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ORIGINAL ARTICLE

# Efficacy of apatinib as third-line treatment of advanced colorectal cancer and prognostic analysis

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## Summary

***Purpose:*** *To explore the efficacy and safety of apatinib mesylate in the third-line treatment of advanced colorectal cancer after the standard second-line treatment failed, and to analyze the possible factors affecting the prognosis.*

***Methods:*** *The clinical data of 52 patients with advanced colorectal cancer who failed or were intolerant of the standard second-line treatment performed in our hospital from January 2017 to December 2018 were collected. All the patients received the third-line treatment with apatinib mesylate tablets that were administered at 500 mg q.d. with 28 d as an administration cycle, and the clinical efficacy of apatinib mesylate and incidence of adverse reactions were recorded and analyzed. Besides, the survival and disease progression of the patients were followed up and recorded, and the influencing factors for the prognosis were analyzed.*

***Results:*** *The remaining 50 patients had efficacy evaluation, and it was found that the overall response rate (ORR) and disease control rate (DCR) were 8.0% (4/50) and 50% (25/50), respectively. The median survival, median progression-free survival (mPFS) and 1-year overall survival (OS) rate were 7.6±2.5, 4.0±1.7 and 26.9% (14/52), respectively. After treatment, the patients had increased scores for all items on the functional scale of the Quality of Life Questionnaire Core 30 (QLQ-C30). Decreases in the scores for all items on the symptomatic scale were also found after treatment, and the mitigation of the symptoms nausea and vomiting and pain was statistically significantly different. According to multivariate analysis results, the mPFS was significantly prolonged in the patients with CerB2$^{++/+++}$, the positivity rate of Ki-67 ≥50% and the presence of hypertension after treatment.*

***Conclusions:*** *Apatinib is effective in the third-line treatment of advanced colorectal cancer, significantly improves the patient quality of life, and causes tolerable adverse reactions. The mPFS is markedly extended in the patients with CerB2$^{++/+++}$, positivity rate of Ki-67 ≥50% and the presence of hypertension after treatment, which are the independent factors affecting the efficacy.*

***Key words:*** *apatinib, third-line treatment, colorectal cancer, late stage, efficacy, prognosis*

## Introduction

Colorectal cancer is the most common malignancy of the digestive system in the clinic and its incidence ranks third among all malignant tumors [1]. Since this disease has atypical symptoms in the early stage, many patients are not definitely diagnosed until the advanced stages of tumors, and they have extensive lymph node or distant organ metastases. If untreated, the patients will have overall survival (OS) of 3-5 months [2,3]. Fluoropyrimidine-based dual-drug combination chemotherapy or its combination with targeted drugs, as the standard first- and second-line therapy schemes for patients with advanced colorectal cancer, has greatly prolonged the survival of such

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patients, with median survival time reaching nearly 2-3 years [4,5]. However, no exactly efficacious treatments have been found after the failure of the second-line treatment.

Apatinib, a self-developed small-molecule tyrosine kinase inhibitor in China, competitively binds to vascular endothelial growth factors receptor-2 (VEGFR-2) to block the transduction of the downstream signaling pathways and inhibit tumor angiogenesis, further exerting an anti-tumor effect [6,7]. At present, apatinib is mainly used to treat gastric cancer and other gastroesophageal junction cancers when the second-line treatment fails, and it exhibits favorable efficacy and tolerability in the treatment of colorectal cancer, lung cancer, breast cancer and liver cancer [8,9]. Few studies now have implied that apatinib mesylate has efficacy benefits and controllable toxicity in treating advanced colorectal cancer [10]. In this study, the clinical data of 52 patients with advanced colorectal cancer who were treated in our hospital from January 2017 to December 2018 were retrospectively analyzed, and the efficacy and safety of apatinib in the third-line treatment of advanced colorectal cancer after the standard second-line treatment failed were analyzed as well. Besides, the possible factors affecting the prognosis were explored.

## Methods

*General data*

The clinical data were collected from 52 patients with advanced colorectal cancer treated in our hospital from January 2017 to December 2018, and among them, there were 31 males and 21 females aged 28-77 years old with a mean age of 57.14±8.34.

