22 OTTOBRE 2020

5 NOVEMBRE 2020

20 GENNAIO 2021

CONDIVISIONE

Incontri di esperienze e punti di vista sulla terapia di condizionamento pre-HSCT

Treosulfano
Questioni Aperte e Potenziali Sviluppi Futuri

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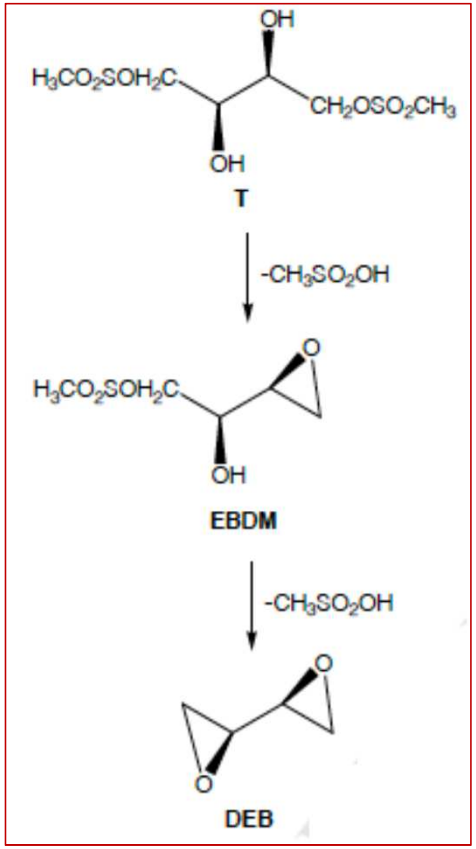
UNIVERSITÀ DEGLI STUDI DI BRESCIA

Sistema Socio Sanitario
Regione Lombardia
ASST Spedali Civili

Treosulfan – Phamacologic Profile

- **Treosulfan** is a water-soluble, bifunctional alkylating agent.
- Treosulfan is a prodrug (pH >5 dependent activation)
  - **NOT require enzymatic activation or hepatic metabolism**
- LOW INTER- and INTRAPATIENT VARIABILITY
- NOT require DRUG LEVEL MONITORING and ADJUSTMENT

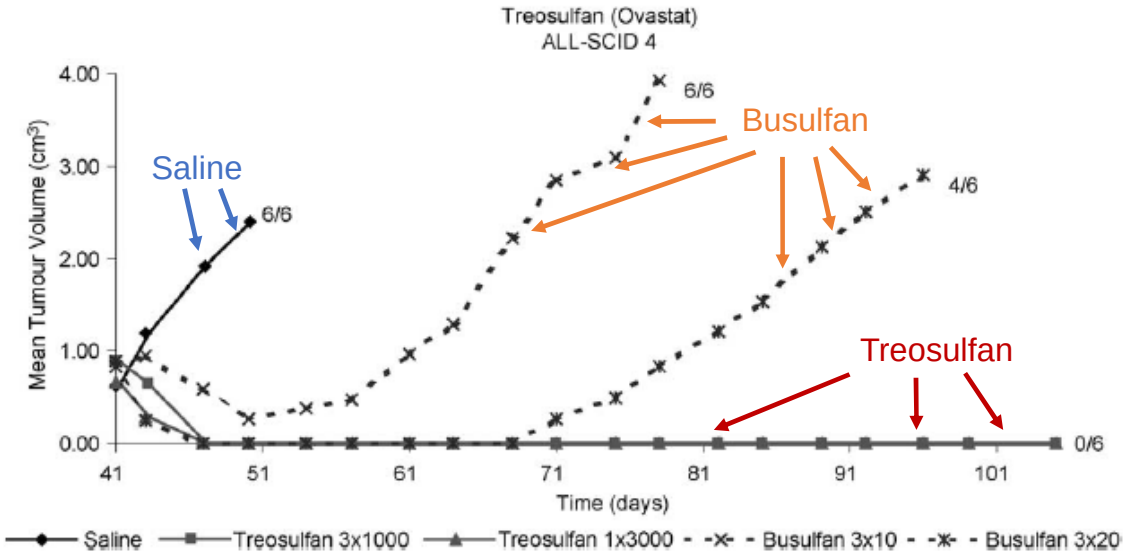


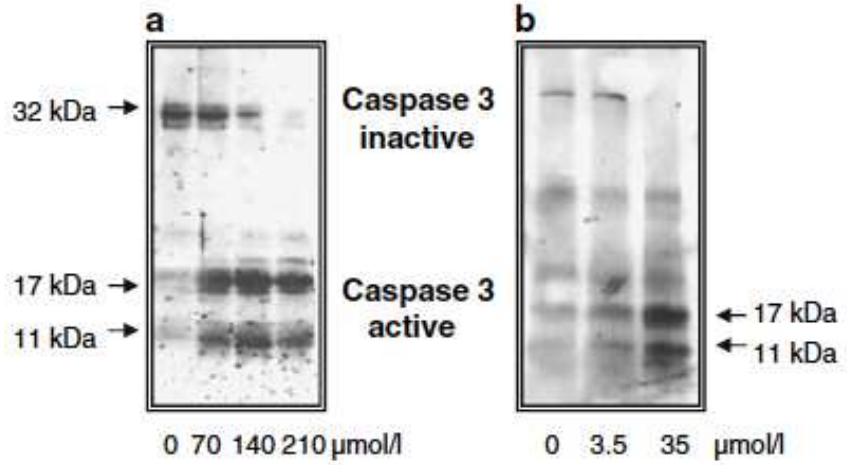
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Danylesko et al., 2011
Romanski et al., 2017
Shimoni et al., 2018

Treosulfan is an attractive candidate for allo- HSCT conditioning regimens

- Preclinical «in vitro» and «in vivo» studies demonstrated that:
- **Treo has intense cytoxicity mediated by Caspase against AML leukemic cells**



