Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

66th ASH Meeting 2024

San Diego & virtuell

KML KONGRESSE

Expert:innen berichten zu Lymphomen & Leukämien

Kompetenznetz Maligne Lymphome

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KML KONGRESSE

Expert:innen berichten zu Lymphomen & Leukämien

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Universitätsklinikum Hamburg Eppendorf

Multiples Myelom (MM)

Offenlegung potentieller Interessenskonflikte

LymphomKompetenz KOMPAKT – ASH2023 wird in Kooperation mit acht unterstützenden Firmen durchgeführt.
Meine persönlichen Disclosures betreffen:

Anstellungsverhältnis, Führungsposition	
Beratungs-/ Gutachtertätigkeit	Abbvie, Adaptive, Amgen, Bristol Myers Squibb, Celgene, Janssen, GSK, Karyopharm, Novartis, Oncopeptides, Pfizer, Roche Pharma, Takeda, Sanofi
Besitz von Geschäftsanteilen, Aktien oder Fonds	
Patent, Urheberrecht, Verkaufslizenz	
Honorare	Abbvie, Adaptive, Amgen, Bristol Myers Squibb, Celgene, Janssen, GSK, Karyopharm, Novartis, Oncopeptides, Pfizer, Roche Pharma, Takeda, Sanofi
Finanzierung wissenschaftlicher Untersuchungen	Amgen, Celgene, Janssen, Sanofi; GSK, Abbvie
Andere finanzielle Beziehungen	
Immaterielle Interessenkonflikte	

Kapitel 1

Smoldering Multiples Myelom – werden wir jetzt doch behandeln?

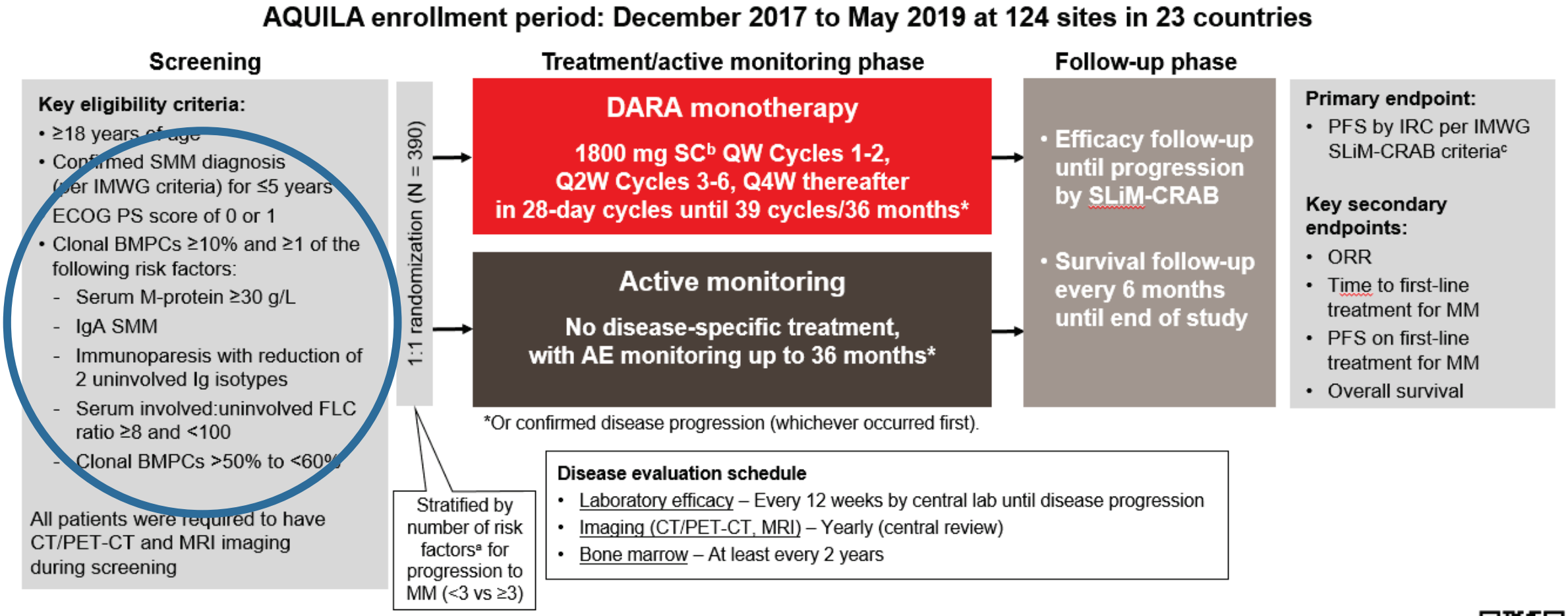
AQUILA Studie

Phase 3 Randomized Study of Daratumumab Monotherapy Versus Active Monitoring in Patients With High-risk Smoldering Multiple Myeloma: Primary Results of the AQUILA Study

Meletios A Dimopoulos et al.

AQUILA-Studie

Phase 3 Randomized Study of Daratumumab Monotherapy Versus Active Monitoring in Patients With High-risk Smoldering Multiple Myeloma: Primary Results of the AQUILA Study



AQUILA-Studie

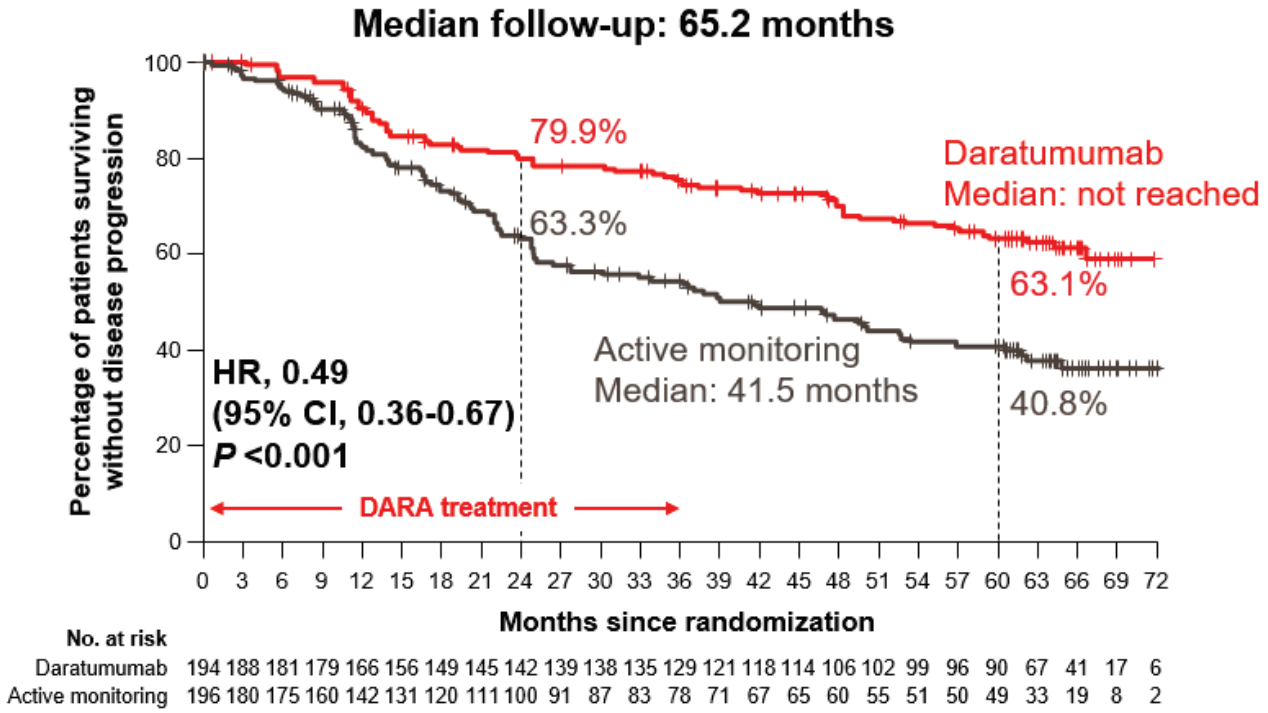
Phase 3 Randomized Study of Daratumumab Monotherapy Versus Active Monitoring in Patients With High-risk Smoldering Multiple Myeloma: Primary Results of the AQUILA Study

