Nová lenalidomidová data v první linii

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Maintenance therapy with lenalidomide

Maintenance TT for Myeloma

- Chemotherapy: NO !

  (SWOG: Arch Intern Med 75; Alexanian: Blood 78; Belch: Br J Cancer 88)

- Interferon: NO !

  - ✓ Mandelli, N Engl J Med 1990: Yes
  - ✓Barlogie, JCO 2006 (US Intergroup): No

- Corticosteroids: NO !

  - ✓Berenson, Blood 2002: Yes (survival and duration of response)
  - ✓ShusTik, JCO 2004: No survival improvement
  - ✓Alexanian, Am J hematol 2000: IFN = Corticoïdes… thus NO!

Thalidomide

Maintenance therapy with thalidomide after ASCT

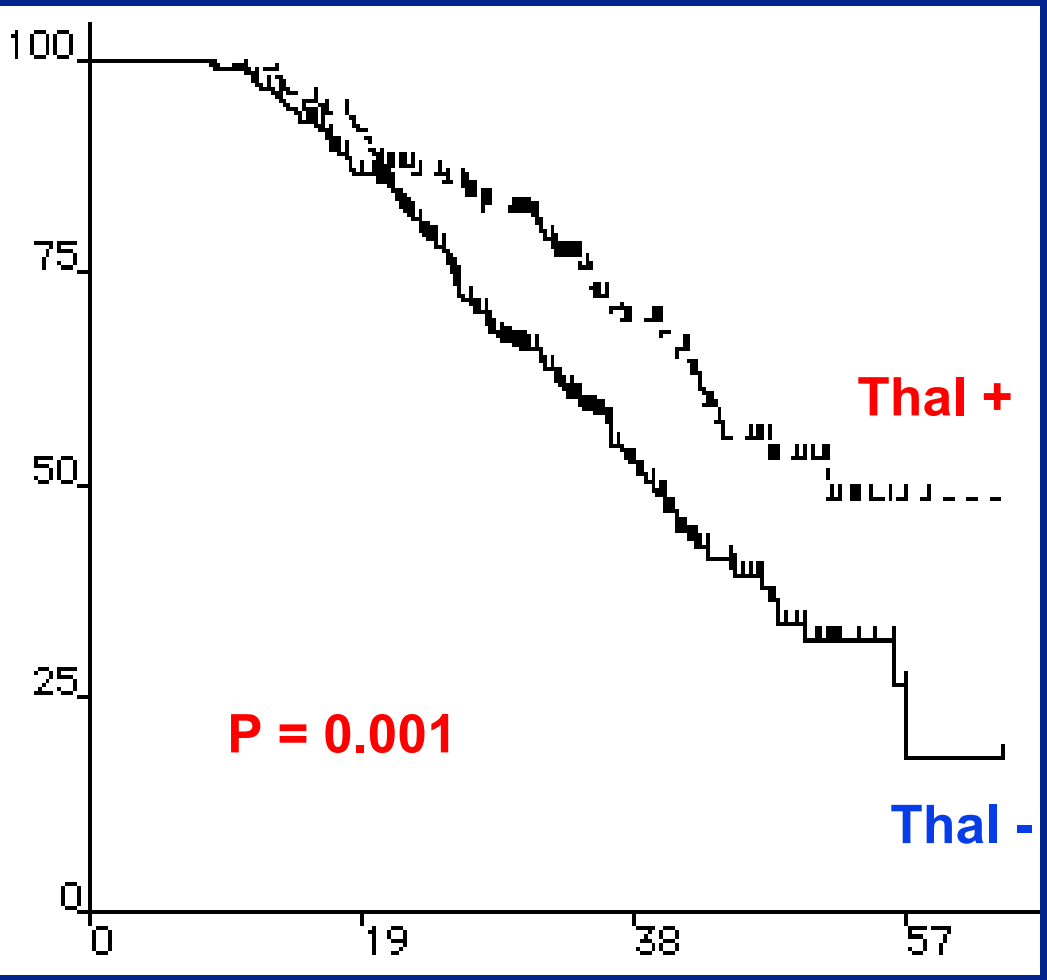
	N	Initial dose, mg	Maintenance versus no maintenance		
			CR, %	EFS or PFS, %	OS, %
Attal et al.[1]	597	400	67 vs 55*	3-year EFS 52 vs 36	4-year OS 87 vs 77
Barlogie et al.[2]	668	400	62 vs 43	5-year EFS 56 vs 44	8-year OS 57 vs 44
Spencer et al.[3]	243	200	63 vs 40*	3-year PFS 42 vs 23	3-year OS 86 vs 75
Lokhorst et al.[4]	535	50	24 vs 66*	Median 22 m vs 34 m	Median 60 m vs 73 m

1. Attal M, et al. Blood. 2006
2. Barlogie B, et al. Blood 2008
3. Spencer A, et al. J clin Oncol. 2009
4. Lokhorst et al . Blood 2010

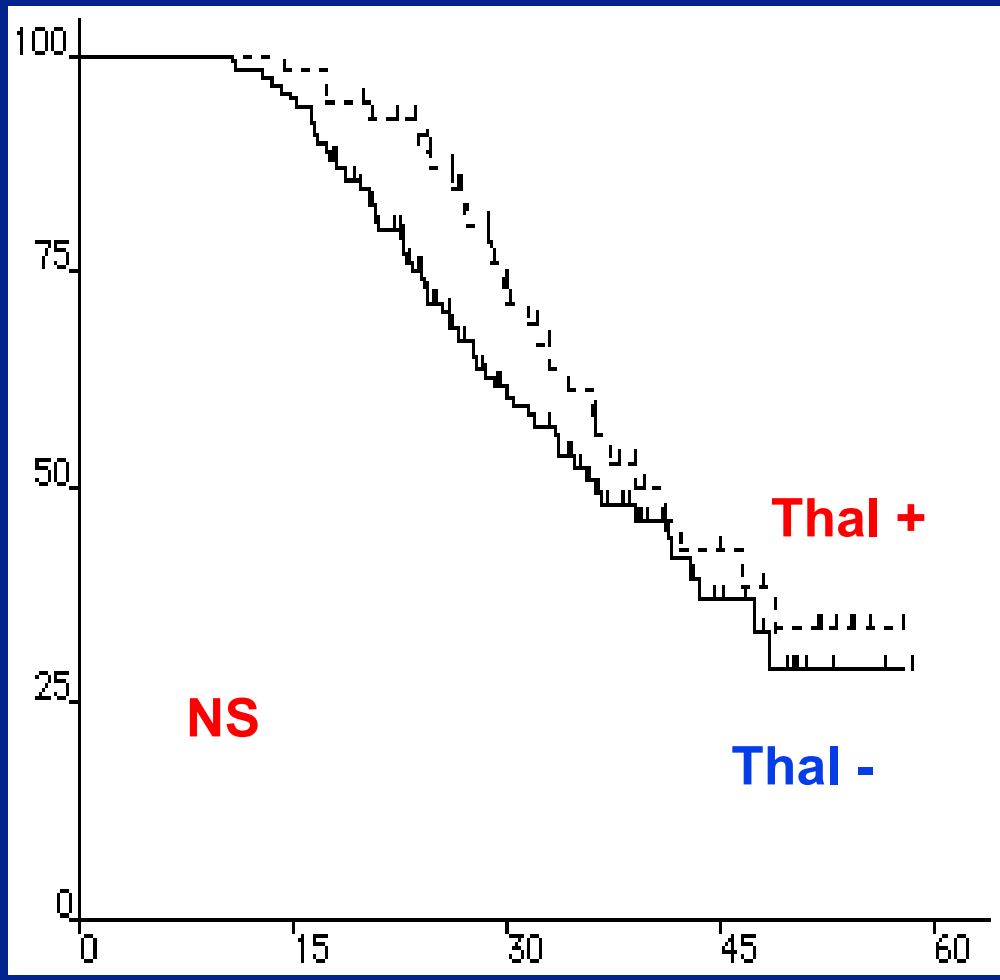
* CR + VGPR rates.

