I, 1 in stage II, 7 in stage III and 18 in stage IV. 16 patients, all with metastatic disease, were treated with crizotinib (15 with 250mg 1x2 and 1 patient with 200mg 1x1). Crizotinib was given to: 0 patients as 1st line, 4 patients as 2d line, 6 as 3d line, 5 as 4th line and 1 as 5th line. At time of data collection 9 patients had discontinued crizotinib-therapy. 7 patients had ongoing treatment with an average duration of 125 days. 12/16 patients obtained partial remission, 3 stable disease and 1 disease progression. 3/9 discontinued crizotinib-therapy due do severe side effects: 1 due to persistant visus toxicity grade ≥2, 1 due to pneumonitis occuring at treatment day 42 and 1 due to liver toxicity with CTCAE grade ≥2 occurring at treatment day 37. Only the case with pneumonitis resultated in death at day 43. No QTc-syndromes and no hematological toxicity CTCAE grade ≥3 occurred.

Conclusion: Identifying patients with ALK-EML4-translocations, the predictive factor for crizotinib-treatment, offers new treatment options and realistically balanced hope in the severe setting of metastatic NSCLC. In our experience, the predictive value of a positive ALK-EML4-test is high on histological material and crizotinib offers good treatment outcomes after progression on platinum-based chemotherapy but for shorter time than what is expected for TKIs in patients with activating EGFR-mutations.

Keyword: ALK-EML4-translocations, metastatic NSCLC, predictive factors

POSTER SESSION 2 - NSCLC NOVEL THERAPIES
TUESDAY, OCTOBER 29, 2013 - 09:30-16:30

P2.11-034 INDIRECT COMPARISONS OF HARM/BENEFIT PROFILE OF EGFR TYROSINE KINASE INHIBITORS AS FIRST LINE TREATMENT IN EGFR MUTATED NSCLC PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: To date, three EGFR Tyrosine Kinase inhibitors (TKIs) gefitinib (G), erlotinib (E), and afatinib (A) have been compared to standard chemotherapy as first line treatment in patients with advanced NSCLC harboring EGFR mutations. We performed a systematic review and meta -analysis in order to estimate through indirect comparisons the relative risk benefit associated to each drug.

Methods: The major databases were searched for published and unpublished randomized control trial up to March 2013. Data extraction was performed by two independent reviewers and focused on benefit (ORR, PFS) and selected harm outcomes (diarrhea, rash, nail disorders, hypertransaminasemia). The adjusted indirect comparisons were performed using the random effect method described by Bucher and Glenny approach for Hazard Ratio (HR) for PFS and relative risk (RR) for the other outcome measures.

Results: All EGFR TKIs fared better when compared with chemotherapy in terms of PFS: overall HR 0.40 (95%CI 0.30-0.54); G vs E HR 1.34 (95%CI 0.63-2.86), G vs A HR 0.74 (95%CI 0.53-1.04), E vs A HR 0.55 (95%CI 0.31-0.99). The relative probability of ORR was G vs E 0.96 (95%CI 0.69-1.34), G vs A 0.79 (95%CI 0.49-1.28), E vs A 0.82 (95%CI 0.49-1.38). Indirect comparisons for safety showed RR for diarrhea G vs E 0.8 (95%CI 0.63-1.01), G vs A 0.32 (95%CI

0.20-0.51), E vs A 0.38 (95%CI 0.24-0.62); for rash G vs E 1.0 (95%CI 0.82-1.22), G vs A 0.31 (95%CI 0.15-0.65), E vs A 0.31 (95%CI 0.15-0.65); for hypertransaminasemia G vs E 2.29 (95%CI 1.63-3.23). Nail disorders affected 57% of patients treated with A, 15% with G, and 4% with E.

Conclusion: Results of our analysis showed that all treatments have similar activity and efficacy while the toxicity profile was less favorable for A with a significant higher risk of diarrhea, rash, and nail disorders. Based on these safety results, we suggest that A may not be the first choice for upfront treatment in EGFR mutated patients. Confirmation is warranted by ongoing prospective head to head RCTs.

Keywords: first line, EGFR-TKI, Metanalysis

POSTER SESSION 2 - NSCLC NOVEL THERAPIES
TUESDAY, OCTOBER 29, 2013 - 09:30-16:30

P2.11-035 ASSOCIATION OF TUMOR PD-L1 EXPRESSION AND IMMUNE BIOMARKERS WITH CLINICAL ACTIVITY IN PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC) TREATED WITH NIVOLUMAB (ANTI-PD-1; BMS-936558; ONO-4538)

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Background: The immune checkpoint receptor programmed death-1 (PD-1) negatively regulates T-cell activation upon interaction with its ligands, PD-L1 and PD-L2. In a Phase 1 dose-escalation/cohort expansion study (CA209-003; NCT00730639), nivolumab, a fully human PD-1 receptor blocking antibody, delivered durable responses in patients with solid tumors, including advanced NSCLC. Immunohistochemistry (IHC) analysis of tumor samples from this study suggested an association between pre-treatment tumor PD-L1 expression and clinical response to nivolumab in patients with melanoma (Grosso JF J Clin Oncol. 2013;31(suppl):abs 3016; Topalian SL NEJM 2012;366:2443-54). Here we investigate the association between PD-L1 expression by IHC and response to nivolumab in patients with NSCLC, and patient response with pre-/post-dose absolute lymphocyte counts (ALC) and selected lymphocyte cell subsets.

