Onkopedia – was ist neu?

Multiples Myelom

Prof. Dr. Martin Kortüm

Medizinische Klinik und Poliklinik II
Direktor: Prof. Dr. H. Einsele

Offenlegung Interessenskonflikte

1. Anstellungsverhältnis oder Führungsposition
Keine

2. Beratungs- bzw. Gutachtertätigkeit
AbbVie, BMS, GSK Janssen, Novartis, Pfizer, Sanofi, Takeda, Stemline

3. Besitz von Geschäftsanteilen, Aktien oder Fonds
Nein

4. Patent, Urheberrecht, Verkaufslizenz
Keine

5. Honorare
AbbVie, BMS, GSK Janssen, Novartis, Pfizer, Sanofi, Takeda, Stemline

6. Finanzierung wissenschaftlicher Untersuchungen
Skyline Diagnostics, Janssen

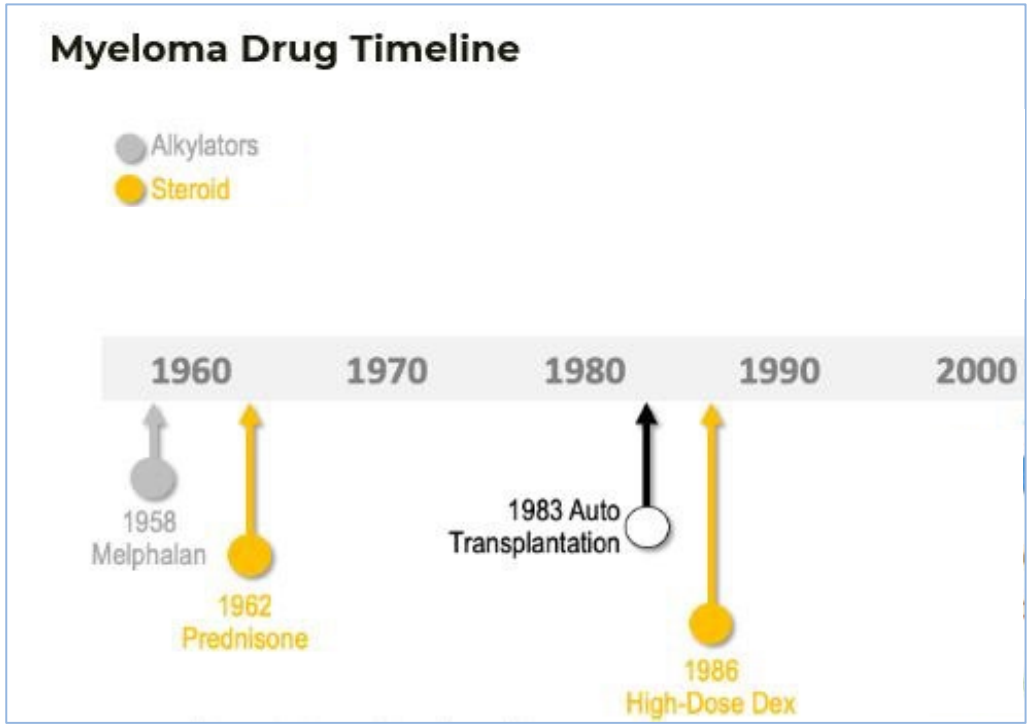
7. Andere finanzielle Beziehungen
keine

8. Immaterielle Interessenkonflikte
keine

Evolving Myeloma Treatment Options

Uniklinikum Würzburg

Vor 2000



2024

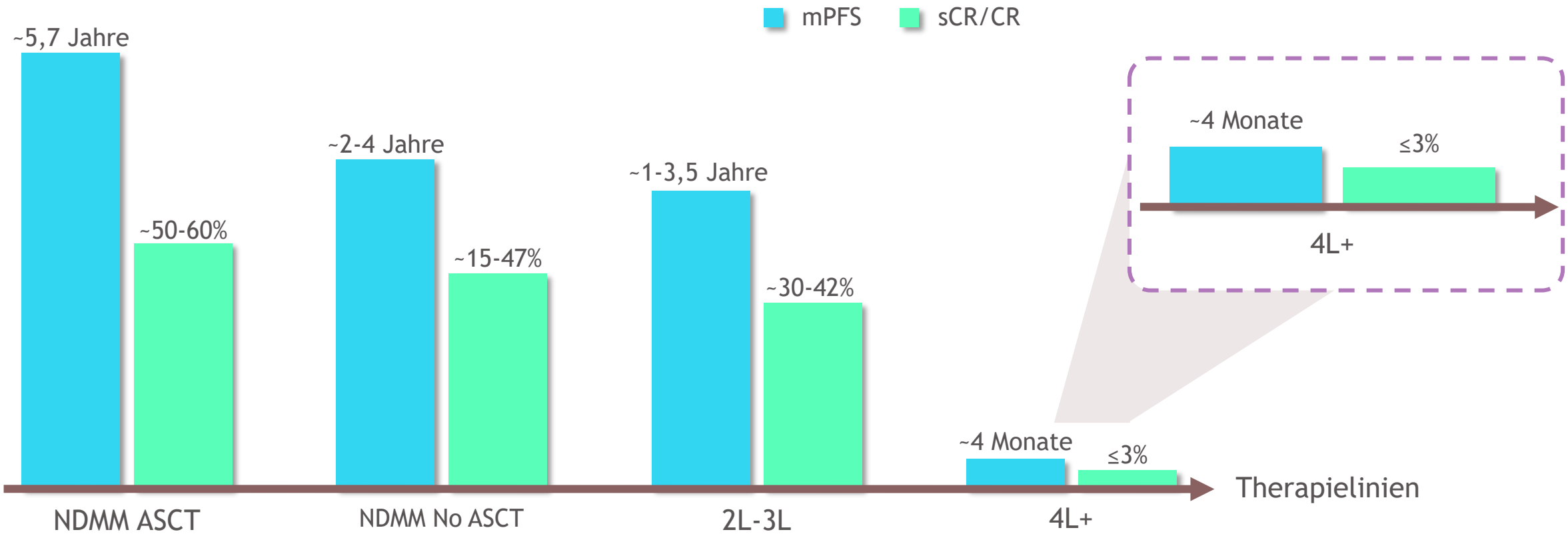
NIH NATIONAL CANCER INSTITUTE

Drugs Approved for Multiple Myeloma and Other Plasma Cell Neoplasms

- Abecma (Idecabtagene Vicleucel)
- Alkeran for Injection (Melphalan Hydrochloride)
- Alkeran Tablets (Melphalan)
- Aredia (Pamidronate Disodium)
- BiCNU (Carmustine)
- Bortezomib
- Carfilzomib
- Carmustine
- Carvykti (Ciltacabtagene Autoleucel)
- Ciltacabtagene Autoleucel
- Cyclophosphamide
- Daratumumab
- Daratumumab and Hyaluronidase-fihj
- Darzalex (Daratumumab)
- Darzalex Faspro (Daratumumab and Hyaluronidase-fihj)
- Doxil (Doxorubicin Hydrochloride Liposome)
- Doxorubicin Hydrochloride Liposome
- Elotuzumab
- Elranatamab-bcmm
- Elrexfio (Elranatamab-bcmm)
- Empliciti (Elotuzumab)
- Evomela (Melphalan Hydrochloride)
- Idecabtagene Vicleucel
- Isatuximab-irfc
- Ixazomib Citrate
- Kyprolis (Carfilzomib)
- Lenalidomide
- Melphalan
- Melphalan Hydrochloride
- Mozobil (Plerixafor)
- Ninlaro (Ixazomib Citrate)
- Pamidronate Disodium
- Plerixafor
- Pomalidomide
- Pomalyst (Pomalidomide)
- Revlimid (Lenalidomide)
- Sarclisa (Isatuximab-irfc)
- Selinexor
- Talquetamab-tgvs
- Talvey (Talquetamab-tgvs)
- Teclistamab-cqyv
- Tecvayli (Teclistamab-cqyv)
- Thalidomide
- Thalomid (Thalidomide)
- Velcade (Bortezomib)
- Xpovio (Selinexor)
- Zoledronic Acid
- Zometa (Zoledronic Acid)

INTERNATIONAL MYELOMA FOUNDATION

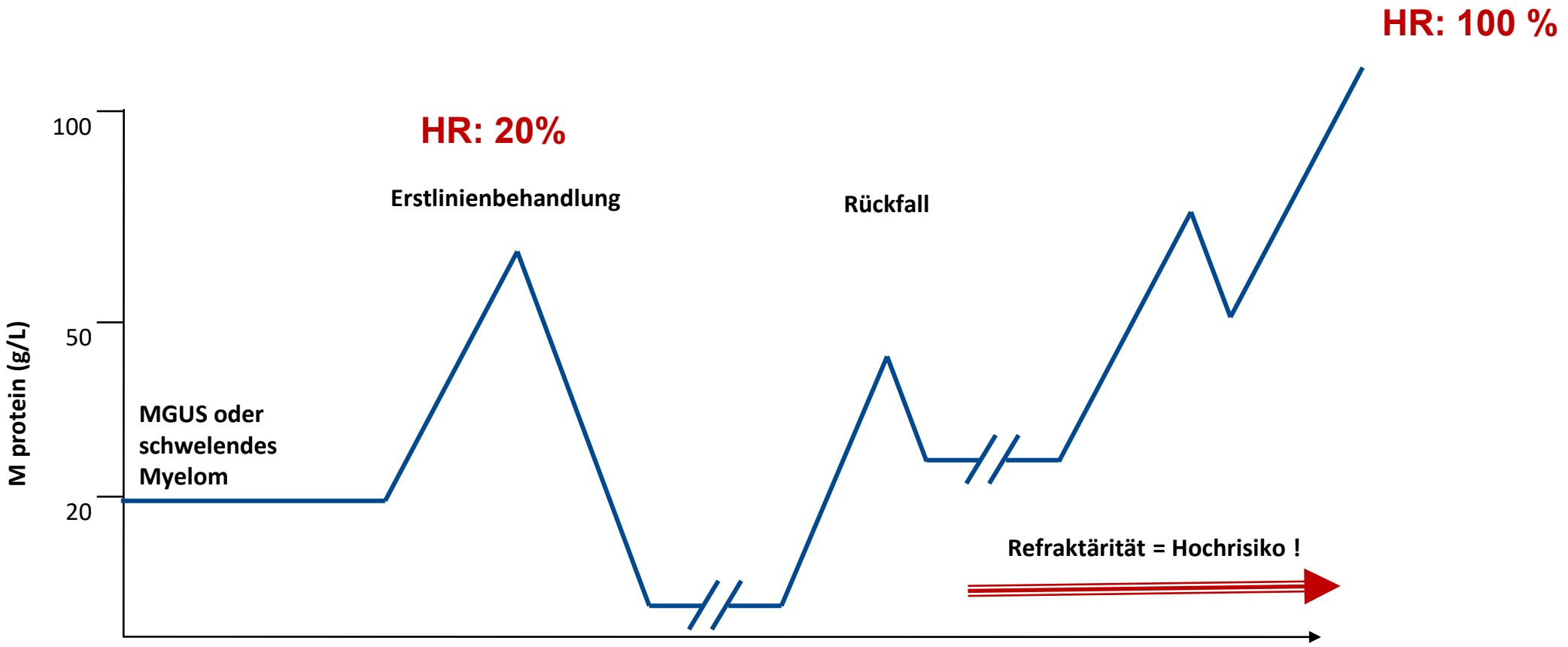
Mit zunehmender Vorbehandlung steigt die Medikamentenresistenz



CR: *complete response*; mPFS: medianes *progression free survival*; NDMM: *neu diagnostiziertes Multiples Myelom*; sCR: *stringent* CR; ASCT: *Autologe Stammzelltransplantation*.

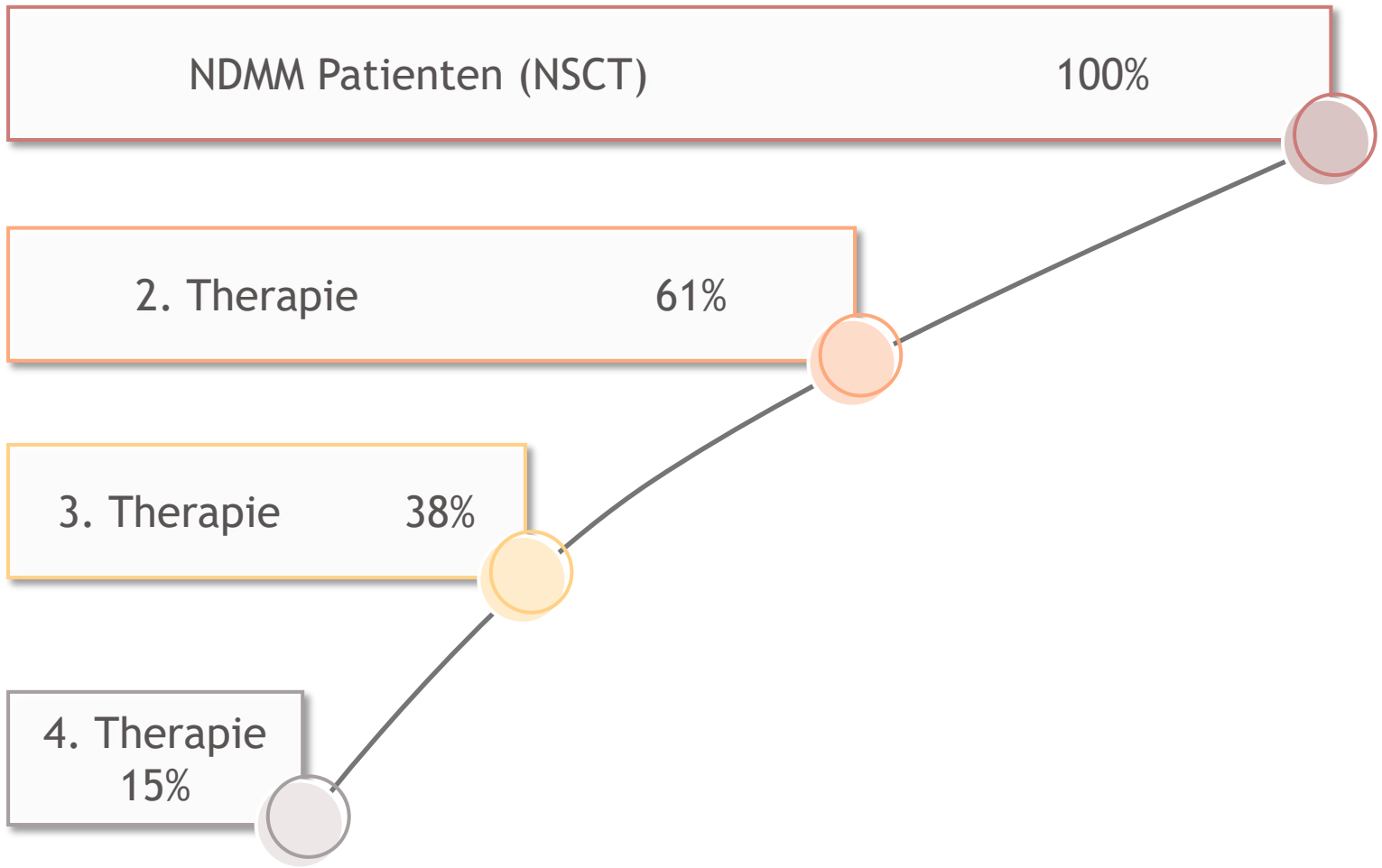
Quelle: Phase-III-Studien oder Packungsbeilagen von SoC-Therapien; Gandhi, et al. Leukemia 33.

Der typische Erkrankungsverlauf



Myeloma Foundation; 2017. Available from www.myeloma.org. American Cancer Society. Cancer Facts & Figures; 2008.

Multiples Myelom - Patientenanteil über die Therapielinien



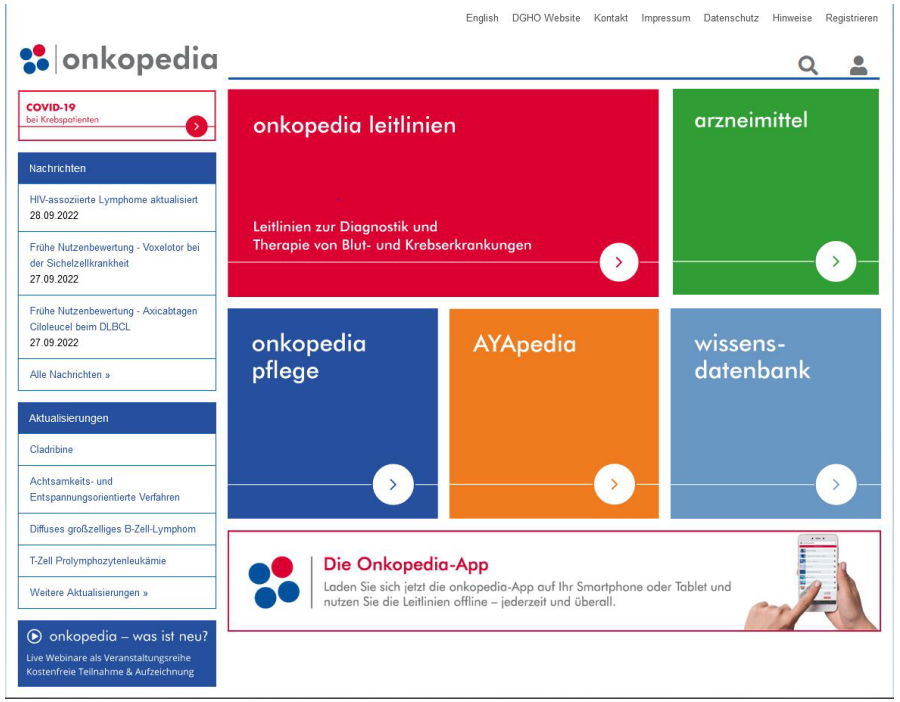
Inzidenz in Deutschland

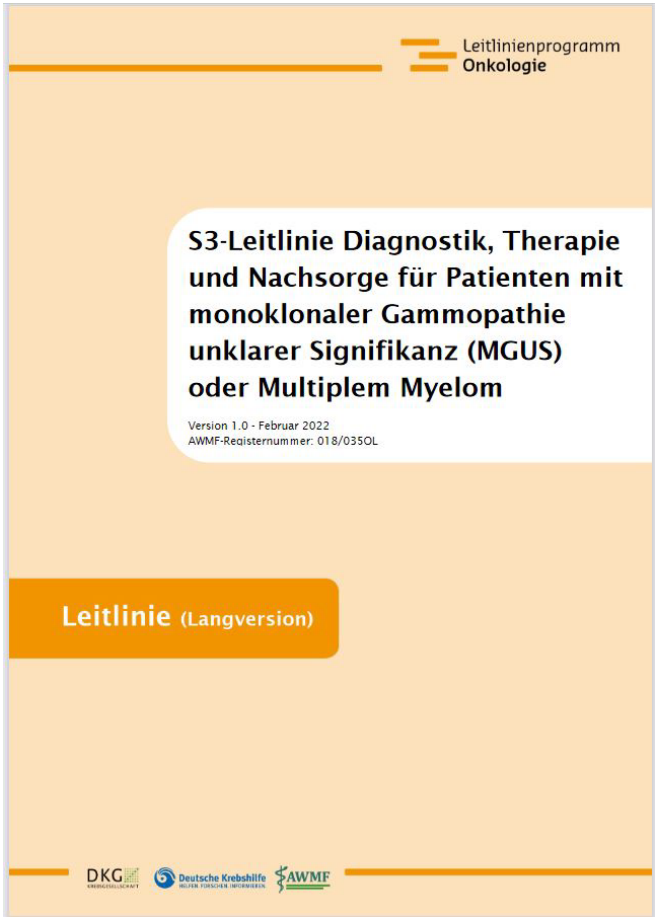
NDMM 2016[2]

6910 Neuerkrankungen

[1]Raab et al., BJH 2016. [2]Krebs in Deutschland für 2015/2016, Zentrum für Krebsregisterdaten, Robert Koch-Institut 2019. [3]Gandhi et al. Leukemia volume 33, pages 2266–2275 (2019).
NDMM: neudiagnostiziertes Multiples Myelom.

Leitlinien für die Diagnostik und Behandlung des MM





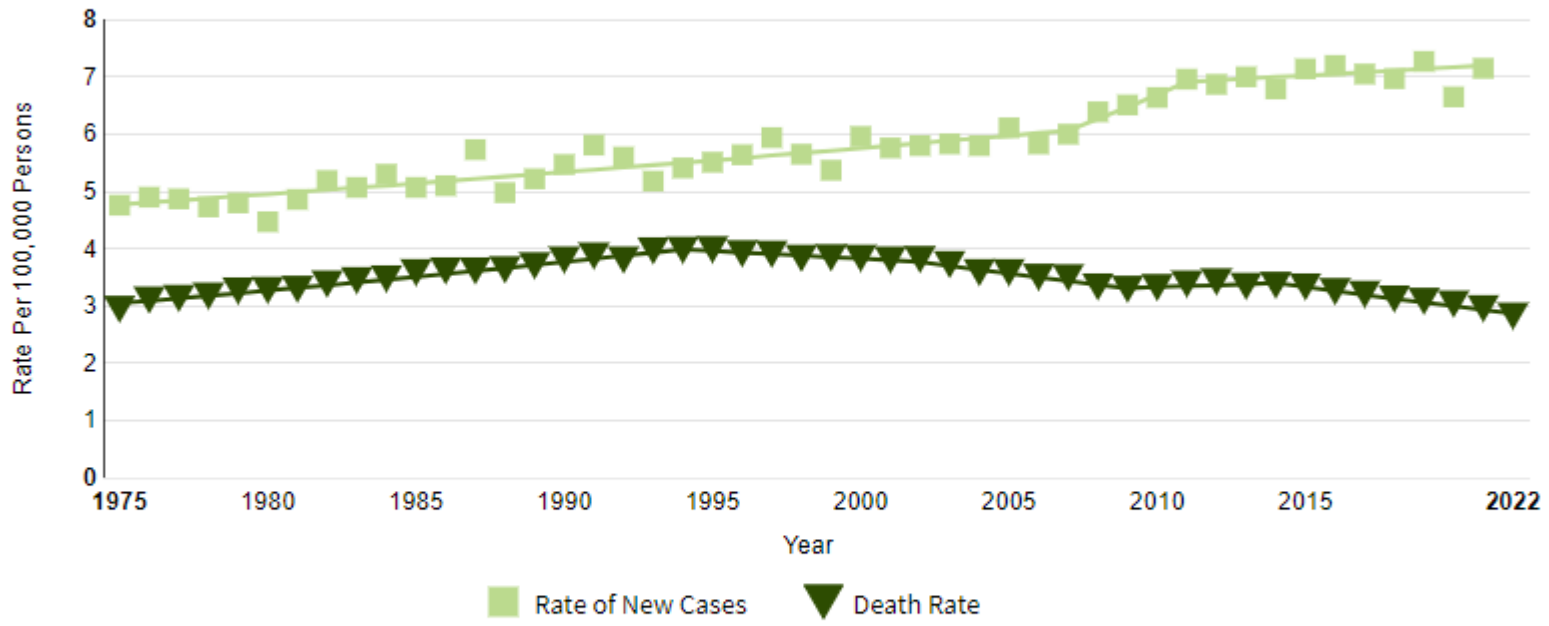
Onkopedia 2018

ESMO 2021

S3 2022

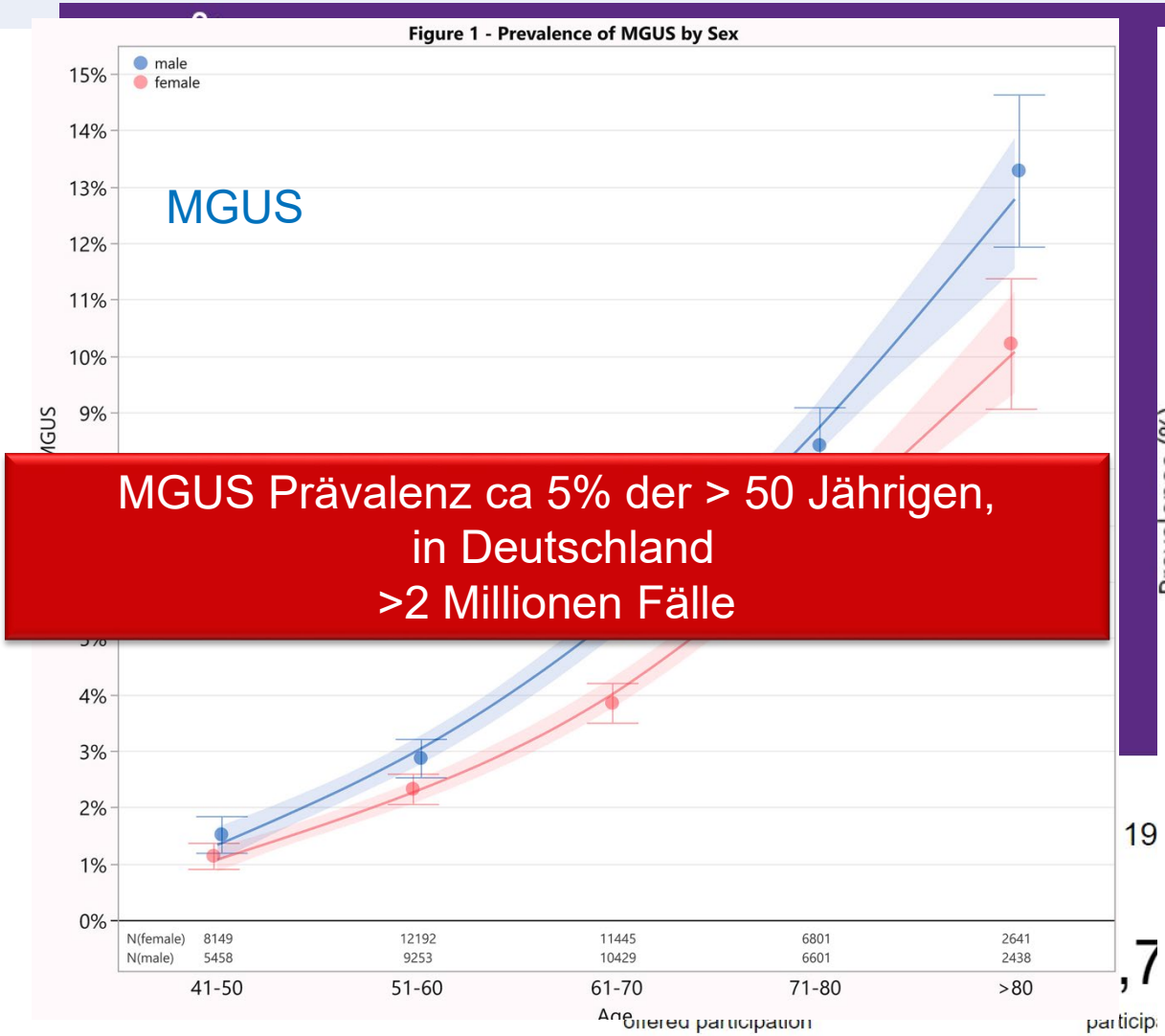
Inzidenz und Prävalenz des MM nehmen zu, die Sterberate nimmt ab

New Cases, Deaths and 5-Year Relative Survival

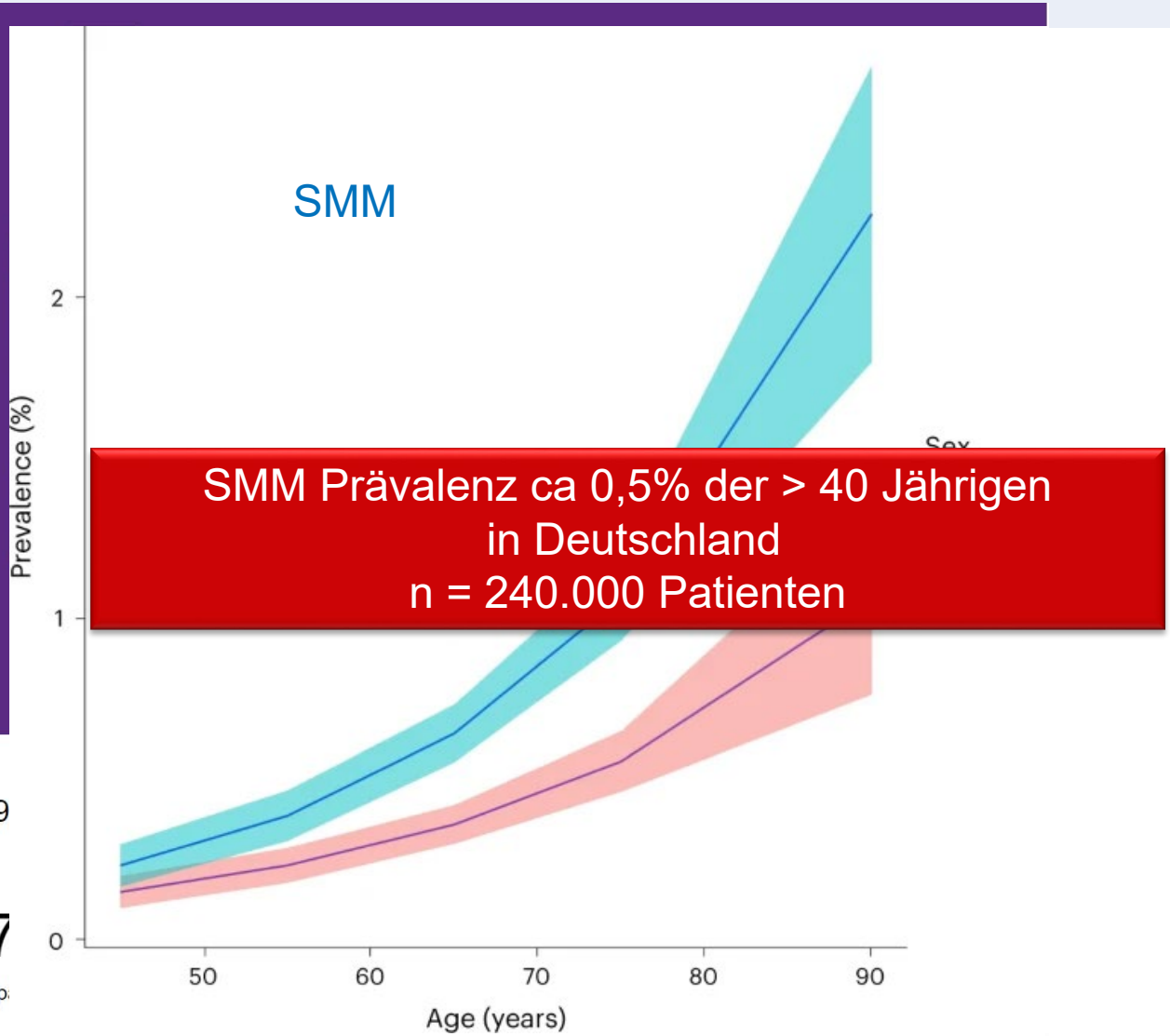


New cases come from SEER 8. Deaths come from U.S. Mortality.
All Races, Both Sexes. Rates are Age-Adjusted.
Modeled trend lines were calculated from the underlying rates using the Joinpoint Trend Analysis Software.
The 2020 incidence rate is displayed but not used in the fit of the trend line(s). Impact of COVID on SEER Cancer Incidence 2020 data

iStopMM – MGUS und SMM Prävalenz höher als vermutet



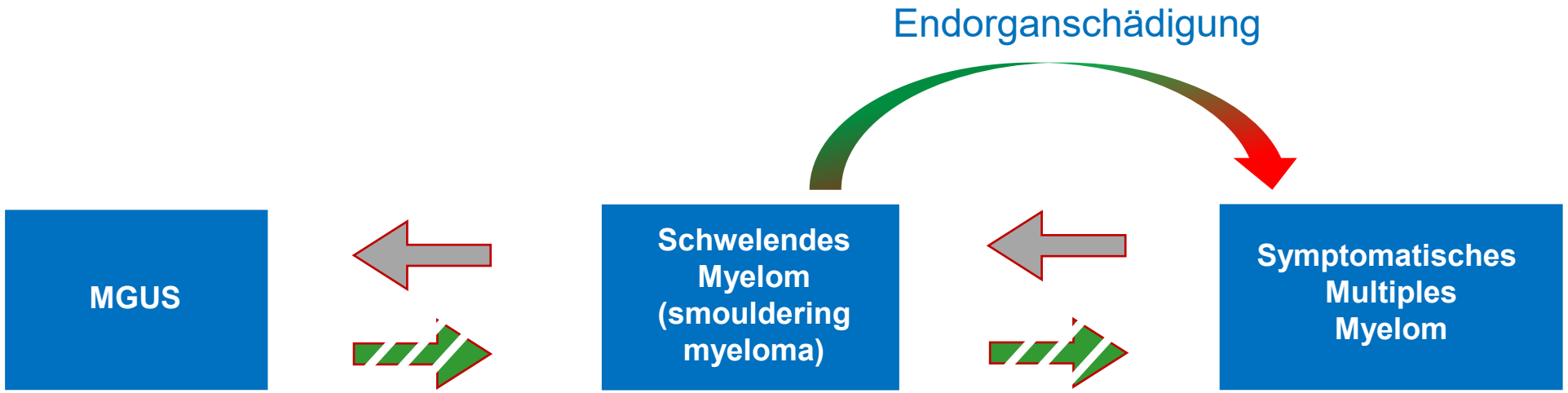
MGUS Prävalenz ca 5% der > 50 Jährigen,
in Deutschland
>2 Millionen Fälle



SMM Prävalenz ca 0,5% der > 40 Jährigen
in Deutschland
n = 240.000 Patienten

Thorsteinsdóttir, S., *Nat Med* (2023).

Stadienhafter **Verlauf der Erkrankung**



Jeder Myelomerkrankung geht eine monoklonale Gammopathie unklarer Signifikanz voraus.

Progressionsauslösende Faktoren sind nicht bekannt.

Biomarkers predicting MGUS /SMM /MM Progression

Smoldering Multiple Myeloma Disease Progression Criteria

Pre-2014

CRAB
C – hypercalcemia
R – renal damage
A – anemia
B – bone lesions

2014, by International Myeloma Working Group (IMWG)

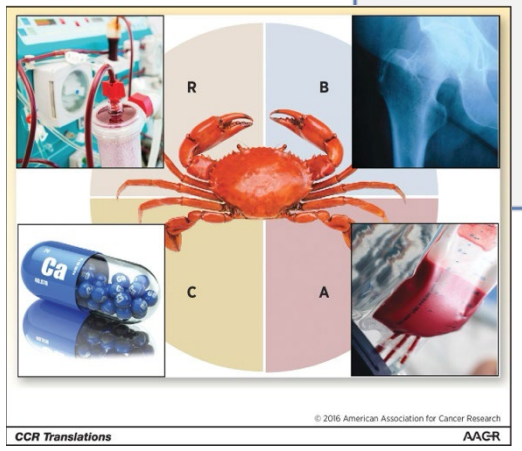
SLiM CRAB
The CRAB remains, plus the following biomarkers of malignancy:
S – 60% or greater plasma cell proliferation
Li -- Free light chain (FLC) ratio greater than 100
M – MRI detected bone lesions (or via PET-CT)

2019, by Mayo/IMWG

20-2-20 criteria for high risk of progression within 2 years; consider starting treatment if high risk.

20 – 20% or greater plasma cell proliferation
2 – M-spike 2.0 or greater
20 – FLC 20 or greater

Low risk: no criteria met
Intermediate risk: 1 criteria met
High risk: 2 or 3 criteria met



S3 Leitlinie SMM: ‚Eine Behandlung *kann* im Einzelfall erfolgen‘

Treating Smoldering Multiple Myeloma - ASH 2023

Uniklinikum Würzburg

757 Genomic Profiling to Interpret the Outcomes of Early Intervention for High-Risk Smoldering Myeloma

Program: Oral and Poster Abstracts
Type: Oral
Session: 652. Multiple Myeloma: Clinical and Epidemiological: Immunological Effects of Sustained Responses in Multiple Myeloma
Hematology Disease Topics & Pathways:
Research, clinical trials, Translational Research, Plasma Cell Disorders, Clinical Research, Diseases, Lymphoid Malignancies

Monday, December 11, 2023: 10:30 AM

Benjamin Diamond, MD[1], *Dickran Kazandjian, MD*[2], *Marios Papadimitriou, MD*[2*], *Bachisio Ziccheddu*[3*], *Patrick Blaney, MS*[4*], *Monika Chojnacka, B.S.*[1], *Michael Durante, PhD*[3*], *Elizabeth Hill, MD*[5*], *Romanos Sklavenitis-Pistofidis, MD*[6], *Kylee H Maclachlan, MBChB, PhD*[7], *Ryan M. Young, PhD*[8*], *Saad Z Usmani, MD*[9], *Faith E. Davies, MD*[10], *Gad Getz, PhD*[11*], *Irene M. Ghobrial, MD*[6], *Gareth J. Morgan, M.D., Ph.D.*[12*], *Francesco Maura, MD*[13] *and Ola Landgren, MD*[3]

Clinical risk scores may <u>not</u> select the right patients and need to be ammended by genetic biomarkers

Bislang keine biomarkerstratifizierte Behandlung

Erstlinientherapie

kein SLiM-CRAB-Kriterium erfüllt[1]

w & w[2]

SLiM-CRAB-Kriterien erfüllt[1]

für Hochdosistherapie geeignet

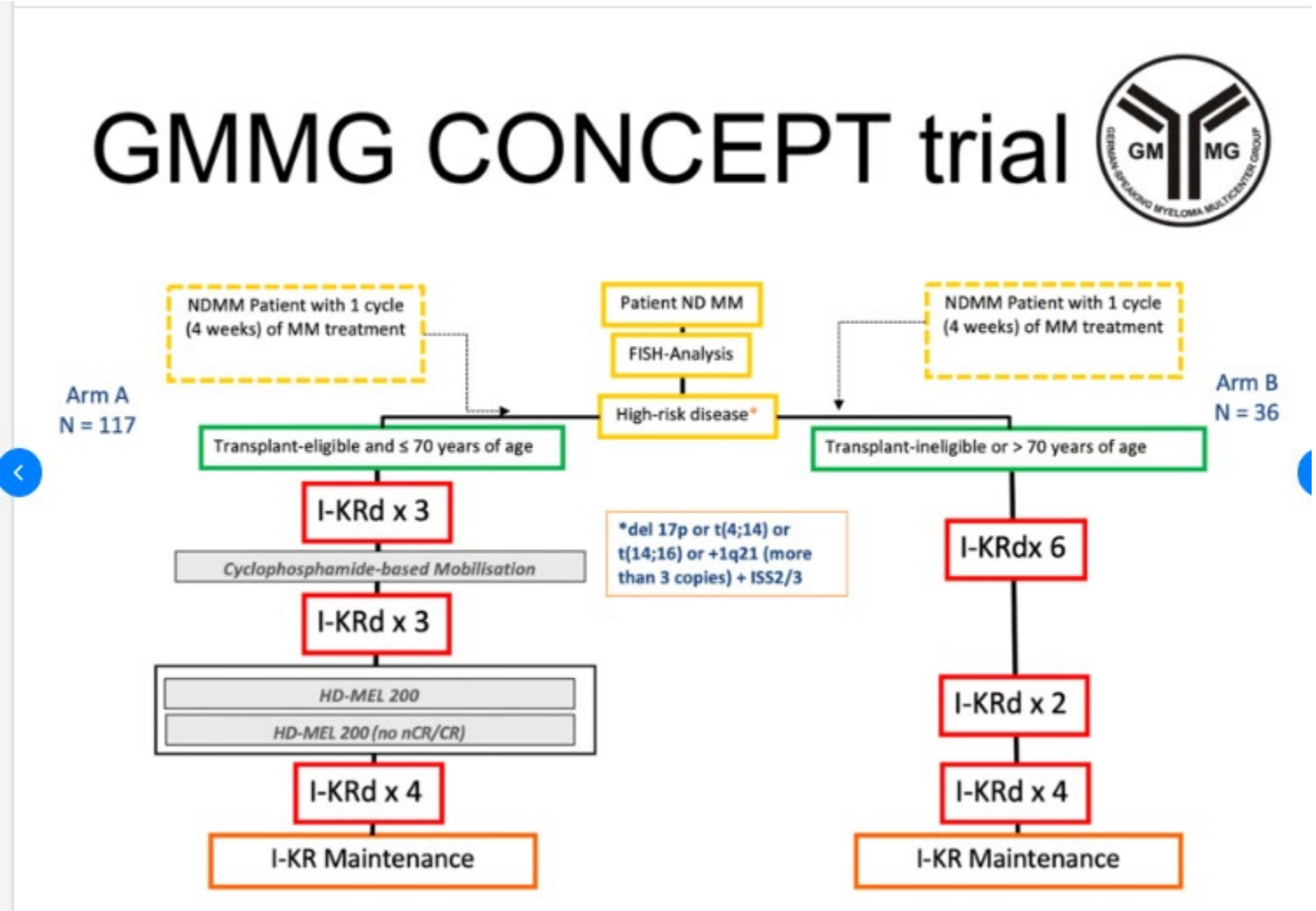
nicht für Hochdosistherapie geeignet

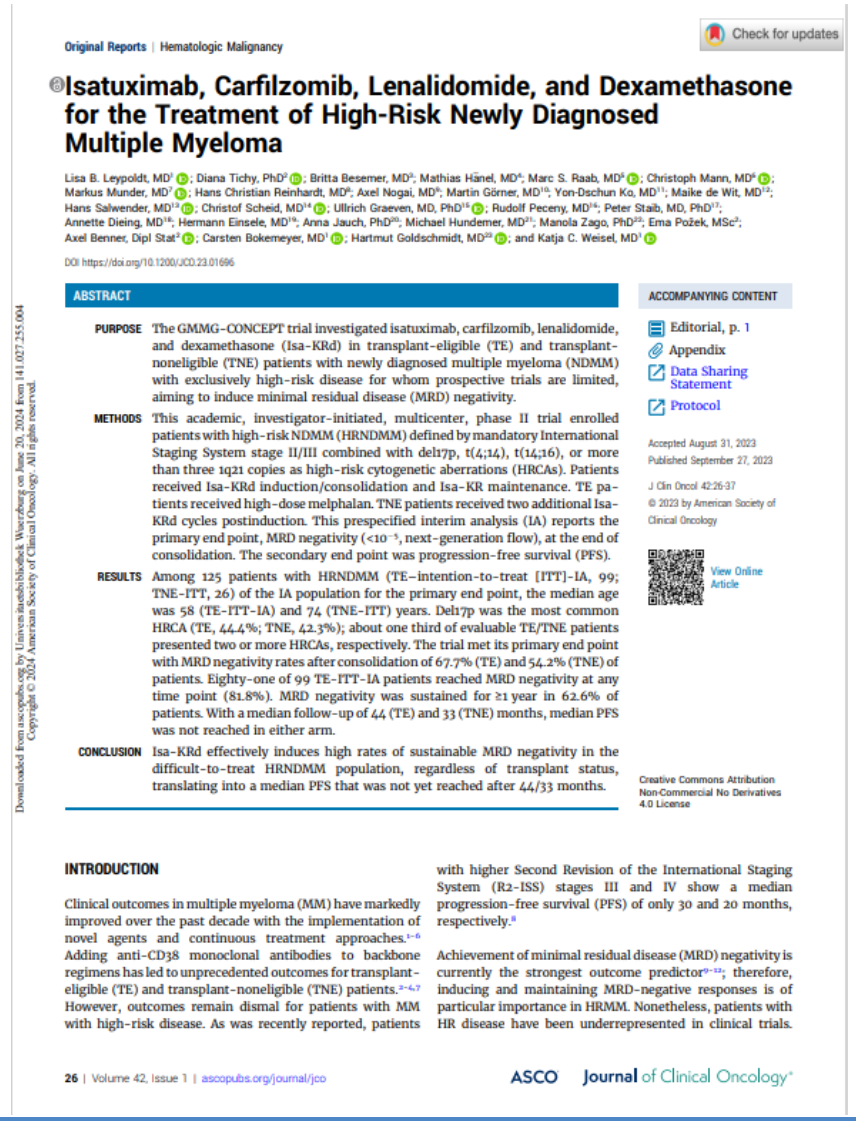
onkopedia

Intensivere Behandlung für genetisch determiniertes Hochrisiko?

