Sistema Socio Sanitario

Regione Lombardia

Fondazione IRCCS Policlinico San Matteo

ATS Pavia

GRAND ROUNDS CLINICI DEL MERCOLEDÌ

con il Policlinico San Matteo

Aula Magna "C. Golgi" & WEBINAR

Trapianto allogenico: attualità e sfide future

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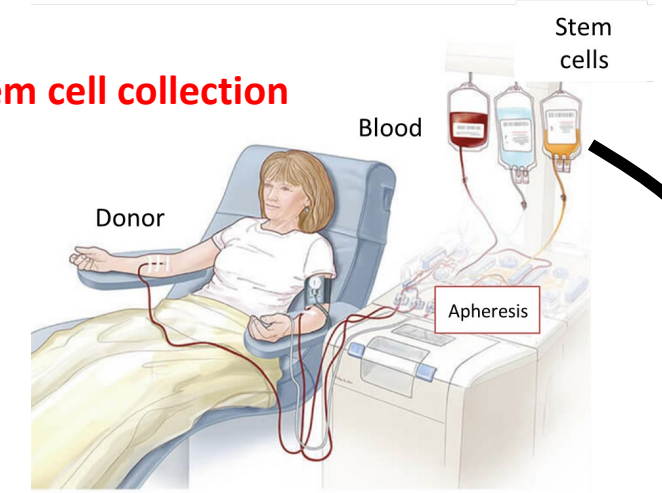
Division of Hematology
Fondazione IRCCS Policlinico San Matteo
Pavia

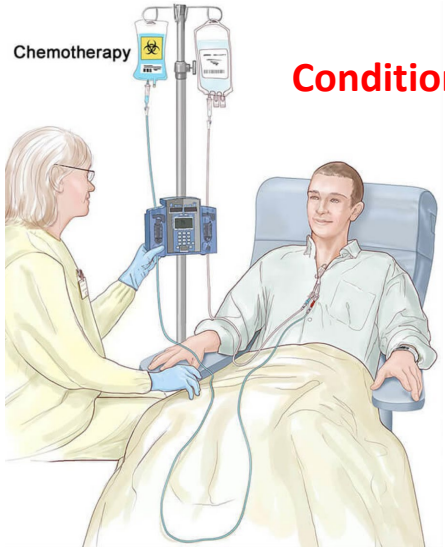
Pavia, 27/3/2024

Principles of allogeneic stem cell transplantation

Stem cell collection



Role of conditioning
1) Elimination of neoplastic cells
2) Creating "space" for donor cells
3) Avoid graft rejection



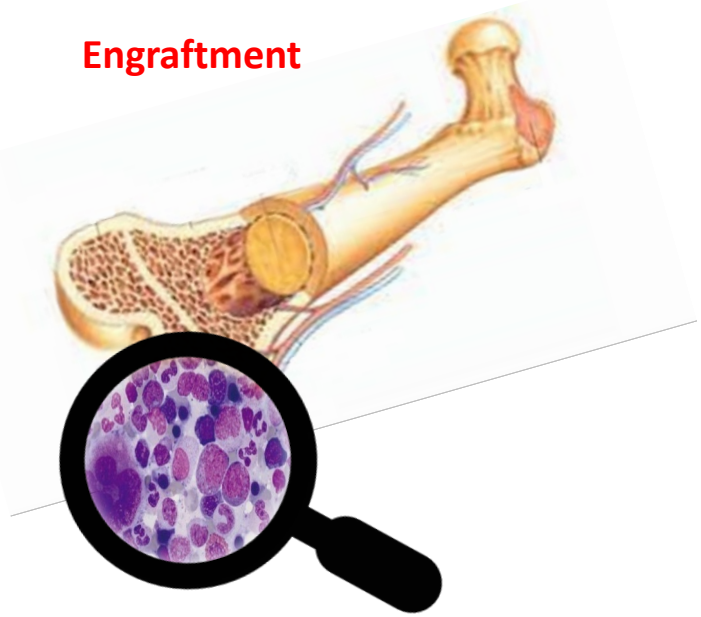
Conditioning

3-7 days

Stem Cell Infusion

14-28 days

Engraftment



Adapted from **National Institute of Health https://www.cancer.gov/about-cancer/treatment/types/stem-cell-transplant**

Clinical history of transplantation

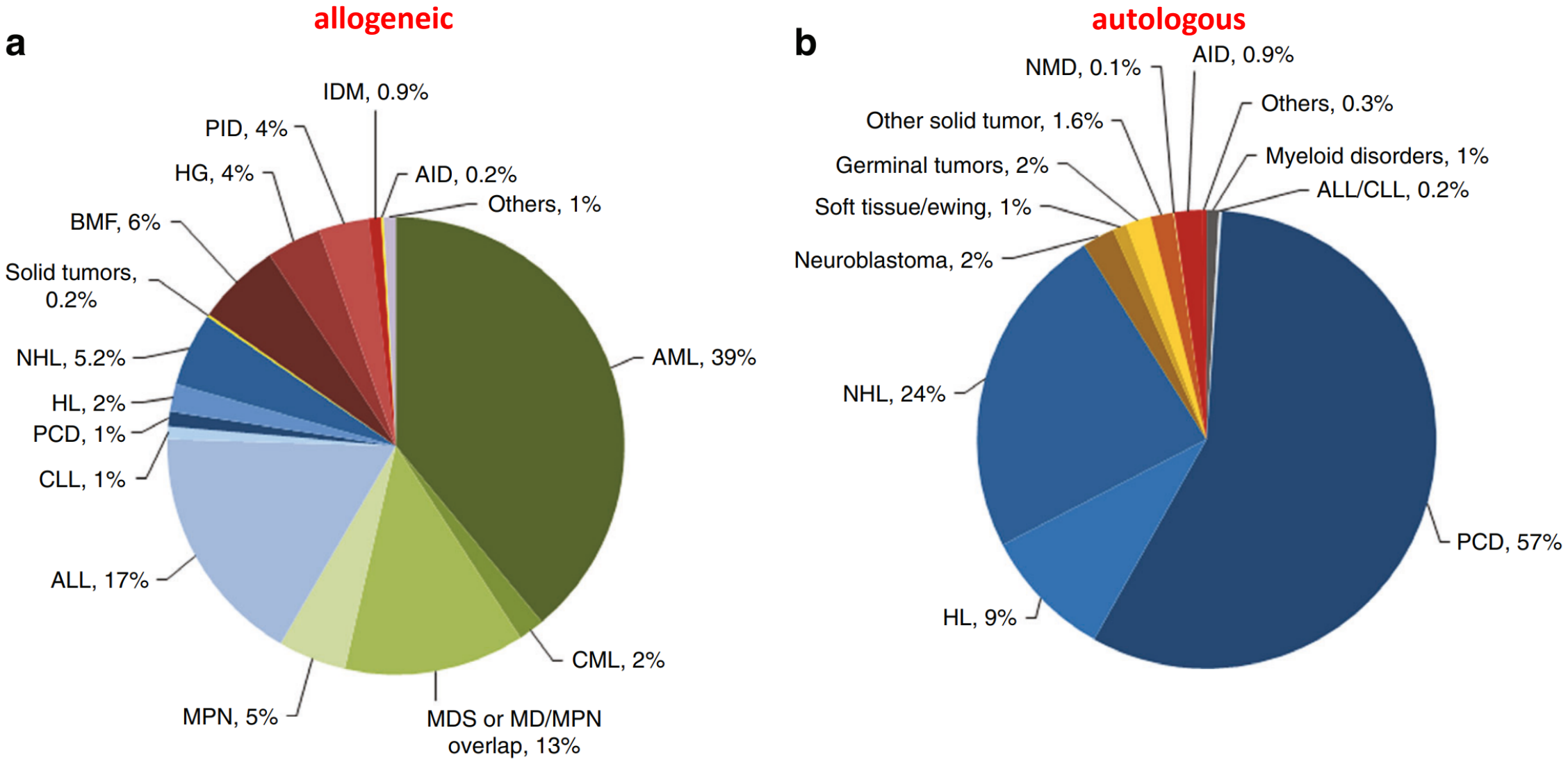
Aplasia	Early period	Late period
Chemo toxicity	Acute GvHD	Chronic GVHD
Anemia	Immunesoppression	Bacterial infections
Thrombocytopenia	Viral infections	Long term AE
Neutropenia		Relapse risk
Opportunistic infections		
Engraftment		

Key components:

- **Supportive therapy** (transfusions/antibiotics/prophylaxis)
- **immunosoppressive therapy**
- **Monitoring** (at least weekly within 3 months)
- **Early** recognition and treatment

Within **one year** of transplantation, it is possible to not receive **any treatment**!

Indications for transplant in Europe



Passweg JR et al. ***BMT 2024***; epub ahead of print

Patients and Methods

•Data Collection

- - **All patients** consecutively **undergoing alloSCT** at the Fondazione IRCCS Policlinico San Matteo in Pavia
- - Transplant period **2013-2023**
- - **Any disease, donor** and **stem cells source**
- - **Medical history** (disease status, HCT-CI, PS, donor features, etc.)

Follow-up after alloSCT

- Acute GVHD
- Chronic GVHD
- Infectious complications
- Record of relapse

Overall outcome

- Date of death
- Causes of Death

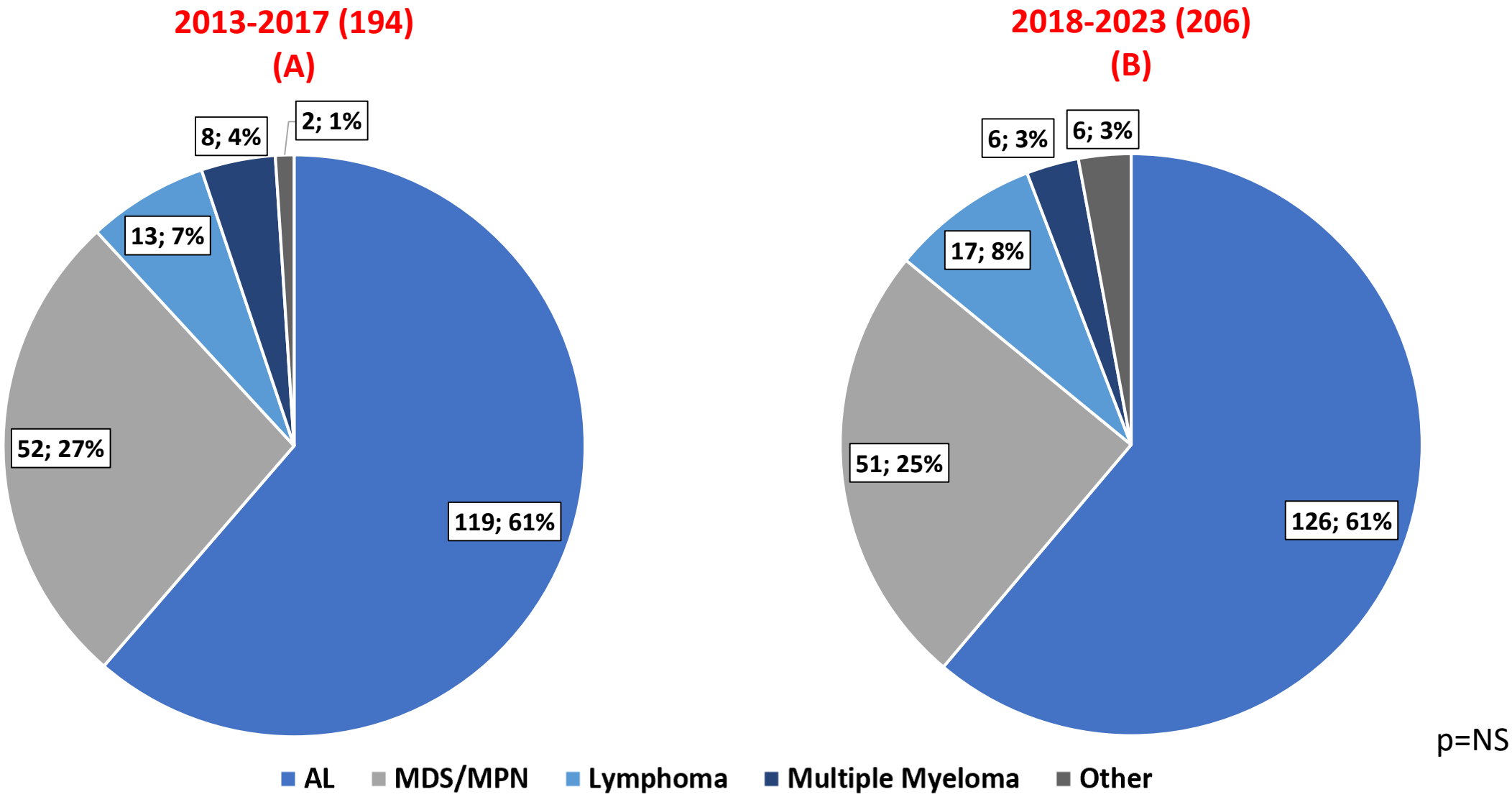
- Overall, **400 patients got allogeneic Stem Cell Transplant (alloSCT)** from 2013 to 2023. Data cut-off is December 2023. **Median follow-up** after allo-SCT was **4,9 years** (95%CI, 4,2-5,4)
- **Acute** and **chronic GvHD** were diagnosed and graded according to **MAGIC** and **2015 NIH criteria**, respectively. **Causes** (NRM, relapse) and **date of death** were recorded
- To assess the evolution of transplants over time, we divided the study cohort into **two transplant periods** (2013-2017[**cohort A**] and 2018-2023 [**cohort B**]).

Harris AC et al. ***Biol Blood Marrow Transplant 2016***; 22(1): 4-10; Jagasia MH et al. ***Biol Blood Marrow Transplant 2015***; 21(3): 389-401

Transplant characteristics

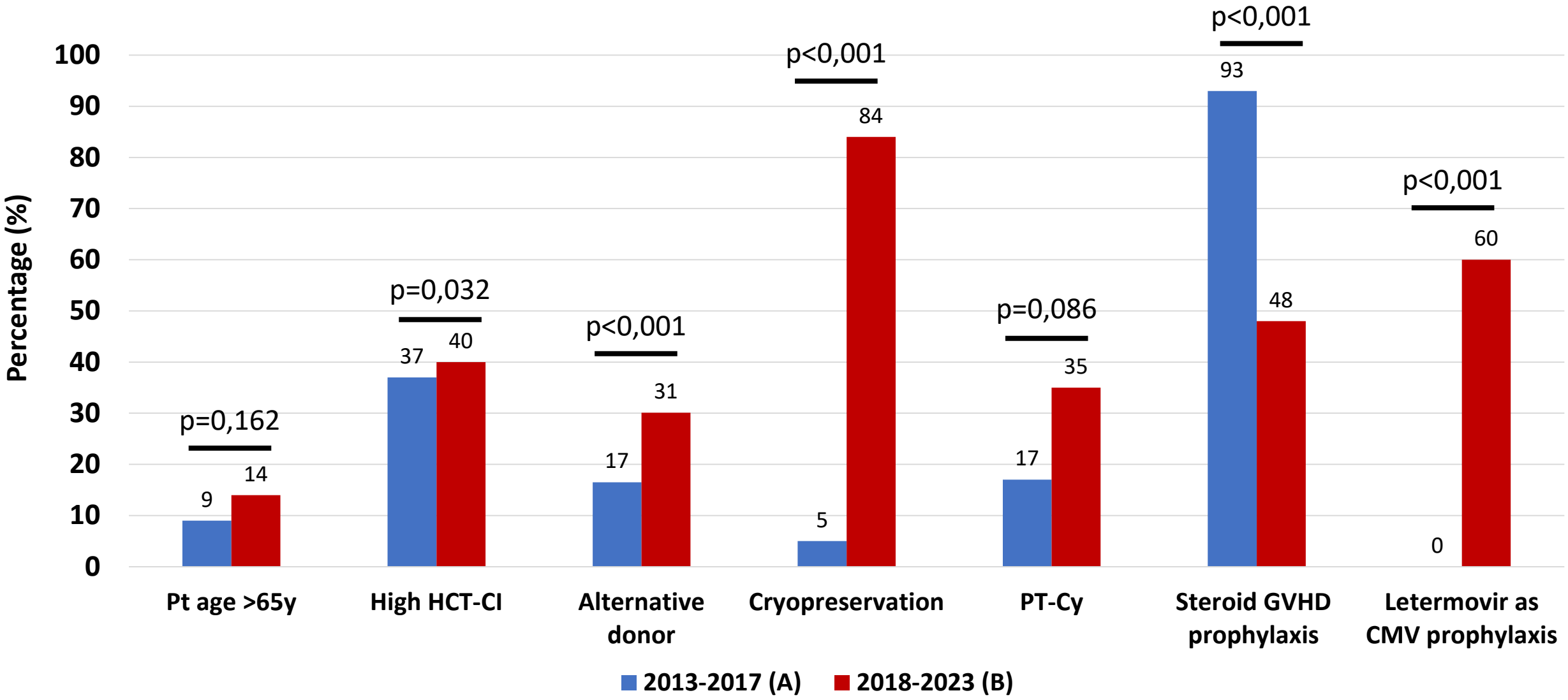
Features	N=400 (%)
Age, median	53,5 years
Male sex	226 (56,5)
HCT-Comorbidity Index class *High*	 155 (38,8)
EBMT risk score *≥3*	 237 (59,3%)
Disease *Acute leukemias* *MDS/MPN* *Lymphoma/Myeloma* *Other*	 246 (61,5) 103 (25,8) 44 (11,0) 7 (1,7)
Disease risk index *High/Very-High*	 136 (34,0)
Transplant Conditioning Intensity (TCI) *High*	 333 (83,7)
Donor *Matched related* *Unrelated* *Haploidentical*	 89 (22,2) 217 (54,2) 94 (23,6)

