# Highlights from IMW 2019

19-20 novembre 2019
Bologna
Royal Hotel Carlton

# La terapia ottimale di induzione e di consolidamento

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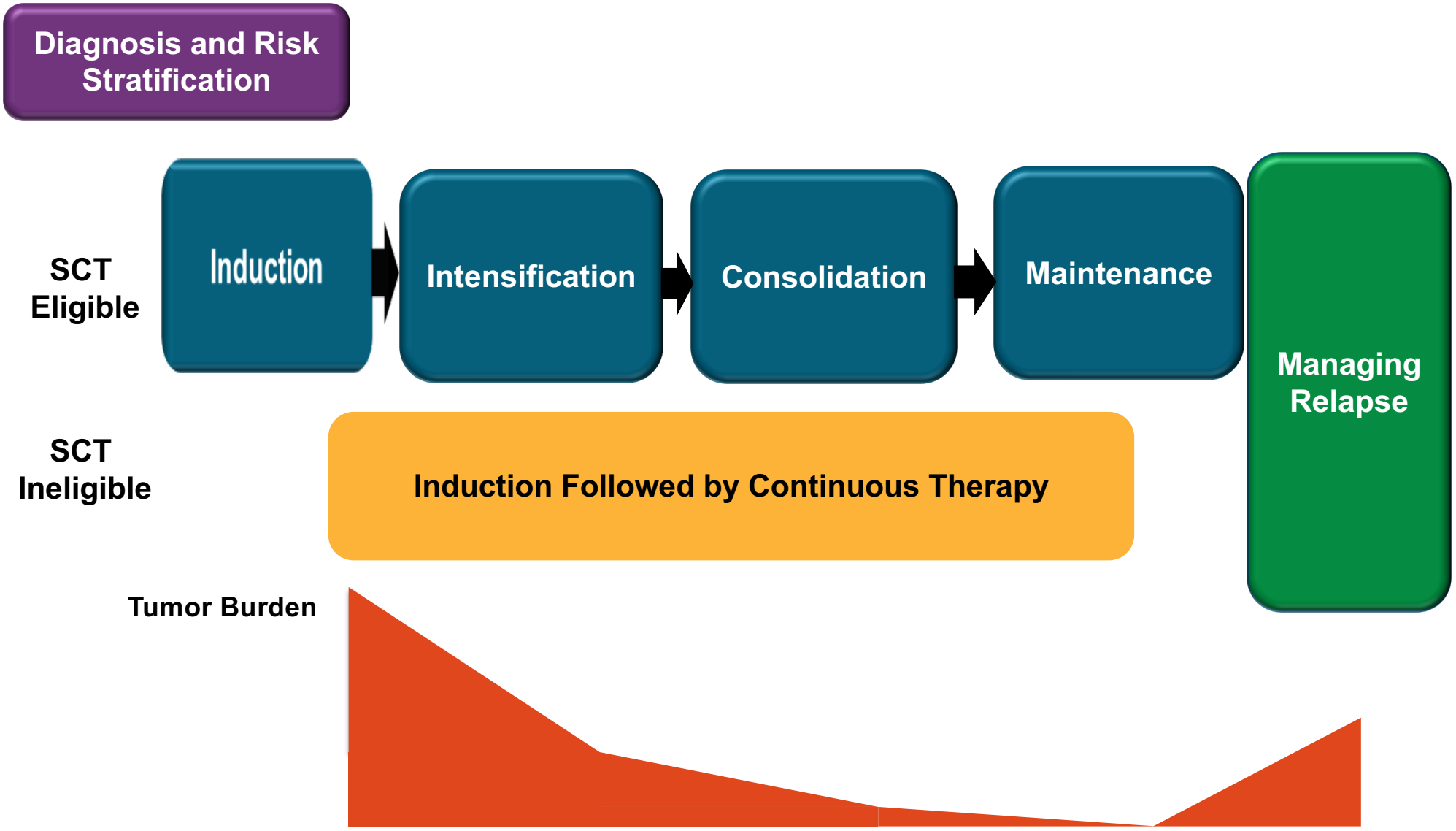
POLICLINICO UMBERTO I

# DISCLOSURE

## Maria Teresa Petrucci

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Honoraria |
|---|---|---|---|---|---|---|---|
| Celgene | | | | | | X | X |
| Janssen-Cilag | | | | | | X | X |
| Takeda | | | | | | X | X |
| BMS | | | | | | X | X |
| Amgen | | | | | | X | X |
| Sanofi | | | | | | X | X |
| | | | | | | | |

# MM Treatment Paradigm



# Quale dovrebbe essere la migliore terapia di induzione per i pazienti eleggibili al trapianto?

**regime di induzione ideale dovrebbe…**

- ✓ **Avere una bassa tossicità;**
- ✓ **Risolvere le problematiche legate alla malattia come la ipercalcemia, anemia, insufficienza renale;**
- ✓ **Migliorare il PS e la QoL;**
- ✓ **Permettere una adeguata raccolta di cellule staminali;**

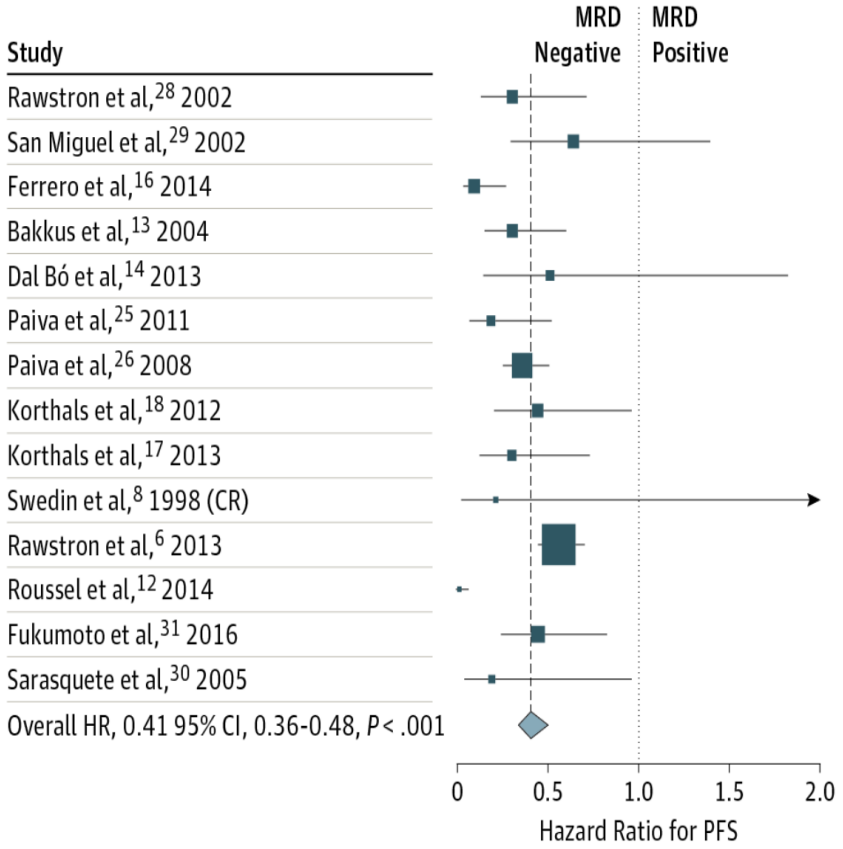
**ma soprattutto…**

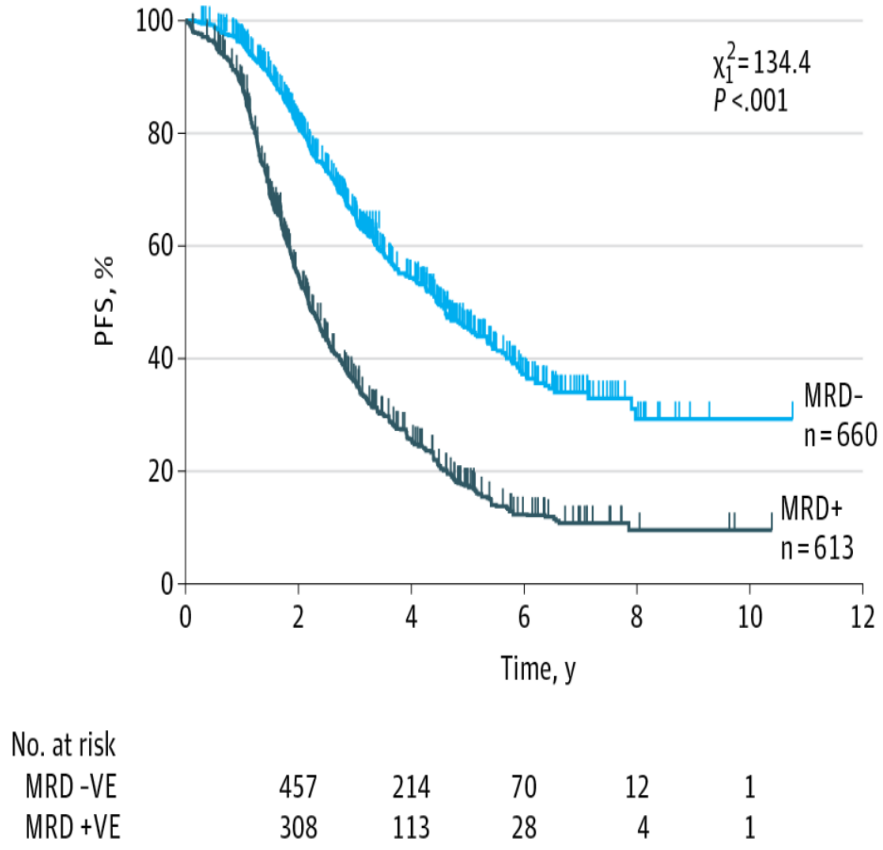
- ✓ **ottenere una rapida e profonda risposta della massa tumorale, perché una ottima qualità della risposta (≥VGPR) è il migliore predittore dell'andamento a lungo termine del paziente con mieloma multiplo;**

**e…. possibilmente a costi contenuti (?!?!).**

# Association of Minimal Residual Disease With Superior Survival Outcomes in Patients With Multiple Myeloma: A Meta-analysis

