**Results:** With excellent spatial and temporal resolution dynamic T1 mapping revealed distinct Gd-DTPA accumulation level changes within the tumor during radiation. The perfusion index (Pi) of Gd-DTPA versus radiation dose showed a significant increase in the first or second week of treatment, then either returned slowly to the pretreatment level or rose again after an intermediate drop. The average Pi- value at the beginning was 0.16 (±0.054) and at the highest level was 0.23 (±0.06). In all groups the rise from the Pi-maximum was statistically significant, revealing an increase within a range of 8.06% to 82.55%.

**Conclusion:** The ultrafast T1 mapping MR-technique described here proved to be a practicable tool for monitoring tumor microcirculation during therapy and offers the potential for customized optimization of therapeutical procedures.

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## Disseminated tumor cells detected by CK 20 RT-PCR in the blood and the bone marrow of patients with colorectal carcinoma represent an independent prognostic factor

I. Vogel, E. Soeth, C. Röder, B. Kremer, H. Kalthoff, D. Henne-Bruns. *University of Kiel, Dep. of Surgery, Kiel, Germany*

**Purpose:** The prognostic impact of the detection of disseminated tumor cells by molecular technics in patients with gastrointestinal carcinoma is so far not proven. The aim of our study was to evaluate the prognostic impact of the detection in bone marrow and blood by CK 20 RT-PCR in patients with colorectal carcinoma.

**Methods:** Bone marrow and venous blood samples of 170 patients with colorectal carcinoma were taken preoperatively. A multivariate analysis to detect independent prognostic factors was performed in 122 patients with curative resection (R0) (Cox regression model).

**Results:** Univariate analysis revealed the lymph node status ($P = 0.0127$) and the detection of tumor cells in the bone marrow ($P = 0.0081$) and in venous blood ($P = 0.0024$) as prognostic factors. The detection of cells in the bone marrow ($P = 0.0405$) as well in the venous blood ($p = 0.0072$) and the combination of both compartments (venous blood and/or bone marrow ($p = 0.0131$)) showed a significance influence on survival in multivariate analysis.

**Conclusion:** The detection of disseminated tumor cells by CK 20 RT-PCR in bone marrow and/or venous blood of patients with colorectal carcinoma is an independent prognostic factor and should therefore lead to randomized studies with adjuvant treatment modalities in positively tested patients.

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## Phase III trial of 5-fluorouracil (5FU) and leucovorin (LV) with or without trimetrexate (TMTX) as first line treatment in advanced colorectal cancer (ACC)

C.J.A. Punt[1], H.J. Keizer, J. Douma, J. Schüller, T. Skovsgaard, C.H.H. ten Napel, H. Lochs, E.W. Muller, L. Russell[2], D.J.T. Wagener[1]. *Dept. of Medical Oncology, University HospitalNijmegen, Netherlands; [2]USBioscience, United States*

**Purpose:** In phase II studies TMTX, a non-classical antifolate, plus 5FU/LV has shown promising response rates but a high incidence of severe diarrhea in untreated ACC patients (pts).

**Methods:** 364 pts were randomized between LV 200 mg/m$^2$ in 1 h i.v. and 5FU 600 mg/m$^2$ bolus i.v. (*arm A*) or TMTX 110 mg/m$^2$ in 1 h i.v. followed after 24 h by LV 200 mg/m$^2$ in 1 h i.v. and 5FU 500 mg/m$^2$ bolus i.v. and LV 7 × 15 mg orally q 6 h starting 6 h after 5FU (*arm B*). Treatment was given weekly x6, q8 wks (one cycle) for a maximum of one year. Primary endpoint was progression free survival (PFS), secondary endpoints were overall survival (OS), response rate, toxicity and quality of life. Eligibility criteria included untreated ACC (adj. therapy with ≥1 yr interval allowed), WHO PS ≤ 2, age ≥ 18 yrs.

**Results:** A planned interim analysis was performed on toxicity and PFS in the first 222 pts entered prior to may '98. Pts characteristics were not significantly (NS) different between arm A (110 pts, 186 cycles) and B (112 pts, 233 cycles). Diarrhea was the major toxicity but occurred less frequently as reported previously due to strict guidelines: grade 3/4 in arm A 25% vs. in arm B 15% (NS). Other grade 3/4 toxicities occurred <10% in both arms. Median PFS was borderline significant (p 0.053) in favor of pts treated with TMTX (3.9 vs.5.3 months).

**Conclusion:** These promising results will be updated together with an analysis on OS in april '99 when the median follow-up will be 17 months. The results will be presented at the meeting.

