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ORIGINAL REPORT

Phase II Study of WEE1 Inhibitor AZD1775 Plus Carboplatin in Patients With *TP53*-Mutated Ovarian Cancer Refractory or Resistant to First-Line Therapy Within 3 Months

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ABSTRACT

Purpose

AZD1775 is a first-in-class, potent, and selective inhibitor of WEE1 with proof of chemopotentiation in p53-deficient tumors in preclinical models. In a phase I study, the maximum tolerated dose of AZD1775 in combination with carboplatin demonstrated target engagement. We conducted a proof-of-principle phase II study in patients with p53 tumor suppressor gene (*TP53*)–mutated ovarian cancer refractory or resistant (< 3 months) to first-line platinum-based therapy to determine overall response rate, progression-free and overall survival, pharmacokinetics, and modulation of phosphorylated cyclin-dependent kinase (CDK1) in skin biopsies.

Patients and Methods

Patients were treated with carboplatin (area under the curve, 5 mg/mL·min) combined with AZD1775 225 mg orally twice daily over 2.5 days every 21-day cycle until disease progression.

Results

AZD1775 plus carboplatin demonstrated manageable toxicity; fatigue (87%), nausea (78%), thrombocytopenia (70%), diarrhea (70%), and vomiting (48%) were the most common adverse events. The most frequent grade 3 or 4 adverse events were thrombocytopenia (48%) and neutropenia (37%). Of 24 patients enrolled, 21 patients were evaluable for efficacy end points. The overall response rate was 43% (95% CI, 22% to 66%), including one patient (5%) with a prolonged complete response. Median progression-free and overall survival times were 5.3 months (95% CI, 2.3 to 9.0 months) and 12.6 months (95% CI, 4.9 to 19.7), respectively, with two patients with ongoing response for more than 31 and 42 months at data cutoff.

Conclusion

To our knowledge, this is the first report providing clinical proof that AZD1775 enhances carboplatin efficacy in *TP53*-mutated tumors. The encouraging antitumor activity observed in patients with *TP53*-mutated ovarian cancer who were refractory or resistant (< 3 months) to first-line therapy warrants further development.

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INTRODUCTION

WEE1 is a tyrosine kinase that regulates cell cycle progression by governing the G_2 checkpoint.[1-3] Binding of cyclin B to cyclin-dependent kinase (CDK1) can trigger mitosis, whereas inhibition of the CDK1/cyclin B complex by WEE1-induced phosphorylation of CDK1 at tyrosine 15 (Y15) will result in cell cycle arrest and allows for DNA repair. Pharmacologic inhibition of WEE1 is a strategy to abrogate G_2 cell cycle arrest and to exploit G_1 checkpoint deficiency of p53-deficient tumor cells, thereby enhancing their apoptotic response to DNA damage.[4]

AZD1775 (formerly MK-1775) is a potent and selective inhibitor of WEE1 (half-maximal inhibitory concentration, 5.18 nM in kinase screens) that demonstrated preclinical proof of principle in in vitro and in vivo models.[5-7] A previous phase I study of AZD1775 in combination with carboplatin, cisplatin, or gemcitabine in patients with different kinds of advanced solid tumors demonstrated an acceptable toxicity profile, linear pharmacokinetics, and target engagement, as defined by reduced phosphorylated

CDK1 (pCDK1) in surrogate tissue (skin biopsies), at tolerable dose levels.[8]

Despite initial therapy consisting of cytoreductive surgery and platinum-based chemotherapy, the majority of patients with epithelial ovarian cancer will experience relapse at some point in time. Approximately 25% of these patients are platinum resistant, with disease recurrence within 6 months after finishing first-line therapy. Refractory patients are patients who experience progression during first-line therapy. Both patients with refractory ovarian cancer and patients with resistant ovarian cancer have a poor prognosis.[9]

We conducted a proof-of-principle phase II study of AZD1775 combined with carboplatin in patients with refractory or early resistant (< 3 months) ovarian cancer after first-line platinum-based therapy because there is an unmet medical need for better treatment options for patients with platinum refractory or resistant ovarian cancer,[9-12] reintroduction of carboplatin in combination with the WEE1 inhibitor AZD1775 provides a setting in which patients serve as their own control, and mutations in the p53 pathway are frequently observed in platinum-resistant and platinum-refractory ovarian cancer.[13-17] The primary objective of this study was to determine the overall response rate (ORR) of AZD1775 plus carboplatin. Secondary objectives included determination of progression-free survival and overall survival, assessment of the safety and tolerability of AZD1775 plus carboplatin, and exploration of the pharmacokinetic and pharmacodynamic parameters of AZD1775 and carboplatin when administered together.

