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Title: A randomised open-label phase III trial evaluating the addition of denosumab to standard first-line treatment in advanced NSCLC – the ETOP and EORTC SPLENDOUR trial

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ABSTRACT

Introduction: RANKL stimulates NF-kB-dependent cell-signalling and acts as the primary signal for bone resorption. Retrospective analysis of a large trial comparing denosumab versus zoledronic acid in bone metastatic solid tumours suggested significant overall survival (OS) advantage for lung cancer patients with denosumab. The randomised open-label phase III SPLENDOUR trial was designed to evaluate whether the addition of denosumab to standard first-line platinum-based doublet chemotherapy improves OS in advanced NSCLC.

Methods: Stage IV NSCLC patients were randomised 1:1 to either chemotherapy with or without denosumab (120mg every 3-4 weeks), stratified by presence of bone metastases (at diagnosis), ECOG performance status, histology and region. To detect an OS increase from 9-11.25 months (HR=0.80), 847 OS events were required. The trial closed prematurely due to decreasing accrual rate.

Results: 514 patients were randomised, 509 receiving ≥1 dose of assigned treatment (chemotherapy:252, chemotherapy-denosumab:257). Median age was 66.1 years, 71% male, 59% former smokers. Bone metastases were identified in 275(53%) patients. Median OS(95%CI) was 8.7(7.6-11.0) in the control versus 8.2(7.5-10.4) months in the chemotherapy-denosumab-arm,

(HR=0.96;95%CI:[0.78-1.19]; 1-sided *P*=0.36). For patients with bone metastasis HR=1.02(95%CI:[0.77-1.35]), while for those without HR=0.90(95%CI:[0.66-1.23]). Grade≥3 adverse events were observed in 40.9%/5.2%/8.7% versus 45.5%/10.9%/10.5% of patients. Conditional power for OS benefit was ≤10%.

Conclusions: Denosumab was well tolerated without unexpected safety concerns. There was no OS improvement for denosumab when added to chemotherapy in the ITT, and in the subgroups with and without bone metastases. Our data do not provide evidence of a clinical benefit for denosumab in NSCLC patients without bone metastases.

KEYWORDS:

NSCLC, RANK, RANKL, Denosumab, bone metastases

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.

Bone metastases are a significant cause of morbidity in advanced cancer and 30–45% of patients with advanced NSCLC will develop bone metastases during the course of their disease, with a post mortem documentation in 36%. Retrospective data demonstrate that in two thirds of patients with bone metastatic disease had bone metastases already at the time of initial diagnosis.[1-4]

Patients with metastatic bone disease may suffer from skeletal-related events (SREs), such as fractures, pain requiring radiation or bone surgery, spinal cord compression, severely affecting quality of life. Lung cancer patients are known to present with high frequency of SREs[5,6] while

the occurrence of NSCLC-associated SREs was shown to predict an unexpectedly short life expectancy with virtually no long-term survivors.[4]

Signalling through binding of the Receptor activator of NF-kB ligand (RANK) to its ligand RANKL, was first discovered as a means of communication between T-cells and dendritic cells. RANKL activates osteoclasts for bone resorption, and enables mammary gland and secondary lymph node organogenesis[7]. RANKL has also profound immune modulating effects since the binding to its receptor induces T-reg cells and chemo-resistance through the activation of multiple signal transduction pathways.[8,9] As a consequence, RANKL-inhibition enhances immune responses and holds promise as immune-therapeutic agent to treat cancer. RANK- and RANKL-expressions have been observed in some tumour types with early clinical data, suggesting a potential anti-tumour effect of RANK-pathway inhibitors.[8]

The RANKL inhibitor denosumab, a fully human monoclonal IgG2 antibody, is approved for the prevention of skeletal-related events in patients with advanced malignancies involving bone, including solid tumours and multiple myeloma.