Transplant indications over time

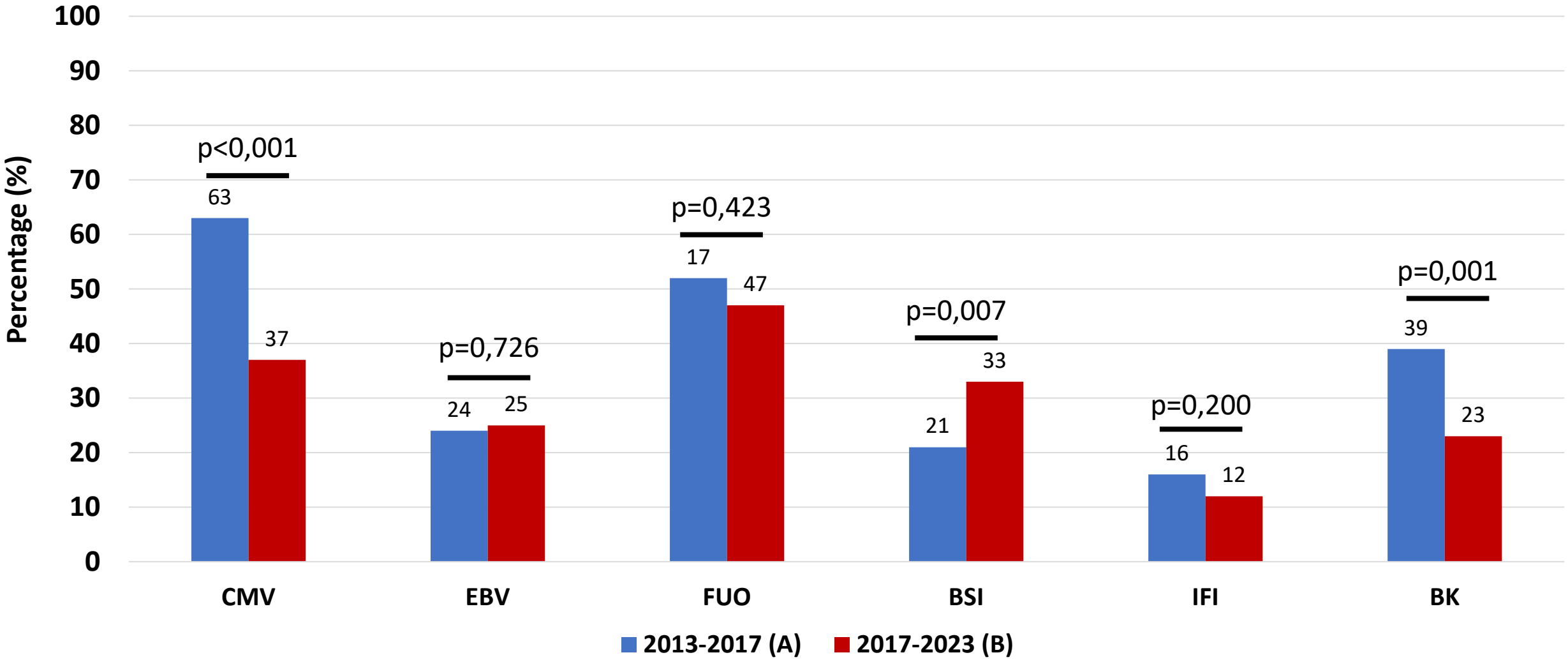


p=NS

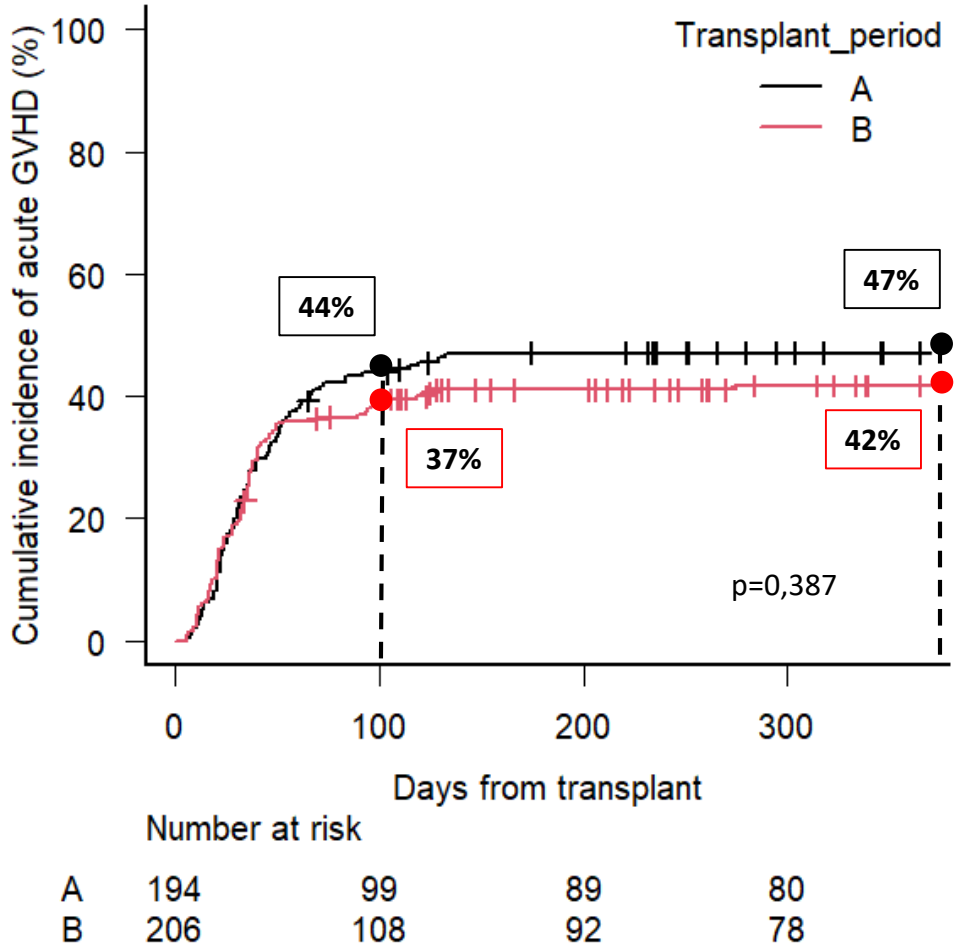
Modifications in transplant platform over time

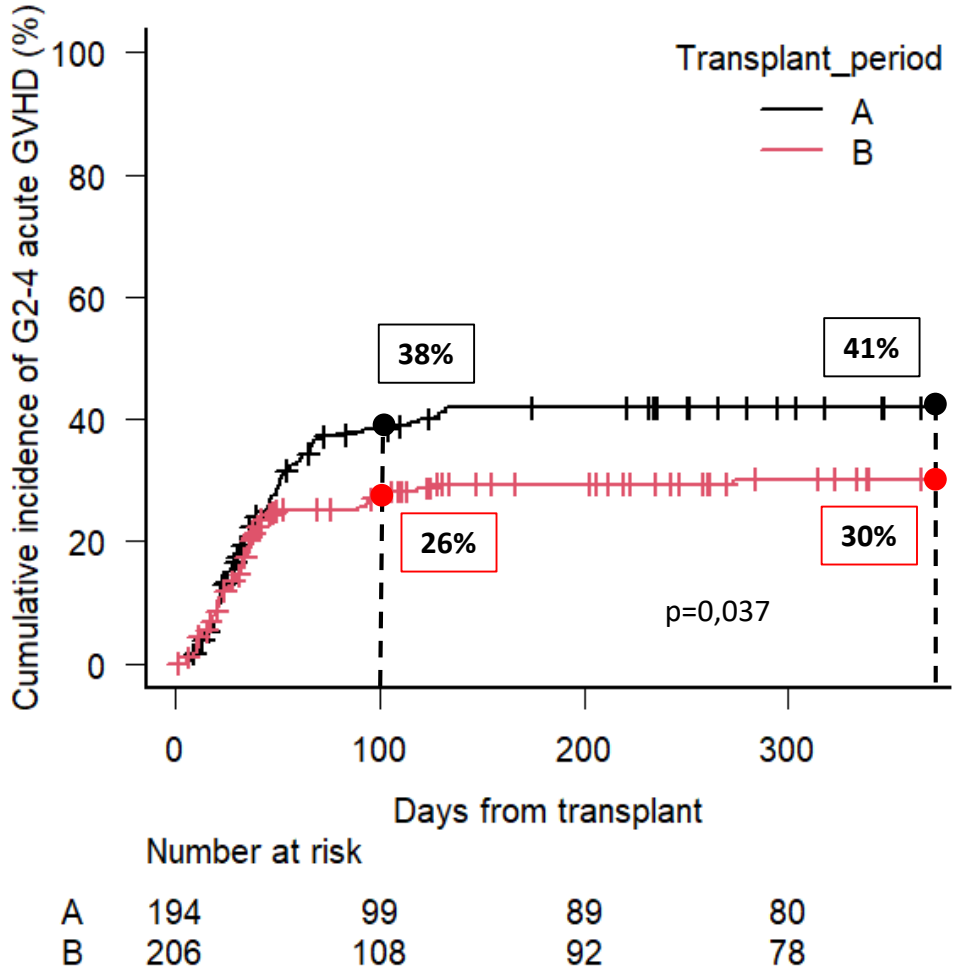


Infections over time

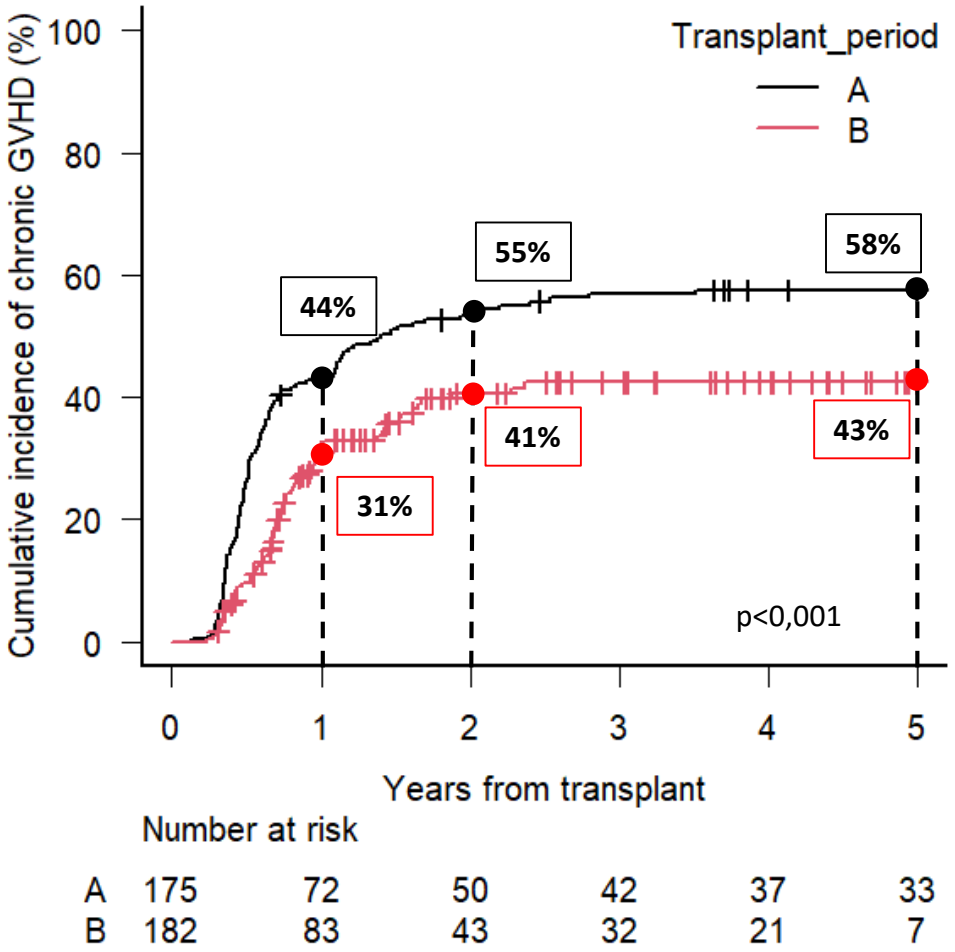


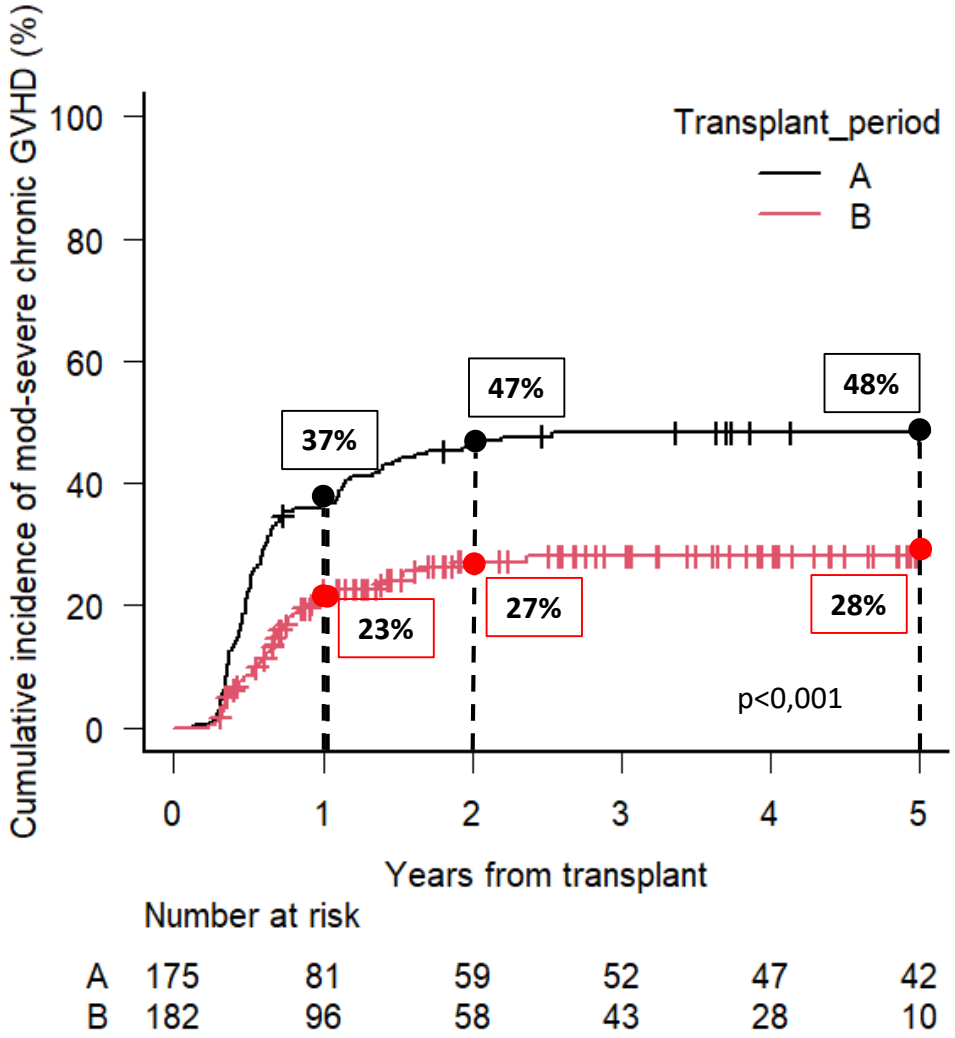
Acute GVHD according to transplant period





