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Original Research

A phase I/II trial of olaparib tablet in combination with eribulin in Japanese patients with advanced or metastatic triple-negative breast cancer previously treated with anthracyclines and taxanes

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Abstract ***Background:*** We conducted a multicenter phase I/II trial of olaparib plus eribulin in Japanese patients with advanced or metastatic triple-negative breast cancer (TNBC) to determine the recommended phase II dose (RP2D) (phase I) and to examine the efficacy and safety (phase II) (UMIN00009498) of the combined therapy.
Patients and methods: In phase I, olaparib tablet was orally administered twice daily from level 1:25 mg BID to level 7:300 mg BID, with 1.4 mg/m^2 of eribulin on days 1 and 8. In phase II, patients were treated with RP2D to assess the response rate (independent review). The planned sample size was 24 with a threshold of 10%.
Results: One of the 24 patients enrolled in phase I experienced dose-limiting toxicity. The RP2D was established as 300 mg twice daily for olaparib and 1.4 mg/m^2 for eribulin. Among the 24 patients in phase II, the median number of administered courses was 5.5 (range: 1–28). Grade ≥III adverse events included neutropenia (83.3%), leucopenia (83.3%), anaemia (41.7%), febrile neutropenia (33.3%) and thrombosis (8.3%). The response rate was 29.2% (independent; N = 7/24; 90% confidence interval [CI]; 14.6–47.9). Median progression-free survival and overall survival were 4.2 (95% CI, 3.0–7.4) and 14.5 (95% CI, 4.8–22.0) months, respectively. Germline *BRCA1/2* mutation status was observed in three patients in phase I and 2 patients in phase II, respectively. The C_{max} and area under the curve for olaparib increased in a dose-dependent manner, and these parameters for eribulin and olaparib were not influenced by each other.
Conclusions: Combination therapy of olaparib with eribulin shows antitumour activity against advanced or metastatic TNBC, but caution must be exercised in the presence of febrile neutropenia.

1. Introduction

Poly(ADP-ribose) polymerase (PARP) inhibitor monotherapy and combination therapy with cytotoxic agents have shown good response in BRCA-mutated cancers [1]. Olaparib (Lynparza™) was the first PARP inhibitor approved (400 mg capsule formulation, twice daily) for patients with germline BRCA-mutated advanced ovarian cancer [2]. During clinical development, the formulation was changed from capsule to tablet, with a recommended dose (RD) for the tablet as 300 mg twice daily [1,3]. Recent phase II trials examined olaparib plus other drugs in patients with various cancers [2–4].

Breast cancer (BC) is classified into various subtypes, among which, triple-negative breast cancer (TNBC), both oestrogen receptor (ER) negative and progesterone receptor (PgR) negative without human epidermal receptor type 2 (HER2) overexpression, remains a poor prognosis type. Therefore, more effective treatment strategies are required. BRCA1-related BC accounts for 5% of all BCs [5]. Although >50% of BC patients who are *BRCA1* mutation carriers have TNBC based on pathological analysis [6,7], TNBC patients do not necessarily harbour *BRCA1* mutations. However, TNBCs with wild-type *BRCA1* frequently exhibit a downregulation of *BRCA1* expression or alterations in *BRCA1* function, which may occur through methylation of the *BRCA1* promoter or overexpression of the protein that regulates *BRCA1* expression [8–11]. Although olaparib is considered a promising drug for TNBC in combination with cytotoxic agents, there are currently few data on its efficacy in patients with or without *BRCA1* mutation.

Several studies have revealed poor tolerability by myelosuppression of olaparib in combination with several cytotoxic agents that are difficult to administer at the standard dose during each monotherapy. Therefore, we previously examined olaparib in combination with various cytotoxic agents, including paclitaxel, gemcitabine, irinotecan, carboplatin and eribulin, using

the combination index method to select an optimal candidate cytotoxic agent [12]. Eribulin is a halichondrin class antineoplastic drug and is a treatment option for patients previously treated with anthracyclines and taxanes for metastatic or recurrent BC, especially patients with TNBC [13–15]. This phase I/II trial was conducted to determine the RD of olaparib tablet plus eribulin in phase I and to evaluate the efficacy in phase II in patients with metastatic or recurrent TNBC, who have been treated with anthracycline and taxanes.

