systemic therapy alone will result in inferior results. Many investigators support the use of radiotherapy after the completion of chemotherapy. The recent and rapid development and application of the microarray technology for identification of patients at risk for relapse should also be focused on identifying those patients who have tumours tending to relapse only locally versus systemically aiming at tailoring the up-front therapy more optimally.

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Epidermal Growth Factor Receptor (EGFR) therapies in colorectal carcinoma - the European data

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EGFR is expressed or upregulated in 60-85% of CRC and its expression is associated with poor survival. The two most extensively evaluated therapeutic approaches targeting the EGFR signalling pathway are the use of monoclonal antibodies (mAb) and tyrosine kinase inhibitors (TKI). Cetuximab is a chimeric mAb that specifically binds to the EGFR. Two US phase II non-randomised studies, conducted in patients with advanced CRC refractory to irinotecan and fluorouracil based chemotherapy, have shown an objective response rate (ORR) of 22.5% when combined with the same dose and schedule of irinotecan and ORR of 10.5% when cetuximab was used as monotherapy. A large European multicentre randomised study was performed comparing combination of cetuximab and irinotecan with cetuximab monotherapy in the same patient population. 218 patients were randomised to the combination arm and 111 to the monotherapy arm. Baseline characteristics were balanced with 63% of patients had prior oxaliplatin exposure. The ORR was 22.9% (95% confidence interval [CI]: 17.5-29.1%) in the combination arm and 10.8% (95% CI 5.7-18.1%) in the monotherapy arm and this difference in ORR was significant (p=0.0074). ORR in both arms were similar in those with prior oxaliplatin treatment and appeared to correlate with the occurrence of skin reaction, although no correlation was seen with the intensity of immunohistochemical EGFR staining on tumour samples. In addition, time to tumour progression was significantly longer in the combination arm compared to the monotherapy arm (median 4.1 months vs. 1.5 months respectively; log rank p

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EGFR inhibitors in the treatment of lung cancer

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Epidermal Growth Factor Receptor (EGFR) is commonly overexpressed in a number of epithelial malignancies and is often associated with an aggressive phenotype (e.g. non-small cell lung cancer (NSCLC), bladder cancer). EGFR is present in over 50% of cases of NSCLC, head & neck squamous cell carcinomas (HNSCC) and colon cancer. Several EGFR-targeting agents have been recently developed (C225, ABX-EGF, E7.6.3, EMD 55900, ICR62, ZD1839, CP358774, PD168393, CGP75166/PKI166, CGP59326A, BIBX1382). The 2 most advanced EGFR inhibitors in development are C225 (CetuximabTM) and ZD1839 (IressaTM). C225 is an antibody directed against the ligand binding domain of human EGFR, which competes for receptor binding with EGF and other ligands. In vitro, CetuximabTM inhibits EGFR tyrosine kinase (TK) activity and proliferation of EGFR-overexpressing squamous cell carcinoma cell lines. Synergy was observed with doxorubicin, cisplatin and radiation in preclinical models. In phase I trials, major toxicity has been dermatological (rash and acneic skin reactions); allergic reactions have also been observed in about 3% of cases. This agent, administered iv. weekly, is presently in phase III trials in HNSCC and colon cancer. IressaTM, a synthetic molecule which targets the EGFR ATP binding site, is a very specific inhibitor of EGFR TK activity. Synergy has been observed with paclitaxel and cisplatin. In phase I trials, responses were seen in advanced NSCLC, and cutaneous toxicity and diarrhea were the most important side effects. Oral chronic administration daily is feasible. Two large randomized trials have been completed in advanced NSCLC in combination with chemotherapy. A large phase II study in second and third line has demonstrated a single agent activity of 18.5%. Another large phase II study in patients who received prior platinum and docetaxel obtained a response rate of 11%. There was no difference in response rate between the 250 and the 500 mg/day doses, but side effects were higher in patients who received the 500 mg dose. A very similar small molecule, OSI-774 (Tarceva), has also shown activity in this setting. Two large randomized phase III studies of Iressa have recently been completed and analyzed in which 2 doses of Iressa (250 or 500 mg/day) or placebo were given in combination with 2 different chemotherapy regimens (carboplatin-paclitaxel or carboplatin-gemcitabine). These studies failed to demonstrate an increase in survival by adding Iressa together with chemotherapy in patients with advanced NSCLC.