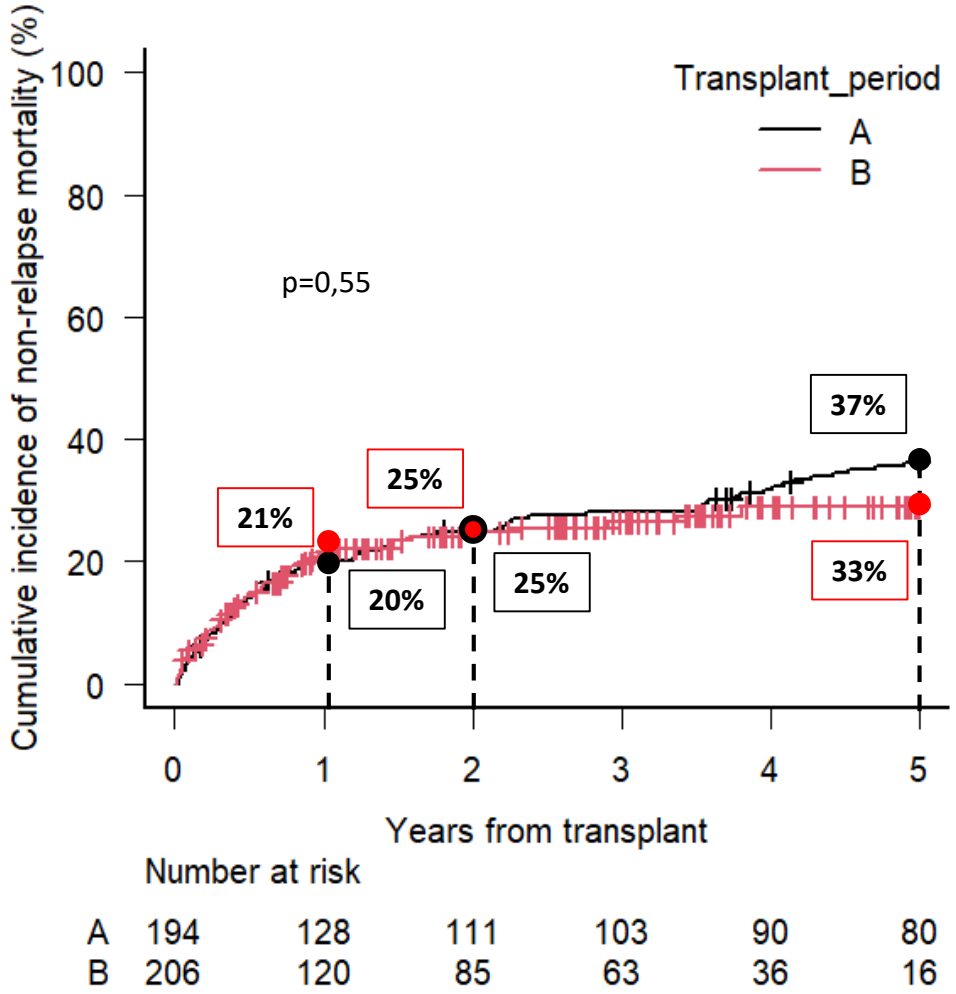
Chronic GVHD according to transplant period



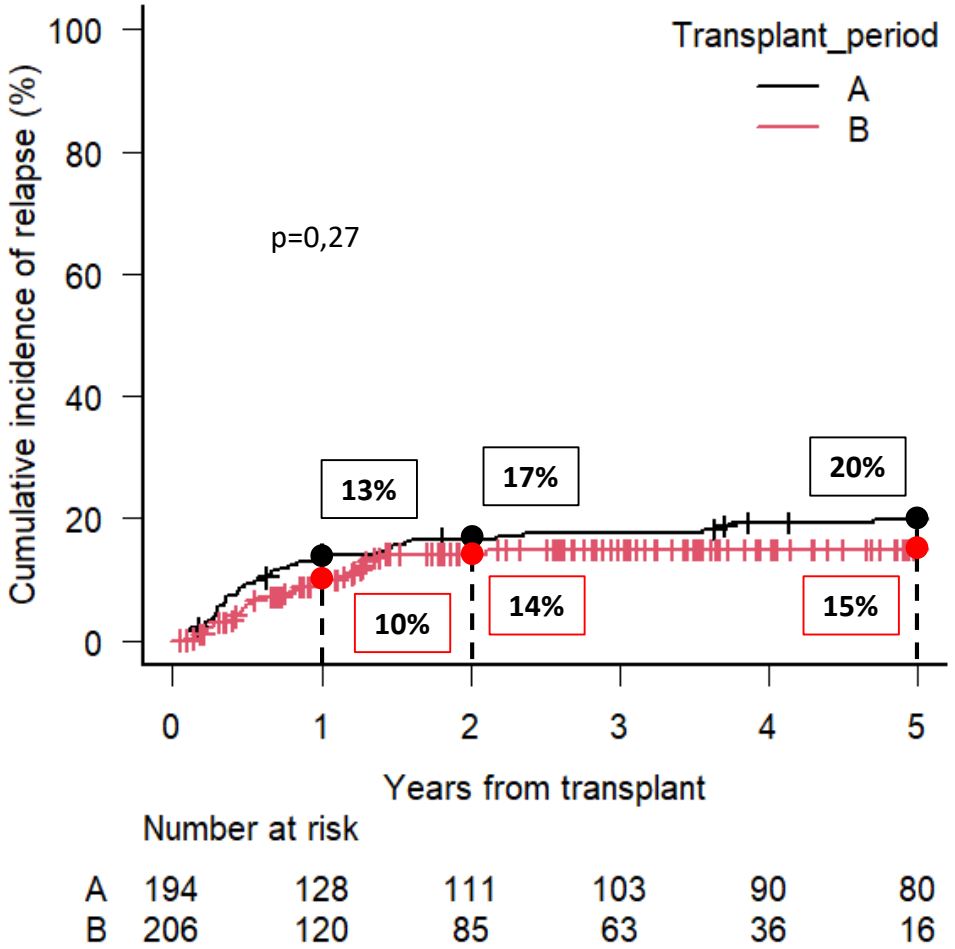


NRM – CIR according to transplant period

NRM

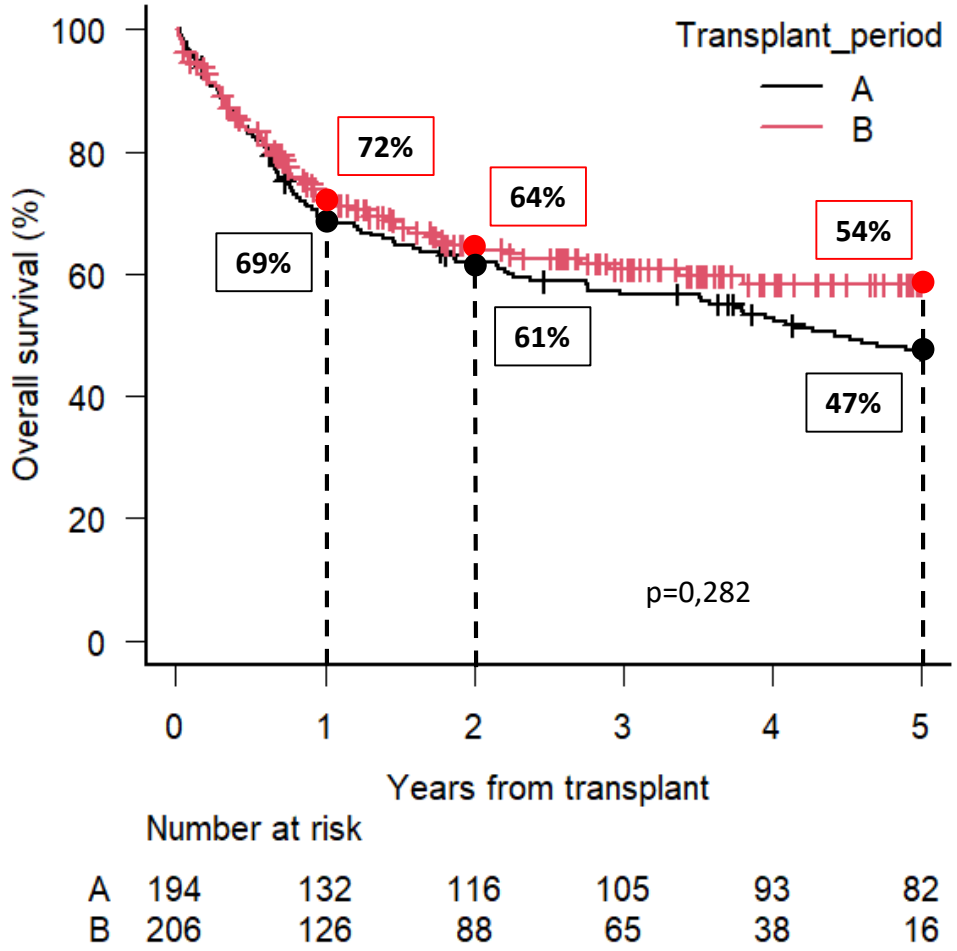


Relapse incidence



Overall survival according to transplant period

Causes of death (Tot=181)	N° (%)
Relapse	55 (30,4)
NRM	
infections	72 (39,8)
aGVHD	12 (6,6)
cGVHD	17 (9,4)
toxicity	3 (1,7)
other	22 (12,2)

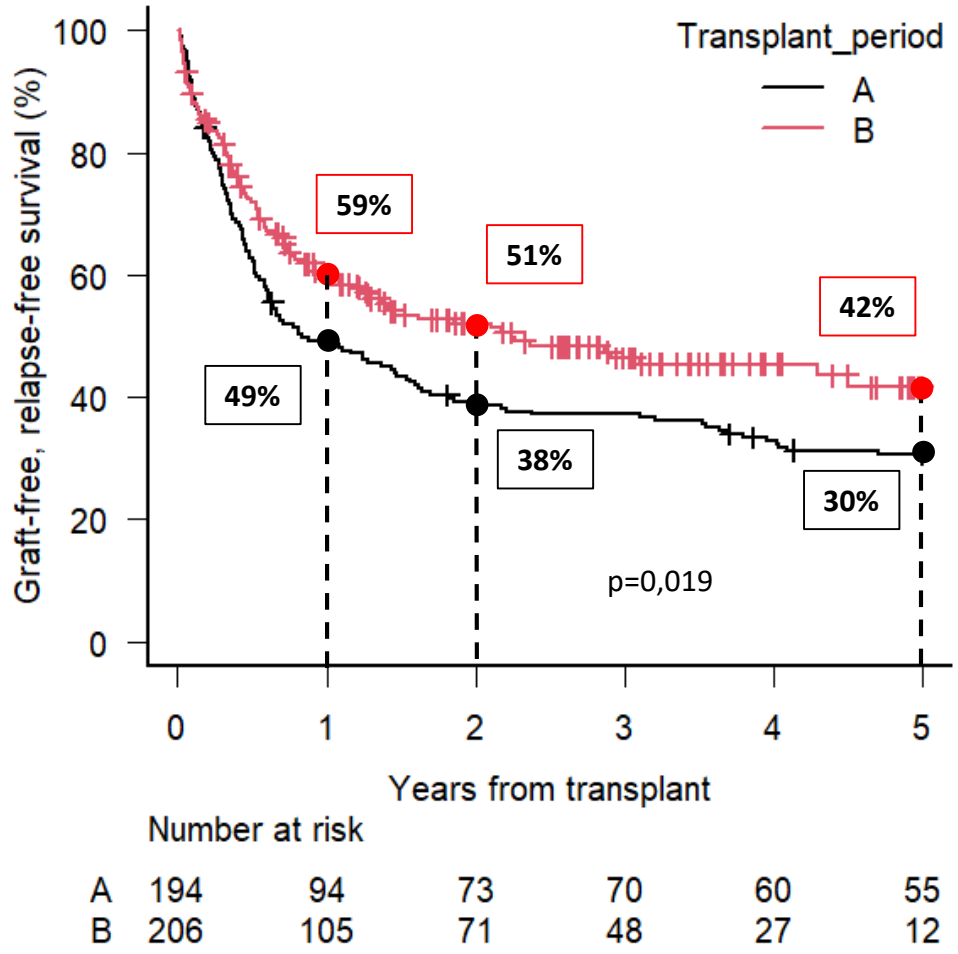


GRFS according to transplant period

GRFS (GVHD-free/relapse-free survival)

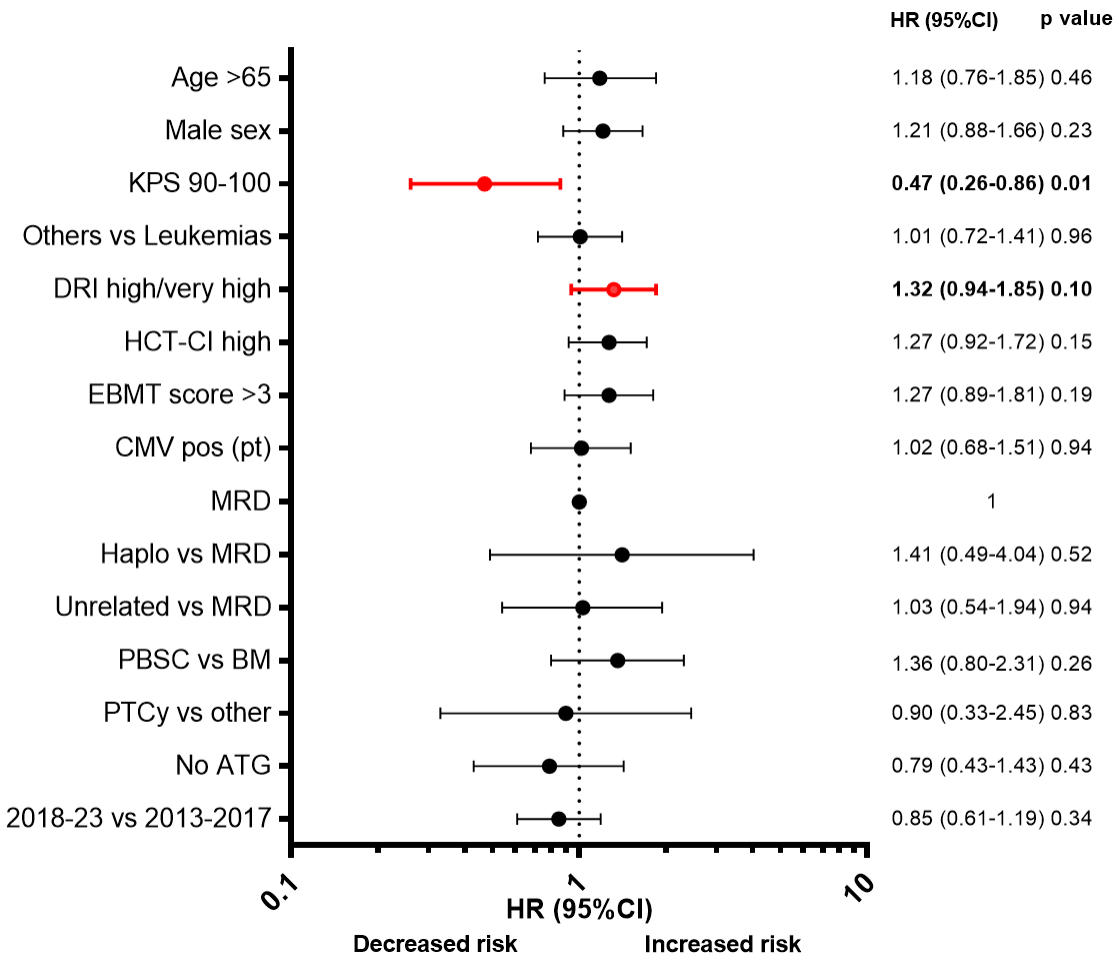
Events of interest:

- **Relapse**
- **Death** (any cause)
- **Grade 3-4 acute GVHD**
- **Severe chronic GVHD**

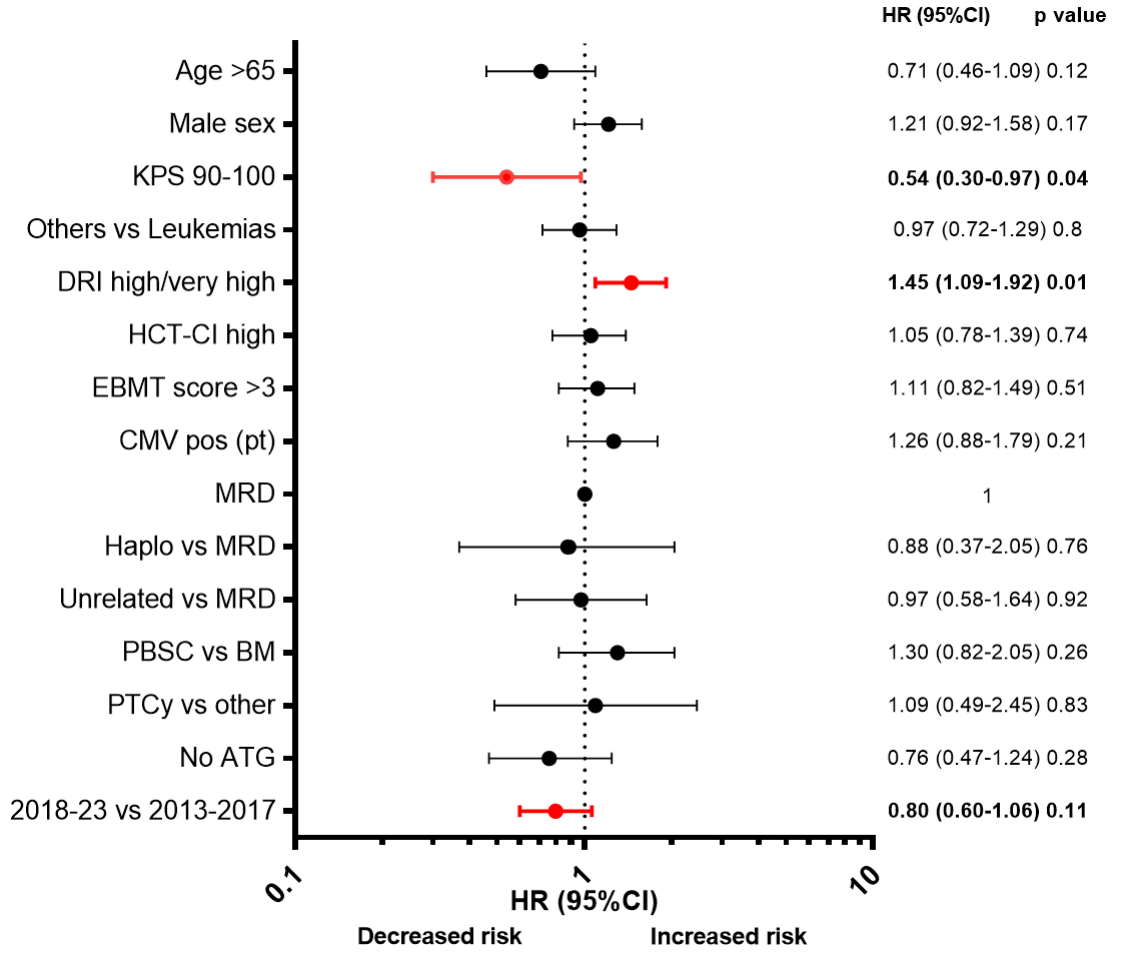


Multivariate analyses on OS and GRFS

Overall survival



GRFS



Summary (I)

- **Allogeneic stem cell transplantation** (allo-SCT) remains a **curative option** for a substantial portion of **hematological diseases**. Despite advancements in transplant procedures, concerns persist regarding **relapse** and **transplant-related mortality**.

- In the past decade, the **Unit of Bone Marrow Transplantation** at the **Fondazione IRCCS Policlinico San Matteo** has performed **400 allo-SCT procedures**, primarily for acute leukemias.

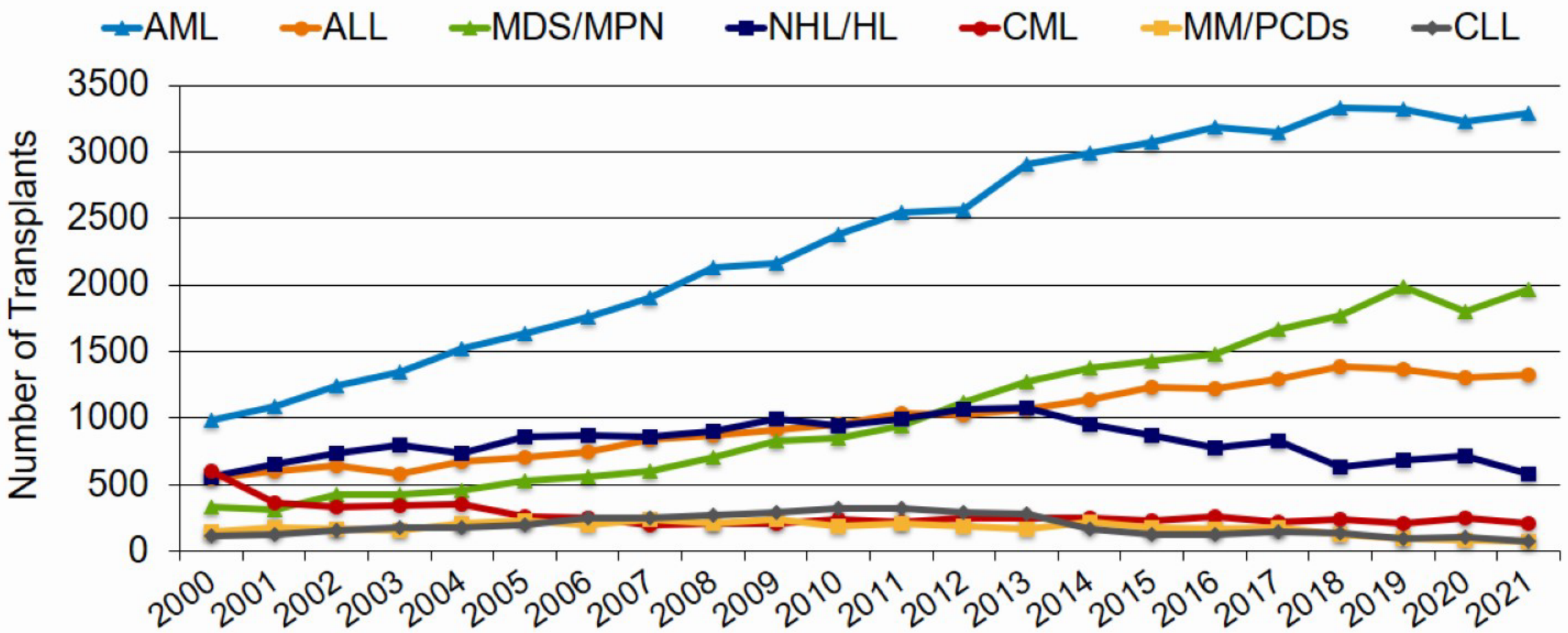
- Over time, we have broadened the application of transplantation to include **older patients** with more **comorbidities**, utilizing a higher proportion of **alternative donors**, and transitioning from steroid-based prophylaxis to a **PTCy platform**, while **maintaining myeloablative conditioning**.

Summary (II)

- **Transplant outcomes** have **improved** during the most recent transplant period. We observed a reduction in **CMV** and **BK virus reactivations**, albeit with a higher incidence of **bloodstream infections**. Additionally, there was a lower occurrence of **severe acute and chronic GVHD**, accompanied by significantly **higher rates of Graft-free, relapse-free survival**.

- The **pre-transplant disease status and PS** continue to play a significant role **in predicting overall survival** and **long-term outcomes**.

Trends in allo-SCT according to indications



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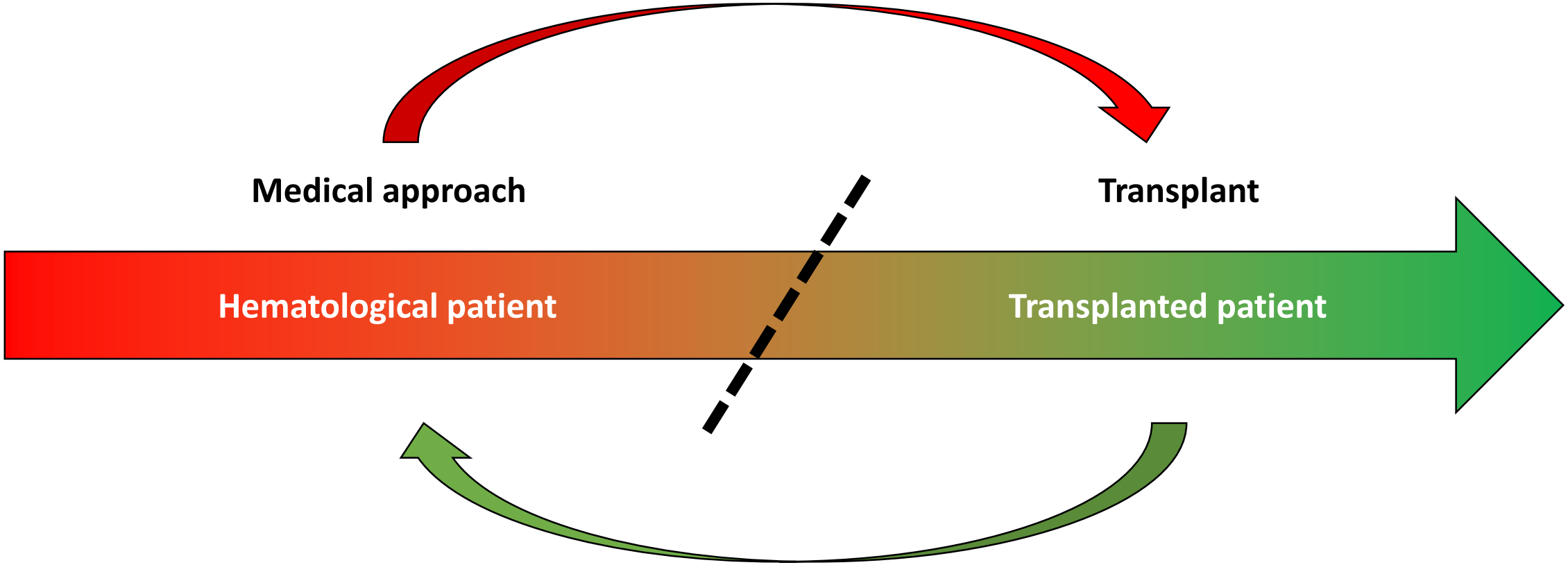
Abbreviations –
AML: Acute Myeloid Leukemia;
ALL: Acute Lymphoblastic Leukemia;
MDS: Myelodysplastic Syndromes;
MPN: Myeloproliferative Neoplasms;
NHL: Non-Hodgkin Lymphoma;
HL: Hodgkin Lymphoma;
CML: Chronic Myeloid Leukemia;
MM: Multiple Myeloma;
PCDs: Plasma Cell Disorders;
CLL: Chronic Lymphocytic Leukemia.

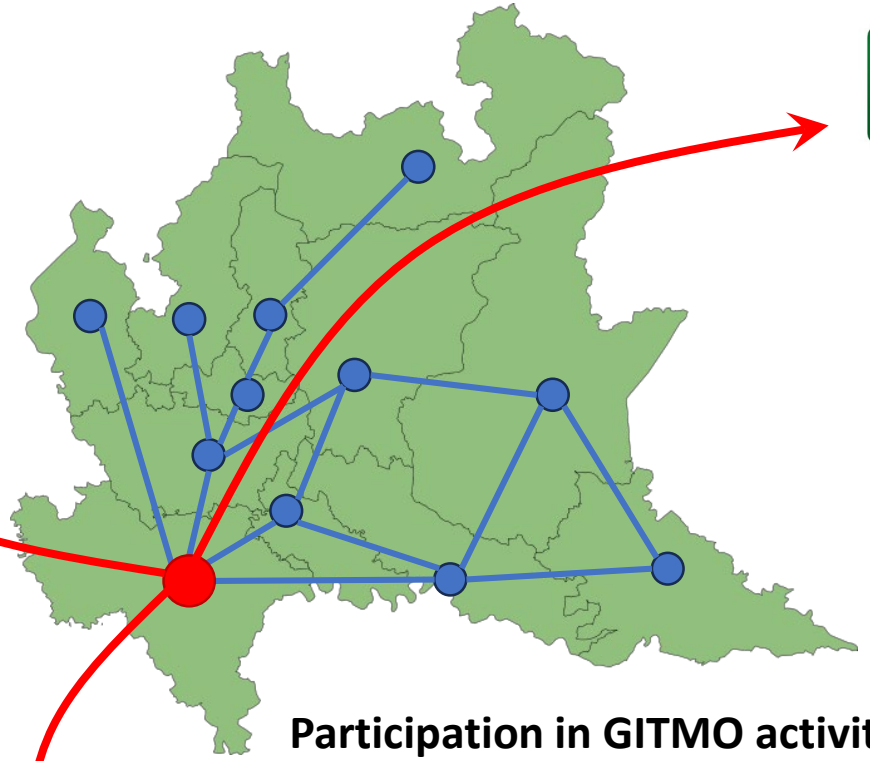
A smooth journey for transplant candidates



Developmental directions of adult allo-SCT in Pavia

Participation in EBMT activities
Multicenter studies
Collaborative guidelines

Ongoing active studies
EBMT recommandations on MDS/MPN
Management of SVT in allo-HCT candidates



Regione Lombardia

Lombardy network
25 Hematology Units
10 Allo-HCT Centers

Patient management
Cooperation between Centers
Clinical Trials

Scientific production
Peer scientific contribution

Participation in GITMO activities
Multicenter studies

Ongoing studies promoted by PV
Survey on GVHD
Role of cryopreservation in allo-SCT
Phase II study on novel pre-transplant conditioning regimens

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Terapie cellulari con CAR-T: "from the bench to the bedside and viceversa"

