Daratumumab (DARA) + Bortezomib/Thalidomide/ Dexamethasone (D-VTd) and DARA Maintenance in Transplant-eligible Newly Diagnosed Multiple Myeloma (NDMM): CASSIOPEIA Minimal Residual Disease (MRD) Update*

*ClinicalTrials.gov Identifier: NCT02541383; sponsored by IFM and supported by HOVON and Janssen Research & Development, LLC.

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Presented by J Corre at the 21st International Myeloma Society (IMS) Annual Meeting; September 25-28, 2024; Rio de Janeiro, Brazil

Disclosure Statement: Jill Corre, PhD

- **Advisory boards:** Sanofi and Bristol Myers Squibb
- **Consultant:** Janssen, Sanofi, Bristol Myers Squibb, Pfizer, and Adaptive
- **Research support:** Sanofi and Bristol Myers Squibb
- **Travel support:** Janssen, Sanofi, Bristol Myers Squibb, and Pfizer

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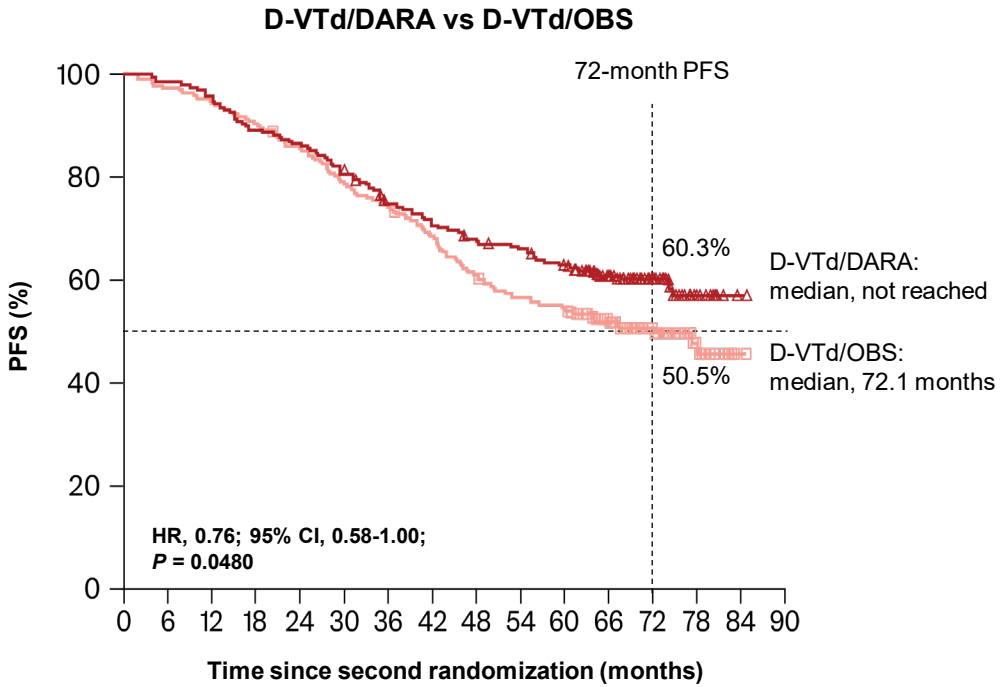
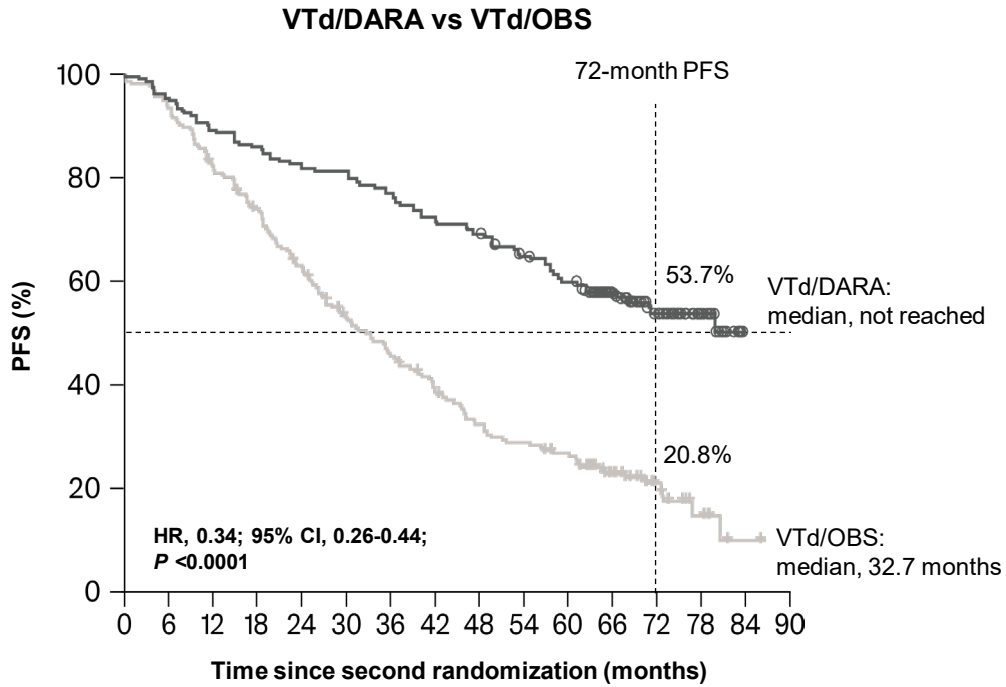
CASSIOPEIA: Introduction

- CASSIOPEIA induction/consolidation established D-VTd as a SoC for transplant-eligible NDMM[1-3]
- Long-term follow-up results from the maintenance phase demonstrated that the longest PFS was observed in patients who received D-VTd followed by DARA maintenance[4]
- **Here we report the effect of DARA on deep and sustained MRD negativity after an 80.1-month median follow-up**





D-VTd, daratumumab plus bortezomib/thalidomide/dexamethasone; SoC, standard of care; NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival; DARA, daratumumab; MRD, minimal residual disease; OBS, observation; HR, hazard ratio; CI, confidence interval; VTd, bortezomib/thalidomide/dexamethasone.

1. Moreau P, et al. *Lancet*. 2019;394(10192):29-38. 2. DARZALEX® (daratumumab) injection [package insert]. Horsham, PA: Janssen Biotech, Inc.; 2023. 3. European Medicines Agency. DARZALEX 20 mg/mL concentrate for solution for infusion [summary of product characteristics]. Accessed May 6, 2024. https://www.ema.europa.eu/en/documents/product-information/darzalex-epar-product-information_en.pdf. 4. Moreau P, et al. EHA 2024. Abstract S204.

