NUOVI FARMACI E TRAPIANTO
Corso educazionale GITMO
Università di Udine 21-22 Gennaio 2016

Anticorpi monoclonali nel condizionamento del trapianto nei linfomi a cellule B

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GITMO ONLUS

ISTITUTO NAZIONALE PER LO STUDIO E LA CURA DEI TUMORI

AGENDA

- **RITUXIMAB**: where do we stand?
  - Survival outcomes - **STUDY EUDRACT 2007- R-ThioFluCy**
  - Immune reconstitution - **STUDY EUDRACT 2007- R-ThioFluCy**

- **TOCILIZUMAB**: study proposal

SURVIVAL OUTCOMES

RITUXIMAB IN ALLO-HCT

1. **Reducing Disease relapse or progression in B cell malignancies**
2. **Reducing GVHD**
3. **Reducing EBV PTLD**

RITUXIMAB IN ALLO-HCT

1. Reducing disease relapse or progression

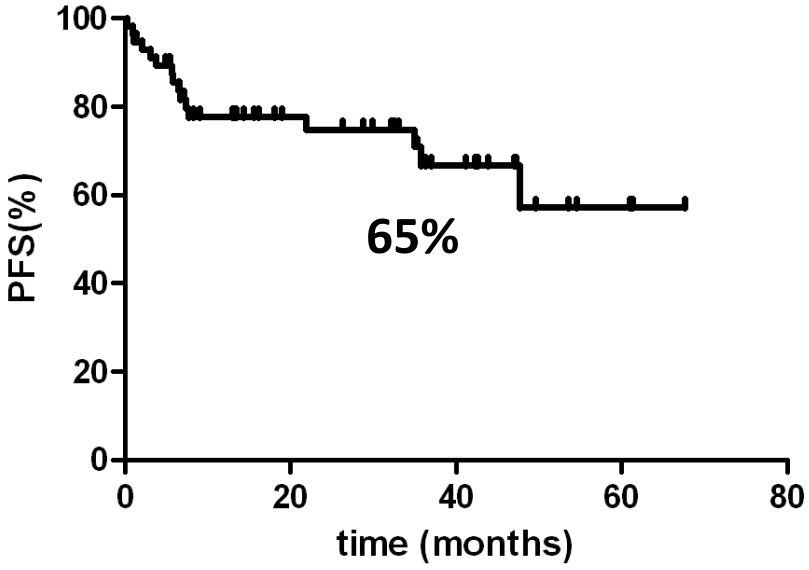
	Study	Disease	PFS
MDACC*	Phase II (#47)	FL	83%(5-year)
Stanford**	Phase II (#35)	CLL, MCL	50% (4-year)
MSKCC°	Phase II (#51)	B-NHL (indolent 80%)	78% (2-year)
Hamburg°°	Phase II randomized (#84)	B-cell 71% vs 74%	45%(3-year)
EUDRACT 2007- R-ThioFluCy§	Phase II vs historical controls (#101)	B-NHL (57%)	3-year FCL 75% CLL 54% DLBCL 30% MCL 46%

**Khouri IF, Blood 2008*
***Arai S, Blood 2012*
°Sauter C, BBMT 2014
°°Glass B, Lancet O 2014
§Dodero A, EBMT 2015

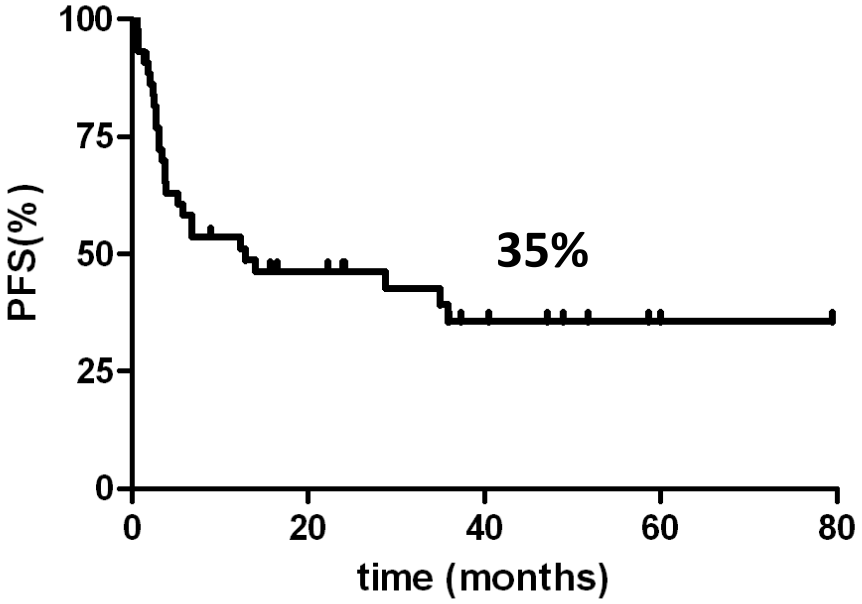
RITUXIMAB IN ALLO-HCT

1. Reducing disease relapse or progression:

PFS at 3 years (EUDRACT 2007 R-ThioFluCy)



Indolent



Aggressive

RITUXIMAB IN ALLO-HCT

2. Reducing GVHD

	Study	Disease	aGVHD 2-4°	cGVHD
MDACC*	Phase II (#47)	FL	11% (5-year)	60% (5-year)
Stanford**	Phase II (#35)	CLL, MCL	6% (4-year)	20% (4-year)
MSKCC°	Phase II (#51)	B-NHL (indolent 80%)	25% (6-month)	29% (2-year)
Hamburg°°	Phase II randomized (#84)	B-cell 71% vs 74%	46% (R) vs 42% (1-year, 0.74)	Extensive 33% vs 41% (3-year, p=0.28)
EUDRACT 2007- R-ThioFluCy§	Phase II vs historical controls (#101)	B-NHL (57%)	24% (R) vs 35% (100-day, p=0.16)	46% (R) vs 47% (3-year, p=0.16)

