Circulating Tumor Cells as a Biomarker to Identify High-risk Transplant-eligible Myeloma Patients Treated With Bortezomib, Lenalidomide, and Dexamethasone With or Without Daratumumab During Induction/Consolidation, and Lenalidomide With or Without Daratumumab During Maintenance: Results From the PERSEUS Study

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Circulating Tumor Cells in Myeloma

- CTCs detected by flow cytometry are a common feature in multiple myeloma (MM) and in MM precursors[1]
- In previous studies, high CTC levels were associated with worse PFS and OS. Conversely, low or undetectable CTC levels were associated with better outcomes[2-5]
- MRD negativity and sustained MRD negativity are associated with longer PFS and OS; MRD negativity is a strong prognostic clinical endpoint in MM[6-8]
- Introduction of daratumumab is revolutionizing the frontline approach in autologous stem cell transplant (ASCT)–eligible NDMM (e.g., CASSIOPEIA, PERSEUS)[9,10]

Abbreviations: CTC, circulating tumor cell; PFS, progression-free survival; OS, overall survival; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma.

1. Sanoja-Flores, et al. (2018) BCJ. 2. Garces, et al. (2022) JCO. 3. Bertamini, et al. (2022) JCO. 4. Kostopoulos, et al. (2023) JCO. 5. Jelinek, et al. (2022) JCO. 6. Munshi, et al. (2020) Blood Adv. 7. Perrot, et al. (2018) Blood. 8. San-Miguel, et al. (2022) Blood. 9. Moreau, et al. (2019) Lancet. 10. Sonneveld, et al. (2024) N Engl J Med.

Circulating Tumor Cells in Myeloma

- No data from recent large clinical trials on the impact of CTCs in patients receiving daratumumab or other CD38 antibodies
- Current standard of care in transplant-eligible NDMM: daratumumab, bortezomib, lenalidomide, and dexamethasone (D-VRd), ASCT, and maintenance
- Most updated clinical endpoints: MRD negativity and sustained MRD negativity
  - A unanimous US FDA ODAC vote supported MRD negativity as an early endpoint for accelerated approval of new MM treatments[1]

Abbreviations: CTC, circulating tumor cell; NDMM, newly diagnosed multiple myeloma; ASCT, autologous stem cell transplant; MRD, minimal residual disease; US FDA ODAC, United States Food and Drug Administration Oncologic Drug Advisory Committee; MM, multiple myeloma.

1. Food and Drug Administration Center for Drug Evaluation and Research. https://www.fda.gov/media/180108/download. Accessed 3 December 2024.

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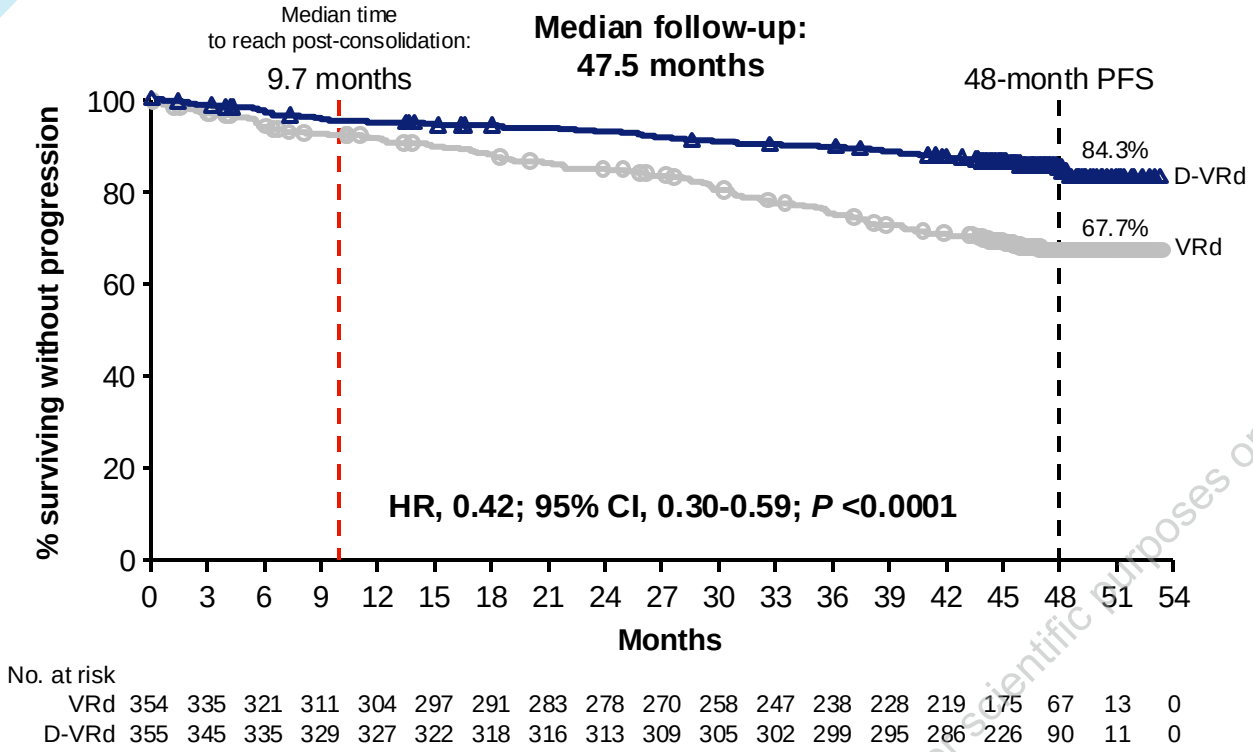
Study aim

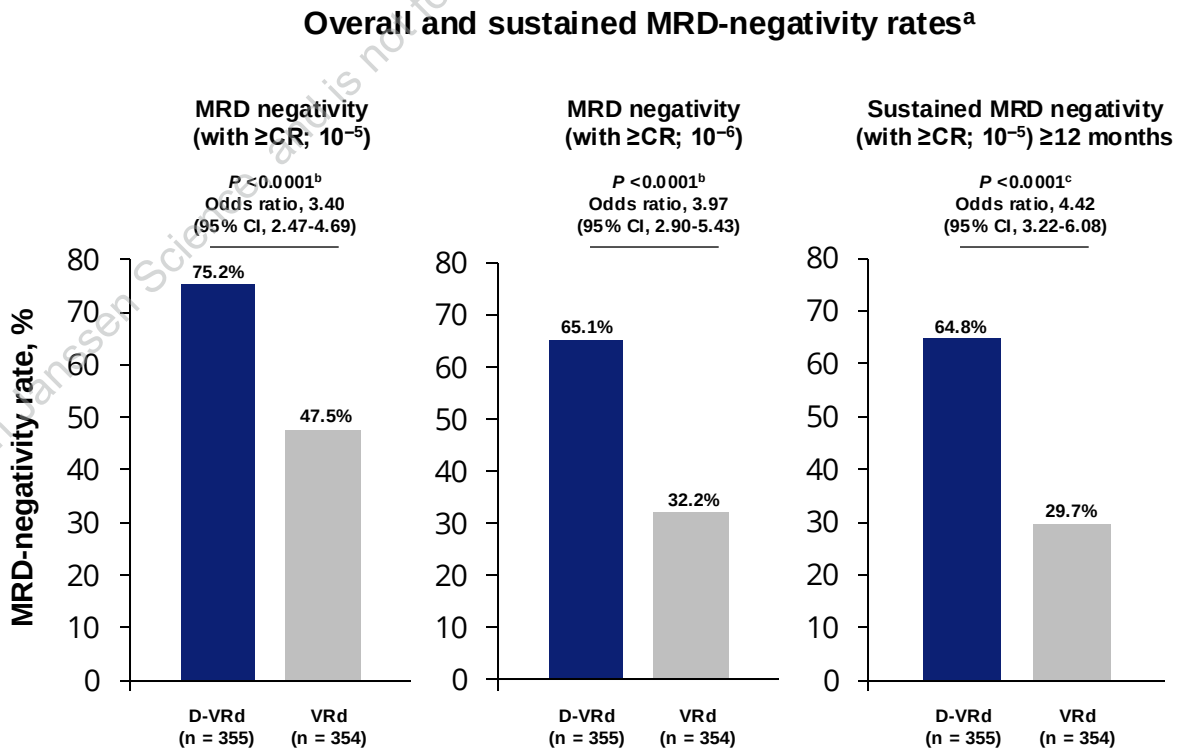
Here, we report results from PERSEUS on the impact of CTCs as a biomarker in transplant-eligible patients with NDMM

