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2013 EMCTO Conference in Thoracic Oncology

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SUMMARY

The European Multidisciplinary Conference in Thoracic Oncology (EMCTO) 2013 Conference integrated the different disciplines and demonstrated how the multidisciplinary team can combine knowledge for personalised treatment of the whole range of thoracic oncology tumours. It was organised in partnership between the European Society for Medical Oncology (ESMO), the European Society for Radiotherapy and Oncology (ESTRO), the European Society of Thoracic Surgeons (ESTS), the European Respiratory Society (ERS), and the European Thoracic Oncology Platform (ETOP). The five partners have created a programme that integrated perspectives from the different disciplines in personalised treatment approach. The scope of this report is to present the scientific highlights from the Conference.

INTRODUCTION

The Conference objectives were to provide interdisciplinary discussions on current standards of care and strengthen knowledge on important milestones in thoracic oncology; to discuss the role of multimodality therapy in thoracic oncology; to translate substantial developments in the management of thoracic tumours into clinical practice tools; to understand the biology and pathohistology of thoracic cancer entities and novel therapies.

There were in total 623 attendees including 522 delegates representing all specialties dealing with lung cancer and other thoracic malignancies: medical oncologists, radiotherapists, pulmonologists, thoracic surgeons, radio diagnosticians, pathologists, basic scientists and epidemiologists. Most of the attendees were European professionals, althoughthere were participants from all continents - Asia and North America were well represented.

From 140 submitted abstracts, the Scientific Committee selected 16 for oral presentation, and 15 for poster discussion. The Scientific Committee saw a significant increase in the number of abstracts in the field of tumour biology. In total 16 travel grants were awarded to enhance participation of young professionals and those practicing in emerging countries. This report summarises the most important scientific findings presented during the conference.

This year one of the main topics of the meeting was combining knowledge towards personalised treatment by a multidisciplinary team. Prof. Rolf Stahel of the University Hospital in Zurich, Switzerland presented key challenges and opportunities for clinical research and practice. Personalised medicine in lung cancer takes into account molecular characteristics thus permitting a departure from empiricism and serendipity towards biology-based therapy; matching the right drug with the right cancer type, and defining biomarkers of response to targeted agents in each individual patient. A broader concept of personalised medicine in lung cancer applies to choosing and combining the right treatment modalities according to patient characteristics and/or tumour characteristics.

According to Prof. Stahel, multidisciplinarity today includes the presence of a pathologist at the multidisciplinary tumour board and in the future, in centres providing whole exon or genome sequencing, the team will include a specialist in bioinformatics. Despite a long history of tumour boards and their relation to patient care, there are still many outcomes not associated with the presence of the tumour board.

The subjects covered in Prof. Stahel's keynote lecture were molecular pathology, fragmentation of the disease, targeted therapies in the curable setting, and combining targeted therapy with chemotherapy, radiotherapy and immunotherapy. He concluded that

- multiplex testing should be used in the context of clinical practice, and whole genome sequencing in the context of research
- new approaches are needed to demonstrate the benefit and survival impact of targeted therapy
- personalised treatment in the curative segment remains investigational
- combination of targeted therapies and local therapies hold promise in patients with oncogenic drivers mutations

Another lecture of great interest was presented by Dr Martin Reck of the Department of Thoracic Oncology, Lung Clinic in Grosshansdorf, Germany, who spoke about targets in squamous cell carcinoma of the lung. In general this tumour subtype is associated more with older patients, smokers, those with more comorbidities, no EGFR mutation, no efficacy of pemetrexed, and poor prognosis. In this lecture Dr Reck focused on targets from the perspective of antiangiogenic treatment, targeted therapies, and immunotherapies (antigen dependent and antigen independent). In

terms of antiangiogenic treatment he highlighted a phase III study which showed higher incidence of pulmonary bleeding and that VEGF tyrosine kinase inhibitors have,in general,a higher rate of toxicities in squamous cell carcinoma.He further focused his talk on novel antiangiogenic strategies. In terms of targeted therapies he covered a role of EGFR-antibodies and growing knowledge about presence of other targets. Dr Reckc oncluded that

- platinum-based doublet therapy is standard of care in this subset of patients;
- new antiangiogenic approaches in clinical investigation are on horizon;
- there is a growing number of molecular targets;
- there are promising early results for immunotherapy.

LUNG CANCER SCREENING

Evaluation of performance of lung cancer screening strategy in the first three rounds of the NELSON trial

The Dutch-Belgian Randomized Lung Cancer Screening Trial (Dutch acronym: NELSON study) was designed to investigate whether screening for lung cancer by low-dose multi-detector computed tomography (CT) in high-risk subjects will lead to a decrease in 10-year lung cancer mortality of at least 25% compared with a control group without screening. The study started in 2003 and Dr Nanda Horeweg of the Department of Public Health and Pulmonology at Erasmus Medical Centre in Rotterdam, Netherlands reported findings from the evaluation of performance of the screening strategy in the first three rounds of the study and risk calculations made for a follow-up period of 5.5 years.

Lung cancer is most often detected in patients who present with already advanced disease, resulting in a poor chance for successful treatment. Therefore, it is necessary to explain the risk of developing lung cancer to smokers, those family members who have been regularly exposed to second hand smoke and other high risk populations Counselling on the potential harms and benefits of the screening procedure and how it could affect lung cancer detection at earlier stage should be provided. Low-dose CT scanning has been proposed as one sensitive screening modality; proponents estimate that it could detect approximately three times as many small lung nodules as chest X-ray. The NELSON screening strategy considers lung nodules with a volume >500mm^3 or a volume-doubling time <400days as positive; volumes 50-500mm^3 or volume-doubling times 400-600 days as indeterminate; and all other nodules as negative.

Dr Horeweg reported that one or more positive screen results were seen in 6% of the subjects and 200 participants were subsequently diagnosed with lung cancer, yielding a positive predictive value of 40.6% for the scans. False positive results were seen in just 1.2% of all scans. Over the 5.5 year

evaluation it was found that the risk of lung cancer detected by screening was influenced by the results of the first scan; the risk was 1.0% after a negative primary scan at baseline, 5.7% after an indeterminate baseline androse to 48.3% in participants with a positive baseline scan.

The authors concluded that the positive predictive value and low false positive rate arising from these results of an analysis of 5.5 years of the program support the use of low-dose CT for lung cancer screening and provide an additional tool for counselling potential candidates for screening.

Is low-dose CT lung cancer screening ready for large-scale population-based implementation?

The 2010 guideline of the European Society for Medical Oncology (ESMO) for diagnosis, treatment and follow-up of early-stage and locally-advanced (non-metastatic) non-small cell lung cancer does not recommend it for screening, but the guideline text summarises the evidence available up to 2010. The ESMO Guidelines Working Group is currently evaluating newer data for an update. However, it seems that in 2013 low-dose CT screening is not ready yet for large-scale population-based implementation, because of remaining questions on definition of the at-risk population, timing, interval and method of CT (especially 2D versus 3D nodule interpretation), how to handle false positive findings, and especially cost-effectiveness in relation to other prevention strategies, mainly smoking cessation. Further analyses of several ongoing European trials are eagerly awaited. Other potential methods of screening, such as sputum, exhaled breath or blood biomarkers lack validation and are not recommended in clinical practice.

The study discussant, Dr Giulia Veronesi said that diagnostic algorithms aim to strike a balance between a too invasive work-up that exposes screened persons to useless invasive procedures and overtreatment, and insufficient surveillance that increases the risks of delayed diagnosis and false negatives. Many screening programmes have adopted 5 mm as the cut-off between positive and negative nodules on CT. The Fleischner guidelines suggested 4 mm as the threshold below which no follow-up was needed. This cut-off was used by the NLST trial and resulted in a very high rate of baseline positivity. Other investigators consider nodule volumes instead of nodule diameter to obtain more reliable assessments of nodule growth.

Dr Veronesi noted that NELSON is the largest randomised controlled trial with LDCT screening in Europe and the first study to incorporate software calculated volume doubling time of nodules into a management algorithm to distinguish between positive and negative. According to Dr Veronesi, remaining questions for the authors to address are the recall rates after baseline and after consecutive screening rounds. When we compare the NELSON recall rate with that of NLST study, the NELSON one is lower even when considering positive and indeterminate nodules together. Dr Veronesi speculated on whether the higher rate of recalls in the NLST was due only to the lower size cut off (4 mm instead of 50 mm3 equal to 5 mm) or whether there may be other causes. Her feeling is

that when the multidisciplinary teamis involved in the decision of how to consider nodules, the rate of recalls is reduced.

