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

F.J. Lejeune. *Centre Hosp. Univ. Vaudois, Multidisiplinary Oncology Centre, Lausanne, Switzerland*

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

A.M.M. Eggermont. *Erasmus Medical Center Rotterdam Daniel den Hoed Cancer Center, Department of Surgical Oncology, Rotterdam, The Netherlands*

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

M. Middleton. *Cancer Research UK Oncology Unit, Churchill Hospital, Oxford, United Kingdom*

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

has not improved over the last 20 years. During this time the mainstay of treatment has been single agent chemotherapy, most often with dacarbazine although other alkylating agents, platinum based drugs and vinca alkaloids are also used. Immunotherapies hold some promise, yet phase II studies of interferon and interleukin 2 have not indicated better outcomes for this group of patients than with chemotherapy. A small minority of patients achieve durable complete responses with interleukin 2. Twice in recent years important advances in treatment appear to have been made, but on both occasions large scale studies have failed to confirm earlier results. In the 1980s phase II trials demonstrated greatly enhanced response rates for combination chemotherapy, particularly the Dartmouth regimen of dacarbazine, BCNU, cisplatin and tamoxifen. Multi-centre phase III trials confirmed this increase in responses, but found no impact upon overall survival. The initial, promising results are likely explained by patient selection, for within the grouping of metastatic melanoma there is a wide variation in survival time. The recent AJCC classification highlights this: 29% of patients with M1a disease will be alive at 2 years, compared with 7% with stage M1c. A similar story is being played out with biochemotherapy. Single institution phase II trials suggested a substantial benefit for this approach in patients able to tolerate treatment. Initial interest centred upon the combination of dacarbazine and interferon. However, an ECOG study involving over 250 patients found no advantage to this combination over chemotherapy alone, a finding borne out in a recent meta-analysis. Other groups have tested a variety of combination chemotherapies with varying regimes of interferon and interleukin 2. Phase III trials of the most promising biochemotherapies, involving hundreds of patients, have shown no survival advantage over chemotherapy alone. In 2003 the best treatment option that we can offer patients with metastatic melanoma, outside of clinical trials, is still single agent chemo- or immunotherapy.

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Design and testing of chemically–defined melanoma vaccines

J.-C. Cerottini. *Ludwig Institute for Cancer Research, Lausanne Branch, Epalinges, Switzerland*

The molecular identification of melanoma antigens recognized by CD8 and CD4 T cells has paved the way to approaches for the design of therapeutic cancer vaccines that are based on the use of chemically defined antigenic peptides and adjuvants. Most of the trials in progress are focused on the vaccination of melanoma patients with peptides derived from cancer germline gene products, such as the MAGE family, and/or melanocyte lineage-associated proteins, such as the Melan-A/MART-1 antigen. The selection of the antigenic peptides to be incorporated in a given vaccine has to take into account the HLA allele pattern expressed by individual patients as well as the antigenic peptide profile of individual tumors. In some instances, the immunogenicity of peptides can be increased substantially by altering specific aminoacid residues at positions that anchor the peptide to the corresponding HLA molecule and/or confer susceptibility to proteolytic degradation by proteases. As the number of variables to be tested for the optimization of antigen-specific T cell responses is very large, the initial evaluation of vaccine-based strategies cannot rely on usual clinical end points, such as tumor regression or time to recurrence, because of the number of patients and years required to achieve meaningful results. Instead, immunological assays that enable quantitative and qualitative monitoring of antigenic peptide-specific T cell responses are being used to evaluate the immunogenicity of candidate vaccines in phase I clinical trials. Although monitoring methodologies have undergone considerable improvement over the past few years, the complexity of the immune response makes the identification of the most effective immunization procedures quite a challenge. Moreover, application of these assays to the monitoring of specific CD8 T cell responses induced by peptide-based vaccines in melanoma patients has revealed significant interindividual differences, which may reflect the preexistence, or lack thereof, of a spontaneous tumor antigen-induced response in these patients. It is thus necessary to use standardized assays to evaluate the development of immune responses triggered by different vaccine strategies in individual patients. In addition, immunological monitoring should include analyses both in the peripheral circulation and at the tumor site because of possible numerical and functional discrepancies between tumor antigen-specific T cells residing in these compartments

