MYELOME MULTIPLE

ACTUALISATIONS THERAPEUTIQUES

Dr Luc Montfort

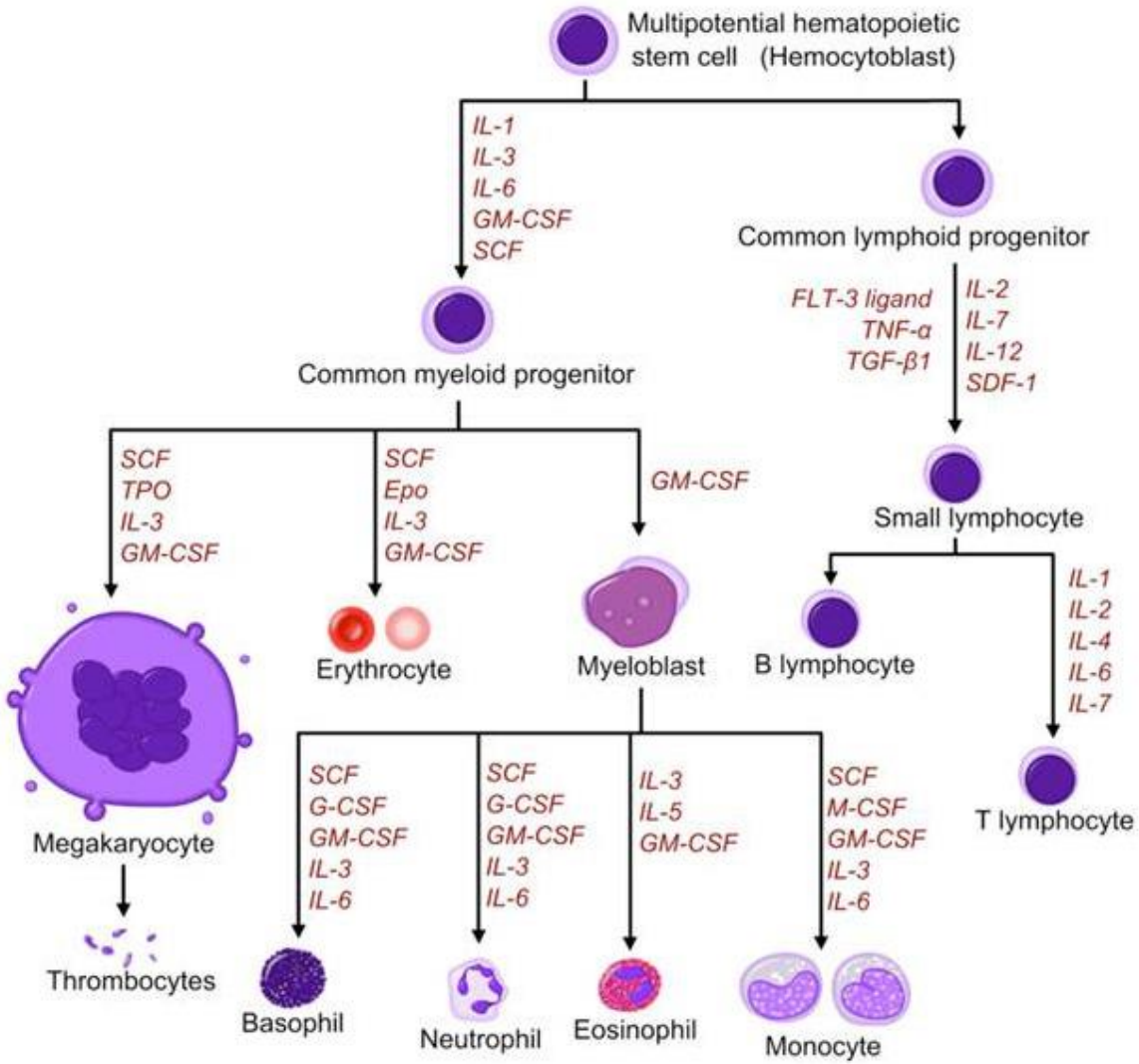
PLAN

- Introduction
- Le myélome multiple
- Les traitements actuels
- La rechute
- Les traitements innovants
- Conclusions