In a pivotal phase III trial of denosumab versus zoledronic acid for the treatment of bone metastases in advanced cancer, denosumab significantly delayed first on-study SREs in NSCLC.[10] In a post-hoc, exploratory analysis of 811 lung cancer patients, denosumab was associated with improved overall survival (OS) versus zoledronic acid. Specifically, in NSCLC, a HR of 0.79 (9.5 versus 8.1 months, 95%CI:[0.65-0.95]) was described.[11]

The SPLENDOUR trial was designed to address in a randomised manner whether the addition of denosumab to standard first-line platinum-based doublet chemotherapy improves OS in advanced NSCLC.

MATERIAL AND METHODS

Design

SPLENDOUR (ETOP 5-12 /EORTC 08111), an international, multi-centre, randomised, open-label phase III trial, evaluated the addition of denosumab to standard first-line anticancer treatment in advanced NSCLC. Safety was monitored by the ETOP Independent Data Monitoring Committee (IDMC). The trial is registered with ClinicalTrials.gov, number NCT02129699.

Patients

Patients were recruited from 55 centres in Austria, Belgium, France, Germany, Ireland, Italy, Slovenia, Spain, Switzerland and the United Kingdom.

Eligible patients were ≥18 years, had measurable or evaluable stage IV NSCLC, (with or without bone metastases), Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2, available tumour tissue for translational research, life expectancy of at least 3 months, and adequate renal, hepatic and haematological functions. Patients with documented sensitising EGFR activating mutation or ALK rearrangements, symptomatic brain metastases, prior chemotherapy or targeted therapy for metastatic disease, or severe, uncorrected hypocalcaemia or hypercalcaemia were excluded. Screening for EGFR/ALK was optional, following local standards, but strongly encouraged in non-squamous histology, while CT scan or MRI of brain was not mandatory and only recommended in case of clinically suspected brain metastasis. Following a protocol amendment, activated when the majority of patients had already been randomised, one line of prior therapy with an immune checkpoint inhibitor was allowed.

Study treatment and assessments

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). Denosumab was continued beyond disease progression and given concomitantly with subsequent treatment lines, for as long as it was tolerated. Zoledronic acid administration was only allowed in the chemotherapy-arm when there were skeletal metastases at baseline, as this is a standard of care. Pemetrexed or erlotinib maintenance treatment after doublet chemotherapy was allowed in both arms.

CT-scans for tumour response assessments were performed at baseline, chemotherapy cycle 3 and then every 12 weeks until progression. All patients underwent a PET-CT or bone scan at baseline for specific bone metastases status assignment. Bone imaging (including bone scan) during treatment and at progression were also performed if clinically indicated, i.e., in case of suspected bone metastases. In the event of equivocal results, further confirmation using bone MRI, CT, X-Ray or biopsy was recommended.

Adverse events were reported following the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0).

Statistical plan

SPLENDOUR used a centralised random assignment of patients using the block design technique, stratified by bone metastases (presence versus absence), ECOG PS (0/1 versus 2), histology (squamous versus other), and geographic region (Eastern versus Western versus Southern Europe) to balance pemetrexed availability, maintenance strategy and standard of care.

The primary endpoint was OS. Secondary endpoints included progression-free survival (PFS), response by RECIST v1.1, and safety. OS and PFS, estimated from time of randomisation, were conducted on the intention-to-treat (ITT) population and analysed using Cox regression. Comparisons between treatment arms were made by score test adjusted for stratification factors.

Sensitivity analysis was performed based on log-rank test and Kaplan-Meier estimates and plots were produced.

For PFS analysis, an event was defined as disease progression or death, whichever occurred first. Alive patients without progression were censored at date of last follow-up.

Using 90% power and one-sided type I error of 2.5%, demonstration of an increase in median OS to 11.25 months in the chemotherapy-denosumab-arm relative to 9 months in the chemotherapy-arm (equivalent to HR=0.80) required observation of 847 deaths. Assuming an accrual rate of 15 patients/month in the first 6 months and 30 patients/month thereafter, 1000 patients were required to be recruited over a period of 37 months and followed for an additional 14 months after the randomisation of the last patient, to reach the required number of events. The trial was designed with a futility interim analysis (IA) at 30% of the information time.

