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30. November 2022

Hämatologie/Onkologie im Dialog – Meet the Expert: Das Multiple Myelom

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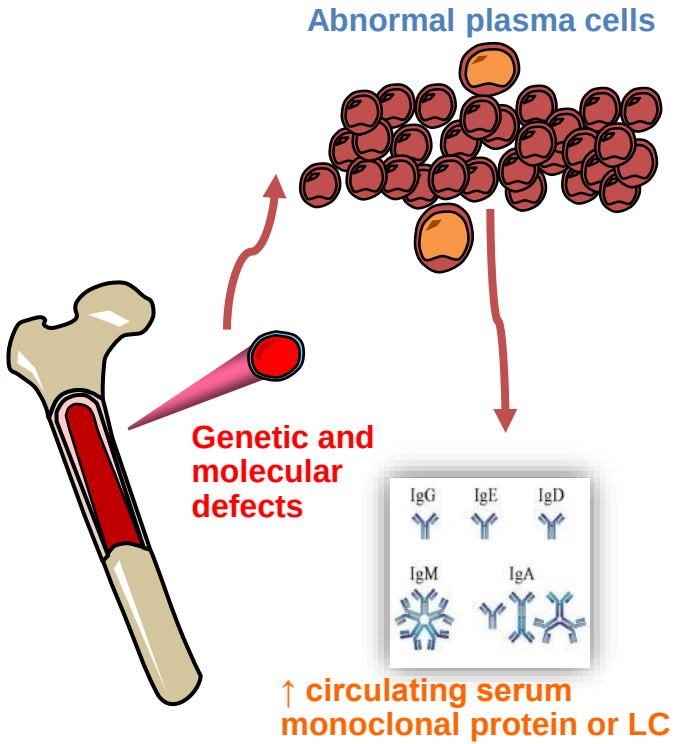
Disclosures

- Honoraria
  - Amgen, BMS, Celgene, Chugai, GSK, Janssen, Novartis, Sanofi
- Consulting or advisory role
  - Adaptive Biotechnology, Amgen, BMS, Celgene, Millenium Pharmaceuticals Inc., Janssen, Sanofi, Takeda
- Research funding
  - Amgen, BMS, Celgene, Chugai, Janssen, Incyte, Merck Sharp and Dohme (MSD), Molecular Partners AG Zürich, Mundipharma, Novartis, Sanofi, Takeda
- Travel, accommodations, expenses
  - Amgen, BMS, Celgene, Chugai, GSK, Janssen, Novartis, Omnia Med Deutschland, Sanofi, Takeda

1 Introduction

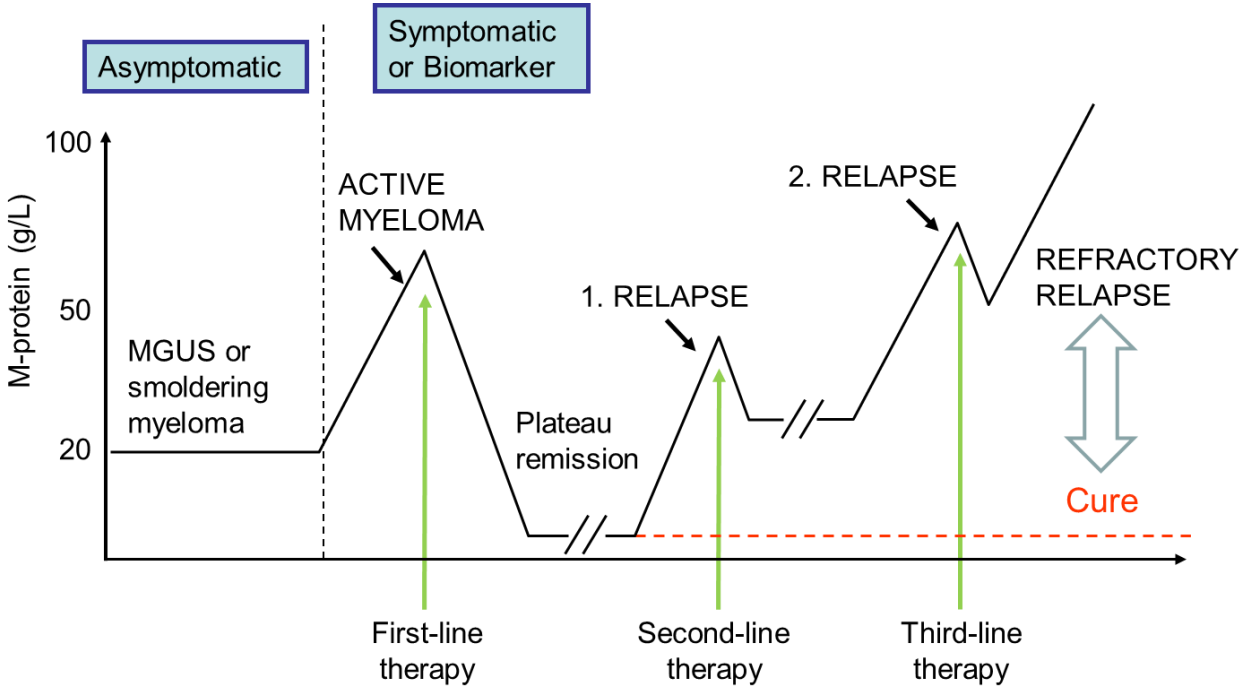
Myeloma Clinical Characteristics

- Cancer of the plasma cells
- 10% of all hematological malignancies
- Europe: 38,900 new cases each year
- Median age: 70 yrs (EU)
- 5-year survival rate: 40-50%
- Newer treatments (PIs, IMiDs and Antibodies) have achieved significant improvement in OS, but **MM remains incurable in the predominant number of patients**



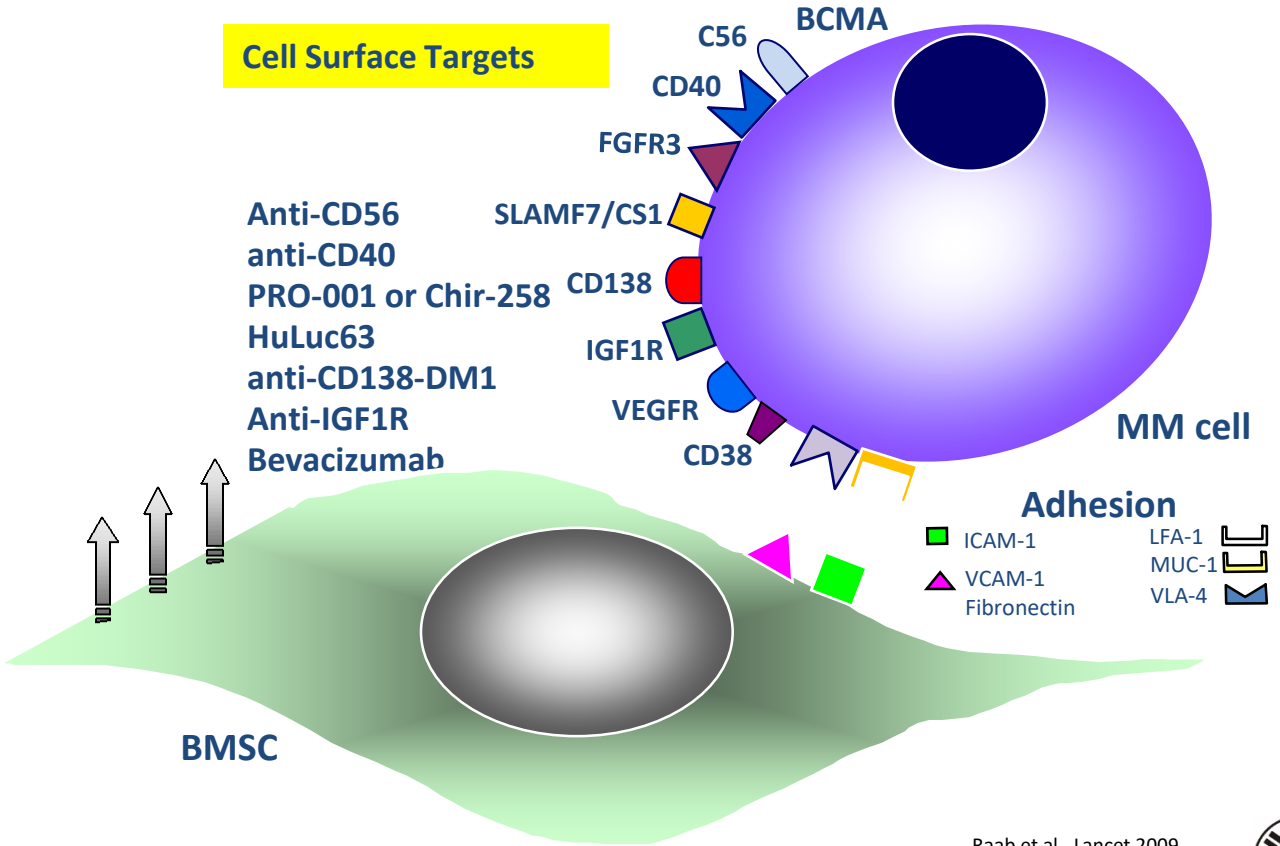
Moreau P et al. Ann Oncol. 2013 Oct;24 Suppl 6:vi133-7.

The Multiple Myeloma Patient Journey



Adapted from Durie 1992, IMF Myeloma Booklet

Targets for MCAB Therapy in MM



Raab et al., Lancet 2009

2 New Definitions

Diagnostic criteria for myeloma

Patient Criteria	MGUS	Smoldering Myeloma	Symptomatic Myeloma
M-protein	< 3 g/dL spike	≥ 3 g/dL spike and/or	In serum and/or urine
Monoclonal plasma cells in bone marrow, %	< 10	≥ 10	≥ 10
End-organ damage or biomarker	None	None	≥ 1 SLiM-CRAB feature

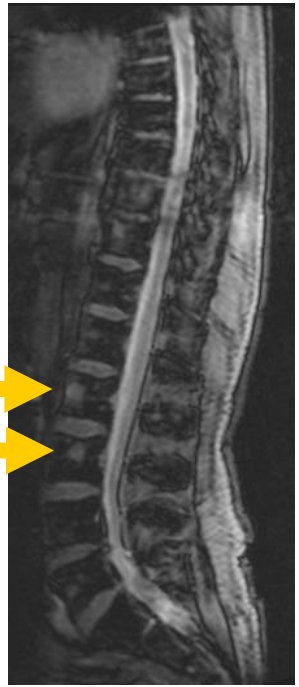
*C: Calcium elevation (> 10.5 mg/L or ULN)
R: Renal dysfunction (serum creatinine > 2 mg/dL) GFR < 40ml/min
A: Anemia (Hb < 10 g/dL or 2 g/dl < normal)
B: Bone disease (lytic lesions or osteoporosis) CT-Scan

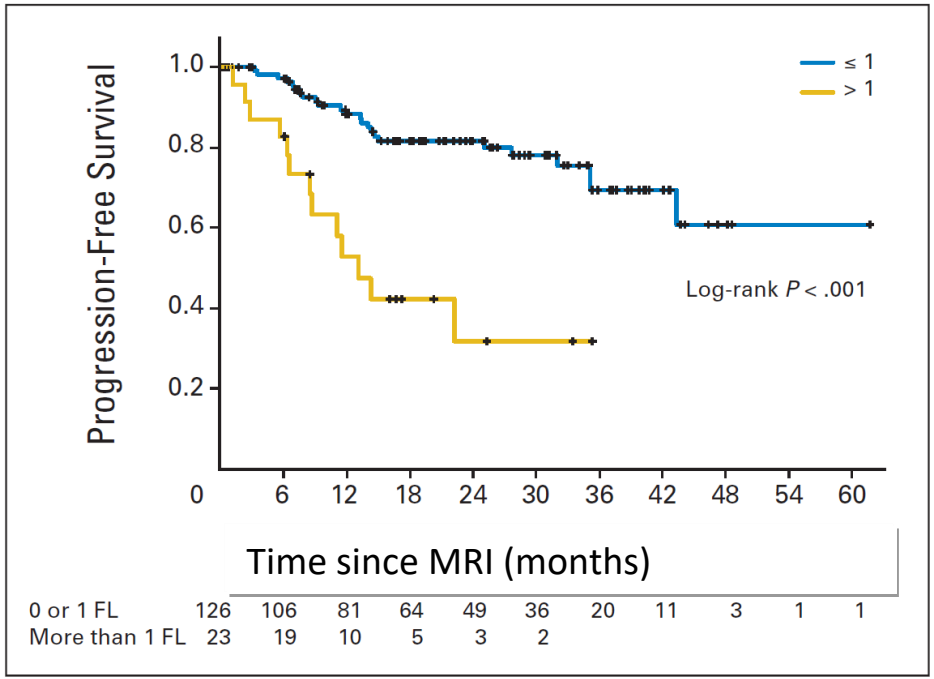
additional; FLC-Ratio > 100 or >1 Lesions in MRI or ≥ 60% BM-Infiltration

