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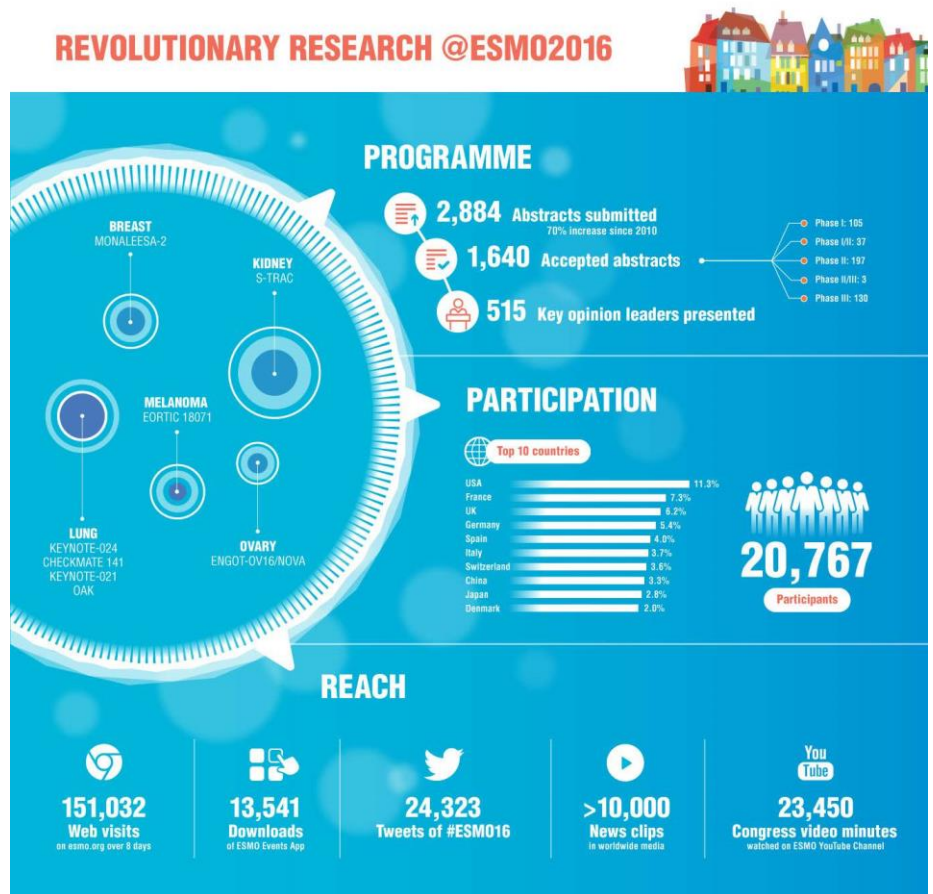
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Summary

The European Society for Medical Oncology (ESMO) 2016 Congress, held October 7 to 11 in Copenhagen, Denmark, was a record-breaker on all levels. It was resounding success and in a dedicated infographic you can find the congress programme statistics. A primary emphasis in the scientific programme was placed on two areas: precision medicine and immunology and immunotherapy across multiple tumour types and how these advances change the treatment landscape in oncology. 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 2016 scientific programme, as well as advances in oncology.



ESMO 2016 record breaking Congress

THORACIC MALIGNANCIES – NSCLC, Metastatic

PD-1 inhibition shows promise as first-line treatment in high PD-L1 expressing patients with advanced NSCLC

Martin Reck of the Lung Clinic Grosshansdorf in Grosshansdorf, Germany and colleagues throughout Europe conducted the phase III KEYNOTE-024 trial of first-line pembrolizumab in patients with tumours expressing levels $\geq 50\%$ of PD-L1 who demonstrated a compelling survival advantage over patients receiving standard first-line platinum-based chemotherapy. The trial was halted early based upon a 45% objective response rate (ORR) and improved progression-free survival (PFS) of 4.3 months over chemotherapy. KEYNOTE-024 enrolled 305 patients having no treatable EGFR mutations or ALK translocations from 16 European countries. Patients were randomised to 35 cycles of 200 mg pembrolizumab (n=154) or to 4 to 6 cycles of investigator's choice of platinum-containing chemotherapy doublet (n= 151). Crossover from the chemotherapy arm at disease progression was allowed. The study's primary end point was PFS and secondary end points included overall survival (OS), ORR, and safety.

An interim analysis done at a median follow-up of 11.2 months showed pembrolizumab-treated patients had median PFS of 10.3 months compared to 6.0 months with chemotherapy, hazard ratio [HR] 95% confidence interval [CI] 0.37, 0.68 ($p < 0.001$); 6-month PFS rates were 62% versus 50%) and 12-month PFS rates were 48% versus 15% with pembrolizumab versus chemotherapy, respectively. Median OS had not been reached in either treatment group but the comparison favoured pembrolizumab; 6-month OS rates were 80% with pembrolizumab compared to 72% with chemotherapy, HR 0.60; 95% CI 0.41, 0.89, ($p = 0.005$). The OS rates were higher with pembrolizumab despite possibly being confounded by crossover of more than 40% from the chemotherapy arm after disease progression. Subgroup analysis revealed a consistent survival advantage with pembrolizumab across all subgroups excepting female-never smokers.

