Praxisrelevante Fortschritte bei MM PatientInnen, die für eine Transplantation in Frage kommen

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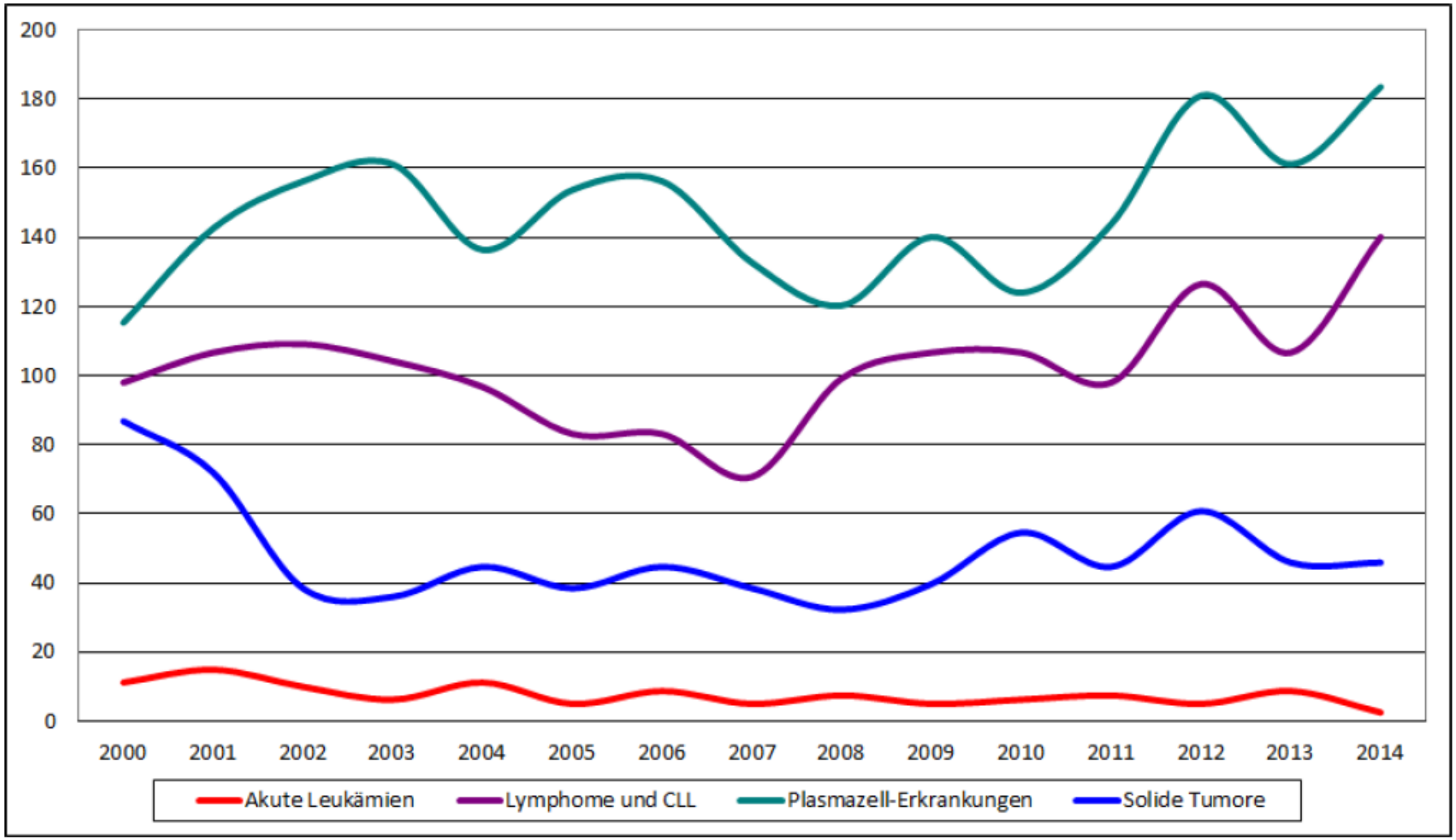
Wilhelminenspital Wien

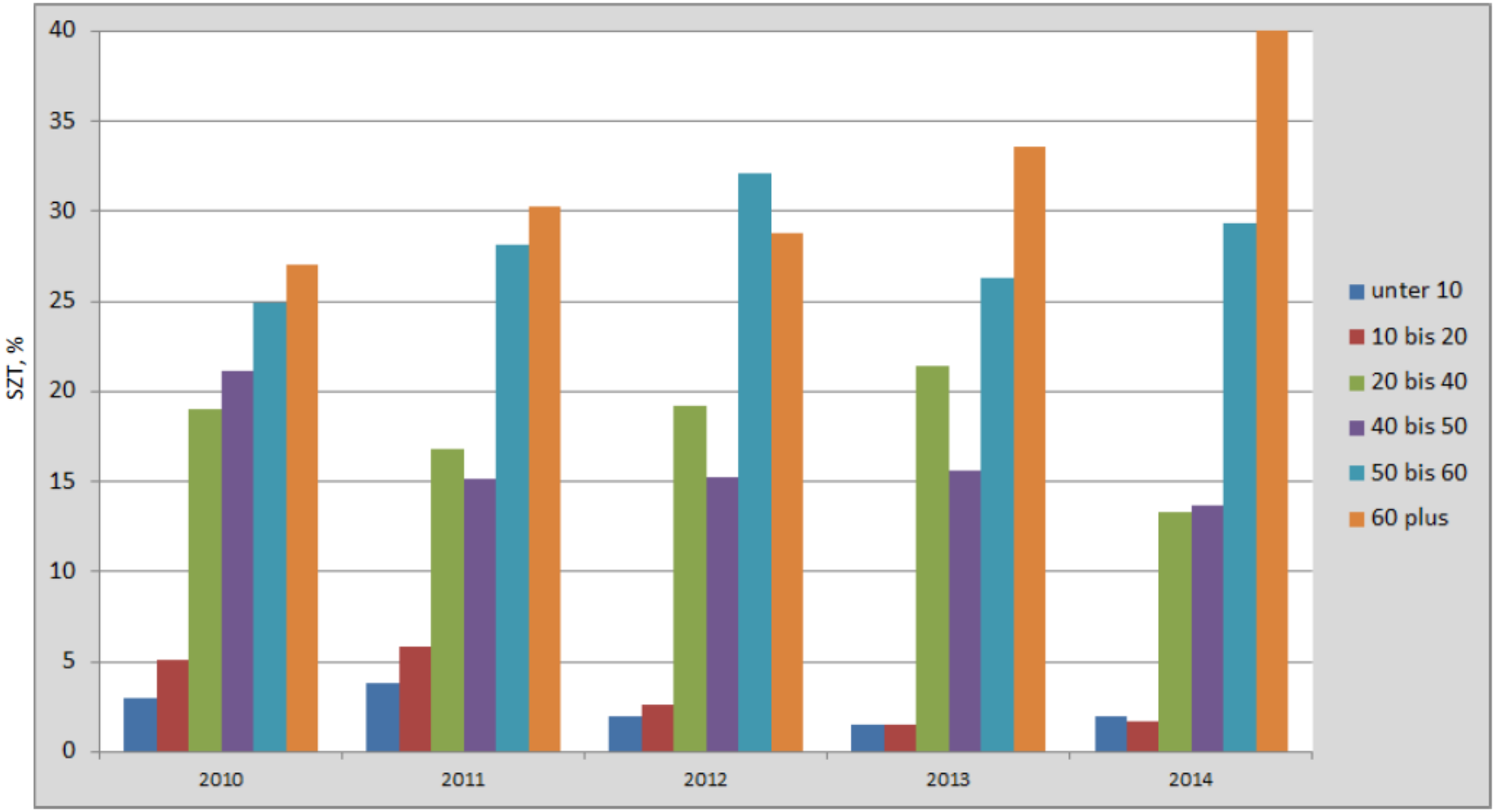
Braille Haus
18. Februar 2016

Entwicklung der autologen SZT
2000 – 2014 pro 10 Mill Einwohner, n=4621



*Nicht in der Darstellung enthalten: andere

Altersverteilung von Patienten mit autologer SZT 2010 - 2014, n=1339 (Angaben in %)