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CASSIOPEIA: Study Design and MRD

MRD results presented:

Induction/consolidation phase (all patients)

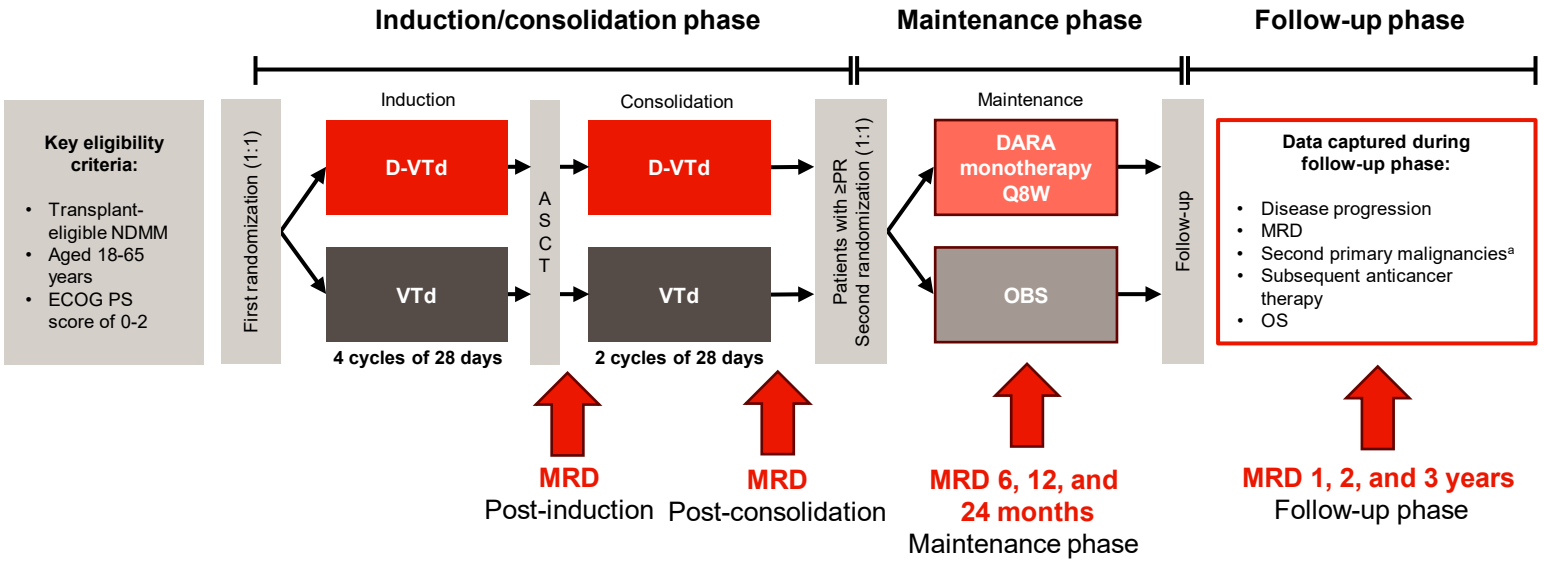
- Post-induction (MFC)
- Post-consolidation (MFC)

Maintenance phase (all patients in ≥VGPR; NGS/MFC 10^{-5}, NGS 10^{-6})

- 6 months
- 12 months
- 24 months

Follow-up phase (all patients with last MRD test negative, NGS/MFC 10^{-5}, NGS 10^{-6})

- 1 year
- 2 years
- 3 years



More patients randomized to D-VTd vs VTd underwent second randomization to maintenance (84.3% vs 79.0%)

MFC, multiparametric flow cytometry; VGPR, very good partial response; NGS, next-generation sequencing; ECOG PS, Eastern Cooperative Oncology Group performance status; ASCT, autologous stem cell transplant; PR, partial response; OS, overall survival.

[a]Aside from second primary malignancies, no additional safety data were collected during the follow-up phase per study protocol, as all patients had completed 2 years fixed duration of maintenance/observation, discontinued study treatment, and completed the 30-day post-treatment window for adverse event reporting at the time of the previous clinical cutoff.

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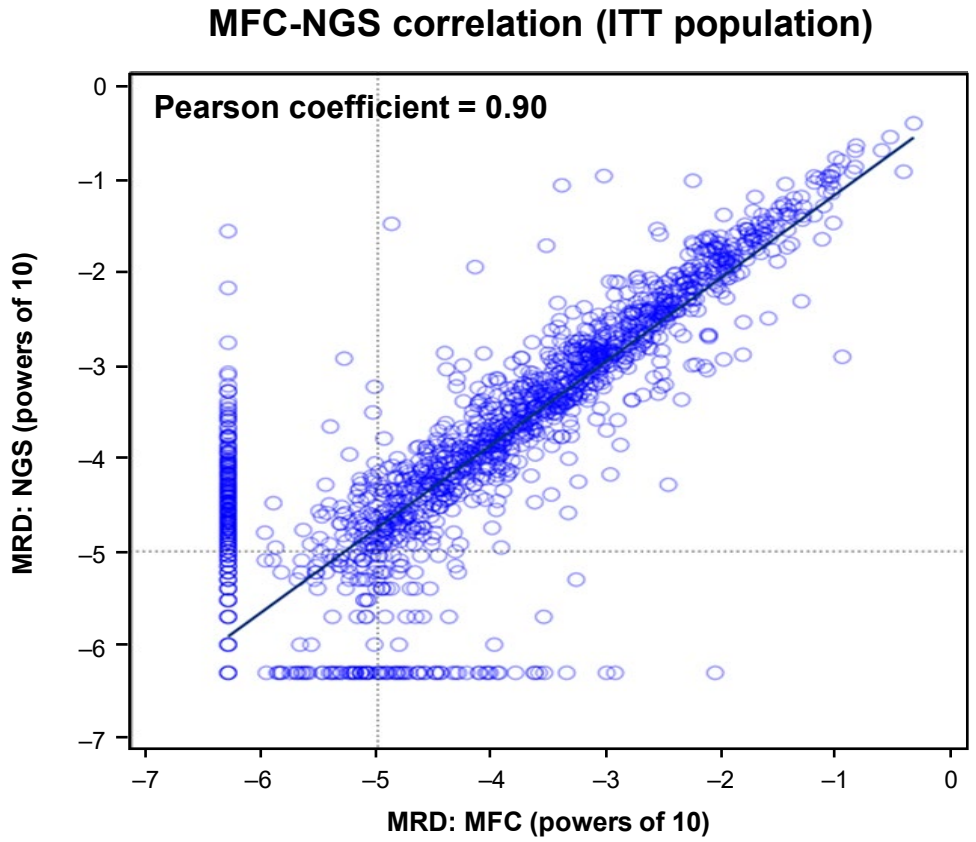
CASSIOPEIA: Sample Compliance and MFC-NGS Correlation at Study Level (ITT/Maintenance Population)

Rates of MRD sample compliance:

- >90% during induction/consolidation
- ~80% during maintenance
- ~60% during follow-up



Rates of MRD sample compliance were generally high, with strong positive correlation between MFC and NGS in the ITT population

ITT, intent-to-treat.