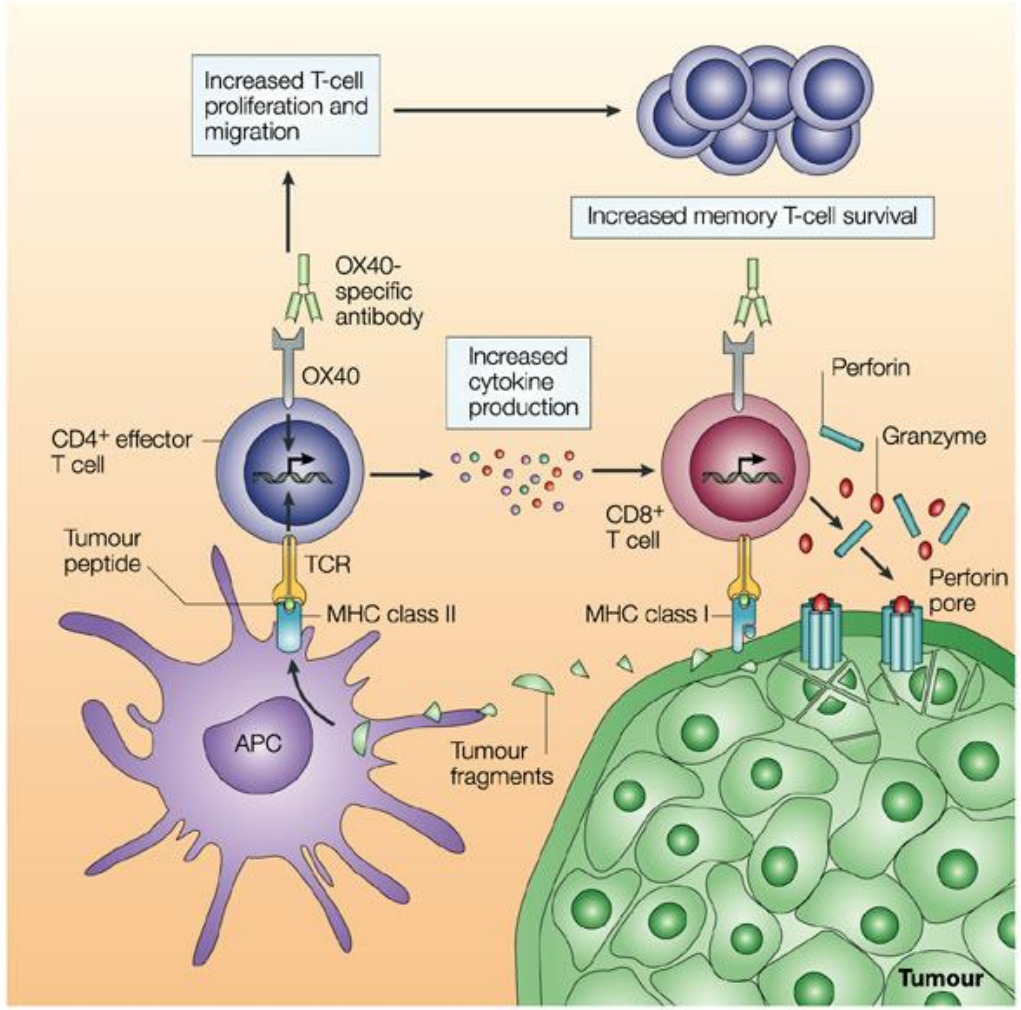
INTRODUCTION

- physiologie de l’hématopoïèse et de la lymphopoïèse
- définition
- physiopathologie du myélome
- définition des entités cliniques

