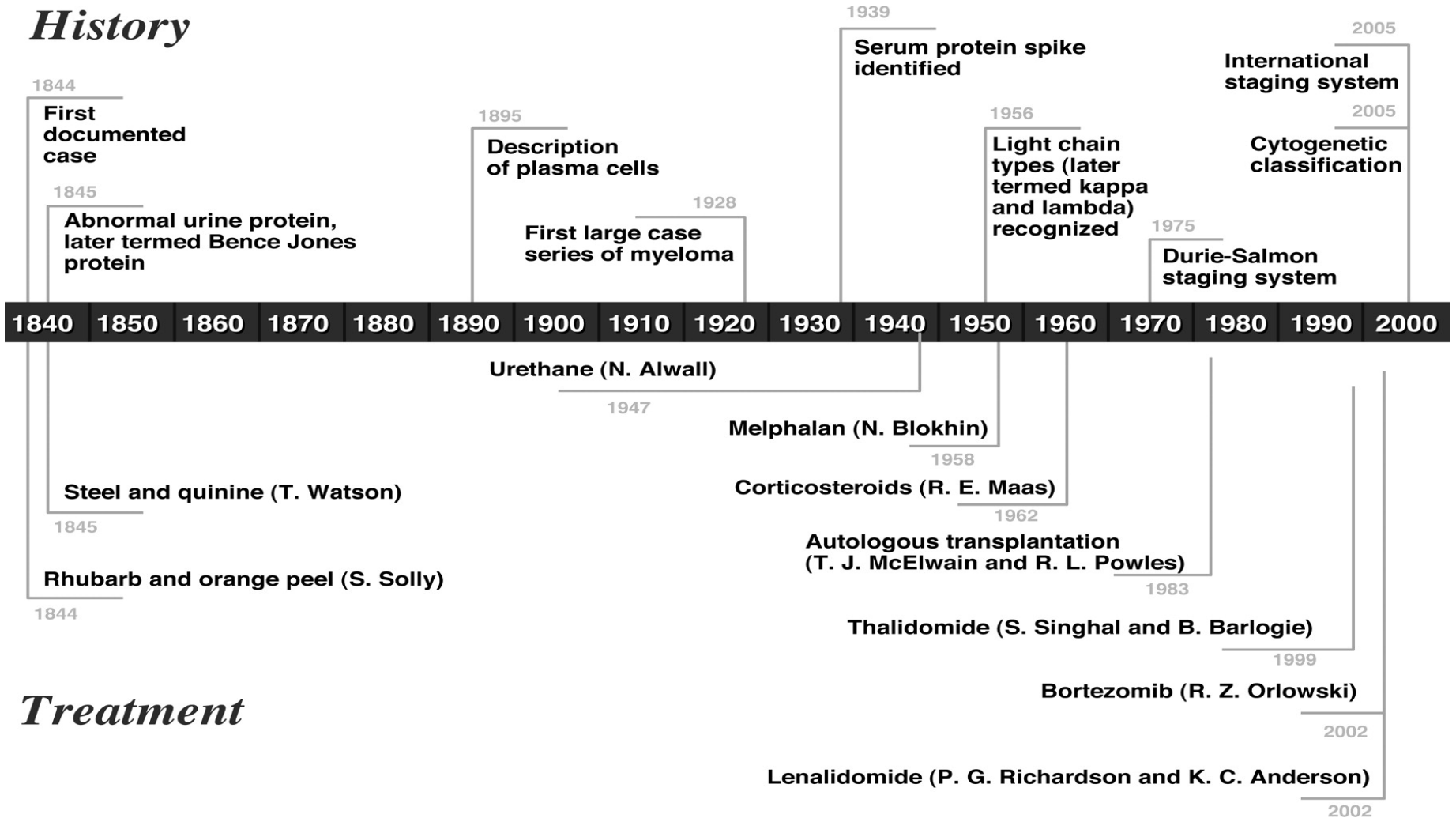
Nuvarande behandlingar och kliniska studier inom myelom

Johan Lund

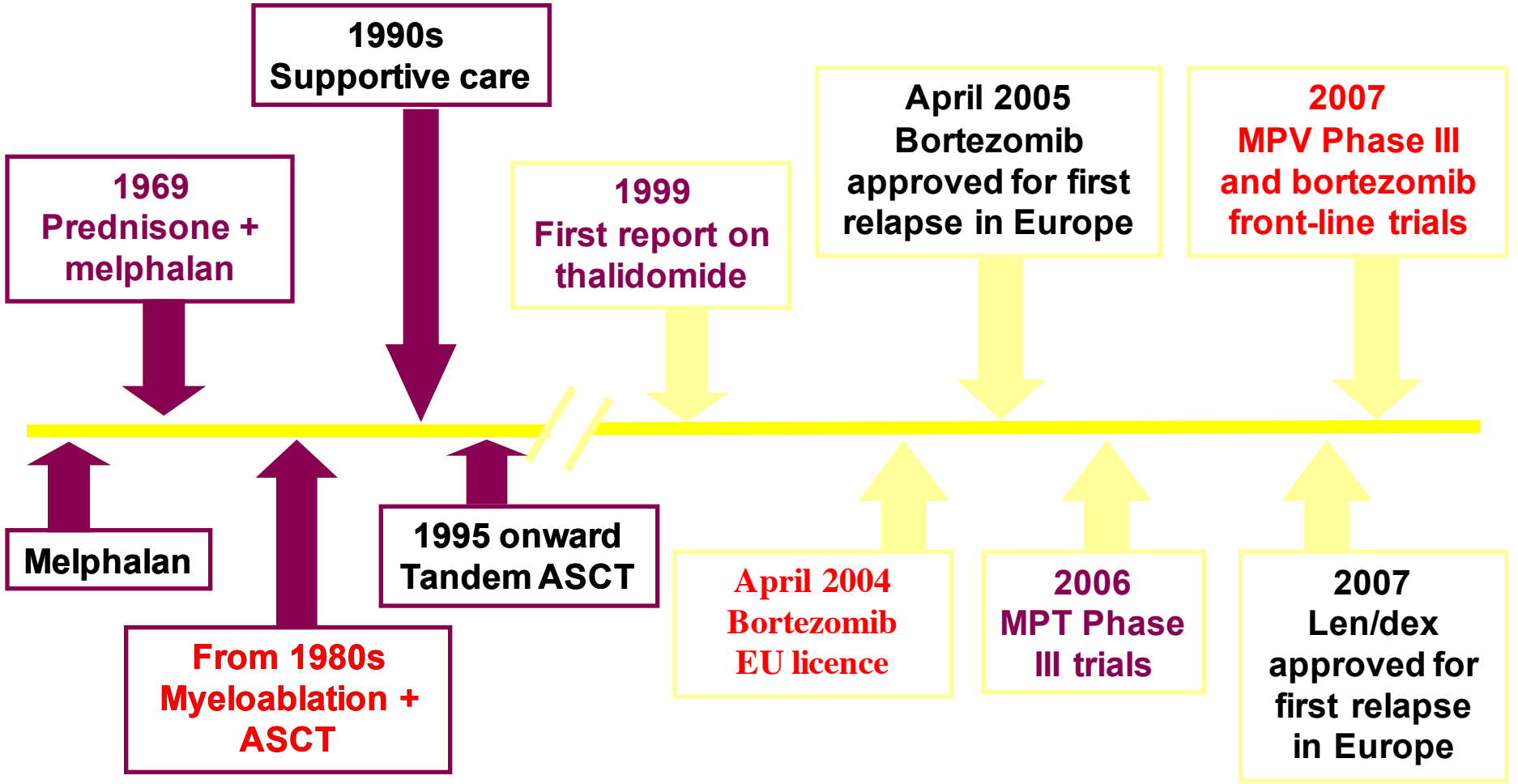
2019-02-09

Timeline depicting the history and treatment of multiple myeloma from 1844 to the present.

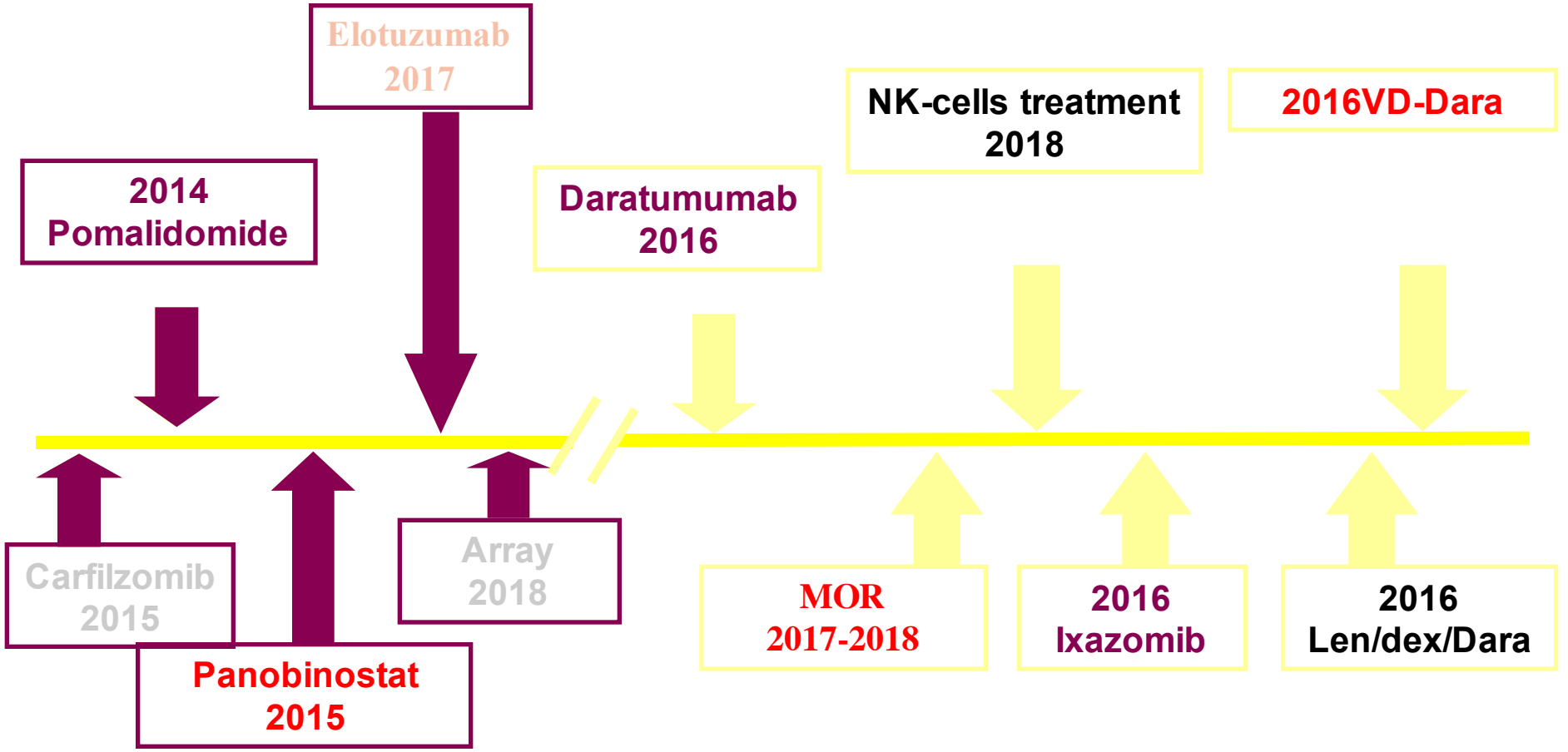


Kyle R A , Rajkumar S V Blood 2008;111:2962-2972

Progress in the treatment of MM over the past 50 years



Progress in the treatment of MM over the past 40 years



Behandling

- Klassiska cellgifter
- Kortison
- Proteasomhämmare
- Immunomodulerande droger – IMiDs
- (Histondeacetylashämmare – HDAC inhibitors)
- Antikroppar
- BiTE – bispecifika antikroppar
- CAR T-celler

Behandling

- MP – melfalan och kortison

-standardterapi från 1969 till början av 2000-talet.

medianöverlevnad strax över 2år

Behandling

- Stamcellstransplantation:

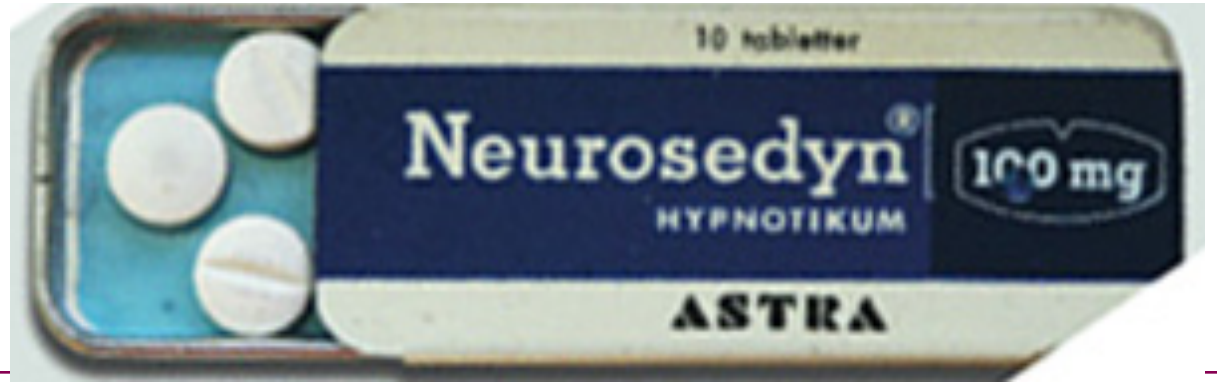
-Högdosbehandling med melfalan

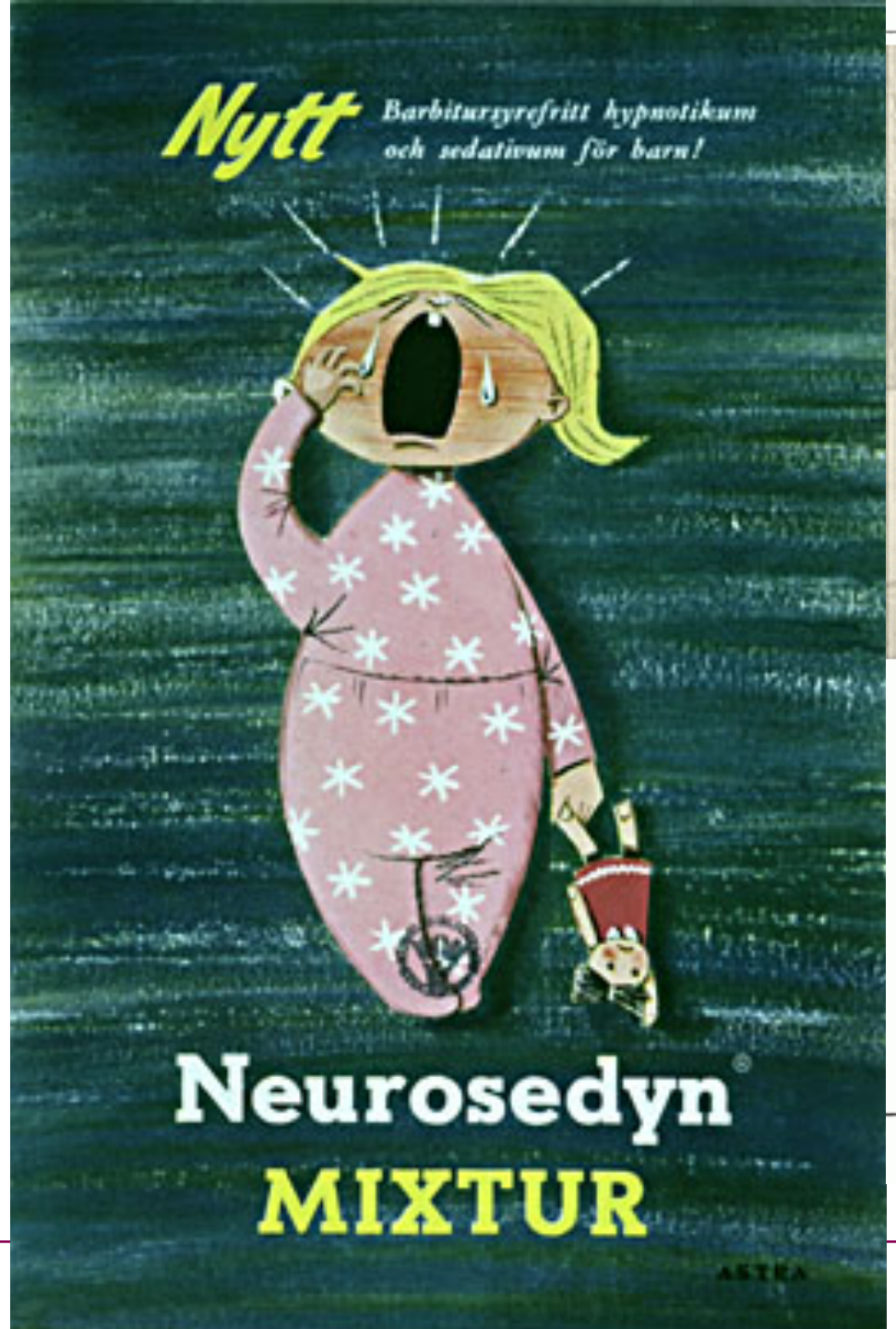
-Ersätter den avdödade benmärgen med egna stamceller.