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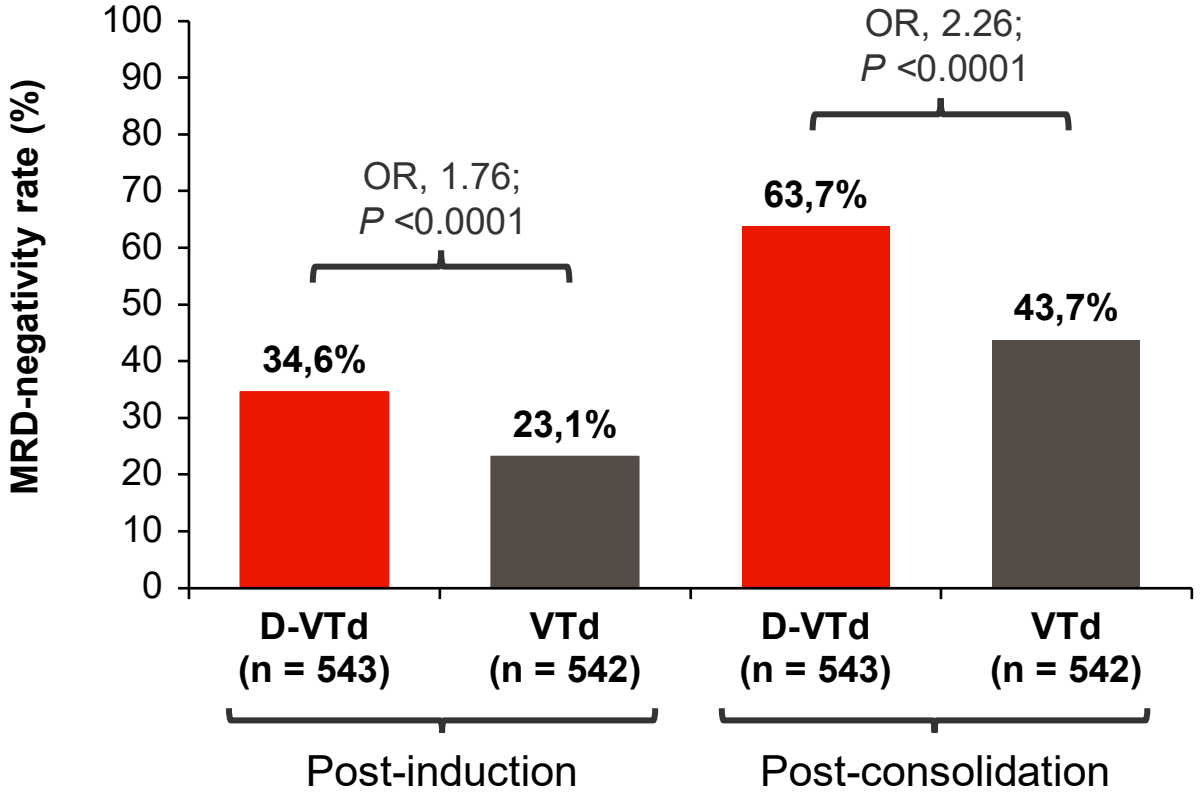
CASSIOPEIA: Post-induction and Post-consolidation Overall MRD-negativity Rates (10^{-5}; ITT)



DARA improved the overall MRD-negativity rates (10^{-5}) achieved post-induction and post-ASCT/consolidation

OR, odds ratio.
MRD-negativity rates shown are regardless of response and were assessed by MFC only at 10^{-5}.

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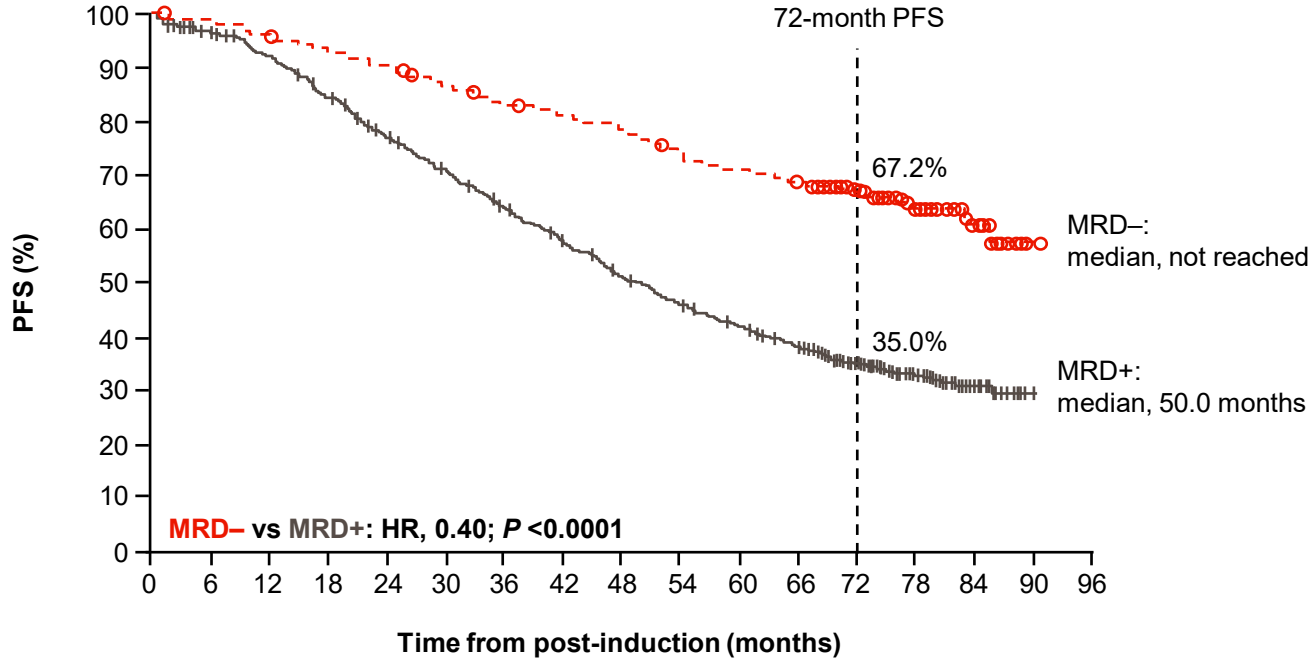
CASSIOPEIA: Landmark PFS Analysis by Post-induction MRD Status in the Overall Study Population (ITT)



No. at risk

MRD+	727	683	648	593	536	489	438	390	343	307	276	247	172	95	38	1	0
MRD–	313	306	297	288	279	265	255	248	239	226	215	209	158	78	38	2	0

- 72-month PFS rates were nearly doubled for patients who achieved MRD negativity post-induction
- Median PFS was not reached for MRD-negative patients versus 50.0 months for MRD-positive patients

Patients who achieved MRD negativity post-induction had improved PFS outcomes

Analysis conducted in the ITT population using post-induction MRD results. MRD results presented here are regardless of response and were assessed by MFC only at 10^{-5}.