## PFS

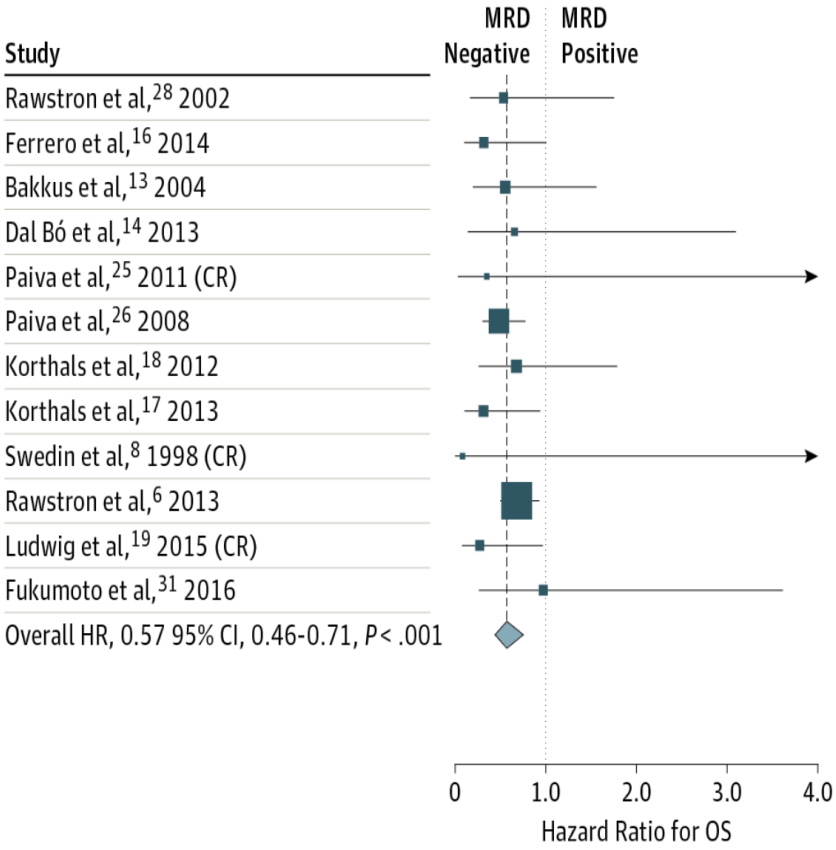


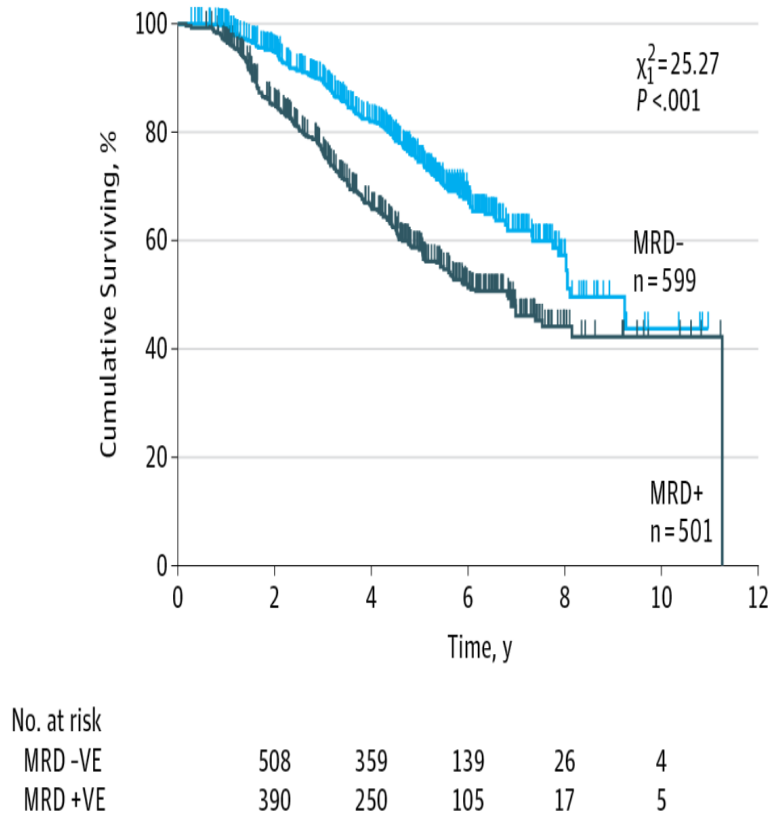




*Munshi NC. JAMA Oncol.* 2017

# Association of Minimal Residual Disease With Superior Survival Outcomes in Patients With Multiple Myeloma: A Meta-analysis

## OS




*Munshi NC. JAMA Oncol.* 2017

# Quale dovrebbe essere la migliore terapia di induzione per i pazienti eleggibili al trapianto?

- **VTD è superiore a TD in RR ≥VGPR and PFS *(Cavo M et al, Lancet 2010);***
- **VTD is superiore a VD in RR ≥VGPR *(Moreau P et al, Blood 2011);***
- **VRD is superiore a RD in ORR, PFS and OS *(Durie BGM et al, Lancet 2017);***

**Consideriamo che "le triplette" contenenti un inibitore del proteasoma (PI) e un immunomedulante (IMiD) hanno "il perfetto numero e tipo" di agenti in combinazione.**

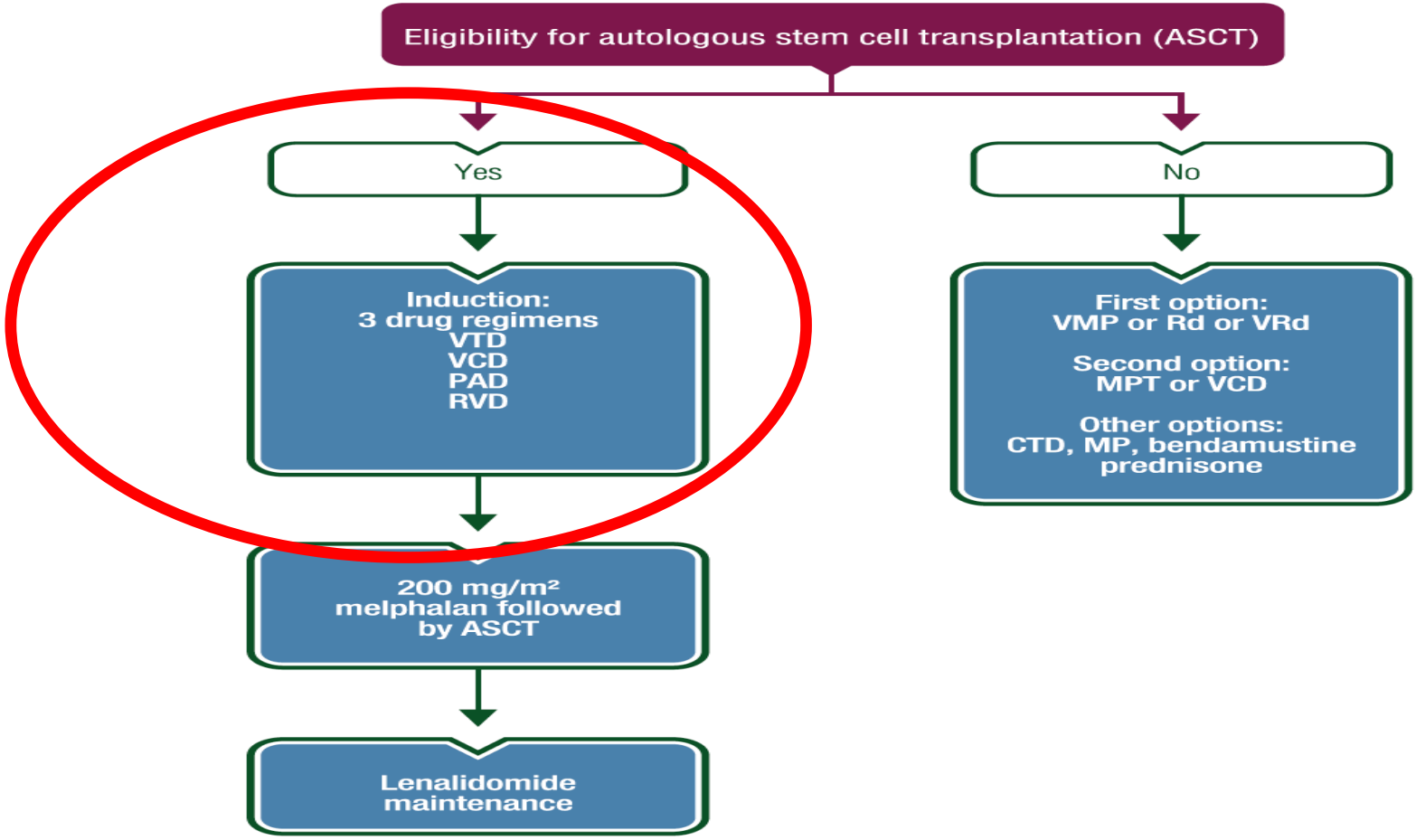
**I regimi preferiti attualmente, per i pazienti di nuova diagnosi eleggibili al trapianto, sono:**

- **VTD: bortezomib, talidomide, desametasone**
- **VRD: bortezomib, lenalidomide, desametasone**

**Ma altre due triplette devono essere considerate in casi particolari:**

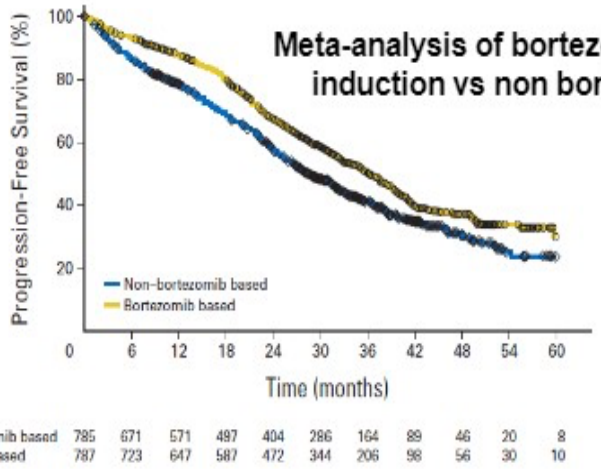
- **VCD: bortezomib, ciclofosfamide, desametasone**
- **KRD: carfilzomib, lenalidomide, desametasone**

# Front-line treatment: ESMO 2017




Moreau P et al. Ann Oncol, 2017

# Induction therapy: state of the art




CR + nCR: 38% vs 24%, P<.0001
median PFS: 35.9 vs 28.6 mos, P<.0001
OS @3-yr: 79.7% vs 74.7%, P=.0402

