ELCC 2014 European Lung Cancer Conference

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Geneva, Switzerland

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Summary

The European Lung Cancer Conference (ELCC) was organised by the European Society for Medical Oncology (ESMO) and the International Association for the Study of Lung Cancer (IASLC). The Conference is built upon the success of previous editions and has now become an annual event. During the intense four-day programme, attendees benefited from educational and scientific updates provided by thoracic oncology specialists. These covered several multidisciplinary topics important for research and clinical practice in the field of lung cancer. The scope of this report is to present a selection of educational highlights and scientific findings presented during the conference.

Introduction

The Conference objectives were to provide a regular update on different multidisciplinary topics important in the lung cancer field, to critically discuss increasing understanding of biology of lung cancer and how it changes diagnostic and treatment landscape and to present the latest advances in translational and clinical research across lung and other thoracic malignancies.

There were, in total, 1396 attendees including 1252 delegates representing all specialties dealing with lung cancer and other thoracic tumours encompassing medical oncologists, radiotherapists, pulmonologists, thoracic surgeons, radiodiagnosticians, pathologists, basic scientists and epidemiologists. Two thirds of the attendees were European professionals, with other participants coming from other continents (approximately 10% from North America, 10% Asia, 5% Central/South America and 5% Middle East).

From 163 submitted abstracts, the Scientific Committee selected 131 abstracts, 16 for oral presentation, 15 for poster discussion and 100 for poster presentation. The most popular categories for abstract submission were advanced non-small cell lung cancer (NSCLC), translational research, tumour biology and pathology. In total 16 travel grants were awarded by the organisers to enhance participation of young professionals and those practicing in emerging countries.

This year of the programme focused on molecular testing in advanced NSCLC, immunotherapy in NSCLC, oncogenic-driven diseases and potential role of local therapies, as well as strategies for overcoming resistance, the worldwide landscape of clinical trials in advanced NSCLC, new developments in targeted therapies, treatment approaches for advanced NSCLC without driver mutations, and oligometastatic NSCLC.

Interaction between the audience and faculty ensured that the data presented were really put into perspective for clinical practice. The format included numerous clinical-world decision questions. Meet-the-Expert sessions provided additional opportunities to interact with the faculty. Specific workshops were designated for certain oncology specialties while the overall conference highlighted the need for multidisciplinary collaboration.

The lectures were designed to analyse and effectively interpret the increasing volume of new clinical data. Top expert faculty gave their opinion on the optimal roles of new diagnostics and therapeutics in clinical scenarios for the treatment of patients with early, locally-advanced and metastatic disease.

Highlights from the educational and scientific sessions

The place of targeted agents in multimodality treatment of stage III NSCLC

Dr Solange Peters of the Lausanne Cancer Center, Switzerland discussed targeted agents (cetuximab/erlotinib/crizotinib/bevacizumab) with definitive chemoradiotherapy and induction therapy with same agents in surgical stage III.

Cetuximab added to chemoradiotherapy does not improve overall survival (OS) or progression-free survival (PFS) in patients with unresectable stage III NSCLC, and it is associated with a significant increase in grade 3-5 toxicities. Greater benefit with cetuximab may occur in patients with high epidermal growth factor receptor (EGFR) expression, although further study including prospective validation is required.

Concomitant administration of EGFR tyrosine kinase inhibitors (TKIs) and radiotherapy is feasible. In unselected NSCLC patients, benefit of a such strategy is unlikely to be shown. In EGFR mutation positive disease, concomitant EGFR TKI with radiotherapy is under evaluation in several clinical trials.

Regarding induction strategy and the role of EGFR TKIs before surgery, neoadjuvant administration is feasible. Again in unselected patients, the benefit of such strategy is unlikely to be shown. In EGFR mutation positive disease, induction EGFR TKI is under evaluation in several clinical trials.

Summarising what we have learnt about radiotherapy and targeted agents, Dr Peters said that OS of 29 months can be expected in stage III NSCLC treated with a concomitant approach in the era of PET-CT. Stage III clinical trials require an enormous collaborative effort and are difficult to complete. Therefore, only rigorous scientific questions should be addressed. There are several ongoing phase I trials with PARP inhibitor olaparib, nelfinavir, and Notch Hedgehog, WNT inhibitors. The place of vaccination in early disease is still under evaluation.

Definition of oligometastatic disease

Dr Christophe Dooms of the Respiratory Division, University Hospitals Leuven, Belgium said in his lecture that 10-15% of all patients with NSCLC have single organ oligometastatic disease. But that there are distinct cohorts with probably different prognoses: 1. patients with

"oligometastases", who are diagnosed with oligometastatic disease; 2. Patients with "oligoreccurence", who relapsed with presentation of oligometastatic disease; and 3. patients with "oligoprogressive" status, a status after cytoreductive therapy.

In terms of a definition for "synchronous" oligometastases, he said that the current definition was merely based on personal opinion. At present, a precise definition is lacking. The turning point between terms oligometastases and poly-metastases is somewhere between 1 and 5 distant metastases in ≤ 2 organs.

Clinical features which areprognostic for outcomes are fit patients (performance status - PS 0-1), limited nodal involvement (N0/1), disease radically treatable by surgical and/or radiotherapy modalities, gross tumour volume < 125 cm3, lung planned tumour volume < 639 cm3, lack of progression on systemic therapy, and presence of 3 or less distant metastases.

First-line management of EGFR/ALK positive NSCLC

Prof. Mark Socinski of the University of Pittsburgh Lung Cancer Center of Excellence said that EGFR and ALK represent two examples in NSCLC where molecularly targeted therapies in molecularly defined patient populations are superior to traditional cytotoxic chemotherapy. All trials in EGFR mutant NSCLC have shown for predominantly exon 19/21 mutations that first-line EGFR TKIs improve overall response rate (ORR) and PFS in comparison to platinum doublets, but a difference in OS was not seen due to cross-over effect (but 100% of patients do not cross-over) and development of resistance. Toxicity is more favourable with TKIs vs. platinum doublets. In term of uncommon EGFR mutations, some may be sensitive, but not all.

According to Prof. Socinski, the treatment options in case of progression are to continue first generation TKIs, local radiotherapy limited to the site of progression while continuing TKI, chemotherapy (either a single agent or combination) added to first generation TKI or alone, and novel therapies (cetuximab/afatinib, CO-1686 trial, AZD9291 trial, anti-PD1 or an anti-PD-L1 trial).

If the mutation status is unknown and the patient needs treatment, the lesson from the IPASS trial is that chemotherapy must be given. But what to do if, after starting chemotherapy, the mutation test returns and shows a sensitive mutation? Options could be to continue chemotherapy plus/minus maintenance and to give EGFR TKI in second-line treatment; to stop chemotherapy and start treatment with EGFR TKI; or to add EGFR TKI to chemotherapy. But there is no published data on that scenario. The decision should be made based on disease response and treatment tolerance.

In the case of ALK translocation positive NSCLC, there is no first-line data to date, but it is common practice to use ALK inhibitors in this setting. Crizotinib improves ORR and PFS in the second-line setting vs. standard second-line options with no difference in OS.

Beyond crizotinib, first and second generations of ALK TKIs in clinical development are LDK378, AF802, AP26113, ASP3026, CEP-28122, NMS-E628 and X276/396.

