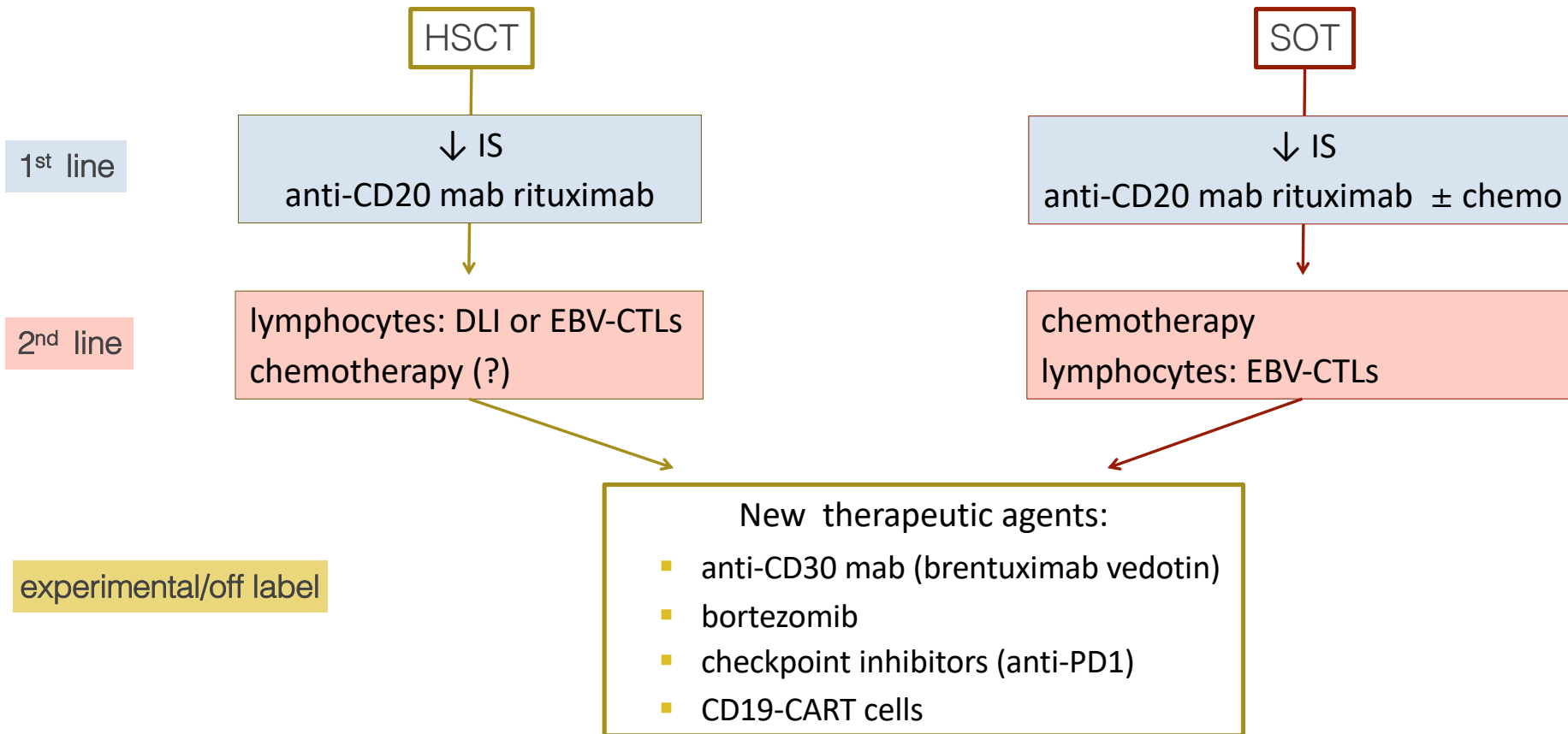# Disclosures

- Atara Biotherapeutics: consultancy/advisory role
- Pierre Fabre Pharma: consultancy/advisory role

Treatment of PTLD after transplantation

HSCT

SOT

1st line

↓ IS
anti-CD20 mab rituximab

↓ IS
anti-CD20 mab rituximab ± chemo

2nd line

lymphocytes: DLI or EBV-CTLs
chemotherapy (?)

chemotherapy
lymphocytes: EBV-CTLs

experimental/off label

New therapeutic agents:
- anti-CD30 mab (brentuximab vedotin)
- bortezomib
- checkpoint inhibitors (anti-PD1)
- CD19-CART cells

