CLINICAL TRIAL

A phase II study of docetaxel and vinorelbine plus filgrastim for HER-2 negative, stage IV breast cancer: SWOG S0102

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Abstract Docetaxel and vinorelbine have demonstrated Single-agent activity in breast cancer. Preclinical studies suggest potential synergy between these antitubulin chemotherapy agents. This study evaluates these drugs in combination in metastatic breast cancer. Taxane-naive patients with HER-2 negative, stage IV breast cancer without prior chemotherapy for metastatic disease, were eligible. Docetaxel (60 mg/m^2) was given intravenously on Day 1, vinorelbine (27.5 mg/m^2) intravenously on Days 8 and 15, and filgrastim on Days 2–21 of a 21-day cycle. The primary study outcome was one-year overall survival (OS), with secondary outcomes of progression-free survival (PFS), response rate (RR), and toxicity. Of 95 patients registered, 92 were eligible and received treatment. One-year OS was 74 % (95 % CI 64–82 %) with a median OS of 22.3 months (95 % CI 18.8–31.4 months). One-year PFS was 34 % (95 % CI 24–43 %) with median of 7.2 months (95 % CI 6.4–10.3). OS at 2 and 3 years were 49 % (95 % CI 38–59 %) and 30 % (95 % CI 21–40 %), respectively. OS was poorer for women with estrogen-receptor negative disease ($n = 32$) compared to estrogen-receptor positive ($n = 60$) (log-rank $p = 0.031$), but PFS was not significantly different ($p = 0.11$). RR was 59 % among the 74 patients with measurable disease. Grade 3 and 4 adverse events were 48 and 16 %, respectively. Grade 4 neutropenia was 12 % and grade 3/4 febrile neutropenia was 3 %. Common grade 3/4 nonhematologic toxicities were fatigue (14 %), pneumonitis (10 %), and dyspnea (9 %). The combination of docetaxel and vinorelbine is an active first-line chemotherapy in HER-2 nonoverexpressing, metastatic breast cancer. This combination is associated with significant hematologic and nonhematologic toxicity. The safety profile and expense of the filgrastim limit recommendations for routine use.

Keywords Breast cancer · Vinorelbine · Docetaxel · Metastatic

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Introduction

Systemic therapy can decrease tumor burden, palliate symptoms, and lengthen survival in metastatic breast cancer, but is rarely curative. The search for better therapy includes identification of new agents and optimization of established drugs through improved delivery regimens, routes, and combinations.

The taxanes, paclitaxel and docetaxel, bind reversibly and specifically to the β-subunit of the mitotic spindle and promote microtubule polymerization [1]. Polymerized microtubules are quite stable, resulting in inhibition of reorganization of the microtubule network, and blocking cells in the G2-M phase of the cell cycle. Vinorelbine is a semisynthetic vinca alkaloid that inhibits microtubule assembly, interferes with formation of the mitotic spindle, and prevents cell division. Hence, the mechanism of action of taxanes and vinca alkaloids is complementary.

Investigation into the combined use of docetaxel and vinorelbine is supported by synergy shown in preclinical models. Drug-resistant cell lines produced by prolonged exposure to paclitaxel have "tubulin mutant" subunits which have an inherently slow rate of microtubule assembly, and increased sensitivity to vincas [2, 3]. Synergy of docetaxel and vinorelbine has been observed in solid tumors in transgenic mouse models [4].

Studies of docetaxel and vinorelbine in metastatic breast cancer have demonstrated activity of both drugs as single agents and in combination. Docetaxel is commonly given at doses of 60–100 mg/m^2 every 3 weeks. In first-line metastatic breast cancer, docetaxel has response rates (RRs) of 50–68 % [5–8]. RRs of 34–57 % have been reported in anthracycline-resistant patients at 100 mg/m^2 [9–11]. Overall RRs of 44 % have been reported using 60 mg/m^2. [12] The major dose-limiting toxicity of docetaxel is neutropenia, with grade 4 neutropenia occurring in 85–97 % of patients receiving 100 mg/m^2 [5–12].

Single-agent vinorelbine at doses of 25–30 mg/m^2/week shows RRs of 35–50 % first-line and 32–35 % second-line in metastatic breast cancer [13–21]. There may be a dose–response to this agent. A phase I-II trial of weekly vinorelbine with filgrastim achieved a median delivered dose intensity of 27.7 mg/m^2/week, with a 25 % RR in patients with prior taxane and anthracycline exposure [22].

