Highlights from IMW 2021

1-2 febbraio 2022
Bologna
Royal Hotel Carlton

Barbara Gamberi

Condizionamento ad ASCT: con Melphalan ed altri agenti?

IFM 9502: MEL 200 as standard of care

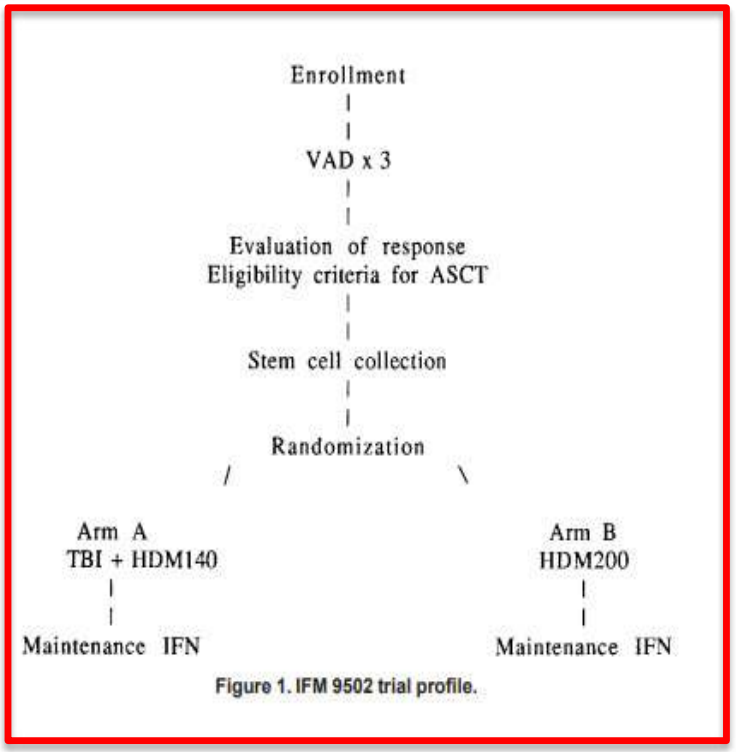


Figure 1. IFM 9502 trial profile.

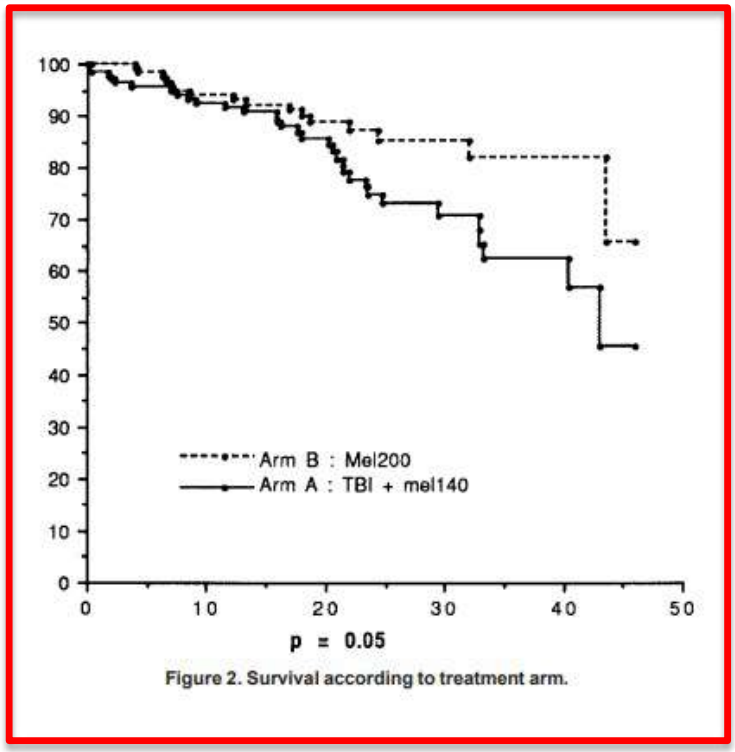


Figure 2. Survival according to treatment arm.

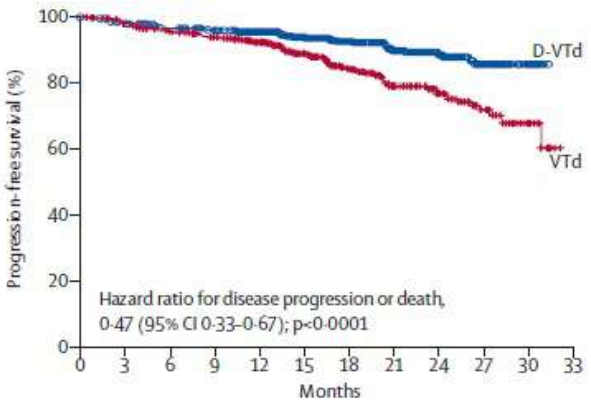
Moreau, 2002

First line: how to do better?

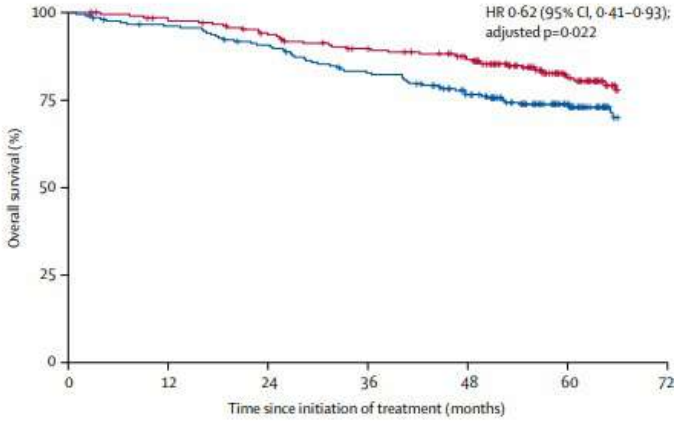
Induction: four instead of three drugs

Transplant: tandem transplant

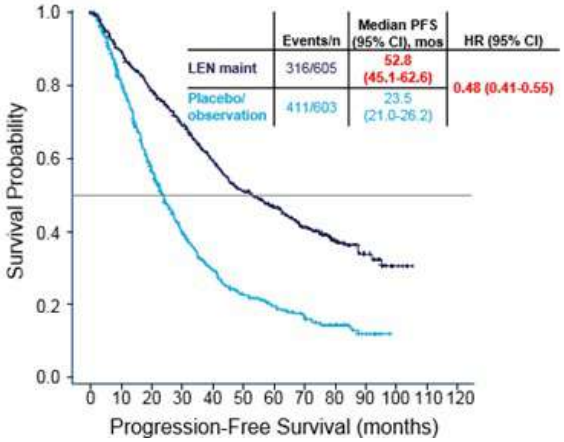
Maintenance: continuous therapy



Moreau, 2019



Cavo, 2020



McCarthy, 2017

Improving the conditioning regimen

- **Increase dose of melphalan**
- **Melphalan derivative**
- **Incorporate new drugs**

