Editorial Commentary

First-line management of advanced non-small-cell lung cancer: can we do better?

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Platin-based chemotherapy (ChT) was the cornerstone of first-line treatment for advanced non-small-cell lung cancer (NSCLC) until 2017, when the results of the first studies comparing immunotherapy to platin doublets became available. Today, it is clearly established that the pembrolizumab–platin-based-doublet combination is superior to the doublet alone, for patients with advanced NSCLCs without oncogenic drivers and Eastern Cooperative Oncology Group performance status (ECOG PS) = 0/1 (1). Recently published long-term efficacy results comparing pembrolizumab-platin-based ChT *vs.* that ChT regimen alone showed that the respective 5-year overall survival (OS) and progression-free survival (PFS) rates were 19.4% *vs.* 11.3%, and 7.5% *vs.* 0.6% (1). Those long-term results were driven by the programmed death-1 ligand (PD-L1) rate, with for patients whose tumor cells expressed ≥50%, 1–49% or <1% PD-L1, respectively, a 5-year OS rates at 29.6%, 19.8% or 9.6%, and 5-year PFS rates at 12.8%, 6.5% or 4.8%. The superiority of the immunotherapy-ChT combination *vs.* ChT was also reported for other immunotherapies, i.e., atezolizumab or cemiplimab (2-4) and other ChTs, e.g., the bevacizumab-platin-doublet combination (5). Unfortunately, those efficacy gains were accompanied by more adverse events (AEs), when immunotherapy was added to chemotherapy.

Therefore, in the first-line setting, all patients with advanced NSCLCs, without oncogenic drivers, can be exposed to ChT-immunotherapy. But can we do better in terms of efficacy or tolerance? Most likely, yes, and several other strategies seem relevant.

First, improve efficacy by increasing the initial therapeutic pressure, e.g., with induction of dual immunotherapy *vs.* combination immunotherapy-ChT, a strategy revived by the recent publication of the phase 3 Poseidon trial (6), or with dual immunotherapy but fewer ChT cycles, like the 9LA scheme (7). Second, identify patients for whom first-line ChT-free management with mono- or dual-immunotherapy is possible.

In the Poseidon trial (6), patients with metastatic, epidermal growth factor receptor (*EGFR)* and anaplastic lymphoma kinase (*ALK*) wild-type NSCLCs were randomized into 3 arms: tremelimumab (T; 75 mg) + durvalumab (D; 1,500 mg) + platin-based ChT (T+D+ChT) for up to 4 21-day cycles, followed by D once every 4 weeks until progression and one additional T dose; D+ChT for up to 4 21-day cycles, followed by D once every 4 weeks until progression; or ChT alone for up to 6 21-day cycles, with or without pemetrexed maintenance. For those 3 arms, respectively, 78.5%, 81.7% and 74.2% of the patients received at least 4 cycles of platin-based induction ChT. PFS was significantly prolonged with D+ChT *vs.* ChT (medians: 5.5 *vs.* 4.8 months; HR: 0.74, 95% CI: 0.62–0.89;

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P<0.0009), with no significant effect on OS (medians: 13.3 *vs.* 11.7 months; HR: 0.86, 95% CI: 0.72–1.02, P=0.0758). T+D+ChT achieved significantly longer PFS (medians: 6.2 *vs.* 4.8 months; HR: 0.72, 95% CI: 0.60–0.86; P=0.0003) and OS (medians: 14.0 *vs.* 11.7 months, HR: 0.77, 95% CI: 0.65–0.92; P<0.003). Interestingly, patients with tumor cells expressing <1% PD-L1 appeared to gain a notable survival benefit from T adjunction to D+ChT, consistent with the role of cytotoxic T-lymphocyte antigen-4 (CTLA-4) and PD-(L)1 checkpoints in the immune response. Intriguingly, PFS and OS benefits with T+D+ChT *vs.* ChT appeared to be greater for patients with non-squamous than squamous histology, but subgroup-analysis results should be interpreted with caution because of small sample sizes. For patients receiving T+D+ChT, D+ChT or ChT, respectively, maximum grade-3/4 treatment-related adverse events (TRAEs) occurred in 51.8%, 44.6% or 44.4%, leading 15.5%, 14.1% or 9.9% to discontinue treatment. Hence there is a moderate but undeniable AE excess, partly ChT-related. According to an exploratory analysis patients with non *KRAS*, *STK11*, or *KEAP1* mutations had a better outcome on the combination of tremelimumab compared with chemotherapy alone. However, small sample sizes precluded any definitive interpretation (6).

