Daratumumab (DARA) + Bortezomib/Thalidomide/ Dexamethasone (D-VTd) Followed by DARA Maintenance in Transplant-eligible Newly Diagnosed Multiple Myeloma (NDMM): >6-year Update of CASSIOPEIA*

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CASSIOPEIA: Introduction

- **Induction/consolidation phase (Part 1) of CASSIOPEIA:** Results established D-VTd as a standard of care for transplant-eligible patients with NDMM[1-3]
  - D-VTd demonstrated superior depth of response (≥CR and MRD negativity) and significantly prolonged PFS and OS versus VTd, with acceptable safety (median follow-up: 18.8 months from first randomization)[1]
- **Maintenance phase (Part 2) of CASSIOPEIA:** DARA monotherapy maintenance Q8W significantly improved PFS and achieved higher rates of MRD negativity versus observation and was well tolerated (median follow-up: 35.4 months from second randomization)[4]
- **Long-term follow-up of CASSIOPEIA:** Here we report the long-term outcomes from the induction/consolidation and maintenance phases after a median follow-up of 80.1 months (nearly 7 years) from first randomization and 70.6 months (~6 years) from second randomization

D-VTd, daratumumab plus bortezomib/thalidomide/dexamethasone; NDMM, newly diagnosed multiple myeloma; CR, complete response; MRD, minimal residual disease; PFS, progression-free survival; OS, overall survival; VTd, bortezomib/thalidomide/dexamethasone; DARA, daratumumab; Q8W, every 8 weeks.

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]. https://www.ema.europa.eu/en/documents/product-information/darzalex-epar-product-information_en.pdf. Accessed May 6, 2024. 4. Moreau P, et al. *Lancet Oncol*. 2021;22(10):1378-1390.

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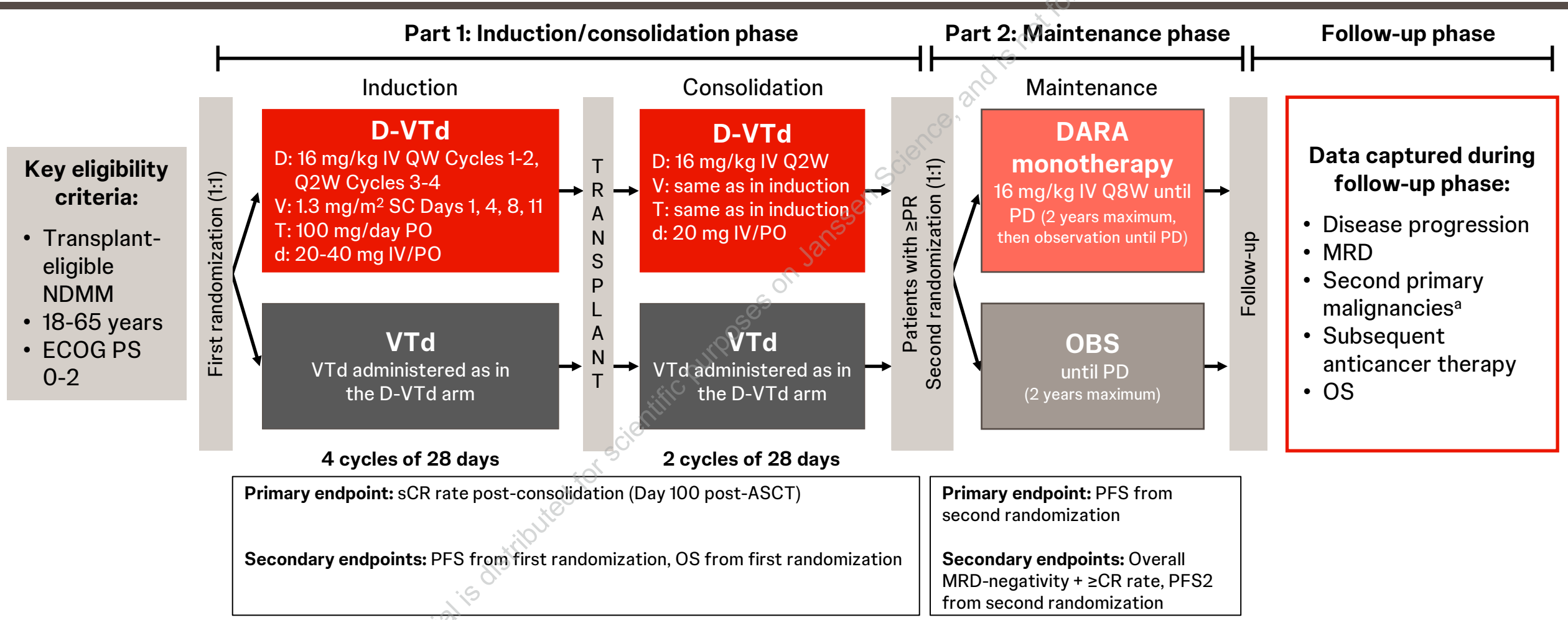
CASSIOPEIA: Study Design



