3rd edition

# Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

**Turin, September 21-22, 2023**

Starhotels Majestic

*Scientific board:*
**Marco Ladetto** (Alessandria)
**Umberto Vitolo** (Candiolo-TO)

# Disclosures of Francesca Gay

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| Janseen, Amgen, Takeda, BMS, Sanofi, Roche, Abbvie | | | | | | x | x |
| Pfizer, Oncopeptides | | | | | | x | |
| | | | | | | | |
| | | | | | | | |

# How I treat high-risk young multiple myeloma patients

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**Università di Torino**
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**Torino**

# High-risk myeloma – the unmet needs

1) **Identify** HRMM patients correctly

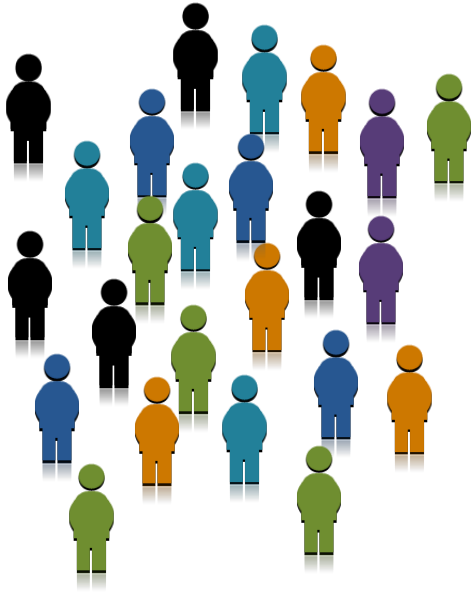
2) **Treat** HRMM effectively vs tolerability

3) **Compare outcomes**

4) **Functional High-risk**

# Identify high-risk myeloma patients

- R-ISS,R2-ISS
- Del17p, p53 mutation
- Ampl 1q, gain1q
- T(4;14), breakpoint location cr4
- Double hit
- Circulating Plasma Cells
- Plasma cell Leukemia
- Extramedullary disease
- Plasmablastic morphology



# Treat high-risk myeloma effectively/torability

- R-ISS,R2-ISS
- Del17p, p53 mutation
- Ampl 1q, gain1q
- T(4;14), breakpoint location cr4
- Double hit
- Circulating Plasma Cells
- Plasma cell Leukemia
- Extramedullary disease
- Plasmablastic morphology

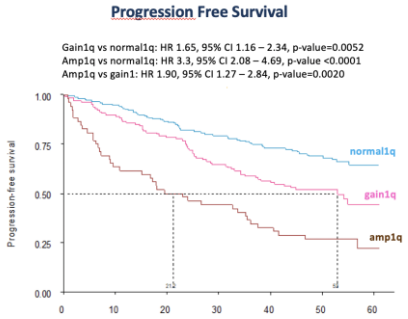
**Patient-related Features**

- Frailty
- Performance Status
- Age
- Renal Failure
- Co-morbidities/Organ Function
- Compliance
- Patient willings

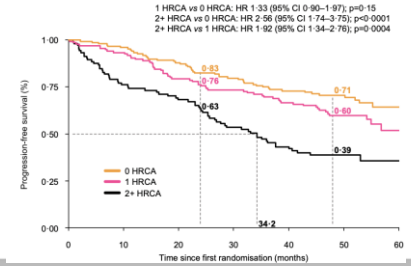
**Drug Access and reimbursement**

# EHA-ESMO 2021 MM guidelines:
## Front-line treatment of ND, TE MM patients

### 1q gain/amp




### High vs Ultra-high risk




**Eligibility for ASCT**

**Induction**

**First option:**
RVd (II, B)
D-VTd (I, A)

**If first option is not available:**
VTd (I, A)
VCd (II, B)

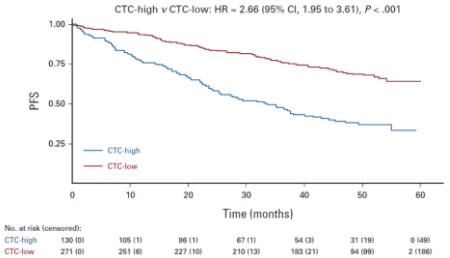
↓

200 mg/m² melphalan (I, A)
followed by ASCT (I, A)

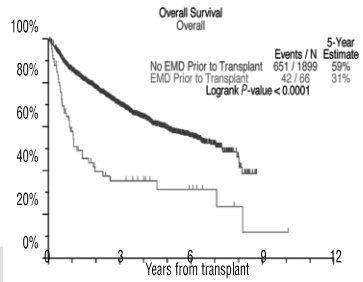
↓

LEN maintenance (I, A)

### Circulating tumor cells




### Extramedullary

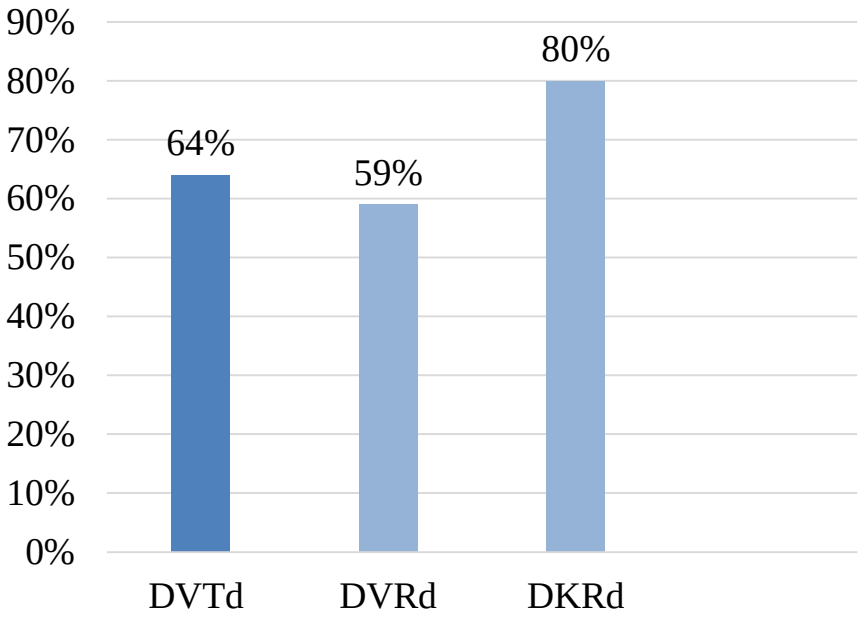





Dimopoulos MA. et al Annals of oncology 2021. D'Agostino M. et al. Manuscript submitted; Mina R. et al. Lancet Oncol 2023; Bertamini L. et al. JCO 2022; Usmani S. et al, Hematologica 2012.

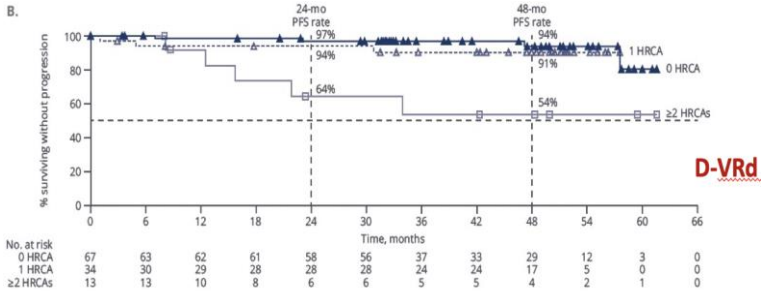
# Are quadruplets reducing the gap with standard risk patients?