**Induction therapy**

VTD
VRD
VCD
PAD
KRD
IxaRD

**3-drug bortezomib-based combinations are the current standard of care for induction therapy**

Which is the best partner for bortezomib?

| Regimens / study | Response | | Safety profile | |
|---|---|---|---|---|
| | ≥ VGPR % | ≥ CR % | SAEs | Grade 3/4 PN |
| PAD vs VCD Prospective[2] | 34.3 vs 37.0 *P* = .58 | 4.4 vs 8.4 *P* = .10 | 32.7% vs 24% *P* = .04 | |
| VTD vs VCD Prospective[3] | 66.3 vs 56.2 *P* = .05 | 13.0 vs 8.9 *P* = .22 | | 7.7% vs 2.9% *P* = .05 |
| VTD vs VCD Case-matched[4] | 64 vs 37 *P*<.001 | 19 vs 6 *P*<.001 | | 7% vs 2% *P* = .009 |


*1. Sonneveld P, et al. J Clin Oncol 2013;31(26): 3279-87;*
*2. Mai EK, et al. Leukemia. 2015;29(8):1721-1729; 3. Moreau P, et al. Blood. 2016;127(21):2569-2574;*
*4. Cavo M, et al. Leukemia. 2015;29(12):2429-2431;*

Management of multiple myeloma in the newly diagnosed patient

*María-Victoria Mateos[1] and Jesús F. San Miguel[2]*

## *How to choose the induction regimen*

After the presentation of the different regimens, the results to date show that most MM patients will respond to triple combinations, with at least one-third achieving CR after 4 to 6 induction cycles (Table 1). Based on the previously reported results, the triplet combination should include a PI and dexamethasone. The election of the third drug must take into account various factors, including prognostic factors; the nature and extent of MM-associated organ impairment; the presence of comorbid conditions such as PN, diabetes, or heart failure; as well as patient preferences and resources and availability in different countries. The triplets combining PI, immunomodulatory drugs (IMiDs), and dexamethasone, VTD, or VRD seem to be the optimal choice, effective in both standard and high-risk patients, with good tolerability; VCD would also be appropriate, especially if IMiDs are not available or comorbid conditions make its use not possible.

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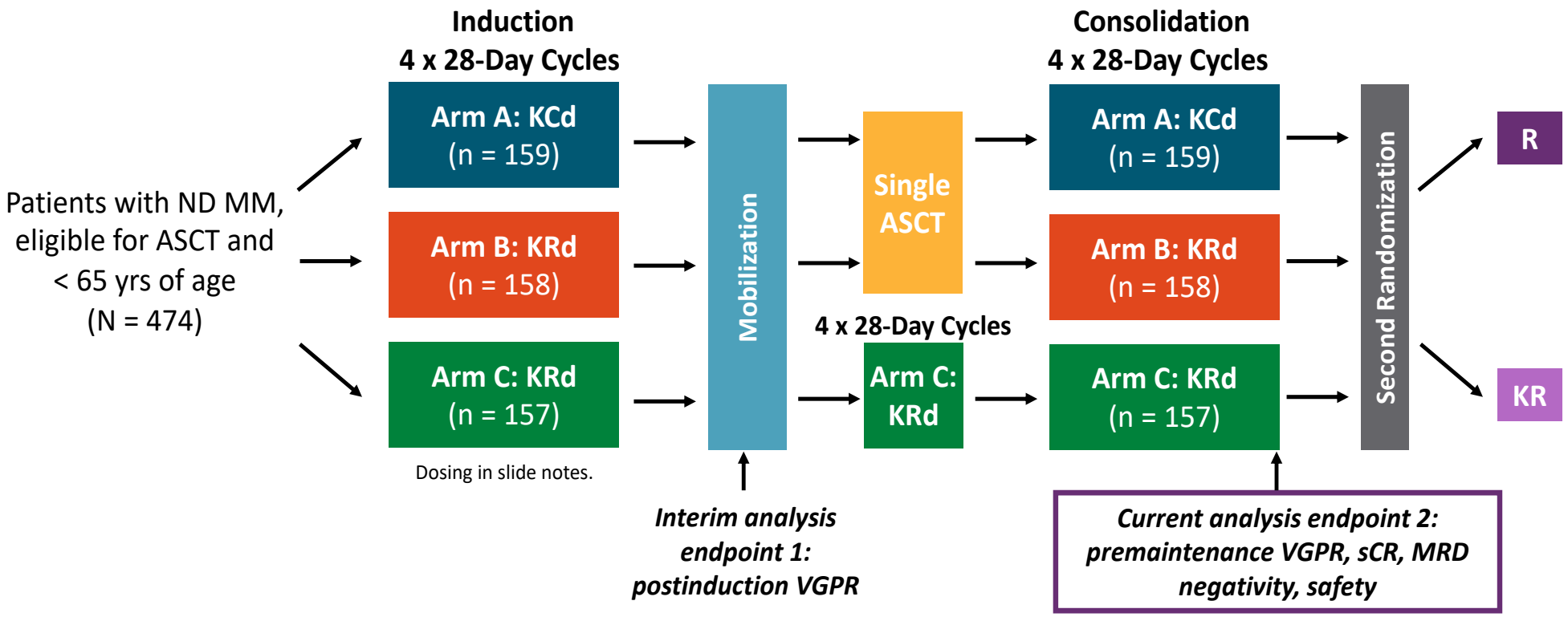
# FORTE KRd in Newly Diagnosed MM

## Multicenter, randomized, open-label II study

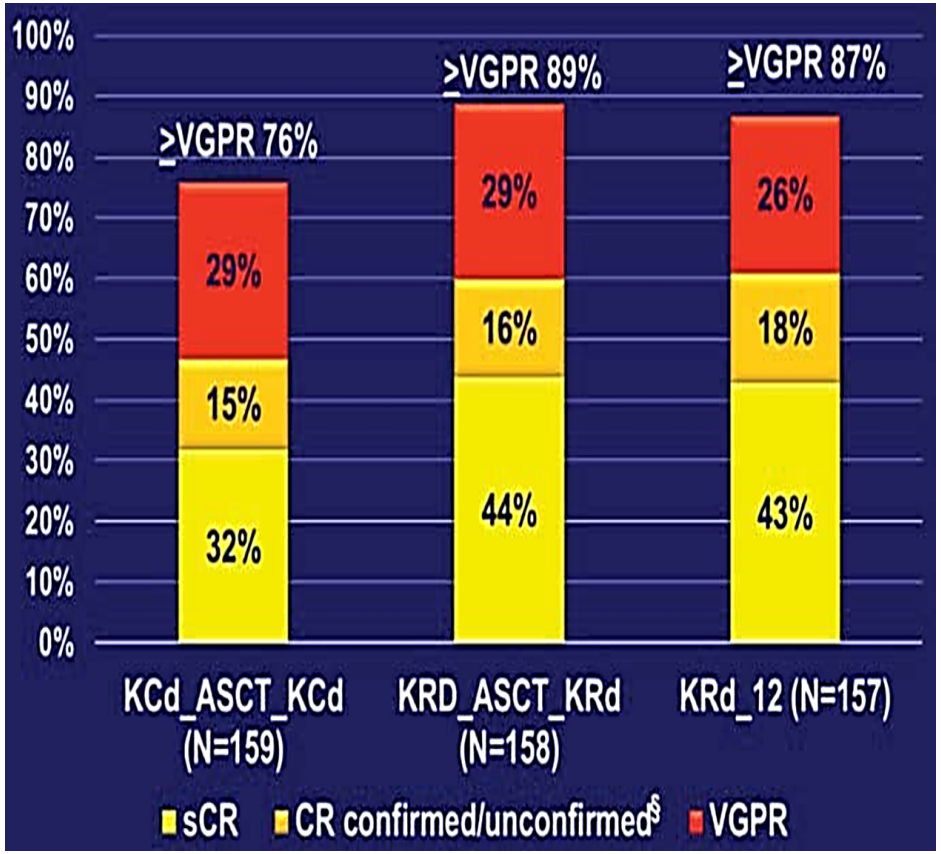



Gay F. et al. ASCO 2019 e IMW 2019

Gay F. et al. ASH 2018

# FORTE KRd in Newly Diagnosed MM
## Responses

| Response Rate | KCd–ASCT–KCd (n = 159) | KRd–ASCT–KRd (n = 158) | KRd x 12 cycles (n = 157) |
|---|---|---|---|
| After ASCT or 8 KRd cycles (ITT), % | | | |
| ▪ ≥ VGPR | 66 | 81 | 85 |
| ▪ sCR | 15 | 23 | 30 |
| ▪ CR* | 9 | 11 | 4 |
| ▪ VGPR | 42 | 47 | 51 |
| Premaintenance, % | | | |
| ▪ ≥ VGPR | 76 | 89 | 87 |
| ▪ sCR | 32 | 44 | 43 |
| ▪ CR* | 15 | 16 | 18 |
| ▪ VGPR | 29 | 29 | 26 |
| MRD negativity† premaintenance, % | 42 | 58 | 54 |




*Confirmed or unconfirmed. †MRD assessed by 2nd generation flow cytometry, with sensitivity of $10^{-5}$.

Gay. ASH 2018. Abstr 121.