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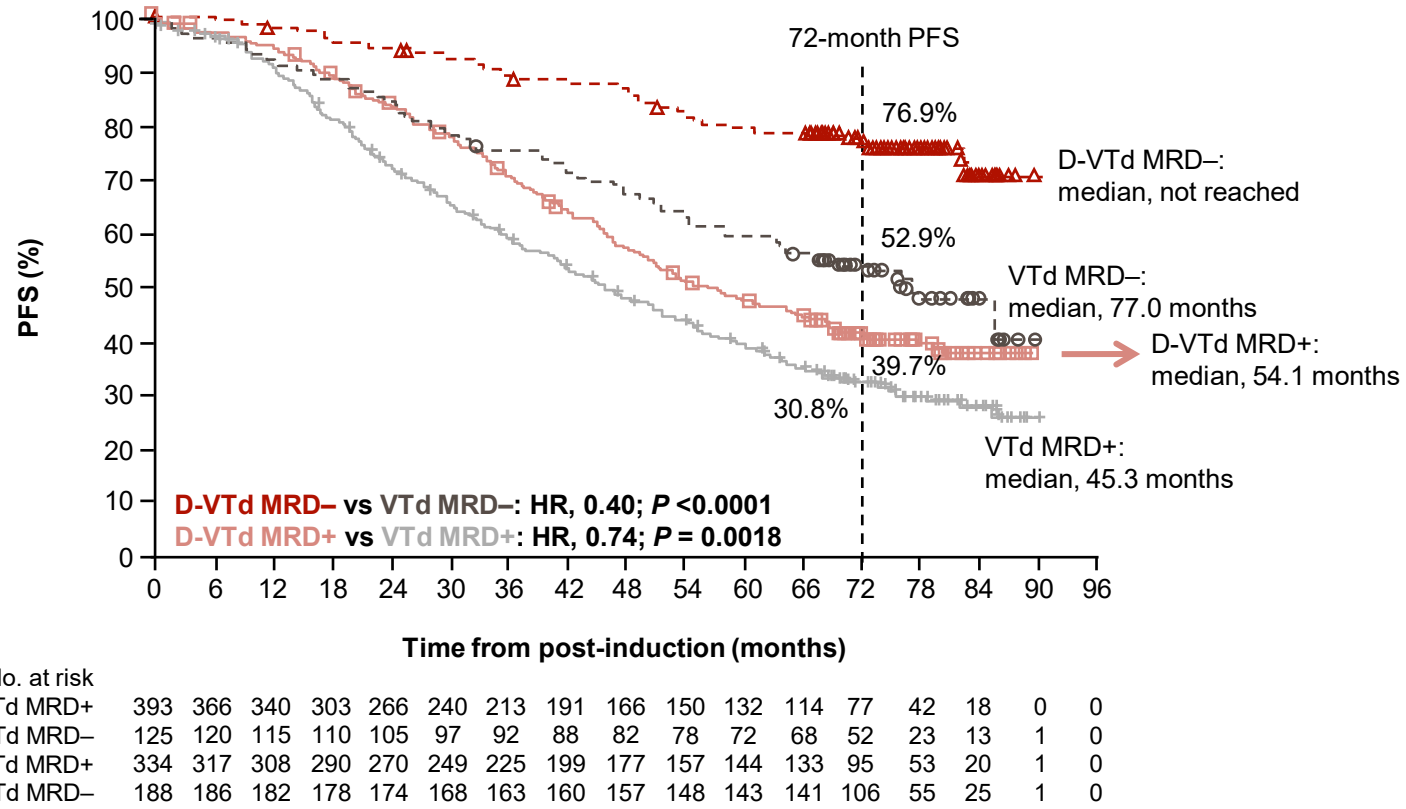
CASSIOPEIA: Landmark PFS Analysis by Post-induction MRD Status and Induction/Consolidation Arm (ITT)



No. at risk																	
VTd MRD+	393	366	340	303	266	240	213	191	166	150	132	114	77	42	18	0	0
VTd MRD–	125	120	115	110	105	97	92	88	82	78	72	68	52	23	13	1	0
D-VTd MRD+	334	317	308	290	270	249	225	199	177	157	144	133	95	53	20	1	0
D-VTd MRD–	188	186	182	178	174	168	163	160	157	148	143	141	106	55	25	1	0

- Patients who achieved MRD negativity post-induction with DARA had the highest 72-month PFS rates

Including DARA in induction/consolidation improved PFS outcomes for *both* MRD-negative and MRD-positive patients

Analysis conducted in the ITT population using post-induction MRD results. MRD results presented here are regardless of response and were assessed by MFC only at 10^{-5}.

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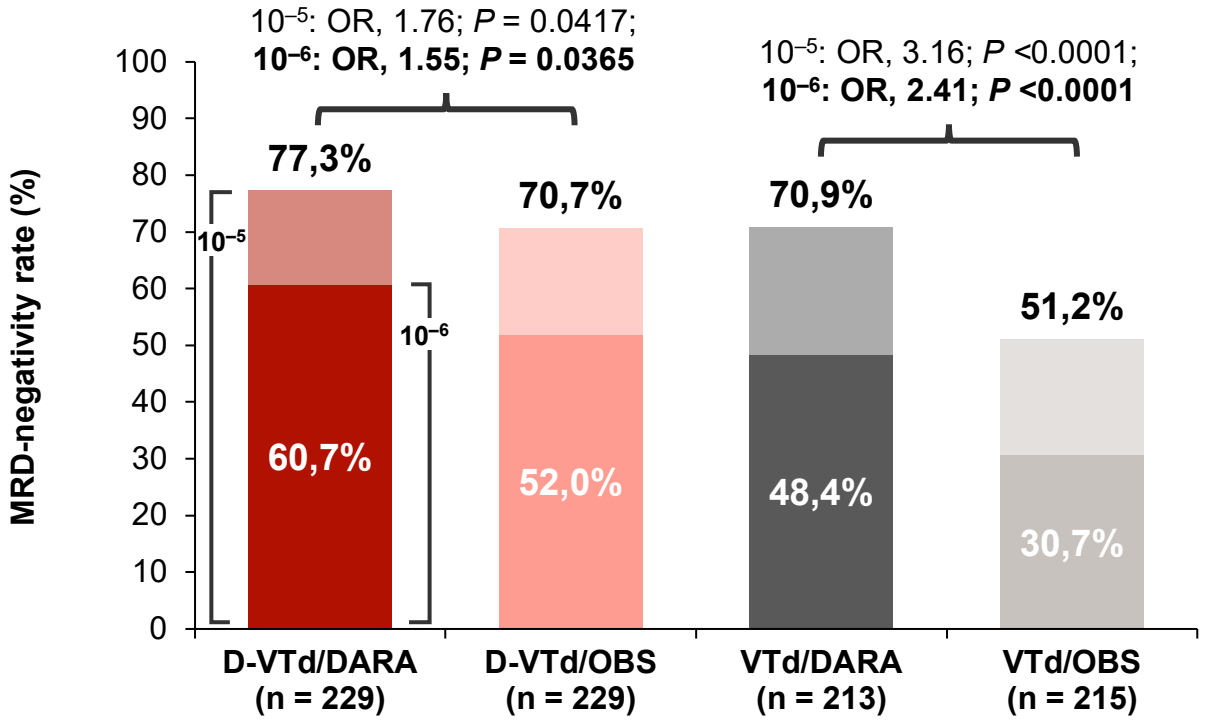
CASSIOPEIA: Overall MRD-negativity Rates (10^{-5} and 10^{-6})[a] From the Maintenance and Follow-up Phases (Maintenance Population)



DARA maintenance increased MRD-negativity rate and depth of MRD negativity regardless of induction/consolidation treatment

[a]MRD was assessed from post consolidation onwards.
MRD-negativity rates shown are regardless of response. MRD data for maintenance and follow-up at 10^{-5} are based on combined NGS/MFC results (MFC data were used only when NGS data were not available).
MRD data presented for maintenance and follow-up at 10^{-6} are based on NGS only due to limitations of MFC at this threshold.