IFM 99 02 : EFS According to del 13

Del 13 -

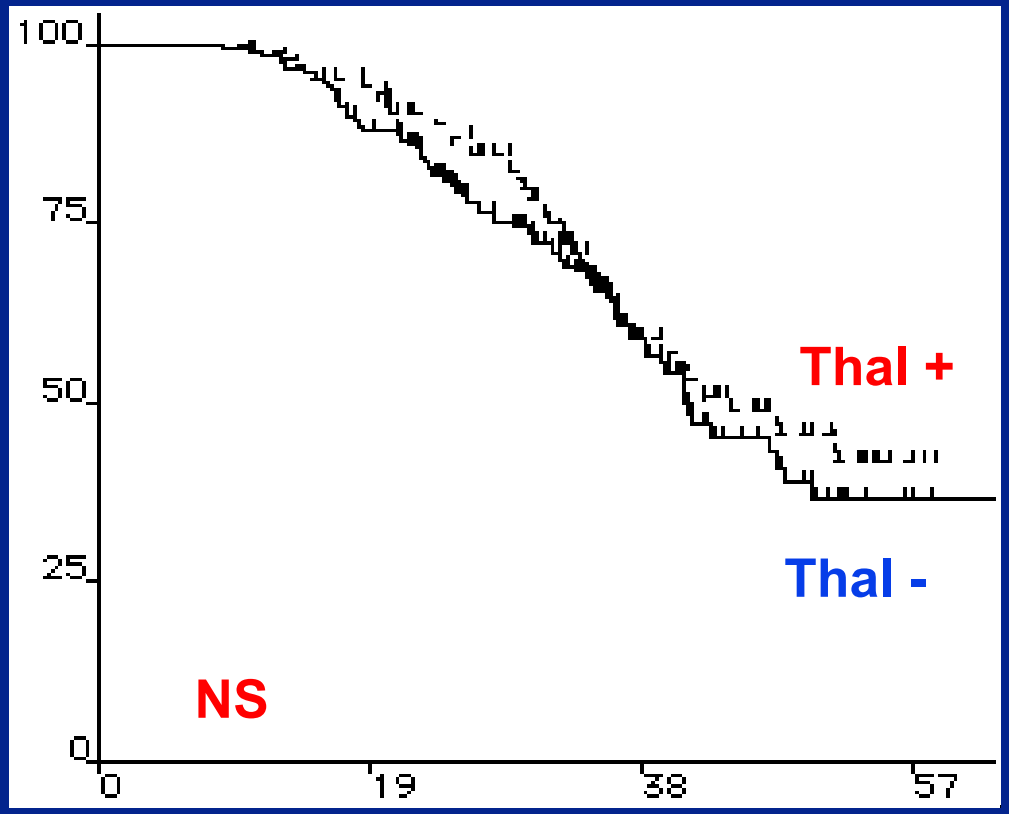


Del 13 +

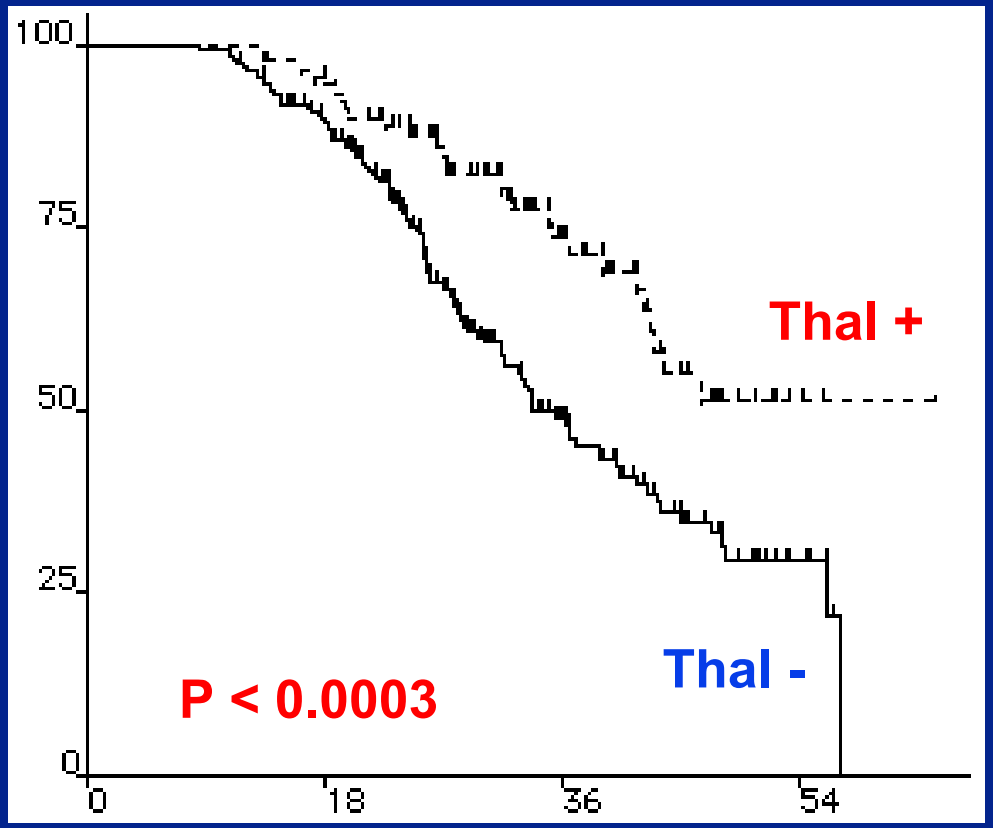


IFM 99 02 : EFS According to Response at Random

Response at Random ≥ 90%



Response at Random < 90%



Consolidation rather than maintenance

Explanation: 68% of PN responsible for short duration of TT ?

Maintenance TT in MM: Thalidomide

- **Thalidomide is an active drug after ASCT:**
  - ✓**Prolongs the PFS in 4/4 studies**
  - ✓ **Prolongs the OS in 3/4 studies**
- **The mechanism of action is unclear:**
  - **Improves the CR rate in 3/3 studies**
  - **Consolidation rather than Maintenance**
  - **Could be proposed for 3 to 6 months**
- **The incidence of neuropathy is a major concern !**

Lenalidomide

Lenalidomide (REVLIMID)

- **Lenalidomide is an attractive drug**
  - ✓**Oral agent**
  - ✓**Without neurological complications**

Thalidomide and Lenalidomide Have Distinct Mechanisms of Action

Efficacy of Thalidomide and Lenalidomide Mechanisms of Action[1]

	Thalidomide	Lenalidomide
Tumouricidal activity	+	+++
Immunomodulatory activity	+	++++
Anti-angiogenic activity	++++	+++

+ = potency factor of 10

- The mechanism of action of thalidomide is anti-angiogenic, while lenalidomide has more potent *tumouricidal and immunomodulatory* effects[1-2]
- Regardless of prior exposure to thalidomide, lenalidomide treatment results in significant efficacy with a manageable safety profile [3-4]

1. Hideshima et al. *Blood* 2000.
2. Mitsiades et al. *Blood* 2002.
3. Wang M et al. *Blood*. 2008.
4. Richardson et al., *Blood* 2009.

IFM 2005-02: Study design

Phase III randomized, placebo-controlled trial
N= 614 patients, from 78 centers, enrolled between 7/2006 and 8/2008

Patients < 65 years, with non-progressive disease, ≤ 6 months after ASCT in first line

Randomization: stratified according to Beta-2m, del13, VGPR

Consolidation:
Lenalidomide alone 25 mg/day p.o.
days 1-21 of every 28 days for 2 months

Arm A=
Placebo
(N=307)
until relapse

Arm B=
Lenalidomide
(N=307)
10-15 mg/d until relapse

Primary end-point: PFS.
Secondary end-points: CR rate, TTP, OS, feasibility of long-term lenalidomide….

ASCT = autologous stem cell transplant. IFM = Intergroupe Francophone du Myelome.

