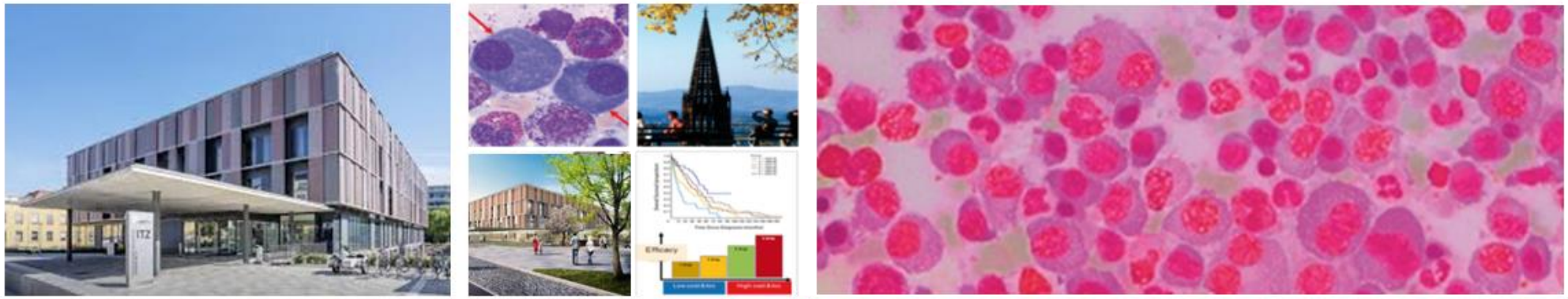
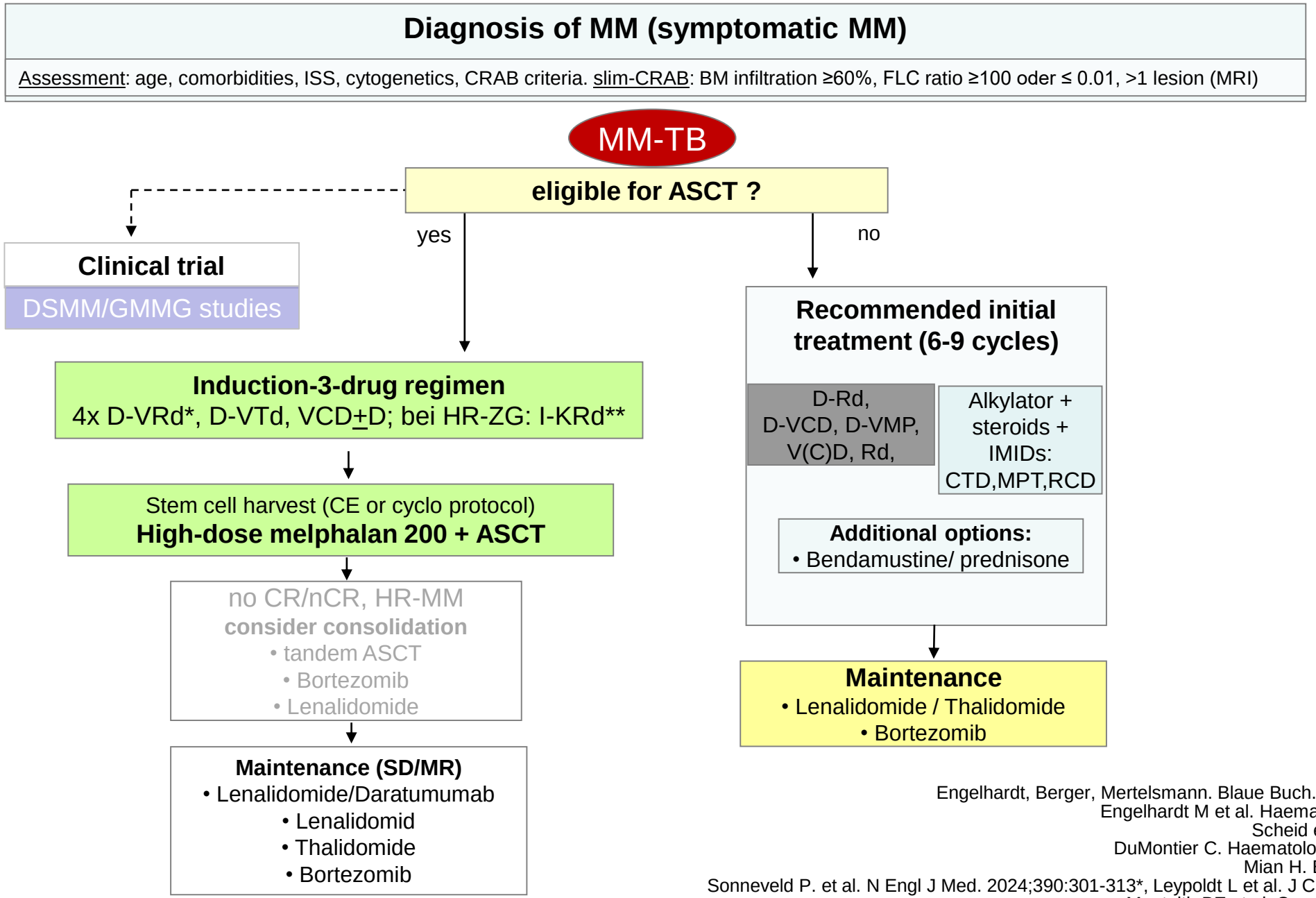
Guideline/Pathway for diagnosis, management and treatment of multiple myeloma (MM)



M.Engelhardt, X.Tonnar, J.Kus, A.Weis, H.Reinhardt, M.Braun, H.Wenger, S.Wenger, M.Pantic, P.Zart, M-A.Calba, J.Neubauer, H.Schäfer, G.Herget, C.Miething, C.Greil, R.Wäsch

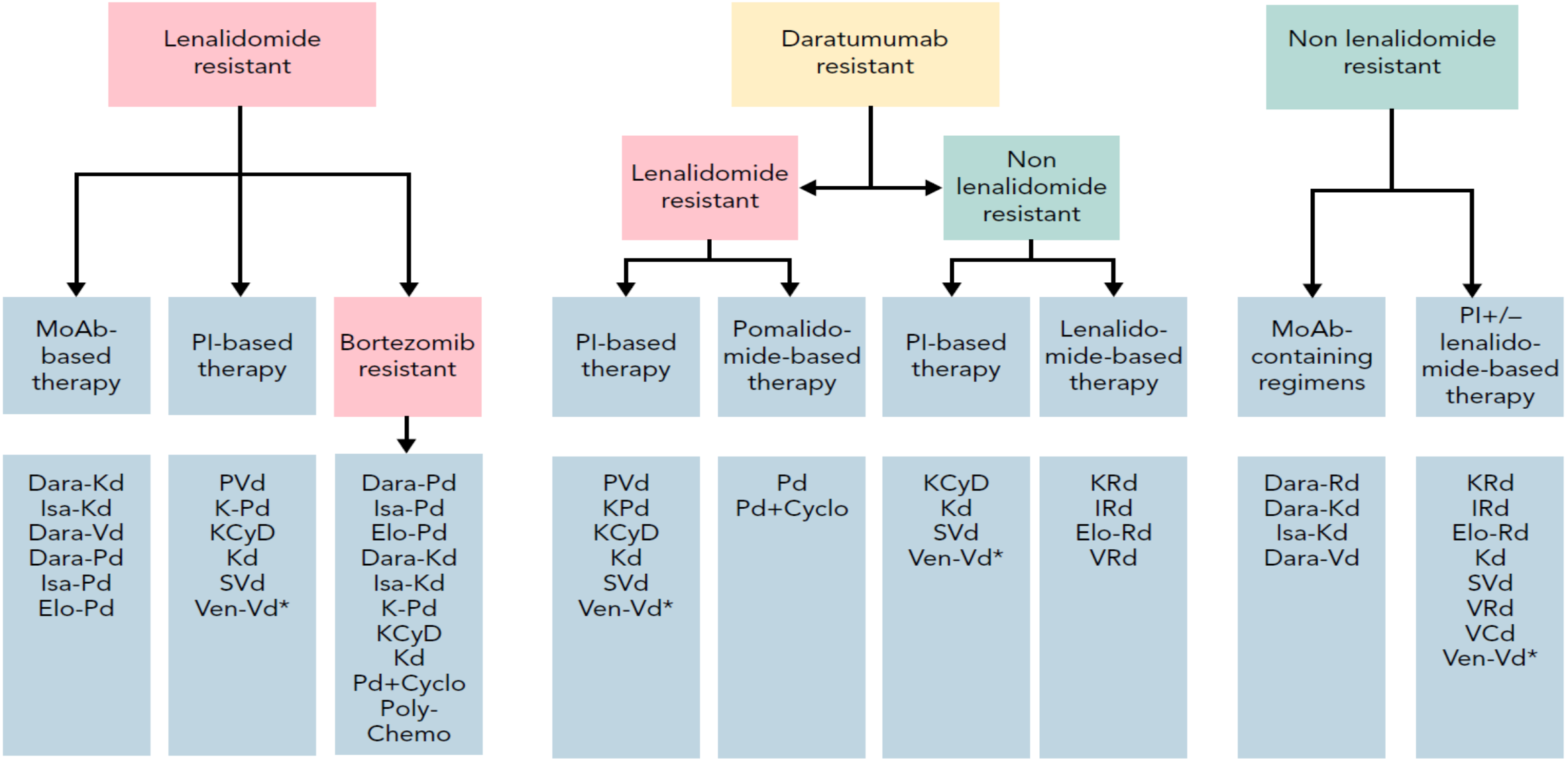
V13, gültig bis 3/2025

UKF-Pathway: Newly diagnosed MM



Engelhardt, Berger, Mertelsmann. Blaue Buch. 8. Auflage. Springer 2023
Engelhardt M et al. Haematologica 2014, 2016, 2017
Scheid et al. S3 Leitlinie MM 2022
DuMontier C. Haematologica. 2022;107:1172-1180
Mian H. Blood Cancer J. 2023;13:6
Sonneveld P. et al. N Engl J Med. 2024;390:301-313*, Leypoldt L et al. J Clin Oncol. 2024;42:26-37**
Monteith BE et al. Curr Oncol 2023;30:4382-4401

