Targeting receptor activator of nuclear factor-kappa B as a new therapy for bone metastasis in non-small cell lung cancer

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Purpose of review
The review aims at comprehensively discussing our current knowledge on bone metastases incidence in non-small cell lung cancer (NSCLC), their related complications as well as clinical impact in patients suffering from advanced disease.

Recent findings
After evoking the use of zoledronic acid as the established standard of care until recently, the new class of drugs available to prevent skeletal related events and targeting receptor activator of nuclear factor-kappa B (RANK) will be emphasized, reporting on denosumab clinical trials, a RANK-ligand (RANKL) targeting monoclonal antibody. Biological hypothesis regarding their mechanisms of action as well a potential direct impact on tumor cells are described according to the most recent laboratory as well as hypothesis-generating clinical data.

Summary
Targeting the RANK pathway is an efficient way to prevent complications of bone metastases in NSCLC. Interesting additional direct effects on tumor biology and evolution are being analyzed and prospectively assessed in clinical trials.

Keywords
bone metastases, non-small cell lung cancer, RANK/RANKL, skeletal-related events, zoledronic acid

INTRODUCTION
Bone metastasis is one of the most frequent sites of secondary lesions in advanced non-small cell lung cancer (NSCLC). In the absence of a standard bone metastasis screening strategy in advanced NSCLC, the real incidence and prevalence of bone metastasis in NSCLC remains somehow unsettled.

Epidemiology of bone metastasis in non-small cell lung cancer
Lung cancer bone metastasis can be accurately detected using single-photon emission computed tomography (SPECT), bone scans or alternatively F-18 fluoride positron emission tomography coupled to computed tomography (18FDG-PET/CT), the most sensitive but also the most expensive technique [1,2]. Systematic use of PET-CT preoperatively in early NSCLC has led to a significant tumor stage migration concerning up to 20% of patients, increasing stage-specific survival and avoiding futile surgery procedures [3,4], including the discovery of asymptomatic bone metastasis in a significant proportion of these cases [5].

Available retrospective data demonstrate a high frequency of bone metastasis in NSCLC, affecting 30–45% of patients in the course of their disease, with a post mortem documentation in 36% of patients [6–8]. In NSCLC, bone metastases are localized in the axial skeleton and most frequently spine, ribs, pelvis, femur and skull. Bone metastases are diagnosed at initial diagnosis in about 2/3 of patients globally and are related to a poor median survival.
KEY POINTS

- Targeting the receptor activator of nuclear factor-kappa B (RANK) pathway by using denosumab, a monoclonal antibody directed against its ligand, has demonstrated a strong efficacy in delaying skeletal-related events in patients suffering from virtually all bone-metastatic advanced solid tumors.

- Lung cancer patients suffering from bone metastases benefit from a bone-targeted protective strategy consisting of zoledronic acid or denosumab administration. The latter might be favored due to a trend of efficiency superiority, an easier mode of delivery and the absence of renal toxicity.

- Data on lung cancer patients suggest denosumab might prolong survival as compared to zoledronic acid, but their interpretation is strongly limited by their unplanned retrospective nature on a specific cancer subgroup only.

- Preclinical reports reveal that RANK pathway and nuclear factor-kappaB might be biologically active in promoting tumorigenesis – impacting cancer early development, subsequent proliferation and metastasization as notably shown in breast, prostate and lung cancer.

overall survival (OS) of less than 6 months and the virtual inexistence of long-term survivors [8,9].

The absence of prospective screening series probably leads to underestimation of the frequency of lung cancer patients with secondary bone localization, despite the particularly painful characteristic of NSCLC bone metastasis being mainly of lytic nature [10]. As life expectancy of NSCLC patients is increasing due to improved systemic treatment, this overall picture reveals the importance of preventing any complication of this condition and of improving survival, symptoms control and quality of life of this large group of patients.

Complications of bone metastasis in non-small cell lung cancer patients

Studies analyzing the impact of bone metastasis complications were designed to examine a range of skeletal-related events (SREs) using a composite of SREs as an endpoint. Despite a dismal survival, patients with advanced NSCLC presenting with bone metastasis will frequently suffer from SREs. Definition of SRE included, in the earliest studies, pathologic fractures, bone pain, hypercalcemia and palliative radiotherapy to bone. This has since evolved such that most subsequent trials have assessed skeletal complications omitting bone pain (and often hypercalcemia), but adding spinal cord compression and the need for orthopedic surgery to bone [11**,12**,13] (given below).

