the addition of irinotecan (hazard ratio [HR]: 0.74; 95% CI 0.57−0.97; interaction p = 0.710). Low and moderate/high Topo1, was not associated with an overall survival benefit with first-line combination chemotherapy (HR 0.91; 95% CI 0.69−1.2, and HR 0.83; 95% CI 0.62−1.1, respectively; interaction p = 0.65).
Conclusions: We did not observe an interaction between Topo1 expression and treatment with capecitabine plus irinotecan in respect to progression free and overall survival. Using the same methodology, we could not confirm the results of Braun et al. This underscores the complexity of this molecular marker and currently prevents the use of Topo1 expression in daily practice.

6004 ORAL

Late toxicity after preoperative (chemo)radiotherapy in non-resectable rectal cancer – results from a randomized phase III study

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Background: Several studies have shown the superiority of preoperative chemoradiotherapy (CRT) versus radiotherapy (RT) alone in locally advanced rectal cancer, but the gains in overall survival are limited. Follow-up of health-related quality of life and late toxicity has therefore become very important. The aim of this study was to compare the two groups, CRT versus RT, with focus on bowel function, urinary complications and sexual function in a long-term follow-up.
Material and Methods: 207 patients with nonresectable rectal cancer were randomized to receive preoperative CRT or RT (2×25 Gy $\pm$ 5FU/leucovorin) before surgery. Extended surgery was often required. Patients in the CRT group were also given adjuvant chemotherapy for 4 months. After a minimum of 4 years (range 4−12) posttreatment, patients alive in Norway and Sweden (n = 105) were contacted. Late toxicity was assessed using validated questionnaires and a telephone interview. Bowel and urinary function were scored with the LENT SOMA scale and the St. Marks score for fecal incontinence.
Results: Of the 105 patients contacted, 78 (74%) answered questionnaires and an interview. There were no statistically significant differences between responders and non-responders. A larger proportion of patients in the CRT group had stoma (73% versus 53%, p = 0.07). A majority of patients in both groups without a stoma (12/44 in the CRT and 16/34 in the RT group) had incontinence for liquid stools and gas. 28% (12/44) of patients in the CRT group suffered from bowel obstruction, half of them needed surgery. In the RT group the comparative figures were 15% (5/34) and 12% (4/34), respectively. In both groups a majority reported no urinary incontinence (73% versus 65%), and importantly, almost all patients in both groups (95% versus 82%) reported that urinary complications had no impact on their social life. More than two-thirds of both males (44/69) and females (27/37) reported on their sexual function. Many males had severe erectile dysfunction, median IIEF scores were 4 (1−29) in the CRT and 5 (1−29) in the RT group. Only 7 and 4 women in the CRT and RT groups, respectively, reported to be sexually active the previous month. However, the majority did not worry about their sex life/lack of sex life, 9/14 and 10/13 in CRT and RT groups, respectively.
Conclusion: There were no statistically significant differences in late toxicity between the CRT and RT groups. Fecal incontinence and erectile dysfunction were frequent in both groups.

6005 ORAL

PIK3CA, BRAF and KRAS mutations and outcome prediction in chemorefractory metastatic colorectal cancer (mCRC) patients treated with EGFR targeting monoclonal antibodies (MoAbs): results of a European Consortium