In the Cosmos 1 study a total of 16 cases were missed at one CT scan and picked up a year later. Most of these were central lesions for which the LDCT scan has a recognised limitation; others had a very high growth rate (usually SCLC) or were below the threshold size in the previous year. Some delayed diagnoses were due to human failure as they were not recognised by the radiologists. Ten per cent of diagnoses were reported as delayed by NY-ELCAP, a proportion similar to that of COSMOS. Dr Veronesi asked the authors of the NELSON study to provide the rate for their study. Dr Veronesi then questioned the NELSON study authors about the standard treatment of positive cases. Did they use CT/PET or routine FNAB in every positive case? She also stressed the treatment of slow growing nodules - how do the NELSON investigators manage slow growing nodules suspicious for malignancy, do they consider a wait and see strategy or surgical resection? In case of surgery, would a limited resection can be an adequate treatment instead of lobectomy? It is expected that the results from the current and other ongoing screening studies will provide answers to these questions.

All authors have declared no conflicts of interest.

Practice point and future research opportunities

The positive predictive value and low false positive rate found in the evaluation of performance of lung cancer screening strategy in the first three rounds of the NELSON trial based on analysis from 5.5 years of the program are supportive for the use of low-dose CT for lung cancer screening. NELSON is the largest randomised controlled trial in Europe and the first study to incorporate software calculated volume doubling time of nodules into a management algorithm to distinguish between positive and negative findings. Remaining questions to address are the recall rate after baseline and after consecutive screening rounds, as well as the standard treatment in positive cases. It is expected that the results from the current and other ongoing screening studies will provide answers to these questions.

EGFR AND BEYOND

A study of simultaneous occurrence of EGFR mutations and HER2 gene amplifications in large series of NSCLC

In a molecular profile analysis of 2271 cases of non-small cell lung cancer (NSCLC), EGFR was mutated in 12% and KRAS in 32% of cases. HER2 gene amplification was confirmed as a rare event

in NSCLC (4%). Coexistence of HER2 gene amplification and EGFR mutation was identified in 3 cases, while KRAS was mutated in 7 HER2-amplified cases. Double EGFR mutations were, however, found in only 2 cases. NSCLC with HER2 amplification was frequently (39%) associated with KRAS activating mutation. A rare A859T mutation was found in one case and was associated with HER2 gene amplification. This mutation was previously associated with resistance to tyrosine kinase inhibitors (TKIs). This novel molecular insight in a large sample of NSCLC cases was presented by Dr Zoran Gatalica, Adjunct Professor of Pathology at Creighton University School of Medicine, Omaha, USA and Director of Oncologic Pathology at Caris Life Sciences International.

HER2 is a member of the EGFR family of receptor tyrosine kinases. It forms heterodimers with other family members enhancing kinase-mediated activation of the downstream signalling pathways. HER2 amplification has been implicated as a mechanism of acquired resistance to EGFR-TKIs that occurs in a subset of tumours that do not show the acquired, somatic resistance EGFRT790M mutation.

Activating mutations in the tyrosine kinase domain of HER2 have been described in a subset of lung adenocarcinomas and as mutually exclusive with EGFR and KRAS mutations. Arcila et al. previously reported (CCR 2012) that HER2 mutation was significantly associated with NSCLC patients who were never smokers but did not associate with sex, race or disease stage. They concluded that HER2 mutations identify a distinct subset of lung adenocarcinomas. Given the high prevalence of lung cancer worldwide and the availability of standard and investigational therapies targeting HER2, they advocated that routine clinical genotyping of lung adenocarcinoma should include HER2. However, no association between HER2 mutation and HER2 overexpression was shown in their study or in results reported by Stephens, et al. (Nature 2004) who determined the prevalence of HER2 mutations in primary NSCLC to be 4.2%, with prevalence increasing to 9.8% in patients with adenocarcinoma.

In this latest analysis, Dr Gatalica headed a team of investigators from Caris Life Sciences, Phoenix, USA and Basel, Switzerland in characterising the molecular profiles of 2271 patients with NSCLC. They used the Molecular Intelligence™ technique to evaluate samples for HER2 protein expression (immunohistochemistry), HER2 gene amplification (FISH), EGFR and KRAS gene mutations (sequencing). Their goal was to analyse the frequency of the simultaneous occurrence of EGFR mutations and HER2 gene amplifications.

As determined by sequencing, EGFR was mutated in 12% and KRAS mutations were seen in 32% of NSCLC patients. Consistent with earlier reports, HER2 gene amplification (HER2/CEP17>2.2) was detected by FISH in 22 (4%) of 589 tested cases, associated with 3+ protein expression. There was no evidence that HER2 amplification associated with T790M mutation. Coexistence of HER2 gene amplification and KRAS mutations were seen in 7 cases. Simultaneous HER2 gene amplification and EGFR mutation was demonstrated in 3 cases (L858R, A859T and E746_A750del, respectively). Double EGFR mutations (L858R/T790M and E746_A750del/T790M) were also rare and found in only

2 cases. The most frequent association was seen between HER2 amplification and KRAS activating mutation, which occurred with a frequency of 39%. One sample showed the rare A859T mutation, which had been reported by Han et al. (JCO 2005) associated with resistance to TKIs (HER2 status was unknown); however this mutation was associated with HER2 gene amplification in the current analysis. The authors speculated that previously reported resistance to TKIs may have been due to HER2 gene amplification rather than an effect of the EGFR mutated protein.

Since earlier studies have suggested that HER2 amplification may cause resistance to erlotinib and gefitnib, NSCLC patients with HER2 amplification and activating EGFR mutation may respond better to afatinib, which inhibits both HER2 and EGFR activity. In January afatinib was granted priority review by the FDA for treatment of patients with advanced NSCLC harbouring EGFR (HER1) mutations. The study authors advocate for using a comprehensive biomarker evaluation in formulating a targeted treatment strategy for patients with NSCLC to obtain the maximum treatment benefit together with minimum side effects. All authors are employed by Caris Life Sciences which funded this study.

Besides this recent recognition that HER2 amplification may be a mechanism of acquired resistance to EGFR-TKI that occurs in a subset of tumours lacking the acquired, somatic resistance EGFRT790M mutation, the amount of research dedicated to HER2 in NSCLC is increasing. At the recent ESMO Signalling Pathways Symposium entitled "Targeting the HER/EGFR family: Focus on breast, lung and colorectal cancers" and data publication in the JCO (2013), it has been acknowledged that HER2 mutated NSCLC represent a small distinct subgroup of oncogene addicted cancers with specific demographics and potentially outcomes. Results of that largest analysis to date in patients with NSCLC and HER2 mutations provide important insights into HER2-driven NSCLC, despite limitations of studying data retrospectively. Furthermore, this largest study in HER2-mutated NSCLC reinforced the importance of screening for HER2 mutations in lung adenocarcinomas and suggests the potential efficacy of HER2-targeted drugs in this population.

Practice point and future research opportunities

Recently, HER2 amplification was recognised as a mechanism of acquired resistance to EGFR-TKI that occurs in a subset of tumours lacking the acquired, somatic resistance EGFRT790M mutation. A novel molecular insight in large sample of NSCLC cases shows that EGFR was mutated in 12% and KRAS in 32% of cases. HER2 gene amplification was confirmed as a rare event in NSCLC (4%). Coexistence of HER2 gene amplification and EGFR mutation was identified in 3 cases, while KRAS was mutated in 7 HER2-amplified cases. Double EGFR mutations were, however, found in only 2 cases. NSCLC with HER2 amplification were frequently (39%) associated with KRAS activating

mutation. A rare A859T mutation was found in one case and was associated with HER2 gene amplification. This mutation was previously associated with resistance to tyrosine kinase inhibitors.

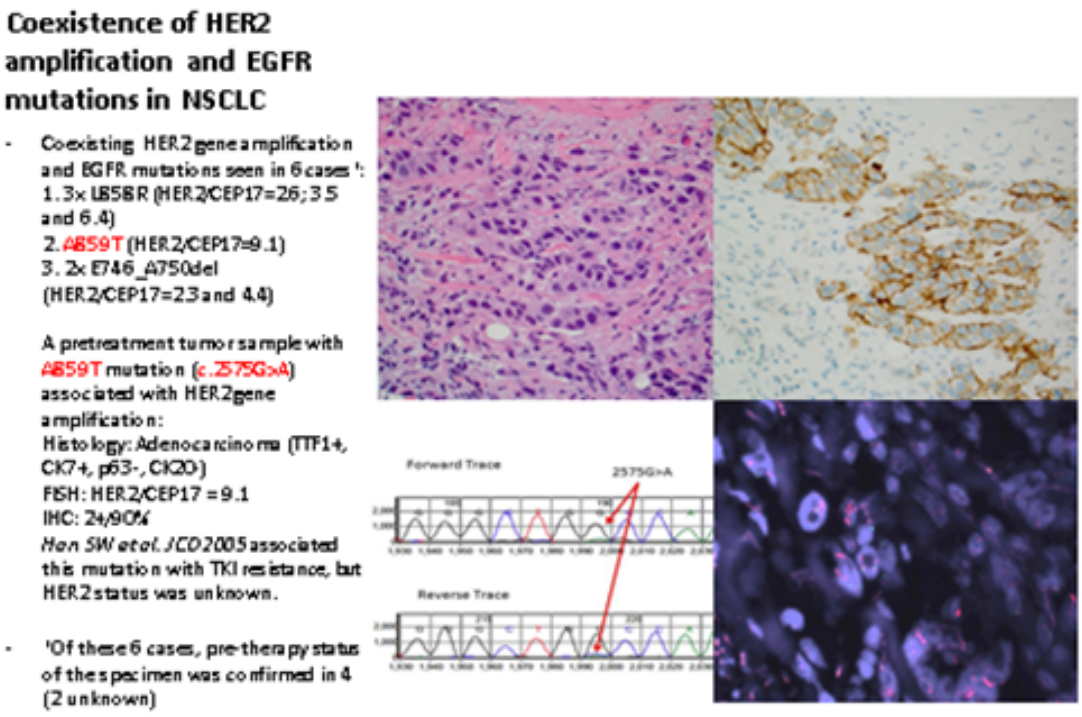


Image: Coexistence of HER2 amplification and EGFR mutations in NSCLC.

