A Phase Ib Study of the DNA-PK Inhibitor Peposertib Combined with Neoadjuvant Chemoradiation in Patients with Locally Advanced Rectal Cancer

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ABSTRACT

Purpose: Peposertib—an orally administered DNA-dependent protein kinase inhibitor—has shown potent radiosensitization in preclinical models. This dose-escalation study (NCT03770689) aimed to define the maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of peposertib plus capecitabine-based chemoradiotherapy (CRT) and assessed its safety and efficacy in locally advanced rectal cancer.

Patients and Methods: Patients were treated for 5 to 5.5 weeks with 50- to 250-mg peposertib once daily, capecitabine 825 mg/m^2 twice daily, and radiotherapy (RT), 5 days per week. Following clinical restaging (8 weeks after CRT completion), patients with clinical complete response (cCR) could opt for surveillance. Total mesorectal excision was recommended upon incomplete response (IR).

Results: Nineteen patients were treated with peposertib at doses of 50 mg ($n = 1$), 100 mg, 150 mg, and 250 mg ($n = 6$ each). Dose-limiting toxicities occurred in one out of five (100 mg), one out of six (150 mg), and three out of six (250 mg) evaluable patients. Peposertib ≤150 mg once daily was tolerable in combination with CRT. After 8 weeks of treatment with peposertib and CRT, the cCR was 15.8% ($n = 3$). Among the three patients with cCR, two underwent surgery and had residual tumors. Among the 16 patients with IR, seven underwent surgery and had residual tumors; five of the remaining nine patients opted for consolidative chemotherapy. The combined cCR/pathologic complete response (pCR) rate was 5.3% ($n = 1$, 100 mg cohort).

Conclusions: Peposertib did not improve complete response rates at tolerable dose levels. The study was closed without declaring the MTD/RP2D.

Introduction

DNA damage response (DDR) pathways—the surveillance and signaling network maintaining genomic integrity of cells—can play a critical role in resistance to antitumor agents by repairing the DNA damage induced by chemotherapy and/or radiotherapy (RT) and allowing cancerous cells to survive treatment (1). The DNA-dependent protein kinase (DNA-PK) is part of a key DDR pathway responsible for repairing DNA double-strand breaks through nonhomologous end joining (NHEJ; ref. 2). Peposertib (formerly M3814) is a potent and selective, orally administered, small-molecule DNA-PK inhibitor that blocks the NHEJ pathway through its high specificity for DNA-PK. Peposertib has demonstrated preclinical activity as a single agent and in combination with RT in a human colon cancer xenograft model and several colon cancer cell lines (3). A first-in-human study showed no significant toxicity for peposertib monotherapy when administered to patients with advanced solid tumors, and 400 mg twice daily was recommended for further evaluation (4).

Here, we report the results of a phase Ib study (NCT03770689) that evaluated the combination of peposertib, capecitabine, and RT in the neoadjuvant setting in patients with locally advanced rectal cancer (LARC).

Patients and Methods

Study design and patients

This open-label, single-arm, phase Ib study evaluated peposertib dose escalation in combination with chemoradiotherapy (CRT) in patients with LARC at nine study sites in the United States and Spain. The study design is illustrated in Supplementary Fig. S1. Eligible patients were ≥18 years old, had pathologically confirmed, resectable, adenocarcinoma of the middle- or distal-third of the rectum (radiologic stages II and III), and an Eastern Cooperative Oncology Group (ECOG) performance status ≤1 (full inclusion and exclusion criteria listed under Methods in Supplementary Material). All patients provided written informed consent for treatment with the Institutional Review Board (IRB)-approved treatment protocol, in accordance with the Declaration of Helsinki. The representativeness of the study population is described in Supplementary Table S1.

Procedures

Patients were treated with peposertib once daily, capecitabine twice daily, and RT, 5 days a week, for 5 to 5.5 weeks. Peposertib was administered orally as a tablet, at doses ranging from 50 to 250 mg 1 hour after a meal (morning) and 1.5 to 2 hours prior to RT.

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Translational Relevance

There is an increasing interest in using inhibitors of the DNA damage response (DDR) as radiosensitizers to enhance the effectiveness of chemoradiotherapy. This phase Ib trial assessed peposertib, a small-molecule inhibitor of DNA-dependent protein kinase (DNA-PK), in combination with neoadjuvant capecitabine-based chemoradiotherapy in patients with locally advanced rectal cancer (LARC). The predicted exposure for efficacy at a safe and tolerable dose level could not be achieved. These results indicate that alternative approaches are needed for integrating peposertib with neoadjuvant therapy in LARC, and add to our understanding of how to optimize combinations targeting the DDR to improve treatment outcomes in cancer.

