GITMO
GRUPPO ITALIANO PER IL TRAPIANTO DI MIDOLLO OSSEO, CELLULE STAMINALI EMOPOIETICHE E TERAPIA CELLULARE

MALATTIA LINFOPROLIFERATIVA POST-TRAPIANTO

FAD SINCRONA
4 dicembre 2024

con il patrocinio di: S·I·T·O· SOCIETÀ ITALIANA DEI TRAPIANTI D'ORGANO E DI TESSUTI

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Disclosures

Honoraria and/or participation of advisory boards in the last 3years for

Incyte, Roche, EUSA Pharm, Takeda, Pierre Fabre

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Clinical case

Background

Age
33 years

Sex
Male

Medical history

1994 → **Diagnosed with congenital Becker's muscular dystrophy (aged 3)**
Family history of Becker's MD: Mother was a healthy carrier, brother had a less severe form of the disease

2012 → **Dilated cardiomyopathy**
→ Placed on the heart transplant list

2013 → **Heart transplant**
Immunosuppressed with cyclosporine and azathioprine

2023
- Paraplegia
- Restrictive dysventilatory lung deficit
- Mild dysphagia to liquids due to a reduction in tongue strength
- Mild cognitive problems
- Non-infectious complications

Before heart transplant | Post transplant | EBV+ PTLD diagnosis | First line treatment | Second line treatment

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Clinical case

10 years after heart transplantation he was admitted to ER

Presenting symptoms:

- abdominal pain, no B symptoms

Performance status:

- ECOG 4

Abdominal CT scan:

- overdistention of jejunal and first ileal loops
- invagination of ileal loops
- many enlarged lymph nodes up to 4 cm

Blood tests:

- Normal blood counts
- Normal renal and hepatic tests
- LDH: normal
- EBV: 30.891 U.I./ml
- CMV: neg

Laparotomy:

20 cm ileal resection + lymph nodes biopsy

Before transplant | **Post transplant** | EBV+ PTLD diagnosis | First line treatment | Second line treatment

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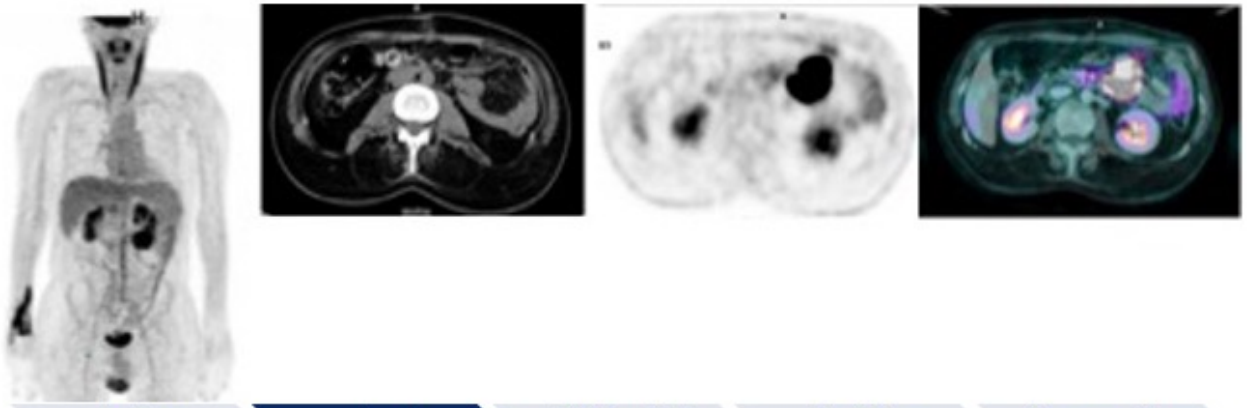
Clinical case

ceCT scan

- persistance of mesentheric lymph nodes up to 4 cm
- Kidneys of normal size with some focal bilateral hypodense alterations, suspected to be neoplastic

[^{18}F]FDG PET/CT scan

- marked accumulation of the tracer mainly anterior to the kidney (SUV max 36.7) where CT showed adenopaties



Before transplant | **Post transplant** | EBV+ PTLD diagnosis | First line treatment | Second line treatment

