

Hemophagocytic lymphohistiocytosis and disseminated intravascular coagulation are underestimated, but fatal adverse events in chimeric antigen receptor T-cell therapy

Supplementary materials:

Supplementary Table S1. Detailed information for each CAR-T products in standard drug name variable “PROD_AI” and supplementary drug name variable “DRUGNAME”

CAR-T products	PROD_AI	DRUGNAME
Axicabtagen-Ciloleucel	"AXICABTAGENE CIOL", "AXICABTAGENE CILOLEUCEL"	"AXI-CEL", "AXICABTAGEN-CILOLEUCEL", "AXICABTAGEN-CILOLEUCEL [KTE C19]", "AXICABTAGENE CILEUCEL", "AXICABTAGENE CILOLAUCAL", "AXICABTAGENE CILOLEUCLEUCEL", "AXICABTAGENE CILOLEUC", "AXICABTAGENE CILOLEUCAL", "AXICABTAGENE CILOLEUCEL", "AXICABTAGENE CILOLEUCEL KITE PHARMA", "AXICABTAGENE CIOLGUCEL", "AXICABTAGENE CLIOLEUCEL", "AXICABTAGENE-CILOLEUCEL CAR T-CELL", "AXICABTAGENE?CILOLEUC", "AXICABTAGENE?CILOLEUCEL CAR T?CELL", "AXICEL (AXICABTAGENE", "CAR T-CELLS NOS [AXICABTAGENE CILOLEUCEL]", "KTE C19", "YESCARTA"
Tisagenlecleucel	"TISAGENLECLEUCEL", "TISAGENLECLEUCEL-T"	"CTL 019", "CTL019", "CTL019(RE-GEN)", "CTL019(RE?GEN)", "KYMRIAH", "M_CTL019_CYCLOPHOSPHAMIDE", "M_CTL019_FLUDARABINE", "TISACEL", "TISAGENLECLEUCEL-T", "TISAGENLECLEUCEL.", "TISAGENLECLEUCEL?T"

Supplementary Table S2. Summarized signal detection of tisagenlecleucel and axicabtagene associated hematologic adverse events in total datasets and different subgroups.

Variables	a	b	c	d	ROR	ROR₀₂₅	ROR₉₇₅	IC	IC₀₂₅	IC₉₇₅
Total	5112	38718	569352	26021252	6.03	5.86	6.21	2.43	2.39	2.48
Tisagenlecleucel	3618	25748	570846	26034222	6.40	6.18	6.63	2.51	2.46	2.57
Axicabtagene	1494	12970	572970	26047000	5.23	4.96	5.52	2.26	2.17	2.34
Tisagenlecleucel vs Axicabtagene	3618	25748	1494	12970	1.22	1.14	1.30	0.08	0.02	0.13
Gender										
Male	2779	21891	224985	8548079	4.82	4.63	5.02	2.12	2.06	2.18
Tisagenlecleucel	1974	14932	225790	8555038	5.00	4.77	5.25	2.17	2.10	2.25
Axicabtagene	805	6959	226959	8563011	4.36	4.05	4.69	2.00	1.88	2.12
Female	1879	14213	264512	14626419	7.30	6.95	7.66	2.71	2.63	2.78
Tisagenlecleucel	1403	9672	264988	14630960	7.99	7.55	8.45	2.82	2.73	2.91
Axicabtagene	476	4541	265915	14636091	5.74	5.22	6.31	2.40	2.25	2.55
Male vs Female	2779	21891	1879	14213	0.96	0.90	1.02	-0.02	-0.08	0.04
Age										
Age<65	3318	24881	242438	10549220	5.80	5.59	6.01	2.37	2.31	2.43
Tisagenlecleucel	2589	18375	243167	10555726	6.11	5.86	6.37	2.44	2.38	2.51
Axicabtagene	729	6506	245027	10567595	4.82	4.46	5.20	2.15	2.02	2.27
Age>=65	824	8245	168297	5932240	3.52	3.27	3.78	1.71	1.60	1.83
Tisagenlecleucel	461	4388	168660	5936097	3.69	3.35	4.06	1.78	1.62	1.93
Axicabtagene	363	3857	168758	5936628	3.30	2.96	3.68	1.63	1.46	1.81
Age<65 vs Age≥65	3318	24881	824	8245	1.33	1.23	1.45	0.08	0.02	0.14
Year										
2017	75	361	81750	3933828	9.44	7.36	12.10	3.01	2.62	3.39
Tisagenlecleucel	75	346	81750	3933843	9.82	7.65	12.60	3.06	2.67	3.44
Axicabtagene	0	15	81825	3934174						
2018	465	3966	112652	5062086	5.24	4.76	5.77	2.26	2.11	2.41
Tisagenlecleucel	276	1604	112841	5064448	7.63	6.71	8.67	2.73	2.53	2.93
Axicabtagene	189	2362	112928	5063690	3.56	3.07	4.13	1.75	1.51	1.99
2019	1289	11296	123992	5440016	5.00	4.72	5.30	2.19	2.09	2.28
Tisagenlecleucel	899	8033	124382	5443279	4.89	4.56	5.24	2.16	2.05	2.27
Axicabtagene	390	3263	124891	5448049	5.19	4.67	5.76	2.24	2.07	2.41
2020	1944	14738	126331	5788178	6.04	5.75	6.33	2.43	2.35	2.50
Tisagenlecleucel	1469	10659	126806	5792257	6.28	5.95	6.64	2.48	2.40	2.57
Axicabtagene	475	4079	127800	5798837	5.26	4.78	5.79	2.26	2.11	2.42
2021	1339	8357	124627	5797144	7.44	7.02	7.88	2.70	2.61	2.79
Tisagenlecleucel	899	5106	125067	5800395	8.13	7.58	8.73	2.81	2.70	2.92
Axicabtagene	440	3251	125526	5802250	6.22	5.63	6.87	2.48	2.32	2.64

