Molecular and immunological features of a prolonged exceptional responder with malignant pleural mesothelioma treated initially and rechallenged with pembrolizumab

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DECLARATIONS

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ABSTRACT

Background

This case represents an exceptional response to pembrolizumab in a patient with epithelioid mesothelioma with a further response on rechallenge.

Case presentation

A 77 year old woman with advanced epithelioid mesothelioma extensively pretreated with chemotherapy demonstrated a prolonged response of 45 months to 52 cycles of pembrolizumab. On rechallenge with pembrolizumab further disease stability was achieved. Serial biopsies and analysis by immunohistochemistry and immunofluorescence demonstrated marked immune infiltration and documents the emergency of markers of immune exhaustion. Whole exome sequencing demonstrated a reduction in tumour mutational burden consistent with sub-clone elimination by immune checkpoint inhibitor (CPI) therapy. The relapse biopsy had missense mutation in BTN2A1.

Conclusion

This case supports rechallenge of PD-1 inhibitor in cases of previous CPI sensitivity and gives molecular insights.

KEYWORDS

Mesothelioma; immunotherapy; PD-1; PD-L1; TMB

BACKGROUND

Mesothelioma is a rare cancer of the pleura and mesothelial membranes associated with asbestos exposure and a poor prognosis. Subtypes include epithelioid, biphasic and sarcomatoid. A multimodal approach that may include surgery, radiotherapy and chemotherapy is often attempted for potentially resectable disease but a proven survival benefit has not, as yet, been demonstrated [1]. The majority of patients have inoperable disease. Treatment for inoperable disease has previously been with chemotherapy though with relatively poor rates and duration of response novel therapeutic strategies are required [2]. Recent trials have assessed the utility of CPI. The documentation of responses suggest that mesothelioma is a relatively "immunogenic" tumour. [3] [4] Pembrolizumab is an anti-programme death receptor 1 (PD-1) antibody investigated in mesothelioma. KEYNOTE-028 recruited 25 patients with PD-L1 positive pleural mesothelioma and has reported interim results; objective response rate of 20%, disease control rate of 52% and a median duration of response of 12.0 months (95% confidence interval of 3.7 – not reached). [5]

CASE PRESENTATION

Clinical Background

The patient is a 77 year old Caucasian woman. She was diagnosed with a left epithelioid mesothelioma on video-assisted thorascopic biopsy in 2009 with pleurally based nodules in the left hemothorax on radiological assessment. She underwent talc pleurodesis and four cycles of cisplatin and pemetrexed. Sixteen months later she developed progressive disease and was treated on a trial of NGR-hTNF (a selective vascular inhibitor) for four months to disease progression. She underwent rechallenge with four cycles of pemetrexed and cisplatin; achieving disease stability for 11 months. She then received six cycles of carboplatin and gemcitabine achieving disease stability for six months.

From June 2014 to June 2016 she received 52 cycles of pembrolizumab (MK-3475) at a dose of 10mg/kg every two weeks on a phase Ib clinic trial (KEYNOTE-028). The tumour biopsy fulfilled criteria for PD-L1 positivity as per trial protocol. She tolerated drug well with immune-related adverse events of grade 2 pruritic rash and grade 1

mucositis, remaining ECOG performance status 1. A partial response was seen on imaging after 3 months, with a 91% reduction in target lesions, that was maintained until June 2016 (figure 1). In April 2018, 21 months after completing two years of pembrolizumab, she developed asymptomatic, small volume, radiological disease progression and recommenced pembrolizumab on study, per protocol, on the same schedule. Following 3 cycles a 12% reduction in tumour size by RECIST criteria from the pre-rechallenge baseline was seen . Stable disease was maintained for 25 cycles when radiological disease progression was confirmed.

Laboratory correlates of immune response

A left pleural biopsy from 2014, taken as baseline biopsy for KEYNOTE-028, and a left pleural biopsy taken in 2018 at relapse prior to pembrolizumab rechallenge were analysed. Histopathology was consistent with malignant epithelioid mesothelioma with cells expressing WT1, calretinin and HBME-1 and negative for BerEP4.

Immunohistochemistry for PD-L1 was performed using Dako 22C3 and Ventana SP263 clones (supplementary data for methods). PD-L1 staining was increased in the relapse compared to baseline biopsy (1-49% in relapse biopsy by SP263, Figure 2).