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Conformal radiotherapy in prostate cancer: development of the new "standard of care"

D.P. Dearnaley. *The Royal Marsden Hospital, Department of Radiotherapy, Sutton, United Kingdom*

The last decade has seen the widespread implementation of CFRT and dose escalated treatments for prostate cancer. Large "phase I" studies, principally from specialist centres in the USA, have documented the safety of these techniques with reports of apparent improvements in disease control. However, it has recently been appreciated that cohort effects in sequentially treated groups of patients may have led to significant bias due to "stage migration". The results of single centre phase III dose escalation trials (MD Andersen and Institute of Cancer Research/Royal Marsden Hospital) indicate improvements in PSA control for men with advanced localised disease, but benefit for patients with good prognosis disease has not yet been confirmed. Assessment of other clinically meaningful endpoints such as metastases free and overall survival will become possible as other larger multicentre trials, which will in total recruit approximately 4,400 men, reach maturity. Data from these trials and other sources should more clearly define dose-volume-complication relationships and individualisation of treatment based on prognostic features for tumour control and complication probabilities may become realistic.

The role of IMRT is yet to be clearly defined but may offer advantages for some anatomic configurations; complex high dose volumes can be shaped and pelvic lymph node irradiation achieved with a significant reduction in bowel volumes treated to high dose. Modelling studies have shown the potential benefit of intra-prostatic boosts, but improvements in MRI and functional imaging are needed to define such "dominant intraprostatic lesions". Such refinements in treatment require attention to the details of all parts of the "technology chain" in particular to the verification of treatment accuracy taking into account the potential for prostate target movement. A variety of localising devices (fiducial markers, localising catheter, ultrasound, rectal balloons) are being assessed to enable development of guided radiotherapy techniques. These methods of "physical optimisation" will be complementary to "biological optimisation" approaches using both altered fractional or combined modality treatments.

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Combination of hormonotherapy (HT) and external irradiation (RT) in prostate cancers. Neo-adjuvant and/ or adjuvant hormonotherapy?

M. Bolla. *Centre Hospitalier de Grenoble, Department of Radiotherapy, Grenoble, France*

Androgen suppression improves the outcome of external irradiation: it possibly eliminates occult systemic disease outside the irradiated volume and has at least an additive effect on local control by inducing apoptosis. RTOG and EORTC trials investigated this combination in locally advanced prostate cancer, cT2c-T4 N0-1 M0 (UICC 1992). Protocol 86-10compared androgen deprivation (flutamide and goserelin) with radiation therapy vs radiation therapy alone in patients with large T2 or T3-4 tumors; androgen deprivation was initiated 2 months prior to starting radiotherapy and stopped at the completion of radiotherapy. Hormonotherapy increased the local control, distant metastases free rate, progression free survival and overall survival in patients with Gleason score 2-6. Protocol 85-31 was devoted to adjuvant androgen suppression with goserelin in T1-2 patients with regional lymph node involvement, T3 regardless of regional lymph node status or pT3 after prostatectomy. Goserelin was started at the end of the radiotherapy and continued indefinitely. There was an increase of the local control, distant metastases free rate, disease free survival; in patients with centrally reviewed tumors with a Gleason score of 8 to 10 there was a difference in survival in favor of the adjuvant goserelin arm. In protocol 92-02, patients with T2c-T4 tumors received goserelin and flutamide two months before and two months during radiation and were randomized to no further therapy or to 24 additional months of goserelin alone (LTAS). The LTAS arm significantly improved the disease free survival, local control, time to distant metastases, time to biochemical failure and showed a favorable trend for disease specific survival. In trial 94-13 the benefits of whole pelvis radiotherapy are manifested when HT is given before and during RT. EORTC trial 22861 has shown that androgen suppression with goserelin given during and for 3 years after external irradiation improves disease free and overall survival whatever the Gleason score is. EORTC trial 22961 closed in 2001, compared surveillance to hormonotherapy with triptoreline for 2·5 years after external irradiation and 6 months of combined androgen blockade. It is now possible to modulate the duration of hormonotherapy