# FORTE KRd in Newly Diagnosed MM
## Safety

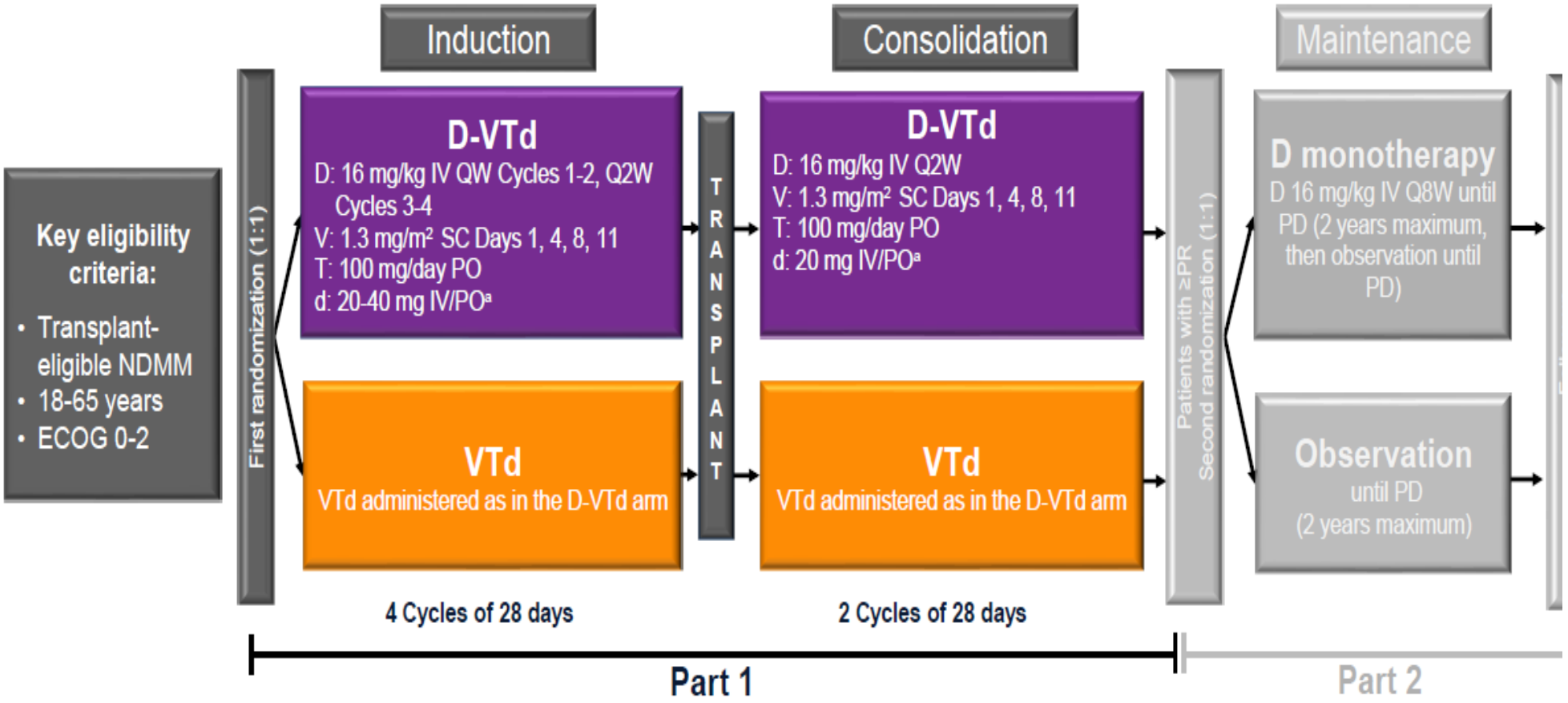
| Safety Outcome, % | KCd–ASCT–KCd (n = 159) | KRd–ASCT–KRd (n = 158) | KRd x 12 cycles (n = 157) |
|---|---|---|---|
| Dose reduction - Reduced ≥ 1 drug | 19 | 32 | 36* |
| **Treatment-Related Grade 3/4** | | | |
| Dermatologic | 1 | 6 | 13* |
| Renal | 1 | 1 | 3 |
| Gastrointestinal | 3 | 4 | 3 |
| Infections | 9 | 10 | 13 |
| Hepatic | 1 | 8 | 10* |
| Deep vein thrombosis/pulmonary embolism | 3 | 1 | 3 |
| Hypertension | 3 | 3 | 8* |
| Cardiac | 3 | 3 | 2 |
| ≥ 1 nonhematologic AE | 26 | 35 | 48* |
| Death due to AE | 2 | 1 | 1 |

*Statistically significant.

Gay. ASH 2018. Abstr 121.

# Phase 3 CASSIOPEIA Study Design

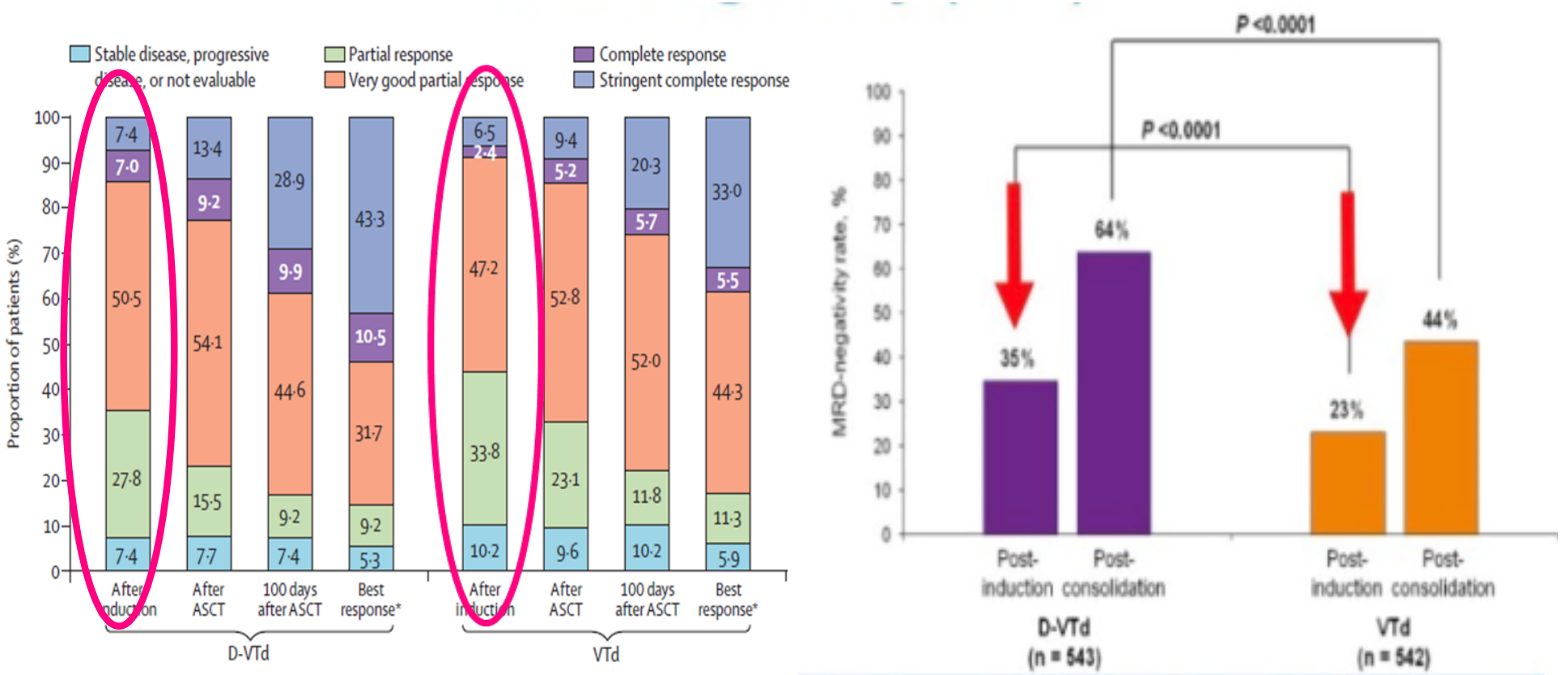
- Phase 3 study of D-VTd versus VTd in transplant-eligible NDMM (N = 1,085), 111 sites from the 9/2015 to 8/2017




***Endpoint primario*: SCR a 100 giorni dall'ASCT**

Moreau P et al. Lancet 2019

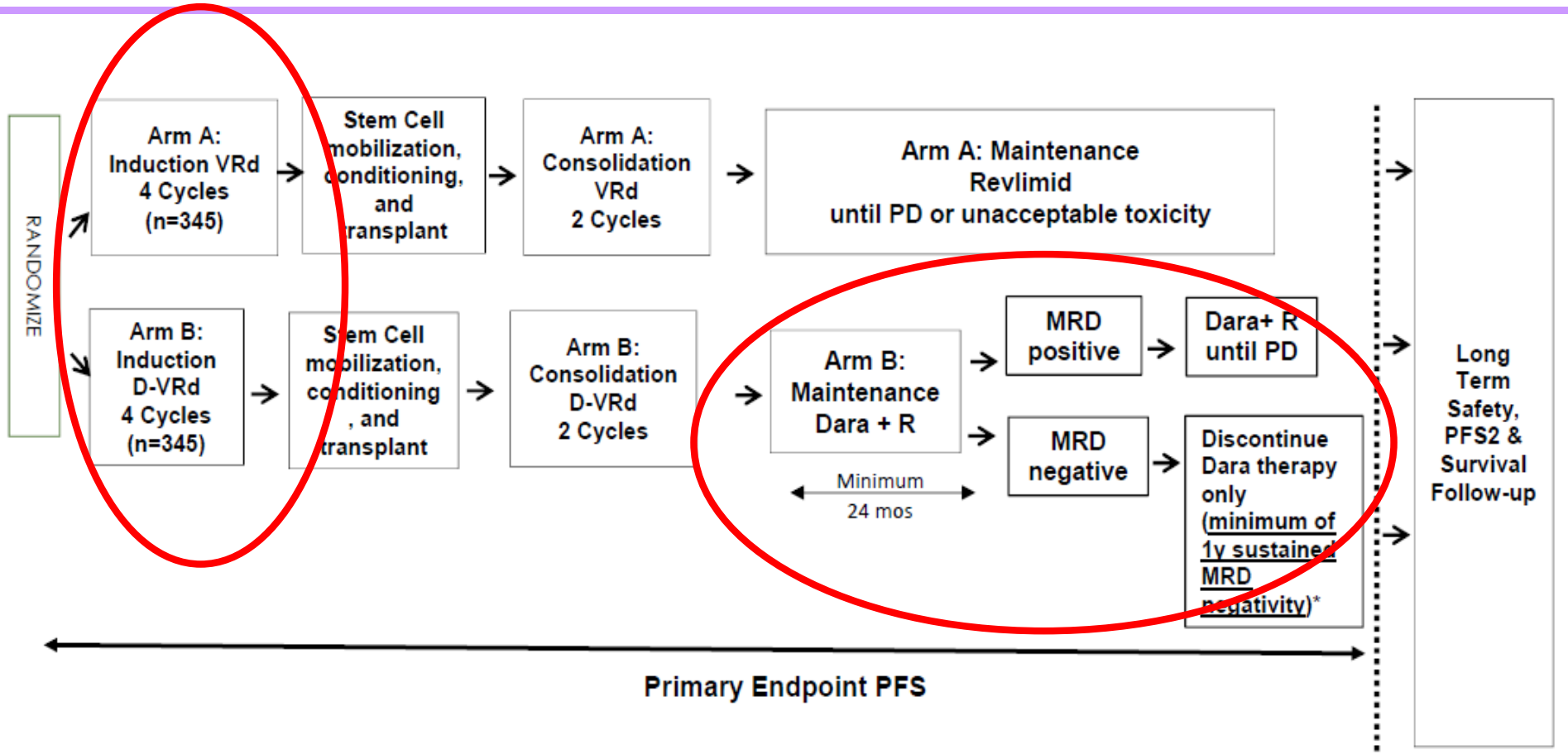
# Post-induction rates of response and MRD-negativity ($10^{-5}$)




