Highlights from IMW 2019

19-20 novembre 2019
Bologna
Royal Hotel Carlton

Trapianto autologo: rimarrà uno standard anche nei prossimi (5) anni?

Francesca Patriarca-
Universita' di Udine

Great debate

P. Sonneveld-Rotterdam

YES

O. Landgren-New Jork

NO

Boston Backbay from the ferry boat September 15, 2019

The reasons of “yes” to ASCT

- Upgrade of response
- Results of randomized studies
- Current guidelines
- Results of new trials

Phases of first-line treatment	objective
1.Induction	Disease control
2. ASCT	3-log tumour reduction
3.Consolidation	Response upgrade
4. Maintenance	Prevent progression

RESPONSE IMPROVEMENT AT DIFFERENT TREATMENT PHASES

Table 2. Response to different treatment phases in the per-protocol population, according to central assessment

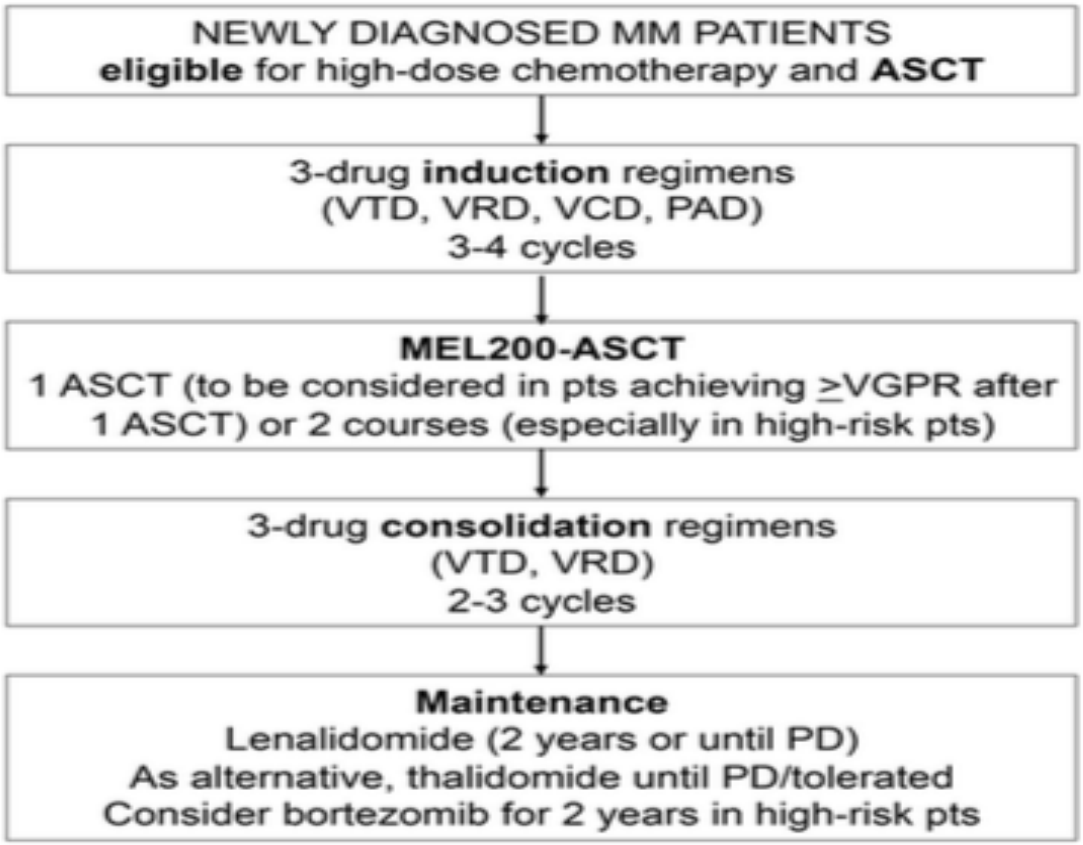
	VTD (n = 160)	TD (n = 161)	*P*
After induction therapy			
CR	36 (22.5%, 16.0-29.0)	9 (5.6%, 2.0-9.1)	< .0001
CR/nCR	53 (33.1%, 25.8-40.4)	22 (13.7%, 8.3-19.0)	< .0001
VGPR or better	100 (62.5%, 55.0-70.0)	50 (31.1%, 23.9-38.2)	< .0001
PR or better	154 (96.2%, 93.3-99.2)	140 (87.0%, 81.7-92.1)	.003
MR or SD	6 (3.7%, 0.8-6.7)	21 (13.0%, 7.8-18.2)	.003
After first ASCT			
CR	70 (43.8%, 36.1-51.4)	49 (30.4%, 23.3-37.5)	.014
CR/nCR	91 (56.9%, 49.2-64.5)	66 (41.0%, 33.4-48.6)	.004
VGPR or better	131 (81.9%, 75.9-87.8)	117 (72.7%, 65.8-79.6)	.049
PR or better	156 (97.5%, 95.1-100)	156 (96.9%, 94.2-99.6)	.742
MR or SD	4 (2.5%, 0.1-0.5)	5 (3.1%, 0.04-5.8)	.742
After second ASCT			
CR	78 (48.7%, 41.0-56.5)	65 (40.4%, 32.8-47.9)	.131
CR/nCR	101 (63.1%, 55.6-70.6)	88 (54.7%, 47.0-62.3)	.123
VGPR or better	138 (86.2%, 80.9-91.6)	131 (81.4%, 75.3-87.4)	.235
PR or better	157 (98.1%, 96.0-100)	157 (97.5%, 95.1-99.9)	.709
MR or SD	3 (1.9%, 0.0-4.0)	4 (2.5%, 0.1-4.9)	.709
After consolidation therapy			
CR	97 (60.6%, 53.0-68.2)	75 (46.6%, 38.9-54.3)	.012
CR/nCR	117 (73.1%, 66.2-80.0)	98 (60.9%, 53.3-68.4)	.020
VGPR or better	147 (91.9%, 87.6-96.1)	142 (88.2%, 83.2-93.2)	.272
PR or better	156 (97.5%, 95.1-99.9)	160 (99.4%, 98.2-100)	.174
MR or SD	1 (0.6%, 0-1.8)	1 (0.6%, 0-1.8)	.996
PD	3 (1.9%, 0-4.0)		.081

Cavo M et al, Blood 2012

Results of prospective randomized studies

autore	terapia	Median PFS	4 y OS
Palumbo et al, NEJM 2014	Induzione: RD Consolidamento: MRP vs Mel 200	**MRP: 22 mesi** **Mel 200:42 mesi**	**MPR : 65%** **Mel 200: 81%**
Gay et al, Lancet Oncology 2015	Induzione RD Consolidamento: CRD vs Mel 200	**CRD: 28 mesi** **Mel 200:43 mesi**	**CRD : 73%** **Mel 200: 86%**
Attal et al, NEJM 2017	Induzione RVD Consolidamento: RVD vs Mel 200	**RVD: 34 mesi** **Mel 200:50 mesi**	MPR : 81% Mel 200: 82%
Cavo et al, SIE 2019	Induzione VCD Consolidamento: VMP vs Mel 200	**VMP:42 mesi** **Mel 200:57 mesi**	VMP: 72% at 5 y Mel 200: 75% at 5 y

