ESPAC-3(v2): A multicenter, international, open-label, randomized, controlled phase III trial of adjuvant 5-fluorouracil/folinic acid (5-FU/FA) versus gemcitabine (GEM) in patients with resected pancreatic ductal adenocarcinoma.

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**Abstract:**

**Background:** Adjuvant 5-FU/FA (ESPAC-1 trial) and GEM (CONKO-001 trial) provide improved survival for patients with resected pancreatic cancer compared to no chemotherapy. The aim of the ESPAC-3 (v2) trial was to compare 5FU/FA vs GEM to identify if either adjuvant chemotherapy was associated with a significantly better survival.

**Methods:** Patients with an R0/R1 resection for pancreatic ductal adenocarcinoma were randomized (stratified for resection margin status and country) <8 weeks of surgery to receive either 5FU/FA (FA, 20 mg/m2, iv bolus injection followed by 5-FU, 425 mg/m2, iv bolus injection given 1-5d every 28 days) or GEM (1,000mg/m2 iv infusion 1d, 8d and 15d every 4 weeks) for 6 months. The primary outcome measure was overall survival; the secondary measures were toxicity, progression free survival and quality of life. 1,030 patients were needed to detect a 10% difference in 2-year survival rates with 90% power.

**Results:** 1,088 patients from 16 countries were randomized from July 2000 to Jan 2007 (5FU/FA = 551, GEM = 537). Median (range) age was 63 (31-85) years; 598 (55%) were men. Median tumor size was 30 (20-350) mm; 384 (35%) were R1 resections; 777 (72%) were node positive; and 263 (25%) were poorly differentiated tumors. Final analysis was carried out on an intention to treat basis with a minimum of 2 years follow-up after 753 (69%) patients had died. Median (IQR) follow-up of 335 alive patients was 34.2 (27.1-43.4) months, equal across treatment groups. Median survival from resection of patients treated with 5FU/FA was 23.0 (95% CI: 21.1, 25.0) months and for patients treated with GEM this was 23.6 (95%CI: 21.4, 26.4) months. Log-rank analysis revealed no statistically significant difference in survival estimates between the treatment groups ($c_2^{LR}=0.7$, p=0.39, HR$_{GEM}=0.94$ (95%CI: 0.81, 1.08)). There was no significant difference in the effect of treatment across subgroups according to $R$ status (test of heterogeneity $c_2^{2}=0.3$, p=0.56).

**Conclusions:** This is the largest adjuvant trial ever conducted for pancreatic ductal adenocarcinoma and showed no significant difference in survival between adjuvant 5FU/FA and adjuvant GEM.