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International Scientific Meeting

## EVOLVING TREATMENT LANDSCAPES IN NON-SMALL-CELL LUNG CANCER

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## Preface

### Dear Colleagues

Twenty-one experts from seven European countries participated in the International Scientific Meeting that took place on 21 March, 2017, at the Boehringer Ingelheim Oncology Research Facilities in Vienna. The meeting focused on the relative importance of various treatment options in non-small-cell lung cancer (NSCLC) against the background of the recent scientific developments. Experts gave talks on state-of-the-art approaches in EGFR-

mutated as well as non-selected NSCLC patients, and a range of subjects was discussed by the faculty in break-out sessions. This publication summarises the lectures and outcomes of the break-out discussions as presented by the group leaders. We hope to provide informative reading on the topic of modern management approaches in a cancer entity the picture of which has undergone dramatic changes over the last few years.



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## EGFR-mutation-positive NSCLC patients

### Long-term response to afatinib

Clinical trials conducted with the EGFR tyrosine kinase inhibitor (TKI) afatinib tend to contain substantial proportions of patients who can be classified as long-term responders (LTRs). According to a combined analysis of the LUX-Lung 3, 6 and 7 trials, 10 % to 12 % of patients have received afatinib for at least 3 years in these studies [1]. “Up to 28 % were treated for at least 2 years, and up to 16 % for 2.5 years or more,” reported Angela Märten, MD, Global Senior Medical Advisor, Boehringer Ingelheim (Figure 1). “Long-term treatment with afatinib had no detrimental impact on subsequent treatment,” Dr. Märten observed.

With respect to the obvious question of whether LTRs share any distinct features, only clinical baseline characteristics are available to date [2-7]. The comparison shows that LTRs tended to be women and to have deletion 19 EGFR mutations more often. “Surprisingly, the group of LTRs included patients with brain metastases,” Dr. Märten noted. Just as unexpected was the finding that significant tumour reduction is not necessarily a prerequisite for long-term response. “Fourteen percent of LTRs experienced only stable disease.” Moreover, LTRs also included patients with uncommon mutations. Importantly, tolerability-guided dose adjustments did not affect long-term response in the LL3 and LL6 trials, where afatinib doses ranged from 20 mg to 50 mg daily.

### Afatinib in the elderly patient

Other analyses from the LUX-Lung studies demonstrate that the clinical benefits conferred by afatinib are independent of age. In the LUX-Lung 3 and 6 trials, progression-free survival (PFS) and overall survival (OS) were significantly in favour of afatinib versus chemotherapy above the pre-specified age cut-off of 65 years [8]. “There was no difference compared to the intent-to-treat population,” Dr. Märten pointed out. According to an exploratory subgroup analysis of

patients aged  $\geq 75$  and  $< 75$  years in the LUX-Lung 7 study, advanced age did not adversely affect the PFS advantage and tolerability of afatinib [6]. For OS, a further post-hoc analysis demonstrated a consistent trend for OS benefit with afatinib, independent of age subgroups. The safety profile of afatinib was generally consistent irrespective of age in the LUX-Lung 3, 6 and 7 trials. Grade-3/4 treatment-related adverse events generally occurred more often in the elderly population, necessitating dose reductions and treatment discontinuations in higher percentages of patients than in the younger age groups. “However, this applied to all of the treatments including chemotherapy and gefitinib,” Dr. Märten said.

