A new radio-enhancer, PEP503 (NBTXR3), in combination with concurrent chemoradiation in locally advanced or unresectable rectal cancer: The dose-finding part of a phase I/II trial.

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Background: PEP503 (as known as NBTXR3) is a novel radio-enhancer composed of functionalized hafnium oxide nanoparticles for a higher energy deposit by radiotherapy comparing to radiotherapy alone without it. A prior phase 3 study for soft tissue sarcoma has demonstrated the clinical benefit. The phase 1b part of the study aimed to test the feasibility of PEP503 intra-tumor injection and examine the safety profile of various dose levels of PEP503 in combination with concurrent chemo-radiation (CCRT) for locally advanced rectal cancers. **Methods:** Patients who had rectal adenocarcinoma of T3-4 or locally unresectable disease suitable for neoadjuvant CCRT were eligible. A single administration of PEP503 intra-tumor injection with multiple needle punctures was applied 24 to 72 hours before the start of IMRT or IMAT at 50 Gy in 25 fractions in combination with capecitabine or infusion 5-FU over 5~6 weeks. Dose escalation of 4 levels of PEP503 injected volume was based on 5%, 10%, 15%, and 22% of the baseline tumor volume by MRI. Intra-tumor dispersion of nanoparticles was inspected by CT-scan and the body kinetics evaluation was performed. The total mesorectal excision was planned around 8~12 weeks later after the completion of CCRT. Preliminary efficacy including tumor response after CCRT and the pathological response with tumor regression grade (TRG) after surgery was collected. **Results:** Twenty patients were enrolled, with 7, 4, 3, and 6 patients at 5%, 10%, 15%, and 22% dose levels, respectively. An injection procedure-related dose-limiting toxicity of urinary tract infection with sepsis was reported in the first treated patient at 5%. There was no adverse event (AE) or serious AE directly caused by PEP503. The most frequently reported AEs related to CCRT across all dose levels were diarrhea (~45%), WBC decreased (~40%), and dermatitis (~25%), but all were grade 1 or 2. The safety profile of CCRT with PEP503 was similar to it of CCRT without PEP503 for rectal cancer patients. The CT scans, before and after CCRT, displayed the dispersion of PEP503 among different tumor shapes and contours without leakage to the surrounding healthy tissues. In most patients, hafnium was not detected in the circulation in 60 minutes after PEP503 injection and not found in urine. Around 70% of patients showed tumor response after the CCRT and half of the patients receiving surgery achieved good tumor regression (AJCC TRG 0 or TRG 1). In the small phase 1b dose-escalation part of the trial, the dose-dependency of the efficacy endpoints could not be assessed. **Conclusions:** Intra-tumor injection of PEP503/NBTXR3 with CCRT is feasible without additional toxicities for rectal cancer patients. The extension phase 2 of the trial to investigate the clinical benefits of PEP503 at 22% of tumor volume is ongoing in Taiwan. Clinical trial information: NCT02465593. Research Sponsor: PharmaEngine, Inc.