Purpose/Objective(s): To improve radiotherapy of cancer patients, development of efficient radiosensitizer is one of the most important issues in clinical cancer treatment. Poly(ADP-ribose) polymerase (PARP)-1 is a nuclear enzyme that promotes base excision repair and DNA strand break repair. Inhibitors of PARP have been shown to enhance the cytotoxic effects of ionizing radiation and DNA damaging agents. We investigated the impact of inhibition of PARP on responses to γ-irradiation (low LET (linear energy transfer) radiation) and carbon-ion irradiation (high LET radiation) in human pancreatic cancer cell line MiaPaCa2.

Materials/Methods: We measured the cell survival by a colony formation assay under combination of PARP inhibitor AZD2281 (one of PARP inhibitors used in clinical trials) and single fraction of γ-irradiation and carbon-ion irradiation (LET 13 and 70 keV/μm). We also analyzed the effect on DNA double and single strand breaks (DSB and SSB) by pulse field gel electrophoresis (PFGE). Western blotting was performed to analyze the effect of PARP inhibition on DNA damage responses (DDR) using antibodies against γ-H2AX, a marker for DSB, and phosphorylated p53 (p-p53) (Ser15).

Results: The colony formation assay showed that addition of PARP inhibitor enhanced the effect of γ-irradiation on cell survival compared to irradiation alone. Increased levels of γ-H2AX and p-p53 (ser15) were observed in the presence of PARP inhibitor. Prolonged increase levels of γ-H2AX and p-p53 (ser15) suggests the enhanced DDR and local delay in DSB processing. Attenuated level of phosphorylated histone H3 was observed in the presence of AZD2281, suggesting the decreased population of the cells arrested in G2/M phase. In the case of carbon-ion irradiation, the PARP inhibitor sensitized the effect of LET13 keV/μm radiation at the range of 1-5 Gy on cell survival (p<0.05). For LET 70 keV/μm radiation, the sensitization effect was also observed at 3 Gy (p<0.05). We observed enhanced levels of γ-H2AX and p-p53 both after LET13 and LET70 keV/μm radiation, suggesting that DDR is also enhanced after carbon-ion irradiation in the presence of PARP inhibitor.

Conclusions: PARP inhibitor AZD2281 sensitized both γ- and carbon-ion irradiated MiaPaCa2 cells. Enhanced and prolonged DDR by AZD2281 were observed. PARP inhibitor may be useful when combined with low or high LET radiation in cancer therapy.