First-in-Human Trial of the Oral Ataxia Telangiectasia and Rad3-Related Inhibitor BAY 1895344 in Patients with Advanced Solid Tumors


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Abbreviations: AE, adverse event; ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia and Rad3-related; BID, twice daily; DDR, DNA damage response; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; MTD, maximum tolerated dose; NGS, next-generation sequencing; NS, not significant; ORR, objective response rate; PARP, poly ADP-ribose polymerase; PCWG3, Prostate Cancer Working Group 3; PD, progressive disease; PR, partial response;
RECIST, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; TEAE, treatment-emergent adverse event.

**Keywords:** ATR inhibitor, DNA damage response, phase I study, ATM mutation, ATM loss

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ABSTRACT

Targeting the ataxia telangiectasia and Rad3-related (ATR) enzyme represents a promising anticancer strategy for tumors with DNA damage response (DDR) defects and replication stress, including inactivation of ataxia telangiectasia mutated (ATM) signaling. We report the dose-escalation portion of the phase I first-in-human trial of oral ATR inhibitor BAY 1895344 intermittently dosed 5–80 mg twice daily (BID) in 21 patients with advanced solid tumors. The maximum tolerated dose was 40 mg BID 3 days on/4 days off. Commonest adverse events were manageable and reversible hematological toxicities. Partial responses were achieved in 4 patients and stable disease in 8 patients. Median duration of response was 315.5 days. Responders had ATM protein loss and/or deleterious ATM mutations and received doses ≥40 mg BID. Overall, BAY 1895344 is well tolerated with antitumor activity against cancers with certain DDR defects, including ATM loss. An expansion phase continues in patients with DDR deficiency.

SIGNIFICANCE

Oral BAY 1895344 was tolerable with antitumor activity in heavily pre-treated patients with various advanced solid tumors, particularly those with ATM deleterious mutations and/or loss of ATM protein; pharmacodynamic results supported a mechanism of action of increased DNA damage. Further study is warranted in this patient population.
INTRODUCTION

The ataxia telangiectasia and Rad3-related (ATR) kinase is a central DNA damage response (DDR) kinase that functions in proliferative cells during DNA replication in order to secure the integrity of the genome and to maintain cell viability (1). ATR is activated in conditions of DNA replication stress induced by a wide range of genotoxic insults which result in double-strand DNA breaks, replication fork stalling, and single-strand DNA/double-strand DNA junctions (1-3). These various lesions are processed to single-strand DNA coated with the replication protein A, which is the stimulus to activate and recruit ATR to DNA damage sites. Once activated, ATR functions to safeguard genomic integrity and ensure replication completion via several downstream effects. These include slowing the progression of replication forks, inhibiting replication origin firing, ensuring sufficient supply of deoxynucleotides, and promoting cell cycle arrest primarily via activation of the S-G2-M cell cycle checkpoint (1).

Whereas ATR(-/-) mice are embryonically lethal and ATR(-/-) cells show extensive chromosomal abnormalities and cannot proliferate in culture, hypomorphic conditional suppression of ATR in adult mice, which maintains a low level of ATR expression, is tolerable and has minimal impact on highly proliferative normal tissues such as bone marrow (4-6). Complete loss of ATR has not been reported in cancer; however, hypomorphic ATR suppression in mice with oncogene-driven tumors has been shown to potently inhibit tumor growth (6, 7). These data indicate that despite the essential role of ATR in both normal and cancer cell proliferation and survival, incomplete ATR inhibition may be a promising anticancer therapy, allowing a sufficient therapeutic window for normal tissues. Furthermore, cancer cells often experience replication stress and acquire inactivating mutations in genes mediating complementary to ATR DNA repair mechanisms, which may
further sensitize tumors to ATR inhibition (8). Next-generation sequencing (NGS) efforts have revealed that the ataxia telangiectasia mutated (ATM) kinase, which senses and mediates repair to double-strand DNA lesions, is among the most commonly aberrant genes in sporadic tumors across many tumor types (9), with the antitumor activity of ATR inhibition being shown to be enhanced in the absence of the ATM tumor suppressor (10).

BAY 1895344 is a potent and selective low-nanomolar ATR kinase inhibitor with antitumor activity in preclinical studies as a single agent in models with certain DDR defects or oncogenic mutations mediating replication stress, including ovarian, prostate, colorectal, and lymphoma tumor models (11). In vivo studies have demonstrated dose-dependent antitumor activity correlating with BAY 1895344 plasma exposure and increased DNA damage. The biological effects were time-, dose-, and schedule-dependent, with the optimal dose and dosing schedule of BAY 1895344 identified in preclinical models as 50 mg/kg twice daily (BID) for 3 days on/4 days off (11). We conducted a first-in-human clinical trial following the Pharmacological Audit Trail (12) to evaluate the safety and tolerability, maximum tolerated dose (MTD), pharmacokinetic–pharmacodynamic profile, and antitumor activity of BAY 1895344 in patients with advanced solid tumors (NCT03188965), and demonstrate that this ATR inhibitor is tolerated at biologically active doses with single-agent antitumor activity against cancers with certain DDR defects, including ATM protein loss.

RESULTS

Patient Characteristics and Treatment

From July 6, 2017 through June 17, 2018, 22 patients were enrolled and treated with BAY 1895344 in the dose-escalation portion of the study. Based on preclinical experiments indicating that optimal antitumor activity and tolerability of BAY 1895344 were achieved via
interruption administration (11), and the human pharmacokinetic parameters of BAY 1895344, 18 patients received BAY 1895344 BID 3 days on/4 days off weekly and 4 patients received a less dose-intense variation of this schedule (3 days on/4 days off for 2 weeks followed by 1 week off) (Supplementary Fig. S1 and S2).

