CORSO EDUCAZIONALE

GRUPPO LINFOMI IN PAZIENTI CON IMMUNODEFICIT

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EBV-driven lymphoproliferative disorders: il ruolo dell'immunoterapia tabelecleucel nei PTLD

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Disclosures of Chiara Consoli

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

PTLD: intro

Post-transplant lymphoproliferative disorders (PTLD) → rare and heterogeneous complications occurring either after solid organ (SOT) or hematopoietic stem cell (HSCT) transplantation due to the immunosuppressive state

Classification: ICC & WHO 2016* → WHO-HAEM5 2022**: Lymphomas arising in immune deficiency/dysregulation

Clinical presentation: heterogeneity

* Blood. 2016 Mar 15;127(20):2375–2390. **Leukemia. 2022 Jul;36(7):1720-1748

PTLD: diagnosis

- **Quantitative determination of EBV-DNA-emia**
- Imaging: CT scan, PET scan, MRI
- **Biopsy** of the lymph node and/or other suspected sites ± endoscopy (if GI symptoms present)
- Histological examination:
  - Detection of viral antigens or in situ hybridisation for EBV-encoded RNA transcripts
  - Immunohistochemistry
  - Flow cytometry for B-cell, T-cell, and plasma cell lineage-specific antigens

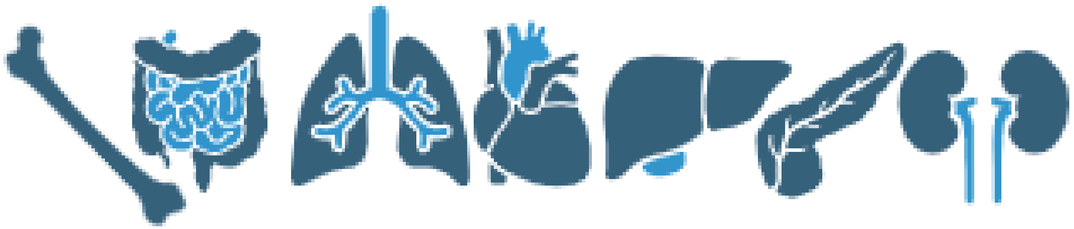
PTLD: epidemiology and risk factors

The overall incidence is about 1% at 10 years:
- Post SOT: 1-25% (10-15%)
- Post HSCT: 1-10% (2%)

Latency (24 m):
- Early PTLD
- Late PTLD

EBV:
- related
- non related

Risk factors:
- Type of transplant
- EBV status and EBV serology donor/recipient mismatch
- HSCT characteristics: ATG use, mismatch donor, severe GVHD
- Young and older recipient age
- Duration and type of immunosuppression



PTLD: treatment

RESTORING T-CELL FUNCTION

- Reduction of immune suppression (RIS)
- **Adoptive immunotherapy (DLI, EBV+ CTLs, CAR-Ts)**

REDUCING TUMOR MASS

- Local therapy (surgery/radiation)
- Rituximab and/or chemotherapy
- Novel therapy (Ab anti-CD30, BTKi)

