from the tumour. Proliferation (as measured by the nuclear antigen, Ki67) is substantially reduced in ER+ primary tumours by SERMs such as tamoxifen and aromatase inhibitors. With aromatase inhibitors at least 90% of patients show a reduction in Ki67 indicating that the large majority of ER+ breast carcinomas have some dependence on oestrogen although the withdrawal of this may lead to an insufficient change to elicit response. No increase in apoptosis has been measured, indeed significant decreases occur with aromatase inhibitors probably as a result of the close association between proliferation and cell death. Changes in Ki67 are only modestly predictive of clinical response but in the IMPACT trial they were predictive of the improved RFS seen with anastrozole over tamoxifen and the combination of tamoxifen and anastrozole. In keeping with this, Ki67 levels after 2 weeks treatment with endocrine therapy is more closely associated with recurrence free survival than pretreatment levels suggesting that the treatment induced change contributes to prediction of long-term outcome. The potential for this to be used for improved prediction of outcome in individual patients will be tested in the PeriOperative Endocrine Therapy for Indiividualising Care (POETIC) trial. Expression array analysis of biopsies before and after treatment with aromatase inhibitors reveals the profound changes in transcription that result from estrogen deprivation. The changes can be summarised as a Global Index of Dependence on Estrogen (GIDE) that may provide an additional index of benefit from the therapy. It is higher in patients with high ER+ tumours and lower in patients with HER2 positive disease. The study of the expression of other such markers or activity of biological pathways with ?Ki67 and/or the GIDE as indices of response should shed further light on the importance of the respective markers/pathways. Detailed analysis of the changes in gene expression after estrogen deprivation may identify pathways other than proliferation that determine the progression of estrogen independent disease and its response to endocrine therapy.

Symposium (Tue, 25 Sep, 14:45−16:45)
Treatment of advanced colorectal cancer in the era of biologics

89 INVITED

Molecular markers and patient selection in colorectal cancer

P. Johnston. *UK*

Abstract not received.

90 INVITED

Signal transduction pathways in colorectal cancer (CRC)

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An emerging understanding of the molecular pathways that characterize cell growth, cell cycle, apoptosis, angiogenesis and invasion has provided novel targets in cancer therapy. Numerous proteins have been implicated as having a crucial role in CRC. There are different targets according to their cellular localization like: (a) membrane receptor targets (epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), insulin-like growth factor receptor (IGFR), platelet-derived growth factor receptor (PDGFR), tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)); (b) intracellular signaling targets (Ras/Raf/MEK/MAPK pathway, phosphoinositol-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR), src kinase and the hdm2/p53 complex, among others); and (c) other protein kinases that regulate cell division (Aurora and Polo kinases and cyclin dependent kinases (CDK)). In this session we aim to review the current knowledge of some of these signaling pathways as well as the potential targets for innovative drugging in CRC.
The PI3K/AkT/mTOR pathway controls many cellular processes that are important for the formation and progression of cancer, including apoptosis, transcription, translation, metabolism, angiogenesis and cell cycle progression. The PI3K signaling pathway is upregulated in many CRC, and this upregulation positively correlates with increased tumorigenic potential of colon adenocarcinoma cell lines. Mutations in PI3CA (which encodes the P110α catalytic subunit) have been identified in up to 40% of CRC. A correlation between PI3K mutations and advanced stage of tumorigenesis, just before cell invasion, has been observed. Increased expression and activation of Akt has been noted in CRC. mTOR downstream and upstream effectors have been shown to be activated in around 1/3 of CRC.
C-src is a non-receptor tyrosine kinase protein overexpressed and activated in many human cancers, including CRC and is associated with advanced-stage and distant metastases. C-src is also of particular interest in colon cancer because it is overexpressed and/or activated in a wide range of tumors that also overexpress several receptor tyrosine-kinases, indicating the potential role for cross-talk interactions in promoting tumorigenesis.
Emerging data from the clinical development of new drugs directed to these targets is providing novel opportunities in the treatment of patients with CRC that will probably translate in efficacy advantage in the next years.

