RESEARCH ARTICLE

First-in-Human Trial of the Oral Ataxia Telangiectasia and RAD3-Related (ATR) Inhibitor BAY 1895344 in Patients with Advanced Solid Tumors

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Illustration by Bianca Dunn

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 to 80 mg twice daily in 21 patients with advanced solid tumors. The MTD was 40 mg twice daily 3 days on/4 days off. Most common adverse events were manageable and reversible hematologic 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 twice daily. 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 pretreated 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.

See related commentary by Italiano, p. 14.

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 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 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–G_2–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 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 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 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

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Note: Supplementary data for this article are available at Cancer Discovery Online (http://cancerdiscovery.aacrjournals.org/).

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Cancer Discov 2021;11:80–91

doi: 10.1158/2159-8290.CD-20-0868

and tolerability, MTD, pharmacokinetic–pharmacodynamic profile, and antitumor activity of BAY 1895344 in patients with advanced solid tumors (NCT03188965), and demonstrated 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. On the basis of preclinical experiments indicating that optimal antitumor activity and tolerability of BAY 1895344 were achieved via intermittent administration (11), and the human pharmacokinetic parameters of BAY 1895344, 18 patients received BAY 1895344 twice daily 3 days on/4 days off weekly, and 4 patients received a less dose-intensive variation of this schedule (3 days on/4 days off for 2 weeks followed by 1 week off; Supplementary Figs. 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 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 cutoff, 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 adverse events (AE; Supplementary Fig. S1).

Table 1. Patient demographics and baseline cancer characteristics

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

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

[a]1 patient with a *BRCA1* mutation had a prior PARP inhibitor.

[b]No patient with a *BRCA2* mutation had a prior PARP inhibitor.

[c]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.

[d]Includes 2 patients diagnosed with colon cancer.

Safety

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

Among all dose cohorts and schedules, the most common all-grade treatment-emergent adverse events (TEAE) 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 nonhematologic TEAEs were of low frequency and primarily grade 1 and 2 (Table 2; 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 twice daily 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 twice daily, including the MTD (Table 2; 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

Table 2. Summary of the most common all-cause TEAEs occurring in ≥10% of the total population by grade and cycle

	Cycle 1 ($n = 22$)		Cycle ≥2 ($n = 22$)		Total ($N = 22$)	
n (%)	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
TEAEs						
Anemia	6 (27.3)	6 (27.3)	2 (9.1)	16 (72.7)	0	18 (81.8)
Neutropenia/decreased neutrophil count	5 (22.7)	8 (36.4)	4 (18.2)	11 (50.0)	4 (18.2)	12 (54.5)
Fatigue	8 (36.4)	0	8 (36.4)	2 (9.1)	13 (59.1)	2 (9.1)
Nausea	5 (22.7)	1 (4.5)	6 (27.3)	1 (4.5)	9 (40.9)	2 (9.1)
Thrombocytopenia/ decreased platelet count	4 (18.2)	4 (18.2)	7 (31.8)	0	6 (27.3)	4 (18.2)
Back pain	3 (13.6)	0	5 (22.7)	0	7 (31.8)	0
Pyrexia	2 (9.1)	0	5 (22.7)	0	6 (27.3)	0
Diarrhea	0	0	4 (18.2)	1 (4.5)	4 (18.2)	1 (4.5)
Headache	4 (18.2)	0	1 (4.5)	0	5 (22.7)	0
Abdominal pain	2 (9.1)	1 (4.5)	2 (9.1)	0	3 (13.6)	1 (4.5)
Hypokalemia	0	0	4 (18.2)	0	4 (18.2)	0
Leukopenia/decreased white blood cell count	0	3 (13.6)	0	2 (9.1)	0	4 (18.2)
Vomiting	1 (4.5)	0	3 (13.6)	1 (4.5)	3 (13.6)	1 (4.5)
Constipation	2 (9.1)	0	1 (4.5)	0	3 (13.6)	0
Decreased appetite	1 (4.5)	0	2 (9.1)	0	3 (13.6)	0
Dyspnea	1 (4.5)	0	2 (9.1)	0	3 (13.6)	0
Gastroesophageal reflux disease	0	0	3 (13.6)	0	3 (13.6)	0
Hypotension	1 (4.5)	1 (4.5)	1 (4.5)	0	2 (9.1)	1 (4.5)
Oropharyngeal pain	2 (9.1)	0	2 (9.1)	0	3 (13.6)	0
Productive cough	0	0	3 (13.6)	0	3 (13.6)	0
Stomatitis	1 (4.5)	0	3 (13.6)	0	3 (13.6)	0