IFM 2005 02 Trial: Patient characteristics

	Arm A (placebo) N = 307	Arm B (Len) N = 307
· Age (y)	55	55
· Sex (M/F)	59% / 41%	55% / 45%
· ISS		
I	48%	43%
II	36%	35%
III	16%	22%
· Beta-2 m (≤3 / >3)	45% / 55%	45% / 55%
· Del 13 (present /eval)	41%	42%
· t(4-14) (present /eval)	7%	12%
· Del 17 (present /eval)	5%	7%

IFM 2005 02 Trial: Patient characteristics

	Arm A (placebo) N = 307	Arm B (Len) N = 307
Induction regimen		
VAD	52%	46%
Vel-Dex	44%	46%
Others	5%	8%
Number of transplant (1 /2)	79% / 21%	79% / 21%
VGPR post ASCT	58%	62%
Interval diagnosis-randomization	10 m (8-12)	10 m (8-12)
Interval transplant-Consolidation	4 (3-5)	4 (3-5)

IFM 2005 02 : Response[a] After Consolidation (n= 572)

	PRE	POST	p value [b]
CR (IF -)	**14%**	**20%**	**<0.0001**
≥ VGPR	**58%**	**67%**	**<0.0001**

[a] IMW Criteria
[b] Mc Nemar test

IFM 2005 02 : Best Response[a]

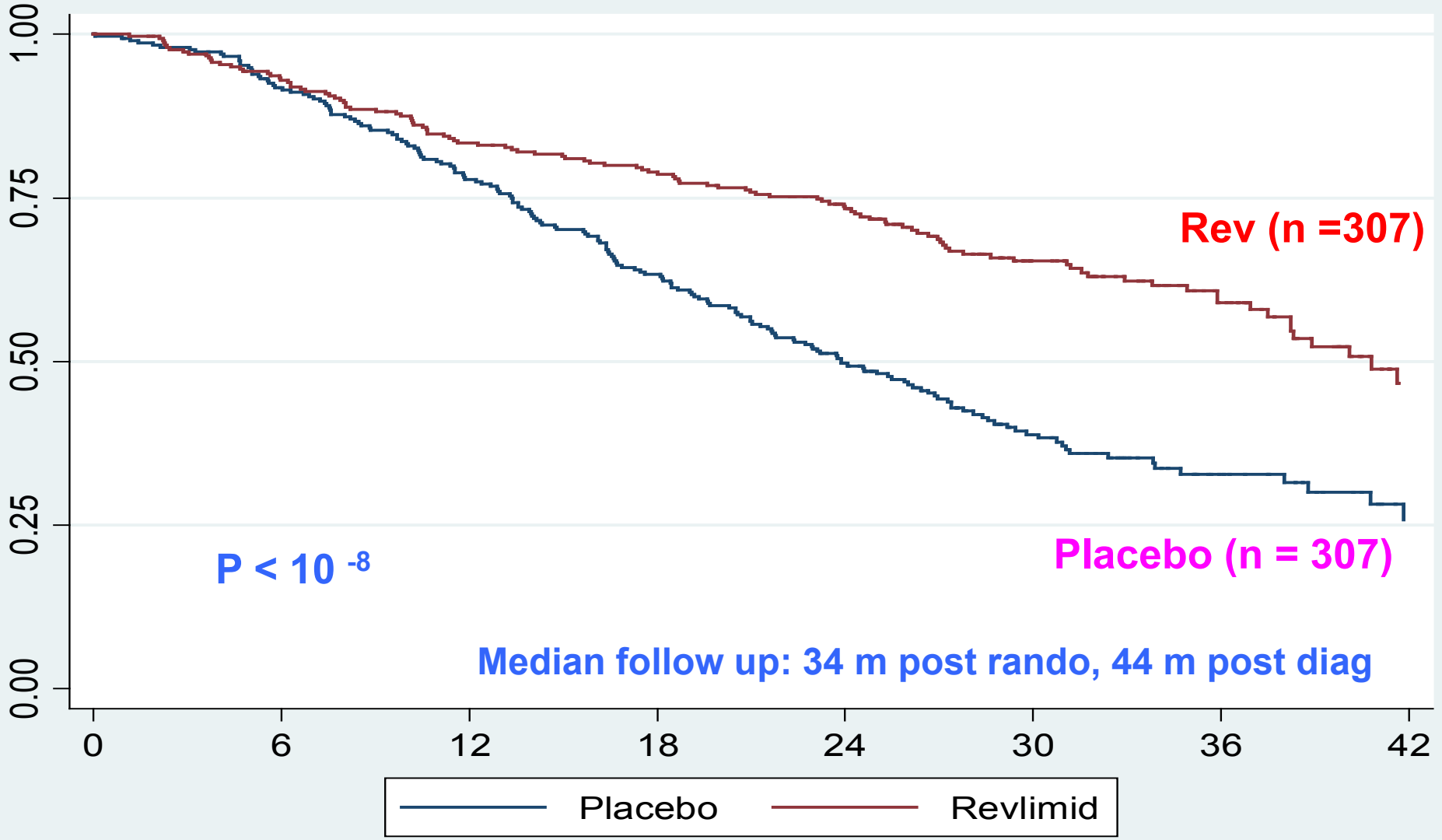
	Placebo (N= 307)	Revlimid (N=307)	p value
CR (IF -)	**23 %**	**25 %**	**0.495**
≥ VGPR	**71%**	**76 %**	**0.13**

[a] ***IMW Criteria***

IFM 2005-02 : PFS

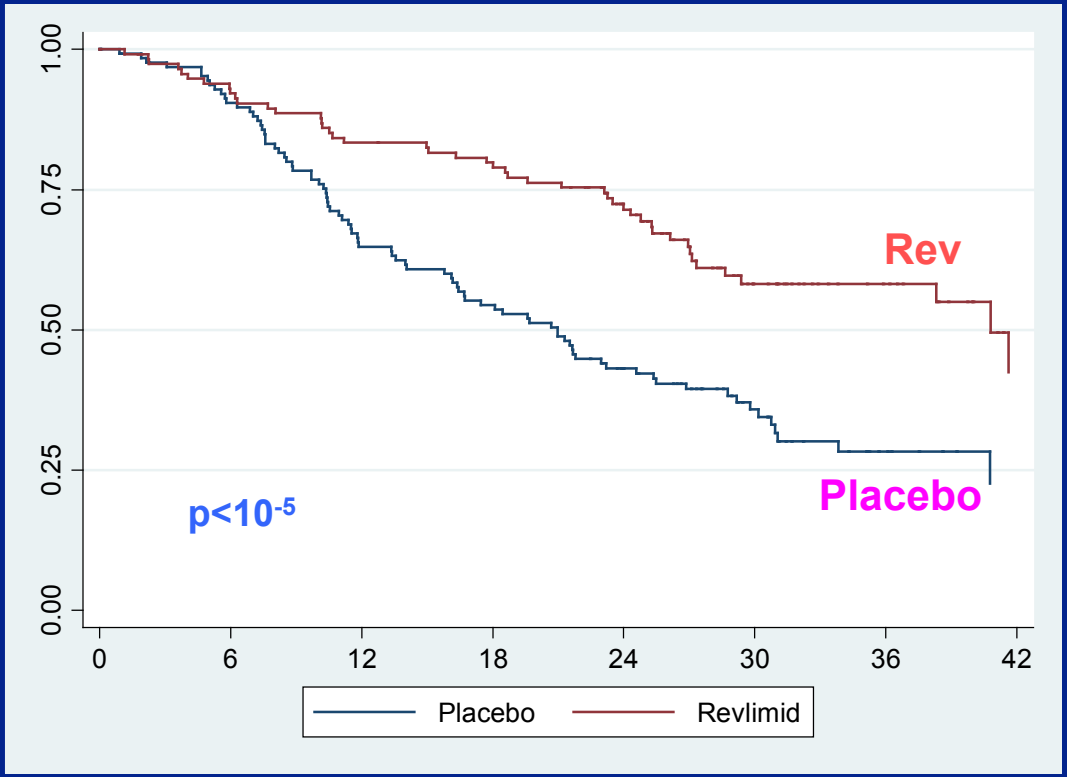
	Arm A N = 307	Arm B N = 307	P
Progression or Death	185	117	
Median PFS post rando (m)	24	42	
4-year post diag PFS (or 3-year post rando)	33%	60%	
Hazard Ratio	1	0.5	$< 10^{-8}$

