Supplementary Materials

Table S1: Definitions of dose-limiting toxicity (DLT) and maximum tolerated dose (MTD)

DLT was defined as any of the following occurring within 30 days of the last infusion of 19-28z CAR T-cells:	
	Grade 4 neutropenia (<500/μL) lasting 30 days or more from time of infusion (in patients with pretreatment absolute neutrophil count >500/μL) unless due to persistent disease.
	Grade 3 or 4 thrombocytopenia that fails to recover to grade ≤2 at 30 days post-infusion (in patients with pretreatment platelet count >50,000/μL) unless due to persistent disease.
	New grade 3 or 4 non-hematologic toxicities lasting ≥14 days, probably or definitively attribued to CAR T-cell infusion, not attributed to chemotherapy received or to persistent disease.
	Grade 4 neurologic toxicity, grade 4 cytokine release syndrome (CRS; see Table S2), or protocol-defined severe CRS, including hypotension with systolic blood pressure <90 mmHg refractory to fluid challenge or requiring vasopressors, or hypoxia/respiratory distress requiring increasing supplemental oygen or ventilatory support, or acute coronary syndrome with detectable troponin and electrocardiogram changes, or seizure (clinically suspected or documented by electroencephalogram) not improving after 24 hours of systemic corticosteroids.
	Any grade 4 seizure.
	Any grade 5 toxicity (death) attributable (possibly, probably, or definitely) to CAR T-cell infusion.
MTD was defined as the highest dose studied for which the incidence of DLT was <33%.	

Table S2: Cytokine release syndrome (CRS) grading criteria

Grade	Definitions
Grade 1	Mild symptoms, requiring observation or symptomatic management only (e.g., antipyretics, antiemetics, pain medications, etc.)
Grade 2	Moderate symptoms Hypotension requiring vasopressors <24 hours, or Hypoxia or dyspnea requiring supplemental oxygen <40% (up to 6L by nasal cannula)
Grade 3	Severe symptoms Hypotension requiring vasopressors ≥24 hours, or Hypoxia or dyspnea requiring supplemental oxygen ≥40%
Grade 4	Life-threatening symptoms Hypotension refractory to vasopressors, or Hypoxia or dyspnea requiring mechanical ventilation
Grade 5	Death

Table S3: Disease burden at time of conditioning chemotheray (if applicable) and CAR T-cell infusion

Pt #	Inf #	Disease	ALC (K/mcL)	BM disease burden		Spleen size (longest axis)	Nodal disease burden
				Cellularity	Involvement		
1		CLL	196.6	90%	100% (IHC); 98% lymphs (BMA)	15.9 cm	Extensive; above and below diaphragm, up to 4.4 cm in longest axis
2		CLL	1.4	Unknown	Unknown	Normal	Extensive; in neck and above and below diaphragm, up to 7.0 cm in longest axis
3		CLL	117.4	80%	100% (IHC); 78% (BMA)	14.8 cm	Extensive; above and below diaphragm, up to 7.7 cm in longest axis
4		CLL	148.5	80%	100% (IHC); 79% lymphs (BMA)	Normal	Extensive; bulky disease above and below diaphragm, with two largest nodal masses each >22 cm in longest axis
5		CLL	44.5	60-70%	67% lymphs (BMA)	17 cm	Extensive; above and below diaphragm, with largest bulky abdominal nodal mass 12.9 cm in longest axis
6		CLL	92.2	70%	97% lymphs (BMA)	s/p splenectomy	Extensive; in neck and above and below diaphragm, with two largest bulky nodal masses each >10 cm in longest axis
7		CLL	1.0	20-50% (patchy)	10% (IHC); 36% lymphs (BMA)	Normal	Extensive; above and below diaphragm; largest abdominal nodal mass 4.4 cm in longest axis
8	1st	CLL	3.3	60-70%	70-80% (IHC); 47% lymphs (BMA)	21 cm	Extensive; in neck and above and below diaphragm, up to 8.5 cm in longest axis; also w/ hepatomegaly (22 cm)
	2nd		9.1	60%	50% (IHC); 48% lymphs (BMA)	20.5 cm	Extensive; in neck and above and below diaphragm, up to 8.7 cm in longest axis; also w/ hepatomegaly (21.6 cm)
9		CLL	2.9	No trephine biopsy	32% lymphs (BMA)	Normal	Mild diffuse adenopathy above and below diaphragm, up to 2.1 cm in longest axis
10		CLL	1.3	No trephine biopsy	11% lymphs (BMA)	Normal	Mild diffuse adenopathy in neck and above and below diaphragm, up to 2.2 cm in longest axis
11		CLL	3.3	Inadequate biopsy	71% lymphs (BMA)	Normal	Mild diffuse adenopathy above and below diaphragm, up to 2.6 cm in longest axis
12		CLL	0.6	50%	NED (IHC); 16% lymphs (BMA); 0.63% (FACS)	Normal	Borderline adenopathy above and below diaphragm, all <1.5 cm in longest axis
13		CLL	1.8	50-60%	10-15% (IHC); 18% lymphs (BMA)	Normal	Borderline adenopathy above and below diaphragm, all <1.5 cm in longest axis; also w/ hepatomegaly (21 cm)
14		CLL	0.6	30%	20-30% (IHC); 59% lymphs (BMA)	12.3 cm	Borderline abdominopelvic adenopathy, all <1.5 cm in longest axis
15	1st	CLL	1.3	80%	70-80% (IHC); 75% lymphs (BMA)	15.1 cm	Diffuse; above and below diaphragm (largely below), up to 4.6 cm in longest axis
	2nd		Total WBC 0.2	50%	90% (IHC); 89% lymphs BMA	15.4 cm	Diffuse; above and below diaphragm (largely below), up to 3.3 cm in longest axis
16	1st	CLL	1.3	90%	60% (IHC); 54% lympjhs (BMA)	15 cm	Diffuse; in neck and above and below diaphragm, up to 3.7 cm in longest axis; also with hepatomegaly (22-23 cm)

