

Supplementary Table S1: Review of HLH cases associated with ICI treatment reported in literature.

Study design	Patients, gender	Cancer type	ICI	HLH criteria	HLH treatment	Time to onset (days)	Outcome	Reference
Case report	n=1 F/35	Melanoma	Ipilimumab/nivolumab	Splenomegaly, cytopenias hypertriglyceridemia, hemophagocytosis, elevated ferritin, and elevated soluble CD25 levels	1.5 mg/kg of methylpredni- sone	21	Recovered	Hantel A <i>et al.</i> , 2018
Case report	n=1 F/52	Metastatic melanoma	Ipilimumab	Fever, hepatitis, pancytopenia, disseminated intravascular Coagulation Ferritin elevated, triglyceride elevated	Methylpredni- solone, Etoposide	56	Fatal outcome	Michot JM <i>et al.</i> , 2018
Case report	n=1, M/58	Metastatic melanoma	Pembrolizumab	Fever, anemia, thrombocytopenia, hypertriglyceridemia, hyperferritinemia reduced NK cell activity, elevated sCD163 levels	Oral prednisone	31	Recovered from HLH, permanently stopped pembrolizuma b	Sadaat M <i>et al.</i> , 2018
Case report	n=1 F/36	Melanoma	Ipilimumab/nivolumab	Fever, increased soluble IL-2R (CD25), hepatitis, activation of resident von Kupffer macrophages, pancytopenia, hyperferritinemia hypofibrinogenemia	Prednisone, mycophenolate mofetil	NR >84	Recovered	Satzger I <i>et al.</i> , 2018
Case report	n=1 F/69	Metastatic melanoma	Ipilimumab/nivolumab	Fever, hepatosplenomegaly, anemia, thrombocytopenia, hyperferritinemia, hypofibrinogenemia, hypertriglyceridemia, hemophagocytosis, elevated soluble CD25, reduced functional NK cell activity	Methylprednisol one, prednisolone	NR	Recovered TSO : four cycle of Ipi/nivo and continued fortnightly on nivolumab	Chin CK <i>et al.</i> , 2019
Pharmaco vigilance study	n=26, 77% M	Melanoma 58% NSCLC 11% Renal cell carcinoma 8% Other/unknown 23%	Anti-CTLA-4 50% Anti-CTLA-4+anti- PD-1 8% Anti-PD-1 38% Anti-PD-L1 4%	Not reported	Not reported	26 (5–116)	46% recovered 23% fatal outcome 31% not reported	Davis EJ <i>et al.</i> , 2019
Pharmaco vigilance study	n=38 24% F 76% M	Melanoma 55% Lung cancer 13% Bladder cancer 8% Other 24%	Nivolumab 37% Ipilimumab 18% Pembrolizumab 18% Ipilimumab+nivolu- mab 13%	haematological and coagulation features 15%		46.9 (median)	Recovered 61% Fatal outcome 26%	Noseda R <i>et al.</i> , 2019
Pharmaco vigilance study	n=5 M/54	Pulmonary sarcomatoid carcinoma	Pembrolizumab	Fever, thrombopenia, anemia, hyperferritinaemia	Prednisolone	7	Partial control of HLH, dead from cancer	Dupré A <i>et al.</i> , 2020
	F/35	Melanoma	Ipilimumab/nivolumab	Pancytopenia, hyperferritinemia, hypertriglyceridemia, hemophagocytosis	Corticosteroids etoposide, tocilizumab	21	progression Hscore 188 Partial control of HLH.	
	F/52	Melanoma	Ipilimumab/nivolumab	Fever, pancytopenia, hypofibrinogenemia, hyperferritinemia, hypertriglyceridemia, hemophagocytosis	Prednisone, etoposide	28	Rechallenge Hscore 221 Death from HLH with cerebral	
	M/69	Melanoma			Corticotherapy	35	hemorrhage Hscore 263	

