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Concurrent Chemoradiation, Adjuvant Durvalumab, and *KEAP-1/NRF-2* Mutations: A Happy Marriage?

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Adjuvant programmed death-ligand 1 blockade after concurrent chemoradiation (CCRT) for stage III NSCLC was found to significantly prolong progression free and overall survival[1] at five-year follow-up of the PACIFIC phase 3 trial.[2] Nevertheless, a significant proportion of patients experience disease relapse and factors underlying this phenomenon are not well understood. In this issue of the *Journal of Thoracic Oncology*, Sheridan et al.[3] present a welcomed retrospective analysis of an institutional series of patients with stage III NSCLC treated with CCRT with or without adjuvant durvalumab. In particular, their analysis focuses on local-regional control, a known prognostic factor for survival after CCRT, and the potential role of *KEAP-1/NRF-2* mutations. These mutations, occurring in approximately 10% of NSCLC, clustering in *KRAS*-mutated lung cancers, are implicated in both resistance to radiotherapy and resistance to immune checkpoint blockade. *KEAP-1* is a negative regulator of *NRF2*, a transcription factor that binds to antioxidant response elements on DNA and initiates the transcription of a number of genes involved in regulation of redox balance and cellular detoxification.[4] The *KEAP-1-NRF2* pathway is an established mechanism of radiotherapy resistance in many cancers, including NSCLC, owing to the enhanced expression of ROS scavengers and detoxification pathways.[5,6] Others have revealed that at least in the context of *KRAS*-mutant NSCLC, comutations of *STK11-LKB1* and *KEAP-1* result in suppressed immune tumor microenvironment, including impaired programmed death-ligand 1 expression.[7] The potential negative predictive value of these mutations in immune checkpoint inhibitor-treated metastatic NSCLC is currently a subject of intense clinical research.

In the PACIFIC trial, local-regional control is unknown (because of missing radiotherapy details) but intrathoracic disease progression was observed in 48.1% of all relapsed patients in the placebo arm,[8] comparable with the 39% local-regional relapse rate reported by Sheridan et al.[3] in the cohort of patients treated with CCRT alone. In keeping with the negative influence of *KEAP-1-NRF2* mutations, the latter patients had a significantly higher local-regional relapse rate than wild-type *KEAP-1-NRF2* patients. Surprisingly, this difference was negated by the addition of durvalumab. Although 18% of the patients treated with CCRT and adjuvant durvalumab (n = 66) experienced a local-regional failure at 12 months, there was no difference between patients with or without *KEAP-1-NRF2* mutations in this respect. Other retrospective cohort studies comparing outcome after CCRT plus durvalumab report local-regional outcomes that seem improved to historical data of CCRT alone. In a Japanese cohort study[9] including 120 patients of whom 76 were treated with CCRT and 44 with CCRT and durvalumab, the 1-year local control was 86% in the CCRT plus durvalumab group and 62% in the CCRT group ($p = 0.005$). Radiotherapy is known to alter the tumor microenvironment attracting immune cells to the tumor site which triggers innate and adaptive responses leading to potentially prolonged tumor regression.[10] Why this should be true in particular for *KEAP-1-NRF2*–mutated tumors as compared with tumors with other known negative prognostic mutations, for example, *TP53*, is unknown. In their report, Sheridan et al.[3] formally analyzed the influence of other genes implicated in radiotherapy resistance (notably *STK11/PBRM1/SMARC4*), but sample size precludes probably firm conclusions in this respect.

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Distant relapse rate was similar between patients with or without *KEAP-1-NRF2* mutations treated either with CCRT alone or CCRT and durvalumab. This finding suggests that the beneficial effects of combining CCRT and checkpoint inhibition for patients with NSCLC with *KEAP-1-NRF2* mutations do not extend outside the radiation port. At first glance, this may seem at variance with recent reports suggesting the addition of local ablative radiotherapy to immune checkpoint inhibition improves the response rate of the latter in the metastatic setting.[11] Nevertheless, none of these studies provided an analysis of mutational status of the patients included. Stage III NSCLC may be the ideal in vivo model to dissect the influence of *KEAP-1-NRF2* mutations on response to immune checkpoint inhibition beyond radiotherapy.

