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Evaluation of pharmacokinetics and safety profiles between S-1 granule and S-1 capsule in patients with solid tumors

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Background: S-1 capsule contains tegafur (FT), 5-chloro-2,4-dihydropyrimidine (CDHP), and potassium oxonate (Oxo) at a molar ratio of 1:0.4:1, and is widely used for the treatment of various solid tumors in Japan. However, some patients are unable to intake the capsule formulation due to dysphagia caused by old age or tumor status. To circumvent this problem, we have developed S-1 granule and studied the bioequivalence between these 2 formulations.
Materials and Methods: This study consisted of 2 parts: Part 1: Single-dose, randomized crossover pharmacokinetics (PK) study in pts' with solid tumors; Part 2: Safety evaluation study using S-1 granule in patients enrolled in part 1. The main inclusion criteria were as follows: written informed consent; histologically or cytologically proven solid tumor; aged 20−74; adequate bone marrow, liver and renal functions. In Part 1, we evaluated PK parameters of FT, 5-fluorouracil (5-FU), CDHP, and Oxo. In Part 2, S-1 granules were administered at a dose of 40−60 mg based on pts' body surface area twice daily for 28 consecutive days followed by 14 days rest, and this treatment was continued until disease progression, unacceptable toxicity, or pts' refusal.
Results: A total of 24 pts (17 males, 7 females) were enrolled from Sept 2006 to May 2007. Twenty and 21 patients were evaluated for Part 1 and Part 2, respectively. All patients had advanced solid tumors: 10 lung cancer, 5 colon cancer, 2 gastric cancer, 2 pancreas cancer, 2 billiary tract cancer, and 1 each had rectal cancer, esophageal cancer, and maxillary sinus cancer. In terms of C_{max}, $T_{max,}$ kel and AUC_{∞}, PK properties of S-1 granule are nearly equivalent to those of capsule formulation (shown in the below table). In Part 2, the incidences of grade 1 or higher adverse drug reaction (ADR) and grade 3/4 ADR were 95.2% and 23.8%. The ADR of grade 3/4 with incidences of $\geqslant$10% was anemia (14.3%). There was no unknown or unexpected ADR, and the toxicity profile of S-1 granule was similar to those of S-1 capsule that had been previously reported.

5-FU	S-1 capsule	S-1 granule
C_{max} (ng/mL)	104.5	106.1
t_{max} (hr)	2.3	1.9
kel (hr^{-1})	0.401	0.415
AUC_{∞} (ng$\times$hr/mL)	558.0	532.3

Conclusions: S-1 granule was almost bioequivalent to capsule. Development of S-1 granule may contribute greatly to the patients receiving oral chemotherapy.

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Outcome and characteristics of patients with advanced gynaecological malignancies enrolled in phase I trials

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Background: Gynaecological cancers (GC) account for approximately 20% of all malignancies diagnosed in woman. Greater knowledge in cancer biology led to the identification of new promising molecular targets, actively developed in phase I trials. Early drug development is challenging in the field of advanced gynaecological cancers. This study aims to describe the clinical features of GC patients included in phase I trials and the clinical benefit resulting from their participation.
Patients and Methods: All patients with advanced solid tumors included in Phase I trials at Institut Gustave Roussy between November 2004 and December 2008 were screened and data from all GC patients included was analyzed.
Results: Overall 44 out of 250 (17%) patients were enrolled in 14 different phase I trials
Median age was 56 years (33−77), median ECOG PS was 1 (0−1) and Pts received a median number of 2.5 (0−8) prior lines of treatment before inclusion.
The histological types were: ovarian cancer (19 pts), cervical cancer (6 pts), endometrial cancer (9 pts), uterine leiomyosarcoma (9 pts) and neuroendocrine tumor (1 pts).
Patients received a median number of 2 cycles (1−20), with investigational agents (anti HER therapies: 7 pts; antiangiogenic therapies: 11 pts; new cytotoxic chemotherapy: 21 pts; others: 5 pts) Two objective responses (RECIST criteria) were observed. Stable disease (SD) was observed in 30 pts (68%). Two patients with uterine leiomyosarcoma treated by antiangiogenic agents after a cytotoxic first line showed a prolonged stable disease (more than 12 months). The median PFS and OS were 2 and 10 months for all pts. Post-phase I therapy was as follows: 44 percent of the pts were retreated, among which 5 patients were enrolled in further phase 1 after progression.
Conclusion: This study shows that pts with advanced GU cancers could strongly benefit from phase I trials. The potential clinical benefit resulting from participation to these trials should encourage physicians to refer GC patients for inclusion in phase I trials.