**Khouri IF, Blood 2008*
***Arai S, Blood 2012*
°Sauter C, BBMT 2014
°°Glass B, Lancet O 2014
§Dodero A, EBMT 2015

RITUXIMAB IN ALLO-HCT

2. Reducing GVHD (Hamburg)

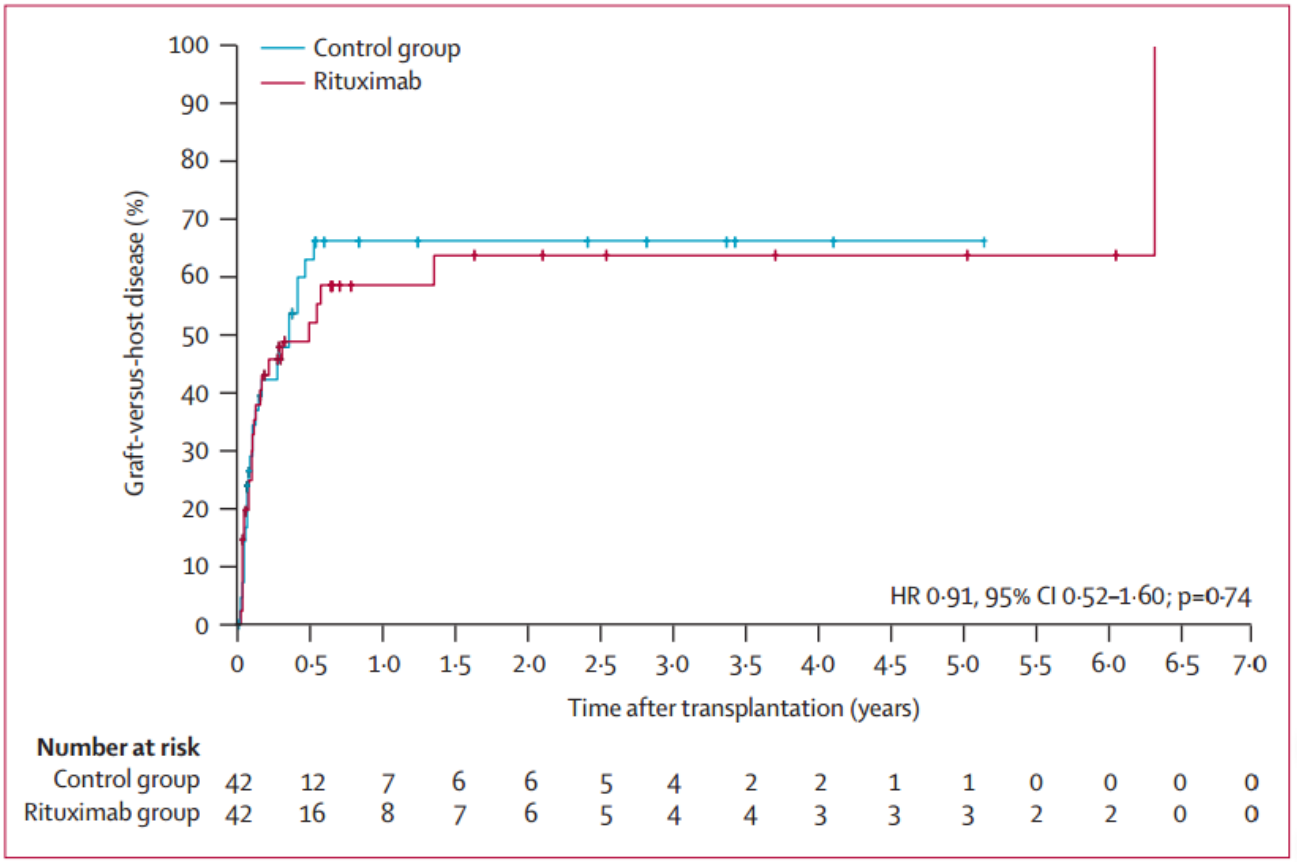
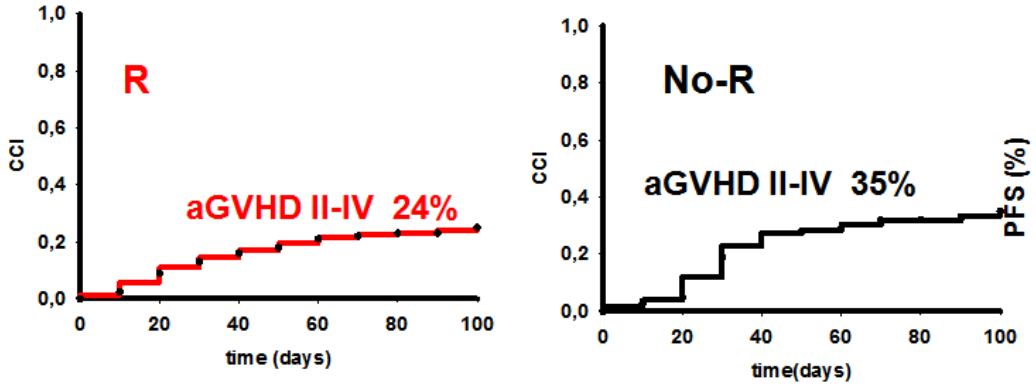


Figure 2: **Kaplan-Meier analysis of acute graft-versus-host disease (grade 2–4) or extensive chronic graft-versus-host disease**

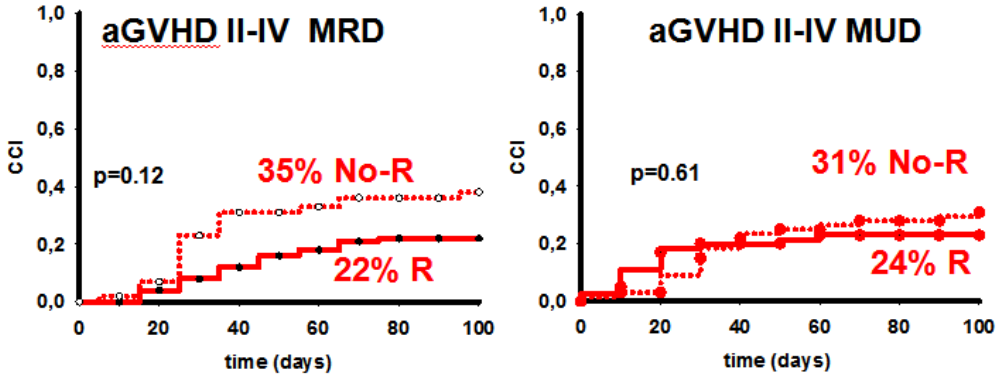
HR=hazard ratio.