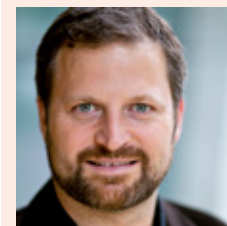
### Brain metastases and leptomeningeal disease

The only available prospective first-line data on patients with EGFR<sup>+</sup> brain metastases are those from a combined analysis of the LUX-Lung 3 and 6 trials [7]. According to the data from 81 patients with stable brain metastases and common mutations, afatinib conferred a significant PFS benefit in this group (PFS, 8.2 vs. 5.4 months with afatinib vs. chemotherapy; HR, 0.50;  $p = 0.03$ ). “The magnitude of this effect resembled the benefit observed in patients without brain metastases,” Dr. Märten stated. Likewise, afatinib treatment was significantly superior to chemotherapy with regard to objective response rates in patients with and without brain metastases, and time to CNS progression was longer. In the majority of patients with brain metastases who experienced disease progression on afatinib, the brain was not the site of first progression. “These data indicate that afatinib controls brain lesions and delays their onset in patients without baseline metastases,” Dr. Märten summarised.

A case series of five patients with multiple symptomatic cerebral lesions who declined whole-brain radiotherapy illustrates the activity of afatinib in this setting [9]. In all of these patients,

afatinib monotherapy induced complete remissions that lasted at least 6 months according to MRI and were accompanied by distinct clinical benefits. For leptomeningeal disease, data are scarce. A study, a case series and reports including a total of 21 afatinib-treated patients demonstrated regression of neurological symptoms and often dramatic improvements in performance status [10, 11]. Cerebral remissions occurred that were long lasting in some cases. This can be explained by the observation that afatinib treatment leads

### Brain metastases



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**Maximilian Hochmair, MD, Otto Wagner Spital, Vienna, Austria**

With regard to brain metastasis, symptomatic patients need to be distinguished from asymptomatic ones. At centres where EGFR-mutation-testing takes weeks, radiotherapy is started first, while at centres that receive test results early, afatinib is the preferred front-line strategy. Afatinib treatment can be followed by radiotherapy as a consolidation measure. Brain irritation should be entirely avoided in these patients, and stereotactic treatment should be performed. In asymptomatic patients, afatinib constitutes a very good option, as other TKIs such as gefitinib and erlotinib do not have similar data in the setting of brain disease.

Monitoring of patients with liquid biopsy is definitely possible. A case series of 100 patients treated at Dr. Hochmair's clinic showed rapid decreases in circulating DNA after 6 weeks in almost all of the patients, including those with brain metastases.

to substantial drug concentrations in the cerebrospinal fluid. “The afatinib penetration through the blood-brain

barrier is sufficient to induce clinical responses,” Dr. Märten concluded.

**Elderly patients and comorbidity**



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Appropriate age thresholds for the so-called elderly patients might be 70 or 75 years. Generally, age itself is not the determining factor when choosing a drug and adjusting the dose, as comorbidities need to be taken into account. If the patient is fit and has no diseases apart from lung cancer, the initial afatinib dose can be 40mg, even in the elderly. Based on the existing data, survival may not be a matter of dose. All patients should be treated individually according to their particular needs. Tolerability-guided dose modification of afatinib is possible without compromising efficacy [12-14]. Physicians should focus on the major group of patients that benefit from the drug for 1 to 2 years. Dosing and tolerability should be adjusted to provide the patient with the best possible quality of life.

**Third-generation EGFR TKI therapy**

The clonal evolution of lung cancer during treatment evokes secondary resistance, and other options are called for. “It is important not to think about the best treatment, but to think about the best treatment strategy,” stressed Egbert Smit, MD, PhD, Netherlands Cancer Institute, Amsterdam, Netherlands.

The T790M mutation is by far the most common acquired alteration after first-generation and second-generation EGFR TKI treatment. Other aberrations, such as MET or HER2 amplifications, occur less frequently (Figure 2) [15]. “The third-generation EGFR TKI osimertinib is effective in tumours with the T790M gatekeeper mutation,” explained Dr. Smit [16]. Acquired resistance following third-generation TKI treatment is highly complex and can be due to secondary gatekeeper mutations or other mechanisms that have not been well characterised yet [17]. The C797S mutation is a major mechanism of acquired resistance to T790M-targeting EGFR inhibitors [17]. This mutation can be diagnosed using next-generation sequencing (NGS) and will also show in liquid biopsy. Several drugs are under development in this area, although they will presumably not become generally available for several years.

