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TITLE

Combined, patient-level, analysis of two randomised trials evaluating the addition of denosumab to standard first-line chemotherapy in advanced NSCLC – the ETOP/EORTC SPLENDOUR and AMGEN-249 trials.

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NSCLC, RANKL, Denosumab, bone metastases

SHORT TITLE

Denosumab addition to first-line chemotherapy in NSCLC – combined analysis

ABSTRACT

Introduction

The efficacy of adding denosumab to standard first-line chemotherapy for advanced NSCLC patients has been evaluated in two separate randomised trials (SPLENDOUR and AMGEN-249). In this pooled analysis, we will assess the combination-treatment effect in the largest available population, in order to conclude about the potential impact of denosumab in NSCLC.

Methods

Both trials included in this combined analysis, were randomised (SPLENDOUR 1:1, AMGEN-249 2:1) multi-centre trials stratified by histology, bone metastasis, geographical region and for SPLENDOUR only, ECOG PS. Cox proportional hazards models, were used to assess the treatment effect with respect to overall survival (OS; primary endpoint) and progression-free survival (PFS; secondary endpoint). Heterogeneity between trials was assessed, and subgroup analyses were performed.

Results

The pooled analysis was based on 740 randomised patients (SPLENDOUR:514; AMGEN-249:226), with 407 patients in the chemotherapy-denosumab arm and 333 in the chemotherapy-alone arm.

In the chemotherapy-denosumab arm, at a median follow-up of 22.0 months, 277 (68.1%) deaths were reported with median OS 9.2 months (95%CI:[8.0-10.7]), while in the chemotherapy-alone arm, with similar median follow-up of 20.3 months, 230 (69.1%) deaths with median OS 9.9 months (95%CI:[8.3-11.2]). No significant denosumab effect was found (HR=0.98; 95%CI:[0.83-1.18]; *P*=0.85).

Among subgroups, interaction was found between treatment and histology subtypes (*P*=0.020), with a statistically significant benefit in the squamous group (HR=0.70; 95%CI:[0.49-0.98]; *P*=0.038), from 7.6-9 months median OS.

With respect to PFS, 363 (89.2%) and 298 (89.5%) events were reported in the chemotherapy-denosumab and chemotherapy-alone arms, respectively, with corresponding medians 4.8 months (95%CI:[4.4-5.3]) and 4.9 months (95%CI:[4.3-5.4]). HR for PFS was 0.97 (95%CI:[0.83-1.15]; *P*=0.76), indicating that no significant denosumab benefit existed for PFS.

Conclusion

In this pooled analysis, no statistically significant improvement was shown in PFS/OS with the combination of denosumab and chemotherapy for advanced NSCLC and no meaningful benefit in any of the subgroups.

INTRODUCTION

Lung cancer is the leading cause of cancer mortality and histologically non-small cell lung cancer (NSCLC) accounts for 85% of lung cancers. Life expectancy of individuals with lung cancer has increased with better treatments, including targeted therapies and immunotherapy.

A considerable and growing number of cytokines, growth factors and immune modulators playing a role in lung cancer development are being identified. Some of them can be considered as prognostic factors, whereas others are also regarded as therapeutic targets.

One such example is the receptor activator of NF-κB (RANK) ligand (RANKL), a tumour necrosis factor (TNF) family member that signals through its receptor RANK, which was first discovered for communication between T-cells and dendritic cells. Through its receptor RANK, RANKL activates osteoclasts for bone resorption, promotes lymphocyte maturation and function, and enables mammary gland and secondary lymph node organogenesis.[1-3]. A link between RANKL-signalling and cancer has been established in recent years. First, and perhaps owing to its bone remodelling capabilities, the RANKL-RANK pathway facilitates bone metastasis formation.[4,5] Second, it promotes seeding of breast tumour cells into the lungs in a T-regulatory–cell-dependent manner. Third, it participates in development of progestin-dependent mammary tumours.[6-8] Importantly, less is known about its contribution in primary

tumours from other carcinomas such as lung cancer. In a large international clinical trial of patients with advanced solid tumours (excluding breast and prostate cancer) or multiple myeloma, denosumab, a fully human monoclonal antibody that binds RANKL and blocks RANKL-RANK interaction, was shown to be non-inferior – with a trend toward superiority – to zoledronic acid in delaying time to first skeletal related event (SRE) (Hazard Ratio (HR), 0.84; 95%CI:[0.71-0.98]; non-inferiority p=0.0007, representing 16% reduction in hazard). Although this trial failed to reveal any difference in overall survival (OS),[9] a pre-specified exploratory subgroup analysis reported that the effect of denosumab on time to first on-study SRE relative to zoledronic acid by tumour stratification factors resulted in a HR of 0.84 for NSCLC (n=702; 95%CI:[0.64-1.10]; P=0.20).