91 INVITED

Optimal strategy for integration of biologics in treatment of metastatic colorectal cancers

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The management of patients with metastatic colorectal cancer (CRC) has changed dramatically over the last years, with increasing chances of prolonged survival. The development of new cytotoxic and targeted agents as well as the multidisciplinary management of patients with resectable and initially non-resectable metastases contribute to the progress. The development of the cytotoxic agents irinotecan, oxaliplatin and capecitabine and of the biological agents bevacizumab, cetuximab and panitumumab has clearly increased the therapeutic options for patients with metastatic CRC.
It has been shown in randomized phase III trials that bevacizumab, when combined with irinotecan plus bolus 5-FU/LV (IFL) in the first-line treatment of metastatic CRC and with FOLFOX in second-line treatment leads to an increased median survival, progression-free survival (PFS) and response rate (RR) compared to the cytotoxic chemotherapy alone. Moreover, it has been demonstrated in a few randomized phase II studies and in a combined analysis of these phase II studies that bevacizumab increases the activity of 5-FU/LV in the first-line setting. The recent randomized phase III study of FOLFOX compared to capecitabine plus oxaliplatin $\pm$ bevacizumab in the first-line treatment shows that capecitabine is as effective as IV 5-FU/LV when combined with oxaliplatin and that bevacizumab increases the PFS of the fluoropyrimidine/oxaliplatin combination. The data from phase 2 studies with irinotecan and capecitabine (without bevacizumab) show also a high activity, although more uncertainty remains on the optimal dose of this combination in view of some reports of higher toxicity of the combination capecitabine plus irinotecan.
Cetuximab is active in epidermal growth factor receptor (EGFR)-expressing irinotecan refractory metastatic CRC. The combination of cetuximab with irinotecan is more active in this setting than cetuximab alone. The combination of cetuximab plus irinotecan leads to an increased RR and TTP compared to cetuximab alone in irinotecan-refractory CRC. It has been shown also that panitumumab, a human monoclonal antibody against the EGFR is active in irinotecan- and oxaliplatin-refractory metastatic CRC. The RR of the anti-EGFR antibodies cetuximab and panitumumab as single agent in EGFR expressing chemorefractory CRC is consistently around 10%. In a large phase III trial it was shown that panitumumab increased significantly the PFS compared to best supportive care in EGFR expressing metastatic CRC refractory to oxaliplatin and irinotecan. In another large randomized trial of cetuximab versus best supportive care, cetuximab prolonged the PFS as well as the survival. The PFS of the combination FOLFIRI/cetuximab was significant longer than that of FOLFIRI alone in a phase 3 trial in the first line treatment of CRC.
With this information in mind, bevacizumab is often used in clinical practice in combination with an active cytotoxic regimen in the first-line treatment of metastatic CRC (FOLFIRI or FOLFOX) and cetuximab plus irinotecan in chemorefractory CRC, at least if patients are fit and if there are no contraindications for these therapeutic options.
Many open questions and challenges remain in relation to the use of the anti-VEGF and anti-EGFR antibodies in metastatic CRC. Answers are needed to optimize the outcome for patients and the more optimal use of the resources. A crucial challenge is to demonstrate which patients are more likely to respond to bevacizumab-containing regimens and to the anti-EGFR antibodies cetuximab and panitumumab. Predictive molecular markers for a benefit on angiogenesis inhibitors are not yet available. Despite intensive research, large studies validating predictive molecular markers for response to anti-EGFR antibodies are not yet available in metastatic CRC. The clinical studies evaluating the activity of cetuximab and panitumumab have been carried out in EGFR-expressing tumors, as determined by immunohistochemistry (IHC). The intensity of EGFR immunostaining is not related to antitumor activity, and a clinical benefit has also be noted in patients whose tumors had no EGFR immunostaining. EGFR gene mutations have not been demonstrated to play a role in the response prediction in CRC. Although it has been reported in a small study that EGFR gene copy number, as assessed by fluorescence in-situ hybridization (FISH), correlates with the propensity of CRC to respond to EGFR-directed antibodies, this finding is at the moment very controversial. In a few other retrospectieve studies K-ras mutations were associated with low activity to cetuximab.