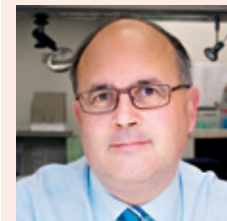
Niederst et al. showed that the allelic context in which C797S was acquired

might predict responsiveness to alternative treatments [18]. Cells will be sensitive to a combination of first and third generation EGFR TKIs if the C797S and T790M mutations are in trans. However, in clinical practice, nearly all cases of acquired C797S are found in cis, which limits the treatment options after third-generation TKI therapy.

**Sequencing of treatment**

Optimal sequences of EGFR TKIs and potential combinations have not been defined yet. Treatment options will diminish if resistance develops after starting third-generation EGFR TKI therapy early on. “The role of cytotoxic chemotherapy and immunotherapy has been

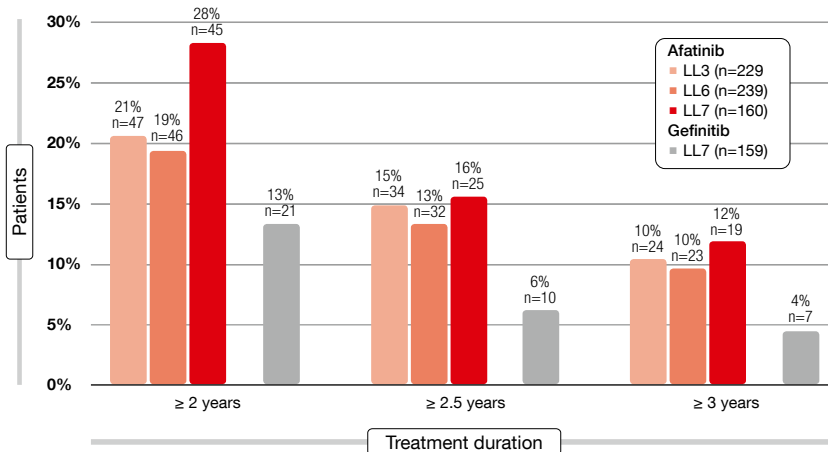
**EGFR testing**



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So-called rare mutations have lost their designation as ‘rare’, because data on them are accumulating, with established clinical consequences. TKI therapy can be used in the setting of combined mutations, but some physicians are inclined to prescribe chemotherapy. T790M mutation occurs only infrequently before the start of EGFR TKI therapy, raising the question of whether these tumours have the same biology as those carrying secondary T790M mutation. Deep sequencing is increasingly being used, which means that T790M frequency will rise. Therefore, physicians need to be aware of the sensitivity of the method employed. From a clinical point of view, treatment is necessary if liquid biopsy reveals T790M mutation in the presence of clinical progression. NGS on liquid biopsy is work in progress; in a small trial conducted in Belgium, NGS showed low sensitivity with regard to this type of mutation.



**Figure 1:** Proportions of afatinib-treated long-term responders in the overall LUX-Lung 3, 6 and 7 populations.

poorly worked out to date,” Dr. Smit noted. Repeated biopsies are an issue in the context of optimisation of treatment strategies based upon biology. Intercalated treatment, i.e., switches from TKIs to cytostatic treatment for 2 or 3 weeks with the objective of obtaining the positive effects of both approaches, was discussed some years ago, but meanwhile it has been dismissed. The IMPRESS study suggested that at least in the resistant setting, the intercalated strategy does not offer more benefits than chemotherapy alone [19]. Cytotoxic chemotherapy is effective in T790M-negative patients experiencing progression, although no prospective trials are available here. Other possible strategies at the time of progression relate to the combination of chemotherapy with EGFR TKIs and the dual TKI blockade. “Afatinib plus cetuximab was quite active in a number of patients,” Dr. Smit reported [20]. Even though the combination was initially designed to target T790M-positive tumours, it also gave rise to durable responses in the T790M-negative population. Side road resistance (e.g., MET, HER2) might call for different targeted agents, such as trastuzumab. After *EGFR* signaling has been exhausted, untargeted drugs will be required in the face of progression.

