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A safe and potent anti-CD19 CAR T cell therapy

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Supplementary Table 1. Prior therapies

| Patient number | First line therapy | First line response | Duration of first line response | Second line therapy | Second line therapy response | Duration of second line response | Third line therapy | Third line therapy response | Duration of third line response | Fourth line therapy | Fourth line therapy response | Duration of fourth line response | Fifth line therapy | Fifth line therapy response | Duration of fifth line response | Sixth line therapy | Sixth line therapy response | Duration of sixth line response | Number of prior lines of therapies | Number of ASCT |
|----------------|----------------------------------|---------------------|---------------------------------|--------------------------|------------------------------|----------------------------------|--------------------------------------|-----------------------------|---------------------------------|---------------------------|------------------------------|----------------------------------|--------------------------|-----------------------------|---------------------------------|--------------------|-----------------------------|---------------------------------|------------------------------------|----------------|
| BZ001 | R-CHOP*4 + HyperCVAD*1 | PR | NA | GEMOX * 5 | SD | NA | | | | | | | | | | | | | 2 | 0 |
| BZ002 | R-CHOP*6 + R*2 | NA | 1 month | DEP * 2 | PD | NA | Radiation therapy | PD | NA | GDP*3 | PD | NA | radioactive seed implant | PD | NA | | | | 5 | 0 |
| BZ004 | R-CHOP*3 | PD | NA | RB + IBRUTINIB /placebo | CR | 5 months | | | | | | | | | | | | | 2 | 0 |
| BZ005 | R-CHOP*8 + R*2 | PD | NA | RB + IBRUTINIB /placebo | PR | 3 months | | | | | | | | | | | | | 2 | 0 |
| BZ006 | R-CHOP*4 | PD | NA | DICE*2 | SD | NA | GDP + Lenalidomide*4 | SD | NA | | | | | | | | | | 3 | 0 |
| BZ007 | R-CHOP *6 | PD | NA | GDP*4 | PD | NA | | | | | | | | | | | | | 2 | 0 |
| BZ008 | R-CHOP * 8 | PD | NA | DICE*3 + MA *1 + ASCT | PD | NA | Radiation therapy + Lenalidomide | CR | 12 months | | | | | | | | | | 3 | 1 |
| BZ009 | CHOP*3 + CHOEP *2 | SD | NA | DICE*6 + RT | PR | 9 months | | | | | | | | | | | | | 2 | 0 |
| BZ010 | ABVD*4 | PD | NA | BEACOPP*2 | PD | NA | R-DICE * 4 | PD | NA | Hyper CVAD *1 | PD | NA | R-EPOCH *1 | PD | NA | R-GEMOX * 1 | PD | NA | 6 | 0 |
| BZ011 | R-CHOP *1 + R-EPOCH/DICE /MTX *7 | PD | NA | GEMOX + Lenalidomide * 3 | PD | NA | | | | | | | | | | | | | 2 | 0 |
| BZ012 | CHOP*3 + RT | CR | 158 months | R-CHOP*4 | PR | NA | R-DICE * 2+ASCT *2 | PD | NA | GDP + Bortezomib *3 + RT | PD | | | | | | | | 4 | 2 |
| BZ013 | R-CHOP/MTX*8 | PD | NA | GEMOX*4 | PD | NA | | | | | | | | | | | | | 2 | 0 |
| BZ014 | R-CHOP*8 | CR | 4 months | R-DICE *4 | PD | NA | | | | | | | | | | | | | 2 | 0 |
| BZ015 | R-EPOCH*6 | PD | NA | DICE*6 | PD | NA | Liposome Encapsulated Mitoxantrone*2 | SD | NA | | | | | | | | | | 3 | 0 |
| BZ016 | R-CHOP*8 | PD | NA | DICE + Chidamide*5 | SD | NA | GEMOX*6 | SD | NA | | | | | | | | | | 3 | 0 |
| BZ017 | R-CHOP*6 | PR | 18 months | DICE + Chidamide*4 | PD | NA | GEMOX*2 + ASCT | PD | NA | | | | | | | | | | 3 | 1 |
| BZ018 | FC*6 | PR | 5 months | R-CHOP*3 | PR | 10 months | Ofatumumab*3 | PD | NA | RB + IBRUTINIB /placebo*6 | PR | 12 months | | | | | | | 4 | 0 |
| BZ019 | R-EPOCH/MTX*7 + ASCT | CR | 28 months | | | | | | | | | | | | | | | | 1 | 1 |
| BZ020 | R-CHOP*2 + R-CHOEP*6 | CR | 10 months | R-DICE*4 + ASCT | CR | 16 months | GDP*2 | PR | 16 months | Radiation therapy | PD | NA | | | | | | | 4 | 1 |
| BZ021 | R-CHOP*8 | PD | NA | DICE*4 | PD | NA | | | | | | | | | | | | | 2 | 0 |
| BZ022 | R-EPOCH*6 | PR | NA | R-DICE + Lenalidomide*3 | PR | 10 months | GDP*2 | PD | NA | | | | | | | | | | 3 | 0 |
| BZ023 | EPOCH*4 | PR | NA | DICE*4 | CR | 14 months | MINE*4 | NA | NA | ESHAP*8 | PR | 4 months | DICE*2 | PR | NA | | | | 5 | 0 |
| BZ024 | R-CHOP*6 | PR | 30 months | R*5 | PD | NA | | | | | | | | | | | | | 2 | 0 |
| BZ025 | R-CHOP*6 | PD | NA | R-EPOCH*1 | PD | NA | R-DICE*6 + ASCT + R maintenance | CR | 3 months | | | | | | | | | | 3 | 1 |
| BZ026 | mini-CCOP*8 | CR | 19 months | GEMOX*8 | PD | NA | mini-CCOP*6 | PR | 2 months | | | | | | | | | | 3 | 0 |

Abbreviations: R: Rituximab. CHOP: Cyclophosphamide, Adriamycin, Vincristine, Prednisone. Hyper CVAD: Cyclophosphamide, Vincristine, Adriamycin, Dexamethasone. GEMOX: Gemcitabine, Oxaliplatin. DEP: Dexamethasone, Etoposide, Cisplatin. RT: Radiation therapy. GDP: Gemcitabine, Cisplatin, Prednisone. RB: Rituximab, Bendamustine. DICE: Dexamethasone, Ifosfamide, Cisplatin, Etoposide.

MA: Methotrexate, Cytarabine. ASCT: Autologous Stem Cell Transplantation. CHOEP: Cyclophosphamide, Adriamycin, Vincristine, Etoposide, Prednisone. ABVD: Adriamycin, Bleomycin, Vincristine, Dacarbazine. BEACOPP: Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone. EPOCH: Etoposide, Prednisone, Vincristine, Cyclophosphamide, Adriamycin. MTX: Methotrexate. FC: Fludarabine, Cyclophosphamide. MINE: Mesna, Ifosfamide, Mitoxantrone, Etoposide. ESHAP: Etoposide, Methylprednisolone, Cisplatin, Cytarabine. RM: Rituximab Maintenance. CDOP: Cyclophosphamide, Liposomal Adriamycin, Vincristine, Prednisone. CR: Complete Remission. PR: Partial Remission. SD: Stable Disease. PD: Progressive Disease. NA: Not Applicable.

Supplementary Table 2. Baseline characteristics of patients

| Patient number | Gender | Age (years) | Lymphoma type | C-Mye (IHC) | BCL-2 (IHC) | BCL-6 (IHC) | FISH assay | Ki67 (IHC) | CD19 status at enrollment (IHC) | Disease stage at enrollment | B symptoms | ECOG score at enrollment | Number of Extranodal disease | LDH (IU/L) | International Prognostic Index score | Bone marrow involved |
|----------------|--------|-------------|-------------------------------------|-------------|-------------------|-----------------------|---------------------|------------|---------------------------------|-----------------------------|------------|--------------------------|------------------------------|------------|--------------------------------------|----------------------|
| BZ001 | male | 65 | FL3a | 20% | - | + | NA | 50-75% | + | IV | Yes | 0 | 2 | 261 | 4 | No |
| BZ002 | female | 68 | Non-GCB DLBCL | 50% | >75% | partial weak positive | NA | 90% | + | IV | No | 1 | 2 | 236 | 3 | No |
| BZ004 | female | 37 | FL2 | NA | + | - | NA | 20% | + | IV | Yes | 0 | 2 | 299 | 3 | No |
| BZ005 | male | 43 | FL2 | NA | + | + | NA | 30% | NA | IV | No | 0 | 1 | 237 | 1 | No |
| BZ006 | male | 48 | Non-GCB DLBCL | <25% | diffused positive | dispersed positive | NA | 20-50% | + | IV | No | 0 | 3 | 172 | 2 | No |
| BZ007 | male | 30 | GCB DLBCL | - | + | + | NA | 80% | NA | II | No | 0 | 1 | 201 | 0 | No |
| BZ008 | male | 26 | Non-GCB DLBCL | 40% | + | + | NA | > 50% | NA | IV | No | 0 | 1 | 184 | 1 | No |
| BZ009 | male | 24 | Non-GCB DLBCL | - | + | + | NA | 50-75% | + | IV | No | 0 | 2 | 193 | 2 | No |
| BZ010 | female | 42 | Non-GCB DLBCL | 20% | 50-75% | + | NA | 80% | + | IV | No | 0 | 4 | 316 | 3 | No |
| BZ011 | female | 30 | HGBL, with MYC and BCL2 R | 70% | + | + | cmy(+) bcl2(+) | 70% | + | IV | No | 1 | 1 | 421 | 2 | No |
| BZ012 | male | 36 | Non-GCB DLBCL | 40% | >75% | + | NA | 80% | + | IV | No | 0 | 3 | 357 | 3 | No |
| BZ013 | female | 63 | Non-GCB DLBCL | NA | + | weak positive | NA | 90% | + | IV | No | 1 | 2 | 661 | 4 | No |
| BZ014 | male | 67 | GCB DLBCL | NA | + | + | NA | 90% | + | IV | Yes | 1 | 1 | 454 | 3 | No |
| BZ015 | male | 48 | Non-GCB DLBCL | NA | - | - | NA | 60% | + | IV | No | 0 | 2 | 178 | 2 | No |
| BZ016 | female | 50 | GCB DLBCL | - | + | + | NA | >75% | + | III | Yes | 0 | 0 | 209 | 1 | No |
| BZ017 | male | 33 | FL with large B cell transformation | NA | + | + | CMYC(-) /BCL2(+) | 60% | + | IV | Yes | 1 | 3 | 232 | 2 | No |
| BZ018 | female | 50 | FL2 | NA | + | + | NA | 80% | + | IV | No | 0 | 2 | 211 | 2 | No |
| BZ019 | female | 66 | Non-GCB DLBCL | 15% | 80% | - | NA | 80% | + | IV | Yes | 0 | 7 | 222 | 3 | No |
| BZ020 | female | 60 | Non-GCB DLBCL | 5% | + | + | NA | 70% | + | IV | Yes | 0 | 6 | 216 | 3 | No |
| BZ021 | female | 66 | Non-GCB DLBCL | 50% | + | - | NA | 50-75% | + | III | No | 0 | 0 | 272 | 3 | No |
| BZ022 | female | 63 | Non-GCB DLBCL | NA | 95% | + | NA | 90% | difused strong positive | IV | Yes | 0 | 2 | 273 | 4 | No |
| BZ023 | male | 47 | FL3a | - | + | + | NA | 30% | + | III | Yes | 0 | 0 | 307 | 2 | No |
| BZ024 | female | 39 | FL2 | <25% | + | + | NA | 50-75% | + | IV | No | 0 | 2 | 203 | 2 | No |
| BZ025 | male | 35 | FL3a | NA | + | + | NA | 50% | + | IV | No | 0 | 2 | 156 | 2 | Yes |
| BZ026 | male | 76 | Non-GCB DLBCL | - | + | - | NA | 50% | + | IV | No | 0 | 3 | 294 | 4 | No |

Abbreviations: IHC: Immunohistochemistry. FISH: Fluorescence In Situ Hybridization. BCL: B Cell Lymphoma. LDH: Lactate Dehydrogenase. FL: Follicular Lymphoma. GCB: Germinal Center B. DLBCL: Diffuse Large B Cell Lymphoma. HGBL: High Grade B Cell Lymphoma. R: Rearrangement. NA: Not Applicable.

Supplementary Table 3. Characteristics of infused CAR T cells

| Patient Number | tEGFR % | CD3 ⁺ % | CD4 ⁺ % | CD8 ⁺ % | Total CAR T cells infused |
|----------------|---------|--------------------|--------------------|--------------------|---------------------------|
| BZ001 | 4% | 97.90% | 8.40% | 88.20% | 6.4×10 ⁶ |
| BZ002 | 10% | 98.30% | 31.60% | 61.60% | 5.7×10 ⁶ |
| BZ004 | 12.80% | 99.40% | 7.71% | 89.90% | 3×10 ⁶ |
| BZ005 | 29.30% | 99.80% | 27.30% | 69.40% | 6×10 ⁶ |
| BZ006 | 6.10% | 99.20% | 13.90% | 85.20% | 6×10 ⁶ |
| BZ007 | 17.70% | 98.70% | 39.30% | 55% | 6×10 ⁶ |
| BZ008 | 11% | 99.50% | 10.50% | 88.40% | 6×10 ⁷ |
| BZ009 | 25% | 99.30% | 21.60% | 76.60% | 6×10 ⁷ |
| BZ010 | 27% | 95.40% | 25.30% | 72% | 6×10 ⁷ |
| BZ011 | 8% | 98.90% | 38.40% | 54.90% | 6×10 ⁷ |
| BZ012 | 19.40% | 96.60% | 12.20% | 82.30% | 1.8×10 ⁸ |
| BZ013 | 53.90% | 98.50% | 50.50% | 47.70% | 1.8×10 ⁸ |
| BZ014 | 60.30% | 98.10% | 36.20% | 61.20% | 1.8×10 ⁸ |
| BZ015 | 25.50% | 97.80% | 47.30% | 49.30% | 3.6×10 ⁸ |
| BZ016 | 9.69% | 98.30% | 8.97% | 81.40% | 3.6×10 ⁸ |
| BZ017 | 4.20% | 95.90% | 4.10% | 91.70% | 2.5×10 ⁸ |
| BZ018 | 12.60% | 84.50% | 44.80% | 53.10% | 4.3×10 ⁷ |
| BZ019 | 22.50% | 99.60% | 34.80% | 60.60% | 3.6×10 ⁸ |
| BZ020 | 12.90% | 98.40% | 9.20% | 89.10% | 2.0×10 ⁸ |
| BZ021 | 55.80% | 98.20% | 28.30% | 70.70% | 2.5×10 ⁸ |
| BZ022 | 31.20% | 98.60% | 34.40% | 65.10% | 3.6×10 ⁸ |
| BZ023 | 58.10% | 98.40% | 25.10% | 68.70% | 3.6×10 ⁸ |
| BZ024 | 21.10% | 99% | 15% | 79.30% | 3.6×10 ⁸ |
| BZ025 | 10.20% | 97.50% | 4.60% | 93.60% | 3.7×10 ⁸ |
| BZ026 | 20% | 99.40% | 23.80% | 77.90% | 3.2×10 ⁸ |

Supplementary Table 4. Cytokine release syndrome (CRS) and neurological toxicities in patients treated with CD19-BBz(86) CAR-T cell therapy.

| | Grade (N=25) | | | | | |
|--|--------------|---------|--------|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 |
| Cytokine Release Syndrome^a | 18 (72%) | 7 (28%) | | | | |
| Fever | 18 (72%) | 5 (20%) | 2 (8%) | | | |
| Hypotension | 25 (100%) | | | | | |
| Acute Kidney injury | 25 (100%) | | | | | |
| Hypoxia | 25 (100%) | | | | | |
| Dyspnea | 24 (96%) | 1 (4%) | | | | |
| Neurological Toxicity^b | 25 (100%) | | | | | |
| Encephalopathy | 25 (100%) | | | | | |
| Delirium | 25 (100%) | | | | | |
| Tremor | 25 (100%) | | | | | |
| Cognitive disturbance | 25 (100%) | | | | | |
| Confusion | 25 (100%) | | | | | |
| Movement involuntary | 25 (100%) | | | | | |
| Memory impairment | 25 (100%) | | | | | |
| Seizure | 25 (100%) | | | | | |
| Dysphasia | 25 (100%) | | | | | |
| Cerebral edema | 25 (100%) | | | | | |
| Somnolence | 25 (100%) | | | | | |

Supplementary Table 5. Cytokine release syndrome and neurological toxicity of individual patients.

| Patient number | CRS and grade | Encephalopathy | Delirium | Tremor | Cognitive disturbance | Confusion | Movement involuntary | Memory impairment | Seizure | Dysphasia | Cerebral edema | Somnolence |
|----------------|---------------|----------------|----------|--------|-----------------------|-----------|----------------------|-------------------|---------|-----------|----------------|------------|
| BZ001 | - | - | - | - | - | - | - | - | - | - | - | - |
| BZ002 | Grade 1 | - | - | - | - | - | - | - | - | - | - | - |
| BZ004 | - | - | - | - | - | - | - | - | - | - | - | - |
| BZ005 | - | - | - | - | - | - | - | - | - | - | - | - |
| BZ006 | - | - | - | - | - | - | - | - | - | - | - | - |
| BZ007 | - | - | - | - | - | - | - | - | - | - | - | - |
| BZ008 | - | - | - | - | - | - | - | - | - | - | - | - |
| BZ009 | - | - | - | - | - | - | - | - | - | - | - | - |
| BZ010 | Grade 1 | - | - | - | - | - | - | - | - | - | - | - |
| BZ011 | - | - | - | - | - | - | - | - | - | - | - | - |
| BZ012 | - | - | - | - | - | - | - | - | - | - | - | - |
| BZ013 | - | - | - | - | - | - | - | - | - | - | - | - |
| BZ014 | - | - | - | - | - | - | - | - | - | - | - | - |
| BZ015 | - | - | - | - | - | - | - | - | - | - | - | - |
| BZ016 | - | - | - | - | - | - | - | - | - | - | - | - |
| BZ017 | Grade 1 | - | - | - | - | - | - | - | - | - | - | - |
| BZ018 | - | - | - | - | - | - | - | - | - | - | - | - |
| BZ019 | - | - | - | - | - | - | - | - | - | - | - | - |
| BZ020 | - | - | - | - | - | - | - | - | - | - | - | - |
| BZ021 | Grade 1 | - | - | - | - | - | - | - | - | - | - | - |
| BZ022 | Grade 1 | - | - | - | - | - | - | - | - | - | - | - |
| BZ023 | - | - | - | - | - | - | - | - | - | - | - | - |
| BZ024 | - | - | - | - | - | - | - | - | - | - | - | - |
| BZ025 | Grade 1 | - | - | - | - | - | - | - | - | - | - | - |
| BZ026 | Grade 1 | - | - | - | - | - | - | - | - | - | - | - |

CRS was assessed and graded according to CRS grading system (Lee et al., Current Concepts in the diagnosis and management of cytokine release syndrome, BLOOD 2014, 124:188-195)

Supplementary Table 6. Other adverse event summary

| Adverse Events | Grade (N=25) | | | | | |
|---|--------------|----------|---------|----------|----------|---|
| | 0 | 1 | 2 | 3 | 4 | 5 |
| General disorders and administration site conditions | | | | | | |
| Fatigue | 23 (92%) | 2 (8%) | | | | |
| Fever | 18 (72%) | 5 (20%) | 2 (8%) | | | |
| Infusion related reaction | 25 (100%) | | | | | |
| Malaise | 23 (92%) | 2 (8%) | | | | |
| Pain | 23 (92%) | 2 (8%) | | | | |
| Appetite decrease | 24 (96%) | 1 (4%) | | | | |
| Cough | 18 (72%) | 7 (28%) | | | | |
| Flu like symptoms | 23 (92%) | 2 (8%) | | | | |
| Skin itch | 24 (96%) | 1 (4%) | | | | |
| Investigations | | | | | | |
| Alanine aminotransferase increased | 15 (60%) | 10 (40%) | | | | |
| Aspartate aminotransferase increased | 23 (92%) | 2 (8%) | | | | |
| Alkaline phosphatase increased | 24 (96%) | 1 (4%) | | | | |
| Blood bilirubin increased | 17 (68%) | 7 (28%) | 1 (4%) | | | |
| CPK increased | 22 (88%) | 1 (4%) | 2 (8%) | | | |
| Creatinine increased | 24 (96%) | 1 (4%) | | | | |
| Lymphocyte count decreased | 0 (0%) | | 1 (4%) | 3 (12%) | 21 (84%) | |
| Neutrophil count decreased | 2 (8%) | 3 (12%) | 6 (24%) | 9 (36%) | 5 (20%) | |
| White blood cell decreased | 0 (0%) | 2 (8%) | 5 (20%) | 15 (60%) | 3 (12%) | |
| Platelet count decreased | 18 (72%) | 3 (12%) | 2 (8%) | 1 (4%) | 1 (4%) | |
| Blood and lymphatic system disorders, Respiratory system disorders, Renal system disorders, Gastrointestinal disorders | | | | | | |
| Anemia | 8 (32%) | 5 (20%) | 8 (32%) | 4 (16%) | | |
| Febrile neutropenia | 24 (96%) | | | 1 (4%) | | |
| Dyspnea | 24 (96%) | 1 (4%) | | | | |
| Hypoxia | 25 (100%) | | | | | |
| Acute kidney injury | 25 (100%) | | | | | |
| Hypotension | 25 (100%) | | | | | |
| Diarrhea | 25 (100%) | | | | | |
| Nausea | 24 (96%) | 1 (4%) | | | | |
| Vomiting | 25 (100%) | | | | | |
| Metabolism and nutrition disorders | | | | | | |
| Hypercalcemia | 25 (100%) | | | | | |
| Hyperglycemia | 11 (44%) | 14 (56%) | | | | |
| Hyperkalemia | 25 (100%) | | | | | |
| Hypermagnesemia | 25 (100%) | | | | | |
| hypernatremia | 25 (100%) | | | | | |
| hypertriglyceridemia | 13 (52%) | 11 (44%) | 1 (4%) | | | |
| hyperuricemia | 16 (64%) | 9 (36%) | | | | |
| Hypoalbuminemia | 24 (96%) | 1 (4%) | | | | |
| Hypocalcemia | 22 (88%) | 3 (12%) | | | | |
| hypoglycemia | 25 (100%) | | | | | |
| Hypokalemia | 20 (80%) | 5 (20%) | | | | |
| Hypomagnesemia | 25 (100%) | | | | | |
| Hyponatremia | 24 (96%) | 1 (4%) | | | | |
| hypophosphatemia | 25 (100%) | | | | | |

All adverse events occurred within one month after CAR T cell infusion were assessed and graded per CTCAE V4.03. For each adverse event, this table summarized the worst adverse event of each patient within one month post infusion.