European Myeloma Network guidelines



Gay F, Haematologica 2018

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2020
Multiple Myeloma

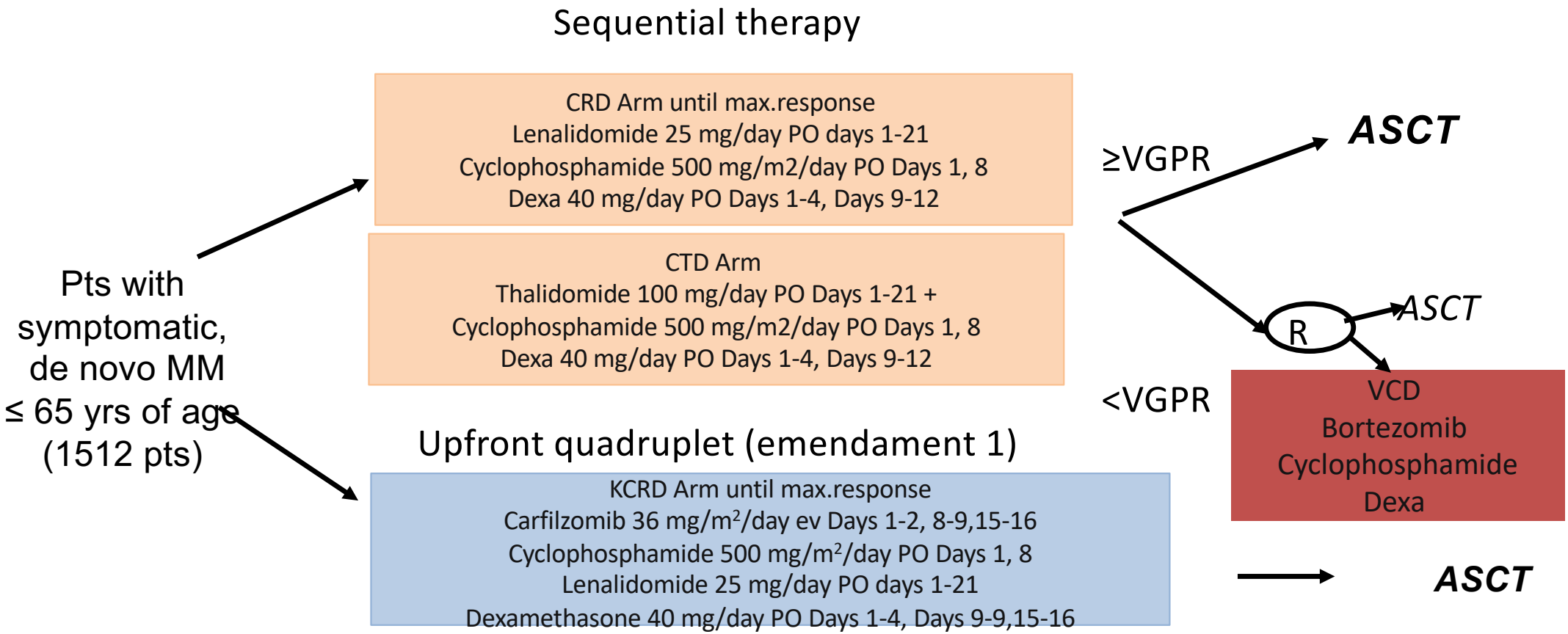
MULTIPLE MYELOMA (SYMPTOMATIC)

Response after primary therapy[n] →

- **Autologous[u,v] stem cell transplant (category 1)**
- **OR**
- **Continuous myeloma therapy or maintenance therapy[r]**
- **OR**
- **Allogeneic[w] stem cell transplant, under certain circumstances**

Category 1 evidence supports proceeding directly after induction therapy to high-dose therapy and stem cell transplant.

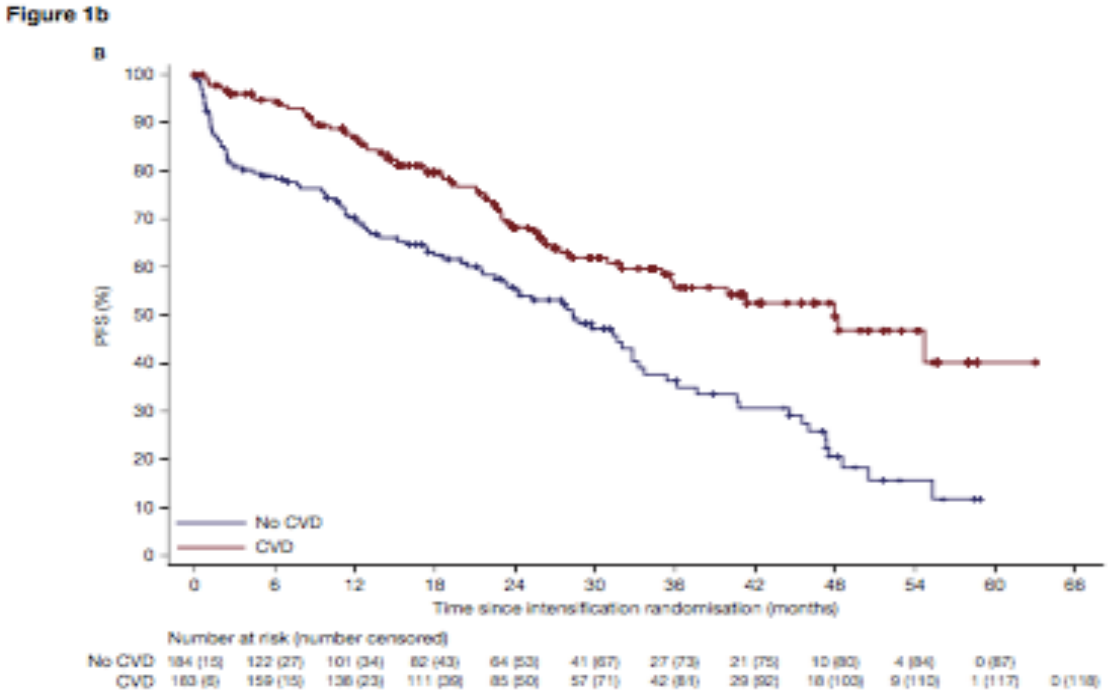
UK NCRI Mieloma XI



1056 patients underwent induction randomization between December 2013 and April 2016
Median follow-up 34.5 months

Pawlyn C, et al. ASH 2015. Abstract 189;Jackson GH et al. ASH 2018. Abstract 302

Impact of response to induction



VCD vs no therapy in pts with MR/PR after induction:

Response-adapted can improve response rates and prolong PFS

Jackson GH, et al, The Lancet Haematology 2019

Table 1

	CTD	CRD	KCRD
Response at end of first induction therapy	*(n=265)*	*(n=265)*	*(n=526)*
CR	18 (6.8%)	19 (7.1%)	93 (17.7%)
nCR	52 (19.6%)	90 (34.0)	203 (38.6)
VGPR	70 (26.4%)	63 (23.8%)	137 (26.0%)
PR	88 (33.2%)	66 (24.9%)	43 (8.2%)
>=VGPR	**140 (52.8%)**	**172 (64.9%)**	**433 (82.3%)**
Response at day 100 after ASCT	*(n=159)*	*(n=179)*	*(n=394)*
CR	40 (25.2%)	41 (22.9%)	122 (31.0%)
nCR	47 (29.6%)	60 (33.5%)	152 (38.6%)
VGPR	34 (21.4%)	46 (25.7%)	88 (22.3%)
PR	28 (17.9%)	26 (14.5%)	23 (5.8%)
>=VGPR	**121 (76.1%)**	**147 (82.1%)**	**362 (91.9%)**

nCR = CR without bone marrow confirmation

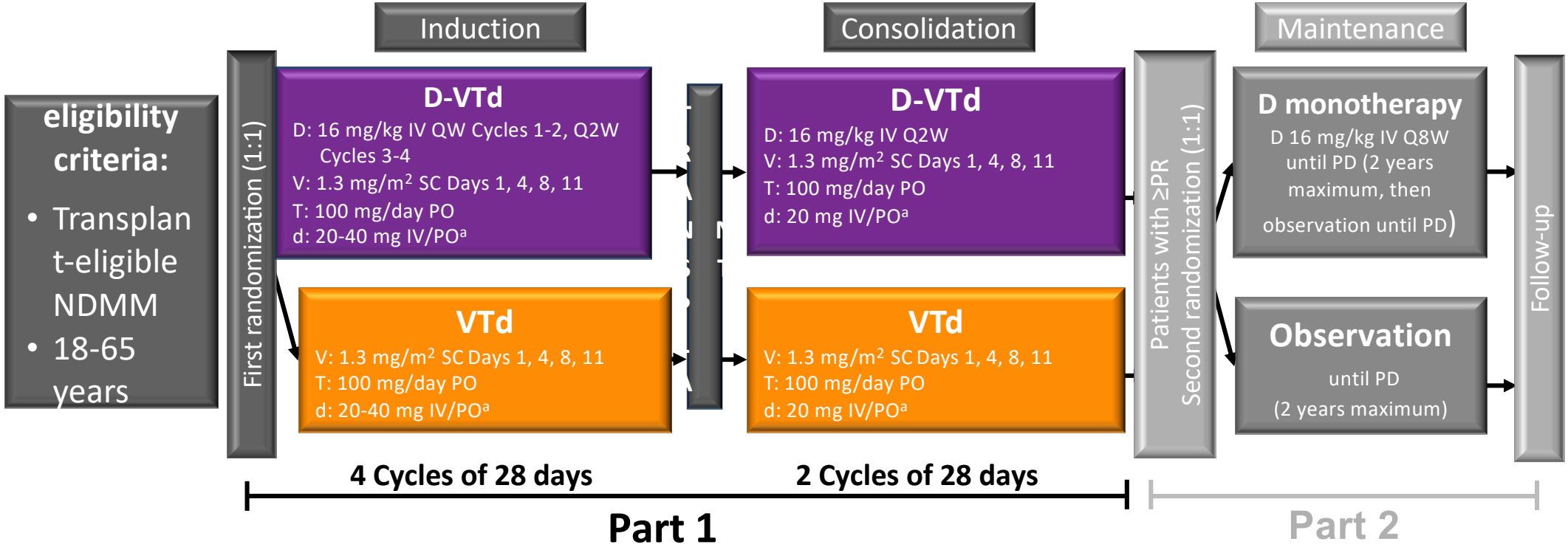
- **KCRD** was associated with a significantly **longer PFS** than triplet therapy (HR 0.63, 95%CI 0.51, 0.76, median PFS KCRD NR vs CTD/CRD 36.2 months, p<0.0001).
- Improved PFS was seen **in all cytogenetic risk groups**.
- **PFS** 0.99
- **The** **sequential triplet approach (HR 0.64, 95% CI 0.52, 0.78, p<0.0001)**.

Frontline therapy for transplant-eligible MM patients: fast start for a long game
Patriarca F. The Lancet Haematology 2019

Jackson et al, ASH meeting 2018

CASSIOPEIA Study Design

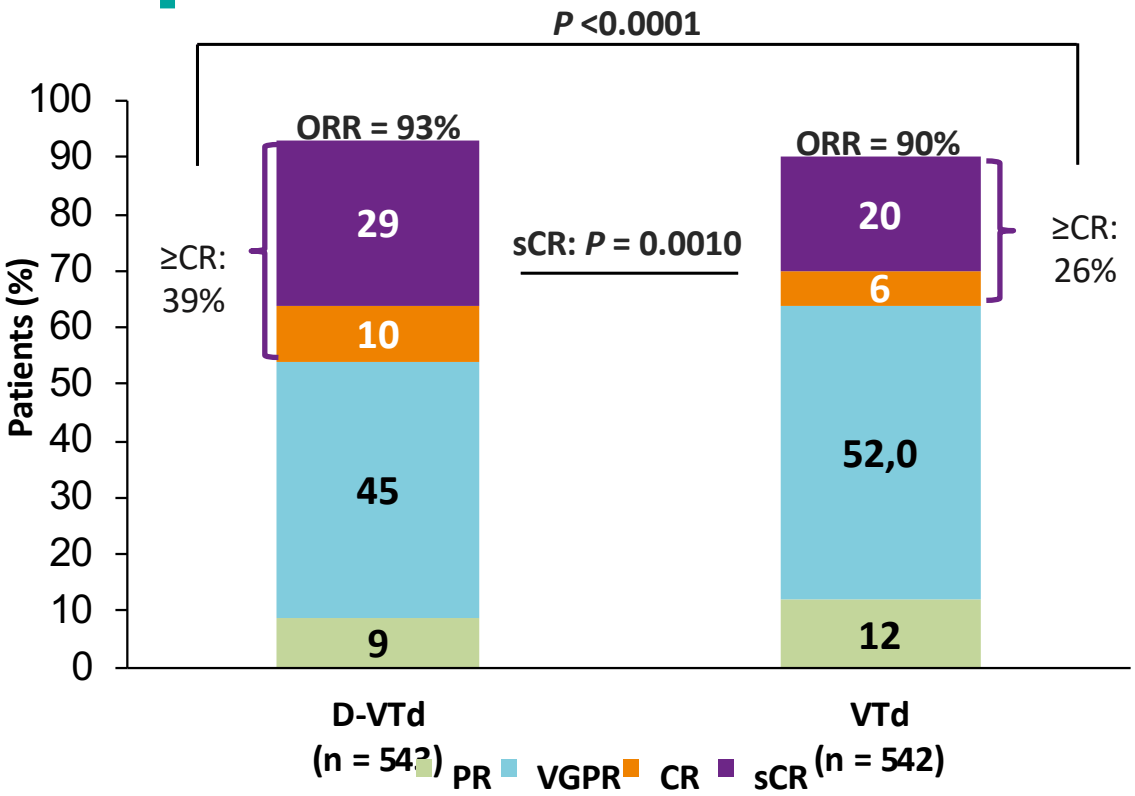
- Phase 3 study of D-VTd versus VTd in transplant-eligible NDMM (N = 1,085)