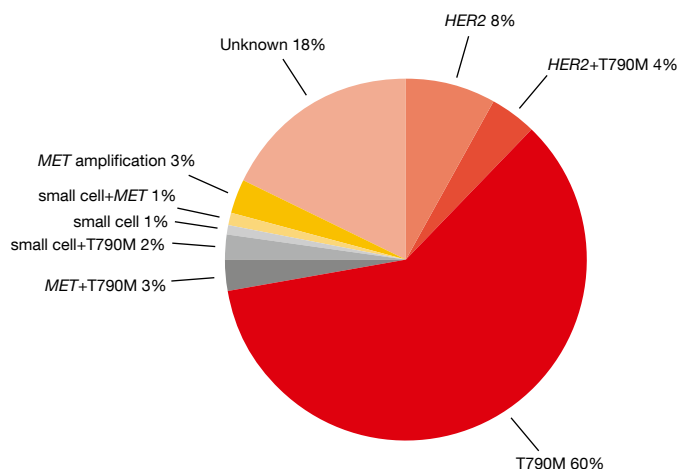
### Sequencing of EGFR TKIs



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From the patients' point of view, it is of course important to have long chemotherapy-free periods, but for reasons of response, *EGFR*-mutant patients should receive chemotherapy at some point in the course of their disease. Further investigation is needed to explore the combination of plasma T790M positivity and lack of progression according to imaging. A trial is going to address this.



**Figure 2:** Distribution of genetic aberrations in tumours with acquired resistance to EGFR TKIs.

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## Non-selected NSCLC patients

### How to proceed in second line?

After failure of first-line treatment, docetaxel used to be the primary second-line option and constituted the comparator in many of the trials investigating new approaches. For patients without driver mutations, current options include immune checkpoint inhibitors (CPIs; i.e., nivolumab, pembrolizumab, atezolizumab), pemetrexed, docetaxel, docetaxel plus nintedanib or ramucirumab, and gemcitabine [1]. Treatment choices depend on PD-L1 expression, age, comorbidity, performance status, patient preference, smoking history, and tumour phenotype (e.g., speed of progression, pattern of metastasis). "Performance status is stronger than age and comorbidity," emphasized Anders Møllema, MD, PhD, Herlev Hospital, Copenhagen, Denmark. Another factor of growing significance is financial considerations, as authorities might increasingly use subgroup analyses to identify patients in whom immunotherapy could be cost-effective.

Short progression-free intervals after first-line therapy indicate decreased efficacy of CPI treatment, as exemplified by data from the CheckMate 057 trial [2]. "On the contrary, LUME-Lung 1 showed that patients whose progression-free intervals are short are doing better with nintedanib plus docetaxel than with docetaxel monotherapy," Dr. Møllema noted [3]. The expert suggested an algorithm according to which the relevance of CPI therapy increases in parallel to the extent of PD-L1 expression and duration of progression-free intervals (Table). In cases with rapid progression and low PD-L1 expression, on the other hand, docetaxel alone or combined with nintedanib appears to be the treatment of choice. "There are no uniform cut-offs," Dr. Møllema pointed out.

Also, older patients tend to benefit less from immunotherapy. This means that CPIs might be preferable in younger patients and in those with good performance status, whereas older patients and those

### PD-L1 testing



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It appears that the majority of physicians wish PD-L1 testing to be conducted as part of the reflex testing after diagnosis of lung cancer, with the purpose of establishing the indication for immunotherapy. Unequivocally negative PD-L1 expression (expression levels of 0) suggest that immunotherapy might not be the best choice in a given patient.