Credit for image: Dr Zoran Gatalica gave permission for publishing the images in the ESMO web news and post-EMCTO Scientific Meeting Report.

Different survival outcome following diagnosis of metastatic bone disease shown for EGFR mutated NSCLC patients in a small retrospective study

The incidence of metastatic bone disease or brain metastasis was not different between EGFR mutated, KRAS mutated and KRAS/EGFR wild type (wt) patients in a small, retrospective study performed by Dutch investigators. Time from diagnosis of metastatic non-small cell lung cancer (NSCLC) to development of metastatic bone disease, first skeletal-related event or brain metastasis and post-brain metastasis survival did not differ. However, survival after diagnosis of metastatic bone disease was longer in EGFR mutated patients. The results were presented by Dr Lizza Hendriks of the Department of Respiratory Medicine, Maastricht University Medical Centre in Maastricht, Netherlands.

Patients with metastatic NSCLC often progress by developing bone and brain metastasis. There is no consensus on whether NSCLC patients develop brain metastasis more frequently or have differing outcomes, including survival following brain metastasis diagnosis according to the underlying genetics of their tumours. Some reports suggest that patients with EGFR mutations are more likely to develop brain metastasis and have longer survival after brain metastasis diagnosis than wt or KRAS mutated patients, but other reports are inconclusive. As yet, there are no similar data for NSCLC patients who develop metastatic bone disease, leading Dutch investigators to conduct a retrospective matched control study comparing the time from metastatic NSCLC diagnosis to the development of metastatic bone disease or brain metastasis, symptoms, skeletal-related events and subsequent survival in EGFR mutated, KRAS mutated and wt patients.

The presented findings concern analysis of all EGFR mutated patients diagnosed with metastatic NSCLC between October 2008 and December 2011 at the study researchers' molecular laboratory, which includes five referral hospitals. Each EGFR mutated patient was paired with a consecutive patient who was KRAS mutated or wt metastatic NSCLC. Patients who experienced another malignancy within two years of diagnosis of metastatic NSCLC or who had no follow-up were excluded from this study. Data regarding age, gender, histology, WHO performance status, treatment, diagnosis of bone and brain metastasis, skeletal-related events and survival following diagnosis of metastatic bone disease/brain metastasis were collected and analysed.

Data from 130 patients were included; 42 (32.3%) patients with EGFR mutations, 48 (36.9%) with KRAS mutations and 40 (30.8%) wt patients. The incidence of bone and brain metastasis at initial presentation did not differ, nor did patterns of time to diagnosis of metastatic bone disease in genetically defined groups. At the time of diagnosis of metastatic NSCLC 70% of patients had already bone metastasis. Median time to metastatic bone disease was 8.4 months in EGFR mutated patients compared with 27.5 months in KRAS mutated patients and 9.3 months in wt patients (p=0.81). The EGFR mutated cohort achieved a longer survival post metastatic bone disease diagnosis, 15.5 months compared with 9.4 and 2.8 months, respectively, for KRAS mutated and wt patients (p=0.001). Time to first skeletal-related event was 3.5, 7.3 and 4.7 months respectively (p=0.82).

At the time of diagnosis of metastatic NSCLC, 38% of patients already had brain metastasis. The time to brain metastasis did not differ significantly between the three groups in this study and was 12.3, 9.1 and 11.6 months, respectively. Survival post brain metastasis was 5.6, 8.9, and 4.6 months, respectively, in EGFR mutated, KRAS mutated and wt patients (p=0.57).

The authors concluded that incidence of metastatic bone disease or brain metastasis was not different between EGFR mutated, KRAS mutated and wt patients. The time from diagnosis of metastatic NSCLC to developing bone metastasis, first skeletal-related event or brain-metastasis and

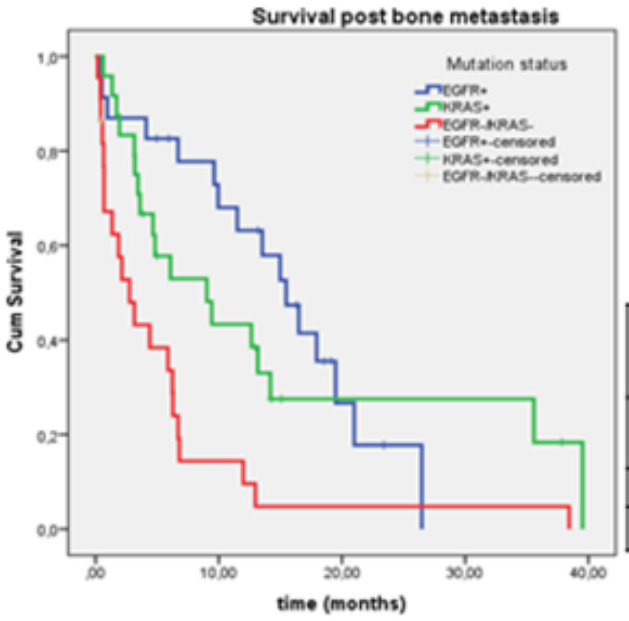
post-brain metastasis survival did not differ in this study. However, survival after metastatic bone disease was significantly longer in EGFR mutated patients. The authors pointed out the importance of prevention and treatment of skeletal-related events in these patients.

The study discussant, Dr Benjamin Besse, congratulated the study team. This is the second study that has compared molecular profile and metastatic pattern, however due to small subgroups, it is hard to draw conclusions about survival and treatment benefit. The wild type subgroup is heterogeneous (ALK, RET, ROS.). Dr Bessespeculated on potential implications in terms of modified work-up for metastatic patients and different follow-up for resected patients. Commenting on results in the cohort of patients with brain metastases, Dr Bessenotedthat EGFR mutated NSCLC patients may be undertreated when brain metastases occur perhaps slow progression influencesthe delay of whole brain radiotherapy. In the small cohort of patients with bone metastases, he speculated that wild type patients may be undertreated and also that bisphosphonates have been poorly prescribed.

All authors have declared no conflicts of interest.

Practice point and future research opportunities

The incidence of metastatic bone disease or brain metastasis was no different between EGFR mutated, KRAS mutated and KRAS/EGFR wild type patients in this small, retrospective study. Time from diagnosis of metastatic non-small cell lung cancer to development of metastatic bone disease, first skeletal-related event or brain metastasis and post-brain metastasis survival did not differ. However, survival after diagnosis of metastatic bone disease was longer in EGFR mutated patients. The findings underline importance of prevention or treatment of skeletal-related events in these patients.



	Median survival (months)	95% CI
EGFR+	15.5	11.5-19.4
- exon 19/21 only	16.5	12.9-20.1
KRAS+	9.4	0.8-18.0
WT	2.8	0.9-4.6

Log rank p = 0.001

Image: Survival curve of post bone metastasis in patients with EGFR mutated, KRAS mutated and wt NSCLC.

Credit for image: Dr Lizza Hendriks gave permission for publishing the figure in the ESMO web news and post-EMCTO Scientific Meeting Report.

A meta-analysis of erlotinib or gefitinib compared to chemotherapy in previously treated patients with metastatic NSCLC

The aim of meta-analysis presented by Dr A. Pochesci of the Sapienza University of Rome, Italy was to compare the efficacy of reversible epidermal growth factor receptor tyrosine kinase inhibitors (rEGFR-TKIs) with chemotherapy in patients who had progressed after at least one line of previous chemotherapy, regardless of EGFR mutational status. His team performed a systematic review of the literature searching for randomised controlled trials (RCT) comparing erlotinib or gefitinib as monotherapy with chemotherapy in previously treated patients with metastatic non-small cell lung cancer (NSCLC).

The endpoints were progression-free survival (PFS), overall survival (OS) and overall response rate (ORR). They conducted subanalysis according to the type of rEGFR-TKI, chemotherapy (docetaxel

vs. other chemotherapy regimens and population (Asian vs. Caucasian). They employed fixed or random-effects models depending on the heterogeneity of the selected trials to calculate the pooled hazard ratio (HR) and risk ratio (RR) with their corresponding 95% confidence intervals (CI).

