- Record patient episode data and associated applied Tacit Knowledge used by Consultant Oncologists during the clinical management of patients diagnosed with advanced breast cancer
- Provide a knowledge resource for oncologists in the domain of advanced breast cancer
- Propose similar episodes of patient care for patients attending outpatient clinics
- Provide an '*ask the expert*' service where junior oncologists can provide anonymous patient data and request advice from acknowledged experts.

It will be fully prototyped and experimented within the key clinical process of cancer care, addressing the substantial problems of bridging clinical expertise between secondary (hospital) care and after care led by the general practitioner and supporting specialist community nurses.
Thus the innovations arising from the project will be piloted and fully validated in two European hospitals, leading to a strong set of case studies and results which will be disseminated to the healthcare and Information and Communication Technologies communities, and to the wider European research area.
This project has been partially funded by the European Commission under the IST initiative.

References

[1] http://oncology.fecs.be

Gastrointestinal Tumours

Oral presentations (Wed, 2 Nov, 9.15–11.15)

GI – metastatic colon cancer

597 ORAL

A randomised phase III multicenter trial comparing irinotecan in combination with either the Nordic bolus 5FU and folinic acid (5FU/FA) schedule (FLIRI) or the bolus/infused de Gramont schedule (FOLFIRI), in patients with metastatic colorectal cancer

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Background: Irinotecan with FU/FA is an established regimen in metastatic colorectal cancer, however, with major uncertainties related to the mode of administration of FU. In the US, a weekly bolus schedule, the Saltz regimen, was used extensively, whereas in Europe, infused 5FU is preferred. We have compared irinotecan in combination with either the Nordic fortnightly 5FU/FA bolus schedule (FLIRI) or the fortnightly Lv5FU2 schedule (FOLFIRI).
Methods: Between August 2001 and March 2004, 567 previously untreated patients with metastatic colorectal cancer at 27 centres in the Nordic countries were randomized to either FLIRI (irinotecan 180 mg/m^2 day 1, 5FU 500 mg/m^2 bolus iv day 1, 2, FA 60 mg/m^2 day 1,2) or FOLFIRI (irinotecan 180 mg/m^2 day 1, FA 200 mg/m^2 day 1, 2, 5FU bolus 400 mg/m^{2}day 1, 2 and infused 5FU 1200 mg/m^2 per 48 hour). The dose of irinotecan, found in a preceding phase II study with the Nordic schedule (210 mg/m^2) was lowered after the first 100 randomized patients to 180 mg/m^2 because of a slight excess of toxicity (any grade 3–4, 49 vs 38 instances, 60 day mortality 3 vs 2) and concerns seen using the Saltz regimen in two American trials. The primary endpoint was progression-free survival with the aim to show non-inferiority (at the most 20% worse or from median 6.7 to 5.4 months, $\alpha = 0.05$, $1 - \beta = 0.80$).
Results: Patient characteristics were well balanced between groups. In the entire patient material, including the first 100 patients, toxicity did not differ between groups (grade 3/4 nausea/vomiting 20 vs 37, diarrhea 23 vs 31, neutropenia 19 vs 8, fever 11 vs 14). The 60 day mortality was 2.4% vs 2.3% (6 patients each in both groups). The primary endpoint, time to progression, did not differ between groups (median 9.1 months in both groups, $p = 0.34$).
Conclusions: Irinotecan with the bolus FU/FA Nordic schedule (FLIRI) is a convenient treatment with efficacy and toxicity comparable to the 'infused' FOLFIRI regimen. Response rates and overall survival will be presented at the meeting.
The work was supported in part by Aventis.

598 ORAL

Randomised comparison of 5-FU/folinic acid plus irinotecan (FOLFIRI) and irinotecan plus oxaliplatin (IROX) in first-line therapy of metastatic colorectal cancer (CRC): the fire-trial

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Objective: This randomised trial compares the 1st-line efficacy and toxicity of infusional 5-FU/FA (AIO regimen) plus irinotecan (FOLFIRI) to the combination of irinotecan plus oxaliplatin (IROX).
Methods: 488 patients (pts) from 56 centres were enrolled between July 2000 and the end of study in September 2004. In the FOLFIRI arm, pts received FA 500 mg/m^2 plus 5-FU 2000 mg/m^2 (24h) and irinotecan 80 mg/m^2 given weekly for 6 times. In the IROX arm pts were treated with oxaliplatin 85 mg/m^2 (d1, 15, 29) and irinotecan 80 mg/m^2 weekly times 6. Treatment cycles were repeated on day 50 in both treatment arms. Patients were stratified according to LDH, adjuvant pretreatment, and Karnofsky performance status (KPS) showing LDH >240 U/ml in 42% vs 39%, adjuvant pretreatment in 31% vs 29%, and a KPS = 100% in 48% vs 47%, in the FOLFIRI- and IROX-arm respectively. The primary end-point of the trial was progression-free survival. At disease progression, pts were offered to switch to the comparator regimen.
Results: Treatment efficacy was evaluable in 478 pts (240 FOLFIRI, 238 IROX). Second-line therapy according to the cross-over protocol was FOLFIRI) of patients. The IROX and 29% (IROX documented in 33% (FOLFIRI complete remission rate (CR) was 7.9% vs 8.3%, the partial remission rate (PR) 36.7% vs 39.5% for an overall remission rate (CR+PR) of 44.6% vs 47.8% in the FOLFIRI- and IROX-arm, respectively. Stable disease (SD) was documented in 44.2% vs 30.7%. Median progression-free survival was 8.2 months vs 7.0 months ($p = 0.377$) with a hazard ratio of 1.093 (95%CI: 0.897–1.330), while median overall survival was 21.9 months vs 19.3 months ($p = 0.249$) with a hazard ratio of 1.159 (95%CI: 0.902–1.49). 60-day mortality was 6.3% and 4.2% (FOLFIRI vs IROX).
Conclusions: FOLFIRI and IROX are comparably effective with regard to response, progression-free survival, and overall survival. Toxicity is similarly acceptable in both treatment arms.

