Versorgungsforschung beim Multiplen Myelom (MM): Beispielhafte Projekte und Ergebnisse

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Klinik für Innere Medizin I,
Hämatologie, Onkologie und Stammzelltransplantation

27.3.2014

Topics

1. Introduction + performance Hem/Onc + CCR-group Freiburg
2. Risk factor analyses in MM and future projects
3. Conditional survival analysis in MM
4. Additional/secondary malignancies in MM
5. CCCF tumorboard analyses in MM
6. CTx error avoidance system Med 1/Hem/Onc

Patient-#, in- and outpts, CTx-#, SCTs 2008 - 2013

Patients	2008	2009	2010	2011	2012	2013
DRG-cases in-pts (n)	3975	3848	3957	2594***	2224***	**2436*** **
Average utilization, in-pts (%)	86	85	86	89	87	**90**
Chemotherapies	23700	23037/ 20524*	24400/ 20270*	25958/ 21946*	26394/ 22528*	**27842 22369***
Patients [teilstat. (d)]	5811	5133	5040	6250	6474	**6850**
Out-pt-visits	16198	17101	18430	19385	20960	**17819♦**
Out-pt-visits, plus Romberg + Naunyn (n)	25323	26621	27714	29189	29493	**26163**
SCTs, entire n	209	196	212	198	206	**239**
- autologous	96	103	103	107	110	**144**
- allogeneic	113	94	109	91	96	**95**

***w/o admission ward (NA/Aufnahmestation)
* exclusively iv-chemotherapies
♦without twice daily check-ups: out-pt- + treatment care

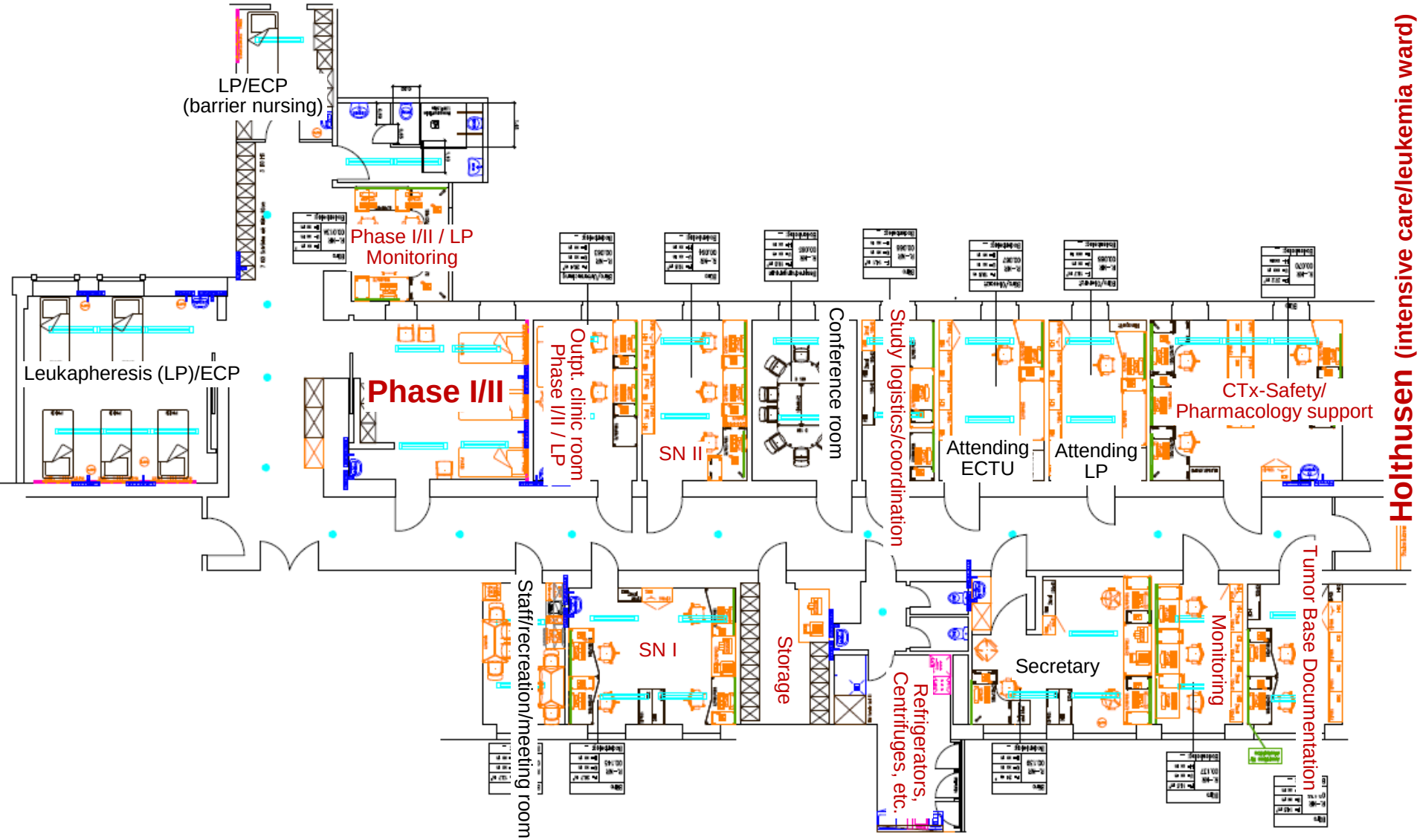
Organigramm
CCRG / Sektion Klinische Forschung, GCP & QM

Leitung: Prof. Dr. M. Engelhardt

Sekretariat	Koordination Studien wissenschaftl. Projekte	Studien-Ass.	BB / Chemo-AS	TBD	EDV	QM
S. Hug	Dr. Kohlweyer H. Hummel	M. Burbeck D. Jakobs I. Surlan K. Scheser C. Messner S- Herzog	H. Reinhardt S. Kaiser M. Szymaniak P. Otte B.Groß	H. Schall J-E.Urban	P. Wolfrum S. Spadaro K. Opeker B. Ladeburg	M. Müller

Section plan

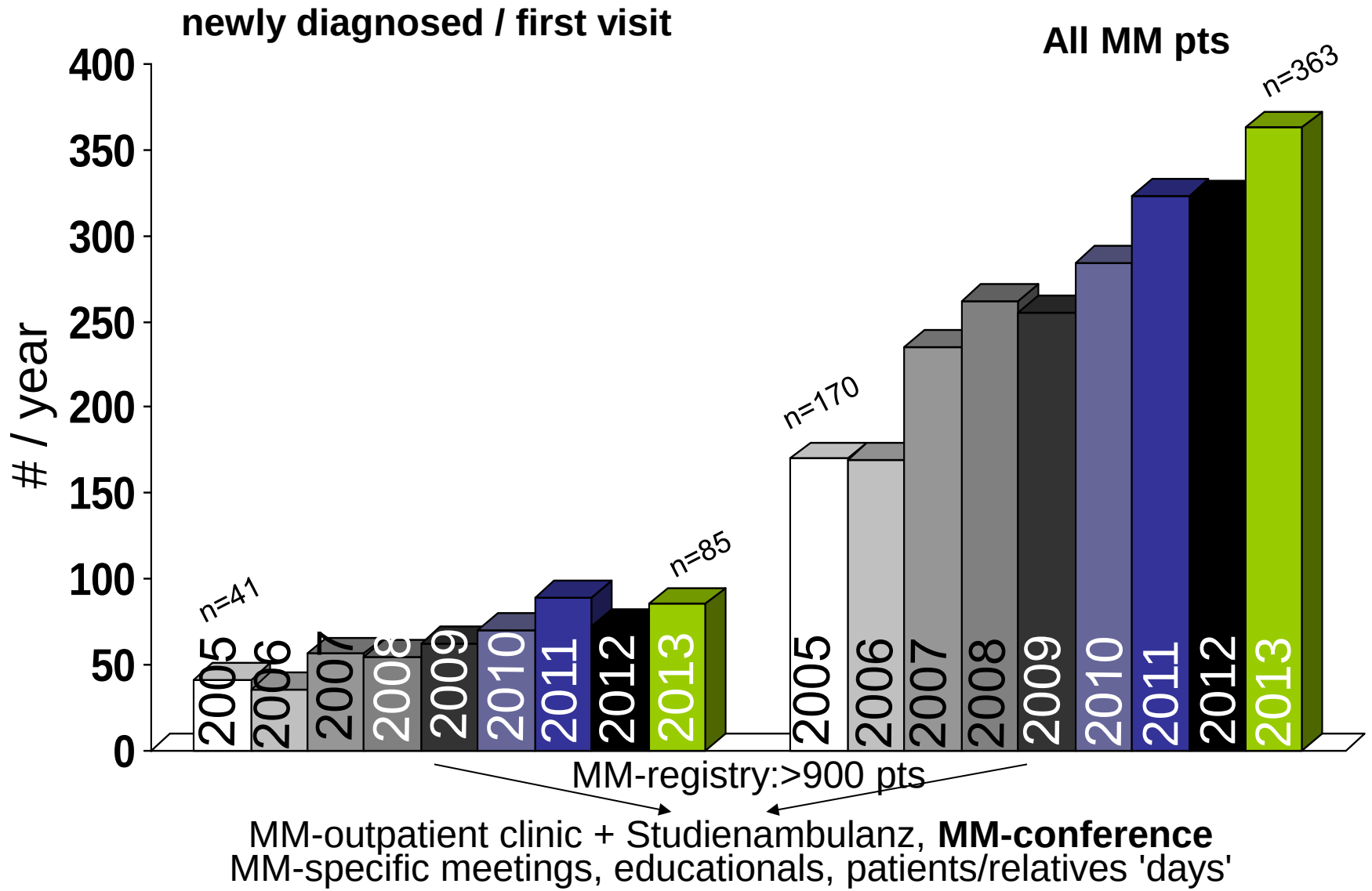
Early Clinical Trial Unit, Leukapheresis + Clinical Cancer Research Group