DECREASING EBV VIRAL LOAD

- Inducers of lytic cycle
- Antiviral agents

PTLD: treatment

RESTORING T-CELL FUNCTION

REDUCING TUMOR MASS

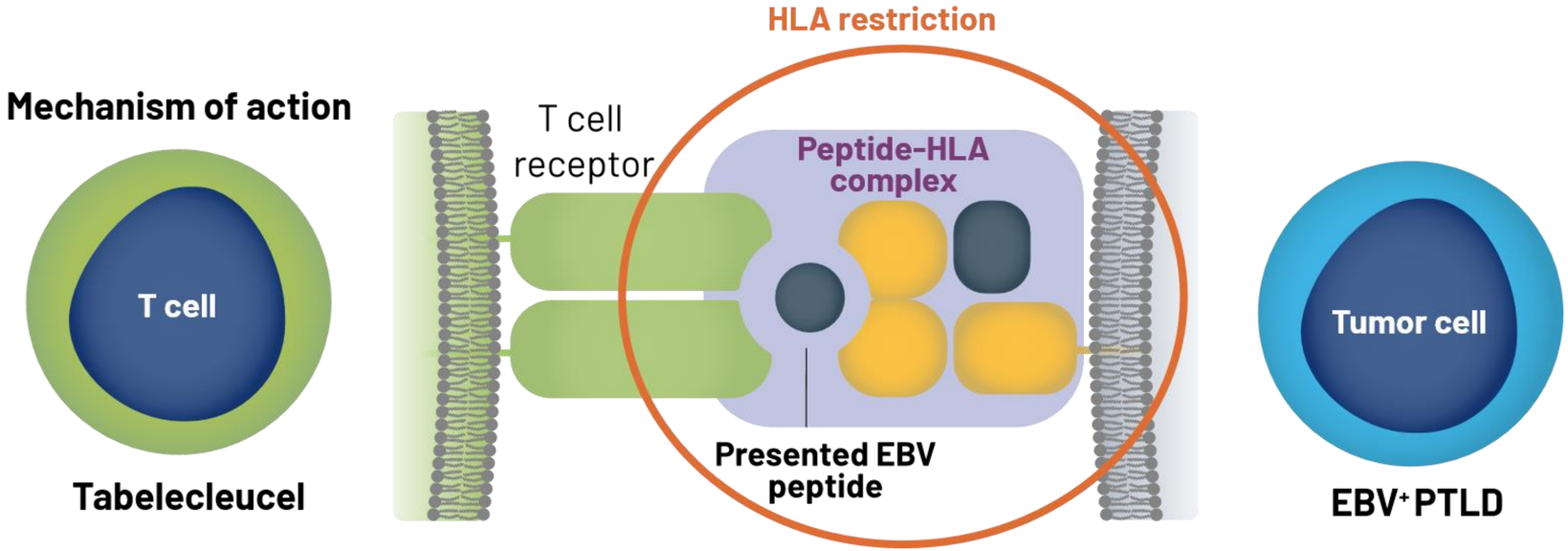
DECREASING EBV VIRAL LOAD

- Reduction of immune suppression (RIS)
- **Adoptive immunotherapy (DLI, EBV+ CTLs, CAR-Ts)**

Tabelecleucel: available as monotherapy in adult and pediatric (>2 years) patients with **R/R EBV-related PTLD**

Tabelecleucel: definition

Tabelecleucel is an **off-the-shelf**, non-genetically modified, **allogeneic**, EBV-specific T cell immunotherapy that targets and eliminates EBV-infected cells in an **HLA-restricted manner**.



Manufacturing: Derived from unrelated third-party donors and cryo-preserved in a bio-bank adapted to cover multiple HLA profiles.

Product selection: Based on the characterization of **HLA restriction** and donor: recipient compatibility.

Administration: No lymphodepletion or pre-medication, 1-hour post-injection monitoring, inpatient or outpatient administration.

Tabelecleucel: scheda tecnica

4.1 Indicazioni terapeutiche

Ebvallo è indicato in monoterapia per il trattamento di pazienti adulti e pediatrici di età pari o superiore a 2 anni con malattia linfoproliferativa post-trapianto positiva al virus di Epstein-Barr (EBV^+ PTLD) recidivata o refrattaria, che hanno ricevuto almeno una terapia precedente. Per i pazienti sottoposti a trapianto di organo solido, la terapia precedente include la chemioterapia, a meno che la chemioterapia non risulti inappropriata.

Posologia

Il trattamento consiste in dosi multiple per iniezione contenenti una dispersione di cellule T vitali in uno o più flaconcini.
La dose raccomandata di Ebvallo contiene 2×10^6 cellule T vitali per kg di peso corporeo del paziente.

EVENTI AVVERSI
Sindrome da tumor flare (TFR, 1%) = impressivo e doloroso aumento delle dimensioni del tumore + possibili diturbi da compressione; dd con la progressione di malattia (rapido aumento dell'LDH di breve durata con conseguente calo dell'LDH stesso)
Sindrome da rilascio di citochine (CRS) (febbre, nausea, vomito, brividi, confusione, capogiro, aumento del battito cardiaco, diminuzione PAO e diminuzione dell'ossigenazione dei tessuti)
Sindrome di neurotossicità associata a cellule effettrici immunitarie (ICANS) = riduzione del livello di coscienza, confusione, crisi convulsive ed edema cerebrale
Reazioni correlate alle infusioni = piressia e dolore toracico non cardiaco Reazioni d'ipersensibilità (inclusa anafilassi)
Malattia del trapianto contro l'ospite (GvHD, 4,9%) o rigetto del trapianto (correlazione con la diminuzione/sospensione delle terapie immunosoppressive per il trattamento della PTLD o con un'azione diretta di Ebvallo)
Trasmissione di agenti infettivi (nonostante i lotti siano testati per HBV/HCV/HIV/micoplasma/CMV)

Il medicinale viene somministrato per più cicli di 35 giorni, durante i quali i pazienti ricevono Ebvallo nei giorni 1, 8 e 15, seguiti dall'osservazione fino al giorno 35. La risposta viene valutata approssimativamente al giorno 28.

Il numero di cicli del medicinale da somministrare è determinato dalla risposta al trattamento mostrata nella Tabella 1. Se non si ottiene una risposta completa o parziale, i pazienti possono passare ad un lotto di Ebvallo con una restrizione HLA diversa (fino a 4 restrizioni differenti) selezionato dalla banca cellulare disponibile.