RITUXIMAB IN ALLO-HCT

2. Reducing GVHD (EUDRACT 2007 R-ThioFluCy)

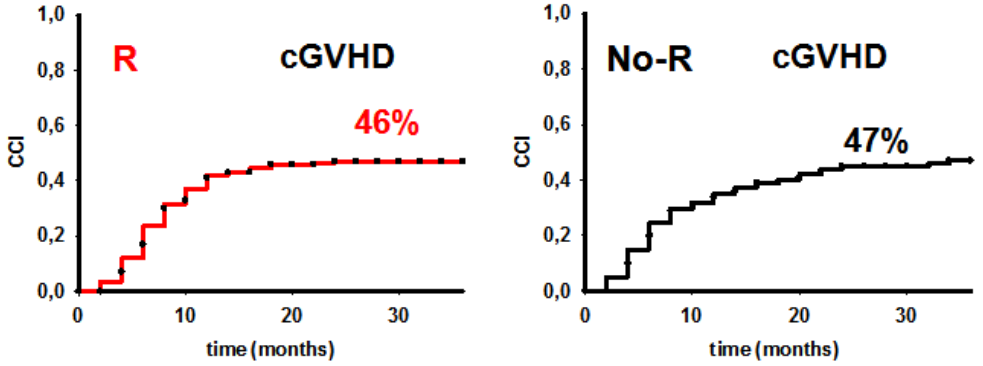


Acute GVHD R versus No-R: p=0.16

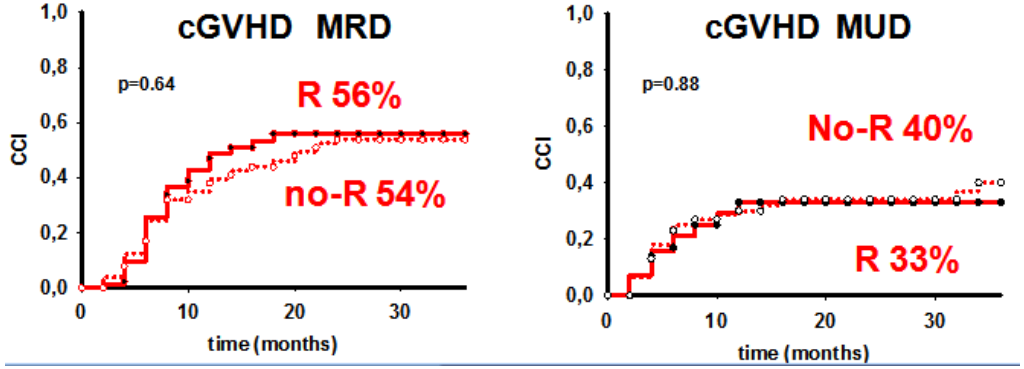


RITUXIMAB IN ALLO-HCT

2. Reducing GVHD (EUDRACT 2007 R-ThioFluCy)

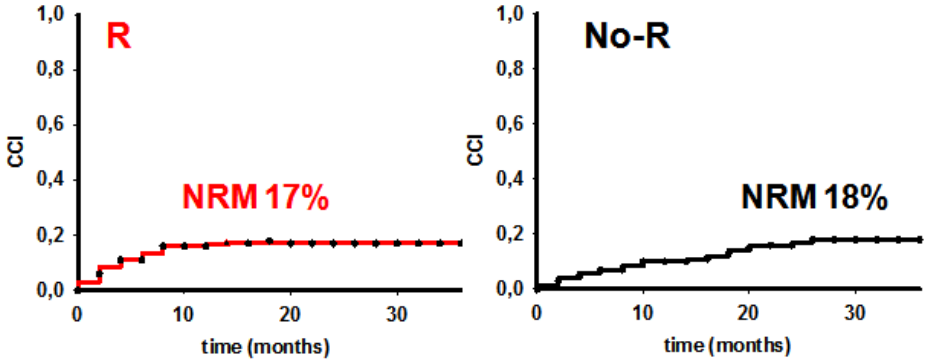


Chronic GVHD R versus No-R: p=0.16



RITUXIMAB IN ALLO-HCT

2. Reducing GVHD (EUDRACT 2007 R-ThioFluCy)



	R	No-R	P Value
NRM Deaths concomitant to GVHD	6/14 (43%)	13/14 (93%)	p=0.01

	R	No-R	P Value
CCI of deaths without GVHD days 0-100	9%	2%	p=0.02

RITUXIMAB IN ALLO-HCT

3. Reducing EBV PTLD

	Study	Disease	EBV PTLD
MDACC*	Phase II (#47)	FL	Not reported
Stanford**	Phase II (#35)	CLL, MCL	No events
MSKCC°	Phase II (#51)	B-NHL (indolent 80%)	No events
Hamburg°°	Phase II randomized (#84)	B-cell 71% vs 74%	Not reported
EUDRACT 2007- R-ThioFluCy§	Phase II vs historical controls (#101)	B-NHL (57%)	Not reported (updating)

**Khouri IF, Blood 2008*
***Arai S, Blood 2012*
°Sauter C, BBMT 2014
°°Glass B, Lancet O 2014
§Dodero A, EBMT 2015

RITUXIMAB IN ALLO-HCT

3. Reducing EBV PTLD (ATG vs no ATG)

	Study	Disease	EBV PTLD	EBV reactivation
Kroger*	Phase III (#168)	Acute leukemias	Not reported	3.2% (ATG) vs 1.4%
Walker**	Phase II (#203)	Leukemias Lymphomas	Not reported	33% (1 death,ATG) vs 2%

**Kroger N, NEJM 2016*
***Walker I, Lancet O 2015*

RITUXIMAB IN ALLO-HCT

1. Reducing RI/POD → not observed
2. Reducing non relapse mortality →

   possible acute GVHD reduction

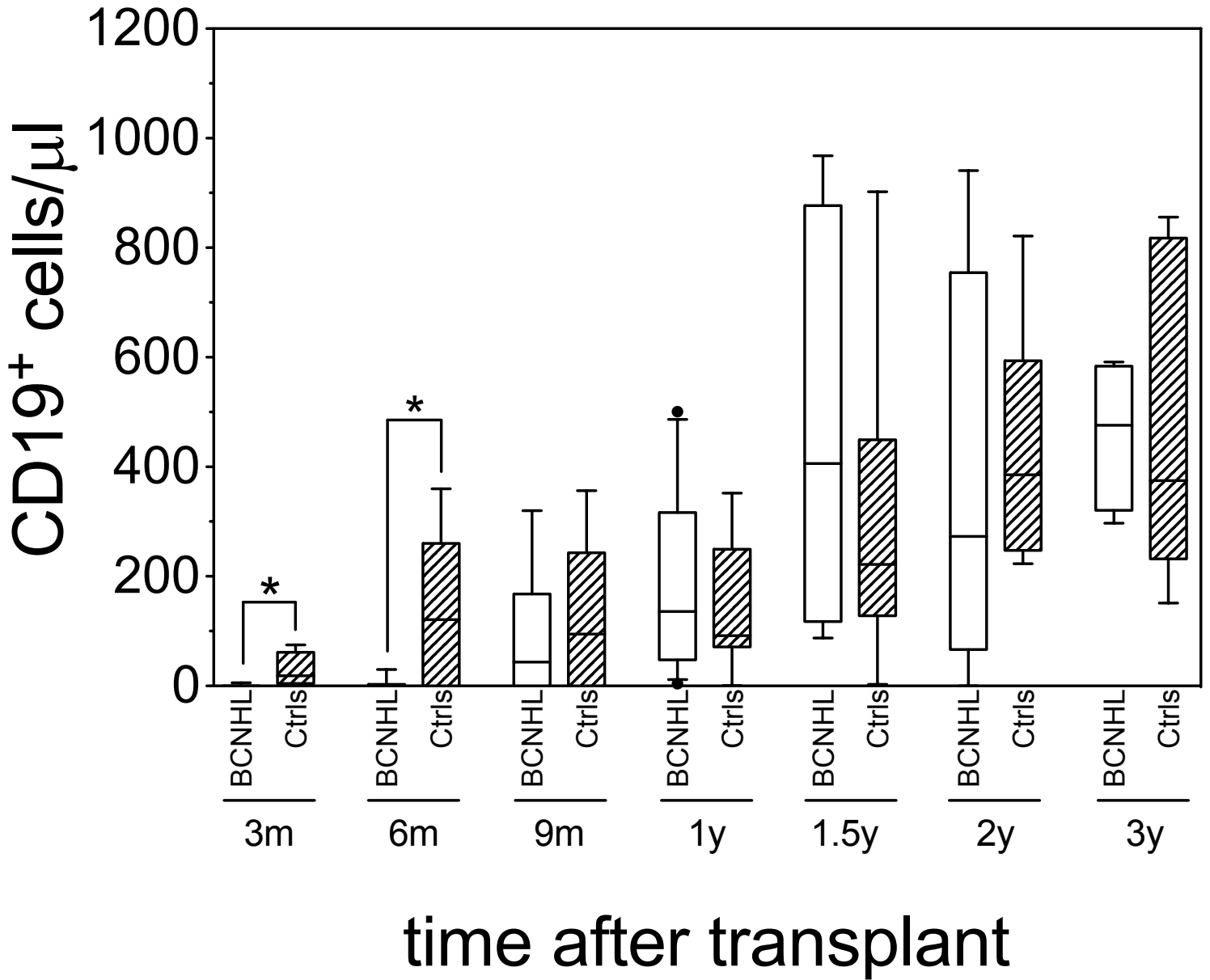
   possible lower GVHD mortality (EUDRACT 2007 R-ThioFluCy)

