

ESMO 2014 Congress Scientific Meeting Report – Lung Cancer Extract

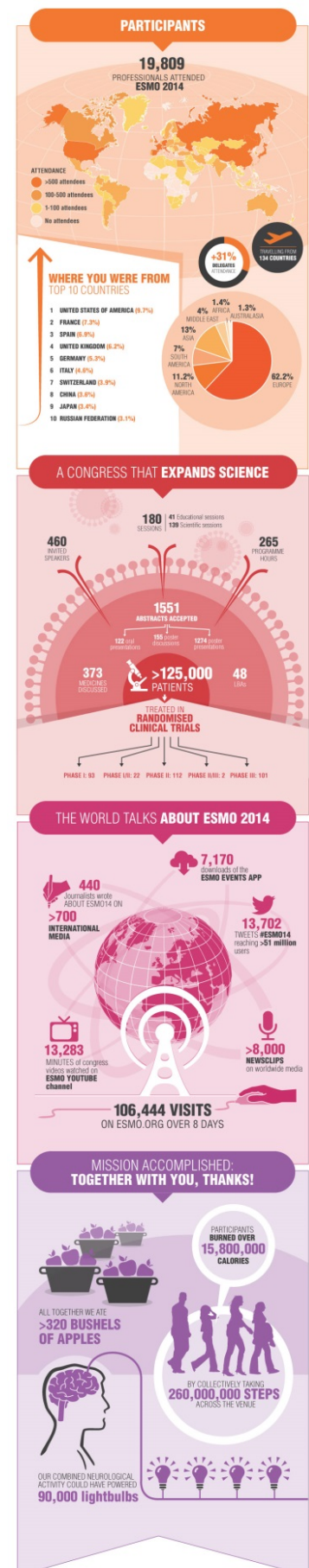
26-30 September 2014

Madrid, Spain

Summary

The European Society for Medical Oncology (ESMO) Congress, held September 26 to 30 in Madrid, Spain, was a record-breaker on nearly all levels. It was resounding success and in a dedicated infographic you can find the congress statistics. A primary emphasis in the scientific programme was placed on precision medicine and how it will change the future treatment landscape in oncology. In addition, a number of scientific presentations were dedicated to cancer immunology and immunotherapy across multiple tumour types. This report is an overview of key scientific presentations made during the congress by leading international investigators. It attempts to represent the diversity and depth of the ESMO 2014 scientific programme, as well as advances in oncology.

Infographic (right): ESMO 2014 record breaking Congress



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Lung Cancer

Final results of the SAKK 16/00 trial: A randomised phase III trial comparing neoadjuvant chemoradiation to chemotherapy alone in stage IIIA/N2 NSCLC

Prof. Miklos Pless of the Kantonsspital Winterthur, Winterthur, Switzerland reported results from the first completed phase III trial that evaluated the role of induction chemoradiotherapy and surgery, in comparison to neoadjuvant chemotherapy alone followed by surgery in patients with stage IIIA/N2 NSCLC. Radiotherapy was active; it increased response, complete resection and pCR rates. However, this failed to translate into an improvement of local control, EFS or OS. Notably, surgery after induction treatment was safe, including pneumonectomy. The OS rates of the neoadjuvant regimen in the study are very encouraging, especially for a multicenter setting.

One standard option in the treatment of stage IIIA/N2 NSCLC is neoadjuvant chemotherapy followed by surgery. Swiss researchers investigated in a randomised trial whether the addition of neoadjuvant radiotherapy would improve the outcome. At ESMO 2014, they presented the final results of the study.

Patients with pathologically proven, resectable stage IIIA/N2 NSCLC, PS 0-1, and adequate organ function were randomised 1:1 to chemoradiation with 3 cycles of neoadjuvant chemotherapy (cisplatin/docetaxel) followed by accelerated concomitant boost radiotherapy with 44 Gy in 22 fractions in 3 weeks, or neoadjuvant chemotherapy alone, with subsequent surgery for all patients. The primary endpoint was EFS (from randomisation to either relapse, progression, second tumour or death).

In total 232 patients were randomised, the median follow-up was 53 months. Two thirds were men, median age was 60 years. Histology was squamous cell in 33%, and adenocarcinoma in 43%.

Response rate to chemoradiotherapy was 61% vs. 44% with chemotherapy. Among all patients 85% underwent surgery, 30-day postoperative mortality was 1%. The rate of complete resection was 91% in chemoradiotherapy patients vs. 81% in chemotherapy patients and the pCR rate was 16% vs. 12%.

The median EFS was 13.1 months for the chemoradiotherapy group vs. 11.8 months in the chemotherapy arm ($p = 0.665$). The median OS in chemoradiotherapy group was 37.1 months, and with chemotherapy 26.2 months ($p = 0.938$). The local failure rate was 23% in both arms.

In the chemotherapy arm, 12 patients were given postoperative radiotherapy for R1 resection, 6 patients received postoperative radiotherapy in violation of the protocol. Patients with a pCR, mediastinal downstaging to ypN0/1 and complete resection had a better outcome. Toxicity of chemotherapy was substantial, especially febrile neutropaenia was common, whereas radiotherapy was well tolerated.

Dr Rafal Dziadziuszko of the Medical University of Gdańsk, Gdańsk, Poland, who discussed the study results, said that the study hypothesis was that addition of sequential radiotherapy to induction chemotherapy followed by surgery improved event-free survival in potentially resectable stage IIIA/N2 NSCLC. He said that chemotherapy plus one local treatment remains the standard of care. Concurrent chemoradiation is most often used. Chemotherapy/surgery is still a valid option in selected patients (based on MDT, patient preference, comorbidities and surgical risk-assessment).

This was an investigator-led study. It was supported by the Swiss State Secretariat for Education, Research and Innovation, Swiss Cancer League (Grant KLS-2745-02-2011), and Sanofi.

Reference

1195O: Final results of the SAKK 16/00 trial: a randomized phase III trial comparing neoadjuvant chemoradiation to chemotherapy alone in stage IIIA/N2 non-small cell lung cancer (NSCLC)

Adjuvant treatment with MAGE-A3 cancer immunotherapeutic in patients with resected NSCLC does not increase DFS: Results of the MAGRIT, a double-blind, randomised, placebo-controlled phase III study

The MAGRIT global trial assessed the efficacy of the recMAGE-A3 + AS15 cancer immunotherapeutic as adjuvant therapy in patients with resected MAGE-A3-positive NSCLC. In this study, treatment with MAGE-A3 cancer immunotherapeutic did not increase DFS compared to placebo in either the overall population or in patients who did not receive adjuvant chemotherapy. The results were presented by Prof. Johann Vansteenkiste of the Respiratory Oncology Unit, University Hospitals Leuven - Campus Gasthuisberg, Leuven, Belgium.

Adjuvant chemotherapy is the standard of care for stage II and IIIA NSCLC, and for high risk stage IB NSCLC. However, the 5-year DFS rate remains poor (35-50%) and about half of the patients will not receive adjuvant chemotherapy for various reasons. Tolerability of adjuvant cisplatin-based chemotherapy is suboptimal.

MAGE-A3 is a tumour-specific antigen. It is expressed in several tumour types, including NSCLC. MAGE-A3 cancer immunotherapeutic is delivered as a recombinant protein, combined with immunostimulants.

MAGE-A3 cancer immunotherapeutic showed activity in metastatic melanoma. The double-blind, placebo-controlled, phase II trial in completely resected MAGE-A3-positive stage IB-II NSCLC showed, at 44 months follow-up, a 25% reduction in the relative risk of cancer recurrence with HR 0.75. It was very well tolerated. Predictive gene signature was discovered in metastatic melanoma and reproduced in NSCLC.

MAGRIT was a randomised, double-blind, placebo-controlled trial that investigated whether the recMAGE-A3+AS15 cancer immunotherapeutic as adjuvant therapy improves DFS in patients with completely resected (R0), anatomically resected, MAGE-A3-positive NSCLC (stages IB, II, and IIIA according to TNM classification version 6) who did or did not receive adjuvant chemotherapy (up to 4 cycles of platinum-based regimen), ECOG PS 0, 1 or 2, adequate bone-marrow reserve, renal function and hepatic function and no auto-immune disease.