To date, literature indicates that material obtained both from the primary site and metastatic lesions can be classified as reliable. Archival material might be problematic from a biological point of view, but results obtained with pembrolizumab were similar in the KEYNOTE-012 trial irrespective of whether archival or rebiptic material was used. Generally, the probability of therapeutic success rises as PD-L1 expression increases. Proper training is mandatory for the assessment of PD-L1 expression. One particular issue in this context relates to the danger of confusion of tumour cells with macrophages, which are highly PD-L1-positive.

with poor performance status would probably fare better with docetaxel.

### The role of nintedanib

The approval of nintedanib plus docetaxel is based on the LUME-Lung 1 trial that revealed a significant PFS benefit for this combination over docetaxel plus placebo (HR, 0.79;  $p = 0.0019$ ) [3]. Likewise, OS significantly favoured the ninte-

danib-treated arm, but as this was restricted to patients with adenocarcinoma (HR, 0.83;  $p = 0.0359$ ), nintedanib was registered for the treatment of tumours with adenocarcinoma histology only. "The other anti-angiogenic compound that received EMA approval was the anti-VEGFR-2 antibody ramucirumab," reported Johan Vansteenkiste, MD, PhD, UZ Leuven, Leuven, Belgium.

Regarding the selection of optimal candidates for immunotherapy, Dr. Van-

### Patients not eligible for immunotherapy



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Absolute contraindications against immunotherapy comprise chronic infections, such as hepatitis C, HIV, and tuberculosis, and autoimmune diseases, such as colitis or pneumonitis. Relative contraindications include an impaired performance status (i.e., ECOG PS >1), fast disease progression, certain histological findings (e.g. PD-L1-negative tumours), and asymptomatic brain metastases. For the latter, radiotherapy should be used. Stereotactic radiotherapy is preferable here, while whole-brain radiation should be avoided as much as possible. It is commendable to assess patients with an increased likelihood of fast progression already 6 weeks after the start of immunotherapy. The timeline of 3 months could be too late in some cases in whom administration of chemotherapy is not possible any more. If the patient does not show any improvement after 6 weeks, treatment should be discontinued.

TABLE

**Proposal for second-line treatment choices between docetaxel and immune checkpoint inhibitor therapy**

Progression-free interval after first line	PD-L1 negativity	Low PD-L1 expression	High PD-L1 expression
PD on doublet chemotherapy	Docetaxel (plus nintedanib)	Docetaxel (plus nintedanib)	Docetaxel (plus nintedanib)/ CPI
PD < 9 months	Docetaxel (plus nintedanib)	CPI	CPI
PD > 9 months	Docetaxel/CPI	CPI	CPI

steenkiste noted that physicians are inclined to prescribe CPIs in patients with squamous-cell carcinoma. "Here, the only alternative is docetaxel." In the setting of non-squamous histology, the presence of PD-L1 expression suggests the use of CPIs, if contraindications are absent. Treatment decisions for patients with PD-L1-negative tumours depend on the speed of tumour progression, as described above.

Dr. Vansteenkiste endorsed PD-L1 staining, because it can be assumed that CPI therapy works more efficiently in patients whose tumours show high PD-L1 expression than in those with low expression. "Thanks to the impressive first-line results obtained with the anti-PD-1 antibody pembrolizumab in the KEYNOTE-024 trial, the discussion on the value of PD-L1 testing has ended", Dr. Vansteenkiste said. Pembrolizumab

was used in tumours expressing PD-L1 levels of at least 50 % [4]. "PD-L1 will remain on our radar as long as no better large-scale applicable predictive biomarkers for immunotherapy are introduced, which will probably be for several years."

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**Evolving treatment algorithms – longer term**

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Immunotherapy notwithstanding, future developments in the targeted area are projected, as NSCLC is a druggable disease. More work will be required on predictors, biomarkers, and patient selection. Combinations will be important, even though it is unknown yet if immunotherapeutic agents should be combined with each other, antiangiogenic drugs or radiotherapy. Cure might be achievable in the future, depending on its definition. Converting lung cancer into a chronic disease can be a valid goal as well.

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