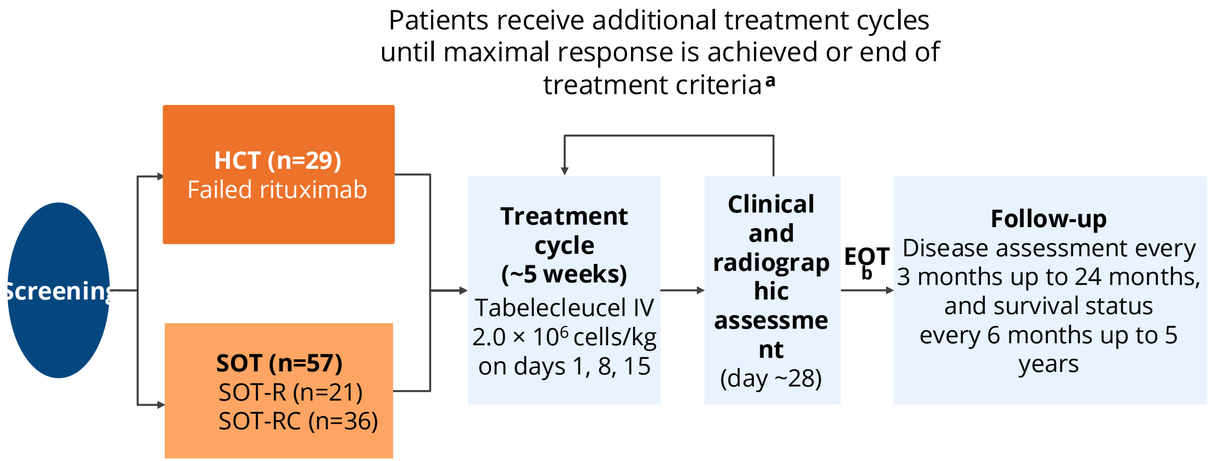
Tabella 1: Algoritmo di trattamento

Risposta osservata[a]	Azione
Risposta Completa (CR)	Somministrare un altro ciclo di Ebvallo con la stessa restrizione HLA. Se il paziente ottiene 2 CR consecutive (risposta massima), non è raccomandato alcun ulteriore trattamento con Ebvallo.
Risposta parziale (PR)	Somministrare un altro ciclo di Ebvallo con la stessa restrizione HLA. Se il paziente ottiene 3 PR consecutive (risposta massima), non è raccomandato alcun ulteriore trattamento con Ebvallo.
Malattia stabile (SD)	Somministrare un altro ciclo di Ebvallo con la stessa restrizione HLA. Se il ciclo successivo determina una seconda SD, somministrare Ebvallo con una restrizione HLA diversa.
Progressione di malattia (PD)	Somministrare un altro ciclo di Ebvallo con una restrizione HLA diversa.
Risposta indeterminata (IR)	Somministrare un altro ciclo di Ebvallo con la stessa restrizione HLA. Se il ciclo successivo determina una seconda IR, somministrare Ebvallo con una restrizione HLA diversa.

[a] La risposta completa alla fine di un ciclo seguita da una risposta parziale o altra risposta a qualsiasi ciclo successivo è considerata progressione di malattia.

Phase 3 ALLELE study

A global, multicentre, open-label Phase 3 study of tabelecleucel after failure of rituximab ± chemotherapy in patients with EBV+ PTLD following allogeneic HCT or SOT[1,2,3]
It demonstrated an overall response rate (ORR) of 51%, with a complete remission (CR) rate of 28% and an overall survival (OS) of 84% at 12 months for responding patients, without significant toxicities.



Key eligibility criteria:
- Prior allogeneic HCT or SOT
- Biopsy-proven EBV+ PTLD
- Previous RTX or RTX-CT[c] failure
- ECOG PS ≤3

Primary endpoint: ORR[d]

Key secondary endpoints:
- TTR and time to best response
- OS in responders vs non-responders

[a]Patients may receive up to 4 (in HCT group) or 2 (in SOT group) different HLA restrictions. [b]Evaluated by independent review. [c]Including R-CHOP. [d]Defined as any of the following: maximal response achieved; unacceptable toxicity; initiation of non-protocol therapy; or failure of up to 4 (in HCT group) or 2 (in SOT group) different HLA restrictions; CT, chemotherapy; EBV+, Epstein–Barr virus-positive; ECOG PS, Eastern Cooperative Oncology Group performance status; HCT, hematopoietic cell transplant; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; RTX, rituximab; SOT, solid organ transplant; TTR, time to response.

1.Mahadeo KM, et al. Lancet Oncol 2024. 2 Ghobadi A et al ASH 2024 3. Nikiforow S et al ASH 2025
EBV+ PTLD, Epstein-Barr virus-associated post-transplant lymphoproliferative disease; HCT, hematopoietic cell transplant; HLA, human leukocyte antigen; SOT, solid organ transplant.