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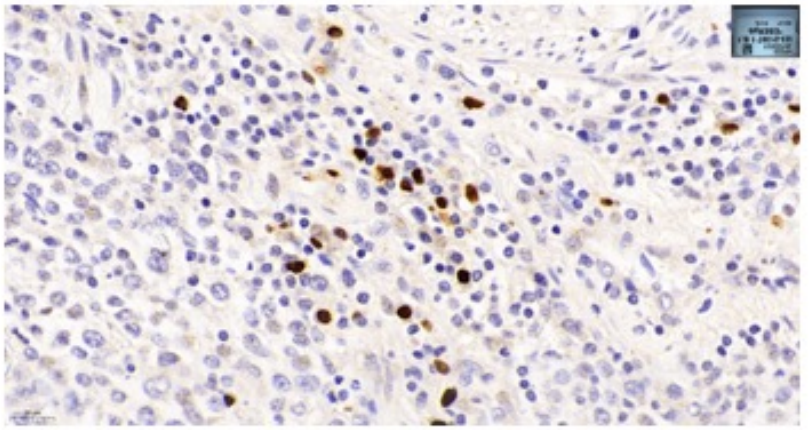
Histology

- Lymph nodes biopsy
- Diffuse large B cell lymphoma (DLBCL)
- GCB subtype (Bcl6+,CD10+/-, MUM 1-)
- EBER +
- FISH: non MYC rearranged



CC: DLBCL EBV driven after heart transplant, stage IV-A, IPI score Int/High

Before transplant → Post transplant → **EBV+ PTLD diagnosis** → First line treatment → Second line treatment

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First line treatment

Treatment details

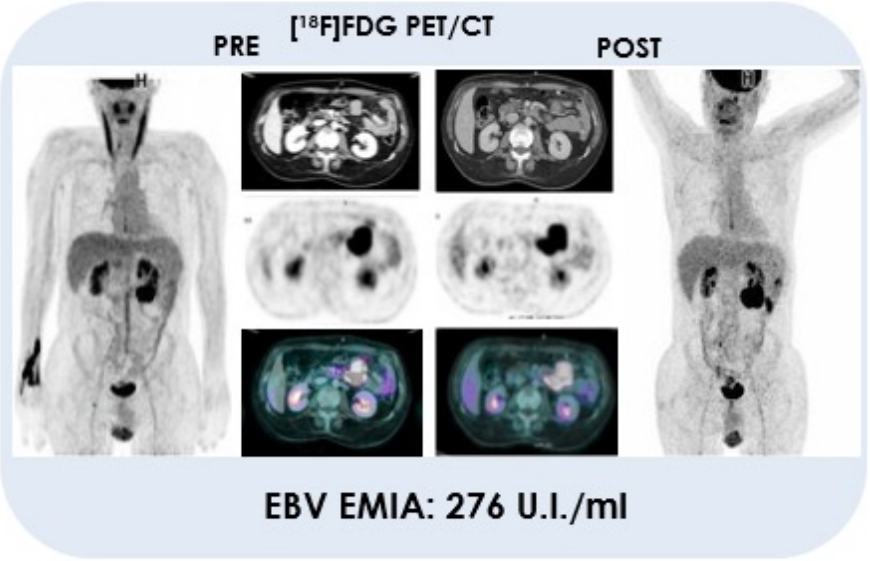
Rituximab monotherapy

Treatment duration

4 times once a week

Tolerability

no hematological/extra-hematological toxicities



EBV EMIA: 276 U.I./ml

Disease progression→ tabelecleucel

Before transplant | Post transplant | EBV+ PTLD diagnosis | **First line treatment** | Second line treatment

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Tabelecleucel is an allogeneic T-cell immunotherapy licensed for the treatment of relapsed/refractory EBV+ PTLD[1]

Tabelecleucel is indicated:[1]

As monotherapy for the treatment of adult and paediatric patients 2 years of age and older with relapsed or refractory EBV+ PTLD who have received at least one prior therapy

For SOT patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate

Tabelecleucel is licensed in Europe, including the UK and Switzerland in the outlined indication[1–3] and is not currently marketed in Italy.

An observational, real world Post-Authorisation Safety Study (PASS) called EBVOLVE is underway, data will be submitted to the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) upon completion.