Combinations of taxanes and vinca alkaloids have been studied in attempt to increase RR and survival. The University of Washington performed a trial of docetaxel (60 mg/m^2 day 1) and vinorelbine (27.5 mg/m^2 days 8 and 15) plus filgrastim in 42 metastatic breast cancer patients, 42 % of whom had received prior taxane [23]. Trastuzumab was allowed for HER-2 overexpressing tumors. The overall RR was 74 %, with median time to progression

(TTP) 6.8 months, and median overall survival (OS) of 30 months.

Based on Single-agent activity, noncross-reactivity, and potential synergy, SWOG tested docetaxel/vinorelbine as first-line chemotherapy in metastatic breast cancer. Filgrastim was added to maximize delivered dose intensity. Because of potential efficacy differences related to HER-2 status and HER-2 targeted therapy, two phase II trials were initiated. S0102, the subject of this report, enrolled HER-2 negative disease. S0215 added trastuzumab to the same chemotherapy regimen in HER-2 overexpressing tumors [24].

Patients and methods

The primary objective was to evaluate 1-year OS in HER-2 negative stage IV breast cancer patients. Secondary objectives included assessment of response, disease progression, and treatment-associated toxicity.

Patient population

Eligible patients were women aged ≥18 with HER-2 nonoverexpressing, stage IV breast cancer. Evaluable and measurable disease was allowed. HER-2 status was determined by local immunohistochemistry or fluorescence in situ hybridization. Adjuvant chemotherapy was allowed if >6 months prior. Prior hormonal and radiation therapies were allowed in any setting. Prior taxane or vinca alkaloid was not permitted. Patients were required to have a Zubrod performance status of 0–2, adequate hematologic values, and normal renal and liver function. Exclusions included central nervous system metastases, ≥grade 2 motor or sensory peripheral neuropathy not due to cancer, sensitivity to *E. Coli*-derived proteins, or history of severe hypersensitivity reaction to polysorbate 80. Patients completed written informed consent documenting that they understood the investigational nature of the study and would comply with study procedures.

Study treatment

Day 1 of each 21-day cycle patients received docetaxel (60 mg/m^2) intravenously over 1-h. Beginning one day prior to docetaxel administration, patients received dexamethasone for a total of 3 days to reduce allergy and fluid retention. Filgrastim (5 μg/kg/day) was given subcutaneously days 2–21. Days 8 and 15 patients received vinorelbine (27.5 mg/m^2) intravenously over 6–10 min. Treatment was terminated for disease progression, unacceptable toxicity, delay of treatment for >2 weeks due to hematologic toxicity or >3 weeks due to other toxicity, physician decision, or patient withdrawal.

Dose modification

If the absolute neutrophil count (ANC) was <1,500/mm^3 on the day of chemotherapy, chemotherapy was delayed for 1 week but filgrastim was continued. After 1 week, if the ANC was ≥1,500/mm^3, both docetaxel and vinorelbine were reduced permanently by 25 % and treatment resumed. If ANC remained <1,500/mm^3, treatment was delayed for another week. If ANC was ≥1,500/mm^3 after 2 weeks, docetaxel and vinorelbine were reduced by 25 % and treatment resumed. If ANC continued <1,500/mm^3 at 2 weeks, the patient was removed from protocol. For neutropenic fever, both docetaxel and vinorelbine were reduced by 25 %.

Patients with platelet counts <100,000/mm^3 were suspended from treatment and rechecked at 1 and 2 weeks. If platelets returned to ≥100,000/mm^3, treatment resumed with 25 % dose reduction in both drugs. If platelets continued <100,000/mm^3 at 2 weeks, patients were removed from study.

If patients developed ≥grade 3 motor or sensory neuropathy, docetaxel and vinorelbine were delayed until recovery to grade ≤ 2. For grade ≥ 2 stomatitis, chemotherapy was delayed until grade ≤ 1. If either condition persisted for 3 weeks, the patient was removed from protocol. If evidence of abnormal liver function, docetaxel was held up to 3 weeks until recovery and resumed with 25 % dose reduction. Protocol treatment was terminated if no recovery was observed within 3 weeks. If grade 4 docetaxel hypersensitivity occurred, the patient was removed from protocol. Dose reductions were not made for docetaxel hypersensitivity or fluid retention.