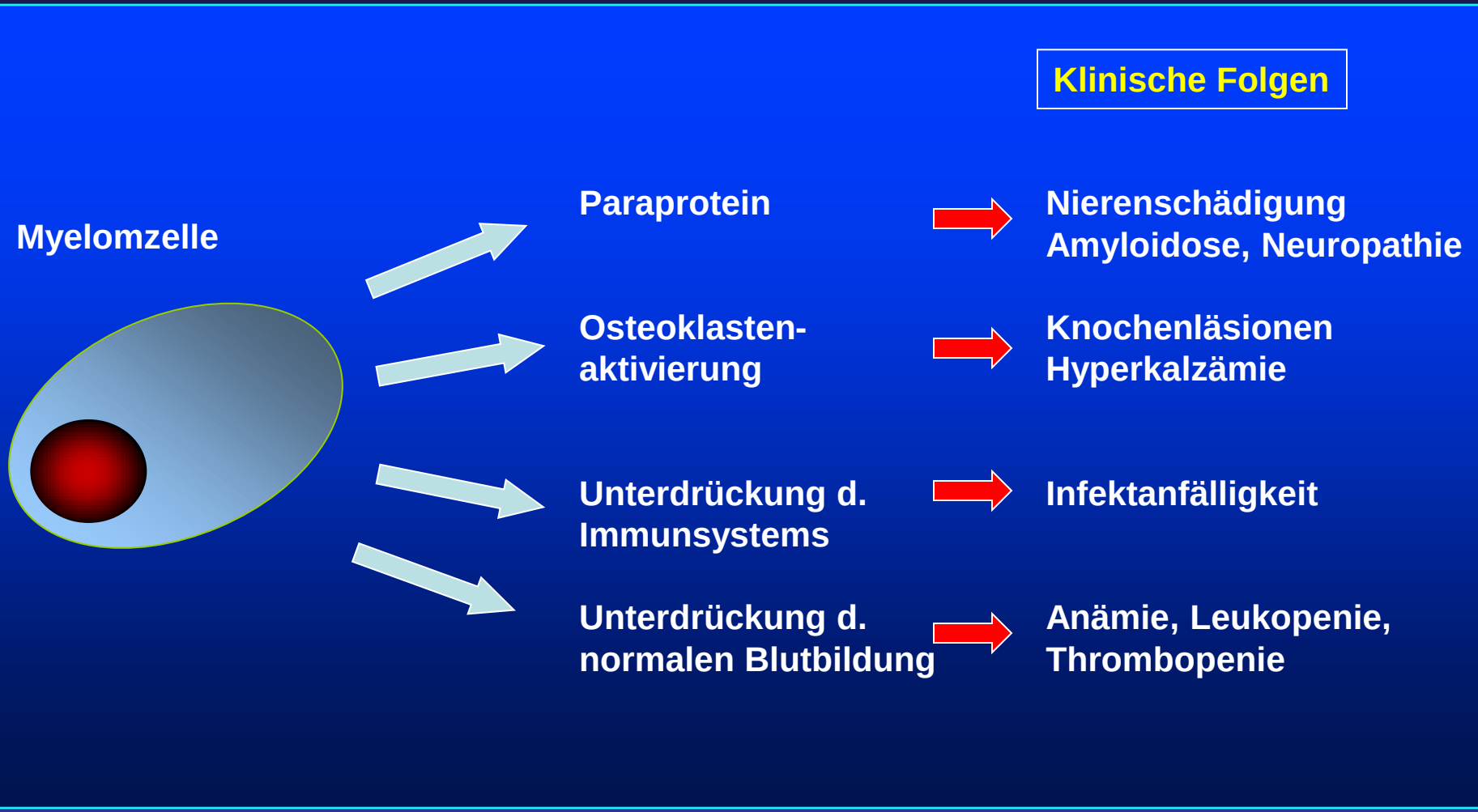
Trends in ASCT for MM in Europe 1991-2010

ASCT bei Patienten ≥ 65 Jahre

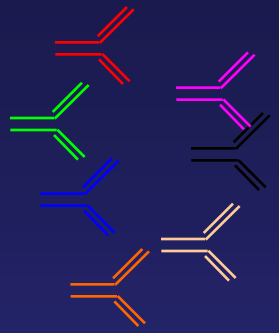
18.8% aller Transplantationen 2006-2010 (3% 1991-1995)
100 Tages Mortalität: ≤ 2.4% (≤ 1.8% < 65 Jahre)
5y OS: ~ 50% (~60% < 65 Jahre)

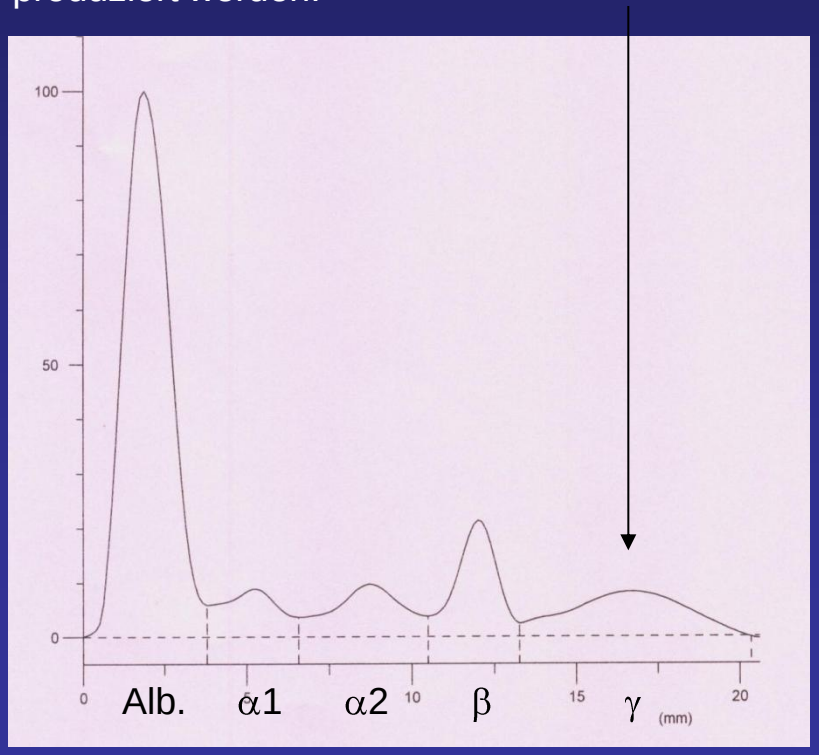
Auner et al., Bone Marrow Transplant, Feb. 2015

Einfluß der Myelomzelle auf das Krankheitsbild



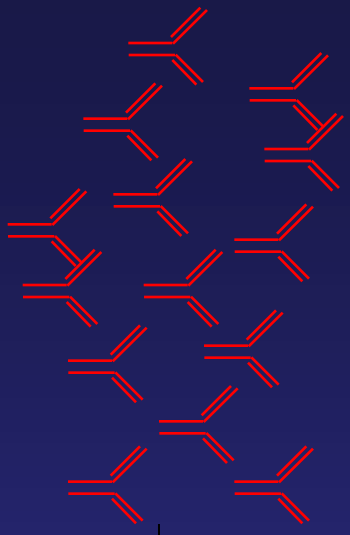
Bei einer Elektropherese einer gesunden Person findet sich im Gamma (γ) –Bereich eine relativ flache Kurve. Diese wird hervorgerufen durch eine Vielfalt von Immun-globulinen, die durch normale Plasmazellen produziert werden.