Molecular testing for clinical practice

Prof. Keith Kerr of the Aberdeen University Medical School, UK, provided some tips for success in biomarker testing. He said that one key is test anticipation. It is important to maximise tissue collection without causing the patient undue harm and to process the tissue appropriately. Any sample type is potentially adequate for biomarker testing. It is important to take steps to "improve" the test sample. He insisted on quality-assured molecular testing. It is crucial to plan the testing strategy as it is a multidisciplinary effort. Everyone in the team should understand why testing is important. He elaborated reflex vs. bespoke testing. Reflex testing (pathologist driven) is fast, cases are not missed, the results are ready for multidisciplinary team decision, but there is a potential for waste of time, tissue and money. Bespoke testing (an order from oncologist) is performed only when needed. It preserves tissue and the cost is higher per test. It is, however, associated with slower turnaround and cases may be missed.

Speaking about how much tumour tissue is needed, Prof. Kerr said that such rules are difficult to establish. And in term what is used for the test, he emphasised collecting whatever is available. Pathologists need tumour cells. Therefore, it is important to maximise tumour cells in material submitted for DNA extraction and minimise non-tumour cells.

Brain metastases: Local therapies in oncogenic-driven diseases

Dr Rafal Dziadziuszko of the Medical University of Gdansk, Poland, reviewed treatment options for NSCLC patients with brain metastases: whole brain radiotherapy (WBRT), stereotactic radiotherapy, surgery, chemotherapy, targeted therapies, and best supportive care.

After giving a general introduction, he reviewed indications for surgery vs. stereotactic radiotherapy in patients with 1-3 metastases. The surgical option should be favoured in cases of single lesions, larger lesions with mass effect, location outside "vulnerable" surgical areas, and no presence for general contraindications to surgery. Stereotactic radiotherapy should be favoured in cases of smaller lesions, multiple (meaning 1-3) lesions, all located in the brain including brain stem and in patients who are not surgical candidates.

WBRT may be deferred in patients until progression in the brain. Stereotactic radiotherapy improves survival when added to WBRT in patients with single metastasis. WBRT improves local control but not survival when added to surgery or stereotactic radiotherapy. WBRT is associated with moderate cognitive dysfunction. In most patients with graded prognostic assessment 3,5-4 surgery or stereotactic radiotherapy without WBRT should be considered, particularly if effective systemic therapy exist.

New approaches in local treatment are hippocampal-sparing radiotherapy, WBRT with simultaneous integrated boost to brain metastases and brain protective agents.

Targeted therapies can significantly prolong survival of NSCLC patients with brain metastases. By trying to answer the question if targeted therapy changes the brain metastases landscape in oncogenic-driven NSCLC subsets, Dr Dziadziuszko said that pharmacokinetic properties of targeted agent in relation to blood-brain barrier are extremely important. Targeted therapies are more effective than chemotherapy in specific subsets of NSCLC patients. Better systemic

control with targeted agents may significantly prolong survival of NSCLC patients with brain metastases and influence the prognostic scoring systems.

ALK-positive NSCLC has a propensity for early brain dissemination, for example it was the case in approximately 30% of patients participating in PROFILE 07 trial. But crizotinib penetration to cerebrospinal fluid is less than 1%. Many progressions occur exclusively in the central nervous system (CNS: brain, meninges, spinal cord), which is defined as pharmacokinetic brain relapses. With continued systemic control, crizotinib may be considered in patients with isolated brain metastases, after WBRT and/or stereotactic surgery, with case stories of prolonged second remissions in the CNS.

Brain penetration of a particular compound in relation to local therapies is very important. Mechanism of CNS progression on EGFR or ALK inhibitors could be pharmacokinetic, making the local treatment essential. In gefitinib treated patients, a switch to erlotinib or afatinib could be considered to achieve higher cerebrospinal fluid concentrations. Several retrospective studies demonstrate some efficacy of erlotinib pulse-dosing and similar observation of efficacy of crizotinib pulse-dosing was published in ALK-positive NSCLC.

First-line treatment of advanced NSCLC in patients without a driver mutation

Prof. Frances Shepherd of the Princess Margaret Cancer Centre in Toronto, Canada said that in first-line chemotherapy trials (ECOG 1594, SWOG 9509, TAX 326, Italian study with doublet therapies) there was no significant or meaningful differences. However, no molecular testing was done for any of these trials. Therefore, some patients with driver mutations may have been included.

In her talk she covered issues such as regimen of choice when selection is based on histology, number of drugs in the regimen, if platinum is necessary, cisplatin vs. carboplatin, treatment of elderly patients, addition of targeted agent, treatment with chemotherapy or a targeted agent, and duration of treatment, in particular duration of maintenance chemotherapy and maintenance targeted agent. She interpreted available data for first-line treatment to conclude that patients should not be selected for EGFR therapy based on clinical characteristics. This may not be the case in second- (including maintenance) or third-line therapy where patients with both EGFR wt and mutant tumours appear to benefit from EGFR TKI therapy.

Prof. Shepherd concluded that there is little new with respect to chemotherapy. The addition of targeted therapy has been disappointing. Vaccine therapy trials, for the most part, have been disappointing as well, although tecemotide may have a role in stage III NSCLC. Immune modulation appears interesting approach, but she warned on the “promising phase II syndrome”. Results of phase III trials are some years away.

Challenges in maintenance treatment in advance NSCLC: Do benefits outweigh the costs?

Speaking about treatment choices in patients with advanced NSCLC without driver mutations, Prof. Giorgio Scagliotti of the University of Turin, Italy, said that the target population for maintenance therapy are those patients with complete response, partial response, or stable disease, following induction therapy with minimal cumulative toxicity.

He stated pro and cons for maintenance treatment. Pros: it maintains disease control, improves PFS, improves OS, maintains quality of life, represents opportunity to treat more patients, and patients support maintenance therapy. Cons: induction chemotherapy of 4 to 6 cycles may accomplish the same improvement in PFS, the marked drop off in number of patients available for second-line therapy in earlier reports, appears not to be the case when patients are carefully followed, grade 3 and 4 adverse events of 30-40% are too high, there is a need for biomarkers, and cost of this intervention is expensive.

Dr Giannis Mountzios of the University of Athens School of Medicine said that maintenance treatment in advanced NSCLC should be individualised taking into consideration efficacy outcomes, adherence to treatment, toxicity and impact on quality of life. Cost-effectiveness of maintenance treatment largely depends on health care systems across Europe and the parameters taken into account in the pharmacoeconomic analysis.

For maintenance treatment, where combinations of novel agents that prolong PFS but not OS, it is highly unlikely that they will represent cost-effective options for most European countries.

Dr Mountzios also asked if a patient achieves stable disease but remains symptomatic, should subsequent therapy be considered as “maintenance” or “early second-line therapy”.

Dr Mountzios also warned that in emerging era of personalised medicine, decisions should be made on individual basis. He stressed on importance of underlying molecular profile of individual patients.