## Overall population, MRD rates

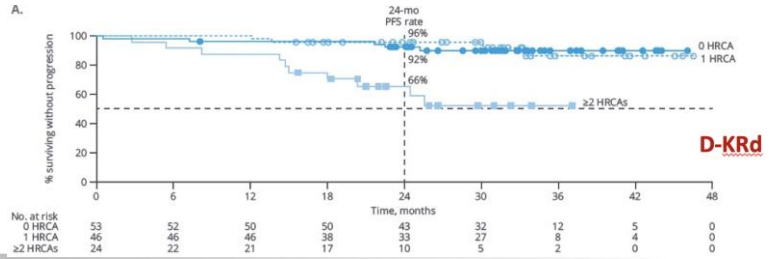



CASSIOPEA GRIFFIN MASTER

## GRIFFIN study: DVRd 0/1 vs 2 HRCA




## MASTER study: DKRd 0/1 vs 2 HRCA

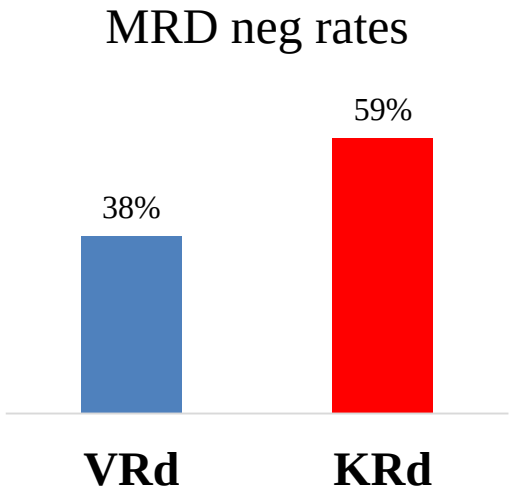




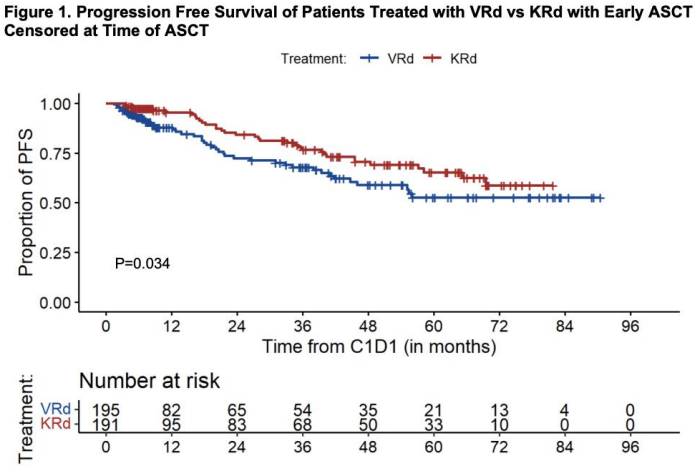

Callander N et al. ASH 2022;abstract 4557 (poster presentation)

# The role of different proteasome inhibitors for high-risk patients: bortezomib vs carfilzomib

## MRD rates in high risk patients: GRIFFIN and FORTE study



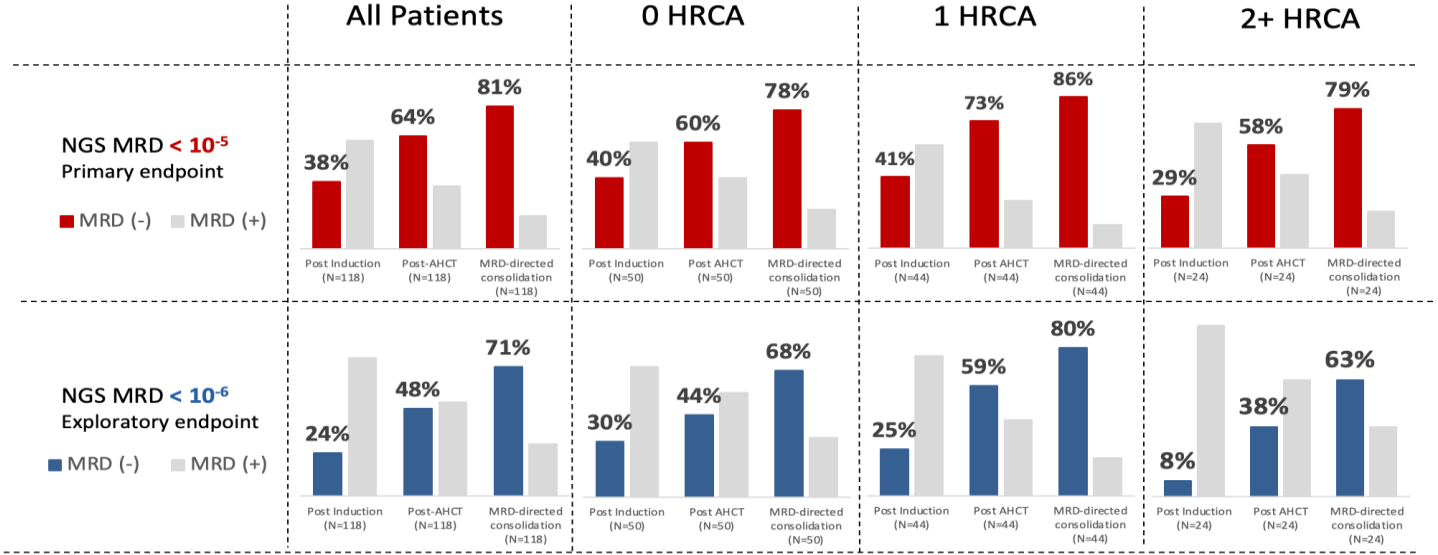

## VRd vs KRd plus upfront ASCT The MSKCC study






Laubach J. Et al. ASH2021 ; Mina R. et al EHA 2021 oral presentation; Rose Tan C. et al. Research square 2023

# MRD Results: MASTER D-KRd



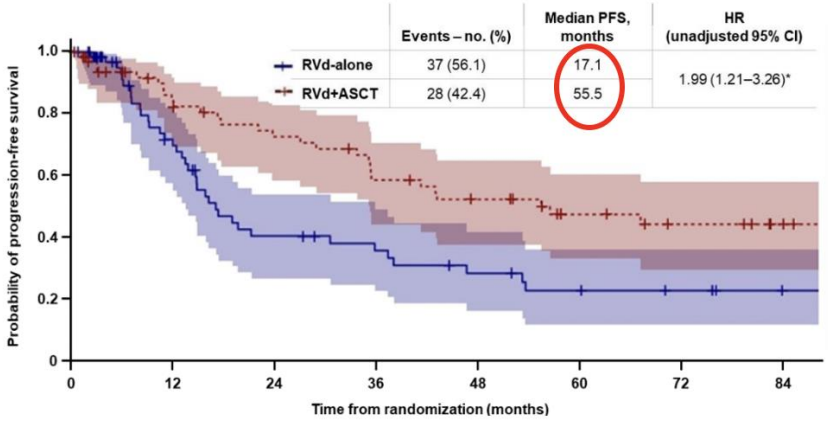

| | All Patients | 0 HRCA | 1 HRCA | 2+ HRCA |
|---|---|---|---|---|
| CR + MRD<$10^{-5}$ | 72% | 76% | 75% | 58% |
| Transition to MRD-SURE | 71% | 66% | 82% | 63% |
| Sustained (12 mo.) MRD <$10^{-5}$ | 65% | 66% | 73% | 46% |

HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20) or del(17p)

# What is the role of ASCT in high-risk patients?

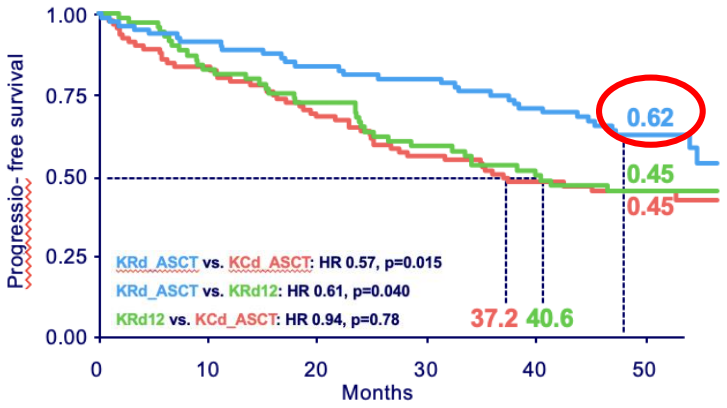
## DETERMINATION study: VRd + ASCT vs VRd alone

*Progression-free survival*




## FORTE study: KRd/KCyd + ASCT vs KRd alone

*Progression-free survival*

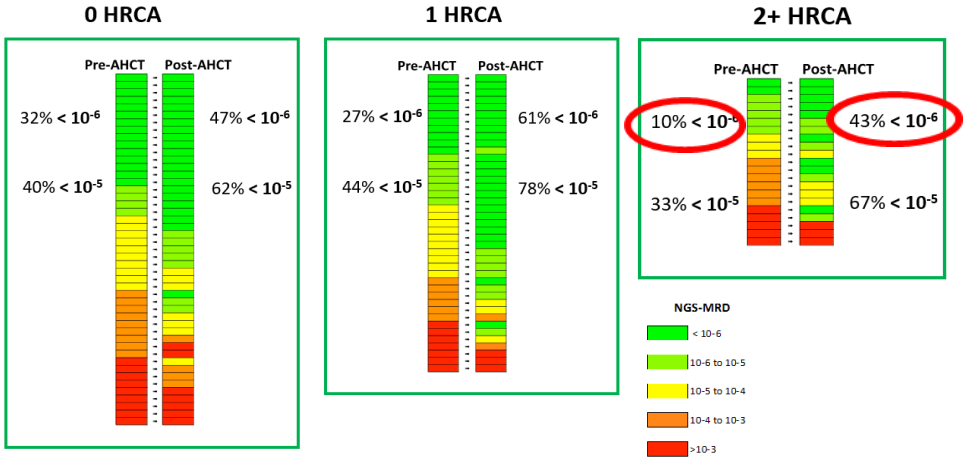





Richardson PG. Et al NEJM 2022. Mina R. et al, Lancet Oncol 2023

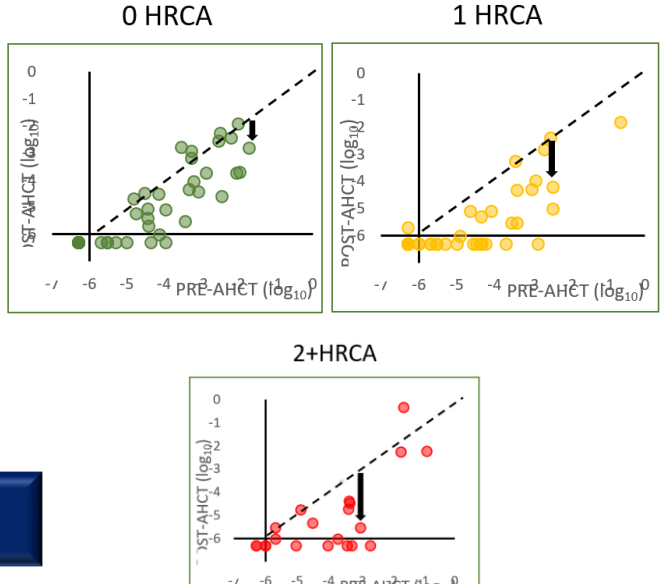
# MASTER study

## Changes in MRD negativity with ASCT




High risk: gain/amp 1q, t(4;14), t(4;16), t(14;20) or del(17p)

## MRD reduction with ASCT in cytogenetic risk group




**Greatest benefit with ASCT was in high-risk MM**

| | 0 HRCA | 1 HRCA | 2+ HRCA |
|---|---|---|---|
| $Log_{10}$ reduction (P=0.02) | **0.91** (range -0.75-2.14) | **1.26** (range -0.21-3.26) | **1.34** (range -1.28-3.41) |
| >1 $Log_{10}$ reduction | 43% | 74% | 71% |
| >2 $Log_{10}$ reduction | 11% | 17% | 43% |

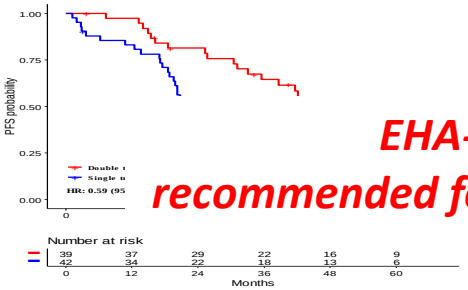
In MVA, presence of HRCA was only factor associated with >1 $Log_{10}$ reduction (OR 3.6, 95% C.I. 1.27-10.2, P=0.016)



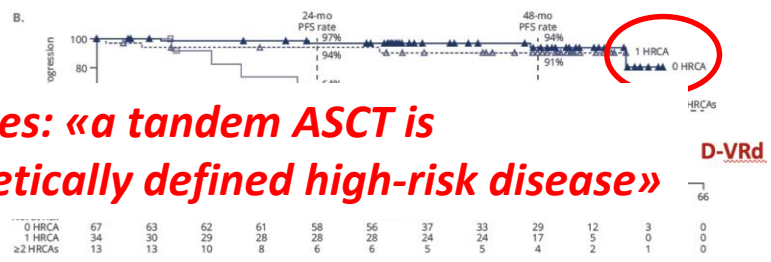
Bal S, et al. Blood 2021;138 (Suppl 1):483.