Abbreviations: CTC, circulating tumor cell; NDMM, newly diagnosed multiple myeloma; ASCT, autologous stem cell transplant; MRD, minimal residual disease; US FDA ODAC, United States Food and Drug Administration Oncologic Drug Advisory Committee; MM, multiple myeloma.

1. Food and Drug Administration Center for Drug Evaluation and Research. https://www.fda.gov/media/180108/download. Accessed 3 December 2024.

PERSEUS: D-VRd-ASCT-D-R as Standard of Care[1]





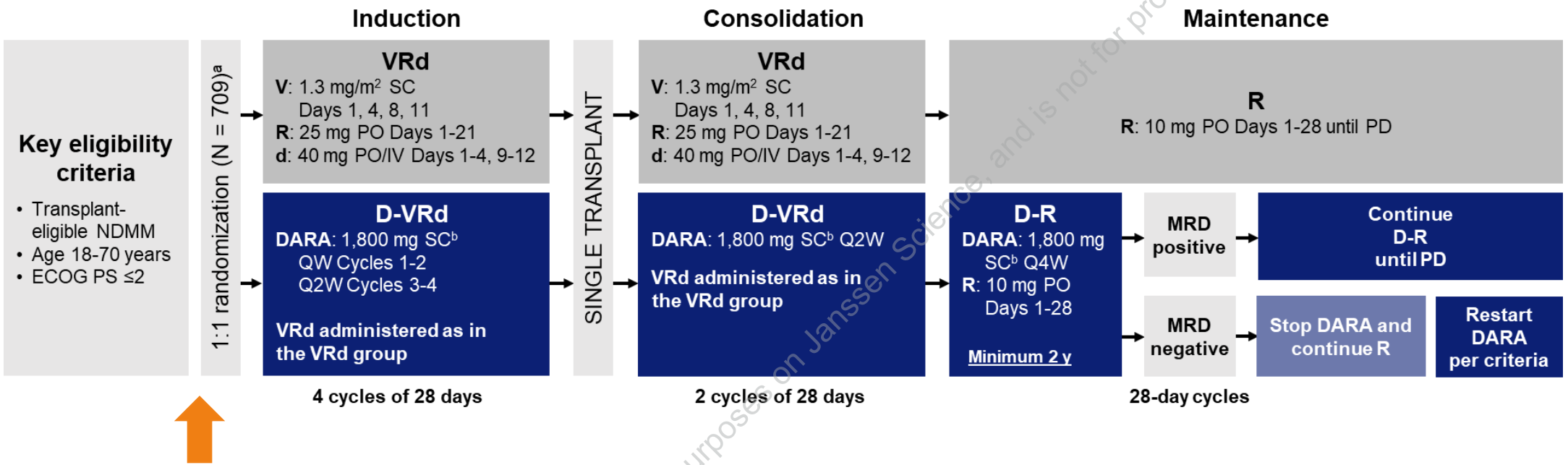
58% reduction in the risk of progression or death in patients receiving D-VRd

Deep and durable MRD negativity achieved with D-VRd

Abbreviations: D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; ASCT, autologous stem cell transplant; D-R, daratumumab plus lenalidomide; PFS, progression-free survival; VRd, bortezomib/lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval; MRD, minimal residual disease; CR, complete response; NGS, next-generation sequencing. [a]MRD-negativity rate was defined as the proportion of patients who achieved both MRD negativity and ≥CR. MRD was assessed using bone marrow aspirates and evaluated via NGS (clonoSEQ assay, version 2.0; Adaptive Biotechnologies, Seattle, WA, USA). [b]*P* values were calculated with the use of the stratified Cochran–Mantel–Haenszel chi-square test. [c]*P* value was calculated with the use of Fisher's exact test.

1. Sonneveld, et al. (2024) N Engl J Med.

PERSEUS: Study Design and CTC Testing



CTC testing performed at screening

Patient flow – CTC testing

CTC testing performed in 451 randomized patients

- 220 in VRd arm
- 231 in D-VRd arm

CTC detection: Euroflow cytometry[c]

	Values
CTCs/mL, median (95% CI)	0.04 (0-22.2)
CTC %, median (95% CI)	0.0094% (0-4.9%)

Abbreviations: CTC, circulating tumor cell; NDMM, newly diagnosed multiple myeloma; ECOG PS, Eastern Cooperative Oncology Group performance status; VRd, bortezomib/lenalidomide/dexamethasone; V, bortezomib; SC, subcutaneous; R, lenalidomide; PO, oral; d, dexamethasone; IV, intravenous; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; DARA, daratumumab; QW, weekly; Q2W, every 2 weeks; PD, progressive disease; D-R, daratumumab plus lenalidomide; Q4W, every 4 weeks; MRD, minimal residual disease; ISS, International Staging System; rHuPH20, recombinant human hyaluronidase PH20. [a]Stratified by ISS stage and cytogenetic risk. [b]DARA 1,800 mg co-formulated with rHuPH20 (2,000 U/mL; ENHANZE® drug delivery technology, Halozyme, Inc., San Diego, CA, USA). [c]Euroflow panel; analyzed at a central laboratory (Erasmus MC, Rotterdam, The Netherlands). Sensitivity was defined as 20 divided by the number of total white blood cell events acquired in the sample (aim: 4-5 million per tube).

