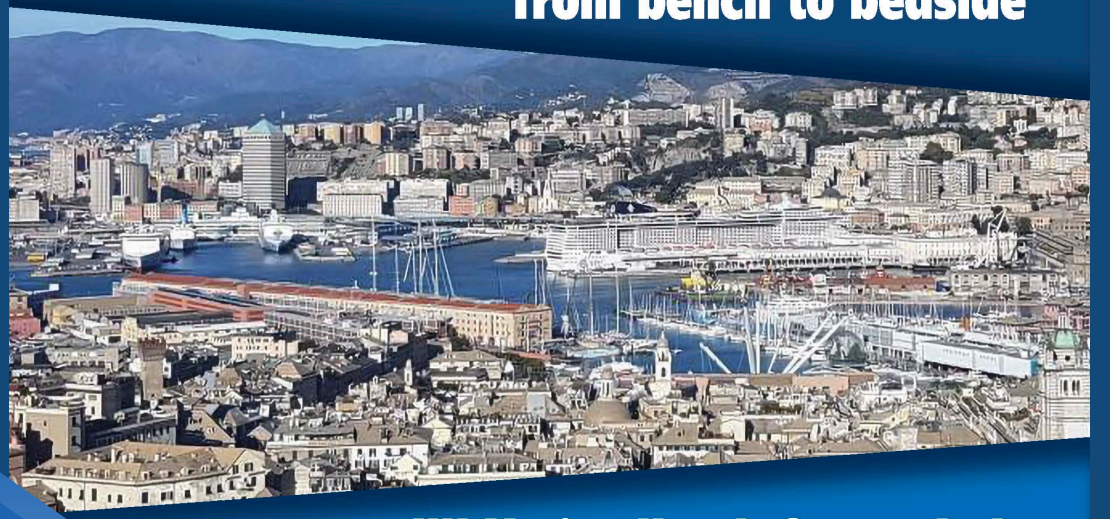
2023 Multiple Myeloma updates:
from bench to bedside



NH Marina Hotel, Genoa, Italy
20-21 November 2023

Dr.
Giuseppe Bertuglia

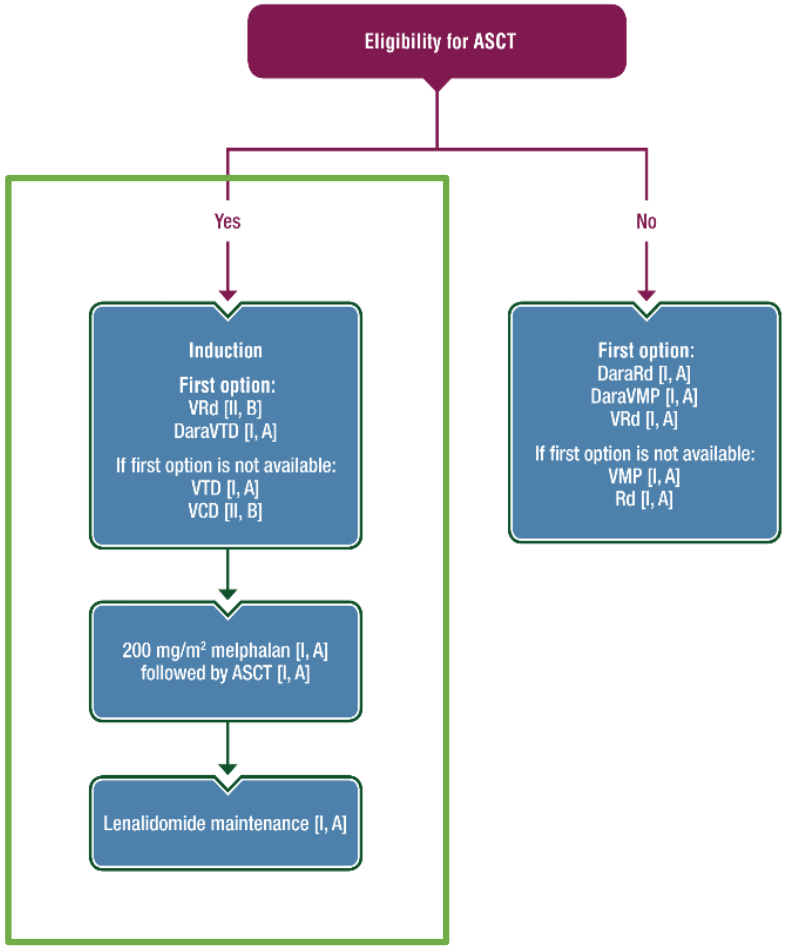
AOU Città della salute e della Scienza
University of Torino, Italy

FRONTLINE THERAPY FOR NEWLY DIAGNOSED YOUNG PATIENTS WITH MULTIPLE MYELOMA

AGENDA

1. What is the impact of the incorporation of anti-CD38 in the induction regimen?
2. Is there still a role of ASCT?
3. Is consolidation recommended?
4. What is the best strategy for maintenance?
5. What's the future?

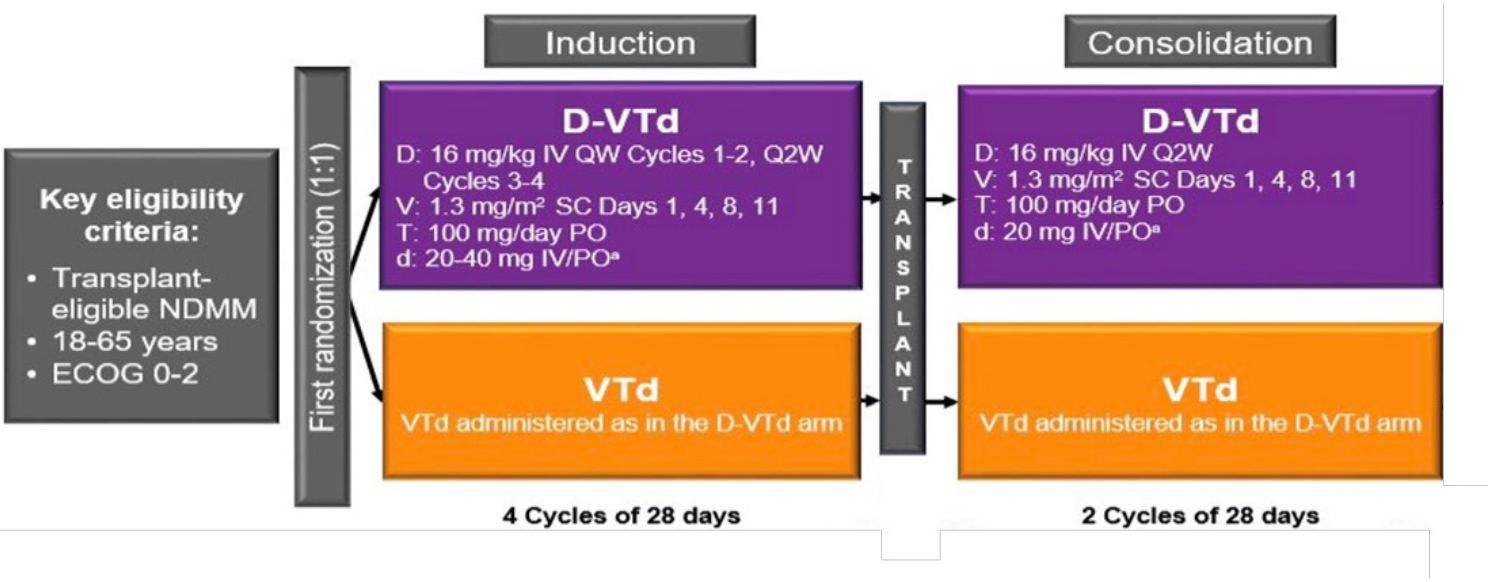
ESMO 2021



ESMO, European Society for Medical Oncology

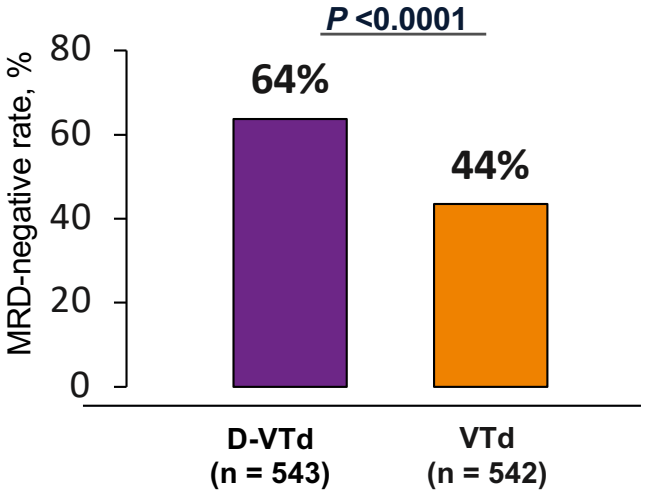
Dimopoulos MA et al. Ann Oncol. 2021 Mar;32(3):309-322.

CASSIOPEIA TRIAL: up-front use of anti-CD38



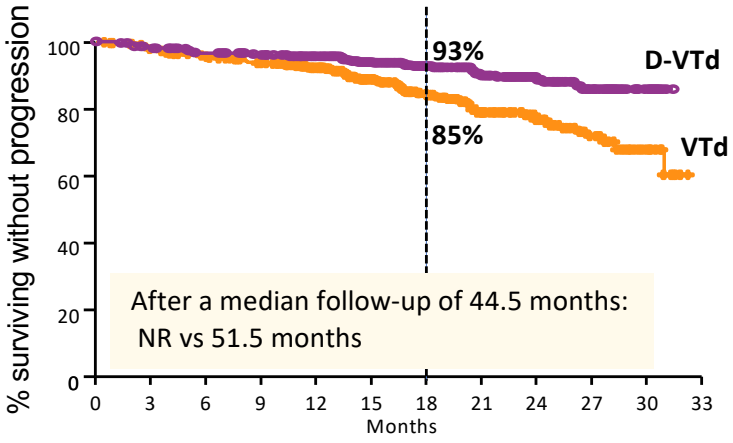
Median (range) follow-up: 18.8 (0.0-32.2) months

MRD (Flow Cytometry; 10^{-5})



PFS From First Randomization

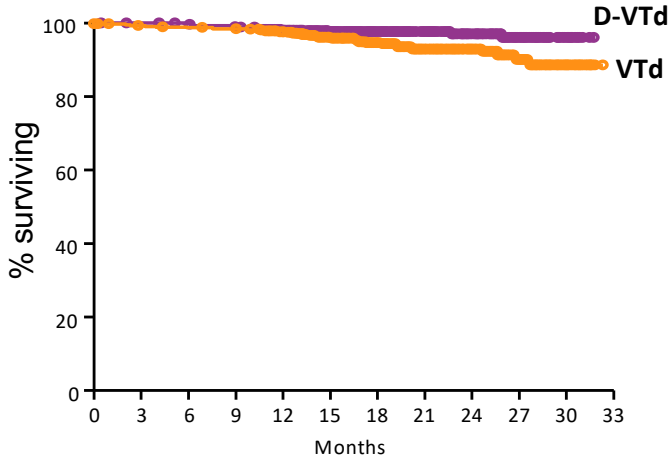
HR (95% CI) 0.47, p <0.0001



After a median follow-up of 44.5 months:
NR vs 51.5 months

OS analysis

18-m OS: 98% vs 95%



HR, hazard ratio; OS, overall survival; PFS, progression-free survival

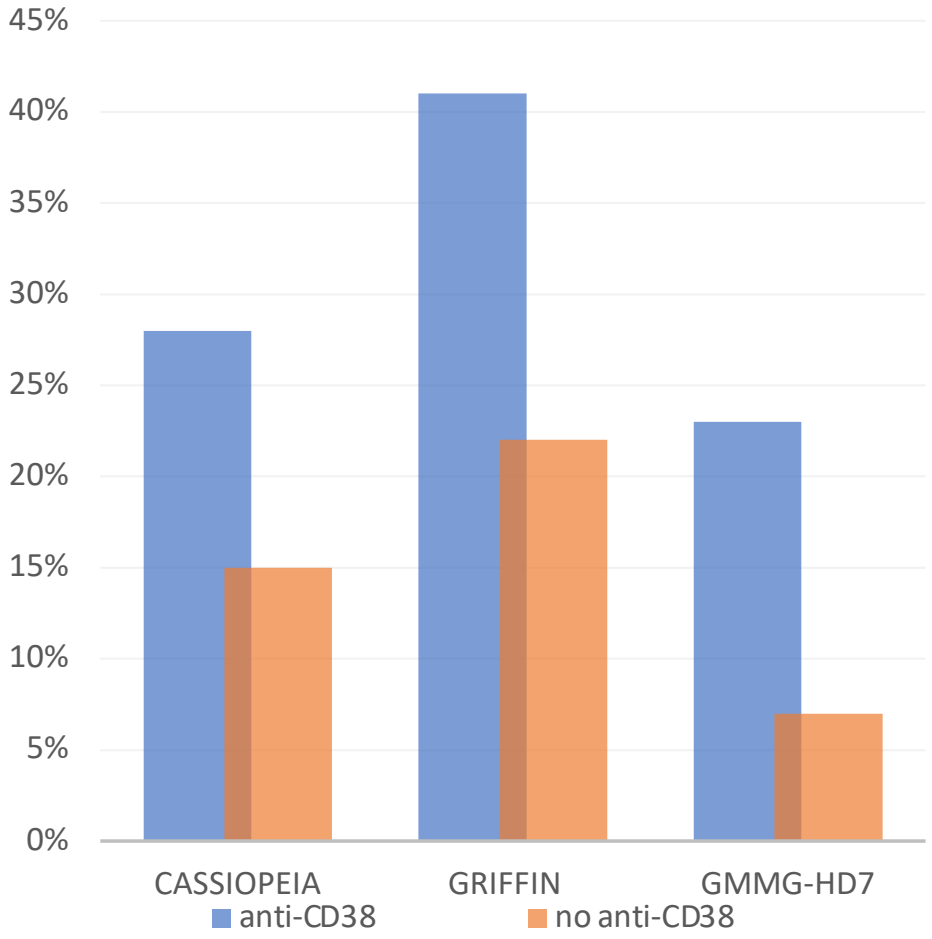
Moreau et al, CASSIOPEIA trial, Lancet 2019
Moreau et al, CASSIOPEIA trial, Lancet 2021

