UNIKLINIK
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Multiples Myelom

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Potentielle Interessenskonflikte

Honorare:

Amgen, BMS, GSK, Janssen, MSD, Novartis, Roche, Takeda

Forschungsunterstützung:

Novartis, Takeda, Janssen

Neu zugelassenen Medikamente bei MM

Farydak (Panobinostat)	EU Zulassung 4.9.15
Kyprolis (Carfilzomib)	EU Zulassung 20.11.15
Empliciti (Elotuzumab)	EU Zulassung 11.5.16
Darzalex (Daratumumab)	EU Zulassung 25.5.16
Ninlaro (Ixazomib)	EU Zulassung 24.11.16
Sarclisa (Isatuximab)	EU Zulassung 30.5.20
Blenrep (Belantamab Mafodotin	EU Zulassung 26.8.20
Nexpovio (Selinexor)	EU Zulassung 26.3.21
Abecma (Idecabtagen vicleucel)	EU Zulassung 18.8.21

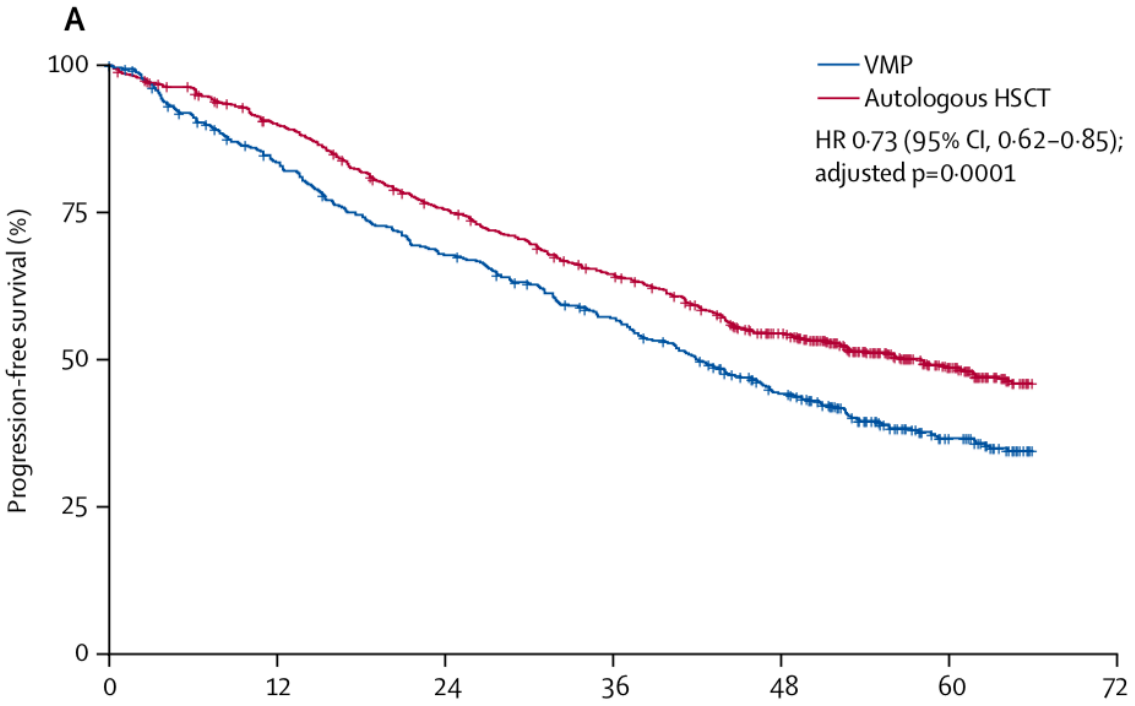
Erwartet: Teclistamab, Ciltacel, ...

Angesichts der vielen neuen Substanzen: Ist die Hochdosistherapie noch nötig?

Hochdosis Melphalan bleibt Standard!

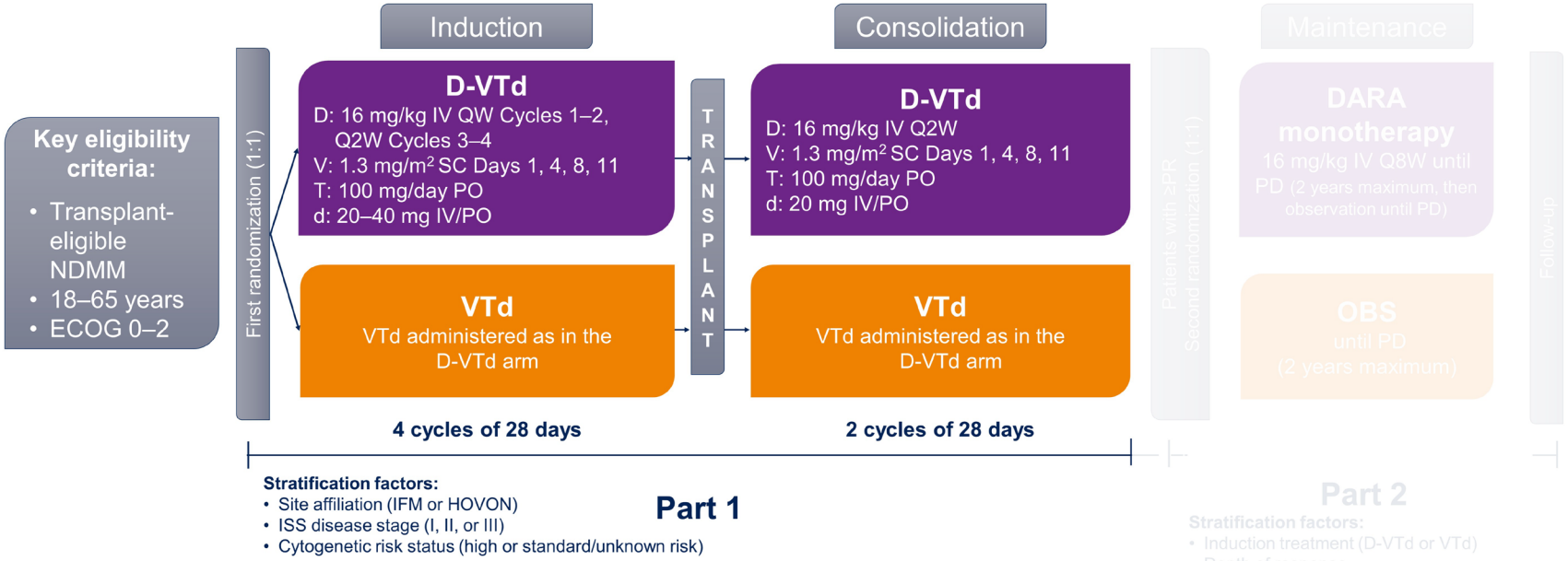
		PFS: HDT	PFS: no HDT	p
Palumbo et al. NEJM 2014	Rd + 2x HDT+/- R vs Rd + MPR +/- R	43.0	22.4	<0.001
Gay et al. Lancet Oncol 2015	Rd + 2x HDT+R vs Rd+CRD + R	43.3	28.6	<0.001
Attal et al. NEJM 2017	3 VRD + HDT + 2 VRD + R vs 8 VRD + R	50	36	<0.001
Cavo et al. Lancet Haematol 2020	3 VCD + HDT+- VRD + R vs 3 VCD + 4 VMP +-VRD + R	56.7	41.9	0.0001

EMN02: PFS mit und ohne Hochdosistherapie



CASSIOPEIA Part 1 Study Design

- Part 1 compared D-VTd vs VTd as induction/consolidation

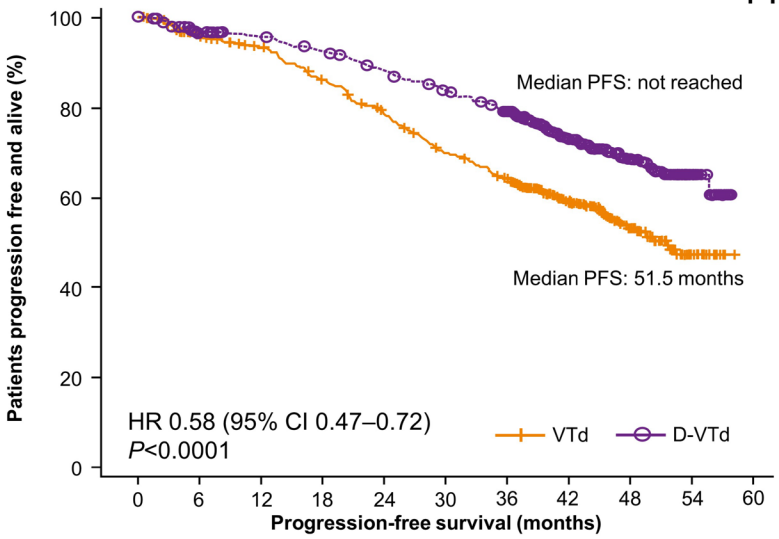


D-VTd, daratumumab, bortezomib, thalidomide, and dexamethasone; ECOG, Eastern Cooperative Oncology Group; IFM, Intergroupe Francophone du Myélome; ISS, International Staging System; HOVON, the Dutch-Belgian Cooperative Trial Group for Hematology-Oncology; IV, intravenous; NDMM, newly diagnosed multiple myeloma; PO, oral; Q2W, every 2 weeks; QW, every week; SC, subcutaneous; VTd, bortezomib, thalidomide, and dexamethasone.