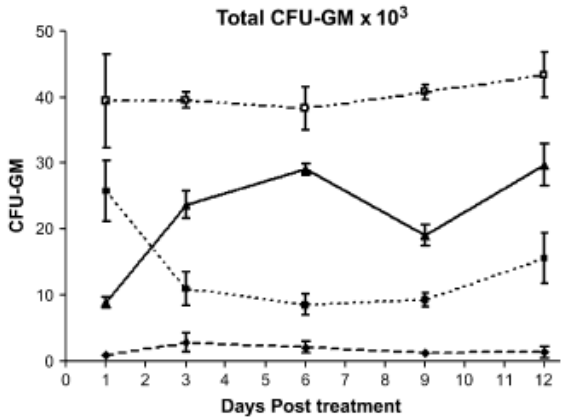


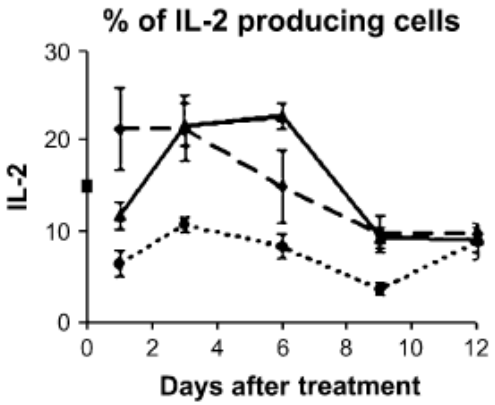
Munkelt et al., 2008
Fichtner et al., 2007

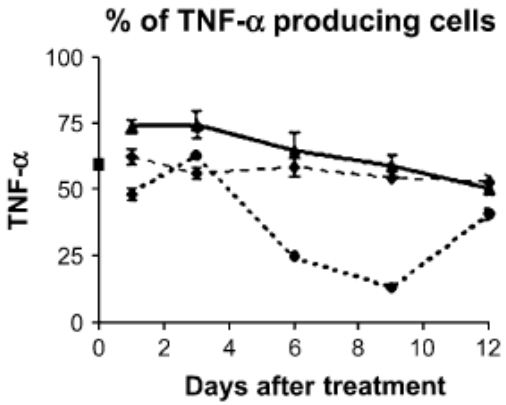
Treosulfan is an attractive candidate for allo- HSCT conditioning regimens

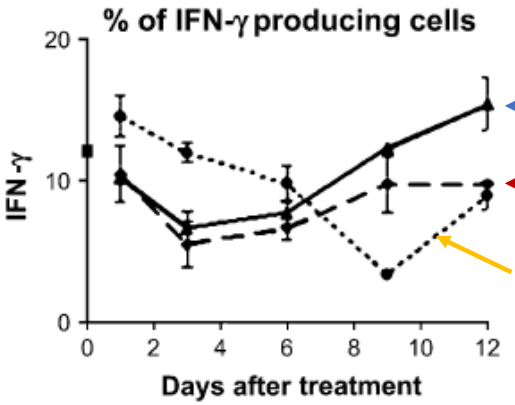
- **Treo** induces deep and stable **Myelosuppression** on committed and non-committed stem cells
- BM suppression at a dose of **10 g/m²**
- Max tolerated cumulative dose from **10 up to 47 g/m²**

  before mucositis, diarrhea, dermatitis, or metabolic acidosis became dose-limiting.
- No episodes of severe hepatotoxicity or central nervous system toxicity were observed.
- **Low pro-inflammatory cytokine release**
  - → Facilitate stem cell engraftment
  - → Low GVHD









Westerhof et al., 2000
Sjoo et al., 2006
Danylesko et al., 2011

Treosulfan doses

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

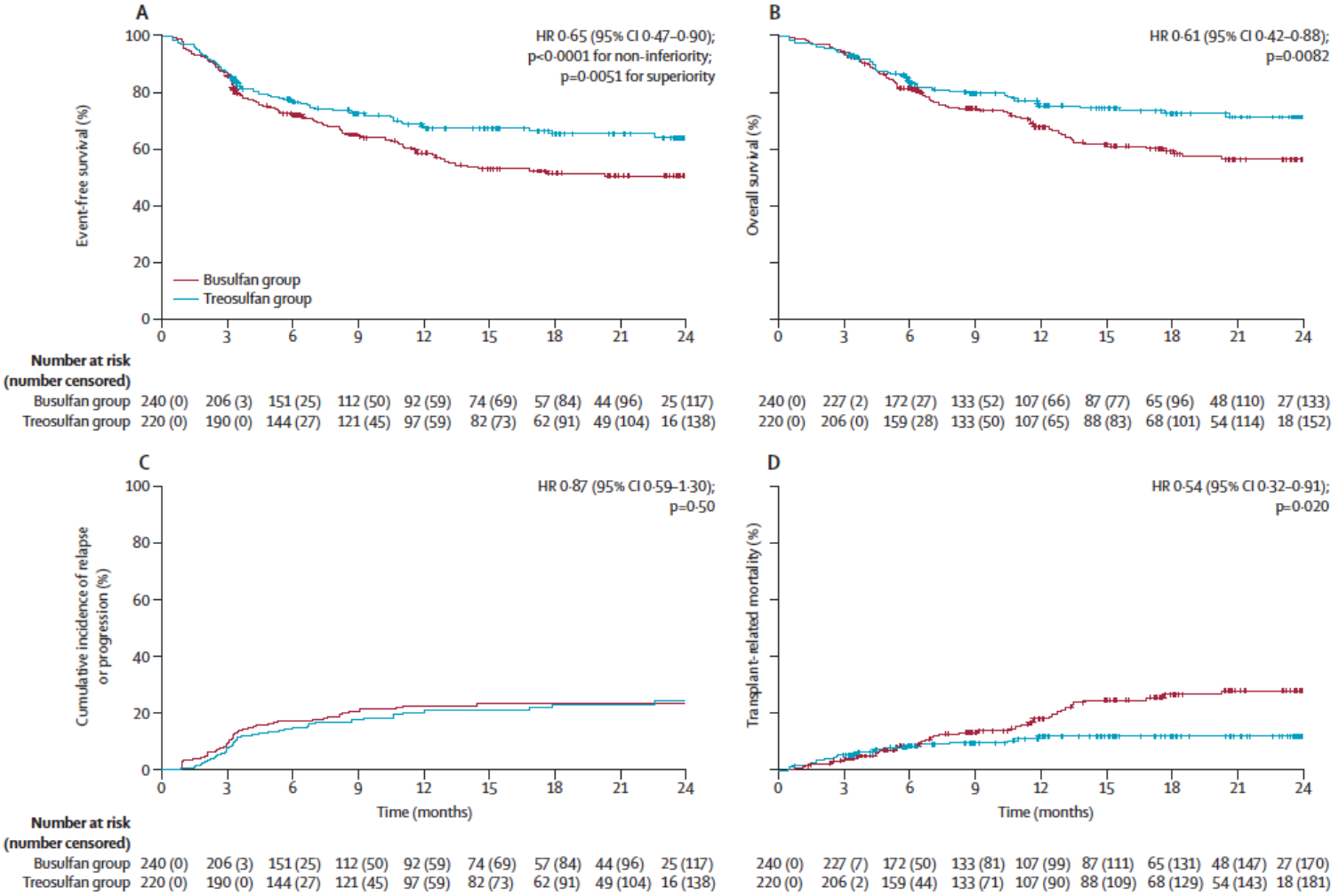
- **EMA - approval : <u>Treo 10-14 g/m² over 3 days in combination with Fluda 5 days</u>**
- ***Adult with malignant disease and NON malignant disease***
- Hematopoietic Stem Cell Transplantation (2019)
- Orphan-Drug (!) (2020)

