CORSO EDUCAZIONALE GITMO

NUOVI FARMACI E TRAPIANTO

MIELOMA – FARMACI IMMUNOMODULANTI E TRAPIANTO ALLOGENICO

Udine, 21-22 Gennaio 2016

Dr. Vittorio Montefusco

FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

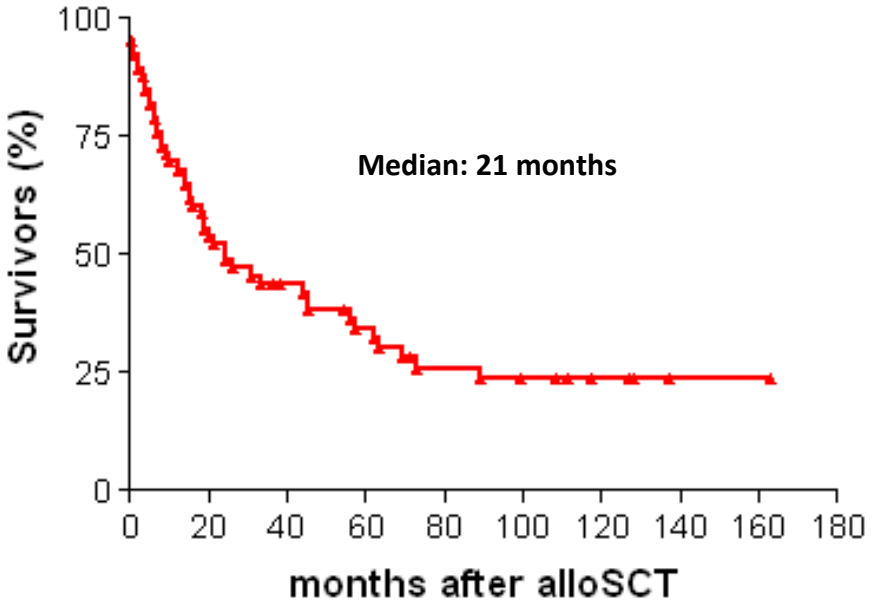
Clinical evidence for the efficacy of allo-HSCT

1. reduced risk of relapse after allo-HSCT compared to auto-HSCT;
2. Clinical response correlates with GVHD;
3. well documented responses to donor lymphocyte infusions (DLI);
4. achievement of durable molecular remissions after allo-HSCT

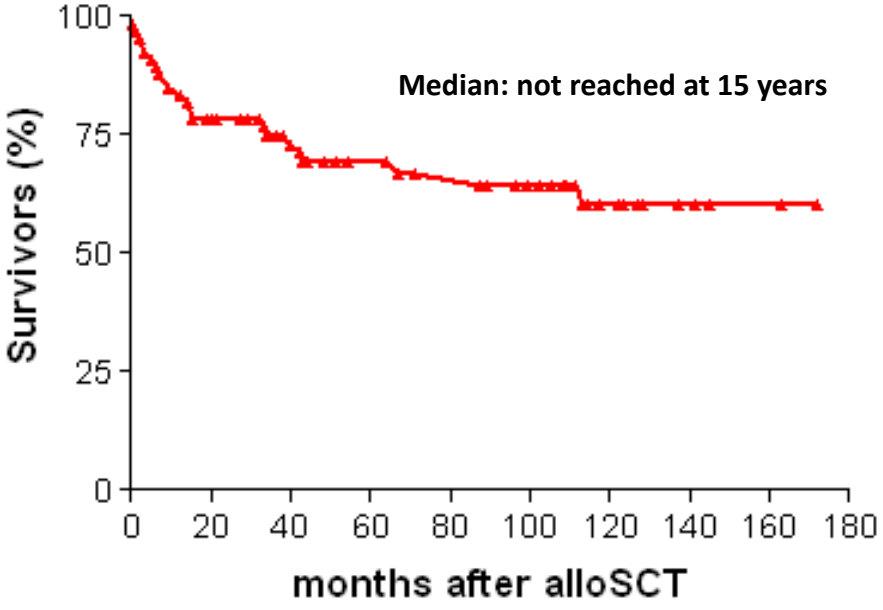
Our experience

In our experience we observed that AlloSCT have an unsatisfactory PFS, while the OS is excellent.

PFS



OS



Personal observation

As observed, PFS is poor, while OS is satisfactory.

Then, it is possible to speculat that the patients benefited from the additional treatments performed after alloSCT.

