Highlights in respiratory oncology

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ESMO 2019 featured the presentation of many interesting studies in the field of lung cancer. Much attention went to non-oncogene driven advanced stage non-small cell lung cancer (NSCLC) in which PD-(L)1 inhibitors are used in monotherapy, in combination with chemotherapy or in combination with CTLA-4 inhibitors. The results of the FLAURA, ALEX and ASCEND-7 trial demonstrated the most recent advances in oncogene-driven advanced stage NSCLC. Finally, the CASPIAN and IMpower 133 trial were the first studies to demonstrate an overall survival benefit with immunotherapy in the field of small-cell lung cancer (SCLC).

NON-ONCOGENE DRIVEN ADVANCED STAGE NSCLC, PD-(L)1 INHIBITORS AS MONOTHERAPY

Long-term survival benefit with pembrolizumab monotherapy in first-line has already been reported as a 3-year overall survival (OS) rate of 43.7 % and a 5-year OS rate of 29.6 % for NSCLC patients with PD-L1 IHC expression ≥50% within KEYNOTE-024 and KEYNOTE-001, respectively. At lower cut-off points for PD-L1 expression, nivolumab (CheckMate-026; cut-off at 5%) and durvalumab (MYSTIC; cut-off at 25%) could not demonstrated a survival benefit for checkpoint inhibitor monotherapy compared to chemotherapy alone.

In the IMpower 110 trial, atezolizumab monotherapy was compared to chemotherapy alone as first-line therapy in advanced stage NSCLC. An interim OS analysis with a median follow-up of 15.7 months demonstrates a survival benefit with atezolizumab monotherapy for high PD-L1 IHC expression (*i.e.* TC3 or IC3) with median overall survival of 20.2 *versus* 13.1 months (hazard ratio [HR] 0.59, p=0.0106), and may become another first-line treatment option for PD-L1 high NSCLC.[1]

NON-ONCOGENE DRIVEN ADVANCED STAGE NSCLC, PD-1 INHIBITOR WITH CHEMOTHERAPY

At median follow-up of 18.7 months, KEYNOTE-189 (platinum-pemetrexed plus pembrolizumab compared to chemotherapy alone) has revolutionised the first-line treatment for advanced stage non-squamous NSCLC with a median overall survival of 22.0 *versus* 10.7 months, respectively, and a HR of 0.56 (p<0.0001).

In the KEYNOTE-407 trial, platinum-(nab)paclitaxel plus pembrolizumab was compared to chemotherapy alone as first-line treatment for advanced stage squamous NSCLC. At this ESMO meeting, the final survival analysis at a median follow-up of 14.3 months *(Figure 1)* further supports the combination of pembrolizumab with chemotherapy as the standard of care therapy with a median OS of 17.1 *vs.* 11.6 months (HR: 0.71) and median PFS2 of 13.8 *vs.* 9.1 months (HR: 0.59), respectively. Grade 3-5 treatment-related adverse events were reported for similar proportions of patients receiving pembrolizumab plus chemotherapy (74%) and chemotherapy alone (70%), leading to treatment discontinuation in 16 *versus* 7%, respectively.[2]

Tissue TMB (mutations/exome) has not proven helpful to select for patients with the highest benefit in the KEYNOTE-189 and KEYNOTE-407 trial, as the combination of pembrolizumab with chemotherapy was more active in both TMB-high and TMB-low tumours at the cut-off of 175 mutations/exome.[3]