Methods: 129 patients with NSCLC from the CA209-003 trial received nivolumab between 2008 and 2012 (1–10 mg/kg IV every 2 weeks) during dose escalation and/or cohort expansion. Archived formalin-fixed paraffin-embedded pre-treatment tumor tissue and pre-treatment and on-treatment peripheral whole blood samples were analyzed to explore potential pharmacodynamic/predictive biomarkers associated with nivolumab therapy. Pre-treatment tumor PD-L1 expression was evaluated by IHC using an automated assay developed by Dako based on a sensitive and specific anti-PD-L1 monoclonal antibody (28-8). Tumors were defined as PD-L1 positive (PD-L1+) when ≥5% of the tumor cells had membrane staining at any intensity. Lymphocyte subsets in the periphery were measured using flow cytometry.

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Results: Tumor membrane PD-L1 expression was measured in 63 patients with NSCLC (29 squamous; 34 non-squamous). 31/63 (49%) NSCLC biopsies were PD-L1+. There was no apparent association between PD-L1 protein expression and NSCLC histology: for squamous and non-squamous tumors, 52% (15/29) and 47% (16/34) were PD-L1+, respective. Objective response rates for PD-L1+ and PD-L1- NSCLC patients with non-squamous and squamous histology are shown in the Table. Objective responses were observed in patients with squamous and non-squamous NSCLC who were negative for PD-L1 expression. Since increases in on-treatment ALC and activated T-cell phenotypes have been shown to positively associate with favorable clinical outcomes in ipilimumab monotherapy (Ku GY Cancer 2010;116:1767-75; Carthon BC Clin Cancer Res 2010;16:2861-71), results from an analysis correlating patient response with pre-/post-dose ALC and T-cell populations in patients with NSCLC receiving nivolumab will be presented.

Table. Patient response according to PD-L1 expression status in patients with NSCLC		
Tumor type	PD-L1 expression status	Objective response rate, n/N (%)
NSCLC (all patients)	+	5/31 (16.1)
	–	4/32 (12.5)
NSCLC (squamous)	+	2/15 (13.3)
	–	3/14 (21.4)
NSCLC (non-squamous)	+	3/16 (18.8)
	–	1/18 (5.6)

Conclusion: Further evaluation of PD-L1 as a molecular marker of nivolumab therapy is required. Association of PD-L1 protein expression with clinical outcome is currently being prospectively assessed in ongoing Phase 3 trials. Clinical Trial Registration Number: NCT00730639

Keywords: nivolumab, non-small cell lung cancer, programmed death-1 receptor ligand 1, biomarker

POSTER SESSION 2 - NSCLC NOVEL THERAPIES
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P2.11-036 ASSOCIATION BETWEEN TUMOR EGFR MUTATION AND PRIMARY TUMOR LOCATION IN PATIENTS WITH ADENOCARCINOMA OF THE LUNGS

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Background: Lung cancer is the leading cause of cancer death in the world, and the non-small cell lung cancer accounts for more than 80% of the lung cancer. Among patients with non-small cell lung cancer, tumor epidermal growth factor receptor (*EGFR*) activating mutations were mostly found in patients with adenocarcinoma and were associated with a better prognosis than *EGFR* wild-type tumors. The relationship between *EGFR* activating mutations and their primary tumor location in the lungs was not reported before.

Methods: We retrospectively reviewed the data of our pulmonary adenocarcinoma patients who had received complete staging and received tumor EGFR mutation analysis. The association between EGFR mutation status, patients smoking status, patient's gender and primary tumor location were analyzed.

Results: 205 cases were reviewed. There are 126 patients with tumor EGFR mutations, including 115 patients with classic EGFR mutations (exon 19 deletions or L858R), and 79 patients were without EGFR mutation. There are statistically significant association between tumor EGFR mutations and primary tumor location in right upper lobe (P=0.007); especially in RB1 segment (P=0.018), and primary tumor location of exon 19 deletions occurred more frequently in right upper lobe (P<0.001). There were no significant associations between patients smoking status and primary tumor location(P=0.659), nor was patients gender and primary tumor location (P=0.473).

Conclusion: There are statistically significant association between *EGFR* mutation and primary tumor location in right upper lobe of patients with adenocarcinoma of the lungs.

Keywords: adenocarcinoma of lung, Tumor EGFR Mutation, tumor location

POSTER SESSION 2 - NSCLC NOVEL THERAPIES
TUESDAY, OCTOBER 29, 2013 - 09:30-16:30

P2.11-037 EGFR ACTIVATING MUTATION AND BONE METASTASIS HAVE ASSOCIATION WITH CNS METASTASIS AT DIAGNOSIS IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Background: CNS metastasis happens not infrequently in patients with non-small cell lung cancer, reaching upto 25%. The presence of CNS metastasis is a major decision factor of planning primary treatment. Furthermore, predictors for CNS metastasis could be used for selecting patients who may get the potential benefit of prophylactic cranial irradiation.

Methods: We retrospectively analyzed the clinicopathologic data of 233 patients with non-small cell lung cancer who underwent brain MRI at the time of diagnosis between Jan 2008 and Dec 2012. Chi-square analysis and multivariate logistic regression model was used to find risk factors for CNS metastasis.

Results: Forty-five (19.3%) patients had initial CNS metastasis (41 brain parenchymal metastasis and 4 leptomeningeal seeding). Chi-square analysis revealed that never-smoking (28.7% vs. 13.7%, P=0.005), lung metastasis (29.6% vs 14.8%, P=0.009), bone metastasis (35.7% vs 13.1%, P<0.001), adenocarcinoma (24.8% vs 10.9%, P=0.008), and EGFR activating mutation (44.4% vs 18.3%, P=0.004) were associated with CNS metastasis. However, pleural,