PATIENTS AND METHODS

Patient Selection

Patients were ≥ 18 years old with a confirmed histologic diagnosis of epithelial ovarian cancer and *TP53* mutation determined by polymerase chain reaction sequencing of exons 2 to 10. All patients previously received first-line platinum plus paclitaxel-based therapy only and showed evidence of disease recurrence during or within 3 months after the end of this treatment according to Response Evaluation Criteria in Solid Tumors (RECIST, version 1.0)[18] or elevated CA-125 levels that could be monitored according to Gynecological Cancer Intergroup (GCIG) criteria.[19] All patients underwent either primary or interval debulking surgery. All patients had an Eastern Cooperative Oncology Group performance status of ≤ 2, adequate organ function, and evaluable or measurable disease according to RECIST version 1.0.[18]

Study Design and Drug Treatment

This investigator-initiated, phase II, open-label, nonrandomized, proof-of-concept study was conducted at the Netherlands Cancer Institute in Amsterdam, the Netherlands. The study (ClinicalTrials.gov identifier: NCT01164995) received approval of the institutional medical ethical review board and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All patients gave written informed consent before inclusion in the study.

Patients received carboplatin intravenously at a dose resulting in a target platinum area under the curve (AUC) of 5 mg/mL·min in a 30-minute infusion, combined with AZD1775 225 mg orally twice a day for 2.5 days in 21-day cycles. Study treatment was continued until disease progression. Carboplatin doses were calculated using the modified Calvert formula, in which glomerular filtration rate was estimated using the Cockcroft-Gault equation. AZD1775 was administered at 12-hour dose intervals, and the first dose was started concomitantly with the start of carboplatin infusion.

Safety and Assessments

Demographic data and medical history were collected during screening. Physical examination, vital signs, and other safety assessments (Eastern Cooperative Oncology Group performance status, registration of concomitant medication, hematology, biochemistry, and urine analysis) were performed at baseline, and hematology and biochemistry assessments were performed throughout treatment.

Radiologic disease assessments were performed by computed tomography scan or magnetic resonance imaging at baseline and every two cycles. Tumor response was evaluated using RECIST version 1.0.[18] Serum CA-125 was investigated as a secondary end point for efficacy and was defined as a 50% reduction during treatment with confirmation after 4 weeks according to the GCIG criteria.[19] Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).[20]

Table 1. Baseline Patient Characteristics

Characteristic	No. of Patients (%) (N = 23)
Median age, years (range)	58 (25-74)
Stage of cancer (at study entry)	
IIB	1 (4)
IIIA	1 (4)
IIIC	12 (52)
IVA	9 (40)
Histologic subtype	
Serous	16 (70)
Clear cell	3 (13)
Mucinous	2 (9)
Mixed epithelial	1 (4)
Unknown	1 (4)
One previous line of therapy	23 (100)
Previous chemotherapy regimen	
Carboplatin plus paclitaxel	20 (87)
Carboplatin plus paclitaxel plus tamoxifen	2 (9)
Carboplatin plus paclitaxel plus bevacizumab	1 (4)
No. of first-line treatment cycles	
< 6	3 (13)
≥ 6	20 (87)
Refractory to first-line therapy	9 (39)
Resistant (≤ 3 months) to first-line therapy	14 (61)
Underwent debulking surgery	23 (100)
TP53 mutation (PCR, exons 2-10)	
Yes*	22 (96)
Missense	19 (83)
Frameshift	3 (13)
Nonsense	1 (4)
Deletion	1 (4)
No	1 (4)
BRCA1 mutation	
Yes	2 (9)
No	21 (91)

NOTE. Twenty-four patients were enrolled onto the study. One patient never started study treatment because of rapid disease progression. In one patient, *TP53* mutation by immunohistochemistry could not be confirmed by sequencing analysis, and therefore, the patient did not meet the inclusion criteria. One patient discontinued study treatment as a result of clinical deterioration during cycle 1. She did not receive at least two cycles of study treatment and did not reach the first computed tomography evaluation after two cycles. Therefore, these two patients were excluded from the response evaluation but included in the toxicity evaluation.

Abbreviation: PCR, polymerase chain reaction.

*Three patients had multiple types of *TP53* mutations. Therefore, percentages do not add up to 100%.

Statistical Analyses

The primary end point of the study was the ORR of AZD1775 225 mg (twice a day for 2.5 days) in combination with carboplatin (AUC, 5) in patients with *TP53*-mutated epithelial ovarian cancer not responding to first-line therapy. According to the A'Hern single-stage phase II design, a sample size of 21 evaluable patients provides a 61% power and a 5% level of significance to demonstrate whether the proportion of patients with a response is $\leq$ 13% or $\geq$ 30%. Accordingly, an ORR of at least 30% was required to declare efficacy, whereas an ORR of 13% or less would indicate no efficacy of interest.