Supplementary Table 7. Adverse events (General disorders)

| Patient number | Fatigue | Fever | Infusion related reaction | Malaise | Pain | Appetite decrease | Cough | Flu like symptoms | Skin itch |
|----------------|---------|---------|---------------------------|---------|---------|-------------------|---------|-------------------|-----------|
| BZ001 | - | - | - | - | - | - | Grade 1 | - | - |
| BZ002 | - | Grade 2 | - | - | - | - | Grade 1 | - | - |
| BZ004 | - | - | - | - | - | - | - | - | - |
| BZ005 | - | - | - | - | - | - | - | - | - |
| BZ006 | - | - | - | - | - | - | - | - | - |
| BZ007 | - | - | - | - | - | - | - | - | - |
| BZ008 | - | - | - | - | - | - | - | - | - |
| BZ009 | - | - | - | - | - | - | - | - | - |
| BZ010 | Grade 1 | - | - | - | - | - | Grade 1 | - | - |
| BZ011 | - | - | - | - | - | - | - | - | - |
| BZ012 | - | - | - | - | Grade 1 | Grade 1 | - | - | - |
| BZ013 | - | - | - | - | - | - | - | - | - |
| BZ014 | - | Grade 1 | - | - | - | - | Grade 1 | - | - |
| BZ015 | - | - | - | - | - | - | - | - | - |
| BZ016 | - | - | - | - | - | - | - | - | - |
| BZ017 | - | Grade 2 | - | Grade 1 | Grade 1 | - | - | - | - |
| BZ018 | - | - | - | - | - | - | - | - | - |
| BZ019 | - | - | - | - | - | - | - | - | - |
| BZ020 | - | - | - | - | - | - | - | - | - |
| BZ021 | - | Grade 1 | - | - | - | - | - | - | - |
| BZ022 | Grade 1 | Grade 1 | - | Grade 1 | - | - | - | - | - |
| BZ023 | - | - | - | - | - | - | - | - | - |
| BZ024 | - | - | - | - | - | - | Grade 1 | Grade 1 | Grade 1 |
| BZ025 | - | Grade 1 | - | - | - | - | Grade 1 | - | - |
| BZ026 | - | Grade 1 | - | - | - | - | Grade 1 | Grade 1 | - |

Supplementary Table 8. Adverse events (Investigations)

| Patient number | Alanine aminotransferase increased | Aspartate aminotransferase increased | Alkaline phosphatase increased | Blood bilirubin increased | CPK increased | Creatinine increased | Lymphocyte count decreased | Neutrophil count decreased | White blood cell decreased | Platelet count decreased |
|----------------|------------------------------------|--------------------------------------|--------------------------------|---------------------------|---------------|----------------------|----------------------------|----------------------------|----------------------------|--------------------------|
| BZ001 | - | - | - | Grade 1 | - | - | Grade 4 | Grade 3 | Grade 3 | Grade 1 |
| BZ002 | - | - | - | - | - | - | Grade 3 | Grade 4 | Grade 3 | - |
| BZ004 | - | - | - | Grade 1 | - | - | Grade 4 | Grade 4 | Grade 3 | - |
| BZ005 | Grade 1 | - | - | - | - | - | Grade 4 | Grade 3 | Grade 3 | - |
| BZ006 | Grade 1 | Grade 1 | - | - | - | - | Grade 4 | Grade 3 | Grade 3 | Grade 2 |
| BZ007 | Grade 1 | - | - | - | - | - | Grade 4 | Grade 2 | Grade 3 | - |
| BZ008 | Grade 1 | - | - | Grade 1 | - | - | Grade 4 | Grade 1 | Grade 2 | - |
| BZ009 | Grade 1 | - | - | - | Grade 2 | - | Grade 4 | Grade 2 | Grade 3 | - |
| BZ010 | Grade 1 | Grade 1 | Grade 1 | Grade 1 | - | - | Grade 4 | Grade 4 | Grade 3 | Grade 4 |
| BZ011 | - | - | - | - | - | - | Grade 4 | Grade 3 | Grade 3 | - |
| BZ012 | Grade 1 | - | - | Grade 1 | - | - | Grade 4 | - | Grade 2 | - |
| BZ013 | - | - | - | - | - | - | Grade 4 | Grade 3 | Grade 3 | - |
| BZ014 | - | - | - | - | - | - | Grade 2 | Grade 4 | Grade 4 | - |
| BZ015 | Grade 1 | - | - | - | Grade 1 | Grade 1 | Grade 4 | Grade 2 | Grade 2 | Grade 1 |
| BZ016 | - | - | - | - | - | - | Grade 4 | Grade 2 | Grade 2 | - |
| BZ017 | Grade 1 | - | - | - | Grade 2 | - | Grade 4 | Grade 3 | Grade 3 | Grade 2 |
| BZ018 | - | - | - | Grade 1 | - | - | Grade 3 | - | Grade 1 | - |
| BZ019 | - | - | - | - | - | - | Grade 4 | Grade 2 | Grade 3 | - |
| BZ020 | - | - | - | Grade 2 | - | - | Grade 4 | Grade 3 | Grade 3 | - |
| BZ021 | - | - | - | - | - | - | Grade 3 | Grade 4 | Grade 3 | - |
| BZ022 | - | - | - | - | - | - | Grade 4 | Grade 3 | Grade 4 | Grade 3 |
| BZ023 | - | - | - | - | - | - | Grade 4 | Grade 2 | Grade 3 | Grade 1 |
| BZ024 | Grade 1 | - | - | Grade 1 | - | - | Grade 4 | Grade 3 | Grade 4 | - |
| BZ025 | - | - | - | - | - | - | Grade 4 | Grade 1 | Grade 1 | - |
| BZ026 | - | - | - | - | - | - | Grade 4 | Grade 1 | Grade 2 | - |

Supplementary Table 9. Adverse events (blood and lymphatic system disorders, respiratory system disorders, renal system disorders, gastrointestinal disorders)

| Patient number | Anemia | Febrile neutropenia | Dyspnea | Hypoxia | Acute kidney injury | Hypotension | Diarrhea | Nausea | Vomiting |
|----------------|---------|---------------------|---------|---------|---------------------|-------------|----------|---------|----------|
| BZ001 | Grade 1 | -- | - | - | - | - | - | - | - |
| BZ002 | Grade 3 | - | - | - | - | - | - | - | - |
| BZ004 | Grade 1 | - | - | - | - | - | - | Grade 1 | - |
| BZ005 | - | - | - | - | - | - | - | - | - |
| BZ006 | Grade 2 | - | - | - | - | - | - | - | - |
| BZ007 | - | - | - | - | - | - | - | - | - |
| BZ008 | - | - | - | - | - | - | - | - | - |
| BZ009 | - | - | - | - | - | - | - | - | - |
| BZ010 | Grade 3 | - | Grade 1 | - | - | - | - | - | - |
| BZ011 | Grade 2 | - | - | - | - | - | - | - | - |
| BZ012 | Grade 1 | - | - | - | - | - | - | - | - |
| BZ013 | - | - | - | - | - | - | - | - | - |
| BZ014 | Grade 2 | Grade 3 | - | - | - | - | - | - | - |
| BZ015 | - | - | - | - | - | - | - | - | - |
| BZ016 | Grade 2 | - | - | - | - | - | - | - | - |
| BZ017 | Grade 2 | - | - | - | - | - | - | - | - |
| BZ018 | - | - | - | - | - | - | - | - | - |
| BZ019 | Grade 2 | - | - | - | - | - | - | - | - |
| BZ020 | Grade 2 | - | - | - | - | - | - | - | - |
| BZ021 | Grade 1 | - | - | - | - | - | - | - | - |
| BZ022 | Grade 3 | - | - | - | - | - | - | - | - |
| BZ023 | Grade 3 | - | - | - | - | - | - | - | - |
| BZ024 | Grade 1 | - | - | - | - | - | - | - | - |
| BZ025 | - | - | - | - | - | - | - | - | - |
| BZ026 | Grade 2 | - | - | - | - | - | - | - | - |

Supplementary Table 10. Adverse events (metabolism and nutrition disorders)

| Patient number | Hypercalcemia | Hyperglycemia | Hyperkalemia | Hypermagnesemia | Hyponatremia | Hypertriglyceridemia | Hyperuricemia | Hypoalbuminemia | Hypocalcemia | Hypoglycemia | Hypokalemia | Hypomagnesemia | Hyponatremia | Hypophosphatemia |
|----------------|---------------|---------------|--------------|-----------------|--------------|----------------------|---------------|-----------------|--------------|--------------|-------------|----------------|--------------|------------------|
| BZ001 | - | - | - | - | - | Grade 1 | - | - | - | - | Grade 1 | - | - | - |
| BZ002 | - | Grade 1 | - | - | - | - | Grade 1 | - | - | - | - | - | Grade 1 | - |
| BZ004 | - | - | - | - | - | - | Grade 1 | - | - | - | - | - | - | - |
| BZ005 | - | - | - | - | - | - | Grade 1 | - | - | - | - | - | - | - |
| BZ006 | - | Grade 1 | - | - | - | Grade 1 | Grade 1 | - | - | - | - | - | - | - |
| BZ007 | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| BZ008 | - | - | - | - | - | - | Grade 1 | - | - | - | - | - | - | - |
| BZ009 | - | Grade 1 | - | - | - | Grade 1 | - | - | - | - | - | - | - | - |
| BZ010 | - | Grade 1 | - | - | - | Grade 1 | - | Grade 1 | - | - | Grade 1 | - | - | - |
| BZ011 | - | Grade 1 | - | - | - | Grade 1 | Grade 1 | - | Grade 1 | - | - | - | - | - |
| BZ012 | - | Grade 1 | - | - | - | Grade 1 | Grade 1 | - | - | - | Grade 1 | - | - | - |
| BZ013 | - | - | - | - | - | Grade 1 | - | - | - | - | Grade 1 | - | - | - |
| BZ014 | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| BZ015 | - | - | - | - | - | Grade 1 | Grade 1 | - | - | - | - | - | - | - |
| BZ016 | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| BZ017 | - | Grade 1 | - | - | - | - | - | - | Grade 1 | - | - | - | - | - |
| BZ018 | - | - | - | - | - | - | - | - | - | - | Grade 1 | - | - | - |
| BZ019 | - | Grade 1 | - | - | - | - | - | - | - | - | - | - | - | - |
| BZ020 | - | Grade 1 | - | - | - | Grade 2 | - | - | - | - | - | - | - | - |
| BZ021 | - | Grade 1 | - | - | - | - | - | - | - | - | - | - | - | - |
| BZ022 | - | Grade 1 | - | - | - | Grade 1 | - | - | Grade 1 | - | - | - | - | - |
| BZ023 | - | Grade 1 | - | - | - | Grade 1 | - | - | - | - | - | - | - | - |
| BZ024 | - | Grade 1 | - | - | - | Grade 1 | - | - | - | - | - | - | - | - |
| BZ025 | - | - | - | - | - | - | Grade 1 | - | - | - | - | - | - | - |
| BZ026 | - | Grade 1 | - | - | - | - | - | - | - | - | - | - | - | - |

Supplementary Table 11. Revised criteria for response assessment

| Response and Site | PET-CT–Based Response | CT-Based Response |
|--------------------------------------|---|--|
| Complete Response | Complete metabolic response | Complete radiologic response (all of the following) |
| Lymph nodes and extralymphatic sites | Score 1, 2, or 3* with or without a residual mass on 5PS _‡ | Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi |
| | In Waldeyer's ring or in extranodal sites with high physiologic uptake or with activation within the spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than in the normal mediastinum and/or liver. In this circumstance, a complete metabolic response may be inferred if the uptake at the sites of initial involvement is no greater than the surrounding normal tissue, even if the tissue has high physiologic uptake. | No extralymphatic sites of disease |
| Nonmeasured lesion | Not applicable | Absent |
| Organ enlargement | Not applicable | Regress to normal |
| New lesions | None | None |
| Bone marrow | No evidence of FDG-avid disease in marrow | Normal by morphology; if indeterminate, IHC negative |
| Partial Response | Partial metabolic response | Partial remission (all of the following) |
| Lymph nodes and extralymphatic sites | Score 4 or 5 _‡ with reduced uptake compared with baseline and residual mass(es) of any size | $\geq 50\%$ decrease in SPD of up to 6 target measurable nodes and extranodal sites |
| | At the interim, these findings suggest responding disease | When a lesion is too small to measure on CT, assign 5 mm \times 5 mm as the default value |
| | At the end of treatment, these findings indicate residual disease | When no longer visible, 0 \times 0 mm |
| | | For a node > 5 mm \times 5 mm, but smaller than normal, use actual measurement for calculation |
| Nonmeasured lesions | Not applicable | Absent/normal, regressed, but no increase |
| Organ enlargement | Not applicable | Spleen must have regressed by $> 50\%$ in length beyond normal |
| New lesions | None | None |
| Bone marrow | Residual uptake higher than uptake in normal marrow but reduced compared with | Not applicable |

| | | |
|---|---|--|
| | baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan. | |
| No response or stable disease | No metabolic response | Stable disease |
| Target nodes/nodal masses, extranodal lesions | Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment | < 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met |
| Nonmeasured lesions | Not applicable | No increase consistent with progression |
| Organ enlargement | Not applicable | No increase consistent with progression |
| New lesions | None | None |
| Bone marrow | No change from baseline | Not applicable |
| Progressive disease | Progressive metabolic disease | Progressive disease requires at least 1 of the following |
| Individual target nodes/nodal masses | Score 4 or 5 with an increase in intensity of uptake from baseline and/or | PPD progression |
| Extranodal lesions | New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment | An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by \geq 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions \leq 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly |
| Nonmeasured lesions | None | New or clear progression of preexisting nonmeasured lesions |
| New lesions | New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered | Regrowth of previously resolved lesions A new node > 1.5 cm on any axis A new extranodal site > 1.0 cm on any axis; if < 1.0 cm on any axis, its presence must be unequivocal and must be attributable to lymphoma |

| | | |
|-------------|--------------------------------|---|
| | | Assessable disease of any size unequivocally attributable to lymphoma |
| Bone marrow | New or recurrent FDG-avid foci | New or recurrent involvement |

Revised criteria for response assessment (Cheson *et al.*, J Clin Oncol. 32: 3059–3067, 2014).

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if it occurs at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as an inadequate response (to avoid undertreatment). Measured dominant lesions: up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Nonnodal lesions include those in solid organs (e.g., liver, spleen, kidneys, and lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake \leq mediastinum; 3, uptake $>$ mediastinum but \leq liver; 4, uptake moderately $>$ liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Duration of response was defined as the time from the first documented response (CR or PR) to the date of relapse, initiation of new treatment, or death due to underlying disease. If a subject did not relapse or die at the time of data cutoff, the duration of the response was censored on the last available visit date.

Supplementary Table 12. Cytokine release syndrome grading form

| CRS grade | Severity | Symptoms and toxicities |
|------------------|------------------|--|
| Grade 1 | Mild | Symptoms are not life threatening, and require symptomatic treatment only, e.g., fever, cough, nausea, fatigue, headache, myalgias, and malaise. |
| Grade 2 | Moderate | Symptoms require and respond to moderate intervention. Oxygen requirement < 40% or Hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity |
| Grade 3 | Severe | Symptoms require and respond to aggressive intervention. Oxygen requirement > 40% or Hypotension requires high dose or multiple vasopressors or Severe hypotension and fever require tocilizumab, or tocilizumab combined with corticosteroids, or Grade 3 organ toxicity or grade 4 transaminitis |
| Grade 4 | Life-threatening | Life-threatening symptoms. Requires ventilator support or Grade 4 organ toxicity (excluding transaminitis) Requires tocilizumab, and/or corticosteroids |
| Grade 5 | Death | Death |

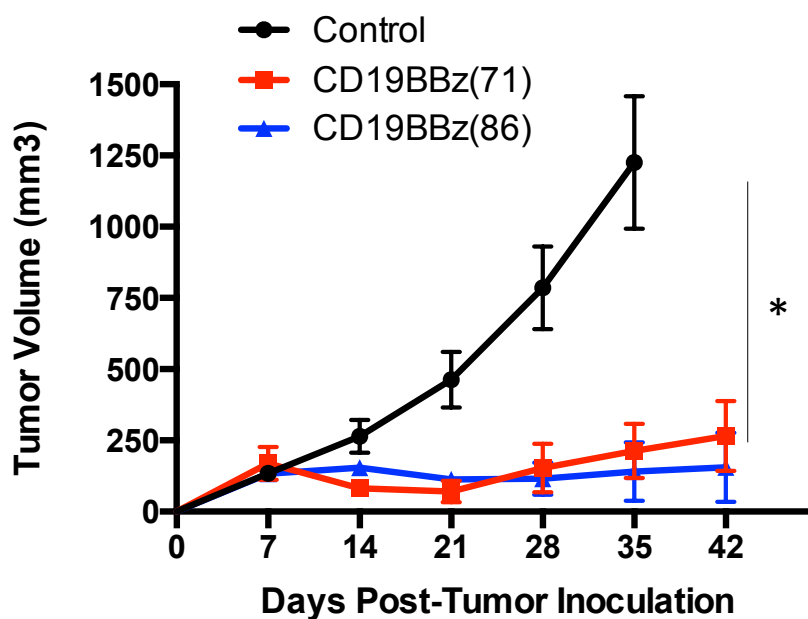
Supplemental Table 13. List of antibodies used in flow cytometry of human specimens

| Antibody name | Clone | Catalog No. | Vendor |
|--|--------------|--------------------|-------------------|
| Anti-EGFR | C225 | Ab00279-10.0 | Absolute antibody |
| FITC anti-human CD3 | UCHT1 | 300406 | BioLegend |
| PERCP anti-human CD4 | RPA-T4 | 300528 | BioLegend |
| PE/Cy7 anti-human CD8a antibody | RPA-T8 | 301012 | BioLegend |
| APC anti-human CD279(PD-1) | EH12.2H7 | 329908 | BioLegend |
| APC Mouse IgG2a,K isotype Ctrl(Fc) | MOPC-21 | 400120 | BioLegend |
| Brilliant Violet 421 anti-human CD45RA | HI100 | 304130 | BioLegend |
| Brilliant Violet 510 anti-human CD45RO | UCHL1 | 304246 | BioLegend |
| APC anti-human CD197(CCR7) | G043H7 | 353214 | BioLegend |
| PE anti-human CD19 | HIB19 | 302208 | BioLegend |

| | | | |
|--|--------|--------|-----------|
| APC anti-human CD20 | 2H7 | 302310 | BioLegend |
| PE/Cy7 anti-human CD27 antibody | M-T271 | 356411 | BioLegend |
| Brilliant Violet 421 anti-human IgD antibody | IA6-2 | 348225 | BioLegend |
| PE anti-human IgG Fc | HP6017 | 409304 | BioLegend |
| HumanTrustain Fcx | | 422302 | BioLegend |

Supplementary Figure 1. Comparable antitumor activity of CD19-BBz(86) variant CAR-T cells and CD19-BBz(71) prototype CAR-T cells *in vivo*.

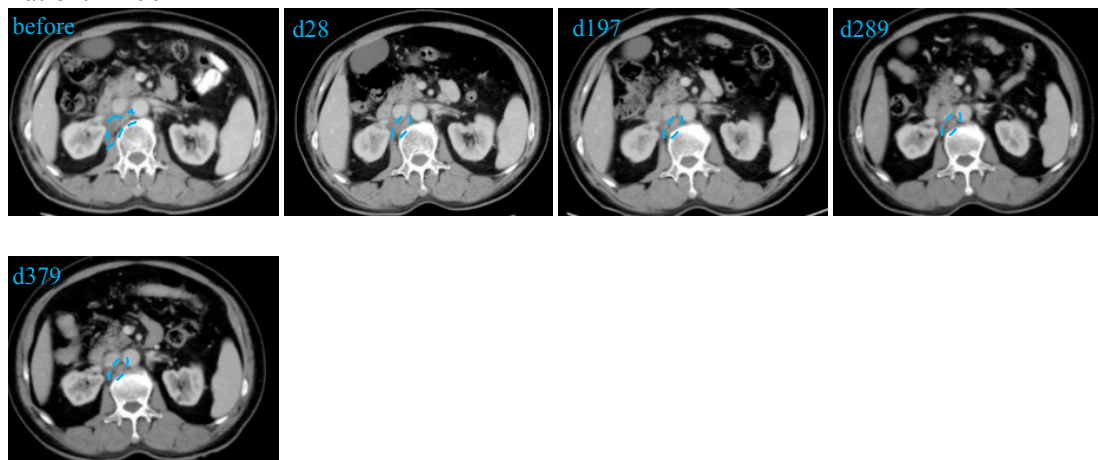
Groups of immunocompromised NSG mice (NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ) (Jackson Laboratory) (n=10) were subcutaneously injected with 2×10^6 CD19⁺ NALM6 tumor cells. The tumor cells were suspended in a solution of 50% PBS and 50% Matrigel (Corning). 7 days later, mice were administered intravenously with 1×10^7 CD19-BBz(86) variant CAR-T cells, CD19-BBz(71) prototype CAR-T cells or control vector-transduced human T cells. Tumors were measured with calipers every 3 days. Tumor volume is calculated as $V=W^2 \times L$. When the longest length reached 12 mm, mice were euthanized. The graph shows the mean tumor size \pm SEM for each time point from one of two independent experiments. * $P < 0.01$, CD19-BBz(86) variant or CD19-BBz(71) vs. control T cells.



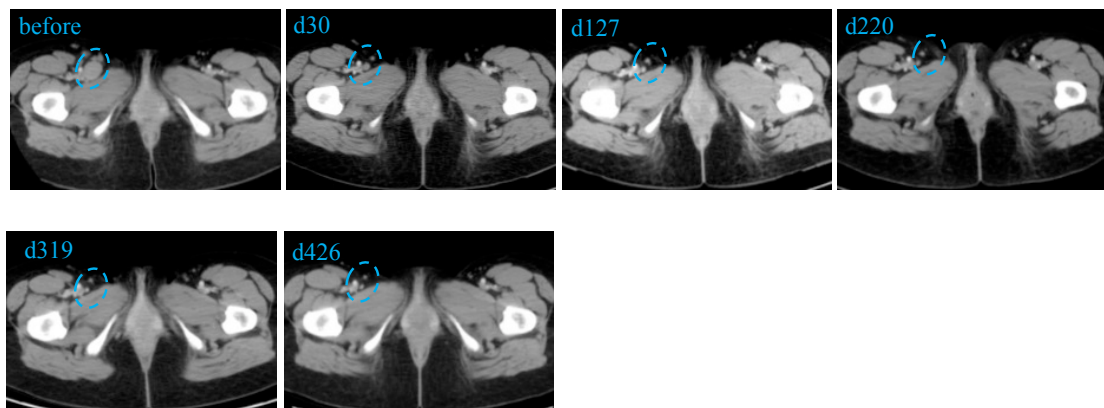
Supplementary Figure 2. Graphs of PET/CT or CT scan before and after CD19-BBz(86) CAR-T cell therapy

PET/CT or CT scans were performed before and after CD19-BBz(86) CAR-T cell therapy. The time point was labelled in the top-left corner of each graph. For patients with multiple lesions, graphs of each lesion were grouped into separated panels to show tumor volume changes over time after CD19-BBz(86) CAR-T cell therapy. The blue arrows or circles indicate sites of lymphoma.