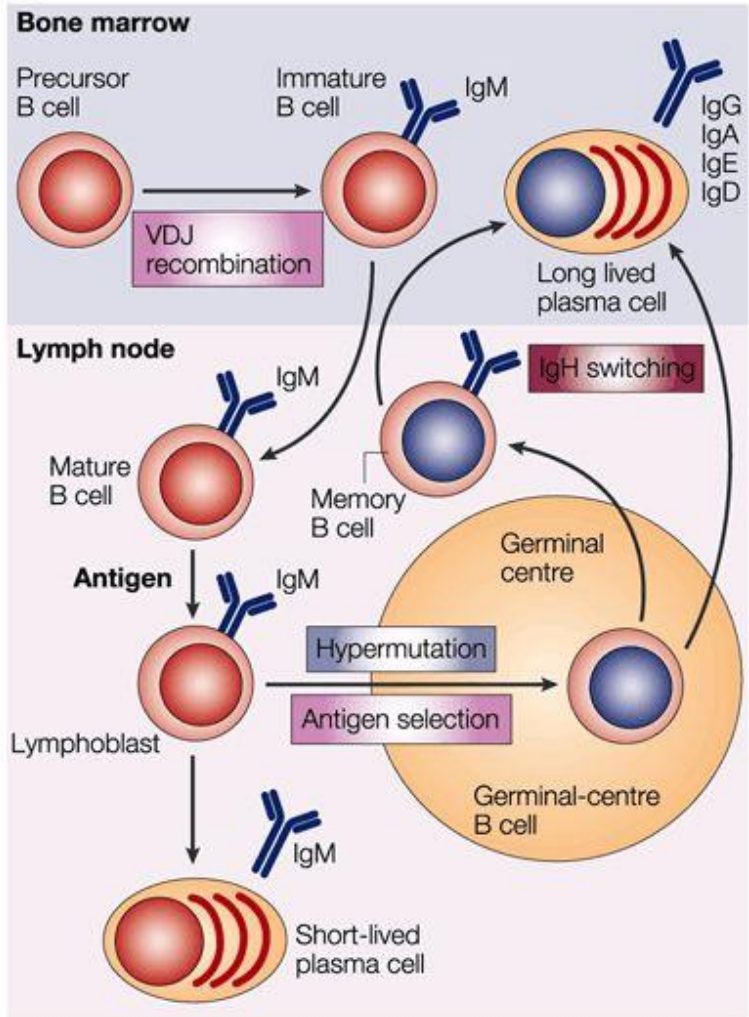
HEMATOPOÏESE



LYMPHOPOÏESE T



LYMPHOPOIESE B