IFM 2005-02 : PFS from randomization



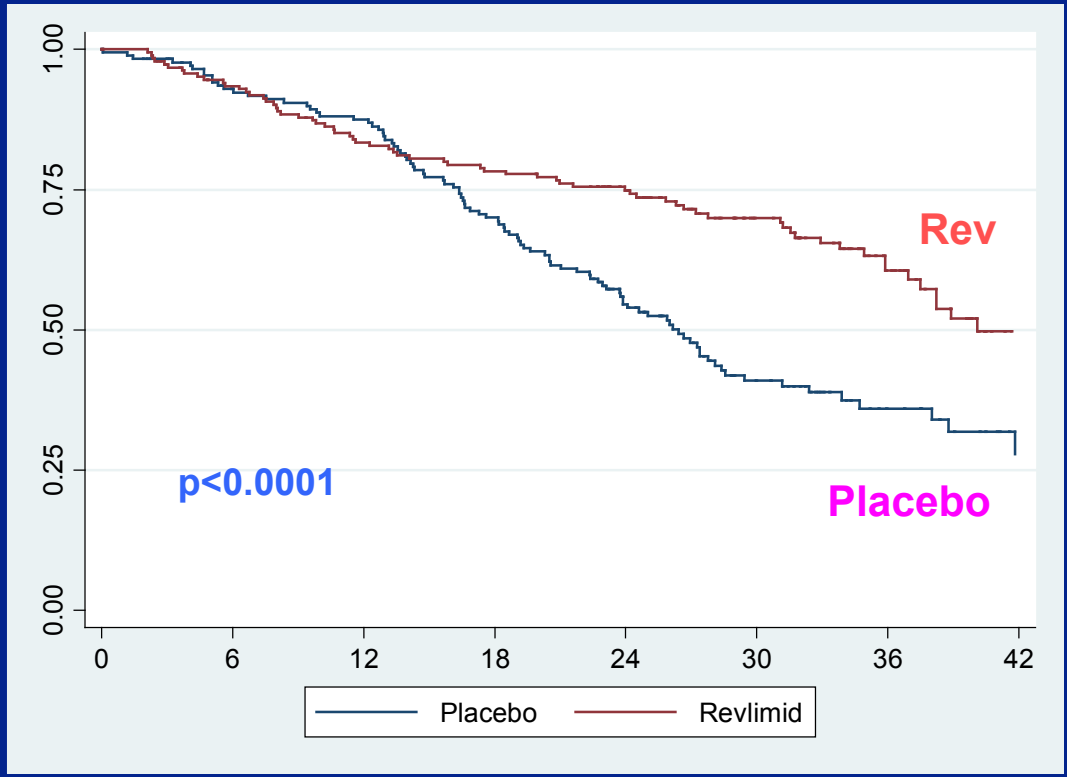
PFS according to Response Pre-Consolidation

PR or SD



HR= 0.46 - CI 95% [0.32-0.66]

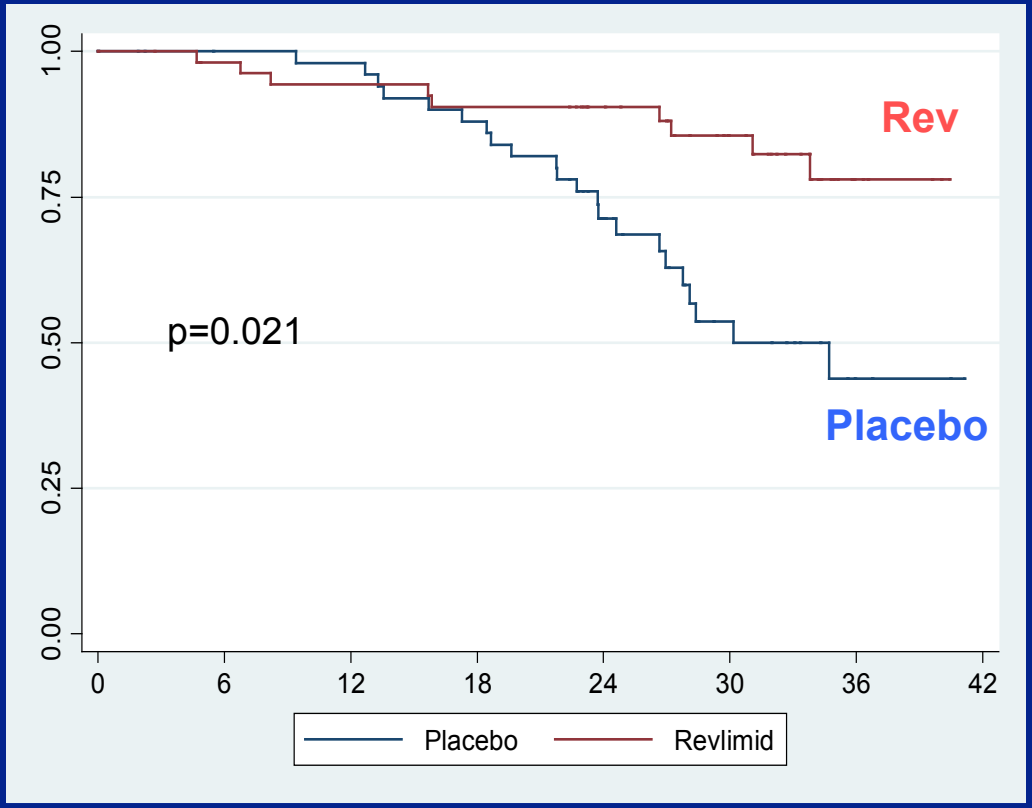
≥ VGPR



HR= 0.53 - CI 95% [0.39-0.72]

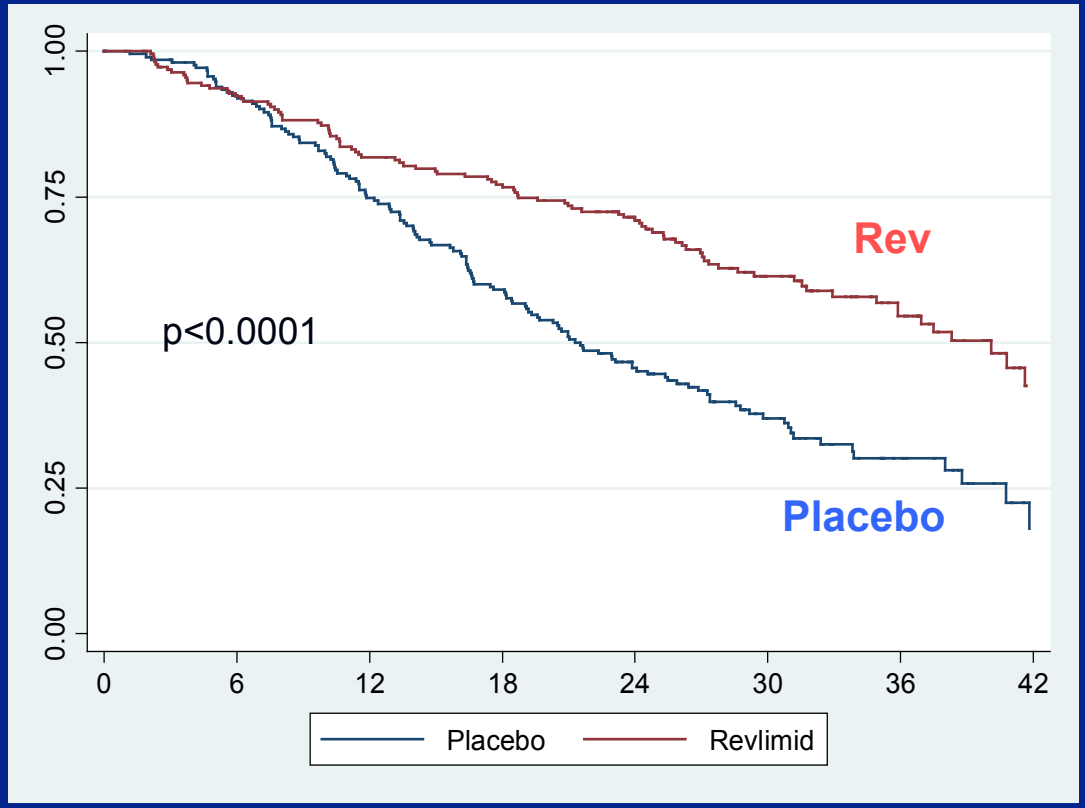
PFS according to Response Post-Consolidation

CR



HR= 0.31 - CI 95% [0.14-0.68]

