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Goshajinkigan (TJ-107) for Oxaliplatin-induced Sensory Neurotoxicity in Colorectal Cancer Patients – a Prospective, Randomized, Double-blinded, Placebo-controlled, Phase II Trial (GONE)

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Background: Cumulative sensory neurotoxicity often results in the early discontinuation of oxaliplatin-based chemotherapy. In a nonrandomized, retrospective study, the Japanese traditional medicine TJ-107 reduced oxaliplatin-related sensory neurotoxicity.
Material and Methods: Between May 2009 and March 2010, ninety-three patients with colorectal cancer receiving infusional fluorouracil, leucovorin, and oxaliplatin(FOLFOX) were randomly assigned to TJ-107 (2.5 g three times daily) or placebo, in a double-blinded manner. The primary endpoint was the incidence of grade 2 or higher sensory neurotoxicity after eight cycles of FOLFOX. The secondary endpoints were the grade of sensory neurotoxicity, response rate (RR), and safety. Sensory neurotoxicity as measured by CTCAE and patient-questionaires were assessed at baseline, every two weeks until cycle eight, and every four weeks until the 26th week.
Results: Eighty-nine patients were available for analysis including 44 in the TJ-107 arm and 45 in the placebo arm. The incidence of grade 2 or higher sensory neurotoxicity was 27.0% and 30.7% at the cycle eight8, 25.7% and 44.1% ($p = 0.109$) at the 26th week in the TJ-107 and placebo arm respectively. The time to grade 2 sensory neuropathy was 5.5 months in the TJ-107 and 3.9 months in the placebo ($p = 0.147$). The RR was 55.5% in the TJ-107 and 39.1% in the placebo. No substantial differences in adverse events are noted between TJ-107 and placebo.
Conclusions: Although little effect was shown at the cycle eight, this study suggests that TJ-107 is effective in reducing oxalipatin-related sensory neurotoxicity without impact on its efficacy. A randomized phase III trial has been started in Japan.

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KRAS Mutational Status and Anti-angiogenic Therapy in Liver Metastatic Colorectal Cancer

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Background: Recently the inhibition of angiogenesis in combination with chemotherapy has become part of the standard care of advanced colorectal cancer. The most frequently found oncogenic mutation in colorectal cancer, namely the mutation of KRAS influences the production of angiogenic factors in malignant cells. Accordingly in the present study we investigated whether the KRAS mutation affects the efficacy of bevacizumab treatment.
Materials and Methods: KRAS mutational status at codon 12 and 13 has been determined from DNA extracted from macrodissected paraffin embedded formalin fixed samples using microcapillary electrophoresis of restriction fragments. In the mutant samples the transitions had been identified by direct sequencing. Thirty five liver metastatic colorectal cancer patients who have received bevacizumab treatment had been analyzed for progression free survival.
Results: In 575 consecutive colorectal cancer samples submitted to the Pathology Department we found KRAS mutated in 31% and 6% of the cases at codon 12 and 13, respectively, yielding an 37% overall mutational frequency. Among the thirty five, anti-angiogenic treatment receiving liver metastatic colorectal cancer patients 16 carried oncogenic mutant allele while 19 patients had wild-type KRAS. Kaplan-Meyer survival analysis had demonstrated that progression-free survival of KRAS mutant patients was highly similar to that of wild-type patients using log-rank test (9.2 ± 5.5 months versus 8.7 ± 5.7 months, respectively).
Conclusions: Our findings support previous studies that KRAS status of colorectal cancer does not interfere with the efficacy of bevacizumab treatment.

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Final Results of a Multicentre Phase II Trial Assessing Sorafenib in Combination With Irinotecan as 2nd or Later-line Treatment in Metastatic Colorectal Cancer (mCRC) Patients With KRas Mutated Tumours (mt) (NEXIRI)