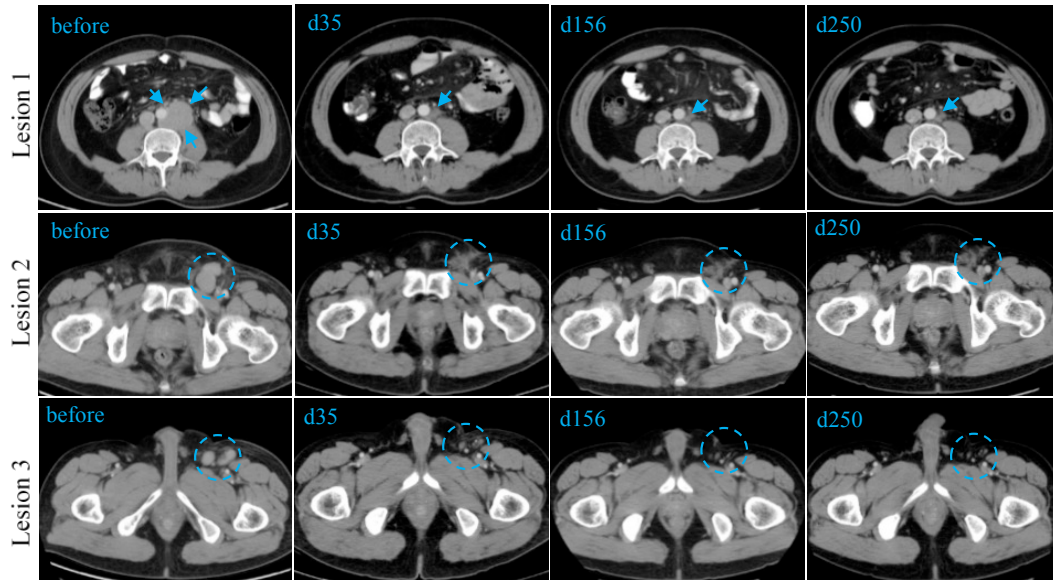
Patient BZ001-PR



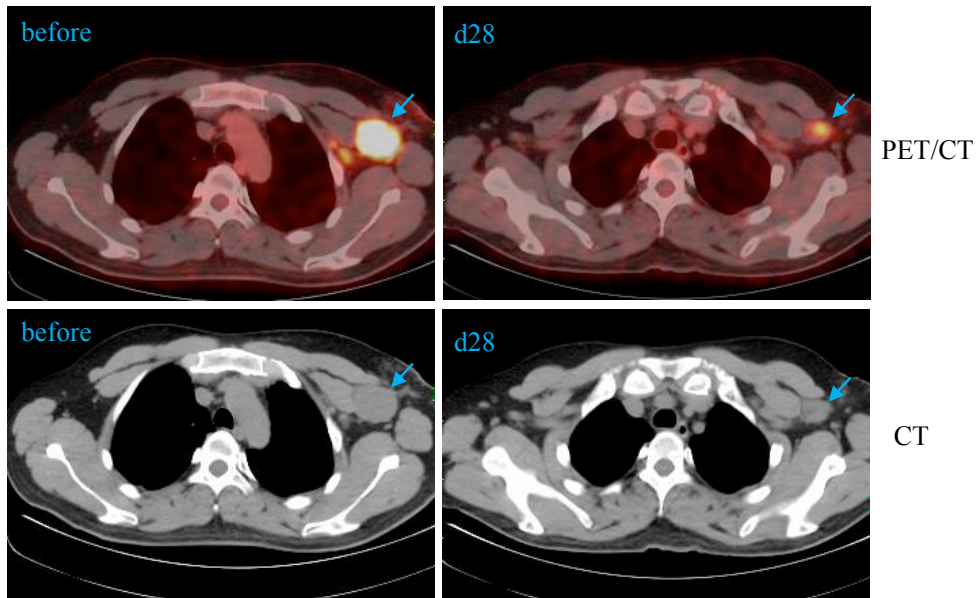
Patient BZ004-PR



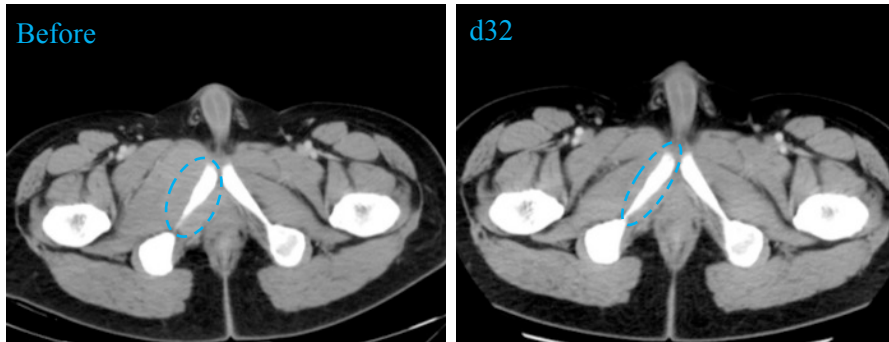
Patient BZ005-CR



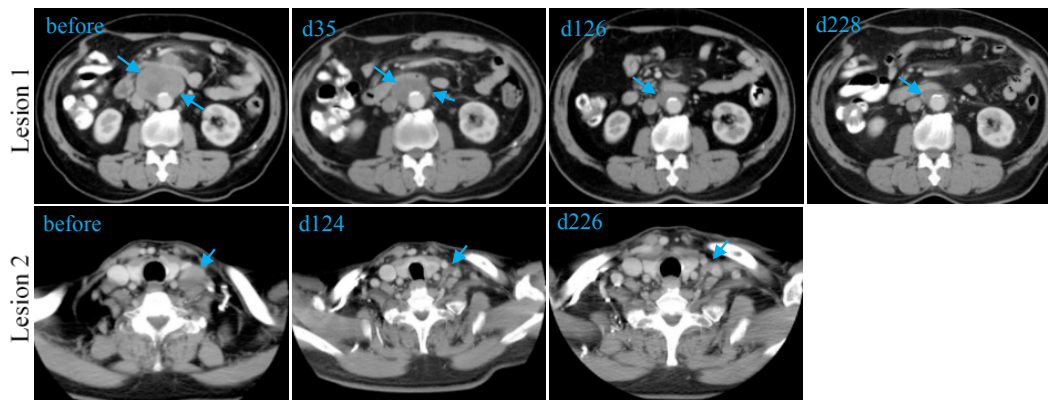
Patient BZ008-PR



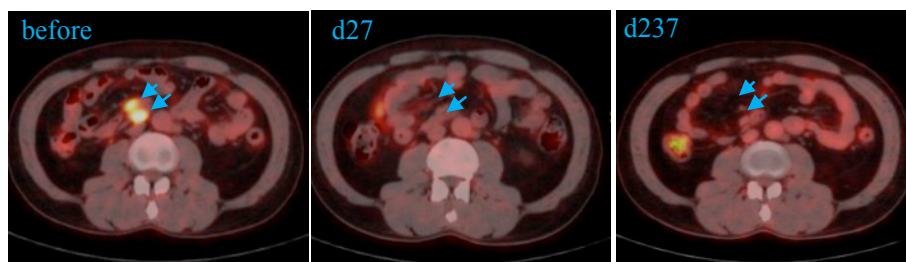
Patient BZ009-PR



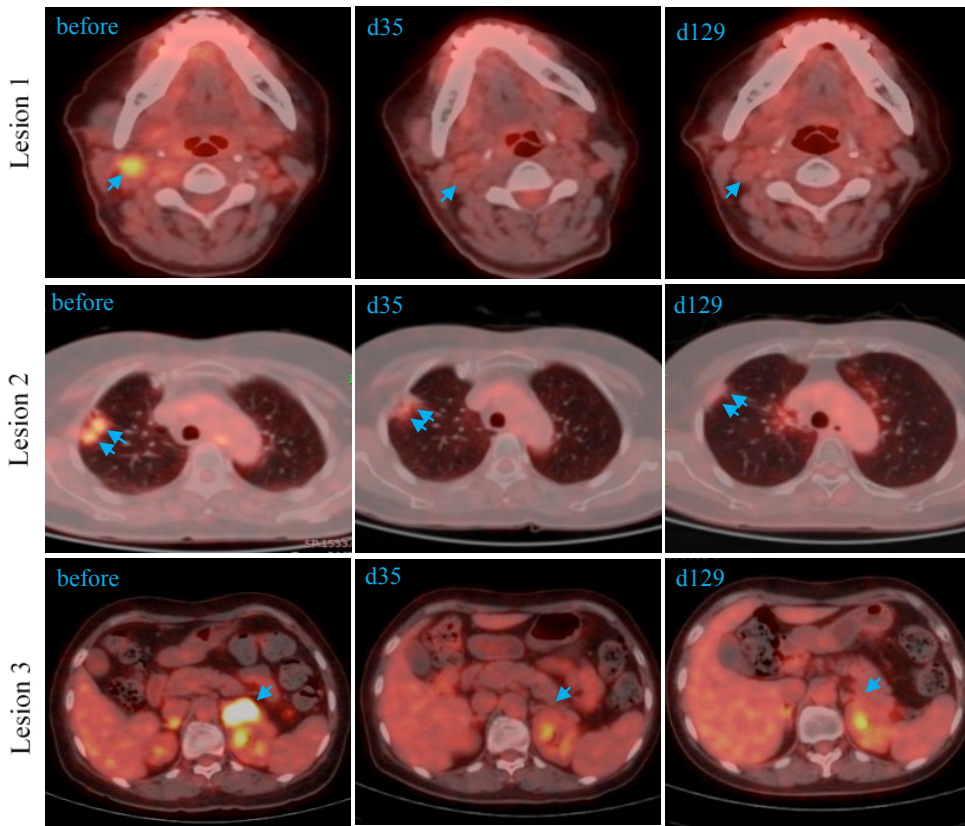
Patient BZ014-PR



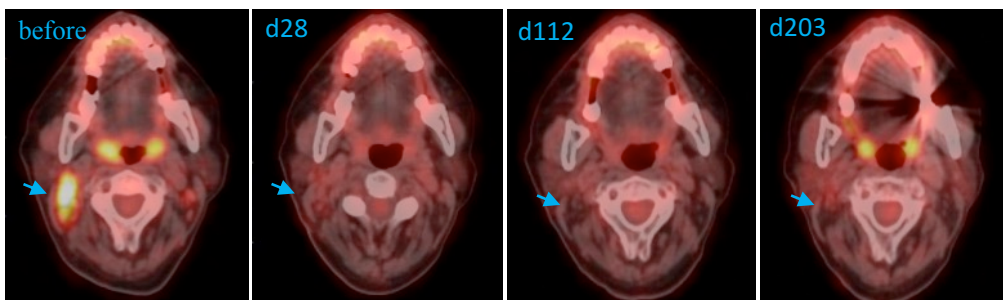
Patient BZ015-CR



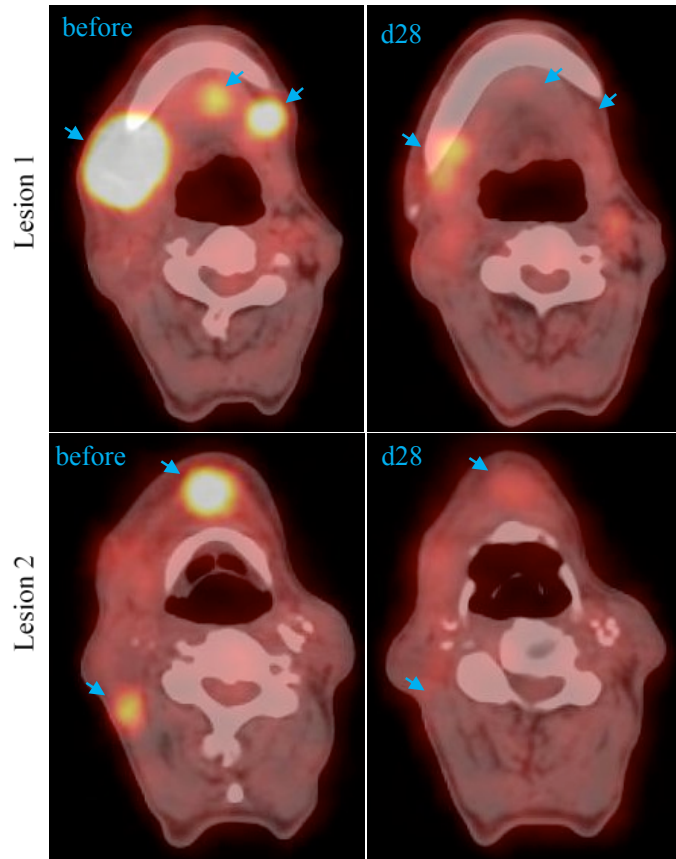
Patient BZ020-CR



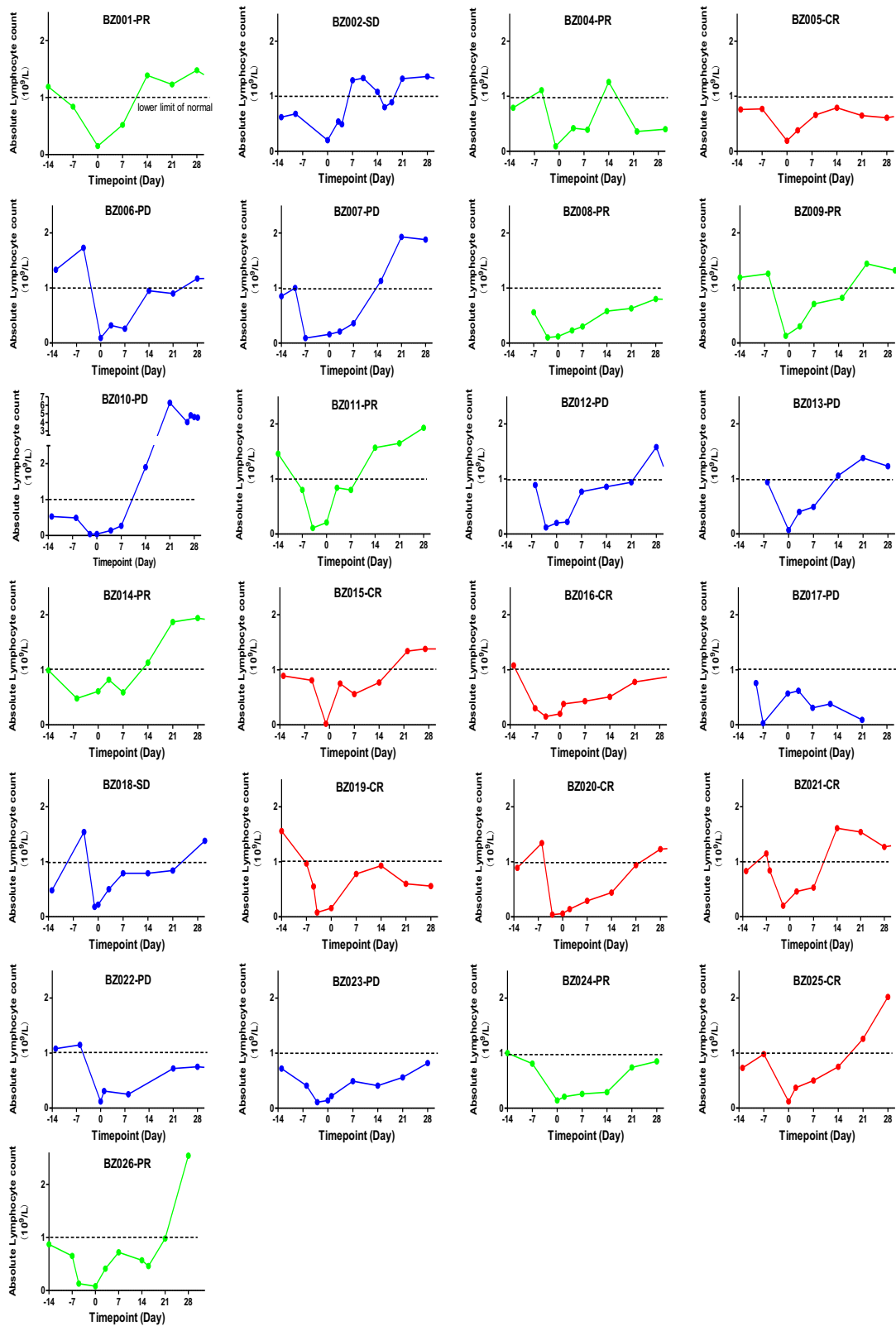
Patient BZ021-CR



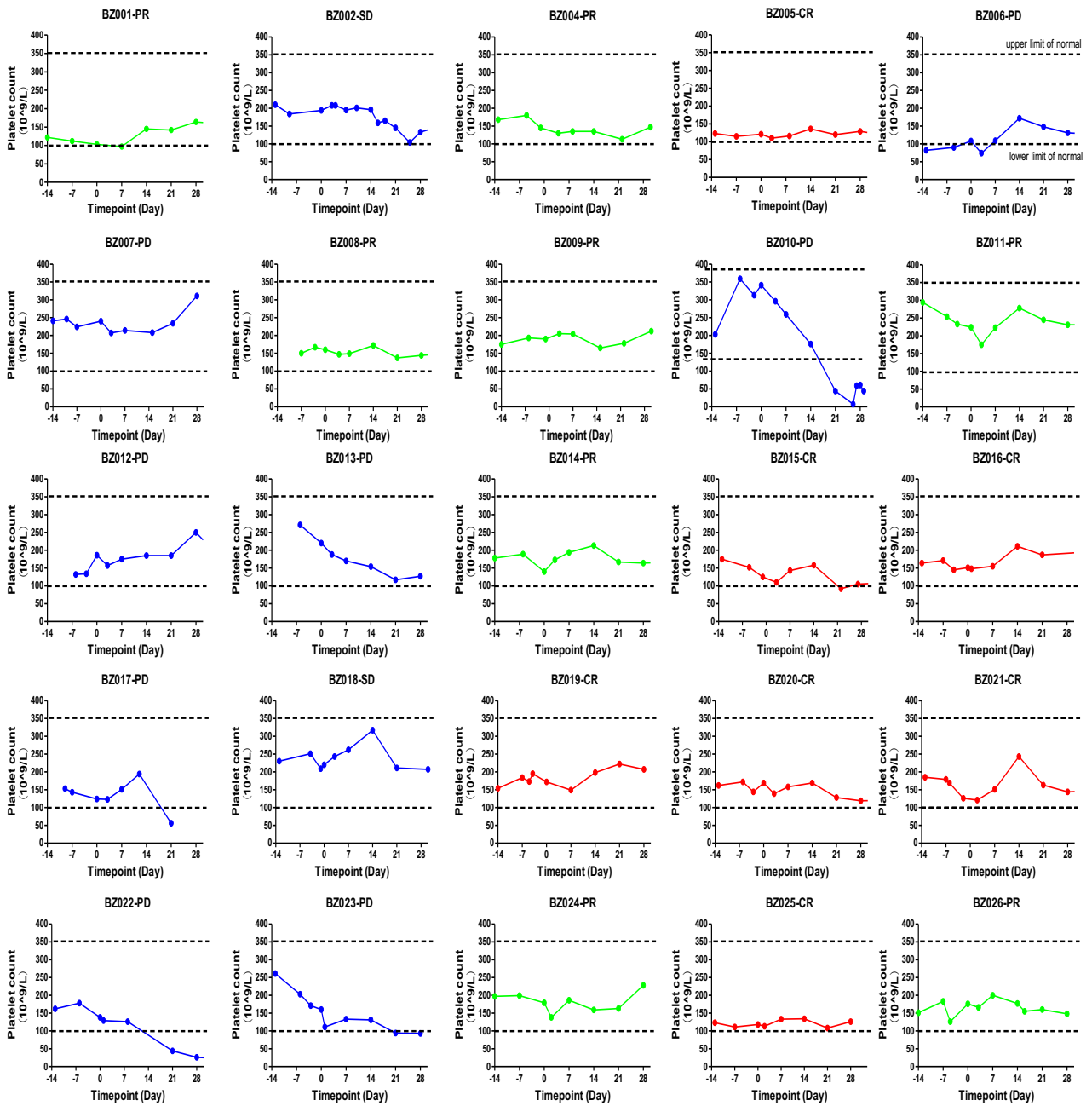
Patient BZ026-PR



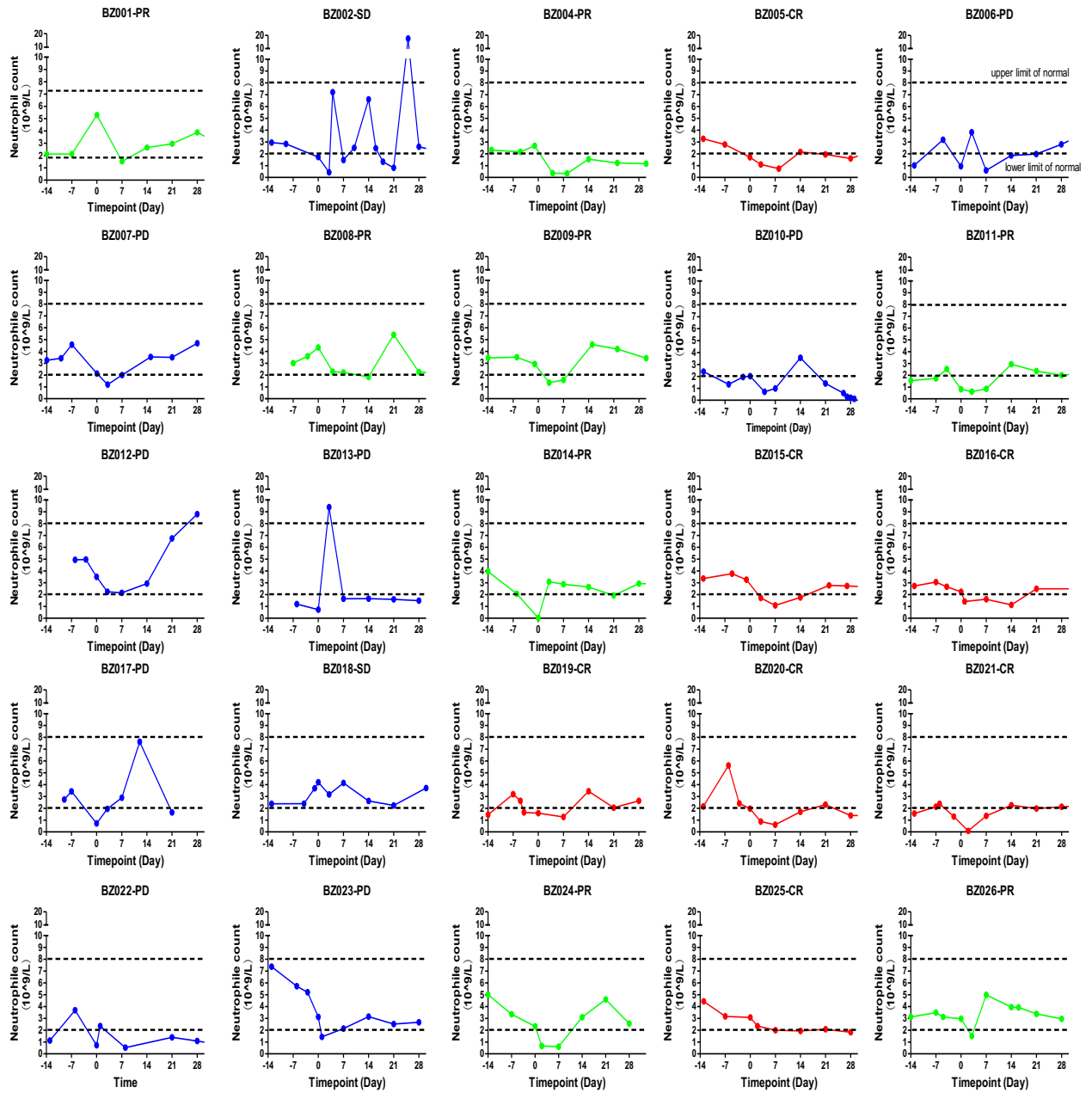
Supplementary Figure 3. Changes of blood absolute lymphocyte count during CD19-BBz(86) CAR-T cell therapy