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## Irinotecan (Iri) in combination with high-dose infusional (HDI) 5FU/FA either weekly or bi-weekly: Evidence of survival advantage and quality of life (QoL) improvement in metastatic colorectal cancer (MCRC)

P. Rougier, D. Cunningham, A.D. Roth, J.R. Germa, R.D. James, P. Karasek, P. Jandik, T. Iveson, J. Carmichael, G. Gruia, M. Alakl, D. Sibaud, J.Y. Douillard. *A. Paré, Boulogne, France; Royal Marsden Hosp. London, United Kingdom; Hosp. Cantonal Geneve, Switzerland; Hosp. Durant y Reynals, Barcelona, Spain; Christie Hosp. Manchester, United Kingdom; Inst. of Oncol. Brno; Univ. Hosp. H. Kralove, Czech Republic; Royal S. Hants Hosp., Southampton; City Hosp., Nottingham, United Kingdom; Rhone Poulenc Rorer, Centre R Gauducheau, St-Herblain, France*

Single agent IRI has been shown to be active in MCRC with significant survival advantage over best supportive care or best 5FU schedule in patients with prior 5FU failure (Lancet, 1998). As of Feb. 1998, 387 pts were randomized to receive (A): combination of IRI at 180 mg/m$^2$ day (d) 1 and 5FU 400 mg/m$^2$ as IV bolus followed by 600 mg/m$^2$/d as a 22 hours (h) continuous infusion (c.i.) + FA on d1–d2 repeated every 2 weeks (wks) or IRI at 80 mg/m$^2$ and 5FU 2.3 g/m$^2$ as a 24-h c.i. + FA weekly × 6 every 7 wks, *versus (vs)* (B): the same regimen of 5FU/FA alone. The main pts characteristics are comparable between groups A (199 pts) and B (188 pts): median age 62 *vs* 59, primary colon/rectum 55/45 *vs* 65/35, performance status 0 52% *vs* 51%, prior adjuvant CT, 26% *vs* 24%, number of organs ≥2 38% *vs* 37%, respectively.

**Efficacy:** group A *vs* B: response rate (RR) 41% *vs* 23% ($p < 0.001$) time to progression (TTP) 6.7 months (m) *vs* 4.4 m ($p < 0.001$) survival 16.8 m *vs* 14.0 m ($p = 0.029$).

**Safety:** The main NCI grade 3/4 adverse events by pts in group A *vs* B are: neutropenia 42% *vs* 11%, diarrhea 22% *vs* 10%; other toxicities were <5% and comparable in both groups.

**QOL:** A better QoL in favor of A was maintained during chemotherapy. Iri in combination with HDI 5FU/FA show a significantly better RR, TTP and survival along with at least an equivalent QoL, as compared to HDI FU/FA alone in pts with MCRC.

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## Medical resource use in a phase III trial (SO 14796) of XelodaTM (capecitabine) in previously untreated advanced/metastatic colorectal cancer

C. Twelves[1], E. Van Cutsem[2], K. Hieke[3], C. Barker[4], C. Jamieson[4], J. Hornberger[4], L. Garrison[4], B. Osterwalder[3], A. Thibault[5]. *[1]Beatson Cancer Center, Western Infirmary, Glasgow, United Kingdom; [2]University Hospital Gasthuisberg, Gastroenterologie, Leuven, Belgium; [3]F. Hoffmann-La Roche, Basel, Switzerland; [4]F. Hoffmann-La Roche, Palo Alto; [5]F. Hoffmann-La Roche, Nutley, United States*

**Introduction:** XELODA(TM) (capecitabine) is a novel, orally administered, tumor-activated fluoropyrimidine carbamate. A randomized phase III clinical trial comparing XELODA (TM) (2500 mg/m$^2$/d × 14 d, q3 weeks, n = 301) vs. Mayo regimen (5-FU 425 mg/m$^2$; LCV 20 mg/m$^2$ d1-5, q4 weeks, n = 301) resulted in a higher response rate (26.6% vs. 17.9%, p = 0.013), and similar duration of response (7.3 vs 9.6 months) and progression-free survival (5.3 vs 4.8 months). The most remarkable differences in adverse events (AEs) were lower rates for XELODA (TM) patients requiring treatment for stomatitis, vomiting, and diarrhea and a higher rate of hand-foot syndrome (HFS).

**Methods:** Patients were recruited from 66 centers in 8 EU-countries, Australia, Russia, Israel and Taiwan. Data on hospital use, IV administration visits, AEs requiring medications or procedures, and all physician encounters were collected alongside the clinical trial for all randomized patients and analyzed.

**Results:** Administration of the Mayo regimen requires 5 visits per monthly cycle for IV administration of 5-FU and LCV. Data were available on 94% (=6,092) of the IV administration visits on the Mayo regimen. 336 of these administrations lasted >24 hours, implying overnight hospitalization for drug administration. 5,718 visits were <8 hours, and 38 visits lasted 8–23 hours. Patients receiving XELODA (TM) required one outpatient visit at the beginning of each cycle and no further visits for drug administration. Total days in hospital for the following AEs – stomatitis/mucosal inflammation, hand-foot syndrome, neutropenia, pyrexia, infections, diarrhea, nausea, and vomiting – was reduced by 184 hospital days (370 vs. 186, −50%) in the XELODA (TM) arm. For these AEs, the use of cephalosporins, quinolones, fluconazole and 5HT3-antagonists was consistently lower (−16%, −39%,