Melanoma Research Review™

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In this issue:

- Outcomes and risk stratification of early-stage melanoma micrometastases
- Indications for sentinel node biopsy in early-stage melanoma
- Therapeutic value of sentinel lymph node biopsy
- T-VEC + pembrolizumab for advanced melanoma
- Histopathological and immunological response to T-VEC
- Scalp melanomas and brain metastases
- Lenvatinib + pembrolizumab after progression on PD-1/ PD-L-1 inhibitor
- Encorafenib + binimetinib vs vemurafenib/encorafenib in BRAF V600-mutant melanoma
- Oestrogen receptors and melanoma in women
- Predicting RFS in stage III melanoma treated with adjuvant immunotherapy

Abbreviations used in this issue:

AE = adverse event; **AJCC** = American Joint Committee on Cancer; **ATP** = adenosine triphosphate; **CI** = confidence interval; **CR** = complete response; **CTLA-4** = cytotoxic T-lymphocyte-associated protein 4; **HR** = hazard ratio; **Ig** = immunoglobulin; **ORR** = objective response rate; **OS** = overall survival; **PD-1** = programmed cell death 1; **PD-L1** = programmed death-ligand 1; **PFS** = progression-free survival; **PR** = partial response; **RFS** = recurrence-free survival; **SN** = sentinel node; **SNB** = sentinel node biopsy; **TRAEs** = treatment-related adverse events; **T-VEC** = talimogene laherparepvec.

Welcome to the 55th issue of Melanoma Research Review

This month's review has a number of publications related to sentinel biopsy of lymph nodes such as predictors of SN+ in thin primaries. There are reviews on the Multicenter Selective Lymphadenectomy trials I and II that make a case for the procedure as having both therapeutic as well as staging value. There are also analyses of large datasets that may help identify patients likely to benefit from the procedure. Articles on T-VEC introduce questions about the effectors induced by T-VEC that may not necessarily be T cells. This may be relevant to the disappointing results of the T-VEC trial.

I hope you find the research in this issue useful to you in your practice and I look forward to your comments and feedback.

Kind Regards,

Professor Peter Hersey
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Clinical outcomes and risk stratification of early-stage melanoma micrometastases from an international multicenter study: Implications for the management of American Joint Committee on Cancer IIIA disease

Authors: Moncrieff MD et al.

Summary: This study aimed to identify adult patients, recruited from an intercontinental (Australia/Europe/North America) consortium of nine high-volume cancer centres, with high-risk sentinel node (SN)-positive American Joint Committee on Cancer (AJCC; eighth edition) stage IIIA melanoma who were more likely to derive benefit from adjuvant systemic therapy. A total of 3607 patients with pathologic stage pT1b/pT2a primary cutaneous melanomas who underwent SN biopsy between 2005 and 2020 were included in the analysis. Over a median follow-up of 34 months there was no significant survival difference between N1a and N2a subgroups. An SN tumour deposit maximum dimension of 0.3 mm was identified as the optimal cut point for stratifying survival. For patients with SN metastatic tumour deposits ≥0.3 mm and <0.3 mm, 5-year disease-specific survival rates were 80.3% and 94.1%, respectively; HR 1.26, $p < 0.0001$. Findings were similar for distant metastasis- and disease-free survival. No survival differences were seen between AJCC IB patients and low-risk (< 0.3 mm) AJCC IIIA patients. The high-risk (≥ 0.3 mm) subgroup comprised 271 (66.4%) of the AJCC IIIA cohort; while only 142 (34.8%) patients had SN tumour deposits >1 mm in their maximum dimension.

Comment: Refining the criteria for treatment of stage IIIA melanoma. This is a follow-up study on 3607 patients that attempts to define which AJCC IIIA patients are most likely to benefit from adjuvant therapy "as it is the early-stage, AJCC IIIA patients whose treatment pathway requires further clarification since their prognosis is excellent, with approximately 90% survival at 10 years." They refer to previous literature that identified the size of the metastasis (1mm) as the main determinant but report that 0.3mm in diameter was a better breakpoint below which recurrence/death was unlikely. This accounted for one-third of patients. Limitations referred to were lack of data on extracapsular spread around lymph nodes and the relatively short follow-up of 34 months.