**Early (post-induction) significant difference in MRD-negativity rates for D-VTD versus VTd**

Avet-Loiseau H et al EHA 2019

# A Phase 3 Study Comparing Daratumumab, [redacted] (bortezomib), Lenalidomide, and Dexamethasone (D-VRd) vs [redacted] Lenalidomide, and Dexamethasone (VRd) in Subjects with Previously Untreated Multiple Myeloma who are Eligible for High-Dose Therapy. The Perseus Study



# **Daratumumab** in Combination with Carfilzomib, Lenalidomide, and Dexamethasone (**KRd**) in Patients With Newly Diagnosed Multiple Myeloma (**MMY1001**): an Open-label, Phase 1b Study

## Study Design

**Open-label, Multicenter, Phase 1b Study (N = 22)**

- NDMM
- Transplant eligible and non-eligible
- Treatment duration: ≤13 cycles or until elective discontinuation for ASCT
- No clinically significant cardiac disease; echo required at screening

**Dosing Schedule (28-d cycles)**

**Daratumumab**:
- **Split dose: 8 mg/kg Days 1-2 of Cycle 1**
- 16 mg/kg QW on Cycles 1-2, Q2W on Cycles 3-6, and Q4W thereafter

**Carfilzomib**:
- 20 mg/m$^2$ C1D1
- Escalated to 70 mg/m$^2$ C1D8+; **weekly (Days 1, 8, 15)**

**Lenalidomide**:
- 25 mg; Days 1-21 of each cycle

**Dexamethasone**: 40 mg/week[a]

**Endpoints**

**Primary**
- Safety, tolerability

**Secondary**
- ORR, duration of response, time to response, IRR

**Exploratory**
- PFS

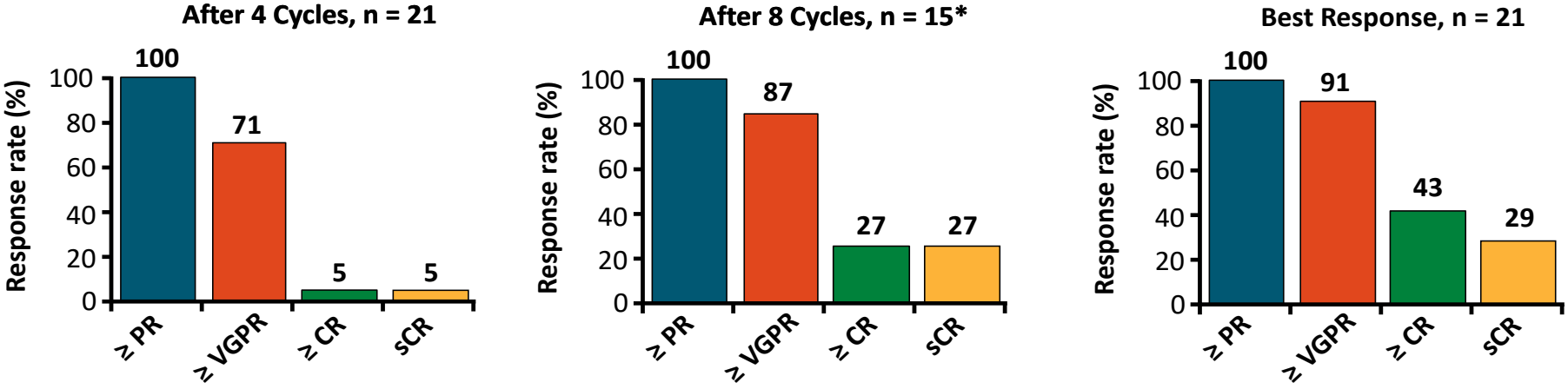


Echo, echocardiogram; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; C1D1, Cycle 1 Day 1; C1D8, Cycle 1 Day 8; IRR, infusion-related reaction; C1D3, Cycle 1 Day 3.
[a]20 mg if >75 y. [b]On daratumumab dosing days, dexamethasone 20 mg IV was administered as pre-medication on infusion day and 20 mg PO the day after infusion; for DARA, split first dose dexamethasone 20 mg IV was administered as a pre-medication on C1D1 and C1D2; on C1D3, administration of low-rose methylprednisolone (≤20 mg PO) was optional. [c]Required before first daratumumab dose, optional for subsequent doses.

Jakubowisk *et al*. ASCO 2017

# Daratumumab + KRd in Newly Diagnosed MM
## Response

- Median number of treatment cycles: 11.5 (range: 1.0-13.0)




**Depth of response improved with duration of treatment**

*5 patients who proceeded to ASCT before cycle 8 and 1 patient who discontinued due to PD at cycle 7 were excluded.

- Median follow-up: 10.8 mos (range: 4.0-12.5)
- OS: 100% at follow-up

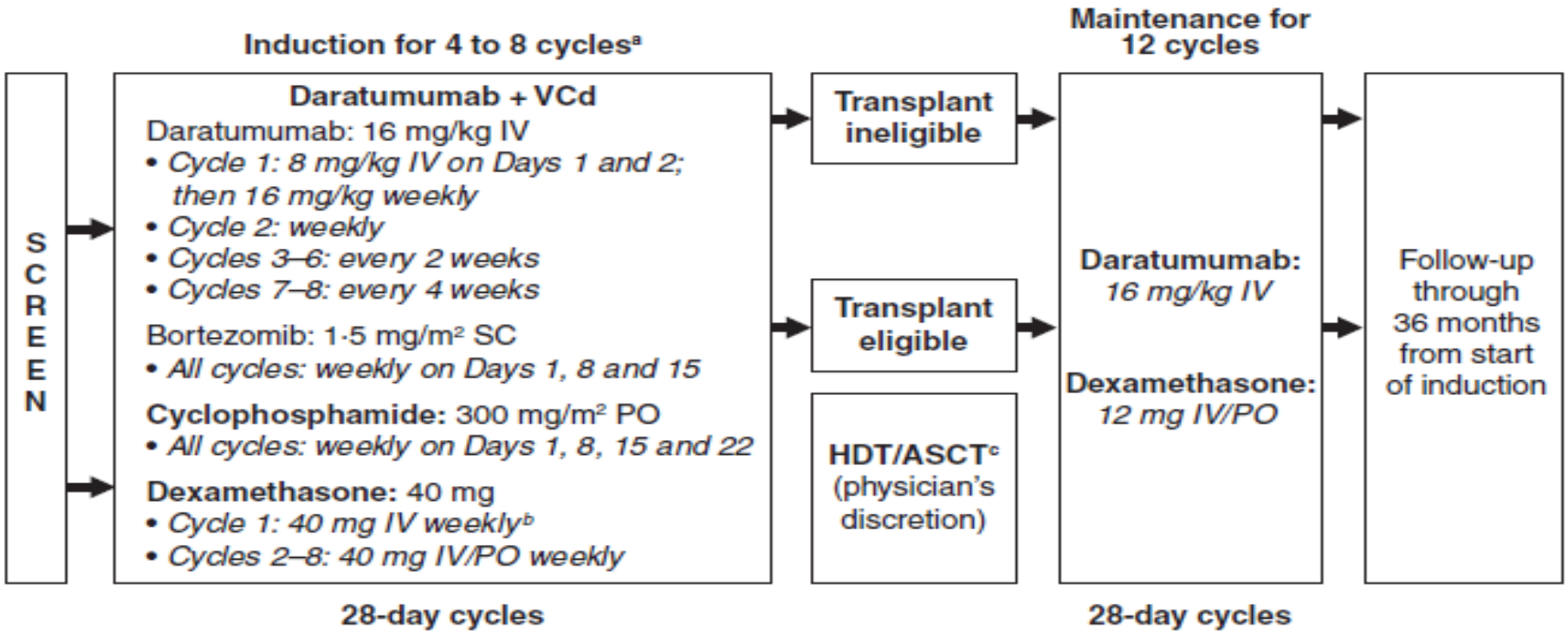
Jakubowisk ASCO2017. Abstr 8000

# Daratumumab + KRd in Newly Diagnosed MM

- **DARA + KRd was well tolerated**
  - Safety is consistent with previous reports of DARA and KRd
  - Low IRR rates associated with split first dose; no grade 3/4
- **Highly effective with 100% ORR**
  - 91% ≥VGPR and 43% ≥CR
  - Depth of response improved with duration of treatment
- **No adverse impact on stem cell collection ($10.4 \times 10^6$ cells/kg)**
  - DARA is feasible as part of induction therapy

Jakubowisk ASCO2017. Abstr 8000

# LYRA: Daratumumab + VCd in Multiple Myeloma



## Key Active and Enrolling Clinical Trials for ASCT-Eligible Patients With Newly Diagnosed MM

| Trial ID | Phase | Status | Investigational Regimen | Primary Endpoint |
|---|---|---|---|---|
| Cassiopeia<br>**NCT02541383** | III | Active, preliminary results available | Dara + VTD vs VDT (induction and consolidation); if PR or better: Dara maintenance vs observation | sCR, PFS |
| GRIFFIN<br>**NCT02874742** | II | Active, preliminary results available | Dara + VRd (induction and consolidation) → Dara + R maintenance vs VRd (induction and consolidation) → R maintenance | sCR |
| GMMG-HD6<br>**NCT02495922** | III | Active, awaiting results | Elo + VRd → Elo + VRd → Elo + R maintenance<br>Elo + VRd → VRd → R maintenance<br>VRd → Elo + VRd → Elo + R maintenance<br>VRd → VRd → R maintenance | PFS |
| ENDURANCE<br>**NCT01863550** | III | Currently enrolling | 1st randomization: VRd vs KRd (induction); 2nd randomization: R maintenance for 24 cycles vs until PD | OS, PFS |
| Perseus<br>**NCT03710603** | III | Currently enrolling | Dara + VRd (induction and consolidation) → Dara + R maintenance vs VRd (induction and consolidation) → R maintenance | PFS |
| GMMG HD7<br>**NCT03617731** | III | Currently enrolling | 1st randomization: Isatuximab + VRd vs VRd (induction)<br>2nd randomization: Isa + R vs R maintenance for 36 months | MRD negativity<br>PFS |
| DSMM XVII<br>**NCT03948035** | III | Currently enrolling | Elo + KRd (induction and consolidation) → Elo + R maintenance vs KRd (induction and consolidation) → R maintenance | MRD negativity<br>PFS |