Up-front use of anti-CD38: impact on rate infection

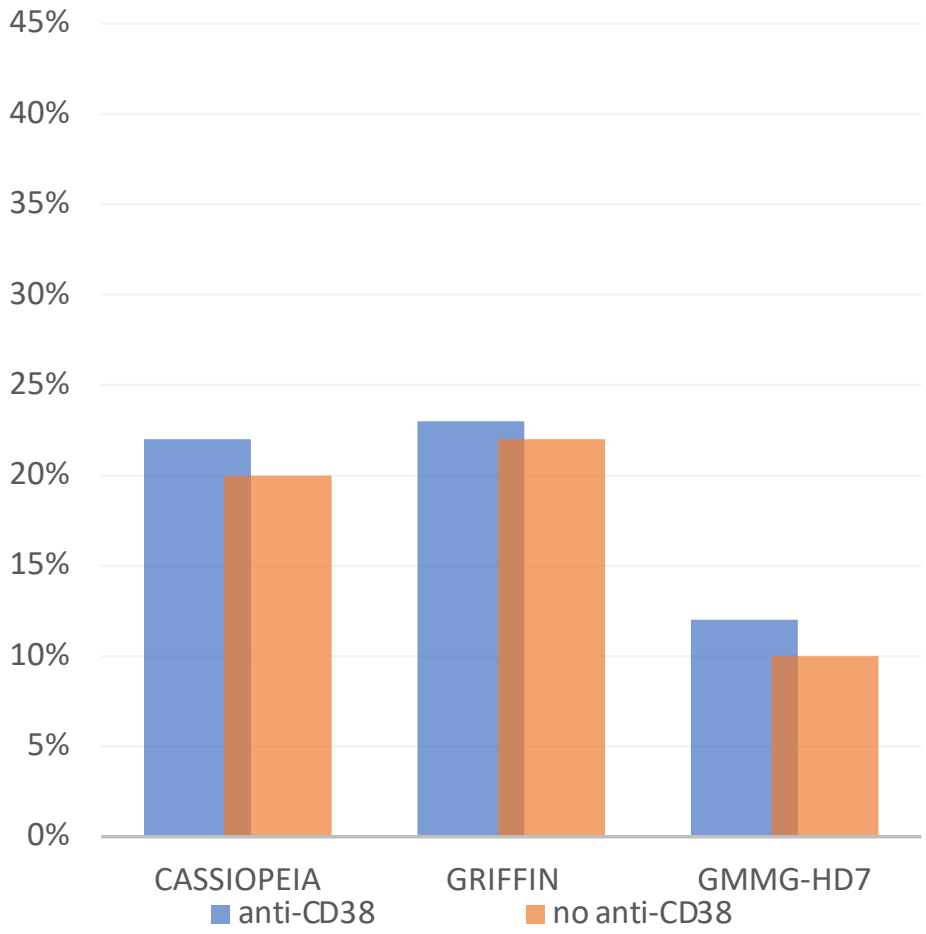
CASSIOPEIA[1]
DVTd vs VTd

GRIFFIN[2,3]
DVRd vs VRd

GMMG-HD7[4]
IsaVRd vs VRd



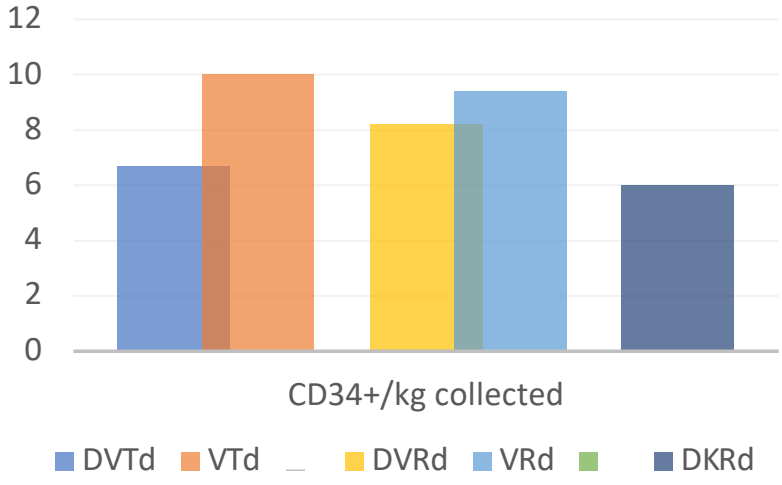
Incidence of ≥ grade 3 neutropenia



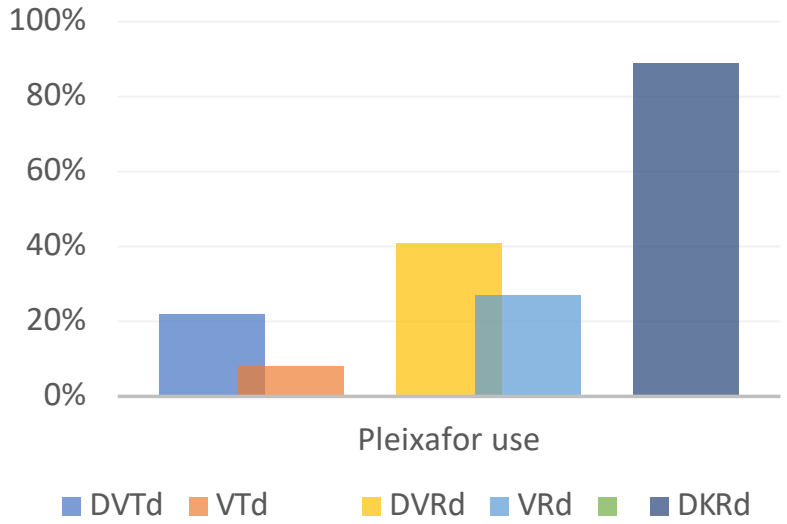
Incidence of ≥ grade 3 infection

1. Avet Loiseau H et al. ASCO 2019;abstract 8017 (oral presentation); 2. Voorhees P et al Blood 2020;136(8):936-945; 3. Sborov WD et al. IMS 2022;abstract OAB-057;4. Goldschmidt H et al. ASH 2021; abstract 463 (oral presentation)

Up-front use of anti-CD38: impact on stem cell mobilization



Hematopoietic stem cell yield



Use of plerixafor as rescue

- Anti-CD38 Moab regimens seem to impact on hematopoietic stem cell yield **(↓)** and the use of plerixafor **(↑)**
- Overall cost **(↑)**
- However, no significantly impact on transplant rates or hematopoeitic engraftment

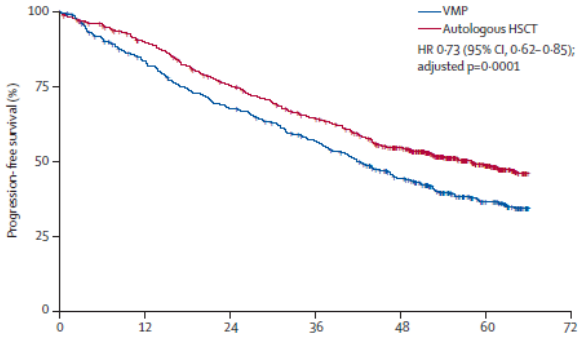
Hulin C et al., CASSIOPEIA study. Haematologica. 2021
S. Chhabra et al., MASTER & GRIFFIN Transplantation and Cellular Therapy 29 (2023)

The role of ASCT: PFS benefits

EMN-02/HO95

Median follow-up: 60 months

VCd x 4 → HDM-ASCT / VMP x 4 → VRd x 2 / No consolidation → R until progression

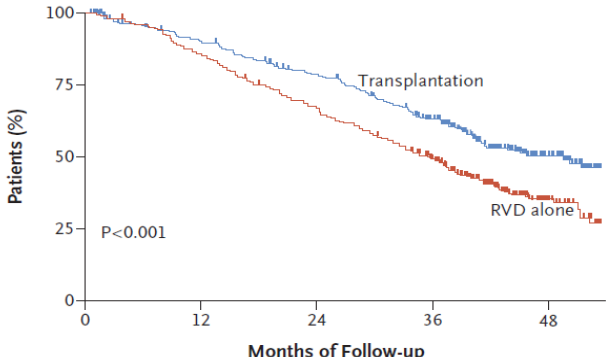


mPFS: **56.7 months** in the ASCT group vs. **41.9 months** in the VMP group

IFM-2009

Median follow-up: 43-44 months

VRd x 3 / VRd x 3 → HDM-ASCT / VRD x 2 / VRd x 5 → R 1 year

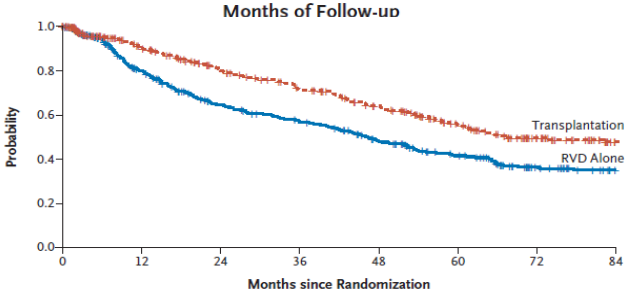


mPFS: **50 months** in the ASCT group vs. **36 months** in the RVD-alone group

DETERMINATION

Median follow-up: 76 months

VRd x 1 → VRd x 2 / HDM-ASCT / VRd x 2 / VRd x2 / VRd x 5 → R until progression



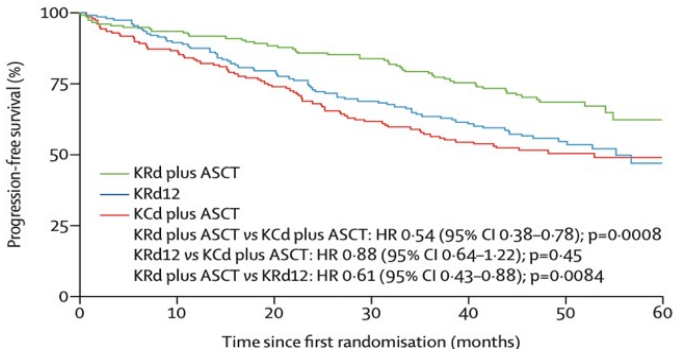
mPFS: 67.5 months in the ASCT group and **46.2 months** in the RVD-alone group

FORTE

Median follow-up: 51 months

KRd x 4 / HDM-ASCT / KRd x 4 → KRd x 4 / KRd x 8 → KR maintenance

KCd x 4 / HDM-ASCT / KCd x 4 → R maintenance



4-y PFS: **69%** in the ASCT group and **56%** in the KRD12 group
mPFS: **NR** vs 55 months

HDM, high-dose melphalan; ASCT, autologous stem-cell transplantation; K, carfilzomib; R, lenalidomide; d, dexamethasone; C, cyclophosphamide; R, lenalidomide, V, bortezomib, KRd plus ASCT, 4 KRD induction cycles, MEL200-ASCT, 4 KRd consolidation cycles; ; KRd12, 12 KRd cycles; HR, hazard ratio; CI, confidence interval; p, p-value; Nr, not reached; PFS, progression free survival

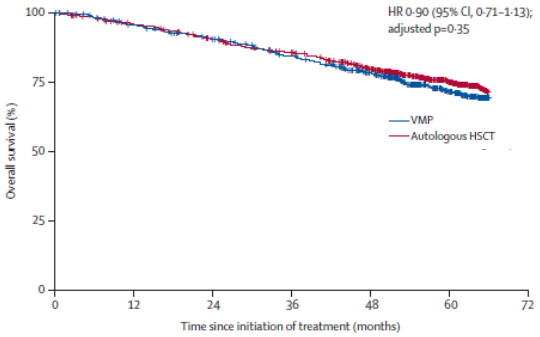
Cavo et al., EMN02, Lancet 2020; Gay F et al., FORTE trial, Lancet Oncol 2021; Attal M et al., IFM-2009, N Engl J Med 2017; Richardson P et al., DETERMINATION study, N Engl J Med 2022