Rajkumar et al. Lancet Oncol. 2014

Smoldering Myeloma – MRI

Progression Risk → Symptomatic MM

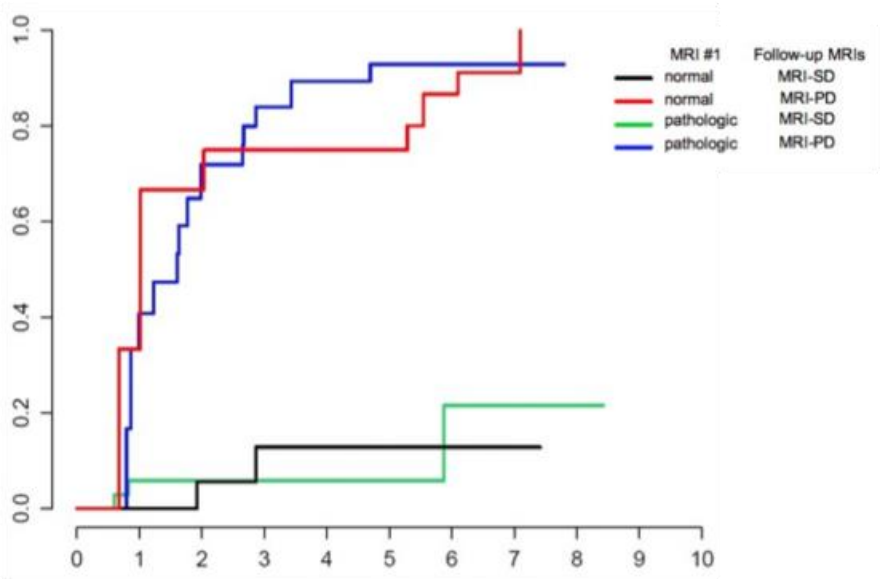




Hillengaß et al, JCO 2010

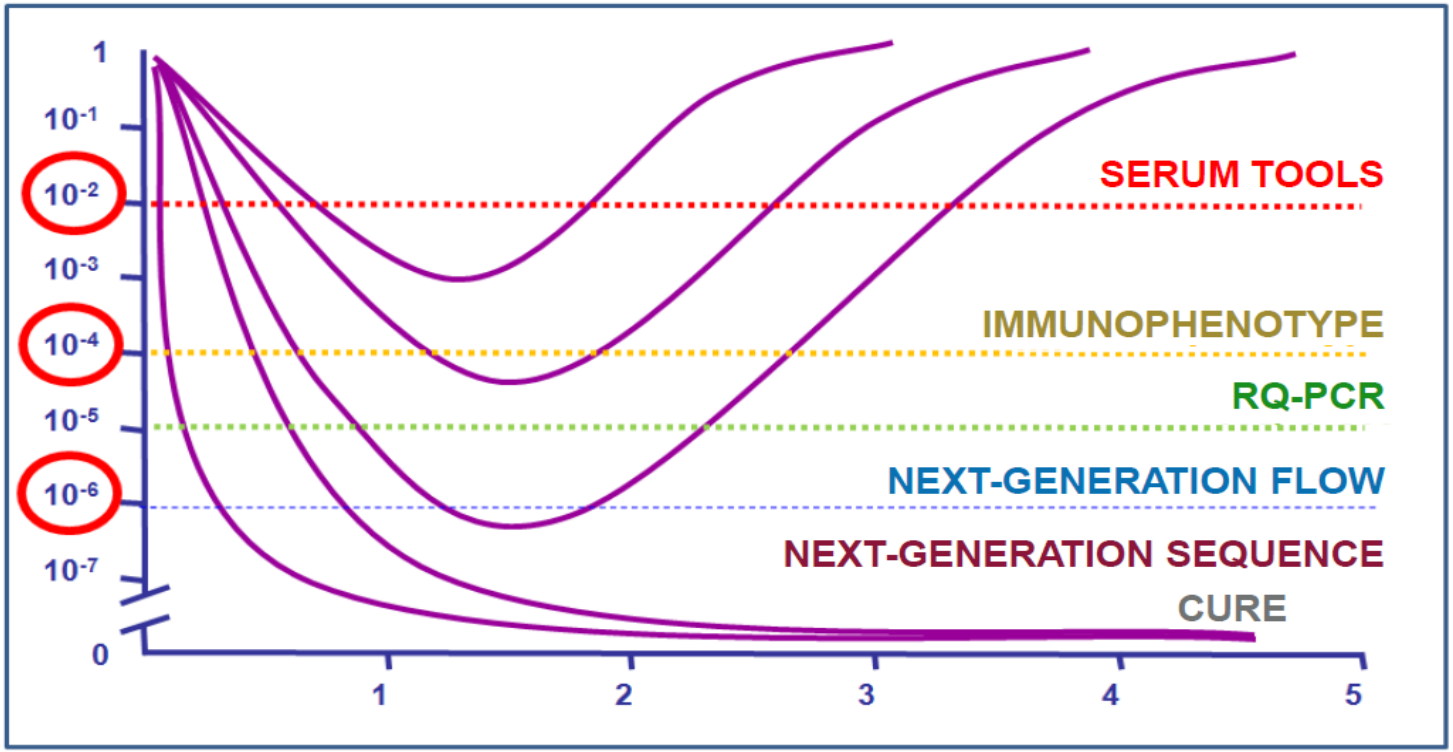
SMM – Dynamics of Focal Lesions

Progression Risk → Symptomatic MM



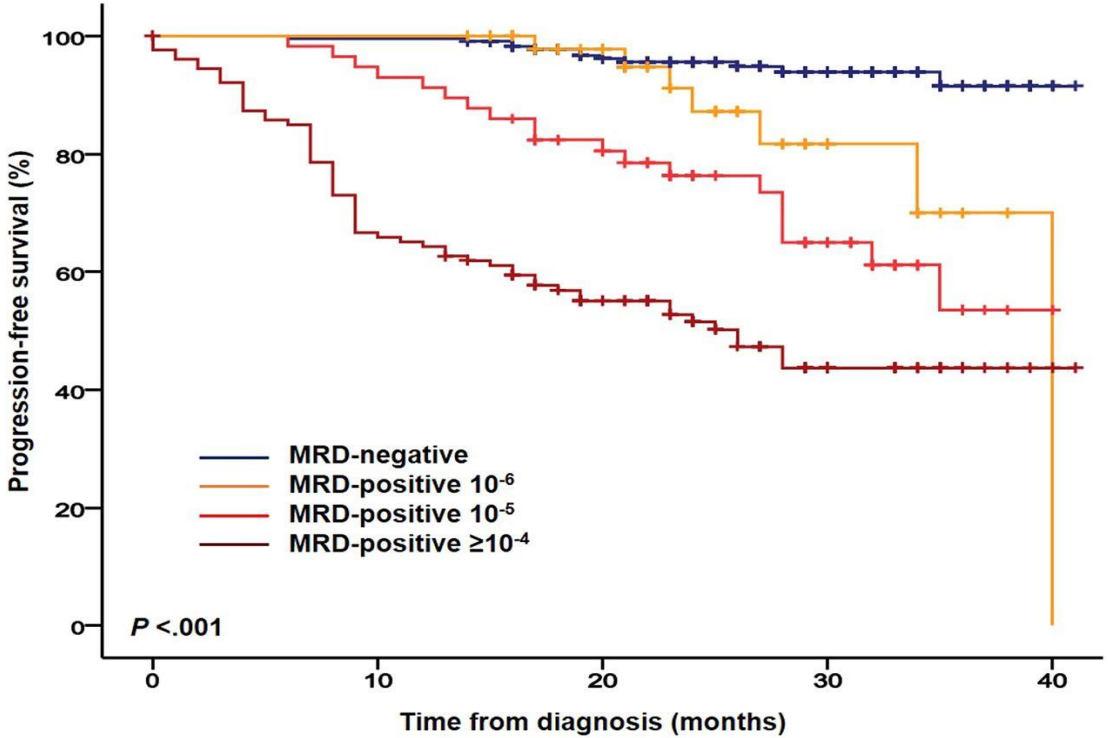
Merz et al, Leukemia 2014

Minimal Residual Disease



Brian GM Durie, MD
Best of ASH 2014
Thursday, January 15th 2015

Prognosis in MM: Role of MRD



- *„Overall, this study defines MRD-negativity as the most relevant clinical endpoint for both standard- and high-risk transplant-eligible MM patients.“*

1. Paiva et al. *Blood (ASH abstr 130)* (2016)

3 Front Line Treatment

Multiple Myeloma:
First Line Treatment – EHA/ESMO Guidelines 2021

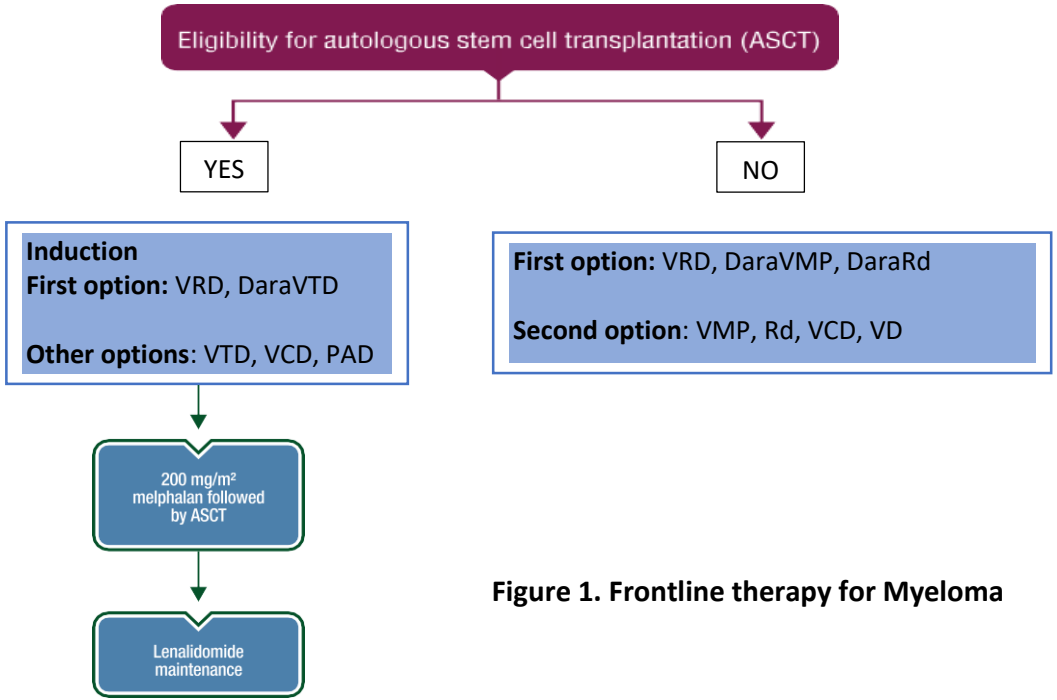
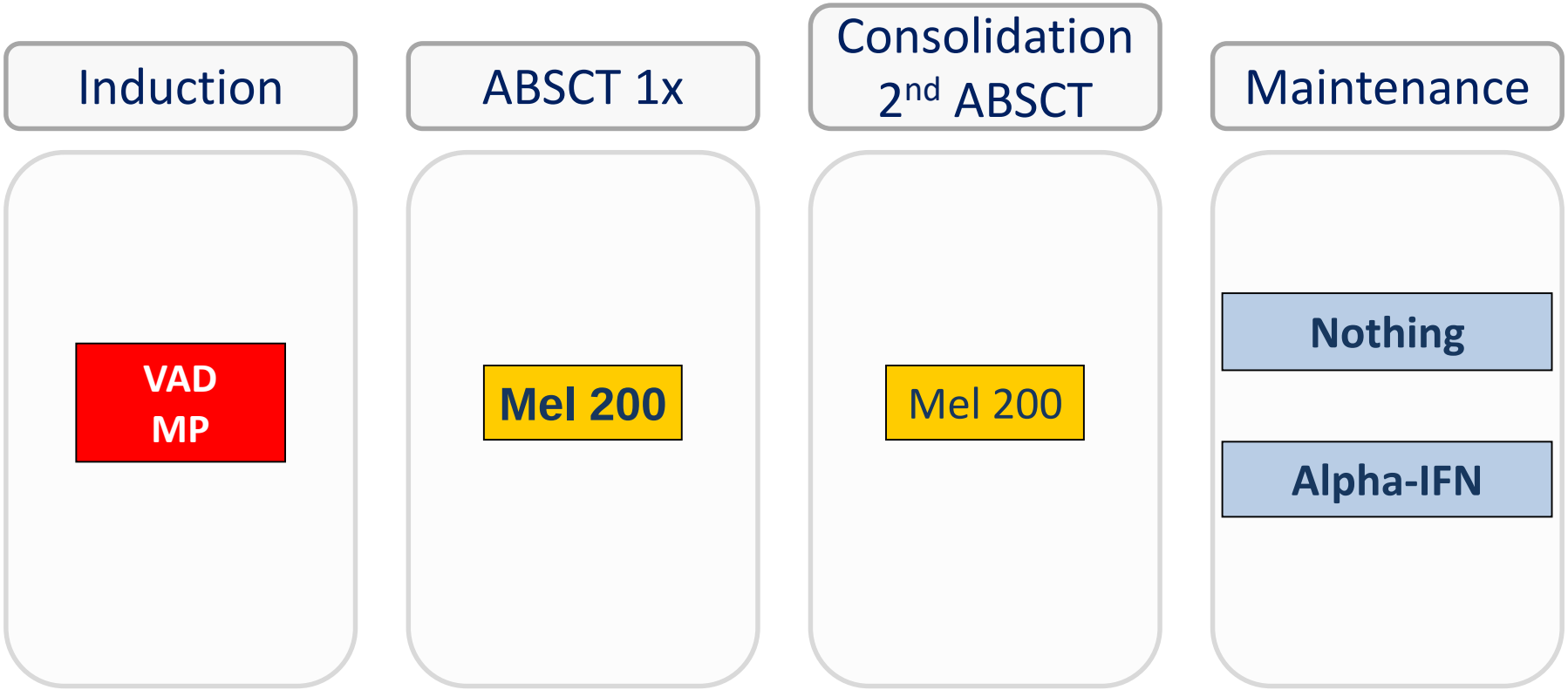