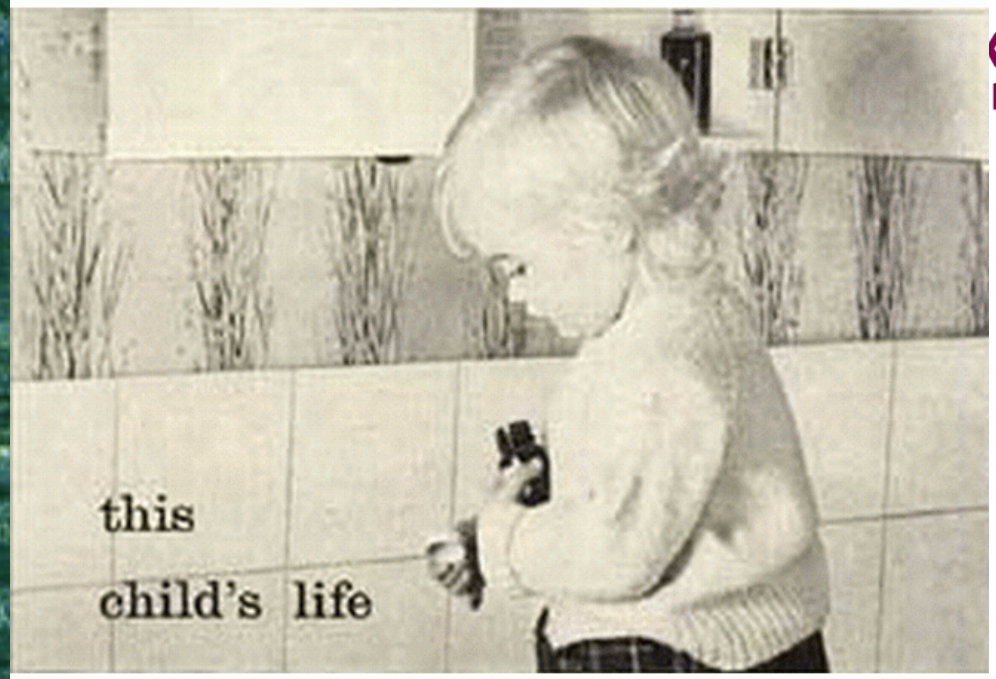
Immunomodulerare - IMiDs

Behandling

- Thalidomide
  - Neurosedynskandalen:
  - Start av försäljning 1957 i Tyskland. 1960 fanns det i mer än 40 länder. Ej i USA då man tyckte att det fanns för dåligt med säkerhetsdata.







may depend on the safety of 'Distaval'

Consider the possible outcome in a case such as this—had the bottle contained a conventional barbiturate. Year by year, the barbiturates claim a mounting toll of childhood victims. Yet it is simple enough to prescribe a sedative and hypnotic which is both highly effective . . . and outstandingly safe. 'Distaval' *(thalidomide)* has been prescribed for over three years in this country, where the accidental poisonings rate is notoriously high; but there is no case on record in which even gross overdosage with 'Distaval' has had harmful results. Put your mind at rest. Depend on the safety of

'DISTAVAL'
TRADE MARK

As a hypnotic at bedtime:
ADULTS: 50 mg. to 200 mg.
INFANTS AND CHILDREN:
25 mg. to 100 mg.

As a daytime sedative:
ADULTS: 25 mg. two or three times daily.
INFANTS AND CHILDREN: Up to 25 mg., according to age, one to three times daily.

'Distaval' (25 mg. tablets).

'Distaval' Forte (100 mg. tablets).
Basic cost to N.H.S. of 12 tablets from dispensing pack of one hundred—1/- or 2/8d. according to strength.

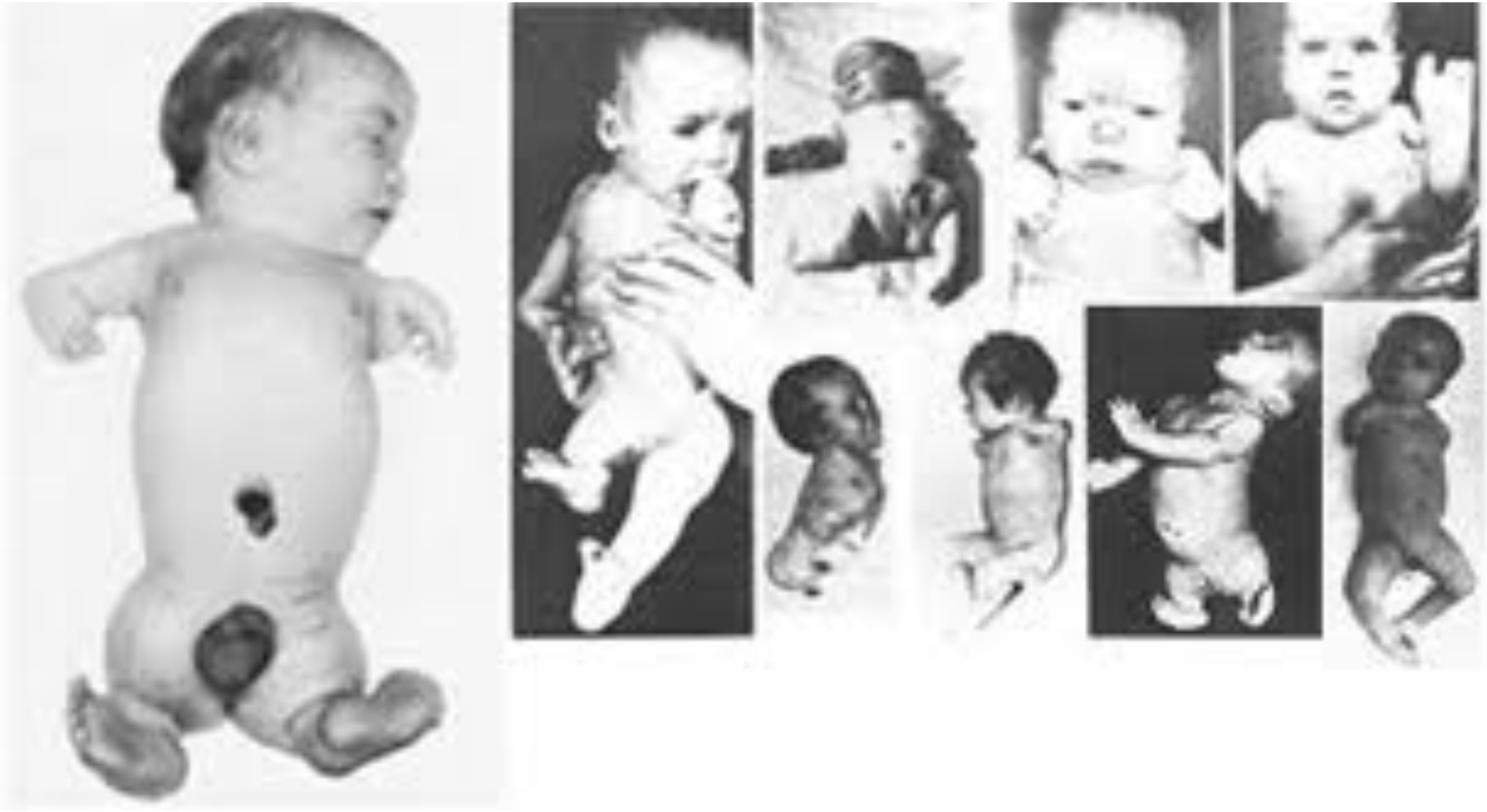
'Distaval' Suspension (50 mg. per 5 ml.)
Basic cost to N.H.S. 3/- per bottle of 60 ml.

REFERENCES:
Practitioner, 1959, *183*, 57.
J. clin. exp. Psychopath., 1959, *20*, 243
J. Coll. gen. Pract., 1958, *1*, 398.
Brit. med. J., 1959, *2*, 635.
Med. Wld. (Lond.), 1960, *93*, 26.
Brit. J. Pharmacol., 1960. *15*, 111.

DCBL THE DISTILLERS COMPANY *(Biochemicals)* LIMITED
Broadway House, The Broadway, Wimbledon, London, S.W.19 Telephone: LIBerty 6020 *Owners of the trade mark 'Distaval'*

Behandling

- Thalidomide
  - December 1961 rapporterades ett troligt samband mellan intag av läkemedlet hos blivande mödrar och uttalade missbildningar hos deras barn.
  - Läkemedet drogs in på alla marknader samma månad, men 10000 barn med missbildningar hade hunnit födas.

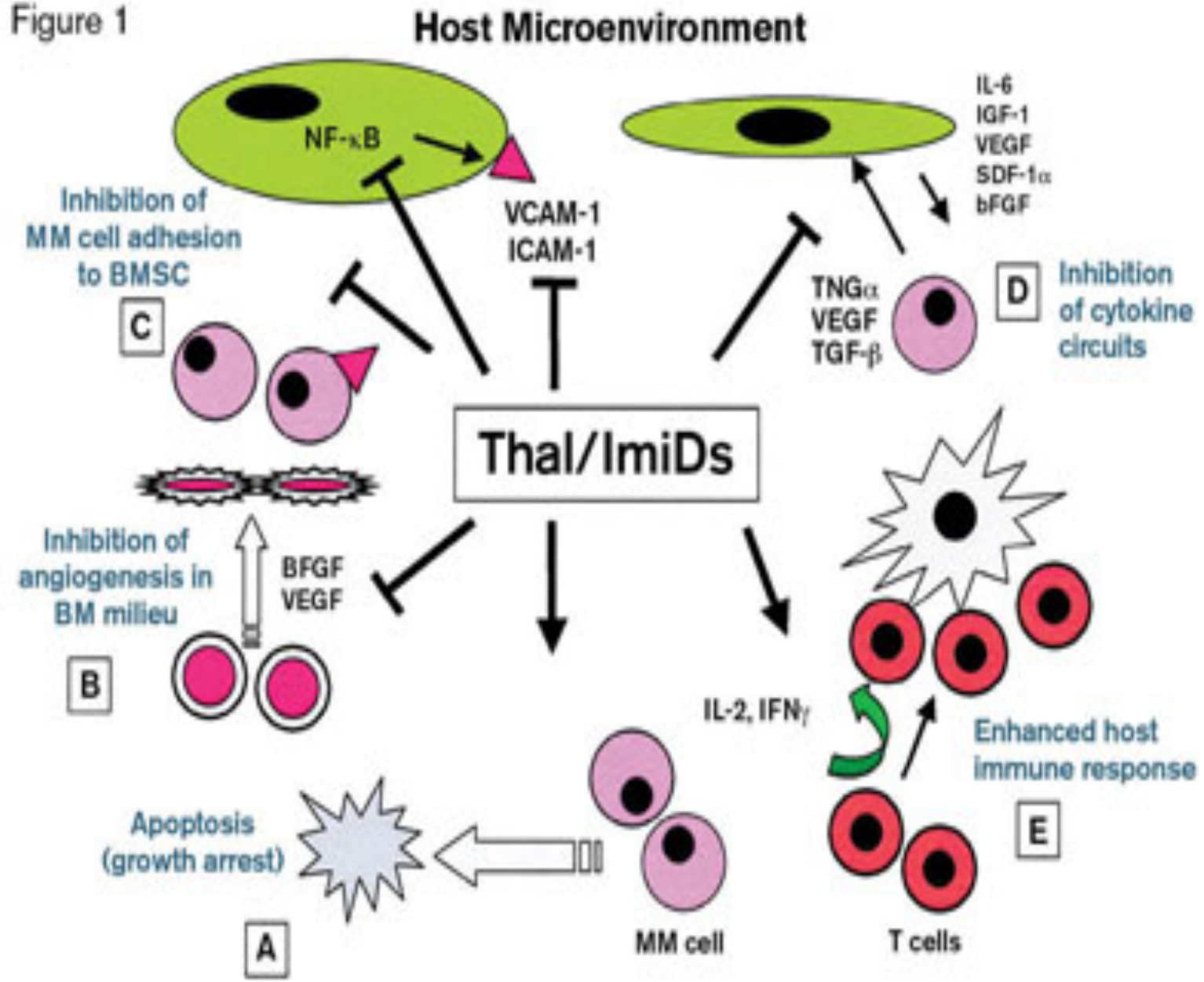


Behandling

- Thalidomide

- Iden från början 1997 var att den hade antiangiogenetiska effekter.
- Därefter pratade man om dess immunomodulerande effekter (höjer IL6 och interferon-gamma och stimulerar T-celler och NK-celler.)

Figure 1



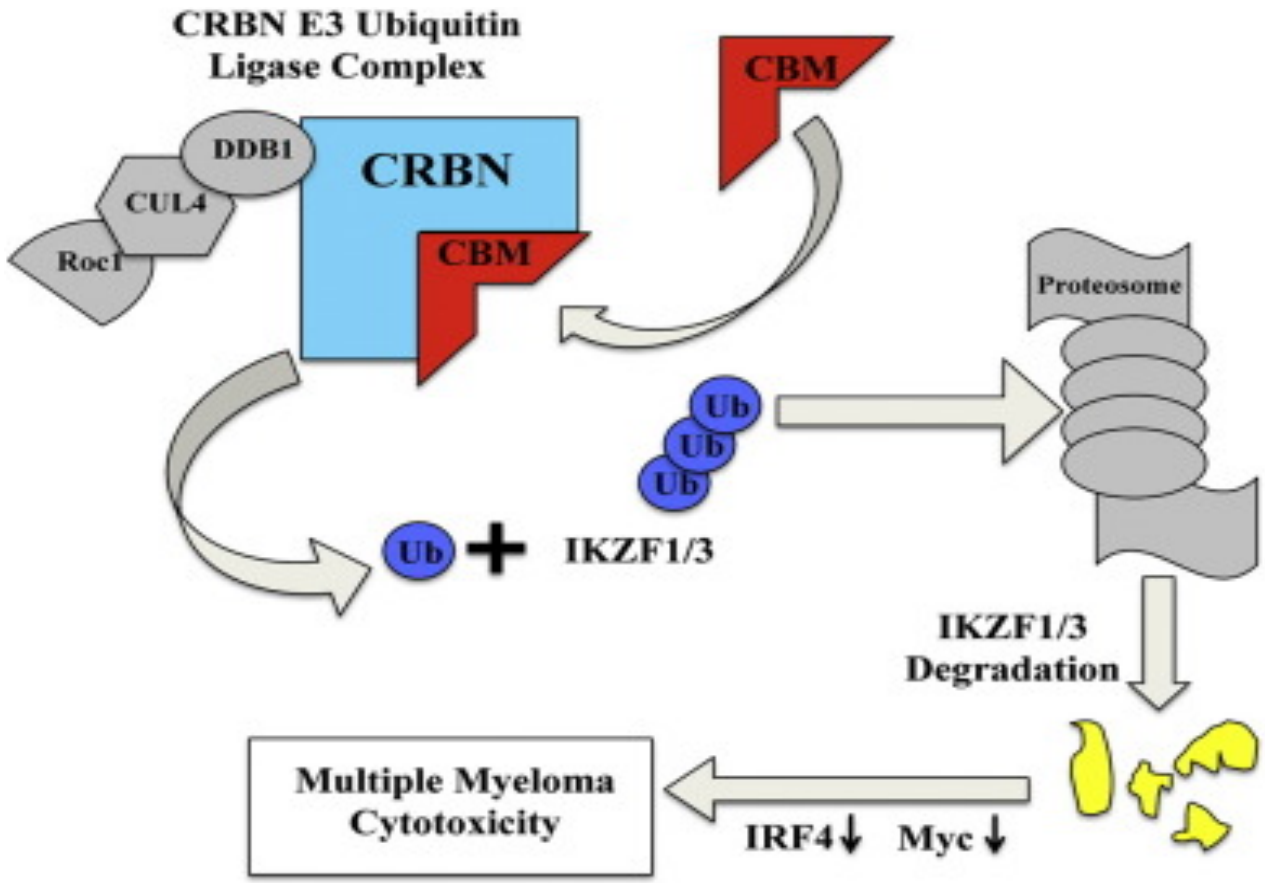


Fig. 1. The CBM action is mediated via CRBN. IMiDs bind to CRBN and cause proteasomal degradation of IKZF1 and IKZF3, consecutively downregulating IRF4 and Myc resulting in MM associated cytotoxicity.