# Tandem autologous transplant for high-risk patients: still a standard?

**EMN02/HO95 study: 1 vs 2 HDM-ASCT**

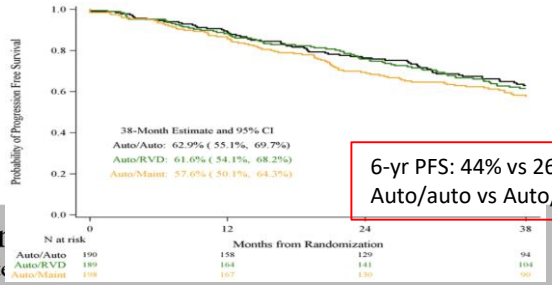



**GRIFFIN study: DVRd**



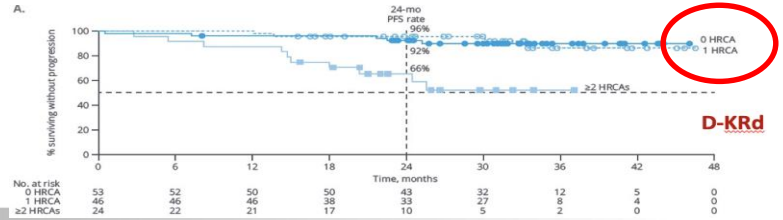

***EHA-ESMO 2021 guidelines: «a tandem ASCT is recommended for patients with genetically defined high-risk disease»***

**STAMINA study: 1 vs 2 HDM-ASCT**




6-yr PFS: 44% vs 26% for Auto/auto vs Auto/Len

**MASTER study: DKRd**



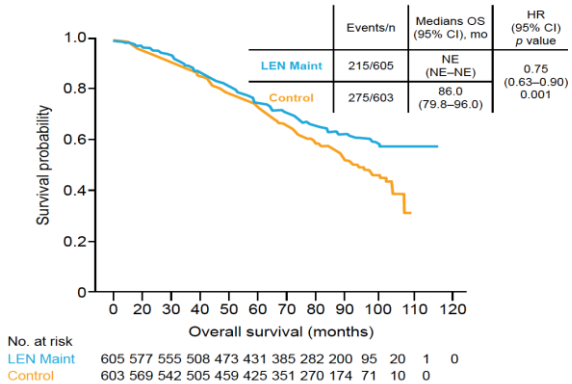


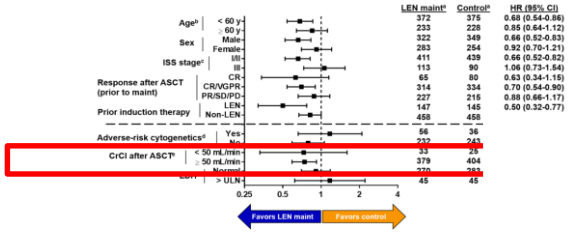

Cavo M. et al. lancet hematology 2020; Stadtmauer EA JCO2019; Natalie Callander et al. – Poster Abstract 4557 ASH 2022

# Maintenance therapy: can we do better?

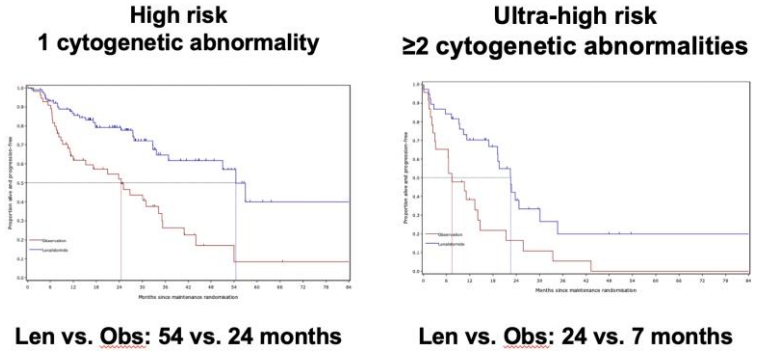
## Lenalidomide maintenance according to FISH risk

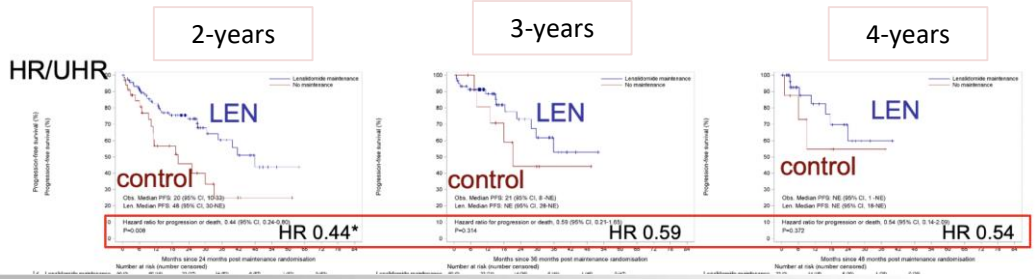
Overall survival




Myeloma XI study: lenalidomide versus observation



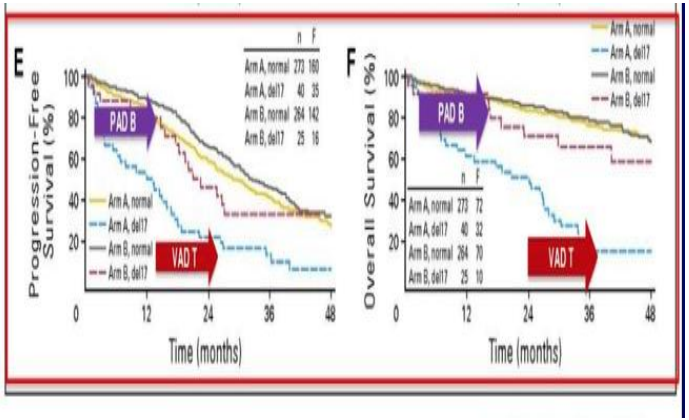



*McCarthy et al. J Clin Oncol 2017; 35(29):3279-3289;* G. Jackson GH. Et al, Lancet Oncol. 2019 Jan;20(1):57-73. Pawlin C. et al ASH22

# Lenalidomide and proteasome inhibitor maintenance

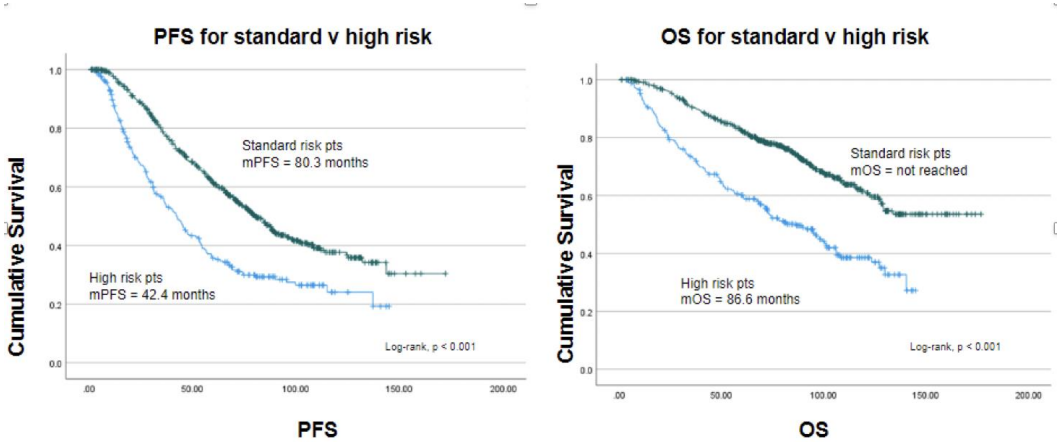
## Bortezomib vs thalidomide

HOVON65




del(17p)