Capecitabine 825 mg/m^2 was administered orally as a tablet, within 30 minutes after a meal (morning and evening). Total RT dose was 50 to 50.4 Gy to the gross tumor with an elective 45.0-Gy dose to at-risk lymph node regions in 25 or 28 fractions (1.8–2.0 Gy, 5 days a week). Patients achieving a clinical complete response (cCR) were offered watch and wait, whereas those without cCR were recommended to undergo surgery by 9.5±2 weeks after completion of CRT, unless the patient declined surgery or if it was contraindicated. Peposertib dose increments were determined using a Bayesian two-parameter logistic regression model with overdose control.

Study endpoints

The primary endpoint was the maximum tolerated dose (MTD), based on the occurrence of dose-limiting toxicities (DLT) from the first study intervention to the end of CRT, with a final assessment 4 weeks after surgery. The recommended phase II dose (RP2D) was also to be determined by the Safety Monitoring Committee (SMC).

Secondary safety endpoints included the occurrence of treatment-emergent adverse events (TEAE) and treatment-related adverse events according to NCI-CTCAE version 5.0, up to at least 1 year from the first study intervention to the final assessment. Secondary efficacy endpoints included cCR defined at 8 weeks after CRT completion according to a modified Memorial Sloan Kettering regression schema (absence of residual tumor in MRI and endoscopy, no irregularity on digital rectal examination; ref. 5). Additionally, pathologic complete response (pCR) was assessed, defined as no residual cancer on pathologic examination of the resected primary tumor and lymph node specimens [ypT$_0$N$_0$], along with the composite endpoint of cCR/pCR, considering patients with cCR who did not undergo surgery (surveillance approach) and those who underwent surgery with pCR.

Other efficacy endpoints were disease-free survival (DFS), local recurrence, and distant metastasis. Neoadjuvant rectal score (NAR) was also reported in patients who underwent surgery. Pharmacokinetic endpoints were estimated during the first 2 weeks of CRT.

Exploratory endpoints included assessment of the ratio of phosphorylated to total DNA-PK [pDNA-PK/tDNA-PK, anti-human DNA-PK, clone 3H6 (Cell Signaling Technology); t-DNA-PK, anti-human DNA-PK, clone 1B9 (AbNova); p-DNA-PK, anti-human p (S2056) DNA-PK, clone MKV-2-99-12, Epitomics (special production for the health care business of Merck KGaA)] to identify the biologically active dose of peposertib, and presence of genetic alterations in tumor tissue to identify biomarkers that might predict the response to peposertib in combination with capecitabine and RT.

Statistical analyses

The dose-escalation analysis set included all patients who had received at least 80% of the planned dose of peposertib and RT, along with 50% of capecitabine, and had completed the DLT period (5 weeks after CRT initiation), and any patient who had experienced a DLT during the DLT period, regardless of treatment dose received (see Supplementary Material for details on all analyses sets).

DLT were confirmed by the SMC during the DLT period. TEAE were summarized according to MedDRA version 24.0 (until 30 days after the last study treatment), with severity graded according to NCI-CTCAE v5.0. Late toxicities, defined as AE that occurred after the on-treatment period, the first occurrence of an AE, a recurring AE with a gap between the first event and recurrence, or a recurring AE with worsened grade, were reported for up to 1 year, or longer for those patients with longer follow-up periods.

Time-to-event analyses were performed using Kaplan–Meier estimates of the survival function [median survival times, rates, and corresponding two-sided 95% confidence intervals (CI)]. Tumor regression was assessed using the modified Ryan scheme (6), wherein a score of 0 denotes CR and a score of 3 denotes poor or no response. The NAR score, designed as a short-term surrogate endpoint for overall survival (7), was also assessed; lower NAR scores indicate better tumor prognosis (see Supplementary Material: Methods for more details on Ryan scheme and NAR score).

Data availability

Any requests for data by qualified scientific and medical researchers for legitimate research purposes will be subject to the health care business of Merck KGaA Darmstadt, Germany's (CrossRef Funder ID: 10.13039/100009945) Data Sharing Policy. All requests should be submitted in writing to the health care business of Merck KGaA Darmstadt, Germany's data-sharing portal (https://www.emdgroup.com/en/research/our-approach-to-research-and-development/healthcare/clinical-trials/commitment-responsible-data-sharing.html). When the health care business of Merck KGaA Darmstadt, Germany, has a coresearch, codevelopment, or comarketing or copromotion agreement, or when the product has been out-licensed, the responsibility for disclosure might be dependent on the agreement between parties. Under these circumstances, the health care business of Merck KGaA Darmstadt, Germany, will endeavor to gain agreement to share data in response to requests.