Characteristic	DARA (n = 194)	Active monitoring (n = 196)
Age		
Median (range), years	63.0 (31-86)	64.5 (36-83)
18 to <65 years, n (%)	106 (54.6)	98 (50.0)
65 to <75 years, n (%)	67 (34.5)	74 (37.8)
≥75 years, n (%)	21 (10.8)	24 (12.2)
Sex, n (%)		
Female	99 (51.0)	103 (52.6)
Male	95 (49.0)	93 (47.4)
ECOG PS score, n (%)		
0	165 (85.1)	160 (81.6)
1	29 (14.9)	36 (18.4)
Median time from diagnosis of SMM to randomization (range), years	0.80 (0-4.7)	0.67 (0-5.0)
Median BMPCs (range), %	20.0 (8.0-59.5)	20.0 (10.0-55.0)

Characteristic	DARA (n = 194)	Active monitoring (n = 196)
Type of SMM, n (%)		
IgG	127 (65.5)	138 (70.4)
IgA	55 (28.4)	42 (21.4)
Other	12 (6.2)	16 (8.2)
AQUILA risk factors for progression to MM, n (%)[a]		
<3	154 (79.4)	156 (79.6)
≥3	40 (20.6)	40 (20.4)
Cytogenetic risk profile[b]	n = 167	n = 170
≥1 of del(17p), t(4;14), and/or t(14;16), n (%)	29 (17.4)	22 (12.9)
Mayo 2018 risk criteria, n (%)[c]		
Low	45 (23.2)	34 (17.3)
Intermediate	77 (39.7)	76 (38.8)
High	72 (37.1)	86 (43.9)

AQUILA-Studie

Phase 3 Randomized Study of Daratumumab Monotherapy Versus Active Monitoring in Patients With High-risk Smoldering Multiple Myeloma: Primary Results of the AQUILA Study



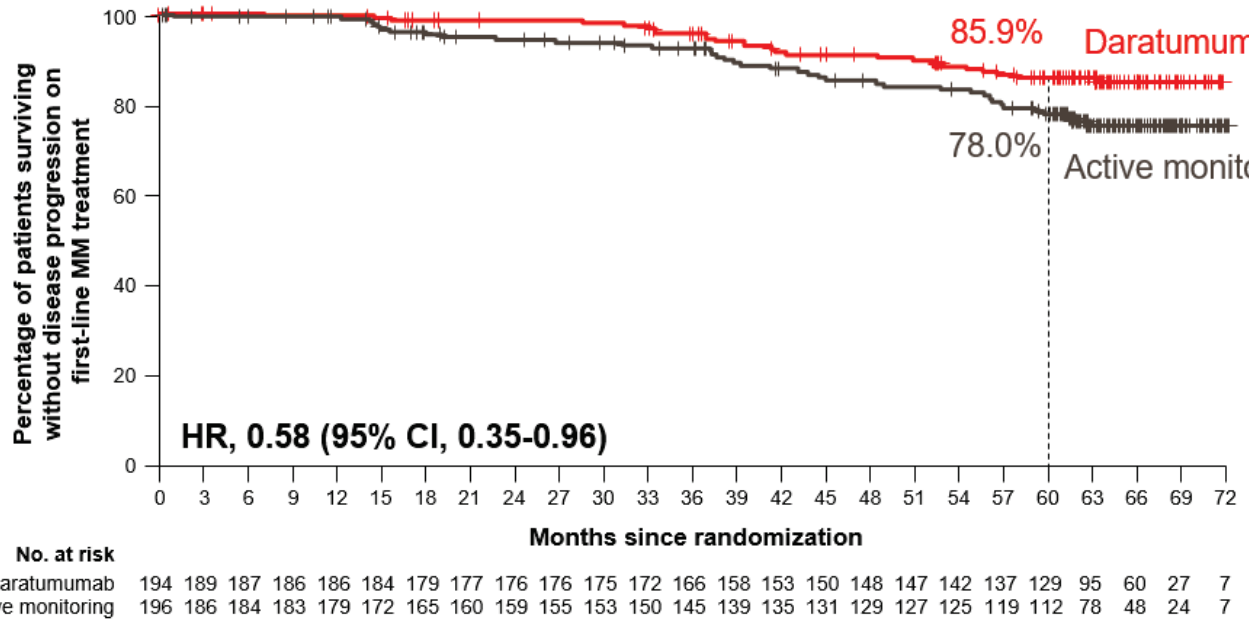
	DARA (n = 194)	Active monitoring (n = 196)
PFS event, n (%)	67 (34.5)	99 (50.5)
Death without disease progression	5 (2.6)	5 (2.6)
Disease progression[a]	62 (32.0)	94 (48.0)
CRAB criteria	12 (6.2)	34 (17.3)
Calcium elevation	0	2 (1.0)
Renal insufficiency[b]	0	0
Anemia	2 (1.0)	14 (7.1)
Bone disease	10 (5.2)	18 (9.2)
SLiM criteria	50 (25.8)	65 (33.2)
Clonal BMPCs	5 (2.6)	16 (8.2)
Serum FLC	33 (17.0)	33 (16.8)
Focal lesion by MRI	12 (6.2)	16 (8.2)

DARA significantly reduced the risk of progression to MM or death by 51% versus active monitoring; the benefit continued beyond 36 months

AQUILA-Studie

Phase 3 Randomized Study of Daratumumab Monotherapy Versus Active Monitoring in Patients With High-risk Smoldering Multiple Myeloma: Primary Results of the AQUILA Study

AQUILA: PFS on First-line Treatment for MM (PFS2)[a]



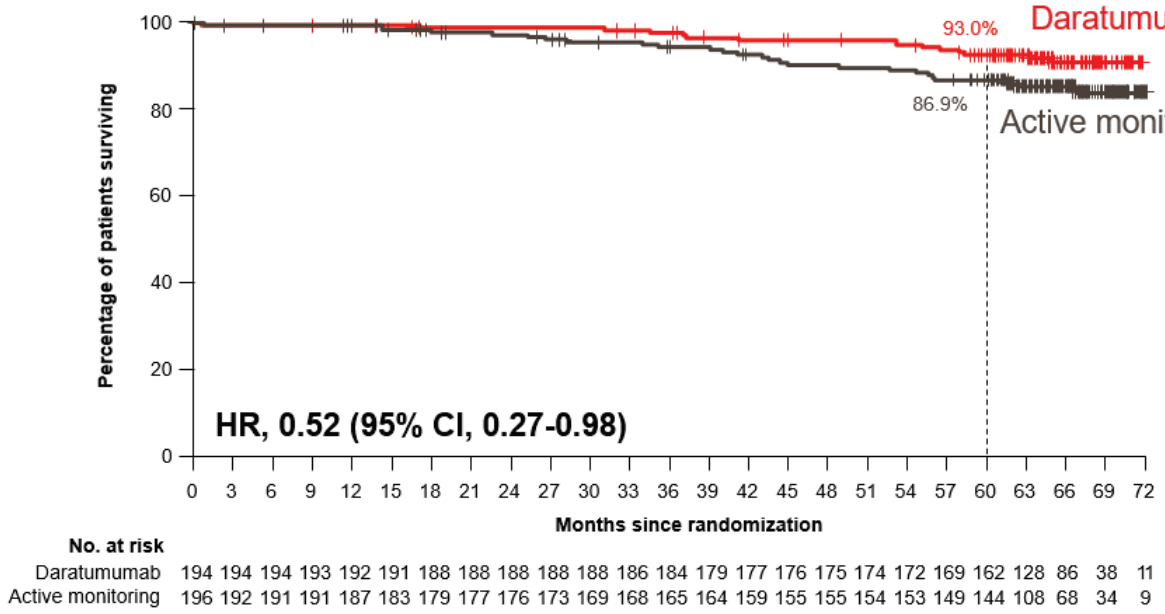
- VRd most common first-line regimen
  - 29.7% (19/64) in DARA arm
  - 27.6% (29/105) in active monitoring arm
- Received anti-CD38 mAb-based therapy (varied):
  - 25.0% (16/64) in DARA arm
  - 33.3% (35/105) in active monitoring arm