	2nd		Total WBC 0.2	80%	20% (IHC); 49% lymphs (BMA)	Not reassesed	Not reimaged prior to CAR T-cell infusion
	3rd		0.7	50%	NED (IHC); 13% lymphs (BMA); 0.032% (FACS)	12 cm	Diffuse; in neck and above and below diaphragm, up to 4.3 cm in longest axis; also with hepatomegaly (22-23 cm)
	4th		0.5				
17		FL	0.3	50-60%	NED (IHC, FACS)	Normal	Extensive; above and below diaphragm, up to 10.1 cm in longest axis
18		MZL	0.3	Inadequate biopsy	NED (FACS)	Normal	No significant adenopathy
19		MZL	2.5	30%	NED (IHC, FACS)	s/p splenectomy	No signficant adenopathy
20	1st	MCL	0.1	>80%	NED (IHC, FACS)	Normal	Extensive; in neck and above and below diaphragm (largely below), up to 10.3 cm in longest axis
	2nd		0.1				

Legend: BM, bone marrow; BMA, bone marrow aspirate; CLL, chronic lymphocytic leukemia; FACS, flow cytometry; FL, follicular lymphoma; IHC, immunohistochemistry; Inf, infusion; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NED, no evidence of disease; Pt, patient.

Table S4: Specific therapies administered prior to CAR T-cell therapy among patients with CLL

Pt #	Number of Prior Therapies	Specific prior therapies (lines of therapy are split by semicolon)
1	2	FCR; PCRM
2	5	Flu (single agent); rituximab (single agent); PCR; rituximab (single agent); PCRM
3	3	Chlorambucil (single agent); Cy (single agent); PCR
4	4	Flu (single agent); Cy (single agent); rituximab (single agent); PCRM
5	1	PCR
6	7	RCVP; rituximab (single agent); PCR; Cy + rituximab; rituximab (single agent); Cy + rituximab; Benda (single agent)
7	5	CVP; rituximab (single agent); Cy + rituximab; PCR; PCRM
8	4	RCHOP; alemtuzumab (single agent); alemtuzumab + rituximab; RCVP
9	3	FC; RCV (then Cy + rituximab); BR
10	2	FCR, BR
11	11	FC; Dex (single agent); PC; Cy + rituximab; lenalidomide; idelalisib; Dex (single agent); Ofa (single agent); ibrutinib; dasatinib (single agent); ibrutinib + dasatinib
12	4	RCHOP; FCR; BR; ibrutinib
13	1	Ibrutinib + rituximab
14	5	FR; BR; second course of BR; RICE; ibrutinib
15	6	FCR; second course of FCR; Dex + rituximab; Cy + rituximab; Ofa (single agent); ibrutinib
16	8	FCR; BR; lenalidomide; ibrutinib; HDMP; obinutuzumab (single agent); idelalisib; venetoclax