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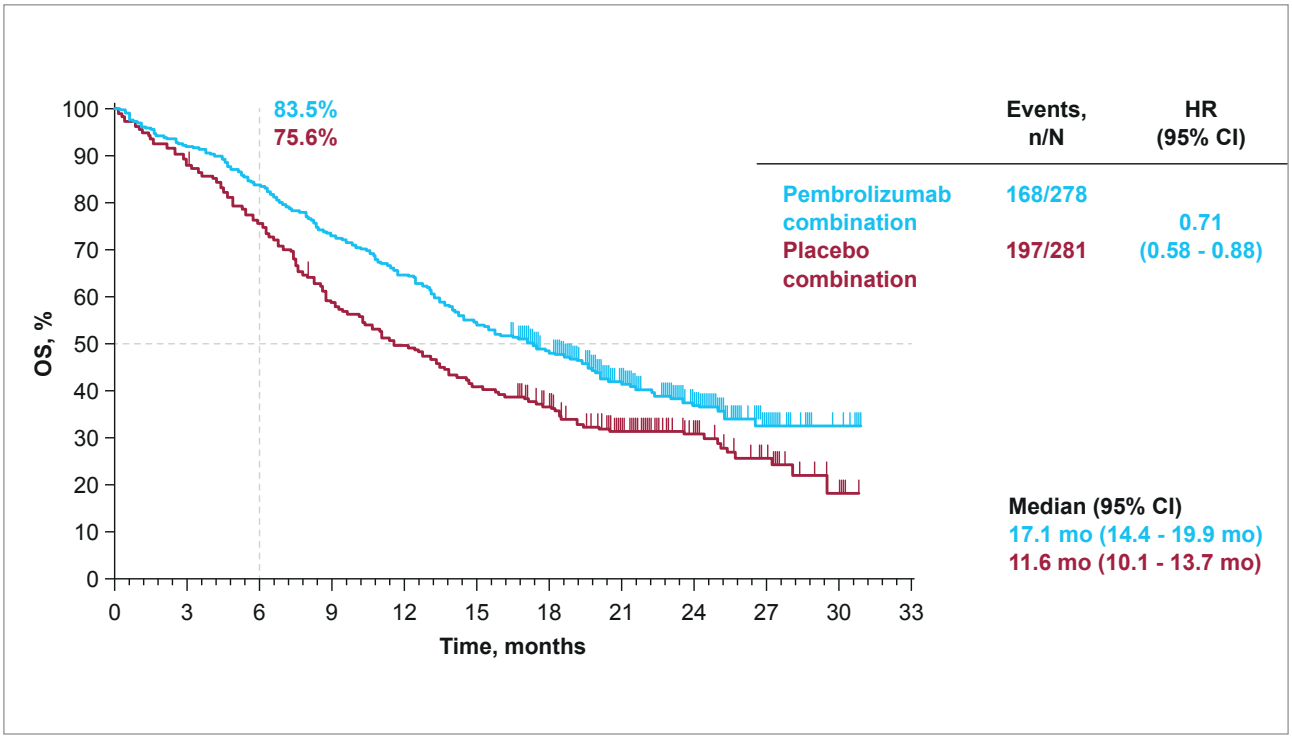

FIGURE 1. Significantly longer overall survival for squamous NSCLC patients treated with first-line pembrolizumab plus chemotherapy compared with chemotherapy alone in the phase III KEYNOTE-407 trial.[2]

NON-ONCOGENE DRIVEN ADVANCED STAGE NSCLC, PD-(L)1 INHIBITOR WITH CTLA-4-INHIBITORS

The combination of durvalumab plus tremelimumab could not improve OS compared with chemotherapy alone in first-line advanced stage NSCLC with PD-L1 ≥25%.

In the CheckMate 227 trial, nivolumab (3mg/kg q2w) plus low dose ipilimumab (1mg/kg q6w) was compared to chemotherapy alone as first-line therapy in NSCLC with PD-L1 ≥1% and no sensitizing *EGFR* mutation or known *ALK* alteration. Overall survival was the co-primary end-point of part 1 of the 2-part phase III trial. The minimum follow-up was 29.3 months. Among the 1,189 patients with PD-L1 ≥1%, OS *(Figure 2)* was significantly prolonged with nivolumab plus low dose ipilimumab compared to histology-based chemotherapy (median 17.1 *versus* 14.9 months; HR: 0.79, p=0.007). This overall survival benefit was supported by favourable results for progression-free survival, objective response rate (ORR, 35.9 *vs.* 30.0 %) and duration of response (median 23.2 *vs.* 6.2 months). In an exploratory analysis, prolonged overall survival with nivolumab plus low dose ipilimumab compared to chemotherapy was also observed among the 550 patients with PD-L1 <1% (median 17.2 *vs.* 12.2 months; HR: 0.62). Grade 3-4 treatment-related adverse events were reported for similar proportions of patients receiving nivolumab (33%) and chemotherapy (36%), leading to treatment discontinuation in 12 *vs.* 5% respectively. This combination of nivolumab and ipilimumab represents a potential chemotherapy-free first-line treatment option for patients with advanced NSCLC. Neither tissue biomarker PD-L1 nor TMB alone (mutations/megabase) was found discriminatory for overall survival benefit with nivolumab plus ipilimumab *versus* chemotherapy alone.[4]

