

# ESMO Copenhagen 2016: a lung cancer 'grand cru'



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Lung cancer has been the queen tumour of the Annual ESMO Congress in Copenhagen 7–11 October 2016. Much awaited studies have been presented with an impact for oncology practice in terms of treatment choice and option. Most of these studies confirmed that the identification of predictive biomarkers of treatment efficacy are key in the management of non-small cell lung cancer (NSCLC). More than ever, biomolecular characterisation is needed and now mandatory in the management of NSCLC to offer the best treatment to patients at all lines of treatment. These results emphasise the need for a strong collaboration between oncologists, pathologists, molecular biologists and other stake holders in a multi-disciplinary approach.

## FURTHER BREAKTHROUGH OF IMMUNE CHECK POINT INHIBITORS

Four studies were presented in a much-attended presidential session, comparing the use of immune check point inhibitors (ICPI) as single agents or combined to chemotherapy with conventional chemotherapy, three of them in upfront, first-line treatment: Keynote-024,<sup>1</sup> Keynote-021<sup>2</sup> (both published on the day of the presentation) and Checkmate 026<sup>3</sup>. Keynote-024 is a randomised phase III comparing the anti-PD-1 antibody pembrolizumab to a platinum-based chemotherapy in NSCLC, first line, without Epidermal Growth Factor Receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) translocation and selected on PD-L1 expression in >50% of cancer cells. The primary endpoint of progression-free survival (PFS) was met (HR 0.50 (95% CI 0.37 to 0.68),  $p < 0.001$ ). Overall survival (OS) is still preliminary but already showed a significant advantage at 6 months for pembrolizumab (HR 0.60,  $p = 0.0059$ ) and objective response rate (ORR) was also improved (44.8% vs 27.8%). When added to and compared with first-line pemetrexed–carboplatin in the randomised phase II for non-squamous NSCLC Keynote-021 cohort G study, the pembrolizumab combination

arm improved ORR (primary endpoint) over chemotherapy alone by 26%. In Keynote-021, level of PD-L1 expression was not an inclusion criterion and ORR was improved independently of the per cent cell stained but with an increased difference in tumours with  $\geq 50\%$  expression level. PFS was also longer in the pembrolizumab combination arm (HR 0.53,  $p = 0.01$ ), but a longer follow-up is needed. OS is not really evaluable and showed no difference at 6 months, considering that of cross-over occurred in 74% of patients who discontinued chemotherapy. These two new Keynote studies are concordant and establish the value of pembrolizumab in first line leading to its approval recently for patients expressing PD-L1 in  $\geq 50\%$  of cancer cells. The phase III Checkmate 026 similarly compared the anti-PD-1 antibody nivolumab as a single agent with investigator choice platinum-based chemotherapy in first-line PD-L1  $\geq 5\%$  positive NSCLC. The primary endpoint of PFS in the population with PD-L1  $\geq 5\%$  was not met (HR 1.15,  $p = 0.25$ ). No difference was observed neither on secondary endpoints of OS and ORR nor on histology as a stratification factor. These results were quite disappointing considering the effect observed in second line in Checkmate 012 and raised interesting hypothesis for discussion. The OAK trial, a phase III randomized study<sup>4</sup> evaluated atezolizumab, an anti-PD-L1 ICPI in the second-line and third-line setting versus docetaxel in all histology NSCLC. The primary endpoint of OS was met in the Intent To Treat (ITT) population (HR 0.73 (95% CI 0.62 to 0.87),  $p = 0.0003$ ) independent of histology, but neither PFS nor ORR was different. Outcomes were also measured according to the level of PD-L1 expression both on tumour and immune cells by the specific for atezolizumab TC/IC score (Tumor Cells/Immune Cells PD-L1 staining intensity). A gradient of efficacy was observed by TC/IC scoring on the HR for OS ranging from 0.75 in TC0/IC0 to 0.41 in TC3/IC3, all HRs showing statistical significance. A similar gradient was also reported for PFS and ORR.

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These four randomised studies confirmed the efficacy of ICPI in metastatic NSCLC. The results of Keynote-024 and the approval of pembrolizumab will potentially change practice in first line for roughly 30% of metastatic NSCLC with PD-L1 expressing tumours on  $\geq 50\%$  of the cells if the drug becomes accessible and affordable. The failure of Checkmate 026 in first line, however, raised questions about the equivalence of effect among the two anti-PD-1 antibodies, and several points need to be addressed. The main issue may reside in testing and patient selection. The Keynote studies in first line identified a patient population benefiting at the most from pembrolizumab, and a 50% staining score has been retained as a criterion by regulation agencies. However, we know from other Keynote studies (-010 and -021) that even when using a lower cut-off at 1%, a favourable outcome occurs as well and 50% may in fact be too restrictive. The same is true for atezolizumab in second line where the high expressors TC3/IC3 showed the best HR for survival but the other group still benefits with a magnitude of effect not clearly different from the TC0/IC0. With nivolumab in the Checkmate studies in second line, staining for PD-L1 was not discriminant and the drug actually approved without a need for testing; but Checkmate 026 in first line failed in patients selected at a cut-off value of 1%. In the Checkmate 026 study, a cut-off value of 5% was used and the population treated included 32% of patient with  $\geq 50\%$  stained cells, and even in this subgroup of high expressors no effect was observed.