ECOG PS, Eastern Cooperative Oncology Group performance status; D, daratumumab; IV, intravenous; QW, weekly; Q2W, every 2 weeks; V, bortezomib; SC, subcutaneous; T, thalidomide; PO, oral; d, dexamethasone; PR, partial response; PD, progressive disease; OBS, observation; sCR, stringent complete response; ASCT, autologous stem cell transplant; PFS2, progression-free survival on next line of therapy.
[a]Aside from second primary malignancies and deaths, 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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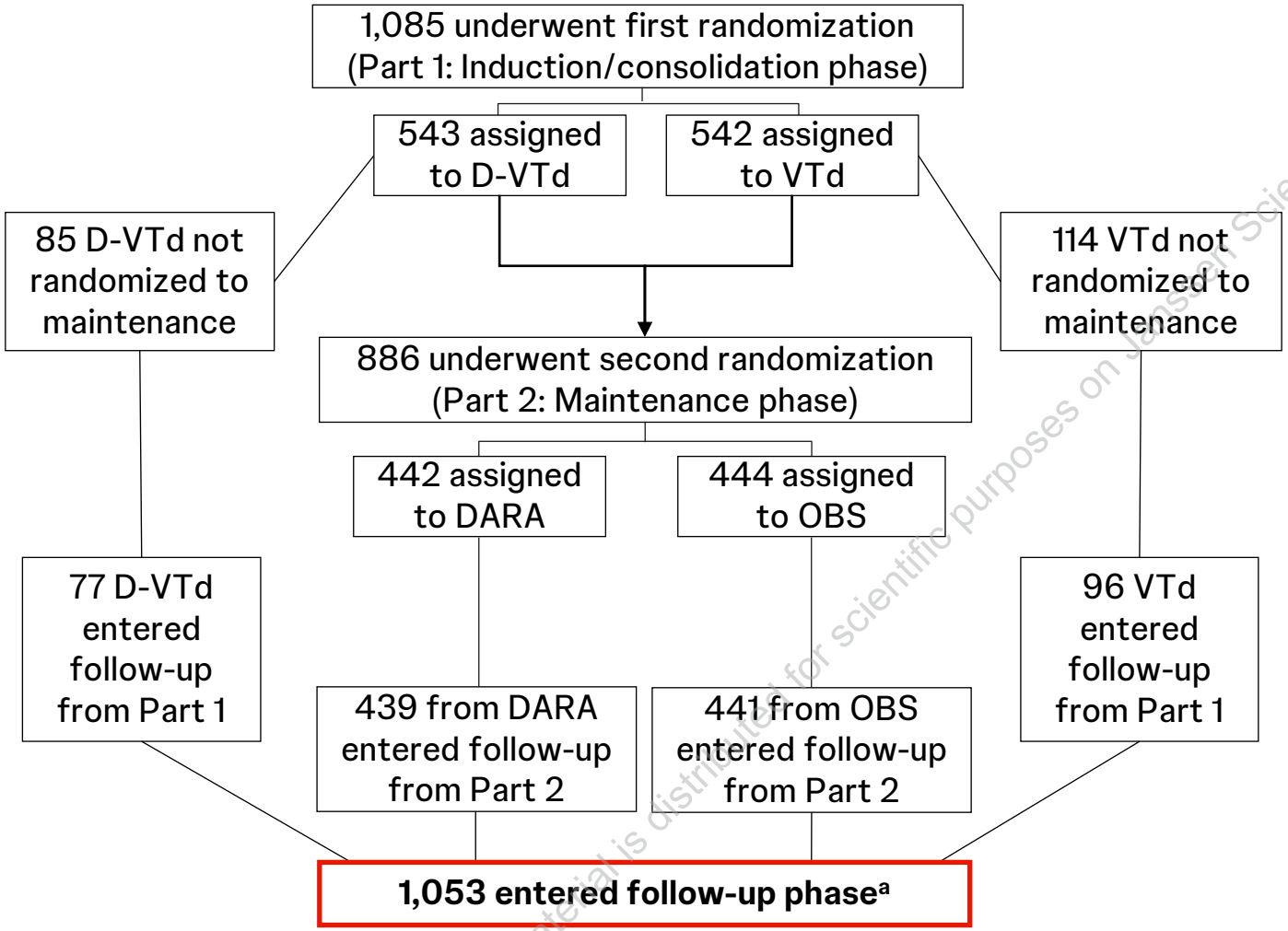
CASSIOPEIA: Patient Disposition



- 1,085 patients were enrolled from 111 sites from Sep 22, 2015 to Aug 1, 2017
- More patients in the D-VTd group versus the VTd group completed induction/consolidation per protocol (84.3% vs 79.0%) and underwent second randomization into the maintenance phase
  - 199 patients (85 from D-VTd and 114 from VTd) did not proceed to second randomization
- Nearly all patients entered the follow-up phase (1,053/1,085; 97.1%)

[a]During the follow-up phase, the following data were captured: disease progression, development of second primary malignancy, start of subsequent anticancer therapy (including best response and disease progression on subsequent therapy), and OS.

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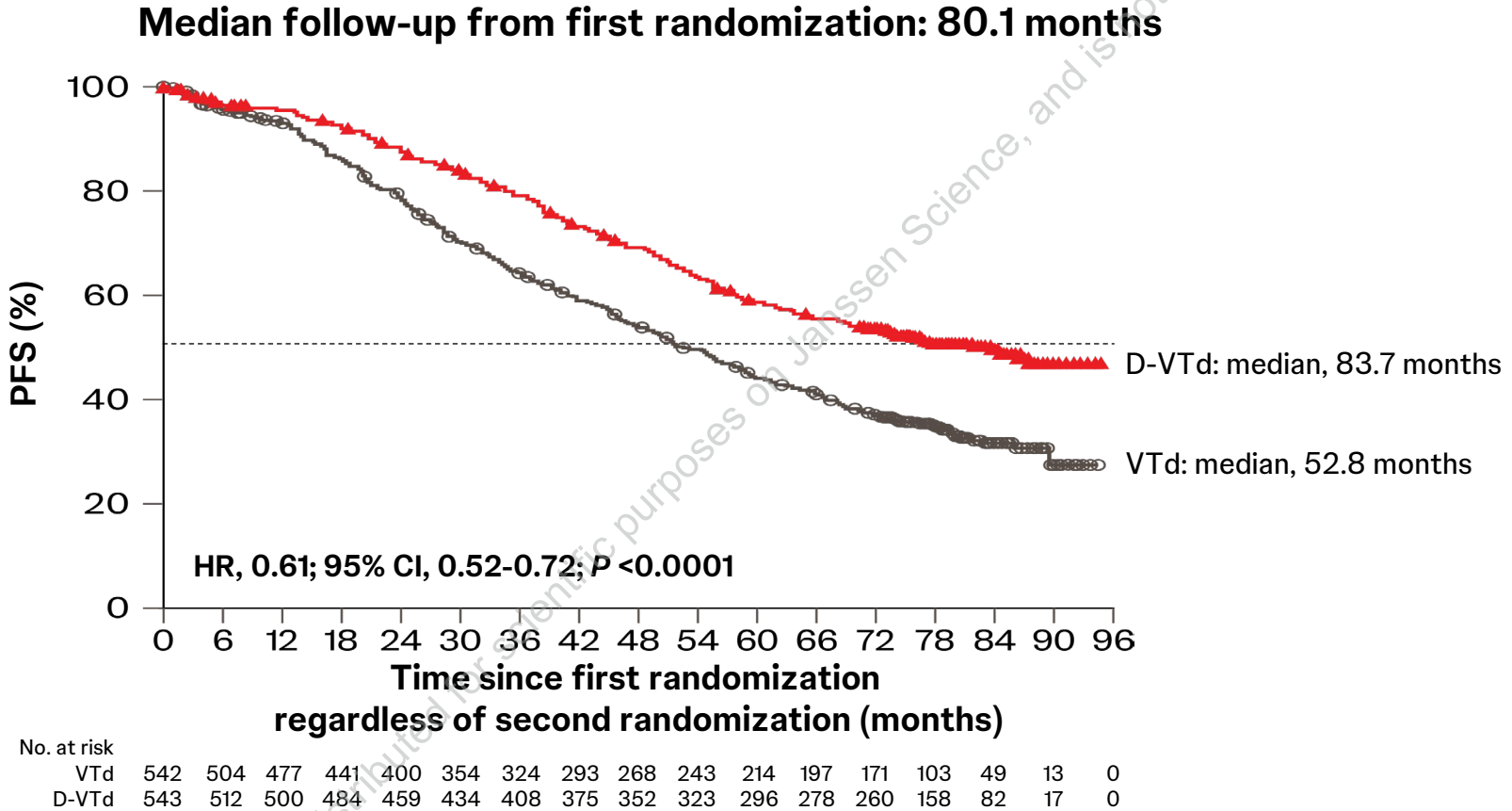
CASSIOPEIA: Updated PFS From First Randomization



