19th Post-ASH : Focus on multiple myeloma

Philip Vlummens

Universitair Ziekenhuis Gent

UNIVERSITEIT GENT

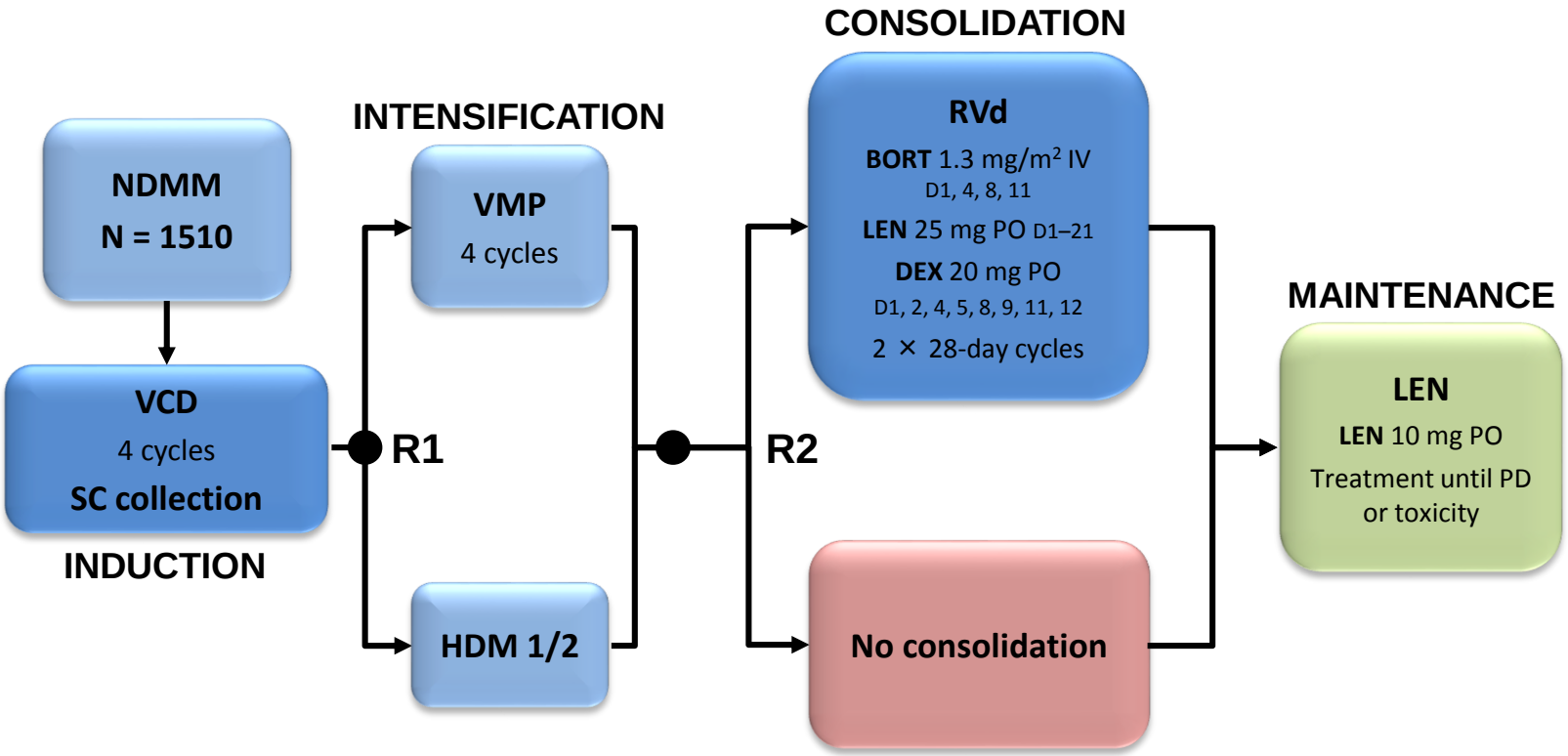
Presentation outline

- Consolidation therapy demystified?
- The role of maintenance therapy
- MRD beyond first line
  - Transplant-ineligible patients (Myeloma XI)
  - Relapse setting (CASTOR/POLLUX)
- New treatment strategies : Venetoclax/Selinexor

Abstract 242 Sonneveld et al.

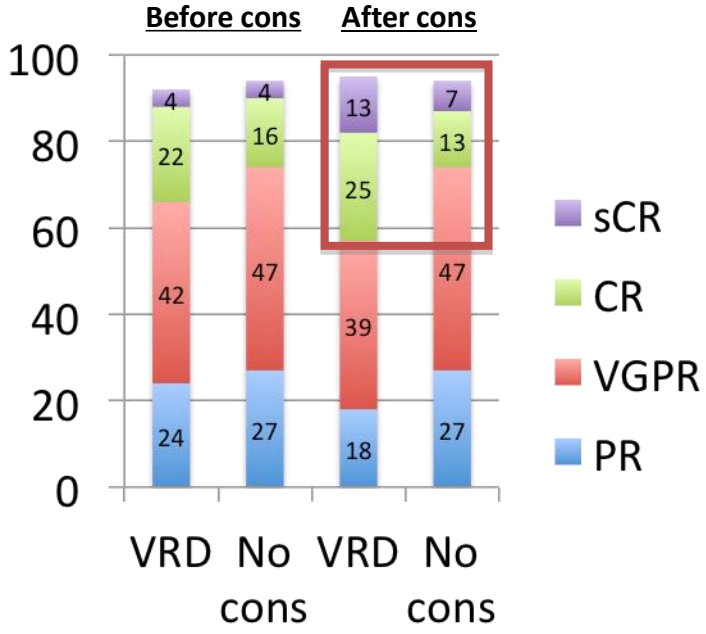
EMN02/HOVON95 MM : A Randomized Phase III Study to Compare Bortezomib, Melphalan, Prednisone (VMP) With High-Dose Melphalan Followed by Bortezomib, Lenalidomide, Dexamethasone (RVd) Consolidation and Lenalidomide Maintenance in Patients With Newly Diagnosed Multiple Myeloma

Consolidation therapy



	No consolidation (444)	VRD (459)
Median age, years (range)	58 (33-66)	57 (29-66)
Male/female	56/44	57/43
ISS I, II, III, %	43/40/17	42/37/21

Patient outcome EMN/HOVON trial



	RVd	No consolidation
PFS	N = 450	N = 435
	65% vs 60% Hazard rate 0,78 (0,61 – 1,00) p = 0,045	
OS	N = 451	N = 438
	Hazard rate 1,16 (0,76 – 1,75) p = 0,50	

- PFS was prolonged with RVd consolidation vs no consolidation (median follow-up 25 mo) from R2
- Benefit in low-risk cytogenetics (HR 0,68, p=0,03), not in high-risk disease (consisting of 25% of patients)
- OS was equal at 86% in both arms

Conclusions

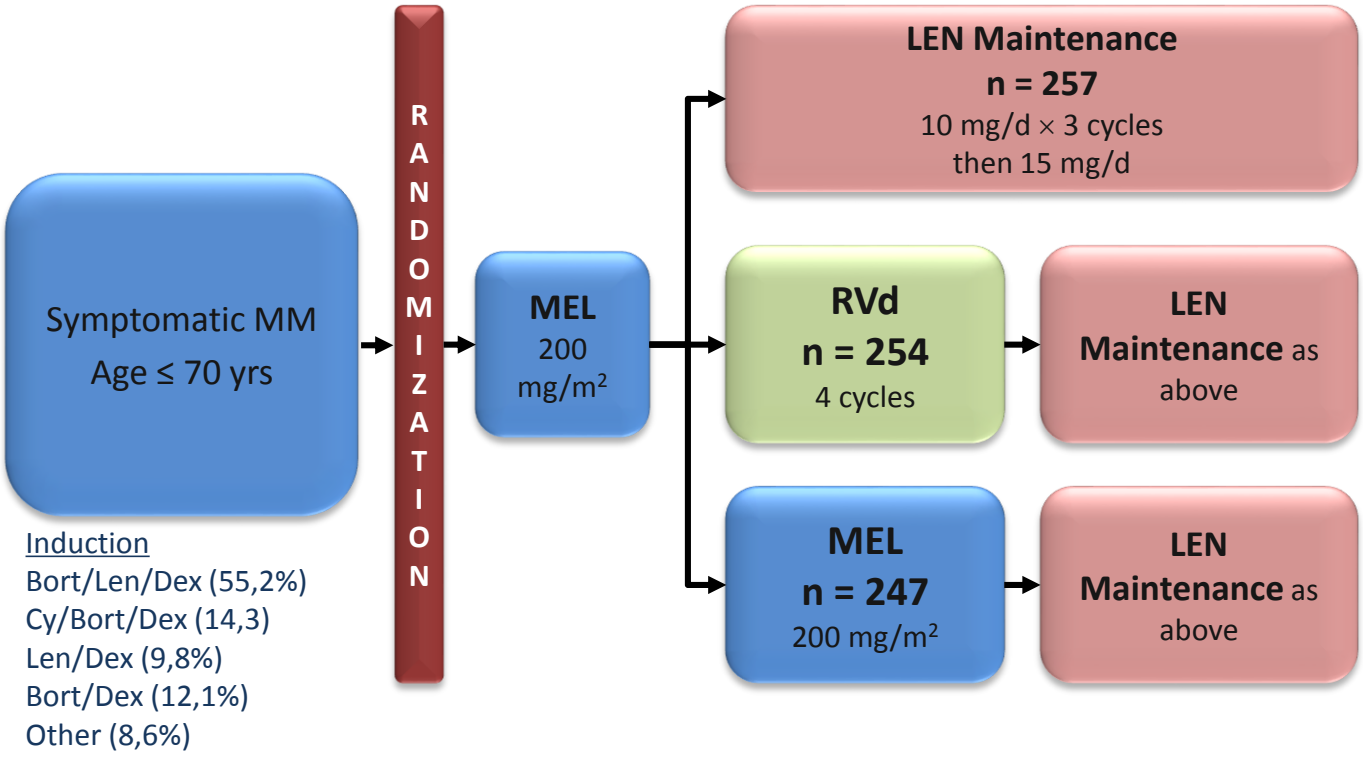
- sCR/CR rate improved following consolidation
- Consolidation therapy with RVd improved PFS when compared to a no consolidation strategy
- Result were independent of ISS stage and were primarily seen in patients without high-risk cytogenetics (planned subgroup-analysis)

