lead to early detection of MBTs. It also informs the patient and their families about multiple modality therapy options for patients with BM including surgery, radiation, radiosurgery and chemotherapy so that they may get more tailored treatment. B-Aware[SM] patient brochures have been circulated throughout Cleveland Clinic cancer centers to help improve patient education. A dedicated webpage (www.clevelandclinic.org/b-aware) has been created to further this endeavor and information may be obtained through the American Cancer Society. There is also a dedicated patient hotline that answers the questions that patient or their families may have regarding MBTs.
Conclusion: B-Aware[SM] is a unique program that has stemmed from a partnership between a tertiary care center (Cleveland Clinic) and the American Cancer Society that endeavors to improve the outcomes of patients with MBTs by improving the awareness of potential patients regarding the risks, signs and symptoms of MBTs and the therapy options for such patients.

8759 POSTER

A Brain Cancer Pathway − 2 Years Experience in Clinical Practice

E.L. Laursen[1], B.K. Rasmussen[1]. *[1]Hilleroed Hospital, Department of Neurology, Hilleroed, Denmark*

Background: The Danish Health Care Sector seeks to improve cancer survival through better diagnostics, faster treatment and increased focus on cancer prevention and early help-seeking. In neuro-oncology this has resulted in the National Integrated Brain Cancer Pathway (NIBCP). We analyze how the pathway works in the initial phase in a clinical setting with emphasis on referral manner and pathway criteria.
Materials and Method: All patients admitted during the first 2-year period to a regional neurology department in Denmark and fulfilling the NIBCP inclusion criteria were included. The clinical inclusion criteria encompass recent onset of focal neurological symptoms or epileptic seizures, changes in personality or behavior or cognitive deterioration or marked changed in headache pattern and in all cases symptoms progressing over time without any other likely cause.
Data regarding referral, symptoms, diagnosis and time for work-up was obtained and supplemented by retrospective review of patient charts. Sensitivities, specificities and positive predictive values of the inclusion criteria were calculated with MRI scan of the cerebrum as index of validity.
Results: The strength of the pathway inclusion criteria is found to be determined largely by the number of criteria fulfilled and by which symptoms predominate at the time of admission. The criteria are found to pick up on the majority of patients with symptomatic brain malignancy but are also found to be highly sensitive of general structural brain lesions.
Conclusion: The pathway is a major step forward in the effort of optimizing the illness trajectory for brain cancer patients. More patients suspected of brain cancer are expected to go through expedient work-up as general practitioners become increasingly familiar with the pathway.

8760 POSTER

Should the Management of Brain Metastases Be Influenced by the Age of the Patient?

P. Hanssens[1], G. Beute[1], B. Karlsson[2]. *[1]St. Elisabeth Ziekenhuis, Tilburg, The Netherlands; [2]National University Hospital, Division of Neurosurgery, Singapore, Singapore*

Objectives: The radiation Therapy Oncology Group (RTOG) defined age as one of the key factors predicting survival time in patients with brain metastases treated with whole brain radiation therapy (WBRT). As most patients with BM succumb from the intracerebral manifestation of their disease we hypothesized that the likelihood of distant recurrences should be higher in elderly patients.
Method: All visible brain metastases were treated with Gamma Knife® surgery (GKS) in 1397 patients treated in St. Elisabeth Hospital, Tilburg, The Netherlands and West Virginia University, Morgantown, WV, USA, All patients were followed prospectively with MR imaging every 3rd months as long as deemed clinically meaningful. The time at risk for distant recurrences was defined as the time between GKS and the first of the following event: the diagnosis of a distant recurrence, the time to death, the time to the last information of the patient or treatment with WBRT without evidence of distant recurrences.
Results: There was no significant relation between the risk of developing distant recurrences and age ($P = 0.033$) comparing $<$ to $\geqslant$ 65 years of age. However, the difference became significant when 75 years was used as age limit ($P = 0.0074$).
Conclusions: Age has a predictive value not only for predicting survival but also for intracranial tumour control following GKS. However, a relavant age limit should probably be older than the 65 years set by RTOG.