- **PFS from first randomization was significantly improved with D-VTd versus VTd**
- **Median PFS was ~2.5 years longer with addition of DARA to VTd (~7 vs ~4.5 years)**

HR, hazard ratio; CI, confidence interval.
P value was calculated using the log-rank test.

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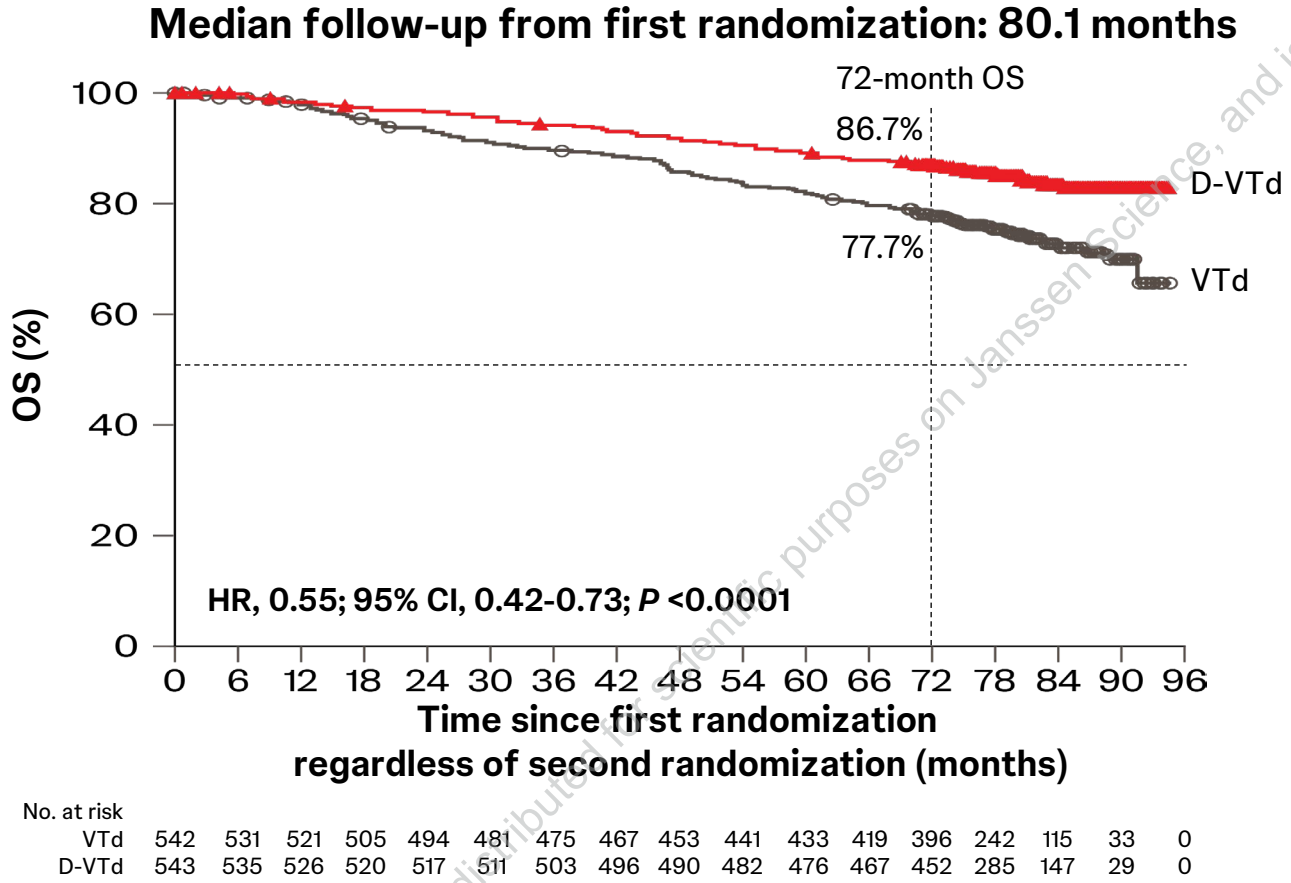
CASSIOPEIA: Updated OS From First Randomization



- **Number of deaths**
  - D-VTd: 83 (15.3%)
  - VTd: 139 (25.6%)

D-VTd significantly reduced the risk of death by 45% versus VTd

P value was calculated using the log-rank test.