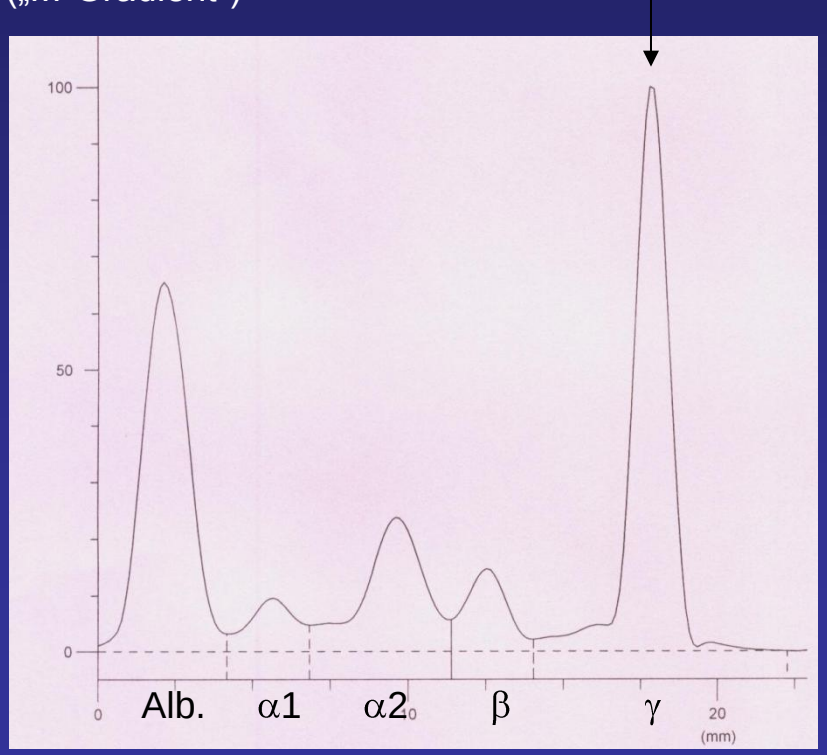




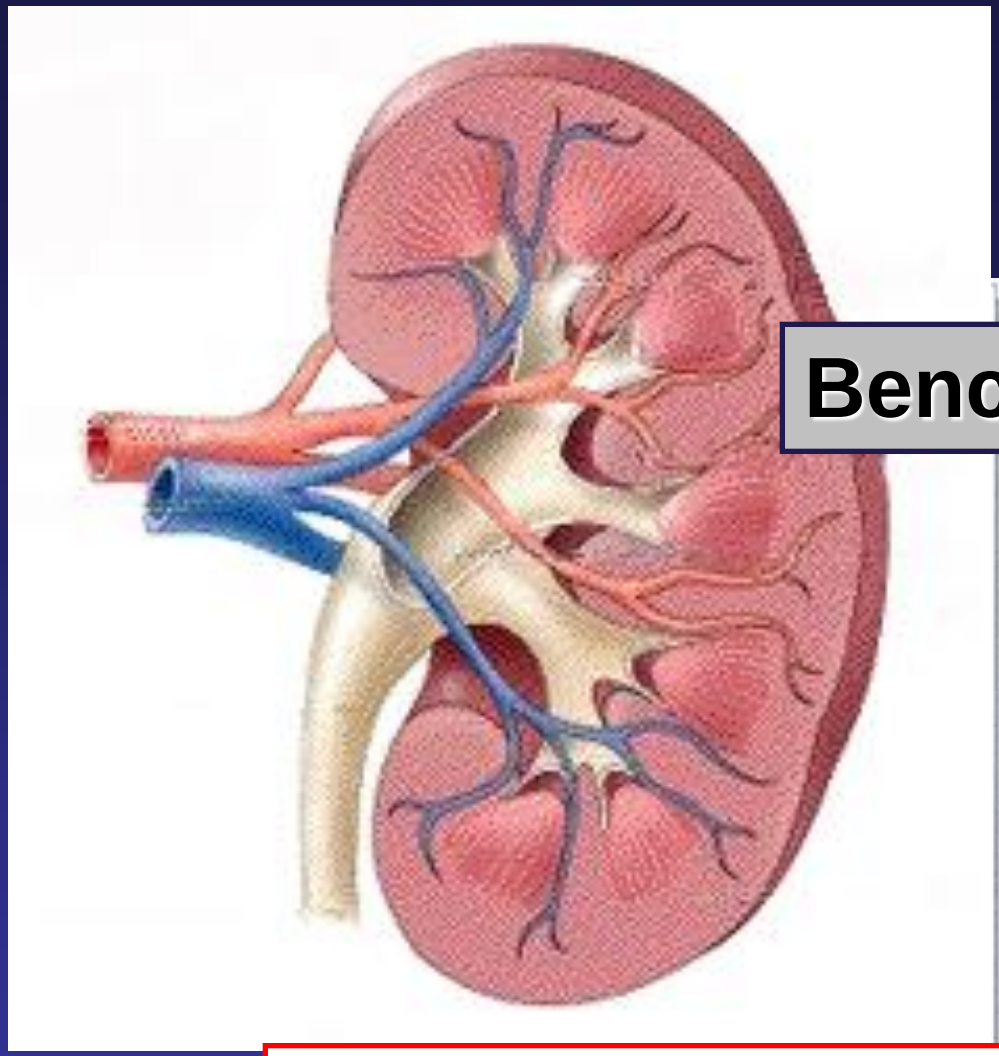
Elektropherese: gesunde Person

Eine klonale Plasmazelle (Myelomzelle) produziert große Mengen eines Immunglobulins eines einzigen Typs. Dieses Immunglobulin („Paraprotein“) Erscheint in der Elektropherese als Zacke („M-Gradient“)

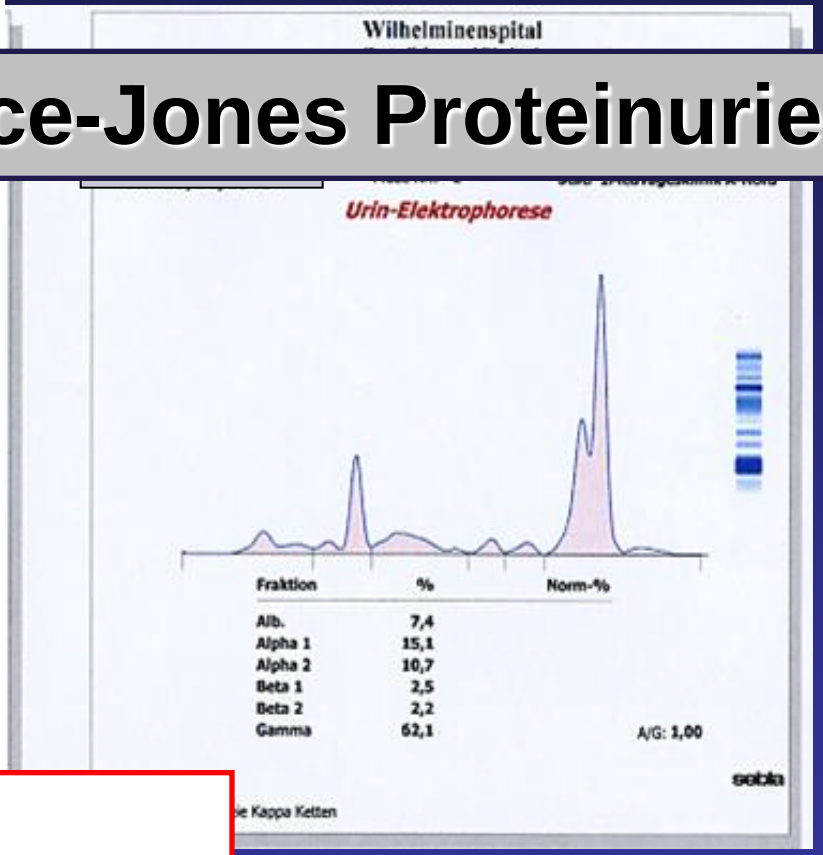




Elektropherese: Myelompatient



Bence-Jones Proteinurie



- Messung 24 h Harn
- ev. Harn-Ephorese
- Myelomniere

Plasmazell-Erkrankungen

- MGUS (monoklonale Gammopathie unbekannter Signifikanz)
- „Smoldering“ Myelom=

  asymptomatisches Myelom
- Multiples Myelom
- Extramedulläres Plasmozytom
- Solitäres Plasmozytom
- AL Amyloidose
- Plasmazell-Leukämie

Asymptomatisches Myelom (Smoldering Myelom)

- Serum M Protein ≥ 3 g/dl

  und/oder

- KM Plasmazellinfiltration ≥ 10%
- Keine Organschäden
- Bei Organschäden → symptomatisches Myelom

International Myeloma Working Group. Br J Haematol. 2003;121:749-57.

Organdysfunktion als „CRAB“ klassifiziert

C- Kalziumerhöhung (> 10mg/L)
R- Renale Dysfunktion (Kreatinin > 2mg/dL)
A- Anämie (Hämoglobin < 10g/dL)
B- Knochenerkrankung (lytische Läsionen oder Osteoporose)

ZUMINDEST EIN Faktor erforderlich für die Diagnose
SYMPTOMATISCHES MYELOM

International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma

S Vincent Rajkumar, Meletios A Dimopoulos, Antonio Palumbo, Joan Blade, Giampaolo Merlini, María-Victoria Mateos, Shaji Kumar, Jens Hillengass, Efstathios Kastritis, Paul Richardson, Ola Landgren, Bruno Paiva, Angela Dispenzieri, Brendan Weiss, Xavier LeLeu, Sonja Zweegman, Sagar Lonial, Laura Rosinol, Elena Zamagni, Sundar Jagannath, Orhan Sezer, Sigurdur Y Kristinsson, Jo Caers, Saad Z Usmani, Juan José Lahuerta, Hans Erik Johnsen, Meral Beksac, Michele Cavo, Hartmut Goldschmidt, Evangelos Terpos, Robert A Kyle, Kenneth C Anderson, Brian G M Durie, Jesus F San Miguel

Lancet Oncol 2014; 15: e538–48

Neue Kriterien für behandlungspflichtiges Myelom

Panel: **Revised International Myeloma Working Group diagnostic criteria for multiple myeloma and smouldering multiple myeloma**

Definition of multiple myeloma

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

- Myeloma defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcaemia: serum calcium >0·25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2·75 mmol/L (>11 mg/dL)
    - Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 μmol/L (>2 mg/dL)
    - Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡
  - Any one or more of the following biomarkers of malignancy:
    - Clonal bone marrow plasma cell percentage* ≥60%
    - Involved:uninvolved serum free light chain ratio§ ≥100
    - >1 focal lesions on MRI studies¶

Knochenmark
Serum
MR

Definition of smouldering multiple myeloma

Both criteria must be met:

- Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10–60%
- Absence of myeloma defining events or amyloidosis

PET-CT=^{18}F-fluorodeoxyglucose PET with CT. *Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used. †Measured or estimated by validated equations. ‡If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement. §These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L. ¶Each focal lesion must be 5 mm or more in size.