Reference: J Clin Oncol. 2022;Jul 18 [Epub ahead of print]
Abstract

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Evaluation of the indications for sentinel node biopsy in early-stage melanoma with the advent of adjuvant systemic therapy: An international, multicenter study

Authors: Moncrieff MD et al.

Summary: The purpose of this multinational, retrospective, cohort study was to assess the sentinel node biopsy (SNB) positivity rate in 3610 patients with early-stage melanoma (0.8-2.0 mm in Breslow thickness; pT1b-pT2a) and to identify predictors of high-risk nodal disease suitable for adjuvant systemic therapy. Overall SNB-positivity rate was 11.4%, with 99.3% of SNB-positive patients reclassified to AJCC stage IIIA. Multivariate analysis suggested that sentinel node status was independently predicted by age, T-stage, mitotic rate, primary site and subtype, and lymphovascular invasion. A mitotic rate of >1 per mm^2 was associated with an increased SNB-positivity rate and predicted high-risk SNB metastases (>1 mm).

Comment: Refining primary tumour characteristics associated with high-risk nodal disease. Large multicentre study groups in melanoma have made it possible to assess risk of metastatic spread to lymph nodes in relatively thin melanoma pT1b-pT2a. To quote from the article, "the primary rationale for offering the procedure [SNB] has altered to identifying those most likely to benefit from adjuvant systemic therapy" (see, however, the article by Crystal et al., and the commentary on this below). The focus of the current study was therefore to reappraise those who are least likely to benefit from being staged by the procedure, particularly if the outcome does not alter subsequent management of the patient. The focus of the analysis was to assess primary melanoma that was associated with early-stage invasive melanoma (i.e., stage IIIA). Although mitotic rate was identified as the main independent predictor of lymph node metastasis, there was little discussion about how practical this would be in prediction of lymph node status given that mitotic rate was not included in AJCC staging because of its lack of reproducibility between centres. They also point to other limitations such as absence of data on tumour-infiltrating lymphocytes. No mention was made of gene expression studies that might be considered in future studies.

Reference: Ann Surg Oncol. 2022;29(9):5937-5945
Abstract

Therapeutic value of sentinel lymph node biopsy in patients with melanoma. A randomized clinical trial

Authors: Crystal JS et al., for the Multicenter Selective Lymphadenectomy Trials Study Group

Summary: This analysis of the prospective, randomised Multicenter Selective Lymphadenectomy Trial (MSLT-II), sought to determine how frequently SLN biopsy without completion lymph node dissection (CLND) resulted in long-term regional nodal disease control in 823 patients (58.2% male; mean age 52.8 years) with SLN metastases. After 10 years, among 855 observed basins, 80.2% (95% CI 77-83) were free of nodal recurrence. Multivariate analysis suggested that freedom from regional nodal recurrence in the observed basins was associated with younger age (HR 0.57; 95% CI 0.39-0.84; p = 0.004), thinner primary melanoma (HR 0.40; 95% CI 0.22-0.70; p= 0.002), axillary basin (HR 0.55; 95% CI 0.31-0.96; p = 0.03), SLN metastasis diameter <1 mm (HR 0.52; 95% CI 0.33-0.81; p = 0.007), and area <5% (HR 0.58; 95% CI 0.38-0.88; p = 0.01). Basin disease-free rates at 5 years were 96% (95% CI 88-100) in patients with no risk factors, 89% (95% CI 82-96) with 1 risk factor, 86% (95% CI 80-93) with 2 risk factors, 80% (95% CI 71-89) with 3 risk factors, 61% (95% CI 48-74) with 4 risk factors, and 54% (95% CI 36-72) with 5-6 risk factors.

