This difference in the time patterns of recurrence and impact of AT may ultimately explain why MMR is predictive of AT benefit.

6010 ORAL

A three-arm phase III randomized trial of FOLFOX-4 vs. FOLFOX-4 plus bevacizumab vs. XELOX plus bevacizumab in the adjuvant treatment of patients with stage III or high-risk stage II colon cancer: results of the interim safety analysis of the AVANT trial

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Background: Bevacizumab (Bev) and capecitabine (Cap) are established drugs for patients (pts) with metastatic colorectal cancer (mCRC). The AVANT trial is evaluating the efficacy and safety of Bev in combination with either intermittent Cap plus oxaliplatin (XELOX+Bev) or fluorouracil/leucovorin with oxaliplatin (FOLFOX-4+Bev) vs. FOLFOX-4 in the adjuvant treatment of pts with stage III or high-risk stage II colon cancer.
Materials and Methods: Pts were randomized to receive 12 cycles (q2 weeks) of FOLFOX-4 (Arm A), 12 cycles (q2 weeks) of FOLFOX-4+Bev (Arm B) or 8 cycles (q3 weeks) of XELOX+Bev (Arm C) followed by a further 8 cycles (q3 weeks) of Bev in Arms B and C (1 year of total Bev duration). Primary objective is to show superiority of Arm B or Arm C vs. Arm A in pts with stage III colon cancer in terms of disease-free survival (DFS). An interim safety analysis was planned 6 months after the last randomized pt ended treatment.
Results: Between December 2004 and June 2007, 3451 pts were randomized (stage III/high-risk stage II: 2867/573). Arm A, 955/192; Arm B, 960/194; Arm C, 952/187. Treatment arms were well balanced for disease stage, age, ECOG status and ethnicity. Median duration of oxaliplatin-containing chemotherapy was 5.3, 5.2 and 4.9 months, respectively, and median duration of Bev treatment was 10.6 months (Arm B) and 10.4 months (Arm C). Main toxicities of interest for Bev are shown in the table. All-cause mortality within 60 days of treatment start was 2 (0.2%) pts in Arm A, 4 (0.3%) in Arm B and 6 (0.5%) in Arm C. Number of deaths not due to colon cancer within 28 days after last drug administration were: Arm A, 8 (0.7%); Arm B, 4 (0.3%); Arm C, 10 (0.9%).
Conclusions: Bev plus fluoropyrimidine/oxaliplatin combination is safe in the adjuvant treatment of colon cancer pts. The adverse event profile is comparable to the safety profile in mCRC and in the NSABP C-08 trial (ASCO 2008–2009).

Table. Grade 3−5 AEs within 6 months of last treatment

No. (%) of pts	Arm A FOLFOX-4* n = 1126	Arm B FOLFOX-4 + Bev** n = 1145	Arm C XELOX + Bev** n = 1135
Venous thrombotic events	62 (5.5)	95 (8.3)	52 (4.6)
Hypertension	12 (1.1)	119 (10.4)	109 (9.6)
Arterial thrombotic events	11 (1.0)	18 (1.6)	17 (1.5)
Bleeding/haemorrhage	7 (0.6)	14 (1.2)	5 (0.4)
Wound healing complications	4 (0.4)	3 (0.3)	5 (0.4)
Abscess/fistula	3 (0.3)	16 (1.4)	9 (0.8)
Gastrointestinal perforations	1 (0.1)	8 (0.7)	2 (0.2)
Proteinuria	1 (0.1)	11 (1.0)	11 (1.0)

*planned treatment duration 5.5 months; ** planned treatment duration 11 months.

6011 ORAL

Calcium and magnesium (Ca/Mg) infusions to reduce oxaliplatin-induced neurotoxicity and outcome in advanced colorectal cancer (ACC) patients (pts) treated with oxaliplatin- and cetuximab-based therapy