DARA improved PFS on first-line treatment for MM versus active monitoring and does not appear to impair later treatment for MM

AQUILA-Studie

Phase 3 Randomized Study of Daratumumab Monotherapy Versus Active Monitoring in Patients With High-risk Smoldering Multiple Myeloma: Primary Results of the AQUILA Study

AQUILA: Overall Survival



	DARA (n = 194)	Active monitoring (n = 196)
Deaths, n (%)	15 (7.7)	26 (13.3)
Primary cause, n		
Disease progression	3	9
AE	2	4
Other*	10	13

*Deaths due to an event occurring after the AE reporting window (ie, events that happened after patient started subsequent therapy or >30 days after last dose) or deaths with unknown reason.

Early intervention with fixed duration DARA extended overall survival versus active monitoring

AQUILA-Studie

Phase 3 Randomized Study of Daratumumab Monotherapy Versus Active Monitoring in Patients With High-risk Smoldering Multiple Myeloma: Primary Results of the AQUILA Study

Daratumumab Monotherapie über 3 Jahre verhindert effektiv die Progression des Hochrisiko-SMM in ein behandlungsbedürftiges Myelom

Kein Hinweis auf nachteiliges Outcome in der Erstlinien-Myelombehandlung durch die Daratumumab Vortherapie

OS Outcome günstiger in der Daratumumab-Gruppe

Zulassung für Daratumumab zur Behandlung des SMM wird erwartet

Kapitel 2

Quadruplet in der Behandlung transplantierbarer Patienten

GMMG-HD7 Studie

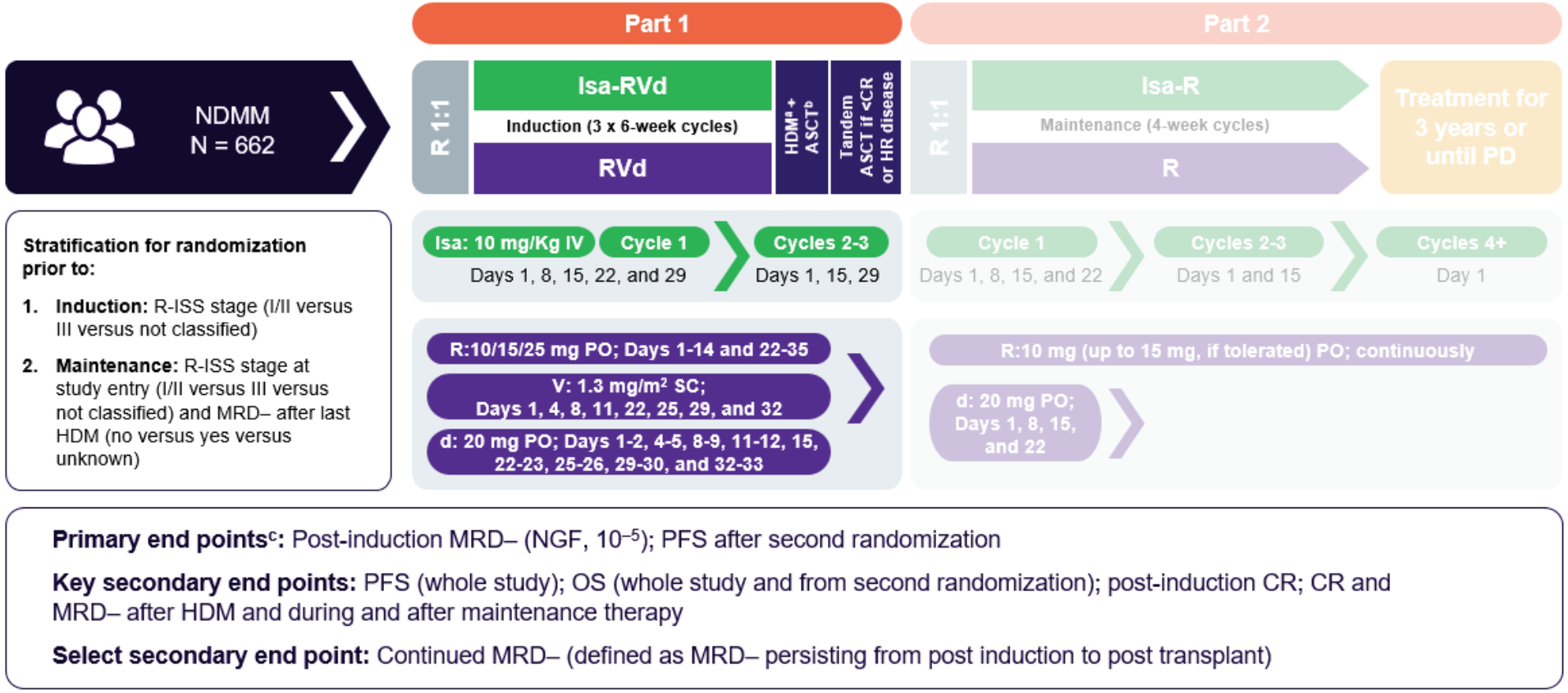
Isatuximab, Lenalidomide, Bortezomib and Dexamethasone Induction Therapy for Transplant-Eligible Patients With Newly Diagnosed Multiple Myeloma: Final Progression-Free Survival Analysis of Part 1 of an Open-label, Multicenter, Randomized, Phase 3 Trial (GMMG-HD7)

Hartmut Goldschmidt et al.

GMMG-HD7 Studie

Isatuximab, Lenalidomide, Bortezomib and Dexamethasone Induction Therapy for Transplant-Eligible Patients With Newly Diagnosed Multiple Myeloma: Final Progression-Free Survival Analysis of Part 1 of an Open-label, Multicenter, Randomized, Phase 3 Trial (GMMG-HD7)