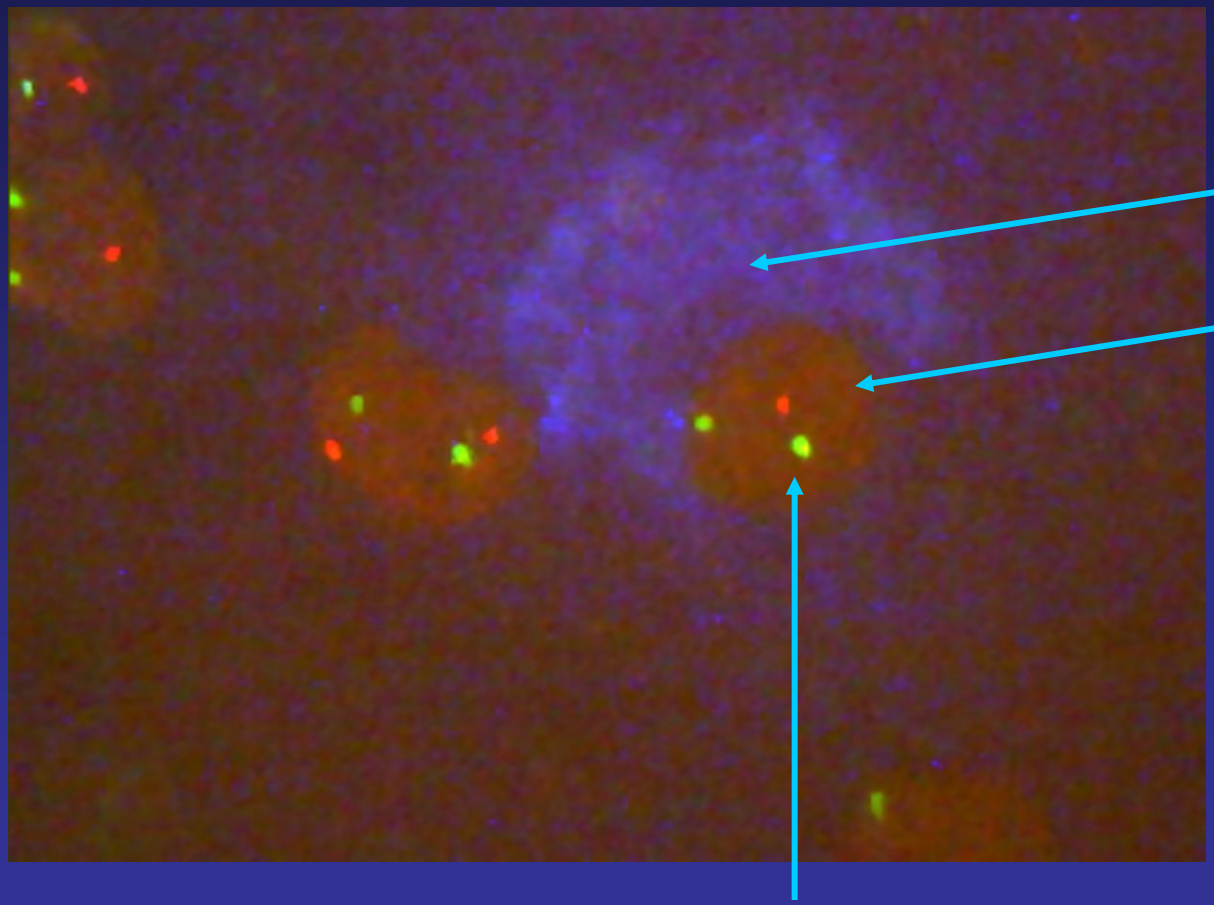
Mayo Stratifizierung (mSMART)

High risk	Intermediate risk	Standard risk
FISH	FISH	All others including:
Del 17p	t(4;14)	FISH
t(14;16)	Cytogenetic del 13	t(11;14)
t(14;20)	Hypodiploidy	t(6;14)
GEP High risk signature	PCLI ≥3%	

Factor	High risk	Intermediate risk	Standard risk
Incidence (%)	20	20	60
Median OS (y)	3	4-5	8-10

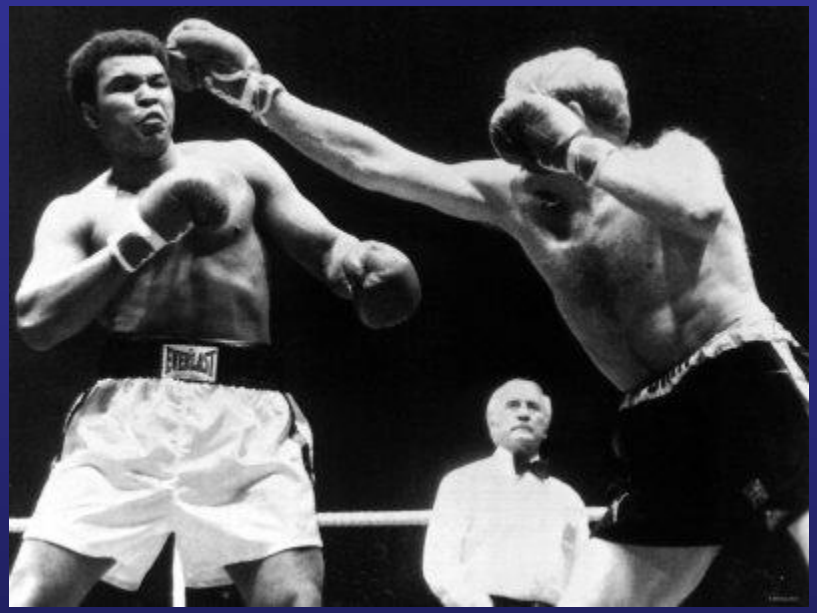
Mikhael et al., Mayo Clinic Proceedings April 2013

FISH Bild mit Nachweis von Chromosomenveränderungen



Grüne und rote Punkte im Zellkern entsprechen bestimmten Chromosomenregionen. In dieser Zelle findet sich nur ein rotes Signal (normalerweise: zwei Signale). Entspricht einem Verlust von Chromosom 13 = Deletion.

Risiko-adaptierte Therapie?



„A clash of philosophies“

- Maximale Therapie für alle?

Rajkumar et al., Blood Sept. 2011

Chemotherapie: Melphalan, Cyclophosphamid, Bendamustin ….

Steroide: Dexamethason, Prednisolon ….

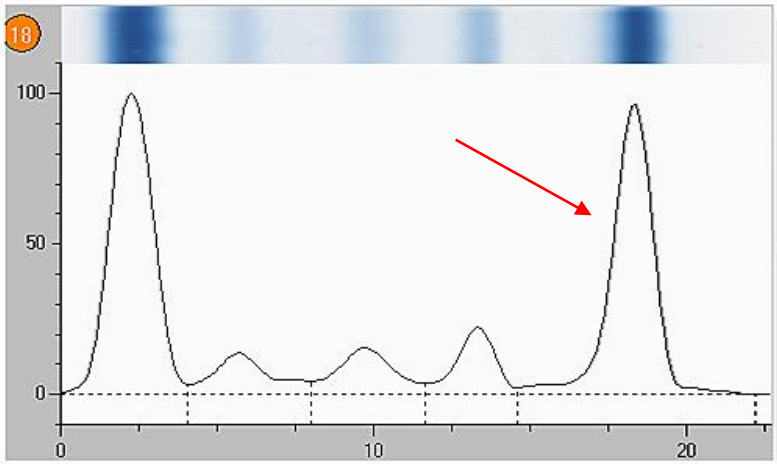
Proteasomhemmer: Bortezomib, Carfilzomib, Ixazomib….

IMiDs: Thalidomid, Lenalidomid, Pomalidomid

HDAC-Hemmer: Panobinostat

Antikörper: Daratumumab, Elotuzumab ….