Updated Analyses From First Randomization Confirm Benefits of D-VTd vs VTd Induction/Consolidation

Median follow-up: 44.5 months

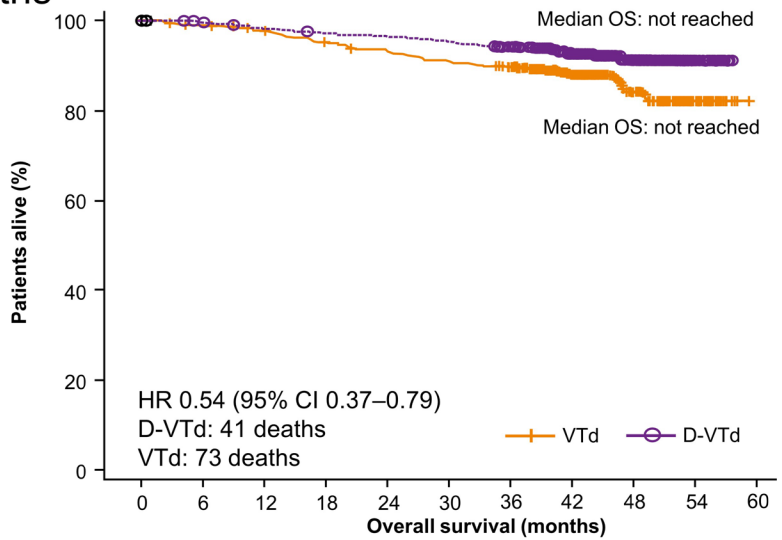
PFS



Patients at risk

VTd	542	499	472	434	391	345	312	191	90	26	0
D-VTd	543	507	495	478	452	426	395	237	119	29	0

OS



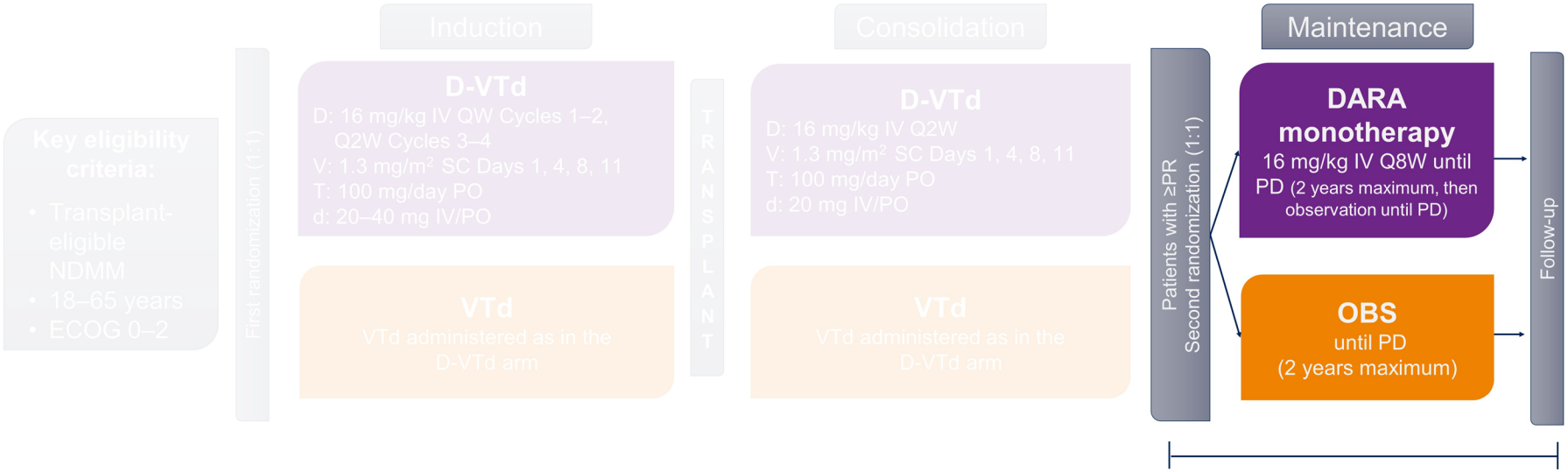
Patients at risk

VTd	542	531	521	505	494	481	468	305	151	42	0
D-VTd	543	536	526	520	517	510	498	327	162	37	0

CI, confidence interval; D-VTd, daratumumab, bortezomib, thalidomide, and dexamethasone; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; VTd, bortezomib, thalidomide, and dexamethasone.

CASSIOPEIA Part 2 Study Design

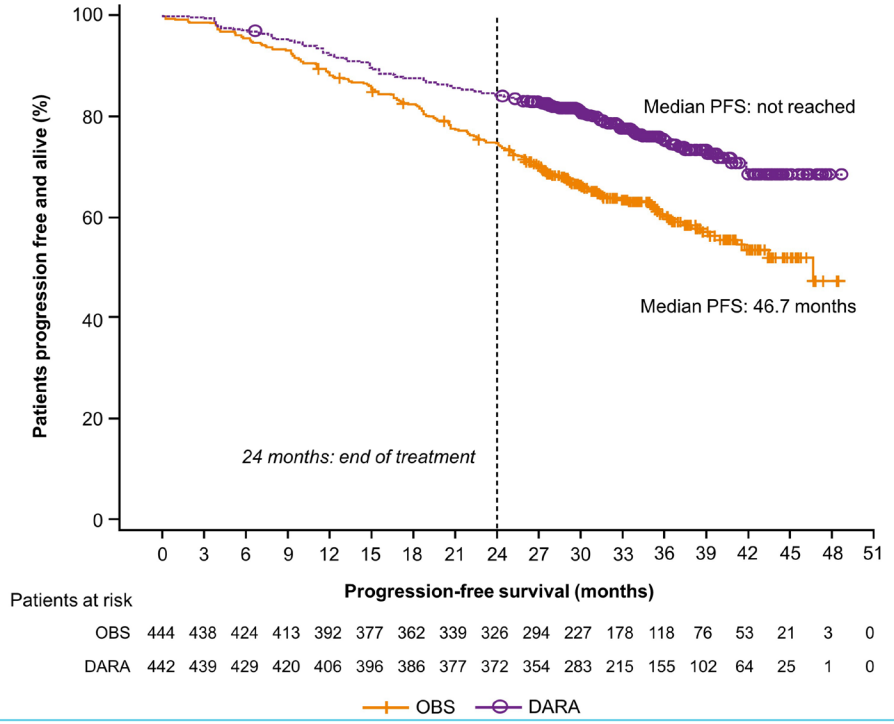
- Patients who completed consolidation and achieved ≥PR were re-randomized 1:1 to DARA 16 mg/kg IV every 8 weeks or OBS (no maintenance) for 2 years



≥PR, partial response or better; DARA, daratumumab; D-VTd, daratumumab, bortezomib, thalidomide, and dexamethasone; IV, intravenous; OBS, observation; PD, progressive disease; Q8W, every 8 weeks; VTd, bortezomib, thalidomide, and dexamethasone.

DARA Significantly Improved PFS From Second Randomization vs OBS

Median follow-up: 35.4 months from second randomization

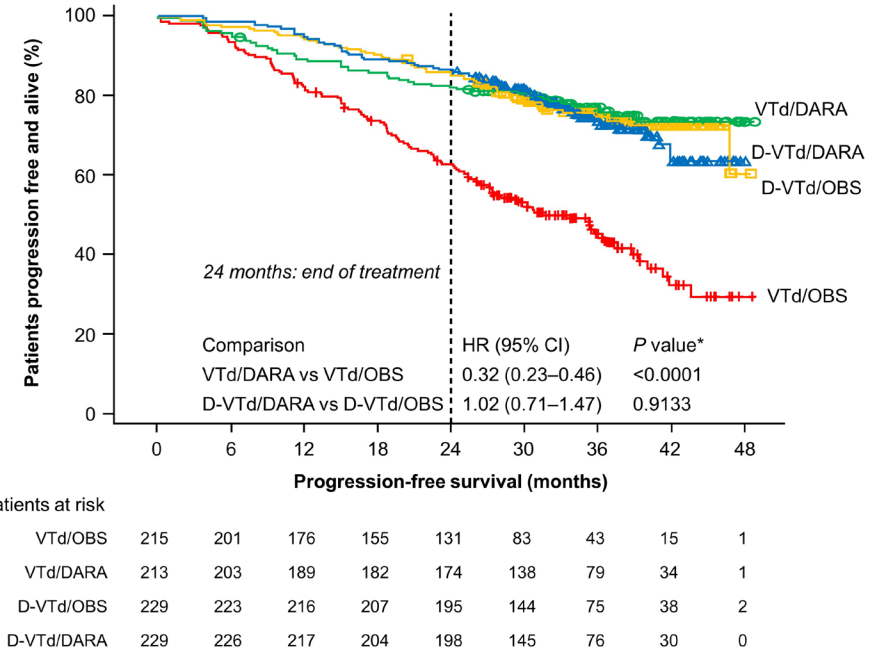


HR 0.53
(95% CI 0.42–0.68)
P<0.0001

CI, confidence interval; DARA, daratumumab; HR, hazard ratio; OBS, observation; PFS, progression-free survival.