The authors selected 9 RCT (2 phase II and 7 phase III) including a total of 3576 patients. Chemotherapy regimens used were docetaxel, pemetrexed and pralatrexate. No statistically significant differences were found in terms of PFS (HR 0.95; 95% CI 0.79-1.14; p=0.62), OS (HR 1.02; 95% CI 0.93-1.11; p=0.71), and ORR (RR 1.21; 95% CI 0.84-1.74; p=0.29) between r-EGFR-TKIs and chemotherapy. Only gefitinib showed an increased ORR vs.chemotherapy (RR 1.34; 95% CI 1.08-1.66; p=0.007), while docetaxel demonstrated less efficacy than rEGFR-TKIs in terms of ORR (RR1.37; 95%CI 1.06-1.76; p=0.013), in the whole population. In Asian patients PFS was significantly higher in those receiving r-EGFR-TKIs (HR 0.77; 95% CI 0.65-0.91; p=0.002) and a trend toward an improvement of ORR was registered with erlotinib or gefitinib compared withchemotherapy (RR 1.74; 95% CI 0.95-3.18; p=0.07).

All authors have declared no conflicts of interest.

Practice point and future research opportunities

Reversible epidermal growth factor receptor tyrosine kinase inhibitors and chemotherapy showed the same efficacy in pre-treated non-small cell lung cancer patients, regardless of EGFR mutational status. Overall response rate seemed to be improved when gefitinib was used, while it was reduced when docetaxel was preferred to reversible epidermal growth factor receptor tyrosine kinase inhibitors. In Asian patients reversible epidermal growth factor receptor tyrosine kinase inhibitors should represent the first choice of treatment after the failure of a first line chemotherapy.

Impact of EGFR status on the presence of liver metastases in NSCLC patients and survival implications

Liver metastases occur in 20-30% of patients diagnosed with non-small cell lung cancer (NSCLC). Liver metastases are considered as a poor prognosis feature and may also indicate a more treatment-resistant condition. However, whether the clinical outcome of NSCLC patients with liver metastasesharbouring molecular alterations in EGFR, KRAS and EML4-ALK genes is substantially different depending on their distinct status is still unknown.

Dr E. Castanon Alvarez of the Department of Oncology, University Clinic of Navarra, Pamplona,

Spain analysed268 consecutive cases with stage IV NSCLC. The tumour molecular analysis for EGFR, KRAS and EML4-ALK was available in 205 patients (76.5%), 136 patients (50.7%) and 31 patients (11.6%), respectively. An EGFR mutation was observed in 32 patients (15.6%), KRAS was mutated in 28 patients (20.6%) and an ALK gene rearrangement was observed in three patients (9.6%). Thirteen of the 31 patients with a complete molecular analysis available showed wild-type tumours for all 3 oncogenes (41.9%). The aim of further analysis was to evaluate the incidence of liver metastases in these patients and the differences in clinical outcome regarding the status of EGFR, KRAS and EML4-ALK.

Most of the patients were men (71.3%). The most common histologies were adenocarcinoma (59.3%) and squamous-cell carcinoma (23.1%). Overall, 34% of the patients showed liver metastases at any time of the disease course. Among the whole cohort, median overall survival for patients with liver metastases was 16 months vs. 42 months for patients with metastases affected other organs than liver (p=0.002). Among patients with liver metastases and EGFR mutations, the one-year survival rate was 85.7% vs. 54.3% for patients with liver metastases and EGFR wild-type (p=0.03). In the subgroup of patients showing metastases in other locations but not liver, the difference in the one-year survival rate (87.5% vs. 78.2%) in favour of patients with EGFR mutations did not reach statistical significance (p>0.05).

The study author has declared no conflicts of interest.

Practice point and future research opportunities

In this series of patients, the presence of liver metastases at any time of the disease course had negative impact on the clinical outcome in patients with non-small cell lung cancer. However, the presence of EGFR activating mutations significantly improved the one-year survival rate in patients with liver spread as opposed to those with metastases in other organs. This observation may suggest that the survival benefit in case of EGFR mutations could have an earlier impact in non-small cell lung cancer patients with liver metastases compared to those with metastases in other organs.

Findings support the value of tumour rebiopsy in NSCLC patients

Many patients are reluctant to undergo rebiopsy of their tumours since it is invasive. At the same time, most oncologists feel that this procedure may yield information about mutations occurring during treatment that can affect response. Treatment with tyrosine kinase inhibitors (TKIs) directed to the epidermal growth factor receptor (EGFR) is known to increase progression-free survival (PFS) to a median value of 12 months in patients with EGFR mutated non-small cell lung cancer (NSCLC)

although resistance to treatment may also develop. To date, several mechanisms have been described by which resistance to EGFR TKIs is acquired, but the data are sparse, and T790M mutations in the tumour are thought to play a role. New findings were presented and detailed the mutations acquired during TKI treatment in a retrospective cohort of patients with NSCLC. These findings support rebiopsy as a valuable tool for directing treatment in these patients.

Dr Justine Kuiper of the Department of Pulmonary Diseases and colleagues at the VU University Medical Center in Amsterdam, the Netherlands, conducted a retrospective analysis to define the EGFR mutation spectrum in 63 patients with NSCLC whose tumours became resistant to treatment with TKIs. They analysed medical records that included biopsies taken before and after TKI treatment in patients with either EGFR mutation or who had demonstrated a duration of response to TKIs of more than 24 weeks. All patients were treated with TKIs. Additionally one, two or three lines of chemotherapy were given to 24 (38%), 6 (10%) and 2 (3%) patients prior to TKI and 8 (13%), 7 (11%), 2 (3%) and 1 (2%) patients received one, two, three or five lines of chemotherapy, respectively, following TKI treatment. The objective response rate to TKI treatment was 61.9% according to RECIST criteria and the median PFS was 12.3 months (range: 1.4 - 43.2).

Comparison of pre- and post-TKI biopsies showed that the frequency of T790M mutation was 47.6% following TKI treatment, which was considered to be consistent with other reports. Two patients lost T790M and exon 21 mutations that were recorded prior to treatment. Thirteen patients developed mutations in EGFR exon 19, and mutations in T790M plus exon 19 were observed in 17 patients following TKI treatment. Transformation to small cell lung cancer occurred in one patient, which is less than reported in the literature; this patient showed an exon 19 deletion in the pre-TKI treatment biopsy. One patient with exon 18 plus exon 21 mutations prior to TKI treatment developed a KRAS mutation afterwards but the authors in that case could not exclude the existence of a second primary tumour.

The study by Kuiper et al illustrated that rebiopsy can be a powerful tool, especially in patients who become resistant to TKI treatment, that yields information on altered tumour characteristics that may direct treatment decision and define the mechanisms behind the development of resistance.

The study discussant, Dr Luis Paz-Ares, said that currently known mechanisms of acquired resistance to EGFR TKIs are secondary EGFR mutations (T790M), MET amplification, HGF high levels, HER2 amplification, downstream effectors (PTEN loss, PI3K and BRAF mutations), small-cell lung cancer (SCLC) transformation, epithelial to mesenchimal transition (EMT), DRG: BRCA1 mRNA levels, FAS and NFKB signalling, VEGF/VEGFR, and IGFR1, IGFBP. He questioned if re-biopsy should be done in patients in the regular clinic after progression of the disease. There is not much data available, but also not much morbidity associated to it from the clinicians' perspective. Rebiopsy could be done in case of trial opportunities, but also some patients' treatment could be tailored to the

pheno- or genotype, especially in case of SCLC transformation, where widely available cisplatin and etoposide are effective. Alternatives to be further explored in this setting are liquid biopsies and functional imaging.

Practice point and future research opportunities

New findings detail the mutations acquired during tyrosine kinase inhibitor treatment in a retrospective cohort of patients with NSCLC. Nearly half of patients with acquired resistance to tyrosine kinase inhibitor treatment developed mutations in T790M over the course of treatment. The findings support rebiopsy as a valuable tool for directing treatment in these patients.