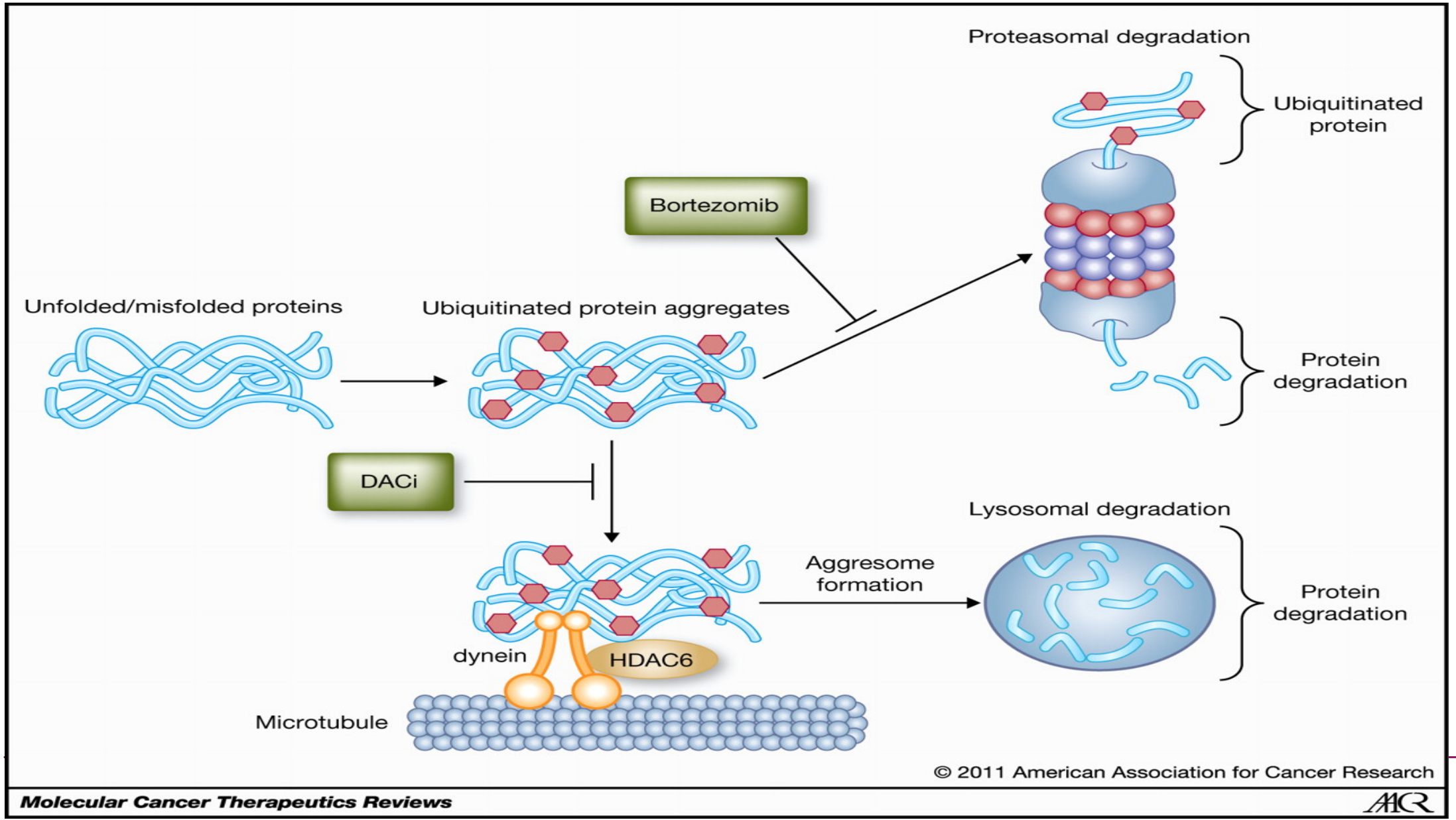
Blood Reviews, Volume 29, Issue 5, 2015, 329–334

http://dx.doi.org/10.1016/j.blre.2015.03.003

Proteasomhämmare

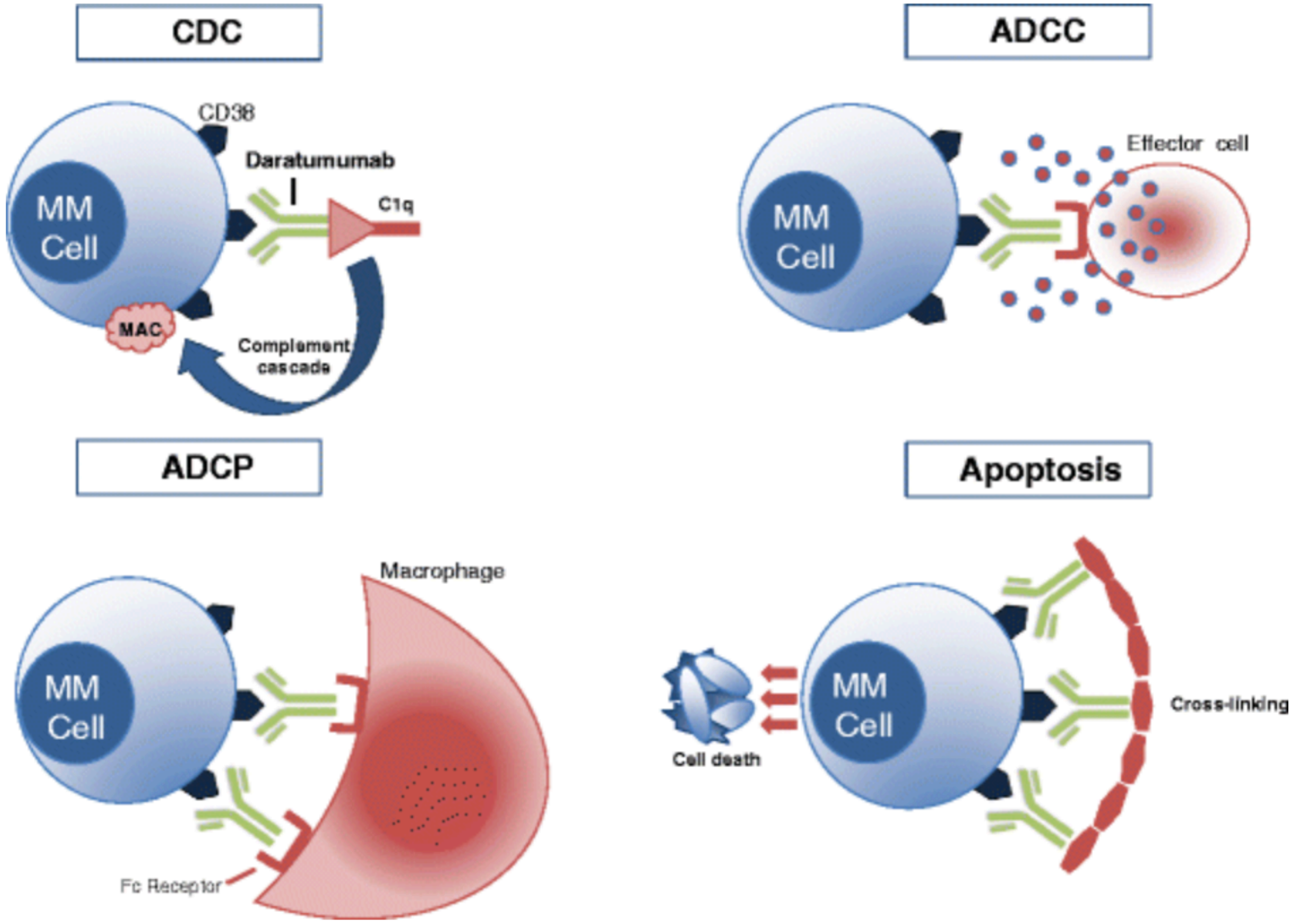
- Proteasomen är en organell som svarar för nedbrytning av abnormala proteiner.

- Blockering av den ger ansamling av pro-apoptotiska signalmarkörer och cellen dör.

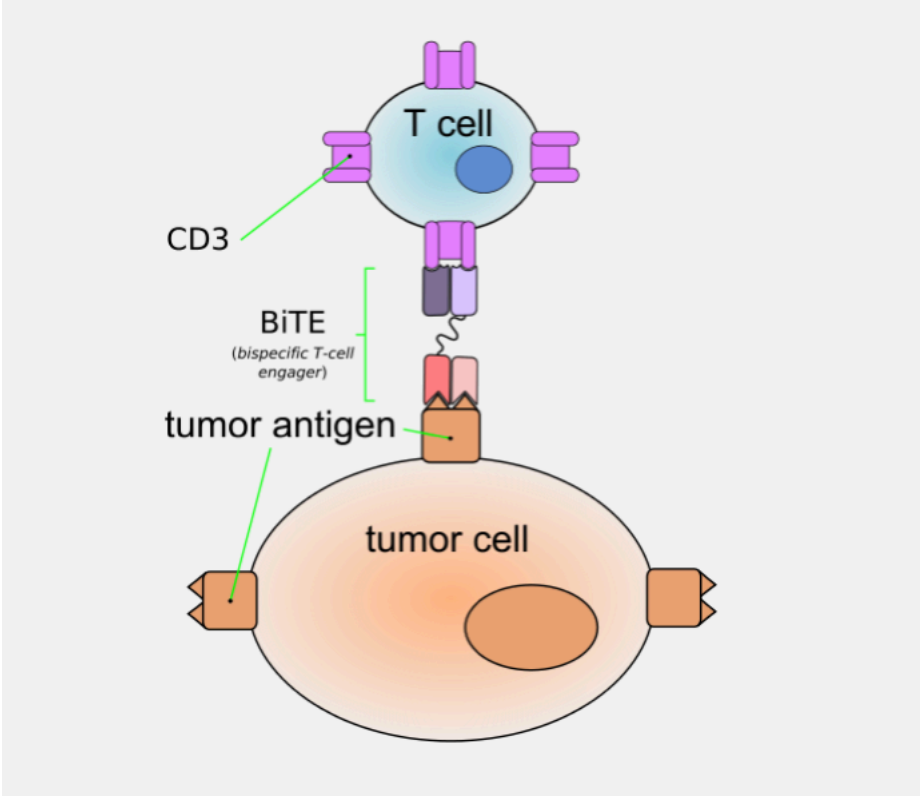

Proteasomal degradation
Ubiquitinated protein
Bortezomib
Unfolded/misfolded proteins
Ubiquitinated protein aggregates
Protein degradation
DACi
Lysosomal degradation
Aggresome formation
Protein degradation
dynein
HDAC6
Microtubule
© 2011 American Association for Cancer Research
Molecular Cancer Therapeutics Reviews
AACR

Antikroppar

- Daratumumab - antikropp mot CD38
- Elotuzumab - antikropp mot SLAMF7
- Nya antikroppar BCMA


CDC
CD38
Daratumumab
C1q
MM Cell
MAC
Complement cascade
ADCC
Effector cell
MM Cell
ADCP
Macrophage
MM Cell
Fc Receptor
Apoptosis
Cell death
MM Cell
Cross-linking

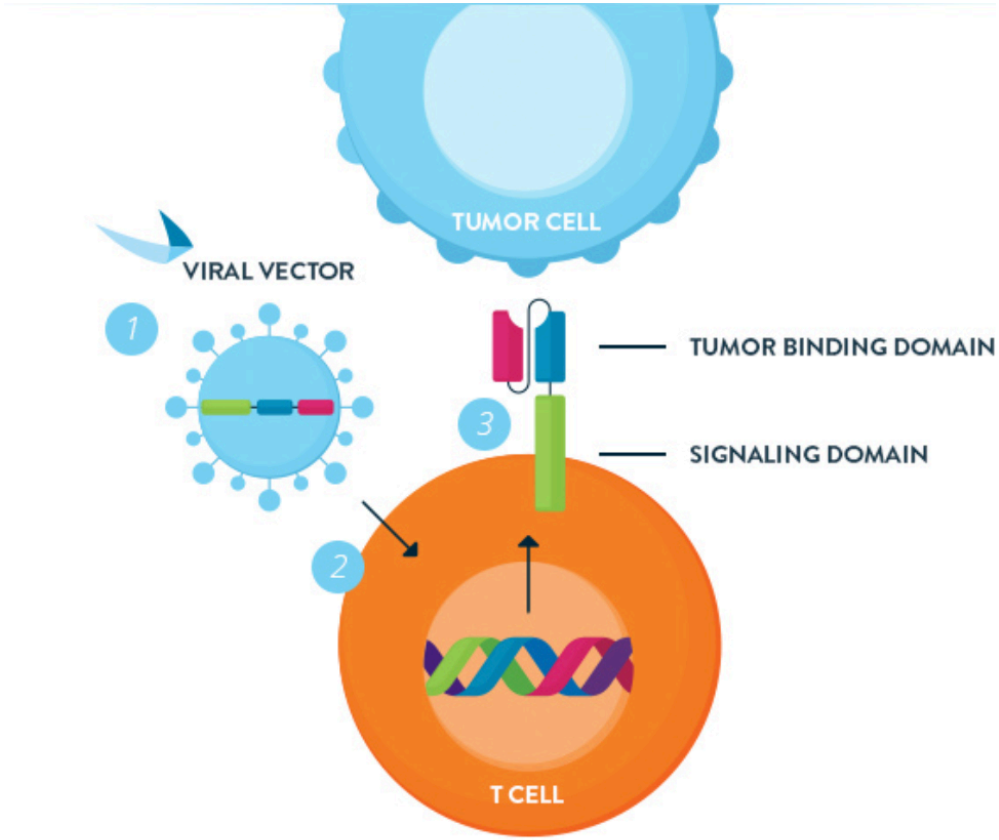
BiTE – bispecifik antikropp



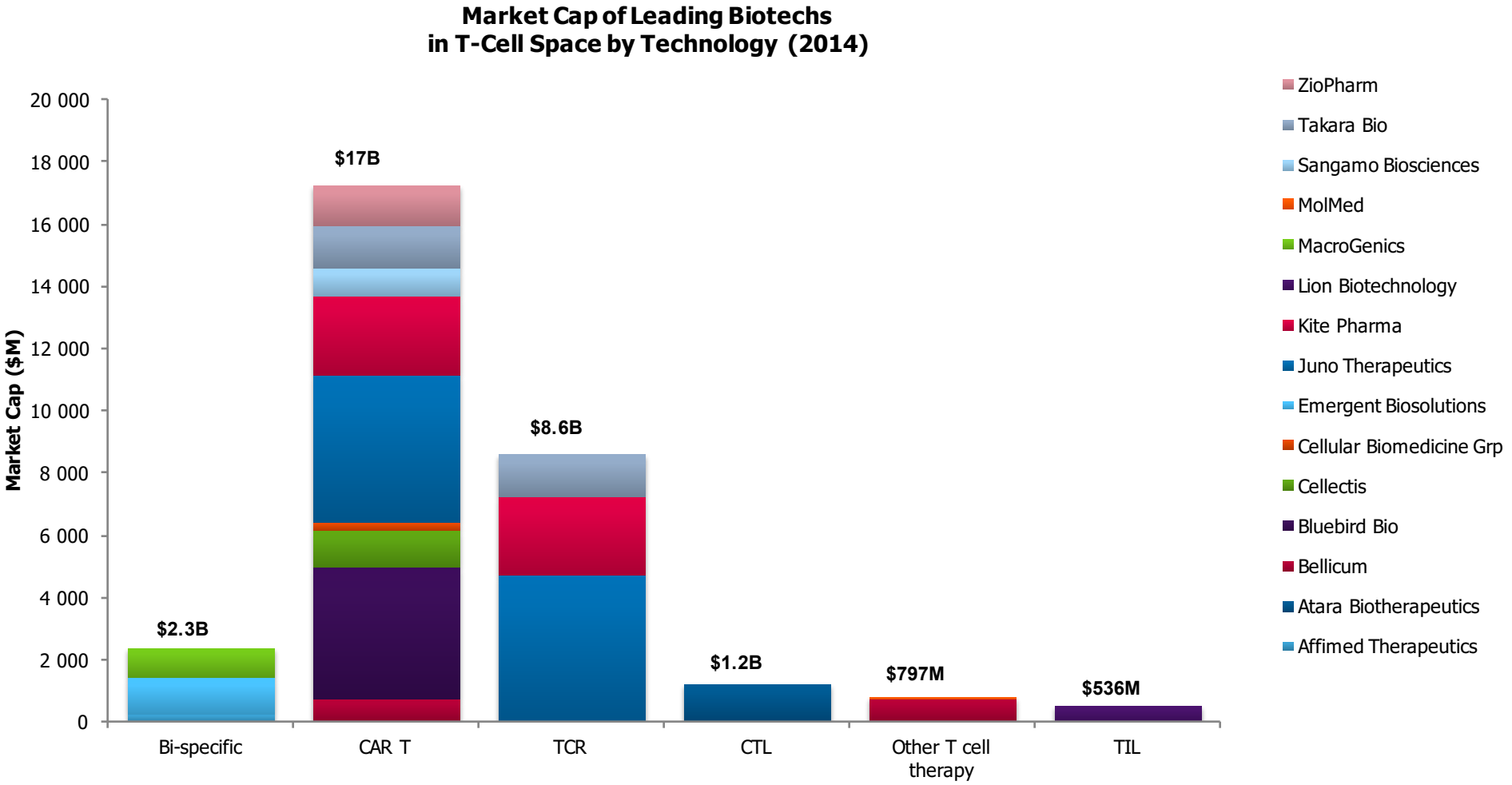
Myeloma Clinical Trials Oct 07, 2017

- Två sammankopplade antikroppar – den ena mot CD3 på T-cellen och den andra mot FCRH5, som uttrycks på plasmaceller.
- Pågår studier. Resultat väntas 2020.

