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A randomized phase III study comparing cisplatin-pemetrexed (cis-pem) with carboplatin (C)-paclitaxel (P)-bevacizumab (B) in chemotherapy naïve patients (pts) with advanced KRAS mutated non-small cell lung cancer (NSCLC): NVALT22

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Background

We previously showed in a retrospective multi-center analysis in pts with *KRAS* mutated NSCLC that outcome with first-line platinum-based chemotherapy was improved with taxane-based combinations compared to other regimens (Mellema, Lung Cancer 2015; 90:245). Therefore, we initiated NVALT22, a multi-center open-label randomized phase III study comparing cis-pem and CPB in pts with advanced *KRAS* mutated NSCLC. Here we present the progression free survival (PFS) as assessed by local investigator.

Methods

Pts with stage IIIB/ IV *KRAS* mutated NSCLC were randomized 1:1 to up to 6 cycles of C (AUC6), P (200 mg/m²), and B (15 mg/kg), every 3 weeks (Q3W), followed by B maintenance; or cis (75 mg/m²) and pem (500 mg/m²), Q3W, followed by pem maintenance. Stratification factors: *KRAS* mutation (G12C/G12V/other), performance status (ECOG 0-1/2), brain metastases (y/n). In 2018 the study was amended: prior pembrolizumab was allowed and added as stratification factor (y/n). Response assessment was performed every 6 weeks (RECIST 1.1). Primary endpoint: PFS. Secondary endpoints: overall response rate, disease control rate and overall survival. The trial was designed to demonstrate superiority of CPB over cis-pem, assumed hazard ratio (HR) 0.67. 201 events and a total sample size of 240 pts were required.

Results

Inclusion was closed prematurely due to slow accrual, mainly due to change of first-line treatment landscape. 203 pts (53% female, median age 65 (range 59 – 70), 45% G12C mutation, 95% ECOG ≤1, 13% history of brain metastasis, 13% prior pembrolizumab) were randomized. At data cutoff (August 16, 2021) median follow-up was 38.3 mo (95% confidence interval (CI) 33.5 – 47.6) and 184 events occurred. Median (95% CI) PFS was 5.2 mo (4.4 – 6.2) for CPB vs 4.7 mo (3.9 – 5.9) for cis-pem, HR 0.96 (95% CI 0.70 – 1.31), *p* = 0.81. In pts with a G12C mutation CPB showed a HR of 0.74 (95% CI 0.47 – 1.16), *p* = 0.22.

Conclusions

CPB did not improve PFS compared to cis-pem in pts with advanced *KRAS* mutated NSCLC.

Clinical trial identification

NCT02743923 (April 19th, 2016); EudraCT 2015-003121-34.

Legal entity responsible for the study

Stichting NVALT studies.

Funding

Eli Lilly; Roche.

Disclosure

A.C. Dingemans: Financial Interests, Institutional, Advisory Board: Roche; Financial Interests, Institutional, Invited Speaker: Takeda; Financial Interests, Institutional, Advisory Board: Sanofi; Financial Interests, Institutional, Advisory Board: Amgen; Financial Interests, Institutional, Advisory Board: Bayer; Financial Interests, Institutional, Invited Speaker: Lilly; Financial Interests, Institutional, Invited Speaker: Janssen; Financial Interests, Institutional, Invited Speaker: Pfizer; Financial Interests, Institutional, Invited Speaker: AstraZeneca; Financial Interests, Institutional, Research Grant: Amgen; Financial Interests, Institutional, Invited Speaker: Lilly; Financial Interests, Institutional, Invited Speaker: Amgen; Non-Financial Interests, Other, Chair EORTC lung cancer group: EORTC; Non-Financial Interests, Member: IASCL; Non-Financial Interests, Member: ASCO; Non-Financial Interests, Member: AACR. S. Burgers: Financial Interests, Institutional, Research Grant: MSD; Financial Interests, Institutional, Advisory Board: Roche; Financial Interests, Institutional, Advisory Board: AstraZeneca; Financial Interests, Institutional, Advisory Board: Boehringer Ingelheim. L.E.L. Hendriks: Financial Interests, Institutional, Advisory Board: Amgen; Financial Interests, Institutional, Advisory Board: BMS; Financial Interests, Institutional, Advisory Board: Boehringer Ingelheim; Financial Interests, Institutional, Advisory Board: Eli Lilly; Financial Interests, Institutional, Invited Speaker: MSD; Financial Interests, Institutional, Advisory Board: Pfizer; Financial Interests, Institutional, Advisory Board: Roche; Financial Interests, Institutional, Advisory Board: Takeda; Financial Interests, Institutional, Research Grant: Boehringer Ingelheim; Financial Interests, Institutional, Research Grant: AstraZeneca; Financial Interests, Institutional, Research Grant: Roche. T.J.N. Hiltermann: Financial Interests, Institutional, Advisory Board: AZD; Financial Interests, Institutional, Advisory Board: BMS; Financial Interests, Institutional, Advisory Board: Boehringer Ingelheim; Financial Interests, Institutional, Advisory Board: Roche; Financial Interests, Institutional, Research Grant: AstraZeneca; Financial Interests, Institutional, Research Grant: BSM; Financial Interests, Institutional, Research Grant: Roche. E.F.F. Smit: Financial Interests, Institutional, Advisory Board: AstraZeneca; Financial Interests, Institutional, Advisory Board: BMS; Financial Interests, Institutional, Advisory Board: Bayer; Financial Interests, Institutional, Advisory Board: cellgene; Financial Interests, Institutional, Advisory Board: dsi; Financial Interests, Institutional, Advisory Board: Eli Lilly; Financial Interests, Institutional, Advisory Board: MSD; Financial Interests, Institutional, Advisory Board: Merck; Financial Interests, Institutional, Advisory Board: Novartis; Financial Interests, Institutional, Advisory Board: Pfizer; Financial Interests, Institutional, Advisory Board: Takeda; Financial Interests, Institutional, Advisory Board: Regeneron; Financial Interests, Institutional, Advisory Board: Roche; Financial Interests, Institutional, Research Grant: AstraZeneca; Financial Interests, Institutional, Research Grant: BMS; Financial Interests, Institutional, Research Grant: Merck; Financial Interests, Institutional, Research Grant: MSD; Financial Interests, Institutional, Research Grant: Roche. J.A. De Langen: Financial Interests, Institutional, Advisory Board: AstraZeneca; Financial Interests, Institutional, Advisory Board: bms; Financial Interests, Institutional, Advisory Board: boehringer ingelheim; Financial Interests, Institutional, Advisory Board: Eli Lilly; Financial Interests, Institutional, Advisory Board: MSD; Financial Interests, Institutional, Advisory Board: Pfizer; Financial Interests, Institutional, Research Grant: AstraZeneca; Financial Interests, Institutional, Research Grant: BMS; Financial Interests, Institutional, Research Grant: Merus; Financial Interests, Institutional, Research Grant: MSD. All other authors have declared no conflicts of interest.