POST-ASH 2016
Plasma cell disorders

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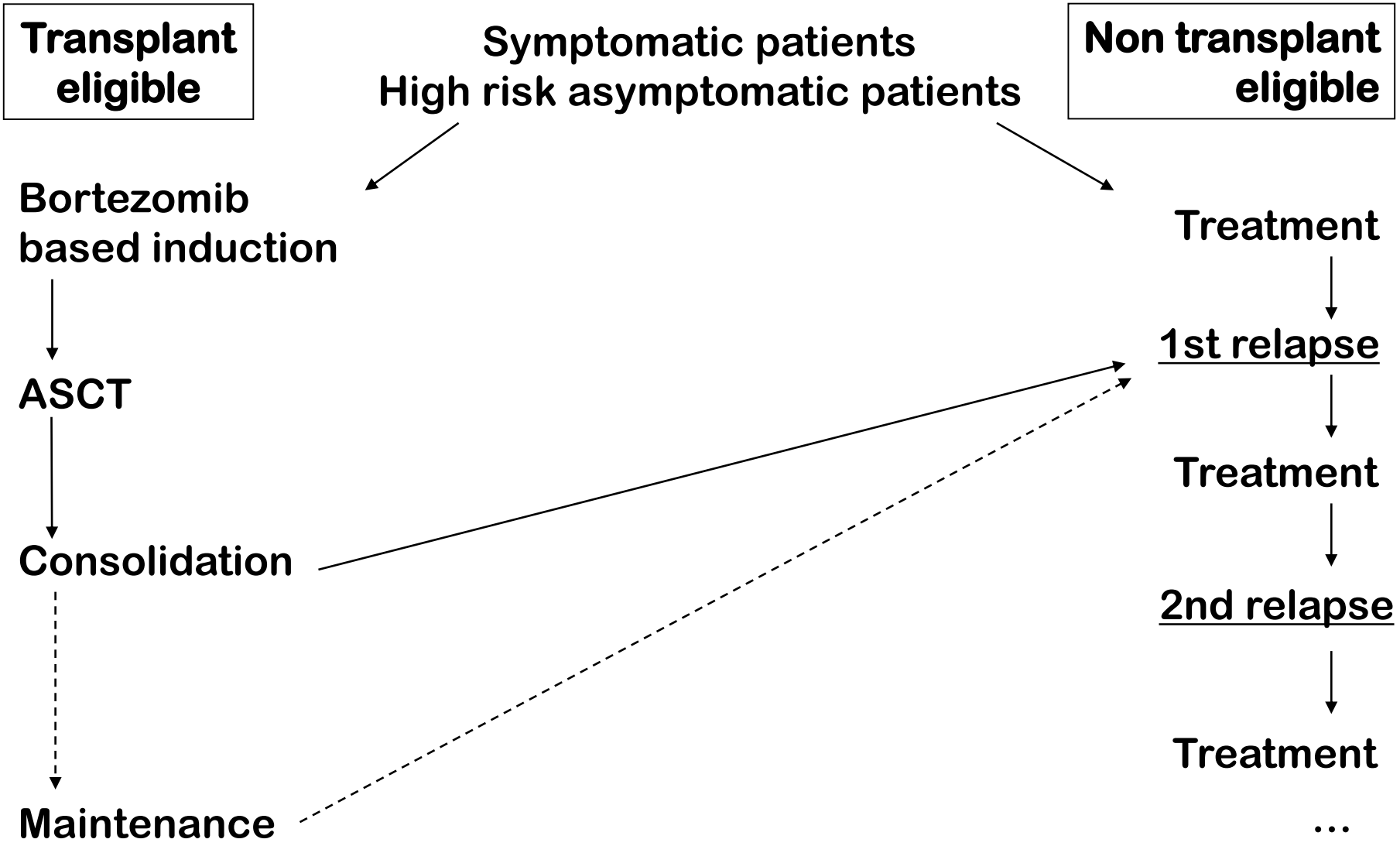
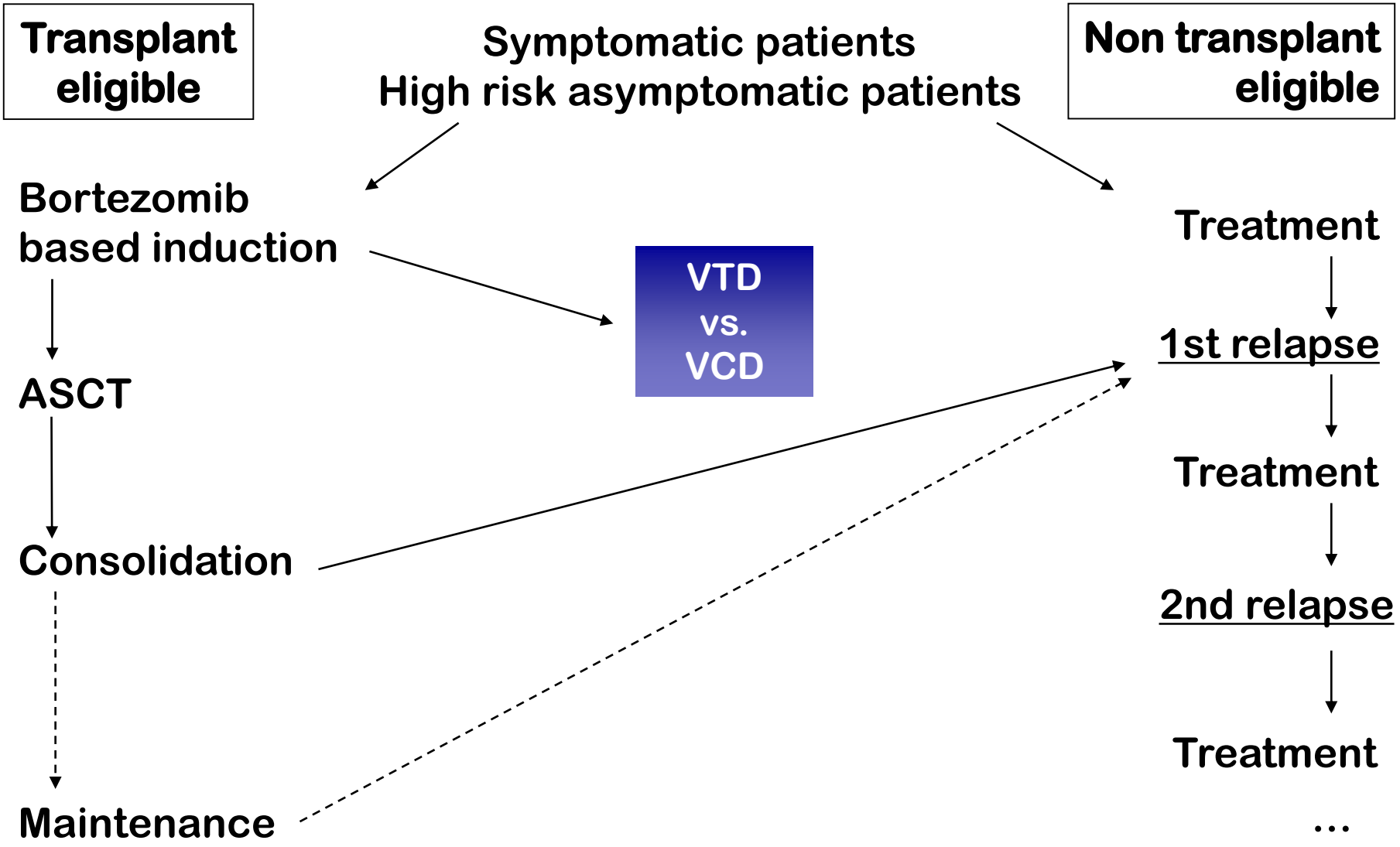
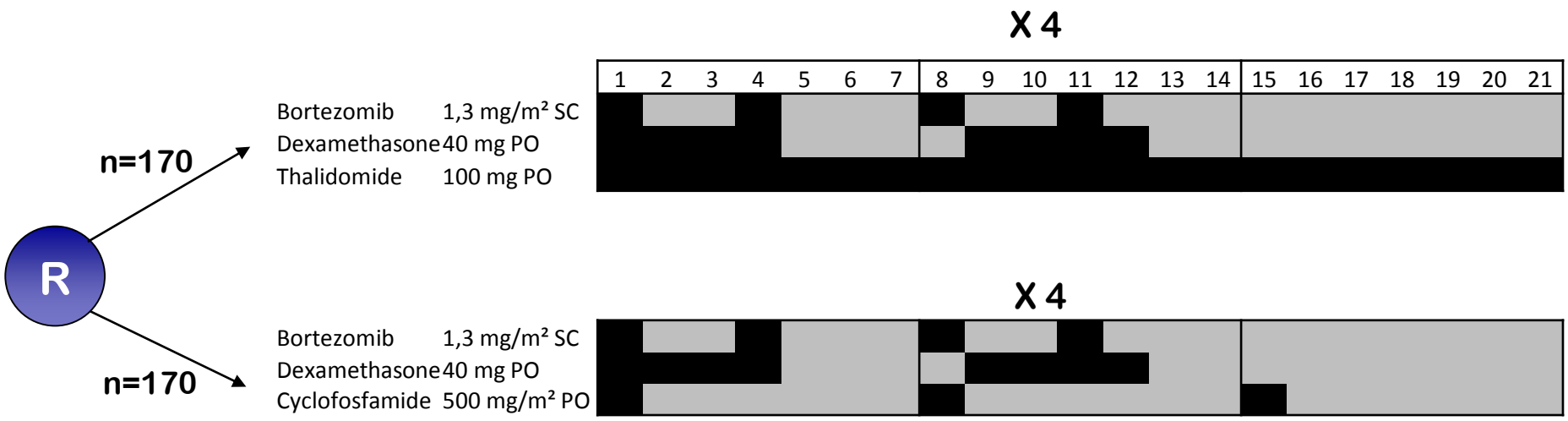
Current treatment paradigm of myeloma in Belgium



Choice of induction regimen ?