-**FT10: Treosulfan 10 g/m² x 3** days (-4 to -2) (total dose: 30 g/m²)
-+ Fludarabine 30 mg/m² x 5 days (-6 to -2)
-*Treosulfan should be administered before fludarabine on days -4, -3, -2*

-**FT14: Treosulfan 14 g/m² x 3** days (-6 to -4) (total dose: 42 g/m²)
-+ Fludarabine 30 mg/m² x 5 days (-7 to -3)
Treosulfan should be administered before fludarabine on days -6, -5, -4
(+/- Thiotepa 5 mg/kg twice a day on day -2)

Scheulen ME et al.; 2000; Nagler et al. 2017

MC-FludT.14/L study



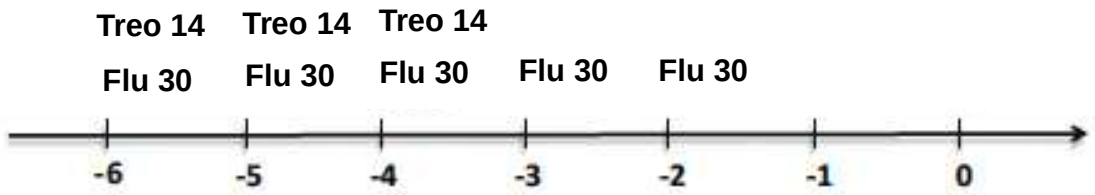
Beelen et al., 2020

MC-FludT.14/L study

Prospective Randomised controlled clinical trial

Objective:

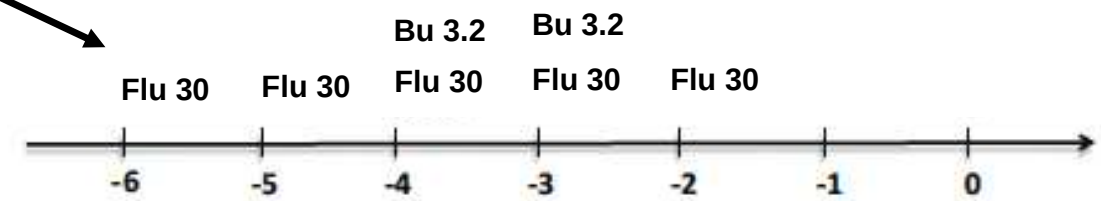
- **Non-inferiority** of treo-based conditioning vs. busulfan based regime
- To compare the associated **safety profiles**



FT14: Treosulfan 14 g/m² x 3 days + Fludarabine 30 mg/m² x 5 days

Inclusion criteria:

- **AML** in CR or **MDS** aged **≥ 50 ys** at HSCT and/or a HCT-CI score >2
- 18-70 years of Age
- Karnofsky Index ≥ 60%
- Availability of an HLA-identical sibling donor (MRD) or HLA-identical unrelated donor (MUD).



FB2: Busulfan 3.2 mg/kg/d x 2days + Fludarabine 30 mg/m² x 5 days

Primary Endpoint

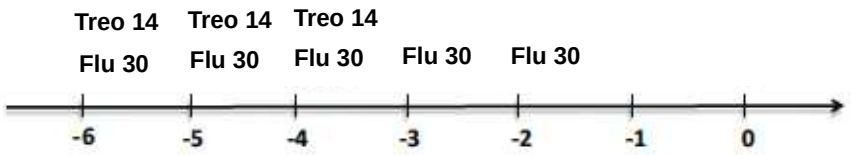
- **EFS at 1 year**

Secondary Endpoint

- OS, RI, NRM, TRM
- CTCAE grade III-IV between -6 and +28
- Engraftment, chimerism, GVHD

MC-FludT.14/L study

On Feb 20, 2012 results of the **interim analysis** prompted the independent data monitoring committee to **temporarily suspend** patient accrual due to concerns about prolonged neutropenia and subsequent serious infectious complications in the treosulfan group



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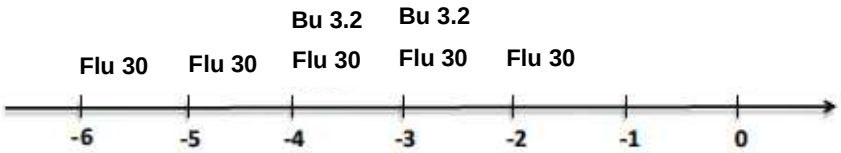
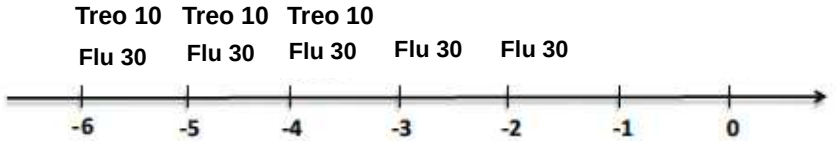
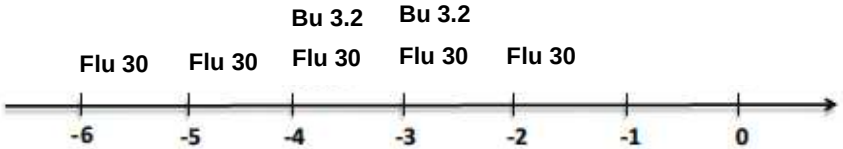