Study design



GMMG-HD7 Studie

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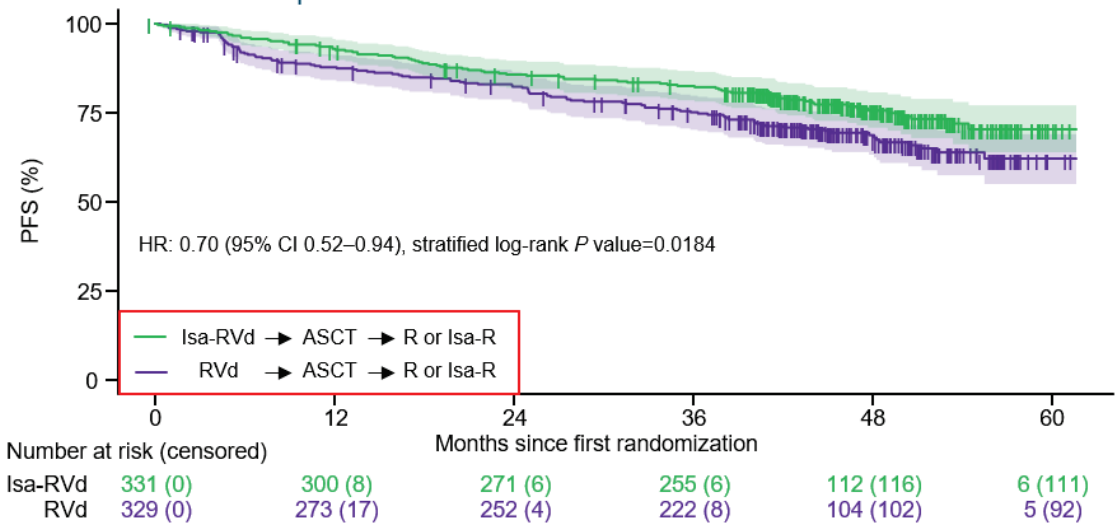
Internal

Secondary endpoint: PFS from first randomization

Kaplan-Meier estimates for PFS from the first randomization

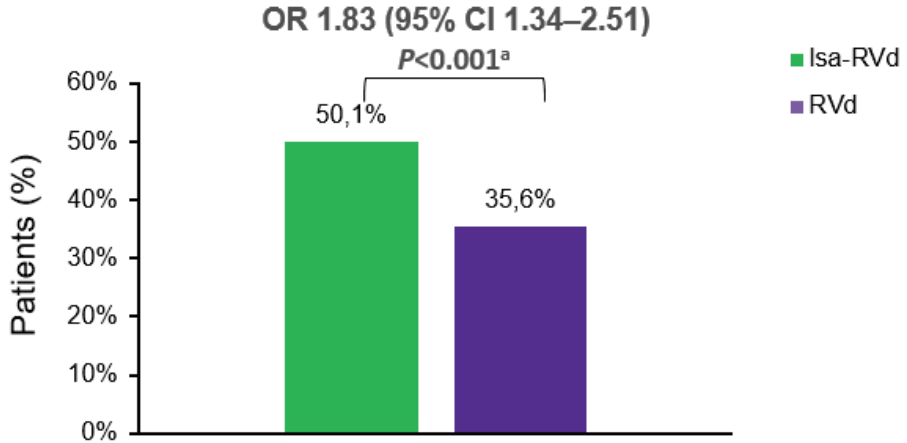


Number at risk (censored)

Isa-RVd	331 (0)	300 (8)	271 (6)	255 (6)	112 (116)	6 (111)
RVd	329 (0)	273 (17)	252 (4)	222 (8)	104 (102)	5 (92)

At a median follow-up of 48 months from first randomization, the addition of Isa to RVd during 18-week induction therapy led to a significant and clinically meaningful PFS benefit independent of maintenance therapy

Patients with MRD– at the end of induction therapy



GMMG-HD7 Studie

Isatuximab, Lenalidomide, Bortezomib and Dexamethasone Induction Therapy for Transplant-Eligible Patients With Newly Diagnosed Multiple Myeloma: Final Progression-Free Survival Analysis of Part 1 of an Open-label, Multicenter, Randomized, Phase 3 Trial (GMMG-HD7)

Isa-VRd in Induktion zeigt PFS Vorteil im Vergleich zur Triplet VRd Induktion unabhängig von der Erhaltungstherapie

Daten bestätigen die bereits publizierten Ergebnisse der PERSEUS Studie

Nach der erfolgten Zulassung des PERSEUS Regimes im Oktober durch die EMA sollte die Dara-VRd Induktion, Dara-VRd Konsolidierung und Dara-R Erhaltung Standard für alle Patient:innen im Kontext der Hochdosistherapie sein

Kapitel 3

Quadruplet in der Behandlung nicht-transplantierbarer Patient:innen

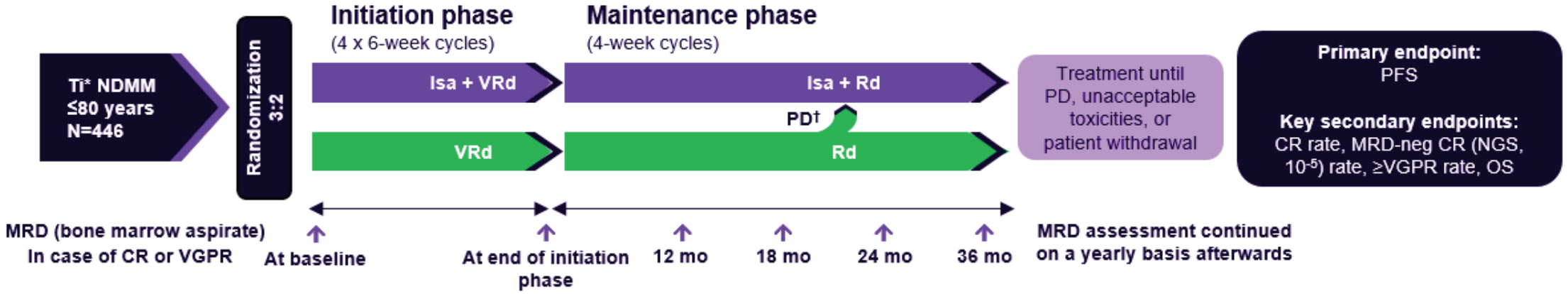
IMROZ-Studie/CEPHEUS-Studie

Isatuximab, Bortezomib, Lenalidomide, and Dexamethasone (Isa-VRd) in Patients with Newly Diagnosed Multiple Myeloma (NDMM): Analyses of Minimal Residual Disease (MRD) Negativity Dynamics in the Phase 3 IMROZ Study – Orlowski et al.

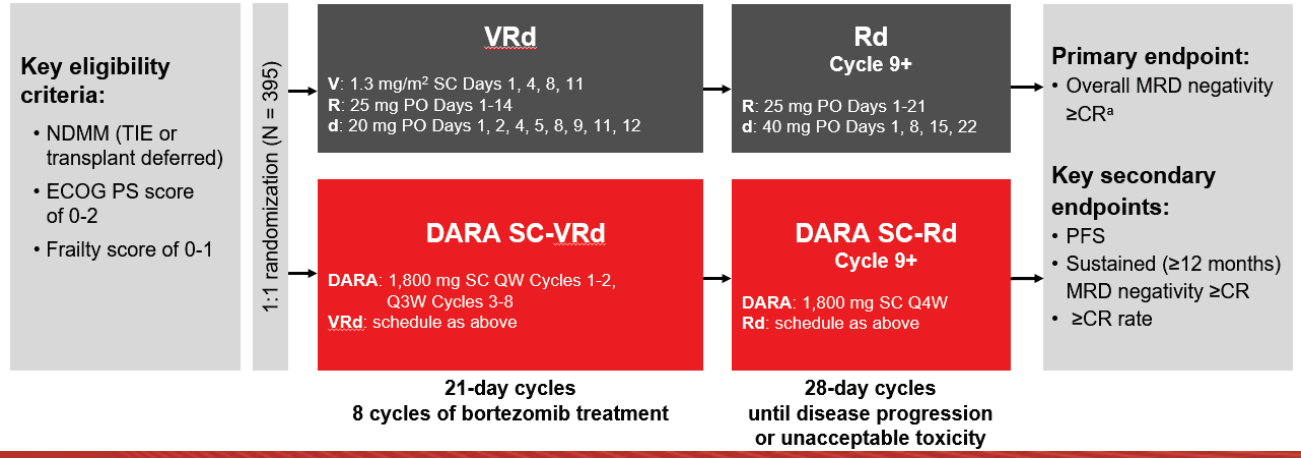
Daratumumab + Bortezomib, Lenalidomide, and Dexamethasone (VRd) Versus VRd Alone in Patients With Newly Diagnosed Multiple Myeloma Ineligible for SCT or for Whom SCT is Not Planned as Initial Therapy: Analysis of Minimal Residual Disease in the Phase 3 CEPHEUS Trial – Zweegman et al.