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 cutoff.

Serious AEs related to study treatment included medication error (reported in 1 patient receiving BAY 1895344 10 mg twice daily); grade 3 diarrhea, grade 3 hypotension, and grade 3 nausea (reported in 1 patient receiving BAY 1895344 60 mg twice daily); and grade 4 neutropenia and grade 2 pyrexia (reported in 1 patient receiving BAY 1895344 80 mg twice daily). Most patients (68.2%) experienced at least 1 dose interruption due to drug-related TEAEs. Two patients (9.1%) permanently withdrew from treatment due to TEAEs (grade 3 hemoptysis in 1 patient receiving BAY 1895344 80 mg twice daily, and increased alanine aminotransferase, aspartate aminotransferase, and total bilirubin in another patient receiving BAY 1895344 60 mg twice daily), 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 and 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 to 17.8 hours, a 1.4- to 2.4-fold accumulation of BAY 1895344 exposure was observed on repeat dosing. There was moderate interpatient variability; however, exposure was broadly dose-proportional across the dose range investigated (5–80 mg twice daily), with no evidence of saturable absorption. Clinical exposure at the MTD was observed to be in the range associated with antitumor activity in nonclinical models, substantially exceeding the biochemical and cellular antiproliferative IC_{90} observed preclinically in sensitive mantle cell lymphoma cell lines, such as GRANTA-519, and in the range of the cellular anti-proliferative IC_{90} of moderately sensitive cell lines (11).

Pharmacodynamic Studies

As of the data cutoff, 17 baseline and on-treatment paired biopsies were available from patients receiving BAY 1895344 at doses of 40, 60, and 80 mg twice daily. 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 (γH2AX)