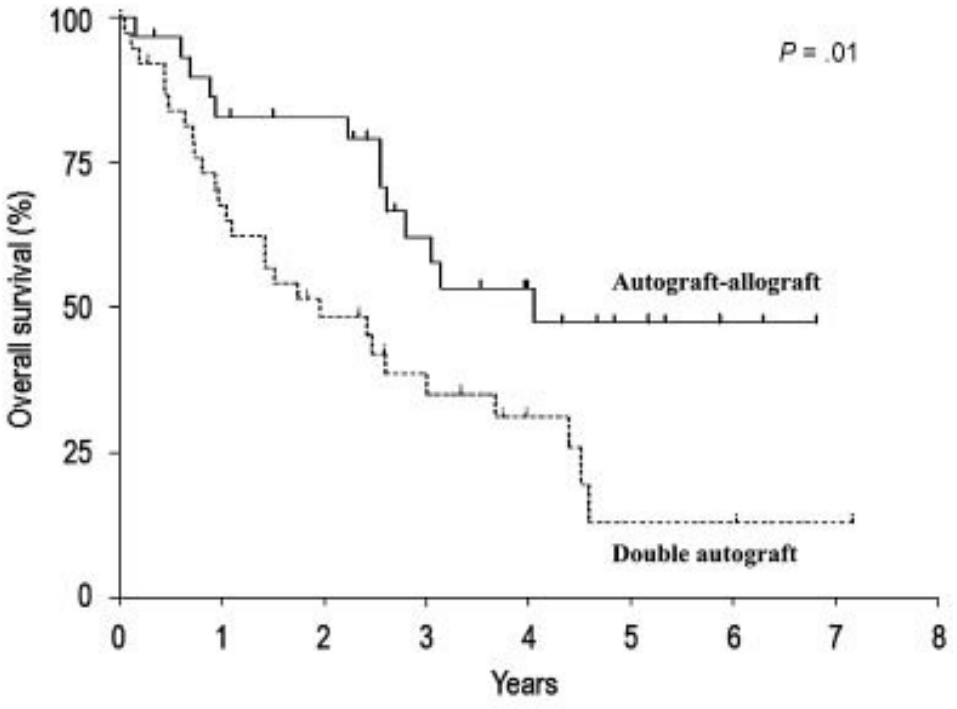
Is the graft-versus-myeloma effect the key element that justify this outcome?

The GITMO study

The GITMO study compared auto vs Auto-Allo (TBI 200). Auto-Allo was superior in terms of PFS and OS.

Moreover, patients relapsed after Allo did better in terms of OS.

OS after 1° relapse



Giaccone et al. Blood 2011

The NMAM 2000 study

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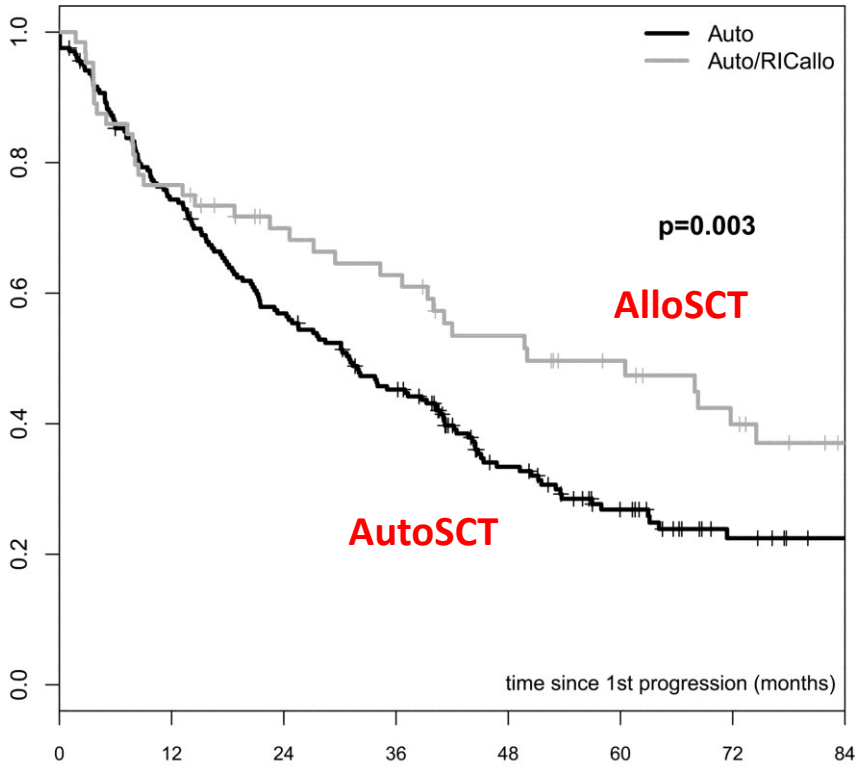
OS after 1° relapse



Gahrton et al. Blood 2013

Thalidomide + DLIs after alloSCT

Kroger et al. first suggested that a specific treatment may be more effective if done in the alloSCT setting (immunemodulating effect?).