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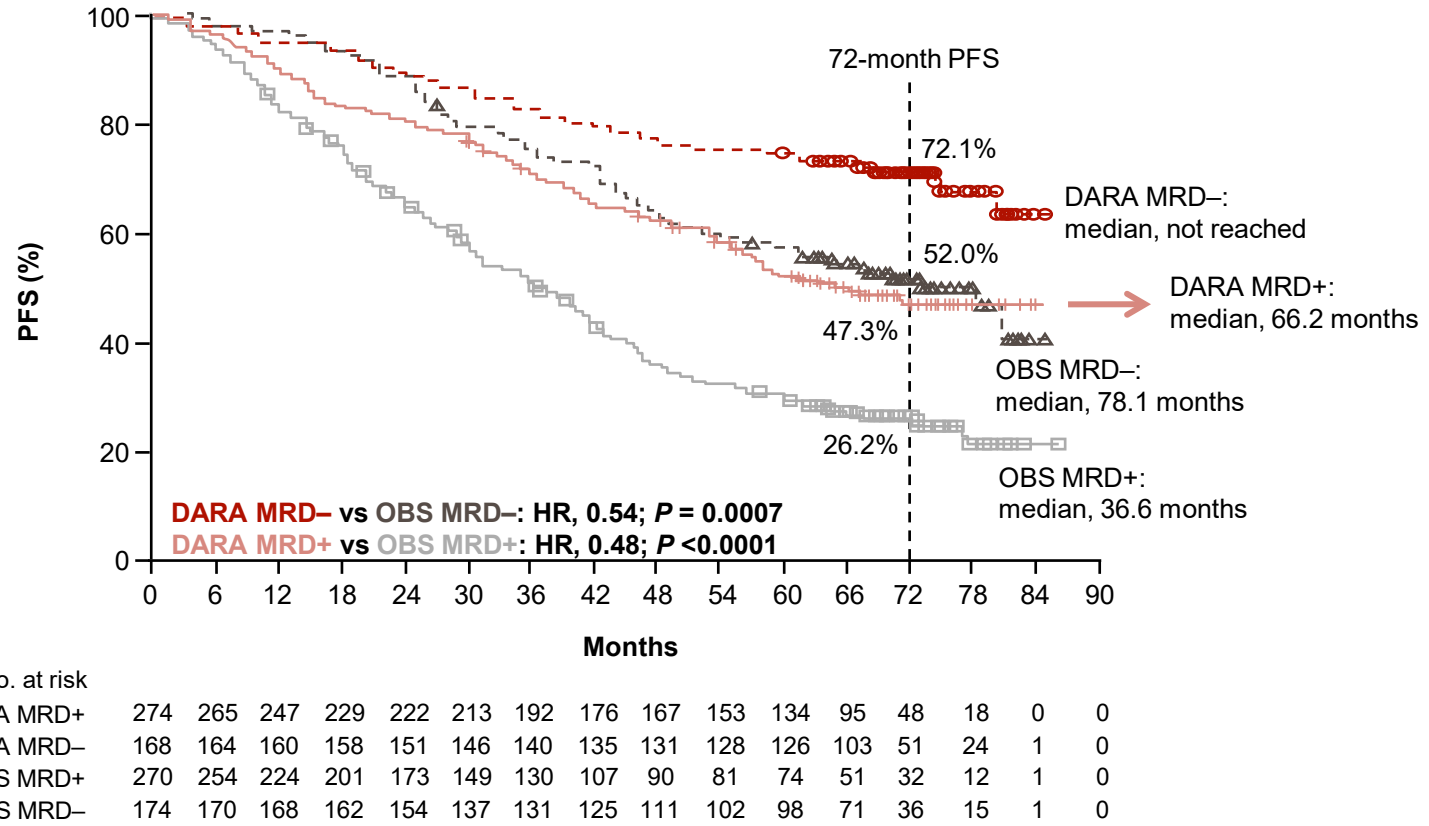
CASSIOPEIA: Landmark Analysis of PFS From Second Randomization by Post-consolidation MRD Status (Maintenance Population)



No. at risk																
DARA MRD+	274	265	247	229	222	213	192	176	167	153	134	95	48	18	0	0
DARA MRD–	168	164	160	158	151	146	140	135	131	128	126	103	51	24	1	0
OBS MRD+	270	254	224	201	173	149	130	107	90	81	74	51	32	12	1	0
OBS MRD–	174	170	168	162	154	137	131	125	111	102	98	71	36	15	1	0

- After achieving MRD negativity post-consolidation, DARA maintenance provided the best PFS outcomes
- Among patients who remained MRD positive post-consolidation, DARA maintenance continued to improve PFS

DARA maintenance improved PFS irrespective of induction/consolidation treatment and post-consolidation MRD status

Analysis conducted in the maintenance population using post-consolidation MRD results. MRD results presented here are regardless of response. MRD data for maintenance and follow-up at 10^{-5} were based on NGS only.

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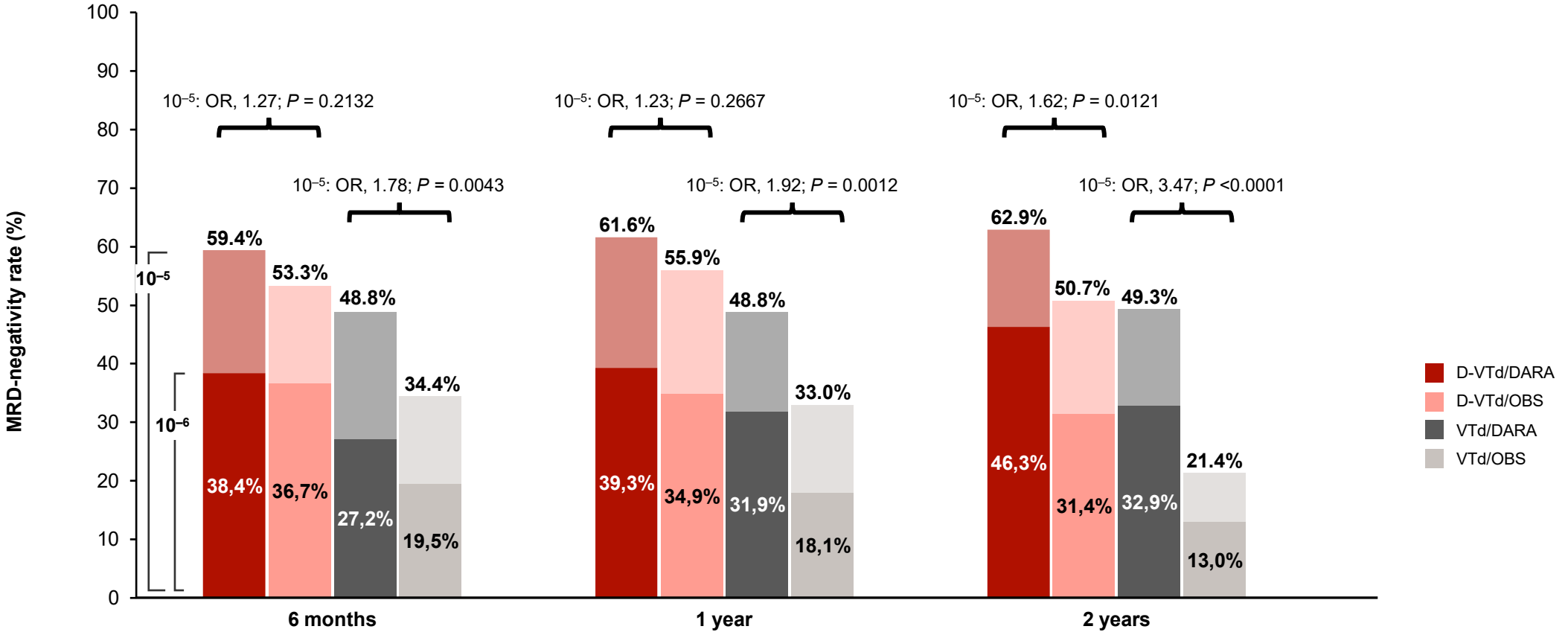
CASSIOPEIA: Landmark MRD-negativity Rates During Maintenance (10^{-5} and 10^{-6}; Maintenance Population)