A lower incidence of any grade adverse events (AEs) of 73% was seen in the pembrolizumab arm versus 90% with chemotherapy. Grade 3/4 AEs were also more frequent in the chemotherapy arm, wherein 53% of patients reported an AE compared to 27% of patients receiving pembrolizumab. Study discontinuation due to AEs occurred in 7% of pembrolizumab and 11% of chemotherapy treated patients. One death in the pembrolizumab arm and 3 deaths in the chemotherapy arm were determined to be treatment-related. These results were simultaneously published online in *The New England Journal of Medicine* (NEJM). NCT02142738. EudraCT number 2014-000323-25. Reck *et al.* LBA8_PR; *NEJM* 2016; 375:1823-1833.

Practice point and future research opportunities

Pembrolizumab demonstrated PFS and OS that were superior to platinum-based chemotherapy

in patients with advanced NSCLC and tumours expressing PD-L1 levels $\geq 50\%$. Taken together with the safety profile, which showed a lower rate of treatment-related adverse events than chemotherapy, pembrolizumab may be considered as a new standard of care for first-line therapy in high PD-L1–expressing advanced NSCLC with no oncogenic driven disease. The patient population in this trial also had good performance status, no untreated brain metastases, no treatable oncogenic ALK or EGFR aberrations, and had not received prior steroid therapy. In daily clinical practice, perhaps 20% of patients with advanced NSCLC may have disease characteristics similar to this population. These data confirm findings from two previous KEYNOTE trials that also showed promising beneficial effects with pembrolizumab in patients with NSCLC and PD-L1-expression with the most favourable outcomes occurring in patients with tumours having high PD-L1 expression, which supports pembrolizumab over platinum-based chemotherapy as a new standard of care in this population. Further study is warranted to explore whether patients with lower levels of PD-L1 expression also derive more benefit from pembrolizumab than chemotherapy.

Atezolizumab in patients with NSCLC and disease progression following platinum-containing chemotherapy

Atezolizumab is a PD-L1 directed antibody that blocks PD-L1 binding to PD-1 and B7.1 while leaving the PD-L2/PD-1 interaction intact, thereby acting to restore tumour-specific T-cell immunity. Fabrice Barlesi, Aix-Marseille University and the Assistance Publique Hôpitaux de Marseille in Marseille, France presented the first results for a PD-L1 directed antibody from a primary efficacy analysis carried out in the first 850 of a total 1225 patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that had been previously treated with platinum-containing chemotherapies enrolled in the OAK study. The OAK is an ongoing randomised, global, multicentre, open-label phase III study, with the primary endpoint of overall survival (OS) and safety with atezolizumab as compared to the historical standard of care, docetaxel. The patients' median age was 64 years, 61% were male, 25% had received two prior lines of therapies, and 26% of patients' had squamous histology. All patients were stratified according to PD-L1 expression status, the number of prior chemotherapy regimens, and tumour histology then randomised to 1200 mg intravenous atezolizumab every 3 weeks or 75 mg/m² docetaxel every 3 weeks (425 patients per arm).

The overall intent to treat cohort, including patients with low to no PD-L1 expression, showed a 27% improvement in OS with atezolizumab compared to patients receiving docetaxel; median OS was 13.8 months versus 9.6 months, respectively, hazard ratio [HR] 0.73 ($p = 0.0003$).

When patients were stratified according to PD-L1 expression levels in the tumour or surrounding immune cells, OS was 59% greater among patients in the highest tertile of PD-L1 expression receiving atezolizumab, compared to patients with similar expression levels receiving docetaxel; the 16% of patients having $\geq 50\%$ tumour cell or $\geq 10\%$ immune cell PD-L1 expression receiving atezolizumab demonstrated median OS of 20.5 months compared with 8.9 months in the docetaxel arm, HR 0.41 ($p < 0.0001$). The median OS in 55% of patients having moderate PD-L1 expression $\geq 1\%$ was 15.7 months with atezolizumab versus 10.3 months with docetaxel, HR 0.74 ($p = 0.0102$). Similar benefit was also seen in patients with low PD-L1 expression levels

(<1%) who demonstrated median OS of 12.6 with atezolizumab versus 8.9 months with docetaxel, HR 0.75 ($p = 0.0205$). Atezolizumab showed significant OS benefit across subgroups of age, PD-L1 status, and smoking status; however, patients harbouring active EGFR mutations showed no benefit. The OS benefit was observed among patients regardless of histology, although the magnitude of benefit was greater in patients with non-squamous histology where OS was 15.6 versus 11.2 months with atezolizumab versus docetaxel, respectively, HR 0.73, ($p = 0.0015$). Patients with squamous histology demonstrated OS of 8.9 versus 7.7 months with atezolizumab versus docetaxel, respectively, HR 0.77 ($p = 0.0383$).

Secondary endpoint results, including progression-free survival (PFS) per RECIST v1.1 were mixed, with patients overall receiving atezolizumab demonstrating numerically lower PFS of 2.8 months versus 4.0 months with docetaxel, HR 0.95 ($p = 0.4928$). The PFS benefit increased proportionally to higher PD-L1 expression, where median PFS of 4.2 months was observed in the atezolizumab arm compared to 3.3 months in the docetaxel arm. Similarly, the objective response rate (ORR) was 13.6% versus 13.4% in the overall atezolizumab versus docetaxel arms, respectively; however, the ORR was stronger in PD-L1 expressers, who achieved ORR of 31% with atezolizumab compared to 11% of docetaxel patients. The overall duration of response was 16.3 versus 6.2 months in the respective arms. No new safety signals emerged with either treatment. There was a lower incidence of adverse events (AEs) with atezolizumab than docetaxel; treatment-related AEs grades 3/4 occurred in 15% and 43% of patients receiving atezolizumab and docetaxel, respectively. No deaths occurred with atezolizumab and one death related to docetaxel occurred. The results were published in the *Lancet*. NCT02008227. Barlesi *et al.* LBA44_PR; *Lancet* 2017;389(10066):255-265.