PERSEUS CTC Sub-study: Baseline Characteristics in Treatment Groups

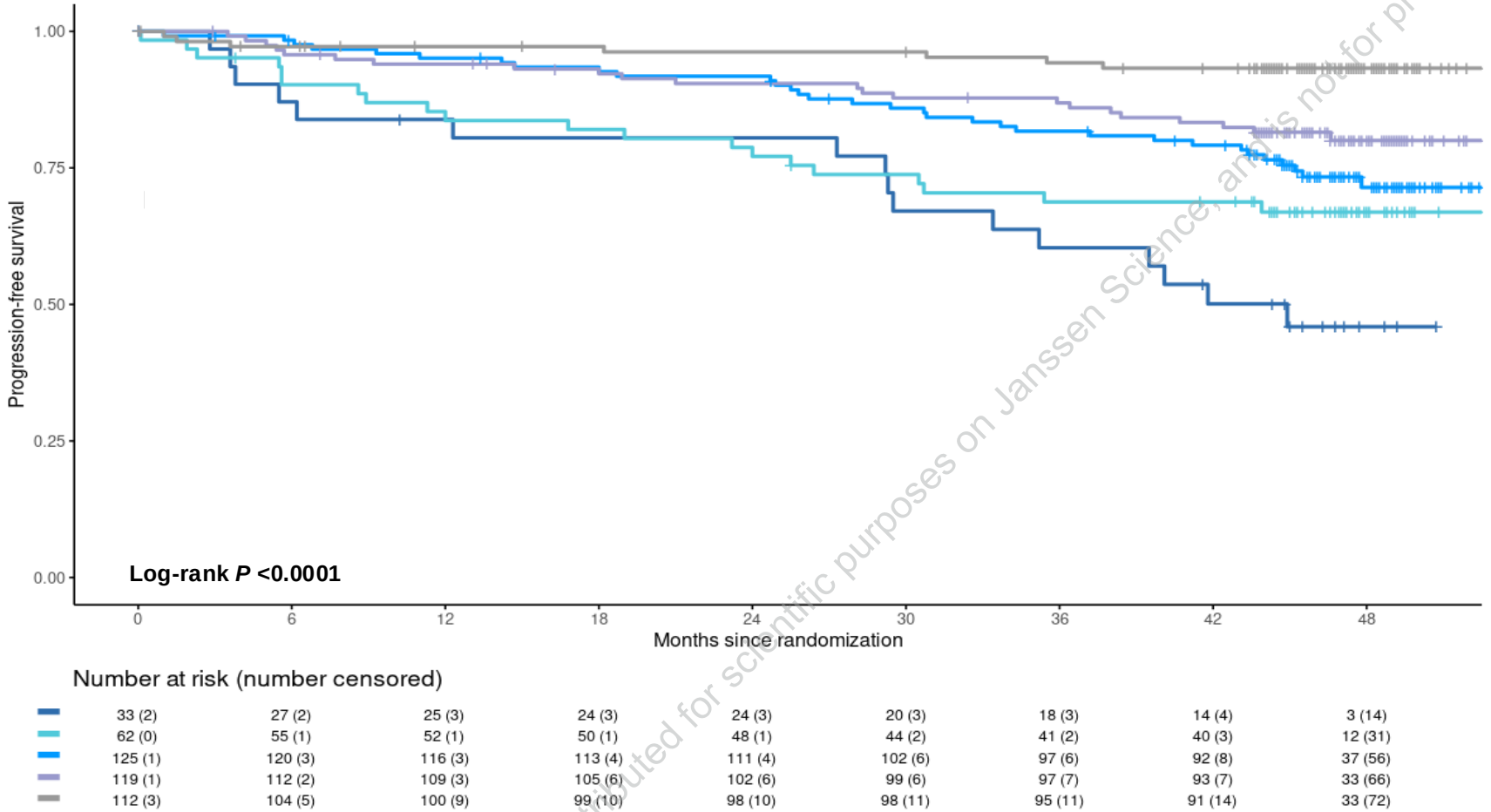
	D-VRd	VRd	*P* value
PERSEUS trial, N	355	354	
CTC sub-study, n (%)	**231 (65.1%)**	**220 (62.1%)**	**0.42**
CTCs detected, n (%)	**183/231 (79.2%)**	**187/220 (85.0%)**	**0.73**
CTC %, median (IQR)	0.0104 (0.0009-0.0738)	0.0088 (0.0012-0.0746)	0.88
Sex female, n (%)	84 (36.4%)	95 (43.2%)	0.14
Age (years), median (IQR)	60 (53.5-65)	59 (52.8-65)	0.71
ISS, % (I / II / III)	53.2% / 31.6% / 15.2%	50.9% / 35.0% / 14.1%	0.76
LDH high, n (%)	63 (27.3%)	42 (19.1%)	0.04
Cytogenetic high risk,[a] n (%)	51 (22.1%)	49 (22.3%)	0.86

Patient characteristics were balanced between treatment groups in this CTC sub-study

Abbreviations: CTC, circulating tumor cell; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; IQR, interquartile range; ISS, International Staging System; LDH, lactate dehydrogenase.

[a]High-risk cytogenetics is defined by the presence of t(4;14) and/or t(14;16) and/or del17p by fluorescence in situ hybridization.

PERSEUS CTC Sub-study: PFS With Varying Levels of CTCs



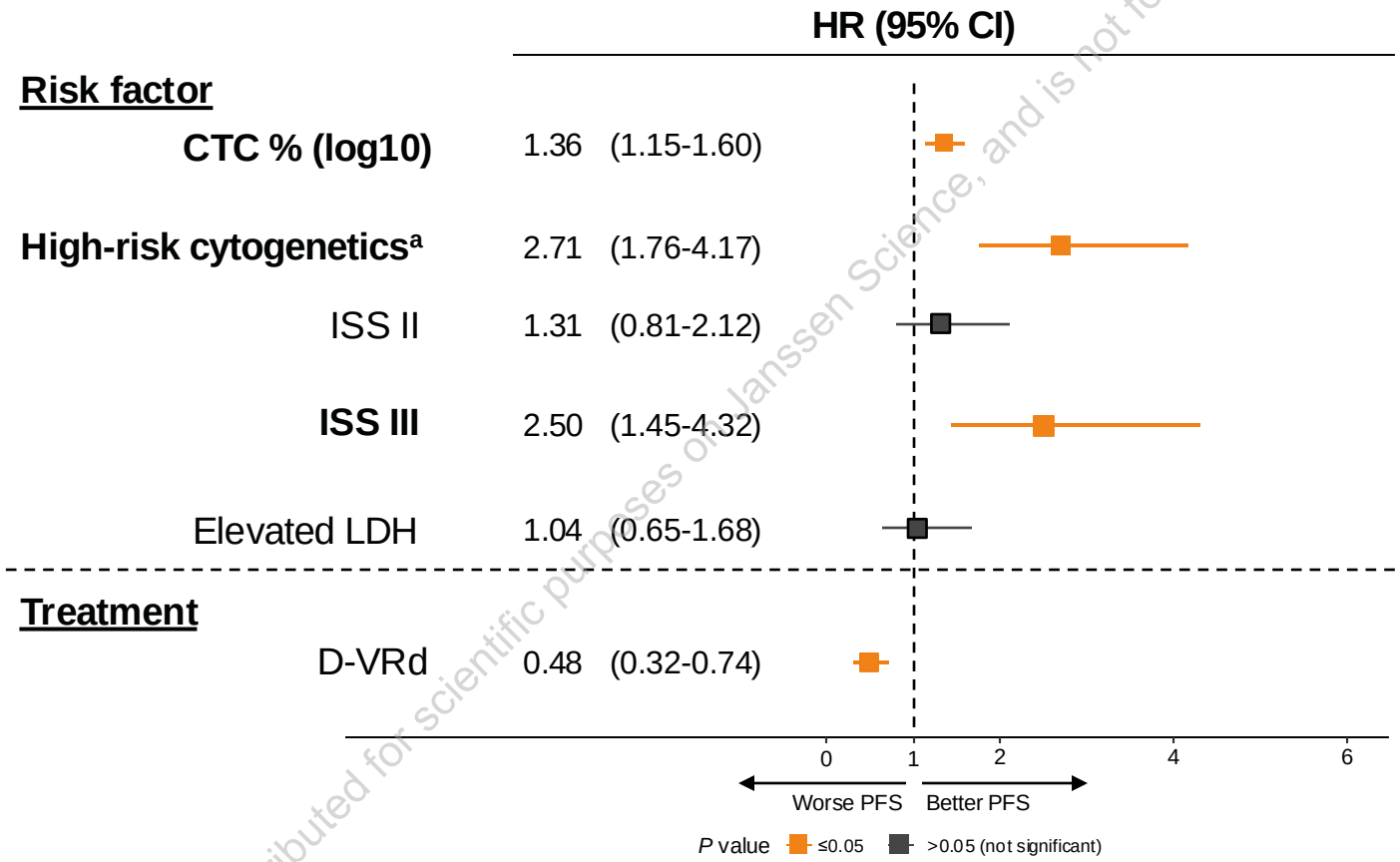
CTC log10	4-year PFS estimates
<0.001%	93%
0.001-0.01%	79%
0.01-0.1%	71%
0.1-1%	67%
≥1%	48%

