

GENE SYMBOL	mRNA	TESTING RANGE
PRF1	NM_005041	Exon2-3
UNC13D	NM_199242	whole exon
STX11	NM_003764	Exon2
STXBP2	NM_006949	whole exon
XIAP	NM_001167	Exon2-7
SH2D1A	NM_002351	whole exon
RAB27A	NM_004580	Exon2-7
MYO5A	NM_000259	whole exon
AP3B1	NM_003664	whole exon
LYST	NM_000081	Exon3-53
ITK	NM_005546	whole exon
SLC7A7	NM_001126105	Exon3-9
BLOC1S6	NM_012388	whole exon
CD27	NM_001242	whole exon
MAGT1	NM_032121	whole exon
ADA	NM_000022	whole exon
BTK	NM_000061	Exon2-19
IL2RA	NM_000417	whole exon
IL2RG	NM_000206	whole exon
MVK	NM_000431	Exon2-11
PNP	NM_000270	whole exon
WAS	NM_000377	whole exon
FAS	NM_000043	whole exon
RECQL4	NM_004260	whole exon
RAG1	NM_000448	Exon2
RAG2	NM_000536	Exon2

Supplemental Table 1. The HLH-related gene panel used for HLH diagnosis by next generation sequencing.

<i>Cases</i>	Primary Treatment		
	CTx (cycles)	Treated time (weeks)	Outcomes
1	ED (1), GED+L-Asp (1), GED (2)	12	PR, Relapse
2	ED (1), GED (2)	8.4	NR
3	ED (1)	11.3	PR, Relapse
4	ED (2)	10.6	PR, Relapse
5	GED (2)	6.3	PR, Relapse
6	ED+CsA (2), GED+CsA (4)	72	Relapse
7	ED (1), GED (1)	11.1	NR

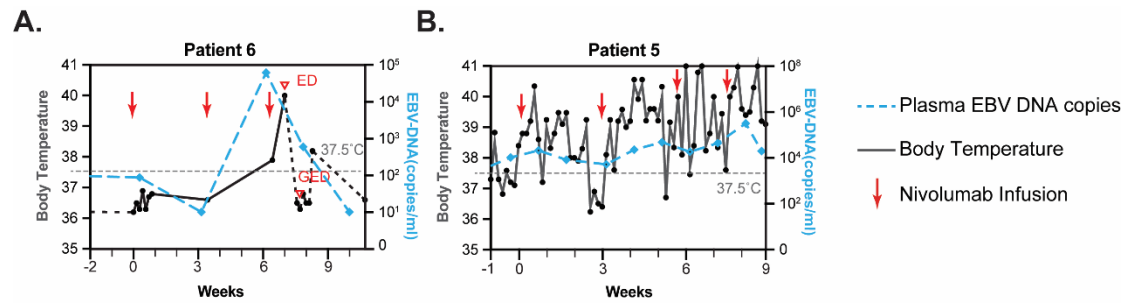
Supplemental Table 2. Primary chemotherapies and outcomes of seven r/r EBV-HLH patients.

Abbr: ED, Etoposide + Dexamethasone; GED, Gemcitabine + Etoposide + Dexamethasone; CsA, Cyclosporin A; L-Asp, L-Asparaginase; PR, partial response; NR, no response.

<i>Case</i>	<i>Nivolumab Treatment</i>				<i>Outcomes</i>	
	<i>Induction</i>		<i>Maintenance</i>		<i>Survival (months)</i>	<i>RFS (months)</i>
	<i>Dose (cycles)</i>	<i>Outcomes</i>	<i>Dose (cycles)</i>	<i>Outcomes</i>		
1	100mg (1), 200mg (2)	cCR	140mg (1) 100mg (1)	cCR	18.9+	18+
2	100mg (6)	cCR and mCR	100mg (4)	cCR and mCR	17.9+	17.4+
3	100mg (3)	cCR and mCR	100mg (2)	cCR and mCR	15.3+	15.3+
4	100mg (2), 120mg (2), 140mg (2)	cCR and mCR	100mg (4)	cCR and mCR	15.3+	13.4+
5	140mg (2), 160mg (1), 180mg (1)	NR, DOD	-	-	5	0
6	160mg (3)	PR, Relapse	-	-	8	1.5
7	100mg (3)	cCR and mCR	100mg (2)	cCR and mCR	11.4+	11+