Results

From March 20, 2019, to April 12, 2021, 19 patients were enrolled in the study (**Fig. 1**); baseline characteristics are summarized in **Table 1**. Notably, three patients who previously received induction chemotherapy were confirmed to have residual disease by endoscopy prior to study entry.

Exposure

Patients were treated with peposertib in dose cohorts of 50 mg ($n = 1$), 100 mg, 150 mg, and 250 mg ($n = 6$ each). The peposertib dose was increased to 250 mg after three patients had been treated with 150 mg. After the first three patients were treated in the 250-mg cohort, the cohort was expanded, and three more patients were treated with 250-mg peposertib. After six patients had been treated with peposertib 250 mg, the dose was de-escalated, and three more patients were treated with peposertib 150-mg. One patient in the 100-mg cohort was excluded from the dose-escalation analysis due to protocol nonadherence; this patient did not have a DLT prior to study discontinuation.

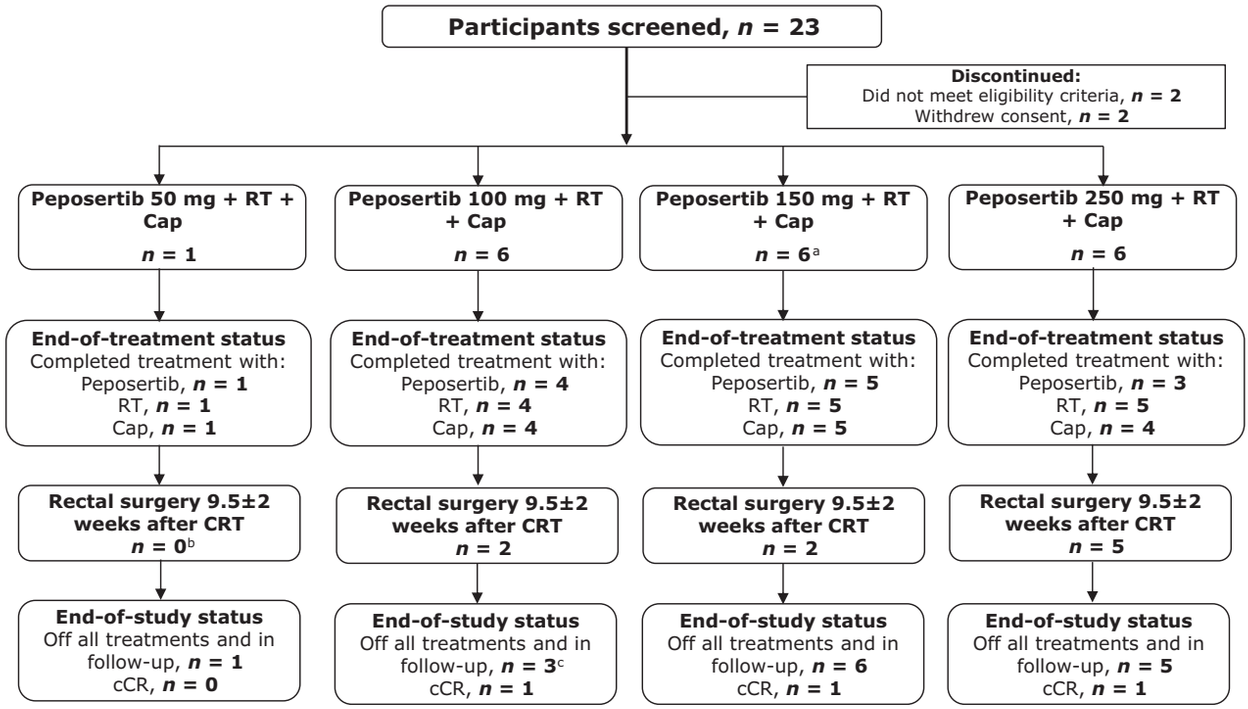

Figure 1.

Patient disposition and patient flow during the study. [a]Three patients were initially treated with 150 mg. After DLT occurred in the 250-mg cohort, the dose was de-escalated and a further three were treated with 150 mg. [b]Patient declined surgery at week 15 in favor of consolidative chemotherapy and underwent surgery outside the protocol window. [c]One patient was removed due to protocol nonadherence. Abbreviations: Cap, capecitabine; cCR, clinical complete response; CRT, chemoradiotherapy; DLT, dose-limiting toxicity; RT, radiotherapy.