# Conclusions
## Induction

**Induction is an important step of high-dose therapy in patients with MM eligible for ASCT**

**VTD/VRD are the best options up-front TODATE**

**KRD > VRD ?**

**Role of quadruplet, including CD38 MoAb will increase MRD negativity rate after induction with increase surrogate for final outcome**

**Conside the global strategy: induction/ASCT and conditioning/consolidation/maintenance**

# Consolidation Therapy

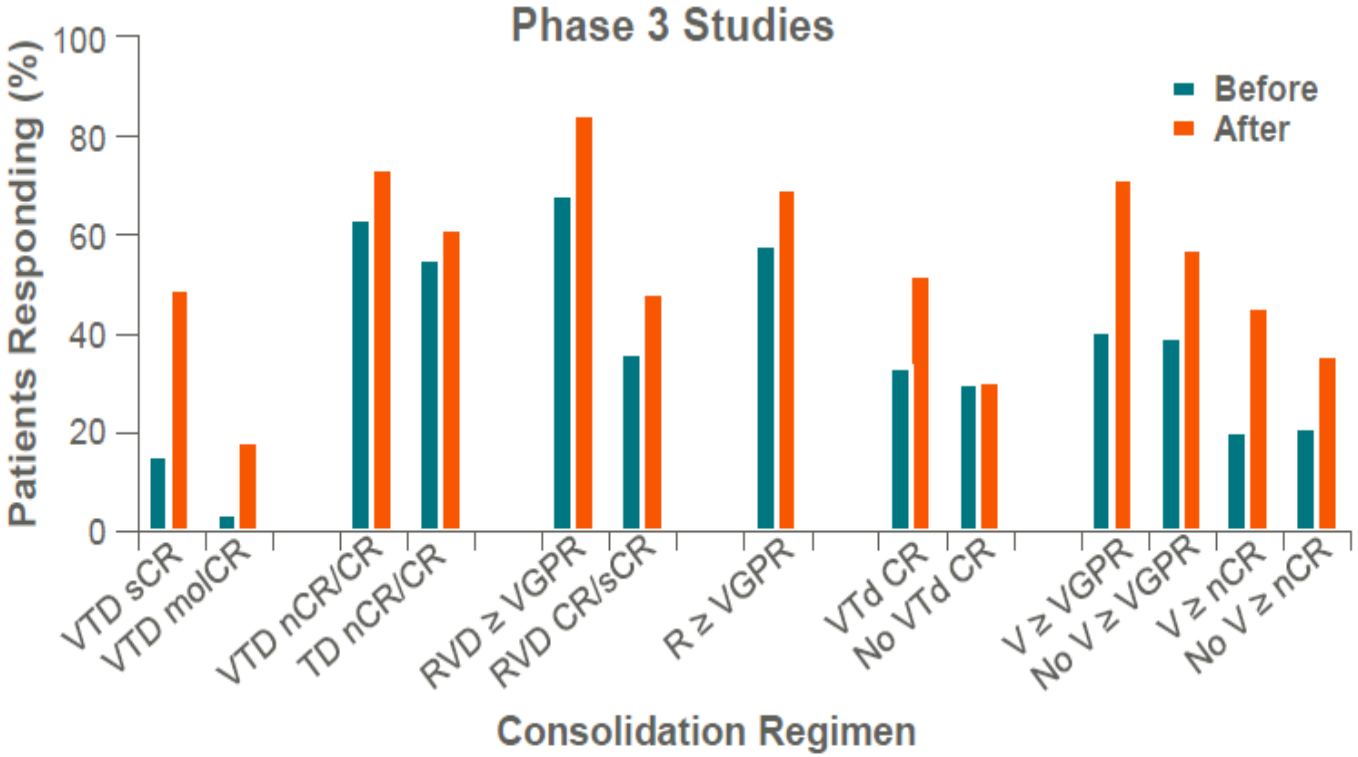
**Short-term** therapy aimed at

- enhancing the depth of response, either conventional CR (in the past) or molecular CR (at present time) after induction therapy followed or not by subsequent ASCT

- Extended PFS and OS
- Possibility of cure

*Cavo M. et al, Blood 2011, Blood 2012*

# Consolidation therapy: phase2/3 studies

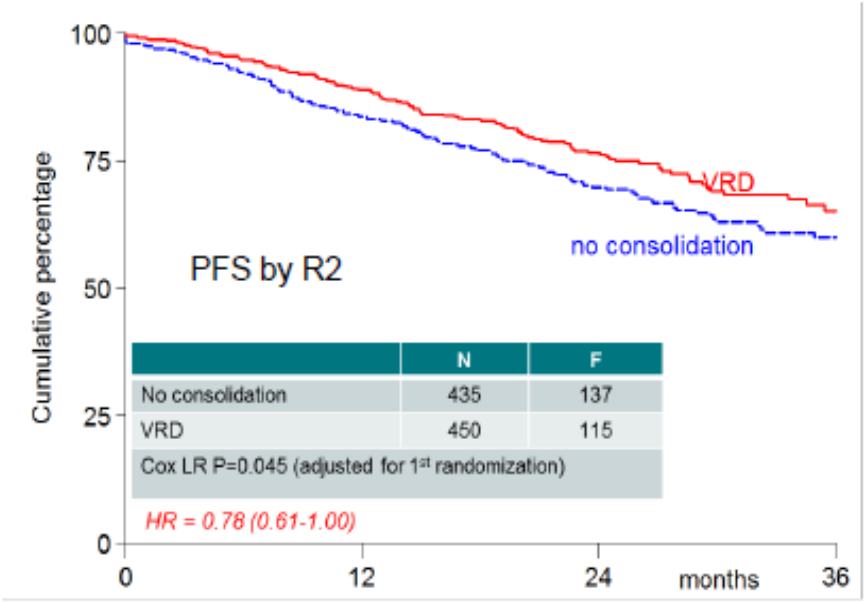



Consolidation therapy resulted in enhanced rates of high-quality conventional responses, in almost all the studies

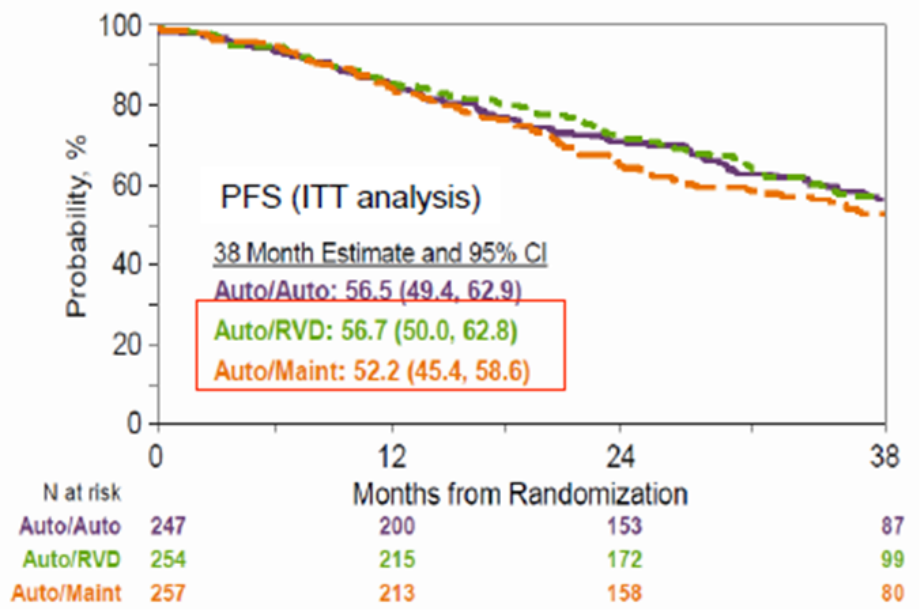
*McCarthy PL, Hahn T. Hematology Am Soc Hematol Educ Program. 2013;2013:496.*

# Consolidation is not yet a standard clinical practice
# Conflicting results emerged from two large randomized phase III trials

## EMN02 phase 3 study
## VRD consolidation vs no consolidation




## STaMINA phase 3 study
## VRD consolidation vs no consolidation



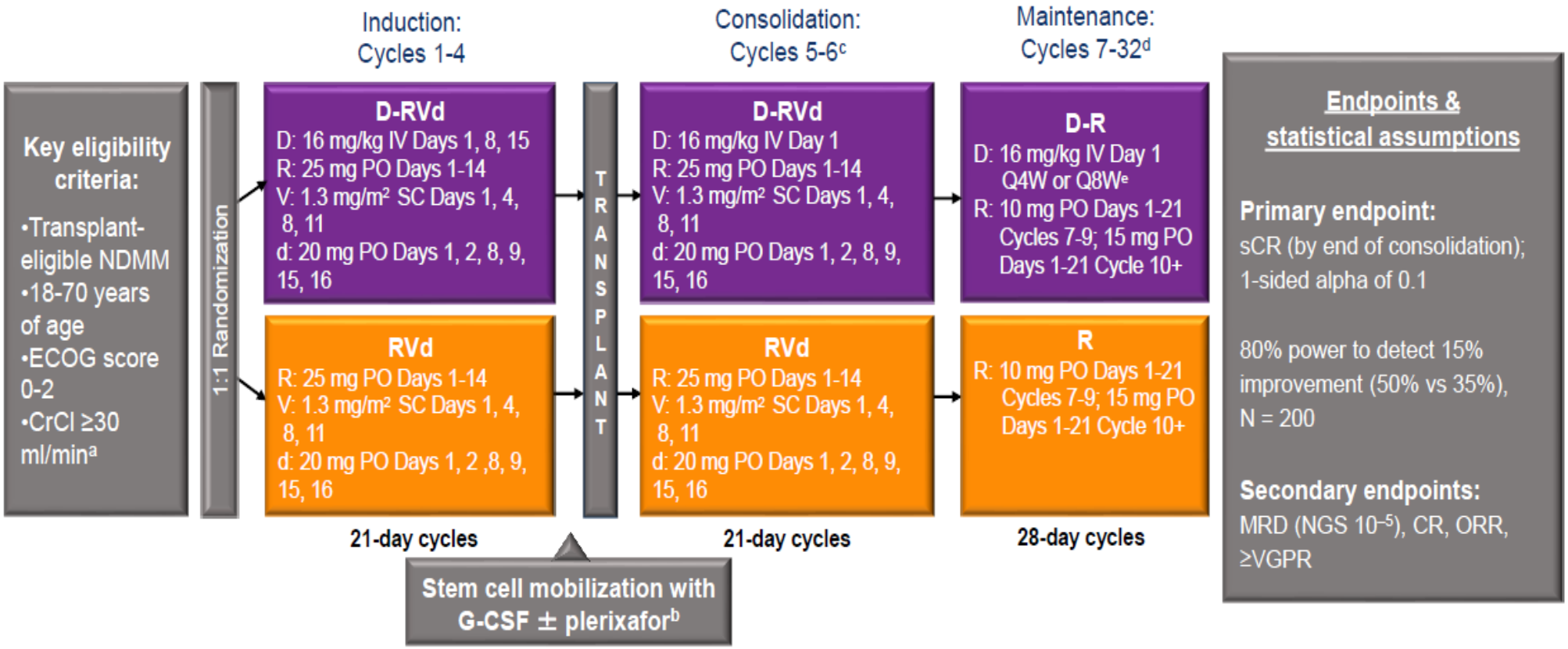

Sonneveld P, et al. EHA 2018, oral presentation; Stadtmauer EA et al. J Clin Oncol 2019;37(7):589-597.

