9164 POSTER

An indirect comparison of the efficacy of bevacizumab plus cisplatin and gemcitabine (BCG) or bevacizumab plus carboplatin and paclitaxel (BCP) versus pemetrexed plus cisplatin (PC) and cetuximab plus vinorelbine and cisplatin (CVC) in patients (pts) with advanced or recurrent non-small cell cancer (NSCLC)

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Background: New treatment options are needed for advanced NSCLC offering improved benefit in terms of progression-free (PFS) and overall survival (OS) over standard chemotherapy (CT). Bevacizumab, a humanised monoclonal antibody (MAb) against vascular endothelial growth factor, when combined with CT increases PFS and OS in pts with advanced NSCLC versus CT alone. [4−5] Cetuximab, a MAb targeting the epidermal growth factor receptor, showed some effect when combined with CT. [3] Also, pemetrexed, a thymidylate synthase inhibitor, has shown non-inferiority over cisplatin plus gemcitabine. [6] This study compared the clinical benefits for pts with NSCLC treated with BCG or BCP to PC and CVC using indirect treatment comparison (ITC) methodology. ITC overcomes the potential problem of different prognostic characteristics between study pts across trials and is valid if the relative efficacy of interventions is consistent across trials.
Material and Methods: In the absence of head-to-head trials, ITC [1] was performed on pts with non-squamous NSCLC to compare the relative benefit of various 1st line therapies BCG/BCP vs. PC, CVC by hazard ratios (HR) adjusted for differences in underlying CT and populations. Where HRs were not reported, HRs [1] and standard errors [7] were estimated. Based on the ITC a statistical disease model was developed to estimate the adjusted time in PFS and OS.
Results: ITC estimated HRs for the primary endpoints in AVAiL [4] and E4599 [5] showed that the adjusted PFS HR for BCG vs. PC and CVC were 0.83 and 0.80 respectively resulting in an expected time spent in PFS for BCG of 9.62 vs. 8.12 and 7.99 months for PC and CVC respectively. Model-derived data showed BCP treatment in pts with adenocarcinoma histology resulted in adjusted BCP HRs of 0.85 and 0.89 vs. PC and CVC respectively. Model data also showed that BCP pts experienced 19.55 vs. 14.52 (PC) and 17.57 (CVC) months of OS. Univariate and probabilistic sensitivity analyses confirmed these findings.
Conclusions: ITC methodology and disease modelling shows that triplet BCG or BCP therapy in pts with advanced non-squamous NSCLC compared with either doublet PC or triplet CVC therapy results in an extension of PFS and OS.

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9165 POSTER

Motesanib or bevacizumab in combination with paclitaxel and carboplatin in patients with advanced nonsquamous non-small cell lung cancer (NSCLC): interim results from a randomized, open-label, phase 2 study

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Background: In nonsquamous NSCLC patients (pts) clinical outcomes may be improved by adding VEGF inhibitors to standard chemotherapy. Motesanib is a highly selective inhibitor of VEGF receptors 1, 2, and 3; PDGF and Kit receptors. This ongoing randomized, open-label, phase 2 study estimated the objective response rates (ORR) between motesanib + paclitaxel/carboplatin (P/C) (2 dosing cohorts) and bevacizumab + P/C (ClinicalTrials.gov ID NCT00369070; sponsor: Amgen Inc.).
Methods: Eligible pts had confirmed unresectable, stage IIIB with pericardial or pleural effusion or stage IV/recurrent nonsquamous NCLSC. Pts were randomized (1:1:1) to receive P/C ($P = 200\ mg/m^2$; C = AUC of 6 mg/mL/min) on day 1 of each 3-week cycle (max 6 cycles) plus motesanib orally from day 1 of cycle 1 at either (Arm A) 125 mg once daily (QD) continuously or (Arm B) 75 mg twice daily (BID) for 5 days followed by 2 treatment-free days; or (Arm C) bevacizumab 15 mg/kg on day 1 of each cycle until disease progression or intolerability. The primary endpoint is ORR per RECIST by independent central review. Secondary endpoints include progression-free survival (PFS), overall survival (OS), and incidence of treatment-emergent adverse events (AEs).
Results: 181 pts received $\geqslant$1 dose of treatment (Arms A/B/C, n = 59/62/60). Baseline demographics/characteristics were similar with some exceptions, eg adenocarcinoma histology (Arms A/B/C, 77/90/86%) and ECOG status (ECOG 0, 43/52/52%). In pts with measurable disease at baseline (Arms A/B/C, n = 56/60/62) ORR in Arms A/B/C was 23/22/29%. At data cut-off, median PFS (95% CI) was 7.4 months (5.3, 8.5) in Arm A, 5.2 (4.2, 6.8) in Arm B, and 6.8 (4.4, 8.8) in Arm C. In Arms A/B/C, grade 3 AEs occurred in 47/50/45%, grade 4 AEs in 8/6/7%, and grade 5 AEs (excluding NSCLC progression) in 5/15/7% of pts. The most common grade 3, 4 or 5 AEs in descending order in Arm A were diarrhea (Arms A/B/C, 19/13/3%), dehydration (17/8/3%), fatigue (17/5/8%), anorexia (12/2/3%), and nausea (10/3/2%). AEs of interest (across all grades) included cardiac toxicity (0/2/2%), cholecystitis (5/6/0%), hemorrhagic events (20/21/18%), deep vein thrombosis (3/0/2%), and pulmonary embolism (3/0/3%).
Conclusions: The ORR was similar between Arms A and B vs C, with a small difference favoring Arm C. PFS was similar between Arms A and B, but Arm B appeared to be worse than Arm C. While this study was not powered to detect a statistically significant difference in ORR or PFS the data support further study of motesanib 125 mg QD + P/C in nonsquamous NSCLC.