CAR T-celler


TUMOR CELL
VIRAL VECTOR
1
TUMOR BINDING DOMAIN
3
SIGNALING DOMAIN
2
T CELL

Cell Therapy Innovators Have Access To Capital for Go To Market Strategy



Bloomberg.com

Behandling

- Klassiska cellgifter
- Proteasomhämmare
- Immunomodulerande droger – IMiDs
- Antikroppar
- BiTE – bispecifika antikroppar
- CAR T-celler

Behandling

- Klassiska cellgifter

Melfalan, Sendoxan

- Proteasomhämmare
- Immunomodulerande droger – IMiDs
- (Histondeacetylashämmare – HDAC inhibitors)
- Antikroppar
- BiTE – bispecifika antikroppar
- CAR T-celler

Behandling

- Klassiska cellgifter
- Proteasomhämmare

Bortezomib, Carfilzomib, Ixazomib

- Immunomodulerande droger – IMiDs
- (Histondeacetylashämmare – HDAC inhibitors)
- Antikroppar
- BiTE – bispecifika antikroppar
- CAR T-celler

Behandling

- Klassiska cellgifter
- Proteasomhämmare
- Immunomodulerande droger – IMiDs

Thalidomide, Lenalidomide, Pomalidomide

- Antikroppar
- BiTE – bispecifika antikroppar
- CAR T-celler

Behandling

- Klassiska cellgifter
- Proteasomhämmare
- Immunomodulerande droger – IMiDs
- (Histondeacetylashämmare – HDAC inhibitors)
- Antikroppar

Daratumumab, Elotuzumab

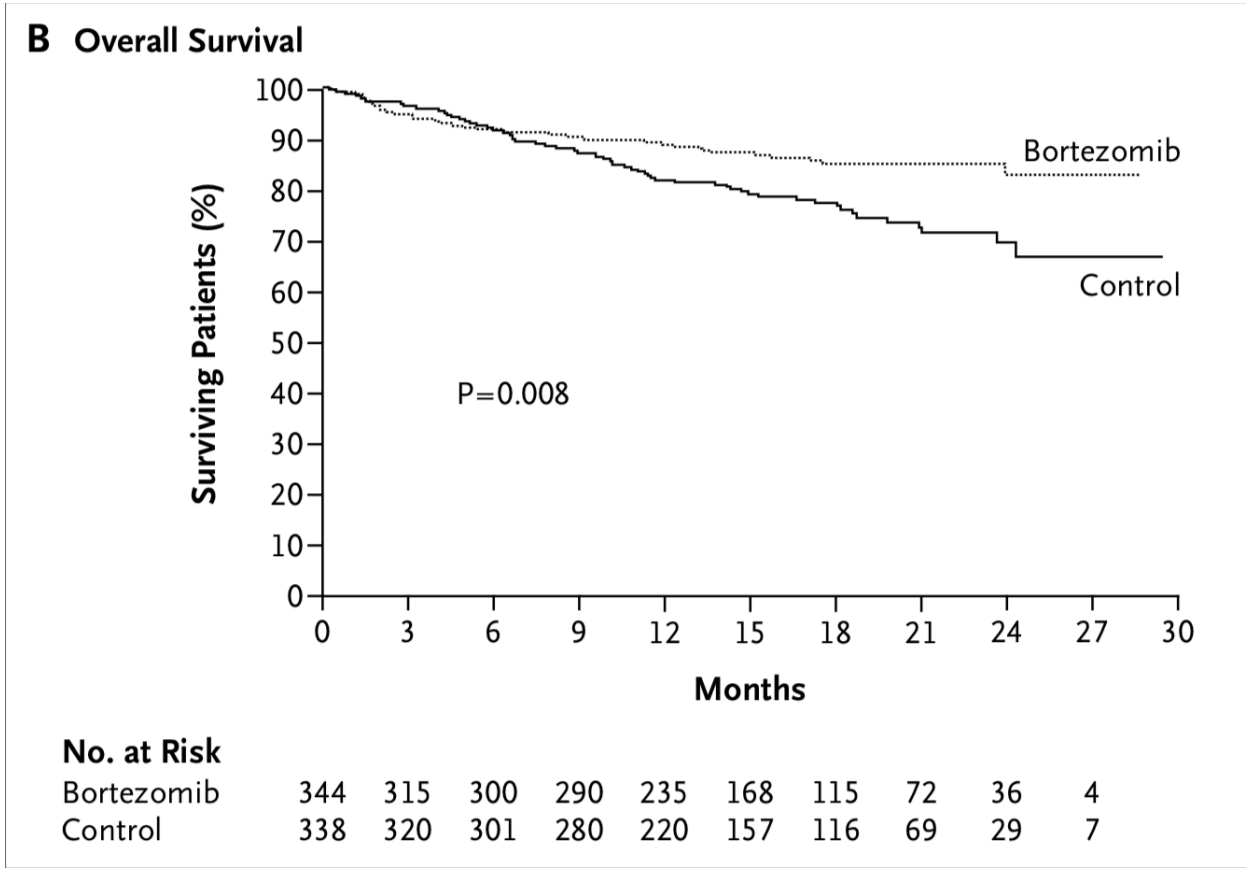
- BiTE – bispecifika antikroppar
- CAR T-celler

Nya behandlingar

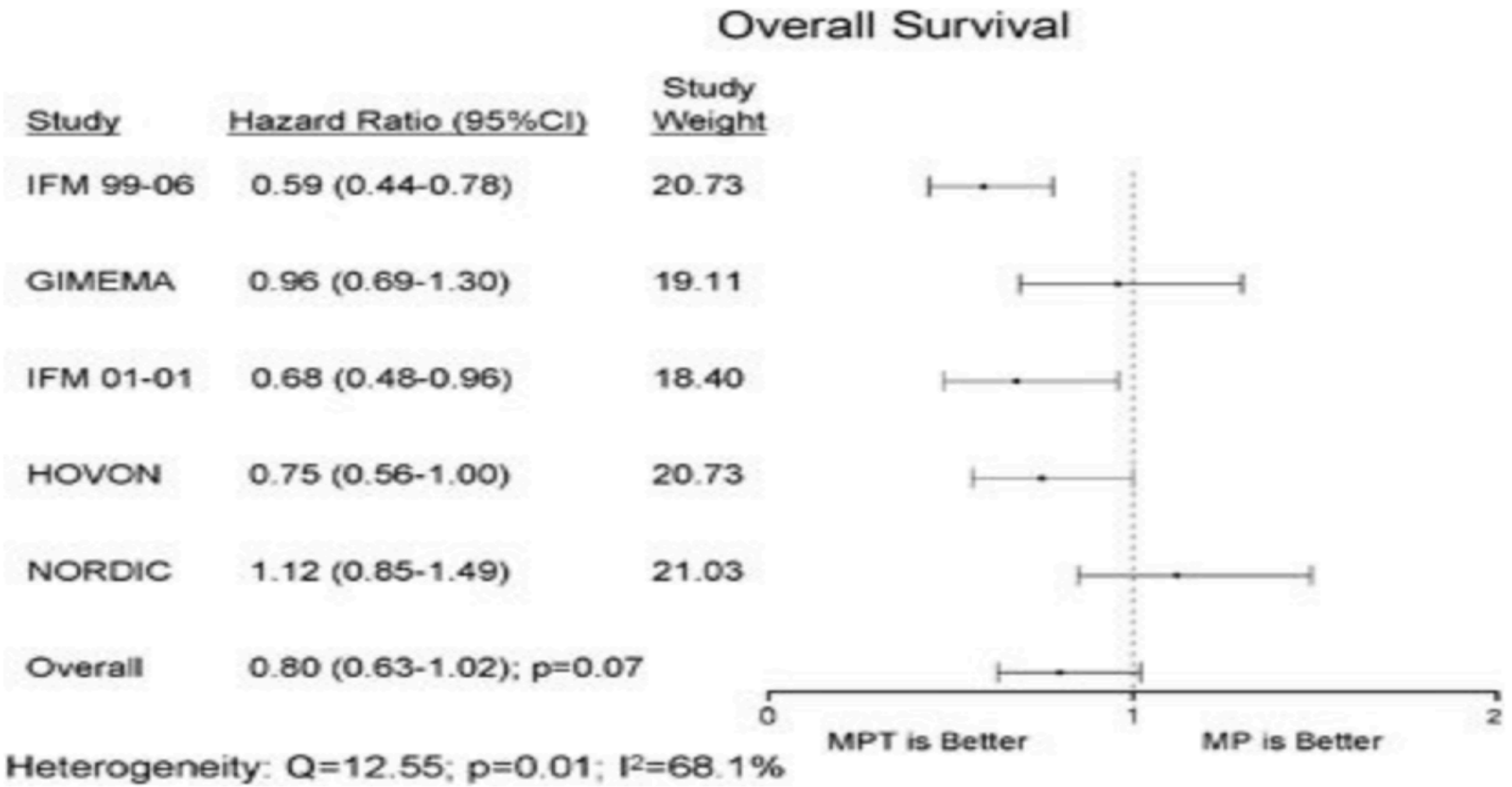
- Hur vet vi vad vi skall använda alla läkemedel och hur vi skall kombinera dem?

- Vad för studier ligger då till grund för alla nya behandlingar?

VISTA-study MP vs MPV



Meta-studie MP vs MPT



Carfilzomib* is an irreversible proteasome inhibitor

ENDEAVOR Study Design

Karolinska Institutet

Randomization 1:1

N=929

Stratification:

- Prior proteasome inhibitor therapy
- Prior lines of treatment
- ISS stage
- Route of V administration

Kd

Carfilzomib 56 mg/m^2 IV

Days 1, 2, 8, 9, 15, 16 (20 mg/m^2 days 1, 2, cycle 1 only)

Infusion duration: 30 minutes for all doses

Dexamethasone 20 mg

Days 1, 2, 8, 9, 15, 16, 22, 23

28-day cycles until PD or unacceptable toxicity

Vd

Bortezomib 1.3 mg/m^2 (IV bolus or subcutaneous injection)

Days 1, 4, 8, 11

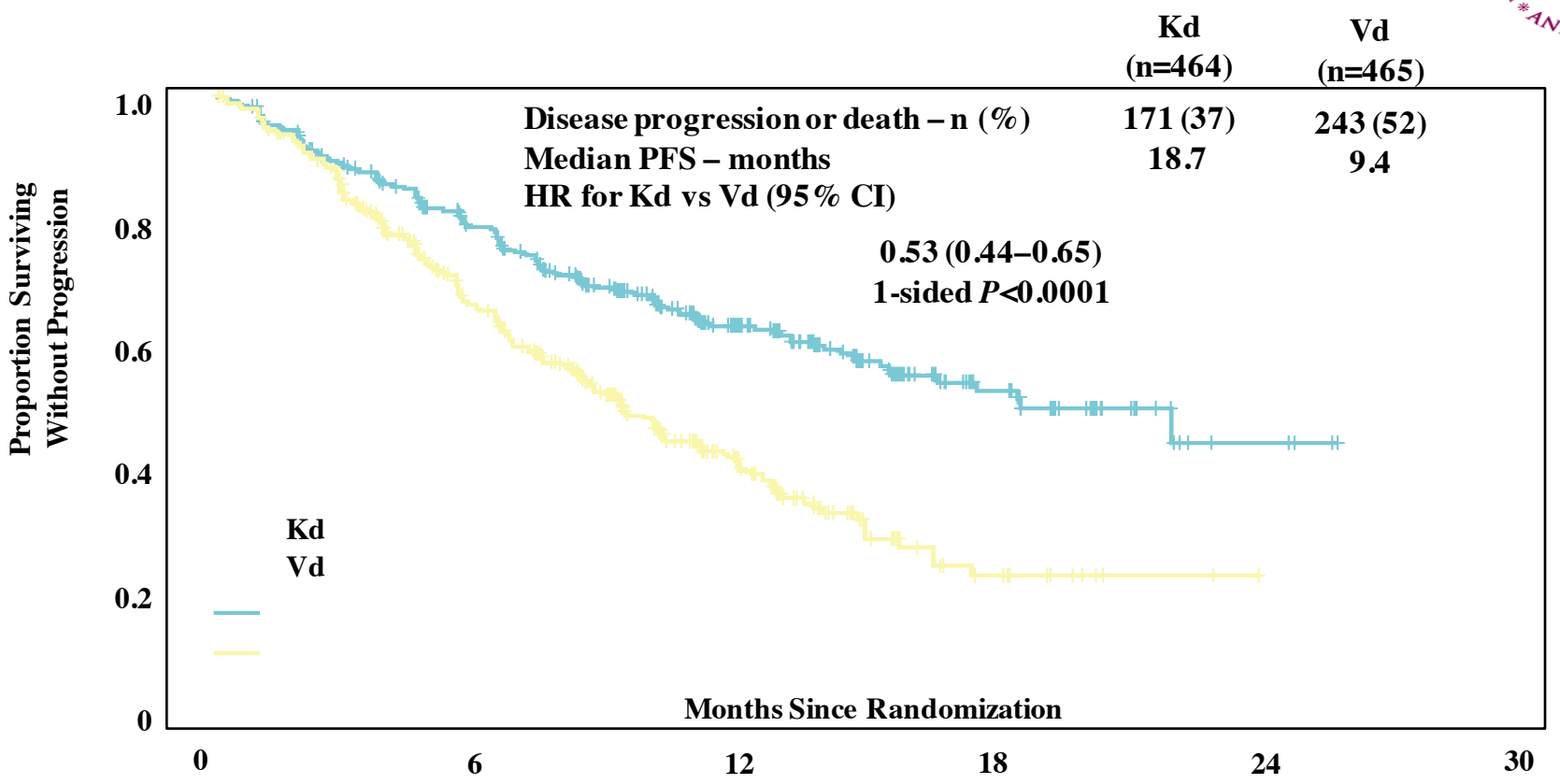
Dexamethasone 20 mg

Days 1, 2, 4, 5, 8, 9, 11, 12

21-day cycles until PD or unacceptable toxicity

ISS, International Staging System; IV, intravenous; Kd, carfilzomib and dexamethasone; PD, progressive disease; Vd, bortezomib and dexamethasone; V, bortezomib.