Oral Presentations (Sat, 24 Sep, 11:15−13:35)
Lung Cancer − Metastatic

9000 ORAL

Epidermal Growth Factor Receptor (EGFR) Expression as a Predictive Biomarker of Survival in Patients With Advanced Non-Small Cell Lung Cancer (NSCLC) Receiving First-Line Therapy With Cetuximab Combined With Chemotherapy in the FLEX Trial

K. O'Byrne[1], L. Paz-Ares[2], J.R. Pereira[3], J. von Pawel[4], R. Ramlau[5], S. Störkel[6], K.M. Schumacher[7], A. von Heydebreck[8], I. Celik[7], R. Pirker[9]. *[1]St James's Hospital, Oncology Department, Dublin, Ireland; [2]Hospital Universitario Virgen del Rocio, Oncology Department, Seville, Spain; [3]Arnaldo Vieira de Carvalho Cancer Institute, Pulmonary Medicine, São Paulo, Brazil; [4]Asklepios Fachkliniken, Oncology Department, München-Gauting, Germany; [5]Poznan University of Medical Sciences, Wielkopolskie Centrum Pulmonologii i Torakochirurgii, Poznan, Poland; [6]HELIOS Hospital Wuppertal, Institute of Pathology, Wuppertal, [7]Merck KGaA, Global Clinical Development Unit − Oncology, Darmstadt, [8]Merck KGaA, Global Biostatistics, Darmstadt, Germany; [9]Medical University of Vienna, Department of Medicine I, Vienna, Austria*

Background: The phase III FLEX study showed that the addition of cetuximab to first-line chemotherapy (CT) statistically significantly improved overall survival (OS) in patients with EGFR-expressing, advanced NSCLC. Prospectively collected tumour immunohistochemistry (IHC) data were analyzed to investigate whether EGFR expression was predictive of outcome in FLEX study patients.
Material and Methods: Tumour EGFR expression was assessed in 1121 (99.6%) of 1125 FLEX study patients according to the proportion of positive cells and intensity of membrane staining on a continuous IHC scale of 0–300. A discriminating threshold IHC score of 200 was selected and used to define groups with low (IHC score <200) and high (IHC score $\geqslant$200) EGFR expression, as previously described. The OS benefit in each group was further analyzed for the overall population and for subgroups defined by tumour histology.
Results: High tumour EGFR expression was scored for 345 (30.8%) of 1121 patients. Baseline characteristics were comparable between treatment arms in both high and low EGFR expression groups. OS time was prolonged in the high EGFR expression group in the CT plus cetuximab compared with CT arm (median 12.0 vs 9.6 months; hazard ratio, HR, 0.73; $p = 0.011$). No corresponding OS benefit was observed in the low EGFR expression group (median 9.8 vs 10.3 months; HR 0.99; $p = 0.88$). A treatment interaction test assessing the difference in HRs between the EGFR expression groups yielded a p-value of 0.044. A multivariable analysis of OS in the EGFR expression groups with adjustment for prognostically relevant baseline factors confirmed the results of the unadjusted analysis. The OS benefit in the high EGFR expression group was observed across tumour histologies: squamous cell carcinoma (median 11.2 vs 8.9 months; HR 0.62); adenocarcinoma (median 20.2 vs 13.6 months; HR 0.74); other histologies (median 8.0 vs 7.6 months; HR 0.75). The safety profile for CT plus cetuximab in the high EGFR expression group was similar to that seen in the overall safety population, with no unexpected adverse events.
Conclusions: The addition of cetuximab to first-line CT substantially prolonged OS in patients with advanced NSCLC and high tumour EGFR expression regardless of histological subtype. The selection of those patients most likely to benefit from first-line treatment with CT plus cetuximab should be based primarily on whether tumours express high or low levels of EGFR, as defined in the current analysis.

9001 ORAL

A Retrospective Subgroup Analysis of EGFR Immunohistochemistry (IHC) Expression by Histo-Score Correlated to Outcomes From the BMS099 1st Line Phase III NSCLC Trial of Cetuximab (Cet) Plus Carboplatin/Taxane

T. Lynch[1], P. Bhagavatheeswaran[2], P. Mukhopadhyay[2], S. Khambata-Ford[3], C.T. Harbison[3]. *[1]Yale School of Medicine, Smilow Cancer Hospital at Yale-New Haven, New Haven CT, [2]Bristol-Myers Squibb, Global Biometric Sciences, Wallingford CT, [3]Bristol-Myers Squibb, Clinical Biomarkers, Princeton NJ, USA*

Background: The phase III FLEX study showed that the addition of Cet to first-line chemotherapy (CT) significantly improved overall survival (OS) in patients (pts) with EGFR-expressing, advanced NSCLC. The phase III BMS099 trial investigated Cet plus first-line CT in advanced NSCLC pts regardless of EGFR expression. In BMS099, the primary end point, progression-free survival (PFS), did not differ significantly between

treatments; overall response rate (ORR) was significantly increased; and OS was greater with Cet, but did not achieve significance. An analysis of the phase III FLEX trial indicated a potential predictive role for tumour EGFR expression levels measured using a continuous scoring system, EGFR IHC Histo-Score (EGFR H-Score). ORR was significantly increased for pts treated with Cet, with tumour EGFR H-Score ⩾200. We report here results from the application of this methodology to BMS099.