IMROZ-Studie/CEPHEUS-Studie

IMROZ

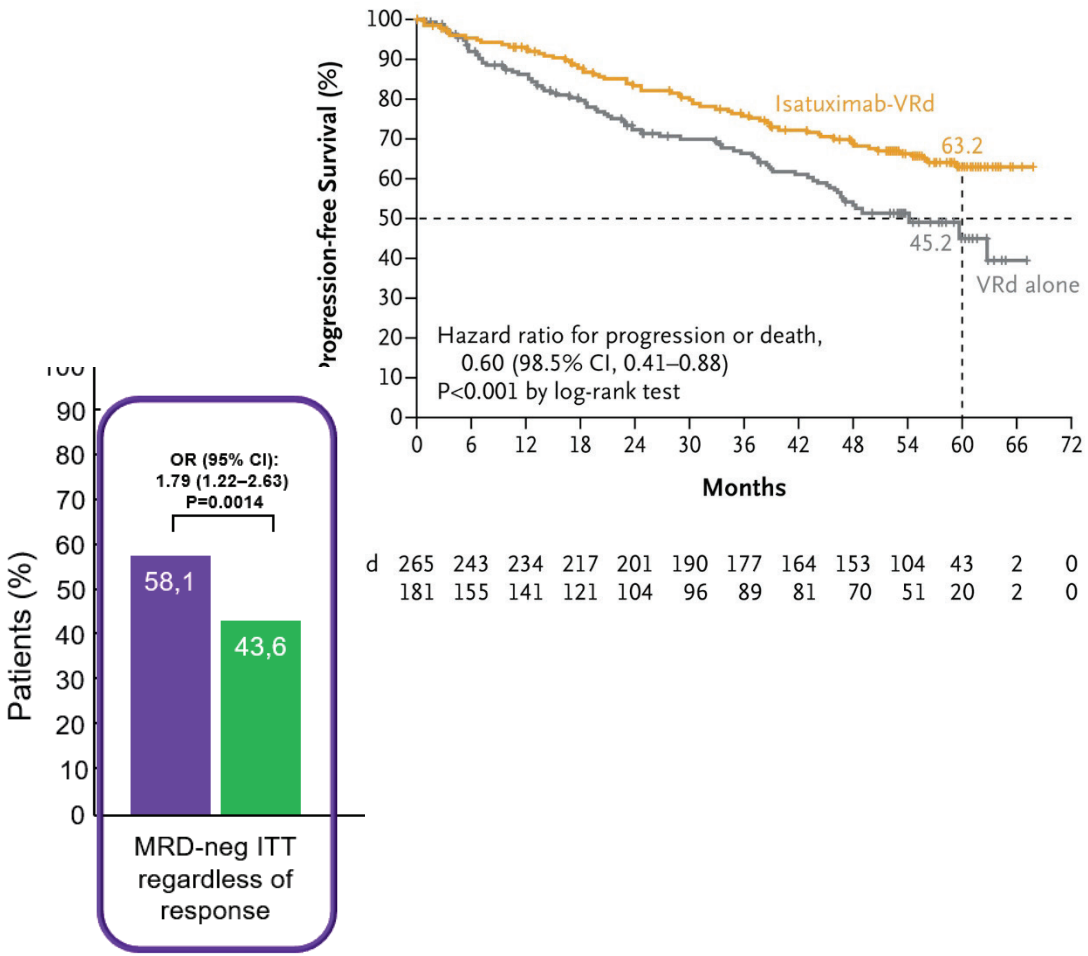


CEPHEUS

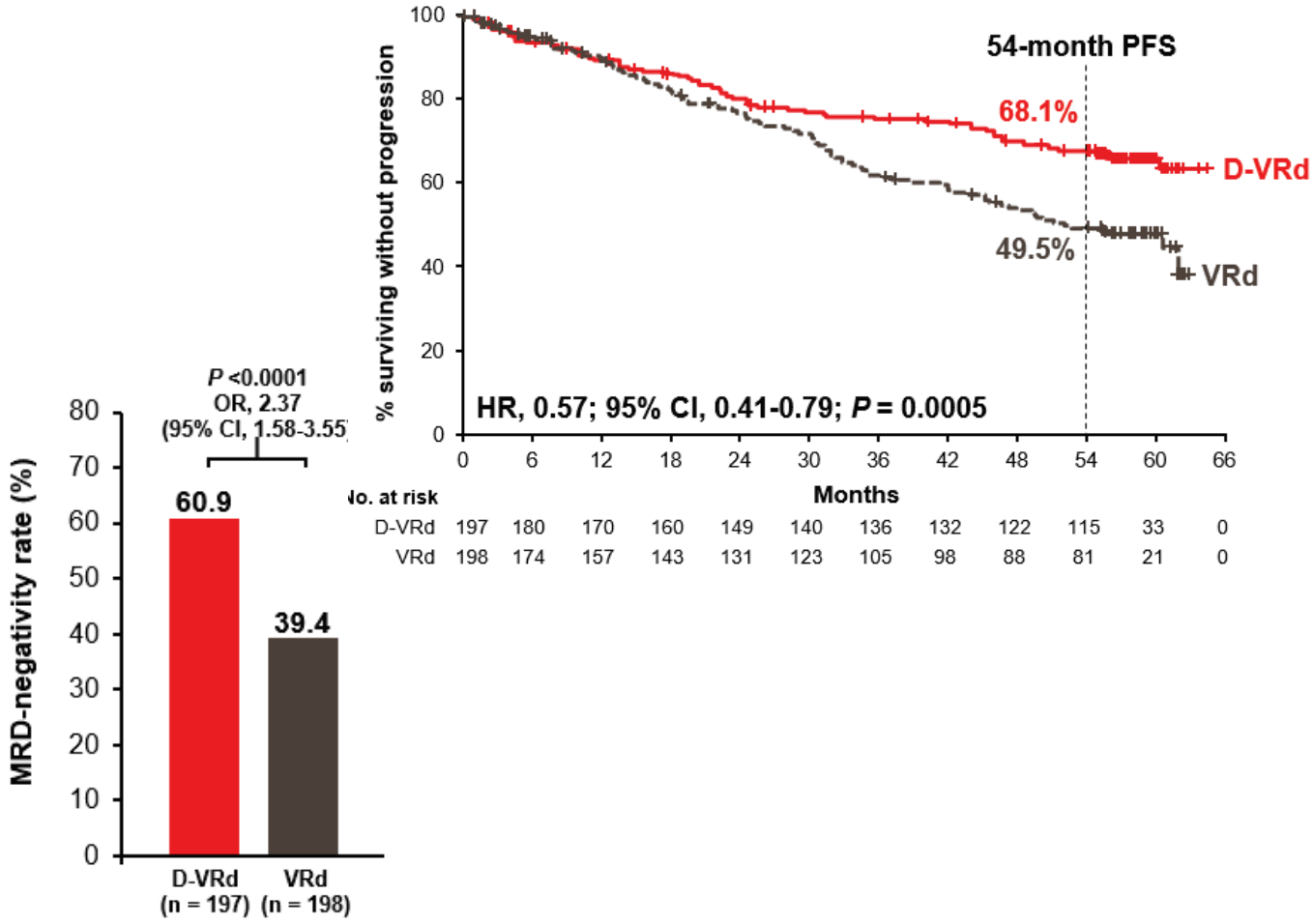


IMROZ-Studie/CEPHEUS-Studie

IMROZ

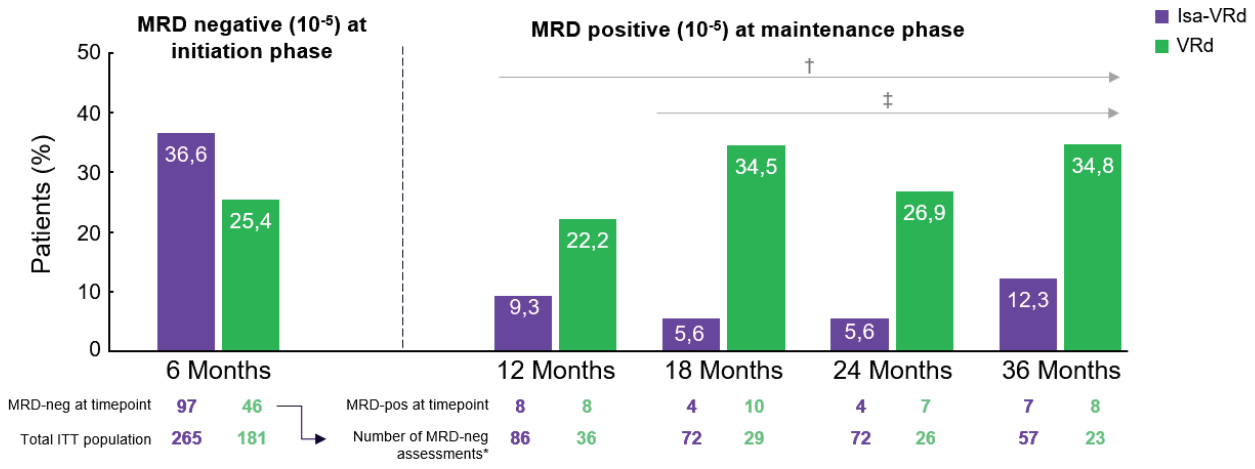


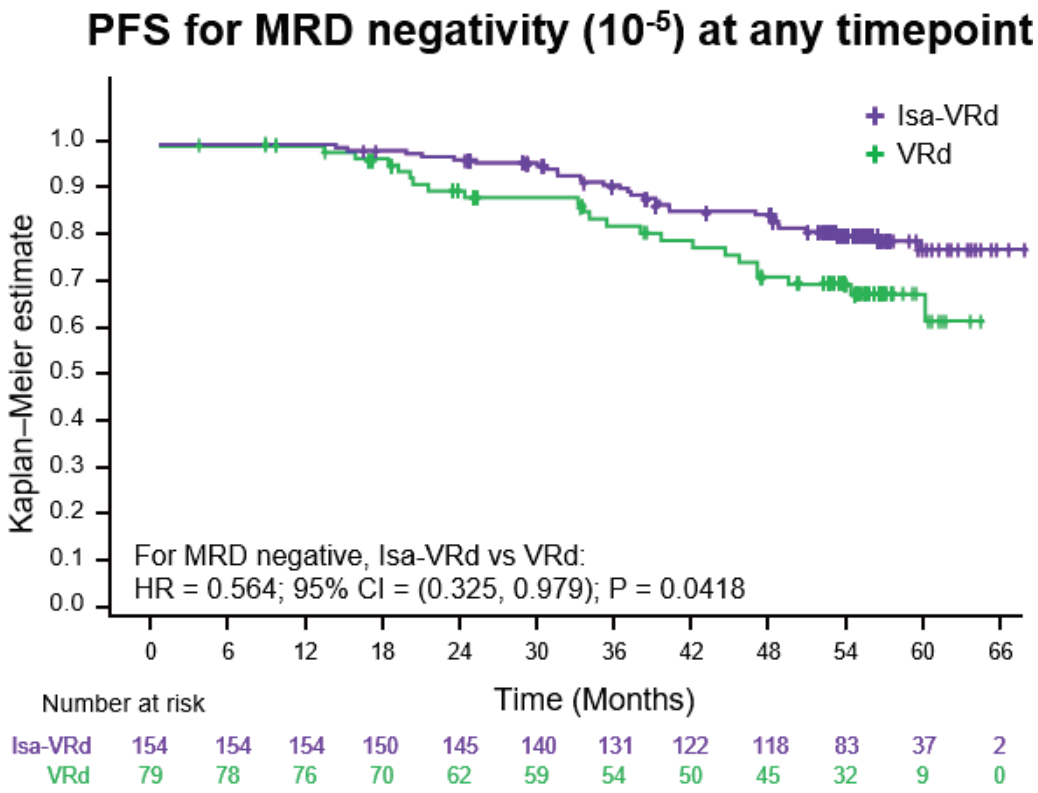
CEPHEUS



IMROZ-Studie

Landmark analysis: Conversion from MRD negativity at initiation phase to MRD positivity at various timepoints during maintenance phase





Weniger Konversionen von MRD-Negativität zu MRD + unter Isa-VRd
PFS bei Erreichen einer MRD-Negativität länger unter Isa-VRd

IMROZ/CEPHEUS

In der IMROZ Studie zeigt Isa-VRd bei nicht-transplantierbaren Patient:innen bis 80 Jahre ein geschätztes PFS > 90 Monate und hohe Raten an MRD-Negativität