*Inclusion criteria:* 1) patients aged ≥18 years old; 2) those who suffered from metastatic colorectal cancer and could not undergo surgery; 3) those who previously failed or were intolerant of a standard second-line chemotherapy with fluoropyrimidines, irinotecan and oxaliplatin and had at least a target lesion with measurable diameter according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1); 4) those able to orally take drugs; and 5) those with an ECOG performance score of 0-1.

*Exclusion criteria:* 1) patients who had been confirmed to be allergic to apatinib mesylate; 2) those with a high blood pressure that failed to be reduced within the normal range after treatment with antihypertensive medications, or severe heart, lung, liver or kidney disease; 3) those with multiple factors affecting oral drugs, such as inability to swallow, nausea, vomiting, chronic diarrhea or ileus; 4) those with an obvious tendency towards gastrointestinal bleeding; 5) those with accompanying central nervous system metastasis; or 6) those complicated with other malignant tumors.

The baseline clinical data of the 52 patients are presented in Table 1. All the participants were informed and signed the informed consent form before the study entry in accordance with the Declaration of Helsinki. This study was approved by the Ethics Committee of Shengzhou People's Hospital.

*Treatment methods*

The patients who were intolerant of the second-line therapy and experienced failure of the second-line treatment were administered apatinib mesylate tablets (Jiangsu Hengrui Medicine Co., Ltd., NMP No.: H20140103) at 500 mg q.d., with 28 d as a treatment cycle. Drug administration was continued for the patients with complete remission (CR), partial remission (PR) and stable disease (SD) until the disease progressed. Finally, the drug administration was stopped when patients developed intolerant toxicity, asked for drug withdrawal or had progressive disease (PD). According to the severity

**Table 1.** Demographics and general clinical data of all studied patients

| *Parameters* | *Cases (n=52) n (%)* |
|---|---|
| Gender (Male/Female) | 31/21 |
| Age (years), mean±SD | 57.14±8.34 |
| BMI (kg/m$^2$), mean±SD | 24.29±3.56 |
| Tumor location | |
| Left colon | 23 (44.2) |
| Right colon | 21 (40.4) |
| Rectum | 8 (15.4) |
| Differentiation grade | |
| Poor | 28 (53.8) |
| Moderate | 24 (46.2) |
| High | 0 (0) |
| Metastasis | |
| Single organ | 33 (63.5) |
| Multiple organ | 19 (36.5) |
| ECOG PS | |
| 0 | 20 (38.5) |
| 1 | 30 (57.7) |
| 2 | 2 (3.8) |
| CEA level (ng/ml) | |
| <25 | 16 (30.8) |
| ≥25 | 36 (69.2) |
| KRAS | |
| WT | 29 (55.8) |
| MUT | 23 (44.2) |
| CerB2 | |
| -, + | 27 (51.9) |
| ++, +++ | 25 (48.1) |
| Ki-67 (%) | |
| <50 | 7 (13.5) |
| ≥50 | 45 (86.5) |

BMI: body mass index; ECOG PS: Eastern Cooperative Oncology Group performance status; CEA: carcinoembryonic antigen

of adverse reactions, the dose could be adjusted to 250 mg q.d. Drug withdrawal and dose reduction were allowed for the cases of grade III hematological toxicity, and grade II non-hematological toxicity. The decreased dose could not be increased to the previous level. Drug dose was adjusted once at most for each patient. In other words, after the dose was decreased to 250 mg q.d., no further dose adjustment was allowed. If patients had grade 3 or above proteinuria after treatment, drug dose needed to be properly adjusted according to their own conditions. Before treatment, the blood pressure of patients with hypertension was controlled within the normal range using antihypertensive drugs, while no preventive antihypertensive treatment was required for those with normal blood pressure.

*Observation indicators*

CT scans were performed on all patients every 8 weeks for efficacy evaluation until disease progression. The efficacy was evaluated based on the RECIST of the USA National Cancer Institute (NCI): CR: disappearance of all target lesions for more than 4 weeks; PR: a 30% decrease in the sum of the longest diameter of target lesions for more than 4 weeks; PD: a 20% increase in the sum of the largest diameter of target lesions or the appearance of one or more new lesions for more than 4 weeks; and SD: neither sufficient shrinkage of lesions to qualify for PR nor sufficient increase in lesions to qualify for PD for more than 4 weeks [6].

