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Current phase II data for ZD0473 in patients with mesothelioma who had relapsed following one prior chemotherapy regimen

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Aims: To examine the tolerability and efficacy of ZD0473, a new generation platinum drug, in patients with mesothelioma who have relapsed after prior chemotherapy.

Methods: Patients were administered ZD0473 by 1-h iv infusion on day 1, at a dose of 120-150 mg/m2, given every 3 weeks, in this Phase II, open-label, multicentre trial.

Results: At this interim analysis, 41 patients had been recruited for the study (F:M [5:36 patients]; performance status 0-1 [31] and 2 [10]; median age 59 years [range 37-75]). In total, 34 patients had received prior cisplatin or carboplatin therapy, the other 7 patients had mainly received either cyclophosphamide or mitomycin C. Time since last treatment was 0-3 months (9 patients), 3-6 months (11), 6-12 months (10), >12 months (4). To date, 91 treatment cycles have been completed (median 2 cycles per patient, [range 1-6]); 6 patients received ~4 cycles. Four patients required treatment delay due to toxicity, only one patient had a delay of ~7 days. Toxicities were experienced by all patients, but were mostly mild in intensity. The most commonly occurring haematological toxicity was grade 3 or 4 (Common Toxicity Criteria) thrombocytopenia (grade 3 [6 patients]; grade 4 [5]). The most common non-haematological events were dyspnoea (grade 3 [7]; grade 4 [3]) and chest pain (grade 3 [6]), irrespective of causality. Overall, 25 patients were evaluated for tumour outcome and 14 had stable disease (including evidence of tumour shrinkage in 3 patients). An improvement in WHO performance status score was observed in four individuals.

Conclusion: The toxicity was manageable and the antitumour activity was mainly seen in terms of disease stabilisation. Continued follow up for response and time to progression is ongoing.

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In vitro schedule dependency in the formation of topoisomerase I and II inhibitor and DNA cleavable complexes

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Topoisomerase targeting chemotherapy is an excellent strategy in lung cancer treatment. We studied that cytotoxic effects of combination use of topoisomerase I inhibitor SN-38 and topoisomerase II inhibitor etoposide (VP-16) were evaluated against the non-small cell lung cancer cell line, Ma-1 and small cell lung cancer cell line, SBC-3 using MTT assay and isobologram analysis. For the mechanism of time dependent antitumor activities, we investigated cleavable complexes of topoiosmerase I and II to DNA using in vivo immunodetection assay. The cells were concurrently or sequentially exposed to drugs for 30 minutes, 2 hours and 24 hours with a total culture time of 7 days. The IC50s in 24 hours exposures for SN-38 and VP-16 were 6325 nM and 54.1μM for in Ma-1 cells, respectively. In SBC-3 cells, the IC50s for SN-38 and VP-16 were 1.36 nM and 0.25μM, respectively. In Ma-1 cells, the short time simultaneous and sequential exposure of VP-16 followed by SN-38 showed antagonistic interaction. However, the long time simultaneous exposure, VP-16 followed by SN-38, and all schedules of SN-38 followed by VP-16 were synergistic interaction. In SBC-3 cells, all schedules showed synergistic interaction. Regarding the cleavable complex, both drugs formed the cleavable complex each other within 30 minutes. In VP-16 exposures, the cleavable complex stabilized along 24 hours. However, the cleavable complex dissociated in 6-8 hours with SN-38 continuous administration along 24 hours. The combination of SN-38 and VP-16 also observed this phenomenon in 24 hours exposure. After drugs washed out with various concentrations and times, the cleavable complex dissociated within 2 hours. These findings suggest that SN-38 preceding VP-16 regimen may be the most favoring regimen, because topoisomerase I to DNA complex was dissociated before VP-16 was administered. Furthermore, prolonged simultaneous exposure may be obtained similar effects. Our results may provide a rationale for the design of administration combining topoisomerase I and II inhibitors.