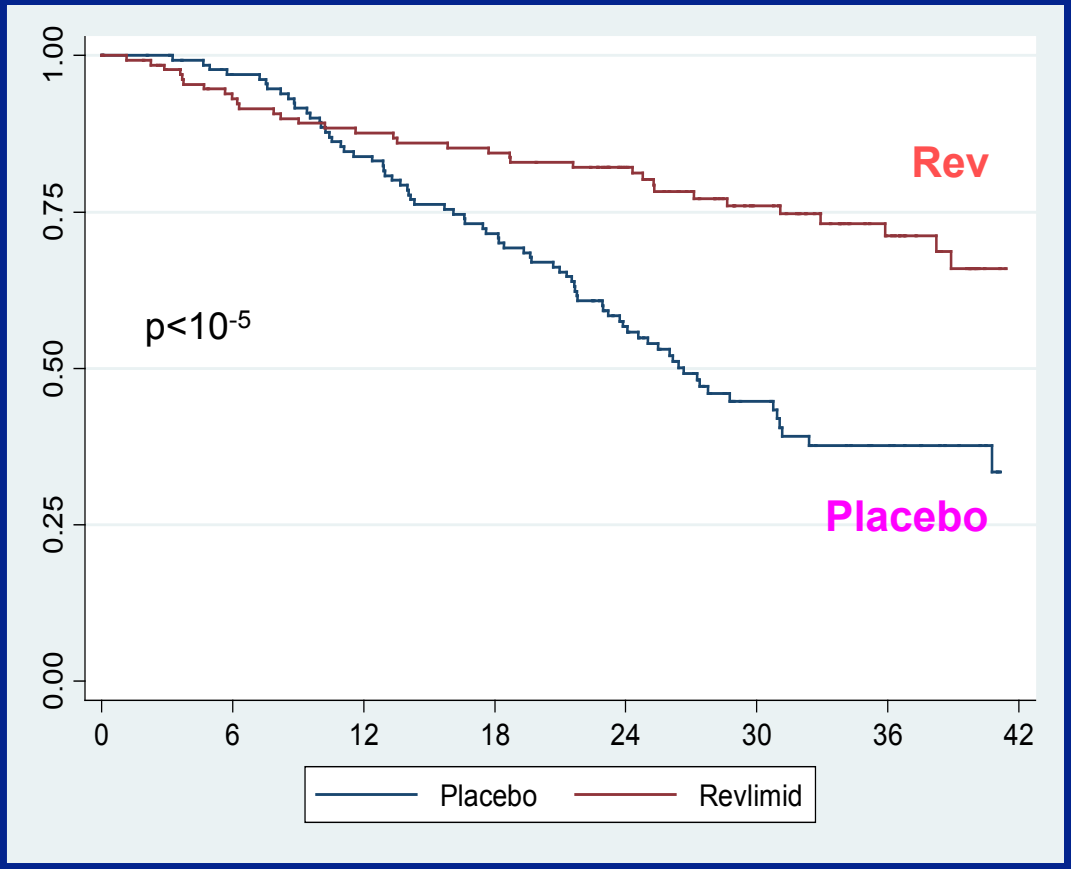
Not in CR



HR= 0.50- CI 95% [0.38-0.65]

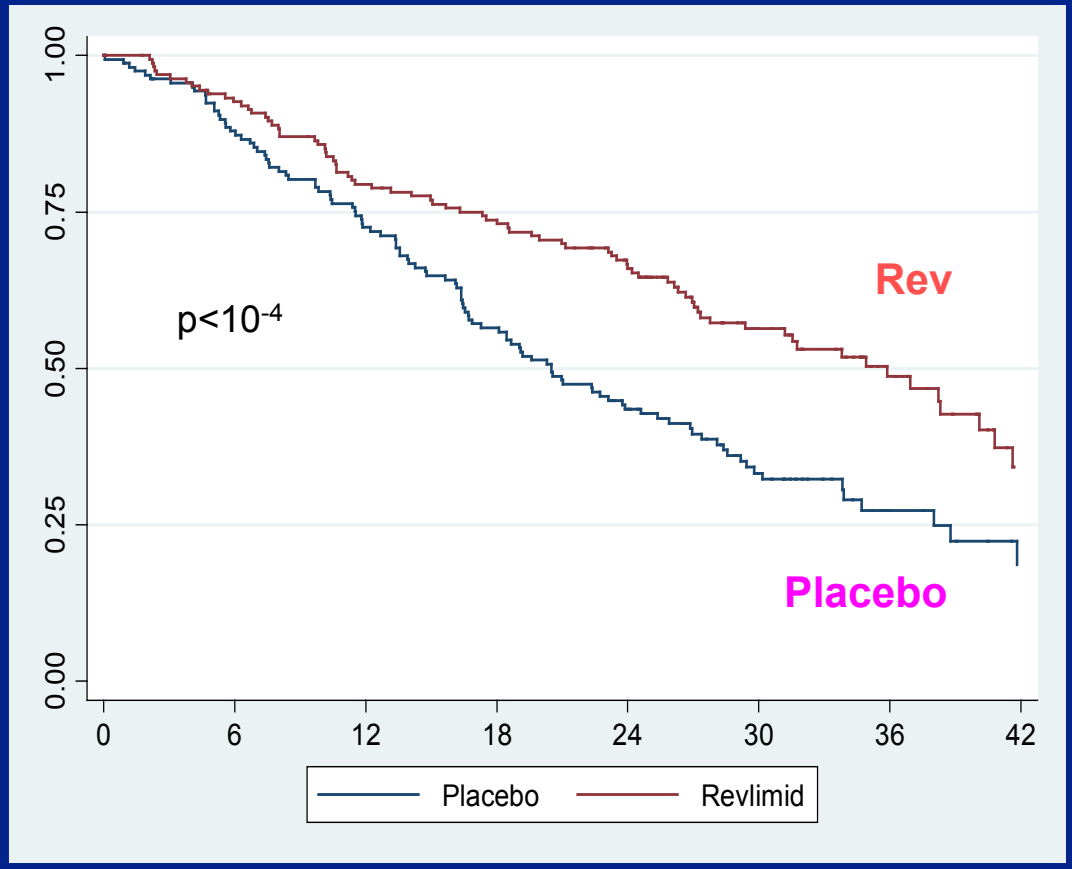
PFS according to initial ß2-m

ß2-m ≤ 3



HR= 0.38 - CI 95% [0.25-0.57]

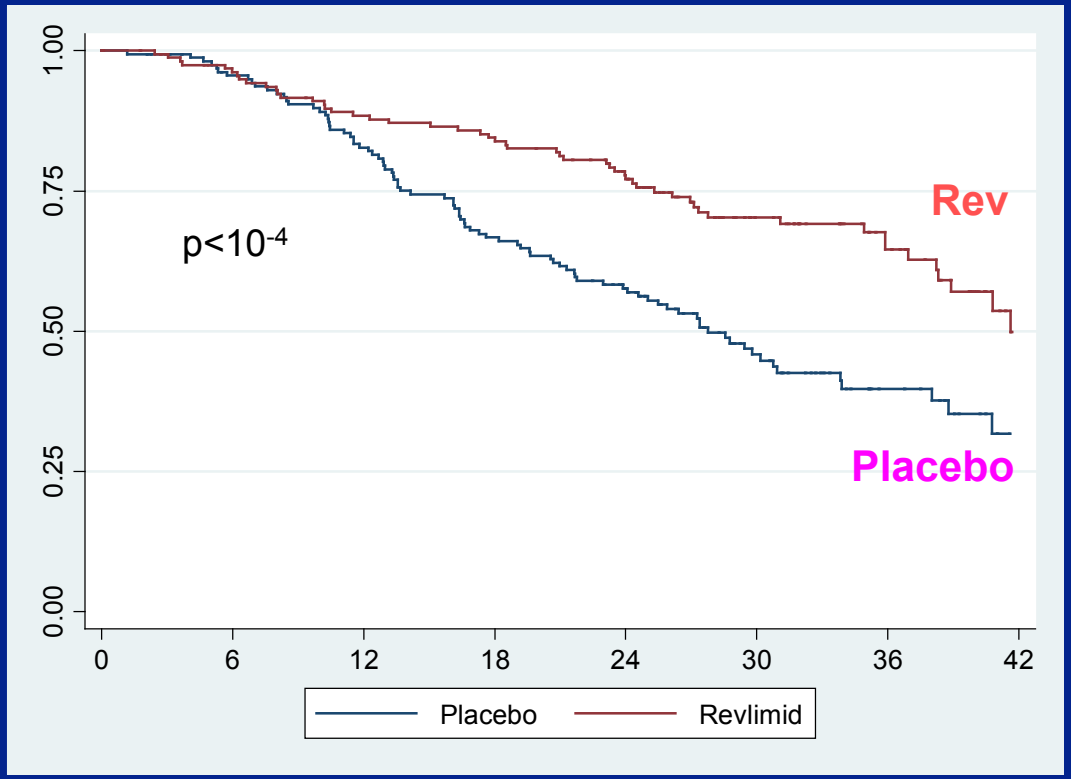
ß2-m > 3



HR= 0.56 - CI 95% [0.42-0.75]