Abbreviations: ROR, reporting odds ratios; IC, information component.

Supplementary Table S3. Hematologic adverse events categorization based on Medical Dictionary for Regulatory Activities (MedDRA) Classification.

HLTs	PTs included
Bone marrow depression	Cytopenia
	Neutropenia
	Thrombocytopenia
	Febrile neutropenia
	Pancytopenia
	B cell aplasia
	Anemia
	Bone marrow failure
	Lymphopenia
	Post-depletion B cell recovery
	Leukopenia
	Febrile bone marrow aplasia
	Neutropenic sepsis
	Agranulocytosis
	Aplastic anemia
	Neutropenic colitis
	Neutrophilia
	Normocytic anemia
	White blood cell disorder
B-lymphocyte abnormalities	
Normochromic normocytic anemia	
Coagulopathies and bleeding diatheses	Coagulopathy
	Disseminated intravascular coagulation
	Hypofibrinogenemia
	Purpura
	Thrombotic microangiopathy
	Petechiae
Hematologic disorders	Hemophagocytic lymphohistiocytosis
	Bone marrow disorder
	Hematotoxicity
Spleen disorders	Splenomegaly
	Hepatosplenomegaly
	Splenic hemorrhage
	Splenic infarction
Hemolyses	Hyperbilirubinemia
	Hemolysis
	Autoimmune hemolytic anemia
	Jaundice
	Hemolytic anemia

Abbreviations: PTs, preferred terms; HLTs, high level terms.

Supplementary Table S4. Signal detection of tisagenlecleucel and axicabtagene associated HLTs in blood and lymphatic system.

Therapy	Events	a	b	c	d	ROR	ROR ₀₂₅	ROR ₉₇₅	IC	IC ₀₂₅	IC ₉₇₅
CAR-T	Bone marrow depression	2351	41479	292615	26297769	5.09	4.88	5.31	2.27	2.21	2.34
	Coagulopathies and bleeding diatheses	278	43552	22780	26567604	7.36	6.54	8.29	2.86	2.66	3.06
	Spleen disorders	31	43799	7643	26582741	2.41	1.69	3.42	1.26	0.66	1.87
	Hematologic disorders	155	43675	7790	26582594	11.69	9.97	13.71	3.52	3.25	3.78
	Hemolyses	56	43774	21213	26569171	1.59	1.23	2.07	0.67	0.22	1.12
	Other events	2241	41589	217311	26373073	6.53	6.26	6.82	2.63	2.56	2.70
Axicabtagene	Bone marrow depression	870	13594	294096	26325654	5.71	5.33	6.12	2.44	2.33	2.55
	Coagulopathies and bleeding diatheses	51	14413	23007	26596743	3.97	3.02	5.23	1.98	1.52	2.45
	Spleen disorders	2	14462	7672	26612078	0.54	0.13	2.14	-0.90	-3.94	2.14
	Hematologic disorders	69	14395	7876	26611874	14.60	11.51	18.51	3.85	3.45	4.25
	Hemolyses	27	14437	21242	26598508	2.29	1.57	3.34	1.19	0.54	1.84
	Other events	475	13989	219077	26400673	4.08	3.72	4.47	1.99	1.84	2.14
Tisagenlecleucel	Bone marrow depression	1481	27885	293485	26311363	4.76	4.51	5.01	2.19	2.10	2.27
	Coagulopathies and bleeding diatheses	227	29139	22831	26582017	8.91	7.82	10.16	3.13	2.91	3.35
	Spleen disorders	29	29337	7645	26597203	3.30	2.29	4.76	1.72	1.09	2.34
	Hematologic disorders	86	29280	7859	26596989	9.45	7.64	11.69	3.22	2.87	3.58
	Hemolyses	29	29337	21240	26583608	1.23	0.86	1.77	0.30	-0.32	0.93
	Other events	1766	27600	217786	26387062	7.74	7.37	8.12	2.86	2.79	2.94