## VRd maintenance in the Emory Cohort






Sonneveld P et al. JCO 2012
Nisha J. et al. JCO 2020

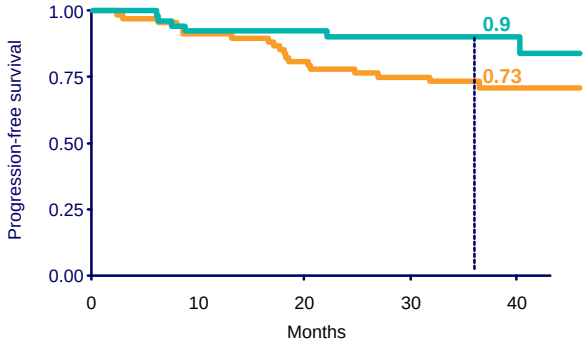
# The FORTE study: Carfilzomib-lenalidomide vs lenalidomide maintenance

## 3-year progression-free survival from random 2

Median follow-up from Random 2: 37 months (IQR 33-42)

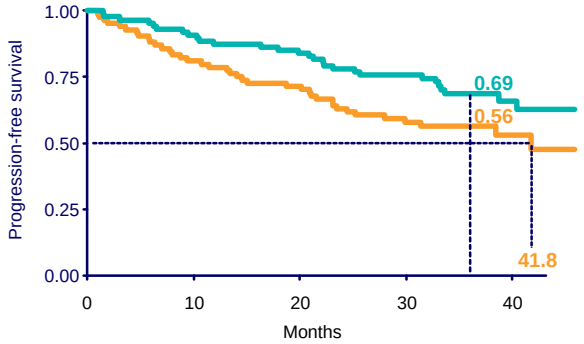
**KR vs. R**

### Standard risk (N=120)



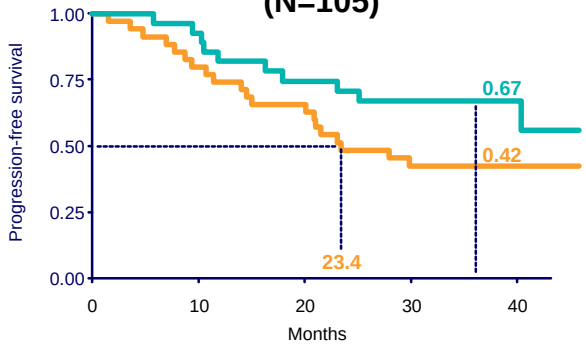

**KR vs. R: HR 0.4, p=0.05**

### High risk (N=172)




**KR vs. R: HR 0.6, p=0.04**

### Ultra-high risk (N=105)



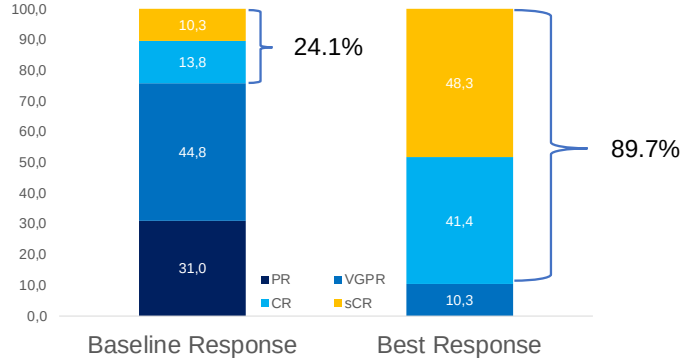

**KR vs. R: HR 0.53, p=0.1**

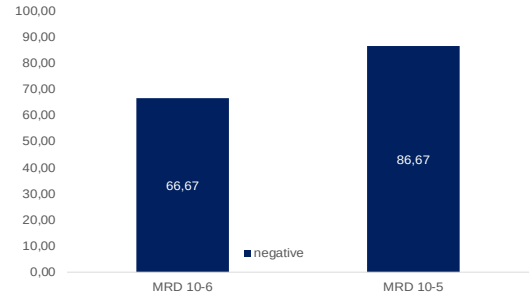


Random 2, second randomization (maintenance treatment); IQR, interquartile range; K, carfilzomib; R, lenalidomide; HR, hazard ratio; CI, confidence interval; p, p-value.

Mina R. et al. Lancet Oncol 2023

# Carfilzomib-pomalidomide-dexamethasone maintenance in high-risk

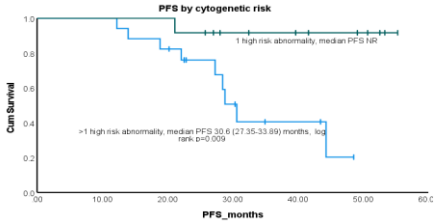


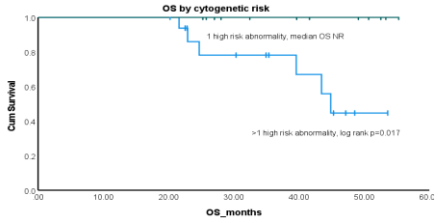




15 samples were analyzed for MRD by NGS clonoseq

## PFS and OS by cytogenetic risk, (1 or >1 cytogenetic abnormalities)

Median follow up: 41.5 months



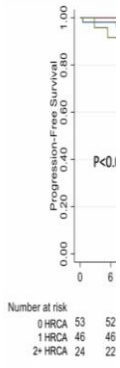



Nooka A et al. ASCO 2023

# MRD and high-risk patients: what do we know?

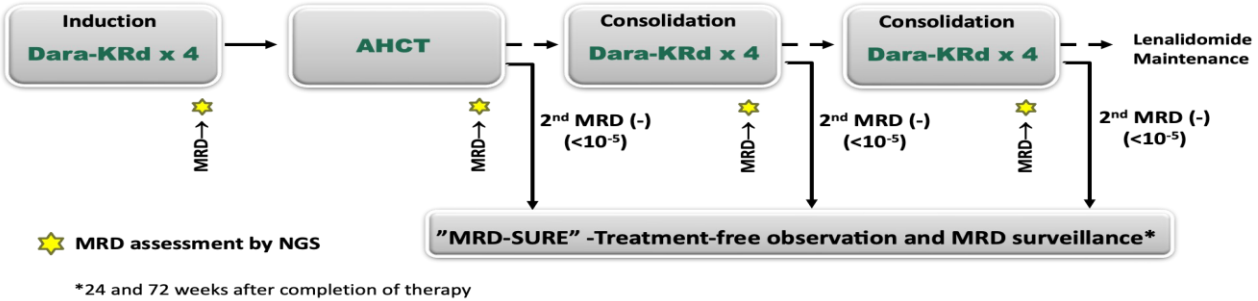
Tre: **Treatment**

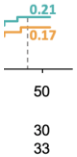
coMMit Myeloma Trials, Innovated




**Dara-KRd**

- Daratumumab 16 mg/m² days 1,8,15,22 (days 1,15 C 3-6; day 1 C >6)
- Carfilzomib (20) 56 mg/m² Days 1,8,15
- Lenalidomide 25 mg Days 1-21
- Dexamethasone 40mg PO Days 1,8,15,22




MRD tested on "first pull" and reported utilizing intent-to-treat principle according to International Harmonization

*Costa LJ et al Leukemia 2021 35:18*



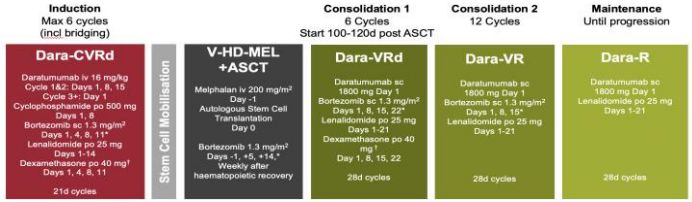
Costa L. et al ASH22; Mina R. et al EHA21; D'Agostino M et al IMS21

