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Immune-related bone marrow failure following anti-PD1 therapy

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1. Background

Anti-PD1s are remarkably effective in the treatment of advanced cancers, particularly melanoma, Hodgkin lymphoma or tumours with a micro-satellite instability phenotype. Other malignancies such as non–small cell lung cancer, kidney or bladder cancer also show significant responses to the blockage of PD1/PD-L1 axis [1]. An increasing number of cancer patients will be exposed to anti-PD1/PD-L1 drugs. The main side-effects of anti-PD1/PD-L1 treatment, also called 'immune-related adverse events', generally mimic

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Table 1
Characteristics of patients that developed an immune-related severe aplastic anaemia following anti-PD1 therapy. All 3 patients received nivolumab intravenously, at a standard dose of 3 mg/kg every 2 weeks for lung adenocarcinoma.

Patient	Gender, age, cancer type and metastatic sites	Previous anti-cancer therapies	Time to aplastic anaemia occurrence[a] (months)	Baseline[b] blood counts	Nadir blood counts	Duration of neutropenia	BM findings	Treatment for aplastic anaemia and supportive care	Outcome
#1	F, 73 years Lung adenocarcinoma, adrenal and brain mets	Thoracic radiation, carboplatin-paclitaxel; carboplatin-pemetrexed	6.2	WBC 10240 ANC 5700 Platelet 295 Haemoglobin 12.0	WBC 500 ANC 10 Platelet 1 Haemoglobin 7.9 Reticulocytes 4	30 days with ANC < 500	Desert BM on aspiration. BM biopsy shows empty marrow spaces, markedly hypocellular bone marrow with cellularity under 10%, activated CD8 pos T-cells in interstitial marrow. Negative PNH screening. CG not done.	IGIV Antibiotics 4 RBC units+ 3 platelets units	No response to IGIV; death at 1 month from febrile neutropenia
#2	M, 70 years Lung adenocarcinoma, adrenal and peritoneum mets	Cisplatin-pemetrexed-bevacizumab; atezolizumab; docetaxel	5.4	WBC 7160 ANC 4761 Platelet 245 Haemoglobin 14.8	WBC 1150 ANC 570 Platelet 15 Haemoglobin 7.6 Reticulocytes 62	91 days with ANC <1000	BM biopsy with hypocellular marrow. Bone marrow cellularity under 10%. CG: loss of Y chromosome in 3 out of 22 metaphases. Negative PNH screening.	Prednisone 1 mg/kg, norethandrolone, GCSF, 4 RBC and 9 platelets units	Partial and transient response to steroids; persistent pancytopenia still ongoing at 4 months
#3	M, 78 years Lung adenocarcinoma, bone, pleura, lung and lymph node mets	Thoracic radiation, carboplatin-paclitaxel	0.5	WBC 5800 ANC 4321 Platelet 144 Haemoglobin 10.0	WBC 670 ANC 252 Platelet 5 Haemoglobin 6.9 Reticulocytes 9	73 days and still ongoing with ANC <500	Hypoplastic, erythroblastic bone marrow with dyserythropoiesis and dysgranulopoiesis. Bone marrow cellularity 20%. Presence of activated CD8 pos T-cells and of rare plasmocytes. PNH screening not done. CG not done.	Prednisolone 1 mg/kg, IGIV, GCSF, antibiotics, 20 RBC and 15 platelets units	No response to steroids and IGIV; death at 3 months from acute coronary syndrome

ANC, absolute neutrophil count; BM, bone marrow; CG, cytogenetics; GCSF, granulocyte colony-stimulating factor; IGIV, intravenous immunoglobulin; mets, metastases; PNH, paroxysmal nocturnal haemoglobinuria; RBC, red blood cells; WBC, white blood count.

[a] Time between the first infusion of anti-PD1 nivolumab and the beginning of aplastic anaemia.

[b] Before anti-PD1 nivolumab treatment.