DARA maintenance consistently led to higher MRD-negativity rates within each induction/consolidation treatment group at all measured time points

Analysis conducted in the maintenance population. MRD-negativity rates shown are regardless of response. MRD data for maintenance and follow-up at 10^{-5} are based on combined NGS/MFC results (MFC data were used only when NGS data were not available). MRD data presented for maintenance and follow-up at 10^{-6} are based on NGS only due to limitations of MFC at this threshold.

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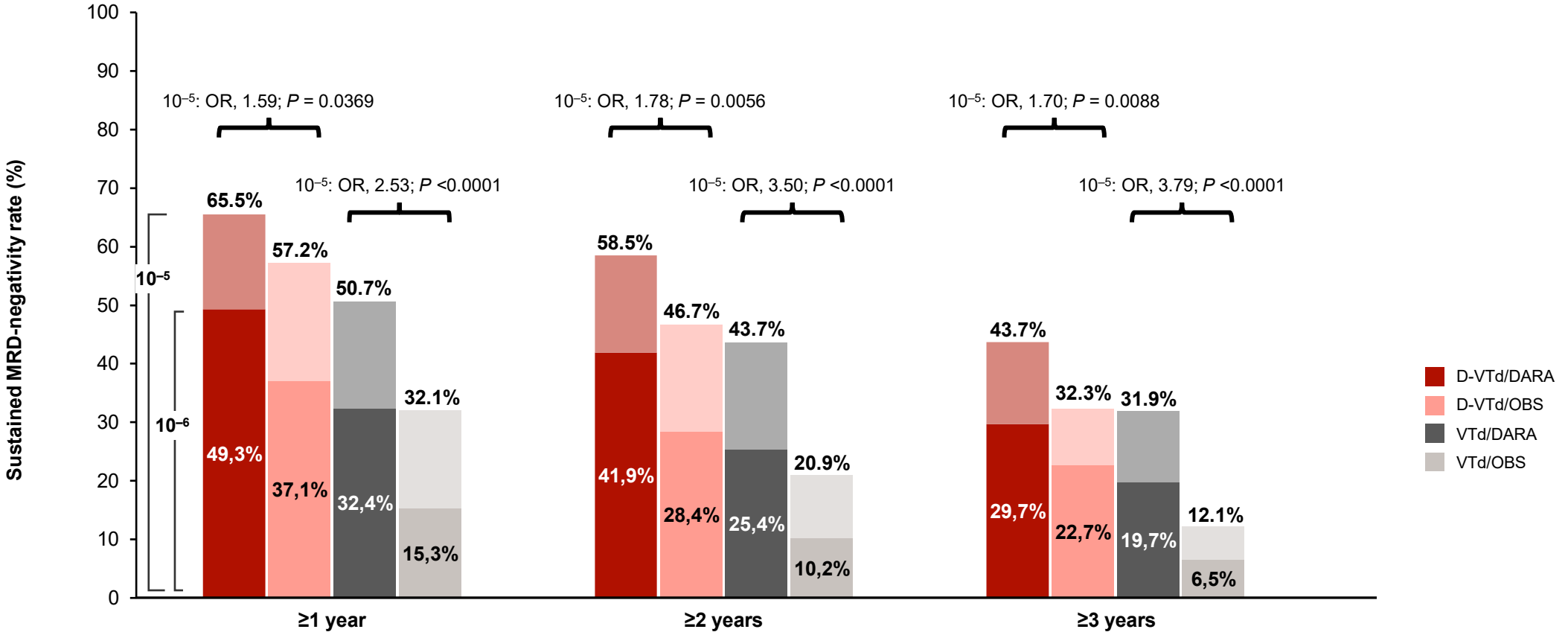
CASSIOPEIA: Sustained MRD-negativity Rates (10^{-5} and 10^{-6}) at Any Time During the Study (Maintenance Population)



DARA maintenance increased sustained MRD-negativity rates versus OBS, including 3-year sustained MRD negativity, within each induction/consolidation treatment group

Analysis conducted in the maintenance population using results from post-induction onwards. Sustained MRD-negativity rates shown are regardless of response. MRD data for maintenance and follow-up at 10^{-5} are based on combined NGS/MFC results (MFC data were used only when NGS data were not available). MRD data presented for maintenance and follow-up at 10^{-6} are based on NGS only due to limitations of MFC at this threshold.