Primary end point: sCR after consolidation

Moreau et al, Oral Presentation, ASCO 2019; Lancet 2019

Efficacy: Post-consolidation Depth of Response

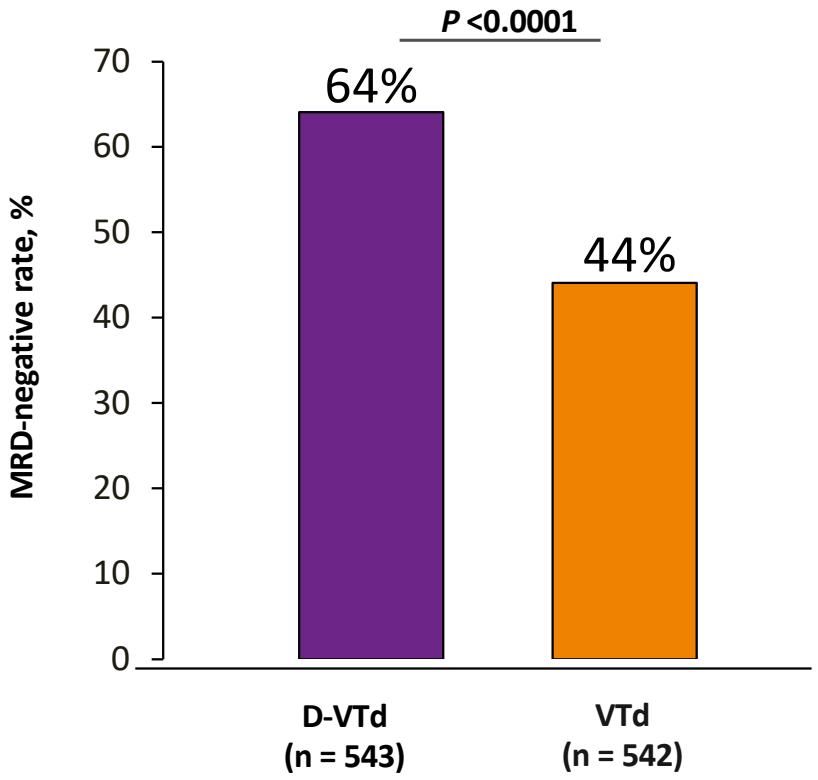


- Primary endpoint
  - Post-consolidation sCR
    - 29% D-VTd vs 20% VTd
    - Odds ratio, 1.60; 95% CI, 1.21-2.12; *P* = 0.0010

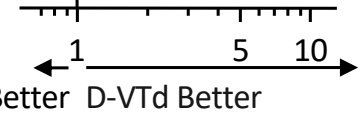
The addition of daratumumab to VTd improved depth of response

Moreau et al, Oral Presentation, ASCO 2019

Efficacy: MRD (Flow Cytometry; 10^{-5})[a,b]



Subgroup	VTd	D-VTd	Odds Ratio (95% CI)
	Minimal residual disease negative, n (%)		
Sex			
Male	131 (41)	192 (61)	2.22 (1.62–3.05)
Female	105 (47)	154 (68)	2.37 (1.62–3.48)
Age			
<50 years	38 (42)	56 (68)	2.84 (1.53–5.28)
≥50 years	198 (44)	290 (63)	2.19 (1.68–2.85)
Site			
IFM	204 (45)	287 (64)	2.16 (1.65–2.81)
HOVON	32 (38)	59 (65)	3.05 (1.65–5.65)
ISS disease stage			
I	103 (45)	137 (67)	2.48 (1.68–3.67)
II	96 (41)	155 (61)	2.21 (1.54–3.18)
III	37 (46)	54 (64)	2.14 (1.15–4.00)
Cytogenetic profile at trial entry[c]			
High risk	38 (44)	49 (60)	1.88 (1.02–3.46)
Standard risk	197 (43)	296 (64)	2.35 (1.80–3.07)
Baseline creatinine clearance			
>90 ml/min	139 (44)	205 (62)	2.07 (1.51–2.84)
≤90 ml/min	97 (43)	141 (67)	2.64 (1.79–3.89)
Baseline hepatic function			
Normal	216 (43)	310 (65)	2.40 (1.85–3.10)
Impaired	20 (48)	36 (57)	1.47 (0.67–3.21)
Type of multiple myeloma[d]			
IgG	122 (39)	201 (61)	2.43 (1.77–3.34)
Non-IgG	59 (49)	61 (66)	2.00 (1.15–3.50)
ECOG performance status			
0	112 (44)	172 (65)	2.39 (1.68–3.41)
≥1	124 (44)	174 (63)	2.17 (1.55–3.04)

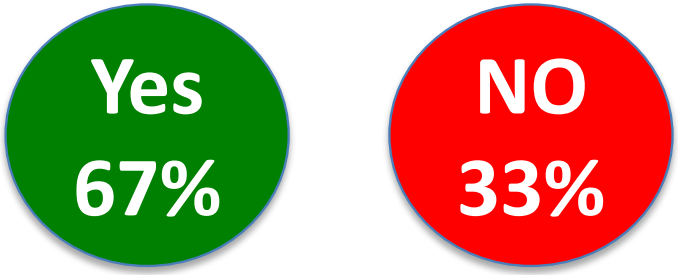


D-VTd superior across all subgroups including high-risk cytogenetics and ISS stage III

Moreau et al, Oral Presentation, ASCO 2019

The reasons of “yes” to ASCT

- Upgrade of response: 30-50% CR
- Results of randomized studies
- 2020 guidelines
- “Fast start” in new trials with carfilzomib or MoAb