Methods: Tumour tissue specimens, previously IHC stained using the Dako EGFR pharmDx kit, were available for 148 of 676 subjects (22%). The proportion of EGFR-positive cells and membrane staining intensity were retrospectively collected and analyzed via a blinded pathology review. EGFR expression levels were determined via a continuous EGFR IHC scoring system ranging from 0–300 based on a composite score consisting of the proportion of positive cells and membrane staining intensity. A cut-off of ⩾200 was applied to this score to classify subjects into high (H) and low (L) groups. The resulting EGFR H-Scores were analyzed for associations with ORR, PFS and OS.

Results: A higher ORR was observed for the H group compared to the L group in the Cet treated-arm, but not in the chemo-alone arm [interaction p-value: 0.087)]. No association was observed between H or L groups and PFS [interaction p-value: 0.73] or OS [interaction p-value: 0.35].

Conclusions: The current analysis demonstrates an observed ORR benefit from the addition of Cet in pts with high EGFR H-Score, compared to those with low EGFR H-Score, however, no significant interaction was seen for OS or PFS. The role of EGFR H-Scores to select NSCLC pts who will receive increased benefit from Cet therapy is still exploratory and requires prospective investigation. The small sample size of the BMS099 biomarker data set limits the interpretation of this analysis. Additional investigations are ongoing to better understand the association of EGFR IHC expression and treatment with Cet therapy.

9002 ORAL

Round Robin Test to Evaluate the Reproducibility of a Therapeutically Relevant Immunohistochemical Score for the Categorization of Non-Small Cell Lung Cancer (NSCLC) Into Tumours With High and Low Epidermal Growth Factor Receptor (EGFR) Expression

J. Rüschoff[1], K.M. Kerr[2], R. Büttner[3], W.T. Olszewski[4], V.A. Alves[5], H.J. Grote[6], P. Middel[7], A. von Heydebreck[8], I. Celik[9], S. Störkel[10]. *[1]Institut für Pathologie Nordhessen, Diagnostic Pathology, Kassel, Germany; [2]Aberdeen Royal Infirmary, Department of Pathology, Aberdeen, United Kingdom; [3]University Hospital Cologne, Institute of Pathology, Cologne, Germany; [4]Institute of Oncology, Department of Pathology, Warsaw, Poland; [5]Hospital Alemão Oswaldo Cruz, LIM14- University of Sao Paulo School of Medicine & CICAP- Pathology, São Paulo, Brazil; [6]Merck KGaA, Histopathology Department, Darmstadt, [7]Targos Advance AG, Department of Pathology, Kassel, [8]Merck KGaA, Global Biostatistics, Darmstadt, [9]Merck KGaA, Global Clinical Development Unit − Oncology, Darmstadt, [10]HELIOS Hospital Wuppertal, Institute of Pathology, Wuppertal, Germany*

Background: Using prospectively collected immunohistochemistry (IHC) data, EGFR expression was evaluated on a continuous scale of 0–300 in patients with advanced NSCLC included in the phase III FLEX study. The addition of cetuximab to first-line chemotherapy was shown to substantially prolong survival in patients whose tumours expressed high levels of EGFR (IHC score ⩾200). This round robin test (RRT) evaluated the inter-observer reproducibility of EGFR IHC scoring.

Material and Methods: After a feasibility study was undertaken that identified factors impacting on reproducibility, a RRT was performed. In a central reference laboratory, serial sections of a tissue microarray (TMA) of NSCLC tumour cores were stained using the DAKO EGFR pharmDX™ kit/autostainer. The EGFR IHC score for each tumour was then evaluated as the sum of the products of tumour cell membrane staining intensity (graded 0−3+) and the percentage of cells at each staining intensity. Following central reference evaluation, and appropriate training, 10 expert lung cancer pathologists independently analyzed EGFR expression for 30 TMA cores without knowledge that these were initially categorized as clearly high (n = 10), clearly low (n = 11) or equivocal (n = 9), relative to the threshold EGFR IHC score of 200. Analysis of between-rater agreement was based on the allocation of the EGFR IHC score into low (<200) and high (⩾200) EGFR expression groups. The overall concordance rate with respect to the reference evaluation was defined as the mean of the per-rater concordance rates with respect to the reference evaluation. Kappa coefficients were calculated for the comparison of each rater with the reference evaluation.

Results: The RRT showed a high inter-observer agreement in EGFR IHC scoring among study participants, with an overall concordance rate of 91% and a mean kappa coefficient of 0.81. Samples with a reference EGFR IHC score <200 or ⩾200 showed mean concordance rates of 95% and 86%, respectively. Tumours with a reference EGFR IHC score clearly below or above the cut-off (<150 or ⩾250) were each categorized with an almost perfect mean concordance rate of 98%. Samples with a reference EGFR IHC score around the cut-off (⩾150–<250) showed a good mean concordance rate of 74%.