Solid tumor + hematology pt-#: initial diagnosis and entire pt-

Tumor entities	Initial contacts /diagnosis pt- #s 2013	Entire pt cohort (in- + outpatients)
ST		
GI (ZGT)	388	570
Lung-, H&N (ZTT)	300	804
Gyn / urology tumors	245	460
Bone / sarcoma pts	86	202
CUP, 2.tumors (SPM)	42	1702
ZNS-,endocrine- tumors	28	102
In situ carcinomas	27	363
∑	**1126**	**4203**
HM		
NHL	209	567
MM / CLL / HL	85 / 43 / 26	363 / 108 / 70
MDS / AML, ALL, other leukemias	65 / 89	84 / 257
MPN	66	90
∑	**583**	**1539**
∑ **ST + HM**	**1709**	**5742**

of MM-pts UKF Med I, 2005 - 2013



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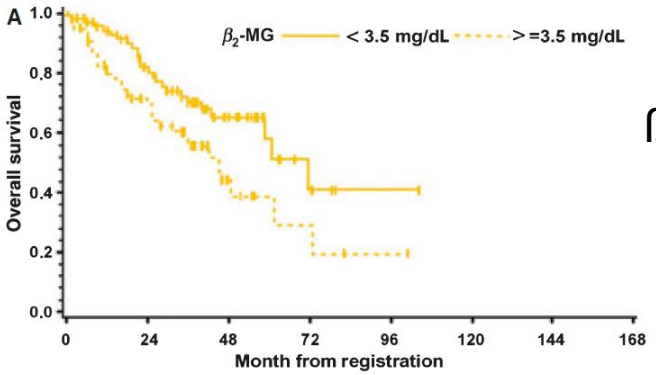
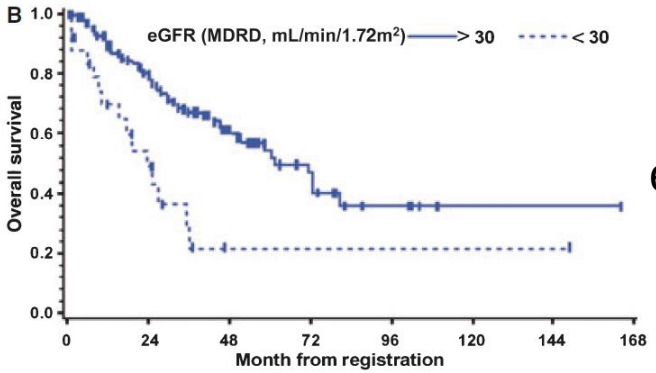
ß2-MG and renal function as defined risk factors in MM

n=198 consecutive MM pts treated in Med 1 1997 and 2003

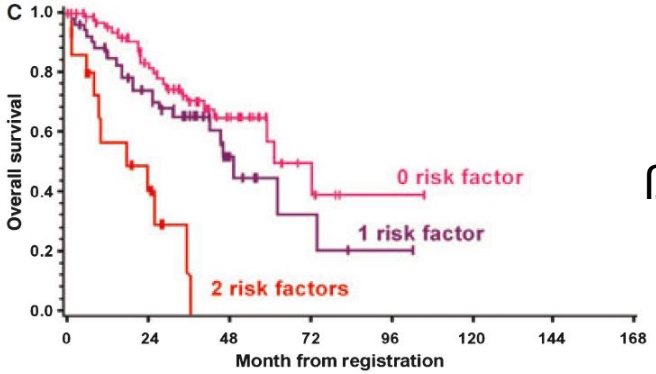
Development of a **MM-specific ß2-MG + eGFR - risk score**



ß2-MG



e-GFR



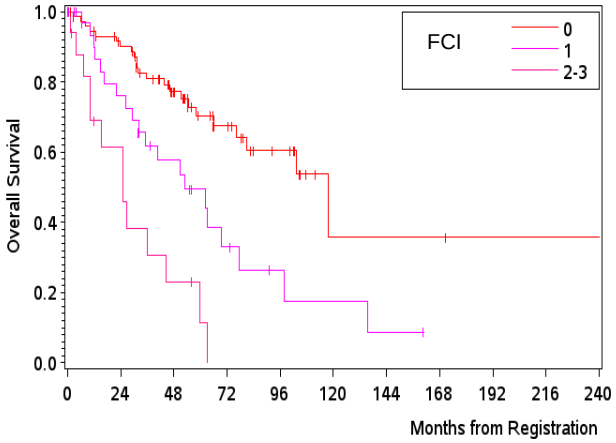
ß2-MG+e-GFR

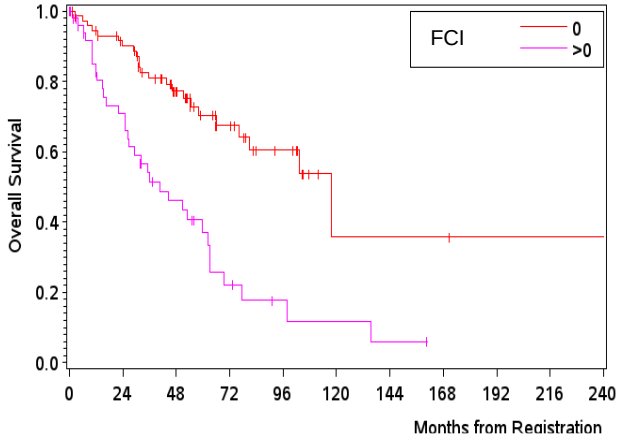
Kleber M, ... Engelhardt M. Eur J Haematol. 2009;83:519-27

Development of the Freiburg Comorbidity Index (iFCI)

Test analysis (n=127)

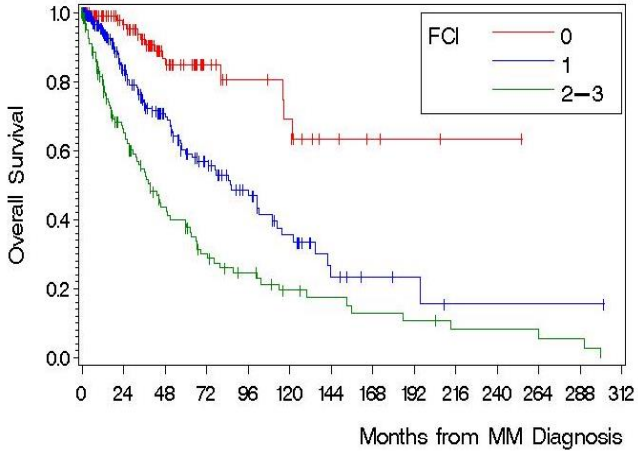
FCI = Freiburg comorbidity index: eGFR≤30ml/min, moderate-severe lung disease, KPS≤70%

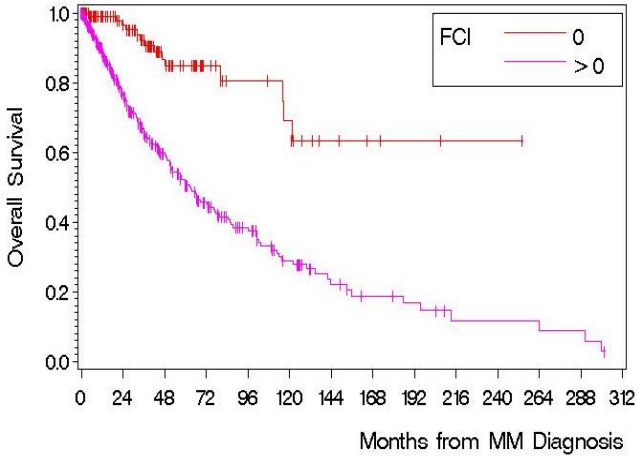




Kleber M, …Engelhardt M. Blood Cancer Journal 2011

Validation analysis (n=466)





Kleber M, ...Engelhardt M. Clin Lymphoma Myeloma Leuk 2013

Development of a MM-specific risk score: Freiburg Comorbidity Index (FCI)

Initial FCI (iFCI)
- eGFR<30
- mod.-sev. lung disease
- KPS≤70%

- Initial analysis (n=127)[1]
- Validation analysis (n=466)[2]

Revised FCI (rFCI)

- Combined **training-** and **validation analysis** to improve the iFCI (n=803)[3]

Prospective validation of the rFCI

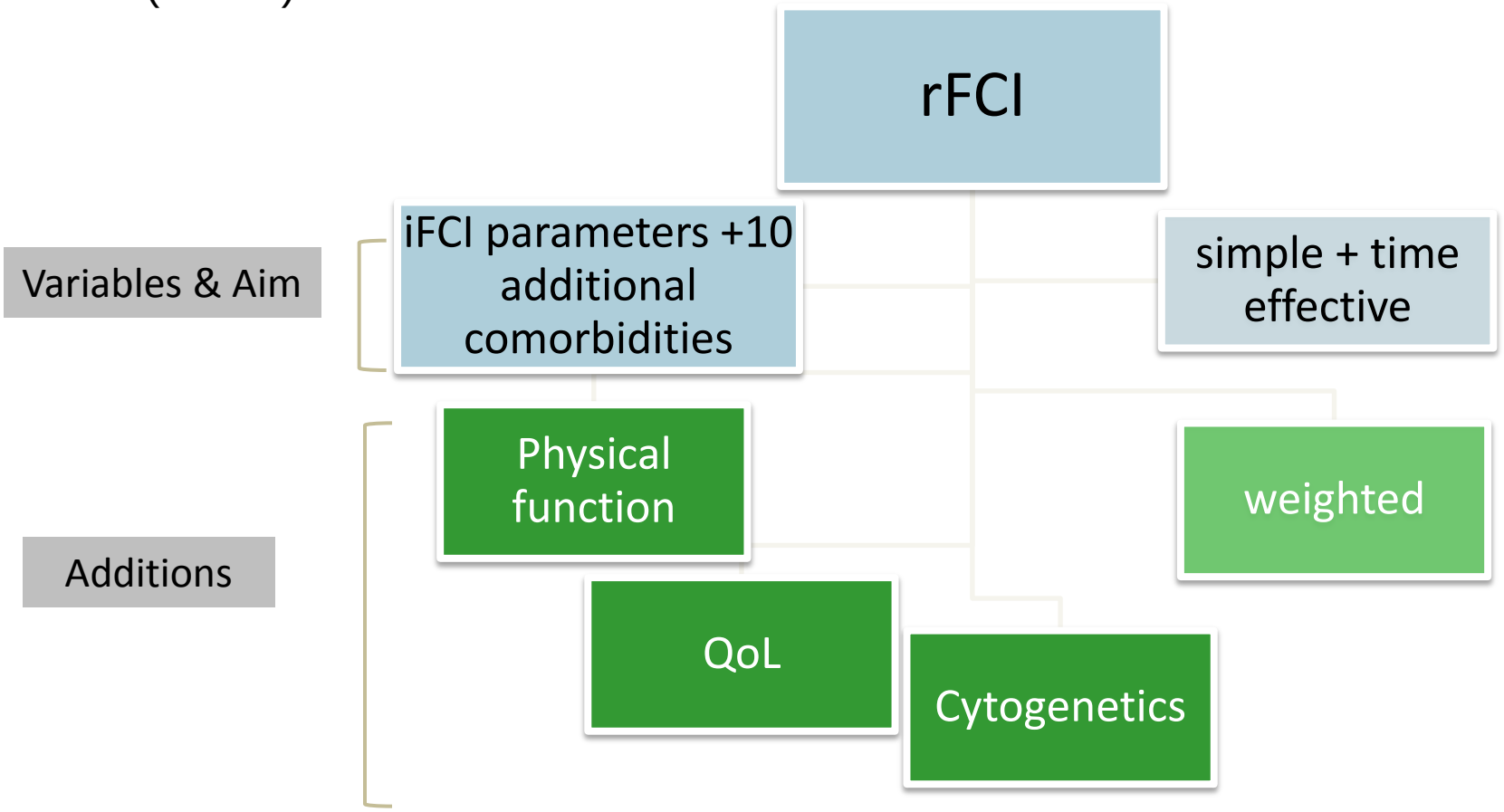
- **Uni-** and **multicenter** analysis[4,5]