However …

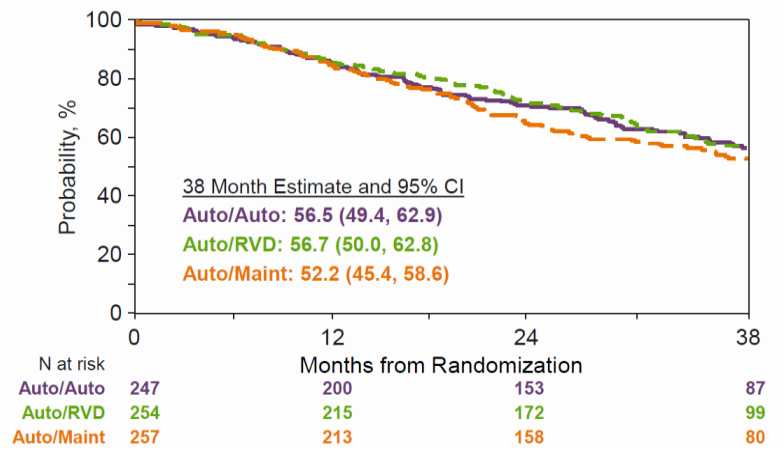
Abstract LBA-1 Stadtmauer et al.

Primary Results From the Randomized Prospective Phase III Trial of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0702 – STaMINA Trial: Autologous Hematopoietic Cell Transplant (AHCT), With and Without Consolidation With Bortezomib, Lenalidomide (LEN) and Dexamethasone (RVd) and LEN Maintenance vs Tandem AHCT and LEN Maintenance for Up-Front Treatment of Patients With Multiple Myeloma