Treatment alogorithm for patients with MM with first relapse



van de Donk, Pawlyn, Yong. Lancet 2021;397:410-27
Engelhardt M et al. Haematologica 2014, 2016, 2017; Onkologe 2018
Scheid et al. S3 Leitlinie MM 2022
van de Donk NWCJ. Hematology ASH Educ.2020:248-258 + Lancman G, Richter J, Chari A. Hematology ASH Educ.2020:264-271
Dimopoulos MA, Ann Oncol. 202;32(3):309-322 + Moreau P. Lancet Oncol. 2021;22:e105-e118 + Kastritis E, Terpos E, Dimopoulos MA. Blood. 2022;139:2904-2917

Phase 3 results for 1.-3.relapse treatment in RRMM

	Dara-Rd	Rd	K-Rd	Rd	Elo-Rd	Rd	Ixa-Rd	Rd	Kd	Vd	Dara-Vd	Vd	Dara-Kd	Kd	Isa-Kd	Kd	SVd	Vd	Ven-Vd	Vd
Median of prior lines of therapy in the study (range)	1 (1-11)		2 (1-3)		2 (1-4)		1 (1-3)		2 (1-3)		2 (1-10)		2 (1-3)		1 (1-3)		1 (1-3)		2 (1-3)	
Exclusion per prior therapy	Lenalidomide-resistant		Lenalidomide-resistant and bortezomib-resistant if at last line		Lenalidomide-resistant		Lenalidomide- or bortezomib-resistant		Bortezomib-resistant		Bortezomib-resistant		previous resistance to carfilzomib, or refractory to anti-CD38		previous treatment with carfilzomib, or refractory to anti-CD38		Bortezomib-resistant		Bortezomib-resistant	
ITT population	283	286	396	396	321	325	360	362	464	465	251	247	312	154	179	123	195	207	194	97
PFS	46	17.5	26.3	17.6	19.4	14.9	20.6	14.7	18.7	9.4	16.7	7.1	NE	15.8	NE	19.1	13.9	9.4	22.4	11.5
HR (95% CI)	0.42 (0.33-0.52)		0.69 (0.57-0.83)		0.71 (0.59-0.86)		0.74 (0.59-0.94)		0.53 (0.44-0.65)		0.31 (0.25-0.39)		0.63 (0.46-0.85)		0.53 (0.32-0.89)		0.70 (0.53-0.93)		0.63 (0.44-0.90)	
1 prior line	149	146	184	157	151	159	212	213	231	229	247	251	144	70	80	55	99	99	91	44
PFS	53.3	19.6	29.6	17.6	NA	NA	20.6	16.6	22.2	10.1	27	7.9					NA	NA	22.4	11.4
HR	0.42 (0.30-0.57)		0.713 (0.532-0.957		0.77 (0.59-1.01)		0.882 (0.65-1.197)		0.447 (0.330-0.606)		0.22 (0.15-0.32)		0.68 (0.40-1.14)		0.589 (0.309-1.123)		0.63 (0.41-0.96)		0.75 (0.45-1.26)	
2-3 prior lines	123	118	212	239	170	166	148	149	232	233	106	107	179	87	99	68	96	108	103	53
PFS	NA	NA	25.8	16.7	NA	NA	NE	12.9	14.9	8.4	NA	NA	NA	NA	NA	NA	NA	NA	NE	14
HR (95% CI)	2 prior lines: 0.39 (0.26-0.58)		0.720 (0.561-0.923)		0.68 (0.53-0.87)		0.58 (0.401-0.838)		0.604 (0.466-0.783)		2 prior lines: 0.46 (0.30-0.72)		0.61 (0.42-0.88)		0.479 (0.294-0.778)		2 prior lines: 0.65 (0.40-1.07)		0.54 (0.33-0.88)	
	3 prior lines: 0.48 (0.25-0.94)										3 prior lines: 0.60 (0.33-1.07)									

Dimopoulos MA, Ann Oncol. 202;32(3):309-322 + Moreau P. Lancet Oncol. 2021;22:e105-e118 + Kastritis E, Terpos E, Dimopoulos MA. Blood. 2022;139:2904-2917

Bispecifics for patients with MM

Bispecific antibody	Antibody structure	Target
AMG 420	BiTE	BCMA × CD3
AMG 701	Extended half-life, scFv plus Fc region	BCMA × CD3
PF-0686135 (elranatamab)	Full-length, humanized IgG2a	BCMA × CD3
REGN5458	Fc Fab arms	BCMA × CD3
Teclistamab	humanized, IgG Fc	BCMA × CD3
CC-93269	2-arm humanized IgG1 Fc, binds bivalently to BCMA and monovalently to CD3 in a 2 + 1 format	BCMA × CD3
TNB-383B	IgG4 Fc. anti-CD3 moiety preferentially activates effector over Tregs; 2 heavy chain-only anti-BCMA moieties	BCMA × CD3
BFCR4350A	Humanized IgG1 Fc	FcRL5 × CD3
Talquetamab	IgG4 Fc	GPRC5D × CD3

Dimopoulos MA, Ann Oncol. 202;32(3):309-322 + Moreau P. Lancet Oncol. 2021;22:e105-e118 + Kastritis E, Terpos E, Dimopoulos MA. Blood. 2022;139:2904-2917

TCEs: Summary

	Teclistamab[1]	Linvoseltamab REGN5458[2]	Elranatamab[3]	Pavurutamab AMG-701[4]	TNB-383B[5]	Alnuctamab CC-93269[6]	Cevostamab[7] (FcRH5-CD3)	Talquetamab[8] (GPRC5D-CD3)
Patients	165	68	55	75	103	30	160	30/44
No. of prior regimens, median	5	5	6	6	5	5	6	6/5
Triple refractory, %	128 (78%)	9 (13%)	50 (91%)	68%	64 (62%)	NR	136 (85%)	77/75
ORR, % (at effective dose level)	63% (1.5mg kg/KG)	73% (96+200 mg)	64% (≥215 µg/kg)	83% (9mg)	64% (≥40mg)	89% (≥6 mg)	55% (160mg)	70/64% (405/800 µg/kg)
CR %	39%	8%	35%	0%	16%	44%	NR	NR
CRS (all grades), %	119 (72%)	28 (38%)	48 (87%)	61%	54 (52%)	23 (77%)	128 (80%)	77/88%
CRS grade 3/4, %	0.6%	0	0	7%	3%	3%	1.3%	3/0%
ICANS, %	14.5	4	NR	8	NR	NR	13	NR
Neutropenia all grade (grade 3/4), %	71 (64)	16 (13)	75 (71)	23 (NR)	17 (NR)	43 (NR)	18 (16)	67/36 (53/23)
Infection %	76	NR	NR	NR/13	28	30	43/19	47/34

(1) Moreau et al. NEJM 2022
(2) Zonder et al. ASH 2021; abs#160
(3) Jakubowiak et al. ASCO 2022; abs #814
(4) Harrison et al. ASH 2020; abs#181
(5) Kumar et al. ASH 2021; abs#900
(6) Costa et al. EHA 2020; abs#S205
(7) Trudel et al. ASH 2021; abs#157
(8) Minnema et al. ASCO 2022; abs#8015
Mouhieddine TH et al. Blood advance 2023;7:1056-64

CAR-T-cells in MM: Idecel-Ciltacel and how to improve

	Ide-cel (bb2121) / KarMMa (phase II)	Cilta-cel (JNJ-4528) / CARTITUDE-1 (phase IB/ II)
Antigen-binding domain	scFv (murine)	Bispecific variable fragments of llama heavy-chain antibodies; two distinct BCMA epitopes are targeted
Signaling domains	CD3ζ/4-1BB	CD3ζ/4-1BB
Vector	Lentiviral	Lentiviral
Other features	Bb21217 uses the same CAR construct as used for ide-cel. During *ex vivo* culture a PI3K inhibitor is added to enrich for CAR-T with memory-like phenotype	Bi-epitope BCMA binding confers high avidity binding
Lymphodepletion	Flu/Cy	Flu/Cy
CAR-T dose	150-450x10^6	Median dose: 0.71x10^6/kg
Number of patients	128 (140 patients underwent leukapheresis)	Data presented for first 97 (113 patients were enrolled/apheresed
Bridging therapy (%)	88	65
Number of prior therapies (median)	6	6
Triple-class refractory (%)	84	88
High-risk cytogenetics (del(17p), t(4;14), or t(14;16) (%)		35 24
Extramedullary disease (%)	39	13
≥PR	150-450x10^6: 73% 150x10^6 : 50% 300x10^6 : 69% 450x10^6 : 82%	97%
≥CR	150-450x10^6: 33% 150x10^6 : 25% 300x10^6 : 29% 450x10^6 : 39%	67%
Median PFS	150-450x10^6: 8.8 months 150x10^6 : 2.8 months 300x10^6 : 5.8 months 450x10^6 : 12.1 months	Median PFS: Not reached; 12-month PFS rate: 77%
CRS (all grades) (%)	84	95
CRS (grade ≥3) (%)	5	4
Median time to CRS onset (any grade) (days)	1	7
Median duration of CRS (any grade) (days)	5	4
Neurotoxicity (all grades) (%)	18	21 (ICANS: 17%; other neurotoxicity*: 12%)
Neurotoxicity (grade ≥3) (%)	3	10 (ICANS: 2%; other neurotoxicity: 9%)
Median time to neurotoxicity onset (any grade) (days)	2	ICANS: 8 days; other neurotoxicities*: 27 days
Median duration of neurotoxicity (any grade) (days)	3	ICANS: 4 days; other neurotoxicities: 75 days
Time to peak CAR-T expansion (days)	11	13
CAR-T persistence 6 months, %	59	42