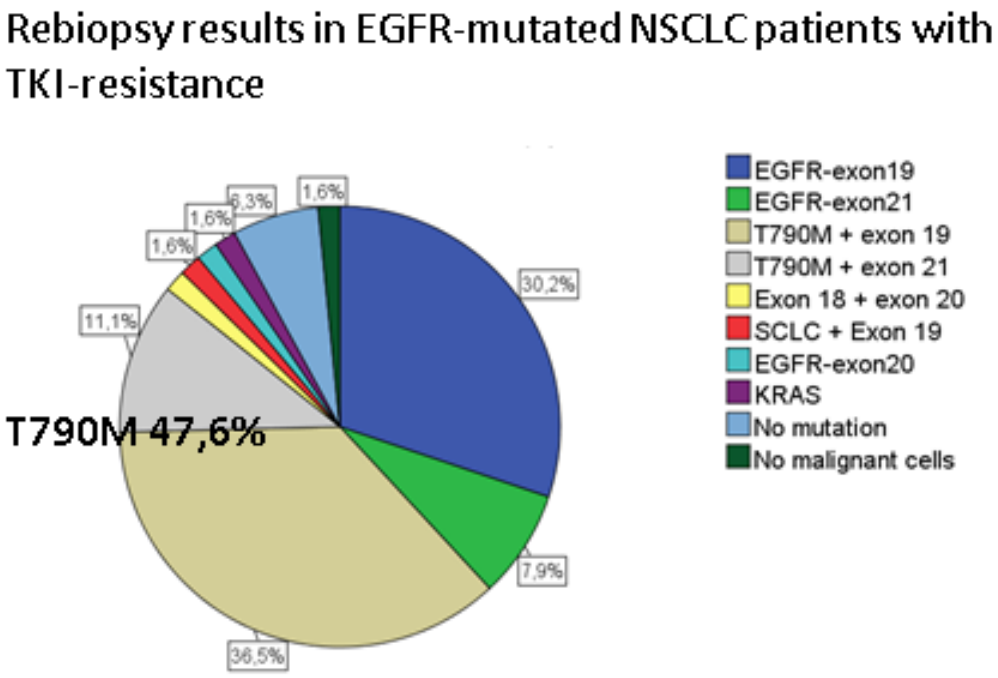


Image: Rebiopsy results in EGFR-mutated NSCLC patients with TKI-resistance

Credit for image: Dr Justine Kuiper gave permission for publishing the image in the ESMO web news and EMCTO post-meeting Scientific Meeting Report.

Molecular follow-up in patients with EGFR mutation-positive NSCLC who progress after oral tyrosine kinase inhibitor treatment

Molecular analysis of rebiopsy specimens taken upon disease progression showed frequent EGFR T790M mutations and/or c-MET amplifications in a cohort of Italian patients with advanced non-small cell lung cancer (NSCLC) with mutation-positive epidermal growth factor receptor (EGFR) who became resistant to oral tyrosine kinase inhibitors (TKIs). The results from this molecular analysis are available in abstract form and were submitted by Dr Bruno Gori of the First Oncological Pulmonary Unit, San Camillo High Specialization Hospital, Rome, Italy.

TKIs are effective treatment options for patients with advanced/metastatic NSCLC who are EGFR mutation-positive. Acquired resistance to TKIs is usually detected concomitantly with disease progression (PD), making efforts to elucidate the underlying mechanisms of molecular resistance crucial to determine optimal treatment for these patients.

Mutations in EGFR exon 20 and c-MET amplifications have been implicated in the development of acquired resistance to TKIs leading the Italian researchers to determine the incidence of these mutations in a cohort of EGFR mutation-positive NSCLC patients who experienced PD following oral TKI treatment. TKIs were administered as first-line treatment to 10 patients and as second-line therapy to 7 patients.

This analysis included data from 17 patients, 12 women and 5 men; 15 patients presented with adenocarcinomas and 2 patients with squamous cell carcinoma. Exon 20 T790M mutation analysis was performed on 14 pre-treatment and all post-treatment specimens by direct sequencing whereas c-MET was evaluated by FISH in 13 rebiopsies. In the initial biopsy EGFR exon 19 deletion was detected in 12 patients and 5 patients had a L858R mutation in exon 21. A second biopsy was performed on the site of the first disease progression post TKI therapy with the intention of reassessing the status of EGFR mutation and c-MET amplification. All studied patients signed a written informed consent.

Results from evaluation of the second biopsy specimen showed T790M mutation had occurred in 8 (47%) patients, and c-MET specific amplification was identified in 4 (31%) of 13 evaluated patients. One patient had both T790M mutation and c-MET amplification while 3 patients exhibited only a c-MET amplification. The authors attributed acquired clinical resistance to TKIs in this cohort by novel EGFR T790M and/or c-MET molecular alterations that occurred following TKI treatment in 11 (65%) assessed patients.In two patients, the EGFR TKI-sensitive mutation originally detected in the first diagnostic specimen was not detected on the site of disease progression. No histotype changes were observed. One of every five pre-treatment EGFR T790M mutations was defined by Real Time PCR and others by direct sequencing.

The authors further concluded thatEGFR T790M mutations and c-MET amplifications were common in patients who were treated with oral TKIs and express acquired drug resistance. They stated that such a 'molecular follow-up', rebiopsy and mutation analysis, will for identification of patients who may benefit from new generation drugs that are currently under development against EGFR (irreversible TKIs) or c-MET.

Practice point and future research opportunities

Molecular analysis of rebiopsy specimens taken upon disease progression showed frequent EGFR T790M mutations and/or c-MET amplifications in a cohort of Italian patients with advanced non-small cell lung cancer with EGFR mutation positive disease who became resistant to oral tyrosine kinase inhibitors.

First-line gefitinib effective and well tolerated in Caucasian patients with EGFR mutation-positive NSCLC

Phase IV study of gefitinib used as first-line treatment in Caucasian patients with epidermal growth factor receptor (EGFR) mutation-positive locally advanced/metastatic non-small cell lung cancer (NSCLC) indicate the treatment is effective and well tolerated. The findings were presented by Dr Jean-Yves Douillard, Professor of Medical Oncology at the University of Nantes and Department of Medical Oncology, Institut de Cancérologie de l'Ouest - René Gauducheau, St Herblain, France, on behalf of a multinational team of investigators.

Gefitinib is a tyrosine kinase inhibitor (TKI) of EGFR that originally showed superior efficacy in trials conducted with non-selected Asian patients. Later, molecular selection was used to enrol EGFR mutated patients in trials and reports began to appear that gefitinib was effective in patients with NSCLC of all races who had mutated EGFR.

This prospective multinational study (NCT01203917) characterises the efficacy and safety/tolerability of gefitinib for first-line treatment of Caucasian patients with EGFR mutation-positive locally advanced/metastatic NSCLC. To be eligible for this study patients were required to be Caucasian, 18 years of age or older, with a performance status 0-2 and have histologically confirmed, previously untreated stage IIIA/B/IV EGFR mutation-positive NSCLC. It was required to provide tumour tissue and matched plasma samples. Patients received gefitinib at 250 mg once daily until disease progression, which was assessed every six weeks using RECIST 1.1 criteria.

The primary endpoint of the study was objective response rate (ORR) by investigator assessment of the full analysis set (FAS). Secondary endpoints included disease control rate (DCR), defined as

complete/partial response or stable disease lasting six or more weeks, progression-free survival (PFS), overall survival (OS) and safety/tolerability. Pre-planned exploratory objectives included comparison of EGFR mutation status between matched tumour and plasma samples.

In all, 1060 patients from 13 countries were screened between September 2010 and February 2012 which yielded in the FAS 106 patients with EGFR mutation-positive NSCLC. The patients were 71% female, 97% had adenocarcinoma and the majority (64%) were never smokers. Baseline analysis determined 31% of patients with L858R mutation, 65% of patients had exon 19 deletions and 4% of patients harboured other mutations.

At data cut off on 15 August, 2012, the primary endpoint ORR in the FAS was 70% and the DCR was 91%. Patients achieved median PFS of 9.7 months and median OS was 19 months (95%CI 17-not calculable, 27% maturity).

Analysis of evaluable samples showed a post treatment mutation rate of 13.7% in tumour and 10.5% in plasma samples. The concordance rate regarding EGFR mutation status between tumour and plasma was 94%.

Gefitinib was well tolerated overall: 8% of patients discontinued treatment due to adverse events. Incidence of serious adverse events was 19%; grades 3/4 adverse events were seen in 15% of patients. The most common adverse events of any grade included rash and diarrhoea which were seen in 45% and 31% of patients, respectively.

From these results, the authors concluded that gefitinib was effective and well tolerated as first-line treatment in Caucasian patients with EGFR mutation-positive NSCLC, as assessed by the study primary endpoint.

The study discussant, Dr Elisabeth Quoix, said that the EGFR mutation rate in Caucasian populations seems to be around 11% to 18% versus 50% in Asian populations with lung adenocarcinoma. Besides lower mutation rate compared to Asian patients there are some similarities, e.g. predominance of exon 19 deletions over exon 21 L858R substitutions, possibly better results in case of exon 19 deletions, overall response rate is around 70% and progression-free survival around 9.2 months in both populations. The current study examined mutation rate and studied gefitinib in a broader European population than the study of erlotinib by Rosell and colleagues, from which results were published last year.

Dr Douillard disclosed receiving principal investigator compensation from AstraZeneca for protocol revision, he also participates in AstraZeneca Advisory Board and meeting symposia. The study co-authors McCormack, Webster and Lilenkova are employees and shareholders of AstraZeneca. All

other authors have declared no conflicts of interest. Editorial assistance was provided and funded by AstraZeneca.

Practice point and future research opportunities

Phase IV study of gefitinib used as first-line treatment in Caucasian patients with epidermal growth factor receptor mutation-positive locally advanced/metastatic non-small cell lung cancer indicate the treatment is effective and well tolerated.