EAP 902 (ATA129-EAP-902): observational study

Characteristic	EBV+ PTLD post-allogeneic HCT (n=10)	EBV+ PTLD post-SOT (n=17)	All (N=27)
Median (range) age, years*	52 (6–64)	48 (12–74)	49 (6–74)
Male, n (%)	5 (50)	7 (41.2)	12 (44.4)
ECOG PS ≥ 2 or Lansky PS ≤ 60, n (%)	2 (20)	4 (23.5)	6 (22.2)
LDH at baseline, n (%)			
Normal	3 (30%)	3 (17.6)	6 (22.2)
Above normal	6 (60%)	14 (82.4)	20 (74.1)
Missing	1 (10%)		1 (3.7)
Median (range) prior lines of therapy	1.5 (1–3)	1 (0–4)	1 (0–4)
Chemotherapy	5 (50%)	10 (58.8%)	15 (55.6%)
Rituximab	10 (100%)	14 (82.4%)	24 (88.9%)
Median rituximab doses (range)	3.5 (1–10)	6 (4–9)	6 (1–10)
Time from transplant to initial diagnosis (n, %)			
Within 1 year	9 (90)	6 (35.3)	15 (55.6)
1 year or more	1 (10)	11 (64.7)	12 (44.4)
Solid organ transplant type, n (%)			
Kidney	--	2 (11.8)	--
Lung	--	6 (35.3)	--
Heart	--	4 (23.5)	--
Intestine	--	2 (11.8)	--
Liver	--	5 (29.4)	--
Pancreas	--	2 (11.8)	--
Small bowel	--	2 (11.8)	--
Multivisceral transplantation	--	3 (17.6)	--

Study population[1]

- 27 patients with EBV+ PTLD for whom tabelecleucel expanded access had been requested consented to secondary use of data

- 24/27 patients with EBV+ PTLD received ≥1 dose of tabelecleucel, including 4 patients with EBV+ primary central nervous system (PCNS) PTLD

EBV+, Epstein-Barr virus positive; ECOG PS, Eastern Cooperative Oncology Group Performance Score; HCT, haematopoietic cell transplant; LDH, lactate dehydrogenase; PS, Performance Score; PTLD, post-transplant lymphoproliferative disorder; R/R, relapsed/refractory; SOT, solid organ transplant.

1. Choquet S, et al. ASCO 2023; Abstract #7521.

EAP 902 (ATA129-EAP-902): results

Efficacy outcomes in patients with EBV+ PTLD who were treated with tabelecleucel[1]

	EBV+ PTLD post-allogeneic HCT (n=8)	EBV+ PTLD post-SOT (n=16)	All (N=24)
Responders*, n (%)	7 (87.5)	9 (56.3)	16 (66.7)
95% CI	47.3, 99.7	29.9, 80.2	44.7, 84.4
CR, n (%)	4 (50.0)	4 (25.0)	8 (33.3)
PR, n (%)	3 (37.5)	5 (31.3)	8 (33.3)
SD, n (%)	0	2 (12.5)	2 (8.3)
PD, n (%)	1 (12.5)	5 (31.3)	6 (25.0)
Median TTR, months (range)	1.0 (0.9–1.6)	1.0 (0.8–2.2)	1.0 (0.8–2.2)

Efficacy outcomes in patients with EBV+ PCNS PTLD who were treated with tabelecleucel[1]

	EBV+ PTLD post-allogeneic HCT (n=2)	EBV+ PTLD post-SOT (n=2)	All (N=4)
Responders*, n (%)	2 (100)	1 (50.0)	3 (75.0)
95% CI	15.8, 100	1.3, 98.7	19.4, 99.4
CR, n (%)	0	1 (50.0)	1 (25.0)
PR, n (%)	2 (100)	0	2 (50.0)
SD, n (%)	0	0	0
PD, n (%)	0	1 (50.0)	1 (25.0)

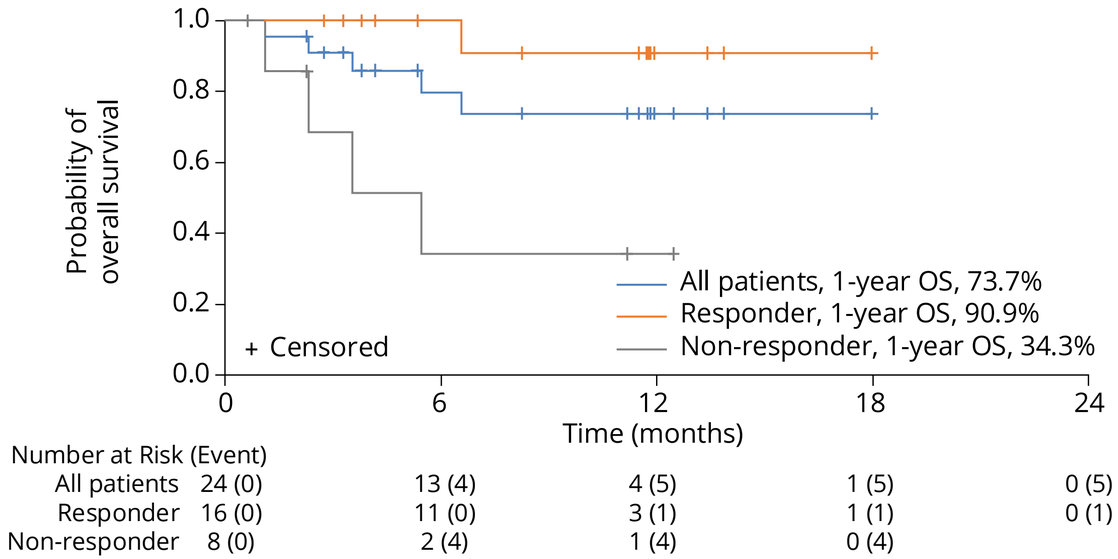
*Best overall response as assessed by the treating physician.
Based on response and availability of product, patients could switch to lots with different HLA restriction match.
CI, confidence interval; CR, complete response; EBV+, Epstein-Barr virus positive; HCT, haematopoietic cell transplant; PCNS, primary central nervous system; PD, progressive disease; PR, partial response; PTLD, post-transplant lymphoproliferative disorder; SD, stable disease; SOT, solid organ transplant; TTR, time to response.
1. Choquet S, et al. ASCO 2023; Abstract #7521.