Immunomodulation with a focus on the clinical development of PD-1/PD-L1 inhibitors in NSCLC

During her lecture, Dr Julie Brahmer of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, USA said that the future of immunotherapy in NSCLC may be in determining the mechanism of immune evasion in each patient. Potential mechanisms for immune evasion in lung cancer are defective antigen presentation, immunosuppressive cell infiltrates, upregulated secretion of immunosuppressive cytokines and checkpoint pathways.

Clinical development of programmed cell death 1 (PD-1) immune checkpoint inhibitors is an exciting area. The antibodies that target PD-1 under development are nivolumab (fully human IgG4), pidilizumab (humanised IgG1) and MK-3475 (humanised IgG4). Programmed cell death 1 ligand 1 (PD-L1) inhibitors under development include BMS-936559 (fully human IgG4), Medl-4736 (engineered human IgG1), MPDL-3280A (engineered human IgG1), and MSB0010718C (engineered human IgG1). They have promising activity in NSCLC, but also a unique set of side effects consistent with the immune mechanism of action.

Common PD-1/PD-L1 blockade immune-mediated toxicities are fatigue, rash, diarrhoea/colitis, hepatitis/liver enzyme abnormalities, infusion reactions and endocrinopathies. Pneumonitis is infrequent. Grade 3 and 4 toxicities are uncommon.

Current trials of PD-1 pathway inhibitors include MPDL-3280A in PD-L1 positive disease, MPDL-3280A vs. docetaxel in the second-line treatment setting, MK-3475 vs. docetaxel in the second-line, MK-3475 as a single agent, nivolumab as a first-line in metastatic disease. A phase III trial of nivolumab vs. docetaxel has completed enrolment. In testing combinations with PD-1 checkpoint inhibitors, other co-inhibitory pathways are important: CTLA-4, TIM-3, LAG-3; co-stimulatory pathways include OX40, 4-1BB, GITR; combinations with standard of care include chemotherapy, TKIs, radiotherapy; then combinations with cancer vaccines and epigenetic therapy are also in research pipeline.

There are open questions regarding testing, in particular assay limitations such as the requirement to assess membrane B7-H1 protein by immunohistochemistry and the number of different commercially available antibodies. Other unanswered questions are what is most important: tumour vs. stroma or both, archived vs. fresh biopsy, how old a biopsy is too old, heterogeneity in expression within tumour tissue, is the presence and composition of tumour infiltrating lymphocytes (TILs) required, is PD-L1 positivity a predictor of response and/or prognostic factor.

Early drug development of targeted therapies in NSCLC: Challenges in collaboration between academia and industry

Dr Thierry Le Chevalier of the Institut d'Oncologie Thoracique, Paris Sud, France, first gave definitions of academic and industry-driven studies. An academic trial is designed to evaluate (phase I/II) and compare (phase III) a drug, a drug combination or a therapeutic modality with existing standard treatments in order to improve the survival of a predefined population. An industry-driven study is mainly focused on the activity of a drug or a drug combination on a predefined disease in order to get a registration or promote its experimental drug.

According to Dr Chevalier, an academic-driven study will mainly evaluate the overall effect of a treatment on a patient's life (OS), while an industry-driven study will focus on the activity of a drug on disease (PFS). However, industry studies are increasingly having co-primary endpoints (PFS and OS). Additionally adverse event reporting is usually more rigorous in industry studies, as there are tighter regulations.

After the general introduction, Dr Chevalier discussed drivers of pharmaceutical regulations in Europe and USA and subsequently about the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use at which the regulatory authorities and pharmaceutical industry of Europe, Japan and the USA discussed scientific and technical aspects of drugs registration.

Dr Chevalier discussed licensing approval scenarios. Regular approval on completion of phase III clinical studies consider full data package with sufficient data to demonstrate safety and efficacy, clinical benefit in in term of OS and PFS. Accelerated approval is intended to make promising products for life-threatening diseases available on the basis of preliminary evidence

prior to formal demonstration of patient benefit. Approval is based on a surrogate endpoint. In addition, it is considered a provisional approval with a written commitment to complete specific clinical studies. The licence may be re-evaluated based on the results of these studies.

Basic principles to be considered for the approval of anticancer drugs are if the drug works and if it is safe. Robust scientific evidence is required, but the views of the Food and Drug Administration and European Medicines Agency may be different. In general, longer survival should be achieved and quality of life improved. In term of safety, the tested drug should be safer than alternatives or the benefit must outweigh the additional risk.

Speaking about clinical trial endpoint selection in last two decades, Dr Chevalier said that strict legal requirements to demonstrate benefit required randomised controlled trials; the primary endpoint must be a valid and reliable measure that provides the most clinically relevant and convincing evidence. Poor design or lack of efficacy are the most important reasons for rejection.

The most commonly used endpoints are based on OS, then PFS, tumour response, symptom assessment and toxicity. OS is historically viewed as the most measure, as it addresses the biology of tumour and the natural history of the disease. It is thought of as a patient-oriented endpoint. PFS is associated with tumour growth; it assesses tumour shrinkage and stabilisation of disease, and therefore it is a disease-oriented endpoint.

In term of future trends, PFS is proving more challenging to employ as a regulatory endpoint. However, it will continue to have a potential role in oncology drug registration if rigorous acceptance criteria and standards are met. There will be increasing regulatory pressure to link or associate PFS with other clinical trial outcomes that show direct clinical benefit (e.g. quality of life benefits, disease-related symptom benefits, OS positive trends). The PFS may have its best future applications in symptomatic disease settings and/or where delay in disease progression correlates with delay in symptom onset. Benefit of delay of progression may also be measured by accessing quality of life benefits pre- vs. post-progression, independent of study arm. PFS can also be an early surrogate for OS where the OS endpoint may be several years away.

Predictive biomarkers do not serve as primary endpoint for drug approval. Further research is required to establish the validity of available tests and determine which biomarkers may predict clinical benefit. Biomarkers may serve as elements of a composite endpoint in the future.

More and more targeted agents are developed in bio-selected populations. And for more and more targeted agents, a companion diagnostic may be required in order to clearly identify the selected population. Whether the companion diagnostics should be developed simultaneously with the agent or independently remains an open question.

Dr Chevalier commented that a change is needed in the regulatory environment in the field of oncology. A paradigm shift from a general population to a more personalised medicine approach is required from the regulatory perspective. In the last two decades, industry has taken the lead on all drug development which explains the increase in disease related endpoints

over patient related endpoints (PFS vs. OS). This fact makes more complex the management of personalised medicine that should be mostly the job of academy.

Academic trials are supposed to be done independently of industry. They are supposed to largely contribute to national and international guidelines. They establish the therapeutic paradigms and the state of the art for defined populations of cancer patients. In ideal world industry develops new drugs and academy uses these drugs which are included in new protocols in combination with other agents and other treatment modalities simultaneously or sequentially. Once the drug is on the market, academy should take the lead in optimising its use. But in the real world, industry develops new drugs; it therefore designs/sponsors/controls most phase III trials; it finances most translational research programs and establishes the dose, schedule and treatment duration.

Discussing Europe as a major partner for research and development in oncology, Dr Chevalier said that EU strengths are approximately 500 million inhabitants; its political and healthcare systems are relatively homogenous compared to rest of the world; there is an established network of academic institutions and national/European cooperative groups; there are several expert centres for translational research; Europe has consistently recruited approximately 50% of total research and development study enrolment targets; it is a still growing market in oncology; and there are specific rules for early access to innovative treatment. But weaknesses are heterogeneity of culture and language; unclear expectations of some national agencies; slow approval process for clinical trial application; slow and complex approval process for license application; and distance from American global headquarters.