	M/27	Melanoma	Ipilimumab	Fever, leukopenia, thrombopenia, hyperferritinemia	Methylprednisolone	28	Recovered. Rechallenge + Hscore 178	
			Ipilimumab/nivolumab	Fever, anemia, hyperferritinemia, hemophagocytosis			Recovered Hscore 247	
Case report	n=1 M/61	Head and neck squamous cell carcinoma	Pembrolizumab	Fever, pancytopenia, hepatomegaly, elevated liver enzymes, splenomegaly, hyperferritinemia, hypofibrinogenemia, hypertriglyceridemia, hemophagocytosis, high soluble interleukin-2 receptor	Dexamethasone 10 mg/m2 Etoposide 150 mg/m2	298	Recovered	Kalmuk J <i>et al.</i> , 2020
Case report	n=1 F/69	Melanoma	Ipilimumab/nivolumab	Fever, liver dysfunction, anemia, thrombocytopenia, hyperferritinemia, hypofibrinogenemia, hepatosplenomegaly, hemophagocytosis	Prednisolone 1 mg/kg	42	Unknown	Mizuta H <i>et al.</i> , 2020
Case reports	n=3, M/42	Melanoma	Ipilimumab/nivolumab	Fever, hyperferritinemia, hypofibrinogenemia, hypertriglyceridemia, pancytopenia, elevated liver enzymes, hemophagocytosis	Tocilizumab	51	Recovered HScore : 319	
	M/36	Melanoma	Nivolumab	Fever, hyperferritinemia, hypertriglyceridemia, pancytopenia, splenomegaly, elevated liver enzymes	Tocilizumab	78	Recovered Hscore 288	Özdemir BC <i>et al.</i> , 2020
	M/32	Melanoma	Ipilimumab/nivolumab	Fever, hyperferritinemia, hypofibrinogenemia, hypertriglyceridemia, pancytopenia, elevated liver enzymes, hemophagocytosis	Tocilizumab	91	Recovered Hscore 317	
Case report	n=1 M/54	Pulmonary metastasis of renal cell carcinoma	Ipilimumab/nivolumab + carbozantinib	Fever, anemia, thrombopenia, elevated liver enzymes, hyperferritinemia, hypofibrinogenemia, hemophagocytosis	Methylprednisolone, anakinra	NR	Recovered Hscore 202 TTO : 6 days after his second infusion of nivolumab/ipilimumab with cabozantinib	Azari A <i>et al.</i> , 2021
Case report	n=1 M 33	Melanoma	Ipilimumab/nivolumab	Fever, elevated liver enzymes thrombopenia, hyperbilirubinemia, hepatomegaly, splenomegaly, hyperferritinemia, hypertriglyceridemia	Prednisone 1mg/kg increased 2mg/kg on day 2	NR	Recovered Diagnosed with encephalitis and hepatitis associated with HLH TTO : Post 2 cycles of Ipi/nivo	Ghous G <i>et al.</i> , 2021
Pharmaco vigilance study (FAERS Database)	n=199 M 119 (59.7%) F 69 (34.6%) UK 11 (5.5%) Median age 65	Melanoma (69, 34.6%), Non-small cell lung cancer (61, 30.6%) Renal cell carcinoma (12, 6%).	Pembrolizumab (60, 30.2%) Nivolumab (54, 27.1%) Ipilimumab/nivolumab (47, 23.6%)	NR	NR	NR	Death 53 (26.6%) Critical Hospitalization 36 (18.1%) 74 (37.2%) Unknown 36 (18.1%)	Grewal US <i>et al.</i> , 2021

Multi-center study	n=2 M/69 M/56	NR NR	Nivolumab Ipilimumab/nivolumab	NR NR	Corticotherapy Corticotherapy	252 168	Recovered Recovered	Kramer R <i>et al.</i> , 2021
Case report	n=2 M/75 F/60	Lung cancer Lung cancer	Pembrolizumab Pembrolizumab	Fever, cytopenia, elevated liver enzymes, hyperferritinemia, hemophagocytosis Cytopenia, coagulation abnormalities, elevated liver enzymes, hyperferritinemia	Corticotherapy Corticotherapy	46 30	Hscore 175 Recovering Hscore 185 Recovering (improved her laboratory finding)	Kurozumi A <i>et al.</i> , 2021
Case report	n=1 M/68	Metastatic renal cell	Nivolumab/ipilimumab	Fever, splenomegaly, pancytopenia, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, high CD25, low NK cell activity	Dexamethasone	90	Recovered Hscore 233	Masood A <i>et al.</i> , 2021
Case report	n=1 F	Melanoma	Nivolumab/ipilimumab	NA	Corticotherapy		Recovered Positive rechallenge	Holmes Z <i>et al.</i> , 2022 ●
Case report	n=1 F/80	Squamous cell carcinoma	Pembrolizumab	Pancytopenia, hepatitis, fever, splenomegaly, hyperferritinemia, hypofibrinogenemia, hypertriglyceridemia, elevated soluble interleukin (IL)-2 receptor, low NK-cell activity	Corticotherapy tocilizumab and etoposide	180	Recovered	Marar R <i>et al.</i> , 2022
Case report	n=1 M/67	Lung adenocarcinoma	Atezolizumab	Fever, hepatomegaly, splenomegaly, pancytopenia, hyperferritinemia, hyperbilirubinemia, hypertransaminitis, elevated IL-6 and CD25, hemophagocytosis	Dexamethasone, tocilizumab, anakinra, mycophenolate mofetil and etoposide	14	Death, neurological dysfunction Hscore 256	Rubio-Perez J <i>et al.</i> , 2022
Case-report	n=2 F/50 M/70	Thymic carcinoma No small cell lung cancer	Pembrolizumab Pembrolizumab	Fever, splenomegaly, elevated liver enzymes, thrombocytopenia, anemia, hypertriglyceridemia, hypofibrinogenemia, hyperferritinemia, decreased natural killer (NK) and elevated soluble CD25 Fever, splenomegaly, elevated liver enzymes, hyperferritinemia, elevated soluble CD25, hypertriglyceridemia, hemophagocytosis,	Dexamethasone, etoposide Dexamethasone, etoposide	7 7	Recovered Recovered EBV+	Wei Y <i>et al.</i> , 2022
Pharmaco vigilance study	n=190 36% M	Melanoma 40% Lung cancer 22.1% Leukemia 3.7% Renal cancer 5.3% Bladder cancer 2.6%	Nivolumab 21.6% Pembrolizumab 30.5% Ipilimumab/nivolumab 34.2%	NA	NA	102 (median, n=50)	Recovered 32.6% Fatal outcome 15.3%	Our series