The adverse reactions of patients were observed and recorded during treatment. Then they were graded and assessed according to the USA NCI-CTCAE v4.03 and the incidence rates of grade I-IV bone marrow suppression, liver and kidney function impairment, hypertension, proteinuria and hand-foot syndrome were analyzed. At 2 weeks after treatment, the quality of life of patients was evaluated using the Quality of Life Questionnaire Core 30 (QLQ-C30) developed by the European Organization for Research and Treatment of Cancer (EORTC), and the results were converted to 0-100 points based on the EORTC scoring guidelines. The higher scores for the functional module and greater sum of the scores for all modules indicated better quality of life, while the quality of life was poorer in the patients with higher scores for the symptomatic module.

All the patients were followed up via outpatient re-examination and telephone until December 2019, and patients' survival and disease progression were recorded. Overall survival (OS) was defined as the duration from the initial oral administration of apatinib to the death of patients or the last follow-up. Progression-free survival (PFS) represented the duration from the initial oral administration of apatinib to tumor progression or the death of patients.

*Statistics*

SPSS 22.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data were presented as mean ± standard deviation and intergroup comparisons were made using pairwise t-test. Enumeration data were expressed as ratio (%) and compared between groups by $x^2$ test. Survival curves were plotted using the Kaplan-Meier method and comparison of survival was determined by log-rank test. The factors affecting the prognosis of patients were analyzed using univariate and multivariate Cox regression analysis. The differences were considered as statistically significant with $p<0.05$.

## Results

*Treatment conditions*

The median duration from the definite diagnosis of the 52 patients to the start of treatment with apatinib was 7.8 months (3-20). A total of 25 patients (48.1%) were administered apatinib at a dose of 500 mg. The drug was discontinued in 2 cases due to intolerable adverse reactions. Of the other 25 (48.1%) patients who stopped apatinib because of disease progression, 17 received interventional therapy, palliative radiotherapy or symptomatic and supportive treatments, 7 patients continued to undergo chemotherapy combined with cetuximab, bevacizumab, or programmed cell death protein-1 antibody therapy and 1 patient was treated with regorafenib.

*Clinical responses to treatment*

The drug was withdrawn at 2 months and 3 months after administration, respectively, for 2 patients who were intolerant to adverse reactions, so their short-term outcomes cannot be evaluated. The efficacy was evaluated in the remaining 50 patients, and it was found that there were 0 cases of CR, 4 cases of PR, 21 cases of SD and 25 cases of PD, with an overall response rate (ORR) of 8.0% (4/50) and a disease control rate (DCR) of 50% (25/50).

**Table 2.** Comparison of adverse reactions of the studied patients

| *Parameters* | *Cases (n=52)* | |
|---|---|---|
| | *Grade I-IV n (%)* | *Grade III-IV n (%)* |
| Leukopenia | 6 (11.5) | 2 (3.8) |
| Anemia | 5 (9.6) | 0 (0) |
| Thrombocytopenia | 3 (5.8) | 0 (0) |
| Nausea and vomiting | 14 (26.9) | 0 (0) |
| Transaminase elevation | 5 (9.6) | 0 (0) |
| Creatinine elevation | 4 (7.7) | 0 (0) |
| Proteinuria | 20 (38.5) | 9 (17.3) |
| Hypertension | 23 (44.2) | 10 (19.2) |
| Hand-foot syndrome | 22 (42.3) | 7 (13.5) |
| Oral mucositis | 11 (21.2) | 0 (0) |
| Arrhythmia | 3 (5.8) | 0 (0) |
| Fatigue | 9 (17.3) | 0 (0) |

**Table 3.** Comparison of pretreatment and posttreatment EORTC-QLQ-C30 scale scores of the studied patients

| *Complications* | *Pretreatment (n=52)* | *Posttreatment (n=52)* | *p value* |
|---|---|---|---|
| QLQ-C30 | | | |
| Functioning scales | | | |
| Physical | 88.68±12.21 | 94.38±11.38 | 0.016 |
| Role | 89.54±11.47 | 93.28±11.56 | 0.101 |
| Emotional | 88.33±13.78 | 94.36±12.46 | 0.021 |
| Social | 89.51±12.67 | 91.12±12.97 | 0.490 |
| Cognitive | 89.89±10.75 | 92.71±11.66 | 0.203 |
| Symptom scales | | | |
| Fatigue | 24.85±11.16 | 26.84±11.81 | 0.379 |
| Nausea and vomiting | 25.08±10.84 | 30.06±13.43 | 0.040 |
| Pain | 35.39±8.79 | 39.31±8.05 | 0.020 |