Challenges in the design of the next generation of clinical trials

Speaking about lessons learned from recent clinical trials, Dr Federico Cappuzzo of the Istituto Toscano Tumori, Ospedale Civile, Livorno, Italy, said that some failures have been found in unselected patients, but that good efficacy has been observed in targeted population. As examples of phase III trials with new targeted agents in unselected NSCLC patients in whom there were no effect on overall survival, he mentioned gefitinib, erlotinib, bexarotene, sorafenib, figitumumab and ASA 404. Cetuximab has shown to have minimal benefit in the same population and bevacizumab has shown a mixed effect.

Dr Cappuzzo concluded that drug development should be fast with patient selection based on tumour biology; studies should be multicentric with mandatory tissue collection. Contribution to clinical trials that mandate tissue is possible for most community sites. Archival tissue, as opposed to new biopsy, is more likely to succeed in the community setting but new tissue is preferable. New sources for biomarker testing are highly recommended (e.g. plasma, effusions,…). Drug toxicity remains a relevant issue when exploring the efficacy of targeted agents.

Bone metastasis in NSCLC: Bisphosphonates and beyond

Dr Vera Hirsh of the McGill University Health Centre in Montreal, Canada discussed the results from a phase III randomised clinical trial in patients with solid tumours (excluding breast and prostate cancer, as well as multiple myeloma) and bone metastases which showed that denosumab was superior to zoledronic acid in delaying time to first on-study skeletal-related event (SRE) and time to first and subsequent SREs.

In an exploratory analysis of a large subgroup of patients bone metastases and either NSCLC or small-cell lung cancer (SCLC), denosumab was associated with significantly improved OS vs. zoledronic acid and better pain control.

Preclinical investigation is underway to evaluate if RANKL inhibition has a direct antitumour effects on lung cancer cells (e.g. apoptosis, inhibition of cancer migration/invasion).

New bone targeted agents such as dasatinib (anti src), RAD 223 (alpha emitter), ACE 011 (Sotatercept) and cabozantinib (anti RET fusion) warrant further investigation.

Thymoma

Dr Giuseppe Giaccone of the Georgetown University Medical Center in Washington DC, USA, highlighted that surgery is the mainstay of treatment in thymoma. In stage I and II, R0 resection rate is close to 100% and recurrence rate less than 10%. However, R0 resection and recurrence rates in stage III and IVA are variable, probably due to the range of experience of centres. There is no role for adjuvant radiotherapy in R0 resected stage I and II disease. Its role is controversial in R0 stage III and it is probably useful in case of R1 resection. In stages III and IVA a good response, increased R0 resection and survival are achieved by preoperative chemotherapy, followed with surgery and adjuvant radiotherapy.

For advanced thymomas cisplatin-containing regimens are most active. Cisplatin, doxorubicin and cyclophosphamide (PAC) regimen has an overall response rate of 50%. The overall 5-year survival rate is only 32-36% in advanced thymomas and 24% in thymic carcinomas even after multimodality therapy. New therapies are needed for the treatment of thymic malignancies and properly conducted phase II studies are necessary.

Dr Giaconne also summarised the results of clinical trials of targeted therapy in thymic malignancies. Activity of octreotide plus prednisone has been shown in octreotide-scan positive thymomas. Activity of cixutumumab has been shown in thymomas and for sunitinib in thymic carcinomas. The biology needs further exploration, in particular the development of more cell lines and in vivo models. Unfortunately, targeted sequencing of known cancer genes did not identify recurrent targetable gene alterations.

Highlights from abstract-related sessions

PD-L1 and PD-1 expression in a cohort of molecularly selected NSCLC patients

A group of Italian and Swiss researchers have found a correlation between PD-L1 expression and EGFR mutation, and between PD-1 expression and KRAS mutations in a cohort of molecularly selected patients with NSCLC. Their findings support a rationale for investigating anti-PD-L1 and anti-PD-1 agents in combination with targeted therapies. The results were presented by Dr Armida D'Incecco of the Department of Medical Oncology, Istituto Toscano Tumori in Livorno, Italy in a proffered papers session.

The cohort included 56 (44.8%) patients with EGFR mutated tumours, 29 (23.2%) KRAS mutated patients, 10 (8.0%) patients with ALK translocation and 30 (24.0%) EGFR/KRAS/ALK wt patients (triple-negative).

PD-L1 and PD-1 expression was assessed by immunohistochemistry, and considered positive with a staining intensity ≥ 2 in more than 5% of cells.

PD-L1 positive expression was observed in 54.4% cases. The researchers found that PD-L1 positivity was significantly associated with presence of EGFR mutations ($p < 0.0001$), while no association was observed with other biomarkers.

PD-1 expression was demonstrated in 34.4% cases. PD-1 positive expression was significantly associated with KRAS mutated status ($p = 0.005$), while no association was observed with other biomarkers.

Among patients treated with gefitinib or erlotinib who were evaluable for response analysis, there were 51.6% positive for PD-L1 expression. They achieved a significantly higher response rate (61.2% versus 34.8%, $p = 0.010$), a significantly longer time to progression (11.7 months versus 5.7 months, $p < 0.0001$) and longer OS (21.9 months versus 12.5 months, $p = 0.087$) compared to PD-L1 negative patients.