Pharmacokinetic and Pharmacodynamic Assessments

To determine the pharmacokinetic parameters of AZD1775, blood samples were collected before dose on day 1, before dose on day 3, and 3 and 8 hours after the last AZD1775 dose of the first cycle. For platinum pharmacokinetic analysis, 4 mL of venous blood were collected in lithium-heparin tubes before dose on day 1, at the end of infusion (EOI), 1 hour after EOI, 5 hours after EOI, and 24 hours after infusion start.

Skin biopsies from the hairy part behind the ear were collected before dose and on day 3 within 2 hours after the fifth dose of AZD1775 to measure pCDK1. pCDK1 levels relative to CDK1 were assessed by immunohistochemistry (IHC). Subsequently, the fold change between the pre- and post-dose pCDK1:CDK1 ratio was calculated. Target engagement was defined as 50% reduction.[21]

p53 Status and Exploratory Genetic Analysis

TP53 mutation status was analyzed in archival tumor tissue, mostly obtained during debulking surgery. Standard IHC and mutation analysis by Sanger sequencing as routinely performed in our laboratory were performed before inclusion, with proven *TP53* mutation as a mandatory inclusion criterion. All samples were analyzed by the AmpliChip (Roche, Basel, Switzerland) p53 test for verification (Data Supplement).[22] Targeted next-generation sequencing of cancer-related genes was performed to explore potential biomarkers predictive for response.

RESULTS

Patient Population

A total of 24 patients were enrolled onto the study, and 23 patients started study treatment (Table 1). One patient never started study treatment because of early progression in the period between registration and study start. The median age of the patients was 58 years (range, 25 to 74 years). The majority of patients (56%) were diagnosed with stage III ovarian cancer according to the International Federation of Obstetricians and Gynecologists staging system for ovarian cancer, and most patients (70%) had an Eastern Cooperative Oncology Group performance status of 0. These findings are in line with what can be expected from this particular patient group.

Twenty-three patients were evaluable for toxicity (ie, received at least one cycle). Within 3 months after first-line therapy, 19 patients had recurrent disease according to RECIST 1.0 criteria, and four patients had recurrent disease according to GCIG criteria for CA-125. All patients showed radiologic measurable or evaluable disease before study start.

Safety

The main treatment-related and clinically significant adverse events per patient are listed in Table 2. Bone marrow toxicity, fatigue, diarrhea, nausea, and vomiting were the most common adverse events. Grade 4 thrombocytopenia and/or grade 2 to 4 neutropenia resulted in dose reductions 11 times (in 11 patients).

Antitumor Activity

Of the 23 patients who started study treatment, one patient did not meet all inclusion criteria, as *TP53* mutation could not be confirmed by sequencing analysis. Therefore, the intent-to-treat population consisted of 22 patients, of whom 21 were considered evaluable for efficacy assessment. One patient did not receive at least two cycles of study treatment and did not reach the first response evaluation after 6 weeks of treatment as a result of clinical deterioration. Of the 21 evaluable patients, five patients (24%) showed progressive disease on the first evaluation after two cycles. Seven patients (33%) experienced stable disease as best response. Eight patients (38%) showed a partial response (PR) as best response, and one patient (5%) had a complete response (CR), resulting in an ORR of 43% (95% CI, 22% to 66%; Fig 1; 41% in the intent-to-treat population). Two patients with a PR discontinued study treatment because of maximum benefit obtained according to their treating physician. Of the 15 patients with serous ovarian cancer, seven (47%) achieved a response, including one

Table 2. Main Treatment-Related Adverse Events, Scored by Highest Grade per Patient (N = 23)

	Grade 1		Grade 2		Grade 3		Grade 4		All Grades	
Adverse Event	No.	%	No.	%	No.	%	No.	%	No.	%
Bone marrow toxicity										
Thrombocytopenia	2	9	3	13			11	48	16	70
Neutropenia			1	4	4	17	5	22	10	43
Anemia			12	52	2	9			14	61
GI toxicity										
Nausea	14	61	3	13	1	4			18	78
Diarrhea	9	39	6	26	1	4			16	70
Vomiting	8	35	3	13					11	48
Pyrosis	2	9	2	9					4	17
Other										
Fatigue	10	43	9	39	1	4			20	87
Hypomagnesemia	7	30	2	9	2	9			11	48
Peripheral sensory neuropathy	2	9	3	13					5	22