VTD vs. VCD : trial design



- Randomised, open label, multicentric phase 3 study
- VTD (x4) vs. VCD (CyBorD) (x4) before ASCT
- Inclusion : newly diagnosed symptomatic MM (< 66 y)
- Primary endpont : percentage of patients reaching VGPR of better (after 4 cycles)
- Stratification based upon ISS (1/2 vs. 3) and adverse cytogenetics (del 17p; t(4;14) vs. all other)

Bortezomib, Thalidomide and Dexamethasone (VTD) Is Superior to Bortezomib, Cyclophosphamide and Dexamethasone (VCD) Prior to Autologous Stem Cell Transplantation for Patients with De Novo Multiple Myeloma. Results of the Prospective IFM 2013-04 Trial Philippe Moreau et al (Abstr. n° 393)

VTD vs. VCD : outcome & safety

Responses

	VTD n = 169	VCD n =169	p
Intention to treat analysis			
≥CR	13,0 %	8,9 %	0,22
≥VGPR	66,3 %	56,2 %	0,05
≥PR	92,3 %	83,4 %	0,01

SAE

	VTD n = 169	VCD n =169	p
Grade III, IV			
Neuropathy	4,0 %	2,2 %	
Neutropenia	11,9 %	22,5 %	

Median number CD34+ stem cells higher in the VTD arm

Bortezomib, Thalidomide and Dexamethasone (VTD) Is Superior to Bortezomib, Cyclophosphamide and Dexamethasone (VCD) Prior to Autologous Stem Cell Transplantation for Patients with De Novo Multiple Myeloma. Results of the Prospective IFM 2013-04 Trial Philippe Moreau et al (Abstr. n° 393)

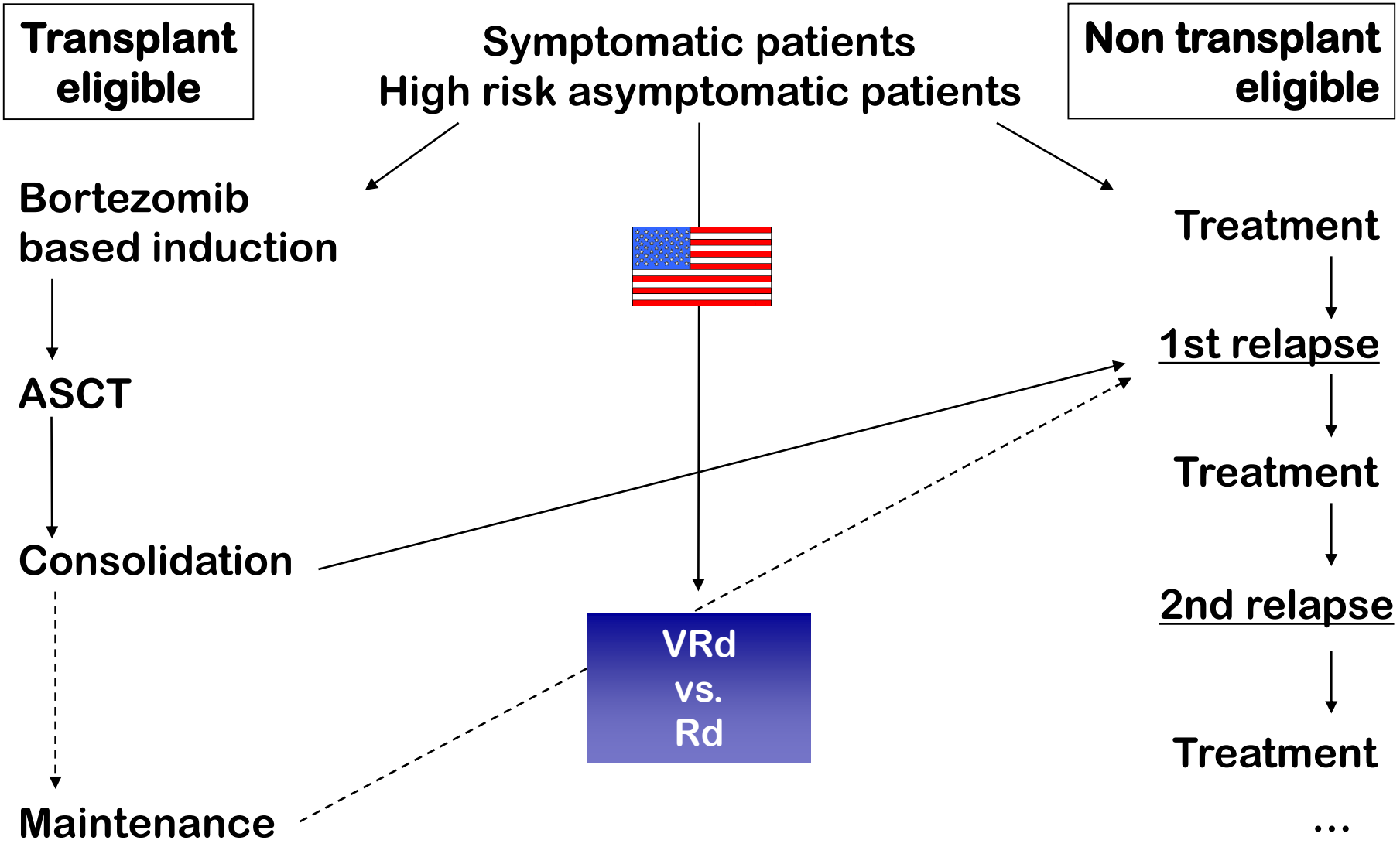
VTD vs. VCD : conclusions

- First prospective randomised trial : VTD vs VCD
- VGPR and PR rates are significantly superior in the VTD arm: synergistic activity of PI + IMiD.
- Median number CD34+ stem cells higher in the VTD.
- Hematologic toxicity increased in the VCD arm, while peripheral neuropathy rate was higher in the VTD arm.

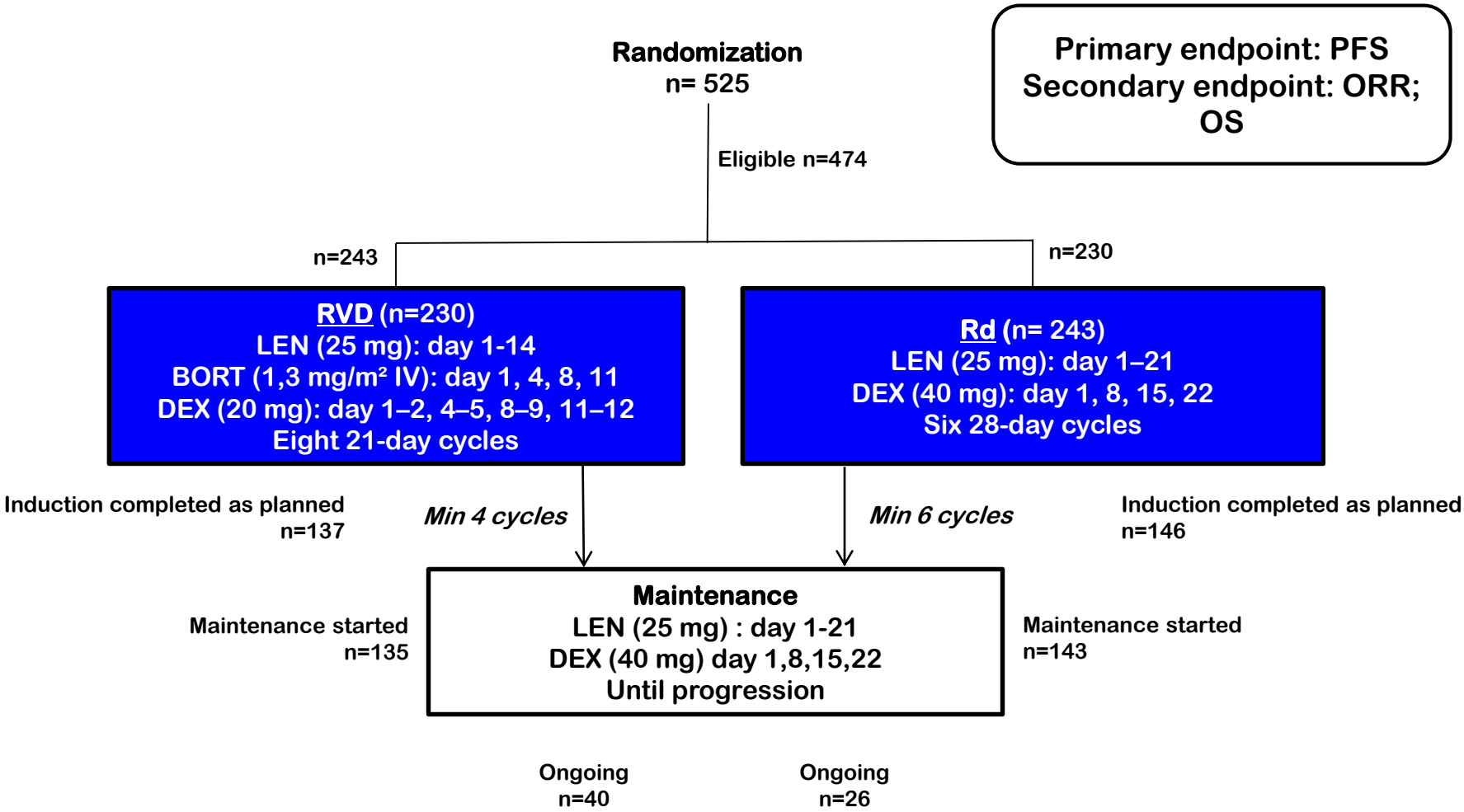
Data supports the preferential use of VTD over VCD prior to ASCT.