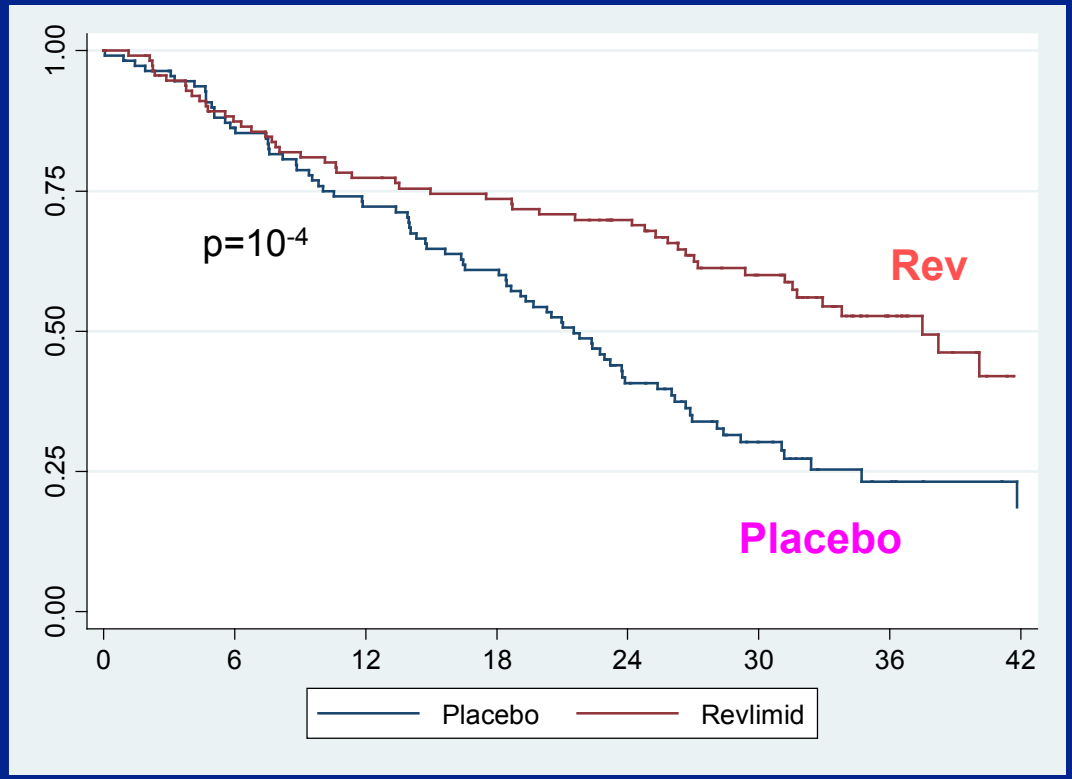
PFS according to cytogenetic

Without del 13



HR= 0.49 - CI 95% [0.35-0.69]

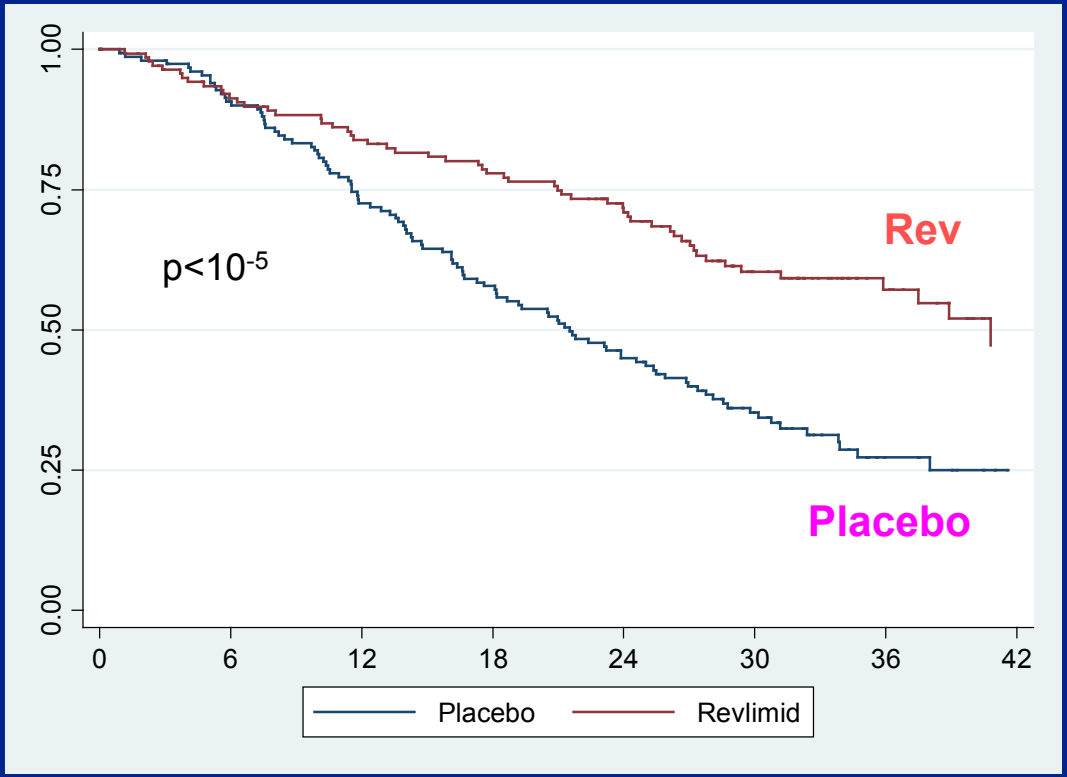
With del 13



HR= 0.49 - CI 95% [0.34-0.70]

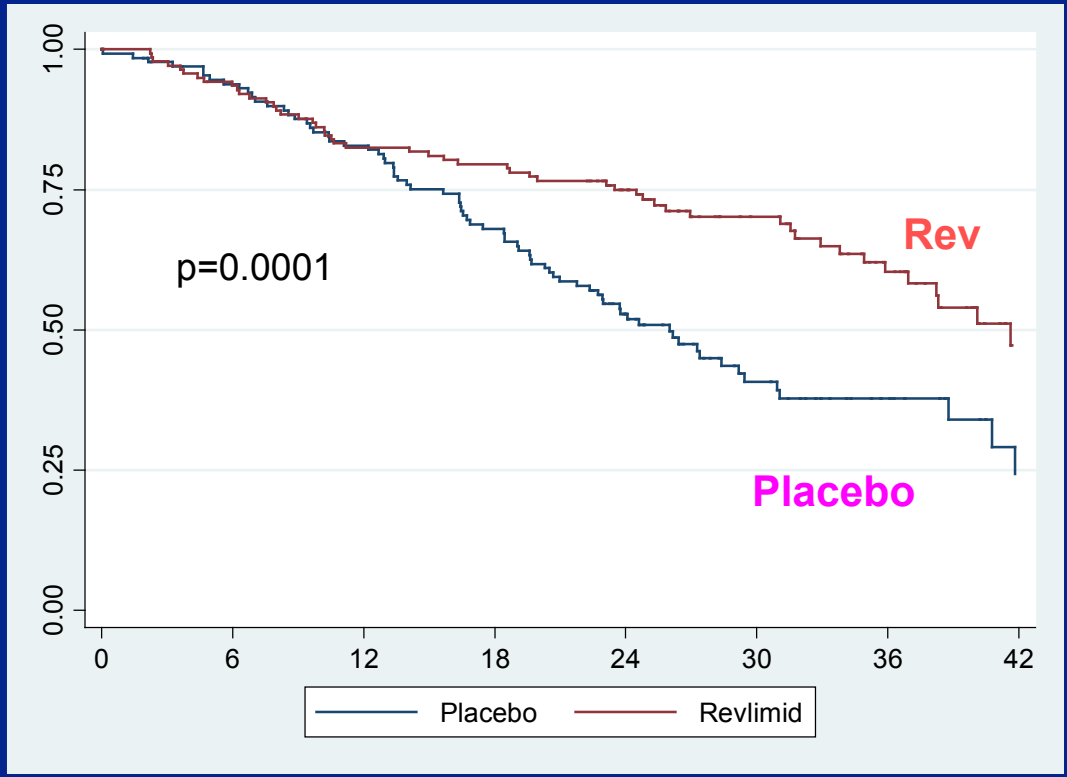
PFS according to induction regimen

VAD



HR= 0.48 - CI 95% [0.35-0.67]