The median age was 63 years. Most patients (72.7%) had received at least 4 lines of prior treatment for advanced disease, with 54.5% of patients resistant to prior platinum-based treatments. The most common tumor types were breast, prostate, and colorectal cancer (18.2% each). Eleven treated patients (50.0%) had 1 or more ATM aberrations detected in baseline tumor biopsies using DNA NGS and/or ATM protein expression immunohistochemistry (IHC) test (Table 1). Six patients (27.3%) had both ATM deleterious mutation and loss of ATM protein expression, 2 (9.1%) had ATM deleterious mutations with ATM protein expression, and 3 (13.6%) had loss of ATM protein expression with wild type ATM gene. In addition, 3 patients (13.6%) and 1 patient (4.5%) had BRCA1 and BRCA2 deleterious mutations, respectively.

At the time of data cut-off, the median duration of treatment was 64.5 days (range 8–472) and 5 patients were ongoing with BAY 1895344 treatment. The most common reason for discontinuation was disease progression in 15 patients (68.2%); 2 patients (9.1%) discontinued due to AEs (Supplementary Fig. S1).

Safety

Oral BAY 1895344 was escalated from 5 mg to 80 mg BID intermittently (Supplementary Fig. S2). The MTD was 40 mg BID 3 days on/4 days off. Dose-limiting toxicities (DLTs) were observed in 6 patients at dose levels higher than the MTD (Supplementary Table S1 and S2). Five of the 6 patients experienced DLTs of hematological nature. One additional
patient treated with BAY 1895344 60 mg BID 3 days on/4 days off presented with grade 2 fatigue requiring dose reduction, which was deemed as a DLT per protocol criteria.

Among all dose cohorts and schedules, the most common all-grade treatment-emergent adverse events (TEAEs) were generally hematologic and comprised anemia (81.8% [all grade 3]), neutropenia (72.7% [grade 3/4, 54.5% (n = 12)]), and thrombocytopenia (45.5% [grade 3/4, 18.2% (n = 4)]). Fatigue (68.2% [grade 2 requiring dose reduction, 4.5% (n = 1); grade 3, 9.1% (n = 2)]) and nausea (50.0% [grade 3, 9.1% (n = 2)]) were also reported. Other non-hematological TEAEs were of low frequency and primarily grade 1 and 2 (Table 2 and Supplementary Table S3).

Grade 3 and 4 neutropenia and thrombocytopenia were dose dependent, occurring primarily during the first cycle of treatment in patients treated with BAY 1895344 at dose levels higher than the MTD (≥60 mg BID across schedules). These AEs were manageable with dose interruption and/or reduction and were not associated with febrile neutropenia or bleeding. The most frequently observed toxicity was grade 3 anemia (hemoglobin <8.0 g/dL or transfusion indicated; 81.8%), presenting at dose levels ≥10 mg BID, including the MTD (Table 2 and Supplementary Table S3). Grade 3 anemia occurred in cycle 2 or later in most patients, was managed by dose interruptions and/or blood transfusion, and did not usually require dose reduction or treatment discontinuation. Of the 2 patients assigned to the MTD, 1 patient experienced recurrent grade 2/3 anemia after cycle 1 requiring a blood transfusion in cycle 4 and fatigue of grade 1/2 starting later in treatment (around cycle 5). The other patient experienced grade 1/2 fatigue starting in cycle 2 with 1 episode of grade 3 fatigue in cycle 7 and recurrent anemia of grade 2/3 requiring a blood transfusion during cycle 2. Both patients achieved a durable objective partial response with treatment durations of 385 and 472 days and were ongoing treatment at the data cut-off.
Serious AEs related to study treatment included medication error (reported in 1 patient receiving BAY 1895344 10 mg BID); grade 3 diarrhea, grade 3 hypotension, and grade 3 nausea (reported in 1 patient receiving BAY 1895344 60 mg BID); and grade 4 neutropenia and grade 2 pyrexia (reported in 1 patient receiving BAY 1895344 80 mg BID). Most patients (68.2%) experienced at least 1 dose interruption due to drug-related TEAEs. Two patients (9.1%) permanently withdrew treatment due to TEAEs (grade 3 hemoptysis in 1 patient receiving BAY 1895344 80 mg BID and increased alanine aminotransferase, aspartate aminotransferase, and total bilirubin in another patient receiving BAY 1895344 60 mg BID), all considered unrelated to treatment. Nine patients (40.9%), all treated at dose levels higher than the MTD, experienced a dose reduction, mainly due to treatment-related neutropenia (5 patients; 22.7%) and fatigue (3 patients; 13.6%).

**Pharmacokinetics**

Pharmacokinetic data are depicted in Fig. 1A–B and in Supplementary Table S4. Following oral administration, BAY 1895344 was absorbed rapidly, with a median time to maximum plasma concentration of 1 hour. Plasma concentration declined with a geometric mean terminal half-life of approximately 11.5 hours. Consistent with the observed half-life of 8.6–17.8 hours, a 1.4–2.4-fold accumulation of BAY 1895344 exposure was observed on repeat dosing. There was moderate inter-patient variability; however, exposure was broadly dose proportional across the dose range investigated (5–80 mg BID), with no evidence of saturable absorption. Clinical exposure at the MTD was observed to be in the range associated with antitumor activity in non-clinical models, substantially exceeding the biochemical and cellular anti-proliferative IC₉₀ observed preclinically in sensitive mantle cell lymphoma cell lines, such as GRANTA-519, and in the range of the cellular anti-proliferative IC₉₀ of moderately sensitive cell lines (11).
**Pharmacodynamic Studies**

As of the data cut-off, 17 baseline and on-treatment paired biopsies were available from patients receiving BAY 1895344 at doses of 40, 60, and 80 mg BID. Nine paired biopsies were obtained from patients treated in the dose-escalation phase; an additional 8 paired biopsies were available from patients treated in the expansion phase. These data demonstrated an on-treatment increase of the DNA damage-induced markers phosphorylated H2AX at Ser 139 (γ-H2AX) and/or pKAP1 in a subset of tumors obtained on cycle 1, day 10, indicating pharmacodynamic target modulation (Fig. 1C–E and Supplementary Fig. S3A and B). On-treatment γ-H2AX induction was not observed in 5/5 patients with ATM loss and with available paired tumor biopsies. The percentage of γ-H2AX positive cells was significantly increased in post-treatment biopsies from patients where ATM protein was expressed (n = 12; P = 0.027, Wilcoxon matched-pairs signed-rank test) (Supplementary Fig. S3C). Only 1 patient had ATM expression with an H-score within the range of 1–30, and γ-H2AX was increased 2-fold in this patient.