SPLENDOUR (ETOP-5-12/EORTC 08111; ClinicalTrials.gov Identifier: NCT02129699) was an open label phase III trial with the primary objective to evaluate whether the addition of denosumab to standard first-line platinum-based doublet chemotherapy in advanced NSCLC improves OS. AMGEN-249 (ClinicalTrials.gov Identifier: NCT01951586) was a randomised, double-blind, multi-centre phase II trial of denosumab in combination with chemotherapy as first-line treatment of metastatic NSCLC.

The current analysis aims at performing an individual data combined analysis of the SPLENDOUR and AMGEN-249 trials, representing the largest number of patients available in order to allow for a conclusion about the potential anti-tumour effect and subsequent OS impact of denosumab in NSCLC. The primary objectives are to assess efficacy in term of OS and progression-free survival (PFS) in the combined data sets.

METHODS

Study designs of included clinical trials

SPLENDOUR was an open label phase III trial with the primary objective to evaluate whether the addition of denosumab to standard first-line platinum-based doublet chemotherapy in advanced NSCLC improves OS. Patient population included those with and without bone metastasis.

AMGEN-249 was a randomised (a ratio 2:1), double blind, multi-centre phase II trial of denosumab in combination with chemotherapy as first-line treatment of metastatic NSCLC.

In both trials, the primary endpoint was OS, while PFS was included among secondary endpoints. The primary objective of this combined individual patient data analysis was to assess the efficacy in terms of OS and PFS in the combined datasets.

The two multicentre trials with similar design were combined to increase the overall statistical reliability of the results. Each trial was a randomised, parallel-group design, comparing addition of denosumab to standard chemotherapy. The stratification factors of both studies were similar. AMGEN-249 stratification factors were histology (squamous vs non squamous); bone metastasis (Yes vs No); region (Western Europe, North America/Australia, Rest of the World). SPLENDOUR stratification factors were histology (squamous vs non squamous); bone metastasis (Yes vs No); region (Eastern Europe, Western Europe, Southern Europe) and ECOG Performance Status (PS) (0/1 vs 2), which was not a stratification factor for the AMGEN-249 trial.

Patients and treatment

Non-small cell lung cancer (NSCLC) patients were pooled from the two clinical trials. The eligibility criteria for both trials are reported in the individual publications.[10,11]

In SPLENDOUR, patients were randomised 1:1 to receive either four to six cycles of platinum-based doublet chemotherapy (platinum compound plus gemcitabine or pemetrexed for non-squamous cell histology) or platinum-based doublet chemotherapy plus denosumab at a dose of 120 mg, subcutaneously every three to four weeks (chemotherapy-denosumab-arm).

In the AMGEN-249 trial, patients were randomised 2:1 to receive four to six cycles of standard of care chemotherapy and denosumab 120 mg or placebo subcutaneously every three to four weeks plus a loading dose on day 8.

Statistical Analyses

The two randomised trials were designed to evaluate the addition of denosumab using OS as the primary endpoint. The pooled statistical analysis was conducted using the same patient populations as those used in both trials. Efficacy data were analysed on intention-to-treat basis. The Cox proportional hazards (PH) model was used to analyse OS and PFS. In all primary analyses, the Cox PH model was stratified by stratification factors (histology, bone metastasis, ECOG PS, geographical region) with the stratification factors nested within each trial. Sensitivity analyses were also performed for both OS and PFS endpoints to account for the

different stratification factors for each study, including Cox models stratified by study and adjusting (in multivariate models) for all the stratification factors. P-values were reported from corresponding stratified log-rank tests. Follow-up time was calculated using the reverse-censoring Kaplan-Meier method.

Subgroup analyses by age (<70 vs ≥70), sex and stratification factors (with ECOG PS 0/1 and 2 exclusively from SPLENDOUR trial) used at randomisation were conducted to assess heterogeneity of the results across specific subgroups using the Cox regression model as in the primary analysis. If the subgroup of interest was one of the stratification factors, in the Cox model this stratification factor was excluded. No adjustment for multiple testing was performed for subgroup analyses.