Conclusions: The RRT showed that after appropriate training, assessing EGFR expression by this IHC scoring method allowed a highly reproducible allocation of NSCLCs into clinically relevant high or low EGFR expression groups.

9003 ORAL

Biomarker Analysis in BO21015, a Phase II Randomised Study of First-line Bevacizumab (BEV) Combined With Carboplatin-gemcitabine (CG) or Carboplatin-paclitaxel (CP) in Patients (pts) With Advanced or Recurrent Non-squamous Non-small Cell Lung Cancer (NSCLC)

T. Mok[1], V. Gorbunova[2], E. Juhasz[3], B. Szima[4], O. Burdaeva[5], C.J. Yu[6], P. Delmar[7], C. Pallaud[7], M. Jonnaert[8], M. Reck[9]. *[1]The Chinese University of Hong Kong, Clinical Oncology, Hong Kong, China; [2]N.N. Blokhin Russian Cancer Research Center, Chemotherapy, Moscow, Russian Federation; [3]Koranyi National Institute for TB and Pulmonology, XIV Department, Budapest, [4]Markusovszky Hospital, Pulmonology Department, Szombathely, Hungary; [5]Arkhangelsk Regional Clinical Oncology Dispensary, Chemotherapy Department, Arkhangelsk, Russian Federation; [6]National Taiwan University Hospital, Internal Medicine Department, Taipei, Taiwan; [7]F. Hoffmann-La Roche Ltd, Biometrics, Basel, [8]F. Hoffmann-La Roche Ltd, Clinical Oncology, Basel, Switzerland; [9]Krankenhaus Grosshansdorf, Thoracic Oncology, Grosshansdorf, Germany*

Background: BO21015 (NCT00700180) is a randomised, multicentre ph II study exploring correlation between biomarker (BM) candidates and best overall response (BOR) to BEV combined with CG or CP in chemonaïve pts with advanced/recurrent non-squamous NSCLC. Here, we present BM analysis data from this study.

Materials and Methods: After Investigator allocation of CG or CP, pts randomised to BEV 7.5 mg/kg (BEV7.5) or 15 mg/kg (BEV15). Pts received up to 6 cycles (q21d) of BEV plus CG or CP followed by BEV until disease progression or unacceptable toxicity. Primary endpoint (EP): correlation of baseline (BL) plasma BM levels (Table) with BOR in pts receiving BEV+chemo; BOR compared in pts with high vs low BM level, adjusting for BL prognostic factors. Sample median used to define high (>median) and low (⩽median) BM level. Significance threshold set at $p \leqslant 0.007$ to account for multiple testing. Secondary EPs: progression-free survival (PFS), BOR, overall survival (OS), safety.

Results: ITT (n = 303) BL characteristics well balanced (BEV7.5 n = 154 [GC 88; PC 66]; BEV15 n = 149 [GC 87; PC 62]). Median age: ~60 yrs; ~60% male; 64% ECOG PS 1; 85% White; former/current smokers 68% and 73%. BM evaluable population (pts with BM sample at BL) represents 95% of the ITT population (BEV7.5, n = 144; BEV15, n = 143). Primary EP: no statistically significant correlation between 7 tested BL BMs and BOR (Table). Pre-specified, exploratory analyses showed a correlation of high BL VEGFA levels with shorter PFS (p = 0.002). Secondary EPs, BEV7.5 vs BEV15: PFS HR 1.01 (95% CI 0.78–1.31, p = 0.945; median 6.8 vs 6.7 months); BOR 37.1% vs 46.4% (p = 0.174); OS data are interim. Safety: no new events reported; full safety data will be presented.

Conclusions: None of the BL candidate BMs statistically significantly correlated with BOR. High BL VEGFA levels had a statistically significant positive correlation with risk of progression. Further exploratory analyses of multi-marker combinations in relation to clinical outcomes will be presented.

	Low BM level		High BM level		Logistic regression		
	N	Responders, %	N	Responders, %	OR*	95% CI	P value
bFGF	142	45.07	141	42.55	1.07	0.63–1.80	0.8127
E-Selectin	142	39.44	141	48.23	1.81	1.06–3.08	0.0285
ICAM	142	44.37	141	43.26	1.09	0.64–1.85	0.7478
PIGF	146	43.84	56	42.86	1.16	0.58–2.33	0.6761
VEGFA	140	43.57	140	45.00	1.22	0.72–2.09	0.4601
VEGFR1	142	48.59	141	39.01	0.77	0.46–1.29	0.3193
VEGFR2	143	39.16	140	48.57	1.44	0.85–2.45	0.1758

*Odds ratio: high vs low BM level