Comment: Sentinel biopsy is not just a staging procedure. Important implications for management of stage II melanoma? The two studies by Moncrieff et al., reviewed above provide a good background to this study by Crystal et al., which makes a case for SNB having not only staging value but also a therapeutic effect. This is based on a 10-year follow-up of 823 patients randomised to SNB alone in the MSLT-II trial that showed no recurrences in the lymph node basin in 96% of patients at 5 years and 80.2% at 10 years. The controls for the study included the nodal recurrence rate in the wide excision alone group in the MSLT-I trial which was almost identical to the rate of SLN metastasis. In that trial of 500 patients in the observation group who had intermediate-thickness melanomas, 87 (17.4%) had nodal metastases at a median of 19.2 months (95% CI 13.6-24.1) after randomisation (Morton DL et al., N Engl J Med. 2014). The present article quotes "It would appear reasonable to assume that this would have been the case for the patients in MSLT-II, meaning all would have developed clinical nodal disease and required full dissection had they not undergone SLN biopsy. However, as demonstrated by the results of this study, performance of the SLN biopsy itself eliminated all nodal disease in the great majority of cases and avoided the need for a significantly more morbid full dissection. Our data, therefore, support the proposition that SLN biopsy may be considered as therapeutic in this regard, rather than merely prognostic." In the commentary on this article by (Rhodin KE et al., JAMA Surg. 2022), the importance of SNB in modern practice is summarised thus "Importantly, grade 3 to 4 treatment-related adverse events (TRAEs) occurred in 16% of patients receiving pembrolizumab. In this scenario, SLN results could be used to potentially avoid the enormous burden of adjuvant immune therapy, including financial toxicity, adverse event (AE) profile, and patient time away from productive life. Therapeutic value is easily measured objectively by overall survival. Measuring therapeutic value subjectively by focusing on patient well-being is much more difficult but critically important. SLN biopsy is a low-risk, outpatient surgery that remains valuable in the treatment of patients with melanoma. Based on the current study, SLN biopsy is the only therapy ever needed to control the SLN basin in the vast majority of patients"!

Reference: JAMA Surg. 2022;Aug 3 [Epub ahead of print]
Abstract

Melanoma Research Review™

Independent commentary by Professor Peter Hersey

Peter Hersey is an honorary Professor of Immuno Oncology in the University of Sydney and a faculty member of the Melanoma Institute Australia. He has conducted a number of phase I to III trials of immunotherapy in melanoma, including use of modified peptide antigens and dendritic cell vaccines. He has taken a leading role in studies investigating properties of melanoma cells that make them resistant to treatment and new treatment approaches to overcome these properties. He is generally recognised as a pioneer of immunotherapy for melanoma in Australia and has participated in most of the key clinical trials on immunotherapy with immune checkpoint inhibitors. He continues translational research on melanoma in the Centenary Institute as joint holder of a NHMRC program grant on melanoma.

Randomized, double-blind, placebo-controlled, global phase III trial of talimogene laherparepvec combined with pembrolizumab for advanced melanoma

Authors: Chesney JA et al.

Summary: This was a multinational, randomised, double-blind, multicentre phase III study of talimogene laherparepvec (T-VEC) plus pembrolizumab versus placebo plus pembrolizumab in 692 patients with advanced melanoma. T-VEC plus pembrolizumab did not improve PFS (HR 0.86; 95% CI 0.71-1.04) or OS (HR 0.96; 95% CI 0.76-1.22) versus placebo plus pembrolizumab. The ORR was 48.6% for T-VEC plus pembrolizumab (complete response rate [CRR] 17.9%) and 41.3% for placebo plus pembrolizumab (CRR 11.6%); durable response rates were 42.2% and 34.1%. Grade ≥3 TRAEs occurred in 20.7% versus 19.5% of patients in the two treatment arms.

Comment: Disappointing results from a large study on combining T-VEC with an anti-PD-1 in treatment of metastatic melanoma. Identification of treatments that improve the efficacy of monotherapy with anti-PD-1 checkpoint immunotherapy is an ongoing aim in treatment of melanoma. T-VEC is a herpes simplexvirus-1-based immunotherapy that promotes intratumoural T-cell infiltration. A phase Ib, single-arm trial (MASTERKEY-265) testing the combination of T-VEC plus pembrolizumab in 21 patients with advanced melanoma showed promising tumour responses (ORR 62%; CRR 43%), and the combination was generally well tolerated with no dose-limiting toxicities. These results prompted the current phase III randomised study on 692 patients. The results did not show significant differences in PFS or OS after an approximate 3-year follow-up. As discussed in the article there were differences in the selection of patients compared to patients entering the OPTIM study on T-VEC that may account for some of the differences. There were also numerical differences in the combination arm in small subgroups. There was no significant increase in immune-related AEs in the combination group. The authors conclude by pointing out that the lack of increased toxicity may still make this combination of interest in patients who are refractory to anti-PD-1 inhibitor therapy for melanoma. Neoadjuvant studies are also in progress: Rohaan MW et al. Neoadjuvant nivolumab plus T-VEC combination therapy for resectable early stage or metastatic (IIIB-IVM1a) melanoma with injectable disease: study protocol of the NIVEC trial. BMC Cancer 2022.