Thalidomide was started at 100 mg daily in R/R MM patients. Soon an excalated DLI program was started (5 x 10^6 CD3/Kg in siblings, 1 x 10^6 CD3/Kg in MUD).

Results:

MR 17%
PR 28%
CR 22%

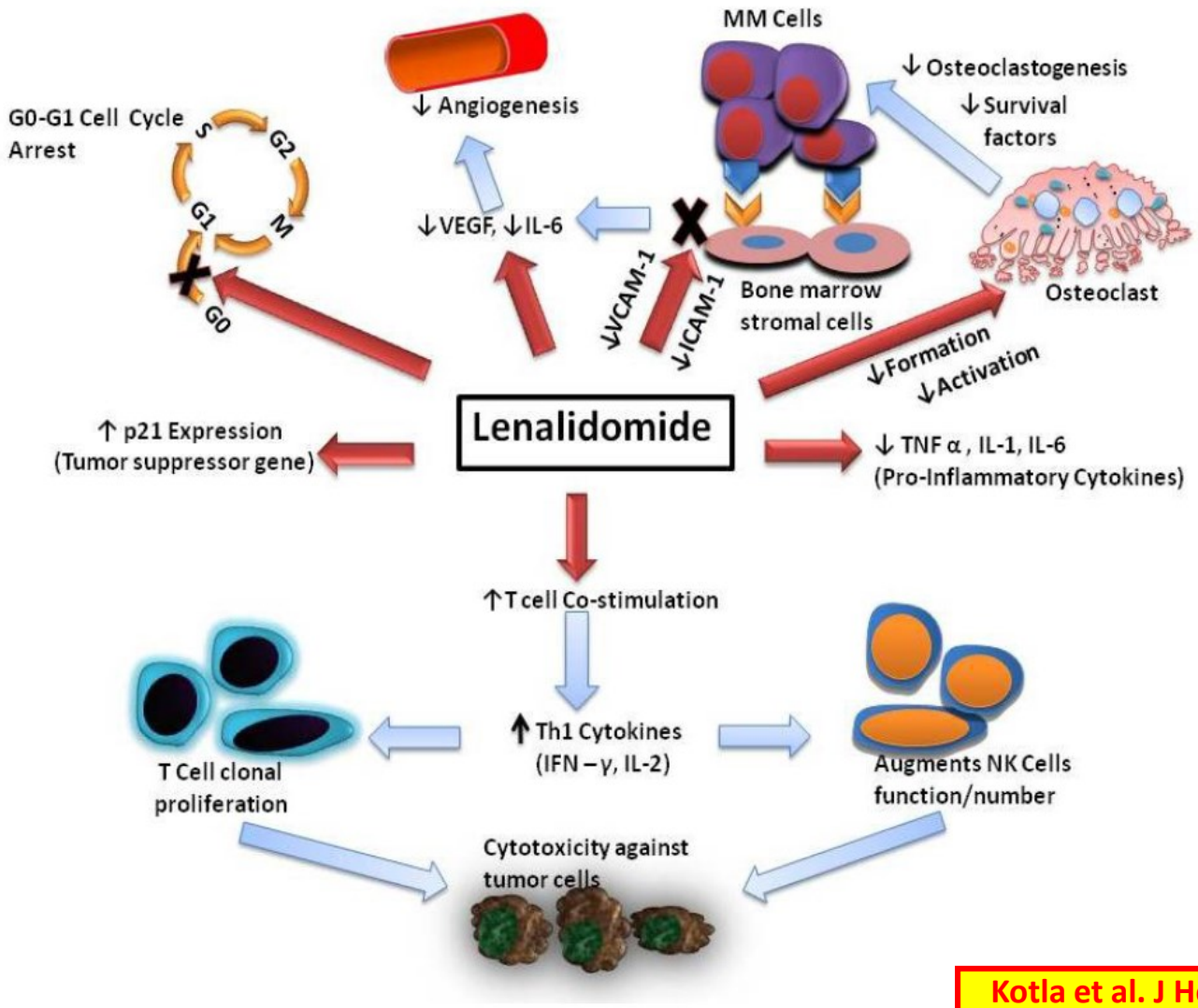
2 yrs PFS: 84%
2 yrs OS: 100%

Toxicity:

aGVHD I° 11%
aGVHD >I° 0%
Limited cGVHD 38%
Extensive cGVHD 0%

Kroger et al. Blood 2004

Lenalidomide immunomodulatory properties



Kotla et al. J Hematol Oncol 2009

1st lenalidomide trial after alloSCT

The Hovon 76 study included 30 MM pts who received alloSCT in 1st line, followed by lenalidomide 10 mg 21/28 days, starting from day +90 (median).