CD3 immunohistochemistry was performed on baseline and relapse biopsies and intensity of staining quantified using the HALO software (supplementary data for methods). Intratumoural T-cells were of a higher density in the relapse compared to baseline biopsy (2092.06/mm^2 versus 348.53/mm^2) (figure 2).

A T-Cell Panel immunofluorescence panel for CD4, CD4+FOXP3+, CD8 and PanCK (pancytokeratin) was performed and analysed with inForm Cell Analysis software (supplementary data for methods). Intratumoural CD8 T-cells demonstrated an almost 5-fold increase in relapse compared to baseline biopsy and CD4+FOXP3+ T-cells demonstrated over a 30-fold increase in relapse compared to baseline (table 1, figure 3).

T-cell Subset	Baseline biopsy (2014)	Relapse biopsy (2018)
CD4	172.03	113.13
CD4+FOXP3+	2.62	88.89
CD8	128.60	565.67
All T-cells	303.26	767.69

Table 1. Intratumoural T-cell density (per mm^2) on baseline and relapse biopsy by immunofluorescence.

Genomics

Whole exome sequencing (WES) was performed on both biopsy samples and a matched germline sample (supplementary data for methods). Tumour content was 80%. The baseline biopsy had 0.92 somatic mutations per Mbp. The relapse biopsy had 0.26. No mutations were found in key drivers such as BAP1, NF2, TP53, LATS2 and SETD2. On copy number variant (CNV) analysis copy number alterations (CNA) were apparent mostly similar in frequently altered genomic region between baseline and relapse biopsy such as chr8q gain, and chr3p and chr9p loss, but also some regions were different such as loss of heterozygosity on chr6q and chr4q in baseline only (figure 4). Three independent measurements of genomic instability (basis of loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions) shows baseline biopsy had instable genome with higher HRD score. Immune related somatic mutations are detailed in table 2. All immune related somatic mutations present in the baseline biopsy were not present in the relapse biopsy. The relapse biopsy had missense mutation in BTN2A1 (c.1352G>C).

Sample	Gene Name	HGVS	Mutation Effect	TUMOR Alternative Allele Depth/Sequencing Depth	Allele Frequency
Baseline	MST1	c.1423+1->CC	Splice_Site	18/103	0.17
	PROS1	c.1030A>G	Missense_Mutation	26/132	0.2
	NLGN1	c.1504_1505insC	Frame_Shift_Ins	12/194	0.06
	NLGN1	c.1507delG	Frame_Shift_Del	12/204	0.06
	MUC4	c.5420T>C	Missense_Mutation	29/657	0.04
	TDP2	c.1037G>A	Missense_Mutation	41/155	0.26
	MUC17	c.8179G>A	Missense_Mutation	12/464	0.03
	VWF	c.1060G>A	Missense_Mutation	12/289	0.04
	MAG	c.1388C>T	Missense_Mutation	12/662	0.02

	LILRB2	c.50C>G	Missense_Mutation	12/55	0.22
	PREX1	c.1489G>A	Missense_Mutation	12/381	0.03
Progression	BTN2A1	c.1352G>C	Missense_Mutation	11/92	0.12

Table 2: Immune related somatic mutations on baseline and relapse biopsy.

DISCUSSION AND CONCLUSION

Dynamic immune changes and changes in tumour mutational burden (TMB) map the clinical response to pembrolizumab

The differences seen in levels of T-cell infiltration between the two biopsies in this patient demonstrate the dynamic changes that occur in the context of CPI treated malignancy. Three cancer-immunity phenotypes have been described. The first is “immune desert”, which can be a result of tolerance, immunological ignorance or lack of priming. In this situation no immune response is mounted to the cancer and little T-cell infiltration is seen. The second is the “immune excluded” tumour in which there is a barrier to immune cell migration to tumour caused by stromal interactions, vascular barrier and, again, no T-cell infiltration is demonstrated. Thirdly, the “inflamed” tumour demonstrate infiltration by immune cells. Inhibitory factors (e.g. PD-L1) and T-cell exhaustion may still impair anticancer immunity in this setting. [6] T-cell exhaustion describes a progressive loss of T-cell function occurring on persistent antigen presentation. [7] Relapse biopsies in this patient demonstrate increased immune cell infiltrate of CD3 CD8 and CD4 T-cells, compared to baseline. This is indicative of immune activation as a result of the primary immunotherapy treatment (a move from an immune desert to inflamed tumour) and is consistent with the prolonged response. However, there is also an increase in FOXP3 positive T-cell, a marker of regulatory T-cells, and PD-L1. Therapeutic targeting of PD-1 is known to effect regulatory T-cell function but not overall number [8]. We may consider the increase in regulatory T-cells a marker of immune exhaustion. These markers of immune exhaustion represent emerging resistance to immunotherapy as evidenced by the clinical progression. Despite these markers of immune exhaustion a response to pembrolizumab rechallenge was achieved thus resistance to immunotherapy was not complete. The finely tuned balance of immunostimulatory and immunosuppressive elements