Legend (in order of appearance): FCR=fludarabine, cyclophosphamide, rituximab; PCRM=pentostatin, cyclophsphamide, rituximab, mitoxantrone; Flu=fludarabine; Cy=cyclophosphamide; RCVP=rituximab, cyclophosphamide, vincristine, prednisone; Benda=bendamustine; CVP=cyclophosphamide, vincristine, prednisone; RCHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; FC=fludarabine and cyclophosphamide; RCV=rituximab, cyclophosphamide, and vincristine; BR=bendamustine and rituximab; Dex=dexamethasone; PC=pentostatin and cyclophosphamide; Ofa=ofatumomab; FR=fludarabine and rituximab; RICE=rituximab, ifosfamide, carboplatin, etoposide; HDMP=high-dose methylprednisolone

Table S5: Management of ibrutinib at the time of CAR T-cell infusion

Pt #	Ibrutinib management pre-CAR T-cell infusion	Ibrutinib management post-CAR T-cell infusion
11	Continued through date of CAR T-cell infusion	Given on day 1 post-CAR T-cell infusion, then held due to development of CRS and neurologic toxicity. Resumed on day 13 post-CAR T-cell infusion after resolution of CRS and neurologic toxicity and subsequent hospital discharge.
12	Continued through date of CAR T-cell infusion	Continued without interruption
13	Held beginning 3 days prior to CAR T-cell infusion	Continued to be held in setting of CRS and neurologic toxicity. Resumed on day 59 post-CAR T-cell infusion in outpatient setting; had been discharged on day 21 post-CAR T-cell infusion following resolution of CRS and neurologic toxicity.
14	Held beginning 5 days prior to CAR T-cell infusion	Continued to be held in setting of CRS and neurologic toxicity. Resumed on day 17 post-CAR T-cell infusion following resolution of CRS and neurologic toxicity.
15	Held beginning 12 days prior to first CAR T-cell infusion	Resumed 24 days following first CAR T-cell infusion and then continued through second CAR T-cell infusion (30 days following the first CAR T-cell infusion) without interruption.

Table S6: Detailed inclusion/exclusion criteria:

Patient population: Patients with chronic lymphocytic leukemia (CLL) or indolent B-cell lymphoma who had relapsed or chemotherapy-refractory disease, or who had evidence of residual disease following therapy were eligible. Chemotherapy-refractory disease was defined by failure to achieve at least a partial response to the last therapy or disease progression within 6 months of the last therapy. Patients who initially responded to therapy but subsequently demonstrated disease progression after 6 months of completion of therapy were considered to have relapsed disease.

Inclusion criteria:

1. Patients must have the following $CD19^+$ B-cell leukemia or lymphoma either with relapsed or chemotherapy-refractory disease or with evidence of residual disease following therapy. In all cases, pathologic confirmation was required at the treating center (Memorial Sloan Kettering Cancer Center).
   --CLL: Patients must have a diagnosis of CLL as evidenced by flow cytometry, bone marrow histology, and/or cytogenetics.
   --Other low grade B-cell neoplasms eligible as well, including small lymphocytic lymphoma (SLL), follicular lymphoma, Waldenstrom macroglobulinemia, hairy cell leukemia, marginal zone lymphomas, and mantle cell lymphomas.
2. Creatinine ≤2.0 mg/100 ml, bilirubin ≤2.0 mg/100 ml, AST and ALT ≤3.0x normal, PT and PTT ≤ 2x normal outside the setting of stable chronic anticoagulation therapy.
3. Adequate cardiac function (left ventricular ejection fraction [LVEF] ≥40%) as assessed by echocardiogram or MUGA scan performed within 1 month of treatment.
4. Adequate pulmonary function as assessed by ≥92% oxygen saturation on room air by pulse oximetry.
5. Life expectancy of >3 months.