DARA Significantly Improved PFS vs OBS in Patients Treated With VTd Induction/Consolidation

- A prespecified analysis showed significant interaction between maintenance and induction/consolidation therapy
- A PFS benefit was observed for VTd/DARA vs VTd/OBS
- PFS was not different for D-VTd/DARA vs D-VTd/OBS



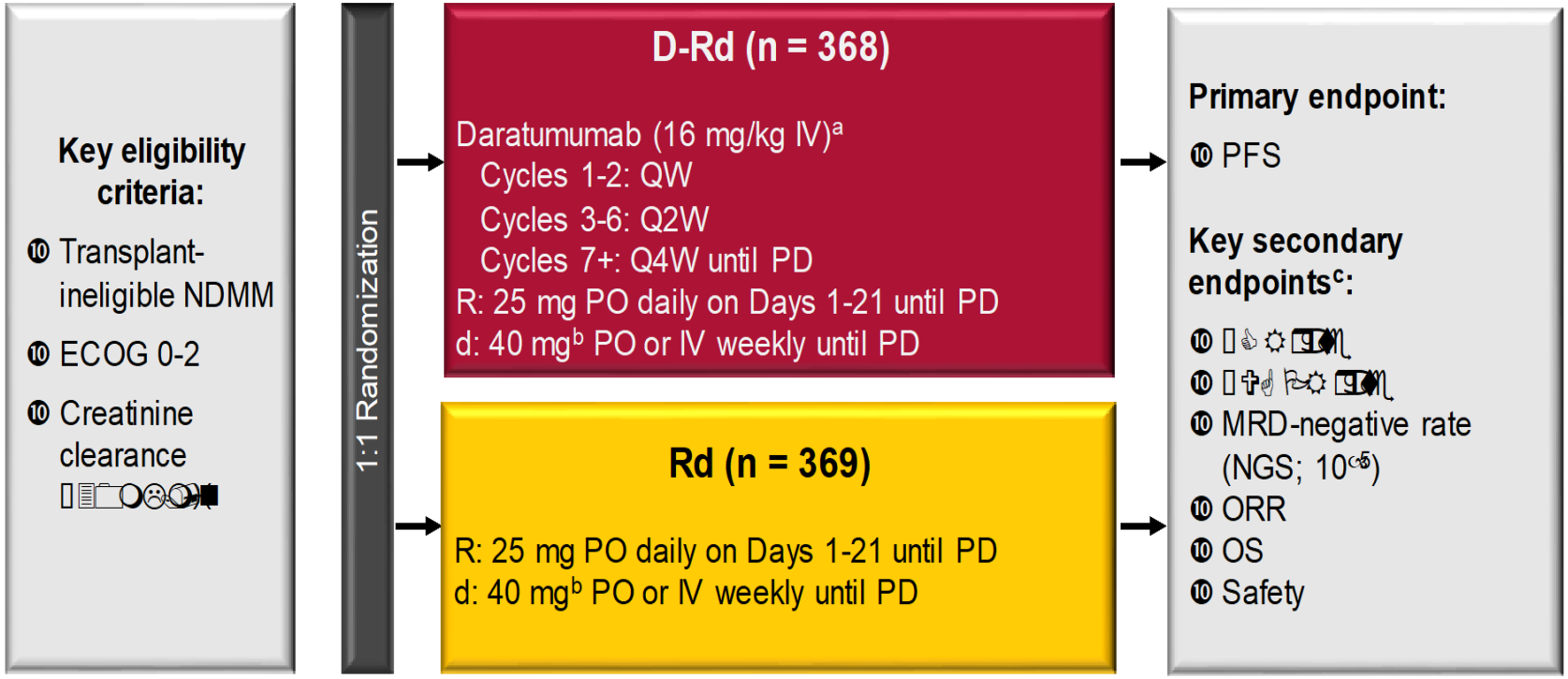
*Nominal *P* value.
CI, confidence interval; D-VTd, daratumumab, bortezomib, thalidomide, and dexamethasone; DARA, daratumumab; HR, hazard ratio; OBS, observation; PFS, progression-free survival; VTd, bortezomib, thalidomide, and dexamethasone.

Und wenn Hochdosistherapie keine Option ist?

Zugelassene Kombinationen:
VRd (besser als Rd)
Daratumumab-VMP (besser als VMP)
Daratumumab-Rd (besser als Rd)

MAIA Study Design

Phase 3 study of D-Rd vs Rd in transplant-ineligible NDMM (N = 737)



Stratification factors
- ISS (I vs II vs III)
- Region (NA vs other)

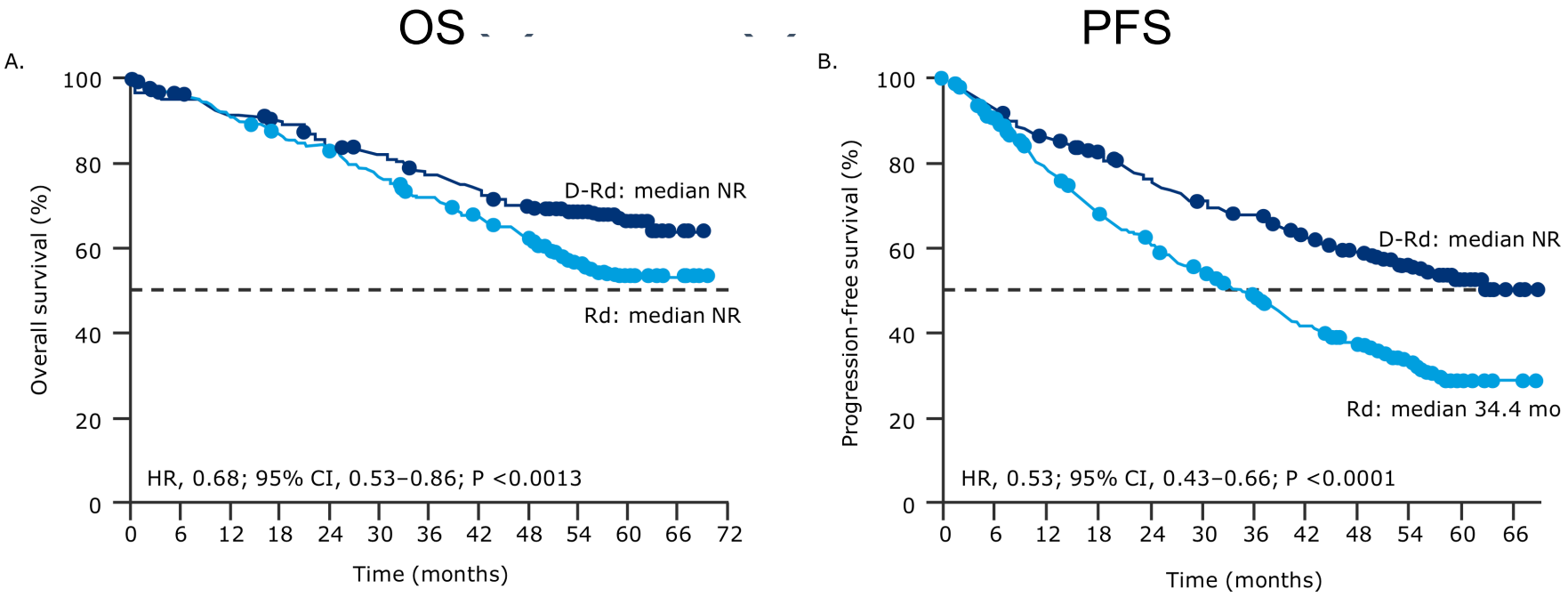
Cycle: 28 days

[a]On days when daratumumab was administered, dexamethasone was administered to patients in the D-Rd arm and served as the treatment dose of steroid for that day, as well as the required pre-infusion medication.
[b]For patients older than 75 years of age or with BMI <18.5, dexamethasone was administered at a dose of 20 mg weekly.
[c]Efficacy endpoints were sequentially tested in the order shown.

ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; NA, North America; IV, intravenously; QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; PD, progressive disease; PO, orally; CR, complete response; VGPR, very good partial response; MRD, minimal residual disease; NGS, next-generation sequencing; ORR, overall response rate; OS, overall survival; BMI, body mass index.

Antikörper in der Erstlinie: DRd vs Rd

Langzeitdaten der MAIA Studie



Facon et al. EHA 2021

Was geben nach DRd?