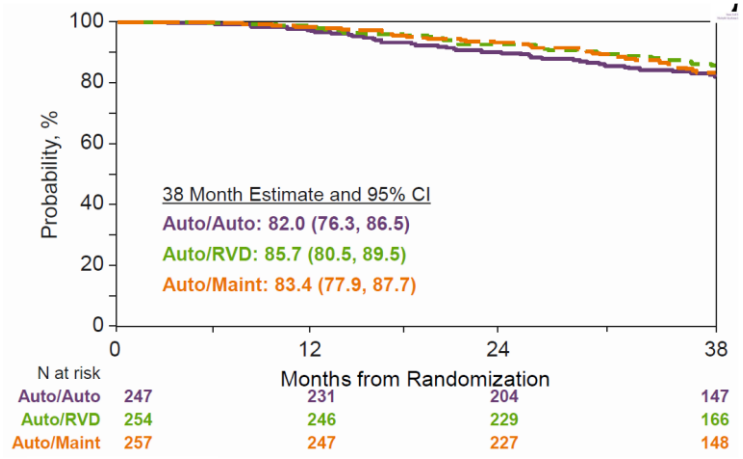
StaMINA - design



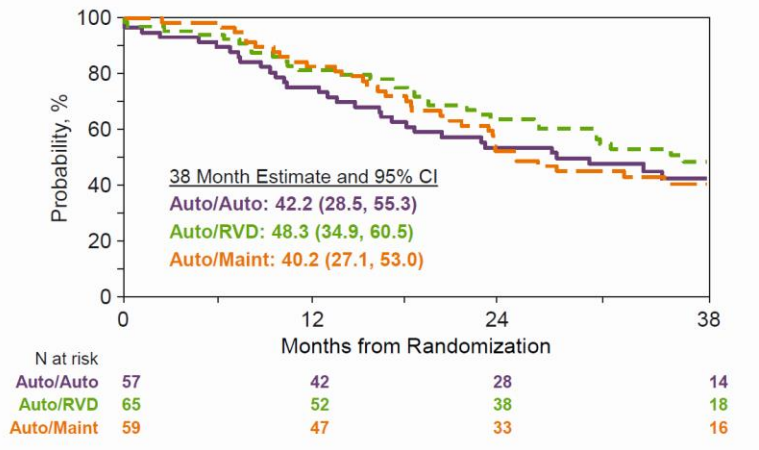
STaMINA – survival data



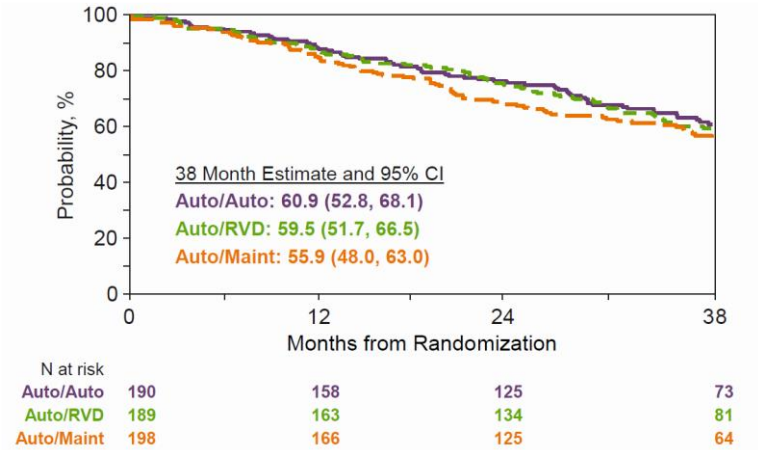
PFS



OS



PFS high-risk



PFS standard risk

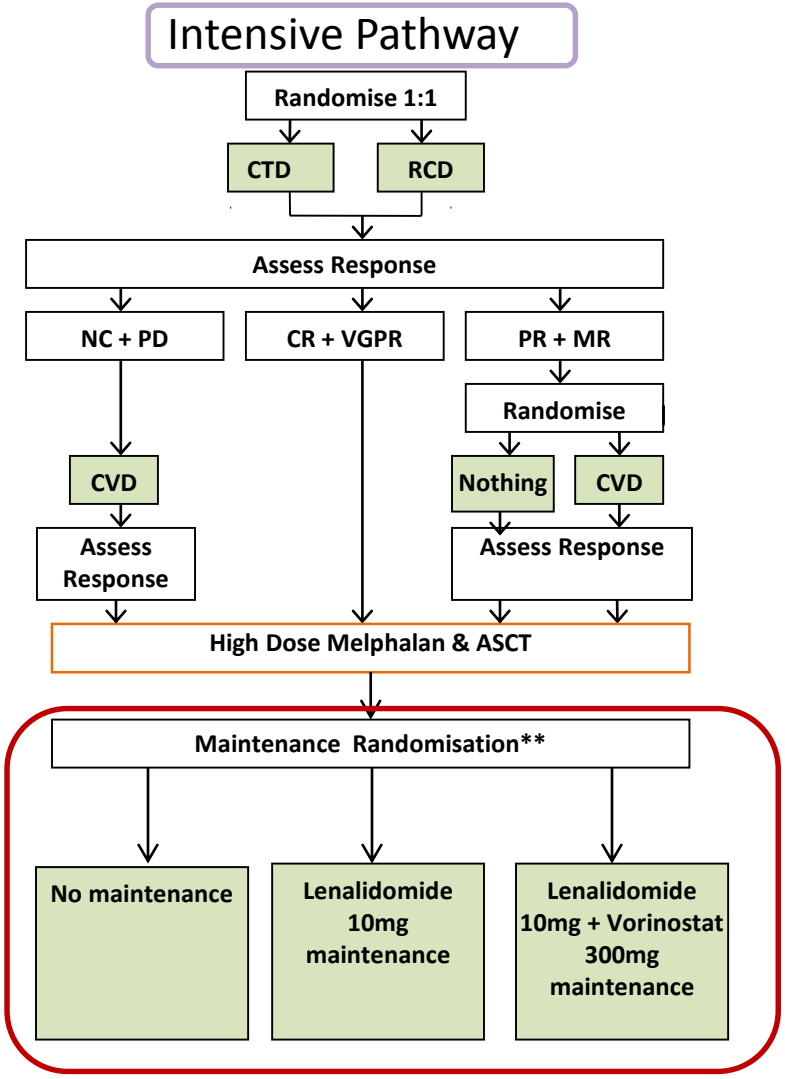
Consolidation therapy

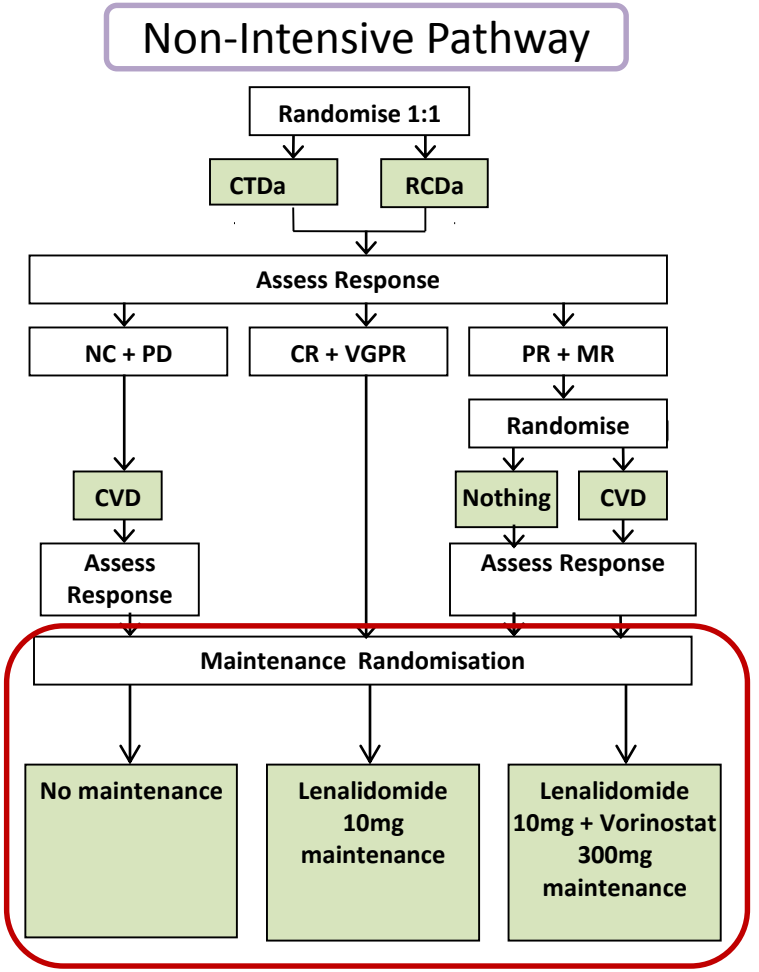
- Consolidation therapy (or a second ASCT) does not seem to provide an incremental outcome benefit in the era of lenalidomide maintenance (EMNO2/HOVON95)
- Results are not uniform between both studies

Abstract 1143 Jackson et al.

Lenalidomide Is a Highly Effective Maintenance Therapy in Myeloma Patients of All Ages: Results of the Phase III Myeloma XI Study

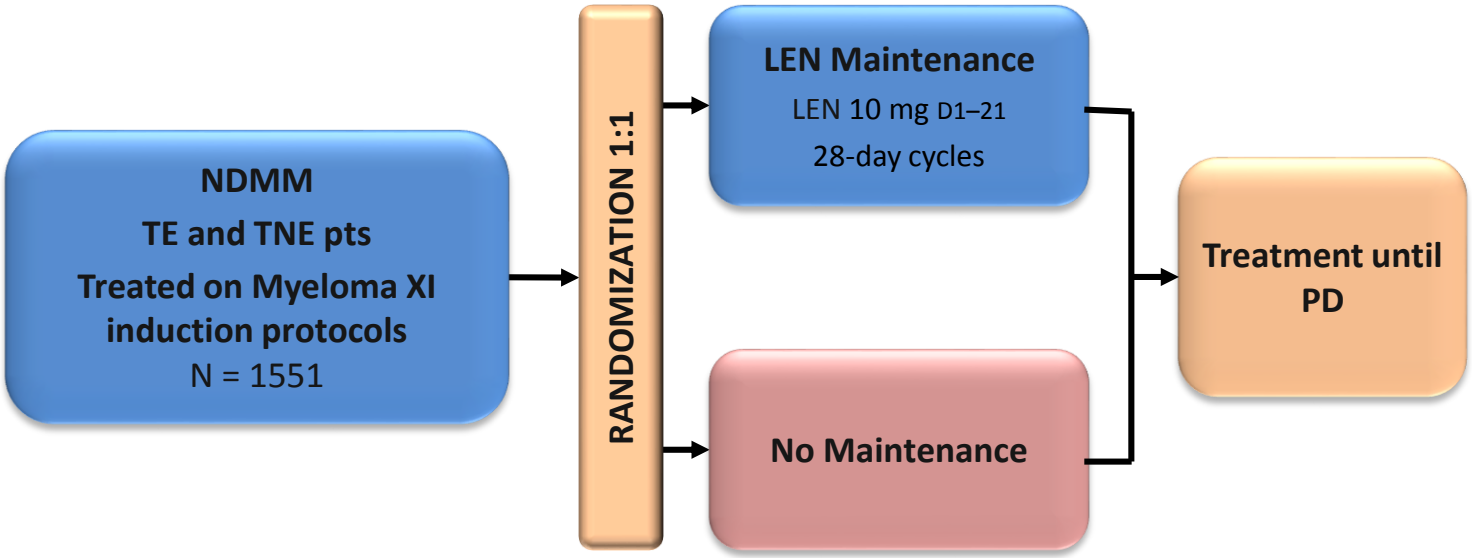
Myeloma XI overview





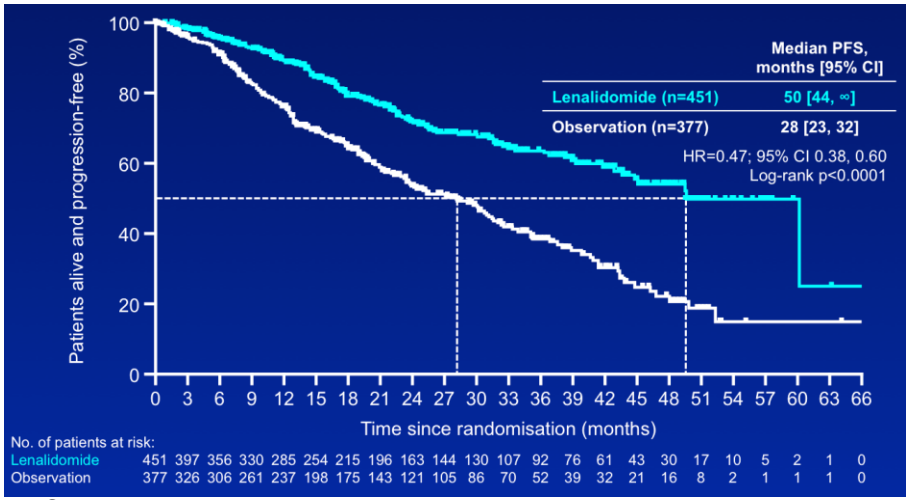
**Patients entered into the RCD arm and assessed as NC or PD at the end of RCD induction are not eligible for the maintenance randomisation

Myeloma XI : Len maintenance

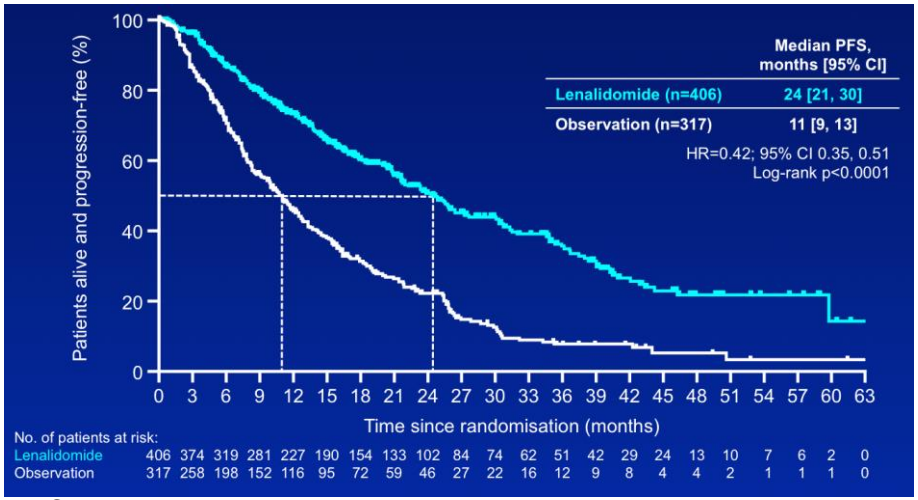


Primary endpoints : PFS and OS
N = 1551 with 828 TE and 723 NTE > 857 maintenance and 694 no maint.
Median age maintenance/no maintenance : 68 (29-89) vs 68 (30-90)
Equal distribution of ISS and cytogenetics between groups
Median follow-up was 27 mo