MAGE-A3 status was assessed in primary tumour by RT-PCR test on formalin-fixed paraffin embedded tissue.

Patients were randomly assigned (2:1) to receive 13 intramuscular injections of MAGE-A3 cancer immunotherapeutic or placebo over a 27 month treatment period.

The three co-primary endpoints were DFS in the overall and in the no-adjuvant chemotherapy population and DFS in patients with a potentially predictive gene signature.

Secondary endpoints included OS, lung cancer specific survival, DFS, immunogenicity, safety, and health-related QoL.

In total 13,849 patients were screened and 4,210 of them had a MAGE-A3 positive tumour sample. However, 2,272 patients were randomised and treated.

One interim analysis was done which concluded that the study may continue as pre-specified boundary was not met and the treatment was well tolerated.

Overall, 52% of the patients received adjuvant chemotherapy. Stage IB disease was recorded in 47%, stage II in 36% and 17% were stage IIIA. Median age was 63 years and 24% of patients were female.

Mean relative dose intensity was above 98% in both groups throughout the treatment period.

Common adverse events present in more than 10% of patients treated with MAGE-A3 cancer immunotherapeutic vs. placebo were: pyrexia (35% vs. 5%), injection site pain (31% vs. 5%), injection site reaction (18% vs. 14%), fatigue (16% vs. 7%), pain (16% vs. 2%), influenza-like illness (13% vs. 3%), and myalgia (12% vs. 2%), respectively.

However, the rate of grade ≥ 3 adverse events did not differ between treatment groups and was below 1%.

Median follow-up at the time of final analysis was 38.8 months. In the overall study population, median DFS was 60.5 months and 57.9 months respectively for MAGE-A3 cancer immunotherapeutic and placebo (HR 1.024, $p = 0.7379$). In patients who did not receive adjuvant chemotherapy, median DFS was 58.0 months and 56.9 months for MAGE-A3 cancer immunotherapeutic and placebo groups, respectively (HR 0.970, $p = 0.7572$).

The OS in the overall population was not reached, but it might be expected to exceed median value of 5 years.

Due to the absence of treatment effect, a gene signature predictive of clinical benefit to MAGE-A3 cancer immunotherapeutic could not be identified.

The authors concluded that MAGRIT is the largest clinical trial in NSCLC and the first one to investigate immunotherapy in the adjuvant setting of early stage NSCLC. Adjuvant treatment with the MAGE-A3 cancer immunotherapeutic did not increase DFS compared to placebo in the overall population nor in patients who did not receive adjuvant chemotherapy. No benefit was observed in any subset analyses. MAGE-A3 cancer immunotherapeutic was generally well tolerated with mainly mild toxicities and no detectable increase in immune-mediated disorders. No predictive gene signature was identified in the training set. The study database is a source for further analysis on global contemporary approach to early stage NSCLC.

Prof. George Coukos of the Centre Hospitalier Universitaire Vaudois - CHUV, Lausanne, Switzerland, who discussed the study results, said that the advantages of vaccine therapy in NSCLC are low toxicity, easiness of administration, and ability to induce anti-tumour protective memory. The disadvantages are low impact at present time. Clinical indication might be in the maintenance/consolidation setting.

The normal function of MAGE-A3 is unknown, but its presence on tumour cells has been associated with a worse prognosis. The MAGE-A3 antigen is expressed in a variety of tumour cells, but not in normal tissues (except for the testes). In NSCLC, expression can be demonstrated

in 35% of early-stage tumours. The 'MAGE-A3 vaccine' is an example of a recombinant protein antigen-based vaccine.

Possible reasons for study failure, according to Prof. Coukos, are retrospective subset analysis that may be deceiving, monovalent molecularly defined vaccines might be too weak to make an impact, metastatic or progressive tumours may be immune escape variants, and/or it could be due to epigenetic mechanisms (association between methylation and lung cancer recurrence).

Prof. Coukos discussed future of vaccines in NSCLC, in particular awaiting the results from other monovalent molecularly defined vaccines and developing polyvalent molecularly defined vaccines.

High mutational rates may contribute to increased immunogenicity. Melanomas and lung tumours display many more mutations than average, with approximately 200 non-synonymous mutations per tumour. These larger numbers reflect the involvement of potent mutagens. Lung cancers in smokers have 10 times as many somatic mutations as those from non-smokers.

Therefore, the future opportunities for vaccines in NSCLC, according to Prof. Coukos, are personalised molecular vaccines based on mutanome analysis and autologous whole tumour antigen vaccines designed to address specific mutations.

GlaxoSmithKline Biologicals SA was the funding source in all stages of the study/project conduct and analysis.

Reference

1173O: MAGRIT, a double-blind, randomized, placebo-controlled Phase III study to assess the efficacy of the recMAGE-A3 + AS15 cancer immunotherapeutic as adjuvant therapy in patients with resected MAGE-A3-positive non-small cell lung cancer (NSCLC)

TARGET: A phase II trial with vintafolide in second-line treatment of folate-receptor-positive NSCLC

A randomised, phase II trial comparing vintafolide vs. vintafolide plus docetaxel vs. docetaxel alone in second-line treatment of folate-receptor-positive NSCLC showed clinically meaningful improvement across all efficacy endpoints (ORR, PFS, and OS) with vintafolide/docetaxel over single-agent docetaxel treatment. The largest benefit was observed in the adenocarcinoma subgroup. The results were presented by Dr Nasser Hanna of the Department Of Medicine, Indiana University, Indianapolis, USA.

The folate receptor is expressed in many epithelial cancers, including NSCLC, and may be a useful biomarker for therapy selection.

Vintafolide, a folate-vinca alkaloid drug conjugate, is a folate receptor-targeted drug. Its companion imaging agent, 99mTc-etarfolatide, enables non-invasive imaging of folate receptor expression.

The TARGET study assessed the benefit of folate receptor-targeted therapy in 199 second-line NSCLC patients with all target lesions expressing folate receptor (100%).

Patients were randomised 1:1:1 to vintafolide, vintafolide plus docetaxel, or docetaxel alone.

Vintafolide was administered on day 1, 4, 8, and 11 and docetaxel on day 1 of a 3-week cycle.

The primary endpoint was PFS; secondary endpoints included OS and ORR. The significance level of each PFS and OS analysis was one-sided $\alpha = 0.10$ with no multiple testing adjustments.

The ORR in the vintafolide/docetaxel arm was 22% in the overall study population; HR for PFS was 0.75 ($p = 0.0696$); and median OS 11.5 months. In the adenocarcinoma subgroup, the ORR was 21%, the HR for PFS 0.73 ($p = 0.0899$) and median OS 12.5 months.

With the pre-specified stratified analysis adjusting for baseline factors (time since last chemotherapy, best response and stage), the OS HR for vintafolide/docetaxel vs. docetaxel were 0.75 (1-sided $p=0.1066$) for all patients, and 0.51 (1-sided $p=0.0147$) for the predefined adenocarcinoma patient subgroup.

Prof. Giorgio Scagliotti of the University of Torino at San Luigi Gonzaga Hospital Regione Gonzole 10, Orbassano, Italy, who discussed the study results, spoke about real-time identification of tumour lesions and response to vintafolide treatment. He said that there was no assessment of any genomic alteration in patients with adenocarcinoma. In addition, there was no information on post-study therapy. In second-line therapy there is still a huge room for improvements in terms of selecting candidate patients and treatments, he concluded.

The study was sponsored by Endocyte, Inc.

Reference

LBA40 PR: TARGET: A randomized, phase II trial comparing vintafolide versus vintafolide plus docetaxel, versus docetaxel alone in second-line treatment of folate-receptor-positive non-small cell lung cancer (NSCLC) patients

BRF113928: A phase II study with dabrafenib in patients with BRAF V600E-mutant advanced NSCLC

Dabrafenib is the first drug of its class to show activity in a prospective trial of NSCLC with BRAF mutations. Treatment of BRAF V600E mutated advanced NSCLC patients with dabrafenib demonstrated significant anti-tumour activity with durable objective responses and an acceptable safety profile in a multicenter, open-label, phase II trial. The findings were reported by Dr David Planchard of the Medical Oncology Department, Institut Gustave Roussy, Villejuif, France.