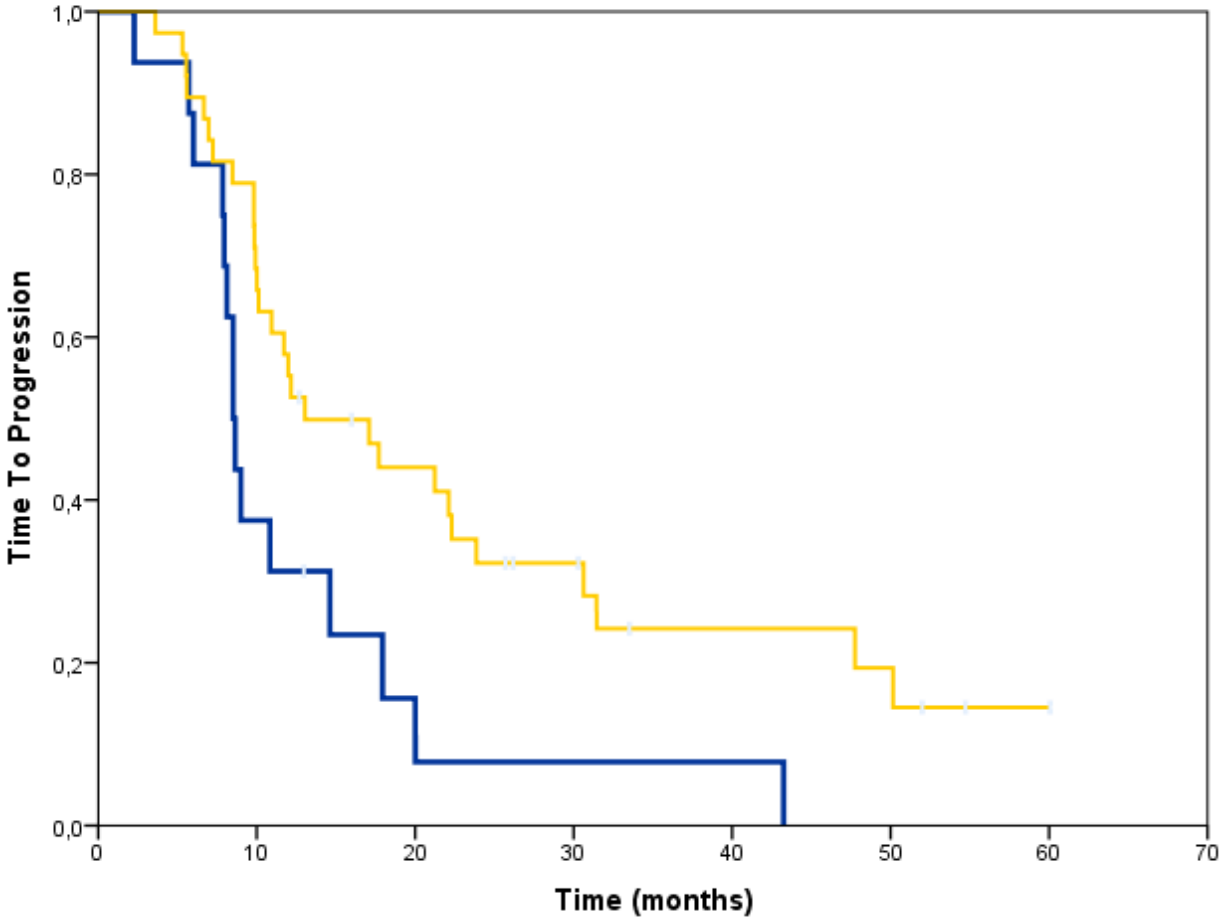
In the subset of EGFR mutated patients treated with EGFR TKIs and evaluable for response, those who were PD-L1 positive (70.9%) showed a longer time to progression (13.0 months versus 8.5 months, $p = 0.011$). The OS was 29.5 months in PD-L1 positive compared to 21.0 months in PD-L1 negative patients. However, no differences were identified in PD-1 positive versus PD-1 negative patients.

PD-1 and PD-L1 expression differ according to clinical and biological characteristics; PD-1 positive patients were generally male, smokers, with adenocarcinoma histology and KRAS mutated disease; while PD-L1 positive patients were generally female, never/former smokers, with adenocarcinoma histology and EGFR mutated or ALK translocated disease.

Dr Fred Hirsch, who discussed the study results said that PD-L1/PD-1 immunohistochemistry needs validation, as no assay is fully validated yet. In addition, he presented PD-L1 expression and driver mutation "map" in NSCLC - a knowledge modified from the work presented by

Kowanetz et al. at 2013 World Conference on Lung Cancer. In lung adenocarcinoma, approximately 47% of the immune infiltrate is PD-L1. Approximately 70% of these PD-L1 positive tumours are also MET positive, KRAS mutant or EGFR mutant. Further, PD-L1 positive NSCLC also expresses other immune checkpoints such as TIM3, LAG-3, B7-H3, B7-H4, and CTLA-4.

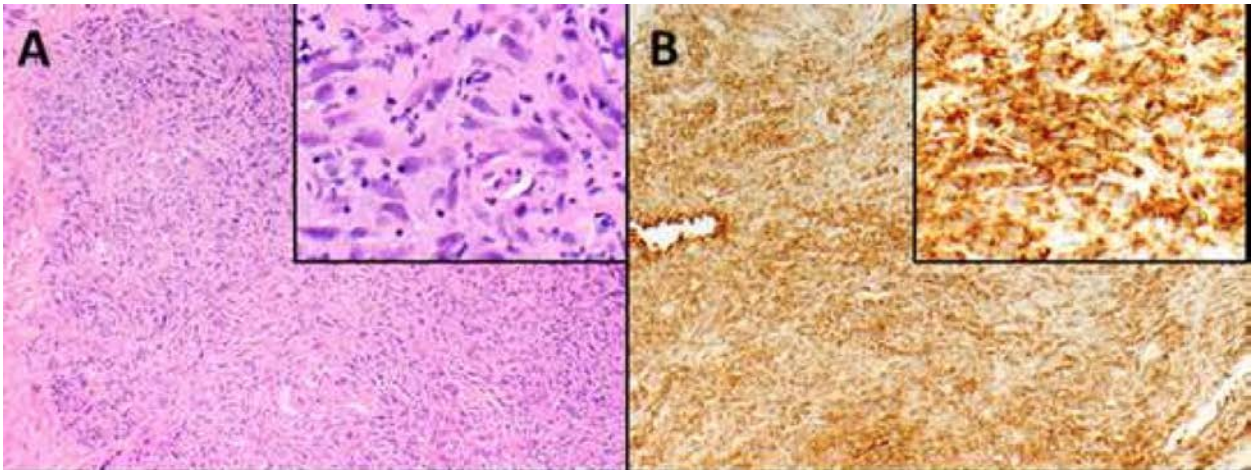
Dr Hirsch pointed out that the study of D'Incecco and colleagues opens an interesting hypothesis that PD-L1 and PD-1 expressing tumours may be two different diseases. Although analysis was done in a small subset, the results are interesting and suggest a correlation between PD-L1 expression and EGFR mutation, as well as between PD-1 expression and KRAS mutations, supporting the idea for further investigation of anti-PD-L1 or anti-PD-1 agents in combination with targeted therapies.



Graph showing time to progression with PD-L1. Although the study sample is small, time to progression was more favourable in PD-L1 positive and EGFR mutated patients treated with EGFR-TKIs (yellow line) than in PD-L1 negative patients (blue line) (8.5 vs. 13 months, p = 0.01). © Armida D'Incecco

PD-L1 expression and association with survival in mesothelioma

Data from the Mayo Clinic, Rochester, USA, shows that PD-L1 is expressed in a substantial number of cases with malignant pleural mesothelioma. In addition, it is associated with poor survival. The researchers led by Dr Aaron Mansfield believe their findings may have important implications for the management of these patients due to availability of agents that target PD-1:PD-L1 interactions. The results were presented in a proffered papers session.



PD-L1 immunohistochemistry staining. © Aaron Mansfield

Diagnosis and targeting lung adenocarcinoma with RET fusion

In a large number of lung adenocarcinoma samples the incidence of RET fusion, as detected by routine diagnostics, was higher than expected, according to a report by Dr Oliver Gautschi of the Clinic for Oncology, Kantonsspital, Luzern, Switzerland, presented during a proffered papers session.

Experience with diagnosis of lung adenocarcinoma with RET fusion and targeted therapy application in this setting is limited. RET fusion is an oncogenic driver in a subset of lung adenocarcinomas. Several RET inhibitors were active in preclinical models and the activity was reported for cabozantinib in several clinical cases.

In November 2012, the investigators integrated RET and KIF5B commercial fluorescence in-situ hybridisation (FISH) probes into diagnostic test algorithms for primary lung adenocarcinoma. Positive cases were recorded from the databases, and clinical outcomes were collected from patients who received RET inhibitors on an individual compassionate use or off-label use basis.