Mit freundlicher Freigabe durch Prof H. Ludwig

Intensivierte Behandlung bei erhöhtem Risiko





Original Reports | Hematologic Malignancy

Check for updates

Isatuximab, Carfilzomib, Lenalidomide, and Dexamethasone for the Treatment of High-Risk Newly Diagnosed Multiple Myeloma

Lisa B. Leypoldt, MD[1]; Diana Tichy, PhD[2]; Britta Besemer, MD[3]; Mathias Hänel, MD[4]; Marc S. Raab, MD[4]; Christoph Mann, MD[4]; Markus Munder, MD[5]; Hans Christian Reinhardt, MD[6]; Axel Nogai, MD[6]; Martin Görner, MD[10]; Yon-Dschun Ko, MD[11]; Maike de Wit, MD[12]; Hans Salwender, MD[13]; Christof Scheid, MD[14]; Ullrich Graeven, MD, PhD[15]; Rudolf Peceny, MD[16]; Peter Staib, MD, PhD[17]; Annette Dieing, MD[18]; Hermann Einsele, MD[19]; Anna Jauch, PhD[20]; Michael Hundemer, MD[21]; Manola Zago, PhD[22]; Ema Požek, MSc[2]; Axel Benner, Dipl Stat[2]; Carsten Bokemeyer, MD[1]; Hartmut Goldschmidt, MD[23]; and Katja C. Weisel, MD[1]

DOI https://doi.org/10.1200/JCO.23.01696

ABSTRACT

PURPOSE The GMMG-CONCEPT trial investigated isatuximab, carfilzomib, lenalidomide, and dexamethasone (Isa-KRd) in transplant-eligible (TE) and transplant-noneligible (TNE) patients with newly diagnosed multiple myeloma (NDMM) with exclusively high-risk disease for whom prospective trials are limited, aiming to induce minimal residual disease (MRD) negativity.

METHODS This academic, investigator-initiated, multicenter, phase II trial enrolled patients with high-risk NDMM (HRNDMM) defined by mandatory International Staging System stage II/III combined with del17p, t(4;14), t(14;16), or more than three 1q21 copies as high-risk cytogenetic aberrations (HRCAs). Patients received Isa-KRd induction/consolidation and Isa-KR maintenance. TE patients received high-dose melphalan. TNE patients received two additional Isa-KRd cycles postinduction. This prespecified interim analysis (IA) reports the primary end point, MRD negativity ($<10^{-5}$, next-generation flow), at the end of consolidation. The secondary end point was progression-free survival (PFS).

RESULTS Among 125 patients with HRNDMM (TE–intention-to-treat [ITT]-IA, 99; TNE-ITT, 26) of the IA population for the primary end point, the median age was 58 (TE-ITT-IA) and 74 (TNE-ITT) years. Del17p was the most common HRCA (TE, 44.4%; TNE, 42.3%); about one third of evaluable TE/TNE patients presented two or more HRCAs, respectively. The trial met its primary end point with MRD negativity rates after consolidation of 67.7% (TE) and 54.2% (TNE) of patients. Eighty-one of 99 TE-ITT-IA patients reached MRD negativity at any time point (81.8%). MRD negativity was sustained for ≥1 year in 62.6% of patients. With a median follow-up of 44 (TE) and 33 (TNE) months, median PFS was not reached in either arm.

CONCLUSION Isa-KRd effectively induces high rates of sustainable MRD negativity in the difficult-to-treat HRNDMM population, regardless of transplant status, translating into a median PFS that was not yet reached after 44/33 months.

ACCOMPANYING CONTENT

Editorial, p. 1
Appendix
Data Sharing Statement
Protocol

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Published September 27, 2023
J Clin Oncol 42:26-37

View Online Article

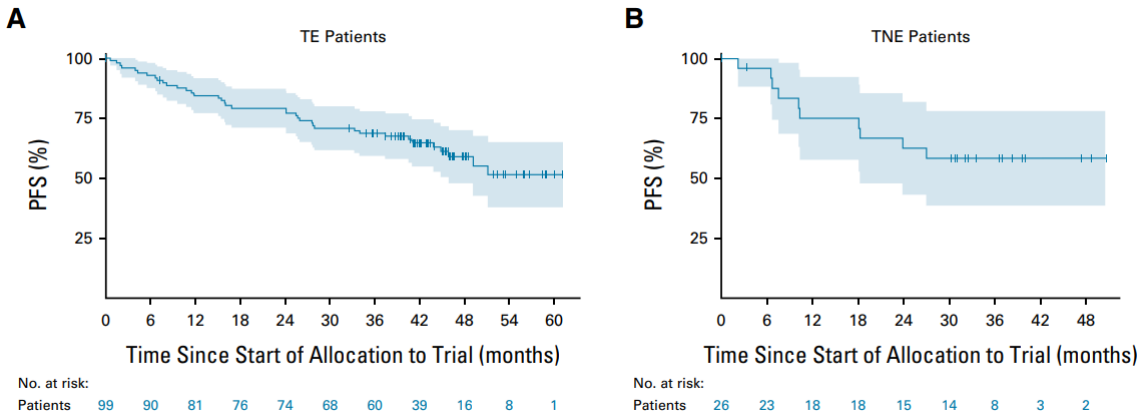
INTRODUCTION

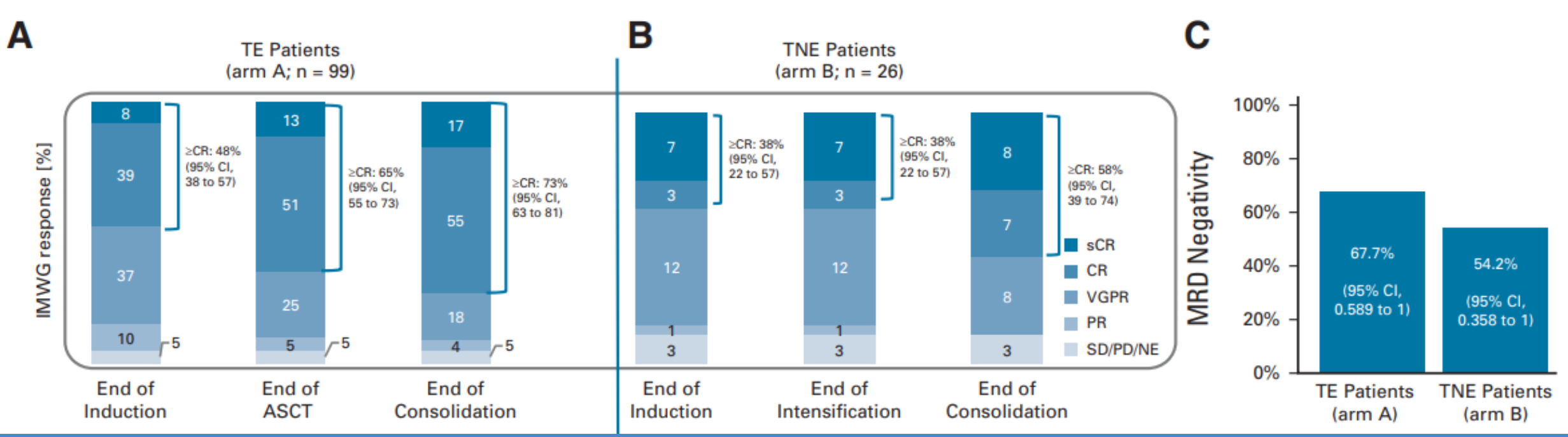
Clinical outcomes in multiple myeloma (MM) have markedly improved over the past decade with the implementation of novel agents and continuous treatment approaches.[1-6] Adding anti-CD38 monoclonal antibodies to backbone regimens has led to unprecedented outcomes for transplant-eligible (TE) and transplant-noneligible (TNE) patients.[2-4,7] However, outcomes remain dismal for patients with MM with high-risk disease. As was recently reported, patients with higher Second Revision of the International Staging System (R2-ISS) stages III and IV show a median progression-free survival (PFS) of only 30 and 20 months, respectively.[8]

Achievement of minimal residual disease (MRD) negativity is currently the strongest outcome predictor[9-12]; therefore, inducing and maintaining MRD-negative responses is of particular importance in HRMM. Nonetheless, patients with HR disease have been underrepresented in clinical trials.

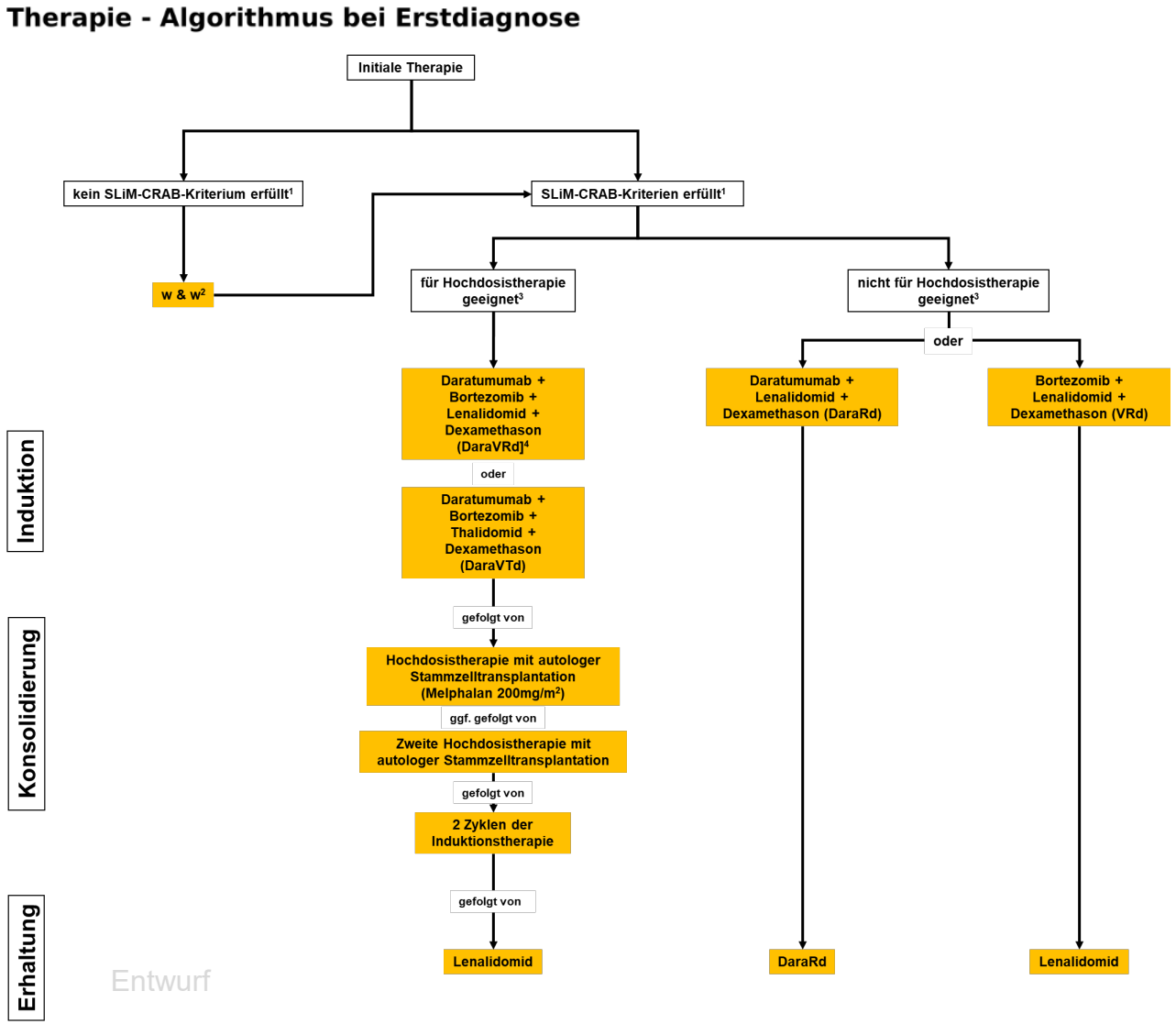
Leypoldt et al J clin oncol 2023

ISA-KRD induziert hohe Rate an MRD Negativität





Erstlinie beim MM 2024



Hochdosisfähige Patienten

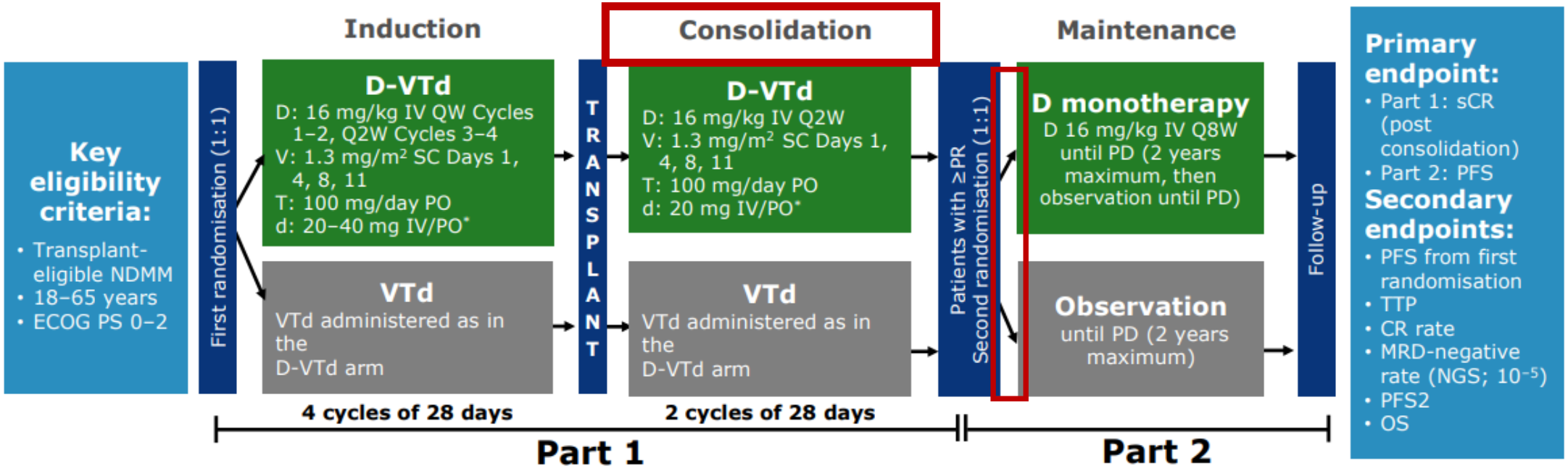
- **PERSEUS (Dara-VRD)** oder
- **CASSIOPEIA (Dara-VTD)**

Nicht transplantable Patienten

- **MAIA (Dara-Rd)** oder
- **SWOG S0777 (VRd)**

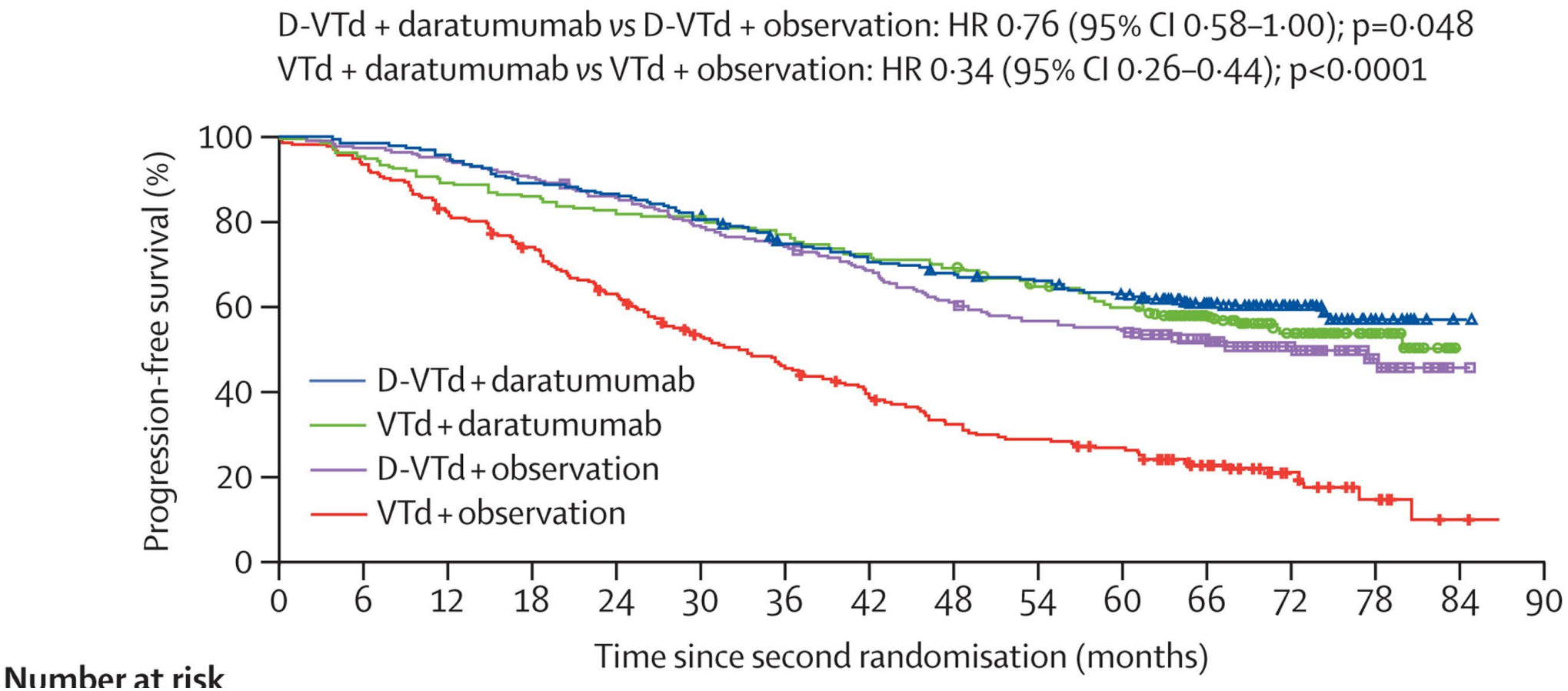
Cassiopeia Studiendesign

- Phase 3 study of D-VTd versus VTd in transplant-eligible NDMM (N=1,085)



Stratification factors:
- Site affiliation (IFM or HOVON)
- ISS disease stage (I, II, or III)
- Cytogenetic risk status (high or standard/unknown risk)

Update EHA 2024: Extended FU 80.1 Monate



Long Term Follow-up der CASSIOPEIA Phase 3 Studie

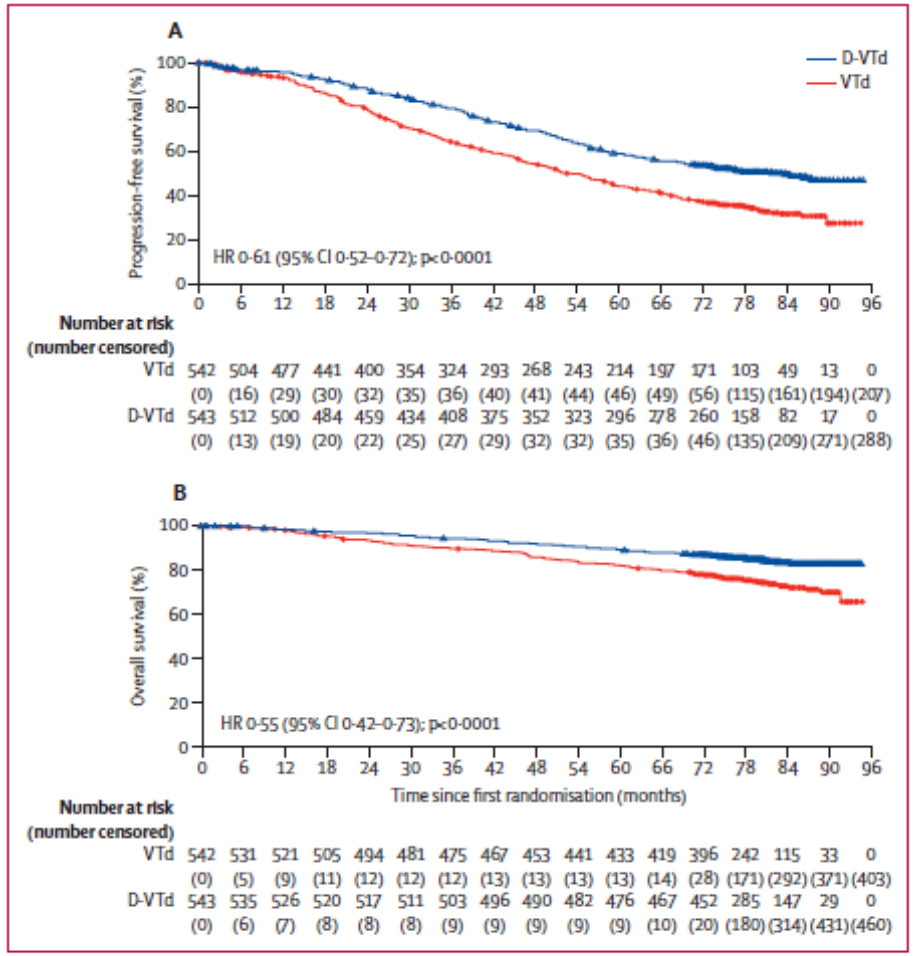


Figure 2: Progression-free survival and overall survival from first randomisation regardless of second randomisation in the intention-to-treat population (n=1085)

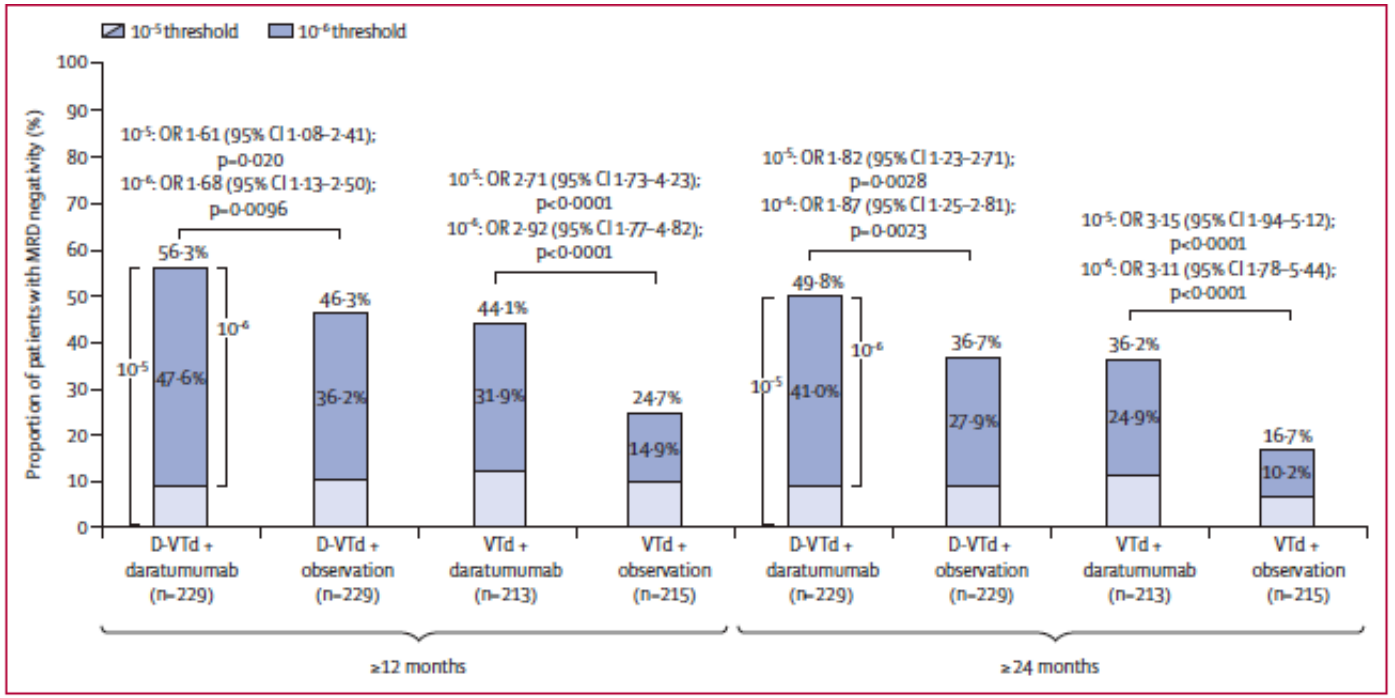
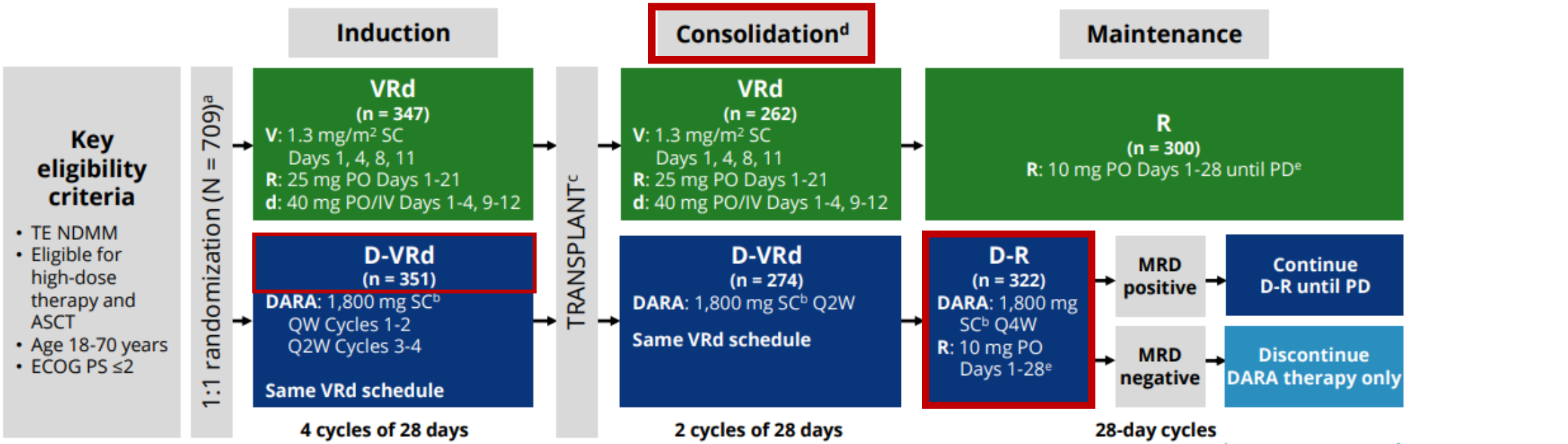


Figure 5: Post-hoc analysis of the proportion of patients with a complete response or better and sustained MRD negativity at any timepoint from post-induction onwards in the maintenance-specific intention-to-treat population (n=886)

Der Anteil von MRD negativen Patienten 12 bzw 24 Monate ist in der Dara-VTD + Dara Erhaltung am höchsten

PERSEUS Studiendesign

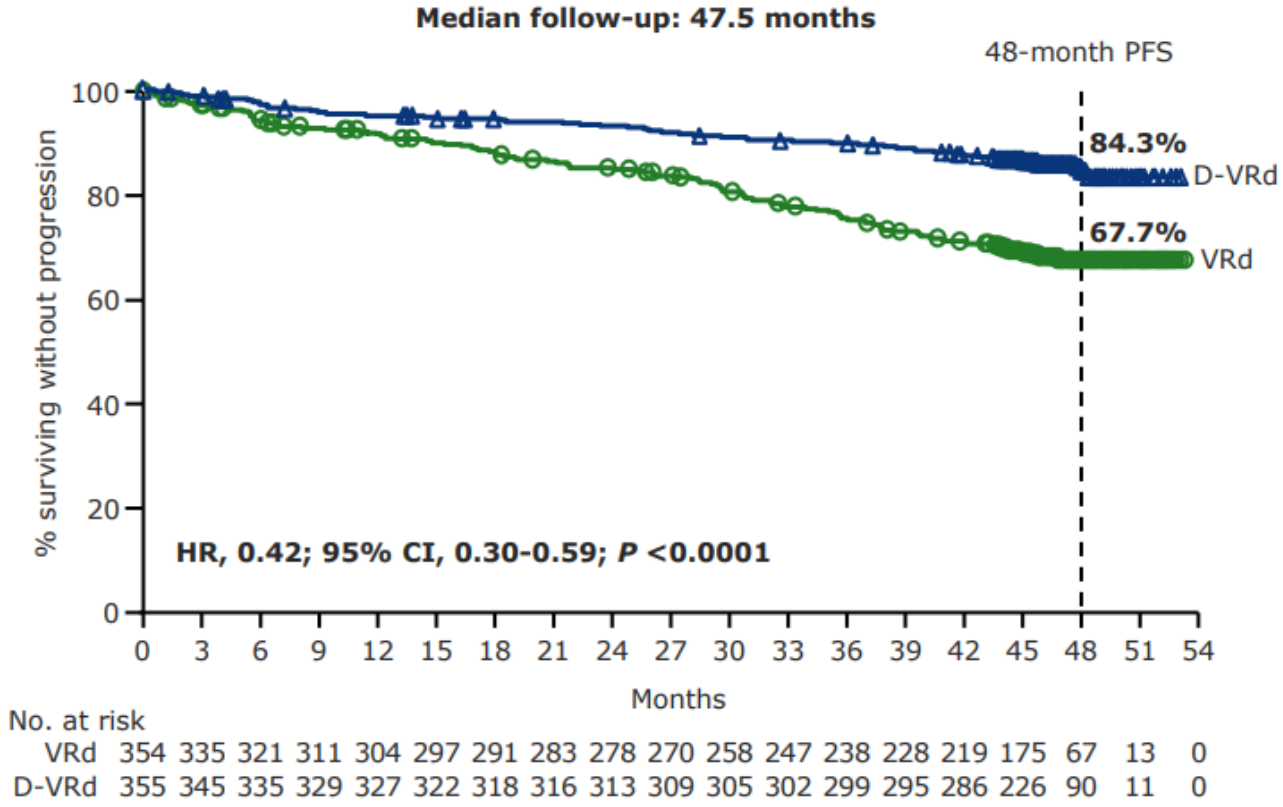
- Open-label, multicenter, randomized phase 3 study with enrollment from January 2019 to January 2020 across 115 sites in 14 countries in Europe and Australia



Primary endpoint: PFS[f]

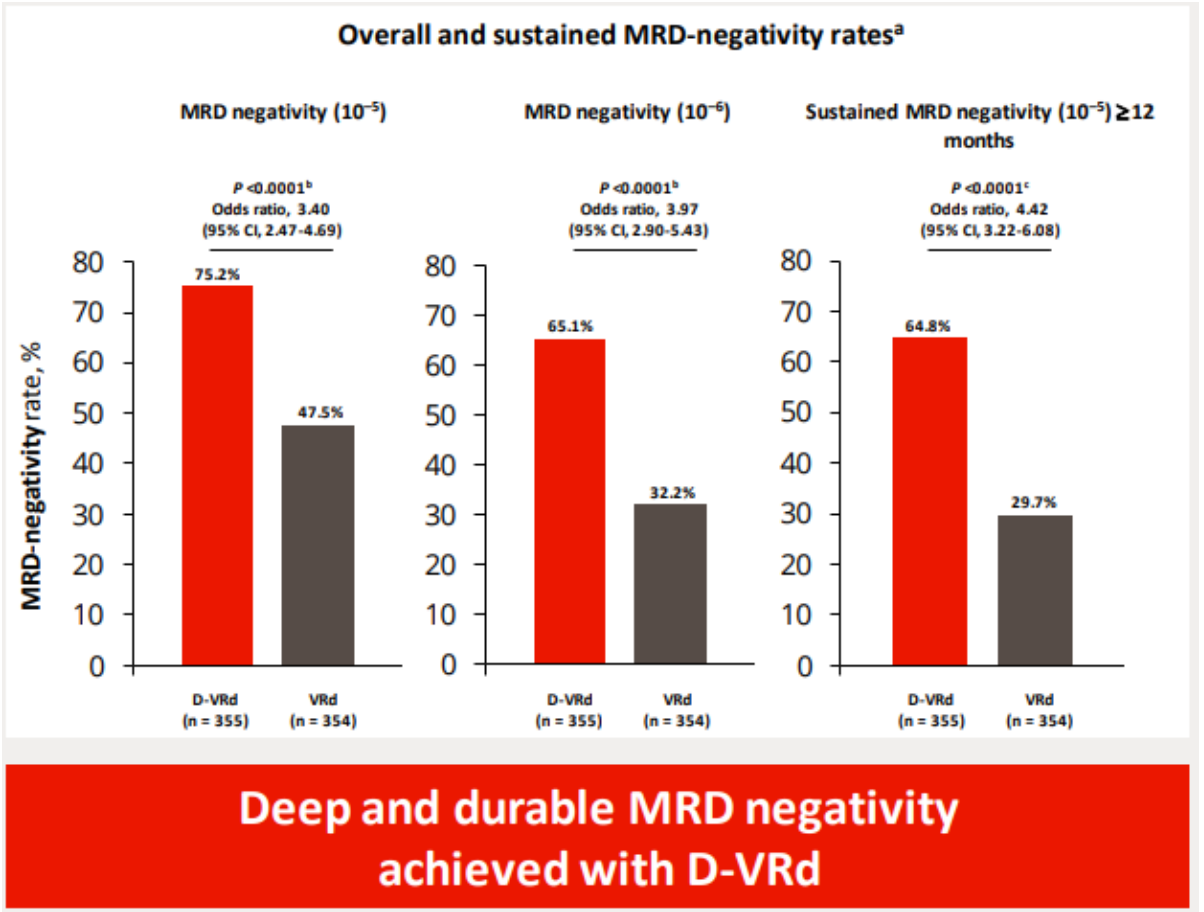
Key secondary endpoints: Overall ≥CR rate, overall MRD-negativity rate,[g] OS

Hohe Ansprechrate und 58% Reduktion des Sterberisikos



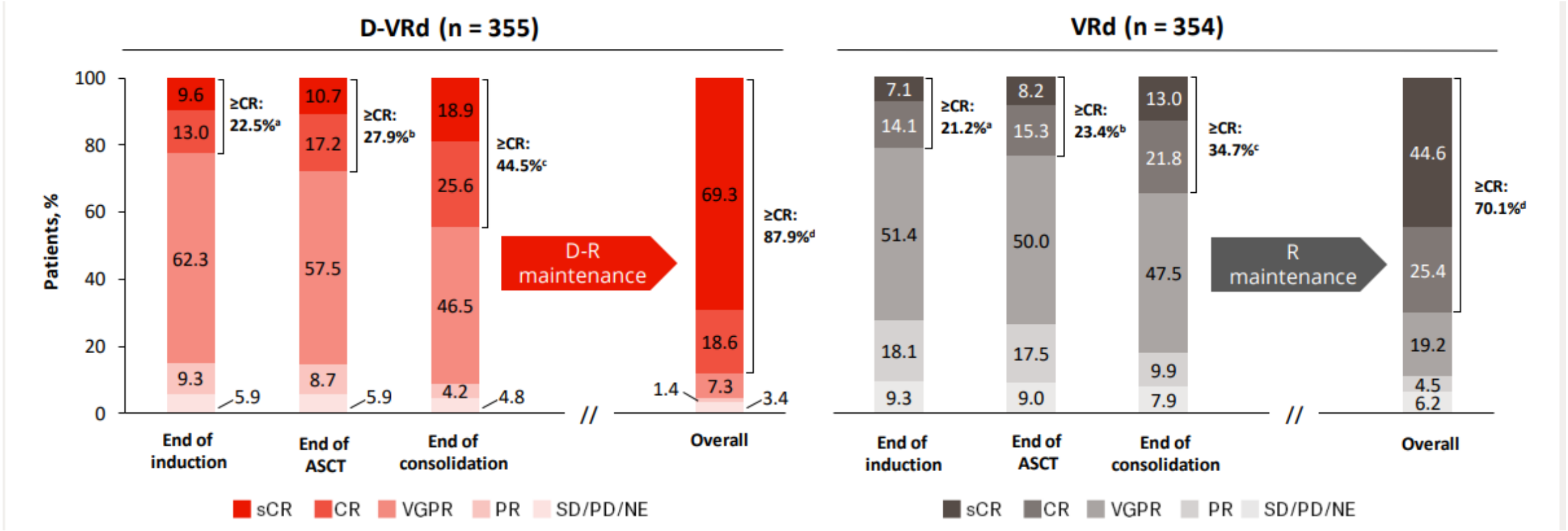
In patients receiving D-VRd versus VRd, there was a 58% reduction in the risk of disease progression or death

(HR, 0.42; 95% CI, 0.30-0.59; P <0.0001)

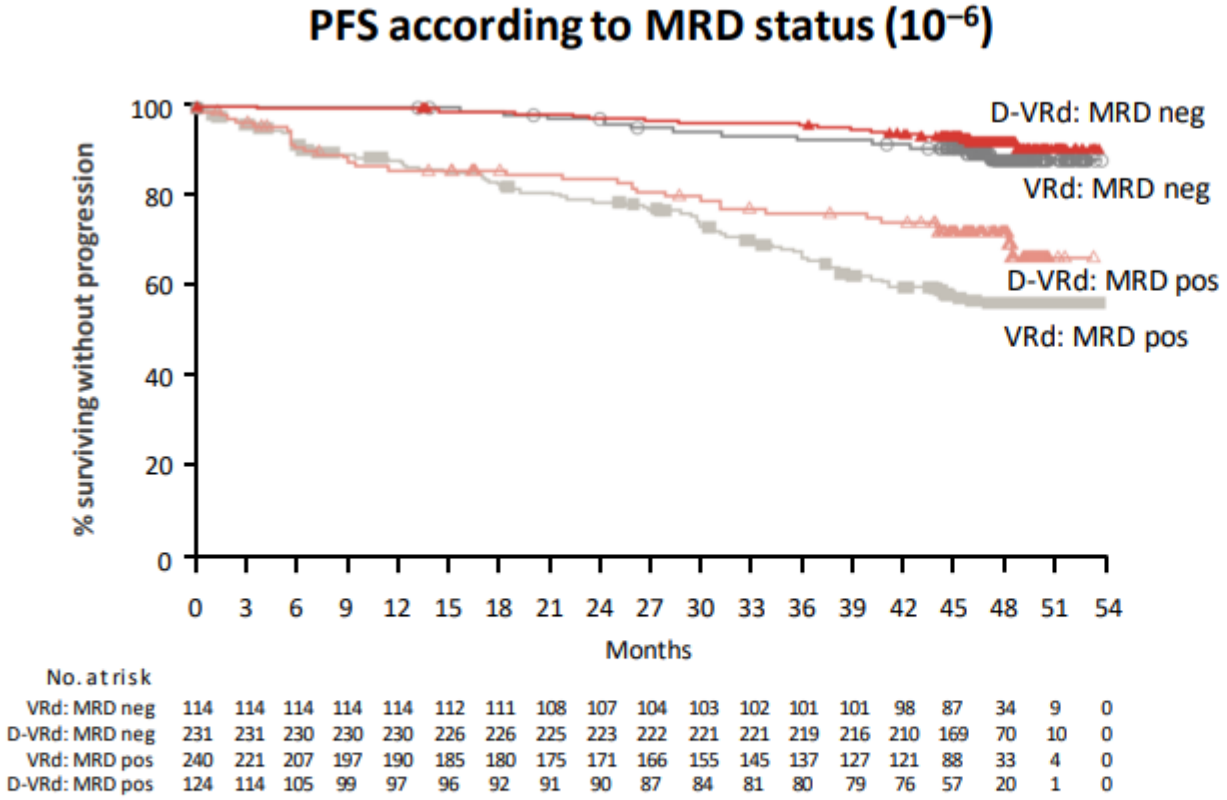


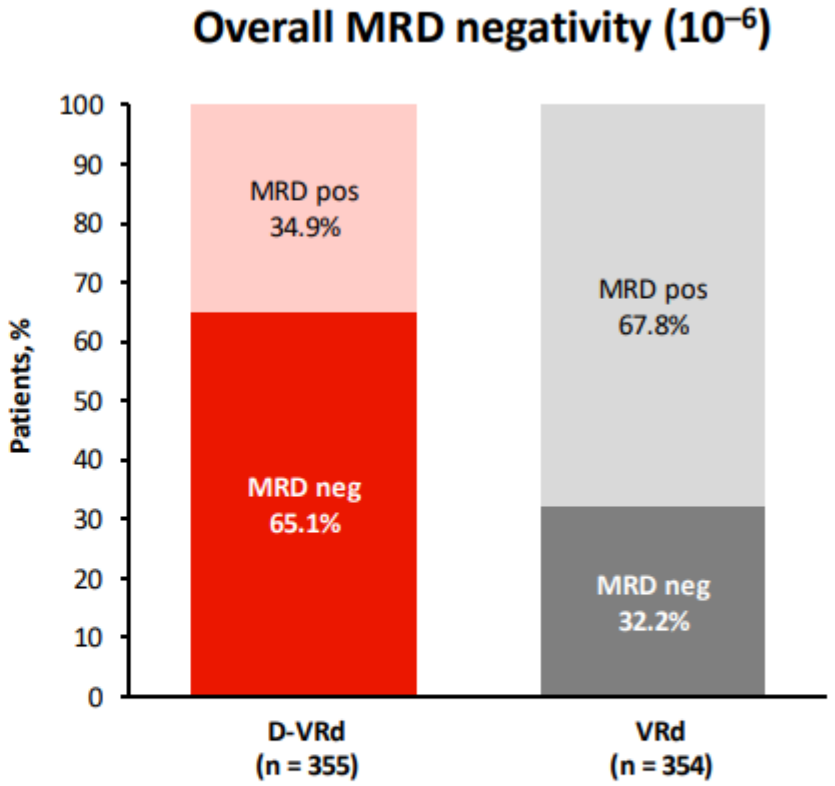
Deep and durable MRD negativity achieved with D-VRd

Die Remissionstiefe nimmt über den Behandlungsverlauf zu



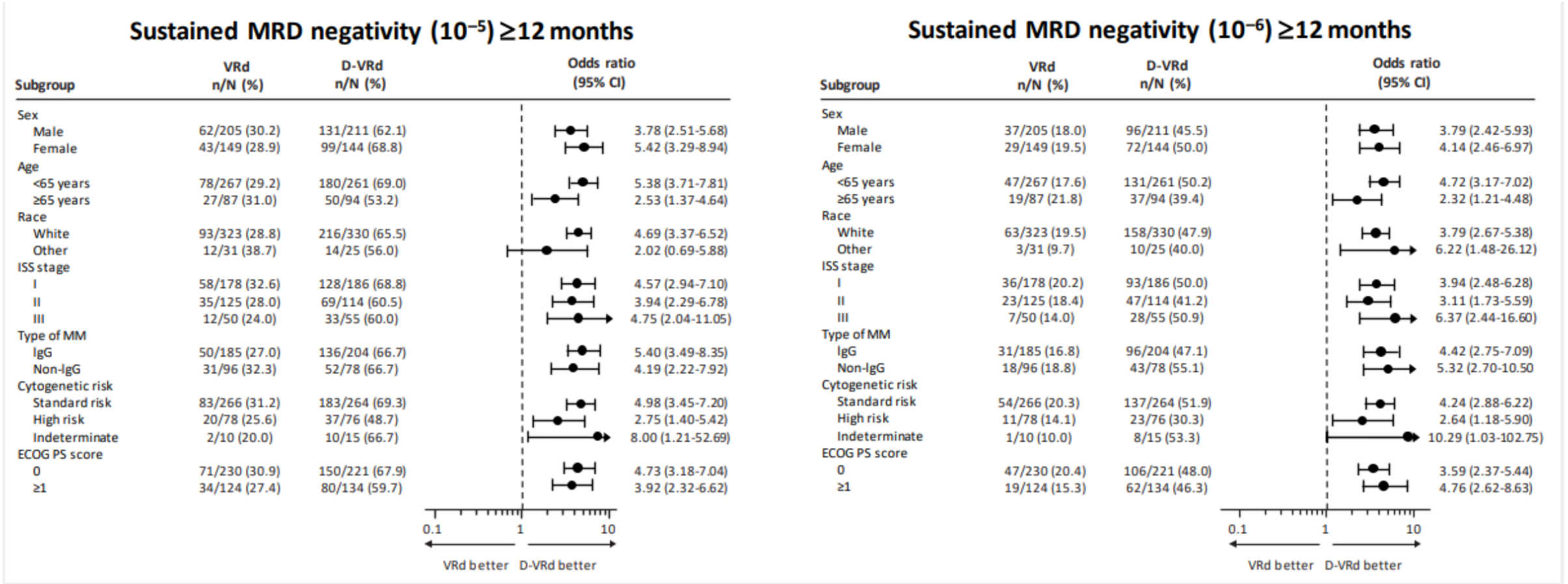
MRD Negativität ist ein Biomarker für verlängertes Überleben