EAP 902 (ATA129-EAP-902): survival

1-year OS Kaplan–Meier estimates[1]

	Allogeneic HCT (n=8)	SOT (n=16)	All (N=24)
1-year OS rate, % (95% CI)	87.5 (38.7, 98.1)	66.5 (32.7, 86.2)	73.7 (47.3, 88.3)
Responders, n	7	9	16
1-year OS rate, % (95% CI)	100	83.3 (27.3, 97.5)	90.9 (50.8, 98.7)
Non-responders, n	1	7	8
1-year OS rate, % (95% CI)	0	41.7 (5.6, 76.7)	34.3 (4.8, 68.5)
Median follow-up, months (range)	9.9 (2.4–13.9)	6.0 (0.7–18.0)	7.4 (0.7–18.0)

Kaplan–Meier plot of OS: Responder vs non-responder[1]



CI, confidence interval; HCT, haemopoietic cell transplant; OS, overall survival; SOT, solid organ transplant.

1. Choquet S, et al. ASCO 2023; Abstract #7521.

Tabelecleucel: European experience

Patient Requests of the 100 first treated patients *(starting date Feb'23)*

163

Formal requests in platform

100

Treated patients

1- Scope: Data from European Union countries only from Feb'23
HCT, Hematopoietic Cells Transplantation; SOT, Solid Organ Transplantation

Lot Match

92%

Match rate: % of patients with at least 1 lot proposed (data 2024-2025)

1,09

Lot selection time: average time in days to perform lot selection and inform medical team

Case and delivery Timing

26

Case time: average time in days from 1st contact to product received at hospital pharmacy

5

Minimal Case time: shorter time in days from 1st contact to product received at hospital pharmacy

3,8

Delivery time: average in days from order to product received at hospital pharmacy

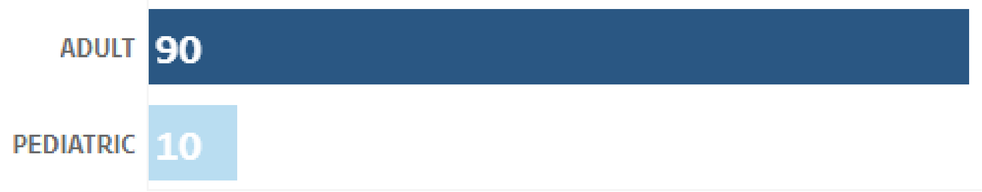
Source: Pierre Fabre Laboratories – Internal data

Tabelecleucel: European experience

Details of the first patients treated

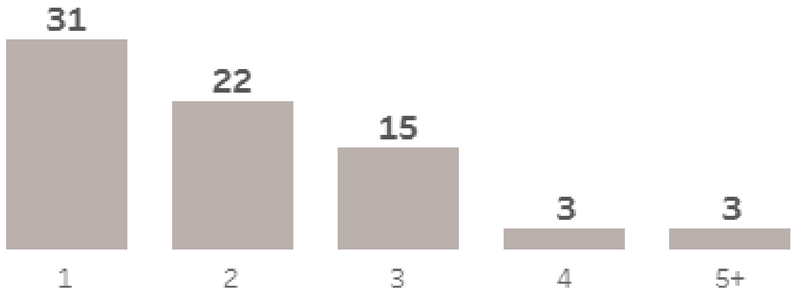
Typology of transplant

Adult / Pediatric patient split



Cycles

Average number of **CYCLES** (initiated) per patient :



Number of cycles received by patients
(including ongoing treatment, including only HCT/SOT until July 2025)