demonstrated in these sequential biopsies in combination with the radiological data present a compelling visualisation of immune activation and exhaustion and clinical implications. A disadvantage of this study is that single biopsies were taken and there may be heterogeneity of immune infiltrates throughout the tumour burden. Ongoing trials address the potential in mesothelioma for drug combinations to move tumours to the inflamed phenotype and overcome CPI resistance. Preclinical evidence suggests chemotherapy causes a degree of immune activation [9] and studies propose rational combination and sequencing of chemotherapy and CPI to achieve this end. The phase II DREAM study of durvalumab in combination with pemetrexed and cisplatin gave an objective treatment response rate of 48% and a phase III is planned [10].

The reduction in the number of somatic mutations between two samples can suggest subclones eliminated by pembrolizumab. This phenomenon is well described previously in melanoma patients treated with nivolumab. [11] On treatment with CPI immunoediting occurs where tumour cells expressing neoantigens targeted by activated T-cells are lost. [12] The resulting loss of cancer heterogeneity results in more homogenous cancer cell population and a lower rate of somatic mutations and a lower TMB.

The case in context as a long-term responder to pembrolizumab and chemotherapy

What is remarkable about this patient's initial response is the depth and duration. The relapse of disease occurred 21 months after the last dose of pembrolizumab. A recent paper suggests nivolumab can be detected more than 20 weeks following administration which is longer than might be anticipated from previous pharmacokinetic data. [13]. Nevertheless the relapse in this patient occurred long after the elimination of all residual drug. Most CPI trials demonstrate a "tail to the curve" with a small number of patients who achieve a prolonged response. [14] Study of these "exceptional responders" can potentially inform on biological features that mark prolonged response and be hypothesis generating for further research into mechanisms of drug resistance and sensitivity.

WES results reveal a TMB low tumour. Mesothelioma is classically a TMB low tumour. Analysis of 74 cases revealed a somatic mutation rate of less than 2 per megabase in all but one case. [15] Also, in keeping with published data is the CNA seen in this case. Others report frequent CNA in keeping with mesothelioma being driven by loss of tumour suppressors rather than an oncogenic driven cancer. [15] Transcriptome analysis was not performed. Others have identified expression of the negative checkpoint inhibitor VISTA commonly in mesothelioma which may have implications on CPI response. [15]

Proposed resistance mechanisms to CPI are numerous and may be multifactorial. [16] The only immune related mutated gene evidenced in the relapse biopsy was BTN2A1. This is a T cell immunomodulatory molecule coregulated with MHC class II.[17] It's role in CPI resistance is not described. As the BTN2A mutation was seen on the relapse biopsy (post relapse but pre rechallenge) the implications of the mutation (if any) is unclear; whether having a role in emerging resistance or sensitivity to rechallenge.

It is also interesting to consider the patient's prior response to chemotherapy. She achieved an unusual (though not unique) 16 month progression free survival with first-line cisplatin-pemetrexed chemotherapy and further response on two chemotherapy rechallenges. The phase II MAPS2 trial of nivolumab or nivolumab-ipilimumab in relapsed mesothelioma included an *post hoc* analysis showing that in the nivolumab group patients who had relapse at least 3 months after pemetrexed-chemotherapy had a small survival benefit [18]. Whether these findings are replicated in other trials and whether this simply represents a more globally indolent disease or whether there is a biological rationale for chemotherapy response correlating with benefit from CPI remains to be seen.

The case in context as a response to pembrolizumab rechallenge

This patient's cancer is also exceptional in its responsiveness to pembrolizumab on rechallenge. This phenomena has not be studied in detail. Though others report the potential for a response with CPI rechallenge,[19] this is the first report, to our knowledge, of disease response on CPI rechallenge in mesothelioma.