The current definition of SREs used in denosumab cancer trials [11**,12**,13] is:

(1) Palliative radiotherapy to bone
(2) Palliative (orthopedic) surgery to bone
(3) Pathologic fracture
(4) Spinal cord compression

SREs severely affect cancer patients’ quality of life and consume significant hospital and financial resources. Typically occurring in periods of disease progression and in situations of expanding tumor load, NSCLC patients are known to present with a high frequency of SREs, as compared to other solid tumors often metastasizing to bone such as breast and prostate cancers [14,15]. Once again, estimation of NSCLC SRE incidence relies on retrospective data extracted from placebo arms of drug-protective trials as well as small retrospective series, and is evaluated to affect between 45 and 65% of bone-metastatic NSCLC, to be often successive and multiple with an evaluated frequency of 2–3 SREs per year, with a time to SRE between 3 and 5 months. The most frequent SRE reported was radiotherapy to bone. Importantly, SRE occurrence was consistently shown to predict a particularly short life expectancy for NSCLC patients [7,8,14–17].

STANDARD TREATMENT OF NON-SMALL CELL LUNG CANCER WITH BONE METASTASIS

Bisphosphonates, such as zoledronic acid, are structural analogues of endogenous pyrophosphate and act on bone metabolism by disrupting the HMG-CoA reductase pathway and blocking osteoclastogenesis, as well as osteoclast cytoskeletal arrangement. A phase III randomized trial in solid tumors excluding breast and prostate carcinoma and including more than 700 patients with long-term follow-up was able to demonstrate a strong activity of zoledronic acid in preventing (risk reduction of 31%), delaying and reducing the annual incidence of SREs [14]. For years, it has become the recommended drug to be administered as part of the overall management of patients with bone metastases but remains of relatively limited use in NSCLC. This might be related to its intrinsic potential nephrotoxicity and requirement for renal function monitoring – in patients often affected by previous cisplatin nephrotoxicity as well as smoking-related arteriosclerosis affecting kidneys, and probably the issue of a short life expectancy.
as the general context of patients suffering from this cancer type being the main reason to renounce to preventive interventions [14,15,18,19].

RECEPTOR ACTIVATOR OF NUCLEAR FACTOR-KAPPA B PATHWAY

Osteoclasts arise from the monocyte–macrophage lineage and, when they are activated, resorb bone and eventually undergo apoptosis. Receptor activator of nuclear factor-kappa B ligand (RANKL) – a tumor necrosis factor (TNF) family member – is a potent osteoclastogenic factor expressed on the surface of osteoblasts and osteocytes and released by activated T cells.

Receptor activator of nuclear factor-kappa B (RANK) is present on osteoclasts and their precursors and stimulates their proliferation, differentiation and adherence and promotes survival and activation of mature osteoclasts.

Whereas RANK signaling is stimulated upon RANKL binding, osteoprotegerin (OPG) is a secreted decoy receptor that acts as a natural inhibitor of the pathway [20]. The whole OPG/RANKL/RANK system tightly regulates physiological bone turnover, bone remodeling as well as bone destruction; in the context of cancer, it is hypothesized that tumor cells lead to increased expression of RANKL on osteoblasts and their precursors, resulting in bone resorption and local bone destruction leading to SREs.

Receptor activator of nuclear factor-kappa B pathway activation beyond bone cells

Apart from bone matrix cells, the transmembrane RANK protein is strongly expressed in lymphocytes, dendritic cells, fibroblasts and mammary gland; RANK mRNA is also found in skeletal muscle, liver, small and large intestine and adrenal gland [21]. Of therapeutic interest, its presence was also demonstrated in some specific types of cancer cells, notably in NSCLC, osteosarcoma as well as in breast and prostate cancer [22–24,25**]. However, laboratory methodologies remain a limiting factor, with available reports using different techniques with very variable sensitivity, whereas immunohistochemistry remains to be standardized and further tested in the context of cancer where RANK protein expression might be low and staining difficult.

TARGETING RECEPTOR ACTIVATOR OF NUCLEAR FACTOR-KAPPA B PATHWAY IN BONE-METASTATIC CANCER

Targeting this pathway has recently been demonstrated to be an interesting strategy in patients suffering from virtually all bone-metastatic advanced solid tumors [11**,12**,13].

Denosumab is a fully human monoclonal IgG2 antibody binding with a high affinity to RANKL. It is specific and does not demonstrate significant binding to other members of the TNF ligand superfamily. As a result of its specific mechanism of action on the bone matrix, denosumab has become a new registered option in the treatment of osteoporosis [26].