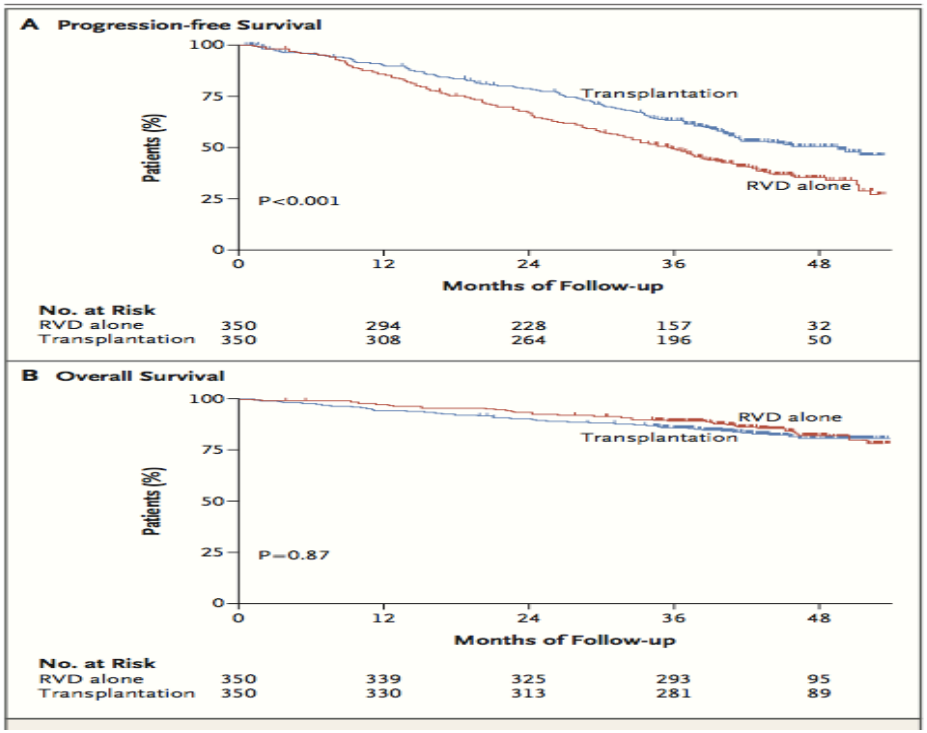
The reasons of “no” to ASCT

- The true need of MM pts is OS
- First line treatments without ASCT have already achieved high rate of MRD negativity
- Sustained MRD negativity have translated in long term PFS and OS
- Melphalan is myelotoxic with substantial risk of MDS/AML

No advantage in OS in ASCT arm in recent randomized studies

N=700 pts
median follow-up 43 months

RVDx3+ASCT+RVDx2+lenax1 year
vs
RVDx8+lenax1 year

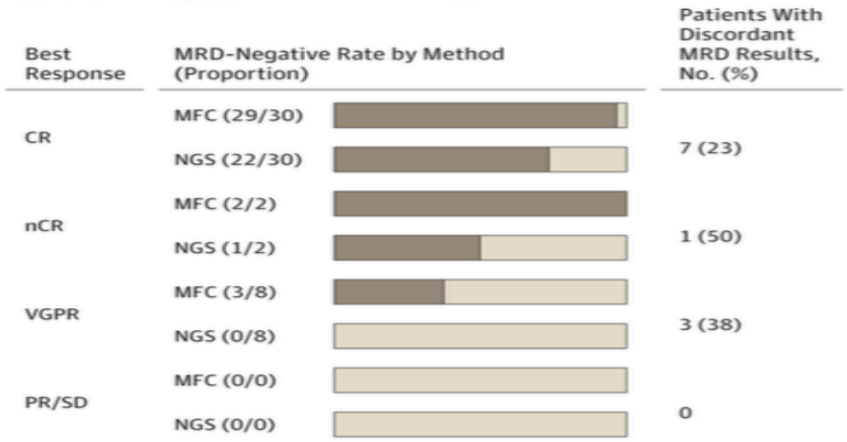


Attal et al, NEJM 2017

KRD induces high rates of MRD negativity

45 NDMM
12 SMM

KRD x 8 cycles
R x 24 months



40/45 at least VGPR

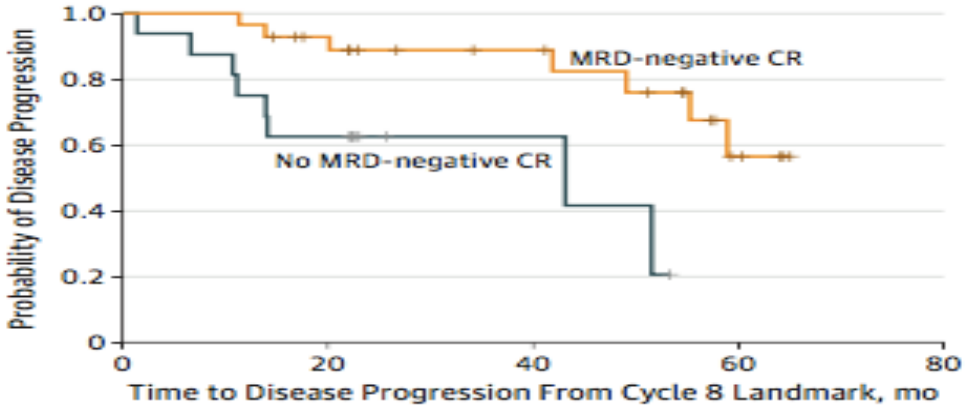
85% MRD neg at MFC
62% MRD neg by NGS
41% MRD neg by TC-PET

Korde et al,JAMA Oncology 2015

MRD negativity is associated with long term PFS

median follow-up 5.2 years
median PFS of MRD neg CR of 5.5 years
m OS not reached

Figure 1. Time to Disease Progression Based on Minimal Residual Disease (MRD)–Negative Complete Remission (CR) Status



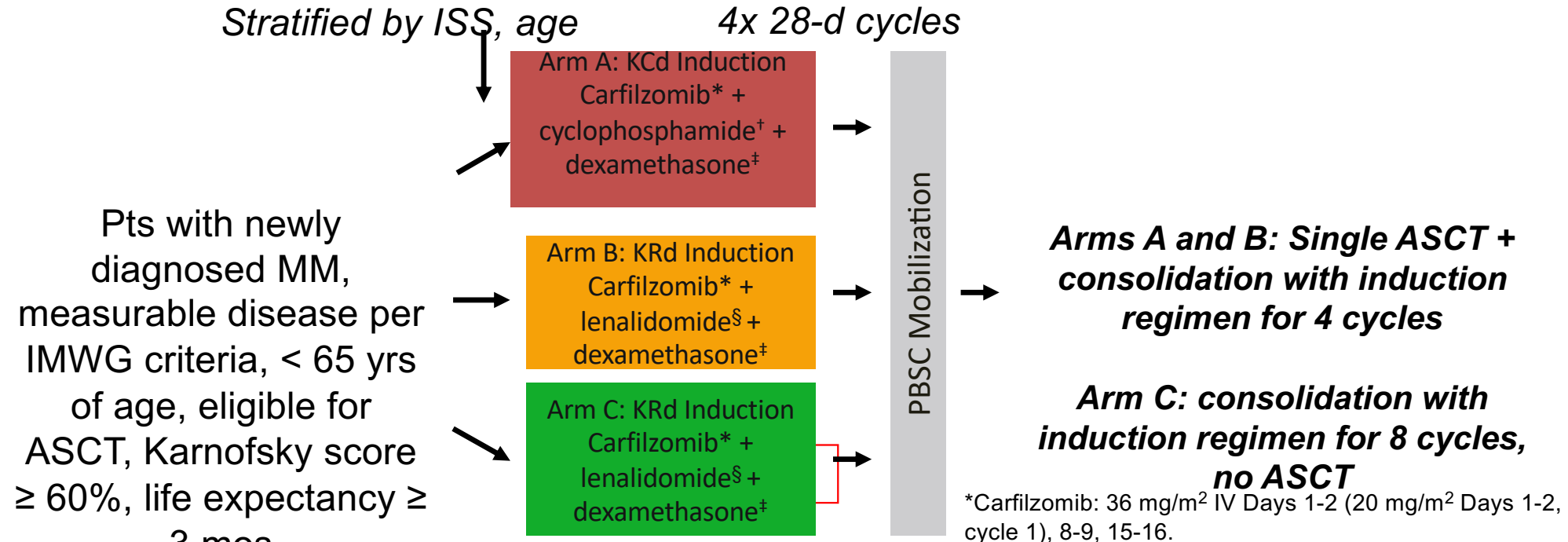
No. at risk					
No MRD-negative CR	16	10	3	0	
MRD-negative CR	28	23	15	4	0