Another point to consider may be in immunohistochemistry testing. There is no standardisation in testing neither with the anti-PD-L1 reagent used nor with the assay methodology. The Food and Drug Administration has approved three diagnostic tests that are drug specific; therefore, when a pathologist is testing a sample, he should be aware of the drug planned to be used if the score is positive, select the proper antibody reagent for testing and apply the described assay procedure in this given setting. In addition, reproducible data have been published showing that all reagents for testing do not perform equally. Two studies have been reported<sup>5,6</sup> and showed that among the three antibodies possibly used in practice, one of them is an outlier and has a lower performance in about 50% of patients otherwise positive. This antibody is used for scoring in atezolizumab trials. Both antibodies used for screening in the Keynote and Checkmate studies behave similarly, with a good concordance among pathologists, and this does not explain the differences on outcome among the two first-line trials. More analysis are being performed on the present studies, other trials are ongoing or planned that hopefully will provide additional data to better understand and improve the present results.

## ONCO-DRIVER ALTERATIONS CONTINUE THEIR JOURNEY IN SELECTED NSCLC

During ESMO 2016 in Copenhagen, several important studies on tyrosine kinase inhibitors (TKIs) have been presented and mature data reported.

ALK/EML4 translocated NSCLC have already largely benefited from crizotinib and second-generation ALK inhibitors are now available. The results of the ASCEND-5<sup>7</sup> phase III study, comparing ceritinib to second-line chemotherapy in ALK+ NSCLC pretreated with crizotinib and one or two lines of chemotherapy were reported at ESMO Copenhagen. PFS (primary endpoint) was 3.5 time longer in median with a HR of 0.49  $p < 0.001$ , response rate was significantly improved. OS will not be evaluable since cross-over was allowed by protocol and quality of life was improved. Another study<sup>8</sup> reported the use of ceritinib in ALK-inhibitor naive patients most of them pretreated with chemotherapy presenting with brain metastasis. In this single-arm study, ORR was 64% (77% in the brain) and median PFS 18.4 months. The median OS was not reached at 30 months and 67% of patients were alive. The journey of ALK inhibitors continues with alectinib and recently long-term results of the Japanese AF-001JP were published<sup>9</sup> with a 3-year survival rate of 78%. More data are expected with the use of brigatinib in the same setting and promising early data have been already reported.<sup>10</sup> This is a major improvement for patients with ALK-translocated tumours, even if it remains a niche representing about 5% of NSCLC adenocarcinomas. These results again emphasise the need of molecular characterisation of NSCLC.

For patients with EGFR mutant NSCLC, several EGFR TKI are now available with first, second, third and now fourth-generation drugs showing activity in EGFR TKI resistance setting. At the ESMO meeting in Copenhagen, the OS data from the LUX-Lung7<sup>11</sup> trial comparing afatinib to gefitinib in first line were presented. The primary endpoint on PFS had already been presented and was met. In terms of OS, no difference was observed neither in the ITT population (HR 0.86,  $p = 0.25$ ) nor according to mutation subtypes (Del 19 or L858R). Tolerance was better with gefitinib with a lower incidence of grade  $\geq 3$  clinical toxicity mainly for diarrhoea and rash. The final results of the IMPRESS trial<sup>12</sup>, an EGFR-mutant NSCLC second-line strategy study evaluating the continuation of gefitinib beyond progression and in combination with cisplatin-pemetrexed versus chemotherapy alone were presented in Copenhagen. This study showed that the continuation of gefitinib beyond progression and combined with chemotherapy had a significant detrimental effect on OS (HR 1.44,  $p = 0.016$ ) and confirmed the preliminary results of a less mature analysis. This study is important in practice and emphasise the need of well-designed clinical trials looking at sequence/strategy considering the numerous agents now available in NSCLC. Another important source of information was the report of the French Nationwide Programme 'Biomarker France'<sup>13</sup> on the routine search for EGFR mutation. This is the largest series (18 679 patients mostly adenocarcinomas) available so far in Caucasian, including 40% present or former smokers. These data confirmed the incidence of sensitising mutation, the largest benefit of TKI is seen in Exons 19 and 21, to a lesser extent in Exon 18, with no difference between Exon 20 mutation

carriers and wild-type EGFR NSCLC. In terms of survival, no difference was observed on PFS between Exons 19 and 21 mutations, and for OS a slight advantage was conferred by Exon 19 over Exon 21 mutations. No difference on OS was seen with the use of TKI in first or second line. This large cohort essentially showed that large-scale nationwide testing is feasible and recommended testing even in smokers.

Two additional randomised studies were presented but failed to reach their primary endpoints. The Sunrise randomised phase III study,<sup>14</sup> an immuno-oncology approach with the antiphosphatidylserine antibody bevacizumab in second line failed to improve OS in the ITT population. A preplanned analysis according to the serum level of  $\beta$ 2-GPI however showed a significant benefit on OS in patients with high circulating  $\beta$ 2-GPI levels. The Select-1<sup>15</sup> randomised phase III with selumetinib in KRAS-mutant NSCLC in second line did not confirm the promising results of the initial phase II on PFS but showed a borderline advantage on ORR.

No doubt that ESMO Copenhagen was a grand cru for lung cancer and confirmed the benefit of immunotherapy with ICPI as well as the use of TKIs in patient with an onco-driver alteration. This very encouraging results are to be improved with appropriate testing of NSCLC upfront and additional studies looking at sequence of use, combination and evaluation at earlier stages of the disease. From an onco-policy point of view, access to testing must be improved to reach out every lung cancer, accessibility to and sustainability of treatment is as well another domain where societies like ESMO and all stakeholders, including patient advocacy groups will have a major role to play.

**Provenance and peer review** Commissioned; internally peer reviewed.

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