to be an acceptable alternative to infusional 5-FU/LV in combination therapy. Updated results including data on second-line treatment will be presented at the meeting.

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Microarray expression analysis indicates a central role for matrix-metalloproteinases MMP-1, MMP-3, MMP-9 and TIMP-3 in the metastatic process of colorectal carcinomas

W.M. Brueckl[1], I. Zeittraeger[1], R.S. Croner[2], A. Jung[3], T. Papadopolous[3], T. Kirchner[3], E.G. Hahn[1], W. Hohenberger[2], A. Wein[1]. *[1]Dept. of Internal Medicine I, [2]Dept. of Surgery, [3]Dept of Pathology, Erlangen, Friedrich-Alexander-University Erlangen-Nuremberg, Germany*

Background/Aims: To date, the molecular basis of the metastatic process is understood only by part. However, the family of matrix-metalloproteinases seems to be involved due to their ability to degrade the extracellular matrix, to induce angiogenesis and to influence apoptosis. In this study the gene expression profile of colorectal carcinomas and their corresponding liver metastases were analysed using gene-expression microarrays to get a deeper view of the genes and pathways involved in metastasis.

Material/Methods: After written informed consent tumour material from nine colorectal primaries and biopsies from the corresponding liver metastases were taken intraoperatively and immediately snap-frozen in liquid nitrogen. The tissues were laser-microdissected, amplified and hybridised to Affymetrix U-133A microarrays according to the manufacturers instructions. 18 gene expression datasets comprising 22,283 human genes and ESTs each were analysed for statistic significance between colorectal carcinomas and liver metastases Results were verified by RT-PCR.

Results: The gene-expression for MMP-1, MMP-3, MMP-9 and TIMP-3 was statistically significant increased in colorectal carcinomas in contrast to liver metastases. Additionally changes in gene expression could be detected for collagens I, III, V, X, laminin, heparansulfate, transmembrane-4 family members and tetraspan. Furthermore, expression changes were obvious for genes involved in angiogenesis, e.g. the endothelin receptor or the plasminogen activator. The increased expression of MMP regulatory genes (CDC42, RAS and FOS) confirm the hypothesis for the involvement by this pathway.

Conclusions: Using genome-wide gene expression analysis we could show a central role for MMP-1, MMP-3, MMP-9 and TIMP-3 in the metastatic process in vivo. Further potential candidates with significant expression differences between primary and metastatic tumours are profen for relevance at present.

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Preliminary phase I results of the oral, once-daily angiogenesis inhibitor PTK787/ZK 222584 (PTK/ZK) in combination with chemotherapy for the treatment of metastatic colorectal cancer

T. Trarbach[1], A.L. Thomas[2], C. Bartel[3], U. Vanhoefer[1], W.P. Steward[2], B. Wiedenmann[3], M. Kowalski[4], U. Riedel[5], D. Reitsma[4], D. Laurent[5]. *[1]University of Essen Medical School, Department of Internal Medicine/Hematology and Onc, Essen, Germany; [2]Leicester Royal Infirmary, Leicester, United Kingdom; [3]Humboldt-Universität zu Berlin, Charité, CVK, Germany; [4]Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States of Amercia; [5]Schering AG, Berlin, Germany*

Background: PTK/ZK is a novel, oral angiogenesis inhibitor that potently inhibits the vascular endothelial growth factor receptor-1 and -2 tyrosine kinases, important receptors contributing to new blood vessel formation during tumor growth and metastasis. Daily administration of PTK/ZK, alone and in combination with chemotherapy, has been generally well tolerated in more than 450 patients, and PTK/ZK significantly reduced tumor blood supply with associated significant reductions in the size of colorectal cancer liver metastases.

Material and Methods: This study assessed safety and preliminary efficacy of PTK/ZK in combination with 2 different chemotherapy regimens. Previously untreated patients with measurable, advanced-stage colorectal cancer were treated with oral PTK/ZK plus either oxaliplatin/5-fluorouracil (5-FU)/leucovorin (FOLFOX4) or irinotecan/5-FU/leucovorin (FOLFIRI) in a phase I/II, dose-escalation study. PTK/ZK was administered at doses ranging from 500 to 2,000 mg/day. Oxaliplatin (85 mg/m^2) or irinotecan (180 mg/m^2) was administered on day 1, and leucovorin (200 mg/m^2 via 2-hour infusion) and 5-FU (400 mg/m^2 bolus followed by 600 mg/m^2 via 22-hour infusion) were administered on days 1 and 2 every 2 weeks. Tumor response was assessed every 12 weeks.