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Background: Peripheral neurotoxicity is a potentially invalidating side effect of oxaliplatin treatment. Ca/Mg infusions are frequently used to prevent this toxicity, but the relationship with outcome is still controversial. Hypomagnesemia (hypoMg) is a frequent side effect of treatment with cetuximab (an epidermal growth factor receptor monoclonal antibody) and is associated with response to this agent. We assessed the effect of Ca/Mg infusions on toxicity and outcome.
Materials and Methods: 755 previously untreated ACC pts received capecitabine, oxaliplatin (to a maximum of 6 cycles) and bevacizumab (CB) or the same combination with the addition of cetuximab (CBC) in a phase III randomized trial (CAIRO2 study of the Dutch Colorectal Cancer Group, Tol et al., N Engl J Med 2009). Pts were divided into 2 groups: group I received Ca/Mg infusions at their first treatment cycle, group II did not. Progression-free survival (PFS), overall survival (OS), response rate (RR), and toxicity (NCI-CTC v.3.0) were assessed per treatment arm in these 2 groups and calculated using a Cox-proportional hazards model and Chi-square analysis.
Results: 732 pts were evaluable for these analyses. Group I consisted of 552 patients (75%), 269 in the CB arm and 283 in the CBC arm, of which 369 (67%) received Ca/Mg at all 6 cycles oxaliplatin. In group II, 133 out of 180 pts (74%) did not receive Ca/Mg during subsequent cycles. Baseline characteristics were comparable between group I and II. The incidence of peripheral neurotoxicity (⩾grade 2) was comparable in group I and group II (39% vs 42%; p = 0.49) in the CB and in the CBC arm. The incidence of all grade hypoMg also did not differ between groups (28% vs 24%; p = 0.32) in both treatment arms. The median PFS (95% confidence interval [CI]) in the CB arm was 10.6 (9.4−12.6) months in group I and 10.7 (9.0−12.7) months in group II (p = 0.54). In the CBC arm the median PFS was 9.2 (8.2−10.3) months in group I and 11.2 (8.6−12.6) months in group II (p = 0.15). The median OS (95% CI) was also comparable between group I and II in both the CB arm (20.0 [17.1−25.4] vs 20.4 [16.7−27.8] months; p = 0.68) and the CBC arm (18.9 [16.2−21.5] vs 20.6 [17.6−25.2] months; p = 0.20). The RR was 35% in group I vs 40% in group II in the CB arm (p = 0.45), and 36% vs 49% in the CB arm (p = 0.06).
Conclusions: Ca/Mg infusions were not correlated with a decreased incidence of peripheral neurotoxicity in pts treated with capecitabine, oxaliplatin and bevacizumab with or without cetuximab. No statistically significant differences in outcome were observed based on Ca/Mg infusions.

6012 ORAL

The FIRIS study; A Phase III trial of 5-FU/l-leucovorin/irinotecan (FOLFIRI) versus irinotecan/S-1 (IRIS) as 2nd-line chemotherapy for metastatic colorectal cancer (mCRC) [FIRIS study group]

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Background: Several phase II studies of irinotecan (IRI) plus S-1 combination therapy (IRIS) conducted in Japan have shown promising efficacy and safety for mCRC, suggesting the potential to replace FOLFIRI. We conducted a randomized phase III trial to demonstrate the

non-inferiority of progression-free survival (PFS) obtained with IRIS in comparison with FOLFIRI.
Methods: IRI-naïve mCRC patients (pts) with one prior chemotherapy regimen, ECOG PS 0–1, and adequate organ function were randomized to receive either FOLFIRI (200 mg/m^2 of l-leucovorin given simultaneously with 150 mg/m^2 of IRI, followed by a 400 mg/m^2 bolus of 5-FU on day 1, and then 2,400 mg/m^2 of 5-FU over 46 h, every 2 weeks) or IRIS (125 mg/m^2 of IRI on days 1 and 15, and 40–60 mg/body of S-1 twice daily for 2 weeks, followed by a 2-week rest). Pts were stratified by institution, prior chemotherapy (with or without oxaliplatin), and PS. The primary endpoint was PFS. Secondary endpoints were overall survival, response, safety, and cost. A sample size of 200 pts per group was estimated to be necessary based on a median PFS of 4.0 months in each group and 80% power to demonstrate non-inferiority of IRIS with a 1-month margin (hazard ratio, HR = 1.333) and 1-sided alpha of 0.025.
Results: Between January 2006 and January 2008, 426 pts were enrolled. Baseline characteristics were well balanced. Pts received an average of 4.7 cycles (1 cycle = 4 weeks) of FOLFIRI (range: 0–20) and 4.9 cycles of IRIS (range: 0–23). The median relative dose intensity of IRI was 78.3% in both arms. Median PFS was 5.1 months (95% CI: 4.2–6.0) with FOLFIRI and 5.8 months (95% CI: 4.5–6.0) with IRIS. The adjusted HR for PFS was 1.077 (95% CI: 0.879–1.319) and the p value for non-inferiority was 0.039. The median survival time was 18.2 months (95% CI: 15.8–20.2) with FOLFIRI and 19.6 months (95% CI: 15.4–23.5) with IRIS (adjusted HR: 0.909; 95%CI: 0.699–1.181). The response rate (RECIST) was 16.7% (29/174) with FOLFIRI and 18.8% (34/181) with IRIS. The safety profile of IRIS was similar to that previously reported, with no unexpected toxicities. Grade 3/4 adverse events (FOLFIRI vs. IRIS) were neutropenia (52 vs. 36%), diarrhea (5 vs. 21%), vomiting (4 vs. 2%), mucositis/stomatitis (1 vs. 3%), fatigue (3 vs. 9%), and febrile neutropenia (1 vs. 5%). The average cost per cycle of chemotherapy (including supportive care) was significantly lower with IRIS.
Conclusion: IRIS was demonstrated to be non-inferior to FOLFIRI with respect to PFS as 2nd-line treatment of mCRC, thus it could replace FOLFIRI.