FB2: Busulfan 3.2 mg/kg/d x 2days + Fludarabine 30 mg/m² x 5 days



FT10: Treosulfan 10 g/m² x 3 days + Fludarabine 30 mg/m² x 5 days



FB2: Busulfan 3.2 mg/kg/d x 2days + Fludarabine 30 mg/m² x 5 days

Treosulfan - Fludarabine conditioning prospective studies

Bone Marrow Transplantation (2012) 47, 1171–1177

www.nature.com/bmt

ORIGINAL ARTICLE

Allogeneic hematopoietic SCT in patients with AML following treosulfan/fludarabine conditioning

J Casper[1,12], J Holowiecki[2,13], R Trenschel[3], H Wandt[4], K Schaefer-Eckart[4], T Ruutu[5], L Volin[5], H Einsele[6], G Stuhler[6], L Uharek[7], I Blau[7], M Bornhaeuser[8], AR Zander[9], K Larsson[10], M Markiewicz[2], S Giebel[2,13], T Kruzel[2], HA Mylius[11], J Baumgart[11], U Pichlmeier[11], M Freund[1] and DW Beelen[3]

- ***75 AML pts*** *(2004-2006);* ***18-60 ys old***
- *Prospective, non-randomized phase II study*
- *Regime:* ***FT14***
- *Low incidences of grade III/IV toxicities*
- ***Infections incidence: 59%***
- *OS and DFS of 61 and 55% at 2 years*

haematologica | 2011; 96(9)

Original Articles

Reduced-toxicity conditioning with treosulfan and fludarabine in allogeneic hematopoietic stem cell transplantation for myelodysplastic syndromes: final results of an international prospective phase II trial

Tapani Ruutu,[1] Liisa Volin,[1] Dietrich W. Beelen,[2] Rudolf Trenschel,[2] Juergen Finke,[3] Marc Schnitzler,[3] Jerzy Holowiecki,[4,13] Sebastian Giebel,[4,13] Miroslaw Markiewicz,[4] Lutz Uharek,[5] Igor W. Blau,[5] Joachim Kienast,[6] Matthias Stelljes,[6] Kajsa Larsson,[7] Axel R. Zander,[8] Martin Gramatzki,[9] Roland Repp,[9] Hermann Einsele,[10] Gernot Stuhler,[10] Joachim Baumgart,[11] Heidrun A. Mylius,[11] Uwe Pichlmeier,[11] Mathias Freund,[12] and Jochen Casper[12,14]

- ***45 MDS pts*** *(2004-2007);* ***18-65 ys old***
- *Prospective, non-randomized phase II study*
- *Regime:* ***FT14***
- *Low incidences of grade III/IV toxicities*
- *OS and DFS of 71 and 67% at 2 years*

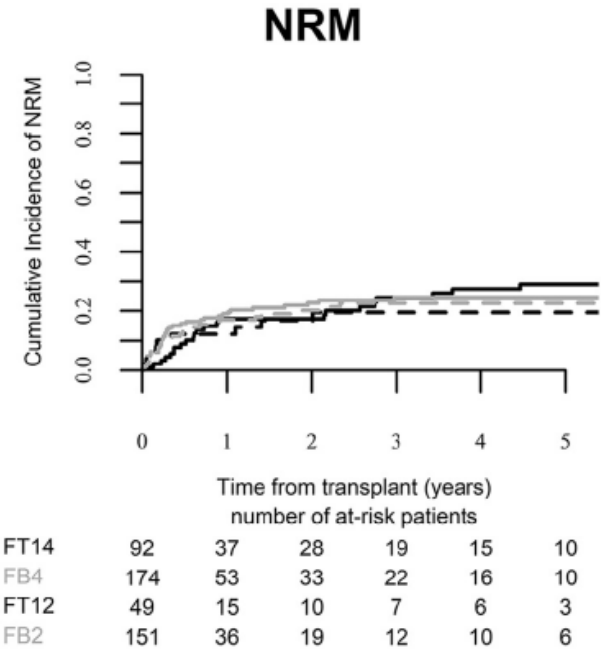
Treosulfan or busulfan plus fludarabine as conditioning treatment before allogeneic haemopoietic stem cell transplantation for older patients with acute myeloid leukaemia or myelodysplastic syndrome (MC-FludT.14/L): a randomised, non-inferiority, phase 3 trial

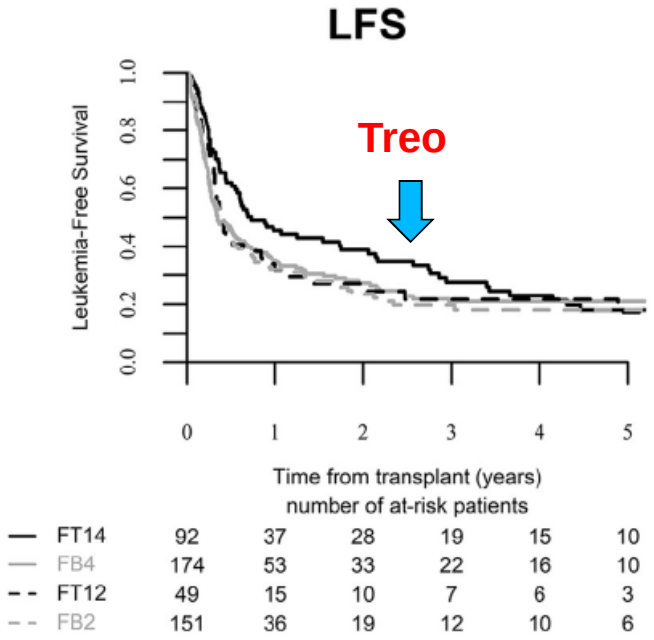
Dietrich Wilhelm Beelen, Rudolf Trenschel, Matthias Stelljes, Christoph Groth, Tamás Masszi, Péter Reményi, Eva-Maria Wagner-Drouet, Beate Hauptrock, Peter Dreger, Thomas Luft, Wolfgang Bethge, Wichard Vogel, Fabio Ciceri, Jacopo Peccatori, Friedrich Stölzel, Johannes Schetelig, Christian Junghanß, Christina Grosse-Thie, Mauricette Michallet, Hélène Labussiere-Wallet, Kerstin Schaefer-Eckart, Sabine Dressler, Goetz Ulrich Grigoleit, Stephan Mielke, Christof Scheid, Udo Holtick, Francesca Patriarca, Marta Medeot, Alessandro Rambaldi,