Increasing levels of CTCs confer inferior prognosis

Abbreviations: PFS, progression-free survival; CTC, circulating tumor cell.

PERSEUS: Prognostic Impact of CTCs and Other Risk Factors on PFS

Cox regression model on PFS



Impact of CTCs is independent of other risk factors

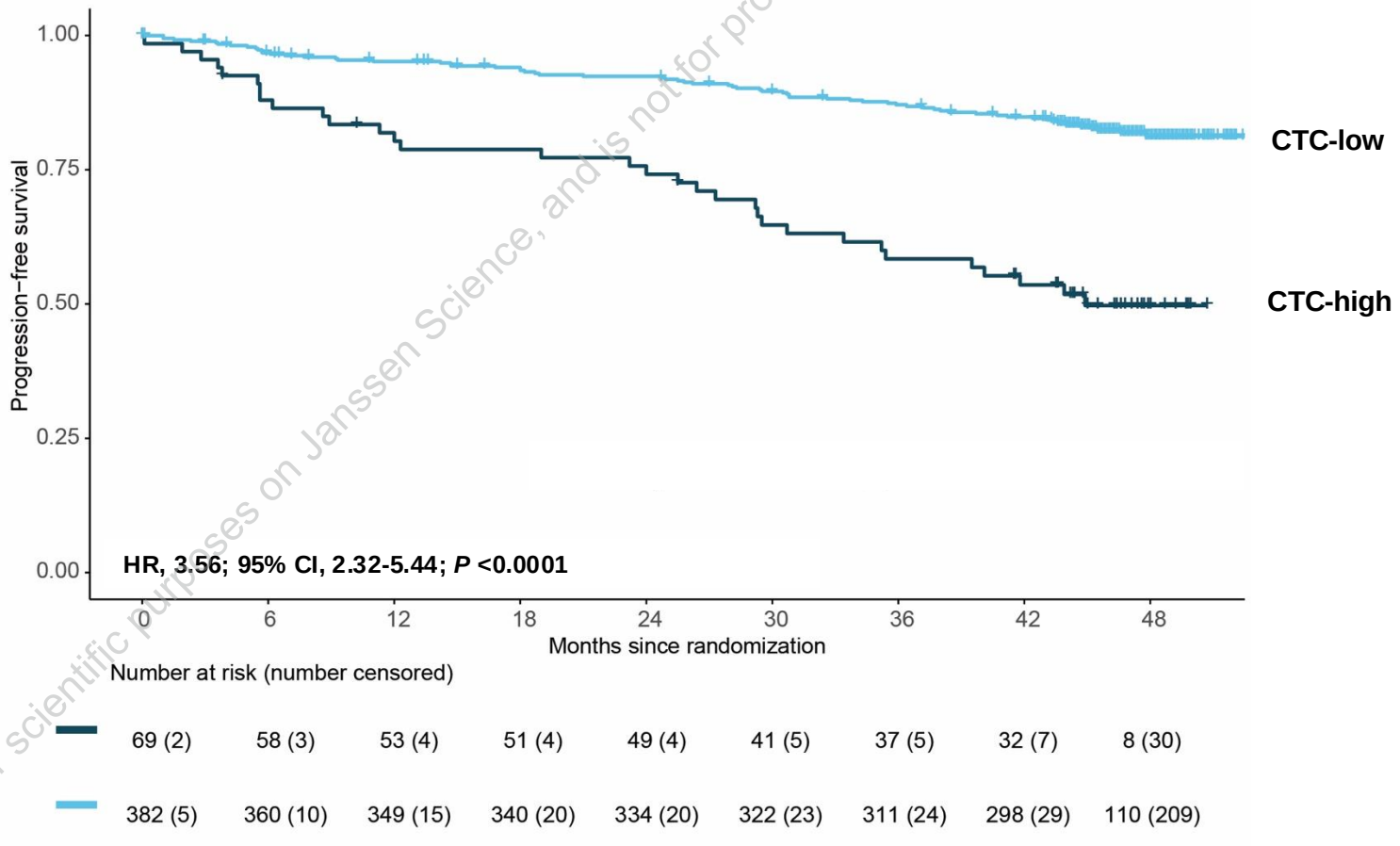
Abbreviations: CTC, circulating tumor cell; PFS, progression-free survival; CI, confidence interval; ISS, International Staging System; LDH, lactate dehydrogenase; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone.

[a]Comparison with standard risk. High-risk cytogenetics is defined by the presence of t(4;14) and/or t(14;16) and/or del17p by fluorescence in situ hybridization. Absence of those is considered standard risk.