PD-L1 expression on tumor and immune cells was evaluated in paired tumor biopsy samples from 15 patients. Five patients had PD-L1 negative tumors in the pre-treatment biopsy (breast cancer, n = 2; prostate cancer, n = 3; Fig. 1F), with those tumors remaining PD-L1 negative post-treatment. Comparison of PD-L1 expression at baseline with on-treatment paired biopsies in patients with gynecological tumors with a PD-L1 positive pre-treatment specimen (ovarian cancer, n = 6; endometrial cancer, n = 2) showed further elevated PD-L1 positivity after treatment with BAY 1895344, which approached statistical significance (P = 0.09, paired t test; Fig. 1G). Treatment effect on tumor infiltration T cells was further evaluated by IHC. A slight increase in CD8+ effector T cells and a slight decrease in
CD4+/FoxP3+ T cells were observed, although neither was statistically significant (Supplementary Fig. S4A–C).

**Antitumor Activity**

Twenty-one patients treated across all dose levels were evaluable for tumor response (1 patient did not have an on-treatment computed tomography scan or clinical progression information, and therefore was not evaluable for response). Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST) partial responses were achieved in 4 patients (Table 3 and Fig. 2A–B). Both patients treated at the BAY 1895344 MTD (40 mg BID, 3 days on/4 days off) had confirmed RECIST partial responses (advanced renal collective duct carcinoma and metastatic appendiceal cancer). Two additional patients commenced treatment at dose levels higher than the MTD (1 patient with hormone receptor positive, human epidermal growth factor receptor 2-negative breast cancer at 60 mg BID and 1 patient with endometrial cancer at 80 mg BID 3 days on/4 days off) and had RECIST partial responses. Both patients were reduced to the MTD after 63 and 34 days of treatment, respectively, due to hematologic toxicities and had sustained RECIST partial responses following dose reduction to the MTD. The objective response rate (ORR) in patients treated at or above the MTD was 30.8% (4/13 patients). The median time to response was 78 days (range 49–211). At the time of data cut-off, 3 of the 4 patients with a RECIST partial response were ongoing with a time on treatment exceeding 1 year (Fig. 2B). Median duration of response was 315.5 days (range 246–357). The disease control rate was 57.1% (12/21) in the overall population and 69.2% (9/13) in patients treated at or above the MTD (Table 3).

Analysis of baseline tumor biopsies by DNA NGS and ATM protein expression by IHC identified ATM aberrations in all 4 patients with a RECIST partial response (Fig. 2A and Supplementary Table S5). The first patient had hormone receptor positive, human epidermal
growth factor receptor 2-negative, platinum-refractory breast cancer and had ATM expression in ≤2% of tumor cells by IHC in a fresh baseline tumor biopsy and an ATM deleterious mutation (ATM_T2333fs*) with an allele frequency of 71%. This patient had received 11 prior lines of systemic therapy and achieved a RECIST partial response (best response of −54% in target lesion size, in addition to −50% and −40% in 2 liver lesions) with a treatment duration of 349 days (Fig. 2C). The second patient had advanced clear cell endometrial cancer and had loss of ATM protein expression in an archival baseline biopsy and an ATM deleterious mutation (ATM_p.I2629fs*) with allele frequency of 40%. This patient had received 1 prior line of systemic therapy and achieved a RECIST partial response (best response of −53%) with a treatment duration of 433 days and was ongoing at data cut-off. The third patient had advanced renal collecting duct carcinoma and had loss of ATM protein expression in archival baseline biopsy with wild type ATM. This patient achieved a RECIST partial response (best response of −69%) with a treatment duration of 385 days and was ongoing at data cut-off. The fourth patient had appendiceal cancer and had an ATM deleterious mutation (ATM_p.V1268fs*) in archival tumor tissue with an allele frequency of 45%; ATM protein was expressed in this patient’s biopsy (60% of tumor cells were positive). The patient achieved a RECIST partial response (best response −35% in all target lesions, including −74% shrinkage in 1 of the target lesions [a rectal lesion]) with a treatment duration of 472 days, and was ongoing at the time of data cut-off. The ORR in patients with ATM aberrations (ATM protein expression loss and/or ATM deleterious mutation) across all dose levels was 36.4% (4/11 patients). An ORR of 33.3% (3 of 9 patients) was observed in patients with ATM protein loss across different dose levels and an ORR of 37.5% (3 of 8 patients) was observed in patients with ATM mutations. All responding patients with ATM aberrations had wild type TP53 (Fig. 2A). Three out of the 11 patients with ATM aberrations
had radiologic progressive disease as best response. Among other aberrations, mutations in the \textit{PIK3} gene were detected in those 3 patients (Supplementary Table S6).

One additional patient with \textit{BRCA1\_Q1401} germline mutation (89% allelic frequency) and high-grade serous ovarian cancer who had received 9 prior lines of chemotherapy including platinum, also refractory to prior poly (ADP-ribose) polymerase (PARP) inhibition, bevacizumab, and immunotherapy (the PD-1 inhibitor nivolumab in a clinical trial), showed a partial response by Gynaecologic Cancer Intergroup cancer antigen 125 (CA-125) criteria (13) (blood CA-125 levels decreasing from 16,693 U/mL at baseline to 6,261 U/mL as best response, which was sustained for more than 28 days), tumor shrinkage (~19% in target lesion size and ~50% in lung lesions), and durable stable disease ongoing after 385 days at the time of data cut-off (Fig. 2D and Supplementary Table S5).

**DISCUSSION**

This first-in-human phase I dose-escalation trial of the potent and selective ATR inhibitor BAY 1895344 provides evidence that ATR inhibition as a single agent is tolerable at biologically active doses using the 3 days on/4 days off schedule. To the best of our knowledge, this study of BAY 1895344 provides the first clinical evidence of an oral ATR inhibitor, with durable single-agent antitumor activity in patients with advanced cancers with ATM aberrations (ATM protein expression loss and/or \textit{ATM} deleterious mutation).