Nicht optimal für Len- + Dara-refraktäre Patienten:

KRd, Ixa-Rd, Dara-Rd, Elo-Rd

Dara-Kd, Dara-Vd, Isa-Kd

Dara-Pd, Isa-Pd

Übrig:

Kd, (Pd), PVD, (Elo-Pd)

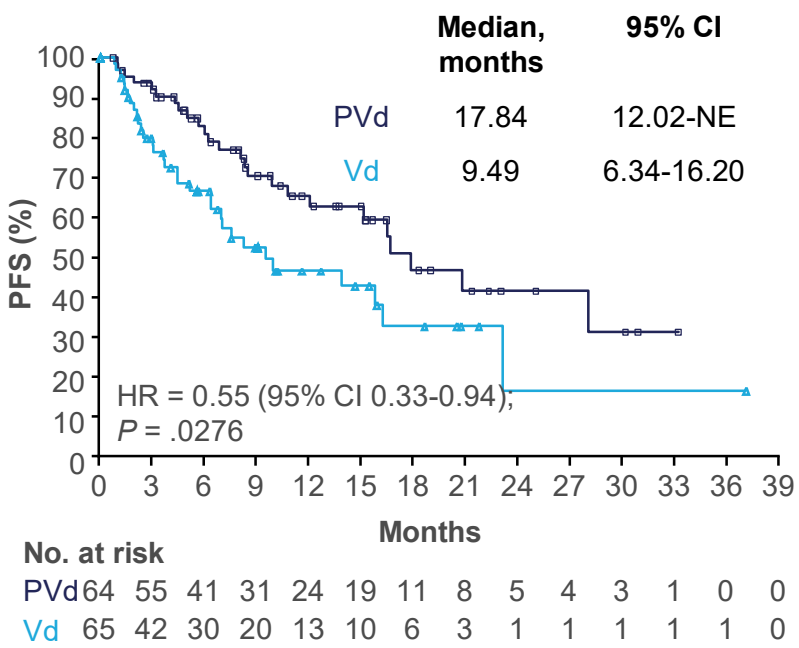
Optimismm: PVd versus Vd in second-line treatment

PFS

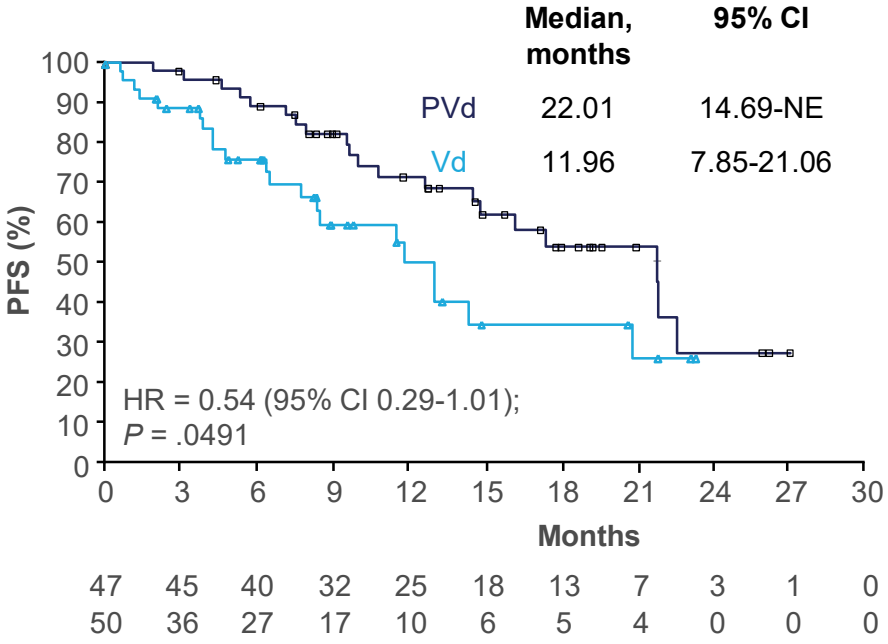
Median follow-up was 16.4 months

PVd reduced the risk of progression or death by 45%-46% after 1 prior line of therapy regardless of LEN refractoriness

LEN Refractory



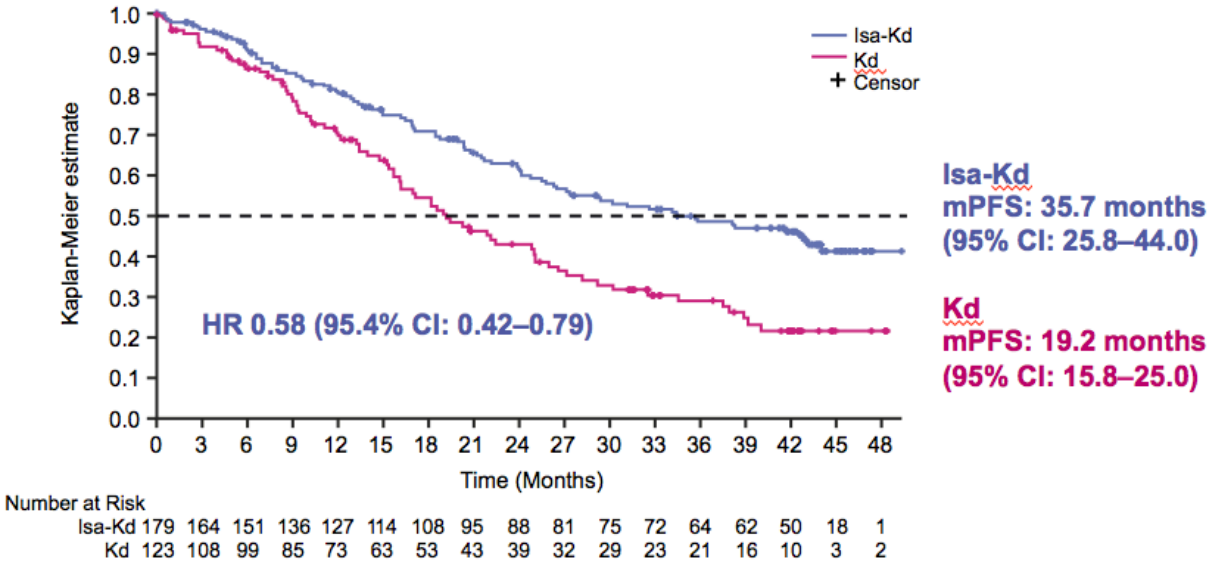
LEN Nonrefractory



Dimopoulos M, et al. Poster presentation at ASH 2018 [abstract 3278].

IKEMA: Isatuximab-Kd vs Kd

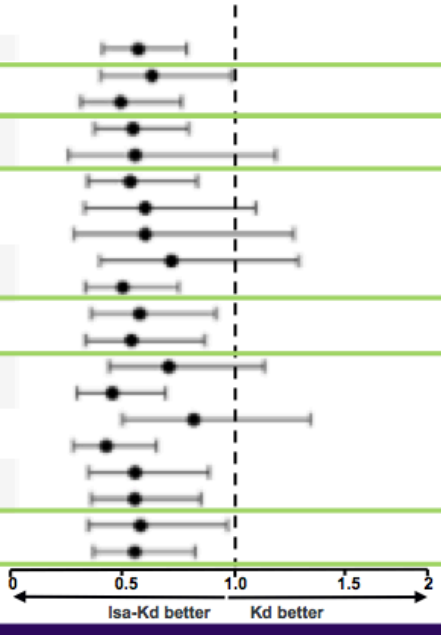
Updated PFS (primary endpoint) – IRC assessment (ITT)



