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A phase 1b study evaluating the safety and preliminary efficacy of berzosertib in combination with gemcitabine in patients with advanced non-small cell lung cancer

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ABSTRACT

Objectives: Berzosertib (formerly M6620, VX-970) is an intravenous, highly potent and selective, first-in-class ataxia telangiectasia and Rad3-related (ATR) protein kinase inhibitor. We assessed the safety, tolerability, preliminary efficacy, and pharmacokinetics (PK) of berzosertib plus gemcitabine in an expansion cohort of patients with advanced non-small cell lung cancer (NSCLC). The association of efficacy with *TP53* status and other tumor markers was also explored.

Materials and methods: Adult patients with advanced histologically confirmed NSCLC received berzosertib 210 mg/m^2 (days 2 and 9) and gemcitabine 1000 mg/m^2 (days 1 and 8) at the recommended phase 2 dose established in the dose escalation part of the study.

Results: Thirty-eight patients received at least one dose of study treatment. The most common treatment-emergent adverse events were fatigue (55.3%), anemia (52.6%), and nausea (39.5%). Gemcitabine had no apparent effect on the PK of berzosertib. The objective response rate (ORR) was 10.5% (4/38, 90% confidence interval [CI]: 3.7–22.5%). In the exploratory analysis, the ORR was 30.0% (3/10, 90% CI: 9.0–61.0%) in patients with high loss of heterozygosity (LOH) and 11.0% (1/9, 90% CI: 1.0–43.0%) in patients with low LOH. The ORR was 33.0% (2/6, 90% CI: 6.0–73.0%) in patients with high tumor mutational burden (TMB), 12.5% (2/16, 90% CI: 2.0–34.0%) in patients with intermediate TMB, and 0% (0/3, 90% CI: 0.0–53.6%) in patients with low TMB.

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Conclusions: Berzosertib plus gemcitabine was well tolerated in patients with advanced, pre-treated NSCLC. Based on the observed clinical efficacy, future clinical trials should involve genomically selected patients.

1. Introduction

For patients with advanced non-small cell lung cancer (NSCLC) and no targetable mutations, cytotoxic chemotherapies, including DNA-damaging or anti-mitotic agents, achieve response rates of 7–21%, as per Response Evaluation Criteria in Solid Tumors (RECIST), when used as single agents in the second- and/or third-line treatment setting [1–7].

Ataxia-telangiectasia-mutated (ATM) and Rad3-related protein kinases (ATR) play critical roles in the DNA-damage response (DDR) by regulating the cell cycle checkpoint control and repairing damaged DNA by homologous recombination [8]. In response to DNA replication stress, induced or exacerbated by chemotherapies such as gemcitabine, ATR is recruited to regions of exposed single-stranded DNA to mediate replication fork stabilization, whereas ATM responds to DNA double-strand breaks [9].

Berzosertib (formerly M6620, VX-970) is an intravenous (IV), highly potent, and selective first-in-class inhibitor of ATR [10]. In preclinical studies, berzosertib sensitizes lung cancer cells to DNA-damage-inducing chemotherapeutics such as gemcitabine [10]. Previous clinical studies have shown that berzosertib in combination with chemotherapy is well tolerated with preliminary efficacy signals in several solid tumors [11,12]. Furthermore, a recent proof-of-concept phase 2 study evaluating the berzosertib–topotecan combination reported an objective response rate of 36% (9/25), with a median duration of response of 6.4 months, in patients with SCLC, including those with platinum-resistant disease [13].

Berzosertib efficacy can be enriched in the presence of specific tumor genetic alterations. Tumor protein p53 (*TP53*) mutational status has been shown preclinically to correlate with response to DNA-damaging agents combined with ATR inhibition [14]. This is explained by the dependence of tumor cells on a functional *TP53* to maintain genomic stability when ATR is inhibited [15], as well as the importance of the ATR-CHK1 axis for G2/M checkpoint control in response to DNA damage when *TP53* is mutated, thus harnessing the synthetic lethal relationship between ATR and *TP53* in *TP53*-mutant tumors. Since mutations of the *TP53* gene are present in approximately 50% of NSCLC [16], ATR inhibition represents a potential therapeutic combination strategy for DNA-damaging chemotherapy in pretreated NSCLC. In addition, recent studies have suggested that molecular alterations in other genes, such as *ATM,* switch/sucrose non-fermentable related, matrix associated, actin dependent regulator of chromatin, subfamily A, member 4 (*SMARCA4*) and AT-rich interaction domain (*ARID1A*), could be potential predictive biomarkers of ATR inhibition by exploiting mechanisms of synthetic lethality related to the DDR or to replication fork stability [17–19]. However, when leveraging the synthetic lethal relationship between ATR and ATM, it may be important to consider the emerging role of ATM in promoting tumor cell ferroptosis [20]. *SMARCA4* is frequently mutated in NSCLC and is involved in the activation of replication stress responses, while *ARID1A* mutations increase tumor cells reliance on ATR-mediated checkpoint activity. Furthermore, *ARID1A*-mutant tumor cells may be more susceptible to oxidative stress due to low levels of antioxidant factors such as glutathione [21].