# Conclusions

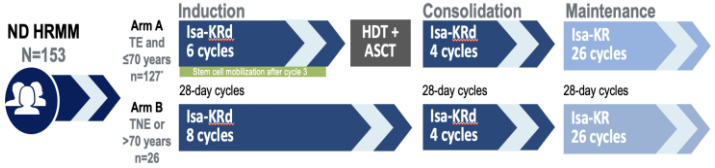
| | High-risk patients |
|---|---|
| • **Induction and consolidation** | • **Quadruplet** (PI + IMID + anti-CD38 MoAb) **induction/consolidation** is the standard, reducing the gap between SR and HR patients; ultra-high risk patients still an unmet medical need. |
| • **High-dose melphalan and autologous stem cell transplant** | • **Upfront ASCT** is a standard of care; *tandem* transplant is recommended in case of triplet induction.<br>• Benefit of tandem ASCT in the context of 4-drug regimens less clear: response/MRD driven/very high-risk? |
| • **Maintenance** | • Lenalidomide is the standard maintenance: in high-risk patients **duration matters**<br>• **2-drug maintenance** (VR/KR) is effective in high-risk patients → best partner to be identified (PI, antiCD38 Moab). |

# Extended consolidation and maintenance for high-risk patients

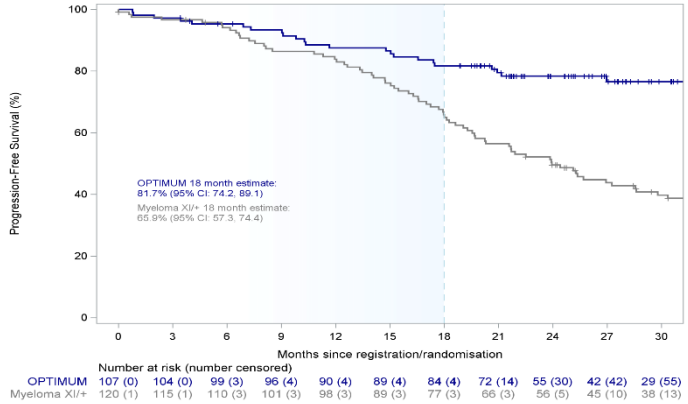
## OPTIMUM




## GMMG-CONCEPT




## Progression-free survival

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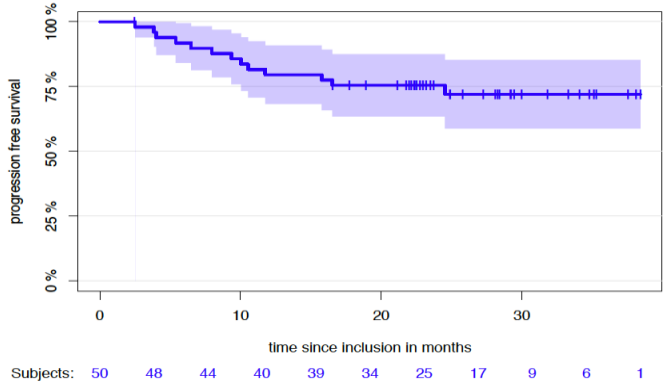




Kaiser M. et al. ASH22
Weisel K. Et al ASH 22

# Conclusions

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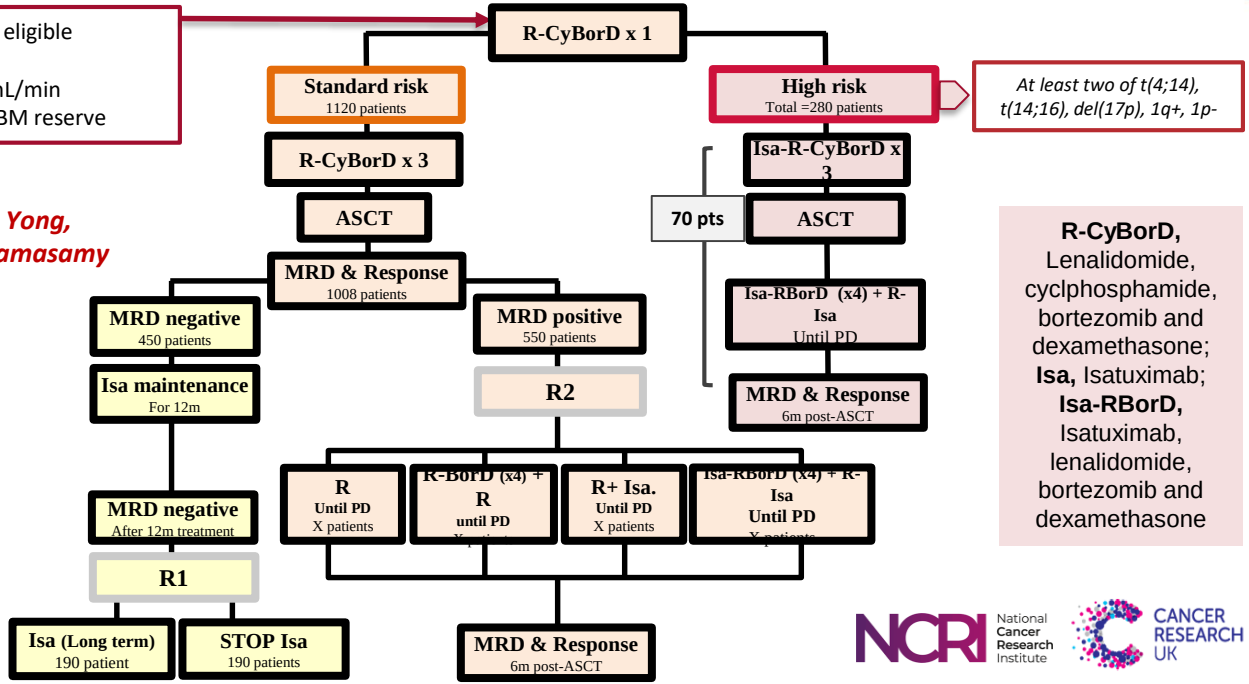
| • **Mesurable residual disease** | • **MRD/sustained-MRD** could provide information to tailor treatment in high-risk patients |