Practice point and future research opportunities

Findings from the first phase III study of atezolizumab confirm the efficacy seen in the POPLAR phase II study. Treatment with atezolizumab resulted in a statistically significant and clinically relevant improvement in OS compared with the current second and third line standard treatment of docetaxel in NSCLC. An improvement in OS was observed even in patients with no PD-L1 expression, therefore PD-L1 negativity cannot be used as an exclusion factor for treatment. Atezolizumab demonstrated a favourable safety profile that appears to be similar to that of other immune-checkpoint inhibitors. Atezolizumab offers a new second-line therapeutic strategy for patients with NSCLC, regardless of the PD-L1 status of the tumour and surrounding immune cells. Since the aim of atezolizumab therapy is to allow the immune system to control and eliminate cancer cells, further investigation of atezolizumab in different types of cancer may be warranted.

Based upon results from the phase III OAK and phase II POPLAR studies, in October, 2016 the US Food and Drug Administration (FDA) approved atezolizumab for the treatment of metastatic NSCLC in patients who have disease progression on platinum-containing chemotherapy, or have progressed on an appropriate FDA-approved targeted therapy if the tumour has EGFR or ALK gene abnormalities.

Second-line ceritinib in crizotinib pre-treated ALK positive NSCLC

Giorgio Scagliotti, Department of Oncology, University of Turin, Turin, Italy and colleagues, conducted ASCEND-5, an open label multicentre, phase III study in 231 patients with advanced ALK-positive NSCLC who had progressed following crizotinib. The ASCEND-5 compared ceritinib to chemotherapy, the current second-line standard in that setting. Patients were randomised to daily ceritinib at 750 mg (n = 115) or the investigator's choice of chemotherapy, pemetrexed at 500 mg/m² (n=40), or 75 mg/m² docetaxel (n=73). Brain metastases at baseline were reported in 65 (56.5%) and 69 (59.5%) patients in the ceritinib and chemotherapy arms, respectively. Crossover to ceritinib was allowed upon disease progression. The primary endpoint was progression-free survival (PFS), as assessed by a blinded independent review committee (BIRC).

The PFS was more than 3 times longer with ceritinib than with chemotherapy; patients with ALK-positive NSCLC had significantly longer median PFS of 5.4 months with ceritinib compared to 1.6 months with chemotherapy, hazard ratio [HR] 0.49 (p < 0.001). Overall survival (OS) was possibly confounded by the crossover of 75 patients to ceritinib. Similar median OS of 18.1 months with ceritinib versus 20.1 months with chemotherapy was observed. The objective response rate by BIRC was 39.1% with ceritinib versus 6.9% with chemotherapy; complete or partial response was achieved by 45 ceritinib versus 8 chemotherapy patients. The disease control rates were 75.5% versus 36.2% with ceritinib versus chemotherapy, respectively.

Toxicities were similar to previously reported studies. The most frequent grade 3/4 adverse events with ceritinib were nausea (7.8%), vomiting (7.8%) and diarrhoea (4.3%), and with chemotherapy grade 3/4 neutropenia occurred in 15.5%, fatigue in 4.4%, and nausea occurred in 1.8% of patients. Patient-reported outcomes, including lung cancer-specific symptoms and overall health status, showed symptom improvement with ceritinib over placebo (p < 0.05); however, two scales for gastrointestinal symptoms showed deterioration. NCT01828112. Scagliotti *et al.* LBA42_PR

Practice point and future research opportunities

The majority of patients treated with the current standard first line treatment for NSCLC, crizotinib, develop resistance due to ALK rearrangement, making a more effective second line agent a priority. This was the first phase III study to assess whether the second generation ALK inhibitor ceritinib is superior to chemotherapy upon progression on crizotinib therapy in NSCLC. Significantly improved PFS and response rates were observed with ceritinib over standard chemotherapy. No improvement in OS was seen with ceritinib, possibly due to the crossover at progression of over two-thirds of patients receiving chemotherapy. Single arm studies have suggested that ceritinib could be a standard option in the second line setting after crizotinib has failed. The positive effect on PFS in this phase III study confirms that there is greater benefit using a second ALK inhibitor over standard chemotherapy. This will establish sequential crizotinib followed by a second generation ALK inhibitor as the standard treatment for patients with metastatic ALK-positive NSCLC.

Nivolumab does not improve survival over platinum-based doublet chemotherapy as first-line therapy in advanced NSCLC despite PD-L1 tumour expression in phase III trial

Mark A. Socinski, Florida Hospital Cancer Institute, USA presented findings from the phase III CheckMate 026 trial investigating the efficacy of first-line treatment with nivolumab compared to platinum-based doublet chemotherapy in 541 patients with histologically confirmed and previously untreated stage IV or recurrent NSCLC and PD-L1 positive tumours (defined as present in 1% or more tumour cells). The patients were randomised 1:1 to receive nivolumab at 3 mg/kg i.v. every 2 weeks or to platinum-based doublet chemotherapy every 3 weeks for up to 6 cycles until disease progression or unacceptable toxicity. Patients in the chemotherapy arm were allowed to crossover to nivolumab upon progression. Patients with EGFR activating mutations and ALK translocations, which are sensitive to targeted therapy, were excluded. The primary endpoint was progression-free survival (PFS), assessed by an independent radiology review committee in patients with PD-L1 in 5% or more tumour cells.