This phase 1 study was separated into six parts (A, B, B2, C1, C2, and C3). In the dose escalation part of this study with berzosertib and gemcitabine (part A), the most common treatment–emergent adverse events (TEAE) of any grade included fatigue, nausea, anemia, and increases in alanine aminotransferase (ALT), and the most common grade $\geq$ 3 TEAEs were neutropenia, increases in ALT and fatigue. These TEAEs were consistent with patient populations treated with gemcitabine [22].

The main purpose of this expansion cohort study (part C1) was to evaluate the safety, tolerability, pharmacokinetics (PK), and preliminary efficacy of berzosertib combined with gemcitabine in patients with advanced NSCLC, with or without *TP53* mutations. An exploratory analysis of potential response biomarkers was also conducted (ClinicalTrials.gov, identifier: NCT02157792).

2. Materials and methods

2.1. Study design

This trial was part of a multicenter, open-label, non-randomized, phase 1 study separated into six parts (A, B, B2, C1, C2, and C3). The initial dose escalation phase of the study (parts A and B) established the recommended phase 2 dose (RP2D) of berzosertib when combined with chemotherapeutic agents, including gemcitabine and cisplatin [22,23]. These doses were further evaluated in the expansion phase of the study in patients with NSCLC (part C1), triple-negative breast cancer (part C2), and small-cell lung cancer (part C3). The focus of this manuscript is part C1; the other parts have been or will be reported separately.

Part C1 was a single-arm expansion cohort study of berzosertib combined with gemcitabine in patients with advanced NSCLC, with or without *TP53* mutations. This part of the study was conducted across three sites in the UK and eight sites in the USA between December 2015 and March 2020. The study was conducted in accordance with the ethical principles of the International Council for Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki, as well as with applicable local regulations.

2.2. Patients

The plan was to enroll approximately 40 patients, including at least 20 patients with *TP53* mutations prospectively determined from archival tumor biopsies.

Eligible patients were adults $\geq$ 18 years of age with advanced (metastatic or locally advanced unresectable tumors and not eligible for definitive treatment), histologically confirmed NSCLC, with available archival tumor biopsies, who were intolerant to standard approved targeted therapies, and measurable disease defined by RECIST v1.1 [24]. Patients who had received more than two lines of cytotoxic chemotherapy in the advanced setting were excluded. Patients who had received treatment with gemcitabine within 6 months were also excluded. Full inclusion and exclusion criteria are shown in the Supplementary Information.

2.3. Treatments

Following screening and baseline evaluations, patients received berzosertib IV (210 mg/m^2; days 2 and 9) approximately 24 h after gemcitabine (1000 mg/m^2; days 1 and 8) in 21-day cycles, which was the RP2D established in part A of this study [22]. The timing of berzosertib relative to gemcitabine was based on the synergy demonstrated when berzosertib was administered 12–24 h after gemcitabine in preclinical models [25]. Patients received treatment until progressive disease (PD) or unacceptable toxicity.

2.4. Objectives

The primary objectives of this study were to evaluate the safety, tolerability, and the objective response rate (ORR) of berzosertib when combined with gemcitabine in patients with advanced NSCLC, with and

without *TP53* mutations. The secondary objectives were to evaluate the preliminary efficacy and PK of berzosertib combined with gemcitabine. The evaluation of potential biomarkers associated with the efficacy of berzosertib in combination with gemcitabine was an exploratory objective.

2.5. Assessments and endpoints

The safety profile was continuously monitored clinically and with standard laboratory parameters. TEAEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) v21.0 [26] and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0 [27].