The researchers performed next generation sequencing on selected diagnostic and repeat biopsy samples, to identify RET kinase mutations and fusion partners. All patients with targeted therapy consented to treatment, translational research and publication.

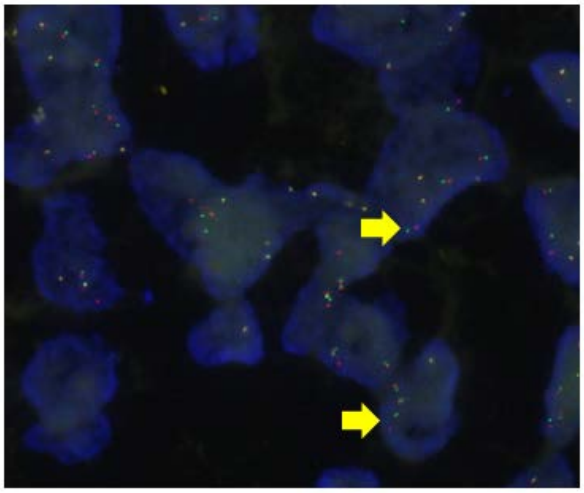
Until November 2013, they analysed by RET-FISH 529 tumour samples. In total, 12 (2.3%) samples were positive by FISH, and none carried a secondary mutation in EGFR, HER2, KRAS, BRAF, ALK, or ROS1.

Four patients with RET fusion and previous chemotherapy received one or more lines of targeted therapy with RET inhibitors after standard treatment. From those, one patient received sunitinib and achieved prolonged disease stabilisation still being alive after follow-up of 56 months, while three patients received vandetanib as first targeted therapy and two of whom had benefit in terms of response. Those three patients received cabozantinib as a second targeted treatment after progression on vandetanib. Two of them achieved partial response to cabozantinib with death recorded at 36 and 34 months after diagnosis. One patient started with ponatinib recently and this patient is alive 50 months from diagnosis.

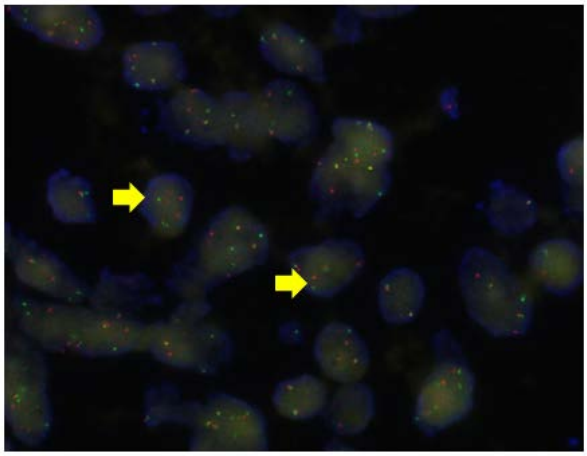
Tumour rebiopsy was performed in all three patients after targeted therapy. No secondary RET mutations have been identified so far.

Chemotherapy is currently standard of care in these patients. The study researchers alerted clinicians that the activation of a global phase II trial with cabozantinib in RET fusion positive lung cancer is ongoing and asked them to refer patients to centres participating in the study.

Dr Mark Kris, who discussed the findings, congratulated the authors for joining forces between institutions. Regarding RET diagnostic screening strategies, he said that immunohistochemistry is ineffective, RT-PCR detects specific fusions, while FISH detects fusion variants. Next generation sequencing is useful for upstream partner identification and concurrent oncogene/tumour suppressor gene aberration identification.



FISH RET analysis shows RET rearrangement. © Joachim Diebold



FISH analzsis shows KIF5B fusion partner. © Joachim Diebold

Phase I study of CO-1686 in patients with EGFR mutated recurrent, advanced NSCLC

CO-1686 has demonstrated a good tolerability and promising efficacy in T790M-positive EGFR mutant NSCLC. It spares wt EGFR signalling according to a presentation given by Dr Heather Wakelee of Thoracic Oncology Unit, Stanford University, USA.

Efficacy of existing EGFR TKIs in NSCLC is limited by the emergence of the T790M mutation in approximately 60% of patients. In addition, skin rash and diarrhoea are significant problems caused by wt-EGFR inhibition. CO-1686 is a novel, oral, selective, covalent TKI that targets common activating EGFR mutations and T790M, while sparing wt-EGFR.

The phase I part of a phase I/II study in EGFR-mutated advanced NSCLC patients has been recently completed. The study was initiated with free-base formulation and early data were presented at the 2013 World Conference on Lung Cancer. However, a superior hydrobromide (HBr) salt tablet form of CO-1686 was adopted in August 2013. All free-base recipients are still on study and converted to HBr in the autumn of 2013. Expansion cohorts are now comparing 500mg, 750mg and 1000mg HBr twice daily. The study is designed to support a potential accelerated approval in the USA.

Patients with EGFR mutated recurrent, advanced NSCLC previously treated with an EGFR TKI were enrolled. Tumour tissue biopsy was mandatory within 28 days before study drug dosing. EGFR genotyping was centrally performed. CO-1686 is administered orally, in continuous 21-day cycles.

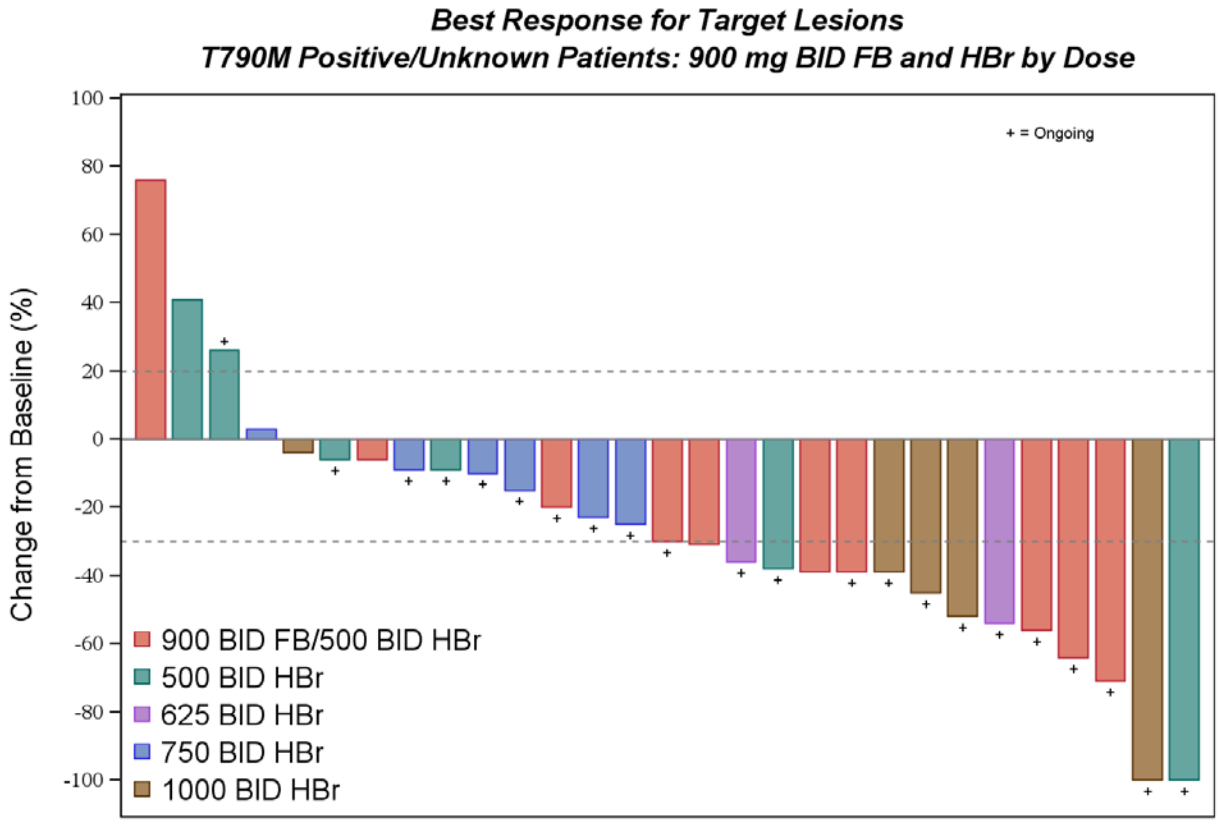
Phase I patient characteristics indicate that approximately 75% immediately terminate TKI therapy on progression, with progressive TKI resistance. Median number of previous TKI lines is two. In total, 62 patients are included with a mean age of 59 years. Females comprise 77% of study population and Asian patients, 16%. ECOG performance status 0 was recorded in 27% of patients.