3. Reducing EBV PTLD → anti EBV reactivation

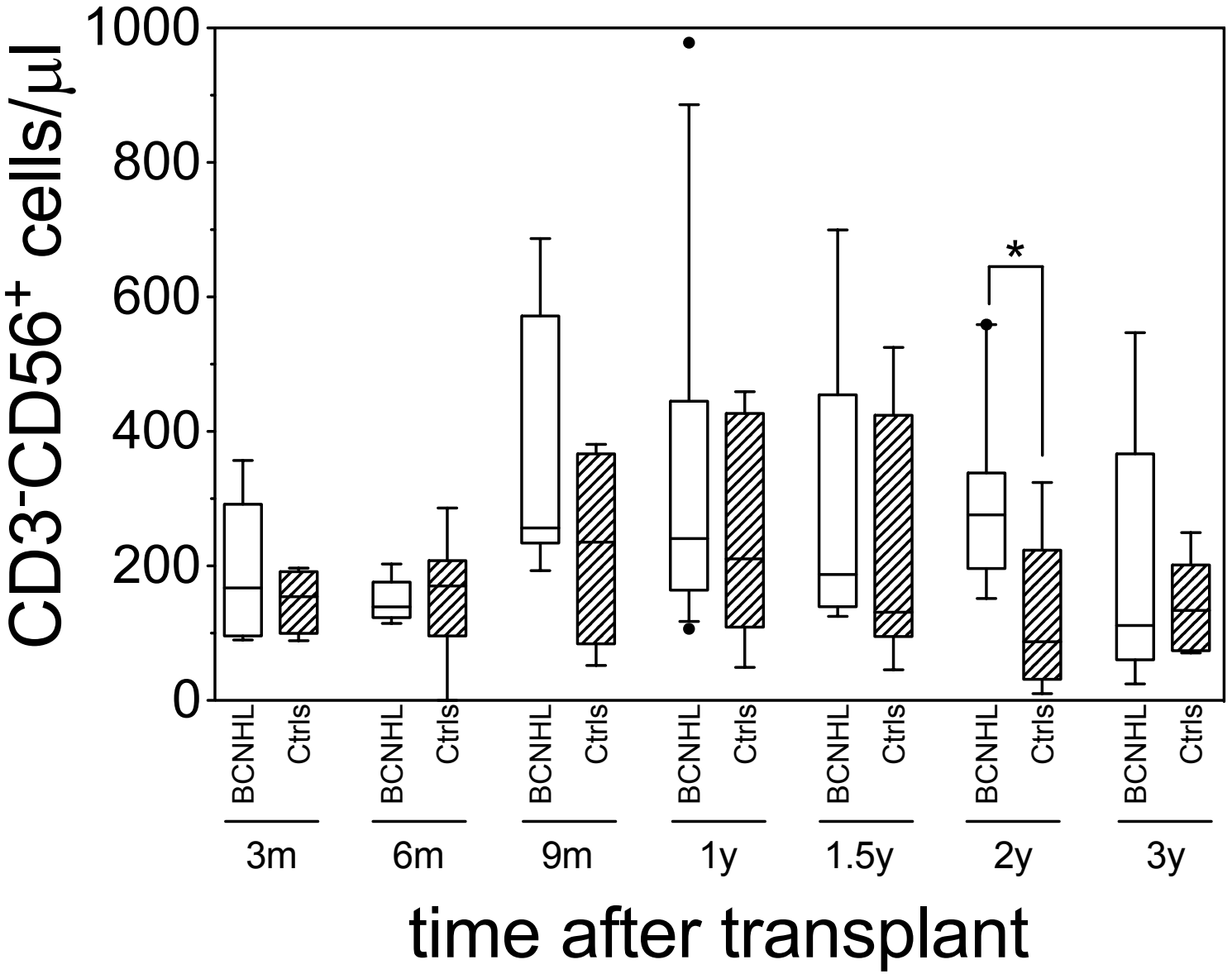
   effect to be verified

IMMUNE RECONSTITUTION (R-ThioFluCy)

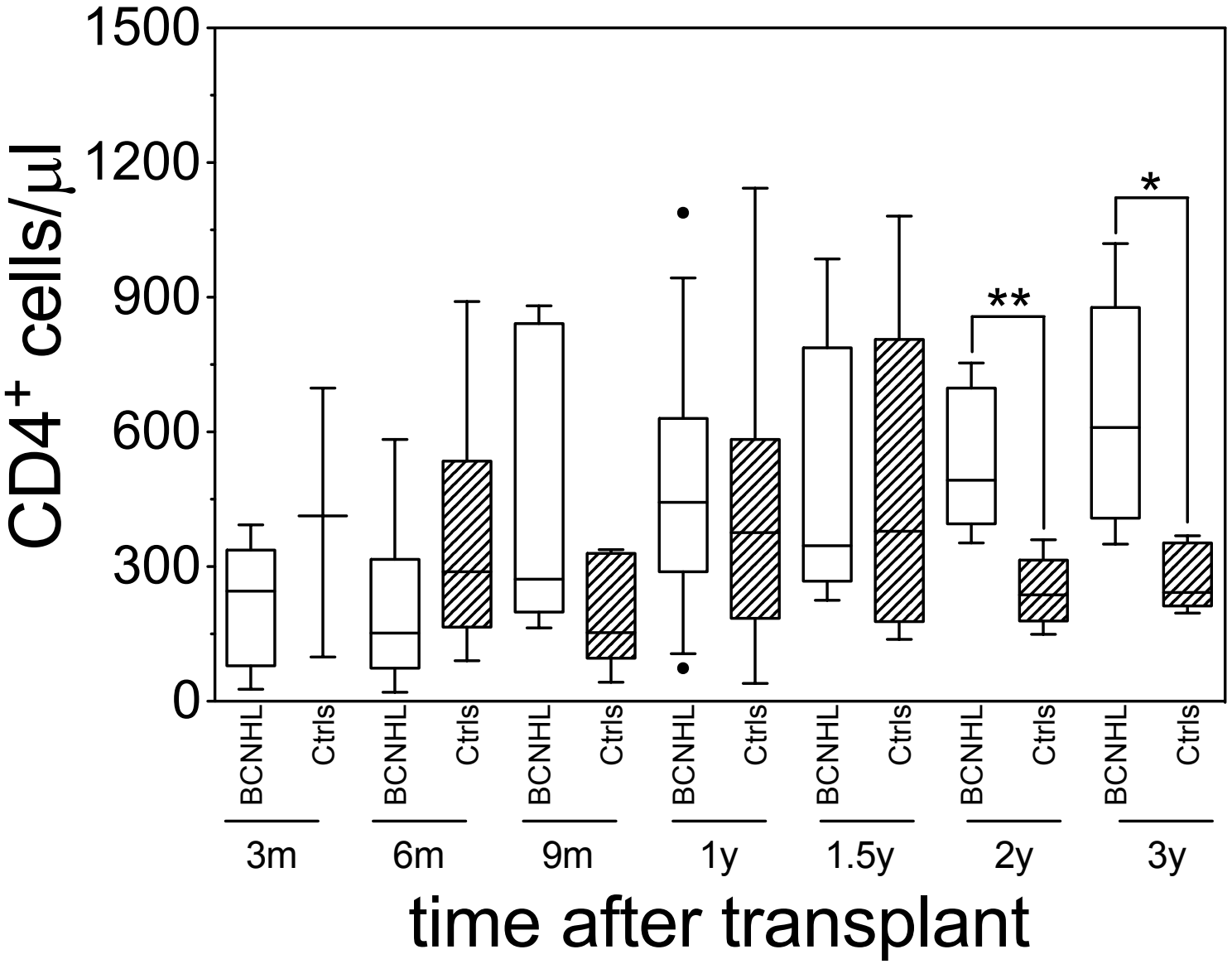
As expected B-cell counts are significantly lower in the BCNHL as compared to the Ctrls in the early phase upon HSCT