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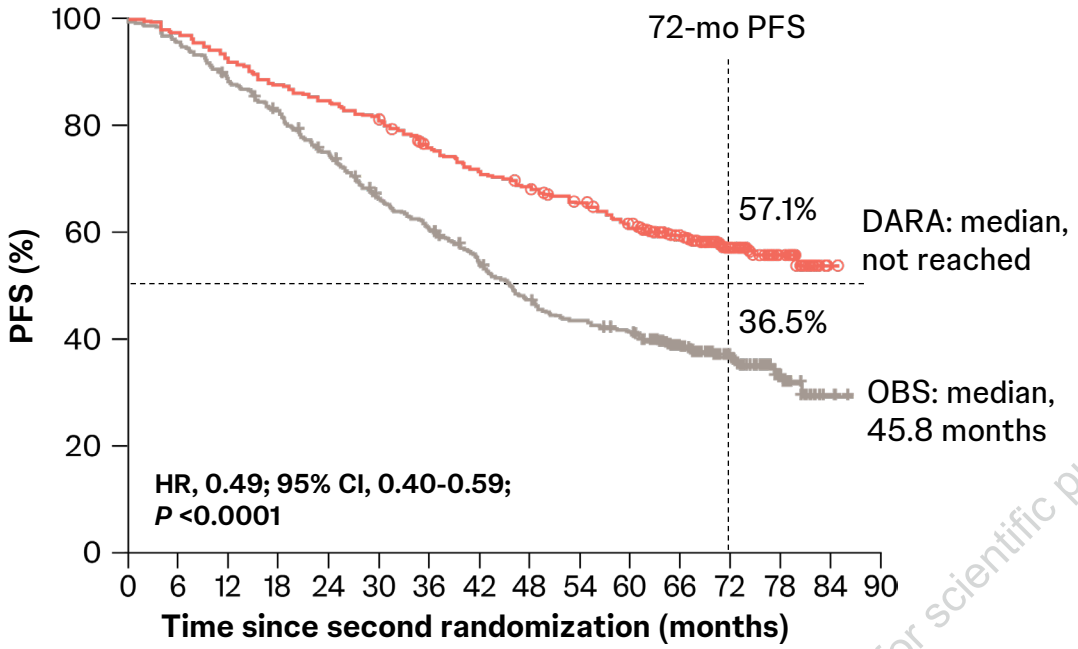
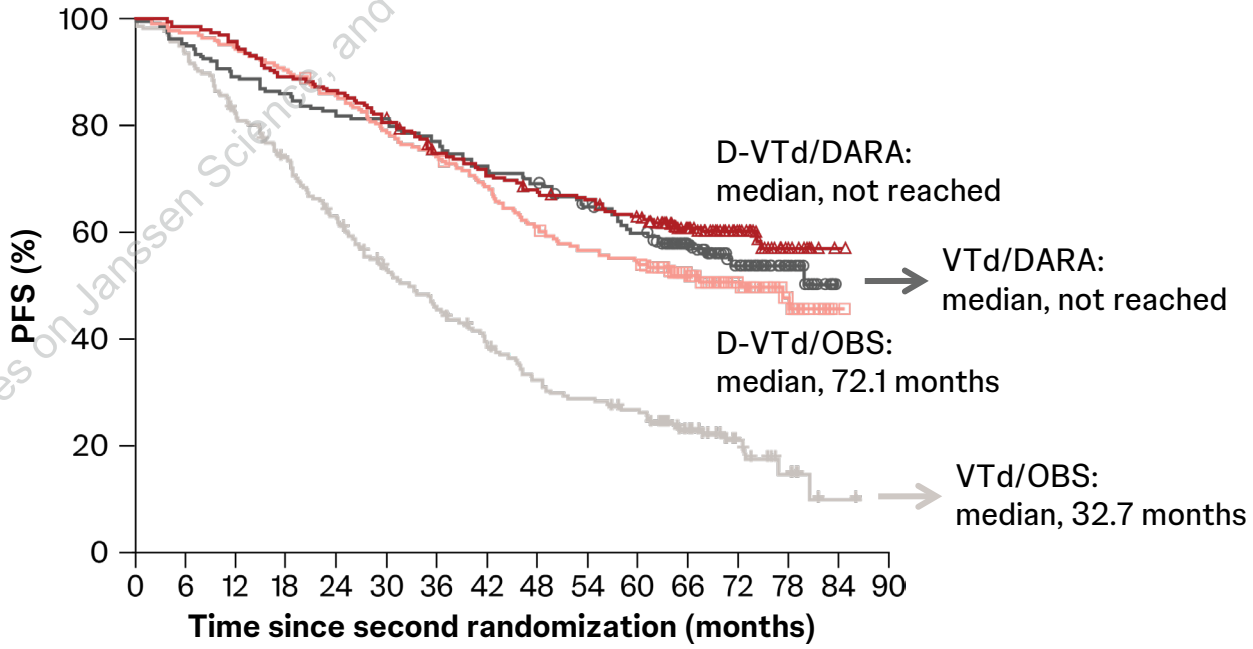
CASSIOPEIA: PFS From Second Randomization

Median follow-up from second randomization: 70.6 months



No. at risk																
OBS	444	424	392	363	327	286	261	232	201	183	172	122	68	27	2	0
DARA	442	429	407	387	373	359	332	311	298	281	260	198	99	42	1	0



No. at risk																
VTd/OBS	215	201	176	156	132	107	92	77	63	56	50	32	13	5	1	0
VTd/DARA	213	203	190	183	175	172	164	153	147	135	123	92	48	23	0	0
D-VTd/OBS	229	223	216	207	195	179	169	155	138	127	122	90	55	22	1	0
D-VTd/DARA	229	226	217	204	198	187	168	158	151	146	137	106	51	19	1	0

- **DARA maintenance reduced the risk of progression or death by 51% versus OBS**
- **The longest PFS was observed in patients who received D-VTd + DARA maintenance**

P value was calculated using the stratified log-rank test with type of induction/consolidation treatment (D-VTd vs VTd) and depth of response (as assessed by MRD status per flow cytometry and post-consolidation response) as the stratification factors.