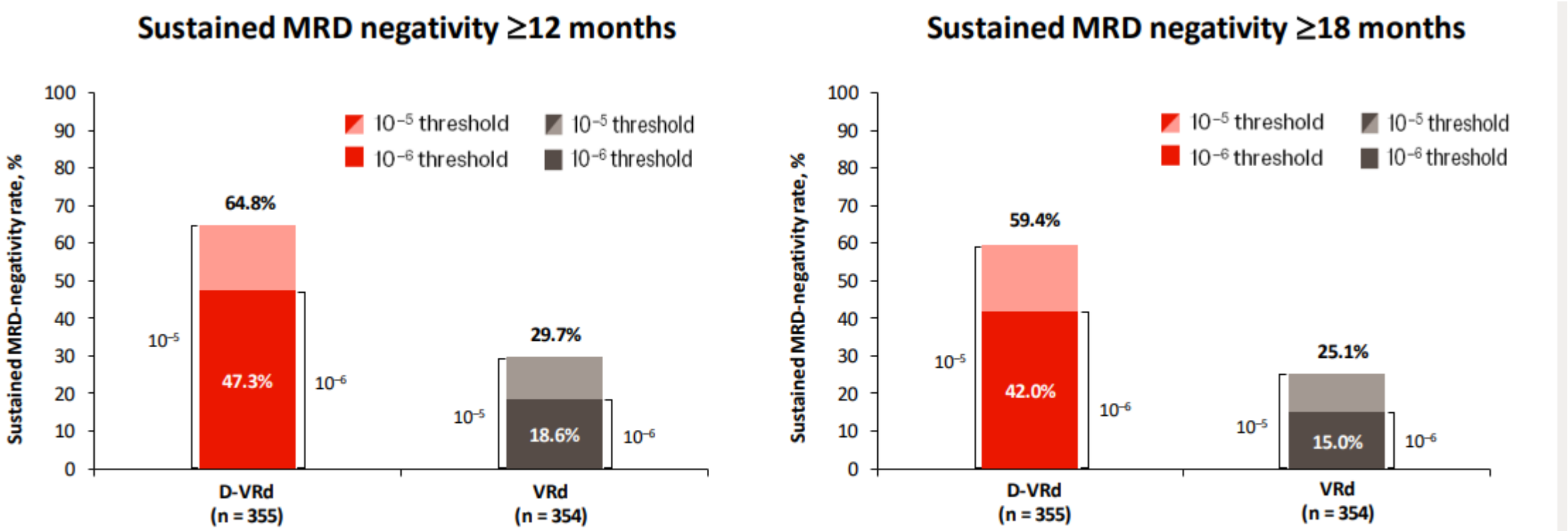
- MRD negativity at 10^{-6} was associated with improved long-term outcomes
- Twice as many patients achieved MRD negativity at 10^{-6} with D-VRd + D-R versus VRd + R
- Patients remaining MRD positive had improved PFS with D-R maintenance versus R alone

Subgruppenanalyse : Vorteil für alle Untergruppen



Sustained MRD-negativity rates were improved with D-VRd + D-R versus VRd + R across subgroups

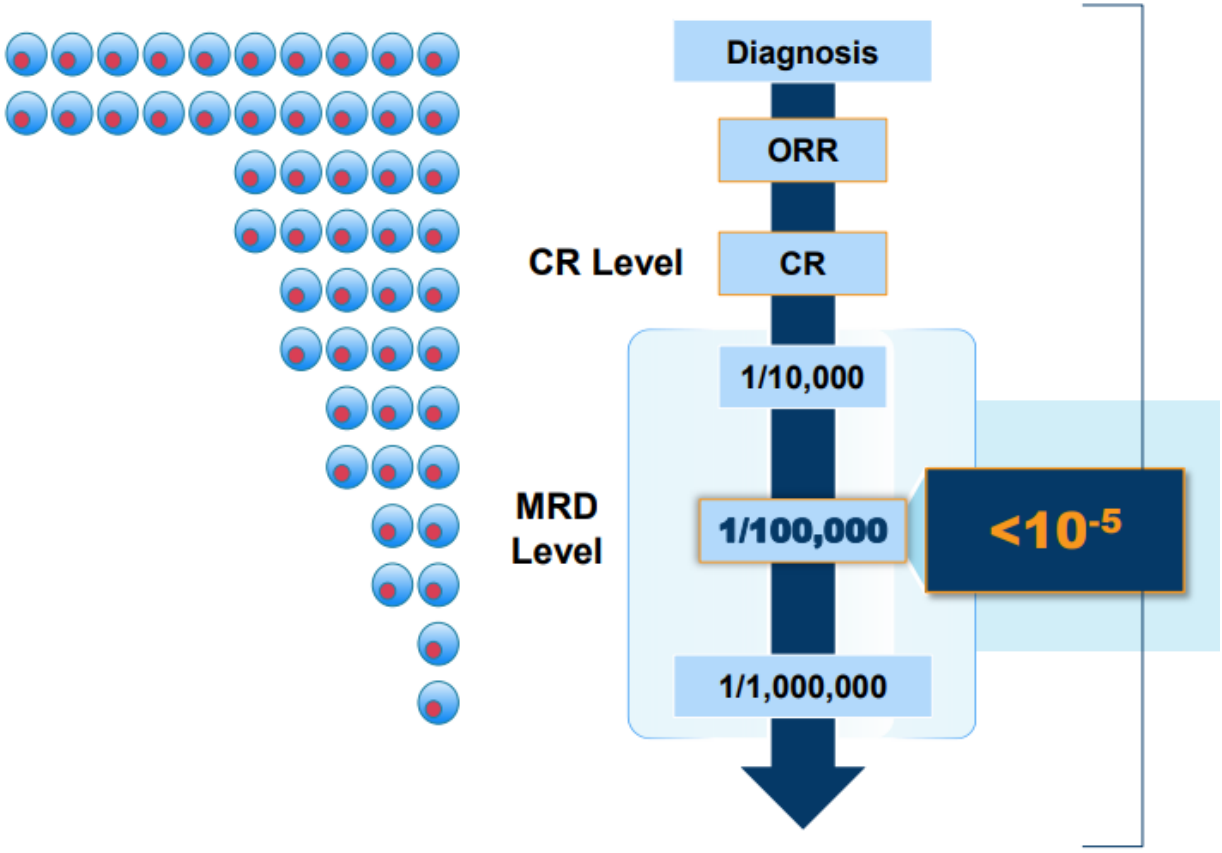
Anhaltende (“sustained“) MRD Negativität (10-6 / 10-5)

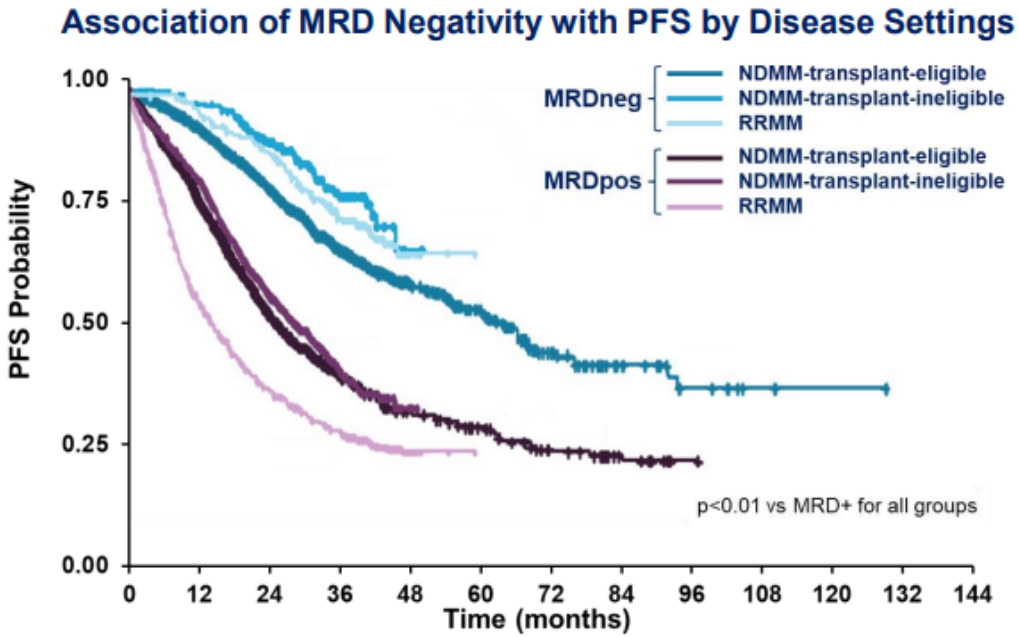


- Rates of sustained MRD negativity at 10^{-6} were 2.5-fold higher for D-VRd + D-R versus VRd + R
- More than 40% of patients had sustained MRD negativity at 10^{-6} for ≥18 months with D-VRd + D-R

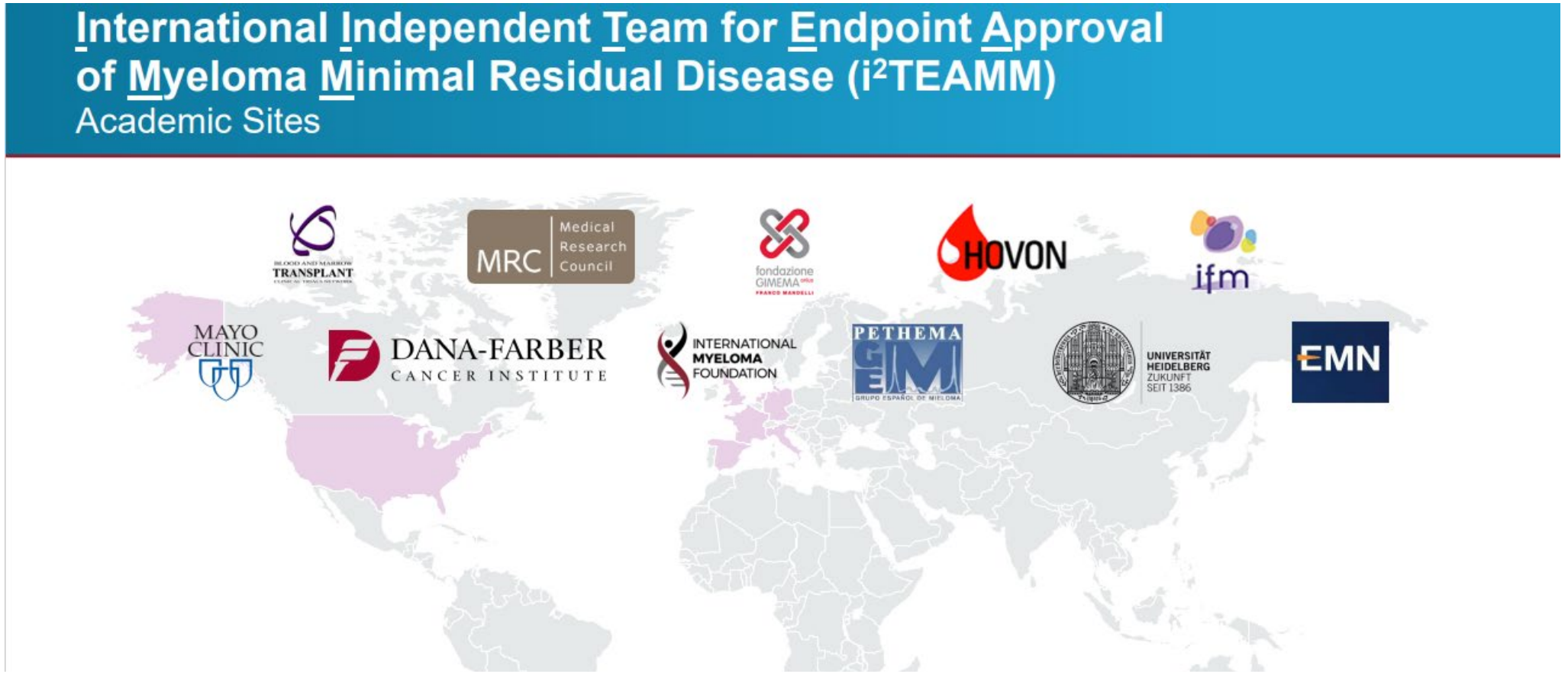
Verlängertes Überleben als Ziel der Therapie

Depth of Response Predicts Longer PFS and OS





MRD Negativität als neuer Endpunkt in Zulassungsstudien

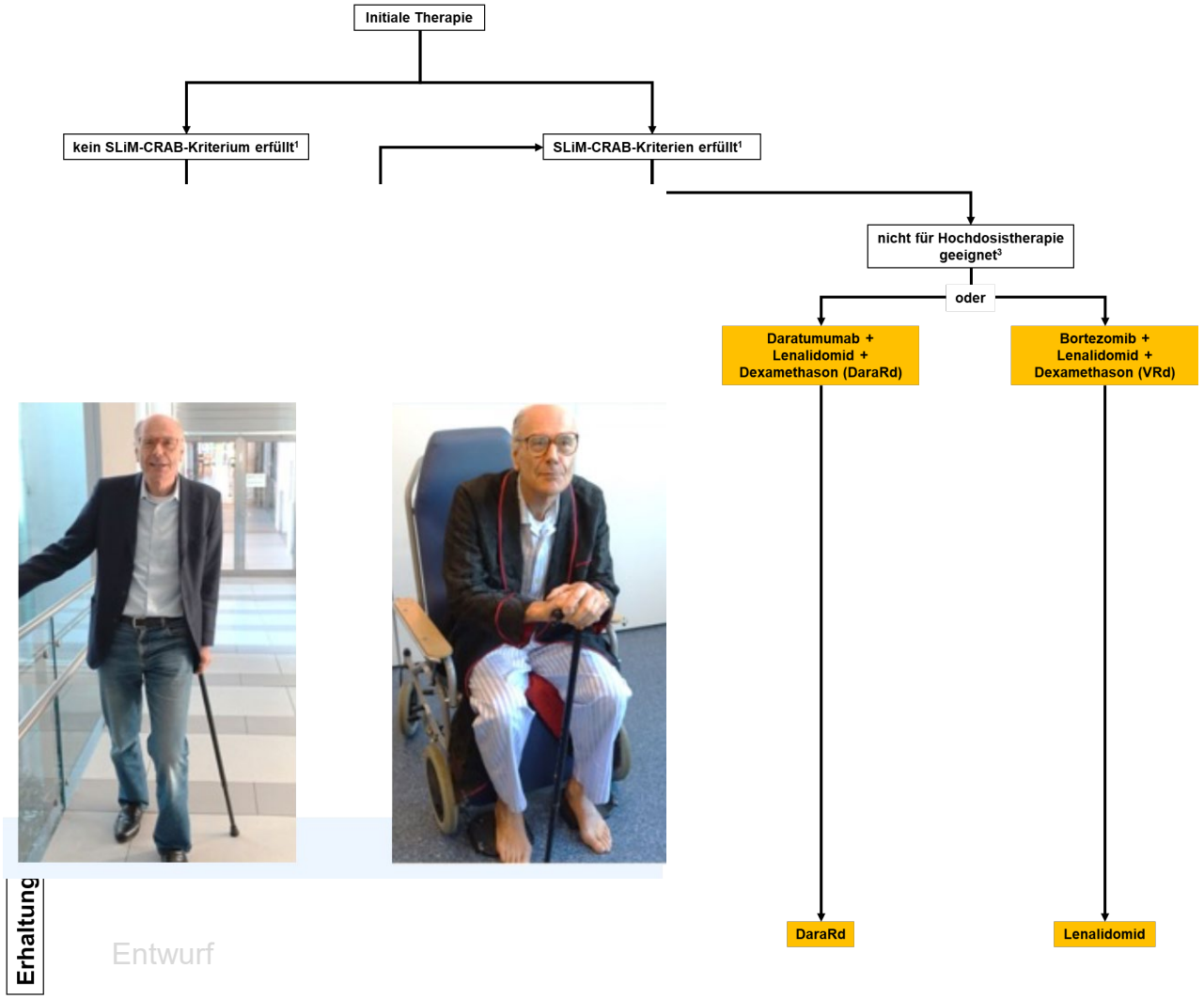


12:0 Abstimmung im Oncologic Drugs Advisory Committee zu Gunsten MRD Negativität als neuer klinischer Endpunkt in Zulassungsstudien

"In myeloma, MRD negativity is the new complete remission."

CC-3

Erstlinie beim MM 2024 - wo stehen wir, was kommt ?



Hochdosisfähige Patienten

- **PERSEUS (Dara-VRD**) oder
- **CASSIOPEIA (Dara-VTD**)

Nicht transplantationsgeeignete Patienten

- **MAIA (Dara-Rd**) oder
- **SWOG S0777 (VRd)**

EHA 2024: Update MAIA Studie, erstmalig OS Daten

NTE-MM: Dara-Rd vs. Rd i

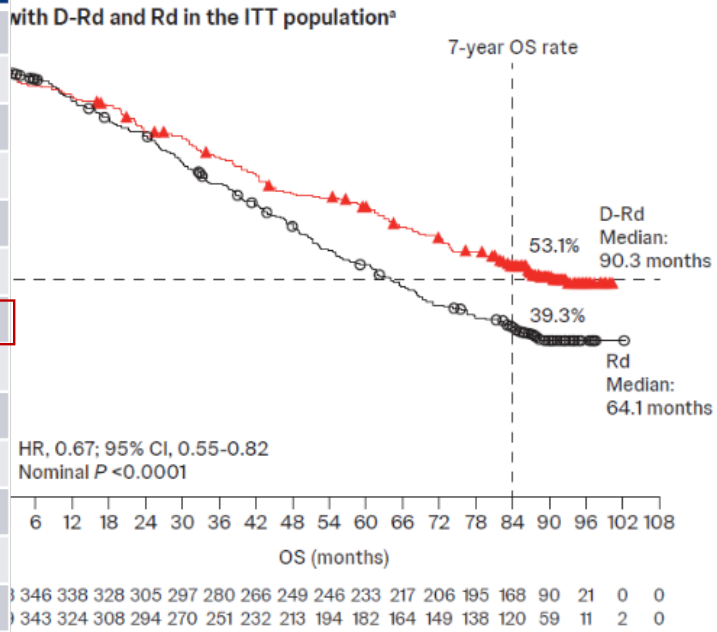
Key eligibility criteria:
NTE NDMM patients
ECOG 0-2
CrCl > 30ml/min

R

DRd
Dara: 16m
q1w (cycle
3-6), then
Len: 25mg
Dex: 40mg
(d1,8,15,2

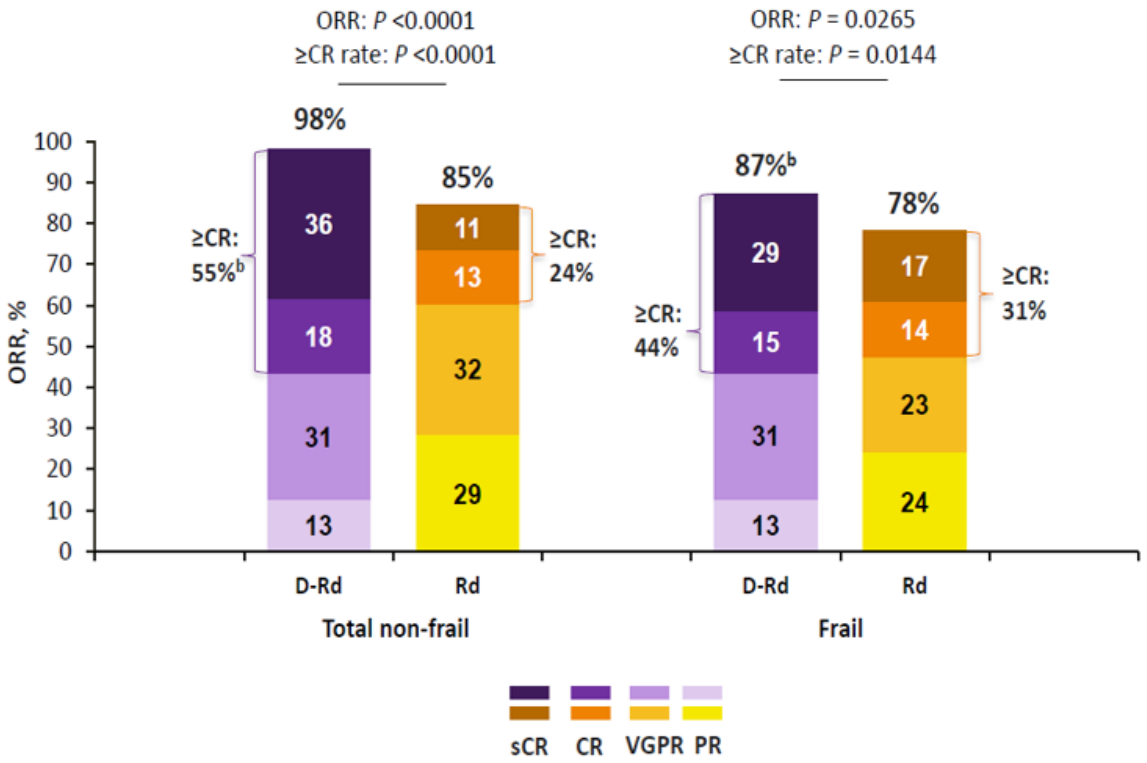
Rd
Len: 25mg
Dex: 40
(d1,8,15,2

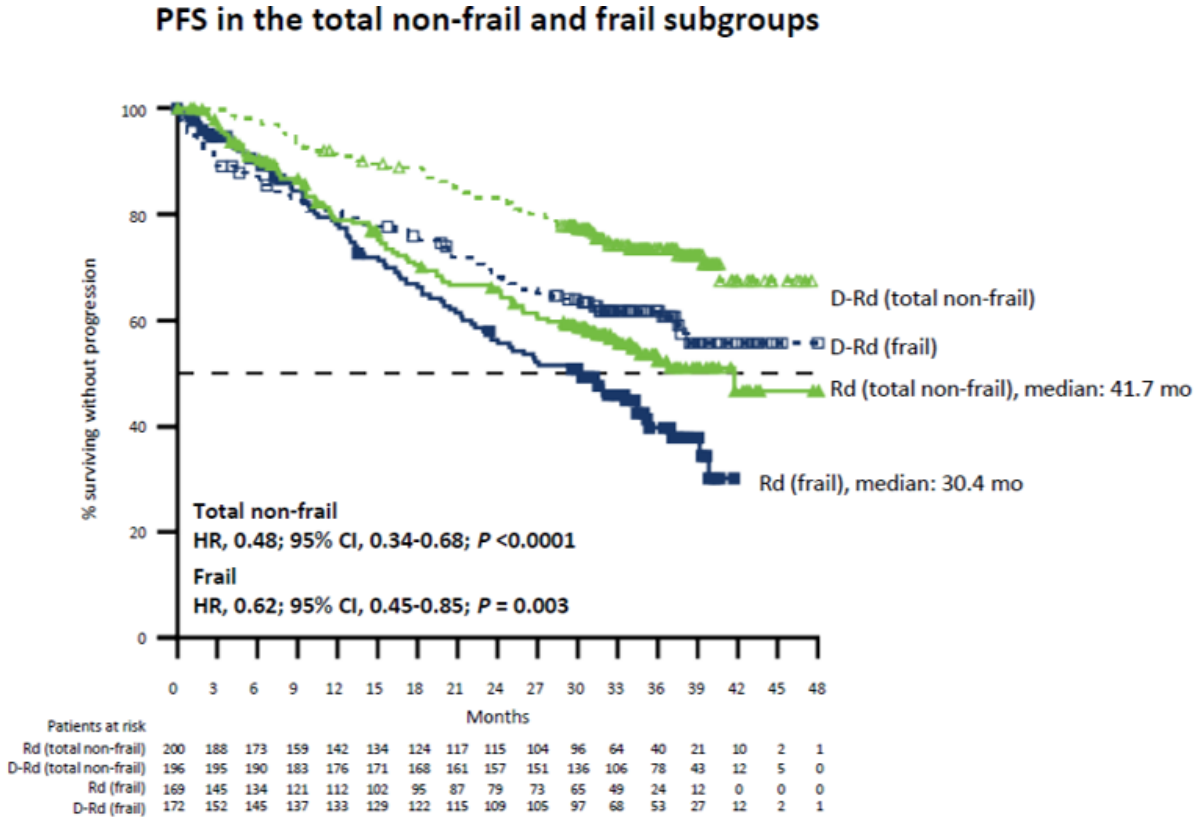
	DRd (n=368)	Rd (n=369)
Age, years		
Median (range)	73.0 (50-90)	74.0 (45-89)
Distribution, n(&)		
<65	4 (1)	4 (1)
65-<70	74 (20)	73 (20)
70-<75	130 (35)	131 (36)
≥75	160 (43)	161 (44)
ECOG PS score[a], n (%)		
0	127 (35)	123 (33)
1	178 (48)	187 (51)
2	63 (17)	59 (16)
ISS Stage, n (%)		
I	98 (27)	103 (28)
II	163 (44)	156 (42)
III	107 (29)	110 (30)



Take Home: 89,3 Monate Follow-up: erstmals OS-Daten (90.3 vs. 64.1 Monate), HR 0.67, medianes Alter 73 Jahre

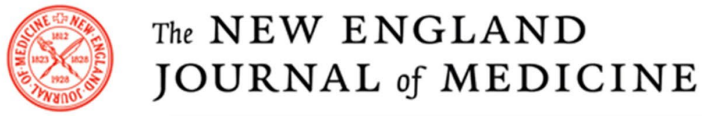
Ansprechen auch beim fragilen Patienten





- Higher ORR and ≥CR with DRd across frailty subgroups
- PFS benefit with DRd after 36.4 months in frailty subgroups

Therapie-Intensivierung beim nicht transplantationsgeeigneten Patienten
Isa-VRd vs VRd



ORIGINAL ARTICLE

Isatuximab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma

T. Facon, M.-A. Dimopoulos, X.P. Leleu, M. Beksac, L. Pour, R. Hájek, Z. Liu, J. Minarik, P. Moreau, J. Romejko-Jarosinska, I. Spicka, V.I. Vorobyev, B. Besemer, T. Ishida, W. Janowski, S. Kalayoglu-Besisik, G. Parmar, P. Robak, E. Zamagni, H. Goldschmidt, T.G. Martin, S. Manier, M. Mohty, C. Oprea, M.-F. Brégeault, S. Macé, C. Berthou, D. Bregman, Z. Klippel, and R.Z. Orlowski, for the IMROZ Study Group*

IMROZ

2024 ASCO ANNUAL MEETING

Phase 3 Study Results of Isatuximab, Bortezomib, Lenalidomide, and Dexamethasone (Isa-VRd) Versus VRd for Transplant-Ineligible Patients With Newly Diagnosed Multiple Myeloma (IMROZ)

Thierry Facon,[1] Meletios-Athanasios Dimopoulos,[2] Xavier Leleu,[3] Meral Beksac,[4,5] Ludek Pour,[6] Roman Hajek,[7] Zhuogang Liu,[8] Jiri Minarik,[9] Philippe Moreau,[10] Joanna Romejko-Jarosinska,[11] Ivan Spicka,[12] Vladimir Vorobyev,[13] Michele Cavo,[14] Hartmut Goldschmidt,[15] Thomas Martin,[16] Salomon Manier,[17] Marie-France Brégeault,[18] Sandrine Macé,[18] Christelle Berthou,[18] Robert Z. Orlowski[19]

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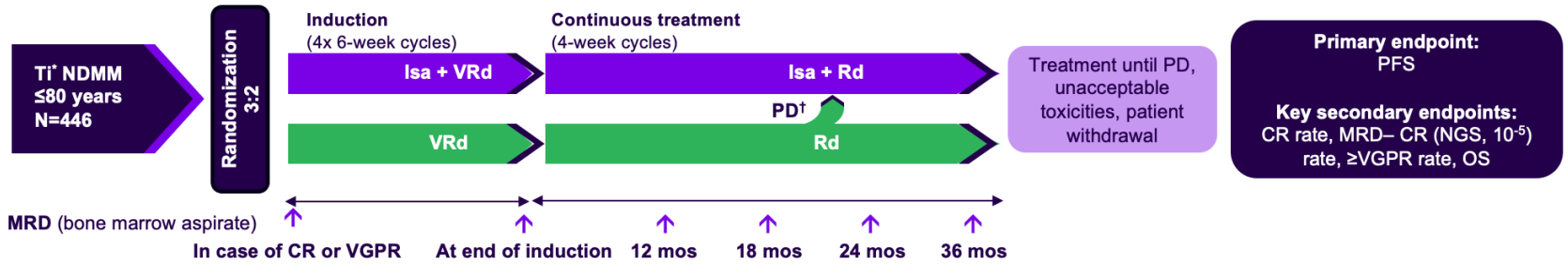
2024 ASCO ANNUAL MEETING #ASCO24

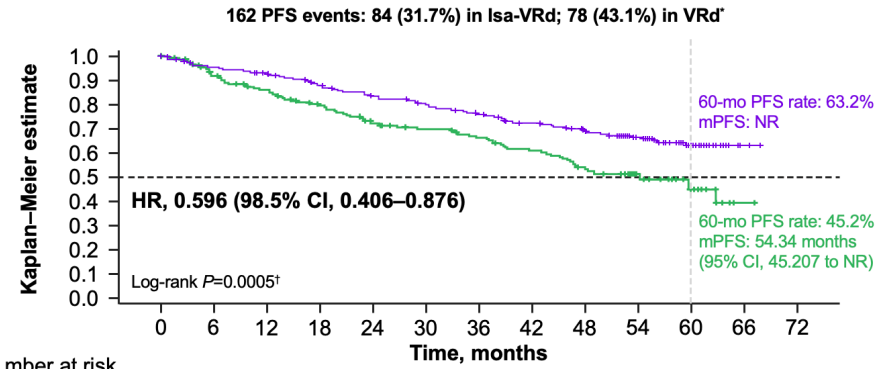
PRESENTED BY: Thierry Facon, MD

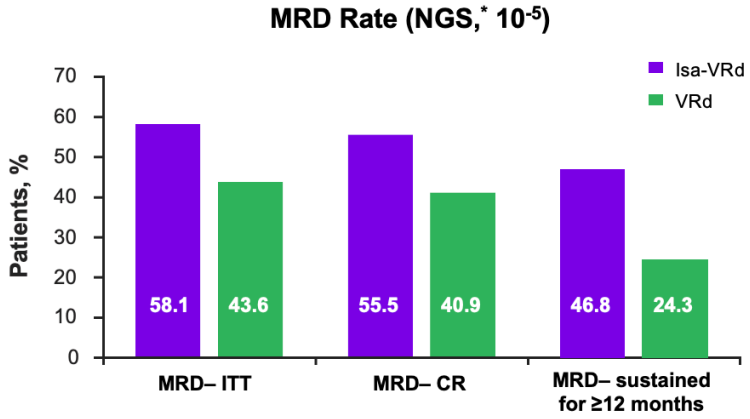
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

IMROZ Studie

NTE-MM: Isa-VRd vs. VRd induction and consolidation (n=446 pts)







Take Home:

- 89,3 mos Follow-up: Erstes Quadruple für NTE-MM
- 5-Jahres-PFS 63% vs. 45%,
- MRD^{neg} (10^{-5}) 56% vs. 41%

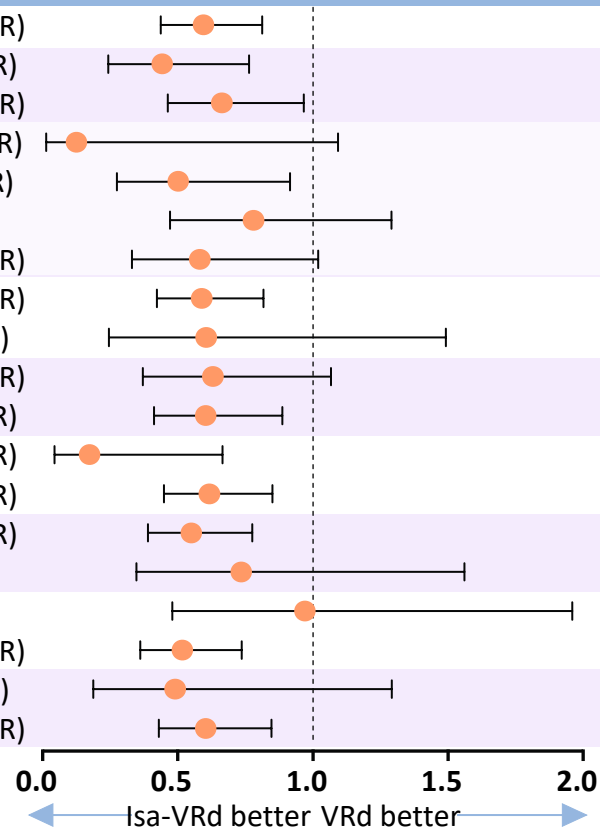
Baseline Characteristics

ITT population	Isa-VRd (n=265)	VRd (n=181)
Age, median (range), years	72.0 (60–80)	72.0 (55–80)
Age by category, years, n (%)		
<65	8 (3.0)	9 (5.0)
65–<70	73 (27.5)	47 (26.0)
70–<75	115 (43.4)	68 (37.6)
75–80	69 (26.0)	57 (31.5)
ECOG PS, n (%)		
0	123 (46.4)	79 (43.6)
1	112 (42.3)	83 (45.9)
2*	29 (10.9)	19 (10.5)
eGFR <60 mL/min/1.73 m² (MDRD), n (%)	66 (24.9)	62 (34.3)

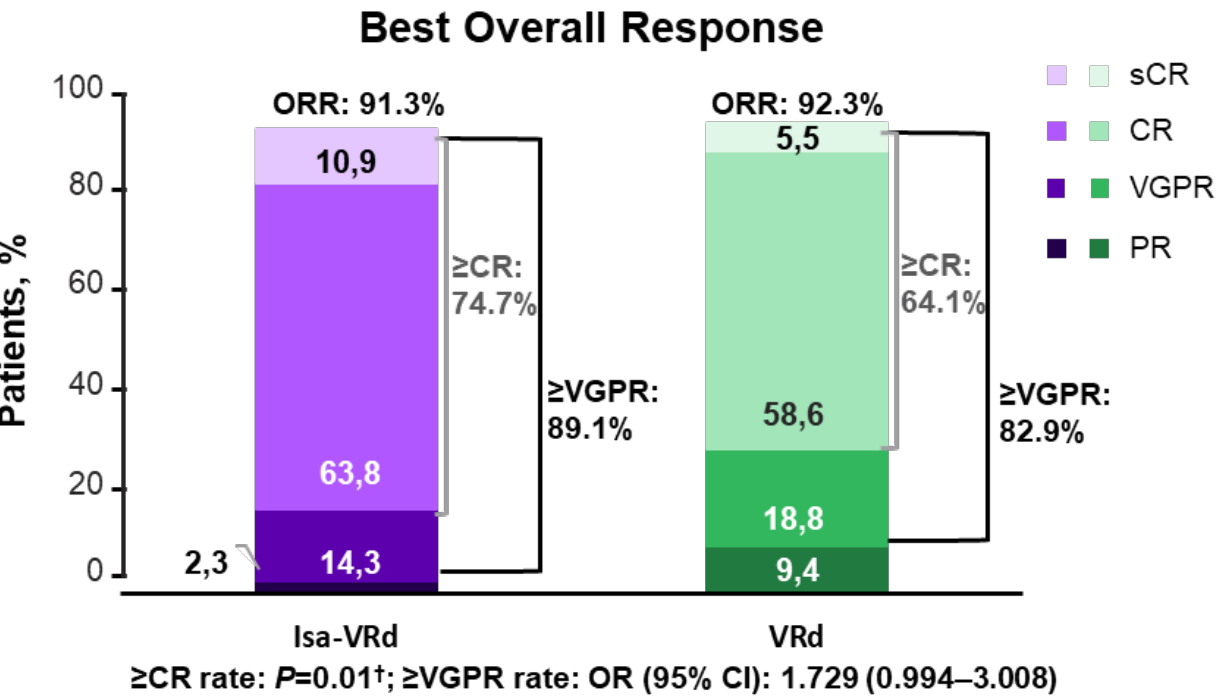
ITT population	Isa-VRd (n=265)	VRd (n=181)
R-ISS stage (IRT strata), n (%)		
I or II	234 (88.3)	157 (86.7)
III	29 (10.9)	21 (11.6)
Not classified	2 (0.8)	3 (1.7)
Cytogenetic risk, n (%)		
Standard	207 (78.1)	140 (77.3)
High†	40 (15.1)	34 (18.8)
High and 1q21+‡	19 (7.2)	15 (8.3)
1q21+/amplification 1q21,§ n (%)	95 (35.8)/ 32 (12.1)	70 (38.7)/ 23 (12.7)
Del(17p) (50% cutoff), n (%)	15 (5.7)	9 (5.0)
Extramedullary disease at study entry¶ (per IRC), n (%)	18 (6.8)	6 (3.3)

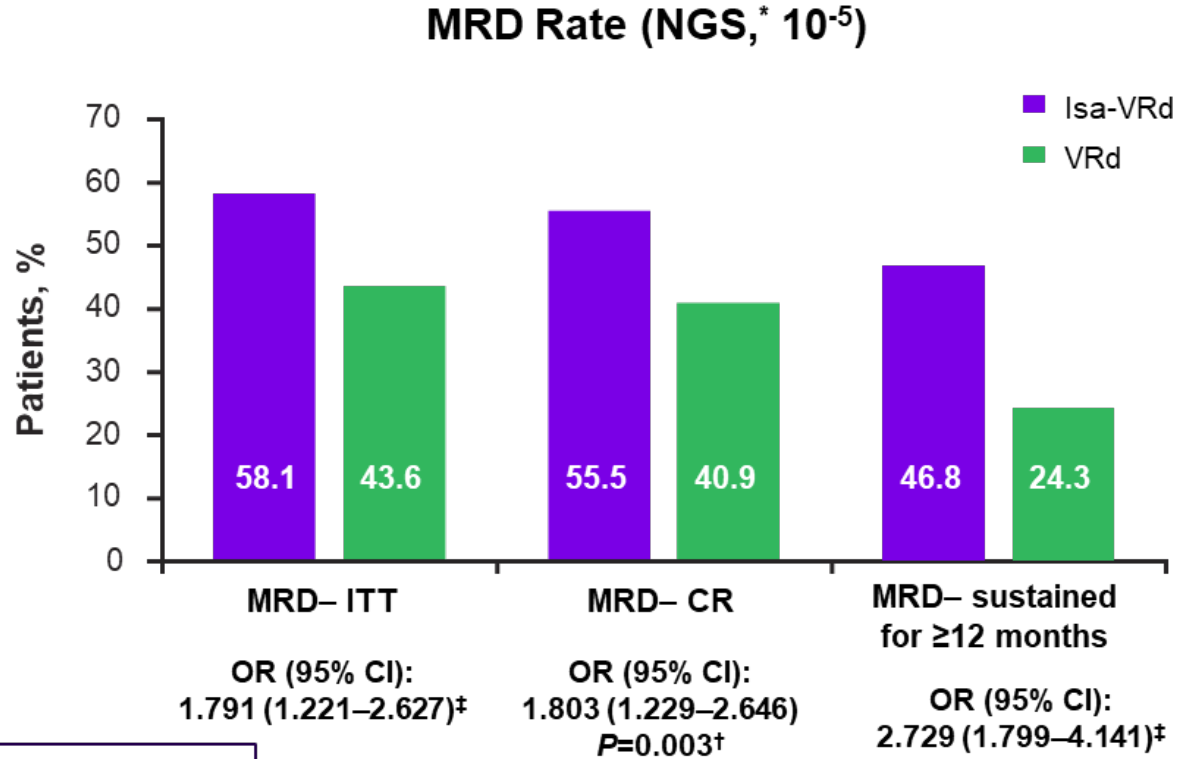
Fast alle Subgruppen profitieren von Isa-VRD vs VRD

Characteristic		Subgroup	Isa-VRd Events/total	Median PFS (95% CI)	VRd Events/total	Median PFS (95% CI)	Hazard ratio (95% CI)
All patients			84/265	NR (NR–NR)	78/181	54.341 (45.207–NR)	0.596 (0.438–0.812)
Age*	**70-year threshold:**	<70 years	22/80	NR (NR–NR)	27/56	53.914 (37.52–NR)	0.441 (0.251–0.775)
		≥70 years	62/185	NR (NR–NR)	51/125	54.341 (43.598–NR)	0.671 (0.463–0.972)
	Multiple subgroups:	<65 years	1/8	NR (48.066–NR)	5/9	31.524 (12.189–NR)	0.126 (0.014–1.095)
		65–<70 years	21/73	NR (NR–NR)	22/47	59.663 (37.52–NR)	0.503 (0.276–0.915)
		70–<75 years	39/115	NR (56.214–NR)	25/68	NR (45.207–NR)	0.781 (0.472–1.291)
		75–80 years	23/69	NR (53.06–NR)	26/57	45.864 (23.819–NR)	0.582 (0.331–1.02)
Baseline ECOG PS		0 or 1	74/235	NR (NR–NR)	69/162	54.341 (45.864–NR)	0.589 (0.424–0.818)
		>1	10/30	NR (29.503–NR)	9/19	43.598 (5.29–NR)	0.606 (0.246–1.493)
Baseline eGFR (MDRD)		<60 mL/min/1.73 m^2	25/66	NR (48.066–NR)	31/62	43.598 (33.117–NR)	0.63 (0.371–1.068)
		≥60 mL/min/1.73 m^2	59/197	NR (NR–NR)	47/119	59.663 (46.62–NR)	0.604 (0.412–0.887)
Extramedullary disease at baseline		Yes	6/19	NR (35.91–NR)	5/7	17.873 (2.825–NR)	0.174 (0.045–0.666)
		No	78/246	NR (NR–NR)	73/174	59.663 (46.16–NR)	0.618 (0.449–0.851)
R-ISS stage at study entry		I or II	67/234	NR (NR–NR)	65/157	59.663 (46.62–NR)	0.551 (0.391–0.776)
		III	16/29	45.602 (21.027–NR)	12/21	37.52 (4.6–NR)	0.736 (0.347–1.561)
Cytogenetic risk at baseline		High	18/40	NR (30.259–NR)	14/34	NR (37.454–NR)	0.971 (0.481–1.96)
		Standard	61/207	NR (NR–NR)	62/140	53.914 (43.006–NR)	0.517 (0.363–0.737)
HRCA† and 1q21+‡		Yes	8/19	NR (22.998–NR)	9/15	37.52 (5.782–NR)	0.491 (0.187–1.293)
		No	70/227	NR (NR–NR)	65/157	59.696 (45.864–NR)	0.604 (0.431–0.847)



Remissionstiefe in ITT Population





Time to MRD–, median (95% CI)
Isa-VRd: 14.72 (11.53–24.08) months
VRd: 32.79 (17.51–45.11) months

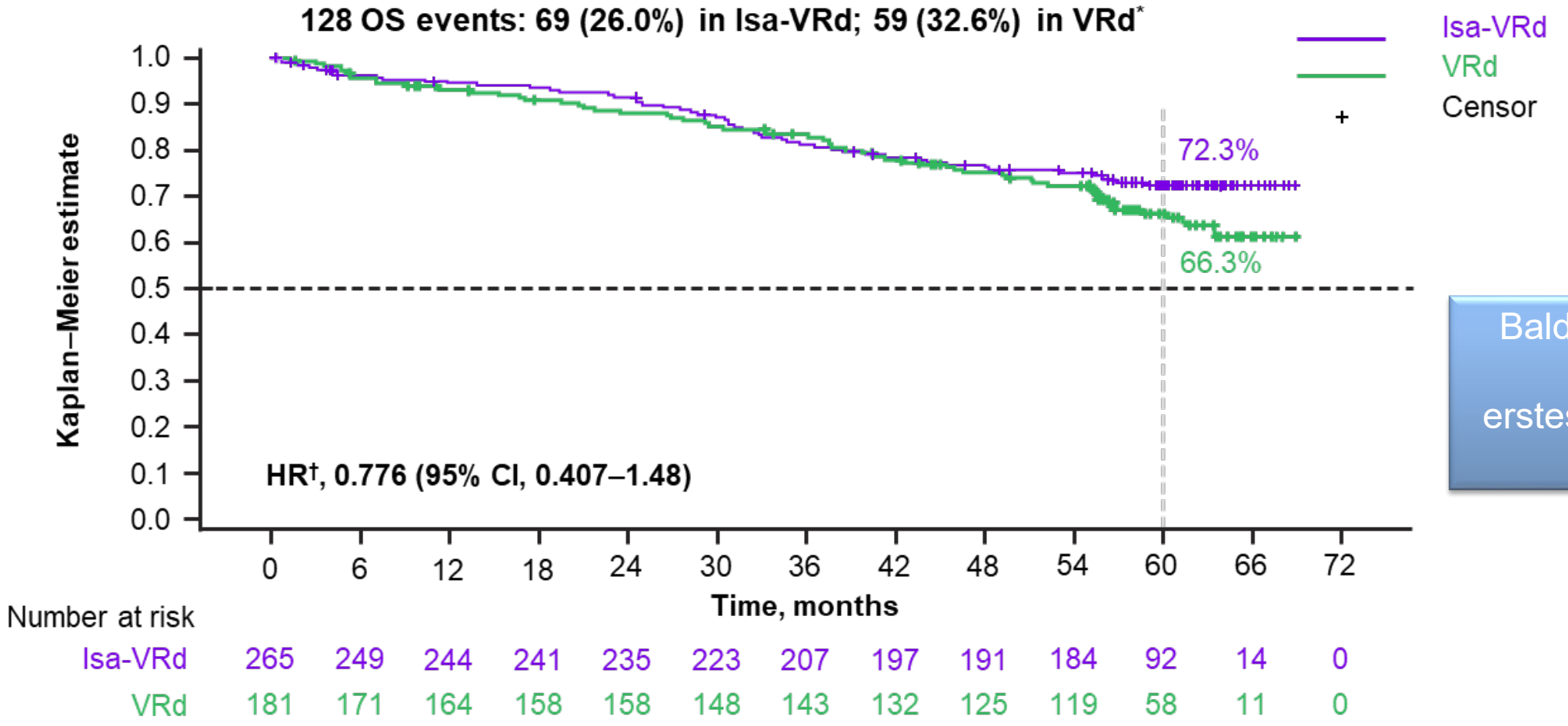
Safety

TEAE overview, n (%)	Isa-VRd (n=263)	VRd (n=181)
Median treatment duration	**53.2 months**	**31.3 months**
Patients still on treatment	**125 (47.2)**	**44 (24.3)**
Any TEAE	262 (99.6)	178 (98.3)
Grade ≥3 TEAEs	241 (91.6)	152 (84.0)
Grade 5 TEAEs*	29 (11.0)	10 (5.5)
Serious TEAEs	186 (70.7)	122 (67.4)
Any TEAE leading to definitive treatment discontinuation	60 (22.8)	47 (26.0)
Event rate per patient-year†		
Any TEAE	13.39	12.69
Grade ≥3 TEAEs	1.17	0.99
Grade 5 TEAEs	0.03	0.02
Serious TEAEs	0.37	0.43
Any TEAE leading to definitive treatment discontinuation	0.07	0.09

Safety

Preferred term, n (%)	Isa-VRd (n=263)		VRd (n=181)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Hematologic laboratory abnormalities				
Neutropenia	230 (87.5)	143 (54.4)	145 (80.1)	67 (37.0)
Nonhematologic adverse events				
Infections	240 (91.3)	118 (44.9)	157 (86.7)	69 (38.1)
Pneumonia	79 (30.0)	53 (20.2)	35 (19.3)	23 (12.7)
Upper respiratory tract infection	90 (34.2)	2 (0.8)	61 (33.7)	2 (1.1)
Diarrhea	144 (54.8)	20 (7.6)	88 (48.6)	15 (8.3)
Peripheral sensory neuropathy	143 (54.4)	19 (7.2)	110 (60.8)	11 (6.1)
Cataract	100 (38.0)	41 (15.6)	46 (25.4)	20 (11.0)
Invasive second primary malignancies				
Solid tumors	22 (8.4)	14 (5.3)	8 (4.4)	6 (3.3)
Hematologic	3 (1.1)	1 (0.4)	2 (1.1)	2 (1.1)
Event rate per patient-year*				
Infections	1.181	-	1.166	-
Secondary primary malignancies†	0.041	-	0.026	-

Trend zum verlängerten Gesamtüberleben



Baldige Zulassung erwartet,
erstes Quadrupel für NTE MM!

