9008 ORAL

Clinical outcomes of bevacizumab in combination with paclitaxel/carboplatin compared with paclitaxel/carboplatin alone in previously untreated Japanese patients with advanced non-squamous non-small-cell lung cancer (NSCLC)

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Background: Bevacizumab (Bev) has been shown to add significant benefit to patients (pts) with advanced NSCLC when combined with platinum-based chemotherapy regimens. However, there has been no investigation with Bev in Japanese NSCLC pts. This randomized, open-label, multicenter, phase II trial evaluated the efficacy and safety of bevacizumab in combination with paclitaxel/carboplatin (PC) as first-line treatment for Japanese pts with advanced or recurrent non-squamous NSCLC.
Material and Methods: A total of 180 pts was planned to be randomly assigned to receive either bevacizumab (Bev) plus pacltaxel/carboplatin (PC), P 200 mg/m^2 and C AUC = 6 q3 wks for up to 6 cycles plus Bev continued to disease progression at 15 mg/kg q3 wks, or PC alone, P 200 mg/m^2 and C AUC = 6 q3 wks for up to 6 cycles. The randomization ratio of PC+Bev:PC was 2:1. The primary endpoints were progression free survival (PFS) and safety. This study was designed to observe a 20% reduction in the risk of a PFS event in the PC+Bev arm compared with PC. Pharmacokinetics of Bev was also investigated. Eligibility criteria: histologically or cytologically documented previously untreated advanced or recurrent non-squamous NSCLC; ECOG PS 0−1.
Results: One hundred eighty (180) pts were enrolled; 121 on PC+Bev and 59 on PC. Baseline patient demographics were well balanced between both treatment arms. As of the clinical-cutoff date, 138 PFS events (PD or death) were reported as assessed by the central review committee. In 175 pts evaluable for efficacy (117 in PC+Bev and 58 in PC), the addition of Bev prolonged PFS significantly: hazard ratio of 0.61 (p = 0.0090), median duration of 6.9 months and 5.9 months for CP+Bev and CP alone, respectively. Bleeding events, hypertension and proteinuria were more frequently observed in PC+Bev arm with one Grade 5 event of hemoptysis and 11 $\geqslant$Grade 3 events of hypertension. However, no new safety signals for Bev were detected. With regard to pharmacokinetics of Bev of 15 mg/kg, its profiles in Japanese pts are comparable to those in EU/US pts: T1/2 = 11.3 $\pm$ 2.1 day, AUCinf = 5314.4 $\pm$ 1012.6 μg·day/mL.
Conclusions: Combination of Bev with PC was efficacious, with prolonging PFS, in this study as previously observed in trials outside Japan. Safety and pharmacokinetics of Bev were also similar to those reported in previous studies. Therefore, as experienced in EU/US, Bev seems to provide Japanese NSCLC pts with significant clinical benefit.

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A meta-analysis of four randomized phase II/III trials adding cetuximab to platinum-based chemotherapy as 1st-line treatment in patients with non-small cell lung cancer (NSCLC)

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Background: Cetuximab added to vinorelbine/cisplatin chemotherapy (CT) significantly improves overall survival (OS) in patients with NSCLC, as demonstrated in the phase III FLEX study. [1] Three other randomized studies have demonstrated the improved efficacy of cetuximab added to different platinum doublets, compared with the platinum doublet alone: a phase III study comparing carboplatin/docetaxel or carboplatin/paclitaxel, $\pm$ cetuximab [2], and two randomized phase II studies investigating cisplatin/gemcitabine or carboplatin/gemcitabine, and cisplatin/vinorelbine, $\pm$ cetuximab.[3,4] A meta-analysis was performed to confirm the robustness of the efficacy results achieved with cetuximab in combination with platinum-based CT.
Materials and Methods: Individual patient data from 2018 patients enrolled in the four randomized controlled phase II/III studies were analyzed for OS, progression-free survival (PFS), and objective response rate (ORR). Hazard ratios (HRs) for the treatment effect on OS and PFS were calculated by applying a Cox proportional hazards model, and logistic regression was used to measure odds ratios for the treatment effect on ORR. The main analyses were adjusted for study and the baseline covariates age, sex, histology, tumor stage, and ECOG performance status. A heterogeneity test of the differences in the treatment effect across studies was performed in addition to three sensitivity analysis models.
Results: The meta-analysis demonstrated a significant benefit across all efficacy endpoints for patients receiving CT + cetuximab over CT alone: OS (HR = 0.878; 95% CI 0.795−0.969; p = 0.010), PFS (HR = 0.899; 95% CI 0.814−0.993; p = 0.036), and ORR (odds ratio = 1.463; 95% CI 1.201−1.783; p < 0.001). The heterogeneity test did not demonstrate a difference in treatment effect across studies and all three sensitivity analyses confirmed the primary analysis results for each endpoint.
Conclusions: Cetuximab improves efficacy (OS, PFS, and ORR) when added to a standard 1st-line CT, independent of the platinum doublet used. These findings are confirmed in this meta-analysis including 2018 patients with advanced NSCLC of all histological subtypes.

References

[1] Pirker et al. J Clin Oncol 2008;26(Suppl. 15): Abstract 3.
[2] Lynch et al. J Thorac Oncol 2008;3(Suppl. 4): S305.
[3] Butts et al. J Clin Oncol 2007;25:5777−5784.
[4] Rosell et al. Ann Oncol 2008;19:362−369.

9010 ORAL

Impact of histology on survival in resected patients with Non Small Cell Lung Cancer (NSCLC): Subgroup analysis of the adjuvant vinorelbine (NVB) cisplatin (CDDP) versus observation ANITA trial

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Background: Platinum-based chemotherapy in advanced NSCLC reported variation in the chemosensitivity according to histology. Data issued from the survival outcome in the ANITA trial are reported according to histology in observation (Obs) (n = 433) and adjuvant (CT) arms (n = 407).
Methods: CT resected stage IB-IIIA NSCLC received NVB 30 mg/m^2 weekly (16 doses), CDDP 100 mg/m^2 on day 1, 29, 57 and 85 versus observation; 5Y OS rates were calculated with Kaplan-Meier for Squamous vs non Squamous, adenocarcinoma (ADK) vs. other histology. Cox models performed with gender (female vs. male), disease stage (IB vs. II vs. IIIA) and WHO performance status (0 vs. 1−2) as cofactors: estimates of cofactor-adjusted hazard ratios (HR) within the above mentioned histological subgroups were obtained.
Results: Histology distribution (CT/Obs): 59/58% squamous-cell carcinoma; 40/41% non squamous-cell carcinoma (1% mixed and missing); 34/33% ADK. NVB-CDDP lead to a benefit of 8.6% in OS at 5 years (5Y), consistent whatever the histology: 7.9% Squamous, 9.3% non Squamous, 13.9% ADK vs. 5.8% other subtypes; 5Y OS Squamous/non Squamous: 51.6/50.7% CT, 43.7/41.4% Obs. 5Y OS suggested poorer prognosis in untreated ADK vs other subtypes (Obs: 38.2 vs 45.0%) which disappeared with NVB-CDDP: 52.1 vs 50.8%. The adjusted HR did not show statistical difference according to histology. In ADK, the HR related to CT vs. Obs was 0.71 [0.52−0.97] and 0.82 [0.65−1.03] in the other subtypes.
Conclusion: Efficacy of NVB-CDDP adjuvant is independent from histology, with similar 5YS OS. The poor outcome of ADK found in Obs was reversed by the positive impact of CT, possibly due to a higher chemosensitivity of this subtype.