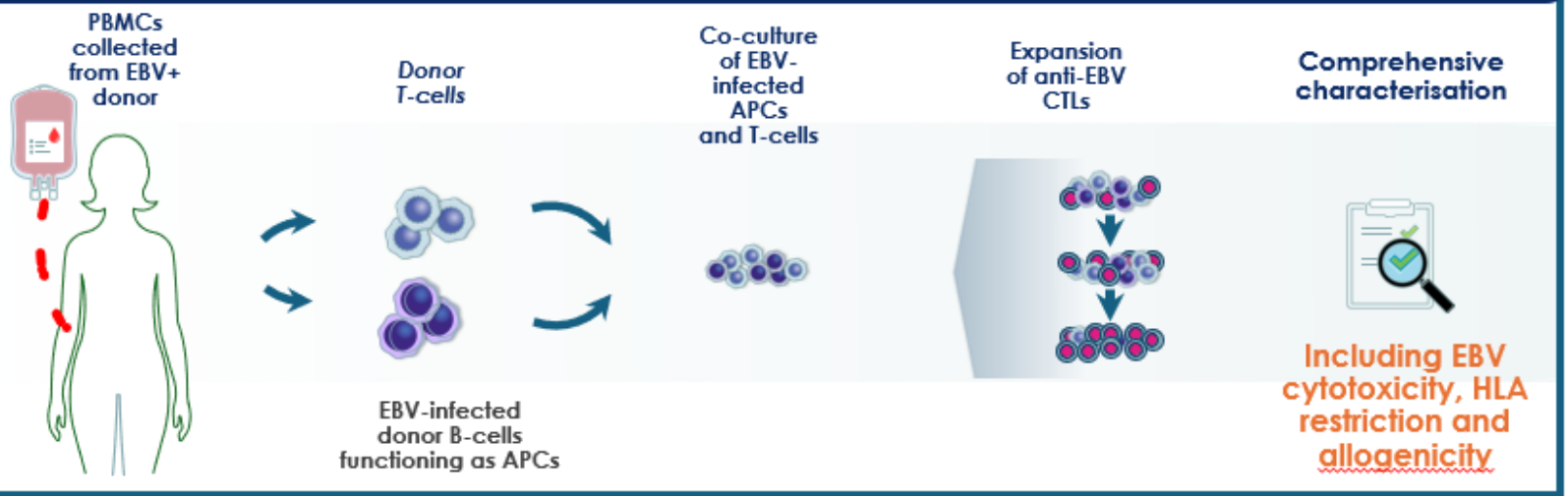
EBVOLVE

EBV+, Epstein Barr virus positive; EU, European Union; PTLD, post-transplant lymphoproliferative disorder; SOT, solid organ transplantation.

1. tabelecleucel EU SmPC; 2. tabelecleucel UK SmPC; 3. tabelecleucel CH SmPC

Manufacturing of tabelecleucel

Tabelecleucel is manufactured from healthy EBV+ donors with diverse HLA profiles to produce expanded CTL lots that are characterised by EBV-specific cytotoxicity and HLA restriction[1–3]



No genetic modification of T-cells

CD4/8, cluster of differentiation 4/8; DNA, deoxynucleic acid; EBV, Epstein-Barr virus; EBV+, Epstein Barr virus positive; FasL, fas ligand; HLA, human leukocyte antigen; PTLD, post-transplant lymphoproliferative disease; TCR, T-cell receptor.

1. Prockop S, et al. Biol Blood Marrow Transplant. 2018:24(3_suppl):S41–S42; 2. Prockop S, et al. J Clin Oncol. 2016:34(15_suppl):Abstract 3012; 3. tabelecleucel EU Summary of Product Characteristics.

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How to establish the suspected origin of EBV+ PTLD disease

The suspected origin of the disease is required to ensure an appropriate tabelecleucel lot is selected from the biobank. This is based on HLA restriction matched to the patient's disease and overall HLA allele profile

BEST OPTION = obtain high resolution HLA typing of the disease biopsy

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

If the patient and donor gender are matched:

Use clinical assumptions:

- Patient/donor EBV serostatus before transplant
- Timing of PTLD diagnosis from transplant
- Disease location (eg. organ involvement

If the patient and donor gender are mis-matched:

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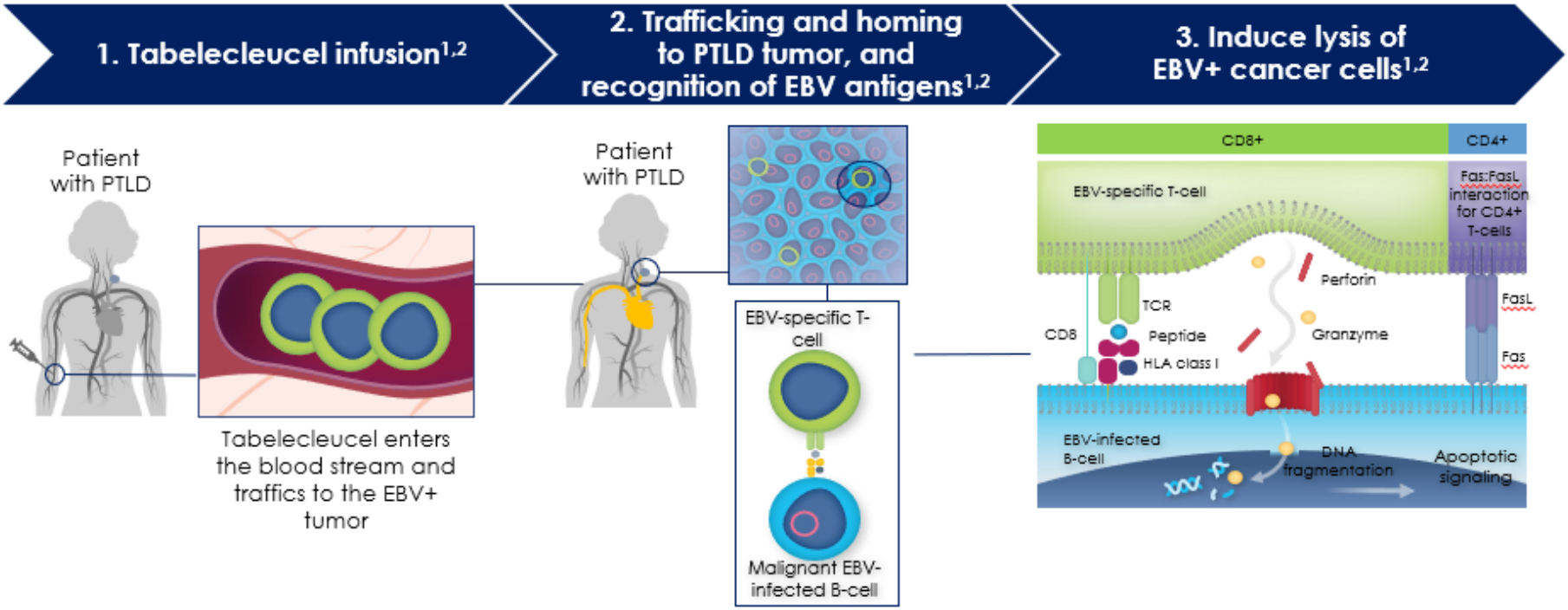
Tabelecleucel mechanism of action



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1. Prockop S, et al. Biol Blood Marrow Transplant. 2018:24(3_suppl):341–342; 2. Prockop S, et al. J Clin Oncol. 2016:34(15_suppl):Abstract 3012.

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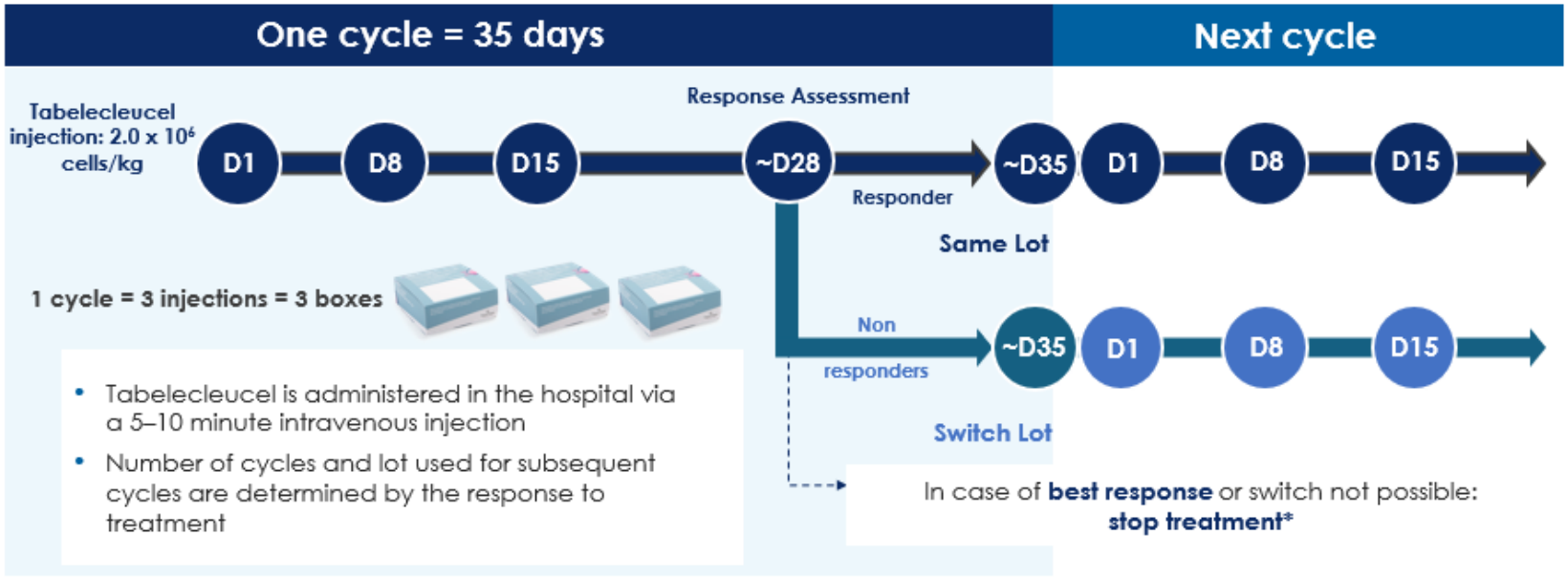
Tabelecleucel administration schedule[1]