Bortezomib, Thalidomide and Dexamethasone (VTD) Is Superior to Bortezomib, Cyclophosphamide and Dexamethasone (VCD) Prior to Autologous Stem Cell Transplantation for Patients with De Novo Multiple Myeloma. Results of the Prospective IFM 2013-04 Trial Philippe Moreau et al (Abstr. n° 393)

Upfront use of triplet regimen without intent of ASCT



VRd vs. Rd : trial design



Bortezomib, Lenalidomide and Dexamethasone Vs. Lenalidomide and Dexamethasone in Patients (Pts) with Previously Untreated Multiple Myeloma without an Intent for Immediate Autologous Stem Cell Transplant (ASCT): Results of the Randomized Phase III Trial SWOG S0777 (Durie, Abstr. n° 5)

VRd vs. Rd : trial population

Median age : 63 y

Factor	Overall %	Treatment arm RVd, %	Rd, %
Female	42	37	47
Age ≥ 65 yr	43	38	48
SWOG PS > 1	14	12	16
sb2m ≥ 4 mg/L	53	51	56
CRP ≥ 8 ml/L	23	21	26
Creatinine ≥ 2 mg/dL	5	5	5
LDH ≥ 190 U/L	36	36	36
Albumin < 3.5 g/dL	42	41	44
Hb < 10 g/dL	32	33	31
Platelet count < 150 x $10^{9/L}$	4	5	4
ISS stage III	33	32	34

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VRd vs. Rd : outcome

- Median follow up : 55 months, median age 63 years ! (28-87)
- ISS stage 3 : 33 %
- Median duration of maintenance : 385 days

FIRST trial
Median age : 73 y
PFS : 25,5 mo

	RVd	Rd
PFS median, months	43	30
	HR: 0.712 (0.560–0.906; *P* = 0.0018	
OS, median, months	75	64
	HR = 0.709 (0.516–0.973); *P* = 0.025	
ORR, %	81	71
CR	16	8
VGPR	28	23

RVd remains superior to Rd for PFS and OS when adjusted for age

Bortezomib, Lenalidomide and Dexamethasone Vs. Lenalidomide and Dexamethasone in Patients (Pts) with Previously Untreated Multiple Myeloma without an Intent for Immediate Autologous Stem Cell Transplant (ASCT): Results of the Randomized Phase III Trial SWOG S0777 (Durie, Abstr. n° 5)

VRd vs. Rd : side effects

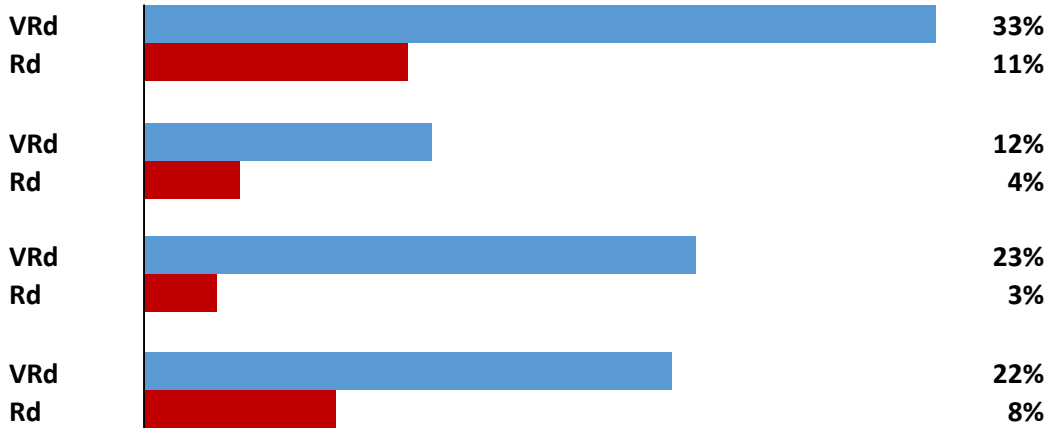
Tolerability

≥ grade 3 Neurologic

≥ grade 3 Pain

≥ grade 3 Sensory

≥ grade 3 Gastrointestinal



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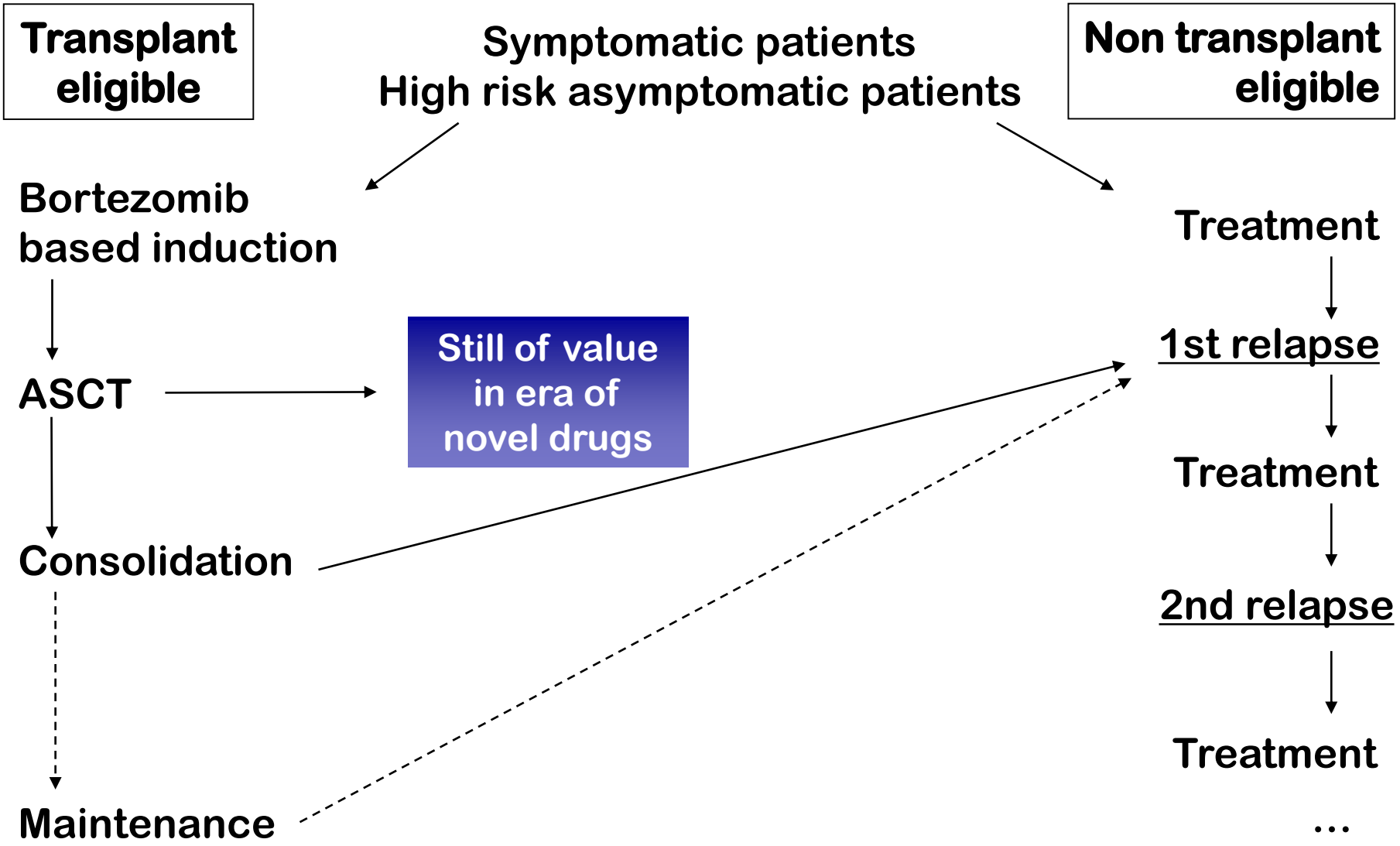
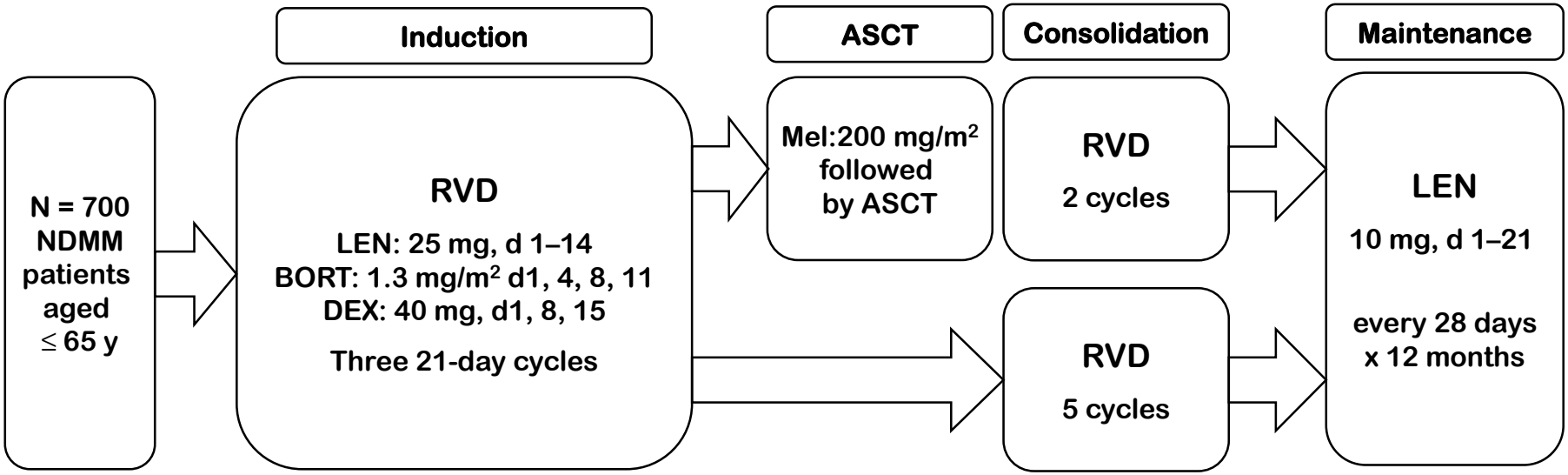
ASCT : still of value ?