To evaluate the efficacy of berzosertib in combination with gemcitabine, tumor assessments were performed every two cycles for the first 12 cycles, then every two to three cycles, and 5 (±1) weeks after completion of therapy. Tumor response assessments were classified according to RECIST v.1.1 [24]. The ORR (primary efficacy endpoint) was defined as the proportion of participants who achieved a best overall response (BOR) of partial response (PR) or complete response (CR) (summarized as objective response [OR]), where both CR and PR were confirmed by repeat assessments performed no $<$ 4 weeks after the criteria for response were first met. The ORR was calculated with the two-sided 90% confidence interval (CI) using the Clopper–Pearson method [28].

The efficacy of berzosertib in combination with gemcitabine was further explored through the assessment of progression-free survival (PFS), duration of response (DOR), overall survival (OS), and disease control.

Blood samples for PK analysis of berzosertib in plasma were collected pre-dose, mid-infusion, and 0, 0.5, 1, 2, 3, and optionally 7 h after the end of the 1-hour berzosertib infusion on cycle 1 day 2. Bioanalysis in plasma was performed using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods [29].

Archival tumor biopsies were collected to assess *TP53* status and other genetic alterations by DNA next–generation sequencing (NGS) with FoundationOne® CDx NGS assay (Foundation Medicine, Cambridge, Massachusetts, US) [30]. A *post-hoc* exploratory analysis was conducted to investigate the potential association between specific genetic tumor alterations and treatment outcomes. The loss of heterozygosity (LOH), tumor mutational burden (TMB) and microsatellite instability (MSI) results were discretized according to the criteria established by Foundation Medicine [31]. LOH levels were reported as a percentage of the affected genome and were discretized to either high LOH (LOH score $\geq$ 16) or low LOH (LOH score $<$ 16). TMB levels were classified as high, if somatic mutations per megabase (MB) were $\geq$ 20; intermediate, if somatic mutations per MB were $\geq$ 6 and $<$ 20; and low, if somatic mutations per MB were $<$ 6.

2.6. Statistical analysis

Based on historical response rates of 10% for single-agent gemcitabine in second-line NSCLC [5], and an enrollment of 30 patients, six responders would result in an exact one-sided 90% CI for ORR of 9.1–35.7%. The probability to observe at least six responders was calculated under the assumption of different response rates. In case of a true response rate of 30%, the likelihood of at least six responders was 84%.

The modified full analysis set included all patients who had a baseline tumor assessment with a measurable target lesion and at least one dose of the study drug. The safety analysis set included all patients who received at least one dose of study drug. The PK analysis set included all patients who received at least one dose of study drug and who provided at least one measurable post-dose concentration.

Summary statistics were provided for berzosertib concentrations by group and time and for berzosertib PK parameters. PK parameters were calculated using standard non-compartmental methods and the actual administered dose. Computation of PK parameters was performed using Phoenix® WinNonlin® Version 8.0 (Certara, L.P., Princeton, New Jersey, USA).

3. Results

3.1. Patient demographics and disposition

Baseline and disease history characteristics of all 38 patients enrolled are presented in Table 1. For those patients whose baseline genotype was determined, *TP53* mutations were found in 60.5% of tumors. All patients except for one (37, 97.4%) received at least one dose of berzosertib and 38 (100.0%) patients received at least one dose of gemcitabine.

3.2. Safety

All 38 patients experienced TEAEs, 36 (94.7%) of whom experienced berzosertib or gemcitabine-related TEAEs (Table 2). The most common TEAEs (of any grade) were fatigue (55.3%), anemia (52.6%), and nausea (39.5%). The most common berzosertib-related TEAEs were fatigue (44.7%), anemia (39.5%), and thrombocytopenia (28.9%). Furthermore, 22 (57.9%) patients experienced berzosertib-related grade $\geq$ 3 TEAEs and 14 (36.8%) patients experienced berzosertib-related serious TEAEs.

Five patients experienced berzosertib-related TEAEs (neutropenia, thrombocytopenia, fatigue, aspartate aminotransferase, and ALT increases) leading to a dose reduction in berzosertib. Eleven (28.9%) patients discontinued treatment with berzosertib, including seven (18.4%) patients who discontinued primarily due to TEAEs; three (7.9%) of whom due to berzosertib-related TEAEs (anemia, thrombocytopenia,

Table 1
Patient demographics and baseline characteristics.