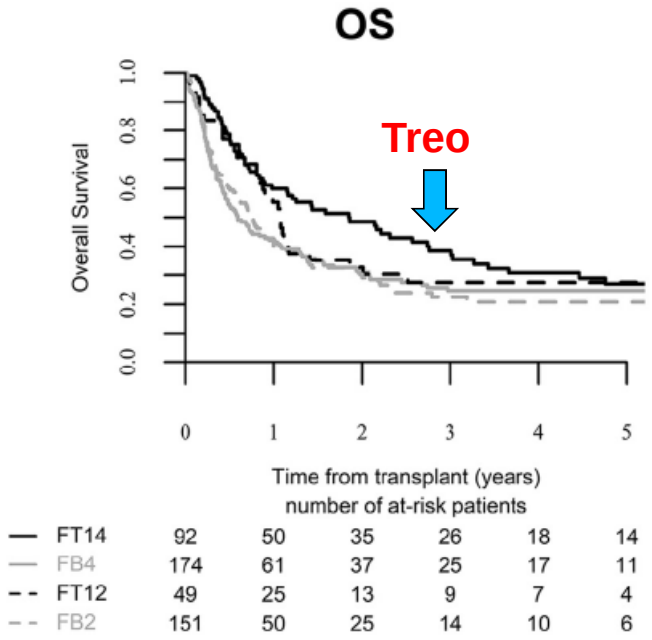
THE LANCET Haematology

2020; 7: e28–39

EBMT Experience: Bu-based vs Treo-based regimens Toxicieties







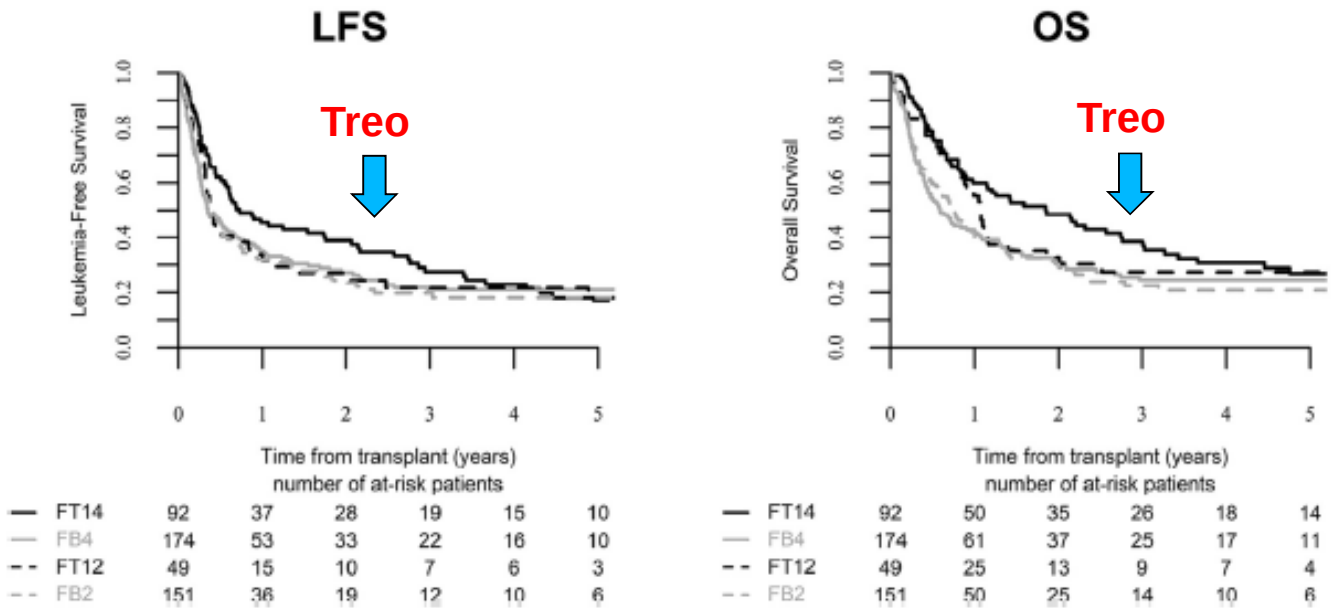
	Relapse		NRM	
	HR (95% CI)	P	HR (95% CI)	P
Conditioning				
FB4	1		1	
FB2	1.21 (1.02-1.43)	.03	.81 (.64-1.01)	.06
FT14	1.03 (.83-1.27)	.80	.95 (.73-1.23)	.95
FT12	1.17 (.89-1.56)	.25	.61 (.40-.94)	.02

	LFS		OS	
	HR (95% CI)	P	HR (95% CI)	P
Conditioning				
FB4	1		1	
FB2	1.04 (.90-1.19)	.63	.94 (.81-1.10)	.42
FT14	.98 (.82-1.17)	.82	.87 (.72-1.05)	.15
FT12	.99 (.78-1.27)	.96	.84 (.64-1.09)	.18
Age per 10 yr	1.14 (1.08-1.21)	<.0001	1.19 (1.11-1.28)	<.0001
Gender, female	.95 (.84-1.07)	.38	.98 (.86-1.12)	.76
Disease status				
CR1	1		1	
CR2/3	1.24 (1.07-1.44)	.005	1.15 (.98-1.36)	.09
Active disease	2.05 (1.78-2.36)	<.0001	1.97 (1.69-2.30)	<.0001