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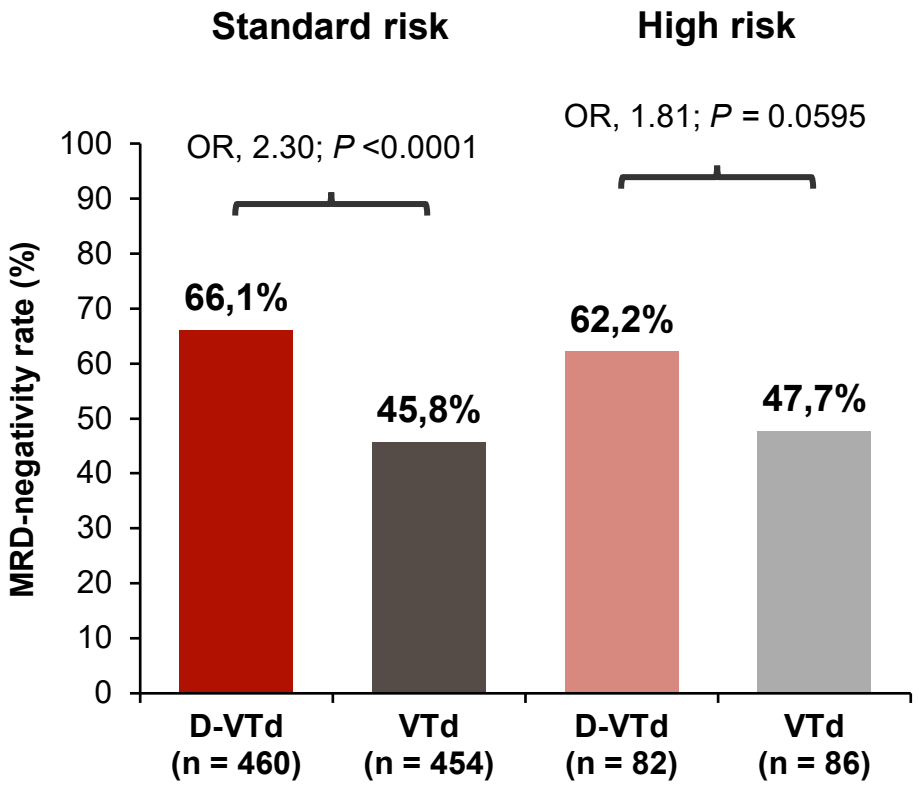
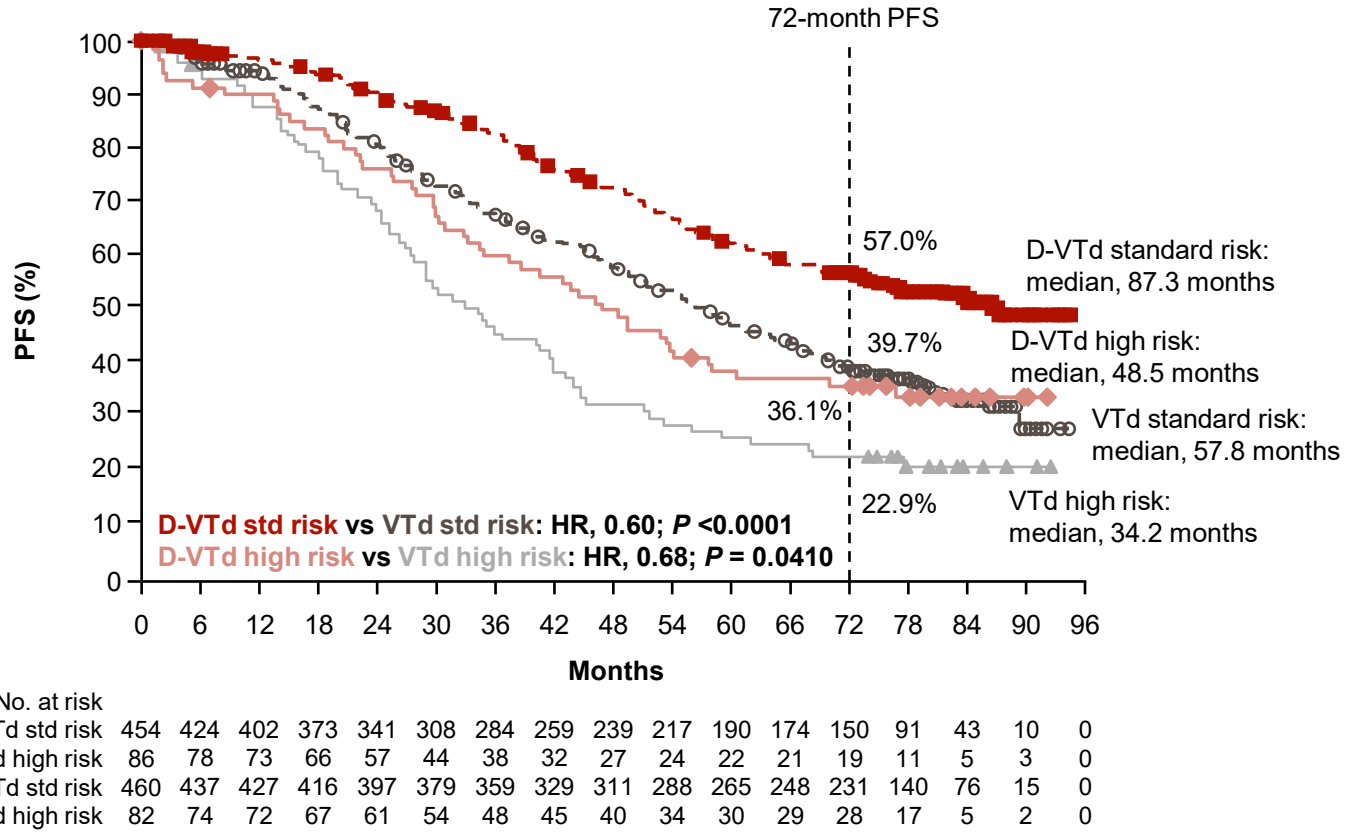
CASSIOPEIA: MRD-negativity Rates (10^{-5})[a] and PFS Based on Cytogenetic Risk Status (ITT)





No. at risk

VTd std risk	454	424	402	373	341	308	284	259	239	217	190	174	150	91	43	10	0
VTd high risk	86	78	73	66	57	44	38	32	27	24	22	21	19	11	5	3	0
D-VTd std risk	460	437	427	416	397	379	359	329	311	288	265	248	231	140	76	15	0
D-VTd high risk	82	74	72	67	61	54	48	45	40	34	30	29	28	17	5	2	0

- **DARA improved MRD-negativity rate in both standard- and high-risk patients**
- **DARA improved PFS regardless of cytogenetic risk status**

Std, standard; FISH, fluorescence in situ hybridization.
[a]MRD was assessed with induction and consolidation periods combined.
MRD-negativity rates shown are regardless of response and were assessed by MFC only at 10^{-5}. High cytogenetic risk was defined as the presence of t(4;14) or del(17p) by FISH testing at screening.