Those findings highlight the interest and originality of the phase 3, 9LA study, which aimed to increase the therapeutic induction pressure while limiting the number of ChT cycles (7), by randomizing patients with *EGFR/ALK*-wild-type advanced NSCLCs and ECOG PS 0/1 to receive nivolumab (360 mg every 3 weeks) + ipilimumab (1 mg/kg every 6 weeks) (N+I) with 2 or 4 ChT cycles. Long-term data from that study showed, after a median follow-up of 30.7 months, a respective 2-year OS and PFS rates of 38% *vs.* 26% and 20% *vs.* 8%. Improved efficacy outcomes in the experimental *vs.* control ChT arm were observed across most subgroups, including by PD-L1 levels. Respective 2-year OS and PFS rates were 37% *vs.* 22% and 20% *vs.* 5%, for patients with tumor cells expressing <1% PD-L1, and 41% *vs.* 28% and 20% *vs.* 9% for those with >1% PD-L1 expression. In addition, efficacy improvements in the experimental *vs.* control arm were observed across non-squamous and squamous histologies (7). Finally, an ongoing randomized phase III study comparing ChT plus pembrolizumab with ChT plus N+I for treatment-naive advanced NSCLC without driver gene alterations, will assess the contribution of bi-immunotherapy in this context (8). The second axis for improvement is ChT-free management. It was first achieved with mono-immunotherapy for patients with high PD-L1 expression (8-10), which represents 20–25% of advanced NSCLCs without oncogenic drivers. In the pivotal trial comparing pembrolizumab *vs.* platin-doublet, and despite a 66.0% effective crossover rate (9), respective median OS rates were 26.3 months (95% CI: 18.3–40.4 months) and 13.4 months (95% CI: 9.4–18.3 months) (HR: 0.62, 95% CI: 0.48–0.81). The Kaplan-Meier estimated respective 5-year OS to be 31.9% and 16.3%. Those results have also been confirmed with other immunotherapies, like atezolizumab for high PD-L1 expressers (10) and cemiplimab (11). Even if the magnitude of the benefit, often linked to the patient-selection methods, varied between studies, a range of arguments supports considering mono-immunotherapy as the reference treatment for these patients with high PD-L1 expression, as also confirmed by real-life data (12).

However, even if some clinical factor, like tumor burden (13,14) can help on the choice of the best strategy, no direct comparison of immunotherapy alone *vs.* combination immunotherapy-ChT is available for this subgroup of patients.

Three ongoing phase 3 studies should help elucidate this important question (15-17). The first, a French, academic study randomized 290, advanced NSCLC patients, without oncogenic drivers, with ECOG PS 0/1 and ≥50% PD-L1 expression to receive pembrolizumab alone or combination pembrolizumab-platin-doublet ChT. PFS was the main outcome criterion (15). The second, a Japanese academic, non-inferiority study, also using PFS as the main endpoint, will enroll 290 patients with advanced NSCLC restricted to non-squamous histology and ECOG PS 0/1 (16). Finally, the US Randomized, Phase III INSIGNA trial (17) plane to randomized, on the same setting, 846 patients. Mono immunotherapy could also become an option for advanced NSCLC patients ineligible for first-line platin-based ChT. The phase III, open-label, randomized, controlled IPSOS trial (18) assessed atezolizumab (1,200 mg every 3 weeks) *vs.* single-agent ChT (vinorelbine or gemcitabine given weekly) for patients with advanced NSCLCs whom investigators deemed unsuitable for platin-doublet ChT because of ECOG PS 2/3 or, alternatively, ECOG PS 0/1 and age ≥70 years with substantial comorbidities and/or contraindication(s) for platin-doublet ChT. Trial results showed an OS benefit, the principal criterion, with respective median OS at 10.3 months (95% CI: 9.4–11.9 months) *vs.* 9.2 months (95% CI: 5.9–11.2 months) (HR: 0.78, 95% CI: 0.63–0.97; P=0.028). Compared with ChT, atezolizumab was associated with fewer grade-3/4

(16% *vs.* 33%) and grade-5 (1% *vs.* 3%) TRAEs.

Another option for ChT-free management is to use dual immunotherapy. We now have long-term follow-up data from the phase III, open-label, randomized controlled CheckMate 227 trial (19) that showed, after a minimum follow-up of 61.3 months, that 5-year OS rates for N+I *vs.* ChT-treated patients, respectively, were 24% *vs.* 14% for tumors expressing >1% PD-L1 and 19% *vs.* 7% for <1% PD-L1-expressing NSCLCs. The median duration of response was prolonged significantly for patients whose tumors expressed >1% PD-L1 (24.5 *vs.* 6.7 months) and <1% PD-L1 (19.4 to 4.8 months). Compared to N alone, the N+I combination seems of little relevance for patients with ≥50% PD-L1 expression and squamous tumor histology; however, because of no predetermined statistical comparison of N+I *vs.* N, drawing a definitive conclusion remains challenging. On the other hand, the phase 3 Keynote-598 trial (20), found no incremental clinical benefit with first-line pembrolizumab–ipilimumab combination compared to pembrolizumab alone for patients whose NSCLCs expressed ≥50% PD-L1. Thus, double immunotherapy does not seem beneficial for those latter patients.