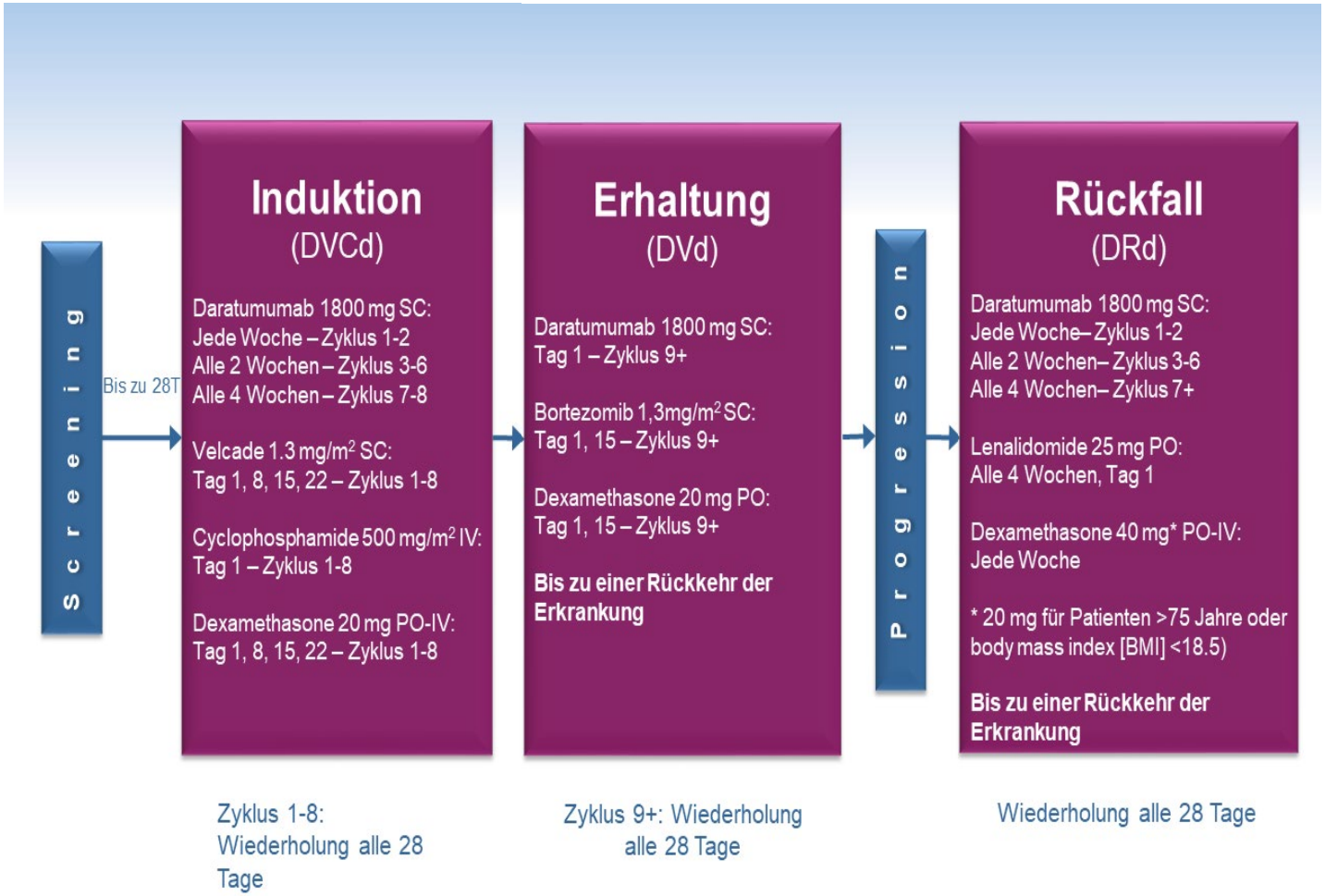
IKEMA: Isatuximab-Kd vs Kd

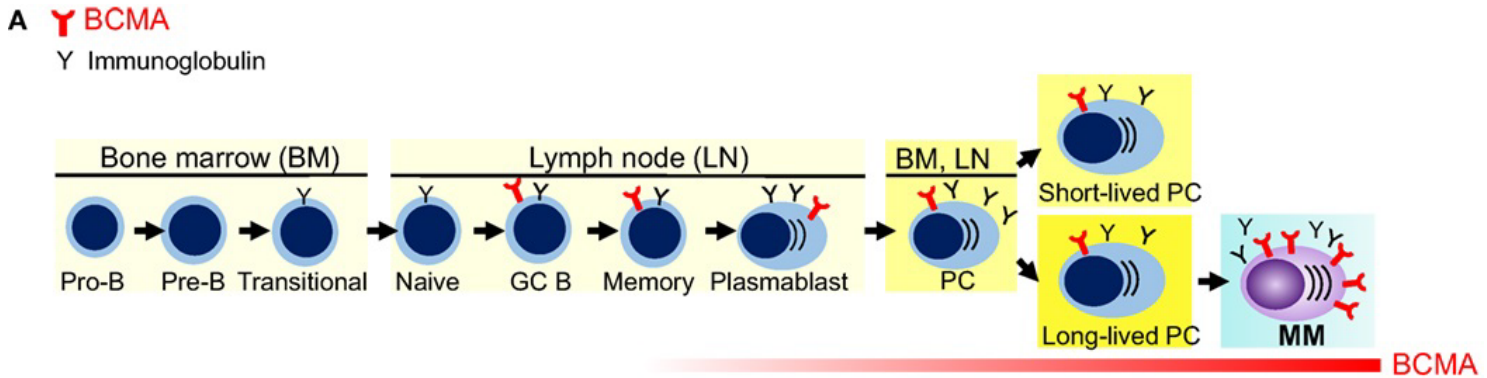
PFS subgroup analyses

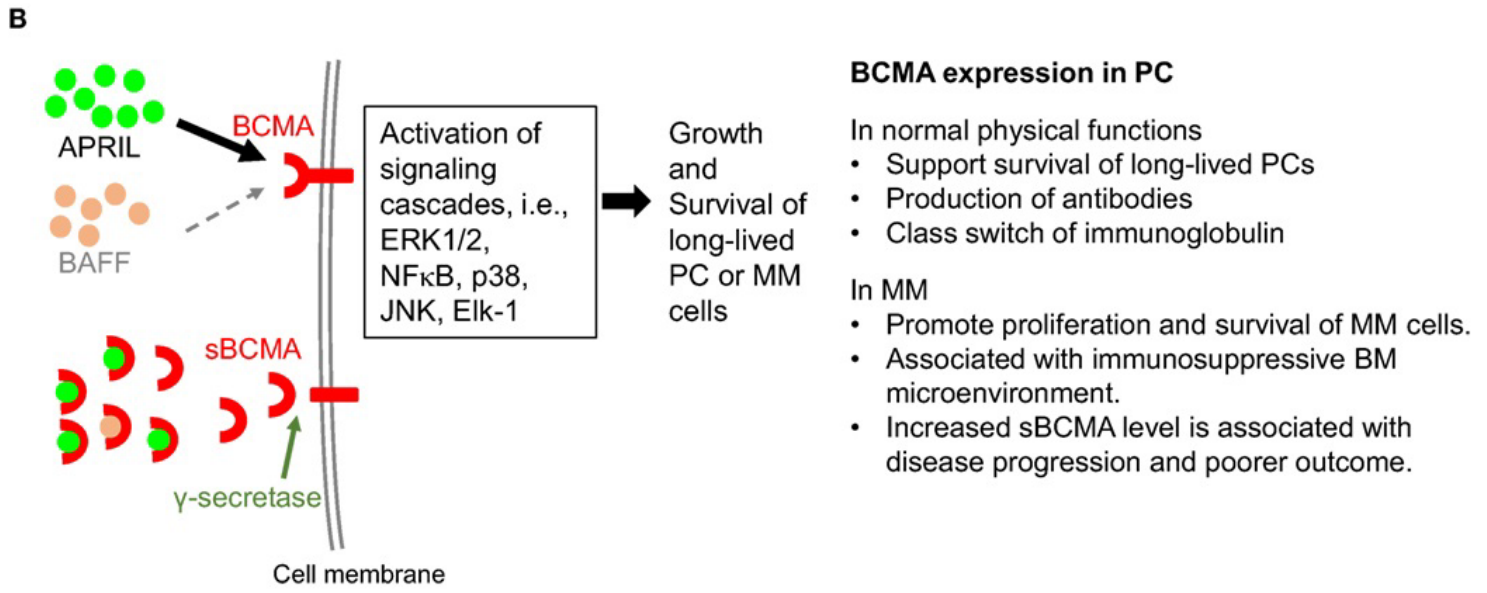
Subgroup		Isa-Kd Events/total	Kd Events/total	Hazard ratio (95% CI)
All patients		86/179	77/123	0.576 (0.418–0.792)
Age	<65 years	43/88	38/66	0.637 (0.410–0.990)
	≥65 years	43/91	39/57	0.497 (0.321–0.771)
Baseline eGFR (MDRD)	≥60 mL/min/1.73 m²	55/122	60/93	0.553 (0.382–0.801)
	<60 mL/min/1.73 m²	23/43	10/18	0.562 (0.266–1.189)
ISS staging at study entry	I	39/89	43/71	0.541 (0.350–0.837)
	II	34/63	17/31	0.608 (0.336–1.099)
	III	13/26	16/20	0.607 (0.290–1.268)
High-risk cytogenetic status	Yes	26/42	21/31	0.724 (0.406–1.290)
	No	50/114	48/77	0.508 (0.341–0.758)
1q21+	Yes	39/75	35/52	0.582 (0.368–0.923)
	No	39/84	33/55	0.546 (0.342–0.873)
Number of prior lines of therapy	1	41/80	31/55	0.712 (0.445–1.138)
	>1	45/99	46/68	0.460 (0.302–0.698)
Prior PI treatment*	Yes	43/81	26/47	0.824 (0.506–1.343)
	No	43/98	51/76	0.434 (0.286–0.657)
Prior IMiD treatment*	Yes	37/81	37/62	0.562 (0.355–0.892)
	No	49/98	40/61	0.560 (0.367–0.854)
Refractory to lenalidomide	Yes	31/57	30/42	0.586 (0.353–0.972)
	No	55/122	47/81	0.560 (0.378–0.829)



