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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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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.

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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.