Erreichte MRD negative Remissionen sind länger anhaltend unter der Quadruplet Therapie und übersetzen sich in besseres PFS

Die CEPHEUS Studie zeigt in der vergleichbaren Patient:innenpopulation vergleichbare Ergebnisse mit Dara-VRd

Bei bereits vorliegendem positiven CHMP Votum wird die Zulassung von Isa-VRd wahrscheinlich noch im Dezember erfolgen und sollte fortan Standard für alle nicht-transplantierbaren Patient:innen bis einschl. 80 Jahre sein

Kapitel 4

Neues aus der Immuntherapie

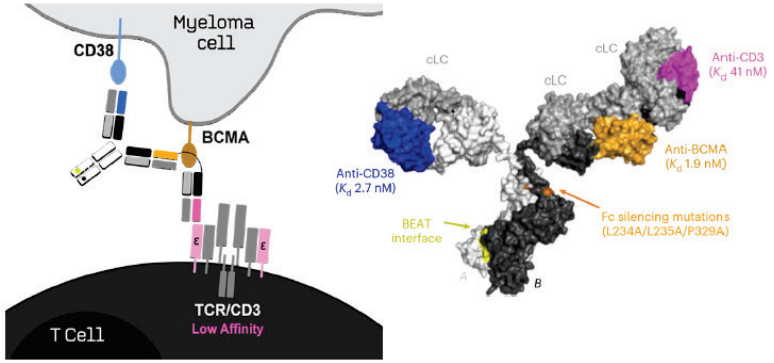
Trispezifischer Antikörper

First Results of a Phase 1, First-in-Human, Dose-Escalation Study of ISB 2001, a BCMAxCD38xCD3 Targeting Trispecific Antibody in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

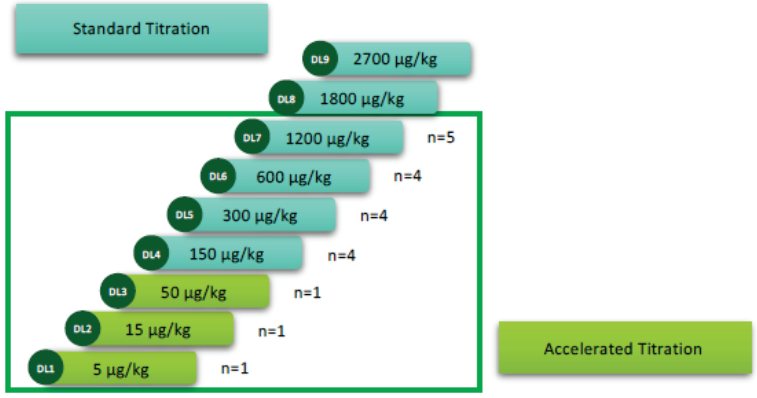
Hang Quach et al.