Characteristic	Total N = 38
Sex, n (%)	
Male	20 (52.6)
Female	18 (47.4)
Race, n (%)	
White	34 (89.5)
Asian	1 (2.6)
Other	1 (2.6)
Unknown	2 (5.3)
Median (range) age, years	62.5 (36–76)
Baseline ECOG PS,[a] n (%)	
0	11 (28.9)
1	27 (71.1)
Prior anticancer therapy, n (%)	
Chemotherapy[b]	38 (100.0)
Investigational therapy	8 (21.1)
Immunotherapy	6 (15.8)
Other	5 (13.2)
Number of previous anticancer chemotherapy regimens, n (%)	
Neoadjuvant	3 (7.9)
Adjuvant	7 (18.4)
1st line, metastatic disease	36 (94.7)
2nd line, metastatic disease	22 (57.9)
>2nd line, metastatic disease	16 (42.1)
TP53,[c] n (%)	
Wild-type	6 (15.8)
Mutant	23 (60.5)
Unknown	9 (23.7)

[a]Data reported for modified Full Analysis Set.
[b]Seven patients received prior treatment with gemcitabine.
[c]Only patients with biomarker status determined by FoundationOne® CDx next-generation sequencing were reported.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; *TP53*, tumor protein p53.

Table 2
Overview of TEAEs for berzosertib + gemcitabine occurring in > 20% of patients by preferred term (N = 38; safety analysis set).

Patients, n (%)	Berzosertib + gemcitabine N = 38	
	Any grade	Grade ≥ 3
All TEAEs	38 (100.0)	33 (86.8)
Berzosertib-related TEAE	34 (89.5)	22 (57.9)
Berzosertib- or gemcitabine-related TEAE	36 (94.7)	24 (63.2)
TEAEs occurring in ≥ 20% of patients	Any grade	Grade 3–4
Fatigue	21 (55.3)	9 (23.7)
Anemia	20 (52.6)	8 (21.1)
Nausea	15 (39.5)	0
Dyspnea	14 (36.8)	5 (13.2)
Pyrexia	13 (34.2)	1 (2.6)
Thrombocytopenia	13 (34.2)	7 (18.4)
Vomiting	12 (31.6)	2 (5.3)
AST increased	11 (28.9)	2 (5.3)
Decreased appetite	11 (28.9)	1 (2.6)
Neutropenia	11 (28.9)	5 (13.2)
ALT increased	10 (26.3)	2 (5.3)
Lower RTI	9 (23.7)	5 (13.2)
Headache	8 (21.1)	0
WBC count decreased	8 (21.1)	1 (2.6)
Serious TEAEs	24 (63.2)	22 (57.9)
Berzosertib-related serious TEAE	14 (36.8)	1 (2.6)
Berzosertib- or gemcitabine-related serious TEAE	14 (36.8)	10 (26.3)
Serious TEAE leading to dose interruption	9 (23.7)	NR
Serious TEAE leading to dose interruption in berzosertib	8 (21.1)	NR
Serious TEAE leading to dose interruption in gemcitabine	8 (21.1)	NR
TEAE leading to dose reduction in ≥ 1 study drug	8 (21.1)	NR
TEAE leading to dose reduction in berzosertib	6 (15.8)	NR
TEAE leading to dose reduction in gemcitabine	7 (18.4)	NR
TEAE leading to permanent discontinuation of ≥ 1 study drug	8 (21.1)	NR
Berzosertib-related TEAE leading to permanent discontinuation of berzosertib	3 (7.9)	NR
Gemcitabine-related TEAE leading to permanent discontinuation of gemcitabine	4 (10.5)	NR
TEAE leading to death		4 (10.5)
Berzosertib-related TEAE leading to death		1 (2.6)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NR, not reported; RTI, respiratory tract infection; TEAE, treatment-emergent adverse event; WBC, white blood cell.

and fatigue). Four (10.5%) patients experienced a TEAE leading to death. One of the four deaths was related to study treatment (hemoptysis, hypovolemic shock, and cardiac arrest); the death occurred after the patient had experienced a grade 3 lower respiratory tract infection and shortness of breath (both unrelated to treatment) for > 1 month.

3.3. Efficacy

The median treatment duration for berzosertib in combination with gemcitabine was 14.0 weeks (2.0–63.0 weeks). There were four confirmed partial responders (10.5%), two of which had a particularly notable response (Table 3, Fig. 1).

Amongst the responders, it is worth noting that a 67-year-old female with epidermal growth factor receptor (*EGFR*) wild-type NSCLC (adenocarcinoma), with evidence of lymph node and lung metastases, achieved a confirmed PR lasting 13.2 months (57.6% maximum tumor shrinkage). This patient was heavily pretreated with several different anticancer regimens (carboplatin + pemetrexed + bevacizumab, followed by pemetrexed + bevacizumab as maintenance, nivolumab, and erlotinib).

