84% of the patients. The patients were screened for HER2 overexpression by the HercepTest™ and were analysed for *TOP2A* abnormalities with the *TOP2A* FISH pharmDx™ (DakoCytomation, Glostrup). Cases were scored as *TOP2A* amplified when the ratio of *TOP2A* gene signals and centromere 17 control signals was * 2. A deletion was scored when the ratio was < 0.8. Recurrence-free survival (RFS) was used as end-point and was defined as the period from enrolment to relapse (local or distant)

Results: So far *TOP2A* gene copy changes have been evaluated in all 307 tumours known to be HER2 2+ or 3+ positive and in 105 tumours known to be HER2 0 or 1+ positive. *TOP2A* amplification or deletion was found in 37% of the patients analysed so far. When adjusted for classical prognosticators, we found that patients with *TOP2A* alterations had a reduced relative risk of recurrence if treated with CEF (HR = 0.42; CI: 0.27-0.66). This in contrast to patients with a normal *TOP2A* genotype for whom similar outcome was observed in the CMF and CEF treated groups, (RFS: HR = 1.01; CI: 0.68-1.49).

Conclusion: *TOP2A* gene copy number changes seem to predict a favourable effect of adjuvant epirubicin therapy in primary breast cancer. *TOP2A* changes were not restricted to HER2 altered tumours and the *TOP2A* analysis will be completed on all tumours.

675 ORAL

Anastrozole is an effective neoadjuvant therapy for patients with hormone-dependent, locally-advanced breast cancer irrespective of cerbB2 status

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Background: the efficacy and safety of anastrozole 1 mg once daily as neoadjuvant therapy in postmenopausal women with locally-advanced breast cancer (LABC) was investigated in an open-label trial.

Methods: 112 patients were included in the trial; patients had histopathologically-confirmed unilateral, oestrogen receptor-positive LABC (stage IIIA/B). After 3 months of neoadjuvant treatment with anastrozole, clinical responses were evaluated. All patients with a complete or partial clinical response (cCR or cPR) underwent surgery (radical modified mastectomy), then continued on 1 mg anastrozole as adjuvant therapy for 2 years or until progression. Primary end point was objective response (cCR+cPR) rate, secondary endpoints included pathological complete or partial response (pCR or pPR) rate. CerbB2 and Ki67 analysis was carried out on all tumours using the histopathological blocks taken at the time of first diagnosis.

Results: tumour response rates for all patients and according to cerbB2 and Ki67 status are presented in the table.

Tumour response	All patients (%)	cerbB2 status (%)		Ki67 status (%)	
		Negative	Positive	<10%	*10%
	n=112	n=79	n=33	n=61	n=51
Clinical response					
cCR	54.5	60.8	39.4	63.9	43.1
cPR	28.6	34.2	15.2	32.8	23.5
No clinical response	17.0	5.1	45.5	3.3	33.3
Objective response					
(cCR+cPR)	83.0	94.9	54.5	96.7	66.7
Pathological response					
pCR	16.1	21.5	3.0	23.0	7.8
pPR	67.0	73.4	51.5	73.8	58.8
No pathological response	17.0	5.1	45.5	3.3	33.3

Conclusions: the response rates following neoadjuvant anastrozole indicate that it is highly effective in postmenopausal women with hormone-dependent LABC, regardless of cerbB2 or Ki67 status. Further follow-up is required to determine the impact of anastrozole on disease-free, and overall, survival following surgery in these patients.

676 ORAL

An assessment of fracture rates over time (between 6 and 48 months) in the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial

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Background: Anastrozole (1 mg once daily [od]) has shown efficacy benefits compared with tamoxifen (20 mg od) for treatment of postmenopausal women with early breast cancer (EBC). An overall assessment of safety data showed a benefit for anastrozole, although incidence of fractures was significantly greater with anastrozole compared with tamoxifen.

Methods: Fracture incidence from the ATAC study was assessed every 6 months up to 48 months of treatment; differences in patterns of time-to-fracture for anastrozole versus tamoxifen were assessed.

Results: At the first analysis (median duration of therapy 31 months), fracture incidence was 5.9 vs 3.7% for anastrozole and tamoxifen, respectively (relative risk [RR] anastrozole/tamoxifen 1.59). Data from a safety update (median duration of therapy 37 months) indicated that risk of fractures did not worsen over time (fracture incidence was 7.1 vs 4.4% for anastrozole vs tamoxifen, respectively; RR 1.60, 95% confidence interval 1.301.97, p<0.0001).