2. Patients and Methods

2.1. Patients

Patients aged ≥18 years with TNBC were enrolled at seven centres in Japan. TNBC type was defined as ER negative and PgR negative and HER2 negative. Patients who had received treatment with both anthracyclines and taxanes were eligible for participation. Patients in phase II were required to have measurable lesions defined in the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. The complete eligibility criteria are listed in the Supplementary information.

The study was approved by the institutional review board of each study centre and complied with the Declaration of Helsinki and the AstraZeneca policy on bioethics [8]. The study was also compliant with the Japanese Good Clinical Practice. The trial was registered in the University Hospital Medical Information Network Clinical Trials Registry (ID: UMIN00009498). All patients provided written informed consent before enrolment.

2.2. Study design and treatments

This was an open-label, multicenter, phase I/II trial of olaparib plus eribulin in Japanese patients with advanced or metastatic TNBC. Phase I included four cohorts with different dose levels and schedules of olaparib and eribulin (Table S1), and dose escalation in each cohort was based on a 3 + 3 design. In cohort 1, patients received eribulin 1.4 mg/m^2 on day 1 and day 8. Olaparib was escalated from 25 mg BID to 300 mg. Doses ≥400 mg BID were not investigated because in Western patients, a tablet dose ≥400 mg BID was not considered suitable for phase III trials [1,16]. The definition of dose-limiting toxicity (DLT) is listed in the Supplementary Information.

2.3. Pharmacokinetics and pharmacodynamics analyses

The secondary objectives in phase I were to characterise the pharmacokinetic profile of olaparib tablet and eribulin, to evaluate drug interactions and to determine the RD. Pharmacodynamics (PD) of PARP inhibition was assessed by peripheral blood mononuclear cell count. Blood samples for the pharmacokinetics (PK) analysis and pharmacodynamics (PD) analysis were collected from all subjects enrolled in phase I according to the schedule shown in the Supplementary Information. Olaparib PK analysis was conducted at Covance, UK, and the PD analysis was conducted at the National Cancer Center.

2.4. BRCA mutation analysis

BRCA mutation status was analysed by central testing using HBOC screening (FALCO Biosystems/Myriad Genetics) or by local testing, where mutation positive was defined as a confirmed deleterious or suspected deleterious germline BRCA mutation. All patients who received BRCA testing received genetic counselling. BRCA mutation status in tumour was not analysed in the trial.

2.5. Efficacy, PD and PK assessments

Objective tumour response assessments were based on RECIST 1.1. The local investigator review was carried out in phase I and phase II, and the independent central review committee (IRC) was only conducted in phase II to evaluate the primary end-point. The secondary and exploratory objectives included best change from baseline tumour size, the relationship between response and BRCA status, progression-free survival (PFS) and overall survival (OS).

During phase I, blood samples for PK analysis were obtained in cycle 1 days 1–3 and in cycle 2 days 1 and 2 for eribulin, and cycle 1 day 21 and cycle 2 day 1 for olaparib. The PK parameters assessed included area under the plasma concentration–time curve (AUC), maximum plasma (peak) drug concentration (C_{max}), time to reach C_{max} (t_{max}), apparent plasma clearance (CL/F) and oral volume of distribution at steady state (Vss/F). All PK parameters were calculated using Phoenix WinNonlin ver 6.3 (CERTARA, USA).

Blood samples for PD analysis were obtained in cycle 1 days 1 and 2, cycle 1 day 21 to cycle 2 day 2 and at the time of disease progression. PARP inhibition by olaparib was assessed by ELISA in the monotherapy phase of eribulin or olaparib and in the combination therapy in phase I. Blood samples were collected before administration of eribulin and 4 and 24 h after cycle 1 day 1, before eribulin, 6 h after olaparib in cycle 1, day 21 (monotherapy) before eribulin and olaparib, 6 h after of olaparib, 4 h after eribulin in cycle 2 day 1 and before olaparib in cycle 2 day 2 (combination).