Exclusion criteria:

1. Karnofsky performance status <70.
2. CLL patients with active transformed disease (Richter syndrome).
3. Patients with following cardiac conditions:
   --New York Heart Association (NYHA) stage III or IV congestive heart failure.
   --Myocardial infarction ≤6 months prior to enrollment.
   --History of clinically significant ventricular arrhythmia or unexplained syncope, not believed to be vasovagal in nature or due to dehydration.
   --History of severe non-ischemic cardiomyopathy with LVEF ≤20%.
4. Patients with HIV, hepatitis B or hepatitis C infection.
5. Patients with any concurrent active malignancies as defined by malignancies requiring any therapy other than expectant observation.

Table S7: Characteristics of commercially available antibodies used for CAR T-cell immunophenotyping

Antibody	Fluorochrome	Manufacturer	Clone
CCR7	FITC	R&D Systems	FAB197F
CD45RA	APC	Thermo Fisher	MED-56
CD62L	FITC	Thermo Fisher	Dreg-56
CD127	eFlour450	eBiosciences	eBioRDR5
CD27	APC	BD Biosciences	L128
CD28	FITC	Invitrogen	10F3

Supplementary Figure Legends:

Figure S1: Timeline of ibrutinib (IBR) exposure in patients undergoing autologous T-cell collection and/or CAR T-cell infusion during ibrutinib therapy.

Figure S2: (A) Median absolute lymphocyte count (ALC) on first day of CAR T-cell infusion following conditioning chemotherapy. (B) Median change in ALC from beginning of conditioning chemotherapy to first day of CAR T-cell infusion. Results are stratified by form of conditioning chemotherapy administered. Bars indicate interquartile range. Cy, cyclophosphamide; Flu, fludarabine.

Figure S3: Course and severity of cytokine release syndrome (CRS) in individual patients, as evaluated each day during inpatient admission following each 19-28z CAR T-cell infusion.

Figure S4: Course and severity of neurologic toxicity following each CAR T-cell infusion in individual patients, as evaluated each day during inpatient admission following each 19-28z CAR T-cell infusion.

Figure S5: Changes in immunoregulatory cytokine levels in evaluable patients receiving conditioning chemotherapy prior to 19-28z CAR T-cell infusion, stratified by status as on ibrutinib (IBR) at CAR T-cell infusion, IBR-naive, or post-IBR, including: (A) IL-6, (B) IL-10, (C) IFN-γ, (D) IL-2, (E) GM-CSF, (F) Flt3L, (G) fractalkine, (H) IL-15, (I) MCP-3.