Activating BRAF V600E mutations in NSCLC are present in approximately 1.5% of tumours, primarily adenocarcinomas, offering an opportunity to test targeted therapy in this subset of patients.

This single-arm, 2-stage design, phase II study enrolled stage IV BRAF V600E-mutant NSCLC patients determined by local laboratory testing.

The primary endpoint was investigator-assessed ORR per RECIST v1.1 criteria.

As of 30 April 2014, 84 patients (female 52%, median age 66, ECOG PS 0–1 86%, Asian 21%, never-smoker 37%, adenocarcinoma histology 96%) were enrolled in the study since August 2011.

Median duration of treatment was 4.3 months (range, 0.3–25.2) with 21 (25%) patients still on treatment.

Six patients had not received any prior regimen for metastatic disease (first-line), 40 patients had one line and 38 patients had received ≥ 2 lines (range 2–9).

The ORR for 78 patients with more than one line of prior therapy (second-line plus patients) was 32%. All of these 25 patients experienced PR. The DCR longer than 12 weeks was 56%. Median DoR was 11.8 months (95% CI 5.4–not reached) with 48% of responders progressed.

Based on assessment by independent review committee, 64 second-line plus patients had measurable disease; ORR and DCR were 28% and 52% respectively, and median DoR has not been reached.

Among the six first-line patients, four patients had measurable disease based on independent review committee with three PRs.

Most common (>25%) adverse events were pyrexia (36%), asthenia (30%), hyperkeratosis (30%), decreased appetite (29%), nausea (27%), cough (26%), fatigue (26%) and skin papilloma (26%). Cutaneous squamous-cell carcinomas, including keratoacanthoma, were reported in 18%.

Grade ≥ 3 adverse events occurred in 45% with one event of grade 5 intracranial haemorrhage.

Dr Enriqueta Felip of the Vall d'Hebron University Hospital Institut d'Oncologia, Barcelona, Spain, who discussed the study results, said that BRAF V600E mutations are present in 1.5% of NSCLC and are mutually exclusive to other driver alterations. BRAF mutations identified in NSCLC are V600E (50%), G469A (40%), D594G (10%). In this study, dabrafenib showed clinically meaningful anti-tumour activity in BRAF V600E mutated NSCLC.

Dr Felip highlighted the recommendation from the 2nd ESMO Consensus Conference on Lung Cancer about optimal treatment for patients with ROS1, RET, BRAF or HER2 genomic alterations after standard treatment: Specific targeted treatments should be discussed with the patients and may be considered in individual patients based on expected risk-benefit, biological plausibility, preclinical data, and limited clinical efficacy data for authorised therapies in different indications.

Dr Felip questioned if in patients with uncommon alterations there is a need for randomised trials if there are good results from single arm phase II trials.

Next steps for researchers would be identification of acquired resistance mechanisms to BRAF inhibitors, testing anti-PD1 and anti-PDL1 strategies and combination of targeted therapies. In the latest one, there is a trial in which a cohort B with dabrafenib/trametinib is actively recruiting.

The study was sponsored by GlaxoSmithKline.

Reference

LBA38 PR: Dabrafenib in patients with BRAF V600E-mutant advanced non-small cell lung cancer (NSCLC): A multicenter, open-label, phase II trial (BRF113928)

A phase II study of neratinib with or without temsirolimus in patients with NSCLC carrying HER2 somatic mutations

In a phase II international randomised study of neratinib with or without temsirolimus in patients with NSCLC and tumours carrying HER2 somatic mutations, the combination therapy with neratinib/temsirolimus met the efficacy criteria in stage 1 study and has been subsequently expanded into stage 2. The results were presented by Dr Benjamin Besse of the Department of Cancer Medicine, Institut Gustave Roussy, Villejuif, France.

Somatic HER2 mutations occur in approximately 2-4% of patients with NSCLC.

In vivo data suggest that combined HER2/mTOR inhibition have synergistic effects in HER2-driven lung tumours. In a phase I study, 5 of 7 HER2-mutated NSCLC patients showed tumour regression (PR/SD) after treatment with neratinib, an irreversible pan-HER TKI and mTOR inhibitor, temsirolimus. However, the effects of neratinib alone are unknown.

This randomised 2-stage phase II study compared neratinib with or without temsirolimus in patients with stage IIIB/IV NSCLC and HER2 somatic mutations.

Patients whose tumours had a documented HER2 mutation were randomised 1:1 to receive oral neratinib 240 mg once daily continuously with or without temsirolimus i.v. 8 mg/week, escalated to 15 mg/week after one 3-week cycle if tolerated.

Addition of temsirolimus was permitted in patients assigned to neratinib alone after progression.

High-dose loperamide prophylaxis for diarrhoea was mandatory throughout cycle 1.

The primary endpoint was ORR. Secondary endpoints included: clinical benefit rate, PFS, and safety.

It was foreseen if ≥ 2 of 13 patients in each arm have a response at 12 weeks in stage 1, a further 26 patients per arm will be enrolled in stage 2.

In stage 1, 27 patients were enrolled (13 in the neratinib arm and 14 in the combined neratinib/temsirolimus arm) with approximately 12 weeks between randomisation of last patient and data cut-off.

Baseline characteristics of these 27 patients included in stage 1 were: male/female 52%/48%; median age 65 year; never smokers 63%. Two patients, both in the neratinib/temsirolimus arm, had not received prior anticancer medications.

In stage 1, ORR was 21% in the neratinib/temsirolimus arm vs. 0% in the neratinib arm. PR was observed in 3 patients in the combined arm and none in the neratinib arm alone. SD was recorded in 6 patients in the combined arm and 4 patients in the neratinib arm.

Median PFS was 4.0 months in the neratinib/temsirolimus arm and 2.9 months in the neratinib arm.

In all 27 patients, the most common all-grade adverse events were diarrhoea, constipation, nausea, dyspnoea, asthenia, and vomiting. Most common grade 3/4 adverse events were dyspnoea, diarrhoea (grade 3 only), vomiting, and nausea.

Grade 3 diarrhoea was recorded in 2 patients in the neratinib/temsirolimus arm and 1 patient in the neratinib arm. It was not a limiting toxicity with aggressive upfront management.

Dr Enriqueta Felip of the Vall d'Hebron University Hospital Institut d'Oncologia, Barcelona, Spain, who discussed the study results, said that NSCLC is divided into subsets by the presence of molecular alterations (EGFR, ALK, KRAS, ROS1, RET, HER2, BRAF, NTRK1, FGFR, among others). Challenges are reflected in genotyping, some molecularly defined subsets are rare and a clear effort is required to identify these patients. There are few trials in these uncommon molecular alterations and directing patients to targeted trials requires collaboration.

HER2 mutations are present in 2% of NSCLC. They are mutually exclusive with other driver alterations. Potential synergistic effect of combined HER2 and mTOR inhibition has been

observed in preclinical models of HER2 mutated NSCLC. In this study encouraging results were seen with the inhibition of both the HER2 and the PI3K pathway. She concluded that neratinib/temsirolimus combination deserves further development in HER2 mutated NSCLC.

The study sponsor was Puma Biotechnology, Inc.

Reference

LBA39 PR: Neratinib (N) with or without temsirolimus (TEM) in patients (pts) with non-small cell lung cancer (NSCLC) carrying HER2 somatic mutations: An international randomized phase II study

IMPRESS: Continuation of gefitinib plus pemetrexed/cisplatin of no clinical benefit in NSCLC patients with acquired resistance to gefitinib

The IMPRESS study is the first and only randomised phase III trial to confirm that continuation of gefitinib in addition to pemetrexed/cisplatin would be of no clinical benefit for patients with NSCLC and acquired resistance to gefitinib. The results were reported by Prof. Tony Mok of the Clinical Oncology Department, The Chinese University of Hong Kong, Hong Kong, China.

The study design was previously presented at the 10th Annual Meeting of the Japanese Society of Medical Oncology, 26–28 July 2012, Osaka, Japan. The latest findings presented as a late breaking abstract at ESMO 2014 report on previously unpublished primary and secondary analysis data.