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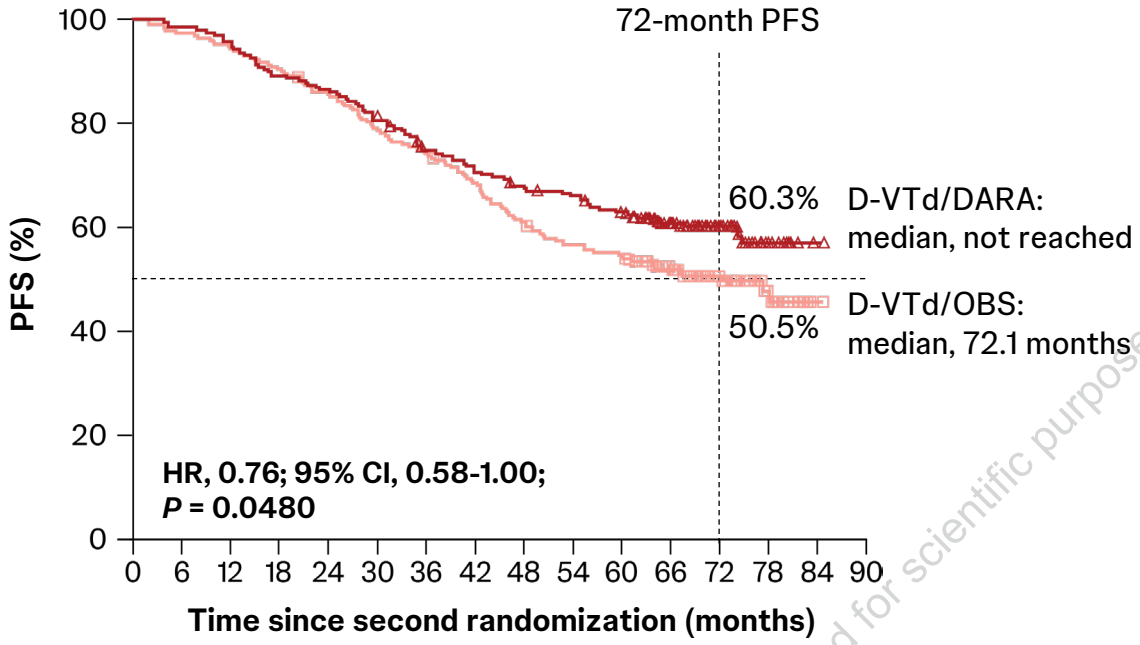
CASSIOPEIA: PFS From Second Randomization

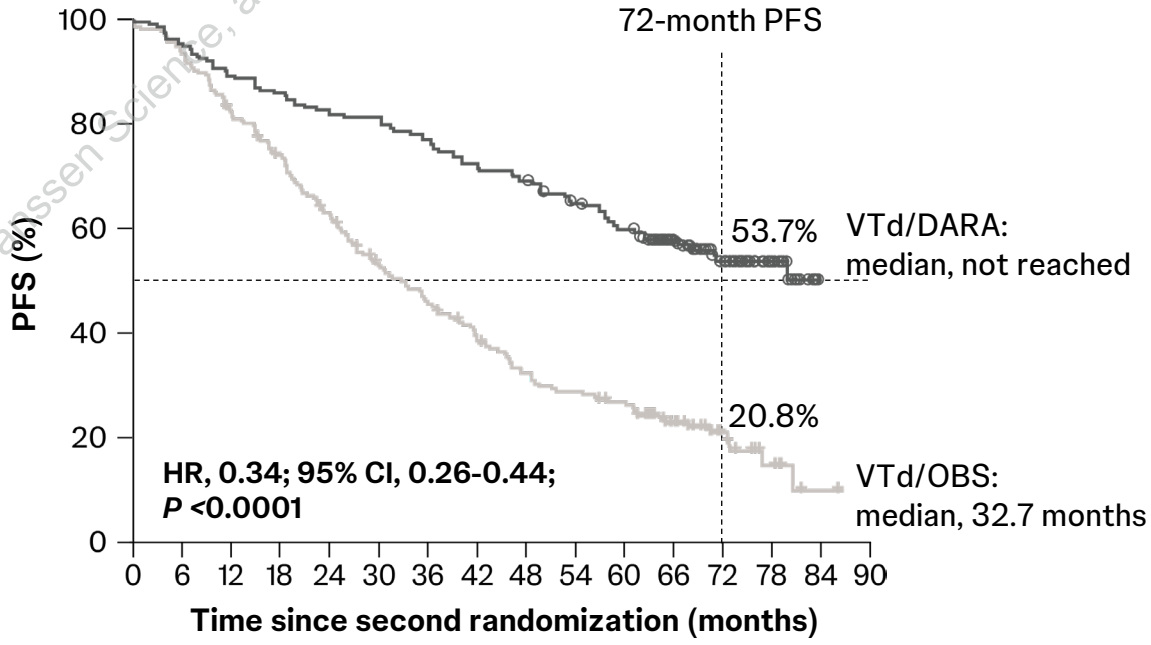
Median follow-up from second randomization: 70.6 months

D-VTd/DARA vs D-VTd/OBS



No. at risk																
D-VTd/OBS	229	223	216	207	195	179	169	155	138	127	122	90	55	22	1	0
D-VTd/DARA	229	226	217	204	198	187	168	158	151	146	137	106	51	19	1	0

VTd/DARA vs VTd/OBS



No. at risk																
VTd/OBS	215	201	176	156	132	107	92	77	63	56	50	32	13	5	1	0
VTd/DARA	213	203	190	183	175	172	164	153	147	135	123	92	48	23	0	0

The longest PFS was observed in patients who received D-VTd + DARA maintenance

P value was calculated using the stratified log-rank test with depth of response (as assessed by MRD status per flow cytometry and post-consolidation response) as the stratification factor.