Shimoni et al., 2018

EBMT Experience: Bu-based vs Treo-based regimens

Role of FT14 in patients with Advanced Disease at SCT



- **In patients with active disease at HSCT the 2-year OS rate was 49% after FT14, compared to 31% of patients who received FB4 (p = 0.004).**
- In Multivariate analysis patients reciving **FT14 subset confirmed a better OS for FT14 compared with FB4 (HR, .60; p = 0.008)**

Shimoni et al., 2018

EBMT Experience: Bu-based vs Treo-based regimens

- Retrospective, multicentric analysis (+500)
- **3293 patients** with de novo (n = 2588) or secondary AML (n = 705)

Inclusion Criteria
•de novo or secondary AML in any disease status at SCT
•After transplants from HLA-matched siblings or 9-10/10 matched unrelated donors
•**between 2000 and 2014**
•Age > 18 ys

FB2: Fludarabine (*30 mg/m² x 5 days*) + Busulfan (*3.2 mg/kg x 2 days*) [***n = 1457***]
FB4: Fludarabine (*30 mg/m² x 5 days*) + Busulfan (*3.2 mg/kg x 4 days*) [***n = 1265***]

Vs.

FT12 : Fludarabine (*30 mg/m² x 5 days*) + Treosulfan (*12g/m2 x 3 days*) [***n = 168***]
FT14 : Fludarabine (*30 mg/m² x 5 days*) + Treosulfan (*14g/m2 x 3 days*) [***n = 403***]

Shimoni et al., 2018

EBMT Experience: Bu-based vs Treo-based regimens

Patient Characteristics

	FB4 (n = 1533)	FT14 (n = 403)	FB2 (n = 1457)	FT12 (n = 168)	*P*
Median age, yr (range)	48 (18-74)	57 (19-73)	60 (18-77)	60 (21-73)	<.0001
Age, yr, IQR	36-56	50-63	54-64	54-65	
Gender, male	55	50	54	52	.26
Disease status					
CR1	73	56	74	52	< .0001
CR2/3	13	21	16	19	
Active disease	14	23	10	29	
Secondary AML	15	25	24	40	<.0001
Donor, sibling	62	36	40	33	<.0001
F → M	22	17	17	18	.007
Stem cell source, PBSC	85	90	95	95	<.0001
CMV status					
D–/R–	13	22	25	19	< .0001
D+/R–	7	6	9	8	
D–/R+	19	28	23	27	
D+/R+	61	44	43	46	
In vivo TCD	50	55	85	65	<.0001
Year of SCT	2012 (2000-2014)	2010 (2003-2014)	2011 (2000-2014)	2010 (2002-2014)	<.0001

75% pts are < 56ys old

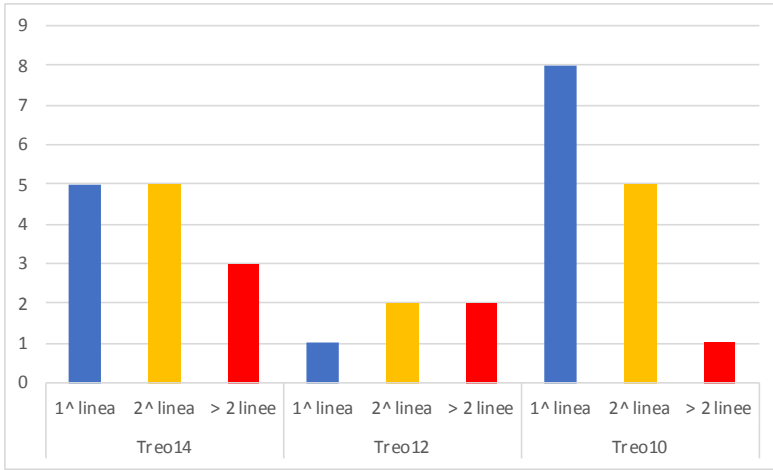
75% pts are > 50ys old !!

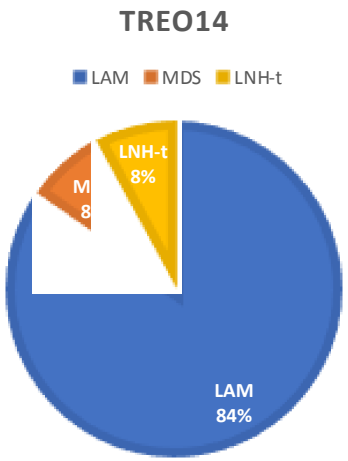
Values are percents unless otherwise defined. F → M indicates female donor to male recipients; CMV, cytomegalovirus; D, donor; R, recipient; TCD, T cell depletion.