Across all dose cohorts, relative peposertib dose intensity was below 80% in five patients (26.3%)—one each in the 100-mg and 150-mg cohorts, and three in the 250-mg cohort. With respect to CRT exposure, three patients (15.8%)—one each in the 100-mg, 150-mg, and 250-mg cohorts—received less than 80% of RT, and six patients (31.6%) received less than 80% capecitabine. Dose-intensity data were unavailable for the single patient in the 50-mg cohort, as the planned treatment schedule was missing.

Safety

DLT and MTD

All patients except one (100-mg cohort, mentioned above) were included for DLT evaluations. Overall, five DLT were reported: one of five patients at peposertib 100 mg (radiation skin injury and enterocolitis), one of six patients at 150 mg (diarrhea), and three of six patients at 250 mg (two enterocolitis and one proctitis). All DLT were grade 3 except for one enterocolitis event in the 250-mg cohort, which was grade 4. The grade 4 enterocolitis event was multifactorial and required hospitalization and treatment with intravenous antibiotics. In addition, cytomegalovirus infection was also diagnosed in this patient.

Surgery was well tolerated with no DLT observed in the postoperative window of 4 weeks. TEAE leading to permanent discontinuation of peposertib were reported in one patient in the 150-mg cohort (diarrhea) and in three in the 250-mg cohort (enterocolitis, $n = 2$, and proctitis, $n = 1$). MTD and RP2D were not declared, as study enrollment was prematurely discontinued.

Other TEAE

Table 2 provides an overview of TEAE; 14 (73.7%) patients experienced grade ≥3 TEAE (none in the 50-mg cohort). The most common grade ≥3 TEAE were lymphocyte count decreased (36.8%), lymphopenia (21.1%), diarrhea (15.8%), and enterocolitis (15.8%). Grade 4 TEAE included lymphocyte count decrease ($n = 1$) and lymphopenia ($n = 1$) in the 100-mg cohort; lymphopenia ($n = 1$) in the 150-mg cohort; and leukopenia and lymphocyte count decrease ($n = 1$) and enterocolitis ($n = 1$) in the 250-mg cohort. TEAE and peposertib-related AE occurring in ≥20% of patients in either treatment arm are listed in Supplementary Table S2. Across all cohorts, the most frequently reported TEAE were diarrhea ($n = 15$, 78.9%), fatigue, nausea, and proctitis ($n = 9$ each, 47.4%).

At data cutoff (March 22, 2022), all patients had completed the 1-year safety follow-up period, and six had completed a longer follow-up. Late toxicities were reported in 18 patients (94.7%), with gastrointestinal disorders ($n = 12$, 63.2%) being the most common. These included proctitis ($n = 3$, 15.8%), intestinal obstruction, nausea, rectal hemorrhage, and vomiting ($n = 2$ each, 10.5%). Anemia ($n = 3$) was the other late toxicity that occurred in more than two patients. Grade ≥3 late toxicities were reported in 11 patients at data cutoff, with no events reported in the peposertib 50-mg cohort (Supplementary Table S3). Late toxicities were seen across the peposertib dose range, with no discernible indication of a dose-dependent effect.

There were no TEAE leading to death. Three patients died during the study [disease progression ($n = 1$; 100 mg; study day 645), pulmonary

Table 1. Patient demographics and baseline characteristics (safety analysis set).