Reference: J Clin Oncol. 2022;Aug 23 [Epub ahead of print]
Abstract

Histopathological and immunological spectrum in response evaluation of talimogene laherparepvec treatment and correlation with durable response in patients with cutaneous melanoma

Authors: Mulder EEAP et al.

Summary: The study examined how often plasma cells were present in biopsy material after T-VEC treatment in 25 patients with stage III-IVM1a cutaneous melanoma. Plasma cells were present in all biopsies taken 3-5 months after starting T-VEC treatment. Among 12 patients with a durable response, angiocentric features (75% vs 29%; p = 0.015) and granulomas (58% vs 15%; p = 0.041) were more frequent versus 13 patients with nondurable responses. In 3 patients with multiple biopsies, there was a class switch of plasma cell infiltration from IgM to IgG with skewing to dominant Ig heavy chain clonotypes. A durable CR (>6 months) was associated with an angiocentric granulomatous pattern in T-VEC injected melanoma lesions.

Comment: A study worthy of thought. Although anti-PD-1 increases T-cell responses, does T-VEC increase something else that is related to clinical responses? Given the heterogeneity of melanoma, this study examined whether humoral responses identified by approaches in tissue sections from T-VEC-treated patients may identify responders to intralesional T-VEC. The study appears to have been meticulously carried out and apparently did not identify responses by T-cells. This contrasts with a previous study that reported such responses (Ribas A et al., Cell 2017). However, they did find evidence of humoral responses by histology methods described in the paper. In discussion, they found no correlation between humoral patterns and persistence of responses, but did find an association with granulomas and durable responses to T-VEC. Granulomatous responses have been identified against herpes simplex virus (HSV)-1 by others and this led to their speculation that a possible explanation for a durable response to T-VEC could be a result of an enhanced immune response to T-VEC due to a previous (latent) infection with HSV-1. They suggest further research is needed to elucidate this hypothesis.

Reference: Melanoma Res. 2022;32(4):249-259
Abstract

Lack of association between anatomical sites of scalp melanomas and brain metastases does not support direct vascular spread

Authors: Li AT et al.

Summary: This retrospective analysis of data (2000-18) from 693 patients who developed distant metastases from cutaneous head and neck melanomas examined locations of metastases from primary scalp and non-scalp melanomas to assess direct venous spread to the brain. Overall, 244 patients developed brain metastases, 44.7% had scalp primaries, and 55.3% had non-scalp primaries. There was no association between sites of primary melanomas and brain metastases. Compared with non-scalp melanomas, scalp melanomas had no greater propensity for first distant metastatic site being in the brain, but did have a shorter time to brain (76.3 vs 168.5 months; $p < 0.001$) and non-brain metastasis (22.6 vs 35.8 months; $p < 0.001$).

Comment: Report on a well conducted clinical study of whether scalp melanoma is associated with a higher incidence of brain metastases. The higher incidence of brain metastases from head and neck melanoma prompted this study in the belief that there may be direct venous spread from scalp to dura. The study was based on data from 693 patients and comparisons made with non-scalp and scalp melanoma. The results appear to clearly establish that the higher incidence was not due to direct spread from the scalp. Connections between the brain and systemic circulation are also of great interest in neurological disorders and apparently lymphatics connect to meningeal outer layers. Whether this is relevant to brain metastases is unknown. See De Mesquita S. J Exp Med. 2022.

Reference: Melanoma Res. 2022;32(4):260-268
Abstract

Phase II LEAP-004 study of lenvatinib plus pembrolizumab for melanoma with confirmed progression on a programmed cell death protein-1 or programmed death ligand 1 inhibitor given as monotherapy or in combination

Authors: Arance A et al.

