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Mode of Histological Diagnosis in Patients With Non-small Cell Lung Cancer Treated With Chemoradiotherapy: Its Prognostic Implication, Especially in Light of the European Durvalumab Licence?

Madam – Chemoradiotherapy is the standard of care in locally advanced non-small cell lung cancer. The PACIFIC trial showed that durvalumab after chemoradiotherapy was associated with a significant survival benefit [1]. However, the European Medicines Agency restricted durvalumab approval to patients with PDL1-positive tumours [2]. Experts criticised this restriction as it was based on an unplanned *post-hoc* analysis [3].

We recently published the outcomes of 100 patients treated with hypofractionated chemoradiotherapy [4] and assessed mechanisms of histological/cytological diagnosis and its prognostic associations as posited by Peters *et al.* [3]. We found that 82% of patients were diagnosed on the first procedure; 21 patients required at least one more procedure to obtain tissue or complete staging. Fifty-one per cent of patients had successful biopsies by bronchoscopy, but 34% were diagnosed on brushes or lavages, which are unlikely to allow PDL1 testing and would not be suitable for analysis within a clinical trial such as PACIFIC (where 15–20 slides or a block of histological sample were required) [1].

We therefore assessed the prognostic impact for patients who were unable to supply an acceptable tissue sample within PACIFIC compared with the rest of the cohort. We found that there was no impact on progression-free survival (median 577 days versus 475 days; $P = 0.52$) or overall survival (median 1224 days versus 1510 days; $P = 0.60$). We were intrigued by the suggestion of a difference in post-progression survival (median 484 days versus 223 days; $P = 0.05$). The reason for this difference is unclear; all patients were treated before the routine use of immunotherapies within the National Health Service.

Although not an end point in PACIFIC, post-progression survival is an important component of health economic models developed to assess the potential cost-effectiveness of new therapies, such as durvalumab. Our data show the potential impact of carrying out a *post-hoc* analysis only in patients with evaluable biomarkers, as there may be subtle differences due to a bias selection of patients. Our analysis supports the assertion of Peters *et al.* [3] that there can be an unintentional introduction of potential bias when this is carried out.

Conflict of interest

The authors declare no conflict of interest.

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