Figure 1. Frontline therapy for Myeloma

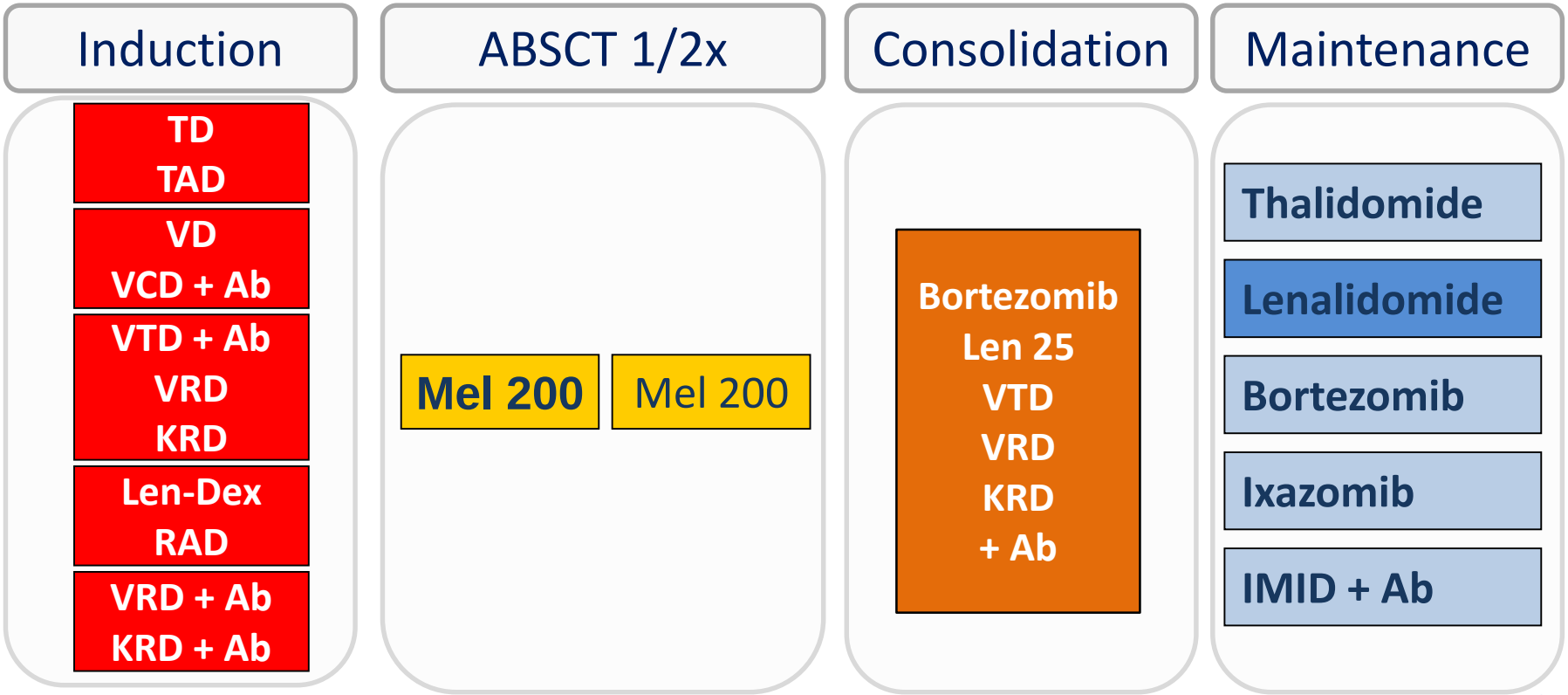
Dimopoulos et al. in review

Drugs Before and After ABSCT in the Early Days of HDT



Adapted from Einsele, DGHO Slides 2012

Increasing Number of New Drugs Before and After ABSCT



Adapted from Einsele, DGHO Slides 2012

As quadruplet combinations increase regimen complexity, a number of factors should be considered

Disease biology
- Cytogenetic risk
- Plasma cell proliferation rate
- LDH
- ISS/R-ISS stage
- DSS stage
- Extramedullary disease

Host factors
- Age
- Frailty
- ECOG PS
- Comorbidities
- Organ function (e.g. cardiac, hepatic)

Therapy factors
- Treatment tolerability/toxicity
- Treatment combinations

Patient preference
- QoL goals
- Treatment burden

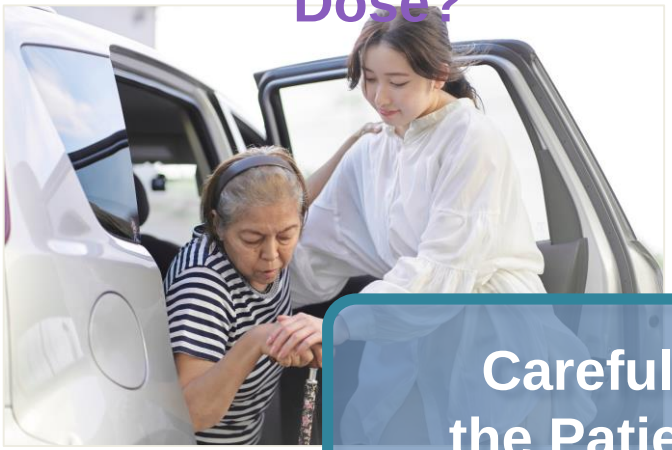
The addition of another agent to a triplet backbone should result in a favorable balance of **increased efficacy** with **minimal additional toxicity**

DSS, Durie-Salmon Staging; ECOG, Eastern Cooperative Oncology Group; (R-)ISS, (Revised-) International Staging System; LDH, lactate dehydrogenase; PS, performance status; QoL, quality of life

1. Delforge M, Ludwig H, Blood 2017;129:2359–67; 2. Chng et al. Leukemia 2014;28:269–77; 3. Mikhael et al. Mayo Clin Proc 2013;88:360–76; 4. Goldschmidt et al. Ann Hematol 2019;98:1–18

The Patient: Frail Versus Fit

Which Dose?

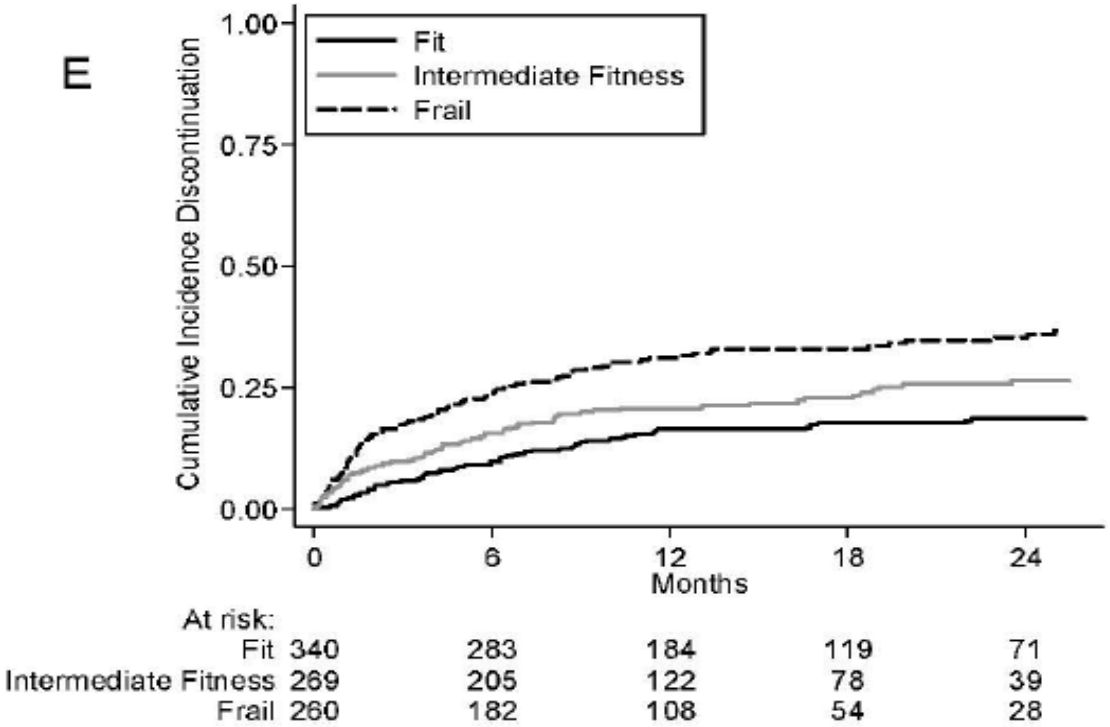


Which of the New Drug(s)?

Carefully Evaluate the Patient Clinically!

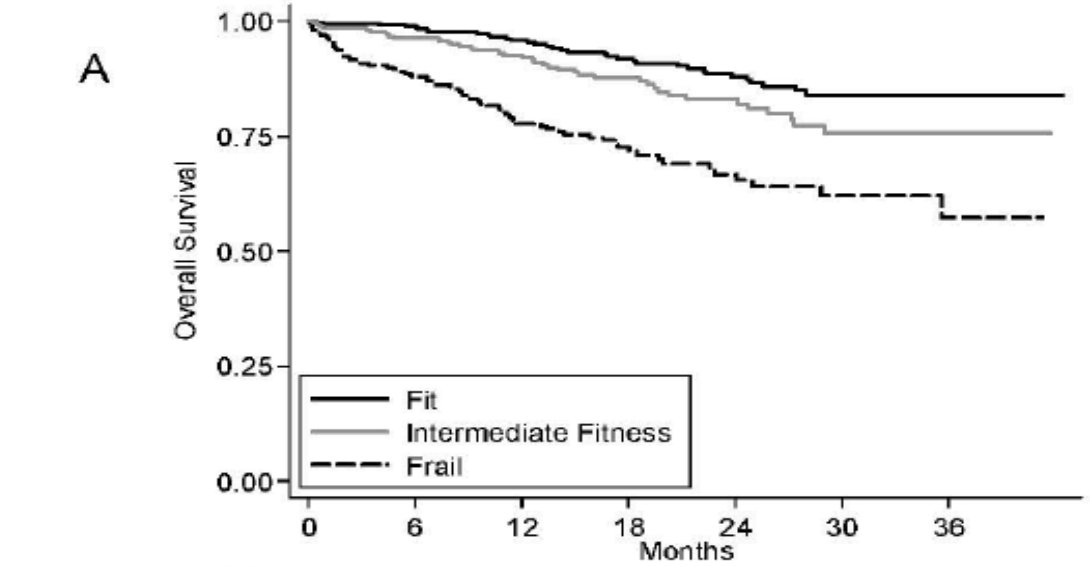
Personal communication of Hartmut Goldschmidt, 2022.
Adapted from Facon/Salwender; IMW 2012

Long Term Outcome - Discontinuation



Antonio Palumbo et al. Blood 2015

Long Term Outcome - Overall Survival



At risk:							
Fit	340	323	248	182	133	84	43
Intermediate Fitness	269	242	183	123	83	47	15
Frail	260	209	151	91	52	27	12

