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,