GMMG-DADA Studie







Cho at al., Front. Immunol. 2018

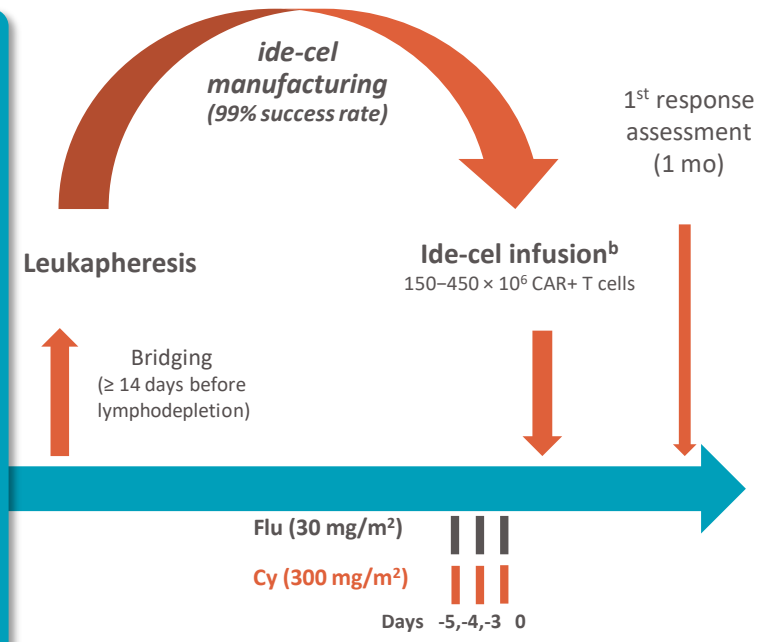
Idecabtagene vicleucel: anti BCMA CART

- Multiple myeloma affects the older population more commonly than younger age groups; median age at diagnosis is 69 years in the US[1]
- Advanced age negatively impacts prognosis and limits treatment options for patients with hematologic malignancies, including multiple myeloma[2,3]
- Ide-cel, a BCMA-directed CAR T cell therapy, showed deep and durable responses across target dose levels of 150−450 × 10^6 CAR+ T cells in the pivotal phase II KarMMa study of patients with triple-class exposed RRMM[4]

Objective: To examine the efficacy and safety of ide-cel in elderly patients in the KarMMa study

Pivotal phase II KarMMa study[4]

Patients with RRMM
- ≥3 prior regimens with ≥2 consecutive cycles each (or best response of PD)
- Previously exposed to
  - IMiD agent
  - Proteasome inhibitor
  - Anti-CD38 antibody
- Refractory to last prior therapy per IMWG criteria[a]



Primary endpoint: ORR (null hypothesis ≤ 50%)

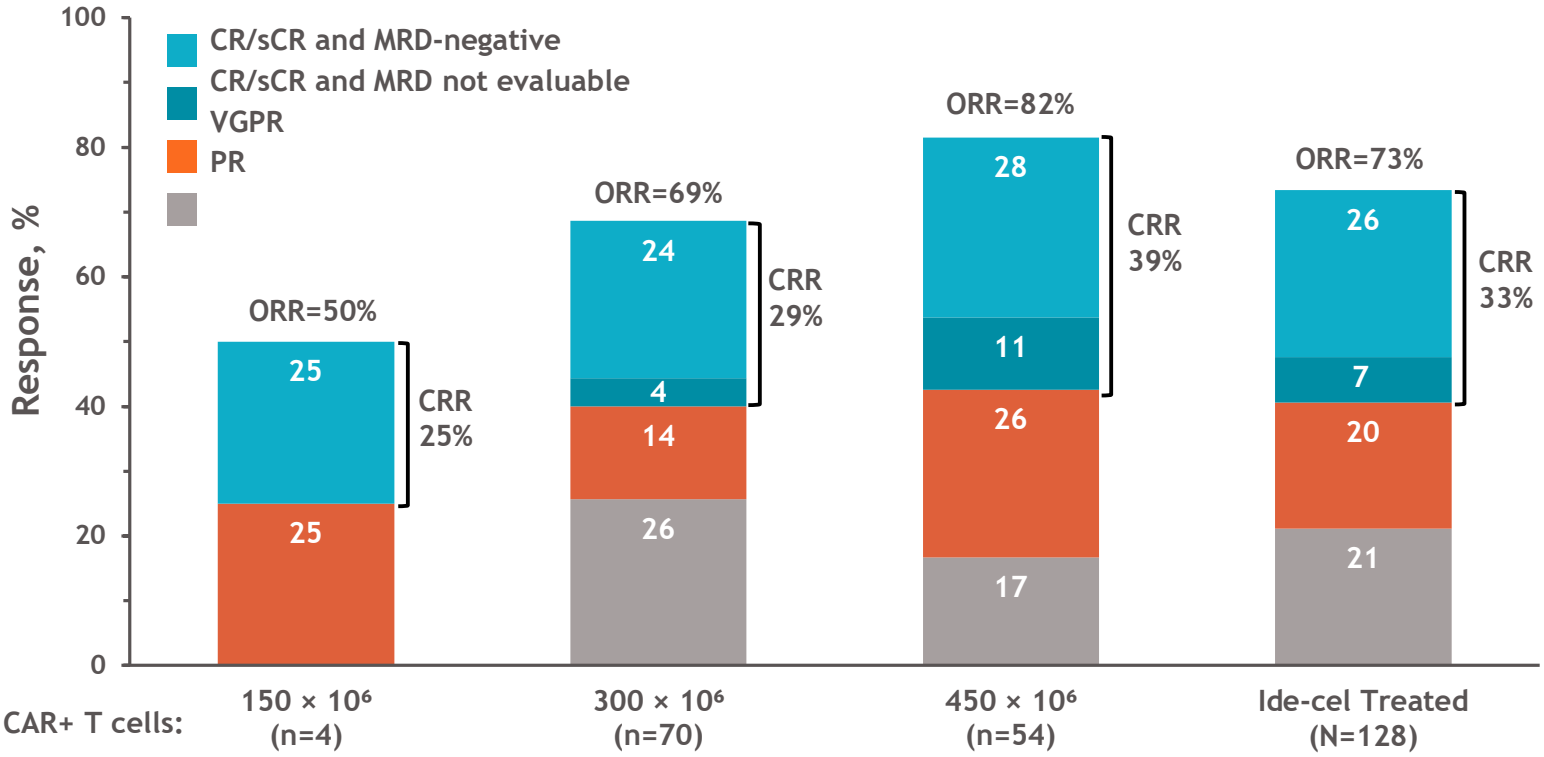
EudraCT: 2017-002245-29
ClinicalTrials.gov: NCT03361748

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; Cy, cyclophosphamide; Flu, fludarabine; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; ORR, overall response rate; PD, progressive disease; RRMM, relapsed and refractory multiple myeloma; US, United States.

[a] Defined as documented PD during or within 60 days from last dose of prior antimyeloma regimen. [b] Patients were required to be hospitalized for 14 days postinfusion. Ide-cel retreatment was allowed at PD for best response of at least stable disease.

1. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database. 2. Hassan M, et al. *Haematologica*. 2014;99:1124-1127. 3. Krok-Schoen JL, et al. *Cancer Med.* 2018;7:3425–3433.
4. Munshi NC, et al. *J Clin Oncol.* 2020;38[suppl, abstr]:8503.

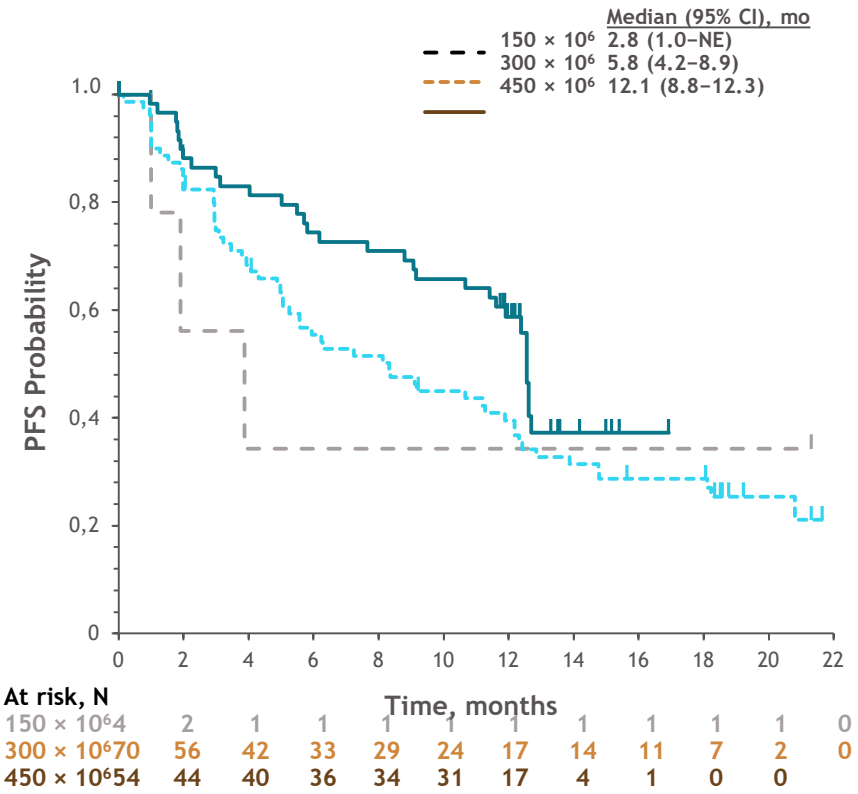
Ide-cel: KarMMa Study



- Primary (ORR >50%) and key secondary (CRR >10%) endpoints met in the ide-cel treated population
  - *ORR of 73% (95% CI, 65.8−81.1; P<0.0001*)*
  - *CRR (CR/sCR) of 33% (95% CI, 24.7−40.9; P<0.0001)*
- Median time to first response of 1.0 mo (range, 0.5−8.8); median time to CR of 2.8 mo (range, 1.0−11.8)
- Median follow-up of 13.3 mo across target dose levels