Most patients with EGFR mutation-positive NSCLC respond to first-line EGFR tyrosine kinase inhibitors (TKIs), but later acquire resistance. Optimal management for patients with acquired resistance has yet to be defined, and options include:

- Discontinuing EGFR TKI therapy and commencing platinum-based doublet chemotherapy
- Continuing EGFR TKI therapy in combination with platinum-based doublet chemotherapy.

The second option is suggested to be beneficial because of the potential tumour heterogeneity at the time of EGFR TKI resistance, and it is also supported by retrospective clinical studies.

The phase III, double-blind IRESSA Mutation Positive Multicentre Treatment Beyond ProgRESSion Study (IMPRESS) evaluated the efficacy and safety of continuing gefitinib plus pemetrexed/cisplatin vs. placebo plus pemetrexed/cisplatin in patients with acquired resistance to first-line gefitinib.

Patients ≥18 years (in Japan ≥20 years) who were chemotherapy-naïve, and who had cytological or histological confirmation of locally advanced/metastatic NSCLC other than predominantly squamous cell histology with an activating EGFR mutation as determined locally, and in whom a prior disease progression was recorded on first-line treatment with gefitinib, were eligible for the study.

Exclusion criteria included prior chemotherapy or other systemic anti-cancer treatment (excluding gefitinib); palliative bone radiotherapy had to be completed at least 2 weeks before start of study treatment with no persistent radiation toxicity; past medical history of interstitial lung disease, drug-induced interstitial disease, radiation pneumonitis which required steroid treatment or any evidence of clinically active interstitial lung disease; other co-existing malignancies or malignancies diagnosed within the last 5 years, with the exception of basal cell carcinoma or

cervical cancer in situ or completely resected intramucosal gastric cancer; any evidence of severe or uncontrolled systemic disease; and treatment with an investigational drug within 4 weeks before randomisation.

Patients from 71 centres in Europe and Asia Pacific were randomised to gefitinib or placebo. The primary endpoint was PFS. Secondary endpoints included OS, ORR, DCR, safety/tolerability, health-related QoL. Exploratory analysis of biomarkers is not yet completed and will be reported separately.

The study researchers estimated that 250 patients would need to be randomised to achieve 190 PFS events (75% PFS maturity); 90% power to demonstrate superiority of gefitinib in combination with chemotherapy vs. chemotherapy alone; and 2-sided 5% significance for assuming a HR of 0.63 for median PFS of 9.5 months vs. 6.0 months.

Randomisation did not include stratification factors, but the analysis was adjusted for two covariates: age (<65 vs. ≥65 years) and prior response to gefitinib (SD vs. PR plus CR).

From March 2014 to December 2013, 265 patients were randomised, 133 in the gefitinib arm and 132 in the placebo arm. Median follow-up in the study was 11.2 months.

The patient demographics in the two arms were well balanced. However, there were more patients ≥65 years in the gefitinib arm and more patients with baseline brain metastases in the chemotherapy arm.

There was no statistically significant improvement in PFS for gefitinib vs. placebo; HR 0.86; $p = 0.273$. Median PFS was 5.4 months in each arm.

The OS was immature (33% of patients had died), with better OS for placebo vs. gefitinib (HR 1.62; $p = 0.029$).

Ad hoc PFS and OS analyses included the addition of brain metastases at baseline as a covariate (brain metastases vs. no brain metastases), but there was no difference in term of PFS.

No treatment differences were found in ORR and DCR.

The safety profile for gefitinib plus pemetrexed/cisplatin was in line with what is already known.

The most common adverse events in the safety population (132 patients in each arm) were nausea recorded in 64% in the gefitinib group and 61% in the placebo group and decreased appetite (49% in the gefitinib treated patients vs. 34% in the placebo arm). No interstitial lung disease was noted. Gefitinib was associated with increased grade 1/2 gastrointestinal toxicities.

Adverse events with outcome of death were reported, in particular 2 casually-related in the gefitinib/chemotherapy arm and 1 casually-related in placebo/chemotherapy group.

Post-discontinuation therapy in ITT population was higher in the placebo arm, where 17% of patients received platinum based regimens in comparison to 5% in the gefitinib arm, and 44% received EGFR TKI vs. 30% of patients in the gefitinib arm.

Prof. Mok concluded that continuation of gefitinib in addition to pemetrexed/cisplatin would be of no clinical benefit for patients with acquired resistance to gefitinib. The IMPRESS study showed no statistically significant improvement in PFS with continuation of gefitinib in addition to chemotherapy beyond RECIST progression to first-line EGFR TKI for patients with EGFR

mutation-positive NSCLC. The OS was immature and not conclusive. There were imbalances in post study treatment in favour of the placebo arm (more doublet platinum chemotherapies and more EGFR TKI rechallenge).

Prof. Solange Peters of the Centre Hospitalier Universitaire Vaudois - CHUV, Lausanne, Switzerland, who discussed the study results, said that there are multiple mechanisms of resistance to EGFR TKIs reported in pre-clinical and clinical trials (MET amplification, HGF overexpression, PIK3CA mutations, PTEN loss, FGFR1/2/3 overexpression, AXL overexpression, CRKL amplification, NFκB activation, BRAF mutation, anti-apoptotic pathway (BIM deletion), loss of EGFR mutant gene, HER2 amplification, PDGFRb expression, and EMT). T790M mutation causes drug resistance by increasing the affinity for ATP. Dynamics of resistance evolution and the question of heterogeneity add to complexity of the problem.

Upon discussing treatment options of EGFR TKI resistance (chemotherapy, immunotherapy, EGFR TKI beyond progression, second generation TKI, third generation TKI, targeting bypass tracks, and chemotherapy plus EGFR TKI - which was tested in the IMPRESS study), she concluded that the IMPRESS study confirms that doublet chemotherapy should continue to be the standard of care for patients who develop resistance to first-line gefitinib. According to her, first-line EGFR TKI should be continued as long as possible and EGFR TKI should be subsequently rechallenged in the course of the disease.

The study was sponsored by AstraZeneca.

Reference

[LBA2 PR: Gefitinib/chemotherapy vs chemotherapy in epidermal growth factor receptor \(EGFR\) mutation-positive non-small-cell lung cancer \(NSCLC\) after progression on first-line gefitinib: The phase III, randomised IMPRESS study](#)

New data on first- and second-line ALK inhibition in NSCLC patients

Two presentations on metastatic NSCLC discussed the use of crizotinib in the first-line setting and efficacy of a second-generation ALK inhibitor, alectinib, in patients with crizotinib-resistant disease. Patients with NSCLC and ALK gene rearranged tumours show dramatic and sustained responses to treatment with ALK inhibitors, with crizotinib being the first-in-class ALK inhibitor. Unfortunately, resistance to crizotinib invariably develops and the researchers are trying to address it with next generation ALK inhibitors.

Overall and intracranial efficacy results and time to symptom deterioration in the PROFILE 1014 study

The efficacy of first-line crizotinib in improving PFS compared with standard pemetrexed/platinum chemotherapy in patients with advanced ALK-positive NSCLC was established in the phase III PROFILE 1014 study which included 343 patients. The results were presented earlier this year during ASCO 2014. Dr Benjamin Solomon from the Peter MacCallum Cancer Centre, Melbourne, Australia, reported additional data from this study during the ESMO 2014.

Crizotinib is an oral small-molecule TKI that targets ALK, ROS1, and MET. It is approved for advanced ALK-positive NSCLC. PROFILE 1014 is the first prospective, randomised phase III trial to compare the efficacy and safety of ALK-targeted therapy with standard chemotherapy for advanced ALK-positive NSCLC in the first-line setting.

Clinical outcomes (overall and intracranial efficacy, lung cancer symptoms) with crizotinib vs. standard chemotherapy as first-line treatment were compared in this ongoing multicentre study in the whole patient population and in patient subgroups.

Patients with previously untreated advanced non-squamous ALK-positive NSCLC were randomised 1:1 to crizotinib (172 patients) or pemetrexed plus cisplatin or carboplatin (171 patients). Continuation of/crossover to crizotinib after progression of disease per independent radiology review was allowed for patients randomised to both arms.