Summary: The phase II LEAP-004 study assessed combination therapy using the multi-kinase inhibitor lenvatinib plus the PD-1 inhibitor pembrolizumab in 103 patients with melanoma who progressed on PD-1 or PD-L1 inhibitors. Over a median follow-up of 15.3 months, the ORR was 21.4% (95% CI 13.9-30.5), with 3 CRs and 19 PRs, and the median duration of response was 8.3 months. Median PFS was 4.2 months (95% CI 3.8-7.1) and OS was 14.0 months (95% CI 10.8 to not reached). In 30 patients with progressive disease on prior anti-PD-1 plus anti-CTLA-4 therapy, ORR was 33.3%. Grade 3-5 TRAEs occurred in 45.6% of patients (hypertension 21.4%) and one patient died from a decreased platelet count.

Comment: Promising results for treatment of patients failing anti-PD1 treatment. As reviewed by the authors, there is a lack of approved treatments for melanoma that progress on anti-PD-1/PD-L1-based therapy, and current guidelines recommend clinical trial enrolment or use of a therapy with a different mechanism of action. Thus, after patients have exhausted targeted therapy (if eligible) and anti-CTLA-4-based regimens, no approved therapies are available. This was a single-arm study and patients were not categorised as primary or secondary resistance to anti-PD-1. Nevertheless, overall responses of 33% and median duration of responses of 8 months were recorded and OS at 1 year was 54.5%. They compared the results to lifileucel adoptive tumour-infiltrating lymphocyte treatment that reported ORR in 66 patients. A randomised trial of pembrolizumab plus lenvatinib (LEAP-003) as first-line therapy is in progress.

Reference: J Clin Oncol. 2022;Jul 22 [Epub ahead of print]
Abstract

COLUMBUS 5-year update: A randomized, open-label, phase III trial of encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with *BRAF* V600-mutant melanoma

Authors: Dummer R et al.

Summary: This paper reports on a 5-year update from the randomised, open-label, phase III COLUMBUS trial of encorafenib plus binimetinib (n = 192) versus vemurafenib (n = 191) or encorafenib (n = 194) in patients with untreated or progressive locally advanced unresectable or metastatic *BRAF* V600-mutant melanoma. The overall 5-year PFS rate with encorafenib plus binimetinib was 23% and OS was 35%, and were 31% and 45% in a subgroup of patients with normal lactate dehydrogenase (LDH) levels; median duration of response was 18.6 months, with disease control in 92.2% of patients. Overall 5-year PFS rate with vemurafenib was 10% and OS rate was 21%, with rates of 12% and 28% in patients with normal LDH levels; median duration of response was 12.3 months, with disease control in 81.2% of patients.

Comment: Long-term results from a popular (no or low fever side effect) targeted therapy for BRAF V600 melanoma. There is nothing particularly new in this follow up, so I have reproduced extracts from the article as follows. This 5-year updated analysis assessed long-term efficacy and safety outcomes with encorafenib plus binimetinib in patients with unresectable or metastatic *BRAF* V600–mutant melanoma. The update confirmed previous reports of prolonged PFS and OS with encorafenib plus binimetinib treatment compared with vemurafenib treatment. In patient subgroup analyses, the observed OS either favoured or trended toward treatment with encorafenib plus binimetinib over vemurafenib. The 5-year OS rate was 35% for both the encorafenib plus binimetinib and encorafenib monotherapy arms; however, combination treatment demonstrated significantly longer PFS (median >5 months) and numerically longer OS (median >10 months). Compared with encorafenib monotherapy, the encorafenib plus binimetinib arm had numerically greater ORR, disease control rate, and duration of response. Furthermore, combination treatment improved tolerability; exposure-adjusted incidence rates for most AEs were lower with encorafenib plus binimetinib compared with encorafenib monotherapy. Among patients with normal LDH levels and <3 organs involved at baseline, the 5-year PFS and OS rates were 39% and 48%, respectively. In conclusion these data demonstrate the long-term benefits of encorafenib plus binimetinib in patients with unresectable or metastatic *BRAF* V600–mutant melanoma.

Reference: J Clin Oncol. 2022;Jul 21 [Epub ahead of print]
Abstract

Female melanoma and estrogen receptors expression: An immunohistochemical pilot study

Authors: Dika E et al.

Summary: This immunohistochemical analysis evaluated the effect of oestrogen receptors (ER)-α and β on melanoma outcome in 28 melanoma specimens from female patients with a previous history of breast carcinoma and female patients undergoing ovarian stimulation versus two control groups matched for age and melanoma staging. ER-β nuclear staining was detected in all women with a history of breast cancer, while cytoplasmatic ER-β was expressed in 7 cases with nuclear and cytoplasmatic ER-β expression much lower in matched controls. Cytoplasmatic ER-α positivity was detected in almost all specimens. In women undergoing ovarian stimulation for assisted reproductive technology, less nuclear ERs were detected, while cytoplasmatic ER-β and ER-α expression varied widely.