In a subgroup of 423 patients with 5% or greater PD-L1 expression, PFS was 4.2 months with nivolumab and 5.9 months with chemotherapy, hazard ratio [HR] 1.15; 95% confidence interval [CI] 0.91 (1.45, $p = 0.25$). Overall survival (OS) was 14.4 months for nivolumab versus 13.2 months for chemotherapy, HR 1.02; 95% CI 0.80, 1.30.

There were no new safety signals with nivolumab and it demonstrated far less toxicity than chemotherapy. Among all treated patients, any and serious treatment-related adverse events were 71% and 18% with nivolumab versus 92% and 51% with chemotherapy, respectively. NCT02041533. Socinski *et al.* LBA7_PR

Practice point and future research opportunities

Nivolumab represents a standard of care as second-line treatment of advanced NSCLC as it improved OS compared to docetaxel in phase III trials, and nivolumab showed a promising response rate in a phase I trial in advanced NSCLC patients with 1% or greater PD-L1 expression in their tumour cells in the first-line setting. However, nivolumab did not show superior survival compared to platinum-based chemotherapy as first-line therapy in stage IV/recurrent NSCLC patients with $\geq 5\%$ PD-L1 tumour expression. There are a number of possible reasons for the disappointing PFS results, but regarding OS, there was a high rate of crossover to immunotherapy on the chemotherapy arm. Also, OS in the chemotherapy arm was better than historical standards. The investigators are conducting further analyses to evaluate these results.

More research is needed about how to use the PD-L1 biomarker to select patients for treatment with nivolumab. In addition, phase I studies suggest that combination immunotherapy improves response rate and outcome, but at the expense of increased toxicity, compared to single agent immunotherapy in NSCLC. Thus, it will be important to investigate this strategy further.

SELECT-1 trial of selumetinib in patients with KRAS-mutant NSCLC did not meet primary endpoint

Principal investigators Pasi Jänne, Dana-Farber Cancer Institute, Boston, US, presented findings from the phase III SELECT-1 trial of the MEK 1/2 inhibitor, selumetinib, in combination with docetaxel chemotherapy as second-line treatment in patients with KRAS mutation-positive locally-advanced or metastatic non-small cell lung cancer (NSCLC). The SELECT-1 was an international trial with 510 randomised patients in over 200 centres. Patients received either oral selumetinib at 75 mg twice daily or placebo in combination with docetaxel, administered intravenously at 75 mg/m² on day 1 of every 21-day cycle.

The results showed that the trial did not meet its primary endpoint of progression-free survival (PFS), and selumetinib did not have a significant effect on overall survival (OS). Median PFS was 3.9 months with selumetinib compared to 2.8 months with placebo, hazard ratio [HR] 0.93 (2-sided p = 0.44) and median OS was 8.7 months versus 7.9 months in the respective groups, HR 1.05 (2-sided p = 0.64). There was a trend towards a higher objective response rate with selumetinib compared to placebo of 20.1% versus 13.7%, respectively, odds ratio 1.61 (p = 0.051).

The adverse event (AE) profiles for selumetinib and docetaxel were consistent with those seen previously. Serious AEs occurred more frequently at 49% in patients treated with the selumetinib plus docetaxel combination compared to 32% with placebo, as did AEs leading to hospitalisation, which occurred in 46% of selumetinib versus 30% of placebo patients. NCT01933932. Jänne *et al.* LBA47_PR

Practice point and future research opportunities

Although a randomised phase II trial showed promising activity of selumetinib in combination with docetaxel in patients with KRAS mutation-positive NSCLC, these results were not confirmed in the phase III SELECT trial. This trial demonstrated that the addition of selumetinib to docetaxel in patients with advanced KRAS mutant NSCLC does not provide clinical benefit in terms of improving PFS or OS; therefore, it is not a treatment approach that should be taken forward.

There remains a desperate need to develop new treatments for the subset of NSCLC patients with KRAS-mutant lung cancer, which is the largest genomically defined subset of NSCLC where there are no effective targeted therapies. Selumetinib inhibits an effector protein immediately downstream from KRAS, which was thought to turn off KRAS-mediated signalling in these cancers.

Selumetinib was granted Orphan Drug Designation by the US Food and Drug Administration for adjuvant treatment of patients with stage III or IV differentiated thyroid cancer.

The SUNRISE phase III trial of bavituximab plus docetaxel in patients with previously treated stage IIIb/IV non-squamous NSCLC is halted after futility analysis

David Spigel, Oncology, Sarah Cannon Research Institute-cancer centre, Nashville, USA, presented the phase III SUNRISE trial comparing bavituximab plus docetaxel with docetaxel and placebo for patients with non-small cell lung cancer (NSCLC), which was halted after a futility analysis. Bavituximab is an IgG3 monoclonal antibody that binds to anionic phospholipids to inhibit tumour growth by stimulating antibody-dependent cellular cytotoxicity.