Study assessments

Prior to study entry, clinical information and tumor assessment were completed. CBC/differential/platelets were evaluated at baseline and weekly thereafter. Serum creatinine, bilirubin, SGOT/SGPT, and alkaline phosphatase were assessed at the beginning of each 21-day cycle. Electrolytes were assessed at baseline and after 6 and 15 weeks of treatment. Toxicity was assessed after each cycle.

Radiologic scans were required at baseline and after three cycles (9 weeks), but could be performed more often. Response was measured by RECIST criteria and applied to measurable and nonmeasurable disease. A patient was considered a responder if there was confirmed or unconfirmed partial or complete response. Others were considered nonresponders. RECIST requires evaluation by the same technique, so patients evaluated by different methods were classified as nonresponders, since disease progression may contribute to choice of a different method of assessment or inability to assess disease.

Adverse events were recorded and graded using the standardized NCI common toxicity criteria version 2.0. Within each toxicity category the highest grade of toxicity was recorded for each patient.

Statistical analysis

The primary outcome was 1-year OS, defined as time from registration to death by any cause. A secondary outcome was progression-free survival (PFS), defined as time from registration to the earliest of death or disease progression. Patients known to be alive were censored at last follow-up. The Kaplan–Meier method was used to compute OS and PFS and log-rank tests used to compare patients by hormone-receptor status. The accrual goal was 90, allowing 1-year OS to be estimated within 11 % with 95 % confidence (2-sided). We did not prespecify expected OS to be obtained for the drug combination to be considered better than standard care. All individuals were included in analysis unless ineligible or did not receive study medication.

Table 1 Descriptive characteristics of evaluable patients enrolled in S0102 (n = 92)

Characteristic	Frequency	Percentage
Age (range 30–88)		
<50	26	28
50–59	34	37
60–69	19	21
70–88	13	14
Race/ethnicity		
nonHispanic White	73	79
Hispanic	3	3
Black	9	10
Asian/Pacific Islander	6	7
Native American	1	1
Estrogen receptor status		
Positive	60	65
Negative	32	35
Prior adjuvant chemotherapy		
None	50	54
Anthracycline	21	23
Non-anthracycline	21	23
Prior hormonal therapy (adjuvant or metastatic)	51	55
Number of metastatic sites		
<3	58	63
≥3	34	37
Measurable disease		
Yes	74	80
No	18	20

Fig. 1 Overall survival in S0102. **a** $n = 92$; 77 deaths. **b** By estrogen–receptor status

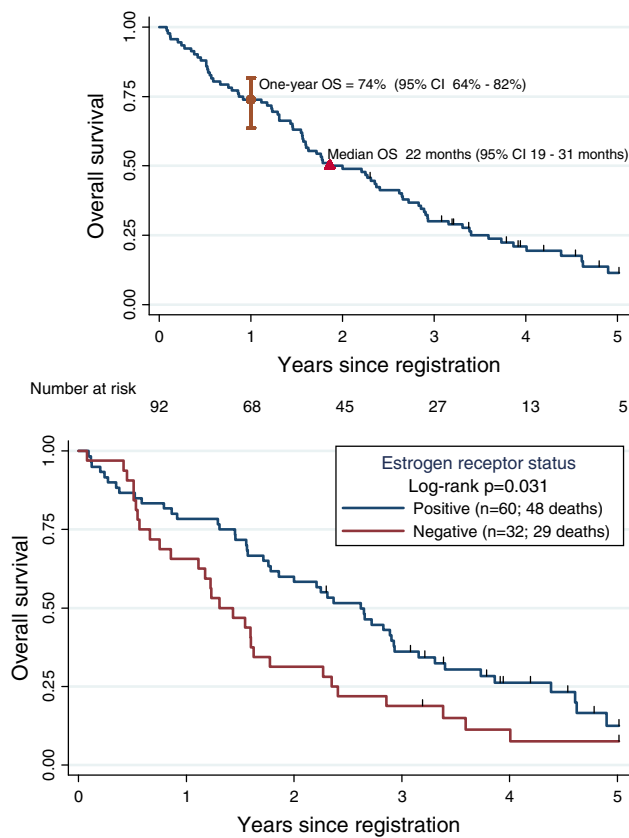**Fig. 2** Progression-free survival in S0102. **a** $n = 92$; 86 events. **b** By estrogen–receptor status