Nature Reviews | Cancer

LYMPHOPOÏESE

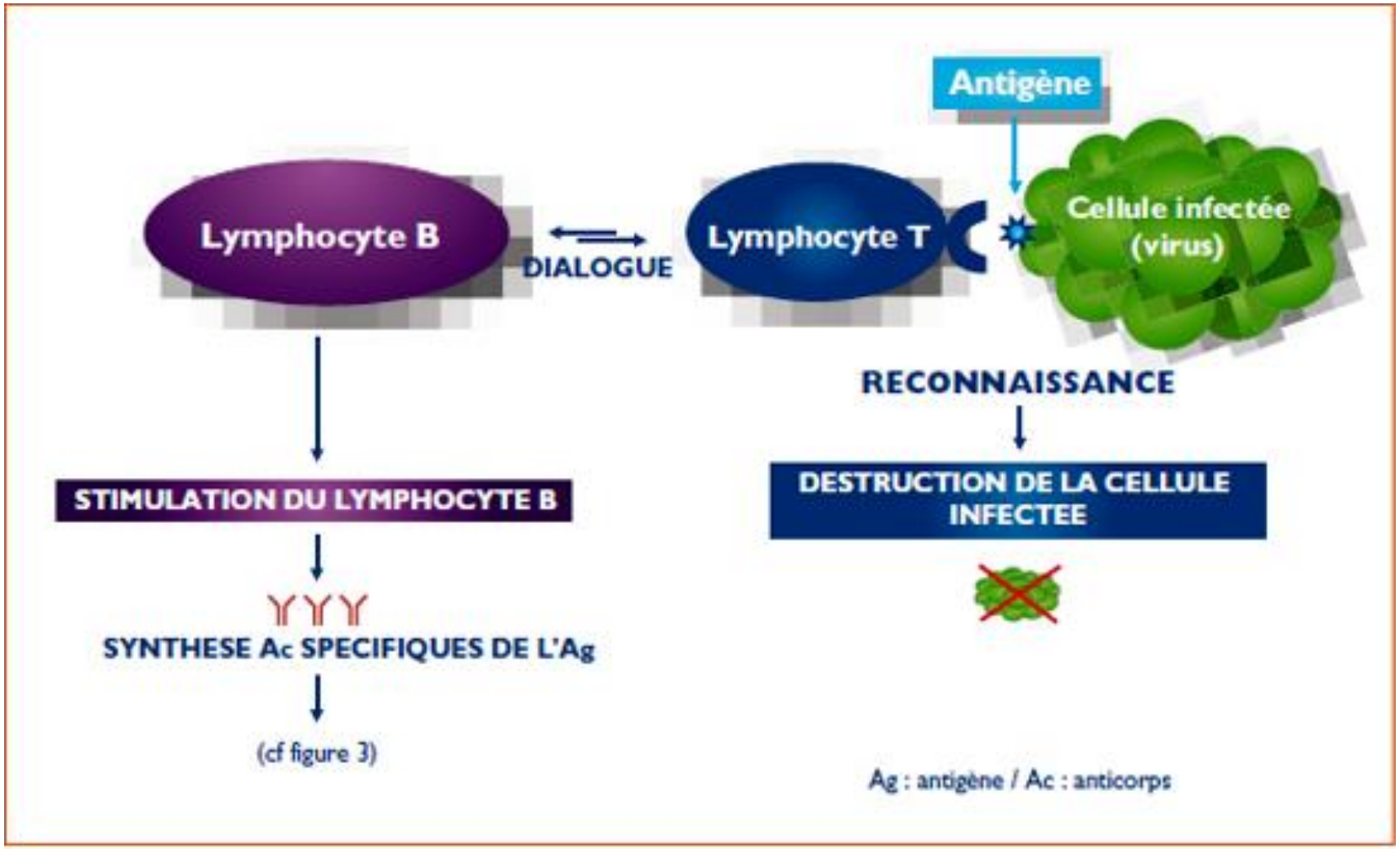
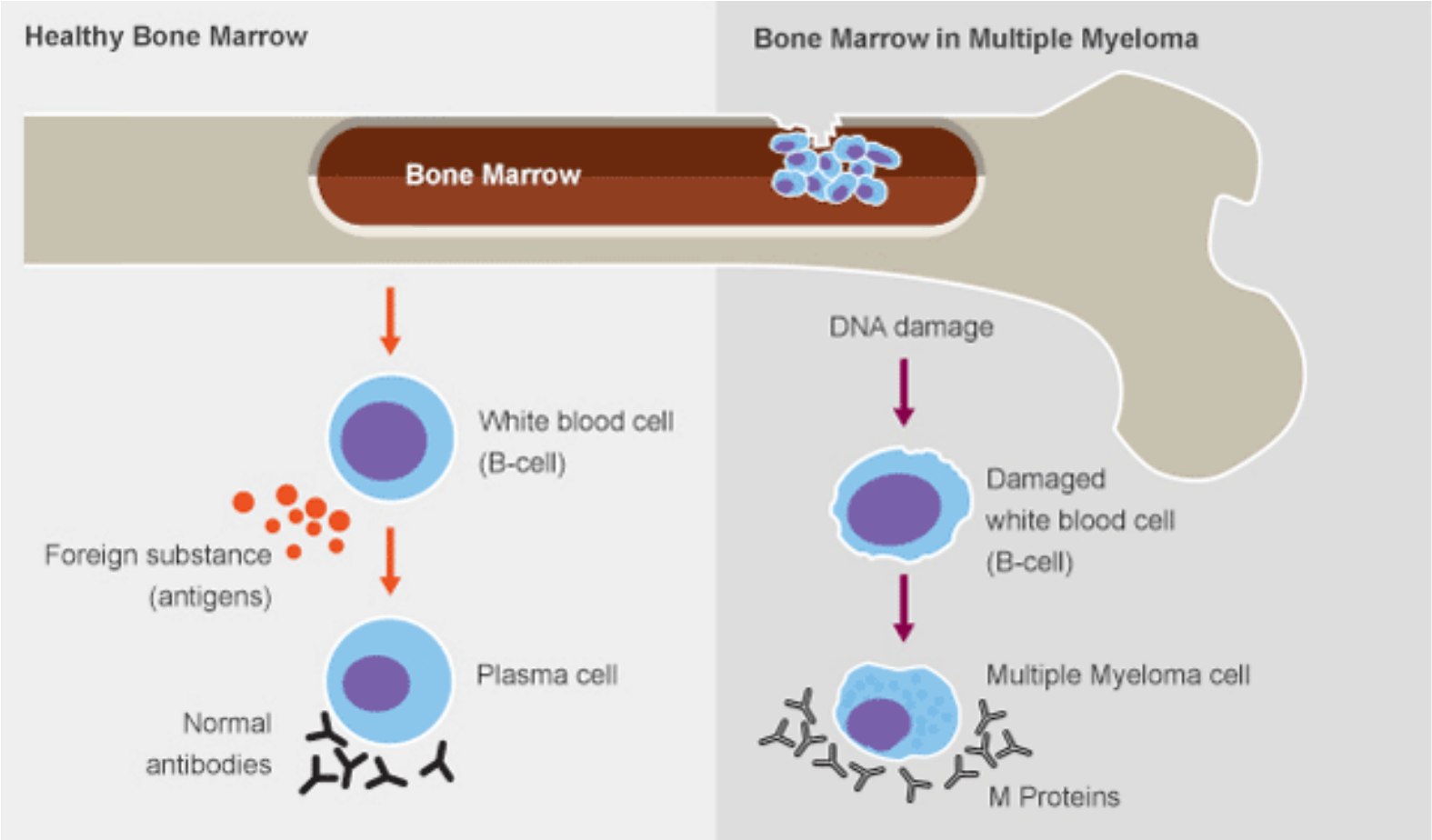