EORTC: European Organization for Research and Treatment of Cancer

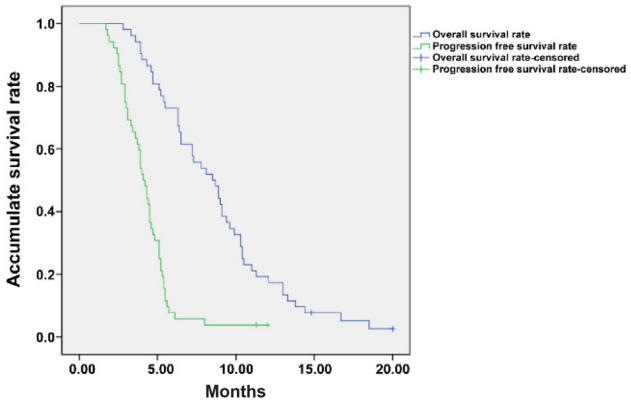


**Figure 1.** Kaplan-Meier survival curves of advanced colorectal cancer patients. Shown are overall survival rate and progression free survival rate of advanced colorectal cancer patients (p<0.05).

*Incidence of adverse reactions*

During treatment, no patients died of severe adverse reactions, and 2 patients were withdrawn from the treatment due to intolerable adverse reactions. Drug dose was decreased in 9 cases for adverse reactions. All the patients had different grades of adverse reactions of which the most common were hand-foot syndrome, secondary hypertension and proteinuria, with the incidence rate significantly higher than those of other adverse reactions including fatigue, bone marrow suppression, nausea and vomiting, transaminase elevation, creatinine elevation, oral mucositis and arrhythmia. Most grade I-II adverse reactions were relieved after symptomatic treatment or reduction in apatinib dose. Grade III and above adverse reactions were mainly leucopenia, proteinuria, hypertension and hand-foot syndrome, which were observed in 2 (3.8%), 9 (17.3%), 10 (19.2%) and 7 (13.5%) cases, respectively (Table 2).

*Quality of life scores*

All the patients were followed up to record the quality of life before treatment and within 2 weeks after treatment. According to the QLQ-C30 scoring method, the patients had an increased score for each item on the functional scale after treatment, and the difference in the improvement in the physical and emotional functioning were statistically significant (p<0.05), with no statistically significant difference in the improvement in the role, social and cognitive functioning (p>0.05). Decreases in the score for each item on the symptomatic scale were also found after treatment, and the mitigation of the symptoms nausea and vomiting and pain was statistically significantly different (p<0.05), but that of fatigue showed no statistically significant difference (p>0.05) (Table 3).

*Postoperative follow-up results of patients in the two groups*

All the patients were followed up for 3-20 months, and the median survival, median PFS (mPFS) and 1-year OS rate were 7.6±2.5 months, 4.0±1.7 months and 26.9% (14/52) months, respectively. The OS and PFS curves of patients in the two groups were generated by the Kaplan-Meier method (Figure 1).

*Influencing factors for patient survival rate and tumor recurrence*

The univariate analysis was conducted to evaluate the effects of gender, age, tumor location, grade of tumor differentiation, number of metastases, level of serum carcinoembryonic antigen (CEA) before treatment, KRAS genotype, CerB2 status, positivity rate of Ki-67 and presence or absence of hypertension and proteinuria after treatment on the mPFS

