Letter to the Editor

NICOLAS, DETERRED and KEYNOTE 799: focus on escalation of conventionally fractionated chemoradiotherapy by immune checkpoint inhibition in unresectable stage III non-small cell lung cancer

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After unprecedented improvement of progression-free survival (PFS) and overall survival (OS) in the ground-breaking PACIFIC trial (1), further intensification of trimodal therapy with concurrent application of immune checkpoint inhibitors (ICIs) and conventionally fractionated concurrent chemoradiotherapy (cCRT) in unresectable stage III non-small cell lung cancer (NSCLC) is being pursued.

Another consolidation therapy following cCRT with pembrolizumab was evaluated in the phase II trial LUN 14-179 in 93 patients and found an improved PFS and OS in comparison with historical controls of chemoradiotherapy (CRT) alone (2). The trial also reported acceptable treatment-related toxicity with a pneumonitis grade ≥III rate of 6.5% (6 patients) similar to the PACIFIC results (1). In addition, the subgroup analysis of Anouti *et al.* (3) found that stage IIIA and longer duration of pembrolizumab (≥4 cycles) were associated with prolonged PFS and OS.

Hereafter, 3 non-randomized multicenter phase II trials: NICOLAS, DETERRED and KEYNOTE 799 have reported results regarding further treatment intensification (4-6).

The NICOLAS trial was designed to initially investigate nivolumab consolidation after cCRT or sequential CRT (sCRT). After proven feasibility of sequential ICI in the PACIFIC study, concurrent use of the PD-1 inhibitor nivolumab with cCRT followed by 12 months of nivolumab maintenance therapy was additionally investigated (4). This multicenter study included 79 patients with stage IIIA/B NSCLC [Union for International Cancer Control (UICC) TNM 7th edition]. The primary endpoint was defined as the number of patients experiencing grade ≥III pneumonitis in the first 6 months. Additionally, the study was designed to show an increase of 1-year PFS from approx. 45% to ≥60%. After a median follow-up time of 21 months, median PFS was 12.7 months and the 1-year PFS was 53.7%. Thus, not meeting the pre-specified efficacy goal. However, significant survival differences were seen between patients with UICC stage IIIA *vs.* IIIB disease. Two-year OS for patients with stage IIIA and IIIB was 81% and 56%, which is identical to the standard arm of the PACIFIC trial (55.6%) (1). A total of nine patients (11.7%) experienced grade ≥ III pneumonitis (8 grade III and 1 grade V pneumonitis), all attributed to nivolumab, whereas four cases were also attributed to thoracic irradiation (TRT) with probable association. In addition, one patient died caused by esophageal ulcer with hemorrhage potentially relation to combined treatment.

The second trial, the DETERRED trial, was divided into two parts (5). Part I included 10 patients who received carboplatin AUC 2 and paclitaxel 50 mg/m^2 weekly concurrent with TRT. Three weeks later, consolidation therapy was continued with carboplatin AUC 6, paclitaxel 200 mg/m^2 and 1,200 mg atezolizumab every 3 weeks for two cycles followed by atezolizumab maintenance for up to 1 year. In part 1, 8 of 10 patients (80%) experienced at least one

grade III or higher adverse events (AE). Two patients were observed with grade III immune-related AEs [dyspnea (n=1) and arthralgia (n=1)]. One patient eventually died from a tracheoesophageal fistula after experiencing a grade IV lung infection.

Part II included 30 patients who received cCRT, as in part I, concurrently with 1,200 mg atezolizumab followed by the same consolidation and maintenance therapies as in part I. The median follow-up time and PFS were 22.5/18.6 months in part I and 15.1/13.2 months in part II. In part 2, 24 (80%) patients showed at least one grade 3 or higher AE. Six (20%) patients experienced grade 3 or higher immune-related toxicity. Only one (3%) patient experienced a grade III pneumonitis. Importantly, both, the NICOLAS and DETERRED trials confirmed safety and feasibility of concurrent application of ICI with cCRT (4,5). Concerning the secondary endpoints, especially PFS, both trials were rather sobering in their results, although the achieved 12-month PFS rates were clearly superior to historical values of cCRT alone.

The results of the phase II KEYNOTE-799 was recently published and investigated pembrolizumab plus cCRT in patients with unresectable stage III NSCLC. This study is a follow-up to a phase I, non-randomized controlled trial, with 21 patients from Jabbour *et al.* (6). They previously showed that intensified treatment is well-tolerated, demonstrating promising PFS rates (estimated 12-month PFS: 69.7%). The authors found that patients with at least 1 dose of pembrolizumab had a median PFS of 18.7, whereas patients with ≥2 doses had a median PFS of 21 months. KEYNOTE-799 subsequently enrolled a significantly larger cohort with 216 patients from 52 academic facilities and community-based institutions in 10 countries.