1. Styczynski J, et al. *Haematologica.* 2016;101: 803–11;   2. Allen UD, et al. *Clin Transplant* 2019; 33(9):e13652

Donor choice: it starts with the transplant

Avoid risk factors:

- EBV serology mismatch
- type of transplant + donor/recipient HLA match

|	HSCT	SOT
EBV serology match	D- for a R-, D+ for a R+	D- for a R-, D+ for a R+
HLA match	identical family > haplo-PTCY > others HLA # or cords	living family donor (haplo)

Choose the best option for cell therapy:

- family donors (prompt availability)
- if not available: third party donor(s) partly HLA compatible

Styczynski et al. Haematologica 2016;

Al Hamed et al. BMT 2020

Donor choice: third party donor for T cell therapy

- Phase II study of cell therapy for EBV PTLD in SOT or HSCT recipients: 52% CR/PR at 6 months (38% long term)
- T-cell allocation: on the basis of HLA typing (HLA A, B, DR) – best match (2-digits)
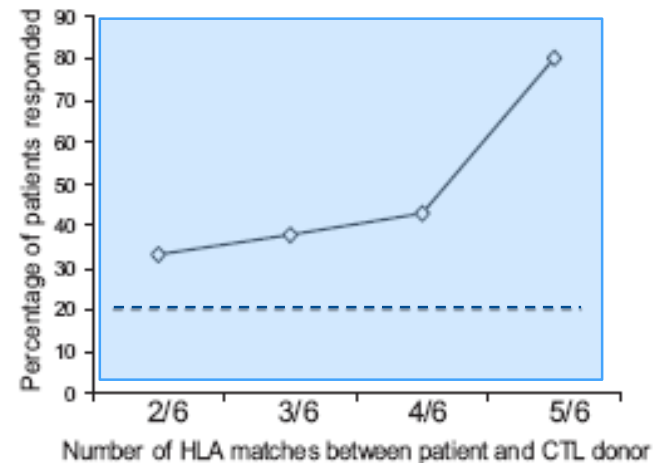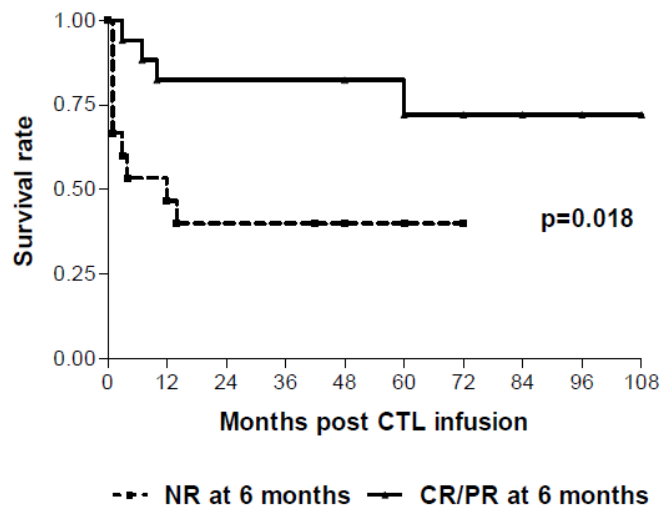
Haque et al. *Lancet* 2002; Blood 2007; Transplantation 2010

Donor choice for CT: what about cellular product function?

Immune surveillance to EBV:

to control infection/disease, donor T cells need to recognize viral protein epitopes presented by infected cells in the host:

- APCs present antigen epitopes to T cells through their MHC complex (HLA class I to CD8+ T cells, HLA class II to CD4+ T cells)
  - T cells need to bind to antigen-HLA complex to start specific immune response: HLA restriction
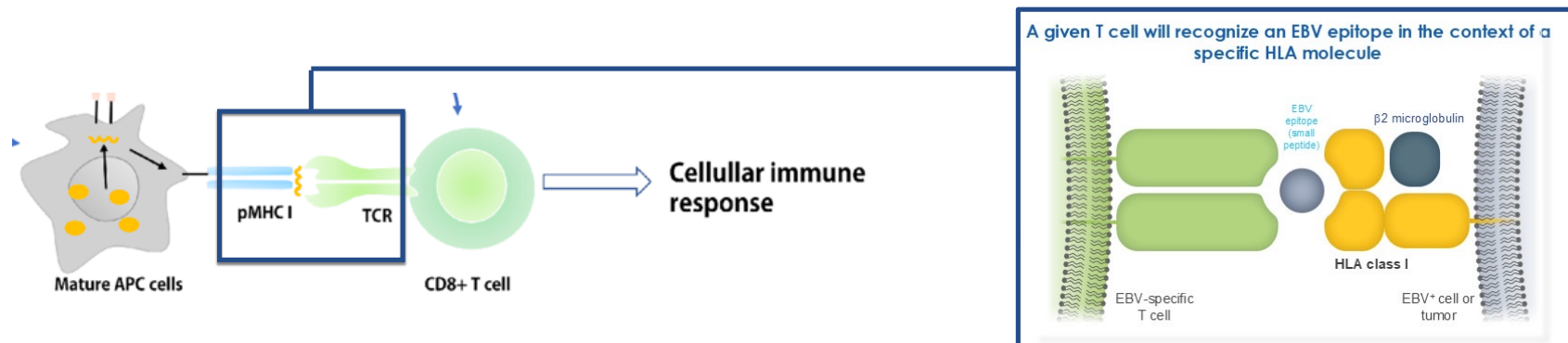
Donor choice for CT: HLA restriction

HLA restriction: HLA locus(i) that needs to match between tumor cell and EBV-specific T cells to allow correct interaction between peptide-HLA complex and T cell receptor (TCR) in order to promote a functional response resulting in tumor cell lysis
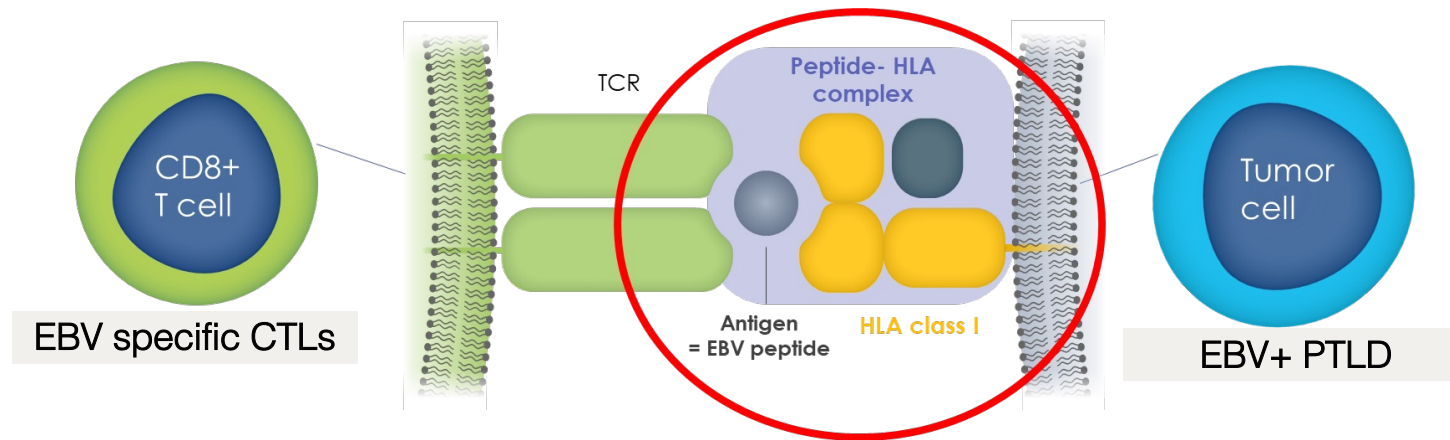

- if HLA is mismatched, donor T cells will not recognize target infected cells
  - according to the degree of matching, Ag presentation will be optimal or suboptimal