The role of ASCT: OS benefits

EMN-02/HO95

Median follow-up: 60 months

VCd x 4 → HDM-ASCT / VMP x 4 → VRd x 2 / No consolidation → R until progression

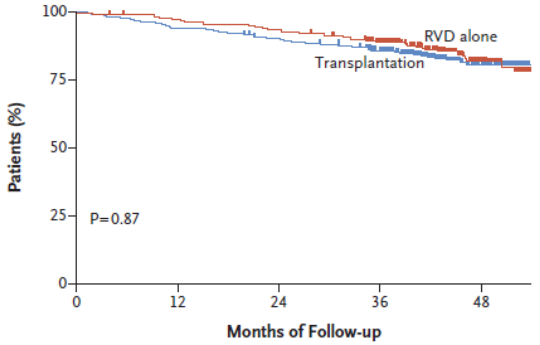


5-year OS: **75.1%** for ASCT vs.**71·6%**

IFM-2009

Median follow-up: 43-44 months

VRd x 3 / VRd x 3 → HDM-ASCT / VRD x 2 / VRd x 5 → R 1 year

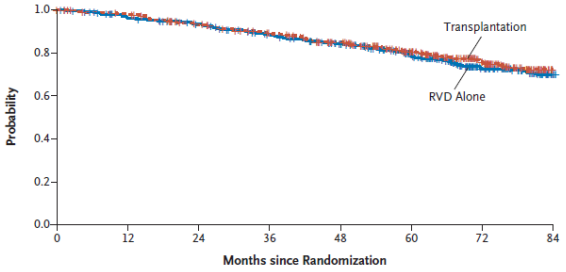


4-y OS: **81%** in the ASCT group vs. **82%** in the RVD-alone group
mOS: **NR** vs **NR**

DETERMINATION

Median follow-up: 76 months

VRd x 1 → VRd x 2 / HDM-ASCT / VRd x 2 / VRd x2 / VRd x 5 → R until progression

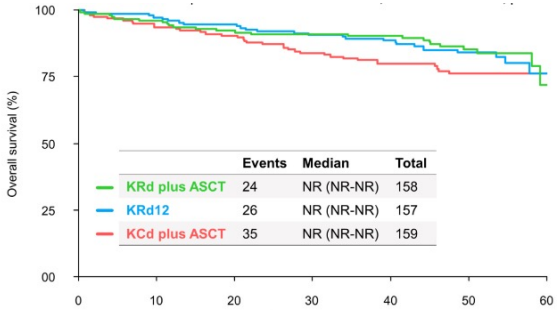


Estimated 5-y OS: **80.7%** in the ASCT group vs. **79.2%** in the RVD-alone group

FORTE

Median follow-up: 51 months

KRd x 4 / HDM-ASCT / KRd x 4 → KRd x 4 / KRd x 8 → KR maintenance
KCd x 4 / HDM-ASCT / KCd x 4 → R maintenance



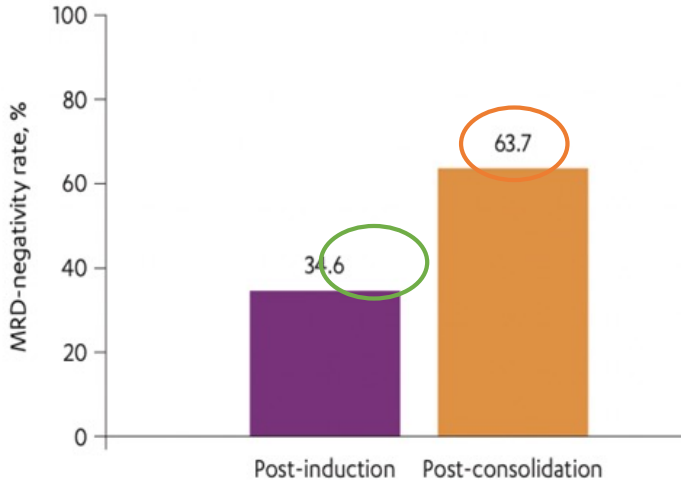
4-y OS: **86%** with KRd plus ASCT vs. **85%** with KRd12

HDM, high-dose melphalan; ASCT, autologous stem-cell transplantation; K, carfilzomib; R, lenalidomide; d, dexamethasone; C, cyclophosphamide; R, lenalidomide, V, bortezomib, KRd plus ASCT, 4 KRD induction cycles, MEL200-ASCT, 4 KRd consolidation cycles; ; KRd12, 12 KRd cycles; HR, hazard ratio; CI, confidence interval; p, p-value; Nr, not reached; PFS, progression free survival

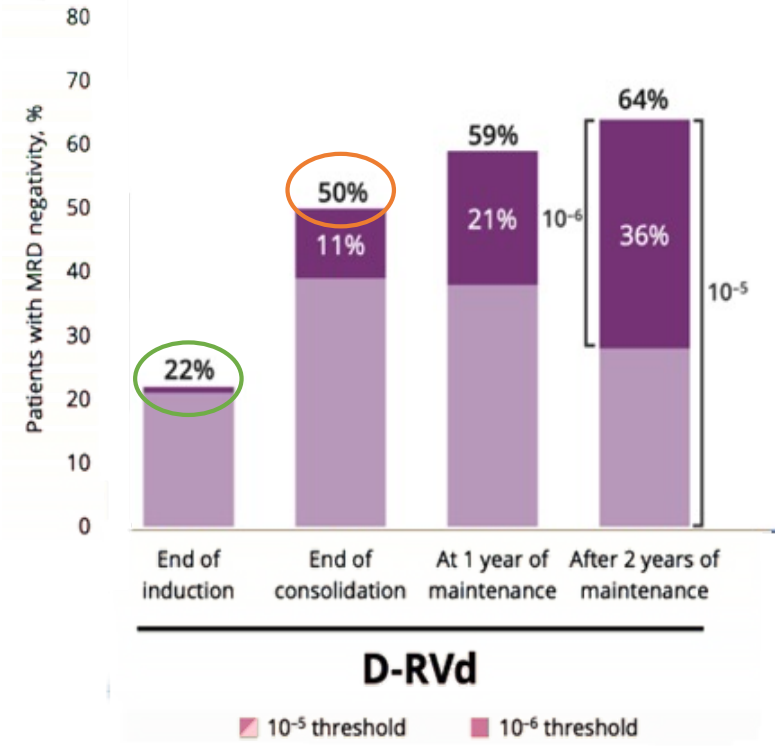
Cavo et al., EMN02, Lancet 2020; Gay F et al., FORTE trial, Lancet Oncol 2021; Attal M et al., IFM-2009, N Engl J Med 2017; Richardson P et al., DETERMINATION study, N Engl J Med 2022

HDM-ASCT incorporated in 4-drug, induction and consolidation regimens increased the rates of MRD negativity

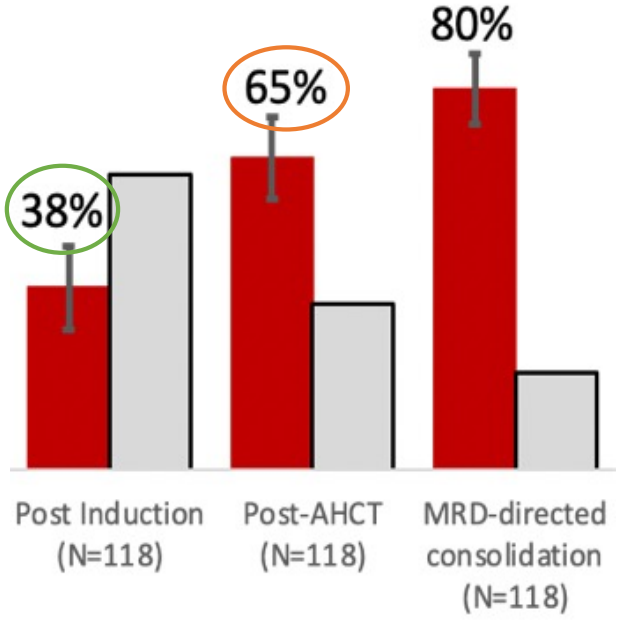
CASSIOPEIA Dara-VTd



GRIFFIN Dara-VRd



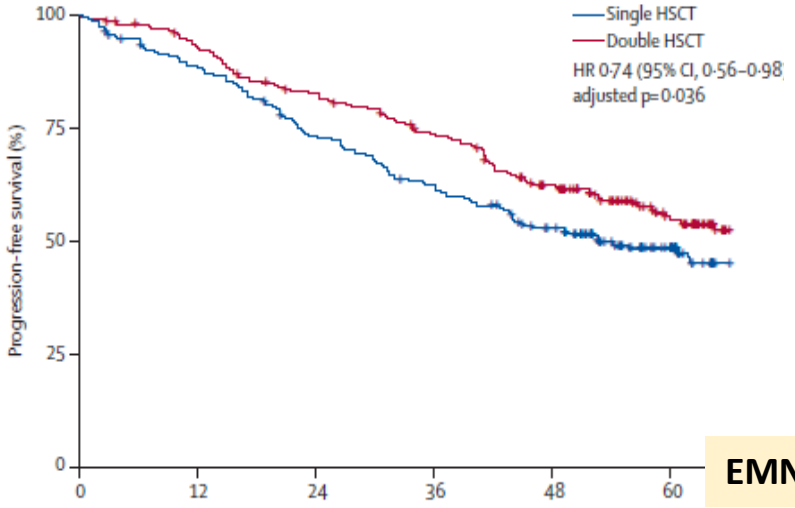
MASTER Dara-KRd

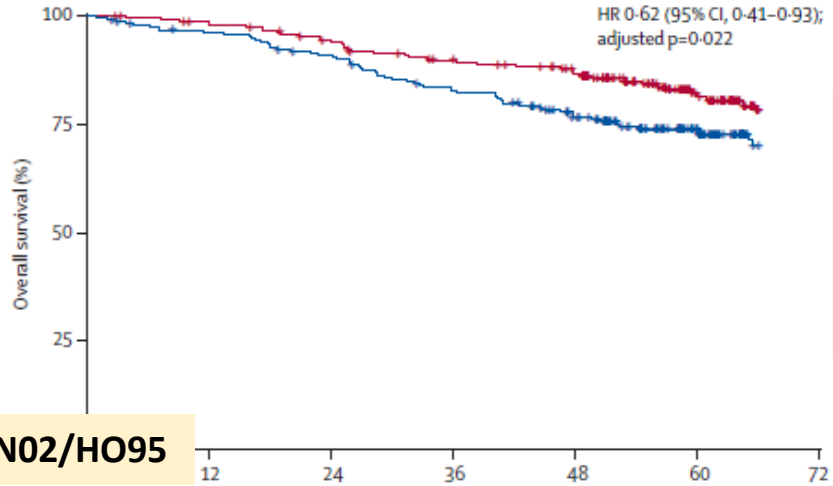


HDM, high-dose melphalan; ASCT, autologous stem-cell transplantation; MRD, minimal residual disease; Dara, D, daratumumab; V, bortezomib; T, thalidomide; d, dexamethasone; R, lenalidomide; K, carfilzomib.

Avet-Loiseau H. et al. Blood. 2021; 138(s1): 82 [abstract, ASH 2021]; Laubach JP et al. Blood. 2021; 138(s1): 79 [abstract, ASH 2021]; Costa LJ et al. Blood. 2021; 138(s1): 481 [abstract, ASH 2021].

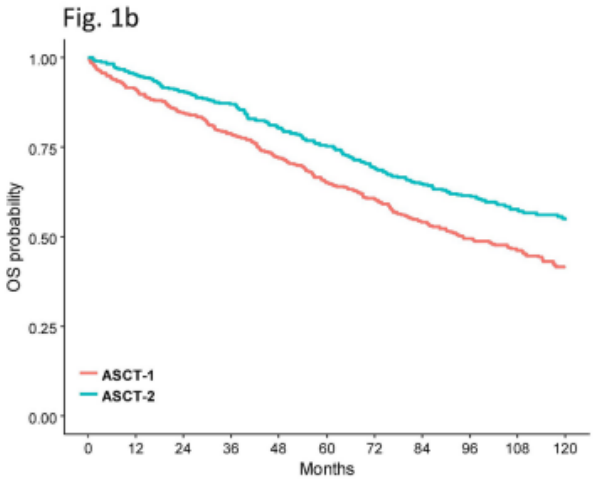
What about the role TANDEM ASCT?