Table 3
Best overall response (modified full analysis set; N = 38).

Efficacy outcome	Patients, n (%)
Best overall response	
CR	0
PR	4 (10.5)
SD	22 (57.9)
PD	7 (18.4)
Not evaluable	5 (13.2)
ORR, n (%), [90% CI]	4 (10.5) [3.7–22.5]
DCR,[a] n (%), [90% CI]	26 (68.4) [53.9–80.7]
Median PFS (months), [90% CI]	4.0 [3.2–5.0]
Median OS (months), [90% CI]	7.4 [5.4–8.5]
Median DOR (months), [90% CI]	6.0 [3.6–nd]

[a]Disease control was defined as a BOR of CR, PR, or SD and the DCR was calculated with a two-sided 90% CI using the Clopper–Pearson method.
Abbreviations: BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; nd, not defined; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

A 75-year-old male patient with anaplastic large-cell lymphoma kinase wildtype, *EGFR* wild-type, programmed death-ligand 1 negative NSCLC (adenocarcinoma), with evidence of lymph node metastases, with progression through two aggressive regimens (carboplatin + pemetrexed, docetaxel + nintedanib followed by nintedanib maintenance), achieved a confirmed, durable PR lasting 6.0 months.

3.4. Exploratory biomarker analyses

Archival tumor biopsies from the 38 patients were analyzed by DNA NGS, of which nine samples did not pass the laboratory quality check process. Overall, 29 samples were included in the data analysis. The subgroup analysis did not demonstrate a clear association between clinical outcome (ORR and PFS) and any alterations in 324 genes explored, including *TP53*, and other potential predictive biomarkers of sensitivity to ATR inhibition including *ATM*, *ARID1A* (Supplementary Table 1) and *SMARCA4* (Table 4).

Regarding genomic signatures, LOH was measurable in 19 patients. The ORR was 30.0% (3/10, 90% CI: 9.0–61.0%) in patients with high LOH, and 11.0% (1/9, 90% CI: 1.0–43.0%) in patients with low LOH. TMB was measurable in 25 patients. The ORR was 33.0% (2/6, 90% CI: 6.0–73.0%) in patients with high TMB, 12.5% (2/16, 90% CI: 2.0–34.0%) in patients with intermediate TMB, and 0% (0/3, 90% CI: 0.0–53.6%) in patients with low TMB.

3.5. Pharmacokinetics

The berzosertib 210 mg/m^2 (IV) dose administered in this study was within the dose range previously shown to exhibit dose-dependent berzosertib PK as monotherapy, or in combination with either carboplatin or gemcitabine [11,22]. The observed berzosertib concentration data in this expansion cohort were consistent with those reported previously at the same dose level [22]. Gemcitabine demonstrated no apparent effect on berzosertib pharmacokinetics (Fig. 2).

The geometric mean (percentage coefficient of variation [%CV]) maximum observed concentration (C_{max}) of berzosertib was 882 ng/mL (55.2%), which was similar to the previously reported C_{max} of 899 ng/mL in part A of this study [22]. A population PK model was developed based on pooled data from two phase 1 studies, including this expansion cohort [32]. The model confirmed that gemcitabine had no apparent effect on berzosertib PK, and that berzosertib PK in patients with NSCLC was comparable to patients with other advanced solid tumors.