Trispezifischer Antikörper

First Results of a Phase 1, First-in-Human, Dose-Escalation Study of ISB 2001, a BCMAxCD38xCD3 Targeting Trispecific Antibody in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)



On-going Part 1 : Dose Escalation (n ≈ 40)



In dose escalation, ISB 2001 is administered subcutaneously (SC) once weekly (q1w) in 28-day cycles, starting with 2 step-up doses on Days 1 and 4, followed by the full target dose from Day 8 onwards.
Backfill to each DL allowed.

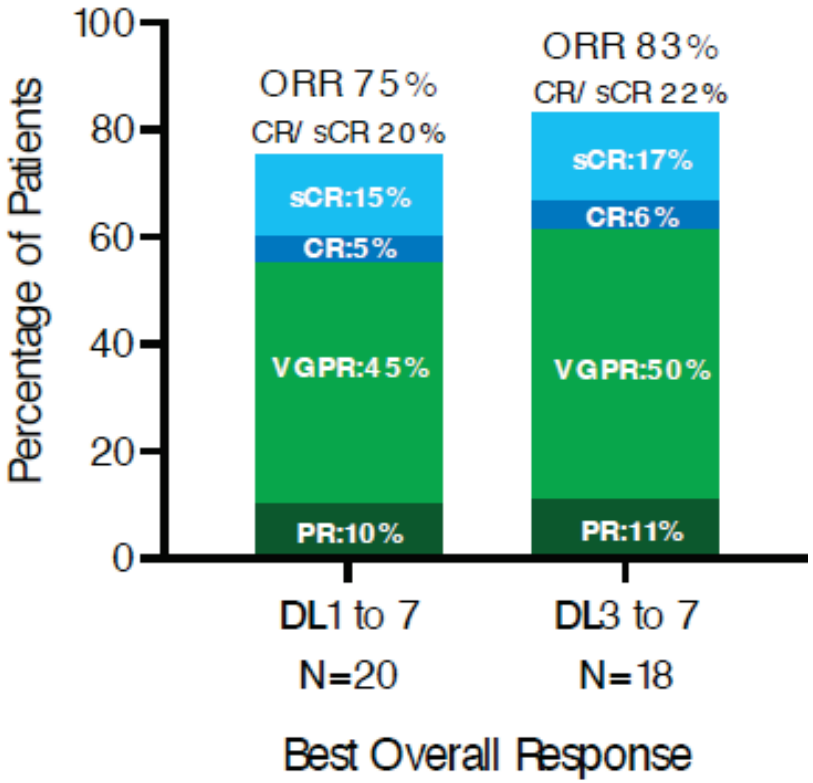
Characteristic	Total (N=20)
Median number of lines of previous therapy (range)	6 (3; 11)
Previous therapy exposure, n (%)	
Triple-exposed	20 (100)
Triple-refractory	5 (25)
Penta-exposed	14 (70)
Penta-refractory	2 (10)
Refractory to last line of therapy	13 (65)
ASCT	19 (95)
Anti-BCMA CAR-T	2 (10)
Bispecifics	9 (45)
BCMA	1 (5)
FcRH5	6 (30)
GPRC5D	4 (20)
Anti-BCMA ADC	5 (25)

Trispezifischer Antikörper

First Results of a Phase 1, First-in-Human, Dose-Escalation Study of ISB 2001, a BCMAxCD38xCD3 Targeting Trispecific Antibody in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

Drug-Related Hematologic TEAEs (N=20)			
AEs, n (%)	All	Grade 3	Grade 4
Any Related Hematologic TEAEs	12 (60)	6 (30)	3 (15)
Anaemia	1 (5)	1 (5)	0
Lymphocyte count decreased	2 (10)	1 (5)	0
Neutropenia	7 (35)	3 (15)	3 (15)
Thrombocytopenia	8 (40)	2 (10)	0

Drug-Related Infections (N=20)			
AEs, n (%)	All	Grade 3	Grade 4
Any Related Infections	9 (45)	3 (15)	0
Lower respiratory tract infection	3 (15)	2 (10)	0
COVID-19	2 (10)	0	0
Upper respiratory tract infection	2 (10)	0	0
Cytomegalovirus viraemia	1 (5)	0	0
Pneumonia	1 (5)	1 (5)	0
Sinusitis	1 (5)	0	0



Non-Hematologic Drug-Related TEAEs (≥ 15%, N=20)			
AEs, n (%)	All	Grade 3	Grade 4
Any Related Non-Hematologic TEAEs	20 (100)	3 (15)	0
Cytokine release syndrome	15 (75)	0	0

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

US Multiple Myeloma Immunotherapy Consortium

Outcomes of Teclistamab in Patients with Relapsed/Refractory Multiple Myeloma with Prior Exposure to BCMA-Directed Therapy: A Multicenter Study from the U.S. Multiple Myeloma Immunotherapy Consortium

Danai Dima, Mariola Vazquez-Martinez, James A Davis, Utkarsh Goel, Aimaz Afrough, Aishwarya Sannareddy, Oren Pasvolsky, Beatrice Razzo, Rahul Banerjee, Jack Khouri, Ariel Grajales-Cruz, Alex Lieberman-Cribbin, Masooma Shifa Rana, Kelley Julian, Shaun DeJarnette, Andrew Portuguese, Mahmoud Gaballa, Gabriel De Avila, Sandra Susanibar-Adaniya, Shahzad Raza, Megan Herr, Evguenia Ouchveridze, Tiffany Richards, Hitomi Hosoya, Lekha Mikkilineni, Gurbakhash Kaur, Daniel Schrum, Omar Castaneda, Adriana Rossi, Chenyu Lin, Peter Forsberg, Yi Lin, Shebli Atrash, Douglas Sborov, Kenneth Shain, Peter Voorhees, Shambavi Richard, Alfred Garfall, Doris Hansen, Surbhi Sidana, Krina Patel, Andrew Cowan, Larry Anderson Jr., Hans Lee, **Faiz Anwer, Christopher Ferreri, Leyla Shune**

Patient Characteristics

Characteristic	Prior BCMA-DT N=193	No Prior BCMA-DT N=192	p-value
Age in years (median, IQR)	67 years (60.4-71.2)	68.3 years (61-75.7)	0.052
Gender, female, n(%)	91 (47.1%)	91 (47.4%)	1.00
Race, n(%)			
White	136 (70.5%)	119 (62%)	0.15
Black	36 (19.7%)	51 (26.6%)	
Other	21 (10.9%)	22 (11.4%)	
ECOG PS (n=379), n(%)	N=189	N=187	
0-1	143 (75.7%)	137 (73.3%)	0.67
2 or more	46 (23.8%)	50 (26.7%)	
Cytogenetic risk, n(%)			
Standard risk	75 (38.9%)	98 (51%)	0.02
High risk (any)	118 (61.1%)	94 (49%)	
Double hit MM	46 (23.8%)	35 (18.2%)	0.22
Extramedullary disease, n(%)	43 (22.3%)	57 (29.7%)	0.12
Plasma cell leukemia, n(%)	7 (3.6%)	5 (2.6%)	0.77
Refractory status			
Triple class refractory	167 (86.5%)	155 (80.7%)	0.16
Penta class refractory	80 (41.5%)	64 (33.3%)	0.12
Median of prior lines of therapy (range)	7 (6-9)	5 (4-6)	<0.001
Prior Autologous SCT	155 (80.3%)	100 (52%)	<0.001