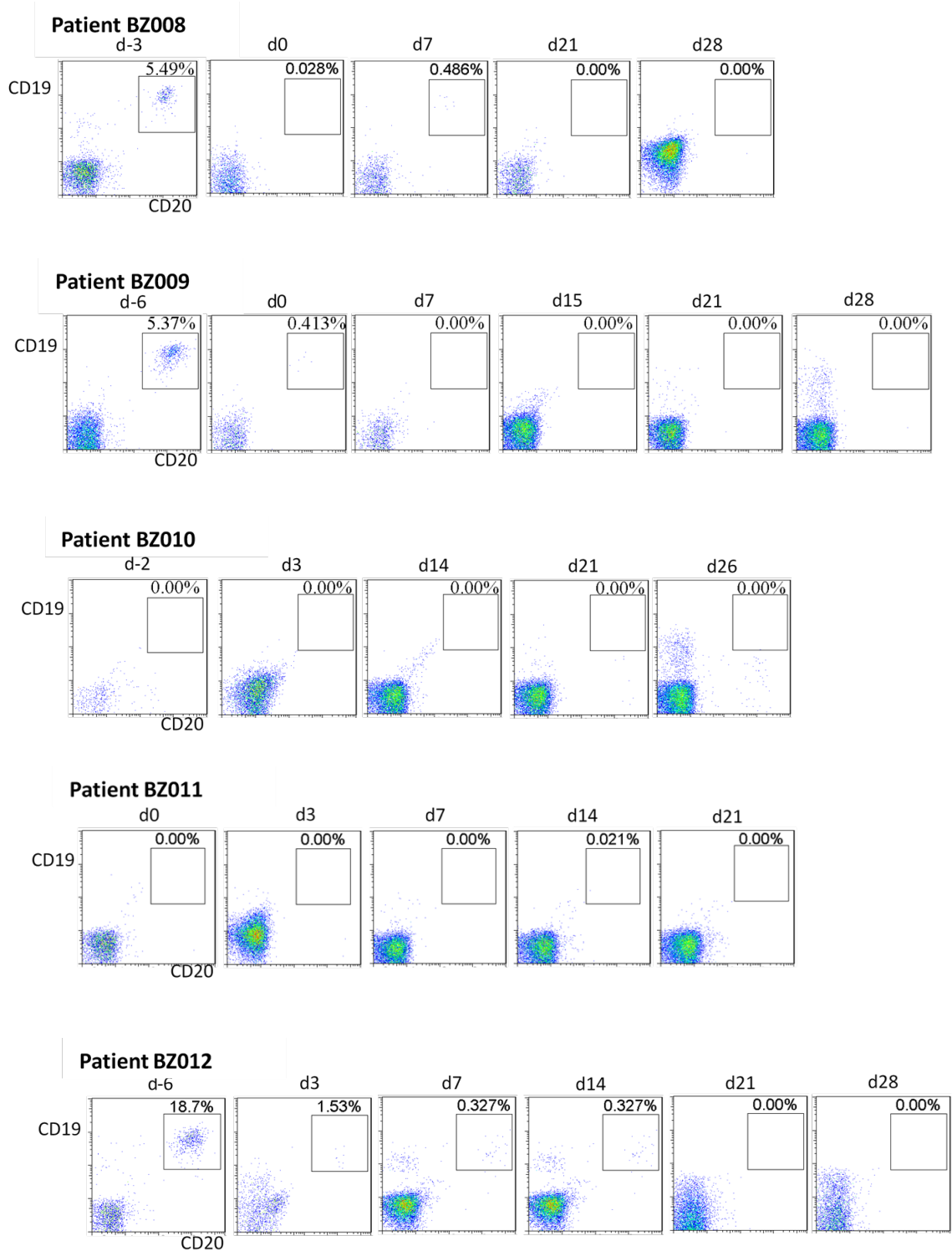
Supplementary Figure 4. Changes of platelet levels during CD19-BBz(86) CAR-T cell therapy

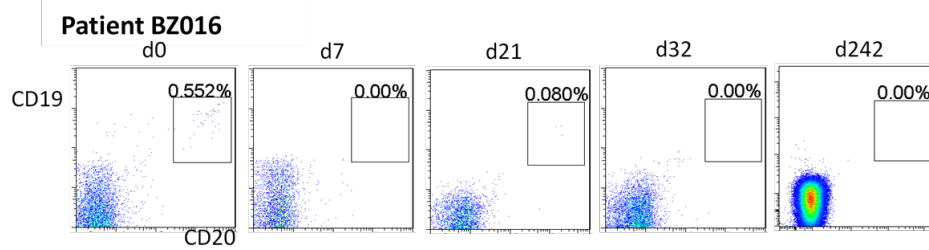
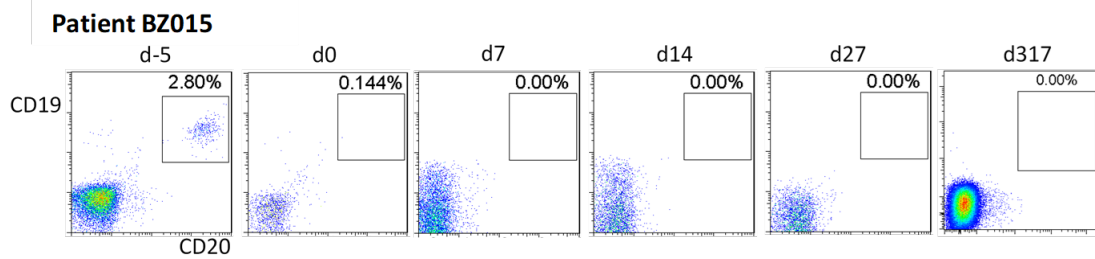
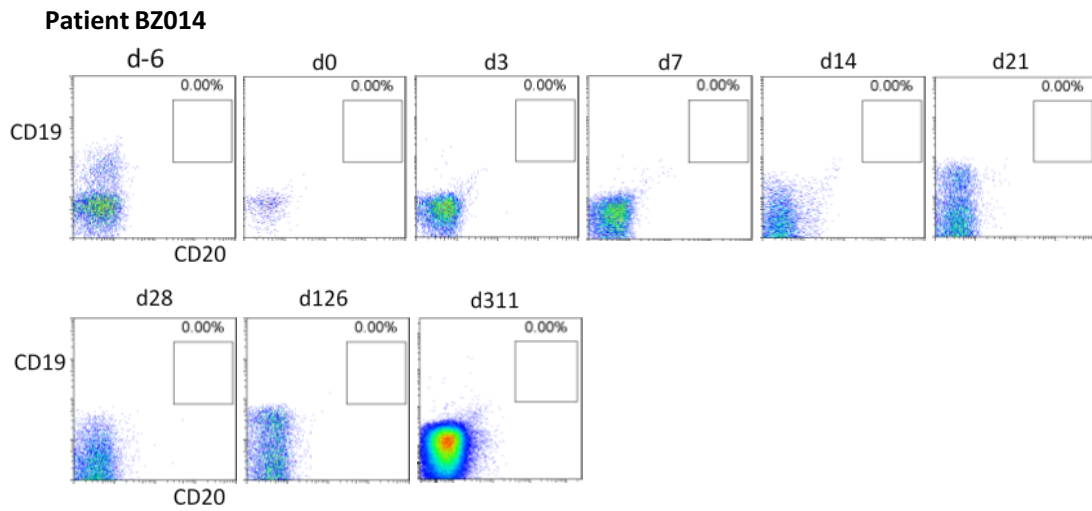
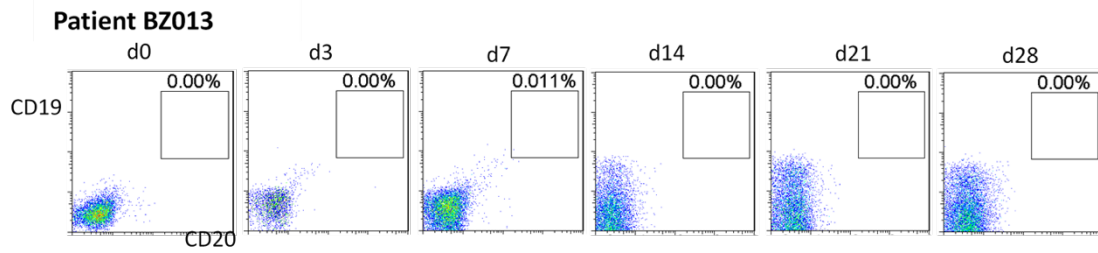


Supplementary Figure 5. Changes of neutrophil cell count during CD19-BBz(86) CAR-T cell therapy

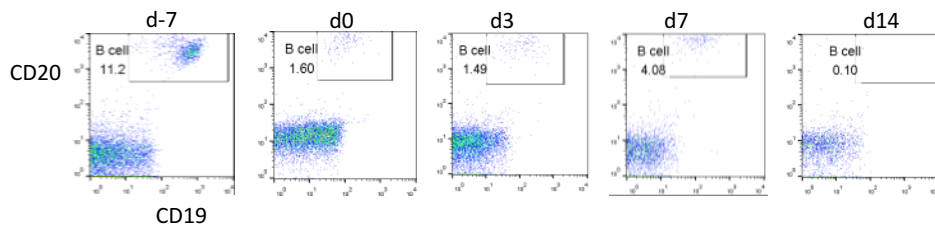


Supplementary Figure 6. Changes of blood CD19+ B-cells after CD19-BBz(86) CAR-T cell therapy

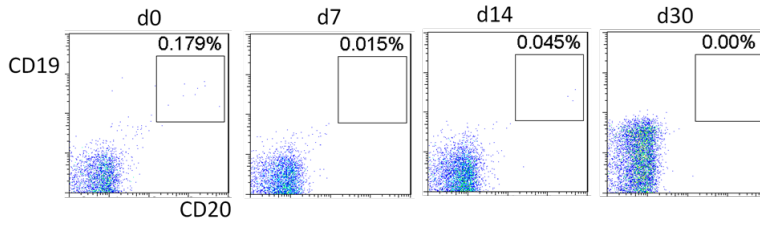




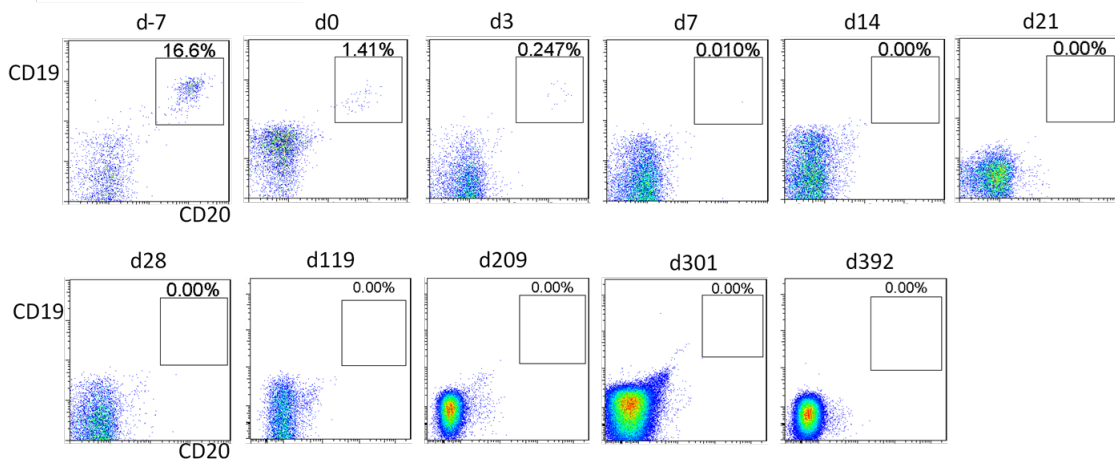
Patient BZ017



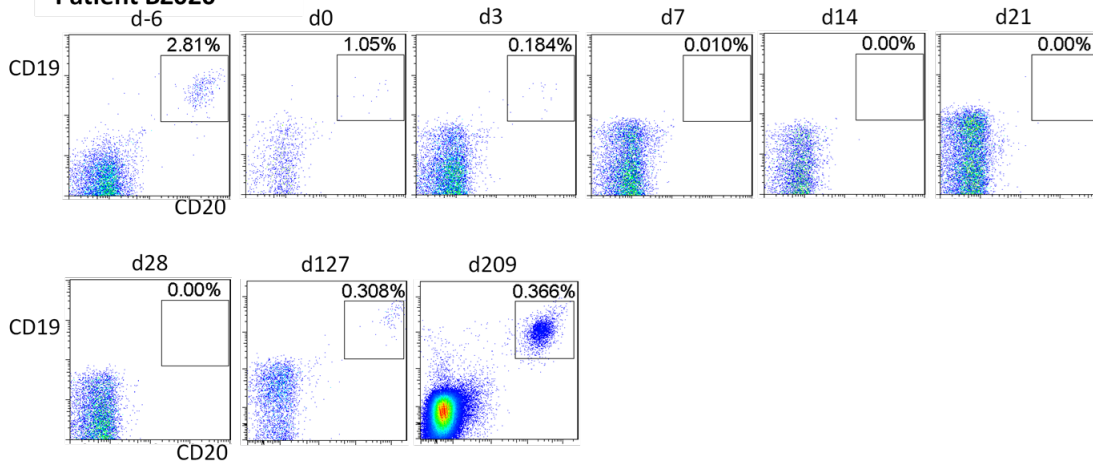
Patient BZ018

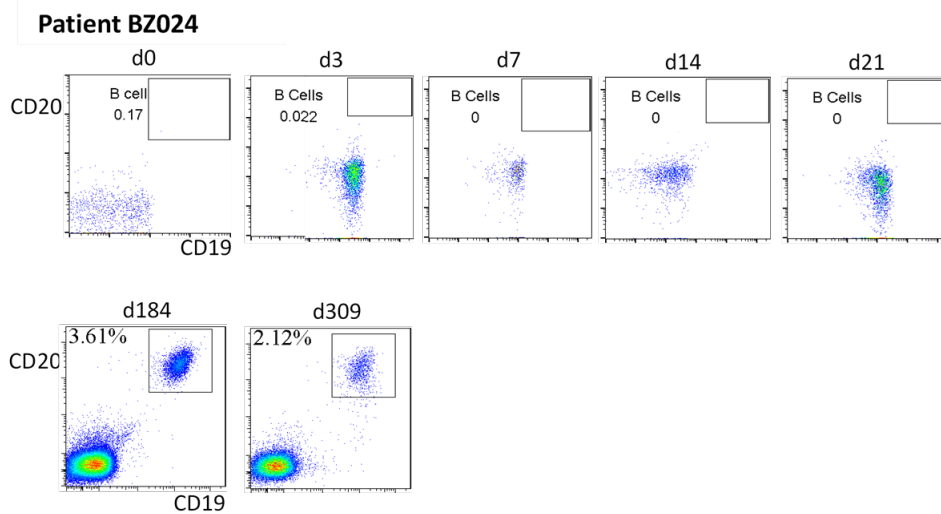
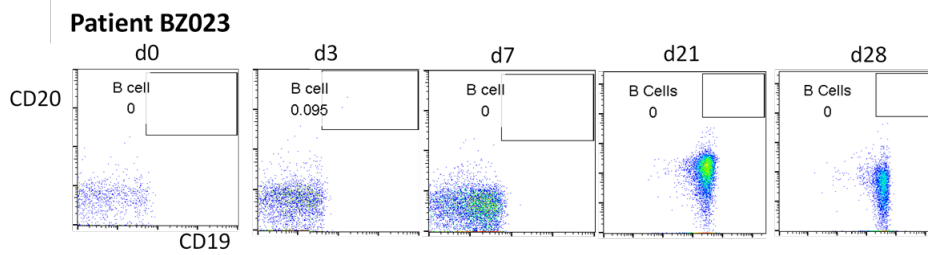
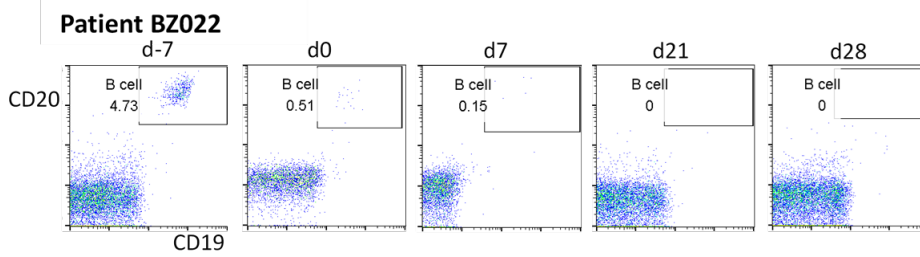
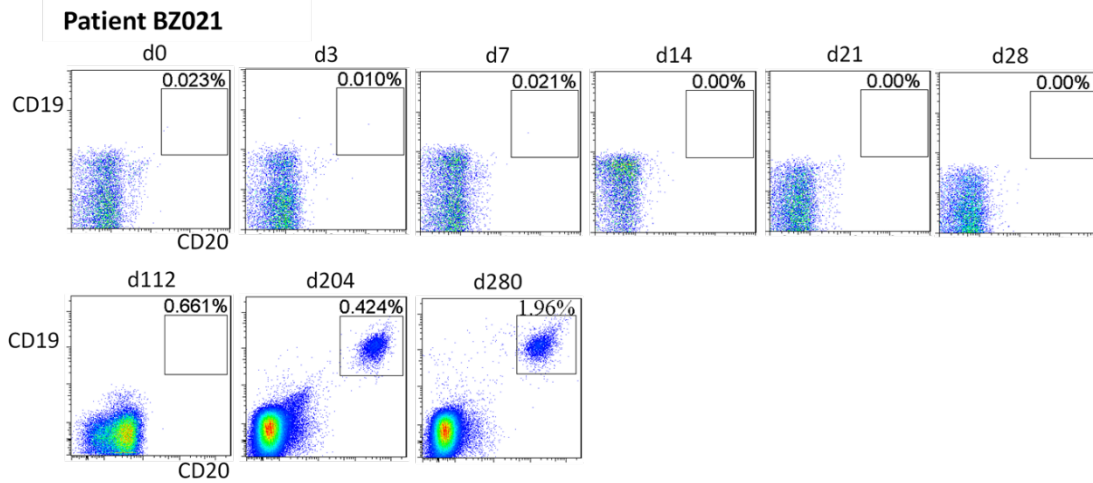