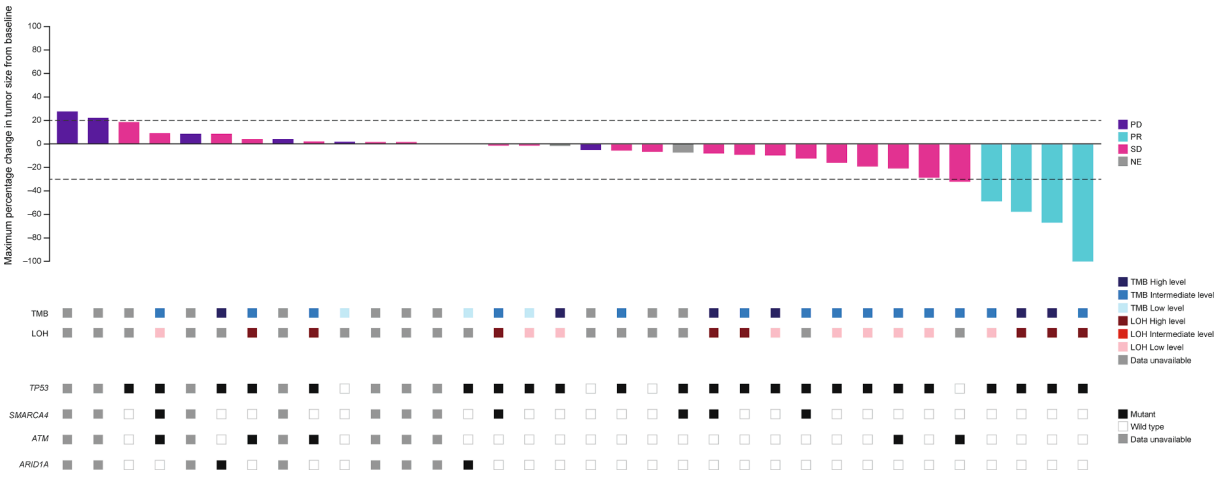

Fig. 1. Best percentage change in tumor size from baseline (modified full analysis set) with genetic profiles. Only patients with a baseline scan, at least one post-baseline assessment, and at least one response assessment are included in Fig. 1 (n = 34). Only patients with biomarker status determined by FoundationOne® CDx next-generation sequencing were reported. The dashed line at 20% represents PD whereas the dashed line at –30% represents PR. *ARID1A*, AT-rich interaction domain 1A; *ATM*, ataxia telangiectasia mutated; LOH, loss of heterozygosity; NE, not evaluable; PD, progressive disease; PR, partial response; *SMARCA4*, switch/sucrose non-fermentable related, matrix associated, actin dependent regulator of chromatin, subfamily A, member 4; SD, stable disease; TMB, tumor mutational burden; *TP53*, tumor protein p53.

Table 4
Objective response rate for selected biomarker subgroups (modified full analysis set).

Subgroups	Mutation status[a]	Responders	ORR [90% CI]
Overall	Overall	4/38	10.5 [3.7–22.5]
TP53	Wild-type	0/6	0.0 [0.0–39.3]
	Mutant	4/23	17.4 [6.2–35.5]
ARID1A	Wild-type	4/27	14.8 [5.2–30.8]
	Mutant	0/2	0.0 [0.0–77.6]
ATM	Wild-type	4/23	17.4 [6.2–35.5]
	Mutant	0/6	0.0 [0.0–39.3]
SMARCA4	Wild-type	4/24	16.7 [5.9–34.2]
	Mutant	0/5	0.0 [0.0–45.1]
LOH	High	3/10	30.0 [8.7–60.7]
	Low	1/9	11.1 [0.6–42.9]
TMB	High	2/6	33.3 [6.3–72.9]
	Intermediate	2/16	12.5 [2.3–34.4]
	Low	0/3	0 [0.0–63.2]

[a]Only patients with high impact or predicted high impact mutations reported. Only patients with biomarker status determined by FoundationOne® CDx next-generation sequencing were reported. The ORR was calculated with the two-sided 90% CI using the Clopper–Pearson method.
Abbreviations: *ATM*, ataxia telangiectasia mutated; *ARID1A*, AT-rich interaction domain 1A; CI, confidence interval; LOH, loss of heterozygosity; ORR, objective response rate; TMB, tumor mutational burden; *TP53*, tumor protein p53; *SMARCA4,* switch/sucrose non-fermentable related, matrix associated, actin dependent regulator of chromatin, subfamily A, member 4

4. Discussion

In this phase 1b expansion cohort study, the combination of the ATR inhibitor berzosertib with gemcitabine, according to the dosing regimen previously determined in the dose escalation portion of the trial (berzosertib 210 mg/m^2 [days 2 and 9] and gemcitabine 1000 mg/m^2 [days 1 and 8] every 3 weeks) [22], was well tolerated in patients with pretreated advanced NSCLC. The safety profile was consistent with that of the individual agents [11,23]. However, the observed clinical efficacy (ORR of 10.5% and median treatment duration of 14.0 weeks) suggests limited benefit of combining an ATR inhibitor with gemcitabine in this unselected population of patients with advanced NSCLC, with and without *TP53* mutations, when compared with historical controls of gemcitabine monotherapy [5]. The ORR was only marginally higher in the subgroup of patients with *TP53* mutations, because there was no responder among the few cases who did not have *TP53* alterations (the study was designed to enrich for tumors with *TP53* mutations). This clinical finding suggests that *TP53* mutations alone are insufficient to enhance the efficacy of the berzosertib–gemcitabine combination in patients with advanced NSCLC, despite the fact that preclinical experiments have highlighted *TP53* mutations as an efficacy surrogate for treatment with ATR inhibitors [14].