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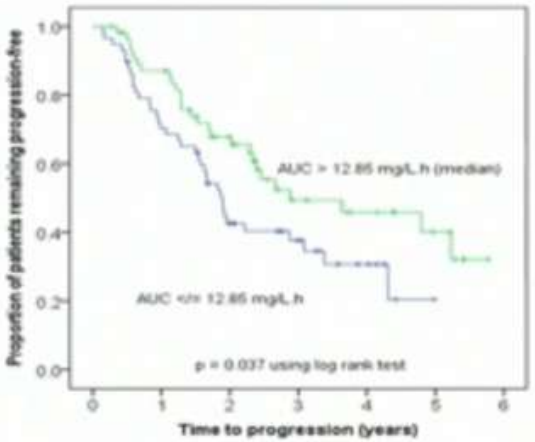
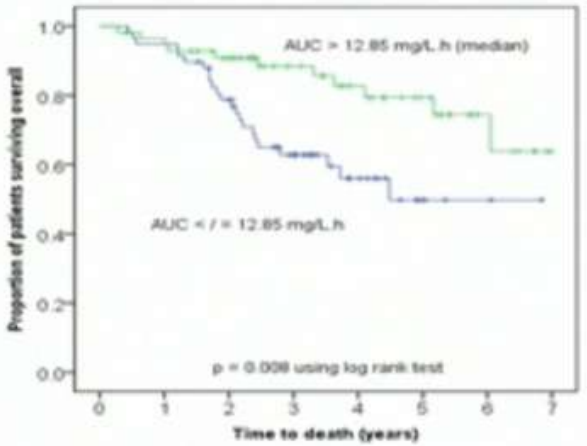
Higher Melphalan AUC Predicts Time to Progression, Overall Survival, and Toxicity

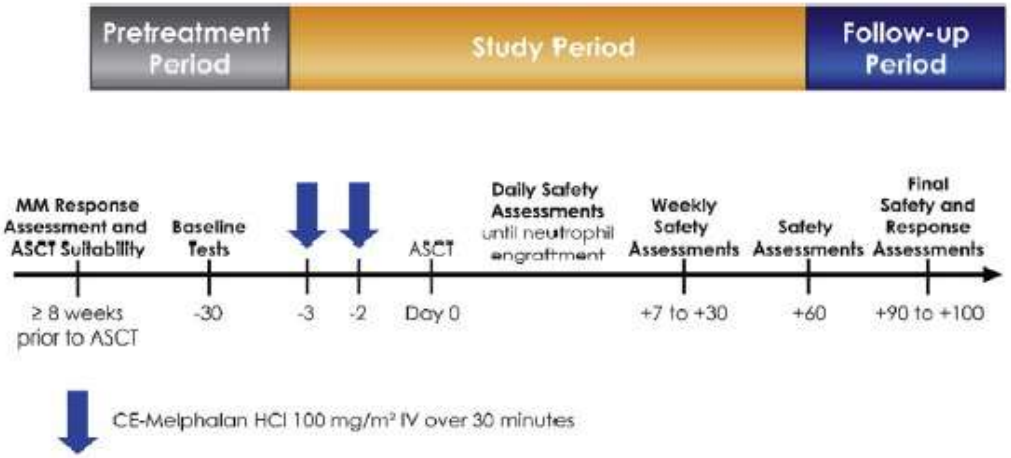


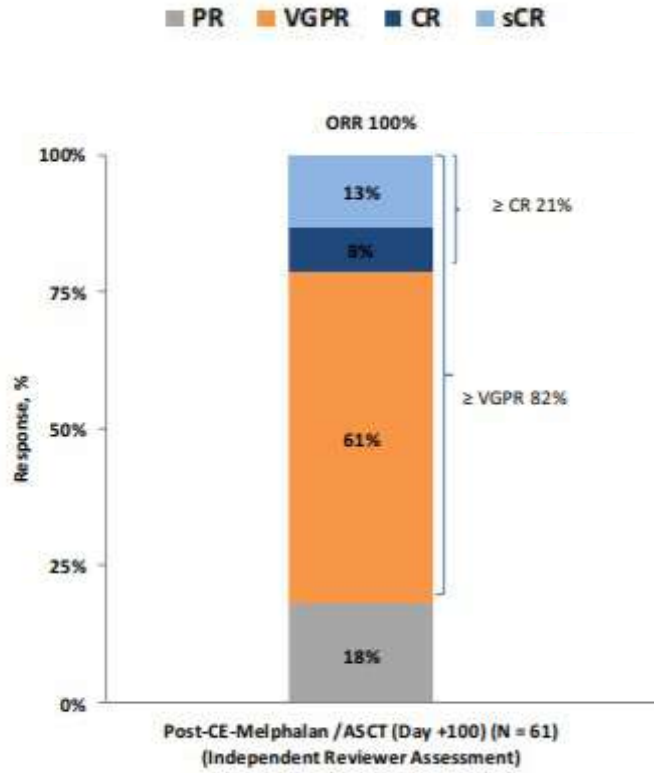


- Melphalan median AUC 12.85 mg/L.h

Shaw, 2012

Evomela





Hari, 2015

Evomela

- more stable and soluble formulation
- eliminates time constraints
- significant variability in exposure: highest quartile had an approximate 3-fold higher AUC then the first quartile
- ongoing studies on long infusion schedule (8-9 hour infusion) and better PK definition

Hari, 2015; Dhakal, 2018; Bashir, 2021

Improving the conditioning regimen

- **Increase dose of melphalan**
- **Melphalan derivative**
- **Incorporate new drugs**