All statistical analyses were conducted at a 0.05 significance level and 95% confidence intervals (CI) were constructed.

RESULTS

The pooled population consisted of 740 patients: 514 patients were derived from the SPLENDOUR trial (255 in chemotherapy-alone and 259 in chemotherapy-denosumab, randomised from 11 December 2014 to 10 January 2018) and 226 from the AMGEN-249 trial (78 in chemotherapy-placebo and 148 in chemotherapy-denosumab, randomised from 31 December 2013 to 21 May 2015) (Figure 1). In total, 407 patients were randomised to the treatment arm (combination of chemotherapy with denosumab), and 333 patients to the control arm (chemotherapy-alone or with placebo). Overall, 70% of the patients were male; median age was 66 years, 92.6% had an ECOG PS of 0/1 and 7.4% had an ECOG PS of 2. The majority of the patients had non-squamous NSCLC (74.9%). Table 1 shows the distribution of patient characteristics for the pooled population. The characteristics were well balanced between treatment arms (except for geographical region, a stratification factor with different levels in the two trials).

Efficacy of treatment on overall survival

The median follow-up for the combined analysis was 20.3 months in the chemotherapy arm and 22.0 months in the chemotherapy-denosumab arm. In the chemotherapy-arm, the total number of deaths was 230 (69.1%) with median OS 9.9 months (95%CI:[8.2-11.2]), while in the chemotherapy-denosumab arm, 277 (68.1%) deaths were recorded with median OS

9.2 months (95%CI:[8.0-10.7]). The Kaplan-Meier curves for OS by treatment arm are depicted in Figure 2A, while respective plots by trial can be found in the supplement (Figures S1A-B).

The primary statistical analysis showed that the combination of denosumab with chemotherapy was not significantly superior to chemotherapy in terms of OS (HR=0.98; 95%CI:[0.82-1.18]; *P*=0.85). Sensitivity results were consistent with those of the primary analysis (indicating no significance). Test for heterogeneity of the treatment effects was not able to detect heterogeneity between the two trials (Figure 2B).

In the subgroup analyses, no heterogeneity was detected, except for histology (interaction *P*=0.02, Figure 3). A statistically significant benefit of the chemotherapy-denosumab combination was detected in the squamous group with median OS 9 months compared to 7.6 months under chemotherapy alone, and HR=0.70 (95%CI:[0.49-0.98]; *P*=0.038), while the effect was not significant for the non-squamous patients (*P*=0.30) (Figures 4A-B). No other subgroup with statistically significant OS benefit was found. For exploratory purposes, the Kaplan-Meier plots for the subgroups of patients with or without bone metastasis are presented in the supplement (Figures S2A-B).

Efficacy of treatment on progression-free survival

In the chemotherapy-arm, 298 (89.5%) patients had progressed or died, and the median PFS was 4.9 months (95%CI:[4.3-5.4]). Similarly, in the chemotherapy-denosumab arm, 363 (89.2%) patients had progressed or died, with median 4.8 months (95%CI:[4.4-5.3]). Figure 5A shows the PFS Kaplan-Meier curves for control and treatment. Corresponding plots by trial can be found in the supplement (Figures S3A-B).

According to the combined statistical analysis performed, the combination of chemotherapy with denosumab was not significantly different to chemotherapy-alone in terms of PFS (HR=0.97; 95%CI:[0.83-1.15]; *P*=0.76). No significant results were also confirmed by sensitivity analyses. Test for heterogeneity of the treatment effects did not detect heterogeneity between the two trials (Figure 5B).

Furthermore, in the subgroup analyses, heterogeneity was detected between PS subgroups (interaction *P*=0.001, Figure 6). A statistically significant benefit of chemotherapy-alone was detected in the ECOG PS=2 group, with HR=2.51 (95%CI:[1.29-4.89]; *P*=0.0045). This result

however should be interpreted cautiously as the sample size of patients with ECOG PS of 2 was very small (n=55; all from the SPLENDOUR trial). Kaplan-Meier plots for patients with PS 0/1 or 2 are provided in the supplement (Figures S4A-B). No other subgroup with significant difference was found. PFS curves for the subgroups of patients with or without bone metastasis and by histology subtype are also reported, for exploratory purposes, in the supplement (Figures S5A- S6B). Of note, the PFS results did not confirm the OS benefit for denosumab that was found for the squamous subgroup.