[1]Kleber M, ...Engelhardt M. Clin Lymphoma, Myeloma Leuk, 2013
[2]Kleber M, ...Engelhardt M. Blood Cancer Journal, 2011
[3]Domm A., Kleber M.,..... Wäsch R, Engelhardt M. Onkologie Suppl 7: 164, 2013
[4]Engelhardt M, Terpos E., Kleber M. et al. Haematologica 2014
[5]DKH grant proposal 2014

Improvement and requirements of the rFCI

Methods:

- Comorbidity assessment in 803 consecutive MM pts, 1997-2013, analyzing 3 iFCI risk factors and 10 additional comorbidities, QoL and cytogenetics
- Revision of the iFCI: complete data set, divided into training- (n=552) + validation set (n=249)



rFCI variables based on backward selection

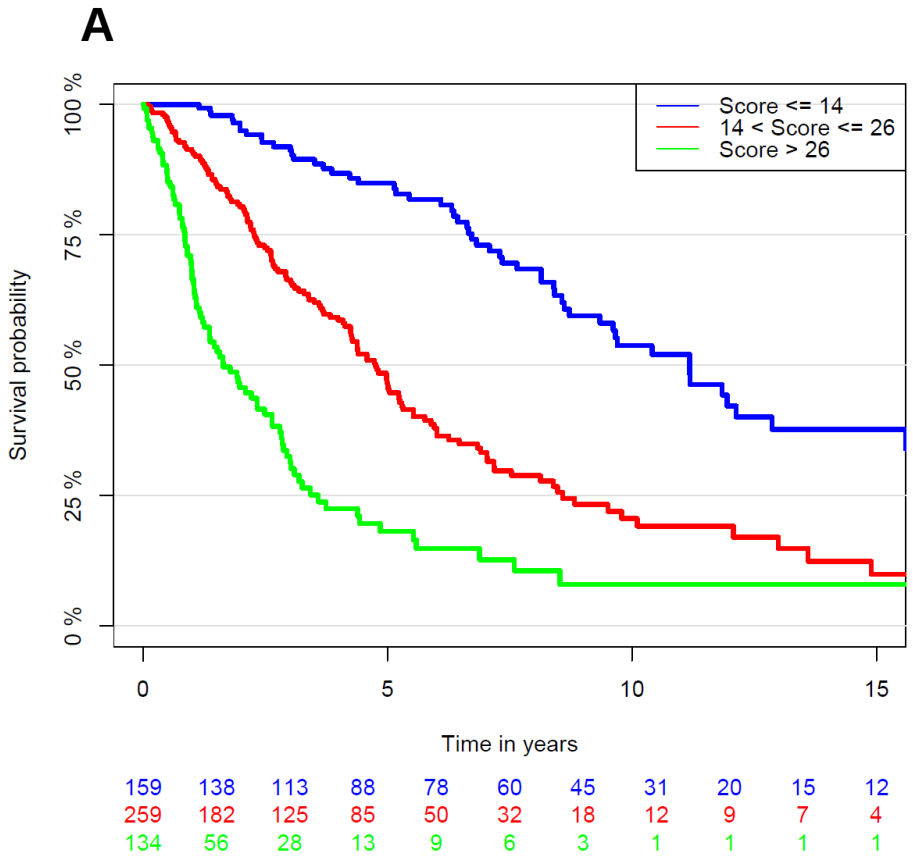
	Comorbidity	Definition	n	log (HR)	2.5%	97.5 %	HR	2.5%	97.5 %	p-value	Weight
Risk factors of the initial FCI	***Lung disease***	No/ Mild	404	0	-	-	1	-	-	***<0.001***	0
		Moderate/ severe	147	0.27	-0.02	0.56	1.32	0.98	1.76		3
	eGFR	≥ 90	184	0	-	-	1	-	-		0
		60 to < 90	192	0.16	-0.14	0.46	1.18	0.87	1.59	***<0.001***	2
		< 60	175	0.59	0.27	0.91	1.80	1.31	2.48		6
	KPS	100%	35	0	-	-	1	-	-		0
		80-90%	207	0.81	0.08	1.55	2.25	1.08	4.69	***< 0.001***	8
		≤ 70%	309	1.16	0.43	1.89	3.19	1.54	6.59		12
New risk faktors	***Age (years)***	≤60	225	0	-	-	1	-	-		0
		>60 to ≤70	184	0.40	0.10	0.69	1.49	1.11	1.99	***< 0.001***	4
		>70	142	0.80	0.48	1.13	2.24	1.61	3.10		8
	Frailty	No/mild	321	0	-	-	1	-	-		0
		Moderate	141	0.36	0.08	0.64	1.44	1.08	1.90	***0.002***	4
		Severe	90	0.62	0.25	0.99	1.85	1.28	2.68		6
	Cytogenetics*	Favourable									0
		Unfavourable								***0.010***	4
		Missing									2

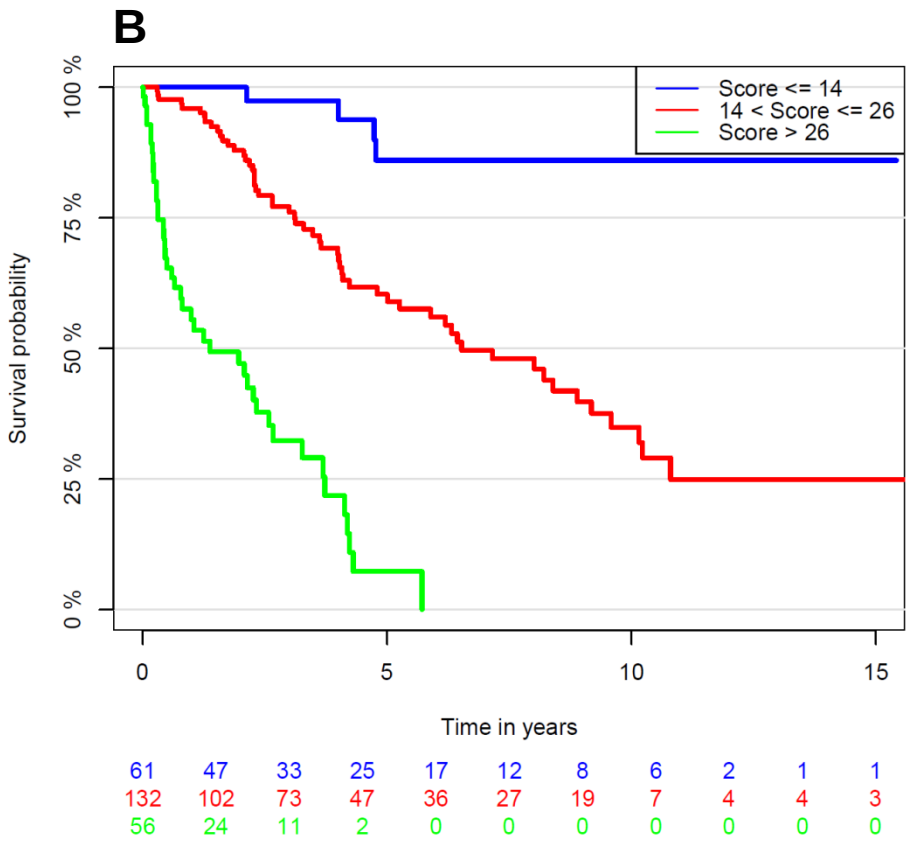
***Favourable**: hyperdiploidy, t(11;14), NK
Unfavourable: del17p, t(4;14), t(14;16), hypodiploidy, 1q gain, del13q, c-myc

max.39

Domm A., Kleber M.,..... Engelhardt M. Onkologie Suppl 7:164,2013

Survival via rFCI:
A. training (552 pts) vs. B. validation set (249 pts)





Domm S. Kleber M... Engelhardt M. Poster Saig 2014

Future goals and projects

Step 1

rFCI: prospective validation

Uni- and multicenter analyses (5 university centers):

1. UK-Freiburg
2. UK-Würzburg (Prof. Einsele/PD Dr. Knop)
3. UK-Ulm (Dr. Langer)
4. UK-Jena (Prof. Hochhaus/Dr. Mügge)
5. UK-Leipzig (Prof. Dr. Niederwieser/Dr. Pönisch)

Step 2

Prospective geriatric assessment* combined with rFCI

Analyses of:

a) treatment toxicity
b) treatment discontinuation
c) AEs
d) early death
e) response
f) outcome (PFS/OS)

*IADL, “Timed Up and Go”-test, malnutrition, pain assessment, physicians' and patients' rating of fitness. SF-12 quality of life assessment, GDS, G8 Screening tool, fTRST

(submitted 1/14)

