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A multicenter Phase Ib/II study of DNA-PK inhibitor peposertib (M3814) in combination with capecitabine and radiotherapy in patients with locally advanced rectal cancer

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STUDY STATUS

50 mg QD
One patient has received peposertib 50 mg QD

100 mg QD
Six patients have received peposertib 100 mg QD

150 mg QD
Three patients have received peposertib 150 mg

250 mg QD
The peposertib 250 mg QD cohort is now open

Study sites
Sites open in the USA and Spain; sites in other countries may open for Phase II recruitment

BACKGROUND

- Preoperative chemo-radiotherapy with or without sequential chemotherapy, followed by surgical intervention, is standard of care for patients with locally advanced rectal cancer; however, not all patients achieve a complete response.[1]
- DNA-dependent protein kinase (DNA-PK) regulates non-homologous end joining (NHEJ), a key DNA damage repair pathway for double-strand break repair.[2,3]
- Peposertib (formerly M3814) is an orally administered, potent and selective DNA-PK inhibitor that blocks NHEJ.[4]
- Peposertib has been shown to potentiate the effect of ionizing radiation in a human colon cancer xenograft model and several colon cancer cell lines.[5]
- This Phase Ib/II study (NCT03770689) aims to evaluate the safety, tolerability, pharmacokinetics, and efficacy of the neoadjuvant treatment combination of peposertib, capecitabine, and radiotherapy (RT) in patients with locally advanced rectal cancer.

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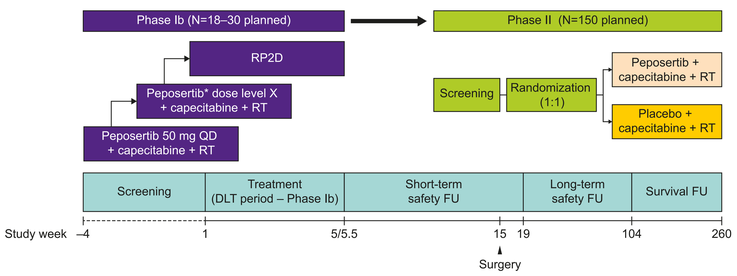
STUDY DESIGN

Phase Ib
- Open-label study (currently enrolling) where patients will receive peposertib + capecitabine (orally, 825 mg/m^2 twice daily) + RT (45–50 Gy), 5 days/week.
- The starting dose of peposertib for the first cohort was 50 mg once daily (QD); additional dose levels are planned to be between 100–800 mg QD (**Figure 1**).

Phase II
- In the double-blind Phase II part of the study (planned), patients will be randomized 1:1 to receive capecitabine (orally, 825 mg/m^2 twice daily) + RT (45–50 Gy), with either oral peposertib (recommended Phase II dose) or placebo, QD for 5 days/week.

Phase Ib and II
- Surgical intervention/imaging/biopsy is scheduled 9.5–10 weeks after end of treatment.
- Eligibility, endpoints, and assessments for both phases are shown in **Tables 1** and **2**.

Figure 1. Study design



*Formerly M3814.
DLT, dose-limiting toxicity; **FU**, follow-up; **QD**, once daily; **RP2D**, recommended Phase II dose; **RT**, radiotherapy; **X**, denoting planned dose level.

ELIGIBILITY, OBJECTIVES AND ASSESSMENTS

Table 1. Key eligibility criteria

Inclusion criteria	Exclusion criteria
≥18 years of age	Contraindications to MRI imaging
ECOG PS ≤1	Concurrent use of other anticancer therapies
Histologically confirmed and localized resectable rectal adenocarcinoma (Stage II or III at original staging)	Major surgical intervention within 4 weeks prior to the first dose of study intervention
Induction chemotherapy permitted if residual disease documented by MRI, digital rectal examination, and endoscopy	Previous radiation therapy to the pelvis
Adequate hematological, renal, and liver function	Unstable cardiovascular function within 6 months prior to enrollment

ECOG PS, Eastern Cooperative Oncology Group performance status; **MRI**, magnetic resonance imaging.