	What may limit CAR-T therapy?	How to improve CAR-T therapy?
Toxicity	On-target, on-tumor	Anti-IL6 treatment and prevention Safeguard designs incorporating drugs such as rituximab/cetuximab
	On-target, off-tumor	Tackling immunogenicity Simplified CAR structures (*e.g.*, heavy-chain-only binding domains)
Resistance	Impaired CAR-T expansion/persistence	Multi-targting therapy (dual-target, OR-target, CARpool) More accurate measurement of expansion/persistence "Suicide switches"
	Immunosuppression induced by BM microenvironment	Combination of immunomodulatory modulation and CAR-T Senolytic CAR-T (?)
	Antigen loss or downregulation	Address trogocytosis Increase antigen density (*e.g.* γ-secretase-inhibition for anti-BCMA therapy)
Management	Suboptimal recognition and treatment of severe events	Increase comparability and knowledge sharing of intensive care unit management and other care settings Outcome prediction
Availability	Lack of scale-up High costs No stockpiling Time	Allogeneic CAR-T Optimize supply chain models (*e.g.*, intermediate players for cryopreservation)

Bruno B, Wäsch R, Engelhardt M, et al. Haematologica 2021;106:2054-2065

Supplements

- MGUS + SMM **slide 9-11**
- CRAB + SLIM-CRAB **slide 12**
- Stage disease categories: ISS/R-ISS **slide 13**
- Diagnostics, includ. Amyloidosis, POEMS **slide 14-20**
- Treatment, including BB protocols + clinical trials **slide 21-22**
- Supportives, response + follow-up **slide 23-26**

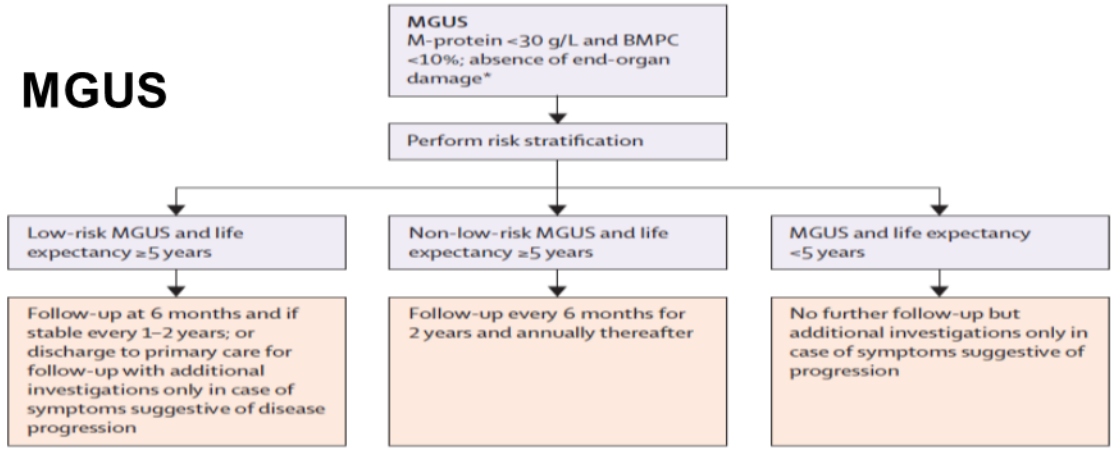
Risk stratification model MGUS

All MGUS patients	Risk stratification		Classification +PD risk/20y->MM	Additional evaluation at diagnosis	Monitoring and evaluation
SPEP, CBC, creatinine	Risk factors for progression[3]: • M-protein, >1.5 g/dL • Non-IgG paraprotein (IgA or IgM) • FLC ratio, <0.26 or >1.65	0 risk factors	Low risk 5%	No additional testing required	Repeat SPEP, CBC, and creatinine in 6 mo and then every 2-3 y if stable, or when symptoms of progression arise
		1 risk factor	Low-intermediate risk 21%	LDH B2-macroglobulin Bone marrow biopsy with FISH IgM MGUS → CT chest and abdomen to evaluate for lymphadenopathy Non-IgM MGUS → skeletal assessment† Light-chain MGUS → NTproBNP, cardiac troponins, urine albumin	If additional testing negative → SPEP, CBC, and creatinine in 6 mo then annually for life if remains stable* If signs of progression → decrease follow-up interval and initiate workup for lymphoplasmacytic malignancy
		2 risk factors	High-intermediate risk 37%		
		3 risk factors	High risk 58%		

Mouhieddine, Weeks, Ghobrial. Blood 2019;133:2484-94

Risk stratification and follow-up MGUS + SMM

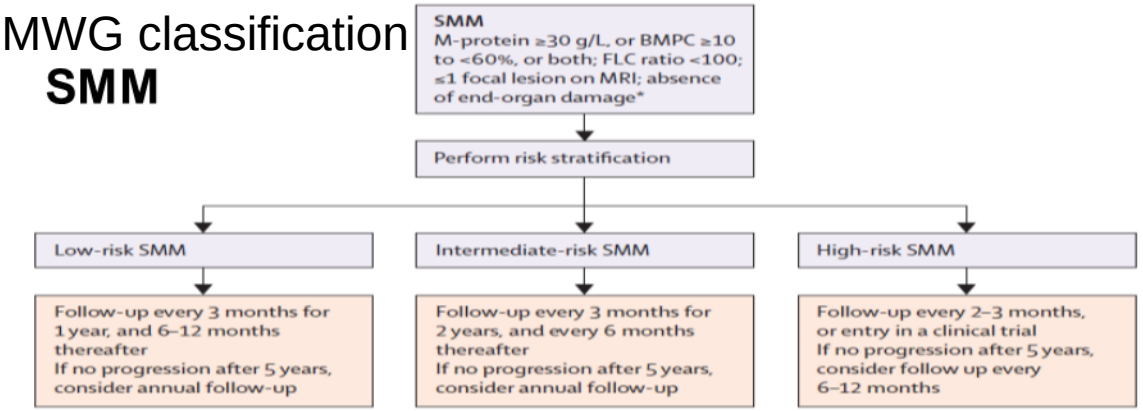
MGUS



Mayo Clinic risk stratification model for MGUS		
Number of risk factors • M-protein ≥15 g/L • Non-IgG subtype • Abnormal FLC ratio	Risk of progression at 20 years	Percentage of total
0: low risk	5%	39%
1: low to intermediate risk	21%	37%
2: intermediate to high risk	37%	20%
3: high risk	58%	5%

IMWG classification

SMM



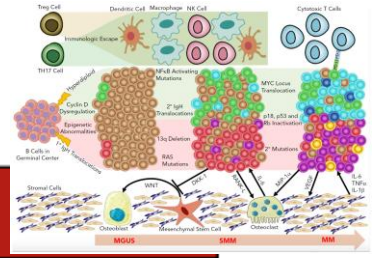
20–20–20 scoring system for smoldering multiple myeloma		
Number of risk factors • Serum M-protein >20 g/L • FLC ratio >20 • BMPC >20%	Risk of progression at 2 years	Percentage of total
0: low risk	5%	37%
1: intermediate risk	17%	27%
2–3: high risk	46%	36%

Mayo classification

Mayo Clinic study group		
# of risks ▪ BMPCs ≥10% ▪ M-protein ≥3g/dL ▪ FLC-ratio <0.125 or >8	# of pts (%)	**5 year** progression (%)
1	76 (28)	**25**
2	115 (42)	**51**
3	82 (30)	**76**
Total	*273 (100)*	*51*

van de Donk, Pawlyn, Yong. Lancet 2021;397:410-27
Caers J,...Engelhardt. The oncologist 21(3):333-42, 2016

MGUS and associated disorders



Clinical disorders	Treatment
Monoclonal gammopathies of renal significance	Fermand JP. Blood 2013;122:3583-90
Immunoglobulin light-chain amylodosis (AL)	Stage 1 and II disease: melphalan + dexamethasone If stage III or severe renal dysfunction: cyclophosphamide/bortezomib/dexamethasone
Immunoglobulin heavy-chain amyloidosis (AH)	
Immunoglobulin light and heavy chain (ALH)	
Type 1 cryoglobulinemia	If plasmacytic IgG or IgA: antimyeloma regimens If lymphoplasmacytic IgM: rituximab containing regimen
Type 2 cryoglobulinemia	Rituximab-containing regimen Treat underlying hepatitis C
Immunotactoid glomerulonephropathy (ITG)	Cyclophosphamide/bortezomib/dexamethasone
Monoclonal immunoglobulin deposition disease (MIDD)	Cyclophosphamide/bortezomib/dexamethasone Successful use of autologous stem cell transplant reported
Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID)	Cyclophosphamide/bortezomib/dexamethasone
Fanconi syndrome (FS)	Cyclophosphamide/bortezomib/dexamethasone
Paraproteinemic neuropathy	Chaudhry Mayo Clin Proc 2017;92:838-50
Distal demyelinating symmetric neuropathy with IgM (DADS-M)	IVIG, consider rituximab
IgG/A axonal neuropathy	Plasmapheresis, IVIG, steroids
IgG/A chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	
Severe and refractory neuropathy	Consider clinical trial or antimyeloma regimens Successful use of autologous stem cell transplant reported