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Tyrosine kinase inhibitor (TKI)-induced macrocytosis

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Background: Several small molecule TKI are routinely used in the clinic or are under clinical development in different cancer types. Treatment with sunitinib in patients (pts) with metastatic renal cell cancer (RCC) induces a significant increase of the mean corpuscular volume (MCV) of peripheral red blood cells (RBC). The pathophysiological mechanism is unresolved but could involve the c-kit dependent signaling pathway in progenitor cells of the bone marrow. We therefore analyzed the effect of imatinib, which acts through c-kit inhibition, on MCV in pts with gastrointestinal stromal tumors (GIST) and this in comparison to the effect of sunitinib in patients with RCC and metastatic breast cancer (MBC).
Patients and Methods: The changes in MCV was studied in 10 pts treated with sunitinib (6 with RCC and 4 with MBC) and in 6 with GIST treated with imatinib. All pts received treatment for >3 month (mo) at the respective recommended dose. In 4 pts showing the increase in MCV under sunitinib a bone marrow aspirate and serum levels of folate, vitamine B12 and thyroid hormones were determined.
Results: Baseline values of MCV in both groups of pts were not different. Sunitinib induced a larger increase in MCV versus baseline than imatinib (mean increase of 12.4%,16.8%,16.6% and 12.7% for sunitinib versus 0.7%, 5.6%, 5.9% and 5% for imatinib at 3, 6, 9 and 12 mo respectively; p-values of <0.005, <0.011, $p < 0.031$ and $= 0.06$ at 3, 6, 9 and 12 mo respectively). Folate, vitamine B12 and thyroid function remained normal in pts treated with sunitinib. Macrocytosis did not result in anemia, was self limiting and recovered completely within 3 to 6 month of drug withdrawal in both groups.
Evaluation of the bone marrow in 4 pts under sunitinib showed *nonspecific dyserythrosis*.
Conclusion: Sunitinib-induced macrocytosis is not limited to RCC cancer but also occurs in MBC. The increase with imatinib in GIST is significantly less than with sunitinib at all time points studied.
Both drugs are used at an effective pharmacodynamic dose (inhibition of c-kit) and moreover sunitinib treated patients often have toxicity related dose reductions. Therefore these data strongly suggest that additional pathways targeted by sunitinib are involved in the drug induced macrocytosis and implicate the VEGF, FLT3 and RET pathways in normal RBC development. The induction of macrocytosis may compromise the blinding process in placebo-controlled trials with known or novel TKI's.

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Safety and pharmacology of the EpCAM/CD3-bispecific BiTE antibody MT110 in patients with metastatic colorectal, gastric or lung cancer

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Background: MT110 is a bispecific antibody construct (BiTE) binding to epithelial cell adhesion molecule (EpCAM), expressed on most solid cancers of epithelial origin, and to CD3 on T cells. MT110 has shown high anti-tumor activity in various preclinical models including a human colorectal cancer (CRC) xenograft. Clinical proof of concept for BiTE antibodies has been demonstrated with blinatumomab (CD19xCD3) in patients (pts) with B cell lymphoma [1].