Time (months)	6-monthly fracture rates/100 patients		Anastrozole/tamoxifen 6-month hazard ratio
	Anastrozole (n=3092)	Tamoxifen (n=3093)	
6	1.11	0.99	1.14
12	0.93	0.58	1.61
18	1.36	0.69	1.98
24	1.57	0.61	2.57
30	1.39	0.96	1.45
36	1.09	0.66	1.66
42	1.50	1.37	1.09
48	1.07	0.80	1.34

Fracture rates (see table), remained fairly constant for both anastrozole (range 0.93 to 1.57) and tamoxifen (0.58–1.37), with the 6-monthly fracture rates for anastrozole plateauing after 24 months. The maximum differences between anastrozole and tamoxifen were seen at 18 and 24 months. Similar patterns were seen for osteoporotic fractures' (hip + spine + wrist).

Conclusions: anastrozole leads to an increased fracture incidence compared with tamoxifen, a drug known to have a positive effect on bone mineral density. Importantly, the fracture rate in the anastrozole-treated group appears to stabilise after peaking at 2 years. Although differences in fracture rates exist, the overall benefit to risk in EBC remains unchanged, favouring anastrozole.

Head and neck cancer

677 ORAL

Results of a phase II study of cetuximab in combination with carboplatin in patients (pts) with recurrent or metastatic nasopharyngeal carcinoma (R&M NPC) who failed to a platinum-based chemotherapy

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Background: Recurrent or metastatic NPC pts usually respond well to palliative platinum-based chemotherapy, indeed for a short period. Relapsing or non-responding patients have few valid therapeutic options, if any. Since studies have revealed a high expression rate of epidermal growth factor receptor (EGFR)- up to 94% in NPC pts with its prognostic significance, cetuximab (Erbitux®), a chimeric anti-EGFR monoclonal antibody, has been evaluated in R&M NPC pts.

Design: a multi-center, single arm phase II study in R&M NPC pts with measurable disease and disease progression on or within 12 months after end of a platinum-based chemotherapy. Experimental therapy: cetuximab (Erbitux™) 400 mg/m^2 loading dose followed by 250 mg/m^2 weekly plus carboplatin AUC 5 administered every 3 weeks.

Results: 60 pts were enrolled into the trial. 85% of pts had metastatic disease. Median age was 45 years (range 23-64) and median KPS at entry was 90 (range 60-100). 53 pts received radiotherapy (RT alone 12 pts, RT/CT 41 pts) and all pts had received a palliative platinum-based therapy. Among 57 out of 60 (14 F, 46 M) pts who were evaluable for efficacy, there were 7 (12.5%) pts with confirmed partial responses (PR), 3 (5.4%) pts having an unconfirmed PR, and 26 (46.4%) pts with stable disease (SD). The clinical benefit (PR+SD) was 64.3%. Median duration of treatment received was 2.5 months. The median time to response was 1.37 months (range 1.27-2.70 months), the median time to progression was 5.70 months (range 4.43-7.23 months), and median overall survival (n=43) was 6.47 months (range 0.17-18.4). Safety profile: skin rash (91% any NCI/CTC grade, 8% grade 3-4), nausea & vomiting (89% any grade, 8% grade 3-4), asthenia (36% any grade, 5% grade 3-4), anemia (33% any grade, 21% grade 3-4), thrombocytopenia (24% any grade, 10% grade 3-4). No serious allergic reactions were encountered.

Conclusion: Cetuximab (Erbitux™) in combination with carboplatin has good activity and acceptable safety profile in heavily pretreated pts with R&M NPC who failed to platinum therapy.

678 ORAL

EGFr expression and histopathological differentiation influence the response to accelerated fractionation in squamous cell carcinomas of the head and neck (HNSCC). Analysis of 702 patients from the randomized DAHANCA 6 and 7 trial.

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Background: Accelerated fractionation of HNSCC results in improved tumor control compared to conventional schedules. However, the response may be heterogeneous and not all tumors benefit from such treatment. A previous study has indicated that poor histopathological differentiation and low expression of EGFr may compromise the ability of tumors to express accelerated regeneration.

Patients and material: 702 patients with available tissue blocks from the DAHANCA 6 & 7 trial were evaluated for tumor differentiation and EGFr expression using immunohistochemistry. Treatment was radiotherapy to a total dose of 66-68 Gy given with 2 Gy/fx. All patients were randomly assigned to receive this in either 5 or 6 fx/wk, resulting in an overall treatment time of 6.5 or 5.5 weeks, respectively. The primary endpoint was actuarial 5-year loco-regional control.