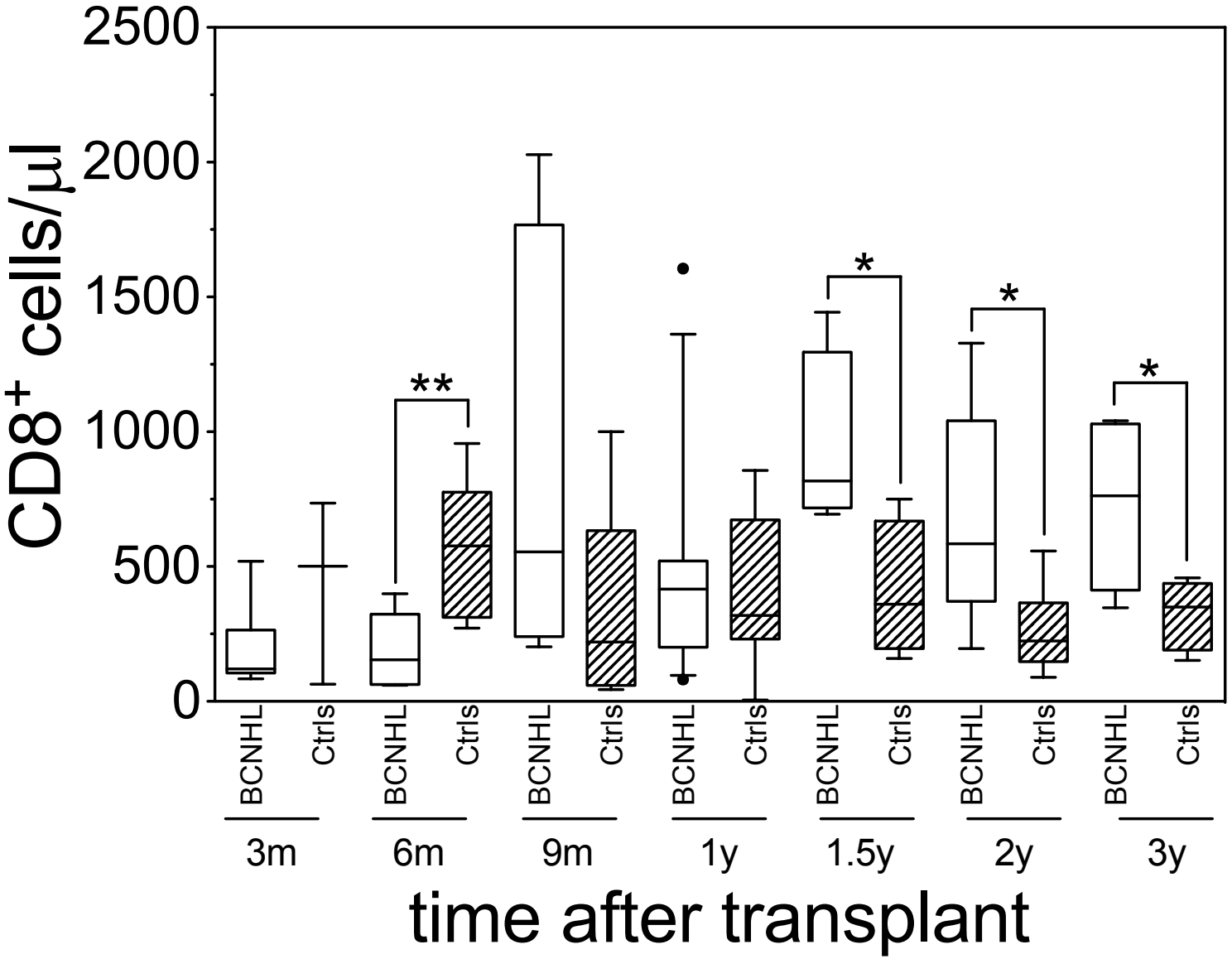
No relevant differences in NK cell Immune Reconstitution



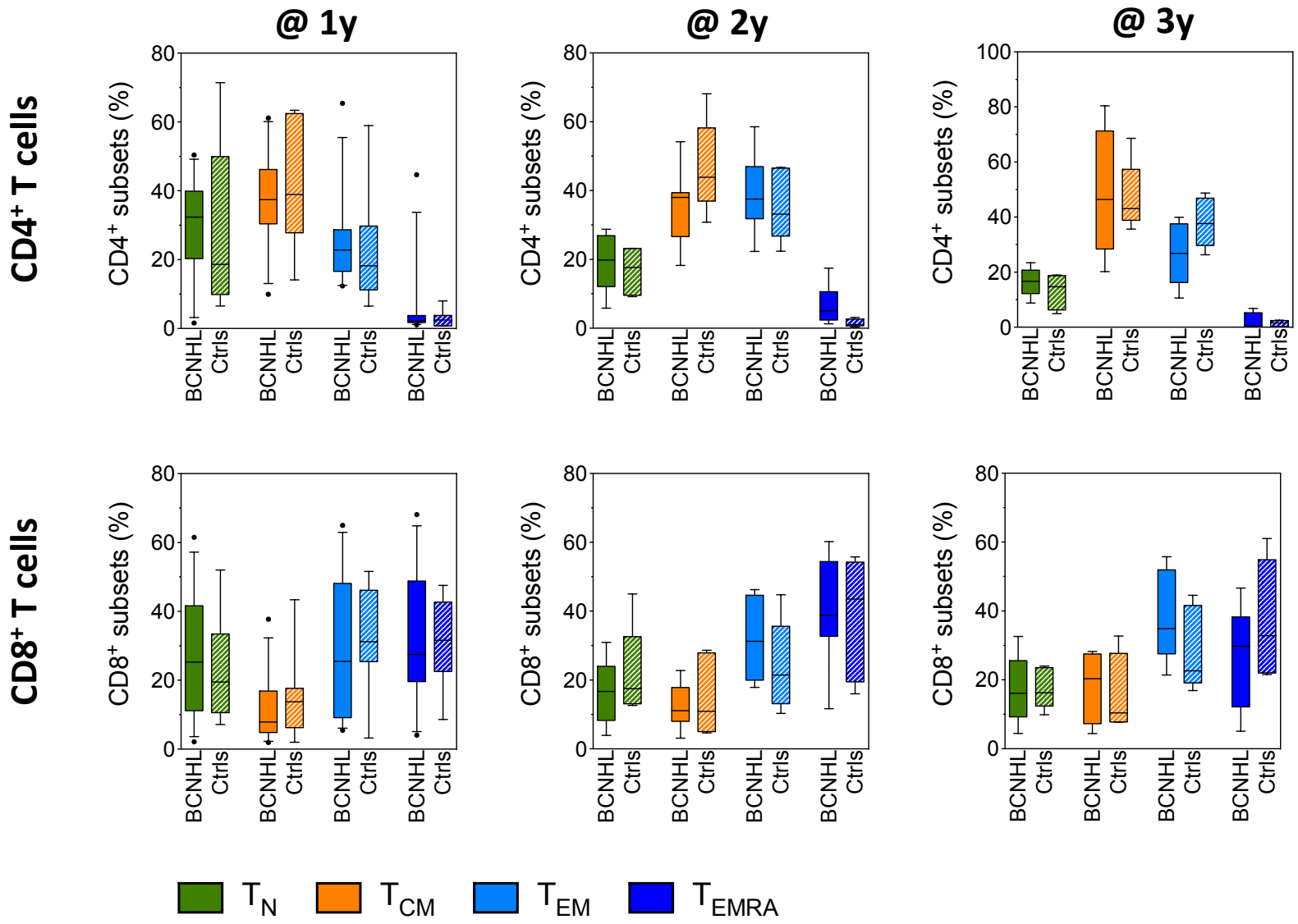
Also for CD4⁺ T cells, BCNHL group shows significantly higher numbers of circulating cells at late time-points after HSCT



CD8+ T cells display superimposable dynamics



No relevant difference in T-cell subset distribution among the two groups analyzed