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Background: The raf kinase inhibitor Sorafenib (S) is the lead compound in a series of raf signalling pathway inhibitors that could inhibit cell growth and proliferation of pts in KRAS mt patients (pts). The aim of this phase II trial was to evaluate the disease control rate (DCR) of Irinotecan (I) combined with S as 2nd or later line treatment (tt) in mCRC pts with KRAS mt.
Methods: In the previous phase I, the recommended dose of I was 180 mg/m^2 in a bi-weekly regimen with a fixed dose of S (400 mg twice daily) (1 cycle= 2 courses of I). In the phase II, pts received this combination until progression or toxicity. Eligibility criteria included: measurable and unresectable mCRC, age >18 years, PS $\leqslant$2, progression after I-based chemotherapy, one or more previous lines and centralized confirmation of KRAS mt in codons 12 or 13 in the primary tumour (PT) or metastases. Primary endpoint was DCR according to RECIST criteria with independent review of CT-scan. Secondary were toxicity, PFS and OS. Tt regimen was considered promising if at least 14 out of 54 pts had DC in a two-stage Simon design. Pharmacokinetic, pharmacogenetic and pathologic studies were also undertaken.
Results: Fifty-four pts were included between 06/09 and 12/09 from 10 centers. Median age was 60 yrs (range: 43−80), 59% were males, 46% PS 0, 63% PT in colon. Previous tts were 5FU 100%, I 100%, oxaliplatin 94%, bevacizumab 89%. The median number of cycles was 4 (1−8) and 13 pts (24%) completed at least 6 cycles. No toxic death was seen. Gr 3 toxicities were: hand-foot syndrome 15%, diarrhea 39%, neutropenia 19% and 16% showed Gr 4 neutropenia. In 46 pts (85%) S dose was reduced to 400 mg daily after two courses due to toxicity, then increased again to 800 mg in 55% of pts. The DCR was 64.9% [IC95%, 51−77] in intention to treat (52 evaluable pts). Median PFS and OS were 3.5 [IC95%, 2.0−3.7] and 7.7 months [IC95%, 4.8−9.7], respectively (follow-up: 9.1 months). Analysis of the CCND1 G870A polymorphism showed that the homozygous A/A genotype was associated with higher DCR ($p = 0.007$).
Conclusion: NEXIRI regimen as 2nd or later-line tt for mCRC pts with KRAS mt shows promising activity in this heavily pre-treated KRAS mt population. These data justify conducting a randomized phase II/III trial to confirm the efficacy of this combination.

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Oxaliplatin/5-Fluorouracil/Leucovorin in Colorectal Cancer With Malignant Ascites, an Observational Study

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Background: Peritoneal carcinomatosis from colorectal cancer (CRC) is a lethal condition with poor prognosis. Malignant ascites is frequently combined with peritoneal carcinomatosis. Efficacy of oxaliplatin with 5-flurouracil and leucovorin (FOLFOX) in advanced CRC is known but efficacy in greatly advanced CRC such as peritoneal carcinomatosis with malignant ascites has not been confirmed yet. Effective treatment modality for peritoneal carcinomatosis with malignant ascites is needed.
Materials and Methods: CRC patients treated with FOLFOX regimen over the period 2001–2010 were screened and medical records of patients with malignant ascites at the beginning of FOLFOX were reviewed.
Results: 731 CRC patients were treated with FOLFOX regimen within the period and 28 patients had malignant ascites at the beginning of treatment. The median patient age was 59.5 years (range 26−80), and 50% (14/28) of the patients were male. 10 patients (35.7%) had treatment history with 1 or more regimen of chemotherapy. Previous surgery history was observed in 14 patients (50%).
Among the 28 patients, 11 patients achieved partial response, 8 patients achieved stable disease, and 7 patients progressed during the treatment period. 2 patients did not have measurable disease. At the time of maximum

response, Ascites disappeared for 15 patients, decreased for 1, showed no change for 4 and increased for 8.
Median progression free survival time was 4.7 months (95% confidence interval (95% CI): 4.7−7.1 months) and median overall survival was 12.3 months (95% CI: 7.3–17.3 months).
Conclusion: FOLFOX in treatment of PC from CRC may be effective but further study is still required.

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The Absolute Rise in Blood Pressure Better Predicts the Outcome of Bevacizumab in Metastatic Colorectal Cancer (mCRC) Patients Compared to CTCAE

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Background: Hypertension (HT) is a common side-effect of bevacizumab, a monoclonal antibody against VEGF which is currently part of standard first-line treatment in patients with mCRC. We investigated the predictive value of early bevacizumab-induced HT for outcome in mCRC patients using both the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) and absolute rise in blood pressure (BP).
Patients and Methods: We evaluated 378 mCRC patients treated in a randomized phase III trial with first-line chemotherapy and bevacizumab (arm A of the CAIRO2 study of the Dutch Colorectal Cancer Group). Patients with and without HT were evaluated using CTCAE and absolute BP data separately. BP was measured at every visit before start of the next treatment cycle. Patients were divided in 2 groups according to the maximal grade hypertension during the first 3 cycles (group with HT defined as grade 2−3, group without HT defined as grade 0−1), and according to a rise in diastolic or systolic BP of 20 or more mmHg during the first 3 cycles (group with and without rise in BP). Patients who received at least 3 cycles of therapy were evaluated.
Results: According to the CTCAE criteria, 55 (16%) of 340 evaluable patients developed grade 2−3 HT during the first 3 cycles. Patient characteristics were comparable between the 2 groups. Patients with HT had a significantly better median overall survival (OS) (Table). Median progression-free survival (PFS) was not significantly different between patients with and without HT. No effect of HT on OS was seen in multivariate analysis (HR 0.70, 95% CI 0.49–1.01).

