Methods: Sixty milimolar NaB was continuously administered intrathecally to 23 patients (pts) with recurrent or progressive MG using a balloon pump system and treatment was continued as long as possible by changing the pump containing NaB weekly. MCT1 expression was also examined by immunohistochemical staining with specific rabbit polyclonal anti-bodies in the center of the tumor and the brain tissue surrounding the tumor in specimens obtained just before commencement of CIA of NaB in 18 pts with recurrent or progressive MG, and the correlation of MCT1 expression with clinical response was evaluated.
Results: Sixteen of 20 evaluable pts showed anti-tumor effects including tumor regression in 11 pts. The overall median survival time of MG was 11.0 (330 days) months. Four of 5 pts with CSF tumor cell dissemination showed a therapeutic response, including temporary negative cytological conversion. However, specimens in all pts responded to the therapy showed marked MCT1 expression in the tumor. By contrast, 4 pts, who did not respond to therapy, showed a low grade of MCT1 expression in the tumor.
Conclusion: The present therapy was well tolerated, resulted in long-term inhibition of tumor growth in some pts, and showed therapeutic safety. The most important favorable factor influencing the response to CIA of NaB was high grade of MCT1 expression in the nucleus and cytoplasma in the center of the tumor.

8737 POSTER

High resolution analyses of loss of heterozigosity (LOH) of chromosome 22 by SNP-arrays and microsatellite markers in meningiomas

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Background: The most frequent chromosomal losses in meningiomas affect the long arm of chromosome 22. Several molecular technologies have been applied to find candidate genes in this chromosome. Microsatellite markers PCR analysis has been used to determine loss of heterozigosity (LOH) and actually single nucleotide polymorphisms (SNPs) arrays are avalaible to search LOH regions, that is consider a key event in the origen of many cancers. Our objective were to perform a genome wide study of LOH of chromosome 22 in meningioma patients using SNP-arrays and results validate with microsatellite markers.
Material and Methods: In the present study, chromosomal 22 LOH regions were analyzed by SNP-arrays in 50 meningioma paired samples with a total of 200 arrays and microsatellite markers were used in a group of tumors too.
Results: The genotype data of 6206 SNPs located on chromosome 22 with an average distance between SNP of 5.8 Kb was obtained. LOH regions were identified in 15 out of 50 cases combining SNP calls of pair normal and tumor samples. The other two third of cases did not presented any LOH region in chromosome 22. The results were verified using a independent method based on microsatellite markers PCR analysis with 8 markers – D22S535, D22S929, nf2CAV, D22S1172, D22S1162, D22S1156, D22S417 and D22S1056 – located in MN1(22q12.1), NF2 (q12.2), LARGE (q12.3), CARD10 (q13.1), FAM152B (q13.2), POLR2F-SOX10 (q13.1), A4GALT (q13.2), ARHGAP8 (q13.31) and TTL8 (q13.33) genes, in a subset of 15 tumors. LOH frequency were higher with PCR microsatellite study than SNP-arrays and both techniques present a high concordance. All cases were informative for more than half of the microsatellite markers analyzed (>5 loci to 11 loci)
Conclusions: In summary, SNP approach allowed extensively map LOH region of chromosome 22 in meningioma tumors. In contrast to diploid tumors (only one present LOH in 1 locus) LOH was a frequent finding in meningiomas with chromosome 22 losses.

8738 POSTER

Efficacy of glycopeptide cancer vaccine with adjuvants for treatment of intracranial transplanted melanoma B16

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Introduction: Despite recent advances in conventional surgical treatment, chemo- and radiotherapy innovative strategies are urgently needed for the successful treatment of brain cancer patients. Consequently, efforts aimed at developing new therapies have focused on new treatment strategies directed on disease elimination, tumor recurrence prevention and inhibition of metastatic dissemination. Cancer vaccines and adjuvants provided the important tools for manipulation of the immunological response to tumors, and therefore can be considered as one of the best alternative to high-toxic conventional anticancer therapies. The main goal of present study was to investigate the efficacy of glycopeptide cancer vaccine (gp50) alone and with adjuvants for therapeutic treatment of intracranial transplanted melanoma B16.
Materials Methods: The gp50 composed of originally prepared autologous 50 kDa-glycopeptide antigens was triply s.c. injected to C57Bl/6 mice with intracranial transplanted melanoma B16. Bacterial CpG DNA (bCpG DNA) and vitamin complex (VC – vitamins C and K_3 in ratio 100:1) were used as vaccine adjuvants. Mice from control group received injections of physiologic saline. The efficacy of immunotherapeutic treatment was evaluated using survival rates of tumor-bearing mice; and cytotoxic activity of splenic lymphocytes and histological examination of changes in mouse brain during vaccinotherapy.
Results: Administration of gp50 alone or combined with bCpG DNA or VC resulted in marked antitumor effect. Median survival rate of mice treated with gp50 alone and combined with bCpG DNA or VC were 27.7 ± 8.0 and 24.6 ± 4.9, 26.0 ± 6.9 days respectively compared with only 13.7 ± 3.8 days in control group. In mice from all treated groups significant increase of lymphocyte cytotoxic activity was also observed. Histological analysis of brain sections showed significant inflammatory lymphocyte infiltrates around tumor masses and necrotizing areas of melanoma cell in brain of mice injected with gp50 alone or with adjuvants as compared with control mice.
Conclusion: Present results suggest that application of gp50 alone or combined with such adjuvants as bCpG DNA and VC can be promising strategy for successful treatment of intracranial tumors.