STEREOTACTIC ABLATIVE RADIOTHERAPY

Stereotactic ablative radiotherapy is an effective alternative in patients with multiple primary lung cancers

Multiple primary lung cancers are not an uncommon clinical presentation. ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of lung cancer state that synchronously detected lesions should be treated as multiple primary tumours. A curative approach for both lesions has been associated with improved survival in the surgical literature. However, many patients with multiple primary lung cancers are elderly and have multiple co-morbidities, which can render them unfit for surgery to both lesions. Findings presented by Dr Gwendolyn Griffioen of the VU University Medical Center, Amsterdam, Netherlands support the use of stereotactic ablative radiotherapy as an alternative treatment in patients with multiple primary lung cancers who were not fit to undergo surgery.

The Dutch researchers evaluated the clinical outcomes of 62 patients who have been diagnosed with multiple primary lung cancers at their institution from 2003 to 2012 and treated by stereotactic ablative radiotherapy. Patients' disease was staged by FDG-PET scan and a pathological diagnosis was available for both lesions in 3%, and for one lesion in 48% of patients. All patient data were reviewed by a multi-disciplinary tumour board. In all, 56 patients were treated by stereotactic ablative radiotherapy as a single modality for both lesions and 6 patients underwent such treatment in combination with surgery for the second lesion. Stereotactic ablative radiotherapy was delivered to a total dose of 54-60 Gy in 3-8 fractions, depending on tumour size and location.

Clinical outcome, including survival, pattern of relapse and toxicity were evaluated. A sub-analysis was performed for ipsilateral and bilateral lung lesions.

The analysis showed a median overall survival of 31 months, with an actuarial survival of 40% at three years post stereotactic ablative radiotherapy. At this time, overall lesion local control was 78%;

local control was significantly associated (p=0.005) with tumour size, with the number of fractions delivered (p=0.013), and with lesion location (p=0.004). At the same follow-up, regional failures were observed in 17% and distant failures were seen in 45% of patients. A sub-analysis performed for ipsilateral and bilateral lung lesions showed lesion control at three years for bilateral lesions of 92% compared to 58% for ipsilateral lesions (p=0.009).

No grade 3 early toxicity was observed and grade 3 late toxicity was reported in 3 (5%) patients that included one case of pneumonitis, one case of rib fracture, and chest wall pain was reported in one patient. No grade 4-5 late toxicity occurred.

These findings suggest that stereotactic ablative radiotherapy either alone or combined with surgery is an effective curative treatment for multiple primary lung cancers in poor surgical candidates. It has limited toxicity and can lead to long-term survival. The authors stated that further studies should be done regarding the disappointing local control rates observed for ipsilateral double lesions following stereotactic ablative radiotherapy. Patients with multiple ipsilateral lesions also had a higher rate of nodal recurrence suggesting that invasive nodal staging may be required for such cases.

The study discussant, Dr Cecile Le Pechoux, said that up to 10% of patients have multiple primary lung cancer with surgery being the standard treatment. Generally, patients with synchronous multiple primary lung cancers show poor survival compared to those with metachronous lesions. In ipsilateral multiple primary lung cancer, second primary lung cancer is technically difficult to operate because of lung adhesion (ipsilateral re-thoracotomy). In contralateral multiple primary lung cancers, there is a risk of deterioration of respiratory function with an impact on quality of life. Regarding surgical results in multiple primary lung cancer, Dr Le Pechoux said that the risk of metachronous lung cancer after resection of early stage lung cancer is around 2% to 3% per year; for metachronous lung cancer 5-year survival rate is between 18% and 51%; for synchronous lung cancer 5-year survival is between 0% and 20%. There is a higher rate of postoperative complications, and in Japanese studies, better results were seen for adenocarcinoma.

Dr Le Pechoux commented that SABR for two synchronous lesions is safe and effective; incidence of grade 3 or higher toxicity is 5%. Local control after SABR for synchronous lesions (85%) is poorer than after SABR for single lung tumours (93%). Incidence of regional relapses overall (17%) is higher for synchronous lesions than for single lesions (12%), therefore Dr Le Pechoux speculated on a possible role for endoscopic nodal staging. Furthermore, she said that the results from the current study are very interesting, but more studies are needed with longer follow-up.

Drs Griffioen, Langerwaard, Haasbeek, Slotman and Senan disclosed that their hospital department has a master research agreement with Varian medical systems.

Practice point and future research opportunities

Findings from a small series support the use of stereotactic ablative radiotherapy as an alternative treatment in patients with multiple primary lung cancers who were not fit to undergo surgery. Three years after receiving stereotactic ablative radiotherapy, poor surgical candidates showed benefit, including good local lesion control and overall survival, and also reported low toxicity.

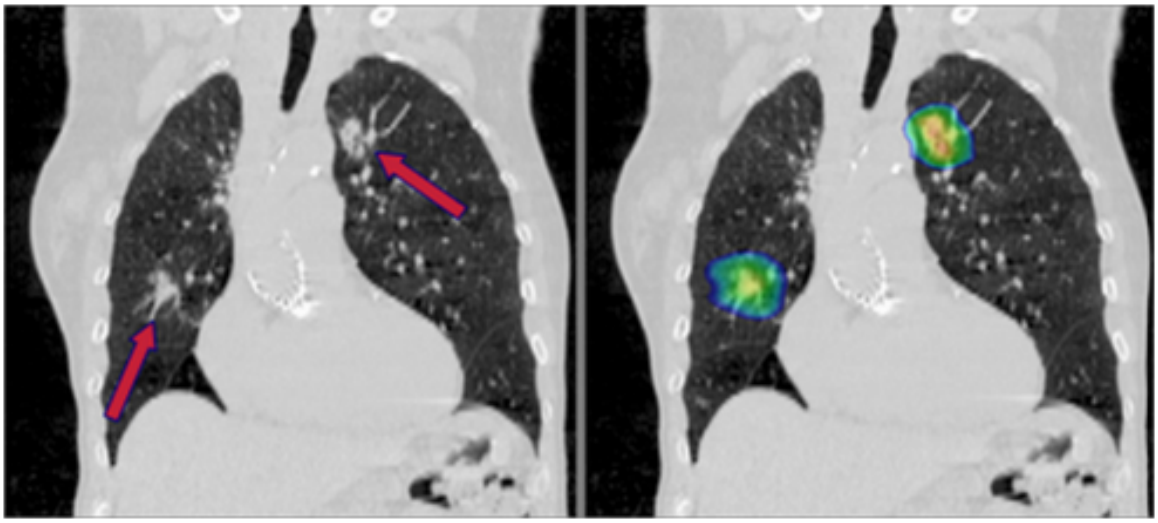


Image: An example of two primary lung cancers, with the right image showing the high-dose radiation region (45 Gray colorwash).

Credit for image: Dr Gwendolyn Griffioen gave permission for publishing the image in the ESMO web news and post-EMCTO Scientific Meeting Report.

SYSTEMIC TREATMENT FOR ADVANCED DISEASE

Meta-analysis slightly favours platinum-based first-line treatment in patients with advanced/metastatic NSCLC

Several meta-analysis conducted in the past suggest that survival of patients with advanced non-small cell lung cancer (NSCLC) is improved if first-line chemotherapy includes platinum derivatives. Results from a new meta-analysis of randomised clinical trials show that platinum-based regimens improve slightly survival in comparison with non-platinum ones and this effect is restricted to cisplatin combinations. The findings were presented by Dr Thierry Berghmans of the Department of Intensive Care and Emergencies and the Clinic of Thoracic Oncology, Institute Jules Bordet in Brussels,

Belgium.

It is well known that cisplatin-based regimens improve survival in comparison to best supportive care alone in patients with advanced NSCLC. However, cisplatin has many adverse events that impact on quality of life while other active agents with different toxicity profiles are currently available. Cisplatin adverse events affect mostly nervous and renal systems, while carboplatin shows a different toxicity profile and it is easier to administer in everyday practice. Several meta-analyses performed in the past suggest that survival is improved in case of platinum-based combination. Since the oncologists aim to improve the treatment outcomes and other active agents are available for clinical use, a thorough evaluation of the literature to include recent large clinical trials was warranted.

The Belgian researchers evaluated all studies published in the French and English languages in the literature that compared first-line platinum to non-platinum regimens in patients with advanced/metastatic NSCLC. For each of 25 studies that were published between 2001 and 2012 and were eligible for the systematic review, the authors extracted an estimate of the hazard ratio (HR) associated with platinum or non-platinum treatment and combined the individual HRs into an aggregate HR for each treatment modality. Either a fixed or a random-effects model (if heterogeneity was statistically significant) was used for this purpose, using data from 23 trials that allowed a quantitative aggregation for meta-analysis.

