Clinical Benefits of and Recent Progress in Eribulin Mesylate Therapy for Breast Cancer Patients

Youngjin Park, Tomoaki Kitahara, Kengo Kadoya, Ryoji Kato

ABSTRACT

Metastatic breast cancer is difficult to completely cure with currently available drug therapy, and the main treatment goals are prolongation of survival and improvement of the quality of life (QOL). Eribulin mesylate (eribulin) is a synthetic analogue of halichondrin B. Because eribulin selectively binds with high affinity to only microtubule plus ends, a small number of molecules can exert antitumor effect through microtubule inhibition. A phase III randomized clinical trial (Study 305) was performed in 762 women with locally recurrent or metastatic breast cancer who had previously received 2 to 5 prior chemotherapeutic regimens, including anthracycline- and taxane-based chemotherapy. The results of this study led to the approval of eribulin in the United States in November 2010, followed by the European Union and Japan. The objective of this study was to evaluate the antitumor effect of eribulin in patients with metastatic and primary breast cancer. We expect that eribulin will be shown to be clinically beneficial, thereby contributing to further progress in the treatment of breast cancer.
article is to comprehensively review the clinical benefits of eribulin in patients with breast cancer. This review is based on the following recent findings: the results of clinical trials in women with heavily pretreated metastatic breast cancer (Study 305); the updated results of Study 305; the outcomes of combination therapy with eribulin and other anticancer agents as postoperative adjuvant, preoperative chemotherapy, or treatment for recurrence; the results of previously unreported studies in women with less heavily pretreated metastatic breast cancer (Study 301); and the results of clinical trials of eribulin as first-line treatment for metastatic breast cancer (Study 206, Study 208). Our ultimate goal is contribute to the improved treatment of patients with breast cancer.

DEVELOPMENT OF ERIBULIN

Eribulin is a synthetic analogue of halichondrin B, a natural anticancer agent that was first isolated from the marine sponge Halichondria okadai by Hirata et al in 1986[12]. H. okadai is a rare species that was collected at Aburatubo beach, located on Miura Peninsula, Kanagawa Prefecture, Japan. Subsequently, Bai et al[8] evaluated the antitumor activity of halichondrin B in vitro. The high antitumor activity of halichondrin B prompted interest in the development of a new anticancer drug, but the supply of halichondrin B was limited severely by its complex chemical structure. Clinical development was thus considered difficult (Figure 1A).

In 1992, however, Aicher et al[4] reported the total synthesis of halichondrin B, leading to the synthesis of halichondrin B derivatives to attempt to develop a new anticancer drug. Consequently, structure-activity relationships were defined for halichondrin B, culminating in the successful total synthesis of eribulin, a chemically and biologically optimized derivative[5]. The antitumor activity of halichondrin B was found to be related to its macrocyclic ketone structure, and eribulin was created as a derivative (Figure 1B).

INHIBITORY PATTERNS OF VARIOUS MICROTUBULE INHIBITORS

Microtubule inhibitors such as taxanes and vinca alkaloids have been reported to be highly effective against breast cancer as well as many other types of cancer. Similar to these drugs, eribulin is a microtubule inhibitor that induces apoptosis of cancer cells by stopping mitosis in the G2/M phase of the cell cycle[6-10]. However, recent studies have demonstrated that the mode of inhibitory action of eribulin differs from mechanisms of conventional microtubule inhibitors.

Taxanes (paclitaxel and docetaxel) bind to the inner surface of microtubules and promote microtubule lengthening (polymerization), while inhibiting microtubule shortening (depolymerization) (Figure 2A). Vinca alkaloids (vincristine, vinblastine, etc.) bind to microtubule plus ends and the outer surface of microtubules, inhibiting microtubule lengthening (polymerization) as well as shortening (depolymerization) (Figure 2B). In contrast, eribulin[6-12] binds to only microtubule plus ends and inhibits only microtubule lengthening (polymerization), without affecting shortening (depolymerization) (Figure 2C).