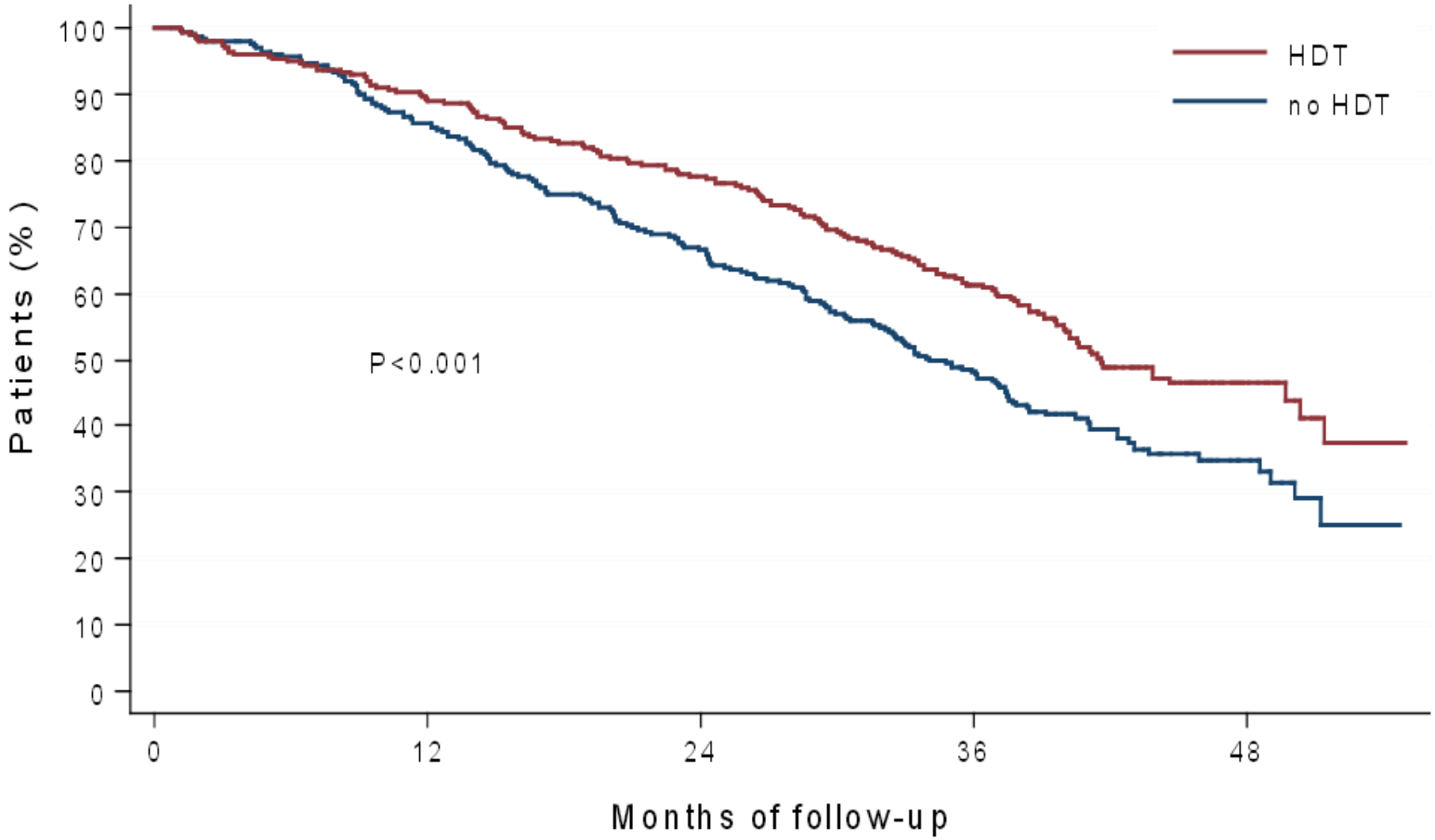


RVD with ASCT vs. RVD without ATSC : trial design



ASCT in the era of novel drugs ? (IFM/DFCI trial 2009)
Attal (Abstr. n° 391)

RVD with ASCT vs. RVD without ATSC : PFS



ASCT in the era of novel drugs ? (IFM/DFCI trial 2009)
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RVD with ASCT vs. RVD without ATSC : outcome

	RVd + ASCT (n = 350)	RVd, no ASCT (n = 350)
PFS median, months	43	34
4-yr PFS, %	47	35
HR = 0.69 (95% CI, 0.56-0.84); P < .001		
4-yr OS, %	81	83
HR = 1.2 (95% CI, 0.7-1.8); NS		
ORR, %	99	98
CR, %	59	49
≥ VGPR, %	88	78
MRD neg by FCM, %	80	65

PFS benefit of ASCT was consistent across subgroups including age (≤ or > 60 yrs), sex, Ig isotype (IgG or others), ISS stage (I or II or III), cytogenetics (standard or high risk), and response after 3 cycles of RVd (CR or not)

ASCT in the era of novel drugs ? (IFM/DFCI trial 2009)
Attal (Abstr. n° 391)

RVD with ASCT vs. RVD without ATSC : toxicity

Grade 3 or 4 Adverse Events of Interest

Grade 3/4 AEs, %	ASCT (n = 350)	RVd (n = 350)
Neutropenia	89	31
Thrombocytopenia	78	9
Infections	18	10
Thromboembolic events	5	4
Peripheral neuropathy	11	11

Cause of death

	ASCT, n = 54	RVD, n =48
Myeloma	33/54 (65 %)	40/48 (83 %)
Toxicity	9/54 (16%)	4/48 (8%)
SPM	6/54 (11 %)	1/48 (2%)
Other	4/54 (7%)	3/48 (6 %)

ASCT in the era of novel drugs ? (IFM/DFCI trial 2009)
Attal (Abstr. n° 391)

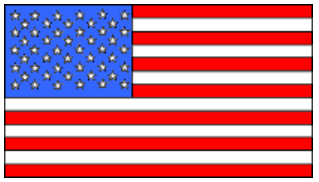
RVD with ASCT vs. RVD without ATSC : conclusions

ASCT after VRD:

- **is feasable**
- **is associated with an acceptable TRM of 1,4 %**
- **increases MRD negativity (80 vs. 65 %, p < 0,01)**
- **increases PFS @ 4 years (47 vs. 35 %, p <0,001)**
- **increases TTP @ 4 years (49 vs. 35 %, p<0,001)**

Long term follow-up is necessary for conclusions regarding OS (@ 4 years – 81% and 83 %)

Impact of continued lenalidomide maintenance ?



ASCT in the era of novel drugs ? (IFM/DFCI trial 2009)
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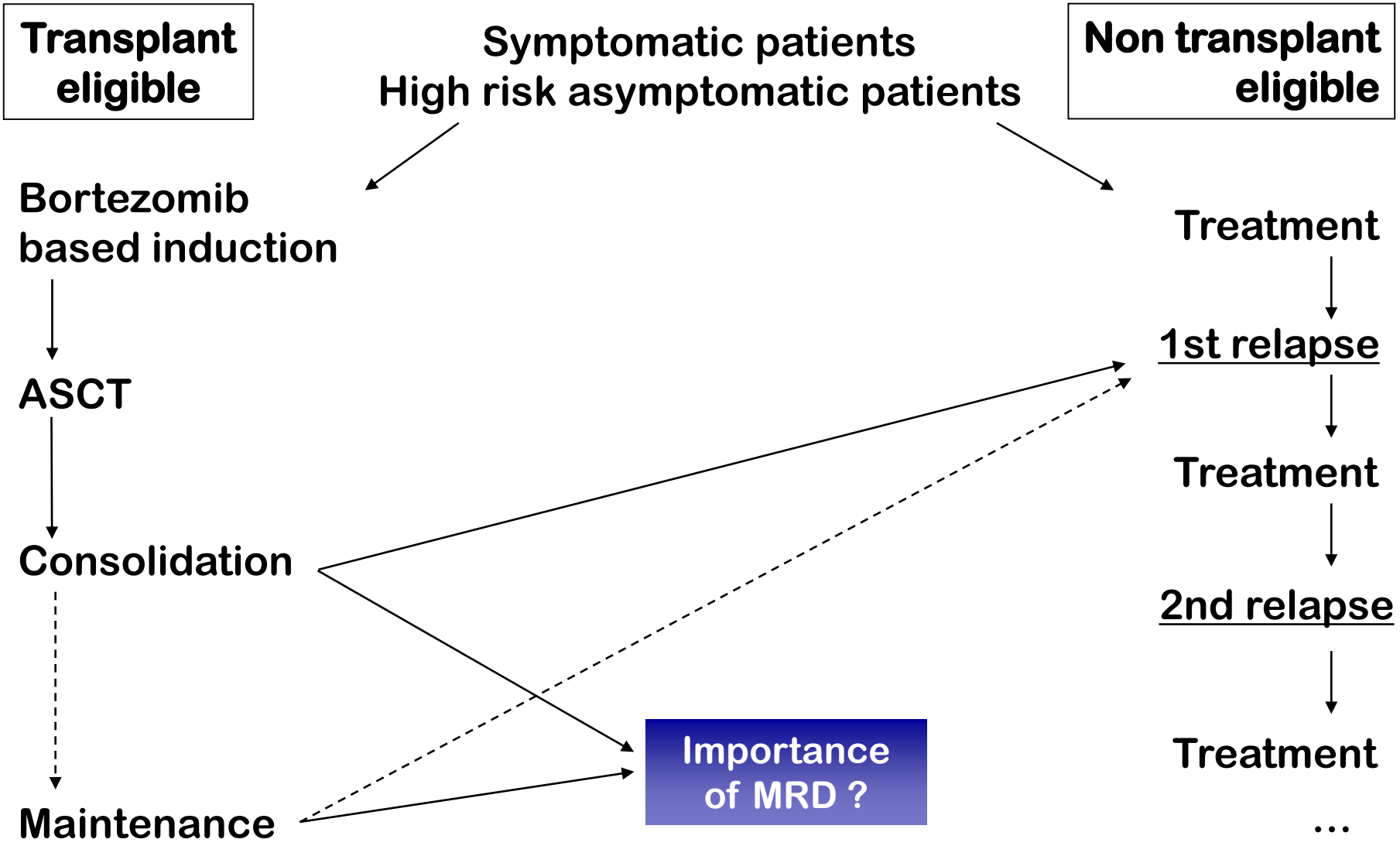
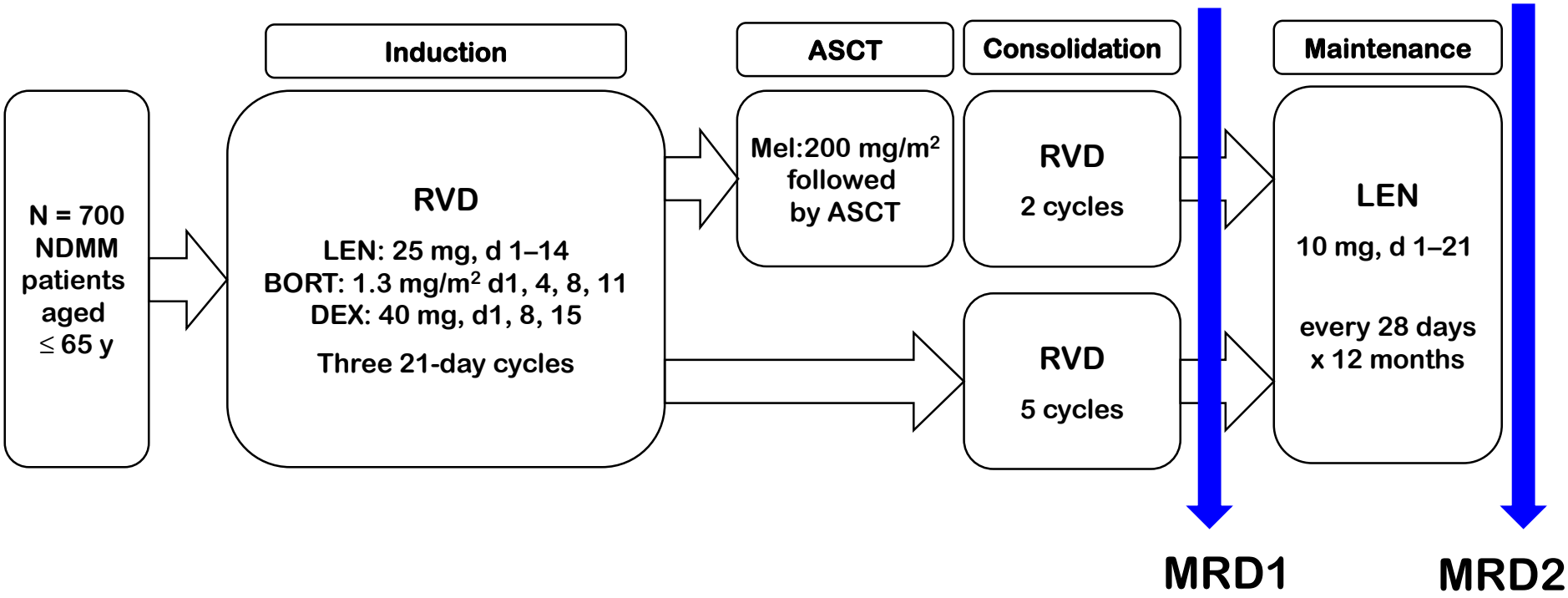
What is the impact of MRD ?



