Toxicity	***Putative Mechanisms***	***Diagnostic Evaluation***	***Therapy after stopping ICI***	***Expected Outcome***	***Retreatment strategy***	***Recurrence after Consider restartinging ICI****
Anemia	Autoantibodies? Cytotoxic T lymphocytes?	CBC, blood smear, reticulocyte count, Coombs testing, cold agglutinins, LDH, indirect bilirubin, haptoglobin; bone marrow aspirate and biopsy when pure red cell aplasia is suspected	Hgb decrease of 2 gm/dL: 1. Corticosteroids -/+ rituximab 2. High-dose IVIG 3. Calcineurin inhibitor 4. Mycophenolic acid	About two-thirds recover within 1 month	Consider restarting ICI when hemolysis parameters stabilize, including during active or tapering immunosuppression	50%
Thrombocytopenia	Autoantibodies? Cytotoxic T lymphocytes?	CBC, blood smear, consider bone marrow aspirate and biopsy*	Platelets < 30,000/μL: 1. Corticosteroids 2. Thrombopoietic agent 3. Rituximab 4. Calcineurin inhibitor	About two-thirds recover within 1 month	Consider restarting ICI when platelet recovery stabilizes, including during active or tapering immunosuppression	33%
Neutropenia	Autoantibodies? Cytotoxic T lymphocytes? NK cells?	CBC, blood smear, bone marrow aspirate and biopsy*, consider vitamin and mineral measurements	Absolute neutrophil count (ANC) < 1,000/μL: 1. Leukocyte growth factor and corticosteroids 2. IVIG 3. Rituximab 4. Calcineurin inhibitor	About two-thirds recover within 1 month	Consider restarting ICI when ANC stabilizes > 1,000/μL, including during active or tapering immunosuppression	66%
Bone marrow failure	Cytotoxic T lymphocytes? NK cells?	CBC, blood smear, reticulocyte count, bone marrow aspirate and biopsy*, consider vitamin and mineral measurements	Cellularity < 25%, ANC < 500/μL, platelets < 20,000/μL, and reticulocytes < 20,000/μL 1. Corticosteroids, transfusions, leukocyte growth factor 2. Antithymocyte globulin + cyclosporine +/- eltrombopag 3. High-dose IVIG	About one-half recover within 2 months	Consider restarting ICI when ANC stabilizes > 1,000/μL, Hgb > 7 gm/dL and platelets > 30,000/μL, including during active or tapering immunosuppression	Unknown
Hemophagocytic lymphohistiocytosis	Macrophage secretion of IL-6?	CBC, reticulocyte count, blood smear, ferritin, fibrinogen, soluble CD25 , triglycerides, bone marrow aspirate and biopsy**	1. Corticosteroids -/+ tocilizumab 2. Etoposide	About three-quarters recover within unknown time-frames	Consider restarting ICI when clinical and laboratory parameters stabilize, including during active or tapering immunosuppression	0
Venous thromboembolism	Macrophage secretion of IL-8?	Ultrasound Doppler and/or CT angiogram	Therapeutic anticoagulation	~ 9% recurrences and ~ 5% major bleeding over median of 8.5 months****	ICI should not be discontinued	ICI should not be discontinued

TABLE 2: CLINICAL APPROACH TO IMMUNE CHECKPOINT INHIBITOR-ASSOCIATED HEMATOLOGICAL TOXICITIES

* Include cytogenetics, flow cytometry, T cell receptor rearrangements and related molecular profiling by next generation sequencing

** Direct identification of hemophagocytosis

*** Based on small case series[18-21]

**** Major bleeding based on International Society of Thrombosis and Haemostasis criteria[23]