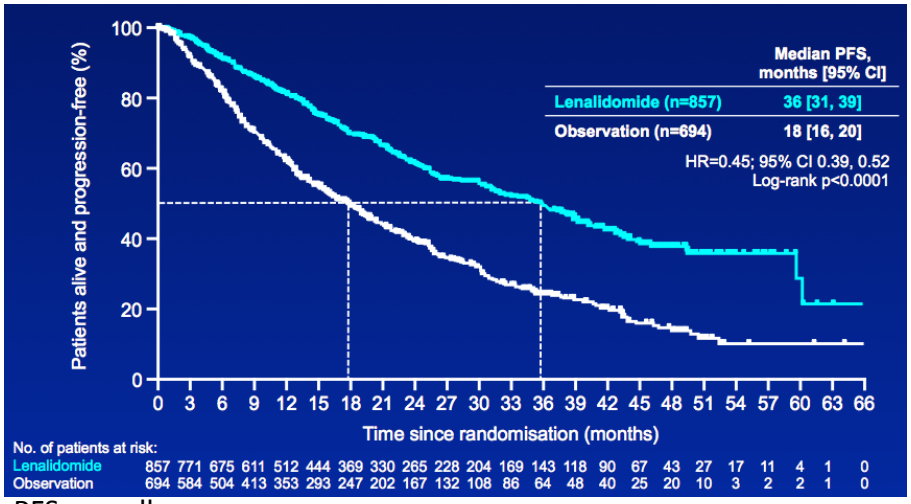
Len maintenance : Results



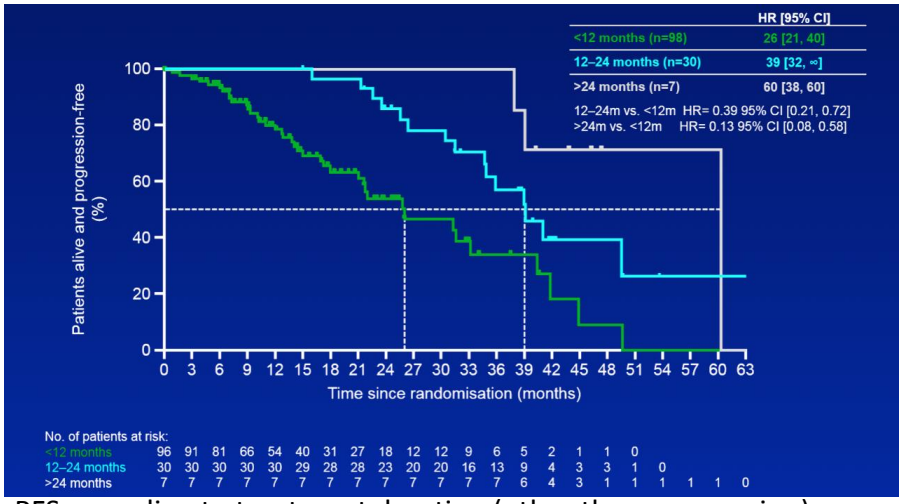
PFS TE



PFS TNE



PFS overall



PFS according to treatment duration (other than progression)

Myeloma XI : Len maintenance

- Maintenance with lenalidomide until progression resulted in a significant PFS improvement
- Longer treatment reduced risk of relapse
- OS data are not available yet
- SPM data :
  - 72 SPMs observed (48 vs 24)
  - No clinically significant increase in invasive SPMs

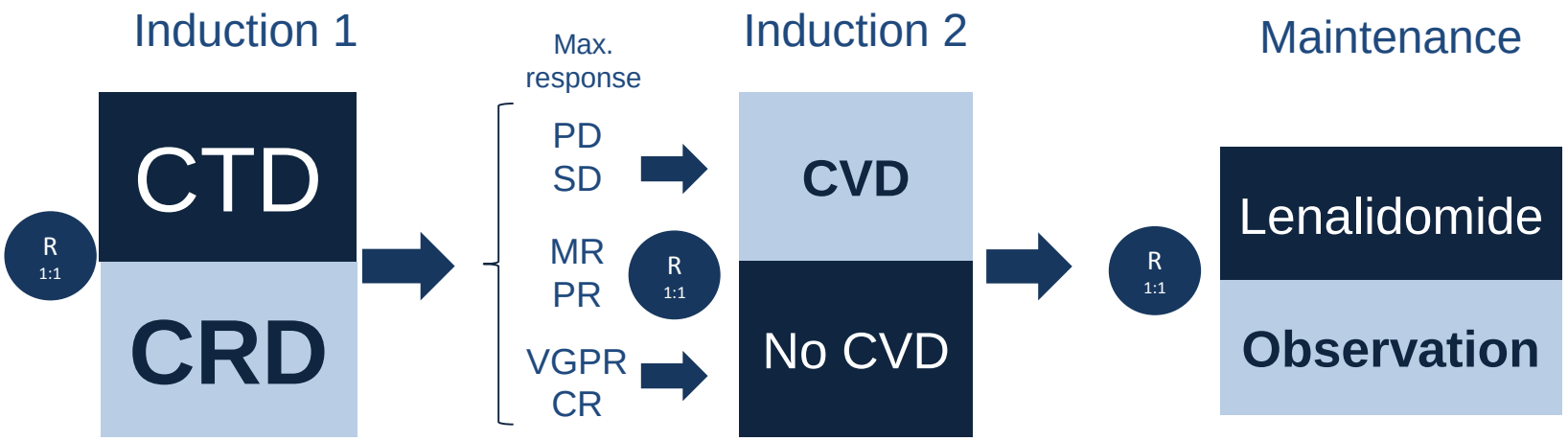
Abstract 245 de Tute et al.

Impact of minimal residual disease in transplant ineligible myeloma patients: results of from the UK NCRI Myeloma XI trial.

MRD in transplant-ineligible patients

- MRD …
  - Independent prediction of outcome
  - Demonstrable quantitative effect
  - Impact is independent of the therapy received
  - Applicable to high- and standard-risk patients
  - **But majority of data available in ASCT-based therapies**