Conclusion

In conclusion, this case represents a prolonged response to pembrolizumab in a patient with epithelioid mesothelioma to PD-1 inhibition with further durable clinical benefit on rechallenge. This supports trial data from Keynote-028 and others that mesothelioma can be responsive to CPI. In this case no reason for prolonged immune sensitivity was identified. The tumour, though PD-L1 positive, did not demonstrate a very high level of PD-L1 expression. WES did not shed light on reasons for prolonged sensitivity to CPI; chromothripsis and loss of heterozygosity are not fully assessed on WES and epigenetic modifications such as methylation are not evaluated by WES.

Serial biopsies demonstrate both the primary immune activation and emerging immune exhaustion. Future research may shed light on the mechanisms of resistance and pave the way for drug combinations to overcome CPI resistance. Cases such as this support attempts to retreat with CPI if a patient clinical condition allows. Further research into the degree to which a “partially exhausted” immune environment can be reactivated by further stimulation are warranted.

ABBREVIATIONS

BAP1	BRCA1 associated protein-1
BTN2A1	Butyrophilin Subfamily 2 Member A1
CD	Cluster of differentiation
CK	Cytokeratin
CAN	Copy number aberration
CPI	Checkpoint inhibitor
ECOG	Eastern Cooperative Oncology Group
FOXP3	Forkhead box P3
LATS2	Large Tumor Suppressor Kinase 2
MHC	Major histocompatibility complex
NF2	Neurofibromin 2
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
SETD2	SET Domain Containing 2
TMB	Tumour mutational burden
TP53	Tumor protein p53
VISTA	V-domain Ig suppressor of T cell activation
WES	Whole exome sequencing
WT1	Wilms tumor protein 1

Figure 1:
A. Axial Enhanced Computer Tomography of thorax.
Upper left panel (a): Baseline prior to commencing pembrolizumab trial (June 2014) with left posterior parietal malignant pleural disease (white circle).
Upper right panel (b): Maintained partial response after 52 cycles pembrolizumab (April 2016) with minimal residual pleural thickening (white arrow)
Lower left panel (c): Disease progression (July 2018) at site of previous disease along the left posterior parietal pleura (white circle)
Lower right panel (d): Partial response in left parietal posterior pleural disease following 3 cycles pembrolizumab rechallenge
B:Tumour response

Figure 2.
A. PD-L1 IHC by Dako 22C3 in baseline (left panel) and relapse (right panel) biopsy.
B. CD3 by immunohistochemistry in baseline (left panel) and relapse (right panel) biopsy.

Figure 3. Multi-coloured immunofluorescence panel for T-cells in baseline (upper panels) and relapse (lower panels) biopsy.

Figure 4. Circos plot of CNA and somatic mutations. From outermost to innermost track: progression sample CNA (log2R), baseline sample CNA (log2R), progression sample mutations, baseline sample mutations