Patients who experienced MRD-negative CR by the end of carfilzomib, lenalidomide, and dexamethasone induction (8 cycles) had a significantly longer time to disease progression, with a 78% reduction in risk of progression (hazard ratio, 0.22; 95% CI, 0.07-0.69; *P* = .005). Hatch marks on the curves indicate censored data.

Kazandjian D et al,JAMA Oncology 2018

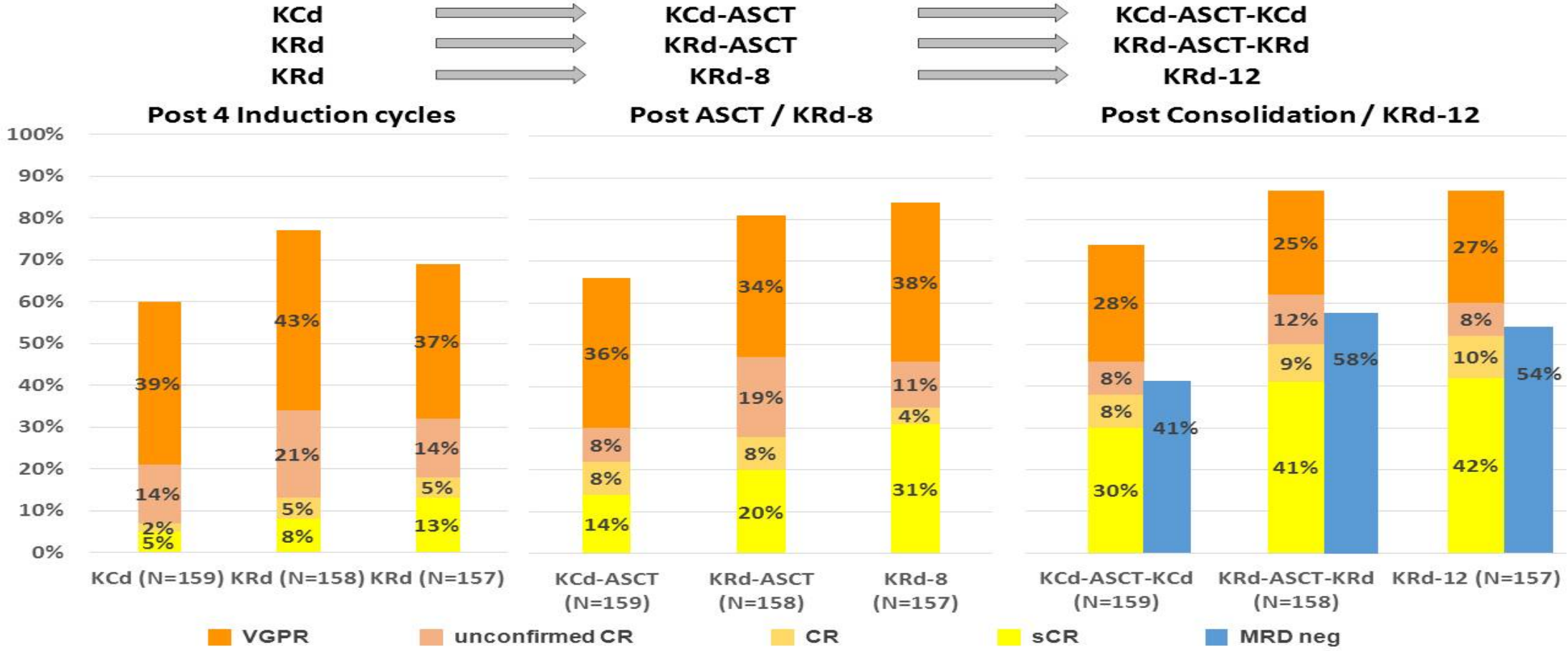
FORTE: Study Design

- Multicenter, randomized, open-label phase II study
- Endpoints: induction phase safety, PBSC mobilization, preliminary efficacy



*Carfilzomib: 36 mg/m^2 IV Days 1-2 (20 mg/m^2 Days 1-2, cycle 1), 8-9, 15-16.
†Cyclophosphamide: 300 mg/m^2 Days 1, 8, 15.
‡Dexamethasone: 20 mg Days 1-2, 8-9, 15-16, 22-23.
§Lenalidomide: 25 mg Days 1-21.