In SUNRISE, 582 patients with stage IIIb/IV non-squamous NSCLC who progressed after standard frontline treatment were randomised in a 1:1 ratio to bavituximab plus docetaxel or docetaxel plus placebo. Patients in each arm received up to six 21-day cycles of docetaxel at 75 mg/m² followed by weekly bavituximab at 3 mg/kg or placebo. Median overall survival (OS) was 10.7 months (95% confidence interval [CI] 8.6,11.5) among 297 patients receiving bavituximab/docetaxel and 10.8 months (95% CI, 9.2, 12.6) with placebo/docetaxel. The prespecified analysis was conducted after 33% of events and an Independent Data Monitoring Committee found that the combination of bavituximab and docetaxel failed to improve OS compared with docetaxel and placebo, the trial's primary endpoint, for patients with previously treated locally advanced or metastatic non-squamous NSCLC. The safety profile was generally similar between the groups, although the rate of grade 3/4 febrile neutropenia was slightly higher at 8.75% with bavituximab/docetaxel versus 5.69% with docetaxel/placebo. NCT01999673. Spigel *et al.* LBA45

Practice point and future research opportunities

A prior, similarly designed phase II trial demonstrated median OS of 11.7 months with bavituximab/and docetaxel compared with 7.3 months with docetaxel/placebo; this study, plus historical data for docetaxel, set the bar for survival expectations in the phase III study. However, the SUNRISE phase III trial did not meet the primary objective of superior OS in patients with previously treated non-squamous NSCLC.

The developing company has planned future trials in HER2-negative and triple negative breast but has placed all bavituximab/chemotherapy combination studies in NSCLC on hold.

Pembrolizumab added to first-line chemotherapy improves outcomes in advanced NSCLC

Corey Langer, Thoracic Oncology Program, Abramson Cancer Center, University of Pennsylvania, USA presented findings from cohort G of the multicentre, open-label, phase II KEYNOTE-021 study, which randomised 123 chemotherapy-naïve patients with stage IIIB/IV, non-squamous non-small-cell lung cancer (NSCLC) containing no EGFR or ALK targetable

mutations, to receive four cycles of carboplatin to an area under the curve of 5 mg/mL per minute and pemetrexed at 500 mg/m² every three weeks, or to the same regimen plus pembrolizumab at 200 mg every three weeks.

After a median follow-up of 10.6 months, an objective response by RECIST was seen in 55% of 60 patients receiving additional pembrolizumab compared to 29% of the 63 patients receiving chemotherapy alone ($p = 0.0016$), yielding a significant estimated treatment difference of 26%. The response with pembrolizumab was rapid, occurring after a median of 1.5 months versus 2.7 months with chemotherapy. Both responses were durable, with a respective 88% and 78% of responders in each group still alive and progression-free at the time of data cut-off. Overall survival rates were similar between groups where a 6-month survival rate of 92% was observed in each arm.

When patients receiving pembrolizumab were assessed by PD-L1 expression levels in their tumour, the investigators noticed a higher response rate of approximately 80% in patients with tumours having PD-L1 expression greater than or equal to 50%.

A higher incidence of adverse events (AEs) of grade 3 severity or above was observed in the pembrolizumab arm compared to the chemotherapy alone arm (39% versus 26%). However, treatment discontinuation rates were similar between groups at 10% for the pembrolizumab arm compared to 13% for the chemotherapy only arm. The most common treatment-related AEs were fatigue and nausea, which were more common in patients receiving pembrolizumab, and anaemia, which was more common in the chemotherapy alone arm. The results presented at ESMO 2016 were published simultaneously online in *The Lancet Oncology*. NCT02039674. Langer *et al.* LBA46_PR; *Lancet Oncology* 2016;17(11):1497-1508.

Practice point and future research opportunities

KEYNOTE-021 is the first randomised phase II trial in advanced, treatment-naïve non-squamous NSCLC to assess the benefit of adding a monoclonal antibody targeting PD-1 to standard chemotherapy and the results indicate that adding pembrolizumab to carboplatin and pemetrexed chemotherapy could be an effective strategy for the first-line treatment of advanced, non-squamous NSCLC. The safety and efficacy of adding pembrolizumab to first-line platinum-based chemotherapy for advanced non-squamous NSCLC is being further assessed in the KEYNOTE-189 and KEYNOTE-047 trials. If these benefits reported here are confirmed in an ongoing phase III trial, the first-line treatment paradigm in advanced NSCLC could be altered to include pembrolizumab.

Data from long-term follow-up of KEYNOTE-010 study with pembrolizumab in previously treated advanced NSCLC

Roy S. Herbst, Medical Oncology, Yale Cancer Center, Smilow Cancer Hospital, Yale School of Medicine, New Haven, USA, presented updated findings on behalf of colleagues from the KEYNOTE-010 trial of first line pembrolizumab versus docetaxel from a 6-month extended follow-up. KEYNOTE-010 has already demonstrated superior overall survival (OS) over

docetaxel in patients with previously treated advanced non-small cell lung cancer (NSCLC). The trial randomised 1034 patients with NSCLC and TPS $\geq 1\%$ that progressed on 2 or more courses of platinum-doublet chemotherapy to pembrolizumab at 2 or 10 mg/kg every 3 weeks or docetaxel at 75 mg/m² every 3 weeks. Crossover upon progression was not permitted until December, 2015.

