A phase II pilot trial with RP101 in advanced pancreatic carcinoma

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R. Fahrig, D. Quietzsch, V. Heinemann, A. Liebert, M. Haenel

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Background: (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU, RP101), which supports apoptosis and prevents the acquisition of chemoresistance, was tested in cultured human pancreatic tumor cells. RP101 down-regulated uridine phosphorylase, a marker of poor prognosis, and APEX1, which is involved in DNA repair, and repressed Stat-3 and its target VEGF. Furthermore, RP101 activated antitumor immunity. These results encouraged us to investigate the effect of RP101 in combination with gemcitabine (GEM) and cisplatin (CIS) in patients with advanced pancreatic cancer.

Methods: A phase II pilot trial was designed to compare the GEM/CIS/RP101 combination to historical GEM/CIS combination. The primary endpoint was survival. 13 pts with histological documented pancreatic carcinoma received GEM 1.000 mg/m2 plus CIS 50 mg/m2 on days 1 and 15 of a 28-day schedule. RP101 treatment was on the same day and for four days after chemotherapy (500 mg/day).

Results: All patients showed at least a stable disease, and 33% of them a PR. As a historical control, 22 pts were selected by random generator from 98 patients enrolled in a previous Phase III study performed in the same centers, 15 with stage IV and 7 with stage III disease, resulting in a similar proportion of stage III to IV patients as in the RP101 co-treatment group (nine stage IV and four stage III). In the RP101-co-treatment group the median survival was significantly longer than that of the historical control group (447 days vs. 186 days, p=0.007). Time to progression (TTP) was also prolonged (280 days vs. 104 days, p=0.004). Ten of the 13 pts lived longer than one year, 4 nearly two years after first treatment.

Conclusions: The combined use of GEM/CIS/RP101 prolonged progression-free and overall survival in locally advanced and metastatic pancreatic cancer when compared to all published studies with all combinations of drugs. A repeat study with GEM/RP101 shows similar promising results indicating that the combination of RP101 with GEM should be explored in larger studies in patients with advance pancreatic cancer.

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Geschäftsführer: Prof. Dr. Rudolf Fahrig
Fiedlerstr. 34
01307 Dresden - Germany