Results

Patient Population

Between May 2001 to January 2004, 95 patients enrolled at 36 institutions. Two patients who did not have disease assessment during the proper time frame were ineligible. One additional patient did not receive treatment and was not evaluable. Of the remaining 92 eligible patients, two did not have toxicity assessments performed, so 90 patients were included in toxicity evaluation. Patient characteristics are summarized in Table 1. Patients ranged in age from 30 to 88 with a median of 56.5 years. Seventeen percent were nonwhite, and 3 % had Hispanic ethnicity. Sixty-five percent had ER-positive tumors. All were HER-2 nonoverexpressing. Fifty-five percent received prior hormonal therapy in the adjuvant or metastatic setting. Forty-six percent had adjuvant chemotherapy, approximately half included anthracycline. Eighty percent of patients had measureable disease, 37 % with ≥3 metastatic sites.

No patients are on protocol treatment at the current time although three patients who have not progressed remain under observation more than 8 years after trial registration. The primary reason for going off treatment was progression
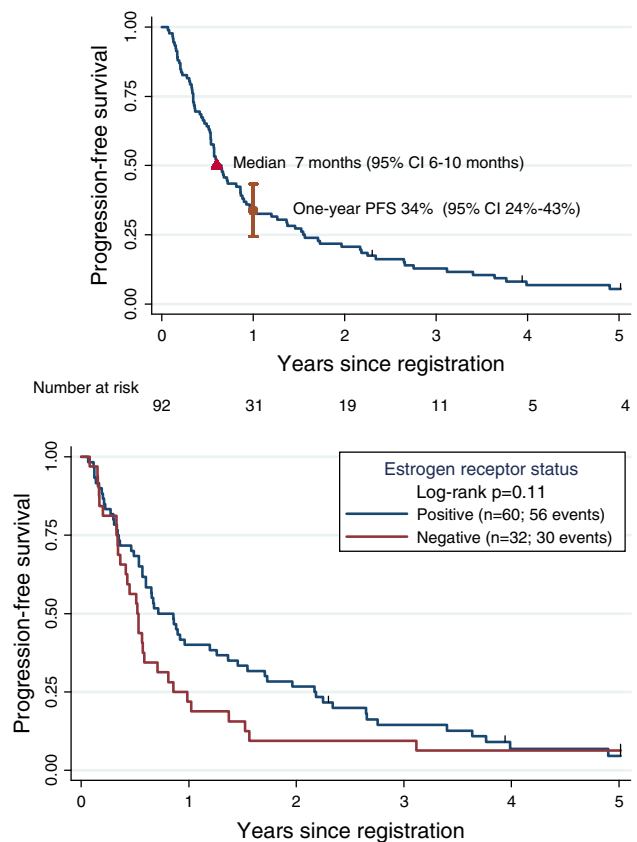
or death (43 %). The remaining reasons were adverse events (27 %), refusal not due to adverse events (15 %), and other unspecified reasons (14 %).

Treatment outcomes

Of the 92 patients, 77 had died by 5 years. Figure 1 shows the Kaplan–Meier plot of OS. OS at 1-year was 74 % (95 % CI 64–82 %), 49 % (95 % CI 38–59 %) at 2-years, and 30 % (95 % CI 21–40 %) at 3-years. Median OS was 22.3 months (95 % CI 18.8–31.4 months). Women with ER-positive disease had longer OS than those with ER-negative disease (log-rank $p = 0.031$) (Fig. 1b). Median OS for the 60 women with ER-positive disease was 31.4 months (95 % CI 21.1–35.0 months) versus 15.7 months for ER-negative disease (95 % CI 9.0–21.3 months).

Of the 92 patients, 86 have progressed or died (Fig. 2). One-year PFS was 34 % (95 % CI 24–43 %), 2-year PFS was 21 % (95 % CI 13–29 %), and 3-year PFS was 13 % (95 % CI 7–21 %). Median PFS was 7.2 months (95 % CI 6.4–10.3 months). Women with ER-positive disease had slightly longer PFS than those with ER-negative disease, though it was not statistically significant (log-rank $p = 0.11$) (Fig. 2b). Since patients continued on treatment

until progression or death, the median duration of treatment was approximately the same as median PFS. For the three off-protocol treatment patients who remain under observation without progression, two have hormone receptor-negative tumors. We did not capture subsequent treatment information after going off-protocol treatment.