**Table 4.** Univariate analysis of predictors for mPFS in advanced colorectal cancer patients after apatinib treatment

| *Parameters* | *Cases (n=52) n (%)* | *mPFS (months)* | *p value* |
|---|---|---|---|
| Gender | | | 0.099 |
| Male | 31 (60.7) | 3.7±0.8 | |
| Female | 21 (39.3) | 4.1±0.9 | |
| Age (years) | | | 0.133 |
| <60 | 36 (18.0) | 3.8±0.9 | |
| ≥60 | 16 (43.8) | 4.2±0.8 | |
| Tumor location | | | |
| Left colon | 23 (44.2) | 4.2±0.7 | 0.123 |
| Right colon | 21 (40.4) | 3.7±0.9 | |
| Rectum | 8 (15.4) | 3.8±0.9 | |
| Differentiation grade | | | 0.064 |
| Poor | 28 (53.8) | 3.6±0.8 | |
| Moderate | 24 (46.2) | 4.1±1.1 | |
| Metastasis | | | 0.102 |
| Single organ | 33 (63.5) | 4.2±0.9 | |
| Multiple organs | 19 (36.5) | 3.8±0.7 | |
| CEA level (ng/ml) | | | 0.016 |
| <25 | 16 (30.8) | 4.4±1.0 | |
| ≥25 | 36 (69.2) | 3.7±0.9 | |
| KRAS | | | 0.155 |
| WT | 29 (55.8) | 3.7±0.9 | |
| MUT | 23 (44.2) | 4.1±1.1 | |
| CerB2 | | | 0.015 |
| -,+ | 27 (51.9) | 3.8±0.7 | |
| ++,+++ | 25 (48.1) | 4.6±1.2 | |
| Ki-67 | | | 0.017 |
| <50 | 7 (13.5) | 3.3±0.6 | |
| ≥50 | 45 (86.5) | 4.5±1.1 | |
| Hypertension after treatment | | | 0.004 |
| Yes | 23 (44.2) | 4.8±1.2 | |
| No | 29 (55.8) | 3.7±0.7 | |
| Proteinuria after treatment | | | 0.478 |
| Yes | 20 (38.5) | 4.1±1.1 | |
| No | 32 (61.5) | 3.9±0.9 | |

mPFS: mean progression free survival; CEA: carcinoembryonic antigen

**Table 5.** Multivariate Cox regression analysis of predictors for mPFS in advanced colorectal cancer patients after apatinib treatment

| *Parameters* | *HR* | *95%CI* | *p value* |
|---|---|---|---|
| CEA level < 25 ng/ml | 1.413 | 0.748-1.964 | 0.231 |
| CerB2 (++,+++) | 0.872 | 0.572-0.985 | 0.037 |
| Ki-67 ≥ 50% | 0.906 | 0.628-0.953 | 0.043 |
| Hypertension after treatment | 0.840 | 0.587-0.978 | 0.033 |

CEA: carcinoembryonic antigen; HR: hazard ratio; CI: confidence interval

of patients. According to the results, the mPFS of patients with advanced colorectal cancer was correlated with serum CEA level before treatment, CerB2 status, the positivity rate of Ki-67 and the presence or absence of hypertension after treatment ($p<0.05$). Moreover, the mPFS was significantly extended in the patients with the level of serum CEA before treatment <25 ng/mL, CerB2$^{++/+++}$, the positivity rate of Ki-67 ≥50% and the presence of hypertension after treatment (p=0.016, p=0.015, p=0.017, p=0.004) (Table 4). Then the above four factors were included into the Cox's proportional hazards regression model for multivariate analysis. It was found that CerB2 status, the positivity rate of Ki-67 and the presence or absence of hypertension after treatment were independent influencing factors for the mPFS of patients, and the mPFS was significantly prolonged in the patients with CerB2$^{++/+++}$, the positivity rate of Ki-67 ≥50% and the presence of hypertension after treatment [hazard ratio (HR)=0.872, 95% confidence interval (CI) (0.572-0.985), p=0.037, HR=0.906, 95%CI (0.628-0.953), p=0.043, HR=0.840, 95%CI (0.587-0.978), p=0.033] (Table 5).

## Discussion

As the third leading malignancy worldwide, colorectal cancer is mainly treated with surgical resection in the early stages and systemic chemotherapy combined with targeted therapy in the late stages for the patients who lack the opportunity for surgery. In the first- and second-line treatments with fluoropyrimidines as the core, are combined with oxaliplatin, irinotecan and anti-vascular endothelial growth factor (VEGF) and anti-epidermal growth factor receptor (EGFR) targeted drugs. The third-line and later-line treatments are difficult to perform in the clinic, since disease progression lowered RR, and weakened body tolerance pose severe challenges to subsequent treatments [11]. As with other malignancies, the key factor for tumor growth and metastasis in advanced colorectal cancer is neovascularization that mainly depends on the overexpression of VEGFRs, of which VEGFR-2 is the most closely related to tumor angiogenesis [12,13]. Currently, the antitumor angiogenesis drugs are dominated by macromolecular antibodies such as aflibercept and bevacizumab and small-molecule tyrosine kinase inhibitors, mainly including regorafenib used for the standard third-line treatment of metastatic colorectal cancer [14,15]. However, there is no effective biomarker for monitoring the prediction of efficacy of such drugs now, so that the therapeutic effect is limited and fails to reach the expected. Therefore, accurate predictive factors for efficacy are particularly important [16].