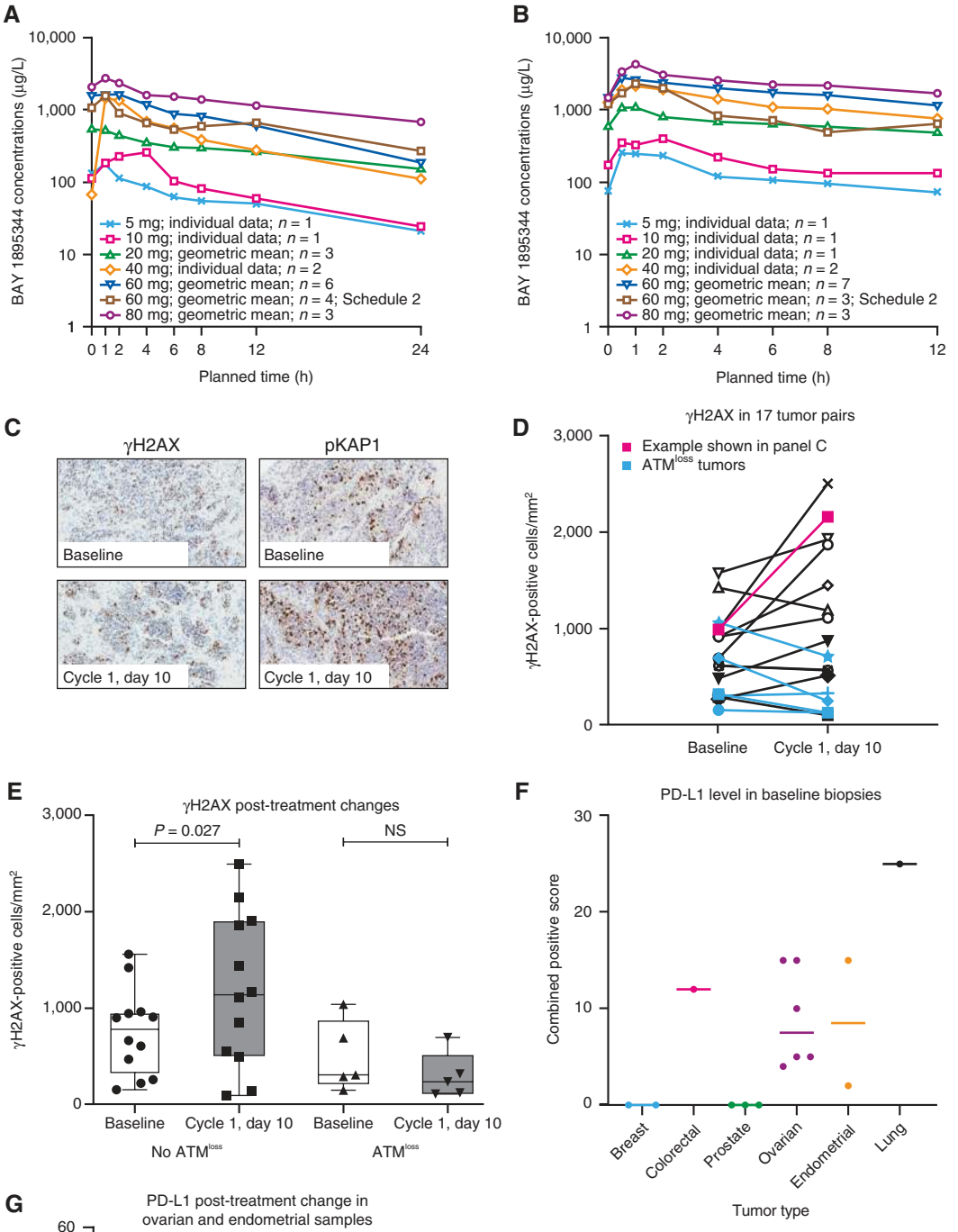

Figure 1. Pharmacokinetic and pharmacodynamic results. **A,** BAY 1895344 geometric mean plasma concentration over time after single-dose administration at cycle 1, day 1. **B,** BAY 1895344 geometric mean plasma concentration over time after multiple-dose administration at cycle 1, day 10. **C,** Example of on-treatment increase of tumor γH2AX 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 γH2AX-positive cells at baseline and post-treatment in biopsy pairs ($n = 17$). **E,** Percentage of γH2AX-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 ($n = 2$) cancer. NS, not significant.

and/or pKAP1 in a subset of tumors obtained on cycle 1, day 10, indicating pharmacodynamic target modulation (Fig. 1C–E; Supplementary Fig. S3A and S3B). On-treatment γH2AX induction was not observed in 5 of 5 patients with ATM loss and with available paired tumor biopsies. The percentage of γH2AX-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 γH2AX 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 pretreatment 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 gynecologic tumors with a PD-L1–positive pretreatment 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-infiltrating 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–S4C).

Antitumor Activity

Twenty out of 21 patients treated across all dose levels were evaluable for tumor response (1 patient did not have an on-treatment CT scan or clinical progression information, and therefore was not evaluable for response). RECIST version 1.1 partial responses were achieved in 4 patients (Table 3; Fig. 2A and B). Both patients treated at the BAY 1895344 MTD (40 mg twice daily, 3 days on/4 days off) had confirmed RECIST partial responses (advanced renal collective ductal carcinoma and metastatic appendiceal cancer). Two additional patients commenced treatment at dose levels higher than the MTD (1 patient with hormone receptor–positive, HER2-negative breast cancer at 60 mg twice daily and 1 patient with endometrial cancer at 80 mg twice daily 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 cutoff, 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; Supplementary Table S5). The first patient had hormone receptor–positive, HER2-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 cutoff. 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 cutoff. 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 cutoff. 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 *PI3K* genes were detected in those 3 patients (Supplementary Table S6).