VD



HR= 0.50 - CI 95% [0.35-0.71]

Prognostic Factors for PFS

Univariate analysis	p
Beta-2 m (<=3 / >3)	<0.001
ISS (I / II + III)	0.07
Del 13 (y / n)	0.001
Induction (VAD / Vel-Dex / Others)	NS
Response post ASCT (VGPR / no)	0.02
Response post consolidation	<0.001
Treatment arm (A / B)	$<10^{-8}$
Multivariate analysis	**p**
Treatment Arm (A / B)	<0.0000001
Response after consolidation (VGPR / no)	0.001
Del13 (y / n)	0.014
Beta-2 m (<=3 / >3)	<0.001

IFM 2005-02 : OS (to November 2010)

	Placebo N=307	Revlimid N=307	p
Death	**45**	**50**	
5-year post diag OS (or 4-year post Rando)	**81%**	**81%**	
Hazard Ratio	1	1.12 (0.75-1.68)	0.57

Grade 3-4 Adverse Events during treatment

AE (grade 4)	Arm A	Arm B
Anemia	2% (1%)	4% (2%)
Thrombocytopenia	6% (2%)	12% (5%)
Neutropenia	14% (3%)	43% (11%)
Febrile Neutropenia	0%	2% (1%)
Infections	5% (1%)	10% (1%)
DVT	0%	2% (0.3%)
Skin disorders	4%	6%
Fatigue	0%	1%
Peripheral Neuropathy	0.3%	0.7%
Hematologic malignancies (n)	2	10
Non hematologic malignancies (n)	1	7

Definitive Discontinuation for AE: placebo = 15% vs lenalidomide = 21%

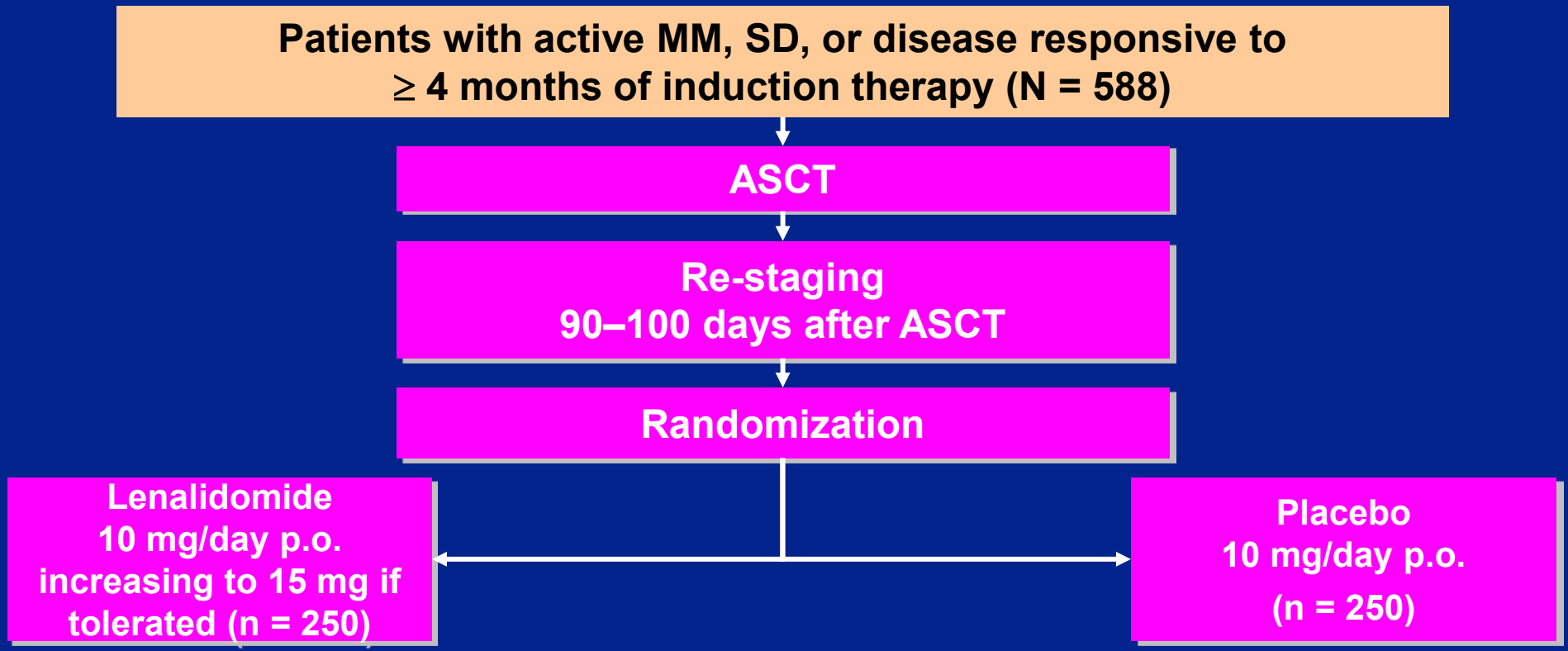
IFM 2005-02: Conclusions

- **Maintenance therapy with Revlimid:**
  - **Is well tolerated:**
    - ✓ Low definitive discontinuation rate due to AE
    - ✓ Low rate of neuropathy and DVT
  - **Is superior to placebo:**
    - ✓ 50% reduction risk of progression
    - ✓ In all stratified subgroups (response, ß2m, FISH)
- **A longer follow-up is required to appreciate the impact on OS :**

  (Today, death are only observed in high risk patients : the median interval Progression-Death being extremely short !! (A vs B = 13 m vs 11 m)

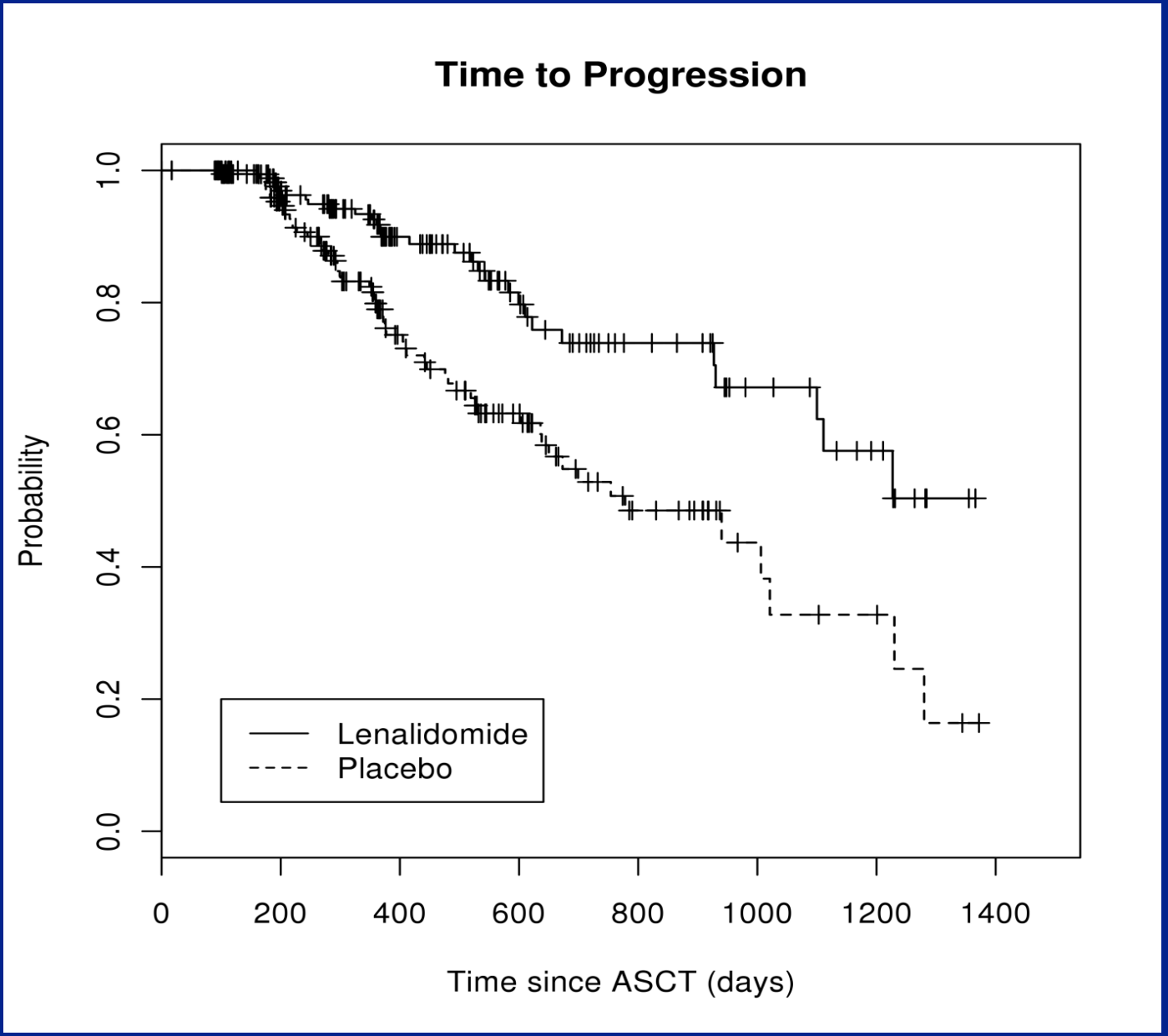
CALGB 100104: Lenalidomide as maintenance therapy after ASCT for MM