As of March 31, 2016, the median follow-up was 19.2 months and median exposure was 106 days with pembrolizumab at both doses versus 62 days with docetaxel. Pembrolizumab continued to show superior OS that was similar between doses. The 18-month OS rates were 37% with pembrolizumab at 2 mg/kg, 43% at 10 mg/kg versus 24% with docetaxel in patients having TPS $\geq 1\%$ and 46%, 52%, and 24%, respectively for TPS $\geq 50\%$. Median OS in TPS $\geq 1\%$ at low and high doses of pembrolizumab versus docetaxel were 10.5 and 13.6 versus 8.6, respectively, hazard ratio [HR] 0.7 (2 mg/kg and HR 0.60 (10 mg/kg). In the TPS $\geq 50\%$ group, median OS was 15.8 months HR 0.54 and 18.8 months, HR 0.48 versus 8.2 months in the respective treatment arms. The objective response rate was also higher for TPS $\geq 1\%$ (19% and 20% versus 10%) and $\geq 50\%$ (29% and 32% versus 9%). At this time-point, 60% of pembrolizumab versus 15% of docetaxel responders in the overall cohort, were alive, and progression free.

Treatment-related adverse event (AE) rates any grade remained lower with pembrolizumab at 64% and 67% versus 81% with docetaxel, as well as grade 3 to 5 AEs of 13% and 17% versus 36% in the respective arms. NCT01905657; EudraCT number 2012-004391-19. Herbst *et al.* LBA48

Practice point and future research opportunities

These and previously reported data formed the basis for the FDA granting a breakthrough therapy designation to pembrolizumab for the treatment of patients with NSCLC who are EGFR mutation- or ALK rearrangement-negative and whose disease has progressed on, or following, platinum-based chemotherapy. Pembrolizumab, a humanised IgG4 PD-1 blocking antibody that exerts dual ligand blockade of the pathway, was previously granted breakthrough status for advanced melanoma, and is being studied across more than 30 types of cancers as monotherapy and in combination. The superior OS for pembrolizumab over docetaxel in patients with previously treated, PD-L1–expressing advanced NSCLC was confirmed in this longer follow-up, as was the lack of difference between pembrolizumab doses, and the durability responses. Taken together with the favourable safety profile despite longer exposure, these data support pembrolizumab as a standard of care for previously treated, PD-L1–expressing, EGFR- and ALK-negative NSCLC.

Continuing gefitinib plus chemotherapy in EGFR mutation-positive NSCLC after progression on first-line gefitinib has deleterious survival effect

Jean-Charles Soria, Department of Medicine, Institut de Cancérologie Gustave Roussy, Villejuif, France reported findings from the final overall survival (OS) analysis of the IMPRESS trial, which evaluated the possible benefit of continuing gefitinib plus cisplatin/pemetrexed versus placebo plus cisplatin/pemetrexed in patients with acquired resistance to first-line gefitinib. Professor Soria and colleagues randomised 265 adult chemotherapy-naïve patients with locally advanced/metastatic NSCLC and activating EGFR mutation that progressed on first-line gefitinib to gefitinib at 250 mg/day or placebo, each in combination with cisplatin 75 mg/m²/pemetrexed 500 mg/m². The primary endpoint was progression-free survival (PFS) and secondary endpoints included OS and safety/tolerability. Primary PFS results confirmed that continuing gefitinib in addition to chemotherapy has little clinical benefit.

A total of 133 patients in the gefitinib and 132 patients in the placebo arms were followed until November, 2015 when 175 (66%) patients had died; most deaths, 65% of gefitinib and 55% with placebo, were due to disease progression. Continuation of gefitinib versus placebo plus cisplatin/pemetrexed was detrimental to OS, hazard ratio [HR] 1.44 (p = 0.016).

A biomarker analyses had been preplanned for EGFR T790M mutation status using plasma circulating free tumour-derived DNA. Subgroup analysis by plasma T790M mutation status showed OS of 10.8 versus 14.1 months, HR 1.49 for T790M-positive, and 21.4 versus 22.5 months, HR 1.15 for T790M-negative with gefitinib versus placebo, respectively. More patients (71%) in the placebo arm received post-discontinuation therapy compared to 61% of patients in the gefitinib arm. Gefitinib plus cisplatin/pemetrexed continued to be well tolerated, with no new unexpected safety findings. NCT01544179. Soria *et al.* Abstract 12010

Practice point and future research opportunities

Although it had been postulated that continuing gefitinib after disease progression could be beneficial as there are multiple causes of acquired resistance to EGFR tyrosine kinase inhibitors and some sites of tumour metastases could continue to be sensitive to treatment, final IMPRESS overall survival data confirm the results published in the *Lancet Oncology* ([http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(15\)00121-7/abstract](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(15)00121-7/abstract)). The final results from this phase III trial indicate that patients with acquired resistance to first-line gefitinib should not continue to receive gefitinib plus doublet chemotherapy beyond progression, due to the observed detrimental effect on OS.

Analysis of the clinical and biological characteristics of EGFR-mutated NSCLC

Charlotte Leduc, Pneumologie, C.H.U. Strasbourg-Nouvel Hopital Civil, Strasbourg, France, presented findings on behalf of the French Cooperative Thoracic Intergroup from a large analysis of a database containing 17,664 patients. The investigators identified 1837 (10.3%) patients with EGFR mutated non-small cell lung cancer (NSCLC) that were evaluated for biological and clinical characteristics. In this large sample set, EGFR exon 18, 19, 20 and 21 mutations were

found in 102 (5.6%), 931 (50.6%), 102 (5.6%), and 702 (38.2%) patients; of these, 70 had never been described. Smokers showed more frequent mutation in exon 18 (20%) and exon 20 (19%) compared to exon 19 (11%) and 21 (11%) ($p = 0.002$). T790M mutated patients ($n=42$) were excluded from the survival analysis.