PERSEUS: CTC Threshold

- Defining an optimal threshold: PFS model including ISS, LDH, and cytogenetics with highest C-index[a]
- Optimal cut-off of 0.175%
- CTC-high: 69/451 (15.3%)
  - Balanced in the 2 arms

	D-VRd	VRd	*P* value
CTC-high (>0.175%), n (%)	36 (15.5%)	33 (15.0%)	0.863

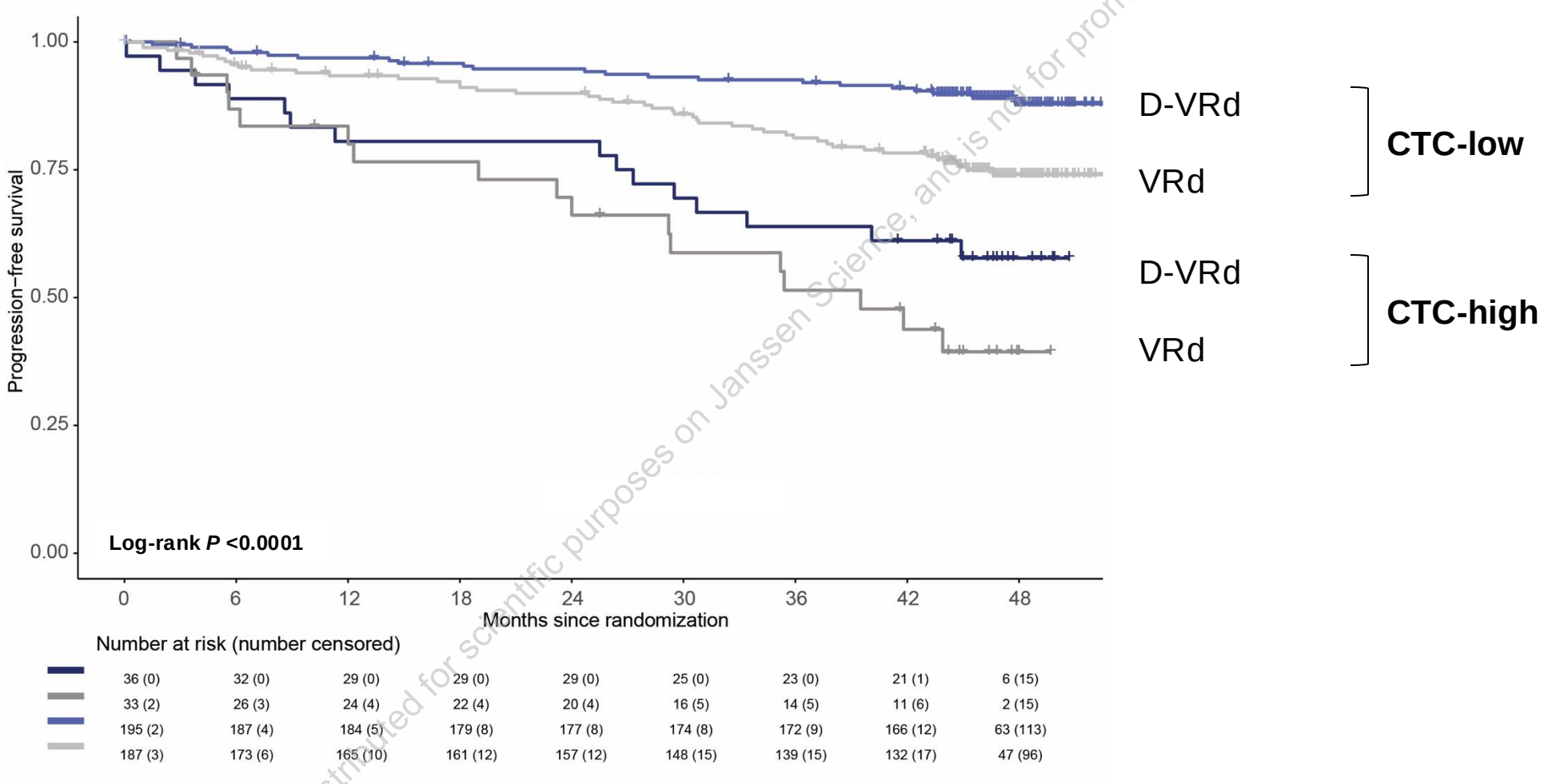


Based on an unbiased method, the optimal CTC threshold for PERSEUS was defined as 0.175%

Abbreviations: CTC, circulating tumor cell; PFS, progression-free survival; ISS, International Staging System; LDH, lactate dehydrogenase; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval.

[a]After testing models with different possible CTC cut-offs in multivariate regression with ISS, LDH, cytogenetics, and treatment, we selected the cut-off that maximized the value (C) of Harrell's C-statistic. The bootstrap method was used to reduce overfitting (as per Bertamini, et al. [2022] JCO).

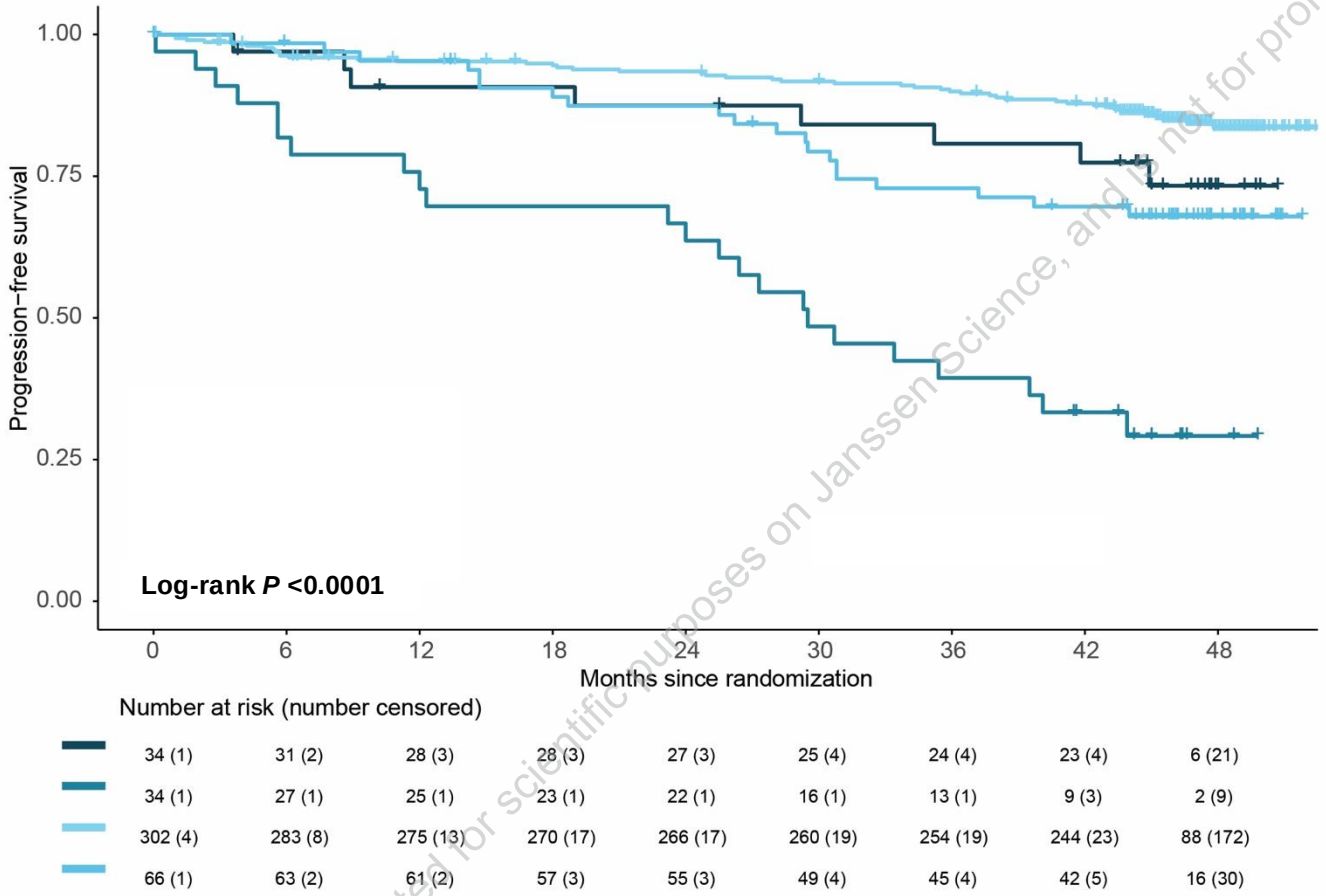
PERSEUS: PFS Based on CTC Levels and Treatment Group



D-VRd significantly improved PFS in CTC-high and -low patients

Abbreviations: PFS, progression-free survival; CTC, circulating tumor cell; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone.
CTC-high is defined by CTC ≥0.175%; CTC-low is defined by CTC <0.175%.