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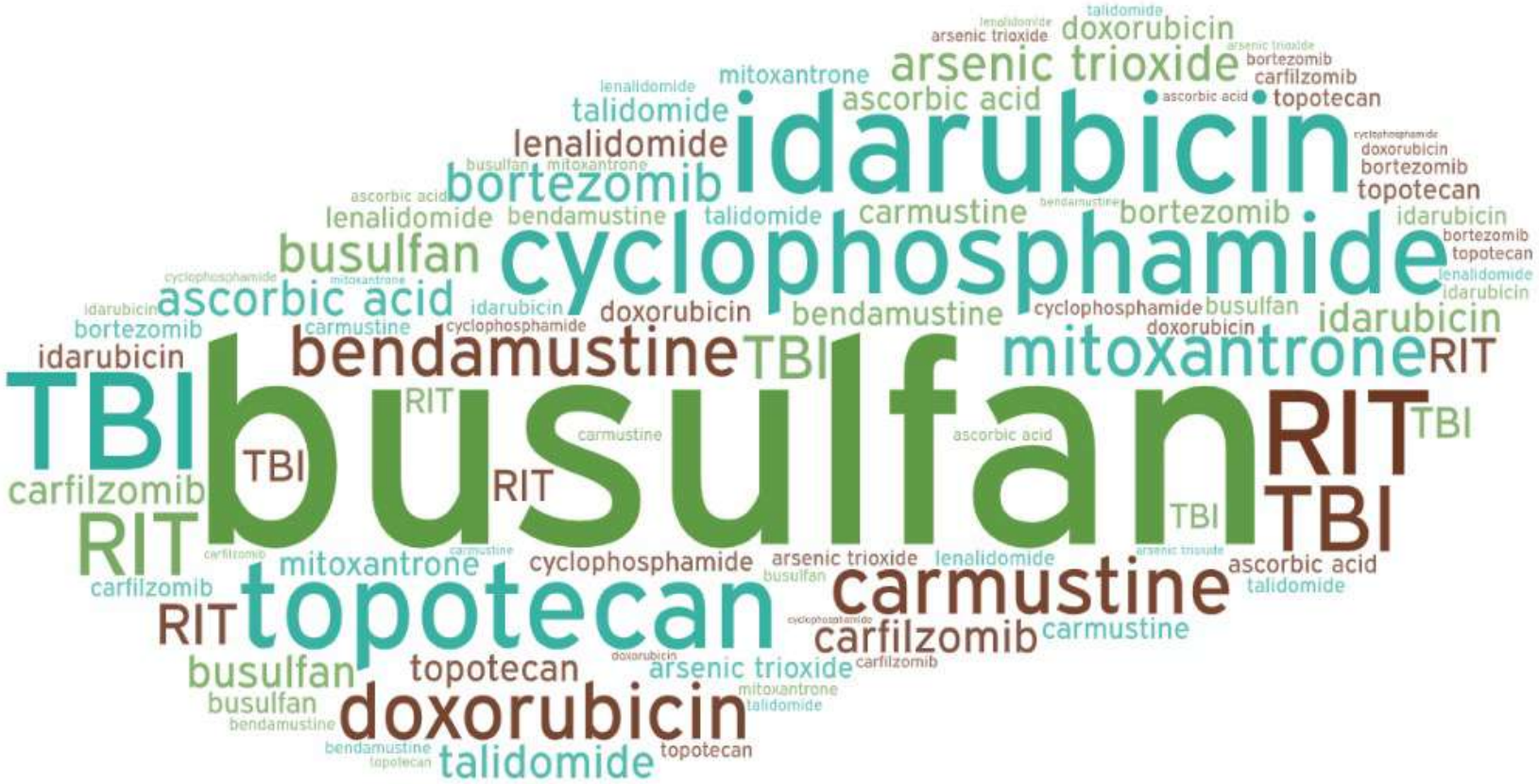
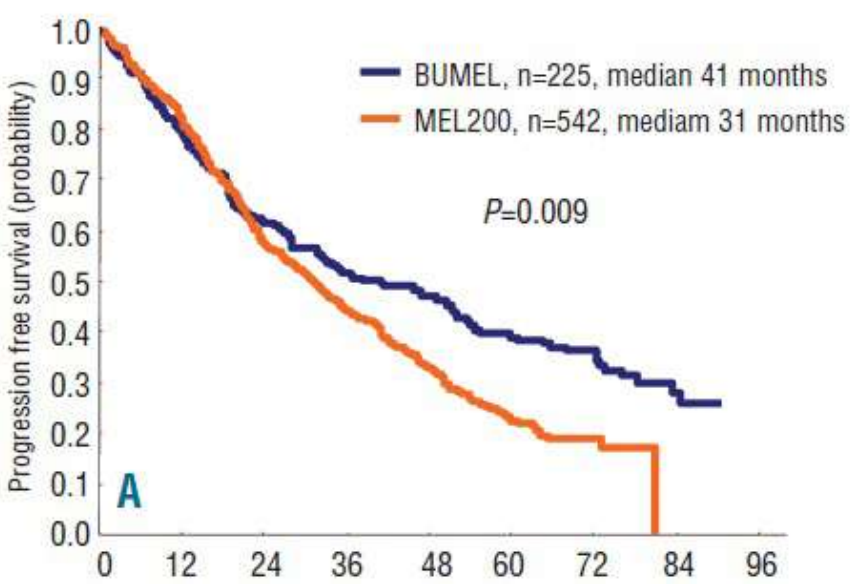
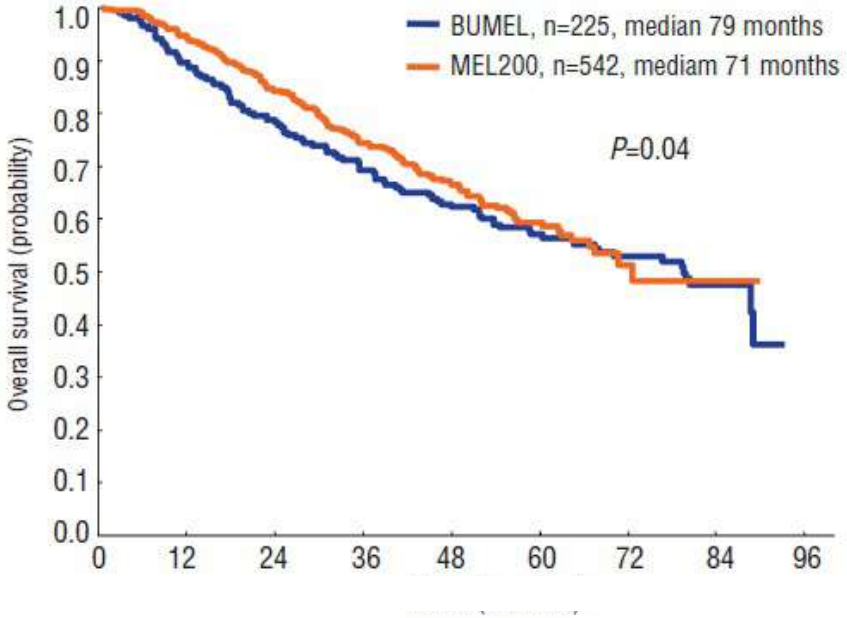


haematologica | 2010; 95(11)

JJ. Lahuerta *et al.*

Busulfan 12 mg/kg plus melphalan 140 mg/m² *versus* melphalan 200 mg/m² as conditioning regimens for autologous transplantation in newly diagnosed multiple myeloma patients included in the PETHEMA/GEM2000 study





Busulfan and VOD: from oral to i.v. formulation

Table 2. Non-hematologic toxicity (excluding VOD) due to high-dose regimens.