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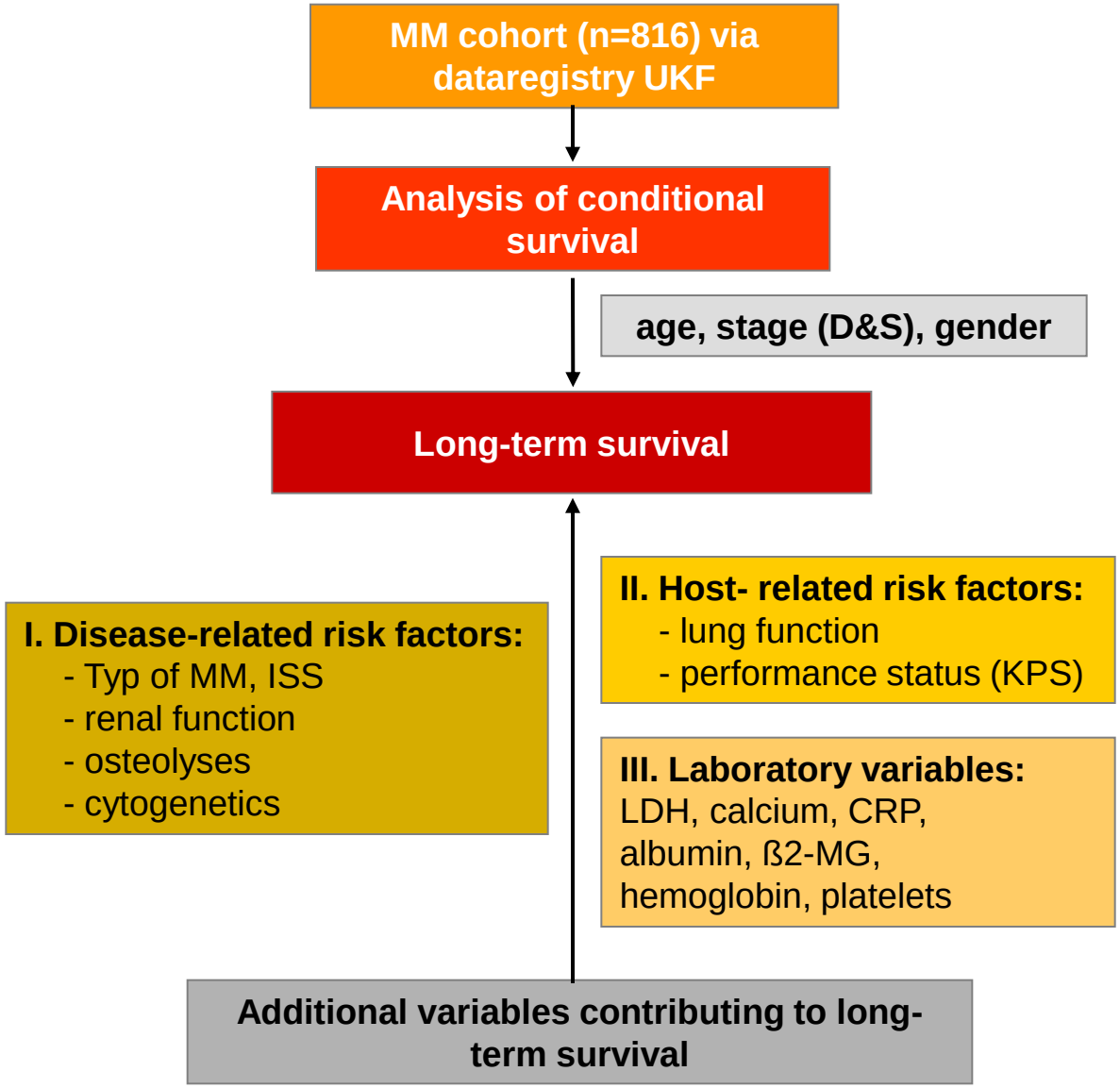
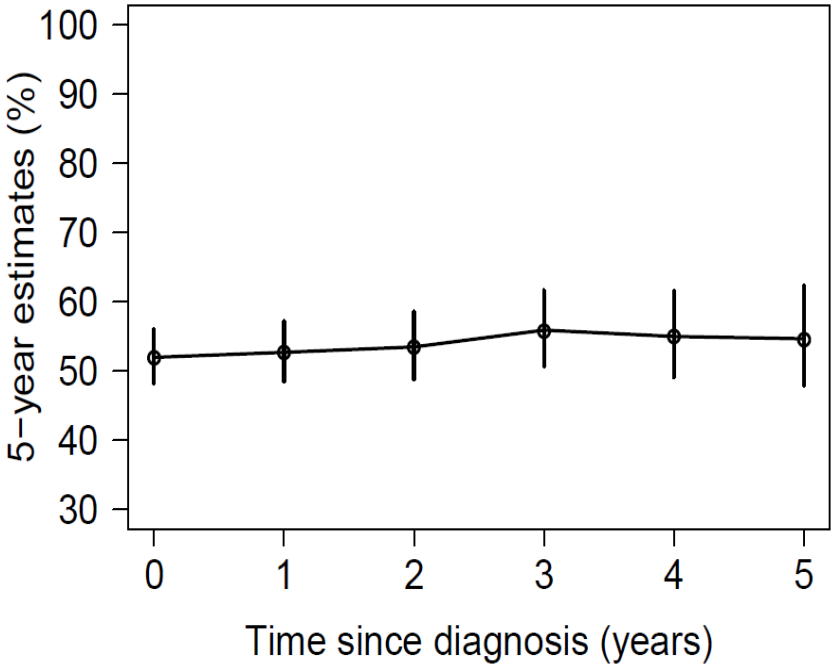
Investigation of conditional surivival risks contributing to long-term survival in MM: Methods

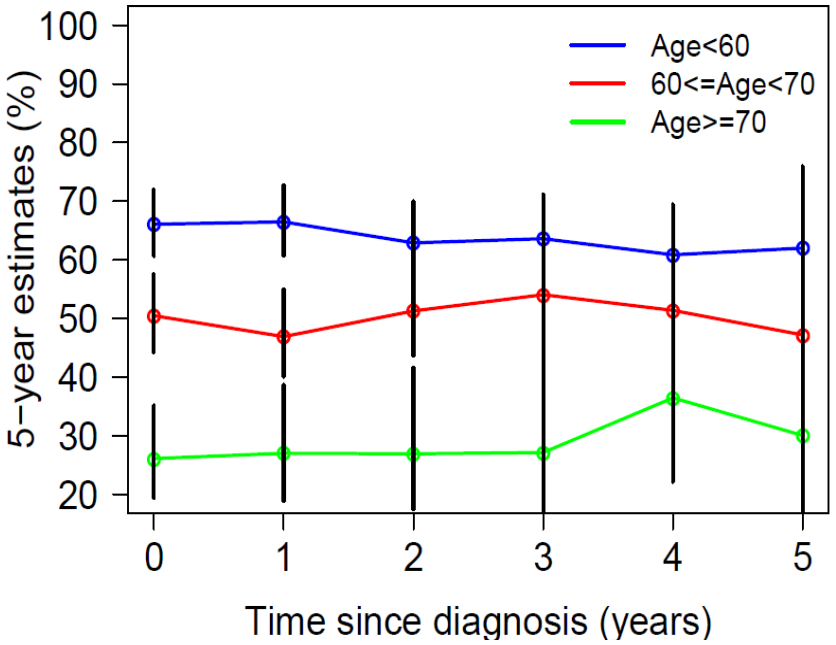


CS in all MM pts and in different age groups (n=816)

1 - 5-yr conditional survival estimates (95% CI)



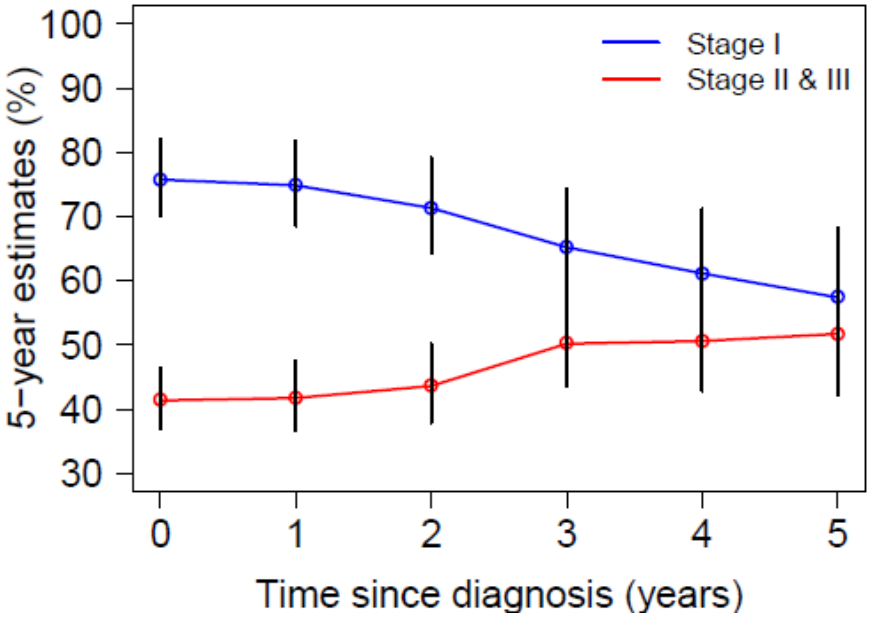
Conditional survival stratified in different age cut-offs



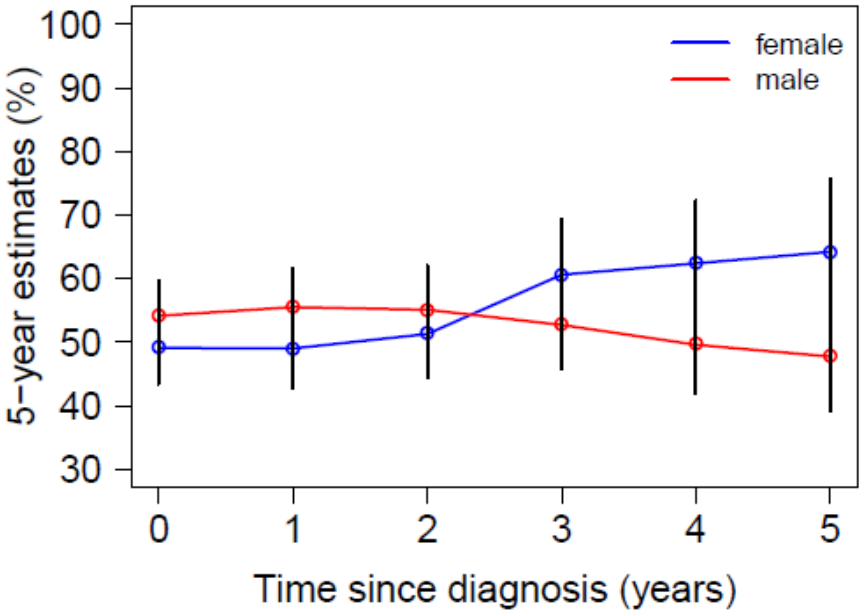
- The 5y-CS probabilities remain almost constant (~53%)
- Age subgroups **<60, 60-70 and >70-years** show substantially different 5y-CS-estimates, but remain constant (60y: ~63%, 60-70y: 51%, >70y: 27%)

CS 5-years estimates stratified by stage and gender at diagnosis (n=816)