Lung cancer

Oral presentations (Mon, 21 Sep, 11:00−12:45)

Lung cancer I

9000 ORAL

Mutations of EGFR (mEGFR) in tumour tissue and serum DNA from stage IV non-small-cell lung cancer (NSCLC) patients (p) prospectively treated with erlotinib

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Background: We evaluated mEGFR in tumor and matched serum at baseline and assessed their role in a multicenter trial of first- and second-line erlotinib in stage IV NSCLC p with mEGFR in tumor.
Material and Methods: mEGFR were detected in 350 of 2105p (16.6%) screened. 217p with mEGFR received erlotinib; 79 did not due to patient or physician decision. mEGFR were assessed in paired serum samples from 164 p with mEGFR in tumor for whom baseline blood samples were available. mEGFR testing in both tumor and serum was performed centrally. EGFR exon 19 deletions (del 19) were studied by length analysis of fluorescently labeled PCR products and the exon 21 L858R by a PCR Taqman assay.
Results: Overall response rate was 70%, time to progression (TTP) was 14 months (m), and median survival (MS) was 27 m. mEGFR status in the serum matched that in the tumor tissue in 97/164 p (59.1%), in 44.1% of p with PS 0, in 57.4% of p with PS 1, and in 78% of p with PS 2 ($P = 0.01$). There were no differences in the metastatic patterns either according to the presence of mEGFR in serum or according to the type of mEGFR. Response rate was 69.8% in 67 p without mEGFR in serum and 71.7% in 97 p with mEGFR in serum. TTP was 19 m for p with mEGFR only in tumor and 12m for p with mEGFR in tumor and serum ($P = 0.14$). TTP for p with del 19 only in tumor was 22 m vs 13 m for p with del 19 in both tumor and serum ($P = 0.36$). TTP for p with L858R only in tumor was 16 m vs 11

m for p with L858R in both tumor and serum (P = 0.13). In the multivariate analysis, male gender, L858R and the presence of mEGFR in serum were independent factors for poor prognosis (Table). MS was 31 m for p with mEGFR only in tumor and 28 m for p with mEGFR in tumor and serum (P = 0.21). When only the 97 p with mEGFR in both tumor and serum were analyzed, p with L858R were older than those with del 19 (73 vs 63 years, respectively; P = 0.01). Response rate was higher in p with del 19 (78.3%) than in p with L858R (59.4%) (P = 0.05). TTP for p with del 19 was 13 m vs 11 m for p with L858R (P = 0.07). MS for p with del 19 was 31 m vs 18 m for p with L8585R (P = 0.01).

Conclusions: mEGFR in serum could be an ancillary non-invasive method for genotyping when there is insufficient tumor tissue. The presence of mEGFR in serum is a prognostic marker for shorter TTP.

	HR	95% CI	p
Sex			
Female	1 (ref.)		
Male	2.39	0.39−0.93	0.001
Exon			
19	0.55	0.36−0.85	0.008
21	1 (ref.)		
Serum (EGFR)			
WT	1 (ref.)		
Mutated	1.63	1.05−2.55	0.03

9001 ORAL

Vandetanib plus docetaxel versus docetaxel as second-line treatment for patients with advanced non-small-cell lung cancer (NSCLC): a randomized, double-blind phase III trial

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Background: Vandetanib (ZACTIMA™) is a once-daily oral inhibitor of VEGFR, EGFR and RET signalling. The addition of vandetanib 100 mg/day to docetaxel (doc) prolonged progression-free survival (PFS) in a randomized phase II study in patients with previously treated advanced NSCLC (Heymach *et al*, JCO 2007).

Methods: The primary objective of this phase III study (ZODIAC; D4200C00032) was to determine whether vandetanib 100 mg/day+doc 75 mg/m^2 every 21 days (max 6 cycles) prolonged PFS vs placebo + doc. Secondary endpoints included overall survival (OS), objective response rate (ORR), time to deterioration of symptoms (TDS) and safety. Efficacy and safety in females were assessed as a co-primary analysis population. Eligibility criteria included stage IIIB/IV NSCLC, performance status (PS) 0−1 and previous chemotherapy.