One additional patient with $BRCA1^{Q1401}$ 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 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 (ref. 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 cutoff (Fig. 2D; 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

Table 3. Best overall response per RECIST or PCWG3 in patients treated with BAY 1895344 monotherapy

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

Abbreviations: BID, twice daily; PCWG3, Prostate Cancer Working Group 3.

[a]1 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.

[b]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.

with advanced cancers with ATM aberrations (ATM protein expression loss and/or *ATM* deleterious mutation).

ATR is known to be essential for normal tissues (4), and complete ATR inhibition is embryonically lethal; however, *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*; ref. 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-day off-treatment period (11). The responses observed were durable, with 3 of 4 responders remaining on treatment for more than 1 year (range 349–472 days) at the time of data cutoff, and an overall median duration of response of 315.5 days. Two responders were treated at the MTD, and 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 twice daily, 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, nonhematologic treatment-related events observed with BAY 1895344 were mild in severity and manageable. Although 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 *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). *ATM* mutations are observed as germline or somatic in human cancers (9). Approximately 1% of the population carries a heterozygous *ATM* germline mutation, while *ATM* somatic

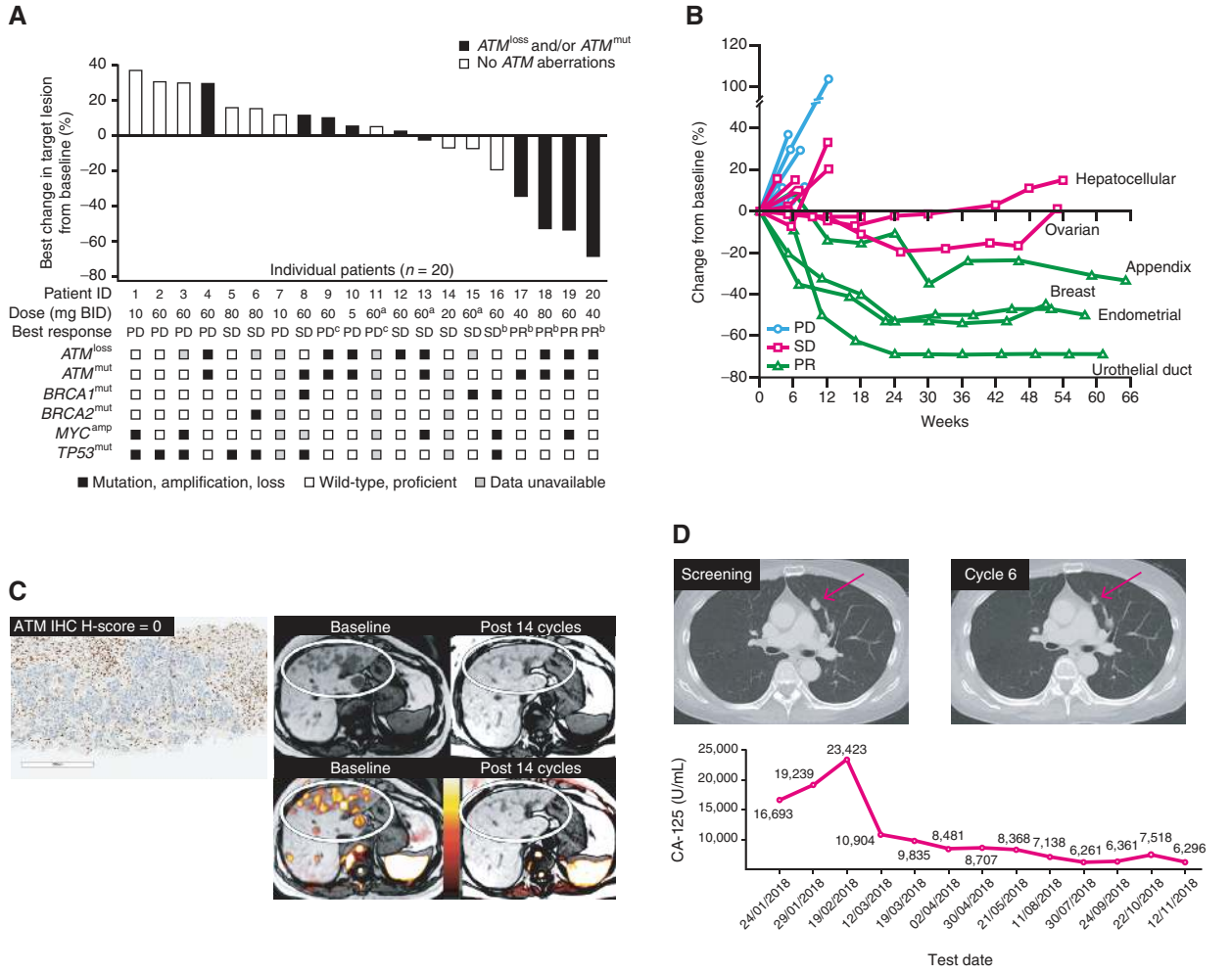

Figure 2. Efficacy and clinical response results of BAY 1895344 in the dose-escalation part. **A,** Change in target lesion size, best response, ATM aberration status, and mutation status in the 20 patients with available data from post-baseline assessments. [a]Alternating dose; [b]Ongoing with study 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,** IHC showing ATM protein loss and CT and FDG PET showing shrinkage of liver metastases (overall tumor shrinkage of −54%) in a patient with tumor ATM protein loss and a germline *ATM* mutation with hormone receptor–positive, HER2-negative platinum-refractory breast cancer and 11 prior lines of systemic therapy. **D,** CT showing shrinkage of lung metastases (overall 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 PARP inhibition and immunotherapy. BID, twice daily; PD, progressive disease; PR, partial response; SD, stable disease.