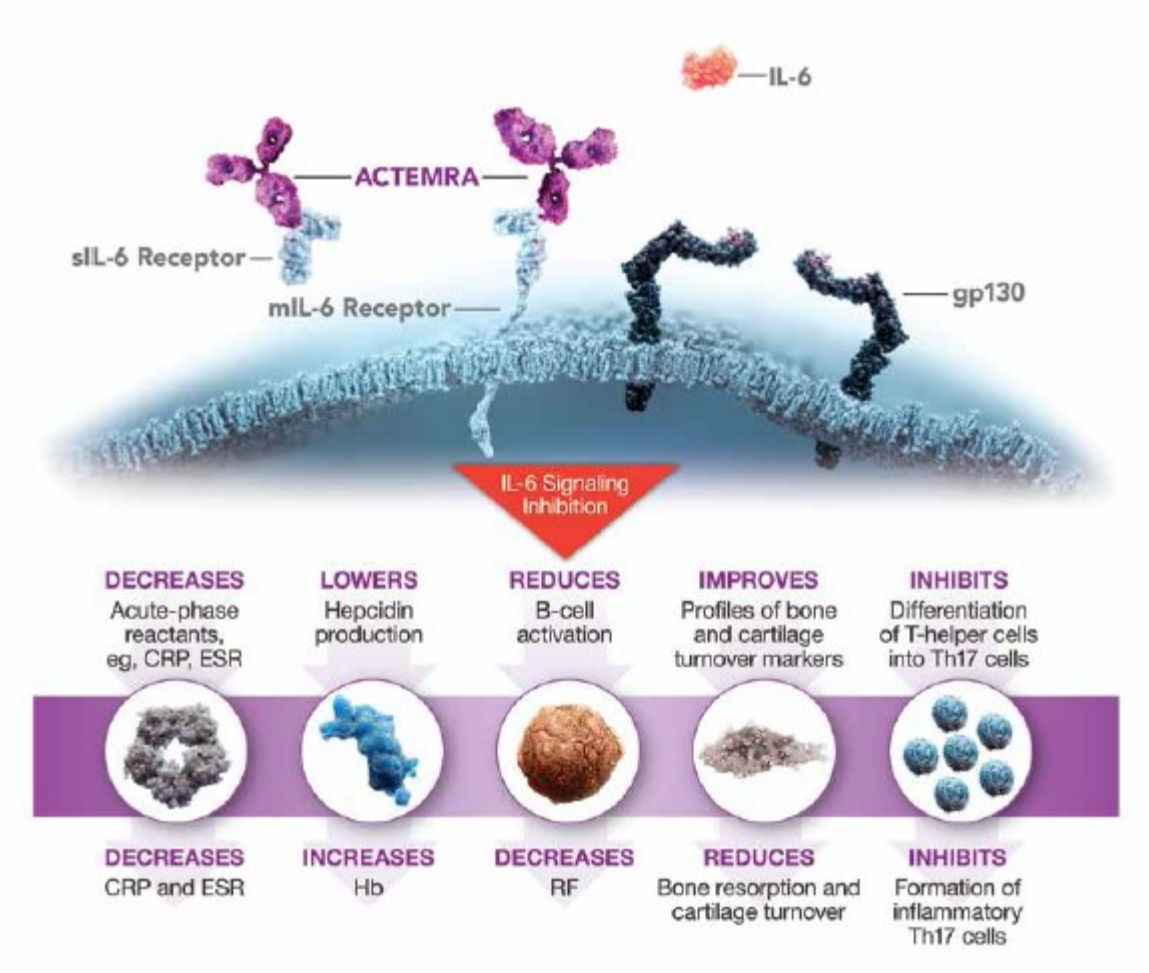
RITUXIMAB IN ALLO-HCT

1. **Delayed CD19 cell recovery (<6 months)**

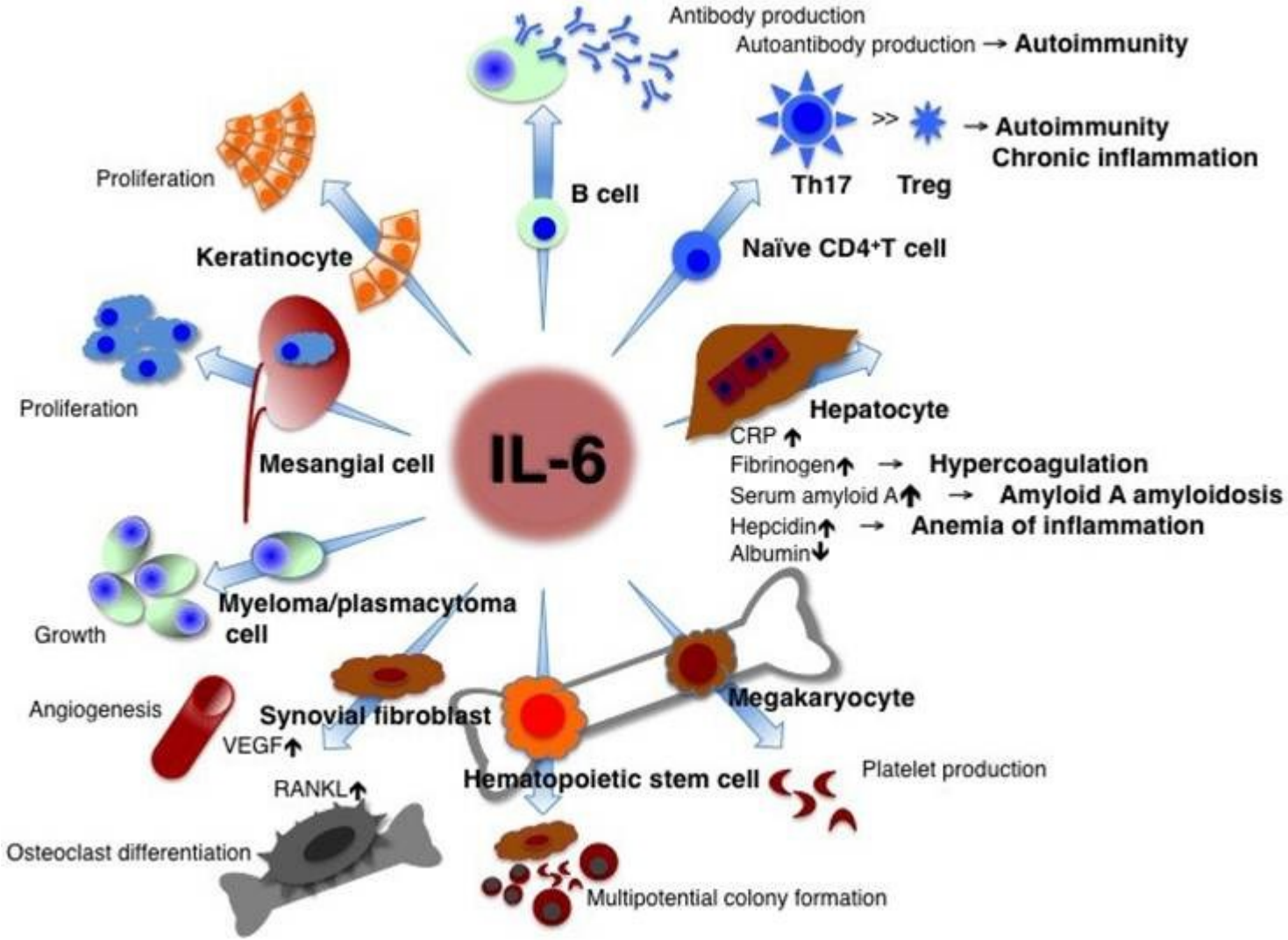
1. **Good CD4/CD8 immune recovery (>2 years)**

NEXT STUDY: TOCILIZUMAB

Tocilizumab



IL-6


Antibody production
Autoantibody production → Autoimmunity
B cell
Th17
>>
Treg
→ Autoimmunity
Chronic inflammation
Naïve CD4+T cell
Proliferation
Keratinocyte
Proliferation
Mesangial cell
IL-6
Hepatocyte
CRP ↑
Fibrinogen↑ → Hypercoagulation
Serum amyloid A↑ → Amyloid A amyloidosis
Hepcidin↑ → Anemia of inflammation
Albumin↓
Growth
Myeloma/plasmacytoma cell
Angiogenesis
VEGF↑
Synovial fibroblast
Megakaryocyte
Hematopoietic stem cell
Platelet production
RANKL↑
Osteoclast differentiation
Multipotential colony formation