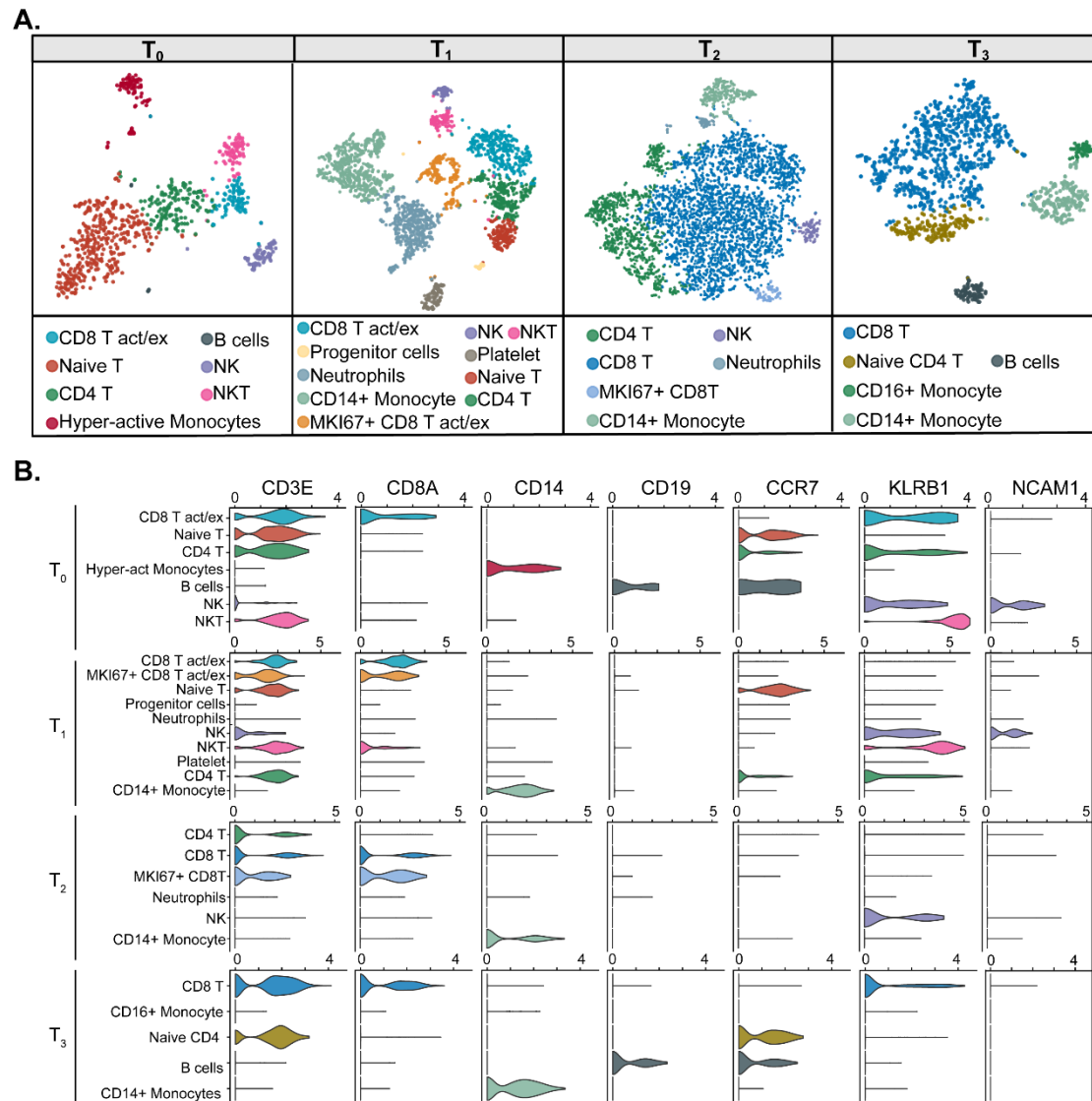
Supplemental Table 3. Treatments and outcomes of nivolumab infusions.

Abbr: cCR, clinical complete response; mCR, molecular complete response; PR, partial response; NR, no response; DOD, dead of disease; RFS, relapse-free survival.



