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

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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)

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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