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EGFR therapies with radiation (the head and neck data)

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Over one half of cancer patients worldwide receive radiation in the treatment of their cancer, and for several tumor types such as squamous cell cancer (SCC) of the head and neck (H&N), radiation represents a central or stand alone form of therapy. The rich overexpression of epidermal growth factor receptor (EGFR) in the vast majority of H&N cancer patients provides a particularly strong clinical/biological rationale for study of EGFR inhibitory strategies in this patient cohort. Substantial preclinical data identifies the capacity of EGFR inhibitory agents to augment the anti-tumor effects of ionizing radiation. Mechanisms for enhanced radiation response following EGFR inhibition include effects on cellular proliferation, apoptosis, damage repair, angiogenesis, invasion and metastases. Clinical trials which specifically evaluate the impact of EGFR inhibition on outcome for advanced H&N cancer patients are maturing. Several phase I/II clinical trials with anti-EGFR monoclonal antibodies and with small molecule inhibitors of the EGFR tyrosine kinase are underway or complete in H&N cancer patients in combination with radiation or with chemoradiation. In the Phase III setting, an international trial has recently completed enrollment of 416 patients treated definitively for advanced SCC of the H&N. Patients received either high-dose radiation alone (majority with hyperfractionation or concomitant boost radiation schedules) or radiation plus weekly infusions of the monoclonal antibody C225 (Erbitux, Cetuximab) during a seven-week treatment course. This represents a very powerful clinical trial for the EGFR field in that it will provide an unencumbered assessment regarding the capacity of EGFR inhibition to modulate radiation response in a large cohort of advanced cancer patients treated with curative intent. Locoregional tumor control and overall survival will be analyzed in this randomized trial. Correlative studies will also be performed from tumor materials gathered from patients for EGFR analysis. In light of consistently high expression levels of EGFR, H&N cancer has also served as a valuable model for examining response rates for EGFR inhibitors in the recurrent and metastatic disease setting. The current status of EGFR inhibitor studies in H&N cancer will be updated during this session.

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EGFR therapies in other tumour types

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The EGFR is expressed in a variety of tumors including non-small cell lung cancer, colorectal cancer, head an neck tumor, renal cell carcinoma, ovarian, prostate and pancreatic tumors, among others. In addition of the antitumor activities reported with anti-EGFR compounds in non-small-cell-cancer and colon carcinomas, antitumor activity has also been reported in other tumor types. Studies with the monoclonal antibody (Mab) IMC-C225 (cetuximab) have been conducted. In patients with refractory head and neck cancer, with documented progression after having received at least two cycles of platinum-based therapy, an 11% response rate was observed when IMC-C225 was added to the platinum regimen. A small phase III study in head and neck tumors comparing cisplatin and placebo to cisplatin and IMC-C225, more than doubling of the response rate was observed in the IMC-C225 arm. IMC-C225 can also be administered safely in patients with head and neck cancer, when given in combination with radiation therapy, with 13 complete responses and 2 partial responses in 16 patients. A phase III study of radiation + IMC- C225 in patients with advanced head and neck tumors has completed accrual. In a phase II study of another anti-EGFR Mab, ABX-EGF, in advanced renal cell carcinoma, clinical activity was also documented in patients that had failed or were unable to receive IL-2. EMD-7200, a humanized Mab, has also shown activity against a variety of tumor types. There is also emerging data of clinical activity with low molecular weight erbB (EGFR and related receptor-family members) tyrosine kinase inhibitors (TKI). In a single agent phase II study with the anti-EGFR TKI ZD1839 in tumors of the head and neck, an 11% response rate was seen. No activity has been seen against prostate carcinoma and minimal activity against breast cancer. Studies with OSI-774, another EGFR inhibitor, have also reported activity in ovarian carcinoma, head neck tumors

and glioblastoma. In ovarian carcinoma, the response rate was 6% and in head and neck, in a multicenter trial of 124 patients that had been previously treated, the overall response rate was 5%. Clinical activity with GW2016, a pan-erbB inhibitor, has also been observed in trastuzumab-refractory HER2 overexpressing breast cancer. In summary, there is growing evidence that anti-EGFR therapies are active in a variety of tumor types in addition to non small cell lung cancer and colon cancer.