The number of patients per trial ranged from 80 to 557 and totalled 6930 for all trials. Cisplatin was the comparator in 15 trials involving 4644 participants and carboplatin was compared in 8 trials comprised of 2286 patients; the HRs for these treatments were 1.099 and 1.75. The value for the heterogeneity test with cisplatin was p=0.53 and with carboplatin was p=0.001. In all 23 studies, the HR was 1.084 (p=0.02).

Only four studies demonstrated a statistically significant survival difference between treatments, with three studies favouring platinum and one in favour of non-platinum therapy. Overall, the data showed a slightly improved survival in patients who received platinum-based regimens over patients treated with non-platinum containing regimens; however this effect was seen only with cisplatin combinations.

Ongoing analyses of patient subgroups according to quality trial assessment (based on Cochrane guidelines) and to the type of non-platinum comparator are underway to better define the role of non-platinum regimens for first-line treatment of patients with advanced NSCLC.

The study discussant, Dr Elisabeth Quoix, said that this meta-analysis confirmed that platinum-based doublets remain the standard treatment. Benefit of platinum-based doublets over non-platinum-based chemotherapy is essentially due to cisplatin (only a trend was seen for carboplatin). However, in special populations (patients with performance status 2, elderly patients) carboplatin-based doublet

should be considered and is probably superior to single new agents. Furthermore she emphasized that the high number of meta-analyses performed in advanced NSCLC reflects probably the heterogeneity of the patients included in randomised controlled trials (regarding age, performance status, etc.) which lead to conflicting or at least inconclusive results. Thus meta-analyses are required to answer important questions, but a good question is why repeated results of repeated meta-analyses do not convince doctors to modify their clinical behaviour.

All authors have declared no conflicts of interest.

Practice point and future research opportunities

Results from a new meta-analysis of randomised clinical trials show that platinum-based regimens slightly improve survival in comparison with non-platinum ones and this effect is restricted to cisplatin combinations.

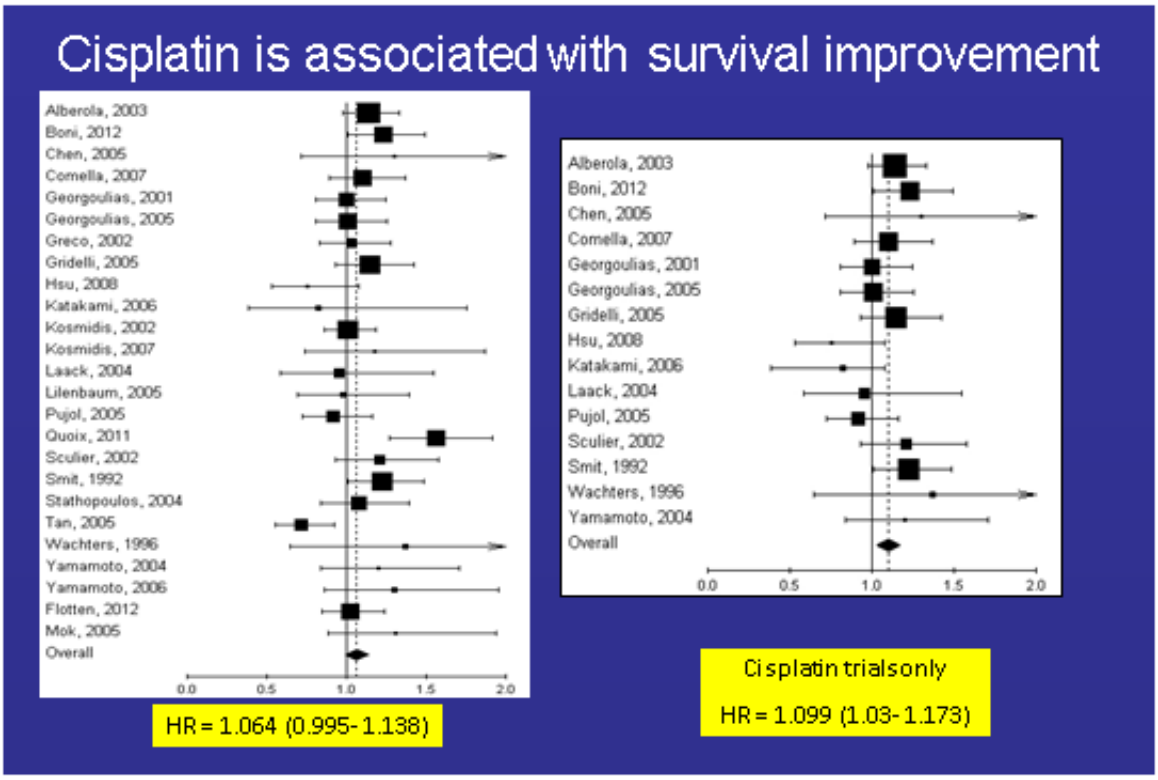


Image:Cisplatin associated with survival improvement in the meta-analysis of randomised clinical trials of first-line platinum- vs. non-platinum-based regimens in patients with advanced/metastatic NSCLC.

Credit for image: Dr Thierry Berghmans gave permission for publishing the images in the ESMO web news and post-EMCTO Scientific Meeting Report.

SUPPORTIVE THERAPY

Enobosarm improves muscle wasting experienced by patients with NSCLC

A randomised, double-blind, placebo controlled phase IIB trial shows that treatment with enobosarm, a non-steroidal selective androgen receptor modulator, significantly improved one measure of physical function and increased lean muscle mass in cancer patients overall and specifically in a cohort of patients with non-small cell lung cancer (NSCLC). Dr Christopher Croot of the Department of Hematology and Oncology, North Mississippi Hematology and Oncology Associates, Ltd. Tupelo, USA is a first author of the study from which findings were presented in a poster-discussion session.

Muscle wasting is a hallmark of cachexia which is caused by by-products of some forms of cancer or by the body's reaction to it. Muscle wasting typically affects skeletal muscles, negatively affecting physical function. It is estimated that more than 50% of lung cancer patients already demonstrate muscle wasting at diagnosis, which increases to affect more than 80% of patients prior to dying from their disease. Enobosarm is non-steroidal selective androgen receptor modulator that is tissue-selective and has anabolic effects in muscle and bone, thus increasing lean body mass.

This randomised, double-blind, placebo controlled study evaluated the effect of enobosarm on lean body mass and physical function in a subset of NSCLC patients. The study enrolled males aged 45 years or more and postmenopausal females, who experienced weight loss of 2% or more over the preceding 6 months. The study participants had been diagnosed with NSCLC, colorectal cancer, non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, or breast cancer.

The study primary and secondary endpoints were change in lean body mass as determined by dual energy X-ray absorptiometry (DEXA) scan and physical function measured by stair climb power, respectively. Response was defined as either a 10% improvement in stair climb power or no loss in lean body mass.

A total of 159 study participants, including a subset comprised of 61 patients with NSCLC, received enobosarm at doses of 1mg or 3mg or placebo for 16 weeks. At 16 weeks, patients treated with enobosarm achieved statistically significant improvements compared to baseline in stair climb power and lean body mass that were not seen in the patients who received placebo. Among 28 NSCLC patients who were evaluable for stair climb power, 18 enobosarm treated subjects showed an

improvement of median 17% over baseline that was statistically significant (p=0.007). Among the 31 NSCLC subjects who were evaluable for lean body mass, the enobosarm cohort of 21 patients showed a median 1.0 kg increase in lean body mass; whereas, a 0.8 kg loss of lean body mass was observed in patients receiving placebo. The responder analysis demonstrated that 78% and 67% of enobosarm treated patients met the criteria defining stair climb power and lean body mass response, respectively.

Enobosarm was well tolerated and commonly reported adverse events were consistent with adverse events seen with chemotherapy and included fatigue, anaemia, nausea, and diarrhoea.

On Friday April 12, 2013, an independent Data Safety Monitoring Board (DSMB) announced that a per protocol safety review of unblinded safety data supported the two pivotal phase III clinical trials of enobosarm that are ongoing to determine the prevention and treatment of muscle wasting in patients with advanced NSCLC.

During the time foreseen for questions and answers, the first author of the study said that two ongoing phase III studies evaluate enobosarm with different type of chemotherapy, one investigate platinum and taxane-based chemotherapy, while the second evaluate platinum and non-taxane regimen. It is important because it is well known that chemotherapy itself can treat symptoms in patients with NSCLC. Each of these phase III studies enrolled 320 patients. The last patient was enrolled oneweek before this conference. The second point raised during the discussion was that the study authors did not prospectively investigate the use of glucocorticoids. It would be also important in such studies to test androgen receptor in tumour tissue, however the study presenter said that the role of testosterone and higher lung cancer rates in men than in womenhave been speculated on for a long time, however he did not believe that the androgen receptor has a major impact on the outcome in NSCLC.

Author MA Johnston disclosed that he is an employee and owns stock in GTx, Inc.; MS Steiner disclosed that he is the CEO and Chairman of the Board of GTx, he and his family own stock in GTx, Inc.; and ML Hancock is employee and owns stock with GTx.