Mouhieddine, Weeks, Ghobrial. Blood 2019;133:2484-94

Diagnosis criteria
International Myeloma Working Group

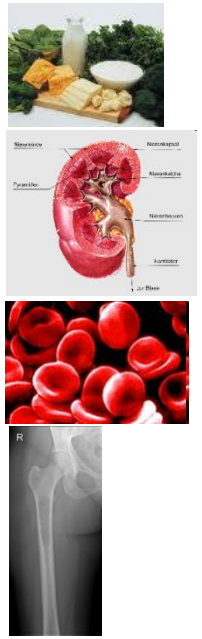
1. Detection of **monoclonal immunglobuline/paraprotein**
   in serum: IgG, IgA, IgD, IgE and/or
   in urine: immunglobulin light chains (Bence-Jones-proteinuria)

2. **>10 % plasma cells** within BM

3. **End organ damage** (1 criterion sufficient)
   - [C] Hypercalcemia *or*
   - [R] Renal insufficiency (crea >1,4 mg/dl) *or*
   - [A] Anemia (Hb <10 g/dl or 2 g/dl < Norm) *or*
   - [B] Osteolytic lesion(s)

or

4. **Revised IMWG criteria** (1 criterion sufficient)
   - [I] Clonal BM PCs >60%
   - [II] Invol/uninv. SFLC ratio >100
   - [III] ≥1 focal lesion on MRI /1 focal lesion on CT with BM infiltration >10% or ≥ 2 focal lesions on CT when BM infiltration <10%



5. **Potential future biomarkers for diagnosis of active MM** (2-y probabilitiy of progression)
   - Unexplained decrease in creatinine clearance by ≥25% plus rise in urinary M-protein or serum free light chain levels (tbd)
   - High BM PC proliferation rate by S-phase assessment on multiparametric flow cytometry (80%)
   - Abnormal PC immunophenotype ≥95% plus immunoparesis (50%)
   - Cytogenetic subtypes: t(4;14) or del17p (50%)
   - High-levels of circulating PCs (80%)
   - Evolving type of SMM (65%)

UK Nordic Myeloma Guidelines 2005
Patriaca F.et al. Eur J Haematol 2008
Ludwig et al. Leukemia 2014
Rajkumar V. et al. Lancet Oncol 2014
Caers J,...Engelhardt. The oncologist 2016; 21(3):333-42

ISS, R-ISS, Durie & Salmon

Stadien	International Staging System (ISS)	R-ISS	Durie & Salmon
Stadium I	ß2-MG < 3,5mg/l, Albumin ≥ 3,5 g/l	ISS I, Nicht-HR-ZG, wie del17, t(4;14), t(14;16), normale LDH	**Alle folgenden Kriterien müssen erfüllt sein** - Hb > 10 g/dl - Serumkalzium normal (≤ 12 mg/dl = ≤ 2,75 mmo/l) - Bildgebung: maximal eine solitäre Läsion - IgG< 5g/dl; IgA< 3 g/dl - Bence-Jones-Proteinurie < 4 g/24h
Stadium II	Nicht ISS I und III	Nicht R-ISS I und III	- Befunde weder denen in Stadium I noch III entsprechend
Stadium III	ß2-MG > 5,5mg/l	ISS III, HR-ZG oder/und erhöhte LDH	**Mindestens eines der folgenden Kriterien muss erfüllt sein** - Hb ≤ 8,5 g/dl - Serumkalzium erhöht (>12mg/dl = >2,75 mmol/l) - Bildgebung ≥ 2 Osteolysen - IgG >7 g/dl; IgA > 5 g/dl - Bence-Jones-Proteinurie >12 g/24h
			Subklassifikation **A** Serumkreatinin < 2 mg/dl **B** Serumkreatinin ≥ 2 mg/dl

Palumbo A et al. J Clin Oncol 2015;33(26):2863-9
Kommentar: M.Engelhardt. Im Fokus Onkologie 2016;19:1-2
Engelhardt M et al. Haematologica. 2017 Feb 2

Initial and subsequence investigations/diagnostics in MM

Screening tests	Tests to establish diagnosis	Tests to estimate tumor burden and prognosis/staging	Tests to assess myeloma-related organ impairment (ROTI)	Special tests indicated in some pts
• Individual and family history and physical examination • Complete blood count (differential; peripheral blood smear) • Serum or plasma electrolytes, urea, creatinine, calcium, albumin and uric acid • Electrophoresis of serum and concentrated urine	• Unilateral bone marrow aspirate, trephine biopsy + FISH (e.g. for 17p13, 13q14, t(4;14), t(14;16), t(14;20), 1q + 1p abnormalities) • Immunofixation of serum and urine • Plasma viscosity • Whole body (WB)-CT • If WB-CT is negative consider WB-MRI, especially in SMM	• Bone marrow cytogenetics: FISH • Quantification of monoclonal protein in serum and urine • Serum free light chain assay (non- or oligo-secretory and smoldering MM) • Calcium • Albumin • β2-microglobulin • LDH	• FBC (anemia) • Serum or plasma urea and creatinine • (e)GFR (measured or calculated) • Calcium • Albumin • Quantification of non-isotypic immunoglobulins • WB-CT • Other organ impairment, e.g. heart: ECHO, proBNP; neurology/PNP	• Bone marrow immunohistology or flow cytometry • Vitamin B_{12} and folate assays • PET-CT or WB-MRI if extramedullary MM is suspected • Quantification of non-isotypic immunoglobulins by nephelometry and densitometry • molecular analysis, i.e. MM-panel, including BRAF V600E

FBC: full blood count
FISH: fluorescence in situ hybridization
* The highest number of plasma cells obtained by either procedure is recorded
grey color: optional, e.g. with clinical symptoms.

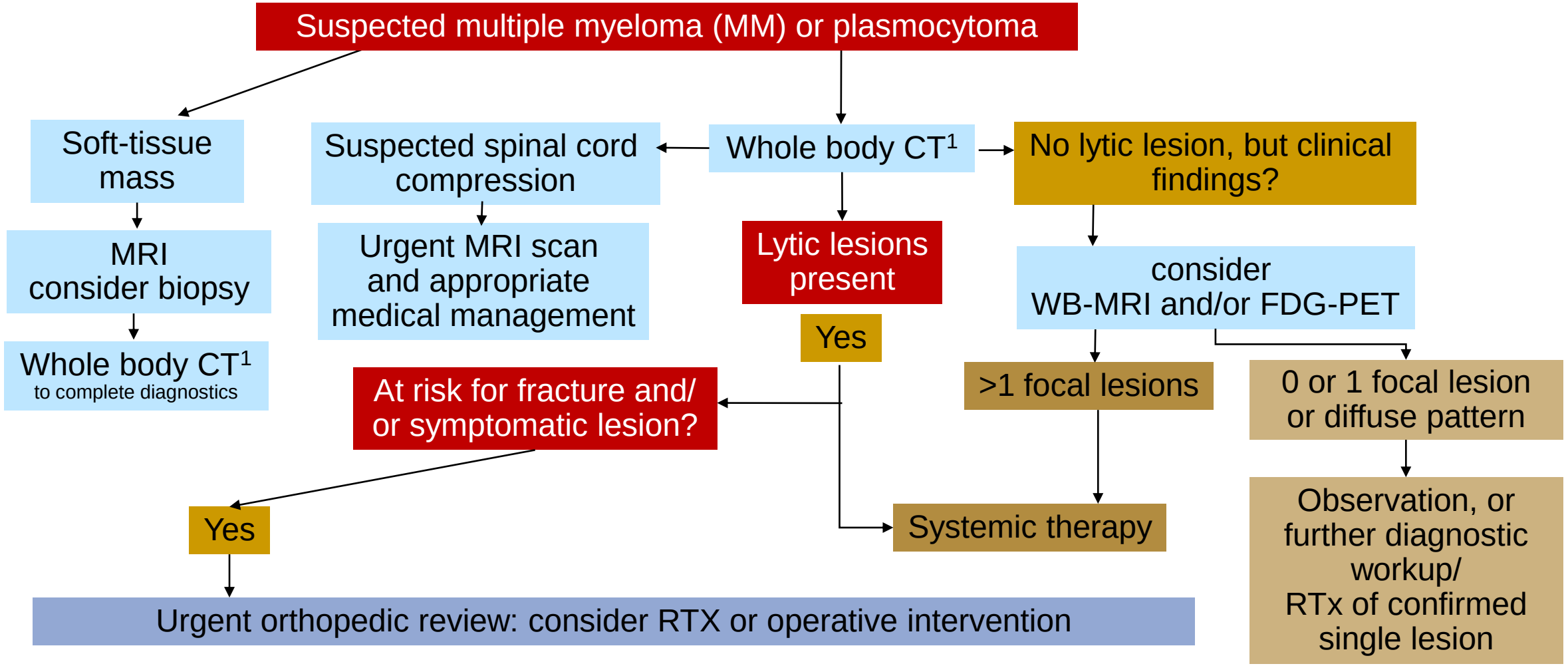
von de Donk. Haematologica 99:984-96, 2014
Engelhardt M. Haematologica 99:232-42, 2014,2015,2016
NCCN guidelines 3.2016
Krönke J, ...Engelhardt M, ...Langer C.Leukemia. 2017 Jan 20