Skeletal-related event as an endpoint

In 2046 breast cancer patients, denosumab – following a monthly 120 mg subcutaneous dose schedule – was demonstrated superior to zoledronic acid in delaying time to first on-study SRE [median not reached for denosumab vs. 26.4 months for zoledronic acid; hazard ratio 0.82; 95% confidence interval (CI) 0.71–0.95; P = 0.01 superiority], associated with a greater reduction in bone turnover markers. OS, disease progression and rates of adverse events were similar between groups [13]. All patients received supplementary vitamin D and calcium. There were no significant differences in the frequency of adverse events, including some cases of osteonecrosis of the jaw in both treatment arms – with denosumab not requiring any control or dose adaptation of renal function. Similar results reproducing superiority of denosumab in delaying SRE events as compared to zoledronic acid were reported in 1901 prostate cancer patients [median of 20.7 months vs. 17.1 months; hazard ratio 0.82 (0.71, 0.95); P = 0.008] [11**].

In a pivotal randomized double-blind phase 3 trial in 1776 patients with advanced solid cancer (other than breast or prostate) or multiple myeloma and no previous intravenous bisphosphonate therapy, denosumab was shown to be noninferior – with a trend toward superiority – to zoledronic acid in delaying time to first SRE (median of 20.6 months for denosumab vs. 16.3 months; hazard ratio 0.84; 95% CI 0.71–0.98; P = 0.0007) (Table 1).

Excluding multiple myeloma patients from analysis, denosumab became superior to zoledronic acid in 1677 patients evaluated (21.4 vs. 15.4 months; hazard ratio 0.81; 95% CI 0.68–0.96; P = 0.034, superiority). Specifically regarding 702 NSCLC patients included, the effect of denosumab on time to first on-study SRE relative to zoledronic acid resulted in a hazard ratio of 0.84 (95% CI 0.64–1.10; P = 0.20) [12**] (Table 1).

Denosumab is well tolerated. A clear picture comes from the analysis of its use in osteoporosis against placebo (at 60 mg every 6 months dose),
where arthralgia, back extremity and musculoskeletal pain, peripheral edemas, cough, dizziness or transient hypocalcemia were reported. In the bone metastasis trial, with higher dose intensity, incidence of osteonecrosis of the jaw was subject to a specific preplanned integrated analysis of the three trials comparing denosumab with zoledronic acid in bone metastases [27] revealing an equal risk (1.8% for denosumab vs. 1.3%; P = 0.13).

In the Henry trial [12**], patients in both treatment groups experienced similar rates of overall adverse events. Hypocalcemia of any grade occurred more frequently with denosumab (10.8% denosumab; 5.8% zoledronic acid). Acute-phase reactions (e.g. pyrexia, fatigue, arthralgia) within the first 3 days after infusion occurred in 14.5% of patients receiving zoledronic acid vs. 6.9% receiving denosumab. No patient developed neutralizing antibodies.

In all recent denosumab trials, effects on bone resorption were assessed as measured at least by changes in urinary and serum N-terminal telopeptide levels and bone-specific alkaline phosphatase. A rapid and strong decline in bone turnover markers was systematically reported under denosumab [28–31], with patients treated with denosumab experiencing a greater suppression of bone turnover markers than observed with zoledronic acid [11**,12**,13].

### Overall survival as an endpoint

OS in solid tumors (excluding myeloma) was similar between both treatment groups [hazard ratio 0.95; 95% CI 0.92 (0.81–1.05); P = 0.215].