Dendrou C, et al. Nat Rev Immunol 2018

Donor choice: third party donor for T cell therapy

- Phase II study of cell therapy for EBV PTLD in SOT or HSCT recipients: 52% CR/PR at 6 months (38% long term)
- T-cell allocation: on the basis of HLA typing (HLA A, B, DR) – best match (2-digits)

effect of HLA restriction · alloreactivity
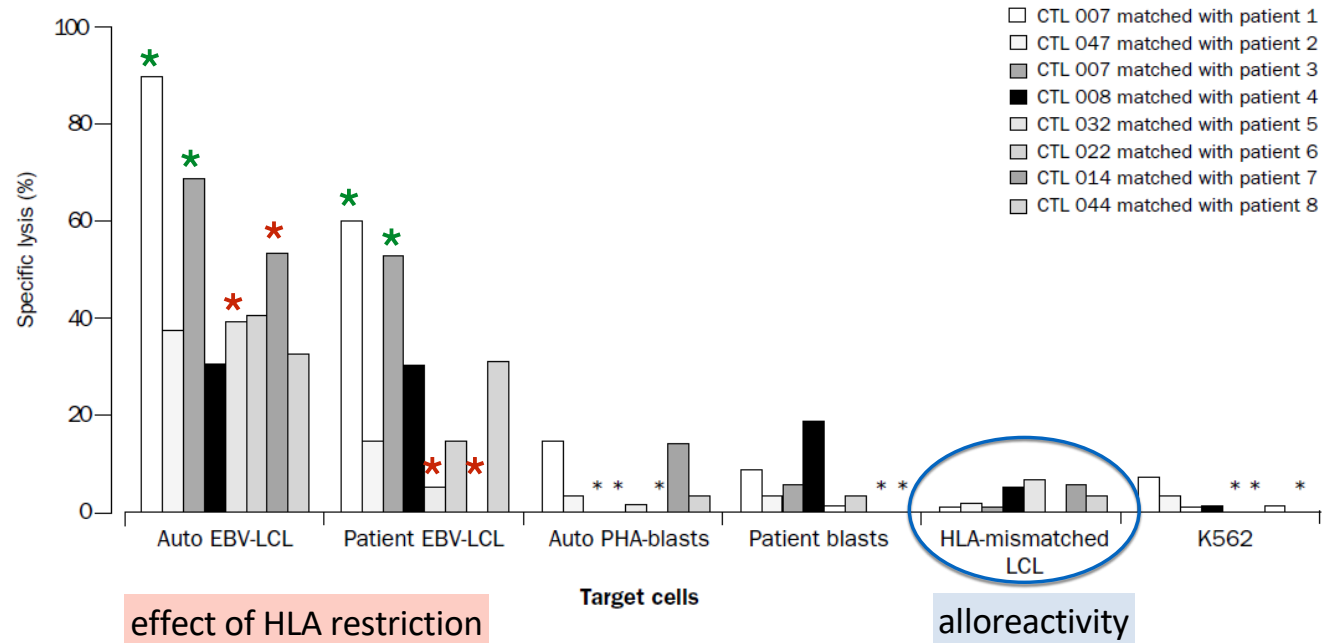
Haque et al. *Lancet* 2002; Blood 2007; Transplantation 2010