The primary endpoint was PFS per independent radiology review. Secondary endpoints included OS, intracranial time to progression, time to deterioration in symptoms of chest pain, dyspnoea, or cough, and safety.

The study met its primary objective: crizotinib was superior to chemotherapy in prolonging PFS (median 10.9 vs. 7.0 months; HR 0.45, $p < 0.0001$). The PFS benefit with crizotinib was observed in most patient subgroups analysed. Median PFS was 6.9 months with pemetrexed/cisplatin (HR 0.49, $p < 0.0001$) and 7.0 months with pemetrexed/carboplatin (HR 0.44, $p < 0.0001$).

Objective responses with crizotinib were rapid and durable when compared with chemotherapy (74% vs. 45%). With 68% of patients still in follow-up, median OS was not reached in either arm. There was a numerical improvement in OS in the crizotinib arm (HR 0.82, $p = 0.361$).

The analysis was not adjusted for the potentially confounding effects of crossover; 70% of patients in the chemotherapy arm received crizotinib after progression.

The intracranial time to progression HR for crizotinib vs. chemotherapy was 0.60 (non-significant difference; only around 15% of patients had intracranial events). In patients with baseline brain metastases, first-line crizotinib showed a numerical improvement in intracranial time to progression and demonstrated a statistically significant improvement in intracranial DCR at 12 ($p = 0.0003$) and 24 weeks ($p = 0.006$).

The time to deterioration in symptoms was around four times longer in the crizotinib arm than in the chemotherapy arm (median 2.1 months vs. 0.5 months; HR 0.62; $p = 0.0004$).

The most common adverse events of any cause with crizotinib were vision disorder and GI symptoms. Adverse events with pemetrexed/platinum chemotherapy were consistent with those previously reported in unselected NSCLC.

The authors concluded that crizotinib showed significant improvements in PFS and the time to deterioration in symptoms vs. pemetrexed/platinum chemotherapy, a numerical improvement in intracranial time to progression, and an acceptable safety profile, establishing crizotinib as the standard of care for patients with treatment-naïve advanced ALK-positive non-squamous NSCLC.

The study was sponsored by Pfizer.

Reference

1225O: Overall and intracranial (IC) efficacy results and time to symptom deterioration in PROFILE 1014: 1st-line crizotinib vs pemetrexed - platinum chemotherapy (PPC) in patients (pts) with advanced ALK-positive non-squamous non-small cell lung cancer (NSCLC)

Antitumour activity of alectinib in crizotinib pre-treated ALK-rearranged NSCLC

Alectinib showed promising a response, including patients with brain metastases, and good tolerability in crizotinib pre-treated NSCLC patients, according to the updated efficacy and safety data from the JP28927 study. The results were presented by Dr Takashi Seto from the National Kyushu Cancer Center, Fukuoka, Japan.

Alectinib is a CNS-penetrant, highly selective ALK inhibitor. It has been approved in Japan since 7 April 2014 and is designated by FDA as a breakthrough therapy. ALEX is a global randomised, phase III, first-line study of alectinib vs. crizotinib that currently recruits treatment-naïve patients with ALK-positive advanced NSCLC.

The JP28927 was a clinical pharmacological study to evaluate the bioequivalence of alectinib in ALK-rearranged NSCLC patients with or without previous treatment with ALK inhibitor. The results for bioequivalence, food effect, efficacy and safety were reported earlier this year at ASCO 2014.

The study included ALK-rearranged NSCLC patients who had to discontinue treatment from crizotinib, a first generation ALK inhibitor, because of drug resistance or intolerance. During the ESMO 2014, the investigators presented updated efficacy and safety data for alectinib in 28 crizotinib pre-treated NSCLC patients included in this study.

As of 11 January, 2014, median follow-up duration was 141 days and 21 patients continued treatment with alectinib without progressive disease. Among 24 patients with target lesions, tumour shrinkage of more than 30% was observed in 18 patients. Confirmed RR was 58.3% and DCR was 83.3 % as assessed by study investigators.

From 19 patients who had brain metastases at baseline, 13 (including 4 patients without prior brain irradiation) were still on study treatment without disease progression.

The safety profile was favourable and continued the same trend previously reported. No patients discontinued study treatment for safety reasons. GI and visual disorders, characteristic for crizotinib treatment, were mild and not so frequent with alectinib.

The authors concluded that their findings suggest that alectinib is a novel therapeutic option for crizotinib pre-treated ALK-rearranged NSCLC.

The study was sponsored by Chugai Pharmaceutical Co., Ltd.

Reference

1224O: Anti-tumor activity of alectinib in crizotinib pre-treated ALK-rearranged NSCLC in JP28927 study

Defining and refining the ALK treatment paradigm in NSCLC

Dr Alice Shaw of the Massachusetts General Hospital, Boston, USA, who discussed the results of both studies, said that for patients with advanced ALK-positive NSCLC crizotinib represents a standard first-line therapy. However, it has modest activity in the CNS. Next generation ALK inhibitors, like alectinib and ceritinib, are active in patients who relapse on crizotinib, and represent a new standard of care.

Further studies are needed to determine the optimal sequencing of ALK inhibitors. The open questions, according to Dr Shaw, are:

- should a next generation ALK inhibitor be used as first-line therapy;
- which ALK inhibitor should be used in the second-line setting in term of CNS efficacy, tolerability, and resistance mechanism;
- is there a role for a third-line ALK inhibitor in terms of CNS disease and resistance mechanism.

Results of LUX-Lung 8, the largest prospective trial to compare EGFR TKIs in patients with relapsed/refractory squamous cell carcinoma of the lung

In the LUX-Lung 8, a global, randomised, phase III study the PFS and DCR were significantly better in patients with relapsed/refractory squamous cell carcinoma of the lung treated with afatinib than in those treated with erlotinib. The study was presented by Prof. Glenwood Goss of the Division of Medical Oncology, University of Ottawa, Ottawa, Canada.

Squamous histology represents approximately 30% of NSCLC cases. Limited progress and therapeutic options exist for these patients in second-line setting. Targetable oncogenic alterations are limited and have not yet translated to a therapeutic paradigm. In addition, patients often have extensive comorbidities.

Erlotinib is the last drug approved (in 2005) based on efficacy vs. placebo in second-/third-line setting. Survival benefit was confirmed in subset analysis of male, ever-smokers with squamous cell carcinoma.

Afatinib is an irreversible ErbB-family blocker that inhibits all kinase-active members (EGFR, HER2 and HER4). Proof of concept in squamous histology was observed in various trials in lung and head and neck cancer. It was approved in the major International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use regions of USA, EU and Japan for the treatment of patients with NSCLC harbouring distinct types of EGFR-activating mutations.

The LUX-Lung 8 study is a randomised, open-label, prospective phase III trial in patients with squamous cell carcinoma of the lung following failure of first-line chemotherapy. It compared afatinib with erlotinib, an EGFR inhibitor.

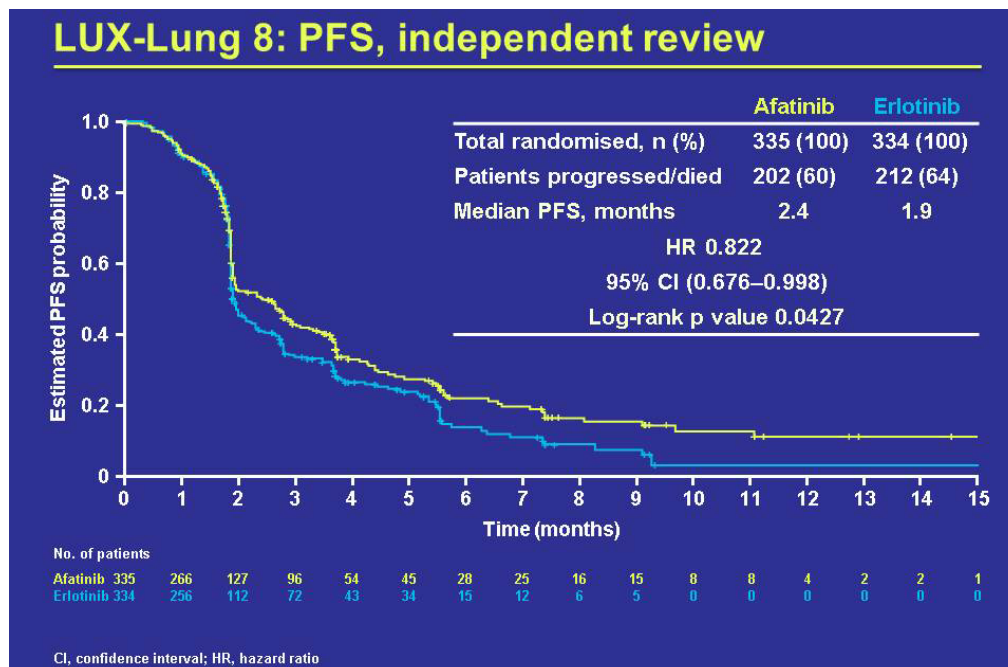
Eligible patients with stage IIIB/IV squamous cell carcinoma of the lung and ECOG PS 0 and 1 were randomised 1:1 to receive afatinib or erlotinib until disease progression. All patients had progressed after ≥4 cycles of platinum-based doublet chemotherapy and had not received prior EGFR TKIs. Patients were stratified based on race (East Asian vs. other).