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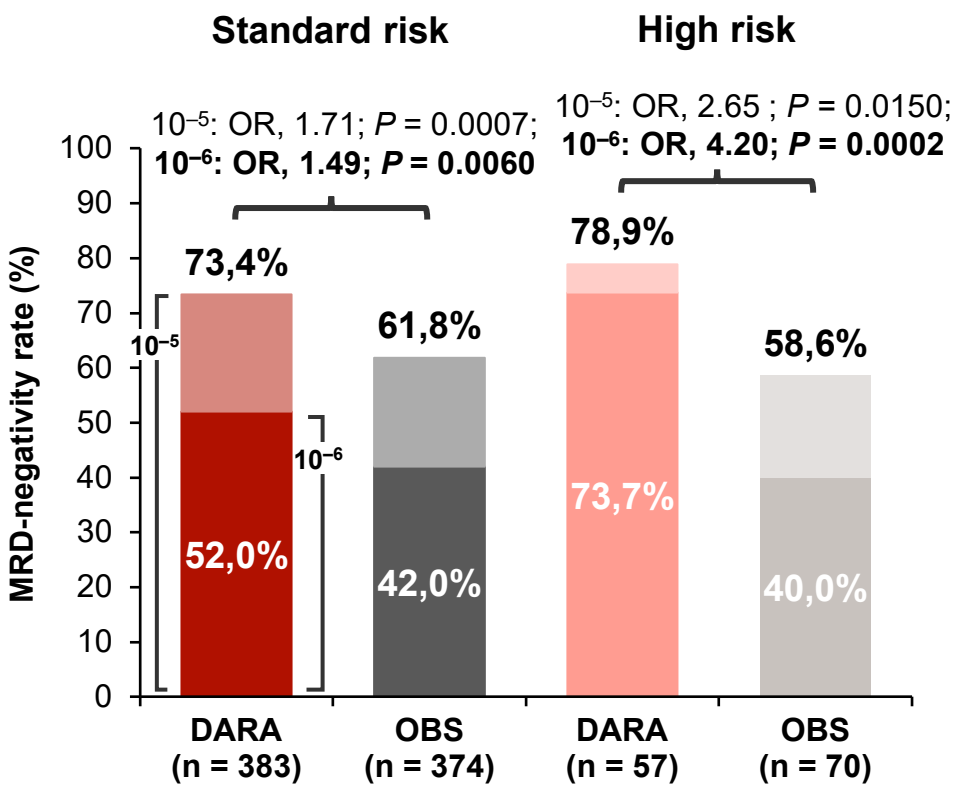
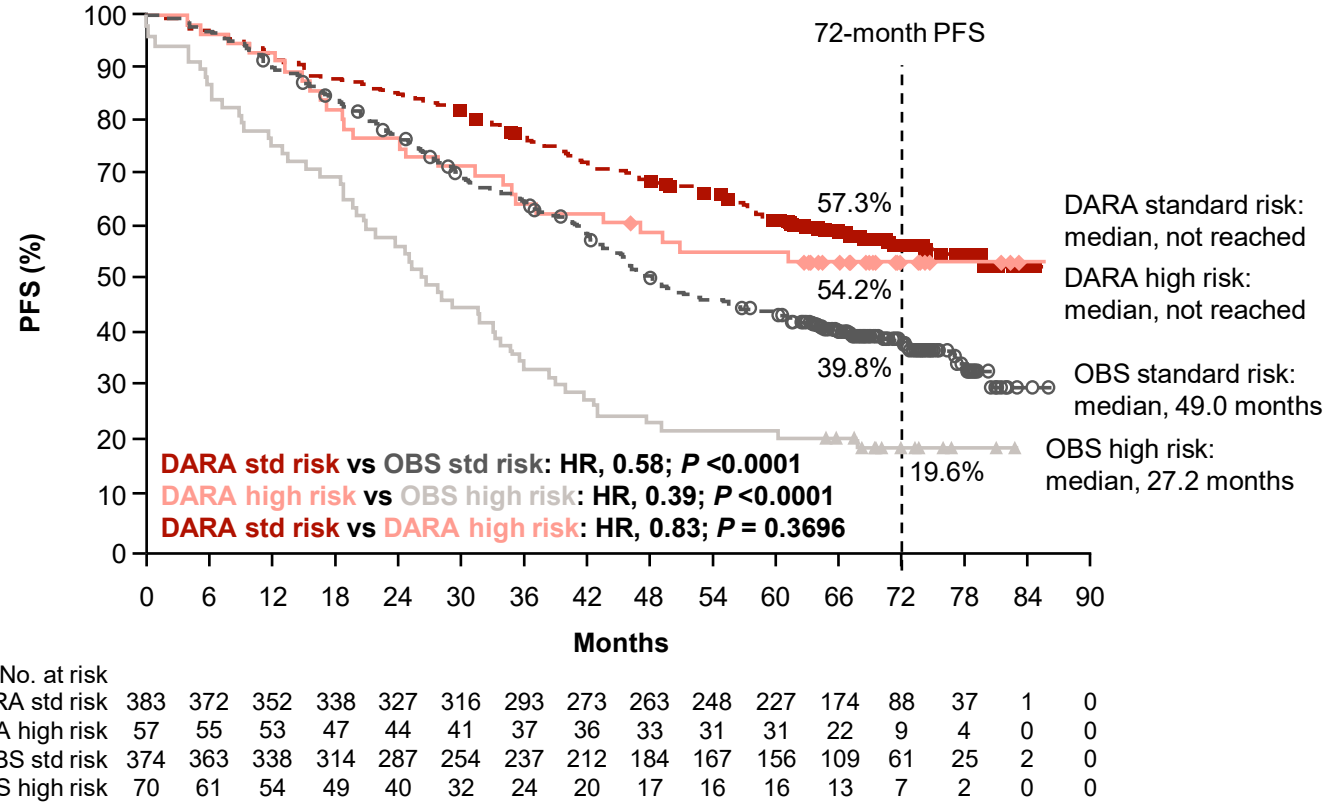
CASSIOPEIA: MRD-negativity Rates (10^{-5} and 10^{-6})[a] and PFS Based on Cytogenetic Risk Status (Maintenance Population)





No. at risk																
DARA std risk	383	372	352	338	327	316	293	273	263	248	227	174	88	37	1	0
DARA high risk	57	55	53	47	44	41	37	36	33	31	31	22	9	4	0	0
OBS std risk	374	363	338	314	287	254	237	212	184	167	156	109	61	25	2	0
OBS high risk	70	61	54	49	40	32	24	20	17	16	16	13	7	2	0	0

- **The highest MRD-negativity rates were seen with DARA in high-risk patients**
- **DARA maintenance improved PFS regardless of cytogenetic risk status**

[a]MRD was assessed from post-consolidation onwards.
MRD-negativity rates shown are regardless of response. MRD data for maintenance and follow-up at 10^{-5} are based on combined NGS/MFC results (MFC data were used only when NGS data were not available). MRD data presented for maintenance and follow-up at 10^{-6} are based on NGS only due to limitations of MFC at this threshold. High cytogenetic risk was defined as the presence of t(4;14) or del(17p) by FISH testing at screening.

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CASSIOPEIA: Conclusions

- Extended follow-up revealed the long-term MRD and PFS benefits of DARA maintenance after DARA-based induction[1]
- DARA maintenance increased the rate of MRD negativity achieved post-induction/consolidation
  - Early achievement of MRD negativity was associated with superior PFS outcomes
- DARA maintenance was associated with improved PFS irrespective of post-consolidation MRD status and prior DARA exposure
  - DARA increased MRD-negativity rates and depth and durability of MRD negativity
- DARA maintenance improved MRD-negativity rates and PFS outcomes in patients with high-risk cytogenetic abnormalities irrespective of prior DARA exposure
- Results are supportive of the deeper and more durable MRD negativity seen with DARA-R maintenance in PERSEUS[2]
  - Results from the phase 3 AURIGA study of DARA-R maintenance in patients with NDMM who were MRD positive following ASCT will be presented at IMS 2024 (Presentation OA-45)

DARA-based induction/consolidation and maintenance resulted in the deepest and most durable MRD negativity, leading to superior PFS outcomes, including in patients with high-risk cytogenetic abnormalities

R, lenalidomide.

1. Moreau P, et al. *Lancet Oncol.* 2024;25(8):1003-1014. 2. Rodríguez-Otero P, et al. ASCO 2024. Abstract 7502.

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CASSIOPEIA: Acknowledgments

- Patients who participated in this study and their families and caregivers
- Staff members at the study sites
- Data and safety monitoring committee
- Staff members involved in data collection and analyses
- Intergroupe Francophone du Myélome (IFM), the Dutch-Belgian Cooperative Trial Group for Hematology Oncology (HOVON), and Janssen

This study was sponsored by Intergroupe Francophone du Myélome (IFM) and supported by the Dutch-Belgian Cooperative Trial Group for Hematology Oncology (HOVON) and Janssen Research & Development, LLC.
Editorial support was provided by Kimberly Carmony, PhD (Lumanity Communications Inc.) and was funded by Janssen Global Services, LLC.

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