Antonio Palumbo et al. Blood 2015

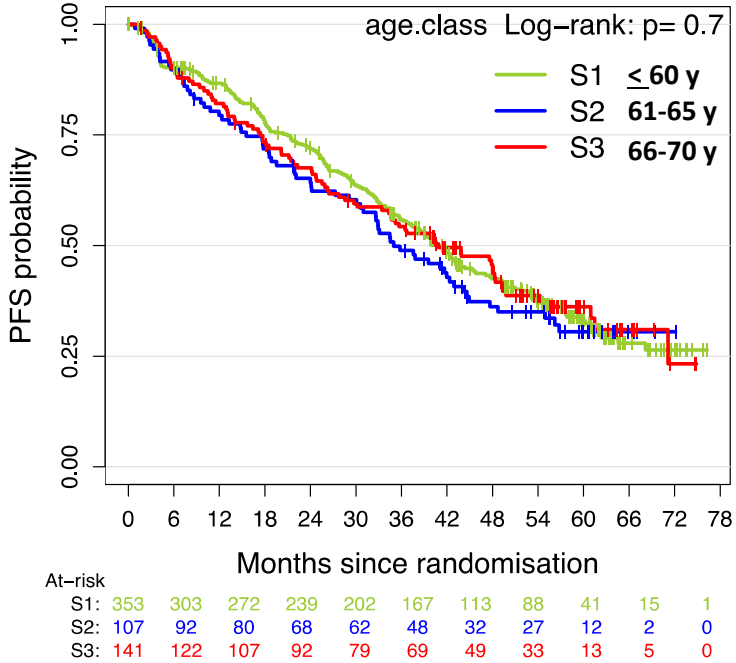
Recommended Starting Dose and Dose Adjustments According to Age Groups and Vulnerability Status

Agent	No Risk Factors*	At least 1 Risk Factor	At least 1 Risk Factor (+ grade 3/4 non-haem AE)
Dexamethasone (mg/day, Weekly)	40	20	10 (or prednisone)
Melphalan (mg/kg, Days 1-4)	0.25	0.18	0.13
Thalidomide (mg/Day)	100	50	50 qod
Lenalidomide** (mg/Day, Days 1-21)	25	15	10
Bortezomib (mg/m^2, Weekly, s.c.)	1.3	1.0	0.7

* Risk factors; age> 75 years, frailty, comorbidities (cardiac, pulmonary, hepatic, renal); ** Dose also adapted according to renal function.

Adapted from Palumbo A, et al. Blood. 2011;118:4519-29.

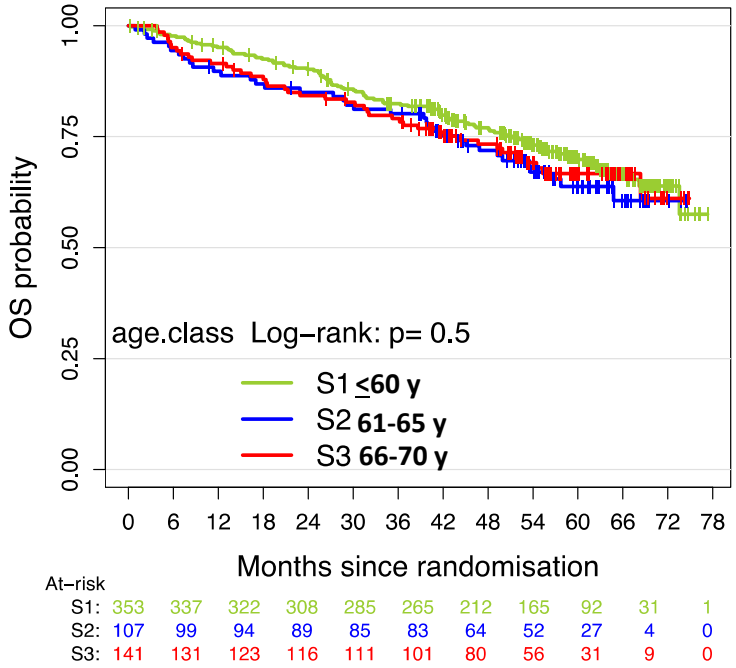
GMMG MM5 - Progression-free survival related to age



- no significant difference regarding PFS and age

Mai et al, Leukemia 2020

GMMG MM5 - Overall survival related to age



- no significant difference regarding OS and age

Mai et al, Leukemia 2020

Trial Results Influences Daily Practice

Liebe DAG-KBT Mitglieder,
26.09.2019

zusammen mit den **Myelom Studiengruppen GMMG und DSMM** hat die DAG-KBT in 2 Treffen mit dem Medizinischen Dienst der Krankenkassen (MDK) eine Vereinbarung hinsichtlich der Erstattung einer autologen Stammzelltransplantation bei Patienten mit Multiplem Myelom in der Altersklasse 66 bis 70 Jahren gefunden. Ab Januar 2019 wird die **autologe Stammzelltransplantation bei Patienten mit Multiplem Myelom im Alter von 66 bis 70 vom MDK nicht mehr als strittig erachtet** wenn eine entsprechende Aufklärung, wie im Anhang ausgeführt, vorgenommen und vom Patienten unterschrieben wird.

Die DAG-KBT ist mit den Studiengruppen DSMM und GMMG weiterhin bemüht auch eine einvernehmliche Lösung hinsichtlich der Altersgruppe 71 bis 75 Jahre und der Tandem Transplantation mit dem MDK in den nächsten Monaten zu erreichen.

Beste Grüße

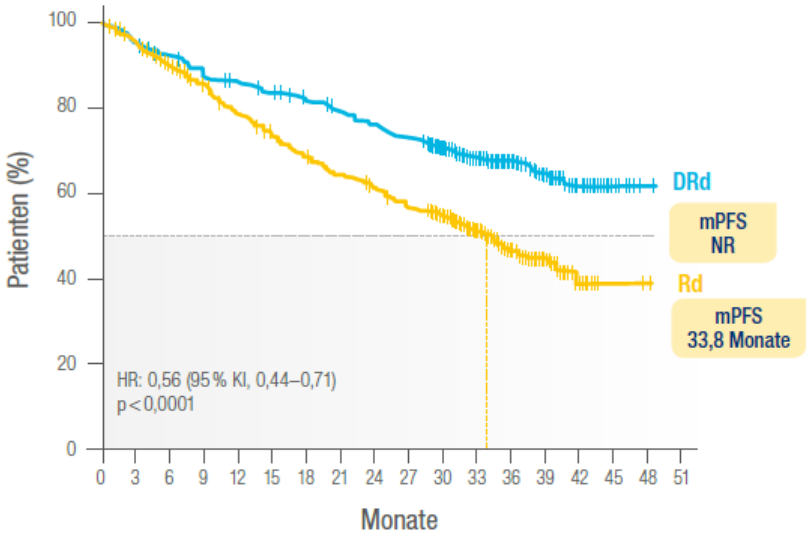
Laura Ruhkopf
Sekretariat Deutsche Arbeitsgemeinschaft für Knochenmark und Blutstammzelltransplantation e.V. (DAG-KBT)
c/o Prof. Dr. Kröger

Front Line Treatment Options for NDMM not

-

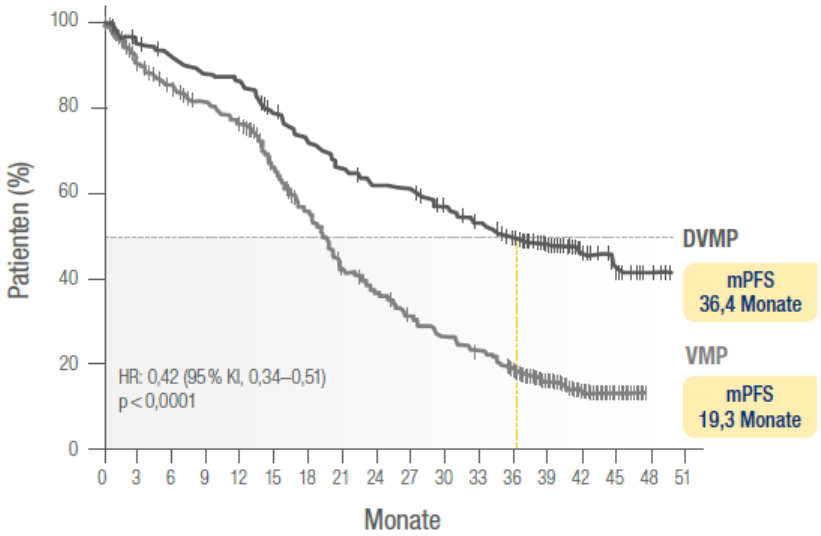
MAIA[2]

Progressionsfreies Überleben
(PFS, medianes Follow-Up: 36,4 Monate)



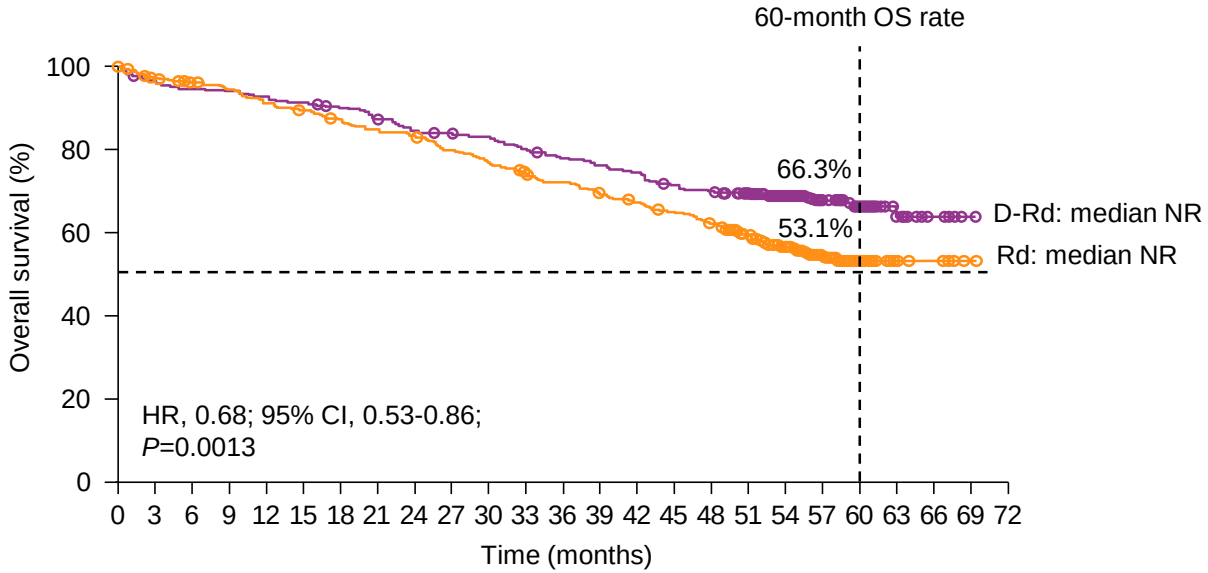
ALCYONE[1]

Progressionsfreies Überleben
(PFS, medianes Follow-Up: 40,08 Monate)



D, Daratumumab; d, Dexamethason; HR, hazard ratio; KI, Konfidenzintervall; M, Melphalan; NR, not reached; NSZT, nicht geeignet für Stammzelltransplantation; P, Prednison; R, Lenalidomid; V, Bortezomib.
Modifiziert nach 1. Bahlis et al. ASH 2019; 2. Mateos et al. *NEJM* 2018.

MAIA: OS



Number at risk

Rd	369	351	343	336	324	317	308	300	294	281	270	258	251	241	232	223	213	183	134	85	42	14	5	1	0
D-Rd	368	350	346	344	338	334	328	316	305	302	297	286	280	273	266	255	249	228	170	118	63	22	6	1	0

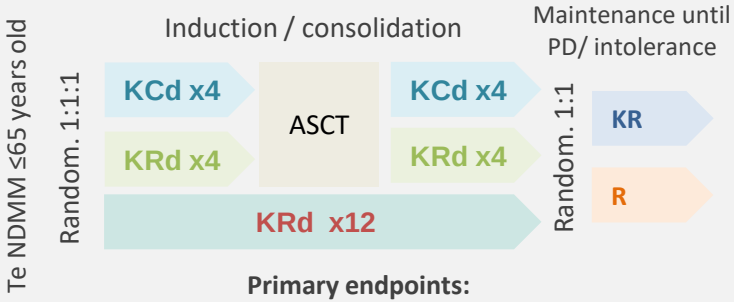
D-Rd demonstrated a significant benefit in OS, with a 32% reduction in the risk of death, in patients with NDMM who are transplant ineligible

4 Role of ABSCT

In the future, will all transplant-eligible patients still require a transplant?