- Tabelecleucel is administered in the hospital via a 5–10 minute intravenous injection
- Number of cycles and lot used for subsequent cycles are determined by the response to treatment

*Best response: two consecutive CRs or three consecutive PRs.[1]

CR, complete response; HLA, human leukocyte antigen; PR, partial response.

1. tabelecleucel EU SmPC

Tabelecleucel treatment algorithm

The Switch and Stop Criteria are determined by the response to treatment[1]

Response observed*	Action
CR	Administer another cycle with the same HLA restriction. If the patient achieves 2 consecutive CRs (maximal response), no further treatment with tabelecleucel is recommended
PR	Administer another cycle with the same HLA restriction. If the patient achieves 3 consecutive PRs (maximal response), no further treatment with tabelecleucel is recommended
SD	Administer another cycle with the same HLA restriction. If the subsequent cycle results in a second SD, administer tabelecleucel with a different HLA restriction
PD	Administer another cycle with a different HLA restriction
IR	Administer another cycle with the same HLA restriction. If the subsequent cycle results in a second IR, administer tabelecleucel with a different HLA restriction

*CR at the end of a cycle, followed by PR or other response at any subsequent cycle, is considered PD.

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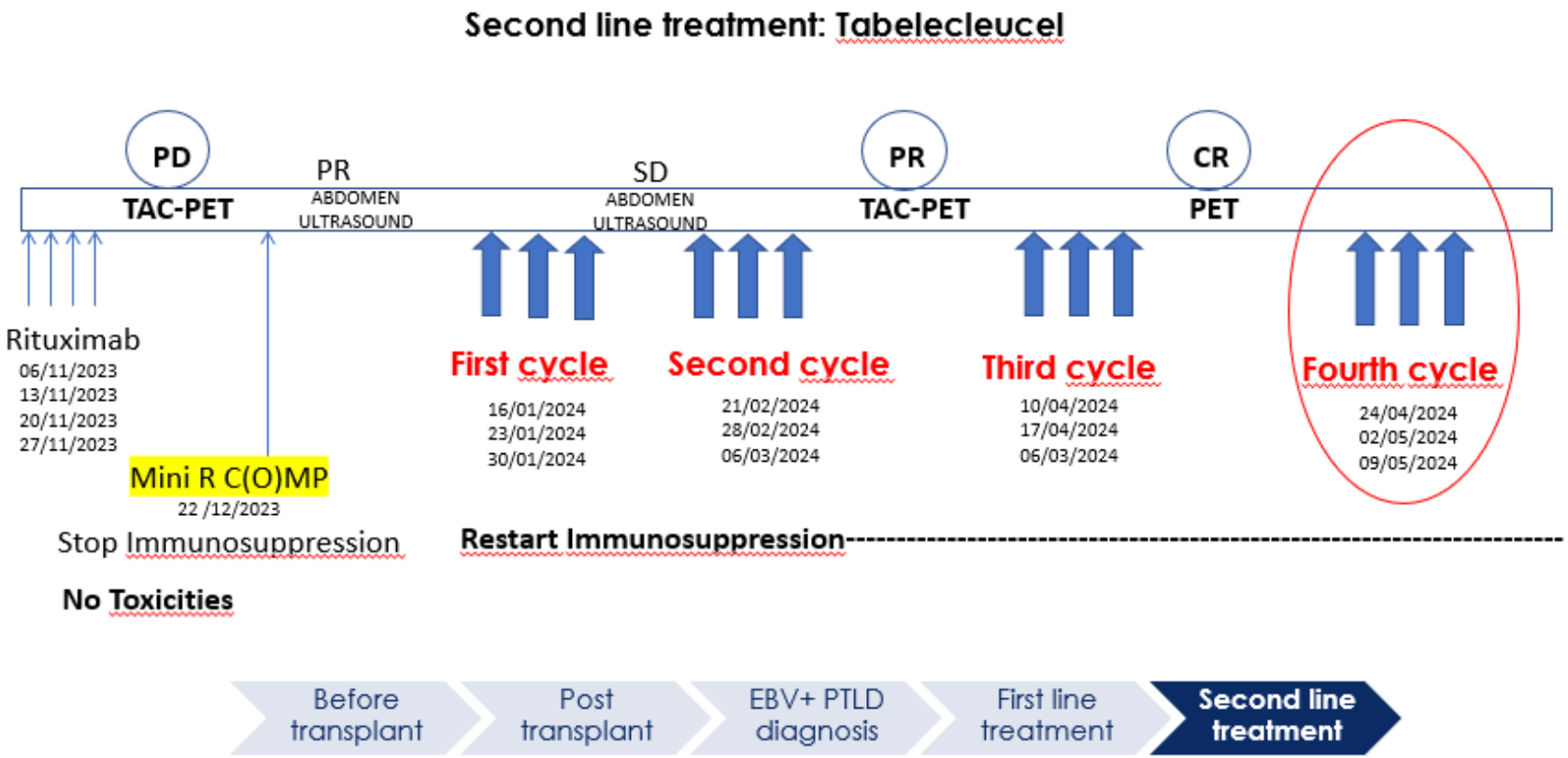