Patient BZ019

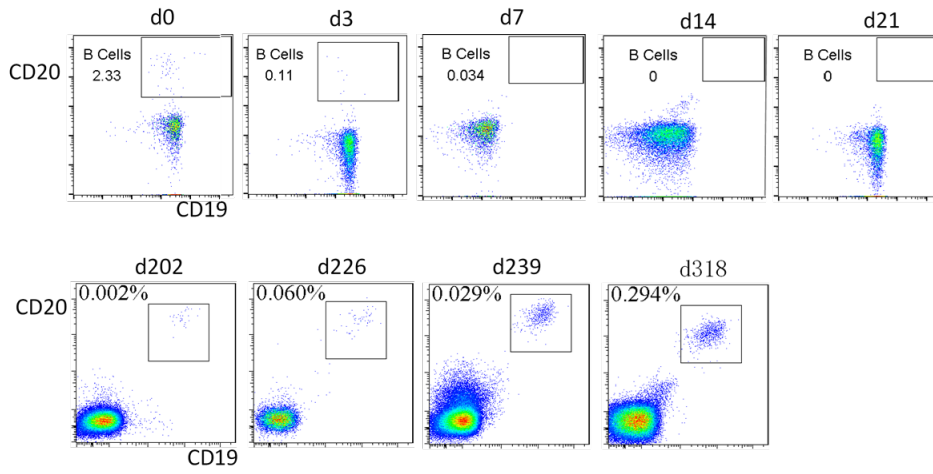


Patient BZ020

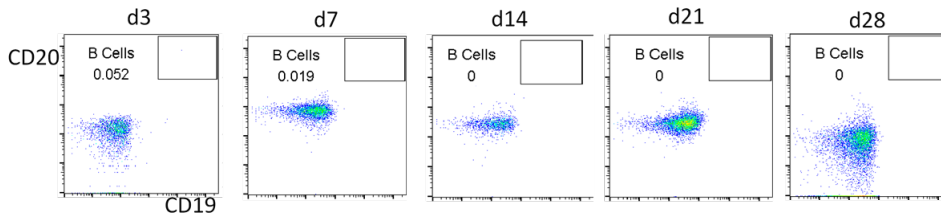




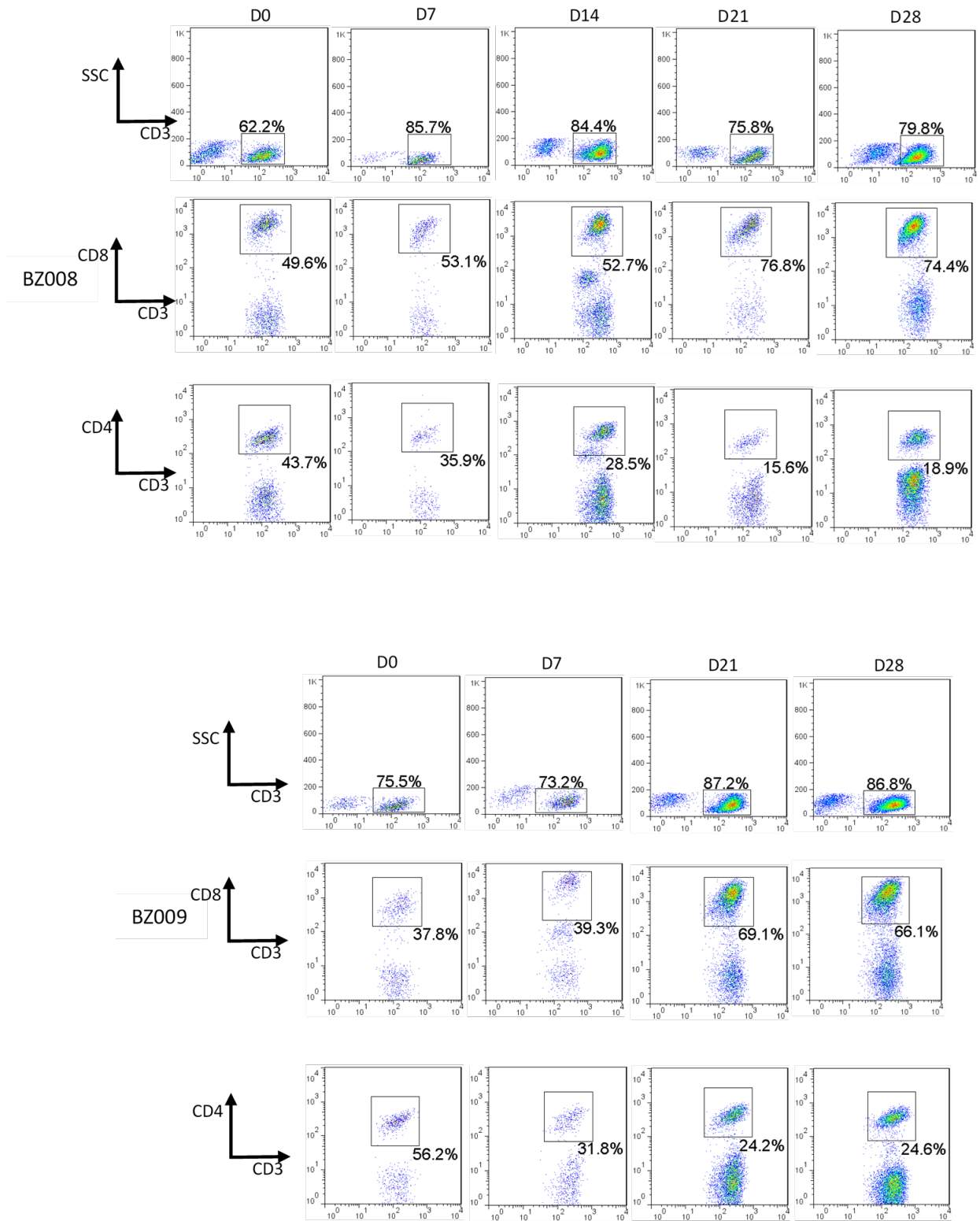
Patient BZ025

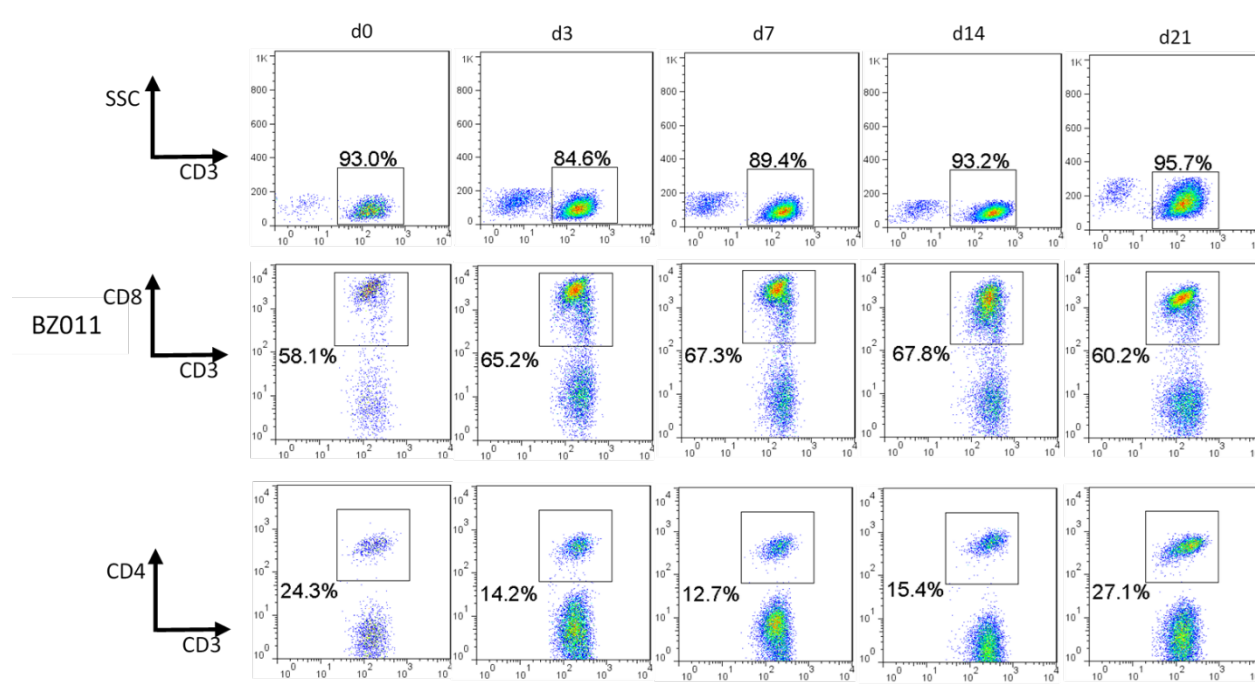
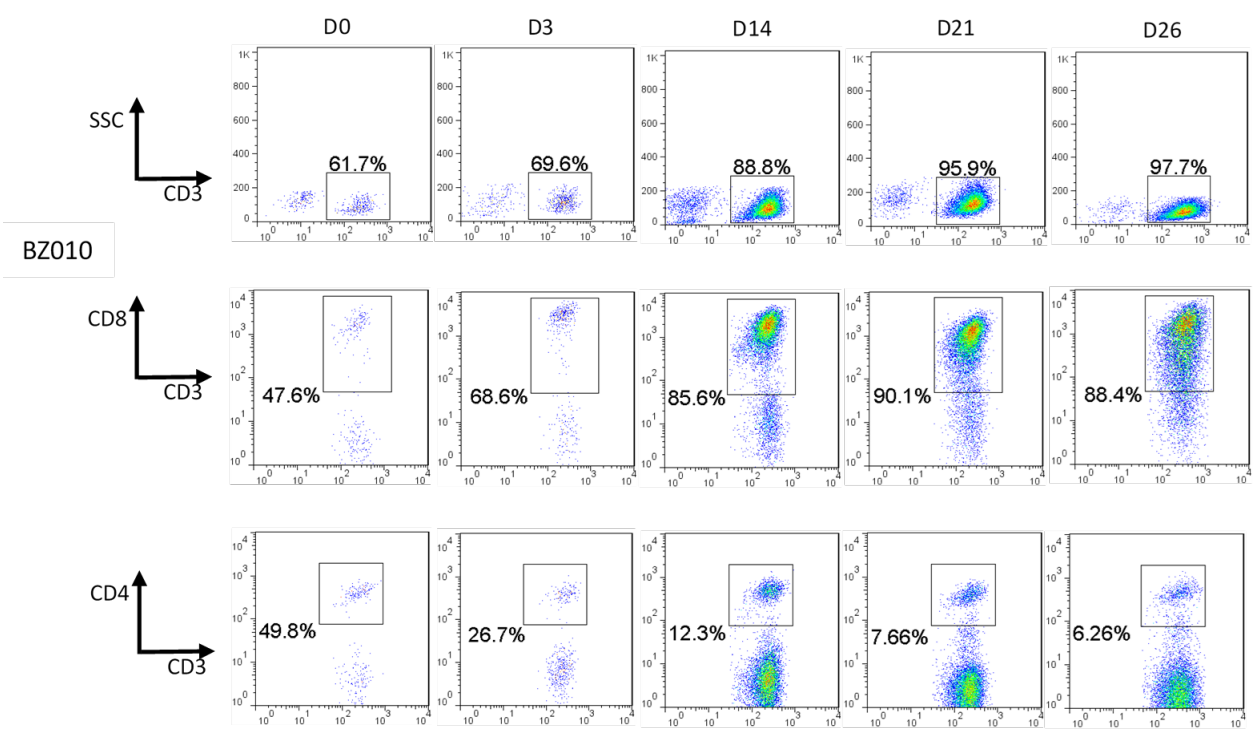


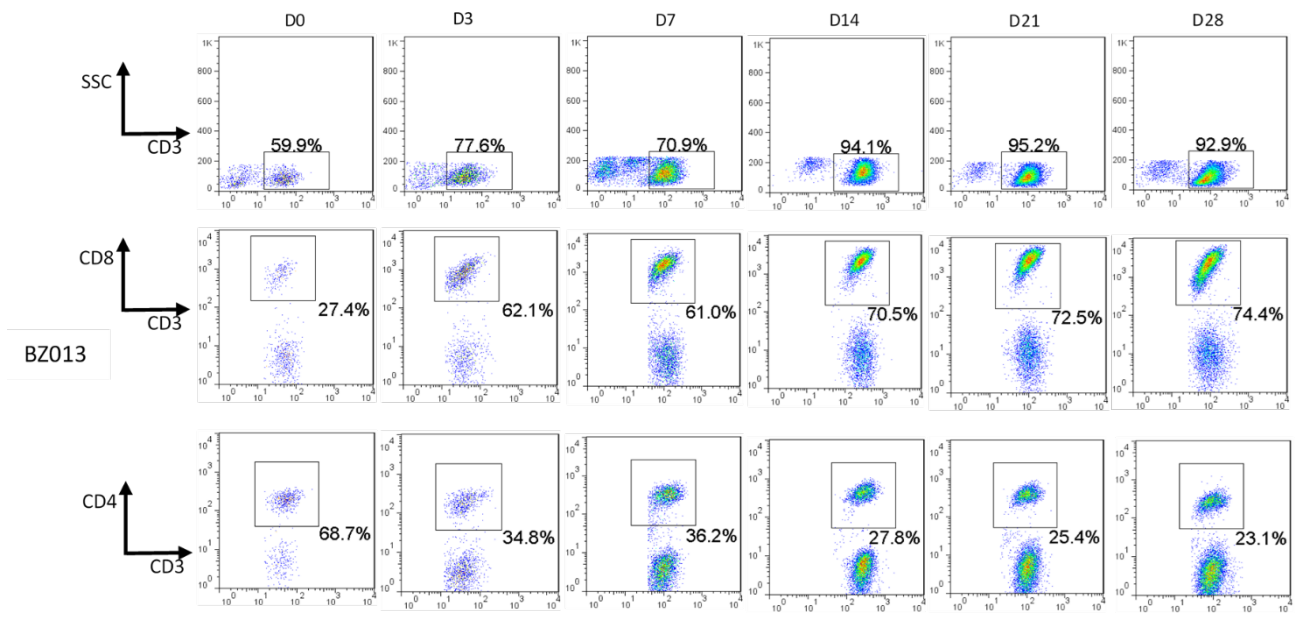
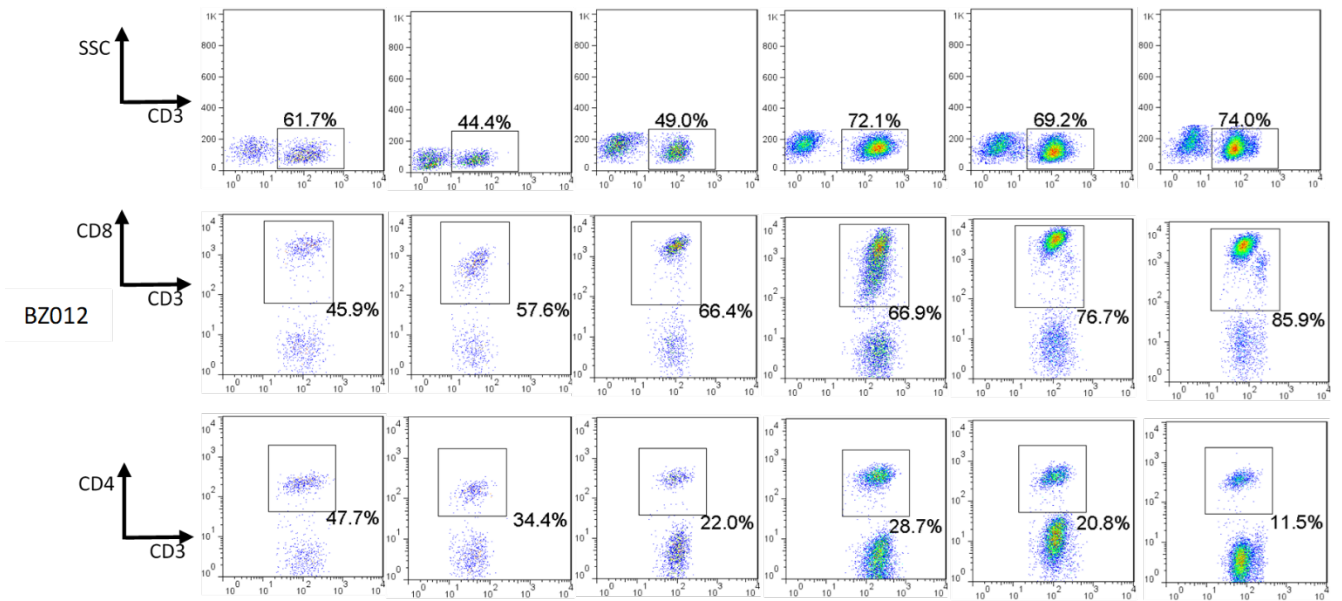
Patient BZ026

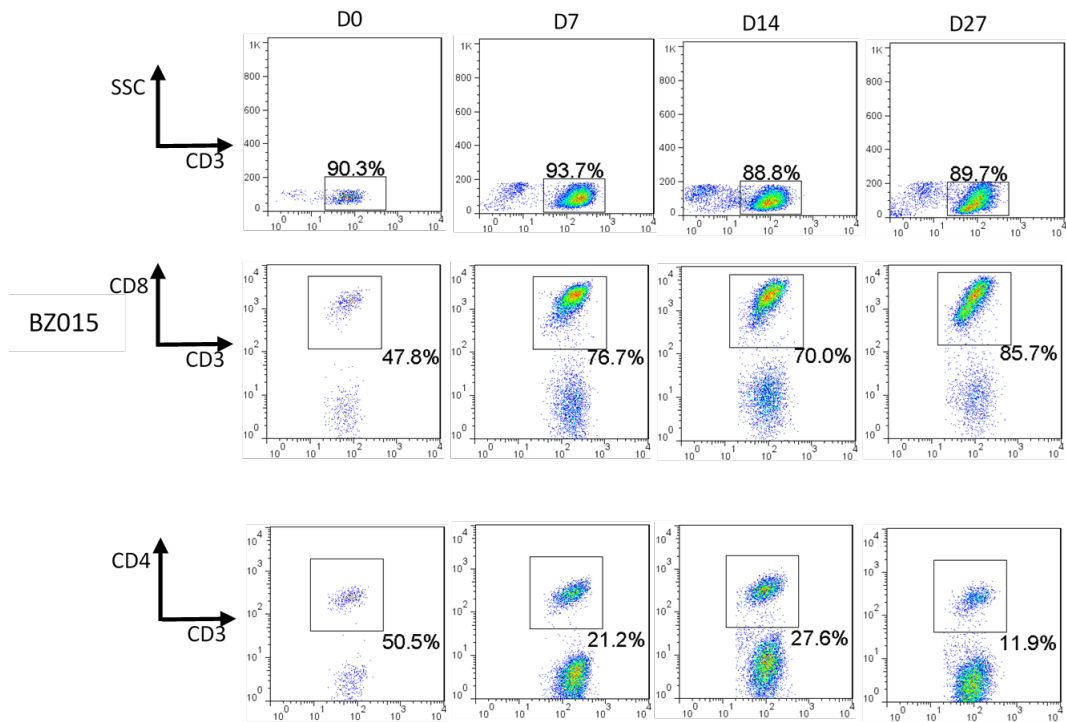
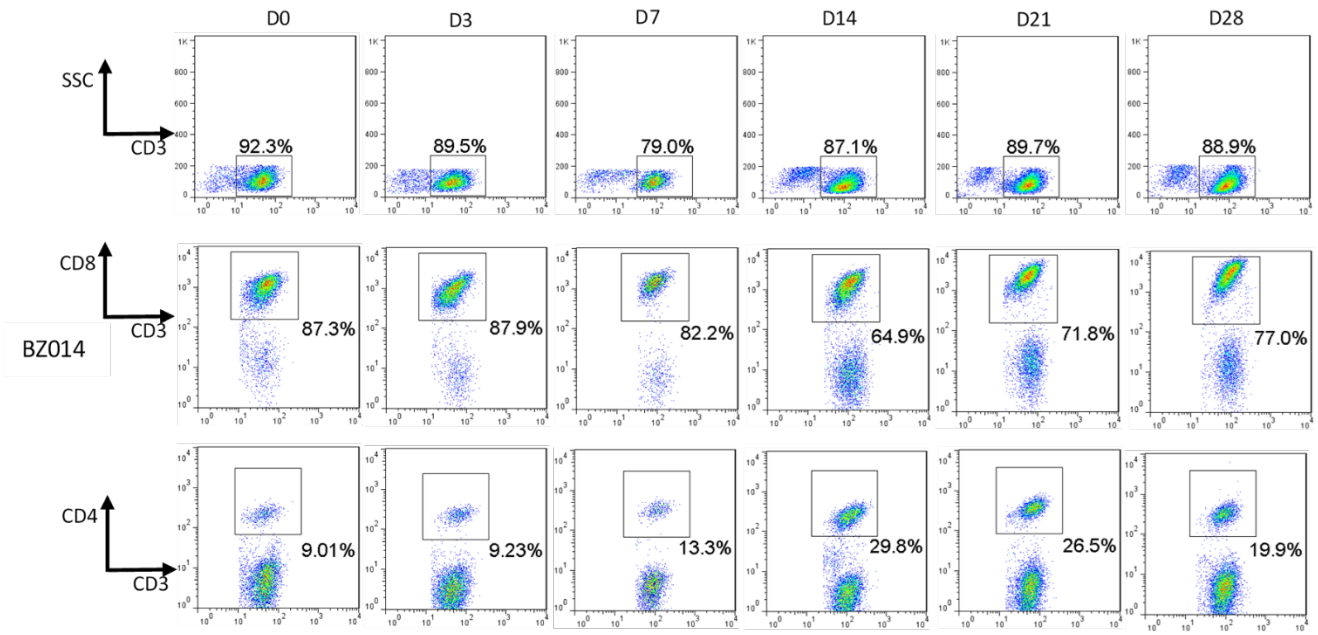


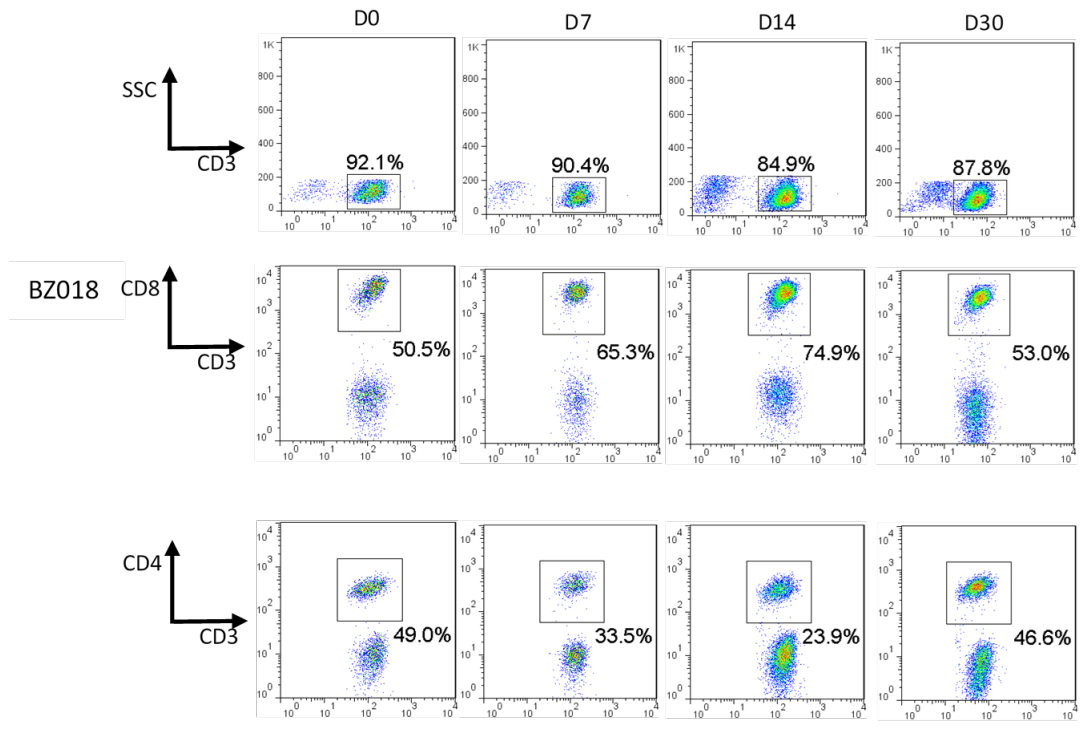
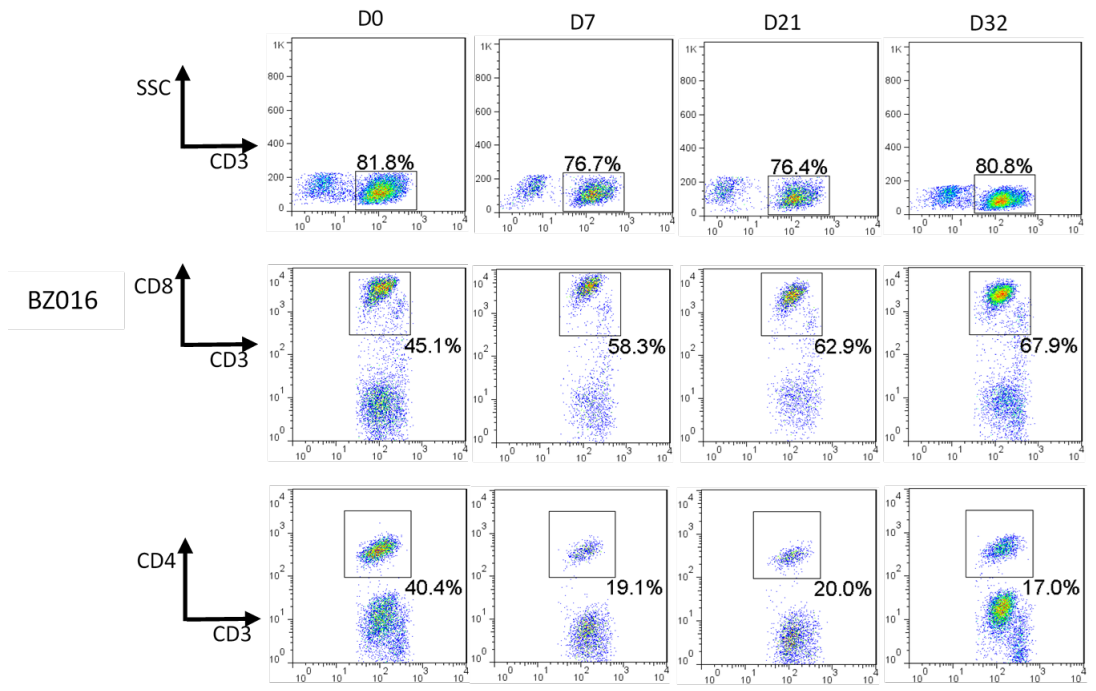
Supplementary Figure 7. Changes of peripheral blood T cells before and after CD19-BBz(86) CAR-T cell infusion (D: day).