mutations are among the most commonly observed mutations in sporadic cancers, including prostate, gastric, endometrial, and breast (9, 18). However, the functional impact of *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 *ATM* mutations (19). In this dose-escalation study, 4 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 of the 4 responders showed ≤2% expression of ATM protein by IHC, whereas the other responder showed an *ATM* mutation regarded as deleterious with abundant ATM protein expression. Furthermore, an *ATM* deleterious mutation was detected in 2 of the 3 responders with ATM protein loss, and the allelic frequency of the *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 *ATM* mutations, respectively. All 4 responding patients with ATM loss and/or *ATM* mutation showed wild-type *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 *BRCA1* deleterious mutation had durable RECIST stable disease ongoing after 385 days, with −19% reduction in tumor size and CA-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 cutoff. 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; ref. 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 that 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 pretreated 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 twice daily 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. On the basis of preclinical studies of BAY 1895344 (11), clinical trials assessing combination regimens of BAY 1895344 are also under way (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 twice daily (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 twice daily and was escalated until the MTD was reached, with the initial doses planned to be doubled up to a dose of 640 mg twice daily. At doses of ≥40 mg twice daily, 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) or a DLT, or if indicated by pharmacokinetic data, the cohort size was increased to 3 patients. Dose-escalation, deescalation, 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, whereas 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 pretreatment 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 pretreatment 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. γH2AX and/or pKAP1 were used as pharmacodynamic biomarkers associated with target and/or pathway engagement. γH2AX 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.

Tumors were assessed by CT or MRI 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://gcigtrials.org/system/files/CA%20125%20Definitions%20Agreed%20to%20by%20GCIG%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.

