Poster Discussions: Oral

New drugs – Phase I-Pharmacogenetics

53 POSTER DISCUSSION

A phase I study of escalating doses of CCI-779 in combination with 5-fluorouracil and leucovorin in patients with advanced solid tumors

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Purpose: CCI-779, a novel ester of rapamycin with a unique cytostatic mechanism of action, has shown antitumor activity preclinically and clinically without prolonged immunosuppressive effects when given intermittently. We report the preliminary clinical results of a phase I study with CCI-779 in combination with 5-FU/LV.

Methods: All drugs were administered once weekly IV for 6 weeks (wks) followed by 1 wk of rest: CCI-779 in 30 min (1st cycle starting in wk 2), followed by LV (200 mg/m2) in 1 hr, and 5-FU (2600 mg/m2)in 24 hrs. Pt characteristics: 28 patients (pts) enrolled, preliminary data available for 24 pts (16 male/8 female); median age 57 yrs (34 to 71). PS (ECOG): 0=17 pts, 1=6, 2=1. Prior chemotherapy (CTx): 6 pts; radiotherapy (Rx): 5; CTx+Rx: 4; surgery only: 6; none: 3. Tumor types: 8 colorectal carcinoma (ca), 4 gastric, 3 esophagus, 3 head & neck, 2 cholangio, 4 other.

Results: CCI-779 was administered at the dose levels of 15 (4 pts), 25 (3), 45 (15), and 75 (6) mg/m2. At 75 mg/m2 CCI-779, stomatitis (6/6 pts) requiring dose reductions and/or discontinuations and medical interventions, was dose-limiting. Thus, additional patients were investigated at 45 mg/m2. Of 11 pts for whom preliminary data are available at this dose, 2 toxic deaths (GI perforation) occurred as well as 15 Gr 3 in 9 pts and 4 Gr 4 toxicities (fatigue, dehydration, leucopenia, acute abdomen) in 1 pt, necessitating dose reductions and/or discontinuations in these pts. Various skin toxicities, eg. rash, folliculitis, pruritus, ulceration, and nail changes, as well as stomatitis and asthenia, represent the most prominent toxicities regardless of the dose level tested. Preliminary antitumor activity data showed as best response a CR in a colon ca pt at 15 mg/m2 CCI-779 in wk 42. Ten SD with a maximum duration of 12 months were observed. The median pt duration on study was 9.0 wks (2 to 52 wks).

Conclusion: Clinical efficacy was observed without a clear dose-response relationship, conceivably due to concomitant optimal 5-FU/LV dosing. The safety profiles at the 4 dose levels suggest an overlap of drug toxicities of CCI-779 and 5-FU/LV. The frequency and severity of toxicities and the number of necessary dose reductions and/or discontinuations even at the 45 mg/m2 dose level suggest a narrow therapeutic index for CCI-779 in combination with 5-FU/LV. In the future, other doses and regimens should be explored.

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A phase I trial of PKC412, an inhibitor of protein kinase C, in combination with bolus 5-Fluorouracil and leucovorin in patients with stage IV colorectal cancer

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PKC412, a N-benzoyl-staurosporine, is a derivate of the naturally occurring alkaloid staurosporine and an inhibitor of the protein kinase C (PKC) enzyme family. PKC412 affects deregulated signalling pathways in malignant cells and has antitumor acticity in vitro and in mouse xenografts and antiangiogenic effects.The primary objective of this study was to determine the MTD of PKC412 in combination with 5-Fluorouracil and leucovorin in patients with stage IV CRC and to assess the safety of the combination of PKC412 with 5-FU and leucovorin.

36 patients (median age 64 yrs, 24 m and 8 f) with previously untreated stage IV CRC were included, 33 patients are evaluable for safety and efficacy. 5 - FU (425 mg/m*) was administered on 5 consecutive days as a bolus, preceded by leucovorin (20 mg/m*). Cycles were repeated every 28 days. PKC412 was given p.o. daily starting with cycle 1 for a scheduled period of 6 cycles. Starting dose for PKC412 was 25 mg/day and was escalated in six cohorts to 225 mg/day based on the MCRM estimate of the MTD.

The mean duration of treatment was 3,5 cycles considering all dose levels. At all doses the most frequent reported adverse events were diarrhea, stomatitis/mucositis, nausea, vomiting, pain and headache. Gr 3/4 toxicities suspected to be due to the combination therapy were neutropenia (2 pts Gr 4, 3 pts Gr 3), diarrhea (4 pts Gr 3), stomatitis (2 pts Gr 3), renal/genitourinary complications (2 pts Gr 3), anorexia (1 pt Gr 3), nausea (1 pt Gr 3), vomiting (1 pt Gr 3) and fatigue (1 pt Gr 3). At 225 mg/day, 2 patients were withdrawn from the study due to emesis after first intakes of PKC412. Another patient reduced PKC412 dose from 225 to 150 mg/day after 9 days of treatment due to nausea and diarrhea. No death occurred during the study. DLTs reported were: grade 3 stomatitis/mucositis at 25 mg/day and 50 mg/day, and grade 4 neutropenia at 150 mg/day. The maximum tolerated dose in this population should be regarded as 150-225 mg/day.

Preliminary efficacy showed that among 33 pts, 5PRs, 9 SDs, 10 PDs were reported and 9 pts were not evaluable.

Pharmacokinetic data will be available for presentation at the meeting.

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Reliable use of Navelbine oral based on pharmacokinetic (PK) bioequivalence

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Oral chemotherapy should significantly improve patients' quality of life. However, depending on the oral bioavailability the required doses are generally different from i.v. to oral. Since oral administration often generates higher inter-individual variabilities than i.v., suitable pharmacokinetic (PK) dose equivalence may be difficult. Therapeutic use of an oral form should be facilitated if its PK behaviour is very close to the i.v. form and if a reliable dose correspondence exists between both forms.

To compare the PK characteristics of Navelbine oral with Navelbine i.v. a bioequivalence analysis of the blood exposure delivered by each form was carried out. Such a statistical analysis, defined by international regulations, is usually aimed at comparing two pharmaceutical forms and therefore to accurately demonstrate that they have the same PK properties and the same degree of variability on PK parameters of parent compound.

To be bioequivalent, PK parameters of two pharmaceutical forms must present no statistical differences in their mean value and the variability expressed as confidence interval around the mean value must be similar and within the range [0.8 - 1.25] defined in regulatory guidelines.

Through an absolute bioavailability study on 24 patients (any solid tumour) receiving Navelbine oral and Navelbine i.v. in a cross-over design, a bioequivalence analysis was performed by comparing doses at 60 mg/m2 oral versus 25 mg/m2 i.v. and 80 mg/m2 oral versus 30 mg/m2 i.v. The demonstration of Navelbine PK linearity has enabled the comparison at different dose levels. No significant statistical differences were observed in the respective blood exposures. Moreover, the respective confidence intervals [0.87-1.09] and [0.97-1.21] were within the required regulatory range [0.8-1.25], which demonstrated a bioequivalence of blood exposure between oral and i.v. doses.

It was also demonstrated that the haematotoxicity, the main dose limiting toxicity (DLT) of Navelbine, was strongly correlated to blood exposure and therefore showing a pharmacokinetic/pharmacodynamic relationship independent of the administration route.

In conclusion, the equivalence of blood exposure that was demonstrated according to strict criteria of bioequivalence clearly establishes the reliable