Source: Pierre Fabre Laboratories – Internal data

Tabelecleucel: Italian experience

Compassionate Use

Open from 02/2024 to 03/2025

14 patients treated

Commercial Use

From 03/2025

14 patients treated

Real-life multicenter Italian experience with tabelecleucel

13 Italian centers

27 patients

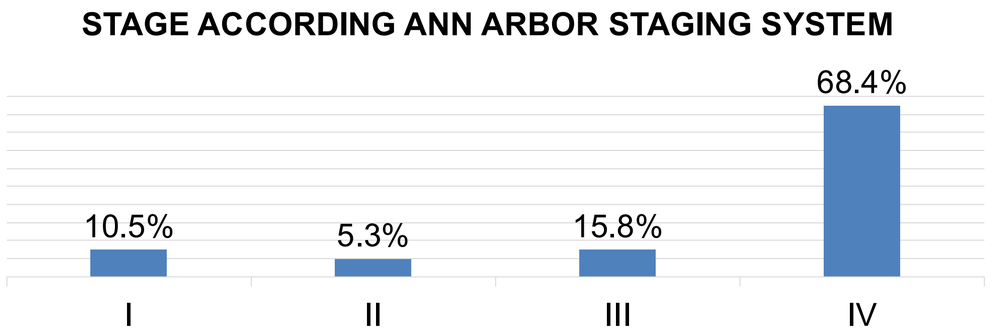
From January 2024 to February 2026

- 15 as compassionate use
- 5 as commercial use
- 4 unknown
- 3 not treated

Unpublished data

Real-life multicenter Italian experience with tabelecleucel

Demographics	Italy (N = 27)	ALLELE* (N = 75)
Age, median (range), years	62 (12–81)	44.4 (2.7–81.5)
Male sex, n (%)	16 (59.3)	44 (58.7)
ECOG PS score, median (range)	1 (0–4)	1 (0–3)
ECOG PS score ≥2, n (%)	10 (37.0)	18 (26.5)
Transplant characteristics		
Transplant type, n (%)		
Kidney	1 (3.7)	14 (28.6)
Heart	6 (22.2)	12 (24.5)
Lung	2 (7.4)	9 (18.4)
Liver	3 (11.1)	4 (8.2)
Multivisceral	3 (11.1)	10 (20.4)
HSCT	12 (44.4)	26 (34.6.4)
Age at transplant, median (range), years	59 (9-75)	



Disease characteristics	Italy (N = 27)	ALLELE* (N = 75)
Age at diagnosis, median (range), years	61 (12-76)	
Extranodal disease at screening, n (%)	22 (81.5)	56 (74.7)
Nodal disease at screening, n (%)	18 (66.7)	
High resolution HLA typing of PTLD, n (%)	12 (44.4)	
PTLD-adapted prognostic index, n (%)[c]	N=18	N = 68
High risk	10 (55.6)	29 (42.6) + 34 (50.0)
Unknown/not applicable	8	1 (1.5)
Monomorphic type, n (%)	19/22 (86.4)	
PTLD morphology, n (%)	N=24	N = 75
Diffuse large B-cell lymphoma	12 (50)	52 (69.3)
Plasmablastic lymphoma	0 (0)	3 (4.0)
T-cell disorders	3 (12.5)	
Other	9 (37.5)	19 (25.3)
Latency: median (range) time, months		
From transplant to EBV^{+} PTLD diagnosis	12 (1-227)	–
Early PTLD, n (%)	16 (70.4)	
Late PTLD, n (%)	11 (40.7)	

Unpublished data

Real-life multicenter Italian experience with tabelecleucel

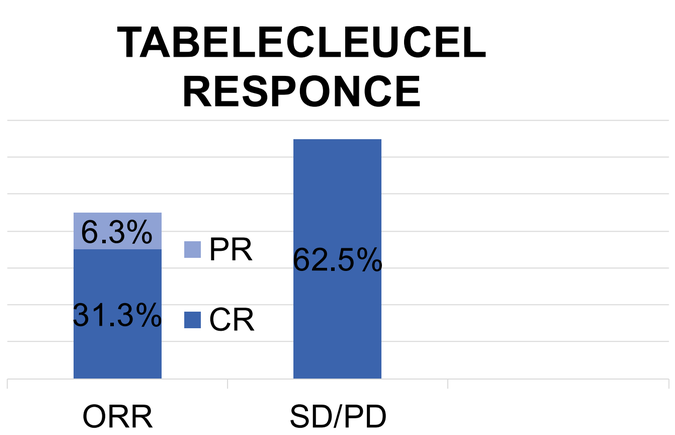
Treatment and prior therapies	Italy	ALLELE* (N=75)
First line rituximab monotherapy, n (%)	21 (77.8)	
Prior rituximab monotherapy, n (%)	22 (81.5)	65 (86.7)
Prior chemotherapy, n (%)	1 (4.3)	35 (46.7)
Prior chemotherapy in combination with rituximab, n (%)	8 (29.6)	28 (37.3)
Median (range) time, months		
From EBV⁺ PTLD diagnosis to first tabelecleucel administration	95 days (12-4723) 3 months (0–155)	4.6 (0.6–190.5)
From EBV⁺ PTLD relapse to first tabelecleucel administration	33 days (7-78)	