# EMN02 and BMT CTN 0702: study inconsistencies

| | EMN02 | STAMINA |
|---|---|---|
| Newly diagnosed (%) | 100 | 85 |
| Induction regimen (%) | VCD (100) | VCD (14)<br>VRD (55) |
| Length of induction therapy (months) | 2-3 | 2-14 |
| Failure to receive double ASCT (%) | 19.8 | 32 |
| Consolidation therapy (%) | Yes (50) | NO (100) |
| Maintenance therapy | Len (10 mg) | Len (10-15) mg |
| PFS at 36-38 mos (%)<br>- All patients<br>- High-risk patients* | <br>73.6<br>64.9 | <br>56.5<br>42.2 |

# GRIFFIN: randomized phase II study

- Phase 2 study of D-RVd vs RVd in transplant-eligible NDMM, 35 sites in US with enrollment from 12/2016 and 4/2018

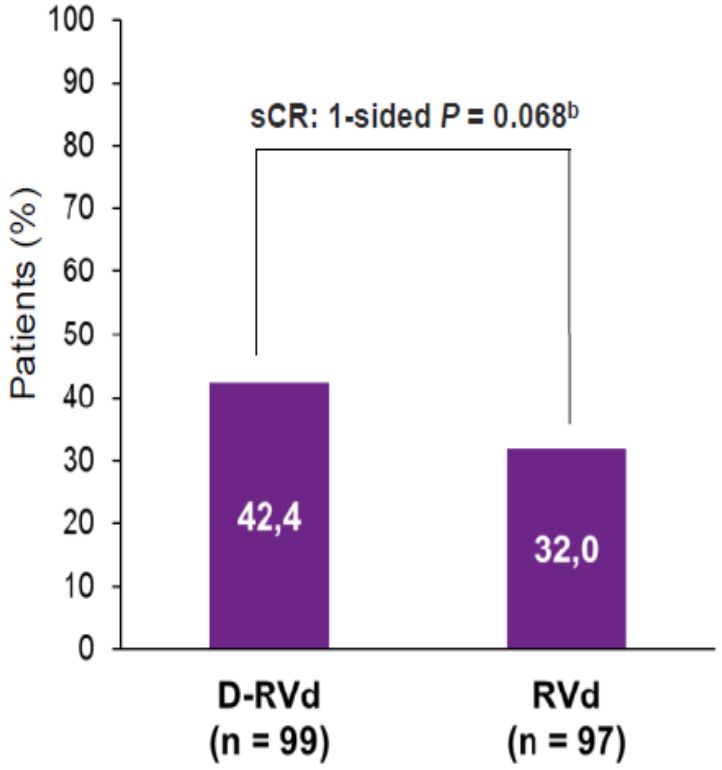



D-RVd, daratumumab-lenalidomide/bortezomib/dexamethasone; RVd, lenalidomide/bortezomib/dexamethasone; NDMM, newly diagnosed multiple myeloma; US, United States; ECOG, Eastern Cooperative Oncology Group; CrCl, creatinine clearance; IV, intravenously; PO, orally; SC, subcutaneously; G-CSF, granulocyte colony-stimulating factor; D-R, daratumumab-lenalidomide; Q4W, every 4 weeks; Q8W, every 8 weeks; sCR, stringent complete response; MRD, minimal residual disease; NGS, next-generation sequencing; CR, complete response; ORR, overall response rate; VGPR, very good partial response.

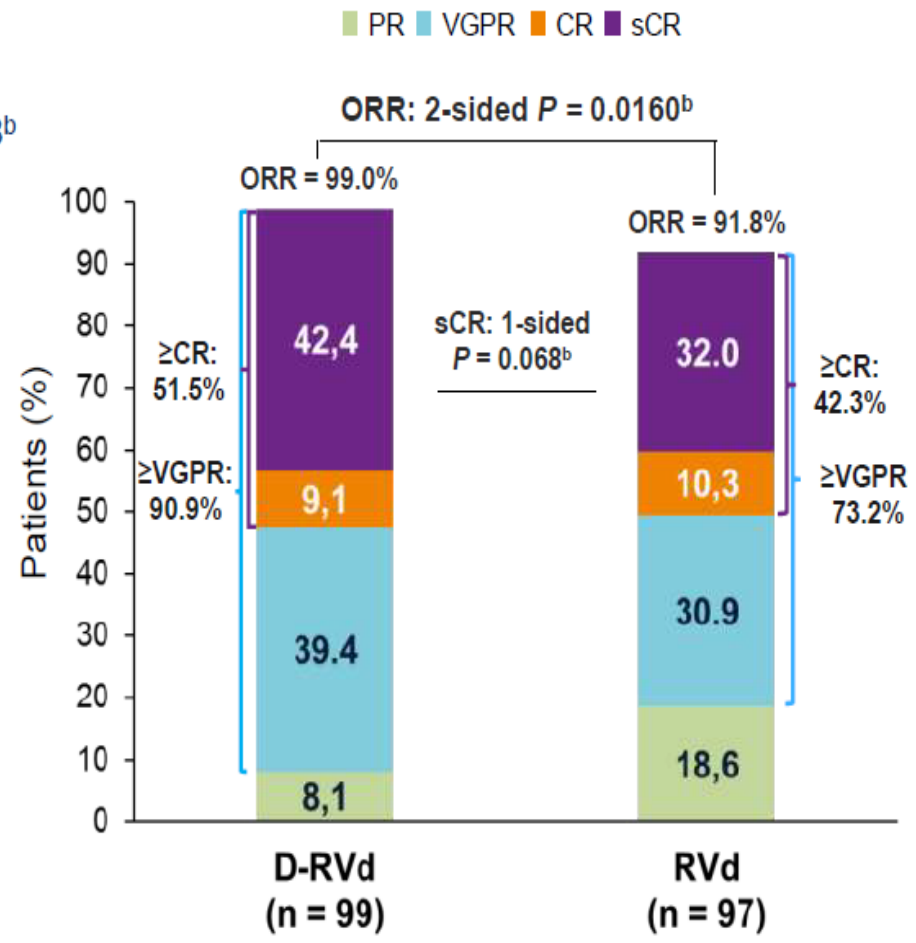
[a]Lenalidomide dose adjustments were made for patients with CrCl ≤50 mL/min. [b]Cyclophosphamide-based mobilization was permitted if unsuccessful. [c]Consolidation was initiated 60-100 days post transplant. [d]Patients who complete maintenance cycles 7-32 may continue single-agent lenalidomide thereafter. [e]Protocol Amendment 2 allowed for the option to dose daratumumab Q4W, based on pharmacokinetic results from study SMM2001 (NCT02316106).

# Primary endopoint: sCR by the end of consolidation

- **Primary endpoint met at pre-set 1-sided alpha of 0.1**
  - sCR by end of consolidation
    - 42.4% D-RVd vs 32.0% RVd
    - Odds ratio, 1.57; 95% CI, 0.87-2.82; 1-sided *P* = 0.068[b]




Post-consolidation depth of response[a]




PR, partial response.
[a]Included patients in the response-evaluable population (all randomized patients with a confirmed diagnoses of MM, measurable disease at baseline, received ≥1 dose of study treatment, and had ≥1 post-baseline disease assessment).
[b]*P* values were calculated with the use of the Cochran–Mantel–Haenszel chi-square test. A 1-sided *P* value is reported for sCR; for all other responses, 2-sided *P* values not adjusted for multiplicity are reported.