599 ORAL

Improved activity with irinotecan, oxaliplatin and infusional 5-FU/LV (FOLFOXIRI) compared with FOLFIRI in metastatic colorectal cancer (MCRC): results of a randomized Phase III trial by the Gruppo Oncologico Nord Ovest (G.O.N.O.)

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Background: The FOLFOXIRI regimen has demonstrated promising antitumor activity coupled with manageable toxicities in Phase II trials in MCRC.
Patients and methods: 244 patients (pts) with measurable, not resectable MCRC and previously untreated with chemotherapy (CT) for advanced disease, were randomly assigned to receive: irinotecan 180 mg/sqm d1, l-LV 100 mg/sqm d1+d2, 5FU 400 mg/sqm bolus d1+d2, 5-FU 600 mg/sqm 22-h infusion on d1+d2 (FOLFIRI, arm A, n = 122) or irinotecan 165 mg/sqm d1, oxaliplatin 85 mg/sqm d1, l-LV 200 mg/sqm d1, 5FU 3200 mg/sqm 48-h infusion starting on d1 (FOLFOXIRI, arm B, n = 122). Both treatments were repeated every 2 weeks and after progression to FOLFIRI an oxaliplatin containing regimen was recommended.

Results: Patients characteristics were (arm A vs arm B): median age 64 vs 62 yrs, ECOG PS 1–2 40% vs 39%, adjuvant CT 24% vs 24%, multiple sites of metastasis 48% vs 55%, liver metastases 79% vs 75%, liver involvement ⩾25% 58% vs 52%. Main observed toxicities were (arm A vs arm B): grade 3–4 diarrhea 12% vs 18%, grade 2–3 vomiting 20% vs 31%, grade 3–4 stomatitis 3% vs 5%, grade 2–3 peripheral neurotoxicity 0% vs 20%, grade 4 neutropenia 28% vs 47%, febrile neutropenia 3% vs 5%. Two pts in each arm died within 60 days, but no toxic deaths have occurred. Among the 230 pts so far evaluated for response (14 too early), responses, assessed by investigators, were (arm A vs arm B): complete 5% vs 8%, partial 35% vs 57%, stable 32% vs 20% progression 25% vs 12%, not evaluable 3% vs 3%. The response rate (complete+partial) was significantly higher in the FOLFOXIRI arm (65% vs 40%, $p = 0.0002$). At a median follow-up of 13.4 months 186 pts have progressed and median PFS is significantly longer in the FOLFOXIRI arm (9.8 vs 6.9 months, $p < 0.0001$) with an hazard ratio of 0.57 in favor of FOLFOXIRI.
Conclusions: This FOLFOXIRI regimen is feasible with manageable toxicities and significantly increases response rate and PFS compared to FOLFIRI. Externally reviewed response rate and updated activity and efficacy results will be presented. (Partially supported by Fondazione ARCO).

600 ORAL

Randomised study of sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (ACC), an interim safety analysis. A Dutch Colorectal Cancer Group (DCCG) Phase III study

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Radboud University Nijmegen Medical Centre, on behalf of the DCCG, Medical Oncology, Nijmegen, The Netherlands