MRD in IFM/DFCI 2009 : trial design



Flow-cytometry (7 colors) : Sensitivity 10^{-4}

NGS : Sensitivity 10^{-6}

Evaluation of Minimal Residual Disease (MRD) By Next Generation Sequencing (NGS) Is Highly Predictive of Progression Free Survival in the IFM/DFCI 2009 Trial

Avet-Loiseau (abstract n° : 191)

MRD in IFM/DFCI 2009 : techniques

	Advantages	Disadvantages
NGS (Sequenta)	Sensitivity ($<10^{-6}$)	Diagnostic sample needed
	Frozen sample	~92 % feasable
	Standardized	
Flow cytometry	No diagnostic sample	Fresh sample (<24-48h)
	100 % feasable	Sensitivity ($<10^{-4}$)
		No standardization

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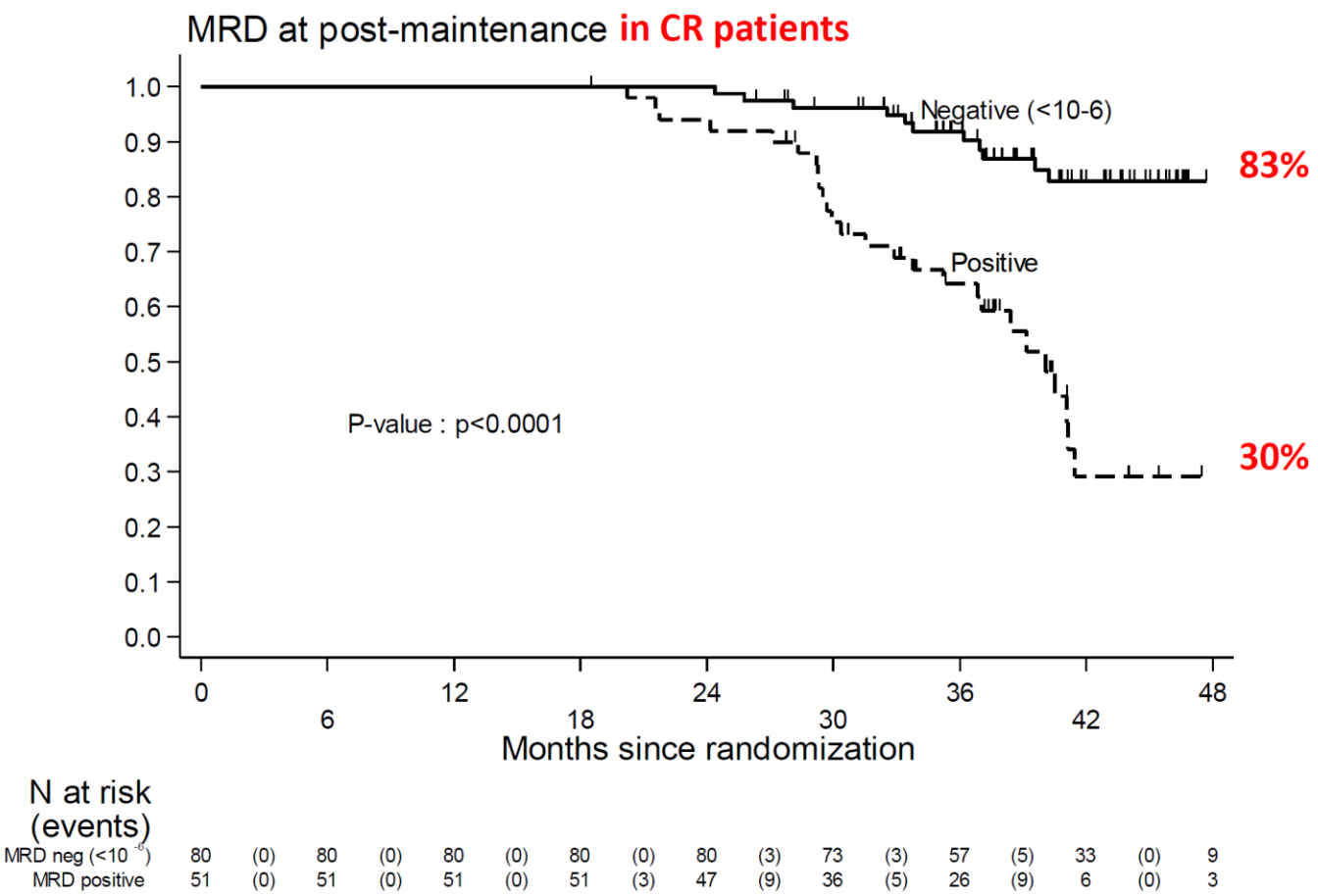
MRD in IFM/DFCI 2009 : impact (post-maintenance)

375 CR/sCR, only 131 MRD



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MRD in IFM/DFCI 2009 : conclusions

- MRD NGS is feasible in 92% of the patients
- MRD NGS is highly sensitive (< 10^{-6})
- This sensitivity is achieved in 100% of the patients
- 10^{-6} level is the most powerful cutoff for PFS
- 13/26 pts with t(4;14) achieved MRD negativity vs. no with del(17p)
- May identify patients cured from myeloma

