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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].