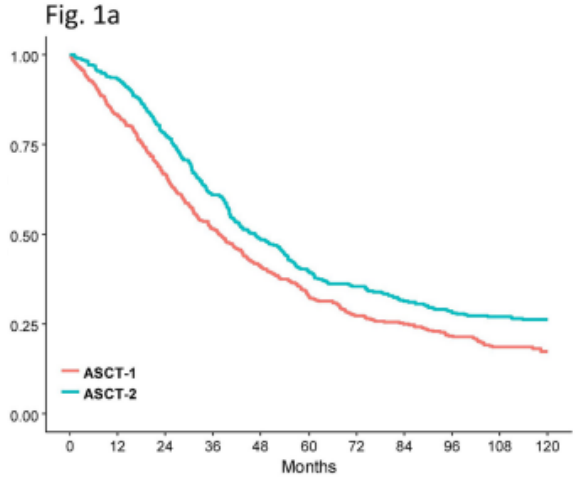




EMN02/HO95

Tandem-ASCT appears to be feasible option especially for patients with high-risk MM

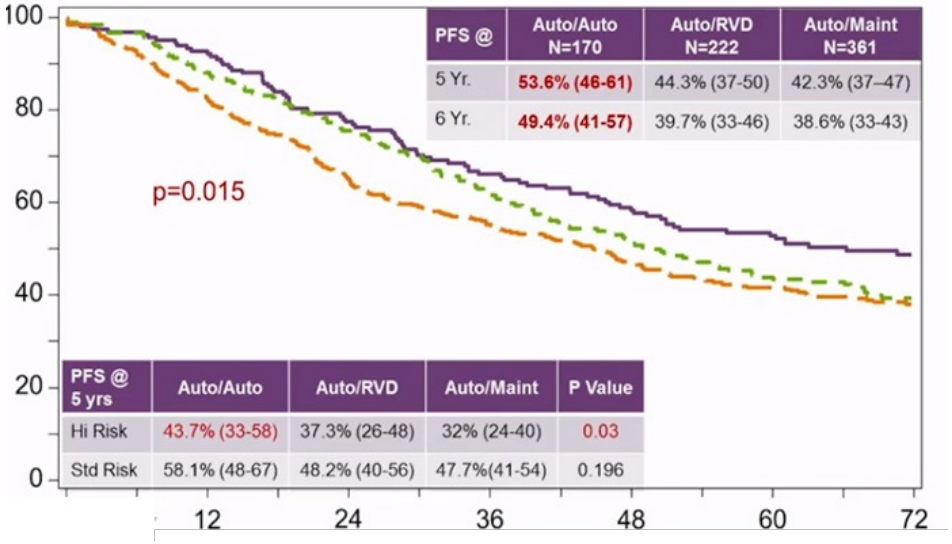




mPFS: 47 vs 38 mo;
HR 0.76, 95%CI=0.65-0.89, p=0.0008

estimated 10-yr OS: 58% vs 47%;
HR 0.69, CI 0.56-0.84, p=0.0002

STAMINA



PFS @	Auto/Auto N=170	Auto/RVD N=222	Auto/Maint N=361
5 Yr.	53.6% (46-61)	44.3% (37-50)	42.3% (37–47)
6 Yr.	49.4% (41-57)	39.7% (33-46)	38.6% (33-43)

PFS @ 5 yrs	Auto/Auto	Auto/RVD	Auto/Maint	P Value
Hi Risk	43.7% (33-58)	37.3% (26-48)	32% (24-40)	0.03
Std Risk	58.1% (48-67)	48.2% (40-56)	47.7%(41-54)	0.196

ultra high-risk pts

mPFS: 35 vs 14 mos; HR 0.45, CI 0.21-0.79; p=0.008)
estimated 10-yr OS: 26% vs 6%, HR 0.44, CI 0.21-0.90; p=0.025)

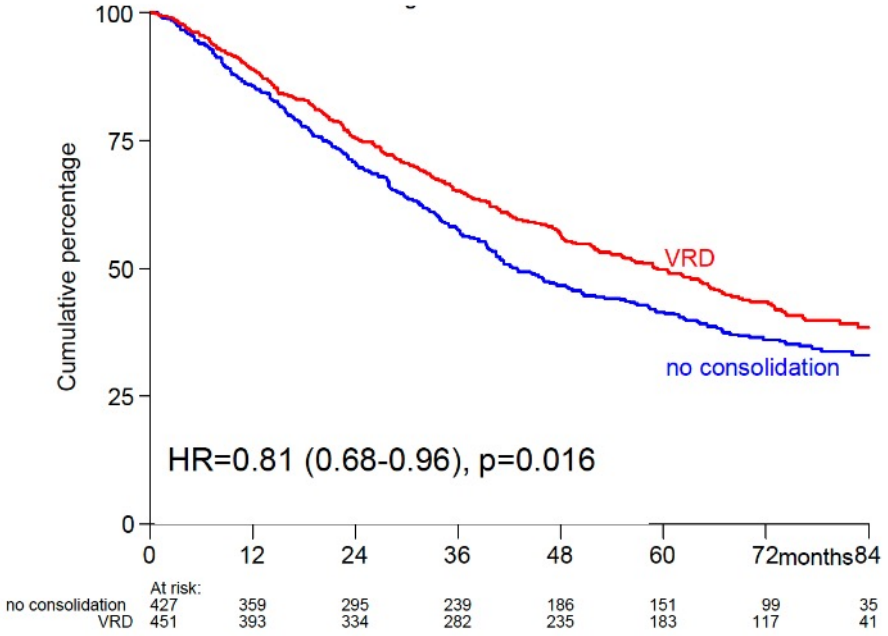
d, dexamethasone; R, lenalidomide; V, bortezomib; ASCT, autologous stem cell transplantation, HR, hazard ratio; p, p value

Cavo et al., single vs. double ASCT, Blood 2018
Hari P, et al. Long term follow of STaMina study, JCO 2020

Is there a role for consolidation in the current treatment scenario?

Median follow-up from R2: 71.3 months

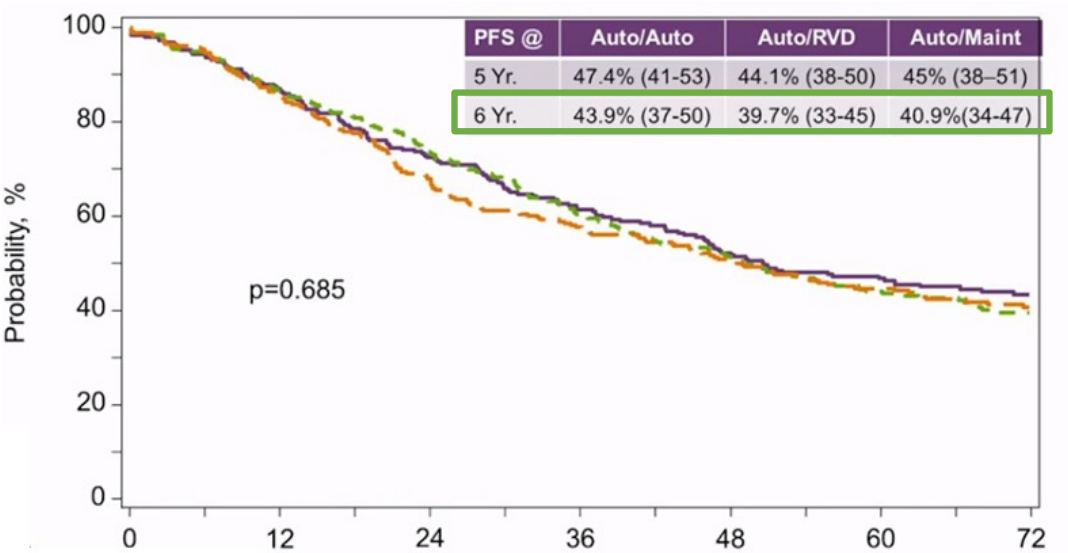
EMN02/HO95: VRd x 2 cycles vs no consolidation
Progression-free survival



5-year PFS: 50% with consolidation vs. 42% no consolidation
mPFS: 59 vs. 43 months

Median follow-up from R2: 76 months

STAMINA: VRd x 4 cycles vs no consolidation
Progression-free survival

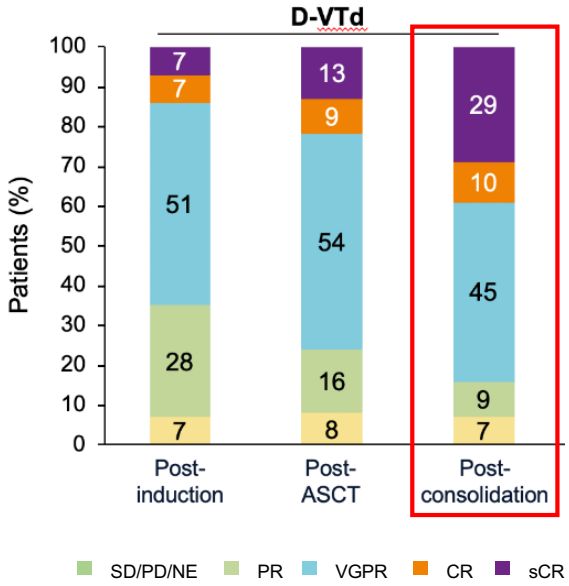


d, dexamethasone; R, lenalidomide; V, bortezomib; ASCT, autologous stem cell transplantation, HR, hazard ratio; p, p value

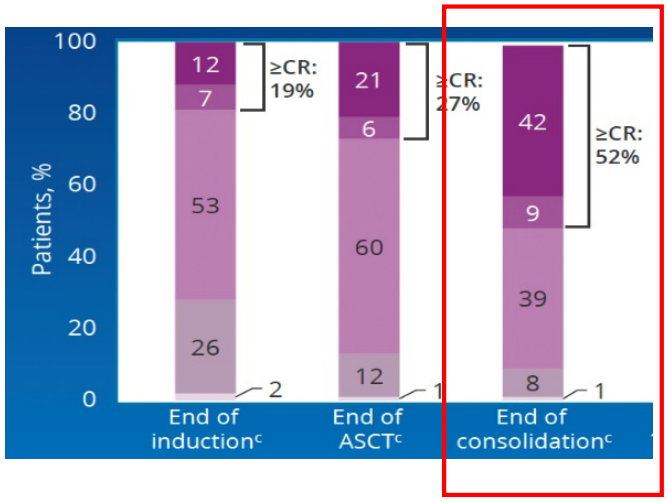
Sonneveld P et al. ASH 2020;abstract 550 (oral presentation); Hari P, et al. Long term follow of STaMina study, JCO 2020

Post-ASCT consolidation improved response rates: a matter of when or for how long?

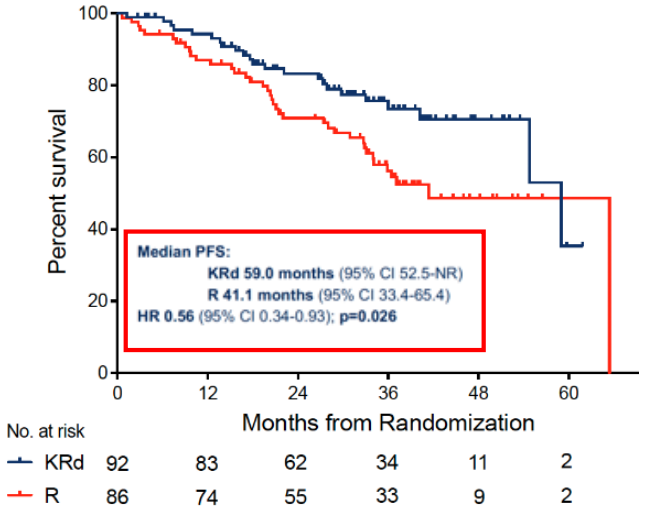
DVTd vs VTd consolidation: CASSIOPEIA study



DVRd vs VRd consolidation: GRIFFIN study



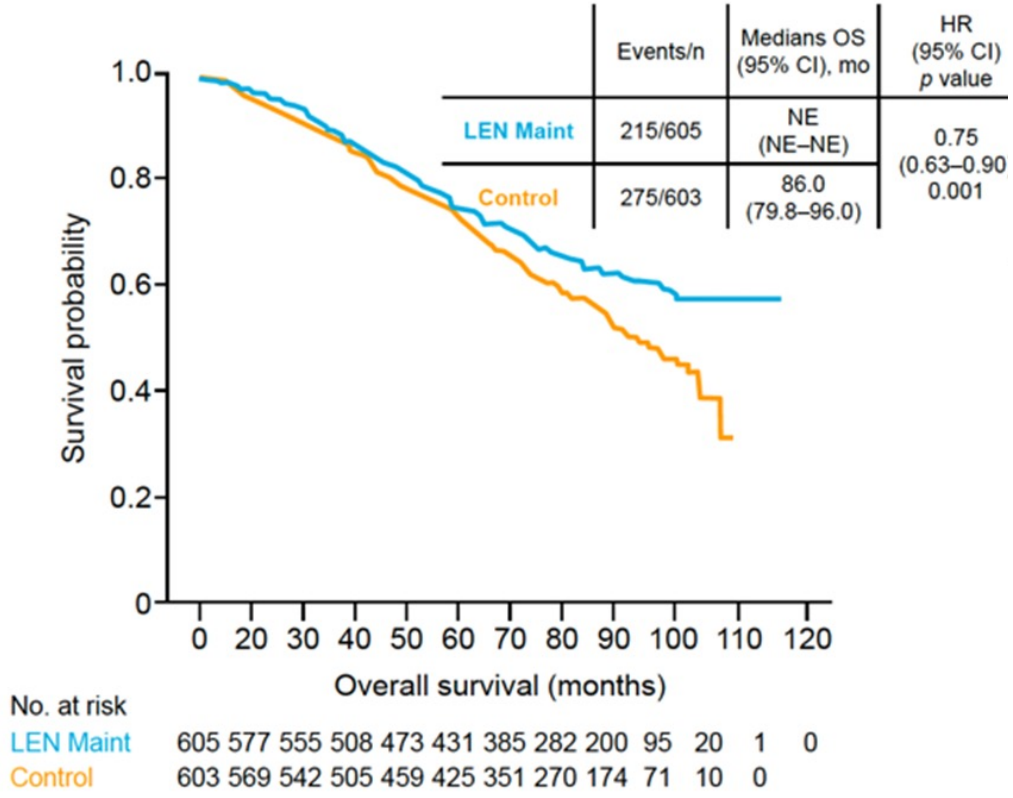
KRd consolidation vs R maintenance: ATLAS study