PERSEUS: PFS Based on Cytogenetic Risk and CTC Levels



Standard-risk cytogenetics – **CTC-low**

Standard-risk cytogenetics – **CTC-high**

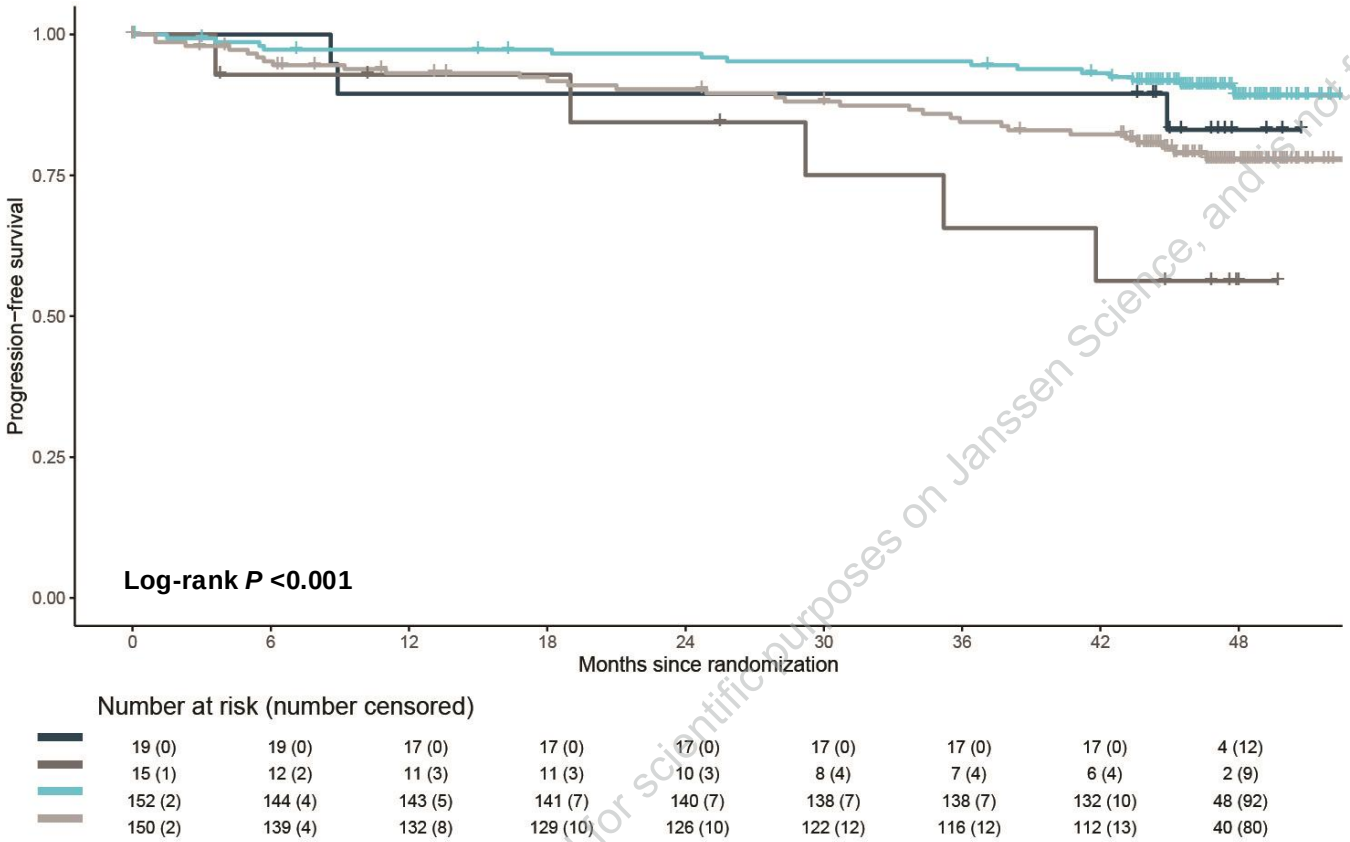
High-risk cytogenetics – **CTC-low**

High-risk cytogenetics – **CTC-high**

Combination of high CTCs and high-risk cytogenetics leads to inferior PFS

Abbreviations: CTC, circulating tumor cell; PFS, progression-free survival.
CTC-high is defined by CTC ≥0.175%; CTC-low is defined by CTC <0.175%.
High-risk cytogenetics is defined by the presence of t(4;14) and/or t(14;16) and/or del17p by fluorescence in situ hybridization.