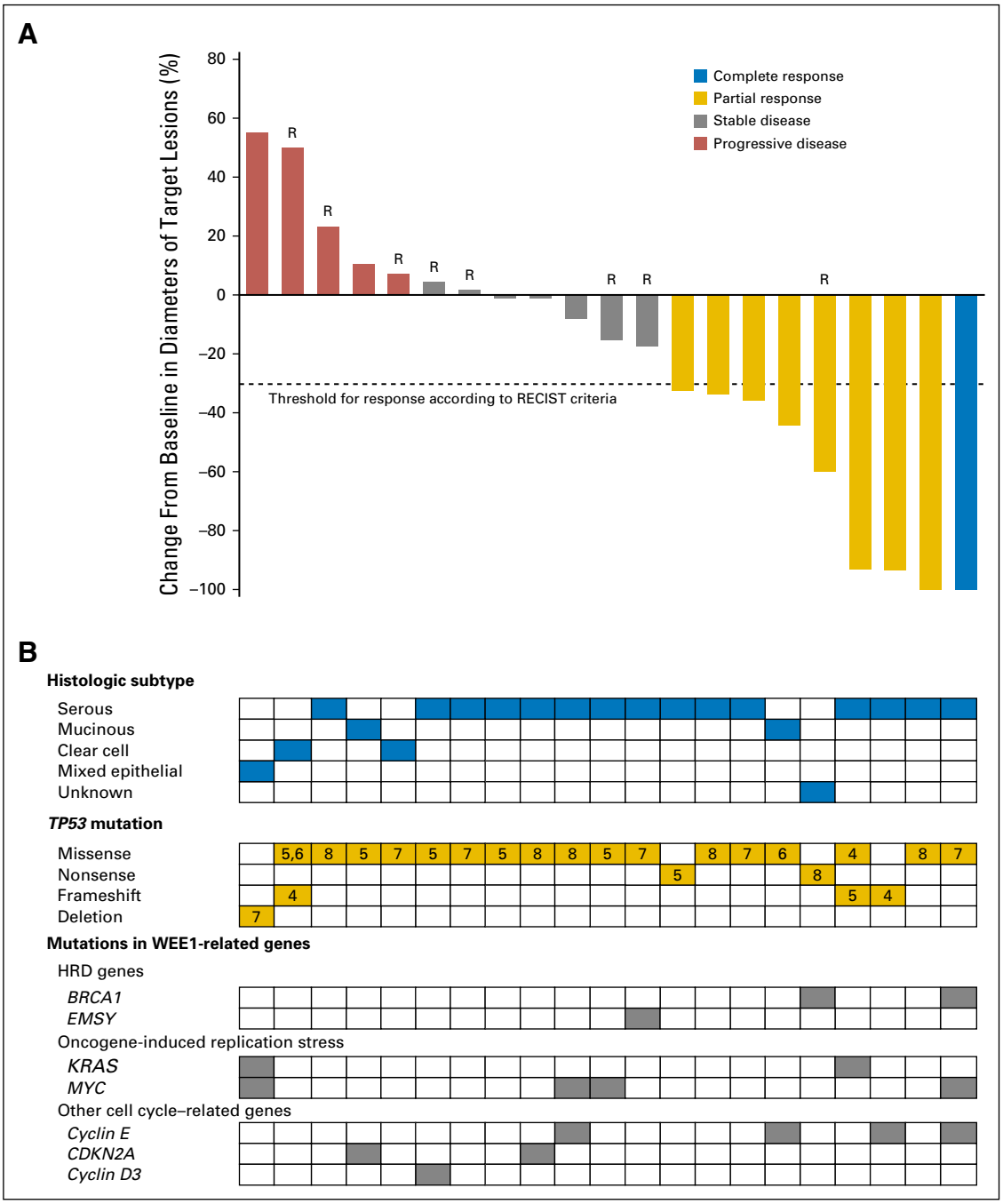

Fig 1. (A) Waterfall plot of best percentage change from baseline stratified by response and (B) correlation with molecular characterization. Patients refractory to first-line treatment are indicated by an R. Numbers in the blue squares represent mutated *TP53* exons. HRD, homologous recombination deficiency; RECIST, Response Evaluation Criteria in Solid Tumors.

CR, and the ORR among the five patients with nonserous subtypes was 20%. One patient with an unknown histologic subtype had a PR. Of 18 patients with *TP53* missense mutations, one patient (6%) achieved a CR and six patients (33%) achieved a PR, and two (67%) of three patients with nonmissense *TP53* mutations achieved a response. All patients with a CA-125 marker response also demonstrated a PR according to RECIST criteria, and two patients had a PR even though CA-125 levels did not reach the threshold of PR according to GCIG criteria. Eight patients (38%) were refractory to first-line therapy, of whom three patients (38%) had progressive disease as best response, four patients (50%) had stable disease, and one patient (12%) had PR. The median progression-free survival time was 5.3 months (95% CI, 2.3 to 9.0 months), with two patients with ongoing response (one PR and one CR) for over 31 and 42 months, respectively, at data cutoff (Figs 2, 3A, and 4). Median overall survival time was 12.6 months (95% CI, 4.9 to 19.7 months; Fig 3B).