Subgroup analyses for the treatment effect on OS and PFS by bone metastasis status at randomisation, ECOG PS and histology were predefined. The accrual in the bone metastases stratum was expected to be 30%. The same OS improvement was assumed for both bone metastases strata in the chemotherapy-denosumab-arm.

The planned IA for futility was conducted when 274 events (32.4% of information) for the primary endpoint were available. Results were presented to the IDMC in September 2017, which recommended continuation of the study as per protocol. However, the Steering Committee closed recruitment as of January 2018, considering that completion of accrual was not feasible in the context of recent immunotherapy advances and the multiplicity of immunotherapy-based ongoing clinical trials in this specific clinical scenario. In fact, subsequent survival improvement and regulatory approval of combined anti-PD(L)-1 and immunotherapy and chemotherapy would have ethically and practically prevented the continuation of this trial.

RESULTS

Patients and Treatment

Between 11/12/2014 and 10/01/2018, 514 patients were randomised from 55 institutions. The patient flow is summarized in the Consort Diagram in Figure 1. The analysis includes data available as of 25 January 2018.

From the 514 randomised patients, 509 started treatment (252 chemotherapy; 257 chemotherapy-denosumab). Thirty-three patients were retrospectively considered ineligible (17 chemotherapy, 16 chemotherapy-denosumab). The primary endpoint analysis was performed on the ITT population of all 514 randomised patients. Safety analysis was based on the 509 patients who started treatment. Of note, three patients randomised to chemotherapy, had actually received denosumab.

Baseline characteristics were well balanced between the two treatment arms (Table 1). The majority of patients had non-squamous histology (72% overall; 73% chemotherapy and 71% chemotherapy-denosumab), ECOG PS of 0/1 (89%; 90% chemotherapy, 89% chemotherapy-denosumab, were from Western Europe (61%; 60% chemotherapy, 63% chemotherapy-denosumab) and had a median age of 66.1 years (65.4 chemotherapy, 66.5 chemotherapy-denosumab). Bone metastases at baseline were observed in 54% of patients (54% chemotherapy, 53% chemotherapy-denosumab). Zoledronic acid was administered in 70 (27.5%) of the chemotherapy patients.

Median duration (range) of trial treatment was 12.4 weeks (3.0-24.9) in the chemotherapy-arm and 21.4 weeks (3.0-148.6) in the chemotherapy-denosumab-arm. Median duration of doublet chemotherapy was similar between the two arms (11.9 versus 12.0 weeks for cisplatin, 12.0 versus 12.0 weeks for carboplatin, 12.4 versus 12.0 weeks for gemcitabine and 12.0 versus 12.0 weeks for pemetrexed) for chemotherapy-arm versus chemotherapy-denosumab-arm, respectively.

Median duration for denosumab treatment was 21.4 weeks (range: 3.0-147.7), with a median cycles number of six. At the time of analysis, eight (3.2%) patients in the chemotherapy-arm and 36 (14%) in the chemotherapy-denosumab-arm were still on treatment (reasons for treatment discontinuation in Table S1).

Efficacy analysis

At the cut-off date for the final analysis (25/01/2018), 159 patients (chemotherapy-arm: 77; chemotherapy-denosumab-arm: 88) were still on follow-up, with median follow-up of 19.8 months (95%CI:[16.8-25.3]) for 25.3 months (95%CI:[19.7-29.0]) for the chemotherapy-arm and chemotherapy-denosumab-arm, respectively.

On the ITT cohort of 514 randomised patients, 355 deaths were observed. Median OS was 8.7 months in the chemotherapy-arm and 8.2 in the chemotherapy-denosumab-arm, corresponding to HR=0.96 (95%CI:[0.78-1.19]; stratified 1-sided *P*-value=0.36) (Figure 2A), confirmed by sensitivity analysis (log-rank *P*=0.34).