Disclosure of Potential Conflicts of Interest

T.A. Yap reports grants from Artios (research support to institution), Constellation (research support to institution), Cyteir (research support to institution), Eli Lilly (research support to institution), Forbius (research support to institution), Genentech (research support to institution), GlaxoSmithKline (research support to institution), ImmuneSensor (research support to institution), Ipsen (research support to institution), Jounce (research support to institution), Karyopharm Therapeutics (research support to institution), Kyowa (research support to institution), Novartis (research support to institution), Regeneron (research support to institution), Ribon Therapeutics (research support to institution), Sanofi (research support to institution), Scholar Rock (research support to institution), Tesaro (research support to institution), and Vertex Pharmaceuticals (research support to institution); grants and personal fees from AstraZeneca (research support to institution; consultant), Bayer (research support to institution; consultant), Clovis (research support to institution; consultant), EMD Serono (research support to institution; consultant); F-star (research support to institution; consultant), Merck (research support to institution; consultant), Pfizer (research support to institution; consultant), Repare (research support to institution; consultant), and Seattle Genetics (research support to institution; consultant), and personal fees from Aduro (consultant), Almac (consultant), Atrin (consultant), Axiom (consultant), Bristol Myers Squibb (consultant), Calithera Biosciences (consultant), Cybrexa (consultant), Guidepoint (consultant), Ignyta (consultant), I-Mab (consultant), Janssen (consultant), Roche (consultant), Rubius (consultant), Schrödinger (consultant), Varian (consultant), and Zai Lab (consultant) outside the submitted work. D.S.P. Tan reports grants and other from Singapore Ministry of Health's National Medical Research Council [NMRC; NMRC Clinician Scientist Award (NMRC/CSA-INV/0016/2017) with grant and salary support]; grants from Singapore Ministry of Health's National Medical Research Council (Centre Grant scheme to National University Cancer Institute, Singapore) during the conduct of the study and grants from Karyopharm Therapeutics; grants and personal fees from AstraZeneca and Bayer; personal fees and nonfinancial support from Eisai, MSD, and Roche; personal fees from Merck Serono outside the submitted work; and charitable research funding from the Pangestu Family Foundation Gynaecological Cancer Research Fund. B.C. Goh reports grants from Bayer Oncology (Bayer Oncology covered the costs of conducting the study) during the conduct of the study; in addition, B.C. Goh has a patent for Detection Of Biomarkers for Non-Small Cell Lung Cancer pending to Sengenics Ltd (PCT patent application no. PCT/SG2019/050611) and a patent for Modulation of Signal Transducer and Activator Of Transcription 3 (STAT3) Expression pending to Apterna (patent filed); and stock ownership (Blueprint Medicines and Gilead Sciences). V. Heong reports grants from National University Cancer Institute Singapore (Yong Loo Lin fellowship grant for salary support to the institution) during the conduct of the study; and honoraria and fees for consulting from AstraZeneca and Pfizer. Y. Drew reports consultancy, honoraria, and advisory boards for AstraZeneca, Clovis, Genmab, Merck, and Tesaro; institution received research funding from AstraZeneca, Clovis, Oncology, Merck, and Tesaro Inc. D.S. Hong reports grants from Bayer (institutional funding for clinical trial) and personal fees from Bayer (advisory board) during the conduct of the study; and disclosures [last 36 months: research/grant funding: AbbVie, Adaptimmune, Aldi-Norte, Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Daiichi Sankyo, Eisai, Eli Lilly, Fate Therapeutics, Genentech, Genmab, Ignyta, Infinity, Kite, Kyowa, LOXO, MedImmune, Merck,