Characteristic	Peposertib (mg) + RT + capecitabine *n* (%, unless otherwise stated)				
	50 mg (*n* = 1)	100 mg (*n* = 6)	150 mg (*n* = 6)	250 mg (*n* = 6)	Overall (*n* = 19)
Sex [*n* (%)]					
Male	1 (100)	3 (50)	4 (67)	3 (50)	11 (58)
Female	0 (0)	3 (50)	2 (33)	3 (50)	8 (42)
Ethnicity [*n* (%)]					
White	1 (100)	6 (100)	6 (100)	6 (100)	19 (100)
Age					
Median, y (min, max)	60	59 (40, 78)	56 (42, 67)	61 (42, 71)	60 (40, 78)
Age by category [*n* (%)]					
<65 y	1 (100)	3 (50)	5 (83)	4 (67)	13 (68)
≥65 y	0 (0)	3 (50)	1 (17)	2 (33)	6 (32)
Weight at baseline					
Median, kg (min, max)	68.6	73.8 (52.9, 125.5)	93.0 (71.0, 110.8)	77.0 (48.8, 102.2)	77.8 (48.8, 125.5)
ECOG PS [*n* (%)]					
0	1 (100)	5 (83)	3 (50)	3 (50)	12 (63)
1	0 (0)	1 (17)	3 (50)	3 (50)	7 (37)
Disease stage at study entry [*n* (%)][a]					
Stage II	0 (0)	1 (17)	0 (0)	0 (0)	1 (5)
Stage IIA	0 (0)	0 (0)	1 (17)	1 (17)	2 (11)
Stage III	0 (0)	2 (33)	2 (33)	0 (0)	4 (21)
Stage IIIA	0(0)	1 (17)	2 (33)	0 (0)	3 (16)
Stage IIIB	1 (100)	2 (33)	1 (17)	4 (67)	8 (42)
Stage IIIC	0 (0)	0 (0)	0 (0)	1 (17)	1 (5)
Clinical T stage					
mrT1	0 (0)	1 (17)	0 (0)	0 (0)	1 (5)
mrT2	0 (0)	1 (17)	2 (33)	0 (0)	3 (16)
mrT3	0 (0)	3 (50)	4 (67)	4 (67)	11 (58)
mrT3b	1 (100)	0 (0)	0 (0)	1 (17)	2 (11)
mrT4	0 (0)	0 (0)	0 (0)	1 (17)	1 (5)
mrT4b	0 (0)	1 (17)	0 (0)	0 (0)	1 (5)
Histopathologic classification, *n* (%)					
Adenocarcinoma	1 (100)	6 (100)	6 (100)	6 (100)	19 (100)
M stage at entry, *n* (%)					
M0	0 (0)	3 (50)	5 (83)	6 (100)	14 (74)
Mx	1 (100)	3 (50)	1 (17)	0 (0)	5 (26)
MRI-EMVI score at study entry, *n* (%)					
Positive	0 (0)	0 (0)	0 (0)	1 (17)	1 (5)
Negative	0 (0)	1 (17)	1 (17)	2 (33.3)	4 (21)
Not done	1 (100)	3 (50)	5 (3)	3 (50)	12 (63)
Not evaluable	0 (0)	1 (17)	0 (0)	0 (0)	1 (5)
Missing	0 (0)	1 (17)	0 (0)	0 (0)	1 (5)
MRI-CRM score at study entry, *n* (%)					
Clear	0 (0)	1 (17)	0 (0)	1 (17)	2 (11)
Involved	0 (0)	0 (0)	1 (17)	3 (50)	4 (21)
Not done	1 (100)	3 (50)	4 (67)	2 (33.3)	10 (53)
Not evaluable	0 (0)	1 (17)	0 (0)	0 (0)	1 (5)
Missing	0 (0)	1 (17)	1 (17)	0 (0)	2 (11)

Note: Before entering the study, two patients (one each in the 100-mg and 150-mg cohorts) received induction chemotherapy with FOLFOX (fluorouracil, leucovorin, oxaliplatin) and one (100-mg cohort) with CAPOX (capecitabine and oxaliplatin). All three patients were confirmed endoscopically to have residual disease.
Abbreviations: CRM, circumferential margin; ECOG PS, Eastern Cooperative Oncology Group Performance Status; eCRF, electronic case report form; EMVI, extramural venous invasion; MRI, magnetic resonance imaging; RT, radiotherapy.
[a]Stage as entered in the eCRF; stage II and stage III rows include only cases where a more specific substage was not entered.

embolism ($n = 1$; 150 mg, study day 169), and SARS-CoV-2 infection ($n = 1$; 250 mg; study day 81)]. All three deaths were considered unrelated to the study treatment and were not classified as treatment-emergent because they occurred more than 30 days after the last study intervention.

Based on the totality of safety data, a peposertib dose of up to and including 150 mg once daily was considered tolerable in combination with RT and capecitabine.

Efficacy

Tumor responses to the combination treatment are shown in **Table 3**, and individual patient outcomes are in Supplementary Table S4.

Tumor response

The cCR rate was 15.8% ($n = 3$), with two of the three patients opting to proceed with surgical resection. During surgery, these two

Table 2. Overview of treatment-emergent adverse events (TEAE; safety analysis set).