Median treatment duration: 2 cycles

Cause of discontinuation: aGVHD in 47%
toxicity in 17%
progression in 17%

The treatment was defined NOT FEASIBLE

Kneppers et al. Blood 2011

German trial with lenalidomide after alloSCT

A German study included 33 MM pts relapsed after autoSCT, who received alloSCT followed by lenalidomide 5 mg 21/28 days (with escalation), starting from day +168(median).

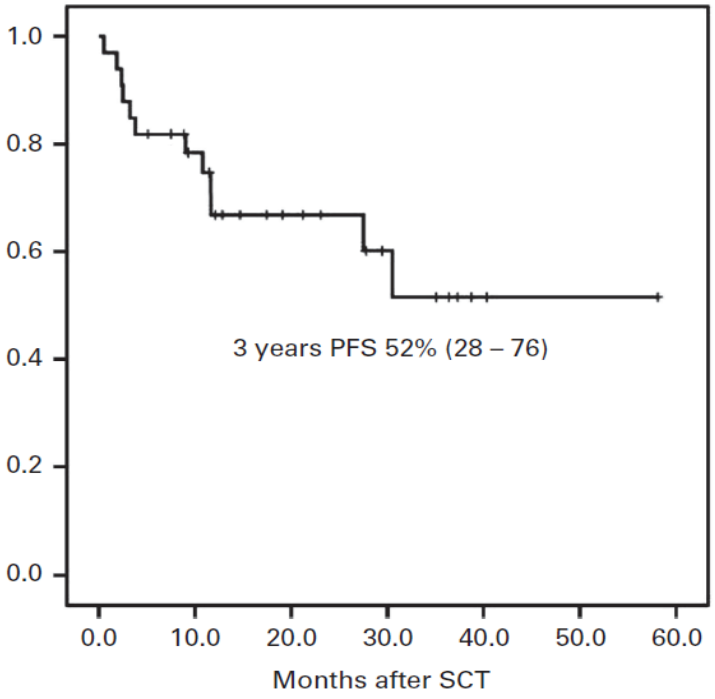
54% of pts discontinued treatment

Cause of discontinuation: aGVHD in 10% [28%]
toxicity in 13%
progression in 20%

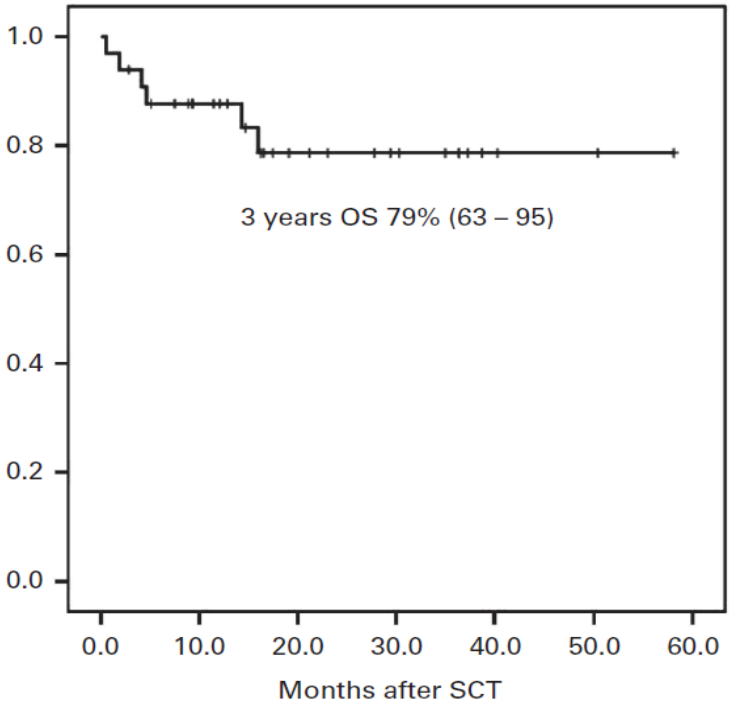
Kroger et al. BMT 2013

German trial with lenalidomide after alloSCT

PFS



OS



The treatment was considered interesting in terms of PFS and OS, but toxic.

Kroger et al. BMT 2013

US trial with lenalidomide after alloSCT

A US study included 30 high risk MM pts who received alloSCT in 1st or 2nd line, followed by lenalidomide 10 mg 21/28 days (with escalation), starting from day +96 (median).