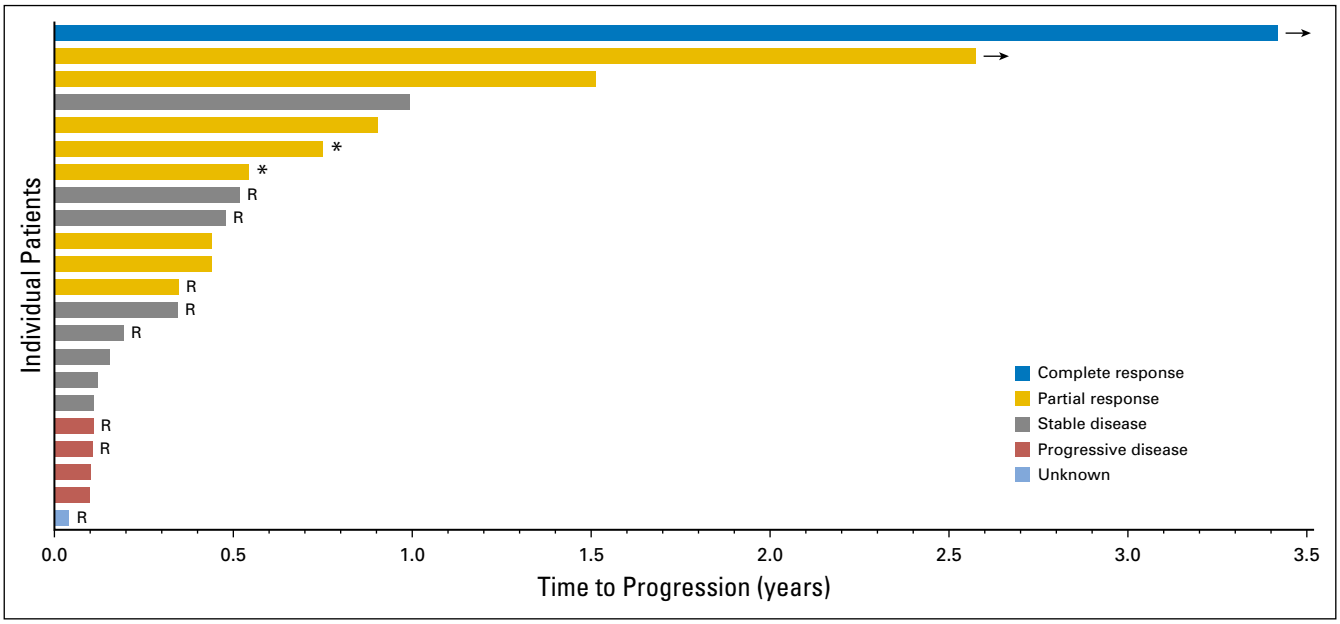

Fig 2. Swimmer plot of progression-free survival by best response. Median progression-free survival was 5.3 months, with two patients with ongoing response at data cutoff (indicated by arrows). Patients refractory to first-line treatment are indicated by an R. (*) Patients who discontinued study treatment because of maximum benefit obtained according to their treating physicians.

Pharmacokinetics and Pharmacodynamics

Blood samples for the measurement of total and free platinum and AZD1775 were obtained in all patients. AZD1775 mean plasma concentration 8 hours after dose, maximum plasma concentration (C_{max}), and AUC from time 0 to 8 hours after dose on day 3 were 834 nM, 1,380 nM, and 8,590 nM·h, respectively. These pharmacokinetic parameters were consistent with data obtained in the previous phase I study with moderate variation on day 3 with a coefficient of variation (CV) in geometric mean C_{max} and AUC of 37% and 40%, respectively (Data Supplement). Mean free platinum C_{max} and AUC from time 0 to infinity were 18.31 μg/mL (CV, 23.8%) and 5.08 mg/mL·min (CV, 26.4%) respectively (Data Supplement).

Skin biopsies were collected in all patients on day 1 (before dose) and day 3 (after dose). Only samples containing more than 50 CDK1-positive cells were scored (n = 20). The geometric mean pCDK1:CDK1 ratio modulation in skin tissue was −58% (range, +56% to −85%) after 3 days of treatment, which was similar to the phase I data of AZD1775 plus carboplatin. Target engagement (ie > 50% pCDK1/CDK1 reduction) was achieved in 13 (65%) of 20 patients who met evaluability criteria (Data Supplement).

p53 Status and Exploratory Genetic Analysis

Results from the p53 status analysis by IHC, direct sequencing, and AmpliChip p53 array are presented in the Data Supplement. In two patients with negative IHC staining for p53, a mutation in one patient and a deletion in one patient were found with polymerase chain reaction/direct sequencing and AmpliChip p53 array. The majority of *TP53* mutations found were in exons 5 to 8, which is in line with results published in the literature (International Agency for Research on Cancer *TP53* database; Data Supplement).