2.6. Statistical analyses

No formal power calculation was performed for sample size determination in phase I. In phase II, an objective response rate (ORR) threshold of 10% was considered clinically meaningful, and a lower limit of the two-sided 90% confidence interval (CI) for the observed ORR greater than this threshold demonstrated the efficacy of the recommended dose combination determined in

phase I. By assuming a 30% true ORR, the chance that the observed ORR exceeded the threshold of 10% was 80.0% with 20 patients, using the normal distribution to approximate the binomial distribution for ORR.

Exact 90% CI for ORR was estimated by the Clopper–Pearson method. PFS was defined as the time from trial registration to disease progression or death by any cause. OS was defined as the time from trial registration to death by any cause. Response duration was defined as the time from the first documentation of partial response/complete response (PR/CR), to disease progression or death by any cause. These time-to-event data were analysed by the Kaplan–Meier method, with the 95% CIs being calculated. A two-sided $P < 0.05$ indicated significance. All statistical analyses were conducted in SAS (version 9.4).

3. Results

3.1. Patient characteristics

In phase I, 25 patients were enrolled in cohort 1 between January 2013 and June 2014. One patient was ineligible after the initiation of the study treatment as the pathological diagnosis was not of the TNBC type. In phase II, 24 patients were enrolled between July 2014 and December 2014. Patient demographics are shown in Table S2. Germline *BRCA* mutation status was obtained in five patients (three with and two without *BRCA*1/2 mutation) in phase I and in seven patients (two with and five without *BRCA*1/2 mutation) in phase II. All other patients were of unknown status.

3.2. Safety

The median total treatment cycles were 5 (range, 2–22) in phase I and 5.5 (1–28) in phase II. In phase I, 11 (45.8%) and five (20.8%) patients had eribulin dose reduction and interruption, respectively, and nine (37.5%) and 14 (58.3%) patients had olaparib reduction and interruption, respectively. In phase II, 18 (75.0%) and seven (29.1%) patients had eribulin reduction and interruption, respectively, and 10 (41.6%) and 19 (79.2%) patients had olaparib dose reduction and interruption, respectively.

After the data cut-off for primary analysis (August 31, 2016), a patient in phase II continued to receive treatment. The remaining 23 patients discontinued because of worsening of the underlying disease, two patients discontinued because of adverse events (AEs), and two patients decided to withdraw from the study.

In phase I, only one of the six patients in level 7 experienced DLT as grade IV neutropenia over 7 days, and omitted eribulin on days 8 and 15. The RD was established as olaparib 300 mg twice daily and eribulin 1.4 mg/m^2 on day 1 and day 8.

All patients in both phases reported AEs, and a toxicity grade ≥III was noted for 91.7% of patients in phase I and 95.8% in phase II (Table 1). The most frequent AEs of any grade were leucopenia, neutropenia, anaemia, malaise, mucositis, anorexia and nausea in both phases. Febrile neutropenia (FN) occurred in 20.8% of patients in phase I and in 33.3% of patients in phase II. The rate of use of gulanulocyte stimulatiog factor (G-CSF) for febrile neutropenia was 16.7% (N = 4/24) in phase II. Although one patient had

Table 1
AEs of all grades and grade ≥III occurring in >10% of patients in phases I and II.

