SCLC is the most aggressive subtype of lung cancer (accounting for about 15% of all lung cancers) with a poor prognosis because most patients are diagnosed in the advanced stages. No major treatment advances have been made in the past 20 years, with the SCLC survival rate being less than 10% of the 5-year overall survival (OS) rates.1,2

For advanced SCLC treatment, the first-line treatment is still the combination of cisplatin or carboplatin (according to patient’s age, performance status, renal function, and comorbidities) and etoposide or irinotecan for Asiatic patients. Second and further treatment lines depend on the timing of progression (platinum-sensitive, refractory, or resistant if progression occurs, respectively, after 6 mo, less than 6 mo, or during first-line treatment), the patient’s performance status, and comorbidities.3,4

In this dreary scenario, cancer immunotherapies (CITs) might be a light of hope because they have already remarkably improved the prognosis of advanced NSCLC, both alone or combined with chemotherapy5 and also as single agents in locally advanced NSCLC.6

SCLC is an immunogenic tumor with high somatic mutation rates owing to tobacco exposure resulting in potential neoantigens, presence of suppressed immune responses, and occurrence of paraneoplastic disorders.7

The initial high expectation raised about the efficacy of CITs in SCLC resulted in disappointment because of the lack of OS benefit, first by “nivolumab single agent versus standard chemotherapy as second-line treatment in patients with advanced SCLC” in the phase III CheckMate 331 trial,9 and afterward by both “the combination of nivolumab and ipilimumab and nivolumab alone as maintenance after first-line chemotherapy in patients with advanced SCLC” in the phase III CheckMate 451 trial.9

In this issue of the Journal, Ready et al.,10 present the updated efficacy and safety results of the randomized cohort of the CheckMate 032 trial.10

The CheckMate 032 is a multicenter, open-label, phase I/II trial testing nivolumab and the combination of nivolumab and ipilimumab at different dose levels in advanced solid tumors. The study design foresaw four single arms testing nivolumab at 3 mg/kg every 2 weeks, nivolumab at 1 mg/kg combined with ipilimumab at 1 mg/kg every 3 weeks for four cycles, followed by nivolumab at 3 mg/kg every 2 weeks until disease progression; nivolumab at 1 mg/kg combined with ipilimumab at 3 mg/kg every 3 weeks for four cycles followed by nivolumab at 3 mg/kg every 2 weeks until disease progression; nivolumab at 3 mg/kg combined with ipilimumab at 1 mg/kg every 3 weeks for four cycles, followed by nivolumab at 3 mg/kg every 2 weeks until disease progression.11

Eligible patients had a diagnosis of advanced solid tumor, were aged 18 years or older, had an Eastern Cooperative Oncology Group performance status of 0 to 1, had undergone treatment at least once or twice; brain metastases were not exclusion criteria if stable. No PD-L1 selection was made.11

On the basis of the safety results and activity signal, a randomized (3:2) cohort was added,10 as reported by Ready et al.,10 comparing in terms of overall response rate (ORR) by blinded independent review, nivolumab at 3 mg/kg every 2 weeks and nivolumab at 3 mg/kg
combined with ipilimumab at 1 mg/kg every 3 weeks for four cycles followed by nivolumab at 3 mg/kg every 2 weeks. The number of previous treatment lines was the only stratification factor.

As the authors concluded, the activity and efficacy in this analysis confirmed the data from the pooled nonrandomized and randomized cohorts in CheckMate 032.11

The combination of nivolumab plus ipilimumab substantially improved the primary end point of ORR compared with nivolumab monotherapy (21.9% versus 11.6%, OR = 2.12, \( p = 0.03 \)) although the combination was associated with increased toxicity (68.8% versus 53.7% overall adverse events [AEs], 37.5% versus 12.9% grade 3 to grade 4 AEs for nivolumab plus ipilimumab and nivolumab, respectively) and treatment-related deaths (three versus one).10 The higher ORR did not translate into longer progression-free survival (PFS) or OS, so the clinical impact of these data remain questionable. In addition, no significant benefit in OS was seen with nivolumab plus ipilimumab versus nivolumab in any patient subgroups analyzed.10

The efficacy of the combination of nivolumab plus ipilimumab in CheckMate 032 is similar to the one reported by the combination of durvalumab and tremelimumab in both the phase I/II trial by Cho et al. (9.5%),12 and the arm A of the phase II BALTIC trial (9.5%).13

However, both combinations had lower ORR than the 33% ORR by pembrolizumab single agent in the PD-L1 expressing SCLC population of the KEYNOTE 028 trial.14

Regarding safety, grade 3 to grade 4 AEs were higher for the combination of durvalumab and tremelimumab in the BALTIC trial (37.5% for nivolumab plus ipilimumab versus 48% for durvalumab and tremelimumab) but lower for the ones in the trial by Cho et al. (37.5% for nivolumab plus ipilimumab versus 23% for durvalumab and tremelimumab), and both were much higher than the single-agent ones (17.6% for atezolizumab,15 12.9% for nivolumab, 8.3% for pembrolizumab,14 and 0% for durvalumab16).

Focusing on efficacy data, although PFS and OS were secondary end points, the analysis was not powered to drive any conclusion, and the ORR benefit did not translate into a survival prolongation, and even the slight PFS advantage at 3 months was lost at 6 months. A reasonable explanation is the higher toxicity of the combination that led to a reduced number of median doses for the combination compared with the single agent (two versus three for nivolumab-ipilimumab and nivolumab, respectively) and a higher number of safety-induced interruptions even among responders (29% versus 18% for nivolumab-ipilimumab and nivolumab, respectively).

As a matter of fact, the dose and schedule of nivolumab and ipilimumab were selected on the basis of activity and safety results of the nonrandomized part and did not follow a classic dose-finding methodology.

Although the safety was overall similar to the one with durvalumab and tremelimumab, the authors, Ready et al.,10 correctly point out that a dose per schedule change should be further tested, similar to the 6-week or 12-week schedule as in the CheckMate 012.17

Finally, another explanation of the efficacy discrepancy, particularly also for OS, could be the fewer number of patients treated with the combination who received a poststudy treatment compared with nivolumab single agent (16.7% versus 32.0%).

No available biomarker identified a benefitting population in the CheckMate 331,8 whereas biomarker data of the CheckMate 4519 have not yet been disclosed.

In CheckMate 332, all the biomarker analyses were exploratory and therefore underpowered, but a signal for a possible predictive role of the tumor mutational burden was identified. Still, the impact of tumor mutational burden on immunotherapy or its combinations was not confirmed in various phase III trials in SCLC.18,19

In conclusion, phase I/II trials may generate an interesting signal but proper validation in adequately powered randomized trials is inevitable. As a matter of fact, besides the combination of checkpoint inhibitors and chemotherapy in first line, so far, no remarkable activity of CIT or CIT combinations could be confirmed in pretreated patients. In addition, no biomarkers are available to characterize benefitting patients.

In this trial, the combination of nivolumab and ipilimumab has shown interesting activity data that are worthy of further investigation, although a study for a careful evaluation of the dose and schedule should be put in place together with a biomarker research strategy.

Certainly, the setting for this combination needs to be reconsidered after the available results of the CASPIAN18 and IMpower133 trials.19

References


