

Clinical and Translational Results of a Phase II Randomized Trial of Maintenance Sunitinib or Observation in Metastatic Pancreatic Adenocarcinoma

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Context To prolong chemotherapy over 6 months in metastatic pancreatic adenocarcinoma (MPA) has unproven benefit and is hampered by cumulative toxicity. **Objective** This phase II trial explored the role of maintenance sunitinib (MS), using an observation (O) group as calibration arm. The predictive role of circulating endothelial cells (CEC) and of functional polymorphisms (SNPs) of genes involved in sunitinib activity, metabolism and transport (*VEGFA*, *VEGFR-2*, *CYP3A5*, *CYP1A1*, *ABCB1*, *ABCG2*) was explored. **Methods** Patients with pathologic diagnosis of MPA, PS >50%, no PD after 6 months of chemotherapy were randomized to O (arm A) or MS (37.5 mg daily) for 6 months (arm B). Primary endpoint was PFS-6. The target enrolment was 26 patients among whom >5 PFS-6 were necessary to declare MS of interest. CEC and SNPs were evaluated on baseline blood samples. **Results** Twenty-eight patients were assigned arm A and 28 arm B, one of whom was ineligible (kidney cancer). Baseline characteristics were balanced; previous chemotherapy was (A/B): gemcitabine 2/3;

combination chemotherapy 25/25. Median duration of MS was 2.8 months. Grade 3-4 toxicity (arm B) was 15% neutropenia; 12% thrombocytopenia and hand-foot syndrome, 8% diarrhea. PFS-6 was 4% and 22%; median PFS was 2.0 and 3.2 months (P=0.01); 2-year OS was 5% and 22% (P=0.12). CEC analysis (n=46; 84%) showed a longer median PFS in untreated patients with CEC <30 when compared to >30 (2.9 versus 1.9 months; P=0.08); a significantly increased PFS in patients with CEC >30 treated by MS versus O (3.4 months; P=0.02); no PFS difference between arms in patients with CEC <30. Genotyping analysis (n=43; 78%) showed a longer median OS among arm B patients with *ABCB1 3435TT* genotype as compared to *3435CC/CT* genotype (26 versus 7 months; P=0.11); and with *VEGFA -634GC-CC* genotype as compared to *-634GG* genotype (11 versus 6 months; P=0.013). **Conclusions** MS fulfilled the primary endpoint of the trial and yielded remarkable OS figures. CEC and SNPs may be useful to predict benefit from MS.