Because eribulin selectively binds with highly affinity to only microtubule plus ends, a small number of molecules can exert antitumor effect through microtubule inhibition. Binding of one molecule of eribulin to two microtubules can inhibit cell proliferation by 50%, and such binding is reversible[10,11]. A recent analysis showed that eribulin binds to a site near the guanosine 5'-triphosphate (GTP) binding site of the β subunit[10]. Because eribulin strongly binds only to this unique site involved in microtubule polymerization, eribulin produces antitumor activity at much lower drug concentrations than conventional microtubule inhibitors.

PHASE I CLINICAL TRIALS FOR SOLID TUMORS (STUDIES 101, 102, 105)

To clarify the dose-limiting toxicity (DLT), maximum tolerated dose (MTD), safety, and antitumor activity of eribulin in patients with solid tumors, three phase I clinical trials (Studies 101, 102, 105) were performed[15].

The DLT was neutropenia, and the MTD was 1.4 mg/m² when given intravenously on days 1 and 8 of 3-week cycles, which was designated as the recommended dose (RD) for the next phase of clinical development (Table 1).

<table>
<thead>
<tr>
<th>Phase</th>
<th>Trial study name</th>
<th>Patient treated No.</th>
<th>DLT</th>
<th>MTD (mg/m²)</th>
<th>Tumor response</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CR PR SD</td>
</tr>
<tr>
<td>101</td>
<td></td>
<td>32</td>
<td>Neutropenia</td>
<td>1.0</td>
<td>1 10</td>
</tr>
<tr>
<td>102</td>
<td></td>
<td>21</td>
<td>Fever neutropenia</td>
<td>2.0</td>
<td>1 12</td>
</tr>
<tr>
<td>105</td>
<td></td>
<td>15</td>
<td>Neutropenia</td>
<td>1.4</td>
<td>3 4</td>
</tr>
</tbody>
</table>

DLT: dose limiting toxicity; MTD: maximum tolerated dose.
PHASE II CLINICAL TRIALS FOR METASTATIC BREAST CANCER (STUDIES 201, 211, 221)

To evaluate the efficacy [overall response rate (ORR), clinical benefit rate (CBR), progression-free survival (PFS), and overall survival (OS)] and safety of eribulin in patients with metastatic breast cancer, three phase II clinical trials were performed\(^{(19-21)}\). The results for efficacy are shown in table 2. In Study 221, response was additionally analyzed according the number of previously received regimens of chemotherapy. The ORR was 36.0% for 0 to 1 regimen, 14.7% for 2 regimens, and 14.3% for 3 regimens, indicating that a lower number of previous regimens were associated with a higher ORR. In addition, two regimens or less were associated with longer PFS and OS (Table 3).

The main types of hematologic toxicity were neutropenia, leukopenia, and lymphopenia. The incidence of febrile neutropenia was low. The main types of nonhematologic toxicity included alopecia, decreased appetite, fatigue, and nausea.

A PHASE III RANDOMIZED CLINICAL TRIAL FOR METASTATIC BREAST CANCER (STUDY 305, EMBRACE)

<table>
<thead>
<tr>
<th>Phase II trial study name</th>
<th>Patient treated No.</th>
<th>ORR (%)</th>
<th>CBR (%)</th>
<th>PFS (median) (days)</th>
<th>OS (median) (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>201</td>
<td>103</td>
<td>11.5</td>
<td>17.2</td>
<td>79</td>
<td>275</td>
</tr>
<tr>
<td>211</td>
<td>291</td>
<td>9.3</td>
<td>17.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>221</td>
<td>81</td>
<td>21.3</td>
<td>27.5</td>
<td>112</td>
<td>331</td>
</tr>
</tbody>
</table>

ORR: objective response rate; CBR: clinical benefit rate; PFS: progression free survival; OS: overall survival.

Table 3 Response according to the number of previously administered regimens of chemotherapy (Study 221).

<table>
<thead>
<tr>
<th>Chemotherapy regimen No.</th>
<th>ORR (%)</th>
<th>Duration of PFS (months)</th>
<th>Duration of OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>14.7</td>
<td>4.0</td>
<td>11.3</td>
</tr>
<tr>
<td>3</td>
<td>14.3</td>
<td>1.9</td>
<td>7.3</td>
</tr>
</tbody>
</table>

ORR: objective response rate; CBR: clinical benefit rate; PFS: progression free survival; OS: overall survival.