D, daratumumab; d, dexamethasone; K, carfilzomib; R, lenalidomide; T, thalidomide; V, bortezomib

Moreau P et al. EHA 2019;abstract S145 (poster presentation); Rodriguez C et al. EHA 2022;abstract P934 (poster presentation); Dytfeld D et al. EHA 2022;abstract S175 (oral presentation)

Lenalidomide maintenance: meta-analysis of 3 randomized studies

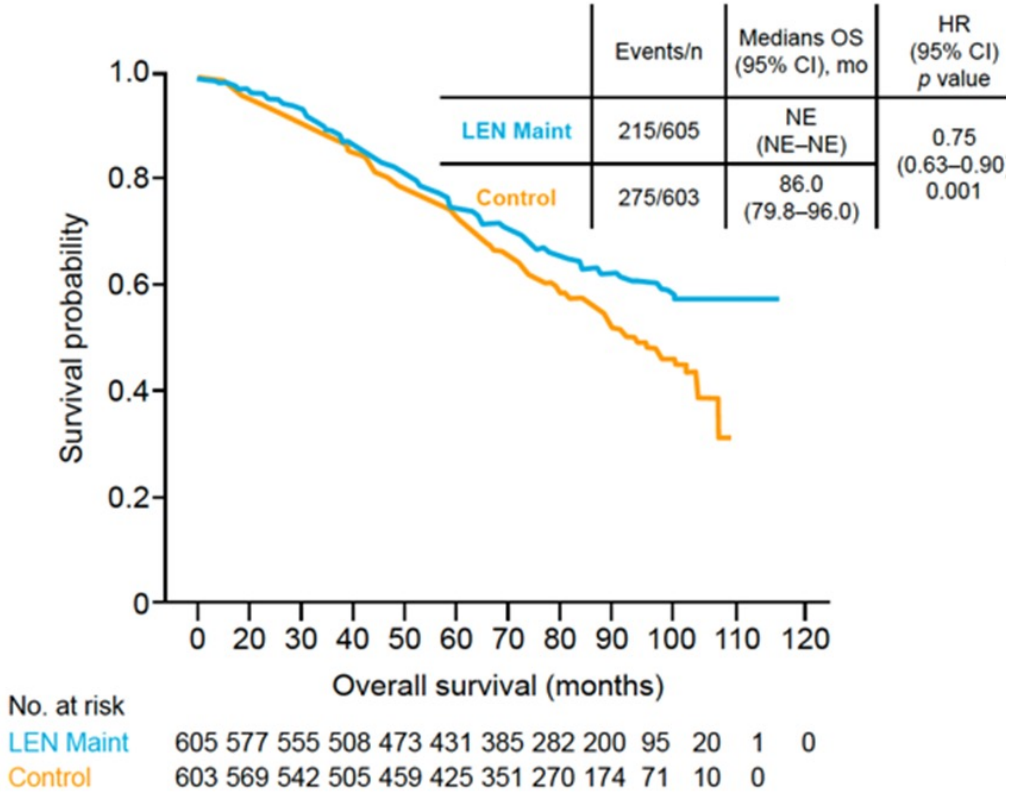


The risk of developing PD was higher than the risk of developing an invasive SPM in both groups.

Len, lenalidomide; Bort, bortezomib; HR, high risk; OS, overall survival; SPM, second primary malignancies; PD progressive disease

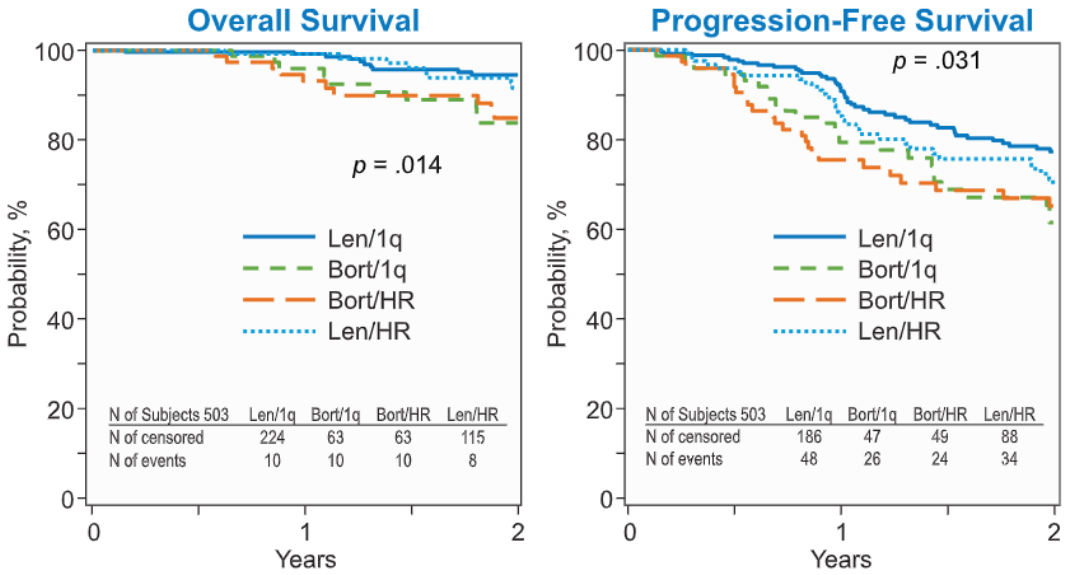
McCarthy P et al. J Clin Oncol 2017; 35(29):3279-3289

Lenalidomide maintenance: meta-analysis of 3 randomized studies



…and bortezomib maintenance?

HOVON-65: bortezomib-based maintenance
96-OS in treated patients are similar with or without deletion 17p13 (52% versus 54%).

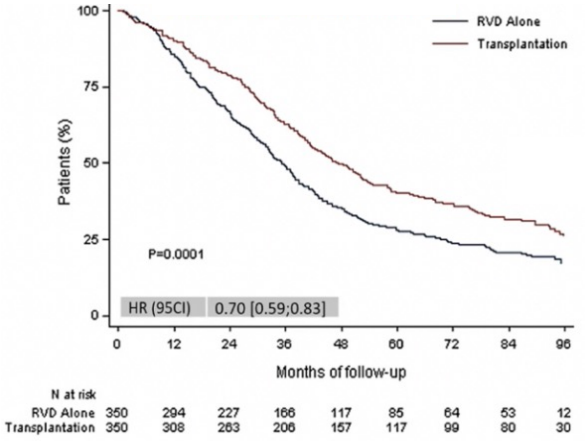


Len, lenalidomide; Bort, bortezomib; HR, high risk; OS, overall survival;

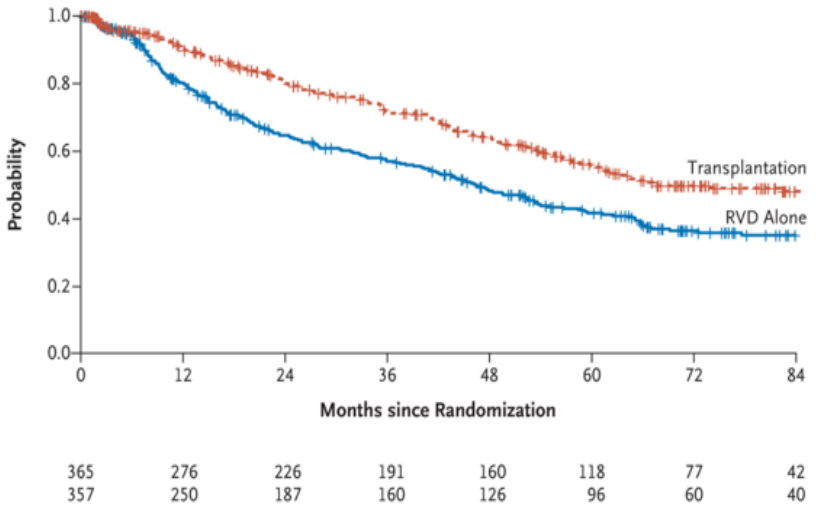
McCarthy P et al. J Clin Oncol 2017; 35(29):3279-3289;
Bumma et al., Cancer 2023

Lenalidomide maintenance: fixed duration or until progression?

IFM 2009: len 1 year
PFS: Median, 47 vs. 35 months



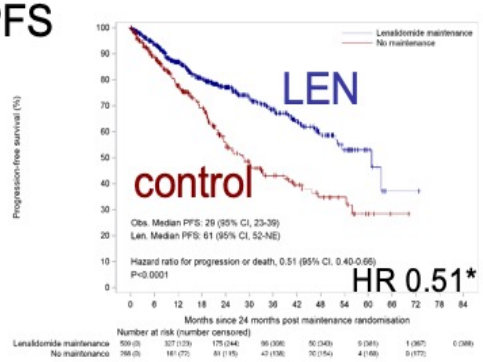
DETERMINATION: len until progression
PFS: Median, 68 vs. 46 months



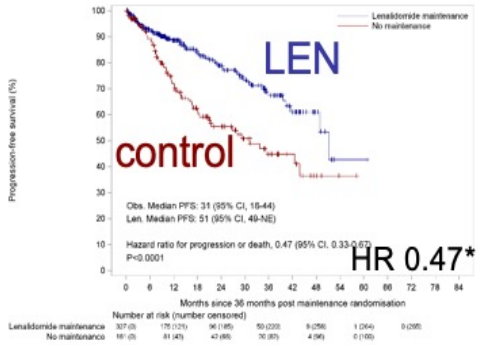
*1-year lenalidomide maintenance in the IFM 2009 study; until progression in the DETERMINATION study.

PFS

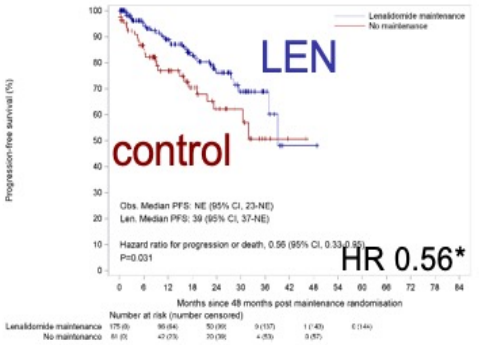
2 years



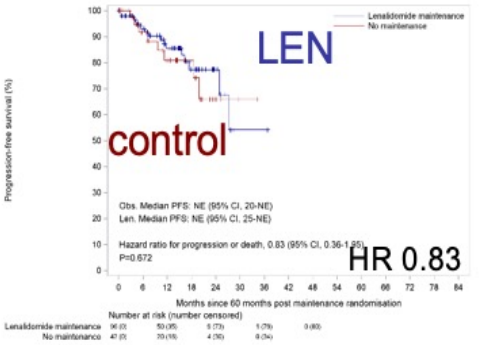
3 years



4 years



5 years



d, dexamethasone; HDM, high-dose melphalan; R, lenalidomide

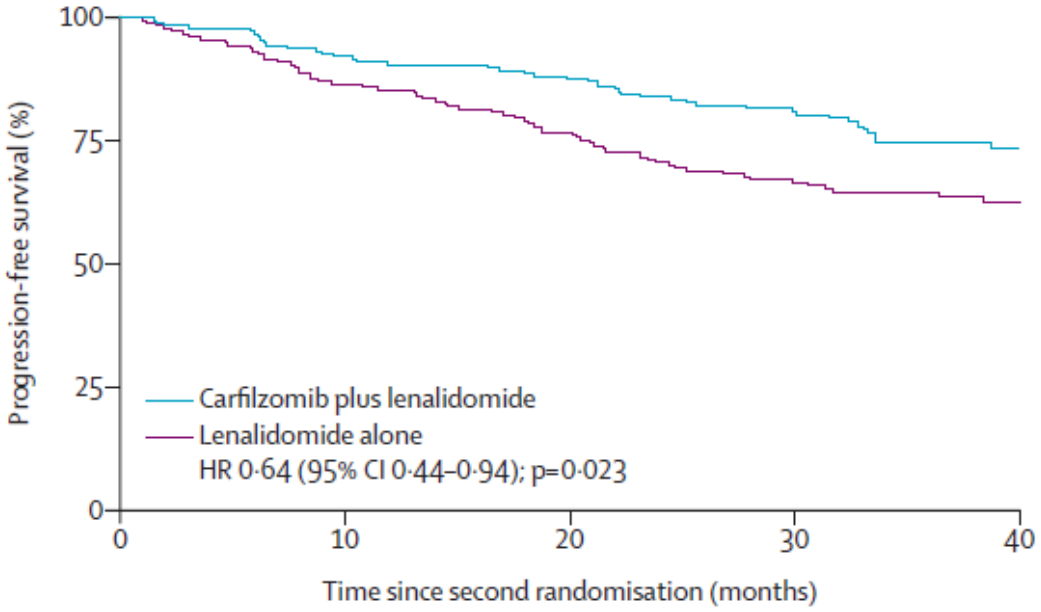
Perrot A et al. ASH 2020;abstract 143 (oral presentation); Richardson PG et al. N Engl J Med 2022;387:132–47.