	Grade I		Grade II		Grade III		Grade IV*		
	BUMEL	MEL200	BUMEL	MEL200	BUMEL	MEL200	BUMEL	MEL200	II/III differences
	n (%)								*P*
Cardiac	2 (0.8)	2 (0.3)	3 (1.3)	8 (1.4)	–	7 (1.2)	–	2 (0.3)	0.2
Renal	–	2 (0.3)	3 (1.3)	8 (1.4)	3 (1.3)	3 (0.5)	–	–	0.2
Pulmonary	–	1 (0.1)	1 (0.4)	2 (0.3)	1 (0.1)	3 (0.5)	–	–	0.6
Hepatic	10 (4.4)	9 (1.6)	6 (2.6)	1 (0.1)	1 (0.1)	–	–	–	0.0004
Central nervous system	–	1(0.1)	2 (0.8)	5 (0.9)	–	1 (0.1)	–	–	0.7
Stomatitis	19 (8.4)	53 (9.7)	73 (32.4)	141 (26.0)	21 (9.3)	34 (6.7)	–	–	0.01
Gastrointestinal	5 (2.2)	45 (8.3)	10 (4.4)	34 (6.7)	2 (0.8)	11 (2.0)	–	–	0.09

**Fatal toxicity.VOD: veno-occlusive disease; BUMEL: oral busulfan 1 mg/kg/8 h plus melphalan 140 mg/m²; MEL200: 200 mg/m².*

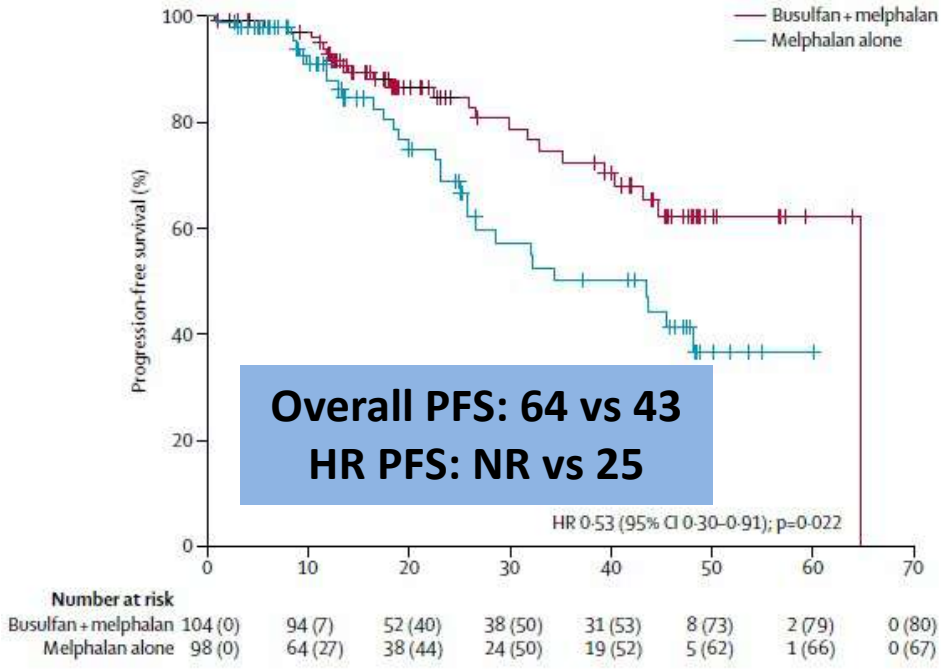
Lahuerta, 2010

BuMel vs Mel alone: a randomized, phase 3 trial

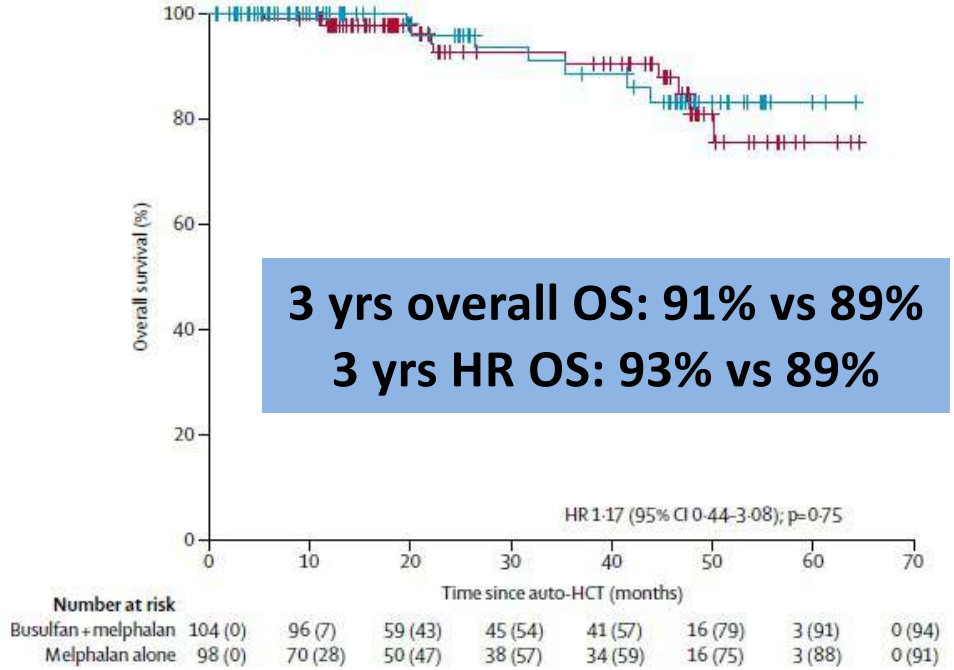
Day	-8	-7	-6	-5	-4	-3	-2	-1
BuMel								
Bu test dose	32 mg/mq							
Bu PK adjusted		*	*	*	*			
Mel 70 mg/mq							*	*
Mel alone								
Mel 200 mg/mq							*	