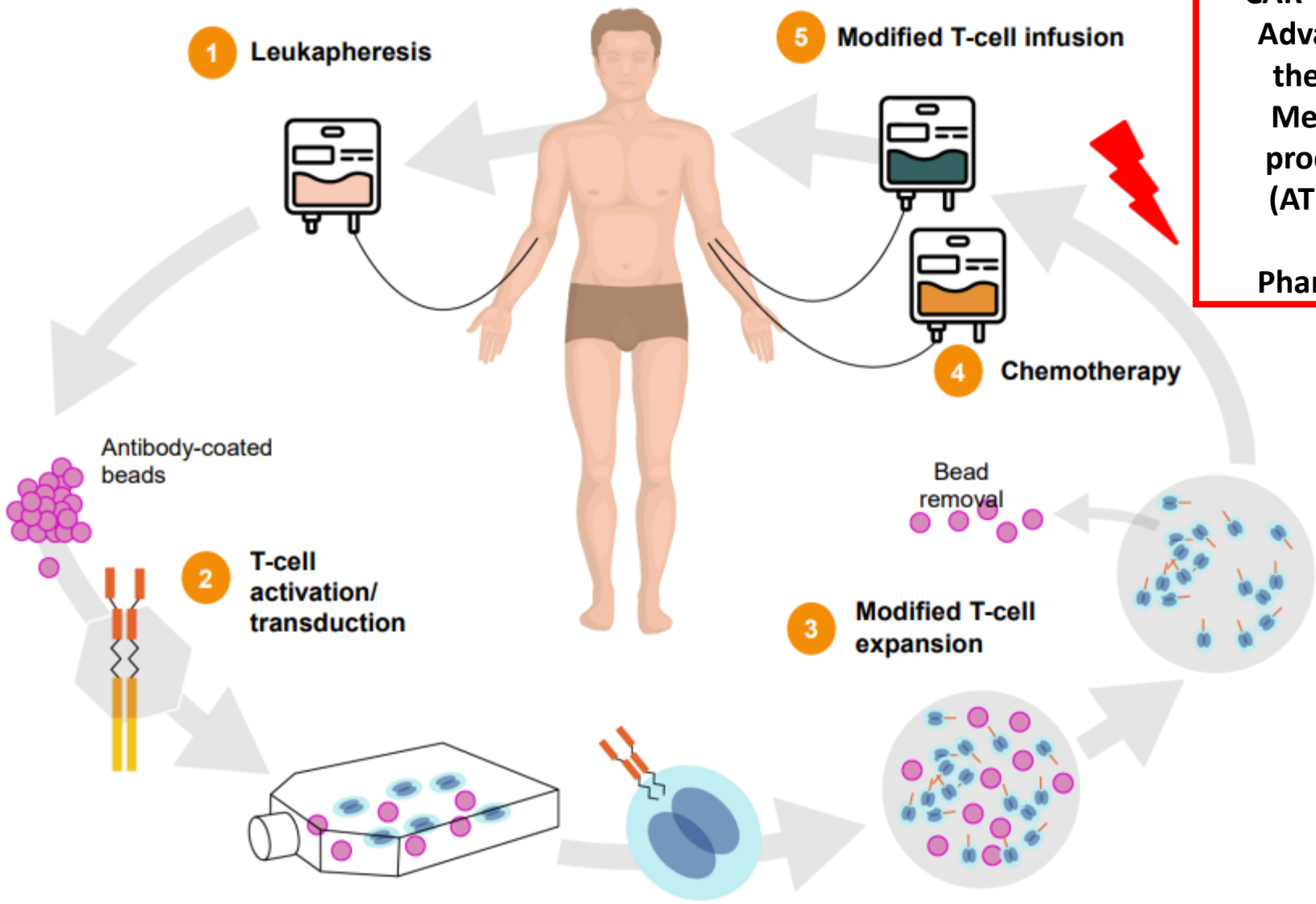
Nicola Polverelli, Antonio Bianchessi, Patrizia Comoli

Unit of BMT
Division of Hematology

Hematology 3
Cell Factory

Pavia, 27/3/2024

CAR-T: Chimeric Antigen Receptor (CAR)- T lymphocytes

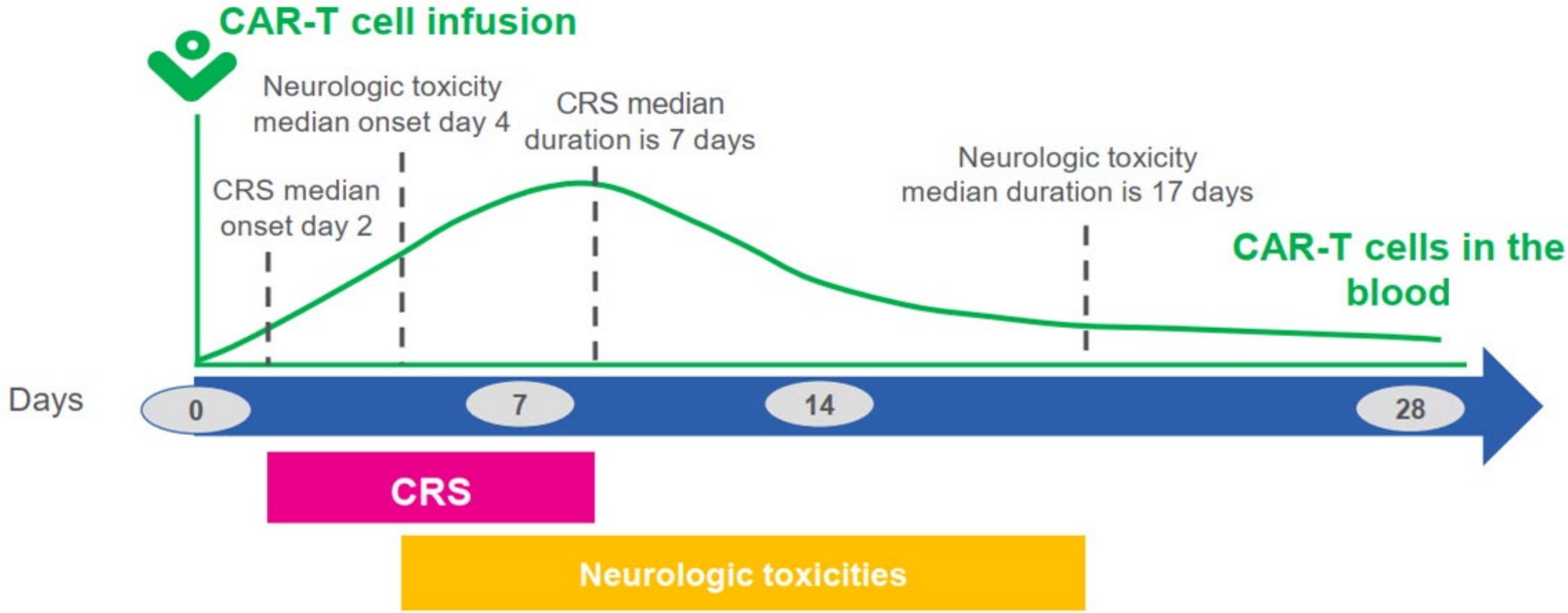


CAR-T cell = Advanced therapy Medical products (ATMPs)

Pharmacy

Main toxicities after CAR-T

- Cytokine Release Syndrome **(CRS)**
- Immune Effector Cell Associated Neurotoxicity Syndrome (**ICANS**)

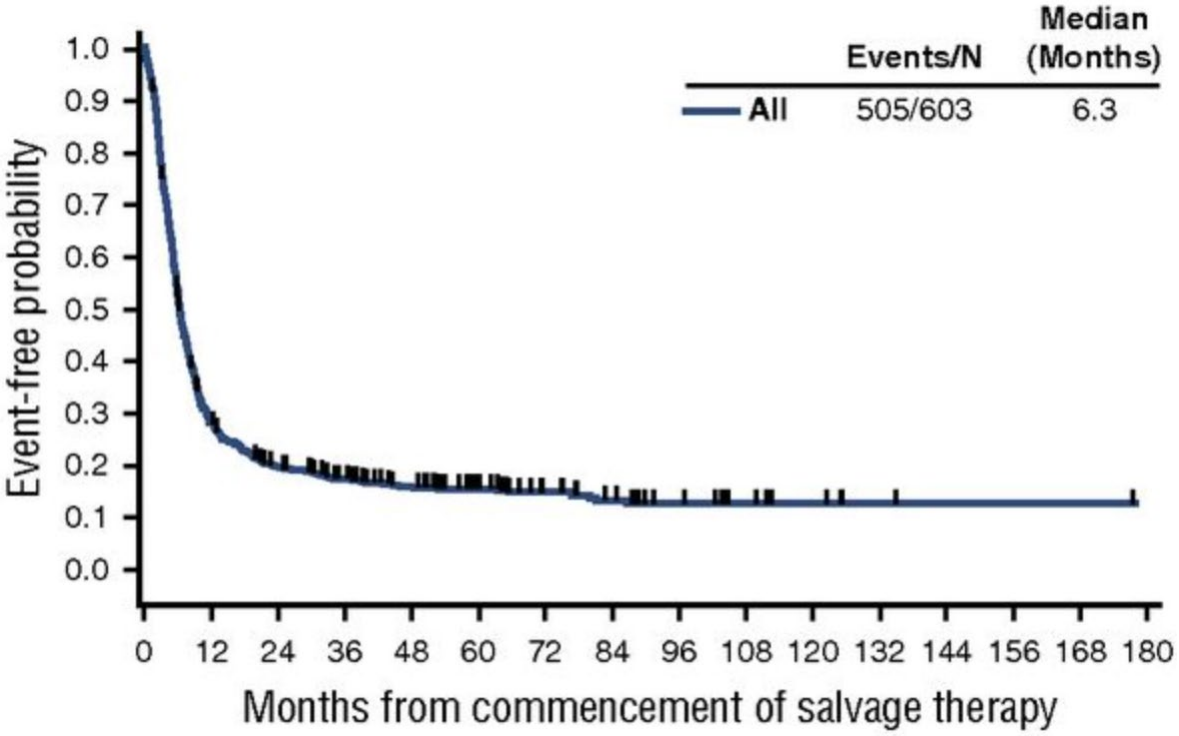


Therapy: anti-cytokines drugs and/or steroids; ICU admission for severe forms

Outcomes of R/R DLBCL and ALL prior to CART availability

R/R DLBCL

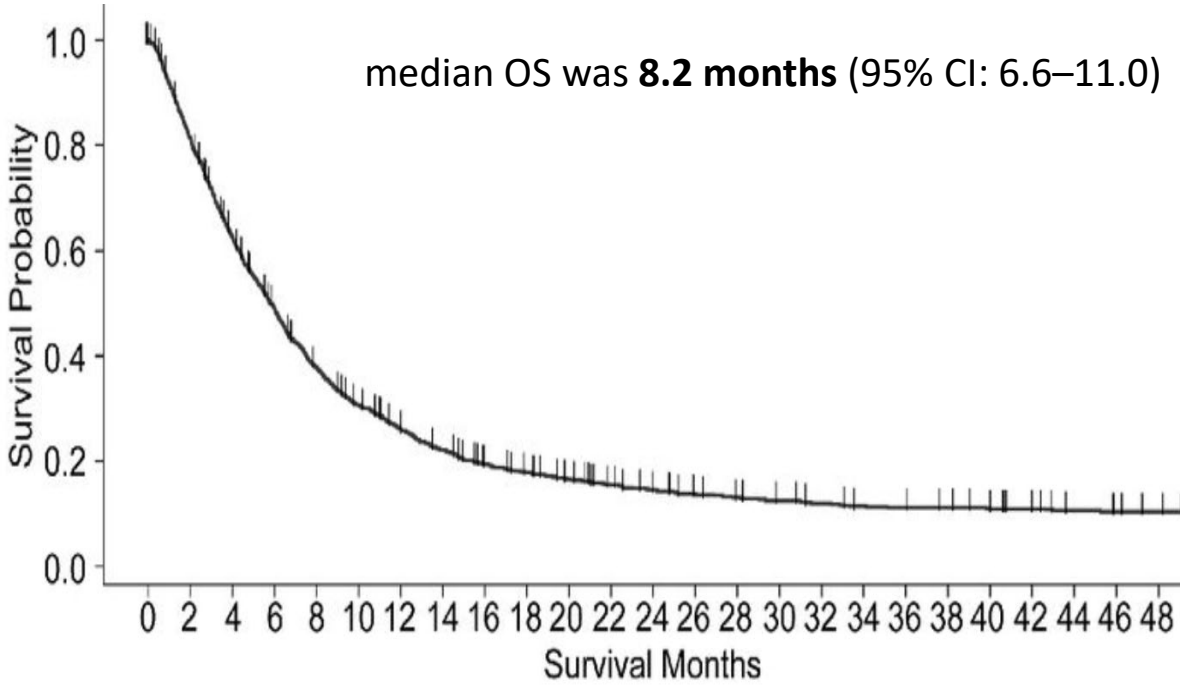
(Primary refractory, refractory to 2° line or later, relapsed ≤12 mo from ASCT)



R/R B-ALL

(Ph-negative relapsed/refractory B-precursor ALL patients)

median OS was **8.2 months** (95% CI: 6.6–11.0)



Crump M et al ***Blood. 2017***;130(16):1800-8; Gökbuget N et al***. Haematologica 2016***; 101(12): 1524-1533

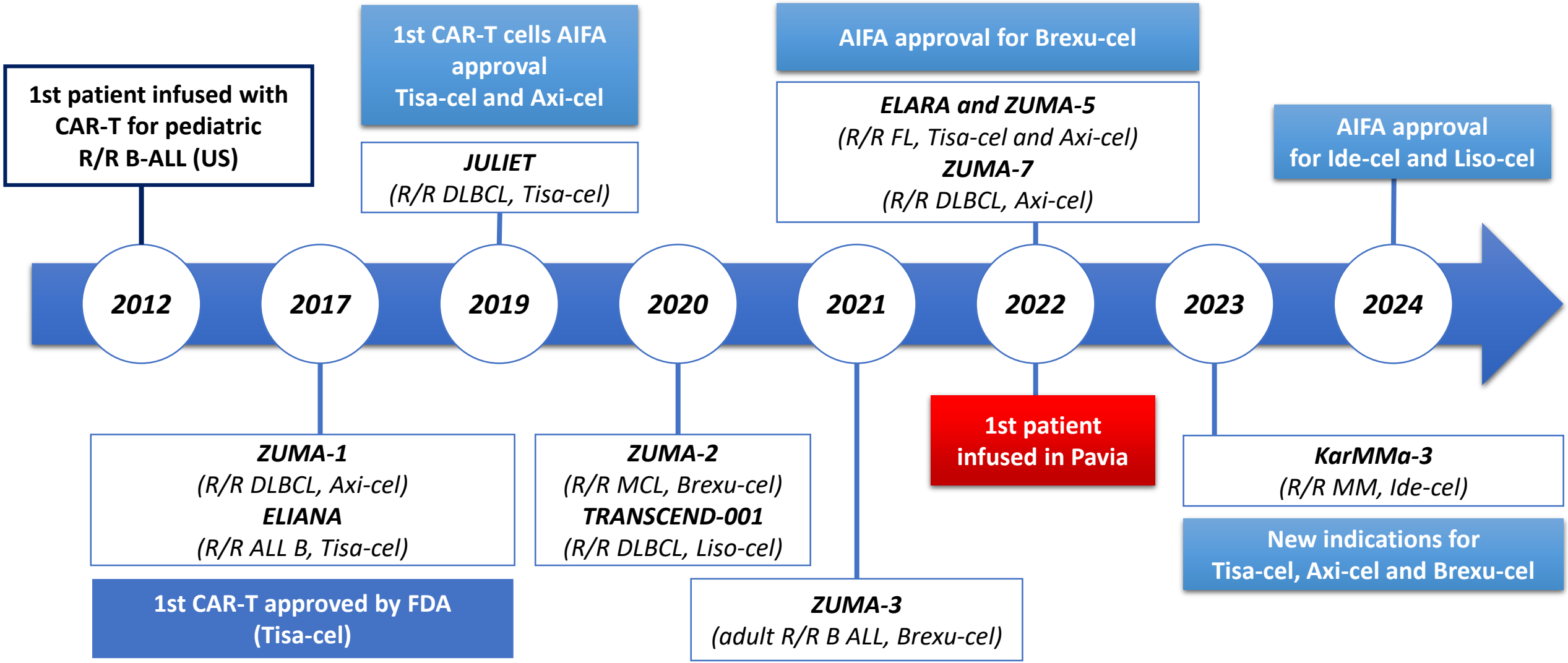
Clinical trials with CART leading to drug approval