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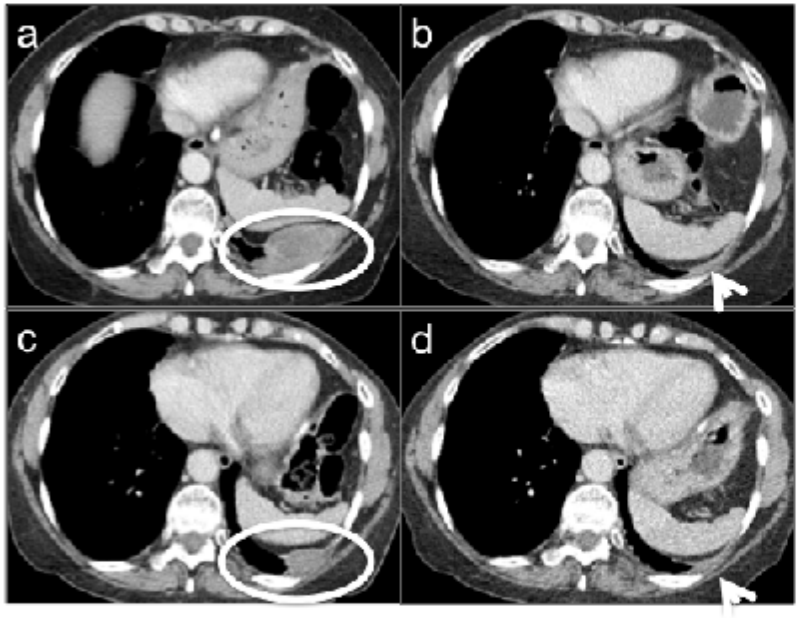
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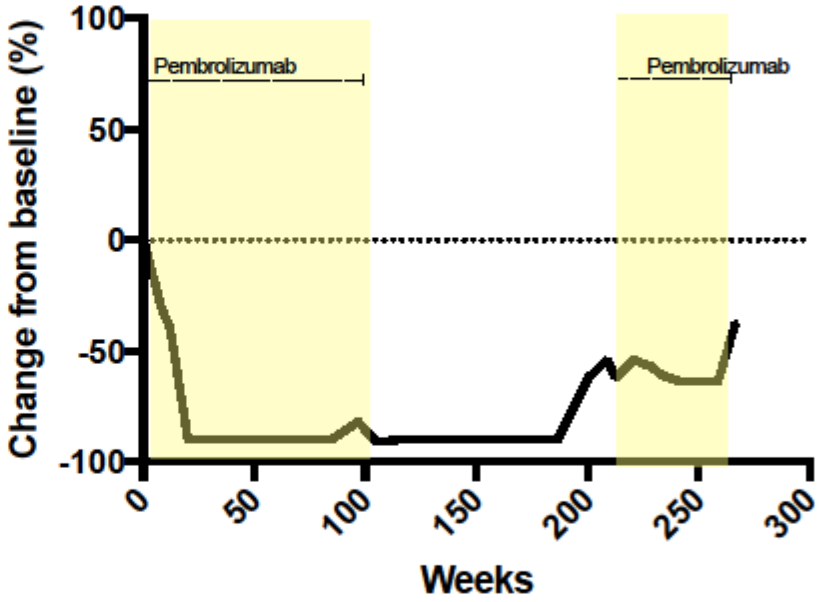