Table 2. Objectives and assessments

Objectives		Endpoints
Primary		
To determine the MTD and RP2D of peposertib* in combination with capecitabine + RT (**Phase Ib**)		Occurrence of DLTs (broadly defined as any drug-induced liver injury meeting Hy's law criteria, any Grade ≥3 toxicity, or any toxicity resulting in less than 80% of the planned study medication intake) (**Phase Ib**)
To evaluate the efficacy of peposertib + capecitabine + RT vs matching placebo arm, in terms of pCR and cCR (**Phase II**)		Composite endpoint of pCR/cCR (**Phase II**)
Secondary		
Efficacy	To explore antitumor activity of combination therapy (**Phase Ib**) and the efficacy of combination therapy vs matching placebo arm (**Phase II**)	pCR/cCR, OS, disease-free survival, BOR, and local/distant recurrence (**Phase Ib and II**) Neoadjuvant rectal score, surgical intervention, and R0 resection (**Phase II only**)
Safety	To evaluate safety and tolerability of combination therapy (**Phase Ib**) vs matching placebo arm (**Phase II**)	TEAEs, lab values, vital signs, ECGs (**Phase Ib and II**)
PK	To assess PK of peposertib (**Phase Ib**) using population PK modelling (**Phase II**)	PK parameter estimates (**Phase Ib and II**)
QoL	To measure QoL (**Phase II**)	Patient-reported outcomes

*Formerly M3814.
BOR, best overall response; **cCR**, clinical complete response; **DLT**, dose-limiting toxicity; **ECG**, Electrocardiographs; **MTD**, maximum tolerated dose; **OS**, overall survival; **pCR**, pathological complete response; **PK**, pharmacokinetics; **QoL**, quality of life; **RP2D**, recommended Phase II dose; **R0**, resection for cure or complete remission; **RT**, radiotherapy; **TEAE**, treatment-emergent adverse event.

STATISTICAL ANALYSES

Phase Ib
- Trial currently recruiting: planned enrollment is 18–30 patients (standard cohort size: n=3).
- After each cohort has completed the treatment period (dose-limiting toxicity period), the safety monitoring committee will review safety, tolerability, and pharmacokinetic data, and will recommend the peposertib dose for the next cohort; dose escalation is guided by Bayesian two-parameter logistic regression model with overdose control.

Phase II
- Planned enrollment is 150 patients.
- An interim futility analysis is planned for Phase II.
- Patients will be considered responders (pathological complete response [pCR]/clinical complete response [cCR]) if they either underwent surgery and had a pCR, or they did not undergo surgery but had a cCR.
- The proportion of patients with pCR/cCR will be indicated per treatment arm, together with the 95% Clopper–Pearson confidence intervals (CI).
- The difference between treatment groups will be presented together with the 95% Newcombe–Wilson CI.[6]

STUDY CONTACT

- The coordinating investigator for this study is Paul Romesser, MD (romessep@mskcc.org).
- For further information, please visit www.ClinicalTrials.gov (NCT03770689) or www.merckgroup.com.

PR reports consulting or advisory role for EMD Serono, Billerica, MA, US, a business of Merck KGaA, Darmstadt, Germany; travel, accommodations, expenses from Elekta; stock and other ownership interests in Pfizer; research funding from EMD Serono, Billerica, MA, US, a business of Merck KGaA, Darmstadt, Germany. **EBH** reports research funding from EMD Serono, Billerica, MA, US, a business of Merck KGaA, Darmstadt, Germany. **TP** reports consulting or advisory role for Novartis, Bayer and Foundation Medicine; travel, accommodations, expenses from Bayer and Novartis. **BS** is an employee of Merck KGaA, Darmstadt, Germany; reports stock and other interests in Merck KGaA, Darmstadt, Germany. **MK** is an employee of Merck KGaA, Darmstadt, Germany; reports stock and other ownership interests in Novartis Pharma SAS and Merck KGaA, Darmstadt, Germany; **ARG** is an employee of Merck S.L., Madrid, Spain, an affiliate of Merck KGaA, Darmstadt, Germany. **IDP** is an employee of Ares Trading S.A. – Merck Group, Eysins, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany; reports stock and other interests in Merck KGaA, Darmstadt, Germany. **EDM** has no relationships to disclose.

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