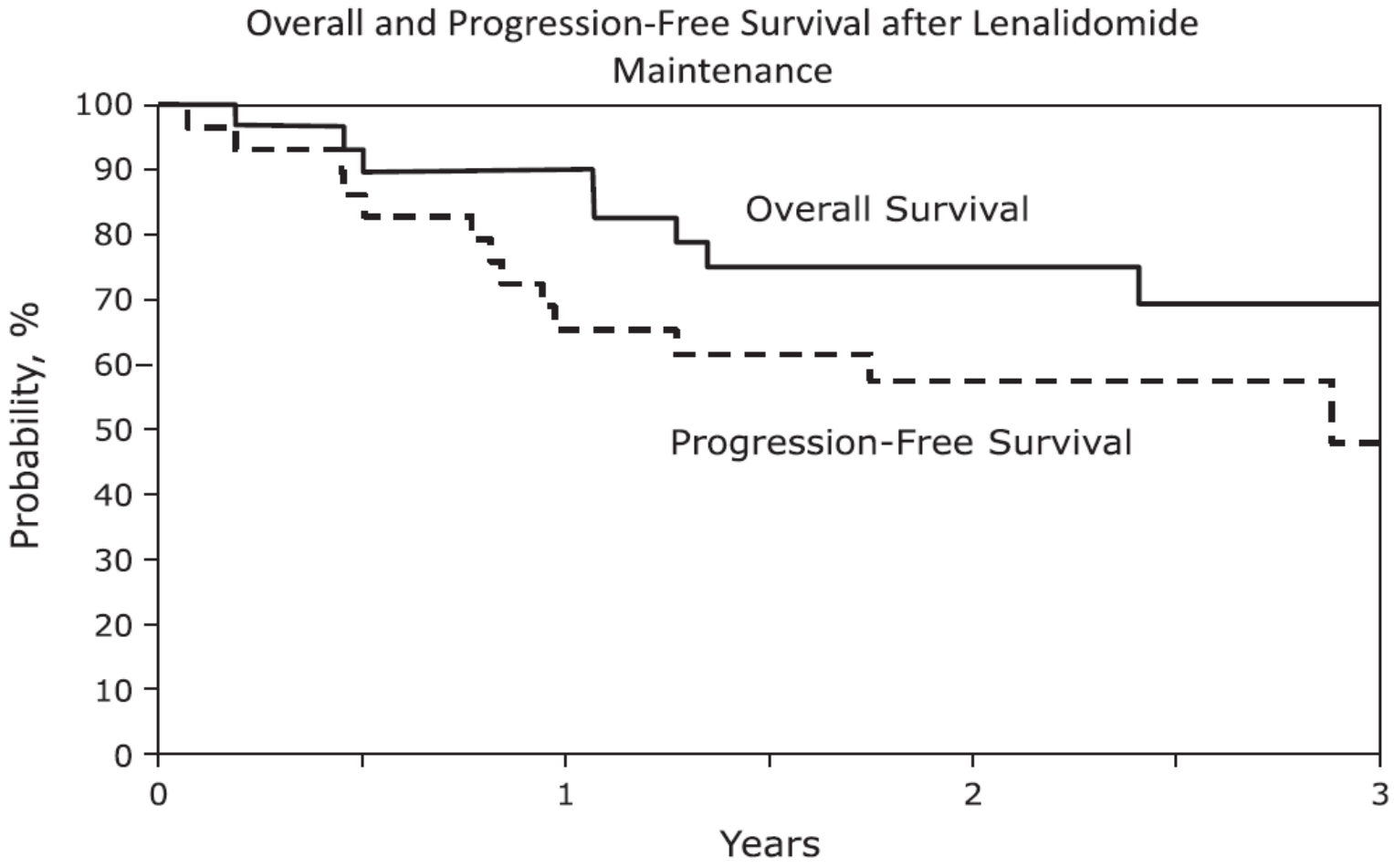
Median treatment duration: 9 cycles

Cause of discontinuation: aGVHD in 23%
toxicity in 13%
progression in 20%

Only 11 pts (30%) completed 12 cycles

Alsina et al. BBMT 2014

US trial with lenalidomide after alloSCT



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Alsina et al. BBMT 2014

A case-matched analysis of lenalidomide after allogeneic or autologous stem cell transplantation

Immunomodulatory properties of lenalidomide

Lenalidomide operates through:

1) **Enhancement of NK cytotoxicity;**
2) **Inhibition of regulatory T cells;**
3) **Inhibition of autocrine cytokines;**
4) **Downregulation of COX-2;**

…….therefore its use after alloSCT appears potentially useful.

Aim of the study

To compare lenalidomide use after autoSCT and alloSCT in a retrospective case-matched analysis.

The survey was conducted among eight Italian centers.

The primary matching criteria was:

The number of treatment lines of therapy, including autoSCT or alloSCT, before lenalidomide administration.

Secondary matching criteria were:

- **ISS stage**
- **FISH unfavourable vs. favourable**

Intra-center matching was encouraged, in order to harmonize treatment strategies.