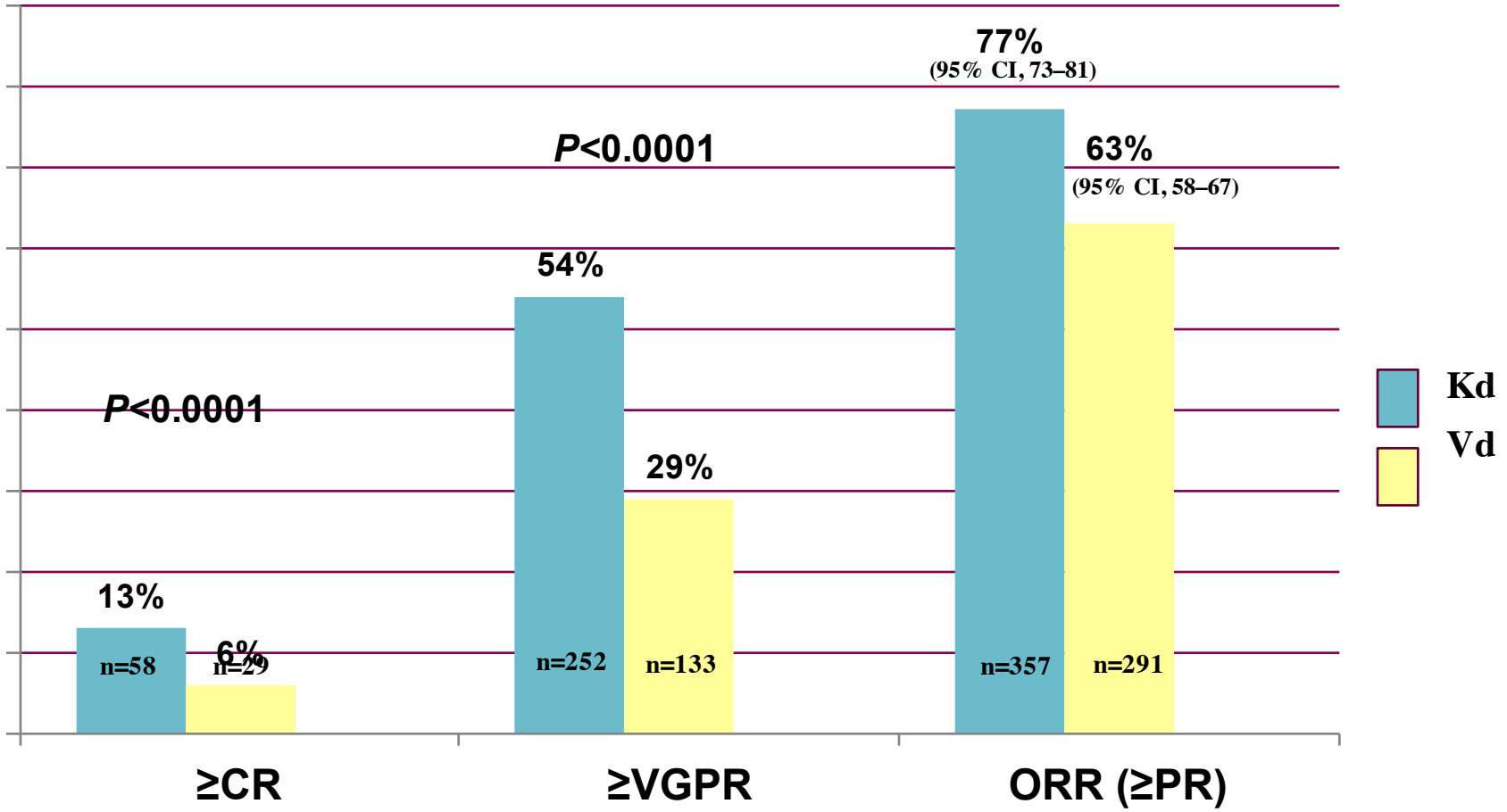
Primary End Point: Progression-Free Survival
Intent-to-Treat Population (N=929)



- **Median follow-up: 11.2 months**

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; Kd, carfilzomib and dexamethasone; PFS, progression-free survival; Vd, bortezomib and dexamethasone.

Secondary End Point: Response Rates

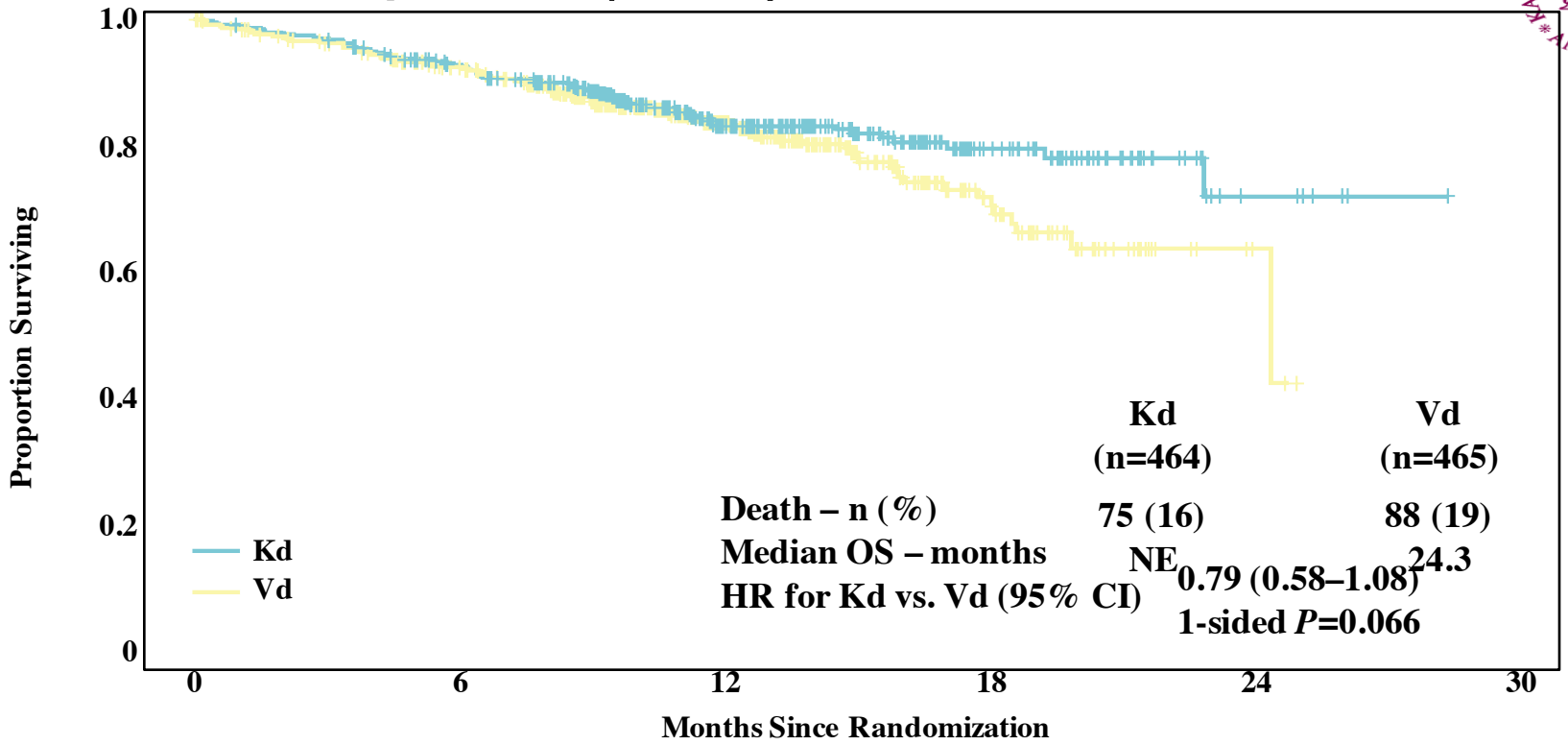


- Median DOR: 21.3 months (95% CI, 21.3–NE) for Kd vs 10.4 months (95% CI, 9.3–13.8) for Vd

CI, confidence interval; CR, complete response; DOR, duration of response; ORR, overall response rate; Kd, carfilzomib and dexamethasone; NE, not estimable; PR, partial response; Vd, bortezomib and dexamethasone; VGPR, very good partial response.

Secondary End Point: Overall Survival

Intent-to-Treat Population (N=929)



OS data were immature; the study will continue until the final OS analysis is performed

CI, confidence interval; HR, hazard ratio; ITT, intent to treat; Kd, carfilzomib and dexamethasone; NE, not estimable; OS, overall survival; Vd, bortezomib and dexamethasone.

Carfilzomib is not approved in EU

	Carfilzomib group (n=464)	Bortezomib group (n=465)
Median age, years	65 (58–72)	65 (60–71)
<65 years	223 (48%)	210 (45%)
65–74 years	164 (35%)	189 (41%)
≥75 years	77 (17%)	66 (14%)
ECOG performance status*		
0	221 (48%)	232 (50%)
1	210 (45%)	203 (44%)
2	33 (7%)	30 (6%)
Cytogenetic risk by FISH†		
High risk	97 (21%)	113 (24%)
Standard risk	284 (61%)	291 (63%)
Unknown/missing	83 (18%)	61 (13%)
Serum β_2-microglobulin concentration		
<3·5 mg/L	220 (47%)	216 (46%)
≥3·5 mg/L	244 (53%)	249 (54%)
ISS stage		
Stage I	205 (44%)	204 (44%)
Stage II or III	259 (56%)	261 (56%)
Previous regimens per interactive voice and web response system		
1	231 (50%)	229 (49%)
2–3	233 (50%)	236 (51%)
Previous therapy‡		
Bortezomib	250 (54%)	252 (54%)
Immunomodulatory drug	326 (70%)	350 (75%)

	Carfilzomib group (n=464)	Bortezomib group (n=465)
Median age, years	65 (58–72)	65 (60–71)
<65 years	223 (48%)	210 (45%)
65–74 years	164 (35%)	189 (41%)
≥75 years	77 (17%)	66 (14%)
ECOG performance status*		
0	221 (48%)	232 (50%)
1	210 (45%)	203 (44%)
2	33 (7%)	30 (6%)
Cytogenetic risk by FISH†		
High risk	97 (21%)	113 (24%)
Standard risk	284 (61%)	291 (63%)
Unknown/missing	83 (18%)	61 (13%)
Serum β_2-microglobulin concentration		
<3·5 mg/L	220 (47%)	216 (46%)
≥3·5 mg/L	244 (53%)	249 (54%)
ISS stage		
Stage I	205 (44%)	204 (44%)
Stage II or III	259 (56%)	261 (56%)
Previous regimens per interactive voice and web response system		
1	231 (50%)	229 (49%)
2–3	233 (50%)	236 (51%)
Previous therapy‡		
Bortezomib	250 (54%)	252 (54%)
Immunomodulatory drug	326 (70%)	350 (75%)

ASPIRE: Carfilzomib + Len/dex vs Len/dex; PFS

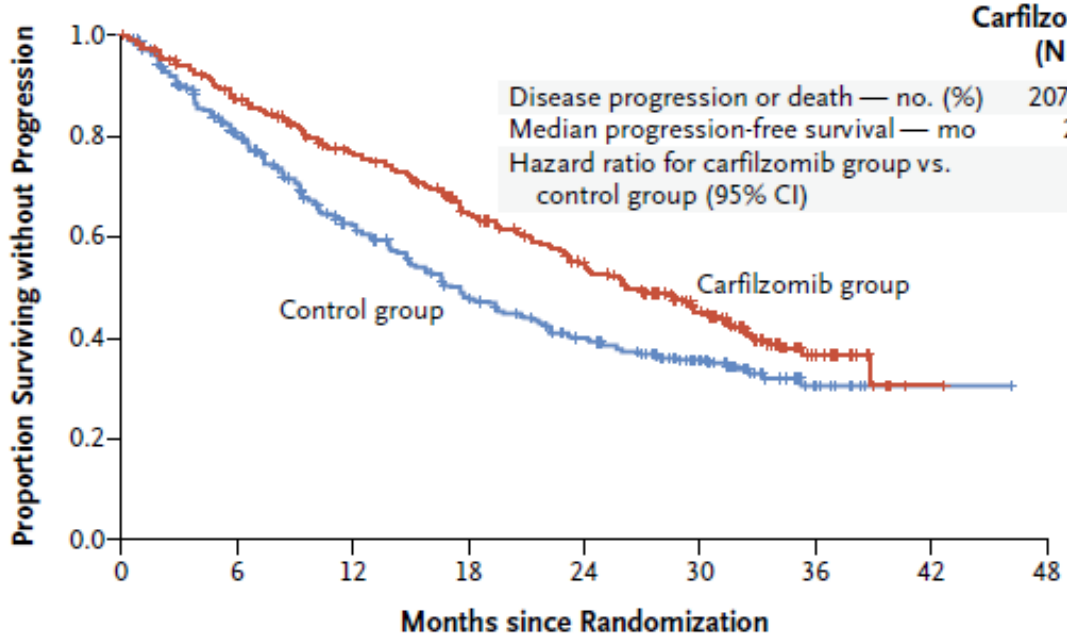
N=792

RANDOMIZE

1:1

KRd
Carfilzomib 20/27 mg/m^2, d 1, 2, 8, 9, 15, 16 (cycles 1-12), d 1, 2, 15, 16 (cycles 13-18)
Lenalidomide 25 mg d 1-21 (cycles 1-19+)
Dexamethasone 40 mg/d QWK (cycles 1-19+)

Rd
Lenalidomide 25 mg d 1-21
Dexamethasone 40 mg/d QWK (cycles 1-19+)



	Carfilzomib Group (N=396)	Control Group (N=396)
Disease progression or death — no. (%)	207 (52.3)	224 (56.6)
Median progression-free survival — mo	26.3	17.6
Hazard ratio for carfilzomib group vs. control group (95% CI)	0.69 (0.57–0.83)	
	P=0.0001	

No. at Risk

Carfilzomib group	396	332	279	222	179	112	24	1
Control group	396	287	206	151	117	72	18	1

Stewart, A K et al. N Engl J Med 2015;372:142-152

Table 3. Adverse Events in the Safety Population.*

Event	Carfilzomib Group (N=392)		Control Group (N=389)	
	All Grades	Grade 3 or Higher	All Grades	Grade 3 or Higher
	number of patients (percent)			
Most common nonhematologic adverse events				
Diarrhea	166 (42.3)	15 (3.8)	131 (33.7)	16 (4.1)
Fatigue	129 (32.9)	30 (7.7)	119 (30.6)	25 (6.4)
Cough	113 (28.8)	1 (0.3)	67 (17.2)	0
Pyrexia	112 (28.6)	7 (1.8)	81 (20.8)	2 (0.5)
Upper respiratory tract infection	112 (28.6)	7 (1.8)	75 (19.3)	4 (1.0)
Hypokalemia	108 (27.6)	37 (9.4)	52 (13.4)	19 (4.9)
Muscle spasms	104 (26.5)	4 (1.0)	82 (21.1)	3 (0.8)
Other adverse events of interest				
Dyspnea	76 (19.4)	11 (2.8)	58 (14.9)	7 (1.8)
Hypertension	56 (14.3)	17 (4.3)	27 (6.9)	7 (1.8)
Acute renal failure†	33 (8.4)	13 (3.3)	28 (7.2)	12 (3.1)
Cardiac failure‡	25 (6.4)	15 (3.8)	16 (4.1)	7 (1.8)
Ischemic heart disease§	23 (5.9)	13 (3.3)	18 (4.6)	8 (2.1)