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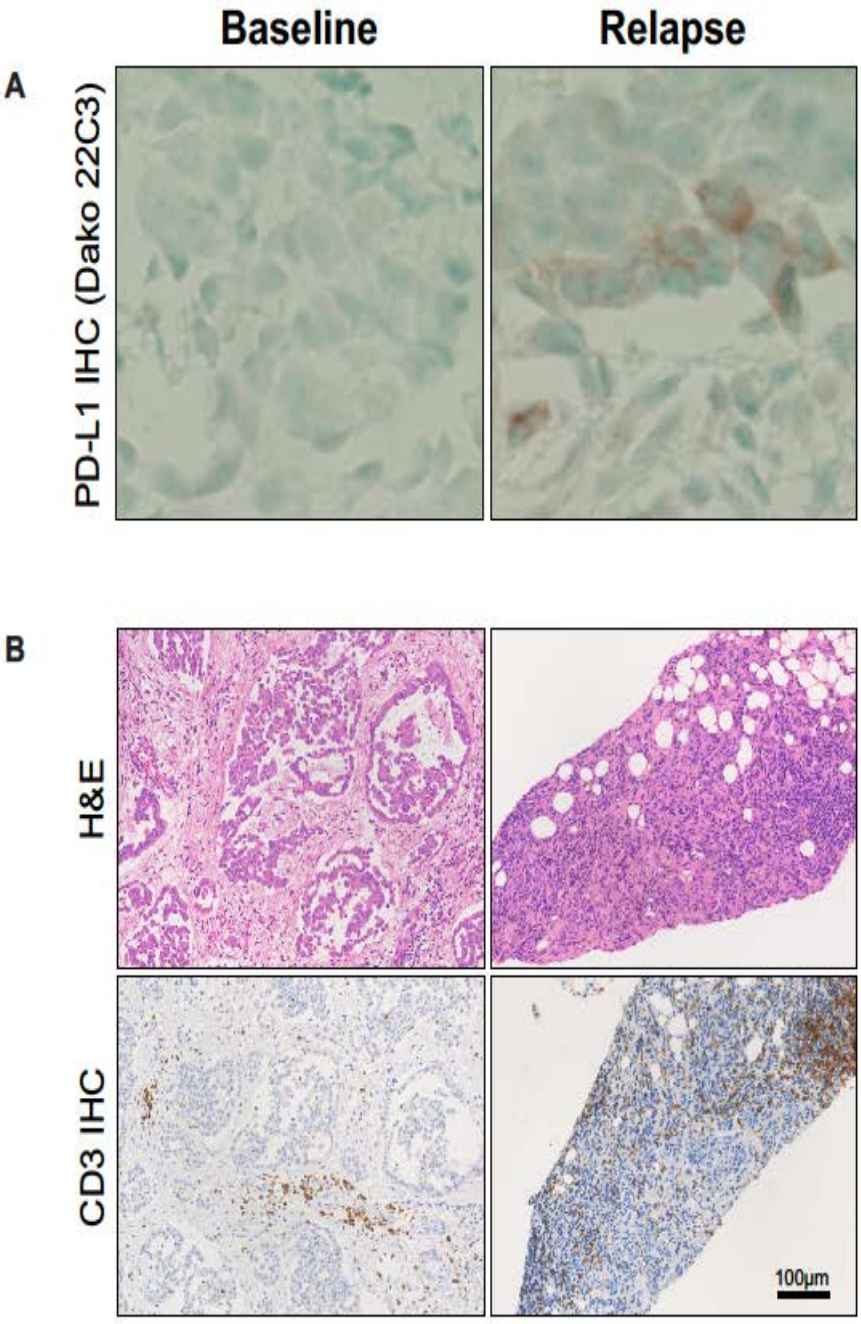
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