Supplementary Figure 1. Effect of CD4+ T cells on LCL EBV Latency stage and EBV gene expression. Western blot images
Western blot images for three donors used for band quantification for graphs in Figure 3 and Supplementary Figure 10.
Supplementary Figure 2. Expression of co-stimulatory molecules and T-helper associated markers in in-vitro T cell-LCL co-culture system. Histogram overlays

Histogram overlays for one representative donor for Figures 4a, b (S2a), Figures 4c, d (S2b) and Figures 4e, f (S2c).

S2a

- **CD40**
- **CD86**
- **ICOS-L**
- **CD80**
- **OX40L**
- **FAS**

Legend:
- **isotype**
- **LCLs (alone)**
- **LCLs (co-culture)**

S2b

- **CD28**
- **ICOS**
- **CD40L**
- **FAS-L**
- **OX40**

Legend:
- **isotype**
- **T cells (alone)**
- **T cells (co-culture)**

S2c

- **IFNγ**
- **IL-13**
- **IL-21**
- **T-bet**
- **GATA3**
- **bcl6**

Legend:
- **isotype**
- **T cells (alone)**
- **T cells (co-culture)**
Supplementary Figure 3. Selection and validation of gRNAs for introduction of IgH/c-myc translocation.

a) Overview of target locations for gRNAs targeting IgH and c-myc regions. b) LCL line was electroporated with IgH targeting or c-myc targeting RNPs. Cells were cultured for 3 days post electroporation, then gDNA was isolated and assessed for presence of mutations using Surveyor Assay kit.
Supplementary Figure 4. Introduction of IgH/c-myc translocation using IgH and c-myc targeting CAS9 RNPs.

a) Overview of gDNA PCR design used to detect IgH/c-myc translocations. **b** LCL line was electroporated with RNPs targeting both IgH and c-myc regions. Cells were cultured for 3 days post electroporation, then gDNA was isolated and assessed for presence of translocation using gDNA PCR. **c** Individual bands were cut out from the agarose gel, cloned into vector and sequenced.

**S4a**

Overview of gDNA PCR design used to detect IgH/c-myc translocations.

**S4b**

Expected size 707bp

\[
\text{t}(8; 14) \quad \text{interest}
\]

Expected size 598bp

\[
\text{t}(14; 8) \quad \text{reciprocal}
\]

**S4c**

\[
t(14; 8) \quad \text{chromosome reciprocal}
\]

Reference seq

clone 1 forward seq

clone 1 reverse seq

clone 2 forward seq

clone 2 reverse seq

\[
t(8; 14) \quad \text{chromosome interest}
\]

Reference seq

clone 3 forward seq

clone 3 reverse seq

clone 4 forward seq

clone 4 reverse seq
Supplementary Figure 5. Generation of ssDNA insert for introduction of GFP tag into IgH/c-myc translocation.

a) Overview of plasmid used for generation of ssDNA insert. ssDNA was generated from PCR product, size and sequence were confirmed by gel electrophoresis (b) and Sanger sequencing (c).

S5a

![Diagram of plasmid showing backbone, c-myc HR, CMV+GFP, IgH HR, and backbone.](Diagram)

S5b

![Image of gel electrophoresis and Sanger sequencing results.](Image)

S5c

![Diagram showing sequencing primers 1 and 2 with IgH HR, TurboGFP, CMV enhancer + promoter, c-myc HR, and SV40 poly(A) signal.](Diagram)
Supplementary Figure 6. Confirmation of presence of IgH/c-myc translocation in CRISPR/CAS9 edited LCL lines

a) Overview of gDNA PCR design used to detect IgH/c-myc translocations. b-d) LCLs from 4 donors either with or without IgH/c-myc translocation were cultured for 3 days. b) Percentage of GFP+ cells was determined by flow cytometry prior to harvesting. c) gDNA was isolated and the presence of the translocation was assessed by gDNA PCR. d) Dual probe FISH for IgH/c-myc translocation was performed. Representative images for each donor for both “wild type” and IgH/c-myc+ LCLs are shown.
Supplementary Figure 7. Effect of IgH/c-myc translocation on LCL gene expression. Western blot images for four donors used for band quantification used for graphs in Figure 6.
Supplementary Figure 8. Effect of IgH/c-myc translocation on LCL phenotype