Table 3. Adverse Events in the Safety Population.*

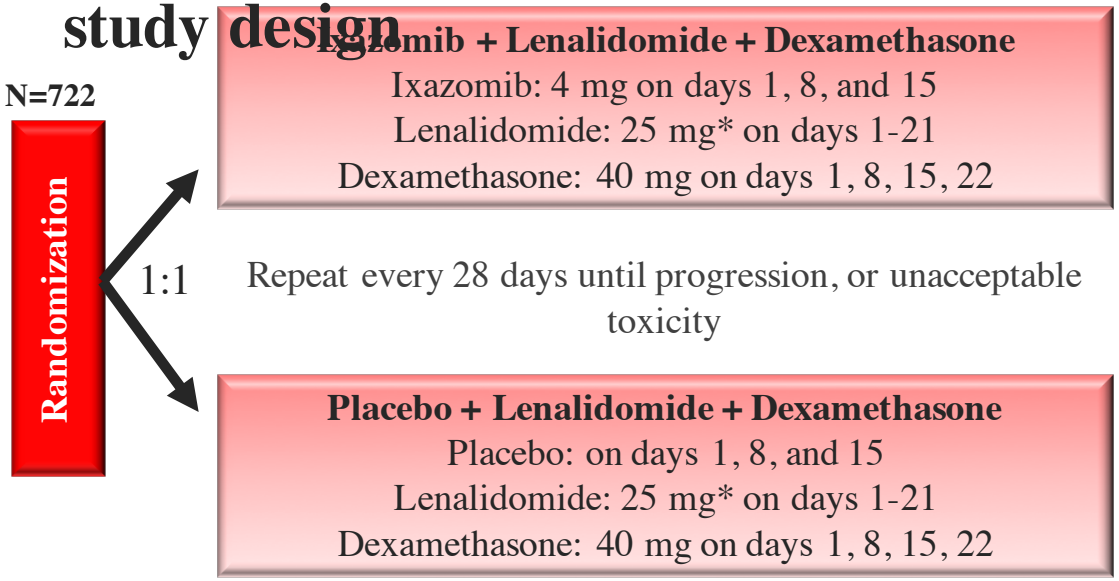
Event	Carfilzomib Group (N=392)		Control Group (N=389)	
	All Grades	Grade 3 or Higher	All Grades	Grade 3 or Higher
	number of patients (percent)			
Most common nonhematologic adverse events				
Diarrhea	166 (42.3)	15 (3.8)	131 (33.7)	16 (4.1)
Fatigue	129 (32.9)	30 (7.7)	119 (30.6)	25 (6.4)
Cough	113 (28.8)	1 (0.3)	67 (17.2)	0
Pyrexia	112 (28.6)	7 (1.8)	81 (20.8)	2 (0.5)
Upper respiratory tract infection	112 (28.6)	7 (1.8)	75 (19.3)	4 (1.0)
Hypokalemia	108 (27.6)	37 (9.4)	52 (13.4)	19 (4.9)
Muscle spasms	104 (26.5)	4 (1.0)	82 (21.1)	3 (0.8)
Other adverse events of interest				
Dyspnea	76 (19.4)	11 (2.8)	58 (14.9)	7 (1.8)
Hypertension	56 (14.3)	17 (4.3)	27 (6.9)	7 (1.8)
Acute renal failure†	33 (8.4)	13 (3.3)	28 (7.2)	12 (3.1)
Cardiac failure‡	25 (6.4)	15 (3.8)	16 (4.1)	7 (1.8)
Ischemic heart disease§	23 (5.9)	13 (3.3)	18 (4.6)	8 (2.1)

Karolinska Institutet

TOURMALINE-MM1: Phase 3 study of weekly oral ixazomib plus lenalidomide-dexamethasone

Karolinska Institutet

Global, double-blind, randomized, placebo-controlled study design



Stratification:
- Prior therapy: 1 vs 2 or 3
- ISS: I or II vs III
- PI exposure: yes vs no

Primary endpoint:
- PFS

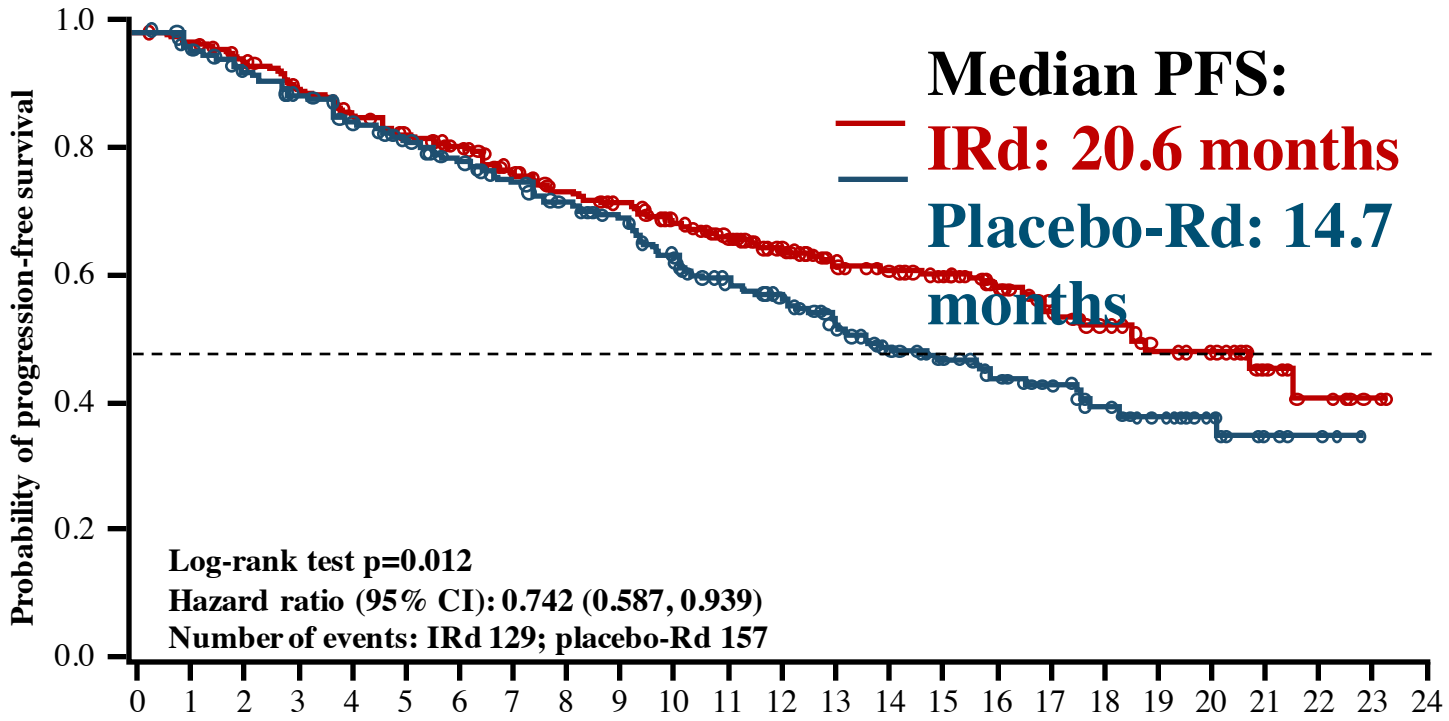
Key secondary endpoints:
- OS
- OS in patients with del(17p)

Response and progression (IMWG 2011 criteria[1]) assessed by an independent review committee (IRC) blinded to both treatment and investigator assessment

*10 mg for patients with creatinine clearance ≤60 or ≤50 mL/min, depending on local label/practice

1. Rajkumar S, et al. Blood 2011;117:4691–5.

Final PFS analysis:
A significant, 35% improvement in PFS with IRd vs placebo-Rd



Number of patients at risk:																								
IRd	360	345	332	315	298	283	270	248	233	224	206	182	145	119	111	95	72	58	44	34	26	14	9	1	0
Placebo-Rd	362	340	325	308	288	274	254	237	218	208	188	157	130	101	85	71	58	46	31	22	15	5	3	0	0

Median follow-up: ~15 months

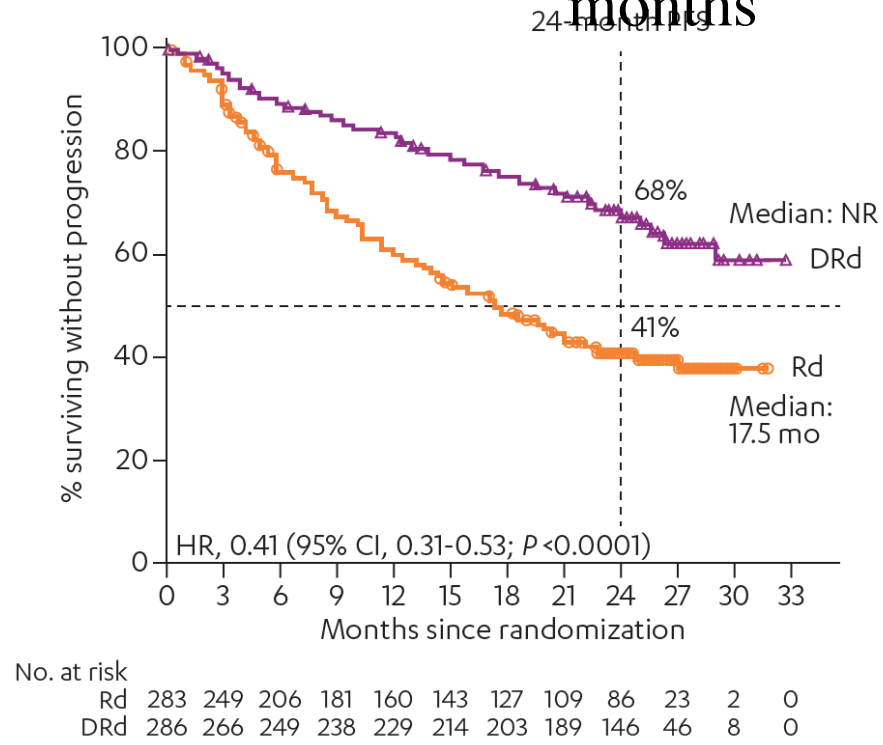
AEs after median follow-up of 23 months: increased rates with IRd driven by low-grade events

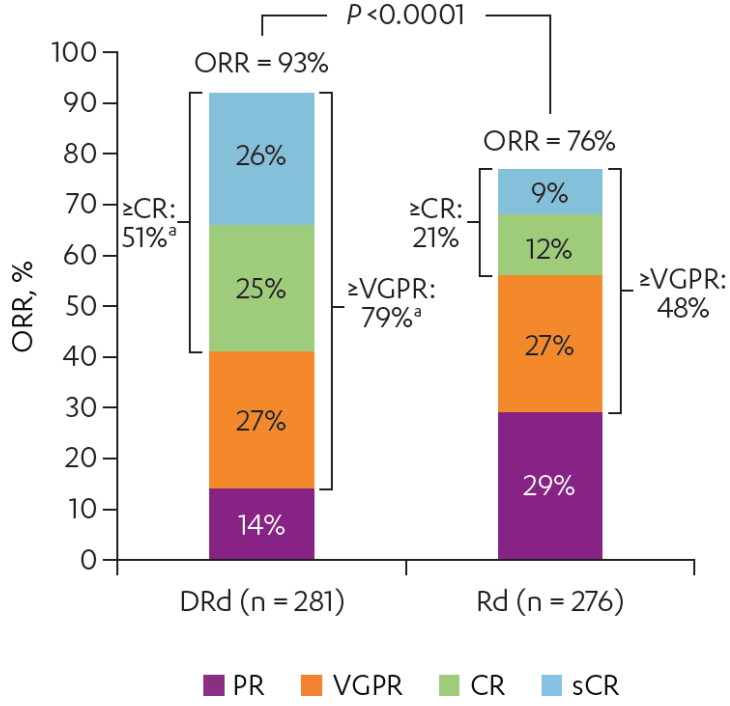
	IRd (N=361), %			Placebo-Rd (N=359), %		
Preferred terms	**All-grade**	**Grade 3**	**Grade 4**	**All-grade**	**Grade 3**	**Grade 4**
AEs overlapping with lenalidomide						
Diarrhea	45	6	0	39	3	0
Constipation	35	<1	0	26	<1	0
Nausea	29	2	0	22	0	0
Vomiting	23	1	0	12	<1	0
Rash*	36	5	0	23	2	0
Back pain	24	<1	0	17	3	0
Upper respiratory tract infection	23	<1	0	19	0	0
Thrombocytopenia	31	12	7	16	5	4
AEs with proteasome inhibitors						
Peripheral neuropathy*	27	2	0	22	2	0
Peripheral edema	28	1	0	20	1	0
AEs with lenalidomide						
Thromboembolism*	8	2	<1	11	3	<1
Neutropenia*	33	18	5	31	18	6

*Represents multiple MedDRA preferred terms.

POLLUX: Daratumumab + Len/dex vs Len/dex; Updated Efficacy

Median follow-up of 25.4 months





DRd-treated patients had a 59% reduction in the risk of disease progression or death in comparison with Rd

Deep responses continue in the DRd group with longer follow-up

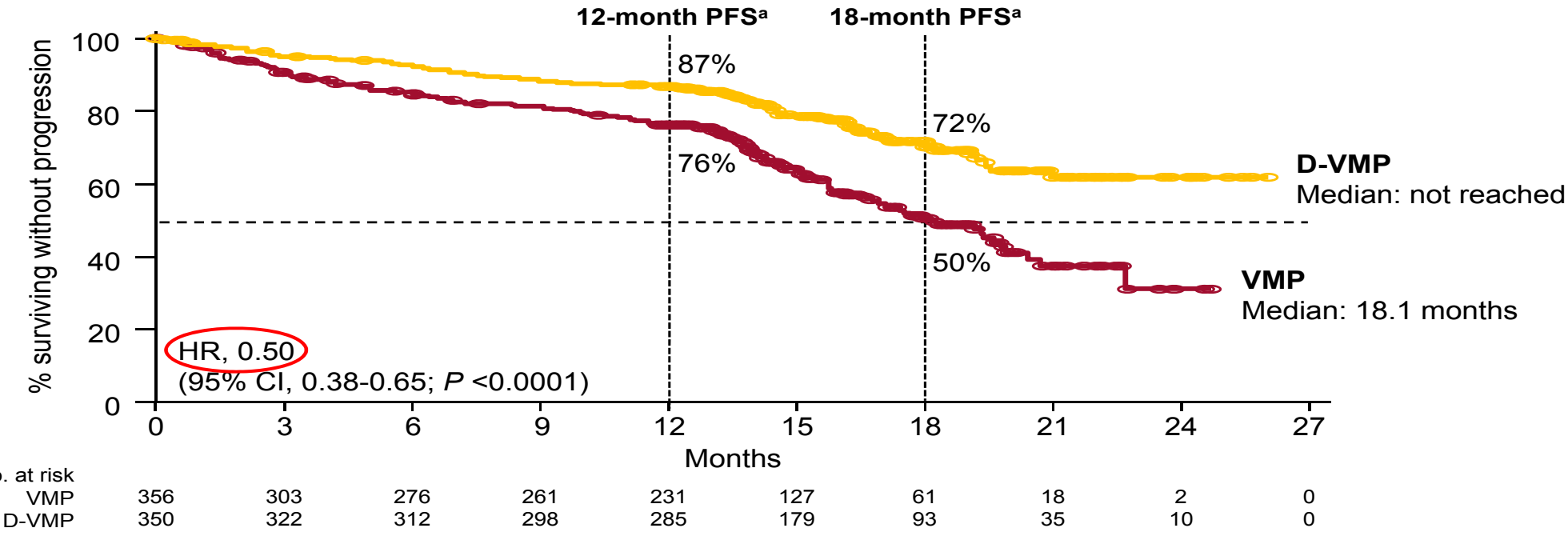
Palisi M, et al. Poster presentation at ASCO 2017. Abstract 8025.

Phase 3 Randomized Study of Daratumumab Plus Bortezomib, Melphalan, and Prednisone (D-VMP) Versus Bortezomib, Melphalan, and Prednisone (VMP) in Newly Diagnosed Multiple Myeloma (NDMM) Patients (Pts) Ineligible for Transplant (ALCYONE).