After a median follow-up of 36.7 (range: 36.4 to 37) months, median overall survival (OS), first-line progression-free survivals (PFS) and disease control rates (DCR) after treatment with a first-line EGFR tyrosine kinase inhibitor (TKI) according to the type of EGFR mutation were analysed. Median OS was 11.8 months in the population of 1270 EGFR wild-type patients; however, OS was prolonged in 555 patients with exon 19 deletions to 26.5 months compared to 21.3 months in 439 patients with L858R mutations ($p = 0.045$). In exon 19, there was no difference in OS based on the length of the deletion. Regarding exon 21, median OS was longer for patients harbouring L858R mutations at 22.4 months versus 14.1 months in patients with L861Q and 14.9 months in patients with other substitutions or 11.8 months in patients with wild-type ($p < 0.0001$). The DCR following treatment with a first-line EGFR-TKI was 82%, 77%, and 54.5% for common, rare and complex mutations, respectively ($p = 0.05$). No difference in DCR was observed with EGFR TKI based on the type of mutation in exon 19 or in exon 21. NCT01700582. Leduc *et al.* Abstract 12020

Practice point and future research opportunities

This large analysis identified common and non-common EGFR mutations and elucidated the different clinical characteristics. Among common mutations, exon 19 mutated patients experienced better outcomes compared to other mutations and wild-type following treatment with an EGFR TKI.

Lenvatinib shows promise in patients with RET fusion-positive adenocarcinoma of the lung

Approximately 1% to 2% of patients with lung adenocarcinoma have tumours that harbour RET fusions that activate RET kinase, prompting Vamsidhar Velcheti, Taussig Cancer Institute, Cleveland Clinic in Cleveland, USA and colleagues to investigate the efficacy of lenvatinib, a multikinase inhibitor with activity to RET, in an open label, phase II trial. The study enrolled 25 patients with RET-positive lung adenocarcinoma, who were treated with lenvatinib at 24 mg per day in 28-day cycles until disease progression or unacceptable toxicity occurred. Previously treated patients were eligible for enrolment, including those receiving prior RET-targeted therapy. KIF5B-RET fusion was seen in 13 patients and 12 patients had other RET fusion. Just 2 (8%) patients had received no prior treatment; 15 (60%) patients received ≥ 2 prior lines of therapy, and 7 (28%) patients had received prior RET therapy. The smoking status of the cohort included 16 (64%) never smokers, one (4%) current smoker, 7 (28%) former smokers, and one (4%) patient with unknown status. The primary endpoint of the trial was objective response rate (ORR) and secondary endpoints included progression-free survival (PFS), overall survival (OS), disease control rate (DCR) defined as complete response (CR) plus partial response (PR) plus

stable disease (SD lasting for ≥ 7 weeks), clinical benefit rate (CBR) defined as CR plus PR plus durable SD (SD lasting for ≥ 23 weeks), and safety.

The primary endpoint, ORR was 16% and consisted entirely of confirmed PRs in 4 patients. The majority of patients experienced tumour shrinkage with lenvatinib and the DCR was 76% (19 patients). Of these, 12 maintained a durable response for 23 or more weeks, yielding a CBR of 48%. Median PFS in the entire study group was 7.3 months (95% confidence interval [CI] 3.6, 10.2 months). Median OS was not reached (95% CI 5.8 months, NE).

Subgroup analysis revealed that the 7 patients previously treated with a RET therapy showed the greatest response. In this cohort, the ORR was 14%, DCR was 86%, and CBR was 57% compared with 17%, 72%, and 44%, respectively, in patients not receiving prior RET inhibitors.

Lenvatinib demonstrated an acceptable safety profile; the most commonly reported treatment-emergent adverse events (TEAEs) were hypertension, which occurred in 68% of patients, nausea in 60%, decreased appetite and diarrhoea, each occurring in 52%, proteinuria in 48%, and vomiting in 44% of patients. TEAEs grade 3 or higher were reported in 23 (92%) patients. TEAEs requiring drug withdrawal occurred in 5 (20%) patients, dose reduction in 16 (64%), and dose interruption occurred in 19 (76%) patients. Three deaths due to AEs occurred on study; one death from pneumonia was possibly related to lenvatinib. NCT01877083. Velcheti *et al.* Abstract 1204PD

Practice point and future research opportunities

RET fusions are detected in 1% to 2% of lung adenocarcinoma and a number of genes, including KIF5B, CCDC6, NCO4 and TRIM33, can act as fusion partners. Lenvatinib is oral multikinase inhibitor of VEGFR 1–3, FGFR 1–4, PDGFR–alpha, and RET and KIT proto-oncogenes.

In this trial, lenvatinib showed promising clinical activity in patients with RET-positive NSCLC with most patients demonstrating tumour shrinkage and disease control; toxicities were manageable in most patients with dose modification. These results support further evaluation of lenvatinib as a potential treatment for patients with RET-positive fusion-positive adenocarcinoma of the lung.