ATR is known to be essential for normal tissues (4), while complete ATR inhibition is embryonically lethal; however, \textit{in vivo} models with ATR expression conditionally reduced to 10% of normal levels showed only a limited effect on the homeostasis of normal tissues (6).

Importantly, the same level of ATR reduction potently and rapidly inhibited growth of oncogene-driven solid and leukemia tumor models, highlighting ATR inhibition as a tolerable
and promising anticancer strategy for a range of human tumors (6). This study of BAY 1895344 provides proof-of-concept clinical evidence in line with these preclinical investigations. A previous study of the intravenous ATR inhibitor M6620 demonstrated a durable response in a patient with advanced colorectal cancer harboring molecular aberrations, including ATM protein loss, 2 heterozygous truncating mutations in ARID1A, and ARID1A protein loss, as well as heterozygous truncating mutations in CHEK1, FANCM, RAD50, POLD1, and FANCP (SLX4) (14). In our study, single-agent ATR inhibition with oral BAY 1895344 resulted in a manageable safety profile and multiple durable RECIST partial responses in patients with a range of different tumor types.

BAY 1895344 was dosed intermittently in a 3 days on/4 days off regimen to achieve tumor targeting while allowing for recovery of normal tissues during the 4 days off-treatment period (11). The responses observed were durable, with 3 out of 4 responders remaining on treatment for more than 1 year (range 349–472 days) at the time of data cut-off and an overall median duration of response of 315.5 days. Two responders were treated at the MTD, while 2 additional responders who commenced treatment at dose levels above the MTD were reduced to the MTD in cycles 2 and 3, respectively, and maintained durable objective responses. The most frequently observed toxicity was grade 3 anemia presenting at dose levels ≥10 mg BID, including the MTD, and occurring in cycle 2 or later in most patients. The observed grade 3 anemia was managed by dose interruptions and/or blood transfusion, and did not require dose reduction or treatment discontinuation. The anemia observed in this clinical trial as the predominant on-target AE is in line with preclinical results showing that rapidly dividing erythrocyte precursors are particularly sensitive to replication stress, which limits their expansion and differentiation (15). Of note, in the ATR inhibitor M6620 first-in-human study, treatment with M6620 as monotherapy was not associated with significant anemia (11). The safety profile of BAY 1895344 indicates that combinations of BAY
1895344 with chemotherapy, which are expected to be synergistic, should be approached with caution due to potential overlapping hematologic toxicity. Besides the hematopoietic-related AEs, non-hematologic treatment-related events observed with BAY 1895344 were mild in severity and manageable. While deletion of ATR in adult mice has also been associated with aging-related phenotypes such as osteoporosis and alopecia (16), such TEAEs were observed in 1 and 0 patients, respectively, in this clinical trial.

The responding population included patients with advanced cancers with a range of different tumor types and pathologies who harbored a defect in ATM (ATM protein loss and/or \textit{ATM} deleterious mutation). These clinical data, in addition to preclinical results of BAY 1895344 and other reported ATR inhibitors, support a synthetically lethal interaction between ATM deficiency and ATR inhibition (11, 17). \textit{ATM} mutations are observed as germline or somatic in human cancers (9). Approximately 1\% of the population carry a heterozygous \textit{ATM} germline mutation, while \textit{ATM} somatic mutations are among the most commonly observed mutations in sporadic cancers, including prostate, gastric, endometrial, and breast (9, 18).

However, the functional impact of \textit{ATM} mutations may vary from deleterious mutations to variants without a functional impact and may depend on the mutation allele frequency (9). To this end, confirmation of loss or reduction of ATM protein expression in tumor tissue may provide additional evidence on the functional significance of \textit{ATM} mutations (19). In this dose-escalation study, 4 out of 11 patients with advanced cancers and ATM aberrations showed durable partial responses. These patients had different tumor histologies (breast, endometrial, appendiceal, and urothelial cancers), indicating that ATM deficiencies may sensitize various tumor types to ATR inhibition. Importantly, 3 out of the 4 responders showed \(\leq 2\%\) expression of ATM protein by IHC, while the other responder showed an \textit{ATM} mutation regarded as deleterious with abundant ATM protein expression. Further, an \textit{ATM} deleterious mutation was detected in 2 out of the 3 responders with ATM protein loss, and the
allelic frequency of the \textit{ATM} mutations in the responding patients ranged from 40% to 71%. In this small patient subgroup, ORRs of 33.3% and 37.5% were observed in patients with ATM loss and in patients with \textit{ATM} mutations, respectively. All 4 responding patients with ATM loss and/or \textit{ATM} mutation showed wild type \textit{TP53} in tumor samples, indicating that the antitumor activity of BAY 1895344 did not require concurrent p53 deficiency in this patient subgroup.

One patient with a \textit{BRCA1} deleterious mutation had durable RECIST stable disease ongoing after 385 days, with −19% reduction in tumor size and cancer antigen 125 reduction corresponding to a partial response per the Gynecological Cancer InterGroup criteria. This patient was platinum refractory, had received 9 prior lines of chemotherapy and prior treatment with a PARP inhibitor (olaparib), bevacizumab, and immunotherapy (nivolumab), and showed stable disease lasting >1 year at data cut-off. The clinical benefit observed in this patient following BAY 1895344 monotherapy is of particular interest in view of preclinical data suggesting that acquired PARP inhibitor resistance may be mediated by ATR-induced protection of the replication fork (20), and is a clinical area of unmet need (21). This also provided the rationale for an ongoing phase Ib clinical trial assessing the combination regimen of BAY 1895344 with the PARP inhibitor niraparib (NCT04267939) (11).