ONCOGENE DRIVEN ADVANCED STAGE NSCLC

In the FLAURA trial, osimertinib (a third-generation EGFR-tyrosine kinase inhibitor) was compared to a first-generation EGFR-receptor tyrosine kinase inhibitor (TKI) in first-line NSCLC patients with an activating *EGFR* mutation in exon 19 (deletion) or exon 21 (L858R). Overall survival was one of the key secondary endpoints, while treatment cross-over to osimertinib was permitted upon confirmation of disease progression and exon 20 T790M positivity within the control arm. The final OS *(Figure 3)* was prolonged for osimertinib compared with the control arm with a median overall survival extending from 31.8 to 38.6 months, corresponding to a hazard ratio of 0.799 (p=0.048). In the control arm, 47% of patients received subsequent osimertinib. The time to first subsequent therapy or death was a median of 13.7 months for the control arm and 25.5 months for the osimertinib arm (HR: 0.478, p=0.0001). Grade 3-5 treatment-related adverse events occurred in 29% (control arm)

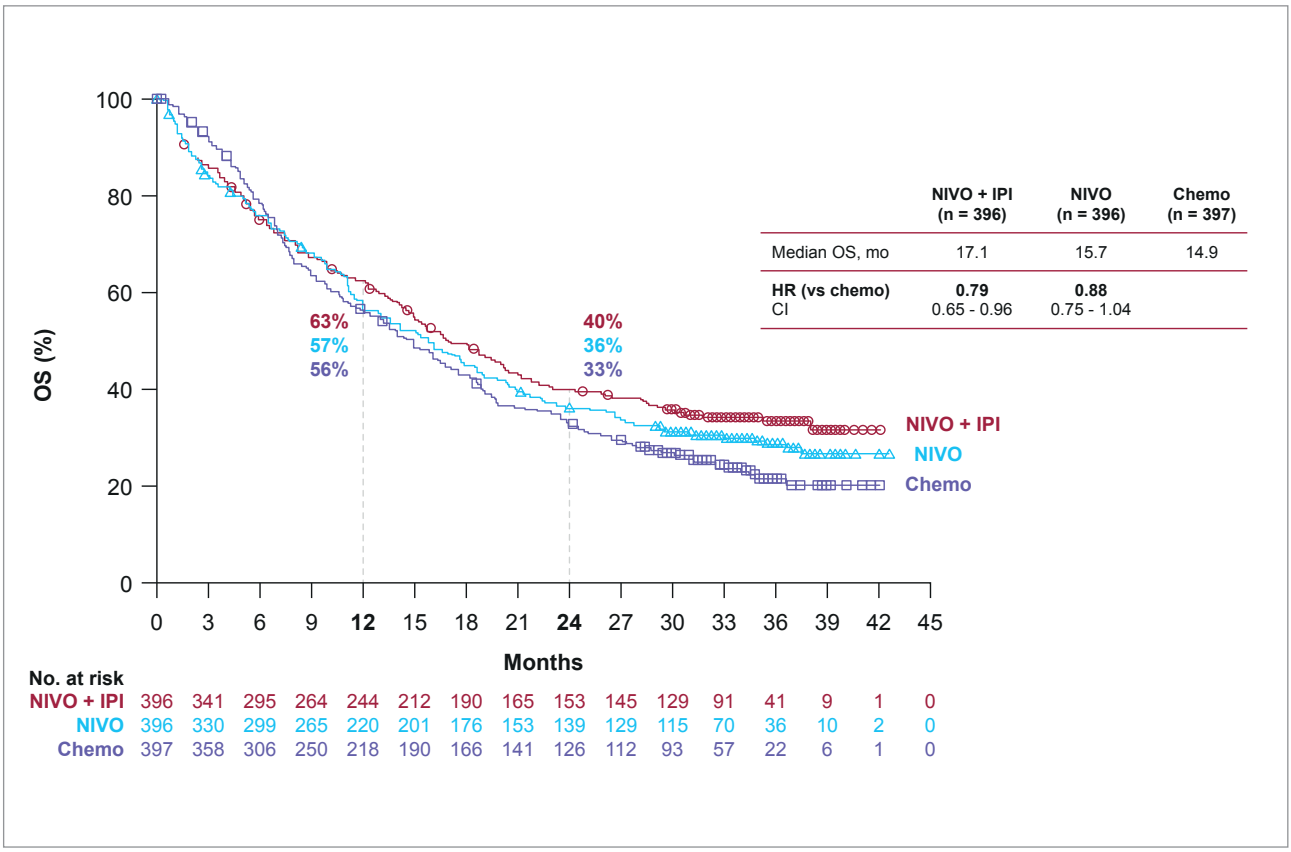

FIGURE 2. Significantly longer overall survival for NSCLC patients treated with first-line nivolumab plus ipilimumab compared with chemotherapy alone in the phase III CheckMate-227 trial.[4]

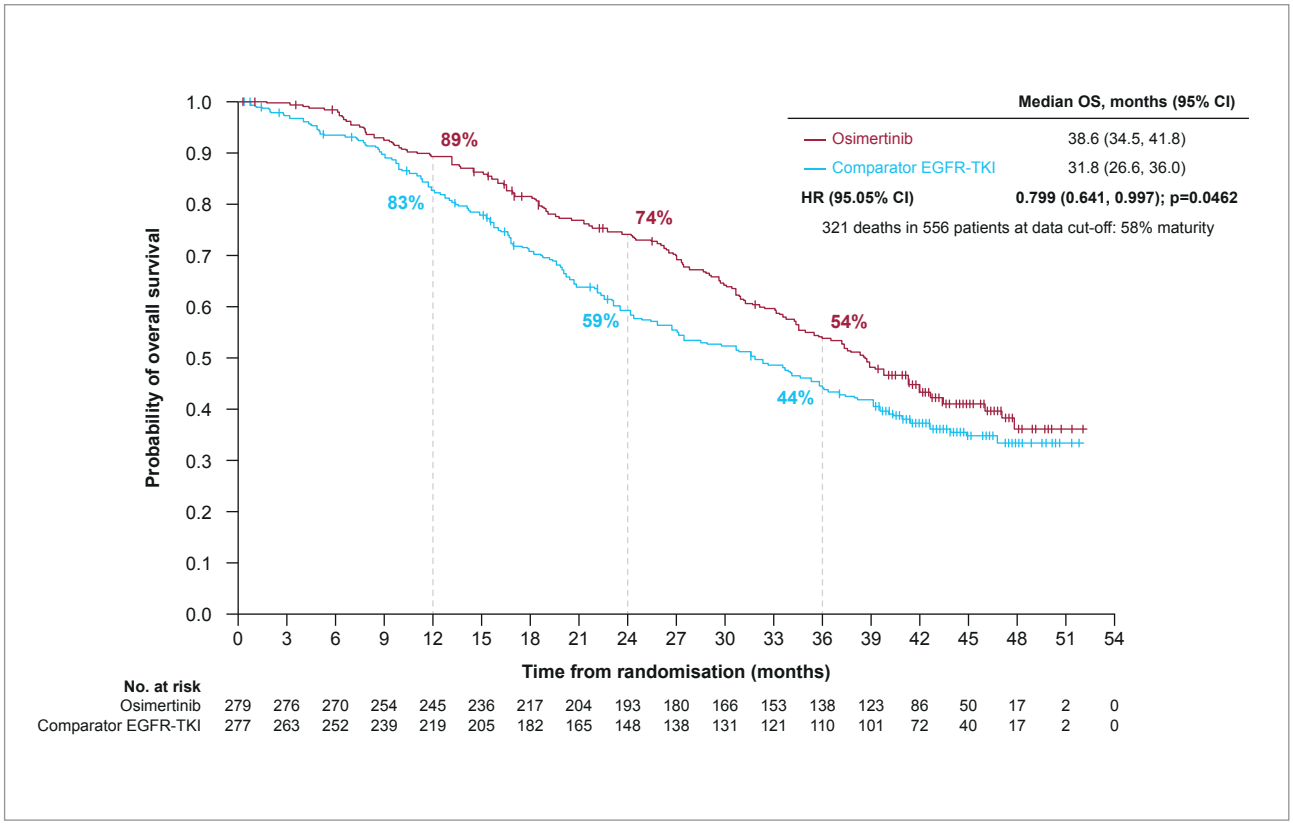

FIGURE 3. Significantly longer overall survival for *EGFR*-mutant NSCLC patients treated with first-line osimertinib compared with first generation EGFR-TKI in the phase III FLAURA trial.[5]

