gastrointestinal tumours, non-colorectal

SCHEDULING NAB-PACLITAXEL WITH GEMCITABINE (SIEGE): RANDOMISED PHASE II TRIAL TO INVESTIGATE TWO DIFFERENT SCHEDULES OF NAB-PACLITAXEL (ABX) COMBINED WITH GEMCITABINE (GEM) AS FIRST LINE TREATMENT FOR METASTATIC PANCREATIC ADENOCARCINOMA (PDAC)

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Background: PDAC carries a poor prognosis. Recently ABX combined with GEM was shown to improve overall survival compared with standard single agent GEM. The mechanism by which ABX and GEM interact is not fully understood, but limited preclinical and clinical data has led to two hypotheses: 1: ABX may act to deplete the tumour stroma by binding to the protein, SPARC (secreted protein acidic and rich in cysteine), facilitating GEM penetration of and access to the tumour; 2: ABX may increase intratumoural levels of the active GEM triphosphate by decreasing cytidine deaminase (CDA) activity, thus enhancing GEM cytotoxicity. Mouse models of PDAC suggest that delivery of ABX 24 hours prior to GEM might result in even higher intratumoural GEM concentrations. Thus, scheduling of these 2 agents may be critical to optimising clinical benefit. Optimal scheduling of ABX + GEM and effect on quality of life is the subject of the SIEGE clinical trial.

Trial design: Patients with previously untreated, histologically or cytologically confirmed metastatic PDAC are randomised to receive a 4-weekly cycle of ABX + GEM until disease progression, administered either concomitantly (IV ABX 125mg/m² d1, d8 and d15 immediately followed by IV GEM 1000mg/m² d1, d8 and d15) or sequentially (the same regimen with GEM given 24hr after ABX). Prior to randomisation, tumour tissue and blood is obtained for analysis of the tumour stroma, SPARC and CDA activity. Blood is collected prior to each treatment cycle and on disease progression. Tumour biopsies are collected prior to starting cycle 3 and at disease progression. The clinical primary endpoint is progression-free survival. Tumour assessments are performed using RECIST every 8 weeks until progression. Recruitment started in January 2014 and a total of 120 patients will be recruited over 2 years at 20 UK sites. Biological samples will be used to determine the mechanism of action of ABX + GEM. Biomarker analyses may identify whether a particular patient subgroup is likely to benefit more than others. The trial is registered as EudraCT 2013-001868-40.

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