Myeloma XI – transplant ineligible patients



MRD

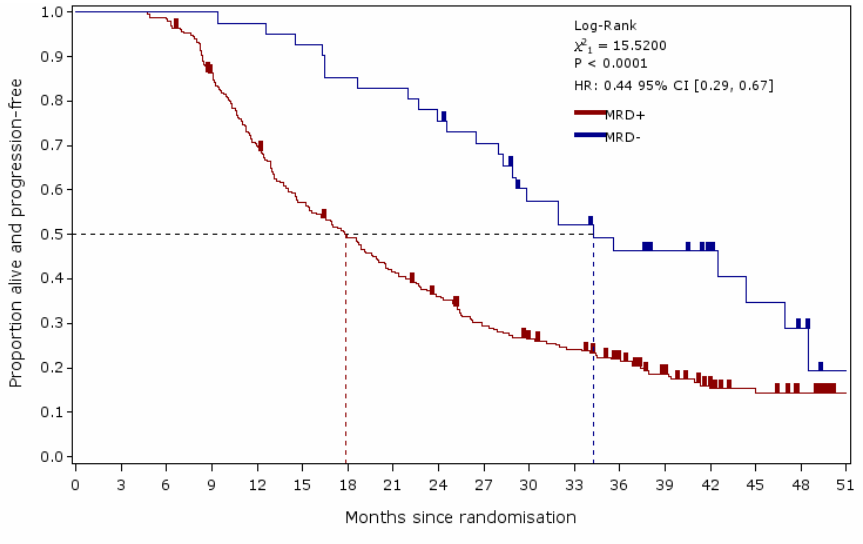
6-colour flow-cytometry

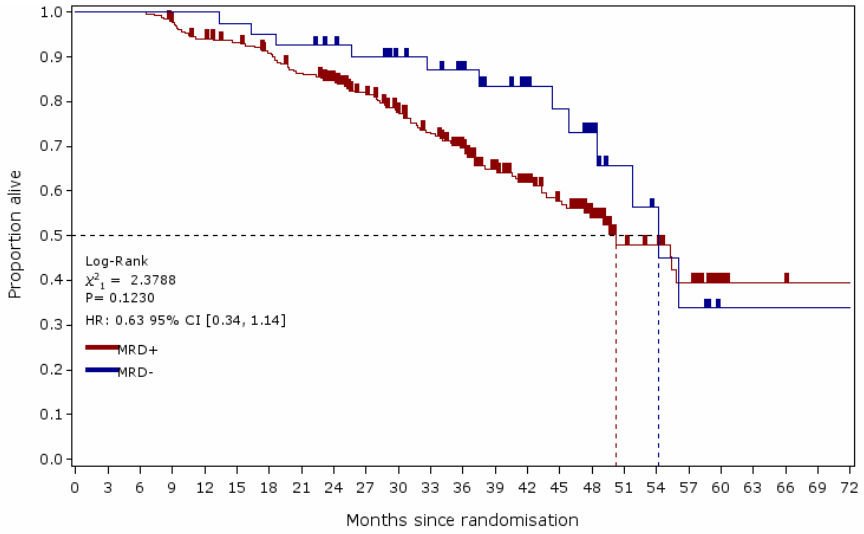
N=297/1852

- Median age 74.0 yrs (56-87)
- 62.8% male
- IgG 60.5%
- ISS III 34.2%

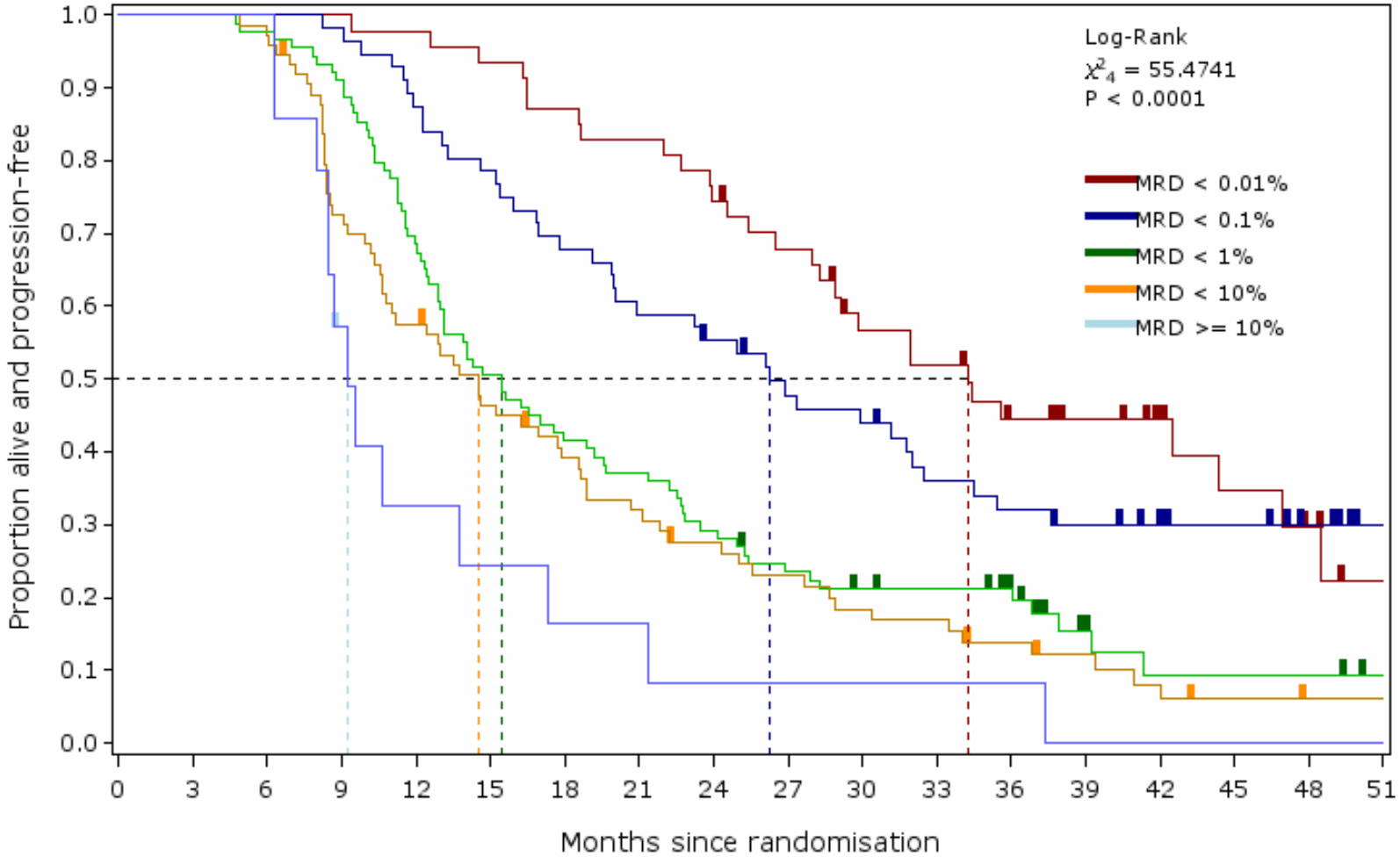
Results

- Overall 41/297 patients (13,8%) achieved MRD-negativity
- No difference between induction therapy was seen
- MRD-status withheld using multivariate analysis





MRD is correlated with PFS



Myeloma XI - MRD

- Feasible using flowcytometry
- Qualitative and continuous variable
- Is a meaningful endpoint/therapeutic goal in transplant-ineligible patients
- Improvement of PFS

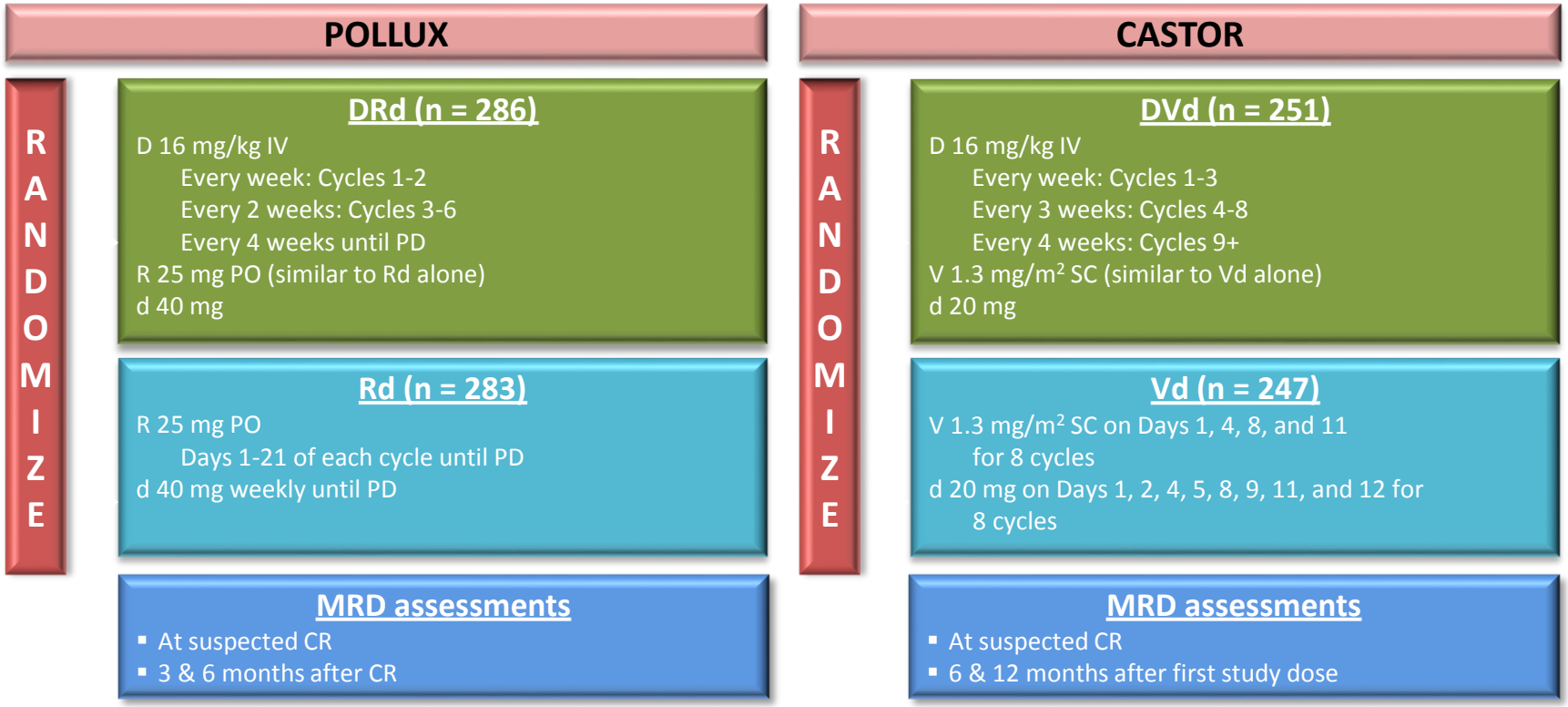
MRD in MM

Abstract 246 Avet-Loiseau et al.

Evaluation of Minimal Residual Disease (MRD) in Relapsed/Refractory Multiple Myeloma (RRMM) Patients Treated With Daratumumab in Combination With Lenalidomide Plus Dexamethasone or Bortezomib Plus Dexamethasone

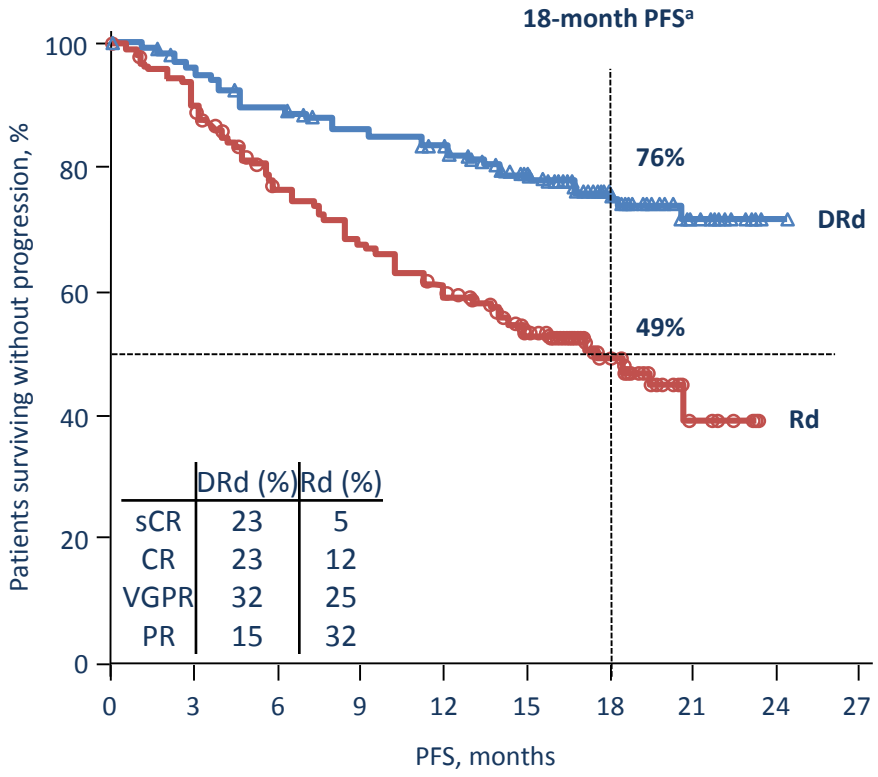
CASTOR & POLLUX

- Multicenter, randomized (1:1), open-label, active-controlled, phase 3 studies in ≥1 prior line of therapy for MM