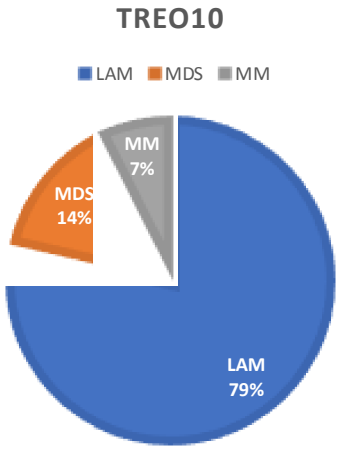
Shimoni et al., 2018

Brescia Experience

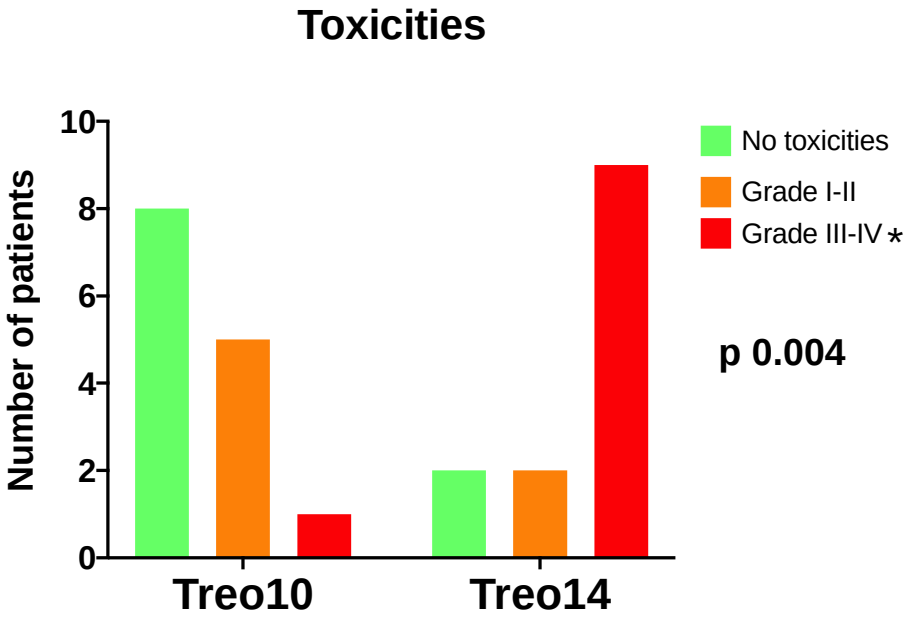
	Total	Treo14	Treo12	Treo10
Patients	32	13	5	14
Male *(%)*	22 (68.8%)	8 (61.5%)	3 (60%)	11 (78.6%)
Age *median (range)*	**57,5** *(43-71)*	**51** *(43-58)*	**60** *(56-63)*	**66,5** *(50-71)*
Diagnosis				
AML	24	11	2	11
1^RC	17	8	1	8
2^RC	5	2	0	10
Molecular RC	12	5	1	6
MDS	4	1	1	2
RAEB I	1	0	0	1
RAEBII	1	0	0	1
LAM oligoblastica	1	0	1	0
MDS with multilinear dysplasia related therapy	1	1	0	0
Multiple Myeloma	3	0	2	1
LNH T	1	1	0	0