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Interleukin-2 in combination with tamoxifen in malignant pleural mesothelioma

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Purpose: Malignant pleural mesothelioma is a rare disease, closely associated to asbest exposure. The naturally chemoresistant tumor has a median survival ranging from 4 to 18 month. In vitro experiments and phase I/II trials with intrapleural Interleukin-2 (IL-2) have shown promising results assumed to be based on natural killer cell mediated immunity.

Methods: We treated outpatient based 25 malignant pleural mesotheliomas in our department, with IL-2 in parallel with Tamoxifen (TAM). Patients received 120mg TAM daily (day 1-7) and 6 Mio. IU IL-2 subcutaneously (day 4-7) every two weeks. Patients were instructed in selfadministration at home and follow up was performed in the outpatient department every 2 month. The patients characteristics: 22 male and 3 female patients; 9 patients in 1st-, 5 in 2nd-, 6 in 3rd-, 5 in more than 3-lines of treatment. In 17 patients we determined occupational disease with asbest exposure. The median age was 57 years. At onset of IL-2 and TAM therapy 2 patients were Butchart stage I, 16 stage II, 5 stage III and 2 stage IV. Relapsing patients received cytostatic treatment, or palliative irradiation.

Results: The median survival is 15,1 month. 19 patients died (5,3 to 92,6 month) while 6 patients are still alive (14.1 to 102.2 month), 2 of them in an objective response, 3 in stable disease. From all 25 patients 3 had a partial response, 7 stable disease, and 15 progressed under therapy. Toxicty was acceptable with local skin rash. As the patients administered IL-2 in the evening, flue-like symptoms were (during sleep) without detrement to patients.

Conclusion: IL-2 combined with TAM offers an additional chance in the outpatient treatment of malignant mesothelioma. Prospective multicenter trials have to verify these results.

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Varying CD97 expression in lung carcinomas and tumour cell lines

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Expression of CD97, a leukocyte differentiation antigen and member of the EGF/TM7 superfamily, has been shown to correlate with the stage of differentiation and metastasis in thyroid carcinomas. The molecule shows structural homology with adhesion molecules, and may thus also be involved in invasive growth and metastasis of other tumours.

First, 5 lung carcinoma cell lines were examined for CD97 expression by FACS analysis. The NCI-H82 and NCI-H69 cell lines of the small-cell lung carcinoma (SCLC) showed no CD97 expression, whereas all non-SCLC (NSCLC) cell lines (A 549, LCLC 103, EPLC 272) were CD97+. The results were confirmed at the mRNA level.

Second, 44 NSCLC of various histophenotypes and their corresponding normal tissues and 10 SCLC were examined for CD97 by immunohistology. Two different CD97 monoclonal antibodies (mab) were used: CD97EGF detects an epitope at the first EGF-like domain of the molecule, whereas CD97stalk binds to the stalk region right before the transmembrane region. An immunoreactive score was set up based on the method devised by Remmele (RS 0-12) and a correlation with the clinical data of the patients was sought. Soluble CD97 (sCD97) was preoperatively determined in the sera of the patients by ELISA.

CD97EGF was only detected at low levels in 10/44 (mean ± SEM; RS 2.3 ± 0.2) NSCLC. We found a different distribution within the various histophenotypes with a tendency towards adenocarcinoma being more than squamous lung cell carcinoma. The corresponding normal bronchiolar epithelium was completely CD97EGF-. In contrast, the CD97stalk epitope was found in 32/44 (RS 5.4 ± 0.5) NSCLC. Scattered cells within one tumour (11/44) were more strongly positive for CD97stalk (RS 7.6 ± 0.8) compared to those grown in tumour cell formations. In a third of all cases, basal cells of the normal bronchiolar epithelium showed a strong staining for CD97stalk, whereas the upper cells were CD97stalk-. The biopsies of SCLC were CD97- for both epitopes, only 1/10 showed a weak staining for CD97stalk. Tumour stage (AJCC) and preoperatively determined sCD97, CYFRA21-1, SCC, CEA and CA19-9 in the sera of the patients showed no correlation with the expression of CD97 in the tumours.