Comprehensive genomic profiling identifies targetable genomic alterations and high mutational burden in lung sarcomatoid carcinoma

Lung sarcomatoid carcinoma (LSC) is a rare, clinically aggressive, heterogeneous and poorly differentiated subtype that involves 3% to 4% of patients with non-small cell lung cancer (NSCLC). LSC is typically difficult to diagnose and is resistant to conventional therapies. LSC harbours a recurrent abnormality known as MET exon 14 skipping mutation that leads to loss of a particular amino acid that is critical to the binding of second protein, which then marks the first protein for degradation. This leads to a drive in cancer growth, according to Balazs Halmos, Clinical Cancer Genomics, Montefiore Medical Center, New York, USA. Dr. Halmos and colleagues queried whether comprehensive genomic profiling (CGP) could identify mutations in LSC that would be susceptible to novel targeted therapies. The investigators performed hybrid-

capture based CGP on 6,923 consecutive FFPE NSCLC samples obtained during the course of clinical care that identified 91 (1.3%) LSCs. The patients in this series had a median age of 67 years (range: 32 to 86), 59% were male, and 82% of tumours were stage IV.

The investigators found that 57% of LSC cases involved a genomic alteration (GA) and 34% of GA involved KRAS. Other GAs were identified in the 7 genes now recommended for testing in the NSCLC National Comprehensive Cancer Network (NCCN) guidelines that included 8.8% in MET, 7.7% BRAF, 6.6% EGFR, 2.2% ERBB2 or 1.1% in RET. No alterations were detected in ALK or ROS1. BRAF alterations included amplification and mutation at V600 or G469. EGFR alterations included amplification, exon 19 deletion, exon 20 insertion, and activating L858R mutation. Notably, MET exon 14 skipping alterations were enriched in this series in 7 (7.7%) samples compared to non-LSC NSCLCs which demonstrated an incidence of 2.8%.

In 39 cases that were wild-type for the 7 NCCN genes and KRAS, potentially actionable GAs were most commonly detected in PTEN at an incidence of 10.3%, PIK3CA at 7.7%, FGFR1 at 7.7%, and in PDGFRA at 7.7%. The median tumour mutation burden (TMB) was 8 mutations/megabase (range: 0 to 165, mean: 14), and 19 (21%) of cases had high TMB \geq 20.

Clinical outcomes were available for a subset of patients that revealed 4 patients with LSC whose tumours harboured alterations in MET, BRAF, and EGFR that received targeted therapies demonstrated clinical benefit and one patient with TMB of 31 has an ongoing response to anti-PD-1 therapy. Halmos *et al.* Abstract 1212PD

Practice point and future research opportunities

This study demonstrated that CGP can be used to inform treatment options in patients with rare, and difficult to treat LSC. Targetable genetic alterations, including MET exon 14 alterations, were found in a majority of LSC patients, some of which occur at greater frequency than that observed in non-LSC NSCLCs. An important portion of LSC cases had high TMB, which suggests an increased likelihood of response to immunotherapy. Thus, CGP can lead to selection of appropriate targeted therapies in this population of patients, which has historically been poorly characterised and difficult to treat.

S-1 is non-inferior to docetaxel in patients with NSCLC who have received a platinum-based treatment

Lead author Makoto Nishio, Department of Thoracic Medical Oncology, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan and colleagues conducted this large phase III trial to demonstrate the non-inferiority of S-1 monotherapy to docetaxel in 1154 patients with previously treated non-small cell lung cancer (NSCLC) in Asia. The study enrolled patients with stage IIIB/IV NSCLC who had received at least one regimen of platinum-based chemotherapy with/without prior exposure to gefitinib or erlotinib. Patients were randomly assigned to S-1 at 80 to 120 mg/day on days 1-28 of a 42-day cycle or to receive docetaxel at

60 mg/m² in Japan, or 75 mg/m² in other countries, on day one of a 21 day cycle. The primary objective was to evaluate whether S-1 is non-inferior to docetaxel in terms of overall survival (OS) and secondary objectives included progression-free survival (PFS), time to treatment failure (TTF), response rate (RR), quality of life, and safety.

At a median follow-up time of 30.75 months, the study satisfied the primary endpoint criteria and found that the median OS of the S-1 group of 12.7 months was non-inferior to 12.5 months with docetaxel, hazard ratio [HR] 0.945; 95% confidence interval [CI] 0.833, 1.073 (p = 0.3818). Similar PFS was demonstrated of 2.86 months with S-1 versus 2.89 months with docetaxel. The investigators did an analysis of response in Japan versus non-Japan, which also demonstrated similar response with S-1 and docetaxel in Japanese and non-Japanese patient populations (HR 0.9; P 0.3374). Grade 3 or higher febrile neutropenia and neutropenia were higher with S-1 at 0.9% and 13.6% with S-1 versus 5.4% and 47.7% with docetaxel. Other non-haematologic toxicities in the S1 and docetaxel groups included, diarrhoea (37.2% versus 18.2%), stomatitis (23.9% versus 14.5%), and decreased appetite (52.6% versus 37.9%), respectively. Nishio *et al.* Abstract 1218PD

Practice point and future research opportunities

This study demonstrated that S-1 is non-inferior to docetaxel in terms of OS and also demonstrated tolerable toxicity. S-1 monotherapy is one of treatment options for patients previously treated with platinum-based chemotherapy for NSCLC.

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Affiliations and Disclosure

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Disclosure

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