In addition to the objective responses observed, analysis of baseline and on-treatment paired tumor biopsies showed evidence of biological effects in tumor tissues consistent with the anticipated mechanism of action of increased DNA damage. Increased pKAP was observed in most tumors treated at or above the MTD, indicative of ATR inhibition in tumor tissue (10). Previous preclinical reports have indicated that DNA damage modulates the tumor microenvironment and may induce inflammatory responses which trigger antitumor
immunity (22). Paired tumor tissues from patients treated in this trial suggest upregulation of PD-L1 expression in a subset of patients with PD-L1 positive tumors following treatment with BAY 1895344, supporting previous studies demonstrating upregulated PD-L1 expression in cancer cells in response to DNA damage (23). These findings, together with previous preclinical studies indicating synergistic activity of BAY 1895344 in combination with immune checkpoint inhibitors in preclinical tumor models, provide evidence for further clinical investigation of the combination of BAY 1895344 with immune checkpoint blockade therapies (11). A clinical trial assessing the combination of BAY 1895344 and the PD-1 inhibitor pembrolizumab is currently ongoing (NCT04095273).

The results from this study provide the first clinical evidence that oral treatment with BAY 1895344 is tolerable and has antitumor activity in heavily pre-treated patients with a range of advanced solid tumors, particularly those with ATM deleterious mutations and/or loss of ATM protein, as well as BRCA1 mutant cancers resistant to PARP inhibitors. BAY 1895344 at the MTD of 40 mg BID in a 3 days on/4 days off schedule is being further evaluated in an ongoing single-agent expansion phase of this study involving patients with DDR deficiency by genetic mutations and/or loss of ATM protein expression by IHC. Based on preclinical studies of BAY 1895344 (11), clinical trials assessing combination regimens of BAY 1895344 are also underway (NCT04095273; NCT04267939).

METHODS

This study was conducted in accordance with protocol requirements, the International Conference on Harmonization for Good Clinical Practice, the guiding principles in the Declaration of Helsinki, and any applicable local laws and regulations. All enrolled patients provided written, informed consent before undergoing study-specific procedures. The
protocol was approved by the Institutional Review Board or ethics committee at each participating institution.

Eligible patients at study sites in Europe, North America, and Asia had to be at least 18 years of age with histologically documented advanced solid tumors or non-Hodgkin lymphoma resistant or refractory to standard treatment, an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate bone marrow, liver, kidney, coagulation, and cardiac function. Patients enrolled were to be enriched for tumors with certain DDR defects (including ATM deleterious mutations or loss of protein expression).

The primary objective was to determine the MTD and/or recommended phase II dose, safety, tolerability, and pharmacokinetics of single-agent BAY 1895344. The secondary objective was to evaluate the response rate of BAY 1895344. Exploratory objectives included assessment of BAY 1895344 on pharmacodynamic biomarkers; assessment of the relationship between BAY 1895344 pharmacokinetic and pharmacodynamic effects based on plasma exposure and effects on safety, tumor response rate, and changes in pharmacodynamic target engagement-associated biomarkers from baseline; and exploration of the predictive capability of putative DDR defect biomarkers.

**Study Design and Treatment**

BAY 1895344 was administered orally as a 1 mg/mL solution BID (every 12 ± 1 hours, except on cycle 1, day 1 when the evening dose was withheld to facilitate pharmacokinetic analyses) in a 3 days on/4 days off schedule. Each cycle comprised 21 days, with 9 treatment days per cycle. Dosing started at 5 mg BID and was escalated until the MTD was reached, with the initial doses planned to be doubled up to a dose of 640 mg BID. At doses of ≥40 mg BID, the plan was to switch to a higher concentration solution (4 mg/mL) for patient
convenience. BAY 1895344 treatment continued until tumor progression, unacceptable
toxicity, or withdrawal of consent. The MTD was defined as the maximum dose at which the
incidence of DLTs (Supplementary Table S1) during cycle 1 was below 30%. Each cohort
was evaluated after patients completed 1 cycle of treatment or had withdrawn during cycle 1
due to a DLT.

Dose escalation followed an accelerated design to minimize the number of patients required
to establish the MTD, with a maximum of 2 patients initially assigned per dose level. If 1 or
more patients experienced a grade ≥2 drug-related toxicity (other than an asymptomatic grade
≥2 laboratory abnormality or constitutional symptoms), a DLT, or if indicated by
pharmacokinetic data, the cohort size was increased to 3 patients. Dose escalation, de-
escalation, or cohort expansion decisions were made in consultation with all investigators and
the sponsor after reviewing all available safety and pharmacokinetic data. A model-based
dose-response analysis of DLT rates was performed to guide dose decisions, considering data
from all dose levels; the dose predicted to yield a maximum DLT rate of 30% was
recommended from the model. Cohort expansion occurred when a previously tested dose
was selected for the next cohort of 3 patients; expansion of up to 10 patients per cohort at any
given dose was allowed. The selection of a next dose level with a predicted DLT rate close
to 30% aimed to ensure that the next tested dose was safe. The maximum dose escalation
was 2-fold for the initial cohorts and 1.5-fold after a DLT in the previous cohort. Intermittent
dose levels and an alternative dosing schedule of 3 days on/4 days off for 2 weeks followed
by 1 week off was to be explored, if indicated by pharmacokinetic and safety data.

Assessments

AEs were summarized according to the Medical Dictionary for Regulatory Activities version
21.1 and graded using the National Cancer Institute Common Terminology Criteria for
Adverse Events version 4.03 (National Cancer Institute. 2010.
https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-
14_QuickReference_5x7.pdf) throughout the study period and up to 30 days after the last
dose. AEs were calculated for cycle 1, cycle ≥2, and overall. Any TEAE starting on or after
the cycle 2 start date was considered to have occurred in cycle ≥2, while events that started in
cycle 1 and continued to cycle ≥2 were included at both time points. For TEAEs with
missing start dates, events were considered to have occurred in cycle 1. Additional safety
evaluations included physical examination, concomitant medications, cardiovascular
assessment, vital signs, and laboratory assessments.

Serial plasma samples were collected for pharmacokinetic analysis on cycle 1, days 1, 2, 3,
and 10, and on cycle 2, day 3 (up to 24 hours post-administration after a single dose of BAY
1895344 and up to 12 hours post-administration after multiple doses). Additional details on
the pharmacokinetic analyses are provided in the Supplementary Material.