María-Victoria Mateos, Meletios A. Dimopoulos, Michele Cavo,3 Kenshi Suzuki,4 Andrzej Jakubowiak,5 Stefan Knop,6 Chantal Doyen,7 Paulo Lucio,8 Zsolt Nagy,9 Polina Kaplan,10 Ludek Pour,11 Mark Cook,12 Sebastian Grosicki,13 Andre Crepaldi,14 Anna Marina Liberati,15 Philip Campbell,16 Tatiana Shelekhova,17 Sung-Soo Yoon,18 Genadi Iosava,19 Tomoaki Fujisaki,20 Mamta Garg,21 Christopher Chiu,22 Jianping Wang,23 Robin Carson,22 Wendy Crist,22 William Deraedt,24 Huong Nguyen,23 Ming Qi,22 Jesus San-Miguel25

Efficacy: PFS

- Median (range) follow-up: 16.5 (0.1-28.1) months

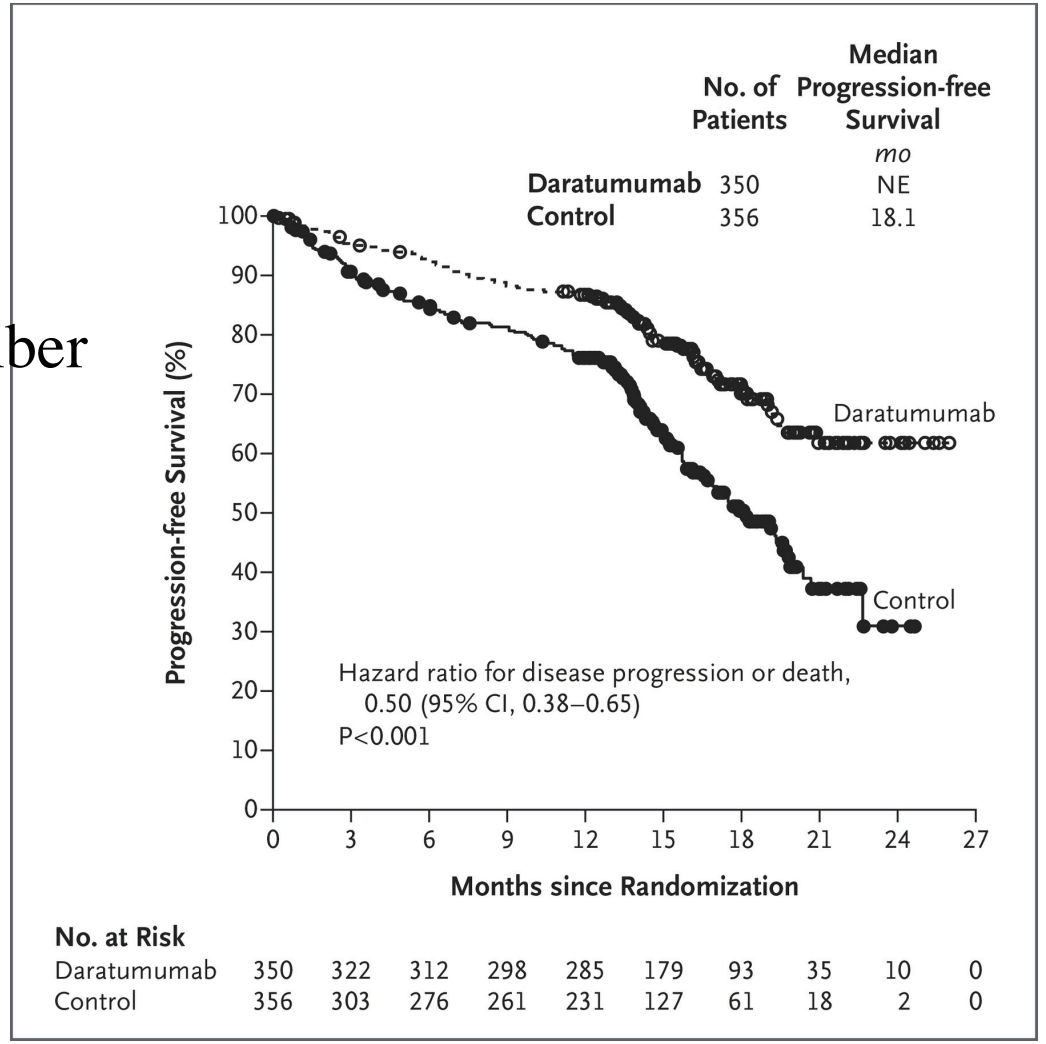


50% reduction in the risk of progression or death in patients receiving D-VMP

HR, hazard ratio; CI, confidence interval.
[a]Kaplan-Meier estimate.

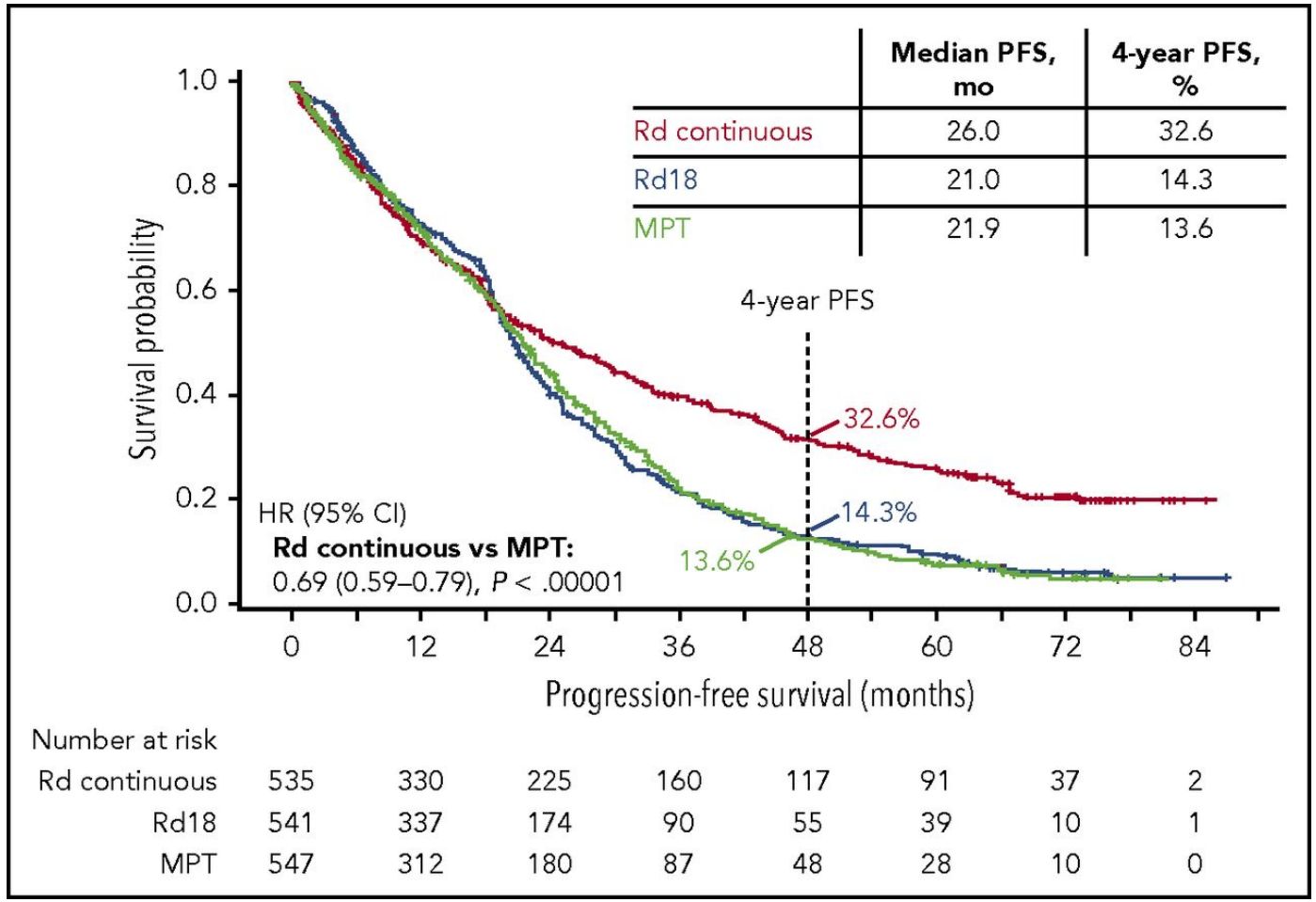
MPV vs DaraMPV

Godkänt av EMA 3 september

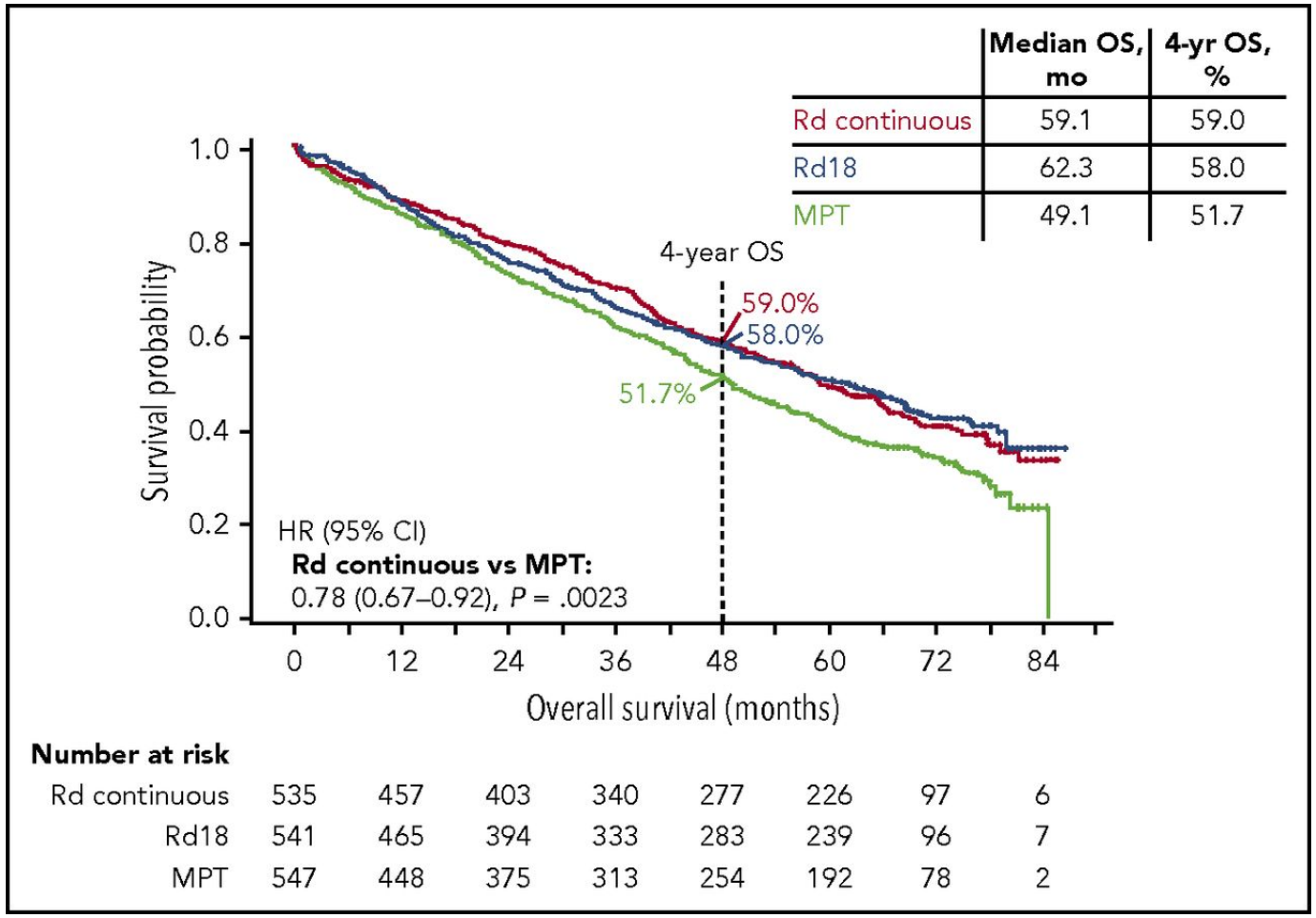


Mateos et al N Engl J Med 2018; 378:518-528
DOI: 10.1056/NEJMoa1714678

FIRST-studien MPT vs RD18 vs RD ; PFS



FIRST-studien MPT vs RD18 vs RD ; OS



Vad gör vi med all data?

- Stor mängd studier
- Sällan man jämför behandlingsregimer mot varandra i helt rättvisa jämförelser

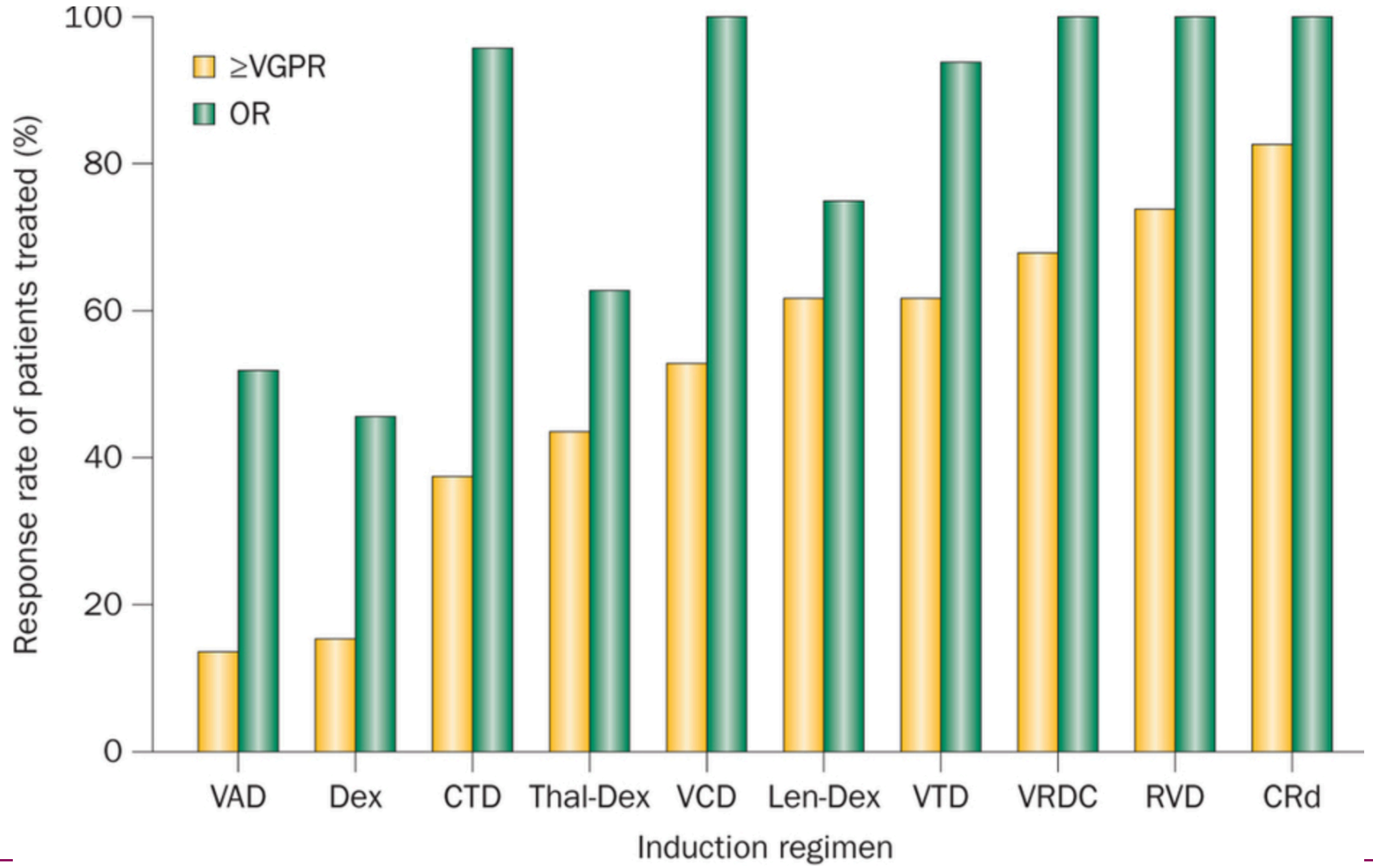
Vad gör vi med all data?

- Tredrogsregimer är bättre än tvådrogsregimer och att blanda fyra läkemedel är nog ännu bättre.