NEW PRESENTATIONS IN RECENT YEARS (2010-2013) AFTER STUDY 305

(1) Updated results of Study 305
San Antonio Breast Cancer Symposium (SABCS) 2010
A stratified analysis of Study 305 was presented. OS was analyzed according to the number of prior chemotherapy regimens in subjects with locally recurrent or metastatic breast cancer treated with eribulin monotherapy or TPC. The median OS was significantly longer in the subjects with 0 to 1 prior chemotherapy regimen compared to those with 2 to 5 regimens.

Table 4 Characteristics of phase III clinical trial (Study 305)

<table>
<thead>
<tr>
<th>Enrolled pt. (total 762)</th>
<th>Region 1 (North America/Western Europe/Australia)</th>
<th>Region 2 (Eastern Europe)</th>
<th>Region 3 (Latin America/South Africa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region 1</td>
<td>488 (64%)</td>
<td>193 (25%)</td>
<td>81 (11%)</td>
</tr>
<tr>
<td>Region 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Region 3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Previous therapy

<table>
<thead>
<tr>
<th>Anthracyclines</th>
<th>Taxanes</th>
<th>Capecitabine</th>
<th>Endocrine therapy</th>
<th>Surgery</th>
<th>Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>752 (99%)</td>
<td>754 (99%)</td>
<td>559 (73%)</td>
<td>640 (84%)</td>
<td>652 (86%)</td>
<td>615 (86%)</td>
</tr>
</tbody>
</table>

No. of previous chemotherapy regimens

| 1               | 1 (41%)  |
| 2               | 96 (13%) |
| 3               | 259 (34%)|
| 4               | 245 (32%)|
| 5               | 136 (18%)|
| 6%              | 22 (5%)  |

Most common metastatic sites

| Bone | 464 (61%) |
| Liver| 455 (60%) |
| Lymph nodes | 338 (44%) |
| Lung | 292 (38%) |

A total of 135 centers located in 19 countries of 3 regions of the world participated in this phase III clinical trial\(^{(19)}\). The subjects were 762 patients with metastatic breast cancer who had previously received 2 to 5 regimens of chemotherapy including anthracyclines and taxanes.

The number of enrolled patients according to region, the treatment history, the number of previously received chemotherapeutic regimens, and metastatic sites are shown in table 4.

The investigators decided the best treatment for each subject (= treatment of physician’s choice, TPC) before randomization. Overall, 508 patients were assigned to eribulin monotherapy, and 254 were assigned to TPC. Patients who were assigned to the TPC group received the designated treatment. In the TPC group (247 patients after excluding dropouts), TPC included chemotherapy, endocrine therapy, radiotherapy, biological agents, and best supportive care. Among the 247 eligible patients in the TPC group, 238 (96%) received chemotherapy, including vinorelbine in 61 patients (25%), gemcitabine in 46 (19%), caprectabine in 44 (18%), taxanes in 38 (15%), anthracyclines in 24 (10%), and other anticancer drugs in 25 (10%). Nine patients (4%) were given endocrine therapy. No patient received other types of treatment.

Results for efficacy in the eribulin group and the TPC group were shown. On an independent review of the results, the median OS was found to be significantly longer in the eribulin group (13.1 months) than in the TPC group (10.6 months) (Figuer 3). However, the median PFS was not significantly longer in the eribulin group (3.7 months) than in the TPC group (2.2 months). The ORR was significantly higher in the eribulin group (12%) than in the TPC group (5%). The CBR was similar in the eribulin group (23%) and the TPC group (17%).

Toxic effects were summarized. The most common hematologic toxicity was neutropenia (eribulin group 52%, TPC group 30%), and the most common non-hematologic toxicity was asthenia/fatigue (eribulin group 54%, and TPC group 40%).
eribulin group than in the TPC group among patients who received up to 3 regimens (13.3 months vs 10.7 months, hazard ratio [HR] 0.774, 95% CI 0.606-0.988; \( p = 0.039 \)). OS was not longer in the eribulin group as compared with the TPC group among patients who received more than 3 regimens (11.7 months vs 10.7 months, HR 0.899, 95% CI 0.600-1.348; \( p = 0.607 \)) [20].