Interestingly, an ad hoc analysis by tumor stratification factors through three reported distinct strata, demonstrated an OS hazard ratio of 2.26 for myeloma (95% CI 1.13–4.50), and 1.08 for other solid tumors (95% CI 0.90–1.30). In the 811 patients with lung cancer, including NSCLC and small-cell lung cancer (SCLC), denosumab treatment was associated with significantly improved OS vs. zoledronic acid [8.9 vs. 7.7 months; hazard ratio 0.80 (95% CI 0.67–0.95); P = 0.01]. Specifically, in NSCLC, a hazard ratio of 0.78 (9.5 vs. 8.0 months; 95% CI 0.65–0.94) was described (Fig. 1 and Table 1), whereas a less convincing signal in a statistically nonsignificant way was reported in SCLC (7.6 vs. 5.1 months; hazard ratio 0.81; 95% CI 0.52–1.26; P = 0.358). Further subgroup analysis could demonstrate this OS difference through distinct NSCLC histological subtypes, maybe to some higher extent in squamous histology (adenocarcinoma 9.6 vs. 8.2 months; hazard ratio 0.80; 9.5 vs. 8.0 months; 95% CI 0.65–0.94) was described (Fig. 1 and Table 1), whereas a less convincing signal in a statistically nonsignificant way was reported in SCLC (7.6 vs. 5.1 months; hazard ratio 0.81; 95% CI 0.52–1.26; P = 0.36). Further subgroup analysis could demonstrate this OS difference through distinct NSCLC histological subtypes, maybe to some higher extent in squamous histology (adenocarcinoma 9.6 vs. 8.2 months; hazard ratio 0.80; 95% CI 0.62–1.02; P = 0.0751) and squamous carcinoma (8.6 vs. 6.4 months; hazard ratio 0.68; 95% CI 0.47–0.97; P = 0.0350) [12**,25**].

### Table 1. Numerical conclusions of pivotal phase III trials in solid tumors (including myeloma and excluding breast and prostate cancers; adapted from [12**])

<table>
<thead>
<tr>
<th>Parameter analyzed</th>
<th>Median time to event (denosumab vs. zoledronate)</th>
<th>HR and (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to first SRE in solid tumors* (n = 1776)</td>
<td>NR</td>
<td>0.84 (0.71, 0.98)</td>
<td>0.06</td>
</tr>
<tr>
<td>Time to first SRE in solid tumors* excluding myeloma and NSCLC</td>
<td>NR</td>
<td>0.79 (0.62, 0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Time to first SRE in NSCLC</td>
<td>NR</td>
<td>0.84 (0.64, 1.1)</td>
<td>0.2</td>
</tr>
<tr>
<td>Overall survival (OS) in solid tumors*</td>
<td>NR</td>
<td>0.95 (0.83, 1.08)</td>
<td>0.43</td>
</tr>
<tr>
<td>OS in NSCLC (n = 702)</td>
<td>9.5 vs. 8.1</td>
<td>0.79 (0.65, 0.95)</td>
<td>0.0104</td>
</tr>
<tr>
<td>OS in adenocarcinoma (n = 400)</td>
<td>9.6 vs. 8.2</td>
<td>0.80 (0.62, 1.02)</td>
<td>0.0751</td>
</tr>
<tr>
<td>OS in squamous carcinoma (n = 163)</td>
<td>8.6 vs. 6.4</td>
<td>0.68 (0.47, 0.97)</td>
<td>0.035</td>
</tr>
<tr>
<td>OS in SCLC (n = 109)</td>
<td>7.6 vs. 5.1</td>
<td>0.81 (0.52, 1.25)</td>
<td>0.358</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio; NSCLC, non-small cell lung cancer; SRE, skeletal-related event.

*Excluding breast and prostate cancer.
Targeting receptor activator of nuclear factor-kappa B pathways as a direct antitumor strategy

A direct impact of RANK and RANKL on tumor cell proliferation has been hypothesized, with a postulated similar pro-survival and activating impact as observed in osteoclasts. Numerous cell types of the osteoblast lineage, but also activated T and narrow stromal cells produce OPG and/or RANKL in order to regulate bone synthesis. Expression of RANKL is controlled by cytokines and hormones, commonly known as regulators of calcium homeostasis, including parathyroid hormone, 1,25 dihydroxyvitamin D3, calcitonin, interleukin (IL)-1, 6, 4 and 18, prostaglandins, corticosteroids, interferon-γ and TGFβ [32]. On the contrary, the regulatory processes of RANKL expression during cancer progression remains unknown; its expression can be induced directly in cancer cells, and growing evidence suggests that normal mammary epithelium and tumor stromal cells – notably lymphocytes and mononuclear cells – can produce RANKL, allowing subsequent paracrine or autocrine activity [33,34]. As an example, both local and systemic levels of RANKL were increased in prostate cancer-bearing mice, generating significant changes in the expression of genes involved in osteolysis, migration and invasion [35]. Breast cancer can induce production of RANKL by stromal cells in bone marrow; in experimental models, breast cancer cells increase local stromal cell expression of RANKL [36–38].