Tocilizumab as antiGVHD prophylaxis

WORKING ON TRM/GVHD

- Phase 1-2 study
- 48 patients: lymphoid and myeloid tumors
- MAC (Cy/TBI) or RIC (Flu/Mel) conditioning
- HLA matched (10/10) related or unrelated
- Standard antiGVHD prophylaxis (CSA/MTX)

Kennedy GA, Lancet 2014

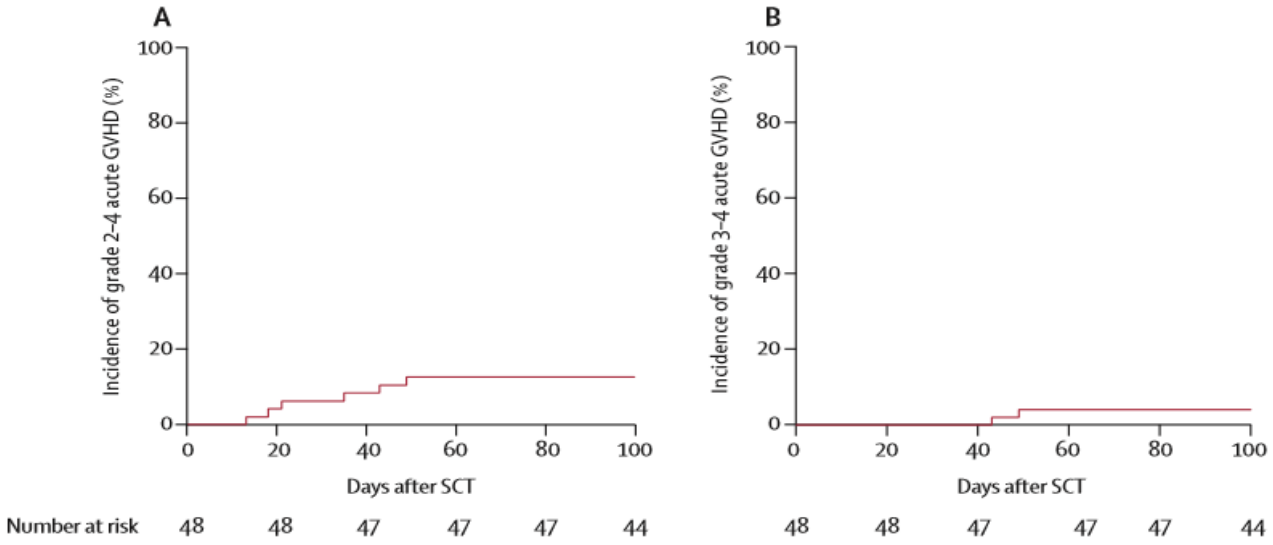
Tocilizumab as antiGVHD prophylaxis

- Median follow up 2 years
- TRM 4%
- RI/POD 27%
- PFS 68%
- OS 84%

Kennedy GA, Lancet 2014

Tocilizumab as antiGVHD prophylaxis

- Grade 2-4 acute GVHD day +100: 12%
- Grade 3-4 acute GVHD day +100: 4%
- Overall chronic GVHD year +2: 51%
- Extensive chronic GVHD year +2: 22%



Kennedy GA, Lancet 2014

TOWARD STUDY

TOcilizumab With ATG in Reducing graft versus host Disease

- Confirm a role for tocilizumab
- Extend donor availability (≥8/10 HLA)
- Decrease chronic GVHD (51% in Kennedy's study)

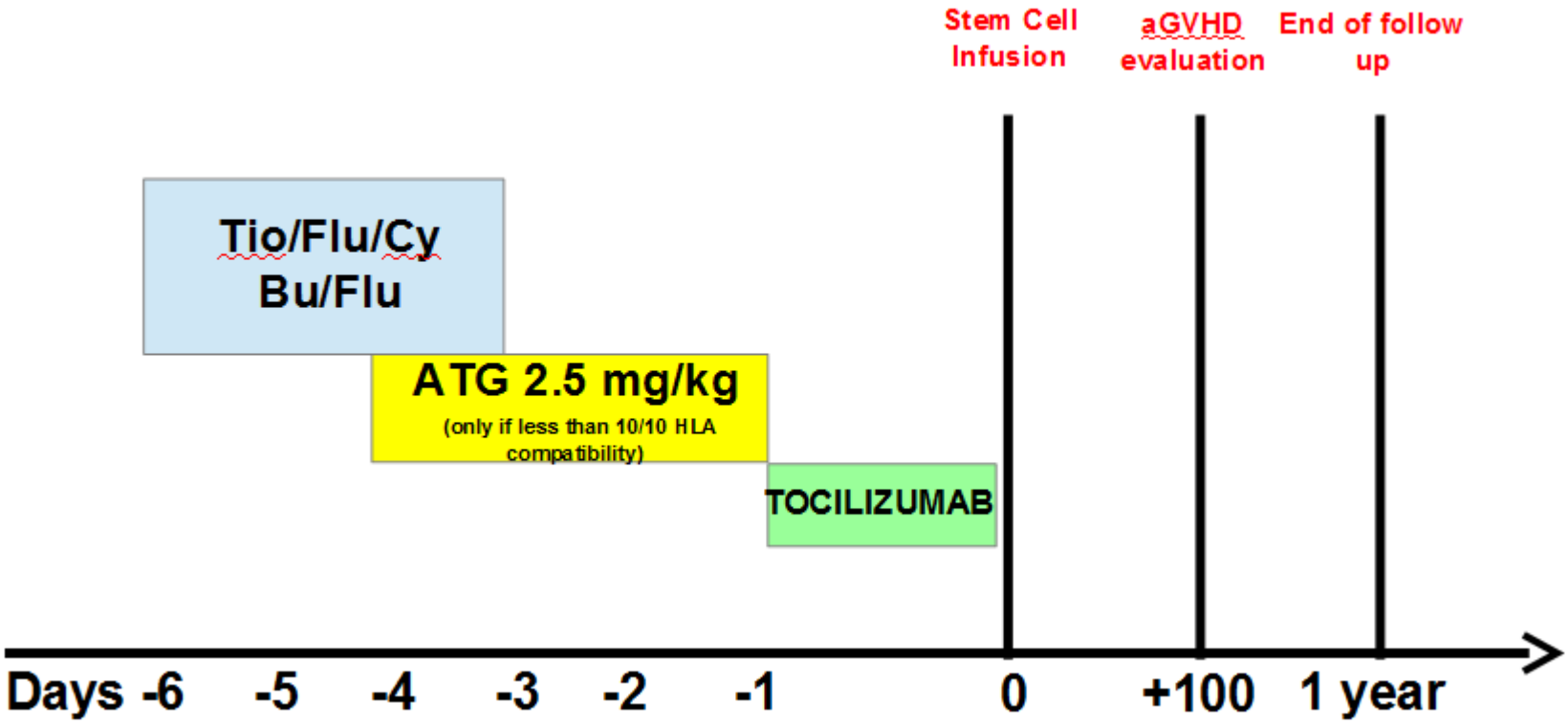
TOWARD STUDY

TOcilizumab With ATG in Reducing graft versus host Disease

Disease	Myeloid + lymphoid malignancies
Donors	-Related or unrelated donors -≥8/10 HLA compatibility
Sample size	30 patients
Primary Endpoint	**Acute GVHD II-IV day +100 (<25%)**
Secondary Endpoint	**Chronic GVHD 1-year (descriptive)**
Statistical design	Phase 2, Simon's optimal two-stage design