Bashir, 2019

BuMel vs Mel alone: PFS and OS



Overall PFS: 64 vs 43
HR PFS: NR vs 25



3 yrs overall OS: 91% vs 89%
3 yrs HR OS: 93% vs 89%

Bashir, 2019

	All patients (n=202)	Busulfan plus melphalan (n=104)	Melphalan alone (n=98)	p value
Overall				
None	0	0	0	<0·0001
Grade 1	17 (8%)	1 (1%)	16 (16%)	..
Grade 2	66 (33%)	16 (15%)	50 (51%)	..
Grade 3	118 (58%)	86 (83%)	32 (33%)	..
Grade 4	1 (<1%)	1 (1%)	0	..
Diarrhoea				
None	67 (33%)	45 (43%)	22 (22%)	0·056
Grade 1	107 (53%)	44 (42%)	63 (64%)	..
Grade 2	21 (10%)	11 (11%)	10 (10%)	..
Grade 3	7 (3%)	4 (4%)	3 (3%)	..
Mucositis				
None	54 (27%)	4 (4%)	50 (51%)	<0·0001
Grade 1	57 (28%)	23 (22%)	34 (35%)	..
Grade 2	76 (38%)	62 (60%)	14 (14%)	..
Grade 3	15 (7%)	15 (14%)	0	..
Nausea				
None	9 (4%)	7 (7%)	2 (2%)	0·91
Grade 1	51 (25%)	22 (21%)	29 (30%)	..
Grade 2	136 (67%)	71 (68%)	65 (66%)	..
Grade 3	6 (3%)	4 (4%)	2 (2%)	..
ALT				
None	167 (83%)	70 (67%)	97 (99%)	<0·0001
Grade 1	25 (12%)	24 (23%)	1 (1%)	..
Grade 2	7 (3%)	7 (7%)	0	..
Grade 3	3 (1%)	3 (3%)	0	..
AST				
None	200 (99%)	103 (99%)	97 (99%)	1·00
Grade 1	1 (0·5%)	0	1 (1%)	..
Grade 2	1 (0·5%)	1 (1%)	0	..
Grade 3	0	0	0	..
Bilirubin				
None	182 (90%)	94 (90%)	88 (90%)	1·00
Grade 1	9 (4%)	5 (5%)	4 (4%)	..
Grade 2	9 (4%)	3 (3%)	6 (6%)	..
Grade 3	2 (1%)	2 (2%)	0	..
Neutropenic fever				
None	99 (49%)	30 (29%)	69 (70%)	<0·0001
Grade 1	1 (0·5%)	1 (1%)	0	..
Grade 2	0	0	0	..
Grade 3	102 (51%)	73 (70%)	29 (30%)	..

Data are n (%). ALT=alanine aminotransferase. AST=aspartate aminotransferase.

Table 2: **Non-haematological toxicity**

Non-haematological toxicity

- **Overall incidence of grade 2-4 non-haematological toxicity was higher in the BuMel arm**
- **No grade 4 mucositis, 14% grade 3 mucositis**
- **Reversible AE; patients fully recovered**
- **No TRM at day 100**
- **Absence of VOD**
- **SPM: one patient per arm**

Bashir, 2019

BuMel vs Mel alone: conclusions

- **busulfan administration was pharmacokinetically adjusted**
- **HR PFS: NR vs 25 m**
- **induction and maintenance were not homogeneous in the protocol**
- **poorer quality of life reported by patients in BuMel arm**
- **minimal residual disease was not assessed**
- **no benefit in overall survival has been reported so far; maybe a longer FU is needed**
- **why such an impressive improvement in progression-free survival was observed in the absence of a higher complete response?**

Bashir, 2019

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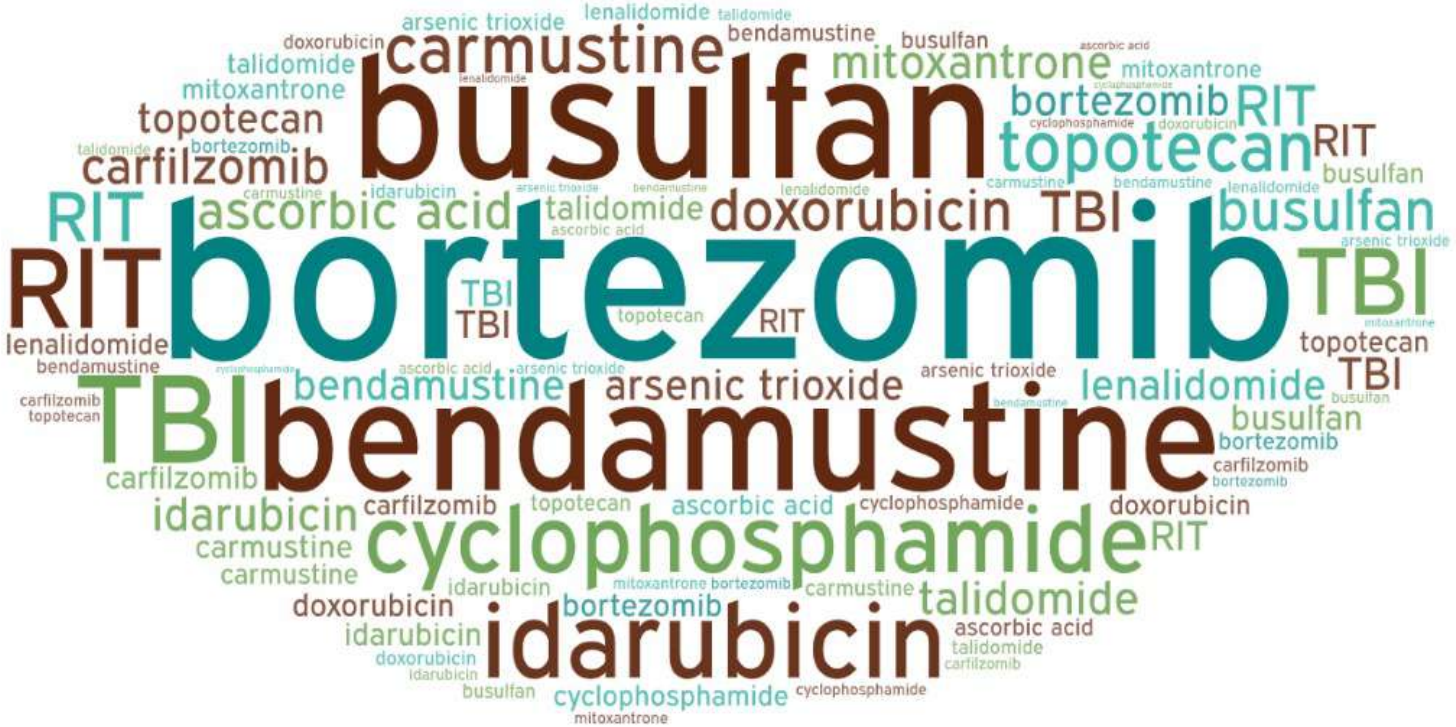
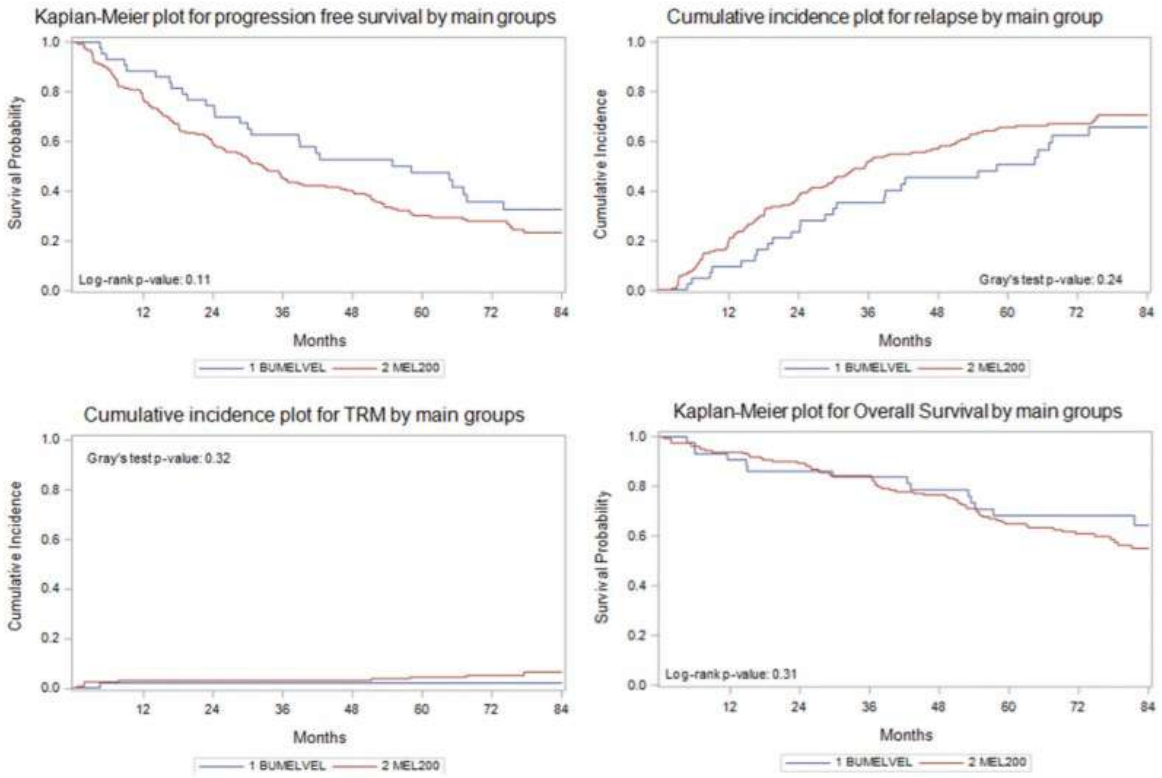