The changes that occur in the breast mammary epithelium at early stages of tumorigenesis and the permissive contribution of progesterone to increased mammary cancer incidence were demonstrated to be dependent on RANK signaling. RANK activation was also shown to result in acceleration of tumorigenesis in mouse mammary tumor virus (MMTV)-RANK transgenic mice as well as in the MMTV-Neu transgenic mouse model. Reciprocally, selective pharmacological inhibition of RANK attenuated mammary tumor development not only in hormone and carcinogen-treated MMTV-RANK and wild-type mice, but also in the MMTV-neu transgenic spontaneous tumor model [39,40]. In animal models, RANKL was shown to increase invasiveness of mammary and prostate cancer as measured by the propensity of the tumors to generate metastatic spread, notably to the lung. Promotion of cell migration was also consistently demonstrated in xenograft models using breast, prostate and melanoma cancer cell lines [41*,42–45].

In lung cancer, RANKL increased intercellular adhesion molecule-1 (ICAM-1) expression and directed the migration of the human lung cancer cell line A549. RANKL stimulation increased MEK (MAP/ERK kinase)/ERK (extracellular signal-regulated kinase) phosphorylation, suggesting that migration of lung cancer cells could be modulated by the RANK-MAPK signal transduction cascade, converging to nuclear factor-kappaB (NF-κB) complex activation [46*].

**Biological Hypothesis of Receptor Activator of Nuclear Factor-Kappa B and Nuclear Factor-Kappa B Signaling in Lung Cancer Biology**

The NF-κB pathway is triggered upon stimulus-mediated activation of the IκB kinase (IKK) complex, which is composed of at least two kinases, IKKα and IKKβ, and an indispensable regulatory subunit, NF-κB essential modulator (NEMO; Fig. 2). The kinases, usually IKKβ, phosphorylate inhibitory molecules of the IκB family. IκBα is a ubiquitously expressed member of the IκB family; it is phosphorylated at two serine residues, an event that precedes its poly-ubiquitination and proteasome-mediated destruction. This enables NF-κB dimers, usually kept inactive through cytoplasmic retention mediated by IκBα, to translocate to the nucleus and activate the transcription of NF-κB target genes. NF-κB transcription factors are either homodimers or heterodimers composed of a combination of the subunits p65 (RelA), p50/p105, cRel, RelB or p52/p100. NF-κB signaling has been investigated in a variety of biological contexts that include inflammation, innate and adaptive immune responses, and cancer [47]. Of particular relevance to cancer were the findings that showed that oncogenic forms of Ras activate the NF-κB pathway [48–50]. In NSCLC, the importance of NF-κB signaling for tumor progression was recently demonstrated, using genetically engineered mouse models of the disease or screens to identify synthetic lethal partners of oncogenic K-ras [51–56,57*]. Additionally, NF-κB signaling was shown to be implicated in EGFR-mutant tumors, since genetic or pharmacologic NF-κB inhibition sensitized EGFR mutant lung tumor cells to targeted therapies [58*]. Recently, activation of NF-κB signaling was demonstrated to confer resistance to apoptosis in three-dimensionally cultured EGFR-mutant lung adenocarcinoma cell lines [59]. Interestingly, NF-κB in lung tumor cells induces the expression of tissue inhibitor of metalloproteinase 1 (TIMP-1), an important regulator of ERK activity and cell proliferation [56]. In K-ras<sub>Lox-STOP-Lox</sub>G12D/WT; p53Flox/Flox mice infected with lentiviruses delivering Cre into the lungs to initiate tumors, we recently used a nonphosphorylatable, dominant negative mutant form of IκBα, which we induced specifically in the lung tumor epithelial cells to inhibit NF-κB activation.
signaling. With this approach, we could demonstrate that NF-κB inhibition substantially decreases the progression of established tumors, highlighting the potential benefit of NF-κB inhibitors as targeted therapies, for example in patients with molecularly defined lung tumors harboring mutant K-ras and p53 [53]. In agreement with this, K-ras\textsuperscript{Lox-STOP-Lox}\textsuperscript{G12D/WT}; p53\textsuperscript{Flox/Flox} lung tumor-bearing mice treated with each one of two selective NF-κB small molecule inhibitory compounds showed, in each case, tumor shrinkage after single-dose treatment, and an increased survival when treated at multiple times [57]. Mechanistically, it is still not completely understood how NF-κB becomes activated in lung tumors. In this respect, p62 (also called Sequestosome-1; gene name Sqstm1) was reported to link ras to NF-κB activation, and to be required for oncogenic K-ras-induced lung tumor development [51]. p62 is a multifunctional protein implicated in NF-κB activation, cell growth and autophagy [60]. In NF-κB signaling, p62 is notably required to transmit responses upon activation of RANK by RANKL during osteoclastogenesis. RANK-mediated NF-κB activation depends on a complex formed between p62 and TRAF6 (Fig. 2). The importance of these two proteins was underscored notably using animal models; mice deficient for Traf6 or Sqstm1 have impaired responses to RANKL and, in the case of TRAF6 deficiency, develop osteopetrosis [61,62]. Additionally, point mutations in SQSTM1 occur in about 10% of patients with Paget’s disease of bone, and a mouse model harboring one of these point mutations, knocked into the endogenous allele of Sqstm1, developed histopathological features reminiscent of the disease, demonstrating the functional implication of mutant p62 [63,64]. In addition to RANK signaling during osteoclastogenesis, TRAF6 and p62 may function together to promote proliferation of lung tumor epithelial cells. Indeed, p62, when activated by oncogenic ras expression, leads to TRAF6 polyubiquitination, which is necessary for NF-κB activation [51]. In lung tumors, TRAF6 levels can become elevated by several mechanisms: the GATA2 transcription factor, which is essential for oncogenic K-ras-dependent lung tumor development, binds to the TRAF6 promoter and enhances its expression [52], and genomic amplifications at the TRAF6 locus have been reported, too [65]. Hence, it is likely that TRAF6 and p62 regulate together NF-κB activity, in different physiological and pathological situations. Whether RANK signaling is directly implicated in lung tumor cells to promote TRAF6 and p62-mediated NF-κB activation is a possibility that...
warrants future investigations. Additionally, it will be important to understand better how NF-κB signaling is orchestrated in lung tumor cells, in order to uncover new ways to inhibit the pathway in NSCLC.