9166 POSTER

Activity of BIBW 2992, an irreversible inhibitor of EGFR and HER2, in adenocarcinoma of the lung with HER2neu kinase domain mutations

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Background: HER2*neu* mutations are found in 2−4% of lung adenocarcinoma and are more common in female, non-smokers and patients with Asian background. BIBW 2992 (Tovok™) is a potent, irreversible inhibitor of EGFR and HER2 (IC50 0.5 and 14 nM, respectively) with preclinical and clinical activity in NSCLC with EGFR mutations. An exploratory Phase II study in demographically and genetically selected NSCLC is being conducted.

Methods: Patients with stage IIIB/IV lung adenocarcinoma who are never or light ex-smokers and their tumors harbor EGFR or HER2*neu* mutations (current report) or are EGFR FISH+ are eligible (Study NCT00730925). Patients receive 50 mg BIBW 2992 qd until disease progression. Tumor assessments are performed every 8 weeks. Based on the criteria set out in the protocol, patients who progress can continue treatment with BIBW 2992 and weekly paclitaxel (80 mg/m^2 weekly, 3/4 weeks). The primary endpoint is objective response rate.
Results: To date eight patients have been included, including 4 patients with EGFR mutations and prior treatment with Erlotinib and four patients with lung adenocarcinoma and HER2 mutations in exon 20. All four patients with a HER2*neu* mutation are female, non smokers with Stage III/IV adenocarcinoma of the lung and had failed prior chemotherapy (up to five lines). Preliminary analysis shows significant improvement of patients' symptoms and performance status as well as tumour size reduction amounting to PR in all three evaluable patients; one patient had early discontinuation of the drug because of grade 3 adverse events and subsequent refusal to reinitiate the treatment. The responding patients have been on Tovok for 9+, 10+ and 10+ months. Diarrhoea and skin rash were the predominant adverse events.
Conclusions: The use of BIBW 2992 in pre-treated patients with NSCLC and activating HER2 mutations in exon 20, can lead to prolonged significant subjective and objective benefit. The use of BIBW 2992, an irreversible and dual EGFR/HER2 inhibitor as a potential new treatment option for these patients warrants further investigations. This clinical observation closely mimics recent results by others with BIBW 2992 in a transgenic HER2 driven lung cancer model. An international Phase III trial program investigating BIBW 2992 in NSCLC, LUX-Lung, is currently recruiting patients.

9167 POSTER

Outcomes with erlotinib in advanced NSCLC: examining the influence of increased EGFR gene copy number and EGFR mutations