The combination of D+T regimen was also compared to ChT as treatment of naïve metastatic NSCLCs in the open-label, phase 3, randomized Mystic trial (21) that examined its effect on OS and PFS. That study failed to meet its primary endpoints. Exploratory analyses identified blood tumor mutational burden (bTMB) ≥20 mutations/megabase (mut/Mb) to be associated with longer OS for D+T than ChT recipients (HR: 0.49, 95% CI: 0.32–0.74). Notably, the phase 3, open-label Neptune study (22), which evaluated first-line D+T *vs.* ChT for patients with metastatic NSCLCs and bTMB ≥20 mut/Mb, also failed to reach its objective, showing that patient selection based on bTMB is not clinically relevant.

For elderly and/or ECOG PS 2 patients, data on the benefit of dual immunotherapy are even rarer. At the 2022 ASCO Congress, the results of a phase 3 trial comparing N+I to platin-doublet ChT for NSCLC patients aged >70 and/or with ECOG PS 2, with OS as the primary endpoint were presented (23); they were negative for the entire population, but subgroup analyses showed a deleterious effect of the dual immunotherapy on patients with ECOG PS 2 but a clear benefit for those >70 years with PS0/1. Median OS rates of N+I and ChT arms, respectively, were 14.7 months (95% CI: 8.0–19.7 months) and 9.9 months (95% CI: 7.7–12.3 months) (HR: 0.85, 95% CI: 0.62–1.16). N+I-treated elderly ECOG PS 0/1 patients obtained a significant benefit compared to ChT, with respective median OS at 22.6 months (95% CI: 18.1–36 months) *vs.* 11.8 months (95% CI: 8.9–20.5 months) (P=0.02). Median PFS significantly favored the N+I arm for the entire population: 5.5 (2.8–8.7) *vs.* 4.6 (3.5–5.6); P=0.015. Safety was similar for the N+I and ChT arms, respectively: 31.4% *vs.* 49.5% of patients with grade ≥3 related TRAEs. Notably, 28.6% *vs.* 22.3% of N+I- and ChT-treated patients, respectively, discontinued treatment because of toxicity. Tolerance of dual N+I immunotherapy was therefore similar on that of a younger population.

That N+I combination was also evaluated for NSCLC patients with ECOG PS 2 or 0/1, and untreated brain metastases, renal impairment, hepatic impairment or controlled human immunodeficiency virus infection as part of cohort 1A of the phase 3B CheckMate 817 study (24). The most common grade-3/4 TRAEs were gastrointestinal (4.0%), cutaneous (3.5%) and endocrine (3.0%) events, with no grade-5 immune-mediated AEs or selected TRAEs. Three (1.5%) treatment-related deaths occurred. The 3-year OS rate was 20.5%.

Smoking status is probably another clinical factor to consider. In the Poseidon, 9LA and CheckMate 227 trials, never-smokers did not seem to benefit from the immunotherapy-ChT combination *vs.* ChT alone in terms of OS with HR >1 for all 3 studies (6,7,19), whereas never-smokers enrolled in the Keynote-189 study benefited from the pembrolizumab-ChT combination (1,25). Finally, certain tumor sites, especially the spinal cord with the risk of its slow compression in the case of hyper-progression, could represent counter indication for mono-immunotherapy.

Conclusions

Even though clinical criteria (ECOG PS, age, etc.) and tumor cell PD-L1-expression level are imperfect markers, they can guide personalization of first-line management of metastatic NSCLCs without oncogenic drivers.

For patients with ECOG PS0/1 whose tumor cells express <1% PD-L1, Poseidon study results suggest a benefit of adding anti-CTLA-4 to D+ChT, with acceptable tolerance. For such patients, a 9LA-type regimen also seems relevant.

For patients with 1–49% PD-L1 expression, first-line ChT-free management alternatives are limited. Although it is an option in some countries, mono-immunotherapy efficacy in this group of patients is only moderate (26,27)

and it is otherwise difficult to draw definitive conclusion about the effectiveness of dual immunotherapy. Therefore, immunotherapy-ChT combination remains the reference treatment.

For patients with >50% PD-L1 expression, mono-immunotherapy should remain the reference treatment. Dual immunotherapy does not seem to provide any additional benefit. Ongoing randomized studies should give us some answers as to the potential contribution of immunotherapy-ChT for these patients.

For elderly patients in good general condition, dual immunotherapy without ChT can be an attractive option. Finally, for patients not eligible for platin-doublet ChT, regardless of the PD-L1-expression level, atezolizumab alone showed a satisfactory risk-benefit balance.

The next steps would be the implementation of prospective strategy trials, taking into account the patients' clinical characteristics (ECOG PS, age, but also smoking status, presence of liver metastases, etc.) to better adapt their management, especially for those with tumors expressing <1% PD-L1.

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