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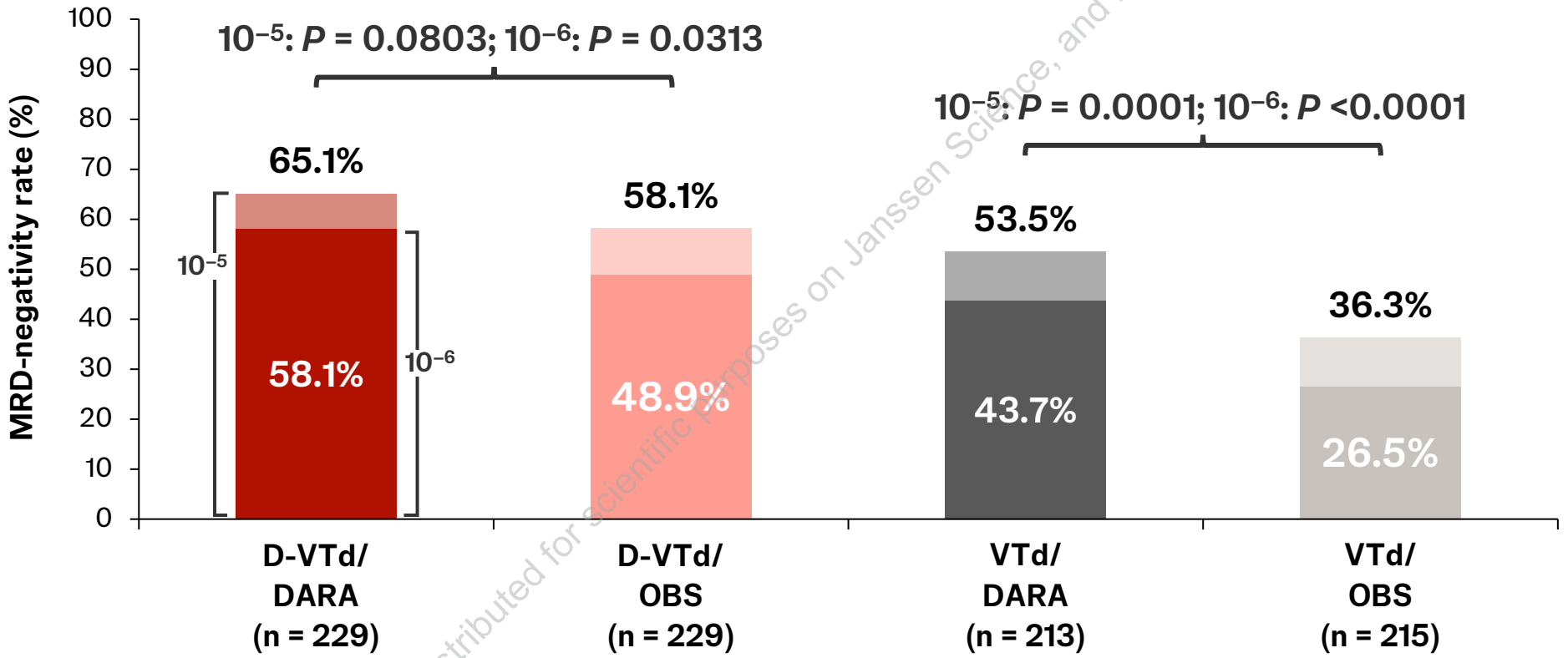
CASSIOPEIA: Overall MRD-negativity Rates[a] at Any Time During Maintenance (10^{-5} and 10^{-6}; Maintenance Population)



MRD-negativity rates at both 10^{-5} and 10^{-6} were highest for D-VTd/DARA

ITT, intent-to-treat.
[a]The proportion of patients who achieved ≥CR and MRD negativity in the maintenance-specific ITT population post-consolidation after the second randomization. MRD was assessed via next-generation sequencing.
P values were calculated using the stratified Cochran–Mantel–Haenszel chi-square test.

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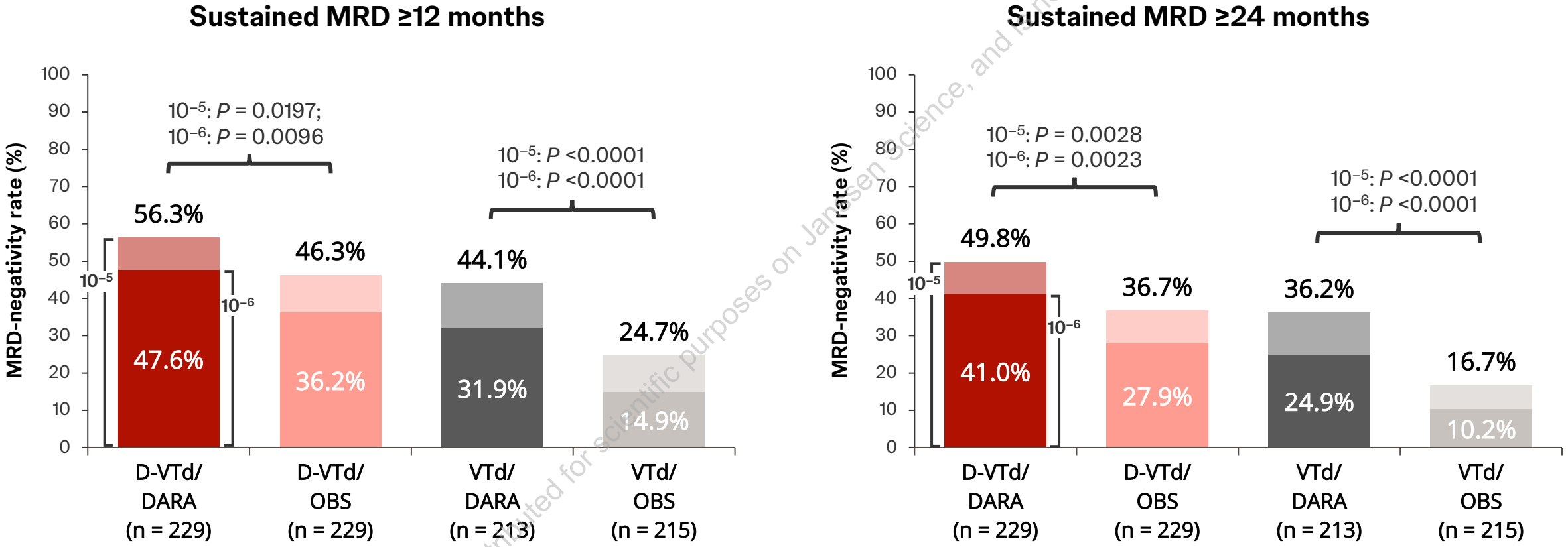
CASSIOPEIA: Sustained MRD-negativity Rates[a] at Any Time During the Study (10^{-5} and 10^{-6}; Maintenance Population)



Rates of sustained MRD negativity for ≥12 and ≥24 months at both 10^{-5} and 10^{-6} were highest for D-VTd/DARA

[a]The proportion of patients who achieved ≥CR and sustained MRD negativity in the maintenance-specific ITT population. MRD was assessed via next-generation sequencing.
P values were calculated using the stratified Cochran–Mantel–Haenszel chi-square test.