Abbreviations: ROR, reporting odds ratios; IC, information component.

Supplementary Table S5. Proportion of death outcome in different PTs within blood and lymphatic system.

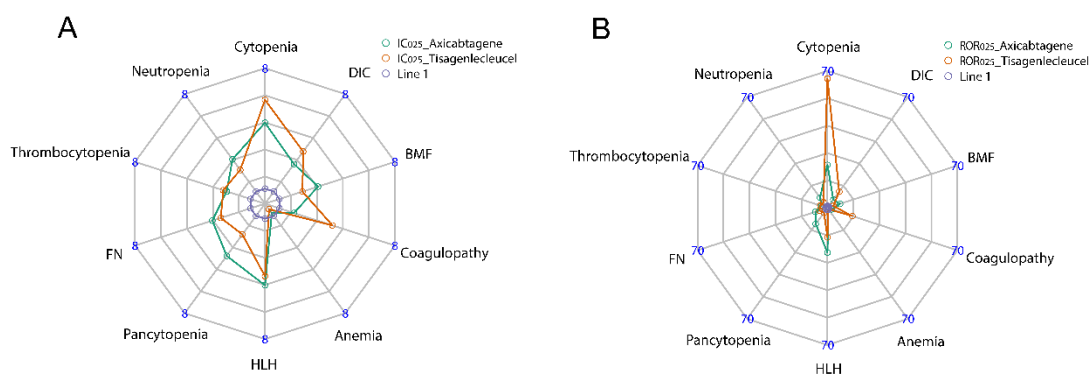
CAR-T	PTs	Death	Total	Rate (%)
Axicabtagene	Anemia	4	51	7.84
Axicabtagene	Bone marrow failure	15	58	25.86
Axicabtagene	Coagulopathy	7	14	50.00
Axicabtagene	Cytopenia	26	90	28.89
Axicabtagene	Disseminated intravascular coagulation	16	24	66.67
Axicabtagene	Febrile neutropenia	26	119	21.85
Axicabtagene	Hemophagocytic lymphohistiocytosis	47	63	74.60
Axicabtagene	Hyperbilirubinemia	6	17	35.29
Axicabtagene	Lymphopenia	10	34	29.41
Axicabtagene	Neutropenia	35	221	15.84
Axicabtagene	Pancytopenia	39	139	28.06
Axicabtagene	Thrombocytopenia	21	99	21.21
Tisagenlecleucel	Anemia	28	78	35.90
Tisagenlecleucel	B cell aplasia	14	82	17.07
Tisagenlecleucel	Bone marrow failure	16	54	29.63
Tisagenlecleucel	Coagulopathy	54	114	47.37
Tisagenlecleucel	Cytopenia	201	427	47.07
Tisagenlecleucel	Disseminated intravascular coagulation	43	75	57.33
Tisagenlecleucel	Febrile neutropenia	42	154	27.27
Tisagenlecleucel	Hemolysis	3	3	100.00
Tisagenlecleucel	Hemophagocytic lymphohistiocytosis	48	73	65.75
Tisagenlecleucel	Hepatosplenomegaly	5	8	62.50
Tisagenlecleucel	Hyperbilirubinemia	11	16	68.75
Tisagenlecleucel	Hypofibrinogenemia	6	17	35.29
Tisagenlecleucel	Leukopenia	5	26	19.23
Tisagenlecleucel	Lymphopenia	17	44	38.64
Tisagenlecleucel	Neutropenia	107	242	44.21
Tisagenlecleucel	Neutropenic colitis	3	3	100.00
Tisagenlecleucel	Neutropenic sepsis	4	4	100.00
Tisagenlecleucel	Normocytic anemia	4	4	100.00
Tisagenlecleucel	Pancytopenia	33	86	38.37
Tisagenlecleucel	Purpura	11	11	100.00
Tisagenlecleucel	Splenic hemorrhage	3	3	100.00
Tisagenlecleucel	Splenomegaly	12	15	80.00
Tisagenlecleucel	Thrombocytopenia	126	219	57.53
Tisagenlecleucel	Thrombotic microangiopathy	5	5	100.00
Tisagenlecleucel	White blood cell disorder	4	4	100.00

Abbreviations: PTs, preferred terms.