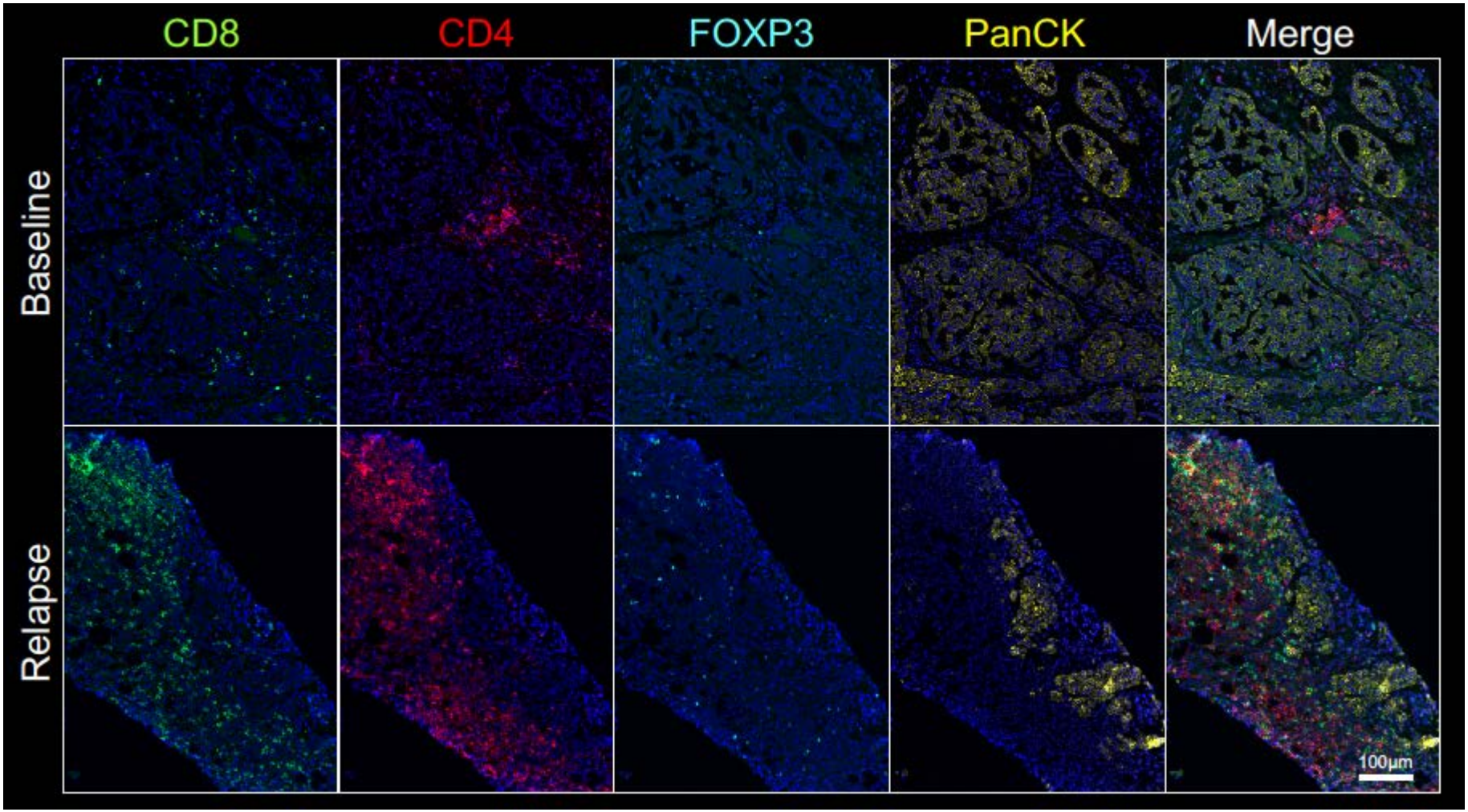
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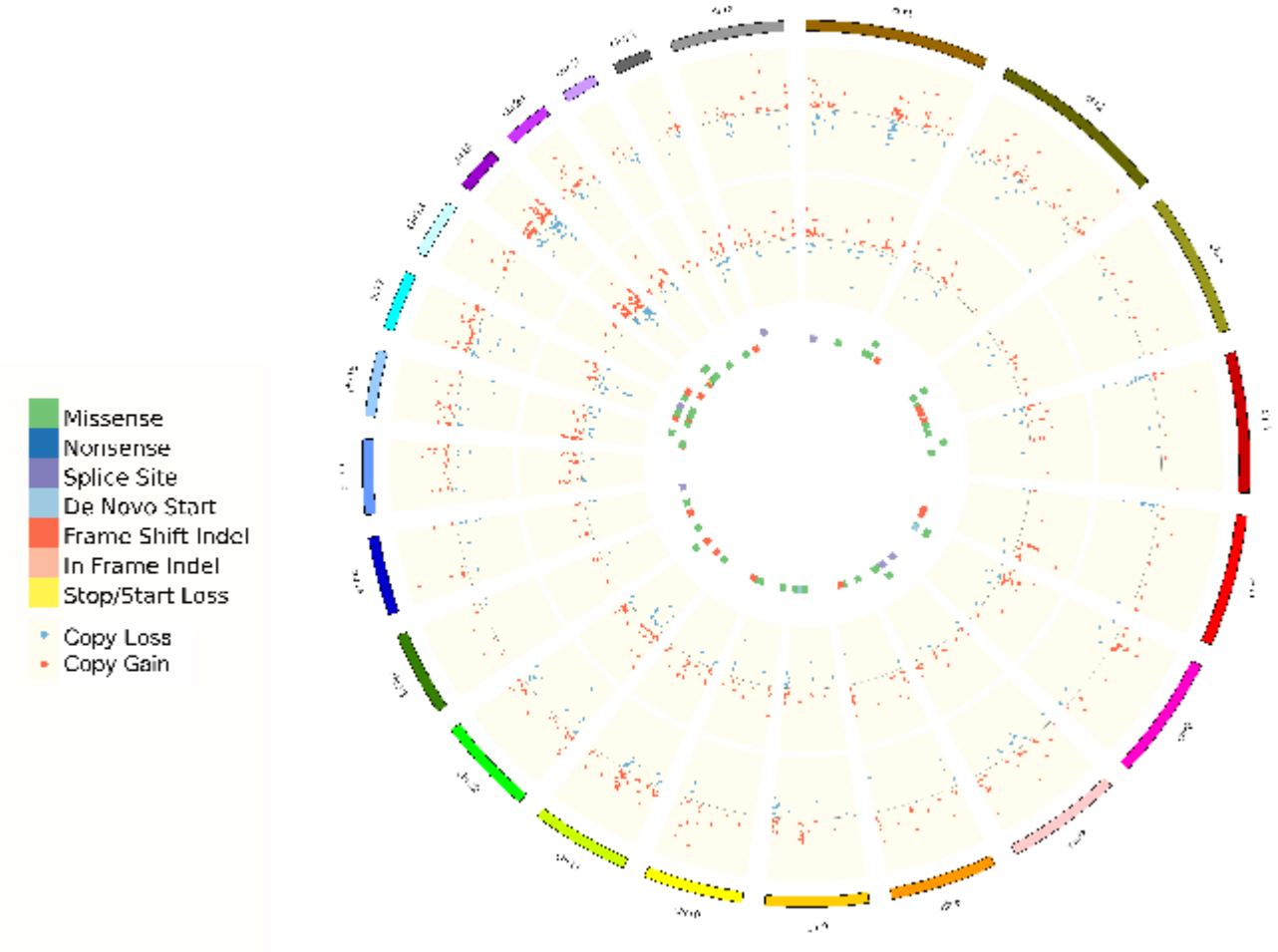
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