Targeted next-generation sequencing revealed mutations in several WEE1-related genes, including DNA damage response genes such as *BRCA1* (n = 2), oncogene-induced stress genes such as *KRAS* (n = 2) and *MYC* (n = 4), and other genes involved in the cell cycle such as *Cyclin E* (n = 4). The two patients with prolonged responses of greater than 31 and 42 months had mutations in *Cyclin E* and in *BRCA1*, *MYC*, and *Cyclin E*, respectively (Fig 1).

DISCUSSION

We report the results of an investigator-initiated, proof-of-principle, phase II study with the first-in-class WEE1 inhibitor AZD1775. AZD1775 in combination with carboplatin was generally well tolerated and demonstrated manageable toxicity. The toxicity profile of the AZD1775 plus carboplatin combination, with nausea, vomiting, diarrhea, fatigue, and bone marrow suppression as major adverse events, is consistent with the toxicity profile observed in the phase I study with AZD1775 and carboplatin (or cisplatin or gemcitabine) in patients with advanced solid tumors.[8] Grade 4 thrombocytopenia and neutropenia events were manageable and did not lead to complications or treatment discontinuation. The results of p53 analysis were in line with data reported in the literature and mainly encountered mutations in exons 5 to 8 of *TP53*, which are known to cause loss of function according to the International Agency for Research on Cancer *TP53* database.

We tested the hypothesis of chemotherapy sensitization by abrogation of the G_2 checkpoint using WEE1 inhibitor AZD1775 in patients with *TP53*-mutated ovarian cancer refractory or resistant (< 3 months) to first-line platinum-based therapy. These patients are known for their poor prognosis, and effective treatment options are currently lacking for these patients. Patients

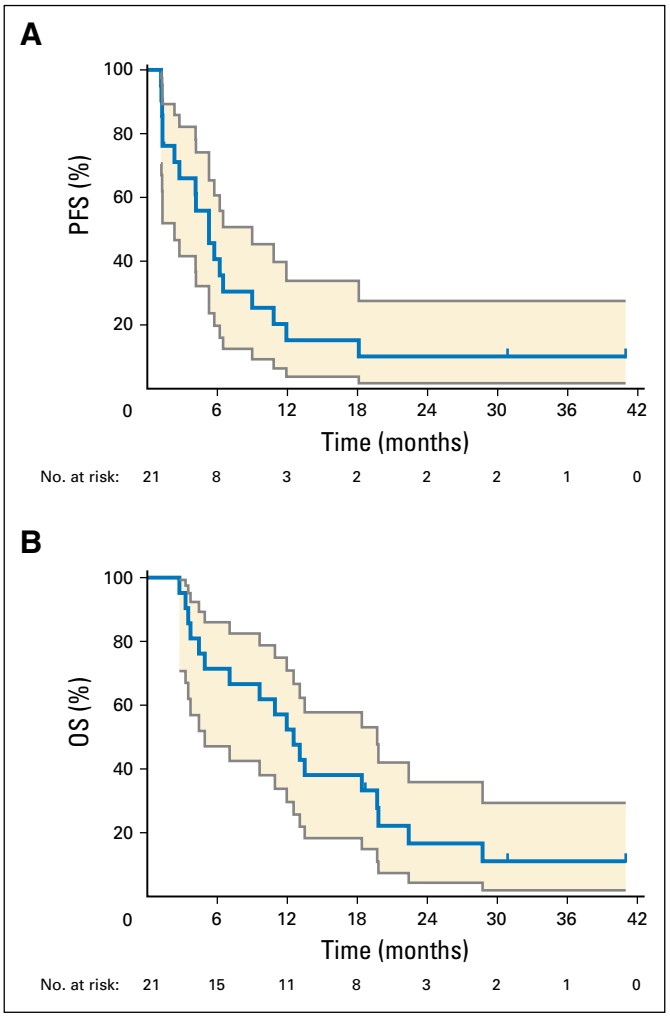

Fig 3. Kaplan-Meier plots of (A) progression-free survival (PFS) and (B) overall survival (OS). Regarding PFS, two patients were censored who remained in follow-up for PFS. Regarding OS, three patients were censored who remained in follow-up for OS. Colored areas represent the point-wise 95% confidence bands, and thick marks indicate censored patients.