Apatinib mesylate can highly and selectively bind to and inhibit VEGFR-2, block the downstream signals, and restrain the VEGF-mediated migration and proliferation of endothelial cells, thereby repressing neovascularization, so this drug excels in antitumor angiogenesis and antitumor activity. Current phase I and II trials have indicated that apatinib mesylate has favorable antitumor activity and controllable toxicity in several solid tumors, such as gastric cancer, breast cancer and non-small cell lung cancer [17,18]. In a phase III clinical trial of advanced gastric cancer, apatinib mesylate treatment enabled a higher DRR, prolonged median survival time and reduced risk of death compared with placebo, and it caused adverse reactions similar to those induced by other drugs of the same type in the incidence rate and type, most of which can be controlled, relieved and reversed by dose adjustment and symptomatic treatment [19]. According to some of previous studies, apatinib mesylate produced benefits and controllable toxicity in advanced colorectal cancer [20]. Therefore, apatinib mesylate was used as third-line treatment for patients with advanced colorectal cancer after the failure of the standard third-line treatment in this study. It was found that the ORR and DCR of patients after treatment were 8.0% (4/50) and 50% (25/50), respectively. According to the follow-up results, the median survival, mPFS and 1-year OS rate were 7.6±2.5 months, 4.0±1.7 months and 26.9% (14/52) months, respectively. These results imply that apatinib mesylate treatment has a tendency to benefit patients with colorectal cancer in the third-line treatment and its efficacy seems to be superior to or at least match with that of single-agent antitumor angiogenesis inhibitor therapy in previous study reports [21], such as the reports of Tournigand et al [22] on the phase III trial of bevacizumab and the regorafenib in the third-line treatment of colorectal cancer. In terms of safety, apatinib mesylate mainly caused grade I-II adverse reactions that were relieved after symptomatic treatment or reduction in apatinib dose, and the main grade III and above adverse reactions were leucopenia, proteinuria, hypertension and hand-foot syndrome, which were observed in 2 (3.8%), 9 (17.3%), 10 (19.2%) and 7 (13.5%) cases, respectively.

The development and progression of tumors are complex and variable, and single-agent antitumor angiogenesis treatment has slightly poorer efficacy, so efficacy limitation is a hotspot that remains to be explored and solved. It is now believed that the factors affecting the therapeutic efficacy and outcome of antitumor angiogenesis drugs include heterogeneity of tumor angiogenesis and

progression, changes in signaling pathways, enhancement of aberrant expression of angiogenic factors, abnormalities in the immune microenvironment, infiltration of inflammatory cells and abnormal perfusion and hypoxia in the tumor cell environment [23]. Studies have suggested that the occurrence of hypertension is correlated with better clinical outcomes of some antiangiogenesis targeted drugs [24,25]. The results of the present study indicated that the patients with CerB2$^{++/+++}$, positivity rate of Ki-67 ≥50% and the presence of hypertension after treatment had a beneficial trend of apatinib mesylate treatment, which agrees with previous literature reports.

This retrospective study was limited by the low number of samples and less comprehensive follow-up contents, so the conclusion of the present study needs to be further corroborated by multicenter, large-sample prospective clinical studies with immunohistochemistry and test of tumor indicators and genes in the future.

## Conclusions

Apatinib has exact efficacy in the third-line treatment of advanced colorectal cancer, significantly improves the quality of life of patients, and causes tolerable adverse reactions. The mPFS is markedly extended in patients with CerB2$^{++/+++}$, positivity rate of Ki-67 ≥50% and the presence of hypertension after treatment, which are independent factors affecting the drug efficacy.

## Conflict of interests

The authors declare no conflict of interests.

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