TOWARD STUDY

TOcilizumab With ATG in Reducing graft versus host Disease



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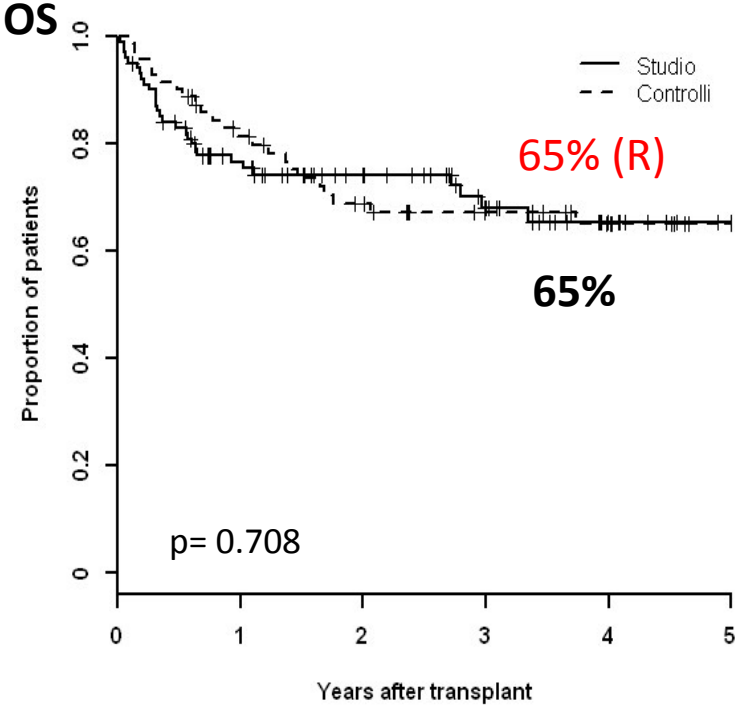
GITMO
GRUPPO ITALIANO TRAPIANTO MIDOLLO OSSEO

Patients characteristics

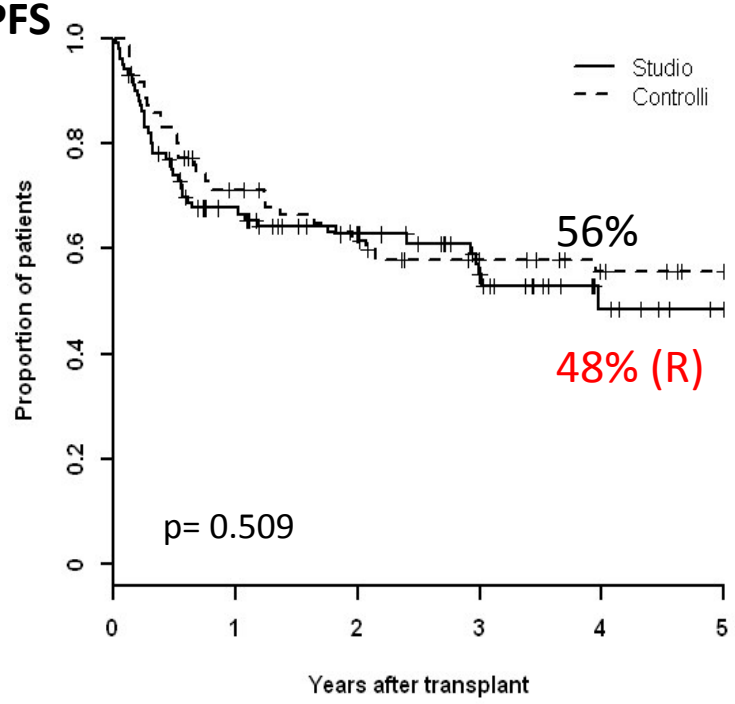
Variable	Study (Rituximab) N=101	Control (No Rituximab) N=71
Age (median)	52 years	51 years
indolent	57 (56%)	32 (45%)
aggressive	44 (44%)	39 (55%)
CR at transplant	40(39%)	31 (44%)
HLA related	54 (54%)	39 (55%)
HLA unrelated	47 (47%)	32 (45%)
HLA unrelated with mismatched	14 (13%)	14 (20%)
N°previous lines (median)	3	3
Prior autoSCT	62 (61%)	46 (65%)

OS e PFS

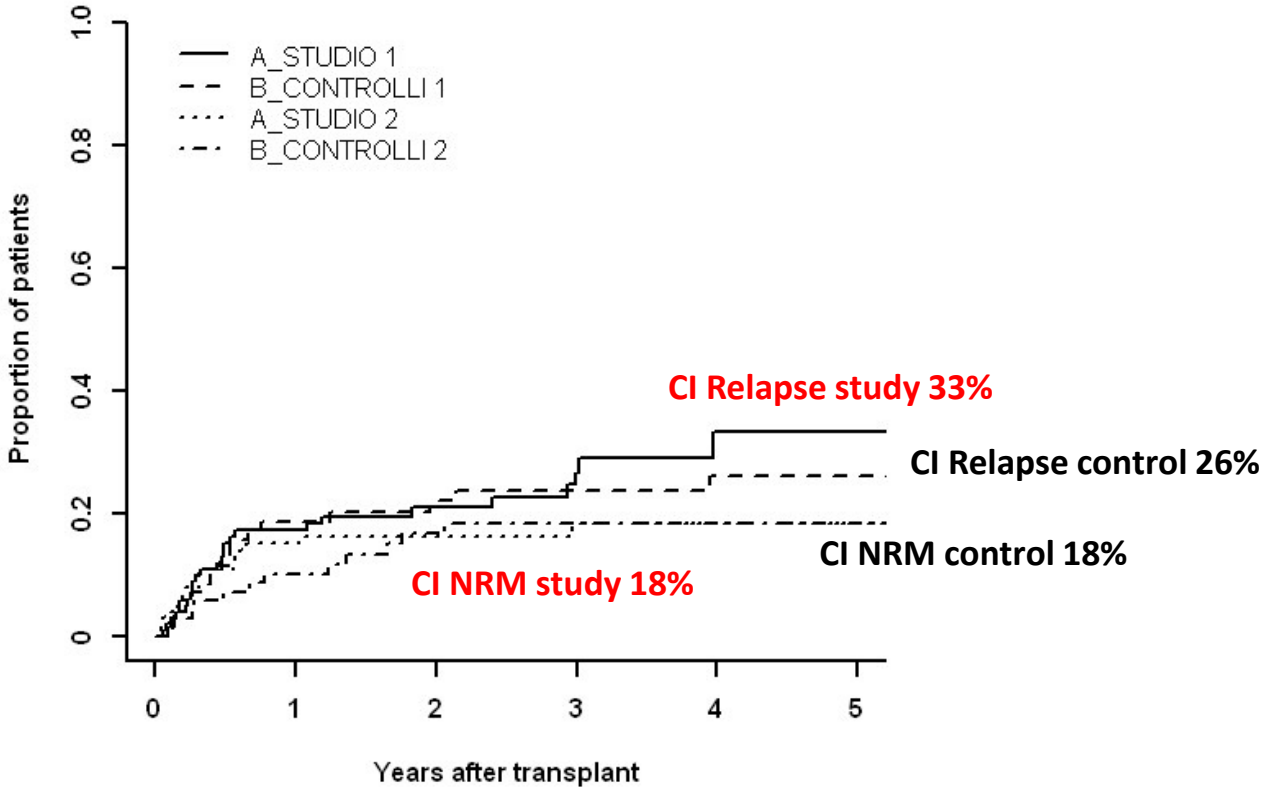
OS



PFS



Relapse/Progression and TRM



CI relapse study versus control (p=0.61); CI NRM relapse versus control (p=0.81)

GFRS composite endpoint

All Patients