Benefit Studie: Isa-VRd vs Isa-Rd beim NTE MM

nature medicine

Article

https://doi.org/10.1038/s41591-024-03050-2

Isatuximab, lenalidomide, dexamethasone and bortezomib in transplant-ineligible multiple myeloma: the randomized phase 3 BENEFIT trial

Received: 18 April 2024

Accepted: 8 May 2024

Published online: 03 June 2024

Check for updates

A list of authors and their affiliations appears at the end of the paper

CD38-targeting immunotherapy is approved in combination with lenalidomide and dexamethasone in patients with newly diagnosed multiple myeloma (NDMM) that are transplant ineligible (TI) and is considered the best standard of care (SOC). To improve current SOC, we evaluated the added value of weekly bortezomib (V) to isatuximab plus lenalidomide and dexamethasone (IsaRd versus Isa-VRd).

This Intergroupe Francophone of Myeloma phase 3 study randomized 270 patients with NDMM that were TI, aged 65–79 years, to IsaRd versus Isa-VRd arms. The primary endpoint was a minimal residual disease (MRD) negativity rate at 10^{-5} by next-generation sequencing at 18 months from randomization. Key secondary endpoints included response rates, MRD assessment rates, survival and safety. The 18-month MRD negativity rates at 10^{-5} were reported in 35 patients (26%, 95% confidence interval (CI) 19–34) in IsaRd versus 71 (53%, 95% CI 44–61) in Isa-VRd (odds ratio for MRD negativity 3.16, 95% CI 1.89–5.28, $P < 0.0001$).

The MRD benefit was consistent across subgroups at 10^{-5} and 10^{-6}, and was already observed at month 12. The proportion of patients with complete response or better at 18 months was higher with Isa-VRd (58% versus 33%; $P < 0.0001$), as was the proportion of MRD negativity and complete response or better (37% versus 17%; $P = 0.0003$). At a median follow-up of 23.5 months, no difference was observed for survival times (immature data). The addition of weekly bortezomib did not significantly affect the relative dose intensity of IsaRd. Isa-VRd significantly increased MRD endpoints, including the 18-month negativity rate at 10^{-5}, the primary endpoint, compared with IsaRd. This study proposes Isa-VRd as a new SOC for patients with NDMM that are TI. ClinicalTrials.gov identifier: NCT04751877.

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Nature Medicine

2024 ASCO ANNUAL MEETING

Isatuximab plus lenalidomide and dexamethasone with weekly bortezomib versus isatuximab plus lenalidomide and dexamethasone in newly diagnosed transplant ineligible Multiple Myeloma. The BENEFIT (IFM 2020-05) study

Xavier Leleu[1] and Cyrille Hulin[2], Lambert Jerome[3], Arthur Bobin[1], Aurore Perrot[4], Lionel Karlin[5], Roussel Murielle[6], Lydia Montes[7], Brieuc Cherel[8], Thomas Chalopin[9], Borhane Slama[10], Marie-Lorraine Chretien[11], Kamel Laribi[12], Claire Dingremont[13], Christophe Roul[14], Clara Mariette[15], Sophie Rigaudeau[16], Claire Calmettes[17], Mamoun Dib[18], Mourad Tiab[19], Laure Vincent[20], Jacques Delaunay[21], Alberto Santagostino[22], Margaret Macro[23], Emmanuelle Bourgeois[24], Frederique Orsini-Piocelle[25], Julie Gay[26], Benoit Bareau[27], Noemie Bigot[3], François Vergez[28], Pierre Lebreton[29], Reza Tabrizi[30], Agathe Waultier-Rascalou[31], Laurent Frenzel[32], Ronan Le Calloch[33], Emilie Chalayer[34], Thorsten Braun[35], Florence Lachenal[36], Selim Corm[37], Celine Kennel[38], Rakiba Belkhir[39], Jean-Sebastien Bladé[40], Bertrand Joly[41], Valentine Richez-Olivier[42], Helene Demarquette[43], Daniela Robu-Cretu[44], Laurent Garderet[45], Muriel Newinger-Porte[46], Amine Kasmi[47], Bruno Royer[48], Olivier Decaux[49], Bertrand Arnulf[48], Karim Belhadj[50], Cyrille Touzeau[51], Mohamad Mohty[52], Salomon Manier[53], Philippe Moreau[51], Hervé Avet-Loiseau[28], Jill Corre[28], Thierry Facon[53]

2024 ASCO ANNUAL MEETING #ASCO24

PRESENTED BY: Xavier Leleu, MD, PhD

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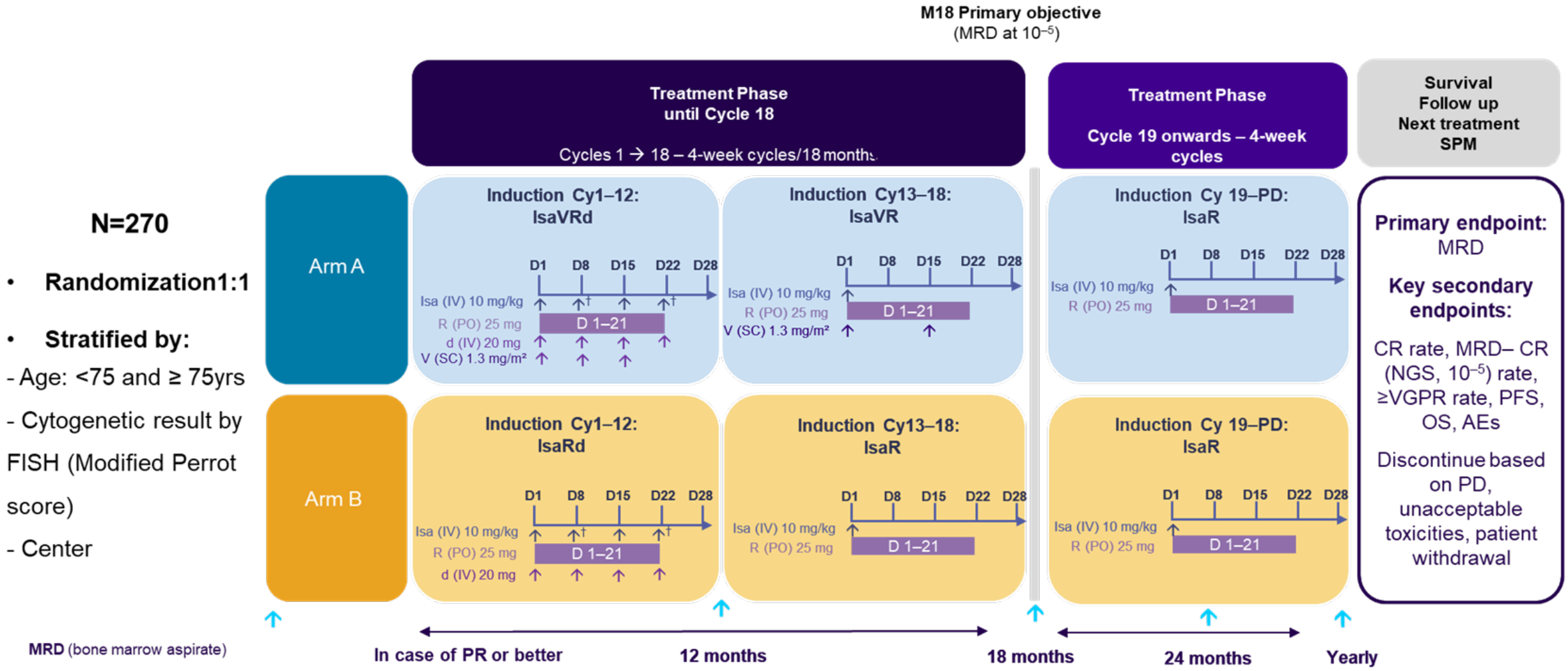
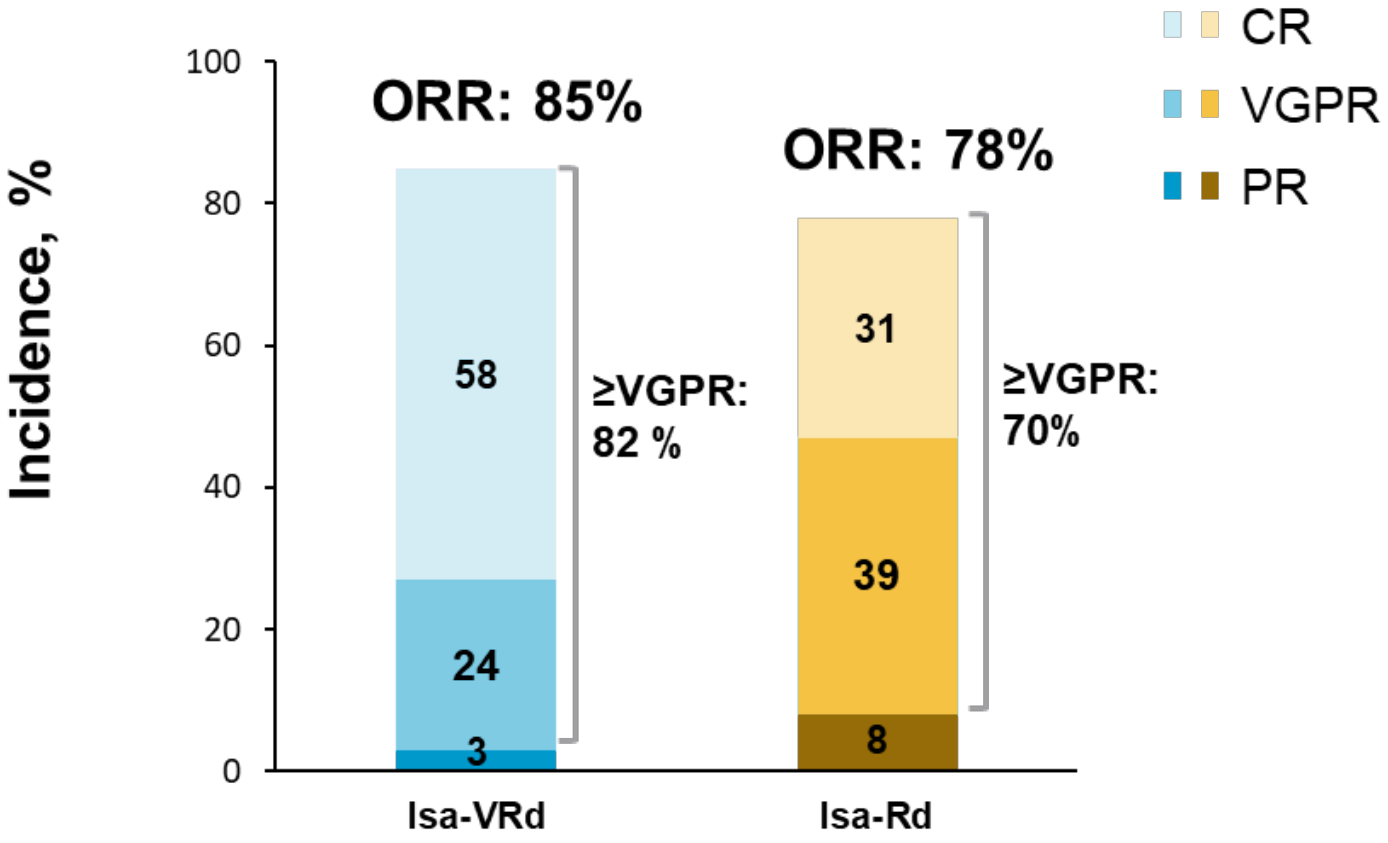
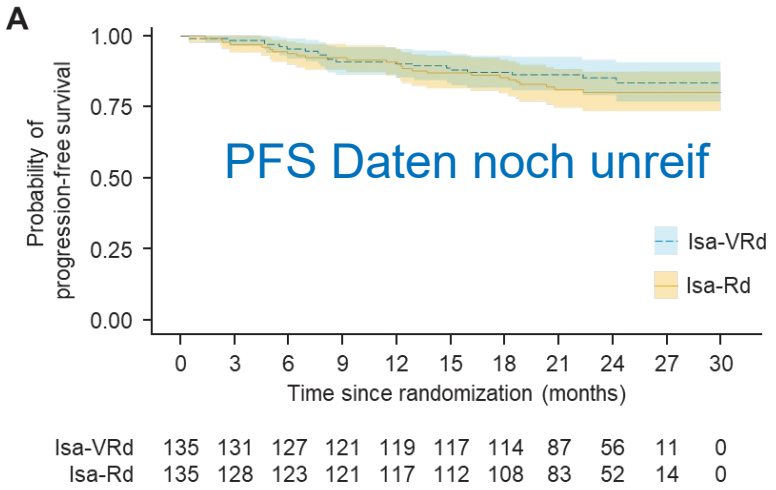
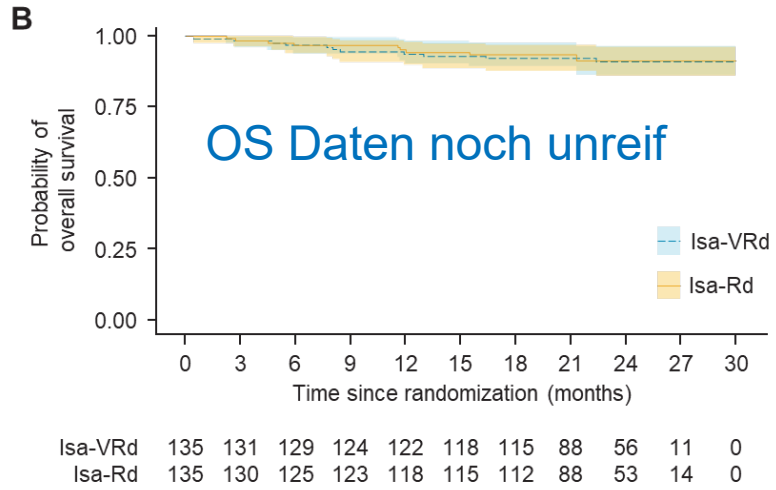
Studiendesign, BTZ weekly



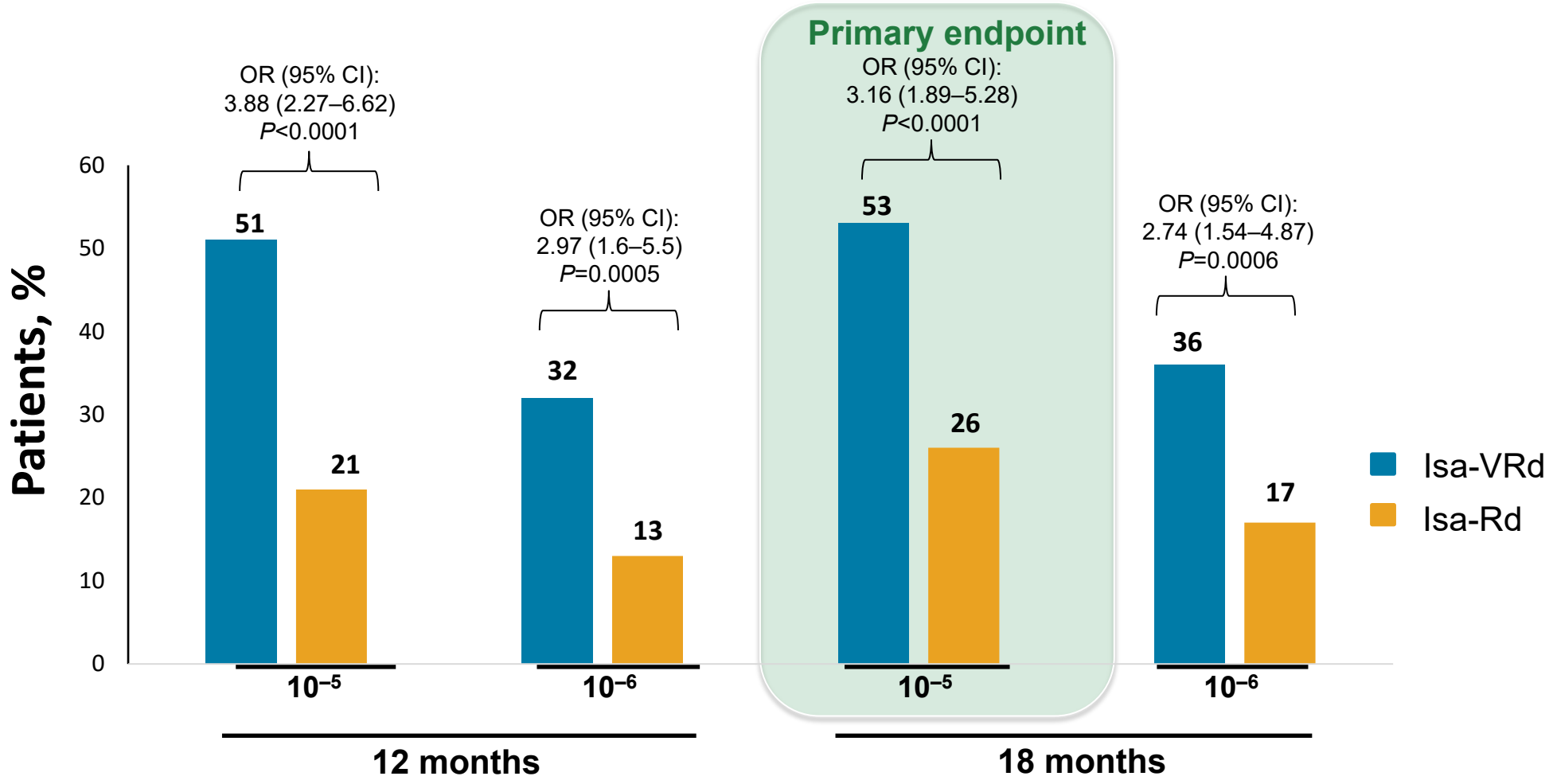
BENEFIT Studie, FU 23.5 Monate



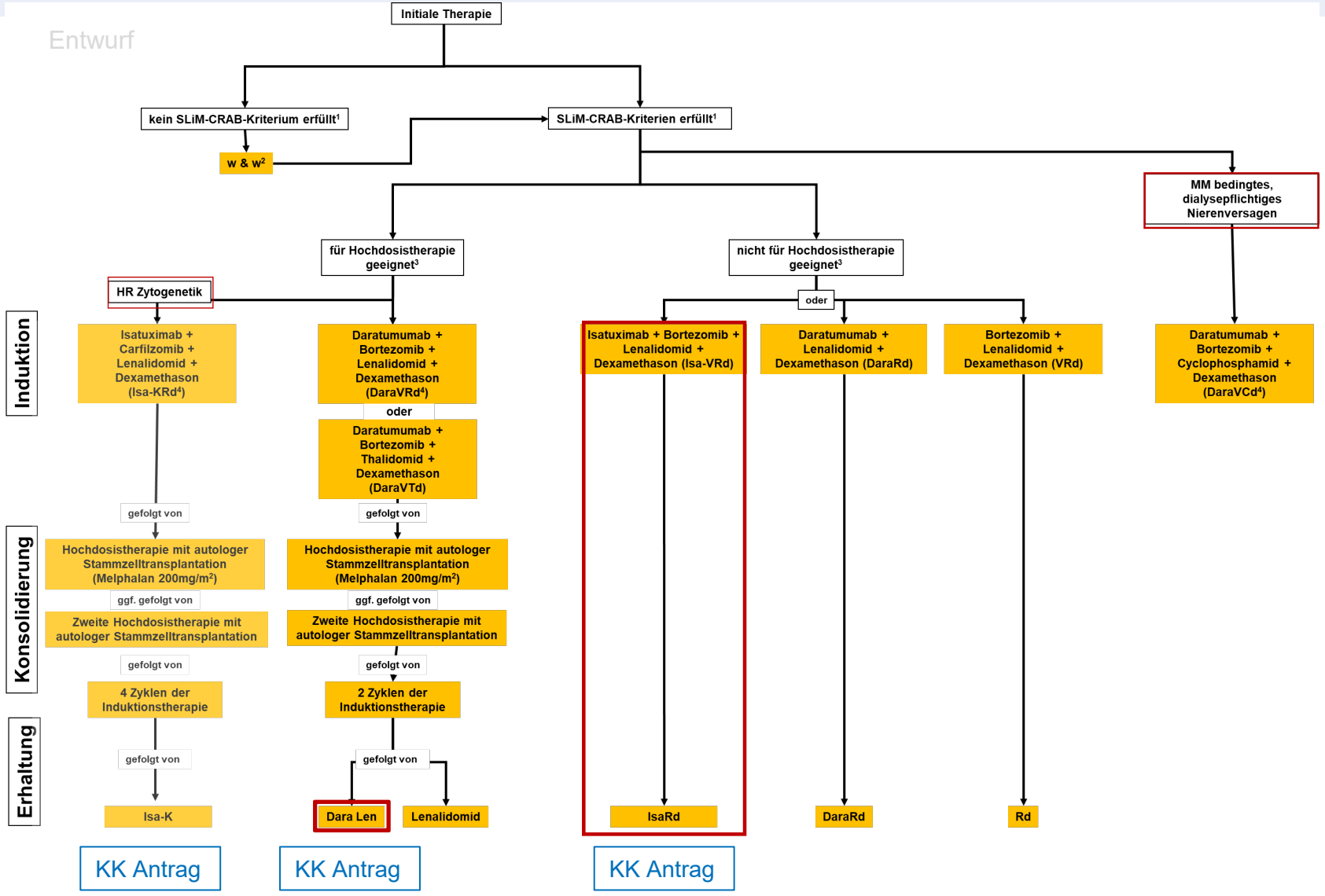




Isa-VRd induziert tiefere Remissionen als ISA-Rd



Ausblick: Erstlinie beim MM - was kommt ?



Hochdosisfähige Patienten

- **PERSEUS (Dara-VRD)** oder
- **CASSIOPEIA (Dara-VTD)**

Nicht transplantable Patienten

- **MAIA (Dara-Rd)** oder
- **SWOG S0777 (VRd)** oder
- **IMROZ (Isa-VRD)**

Rückfall 2018

Rückfall 2022

Therapie - Algorithmus im Rez

Rückfallstudien : direkte Vergleiche fehlen !

TABELLE

Randomisierte Vergleichsstudien zur Therapie des multiplen Myeloms (jeweils alphabetische Reihenfolge)[1]

Studie															
Erstlinie, nicht tr															
ALCYONE (e1, e															
MAIA (e3, e4)															
SWOG S0777 (e															
Rezidiv															
APOLLO (e6)															
ASPIRE (e7)															
BOSTON (e8)															
CANDOR (e9)															
CASTOR (e10)															
ELOQUENT-2 (e															
ELOQUENT-3 (e															
ENDEAVOR (e13, e14)	NCT01568866	Kd	Vd	19	9	0,53 [0,44; 0,65]	48	39	0,76 [0,63; 0,92]	59 %	40 %	77 %	63 %	13 %	6 %
ICARIA-MM (e15)	NCT02990338	Isa Pd	Pd	12	7	0,60 [0,44; 0,81]	NE	NE	0,69 [0,46; 1,0]	62 %	54 %	60 %	35 %	5 %	1 %
IKEMA (e16)	NCT03275285	Isa Kd	Kd	NE	19	0,53 [0,32; 0,89]	NE	NE	-	59 %	57 %	87 %	83 %	40 %	28 %
OPTIMISMM (e17)	NCT01734928	PVd	Vd	11	7	0,61 [0,49; 0,77]	NE	NE	0,98 [0,73; 1,32]	61 %	43 %	82 %	50 %	16 %	4 %
POLLUX (e18)	NCT02076009	Dara Rd	Rd	45	18	0,44 [0,35; 0,55]	NE	NE	-	49 %	42 %	93 %	76 %	57 %	23 %
TOURMALINE-1 (e19, e20)	NCT01564537	Ixa Rd	Rd	21	15	0,74 [0,59; 0,94]	54	52	0,94 [0,78; 1,13]	40 %	44 %	78 %	72 %	14 %	7 %

Therapieprinzipien:

- Klassenwechsel
- Studien
- Re-Exposition.
- Neue Optionen der Immuntherapie nutzen

(ab erstem Rezidiv verfügbar, geeignetes Zentrum !)

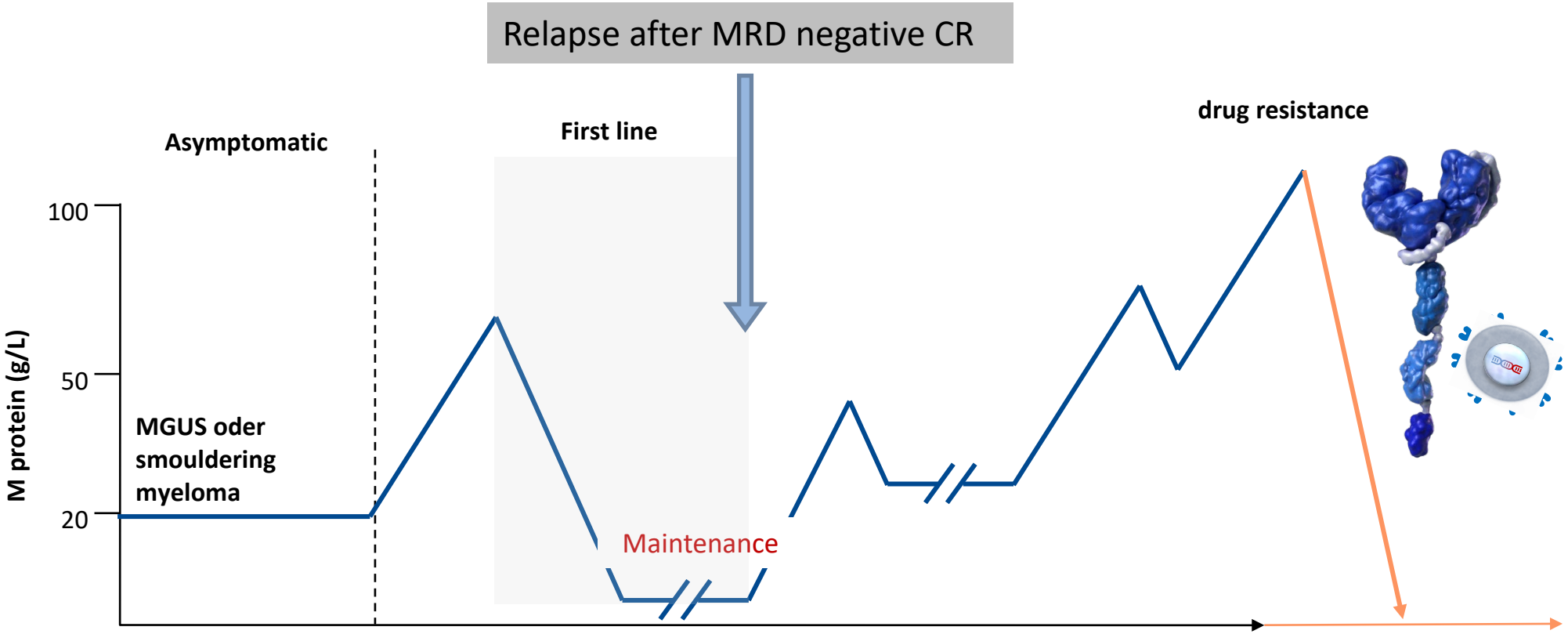
Pomalidomid + (Cyclophosphamid[10] +) Dexamethason (PomCD)

Legende:

[1] *Die Wahl der Arzneimittel richtet sich neben den Zulassungsbedingungen auch nach der Wirksamkeit der Erstlinientherapie und der Verträglichkeit.*

[2] *Anthrazykline, Bendamustin, Cyclophosphamid, Melphalan,*

Der ‘typische Erkrankungsverlauf’ ist Geschichte !



MGUS, monoclonal gammopathy of undetermined significance; M protein, myeloma protein.

Durie BGM. Multiple myeloma: cancer of the bone marrow. Concise review of the disease and treatment options. International Myeloma Foundation; 2017. Available from www.myeloma.org. American Cancer Society. Cancer Facts & Figures; 2008.

Immuntherapie beim Multiplen Myelom

Monoclonal antibodies (mAb)

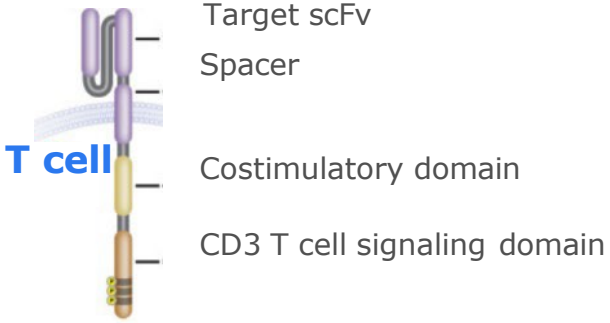
- Daratumumab
- Isatuximab
- Elotuzumab

Antibody-drug conjugate (ADC)

- Belantamab mafodotin

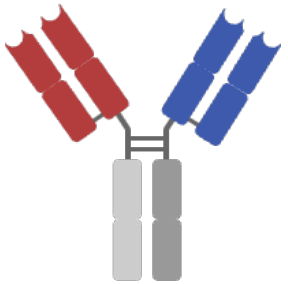
(nicht verfügbar ! Zulassung widerrufen, erneute Zulassung beantragt)

Chimeric antigen receptor T cells (CAR-T)



- Ide-cel
- Cilta-cel

Bispecific antibody



- Teclistamab
- Talquetamab
- Elranatmab

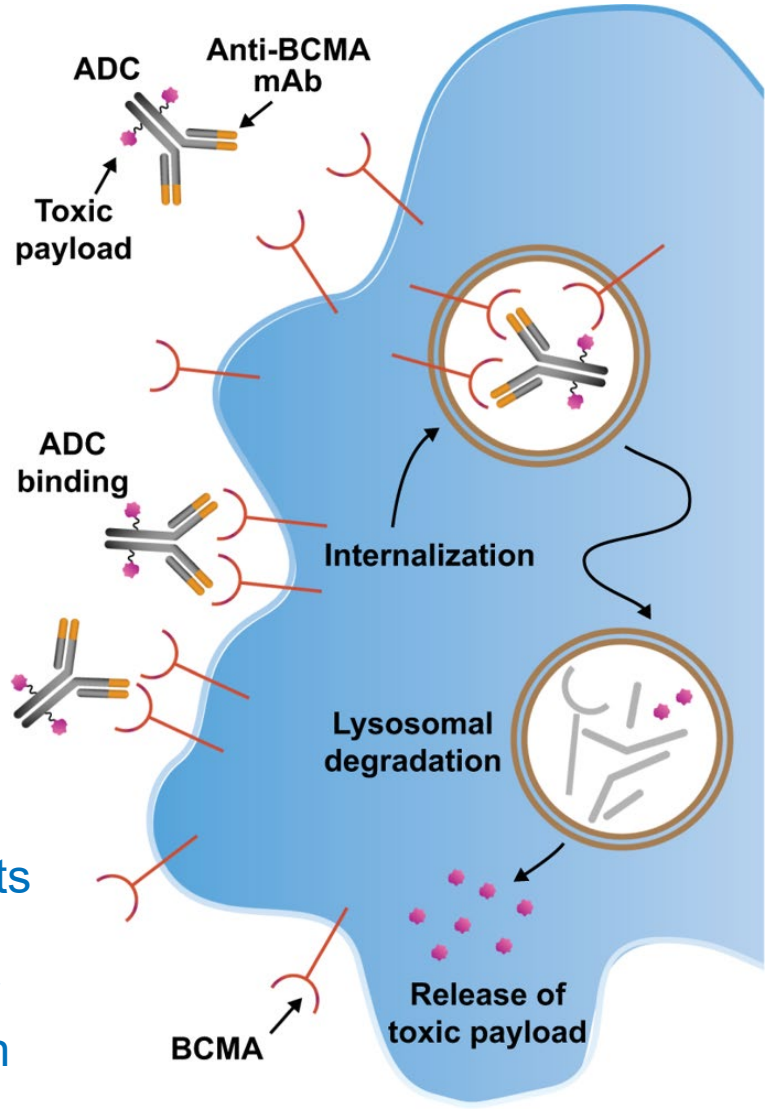
ADC, antibody-drug conjugate; CAR-T, chimeric antigen receptor; CD, cluster of differentiation; mAb, monoclonal antibody; MM, multiple myeloma; scFv, single-chain variable fragment.

1. Castaneda-Puglianini O, Chavez JC. *Drugs Context.* 2021;10:2021-2-4. 2. Cho SF, et al. *Front Immunol.* 2018;9:1821. 3. Shah N, et al. *Leukemia.* 2020;34(4):985-1005; 4. Soekojo CY, et al. *Cells.* 2020;9:601; 5. Tyagarajan *Mol Ther Methods Clin Develop.* 2019;16:136-144.
6. Larson RC, Maus MV. *Nat Rev Cancer.* 2021;21(3):145-161. 7. Radocha J, et al. *Cancers.* 2021;13:1571; 8. Hosny M, et al. *J Clin Med.* 2021;10:4593.

Belantamab war 2020 die erste zugelassene BCMA gerichtete Therapieoption zur Behandlung des MM

GSK2857917 – **Belantamab mafodotin**

- humanisierter IgG1 anti-BCMA Antikörper
- Toxin: Tubulin Polymerisierungs Blocker MMAF
  - ADC Internalisation
  - Lyse des AK und Toxin Freisetzung



- Marktrücknahme im Jahr 2023 - Nicht Erreichen des primären Endpunkts (DREAMM-3: Bela vs Pd).
- Wiederzulassung 2025 erwartet auf Grund positiver Ergebnisse aus der DREAMM-7 (BelaVd vs DVd) und DREAMM-8 (BelaPd vs DPd) Studien

Neue Wirkweise und neues Nebenwirkusspektrum

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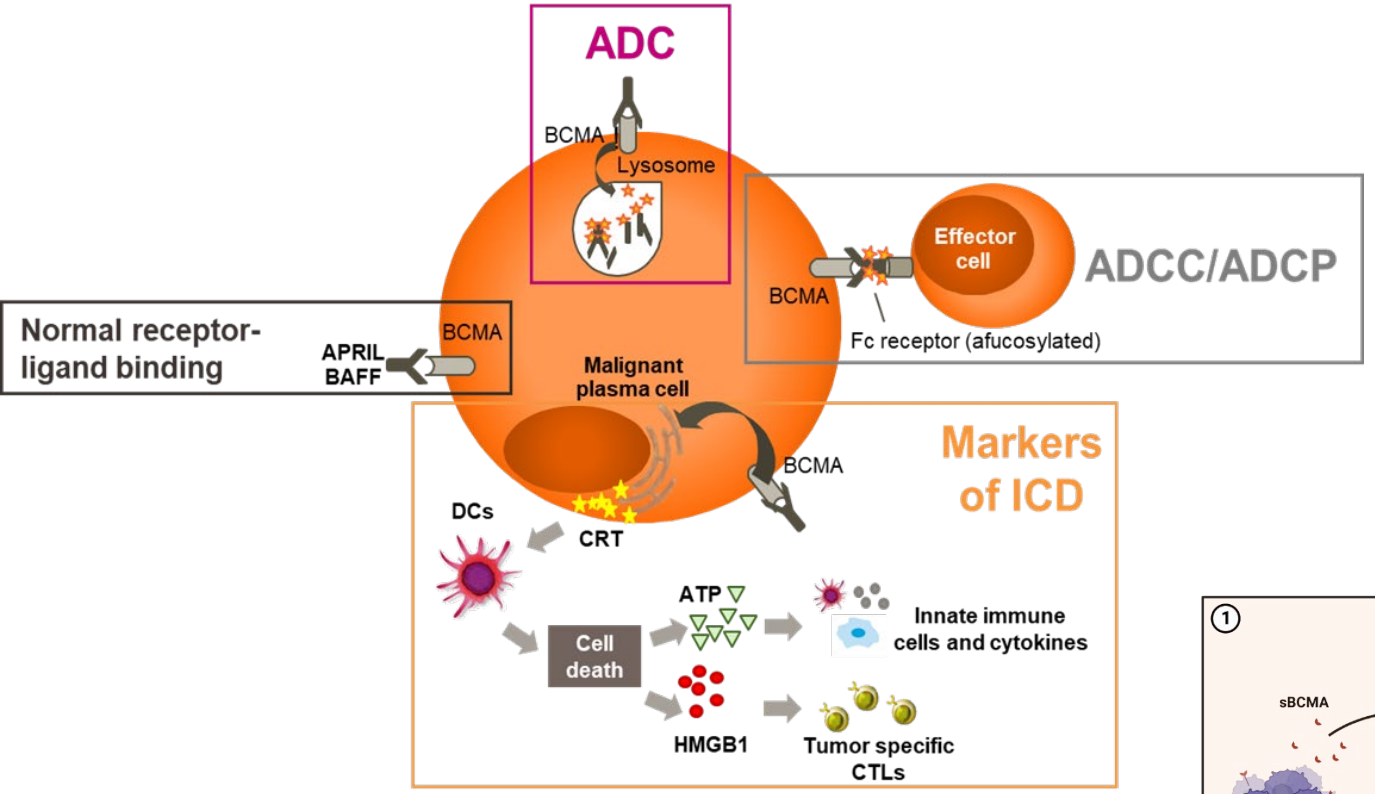
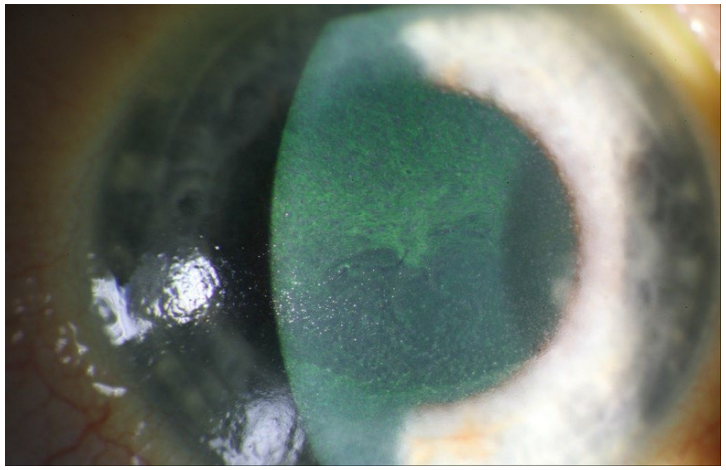
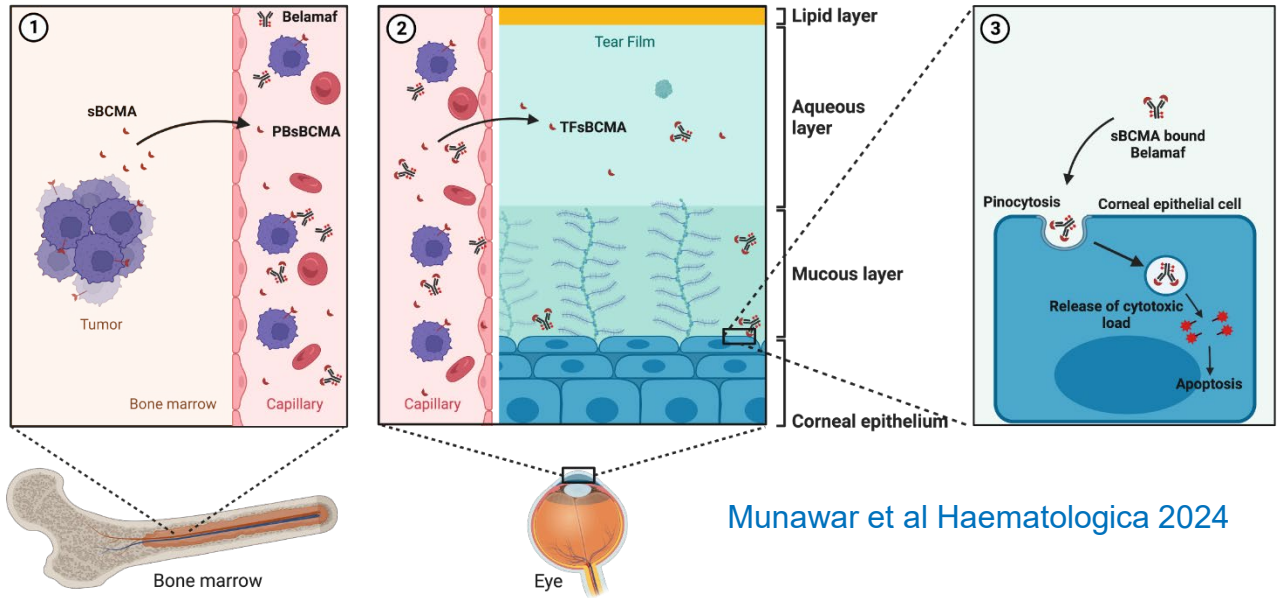