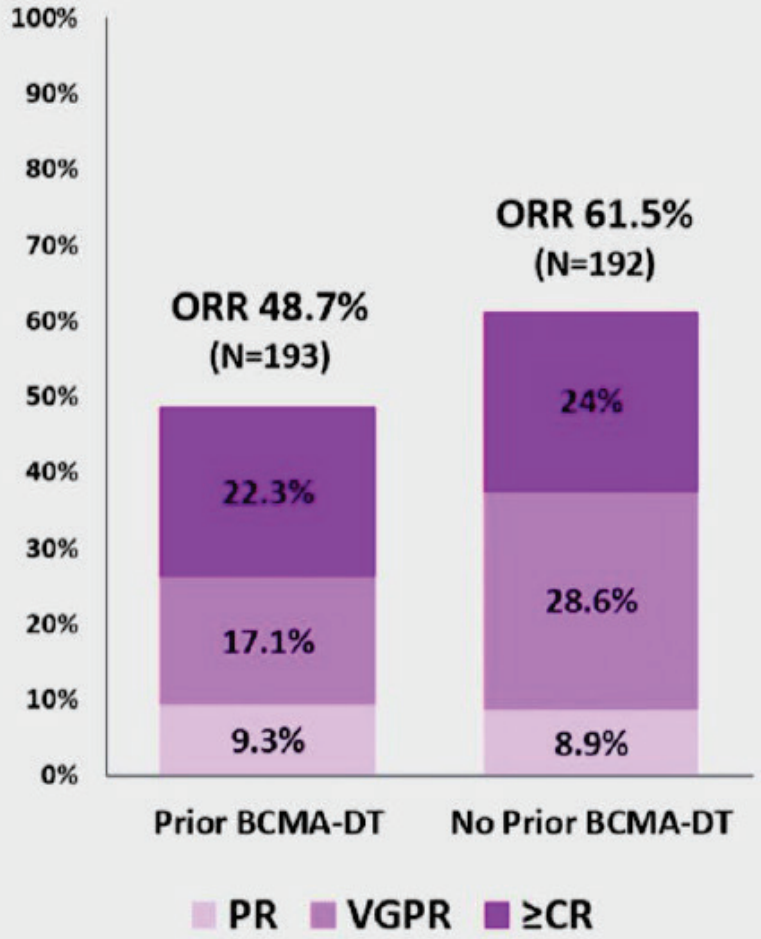
385 patients with RRMM across 14 U.S centers received standard-of-care Teclistamab

Type of prior BCMA-DTs

Number of prior BCMA-directed therapies	
One prior BCMA-DT	N = 149 (77%)
1. ADC	n = 45
Belantamab mafodotin	n = 43
Experimental ADC	n = 2
2. CAR T	n = 98
Idecabtagene vicleucel	n = 76
Ciltacabtagene autoleucel	n = 11
Experimental autologous CAR T	n = 8
Experimental allogeneic CAR T	n = 3
3. Bispecific Antibody	n = 6
Experimental bispecific Ab	n = 6
Two prior BCMA-DT	N = 42 (22%)
Belantamab mafodotin + idecabtagene vicleucel*	n = 29
Belantamab mafodotin + ciltacabtagene autoleucel^	n = 2
Belantamab mafodotin + allogeneic CAR T†	n = 2
Belantamab mafodotin + experimental bispecific Ab‡	n = 2
Belantamab mafodotin + experimental ADC§	n = 2
Experimental ADC + idecabtagene vicleucel¶	n = 2
Experimental ADC + ciltacabtagene autoleucel**	n = 1
Idecabtagene vicleucel** + experimental autologous CAR T	n = 1
Idecabtagene vicleucel + experimental bispecific Ab**	n = 1
Three prior BCMA-DT	N = 2 (1%)
Belantamab mafodotin + Idecabtagene vicleucel + experimental bispecific Ab±	n = 2

Most recent prior BCMA-DT:
*7 belantamab mafodotin, 22 idecabtagene vicleucel
^both ciltacabtagene autoleucel
†1 belantamab mafodotin, 1 allogeneic CAR T
‡ 1 belantamab mafodotin, 1 experimental bispecific Ab
§ both belantamab mafodotin
¶ both idecabtagene vicleucel
± both idecabtagene vicleucel
**indicates most recent

Efficacy Outcomes with Teclistamab: Response



Part of the Univariate/Multivariable Analysis for ORR – All patients

Variable	Simple Logistic Regression		Multiple Logistic Regression	
	OR (95% CI)	P value	OR (95% CI)	P value
Prior BCMA therapy				
No	Ref		Ref	
Yes	0.59 (0.39-0.89)	**0.012**	0.64 (0.41-1.01)	**0.057**
True EMD				
No	Ref		Ref	
Yes	0.46 (0.28-0.73)	**0.0011**	0.47 (0.29-0.77)	**0.003**
ECOG PS				
0-1	Ref		Ref	
≥2	0.36 (0.22-0.58)	**<0.0001**	0.32 (0.19-0.53)	**<0.0001**
Prior Autologous SCT				
No	Ref		Ref	
Yes	0.63 (0.41-0.98)	**0.04**	0.68 (0.42-1.10)	0.12

The prior BCMA-DT cohort had worse **ORR**: 48.7% vs 61.5% (p=0.012) and **≥VGPR**: 39.4% vs 52.6%, p=0.009, but similar **≥CR rates:** 22.3% vs 24%; p=0.78 c/t those without prior BCMA-DT.

In MVA there was a strong signal for worse ORR in the prior BCMA-DT cohort, however, receipt of a prior BCMA-DT was not independently associated with the likelihood of achieving response (HR 0.64, 95% CI: 0.41-1.01, **p=0.057**).

Efficacy Outcomes with Teclistamab: Response based on timing of prior BCMA-DT

- Patients who responded to Tec had a **numerically longer** median time from last BCMA-DT exposure to Tec initiation compared to non-responders: **10.5** vs **7.5 months, p=0.48.**
- Patients who achieved ≥VGPR had a **numerically longer** median time from last BCMA-DT exposure: **11.4** vs **7.5 months, p=0.5**.
- While patients receiving Tec within **6 months** of their last BCMA-DT had a numerically **lower ORR: 42%** vs **51.5%;** p=0.38, and **≥CR rate: 15%** vs **25%;** p=0.19 compared to patients receiving Tec ≥6 months, this did not reach statistical significance.
- The 27 patients receiving Tec within **3 months** of their last BCMA-DT also had a numerically lower **ORR: 37%** vs **51%;** p=0.27) and **≥CR rate: 11%** vs **24%;** p=0.20 compared to those receiving Tec ≥3 months after the last exposure.

Zusammenfassung | Take-Home-Messages

Beim Smoldering Myelom zeigt eine zeitlich begrenzte Daratumumab Monotherapie sehr gute Ergebnisse hinsichtlich der Verzögerung der Progression in ein behandlungsbedürftiges Multiples Myelom

Quadruplet Therapien sind Standard bis einschliesslich 80 Jahre; zugelassen in D (bzw. pos. CHMP Votum)

Für TE Patienten – PERSEUS Regime

Für TNE Patienten – IMROZ Regime

Neue Antikörperkonstruktionen zeigen hohe Effektivität bei stark vorbehandelten Patient:innen

Teclistamab ist effektiv nach vorangegangener anti-BCMA Therapie – Intervall beachten!

Die Kurzpräsentationen sind online unter

www.lymphome.de/ash2024

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