# Quality of life with durvalumab in stage III non-small-cell lung cancer


Published Online
October 7, 2019
https://doi.org/10.1016/
S1470-2045(19)30643-6

See Articles page 1670

In *The Lancet Oncology*, Rina Hui and colleagues report the patient-reported outcomes (PROs) data of the PACIFIC study.[1] The PACIFIC study[2,3] set a new standard of care in patients with stage III non-small-cell lung cancer, finding a significant benefit in survival with adjuvant durvalumab after chemoradiotherapy compared with placebo. Evaluation of health-related quality of life (HRQOL), showed that the addition of durvalumab was not detrimental to HRQOL; for example, physical functioning (mean change from baesline to week 12 0·1 [95% CI −1·10 to 1·28] in the durvalumab group *vs* 2·0 [0·22 to 3·73] in the placebo group) and global health status or quality of life (2·6 [1·21 to 3·94] *vs* 1·8 [−0·25 to 3·81]) remained stable with both treatments.

Hui and colleagues[1] used validated methods, in complement, to analyse HRQOL data, namely the mixed model for repeated measures, the time-to-deterioration approach, and an evaluation of the proportion of patients who showed a clinically relevant improvement of key symptoms relative to baseline.[4] All methods showed concordant results, supporting the hypothesis that durvalumab did not compromise HRQOL. Hui and colleagues analysed five key symptoms—cough, dyspnoea, chest pain, fatigue, and loss of appetite—which are dimensions that have been assessed in other lung cancer trials.[5] Evaluation of specific symptoms, even if HRQOL is a secondary endpoint, is good practice to reduce the incidence of type I errors associated with the multidimensionality of HRQOL. The authors should also be commended for interpreting their results in terms of the minimal clinically important difference (MCID), to ensure the clinical relevance of the difference observed. This approach is not systematically used, particularly in lung cancer trials.[6] Moreover, the results of the PROs analyses are strengthened by the fact that the PACIFIC trial was a double-blind study, because the findings are not affected by patients' knowledge of their treatment allocation, which could introduce a bias in HRQOL evaluation. The PACIFIC trial results are also consistent with previous studies,[7] which showed that immunotherapy did not compromise HRQOL.

Hui and colleagues used European Organisation for Research and Treatment of Cancer (EORTC) questionnaires that have been validated in lung cancer—the Quality of Life Questionnaire-Core 30 (QLQ-C30) and its lung cancer module, the Quality of Life Questionnaire-Lung Cancer 13 (QLQ-LC13)—which are widely used in non-small-cell lung cancer phase 3 trials.[6] These existing questionnaires cannot be adapted to new treatments such as immunotherapy. In fact, the toxicity profile of immunotherapy is different to that of non-immunotherapy interventions, and new approaches might be necessary to capture specific immunotherapy-related changes in HRQOL. Although the QLQ-LC13 broadly covers the respiratory domain, the questionnaire might not capture symptoms specific to immunotherapies, which might affect different organs. The EORTC has developed a new version of the lung cancer module, the QLQ-LC29, which has been validated in stage III non-small-cell lung cancer.[8] However, this questionnaire is not yet validated in all languages, and it has yet to be validated for immunotherapy. This paucity of validated questionnaires for immunotherapy emphasises the need to further develop new questionnaires that are appropriately tailored to new treatment strategies, such as immunotherapy. Meanwhile, since the development and validation of new questionnaires is a lengthy process, addition of items from the EORTC Item Library to validated questionnaires (such as regarding experience of muscle weakness) could improve evaluation of HRQOL in patients being treated with immune checkpoint inhibitors.[9]

Beyond the choice of the questionnaire, the requirements of HRQOL assessment in immunotherapy might differ from that of chemotherapy. Since immune-related adverse events affect few patients and severe adverse events remain infrequent, it is not surprising that, overall, quality of life was unaffected. There is, therefore, a need to detail adverse events in the small proportion of patients who report immune-related adverse events, who might show deterioration of HRQOL. The authors used time-to-first-deterioration of HRQOL, reflecting transient symptoms, and time-to-deterioration in which they only considered deteriorations that were confirmed at the next consecutive

timepoint in a post-hoc, exploratory analysis. Use of time-to-deterioration, with no need for confirmation, might have improved the sensitivity to detect small deteriorations in HRQOL. Another way to improve the sensitivity to detect small HRQOL modifications would be to use a MCID of 5 points, rather than the usual MCID of 10 points. In the PACIFIC study, HRQOL results are reported at a median follow-up of 25 months (IQR 14·1–29·5). Despite this already long follow-up period, long-term side-effects could still occur after the last administration of durvalumab. A longer evaluation of HRQOL would thus be interesting, especially in the present context of potentially curative treatment.