Evaluation of Minimal Residual Disease (MRD) By Next Generation Sequencing (NGS) Is Highly Predictive of Progression Free Survival in the IFM/DFCI 2009 Trial
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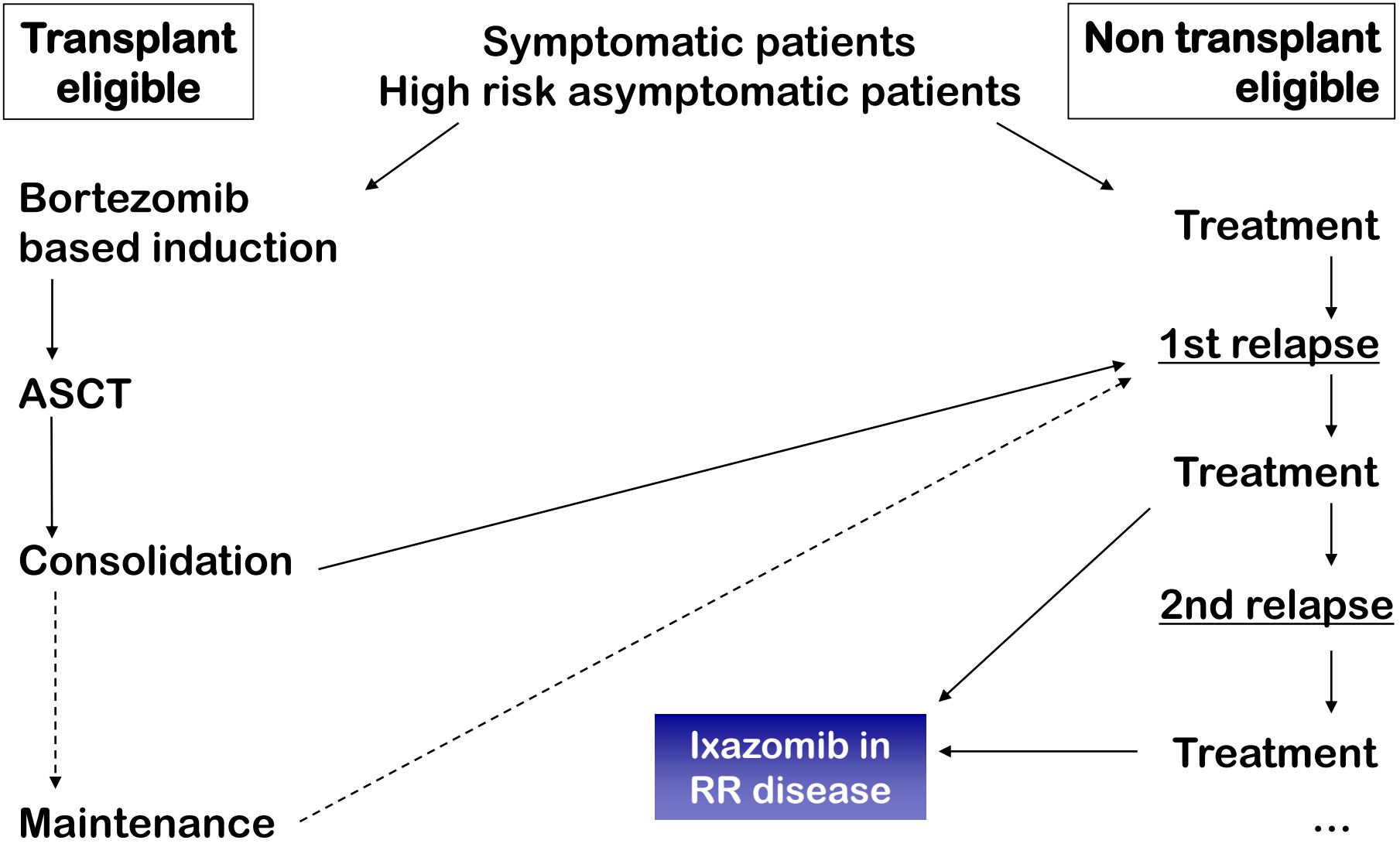
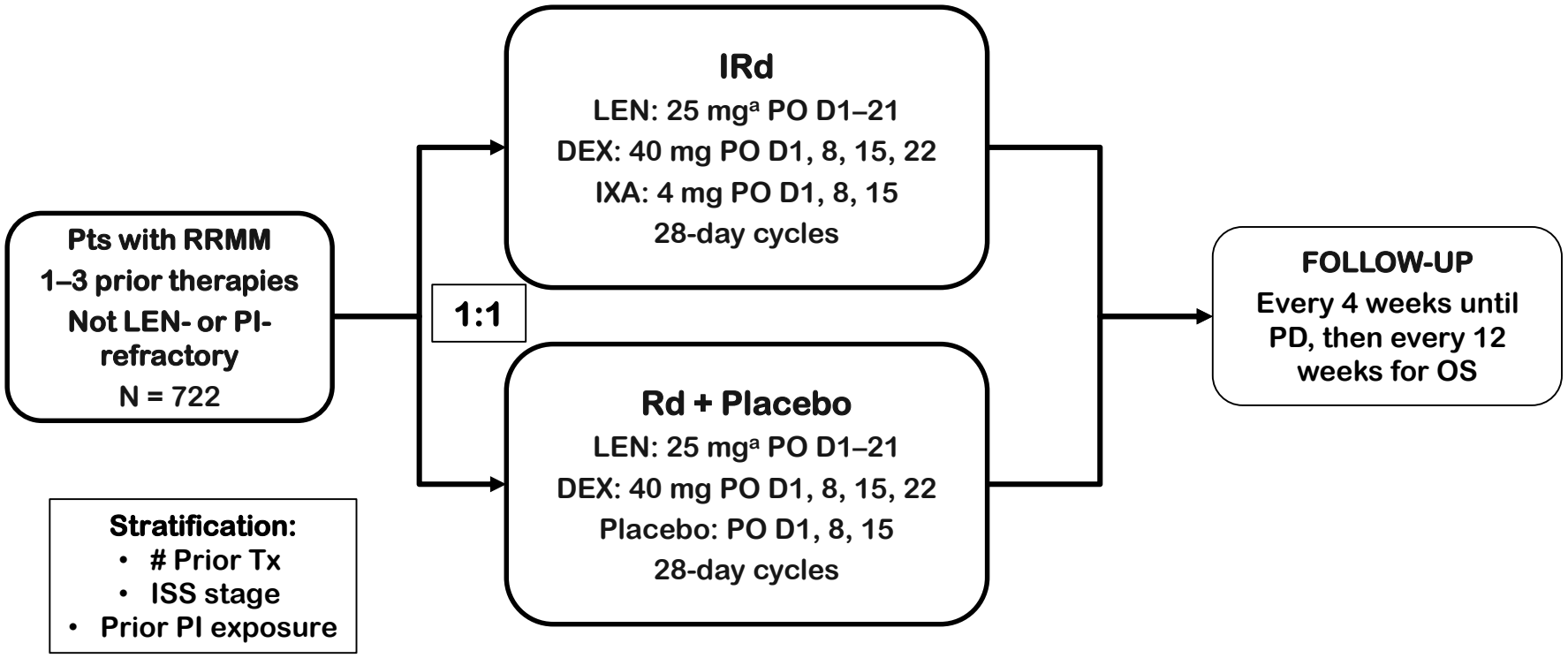
Ixazomib – an oral PI



IRd vs. Rd in RRMM : trial design



Primary endpoint: PFS by independent review committee using IMWG criteria

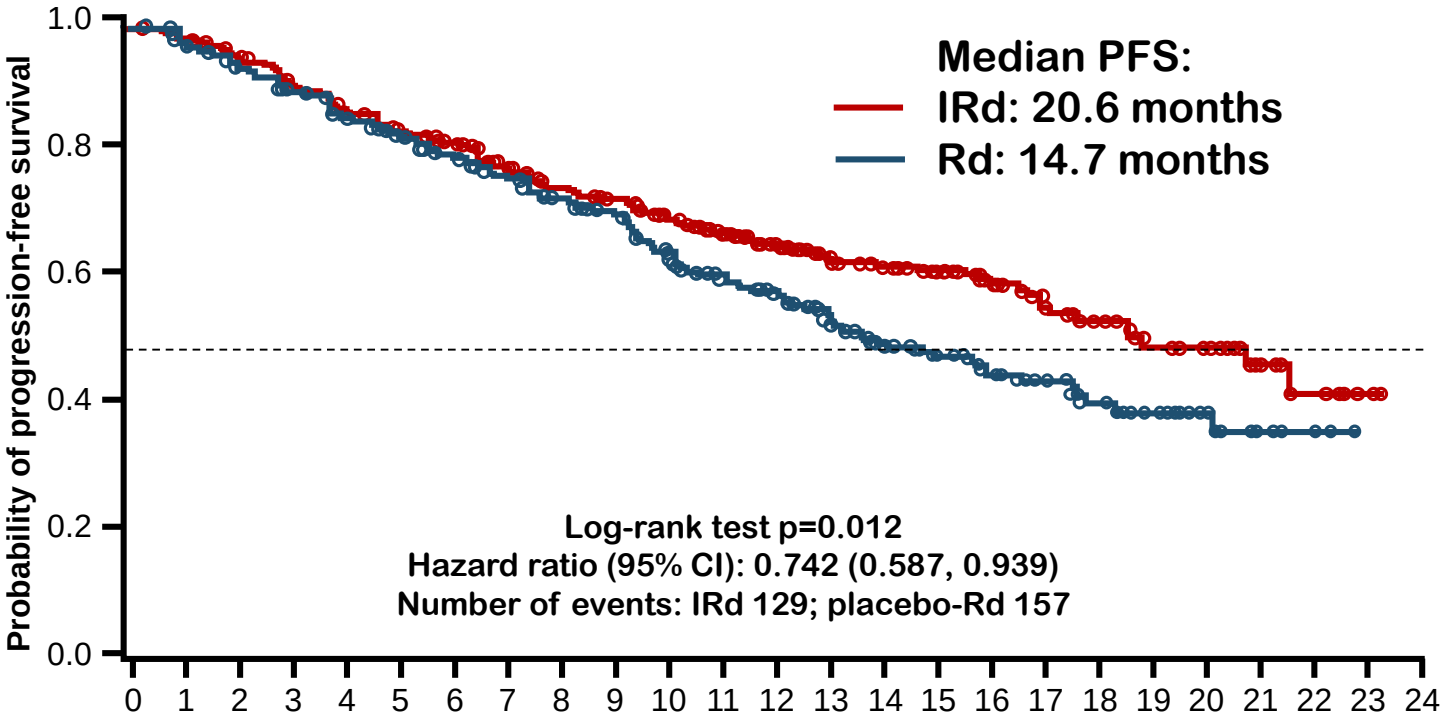
Key secondary endpoints: OS, OS in high-risk pts[b] with del(17)

Data presented are from the 1st of 3 planned interim analyses

Ixazomib, an Investigational Oral Proteasome Inhibitor (PI), in Combination with Lenalidomide and Dexamethasone (IRd), Significantly Extends Progression-Free Survival (PFS) for Patients (Pts) with Relapsed and/or Refractory Multiple Myeloma (RRMM): The Phase 3 Tourmaline-MM1 Study (Moreau, Abst. n° 727)

IRd vs. Rd in RRMM : PFS

Median follow-up: ~15 months



Number of patients at risk:

Time from randomization (months)

IRd	360	345	332	315	298	283	270	248	233	224	206	182	145	119	111	95	72	58	44	34	26	14	9	1	0
Placebo-Rd	362	340	325	308	288	274	254	237	218	208	188	157	130	101	85	71	58	46	31	22	15	5	3	0	0

Ixazomib, an Investigational Oral Proteasome Inhibitor (PI), in Combination with Lenalidomide and Dexamethasone (IRd), Significantly Extends Progression-Free Survival (PFS) for Patients (Pts) with Relapsed and/or Refractory Multiple Myeloma (RRMM): The Phase 3 Tourmaline-MM1 Study (Moreau, Abst. n° 727)

IRd vs. Rd in RRMM : responses

	IRd (n = 360)	Rd (N = 362)	HR / OR (IRd vs Rd)	*P*-value
Confirmed ORR (≥ PR)	78.3	71.5	OR, 1.44	0.035
CR+VGPR	48.1	39.0	OR, 1.45	0.014
CR	11.7	6.6	OR, 1.87	0.019
PR	66.7	64.9	-	-
VGPR	36.4	32.3	-	-
Median time to first response, mos	1.1	1.9	-	-
Median duration of response, mos	20.5	15.0	-	-
Median TTP, mos	21.4	15.7	HR, 0.712	0.007