# Current RADAR Study Design

Transplant eligible
ECOG 0-2
GFR ≥ 30 mL/min
Adequate BM reserve

***PIs: Kwee Yong, Karthik Ramasamy***



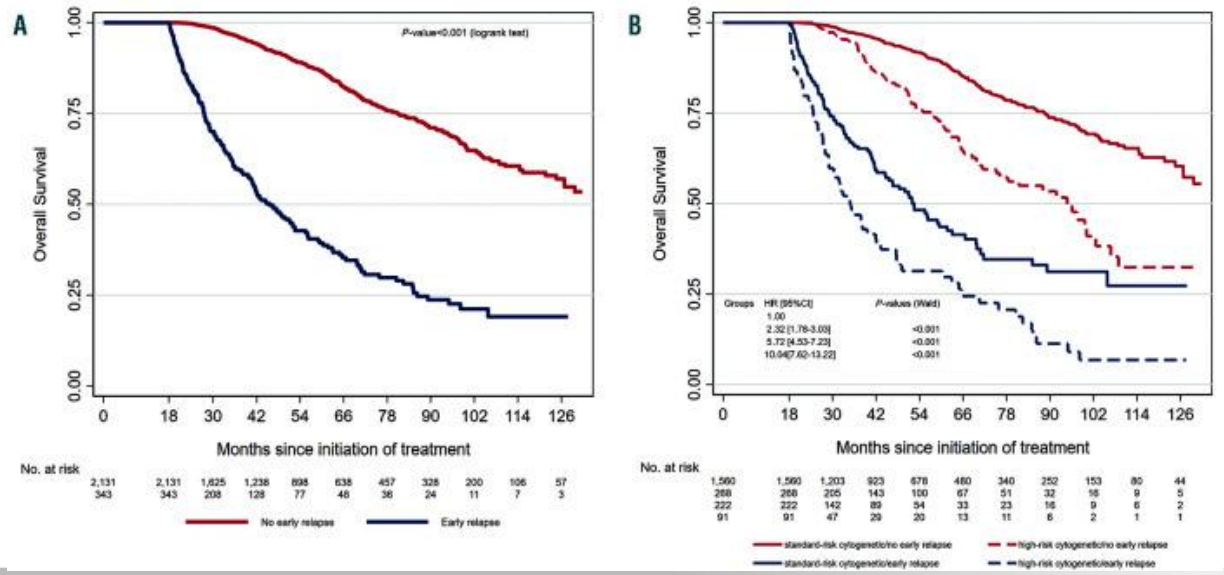

**R-CyBorD,** Lenalidomide, cyclphosphamide, bortezomib and dexamethasone;
**Isa,** Isatuximab;
**Isa-RBorD,** Isatuximab, lenalidomide, bortezomib and dexamethasone

All patients are tested for MRD at 12 and 24 months

# Functional high-risk: early relapse

Early relapse defined as: < 18 months from treatment start or <12 months after ASCT)

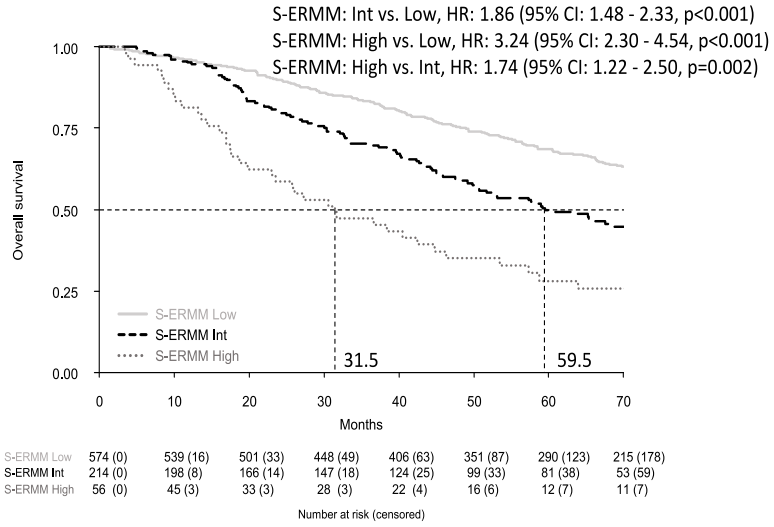
19% of patients experienced early relapse; 12.5% were defined Standard risk





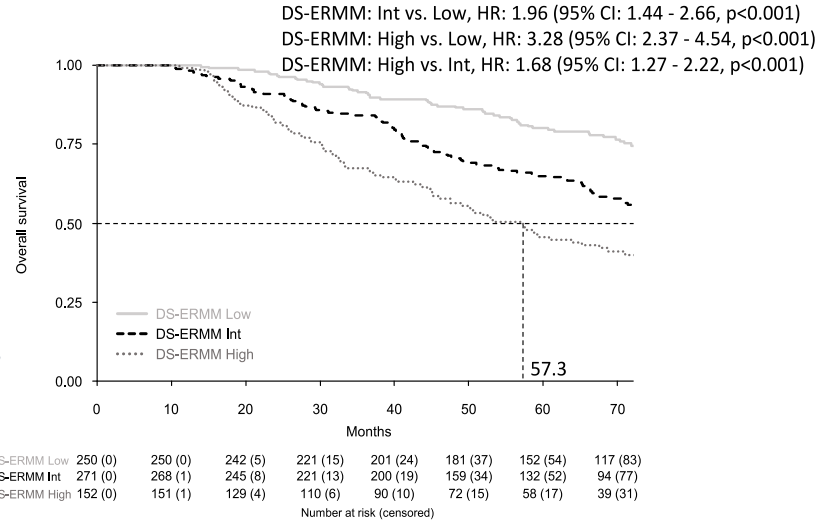

*Corre et al., Haematologica 2020*

## OS according to the risk of early relapse, based on baseline features only




***54% of patients change is risk-status***

## OS according to the risk of early relapse at 9 months, based on baseline features + response



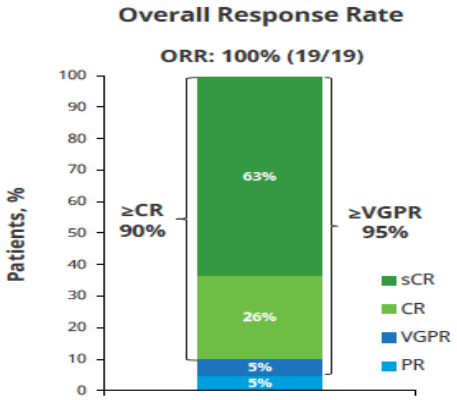



Caccese M, et al. Clin Cancer Res. 2021 Apr 29:clincanres.0134.2021. doi: 10.1158/1078-0432.CCR-21-0134. Online ahead of print.

# THANK YOU

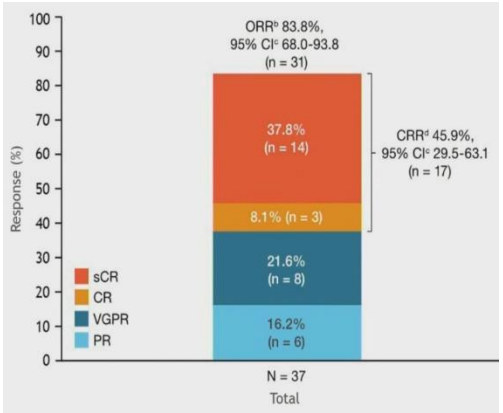
# CAR-T IN EARLY RELAPSE

**CARTITUDE-2 Cohort B:**
Cilta-cel in patients with early relapse after initial therapy (n=19)
Progression ≤12 months from ASCT or induction therapy.