Ideal features of EBV T cell products for donor choice in cell

1. High resolution 4-digit HLA typing

2. EBV HLA restriction

3. Lack of alloreactivity

4. Selective lysis of EBV+ cells

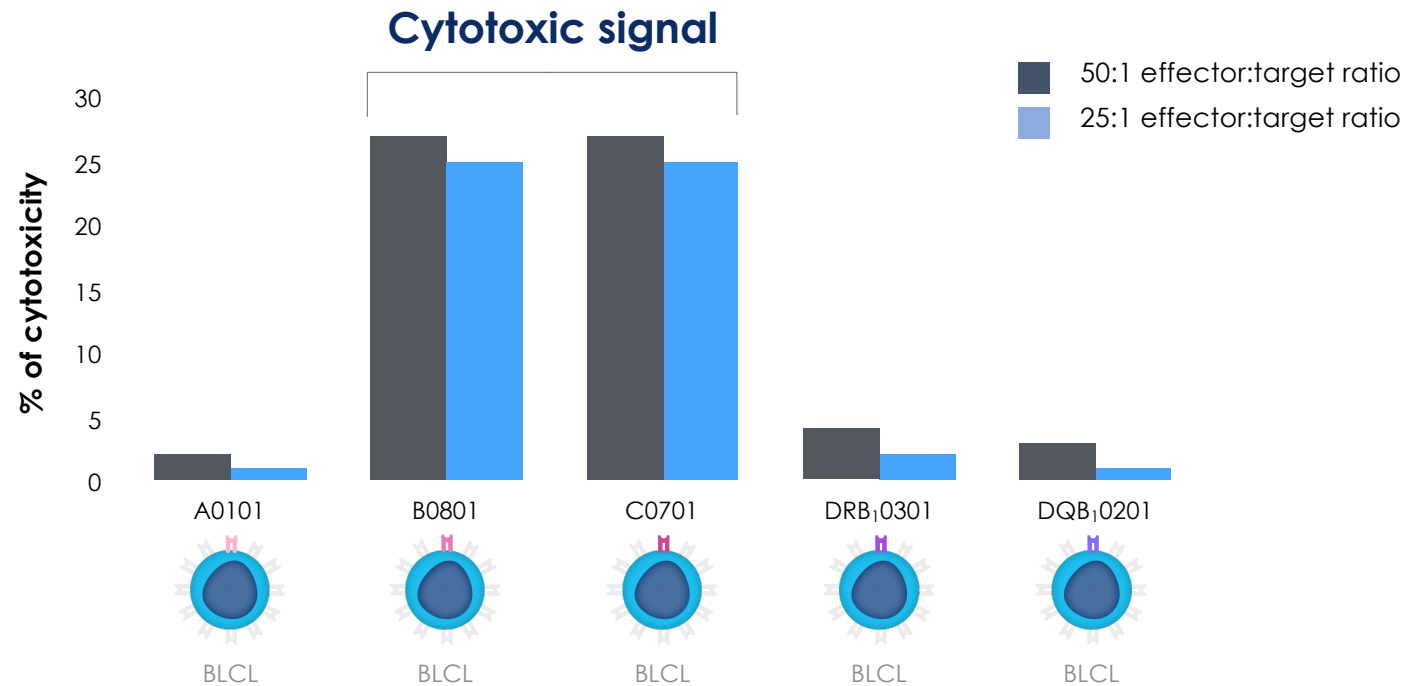Important for third-party cells, but also for HLA-mismatched family donors

Donor choice: how to test a T cell product

EBV-CTLs lot A A0101 B0801 C0701 $DRB_1$0301 $DQB_1$0201
A0301 B3501 C0801 $DRB_1$0701 $DQB_1$0205

Donor T-cells

Co-culture of EBV-infected APCs and T-cells

EBV-infected donor B-cells functioning as APCs

% of cytotoxicity
30
25
20
15
10
5
0

A*0101   B*0801   C*0701 $DRB_1$0301 $DQB_1$0201
BLCL   BLCL   BLCL   BLCL   BLCL
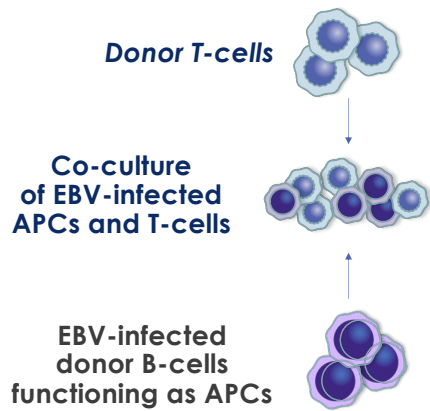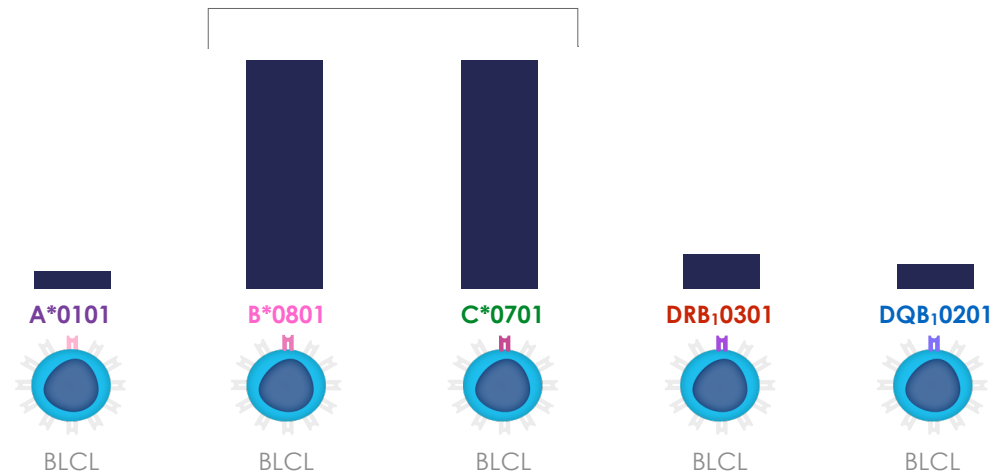
Panel of targets sharing single HLA alleles with the donor