Comment: No conclusions re biologic importance but information about effects of anti-oestrogen therapy on ER. As referred to in previous issues of Melanoma Research Reviews, sex differences in survival from melanoma are now well recognised with females having almost half the death rate of males. Females also have improved response to targeted treatment with BRAF and MEK inhibitors. This was observed in the 5-year follow-up study of dabrafenib and trametinib in treatment of metastatic melanoma reported by Robert C et al. (N Engl J Med. 2015) and recently by Wargo and colleagues in neoadjuvant BRAF/MEK studies showing higher rates of major pathological responses in lymph nodes from females compared to males (Vellano CP et al., Nature 2022). The present article has focused on expression of ERs on melanoma to see if imbalances of α (stimulatory) and β (inhibitory) forms of the receptors may be relevant to melanoma biology. They conclude, "In our cross-sectional cohort study, we found that cutaneous melanoma of women treated with anti-estrogen therapy is generally more prone to express nuclear ER-β and cytoplasmatic ER-α compared to women of the same age and cutaneous melanoma staging. Although the role and the presence of ERs, especially of ER-α, in cutaneous melanoma cells is still debated, its presence in the cytoplasm can suggest a possible role of both anti-estrogen cancer therapy and estrogen non-genomic pathway among these patients. Larger multicenter studies are needed to confirm or reject this hypothesis."

Reference: Melanoma Res. 2022;32(4):231-240
Abstract

Higher proportions of CD39$^+$ tumor-resident cytotoxic T cells predict recurrence-free survival in patients with stage III melanoma treated with adjuvant immunotherapy

Authors: Attrill GH et al.

Summary: This immunohistochemical study examined whether specific cytotoxic CD8$^+$ T-cell subsets (CD39, CD103, PD-1) predicted recurrence in 103 anti-PD-1-treated high-risk patients with stage III melanoma. Over a median 19.3-month follow-up, 36% of patients experienced recurrence. Two CD8$^+$ T-cell subpopulations were associated with recurrence; CD39$^+$ tumour-resident memory cells (CD39$^+$CD103$^+$PD-1$^+$CD8$^+$ [CD39$^+$ TRM]) were a higher proportion of CD8$^+$ T cells in recurrence-free patients (p = 0.0004), while bystander T cells (CD39-CD103-PD-1-CD8$^+$) were a greater proportion of T cells in recurrent patients (p = 0.0002). CD39$^+$ TRMs localised closer to melanoma cells than bystander T cells. Multivariate analysis confirmed improved 1-year recurrence-free survival with a high proportion of intratumoural CD39$^+$ TRMs (78.1% vs 49.9%; HR 0.32; 95% CI 0.15-0.69), without complete lymph node dissection (HR 2.85; 95% CI 1.13-7.19), and with less advanced disease stage (HR 1.29; 95% CI 0.59-2.82). A regression model identified recurrence status at 1 year with an area under the curve of 75.9% in a discovery cohort and 69.5% in a validation cohort.

Comment: A well-conducted study in patients, requiring further study. The aim of this study was to identify whether particular CD8 T-cell populations may be associated with recurrence of melanoma during adjuvant treatment with immune checkpoint inhibitors. It followed previous studies showing that resident CD103/CD69 CD8$^+$ T cells were associated with improved survival in patients with metastatic melanoma treated with anti-PD-1. The studies were on pre-treatment biopsies and hence potentially useful for example identifying patients who will recur following adjuvant anti-PD-1 and who may require additional treatments such as combination with BRAF/MEK inhibitors or alternative therapies to prevent recurrence in high-risk patients. The study appears to have been well conducted although a clear distinction between CD8, CD103, CD39 and CD8, CD103, CD39-$^+$ was not apparent. CD39 is an enzyme that converts ATP to inhibitory adenosine. It is also a marker of T-cell exhaustion and associated with resistance in metastatic disease, so further study appears warranted.

Reference: J Immunother Cancer 2022;10(6):e004771
Abstract

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