Figure S1

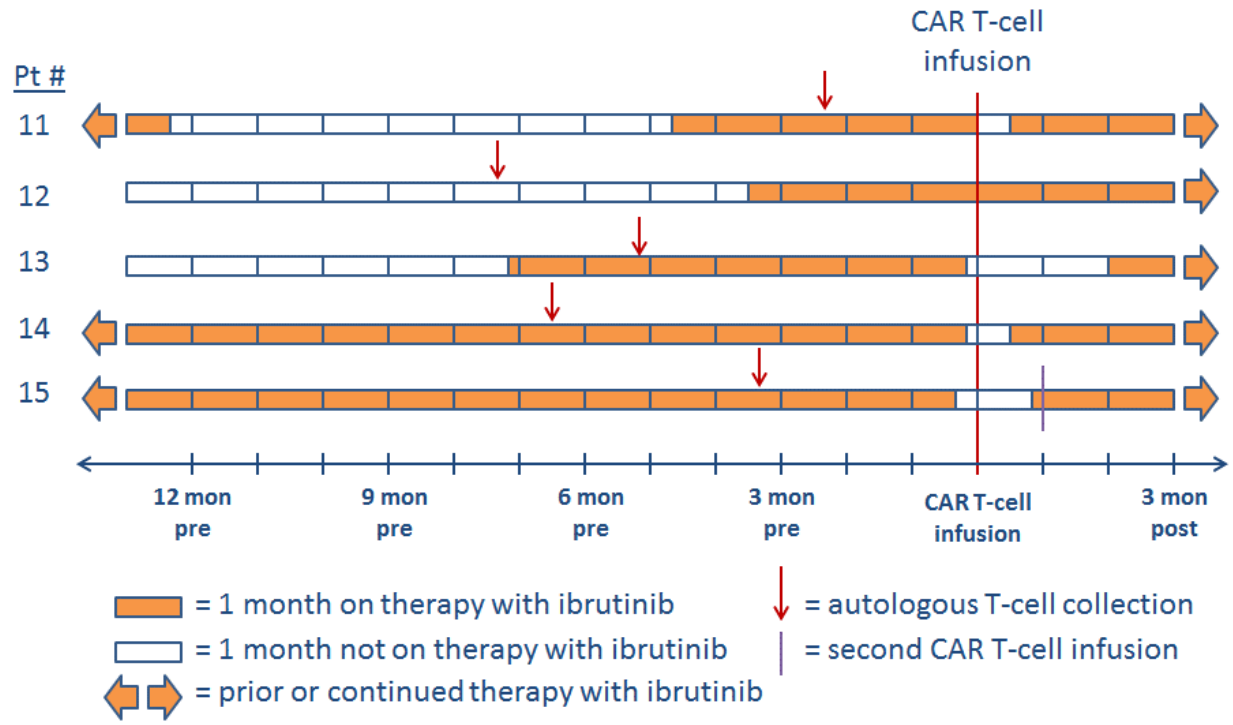

CAR T-cell infusion
Pt #
11
12
13
14
15
12 mon pre
9 mon pre
6 mon pre
3 mon pre
CAR T-cell infusion
3 mon post
= 1 month on therapy with ibrutinib
= 1 month not on therapy with ibrutinib
= prior or continued therapy with ibrutinib
= autologous T-cell collection
= second CAR T-cell infusion

Figure S2

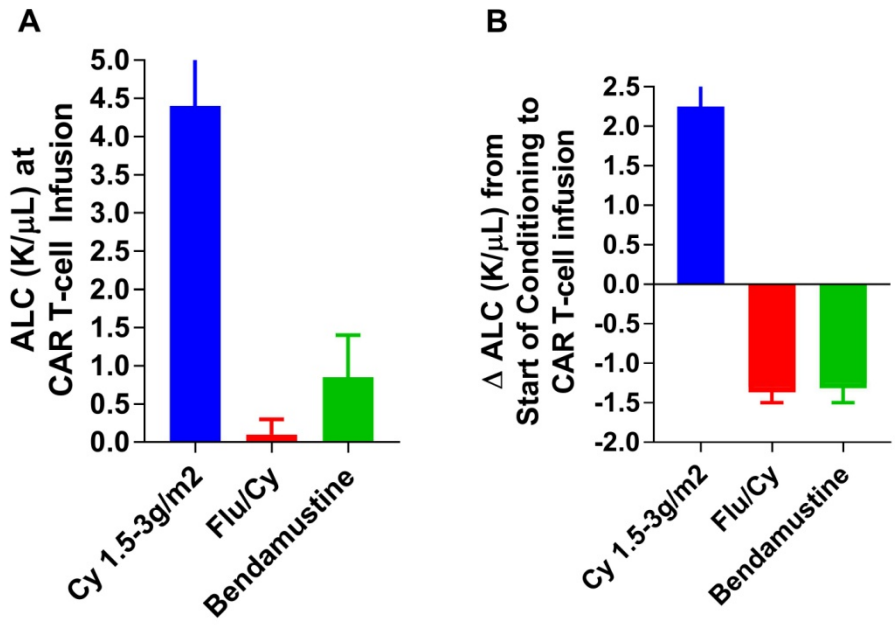

A
ALC (K/μL) at CAR T-cell Infusion
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Cy 1.5-3g/m2
Flu/Cy
Bendamustine
B
Δ ALC (K/μL) from Start of Conditioning to CAR T-cell infusion
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
Cy 1.5-3g/m2
Flu/Cy
Bendamustine