A*0101   B*0801   C*0701 $DRB_1$0301 $DQB_1$0201
BLCL   BLCL   BLCL   BLCL   BLCL

This EBV CTL lot exhibits EBV-directed *in vitro* cytotoxic activity against EBV antigens presented by B*0801 and C*0701 HLA

→ This lot will have increased efficacy for patients with EBV+ PTLD tumour cells expressing B*0801 and/or C*0701 HLA alleles

Adapted from: Barker JN et al. Blood. 2010

Donor choice: how to test a T cell product

Potency and safety test controls
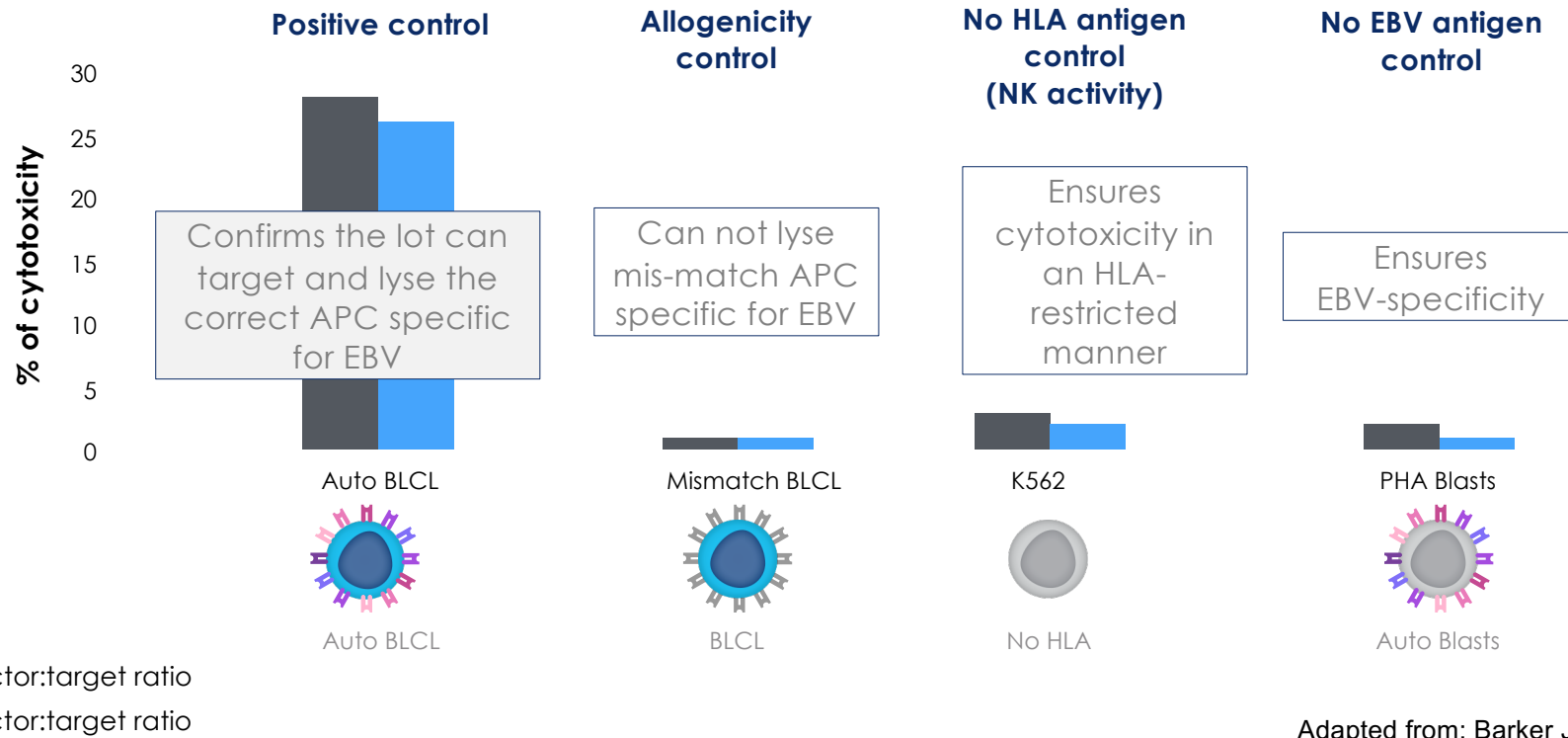
Positive control — Confirms the lot can target and lyse the correct APC specific for EBV — Auto BLCL — Auto BLCL