A subgroup analysis of Study 305 was performed to determine OS among patients in region 1 (North America, Western Europe, and Australia) who received eribulin during phase III studies. The median OS was significantly longer in patients who received eribulin monotherapy than in those who received TPC (13.1 months vs 10.0 months, HR 0.724, 95% CI 0.568-0.924; \( p = 0.009 \)). The median PFS did not differ significantly (eribulin monotherapy 3.3 months vs TPC 2.2 months, HR 0.843, 95% CI 0.666-1.066; \( p = 0.153 \)) [21].

Updated results of Study 305 were also presented. The median OS was reported to be significantly longer in the eribulin group than in the TPC group (12.45 months) than in the TPC group (10.12 months) [24].

American Society of Clinical Oncology (ASCO) 2011
A subgroup analysis of OS in patients with visceral disease in Study 305 was presented. A total of 624 patients were classified as having visceral disease; 413 patients were randomly assigned to eribulin monotherapy and 211 patients were randomly assigned to TPC. The median OS was found to be significantly longer in the eribulin group (12.45 months) than in the TPC group (10.12 months) [24].

Outcomes obtained with eribulin combined with other anticancer agents as treatment for recurrence, postoperative adjuvant therapy, or preoperative chemotherapy
ASCO 2012
The results of a phase I b clinical trial (Study 203, dose-escalation study) of eribulin plus capecitabine as combined therapy for solid cancers (colon cancer 20.6%, lung cancer 17.7%, breast cancer 14.7%) were presented. This combined therapy was well tolerated, with no unexpected safety findings. The MTD (1.4 mg/m² on days 1 and 8) was selected for evaluation in ongoing phase II clinical trials [25].

A phase II clinical trial (Study 210, NCT01328249) of dose-
dense doxorubicin and cyclophosphamide followed by eribulin monotherapy as adjuvant treatment for HER2-negative, early-stage breast cancer was performed (Figure 4). Feasibility was determined by whether the eribulin portion could be completed without treatment delay or dose reduction\(^{26}\).

Phase II clinical trial (NCT01372579) of eribulin plus carboplatin as combined therapy for neoadjuvant treatment of triple-negative breast cancer was performed (Figure 5).

Toxicity will be assessed for the first 10 patients who receive eribulin at a dose of 1.4 mg/m\(^2\) (over 2-5 minutes intravenously on day 1 and 8) followed by carboplatin at a dose calculated to produce an area under the curve of 6 mg/mL/minute (given over the course of 30 minutes only on day 1). If dose reduction is not required, further patients will be evaluated. The primary endpoint was to determine the rate of pathological complete response (pCR). Secondary endpoints included determination of the clinical response rate, toxicity evaluation, and measurement of stem cells and TLE3 as a biomarker of response to eribulin therapy\(^{27}\).

(3) Therapeutic usefulness of eribulin for patients with less heavily pretreated metastatic breast cancer

At SABCS 2012, the results of a phase III randomized clinical trial (Study 301, NCT00337103) comparing eribulin monotherapy with capecitabine monotherapy in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes were presented. Of the 1,102 patients, 554 were randomly assigned to the eribulin group and 548 to the capecitabine group. The median number of treatment cycles was 6 in the eribulin group.

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**Figure 4** Study design of phase II clinical trial (Study 210) of dose-dense doxorubicin and cyclophosphamide followed by eribulin as combined therapy for adjuvant treatment of HER2-negative, early-stage breast cancer.

**Figure 5** Study design of phase II clinical trial of eribulin plus carboplatin as neoadjuvant combined therapy for triple-negative breast cancer.
and 5 in the capecitabine group. The median OS was 15.9 and 14.5 months (HR=0.879, 95% CI 0.932-1.003; p=0.056), and the median PFS was 4.1 and 4.2 months (HR 1.079, p=0.305) in the eribulin group and the capecitabine group, respectively. Among patients with HER2-negative breast cancer, the median OS was 15.9 months in the eribulin group and 13.5 months in capecitabine group (HR 0.838, p=0.030). In this study, eribulin monotherapy was associated with a trend toward better OS than capecitabine monotherapy[28].