served as their own control because they were re-exposed to carboplatin in combination with orally administered WEE1 inhibitor AZD1775. Whereas first-line treatment consists of a predefined number of six carboplatin treatment cycles, in this study, we continued carboplatin plus AZD1775 until disease progression. Encouraging antitumor activity was observed. The ORR was 43%, including one (5%) CR and eight (38%) PRs. This response rate exceeds the effect that could be expected with second-line single-agent treatment options, including paclitaxel, pegylated liposomal doxorubicin, bevacizumab, and topotecan, which have reported response rates of 11% to 21%.[23-25] Three studies investigating combination strategies in patients with ovarian cancer pretreated with platinum-based therapy demonstrated clinical activity in the range of our study. The randomized phase III Avastin Use in Platinum-Resistant Epithelial Ovarian Cancer (AURELIA) study reported a 52% ORR with bevacizumab plus weekly paclitaxel in patients with platinum-resistant ovarian cancer.[26] Two small studies published by Sharma et al[27] and van der Burg et al[28] reported ORRs of 60% and 46% with weekly dose-dense paclitaxel plus carboplatin and weekly cisplatin plus daily etoposide, respectively, in pretreated platinum-resistant patients. However, patients treated in AURELIA and in the study reported by Sharma et al[27] were platinum resistant within 6 months, and the majority of patients had a platinum-free interval of ≥ 3 months. Moreover, in these studies, as well as in the study published by van der Burg et al,[28] platinum-refractory patients were excluded, and a large portion of the patients treated in the study by van der Burg et al[28] (82%) were not pretreated with a paclitaxel-containing regimen. In contrast, our study solely enrolled patients who developed platinum-resistant disease within 3 months, including platinum-refractory patients (40%), which indicates the particularly aggressive disease present in our patients, and all patients were pretreated with the highly active carboplatin plus paclitaxel combination therapy. Therefore, our results suggest that AZD1775 plus carboplatin may improve first-line carboplatin plus paclitaxel chemotherapy in patients with resistant ovarian cancer in terms of progression-free survival, warranting further clinical evaluation in patients with *TP53*-mutated ovarian cancer. However, phase II and III studies are needed to confirm the observed antitumor activity and to give a definite answer about whether the combination of carboplatin and AZD1775 is synergistic or AZD1775 monotherapy is equally effective.

Pharmacokinetic parameters of AZD1775 in our study were consistent with data obtained in the phase I study. Mean plasma concentration of AZD1775 at 8 hours after dose well exceeded the preclinical target of 240 nM, and target engagement, defined as a 50% reduction of pCDK1 in surrogate skin tissue, was observed in 65% of the patients. However, a clear correlation between pCDK1 reduction and efficacy was not observed.

Genetic alterations in the following three gene groups were hypothesized to benefit from WEE1 inhibition: cell cycle–dependent genes (eg, *TP53* and *RB1*); homologous recombination deficiency genes (eg, *BRCA1*); and oncogene-induced replication stress genes (eg, *KRAS* and *MYC*). Although the sample size is too small to draw conclusions, alterations in *BRCA1*, *Cyclin E*, and *MYC* may, in addition to *TP53* mutations, enrich for response to WEE1 inhibition combined with carboplatin.

Two patients discontinued study treatment because of maximum benefit obtained according to their treating physician. However, 2 months after discontinuation, an increase in CA-125 levels was observed in both patients, followed by disease progression on computed tomography scan. Therefore, given the long-lasting (ie, $>$ 1 year) disease control and manageable toxicity observed in four patients enrolled onto this study, treatment continuation beyond maximum benefit needs to be considered in future studies.

Initial preclinical data primarily supported combination therapy of AZD1775 with DNA-damaging agents on the basis that cells defective in the G_1 checkpoint as a result of loss of function of p53 are more dependent on the G_2 checkpoint for DNA repair. However, recent preclinical and clinical research demonstrated AZD1775 single-agent activity on the basis of the role of WEE1 in the stabilization of replication forks and homologous