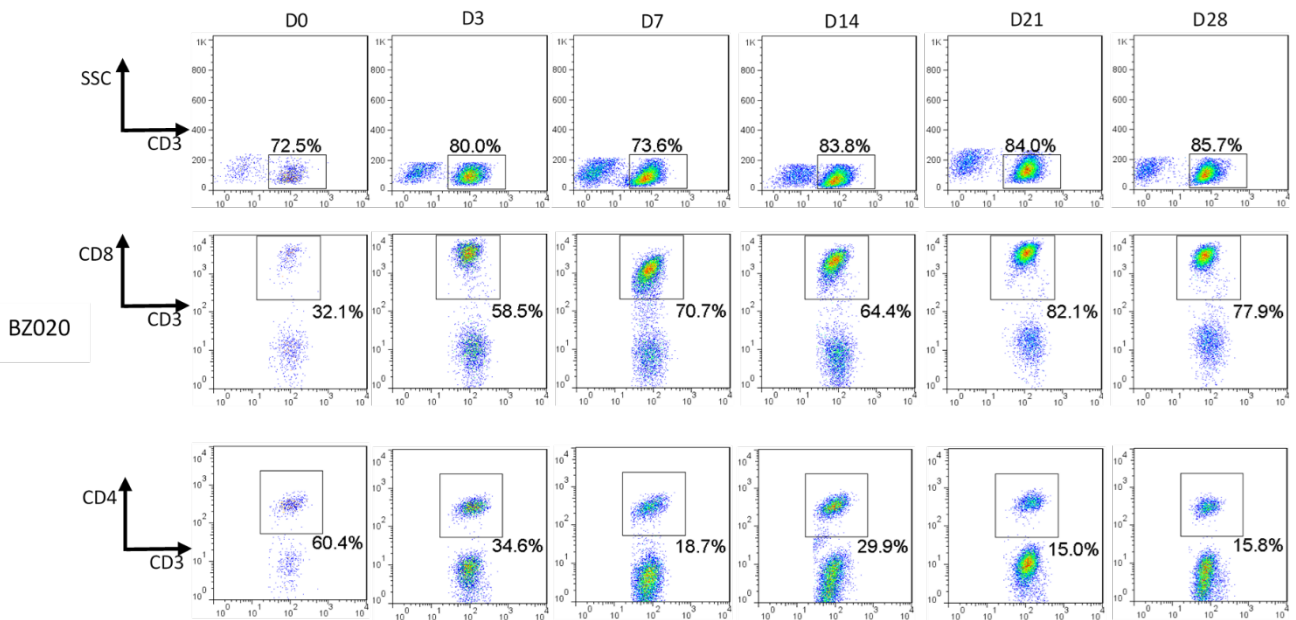
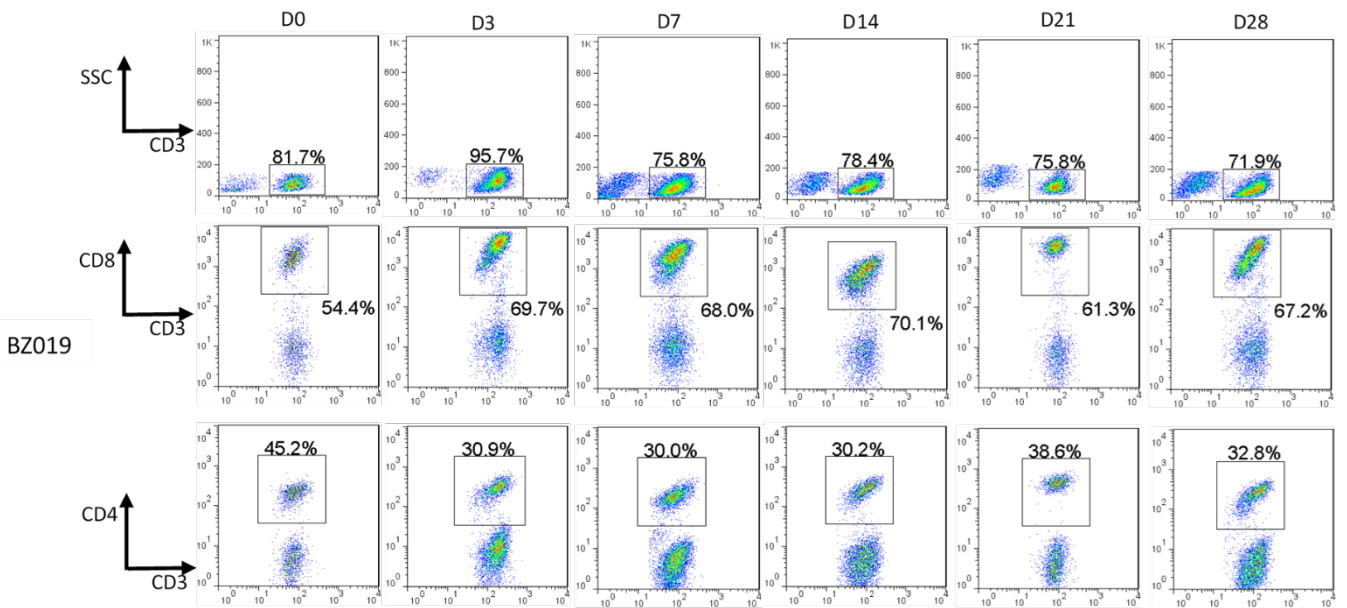


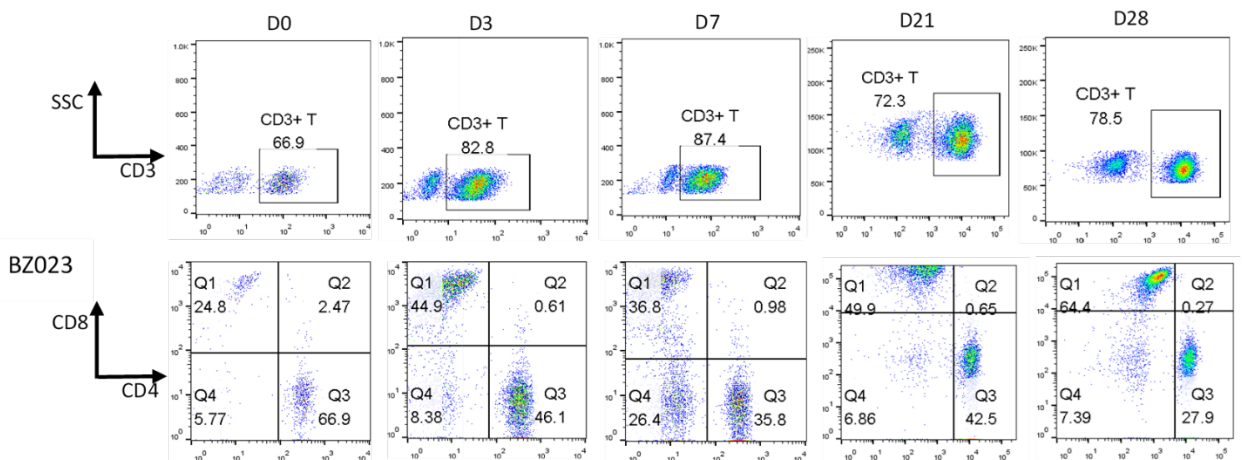
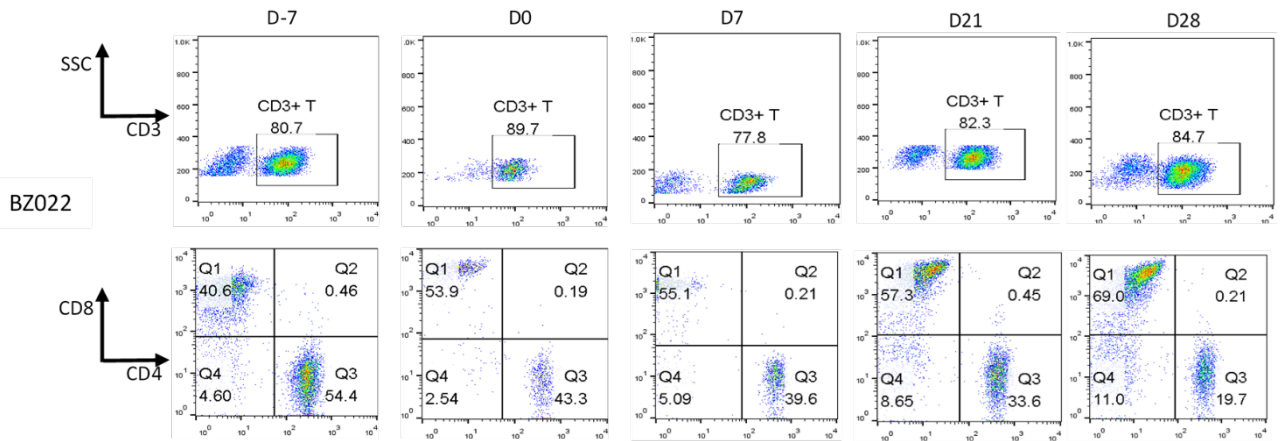
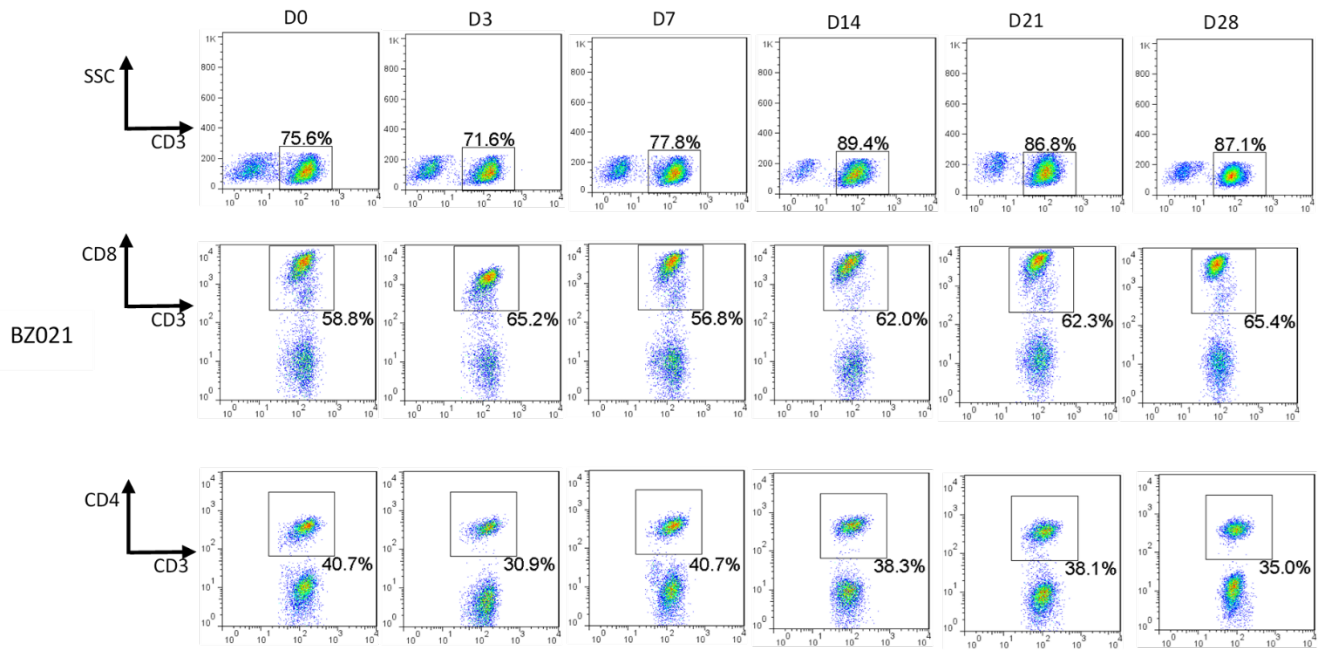


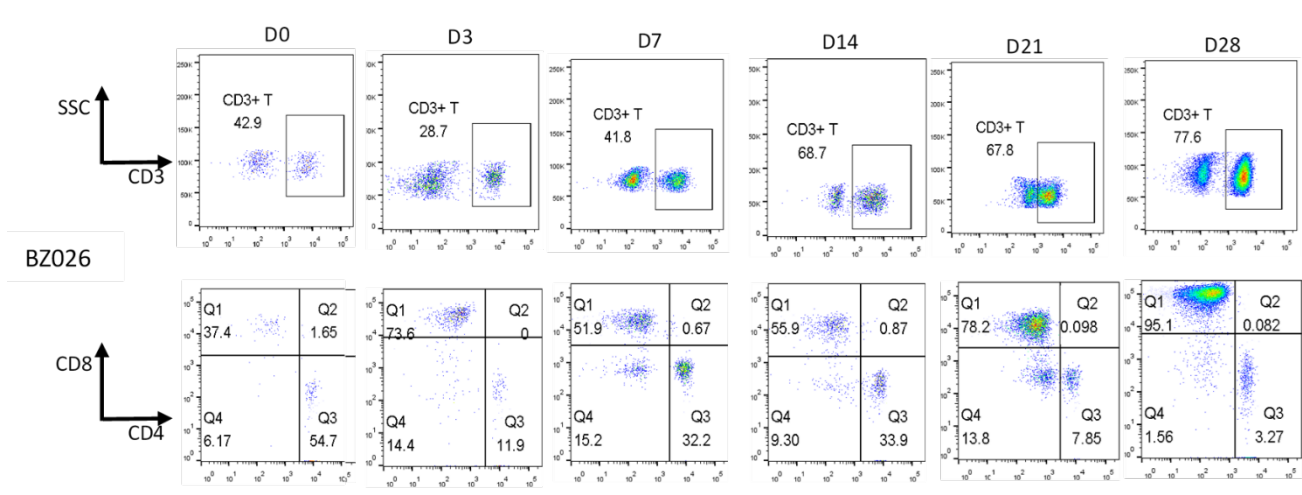
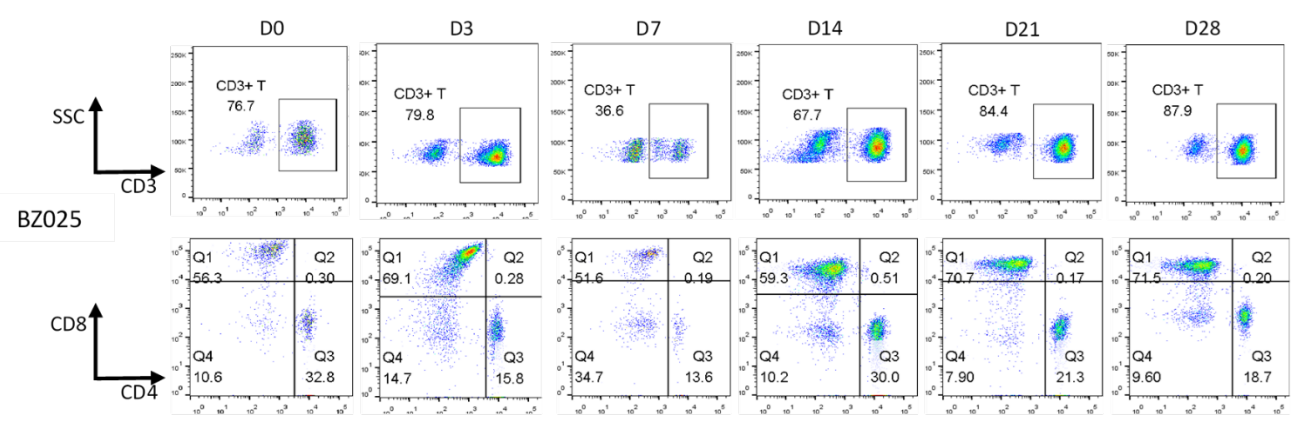
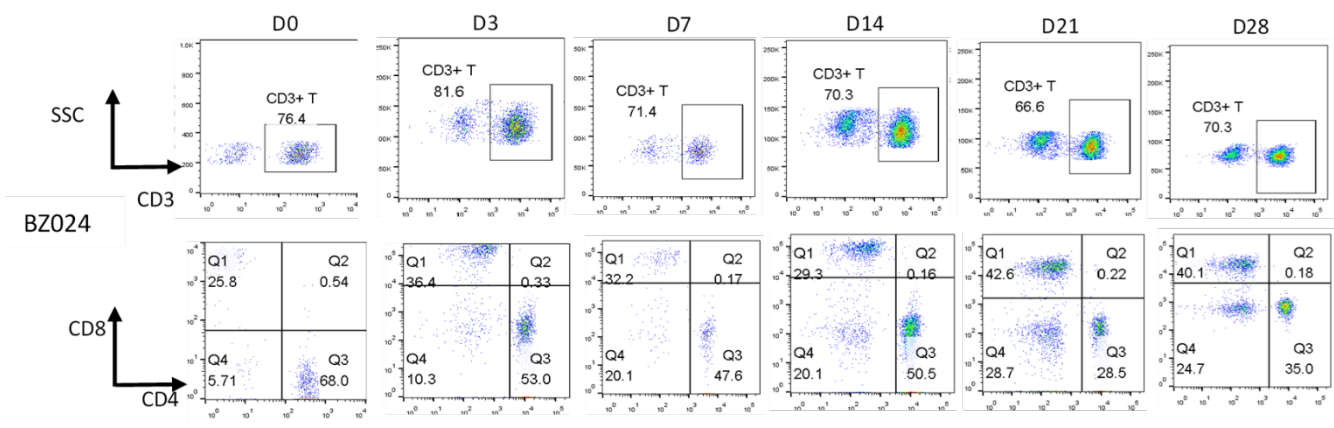