(4) Therapeutic usefulness of eribulin as first-line treatment for metastatic breast cancer

At SABCS 2012, the results of a phase II clinical trial (Study 206, NCT01268150) of eribulin monotherapy as first-line treatment for locally recurrent or metastatic HER2 negative breast cancer were presented. Efficacy and safety were evaluated. Of 56 enrolled patients, 54 had at least 1 post-baseline assessment. ORR was 31% [complete response (CR) 0%, partial response (PR) 31%, stable disease (SD) 48%], and CBR was 48%. The median time to response (TTR), duration of response (DOR), and PFS were 1.4, 5.8, and 6.1 months, respectively. Treatment-related serious adverse events occurred in 5 patients (9%): neutropenia (4%), and febrile neutropenia (5%)[29].

At SABCS 2012, the results of a phase II clinical trial (Study 208, NCT01269346) of eribulin plus trastuzumab as first-line combined therapy for locally recurrent or metastatic HER2-positive breast cancer were presented. Efficacy and safety were evaluated. 37 of 52 planned patients have been treated. The ORR was 60% [CR 5%, PR 54%, SD 30%, progressive disease (PD) 22%], and CBR was 70%. Treatment-related serious adverse events occurred in 4 patients (11%): neutropenia (8%), and febrile neutropenia (6%)[30].

(5) Others

ASCO 2013

Subgroup analyses of a phase ASCO 2013 III randomized clinical trial (Study 301, NCT00337103) comparing eribulin monotherapy with capecitabine monotherapy for locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes was presented. Prespecified exploratory subgroups were defined according to age, receptor status, number and setting of prior chemotherapy regimens, sites of organs involved, and time to progression after the last course of chemotherapy. An analysis of OS suggested that the following subgroups appeared to benefit more from eribulin monotherapy than capecitabine monotherapy (Figure 6): (1) patients with non-visceral disease (HR 0.51, 95% CI 0.33-0.80); (2) patients with >2 organs involved (HR 0.75, 95% CI 0.62-0.90); (3) patients with a time to progression (TTP) of >6 months after the last course of chemotherapy (HR 0.70, 95% CI 0.52-0.95), and (4) patients who had received an anthracycline, a taxane, or both for metastatic disease (HR 0.84, 95% CI 0.72-0.98). For OS, a trend favoring capecitabine was not seen in any subgroup[31].

The results of QOL research in patients with locally advanced or metastatic breast cancer who were previously treated with anthracyclines and taxanes and then received eribulin monotherapy or capecitabine monotherapy (Study 301, NCT00337103) were presented. QOL, a secondary endpoint, was assessed using the EORTC QLQ-C30 and QLQ-BR23 questionnaires at baseline, 6 weeks, and 3, 6, 12, 18, and 24 months after starting treatment (or until PD or treatment change), as well as at unscheduled visits. The primary endpoint was the change from baseline for Global Health Status (GHS)/overall QOL; exploratory endpoints were the change from baseline for each functional domain and signs/symptoms.
GHS/QOL scores improved more in patients who received eribulin monotherapy than in those who received capecitabine monotherapy  

(p=0.048)[32]

The results of a Phase Ⅰ b clinical trial (NCT01554371) of eribulin plus cyclophosphamide as combined therapy for metastatic breast cancer were presented. There was no DLT; the RD for phase Ⅱ was eribulin 1.4 mg/m² on days 1 and 8 plus cyclophosphamide 600 mg/m² on day 1. All grade adverse events included neutropenia (50%), thrombocytopenia, fatigue, nausea, peripheral neuropathy, rash, mucositis, alopecia (38% each) and elevated liver enzymes (17%). Combined therapy with eribulin plus cyclophosphamide was a well-tolerated regimen with promising activity in metastatic breast cancer[30].