Table 2 shows the distribution of responses for the 74 women with measurable disease. There were 44 complete or partial (confirmed or unconfirmed) responses for a RR of 59 % (95 % CI 47–71 %) (Table 2). RR did not differ significantly between ER-positive and ER-negative disease (Table 3; Fisher's exact $p = 0.45$). Three patients were classified as not responding because different imaging techniques were used in response assessments.

Safety

Among the 90 patients evaluable for toxicity, adverse events possibly due to treatment were recorded for 135 different categories. The maximum degree experienced throughout treatment of each adverse event was recorded for each patient. Fourteen (15.6 %) patients reported grade 4 adverse events. Table 4 shows the most common adverse events, including all grade 4 events, and all toxicities with a combined grade 3/4 score of ≥ 5 %.

Three patients (3.3 %) had fatal grade 5 events, rated as possibly treatment-related. One died of progressive respiratory failure following an admission for neutropenic fever and mucositis, and subsequent radiation to an endobronchial mass. Another died following admission for nonneutropenic sepsis and poorly controlled blood sugars. A third died of an acute cardiopulmonary event following

Table 2 Response to treatment ($N = 92$)

Response	Number	Percentage
Complete response	10	11
Partial response	35	38
Stable/no response	25	27
Increasing disease	15	16
Early death	1	1
4Unable to assess	6	7

Table 3 Response to treatment by estrogen receptor status

	ER positive	ER negative	p value
One-year survival	78 % (68–89 %)	66 % (49–82 %)	0.007
Median PFS	10.3 months (6.8–14.4)	6.4 months (4.4–7.1)	0.07
Response rate	32/60 (53 %) (40–66 %)	13/32 (41 %) (24–59 %)	0.28

Table 4 Adverse events possibly related to treatment ($N = 90$)

Adverse event	3	4	5
Any adverse event	43	14	3
Selected hematologic			
Neutropenia/granulocytopenia	12	11	0
Anemia	16	0	0
Thrombocytopenia	1	1	0
Leukopenia	11	5	0
Infection with 3–4 neutropenia	4	1	1
Febrile neutropenia	2	1	0
PRBC transfusion	6	0	0
Selected nonhematologic			
Fatigue/malaise/lethargy	13	0	0
Sensory neuropathy	7	0	0
Hyperglycemia	6	1	0
Stomatitis/pharyngitis	3	2	0
Dyspnea	5	3	0
Hypokalemia	5	0	0
Anorexia	3	1	0
Pneumonitis/infiltrates	6	3	0
Bone pain	6	0	0
Hypocalcemia	4	1	0
Dehydration	5	1	0
Respiratory infect w/neutropenia	1	0	1
Respiratory infect w/o neutropenia	0	0	1
Hypophosphatemia	0	1	0
Hypoxia	1	1	0

admission for presumed community acquired pneumonia without cytopenia. All other deaths occurred after progression.

Discussion

The combination of docetaxel and vinorelbine with filgrastim, as studied in SWOG S0102, is active as first-line chemotherapy in HER-2 nonoverexpressing, metastatic breast cancer. We tested the docetaxel/vinorelbine combination based on potential synergy between these antitubulin agents suggested by preclinical studies. If chemotherapeutic agents with true synergy were identified, the case for combining drugs would be strengthened. While others have studied these agents in combination, the unique features of this study include the schedule of the drugs, the ability to achieve a high dose intensity due to the use of growth factor, and the inclusion of exclusively HER-2 nonoverexpressing breast cancers.

Several groups have studied combinations of the taxanes with other agents. In advanced breast cancer, combination chemotherapy regimens have demonstrated improved

tumor RR, TTP, and prolonged survival when compared to single agents [25, 26]. Most trials have not tested the concurrent administration of two chemotherapy agents versus the same agents given as monotherapy in sequence. When combination chemotherapy regimens have been compared to sequential administration of the same agents, survival has not differed [27]. Combination chemotherapy, with a higher RR, is a reasonable option for some advanced breast cancer patients, particularly those with rapidly progressive, life-threatening disease.