Patients characteristics

	Auto	Allo
Number of patients	40	40
Median age (range), yrs	55 (39-70)	47(29-61)
D&S stage		
I	5 (13%)	9 (23%)
II	8 (20%)	5 (13%)
III	26 (67%)	25 (64%)
ISS stage		
I	19 (49%)	14 (37%)
II	10 (25%)	12 (32%)
III	1 (3%)	1 (3%)
n.a.	9 (23%)	11(28%)

Patients characteristics

	Auto	Allo
Median number of treatment lines before Len start	3 (1-6)	3 (1-6)
Previous thalidomide	35 (87%)	21 (53%)
Previous lenalidomide	2 (5%)	5 (12%)
Previous bortezomib	31 (77%)	36 (90%)
Time from transplant to Len (months)	39 (7-159)	29 (4-216)

Median follow-up after Len start

22 months (range 2-55)

Results - Best response to Len

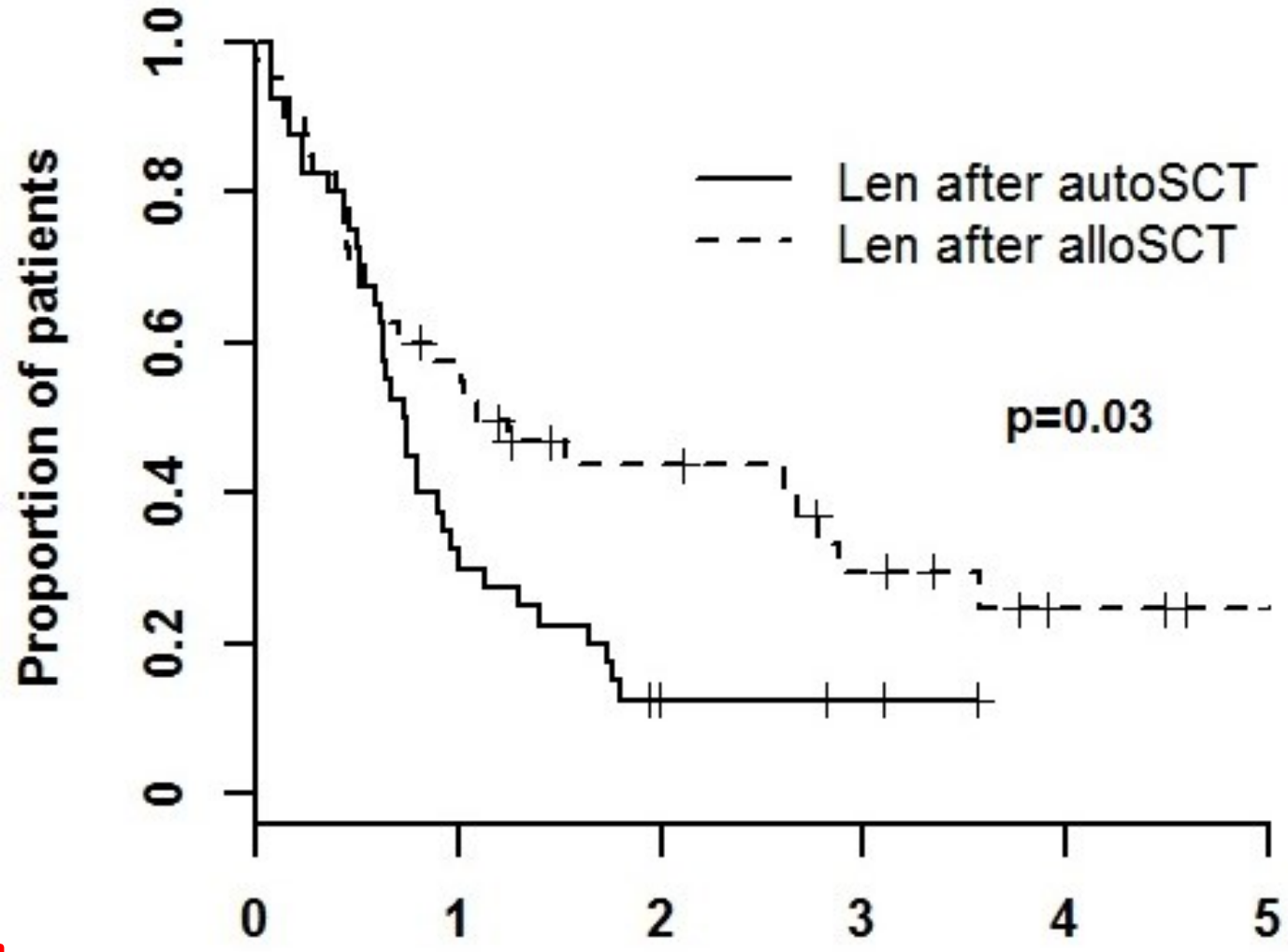
	Auto	Allo
CR	5 (12%)	4 (10%)
VGPR	6 (15%)	8 (20%)
PR	12 (30%)	12 (30%)
SD	11 (28%)	8 (20%)
PD	6 (15%)	8 (20%)