Arm A	CTCAE data (n = 340)				Absolute blood pressure data (n = 311)			
	No HT (n = 285)	HT (n = 55)	HR	p	No HT (n = 218)	HT (n = 93)	HR	p
Median PFS	10.6	12.7	0.81	0.19	10.6	13.5	0.86	0.26
(95% CI), mo	(9.4–12.3)	(9.8–15.0)	(0.59–1.11)		(9.3–12.2)	(10.6–14.5)	(0.66–1.11)	
Median OS	20.2	25.0	0.70	0.05	18.4	27.8	0.61	<0.001
(95% CI), mo	(17.5–24.1)	(20.4–32.2)	(0.49–1.00)		(16.7–21.3)	(23.0–32.6)	(0.46–0.82)	<0.001

Absolute BP data were available of 311 patients, 93 (30%) patients developed HT. Patients with HT had a better median OS, with a HR of 0.61 (95% CI 0.46–0.82). We did observe an increase in median PFS in patients with HT however this difference was not statistically significant. In multivariate analysis, HT was an independent prognostic factor for OS (HR 0.59, 95% CI 0.44–0.80).
Conclusions: We found HT defined as an absolute increase of at least 20 mmHg to be better predictive for the outcome of treatment with bevacizumab plus chemotherapy in mCRC patients compared to HT defined according to CTCAE grade 2−3. When further validated, HT defined as a rise in BP of at least 20 mmHg may be used in clinical practice to identify patients that benefit from bevacizumab treatment.

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Impact of Early Tumour Shrinkage on Long-term Outcome in Metastatic Colorectal Cancer (mCRC) Treated With 5FU+Irinotecan+Leucovorin (FOLFIRI) or Capecitabine+Irinotecan XELIRI Plus Bevacizumab

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Background: The measurement of tumour shrinkage at the first evaluation (8 weeks) was reported to predict long-term outcome in first line mCRC treated with irinotecan based chemotherapy (CT) + cetuximab. In the CRYSTAL study, the predictor power of early tumour shrinkage (ETS) was restricted to pts treated with CT + cetuximab (Piessevaux, et al. ESMO 2010, abstract 596P). This study has for aim to evaluate the impact of ETS on long-term outcome in patients (pts) receiving irinotecan based CT + bevacizumab.
Material and Methods: The pts treated in the randomized phase II trial ACCORD 13 (Folfiri + bevacizumab vs. XELIRI + bevacizumab) previously reported (Ducreux et al, ASCO 2009, abstract 4086) were included in this post-hoc analysis with a 36 months follow-up. Based on the 8-weekly radiological assessments reported by the investigators, relative changes of the tumour size from baseline were dichotomized using a 20% decrease cut-off value. Univariable analyses for progression-free survival (PFS), and overall survival (OS) were based on Kaplan–Meier curves and logrank test. Multivariable analysis used Cox model and included ETS, Köhne prognostic score; age, sex, and treatment arm.
Results: Two pts out of 145 were excluded from this analysis because of early death. One patient had GI perforation at week 6 leading to stop the study treatment and was considered as non responder. Tumour measurements after 8 weeks of treatment were available in the remaining pts. ETS was observed in 87 pts out of 143 (61%). All the RECIST responders (46) had early shrinkage. Median PFS were 10 months and 9 months in pts with and without ETS, respectively. PFS rates were 97% and 75% at 6 months 23% and 20% at 12 months in the pts with and without ETS, respectively, (Hazard ratio [HR] = 0.84; [0.59–1.20], p = 0.35). The multivariable analysis did not show significant impact of adding ETS to the model. Median OS were 33 months and 22 months for pts with or without ETS, respectively. OS rates were respectively 93% and 79% at 12 months in the pts with or without ETS, the corresponding rates at 24 months were 52% and 36% (HR = 0.59; [0.36–0.97], p = 0.04). The multivariable analysis showed that ETS had the strongest independent prognostic value when it was added to the OS prognostic model (HR = 0.54 [0.32–0.92] p = 0.02), age: p = 0.07, other variables: $p \geqslant 0.28$.
Conclusions: Combination of fluoropyrimidines + bevacizumab gives rapid responses. ETS is able to determine a group of patients with prolonged survival that is rarely observed in mCRC. Despite the absence of effect of ETS on PFS, these results are similar or even better to those observed with CT + cetuximab and their relevance in terms of daily clinical practice remains debatable and need to be confirmed on a large population.