Availability of a fresh pre-treatment tumor biopsy, or archival tumor tissue collected within
6 months of starting the trial, was mandated for patient enrollment to evaluate the impact of
DDR deficiency by certain DDR gene mutations and/or ATM protein loss on response to
BAY 1895344. Gene mutations in tumor tissue were determined by local report and/or
central laboratory testing using FoundationOne® CDx NGS assay (Foundation Medicine,
Inc.). DDR genomic variants were prospectively functionally annotated by the Precision
Oncology Decision Support Group at the Khalifa Institute for Personalized Cancer Therapy at
the University of Texas MD Anderson Cancer Center (24). ATM protein expression was
assessed via IHC, with ATM protein loss defined as <1% of evaluated tumor cells’ nuclei
staining positive for ATM. See the Supplementary Material for additional details.
Paired pre-treatment and on-treatment fresh tumor biopsies were collected from the participants enrolled in dose escalation at the dose levels predicted to be biologically active and dose-expansion cohorts. γ-H2AX and/or pKAP1 were used as pharmacodynamic biomarkers associated with target and/or pathway engagement. γ-H2AX was evaluated by IHC in paired biopsies using phosphorylated H2AX rabbit clone 20E3. pKAP1 was evaluated by IHC using rabbit clone 6H11L6. PD-L1 expression was also evaluated in paired biopsies using the Agilent IHC 22C3 pharmDx (Dako Omnis) assay and the combined positive score algorithm (25). All IHC staining was performed by Mosaic Laboratories, LLC (Lake Forest, CA).

Tumors were assessed by computed tomography or magnetic resonance imaging for response via RECIST (26) at the end of every second cycle until cycle 8, and at the end of every 3 cycles thereafter, except for castration-resistant prostate cancer. Castration-resistant prostate cancer was assessed using Prostate Cancer Clinical Trials Working Group 3 criteria (27) at the end of every third cycle until cycle 12, and every 4 cycles thereafter. A best response of stable disease required stable disease to be documented at least once at 6 weeks from baseline.

Blood was assessed for CA-125, a marker of tumor growth, in patients with ovarian cancer and was collected at screening, at the end of every second cycle, and at the end of treatment. Response according to CA-125 was calculated as defined by the Gynecological Cancer InterGroup (Gynecological Cancer InterGroup. 2005. https://gcigttrials.org/system/files/CA%20125%20Definitions%20Agreed%20to%20by%20GCI%20-%20November%202005.pdf).
**Statistical Analysis**

All patients who received at least 1 dose of BAY 1895344 and had post-treatment safety data were included in the safety evaluation. All patients who completed cycle 1 and received at least 80%, and not more than 120%, of the required dose during cycle 1 or discontinued during cycle 1 because of a DLT were included in the MTD evaluation. The incidence of DLTs during cycle 1 was summarized by dose, and modeled as a function of BAY 1895344 dose using Bayesian logistic regression based on previously reported methodology (28). All patients receiving at least 1 dose of BAY 1895344, and with at least 1 valid pharmacokinetic assessment of BAY 1895344 after first dosing and no substantial protocol deviations, were included in pharmacokinetic evaluations; all patients with evaluable pharmacodynamic data, and without substantial protocol deviations, were included in pharmacodynamic evaluations. All patients who received at least 1 dose of BAY 1895344 and had post-baseline tumor scans were included in the evaluation of antitumor activity/response. Summary statistics are provided where appropriate.

**Authors’ Contributions**

**Conception and design:** T.A. Yap, D.S.P. Tan, G. Wilkinson, J. Hreiki, A.M. Wengner, M. Ludwig, L. Liu, S. Bordia, R. Plummer, E. Lagkadinou, J.S. de Bono


**Analysis and interpretation of data:** T.A. Yap, D.S.P. Tan, G. Wilkinson, J. Hreiki, F. Bladt, A. Schlicker, M. Ludwig, Y. Zhou, S. Bordia, E. Lagkadinou, J.S. de Bono
Writing, review, and/or revision of the manuscript: all authors

Administrative, technical, or material support: T.A. Yap, D.S.P. Tan, G. Wilkinson, J. Hreiki, A. Schlicker, M. Ludwig, Y. Zhou, E. Lagkadinou, J.S. de Bono

Study supervision: T.A. Yap, D.S.P. Tan, E. Lagkadinou, J.S. de Bono

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Communications, provided medical writing support with this manuscript, based on detailed discussion and feedback from all the authors; this assistance was funded by Bayer AG.
REFERENCES


Table 1. Patient demographics and baseline cancer characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (N = 22)</th>
</tr>
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<tbody>
<tr>
<td>Female, n (%)</td>
<td>11 (50.0)</td>
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<tr>
<td>Median age, years (range)</td>
<td>63 (45–74)</td>
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<tr>
<td>ECOG PS 0, n (%)</td>
<td>6 (27.3)</td>
</tr>
<tr>
<td>ECOG PS 1, n (%)</td>
<td>16 (72.7)</td>
</tr>
<tr>
<td>Prior lines of systemic chemotherapies, n (%)</td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>2–3</td>
<td>4 (18.2)</td>
</tr>
<tr>
<td>≥4</td>
<td>16 (72.7)</td>
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<tr>
<td>Prior platinum-containing chemotherapy, n (%)</td>
<td>16 (72.7)</td>
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<tr>
<td>Platinum resistant</td>
<td>12 (54.5)</td>
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<td>Platinum sensitive</td>
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<td>Prior immuno-oncology, n (%)</td>
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<tr>
<td>Prior PARP inhibitor, n (%)</td>
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<tr>
<td>DDR deficiency, n (%)</td>
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<tr>
<td>ATM protein loss and/or ATM mutation</td>
<td>11 (50.0)</td>
</tr>
<tr>
<td>ATM proficient and ATM wild type</td>
<td>4 (18.2)</td>
</tr>
<tr>
<td>BRCA1 mutation&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>BRCA2 mutation&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Unknown&lt;sup&gt;c&lt;/sup&gt;</td>
<td>7 (31.8)</td>
</tr>
<tr>
<td>Tumor type, n (%)</td>
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<tr>
<td>Breast cancer</td>
<td>4 (18.2)</td>
</tr>
<tr>
<td>Colorectal cancer&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4 (18.2)</td>
</tr>
<tr>
<td>Castrate-resistant prostate cancer</td>
<td>4 (18.2)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>Endometrial</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (27.3)</td>
</tr>
</tbody>
</table>