LCLs from 4 donors either with or without IgH/c-myc translocation were cultured at same density for 3 days and compared to assess the effect of translocation on LCL phenotype. Different symbols represent different conditions, while different colors represent different TMC donors. P-values were calculated using paired t-test. p>0.05 not significant (n.s.). For flow cytometry experiments, isotype staining was used to determine positive cells.

a) Gene expression was determined using qRT-PCR. Shown are mean ± SD of dCt values normalized to geometric means of TBP and YWHAZ. b, c) Histogram overlays for one representative donor for Figure 6g (S2b) and Figure 6h (S2c)
**Supplementary Figure 9. Effect of CD4+ T cells on proliferation and viability of IgH/c-myc+ LCLs**

LCLs either with or without IgH/c-myc translocation were cultured for 9 days either alone or in co-culture with various ratios of expanded autologous CD4+ T cells activated using anti-CD3/CD28 beads. At given timepoints cells were harvested, stained and analysed using flow cytometer. LCLs were pre-gated based on CD19 expression. Shown are mean ± SD of mean percentage of positive cells from 3 TMC donors. P-values were calculated using two-way Anova with Tukey’s test for multiple comparisons. p>0.05 not significant (n.s.), p<0.1*, p<0.01**, p<0.001***, p<0.0001****.

**a)** Mean percentage of LCLs in co-culture was determined by CD19 and CD4 staining. **b)** Mean percentage of EdU+ LCLs was measured using Click-iT Flow Cytometry kit. **c)** Mean percentage of LCLs in different cell cycle stages was measured using EdU Click-iT Flow cytometry kit and FxCycle dye.

**S9a**

**Percentage of LCLs in co-culture**

1:1 T cell/LCL ratio

- WT (co-culture)
- IgH/c-myc+ (co-culture)

**S9b**

**EdU proliferation assay**

1:1 T cell/LCL ratio

- WT (alone)
- IgH/c-myc+ (alone)
- WT (co-culture)
- IgH/c-myc+ (co-culture)

**S9c**

**Cell cycle assay**

- **5:1 T cell/LCL ratio**
- **1:1 T cell/LCL cell ratio**

- G2
- S
- G1
Supplementary Figure 10. Effect of CD4+ T cells on c-myc and bcl6 expression in LCLs

LCLs were cultured for 7 days either alone or in co-culture with various ratios of expanded autologous CD4+ T cells activated using anti-CD3/CD28 beads. At given timepoints cells were harvested and LCLs were isolated using CD19+ beads and AutoMACS. Different symbols represent different conditions, while different colors represent different TMC donors. P-values were calculated using two-way Anova with Sidak’s test for multiple comparisons. p>0.05 not significant (n.s.), p<0.1*, p<0.01**, p<0.001***. WB images used for quantification can be found in Supplementary Figure 1.

a) Total c-myc protein expression was assessed using Western blotting. Western blot image was quantified and normalized to β-actin as loading control. Shown are mean ± SD of normalized volume of c-myc band.

b) c-myc and bcl6 expression was determined using qRT-PCR. Shown are mean ± SD of dCt values normalized to geometric means of TBP and YWHAZ.
Supplementary Table 1. Part 1. Details eBL patients used for IHC stainings