Background: Survival results in previous studies of mono- versus combination chemotherapy in ACC may have been biased by an imbalance in salvage treatments. This is the first study that prospectively evaluates sequential versus combination chemotherapy with a fluoropyrimidine, irinotecan, and oxaliplatin, and which incorporates capecitabine as fluoropyrimidine.
Patients: Patients were randomised between 1st line capecitabine, 2nd line irinotecan, and 3rd line capecitabine+oxaliplatin (arm A) vs. 1st line capecitabine+irinotecan, and 2nd line capecitabine+oxaliplatin (arm B). Primary endpoint is overall survival. Between Jan. 2003 and Dec. 2004 a total of 820 patients (pts) were randomised.
Results: The first 400 pts included in the study were considered in this analysis. On-study forms were available from 366 pts, and 350 pts were known to have entered the 1st-line treatment period. Median number of cycles (range) in arm A was 1st line 7.0 (1–30), 2nd line 6.0 (1–24), 3rdline 3.5 (1–30), in arm B 1st line 6.0 (1–26), 2nd line 3.0 (1–24). In 1st line, the most importantgrade 3–4 toxicities in arm A versus B were: hand–foot syndrome (11% vs. 2%), diarrhea (11% vs. 23%), nausea (3% vs. 9%), vomiting (3% vs 7%), febrile neutropenia (<1% vs 5%), and all grades cholinergic syndrome (0% vs 20%). In 2nd line: diarrhea (15% vs 10%), febrile neutropenia (6% vs 2%), sensory neuropathy (1% vs 7%), and all grades hypersensitivity reactions (1% vs 11%) and cholinergic syndrome (31% vs 4%). When grade 3–4 toxicity over all lines was considered, the largest differences were observed for the incidence of hand foot syndrome (12% vs 4%) and diarrhea (19% vs 25%). Incidence of thrombo-embolic events (4% vs 5%) and cardiotoxicity (1% vs 0%) was low. Sixty-day all-cause mortality was 5% (19 pts), 3% (6 pts) in arm A and 6.5% (13 pts) in arm B. Cause of death was disease progression (7 pts), sudden death of unknown cause (4 pts, all in arm B), neutropenic sepsis (3 pts), diarrhea, respiratory failure of unknown cause, pulmonary embolism, ruptured abdominal aneurysma, and bowel perforation/bleeding during NSAID use (1 pt each). Overall, 8 pts died by causes which were clearly related to treatment: 6 pts (3%) in arm A (neutropenic sepsis 4, diarrhea 2) and 2 pts (1%) in arm B (neutropenic sepsis 2). In 3/8 pts protocol violations were likely to have contributed significantly.
Conclusions: Toxicity in both arms was acceptable. Sequential treatment had a higher incidence of hand–foot syndrome, and a lower incidence of diarrhea. Many patients are still on treatment, and data are therefore subject to change. Based on these preliminary safety results, combination treatment does not appear to be more toxic to sequential treatment, but the sudden deaths during treatment with capecitabine+irinotecan need further attention.

601 ORAL

Infusional 5-fluorouracil/folinic acid plus oxaliplatin (FUFOX) versus Capecitabine plus oxaliplatin (CAPOX) as first line treatment of metastatic colorectal carcinoma (MCRC): results of the safety and efficacy analysis

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Background: In a previous phase III study the FUFOX regimen has shown superior response rates to bolus 5-FU/FA (Mayo Clinic protocol) in patients with MCRC. The combination of capecitabine (CAP) and oxaliplatin (OX) has demonstrated good efficacy and safety results in recent phase II studies. In August 2002 we initiated a phase III trial to compare FUFOX and CAPOX as first line therapy in patients with MCRC. Here, we present the results of the safety and efficacy analysis.
Patients and methods: From August 2002 to August 2004, 474 patients (m:f = 62% vs 38%; median age 65 (range 32–86)) have been randomized to receive either FUFOX (234 pts. arm A: 5-fluorouracil 2000 mg/m^2 24 h infusion, folinic acid 500 mg/m^2, oxaliplatin 50 mg/m^2 d1, 8, 15, 22; q5 wks) or CAPOX (242 pts arm B: capecitabine 1000 mg/m^2 bid d1–14, oxaliplatin 70 mg/m^2 d1 and 8; q3 wks). All patients had measurable metastatic disease, ECOG performance status 0–2, normal renal and hepatic function.
Results: To date 2123 treatment cycles (1026 FUFOX, 1515 CAPOX) are evaluable for toxicity (median number of cycles per patient: arm A: 4, range 1–10; arm B: 6, range 1–21, table 1). Based on 233 events currently observed, median time to tumor progression (primary study endpoint) was 8 months in the FUFOX arm and 7 months in the CAPOX arm, respectively: p = NS.
Secondary efficacy parameters are detailed in table 1.

Table 1

Response Rates (ITT), %	CAPOX	FUFOX
CR	2	5
PR	45	44
SD	32	23

Table 1: Response rates.

Conclusions: These data show for the first time that both FUFOX and CAPOX have comparable efficacy profiles and response rates. As showed in previous analysis the safety profiles of both regimens are equivalent. Updated toxicity and efficacy results will be reported at the meeting.

602 ORAL

Preliminary safety of bevacizumab with first-line FOLFOX, CAPOX, FOLFIRI and Capecitabine for mCRC – First BEATrial

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Background: In a phase III pivotal trial in patients (pts) with metastatic colorectal cancer (mCRC), bevacizumab (BEV, Avastin®) increased overall survival by 30% when added to first-line IFL chemotherapy (CT). Safety data from controlled BEV trials have been described, and indicate that certain serious adverse events (SAE), primarily gastrointestinal (GI) perforations and arterial thromboembolic events (TE) occurred more often in pts who received CT with BEV than those who received CT alone.