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Treatment with a combination of mMAb17-1A, GM-CSF, alpha-Interferon and 5-Fluorouracil of patients with advanced colorectal carcinoma (CRC).

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Background: The mouse monoclonal antibody MAb 17-1A (IgG) recognizes the tumor associated antigen CO17-1A/ GA 733-3/Ep-CAM, which is abundantly expressed in CRC. The clinical effect of MAb17-1A alone in advanced CRC is modest. Combination with cytokines, as granulocyte/macrophage-colony-stimulating-factor (GM-CSF), improved significantly the clinical response, with some remarkable long-lasting complete remissions. Chemotherapeutics such as 5-fluorouracil (5-FU) can serve as immunomodulating agents. Based on previous clinical studies and on a preclinical animal model, we have conducted this phase II study in patients (pts) with advanced CRC.

Material and methods: Twenty-seven pts were included were treated with the following regimen: Recombinant human α -interferon (α -IFN)(3 X 10^6 IU) was given subcutaneously (s.c.) once daily day 1 through 5. 5-FU (500 mg/m^2) was administered as a daily intravenous (i.v.) bolus injection on days 4 and 5. Two days' rest was followed by GM-CSF (200 μ g/m^2 /day) s.c. once daily day 8 through 14. MAb17-1A (400 mg) was given as a single infusion on day 10. The treatment was repeated every 4th week until disease progression.

Results: Twenty-six of 27 pts were evaluable for response. 54% (14/26) (1 PR, 2 MR, 11 SD) had a clinical response. The median progression-free survival (PFS) and overall survival (OS) were 3.2 months (range 1-17 months) and 17.5 months (range 1-38.5 months), respectively, from start of MAb 17-1A therapy. Each pts received a median of 4 cycles (range 1-9 cycles). The total number of treatment cycles were 119. Treatment was well tolerated with no grade IV toxicity. There was a tendency to reduced frequency of side-effects related to the administrations of cytokines by increasing number of treatment cycles. Allergic reactions to MAb 17-1A increased by each treatment cycle but could significantly be reduced by lowering the MAb dose and increasing the infusion time. The intended full dose of MAb 17-1A had to be reduced at 71% of the infusions.

Conclusion: This phase II study was the 10th consecutive treatment protocols conducted and evaluated by the same group of clinicians evaluating the therapeutic effect of MAb17-1A in pts with advanced CRC. In the present study, the addition of 5-Fu, GM-CSF and α -IFN to MAb17-1A therapy seemed to augment the clinical effect of MAb17-1A in pts with advanced CRC. Compared to MAb17-1A therapy alone the clinical response rate increased from 15% to 54%. The majority of the responses was SD > 3 months. Furthermore, PFS was significantly improved from 1.5 months to 3.5 months. Based on the adjuvant studies using Panorex where this anti-EpCAM MAb seemed to have a clinical effect by itself, with an antitumor mechanism differ from conventional chemotherapeutics and on the results of the present study, it might be suggested to incorporate anti-EpCAM antibodies into current treatment protocols in pts with metastatic CRC.

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Serial monitoring of serum HER-2 extracellular domain (H-ECD) during herceptin-taxol chemotherapy (CT) for metastatic breast cancer (MBC) pts: preliminary results from the French experience (HER.ME.S protocol).

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Rationale: The H-ECD level is increased in the sera of pts with overexpressed MBC. Circulating levels of the H-ECD have been reported to be predict for response to CT. Study: The French protocol HER.ME.S is a phase IV, pharmaco-economic, on-line study in which we were interested to determine whether serum levels of H-ECD (Oncogene Science -Bayer Diagnostics-Elisa kit) would predict the course of disease in HER-2+ MBC pts. 180 HER-2+ MBC pts are planned to be treated in the HER.ME.S protocol with a combination of Taxol (175 mg/m2/3w or 80 mg/m2/w, 6 weeks/8) + Herceptin (4 mg/kg on week 1, followed by 2 mg/kg/w) or Herceptin alone, until progression or unacceptable toxicity. Since 09/01, 72 pts have been screened for HER-2 status; 35 of them were HER-2+. The H-ECD levels were determined during the following periods: pre-inclusion, inclusion (day 0), then days 28, 56, 84, 102 and 120 for HER-2+ pts. Evaluation of the disease was performed according to the RECIST criteria every 2 months until withdrawn of the study.

Results: Results are available today for all the 72 screened pts and the first 30 included pts. At the time of pre-inclusion, the median level of H-ECD for the 72 pts was 105 ng/ml (7-1500). Forty-eight pts (90% of them being HER-2+) were determined above 15 ng/ml (level generally considered as the cut-off value between normal pts and MBC pts). For the first 30 included pts, the median H-ECD level was 156 ng/ml (7-1500). For 16 pts with low metastatic spread (< 3 metastatic sites), the mean H-ECD level was 27 ng/ml (11 - 63). For 14 pts with high metastatic spread (3 or more metastatic sites), the mean H-ECD level was 297 ng/ml (7 - 1500). Nineteen pts were evaluated after one month of treatment: 53% responded, 37% were stable and 10% progressed. No progressive pts had a decrease in H-ECD level; among stable pts, the mean decrease of H-ECD level was 10% (-135% to 41%); no responder pts had an increase in H-ECD level and the mean decrease was 44% (6% - 89%).

Conclusion: ratio of H-ECD variation (initiation vs one month determination) seems to be an early predictive response factor.

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Human phase II/A study of a novel somatostatin analogue, TT-232 in malignant melanoma patients

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TT-232, a novel somatostatin analogue, with a five residue ring structure (D-Phe-Cys-Tyr-D-Trp-Lys-Cys-Thr-NH_2) has shown a strong antitumor effect both in vitro and vivo. TT-232 has practically no growth hormone release inhibitory activity and it is a potent inducer of apoptosis. It seems to act via shortterm induction of tyrosine phosphatase and inhibition tyrosine kinase.

Patients (pts) with histologically proven advance stage malignant melanoma had been treated with 480 μg/kg TT-232. daily 4-hour infusion on the following days 1-7, 15-21. The next cycle has been started on day 29.

Between August 2001 and September 2002 twelve patients (male:6, female:6) were enrolled in the study. The median age was 52 yrs. (rage 27-72). The primary tumor localization was the following: trunk:7, head:1, ocular:1, upper extremity:1, lower extremity:2. All pts had previous surgery, 8 had radiotherapy, all received chemotherapy and 11 had immunotherapy.

Altogether 49 cycles had been given (range 2-8, median 4). One patient had partial remission (lymph nodes) and 3 pts had stable disease (hepatic, mediastinal, rertoperitoneal lymph nodes and pulmonary metastases).

Out of 343 days of treatment fever (gr.1-2) has been observed on 8 days. No other toxicity occurred.

Serum level of TT-232 has been measured with an enzyme immunoassay (ELISA) method. Blood samples were taken on day 1 at 0,2.4,8 hours. The free peptide concentration has raised during the first 2 hours. At 8 hours approx. 25% of the max. serum level was still present.

TT-232 seems to be a promising new agent in the treatment of malignant melanoma with no obvious toxicity.

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Positive correlation between expression of vascular endothelial growth factor (VEGF) and highest microvascular density in esophageal carcinoma

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Purpose: The prognosis and the characteristics are different according to the individual tumor in esophageal carcinoma. It has been suggested that the prognosis of macroscopically infiltrative type of esophageal carcinoma is worse than that of the localized type even if clinical stage was same. The aim of this study was to determine the cause of unfavorable prognosis in