Data cutoff: 14 Jan 2020. MRD-negative defined as $<10^{-5}$ nucleated cells by next generation sequencing. Only MRD values within 3 mo of achieving CR/sCR until progression/death (exclusive) were considered.
Values may not add up due to rounding.
CR/sCR, complete response/stringent CR; CRR, CR rate; MRD, minimal residual disease; ORR, overall response rate (≥PR); PR, partial response; VGPR, very good PR. **P* value at the primary data cutoff with same ORR and 95% CI.

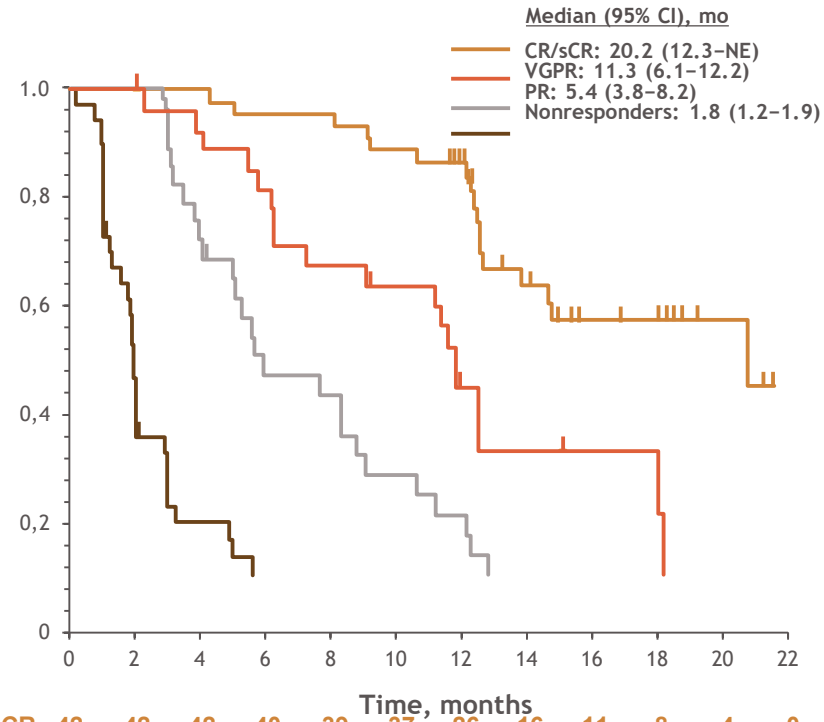
PFS by Target Dose



At risk, N											
150 × 10⁶	4	2	1	1	1	1	1	1	1	1	0
300 × 10⁶	70	56	42	33	29	24	17	14	11	7	2	0
450 × 10⁶	54	44	40	36	34	31	17	4	1	0	0

- PFS increased with higher target dose; median PFS was 12 mo at 450 × 10^6 CAR+ T cells

PFS by Best Response



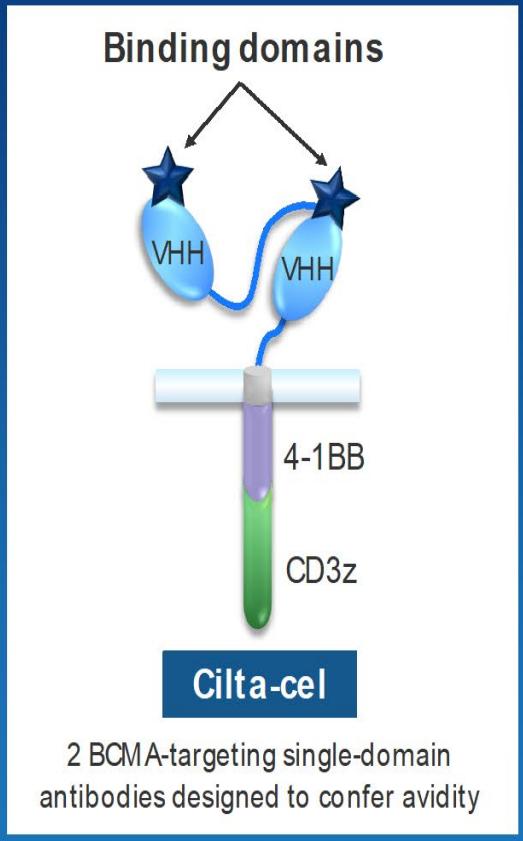
CR/sCR	42	42	42	40	39	37	26	16	11	8	4	0
VGPR	25	25	22	20	16	14	8	3	2	0	0	
PR	27	16	10	9	5	1	0	0	0	0	0	
Nonresponders	34	8	83	70	64	56	35	19	13	8	4	0

- PFS increased by depth of response; median PFS was 20 mo in patients with CR/sCR

Data cutoff: 14 Jan 2020. NE, not estimable; PFS, progression-free survival.

Ciltacabtagene autoleucel (cilta-cel; JNJ-68284528) is a chimeric antigen receptor T-cell therapy for the treatment of patients with RRMM[1]

- In the phase 1b/2 CARTITUDE-1 study, early, deep, and durable responses were observed with a single cilta-cel infusion in heavily pretreated patients with RRMM[1]
  - At a median follow-up of 12.4 months
    - Cilta-cel had a manageable safety profile
    - ORR and sCR were 97% and 67%, respectively
    - Overall 12-month PFS and OS rates were 77% and 89%, respectively
    - Median PFS and duration of response were not reached (95% CI, 16.8–not estimable and 15.9–not estimable, respectively)
- **Here, we report updated results from the CARTITUDE-1 study with a longer duration of follow-up (median ~2 years)[a]**



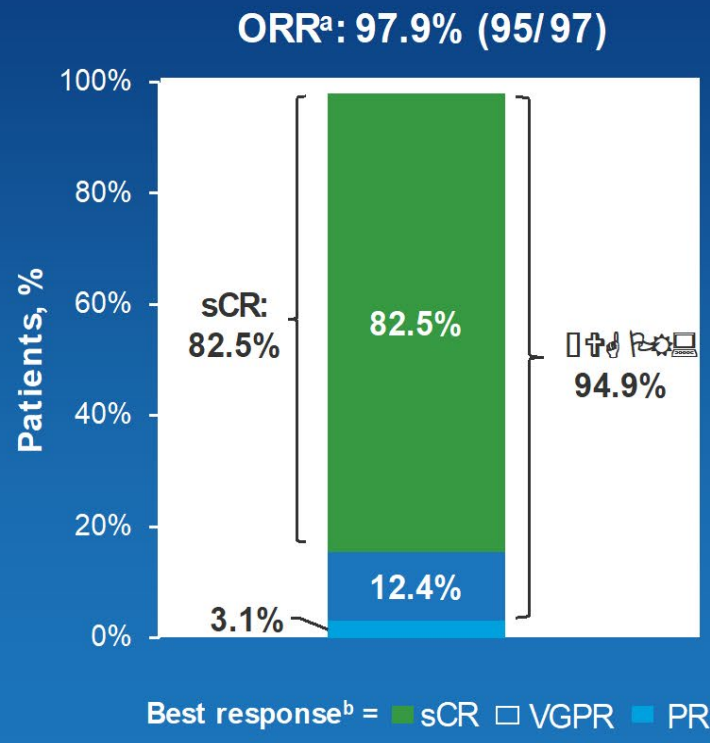
[a]Median 21.7 months, data cut-off July 22,2021

BCMA, B-cell maturation antigen; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma; sCR, stringent complete response; VHH, single variable domain on a heavy chain

1. Berdeja JG, et al. *Lancet* 2021; 398:314-24.

Presented at the 63rd American Society of Hematology (ASH) Annual Meeting & Exposition; December 11-14, 2021; Atlanta, GA/Virtual.