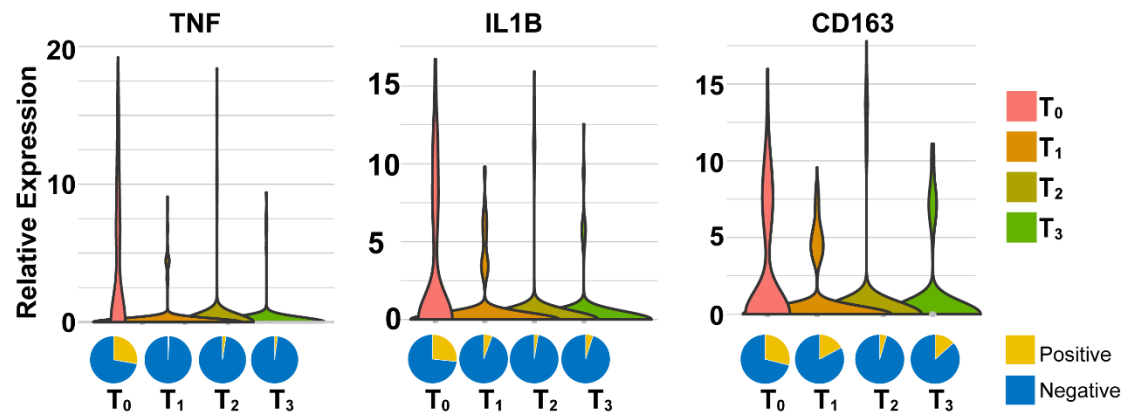
Supplemental Figure 1. Dynamics of clinical and laboratory parameters after nivolumab infusions in two patients without clinical complete response.

Dynamics of body temperature and plasma EBV-DNA copy numbers in NR patients 6 (A) and patient 5 (B) during induction therapy.

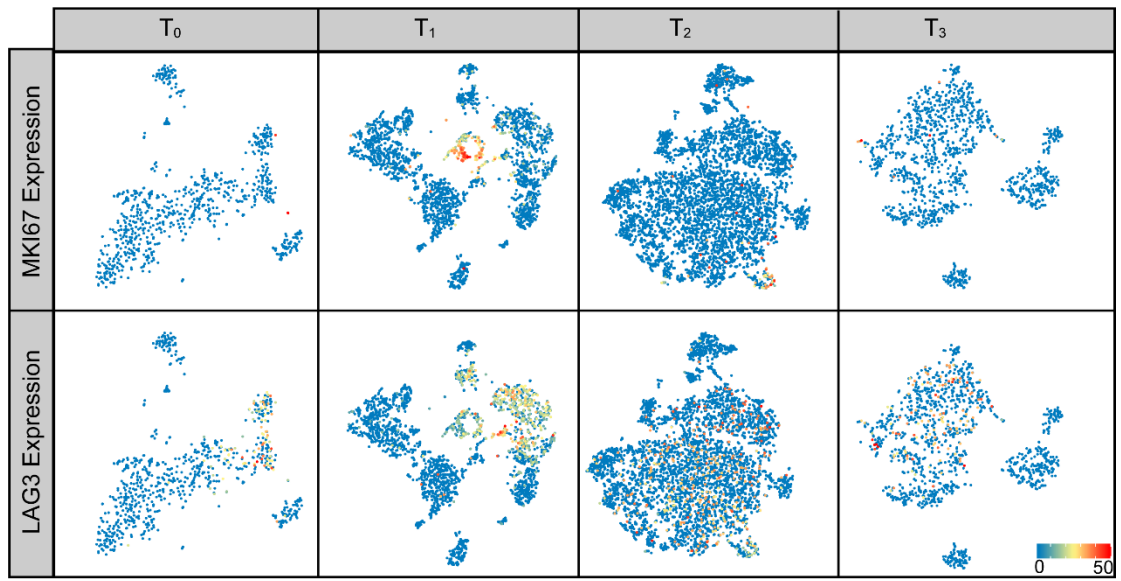


Supplemental Figure 2. Single cell RNA sequencing analysis of peripheral blood cells of patient 7 before and during nivolumab treatment.

(A) t-distributed stochastic neighbor embedding (t-SNE) maps displaying peripheral blood cell subpopulations at T₀ (Day 0, before infusion), T₁ (Day 7 after the first infusion), T₂ (Day 21 when clinical CR) and T₃ (Day 76 when molecular CR). (B) Violin plots showing the expression levels of marker genes in each cell population at different time points.



Supplemental Figure 3. Expression levels of TNF, IL1B and CD163 in monocytes/MΦ in peripheral blood of patient 7 before and during nivolumab treatment. Upper, violin plots showing the expression levels of TNF, IL1B and CD163 in monocytes/MΦ at different time points. Lower, pie charts showing the ratios of TNF, IL1B and CD163 positive monocytes/MΦ at different time points.



Supplemental Figure 4. Expression levels of MKI67 and LAG3 projected on t-SNE plots in the peripheral blood of patient 7 before and during nivolumab treatment.