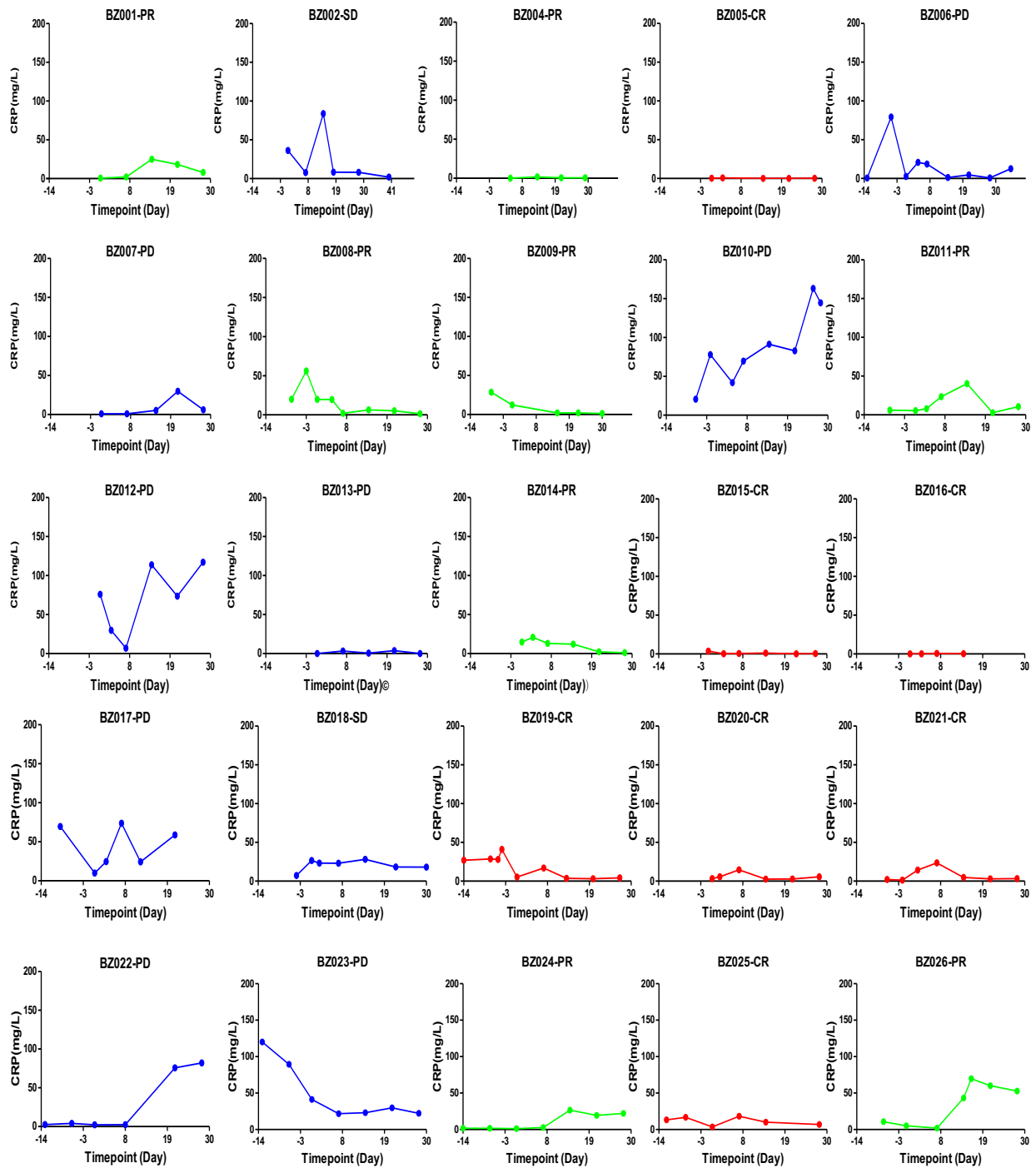




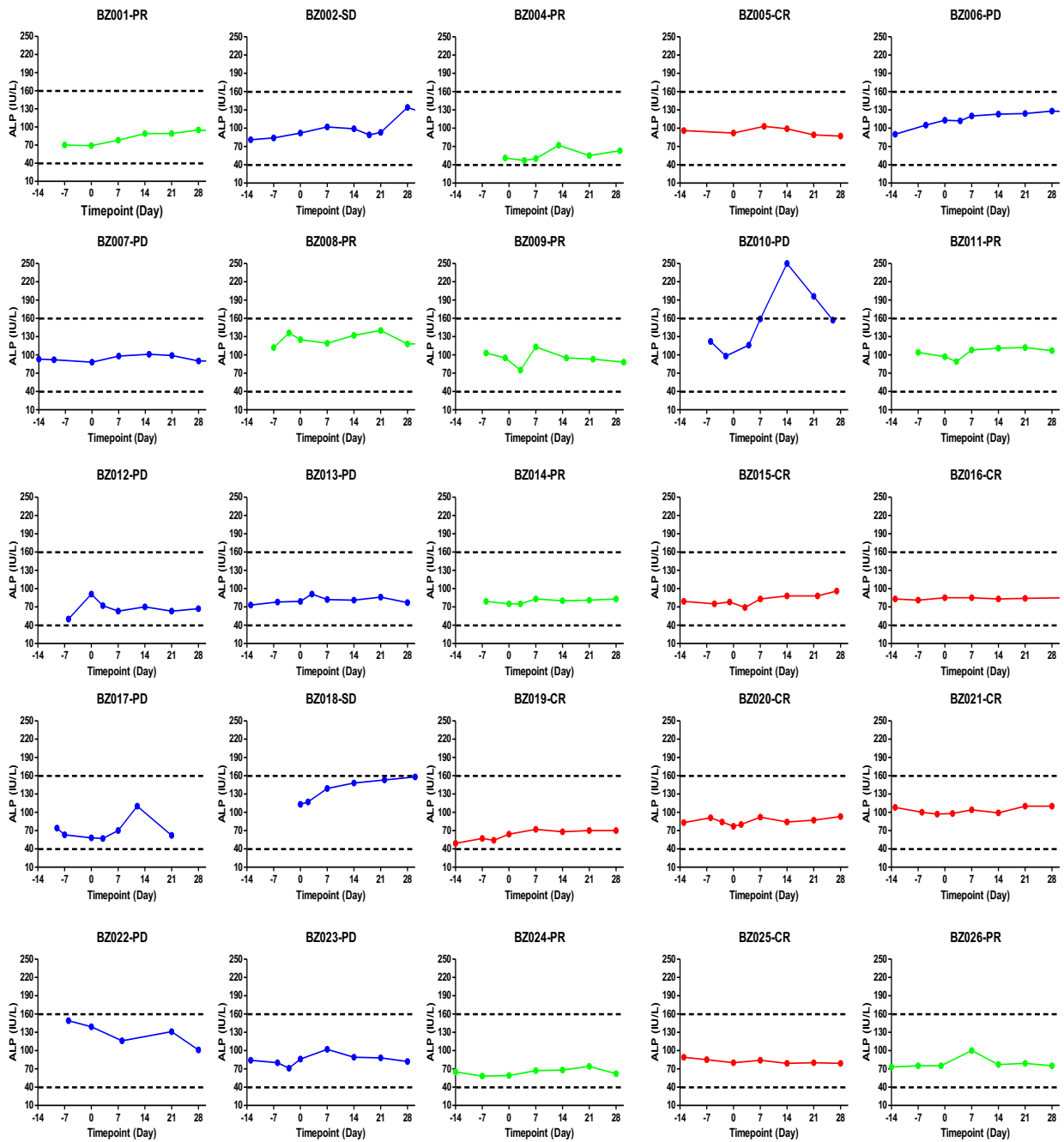




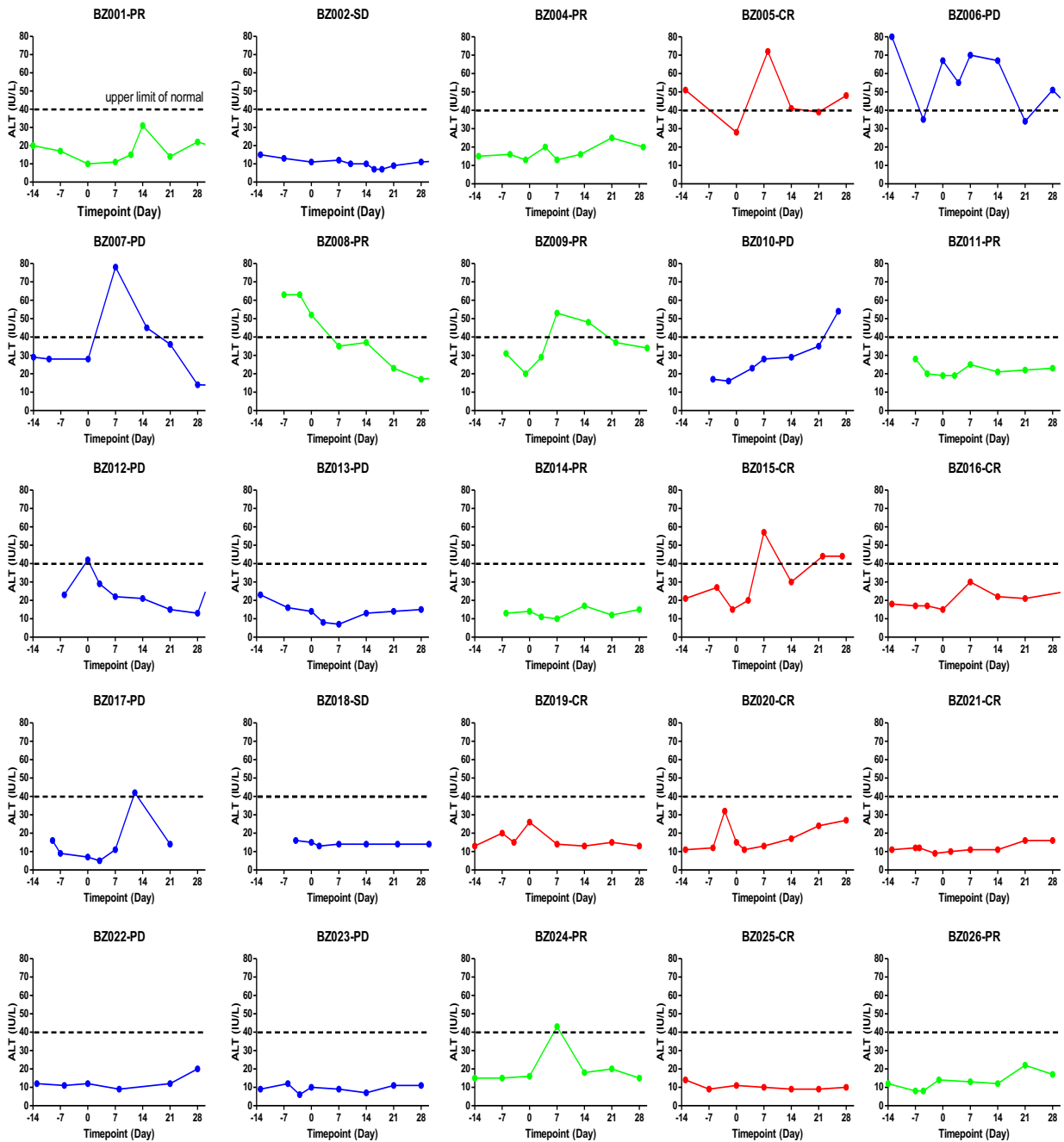
Supplementary Figure 8. Changes of blood c-reaction protein (CRP) during CD19-BBz(86) CAR-T cell therapy



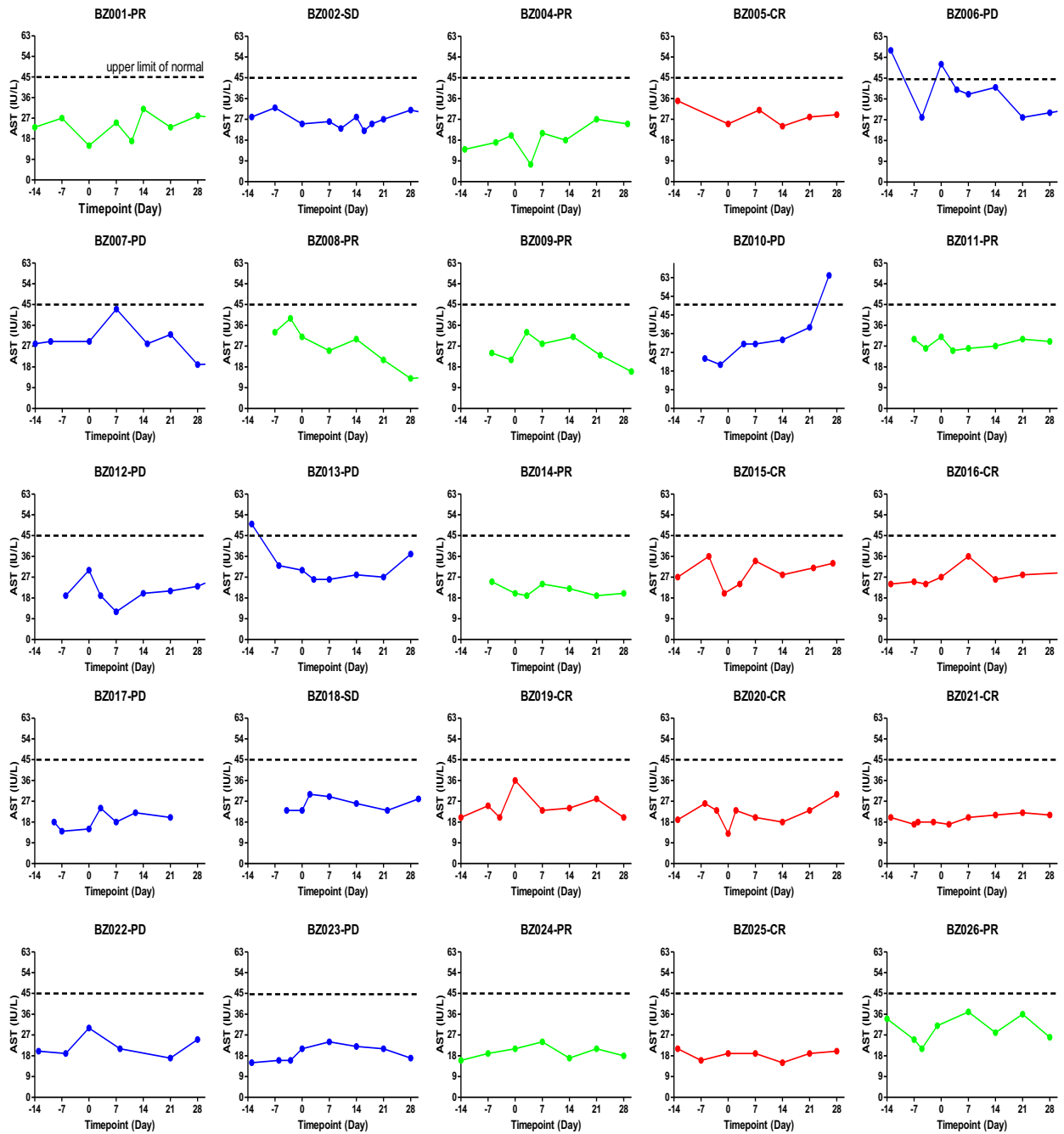
Supplementary Figure 9. Changes of blood alkaline phosphatase (ALP) during CD19-BBz(86) CAR-T cell therapy



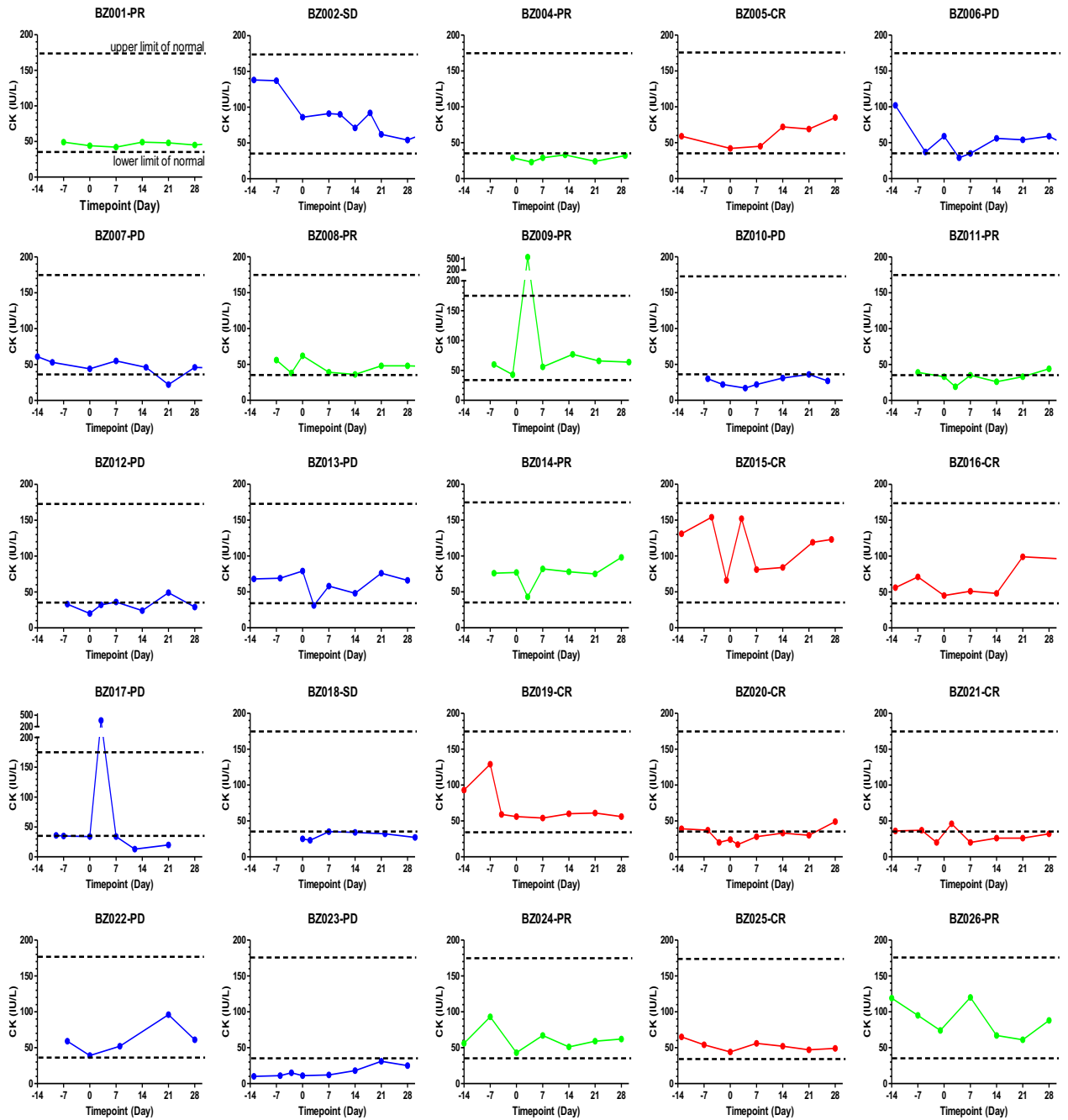
Supplementary Figure 10. Changes of blood alanine aminotransferase (ALT) during CD19-BBz(86) CAR-T cell therapy



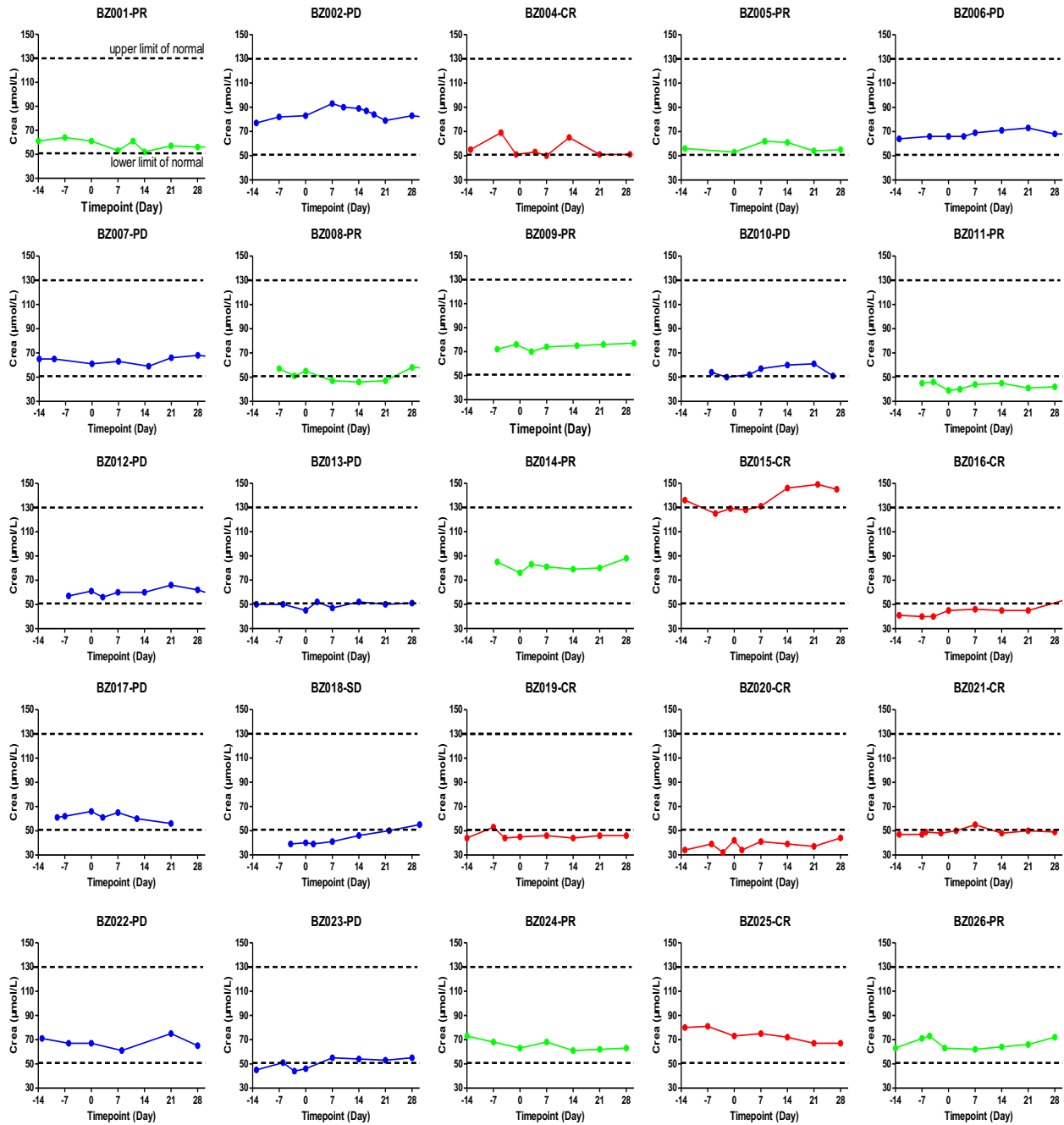
Supplementary Figure 11. Changes of blood aspartate aminotransferase (AST) during CD19-BBz(86) CAR-T cell therapy



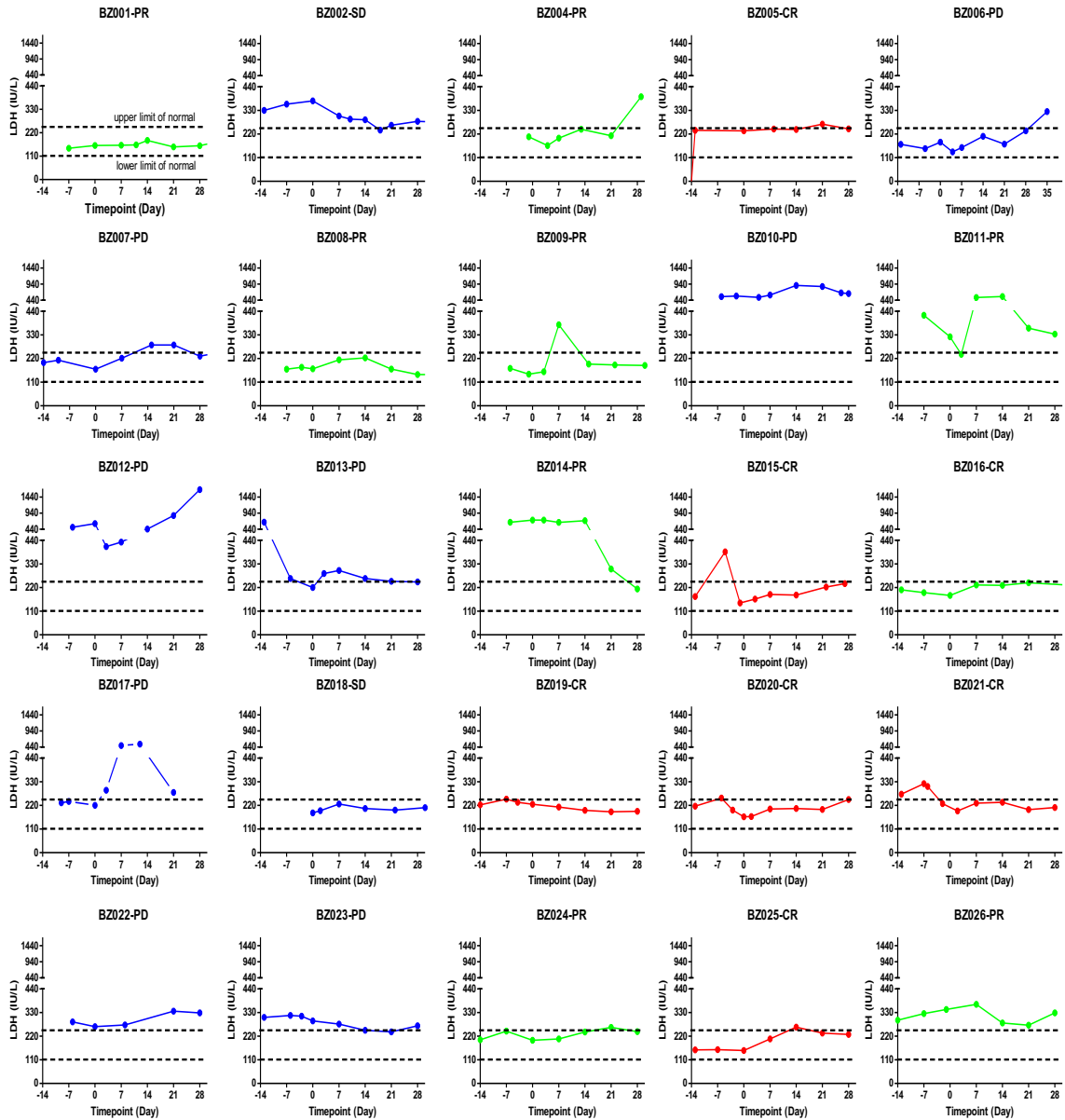
Supplementary Figure 12. Changes of blood creatine kinase (CK) during CD19-BBz(86) CAR-T cell therapy