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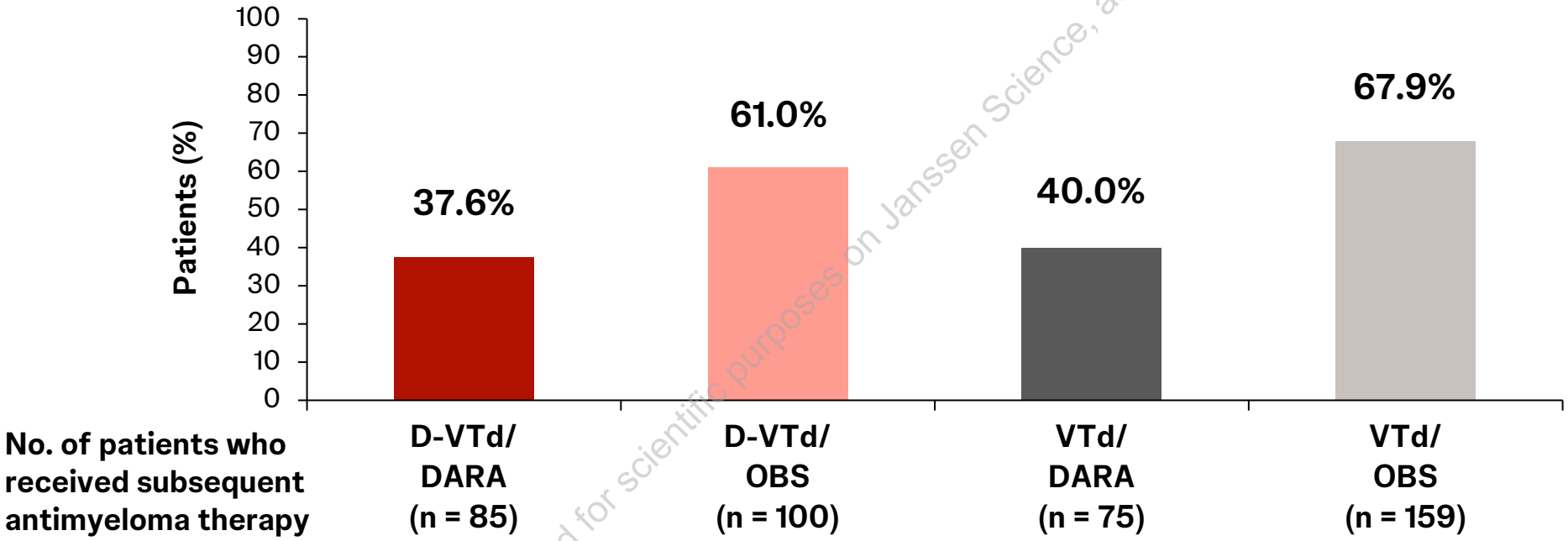
CASSIOPEIA: First-line Subsequent Anti-CD38–based Therapies (Maintenance Population)



- Higher proportions of patients in the OBS versus DARA arms received subsequent antimyeloma therapy; in the OBS arms, these were primarily anti-CD38–based therapies
- The most common subsequent anti-CD38–based regimen received was D-Rd

D-Rd, daratumumab plus lenalidomide/dexamethasone.

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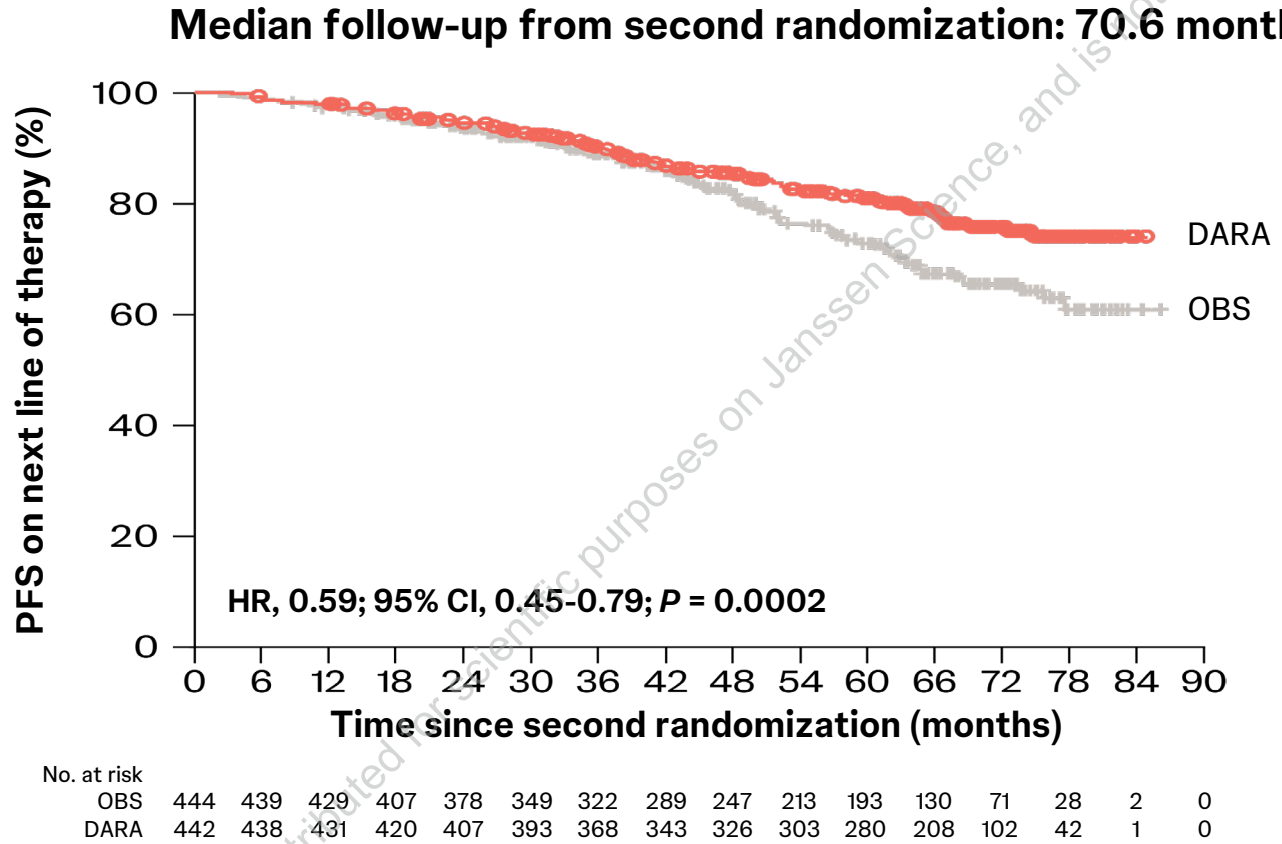
CASSIOPEIA: PFS2 From Second Randomization



PFS2 was significantly improved with DARA maintenance versus OBS

P value was calculated using the stratified log-rank test with type of induction/consolidation treatment (D-VTd vs VTd) and depth of response (as assessed by MRD status per flow cytometry and post-consolidation response) as the stratification factors.