DISCUSSION

Randomized controlled clinical trials of a new anticancer agent are designed to show the superiority of a new anticancer agent to control treatment with standard therapy if such therapy has been established or to demonstrate the non-inferiority of a new anticancer agent to control treatment if toxicity is clearly mild. However, if a standard therapy has not been established and various types of anticancer therapy are used in clinical practice, the trial design may include a control group assigned to receive TPC.

In Study 305, the control group was assigned to TPC. Provided that the TPC was monotherapy, patients could receive chemotherapy, endocrine therapy, radiotherapy, biological therapy, or best supportive care. In this study, patients were randomly assigned to treatment after TPC was decided by the investigator, thereby reducing bias.

The median OS, the primary endpoint, was significantly longer in the eribulin group than in the TPC group. On an independent review of the results, the median PFS, a secondary endpoint, was not significantly longer in the eribulin group. On an investigator review of the results, however, the PFS was significantly longer in the eribulin group (3.6 months) than in the TPC group (2.2 months, p=0.002). The difference between the 2 evaluations is attributed to the fact that data on patients in whom PD was difficult to evaluate on imaging studies were censored in the independent review, thereby decreasing the number of patients eligible for analysis and eliminating the significant difference between the groups.

To our knowledge, no single anticancer agent has been demonstrated to significantly prolong OS in patients with metastatic breast cancer who had previously received anticancer therapy including anthracyclines and taxanes. The fact that eribulin monotherapy significantly prolonged OS will most likely have a significant impact on the future management of metastatic breast cancer.

New randomized clinical trials are now ongoing to evaluate eribulin monotherapy, and eribulin plus other anticancer agent as combined therapy, and to compare eribulin monotherapy with monotherapy with other anticancer agents. We outline the objectives of new clinical trials designed to further define the therapeutic usefulness of eribulin.

Eribulin-based combination chemotherapy

(1) Phase Ⅰ b trial of eribulin plus capecitabine for metastatic breast cancer (dose escalation study, Study 203): To determine the maximum tolerated dose and dose-limiting toxicity of eribulin combined with capecitabine in patients with metastatic breast cancer[29].

(2) Phase Ⅱ trial of doxorubicin and cyclophosphamide followed by eribulin for early breast cancer (adjuvant treatment, Study 210):

To clarify the effectiveness of sequential treatment with doxorubicin, cyclophosphamide, and eribulin as postoperative adjuvant chemotherapy in patients with HER2-negative early breast cancer[30].

(3) Phase Ⅱ trial of eribulin plus carboplatin for triple-negative breast cancer (neoadjuvant treatment): To clarify the effectiveness of combination therapy with eribulin and carboplatin in patients with triple-negative breast cancer[31].

(4) Phase Ⅱ trial of eribulin plus trastuzumab for HER2-positive metastatic breast cancer (Study 208): To clarify the efficacy and safety of eribulin combined with trastuzumab, used as first-line standard treatment for patients with HER2-positive metastatic breast cancer[32].

(5) Phase Ⅰ b trial of eribulin plus cyclophosphamide for metastatic breast cancer: To determine the maximum tolerated dose and dose-limiting toxicity of eribulin combined with cyclophosphamide in patients with metastatic breast cancer[33].

Controlled studies of monotherapy

(1) Phase Ⅲ randomized clinical trial of eribulin monotherapy vs capecitabine monotherapy for metastatic breast cancer (Study 301): This phase III study is designed to compare the therapeutic effectiveness of eribulin monotherapy with that of capecitabine monotherapy in patients with less heavily pretreated metastatic breast cancer[28,31].

(2) Phase Ⅱ trial of eribulin monotherapy for HER2-negative metastatic breast cancer (Study 206): To clarify the efficacy and safety of monotherapy with eribulin as first-line treatment for HER2-negative metastatic breast cancer[29].

All new clinical trial results were abstracted from presentations at many meetings (e.g., ASCO, SABCS, and ESMO) held from 2010 through 2013 and must be interpreted carefully until they are published in peer-reviewed journals. However, new clinical trials of eribulin monotherapy and combined therapy are expected to further clarify clinical benefits in patients with metastatic and primary breast cancer.

CONCLUSIONS

We expect that eribulin will be shown to be clinically beneficial, thereby contributing to further progress in the treatment of breast cancer.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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