	TEAE, *n* (%)				
Patients with any	**50 (*n* = 1)**	**100 (*n* = 6)**	**150 (*n* = 6)**	**250 (*n* = 6)**	**Overall (*n* = 19)**
TEAE	1 (100)	6 (100)	6 (100)	6 (100)	19 (100)
Peposertib-related TEAE	1 (100)	5 (83)	5 (83.3)	6 (100)	17 (90)
RT-related TEAE	1 (100)	6 (100)	6 (100)	6 (100)	19 (100)
Capecitabine-related TEAE	1 (100)	6 (100)	6 (100)	6 (100)	19 (100)
Serious TEAE	0	3 (50)	0	4 (67)	7 (37)
Peposertib-related serious TEAE	0	2 (33)	0	4 (67)	6 (32)
RT-related serious TEAE	0	2 (33)	0	3 (50)	5 (26)
Capecitabine-related serious TEAE	0	2 (33)	0	3 (50)	5 (26)
Grade ≥3 or grade ≥4 TEAE					
Grade ≥3 TEAE	0 (0)	4 (67)	4 (67)	6 (100)	14 (74)
Grade ≥4 TEAE	0 (0)	2 (33)	1 (17)	2 (33)	5 (26)
Peposertib-related grade ≥ 3TEAE	0 (0)	3 (50)	4 (67)	6 (100)	13 (68)
Peposertib-related grade ≥4 TEAE	0 (0)	2 (33)	1 (17)	2 (33)	5 (26)
RT-related grade ≥3 TEAE	0 (0)	2 (33)	2 (33)	5 (83.3)	9 (47)
RT-related grade ≥4 TEAE	0 (0)	1 (17)	1 (17)	2 (33)	4 (21)
Capecitabine-related grade ≥3 TEAE	0 (0)	2 (33)	2 (33)	6 (100)	10 (53)
Capecitabine-related grade ≥4 TEAE	0 (0)	2 (33)	1 (17)	2 (33)	5 (26)
TEAE leading to study discontinuation	0	0	0	0	0
TEAE leading to death	0	0	0	0	0
TEAE leading to permanent discontinuation of peposertib	0 (0)	0 (0)	1 (17)	3 (50)	4 (21)
TEAE leading to permanent discontinuation of RT	0 (0)	0 (0)	1 (17)	1 (17)	2 (11)
TEAE leading to permanent discontinuation of capecitabine	0 (0)	0 (0)	1 (17)	2 (33)	3 (15.8)

Note: TEAE were defined as events with onset date or worsening during the on-treatment period (until 30 days after the last dose of treatment). Related TEAE were events with the relationship of missing, unknown, or yes. Severity was graded according to NCI-CTCAE v5.0.
Abbreviations: CTCAE v5.0, Common Terminology Criteria for Adverse Events, Version 5.0; NCI, National Cancer Institute; RT, radiotherapy; TEAE, treatment-emergent adverse event.

patients were found to have residual disease pathologically and were not considered to have met the composite endpoint of cCR/pCR.

Among the 16 patients without cCR, seven directly underwent surgery, five declined surgery and opted to proceed with consolidative chemotherapy to complete total neoadjuvant therapy (TNT), and the remaining four patients did not have surgery for unspecified reasons. Of the nine patients who opted for surgery (cCR, $n = 2$; others, $n = 7$), none achieved pCR. One patient in the 150-mg cohort had pCR but required rectal surgery at week 5 after CRT, which prevented enumeration as pCR, per protocol.

Overall, one of 19 patients (5.3%, 100-mg cohort) reached the composite endpoint of cCR/pCR.

NAR and Ryan response assessment scores

NAR tended to rise with increasing peposertib dose, with median values of 9.4, 13.8, and 15.0 in the 100-mg, 150-mg, and 250-mg dose cohorts, respectively. A Ryan score of 1 was observed in two patients, one each in the 100-mg and 150-mg cohorts.

DFS and time to recurrence

Among the nine patients who underwent surgery, none experienced locoregional recurrence within the study period (including follow-up of up to 2 years), whereas one experienced a distant recurrence.

At data cutoff, five progression events (three deaths, two progressive disease events) had occurred, and the disease-free survival rate at 18 months was estimated to be 65.9% (95% CI, 25.9–87.9), with a median DFS of 21.2 months (95% CI, 18.0–not done (ND); Supplementary Fig. S2].