Some limitations of the results presented should be mentioned. The authors state that chemoradiation management has remained essentially unchanged in the seven years' time span in which the patients were included in the analysis (2013–2020). This seems rather inconceivable, although the fractionation regimens remained rather stable, as there have been many improvements in radiotherapy planning and execution in this period. For example, the introduction of daily three-dimensional image guidance for lung cancer, especially in stage III disease, became an essential part of quality assurance because it is known that intrathoracic changes do occur during the 6 weeks of treatment.[12] In addition, in view of the small sample size and multiple testing issues, the results obtained cannot be more than hypothesis generating.

The clinical implications of the report by Sheridan et al.[3] are limited. Although intuitively one might assert that patients with stage III NSCLC with *KEAP-1-NRF2* mutations in particular might benefit from the addition of durvalumab to CCRT, such an assumption is not supported by the data presented. Thus, genomic testing for *KEAP-1-NRF2* mutations in patients with stage III NSCLC outside clinical studies in the absence of prospective data is not mandated. Should *KEAP-1-NRF2* mutation results be available, they should not influence clinical decision making. Nevertheless, the report by Sheridan et al.3 constitutes a conceptual framework in which lung cancer research community may build on to disentangle the influence of often-reported genomic mutations on the outcomes of immune checkpoint inhibition in addition to CCRT in stage III NSCLC.

References

1. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Eng J Med*. 2018;379:2342–2350.
2. Spigel DR, Faivre-Finn C, Gray JE, et al. Five-year survival outcomes of durvalumab after chemoradiotherapy in unresectable stage III NSCLC: an update from the PACIFIC trial. *J Clin Oncol*. 2021;39(suppl 15):8511–8511.
3. Shaveridan N, Offin M, Shepherd AF, et al. The impact of durvalumab on local regional control in stage III non-small cell lung cancers treated with chemoradiation and on KEAP1/NFE2L2 mutant tumors. *J Thorac Oncol*. 2021;16:1392–1402.
4. Lee S, Lim MJ, Kim MH, et al. An effective strategy for increasing radiosensitivity of human lung cancer cells by blocking NRF-2-dependent antioxidant responses. *Free Radic Biol Med*. 2012;53:807–816.
5. Jeong Y, Hoang NT, Lovejoy A, et al. Role of KEAP1/NR2 and TP53 mutations in lung squamous cell development and radiation resistance. *Cancer Discov*. 2017;7:86–101.
6. Sitthideatphaiboon P, Galan-Cobo A, Negrao MV, et al. STK11/LKB1 mutations in NSCLC are associated with KEAP1/NRF2-dependent radiotherapy resistance targetable by glutaminase inhibition. *Clin Cancer Res*. 2021;27:1720–1733.
7. Skoulidis F, Byers LA, Diao L, et al. Co-occurring genomic alterations define major subsets of KRAS-mutant adenocarcinoma with distinct biology, immune profiles and therapeutic vulnerabilities. *Cancer Discov*. 2015;5:860–877.
8. Raben D, Rimmer A, Senan S, et al. Patterns of disease progression with durvalumab in stage III non-small cell lung cancer (PACIFIC). *Int J Radiat Oncol Biol Phys*. 2019;105:683.
9. Abe T, Saito S, Iino M, et al. Effect of durvalumab on local control after concurrent chemoradiotherapy for locally advanced non-small cell lung cancer in comparison to chemoradiotherapy alone. *Thorac Cancer*. 2021;12:245–250.
10. Barcellos-Hoff MH, Park C, Wright EG. Radiation and the microenvironment—tumorgenesis and therapy. *Nat Rev Cancer*. 2005;5:867–875.
11. Theelen WSME, Chen D, Verma V, et al. Pembrolizumab with or without radiotherapy for metastatic non-small cell lung cancer: a pooled analysis of two randomized trial. *Lancet Respir Med*. 2021;9:467–475.
12. Kwint W, Conijn S, Schaake E, et al. Intra thoracic changes in lung cancer patients during the course of radiotherapy. *Radiother Oncol*. 2014;113:392–397.