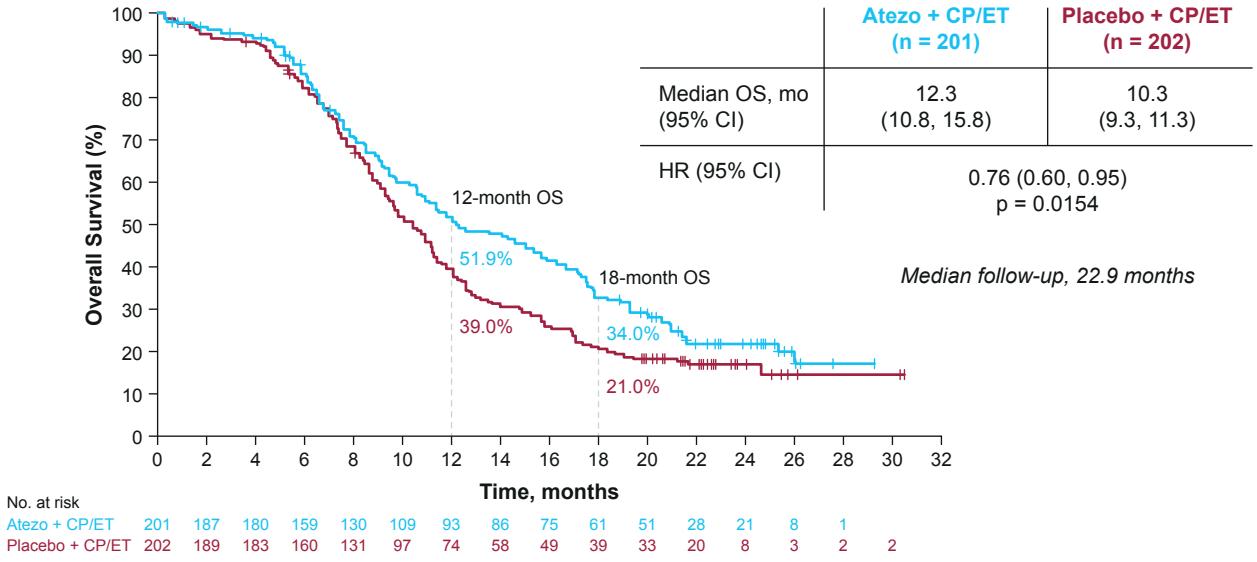

FIGURE 4. Significantly longer overall survival for SCLC patients treated with first-line atezolizumab plus chemotherapy compared with chemotherapy alone in the phase III IMpower 133 trial.[10]

and 18% (osimertinib arm), with diarrhoea (3%) and anorexia (3%) being most frequently reported in the osimertinib arm. These data support the clinical efficacy of osimertinib as the standard of care first-line treatment in non-Asian patients with NSCLC harbouring an exon 19 or exon 21 *EGFR* mutation.[5]

The final progression-free survival (PFS) and updated OS from the randomised phase III ALEX trial compared alectinib to crizotinib in untreated advanced tissue-based *ALK* positive NSCLC. ALEX demonstrates a median PFS of 34.8 *versus* 10.9 months (HR 0.43, p<0.0001), while the OS remains immature with a 4-year OS of 65 *versus* 52%, respectively.[6] In the BFAST trial, a non-randomised cohort of blood-based *ALK*+ screened patients were treated with alectinib 600mg BID. The clinical benefit was evaluated using ALEX alectinib data as a reference. BFAST *ALK*+ and ALEX reported a confirmed ORR of 80% and 71.7%, and a 12-month PFS of 78% and 68%, respectively, demonstrating the utility and high specificity of blood-based next-generation sequencing testing.[7]