CS stratified by D&S stage I vs. II-III



CS 1-5ys after diagnosis in male vs. female



→ advanced disease stage by Durie&Salmon effected CS, gender did not

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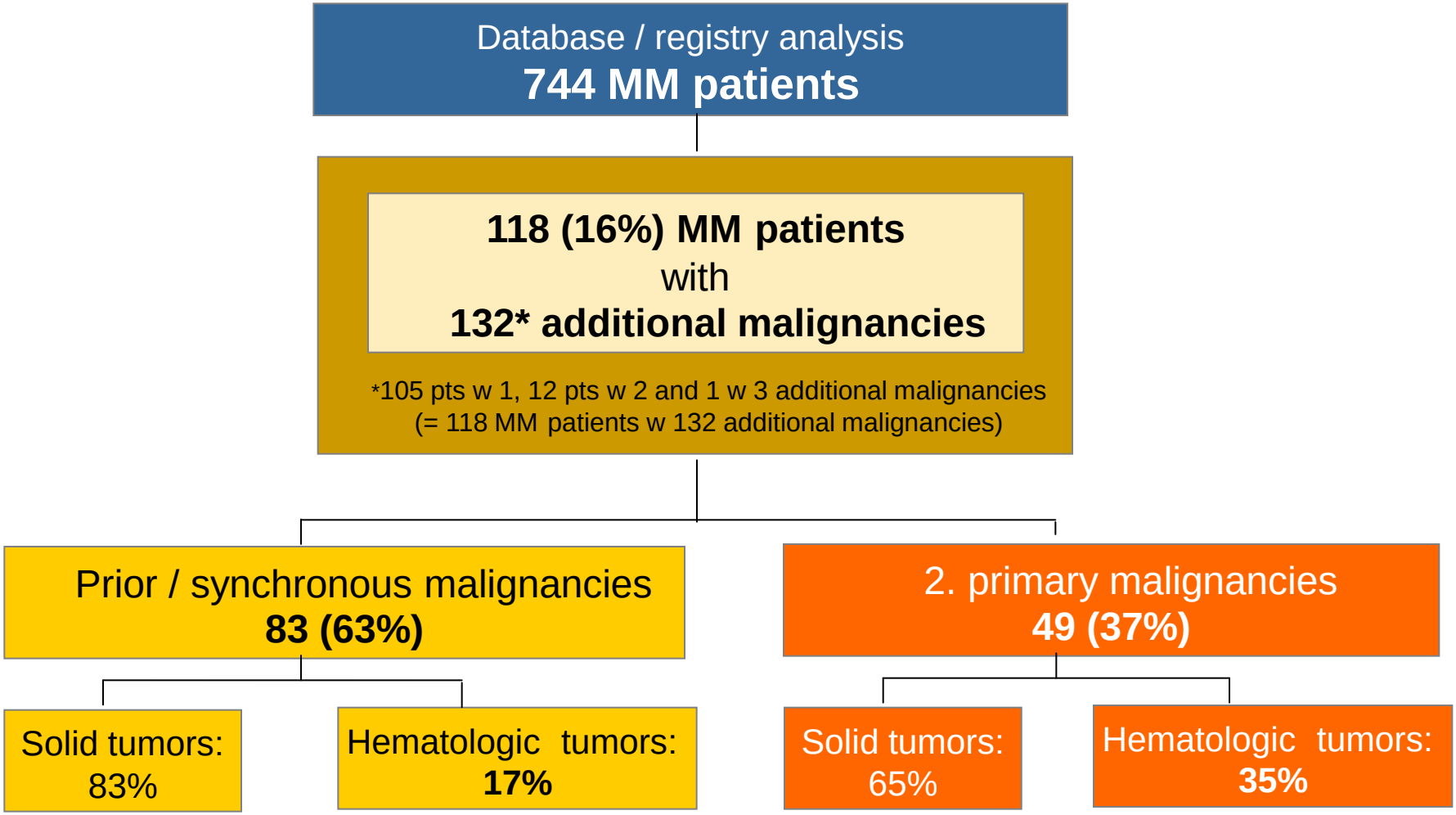
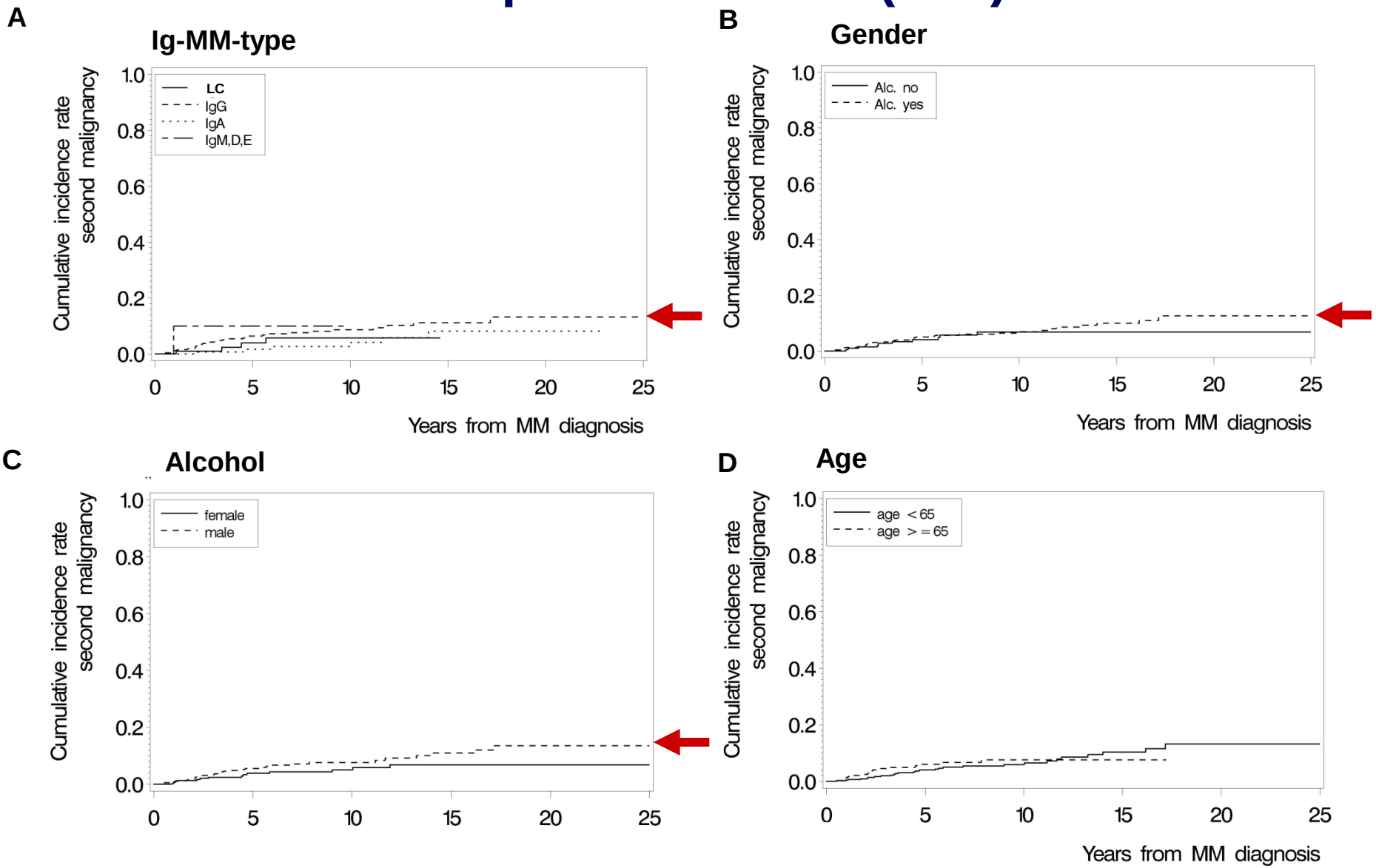
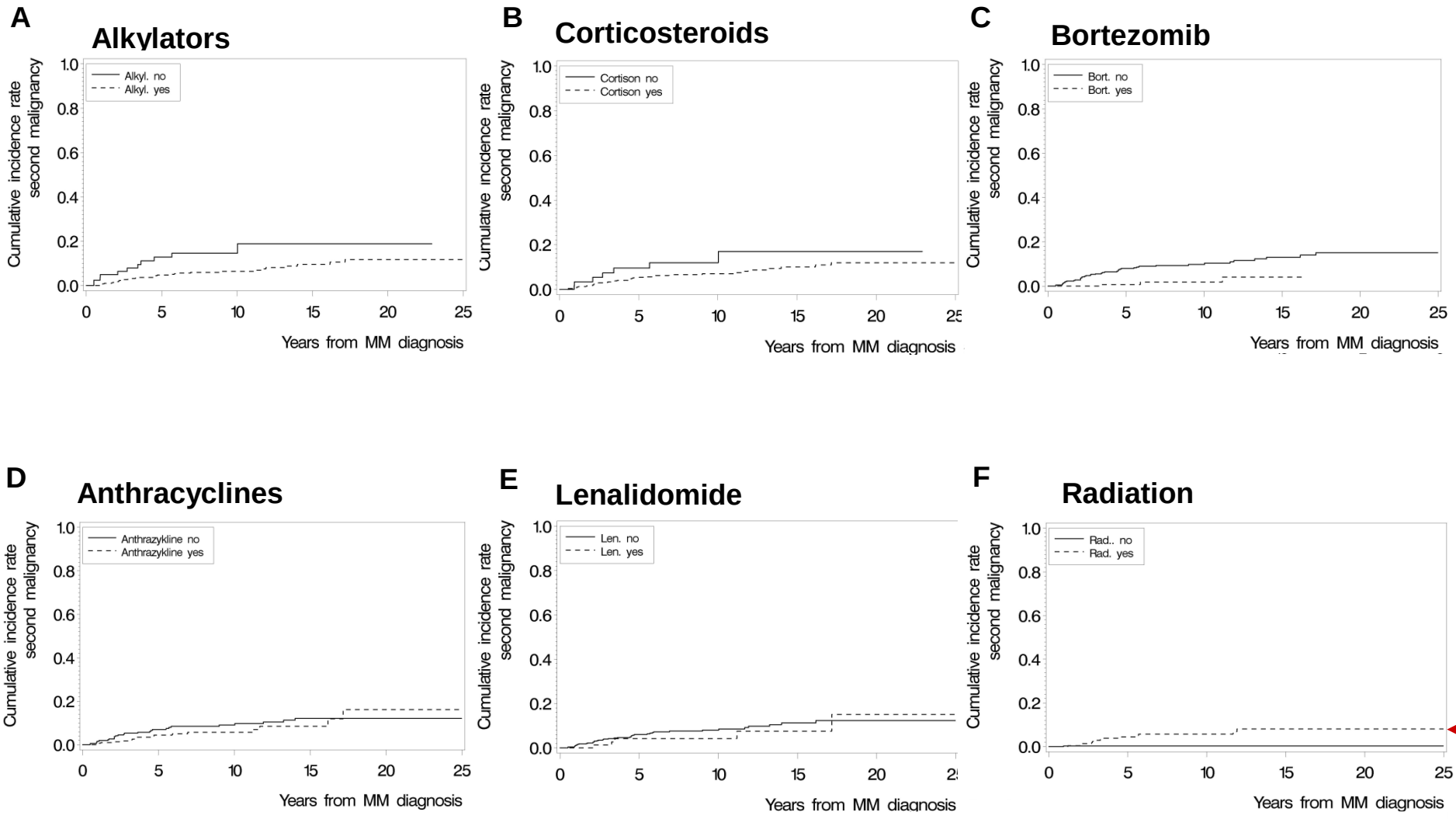
Incidence and onset of additional malignancies