CO-1686 is very well tolerated with hyperglycaemia (grade 3 in 19%) which is typically asymptomatic and managed with a single oral agent. Aetiology of the hyperglycaemia is currently unknown. Other toxicities observed (nausea, diarrhoea, decreased appetite, vomiting, fatigue and myalgia) were mild in most cases. Percentage of diarrhoea and rash indicate no wt EGFR inhibition and the compound represents a truly third-generation of EGFR TKIs. QTc prolongation grade 3 was observed in 5% of patients and resolved in most cases upon dose reduction. However, only one patient discontinued drug due to adverse events.

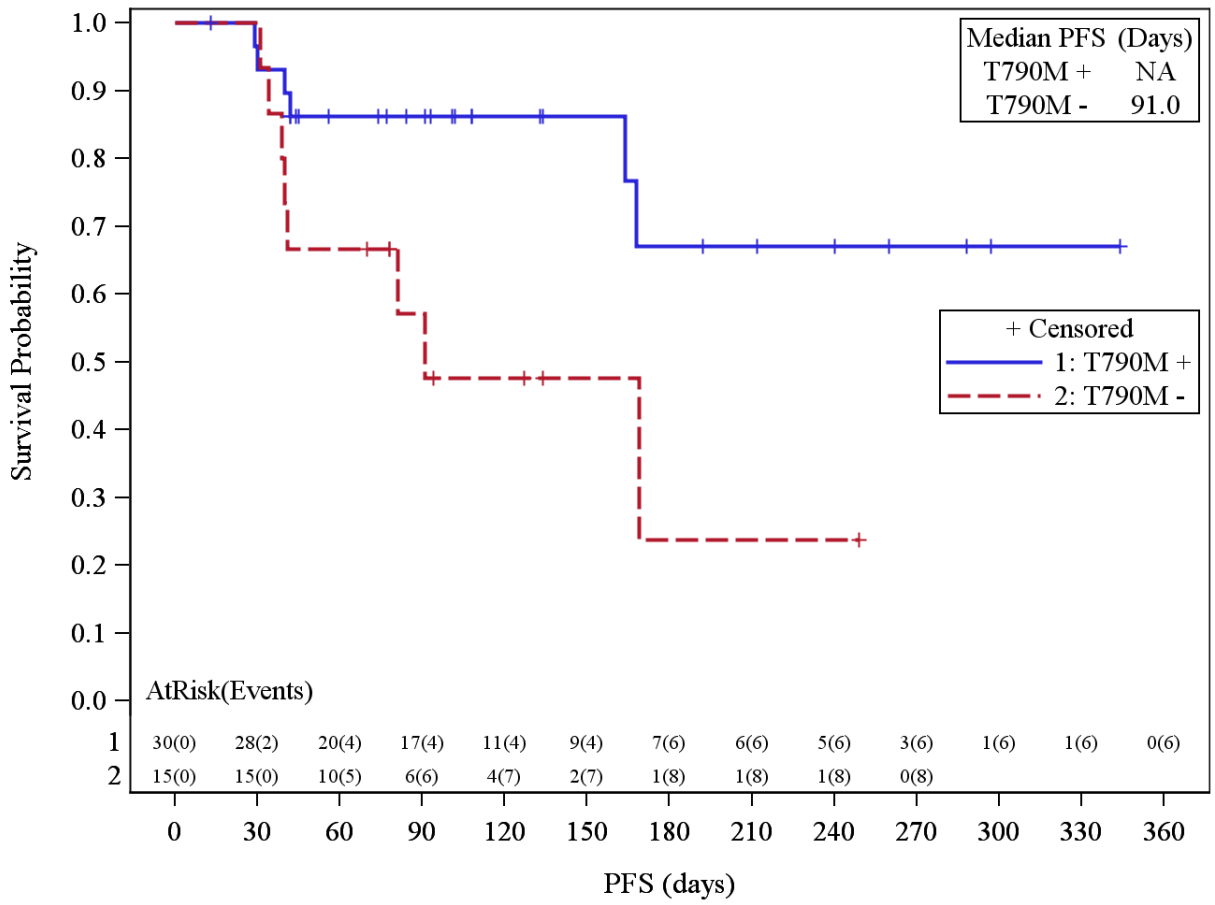
In term of efficacy, it is clear that responses deepen over time. So far, HBr shows a consistent clinical benefit; the data with HBr are immature with >80% of patients still being still ontreatment. Efficacy is clear across all dose levels in centrally-confirmed T790M-positive patients with an ORR of 64%. The response rate remains above 50% even when patients with currently T790M-unknown status are included. Median PFS exceeds six months in T790M-positive patients.

Dr Wakelee listed the phase II/III registration trials which are planned to enrol the patients this year. TIGER1 is a phase II/III study in newly diagnosed EGFR-mutated NSCLC, 1:1 randomisation CO-1686 vs. erlotinib; the primary endpoint is PFS. TIGER2 is a phase II study planned for patients progressing upon first and only TKI treatment with biopsy-proven T790M+ disease; the primary endpoint is ORR. TIGER3 is a phase III study in patients who have progressed on doublet chemotherapy or TKI in T790M+ and T790M- setting. Randomisation will be CO-1686 versus chemotherapy. TIGER4 is a phase II study in the plasma T790M+ setting with a patient population similar to the TIGER2 trial.

Dr Tony Mok, who discussed the study results, compared CO1686's characteristics - as a third generation TKI inhibitor - with the characteristics of first generation TKIs (gefitinib and erlotinib) and second generation TKIs (afatinib, dacomitinib). He characterised the response rate observed with CO1686 as impressive, and emphasised the need to develop T790M as a companion biomarker. As unanswered questions, he wonders if CO1686 works in T790M negative tumours and if yes, why? He also questioned if a T790M EGFR TKI should be used as first line treatment for patients with only sensitising EGFR mutation.