Figure S3

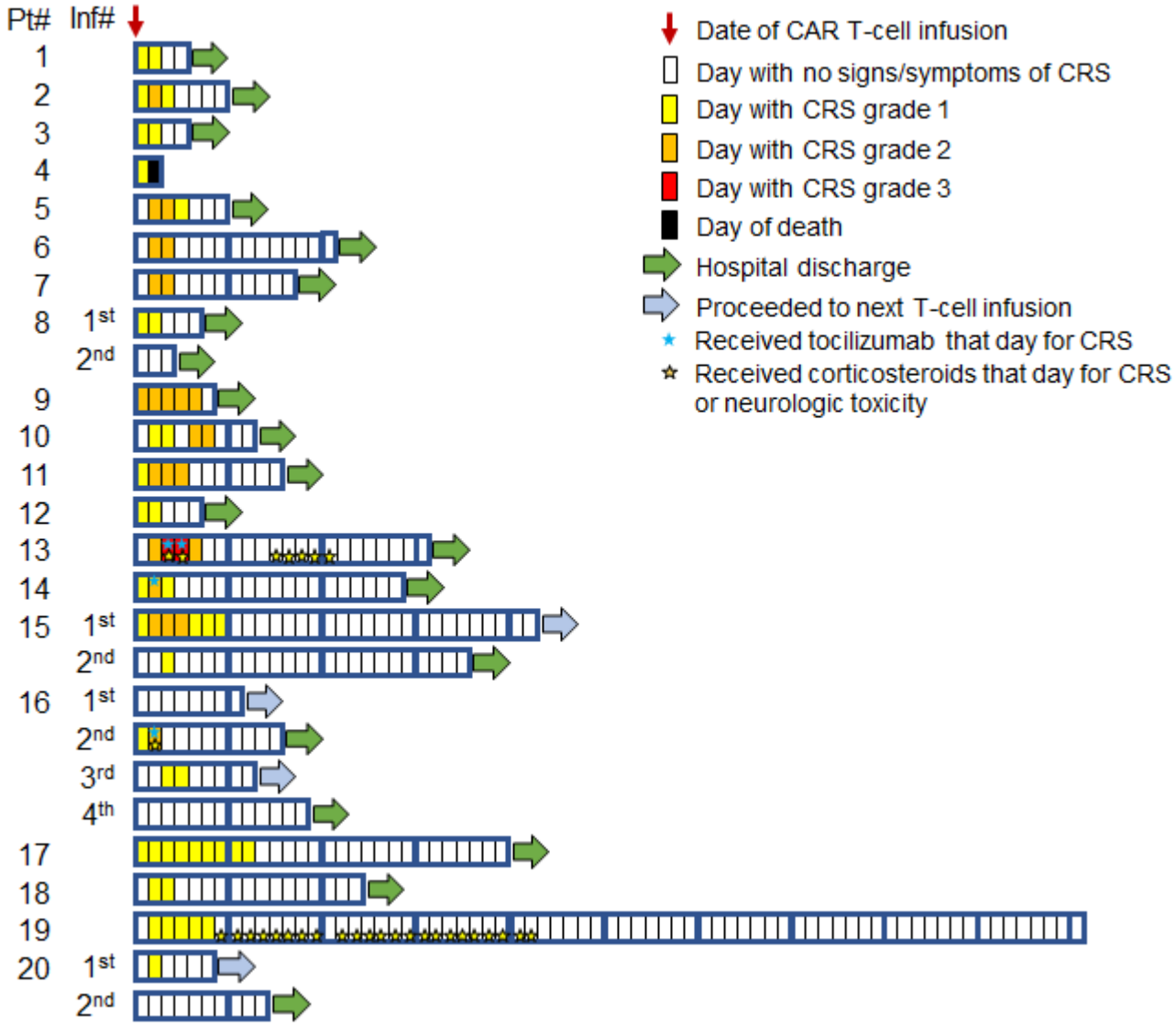

Pt# Inf#
1
2
3
4
5
6
7
8 1st
2nd
9
10
11
12
13
14
15 1st
2nd
16 1st
2nd
3rd
4th
17
18
19
20 1st
2nd
Date of CAR T-cell infusion
Day with no signs/symptoms of CRS
Day with CRS grade 1
Day with CRS grade 2
Day with CRS grade 3
Day of death
Hospital discharge
Proceeded to next T-cell infusion
Received tocilizumab that day for CRS
Received corticosteroids that day for CRS or neurologic toxicity