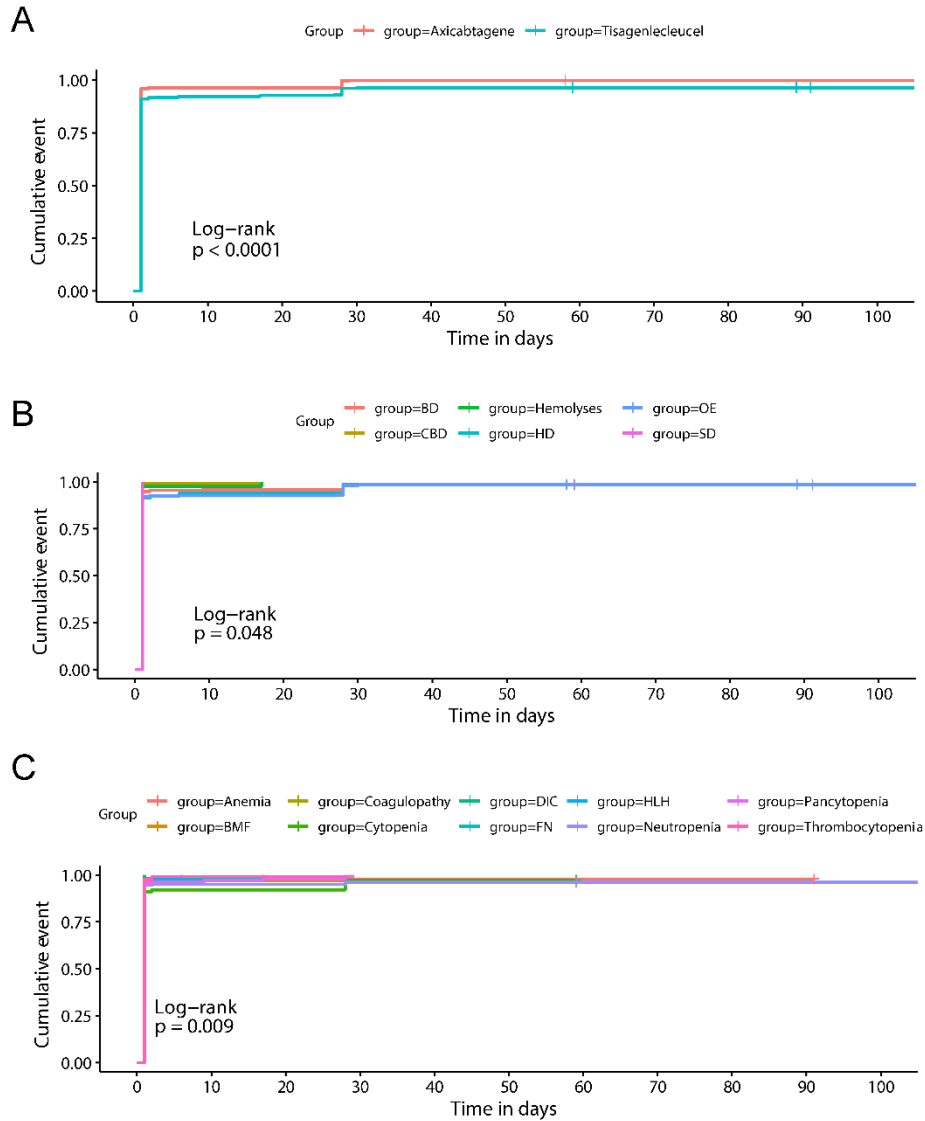
Supplementary Table S6. Proportion of death outcome in different high level terms (HLTs) within blood and lymphatic system.