Median DOR was NR
**12-month PFS rate was 89.5%**

**KarMMa-2:**
Cohort 2a – Ide-cel for patients with an early relapse after ASCT



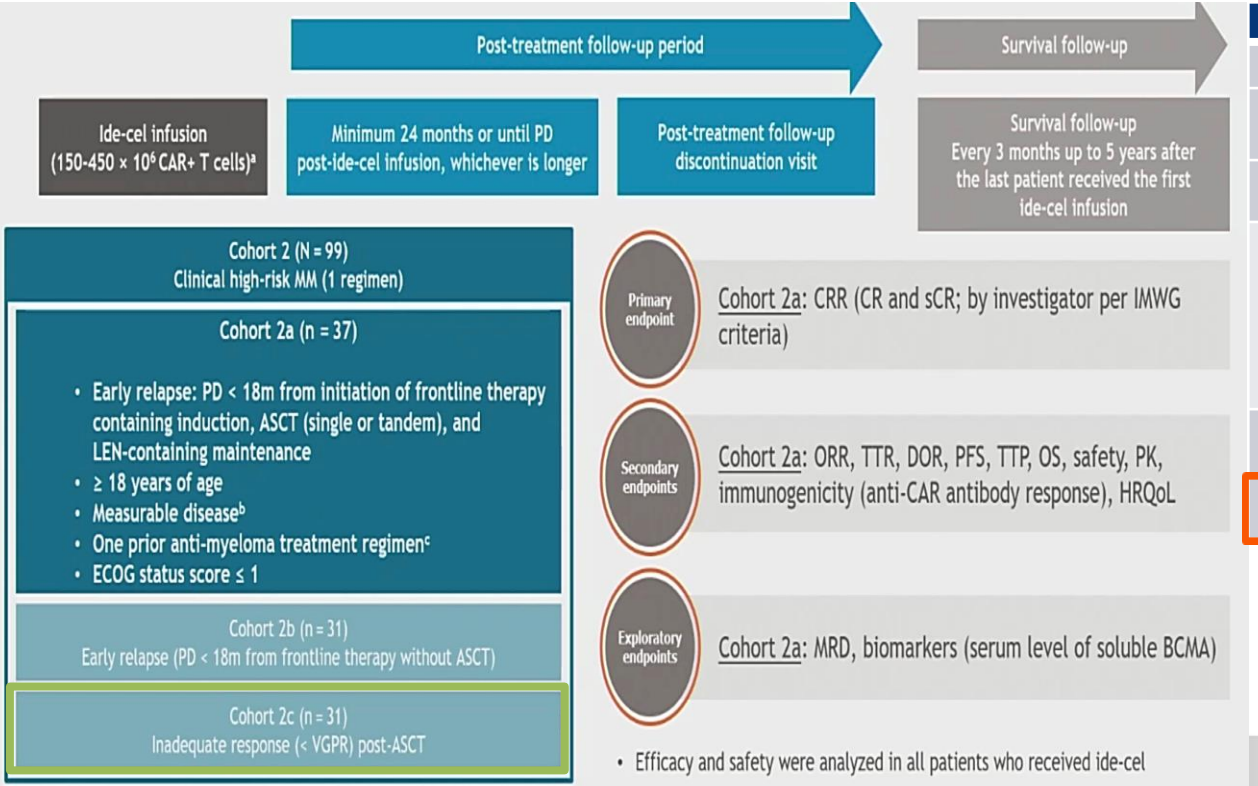

**Median duration of response in responding patients**: 15.7 months
**Median duration of response in patients achieving a ≥CR**: 23.5 months



CAR: chimeric antigen receptor; AE: adverse event; LOT: line of therapies; MNT:Movement and neurocognitive treatment-emergent; EMD: extramedullary disease; ORR: overall survival; CR: complete response; VGPR: very good partial response; DOR: duration of response; PFS: progression free survival; NR: not reached

van de Donk N et al. ASH 2022; abstract 3354 (poster presentation)

# KarMMa-2: Cohort 2c – inadequate response after ASCT




## Baseline characteristics

| Characteristic | n=31 |
|---|---|
| Age, median years (range) | 64.0 (46.0–72.0) |
| Median time from initial diagnosis to screening, years (range) | 1.0 (0.7–1.9) |
| Extramedullary disease, n (%) | 2 (6.5) |
| High-risk cytogenetics, n (%) Includes del17p, t(4;14), t(4;16) | 3 (9.7) |
| Standard risk cytogenetics | 14 (45.2) |
| Not evaluable/missing data | 14 (45.2) |
| Best overall response to ASCT, n (%) | |
| PR | 27 (87.1) |
| MR | 2 (6.5) |
| SD | 2 (6.5) |



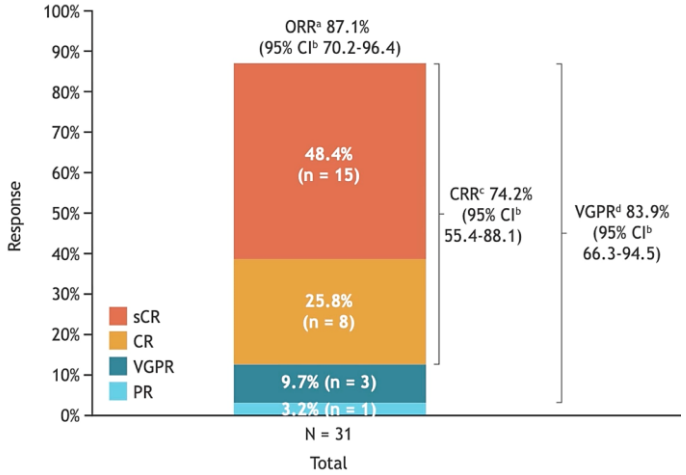
• Dhodapkar M et al. ASH 2022;abstract 3314 (poster presentation)

# KarMMa-2: ORR and MRD

## Cohort 2c – inadequate response after ASCT

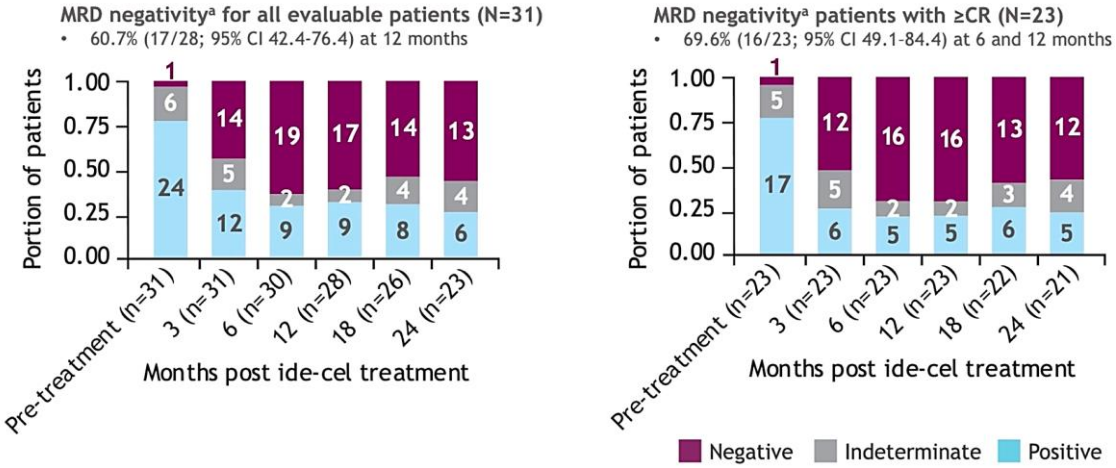
## Upgrade in Response Quality by consecutive CART

### ORR




- **Median follow-up**: 27.9 months

### MRD negativity at $10^{-5}$ by NGS/NGF




[a]MRD negative was defined as minimum of 1 in $10^5$ nucleated cell.



• Dhodapkar M et al. ASH 2022;abstract 3314 (poster presentation)