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Background: Deregulations of the EGFR signaling pathway, including *KRAS*, *BRAF* and *PIK3CA* mutations can impair clinical response to EGFR targeting MoAbs in mCRC. The predictive role of *KRAS* is well validated, however the precise impact of *BRAF* and *PIK3CA* and the combinations needs to be determined. A European Consortium was set up in order to have a large sample set with sufficient power to perform this subgroup analysis.
Methods: Over 1000 formalin-fixed, paraffin-embedded samples of chemorefractory mCRC treated with EGFR targeting MoAbs were collected together with the clinical data. All samples were centrally analyzed by the Sequenom MALDI-TOF MassArray system for the following mutations: *KRAS* p.G12S, p.G12R, p.G12C, p.G12D, p.G12A, p.G12V, p.G13D, p.A146T, p.G13A, p.G13V, p.G13G, p.G13G, p.A59T, p.Q61K, p.Q61E, p.Q61P, p.Q61R, p.Q61L, p.Q61H and p.Q61H; *BRAF* p.V600E, p.V600M, p.K601E and p.D594G; *PIK3CA* p.N345K, p.R38H, p.C420R, p.P539R, p.E542K, p.E542Q, p.E545K, p.E545G, p.E545Q, p.Q546K, p.Q546E, p.E81K, p.R88Q, p.C901F, p.M1004I, p.G1007R, p.H1047Y, p.H1047R, p.H1047L, p.G1049R, p.G1049S, p.G106V, p.R108H, p.G12D, p.G118D, p.P134S, p.S158L, p.H160N, p.H701P, p.K184E and p.K179T. We correlated the mutation status with objective response, progression-free and overall survival. Furthermore we studied the associations between the mutations and their frequency.
Results: An interim analysis on 705 patients was performed looking at mutation frequency and associations between mutations. *KRAS* mutations were found in 38%, *BRAF* in 4% and *PIK3CA* in 12.2% of patients. 40/244 (16%) *KRAS* mutants and 40/402 (10%) *KRAS* wild-types had a *PIK3CA* mutation (p = 0.016 Pearson's chi-square). 1/27 (3.7%) *BRAF* mutants and 78/631 (12%) *BRAF* wild-types had a *PIK3CA* mutation (p = 0.235 Fisher's exact test). *BRAF* and *KRAS* mutations were mutually exclusive. The mutation analysis will be completed on all patients. Not all samples were analyzed at the time of abstract submission. The success rate in the first series was higher than 90%. The outcome analysis is ongoing and will be presented at the meeting for all patients.
Conclusion: This series will be the largest one presented that will define the role of EGFR pathway deregulations in patients with mCRC treated with EGFR MoAbs in the chemorefractory setting.

6006 ORAL

PIK3CA mutations predict local recurrences in rectal cancer patients

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Background: Identifying rectal cancer patients who are at risk for local recurrence would allow for refinement in selection of patients who would benefit from preoperative radiotherapy. PIK3CA, KRAS and BRAF mutations are commonly found in colon cancers, but their prevalence has not been clearly assessed in rectal cancer. In this study, we aimed to determine the mutation frequencies of PIK3CA, KRAS and BRAF and to investigate whether a mutation may be used as parameter for predicting local recurrences in rectal cancer patients.
Material and Methods: Non-irradiated tumor samples from 240 stage I-III rectal cancer patients were available from the Dutch Total Mesorectal Excision (TME) trial, in which rectal cancer patients were randomized for treatment with standardized surgery and preoperative radiotherapy or surgery only (median follow-up surviving patients 7.2 years). The sequences of exons 9 and 20 of PIK3CA, exon 1 of KRAS and exon 15 of BRAF were evaluated by PCR and sequencing using DNA extracted from freshly frozen tumor tissue.
Results: PIK3CA, KRAS and BRAF V600E mutations were identified in 19 (7.9%), 81 (33.9%) and 5 (2.1%) rectal cancers, respectively. Mutations in KRAS and BRAF were mutually exclusive (P = 0.17), which is consistent with previous studies. Although 10 tumors showed both PIK3CA and KRAS mutations, this association was not statistically significant (P = 0.07). Interestingly, PIK3CA mutations revealed a strong association with increased local recurrences (5-year risks, 27.8% vs 9.4%; P = 0.006) and the significance was unaffected when patients who received postsurgery radiotherapy were excluded (5-year risks, 26.7% vs 6.4%; P = 0.002). In univariate analysis, a PIK3CA mutation was predictive of local recurrence (hazard ratio (HR) 3.48; 95%CI 1.3−9.34; P = 0.01). In multivariate analysis, PIK3CA mutations remained as an independent predictor for the development of local recurrences (HR 3.38; 95%CI 1.24−9.18; P = 0.02), next to tumor-node-metastasis (TNM) stage.
Conclusion: PIK3CA mutations can be used as a biomarker to identify rectal cancer patients with an increased risk for local recurrences. Comparison with patients within the TME trial who did receive preoperative radiotherapy should reveal whether these patients indeed benefit from preoperative radiotherapy. Currently, our findings suggest that prospective evaluation of PIK3CA mutation status would reduce overtreatment by preoperative radiotherapy for the low risk patients who would only experience the side-effects.