CASTOR & POLLUX

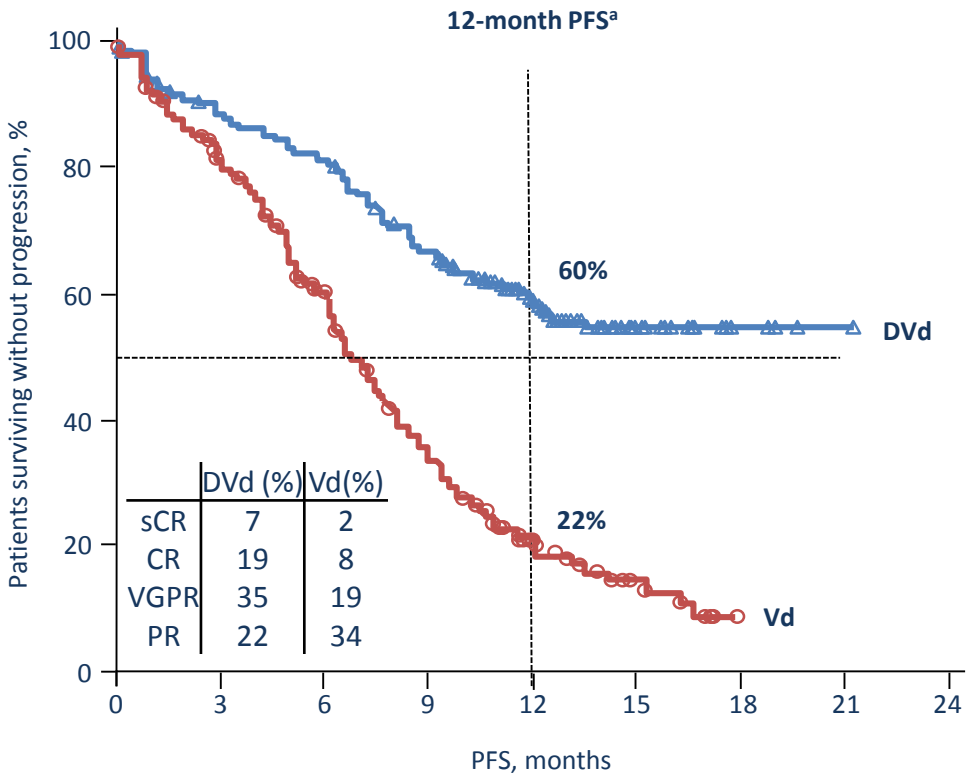
POLLUX



Median (range) follow-up:
17.3 (0-24.5) months

- **Median PFS**
  - DRd: not reached; Rd: 17.5 months
  - HR: 0.37 (95% CI, 0.28-0.50; *P* <0.0001)

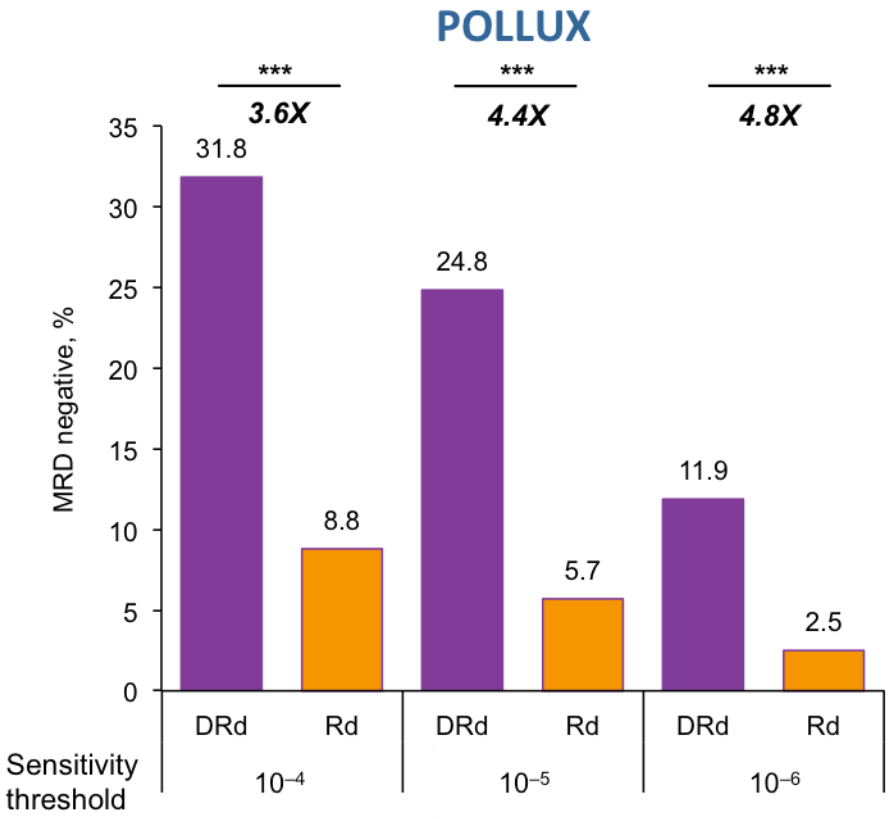
CASTOR

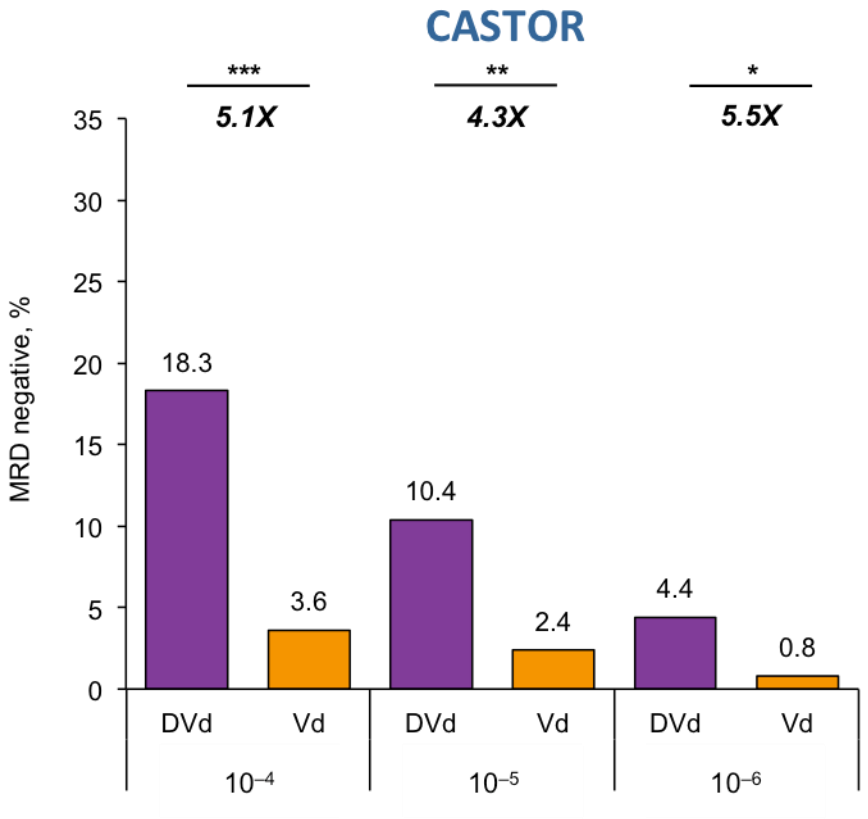


Median (range) follow-up:
13.0 (0-21.3) months

- **Median PFS**
  - DVd: not reached; Vd: 7.1 months
  - HR: 0.33 (95% CI, 0.26-0.43; *P* <0.0001)

MRD-negativity in CR patients



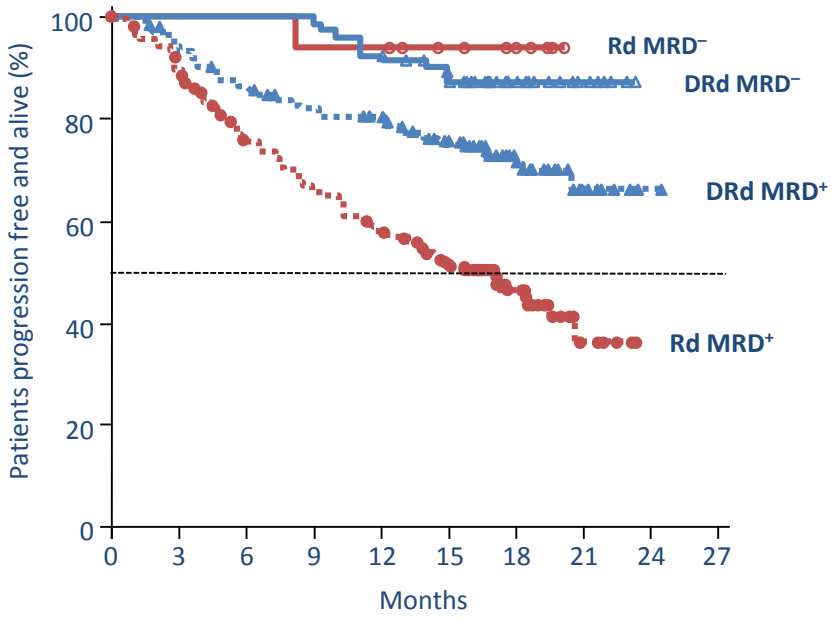


- Daratumumab in combination with standard of care significantly improved MRD-negative rates at all thresholds

