Introduction:
Chemotherapeutic agent-induced nuclear factor kappa b (NF-κB) activation has been reported as a key mechanism of chemoresistance. We previously reported that nafamostat mesilate (NAM), a synthetic serine protease inhibitor, inhibits NF-κB activation by inhibiting phosphorylation of IκBα. Based on these facts, phase II study of gemcitabine (GEM) with regional arterial infusion of NAM for advanced pancreatic cancer was conducted as a translational research. Overall survival of NAM/GEM was 10.0 months. Subsequently, a novel phase II study of combination chemotherapy of NAM/GEM with S-1, an oral fluoropyrimidine was planned (UMIN 000008413).

Methods:
Patients, who could finish at least 1 course of this treatment, with more than 12 months follow-up time were investigated in this first report. Parameters evaluated consisted of overall survival (OS), progression-free survival (PFS), one-year survival rate, serum value of CA19-9 and adverse events. Patients received GEM (1,000 mg/m² i.v. for 30 min), NAM (continuous regional arterial infusion for 24 h via a port-catheter system) on days 1 and 15, and oral S-1 [(80 mg/day (BSA < 1.25 m²), 100 mg/day (1.25 BSA < 1.5 m²), or 120 mg/day (BSA 1.5 m²)] on days 1-14 or, days 1-7 and 15-21. This regimen was repeated at 28-day intervals.

Results:
Twenty-seven out of 37 enrolled and evaluable patients (Male/Female: 16/11, Age (median): 67 (range 35-78) yrs, Stage III/IV 8/19.) were candidates in this report. Two of 8 patients in stage III (25%) could undergo conversion surgery. Ten of the 27 patients (37%) underwent subsequent treatment (FOLFIRINOX: 3, GEM/ nab-PTX: 3, TAS-118: 3, chemoradiation with S-1: 1, GEM/intraarterial 5-FU: 1, surgery: 2). Median OS and PFS were 12.2 (95% CI, 10.8 -17.2 mo) and 8.8 months (95% CI, 7.8-11.6 mo), respectively. One-year survival rate was 59.3%. Twenty-two patients had an abnormally high value of serum CA19-9 before the treatment, of whom 21 (96%) showed reduction after the treatment. As for adverse events, Grade 4 treatment-related hematological toxicities were encountered in 3 patients (neutropenia: 2, creatinine elevation: 1). So far, no febrile neutropenia has been observed. No patients developed Grade 3/4 non-hematological toxicities. Although no patients showed port-catheter system-related problems, one patient was allergic to the material of port-catheter, who was excluded from this evaluation according to the protocol.

Conclusion:
This study is ongoing. However, NAM/GEM/S-1 therapy is safe, and our initial data suggest that this regimen seems promising as a novel treatment for advanced unresectable pancreatic cancer.