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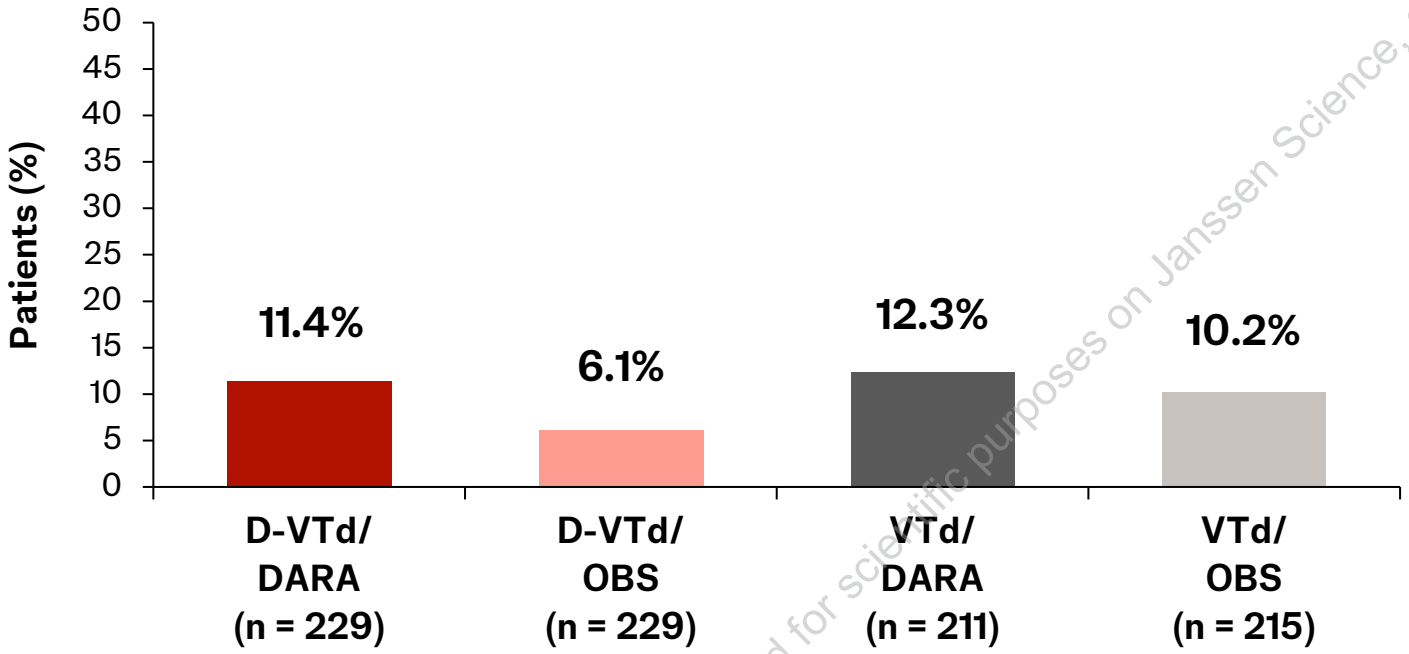
CASSIOPEIA: Second Primary Malignancies (Maintenance Population)



- **Type of second primary malignancy**
  - Non-cutaneous: 47 (5.3%)
  - Cutaneous: 27 (3.1%)
  - Hematologic: 16 (1.8%)

Occurrence of second primary malignancies remained low and relatively consistent with ~6 years of follow-up

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CASSIOPEIA: Conclusions

- **In the induction/consolidation phase (median follow-up of nearly 7 years):**
  - PFS and OS were significantly improved with D-VTd versus VTd
  - Median PFS was ~2.5 years longer with addition of DARA to VTd (~7 vs ~4.5 years)
  - D-VTd reduced the risk of death by 45% versus VTd
- **In the maintenance phase (median follow-up of ~6 years):**
  - DARA reduced the risk of progression or death by 51% versus OBS
  - 72-month PFS rates were 20% higher with DARA versus OBS (57.1% vs 36.5%)
  - D-VTd induction/consolidation + DARA maintenance led to the most pronounced PFS benefit
  - D-VTd induction/consolidation + DARA maintenance achieved the highest and most durable rates of MRD negativity, which translated to superior PFS outcomes

These results confirm D-VTd induction/consolidation as a standard of care and demonstrate the benefit of DARA monotherapy maintenance for transplant-eligible patients with NDMM

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CASSIOPEIA: Acknowledgments

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

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THE LANCET
Oncology

Bortezomib, thalidomide, and dexamethasone with or without daratumumab and followed by daratumumab maintenance or observation in transplant-eligible newly diagnosed multiple myeloma: long-term follow-up of the CASSIOPEIA randomised controlled phase 3 trial

Philippe Moreau, Cyrille Hulin, Aurore Perrot, Bertrand Arnulf, Karim Belhadj, Lotfi Benboubker, Sonja Zweegman, Hélène Caillon, Denis Caillot, Hervé Avet-Loiseau, Michel Delforge, Thomas Dejoie, Thierry Facon, Cécile Sonntag, Jean Fontan, Mohamad Mohty, Kon-Siong Jie, Lionel Karlin, Frédérique Kuhnowski, Jérôme Lambert, Xavier Leleu, Margaret Macro, Frédérique Orsini-Piocelle, Murielle Roussel, Jean Marc Schiano de Colella, Niels WCJ van de Donk, Soraya Wuillème, Annemiek Broijl, Cyrille Touzeau, Mourad Tiab, Jean-Pierre Marolleau, Nathalie Meuleman, Marie-Christiane Vekemans, Matthijs Westerman, Saskia K Klein, Mark-David Levin, Fritz Offner, Martine Escoffre-Barbe, Jean-Richard Eveillard, Réda Garidi, Winnie Hua, Jianping Wang, Alba Tuozzo, Carla de Boer, Melissa Rowe, Veronique Vanquickelberghe, Robin Carson, Jessica Vermeulen, Jill Corre, Pieter Sonneveld, on behalf of the Intergroupe Francophone du Myélome, the Dutch-Belgian Cooperative Trial Group for Hematology Oncology and the CASSIOPEIA Investigators

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