Checkliste für Erstdiagnose MM

- **Labor**: Blutbild mit diff. BB, Nierenretentionsparameter, Gesamteiweiß, Albumin, Immunglobuline, k-/l-Leichtketten, Elektrolyte, incl. Calcium, LDH, GPT
- Serumprotein-Elektrophorese mit Bestimmung des M-Gradienten
- **Immunfixations-Elektrophorese** in Serum und Urin
- **CT-Multiregion** durchführen -> evtl. stabilitätsgefährdende Osteolysen strahlentherapeutisch und ggf. unfallchirurgisch abklären; extramedulläre Manifestationen bestrahlen lassen
- **Knochenmarkpunktion**
- Zahnstatus klären und evtl. sanieren -> **Bisphosphonat- od. RANK-L-Therapie** einleiten
- An AL-Amyloidose denken

Engelhardt. Haematologica 2014
van de Donk. Haematologica 2014
Schnerch,....Engelhardt. IF Onkologie 2014
Engelhardt M. et al. Onkologe 3:217-28, 2014+2015 + 2018

Algorithm for imaging + bone disease management



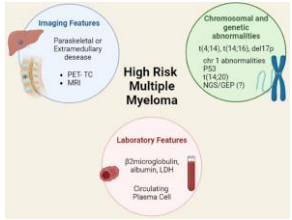
[1] WB-CT must include humeri/femura. In particular, the humeri may not be fully visualized on whole-body CT and whole-body MRI in obese patients, in which case supplemental radiographs in 2 planes should be obtained.

Consider PET-CT before and after CAR T cell therapy

Terpos E. et al. Haematologica. 100(10):1254-66, 2015
Rajkumar V. et al. Lancet Oncol 15:e528, 2014
Marshall C et al. AJR 2020;214:1321-34
Kanellias N et al. J Clin Med. 2022 May 30;11(11):3088

[1] MM-TB: Prof. Dr. G.Herget, Orthopädie, PD Dr. J.Neubauer, Radiologie UKF

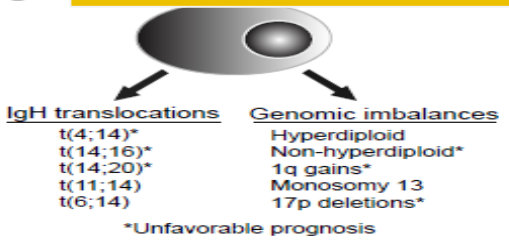
Risk stratification via cytogenetics and others



1

	High risk	Potentially high risk (more data needed)
Currently Utilized Staging systems:	R-ISS stage 3 IMWG high-risk mSMART high risk	
High-risk cytogenetic changes[a]	• t(14;16) • t(4;14) • IgL-MYC translocation • +1q amplification (≥4 copies): 20% CCF • 1p- • del(17p): 55–60% CCF	• t(14;20) • t(8;14) and other MYC translocations • +1q gain (3 copies) • del 13q/-13
GEP-results	EMC92/SYK92 (MMprofiler): high-risk UAMS GEP70 (MyPRS): high risk	
Mutations obtained by whole-genome/ exome sequencing	• TP53 deletion • LOH and APOEBEC signature • CKS1B amplification • "High Risk Genomic Clusters"[b]	• TRAF3 • TGDS • PRDM1 • DNAH11 • FAT1 • NRAS • SP140 • IGLL5 • Driver gene mutational burden
Clinical Features and disease burden:	• High Plasma Cell Labeling Index • Extramedullary Myeloma • Focal Lesions (FL): 3 large FLs with a product of the perpendicular diameters >5 cm^2 • Clinical frailty by objective geriatric assessment	Socioeconomic status

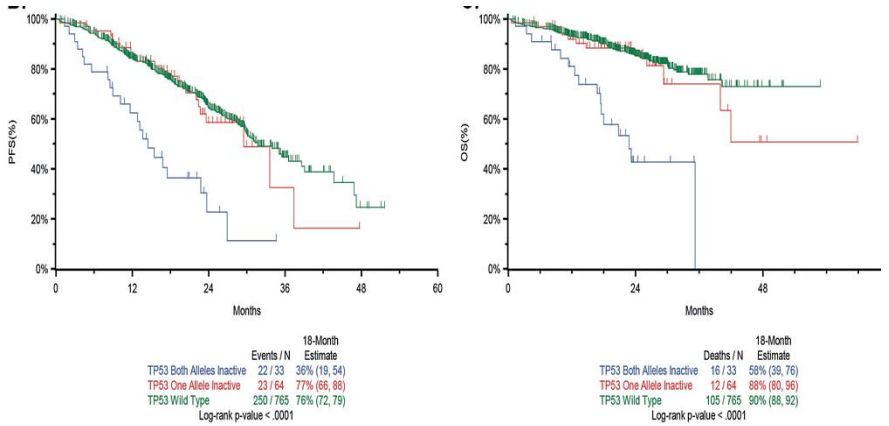
2 Sonneveld P. Blood 127, 2955-62, 2016, IMWG consensus



Standard	High Risk
all others	**del 17p, t(4;14), t(14;16)**
t(11;14)	**gain (1q)**
t(6;14)	Nonhyperdiploid
	del 13q karyotyp
	GEP high risk profile

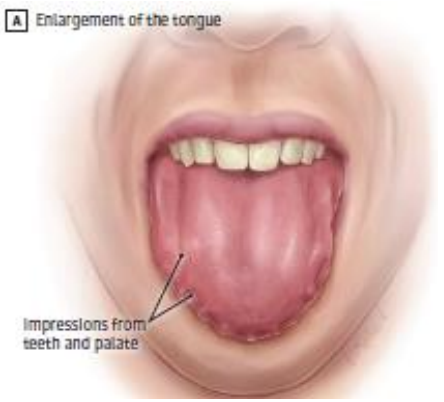
3 Double-Hit MM
Walker B. et al. Leukemia 33:159-170, 2019

4 Pawlyn C, Davies FE. Blood 133:660-675, 2019



van de Donk. Lancet. 2021;397:410; Schinke, Ihorst, …Wäsch, Schumacher, Engelhardt. Cancer 2020;126:3504; Hagen, Zhang, Barton. Blood Cancer J. 2022;12:83

AL-Amyloidose-Diagnostik



Bei welchen Patienten?

- Prinzipiell kann bei jedem MGUS AL-Amyloidose bestehen; bevorzugt bei:
  - Paraprotein vom Typ Lambda
  - Zytogenetik t(11;14)
  - Erhöhten freie Leichtketten im Serum

Klinische Symptome?

- Makroglossie, periorbitale Einblutungen, Synkopen, Durchfälle, Herzinsuffizienz, Ödeme, Polyneuropathie

Symptom	Immunoglobulin light chain amyloidosis	Wild-type transthyretin amyloidosis	Variant transthyretin amyloidosis
Atypical MGUS or smoldering myeloma	X		
Diastolic dysfunction, HFpEF	X	X	X
Proteinuria, nondiabetic	X		
Small fiber neuropathy	X		X
Autonomic dysfunction	X		X
Hepatomegaly, no imaging defects	X		
Purpura on the face and/or neck	X		
Macroglossia	X		
Bilateral carpal tunnel	X	X	X
Spinal stenosis/pseudoclaudication	X	X	X
Biceps rupture		X	

Welche Diagnostik ist geeignet?

- EKG, NT-Pro-BNP,TropT, Albuminurie, Serum freie Leichtketten
- Echokardiografie, Neurologische Untersuchung, Oberbauch-Sonographie/ Gamma-GT

Diagnostik zum Amyloidosenachweis:

- Fat pad*, KMP*, Rekto-/Gastroskopie (tiefe+serielle Biopsien), *fat pad Aspirat + KMP erlauben in 85% der Pat., Amyloidose nachzuweisen; Niere+Herz (letztere biopt. Sicherung erfolgt aufgrund Biopsie-Risiko seltener, stattdessen typischer Herzechobefund maßgebend)
- Histopatholog. Nachweis AL-Amyloidose (vs. z.B. ATTR od. senile Amyloidose); Nachweis, dass Amyloid v. Ig-/Paraprotein abstammt obligat; zudem: Serum-/Urin-Paraproteinnachweis, vor anti-MM/AL-Amyloidosetherapie

Gertz MA. Am J Hematol 88:416-25, 2013
Müller AM, ...Engelhardt M.Oncologist. 11:824-30, 2006
Gertz MA, Dispenzieri A. JAMA 2020;324:79-89

Amyloidose-Diagnostik + Staging systems

Major diagnostic tools for amyloidosis

Serum immunofixation
- Useful in detecting a monoclonal protein raising suspicion of immunoglobulin light chain (AL) amyloidosis

Urine immunofixation
- Useful in detecting a monoclonal protein raising suspicion of AL amyloidosis

Serum immunoglobulin free light chain
- Useful in detecting a monoclonal protein raising suspicion of AL amyloidosis

Echocardiography with left ventricular longitudinal strain
- Findings of wall thickening, impaired relaxation, and abnormal strain consistent with infiltrative cardiomyopathy amyloidosis; not seen with ischemia or valve disease