PERSEUS: PFS Based on CTC Levels in Patients With Standard Cytogenetic Risk

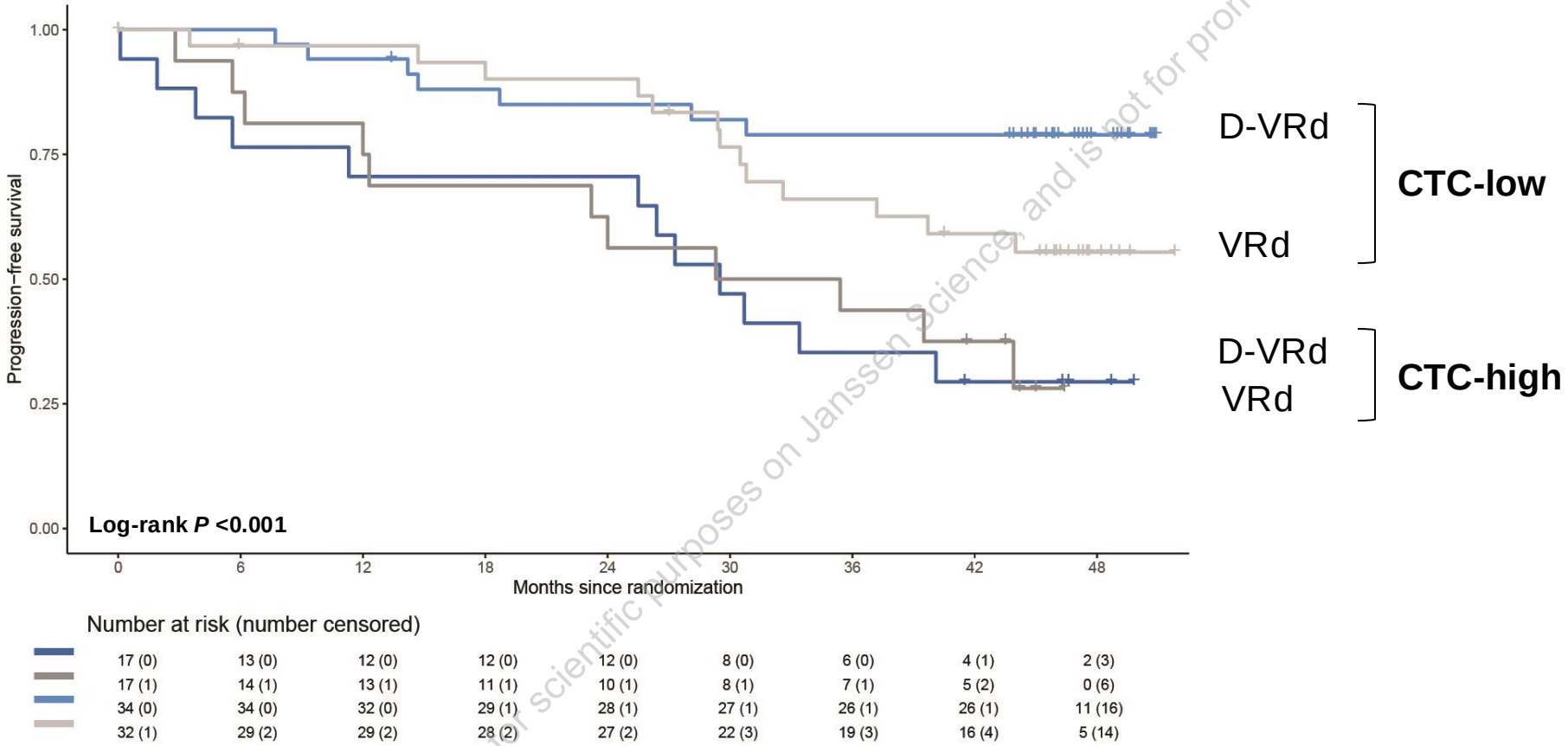


D-VRd **CTC-low**
D-VRd **CTC-high**
VRd **CTC-low**
VRd **CTC-high**

D-VRd improved outcomes regardless of CTC levels in patients with standard cytogenetic risk

Abbreviations: PFS, progression-free survival; CTC, circulating tumor cell; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone.
CTC-high is defined by CTC ≥0.175%; CTC-low is defined by CTC <0.175%.
Standard-risk cytogenetics is defined by the absence of t(4;14) and t(14;16) and del17p by fluorescence in situ hybridization.

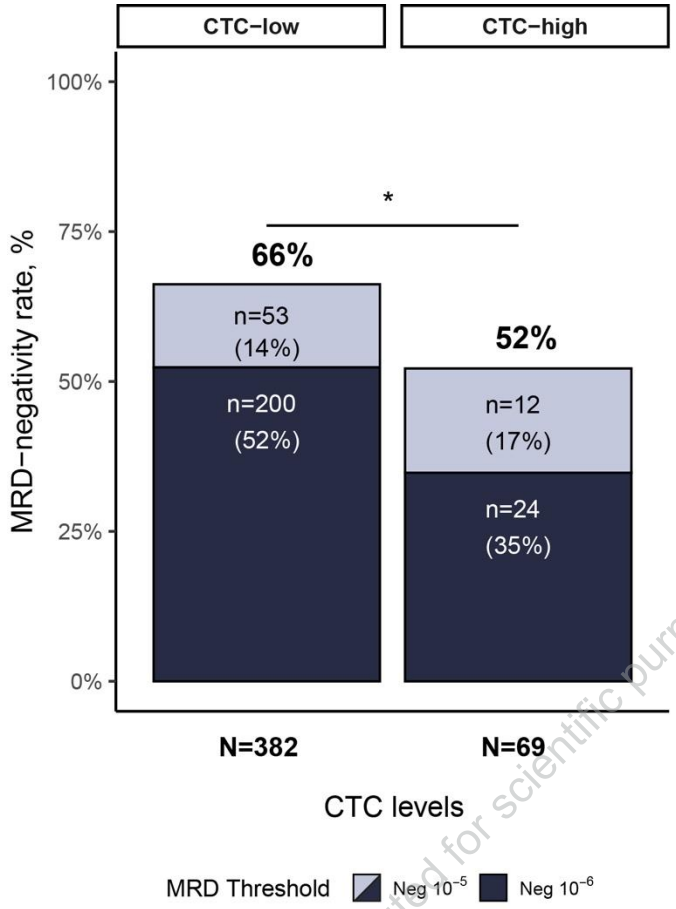
PERSEUS: PFS Based on CTC Levels in Patients With High Cytogenetic Risk

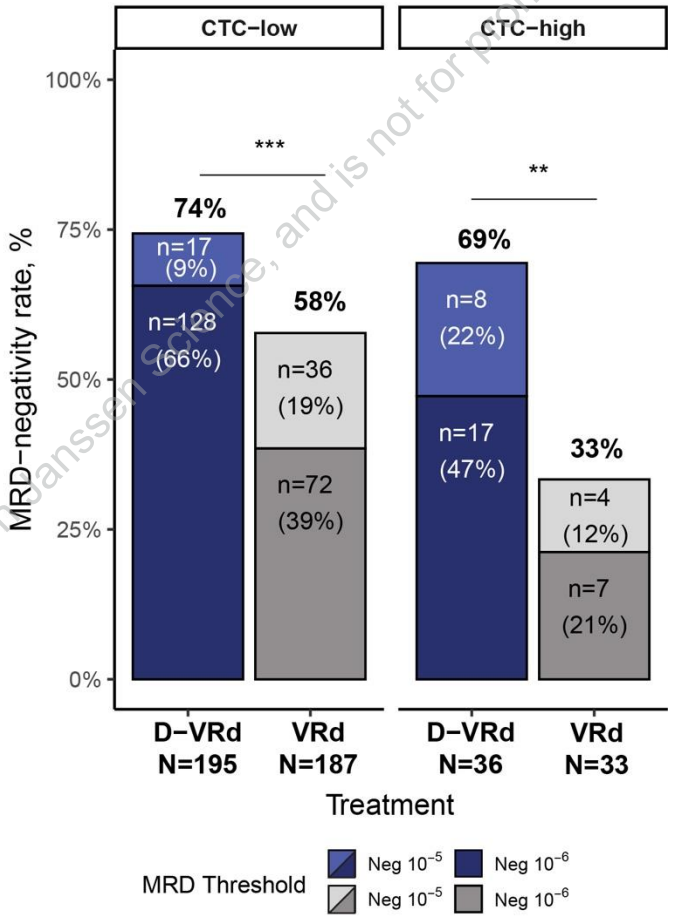


D-VRd improved outcomes with high cytogenetic risk and low CTC levels but did not ameliorate outcomes with high cytogenetic risk combined with high CTC levels

Abbreviations: PFS, progression-free survival; CTC, circulating tumor cell; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone.
CTC-high is defined by CTC ≥0.175%; CTC-low is defined by CTC <0.175%.
High-risk cytogenetics is defined by the presence of t(4;14) and/or t(14;16) and/or del17p by fluorescence in situ hybridization.