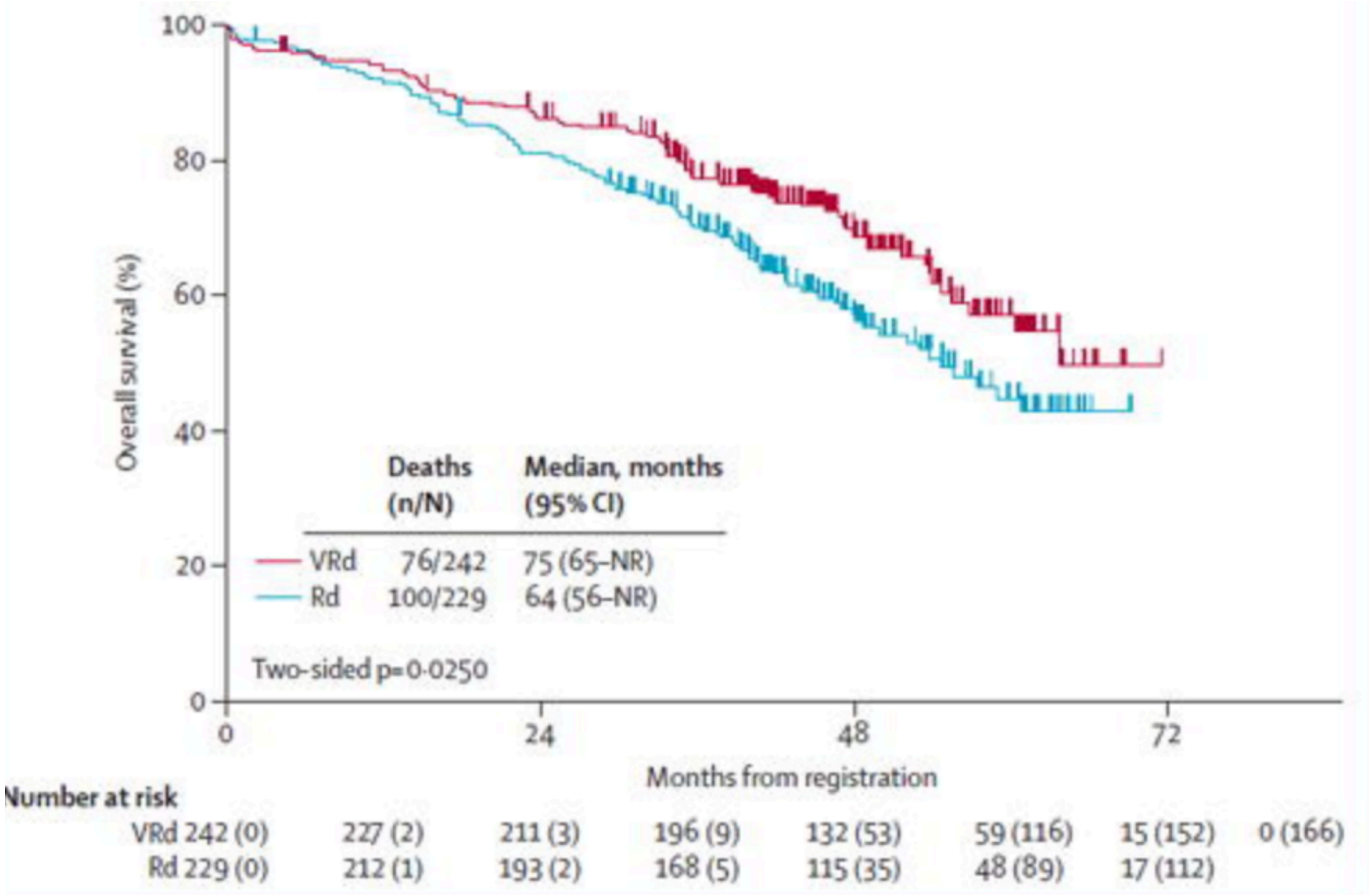
- Alla patienter tål inte för tuff behandling. Man måste tänka på biverkningar.

- Kostnadsaspekten!

Induction Treatment



VRD vs RD

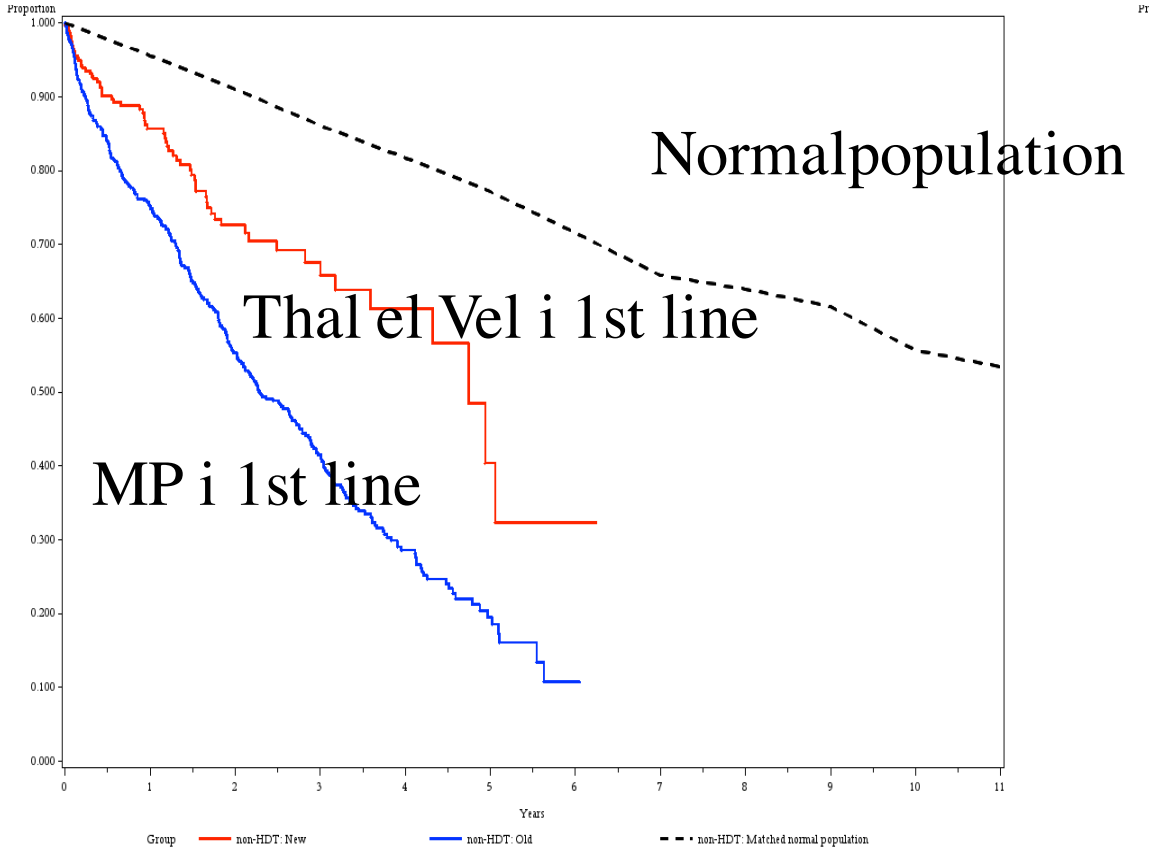


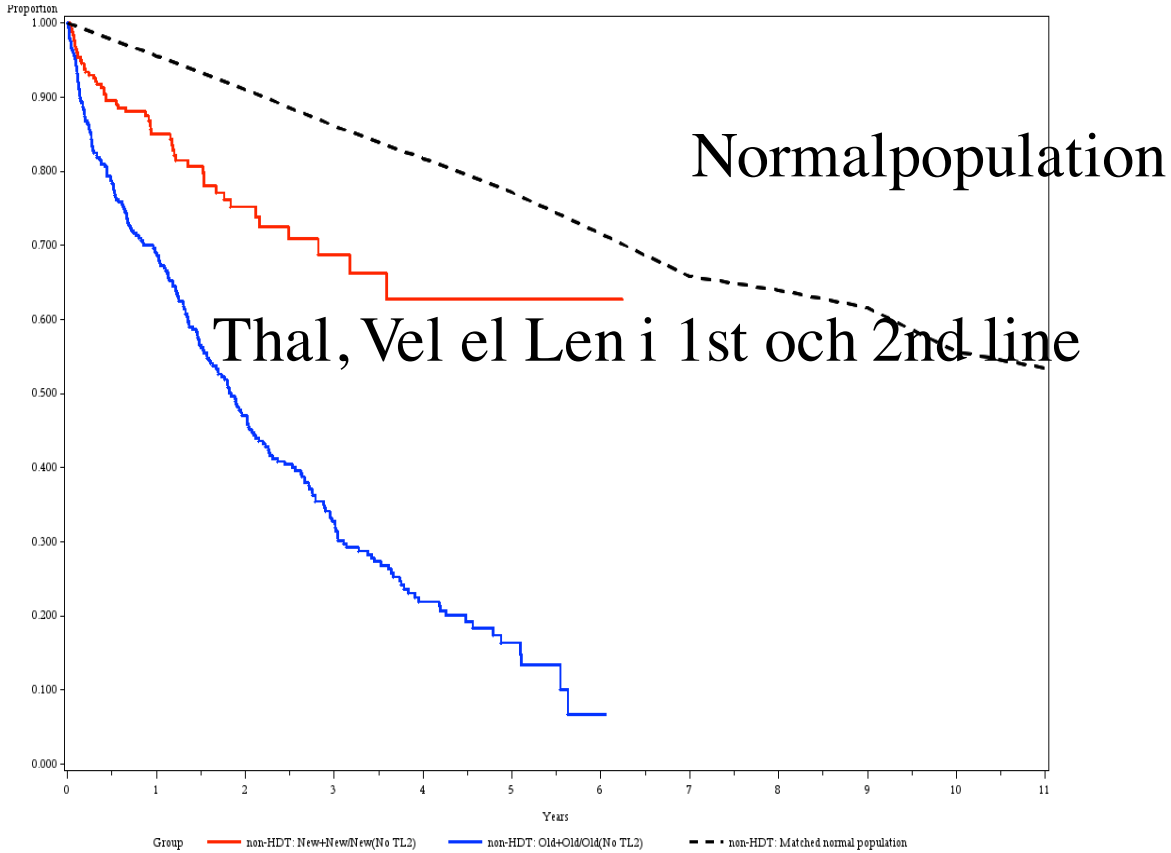
Durie et al Lancet. 2017 Feb 4; 389(10068): 519–527.

Får det någon effekt?

Ja; överlevnaden ökar inte bara i studier utan också i verkligheten

OS non-HDT

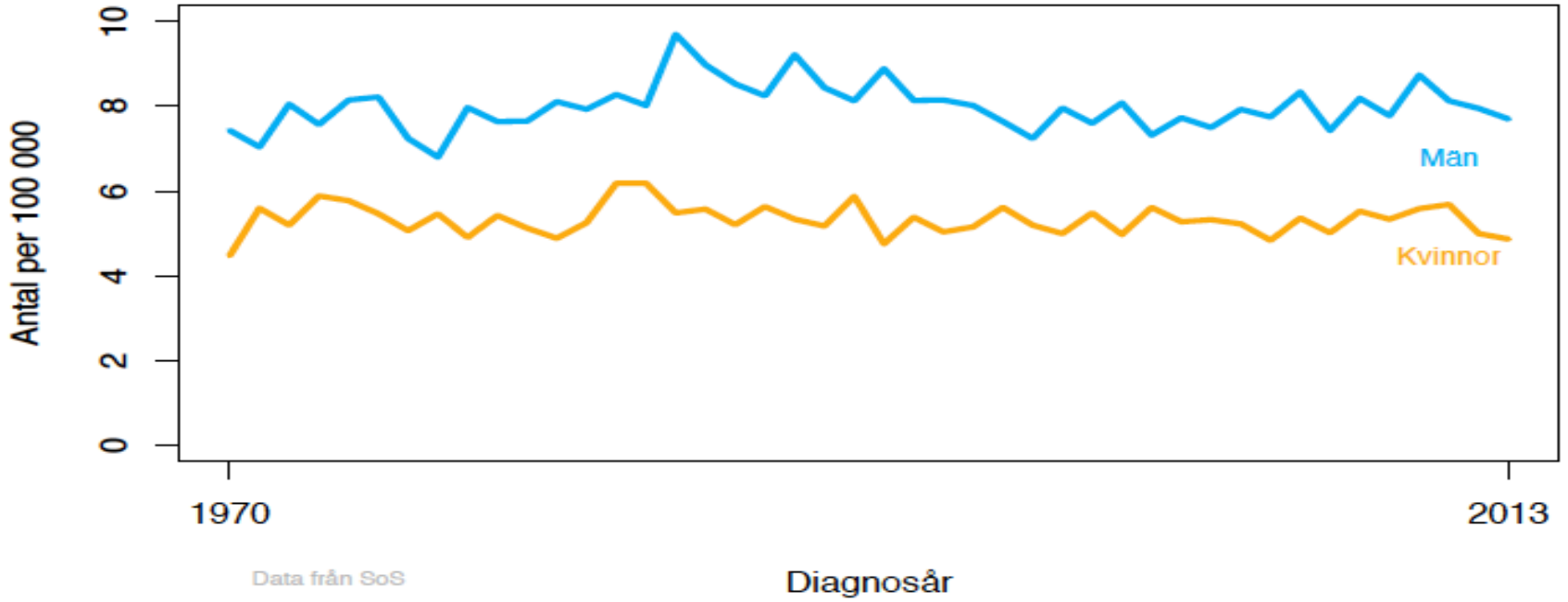

Proportion
1.000
0.900
0.800
0.700
0.600
0.500
0.400
0.300
0.200
0.100
0.000
0
1
2
3
4
5
6
7
8
9
10
11
Years
Group
non-HDT: New
non-HDT: Old
non-HDT: Matched normal population
Normalpopulation
Thal el Vel i 1st line
MP i 1st line


Proportion
1.000
0.900
0.800
0.700
0.600
0.500
0.400
0.300
0.200
0.100
0.000
0
1
2
3
4
5
6
7
8
9
10
11
Years
Group
non-HDT: New+New/New(No TL2)
non-HDT: Old+Old/Old(No TL2)
non-HDT: Matched normal population
Normalpopulation
Thal, Vel el Len i 1st och 2nd line

OS

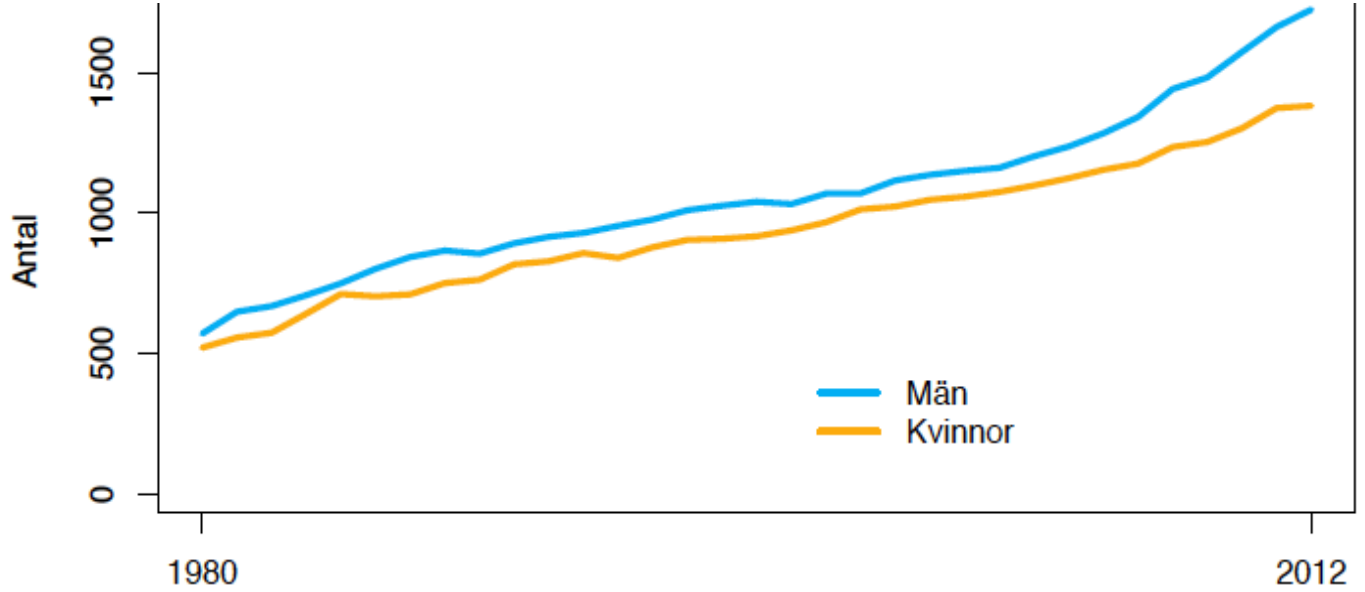
	Median (month)	
HDT digan. 2000-2005	84,2	
HDT diagn. 2006-2010	NR	p=0,6907

Incidens



Data från SoS

Prevalens



Data från NORDCAN

Data från SoS