Tabelecleucel exposure	Italy (N=24)	ALLELE (N = 75)
Number of tabelecleucel cycles, median (range)	2 (1–8)	2 (1–6)
Number of tabelecleucel infusions, median (range)	4.5 (1–24)	6 (1–18)
Location of infusion administration, n (%)		
Inpatient, n (%)	10/24 (41.7)	175 (33.1)
Outpatient, n (%)	10/24 (41.7)	353 (66.9)
Unknown, n (%)	4/24 (16.7)	
Number of lots received, n (%)	**N=24**	
1	22 (90.9)	49 (65.3)
2	1 (4.2)	23 (30.7)
3	1 (4.2)	3 (4.0)
Adverse events, n (%)	2 (8.3)	8 (9.3)

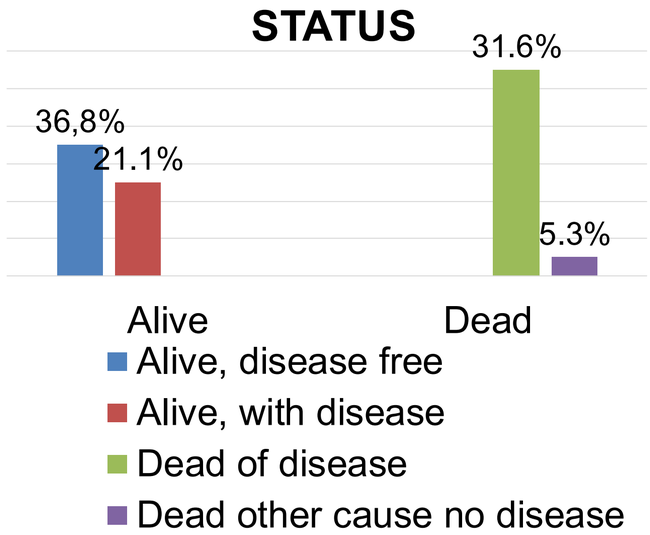
Unpublished data

Real-life multicenter Italian experience with tabelecleucel

Tabelecleucel response and follow-up	
Response	**N=24**
Overall response rate (ORR), n (%)	9/24 (37.5)
Complete response (CR), n (%)	7 (29.2)
Partial response (PR), n (%)	2 (8.3)
Stable disease (SD) or no response (NR) or progression disease (PD), n (%)	15 (62.5)
Status	**N=24**
Dead, n (%)	12 (50)
Alive, n (%)	12 (50)
Alive, disease free, n (%)	7 (29.2)
Alive, with disease, n (%)	5 (20.8)
Dead of disease, n (%)	11 (45.8)
Dead other cause and disease, n (%)	0 (0)
Dead, other cause no disease, n (%)	1 (4.2)
Dead, allograft rejection, n (%)	0
Dead, reason and disease status unknown, n (%)	0
Overall survival, median (range), months	8 (1-159)
Median follow-up, median (range), months	5 (1-25)



ORR: overall response rate; CR: complete responce; PR: partial responce; SD; stable disease; PD progressive disease