CONCLUSION
Bone-protective therapy should be considered at the time of bone metastases detection before debilitating complications — including devastating pain — develop and SREs are experienced. The impressive prevalence of bone metastasis and SRE incidence in advanced NSCLC raise the question of the rational for a general screening of bone metastasis. This uncertainty translates into somewhat discrepant international guidelines and recommendations [66,67,68*], where relevance of a general bone metastasis screening procedure or an early upfront administration of skeletal protective drug in all advanced NSCLCs are being discussed, in the perspective to ensure an early exposure to the efficient drugs available. Further clinical studies will be needed to predict which patients might benefit most from early or prophylactic treatment, as well as to specify the utility of markers of bone resorption and tumor biomarkers in choosing treatment strategy.

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 tumor growth in bone by mechanically facilitating cancer cell establishment. In addition, RANK expression per se has been observed in some tumor types, whereas RANK was shown to be expressed at least in some cancer cell types. In addition, there is an increased expression of the RANK/RANKL proteins and abnormal OPG/RANKL ratio in patients having cancer with bone metastases. The retrospective, unplanned nature of lung cancer survival data implies bias risks and imposes some caution in their interpretation. However, based on previous data involving the RANK pathway in tumor biology, it is obvious that this warrants further preclinical and clinical investigation.

Undoubtedly, the potential for RANK pathway inhibitors to interfere with bone metastasis appearance and/or progression by affecting the bone microenvironment but also potentially reducing tumor aggressiveness and metastatic capabilities via distinct mechanisms should constitute a research priority. The European thoracic platform (ETOP) is planning a phase III prospective trial evaluating the potential of denosumab as an antitumor agent to increase survival of patients with advanced NSCLC with or without bone metastasis, in the context of a strong and unique European collaboration with EORTC.

Acknowledgements
None.

Conflicts of interest
The authors disclose no conflict of interest.

REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as:
* of special interest
** of outstanding interest
Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

13. Phase II trial showing superiority of denosumab as compared to zoledronic acid in delaying SREs in prostate bone-metastatic cancer.
15. Phase II trial showing superiority of denosumab as compared to zoledronic acid in delaying SREs in solid bone metastatic cancer (excluding breast and prostate cancers and including myeloma), showing a noninferiority of denosumab (superiority if myeloma excluded). From this trial are extracted the subgroup restrospective survival data in lung cancer.
Lung and mediatinum


40. Unplanned subgroup analysis of SRE PHASE III preventive trial looking at survival in both arms in lung cancer patient group.


46. Unplanned subgroup analysis of SRE PHASE III preventive trial looking at survival in both arms in lung cancer patient group.


53. Unplanned subgroup analysis of SRE PHASE III preventive trial looking at survival in both arms in lung cancer patient group.


59. Unplanned subgroup analysis of SRE PHASE III preventive trial looking at survival in both arms in lung cancer patient group.