Allogenicity control — Can not lyse mis-match APC specific for EBV — Mismatch BLCL — BLCL

No HLA antigen control (NK activity) — Ensures cytotoxicity in an HLA-restricted manner — K562 — No HLA

No EBV antigen control — Ensures EBV-specificity — PHA Blasts — Auto Blasts

% of cytotoxicity (30, 25, 20, 15, 10, 5, 0)

■ 50:1 effector:target ratio
■ 25:1 effector:target ratio

Adapted from: Barker JN et al. Blood. 2010

Donor choice: what is needed to select the best T cell product

The suspected **origin of the disease** is required to ensure an appropriate T cell lot is selected
The best option is to obtain **high resolution HLA typing** of the **tumor biopsy**

If biopsy high resolution HLA typing is not available, the origin of the disease must be defined:

If the patient and donor gender are mis-matched:	**If the patient and donor gender are matched:**
On tumor: perform a chromosome FISH test If tumor cells are circulating (HSCT): chimerism	**If tumor cells are circulating (HSCT):** chimerism **Otherwise, use clinical assumptions:** • Patient/donor EBV serostatus before transplant • Timing of PTLD diagnosis from transplant • Disease location (eg. organ involvement)

Donor choice: how to select a T cell product

	HLA profile of the tumour (patient)	A	B	C	DRB$_1$	DQB$_1$
		1101/2902	4403/3502	0401/1601	0701/1104	0401/0404

PTLD patient

The appropriate tabelecleucel lot for this patient must include: **1 shared HLA restriction** ✚ **≥ 1 other compatible HLA allele**

Tab-cel inventory

	A	B	C	DRB$_1$	DQB$_1$
T-cel lot A	0101/0101	0801/0801	0701/0701	0301/0301	0201/0201
T-cel lot B	1101/3303	0701/1503	0702/0210	0701/0401	0305/0906
T-cel lot C	1101/0201	3520/1513	0401/0701	0501/0601	0203/0205
T-cel lot D	1101/2402	3503/4002	0401/0202	0301/0604	0104/0403
T-cel lot E	0201/3004	4403/3701	0702/0701	0701/0202	0205/0201

Alleles in blue highlight the specific HLA restriction that mediates cytotoxicity

Donor choice: how to select a T cell product

HLA profile of the EBV+ PTLD (patient)

PTLD patient

	A	B	C	DRB$_1$	DQB$_1$
	● **1101**/2902	● **4403**/3502	▲ **0401**/1601	▲ **0701**/1104	0401/0404

The appropriate tabelecleucel lot for this patient must include:

1 shared HLA restriction ● + ≥ 1 other compatible HLA allele ▲
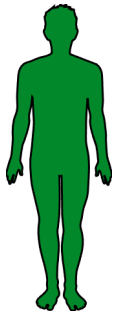
Tab-cel inventory

Alleles in blue highlight the specific HLA restriction that mediates cytotoxicity

	A	B	C	DRB$_1$	DQB$_1$
T-cel lot A	0101/0101	**0801/0801**	0701/0701	0301/0301	0201/0201
T-cel lot B	● **1101**/3303	0701/**1503**	0702/**0210** ▲0701/0401		0305/0906
T-cel lot C	● **1101**/0201 ▲3502/1513	▲**0401**/0701		0501/0601	0203/0205
T-cel lot D	● **1101/2402**	3503/4002 ▲**0401**/0202		0301/0604	0104/0403
T-cel lot E	0201/3004	● **4403**/3701	0702/0701 ▲0701/0202		0205/0201

T-cell lots that can be selected for this PTLD patient

Donor choice: what is needed to select the best T cell product

① Patient Information

T-cells must be specifically selected for each patient, based on their disease HLA profile

Patient information required to obtain a EBV T cell product for cell therapy:

- **Patient HLA genotyping*** in high resolution

- **Donor HLA genotyping*** in high resolution (highly recommended), or low resolution (donor ethnicity required)

- **Suspected origin of EBV+ PTLD disease** (i.e., donor or patient)

*HLA for alleles: A, B, C, DRB1, DQB1. High resolution: 4 digits (00:00).