6013 ORAL

Quality assurance in rectal cancer treatment in the Netherlands: a catch up compared to colon cancer treatment

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Background: In the last two decades, treatment of rectal cancer has been substantially improved by the introduction of the Total Mesorectal Excision (TME) surgical technique together with effective neoadjuvant treatment regimens. In the Netherlands, TME surgery was implemented in a structural way within the framework of the TME trial (1996–1999). For the treatment of colon cancer, adjuvant chemotherapy was introduced in the late 1990's. Traditionally, survival after rectal cancer was inferior compared to colon cancer. The aim of this study is to examine the effects of the structural changes in rectal cancer care on survival compared to colon cancer for patients treated before, during and after the TME trial.
Material and Methods: We compared two-year overall survival of all patients with curatively resected colon (n = 15266) and rectal cancer (n = 5839) in the regions of Comprehensive Cancer Centres South and West between 1990 and 2005.
Results: Using a Cox proportional hazard model adjusting for age, gender and tumor stage, there was no difference in two-year survival between rectal cancer and colon cancer in the pre-trial period. However, in the post-trial period, two-year survival was higher for rectal cancer than for colon cancer. When comparing the pre-trial period with the post-trial period, two-year survival improved significantly for stage II and III colon cancer patients and for stage II and III rectal cancer patients.

		1990–1995	2000–2005	P
Rectal vs Colon	Hazard Ratio[1]	1.088		0.14
	Hazard Ratio[2]		0.844	0.003
Colon cancer	2 yr surv stage II	77.7%	80.1%	0.029
	2 yr surv stage III	62.3%	69.1%	<0.001
Rectal cancer	2 yr surv stage II	77.6%	85.1%	<0.001
	2 yr surv stage III	64.0%	78.6%	<0.001

[1]Compared to colon cancer 1990–1995. [2]Compared to colon cancer 2000–2005.

Conclusion: In the past 15 years, survival improved significantly for both colon and rectal cancer. Remarkably, the traditional survival backlog for rectal cancer compared to colon cancer has changed to a lead in the most recent years. This study shows the lasting effects that structural surgical training and quality assurance can have on survival outcome.

Poster presentations (Wed, 23 Sep, 09:00–12:00)
Gastro-intestinal malignancies – Colorectal cancer

6014 POSTER

Transanal Endoscopic Microsurgery (TEM) in Tubulovillous Adenoma and T1 rectal lesions

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Background: Transanal Endoscopic Microsurgery (TEM) is a minimal invasive technique for the local resection of Tubulovillous Adenoma and stage T1 rectal carcinomas in selected patients, associated with lower morbidity and mortality rates than open surgery. We report our initial results using TEM.
Methods: In 2002, TEM was introduced in our clinic. All patients undergoing TEM for tubulovillous adenoma or carcinoma between May 2002 and December 2007 were included in a prospective database.
Results: We included 105 patients: 54 men and 51 women. The median age was 68 years (range 46–94 years). The procedure was performed in 104 patients with curative intention and in 1 patient in a palliative setting. The median distance from the tumour to the anal verge was 7.0 centimetres and the median operating time was 90 minutes.
Peroperatively, 10 perforations occurred, all in high ventral or lateral situated tumours. In 2 of those 10 patients TEM was converted to (low) anterior resection. As a result of difficult access to the lesion or size of the lesion, but with an intact peritoneum, conversion to (low) anterior resection was also performed in 4 other patients (total conversion rate 5.7%).
Postoperative staging revealed 77 stage T0 tumours, 22 stage T1 tumours, 5 stage T2 tumours and 1 stage T3 carcinoma. In 89% of patients tumour resection was radical. In 6 patients an additional open resection was performed.
8 patients suffered from one of the following postoperative complications; urinary infection, urinary retention, pneumonia, atrial fibrillation, rectal bleeding or late perforation. (postoperative complication rate 7.6%).
Median length of stay in our hospital was 4 days. At this moment 8 recurrences occurred after a follow up ranging from 3 to 59 months (median follow up 27 months; recurrence rate 7.6%).
Conclusion: TEM is a safe curative operating technique, with low morbidity and recurrence rates. As such, TEM is the treatment of choice for tubulovillous adenoma and selected stage T1 rectal tumours.

6015 POSTER

Extended TME and MRI assisted pathology show high incidence of pT4 after neoadjuvant treatment

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Background: The clinical ability of pre- and post neoadjuvant magnetic resonace imaging (MRI) to predict the necessary extension of total mesorectal excision (ETME) in evaluation of the areas at risk in locally advanced rectal cancer. Evaluation of treatment response to chemoradiotherapy/radiation therapy in T4 stage tumours is difficult. MRI cannot detect small islets of tumour within fibrosis or mucin and not discriminate between different tissue components within a voxel. Increasing rate of late local relapses, also later than five years after treatment, have been reported from different studies.
Material and Methods: Prospective registration of 92 MRI evaluated T4a cancers undergoing multimodal treatment for rectal cancer between 2002 and 2007 in a Norwegian tertiary referral cancer centre. MRI was found to predict T-downstaging in 10% after neoadjuvant treatment. In 35% both MRI and histopathological examination staged the patients as T4 after treatment. Fifty-five percent (n = 51) of the patients were downstaged after the routine postoperative pathology work-up. A new technique with MRI-based sampling of areas of infiltration was introduced and dedicated histopathological evaluation of these threatened areas was performed.
Results: ETME was performed in 95% of the patients, mostly as en-bloc resections. After MRI focused pathology 50% of these 51were reclassified