FORTE (Phase 2)[1]

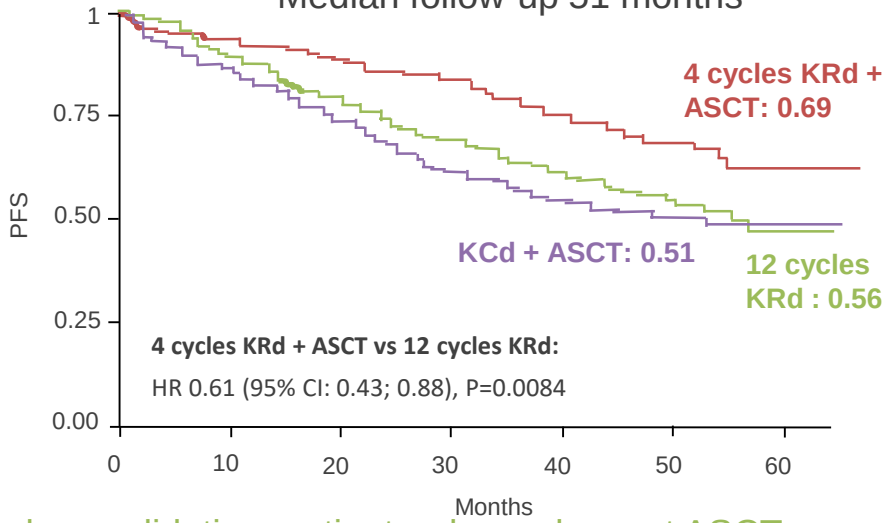
Aim: to evaluate efficacy and safety of different K-based induction and consolidation regimens ± ASCT, and maintenance with KR versus R alone in Te NDMM



Primary endpoints:
≥VGPR (KRd vs KCd induction)
PFS from maintenance randomization

3-year PFS in FORTE (N=474)

Median follow-up 51 months[2]



Of the patients treated with KRd induction and consolidation, patients who underwent ASCT had a longer PFS than patients who received an additional 4 cycles of KRd without ASCT

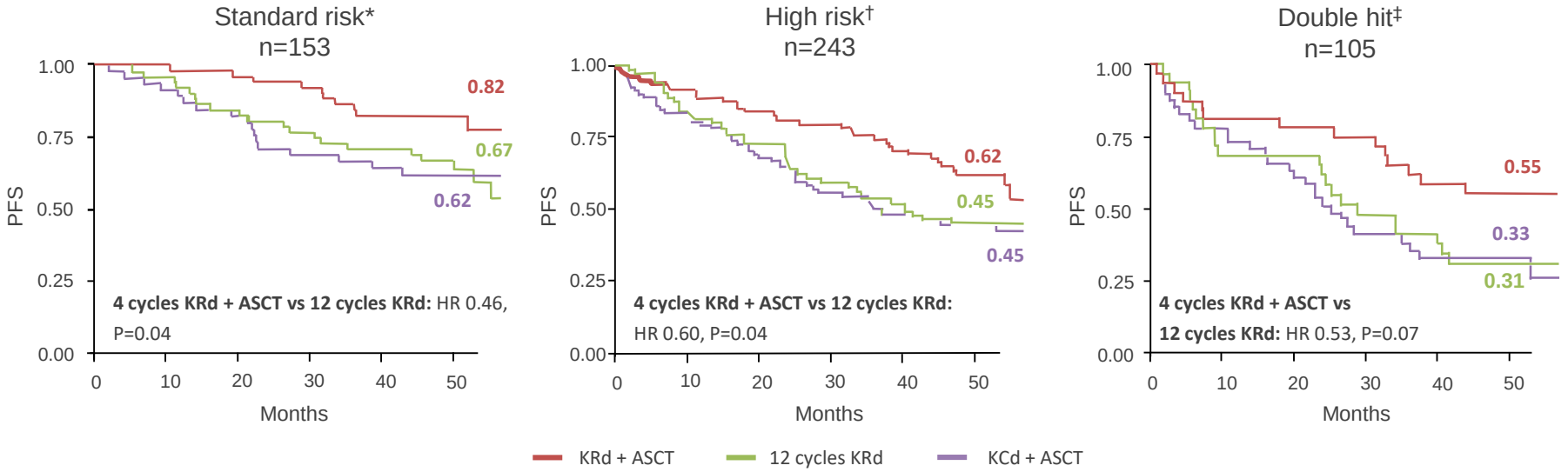
Study includes an investigational combination that has not been approved by any health authorities. ASCT, autologous stem cell transplant; C, cyclophosphamide; CI, confidence interval; d, dexamethasone; HR, hazard ratio; K, carfilzomib; NDMM, newly diagnosed multiple myeloma; PD, progressive disease; PFS progression-free survival; R, lenalidomide; Te, transplant eligible; VGPR, very good partial response

1. Gay et al. Lancet Oncol. 2021;22:1705–20;
2. Mina et al. EHA 2021; Abstract #S182

In the future, will all transplant-eligible patients still require a transplant?

4-year PFS by cytogenetic risk in the FORTE study

Median follow-up 51 months



Of the patients treated with KRd induction and consolidation, patients who underwent ASCT had a longer PFS than patients who received an additional 4 cycles of KRd without ASCT, regardless of cytogenetic risk

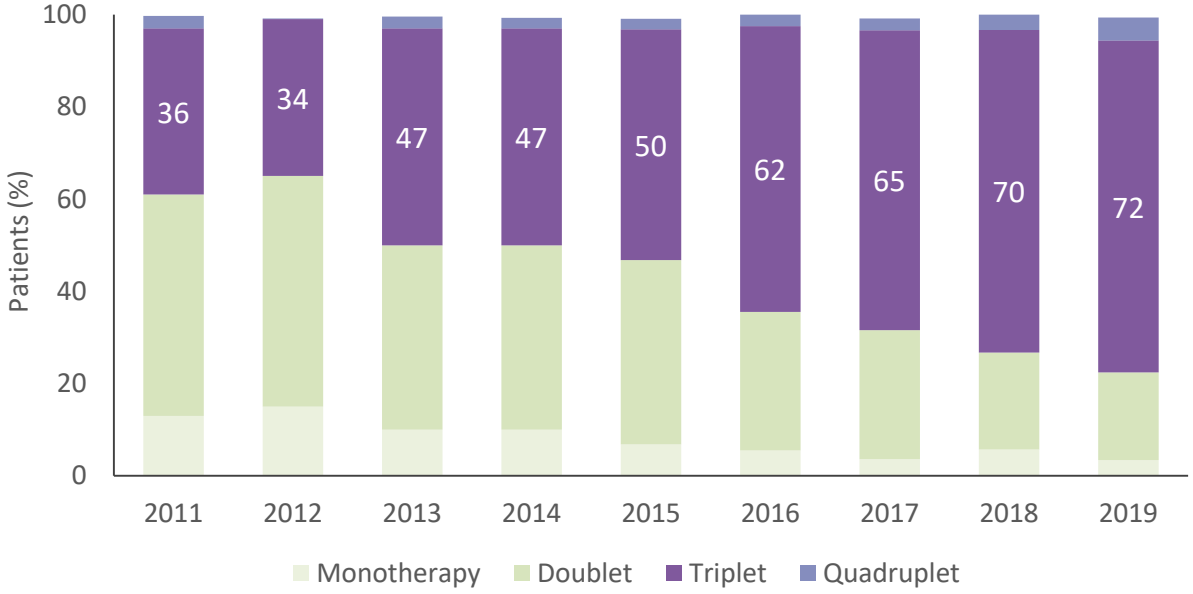
an investigational combination that has not been approved by any health authorities. Adverse cytogenetic abnormalities included: ≥15% t(4;14), t(14;16) (cut-off not reported), ≥10% del(17p), ≥10% del(1p), ≥10% gain(1q), ≥20% amp(1q). *Defined as the absence of any adverse cytogenetic abnormalities. †Defined as ≥1 cytogenetic aStudy includes bnormalities. ‡Defined as ≥2 cytogenetic abnormalities. ASCT, autologous stem cell transplant; C, cyclophosphamide; CI, confidence interval; d, dexamethasone; HR, hazard ratio; K, carfilzomib; NDMM, newly diagnosed multiple myeloma; PFS progression-free survival; R, lenalidomide;

Mina et al. EHA 2021; Abstract #S182

Over the last decade, the use of triplet regimens in frontline MM treatment has increased

Frontline prescribing trends in the US (regardless of transplant eligibility)

Flatiron Health electronic-health records database (N=6271)



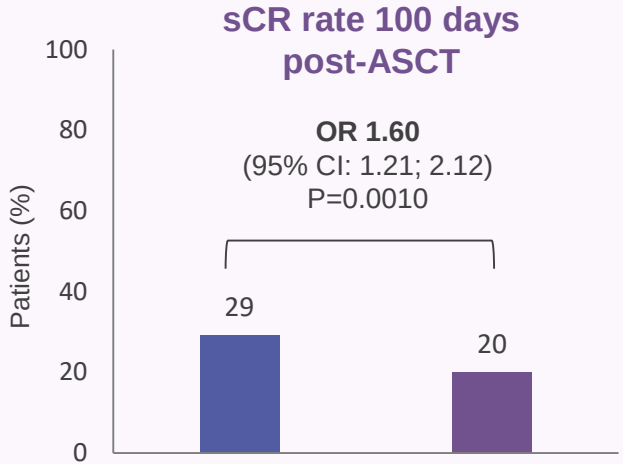
Use of triplet regimens **doubled** between 2011 and 2019

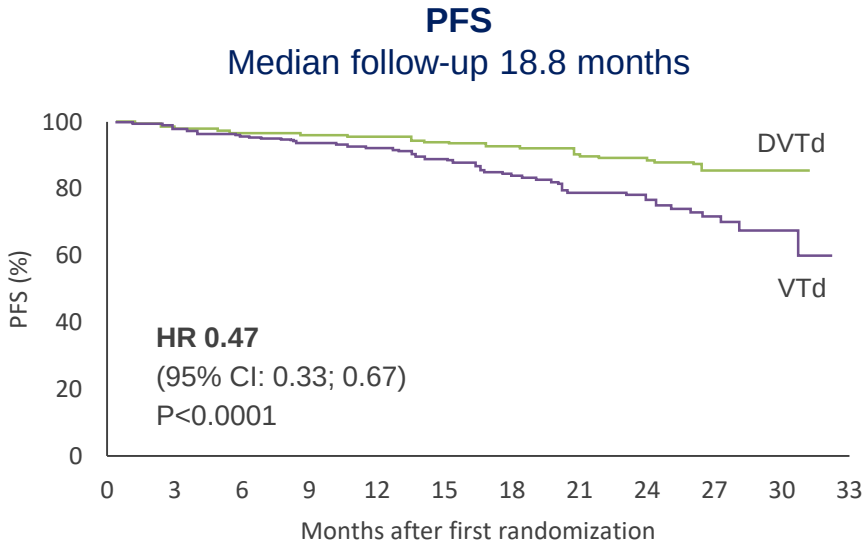
Kumar, et al. Cancer Med 2021;10:5866–77

CASSIOPEIA: DVTd vs VTd in transplant-eligible NDMM

Efficacy (Part 1 - induction, ASCT, and consolidation)

Primary endpoint (Part 1)



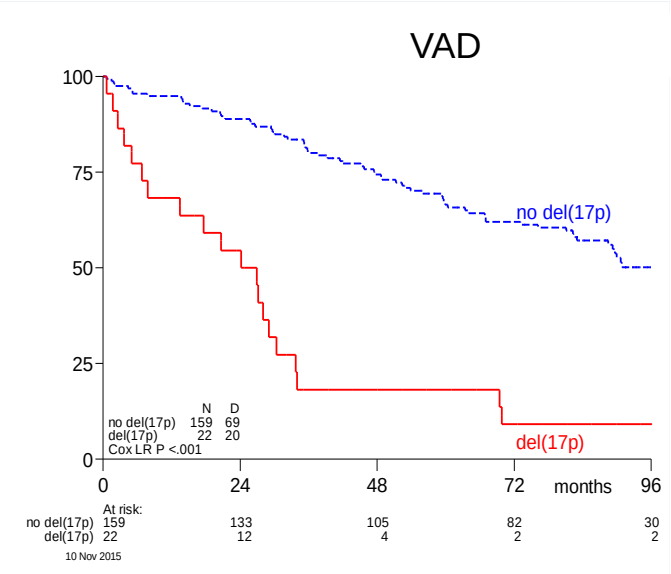


There was a statistically significant improvement in 100-day post-ASCT sCR rate with the addition of daratumumab to VTd. After 18.8 months median follow-up, the PFS HR favored the DVTd arm

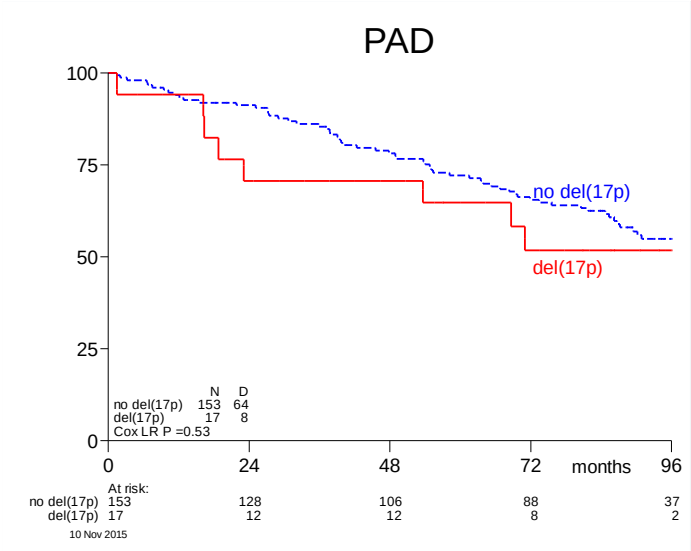
Moreau, et al. Lancet 2019;394:29–38;