PERSEUS: Overall MRD Negativity (With ≥CR; 10^{-5} and 10^{-6})[a] and CTC Levels

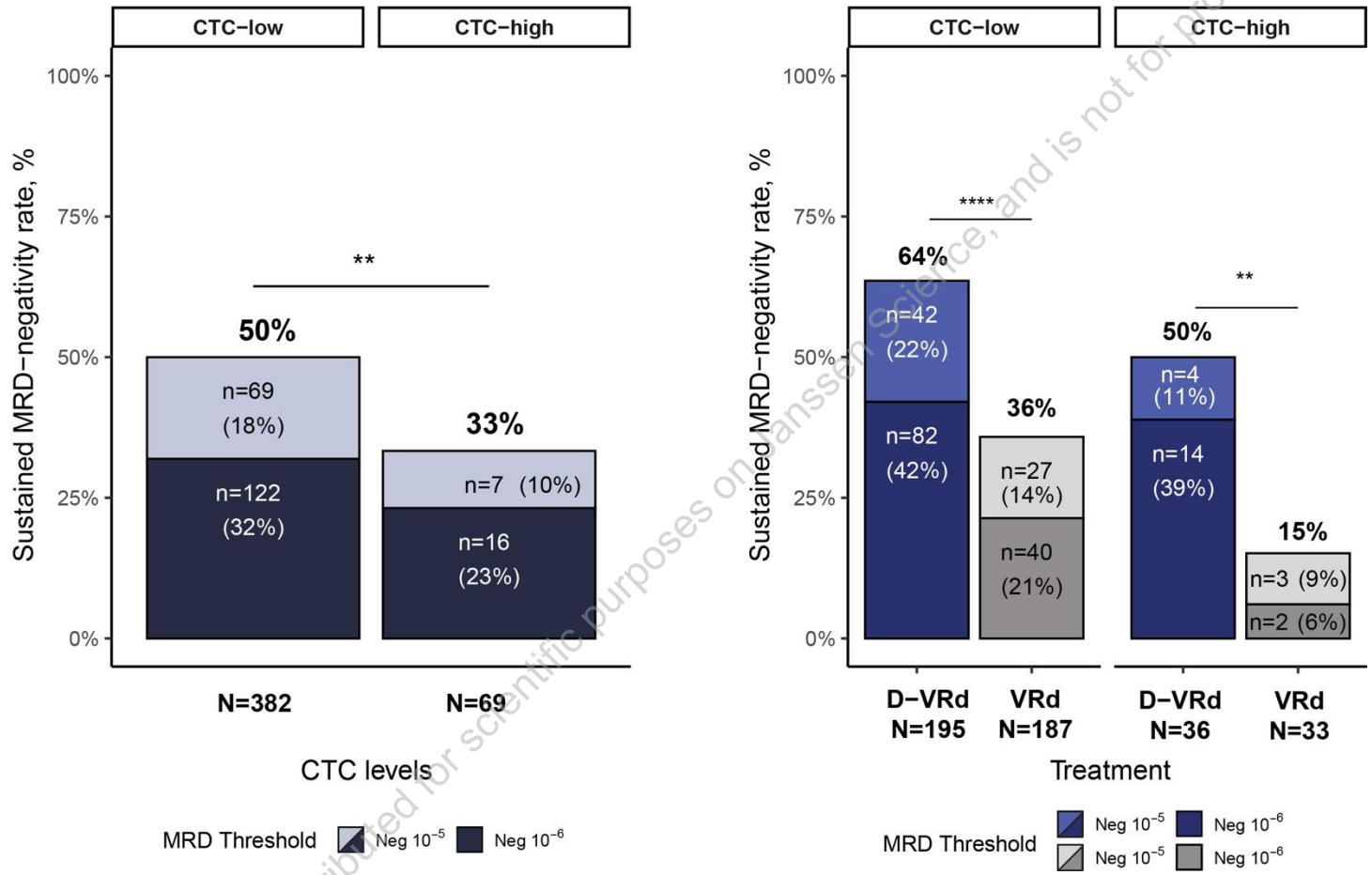




D-VRd improves MRD-negativity rates at both 10^{-5} and 10^{-6} in CTC-high and -low patients

Abbreviations: MRD, minimal residual disease; CR, complete response; CTC, circulating tumor cell; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; neg, negative; ITT, intent-to-treat. CTC-high is defined by CTC ≥0.175%; CTC-low is defined by CTC <0.175%. Bars over bar plots represent results of statistical test of 10^{-5} threshold comparison (adjusted *P* values: ****<0.0001, ***<0.001, **<0.01, *<0.05. *P* values >0.05 are not shown. Chi-square test is shown). [a]Proportion of patients who achieved both MRD negativity and ≥CR in the randomized (ITT) population.

PERSEUS: ≥12-Month Sustained MRD Negativity (With ≥CR; 10^{-5} and 10^{-6})[a] and CTC Levels



D-VRd improves sustained MRD negativity in CTC-high and -low patients

Abbreviations: MRD, minimal residual disease; CR, complete response; CTC, circulating tumor cell; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; neg, negative. CTC-high is defined by CTC ≥0.175%; CTC-low is defined by CTC <0.175%. Bars over bar plots represent results of statistical test of 10^{-5} threshold comparison (adjusted *P* values: ****<0.0001, ***<0.001, **<0.01, *<0.05. *P* values >0.05 are not shown. Fisher's test is shown). [a]2 consecutive MRD-negative results ≥12 months apart with no MRD-positive results in between.

PERSEUS CTC Sub-study: Conclusions

- Results from PERSEUS support the impact of CTC as a biomarker in transplant-eligible patients with NDMM
- High CTC levels as a prognostic marker are associated with worse PFS independently of other risk factors (i.e., cytogenetics, ISS, LDH)
- High CTC levels combined with high-risk cytogenetics identifies a possible ultra high-risk group with poor prognosis
- Treatment with D-VRd improves outcomes over VRd in both patients with high and low CTC levels, leading to improved MRD-negativity and sustained MRD-negativity rates at both 10^{-5} and 10^{-6} and improved PFS

High CTC levels should be considered as a risk factor assessed at diagnosis in clinical trials and in clinical practice

Abbreviations: CTC, circulating tumor cell; NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival; ISS, International Staging System; LDH, lactate dehydrogenase; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; MRD, minimal residual disease.

Acknowledgments

- Patients who participated in this study and their families/caregivers
- Staff members at the study sites
- Data and safety monitoring committee
- European Myeloma Network (EMN) and Janssen
- Depts. of Hematology and Immunology at Erasmus MC, Rotterdam
- EMN acknowledges the valuable contributions and participation of the National Myeloma Study Groups of all participating countries in Europe and Australia

- This study was sponsored by EMN in collaboration with Janssen Research & Development, LLC

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Editorial support was provided by Kimberly Carmony, PhD (Lumanity Communications Inc.) and was funded by Janssen Global Services, LLC.

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