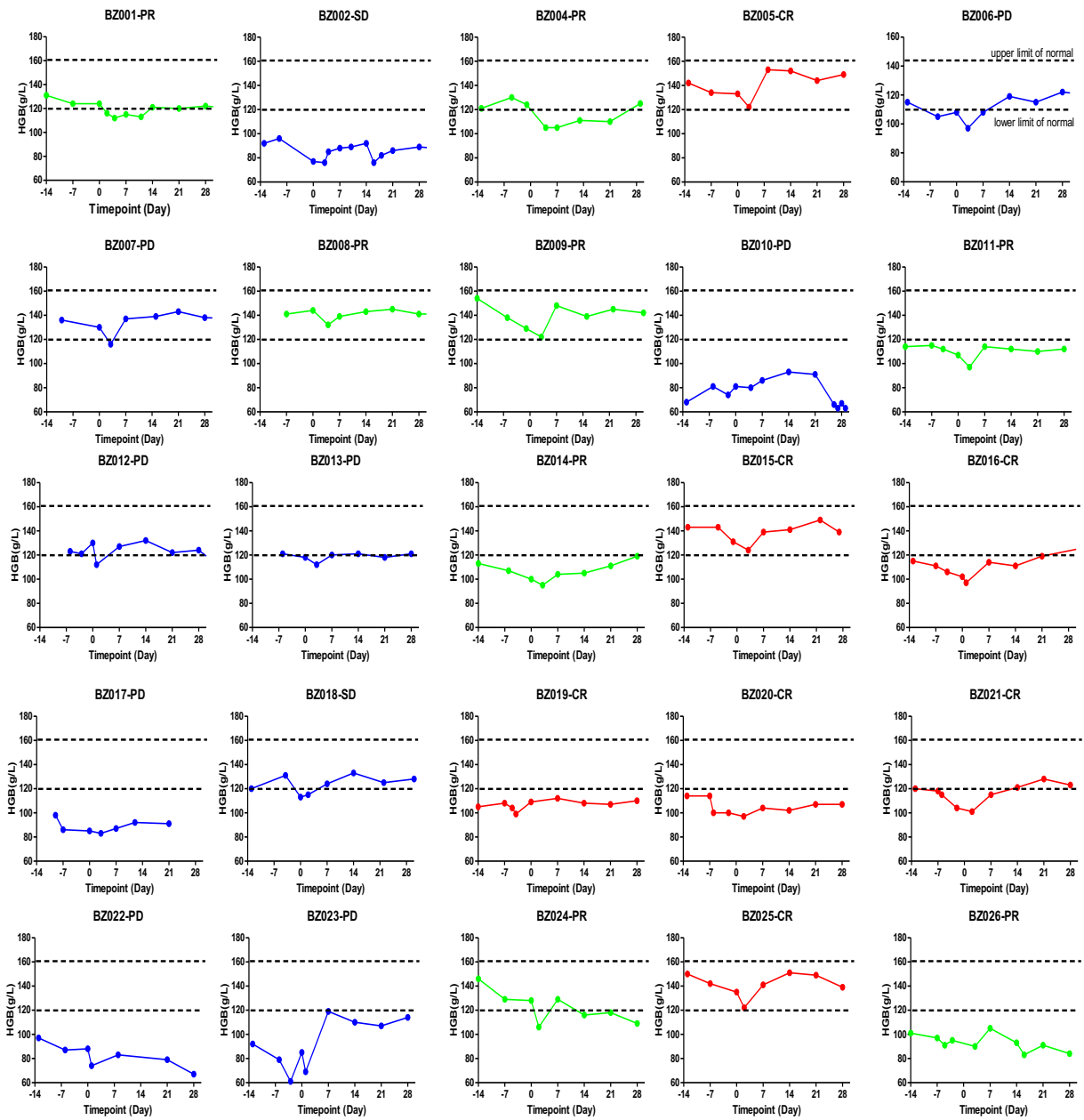
Supplementary Figure 13. Changes of blood creatinine (Crea) during CD19-BBz(86) CAR-T cell therapy



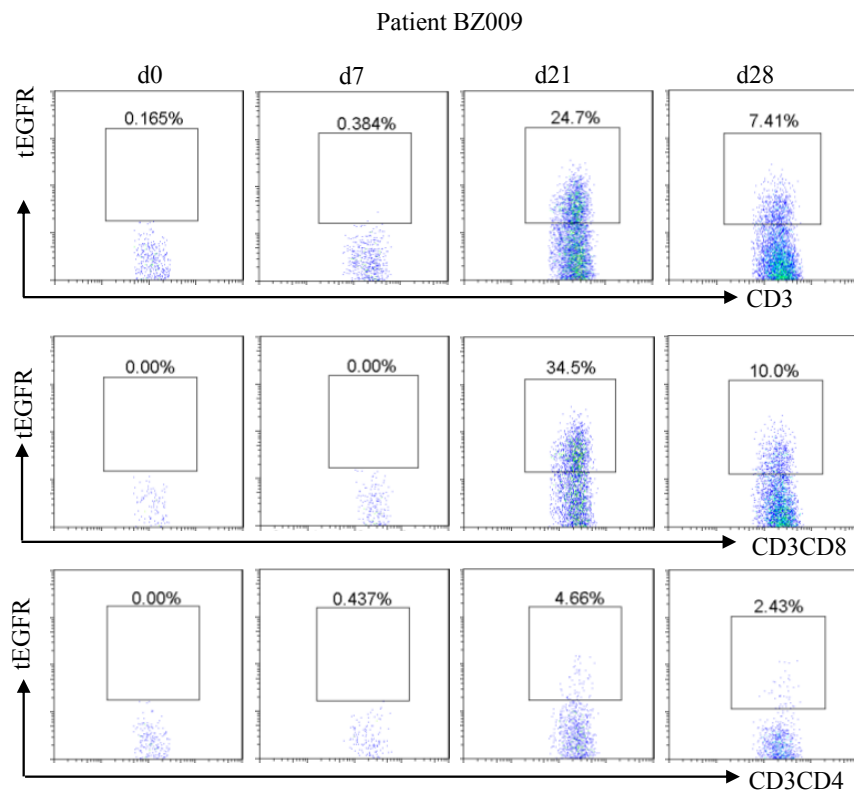
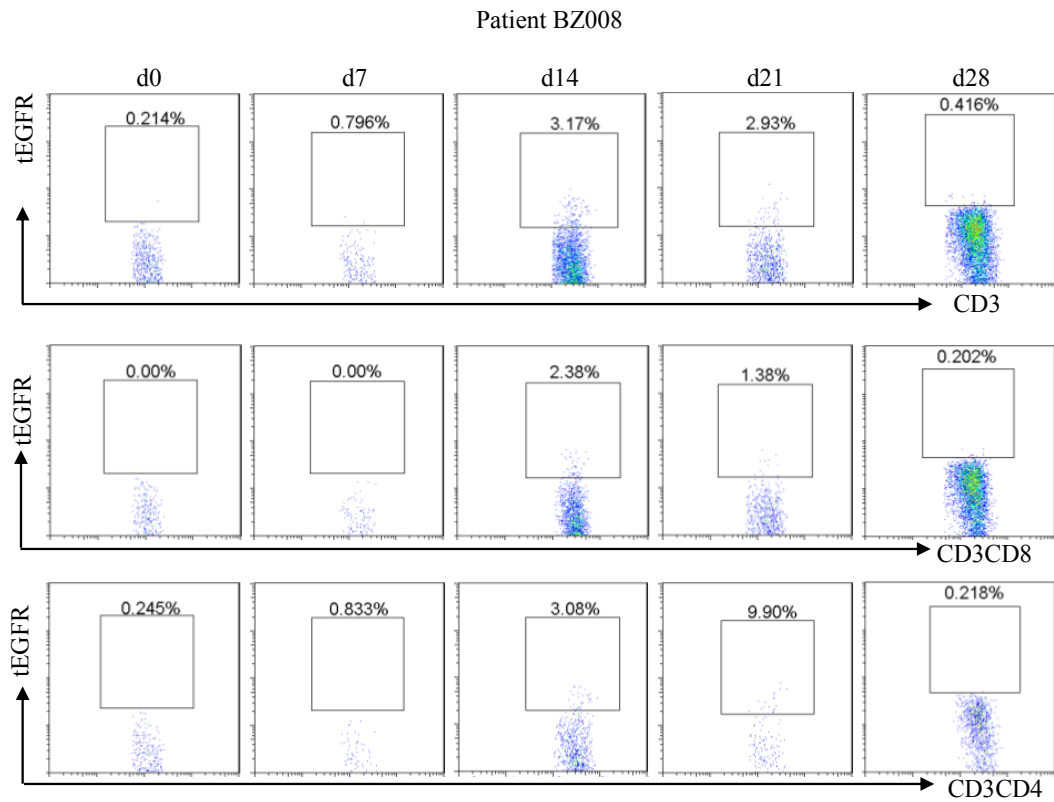
Supplementary Figure 14. Changes of blood lactate dehydrogenase (LDH) levels after CD19-BBz(86) CAR-T cell therapy



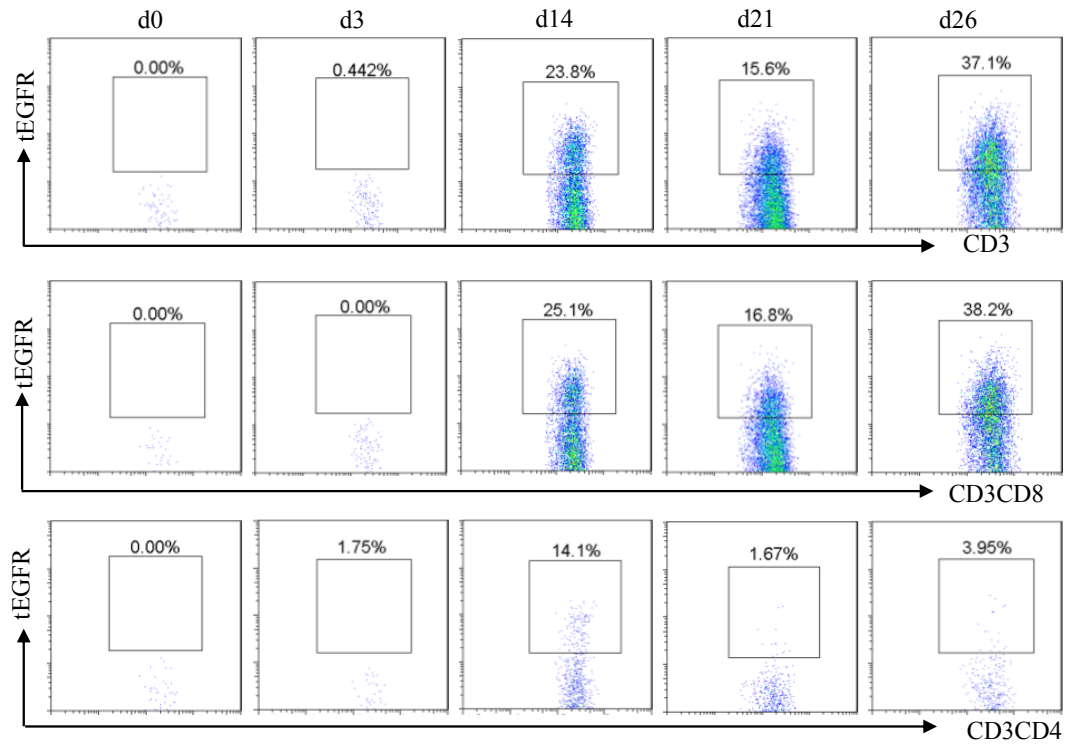
Supplementary Figure 15. Changes of blood hemoglobin (HGB) levels during CD19-BBz(86) CAR-T cell therapy



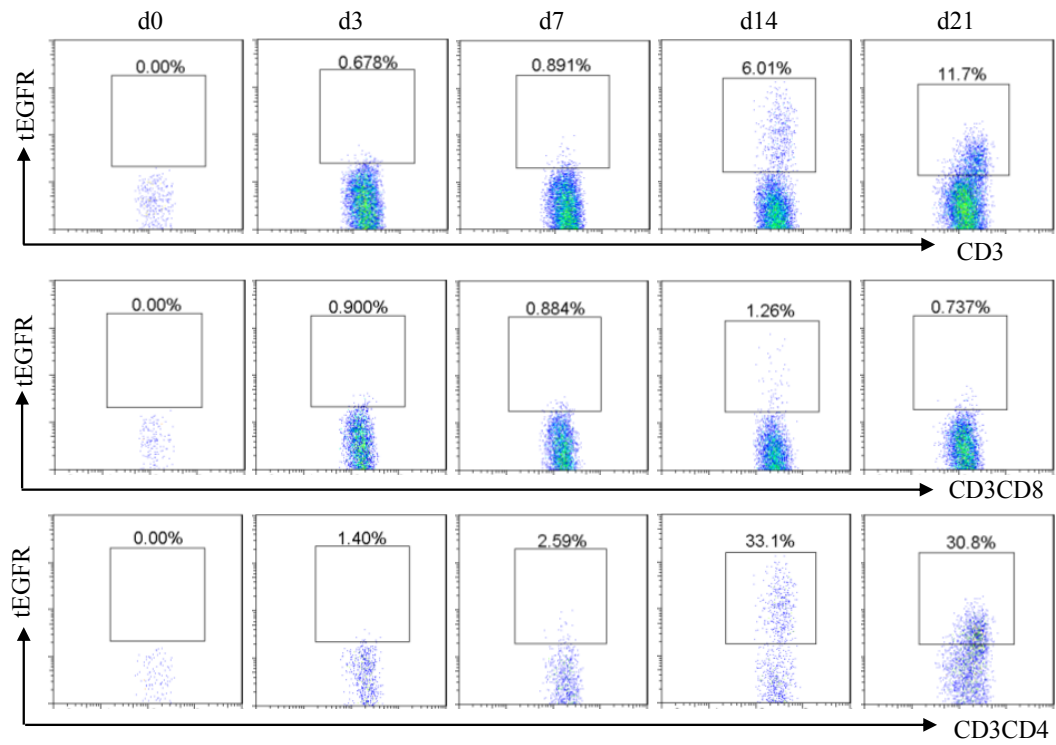
Supplementary Figure 16. CD19-BBz(86) CAR-T cell *in vivo* expansion detected by flow cytometry



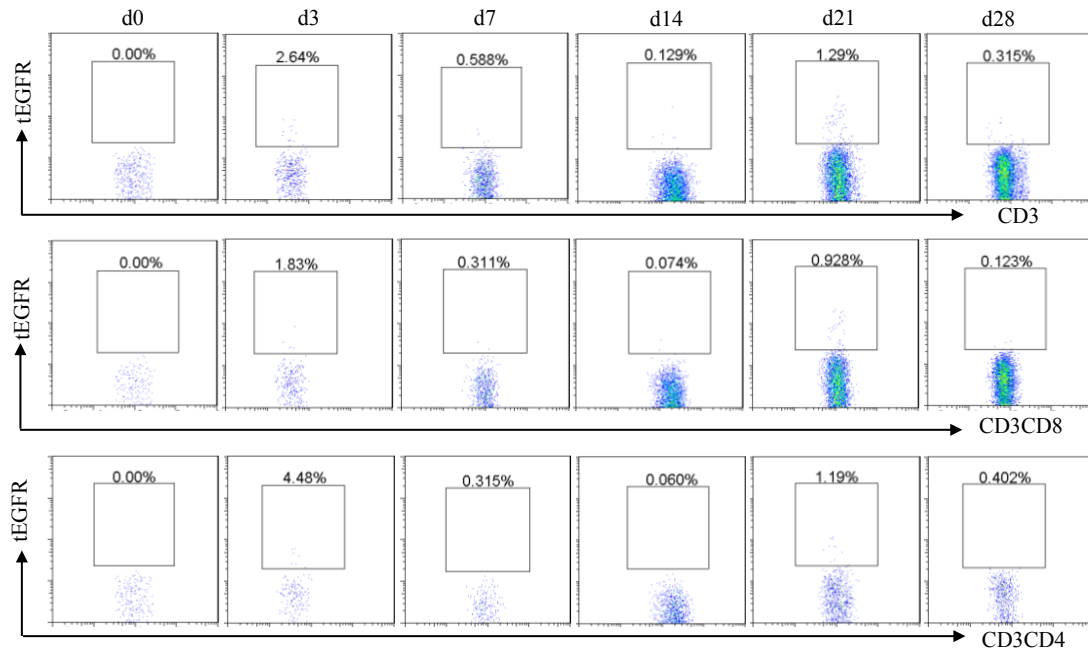
Patient BZ010



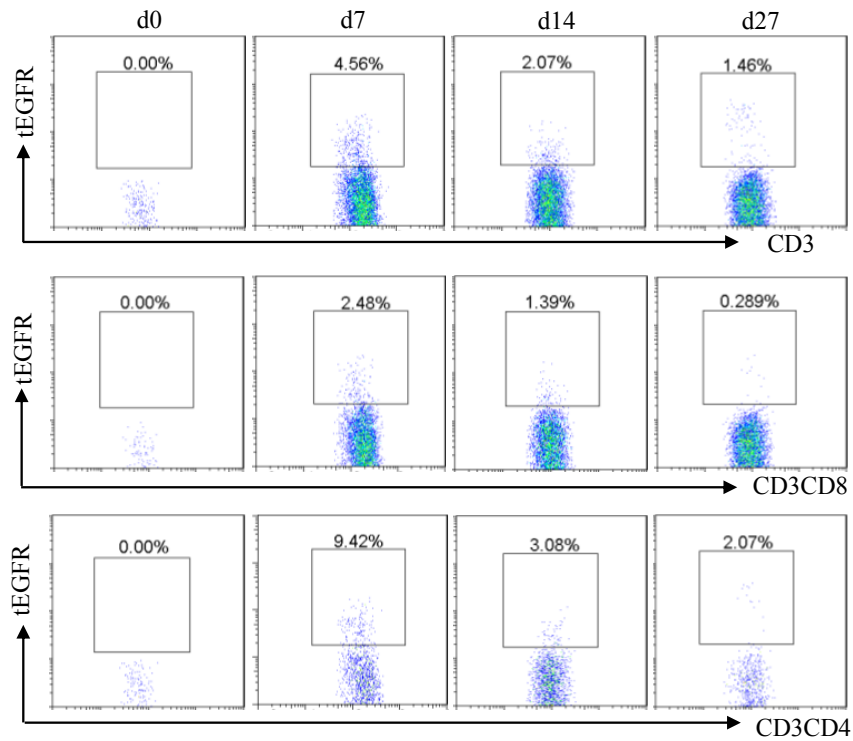
Patient BZ011



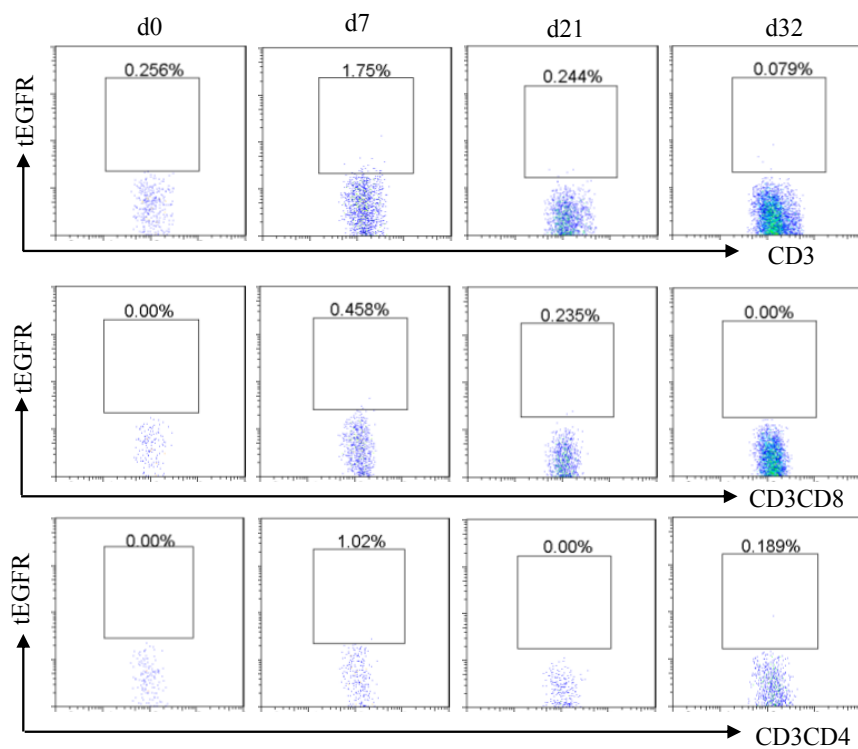
Patient BZ012



Patient BZ015



Patient BZ016



Patient BZ018