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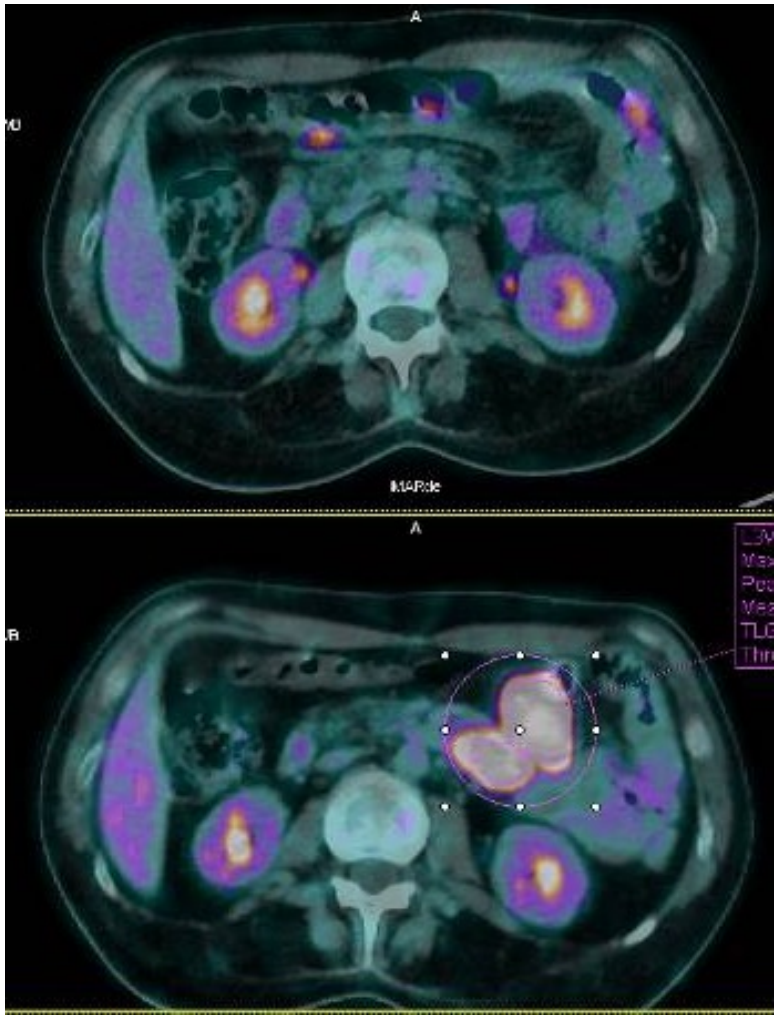

TC-PET response
After the third cycle of Tabelecleucel

TC-PET after Rituximab