Practice point and future research opportunities

A randomised, double-blind, placebo controlled phase IIB trial shows that treatment with enobosarm, a non-steroidal selective androgen receptor modulator, significantly improved one measure of physical function and increased lean muscle mass in cancer patients overall and specifically in a cohort of patients with non-small cell lung cancer. Per protocol safety review of unblinded safety data support two pivotal phase III clinical trials of enobosarm that are ongoing to determine the prevention

and treatment of muscle wasting in patients with advanced non-small cell lung cancer.

PULMONARY METASTASECTOMY IN CRC

Initial results from the largest prospective study of pulmonary metastasectomy in patients with colorectal cancer

The largest-to-date and only prospective Spanish series of 549 patients who underwent surgical resection of lung metastases from colorectal carcinoma demonstrated a good postoperative recovery from the procedure. A further analysis on morbidity, the correlation between imaging studies and pathological findings and survival after three years is underway. The initial findings from this study have been presented by Dr Laureano Molins of the Department of Thoracic Surgery, Sagrat Cor University Hospital and Hospital Clinic, Barcelona, Spain.

Pulmonary metastasectomy is a commonly performed surgical treatment in patients with lung metastases from colorectal cancer despite the lack of evidence from any controlled study of survival benefit. Claims for a survival benefit derive from case series.

Dr Molins headed a team of investigators at cancer centres throughout Spain in conducting a prospective cohort study using data from the Registry of the Spanish Group for Surgery of Lung Metastases from Colorectal Carcinoma (GECMP-CCR-SEPAR). The study objective was to analyse the main clinical factors involved in the prognosis of patients undergoing surgery for lung metastases from colorectal carcinoma.

From March 2008 to March 2010 a total of 549 patients underwent at least one episode of radical lung metastasectomy and were enrolled in this study. The mean number of nodules detected by computed tomography (CT) was 1.88 (range 1-12); 314 (59%) patients presented with a single node, 96 (18%) with multiple unilateral nodules and 120 (23%) patients had multiple bilateral nodules in lung. Synchronous lung metastases and colorectal carcinoma was detected in 78 (15%) patients. Patients with metachronous lesions showed a mean disease free interval of 24 months.

A video-assisted thoracoscopic approach was decided for 75 (17%) of the 446 patients who had unilateral clinical involvement. Wedge resection was performed in 80% of patients. Occult metastases were detected by CT in 23% of patients showing bilateral pathological involvement compared to 7% of patients without bilateral involvement ($p<0.001$). Staging was done by PET or PET-CT in 75% of patients with the following diagnostic values: sensitivity 84%, specificity 78%, positive predictive value 98%, and negative predictive value 26%.

Patients who underwent pulmonary metastasectomy experienced few complications in this series; postoperative morbidity was observed in 81 (15%) patients. Postoperative mortality was exceptionally low, with two deaths (0.4%) occurring after resection of lung metastasis from colorectal cancer.

Thoracotomy and wedge resection were the most frequently performed surgical techniques in this setting. The authors commented that the imaging tests used, CT and PET or PET-CT, had clear limitations in preoperative evaluation of patients as candidates for lung metastasectomy. They pointed out that it is the only prospective data collection regarding pulmonary metastasectomy in their country with a larger data base than previously seen in the literature. Resection of lung metastases from colorectal carcinoma is a procedure with low morbidity and mortality. The analyses are ongoing and three year follow-up data on morbidity, the correlation between imaging studies and pathological findings, and survival will be reported as data becomes mature.

The study discussant, Dr Paul Van Schil, said that 30% of all cancer patients will develop lung metastases. Five-year survival rates in untreated patients is about 5-10% and 30-50% in resected patients. There is a lack of prospective randomised studies in this field and he discussed the results of PulMiCC trial: a multi-centre, randomised trial evaluating pulmonary metastasectomy in colorectal cancer (published by Hornbech et al. in the European Journal of Cardiothoracic Surgery in 2011) and long term results of lung metastasectomy: prognostic analysis based on 5206 cases published by Pastorino et al. in the Journal of Thoracic Cardiovascular Surgery in 1997.

Furthermore, he discussed how to improve local control and specifically chemo-embolization (embolic trapping), pulmonary artery infusion, isolated lung perfusion, as well as non-resectional therapies, such as radiofrequency ablation (RFA) and stereotactic radiotherapy (SRT). He continued with the role of VATS in surgery for lung metastases, and referred to a previously published treatment algorithm for lung metastases (Zheng Y. SurgClinNorh Am 2010; 90: 1041-51). In case of low operative risk and 1-2 peripheral metastases, the algorithm suggests considering VATS, in case of more than 2 metastases an open intervention; in case of increased operative risk it suggests RFA/SRT; and in case of recurrent lung metastases after prior resection to consider RFA/SRT or to repeat resection.

All authors have declared no conflicts of interest.

Practice point and future research opportunities

The largest-to-date and only prospective Spanish series of patients who underwent surgical resection of lung metastases from colorectal carcinoma demonstrated a good postoperative recovery from the procedure. Low morbidity and mortality were observed; thoracotomy and wedge resection were most

frequently performed surgical techniques in the study cohort. A further analysis on morbidity, the correlation between imaging studies and pathological findings and survival after three years is underway.

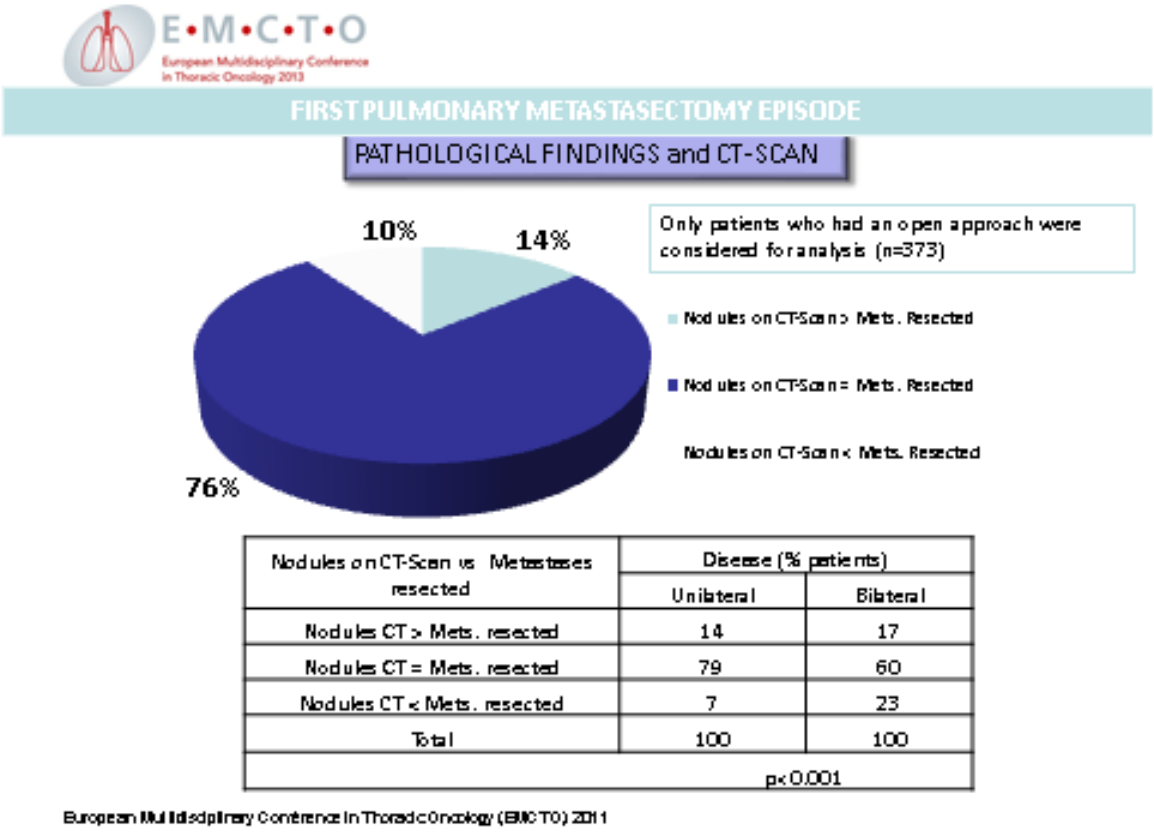


Image: Analysis of pathological findings and CT scan at first pulmonary episode resection.

Credit for image: Dr Laureano Molins gave permission for publishing the image in the ESMO web news and EMCTO post-meeting Scientific Meeting Report.

RELATED INFORMATION

The conference abstracts can be found in Vol 80 May 2013 p S1-S76 - Supplement 1 here:

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Save the date:ELCC 2014 European Lung Cancer Conference organized by the European Society for Medical Oncology (ESMO) and the International Association for the Study of Lung Cancer (IASLC), 26-29 March 2014, Geneva, Switzerland.

AFFILIATION AND DISCLOSURE

Dr Svetlana Jezdic, ESMO Head Office.

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