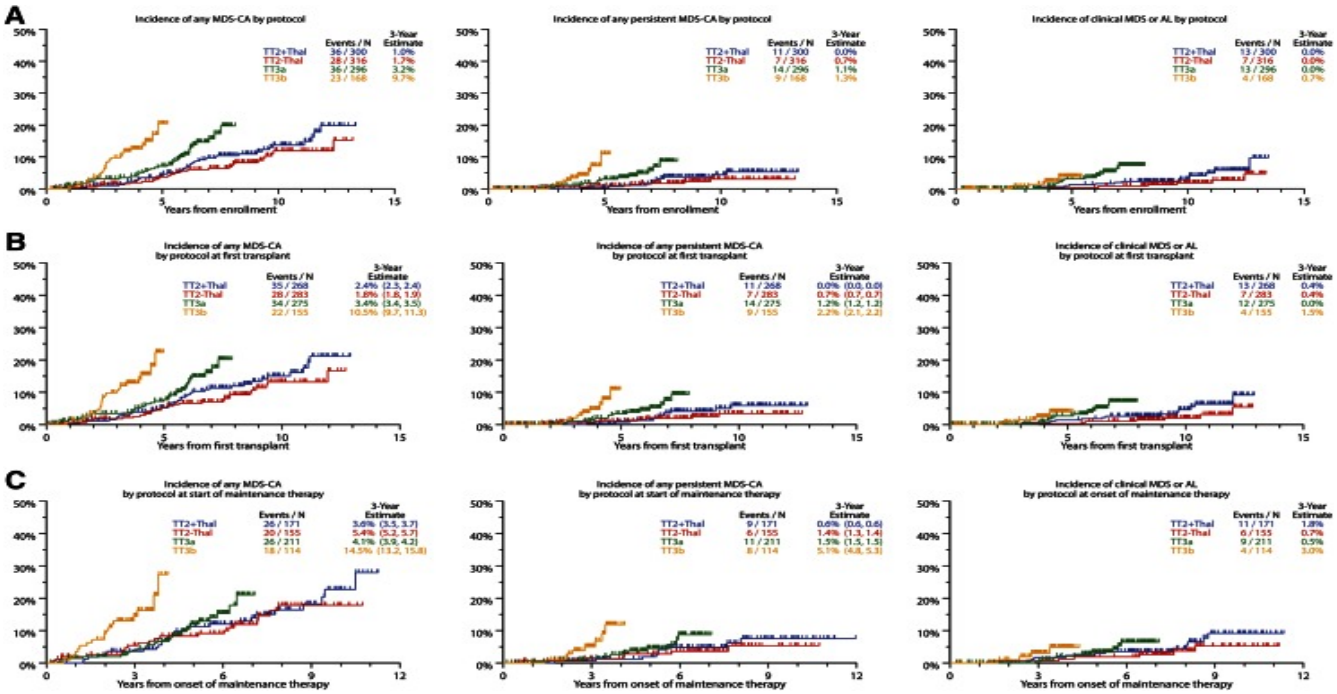
Gay FM, et al. ASH 2018. Abstract 8003.
ClinicalTrials.gov. NCT02203643



Gay F et al, ASH meeting 2018

t-MN in Total Therapy (1080 pts)

11%
MDS-CA

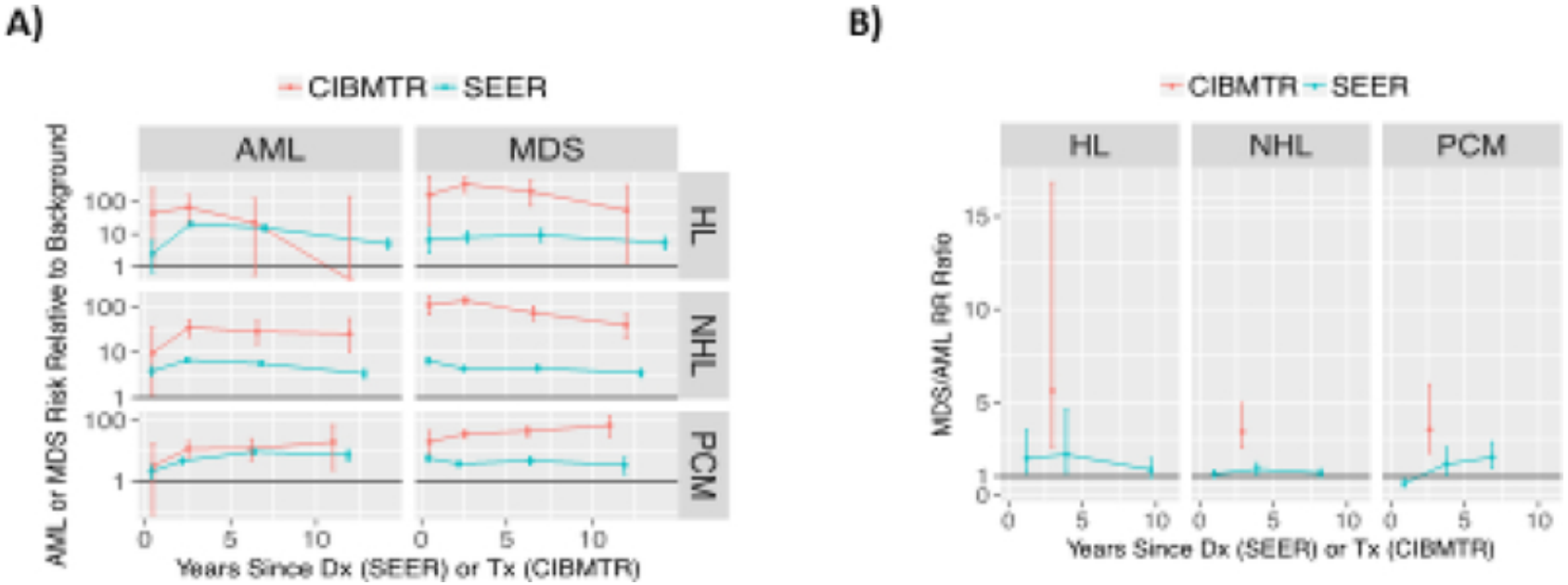


3%
Clinical MDS/AML

Risk factors for MDS-type cytogenetic abnormalities included immunomodulatory drugs, older age, male gender, and low CD34 dose (<5 million/kg) given with first transplant.