Response rate above 50% observed even when patients with T790M-unknown status (for whom central testing results are awaited) are included in the analysis. © Heather Wakelee

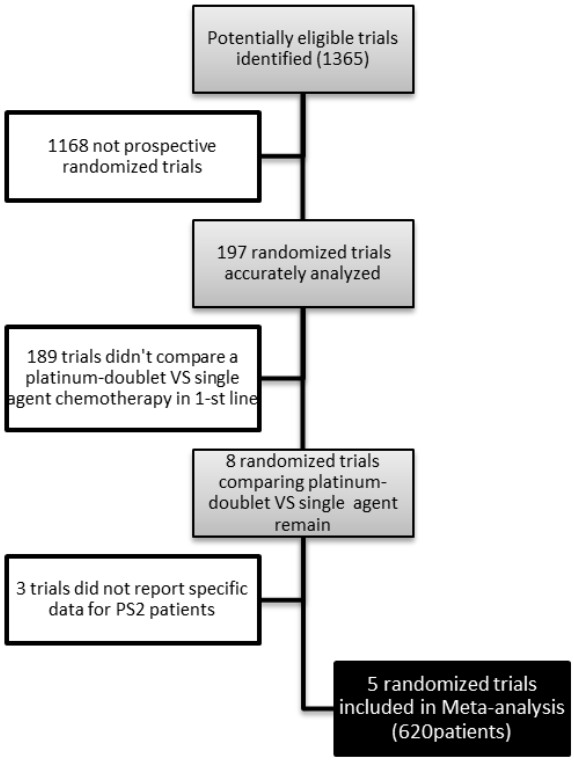


Durable benefit with median PFS that exceeds 6 months in T790M-positive patients. © Heather Wakelee

A meta-analysis of platinum-based vs. single agent chemotherapy in NSCLC patients with performance status 2

A literature-based meta-analysis of randomised trials comparing platinum-based doublets and single-agent chemotherapy, performed by Prof. Christian Rolfo of Phase I - Early Clinical Trials Unit, Antwerp University Hospital in Edegem, Belgium and colleagues from Italy, suggests that carboplatin-based combination regimens are a feasible treatment option in first-line therapy of wt patients with NSCLC with PS 2. The results were presented in a general poster session.

The findings suggest that platinum-based combination regimens are superior to single-agent chemotherapy, both in terms of ORR and survival rate, however they are associated with increase in severe haematological toxicities. The authors underlined the need to better understand which factors induce a worse PS, e.g. comorbidities or tumour burden. It is of paramount importance to select a favourable subgroup of patients who can better tolerate platinum-based doublet chemotherapy.



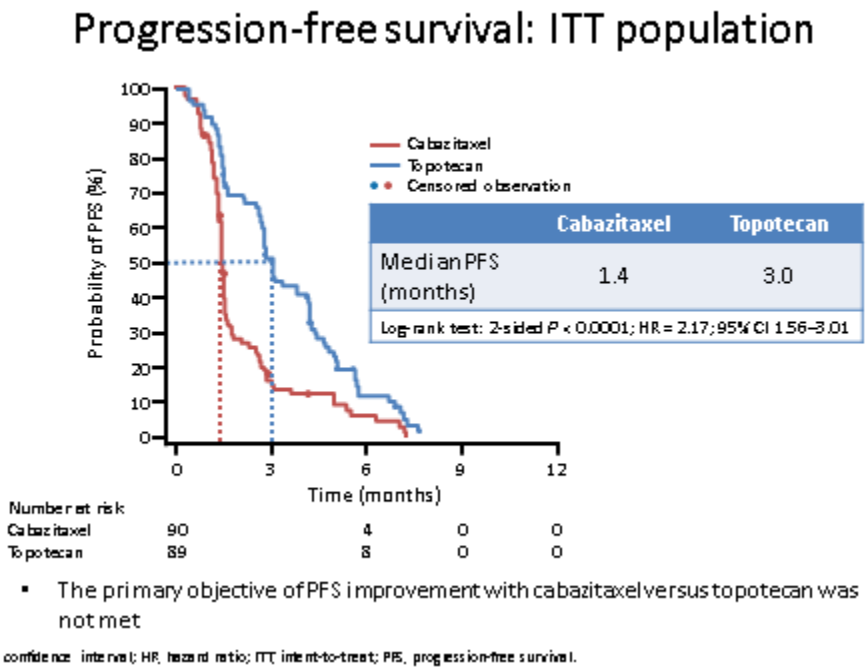
Flow-chart of trials selection. © Christian Rolfo

Quality of life in ENSURE study of first-line erlotinib vs. gemcitabine/cisplatin in Asian patients with EGFR mutation-positive NSCLC

ENSURE, a randomised, phase III study, met its primary endpoint of improved PFS with erlotinib vs. gemcitabine/cisplatin in Asian patients with EGFR mutation-positive NSCLC. Quality of life is important in assessing treatment benefit and its assessment in the ENSURE study is associated with improved domains that favour elotinib to gemcitabine/cisplatin. The findings were presented by Dr Yi-Long Wu of the Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences in Guangzhou, China, on behalf of researchers from multiple sites in Asia in a proffered papers session.

Cabazitaxel fails to meet the primary endpoint in a randomised phase II study in SCLC patients

Cabazitaxel failed to meet its primary endpoint of showing superior PFS and additionally showed less favourable median OS compared to topotecan in an international, randomised open-label phase II trial performed in patients with SCLC, who had progressed during or after first-line platinum-based chemotherapy. The results were presented by Dr Tracey Evans of the Perelman Center for Advanced Medicine, University of Pennsylvania, Philadelphia, USA in a proffered papers session.



The primary objective of PFS improvement with cabazitaxel vs. topotecan was not met. © Tracey Evans

Dr Pilar Garrido, who discussed the study results, said that a strong signal forcabazitaxel activity in SCLC was not actually seen in phase I studies. She said that SCLC is a genetically complex cancer. The oncology community should focus on identifying the underlying mechanism for rapid development of resistance to find more effective treatments for SCLC patients.

Related information

The conference abstracts can be found in Journal of Thoracic Oncology 2014; 9 (Suppl. 1): http://journals.lww.com/jto/toc/2014/04001

Click here to access the meeting webcast page: http://oncologypro.esmo.org/Meeting-Resources/ELCC-2014

All ELCC 2014 news can be found here: http://www.esmo.org/Conferences/Past-Conferences/ELCC-2014-Lung-Cancer/News-Videos

Save the date: ELCC 2015 European Lung Cancer Conference organised by the European Society for Medical Oncology (ESMO) and the International Association for the Study of Lung Cancer (IASLC) in partnership with European Society for Radiotherapy & Oncology (ESTRO), European Society of Thoracic Surgeons (ESTS) and European Thoracic Oncology Platform (ETOP), 15-18 April 2015, Geneva, Switzerland. http://www.esmo.org/Conferences/ELCC-2015-Lung-Cancer

Affiliation and disclosure

Dr Svetlana Jezdic, ESMO Head Office.

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