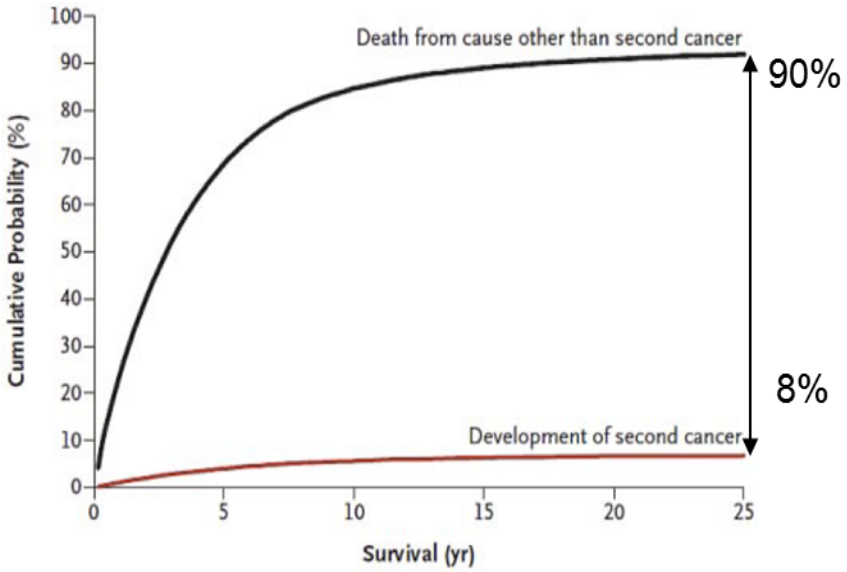
CI for developing 2. malignancies for disease- (A) and host-specific factors (B-D)

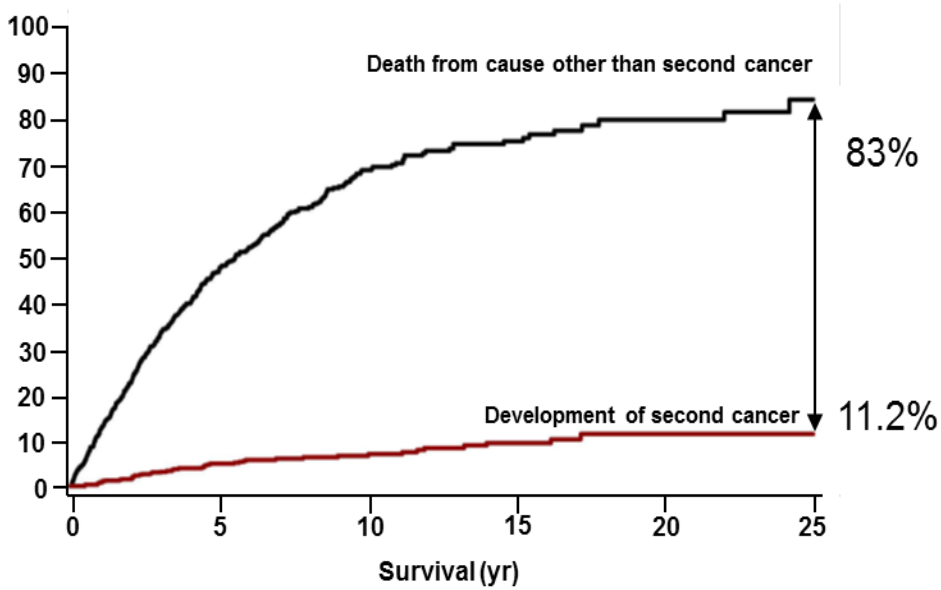


CI for developing 2. malignancies for various therapies



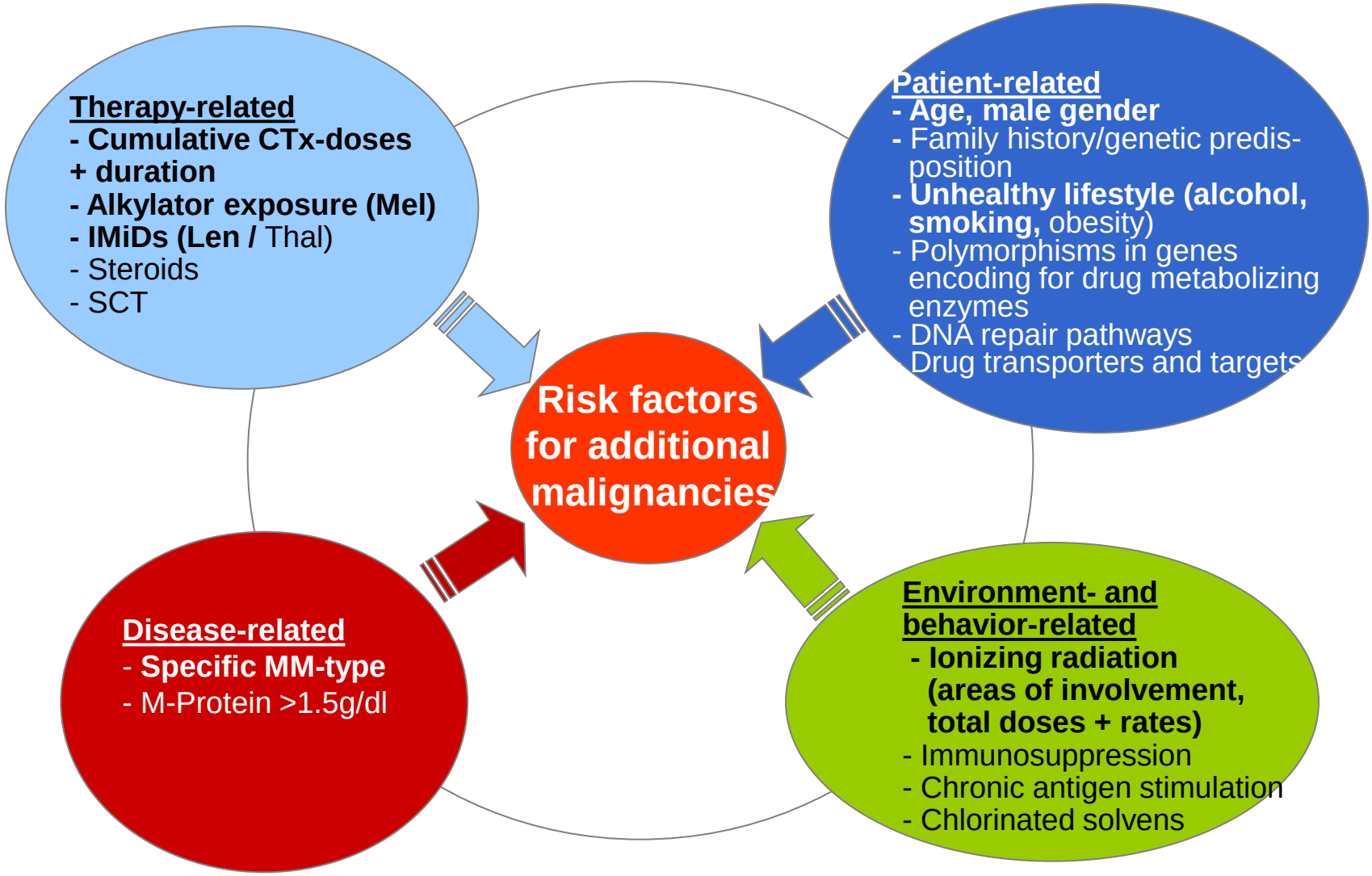
CI of developing 2. malignancies and of death from other causes than 2. cancer in MM





Landgren O. et al., N Engl J Med 2011;365: 2241-2
Engelhardt M, Wäsch R, Landgren O, Kleber M. Clin Lymphoma Myeloma Leuk. 2014;14:98-101

Risk factors of additional malignancies in MM



Engelhardt M, Wäsch R, Landgren O, Kleber M. Clin Lymphoma Myeloma Leuk. 2014;14:98-101

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Procedures within MM-Tumorboard

- Initiated 6/2012
- Physicians and referring oncologists present and discuss difficult-to-treat MM patients.
- Weekly interdisciplinary conference (hem/onc, orthopedics, pathology, radiation therapy, cytogenetic specialists/pathology, etc.)
- Shared goal of providing best possible patient care

in Medoc - under 'pt documents'

Protokoll

Multiple Myelom (M. Waldenström / AL-Amyloidose) - Konferenz

Patient: XY, Geburtstdatum, Wohnort, PIZ

Diagnose:

ED:
Stadium nach Durie & Salmon:
Stadium nach ISS:
Grad der KM-Infiltration (%):
Zytogentikbefund (FISH):
Bestehende CRAB-Kriterien (Hyperkalzämie, Nierensuffizienz, Anämie oder Osteolysen):
Serum-Kalzium (mg/dl):
Serum Kreatinin (mg/dl):
eGFR (ml/min/1.73m^2, MDRD):
Hämoglobin (g/dl):
Osteolysen (Anzahl / Ort / Stabilität):

Karnofsky Performance Status (%): 50%
Komorbiditäten:

Bisherige Therapie und Response:

Fragestellung an die Konferenz/Therapievorschlag:

Nach Vorstellung in der Myelomkonferenz, unter Berücksichtigung der Aktenlage, wird folgende Therapieempfehlung festgelegt:

Referring physician presents pt: Diagnosis, MM-parameters, pt characteristics (e.g. comorbidities)