Keratopathie (reversibel) bei >70% der Patienten



Munawar et al Haematologica 2024

Ab 2. Linie: DreaMM- 7 Studie BelaVd vs DVd

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Recruitment period
~13-month from FPI (May 7, 2020) to LPI (June 28, 2021)

Treatment period
Until end of study, withdrawal of consent, disease progression, death or unacceptable toxicity

Follow-up period

Eligibility criteria

- Adults with MM
- ≥1 prior line of MM therapy, and documented PD during or after their most recent therapy
- No prior treatment with anti-BCMA
- Not refractory or intolerant to daratumumab or bortezumib

1:1 Randomization

	Cycle 1-8	Cycle 9+
Arm A (BVd)[1]	**Belantamab mafodotin** IV 2.5 mg/kg Q3W + **Bortezomib** 1.3 mg/m² SC on days 1,4,8, and 11 of cycles 1-8 (21-day cycle) + **Dexamethasone** 20 mg[a] on the day of, and day after bortezomib for cycles 1-8	**Belantamab mafodotin monotherapy** IV 2.5 mg/kg Q3W
Arm B (DVd)[1]	**Daratumumab** IV 16 mg/kg cycles 1-3; Q1W and cycles 4-8; Q3W + **Bortezomib** 1.3 mg/m² SC on days 1,4,8, and 11 of cycles 1-8 (21-day cycle) + **Dexamethasone** 20 mg[a] on the day of, and day after bortezomib for cycles 1-8	**Daratumumab monotherapy** IV 16 mg/kg Q4W

End of treatment visit

Follow-up for PFS Q3W (for patients who discontinue due to reasons other than PD)

Disease assessments Q3W

Follow-up for OS Q12W (for patients who discontinue due to PD, or other reasons)

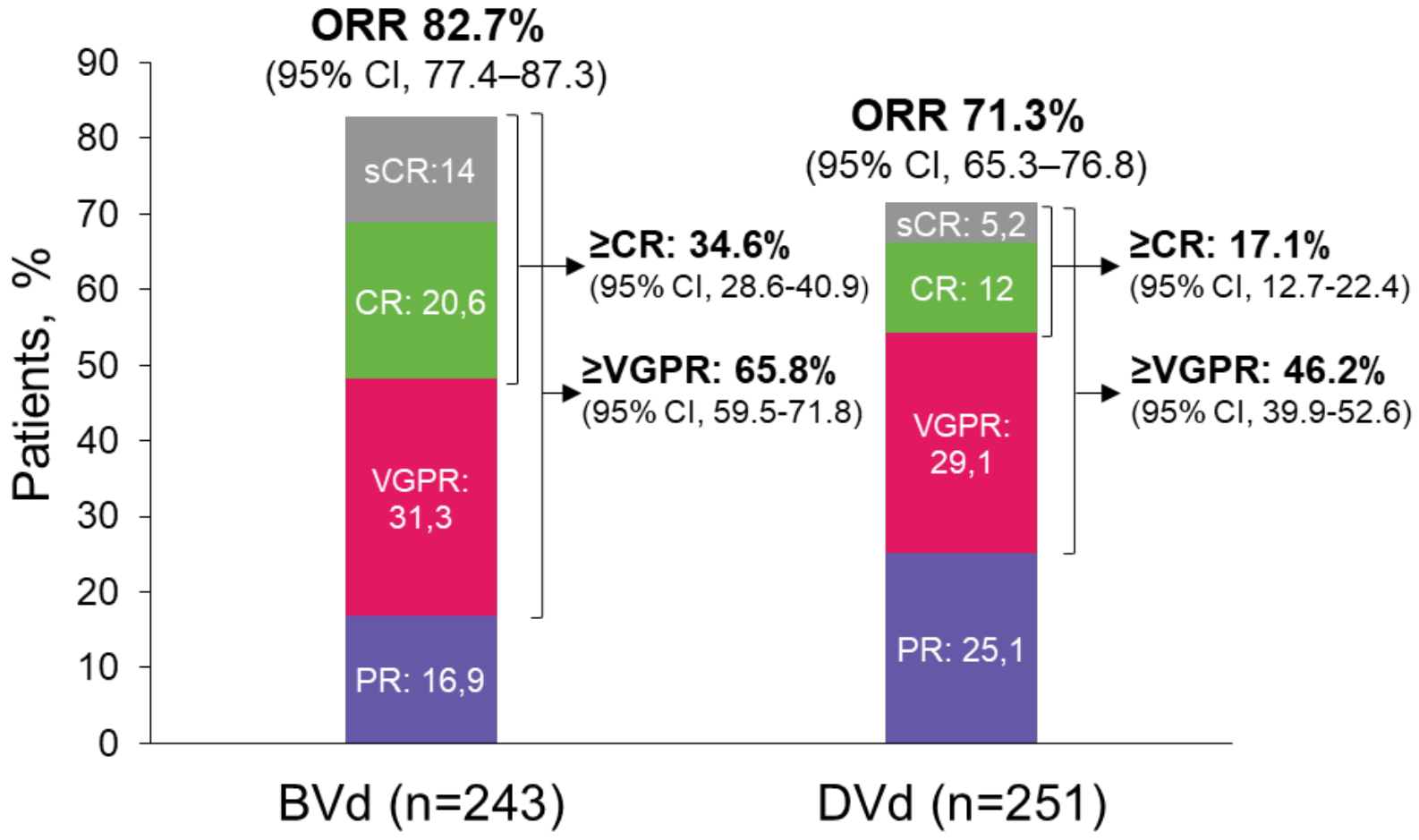
Disease assessment visits: Q3W from cycle 1 day 1 until disease progression

Stratification:
- Prior lines of treatment (1 vs 2 or 3 vs ≥4)
- R-ISS (I vs II/III)
- Prior bortezomib (yes vs no)

- **Primary endpoint:** PFS
- **Key secondary endpoints:** OS, DOR, MRD
- **Additional secondary endpoints:** CRR, ORR, CBR, TTR, TTP, PFS2, AEs, Ocular findings, QOL

[a] Reduce starting dose of dexamethasone to 10 mg for patients >75 years of age, who have a body-mass index <18.5, who had previous unacceptable side effects associated with glucocorticoid therapy, or who are unable to tolerate the starting.
AE, adverse event; BVd, belantamab mafodotin plus Bor/Dex; CBR, clinical benefit rate; CRR, complete response rate; DOR, duration of response; DVd, daratumumab plus Bor/Dex; FPI, first-patient-in; IV, intravenous; LPI, last-patient-in; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; q3w, every 3 weeks; q4w, every 4 weeks; q12w, every 12 weeks; qw, every week; QOL, quality of life; R-ISS, Revised International Staging System; SC, subcutaneous; TTP, time to progression; TTR, time to response.
Mateos MVM et al. Presented at the February American Society of Clinical Oncology Plenary Series. 2024 Abstract 439572.

Gesamtansprechen (ORR)



CR 34.6% vs 17.1%

- MRD Negativität (10-5)
  - 24.7% vs 9.6%
- Infektionen (all)
  - 51.1% vs 55.4%
- Infektionen >= Grad 3
  - 22.5% vs 16.4%
- Okuläre AESIs >=3
  - 34% vs 3%

Medianes PFS 36.6 Monate vs 13.4 Monate

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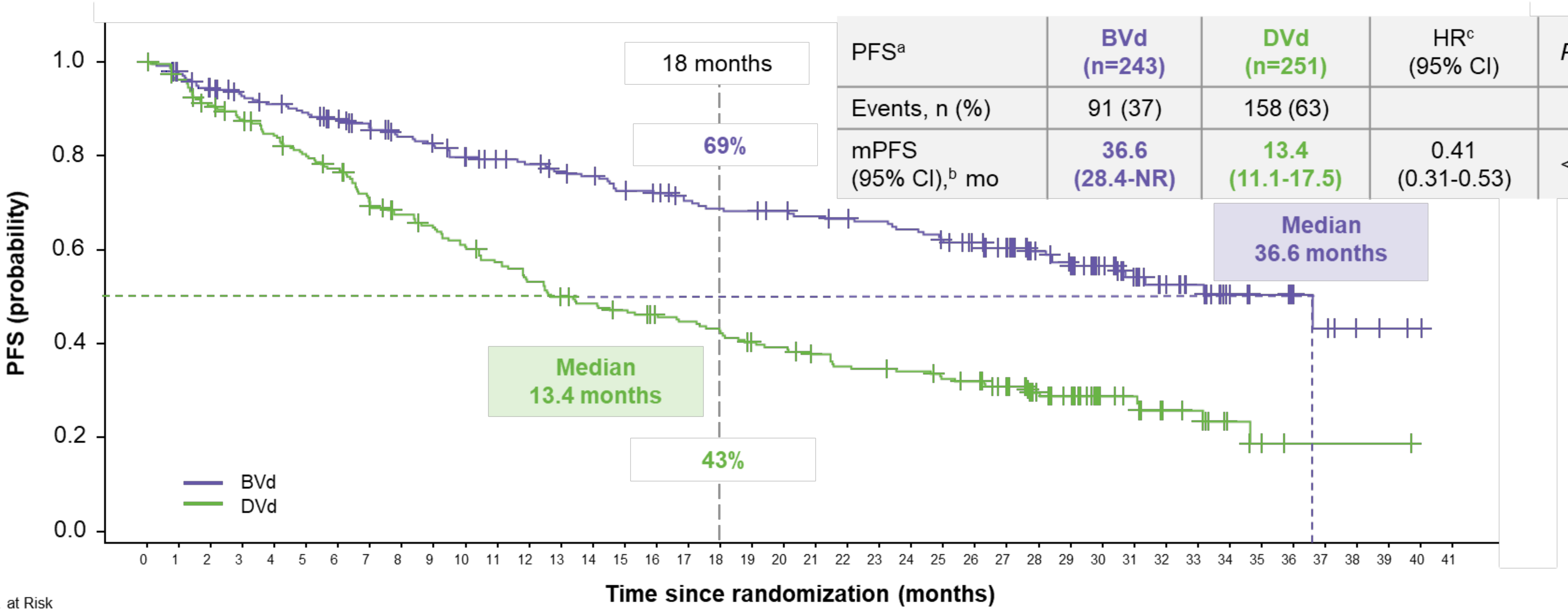


PFS[a]	BVd (n=243)	DVd (n=251)	HR[c] (95% CI)	*P*-value[d]
Events, n (%)	91 (37)	158 (63)		
mPFS (95% CI),[b] mo	36.6 (28.4-NR)	13.4 (11.1-17.5)	0.41 (0.31-0.53)	<.00001

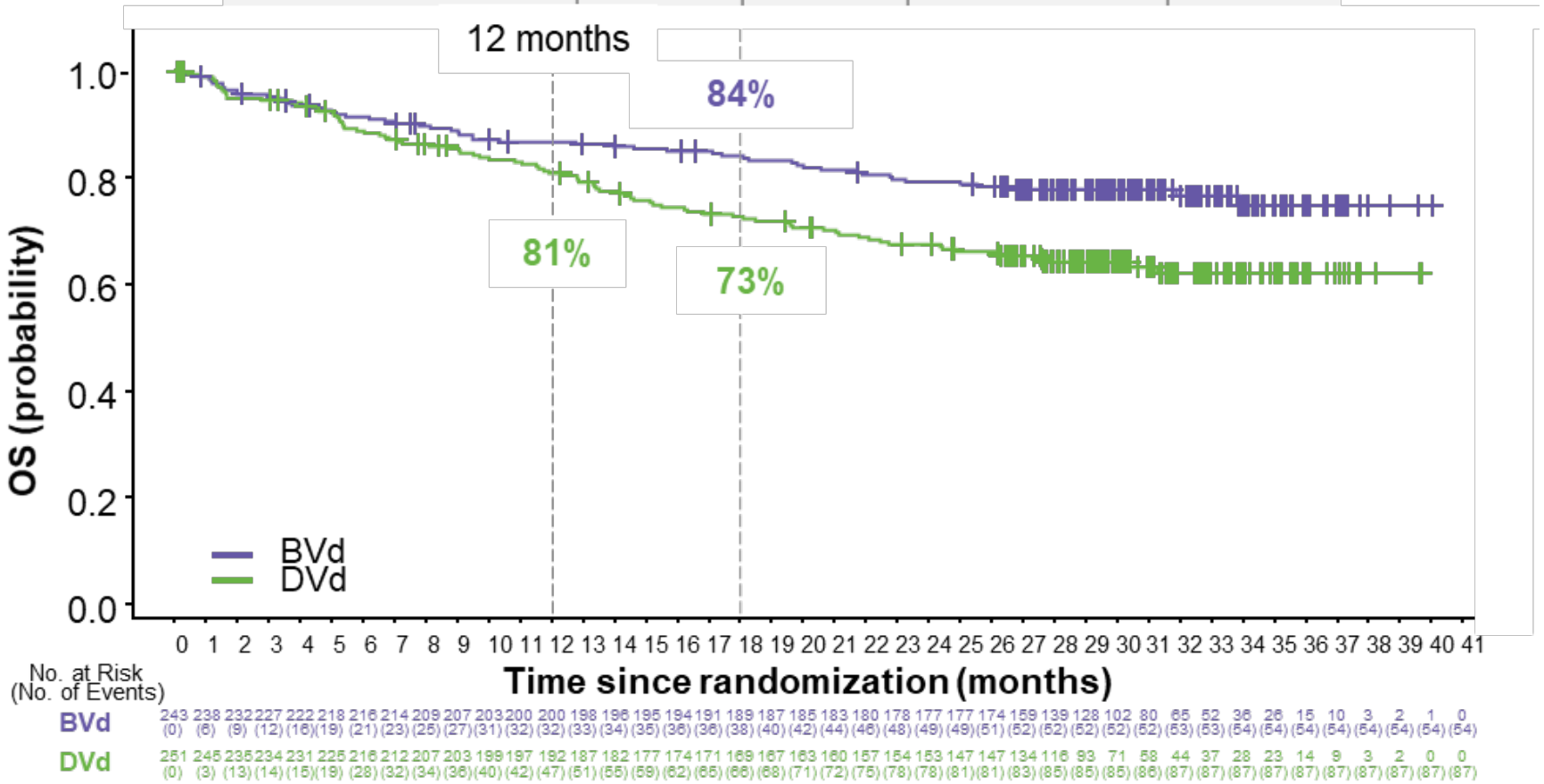
No. at Risk (No. of Events)

Month	BVd	DVd
0	243 (0)	251 (0)
1	230 (6)	230 (9)
2	220 (13)	214 (22)
3	211 (17)	205 (29)
4	205 (21)	194 (37)
5	200 (25)	183 (47)
6	192 (28)	176 (53)
7	183 (32)	155 (71)
8	175 (36)	148 (75)
9	171 (39)	141 (81)
10	163 (45)	132 (90)
11	158 (46)	124 (97)
12	155 (48)	115 (106)
13	150 (51)	107 (113)
14	147 (53)	103 (116)
15	140 (59)	99 (119)
16	137 (60)	94 (121)
17	131 (63)	91 (124)
18	128 (66)	87 (128)
19	127 (67)	80 (133)
20	125 (67)	78 (135)
21	122 (69)	73 (138)
22	120 (70)	68 (143)
23	118 (71)	67 (144)
24	115 (74)	65 (145)
25	110 (78)	61 (148)
26	105 (79)	59 (149)
27	94 (81)	52 (151)
28	79 (82)	39 (153)
29	72 (86)	33 (154)
30	56 (86)	22 (154)
31	41 (88)	19 (154)
32	31 (89)	12 (156)
33	25 (89)	11 (156)
34	15 (90)	5 (157)
35	11 (90)	2 (158)
36	8 (90)	1 (158)
37	6 (91)	1 (158)
38	3 (91)	1 (158)
39	2 (91)	1 (158)
40	1 (91)	0 (158)
41	0 (91)	0 (158)

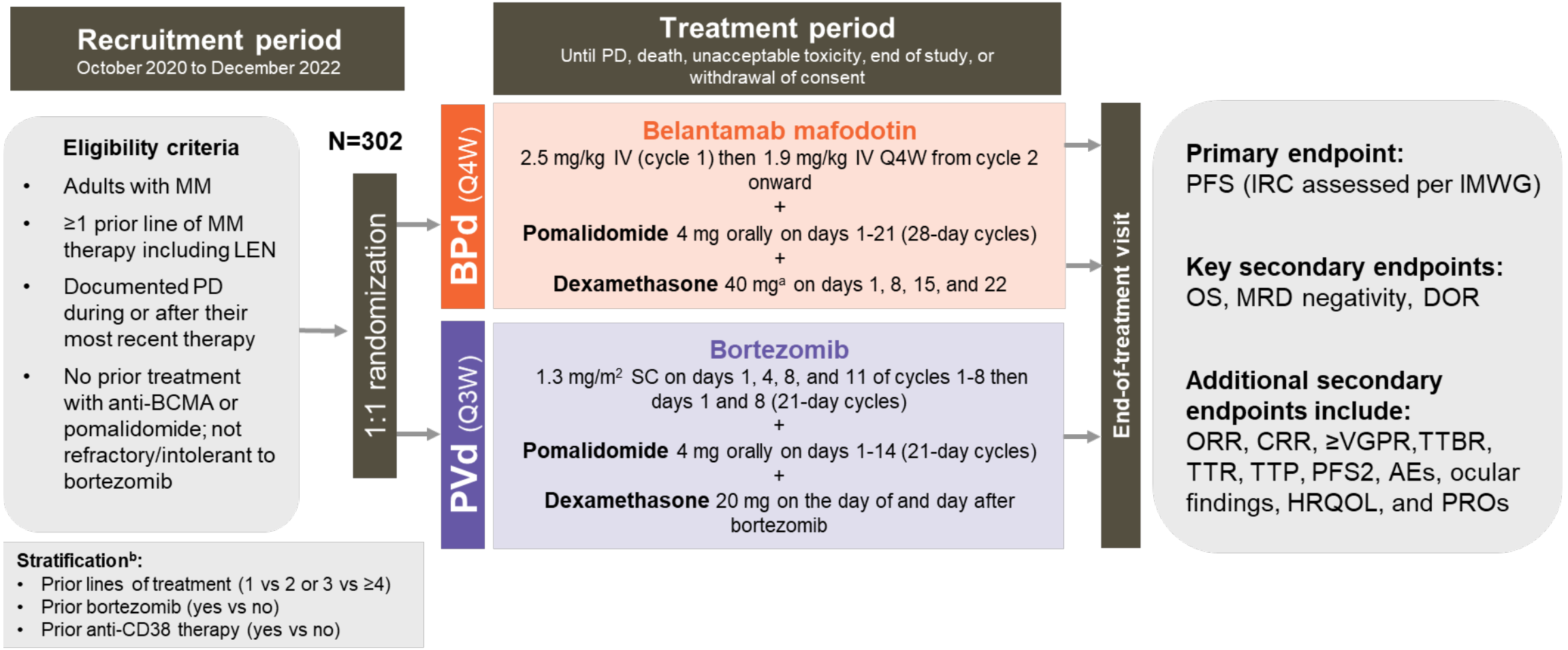
Medianes Gesamtüberleben noch nicht erreicht

Uniklinikum Würzburg

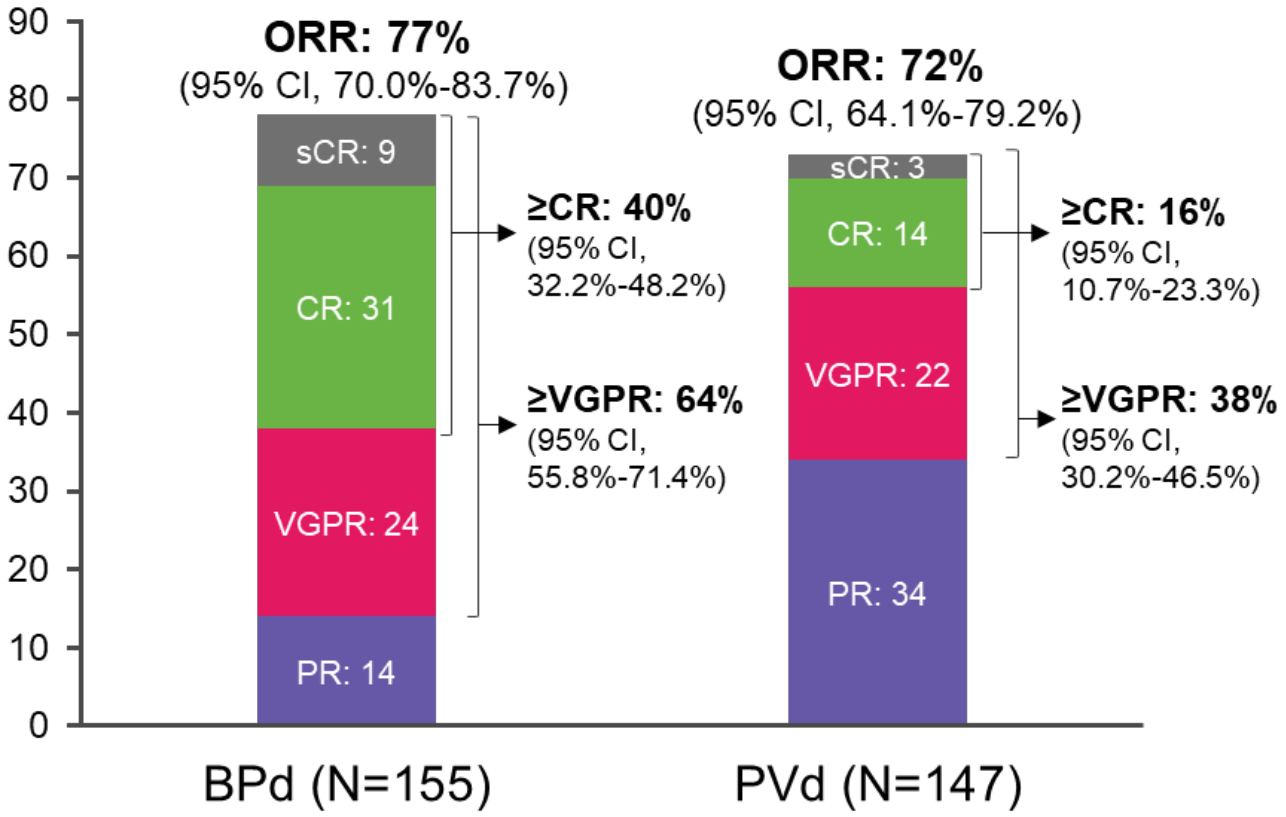
OS[a]	BVd (n=243)	DVd (n=251)	HR[c] (95% CI)	*P*-value[d]
Events, n (%)	54 (22)	87 (35)		
mOS (95% CI),[b] mo	NR	NR	0.57 (0.4-0.8)	.00049[e]



Ab 2. Linie: DreaMM- 8, BelaPd vs DPd



ORR und Sicherheit



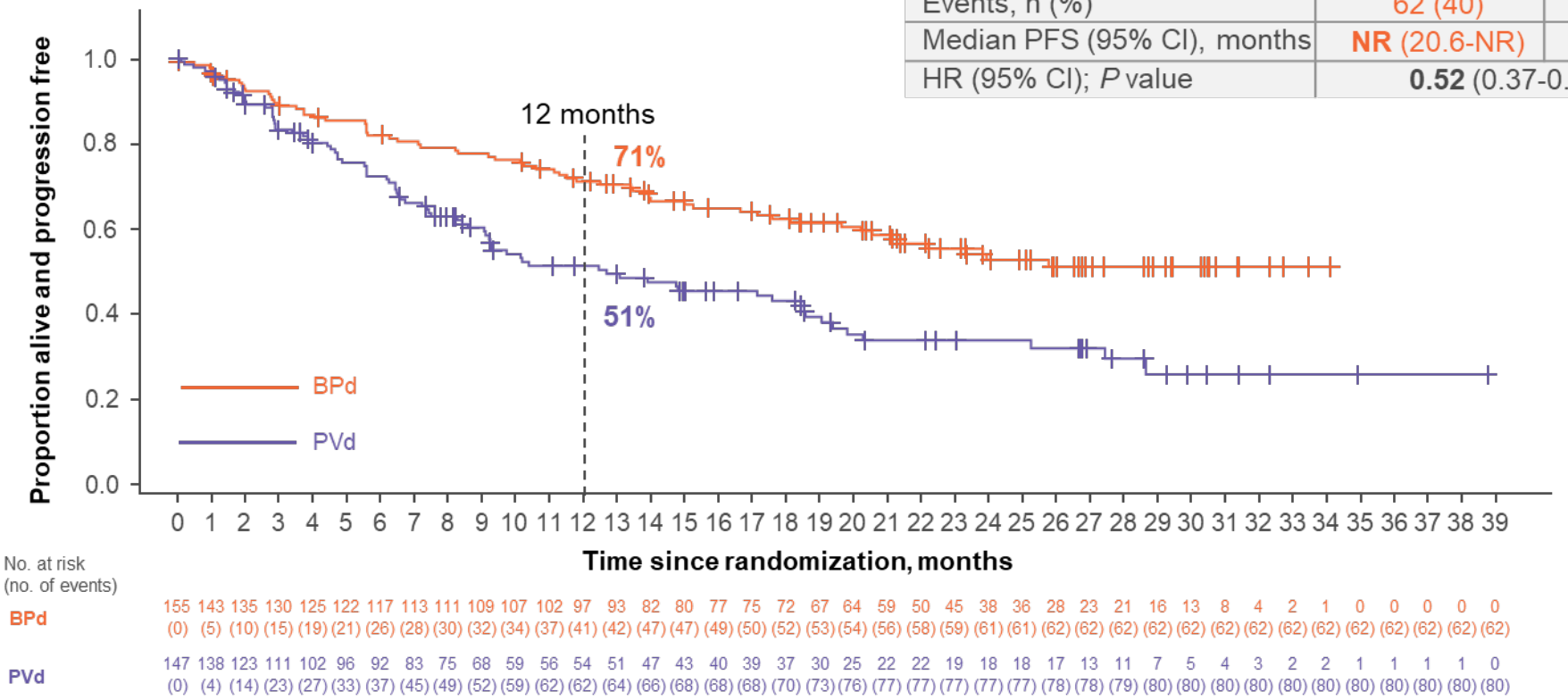
CR 40% vs 16%

- MRD Negativität (10-5)
  - 23.9% vs 4.8%
- Infektionen (all)
  - 82% vs 68%
- Infektionen >= Grad 3
  - 49% vs 26%
- Okuläre AESIs >=3
  - 43% vs 2%

Medianes PFS NR Monate vs 12.7 Monate

Uniklinikum Würzburg

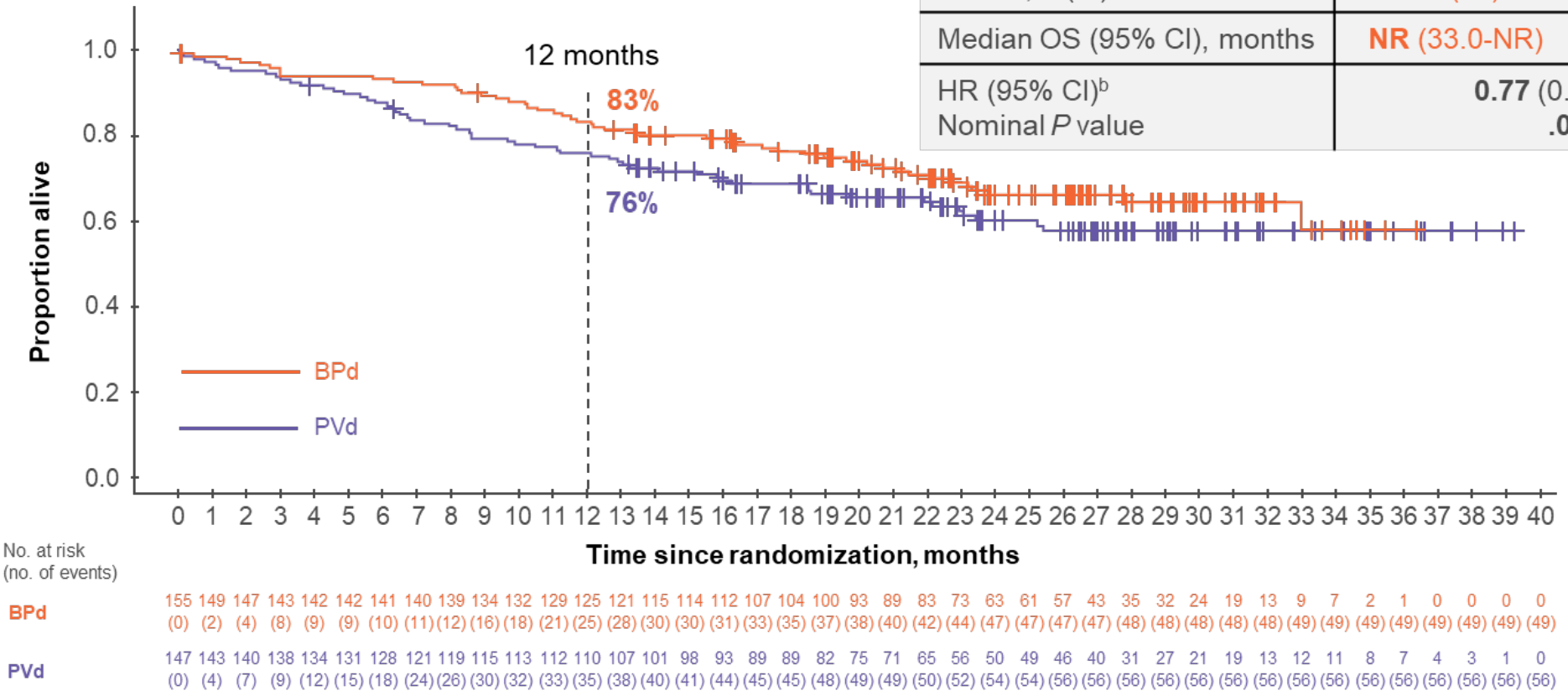
PFS	BPd (N=155)	PVd (N=147)
Events, n (%)	62 (40)	80 (54)
Median PFS (95% CI), months	**NR** (20.6-NR)	**12.7** (9.1-18.5)
HR (95% CI); *P* value	**0.52** (0.37-0.73); **<.001**	



Medianes Gesamtüberleben noch nicht erreicht

Uniklinikum Würzburg

Interim OS	BPd (N=155)	PVd (N=147)
Events, n (%)[a]	49 (32)	56 (38)
Median OS (95% CI), months	**NR** (33.0-NR)	**NR** (25.2-NR)
HR (95% CI)[b] Nominal *P* value	**0.77** (0.53-1.14) **.095**	



Zulassung für 2025 erwartet

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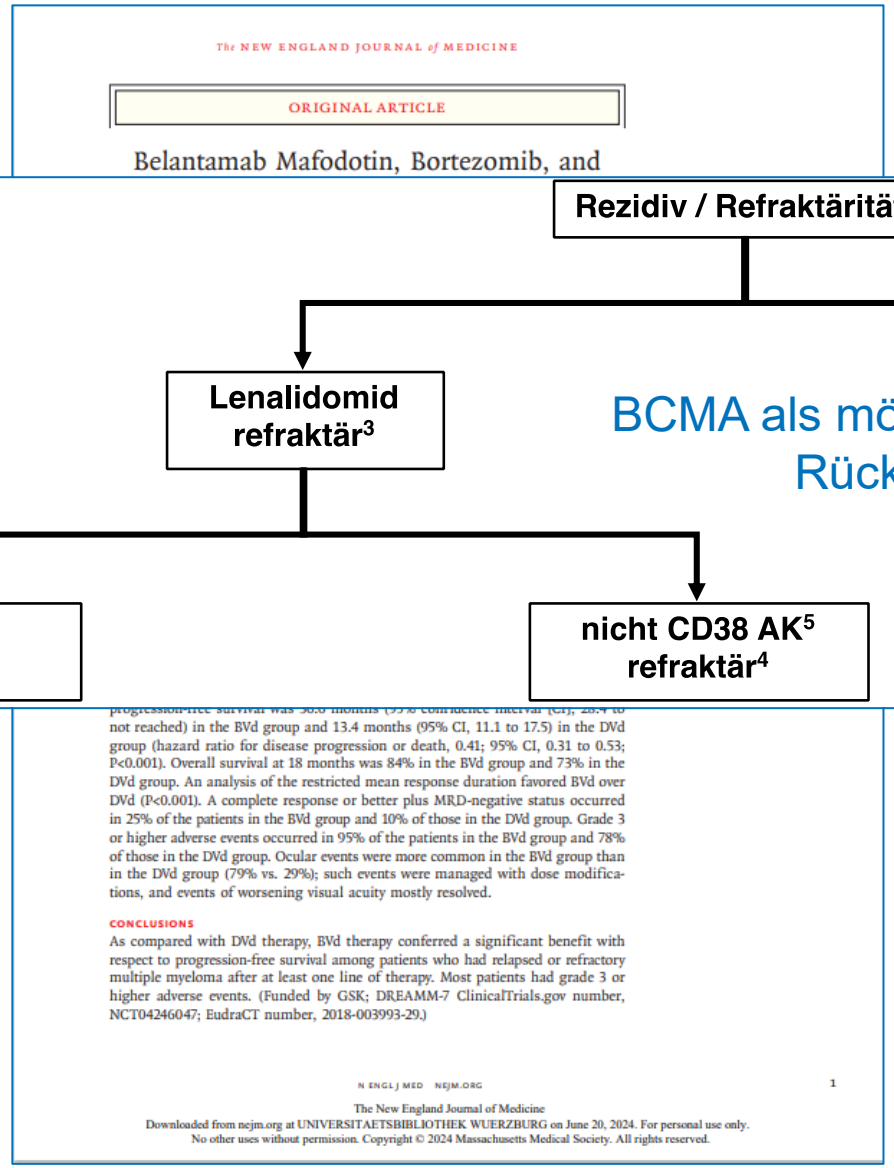
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Belantamab Mafodotin, Bortezomib, and

progression-free survival was 36.6 months (95% confidence interval [CI], 28.4 to not reached) in the BVd group and 13.4 months (95% CI, 11.1 to 17.5) in the DVd group (hazard ratio for disease progression or death, 0.41; 95% CI, 0.31 to 0.53; P<0.001). Overall survival at 18 months was 84% in the BVd group and 73% in the DVd group. An analysis of the restricted mean response duration favored BVd over DVd (P<0.001). A complete response or better plus MRD-negative status occurred in 25% of the patients in the BVd group and 10% of those in the DVd group. Grade 3 or higher adverse events occurred in 95% of the patients in the BVd group and 78% of those in the DVd group. Ocular events were more common in the BVd group than in the DVd group (79% vs. 29%); such events were managed with dose modifications, and events of worsening visual acuity mostly resolved.

CONCLUSIONS

As compared with DVd therapy, BVd therapy conferred a significant benefit with respect to progression-free survival among patients who had relapsed or refractory multiple myeloma after at least one line of therapy. Most patients had grade 3 or higher adverse events. (Funded by GSK; DREAMM-7 ClinicalTrials.gov number, NCT04246047; EudraCT number, 2018-003993-29.)

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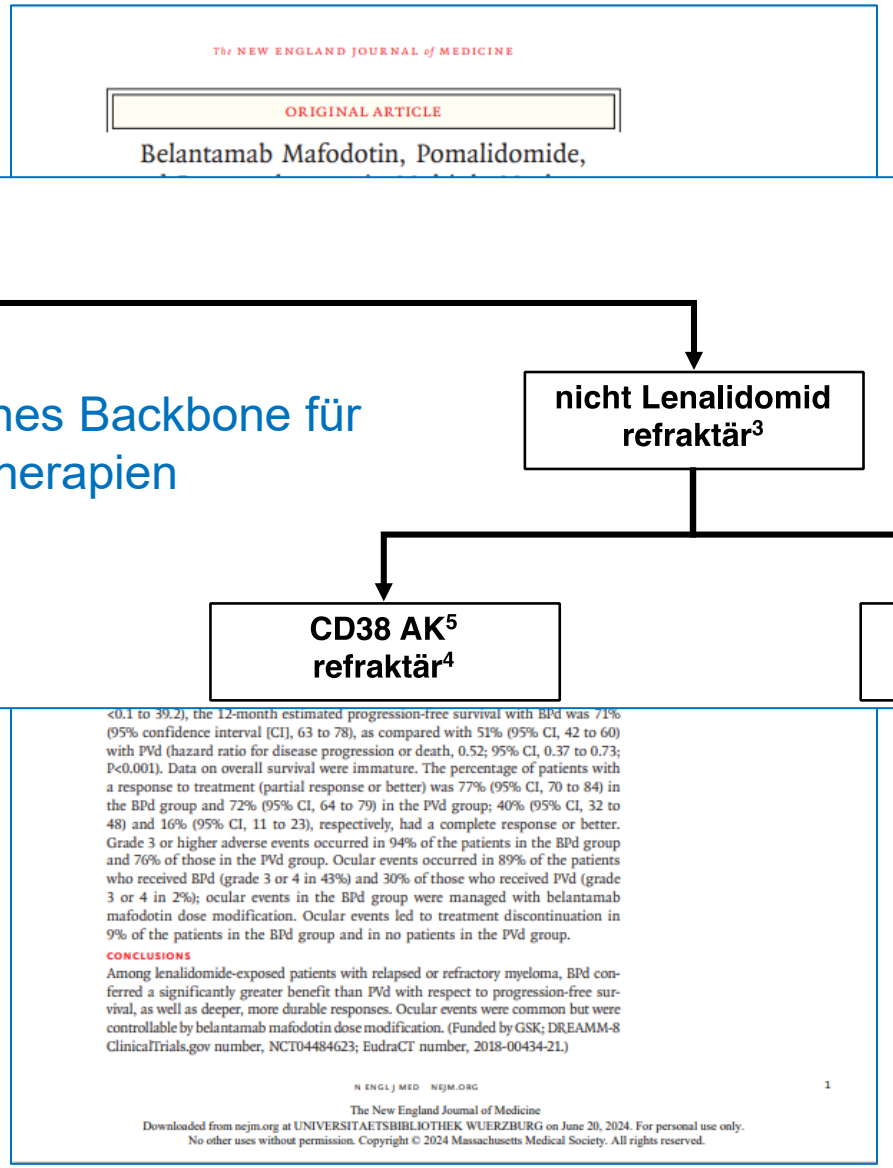

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Belantamab Mafodotin, Pomalidomide,

<0.1 to 39.2), the 12-month estimated progression-free survival with BPd was 71% (95% confidence interval [CI], 63 to 78), as compared with 51% (95% CI, 42 to 60) with PVd (hazard ratio for disease progression or death, 0.52; 95% CI, 0.37 to 0.73; P<0.001). Data on overall survival were immature. The percentage of patients with a response to treatment (partial response or better) was 77% (95% CI, 70 to 84) in the BPd group and 72% (95% CI, 64 to 79) in the PVd group; 40% (95% CI, 32 to 48) and 16% (95% CI, 11 to 23), respectively, had a complete response or better. Grade 3 or higher adverse events occurred in 94% of the patients in the BPd group and 76% of those in the PVd group. Ocular events occurred in 89% of the patients who received BPd (grade 3 or 4 in 43%) and 30% of those who received PVd (grade 3 or 4 in 2%); ocular events in the BPd group were managed with belantamab mafodotin dose modification. Ocular events led to treatment discontinuation in 9% of the patients in the BPd group and in no patients in the PVd group.

CONCLUSIONS

Among lenalidomide-exposed patients with relapsed or refractory myeloma, BPd conferred a significantly greater benefit than PVd with respect to progression-free survival, as well as deeper, more durable responses. Ocular events were common but were controllable by belantamab mafodotin dose modification. (Funded by GSK; DREAMM-8 ClinicalTrials.gov number, NCT04484623; EudraCT number, 2018-00434-21.)

N ENGL J MED NEJM.ORG 1

Rezidiv / Refraktärität[1]

Lenalidomid refraktär[3]

nicht Lenalidomid refraktär[3]

CD38 AK[5] refraktär[4]

nicht CD38 AK[5] refraktär[4]

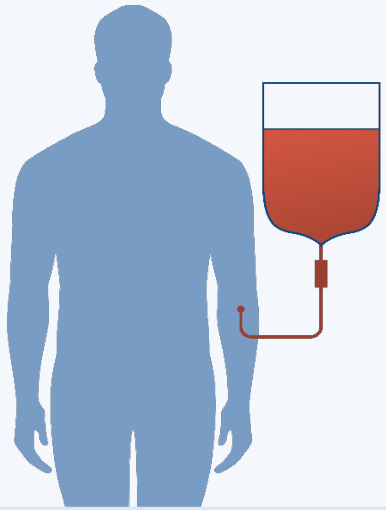
CD38 AK[5] refraktär[4]

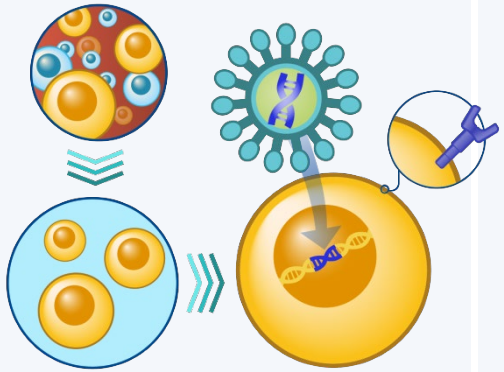
nicht CD38 AK[5] refraktär[4]

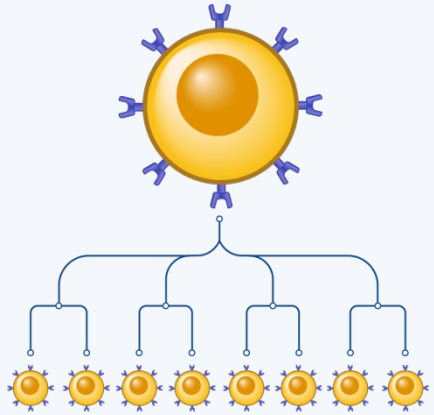
BCMA als mögliches Backbone für Rückfalltherapien

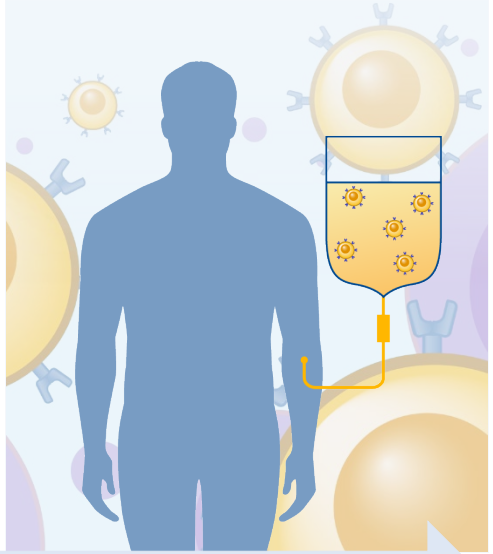
CAR-T-Zelltherapie: Herstellung und Therapieablauf

LEUKAPHERESE	CAR-T-HERSTELLUNG	CAR-T-EXPANSION	CAR-T-INFUSION	MONITORING
Im Klinikzentrum	In hochspezialisierten Zentren		Im Klinikzentrum	
T-Zellen aus peripherem Blut werden per Leukapherese entnommen und zum Hersteller transportiert.	T-Zellen werden isoliert, aktiviert und expandiert. Das genetische Material für CAR wird durch viralen Gentransfer in die T-Zellen stabil eingeschleust.	CAR-T-Zellen werden bis zur therapeutischen Dosis expandiert, formuliert und kryokonserviert. Nach QC/QA Check und Freigabe erfolgt der Transport zurück zum Behandlungszentrum.	CAR-T-Zellen werden dem Patienten nach Lymphodepletion infundiert.	Es erfolgt ein stationäres oder ambulantes Monitoring nach der Infusion der CAR-T-Zellen.