Results: Between May 06−April 08, 1391 patients (mean age, 58 yrs; 30% female; 25% squamous; 10% brain mets; 85% stage IV; 35%/65% PS 0/1) were randomized to vandetanib+doc (n = 694) or placebo+doc (n = 697). Baseline characteristics were similar in both arms. At data cut-off, the median duration of follow-up was 12.8 months, 87% patients had progressed and 59% had died. The addition of vandetanib to doc showed a statistically significant improvement in PFS vs doc (hazard ratio [HR] 0.79, 97.58% CI 0.70−0.90; 2-sided $P < 0.001$), and a similar advantage in females (HR 0.79; 2-sided $P = 0.024$). Significant advantages for vandetanib + doc were also seen for ORR (17% vs 10%, 2-sided $P < 0.001$) and TDS (HR 0.77, 2-sided $P < 0.001$; FACT-L Lung Cancer Subscale). OS showed a positive trend for vandetanib+doc that was not statistically significant (HR 0.91, 97.52% CI 0.78−1.07; 2-sided $P = 0.196$). Exploratory clinical and molecular subgroup analyses for PFS and OS were generally consistent with the results seen in all patients. The adverse event profile was consistent with that previously observed for vandetanib in NSCLC. The vandetanib arm had a higher incidence of diarrhoea (42% vs 33%), rash (42% vs 24%), neutropenia (32% vs 27%) and hypertension (6.0% vs 1.7%). Nausea (23% vs 32%), vomiting (16% vs 21%) and anaemia (10% vs 15%) were less frequent in the vandetanib arm. The incidence of protocol-defined QTc prolongation in the vandetanib arm was 1.9%.

Conclusions: This study met its primary objective of PFS prolongation with vandetanib+doc vs doc alone. Vandetanib is the first and only targeted therapy to show significant clinical benefits when added to chemotherapy in phase III studies in second-line advanced NSCLC. An OS update will be performed in 2009.

9002 ORAL

A phase III, first-line trial of gefitinib versus cisplatin plusdocetaxel for patients with advanced or recurrent non-small cell lungcancer (NSCLC) harboring activating mutation of the epidermal growthfactor receptor (EGFR) gene: a preliminary results of WJTOG 3405

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Background: Patients with non-small cell lung cancer (NSCLC) harboring activating mutations of the EGFR gene respond remarkably well to EGFR specific tyrosine kinase inhibitor, gefitinib. However, its superiority to standard platinum doublet chemotherapy in terms of progression free survival (PFS) or overall survival (OS) is not known.

Material and Methods: Chemo naive patients with stage IIIB/IV or recurrent NSCLC, harboring activating EGFR mutation (either exon 19 deletion or L858R in exon 21) aged 75 years or younger, with PS of 0 or 1 were enrolled. Patients were randomized to receive either gefitinib (250 mg/day) until progression or cisplatin (80 mg/sqm) plus docetaxel (60 mg/sqm) day 1, given every 21 days for three cycles to six cycles. PFS was the primary endpoint. Assuming that PFS for gefitinib was 12.5months and for chemotherapy was 7 month based on the previous reports, hazard ratio would be 0.56. With this HR, 146 patients would be required to have a power of 0.8. However, sample size was set at 200 patients to allow HR up to 0.64.

Results: As of April 25, 164 patients had been randomized. Here, we report the preliminary data for 122 patients of the 164. Of 122, 55 patients were postoperative recurrence and 67 were with stage IIIB/IV diseases. Age, sex, stage, smoking history and absence or presence of postoperative adjuvant chemotherapy were well balanced between two groups. Percentages of the patients with age of 65 or older, female, non-smokers were 49%, 74%, and 75%, respectively. For all patients, median PFS was 8.4 months and one-year PFS rate was 32.4% (95% confidence interval (CI); 22.4−42.9%). Median survival was not reached and one-year OS rate was 94.0% (95% CI; 84.7−97.7%).

Conclusions: The enrollment of this phase III trial is ongoing. NSCLC patients with EGFR mutations had good prognosis irrespective of the treatments confirming the previous reports. Subset analysis of IPASS (Phase III study of gefitinib vs. carboplatin/paclitaxel in Asian, non-/light smokers with adenocarcinoma of the lung) suggested that NSCLC patients with EGFR mutation treated with gefitinib had a significantly longer PFS than those treated with chemotherapy with a HR of 0.48 (~10 months vs. ~6 months). Our study appears to have similar PFS and it would be positive if this HR is reproduced. Data on response rates and safety profile will be available at the presentation. The final analysis is expected in early 2010.

9003 ORAL

Response and progression-free survival in 1006 patients with known EGFR mutation status in phase III randomized trials of gefitinib in individuals with non-small cell lung cancer

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Background: Gefitinib (Iressa®) inhibits tyrosine kinase activity of the epidermal growth factor receptor (EGFR). The EGFR kinase can be constitutively activated by mutations in exon 19 or 21 of the *EGFR* gene. Cells harboring these mutations are “addicted” to EGFR signaling and are exquisitely sensitive to blockade of the kinase. These mutations are often found in the tumors of patients (pts) with marked benefit to gefitinib. We