Study	Product	Indication	Line of therapy	Target	Outcome CAR-T study
ZUMA-1	Axi-cel	R/R DLBCL & PMBCL	3	CD-19	18m-OS 52%, ORR 82%
ELIANA	Tisa-cel	R/R B ALL (≤ 25y)	≥2	CD-19	12m-EFS 50%, ORR 81%
JULIET	Tisa-cel	R/R DLBCL	3	CD-19	12m-OS 49%, ORR 52%
ZUMA-2	Brexu-cel	R/R MCL	3	CD-19	12m-PFS 61%, ORR 85%
TRANSCEND-001	Liso-cel	R/R DLBCL	3	CD-19	2y-PFS 41%, ORR 73%
ZUMA-3	Brexu-cel	R/R B ALL (> 25y)	≥2	CD-19	Median OS 25.4m, ORR 71%
ELARA	Tisa-cel	R/R FL	3	CD-19	1y-PFS 67%, ORR 86%
ZUMA-5	Axi-cel	R/R FL	4	CD-19	Median PFS 40.2m, ORR 92%
ZUMA-7	Axi-cel	R/R DLBCL	2	CD-19	24m-EFS 41%, ORR 83%
KarMMa-3	Ide-cel	R/R MM	4	BCMA	Median PFS 13.3m, ORR 71%

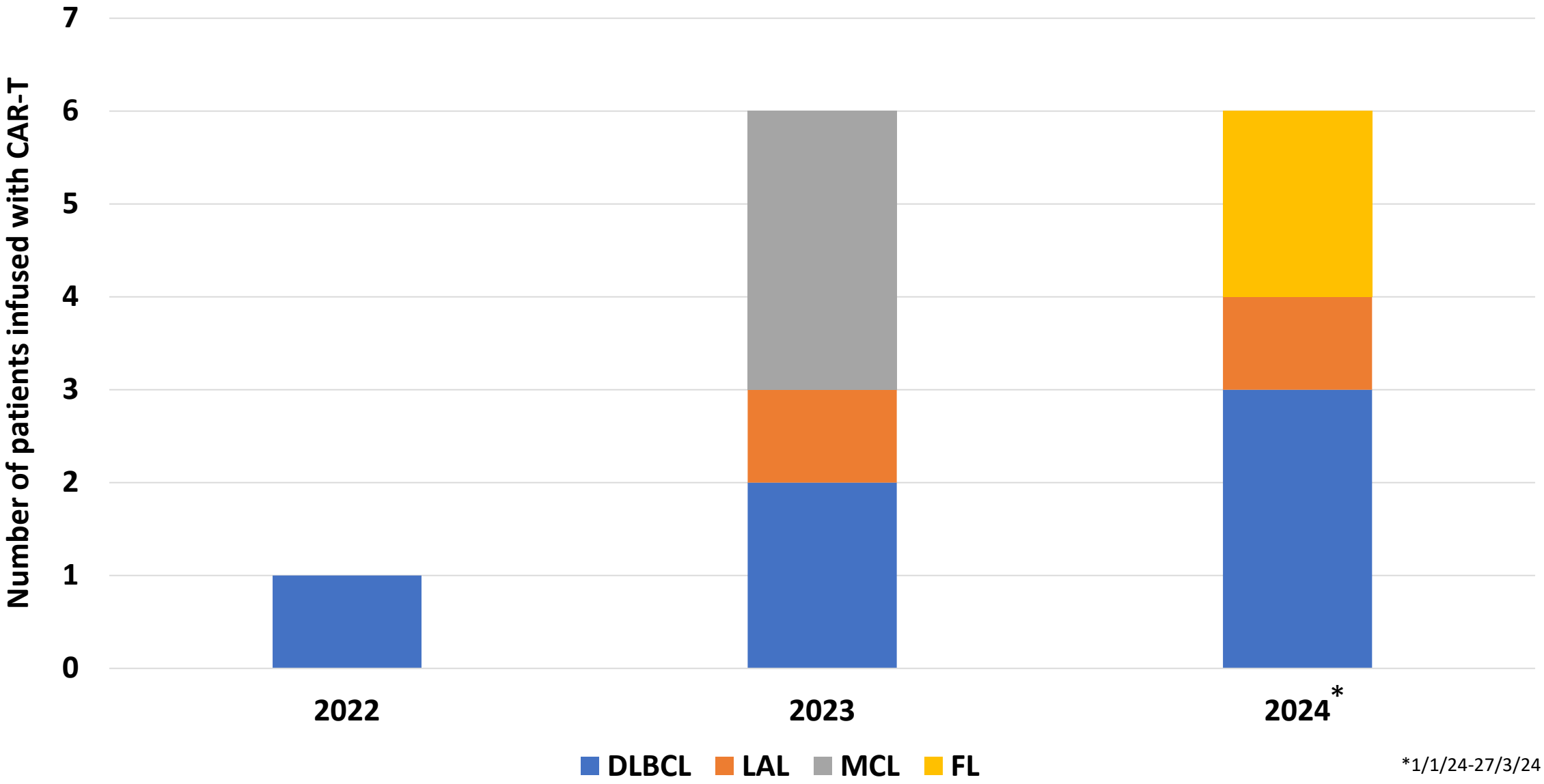
ALL B: B cell acute lymphoblastic leukemia; **BCMA**: B-cell maturation antigen; **DLBCL**: diffuse large B cell lymphoma; **FL**: follicular lymphoma; **MCL**: mantle cell lymphoma; **MM**: multiple myeloma; **PMBCL**: primary mediastinal B cell lymphoma; **R/R**:refractory/relapsed

Neelapu S et al. ***N Engl J Med 2017***; 377(26):2531-2544; Maude SL et al. ***N Engl J Med 2018***; 378(5):439-448; Schuster SJ et al. ***N Engl J Med 2019***; 380(1):45-56; Wang M et al. ***N Engl J Med 2020***; 382(14):1331-1342; Abramson JS et al. ***Lancet 2020***; 396(10254):839-852; Shah BD et al. ***Lancet 2021***; 398(10299):491-502; Fowler NH et al. ***Nat Med. 2022***;28(2):325-332; Jacobson CA et al. ***Lancet 2022*** ;23(1):91-103; Locke FL et al. ***N Engl J Med 2022***; 386(7):640-654; Rodriguez-Otero P et al. ***N Engl J Med. 2023***;388(11):1002-1014.

CAR-T therapy: an history of success



CAR-T activity (Oct 2022- Mar 2024)

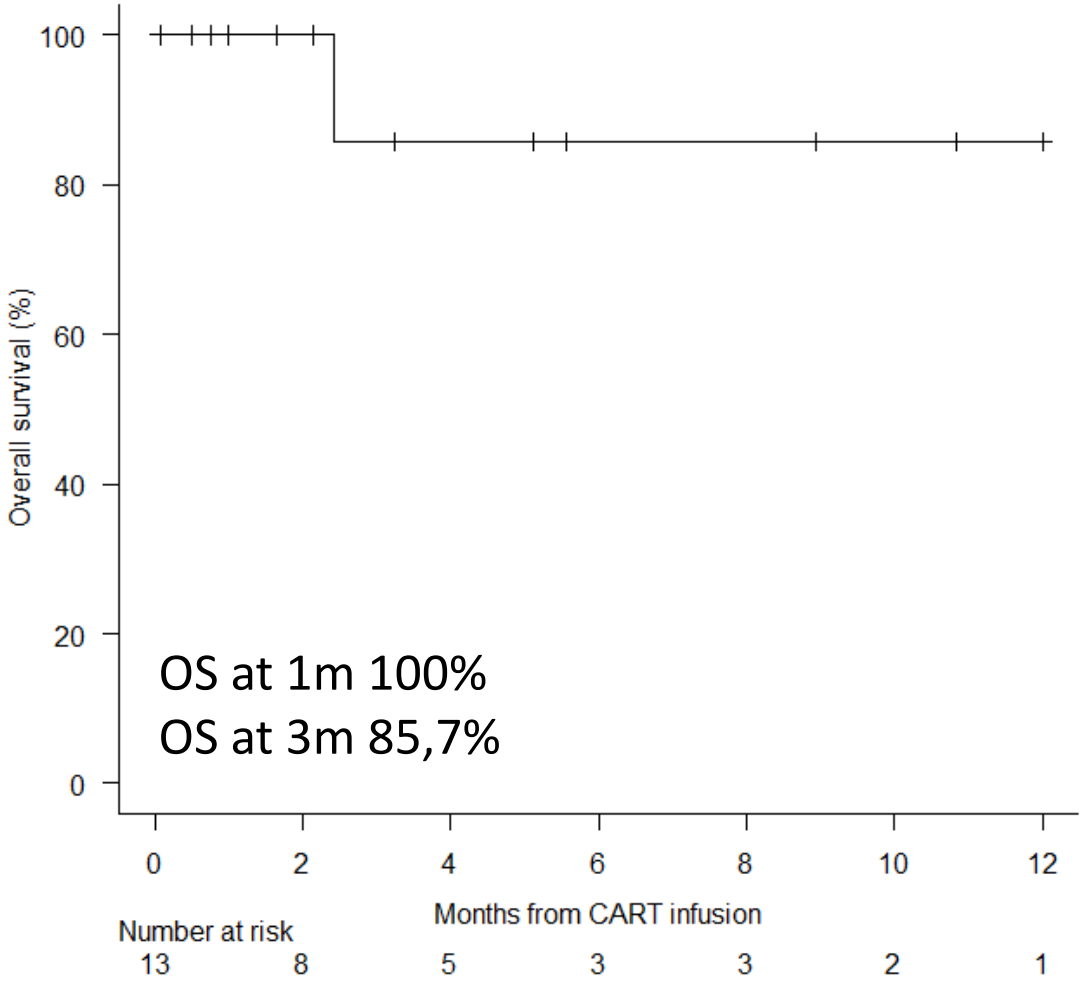


*1/1/24-27/3/24

Clinical characteristics

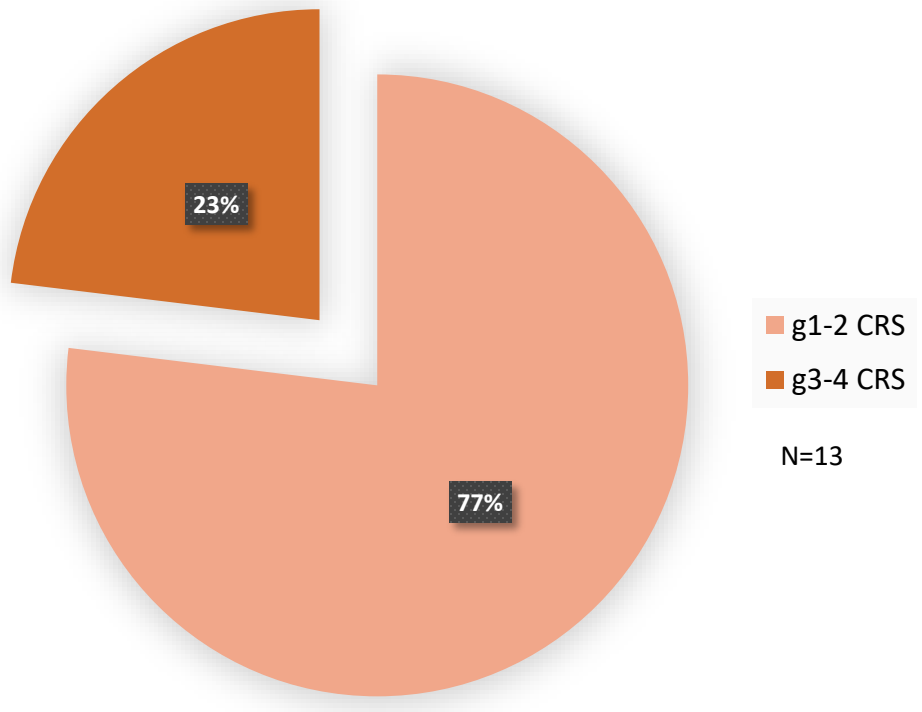
Patients characteristics	N=13
Age, median	61
Sex (M/F)	9/4
Diagnosis, n (%) • *DLBCL* • *ALL B* • *MCL* • *FL*	 6 (47) 2 (15) 3 (23) 2 (15)
Lines of therapy pre-CAR-T • *≥ 2*	 13
Product (%) • *Axi-cel, anti-CD19 (Yescarta)* • *Brexu-cel, anti-CD19 (Tecartus)* • *Tisa-cel, anti-CD19 (Kymriah)*	 4 (31) 4 (31) 5 (38)

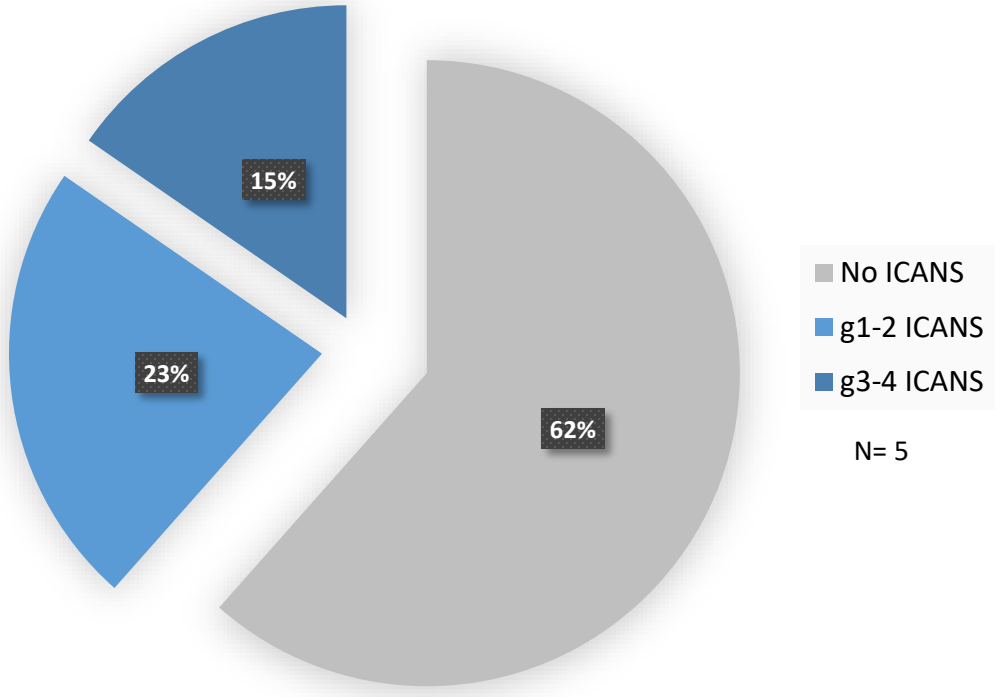
Treatment outcomes after CART infusion



Clinical outcomes	N=13
Response to CAR-T (%) • *Complete remission* • *Partial remission*	 12 (92) 1 (8)
Median time to response (days)	30
Median Follow-up (months)	3,2

Treatment toxicities after CART infusion



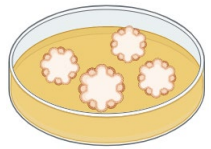


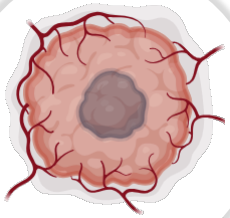
CRS all grades 13 (100%); severe 3 (23%)

ICANS all grades 5 (38%); severe 2 (15%)

Overall, **5 patients** required **ICU admission** due to severe forms of CRS/ICANS