The trial was powered for PFS and OS. The primary endpoint was PFS according to RECIST v1.1 criteria as assessed by independent radiological review (IRR). Secondary endpoints included OS planned at 632 events, ORR, DCR, safety and health-related QoL.

An interim futility analysis was performed by an independent data monitoring committee and the trial was allowed to accrue to the planned 800 patients. Overall 795 patients were recruited between March 2012 and January 2014. Planned primary analysis was based on 414 PFS events by IRR in the first 669 patients randomised (afatinib 335, erlotinib 334) while recruitment was ongoing.

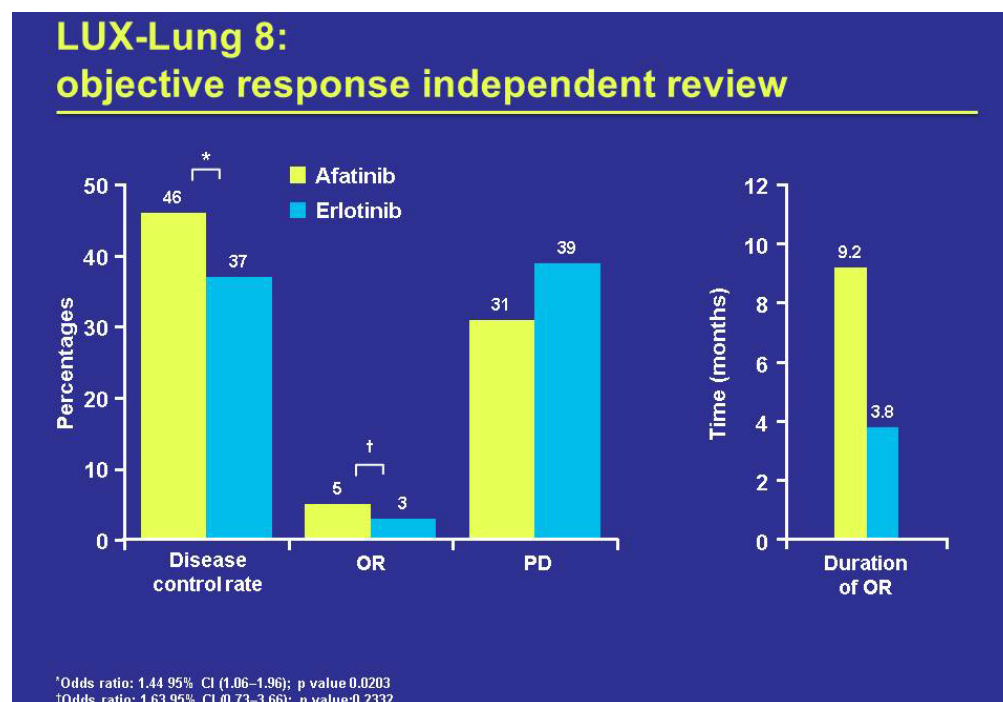
Baseline characteristics were well balanced between the arms. Median age was 65 years, 85% of patients were male, East Asians accounted of 22% of the study population, and never smokers 5%.

Median PFS was significantly higher for afatinib than erlotinib, both by IRR (2.4 vs. 1.9 months; $p=0.0427$) and investigator review (2.7 vs. 1.9 months; $p=0.0053$), respectively.



Caption: PFS by independent review in the LUX-Lung 8 study. © Glenwood Goss

The ORR was 4.8% vs. 3.0% ($p=0.233$), but DCR 45.7% vs. 36.8% ($p=0.020$) was significantly higher with afatinib vs. erlotinib.



Caption: The ORR was 4.8% vs. 3.0% ($p=0.233$), but DCR (45.7% vs. 36.8%; $p=0.020$) was significantly higher with afatinib vs. erlotinib.

The overall adverse event profile was comparable and consistent with the mechanistic profile of EGFR inhibition (patients with \geq grade 3 adverse events: 50.2% and 49.1% for afatinib and erlotinib with higher incidence of drug-related \geq grade 3 diarrhoea (9.7% vs. 2.4%) and grade 3 stomatitis (3.3% vs. 0.0%) with afatinib and higher incidence of grade 3 rash/acne with erlotinib (5.5% vs. 9.0%).

The authors concluded that LUX-Lung 8 is the largest prospective trial to compare EGFR TKIs in patients with relapsed/refractory squamous cell carcinoma of the lung. The PFS was statistically significantly increased with afatinib than erlotinib. Tumour shrinkage was greater, response rate higher, and DCR significantly higher in the afatinib arm compared to the erlotinib arm. Overall adverse event profile was consistent with mechanistic profile of EGFR inhibition and was manageable. Patient-reported outcomes favoured afatinib versus erlotinib. The OS data are awaited.

Dr Pasi Janne of the Dana-Farber Cancer Institute, Boston, USA, in his discussion entitled “Who should be treated with EGFR TKI”, said that the clinical implications of LUX-Lung 8 study are marginal benefit of afatinib over erlotinib and increased toxicity. EGFR-inhibitors are used less (if at all) in squamous cell lung cancer, chemotherapy is generally more effective in this disease and more than 99% of EGFR mutations actually occur in adenocarcinoma. New therapies are emerging for squamous cell cancer in particular anti-PD 1, anti-PD-L1 and anti-PD-L2 inhibitors.

The study was sponsored by Boehringer Ingelheim.

Reference

1222O: A randomized, open-label, phase III trial of afatinib (A) vs erlotinib (E) as second-line treatment of patients (pts) with advanced squamous cell carcinoma (SCC) of the lung following first-line platinum-based chemotherapy: LUX-Lung 8 (LL8)

Antitumour activity of pembrolizumab and correlation with PD-L1 expression in a pooled analysis of patients with advanced NSCLC

The anti-PD-1 antibody pembrolizumab has shown durable antitumour activity and acceptable toxicity in treatment-naïve and previously treated advanced NSCLC patients. Correlation between tumour PD-L1 expression and improved pembrolizumab antitumour activity has been observed. Prof. Edward Garon of the David Geffen School of Medicine at UCLA, Santa Monica, USA presented analysis in 282 patients with treatment-naïve or previously treated advanced NSCLC enrolled in randomised and non-randomised cohorts of the phase I KEYNOTE-001.

PD-1 is a negative co-stimulatory receptor expressed primarily on activated T cells. Binding of PD-1 to its ligands inhibits effector T-cell function. Expression of PD-L1 on tumour cells and macrophages can suppress immune surveillance and permit neoplastic growth. Pembrolizumab is able to achieve a dual blockade (PD-L1 and PD-L2). It shows no cytotoxic (ADCC/CDC) activity.

In this study, tumour PD-L1 expression was determined prospectively by a prototype IHC assay in all patients. Samples were independently reanalysed using a clinical trial IHC assay.

Pembrolizumab was given at 2 mg/kg every 3 weeks (Q3W), 10 mg/kg Q3W, or 10 mg/kg Q2W until progression, death, or unacceptable toxicity.