Figure S4

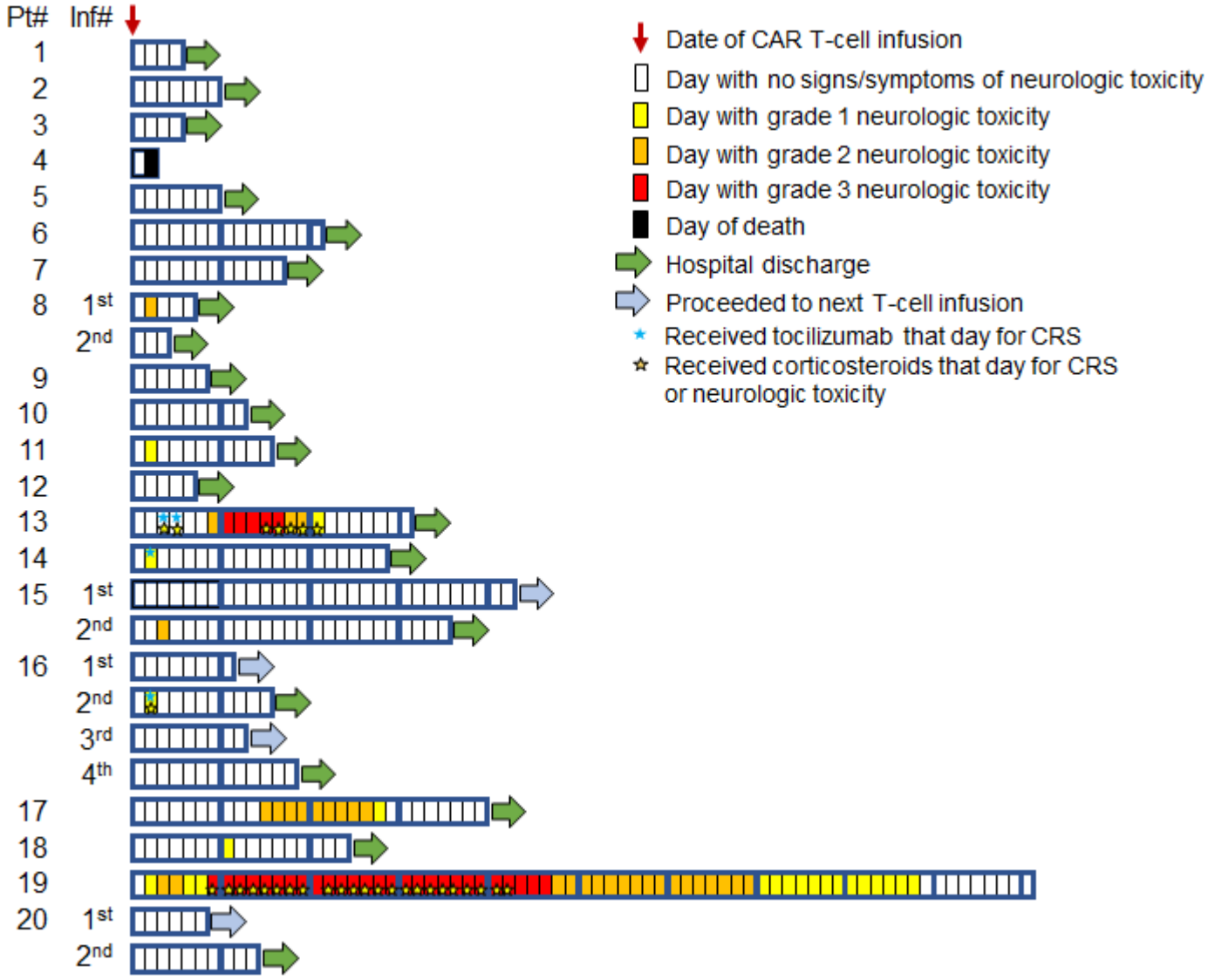
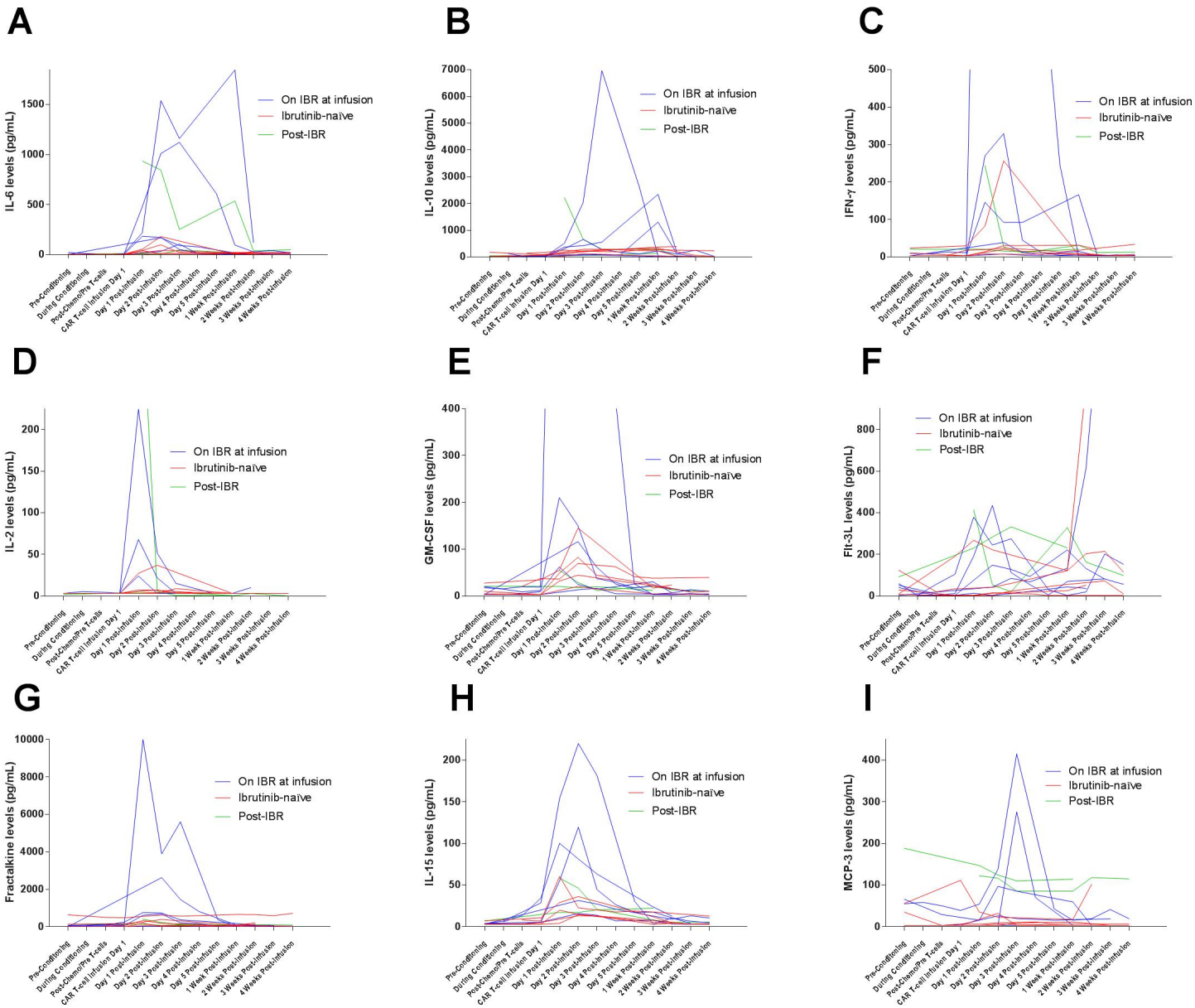