Across all patients, the primary endpoint was the objective response rate (ORR) and the incidence of grade ≥3 pneumonitis. It should also be emphasized that the KEYNOTE-799 is lacking a control arm and treatment response was assessed by the investigators which may impact the study results. Cohort A with 112 patients (squamous and non-squamous histology) who received carboplatin (AUC 6) and paclitaxel (200 mg/m^2) on day 1 of a 3-week cycle. Subsequently, patients received carboplatin (AUC 2) and paclitaxel (45 mg/m^2), weekly for 6 weeks and 2 cycles of pembrolizumab (200 mg) every 3 weeks concurrently with TRT. Cohort B included 102 patients with non-squamous histology. They received 3 cycles of cisplatin (75 mg/m^2) and pemetrexed (500 mg/m^2) plus pembrolizumab (200 mg) on day 1 of each 3-week cycle and standard TRT during cycles 2 and 3. After concurrent chemo radioimmunotherapy, both groups continued pembrolizumab (200 mg) every 3 weeks up to one year unless SAEs occurred. The median time from the first dose to the database cutoff date was 18.5 months in cohort A and 13.7 months in cohort B. ORR in groups A and B was very promising with 70.5% and 70.6%, respectively. Median PFS, OS and ORR were neither achieved in group A nor in group B. The 12-month PFS was 67.1% in group A and 71.6% in group B. In group B, this was the highest 12-month PFS rate published for unresectable stage III disease. Grade ≥III pneumonitis occurred in 16 patients, 8% in group A and 6.9% in group B. Overall, KEYNOTE-799 reported 16 (7.4%) patients with grade ≥III pneumonitis and 5 (2.3%) patients with pneumonitis-related death.

The significantly higher number of included patients, due to more participating centers, increases the impact of this phase II study. In addition, follow-up imaging (up to 54 weeks), as well as the strict radiation treatment constraints, including mean lung dose, total lung V5 and V20 seems to also be favorable. Furthermore, especially group B showed a very low discontinuation rate (<20%), as well as encouraging tolerability and a low incidence of severe toxicity, despite this intensified treatment. However, the relatively short median follow-up must be noted and longer-term results are eagerly awaited. Also, the multinational design may lead to bias, as decision concerning tumor resectability may not be uniform. Furthermore, the exclusion of patients with Eastern Cooperative Oncology Group (ECOG) performance status 2 and the lack of information on tumor volume, i.e., gross tumor volume should be noted.

Intensifying the concurrent phase of trimodal therapy by introducing pembrolizumab to cCRT in KEYNOTE 799 likely achieved two important goals.

Firstly, a significant increase in ORR (tumor shrinkage) directly during the course of chemoradioimmunotherapy and/or just before the start of maintenance therapy with ICI. It is likely that this goal was reached with significantly higher reported complete and partial remission rates.

Secondly, an accelerated effect on the establishment (velocity) of the anti-tumor immune response by early addition of pembrolizumab. Based on reported duration of response (DoR) rates at 12 months. Objective confirmation by comprehensive analysis of markers of immune response such as peripheral and tumor-infiltrating lymphocyte subsets, circulating cytokines, and circulating cell-free deoxyribonucleic acid (DNA) is of interest and is planned to

be investigated via exploratory biomarker research. Despite the planned analysis of the T-cell repertoire from tumor tissue and blood, the lack of dynamic analysis of absolute lymphocyte counts within the competitive treatment phase and thereafter may be considered as a limitation.

In summary, concurrent chemoradioimmunotherapy followed by maintenance treatment with ICI appears safe. Nevertheless, compared with PACIFIC (30.5% AEs of grade III or higher and 4.8% of patients with a pneumonitis of grade III or higher) and LUN 14-179, KEYNOTE-799 and the NICOLAS trial seem to have slightly higher immune-related pneumonitis rates. Nevertheless, it must be emphasized that potential biases play a pivotal role here. For example, the PACIFIC study only included the fittest patients after cCRT compared to the NICOLAS trial.

Concurrent chemoradioimmunotherapy may be associated with acceleration of objective tumor response (tumor shrinkage) and response duration. The historically unprecedented 12-month DoR rate in the PACIFIC (72.8%) was further improved in KEYNOTE-799 trial (cohort A: 79.7%, cohort B: 75.6%). Nevertheless, ongoing studies, need to pay more attention to firstly deciphering treatment-related lymphocytopenia, monitoring of peripheral and tumor-infiltrating immunocompetent cell subsets and circulating markers of continuous disease activity such as circulating tumor DNA (ctDNA), specific genetic mutations such as Serine/threonine kinase 11 (STK11) mutation (7) to make more precise statements about residual disease, potential patterns of failure and response duration. Additionally, new combinations such as oleclumab or monalizumab to consolidation durvalumab therapy after cCRT showed promising early results and acceptable toxicity profile but needs longer follow-up time (8).

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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