ASCT, autologous stem cell transplant; CI, confidence interval; CR, complete response; D, daratumumab; d, dexamethasone; HR, hazard ratio; NDMM, newly diagnosed multiple myeloma; OR, odds ratio; PFS, progression-free survival; sCR, stringent complete response; T, thalidomide; Te, transplant eligible; V, bortezomib; VGPR, very good partial response

HOVON 65/GMMGHD4: OS by Treatment Arm Subgroup with del(17/17p)



p<0.001

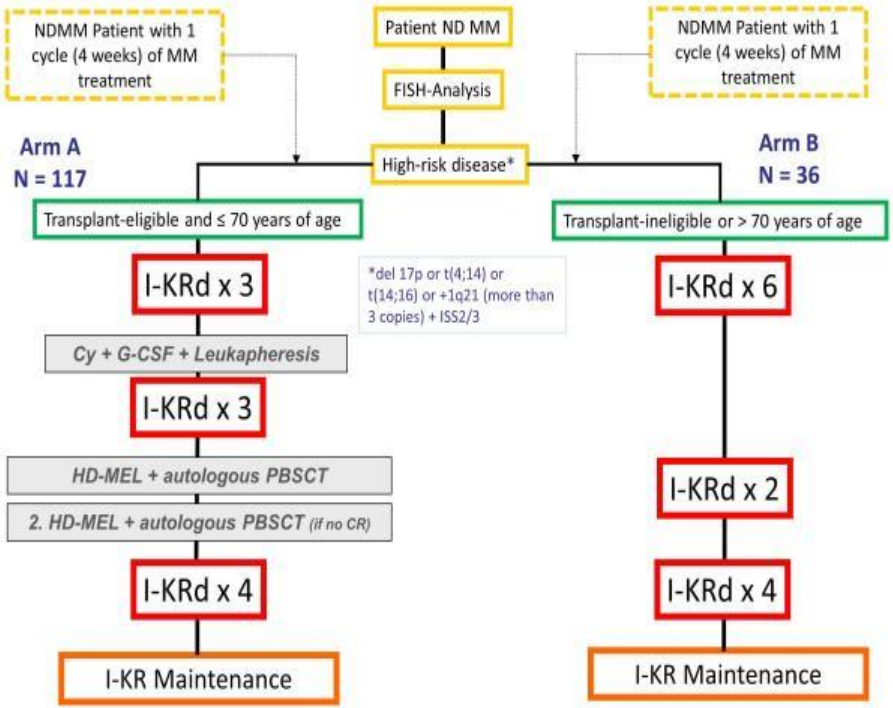


p=0.5

Neben et al., Blood 2012

Goldschmidt et al., Leukemia 2017

GMMG-CONCEPT-Trial

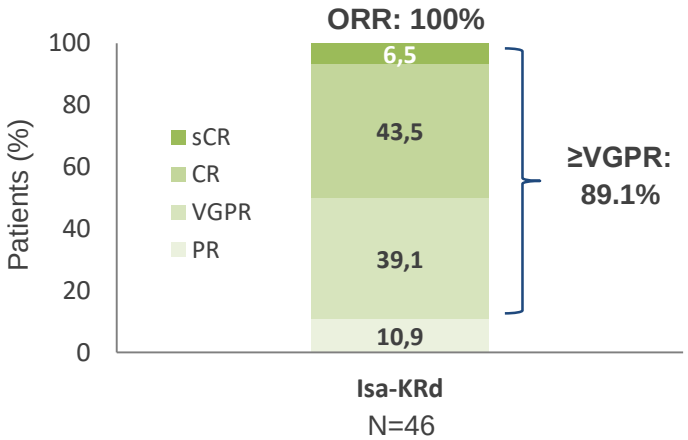


Lead PI: Katja Weisel, Sponsor: University Medical Center of Hamburg-Eppendorf

GMMG-CONCEPT: Isa-KRd (Phase 2)
Efficacy Interim analysis of first 50 patients

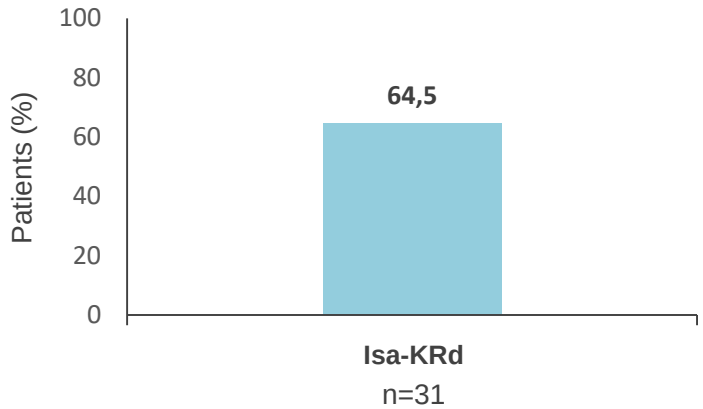
Best response during induction

Arm A (transplant-eligible NDMM)



MRD– (10^{-5} by NGF) during induction*

Arm A (transplant-eligible NDMM)



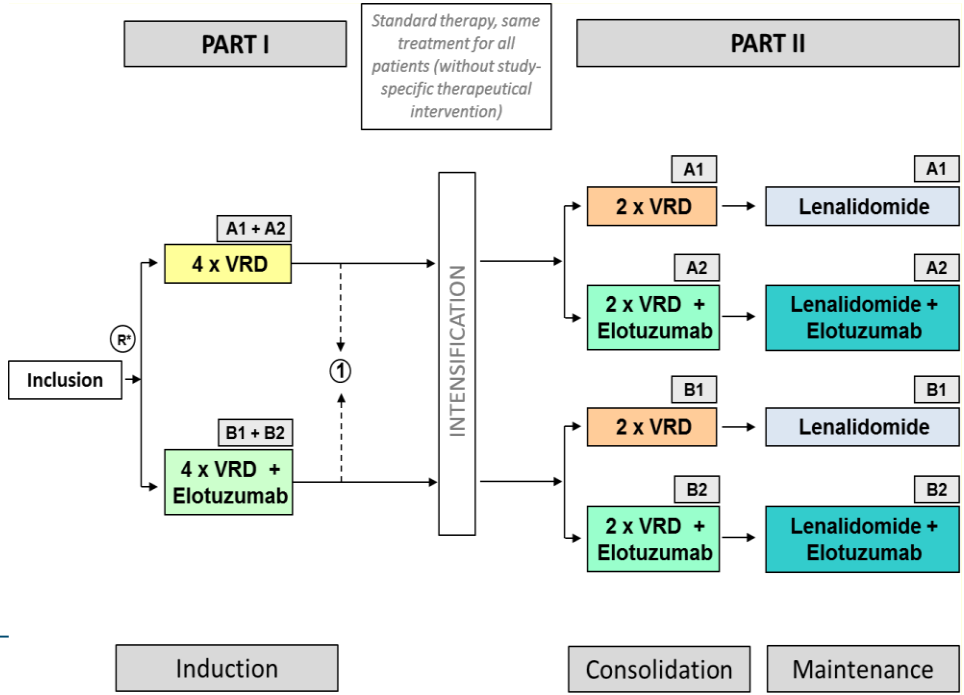
Rates of early, deep responses were encouraging, with almost two-thirds of patients achieving MRD– during induction

Leypoldt, et al. Leukemia 2022;36:885–8

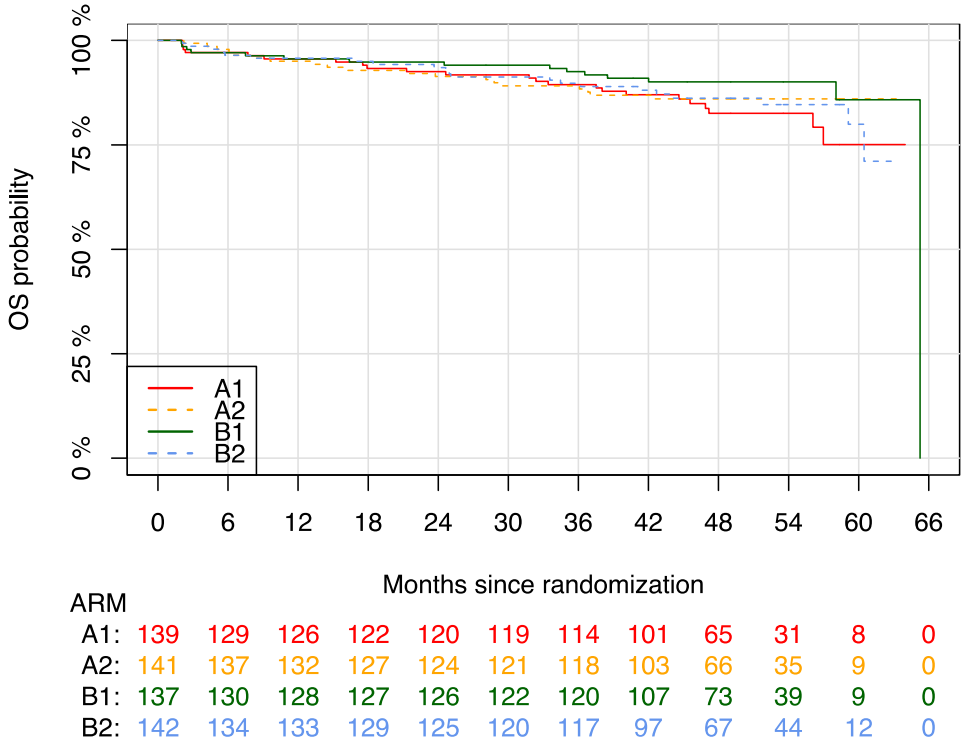
Bortezomib, lenalidomide and dexamethasone with or without elotuzumab as induction therapy for newly-diagnosed, transplant-eligible multiple myeloma

Hartmut Goldschmidt[1,2], Elias K. Mai[1,2], Hans J. Salwender[3], Uta Bertsch[1,2], Kaya Miah[4], Christina Kunz[4,5], Roland Fenk[6], Igor W. Blau[7], Christof Scheid[8], Hans Martin[9], Jörg Thomalla[10], Rolf Mahlberg[11], Marc. S. Raab[1], Stefanie Huhn[1,2], Dirk Hose[1], Anna Jauch[12], Ullrich Graeven[13], Mohammed Wattad[14], Britta Besemer[15], Andrea Seidel-Glätzer[16], Roland Schroers[17], Andreas Neubauer[18], Jan Dürig[19], Markus Munder[20], Mathias Hänel[21] and Katja C. Weisel[15, 22] for the German-speaking Myeloma Multicenter Group (GMMG)

- The addition of elotuzumab to VRD did not increase VGPR rates or better after four cycles of induction therapy
- Determination of CR rates is impeded by elotuzumab → MRD results may provide further insights in possible differences
- Overall toxicities for VRD vs. VRD + elotuzumab are comparable
- PFS results being awaited for 2021 (including results on maintenance strategies lenalidomide vs. elotuzumab + lenalidomide)