Cardiac magnetic resonance imaging
- Demonstrates wall thickening; late gadolinium enhancement specific for amyloidosis

Technetium pyrophosphate or methylene diphosphonate scintigraphy (cardiac amyloid transthyretin [ATTR] amyloidosis only)
- Uptake in myocardium seen in ATTR amyloidosis; diagnostic if no monoclonal gammopathy (mass spectroscopy is required if there is monoclonal gammopathy and a positive PYP scan)

Subcutaneous fat aspiration for Congo red staining
- Least invasive technique to obtain tissue biopsy verification of amyloidosis

Bone marrow biopsy, Congo red staining, and fluorescence in situ hybridization (FISH) genetics
- Alternate source of tissue for tissue verification of amyloidosis; required to exclude myeloma in AL amyloidosis; FISH genetics prognostic for outcomes in AL amyloidosis

Lip biopsy for Congo red staining
- Alternate noninvasive tissue source for demonstrating amyloid deposits

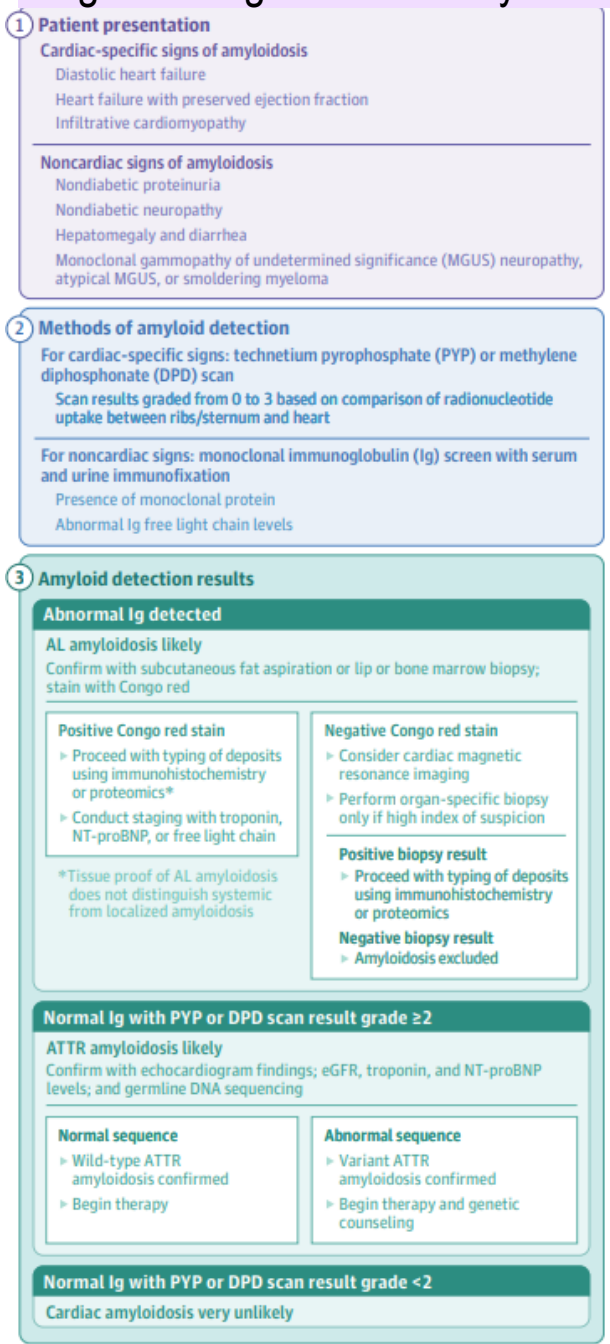
N-terminal fragment of the prohormone brain natriuretic peptide
- Cardiac biomarker used in staging of all forms of amyloidosis

Troponin
- Cardiac biomarker used in staging of all forms of amyloidosis

Amyloid typing with tissue mass spectrometry or immunohistochemistry completed by very experienced clinicians
- Required for all positive Congo red tissue specimens to verify the subunit protein composition

Germline DNA testing (transthyretin and other rare hereditary amyloid precursor proteins)
- Required to distinguish wild-type ATTR from variant ATTR amyloidosis

Diagnostic algorithm for amyloidosis



Staging systems for Immunoglobuline light-chain amyloidosis

	Threshold			Survival			
Staging system	NT-proBNP, pg/mL	Troponin T, ng/mL	dFLC, mg/L	Stage I	Stage II	Stage III	Stage IV
				Median survival, mo			
Mayo 2004	332	0.035		27.2	11.1	4.1	
Mayo 2012	1800	0.025	180	94.1	40.3	14	5.8
				Survival at 3 y, %			
European 2016	332	.035		100	52	55	19 (NT-proBNP >8500)

Gertz MA, Dispenzieri A. JAMA 2020;324:79-89

Checkliste POEMS – Syndrom

Für:

Kategorien	Diagnostische Kriterien	Diagnostik bzw. Definition des Kriteriums	Ja/ Nein	Summe
Mandatory Mind. 2	Plasmazelldyskrasie / **M**onoklonale Gammopathie	Serumelektrophorese / Knochenmark-Biopsie		
	Polyneuropathie (PNP)[1]	Fragebogen (siehe Anhang)		
Major Mind. 1	Castleman	Bildgebung: GK-CT nativ, ggf. FDG-PET		
	Osteosklerose	Bildgebung: GK-CT nativ, ggf. FDG-PET		
	VEGF[2]	Serumspiegelbestimmung: IMD Labor Berlin: >380 pg/ml im Serum (Grenzwert laborspezifisch)		
Minor Mind. 1	**O**rganomegalie	Klinisch / Bildgebung (s.o.)		
	Extravask. Volumen↑	Klinisch / Bildgebung (s.o.): Ödeme, Aszites, Pleuraerguss, Perikarderguss		
	Endokrinopathie	Gonadal, Adrenerg, Prolactin↑,Gynäkomastie, Galactorrhö, Diabetes mellitus, Hypothyreoidismus		
	Hautveränderungen (**S**kin changes)	Hyperpigmentation, Akrozyanose, Plethora, Hämangiome, Teleangiektasien, Hypertrichosis, Verdickung		
	Papillenödem	Ophthalmoskopie / OCT (OCT=Optische Cohärenztomographie)		
	Thrombozytose/Polyzythämie	Blutbild		
Sonstige	*Sonstige Symptome können lediglich den Verdacht erhärten, aber gehören nicht zur POEMS-Definition!* Gewichtsverlust, pulmonale Hypertonie, Fatigue, Trommelschlegelfinger, restriktive Lungenfunktionsstörung, Hyperhidrose, thrombotische Diathese, Diarrhoe, Vitamin-B-Werte↓			

Interpretation:	**POEMS:**	Mind. 2+1+1, d.h.: Beide mandatorischen + mind. 1 Major + mind. 1 Minor	
	POEMS möglich:	Maximal ein fehlendes Kriterium in maximal einer Kategorie	
	Kein POEMS:	Alles andere. DD M. Castleman, MG+PNP, SMM, MM etc.	

[1] PNP-Fragebogen

Sie können helfen, der 'peripheren Polyneuropathie' vorzubeugen oder mögliche Symptome zu verringern.

Die genaue Selbstbeobachtung auf erste Anzeichen ist von besonderer Bedeutung.

Wenn Sie eine der folgenden Fragen mit „Ja“ beantworten, ist es wichtig, dass Sie sich sofort mit Ihrem Arzt und Pflegekraft in Verbindung setzen.

Datum der Erfassung: .....

1. Meine Hände oder Füße sind taub oder kribbeln	Ja	Nein
2. Meine Hände oder Füße fühlen sich unangenehm an	Ja	Nein
3. Ich habe Gelenkschmerzen oder Muskelkrämpfe	Ja	Nein
4. Ich höre schlecht oder höre ein Pfeifen oder Brummen	Ja	Nein
5. Ich habe Probleme beim Zuknöpfen, z.B. von Hemden	Ja	Nein
6. Ich habe Probleme, kleine Gegenstände zu ertasten, wenn ich sie in den Händen halte	Ja	Nein
7. Ich habe Probleme beim Gehen	Ja	Nein
Ergebnis / ∑:		

[2] VEGF-Bestimmung: Weitere Infos

IMD Berlin MVZ

Nicolaistraße 22
12247 Berlin (Steglitz)

Tel. +49 (0)30 77001-220
Fax +49 (0)30 77001-236

Info@IMD-Berlin.de
IMD-Berlin.de

Material

1 ml abgetrenntes Serum

Abrechnung

Eine Abrechnung ist nur im privatärztlichen Bereich (GOÄ) gegeben. Für Selbstzahler (IGeL) kostet die Untersuchung 28,86 €.