| Case | Gender | Age (YRS) at diagnosis | Topography            | Morphology | FISH                                      |
|------|--------|------------------------|-----------------------|------------|------------------------------------------|
|      |        |                        | Cell size             | Starry-sky (NP) Not Present (P) Present | t8; 14 (c-myc translocation) |
| BL 1 | M      | 45                     | DUODENAL LESION       | MEDIUM     | NP                                       | POSITIVE t(8;14) |
| BL 2 | F      | 32                     | LYMPH NODE            | MEDIUM     | P                                        | NEGATIVE t(8;14); NEGATIVE c-MYC translocation |
| BL 3 | M      | 70                     | PAROTID GLAND         | MEDIUM     | P                                        | POSITIVE t(8;14) |
| BL 4 | F      | UNSPECIFIED            | LEFT AXILLARY NODE    | MEDIUM     | P                                        | POSITIVE t(8;14) |
| BL 5 | M      | 39                     | AXILLARY NODE         | MEDIUM     | P                                        | POSITIVE t(8;14) |
| BL 6 | M      | 26                     | LYMPH NODE            | MEDIUM     | P                                        | POSITIVE c-MYC rearrangement, NEGATIVE BCL2 & BCL6 rearrangement |
| BL 7 | F      | 30                     | FALLOPIAN TUBE        | MEDIUM     | P                                        | POSITIVE t(8;14) |
| BL 8 | F      | 29                     | AXILLARY NODE         | MEDIUM     | P                                        | POSITIVE t(8;14) |
| BL 9 | M      | 29                     | AXILLARY NODE         | MEDIUM     | P                                        | NEGATIVE t(8;14); NEGATIVE c-MYC rearrangement |
| BL 10| F      | 32                     | PAROTID GLAND         | MEDIUM     | P                                        | UNSUCCESSFUL FISH |
| BL 11| M      | 42                     | LEFT CERVICAL NODE    | MEDIUM     | P                                        | UNSUCCESSFUL |
| BL 12| M      | 32                     | INGUINAL NODE         | MEDIUM     | P                                        | POSITIVE C-MYC REARRANGEMENT |
| BL 13| M      | 40                     | AXILLARY LYMPH NODE   | MEDIUM     | P                                        | POSITIVE t(8;14) |
Supplementary Table 1. Part 2. Details eBL patients used for IHC stainings

| Case | CD20 | CD10 | Bcl6 | bcl2 | Ki67 | TdT | MuM1 | Cyclin D1 |
|------|------|------|------|------|------|-----|-------|-----------|
| BL 1 | P    | P    | P    | P    | N    | 100%| NP    | N         |
| BL 2 | P    | P    | P    | P    | N    | 100%| NP    | N         |
| BL 3 | P    | P    | P    | P    | N    | 100%|       | N         |
| BL 4 | P    | P    | P    | P    | N    | 100%| N     | N         |
| BL 5 | P    | P    | P    | P    | N    | 100%| NP    | N         |
| BL 6 | P    | P    | P    | P    | N    | 100%| NP    | N         |
| BL 7 | FOCAL | P  | P    | P    | N    | 100%| N     | P         | CD138 NEG |
| BL 8 | P    | P    | P    | P    | N    | 100%| N     | NP        |
| BL 9 | P    | P    | P    | P    | N    | 100%| N     | NP        |
| BL 10| P    | P    | P    | P    | N    | 100%| N     | N         |
| BL 11| P    | P    | P    | P    | N    | 100%| N     | N         |
| BL 12| P    | P    | P    | P    | N    | 100%| N     | N         |
| BL 13| P    | P    | P    | P    | N    | 100%| N     | NP        |

Supplementary Table 2. eBL tumour IHC data

| Case | CD3 | CD4 | CD8 |
|------|-----|-----|-----|
| BL 1 | 2   | 1   | 2   |
| BL 2 | 2   | 2   | 2   |
| BL 3 | 3   | 1   | 3   |
| BL 4 | 2   | 2   | 2   |
| BL 5 | 2   | 1   | 2   |
| BL 6 | 5   | 3   | 4   |
| BL 7 | 2   | 2   | 2   |
| BL 8 | 5   | 4   | 4   |
| BL 9 | 3   | 2   | 3   |
| BL 10| 2   | 2   | 2   |
| BL 11| 2   | 2   | 2   |
| BL 12| 2   | 2   | 2   |
| BL 13| 2   | 1   | 3   |

numbers in % of total infiltrate

n/a: not available
FN: false negative
0: negative
1: < 1%
2: 1-5%
3: 10%
4: 10-20%
5: 21-30%