Usmani S, Blood 2013

RISK OF MDS/AML AFTER AUTOLOGOUS TRANSPLANT

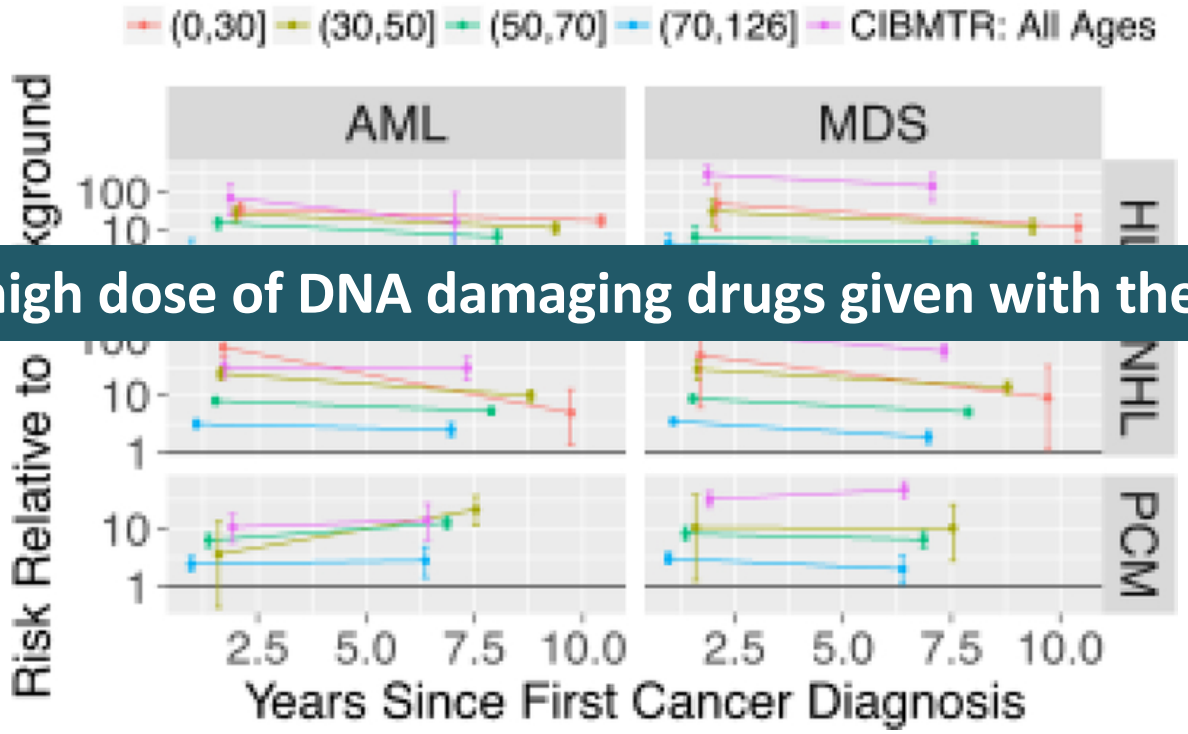


3,7% MDS/AML out of 9029 lymphoma/MM recipients of autotranplants in CIBMTR

Radivoyeevitch T, Leukemia Research 2018

Risks of developing t-MN after autotransplants for plasma cell myeloma (n=4653)

Parameter	n	Hazard Ratio (95% CI)	P-value
Age at transplant, years			
18-54	1661	1.00	
55+	2902	2.47(1.55 - 3.93)	<.01
Prior Lines of chemotherapy			0.08
1	2472	1.00	
2	1252	1.21(0.78 - 1.88)	0.39
3+	655	1.77(1.06 - 2.96)	0.03
Missing	184	0.28(0.04 - 2.06)	0.21
Sex			
Female	1859	1.00	
Male	2704	2.27(1.45-3.53)	<.01

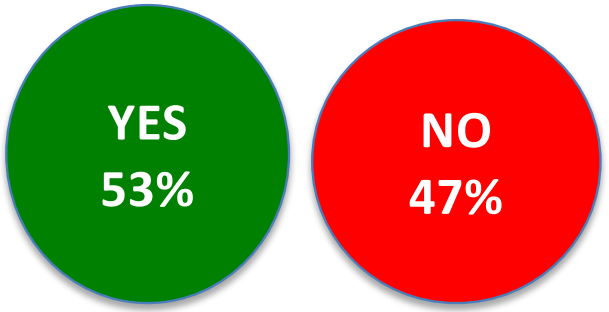


Expose to high dose of DNA damaging drugs given with the autotransplant

Higher RR for developing t-MN after autotransplant (CIBMTR data-purple line) in comparison with similar subjects, most of whom did not receive autotransplant (SEER data-blu line)

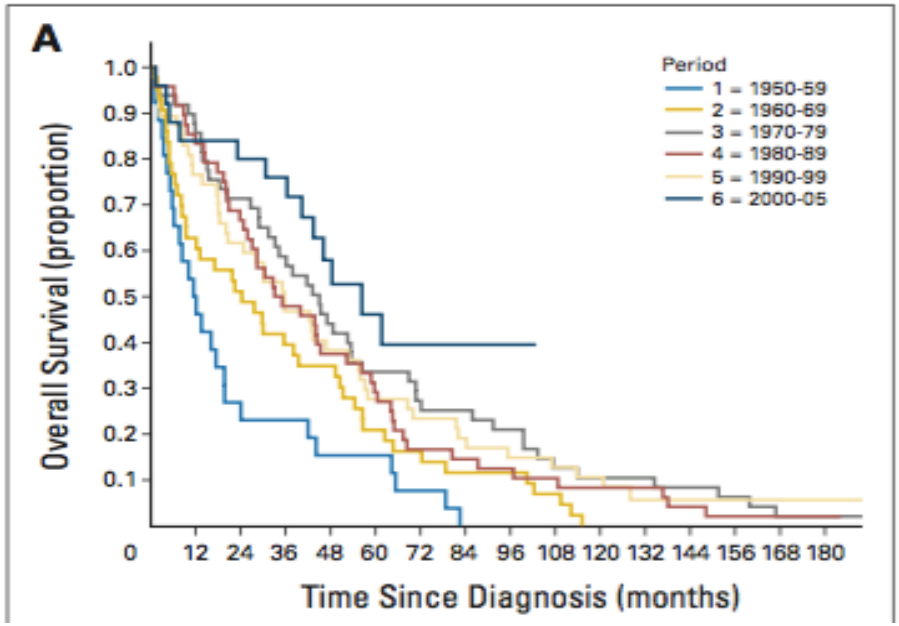
The reasons of “no” to ASCT

- No OS advantage in randomized studies
- First line treatments without ASCT have already achieved high rate of MRD negativity and long term PFS and OS
- Low risk patients with sustained MRD negativity could avoid ASCT
- Melphalan is myelotoxic with substantial risk of MDS/AML

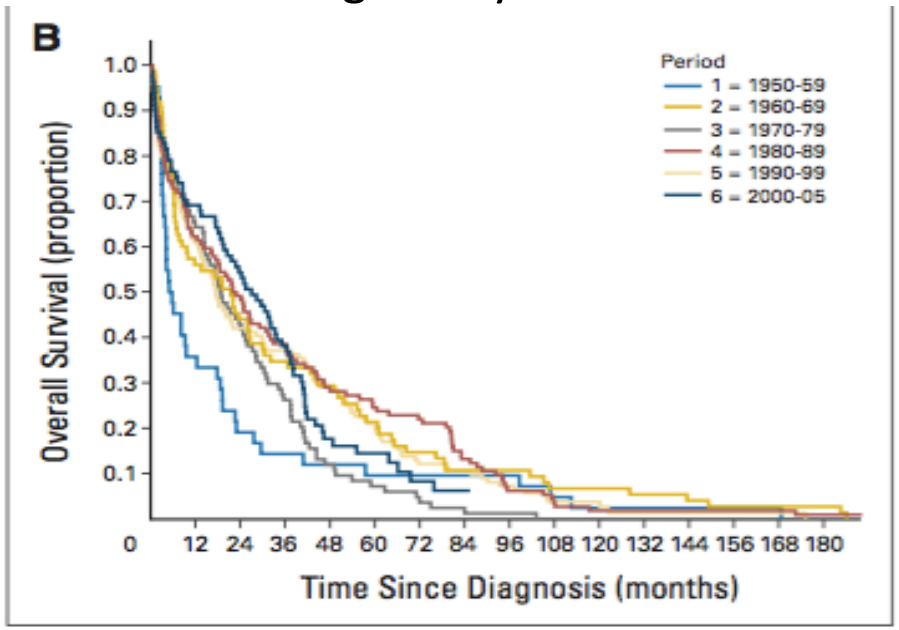


The true needs for MM patients.
OS improvement in registry based studies

Age ≤ 65 years



Age>65 years



Turesson I JCO 2010