Pharmacokinetics and pharmacodynamics

Peposertib exposure was dose proportional across all dose levels after single and multiple dosing (Supplementary Fig. S3; Supplementary Table S5). Geometric mean exposure AUC_{0-24h} was 3,000, 4,100, and 7,210 ng*h/mL at fraction day (FD) 1 and 3,470, 5,020, and 9,440 ng*h/mL at FD 9 for the 100-mg, 150-mg, and 250-mg dosing groups. Statistical analysis for the 50-mg group was not done. The mean terminal half-life was around 5 to 6 hours for all dosing groups, independent of the dose level. No relevant peposertib accumulation was observed after multiple once-daily dosing, and the average exposure proportion of M467 (the major metabolite of peposertib), compared with peposertib, was <16% for C_{max} and <25% for AUC. In pharmacodynamic assays, inhibition of DNA-PK autophosphorylation was observed only at peposertib ≥150 mg, providing evidence of target engagement (Supplementary Fig. S4).

Mutation frequencies

Adequate samples for whole-exome sequencing were available from 10 patients. High-impact mutations (frameshift/nonsense mutations deleterious to protein function) in *TP53* were observed in three (30%) patients, whereas moderate-impact mutations (missense mutations) were observed in five (50%) patients (Supplementary Table S6); none of these patients showed pCR/cCR. No patients had deleterious mutations in *ATM*, but one patient had a missense mutation, leading to an amino acid change. High-impact mutations in *APC* were observed in eight out of 10 patients, and among these was the patient with the composite endpoint of cCR/pCR.

Tumor mutational burden (Supplementary Table S7) ranged between six and eight mutations/10^6 base pairs, except in one patient (11.4/10^6 base pairs); this patient did not show a response to treatment and was microsatellite stable.

Discussion

This study showed that peposertib has a potent radiosensitizing effect when combined with capecitabine-based CRT in patients with

Table 3. Efficacy analysis: full analysis set at follow-up (March 2022).

	Peposertib (mg) + RT + capecitabine				
	50 (*n* = 1)	**100 (*n* = 6)**	**150 (*n* = 6)**	**250 (*n* = 6)**	**Overall (*n* = 19)**
Number of subjects with tumor assessment at ETT, *n* (%)	1 (100)	4 (67)	5 (83.3)	5 (83.3)	15 (78.9)
Clinical response, *n* (%)					
Complete response	0 (0)	1 (16.7)	1 (16.7)	1 (16.7)	3 (15.8)
Near-complete response	1 (100)	2 (33.3)	2 (33.3)	3 (50.0)	8 (42.1)
Incomplete response	0 (0)	1 (16.7)	2 (33.3)	1 (16.7)	4 (21.1)
Progressive disease	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Missing[a]	0 (0)	2 (33.3)	1 (16.7)	1 (16.7)	4 (21.1)
Composite endpoint cCR/pCR[b]					
Responders, *n* (%)	0 (0)	1 (16.7)	0 (0)	0 (0)	1 (5.3)
95% CI (exact)[c]	(0–97.5)	(0.4–64.1)	(0–45.9)	(0–45.9)	(0.1–26.0)
Individual endpoints					
Clinical complete response					
Responders, *n* (%)[d]	0 (0)	1 (16.7)	1 (16.7)	1 (16.7)	3 (15.8)
95% CI (exact)[b]	(0–97.5)	(0.4–64.1)	(0.4–64.1)	(0.4–64.1)	(3.4–39.6)
Pathologic complete response					
Responders, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
95% CI (exact)[b]	(0–97.5)	(0–45.9)	(0–45.9)	(0–45.9)	(0–17.6)
Disease-free survival time[c]					
Number of events (PD, deaths), *n* (%)	—	—	—	—	5 (26.3)
Median (mo)	—	—	—	—	21.2
Minimum, maximum (mo)[d]	—	—	—	—	0, 23.5
95% CI	—	—	—	—	(18.0, ND)

Abbreviations: cCR, clinical complete response; CI, confidence interval; ETT, end-of-trial treatment; ND, not done or could not be calculated; pCR, pathologic complete response; PD, progressive disease; RT, radiotherapy.

[a]Data are missing for patients who stopped treatment in the first 5 weeks of the study.

[b]Participants were cCR/pCR responders if participants had surgery and had pCR, or if participants did not have surgery but had cCR. One participant in the peposertib 150-mg cohort with a pCR had rectal surgery before week 15 (study day 70); as per the protocol, only participants who underwent surgery at week 15 could be considered as pCR for the primary endpoint.

[c]95% exact CI using the Clopper–Pearson method.

[d]Two patients with cCR opted for surgery and were found to have residual disease pathologically, and thus were not considered to meet the endpoint of cCR/pCR.