Time from Len start to best response

Auto — 4 months (range 1-21)

Allo — 4 months (range 1-19)

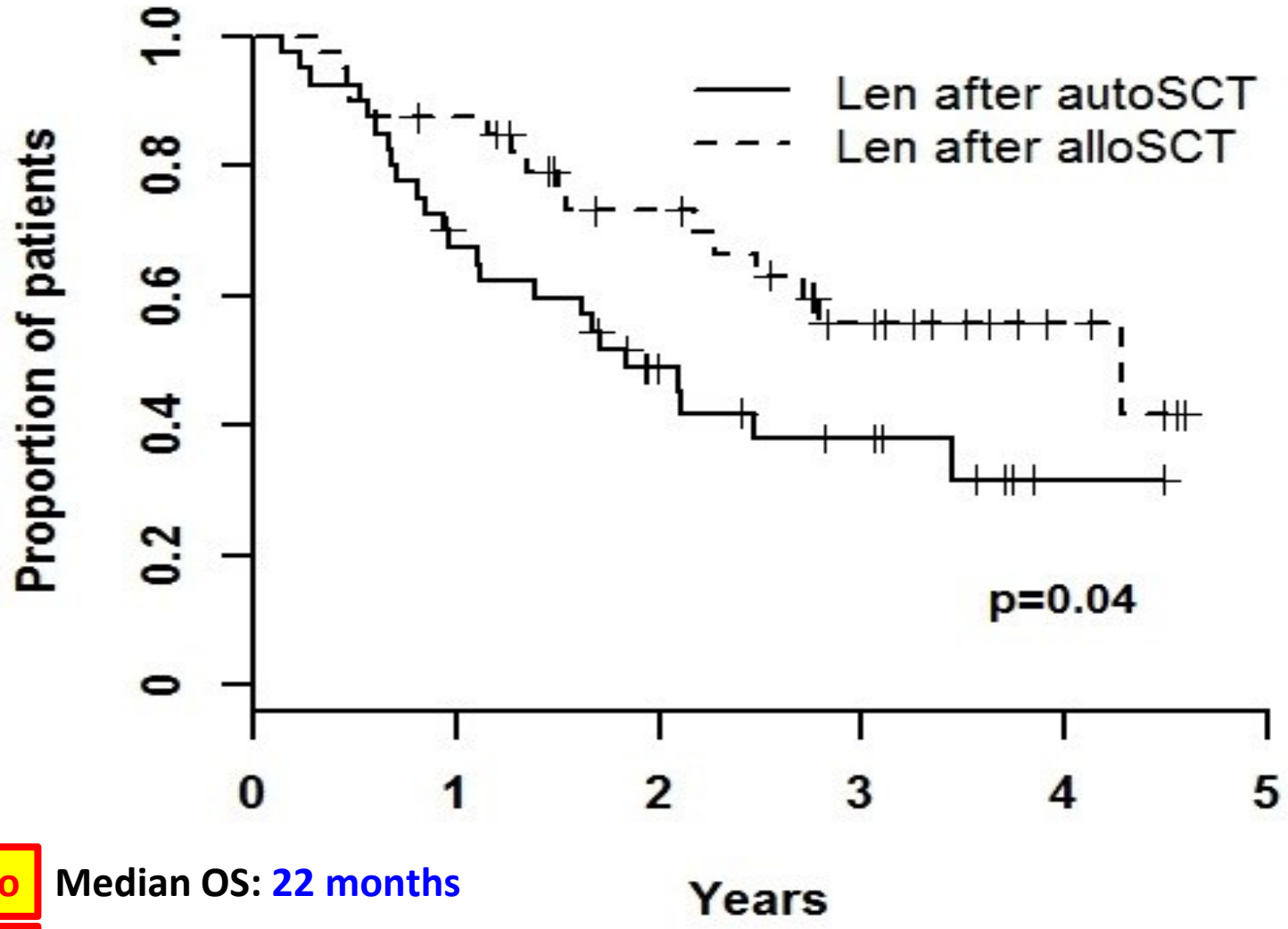
Results - PFS



Auto Median PFS: 9 months

Allo Median PFS: 13 months

Results - OS



Auto Median OS: 22 months

Allo Median OS: 51 months

Toxicity

No unexpected toxicities were observed

	AutoSCT	AlloSCT
Neutropenia G3-G4	12 (30%)	10 (25%)
Thrombocytopenia G3-G4	3 (8%)	4 (10%)
Gastrointestinal G3-G4	2 (5%)	
Peripheral neuropathy G3-G4	2 (5%)	4 (10%)
Deep venous thrombosis	1 (3%)	1 (3%)

No aGVHD.

