Editorial Commentary

Immediate start of durvalumab after chemoradiotherapy in unresectable non-small cell lung cancer UICC stage III: early results from the TORG1937/DATE study

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The authors of the TORG1937/DATE study should be commended on their well-designed "Phase II study of Durvalumab immediately after completion of chemoradiotherapy in unresectable stage III non-small cell lung cancer" published in *Clinical Cancer Research* (1). The primary aims of the study were efficacy and toxicity of Durvalumab treatment started immediately, i.e., one day, after the end of concomitant chemoradiation (cCRT). The primary endpoint was 1-year progression-free survival (PFS) indexed by the date of registration for cCRT. Additionally, the 1-year PFS from initiation of durvalumab was also assessed as a secondary endpoint, which is better comparable to the results from the PACIFIC trial (2-4). The other co-secondary endpoints were toxicity, objective response rate (ORR), 2-year PFS and four endpoints regarding overall survival (1- and 2-year OS, OS from registration, OS from start of durvalumab). The number of patients was calculated based on an assumed 1-year PFS of 63%. Forty-two of the initially registered 47 patients received Durvalumab therapy, two of which were not evaluable because of consent withdrawal and loss to follow-up. With a median follow-up of 14.0 months, this study revealed a 1-year PFS of 75% and a median PFS (mPFS) of 14.2 from registration. The mPFS as of the start of durvalumab was 12.7 months. Pneumonitis was the main adverse event of special interest (AESI) with a rate of 78.7% any grade and 4.3% grade 3 or more. The 1-year OS rates were well above 95%, which has to be taken with a grain of salt regarding the relative immaturity of the data. Concluding, the authors state that the primary endpoint was met with 1-year PFS of 75% and that pulmonary toxicity was in the range of the Japanese sub cohort of PACIFIC.

Since lung cancer is still the main cause for cancer-related deaths worldwide it constitutes an ongoing medical problem, which continues to involve all clinical disciplines related to thoracic oncology. Approximately 80% of the patients are diagnosed with non-small cell lung cancer (NSCLC), 30% of which present in locally advanced Union for International Cancer Control (UICC) stage III (5,6). The established standard of care (SoC) treatment is concomitant chemoradiotherapy (cCRT) with 60–66 Gy in 2 Gy fractions followed by durvalumab for 1 year (2,3,7,8). The 5-year results of the PACIFIC trial are consistent with prior publications demonstrating continuous clinical benefit of durvalumab maintenance treatment compared to placebo after CRT. The 1-year and mPFS rates with this regimen were 55.7% and 16.9 months, respectively, regardless of the patients' programmed cell death ligand-1 (PD-L1) status (4). While all grade pneumonitis of any cause occurred in 32.8% of the Durvalumab patients, the rate for grades 3–4 was 3.4%. Additionally, pneumonia was observed in 13.3% and 4.4%, respectively.

The immunogenic effect of chemotherapy and irradiation has been documented in multiple preclinical studies

partially quoted by the authors (9-11). Hence, in order to take advantage of the synergy between these two clinical treatment modalities and immunotherapy, the idea of a short interval between end of CRT and start of durvalumab seems plausible. Even more so as the results from PACIFIC (2-4) corroborate this notion. In this context TORG1937/DATE highlights the importance of quick initiation of durvalumab initiation after CRT. More than 70% of the patients started durvalumab on the day after completion of cCRT, 1 (2.4%) patient had a lag time of eight days. This focus on the time factor is of interest since accelerated repopulation is an important issue in NSCLC. The 5-year outcome data of PACIFIC corroborate the beneficial effect of early Durvalumab administration within 14 days after the end of CRT (4), with a HR of 0.54 [95% confidence interval (CI): 0.37–0.80]. In two real world data (RWD) studies—one Japanese analysis (12) and one Austrian (13)—the intervals between the end of CRT and the start of immune checkpoint inhibition are 13 and 14 days, respectively. Mostly, however, the median delay in RWD studies amounts to approximately 40 days (14-18) with up to 72 days in the S-REAL study (19). Hence, it seems hard to implement early durvalumab administration in daily clinical practice (19,20). Since the 14 days cut-off is apparently beyond reach in most clinical contexts as described by multiple RWD studies (14-19), TORG1937/DATE poses the question of how to manage the start of durvalumab precisely on the next day after CRT completion.