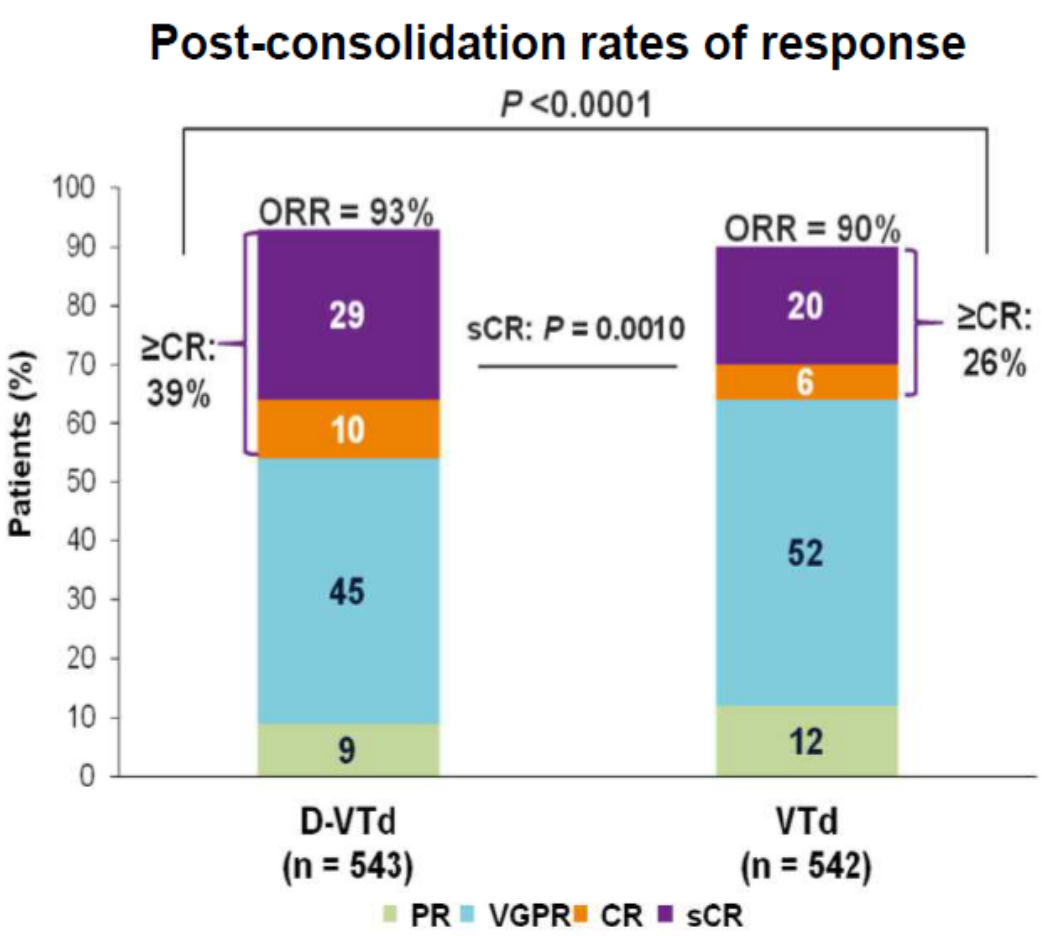
# Post-Consolidation MRD Negativity

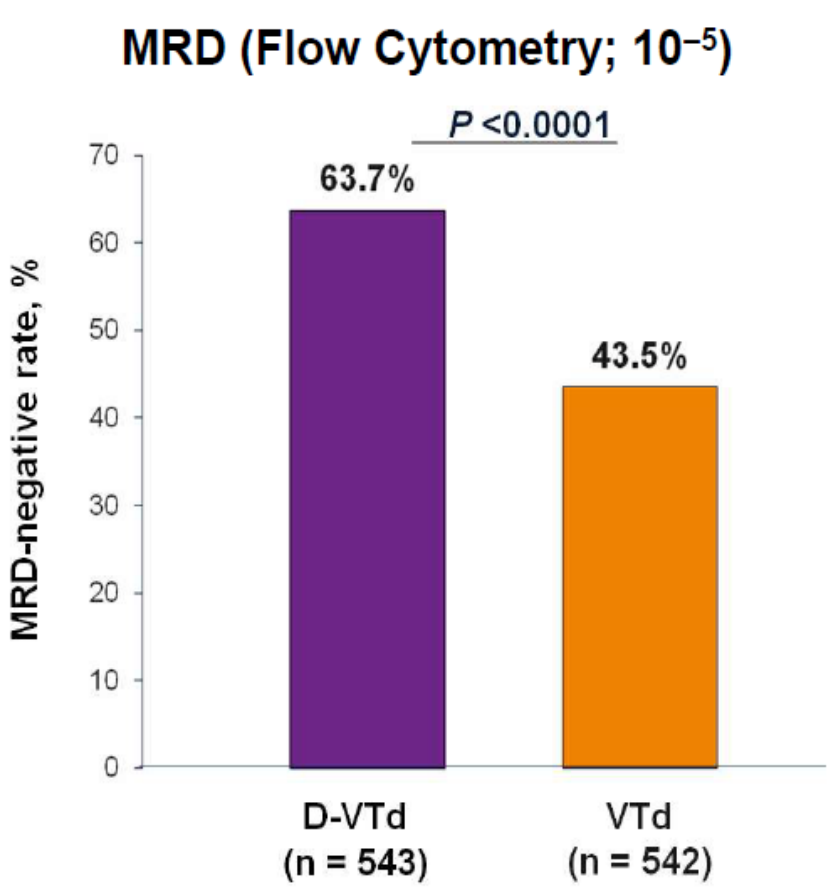
| MRD-Negative Status ($10^{-5}$),[a] n (%) | D-RVd | RVd | Odds Ratio (95% CI) | *P* value[b] |
|---|---|---|---|---|
| In ITT population | | | | |
| MRD negative regardless of response | 46/104 (**44.2**) | 15/103 (**14.6**) | 4.70 (2.38-9.28) | <0.0001 |
| MRD negative with CR or better | 30/104 (**28.8**) | 10/103 (**9.7**) | 3.73 (1.71-8.16) | 0.0007 |
| In patients achieving CR or better | 30/51 (**58.8**) | 10/41 (**24.4**) | 4.65 (1.76-12.28) | 0.0014 |
| In patients who received ASCT | 45/94 (**47.9**) | 14/78 (**17.9**) | 4.31 (2.10-8.85) | <0.0001 |

**D-RVd improved MRD-negativity ($10^{-5}$) rates at the end of consolidation**

[a]The threshold of MRD negativity was defined as 1 tumor cell per $10^5$ white cells. MRD status is based on assessment of bone marrow aspirates by next-generation sequencing in accordance with International Myeloma Working Group criteria. MRD assessments occurred in patients who had both baseline (with clone identified/calibrated) and post-baseline MRD (with negative, positive, or indeterminate result) samples taken (D-RVd, n = 71; RVd, n = 55). Patients with a missing or inconclusive assessment were considered MRD positive. [b]*P* values were calculated from the Fisher's exact test.

# CASSIOPEIA study: depth of response




**D-VTd improved the rate of sCR (primary study endpoint), ≥CR and MRD negativity**

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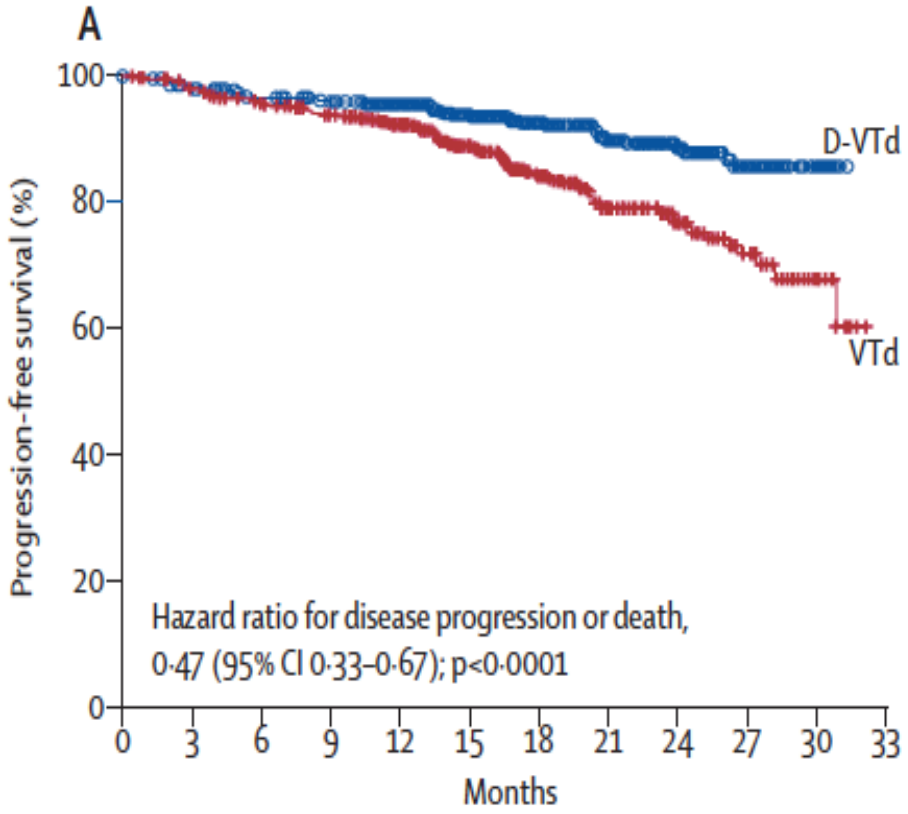
# Phase 3 CASSIOPEIA Study




| | D-VTd (n=536) | | VTd (n=538) | |
|---|---|---|---|---|
| | Any grade | Grade 3 or 4 | Any grade | Grade 3 or 4 |
| Haematological adverse events | | | | |
| Neutropenia | 157 (29%) | 148 (28%) | 89 (17%) | 79 (15%) |
| Thrombocytopenia | 109 (20%) | 59 (11%) | 73 (14%) | 40 (7%) |
| Lymphopenia | 99 (18%) | 91 (17%) | 67 (12%) | 52 (10%) |
| Non-haematological adverse events | | | | |
| Peripheral sensory neuropathy | 314 (59%) | 47 (9%) | 340 (63%) | 46 (9%) |
| Constipation | 272 (51%) | 7 (1%) | 262 (49%) | 7 (1%) |
| Asthenia | 171 (32%) | 7 (1%) | 155 (29%) | 6 (1%) |
| Peripheral oedema | 162 (30%) | 3 (<1%) | 148 (28%) | 7 (1%) |
| Nausea | 162 (30%) | 21 (4%) | 130 (24%) | 12 (2%) |
| Pyrexia | 140 (26%) | 14 (3%) | 114 (21%) | 12 (2%) |
| Paraesthesia | 118 (22%) | 4 (<1%) | 108 (20%) | 6 (1%) |
| Stomatitis | 86 (16%) | 68 (13%) | 104 (19%) | 88 (16%) |
| Second primary malignancy | 10 (2%) | NA | 12 (2%) | NA |
| Any infusion-related reaction | 190 (35%) | 19 (4%) | NA | NA |

Data are n (%). D-VTd=daratumumab plus bortezomib, thalidomide, and dexamethasone. VTd=bortezomib, thalidomide, and dexamethasone. NA=not applicable. *Adverse events of any grade that were reported in at least 20% of patients in either treatment group and grade 3 or 4 adverse events that were reported in at least 10% of patients in either treatment group are listed.

***Table 3:* Most common adverse events during treatment in the safety population***

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## Novel agent-based consolidation therapy of the ASCT: state of art

Modern induction and post-ASCT consolidation therapies including a PI combined with an IMiD with or without a MoAb

RESULT IN

Rates of MRD negativity $10^{-5}$ up to $\sim$ 60%

# Future directions

- **Incorporation of immunotherapy (Daratumumab, Elotuzumab) into induction regimens.**
- **Incorporation of novel oral agent (carfilzomi, ixazomib,) into induction regimens.**
- **Choosing induction regimens based on patient's risk-class.**
- **Extending treatment on evaluation of MRD.**


Grazie!!