In the ASCEND-7 phase II study, ceritinib demonstrated intra- and extra-cranial activity, regardless of prior treatment in patients with *ALK*+ NSCLC and brain or leptomeningeal metastases.[8]

ADVANCED STAGE SCLC

In the CASPIAN trial, durvalumab plus platinum-etoposide and maintenance durvalumab resulted in improved OS compared with 4-6 cycles of chemotherapy alone for patients with advanced stage SCLC with a median OS of 13.0 *vs.* 10.3 months (HR: 0.73, p=0.0047), respectively, and without significant interaction based on PD-L1 expression (1% cut-off or continuous).[9]

In IMpower 133, first-line atezolizumab plus carboplatin-etoposide and maintenance atezolizumab was compared with 4 cycles of chemotherapy. An updated OS analysis (median follow-up 22.9 months; *Figure 4*) confirms the continued survival benefit of the first-line atezolizumab arm over chemotherapy alone (median OS of 12.3 *versus* 10.3 months, respectively; HR: 0.76, p=0.0154), and without significant interaction based on PD-L1 expression (1% or 5% cut-off) or blood TMB.[10]

REFERENCES

1. Spigel D, de Marinis, F, Giaccone G, et al. IMpower110: Interim overall survival (OS) analysis of a phase III study of atezolizumab (atezo) vs platinum-based chemotherapy (chemo) as first-line (1L) treatment (tx) in PD-L1–selected NSCLC. Ann Oncol. 2019;30(suppl5):LBA78.

2. Paz-Ares L, Vicente D, Tafreshi A, et al. Pembrolizumab (pembro) + chemotherapy (chemo) in metastatic squamous NSCLC: Final analysis and progression after the next line of therapy (PFS2) in KEYNOTE-407. Ann Oncol. 2019;30(suppl5):LBA82.

3. Paz-Ares L, Langer CJ, Novello S, et al. Pembrolizumab (pembro) plus platinum-based chemotherapy (chemo) for metastatic NSCLC: Tissue TMB (tTMB)

and outcomes in KEYNOTE-021, 189, and 407. Ann Oncol. 2019;30(suppl5):LBA80.
4. Peters S, Ramalingam SS, Paz-Ares L, et al. Nivolumab (NIVO) + low-dose ipilimumab (IPI) vs platinum-doublet chemotherapy (chemo) as first-line (1L) treatment (tx) for advanced non-small cell lung cancer (NSCLC): CheckMate 227 part 1 final analysis. Ann Oncol. 2019;30(suppl5):LBA4_PR.
5. Ramalingam SS, Gray JE, Ohe Y, et al. Osimertinib vs comparator EGFR-TKI as first-line treatment for EGFRm advanced NSCLC (FLAURA): Final overall survival analysis. Ann Oncol. 2019;30(suppl5):LBA5_PR.
6. Mok TSK, Shaw AT, Camidge RD, et al. Final PFS, updated OS and safety data from the randomised, phase III ALEX study of alectinib (ALC) versus crizotinib (CRZ) in untreated advanced ALK+ NSCLC. Ann Oncol. 2019;30(suppl5):1484PD.
7. Gadgeel SM, Mok TSK, Peter S, et al. Phase II/III blood first assay screening trial (BFAST) in patients (pts) with treatment-naïve NSCLC: Initial results from the ALK+ cohort. Ann Oncol. 2019;30(suppl5):LBA81_PR.
8. Chow LQ, Barlesi F, Bertino EM, et al. Results of the ASCEND-7 phase II study evaluating ALK inhibitor (ALKi) ceritinib in patients (pts) with ALK+ non-small cell lung cancer (NSCLC) metastatic to the brain. Ann Oncol. 2019;30(suppl5):1478O.
9. Paz-Ares L, Goldman JW, Garassino MC, et al. PD-L1 expression, patterns of progression and patient-reported outcomes (PROs) with durvalumab plus platinum-etoposide in ES-SCLC: Results from CASPIAN. Ann Oncol. 2019;30(suppl5):LBA89.
10. Reck M, Liu SV, Mansfield AS, et al. IMpower133: Updated overall survival (OS) analysis of first-line (1L) atezolizumab (atezo) + carboplatin + etoposide in extensive-stage SCLC (ES-SCLC). Ann Oncol. 2019;30(suppl5):1736O.