CAR-T products	HLTs	Death	Total	Rate (%)
Axicabtagene	Bone marrow depression	180	870	20.69
Axicabtagene	Hematologic disorders	47	69	68.12
Axicabtagene	Coagulopathies and bleeding diatheses	26	51	50.98
Axicabtagene	Hemolyses	7	27	25.93
Axicabtagene	Other events	224	475	47.16
Tisagenlecleucel	Bone marrow depression	607	1481	40.99
Tisagenlecleucel	Coagulopathies and bleeding diatheses	120	227	52.86
Tisagenlecleucel	Hematologic disorders	50	86	58.14
Tisagenlecleucel	Spleen disorders	22	29	75.86
Tisagenlecleucel	Hemolyses	18	29	62.07
Tisagenlecleucel	Other events	816	1765	46.23

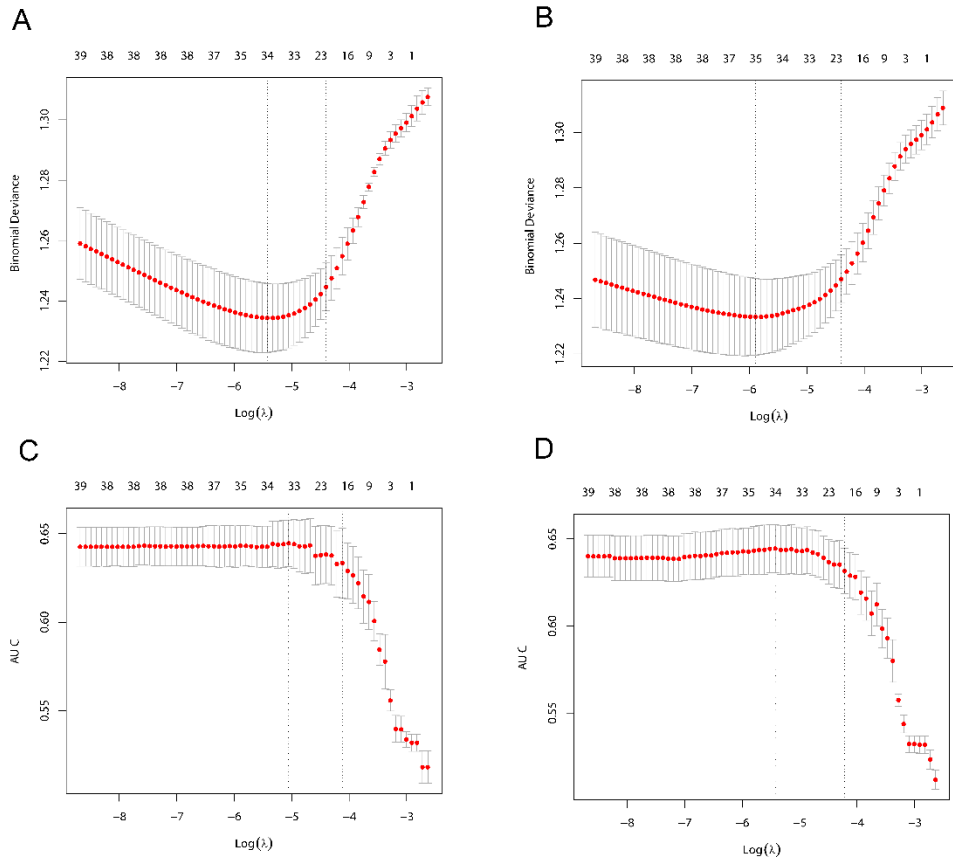
Abbreviations: HLTs, high level terms.



Supplementary Figure S1. (A) Signal value IC_{025} of top 10 frequently reported hematologic adverse events following CAR-T therapy. (B) Signal value ROR_{025} of top 10 frequently reported hematologic adverse events following CAR-T therapy. FN, febrile neutropenia; HLH, hemophagocytic lymphohistiocytosis; DIC, disseminated intravascular coagulation; BMF, bone marrow failure; IC_{025} , lower limit of the information component 95% confidence interval; ROR_{025} , lower limit of the reporting odds ratios 95% confidence interval.



Supplementary Figure S2. (A) Days from CAR-T infusion to adverse event onset grouped by CAR-T products. (B) Days from CAR-T infusion to adverse event onset grouped by HLTs. (C) Days from CAR-T infusion to adverse event onset grouped by PTs. BD, bone marrow depression; CBD, coagulopathies and bleeding diatheses; SD, spleen disorders; HD, Hematologic disorders; FN, febrile neutropenia; HLH, hemophagocytic lymphohistiocytosis; DIC, disseminated intravascular coagulation; BMF, bone marrow failure; OE, other events.



Supplementary Figure S3. (A) Deviance of 3-fold cross-validation lasso regression. (B) Deviance of 6-fold cross-validation lasso regression. (C) AUC of 3-fold cross-validation lasso regression. (D) AUC of 6-fold cross-validation lasso regression.