Results: Poor differentiation was observed in 236 (34%) patients and low EGFr in 112 (16%) patients. There was some correlation between poor differentiation and lack of EGFr but otherwise there was no correlation between these parameters and classical prognostic factors. As shown in the full DAHANCA 6 & 7 trial, acceleration in this cohort of patients resulted in a significant improved 5-year loco-regional control rate (53% vs. 66%, $p<0.001$ for 5 fx/wk or 6 fx/wk, respectively). There was no effect of acceleration in poorly differentiated tumors (57% vs. 64%, n.s.), whereas well to moderate differentiated tumors showed a significant benefit (50% vs. 67%, $p<0.001$). Similarly, there was no effect of acceleration in tumors with low expression of EGFr, whereas high expression was related to a better outcome in tumors treated with 6 fx/wk (53% vs. 65%, p=0.004). By combining the two parameters it was apparent that the presence of either low EGFr *or* poor differentiation, which was found in 294 patients, resulted in lack of response to acceleration (57% vs. 63%, n.s.), whereas the other 408 tumors with well to moderate differentiation *and* high EGFr showed a marked response to acceleration with loco-regional control rates of 49% vs. 67%, p=0.0005. Multivariate analysis confirms that acceleration has no influence on loco-regional control in tumors with low EGFr or poor differentiation, whereas it is the case for well to moderate differentiated tumors with high EGFr.

Conclusion: The study illustrates the complexity of EGFr: EGFr alone has no predictive value whereas the predictive value of EGFr in combination with tumor differentiation is dependent of the overall treatment time of radiotherapy. Tumor repopulation may be linked with factors influencing control of tumor differentiation and proliferation. Poor histopathological differentiation and lack of EGFr expression indicate that such mechanisms are not functioning. From that follows that the beneficial use of anti-EGFr drugs could be more limited than expected.

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679 ORAL

Pretreatment gene expression profiling value in predicting the clinical outcome of patients with oropharyngeal carcinoma

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Background: Individual tumors display a wide range of responses to radiotherapy and/or chemotherapy and consequently unpredictable outcome. The aim of the present study was to assess the predictive value of the pretreatment gene expression profiles of oropharyngeal squamous cell carcinomas.

Material and Methods: Twenty-six pretreatment biopsies from patients managed with radical radiotherapy were analyzed with microarrays containing 4132 cDNAs of human genes. Twelve from patients who were disease-free at a minimum follow-up of 12 months and 10 presenting with any event (locoregional or distant), while four patients served as a test.

Results: The selection of 738 genes expressing signal over background enabled the clustering of the whole group into two distinct groups according to their oncological outcome (with and without event). The profiles that best discriminate between the two groups are those from the first cluster of 11 genes, particularly 5 genes that showed a clear distinct pattern. To evaluate the predictive strength of the method, we examined 4 additional biopsies in a blind test and correctly predicted them to be in the disease-free group.

Conclusions: Pretreatment gene expression profiling represents a promising tool in predicting the clinical outcome of patients suffering from oropharyngeal squamous cell carcinoma and treated with radical radiotherapy.

680 ORAL

HPV infection as prognostic factor in squamous cell cancers (SCC) of oropharynx treated with surgery with or without radiotherapy (RT)

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Background: Head and neck squamous cell carcinomas (HNSCC) are generally associated with alcohol abuse and smoking, but for a subgroup of these tumors increasing data suggest a link to HPV infection. HPV positive (pos) oropharyngeal cancer seems to represent a distinct clinical entity. HPV pos cancers have been reported to have a better outcome although published series are heterogeneous in patient selection and treatment. Two studies showed a better radiosensitivity for HPV pos neoplasms. To verify the prognostic role of HPV infection in oropharyngeal SCC cancer we retrospectively analyzed a series of patients treated with surgery with or without RT.

Patients and Methods: Genomic DNA from paraffin embedded surgical samples of 55 patients treated at our Institution from April 1990 to June 1999 was extracted. The amount of HPV 16 and 18 DNA was analyzed by absolute quantitative PCR and then HPV16 pos cases were tested for E6 and E7 mRNA. Overall and cause-specific survival rates were tested according to Kaplan-Meier analysis.

Characteristics	HPV pos *n (%)*	HPV neg *n (%)*
Sex		
Male	7 (54)	34 (81)
Female	6 (46)	8 (19)
Median age (years)	58	57
Stage		
II-III	7 (54)	15 (36)
IV	6 (46)	27 (64)
Node status		
Negative	4 (31)	13 (31)
Positive	9 (69)	29 (69)
Site		
Tonsil	4 (31)	16 (38)
Base of tongue + GlossoTonsillar Sulcus	7 (54)	14 (33)
Other	2 (15)	12 (29)
Treatment		
Only surgery	4 (31)	17 (40)
Surgery plus radiotherapy	9 (69)	25 (60)
Relapse	4 (31)	23 (55)
Metachronous second tumors	0	5 (12)