Methods: This phase 1 study evaluates safety, tolerability, pharmacokinetics/-dynamics and anti-tumor effects of MT110 in pts with advanced solid tumors expressing EpCAM. A dose escalation with 3−6 pts per cohort is used to determine the maximum tolerated dose (MTD). Starting dose was 1 μg/d given as continuous i.v. infusion for 1 or more 28-day cycles.
Results: To date, a total of 14 pts (3 gastric, 9 CRC, 1 NSCLC, 1 SCLC; up to 7 previous chemotherapies) have been treated in 4 cohorts up to 10 μg/d. Overall, MT110 was very well tolerated with few clinical adverse events. All but 1 of the treated pts completed at least 4 wks of therapy. Besides initial lymphopenia, an increase in liver enzymes, up to grade 3/4, was the most frequent laboratory abnormality. These events were transient in nature and not found to impact on liver synthesis nor were any abnormal results seen in imaging (ultrasound, CT scan, and/or MRI of the liver). The increase in liver enzymes did not occur on re-exposure to MT110. Concomitant corticosteroids were found to mitigate increases in liver enzymes and further optimization of the treatment schedule is currently ongoing. As observed with blinatumomab, MT110 caused a rapid redistribution of lymphocytes shortly after start of infusion. Signs of T cell expansion/-activation were seen in pts with clinical benefit after 4 wks. Disease stabilization according to RECIST was confirmed in 6 of 13 pts, lasting 12 wks in median. In one patient, a lung metastasis was resected 11 wks after initiation of MT110 treatment. Immunohistochemistry revealed tumor cell necrosis and a massive T cell infiltration as possible evidence of MT110 activity. None of the pts developed antibodies against MT110.
Conclusion: First signs of biological activity of MT110 in pts with advanced EpCAM-expressing tumors have been observed at clinically well tolerated doses. Optimization of the treatment schedule and evaluation of BiTE antibody MT110 at higher doses is currently ongoing.

References

[1] Bargou R et al. (2008) Science 321:974.

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Clinical and preclinical development of 4SC-201, a new oral histone deacetylase (HDAC) inhibitor

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Background: 4SC-201 is a new, specific, potent, pan-HDAC inhibitor under evaluation as mono or combination therapy for solid and haematological malignancies.
Methods: Preclinical studies of anti-cancer activity of 4SC-201 alone or in combination with other cancer drugs in cell lines and in xenograft models were performed. In a First-in-Man (FIM) study, patients (pts) with advanced refractory solid tumours were dosed once daily, d1−5, in a 14-day cycle in sequential cohorts. Objectives included determination of safety, tolerability, pharmacokinetics (PK), pharmacodynamics, maximum tolerated dose and anti-cancer activity.
Results: In preclinical studies 4SC-201 demonstrated potent activity across a broad range of tumour cell lines originated from different cancers. Xenograft studies revealed strong dose-dependent anti-tumour activity and good tolerability. 4SC-201 enhanced the anti-tumour activity of a variety of approved cancer drugs when tested in combination. In a FIM study, 18 pts were treated at dose levels of 100 mg, 200 mg, 400 mg, 600 mg (3 pts each) and 800 mg (6 pts). Grade 3 DLT of nausea and vomiting occurred in 1 pt dosed at 800 mg. Most common adverse events included nausea, vomiting and fatigue. 8 of 9 pts treated at the two highest dose levels had stable disease during the main phase of the study (4 cycles). A patient with metastatic thymoma (minor response) continued treatment until cycle 18 and stopped without evidence of progressive disease. Another patient with liposarcoma remains on treatment for over a year. Following single oral administration high plasma exposure of 4SC-201 was obtained indicating good bioavailability with a dose-proportional PK profile and low inter-individual variability for all dose levels. Biomarker assays revealed that HDAC inhibition in PBMC ranged from 50 to 100% and was dose-dependent.
Conclusions: In summary, preclinical studies testing 4SC-201 alone or in combination with several cancer drugs showed substantial synergistic anti-tumour activity. Phase I data confirmed the favorable oral drug profile and good tolerability of 4SC-201. Efficient target modulation and anti-tumour activity were observed. Consequently, phase II development will be initiated aiming for clinical proof-of-concept in specific tumour indications, including combination studies with e.g. STIs such as sorafenib or chemotherapeutic agents.