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Melanoma biology and surgical margins

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Skin melanoma, unlike other cancers, occurs at the body surface: it can be detected and treated before it reaches competence for metastasis. The impact of surgery is unrivalled in this condition only. Beyond 0.75-1.00 mm thickness, an increasing proportion of melanomas acquire metastatic properties.

There is today evidence that wide surgery does not help and that surgery is limited to local control of the disease.

Local resection margins. According to randomised trials, the territory of early spread - without concomitant distant micrometastases -that can be eradicated by surgery, is shrinking. It was demonstrated that 3-4 cm resection margins are not better in term of recurrence and survival than 1 or 2 cm. Nowadays, most melanomas can be adequately resected without skin graft.

Regional lymph nodes metastases. Regional *elective* lymph node dissection, for high-risk melanoma (1.5 mm thick or more) does not improve survival, as compared to delayed lymph node dissection performed when clinical metastases appear. It is the same for prophylactic isolated limb perfusion with melphalan, which reduces the rate of in-transit metastases but does not improve survival.

Sentinel node biopsy allows early detection of regional lymph node metastases, with minimally invasive surgery. Ongoing randomised study will evaluate its impact on survival. Considering the experience with elective lymph node dissection, it is unlikely that *selective* - as opposed to *elective*- lymph node dissection, for positive sentinel node, will influence survival. The already extensive experience with sentinel node biopsy provides a death risk hierarchy:†one N2 node (with clinical metastasis), N1 node -or sentinel node- with micrometastasis and N0 node with no histologically detectable micrometastasis but PCR positive, give, respectively, 50%, 60% and 70% 5 years survival. In other terms, the earlier the detection of metastasis, the longer the survival. In terms of growth kinetics, the earlier the detection of metastasis, the longer the time to death, without evidence that surgery would have an impact. Only in a yet unpredictable subset of patients with lymph node confined disease, surgery might have an impact. It is hoped that, in the future, gene expression profiles of primary melanoma will help to pick out these patients. Multivariate analysis showed that the status of sentinel node is the most powerful prognosis factor of primary melanoma.

Sentinel node biopsy is a valuable tool for selecting patients for adjuvant treatments, in the frame of clinical trials, where micrometastatic and clinically involved lymph nodes are separately entered.

In-transit metastases. In-transit metastases can be eradicated in 50% of cases by isolated limb perfusion with melphalan, under mild hyperthermia. When in-transit metastases are recurrent, or deep seated, or bulky, the combination of tumour Necrosis Factor (TNF) to melphalan and Interferon gamma gives around 80% complete responses. This is the first antivascular treatment of cancer efficient in clinic, but it has no effect on survival.

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Adjuvant therapy in melanoma

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Adjuvant therapies for patients with melanoma at high risk of relapse whether local such as excision margins, elective regional lymph node dissection and prophylactic isolated limb perfusion, or systemic such as chemo-immuno-, immunochemo- or vaccination therapy have little or no impact on survival when evaluated in randomized trials. The European approach to the treatment of each stage of malignant melanoma is characterized by thoughtful caution with particular atttention being paid to the avoidance of unwarranted mutilation or toxicity because phase III studies have failed to demonstrate unequivocal benefits for a more aggressive approach.

In Europe there is no standard adjuvant systemic therapy; high dose interferon is used sporadically in individual patients by some doctors but there is little enthusiasm for adopting this regimen as the standard of care because of its high toxicity profile and the lack of a clear beneficial impact on longterm survival. Less toxic lower dose maintenance IFN regimens, antiangiogenic agents and vaccine therapies are currently being explored.