Dauer ca. 4-5 Wochen[1]

QC, Qualitätsmanagement; QA, Quality Assurance; [1]Abecma® aktuelle Fachinformation

CAR-T Zell Therapie in frühen Linien zugelassen

- Cilta-cel: Zugelassen im ersten Rückfall für
  - PI und IMid vorbehandelte, Len refraktäre Patienten mit Progression auf die letzte Therapie
- Ide-cel: Zugelassen im zweiten Rezidiv
  - IMiD, PI und CD38 moAB vorbehandelte Patienten mit Progression auf die letzte Therapie

	Approved CAR-T cells		Academic	Alternative manufacturing	Human scFv		Allo-CAR	GPRC5D	
	Ide-cel KarMMa[1] (n = 128)	Cilta-cel CARTITUDE-1 (n = 97) [2,3]	ARI0002h[4] (n = 30)	P-BCMA-101 PRIME[5,6] (n = 53)	CT053[6] LUMMICAR (n = 24)	CT103A[7] (n= 79)	ALLO-715 UNIVERSAL[8] (n = 43)	MCARH 109[9] (n= 17)	OriCAR -017[90] (n= 13)
Specificity	Auto	Auto	Auto		Auto	Auto		Auto	Auto
ORR, %	81	98	100	67	87	95	71	71	100
CR/sCR, %	39	82	63	NA	NA	68	25	25	60
PFS	12.2 m	34.9 m	53%@18 m	NR	NR	NR	NR	NR	NR

*There, are no head-to-head comparisons of these data and naïve comparison should be conducted with caution
BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; EMD, extramedullary disease; HR cytog, high-risk cytogenetics; NA, not available; NR, not reached/not reported; ScFv, single-chain variable fragment; TCR, T-cell receptor; triple-R, triple-class refractory

Accelerated approval

1. Anderson L et al. ASCO 2021;abstract;8016 (poster presentation); 2. Berdeja J et al. Lancet 2021;398;314-24; 3. Lin Y et al. EHA 2022;abstract P961 (poster presentation); 4. Fernández de Larrea C, et al. EHA 2022;abstract S103 (oral presentation); 5. Costello C, et al. ASH 2020;abstract 134; 6. Mohyuddin GR et al. Blood Adv 2021;5(4):1097-1101; 7. Li C et al. EHA 2022;abstract S187 (oral presentation); 7. Li C, et al. ASH 2021;abstract 143; 8. Mailankody S, et al. ASH 2021;abstract 651; 9. Mailankody S, et al NEJM 2022. 10. Zhang et al Lancet Hematology 2023

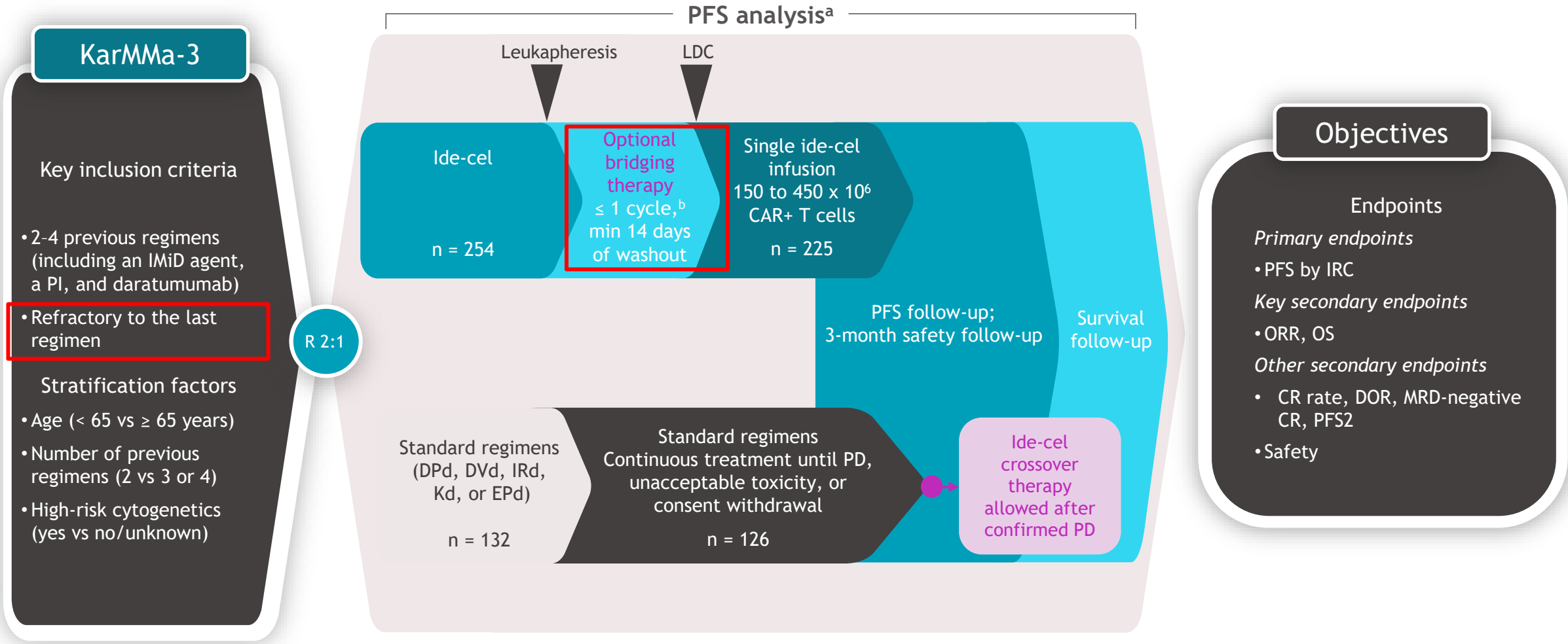
Idecabtagene vicleucel versus standard regimens in patients with triple-class–exposed relapsed and refractory multiple myeloma: updated analysis from KarMMa-3

Paula Rodríguez-Otero,[1] Sikander Ailawadhi,[2] Bertrand Arnulf,[3] Krina K. Patel,[4] Michele Cavo,[5] Ajay K. Nooka,[6] Salomon Manier,[7] Natalie Callander,[8] Luciano J. Costa,[9] Ravi Vij,[10] Nizar J. Bahlis,[11] Philippe Moreau,[12] Scott Solomon,[13] Ingerid Weum Abrahamsen,[14] Rachid Baz,[15] Annemiek Broijl,[16] Christine Chen,[17] Sundar Jagannath,[18] Noopur Raje,[19] Christof Scheid,[20] Michel Delforge,[21] Reuben Benjamin,[22] Thomas Pabst,[23] Shinsuke Iida,[24] Jesus Berdeja,[25] Anna Truppel-Hartmann,[26] Rashmi Bhatnagar,[27] Fan Wu,[28] Julia Piasecki,[28] Laurie Eliason,[28] Devender Dhanda,[28] Jasper Felten,[29] Andrea Caia,[29] Mark Cook,[29] Mihaela Popa McKiver,[28] Sergio Giralt[30]

[1]Clínica Universidad de Navarra, Pamplona, Spain; [2]Mayo Clinic, Jacksonville, FL, USA; [3]Hôpital Saint-Louis, Paris, APHP, Université Paris cite, France; [4]MD Anderson Cancer Center, University of Texas, Houston, TX, USA; [5]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Seràgnoli Institute of Hematology, Bologna University School of Medicine, Bologna, Italy; [6]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [7]CHU Lille, Université de Lille, Lille, France; [8]Univeristy of Wisconsin Carbone Cancer Center, Madison, WI, USA; [9]University of Alabama at Birmingham, Birmingham, AL, USA; [10]Washington University School of Medicine in St. Louis, Saint Louis, MO, USA; [11]Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, AB, Canada; [12]University Hospital of Nantes, Nantes, France; [13]Northside Hospital Cancer Institute, Atlanta, GA, USA; [14]Oslo University Hospital, Oslo, Norway; [15]Moffitt Cancer Center, Tampa, FL, USA; [16]Erasmus MC Cancer Institute, Rotterdam, The Netherlands; [17]Princess Margaret Hospital, Toronto, ON, Canada; [18]Mount Sinai Medical Center, New York, NY, USA; [19]Massachusetts General Hospital, Boston, MA, USA; [20]University of Cologne, Cologne, Germany; [21]Universitaire Ziekenhuizen Leuven, Leuven, Belgium; [22]Kings College Hospital, London, UK; [23]Bern University Hospital, Bern, Switzerland[24]Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; [25]Sarah Cannon Research Institute, Nashville, TN, USA; [26]2seventy bio, Cambridge, MA, USA; [27]Syneos Health, Haryana, India; [28]Bristol Myers Squibb, Princeton, NJ, USA; [29]Bristol Myers Squibb, Boudry, Switzerland; [30]Memorial Sloan Kettering Cancer Center, New York, NY, USA

ASH 2023, Abstract number 1028

KarMMa-3 Studiendesign (NCT03651128)



Rodríguez-Otero, ASH 2023

Baseline characteristics

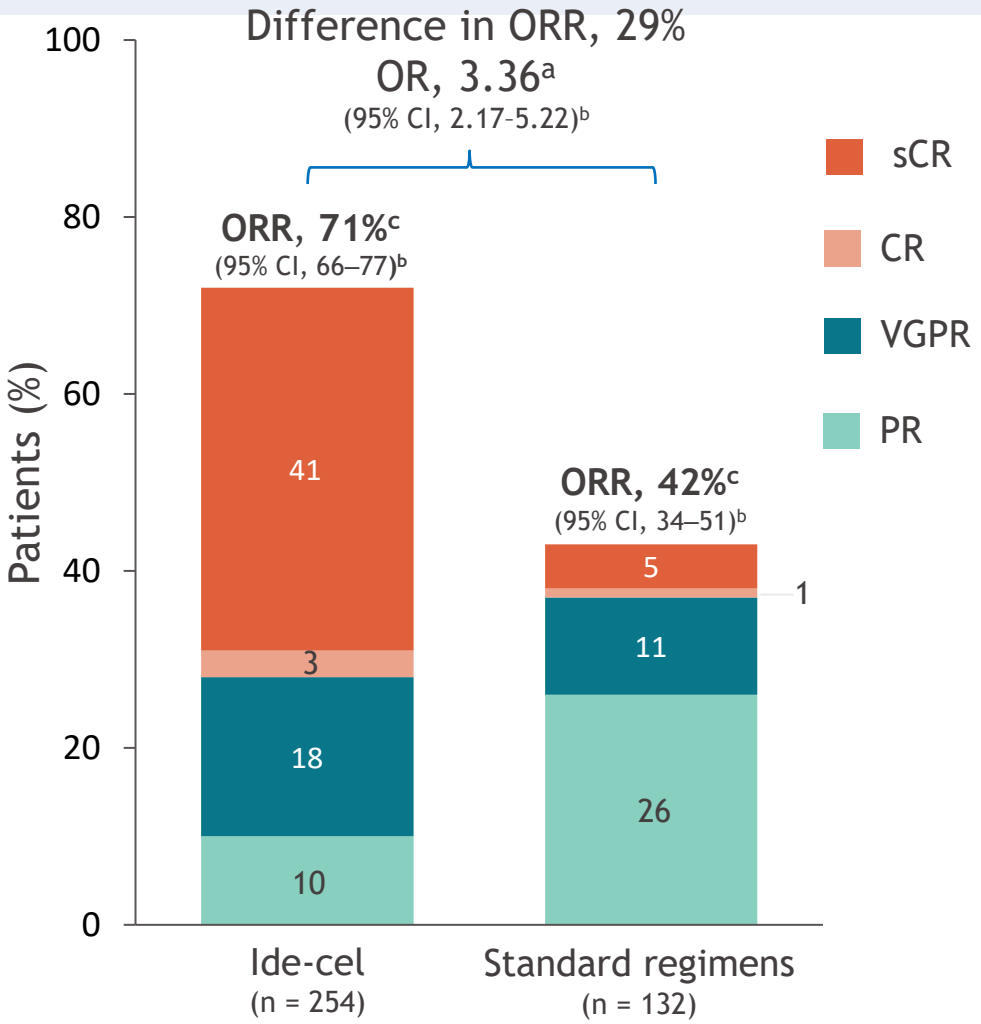
Characteristic	Ide-cel (n = 254)	Standard regimens (n = 132)
Median (range) age, years	63 (30-81)	63 (42-83)
Median (range) time from diagnosis to screening, years	4.1 (0.6-21.8)	4.0 (0.7-17.7)
Previous autologous HSCT	214 (84)	114 (86)
R-ISS disease stage		
I	50 (20)	26 (20)
II	150 (59)	82 (62)
III	31 (12)	14 (11)
EMP	61 (24)	32 (24)
High tumor burden[a]	71 (28)	34 (26)
High-risk cytogenetics[b]	166 (65)	82 (62)
del(17p)	66 (26)	42 (32)
t(4;14)	43 (17)	18 (14)
t(14;16)	8 (3)	4 (3)
1q gain/amplification	124 (49)	51 (39)
Ultra-high-risk cytogenetics[c]	67 (26)	29 (22)
Median (range) time to progression on last prior antimyeloma therapy, months	7.1 (0.7-67.7)	6.9 (0.4-66.0)
Daratumumab refractory	242 (95)	123 (93)
Triple-class-refractory[d]	164 (65)	89 (67)

Baseline characteristics were generally balanced between treatment arms

Overall, 66% of patients had TCR RRMM and 95% were refractory to daratumumab, indicating a difficult-to-treat patient population

Rodríguez-Otero, ASH 2023

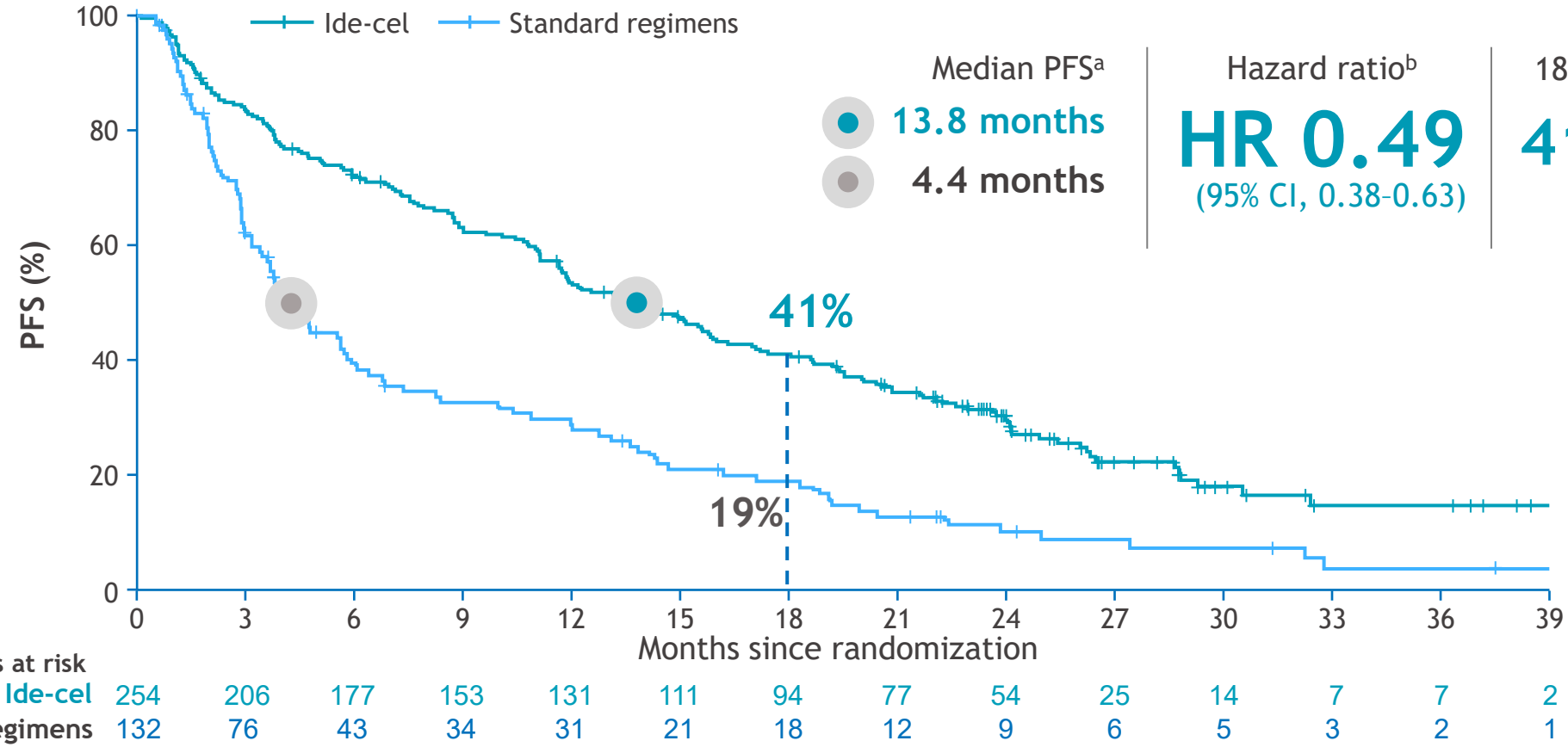
Update ASH 2023: Tiefes und dauerhaftes Ansprechen unter Ide-cel,



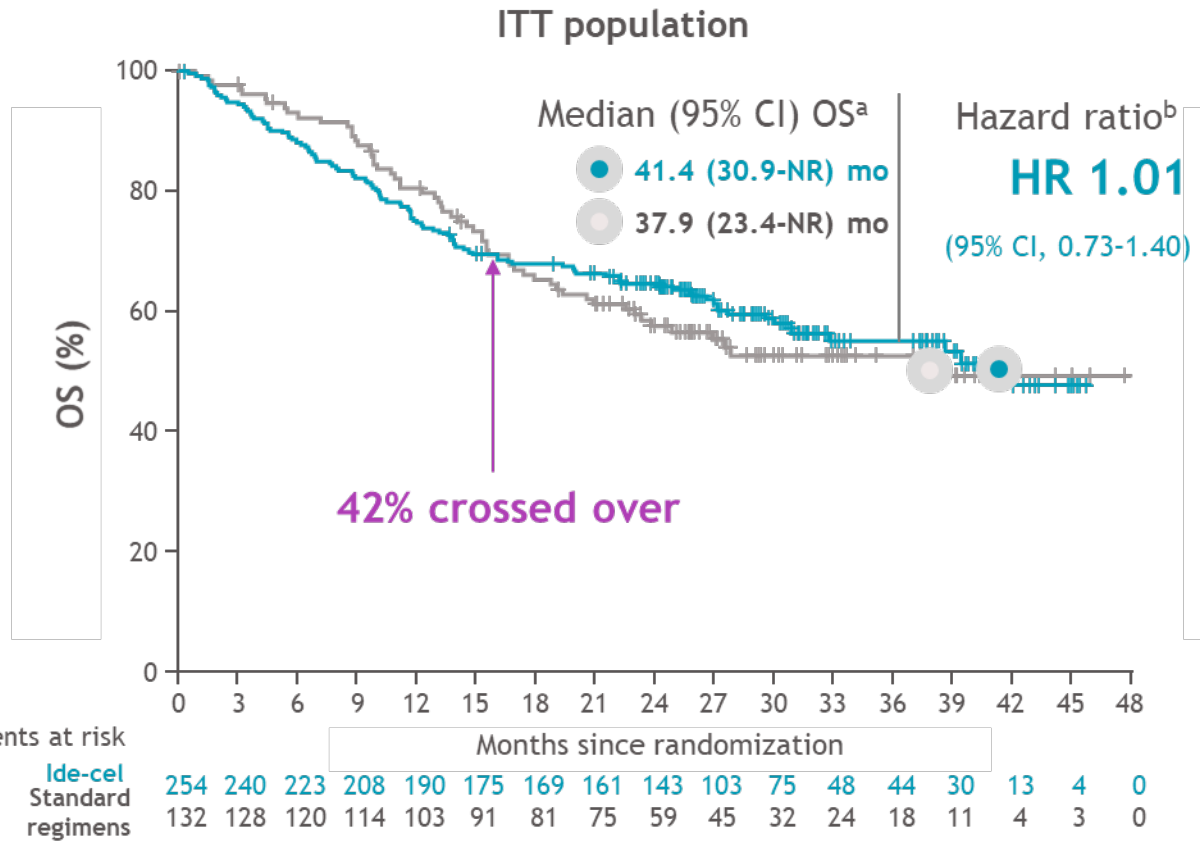
Secondary endpoint	Ide-cel (n = 254)	Standard regimens (n = 132)
CR rate (95 % CI), %[d] increased by 5% from the interim analysis.	44 (38–50)	5 (2–9)
MRD-negative CR rate, n/N (%) (95% CI)[e]	57/163 (35) (28–42)	1/54 (2) (0–5)
Median (95% CI) DOR, months	16.6 (12.1–19.6)	9.7 (5.5–16.1)
Median PFS2, months	23.5	16.7
HR (95% CI)	0.79 (0.60–1.04)	

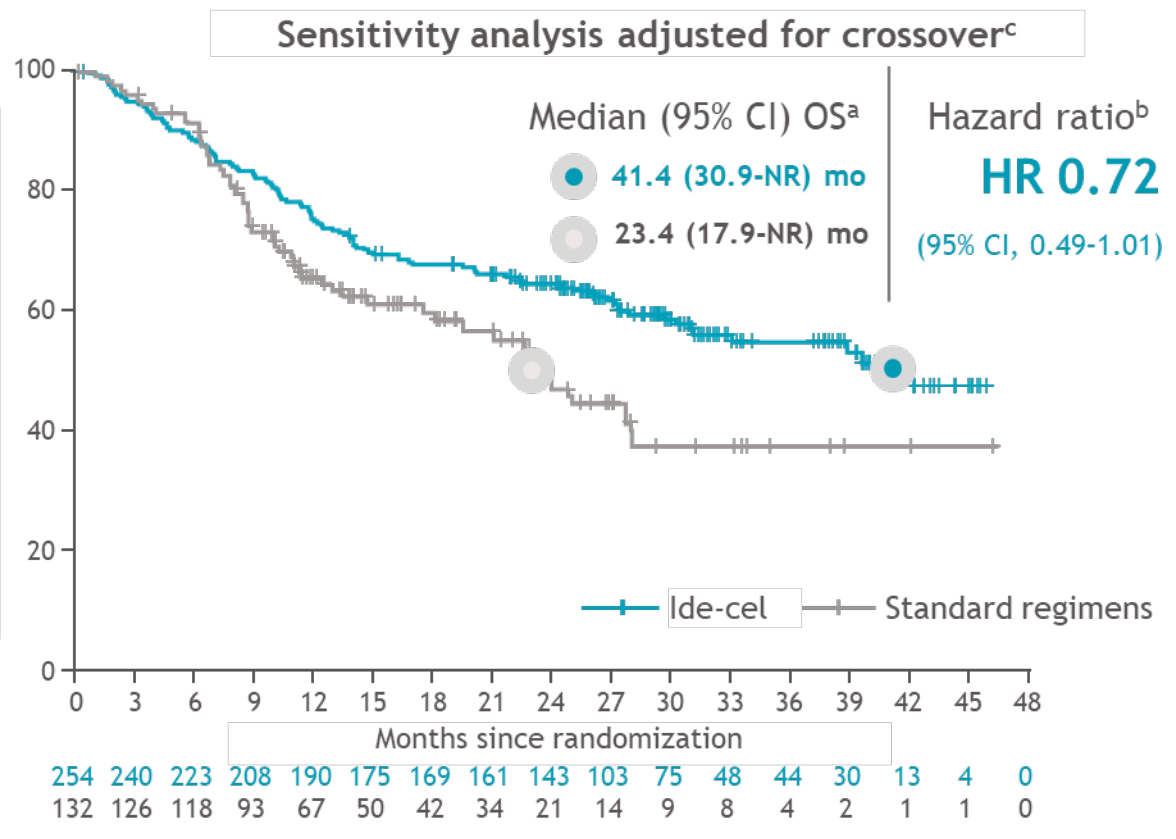
Signifikanter PFS Benefit mit, 51% Risikoreduktion für Progress oder Tod

median follow-up of 30.9 months (range: 12.7-47.8)



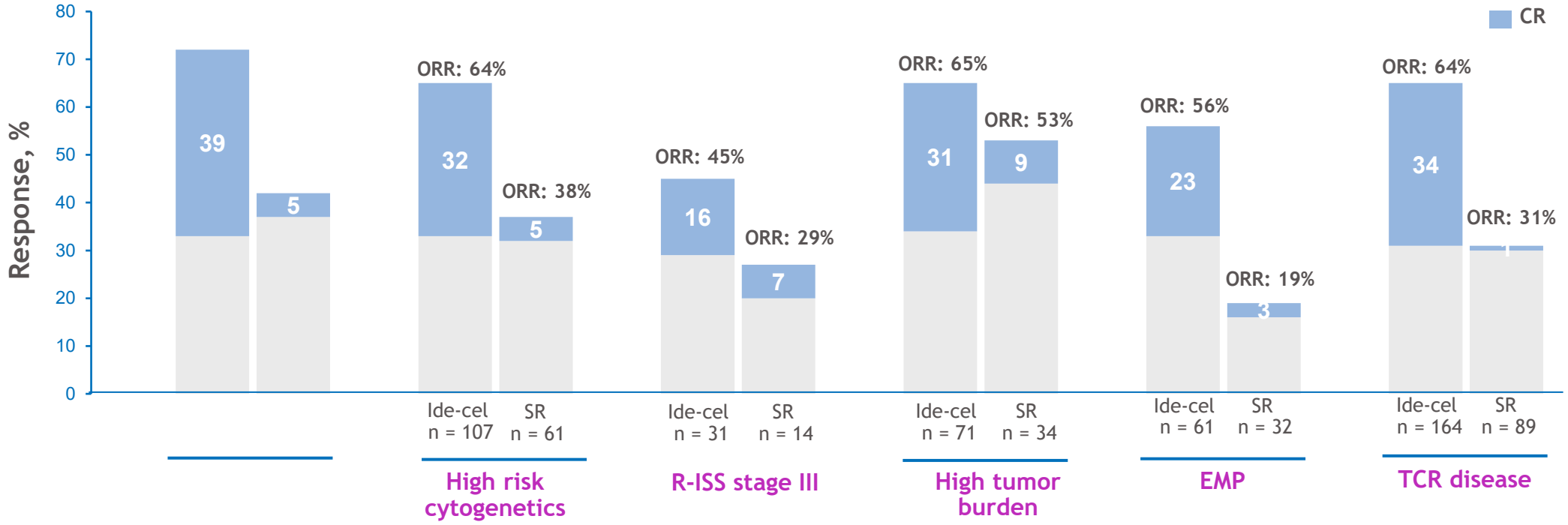
Cross-over zu ide-cel nach Progress im Standard Arm





>50% der Patienten im Standard Arm erhielten Ide-cel als nachfolgende Therapie (nach PD), die Mehrheit innerhalb 3-16 Monate nach Randsomisierung

Ansprechen bei Hochrisiko Myelom



mPFS[a]	**13.3**	4.4	**11.9**	4.2	**5.2**	3.0	**11.0**	4.9	**7.2**	2.0	**11.2**	3.5
HR[b]	0.49		0.61		0.86		0.60		0.40		0.46	

Treated population, n (%)	Ide-cel (n = 225)	Standard regimens (n = 126)
Any-grade AE	225 (100)	124 (98)
Serious AE	105 (47)	52 (41)
ITT population, n (%)	**Ide-cel (n = 254)**	**Standard regimens (n = 132)**
Overall deaths	106 (42)	58 (44)
Cause of death		
Disease progression	64 (25)	37 (28)
AEs	17 (7)	8 (6)
Other causes	23 (9)	12 (9)
SPMs[a]	2 (1)	1 (1)

Treated population, n (%)	Ide-cel (n = 225)
CRS[b]	
Any grade	197 (88)
Grade 3/4	9 (4)
iiNT[c]	
Any grade	34 (15)
Grade 3/4	7 (3)
Infections	
Any grade	125 (56)
Grade 3/4	50 (22)

ide-cel safety profile remained consistent :

- No new CRS or iiNT events with ide-cel since the interim analysis and no parkinsonism or Guillain-Barré syndrome reported in KarMMa-3
- No SPMs of T-cell origin in the ide-cel arm
- No new safety signals

[a]Deaths due to SPMs in the ide-cel arm were leukemia (n = 1) and pancreatic adenocarcinoma (n = 1); death due to SPMs in the standard regimens arm was malignant neoplasm of unknown primary site (n = 1); [b]CRS was graded according to modified Lee's criteria; maximum-grade events are reported, patients could have >1 event; [c]Includes immune effector cell-associated neurotoxicity syndrome reported by investigator as a neurologic toxicity.

Rodriguez-Otero P, et al. ASH 2023. [oral #1028]

Abbreviations are defined in the Notes Page section.

KarMMa-3: Entscheidende Rolle der Bridging Therapie

Of 213 patients who received bridging therapy, 200 were evaluable for change in disease burden before ide-cel

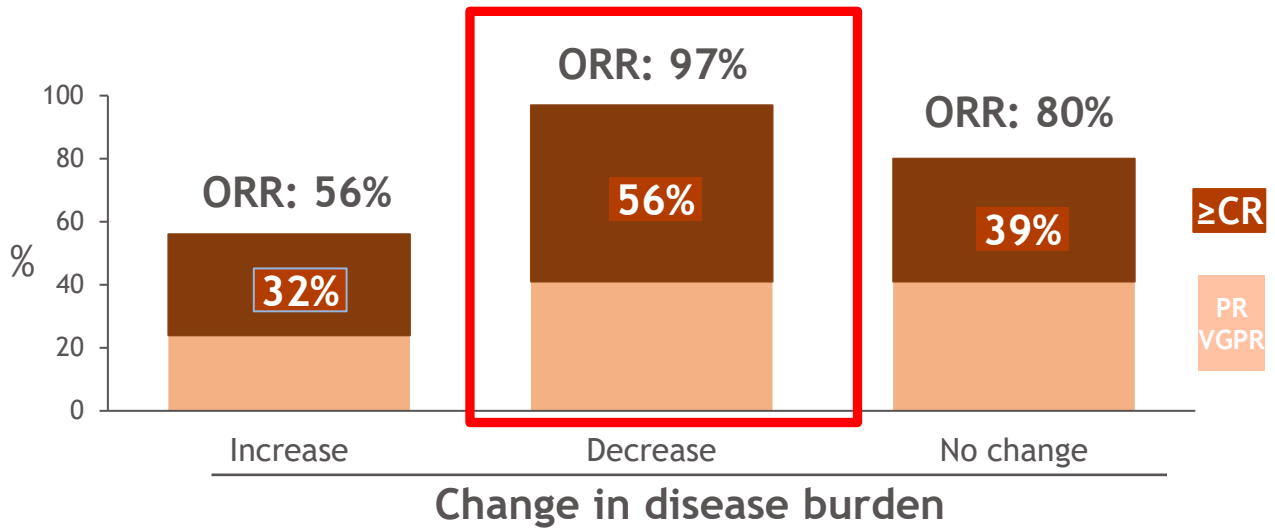
- **DPd: 45 patients**
- **DVd: 20**
- **IRd: 25**
- **Kd: 26**
- **EPd: 59**
- **Other: 25**

A higher proportion of patients with DB increase, had:

EM disease, high-risk cytogenetics, TCR disease, shorter time to progression after last Tx at baseline vs those with DB decrease or no change

Median number of cycles:
1 for all BTx regimens

Change in disease burden		
Increase	Decrease	No change
28%	15%	51%

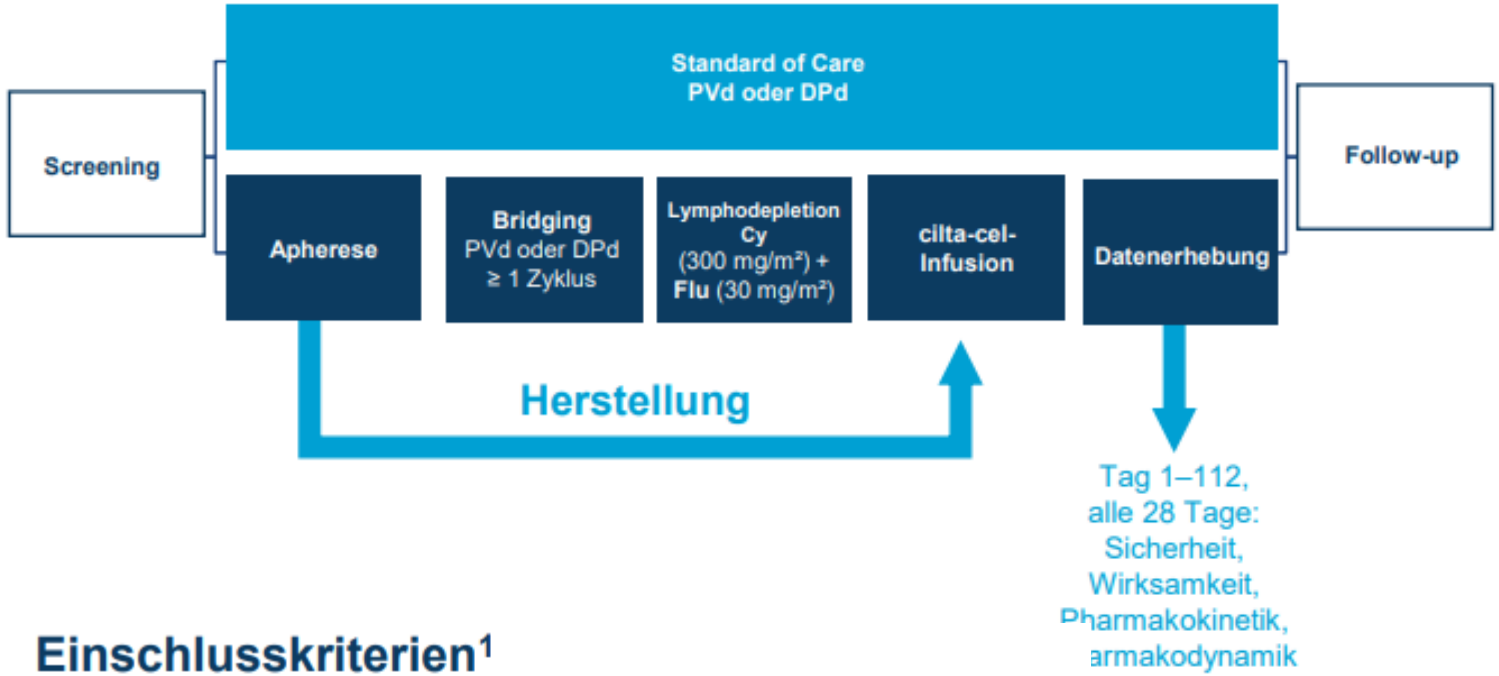


Median PFS, months (95% CI)	**6.9 (2.4-11.8)**	**20.7 (11.2-NR)**	**15.1 (12.4-17.3)**

Einsele et al. IMS 2023.

Ide-cel is approved for patients with RRMM after ≥ 4 (FDA) or ≥ 3 (EMA) prior therapies including an IMiD agent, a PI, and an anti-CD38 mAb and who have demonstrated disease progression on the last therapy (EMA).
Einsele H, et al. IMS 2023; Poster #P008; BTx- bridging therapy; Tx-therpy; DB disease burden; TCR- triple refractory disease; EM - extramedullary disease; GBS - Guillain-Barré syndrome

Cartitude 4 Studiendesign



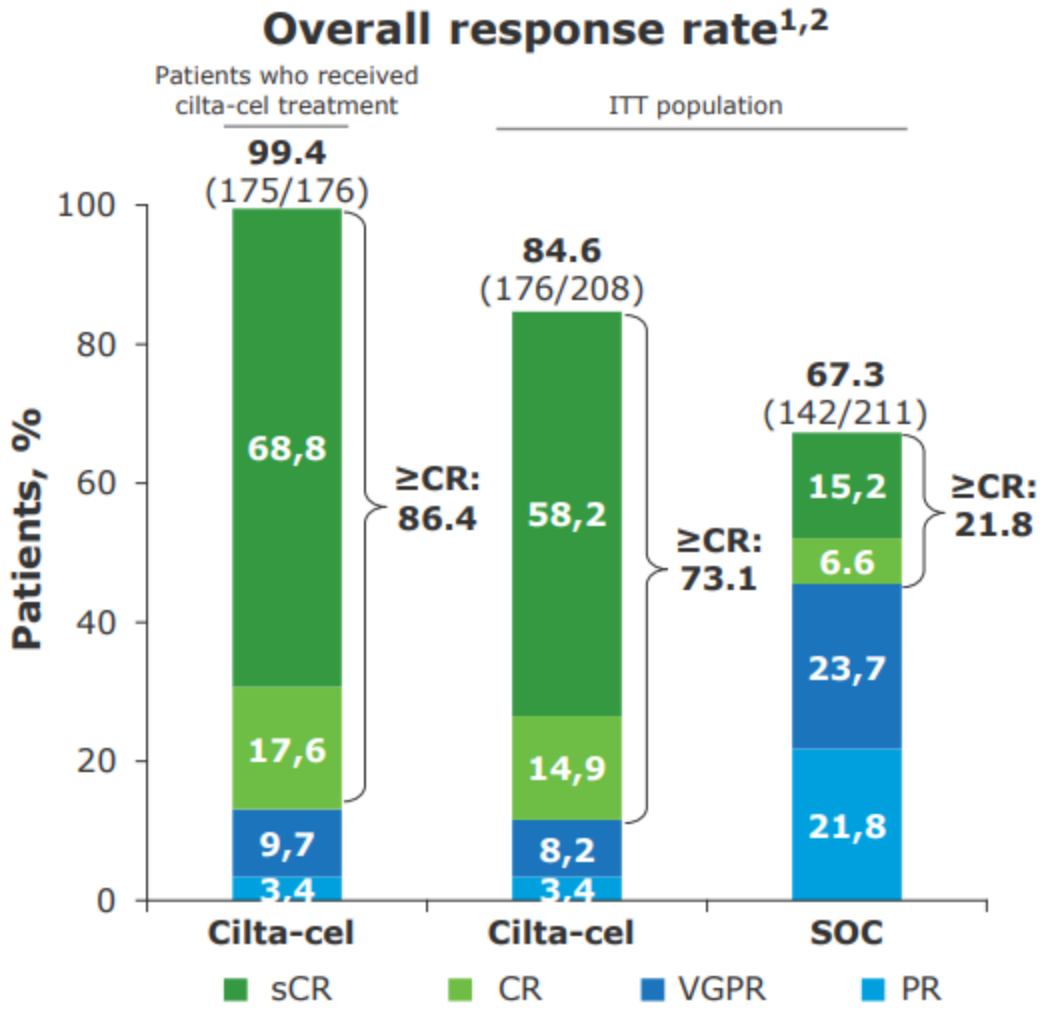
Baseline-Charakteristika	ITT-Population cilta-cel (N = 208)	SOC (N = 211)
Zytogenetisches Hochrisikoprofil, n (%)	123 (59,4)	132 (62,9)
del(17p)	49 (23,7)	43 (20,5)
t(14;16)	3 (1,4)	7 (3,3)
t(4;14)	30 (14,5)	30 (14,3)
gain/amp(1q)	89 (43,0)	107 (51,0)
≥ 2 Hochrisikomutationen	43 (20,8)	49 (23,3)
del(17p), t(14;16) oder t(4;14)	73 (35,3)	69 (32,9)
Therapie mit 3 Wirkstoffklassen, n (%)[d]	53 (25,5)	55 (26,1)
Therapie mit 5 Wirkstoffklassen, n (%)[d]	14 (6,7)	10 (4,7)
Refraktär, n (%)		
Dreifach refraktär[e]	30 (14,4)	33 (15,6)
Bortezomib	55 (26,4)	48 (22,7)
Pomalidomid	8 (3,8)	9 (4,3)
Daratumumab	48 (23,1)	45 (21,3)
Beliebiger PI	103 (49,5)	96 (45,5)

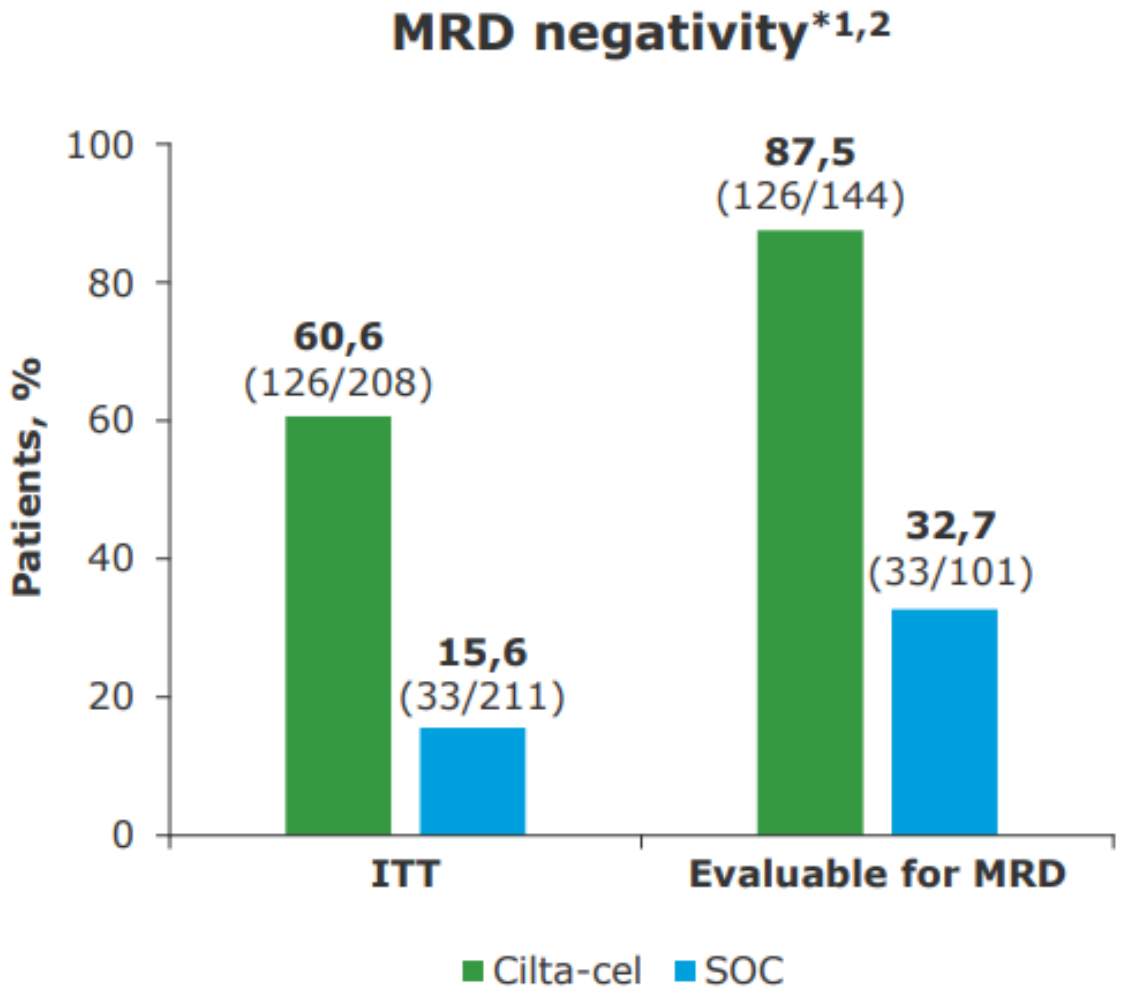
Einschlusskriterien[1]

- Alter ≥ 18 Jahre und Multiples Myelom nach IMWG-Kriterien
- ECOG Performance Score 0 oder 1
- 1–3 vorherige Behandlungslinien einschließlich PI und IMiD
- Lenalidomid-refraktär
- Keine Vorbehandlung mit CAR-T oder BCMA-gerichteten Therapien

Primär:
Progressionsfreies Überleben (PFS)

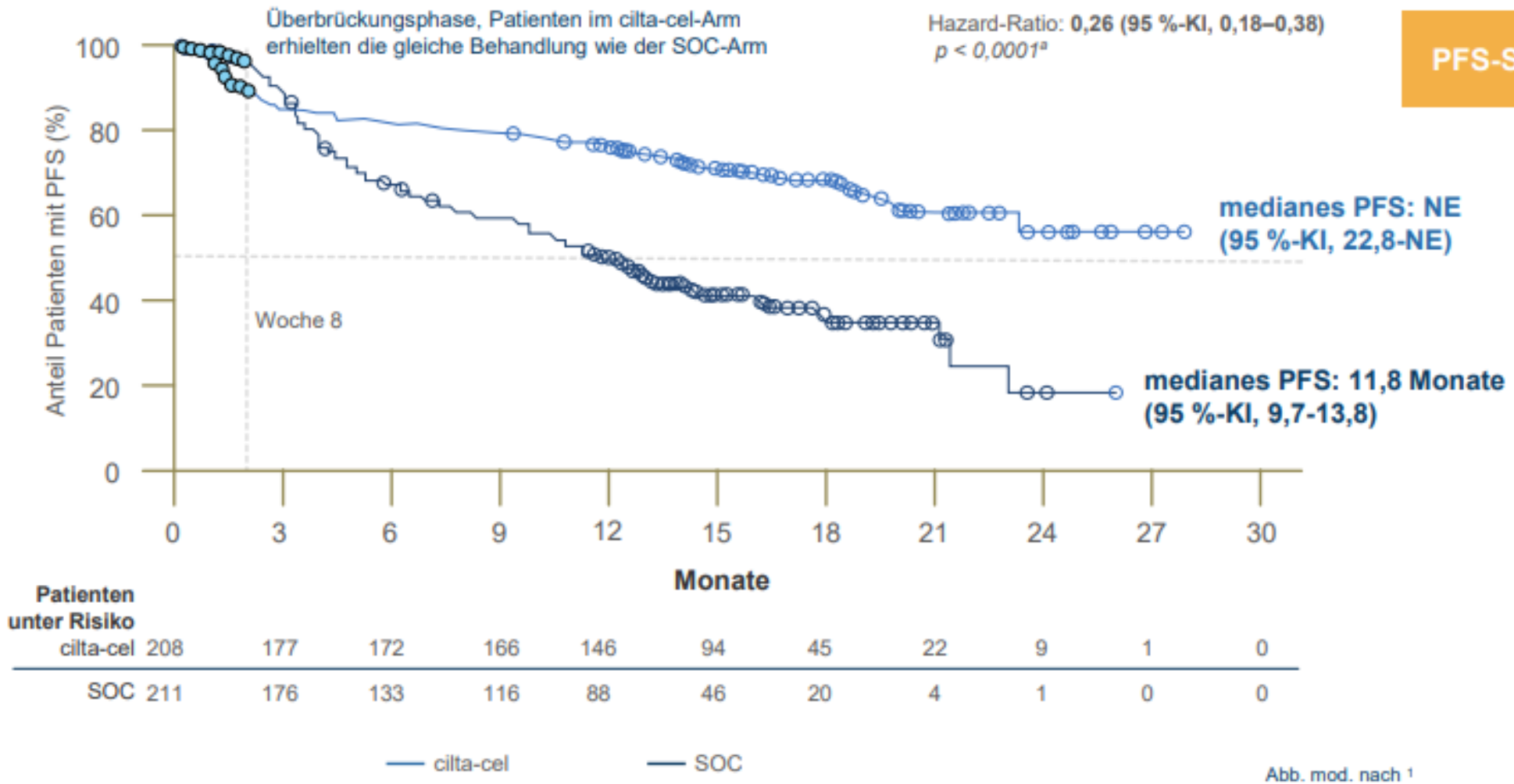
Sekundär:
Erreichen von ≥ CR, Gesamtansprechrate (ORR), Erreichen von MRD-Negativität, Gesamtüberleben (OS), Sicherheit, patient-reported outcomes (PRO)





1. San-Miguel J, et al. N Engl J Med 2023;389:335–347; 2. Dhakal B, et al. ASCO, Chicago, USA, and Virtual, 2–6 June 2023. 106.