Others have reported on combinations of docetaxel and vinorelbine in different schedules and doses in metastatic breast cancer. Most of these studies delivered the two drugs same day, without growth factor, which led to high RRs but also high toxicity [28–31]. Because of significant neutropenia seen in combining docetaxel and vinorelbine, subsequent studies incorporated growth factor to maintain dose intensity, but still included overlapping same-day dosing of the two drugs [32, 33]. Despite the addition of filgrastim in these trials, neutropenia remained a common toxicity. Other common grade 3/4 toxicities included fatigue, myalgias, and nail toxicities.

The response rate of 59 % in S0102 was comparable to that reported in other docetaxel/vinorelbine trials, which ranged between 43 and 80 % [28–33]. One-year OS, the primary study endpoint for S0102, was 74 % in this multicenter, cooperative group trial. This endpoint is not reported in the other trials, and is, therefore, difficult to compare.

A unique feature of the S0102 regimen was the scheduling of drug administration on separate weeks, as well as the inclusion of growth factor support throughout. Myelosuppression was the primary toxicity, despite use of filgrastim. This study provides further data on the previously reported safety of same-day administration of vinorelbine and filgrastim [22].

A parallel study for patients with HER-2 overexpressing cancers, SWOG S0215, including the addition of trastuzumab to the S0102 docetaxel/vinorelbine regimen has been reported [24]. OS at 1-year in S0215 was 93 %, with a median of 40 months. One-year PFS was 70 %, with median PFS of 21 months. The RR was 66 %. Grade 4 toxicity was 19 % and grade 3 was 33 %. Grade 4 neutropenia was 15 %. No deaths were attributed to treatment in S0215.

Given that S0102 excluded HER-2 overexpressing disease and accrued patients with relatively low prior anthracycline exposure and no prior taxane, it is difficult to find trials with similar populations for comparison. Docetaxel/capecitabine is an FDA approved combination chemotherapy regimen in metastatic breast cancer. Patients in the trial leading to its approval had anthracycline exposure, and up to three prior metastatic chemotherapy

regimens [25]. The trial included cancers with a mix of HER-2 status. The RR was 42 %, TTP 6.1 months, median OS 14.5 months, and 1-year TTP < 20 %. Another approved combination taxane regimen in metastatic breast cancer is paclitaxel/gemcitabine [26]. This regimen was also studied in cancers with a mix of HER-2 expression. Patients had anthracycline exposure, no prior chemotherapy for metastatic disease, and no prior taxane or gemcitabine. The RR was 41.4 %, median PFS 5.9 months, median OS 18.6 months, and 1-year PFS 23 %. E2100, a trial of weekly paclitaxel ± bevacizumab, is a taxane combination trial with a more similar patient population to S0102 [34]. The combination arm in E2100 was taxane plus a biologic and not chemotherapy. Patients in E2100 were essentially HER-2 negative, without prior chemotherapy for metastatic disease, but prior adjuvant chemotherapy, including taxane, was allowed if >12 months prior. This combination strategy showed superiority to Single-agent taxane in RR and PFS. The paclitaxel/bevacizumab arm reported a 36.9 % RR, 11.8 month PFS, 26.7 month OS, and 1-year PFS of 50 %. Two-year PFS was ~15 %. Tolerability of the combination arm was favorable compared to that reported for most taxane combination chemotherapy regimens.

Docetaxel and vinorelbine are active in combination in HER-2 nonoverexpressing, stage IV breast cancer. Both the efficacy and the toxicity of this combination may be schedule and dose dependent. The combination taxane/vinca regimen tested in S0102 is highly effective in first-line metastatic breast cancer, and may have a role in aggressive, rapidly progressive disease. However, safety concerns, including high rates of neutropenia despite the inclusion of filgrastim, as well as the expense of the filgrastim required with this regimen, limit recommendations for routine clinical use. For the majority of metastatic breast cancer patients, use of sequential Single-agent chemotherapies instead of combinations offers less side effects and improved quality of life. Combinations of chemotherapy agents and biologically targeted agents with reduced and/or nonoverlapping toxicities should be explored as a preferred strategy to improve antitumor efficacy and minimize the impact of therapy on patients' quality of life.

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