Three (8%) patients had a cGVHD worsening.

The French experience

52 patients treated with Len after AlloSCT.

Patients' characteristics

Median age	48 (32 - 61)
Previous thalidomide	26 (50%)
Previous lenalidomide	5 (10%)
RIC conditioning	44 (85%)
Myeloablative conditioning	8 (15%)
Matched related donor	40 (77%)
Matched unrelated donor	9 (17%)
Mismatched donor	3 (6%)
Months from transplant to Len	24 (1-97)
Active aGVHD at Len start	3 (6%)
Active cGVHD at Len start	13 (26%)

Coman et al. Haematol 2013

Results - Best response to Len

Median follow-up after Len start

16 months (range 4-50)

	With steroids	W/o steroids
CR	28%	33%
VGPR	25%	17%
PR	32%	25%
SD	8%	8%
PD	7%	17%

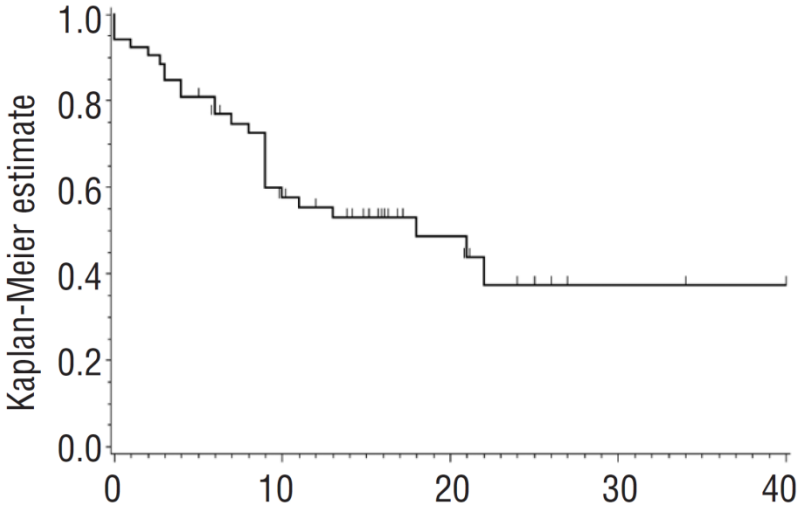
Time from Len start to best response

3 months (range 1-11)

Coman et al. Haematol 2013

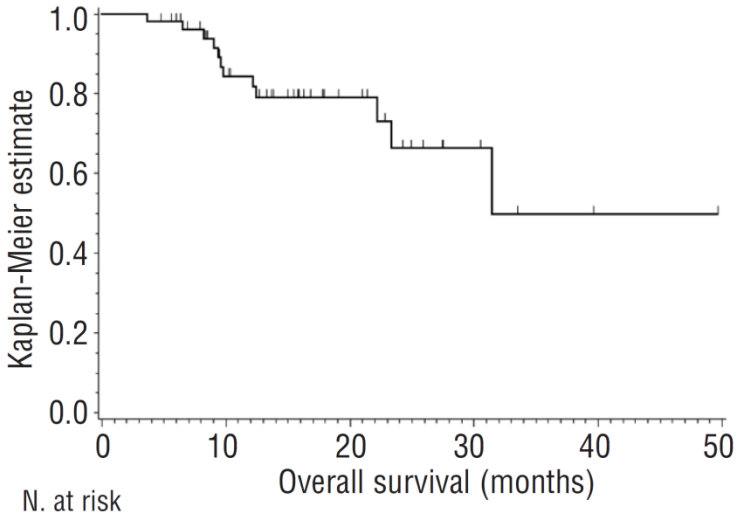
Results – PFS & OS

PFS



Median PFS: 18 months

OS



Median OS: 30 months

Coman et al. Haematol 2013

Results – Toxicity

Neutropenia G3-G4	29%
Thrombocytopenia G3-G4	13%
Infections G3-G4	24%
Thromembolism	14%

13 (26%) pts developed *a*GVHD

6 (11%) pts developed *c*GVHD

The combination with dexamethasone reduced by 50% the risk of GVHD.

GVHD rapidly resolved after Len withdrawal

Coman et al. Haematol 2013

Conclusions

- AlloSCT is a treatment option for young MM patients.

- Molecular remissions and prolonged survival are described

- AlloSCT may be also considered as a platform for subsequent treatments, in particular using of immunomodulationg drugs.

- IMiDs have probably an enhanced effect after AlloSCT

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