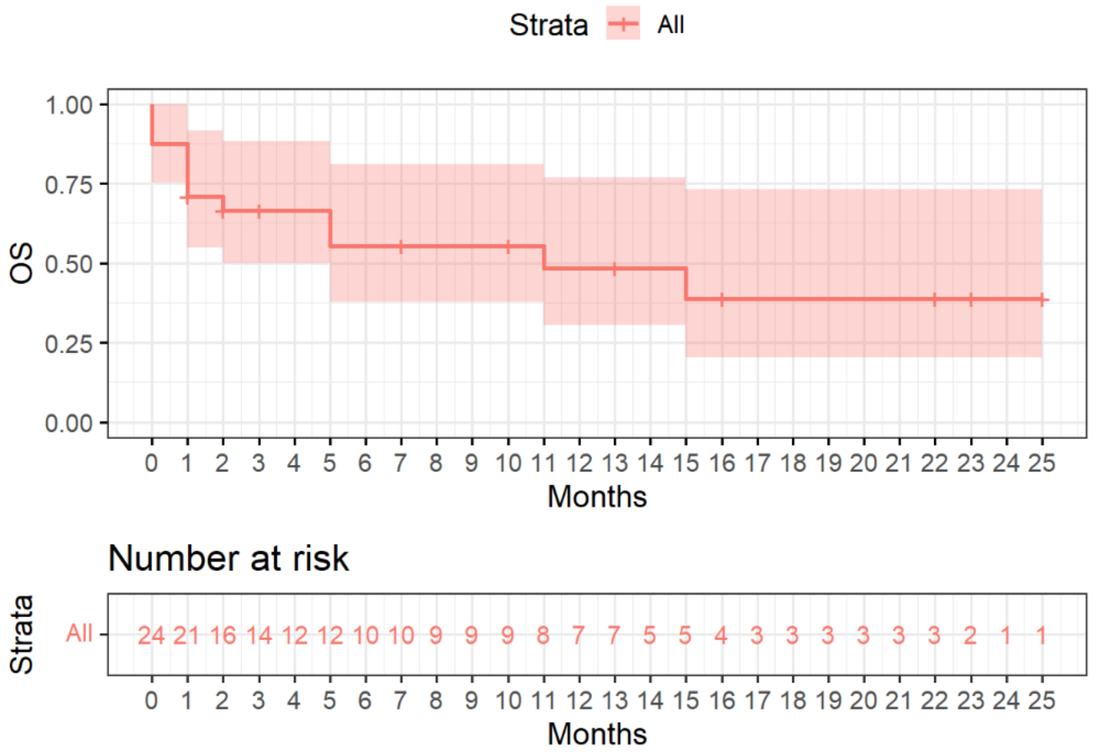


- The ORR was 37.5%, with 7 of 24 treated cases (29.2%) achieving CR.
- In the subcohort of SOT recipients, ORR was 46%, with 5 of 13 patients (39%) achieving CR; while, among HSCT recipients ORR was 27%, with 2 of 11 achieving CR.
- After a median follow-up of 5 months, 12 of 27 patients were alive.

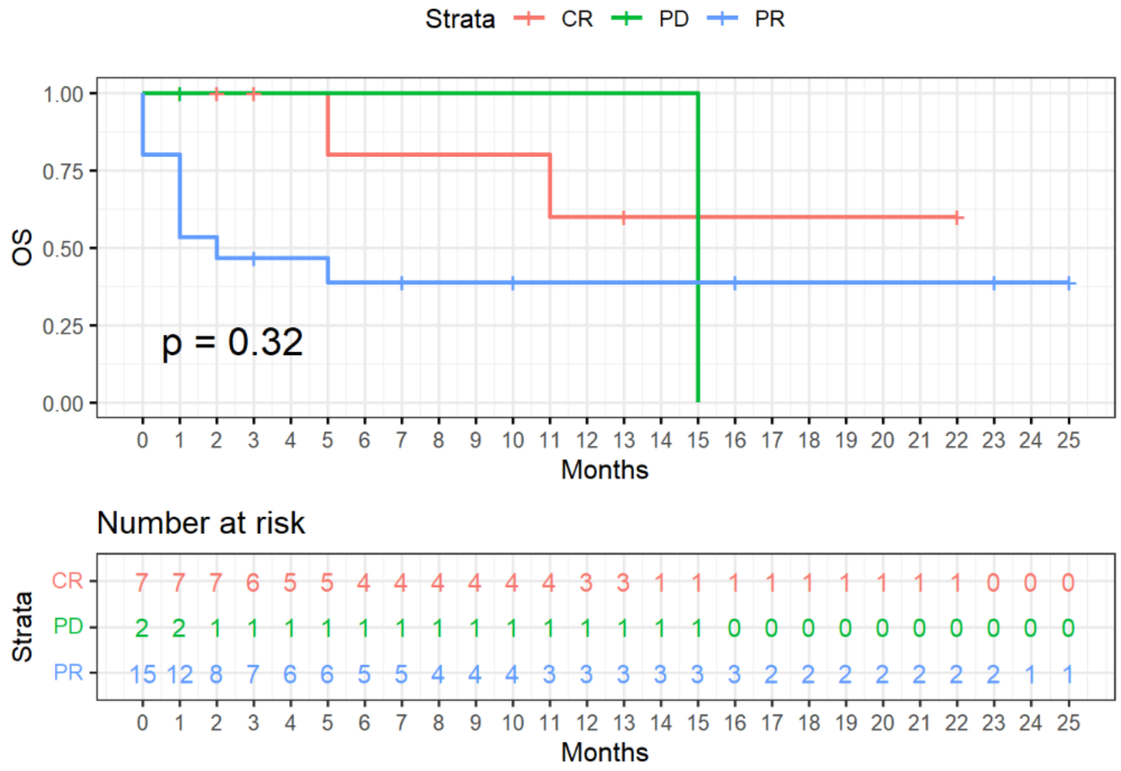
Unpublished data

Real-life multicenter Italian experience with tabelecleucel

Kaplan–Meier survival curve of the overall study population



Kaplan–Meier survival curves stratified according to response to cellular therapy



Conclusion

- PTLD are **rare** and **heterogenous** diseases: multidisciplinary approach
- Tabelecleucel **easily available** in the real world setting and **safe**
- Preliminary experience supports the efficacy and safety of tabelecleucel, consistent with the results of the ALLELE trial, expecially in SOT.
- **Early detection** of potential candidates for tabelecleucel treatment
- **Longer follow-up** and larger cohorts are needed to better define outcomes, particularly in HSCT recipients.
- Additional studies are warranted to define prognostic factors influencing response to tabelecleucel.

GRAZIE PER L'ATTENZIONE

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