Initial treatment and response

Questions concerning conference, therapy proposals

TB- Recommendation

Preliminary MM tumor board results

Table 1. # of pts presented at TB

Month / Year	# pts in MM- conference
2012	
1 June	16
2 July	24
3 August	11
4 September	8
5 October	19
6 November	18
7 December	16
Overall 2012	**112 (: 7 = 16 → 4/week)**
2013	
1 January	29
2 February	37
3 March	26
4 April	17
5 May	20
6 June	13
7 July	27
8 August	12
9 September	25
10 October	19
11 November	18
12 December	15
Overall 2013	**258 (: 12 = 22 → 6/week)**
Overall 2012 + 2013	**370**

Fig. 1. Increase of assessed MM-pts within TB: 2011 vs. 2012/13

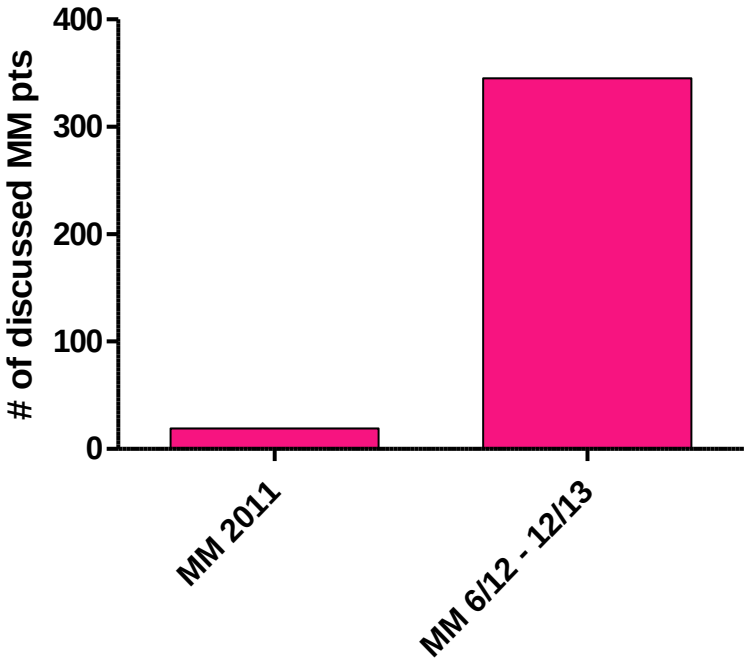

Table 2. Coverage of pts presented in MM-TB of entitre cohort

	# of all MM pts (12 ms)	# of all MM pts (7 ms)	# of pts discussed in MM-TB	Coverage
6 - 12 /2012	322	188	112	112/188 → **65%**
1 - 12 /2013	363	363 (12 ms)	258	258/363 → **71,1%**
→ Increase of presentation rate 2012 → 2013: **10%**				

Engelhardt, DGHO 20.10.13
R.Selder, Saig-Workshop 2014

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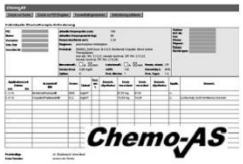
CTx ordering/monitoring via Chemo-AS