VERLAUF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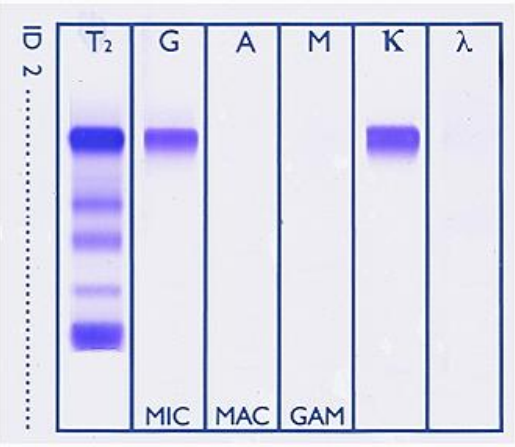
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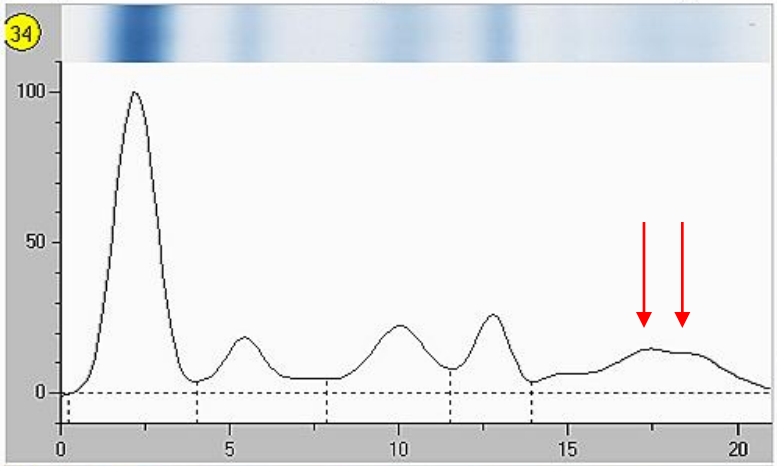
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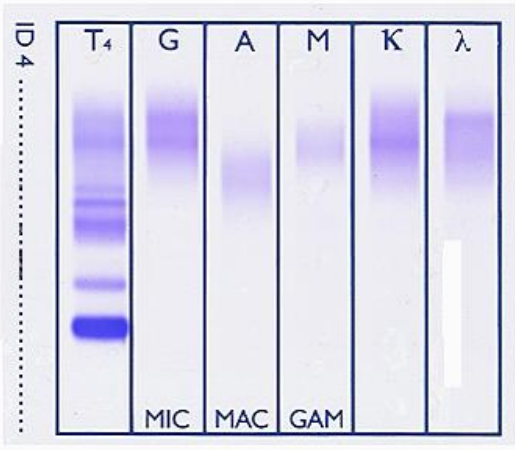
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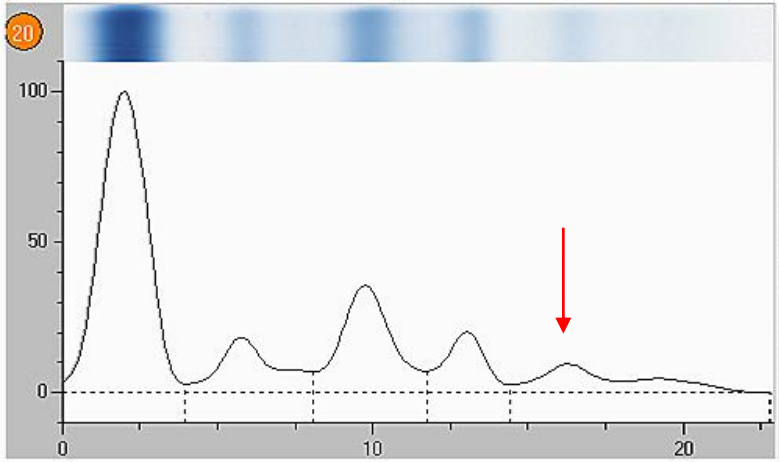
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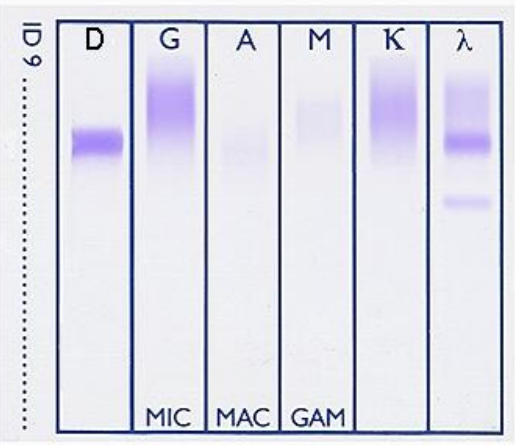
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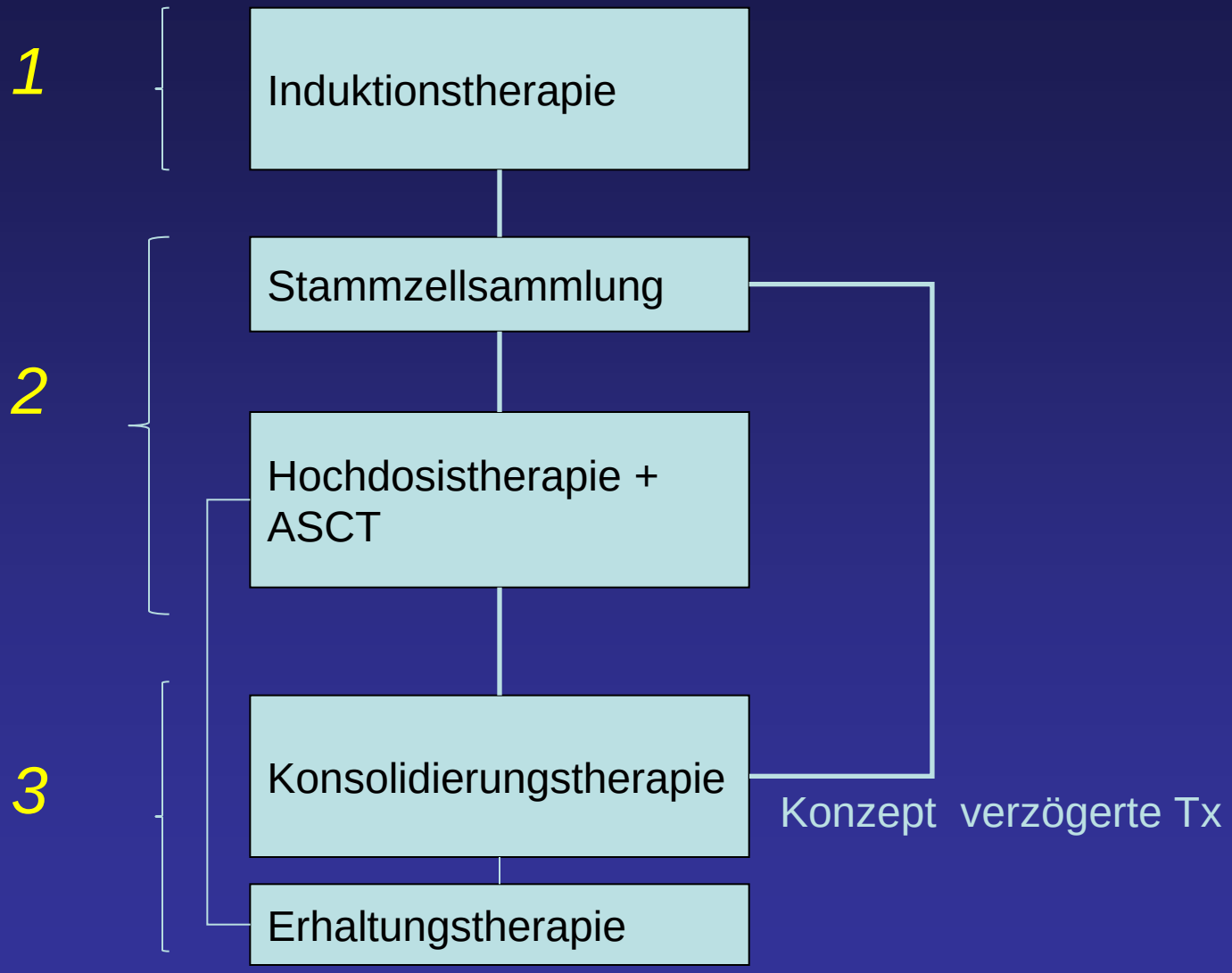
First Line Therapie Patienten fit für ASCT



THIS EVENING,

At the City-Tavern, will be Performed, a CONCERT,
for the *Benefit* of Mr. REHINE.

CONCERT.

FIRST ACT.

Overture	by	Stamitz
Song, *The Lover's Petition,*		Rehine
Solo Violino		Phile
Song, *No, 'twas neither Shape nor Feature,*		Harper
Quartet		Daveaux
Song, *O gentle Maid,*		Rehine
Sinfonia		Stamitz

SECOND ACT.

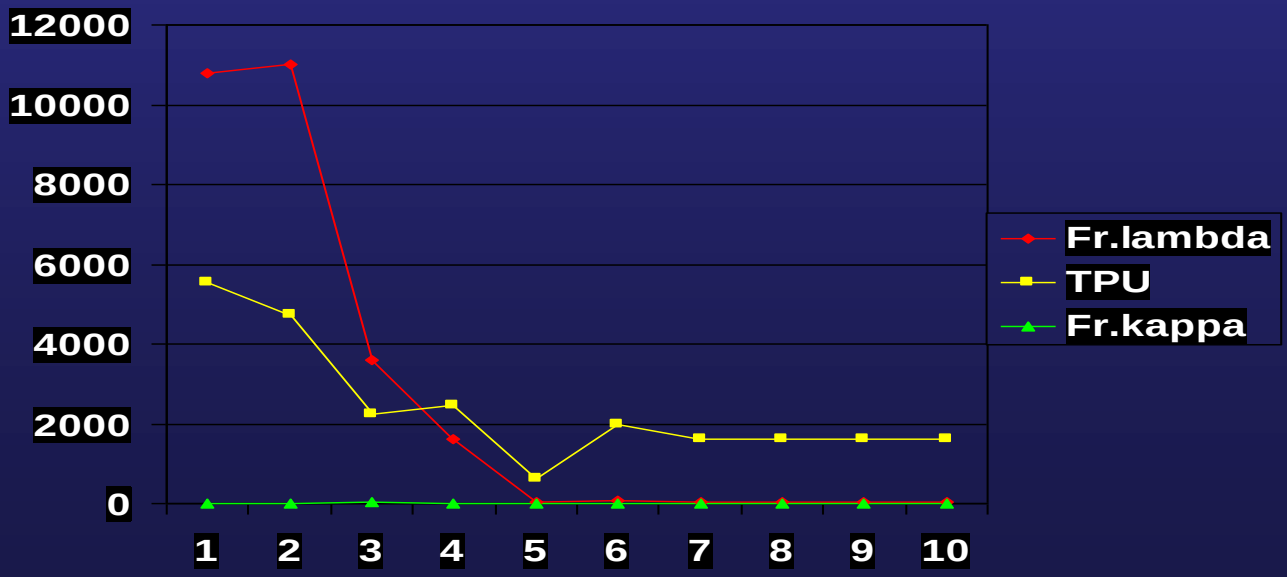
Sinfonia	by	Vanhall
Song, *Mary's Dream,*		Rehine
Concert Clarinetto		Wolf
Hunting Song		Harper
Quartet		Kammel
Song, *Ma Cher Amie,*		Rehine
Sinfonia		Kammel

After the CONCERT a BALL.

Tickets, to admit a Gentleman and Lady, may be had at the City-Tavern, and of Mr. *Oswald*, at the Coffee House. Price, *One Dollar.*

The *Concert* to begin precisely at 7 o Clock.

Philadelphia, *Nov.* 28.