Median number of treatment cycles: 17 (range 1–34) for IRd and 15 (range 1–34) for Rd

- 48% and 43% of patients had received ≥ 18 cycles respectively
- 20% and 19% of patients had received ≥ 25 cycles respectively

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IRd vs. Rd in RRMM : PFS in prespecified subgroups

	IRd (n = 360)	Rd (N = 362)	HR (IRd vs Rd)	*P*-value
Median PFS, mos				
All patients	20.6	14.7	0.742	0.012
Standard-risk patients	20.6	15.6	0.640	<0.05
All high-risk patients	21.4	9.7	0.543	-
Patient with del(17p)*	21.4	9.7	0.596	-
Patients with t(4;14) alone	18.5	12.0	0.645	-

* Alone or in combination with t(4;14) or t(14;16)

* Alone or in combination with t(4;14) or t(14;16)

- Median OS was not reached in either arm
- In the IRd am, median PFS in high-risk patients was similar to that in the overall patient population and in patients with standard-risk cytogenetics

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IRd vs. Rd in RRMM : conclusions

- IRd (compared to Rd) in RRMM was associated with:
  - An improvement in PFS
  - Improved TTP and response rates
  - Improved PFS in high-risk patients, similar to standard-risk patients
- Ixazomib added limited additional toxicity to that seen with Rd
  - Low rates of PN and no cardiovascular or renal signals

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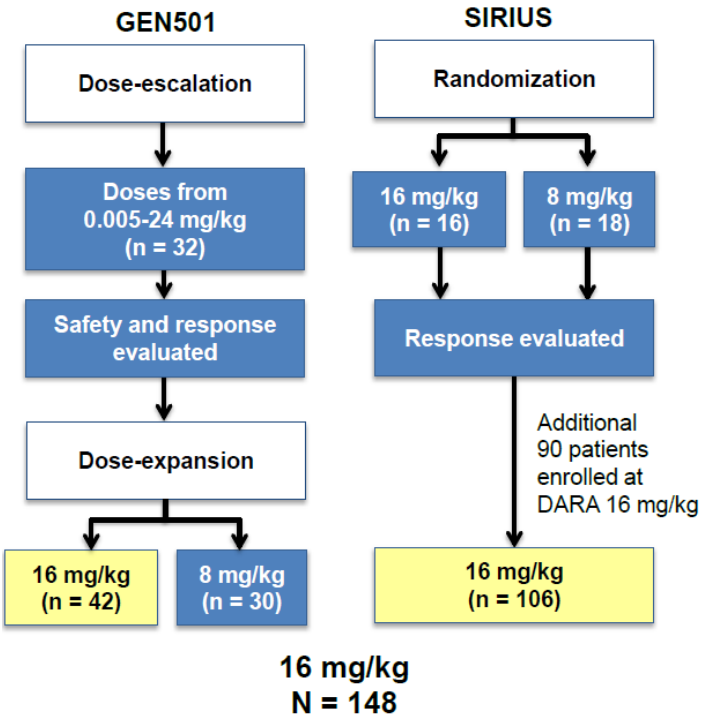
Daratumumab monotherapy in RRMM : trial design



GEN501[1]

- Open-label, multicenter, phase 1/2, dose-escalation and dose-expansion study
- Relapsed from or refractory to ≥2 prior lines of therapy including PIs and IMiDs

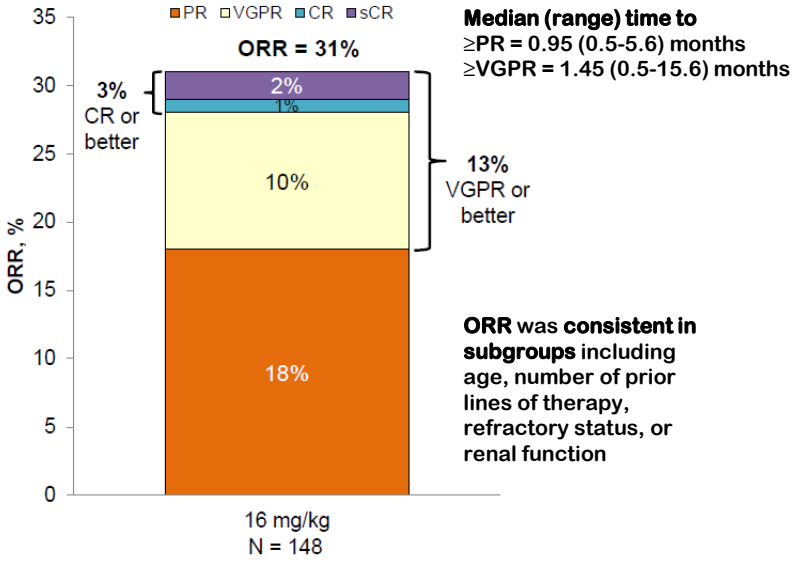
SIRIUS[2]

- Open-label, multicenter, phase 2 study
- Patients had received ≥3 prior lines of therapy, including a PI and an IMiD, or were double refractory to a PI and an IMID

Clinical Efficacy of Daratumumab Monotherapy in Patients with Heavily Pretreated Relapsed or Refractory Multiple Myeloma
Usmani (abstr. n° 29)

Daratumumab monotherapy in RRMM : outcome

Response Rate

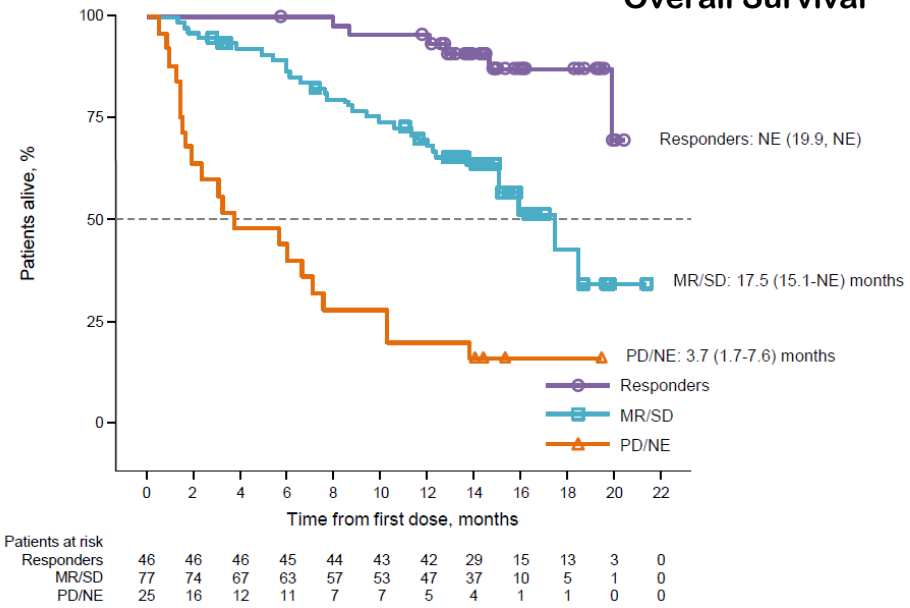


Median (range) time to
≥PR = 0.95 (0.5-5.6) months
≥VGPR = 1.45 (0.5-15.6) months

ORR was consistent in subgroups including age, number of prior lines of therapy, refractory status, or renal function

- Median duration of response = 7.6 months (95% CI, 5.6-NE)
- At a median follow-up of 14.8 months, 50% (95% CI, 33.6-63.9) of responders were progression-free at 12 months.

Overall Survival



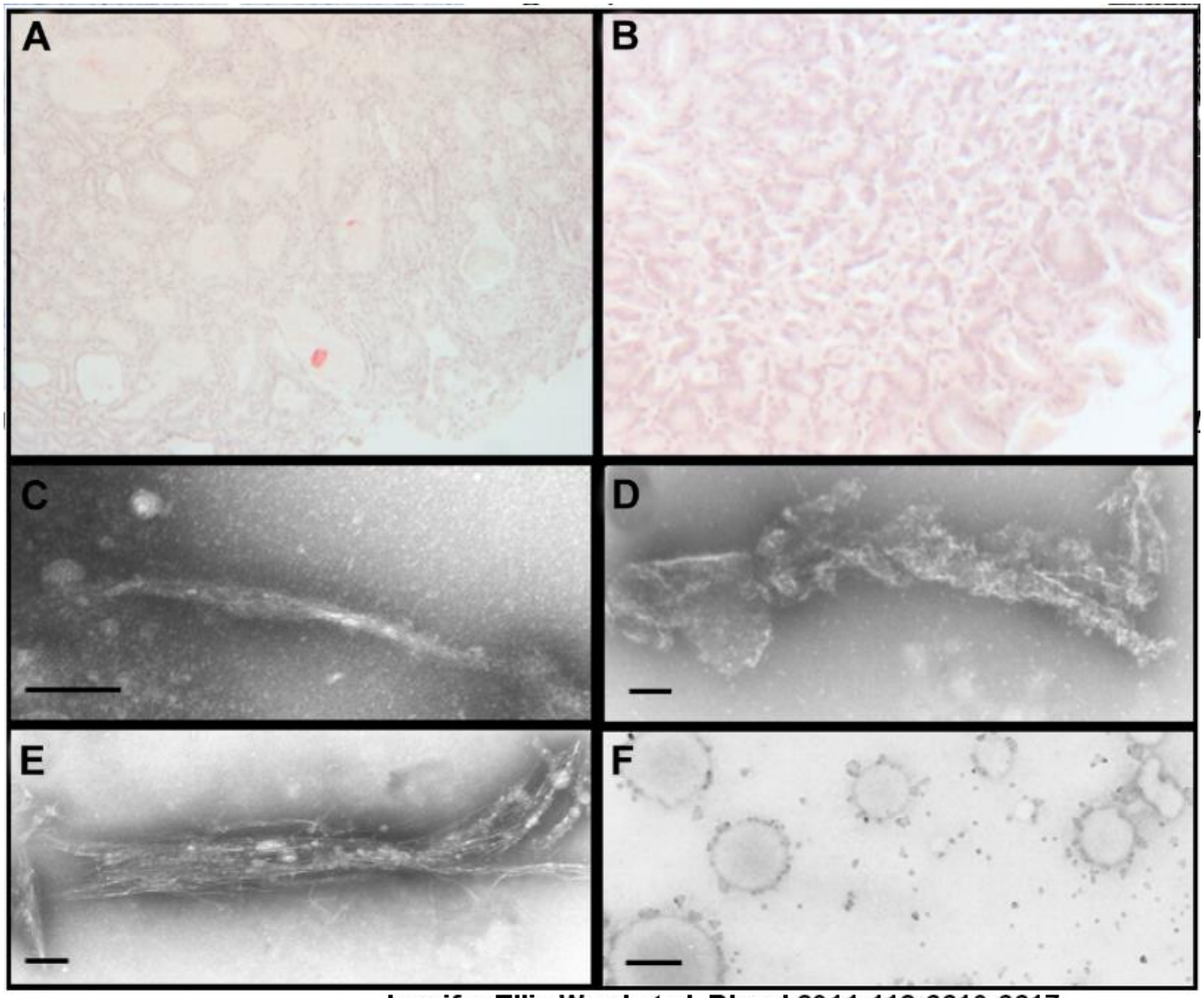
- In the combined analysis, median OS = 19.9 months (95% CI, 15.1-NE)
- 1-year overall survival rate = 69% (95% CI, 60.4-75.6)