*** *P* <0.0001.
** *P* <0.005.
* *P* <0.05.

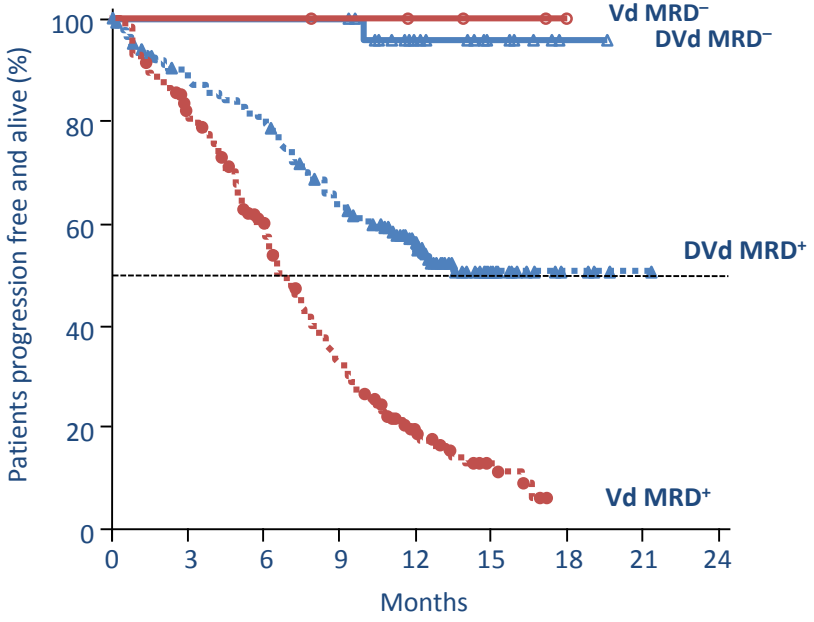
PFS data (MRD 10^{-5})

POLLUX



Patients at risk										
Rd MRD negative	16	16	16	15	15	12	10	0	0	0
DRd MRD negative	71	71	71	70	66	57	28	6	0	0
Rd MRD positive	267	233	190	166	144	120	38	5	0	0
DRd MRD positive	215	195	178	167	161	137	54	9	1	0

CASTOR



Patients at risk										
Vd MRD negative	6	6	6	5	3	2	0	0	0	
DVd MRD negative	26	26	26	26	15	7	1	0	0	
Vd MRD positive	241	176	123	68	20	7	0	0	0	
DVd MRD positive	225	189	172	134	76	26	4	1	0	

- Lower risk of progression in MRD-negative patients (ITT analysis)
- PFS benefit in MRD-positive patients who received daratumumab-containing regimens versus standard of care

Conclusions

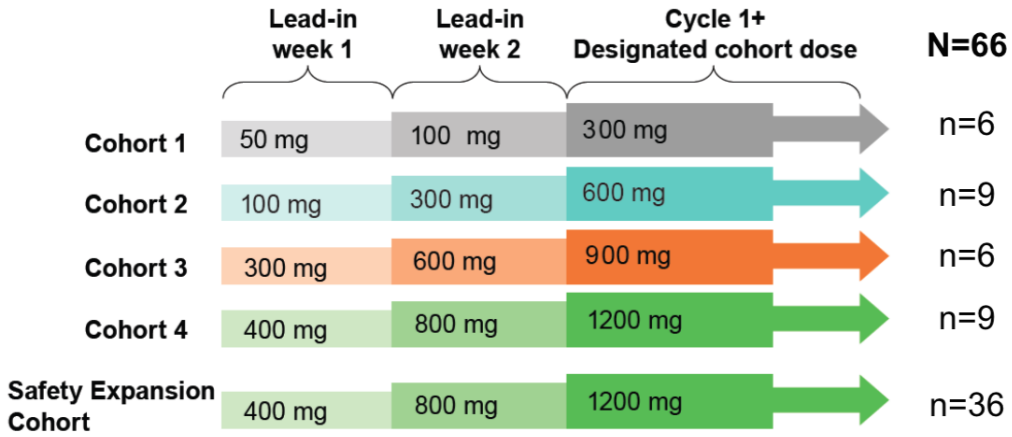
- MRD-negativity is associated with a lower risk of progression in relapsed patients
- Daratumumab induced MRD-negativity in over 4 times as many CR patients as standard of care regimens
- Addition of Daratumumab prolongs PFS even when MRD-positive
- The higher rate of MRD-negativity and deep clinical responses may lead to improved OS (data not mature)

Abstract 488 Kumar et al.

Venetoclax monotherapy for relapsed/refractory multiple myeloma: Safety and efficacy results from a phase I study

Characteristics

- Phase 1, open-label multicenter study of venetoclax, a BCL-2 inhibitor, in RRMM.



- Patients were treated on a 21-day cycle with daily venetoclax
- Patients who progressed on monotherapy could have dexamethasone added

Patient characteristics and adverse events

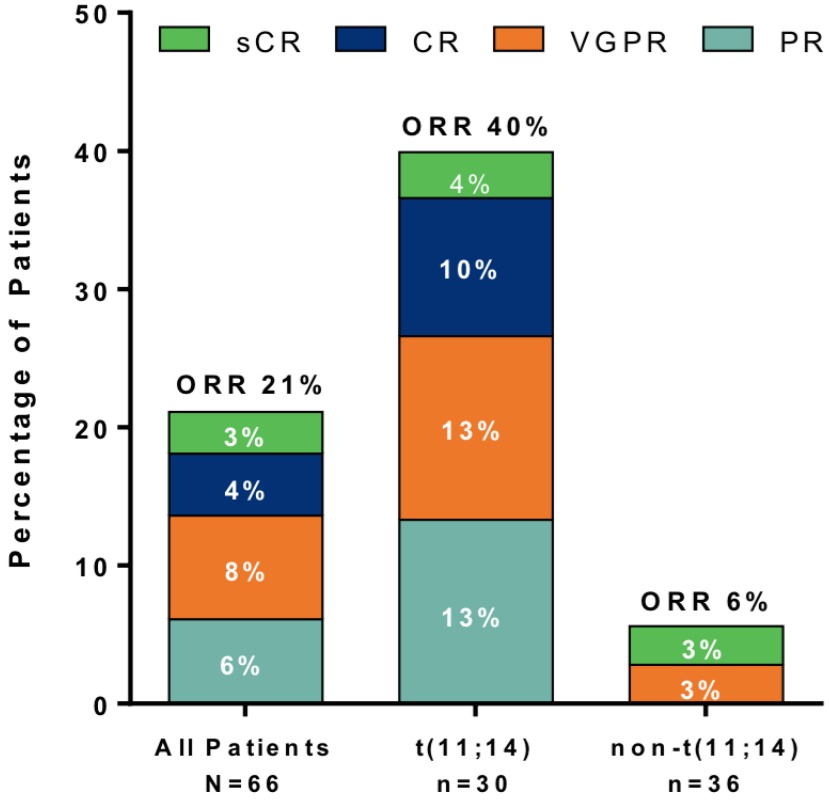
		N = 66
Age, median (range), years		63 (31-79)
ISS		
	I	24 (38)
	II/III	39 (62)
	Unknown	3
Cytogenetics		
	t(11;14)	30 (46)
	t(4;14)	6 (9)
	del(17p)	12 (18)
	del(13q)	32 (48)
	Hyperdyploid	27 (41)
No. of prior lines of therapy, median (range)		5 (1-15)
ASCT, n (%)		50 (76)
Bortezomib/refractory, n (%)		62 (94) / 46 (70)
Lenalidomide/refractory, n (%)		62 (94) / 51 (77)
Bortezomib and lenalidomide refractory, n (%)		40 (61)
Refractory to last prior therapy, n(%)		52 (79)

AEs for 20% or more of patients for any grade AE or for 10% or more with grade 3 or 4.

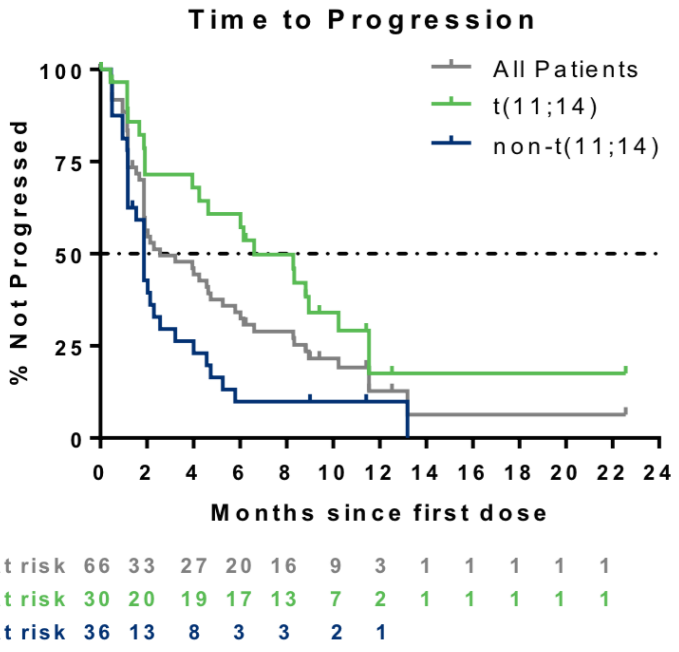
N (%)	Any grade	Grade 3/4
Total	66 (100)	45 (68)
Hematologic		
Thrombocytopenia	21 (32)	17 (26)
Neutropenia	18 (27)	14 (21)
Anemia	15 (23)	9 (14)
Leukopenia	15 (23)	9 (14)
Lymphopenia	12 (18)	10 (15)
Non-hematologic		
Nausea	31 (47)	2 (3)
Diarrhea	24 (36)	2 (3)
Fatigue	18 (27)	3 (5)
Back pain	14 (21)	5 (8)
Vomiting	14 (21)	2 (3)

- Two patients had dose-limiting toxicities of abdominal pain and nausea at 600 mg
- No events of TLS
- Serious AEs : pneumonia (8%), sepsis (5%), pain, pyrexia, cough and hypotension (3% each)

Response and time to progression



15 patients received add-on dexa



	All patients
Active, n (%)	11 (17)
Discontinued, n (%)	55 (83)
Progression	41 (62)
Adverse events	5 (8)
Deaths, n (%)	8 (12)