1. Induktionstherapie

Vel/Dex
Rev/Dex
Thal/Dex

Vel/Thal/Dex
Vel/Cyc/Dex
Vel/Rev/Dex

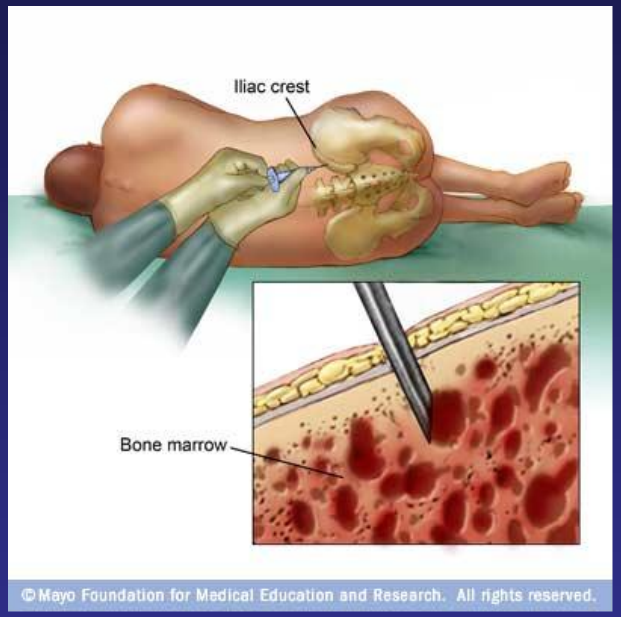
Vel/Thal/Cyc/Dex

2. Hämatopoietische Stammzellen (Blutbildende Stammzellen)

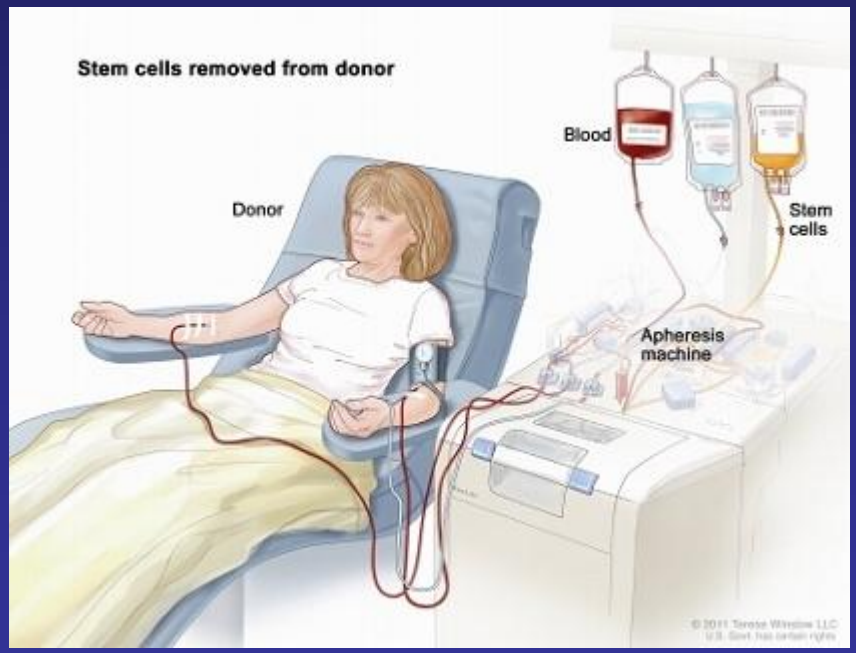
- Stammzellen – Woher?
- Peripheres Blut
  - Knochenmark

- Stammzellen – Von wem?
- Vom Patienten selbst = Autolog
- Von einer anderen Person = Allogen
- Syngen (Eineiiger Zwilling)
- Verwandt (Bruder/Schwester)
- Fremdspender (Register)

Stammzellsammlung – Damals



Stammzellsammlung – Heute



Pherese

Auftauen Stammzellen - Transplantation

Autologous Transplantation and Maintenance Therapy in Multiple Myeloma

A. Palumbo, F. Cavallo, F. Gay, F. Di Raimondo, D.B. Yehuda, M.T. Petrucci, S. Pezzatti, T. Caravita, C. Cerrato, E. Ribakovsky, M. Genuardi, A. Cafro, M. Marcatti, L. Catalano, M. Offidani, A.M. Carella, E. Zamagni, F. Patriarca, P. Musto, A. Evangelista, G. Ciccone, P. Omedé, C. Crippa, P. Corradini, A. Nagler, M. Boccadoro, and M. Cavo

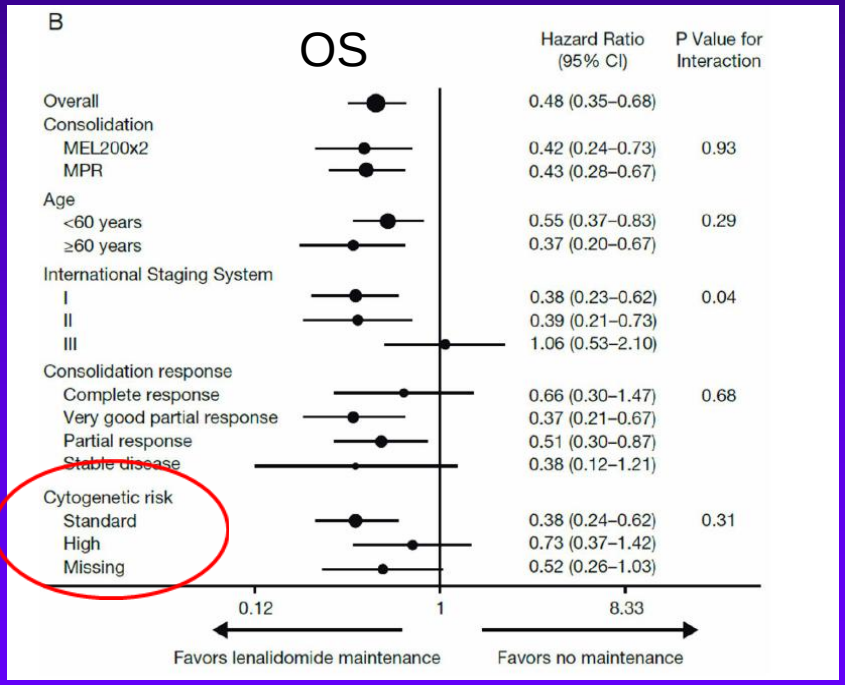
Len/Dex x 4 → STZ-Pherese → MPR x 6 oder MEL200 x2
→ Len Maintenance oder keine Maintenance

Hochdosis (MEL200) besser

Palumbo et al., New Engl. J.Med., Sept. 2014

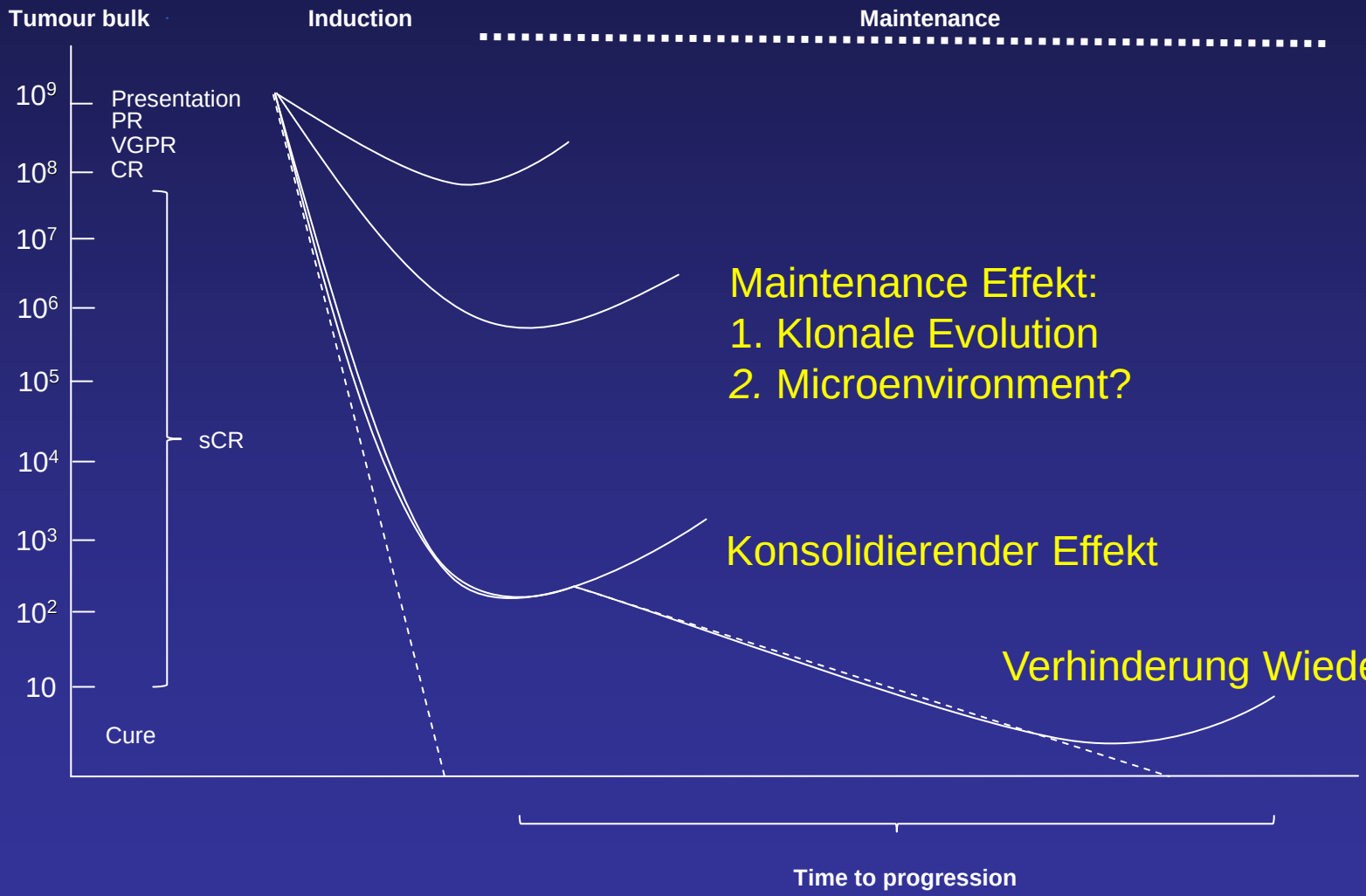
Autologous Transplantation and Maintenance Therapy in Multiple Myeloma