Primärer Endpunkt PFS (ITT-Population)



PFS nach Anzahl der Vortherapielinien

PFS-Subgruppenanalyse

Abb. mod. nach [1]

Ciltacabtagene Autoleucel vs Standard of Care in Patients With Functional High-Risk Multiple Myeloma: CARTITUDE-4 Subgroup Analysis

Luciano J Costa[1], Katja Weisel[2], Niels WCJ van de Donk[3], Surbhi Sidana[4], Yaël C Cohen[5], Duncan Purtill[6], Cyrille Touzeau[7], Carlos Fernández de Larrea[8], Joaquin Martinez-Lopez[9], Nikoletta Lendvai[10], Ana Slaughter[11], Carolina Lonardi[12], Man Zhao[13], Katherine Li[14], Martin Vogel[15], Mythili Koneru[16], Nitin Patel[16], Erika Florendo[16], Octavio Costa Filho[16], María-Victoria Mateos[17]

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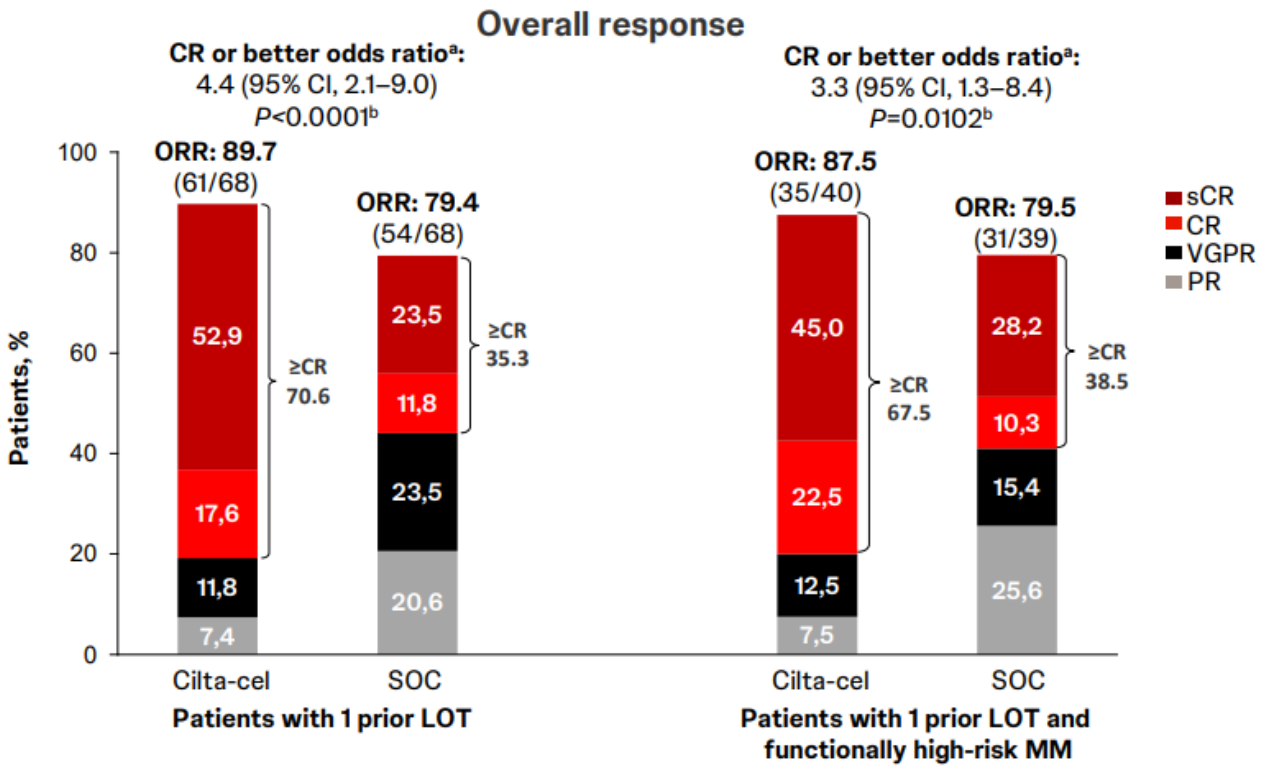
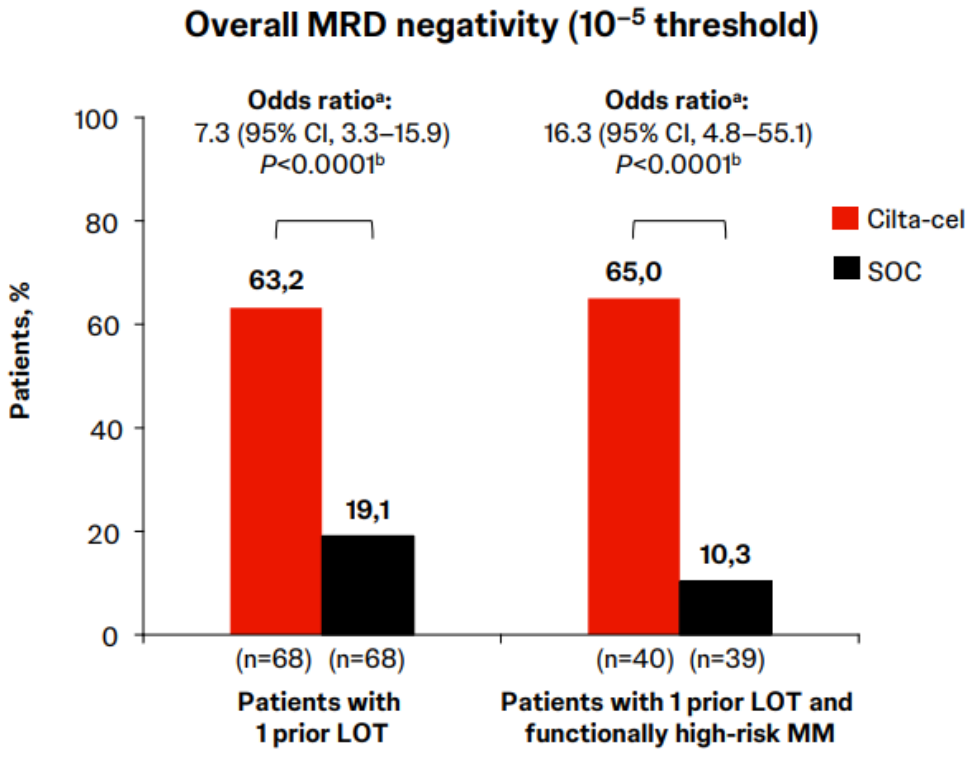
Functionally high-risk MM defined as PD ≤18 months after receiving ASCT or the start of initial frontline therapy in patients with no ASCT

Presented by LJ Costa at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting; May 31–June 4, 2024; Chicago, IL, USA

Ansprechen bei Patienten mit Rückfall <18 Monate nach ASCT oder Therapiestart mit geringem Unterschied

Uniklinikum Würzburg



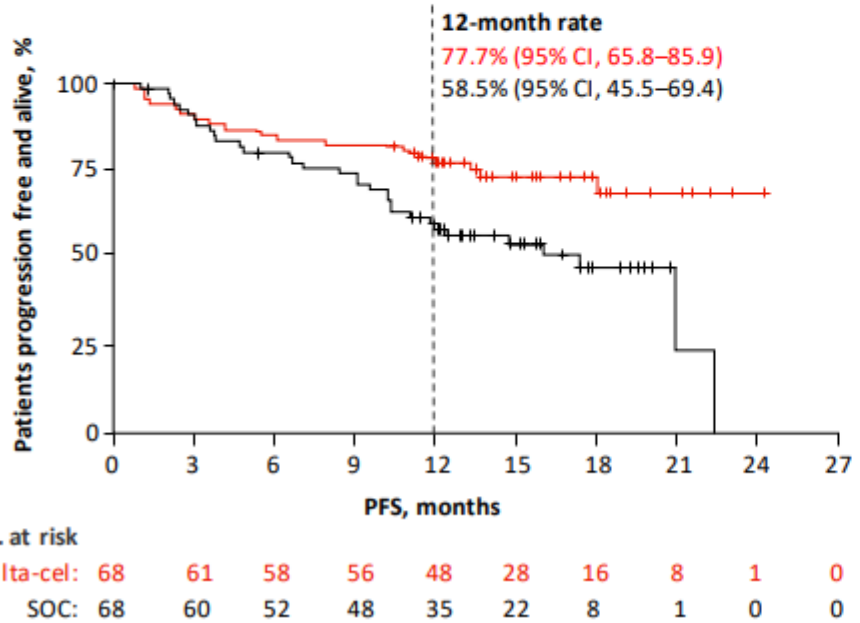


Presented by LJ Costa at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting; May 31–June 4, 2024; Chicago, IL, USA

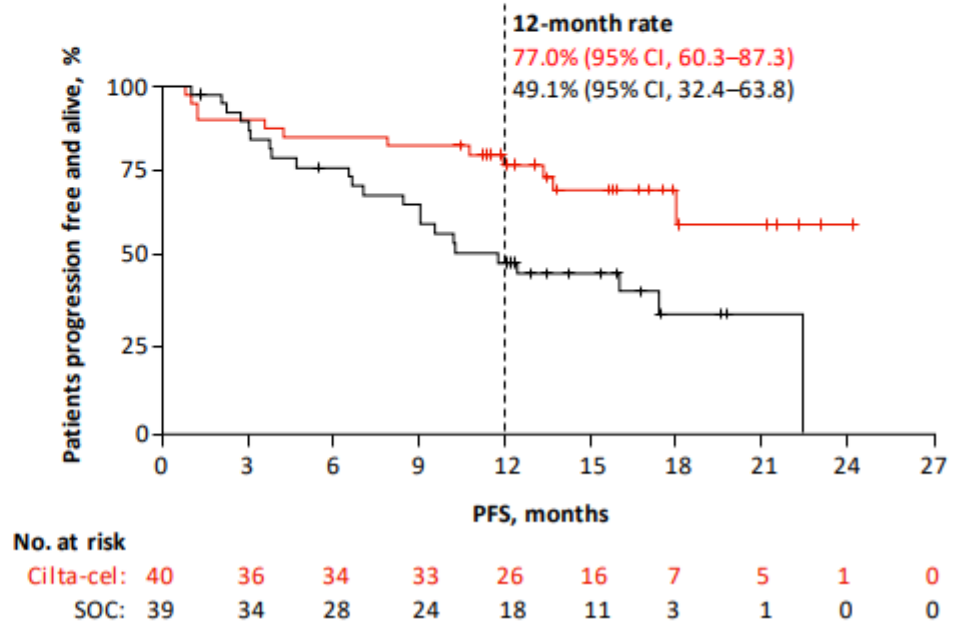
Ansprechdauer bei Patienten mit Rückfall <18 Monate nach ASCT oder Therapiestart mit geringem Unterschied

Uniklinikum Würzburg

	Patients with 1 prior LOT	
	Cilta-cel (n=68)	SOC (n=68)
Median PFS (95% CI), months[a]	NR (NE–NE)	17.41 (11.10–NE)
HR (95% CI); *P* value[b,c]	0.35 (0.19–0.66); 0.0007	



	Patients with 1 prior LOT and functionally high-risk MM	
	Cilta-cel (n=40)	SOC (n=39)
Median PFS (95% CI), months[a]	NR (18.00–NE)	11.79 (8.44–NE)
HR (95% CI); *P* value[b,c]	0.27 (0.12–0.60); 0.0006	



Presented by LJ Costa at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting; May 31–June 4, 2024; Chicago, IL, USA

Uniklinikum Würzburg

Ciltacabtagene Autoleucel vs Standard of Care in Lenalidomide-Refractory Multiple Myeloma: Phase 3 CARTITUDE-4 Subgroup Analysis by Cytogenetic Risk

Roberto Mina[1], Binod Dhakal[2], Jesús San-Miguel[3], Mi Kwon[4], Duncan Purtill[5], Hila Magen[6], Magdalena Dutka[7], Michel Delforge[8], Ravi Vij[9], Stina Wichert[10], Sung-Soo Yoon[11], Monique C Minnema[12], Nikoletta Lendvai[13], Carolina Lonardi[14], Ana Slaughter[15], Martin Vogel[16], Katherine Li[17], Diana Chen[18], Man Zhao[19], Tzu-min Yeh[13], Nina Benachour[20], Tamar Lengil[21], Mythili Koneru[22], Nitin Patel[22], Erika Florendo[22], Octavio Costa Filho[22], Hermann Einsele[23], Salomon Manier[24], Joaquin Martinez-Lopez[25]

[1]A.O.U. Città della Salute e della Scienza di Torino, Turin, Italy; [2]Medical College of Wisconsin, Milwaukee, WI, USA; [3]Cancer Center Clinica Universidad Navarra, CIMA, IDISNA, Pamplona, Spain; [4]Hospital General Universitario Gregorio Marañón and Gregorio Marañón Health Research Institute (IiSGM), Madrid, Spain; [5]Fiona Stanley Hospital, Perth, Western Australia, Australia; [6]Chaim Sheba Medical Center, Ramat-Gan, and Sackler Faculty of Medicine and Health Sciences, Tel Aviv University, Tel Aviv, Israel; [7]Medical University of Gdańsk, Gdańsk, Poland; [8]University of Leuven, Leuven, Belgium; [9]Washington University School of Medicine, St. Louis, MO, USA; [10]Skåne University Hospital in Lund, Lund, Sweden; [11]Seoul National University College of Medicine, Seoul, Republic of South Korea; [12]University Medical Center Utrecht, Utrecht, Netherlands; [13]Janssen Research & Development, Raritan, NJ, USA; [14]Janssen, Buenos Aires, Argentina; [15]Cilag GmbH International, Zug, Switzerland; [16]Janssen Research & Development, Neuss, Germany; [17]Janssen Research & Development, Spring House, PA, USA; [18]Janssen Research & Development, Shanghai, China; [19]IQVIA, Shanghai, China; [20]Janssen Research & Development, Beerse, Belgium; [21]Janssen Global Services, Raritan, NJ, USA; [22]Legend Biotech USA Inc., Somerset, NJ, USA; [23]Universitätsklinikum Würzburg, Medizinische Klinik und Poliklinik II, Würzburg, Germany; [24]University of Lille, CHU Lille, Lille, France; [25]Hematological Malignancies Clinical Research Unit, Hospital 12 de Octubre Universidad Complutense, Centro Nacional de Investigaciones Oncológicas CIBERONC, Madrid, Spain

Presented by Mina R et al. at the 2024 European Hematology Association Annual Meeting; June 13-16, 2024; Madrid, Spain & Virtual

Cilta-cel bei Len refraktärer Erkrankung und genetisch determiniertem Hochrisiko

Uniklinikum Würzburg

Figure 2: Treatment response by cytogenetic risk abnormality

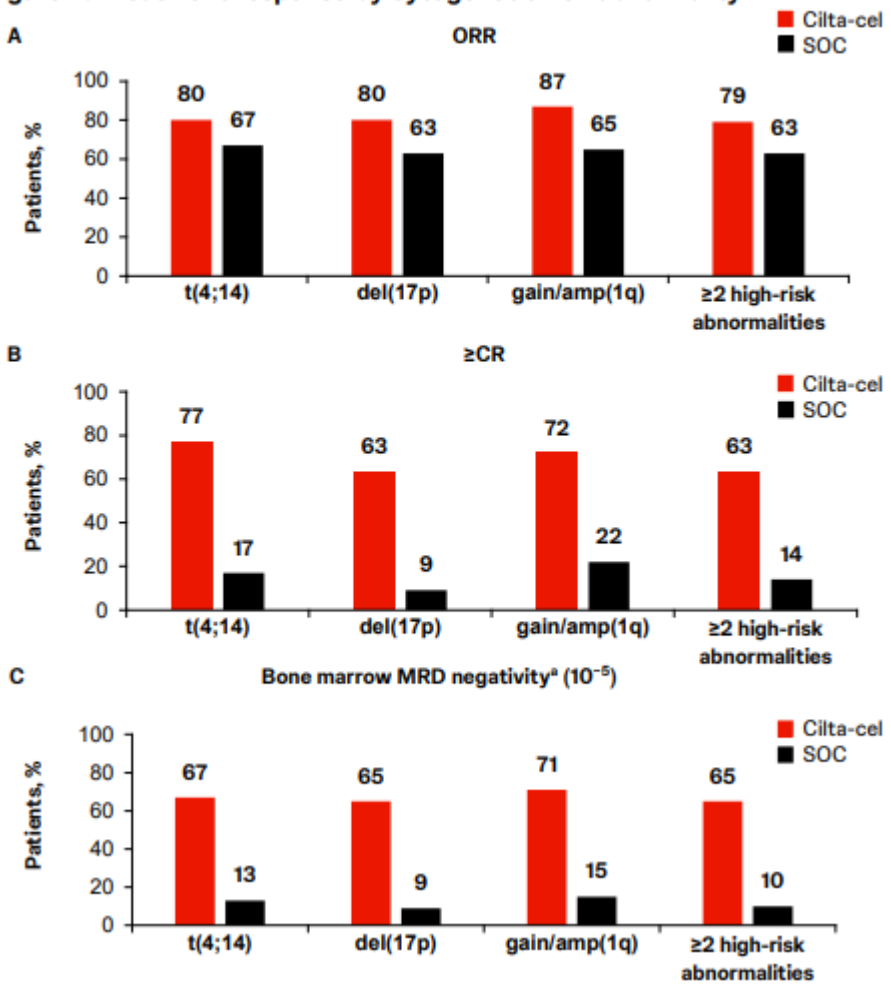
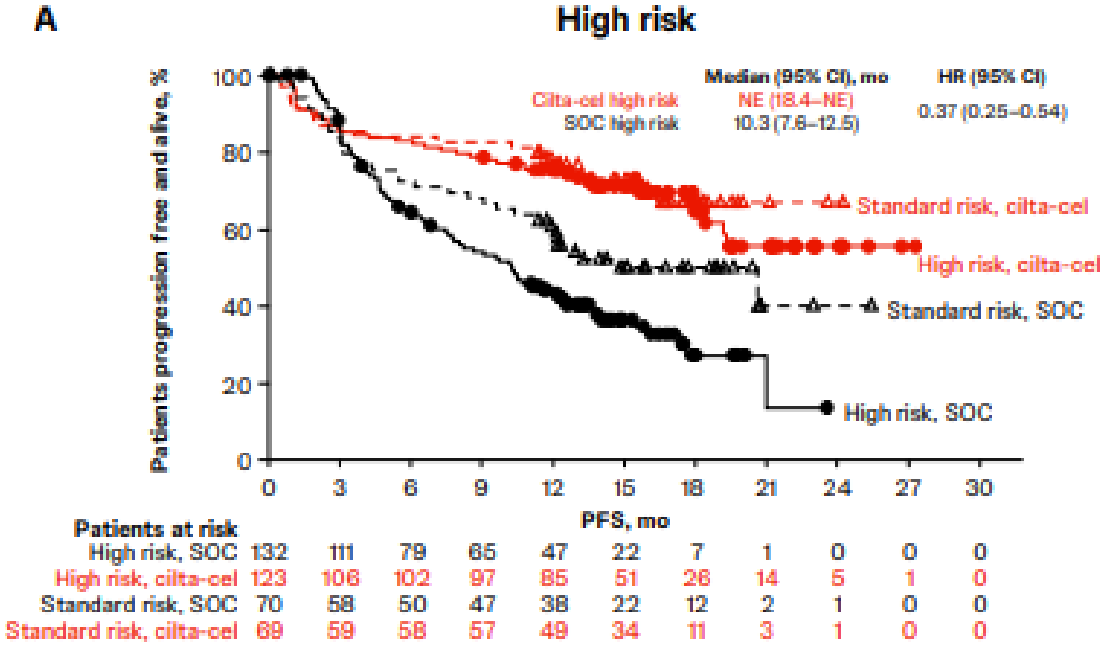


Figure 3: PFS by high-risk cytogenetic abnormalities



Presented by Mina R et al. at the 2024 European Hematology Association Annual Meeting; June 13-16, 2024; Madrid, Spain & Virtual

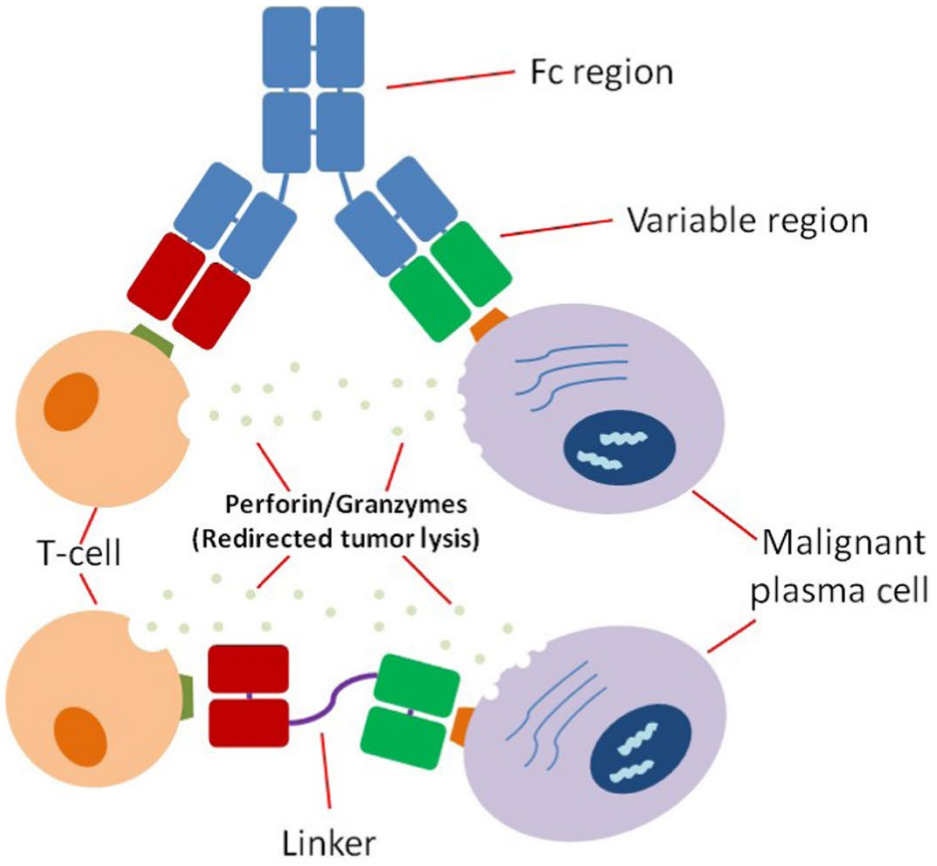
Ab der 4. Linie: Bispezifische Antikörper rekrutieren aus dem gesamten T-Zell Pool des Patienten !

IgG-like BiAb

- Elranatamab
- REGN-5458
- Teclistamab
- CC-93269
- TNB-383B
- Cevostamab
- Talquetamab

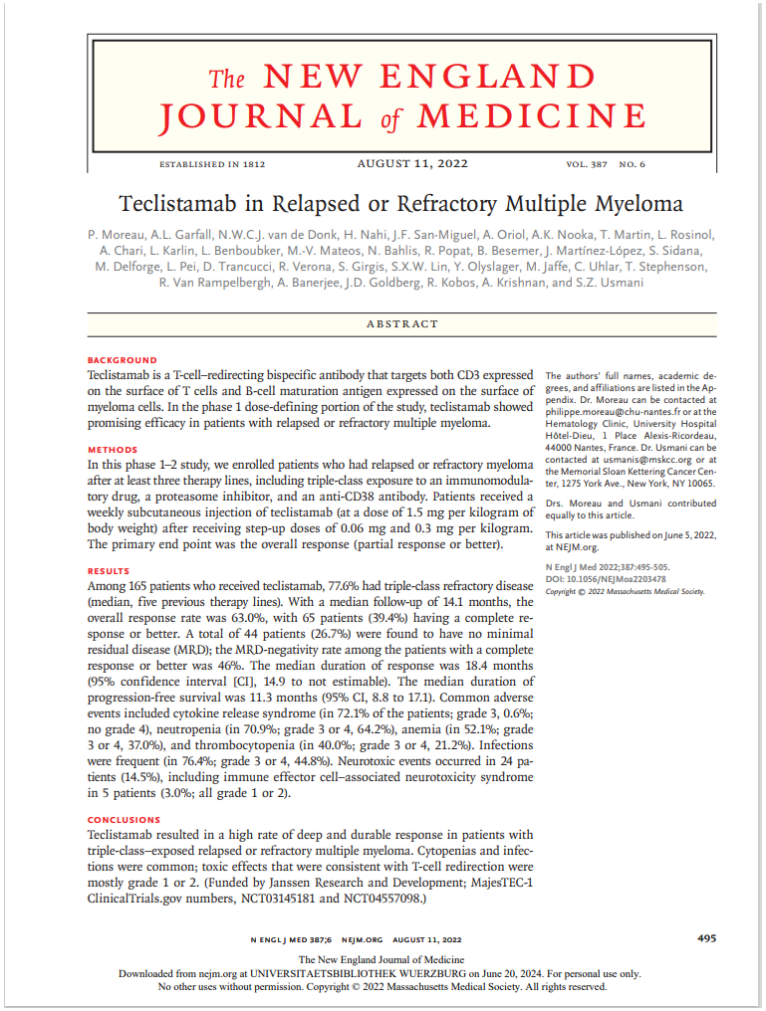
Non-IgG-like BiAb

- AMG 420
- AMG 701 (Extended half-life)



Christopher Cipkar,Christine Chen,Suzanne Trudel, Antibodies and bispecifics for multiple myeloma: effective effector therapy, Hematology Am Soc Hematol Educ Program, 2022, Figure 2.

Zwei zugelassene BCMA gerichtete bispezifische AK



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Teclistamab in Relapsed or Refractory Multiple Myeloma

P. Moreau, A.L. Garfall, N.W.C.J. van de Donk, H. Nahi, J.F. San-Miguel, A. Oriol, A.K. Nooka, T. Martin, L. Rosinol, A. Chari, L. Karlin, L. Benboubker, M.-V. Mateos, N. Bahlis, R. Popat, B. Besemer, J. Martínez-López, S. Sidana, M. Delforge, L. Pei, D. Trancucci, R. Verona, S. Girgis, S.X.W. Lin, Y. Olyslager, M. Jaffe, C. Uhlar, T. Stephenson, R. Van Rampelbergh, A. Banerjee, J.D. Goldberg, R. Kobos, A. Krishnan, and S.Z. Usmani

ABSTRACT

BACKGROUND

Teclistamab is a T-cell–redirecting bispecific antibody that targets both CD3 expressed on the surface of T cells and B-cell maturation antigen expressed on the surface of myeloma cells. In the phase 1 dose-defining portion of the study, teclistamab showed promising efficacy in patients with relapsed or refractory multiple myeloma.

METHODS

In this phase 1–2 study, we enrolled patients who had relapsed or refractory myeloma after at least three therapy lines, including triple-class exposure to an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 antibody. Patients received a weekly subcutaneous injection of teclistamab (at a dose of 1.5 mg per kilogram of body weight) after receiving step-up doses of 0.06 mg and 0.3 mg per kilogram. The primary end point was the overall response (partial response or better).

RESULTS

Among 165 patients who received teclistamab, 77.6% had triple-class refractory disease (median, five previous therapy lines). With a median follow-up of 14.1 months, the overall response rate was 63.0%, with 65 patients (39.4%) having a complete response or better. A total of 44 patients (26.7%) were found to have no minimal residual disease (MRD); the MRD-negativity rate among the patients with a complete response or better was 46%. The median duration of response was 18.4 months (95% confidence interval [CI], 14.9 to not estimable). The median duration of progression-free survival was 11.3 months (95% CI, 8.8 to 17.1). Common adverse events included cytokine release syndrome (in 72.1% of the patients; grade 3, 0.6%; no grade 4), neutropenia (in 70.9%; grade 3 or 4, 64.2%), anemia (in 52.1%; grade 3 or 4, 37.0%), and thrombocytopenia (in 40.0%; grade 3 or 4, 21.2%). Infections were frequent (in 76.4%; grade 3 or 4, 44.8%). Neurotoxic events occurred in 24 patients (14.5%), including immune effector cell–associated neurotoxicity syndrome in 5 patients (3.0%; all grade 1 or 2).

CONCLUSIONS

Teclistamab resulted in a high rate of deep and durable response in patients with triple-class–exposed relapsed or refractory multiple myeloma. Cytopenias and infections were common; toxic effects that were consistent with T-cell redirection were mostly grade 1 or 2. (Funded by Janssen Research and Development; MajesTEC-1 ClinicalTrials.gov numbers, NCT03145181 and NCT04557098.)

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Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results

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Check for updates

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Elranatamab is a humanized B-cell maturation antigen (BCMA)-CD3 bispecific antibody. In the ongoing phase 2 MagnetisMM-3 trial, patients with relapsed or refractory multiple myeloma received subcutaneous elranatamab once weekly after two step-up priming doses. After six cycles, persistent responders switched to biweekly dosing. Results from cohort A, which enrolled patients without prior BCMA-directed therapy ($n = 123$) are reported. The primary endpoint of confirmed objective response rate (ORR) by blinded independent central review was met with an ORR of 61.0% (75/123); 35.0% ≥complete response. Fifty responders switched to biweekly dosing, and 40 (80.0%) improved or maintained their response for ≥6 months. With a median follow-up of 14.7 months, median duration of response, progression-free survival and overall survival (secondary endpoints) have not been reached. Fifteen-month rates were 71.5%, 50.9% and 56.7%, respectively. Common adverse events (any grade; grade 3–4) included infections (69.9%, 39.8%), cytokine release syndrome (57.7%, 0%), anemia (48.8%, 37.4%), and neutropenia (48.8%, 48.8%). With biweekly dosing, grade 3–4 adverse events decreased from 58.6% to 46.6%. Elranatamab induced deep and durable responses with a manageable safety profile. Switching to biweekly dosing may improve long-term safety without compromising efficacy. ClinicalTrials.gov identifier: NCT04649359.

The introduction of immunomodulatory drugs, proteasome inhibitors and anti-CD38 monoclonal antibodies has transformed the treatment landscape in multiple myeloma. The addition of these agents has substantially improved patient survival; however, outcomes for patients with disease progression after these agents remain poor with a median progression-free survival (PFS) of 4.6 months and median overall survival (OS) of 12.4 months with a standard of care therapy, highlighting an unmet medical need in the relapsed or refractory multiple myeloma

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Lesokhin et al Nature Medicine 2023

Original Reports | Hematologic Malignancy

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Linvoseltamab for Treatment of Relapsed/Refractory Multiple Myeloma

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DOI https://doi.org/10.1200/JCO.24.01008

ABSTRACT

PURPOSE We present a phase I/II first-in-human trial evaluating the safety and efficacy of 50 mg and 200 mg doses of linvoseltamab, a B-cell maturation antigen × CD3 bispecific antibody in relapsed/refractory multiple myeloma (RRMM).

METHODS Phase II eligible patients had RRMM that either progressed on/after ≥three lines of therapy including a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an anti-CD38 antibody or was triple-class (PI/IMiD/anti-CD38) refractory. Phase II treatment was once a week through week 14 and then once every 2 weeks. Phase II 200 mg patients who achieved a ≥very good partial response by week 24 received linvoseltamab once every 4 weeks. The primary end point in phase II was overall response rate (ORR).

RESULTS Among the 117 patients treated with 200 mg, the median age was 70 years, 39% had high-risk cytogenetics, and 28% had penta-refractory disease. At a median follow-up of 14.3 months, the ORR was 71%, with 50% achieving ≥complete response (CR). In 104 patients treated with 50 mg at a median follow-up of 7.4 months, the ORR was 48%, with 21% achieving ≥CR. The median duration of response (DOR) for 200 mg patients (n = 83) was 29.4 months (95% CI, 19.2 to not evaluable). Among 200 mg patients, the most common adverse events included cytokine release syndrome (35.0% Gr1, 10.3% Gr2, 0.9% Gr3), neutropenia (0.9% Gr2, 18.8% Gr3, 23.1% Gr4), and anemia (3.4% Gr1, 4.3% Gr2, 30.8% Gr3). Immune effector cell-associated neurotoxicity syndrome occurred in 7.7% of patients (2.6% each Gr1, Gr2, Gr3). Infections were reported in 74.4% of patients (33.3% Gr3, 2.6% Gr4); infection frequency and severity declined over time.

CONCLUSION Linvoseltamab 200 mg induced deep and durable responses, with a median DOR of 29.4 months, in patients with RRMM with an acceptable safety profile.

ACCOMPANYING CONTENT

- Appendix
- Data Sharing Statement
- Data Supplement
- Protocol

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J Clin Oncol 00:1-11

View Online Article

INTRODUCTION

Multiple myeloma (MM) remains an incurable hematologic malignancy despite advances in antimyeloma therapies. With repeated cycles of relapse and remission, patients with myeloma experience increasingly shorter periods of remission and their disease often becomes refractory to the three principal antimyeloma drug classes: proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and anti-CD38 antibodies.[1,2] Therapies utilizing different mechanisms of action that are well tolerated and induce deep and durable remission are needed.[1,3]

B-cell maturation antigen (BCMA; also known as TNFRSF17) expression is restricted to plasmablasts and plasma cells[4–6] and has emerged as an important drug target for both chimeric antigen receptor T-cell (CAR-T) therapies and bispecific antibodies in the treatment of MM.[7–11] In heavily treated patients with relapsed/refractory MM (RRMM), approved BCMA-targeted CAR-T therapies have shown overall response rates (ORRs) of 73%–97%,[8,12] whereas bispecific BCMA × CD3 (BCMA×CD3) antibodies have shown ORRs of 61%–63%.[10,11,13] CAR-T therapies are complicated by manufacturing and access challenges and usually require bridging therapy, which may lead to delays

Bumma et al JCO 2024

Uniklinikum Würzburg

Effektivität der BCMAxCD3 bispecifischen Antikörper

Bispecific Antibody	Teclistamab (JNJ-64007957)	Elranatamab (PF-06863135)	Linvoseltamab (REGN5458)	ABBV-383	Alnuctamab BMS-93269	HPN217
Structure/Function	Humanized antibody	Humanized antibody	*Veloci-Bi*® platform fully human antibody	Low CD3 affinity fully human antibody	Humanize antibody 2 BCMA + 1 CD3	Trispecific 50kDa (albumin)
Treatment	Weekly SC	Weekly SC	Weekly IV	IV q3w	Qwk -> Q4wk SQ	Q2wk IV
Patients	n= 165	n= 123	n= 221	n= 174	n= 68	n= 62
Median prior lines	5	5	5	5	4	6
Triple-class refractory	78%	97%	82%	80%	63%	76%
ORR at RP2d	63%	61%	71%	58-61%	65%	73%
RP2D (n)	1.5 mg/kg SC **(n=165)**	76 mg SQ **(n=123)**	200 mg IV (n=117)	40 to 60 mg IV (n=52 n=59)	30 mg SQ (n=26)	?12 or 24 mg (n=13)
PFS	11.3 mos (8.8-17.1)	17.2 mos (9.8-NE)	NR (17.3 –NE)	13.7 or 11.2 mos	NR	NR
DOR	18.4 mos (14.9-NE)	NE @12 mos	29.4 mos	NE	NE	NR

Zulassung: für Patienten, die zuvor drei Therapien erhalten haben, darunter IMiD, PI und Anti-CD38- AK und die während der letzten Therapie eine Krankheitsprogression gezeigt haben

Moreau et al. *N Engl J Med.* Jun 5 2022. Lesohkin et al Nature med 2023 Bumma et al ASH 2022; Voorhees et al ASH 2022 Wong et al ASH 2022;; Abdallah et al ASH 2022. Van de Donk IMS 2023

D'Souza et al. JCO 2022

Non-BCMA gerichtete *CD3 Bispezifische Antikörper

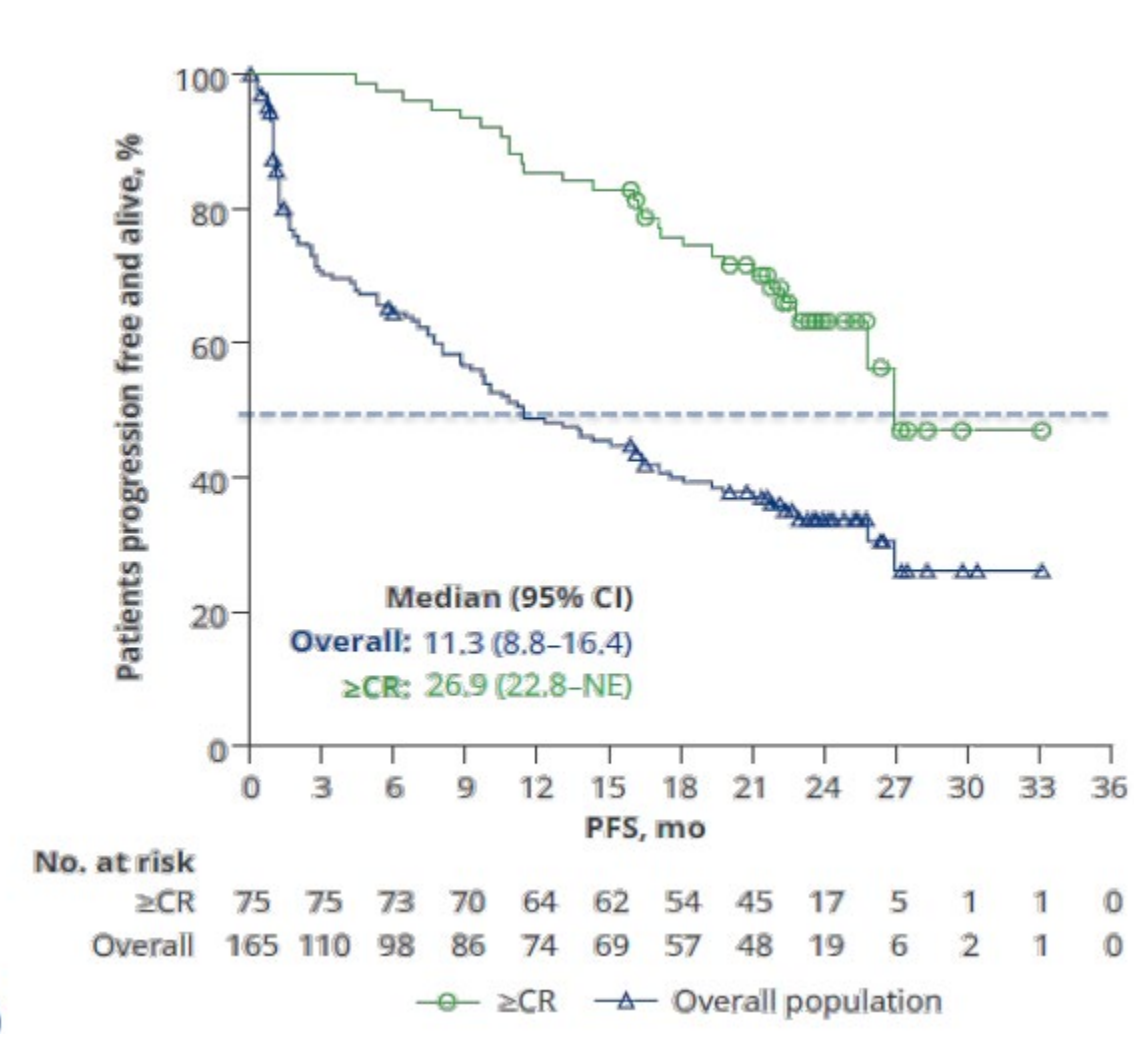
Bispecific Antibody	Talquetamab Phase 1/2 MonumenTAL-1 Study GPRC x CD3			Forimtamig (RG6234) Phase 1 GPRC X CD3 (2:1)	Cevostamab (GO39775) Phase 1 FcRH5 X CD3
Treatment	0.4 mg/kg SQ QW	0.8 mg/kg SC Q2W	Either dose	SQ q 2wk *12 mos	IV q3w * 12 mos
Patients	n=143	n=145	n=51	n=57	n=161
Median prior lines	5	5	6	5	6
Triple-class refractory	74%	69%		63%	85%
ORR @RP2D	**74%**	**72%**	**65% (prior CART/bisp 75%/44%)**	**64% (at 30-7200 ug)**	**132-198 mg: (56.7%)**
PFS	**7.5 mos**	**14.2 mos**	**5.1**		
DOR	**9.5 mos**	**NR**	**11.3 mos**	**12.5 mos**	