<sup>a</sup>1 patient with a BRCA1 mutation had a prior PARP inhibitor;<sup>b</sup>No patient with a BRCA2 mutation had a prior PARP inhibitor; <sup>c</sup>Includes 3 samples with wild type ATM that failed IHC testing, and 1 sample with high expression levels of ATM protein that failed NGS testing; <sup>d</sup>Includes 2 patients diagnosed with colon cancer.

ECOG PS, Eastern Cooperative Oncology Group performance status.
<table>
<thead>
<tr>
<th>TEAEs</th>
<th>Cycle 1 (n = 22)</th>
<th>Cycle 2 (n = 22)</th>
<th>Total (N = 22)</th>
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<tr>
<td></td>
<td>Grade 1/2</td>
<td>Grade 3/4</td>
<td>Grade 1/2</td>
</tr>
<tr>
<td>Anemia</td>
<td>6 (27.3)</td>
<td>6 (27.3)</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>Neutropenia/decreased neutrophil count</td>
<td>5 (22.7)</td>
<td>8 (36.4)</td>
<td>4 (18.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (36.4)</td>
<td>0</td>
<td>8 (36.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (22.7)</td>
<td>1 (4.5)</td>
<td>6 (27.3)</td>
</tr>
<tr>
<td>Thrombocytopenia/decreased platelet count</td>
<td>4 (18.2)</td>
<td>4 (18.2)</td>
<td>7 (31.8)</td>
</tr>
<tr>
<td>Back pain</td>
<td>3 (13.6)</td>
<td>0</td>
<td>5 (22.7)</td>
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<tr>
<td>Pyrexia</td>
<td>2 (9.1)</td>
<td>0</td>
<td>5 (22.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>0</td>
<td>4 (18.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (18.2)</td>
<td>0</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (9.1)</td>
<td>1 (4.5)</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>0</td>
<td>0</td>
<td>4 (18.2)</td>
</tr>
<tr>
<td>Leukopenia/decreased white blood cell count</td>
<td>0</td>
<td>3 (13.6)</td>
<td>0</td>
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<tr>
<td>Vomiting</td>
<td>1 (4.5)</td>
<td>0</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (9.1)</td>
<td>0</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1 (4.5)</td>
<td>0</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1 (4.5)</td>
<td>0</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>0</td>
<td>0</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1 (4.5)</td>
<td>1 (4.5)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>2 (9.1)</td>
<td>0</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>Productive cough</td>
<td>0</td>
<td>0</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>1 (4.5)</td>
<td>0</td>
<td>3 (13.6)</td>
</tr>
</tbody>
</table>
Table 3. Best overall response per RECIST or PCWG3 in patients treated with BAY 1895344 monotherapy

<table>
<thead>
<tr>
<th>Best response, a n (%)</th>
<th>Total (N = 21)</th>
<th>3 days on/4 days off schedule (n = 17)</th>
<th>Doses ≥40 mg BID 3 days on/4 days off (n = 13)</th>
<th>Patients with ATM loss and/or ATM mutation (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>4 (19.0)</td>
<td>4 (23.5)</td>
<td>4 (30.8)</td>
<td>4 (36.4)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>8 (38.1)</td>
<td>6 (35.3)</td>
<td>5 (38.5)</td>
<td>3 (27.3)</td>
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<tr>
<td>Progressive disease b</td>
<td>9 (42.9)</td>
<td>7 (41.2)</td>
<td>4 (30.8)</td>
<td>4 (36.4)</td>
</tr>
<tr>
<td>Objective response rate, n (%)</td>
<td>4 (19.0)</td>
<td>4 (23.5)</td>
<td>4 (30.8)</td>
<td>4 (36.4)</td>
</tr>
<tr>
<td>Disease control rate, n (%)</td>
<td>12 (57.1)</td>
<td>10 (58.8)</td>
<td>9 (69.2)</td>
<td>7 (63.6)</td>
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<tr>
<td>Median duration of response, days (range)</td>
<td>315.5 (246–357)</td>
<td>315.5 (246–357)</td>
<td>315.5 (246–357)</td>
<td>315.5 (246–357)</td>
</tr>
<tr>
<td>Median duration of stable disease, days (range)</td>
<td>89 (51–378)</td>
<td>89 (51–378)</td>
<td>86 (51–371)</td>
<td>86 (51–127)</td>
</tr>
<tr>
<td>Median time to response, days (range)</td>
<td>78 (49–211)</td>
<td>78 (49–211)</td>
<td>78 (49–211)</td>
<td>78 (49–211)</td>
</tr>
</tbody>
</table>

a1 patient receiving treatment on the 3 days on/4 days off schedule did not have a post-baseline tumor assessment and therefore was not evaluable for best response; b2 patients who achieved stable disease as RECIST best response had investigator-assessed clinical disease progression at the same time point and were therefore reported as having progressive disease.

PCWG3, Prostate Cancer Working Group 3.
Figure 1. Pharmacokinetic and pharmacodynamic results. A, BAY 1895344 geometric mean plasma concentration over time after single-dose administration at cycle 1, day 1. B, BAY 1895344 geometric mean plasma concentration over time after multiple-dose administration at cycle 1, day 10. C, Example of on-treatment increase of tumor γ-H2AX and pKAP1 at baseline and cycle 1, day 10 in a patient with a *BRCA1* germline mutation and high-grade serous platinum-refractory ovarian cancer. D, Percentage of γ-H2AX positive cells at baseline and post-treatment in biopsy pairs (*n* = 17). E, Percentage of γ-H2AX positive cells at baseline and post-treatment in biopsy pairs from patients with (*n* = 12) or without (*n* = 5) ATM protein expression. F, PD-L1 expression in baseline tumor biopsy samples. G, Comparison of PD-L1 expression at baseline with on-treatment paired biopsies in patients with ovarian (*n* = 6) and endometrial cancer (*n* = 2). NS, not significant.