A. Palumbo, F. Cavallo, F. Gay, F. Di Raimondo, D.B. Yehuda, M.T. Petrucci, S. Pezzatti, T. Caravita, C. Cerrato, E. Ribakovsky, M. Genuardi, A. Cafro, M. Marcatti, L. Catalano, M. Offidani, A.M. Carella, E. Zamagni, F. Patriarca, P. Musto, A. Evangelista, G. Ciccone, P. Omedé, C. Crippa, P. Corradini, A. Nagler, M. Boccadoro, and M. Cavo



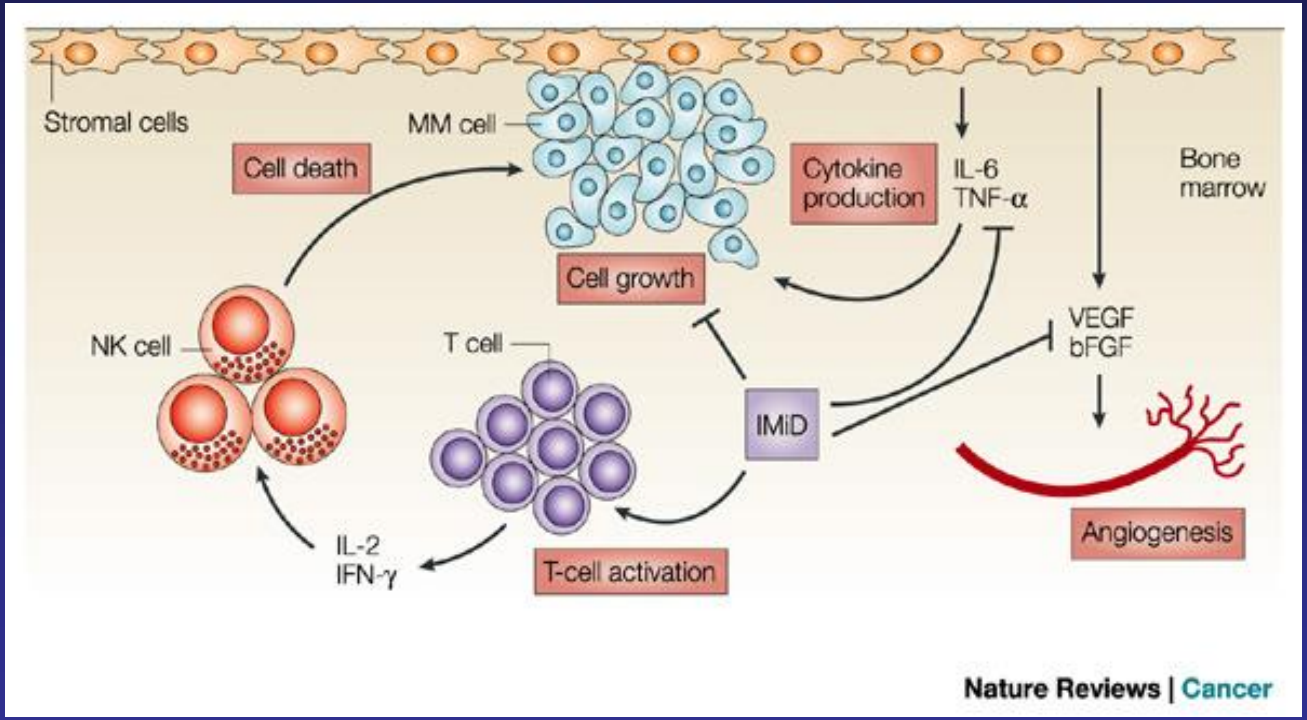
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 SEPTEMBER 4, 2014 VOL. 371 NO. 10

3. Erhaltungstherapie (Maintenance)



Morgan G, oral presentation modified

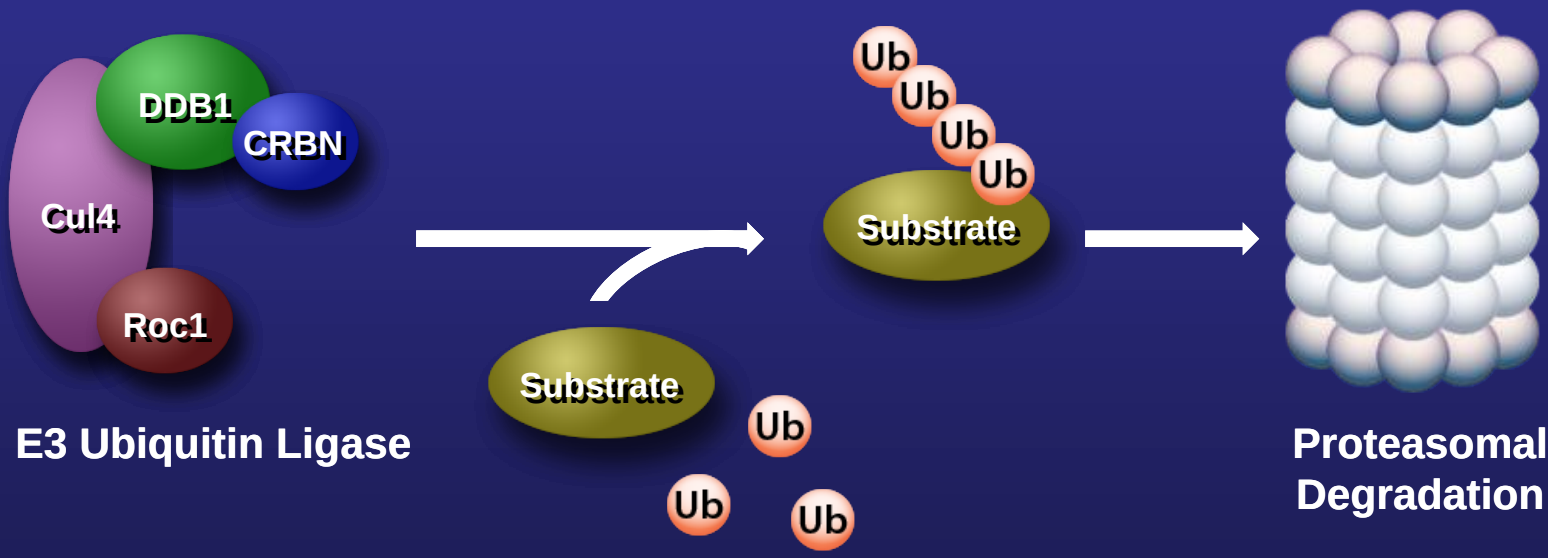
IMiDs – immunomodulatorische Substanzen



Bartlett et al., 2004

Thalidomid
Lenalidomid (Revlimid®)
Pomalidomid (Imnovid®)

Cereblon, a Component of an E3 Ubiquitin Ligase, Is a Target of Lenalidomide and Other IMiD® Drugs[1-3]



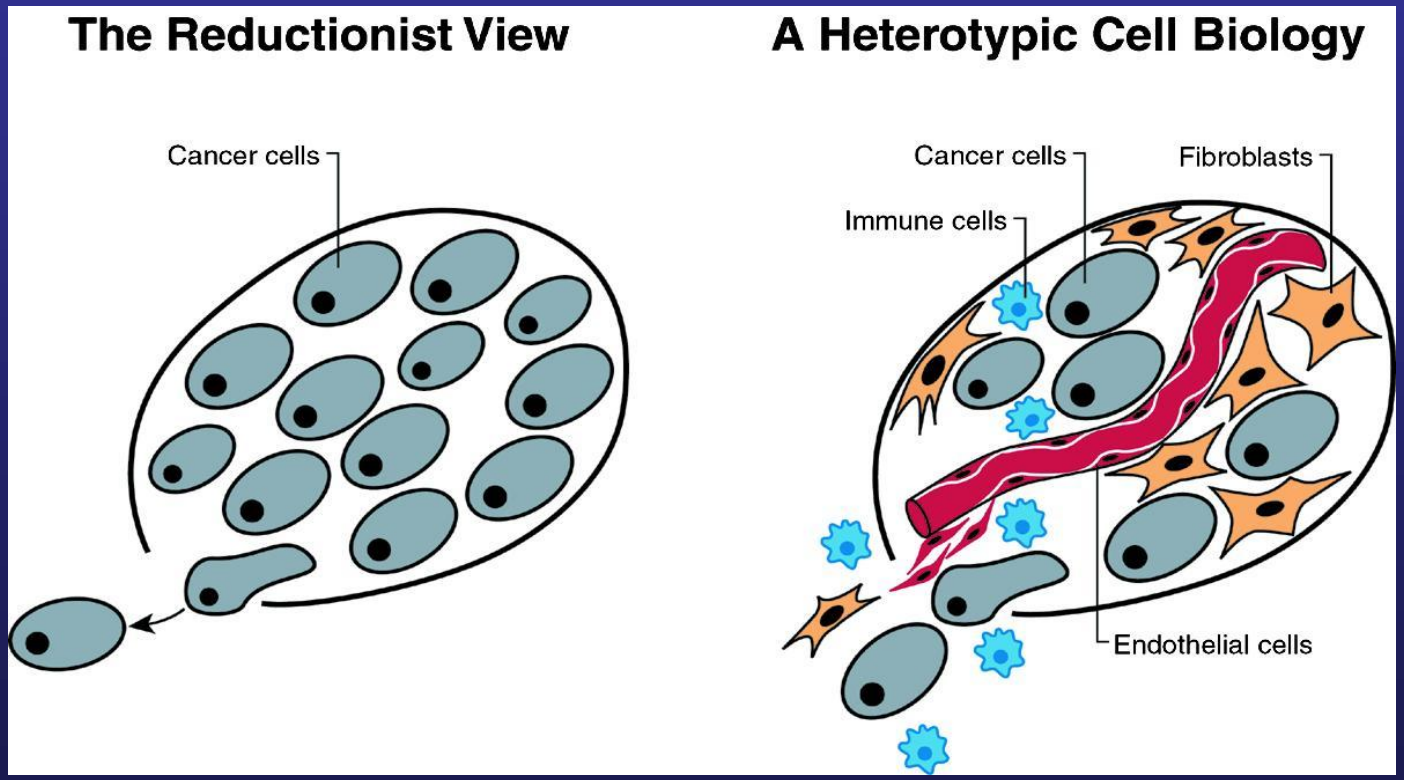
CRBN: cereblon; Cul4: culln 4; DDB1: DNA damage-binding protein 1; Roc1: regulator of cullins 1; Ub: ubiquitin.