AE	Phase I (N = 24)		Phase II (N = 24)	
	All grades	Grade ≥III	All grades	Grade ≥III
Low albumin	1 (4.2)	0	5 (20.8)	0
Elevated aspartate aminotransferase	10 (41.7)	0	2 (8.3)	0
Elevated alanine aminotranferase	10 (41.7)	1 (4.2)	1 (4.2)	0
Elevated alkaline phosphatase	3 (12.5)	0	0	0
Elevated GGTP	3 (12.5)	1 (4.2)	0	0
Elevated creatinine	3 (12.5)	0	6 (25.0)	0
Hair loss	11 (45.8)	0	10 (41.7)	0
Headache	5 (20.8)	0	1 (4.2)	0
Insomnia	1 (4.2)	0	3 (12.5)	0
Fatigue	1 (4.2)	0	3 (12.5)	0
Malaise	19 (79.2)	0	7 (29.2)	0
Decreased body weight	3 (12.5)	0	4 (16.7)	0
Pain	1 (4.2)	0	3 (12.5)	0
Myalgia	3 (12.5)	0	1 (4.2)	0
Musculoskeletal disorder, not	4 (16.7)	0	1 (4.2)	0
Oral mucositis	10 (41.7)	0	13 (54.2)	0
Dysgeusia	7 (29.2)	0	6 (25.0)	0
Loss of appetite	15 (62.5)	0	3 (12.5)	0
Nausea	14 (58.3)	0	12 (50.0)	0
Vomiting	10 (41.7)	0	8 (33.3)	0
Gastritis	3 (12.5)	0	0	0
Abdominal pain	3 (12.5)	0	1 (4.2)	0
Diarrhoea	10 (41.7)	1 (4.2)	4 (16.7)	1 (4.2)
Constipation	8 (33.3)	0	3 (12.5)	0
Oedema	3 (12.5)	0	1 (4.2)	0
Urticaria	3 (12.5)	0	0	0
Maculopapular rash	10 (41.7)	0	4 (16.7)	0
Peripheral sensory	4 (16.7)	0	10 (41.7)	0
Acneiform eruptions	3 (12.5)	0	0	0
Cough	0	0	4 (16.7)	0
Infection, not specific	3 (12.5)	0	6 (25.0)	0
Leucopenia	24 (100.0)	21 (87.5)	24 (100.0)	20 (83.3)
Anaemia	23 (95.8)	4 (16.7)	22 (91.7)	10 (41.7)
Decreased neutrophil count	23 (95.8)	21 (87.5)	24 (100.0)	20 (83.3)
Fever	12 (50.0)	0	8 (33.3)	0
Febrile neutropenia	5 (20.8)	5 (20.8)	8 (33.3)	8 (33.3)

GGTP, γ-glutamyl transpeptidase; AE, adverse effect.

secondary prophylactic G-CSF, no patient had febrile neutropenia in the subsequent cycle.

3.3. Efficacy

In phase I, there were four cases with PR as assessed by the local investigators. In phase II, the ORR as assessed by the local investigators was 37.5% (95% CI, 18.8–59.4%) (Table 2 and Fig. 1). The ORR by IRC assessment was 29.2% (90% CI, 14.6–47.9%), as the IRC evaluated three patients with no measurable lesions. Therefore, the null hypothesis of a 10% ORR was rejected ($P < 0.001$). The relationships between response—as assessed by the local investigators—and BRCA status are shown in Table S4. Median response duration was 5.3 months (95% CI, 2.0–12.4 months), and median PFS and OS were 4.2 (95% CI, 3.0–7.4) and 14.5 (95% CI, 4.8–22.0) months, respectively.

3.4. Pharmacokinetics and pharmacodynamics

The AUC of eribulin was hardly affected by combination with olaparib (Fig. S1). C_{max} and AUC of olaparib increased with increasing dose in both olaparib-only and eribulin plus olaparib combined therapy (Fig. S2). C_{max} and AUC of olaparib were lower when combined with eribulin (Fig. S3). Olaparib reduced PARP activity in all cases and to <20% of baseline or the lower limit of quantification in 71% of patients. Eribulin mesylate-only elevated and reduced PARP activity in 50% and 21% of patients, respectively, while eribulin mesylate plus olaparib reduced PARP activity in 79% of patients. Therefore, olaparib inhibited PARP activity in both monotherapy and in combination therapy. PARP activity was increased in 50% and reduced in 20.8% of patients undergoing eribulin monotherapy.

Table 2
Tumour response (phase II).

Tumour response (local), N (%)	
CR	1 (4.2%)
PR	8 (33.3%)
SD	9 (37.5%)
PD	5 (20.8%)
NE	1 (4.2%)
Clinical benefit rate (local, CR+PR+SD)	18(75%)
ORR	9 (37.5%)
95% CI	18.8–59.4
Tumour response (independent), N (%)	
CR	0 (0%)
PR	7 (29.2%)
SD	7 (29.2%)
PD	6 (25%)
Clinical benefit rate (independent, CR+PR+SD)	14(58.3%)
NE[a]	4 (16.7%)
ORR	7 (37.5%)
95% CI	12.6–51.1
Median duration of response in months	5.26
95% CI	2.03–12.39
Median PFS in months	4.2
95% CI	3.0 to 7.4
Median OS in months	14.5
95% CI	4.8 to 22.0

CI, confidence interval; CR, complete response; NE, not evaluable; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

[a] Three patients had no target lesion as observed by the independent review committee and one patient discontinued treatment due to adverse events before efficacy evaluation.