BuMelVel vs Mel alone: a phase II trial

Day	-6	-5	-4	-3	-2	-1
BuMelVel						
Bu test dose	130 mg/mq	130 mg/mq				
Bu PK adjusted			*	*		
Mel 70 mg/mq					*	*
Vel 1,6 mg/mq					*	*
Mel alone						
Mel 200 mg/mq					*	

Hagen, 2020

BuMelVel vs Mel alone



Hagen, 2020

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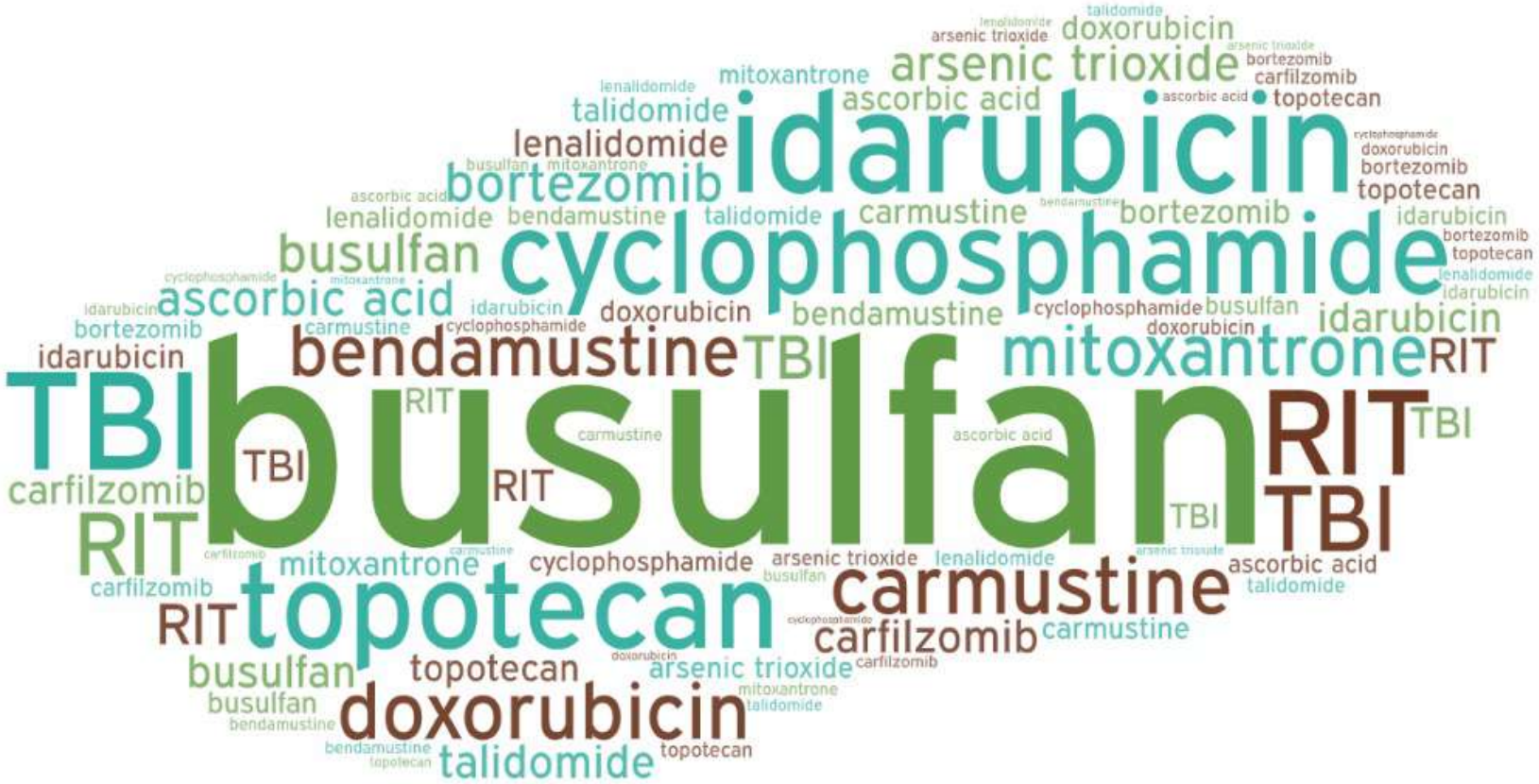

Conclusions

- small and retrospective studies, heterogenous patients, no MRD
- high-dose melphalan chemotherapy remains the standard conditioning therapy
- participation in clinical trials looking at improving the efficacy of conditioning with novel agent is preferred if available
- BuMel combination may offer an alternative to standard Mel 200; looking forward to phase III, randomized, multicentre study GEM 2012 results
- ideally we will need to stratify patients identifying prognostic biomarkers
- MM treatment is a complex strategy that integrates the use of novel agents in induction and consolidation/maintenance with high dose chemotherapy in conditioning