Clinical Efficacy of Daratumumab Monotherapy in Patients with Heavily Pretreated Relapsed or Refractory Multiple Myeloma
Usmani (abstr. n° 29)

New drugs in myeloma

PD-1 antibodies	Study phase	Abstr. N°
Pembrolizumab		
+ LEN/DEX	**1**	**505**
+ POM/DEX	**2**	**506**
Pidilisumab		
+ LEN/DEX	**1/2**	**1838**
+ DC fusion vaccine	**1**	**4218**
Bruton tyrosine kinase inhibitor		
Ibrutinib		
+ CFZ	**1/2b**	**377**
Kinesin spindle protein inhibitor		
Finalisib		
+/- CFZ	**2**	**728**
+ CFZ	**1**	**376**
Anti-CD38		
Daratumumab	**1/2a + 2**	**29**
+ LEN/DEX	**1/2a**	**507**
+ POM/DEX	**1b**	**508**
Isatuxumab	**2**	**509**
MOR202	**1/2a**	**3035**
BCL-2 inhibitor		
Venetoclax	**1**	**4219**
+ BOR/DEX	**1b**	**3038**
HDAC inhibitor		
Panabinostat		
+ LEN/DEX	**2**	**4226**
Ricolinostat		
+ POM/DEX	**1b**	**4228**
+ BOR/DEX	**1b**	**1827**
Vorinostat		
+ BOR/DOXO/DEX	**1/2**	**4260**
+ BOR/DEX	**2**	**1852**
+ LEN/DEX	**2b**	**4264**

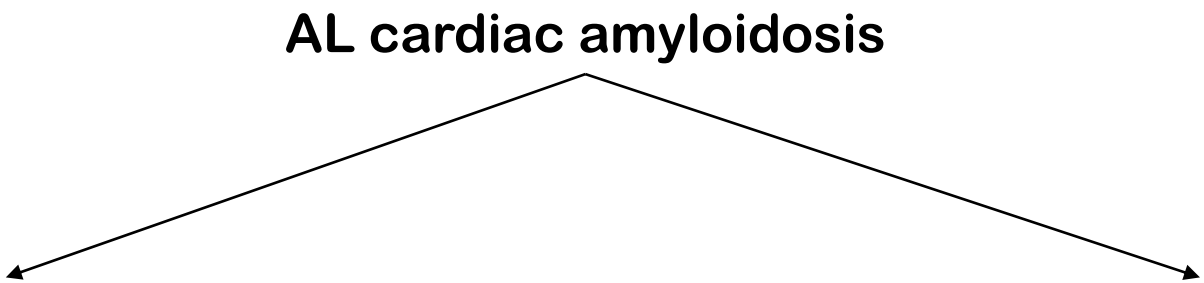
Docycyclin reduces amyloid deposition



Jennifer Ellis Ward et al. Blood 2011;118:6610-6617

Oral Doxycycline Improves Outcomes of Stage III AL Amyloidosis - a Matched Case Control Study
Wechalekar (Abstr. N° 653)

Docycyclin in AL cardiac amyloidosis : trial design



Doxycyclin 100 mg q12h during treatment

Investigational cohort (n=30)

Control arm

Random matched historical cohort (n = 73)

Median age : 65 y (47-87y)
- 72 % : Bortezomib based
- 23 % : Thalidomide based
- 5% : Melphalan based

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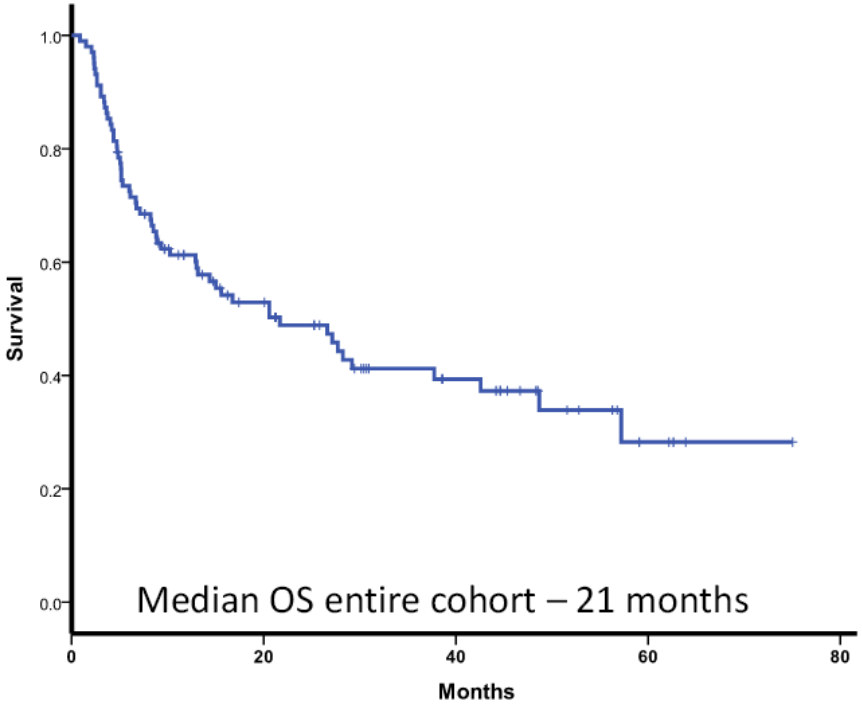
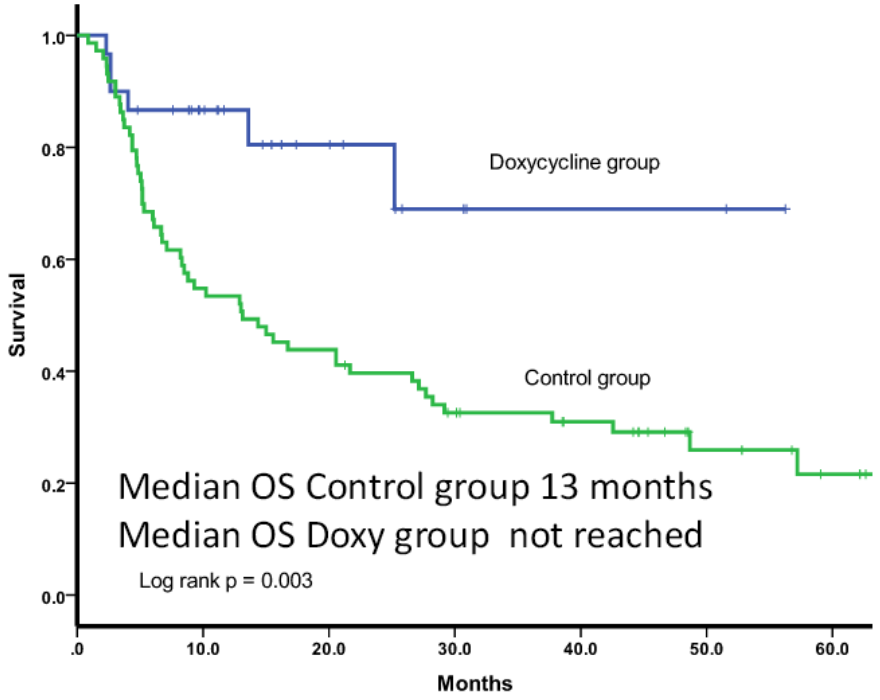
Wechalekar (Abstr. N° 653)

Docycyclin in AL cardiac amyloidosis : outcome





Oral Doxycycline Improves Outcomes of Stage III AL Amyloidosis - a Matched Case Control Study
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Docycycline in AL cardiac amyloidosis : conclusions

Stage	NT-proBNP (< 332 ng/L)	cTnT (<0.035 µg/L) or cTnI(< 0.1 µg/L)
I	LOW	LOW
II	Only one elevated	
III	HIGH IIIa (≤ 8500 ng/l) IIIb (>8500 ng/l)	HIGH

- Oral doxycycline + chemotherapy improves OS
- Only in stage II and IIIa patients
- Higher CR/VGPR rate > higher cardiac responses
- Low toxicity – low costs
- Randomized trial needed

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ASH 2015 Plasma Cell disorders : Take home messages

- VRd is superior to Vd in terms of PFS and OS in newly diagnosed patients (without intent of ASCT)
- VTD is superior to VCD as induction regimen before ASCT
- Even in the era of new drugs and with triplet induction therapy an upfront ASCT still prolongs PFS
- MRD analysis may identify potentially cured myeloma patients and may influence decision making on maintenance duration
- All oral Ixazomib-Rd prolongs PFS by 5,9 months in relapsed and/or refractory patients compared to Rd
- Daratumumab in monotherapy shows impressive single agent activity in heavily pretreated patients with low toxicity
- Adding oral doxycycline to standard therapy in cardial AL amyloidosis may mitigate the dismal prognosis