2 electronic CTx order

CCR-Group

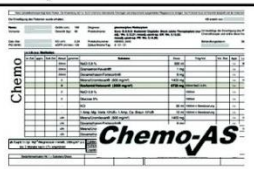
3 check CTx order

1 IC

electronic CTx order

check CTx order

4 patient-specific CTx chart



5 CTx delivery

interactive check

6 CTx - application

Patient

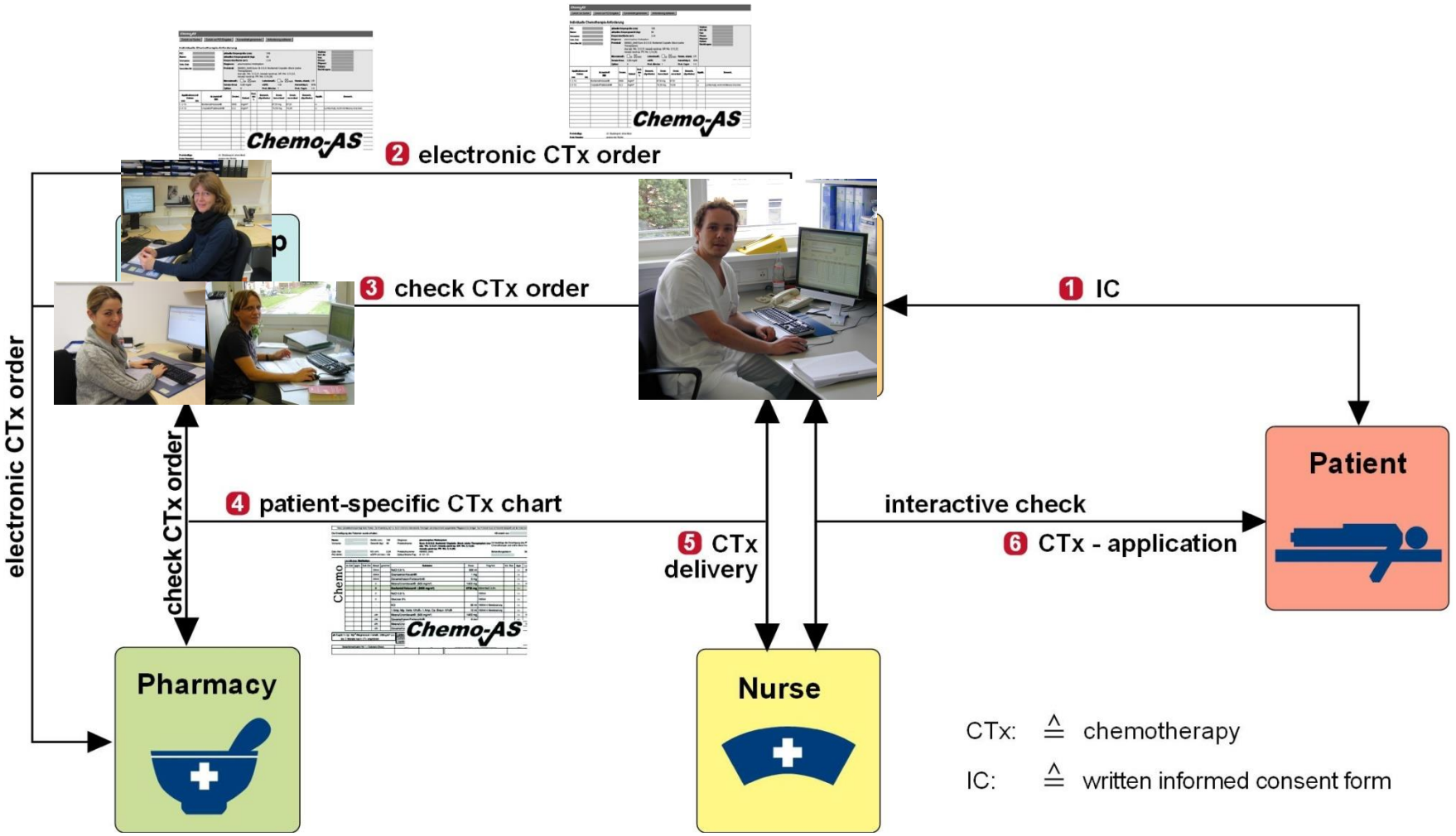
Pharmacy

Nurse

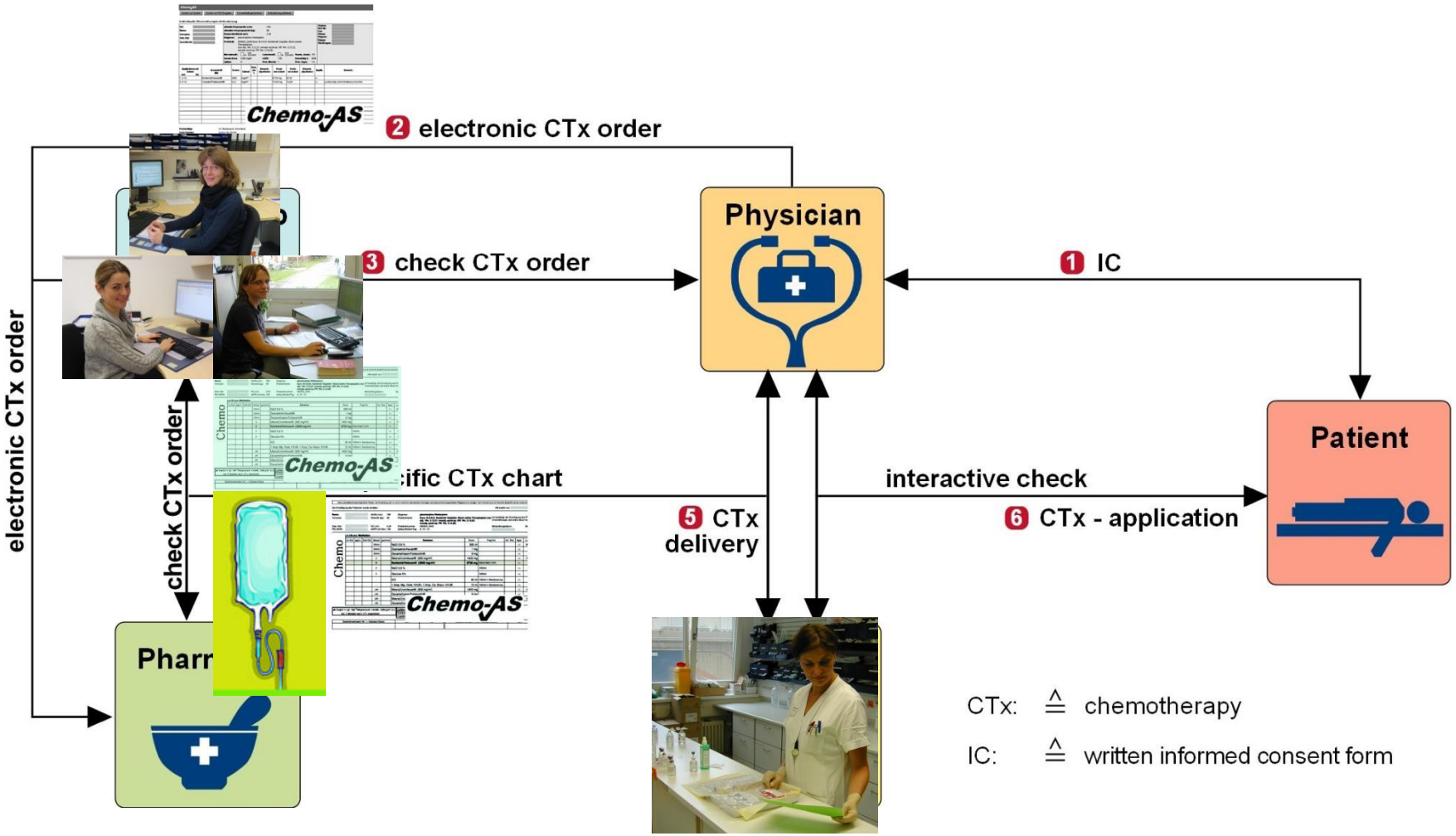
CTx: ≙ chemotherapy

IC: ≙ written informed consent form

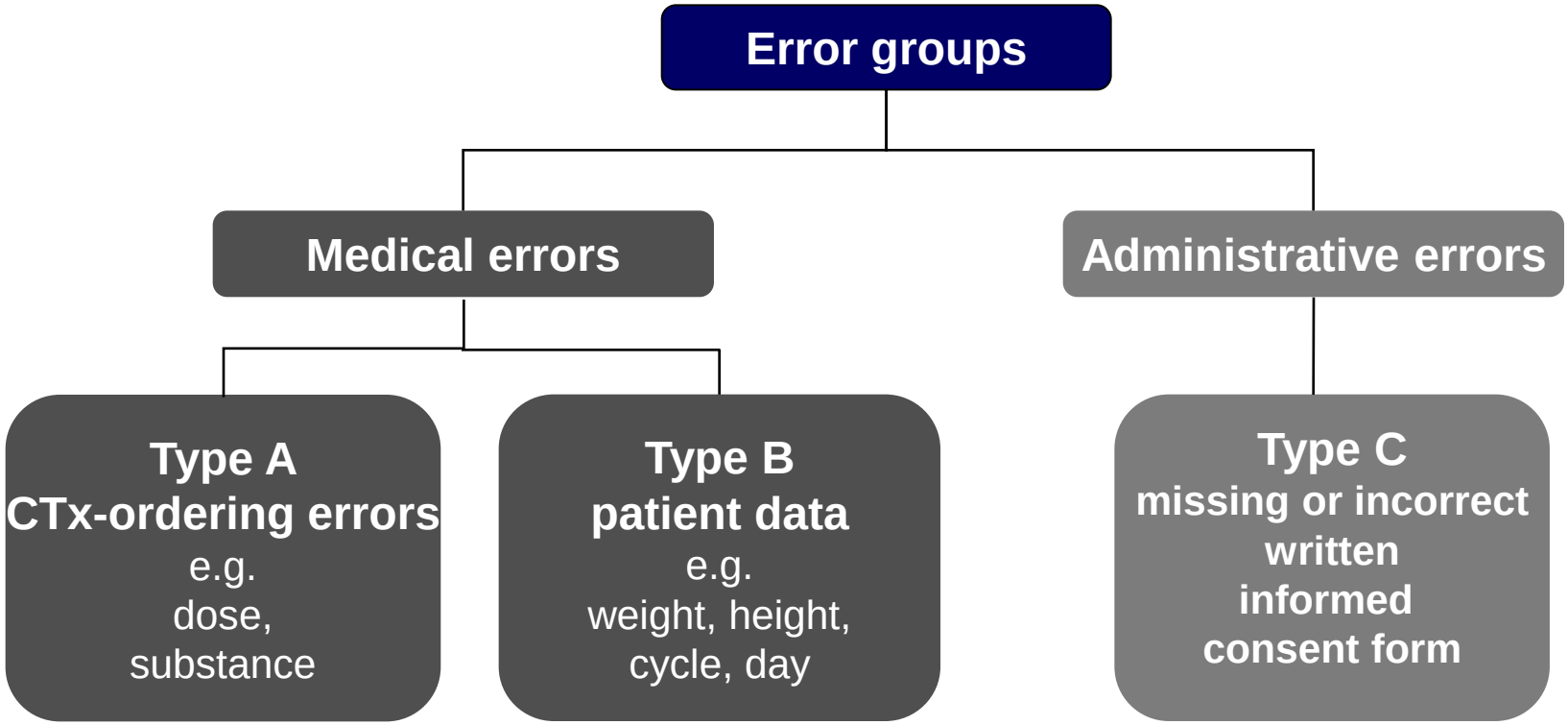
CTx ordering/monitoring via Chemo-AS



CTx ordering/monitoring via Chemo-AS



Error assessment on CTx-ordering



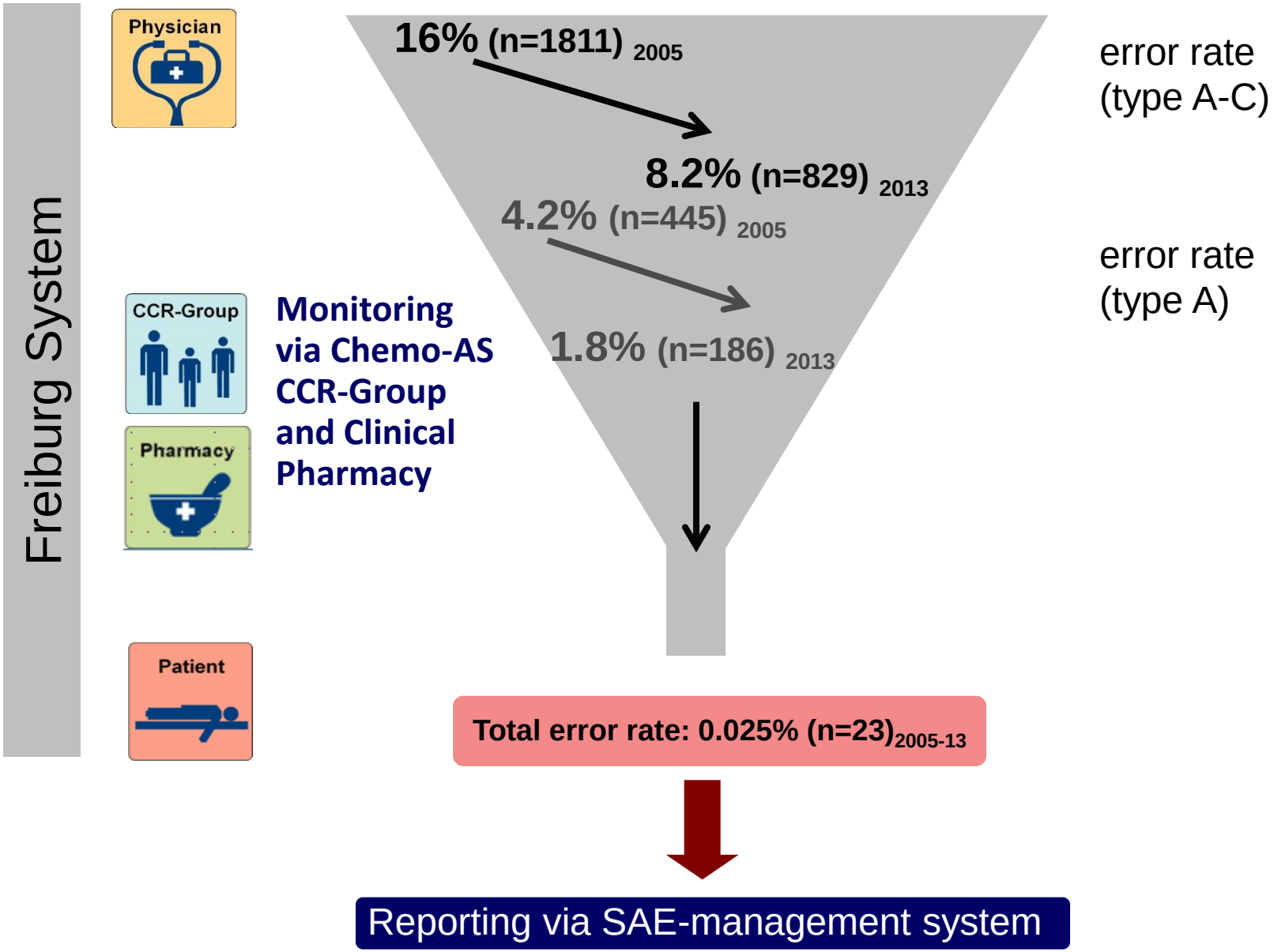
Markert A et al. Int J Cancer 2009;124:722-28

Chemo-AS: Reduction of error rates (type A-C)

	2005	2006	2007	2008	2009	2010	2011	2012	2013
# CTx-order	10885	11331	10674	11420	11429	8510	8956	8888	10155
Error free	9138 (84%)	9406 (83%)	8843 (82.8%)	10049 (88%)	10046 (87.9%)	7520 (88.4%)	8353 (93%)	8194 (92.2%)	9326 (91.8%)
*Total correction rate**	*1811 (16.6%)*	*1978 (17.5%)*	*1691 (15.8%)*	*1429 (12.5%)*	*1406 (12.3%)*	*1076 (12.6%)*	*632 (7%)*	*763 (8.6%)*	*829 (8.2%)*
*Correction rate * Typ A: CTx*	*445 (4.2%)*	*409 (3.6%)*	*201 (1.9%)*	*222 (1.9%)*	*213 (1.9%)*	*112 (1.3%)*	*140 (1.6%)*	*128 (1.4%)*	*186 (1.8%)*
*Correction rate * Typ B: patient data*	*485 (4.5%)*	*507 (4.8%)*	*519 (4.9%)*	*537 (4.7%)*	*563 (4.9%)*	*746 (8.8%)*	*310 (3.5%)*	*323 (3.6%)*	*341 (3.4%)*
*Correction rate * Typ C: Ø IC*	*881 (8.1%)*	*1062 (9.4%)*	*971 (9.1%)*	*670 (5.9%)*	*630 (5.5%)*	*218 (2.6%)*	*182 (2.0%)*	*312 (3.5%)*	*302 (3.0%)*

* Correction rate by CCR-Group

Effective CTx-error avoidance



Summary on CTx-management Med 1/CCCF

- State-of-the-art tumor therapy according to international standards
- Highest safety of CTx ordering and CTx administration
- Major support and work simplification for physicians, nurses
- and pharmacy staff
- User-friendly and long-term, well established application system
- Transparent documentation and information concerning CTx administration
- Transferable to other CTx applying units (gynecology + neurology/neurosurgery)

Improved quality of CTx-treatment and

maximum patient safety

12 Top oncology centers Germany

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TUMORZENTRUM

DEUTSCHE KREBSHILFE

deutsche studiengruppe multiples myelom
dsmm
doing studies on multiple myeloma

EMN
Trialist Group