1. Lopez-Girona A. *Leukemia.* 2012;26:2326-2335. 2. Ito T. *Science*. 2010;327:1345-1350. 3. Zhu YX. *Leuk Lymphoma*. 28 Sep 2012. [Epub ahead of print]. DOI: 10.3109/10428194.2012.728597.

Bailar and Smith: „Progress against cancer?“

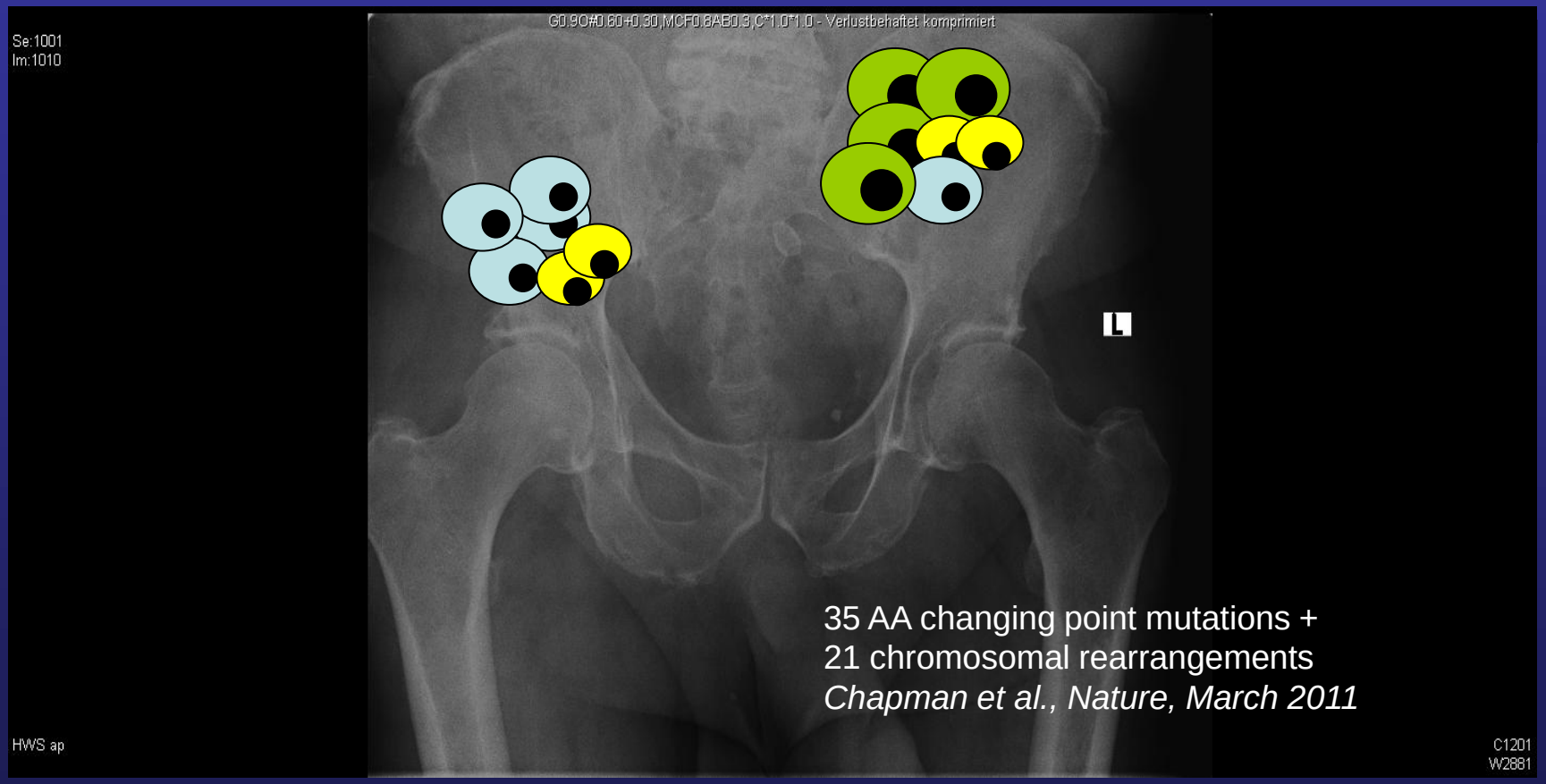
Vergleich Alters-adaptierte Mortalitätsrate 1950-82

New England Journal of Medicine, Mai 1986

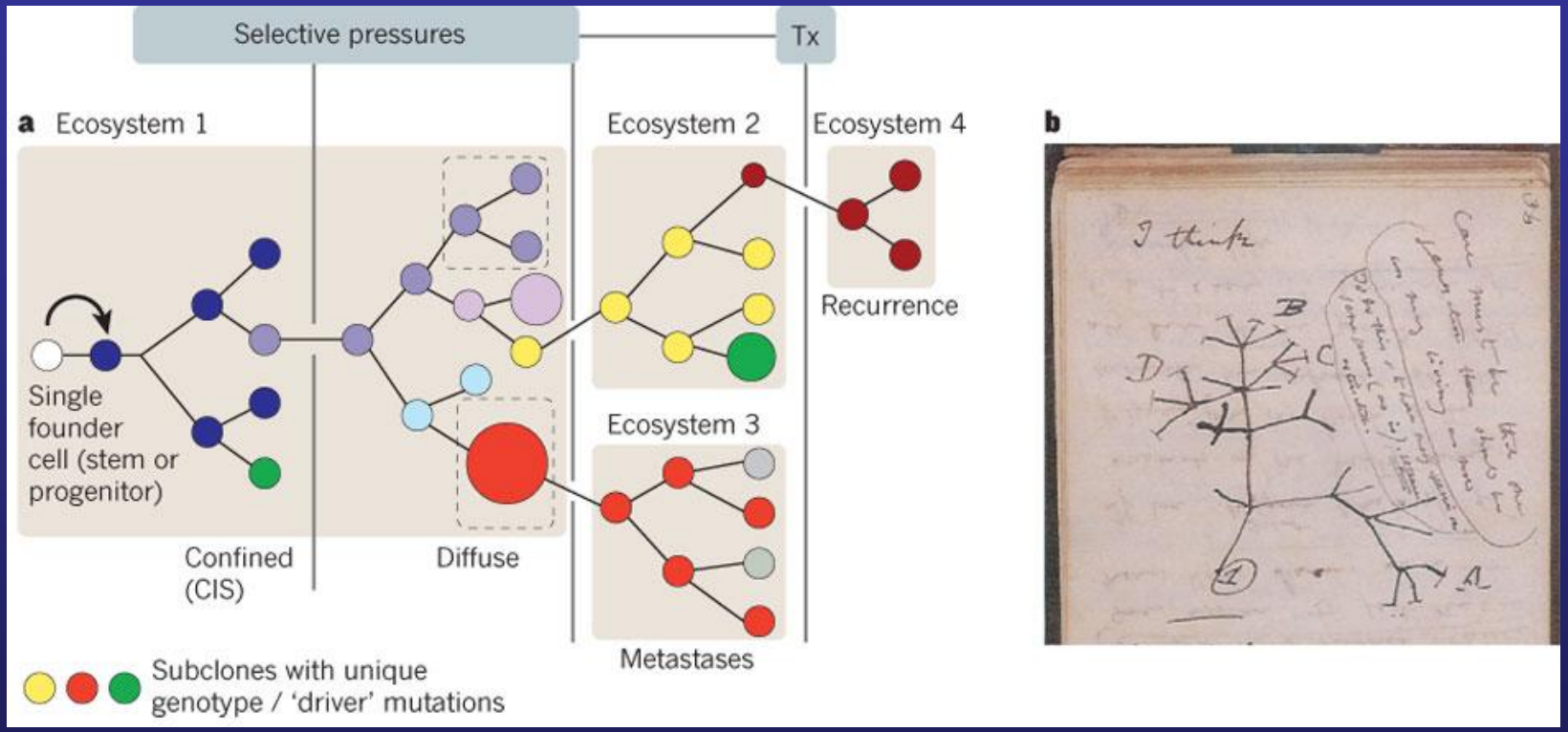


MM Heterogenität

Tumor cell heterogeneity = intraclonal (all MM cells share VDJ signature)



Not all mutations occur in the same cell
Spatial variation in tumor composition
Expansion and decline of clonal populations over time
Partial tumor responses to therapy and emergence of drug-resistant cells
Seeding from subclones (rare or common in the original population)



Greaves and Maley: „Clonal evolution in cancer“, Nature, Jan. 2012

Danke für die Aufmerksamkeit!