CARTITUDE-1: Efficacy Response



Responses deepened over time from the 1-year follow-up

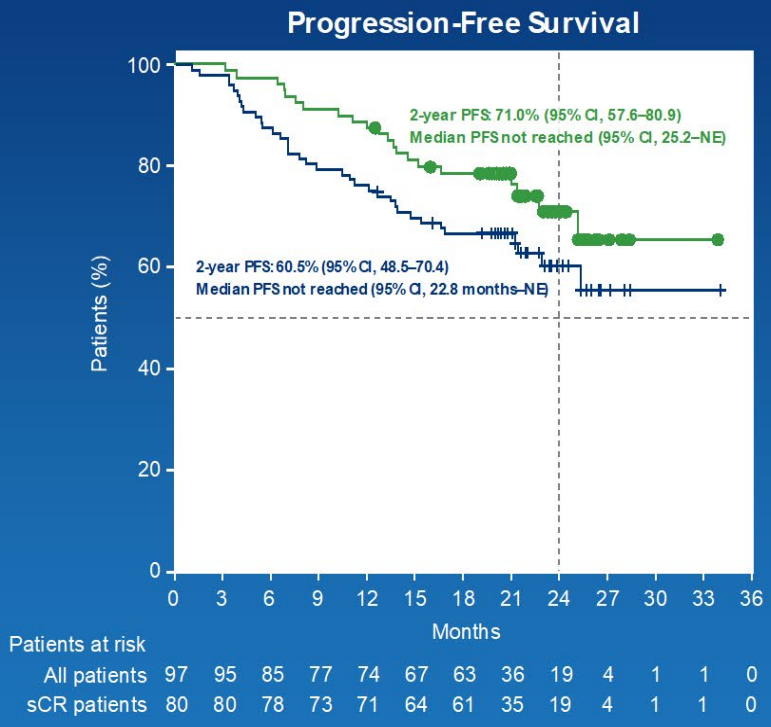
Best response at any time	Median–1 year follow-up	Median–2 years follow-up
sCR, %	67	83

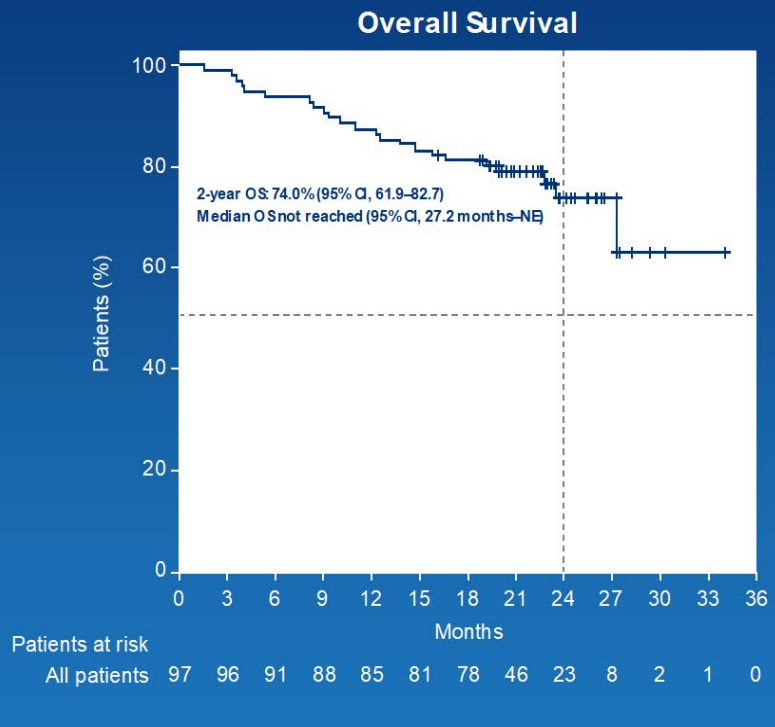
- Median time to first response was 1 month (range, 0.9–10.7)
- Median time to best response was 2.6 months (range, 0.9–17.8)
- Median time to CR or better was 2.9 months (range, 0.9–17.8)
- Median duration of response was not estimable (21.8 months–NE)
- 60.5% of patients are still progression-free at 2 years

[a]ORR assessed by independent review committee; [b]No patient had CR or stable disease as best response.
CR, complete response; NE, not estimable; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

Presented at the 63rd American Society of Hematology (ASH) Annual Meeting & Exposition; December 11-14, 2021; Atlanta, GA/Virtual.

CARTITUDE-1: Progression-Free Survival and Overall Survival





All patients sCR patients

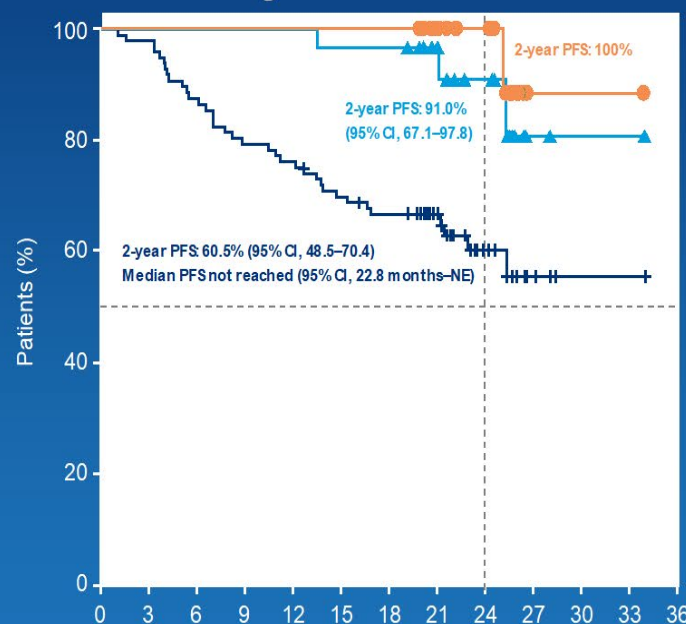
MRD, minimal residual disease; NE, not estimable; OS, overall survival; PFS, progression-free survival; sCR, stringent complete response

Presented at the 63rd American Society of Hematology (ASH) Annual Meeting & Exposition; December 11-14, 2021; Atlanta, GA/Virtual.

CARTITUDE-1: Progression-Free Survival and Overall Survival by MRD Negativity (10^{-5}) [illegible]

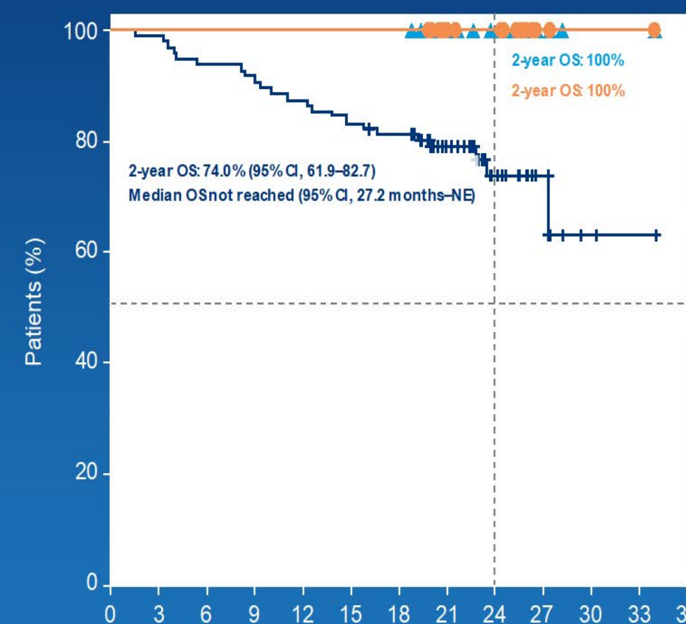
- Of the 61 patients evaluable for MRD, 92% were MRD-negative (at 10^{-5})

Progression-Free Survival



Patients at risk	0	3	6	9	12	15	18	21	24	27	30	33	36
All patients	97	95	85	77	74	67	63	36	19	4	1	1	0
[illegible]	30	30	30	30	30	29	29	17	12	2	1	1	0
[illegible]	18	18	18	18	18	18	18	12	10	1	1	1	0

Overall Survival



Patients at risk	0	3	6	9	12	15	18	21	24	27	30	33	36
All patients	97	96	91	88	85	81	78	46	23	8	2	1	0
[illegible]	30	30	30	30	30	30	30	17	13	3	1	1	0
[illegible]	18	18	18	18	18	18	18	12	11	2	1	1	0

All patients — [illegible] — [illegible]

MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival

Presented at the 63rd American Society of Hematology (ASH) Annual Meeting & Exposition; December 11-14, 2021; Atlanta, GA/Virtual.

Zusammenfassung und Ausblick

Primärtherapie:

Bortezomib+- Daratumumab-Induktion, Hochdosistherapie, Len-Erhaltung

VRd, Dara-VMP und Dara-Rd neue Standards für HDT-ungeeignete Patienten

Offene Studien: GMMG-DADA, GMMG-CONCEPT

Frühes Rezidiv:

Carfilzomib oder Pomalidomid in Kombinationen, Bortezomib oder Lenalidomid in Kombinationen

Spätes Rezidiv:

Belantamab-Mafodotin, Idecabtagene vicleucel

Dringend erwartet: weitere CAR-T, bispezifische Antikörper

Studien in Vorbereitung: CART und bispezifische Ak in der Primärtherapie

Vielen Dank für Ihre Aufmerksamkeit!