LARC, as evidenced by the increase in RT-associated toxicities, and the consequent narrow therapeutic index of the drug. Overall, peposertib doses up to and including 150 mg once daily, in combination with concurrent CRT, were considered tolerable. However, they did not appear to improve complete response rates as compared with historical reports suggesting a pCR after neoadjuvant CRT is ∼10% to 25% (8). The SMC halted dose escalation after cohort 5 (150 mg, de-escalation after the 250-mg dose cohort) given concerns that peposertib had a narrow therapeutic index when combined with capecitabine-based CRT in rectal cancer, and the MTD and RP2D were not formally declared.

Currently, organ preservation through nonoperative, personalized treatment strategies that are safe (9), improve quality of life (10), and cost-effective (11), are being increasingly sought by patients with rectal cancer (12). Hence, selective radiosensitizers represent strong candidates for optimizing neoadjuvant treatment strategies. However, we found that the combination of peposertib with RT and capecitabine was tolerable only at doses that yielded insufficient exposure, suggesting that a better understanding of how DNA-PK inhibitors may augment the radiosensitizing effects of capecitabine and other chemotherapeutic agents is needed. Ongoing studies evaluating peposertib in multiple disease settings (13–18), and studies with other DNA-PK inhibitors, such as XRD-0394 and AZD7648 (19), may further inform our understanding of the safety, tolerability, and efficacy of DNA-PK inhibitors in combination with RT and/or other therapeutic agents in the treatment of cancer.

An earlier study of peposertib in patients with locally advanced head and neck cancer (NCT02516813) showed that it could not be safely combined with RT and full doses of cisplatin, a very potent radiosensitizer itself (20). When analyzed in the context of results from our study, these observations indicate that the concomitant use of two radiosensitizers may be infeasible. However, it is also worthwhile to note that the majority of TEAE observed in our study were gastrointestinal disorders, distinct from the toxicity reported by Samuels and colleagues (20), suggesting the AE profile is dependent on anatomy, radiation fields, and concurrent chemotherapies. Currently, the combination of peposertib with RT alone is under investigation in patients with advanced head and neck cancer who are not eligible for platinum-based CRT (15).

At the time of initiating this study, the standard of care for patients with LARC included neoadjuvant chemotherapy and radiation; however, treatment paradigms have since shifted with wider adoption of TNT, intensive surveillance, and short-course RT. Incorporating peposertib into short-course RT without capecitabine, or administering it during the boost phase of CRT, could help reduce exposure of normal rectal tissue to DNA-PK inhibitors and potentially widen the therapeutic index. Additionally, more conformal radiation modalities could be considered, for example, MR-guided adaptive radiotherapy or even proton therapy (21). Response to treatment can also be improved by patient stratification based on predictive biomarkers, such as loss-of-function mutations in *TP53* or *ATM*. Alternatively, less potent radiosensitizing DDR inhibitors, such as those against ataxia telangiectasia–mutated (ATM) or ataxia telangiectasia and Rad3-related (ATR) kinases, may be more suitable when combined with RT in rectal cancer (22, 23).

The use of the Bayesian 2-parameter logistic regression model for dose optimization and the inclusion of biomarker analysis to identify potential markers for future patient stratification are important strengths of the study. However, small patient numbers and the single-arm design in a selected population limit the interpretation of our findings. Although the variable post-CRT treatment (consolidative chemotherapy vs. surgery) may reflexively be considered a limitation of our study, it can also be considered a strength given we assessed the safety and tolerability of peposertib in patients treated with induction CRT who then proceeded directly to surgery as well as in patients treated with induction CRT followed by consolidative chemotherapy, which is the current standard-of-care arm for patients with low rectal cancers hoping for organ preservation as established by the OPRA trial (9). In fact, induction chemoradiation followed by consolidative chemotherapy is the current standard-of-care arm for the ongoing NCTN JANUS rectal cancer study (NCT05610163) being led by the Alliance for Clinical Trials in Oncology.

In conclusion, peposertib + CRT proved to have a narrow therapeutic index, limiting the clinical utility of the DNA-PK inhibitor peposertib when combined with capecitabine-based chemoradiation for locally advanced rectal cancer. However, inhibition of DNA-PK remains an important strategy and avenue of research for modifying the DDR to improve the efficacy of radiation and other anticancer treatments.

Ethics approval and consent to participate

This study was performed in compliance with the International Council for Harmonization Good Clinical Practice guideline and in accordance with the Declaration of Helsinki. The study protocol and other relevant documents were reviewed and approved by an Institutional Review Board/Independent Ethics Committee before study start, and all patients provided their written informed consent.

Authors' Disclosures

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Authors' Contributions

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Note

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