Lenalidomide maintenance: Len-base combinations are better?

R vs KR maintenance

FORTE

Median follow-up from random 2: 37 months

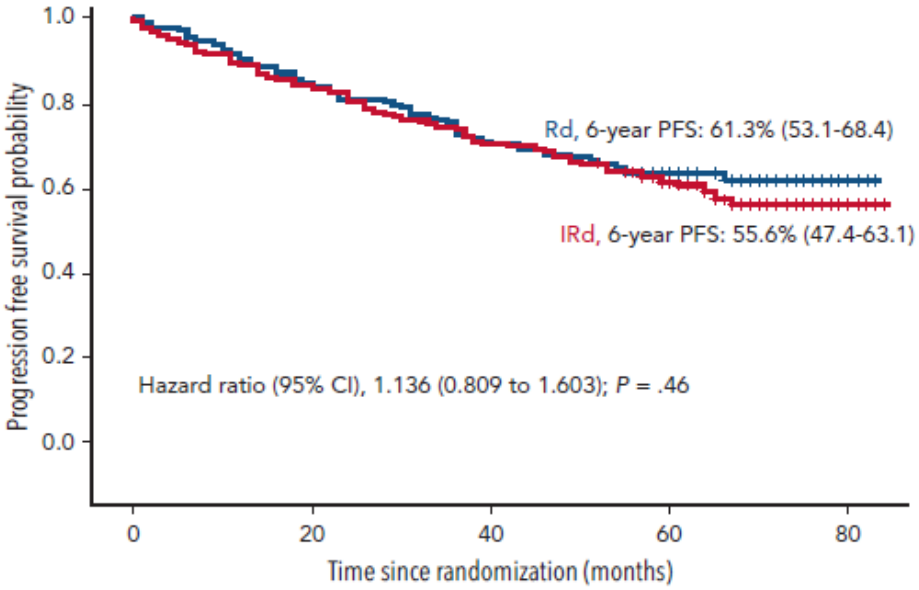


3-year PFS: 75% with KR vs. 65% with R
HR 0,64 [95% CI 0,44–0,94], **p=0,023**

Rd vs IRd maintenance

GEM2014

Median follow-up: 69 months



6-year PFS: 61.3% with Rd vs. 55.6% with IRd
HR 1,1 [95% CI 0,81–1,60], p=0,46

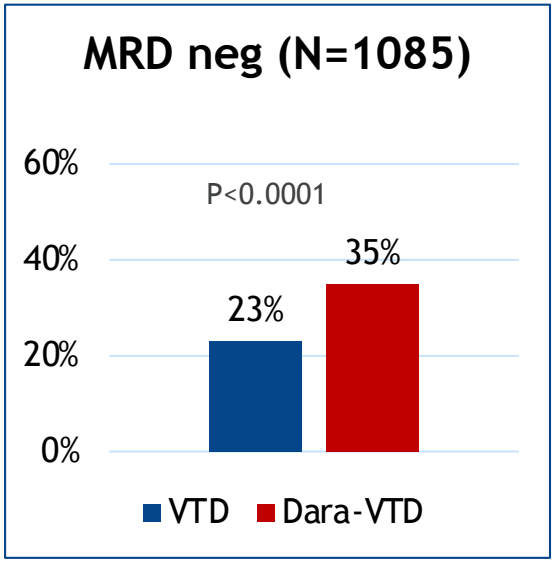
R, lenalidomide; k, carfilzomib; I, Ixazomib; PFS, progression-free survival; OS, overall survival

Gay F et al., FORTE trial, Lancet Oncol 2021 ; Rosinol et al., Blood 2023

WHAT'S THE FUTURE?

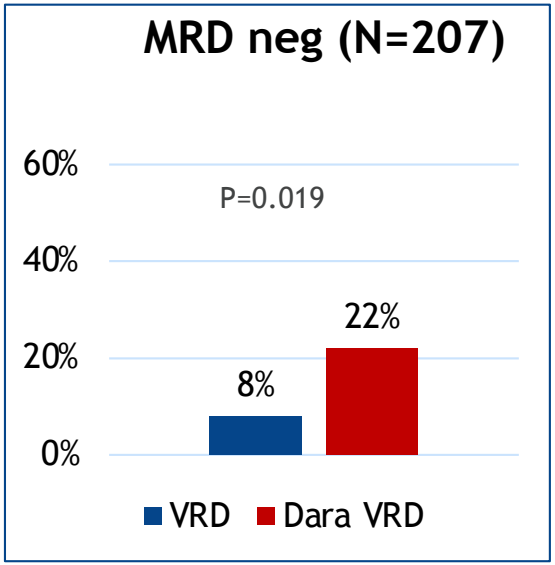
In the era of quadruplets: alternative to DVTd

CASSIOPEIA[1]
DVTd vs VTd (4x4w cycles)



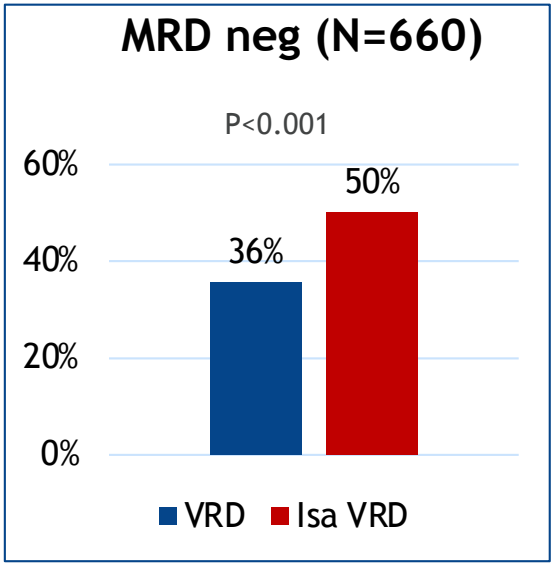
Duration of induction therapy: 112 days

GRIFFIN[2,3]
DVRd vs VRd (4x4w cycles)



Duration of induction therapy: 84 days

GMMG-HD7[4]
IsaVRd vs VRd (3x6w cycles)



Duration of induction therapy: 126 days

Median follow-up of 44.5 months:
NR vs 51.5 months

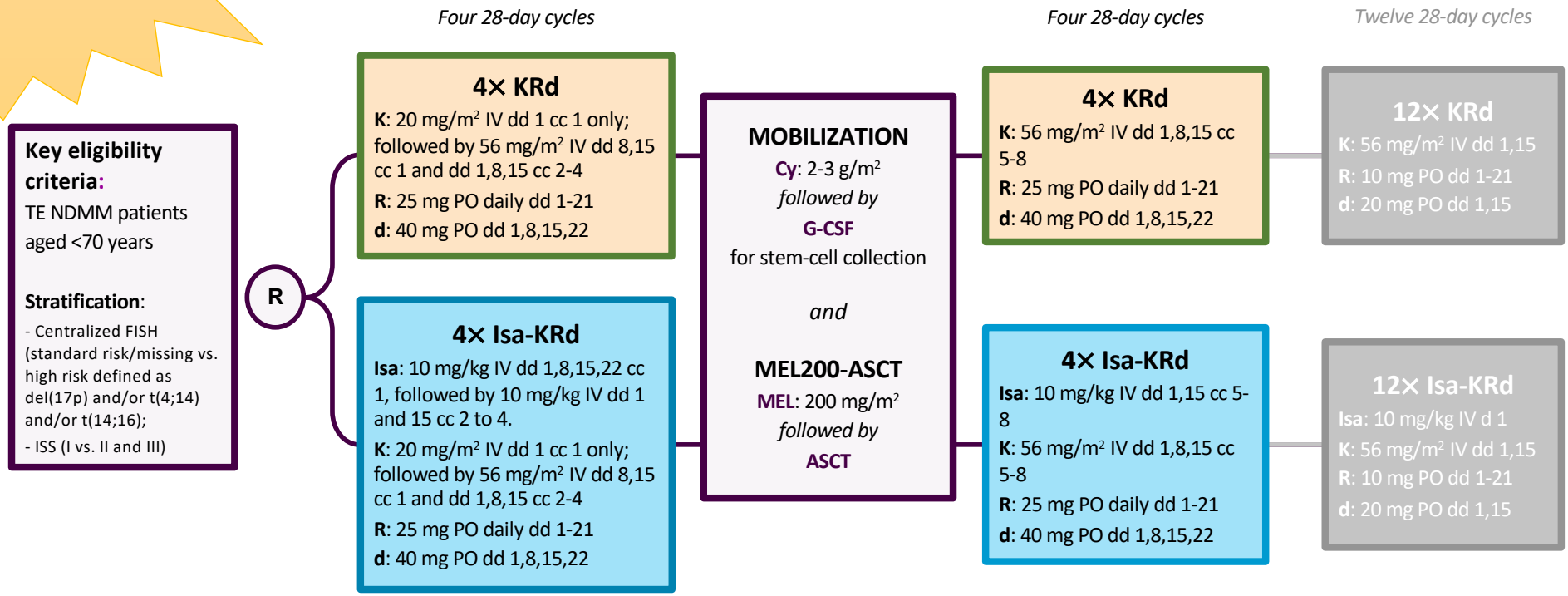
Follow-up: 38.6 months
mPFS: NR either arm
Estimated 36-month PFS: 88.9% vs. 81.2%

D, daratumumab; d, dexamethasone; Isa, isatuximab; MRD, minimal residual disease; R, lenalidomide; TE, transplant eligible; T, thalidomide; V, bortezomib

1. Avet Loiseau H et al. ASCO 2019;abstract 8017 (oral presentation); 2. Voorhees P et al Blood 2020;136(8):936-945; 3. Sborov WD et al. IMS 2022;abstract OAB-057;4. Goldschmidt H et al. ASH 2021; abstract 463 (oral presentation)

WHAT'S THE FUTURE?

In the era of quadruplets: alternative to DVTd



ASH | Annual Meeting & Exposition

4 Results of the Phase III Randomized Iskia Trial: Isatuximab-Carfilzomib-Lenalidomide-Dexamethasone Vs Carfilzomib-Lenalidomide-Dexamethasone As Pre-Transplant Induction and Post-Transplant Consolidation in Newly Diagnosed Multiple Myeloma Patients

Program: General Sessions
Session: Plenary Scientific Session
Hematology Disease Topics & Pathways:
Research, clinical trials, adult, Clinical Research, Combination therapy, Therapies, Adverse Events, Study Population, Human, Minimal Residual Disease

Sunday, December 10, 2023, 2:00 PM-4:00 PM

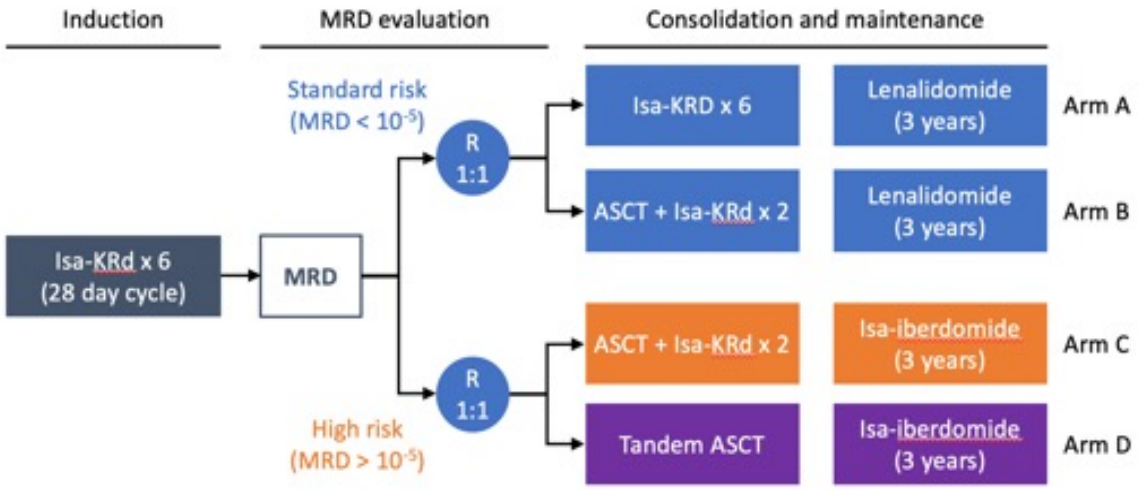
Francesca Gay, MD, PhD[1,2], *Wilfried Roeloffzen, MD, PhD*[3*], *Meletios A. Dimopoulos, MD, PhD*[4], *Laura Rosiñol, MD, PhD*[5*], *Marjolein van der Klift, MD, PhD*[6*], *Roberto Mina, MD*[1,2*], *Albert Oriol Rocafiguera, MD*[7*], *Eirini Katodritou, MD*[8*], *Ka Lung Wu, MD, PhD*[9], *Paula Rodriguez Otero, MD, PhD*[10*], *Roman Hajek, MD*[11,12], *Elisabetta Antonioli, MD*[13*], *Mark van Duin, PhD*[14*], *Mattia D'Agostino, MD*[1,2*], *Joaquin Martinez-Lopez, MD, PhD*[15*], *Elena M. van Leeuwen-Segarceanu, MD, PhD*[16*], *Paola Tacchetti, MD, PhD*[17*], *Niels W.C.J. van de Donk, MD, PhD*[18], *Katja Weisel, MD*[19], *Luděk Pour, MD*[20*], *Jakub Radocha, MD, PhD*[21], *Angelo Belotti, MD*[22*], *Fredrik Schjesvold, MD, PhD*[23,24], *Joan Bladé, MD, PhD*[25*], *Hermann Einsele, MD, PhD*[26*], *Pieter Sonneveld, MD, PhD*[14], *Mario Boccadoro, MD*[27] *and Annemiek Broijl, MD, PhD*[28]

TE, transplant-eligible; NDMM, newly diagnosed multiple myeloma; del, deletion; t, translocation; ISS, International Staging System stage; R, randomization; Isa, isatuximab; K, carfilzomib; R, lenalidomide; d, dexamethasone; IV, intravenous; dd, days; cc, cycles; PO, orally; Cy, cyclophosphamide; G-CSF, granulocyte colony-stimulating factor; MEL, melphalan; ASCT, autologous stem-cell transplantation; MRD, minimal residual disease; NGS, next-generation sequencing; PFS, progression-free survival.