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Background: Increased *EGFR* gene copy number and the presence of *EGFR* mutations have been discussed as predictive markers for benefit with erlotinib. We conducted exploratory analyses to investigate the reported association between *EGFR* gene amplification and *EGFR* mutations, using data from the phase III placebo-controlled SATURN study (BO18192, F. Hoffmann-La Roche, complete) of erlotinib as maintenance therapy for advanced NSCLC.
Materials and Methods: Following 4 cycles of 1st-line chemotherapy, patients (pts) who had non-PD (n = 889) were randomised to erlotinib 150 mg/day or placebo. 874 baseline tumour samples were available. *EGFR* gene copy number was assessed using FISH; FISH+ status = high polysomy (⩾4 gene copies in ⩾40% of nuclei) and/or gene amplification (gene/chromosome ratio ⩾2, or ⩾10% of nuclei with *EGFR* clusters, or ⩾10% of nuclei with ⩾15 gene copies). *EGFR* mutation (mut) status was assessed using DNA sequencing. Tumours were *EGFR* mut+ if exon 19 deletions and/or L858R mutations (exon 21) were identified.
Results: *EGFR* FISH results were available for 488 pts; high polysomy and/or amplification (FISH+) 232 (48%), high polysomy 228 (47%), *EGFR* amplification (amp)+ 116 (24%). A PFS benefit was seen with erlotinib in both *EGFR* FISH+ and FISH− groups (see table). Pts with *EGFR* amp+ only had substantially greater benefit from erlotinib than pts with *EGFR* amp−. *EGFR* amplification was significantly more common in *EGFR* mut+ than wild-type (wt; 44 vs 20%, $p < 0.01$). Irrespective of FISH status, the *EGFR* mut+ group had a very large PFS benefit with erlotinib. In pts with *EGFR* wt tumours, the improvement in PFS observed with erlotinib was similar in the *EGFR* amp+ and amp− groups.
Conclusions: There was no significant difference in PFS between the predefined FISH+ and FISH- groups; however, in subgroup analyses, pts with *EGFR*-amplified tumours obtained a greater PFS benefit from erlotinib than pts without amplified tumours. There was a clear link between the presence of *EGFR* amplification and *EGFR* mutations (which are themselves associated with better outcomes with erlotinib). Further studies are warranted to investigate the relationship between *EGFR* gene amplification and *EGFR* mutations.

	n	HR for PFS	95% CI	Interaction p value
EGFR FISH+	231	0.68	0.51−0.90	0.35
EGFR FISH−	255	0.81	0.62−1.07	0.35
EGFR amp+	115	0.47	0.31−0.72	0.01
EGFR amp−	371	0.86	0.69−1.08	0.01
EGFR mut+	49	0.10	0.04−0.25	0.0004
EGFR wt	388	0.78	0.63−0.96	0.0004
EGFR wt/*EGFR* amp+	61	0.72	0.41−1.25	0.71
EGFR wt/*EGFR* amp−	233	0.84	0.64−1.11	0.71

9168 POSTER

Safety and efficacy of first-line bevacizumab-based therapy in advanced non-small cell lung cancer (NSCLC): results of the SAiL study (MO19390)

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Background: Bevacizumab in combination with chemotherapy for first-line treatment of advanced NSCLC has been shown to improve outcomes in pivotal phase III clinical trials (E4599 and AVAiL). SAiL (MO19390, Roche) is an international, multicentre, single-arm study to assess the safety and efficacy of first-line bevacizumab plus chemotherapy in a real-life clinical population. Here, we report interim safety and efficacy data from SAiL.
Methods: The primary endpoint was safety, and secondary endpoints included time to disease progression (TTP) and overall survival (OS). Pts with untreated locally advanced, metastatic or recurrent non-squamous NSCLC (ECOG PS 0−2) received bevacizumab (7.5 or 15 mg/kg every 3wks) plus standard chemotherapy for up to six cycles, followed by bevacizumab until disease progression.
Results: This interim analysis (data cut-off April 2009) was based on 2,116 pts (mean age 59 years). Pts (%) were: male 60.2; stage IIIB/IV 19.6/80.4; adenocarcinoma/large cell/other (for available samples) 85.8/7.1/7.1; ECOG PS 0/1/2 37.4/56.4/6.2. Pts received a median of 7 Bv cycles and 5 chemotherapy cycles. 671 (31.0%) pts experienced grade ⩾3 serious adverse events (SAEs); 227 (10.5%) pts experienced grade ⩾3 (G⩾3) SAEs related to Bv. AEs of special interest (all grades) were reported in 1,407 (65.0%) pts and resolved or improved in 1,154/1,407 pts (82%). AEs of special interest included hypertension (26.8%; G⩾3: 0.4%), epistaxis (26.1%; G⩾3: 0.7%), proteinuria (24.2%; G⩾3: 0.1%), bleeding (17.3%; G⩾3: 2.1%), thromboembolism (11.9%; G⩾3: 4.8%), CHF (4.8%; G⩾3: 1.1%) and GI perforation (1.2%; G⩾3: 0.9%). Temporary interruption (5.5% of pts) or discontinuation (12.1% of pts) of Bv due to AEs of special interest was infrequent. The number of deaths due to bleeding events was 0.7% (including haemoptysis [0.2%] and pulmonary haemorrhage, [0.1%]). No new safety signals were reported. At this analysis, median TTP for the overall population was 7.8 months and median OS was 15.3 months; 80.1% of patients had a best RECIST response (at any visit) of SD or better.
Conclusions: This interim analysis of SAiL confirms the well-established and manageable safety profile of first-line bevacizumab in combination with chemotherapy for advanced NSCLC. The clinical outcomes in this real-life population are consistent with those seen in the pivotal trials of bevacizumab in NSCLC (E4599 and AVAiL).