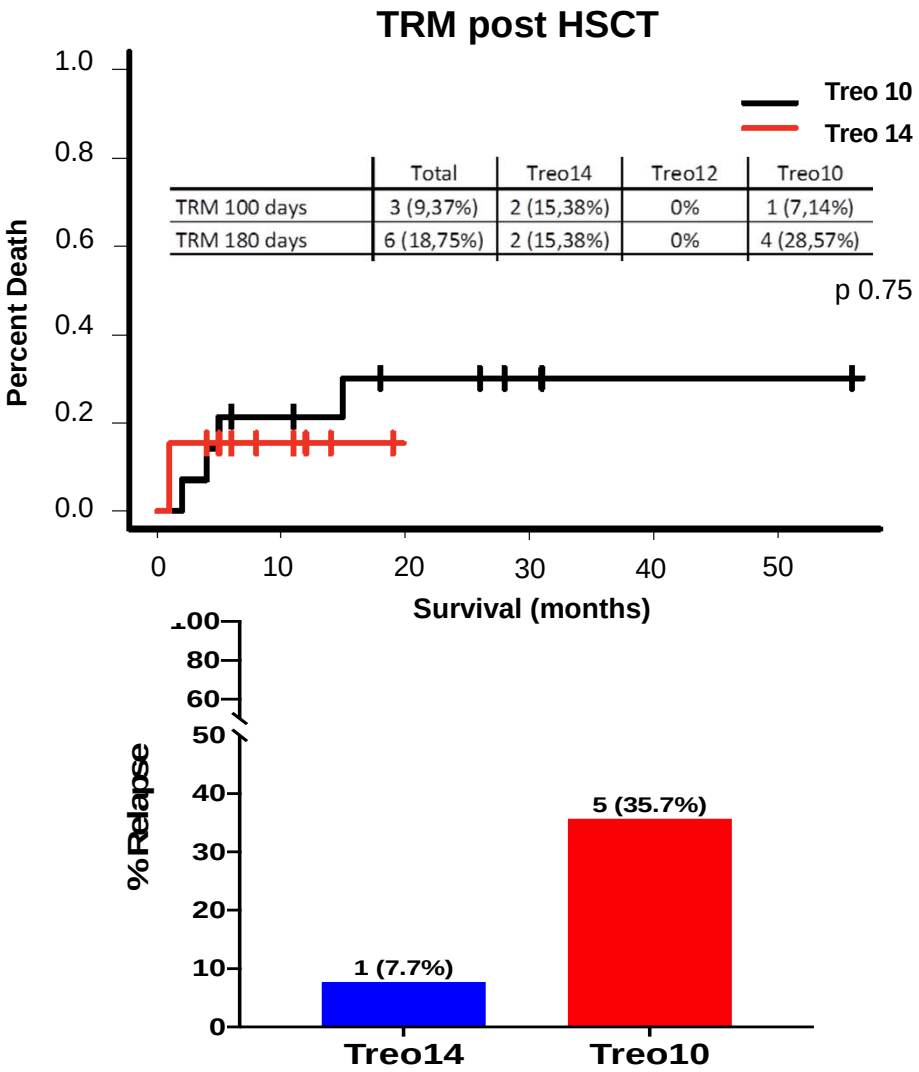
Brescia Experience



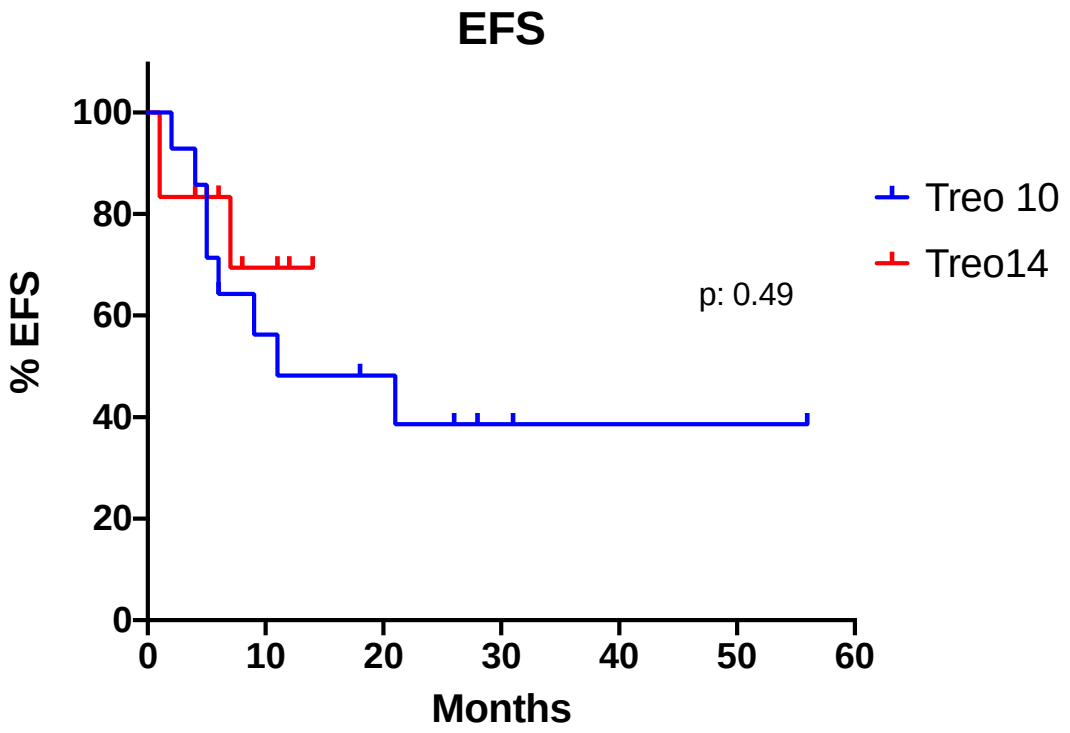
	Total	Treo14	Treo12	Treo10
Graft MPN *median days (range)*	23.5 (14-29)	25 (14-29)	19 (17-28)	22 (17-39)
Graft PLT *median days (range)*	25 (13-86)	24,5 (18-86)	22.5 (14-30)	25 (13-45)
Infections	31 (96.8%)	13 (100%)	5 (100%)	13 (92.9%)
Viral	22 (68.8%)	8 (61.5%)	5 (100%)	9 (64.3%)
IFI	7 (21.9%)	3 (23%)	0 (0%)	4 (28.6%)
aGVHD	13 (40.1%)	5 (38.5%)	3 (60%)	5 (35.8%)
Gr I-II	10 (31.2%)	3 (23%)	3 (60%)	4 (28.6%)
Gr III-IV	3 (9.4%)	2 (15.4%)	0 (0%)	1 (7.14%)
St I-II	9 (28.1%)	3 (23%)	3 (60%)	3 (21.4%)
St III-IV	4 (12.5%)	2 (15.4%)	0 (0%)	2 (14.3%)
cGVHD	8 (25%)	4 (30.7%)	0 (0%)	4 (28.6%)
Mild/moderate	5 (15.6%)	2 (15.4%)	0 (0%)	3 (21.4%)
Serious	3 (9.4%)	2 (15.4%)	0 (0%)	1 (7.14%)

*In 8 of 9 (88,9%) of grade III-IV toxicities Treo was associated with Melphalan

Brescia Experience



	Total	Treo14	Treo12	Treo10
TRM 100 days	3 (9,37%)	2 (15,38%)	0%	1 (7,14%)
TRM 180 days	6 (18,75%)	2 (15,38%)	0%	4 (28,57%)



Median EFS: Treo10: 11 months *(median FU: 18 months)*
Treo14: not reached *(median FU: 8 months)*

Treosulfan- Discussion

- *GITMO Retrospective Analysis on FT14 - FT12 (5 or 3 years)*
- *FT14 / FT12 prospective investigational studies*
- *Correlative biological studies on FT antileukemic activity and AML/MDS - NGS mutational profile*
- *Treo in combination with Tiotepa (TTF) for conditioning regimen in Hemat. Malign. Diseases*
- *FT in combination with molecular targeted drugs (FLT3-IDH1-2)*

FT14 study proposal

Prospective Phase II study on Safety and Efficacy of Fludarabine plus Treosulfan (14mg) (FT14) conditioning regimen for allogeneic Stem Cell Transplantation (allo-SCT) in Acute Myeloid Leukemia (AML) patients (≥40 <65years)

FT14 - Study

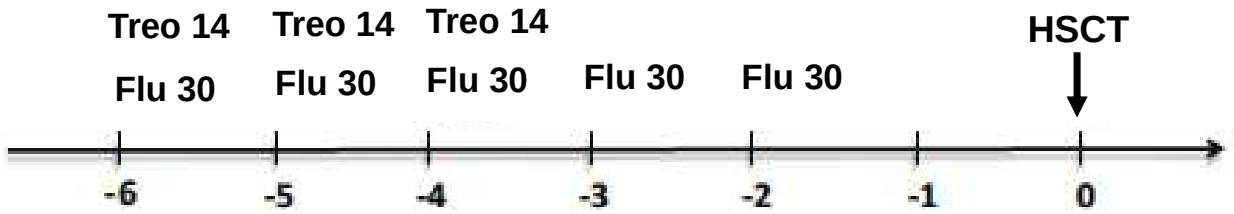
FT14 Study Proposal

Primary Objective

To prospectively evaluate the safety and efficacy of the FT14 conditioning regimen for allo-SCT in AML pts (≥40 <65years).

Primary endpoint is :

- **Event-free survival 2 year after allo-SCT**



FT14 : Fludarabine (*30 mg/m² x 5 days*) + Treosulfan (*14g/m2 x 3 days*)

FT14 study proposal

Inclusion criteria (the same as FB4)

- Patients ≥40 <65 years of age
- Diagnosis of AML in first CR/CRi/
- Eligible for allo-SCT from HLA-identical matched related or unrelated donor as defined by molecular high-resolution typing (4 digits)
- Adequate hepatic function (bilirubin ≤2 UNL; ALT/AST ≤2,5 UNL)
- Adequate renal function (creatinine clearance ≥50 ml/min)
- ECOG Performance Status ≤ 2
- Willing and able to comply with all of the requirements and visits in the protocol.
- Written and signed informed consent

FT14 study proposal

Sample size: 67 patients

This sample size has been calculated on the basis of expected LFS after allo-HCT with FB4 conditioning regimen in AML patients in complete hematological remission (LFS 65% at 1y) compared to that expected after a regimen including treosulfan, an agent associated to lower toxicity and higher anti-leukemic activity compared to busulfan.

→ Our hypothesis is that this new conditioning regimen could allow to reach an **LFS of 80% at 1 year.**

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