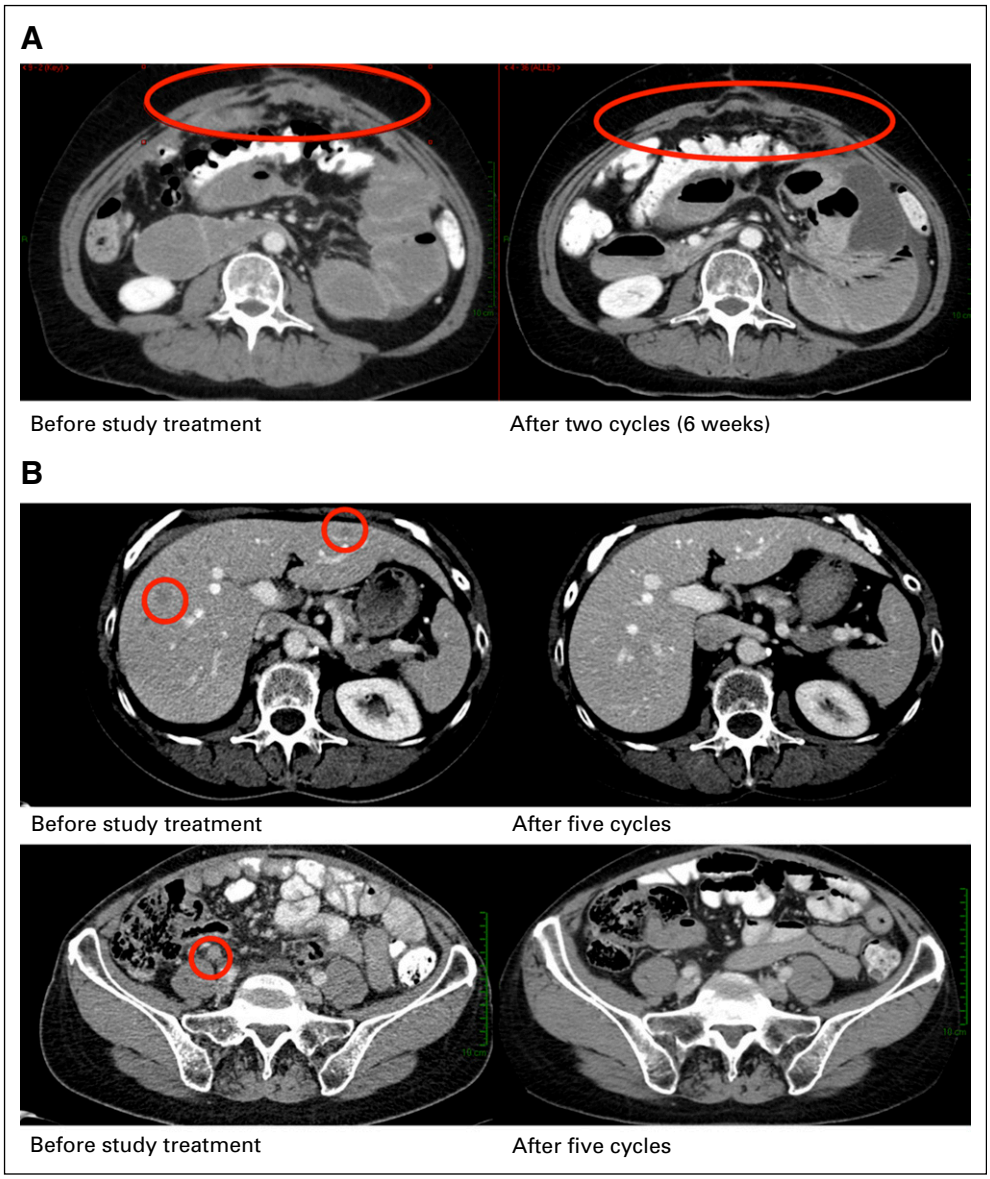

Fig 4. Computed tomography scan images of two patients. (A) In the first patient, peritoneal lesions growing into the abdominal wall decreased to residual lesions after two cycles of study treatment. (B) In the second patient, liver lesions and a pathologic lymph node before start of treatment disappeared after five cycles of study treatment.

recombination repair.[29,30] Do et al[30] demonstrated that some patients obtained benefit from AZD1775 monotherapy for a prolonged period of time. However, responses were only seen in patients with *BRCA1/2* mutations and not in patients with *TP53* mutations or patients with concurrent *BRCA1/2* and *TP53* mutations. Nevertheless, a possible role for maintenance therapy with AZD1775 as a single agent after combined carboplatin plus AZD1775 is worth exploring in patients with *TP53*-mutated ovarian cancer, particularly because AZD1775 is orally administered and will be less onerous than the combination with additional intravenous chemotherapy.

Another attractive option for future studies is to explore simultaneous inhibition of multiple DNA repair mechanisms, for instance, dual inhibition of WEE1 and poly (ADP-ribose) polymerase in combination with DNA-damaging anticancer agents in patients with tumors harboring aberrations in DNA repair mechanisms, such as *BRCA* mutation,[31] or the combination of AZD1775 and a Chk1 inhibitor, another key player with a coordinating role in the cell cycle and DNA damage response.[32]

In conclusion, our study provides clinical evidence that AZD1775 enhances the antitumor efficacy of carboplatin in patients with *TP53*-mutated ovarian cancer resistant to first-line therapy and suggests that AZD1775 plus carboplatin may outperform first-line platinum-based chemotherapy in these patients. On the basis of these encouraging results, further development starting with a randomized phase II or III study is warranted in this particular patient group and in other p53-deficient tumors to substantiate the true value of AZD1775.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

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Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Phase II Study of WEE1 Inhibitor AZD1775 Plus Carboplatin in Patients With *TP53*-Mutated Ovarian Cancer Refractory or Resistant to First-Line Therapy Within 3 Months

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