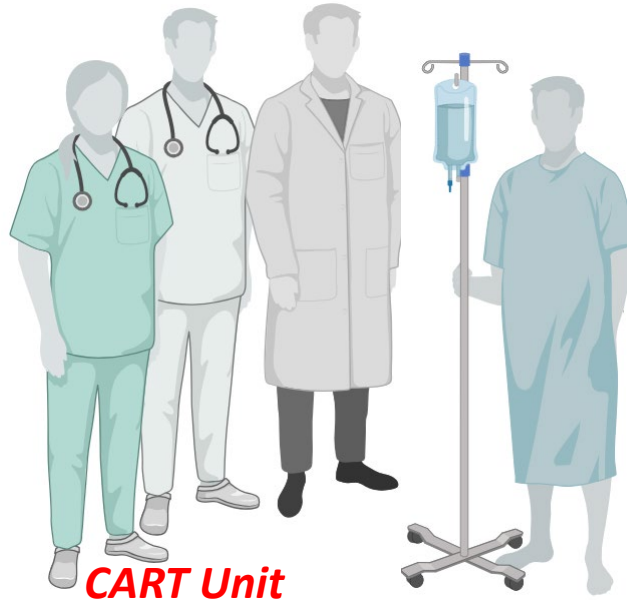
Microbiology & Virology
Advanced diagnosis
Monitoring
Lab research

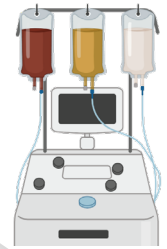




Pathology & Laboratory
Diagnostics
Mechanisms of resistance/tumor escape
Microenvironment/Immune reconstitution

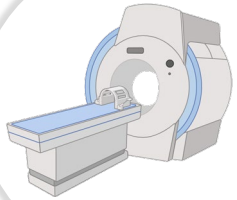
Infectious diseases
Prophylaxis
Patient care
Clinical research

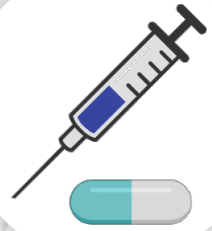




Transfusion Medicine
Timely apheresis
Quality production
Cryopreservation

Radiology
CT/MRI
Differential diagnosis

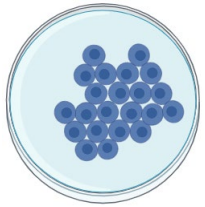




Pharmacy
Drug supply
Interaction check
Pharmacokinetics

CART Unit
Division of Hematology

Neurology & Neurophysiology
ICANS monitoring
Identification of RF
Guidelines on ICANS

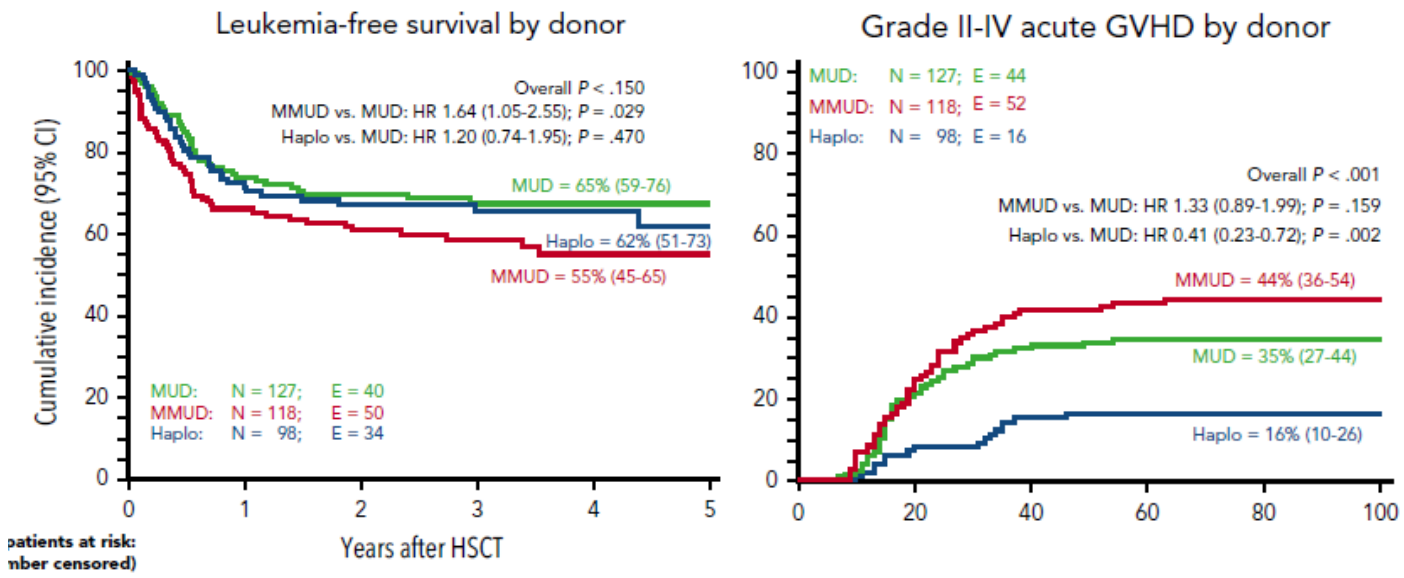


Intensive Care Unit
Venous access
Patient management
Strict clinical monitoring

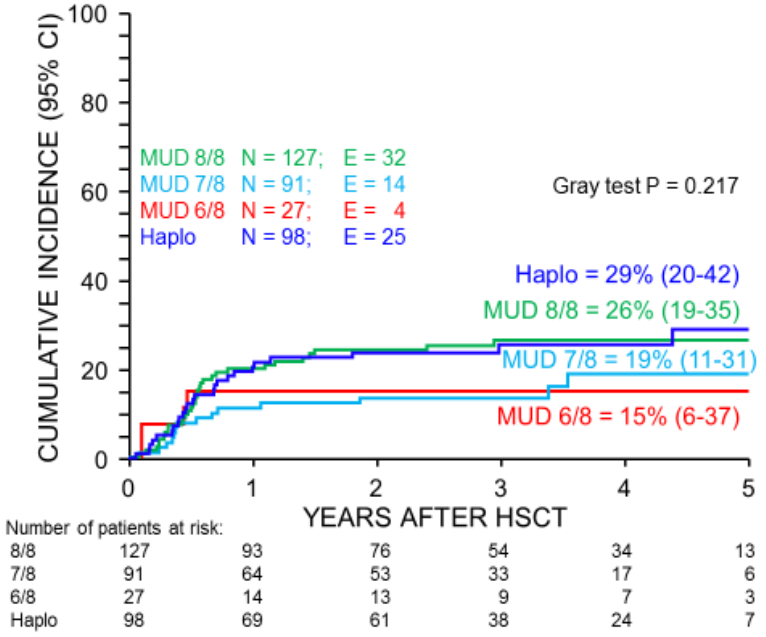
Ped Onco-hematology & Cell Factory
Academic products

Terapia con CAR-T presso la Fondazione: clinical need

HSCT from HLA-haploidentical family donors in children: the AIEOP data (2010-2015)



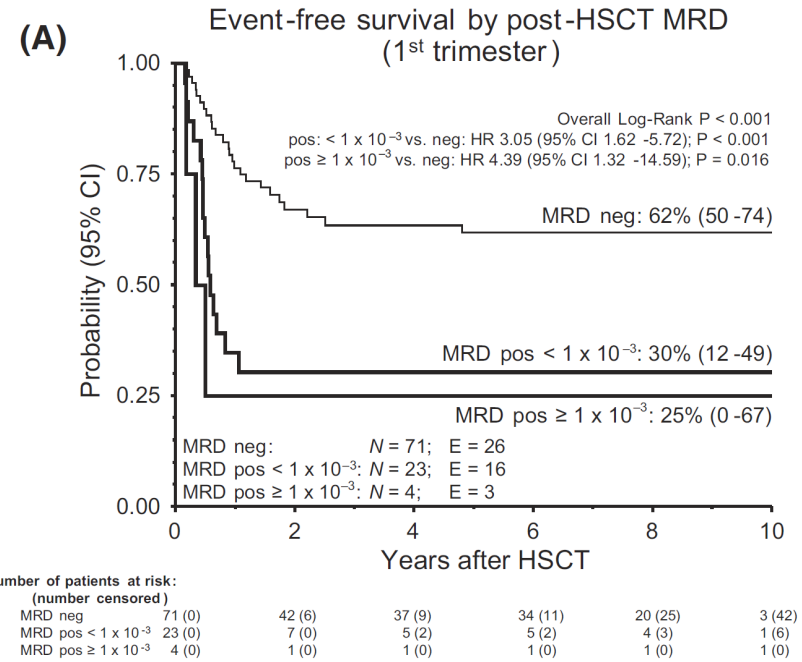
Relapse

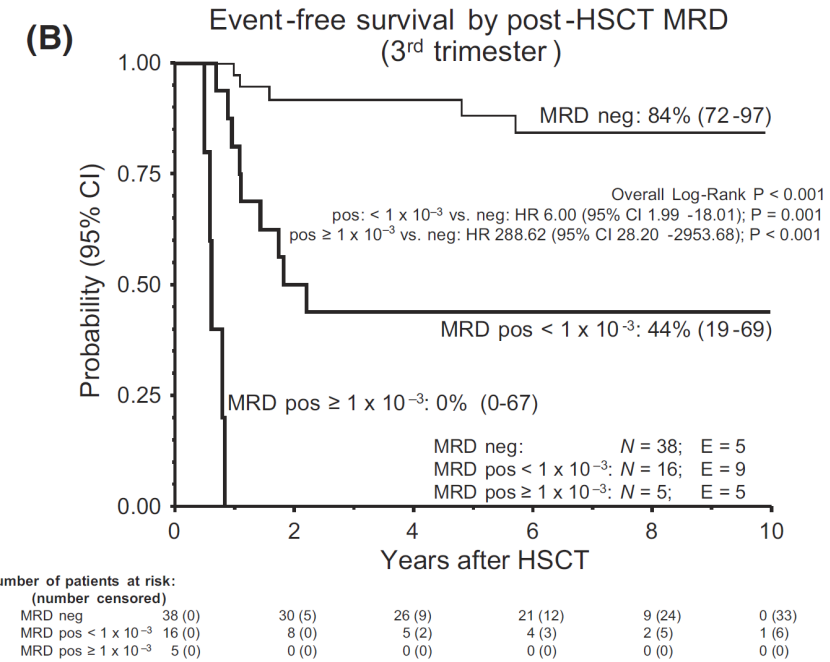


Bertaina A*, Zecca M*, Buldini B, et al, *Blood* 2018

Terapia con CAR-T presso la Fondazione: clinical need

Prognostic significance of MRD levels after HSCT





Lovisa F., Zecca M., Rossi B. *et al*. British Journal of Haematology 2018; 180:680-693.

Terapia con CAR-T presso la Fondazione: clinical need

How we control relapse after haplo-HSCT in children

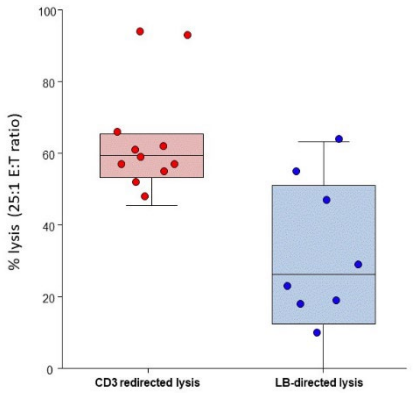
- In pediatric T-cell depleted haplo-HSCT, no post-transplant immunosuppression for GVHD prevention:
  - modulation of IS is not feasible
- The only available option, in the absence of targeted drug therapy: donor lymphocyte infusions (DLI):
  - unmanipulated DLI: high CI of aGVHD
  - modified DLI

Terapia con CAR-T presso la Fondazione: clinical need

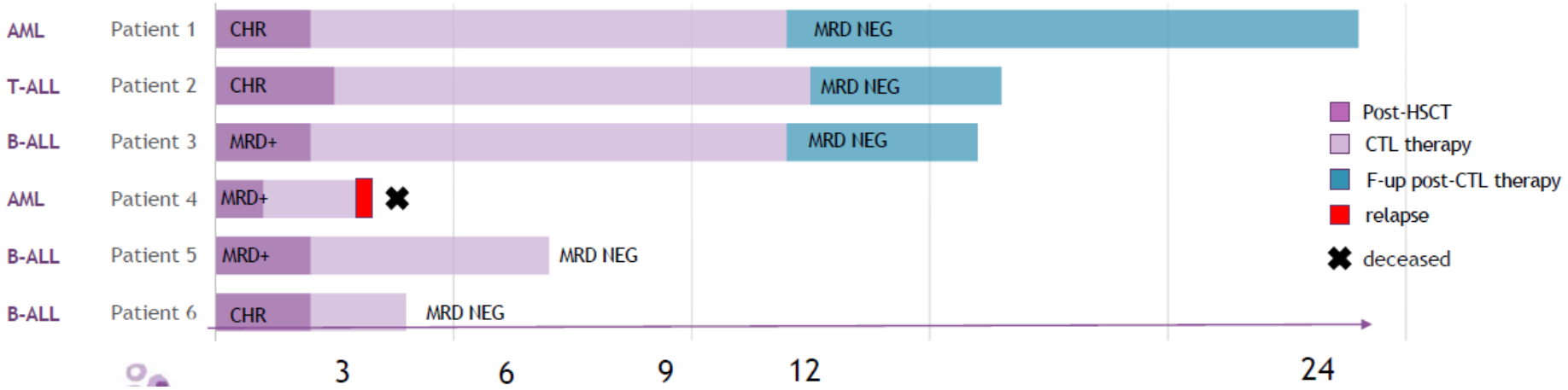
Cell therapy for prevention of relapse after haplo-HSCT for pediatric leukemia Leuk-CTL-001 trial:

Anti-leukemia CTLs:

LB-stimulated donor T cells



Escalating doses of donor leuk-CTL
from 10^4 cells/dose, ½ log every 3 wks, to $8x10^6$ cell/dose



Terapia con CAR-T presso la Fondazione: clinical need

- There is a further clinical need: production of CTLs for those patients lacking cryopreserved leukemic blasts
  - We are working on identifying leukemic targets for cell therapy, in order to expand CTLs with synthetic peptides.
  - alternative: use of CAR-T as a prophylactic/preemptive therapy of relapse after HSCT

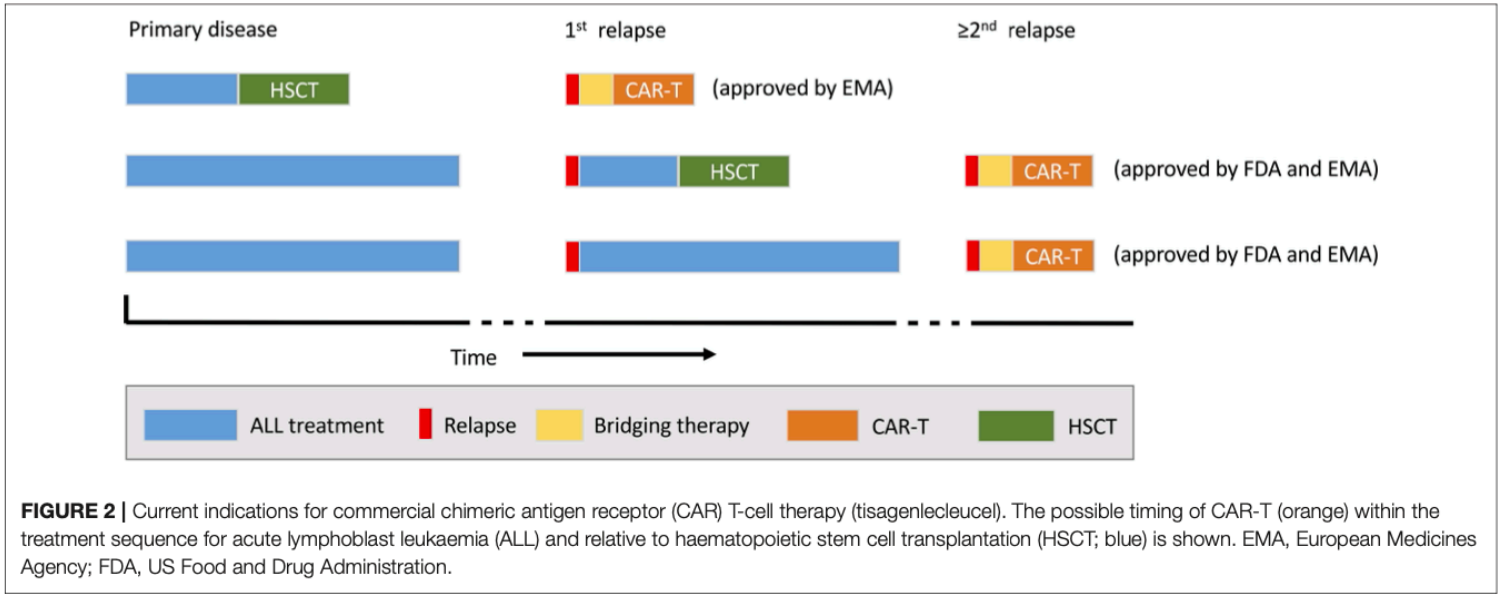


FIGURE 2 | Current indications for commercial chimeric antigen receptor (CAR) T-cell therapy (tisagenlecleucel). The possible timing of CAR-T (orange) within the treatment sequence for acute lymphoblast leukaemia (ALL) and relative to haematopoietic stem cell transplantation (HSCT; blue) is shown. EMA, European Medicines Agency; FDA, US Food and Drug Administration.