ClinicalTrials.gov Identifier: NCT04483739

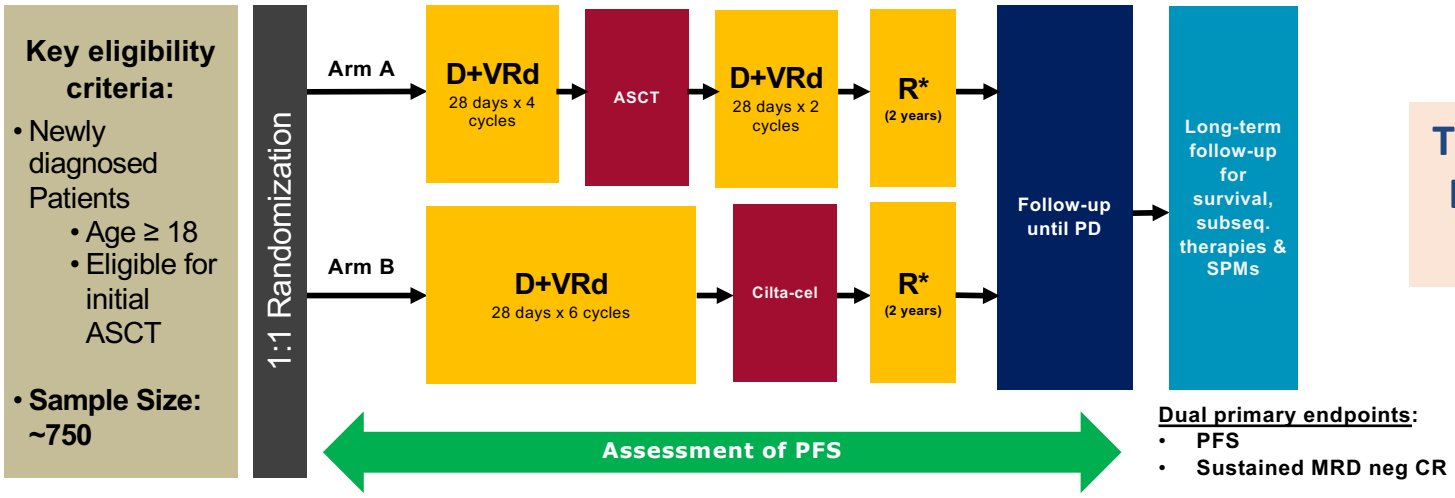
WHAT'S THE FUTURE?

Will ASCT be necessary in all NDMM patients?



The randomized, phase III IFM 2020-02 Minimal Residual Disease Adapted Strategy (MIDAS) study

Will CAR T-cell therapy replace HDM-ASCT as upfront treatment in NDMM patients?



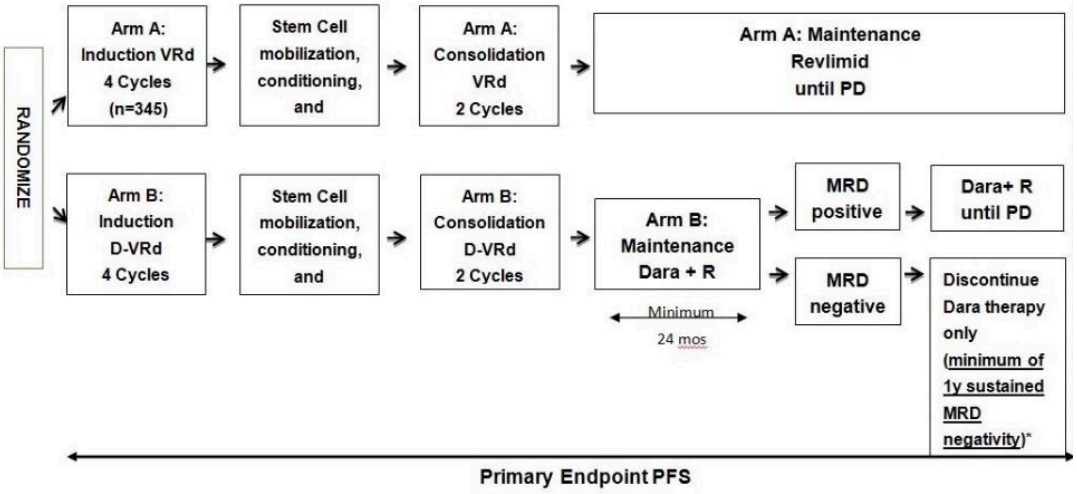
The randomized, phase III EMAGINE/CARTITUDE-6 (EMN28) study

CAR, chimeric antigen receptor; HDM, high-dose melphalan; ASCT, autologous stem-cell transplantation; NDMM, newly diagnosed multiple myeloma; D, daratumumab; V, bortezomib; R, lenalidomide; d, dexamethasone; Cilta-cel, ciltacabtagene autoleucel; PFS, progression-free survival; PD, progressive disease; SPMs, second primary malignancies; subseq., subsequent; ISS, International Staging System; MRD, minimal residual disease; neg, negativity; CR, complete response; Isa, isatuximab; K, carfilzomib

ClinicalTrials.gov Identifier: NCT05257083
ClinicalTrials.gov Identifier: NCT04934475

WHAT'S THE FUTURE?

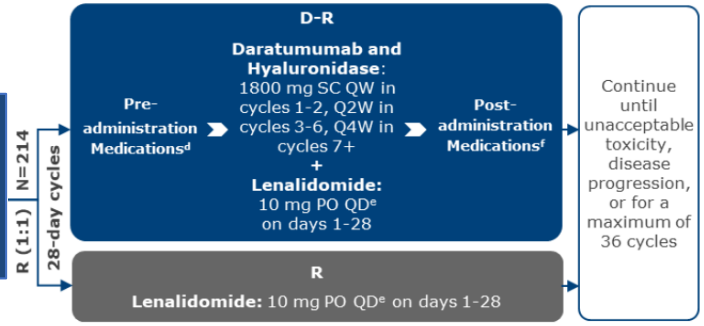
Maintenance therapy: the role of MRD and anti-CD38



*opportunity to restart therapy upon relapse from CR or loss of MRD status

The randomized, phase III PERSEUS (EMN17) study

NDMM with ≥ 4 cycles of induction treatment and/or consolidation, HDC and ASCT, reaching ≥ VGPR with MRD positive (NGS 10^{-5})



The randomized, phase III AURIGA study

CR, complete response; Dara/D, daratumumab, V, bortezomib; R, lenalidomide; d, dexamethasone, MRD, minimal residual disease; PD, progressive disease, VGPR, very good partial response; NG, next generation sequencing

ClinicalTrials.gov Identifier: NCT03710603
ClinicalTrials.gov Identifier: NCT03901963

Conclusions

- Quadruplets (PI + IMiDs + anti-CD38 mAb) have replaced triplets as induction and consolidation for TE MM patients: ↑ MRD rates and longer PFS.
- Upfront ASCT was a SoC in the era of triplets (↑ MRD rates and longer PFS as compared to a non transplant approach) and still is a backbone in studies with quadruplets.
- Consolidation is a matter of debate: biological rationale vs treatment duration?
- Lenalidomide maintenance is the current SoC:
  - Duration of maintenance matters, particularly in high-risk patients: the longer the better
  - Two-drug maintenance (e.g. lenalidomide plus carfilzomib) maintenance could prolong PFS

The ongoing trials could change the current scenario in the coming years (induction quadruplets, ASCT replacement, MRD-driven therapy)

ACKNOWLEDGEMENTS

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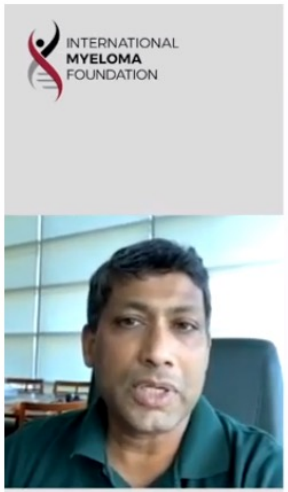
Dr. Stefania Oliva
Dr. Mattia D'Agostino
Dr. Lorenzo Cani
Dr. Andrea Casson
Dr. Tommaso Picardi

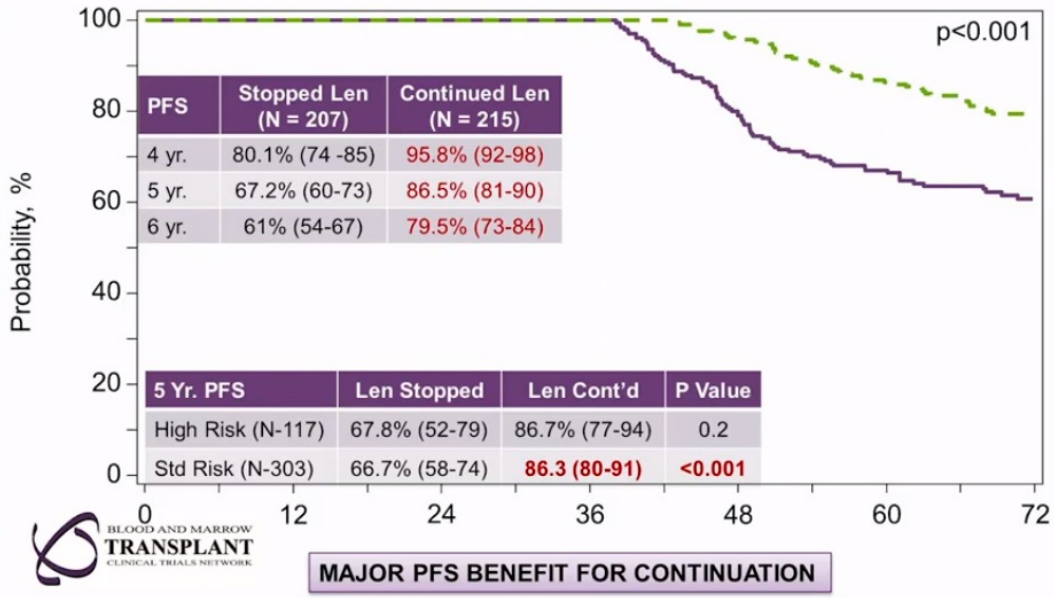
Laboratory Staff
Transplant Unit
Nurses
Data Managing Staff
Statisticians

European Myeloma Network (EMN)
Prof. Mario Boccadoro



Parmeswaran Hari, MD
Center for International Blood and Marrow Transplant Research
Medical College of Wisconsin
Milwaukee, WI, USA

PFS Landmark Analysis: Len continued beyond 38 mo. vs. Not



PFS	Stopped Len (N = 207)	Continued Len (N = 215)
4 yr.	80.1% (74 -85)	95.8% (92-98)
5 yr.	67.2% (60-73)	86.5% (81-90)
6 yr.	61% (54-67)	79.5% (73-84)

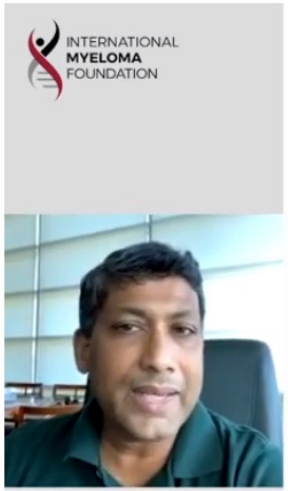
5 Yr. PFS	Len Stopped	Len Cont'd	P Value
High Risk (N-117)	67.8% (52-79)	86.7% (77-94)	0.2
Std Risk (N-303)	66.7% (58-74)	**86.3 (80-91)**	**<0.001**