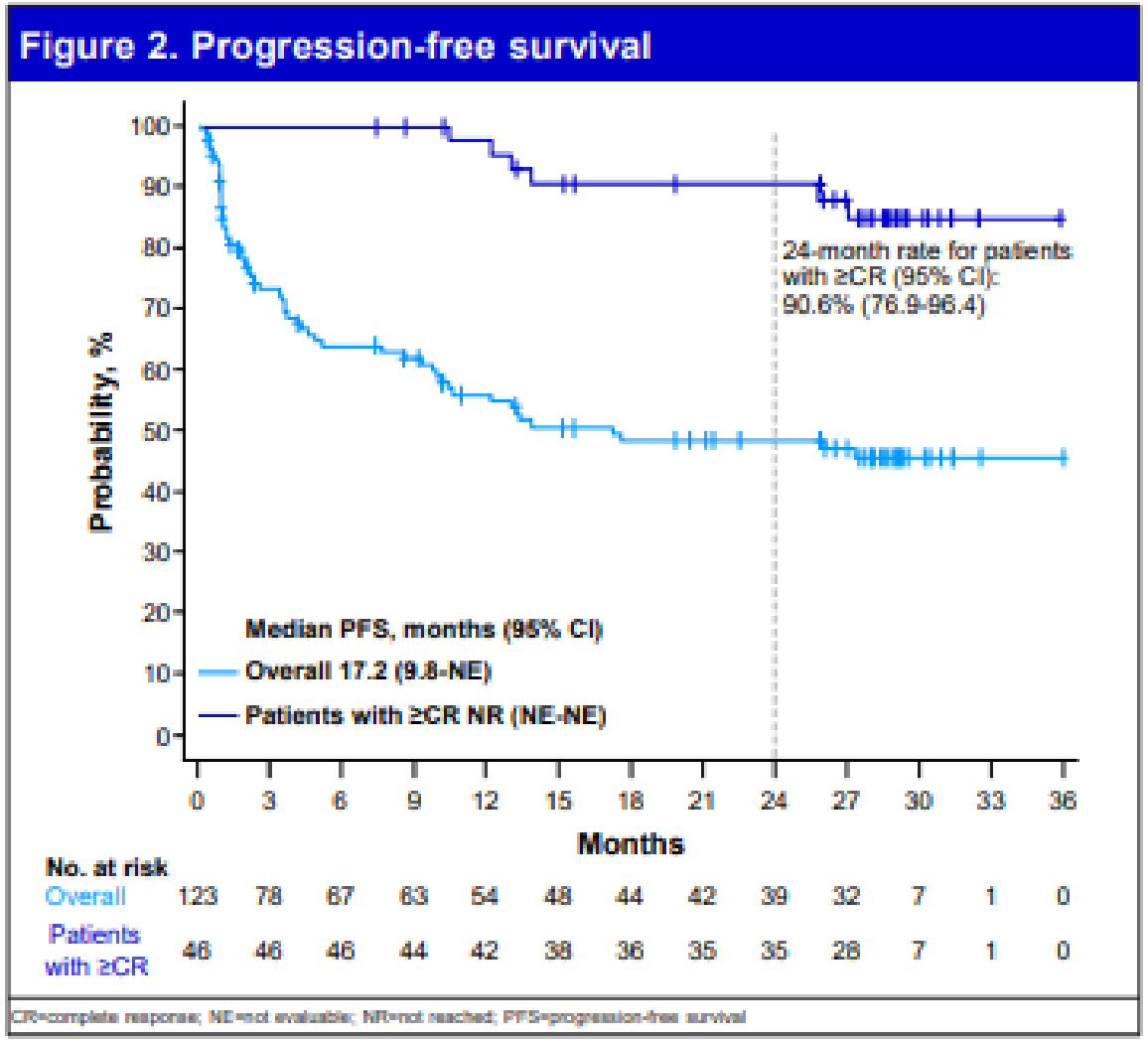
Accelerated approval

Zulassung: für Patienten, die zuvor drei Therapien erhalten haben, darunter IMiD, PI und Anti-CD38- AK und die während der letzten Therapie eine Krankheitsprogression gezeigt haben

Chari et al ASH 2022 ; Touzeau et al EHA 2023 Carlo-Stella ASH 2022. Trudel S et al, ASH 2021; Trudel et al ASH 2022

PFS in MajesTEC-1 und MagentisMM-3, schnelles Ansprechen





Zytokinstürme treten insbesondere bei Behandlungsbeginn auf und können wirksam mit Tocilizumab behandelt werden

CRS Definition

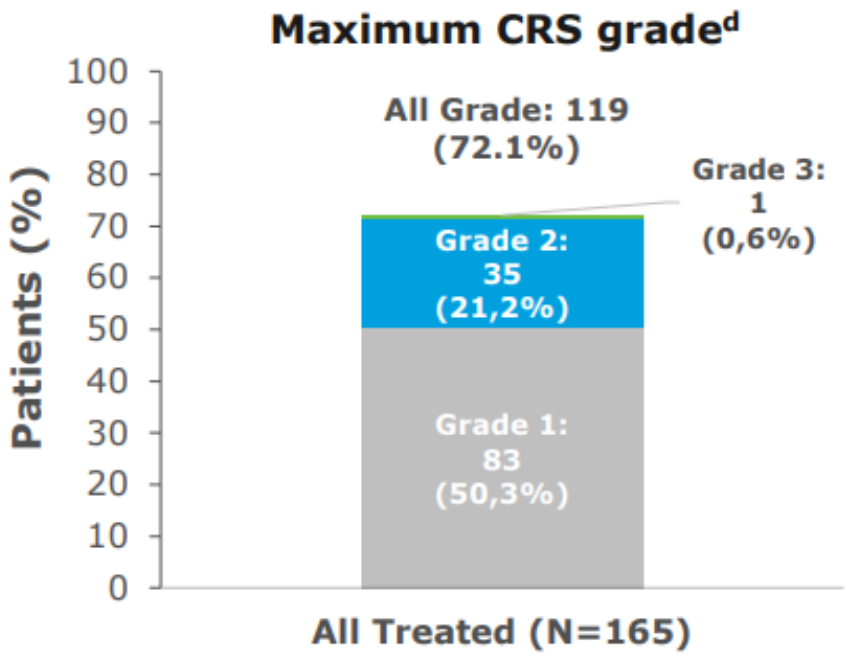
A clinical syndrome characterized by systemic immune activation, including excessive elevation of cytokines and other inflammatory markers that can be triggered by infections or certain therapies[1,2]

Typical Mild Symptoms[1,2]
Fever
Fatigue
Headache
Tachycardia
Rash
Tachypnea
Arthralgia/myalgia

More Severe Symptoms[1,2]
High fever
Hypotension
Vascular leakage
Seizure
Disseminated intravascular coagulation
Dyspnea
Acute respiratory distress syndrome
Multiorgan system failure • Renal failure • Cardiac dysfunction • Vascular leakage with peripheral and pulmonary edema

Neurologic Symptoms[1,2]
Confusion
Headaches
Hallucinations
Aphasia
Hemiparesis
Seizures

Beispiel: CRS in der MajesTEC-1 Studie



Parameter	N=165
Patients with CRS, n (%)	119 (72.1)
Patients with ≥2 CRS events	55 (33.3)
Time to onset (days), median (range)	2 (1–6)
Duration (days), median (range)	2 (1–9)
Received supportive measures[a] for CRS, n (%)	110 (66.7)
Tocilizumab[b]	60 (36.4)
Low-flow oxygen by nasal cannula[c]	21 (12.7)
Steroids	14 (8.5)
Single vasopressor	1 (0.6)

- Most CRS events were confined to step-up and first full treatment doses
- All CRS events fully resolved without treatment discontinuation or dose reduction

ICANS sind Immune Effector Cell-associated Neurotoxicity Syndrome

ICANS (ASTCT definition)[1]

A disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells

Symptoms of ICANS[1-3]

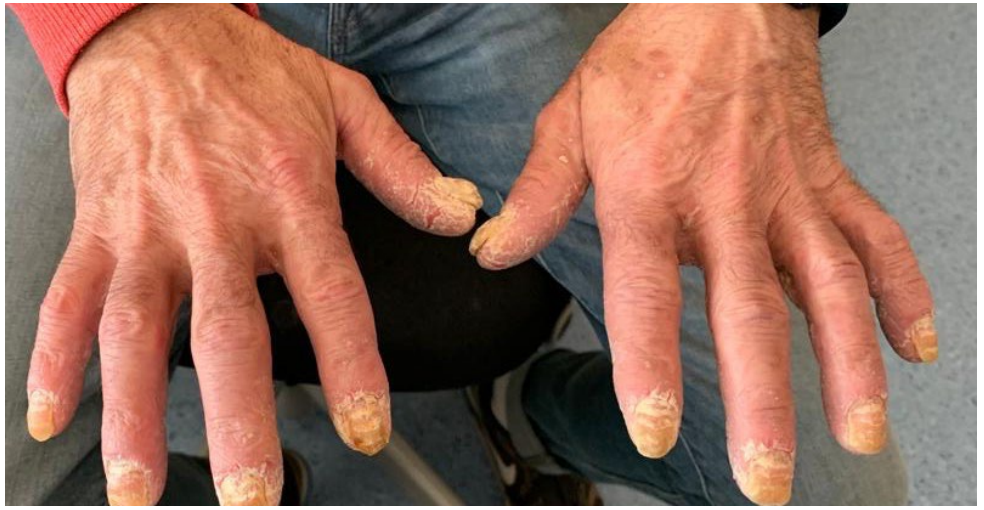
- Aphasia (often the first and most characteristic symptom[4,5])
- Altered level of consciousness
- Agitation
- Delirium
- Encephalopathy
- Impairment of cognitive skills/difficulty concentrating
- Lethargy
- Motor weakness

Nonspecific symptoms, such as headache and weakness, frequently occur with ICANS, but can often develop without broader neurologic dysfunction due to fever, chemotherapy, or other events[1]

GPRC5D spezifische NW unter Talquetamab

Uniklinikum Würzburg

Häufig: Verlust oder Verminderung von Geschmacks- und Geruchssinn!



Hauttoxizität nach GPRC5D gerichteter bispezifischer AK Therapie

„Sniffin‘ sticks“

„Taste-strips“

Leo Rasche

MonumenTAL-1: niedrige Rate an Grad 3/4 Infektionen

Hematologic AEs

- Most high-grade AEs were cytopenias

Infections

- In QW, Q2W, and prior TCR cohorts, respectively:
  - All-grade (grade 3/4) infections occurred in 58.7% (19.6%), 66.2% (14.5%), and 72.5% (27.5%)
  - Infections led to discontinuation in 1.4%, 0%, and 2.0%
  - Infections led to death in 2.1%, 1.4%, and 0%
  - Opportunistic infections were low at 3.5%, 5.5%, and 5.9%

AEs (≥30% in any cohort), n (%)	0.4 mg/kg SC QW (n=143)		0.8 mg/kg SC Q2W (n=145)		Prior TCR (n=51)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Hematologic AEs						
Anemia	64 (44.8)	45 (31.5)	66 (45.5)	40 (27.6)	25 (49.0)	14 (27.5)
Neutropenia	50 (35.0)	44 (30.8)	41 (28.3)	32 (22.1)	28 (54.9)	27 (52.9)
Thrombocytopenia	39 (27.3)	29 (20.3)	43 (29.7)	27 (18.6)	19 (37.3)	15 (29.4)

Data cut-off date: January 17, 2023.
AEs were graded by Common Terminology Criteria for Adverse Events v4.03.
AE, adverse event; Q2W, every other week; QW, weekly; SC, subcutaneous; TCR, T-cell redirection therapy.

See Poster P892 at EHA for additional infection analyses with talquetamab monotherapy in MonumenTAL-1
Presented June 9, 2023; 18:00–19:00

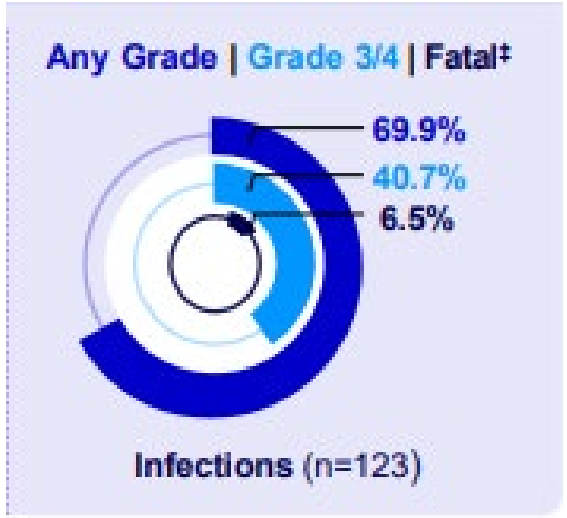
Problem bei der Therapie mit BCMA-Directed BsAb ist die hohe Infektgefährdung

Prof Ajai Chari, UCSF

MaiesTEC-1:

Efficacy and safety[2]	N=165
Median follow-up, months	23
ORR, %	63.0
Median DOR, months	21.6
Median PFS, months	11.3
CRS, %	
Any grade	72.1
Grade 3-4	0.6
ICANS, %	
Any grade	3.0
Grade 3-4	0
Infections, %	
Any grade	80.0
Grade 3-4	55.2
Treatment discontinuation due to AEs, %	<5

MagentisMM-3



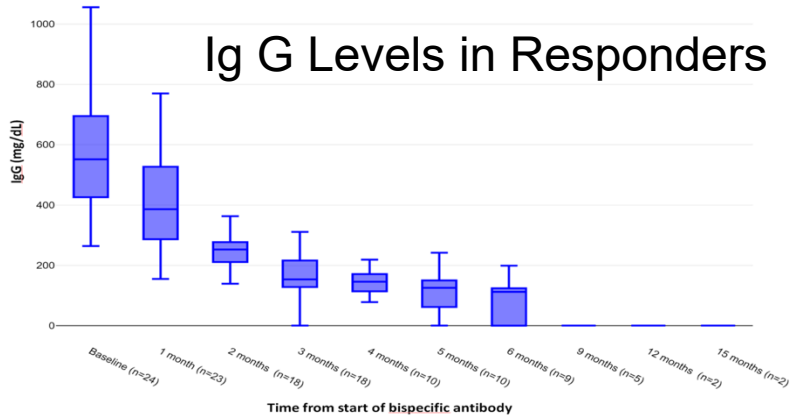
“Non-PD” Todesfälle sind Klasseneffekt BCMA gerichteter bispez AK !

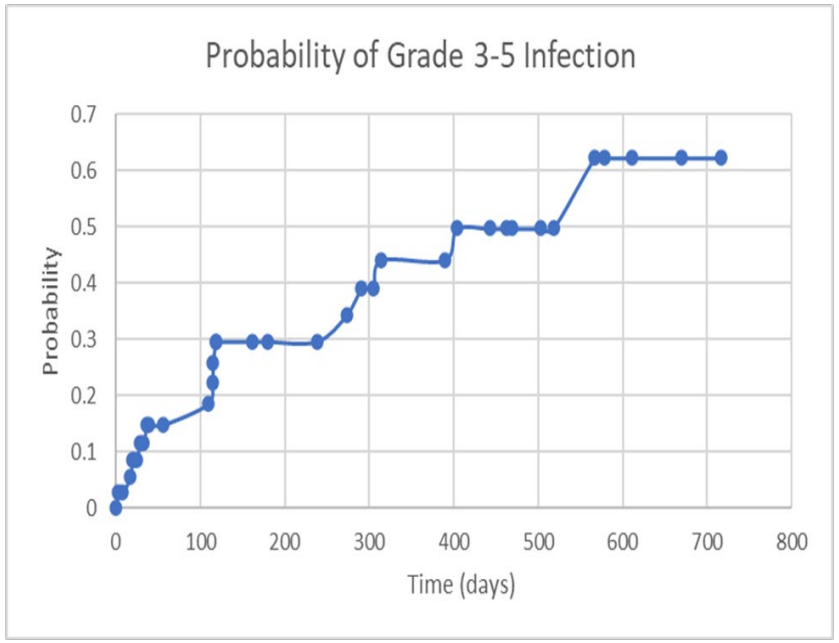
[a]Soft tissue plasmacytomas not associated with bone were included. [b]Of 162 patients evaluable.

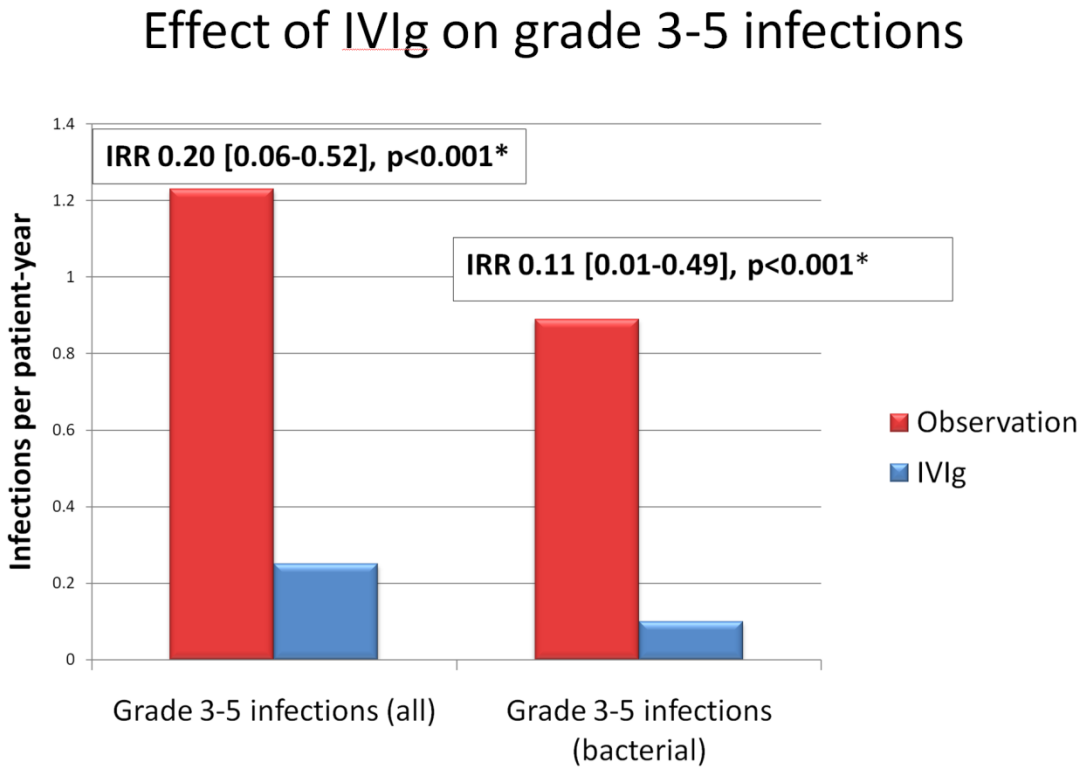
AE, adverse event; BCMA, B-cell maturation antigen; BsAb, bispecific antibody; CRS, cytokine release syndrome; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ICANS, immune effector cell-associated neurotoxicity syndrome; ISS, International Staging System; MM, multiple myeloma; ORR, overall response rate; PFS, progression-free survival; Q2W, every 2 weeks; Q4W, every 4 weeks; RRMM, relapsed or refractory multiple myeloma; TCE, triple-class exposed.

1. Moreau P, et al. *N Engl J Med.* 2022;387(6):495-505. 2. van de Donk N, et al. Abstract presented at: 59th ASCO Annual Meeting; June 2-6, 2023; Chicago, IL.

BCMA Bispecs: IgG Levels, Grade 3-5 Infektionen und Benefit von IVIg

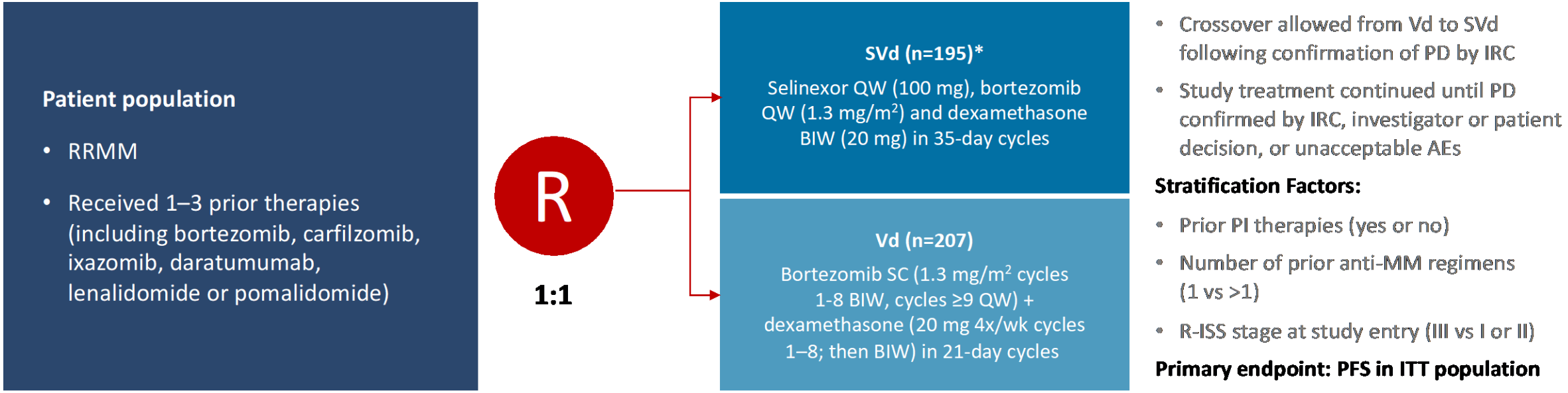






- IVIg Substitution essentiell für BCMA bispecifics
- Therapiedauer von BCMA gerichteten bispecifics unklar !

Selinexor ist ein „first in class“ XPO1 Inhibitor



Selinexor ist in Kombination mit Bortezomib und Dexamethason zugelassen für Patienten mit Multiplen Myelom, die zuvor mindestens eine Therapie erhalten haben.

Bortezomib wurde im Selinexor-Arm einmal wöchentlich, im Kontrollarm zweimal wöchentlich appliziert.
Selinexor führte gegenüber dem Kontrollarm zur statistisch signifikanten Verlängerung des progressionsfreien Überlebens und zur Erhöhung mindestens partieller Remissionen.
Die Gesamtüberlebenszeit wurde nicht verlängert.

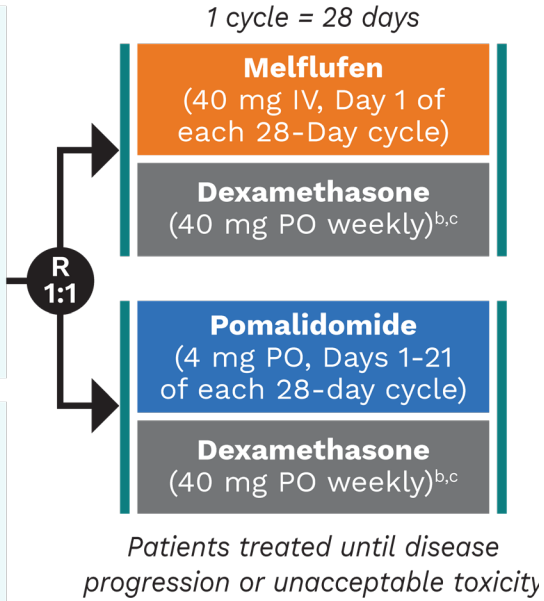
Melflufen – eine den Peptid-Wirkstoff-Konjugaten zugeordnete Weiterentwicklung von Melphalan

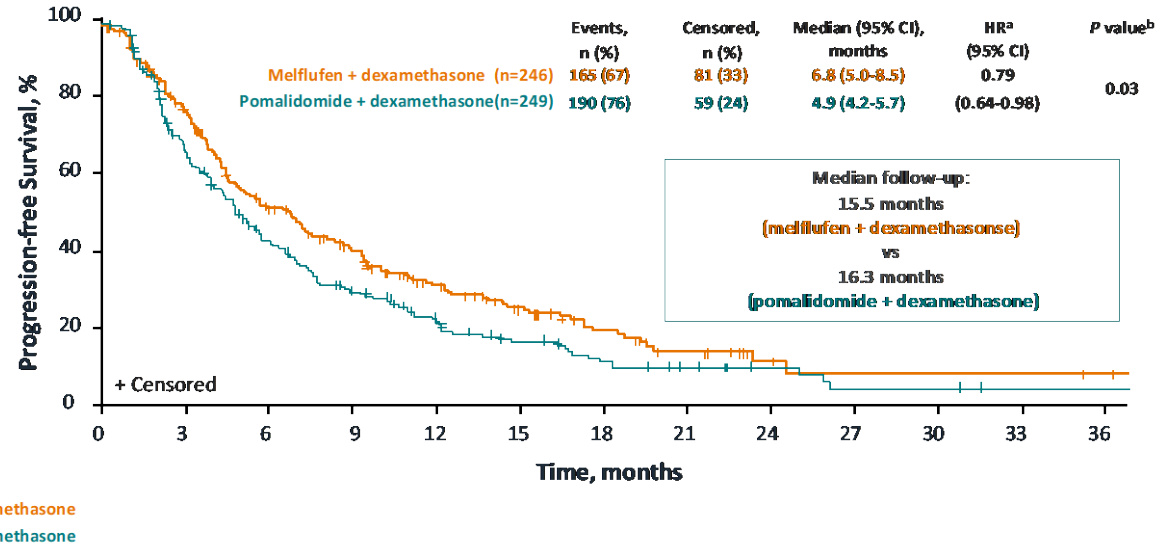
Ocean Studie

Patients with RRMM[a]
- Aged ≥18 years
- 2-4 prior lines of therapy including lenalidomide and a PI
- Refractory to lenalidomide and last line of therapy
- ECOG PS ≤2

(N=495)

Patients stratified by:
- Age (<75 vs ≥75 years)
- Prior lines of therapy (2 vs 3-4)
- ISS score (I vs II/III)

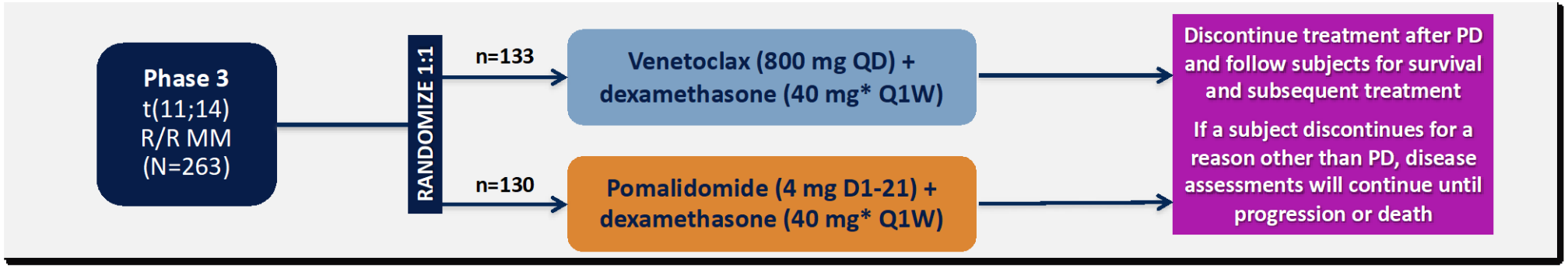




- Zugelassen in Kombination mit Dexamethason für Patienten, die mindestens 3 Therapielinien erhalten haben, deren Erkrankung gegenüber mindestens einem PI, einem IMiD und einem CD38 moAB refraktär ist und die ein Fortschreiten der Erkrankung während oder nach der letzten Therapie gezeigt haben.
- Bei Patienten mit vorangegangener autologer Stammzelltransplantation sollte die Zeit bis zur Progression nach der Transplantation mindestens 3 Jahre betragen.

Venetoclax für t(11;14) positives MM (off-lable)

CANOVA (NCT03539744) – A Phase 3, Multicenter, Randomized, Open Label Study of Venetoclax and Dexamethasone Compared With Pomalidomide and Dexamethasone in Subjects With t(11;14)-Positive R/R MM



INCLUSION CRITERIA

- t(11;14)-positive multiple myeloma by FISH
- ≥ 2 prior lines of therapy
- ECOG PS ≤2
- Documented disease progression on or within 60 days after completion of their last therapy
- Received at least 2 cycles of both lenalidomide and a proteasome inhibitor, alone or together
- Refractory to lenalidomide

EXCLUSION CRITERIA

- Prior venetoclax or pomalidomide

OBJECTIVES

Primary: ***PFS***

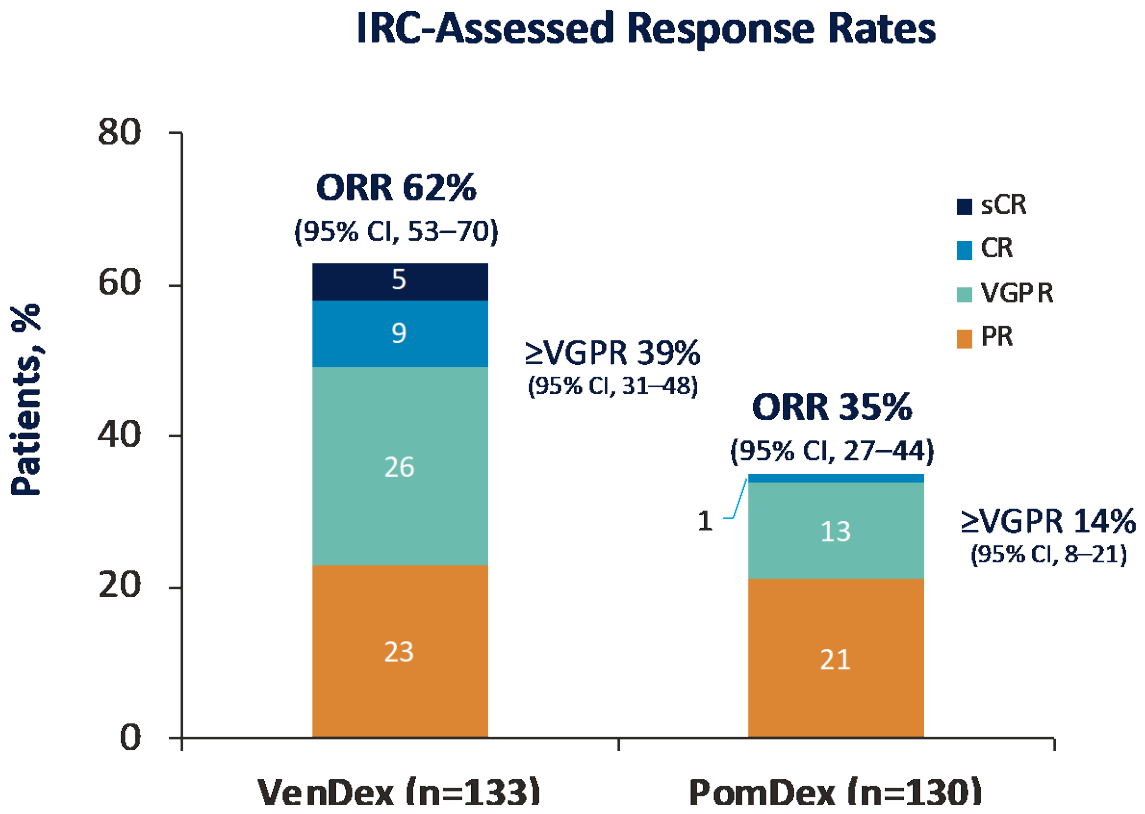
Secondary: ***Response rates (ORR, VGPR or better), OS, DOR, TTP, TTR, MRD, PK, Safety, PROs***

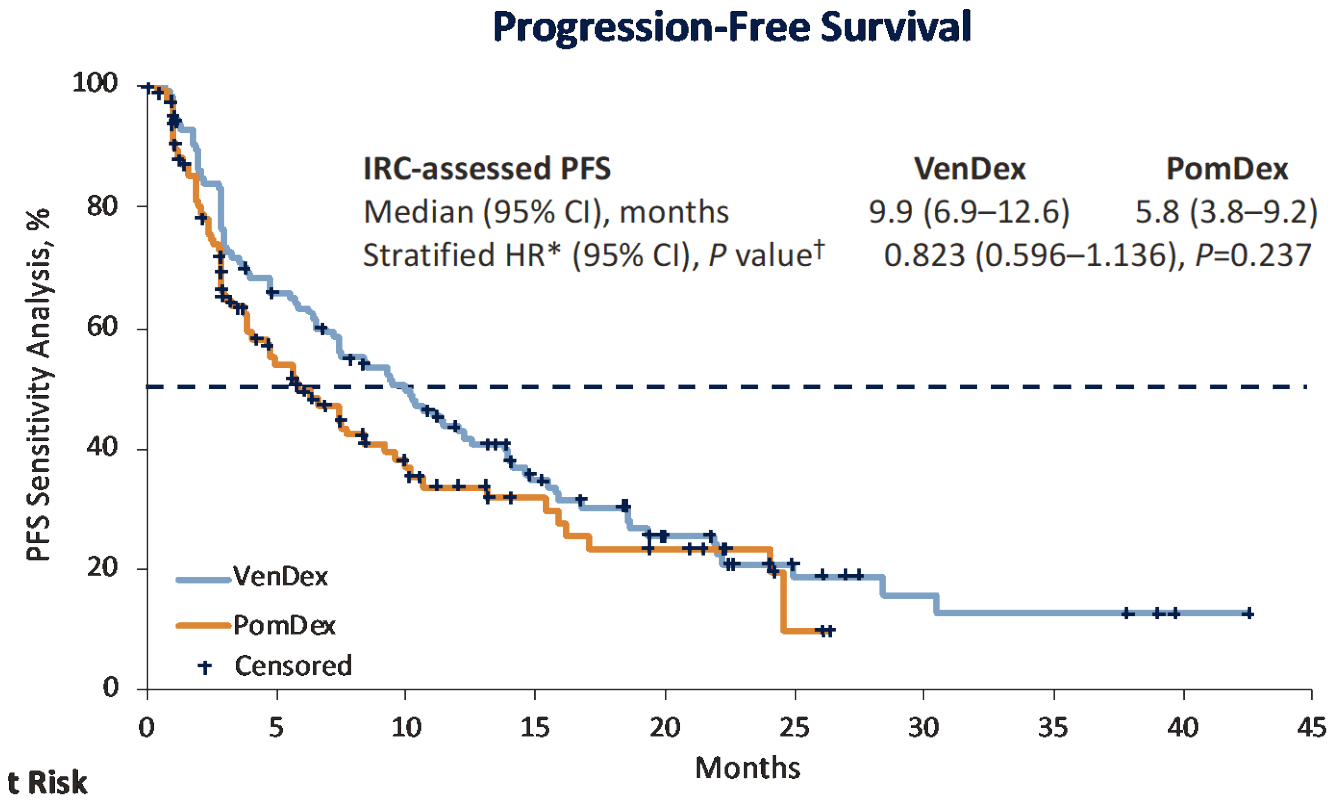
Data cutoff date: July 24, 2023.
*Patients aged ≥75 years received dexamethasone 20 mg QW.
Dexamethasone could be administered IV when PO was not possible.

D=Day. DOR=Duration of Response. ECOG PS=Eastern Cooperative Oncology Group Performance Score. FISH=Fluorescence In Situ Hybridization. IV=Intravenously. MM=Multiple Myeloma. MRD=Minimal Residual Disease. ORR=Overall Response Rate. OS=Overall Survival. PD=Progressive Disease. PFS=Progression-Free Survival. PK=Pharmacokinetics. PO=Orally. PRO=Patient Reported Outcome. Q1W=Once Weekly. QD=Daily. R/R=Relapsed/Refractory. TTP=Time to Progression. TTR=Time To Response. VGPR=Very Good Partial Response.

Mateos M, et al. Oral Abstract 52. IMS Annual Meeting; Sept 27-30, 2023; Athens, Greece.

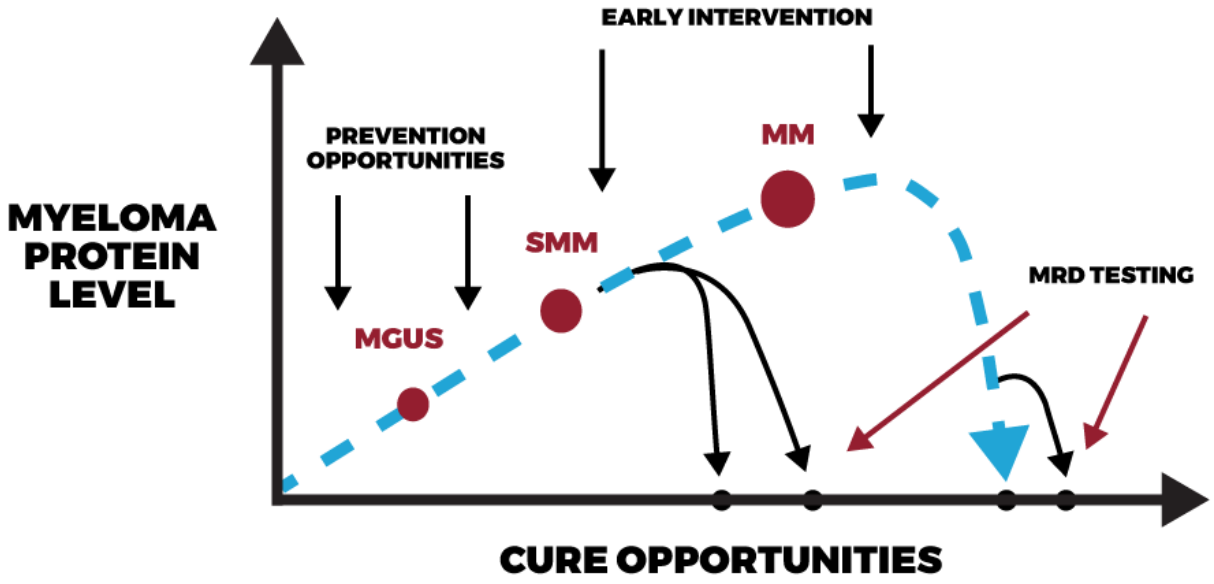
Der primäre Endpunkt der Studie wurde nicht erreicht

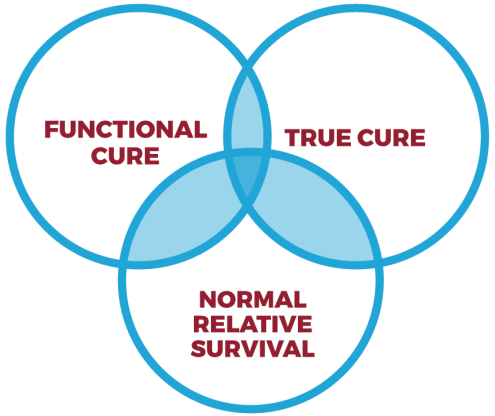


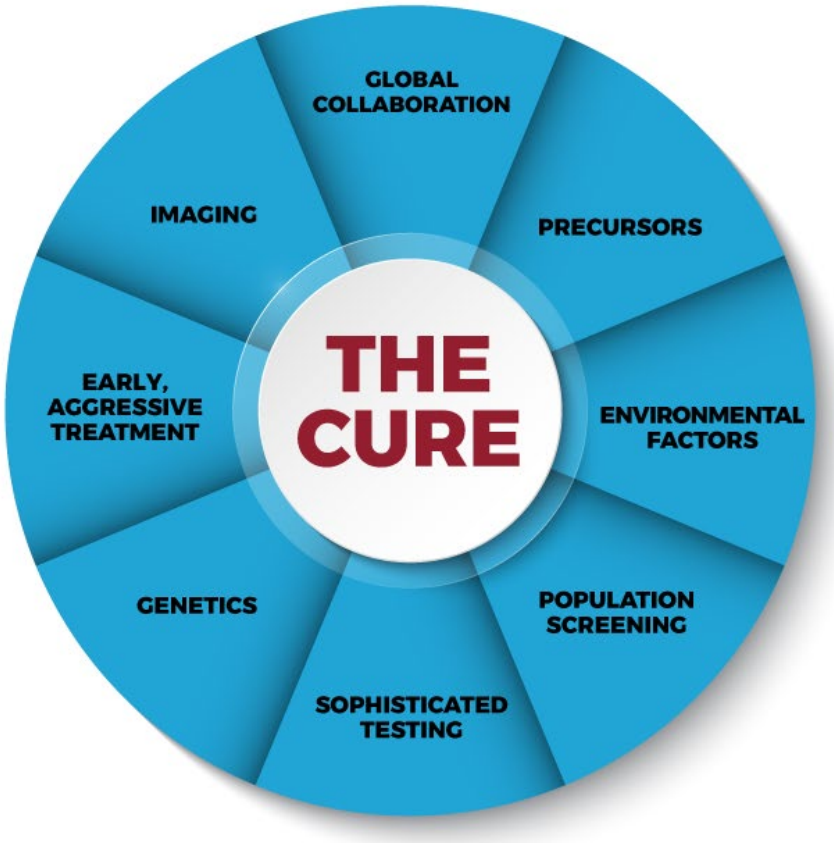


Cure Myeloma

Uniklinikum Würzburg







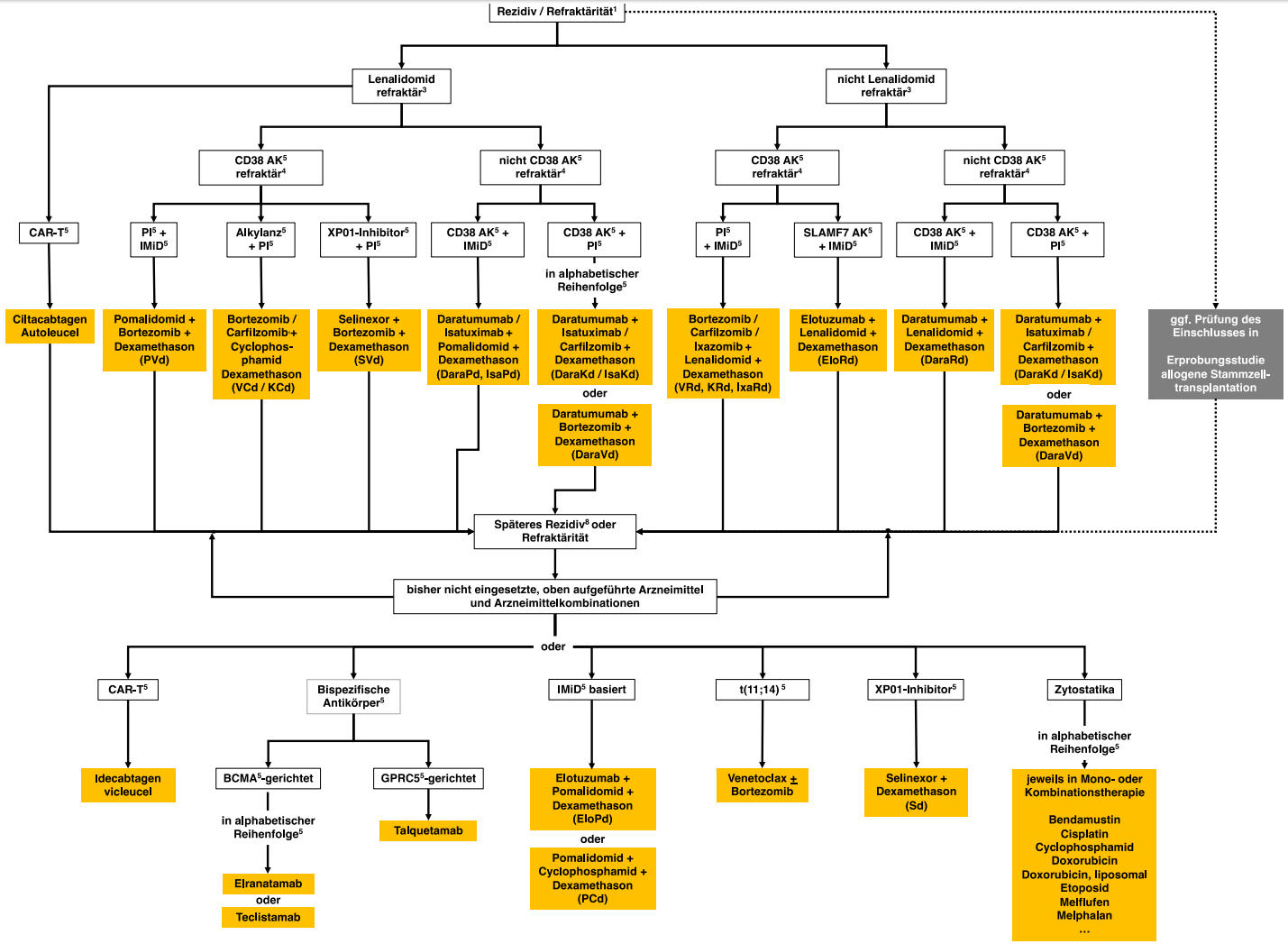
MANY APPROACHES. ONE TARGET:

THE IMF ON THE ROAD TO THE CURE.

Road to the Cure | International Myeloma Foundation

Zusammenfassung: Myelom - Algorithmus 2024

Rückfall



Entwurf

Vielen Dank für Ihre Aufmerksamkeit

Prof. B. Wörmann