Results: To date, 35 patients have been treated with PTK/ZK plus FOLFOX4, and 16 patients have received PTK/ZK plus FOLFIRI. Both combinations were generally well tolerated. In the FOLFOX4 arm, lightheadedness and dizziness were dose limiting at 2,000 mg/day PTK/ZK; the maximum tolerated dose has not yet been reached in the FOLFIRI arm (with dosing currently at 1,250 mg). Preliminary results suggest that PTK/ZK did not affect the safety profile of either chemotherapy regimen or alter the pharmacokinetics of oxaliplatin. Among 21 evaluable patients treated with PTK/ZK + FOLFOX4, 9 (43%) had a partial response (PR), 8 (38%) had stable disease, and 4 (19%) had progressive disease. For 29 patients to date, median time to progression is 10.8 months (95% CI, 6.9-13.4 months). Among 9 evaluable patients treated with PTK/ZK + FOLFIRI, 4 (44%) had a PR and 5 (56%) had stable disease.

Conclusions: These preliminary results suggest that PTK/ZK combined with FOLFOX4 and FOLFIRI is feasible and well tolerated. The results are promising, particularly with regard to time to progression, and patients continue to be accrued to this trial.

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Comparison between radiotherapy and neoadjuvant chemotherapy and radiotherapy in a population based series of epidermoid anal carcinomas

P.J. Nilsson[1], C. Svensson[2], S. Goldman[1], O. Ljungqvist[1], B. Glimelius[3]. *[1]Ersta Hospital, Centre of Gastrointestinal Disease, Stockholm, Sweden; [2]Huddinge University Hospital, Dept. of Oncology, Stockholm, Sweden; [3]Karolinska, Dept. of Oncology and Pathology, Stockholm, Sweden*

Background: Primary treatment of epidermoid anal cancer is radiotherapy (RT) alone, or in combination with chemotherapy. Radical surgery is reserved for poor responders or recurrences. The use of concomitant chemoradiotherapy as well as neoadjuvant chemotherapy followed by RT has been reported in the literature. This study presents results from a large population-based material and provides comparison between different treatments.

Material and methods: Between 1985 and 2000, 308 patients with invasive epidermoid anal cancer were diagnosed in the Stockholm Health Care Region. All patients were prospectively recorded. Treatment was given according to defined protocols. Between 1985 and 1991 RT+/-concomitant bleomycin was used for all tumours. Between 1989 and 2000 patients with locally advanced tumours (T>4 cm or N+) received neoadjuvant platinum based chemotherapy followed by RT, whereas smaller lesions were treated with RT alone.

Results: Among the 276 patients (90%) who were treated with curative intent, 264 (96%) received treatment in accordance with the protocols. Among 142 patients with locally advanced tumours treated with either RT+/-concomitant bleomycin (n=51) or neoadjuvant platinum based chemotherapy and RT (n=91), the complete response rate (CR) was 87%. Patients receiving neoadjuvant chemotherapy had a significantly higher CR-rate compared to those treated with RT+/-bleomycin (92 vs. 76%, p<0.01). The overall 5-year survival rate among patients with locally advanced tumours was 59%. A significantly higher 5-year survival rate was found in the neoadjuvant group (63 vs. 44%, p<0.05). Isolated locoregional failures, either as residual tumour after completion of therapy or as recurrences, occurred significantly more frequent among patients receiving RT+/-bleomycin (31 vs. 14%, p<0.05). Multivariate analyses revealed treatment as an independent prognostic factor.

Conclusions: The results suggest that neoadjuvant platinum based chemotherapy and RT is superior to RT alone or with bleomycin in the treatment of locally advanced cases of epidermoid anal cancer. For confirmation of superiority to the present reference regimen, being RT with concomitant 5-FU and mitomycin C (or cisplatinum), a randomised trial is needed.

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Screening for single nucleotide polymorphism (snp) in association with sporadic colorectal cancer.

N. Tørring, K. Bihl, T. Ørntoft. *Molecular Diagnostics Laboratory, Department of Clinical Biochemistry, Aarhus University Hospital-Skejby Sygehus, Aarhus, Denmark*

Background: The cumulative life time risk of developing sporadic colorectal cancer (CRC) in the Western Europe is approximately 6%. A first-degree relative to patients with sporadic CRC is twice as likely to develop the disease. We believe that single nucleotide polymorphism (SNP) may be important for susceptibility for disease development. However screening of