

AZD1775 plus chemoradiotherapy for pancreatic cancer

A new study has shown that the Wee1 inhibitor AZD1775 (adavosertib) is well tolerated in combination with gemcitabine and radiotherapy in patients with pancreatic cancer.

The phase 1, dose-escalation trial involved 34 patients with locally advanced, unresectable adenocarcinoma of the pancreas. The patients received four 21-day cycles of 1000 mg/m² intravenous gemcitabine on days 1 and 8, and 100–175 mg of oral AZD1775 on days 1, 2, 8, and 9. Patients also received radiotherapy during cycles 2 and 3, followed by a 3-week break and a fourth cycle of gemcitabine-AZD1775. The primary objective was to determine the maximum tolerated dose of AZD1775. Secondary objectives included overall survival and progression-free survival.

Eight (24%) of 34 patients reported dose-limiting toxicities, mostly

anorexia or nausea (two [6%]) and fatigue (two [6%]). On this basis, 150 mg was selected as the recommended phase 2 dose. Median overall survival was 21.7 months (90% CI 16.7–24.8) and median progression-free survival was 9.4 months (90% CI 8.0–9.9).

Co-author Theodore Lawrence (University of Michigan, Ann Arbor, MI, USA) commented that there have been many attempts to use radiotherapy in patients with pancreatic cancer. “The big issue has been that systemic therapy has not worked well in this disease, but it is finally getting better”, he explained. “So, combinations such as the one used in our trial, which are much more intensive in a primary tumour that cannot be controlled by chemotherapy alone, could help us to prolong survival.”

Andrew Biankin (University of Glasgow, Glasgow, UK) noted that

combining Wee1 inhibition with radiotherapy makes sense. “Radiation therapy induces DNA damage and Wee1 inhibition prevents the damage from being repaired”, he said. However, he cautioned that it was too early to draw any conclusions on whether the combination will improve survival.

Lawrence outlined potential future studies involving Wee1 inhibition in patients with unresectable pancreatic cancer. One possibility would be to compare the FOLFIRINOX regimen with gemcitabine-AZD1775. The preferred option would be two or three cycles of FOLFIRINOX followed by gemcitabine-AZD1775 versus the preferred regimen at each institution. “I think a trial of that nature has the potential to be the most clinically impactful”, he told *The Lancet Oncology*.

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