Buechner J *et al*. Front Ped 2022; 9:784024.

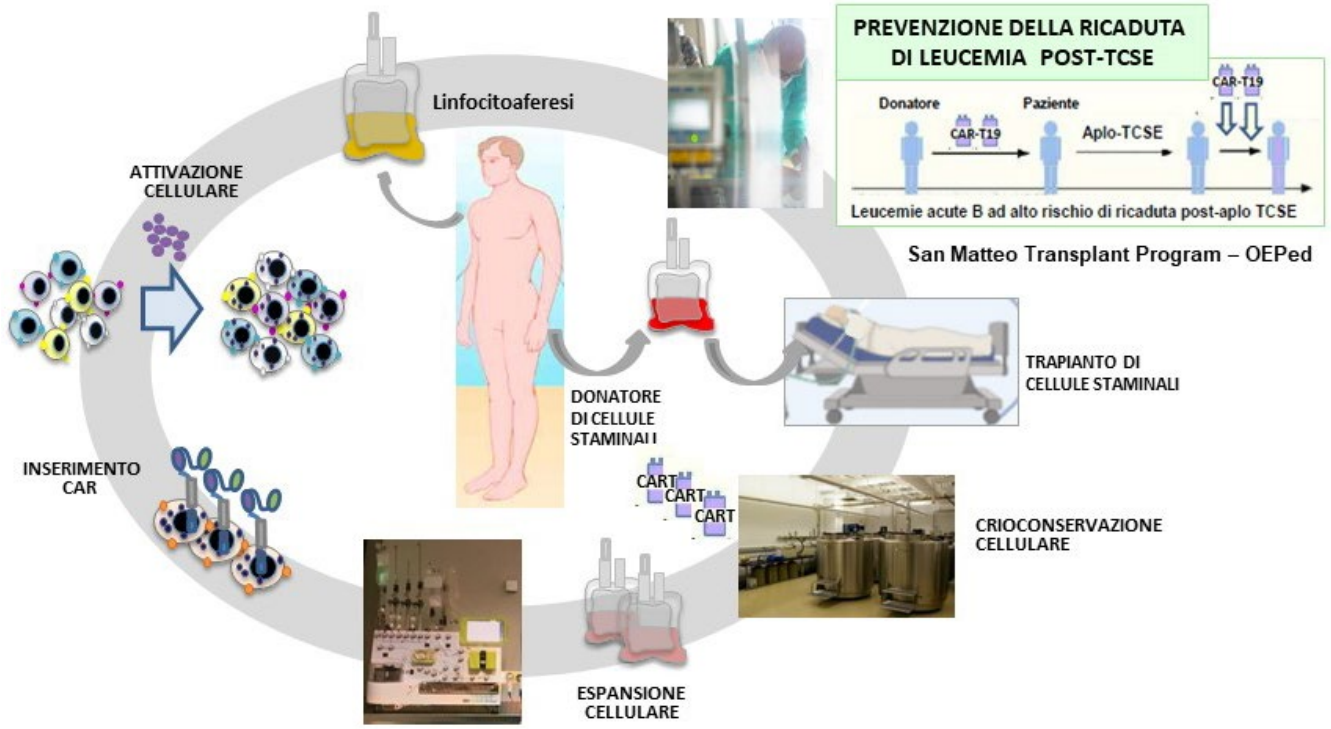
Terapia con CAR-T presso la Fondazione: progetto

- La Fondazione è uno dei centri selezionati da Regione Lombardia per il Programma Regionale e Nazionale CAR-T

Obiettivi strategici 2023-2025

- Protocollo cellule CAR-T CD19 allogeniche dopo aplo-HSCT in pz pediatrici ed adulti

- Protocolli in pipeline:
  - altri tumori ematologici
  - tumori solidi



Terapia con CAR-T presso la Fondazione: progetto

G0

Cell preparation

Selection

Activation

Expansion

Transduction

Formulation (wash)

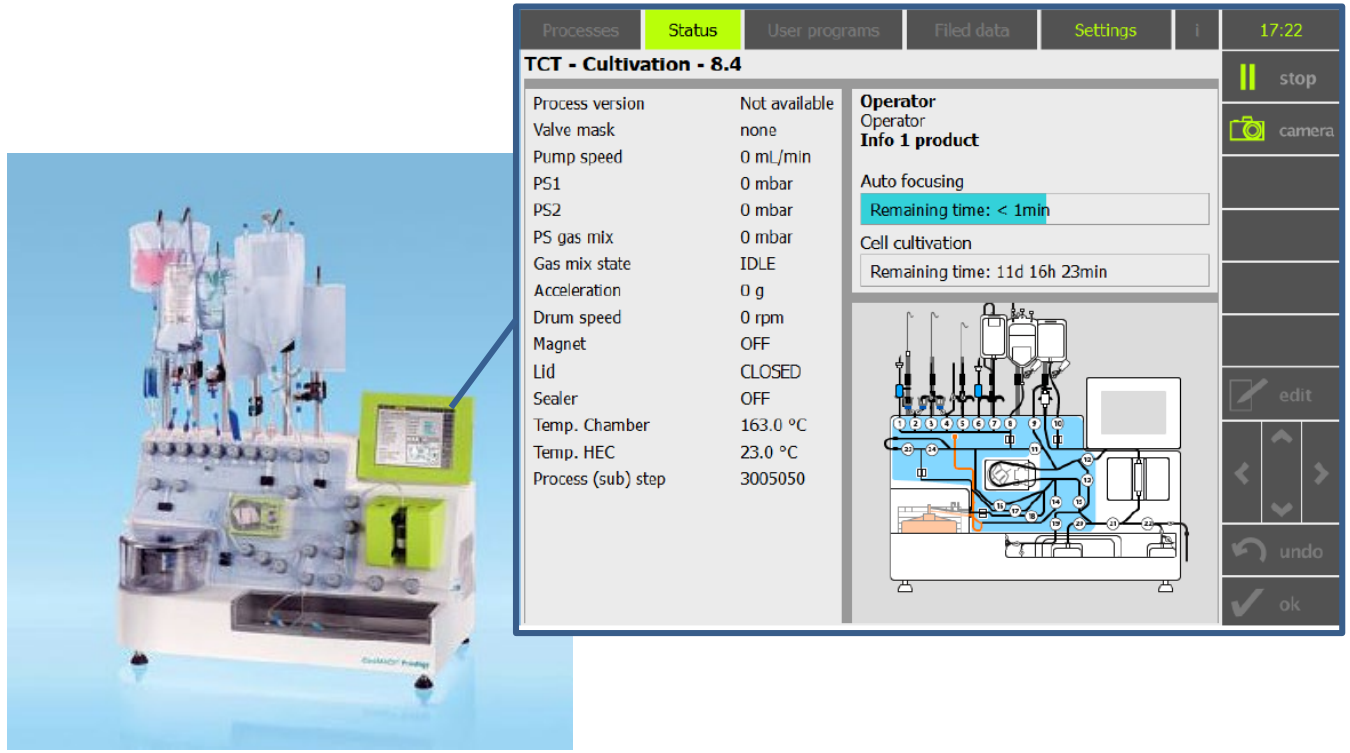
Formulation (concentrate)

G12

Cryopreservation

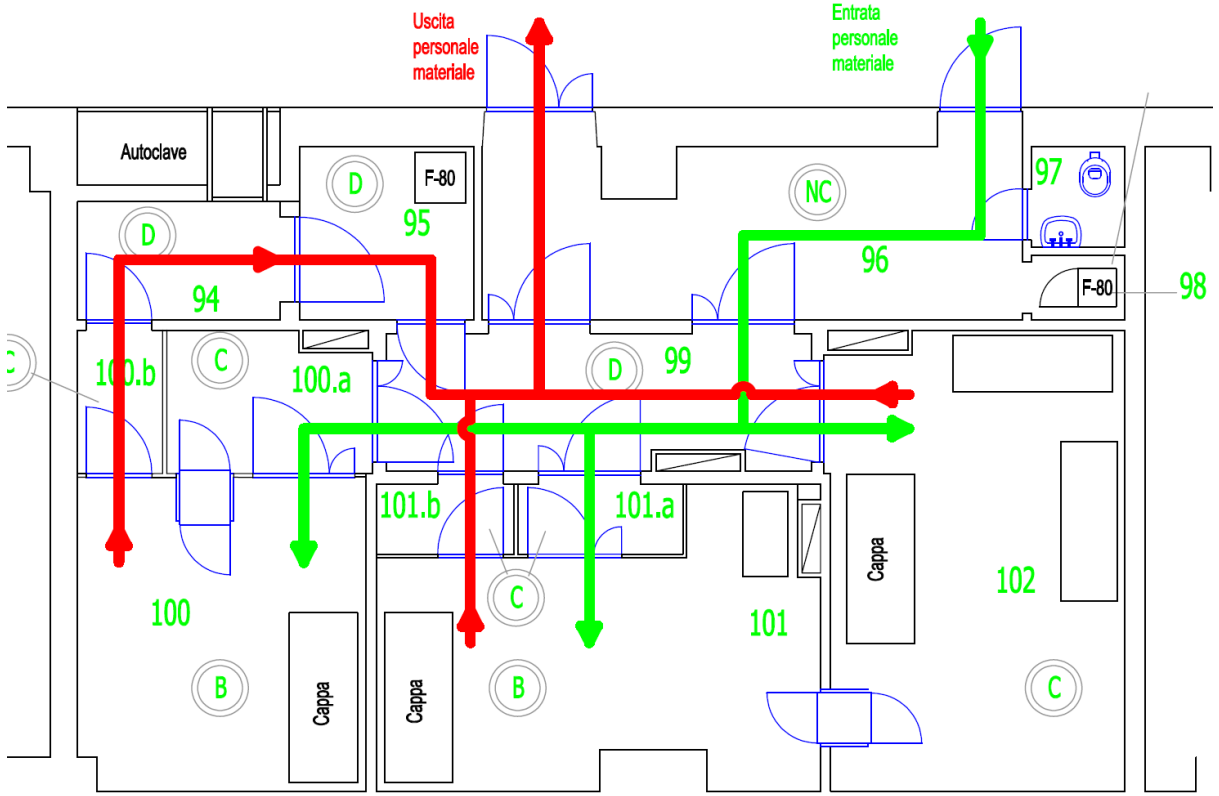
QC (Flow cytometry-based)

- Protocollo allo CAR-T CD19 dopo aplo-TCSE:
  - vettore virale fornito da Miltenyi biotec
  - cellule CAR-T espanse in bioreattore Miltenyi Prodigy: protocollo automatizzato



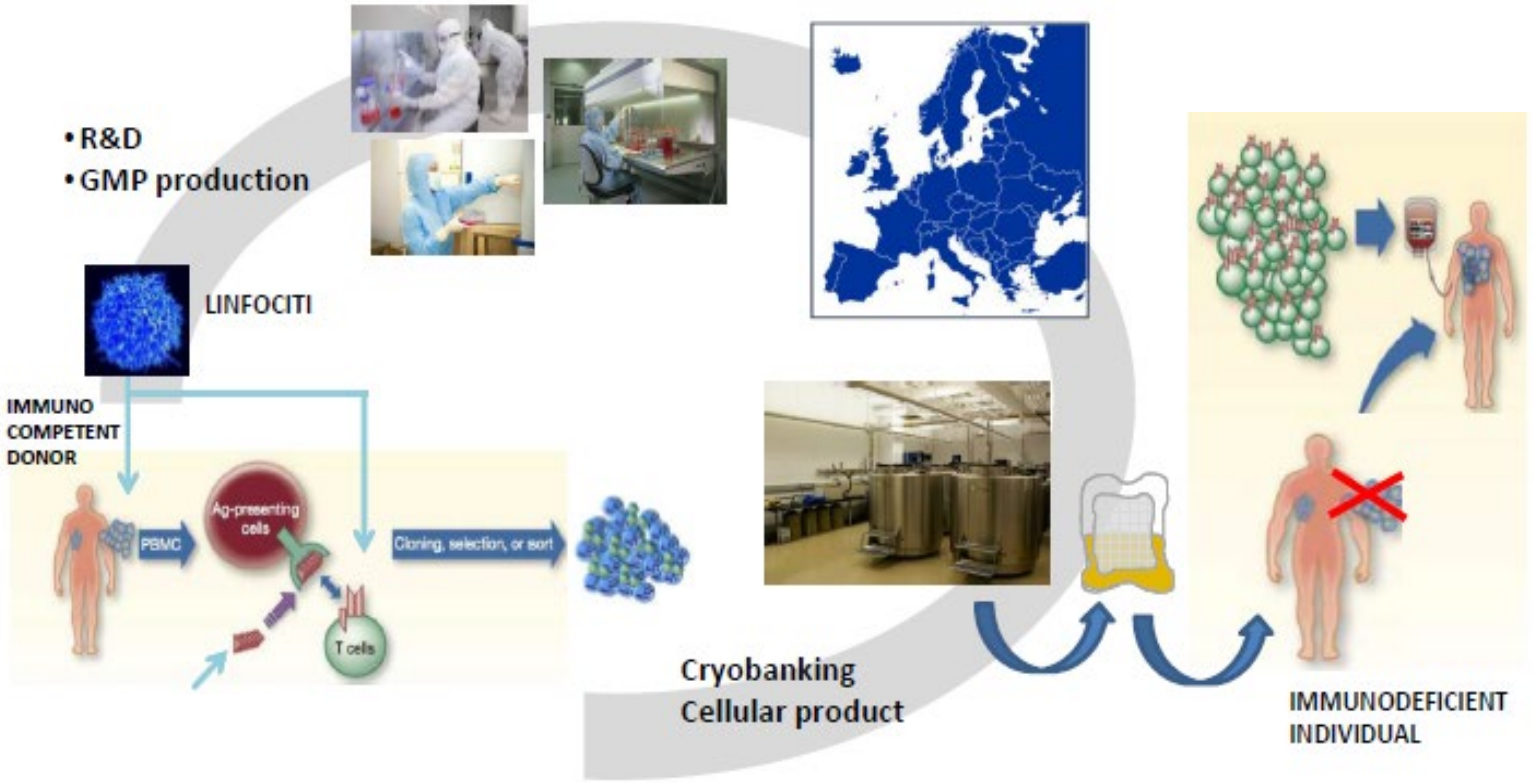
Terapia con CAR-T presso la Fondazione: progetto

- Effettuato audit AIFA dei laboratori disponibili: richiesta di revamping area BL3
- Conclusa la progettazione: avvio lavori previsto per settembre 2024



CAR-T accademiche

The future: banking of third party allogeneic CAR-T



Sistema Socio Sanitario

Regione Lombardia

Fondazione IRCCS Policlinico San Matteo

ATS Pavia

GRAND ROUNDS CLINICI DEL MERCOLEDÌ

con il Policlinico San Matteo

Aula Magna "C. Golgi" & WEBINAR

Grazie per l'attenzione!!

Unit of BMT
Division of Hematology

Hematology 3
Cell Factory