Based on these results, the null hypothesis H_0 cannot be rejected and thus OS chemotherapy-denosumab-arm was not found to be significantly superior to the chemotherapy-arm. Conditional power calculations indicated that, even if recruitment had been completed, the power of detecting a significant OS benefit would be less than 10%.

Similarly, PFS did not display a significant difference between the two treatment arms (Figure 2B). The same number of 228 PFS events, were observed in both arms (chemotherapy: 192 progressions and 36 deaths without progression; chemotherapy-denosumab: 186 and 42), with almost identical median PFS (chemotherapy: 4.7 months, 95%CI:[4.1-5.2]; chemotherapy-denosumab: 4.7 months, 95%CI:[4.2-5.3]; stratified Cox 1-sided *P*=0.46).

One complete response was observed in each treatment arm, while objective response rate (ORR) was 29.4% on chemotherapy-arm and 30.5% on chemotherapy-denosumab-arm (Fisher's exact *P*-

value=0.85). Stable disease occurred in 39.6% on chemotherapy and 33.6% on chemotherapy-denosumab, respectively (Table 2).

Subgroup analyses on the primary endpoint OS are presented in Figure 3 (unadjusted Cox analysis). No significant treatment effect was found in any of the subgroups examined, including for presence or absence of bone metastases at randomization. Hazard ratios for patients with and without bone metastases at randomization were 1.02 (95% CI: [0.77-1.35]) and 0.90 (95% CI: [0.66-1.23]), respectively (interaction P=0.55). Of note, the interaction of treatment with ECOG performance status was found significant (*P*=0.027) (Figure 3). Analogous stratified subgroup results for both OS and PFS are summarized in Table S2.

Bone events were recorded in 48 patients (9.3%) overall, 7.7% and 11% on chemotherapy and chemotherapy-denosumab respectively (Fisher's exact *P*-value=0.13, Table S3).

Safety analysis

The number of patients with grade 3/4/5 AEs were 103(40.9%)/13(5.2%)/22(8.7%) on chemotherapy versus 117(45.5%)/28(10.9%)/27(10.5%) on chemotherapy-denosumab, respectively. The most common grade≥3 AEs on chemotherapy were hypertension in 20(7.9%) of the patients (2 grade4), lung infection in 19(7.5%) patients (3 grade5), dyspnoea and fatigue each in 13(5.2%) patients, and sepsis in 10(4%) patients (7 grade5; 3 grade4). Similarly, on chemotherapy-denosumab, hypertension was the most frequent AE (40 patients; 15.6%; 3 grade4). Lung infection is recorded for 28(10.9%) patients (2 grade4; 3 grade5). Other common AES on chemotherapy-denosumab included fatigue in 31(12.1%) patients, dyspnoea in 21(8.2%; 1 grade4), nausea in 17(6.6%) and febrile neutropenia in 13(5.1%, 4 grade4; 2 grade5). Sepsis was reported for 11(4.3%) patients (7 grade4, 4 grade5). The full table of grade≥3 AEs by treatment arm as well as lab toxicities are available in supplement Tables S4 and S5.

Twenty-two (8.7%) patients on chemotherapy had serious AEs (SAEs) with a fatal outcome (nine of which were toxic deaths); while on chemotherapy-denosumab, 32 (12.4%) had a SAE of fatal outcome and nine toxic deaths were observed.

DISCUSSION

While a link between RANKL-signalling and breast cancer bone and systemic progression has been established,[12-14] much less is known about RANKL-signalling in primary tumours from other carcinomas such as lung cancer.