The exploratory biomarker subgroup analysis also demonstrated no clear association between treatment outcome (ORR and PFS) and gene alterations, including *ATM, ARID1A* and *SMARCA4*, which have previously been associated with sensitivity to ATR inhibition [17–19]. There was also no association observed between treatment response and alterations in other cell cycle genes such as *CCNE1*, *MYC*, or *RB*, whose dysregulation is associated with DNA replication stress [33,34].

However, since only single digit cases carrying genetic alterations in each of these genes were identified, the relationship between treatment response and these individual genomic alterations could not be determined. Additionally, there were limitations to our analyses, including the lack of genomic data that would have enabled the evaluation of biomarker zygosity status of tumor suppressor genes on treatment outcomes. Another limitation was the lack of confirmation of the observed *ATM, SMARCA4, ARID1A* or other tumor suppressor loss at the protein level. Although ATM immunohistochemistry was planned, the available tumor samples were largely exhausted after DNA NGS. As the clinical development of berzosertib continues, further investigations are required to identify genomic alterations that confer susceptibility to ATR inhibition. Identifying such alterations, with confirmation at the protein level, may ultimately help define patient populations most likely to benefit from the addition of berzosertib to DNA damage-inducing chemotherapies or other anticancer therapies.

We observed a trend towards increased response rate in patients with high TMB (33.0%) and LOH scores (30.0%), versus those patients with low TMB and LOH scores, respectively. TMB and LOH are markers of genetic instability and homologous recombination deficiency [35,36]. High TMB is also indicative of DNA DSB repair deficiency [37]. In fact, both TMB and LOH are emerging as predictive biomarkers to poly (ADP-ribose) polymerase and immune checkpoint inhibitors [36,38–40], which could well synergize with increased DNA damage resulting from the combination of berzosertib and gemcitabine. However, the associations were not statistically significant, likely due to the small sample size. Nevertheless, given the biologic rationale for an association