Pt#
Inf#
1
2
3
4
5
6
7
8
1st
2nd
9
10
11
12
13
14
15
1st
2nd
16
1st
2nd
3rd
4th
17
18
19
20
1st
2nd
Date of CAR T-cell infusion
Day with no signs/symptoms of neurologic toxicity
Day with grade 1 neurologic toxicity
Day with grade 2 neurologic toxicity
Day with grade 3 neurologic toxicity
Day of death
Hospital discharge
Proceeded to next T-cell infusion
Received tocilizumab that day for CRS
Received corticosteroids that day for CRS or neurologic toxicity

Figure S5


A
IL-6 levels (pg/mL)
B
IL-10 levels (pg/mL)
C
IFN-γ levels (pg/mL)
D
IL-2 levels (pg/mL)
E
GM-CSF levels (pg/mL)
F
Flt-3L levels (pg/mL)
G
Fractalkine levels (pg/mL)
H
IL-15 levels (pg/mL)
I
MCP-3 levels (pg/mL)
On IBR at infusion
Ibrutinib-naïve
Post-IBR
Pre-Conditioning
During Conditioning
Post-Chemo/Pre T-cells
CAR T-cell Infusion Day 1
Day 1 Post-Infusion
Day 2 Post-Infusion
Day 3 Post-Infusion
Day 4 Post-Infusion
Day 5 Post-Infusion
1 Week Post-Infusion
2 Weeks Post-Infusion
3 Weeks Post-Infusion
4 Weeks Post-Infusion