Ongoing phase III, randomized, placebo-controlled trial



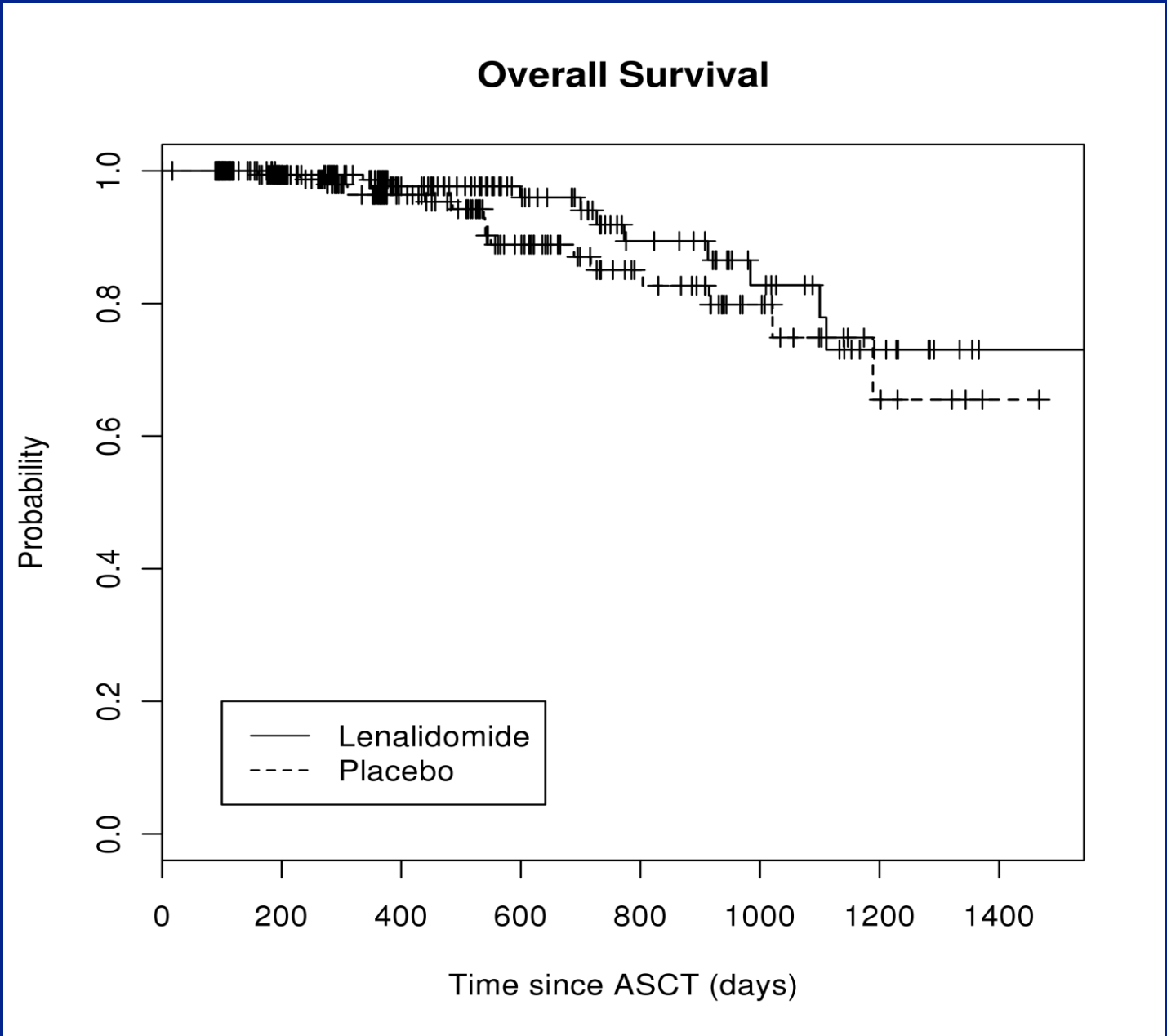
Primary end-point: time to disease progression after autologous ASCT
Secondary end-points: CR rate, PFS, OS, and feasibility of long-term lenalidomide

Trial NCT00114101. Available from: www.ClinicalTrials.gov.



CALGB 100104, Nov 2009

Median Follow up is 12 months



CALGB 100104, Nov 2009

Limitations !

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Safety of the long-term use of lenalidomide

2 years of maintenance – cut off ?
(under investigation)

Safety of the long-term use of lenalidomide

Three large studies presented at ASH 2010 raised questions about the occurrence of second primary cancers in the setting of lenalidomide maintenance

In the clinical trial setting, it is a priority to ensure consistent data collection and reporting of second cancers.

„Lenalidomide (Revlimid) maintenance treatment in Czech Republic

„CMG 2008 junior“
Protokol RV-MM-EMN-441

and

„CMG 2010 senior“
Protokol EMN 01

Clinical trials active in the Czech Republic for newly diagnosed patients

CZECH MYELOMA GROUP
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Protokols RV-MM-EMN-441 and EMN01

- **Main coordinator:**

  Fondazione Neoplasie Sangue Onlus (FO.NE.SA Onlus), Itálie

- **Coordinator for CR, SR, Hungary and Poland:**
  CMG, foundation

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„CMG 2008 junior“
Trial RV-MM-EMN-441

Induction: RD 4 cycles

Collection of PBSC (Cy 3g/m2+ G-CSF)

Randomization 1:

Arm A: CRD 6 cycles

Arm B: ASCT (MEL 200)

Randomization 2: maintenance

Arms: A1, B1: Lenalidomid

Arms: A2, B2: Lenalidomid+Prednison

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„CMG 2008 junior“
Trial RV-MM-EMN-441

Actual Status

Planned numbers of enrolled patients:

Total: 380

Actual status of enrollment (11.4.2011):

Italy – 254 (and STOP)	Slovak Rep. – 4
Australia – 48	Hungary – 7
Czech Rep. – 54	Poland – 0

Total of 367 pts. were enrolled until 11.4.2011

Total of 13 pts. remaining to be enrolled

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„CMG 2010 senior“
Trial EMN 01

Randomization 1:

Arm A:	**RD**	**9 cycles**
Arm B:	**MPR**	
Arm C:	**CPR**	

Randomization 2: maintenance

Arm A1, B1, C1: Lenalidomid

Arm A2, B2, C2: Lenalidomid+Prednison

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„CMG 2010 senior“
Trial EMN 01
Actual Status

Planned numbers of enrolled patients:

Total: 660

Actual status of enrollment (11.4.2011):

Italy – 338
Czech Rep. – 8 (just started)
Israel – 0
Germany – 0

Total of 346 pts. were enrolled until 11.4.2011

Total of 314 pts. remaining to be enrolled

Conclusion

Lenalidomide has strong immunomodulatory feature with durable response

The maintenance therapy with lenalidomide is beneficial

Longer follow –up and further safety analysis can define optimal duration of maintenance therapy

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Thank you for your attention