Figure 2. Efficacy and clinical response results of BAY 1895344 in the dose-escalation part. A, Change in target lesion size, best response, ATM aberration status, and mutation status in the 20 patients with available data from post-baseline assessments. \(^a\)Alternating dose; \(^b\)Ongoing with study treatment; \(^c\)2 patients who achieved stable disease as RECIST best response had investigator-assessed clinical disease progression at the same time point and were therefore reported as having progressive disease. B, Durability of response in the 17 patients treated on the 3 days on/4 days off schedule who had post-baseline tumor assessments. C, Tumor reduction of −54% in a patient with tumor ATM protein loss by IHC and a germline *ATM* mutation with hormone receptor positive, human epidermal growth factor receptor 2-negative platinum-refractory breast cancer and 11 prior lines of systemic therapy. D, Tumor shrinkage of −19% and a significant cancer antigen 125 reduction in a patient with a *BRCA1* germline mutation and high-grade serous platinum-refractory ovarian cancer, also refractory to prior poly (ADP-ribose) polymerase inhibition and immunotherapy. PD, progressive disease; PR, partial response; SD, stable disease.
**PD-L1 level in baseline biopsies**

- Breast
- Colorectal
- Prostate
- Ovarian
- Endometrial
- Lung

**Combined positive score**

**Tumor type**

**Figure 1**

**BAY 1895344 concentrations (µg/L)**

- Planned time (h)
  - 10 mg; individual data; n = 1
  - 20 mg; individual data; n = 1
  - 40 mg; individual data; n = 2
  - 60 mg; individual data; n = 6
  - 60 mg; geometric mean; n = 4; Schedule 2
  - 80 mg; geometric mean; n = 3

**γ-H2AX positive cells/mm²**

- Baseline
- Cycle 1, day 10

**Example shown in Fig. 1C**

**ATM loss tumors**

**P = 0.027**

**NS**

**PD-L1 post-treatment change in ovarian and endometrial samples**

- Planned time (h)
  - 5 mg; individual data; n = 1
  - 10 mg; individual data; n = 1
  - 20 mg; individual data; n = 1
  - 40 mg; individual data; n = 2
  - 60 mg; geometric mean; n = 7
  - 60 mg; geometric mean; n = 3; Schedule 2
  - 80 mg; geometric mean; n = 3

**Combined positive score**

**Tumor type**

**Figure 1**

**BAY 1895344 concentrations (µg/L)**

- Planned time (h)
  - 10 mg; individual data; n = 1
  - 20 mg; individual data; n = 1
  - 40 mg; individual data; n = 2
  - 60 mg; individual data; n = 6
  - 60 mg; geometric mean; n = 4; Schedule 2
  - 80 mg; geometric mean; n = 3

**γ-H2AX in 17 tumor pairs**

- Example shown in Fig. 1C
- ATM loss tumors

**P = 0.027**

**NS**

**PD-L1 post-treatment change in ovarian and endometrial samples**

- Planned time (h)
  - 5 mg; individual data; n = 1
  - 10 mg; individual data; n = 1
  - 20 mg; individual data; n = 1
  - 40 mg; individual data; n = 2
  - 60 mg; geometric mean; n = 7
  - 60 mg; geometric mean; n = 3; Schedule 2
  - 80 mg; geometric mean; n = 3

**Combined positive score**

**Tumor type**

**Figure 1**

**BAY 1895344 concentrations (µg/L)**

- Planned time (h)
  - 10 mg; individual data; n = 1
  - 20 mg; individual data; n = 1
  - 40 mg; individual data; n = 2
  - 60 mg; individual data; n = 6
  - 60 mg; geometric mean; n = 4; Schedule 2
  - 80 mg; geometric mean; n = 3

**γ-H2AX in 17 tumor pairs**

- Example shown in Fig. 1C
- ATM loss tumors

**P = 0.027**

**NS**

**PD-L1 post-treatment change in ovarian and endometrial samples**

- Planned time (h)
  - 5 mg; individual data; n = 1
  - 10 mg; individual data; n = 1
  - 20 mg; individual data; n = 1
  - 40 mg; individual data; n = 2
  - 60 mg; geometric mean; n = 7
  - 60 mg; geometric mean; n = 3; Schedule 2
  - 80 mg; geometric mean; n = 3

**Combined positive score**

**Tumor type**
Figure 2

A

Best change in target lesion from baseline (%)

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Dose (mg BID)</th>
<th>Best response</th>
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<tr>
<td>1</td>
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<td>PD</td>
</tr>
<tr>
<td>2</td>
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</tr>
<tr>
<td>3</td>
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<td>PD</td>
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<tr>
<td>4</td>
<td>80</td>
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<tr>
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<td>SD</td>
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ATM\textsuperscript{mmt} and/or ATM\textsuperscript{mut}

No ATM aberrations

Patient ID

Dose (mg BID)

Best response

- ATM\textsuperscript{mmt}
- ATM\textsuperscript{mut}
- BRCA1\textsuperscript{mmt}
- BRCA2\textsuperscript{mmt}
- MYC\textsuperscript{amp}
- TP53\textsuperscript{mut}

Mutation, amplification, loss
Wild type, proficient
Data unavailable

B

Change from baseline (%)

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<th>SD</th>
<th>PR</th>
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Hepatocellular
Ovarian
Appendix
Breast
Endometrial
Urothelial duct

C

ATM IHC H-score = 0

Baseline Post 14 cycles

Baseline Post 14 cycles

D

Screening

Cycle 6

CA-125 (U/mL)

Test date

16,693 10,904 9,835 8,481 8,707 8,368 6,261 6,351 6,296