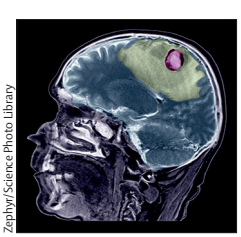
With an adequate method of PRO analysis that was based on current standards, the PRO results of the PACIFIC study confirm that adjuvant durvalumab is a drug of interest after chemoradiotherapy for stage III non-small-cell lung cancer. This study highlights the need for more data on HRQOL and new approaches, including new questionnaires items and strategies, to capture clinically meaningful changes in HRQOL in patients receiving immune checkpoint inhibitors.

*Amélie Anota, Virginie Westeel*
Methodology and Quality of Life in Oncology Unit (AA, VW), and Chest Disease Department (VW), University Hospital of Besançon, 25 000 Besançon, France; INSERM UMR 1098 (Host–Graft–Tumour Interactions and Cell and Tissue Engineering), University of Franche-Comté, Besançon, France (AA, VW); and French National Platform Quality of Life and Cancer, Besançon, France (AA)
aanota@chu-besancon.fr

AA reports grants and personal fees from Bristol-Myers Squibb, honoraria and speakers' fees from AstraZeneca, and honoraria from Roche, outside the submitted work. VW reports personal fees from Bristol-Myers Squibb, AstraZeneca, Roche, Boehringer Ingelheim, Merck Sharp & Dohme, and Lilly, outside the submitted work.

1 Hui R, Özgüroğlu M, Villegas A, et al. Patient-reported outcomes with durvalumab after chemoradiotherapy in stage III, unresectable non-small-cell lung cancer (PACIFIC): a randomised, controlled, phase 3 study. *Lancet Oncol* 2019; published online Oct 7. https://doi.org/10.1016/S1470-2045(19)30519-4.
2 Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med* 2017; **377:** 1919–29.
3 Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med* 2018; **379:** 2342–50.
4 Bonnetain F, Fiteni F, Efficace F, Anota A. Statistical challenges in the analysis of health-related quality of life in cancer clinical trials. *J Clin Oncol* 2016; **34:** 1953–56.
5 Lee C, Novello S, Rydén A, et al. Patient-reported symptoms and impact of treatment with osimertinib versus chemotherapy in advanced non-small-cell lung cancer: the AURA3 trial. *J Clin Oncol* 2018; **36:** 1853–60.
6 Fiteni F, Anota A, Westeel V, Bonnetain F. Methodology of health-related quality of life analysis in phase III advanced non-small-cell lung cancer clinical trials: a critical review. *BMC Cancer* 2016; **16:** 122.
7 Tykodi SS, Schadendorf D, Cella D, et al. Patient-reported outcomes with nivolumab in advanced solid cancers. *Cancer Treat Rev* 2018; **70:** 75–87.
8 Koller M, Hjermstad MJ, Tomaszewski KA, et al. An international study to revise the EORTC questionnaire for assessing quality of life in lung cancer patients. *Ann Oncol* 2017; **28:** 2874–81.
9 Kulis D, Bottomley A, Whittaker C, et al. The use of the EORTC item library to supplement EORTC quality of life instruments. *Value Health* 2017; **20:** A775.

# Untapped potential: recognising CNS opportunities in early oncology drug development


Zephyr/Science Photo Library

Published Online
October 3, 2019
https://doi.org/10.1016/S1470-2045(19)30633-3
See Articles page 1681

In *The Lancet Oncology*, Myung-Ju Ahn and colleagues[1] describe what, at first glance, appears to be a standard phase 1–2 study of a novel third-generation EGFR tyrosine kinase inhibitor, lazertinib. In thoracic oncology, third- generation EGFR inhibitors are characterised by their ability to inhibit not only the standard sensitising *EGFR* mutations occurring in non-small-cell lung cancer (NSCLC), but also T790M, an exon 20 point mutation, which commonly emerges as a resistance mechanism during treatment with first-generation or second- generation inhibitors. Osimertinib, another third-generation inhibitor, is already approved by the US Food and Drug Administration for use in the presence of a detectable *T790M* mutation after first-generation or second-generation inhibitor therapy, and as first-line therapy, before acquired resistance has emerged.[2,3]

In the trial,[1] lazertinib was escalated from 20 mg daily to 320 mg daily, without dose-limiting toxicities. Treatment-related grade 3 or 4 adverse events occurred in 3% of patients without apparent dose dependence; however, the proportion of patients requiring dose reductions seemed to increase with dose, from 8% at 120 mg to 17% at 240 mg to 20% at 320 mg. 62 (57%, 95% CI 48–67) of 108 patients with T790M-postive tumours had an objective response. Among those who received doses 120 mg or more versus 80 mg or less, the objective response appeared similar at 60% (95% CI 47–72) versus 54% (40–69) but the median progression-free survival was 12·3 months (95% CI 8·3–not reached)