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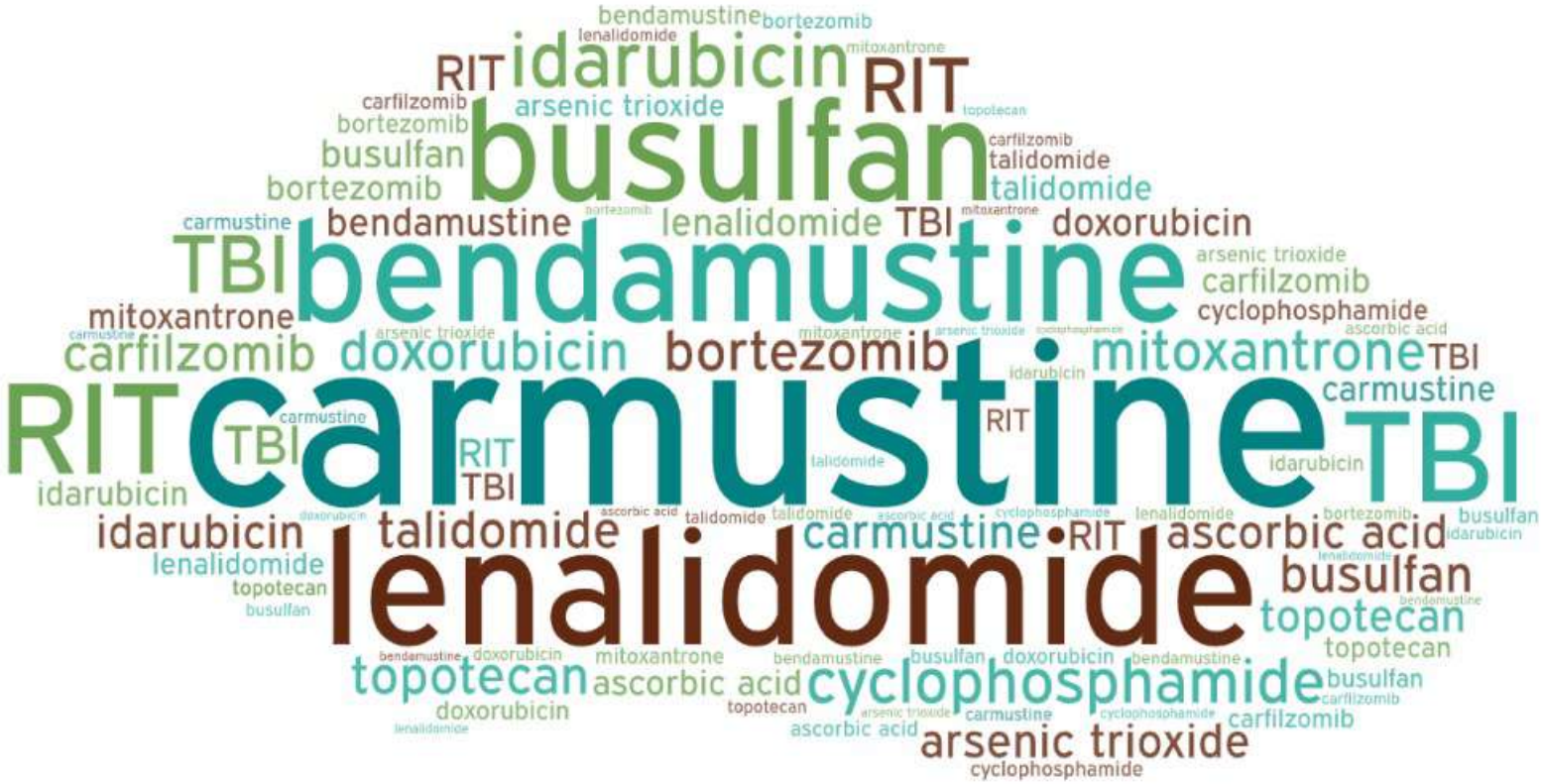
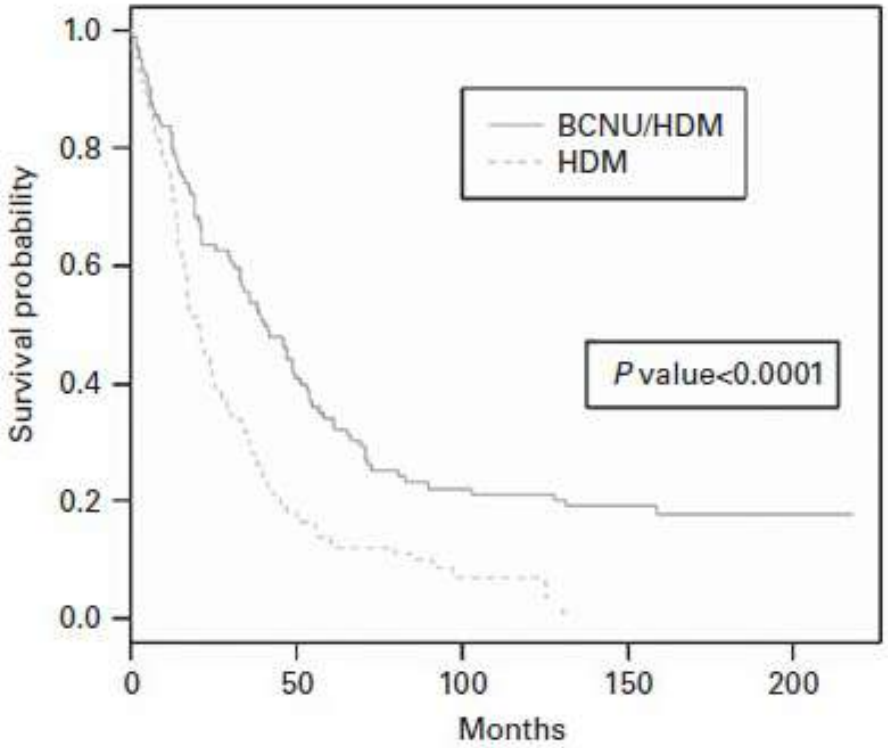
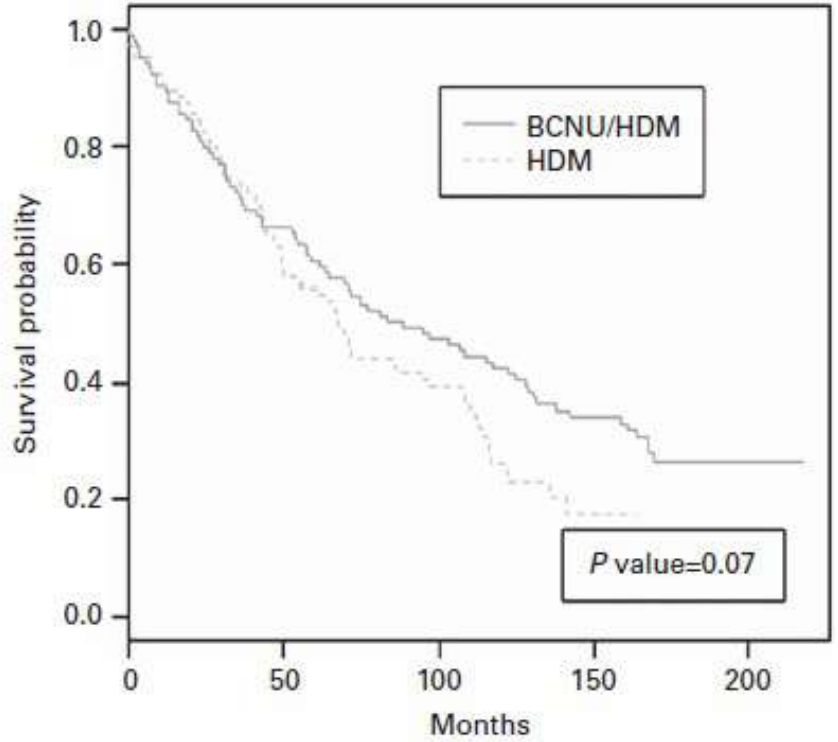