Also in Europe, for the last last decade, the main focus has been on Interferon-alpha (IFNα), a pleiotropic cytokine with various direct and indirect inflammatory response modulating activities. Some of these activities may have direct or indirect antitumor effects. For such a wide range of biologic activities the dose for optimal biologic activity may differ greatly from the maximally tolerated dose as different effects are mediated by different concentrations of the IFNα. Because of its immunomodulatory effects it has been extensively studied in melanoma patients. Little antitumor activity has been demonstrated in metastatic stage IV melanoma, with overall response rates 10-15%, which was not dose-related. Yet, IFNα has been widely studied in the adjuvant setting for stage II and stage III disease. Many trials have been underpowered, have used very heterogeneous mixed patient populations, a wide variety of doses and treatment schedules, and have suffered from early and unplanned analyses.

Mature data are still pending in some 3000 patients of the overall 6000 patients that participated in adjuvant trials. A metaanalysis has demonstrated a similar impact on relapsefree survival across various dose-ranges of IFNα, but *no* significant impact on overall survival. In light of the lack of impact on overall survival and the considerable to serious dose-dependent toxicity of IFNα we do not have a clearly dose- and schedule-defined role for IFNα in the adjuvant setting and have no evidence for a benefit of IFNα in stage IV melanoma. For the adjuvant setting the main question: efficacy of very toxic high dose therapy versus efficacy of non-toxic longterm treatment will be answered by the mature data of the large US-Intergroup high-dose and EORTC intermediate-dose and long term maintenance therapy trials.

Mature data of the largest trial, EORTC 18952, will be presented at ECCO 12

EORTC 18952 is the largest adjuvant IFN trial ever conducted in melanoma. The efficacy of intermediate doses of IFN-α2b (10 MU qd, 5d/wk,sc,4 wks followed by either (arm A) 10MU, sc, tiw, for ONE YEAR, or by (arm B) 5MU, tiw, sc for TWO YEARS, was compared to observation (arm C). in 1388 patients with high risk melanomas (T4N0M0, anyTN1-2M0). The intent-to-treat analysis has been used.

Results: A total of 740 pts developed distant metastases and 648 died; the median follow up was 4.2 yrs. The differences between the 3 arms were not statistically different neither in terms of distant metastasis free interval (DMFI) (p=0.22) not in terms of survival (p=0.40). An UPDATE will be presented at ECCO 12

Endpoint		Control	1-year IFN-α 2b	2-year IFN-α 2b
Distant Metastasis	4-year rate (SE)	44.4% (3.1%)	44.6% (2.2%)	48.7% (2.2%)
-Free Interval	HR (95% CI)	1	0.95 (0.79-1.16)	0.85 (0.70-1.04)
	P2-value		0.62	0.11
Survival	4-year rate (SE)	51.8% (3.1%)	53.0% (2.2%)	55.1% (2.2%)
	HR (95% CI)	1	0.99 (0.80-1.21)	0.89 (0.72-1.10)
	P2-value		0.88	0.27

HR: Hazard ratio

Treatment regimens were relatively well tolerated with an overall reporting of grade 3-4 toxicities in about 10% of the patients in the treatment arms A and B. In contrast to a very low rate of haematologic and hepatotoxic events the constitutional symptoms such as fatigue, anorexia and mood changes including severe depression were the most frequent causes for reductions, interruptions and for going of treatment early.

Conclusions: One year treatment with high–intermediate dose (10 MU) IFN-α 2b showed no effect at all whereas 2-year treatment with the lower dose with 5 MU had a marginal effect that failed to reach significance. Duration may therefore well be of more importance than dose.

The question whether IFN is a cytokine that requires long term maintenance treatment for a significant improvement of outcome is presently addressed in the EORTC18991 trial which recently completed accrual of 1200 patients and investigates the impact of 5 years of treatment with PEG-Intron in comparison to observation in stage III melanoma.

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Chemo versus biochemotherapy in metastatic melanoma

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Treatments for metastatic melanoma remain far from satisfactory: approximately one fifth of patients respond and median survival, at 6 months,