The ORR was assessed per RECIST v1.1 by central review and per immune-related response criteria (irRC) by investigator review.

Mature data are available for 262 patients with 5.4 months of median follow-up.

Grade 3-5 drug-related adverse events occurred in 24 (9%) patients, most commonly pneumonitis.

The ORR in patients with measurable disease at baseline was 21% according to RECIST v1.1 and 23% according to irRC in overall study population (26%/47% in treatment naive, 20%/18% in previously treated, respectively) and was 18% in patients with squamous and 23% in patients with non-squamous histology. The ORR was 33%/67% at 2 mg/kg Q3W, 21%/22% at 10 mg/kg Q3W, and 21%/22% at 10 mg/kg Q2W. The ORR was 23%/25% in patients with $\geq 1\%$ PD-L1 staining and 9%/13% in patients with negative PD-L1 staining.

In all treatment-naive patients, responses are still ongoing, in 77% of previously treated patients.

In treatment-naive patients the PFS is 27 weeks with a 24-week PFS rate of 51%. In the same group, median OS has not yet been reached and the 6 month OS rate is 86%. In previously treated patients the median PFS is 10 weeks, and 24 week PFS rate is 26%. The median OS is 8.2 months and 6 month OS rate is 59%.

In the pooled population, median PFS is 13 weeks and 24 week PFS rate 30%. The median OS is 8.2 months with a 6 month OS rate of 64%.

The data for PD-L1 staining using the clinical trial IHC assay are available for nearly half of the patients. In these patients, the ORR was higher in patients with strong PD-L1 expression ($\geq 50\%$ staining) than in patients with weak/negative PD-L1 expression.

The PFS was longer in patients with PD-L1 strong-positive vs. PD-L1 weak-positive/negative tumours (HR, 0.52). The OS was longer in patients with PD-L1 strong-positive v. PD-L1 weak-positive/negative tumours (HR 0.59).

Prof. Garon concluded that pembrolizumab is tolerable and provides antitumour activity in treatment-naive or previously treated advanced NSCLC, regardless of dose/schedule. Patients with strong PD-L1 tumour expression may derive particular benefit from pembrolizumab. Validation of the prospective PD-L1 cut point will be performed in an additional 300 patients enrolled in KEYNOTE-001. Ongoing studies with pembrolizumab in NSCLC are KEYNOTE-010, -024, and -042.

The study was supported by Merck Sharp & Dohme Corp.

Reference

LBA43: Antitumor activity of pembrolizumab (Pembro; MK-3475) and correlation with programmed death ligand 1 (PD-L1) expression in a pooled analysis of patients (pts) with advanced non-small cell lung carcinoma (NSCLC)

How to guide the selection of chemotherapy regimen for non-squamous NSCLC

Although docetaxel plus cisplatin vs. pemetrexed plus cisplatin showed similar PFS and RR in a phase III study of first-line treatment for non-squamous NSCLC, more frequent adverse events and higher toxicities were observed in the docetaxel arm. In another Korean, biomarker-stratified, randomised phase II study, RR and PFS with pemetrexed/cisplatin regimen compared to gemcitabine/cisplatin chemotherapy were more prominent in the thymidylate synthase (TS)-negative group than in TS-positive group, suggesting that TS can be used as a predictive biomarker.

Docetaxel plus cisplatin vs. pemetrexed plus cisplatin in first line non-squamous NSCLC

For patients with non-squamous-NSCLC, pemetrexed plus cisplatin is superior to gemcitabine plus cisplatin in terms of efficacy and toxicity. Docetaxel/cisplatin is an active regimen for first-line NSCLC. Median PFS of pemetrexed/cisplatin is 6.4 months in East Asians compared with 5.3 months in all ethnic patients. However, there was no prospective phase III trial that directly compared the efficacy of the two regimens. The objective of the study presented by Prof. Young-Chul Kim of the Pulmonology Unit, Chonnam National University Hwasun Hospital Lung Cancer Clinic, Hwasun Gun, Korea was to prove the non-inferiority of PFS of docetaxel/cisplatin compared with pemetrexed/cisplatin.

The researchers performed an open-label phase III trial. The study recruitment was between August 2011 and December 2013 at 14 centers in Korea. Patients with chemotherapy-naïve non-squamous-NSCLC were randomised into 3 weekly cisplatin-based chemotherapies, with either docetaxel or pemetrexed, for up to 4 cycles with stratification by PS and sex. Thereafter, the patients continued treatment with either pemetrexed, EGFR TKI or docetaxel.

The primary objective was to assess PFS and the secondary endpoints were RR assessed by RECIST v1.1 criteria, OS and safety.

In total, 156 patients were randomised, but after 149 patients had been enrolled - pemetrexed/cisplatin (77) and docetaxel/cisplatin (72) - the study team finished enrolment due to the approval and popular use of maintenance treatment with pemetrexed in Korea.

Clinical characteristics including sex, age, and performance status were well balanced between the arms. The number of cycles and relative dose intensity were not significantly different between the arms.

In ITT population, PR was observed in 24 (31.2%) and 24 (33.3%) patients in pemetrexed/cisplatin and docetaxel/cisplatin group, respectively.

Median PFS was 4.7 months in the pemetrexed/cisplatin arm and 4.6 months in the docetaxel/cisplatin arm. Median OS was 19.7 month in the pemetrexed/cisplatin arm and 28.0 month in the docetaxel/cisplatin arm.

Rate of grade 3 or 4 neutropaenia and febrile neutropaenia, number of serious adverse events were significantly higher in the docetaxel arm.

Prof. Kim concluded that in non-squamous NSCLC without driver mutations, both regimens showed similar PFS and RR. However, more frequent adverse events and higher toxicities were observed in the docetaxel/cisplatin arm. Numerically shorter PFS were seen in both arms in this trial in comparison to the East Asian and overall population in other trials which suggests that maintenance treatment should be considered unless disease progression is noted.

Dr Giorgio Scagliotti of the University of Torino at San Luigi Gonzaga Hospital Regione Gonzole 10, Orbassano, Italy, who discussed the study results, said that it was planned as a non-inferiority study with a margin of 1.5 months. The original sample size was 562 patients, however, it was stopped after enrollment of 159 patients (28%) and for him this is just a randomised phase 2 study, therefore no meaningful conclusion could be drawn because of the limited number of patients. The PFS data are comparable to Caucasian patients, longer OS data in both arms are typical for data seen in Asian patients. As expected lung toxicity is higher with the

docetaxel/cisplatin treatment. Pemetrexed-based chemotherapy remains the preferred doublet in non-oncogene addicted non-squamous NSCLC.

Reference

LBA41 PR: A randomized phase III study of docetaxel plus cisplatin versus pemetrexed plus cisplatin in first line non-squamous non-small cell lung cancer (NSq-NSCLC)

Pemetrexed plus cisplatin vs. gemcitabine plus cisplatin according to thymidylate synthase expression in non-squamous NSCLC

Prof. Myung-Ju Ahn of the Department Of Internal Medicine, Hematology, Oncology, Sungkyunkwan University, School of Medicine, Seoul, Korea presented results of a biomarker-stratified randomised phase II trial. The primary endpoint was to determine the predictive value of TS in non-squamous NSCLC in term of ORR by testing the interaction between treatment arms and TS positivity.

As background, the Korean researchers explained that pemetrexed/cisplatin showed superior outcomes in non-squamous NSCLC compared with gemcitabine/cisplatin; however a phase III trial showed it was inferior in squamous NSCLC. One of culprits for this phenomenon is the different expression level of TS according to histotypes where TS expression is higher in squamous NSCLC than in non-squamous NSCLC.

TS is an important enzyme in de novo DNA synthesis and one of target proteins of pemetrexed. Many retrospective analyses showed better clinical outcomes of pemetrexed-based therapy in NSCLC patients with low TS-expressing tumours. This study was conducted to evaluate whether TS expression is a predictive factor for pemetrexed/cisplatin compared with gemcitabine/cisplatin in non-squamous NSCLC patients.

The main inclusion criteria were patients ≥ 18 years with histologically or cytologically confirmed advanced stage (IIIB or IV, or recurrent disease at least 6 months after complete resection), non-squamous NSCLC except large cell neuroendocrine carcinoma, at least one measurable lesions, ECOG PS 0 or 1, adequate organ function, and no prior chemotherapy for advanced disease. Written consent was obtained from eligible patients.

