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## **Promising efficacy of anti-PD-1 for pretreated advanced anal carcinoma: for which patients?**

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Aurélien Marabelle and colleagues<sup>1</sup> reported on the efficacy and safety of pembrolizumab in the anal squamous cell carcinoma (ASCC) cohort of the multicohort, multicentre, phase 2 KEYNOTE-158 study. The results reported by Marabelle and colleagues are promising, showing durable antitumour activity with pembrolizumab monotherapy in a subset of patients, with objective responses observed in 11% of patients and a median duration of response not being reached after a long median follow-up. The study also reports of an encouraging median overall survival (OS) of 11.9 months and provides the first efficacy data according to PD-L1 expression in this tumour type.

Although its incidence has increased over the past 20 years, ASCC is rare, with less than 50,000 new cases being reported per year worldwide. For patients with unresectable recurrent or metastatic disease, survival is poor, and data are scarce. After failure to first-line chemotherapy (carboplatin-paclitaxel or 5-FU-cisplatin +/- docetaxel)<sup>2,3</sup>, no antitumour treatment has proven to be effective thus far.

More than 90% of ASCC cases are related to human papilloma virus (HPV) infection. The viral oncoproteins E6 and E7 can upregulate immune checkpoint proteins such as PD-L1 but can also promote the recruitment of tumour-infiltrating lymphocytes that can trigger an antitumour host immune response. For this reason, PD-1 inhibition is of particular interest in the treatment of HPV-induced cancers, such as ASCC. The first two studies that investigated anti-PD-1 monotherapy (pembrolizumab and nivolumab) in advanced ASCC showed promising effects in terms of objective response (17-24%) and stabilization (42-47%) in 25 and 37 patients, respectively, who progressed on chemotherapy<sup>4,5</sup>. Additionally, median overall survival (OS) (9.3-11.5 months) was encouraging compared to historical data with chemotherapy alone<sup>6</sup>. Given these promising initial results, as well as unmet needs and lack of other treatment options in this setting, the ESMO guidelines recommend that anti-PD-1 inhibitors be considered where possible in clinical trials<sup>7</sup>. The recently reported results of the phase 2 PODIUM-202 trial, which evaluated retifanlimab (another anti-PD-1 antibody) in 94 previously treated patients, support this idea<sup>8</sup>.

To date, the KEYNOTE-158 study is the largest study showing the antitumour activity of an anti-PD-1 antibody in 112 pretreated ASCC patients, with a much longer follow-up period than that of previous studies (34.7 months vs. < 11 months). This confirms the interest of immunotherapy in this orphan disease. Six of the 12 (50%) patients responding to pembrolizumab had a complete response, and 90% of the responders had a prolonged duration of response at  $\geq 24$  months. Pembrolizumab was well tolerated, further supporting its value in a situation where a favourable benefit-to-risk ratio is expected.

However, although they are very encouraging, the results of this study still raise certain questions. Indeed, only a small subset (11%) of patients responded to the PD-1 blockade. Therefore, efforts should now focus on identifying responder patients who may benefit from immunotherapy in ASCC.

The study suggests a higher ORR in patients with PD-L1-positive tumours than in PD-L1-negative tumours (15% vs. 3%, respectively). However, these data should be interpreted with caution for several reasons. First, the improved ORR had no impact on survival. Second, previous studies do not support such a predictive value of PD-L1 expression, as they reported similar ORRs regardless of PD-L1 status<sup>4-5,8</sup>. Third, the definition of PD-L1-positive status is not standardized. In this reported study, PD-L1 positivity was defined as a PD-L1 combined positive score (CPS)  $\geq 1$ , whereas other definitions were previously used<sup>4</sup>. Finally, the prognostic value of PD-L1 expression cannot be excluded, given the single-arm design of the study.

Tissue tumour mutational burden (tTMB) may be another interesting predictive biomarker<sup>9</sup>. However, in contrast to what was observed in all of the KEYNOTE-158 study cohorts, the tTMB-high group had a surprisingly lower ORR to pembrolizumab than the tTMB-low group (7% vs. 11%, respectively) in the anal carcinoma cohort. Among other potential biomarkers, HPV circulating tumour DNA (ctDNA) could be useful as a noninvasive early dynamic biomarker to monitor the efficacy of immunotherapy and have the advantage of rapidly distinguishing pseudoprogressions that can be observed with PD-1 inhibitors from true tumour progressions<sup>10</sup>. The clinical value of HPV ctDNA detection needs to be investigated (beyond the proof-of concept) in large studies.

For the first time, the KEYNOTE-158 study reported of a better ORR to anti-PD-1 as a second-line therapy than as a third-line therapy or more, thus suggesting better efficacy with earlier use. This reinforces the evaluation of immunotherapy in first-line treatment, as is the case in combination with chemotherapy in several ongoing trials, including the phase 3 EA2176 study (NCT04444921) of carboplatin-paclitaxel +/- nivolumab and the POD1UM-303/InterAACT 2 study (NCT04472429) of carboplatin-paclitaxel +/- retifanlimab.

The results of the KEYNOTE-158 anal cancer cohort clearly confirm the value of immunotherapy in advanced ASCC, but they also call for further research to determine biomarkers to identify patients who will truly benefit from this therapy.

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