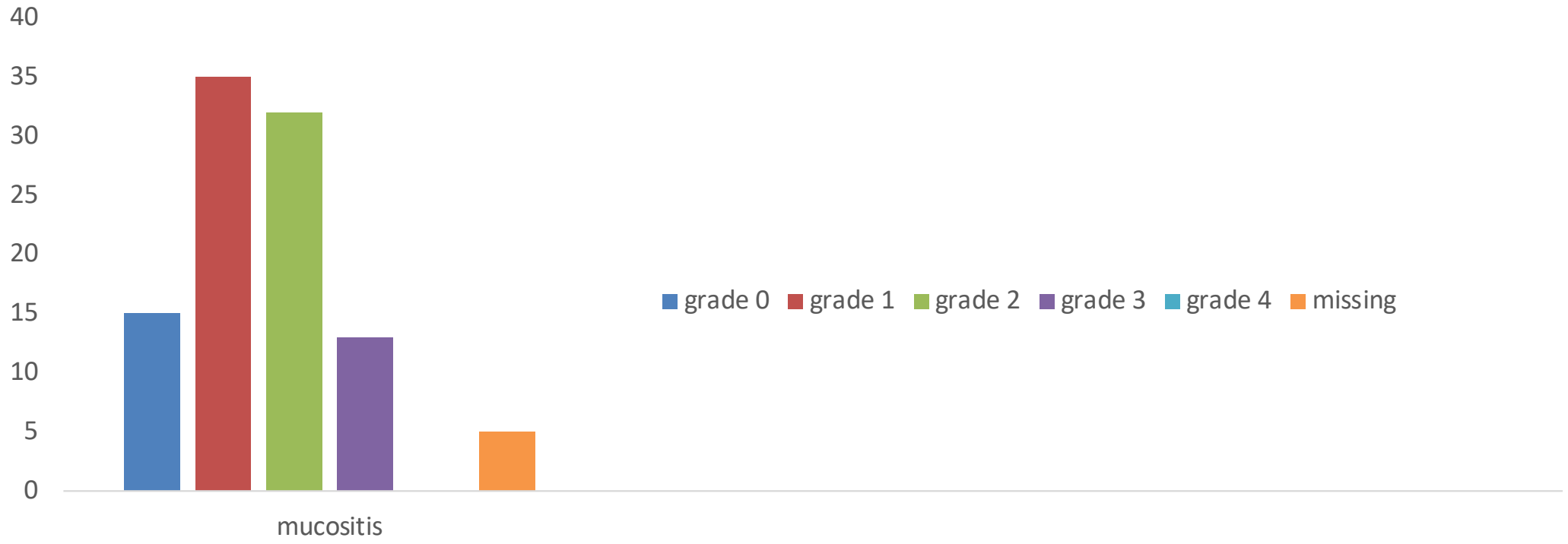
BCNU/Melphalan



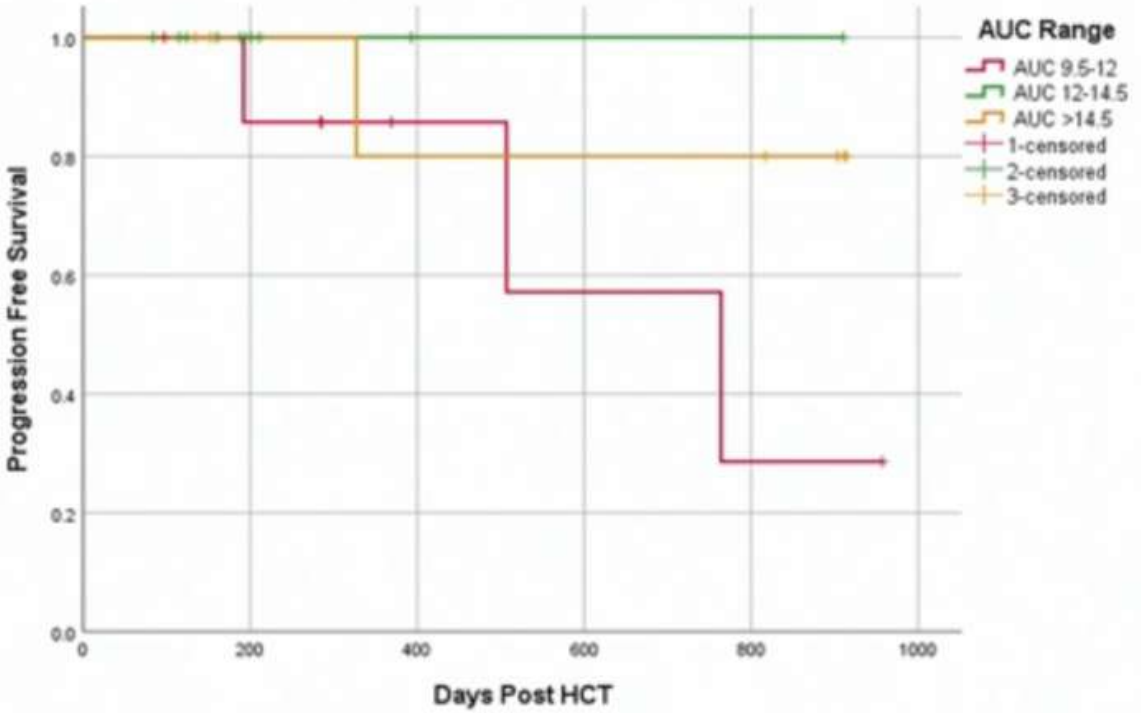


Saviraj, 2020

Worst mucositis results



PFS by AUC (n=25)



Shaw, 2012