Abkürzungen:

GK-CT: Ganzkörper-CT
OCT: Optische Cohärenztomographie
DD: Differentialdiagnose
PNP: Polyneuropathie
MG: Monoklonale Gammopathie
SMM: Smouldering Multiple Myeloma
MM: Multiples Myelom

Für eine druckbare Version auf dieses Logo doppelklicken→ PDF DRUCKVERSION

Blaue Buch-Therapieprotokolle MM/Amyloidose

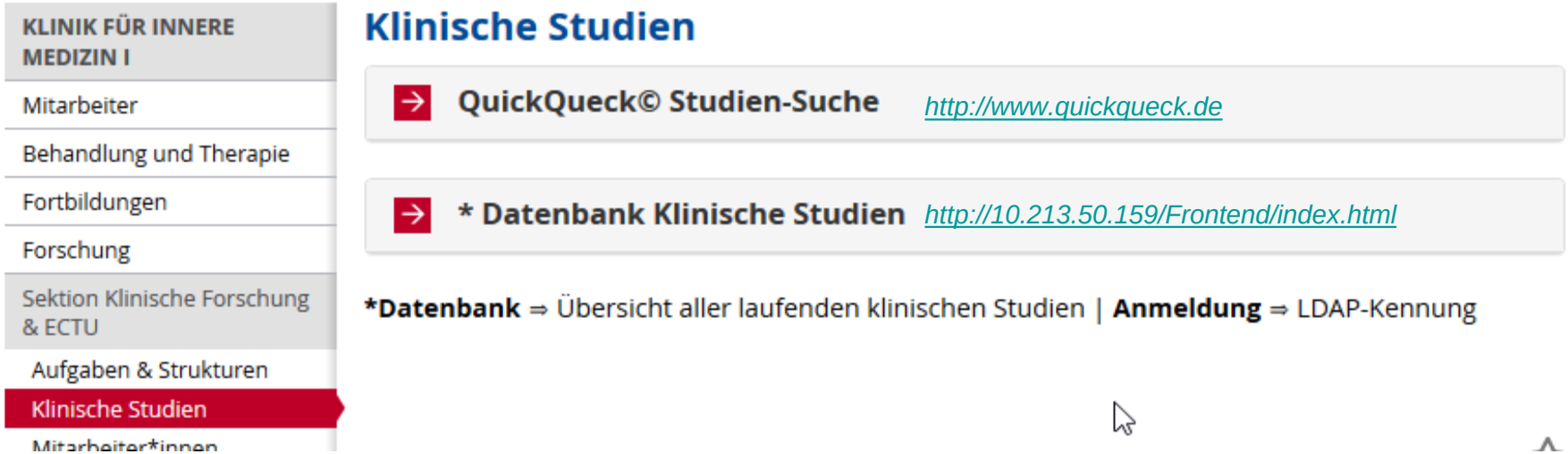
	NDMM	Mobili-sation	ASCT (allo-SCT)	RRMM	Maintenance	CAR-T	Amyloidosis
Standard Protocols	VCD VRD VD RD Dara-VRD Dara-VCD Dara-VMP Dara-VTD Dara-RD VMP MPT MP (Alexanian) Mel i.v. Bendamustin Benda/Thal/Pred Benda/Borte/Pred (±Thal) CTD HD-Dex	Cyclo 2g/m^2 (1-4g/m^2) CE CE- Amyloidosis	Mel 200 Mel 140 Bu-Mel BEAM TEAM BM TM	Dara mono, Dara-RD, Dara-VD, Dara/Pom/Dex, Elo-RD, Elo/Pom/Dex, Elo-VD, Isa/Carf/Dex, Isa/Pom/Dex, Car/Len/Dex, Carf/Cyclo/Dex, Carf/Benda/Dex, Carf/Dex, Carf/Pom/Dex, Carf/Dara/Dex, Ixa/Len/Dex, Ixa/Dex/Benda, Ixa/Pom/Dex, Pom/Dex, Pom-VD, Pom/Cyclo/Dex, VDD, Panobinostat-VD, Venetoclax-VD, Belantamab, Belantamab-VD, Selinexor-Dexa, Sel-VD, Sel/Carf/Dex, Vd-PACE Teclistamab, Talquetamab q2w	Lena/Dara Lenalidomid Bortezomib VD Erhaltung Carf/Dex Ixa/Dex LD Thal/Dex	FluCy vor ABECMA® FluCy vor CARVYKTY®	all MM protocols + Palladini VD VCD Dara-VD Dara-VCD
Clinical Trials	**DMMXIX (Ph III)** **DSMM XX (Ph II)**		**AlloRelapse (Ph III)**	**AlloRelapse (Ph III)**	**DSMM XX (Ph II)**		
	18**+2**	3	7+**1**	32**+1**	7**+1**	2	5

total: 79

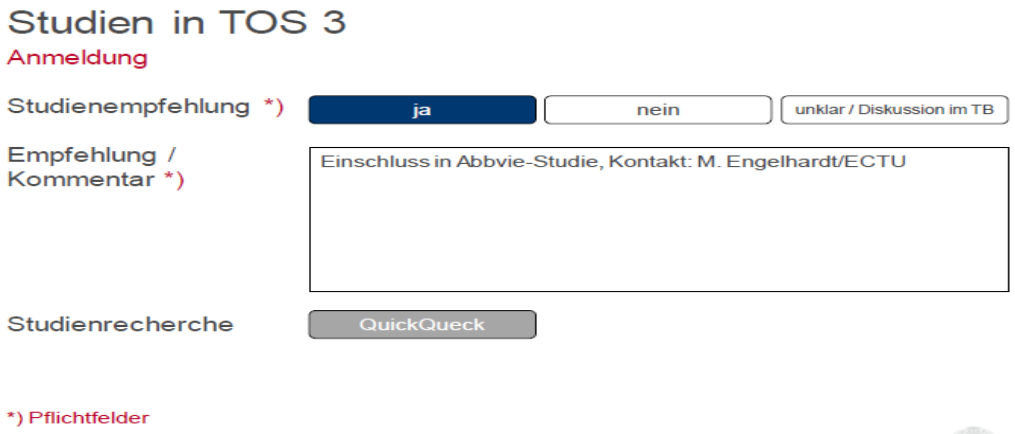
Engelhardt, Mertelsmann, Duyster. Das Blaue Buch. Springer 8. Ed. 2023
Rasche, Wäsch et al. Novel IOs. Haematologica 2021;106:2555-65

Studiensuche Med.1

Übersicht der rekrutierenden Studien in QuickQueck, Studien Datenbank &Tumorboard



Verlinkung der MM-Studien aus QuickQueck mit TOS 3 System



Rekrutierende MM Studien

Linie	Studie
1-Line	GMMG HD10/DSMM XX Phase 2 of Teclistamab + Daratumumab, Lenalidomide and Dexamethasone +/- Bortezomib as Induction Therapy and Teclistamab + Daratumumab and Lenalidomide as Maintenance Therapy in NDMM
2-Line	AlloRelapseMM Allo Tx vs konventionelle Therapie als Salvagetherapie für rrMM
NIS	MYRIAM Clinical research platform for molecular testing, treatment & outcome of MM patients

Supportives + monitoring on induction or salvage therapy

	Type
Infection prophylaxis	Trimethoprim-sulfamethazole (if on steroids) Aciclovir (all pts irrespective of whether on therapy or not)
Vaccination	Seasonal influenza + SARS-CoV-2 vaccine Vaccination against Streptococcus pneumoniae + Haemophilus influenzae, response may be suboptimal Currently available zoster vaccine (Shingrix)
Ulcer/gastritis prophylaxis	If on steroids, PPI or H2-blocker
Deep venous thrombosis (DVT)	Warfarin, if history of prior venous thrombo-embolism or risk of thrombosis LMW heparin (safer alternative than warfarin, particularly in RI) or DOACs (Rivaroxaban/Dabigatran)
Regular blood counts + chemistry	At the time of every infusion of Bortezomib (B) on B-based regimens Initially, every 2 weeks on Lenalidomide-containing regimens Every 2-4 weeks on Dexamethasone- or Thalidomide-containing regimens
Regular clinical evaluation	Every 1-4 weeks to start with based upon regimen Blood pressure and blood sugar monitoring + secondary primary malignancies[#]
Bone mineralization	Bisphosphonates*, Denosumab*, Ca/VitD3, sport activities *oral substitution of min. 500mg Ca+400 IE Vit D3/d

Mehta J. How I treat elderly patients with myeloma. Blood 116: 2215-23, 2010
[#]Engelhardt. Haematologica 2014. 2016, 2017, 2020
Baden LR, COVE Study Group. N Engl J Med. 2021 Feb 4;384(5):403-416
Bauersachs R. Res Pract Thromb Haemost. 2020 Apr 4;4(4):532-549
Bosch FTM. Blood Adv. 2020 Oct 27;4(20):5215-5225
Ludwig H. Lancet hematol 2021:e934-46
Delforge M, Ludwig H. Blood. 2017 Apr 27;129(17):2359-2367
Möller MD. Curr Optin Oncol 2021;33:648-57

MM-Bisphosphonat-Therapie

Wer sollte Bisphosphonate erhalten?

- Symptomatisches MM oder solitäres Plasmozytom, nicht MGUS oder SMM

Welches Bisphosphonat?

- Zoledronsäure 4mg als KI (15 min) alle 4 Wochen oder Pamidronsäure 60-90mg als Infusion über 3-4 Stunden alle 4 Wochen (mit normaler Nierenfunktion)

Bisphosphonattherapie bei Niereninsuffizienz (Creatinin-Cl <30ml/min)?

- Ø Pamidronat und Zoledronat, ggf. bei Osteolysen + NI: Pamidronat 30mg/3h
- od. Empfehlung für Clodronat: 50-80CrCL (75% DR), 12-50CrCL (50-75% DR), <12 (50% oder Unterbrechung)

Applikationsdauer der Bisphosphonate?

- Jahr 1 + 2: alle 4 Wochen, ab 3. Jahr gemäß individuellem Remissionsstatus: bei CR 1x jährlich, sonst 1x alle 3 Monate; bei Progress erneut: 1x monatlich

Prophylaxe von Kieferosteonekrosen?