Additionally, several issues concerning endpoints and statistics as well as the comparability to PACIFIC with respect to outcome and toxicity arise. As the authors state, the statistics tool required 42 patients under the prerequisites quoted above. The authors included 47 patients to account for drop outs. As a matter of fact, 5 patients did not receive durvalumab and 2 of the remaining 42 could not—as the authors dually note—be evaluated for 1-year PFS because of withdrawal of consent and loss to follow-up. It seems questionable in how far the final cohort of 40 patients fulfil the initial statistical criteria. The authors might have wanted to discuss this aspect since the small patient number of 42, was finally not met, which may question the validity of the study. With regard to the comparability to the current SoC the authors state that with 12.7 months mPFS from start of durvalumab was not notably different from mPFS in PACIFIC (2-4) and PACIFIC-R (14,21). Of note, the mPFS in PACIFIC and PACIFIC-R were 16.9 and 21.7 months. Hence, the mPFS in TORG1937/DATE is shorter by 25% and 42%, respectively, which constitutes a substantial difference. This is even more striking as the 1-year PFS of 55.7% in the long-term analysis of the PACIFIC trial (4) was markedly lower than in the current analysis with 75%. The authors claim that the study met the primary endpoint of 1-year PFS from registration before cCRT, which would mean approximately 12 months from the start of durvalumab. With a median follow-up of 14.2 months, however, the data at the present stage seem rather immature to infer definite conclusions. Hence, the results from TORG1937/DATE appear somewhat inconclusive thus far. A longer follow-up period might potentially resolve this issue. Lung toxicity as a consequence of thoracic chemoradioimmunotherapy is a side effect that merits special interest in prospective and RWD studies. The authors report an extremely high rate of almost 80% all grade pneumonitis. While there are only two studies (22,23) that report a similar level of pulmonary toxicity, PACIFIC lists all grade pneumonitis at a rate of 32.8% (3). This large discrepancy is only explainable by a very comprehensive definition of lung toxicity (22,23) summarizing pneumonia, pneumonitis, fibrosis, pleural effusion, hypoxia and respiratory distress under one term. Unfortunately, the TORG1937/DATE study group neither gives a clear definition of pulmonary toxicity nor discusses the huge difference with literature. Likewise, the lack of data on grade 2 pneumonitis, which is clinically highly relevant as it causes respiratory distress that is usually treated with corticosteroids, hampers a clear understanding of the toxicity profile.

The authors themselves mention the following limitations, which may have influenced outcome: small sample size, median age 65 years (exclusion of patients above 75 years), PD-L1 status known only in 85% of patients and radiation techniques [almost 70% three-dimensional radiotherapy (3D-RT)]. With respect to the primary endpoint, i.e., PFS, the first three may have an influence. As for the radiation techniques, it seems astonishing that almost 70% were treated with 3D radiation, whereas IMRT/VMAT is nowadays routinely used in radiation oncology departments. Nevertheless, while advanced radiation techniques improve LRC (24) their impact on PFS is limited.

In summary, as only 2% of the patient population qualifies for prospective studies (25) there are several structural difficulties, which hamper the direct comparison of studies that test the PACIFIC regimen prospectively with RWD (25). This seems important in the given context, as this small prospective phase II trial with 42 patients

presents results, which have to be corroborated not only by larger prospective trials but also in the clinical setting. Although PACIFIC demonstrated that an interval of less 14 days between CRT and Durvalumab is beneficial for outcome, the question whether a further shortening of the interval to zero results in an outcome benefit is—thus far—inconclusively answered by TORG1937/DATE. Likewise, toxicity remains an unresolved issue, especially since elderly patients >75 years were excluded. Finally, with RWDs in mind, an immediate start of immunotherapy on the day after finishing chemoradiotherapy seems hard to achieve in daily practice.

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Footnote

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