4. Discussion

A previous phase I dose-finding study evaluated olaparib tablet in Japanese patients with advanced solid tumours [1]. No DLTs were reported at 300 mg BID; thus, this dose was considered tolerable [1]. Multiple studies have investigated the tolerability of olaparib capsule combined with other drugs. These studies established olaparib capsule combination regimens and RD; however, the RD in these studies was generally lower than the standard doses of combination drugs [17–22]. In addition, topotecan plus olaparib capsule was not tolerable because of the associated severe haematological toxicity and a subtherapeutic maximum tolerated dose [23]. The present study recommends the phase II dose of eribulin plus olaparib tablet based on information obtained during the cycle 1 DLT evaluation period, which corresponds to the standard monotherapy dosages.

Anaemia and FN reportedly were 32.1% and 14.8%, respectively, in a phase II study of eribulin in Japanese BC patients previously treated with anthracyclines and taxanes [24]. Pyrexia, neutropenia and FN were often observed in eribulin. Frequencies of bone-marrow toxicity, and FN have been suggested to be generally higher in Japanese patients than in Western patients [14,15,24]. Therefore, we did not include the low-risk grade III FN patients, as they could be safely treated by oral antibiotics, to define DLT in this phase I study. FN was observed in 20.8% patients in phase I, similar to that previously reported for eribulin in Japanese patients. Phase I trials of weekly paclitaxel plus olaparib or cisplatin plus olaparib required primary prophylaxis with granulocyte-colony stimulating factor because of severe myelosuppression, even though the doses were lower than the recommended monotherapy doses for each drug. According to the safety profile for long-term tolerability in the total treatment courses of the phase II, especially for the frequency of febrile neutropenia and dose modification, the initial dose modification of this combination is more suitable when further developments are performed.

The ORRs in the study were higher than that reported for eribulin in metastatic or recurrent BC patients, previously treated with anthracyclines and taxanes. The ORR for eribulin for TNBC in Study 305 was 12% [14], and 11.0% in Study 301 [15]. The ORR

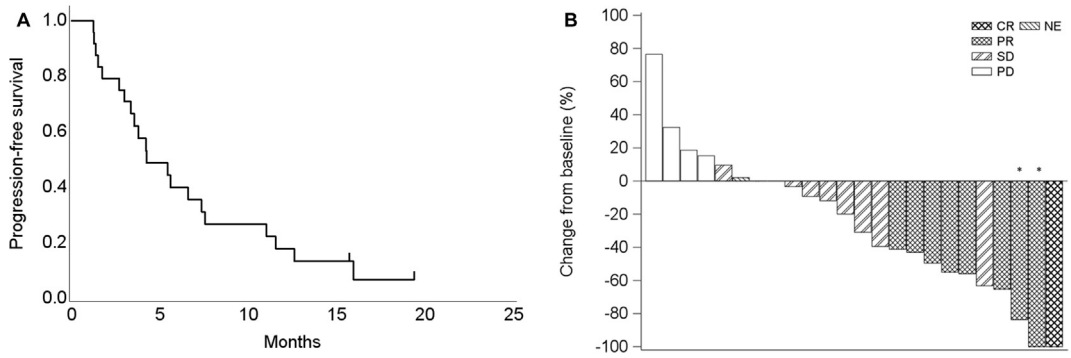

Fig. 1. Efficacy in phase II (N = 24). (A) Progression-free survival (local investigator assessment) and overall survival. Dotted line indicate progression-free survival, and solid line, overall survival. (B) Maximum decline in tumour size from baseline (local investigator assessment). *Patients with BRCA-mutated status. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; NE, not evaluable.