GMMG HD-6 Overall Survival



3-year OS rates

A1: 89.4%

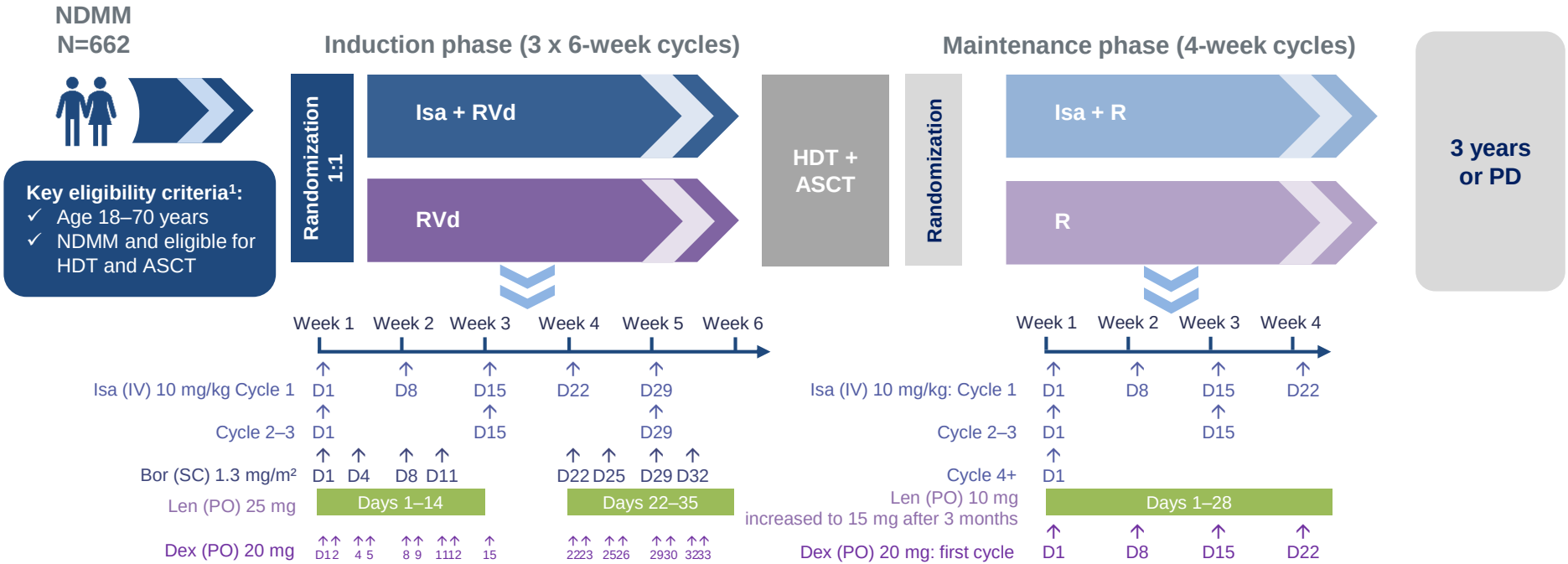
A2: 89.1%

B1: 92.5%

B2: 89.7%

- stratified log rank p=0.43

The first phase 3 study evaluating Isa + RVd for induction and maintenance in Te NDMM patients



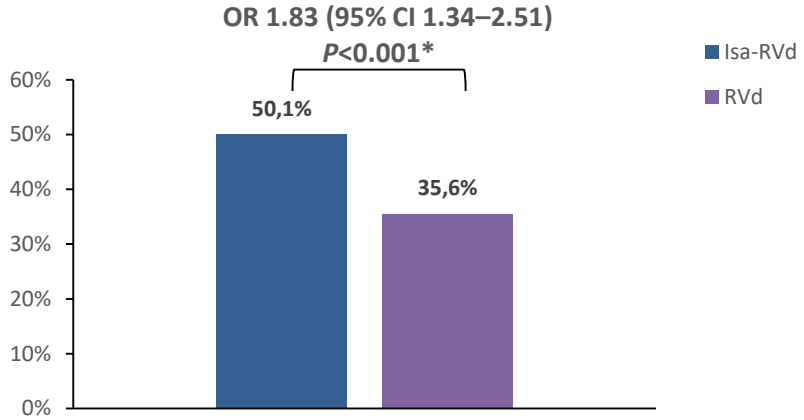
Goldschmidt, Mai et al. Lancet Haematol. Accepted 2022

ASCT, autologous stem cell transplant; D, day; d/Dex, dexamethasone; HDT, high-dose therapy; Isa, isatuximab; IV, intravenous; NDMM, newly diagnosed multiple myeloma; PD, progressive disease; PO, oral; R/Len, lenalidomide; SC, subcutaneous; Te, transplant eligible; V/Bor, bortezomib; RVd is off label use in some countries according to the lenalidomide summary of product characteristics.

1. ClinicalTrials.gov: NCT03617731

First primary endpoint, end of induction MRD negativity by NGF (10^{-5}), was met in ITT analysis

Patients with MRD negativity at the end of induction therapy

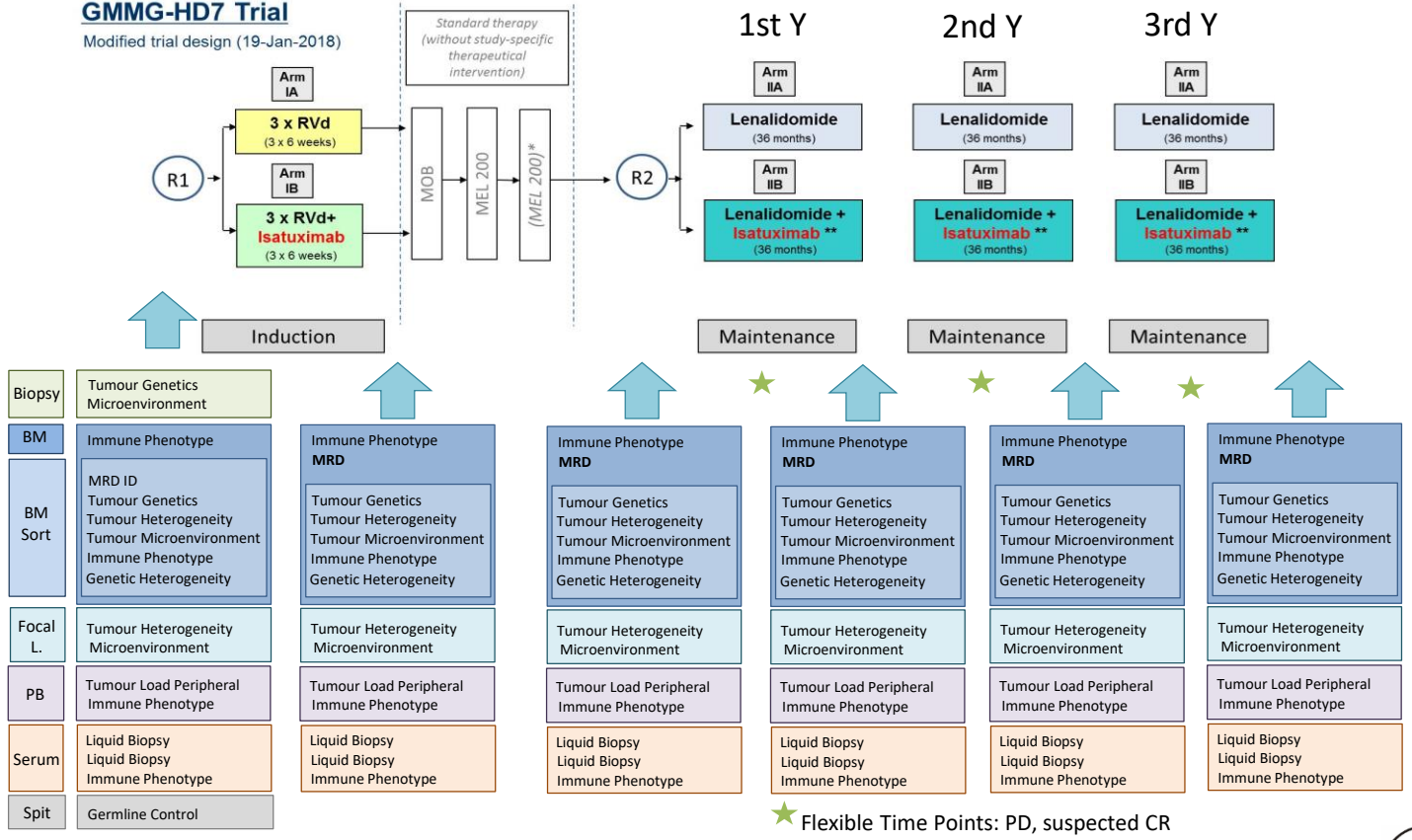


Low number of not assessable/missing† MRD status: Isa-RVd (10.6%) and RVd (15.2%)

Isa-RVd is the first regimen to demonstrate a rapid and statistically significant benefit from treatment by reaching a MRD negativity of 50.1% at the end of induction and to show superiority vs. RVd in a Phase 3 trial

Goldschmidt, Mai et al. Lancet Haematol. Accepted 2022

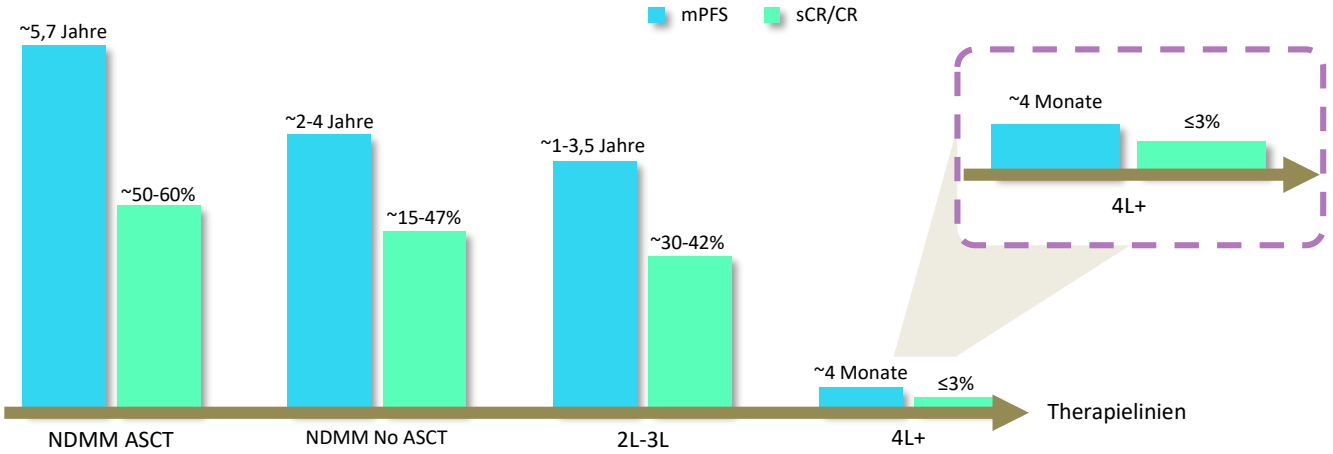
Biobanking in HD7 - Time Points For Sampling



gmmg.info

4 Relapse Treatment and Future Directions

High therapeutic requirement in advanced lines in multiple myeloma



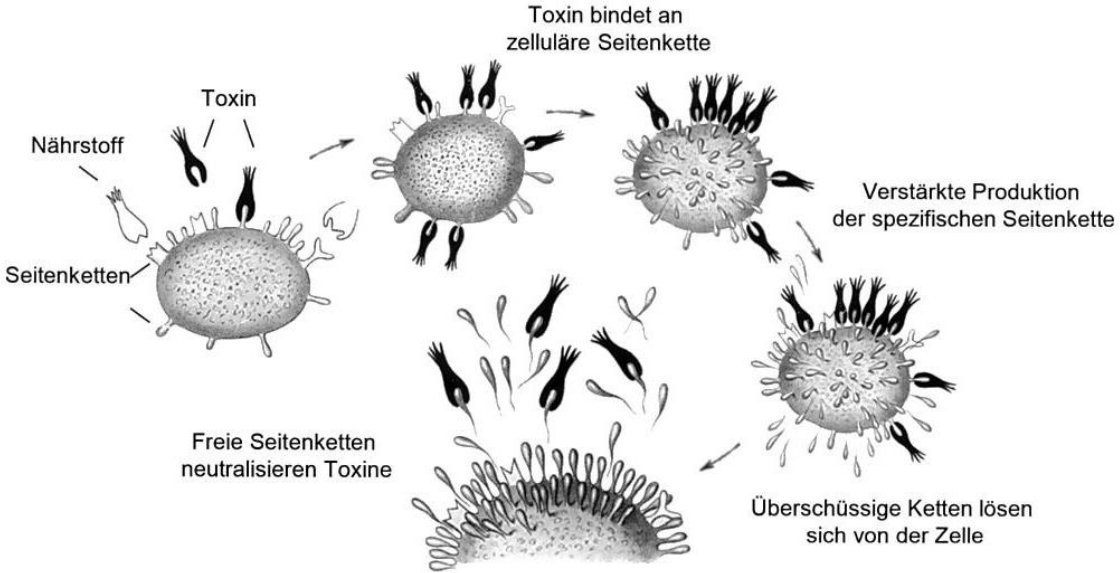
CR: *complete response*; mPFS: medianes *progression free survival*; NDMM: *neu diagnostiziertes Multiples Myelom*; sCR: *stringent* CR; ASCT: *Autologe Stammzelltransplantation*.

Gandhi, et al. Leukemia 2019.

