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Letter to the Editor

Metachronous malignancies after response to checkpoint inhibition

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To the Editor,

Immune checkpoint inhibitors (ICIs) targeting the CTLA-4 and/or PD(L)1 receptors on immune and cancer cells have drastically changed the outcomes for some patients with cancer [1,2]. Patients achieving an objective response to ICI treatment have a high chance for benefitting form a durable remission of their disease, even after the discontinuation of ICI treatment [3]. As such, unprecedented numbers of patients with advanced melanoma are becoming long-term survivors with little risk for recurrence when more than 5 years have passed since they initiated successful ICI [4,5].

This long-lasting immunologically driven response in patients with poor prognosis advanced disease is unprecedented by prior anticancer therapies and therefore necessitates a shift in clinical reasoning with respect to the specific needs of these cancer survivors. For instance, new symptoms or abnormalities on imaging should not be promptly attributed to disease progression and require thorough investigation. Here, we report 15 patients treated in two academic hospitals in whom new symptoms or abnormalities after response to ICI were found to be attributable to a metachronous new primary malignancy.

Patient characteristics, ICI treatment, second primary malignancy and diagnostic indicators that led to the diagnosis of the metachronous malignancy are summarised in Table 1.

All patients were treated for metastatic or unresectable melanoma, except for patient 5, who was treated for stage IV squamous cell carcinoma. Patients received monotherapy with either a PD-1 (12/15) or anti-CTLA4 (7/15)-blocking monoclonal antibody. Patient 14 was treated with dual ICI therapy after failing PD-1 inhibition monotherapy. The median time from start of checkpoint inhibition to the diagnosis of the metachronous primary malignancy was 48 months (range 5–110 months). At time of diagnosis of the metachronous primary tumour, four patients had a partial response to treatment, whereas 11 patients had reached a complete response. Two patients (patients 4 and 6) were still on treatment at time of the diagnosis; in all other patients, ICI had been discontinued. In five patients, further diagnostics were initiated due to the onset of new clinical symptoms (haematuria, self-palpated breast mass, new suspected skin lesion). In two patients, laboratory abnormalities were the diagnostic indicators that resulted

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Table 1
Patient characteristics, ICI treatment, second primary malignancy and diagnostic indicators revealing the second primary malignancy.

	Gender (age at diagnosis)	ICI	Response at time of SPM	Second malignancy	Time after start ICI	Diagnostic indicator
1	F (75 Y)	Pembrolizumab	PR	Oesophageal carcinoma	36 months	Increasing FDG activity oesophagus, peritoneal carcinomatosis, pleural fluid at PET-CT
2	F (54 Y)	Pembrolizumab, followed by ipilimumab	PR	Non-small cell lung cancer	47 months	Multiple new pulmonary nodules at CT
3	M (79 Y)	Ipilimumab	PR	Colorectal carcinoma (MSS)	5 months	Circumferential wall thickening of the colon at CT
4	M (80 Y)	Cemiplimab	CR	Colorectal carcinoma (MSS)	7 months	New liver lesion at CT
5	F (42 Y)	Pembrolizumab	CR	Tenosynovial giant cell tumour	40 months	FDG-active nodule behind the patella at PET-CT
6	M (75 Y)	Nivolumab	PR	Colorectal carcinoma (MSS)	5 months	Iron deficiency anaemia in routine lab + colon mass at MRI
7	M (51 Y)	Ipilimumab	CR	Dermatofibrosarcoma protuberans	30 months	Suspicious skin lesion at dermatological follow-up
8	F (56 Y)	Pembrolizumab	CR	Non-small cell lung cancer	85 months	Solitary lung nodule at CT
9	F (53 Y)	Pembrolizumab	CR	Triple negative breast carcinoma	62 months	Self-detected breast mass
10	F (66 Y)	Ipilimumab, followed by pembrolizumab	CR	Triple negative breast carcinoma	48 months	FDG-active breast nodule at PET-CT
11	M (59 Y)	Ipilimumab	CR	Prostate carcinoma	110 months	Increasing PSA at screening
12	M (74 Y)	Ipilimumab, followed by pembrolizumab	CR	Urothelial cell carcinoma	65 months	Increasing FDG activity bladder wall at PET-CT
13	M (72 Y)	Pembrolizumab	CR	Urothelial cell carcinoma	68 months	Haematuria
14	M (68 Y)	Pembrolizumab, followed by nivolumab + ipilimumab	CR	Urothelial cell carcinoma	88 months	Increasing FDG activity bladder at PET-CT + haematuria
15	M (61 Y)	Ipilimumab, followed by pembrolizumab	CR	Urothelial cell carcinoma	59 months	Haematuria

Definitions: F, female; M, male; Y, year; PR, partial response; CR, complete response; SPM, second primary malignancy; MSS, microsatellite stable; PSA, prostate-specific antigen.

in the discovery a second malignancy. Most patients however showed growing or new lesions on follow-up imaging, while their known disease remained in ongoing response. For this reason, histology was obtained from these new lesions that revealed the presence of a metachronous new malignancy.

We report the characteristics of 15 patients in which a metachronous malignancy was diagnosed during the treatment or surveillance period following ICI treatment, 11 of whom had a complete response of their primary metastatic disease. Eleven patients developed new lesions more than 3 years after starting ICI. Follow-up studies of ICI-treated advanced melanoma patients consistently show a plateau in overall survival at approximately 2–3 years; thereafter, the risk of death or progression of disease becomes low [1,6] and new lesions or symptoms after this time period should therefore also trigger a critical reflection on the possibility of a metachronous new malignancy. However, there were also patients who presented with new lesions relatively soon after initial response to ICI. These lesions might therefore have been more easily interpreted as progression of the primary malignancy yet proved to be metachronous primary malignancies.

The patients presented here were all treated for advanced melanoma or cutaneous squamous cell carcinoma. However, as data suggest that other malignancies may be approaching similar survival plateaus with ICI treatment [7], awareness for second malignancies will likely be relevant for other ICI-treated patients as well. Little is known at present about the incidence of metachronous primary malignancies during or after ICI [8]. A recent study suggested that ICI might have a protective effect against the development of a second primary cancer [9]. However, there are also concerns that ICI-treatment might increase this risk [10], either directly as a long-term effect of the treatment on healthy tissue or indirectly by increasing the life expectancy of cancer survivors. Nonetheless, this case series stresses the importance of obtaining histological proof of suspected progression in patients that develop new lesions after an initial response to ICI.

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Conflict of interest statement

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