was 13% in 62 BC patients with BRCA mutation–positive status, treated with olaparib [25]. Another study reported no confirmed response in 26 patients with TNBC, including 10 patients with BRCA mutation–positive status [26]. In the OlympiAD study, a phase III trial of olaparib in patients with BRCA mutation–positive advanced BC, the ORR was 59.9%, with 9.9% of patients exhibiting CR [27]. In this study, in five of the 23 patients, the tumour shrunk >30% from baseline, and all patients were BRCA mutation positive. Two patients with known BRCA mutation status and 40% of BRCA mutation–negative patients showed PR. These findings suggest that *BRCA* mutation status may be related to the response to olaparib; however, the response rate to olaparib based on a *BRCA* mutation–positive status may not necessarily be high. A limitation of the present study was that *BRCA* mutation status was not available for most of the patients. In the five patients with *BRCA* mutation-positive status, in the present study, one of the three patients in phase I and two of the two patients in phase II achieved PR. In this exploratory phase I/II trial, we explored the potential predictive factor of efficacy using TNBC patient samples. This correlation analysis of homologous recombination deficiency in tumour samples might shed more light on the predictability of the response to olaparib plus eribulin on the basis of *BRCA* mutation status. We will report the correlative analysis results from this trial in an upcoming report. In addition, several recent challenges to explore promising drug developments for TNBC are ongoing. This is in efforts to find other predictors of efficacy for DNA damage repair inhibitors, including the PARP inhibitor, classified by homologous recombination DNA repair-deficient status. Homologous recombination DNA repair-deficient status encompasses a broader criteria than BRCA-mutated status, immunotherapy combination, epigenetic drug and other solid cancers [28–31].

In the pooled analyses of eribulin, median PFS and OS in eribulin were 2.8 months and 12.4 months, respectively [15]. PFS and OS were significantly longer for TNBC than for non-TNBC subtypes. In olaparib, median PFS and OS were 3.7 months and 11 months, respectively, in BC patients with BRCA mutation–positive status [25]. In another study, median PFS in total TNBC patients and patients with BRCA mutation–positive status were 54 and 109 days, respectively [26]. In the OlympiAD study, all patients were of a *BRCA* mutation–type population, and a favourable PFS tendency was observed in *BRCA*-mutated TNBC compared to *BRCA*-mutated hormone positive BC [27]. Median PFS and OS in the present study were deemed better than those reported in other studies of monotherapy; however, the additional treatment benefit by the combination regimen could not be quantified as this study was not a randomized controlled trial. The ORR and PFS of this study appeared less favourable than olaparib in the OlympiAD study. A potential reason for this result is the difference in the patient population having TNBC with or without *BRCA*-mutated status. In addition, most patients in phase II were a part of a heavily treated status as 80% of patients received three or more chemotherapy regimens including both anthracycline and taxanes before enrolment. On the other hand, the OlympiAD study having enrolled patients with BRCA-mutated status was able to enrol patients with all subtypes including hormone receptor positive status and patients treated with no more than two previous chemotherapy regimens for metastatic disease [27].

5. Conclusion

This was the first study to evaluate the safety, efficacy and drug interaction of olaparib combined with eribulin in metastatic or recurrent patients with TNBC, previously treated with anthracycline and taxane. Eribulin standard dose plus olaparib tablet, 300 mg BID, resulted in a high frequency of febrile neutropenia and was not well tolerable in the metastatic or recurrent

setting. There was no significant interaction between olaparib and eribulin that may have influenced the clinical safety of this combination, and PARP inhibition was guaranteed even at the lowest dose of olaparib.

Conflict of interest statement

KY received honorarium from Eisai, Mochida Pharmaceutical, and Taiho Pharmaceutical (honorarium, advisory board), research fund from Novartis, and is a member of the advisory board for Eisai. AH received honoraria/consultancy fees from Ono Pharmaceuticals Co., Ltd., Kissei Co., Ltd., AbbVie GK, Nippon Boehringer-Ingelheim Co., Ltd., Astellas Pharm Inc., Nippon Shinyaku Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd. NM received honoraria from Chugai, AstraZeneca, Pfizer, Eisai, Kyowa-Kirin and Takeda and research funding from Chugai, AstraZeneca, Kyowa-Kirin, MSD, Novartis, Pfizer, Eli-Lilly, Eisai and Daiichi Sankyo. YN received honoraria from Eisai, Chugai, Taiho and research funding from Eisai. KA received honoraria from Eisai and AstraZeneca. MT received honoraria from Eisai and AstraZeneca.

KT received honoraria from Eisai and AstraZeneca and recived grant from Eisai and AstraZeneca. YF received honoraria from Eisai and AstraZeneca. The other authors have no conflicts interest to disclose.

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Appendix ASupplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2018.11.014.

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