- Vor Beginn und im Verlauf einer BP-Therapie alle 6 Monate: Kontrolluntersuchung beim Zahnarzt.
- Vor Beginn eines zahnärztlichen Eingriffs (Zahn-Extraktion, Wurzelbehandlung, Kiefer-OP): Unterbrechung BP-Therapie 30-60d vor + nach Eingriff; prophylaktische Antibiotika-Therapie (z.B. Clindamycin 4 x 300mg oder Amoxicillin 3x1g über 10 Tage mit Beginn 2 Tage vor dem Eingriff)

Terpos et al. Blood.121:3325-8, 2013
Kortüm, Engelhardt, Rasche, Knop, Einsele. Internist 54:963-77, 2013
Terpos E et al. Expert Rev. Hematol. 7:113-125, 2014
Poxleitner, Engelhardt, Schmelzeisen, Voss. Dtsch Ärztebl Int 2017;114:63-9

Response criteria

International myeloma working group (IMWG)

Response category	Response criteria
Stringent CR (sCR)	CR as defined below plus: Normal FLC-ratio, no clonal BM PCs by immunohistochemistry or Flow cytometry
CR	Serum/urine IF-, <5% BM PCs, no soft tissue plasmocytomas
VGPR	Serum/urine IF+, not via electrophoresis or ≥90% serum M-protein reduction plus urine M-protein level <100mg/24h
PR	≥50% reduction of serum M-protein and reduction in 24h urinary M-protein by ≥90% or to <200mg/24h If serum and urine M-protein are unmeasurable, ≥50% decrease in difference between involved and uninvolved FLC levels required If serum and urine M-protein are unmeasurable, and SFLC assay is also unmeasurable, ≥50% reduction in PCs reqiured, provided baseline BM PCs were ≥30% If present at baseline, ≥50% reduction in soft tissue plasmocytomas
SD	Not meeting criteria for CR, VGPR, PR or PD
PD	Increase of ≥25% from baseline in: • Serum M-component and/or • Urine M-component and/or • only in pts w/o measurable serum and urine M-protein: difference between involved and uninvolved FLC levels: absolute increase >10mg/dl • BM PCs ≥10% • New bone lesions or soft tissue plasmocytomas or increase of existing bone lesions or soft tissue plasmocytomas • hypercalcemia (corrected serum calcium >11.5mg/dl), attributed solely to MM

Rajkumar SV. et al. Blood 117: 4696-4700, 2011
Lonial S & Anderson KC. Leukemia 28:258-68, 2014

Verlaufsdiagnostik nach MM-Therapie (außerhalb von Studien)

- **Anamnese:** Karnofsky-Index, Infektionen und Begleiterkrankungen
- **Körperlicher Untersuchungsbefund inklusive Größe und Gewicht:** Polyneuropathien?, Infektionen? Schmerzen (Lokalisation, Charakter) ?
- **Laboruntersuchungen (Blut):** Blutbild mit Differentialblutbild, Gesamtprotein, Albumin, Kreatinin, Harnstoff, Natrium, Calcium, Kalium, GOT, GPT, g-GT, Bilirubin, LDH, AP, Harnsäure, CRP, ß2-MG, Serum-Elektrophorese mit Immunfixation, freier Leichtkettentest (SFLC), eGFR (MDRD), quantitative Immunglobulin-Bestimmung, Immunfixation im Urin
- **Knochenmark-Diagnostik**:

Therapiemodus	Initial	30d	100 d	1 Jahr	Rezidiv
Standard Ø SCT	x	ø	ø	x (post Therapiebeginn)	x
ASCT	x	x	ø	x post ASCT	x
Allo SCT	x	x	x	x post allo SCT	x

- **Bildgebung:** im Verlauf bei klinischer Indikation
- **MM-Patientenvorstellung ED und Rezidiv bzw. bei jeglichem Diskussionsbedarf**: UKF MM-TB-Konferenz, jeden Mo, 15.30h, ITZ Raum 153

Engelhardt. Haematologica 2014
van de Donk. Haematologica 2014
Engelhardt M. et al. Onkologe 3:217-28, 2014+2015 + 2018
Herget, Kälberer...Engelhardt. Leuk Lymphoma 2021
Lin C-M et al. BMC cancer 2023;23:446
Reymolds GK. Crit Rev Oncol/Hematol 2023;192: 104134

UKF: Universitätsklinik Freiburg

Gültigkeit	Datum der Aktualisierung	Version	Änderung	Verantwortliche
-	05.2011	1	-	M.Engelhardt, J.Udi, J.Waldschmdt, H.Reinhardt, S.Kaiser, M.Vits, M.Pantic, G.Herget, K.Henne, E.Kotter, U.Salzer, A. May, R.Voll, R. Wäsch
-	05.2012	2	-	M.Engelhardt, J.Udi, J.Waldschmdt, H.Reinhardt, S.Kaiser, M.Vits, M.Pantic, G.Herget, K.Henne, E.Kotter, U.Salzer, A. May, R.Voll, R. Wäsch
-	06.2013	3	-	M.Engelhardt, J.Udi, J.Waldschmdt, H.Reinhardt, S.Kaiser, M.Vits, M.Pantic, G.Herget, K.Henne, E.Kotter, U.Salzer, A. May, R.Voll, R. Wäsch
November 2014 – Dezember 2015	24.11.2014	4		M.Engelhardt, J.Udi, J.Waldschmdt, H.Reinhardt, S.Kaiser, M.Vits, M.Pantic, G.Herget, K.Henne, E.Kotter, U.Salzer, A. May, R.Voll, R. Wäsch
November 2015 – Dezember 2016	18.11.2015	5	Aktualisierung der Verantwortlichen, Aktualisierung der Folien	M.Engelhardt, J.Waldschmidt, A.Zober, H.Reinhardt, S.Kaiser, M.Vits, S.Dold, M.Pantic, G.Herget, K.Henne, Zadeh, F+C.Neubauer, U.Salzer, A.May, R.Wäsch
Dezember 2016 - September 2017	25.02.2017	6	Aktualisierung der Verantwortlichen, Aktualisierung der Folien	M.Engelhardt, J.Waldschmidt, A.Zober, H.Reinhardt, S.Kaiser, M.Vits, S.Dold, M.Pantic, G.Herget, K.Henne, Zadeh, F+C.Neubauer, U.Salzer, A.May, R.Wäsch

Gültigkeit	Datum der Aktualisierung	Version	Änderung	Verantwortliche
September 2017 - Oktober 2018	27.09.2017	7	Aktualisierung der Verantwortlichen, Aktualisierung der Folien	M.Engelhardt, J.Waldschmidt, H.Reinhardt, S.Dold, S.Müller, C.Kiote-Schmidt, M.Pantic, C.Greil, S.Ajayi, M.Vits, H.Schäfer, J.Neubauer, U.Salzer, A.May, M.Boeker, G.Herget, R.Wäsch
Oktober 2018 - November 2019	10.10.2018	8	Aktualisierung der Verantwortlichen, Aktualisierung der Folien	M.Engelhardt, M.Weiß, H.Reinhardt, S.Dold, S.Müller, C.Kiote-Schmidt, M.Pantic, G.Graziani, C.Greil, C.Miething, M.Rassner, S.Ajayi, H.Schäfer, J.Neubauer, A.May, K.Aumann, M.Seidl, G.Herget, R.Wäsch
Novembe 2019 - Januar 2021	15.11.2019	9	Aktualisierung der Verantwortlichen, Aktualisierung der Folien	M.Engelhardt, M.Weiß, H.Reinhardt, J.Hung, C.Kiote-Schmidt, M.Pantic, G.Graziani, C.Greil, C.Miething, M.Rassner, S.Ajayi ,H.Schäfer, J.Neubauer, K.Aumann, G.Herget, R.Wäsch
Januar 2021 – Februar 2022	09.02.2021	10	Aktualisierung der Verantwortlichen, Aktualisierung der Folien	Engelhardt, Rassner, Jung, Waldschmidt, Weiß, Reinhardt, Rösner, Braun, Surlan, Gengenbach, Möller, Pantic, Greil, Miething, Bartsch, Calba, Schäfer, Neubauer, Herget, Wäsch
Februar 2022 – Februar 2023	17.02.2022	11	Aktualisierung der Verantwortlichen, Aktualisierung der Folien	Engelhardt, Jung, Waldschmidt, Rassner, Reinhardt, Rösner, Braun, Pantic, Greil, Miething, Calba, Neubauer, Schäfer, Herget, Wäsch

Gültigkeit	Datum der Aktualisierung	Version	Änderung	Verantwortliche
Februar 2023 –März 2024	22.02.2023	12	Aktualisierung der Verantwortlichen, Aktualisierung der Folien	M.Engelhardt, C.Miething, C.Greil, A.Kutilina, M.Schinke, L.Gengenbach, X.Tonnar, G.Mostufi, S.Ganz, J.Zillinger, Z.Brugger, H.Reinhardt, A.Rösner, M.Braun, S.Wenger, M.Pantic, P.Zart, M-A.Calba, J.Neubauer, H.Schäfer, G.Herget, R.Wäsch
März 2024 – März 2025	28.02.2024	13	Aktualisierung der Verantwortlichen, Aktualisierung der Folien	M.Engelhardt, X.Tonnar, J.Kus, A.Weis, H.Reinhardt, M.Braun, H.Wenger, S.Wenger, M.Pantic, P.Zart, M-A.Calba, J.Neubauer, H.Schäfer, G.Herget, C.Miething, C.Greil, R.Wäsch