Mirati, miRNA, Molecular Templates, Mologen, NCI-CTEP, Novartis, Pfizer, Seattle Genetics, Takeda, and Turning Point Therapeutics; travel, accommodations, and expenses: AACR, ASCO, Bayer, Genmab, LOXO, miRNA, and SITC; consulting or advisory role: Acuta, Adaptimmune, Alpha Insights, Amgen, Axiom, Baxter, Bayer, COG, Ecor1, Genentech, GLG, groupH, Guidepoint, Infinity, Janssen, Medscape, Merrimack, Numab, Pfizer, prIME Oncology, Seattle Genetics, Takeda, Trieza Therapeutics, and WebMD; and other ownership interests: Molecular Match (advisor), OncoResponse (founder), Presagia Inc (founder and advisor)]. F. Meric-Bernstam reports grants and personal fees from Debiopharm (consulting; sponsored research), eFFECTOR Therapeutics (consulting; sponsored research), Genentech (consulting; sponsored research), and Puma Biotechnology (advisory committee; sponsored research); personal fees from Aduro BioTech (consulting), Alkermes (consulting), F. Hoffman-La Roche Ltd. (consulting), IBM Watson (consulting), Immunomedics (advisory committee), Inflection Biosciences (advisory committee), Jackson Laboratory (consulting), Kolon Life Science (consulting), Mersana Therapeutics (advisory committee), OrgiMed (consulting), PACT Pharma (consulting), Parexel International (consulting), Pfizer (consulting), Samsung Bioepis (consulting), Seattle Genetics (consulting; advisory board), Silverback Therapeutics (advisory committee), Spectrum Pharmaceuticals, (advisory committee), Tyra Biosciences (consulting), Xencor (consulting), Zentalis (advisory committee), and Zymeworks (consulting); grants from Aileron Therapeutics (sponsored research), AstraZeneca (sponsored research), Bayer HealthCare Pharmaceuticals (sponsored research), Calithera Biosciences (sponsored research), Curis, Inc. (sponsored research), CytomX Therapeutics (sponsored research), Daiichi Sankyo (sponsored research), Guardant Health (sponsored research), Millennium Pharmaceuticals (sponsored research), Novartis (sponsored research), and Taiho Pharmaceuticals (sponsored research); other from Beth Israel Deaconess Medical Center (travel related), Chugai Biopharmaceuticals (honoraria - speaking engagement), Mayo Clinic (honoraria - speaking engagement), and Rutgers Cancer Institute of New Jersey (honoraria - speaking engagement) outside the submitted work. G. Wilkinson reports other from Bayer AG (employee and shareholder) outside the submitted work. A.M. Wengner reports personal fees from Bayer AG (employed at Bayer AG) during the conduct of the study; in addition, A.M. Wengner has several patents pending and ownership interest in Bayer, including patents. F. Bladt reports personal fees from Bayer AG (Bayer AG employee) during the conduct of the study and outside the submitted work. A. Schlicker reports personal fees from Bayer AG and other from Bayer AG (shareholder) during the conduct of the study; in addition, A. Schlicker has a patent for use (for 2-[(3R)-3-methylmorpholin-4-yl]-4-(1-methyl-1H-pyrazol-5-yl)-8-(1H-pyrazol-5-yl)-1,7-naphthyridine (BAY 1895344) for treating hyperproliferative diseases which are characterized by biomarkers) pending. M. Ludwig reports employment with Bayer Pharma AG, Berlin, Germany. Y. Zhou reports other from Bayer (employee) during the conduct of the study and outside the submitted work. L. Liu reports other from Bayer (employee) during the conduct of the study; other from Bayer (stock holder) outside the submitted work; in addition, L. Liu has a patent for US/08.12.17/USP210762596356 pending and issued. S. Bordia reports other from Bayer (part of Bayer Clinical Trial Team) during the conduct of the study. R. Plummer reports other from Bayer (clinical trial costs to institution) during the conduct of the study; and personal fees from Bayer (honorarium for SAB) outside the submitted work. J.S. de Bono reports grants and other from Bayer (trial funding and grant for preclinical studies to the ICR) during the conduct of the study; and personal fees from Astellas (advisory board), AstraZeneca (advisory board), Bayer (advisory board), Daiichi Sankyo (advisory board), Janssen (advisory board), Merck Serono (advisory board), MSD (advisory board), and Sanofi Aventis (advisory board), outside the submitted work; in addition, J.S. de Bono has a patent for PARP inhibition for patients with DNA Repair defects licensed and with royalties paid from The Institute of Cancer Research (no personal income). No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

