



# Evolving Management with Molecular-Targeted and Bone-Targeted Medicine in Patients with Advanced Non – Small Cell Lung Cancer

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## Introduction

### Molecular targeted medicine

In the field of advanced non-small cell lung cancer (NSCLC), the driver mutations such as epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) fusion gene have been discovered in recent years. Of the mutated genes in cancer, driver gene with oncogene addiction is strongly involved in the development and progression of cancer and dependent on tumor survival. Crizotinib which is ALK tyrosine kinase inhibitors (TKI) is recommended for the patients with previously treated advanced NSCLC with ALK-rearrangement [1] and erlotinib is recommended for the patients with EGFR mutated advanced NSCLC [2,3] in National Comprehensive Cancer Network (NCCN) guidelines 2013. Gefitinib is also used for the patients with EGFR mutated NSCLC in Japan and several countries on the basis of large scale phase III trials [4-6]. Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), has been shown to benefit patients with untreated NSCLC in addition to carboplatin and paclitaxel [7]. More recently, new driver genes such as RET fusion [8], ROS1 rearrangement [9], BRAF mutations, HER2 insertions, PIK3CA mutations, FGFR1 amplifications, and DDR2 mutations were also identified and these driver mutations are expected as a target for new therapeutic medicines. Novel molecular targeted medicines such as afatinib, an irreversible inhibitor of the ErbB family of tyrosine kinases [10], and CH5424802, selective ALK inhibitor [11], are studied in clinical trials. “Next Generation DNA Sequencer” has been developed and analyzing nucleotide sequence of the gene is faster than before and rapid identification of key driver mutations in advanced NSCLC is becoming more and more important.

The personalized medicine based on genetically identified oncogenes in advanced NSCLC is going to be standard in daily clinical practice. Elucidation of these oncogenic drivers and development of molecular-targeted agents will cause the expansion of knowledge about molecular pathways including genesis of the lung cancer and result in a radical change of treatment strategies leading to improved overall survival and quality of life in the future.

### Bone-targeted medicine

It has been reported that the incidence of bone metastases in lung cancer patients is approximately 30-40% [12]. Bone metastasis causes skeletal-related events (SREs) such as fracture, need for radiation, and surgery to bone, spinal cord compression, and hypercalcemia. These complications lead to decreased performance status (PS), quality of life (QOL), and shortening of overall survival (OS). It is very important to delay and prevent SREs in clinical practice with bone-modifying agents (BMA) such as zoledronic acid and denosumab.

Denosumab is a kind of molecular targeted medicines and a fully human monoclonal anti-receptor activator of nuclear factor kappa-B ligand (RANKL) antibody. Stimulation of osteoblasts by tumor increases the expression of RANKL in bone metastasis and leads to increased

bone resorption. Denosumab interrupts this vicious cycle by binding to RANKL and preventing the formation and function of osteoclasts [13]. In a phase III trial, denosumab was non-inferior to zoledronic acid in delaying time to first on-study SRE in patients with advanced cancer metastatic to bone (excluding breast and prostate) or myeloma [14]. Overall survival and disease progression were similar between groups. By the two randomized trial, Denosumab was superior to zoledronic acid in delaying time to first on-study SRE in patient with advanced breast cancer and prostate cancer [15,16]. A combined analysis of 3 pivotal, randomised, phase 3 trials showed denosumab's superiority to zoledronic acid in preventing SREs [17]. Even if there is a subgroup analysis, Scagliotti et al. showed denosumab was associated with improved overall survival compared with zoledronic acid in patients with metastatic lung cancer [18]. Denosumab has the merits that there is no need to adjust the dose according to renal function and we can give by subcutaneous injection. But, the death due to hypocalcemia was reported and monitoring of serum calcium is necessary.

Although Strontium-89 and samarium-153 are beta-emitting radioisotope radiopharmaceuticals approved already for palliation of bone metastases [19], the results of ALSYMPCA study has been published recently [20]. In this phase III study, radium-223 chloride which is a kind of alpha-emitting radioisotope delayed SREs and significantly improved OS as compared with placebo in patients with castration-resistant prostate cancer and bone metastases. In NSCLC, future trials with radium-223 may reveal its decrease of SREs and survival effectiveness.

The purpose of the treatment with bone-targeted agents is decrease of SREs in patients with bone metastases now. We must start treatment early when bone metastasis became clear and also continue bone-targeted agents as long as possible to draw a maximum effect.

## Communication

Even if molecular targeted treatment causes good response against advanced NSCLC, radical cure is not obtained in the current medical standard. It goes without saying that the development of the further medicine is necessary, but communication with patients is very important in the choice of treatment. For example, to think either cytotoxic chemotherapy or EGFR-TKI therapy in patients with EGFR mutated advanced NSCLC as first line treatment is very important

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for the patient and needs good communication between health care workers and the patient. In this case, It is also necessary that the choice of treatment should be determined by the patient's wish, patient's status, social background such as family, job, and life style, and medical condition, because QOL and daily life is significantly changed by the treatment. Communication is not only between health care workers and patients but also between health care workers and team medicine is very important, of course.

The genuine personalized medicine is to manage patients' symptom, to adjust family's support, and to control complications considering PS, age, histological type, clinical stage, genetic mutation, and metastasis (brain, adrenal, pleural, and bone). Appropriate communication between not only health care workers as team medicine but also medical staff and patients is more and more important in order to perform a patient-centered medicine.

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