Paul Ehrlich 1854 - 2015

Wikipedia

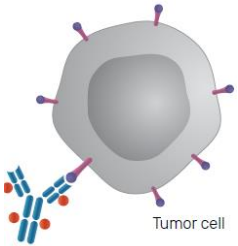
Paul Ehrlich Nobel Prize 1908



Quelle: Trillium Immunologie 2018; 2(4) – Eine kurze Zeitreise
Von Ehrlichs Seitenkette bis zur Entdeckung der Plasmazelle – Autoren: S.R. Schulz, H-M Jäck, K. Pracht

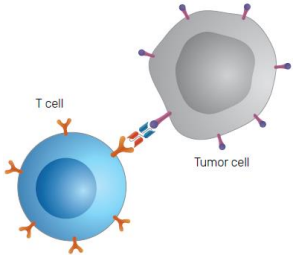
BCMA: One target, several approaches

Deliver



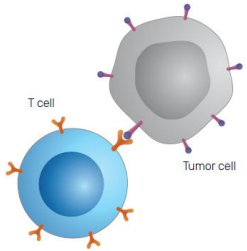
Antibody Active substance Conjugate
e.g. Belantamab mafodotin

Link



T cell Engager

Arm



Chimera Antigen Receptor T Cell

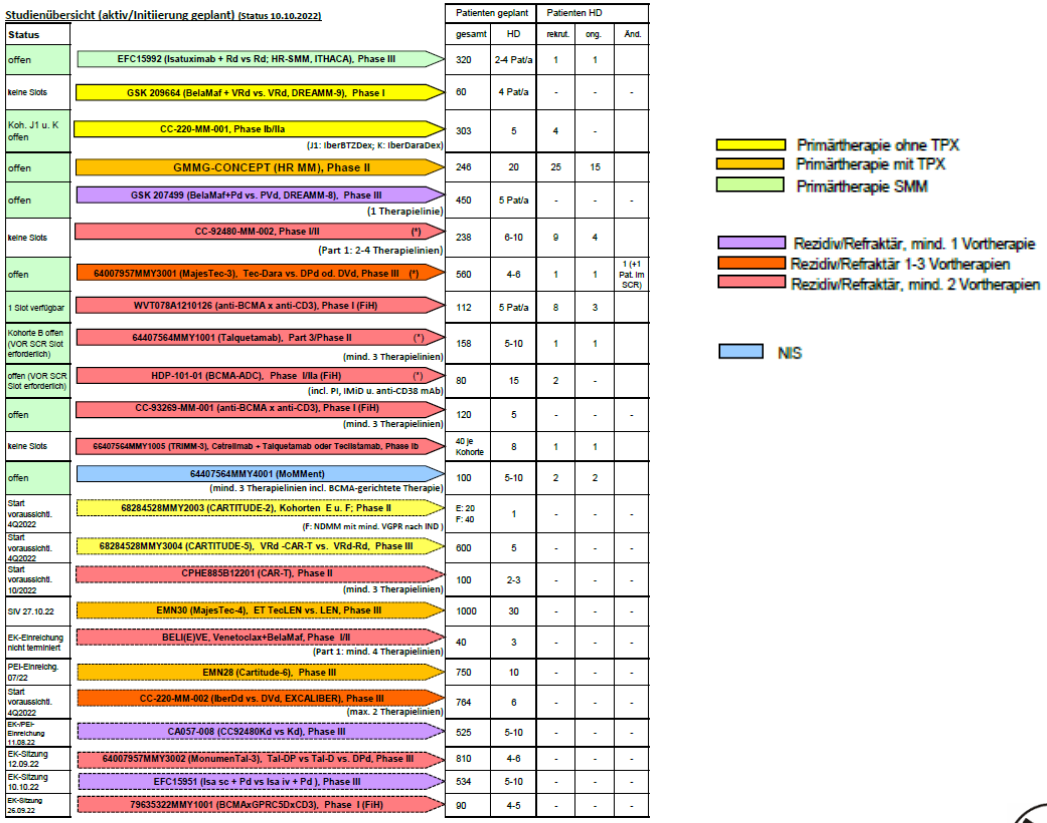
Batlevi CL, et al. Nat Rev Clin Oncol. 2016;13(1):25-40.
Marin-Acevedo JA, et al. J Hematol Oncol. 2018;11(1):8.
Thomas A, et al. Lancet Oncol. 2016;17(6):e254-e262.
Baeuerle PA, et al. Cancer Res. 2009;69(12):4941-4944.
Brudno JN, et al. Blood Rev. 2019;34:45-55.
Porter DL, et al. N Engl J Med. 2011;365(8):725-733.

Studienübersicht (aktiv/Initiierung geplant)

(Status 10.10.2022)

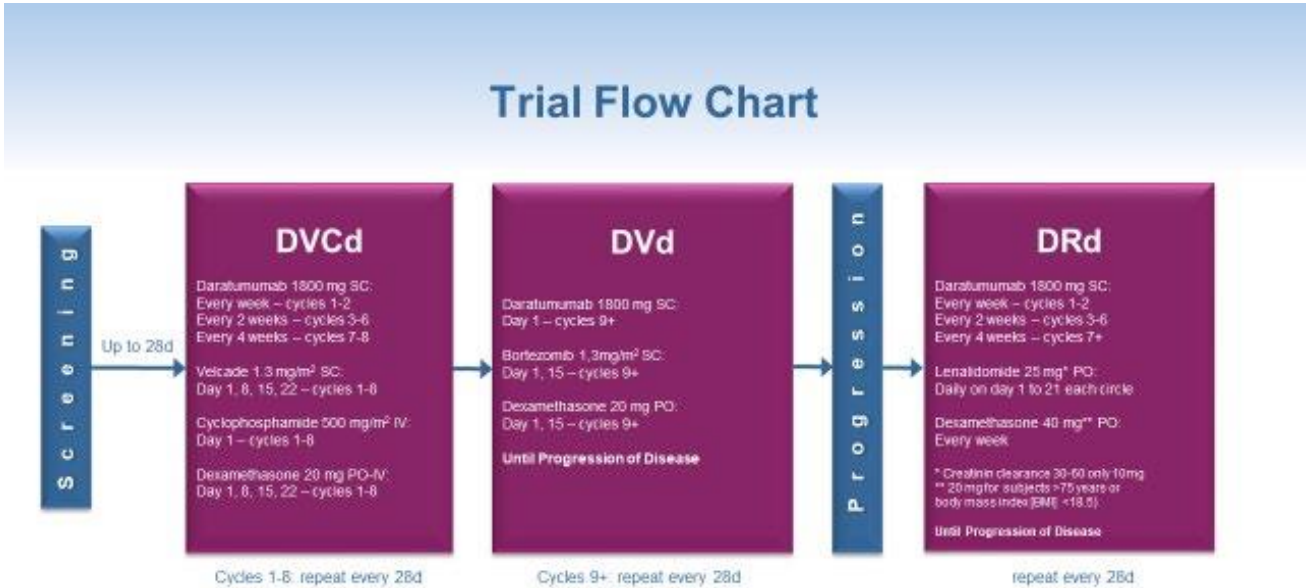
Prof. Raab

Dr. Schlenzka



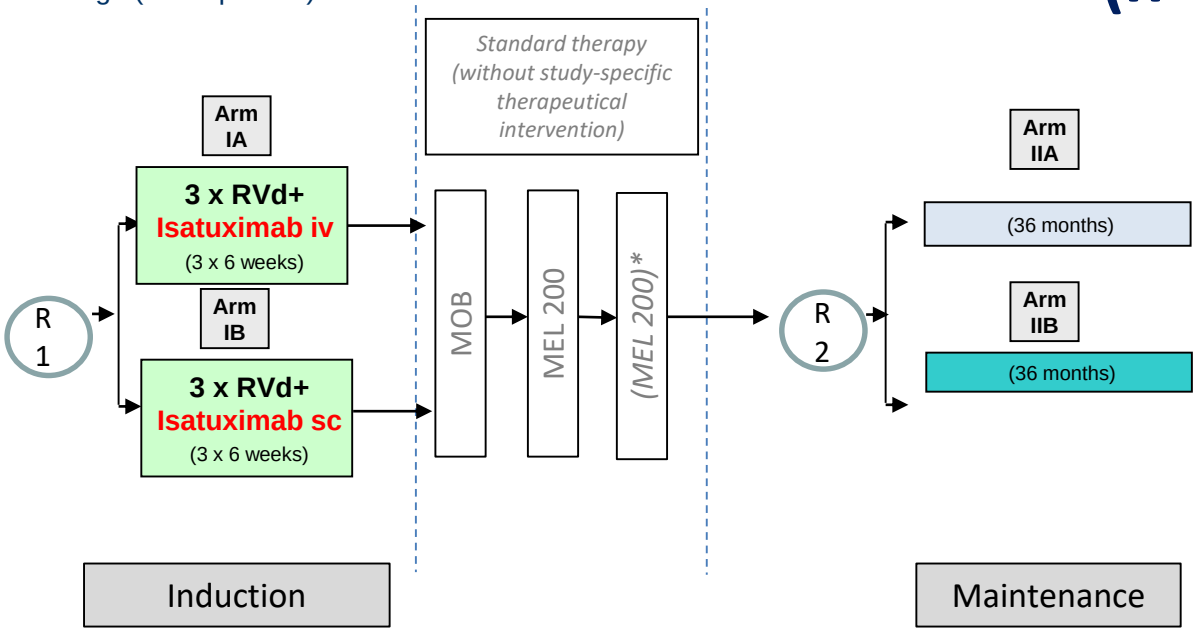
GMMG DaDa Trial - LKP Prof. Scheid, Köln

Figure 1: Trial flowchart



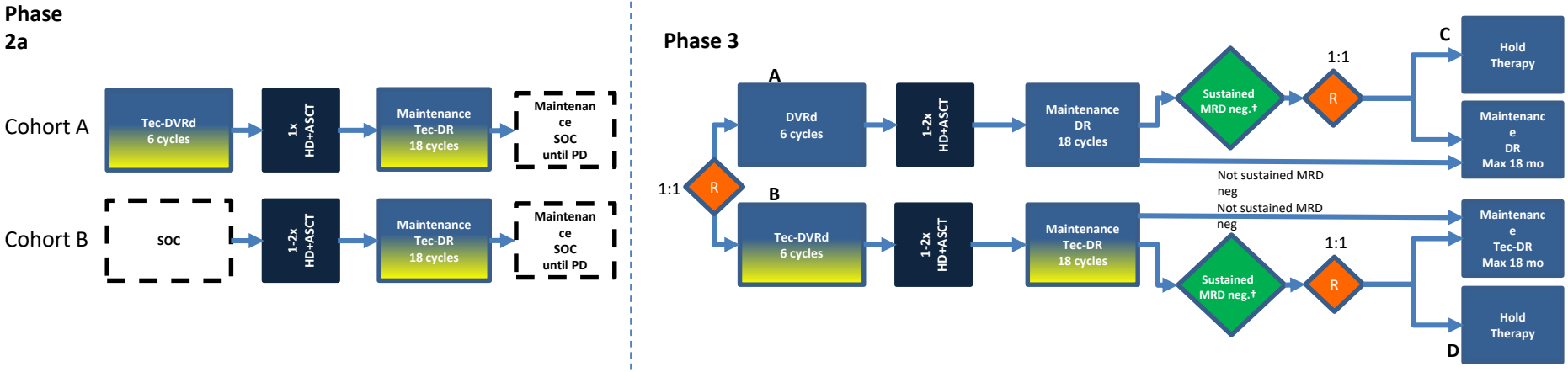
Joint German Study: Proposal NDMM up to 70 Years (n=514 pts.)

Modified trial design (20-Sep-2021)



R1 = 1st randomization (at study inclusion); R2 = 2nd randomization (prior to maintenance)

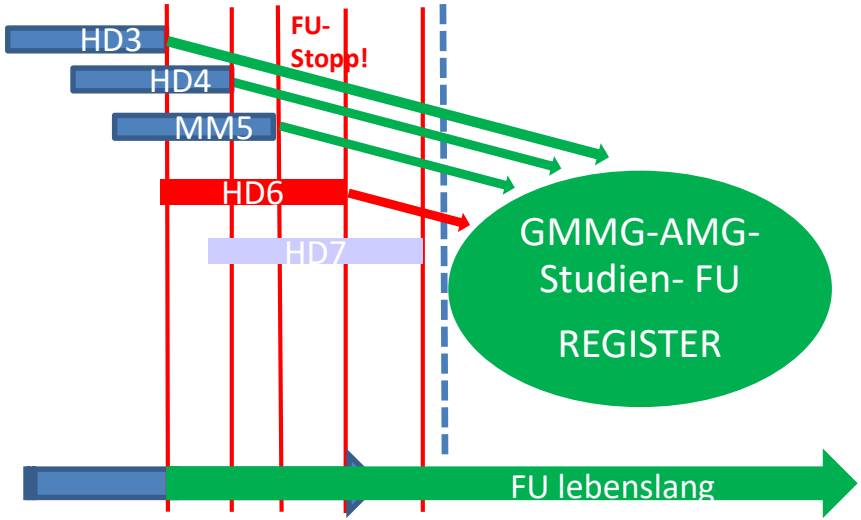
German Intergroup Trial GMMG/DSMM: Phase 2/3 Teclistamab in Transplant-Eligible NDMM



Myeloma Register Expansion Follow-Up: GMMG-Studies MM

AMG-Studien MM max. 3 Jahre FU

GMMG-MM-FU-Register (in Vorbereitung)



Danke!

Heidelberg, Germany

GMMG Study Group Meeting Heidelberg September 2019