T.A. Yap: Conceptualization, data curation, formal analysis, supervision, methodology, writing-original draft, project administration, writing-review and editing. **D.S.P. Tan:** Conceptualization, data curation, formal analysis, supervision, methodology, writing-original draft, project administration, writing-review and editing. **A. Terbuch:** Conceptualization, data curation, formal analysis, supervision, methodology, writing-original draft, project administration, writing-review and editing. **R. Caldwell:** Data curation, writing-original draft, writing-review and editing. **C. Guo:** Data curation, writing-original draft, writing-review and editing. **B.C. Goh:** Data curation, writing-original draft, writing-review and editing. **V. Heong:** Data curation, writing-original draft, writing-review and editing. **N.R.Md. Haris:** Data curation, writing-original draft, writing-review and editing. **S. Bashir:** Data curation, writing-original draft, writing-review and editing. **Y. Drew:** Data curation, writing-original draft, writing-review and editing. **D.S. Hong:** Data curation, writing-original draft, writing-review and editing. **F. Meric-Bernstam:** Data curation, writing-original draft, writing-review and editing. **G. Wilkinson:** Conceptualization, data curation, methodology, writing-original draft, project administration, writing-review and editing. **J. Hreiki:** Conceptualization, formal analysis, methodology, writing-original draft, project administration, writing-review and editing. **A.M. Wengner:** Conceptualization, data curation, formal analysis, methodology, writing-original draft, project administration, writing-review and editing. **F. Bladt:** Conceptualization, data curation, formal analysis, methodology, writing-original draft, writing-review and editing. **A. Schlicker:** Formal analysis, methodology, writing-original draft, project administration, writing-review and editing. **M. Ludwig:** Conceptualization, formal analysis, methodology, writing-original draft, project administration, writing-review and editing. **Y. Zhou:** Conceptualization, formal analysis, methodology, writing-original draft, project administration, writing-review and editing. **L. Liu:** Conceptualization, formal analysis, methodology, writing-original draft, project administration, writing-review and editing. **S. Bordia:** Conceptualization, formal analysis, methodology, writing-original draft, writing-review and editing. **R. Plummer:** Conceptualization, formal analysis, methodology, writing-original draft, writing-review and editing. **E. Lagkadinou:** Conceptualization, formal analysis, supervision, methodology, writing-original draft, project administration, writing-review and editing. **J.S. de Bono:** Conceptualization, data curation, formal analysis, supervision, methodology, writing-original draft, project administration, writing-review and editing.

Acknowledgments

This study was supported by research funding from Bayer AG. This work at The University of Texas MD Anderson Cancer Center was supported in part by the Cancer Prevention and Research Institute of Texas (RP1100584, to F. Meric-Bernstam), the Sheikh Khalifa Bin Zayed Al Nahyan Institute for Personalized Cancer Therapy (1U01 CA180964, to T.A. Yap, F. Meric-Bernstam), the Center for Clinical and Translational Sciences grant (UL1 TR000371, to F. Meric-Bernstam), and the MD Anderson Cancer Center support grant (P30 CA016672, to T.A. Yap, D.S. Hong, F. Meric-Bernstam). Participating UK sites received support from the Experimental Cancer Medicine Centre, jointly funded by Cancer Research UK, the National Institute for Health Research in England, and the Departments of Health for Scotland, Wales, and Northern Ireland (to A. Terbuch, R. Caldwell, C. Guo, N.R. Md. Haris, S. Bashir, Y. Drew, R. Plummer, J.S. de Bono). This work was supported by funding from the Singapore Ministry of Health's National Medical Research Council under its Centre Grant scheme to National University Cancer Institute

and Clinician Scientist Award (NMRC/CSA-INV/0016/2017, to D.S.P. Tan). The authors wish to thank the patients and their families, coinvestigators, and referring physicians who participated in this study. DDR genomic variant functional annotation was undertaken prospectively by the Precision Oncology Decision Support Group at the Khalifa Institute for Personalized Cancer Therapy at The University of Texas MD Anderson Cancer Center. Laura Valenzo, PhD, of Complete HealthVizion, McCann Health Medical Communications, provided medical writing support for this manuscript, based on detailed discussion and feedback from all the authors; this assistance was funded by Bayer AG.

Received June 19, 2020; revised July 31, 2020; accepted August 21, 2020; published first September 28, 2020.

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