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Phase I trial of oral Deforolimus in combination with Bevacizumab in patients with advanced solid tumours

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Background: Deforolimus (DF) is a unique inhibitor of mammalian target of rapamycin (mTOR). One of mTOR's many functions is to regulate vascular endothelial growth factor (VEGF) secretion and VEGF receptor (VEGFR) signaling in endothelial target cells. Combination of bevacizumab (BV), a humanized monoclonal antibody that inhibits VEGF, with DF would be expected to diminish VEGF production and VEGFR signaling, and offer a promising therapeutic approach. The goal of the study was to identify an optimal phase 2 dose of DF combined with each of the two approved BV regimens.
Methods: Three dose combinations were tested in this phase 1, dose-escalation design in adult patients with advanced solid cancers (Clinical Trials ID: NCT00781846). The 3 dose combinations were: Cohort 1, DF 30 mg PO daily for 5 days/week (QD×5/wk) with BV 10 mg/kg IV every 2 weeks (4 wk cycles); Cohort 2a: DF 40 mg PO QD×5/wk and BV 10 mg/kg IV Q2 wks (4 wk cycles); and Cohort 2b: DF 40 mg PO QD×5/wk and BV 15 mg/kg IV Q3 wks (3 wk cycles). DLTs were protocol-defined events related to study drug that occurred during cycle 1.
Results: Seventeen patients (10F, 7M) were enrolled and treated; 16 were evaluable for DLTs (3 in Cohort 1; 6 in Cohort 2a; 7 in Cohort 2b). Median age was 60 years (range 24−72). Patients had 12 solid tumor types: 3 had ovarian carcinoma, 2 leiomyosarcoma, 2 pancreatic cancer, 2 colorectal carcinoma, 2 uterine carcinoma, and 6 had other distinct tumor types. No DLTs were noted in the 3 cohorts. One patient had 2 SAEs (G2 abdominal wall abscess and a G2 colonic fistula) related to BV per the investigator's assessment. Ten patients experienced treatment related AEs. The most common AEs were stomatitis, mucosal inflammation, neutropenia, thrombocytopenia, proteinuria, and headache. In this heavily pre-treated population, the median duration of treatment is currently 7 wks (range 2.3−24 wks). Six patients have discontinued treatment (4 for PD and 2 for unrelated SAEs) and 11 remain on treatment. Two patients have had stable disease for more than 4 months (1 patient with pancreatic cancer had a 13% reduction in tumor for more than 6 months and a patient with ovarian carcinoma that has been stable for 4+ months).
Conclusions: DF 40 mg QDx5/wk combined with two approved dosages and schedules (10 mg/kg q2 wks & 15 mg/kg q3 wks) of BV is feasible, well tolerated, and shows potential anti-tumor activity. The combination of DF/BV warrants further investigation in phase 2 trials.

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Retrospective analysis of unplanned hospital admissions: an early surrogate indicator of patient (pt) attrition in phase-I trials

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Background: We have previously reported a high Royal Marsden Hospital (RMH) prognostic score (RPS) of 2−3 predicts 90-day mortality and reduced overall survival (Arkenau et al BJC & EJC 2008). In this study, we explored the significance of unplanned hospital admissions (UHA) as a potential surrogate indicator of poor clinical outcome.
Methods: All pts admitted to RMH Phase I Unit, UK, during 2-month intervals over 3 consecutive years were included in this analysis (2005–2007). We collated pt baseline characteristics, demographic and laboratory profiles, reasons for hospital admissions and relevant clinical trial data.
Results: A total of 172 pts accounting for 310 admissions were seen on the Phase I unit during the stipulated time periods (amounting to 6 months in total). Median age: 61 years (range: 19−84); male to female admissions ratio 1.3:1. Pts were on trials of single-agent targeted therapies (69%), cytotoxic combinations (26%), vaccine/viruses (3%) and hormonal modulation (2%). Reasons for planned admissions (n = 246) included treatment commencement, PK/PD sampling, paired pre/post treatment biopsies and insertion of central lines. 20.6% (64/310) of overall admissions were unplanned: 50 (78%) were due to disease-associated symptoms/complications and 14 (22%) treatment-related toxicities (TRT). 71% of pts with TRT were on cytotoxic combination trials. Median duration of UHA was 2 days (range:1−20) and there was no relation between length of stay and predicted outcome. 78% of pts in the UHA cohort had a high RPS of 2−3 (i.e. poor outcome) vs 43% in patients whose admission was