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

MAJOR PFS BENEFIT FOR CONTINUATION

13

Long term follow up of BMT CTN 0702 (STaMINA) of



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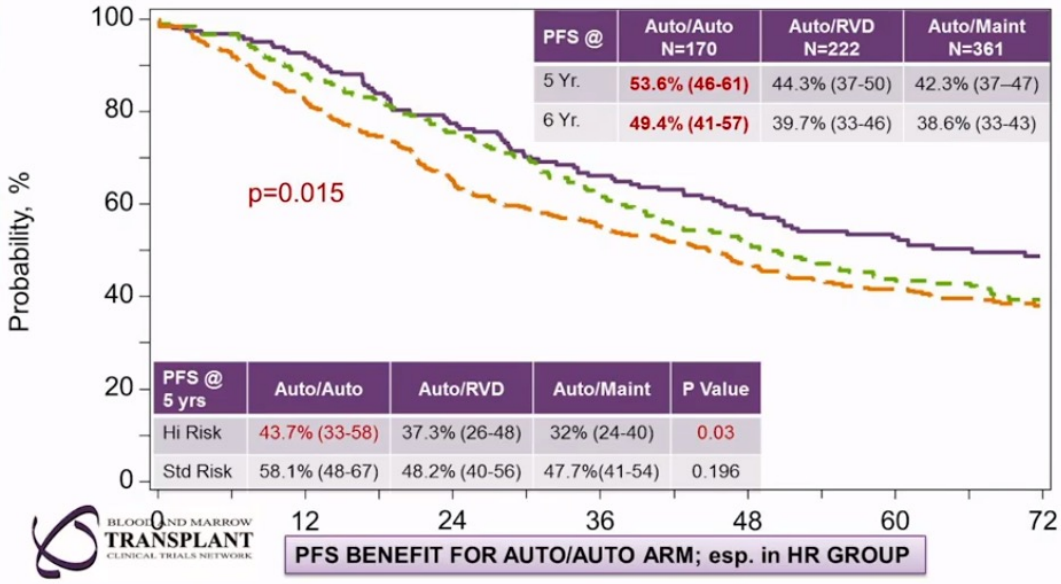
Center for International Blood and Marrow Transplant Research
Medical College of Wisconsin
Milwaukee, WI, USA

STaMINA: PFS by Treatment Received



PFS @	Auto/Auto N=170	Auto/RVD N=222	Auto/Maint N=361
5 Yr.	53.6% (46-61)	44.3% (37-50)	42.3% (37–47)
6 Yr.	49.4% (41-57)	39.7% (33-46)	38.6% (33-43)

PFS @ 5 yrs	Auto/Auto	Auto/RVD	Auto/Maint	P Value
Hi Risk	43.7% (33-58)	37.3% (26-48)	32% (24-40)	0.03
Std Risk	58.1% (48-67)	48.2% (40-56)	47.7%(41-54)	0.196

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

PFS BENEFIT FOR AUTO/AUTO ARM; esp. in HR GROUP

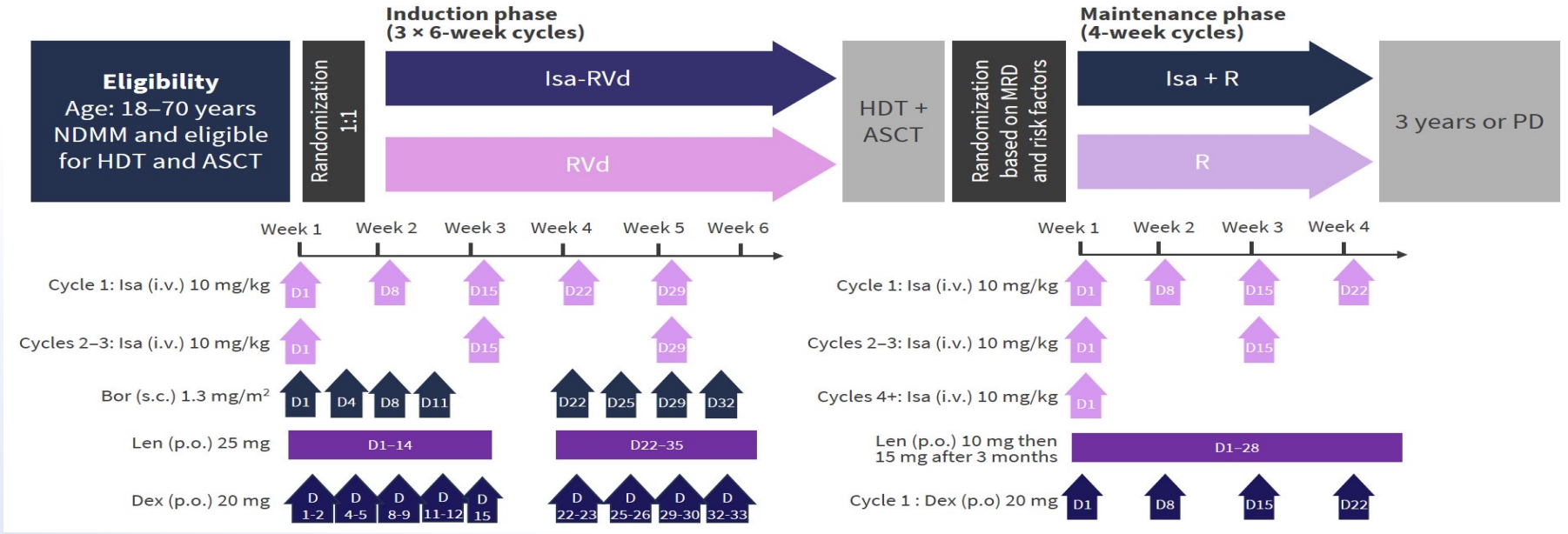
15

IMF

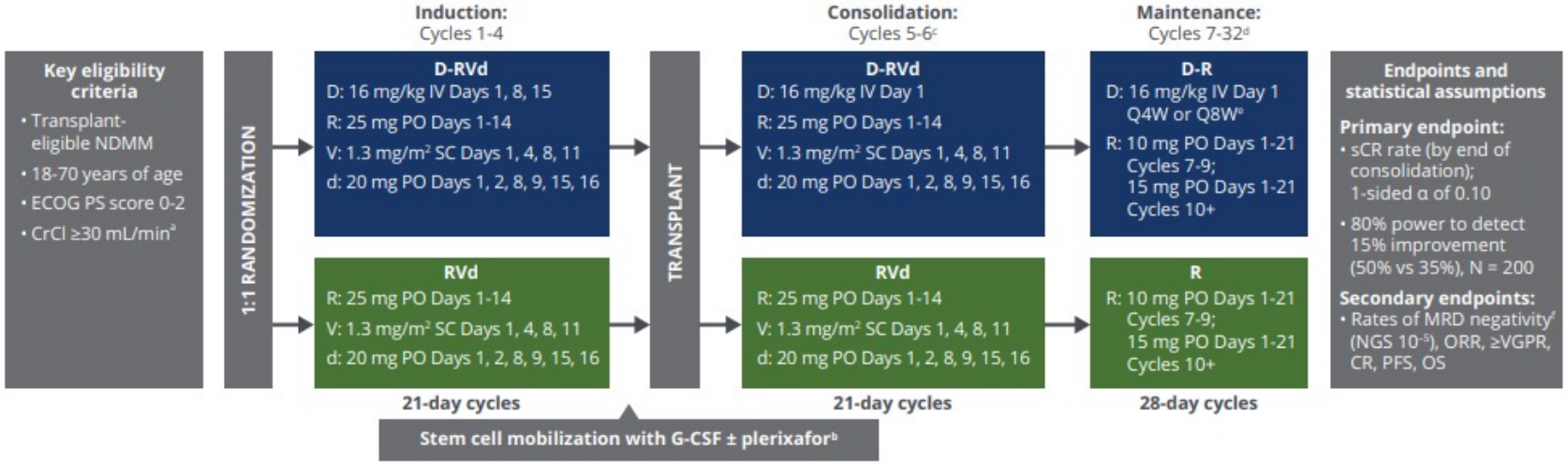
Long term follow up of BMT CTN 0702 (STaMINA) of

In the era of quadruplets: alternative to DVTd

GMMG-HD7



GRIFFIN

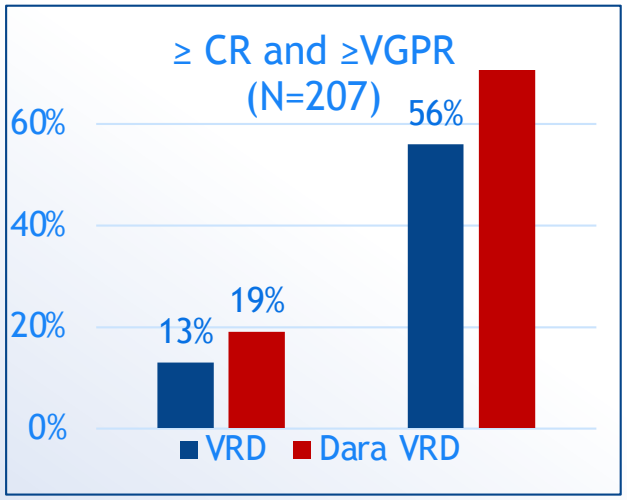


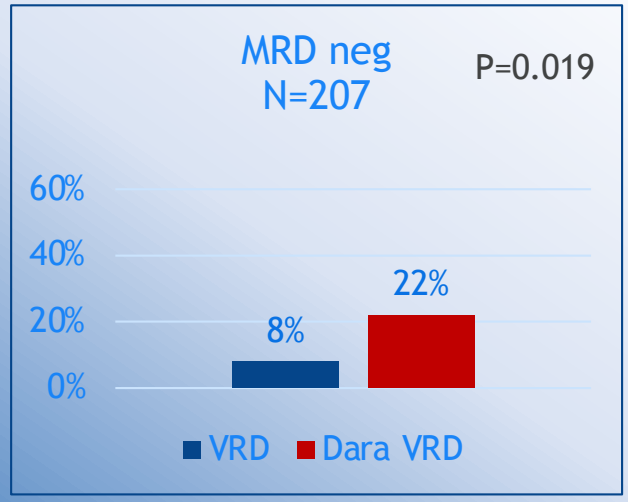
In the era of quadruplets: alternative to DVTd

Post Induction response rates and MRD neg (10^{-5}) with the addition of Anti-CD38 monoclonal antibodies to standard triplets

GRIFFIN

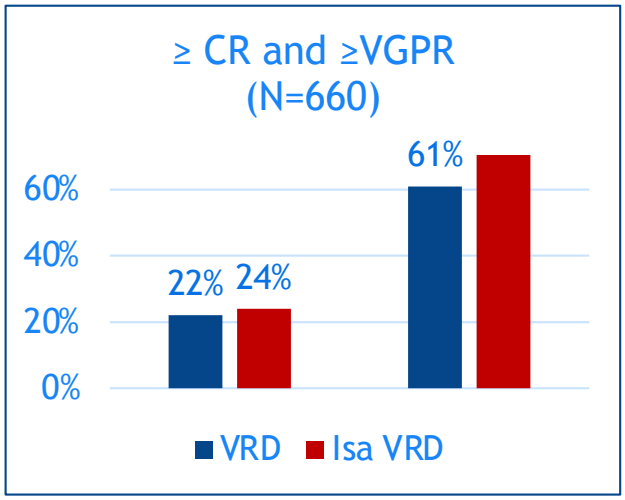
DVRd vs VRd (4x4w cycles)

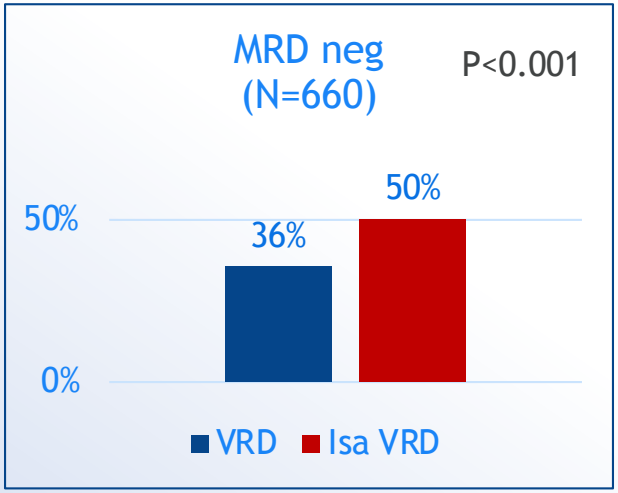




GMMG-HD7

IsaVRd vs VRd (3x6w cycles)





Up-front use of anti-CD38: impact on stem cell mobilization

Incidence of ≥ grade 3 neutropenia		
	Anti-CD38	No anti-CD38
CASSIOPEIA (DVTd vs. VTd)	28%	15%
GMMG-HD7 (Isa-VRd vs VRd)	23%	7%
GRIFFIN (DVRd vs VRd)	41%	22%

Incidence of ≥ grade 3 infection		
	Anti-CD38	No anti-CD38
CASSIOPEIA (DVTd vs. VTd)	22%	20%
GMMG-HD7 (Isa-VRd vs VRd)	12%	10%
GRIFFIN (DVRd vs VRd)	23%	22%

1. Avet Loiseau H et al. ASCO 2019;abstract 8017 (oral presentation); 2. Voorhees P et al Blood 2020;136(8):936-945; 3. Sborov WD et al. IMS 2022;abstract OAB-057;4. Goldschmidt H et al. ASH 2021; abstract 463 (oral presentation)