DISCUSSION AND CONCLUSION

Retrospective data on bone metastasis, a significant cause of morbidity in advanced cancer, demonstrate that 30-45% of NSCLC patients are affected during the course of their disease, with a post mortem documentation in 36% of patients. Bone metastases at initial diagnosis occur in about two thirds of patients.[12-15] Cancer metastasis to the bone results from the active engagement and interaction with the bone microenvironment. RANKL-mediated increased bone turnover and osteoclast activity may enhance tumour growth in bone by mechanically facilitating cancer cell establishment.

A direct impact of RANK and RANKL on tumour cell proliferation has been hypothesised, with a potential similar stimulatory effect as observed on osteoclasts. RANK-signalling accelerated tumourigenesis in mouse mammary tumour virus (MMTVneu)-RANK transgenic mice as well as in the MMTVneu transgenic mouse model.[6,16] In addition, RANKL expression per se has been observed in some tumour types, while RANK was shown to be expressed at least in some cancer cell types. In parallel, early clinical data suggest a potential anti-tumoural effect of RANK pathway inhibitors. Undoubtedly, the potential for RANK pathway inhibitors to reduce tumour aggressiveness and metastatic capabilities via distinct mechanisms should deserve specific investigations. The apparent survival benefit of denosumab compared to zoledronic acid for patients with lung cancer and bone metastases, in a post-hoc analysis of a randomised phase III trial, gave additional reason to prospectively investigate the impact of denosumab.[9,17]

Our present analysis is aiming at establishing a final conclusion about the role of denosumab as an anti-tumour agent in advanced NSCLC particularly in subgroups underrepresented in either study alone. Both trials in this combined analysis, were randomised multi-centre trials seeking to investigate whether the addition of denosumab to standard first-line platinum

chemotherapy improves OS in advanced NSCLC. The SPLENDOUR trial planned to randomise 1000 patients. However, the recruitment stopped prematurely in January 2018 after the randomisation of 514 patients, due to slow accrual, related to the advent of frontline immunotherapy becoming available in competitive clinical trials and subsequently established as standard of care. The final analysis of SPLENDOUR did not show an improvement in OS for the addition of denosumab compared to chemotherapy. Subgroup analyses did not show survival differences between patient cohorts with and without bone metastases and irrespective of histological subtypes. The combined analysis allows the effects of the treatment to be assessed in a larger cohort. The patient characteristics and the follow-up duration were similar in both trials. Although the size of the SPLENDOUR trial was more than double that of the AMGEN-249 trial, combining them provides a larger clinically homogenous cohort. The results were weighted towards the SPLENDOUR trial since it was comparatively larger.

This combined analysis using patient individual data found no statistically significant improvement in PFS with the combination of denosumab and chemotherapy versus chemotherapy alone, in the overall population and across the important clinical subgroups as defined by age, gender, PS and presence of bone metastases, histology, and region with the exception of a divergent poorer outcome for the small subgroup of PS 2 patients. No statistically significant improvement in OS with the combination of denosumab and chemotherapy was shown, with the exception of a differential treatment effect by histology, which was a stratification factor in both studies. A statistically significant improvement in OS was demonstrated in patients with histologically squamous NSCLC, while such a benefit was not found in non-squamous NSCLC. This difference was interestingly not statistically significant for PFS. Whether this improvement of median OS from 7.6 to 9.0 months, with the survival curves tending to come together at approximately 18 months (even though with only a few patients still at risk), represents a true effect of RANK-signalling pathway inhibition, or is the effect of any confounding factors that would have impacted OS differentially in these subgroups, including for example subsequent lines of treatments, remains unknown. Of note, two smaller randomised trials that tested zoledronic acid added to second-line chemotherapy with docetaxel, also failed to show a positive PFS signal in patients with NSCLC.[18,19]

While the efficacy and safety of denosumab in the treatment of patients with bone metastases from lung cancer has been firmly established, our compiled data set from two prospective clinical trials fails to demonstrate a positive survival impact for denosumab when added to

chemotherapy. However, with the emergence new strategies for immune- and targeted therapies, the treatment paradigm for metastatic NSCLC has been dramatically modified. New combined strategies on the role of the RANK pathway blockade in cancer are being considered, including combinations with immune-checkpoint blockade.[20-22] The DENIVOS trial is evaluating denosumab and nivolumab combination as second-line treatment in stage IV NSCLC with bone metastases (NCT03669523). In priority and specifically, the potential of denosumab to enhance the response to immuno-oncology agents deserves further evaluation in NSCLC.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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