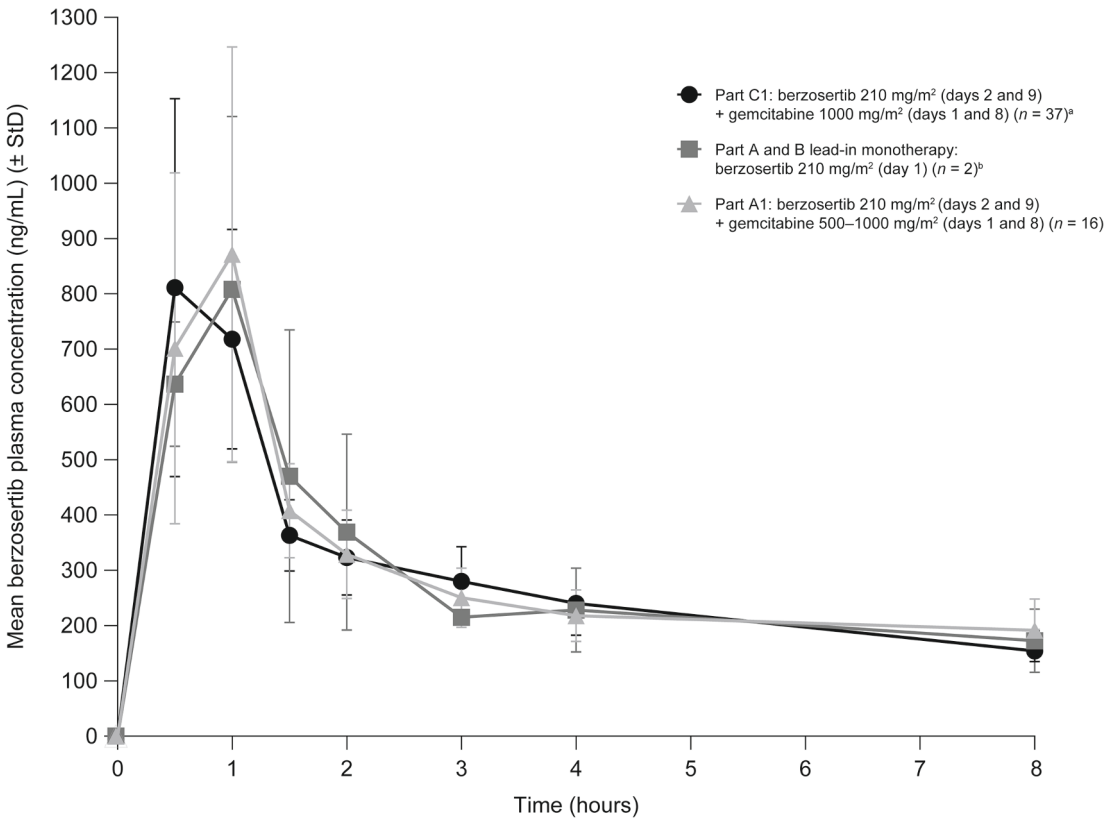

Fig. 2. Plasma berzosertib concentration–time profile after the first intravenous infusion of berzosertib monotherapy and of berzosertib in combination with gemcitabine. [a]$n = 3$ for the 8-hour timepoint. [b]$n = 1$ for the 3-hour timepoint. StD, standard deviation.

between TMB and LOH and a higher sensitivity to DDR inhibitors, further investigations in this direction are warranted.

5. Conclusions

The combination of berzosertib and gemcitabine in patients with advanced, pre-treated NSCLC was well tolerated, but given the observed clinical efficacy, future clinical trials may best be undertaken in a genomically selected patient population. In other malignancies, such as platinum-resistant ovarian cancer, the combination of berzosertib and gemcitabine has shown an encouraging efficacy signal, serving as a reminder of the molecular heterogeneity and notable clinical differences between disease entities [12].

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CRediT authorship contribution statement

Ruth Plummer: Conceptualization, Formal analysis, Investigation, Resources, Writing – review & editing, Supervision. **Emma Dean:** Investigation, Resources, Data curation, Writing – review & editing, Supervision. **Hendrik-Tobias Arkenau:** Investigation, Resources, Writing – review & editing. **Charles Redfern:** Investigation, Resources, Writing – review & editing. **Alexander I. Spira:** Investigation, Resources, Data curation, Writing – review & editing, Project administration, Funding acquisition. **Jason M. Melear:** Investigation, Resources, Writing – review & editing. **Ki Y. Chung:** Investigation, Resources, Data curation, Writing – review & editing. **Jordi Ferrer-Playan:** Writing – review & editing, Supervision, Project administration. **Thomas Goddemeier:** Formal analysis, Writing – review & editing, Visualization. **Giuseppe Locatelli:** Conceptualization, Formal analysis, Investigation, Resources, Writing – review & editing, Visualization, Supervision. **Jennifer Dong:** Formal analysis, Writing – review & editing. **Patricia Fleuranceau-Morel:** Formal analysis, Writing – review & editing. **Ivan Diaz-Padilla:** Writing – review & editing, Supervision. **Geoffrey I. Shapiro:** Conceptualization, Investigation, Resources, Writing – review & editing, Supervision.

Declaration of competing interest

Ruth Plummer: received honoraria for serving on advisory boards on behalf of Vertex and Merck Healthcare KGaA, Darmstadt, Germany relating to this compound; reimbursement for her institution for clinical trials costs; consultancy services to Pierre Faber, Bayer, Octimet, Clovis Oncology, Novartis, Karus Therapeutics, Biosceptre, BMS, Cybrexa, Ellipses, CV6 Therapeutics, Astex Therapeutics, and Sanofi Aventis; research funding from AstraZeneca; and medical writing support for developing this manuscript from Merck Healthcare KGaA, Darmstadt Germany.

Emma Dean: is an employee and stakeholder of AstraZeneca; and received medical writing support for developing this manuscript from Merck Healthcare KGaA, Darmstadt Germany.

Hendrik-Tobias Arkenau: reports honoraria from Bicycle Therapeutics, Biontech, Bayer, Beigene, Servier, Roche and Guardant Health; served as an advisor/consultant for Bicycle Therapeutics, Biontech, Bayer, Beigene, Servier, Roche and Guardant Health; received support

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Alexander I Spira: reports grants or contracts from BMS, Mirati, Amgen, Novartis, Merck KGaA, Darmstadt, Germany, AstraZeneca, Sanofi, Abbvie, Cytomx, Macrogenics, Pfizer; and consulting fees from Mirati, Amgen, Sanofi, AstraZeneca, Merck KGaA, Darmstadt, Germany, BMS; and received medical writing support for developing this manuscript from Merck Healthcare KGaA, Darmstadt Germany.

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Appendix A. Supplementary data

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