NF-kB-signalling in tumour epithelial cells played an important role in the development of lung tumours in NSCLC mouse models[15-20] and RANKL could theoretically participate in the elaboration of an NF-kB response in lung tumour cells.[21] Of particular interest and supporting the design of this trial was the finding that RANKL blocking agents can impair the growth of primary tumours in several mouse models of lung adenocarcinoma with a predominant effect observed in the presence of KRAS mutation.[22]

SPLENDOUR was designed to evaluate whether denosumab, given in addition to standard first-line platinum-based doublet chemotherapy and continued across subsequent lines of treatments, improves OS in advanced NSCLC. Denosumab in addition to standard chemotherapy was well tolerated without major safety concerns. However, the final analysis of SPLENDOUR did not show an improvement in OS for the addition of denosumab compared to chemotherapy. Subset analyses did not show survival differences between patient cohorts with and without bone metastases and irrespective of histological subtypes.

Our results align with the data from a company sponsored randomised phase II biomarker-driven trial of denosumab versus placebo in NSCLC (NCT01951586), which recruited a similar group of 226 patients in parallel to SPLENDOUR. The reported OS was better at 10.9 months for placebo

and 10.7 months for denosumab, respectively (HR=1.06, 95%CI:[0.75-1.59]) than in SPLENDOUR (median OS around 8 months). There was no correlation between OS and RANK-expression on tissue (data obtained from clinicaltrials.gov).

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. Recruitment, initially very fast, was negatively impacted by a rapidly changing treatment landscape, especially with the advent of frontline immunotherapy becoming available in competitive clinical trials and subsequently as standard of care.

While chemotherapy, concomitantly or not with immunotherapy, will most probably remain a key component of lung cancer treatment, SPLENDOUR was unable to demonstrate any improvement of its activity by adding denosumab. An overall survival of less than one year is in keeping with the historical results pre-targeted and pre-immunotherapy, in a trial with unselected NSCLC patients, notably including PS2 patients.[23] Serum and tumour samples were collected from patients and translational analyses are ongoing, aiming at identifying a subset of patients who might benefit from the addition of denosumab.

Conclusion

In conclusion, denosumab in combination with doublet chemotherapy in patients with stage IV NSCLC did not improve OS, ORR or PFS overall or in any subgroup analysed. There were no new safety concerns.

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DISCLOSURE

Solange Peters has received education grants, provided consultation, attended advisory boards, and/or provided lectures for: Abbvie, Amgen, AstraZeneca, Bayer, Biocartis, Bioinvent, Blueprint Medicines, Boehringer-Ingelheim, Bristol-Myers Squibb, Clovis, Daiichi Sankyo, Debiopharm, Eli Lilly, F. Hoffmann-La Roche, Foundation Medicine, Illumina, Incyte, Janssen, Merck Sharp and Dohme, Merck Serono, Merrimack, Novartis, Pharma Mar, Pfizer, Regeneron, Sanofi, Seattle Genetics and Takeda , from whom she has received honoraria.

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Michael Mark attended advisory boards for: AstraZeneca, Merck Sharp and Dohme, Bristol-Myers Squibb.

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Rolf A Stahel has received honoraria as a consultant at advisory boards from Abbvie, Astra Zeneca, MSD, Pfizer, Regeneron, Roche, Seattle Genetics and Takeda, speaker honoraria in the last two years from Astra Zeneca, Boehringer Ingelheim, Eli Lilly, MSD and Roche and DMC honoraria for Genentech/Roche and Takeda and in the function of ETOP president and scientific chair financial support for ETOP trials from AstraZeneca, AMGEN, BMS, Boehringer Ingelheim, Genentech, MSD, Roche, and Pfizer.

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TABLE AND FIGURE LEGENDS

Figure 1: Study design and Consort diagram.

Figure 2: A) Overall survival by treatment arm in the intention-to-treat population. B) Progression-free survival by treatment arm in the intention-to-treat population.

Figure 3: Overall survival: Sub-group analysis (Forest Plot)

Notes: HR: Hazard Ratio, CI: Confidence Interval

HRs are based on unadjusted univariate Cox models

Table 1: Stratification Factors and Baseline Characteristics of patients (ITT population)

Table 2: Best Overall Response by arm (Intention-to-treat population)

LIST OF SUPPLEMENTARY MATERIAL

Supplementary Tables

Supplementary Figures