TS expression was measured by IHC. The patients with more than 10% of tumour cells expressing TS were grouped as a TS-positive and those with 10% or less were grouped as a TS-negative. In a retrospective study by the same investigators, the median H score of 15 as the cut-off value for TS-positive or TS-negative tumours was identical to the expression in 10% of tumour cells irrespective of staining intensity.

After being stratified as TS-positive or TS-negative, patients were randomised to either pemetrexed/cisplatin or gemcitabine/cisplatin arms in a 1:1 fashion.

The study primary endpoint was interaction between TS and treatment allocation as assessed by response rate. Secondary endpoints included interaction between TS and treatment allocation in terms of PFS or OS, and safety of treatment.

This trial was designed to provide 90% power to detect an interaction term of $b=1.294$ based on the response rate of each group as estimated from the investigators' previous study. One-sided α of 0.1 was used for the analysis of interaction term, whereas two-sided α of 0.05 was used for other endpoints.

Chemotherapy in both arms was administered until disease progression or unacceptable toxicity with maximum 6 cycles. Response evaluation by RECIST v1.1 was done every 2 cycles during treatment and every 2 months after completion of study chemotherapy.

For 315 evaluable patients, the RR calculated by investigators in pemetrexed/cisplatin and gemcitabine/cisplatin was 47.0% and 21.1% in the TS-negative group, and 40.3% and 39.2% in the TS-positive group ($p = 0.008$), respectively. The RR in the pemetrexed/cisplatin and gemcitabine/cisplatin arms as evaluated by independent reviewers were 38.6% and 21.1% in TS-negative group, and 40.3% and 48.1% in TS-positive group ($p = 0.007$), respectively.

The median PFS in the pemetrexed/cisplatin and gemcitabine/cisplatin arms were 6.4 and 5.5 months in TS-negative group ($p = 0.013$), and 5.9 and 5.3 months in TS-positive group ($p = 0.64$) (interaction $p = 0.07$), respectively.

Out of 88 patients with tumours harboring EGFR mutations, 74 received gefitinib or erlotinib, while 9 had not commenced post-discontinuation therapy because their disease had not yet progressed at the time of data cut-off.

The median OS in the pemetrexed/cisplatin and gemcitabine/cisplatin arms were not different in TS-negative group (not reached vs. 28.3 months, $p = 0.86$), or the TS-positive group (19.0 vs. 14.4 months, $p = 0.36$) (interaction $p = 0.31$). However, in multivariate analyses, TS-negative expression was significantly associated with longer survival (HR 0.64), along with younger age (HR 0.62) and EGFR mutation (HR 0.45).

The authors concluded that in terms of RR and PFS, clinical benefits with pemetrexed/cisplatin chemotherapy compared with gemcitabine/cisplatin were more prominent in the TS-negative group than in the TS-positive group, suggesting that TS can be used as a predictive biomarker. Furthermore, given that low TS expression was associated with prolonged OS irrespective of chemotherapeutic regimens, the authors noted that TS expression can also serve as a prognostic biomarker.

Dr Giorgio Scagliotti of the University of Torino at San Luigi Gonzaga Hospital Regione Gonzole 10, Orbassano, Italy, who discussed the study results said that it was a reasonably well designed study, however, prognostic/predictive role of TS remains unsolved. IHC, according to Dr Scagliotti, should not be used, while a role of RT-PCR detection would be more appropriate.

Pharmacogenomic markers are still restricted to clinical research settings and no data support their use in clinical practice to select patients.

Reference

LBA42 PR: Cisplatin plus pemetrexed (CP) versus cisplatin plus gemcitabine (CG) according to thymidylate synthase expression in non-squamous NSCLC: A biomarker-stratified randomized phase II trial

Prospective molecular evaluation of small cell lung cancer utilising the comprehensive mutation analysis programme at Memorial Sloan Kettering Cancer Center

Dr Lee Krug of the Memorial Sloan Kettering Cancer Center (MSKCC), New York, USA reported that comprehensive molecular evaluation of small-cell lung cancer (SCLC) is feasible on clinical specimens. Prospective collection of SCLC tumour samples and mutational analyses in the study

continue. Such analyses will allow characterisation of SCLC molecular diversity and identification of patients who may be candidates for targeted therapies.

Recent studies using next generation sequencing (NGS) on resected SCLC specimens have led to insights into the molecular heterogeneity of this disease. However, comprehensive, prospective molecular profiling of patients with advanced SCLC using the biopsy specimens available in clinical practice has not been performed, the authors explained in study background.

Utilising an institutional review board-approved protocol, the MSKCC researchers prospectively evaluated the SCLC tumours of patients in active treatment. The biopsies were evaluated by fluorescence in situ hybridisation (FISH) for FGFR1 and MET copy number, point mutation genotyping for known oncogenes by a mass spectrometry based assay (Sequenom), and NGS with a panel of 300 cancer-related genes. They first tested the feasibility of this approach in a series of patients with SCLC identified retrospectively, with matched tumour and normal pairs, and performed NGS, confirming the findings by FISH.

In the feasibility cohort, 21 patients with SCLC had FFPE samples available. After histologic review and DNA extraction, 10 patients had adequate material for NGS. The researchers observed recurrent mutations in RB1 (7 cases) and TP53 (8 cases) and amplifications of FGFR1 (2 cases) and MET (1 case), using as little as 15 nanograms of DNA. FISH confirmed FGFR1 and MET amplification in the identified cases.

Since February 2013, SCLC patients undergoing active treatment, with sufficient archived tissue, provided consent for the SCLC mutational analysis programme. Thus far, 43 patient samples have been tested. Sequenom in 32 patients identified an AKT1 E17 mutation in one case and a PIK3CA E542K mutation in one case. NGS in 25 patients has yielded the following: loss of RB1 (18 mutations, 4 deletions); mutations in TP53 (24), MLL3 (9), and EPHA 5 (9); and amplifications of CDKN2C (5), MYCL1 (3), SOX2 (2), and FGFR1 in one case confirmed by FISH. Four patients had insufficient material.

The findings are confirmatory of previous retrospective studies with frequent inactivation of TP53, RB1 and comparable frequency of alterations such as SOX2 and FGFR1 amplifications, and PTEN loss. Homozygous deletions are more common in refractory disease. In this series, extensive stage disease is not associated with an increased number of mutations relative to limited stage disease. When further evaluated for response, several mutations appear to be specific to sensitive disease patients. Ongoing analyses are focused on correlating SCLC gene alterations with outcomes and associating these patients with appropriate targeted therapy.

Prof. Caroline Dive of the Christie Hospital, Manchester, UK said that obtaining serial and sufficient biopsies from SCLC is possible, but difficult. There is an urgent need for better therapies, useful biomarkers for drug development and patient relevant mouse models to explore biology and test new treatments.

SCLC is not routinely resected and therefore there is a limited amount of tissue for research. SCLC cell lines were amongst the first to be developed, but the generated hypotheses have mainly not been upheld in the clinic. Patient derived explant models to explore biology and pharmacology require fresh tissue, but it remains challenging to get SCLC biopsies (small, necrotic masses). It has been done in this study and the data are pioneering. Some key issues are

if this approach is realistic for SCLC patients who don't attend large well funded comprehensive cancer centres, with what frequency should progression biopsies be obtained to study drug resistance mechanisms, how many targeted therapies are available now for patients with molecular analyses to hand, how many molecular hits were actionable and in how many patients, does a small biopsy miss important subclonal drivers, and what do we really know about intratumour heterogeneity and evolution of SCLC? The authors noted that a greater number of genes are altered in patients with sensitive disease compared to refractory disease, but these results require validation, according to Prof. Dive.

The study was funded, in part, by the Lung Cancer Research Foundation.

Reference

1463O: Prospective molecular evaluation of small cell lung cancer (SCLC) utilizing the comprehensive Mutation Analysis Program (MAP) at Memorial Sloan Kettering Cancer Center (MSKCC)

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Affiliations and Disclosure

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Disclosure

No conflicts of interest to disclose.

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