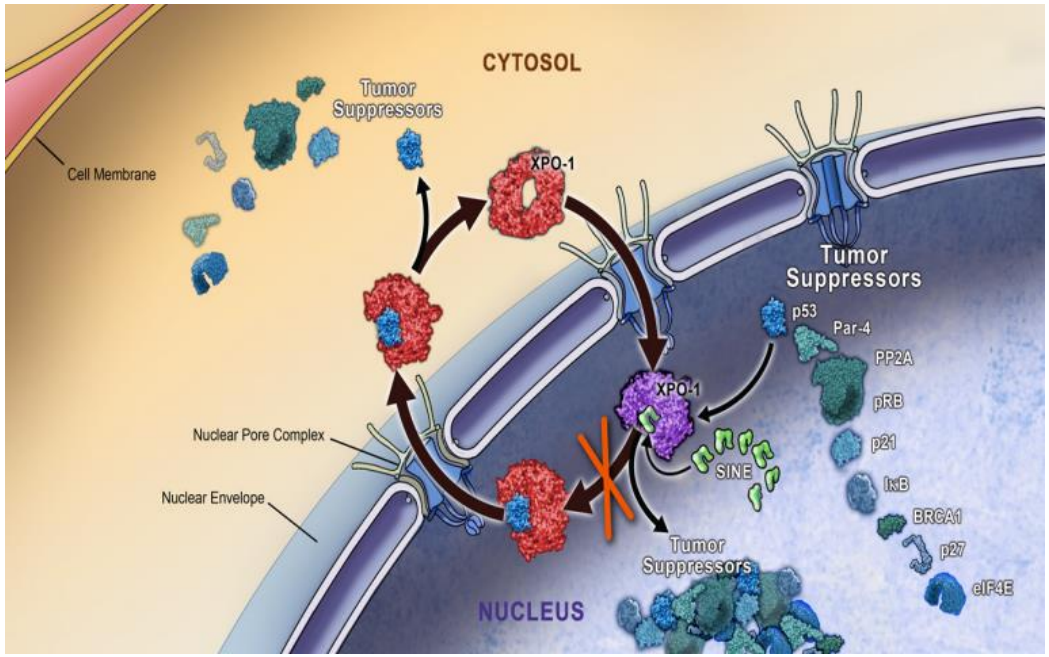
Conclusions

- Data suggests Venetoclax monotherapy is safe
- An ORR of 21% was seen in all patients
- In patients with t(11;14), a higher ORR (40% vs 6%) was seen
- Other treatment combinations (Bort) are being actively investigated based on pre-clinical data (Moreau et al., abstract 975) and show promising results

Abstract 491 Vogl et al.

Selinexor and low dose dexamethasone (Sd) in patients with lenalidomide, pomalidomide, bortezomib, carfilzomib and anti-CD38 ab refractory multiple myeloma (MM): STORM study.

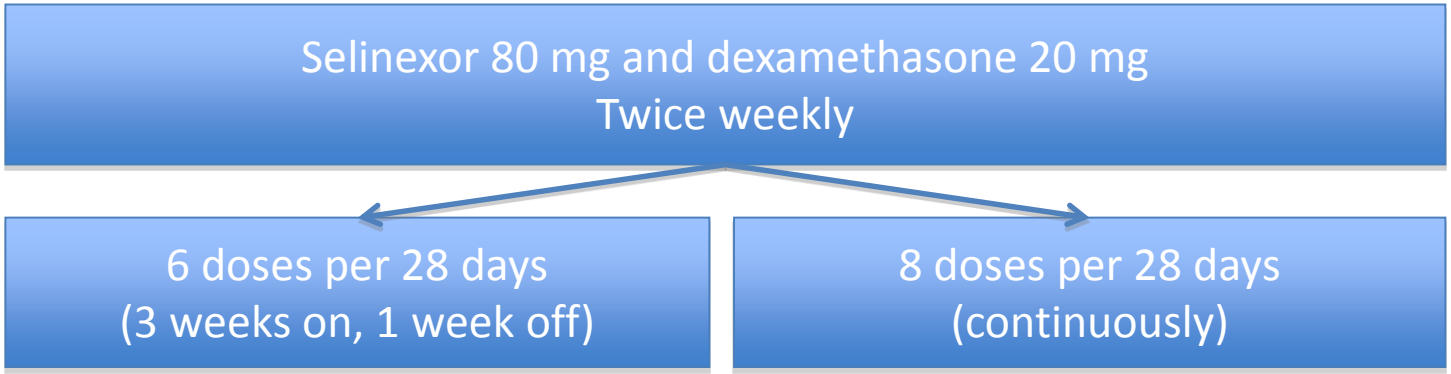
Mechanism of Selinexor



- Exportin 1 (XPO1) is the nuclear exporter for tumor suppressor proteins and the glucocorticoid receptor
- Inhibition of XPO1 induces retention of these proteins
- Suppression of oncoprotein expression

STORM-trial

- Patients refractory to
  - Bort, Carf, Len, Pom = quad-refractory
  - Also refractory to anti-CD38 = penta-refractory



* Dose modification for toxicity possible

Patient characteristics

	Quad-refractory	Penta-refractory
	N = 48	N = 31
Median age, years (range)	62 (41-78)	68 (31-78)
Males : females	24 (50%) : 24 (50%)	13 (42%) : 18 (58%)
Median prior regimens (range)	7 (3-16)	7 (5-17)
Median years from diagnosis (range)	4 (1-16)	4 (1-35)
Prior therapies		
Glucocorticoids	48 (100%)	31 (100%)
Alkylating agents	47 (98%)	30 (97%)
Stem cell transplant	37 (77%)	24 (77%)
Anthracyclines	20 (42%)	12 (39%)
Treatment 6 doses : 8 doses/cycle	40 (83%) : 8 (17%)	11 (35%) : 20 (65%)

STORM results

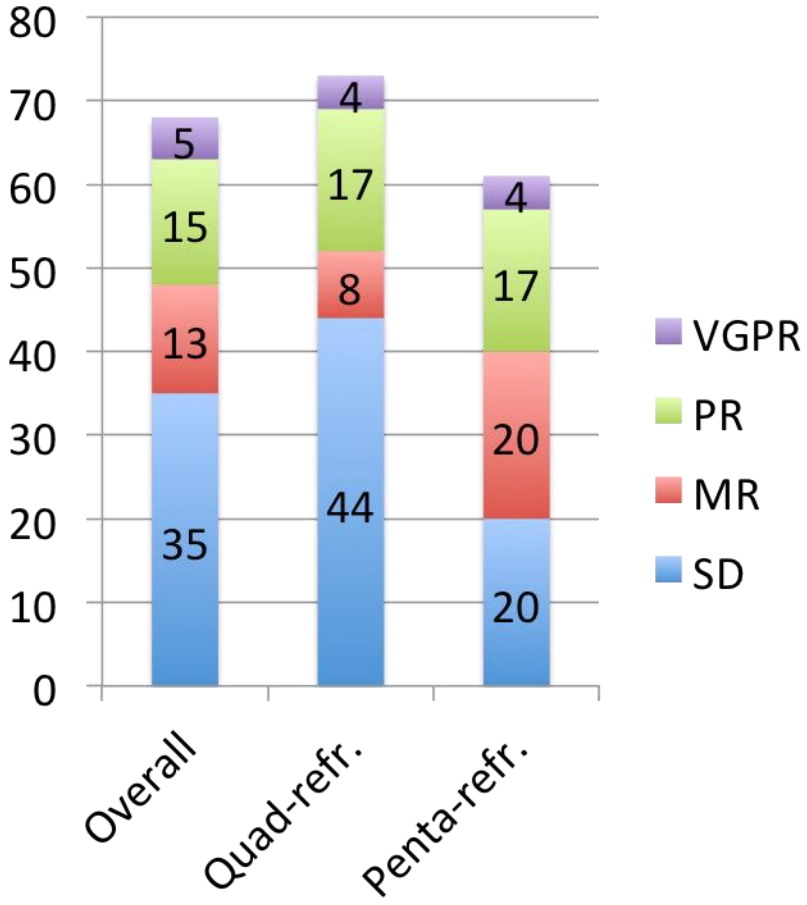
- At time of analysis 70 patients (%) had discontinued treatment
  - Progression (70%)
  - Adverse events (17%)

Most frequent 3/4 AEs	
Trombocytopenia	59%
Anemia	28%
Neutropenia	17%
Fatigue	15%
Hyponatremia	22%

Dose interruptions : 52%
Dose reductions : 37%
Discontinuation : 18% (14 pt)

Using supportive care:
- Anti-emetics
- Growth factors
- Salt supplementation

STORM results



- ORR 20 – 21% (6-8/mo no diff)
- CR?
- Med. time to response : 1 mo
- Med. duration response : 5 mo

	All patients	MR or better
Median OS	9,3 mo	NR
Median PFS	2,3 mo	5,5 mo

Conclusions

- The results suggest that Sd displays anti-tumor activity in heavily pretreated patients
- An ORR of 20 – 21% is seen and responses are associated with a benefit in PFS and OS

Key points

- The exact role of consolidation therapy, especially in the era of lenalidomide maintenance, remains unclear.
- Maintenance therapy with IMiDs is well tolerated and should be considered in the future treatment of MM patients if available.
- MRD is an important marker of response and leads to prolonged PFS, even in elderly and RRMM patients.
- The interplay between MRD and OS looks promising and will hopefully be elucidated in the near future.
- Agents such as Selinexor and Venetoclax exhibit noteworthy activity in RRMM patients.