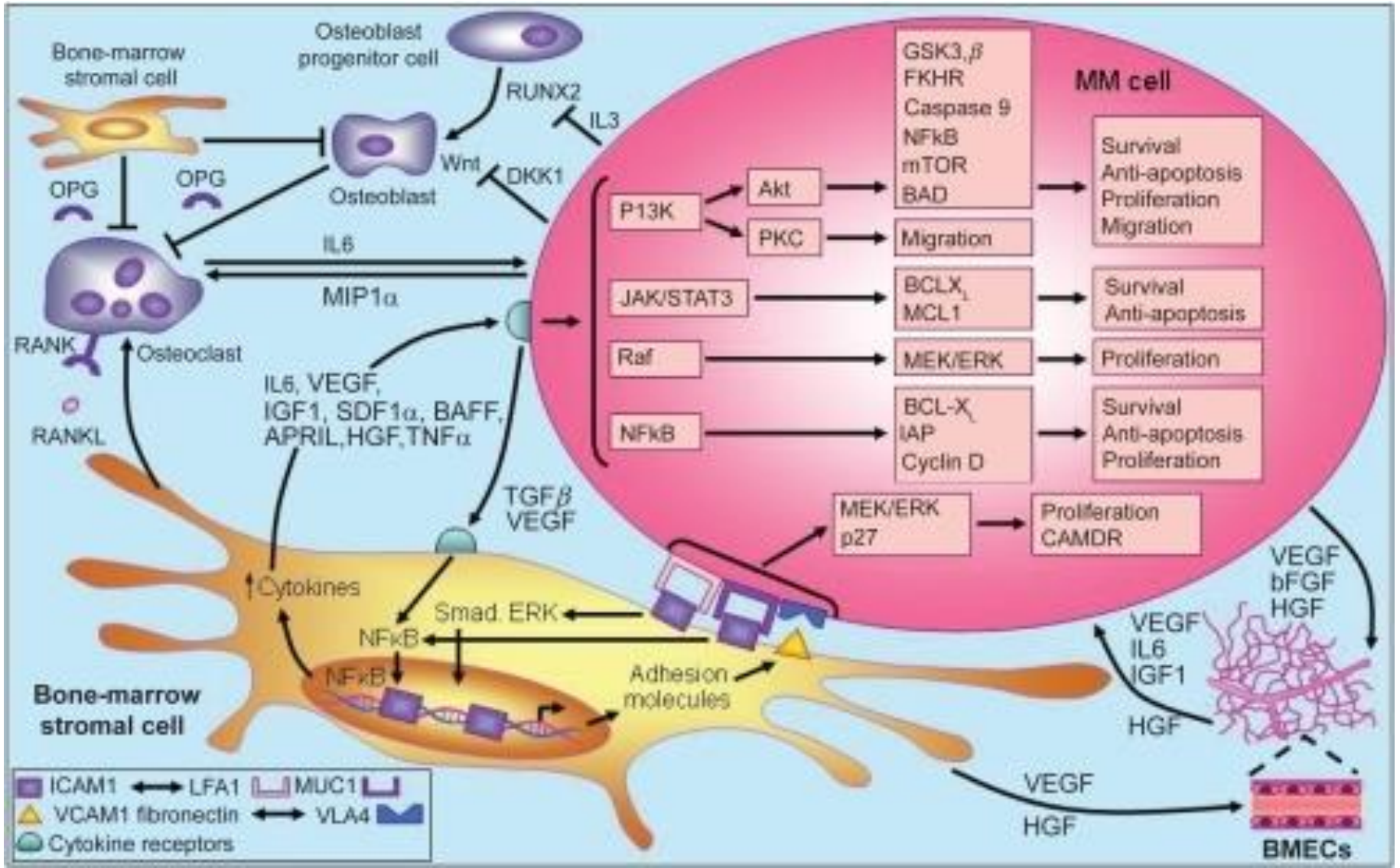


Figure 2 : Exemple d'actions des lymphocytes T

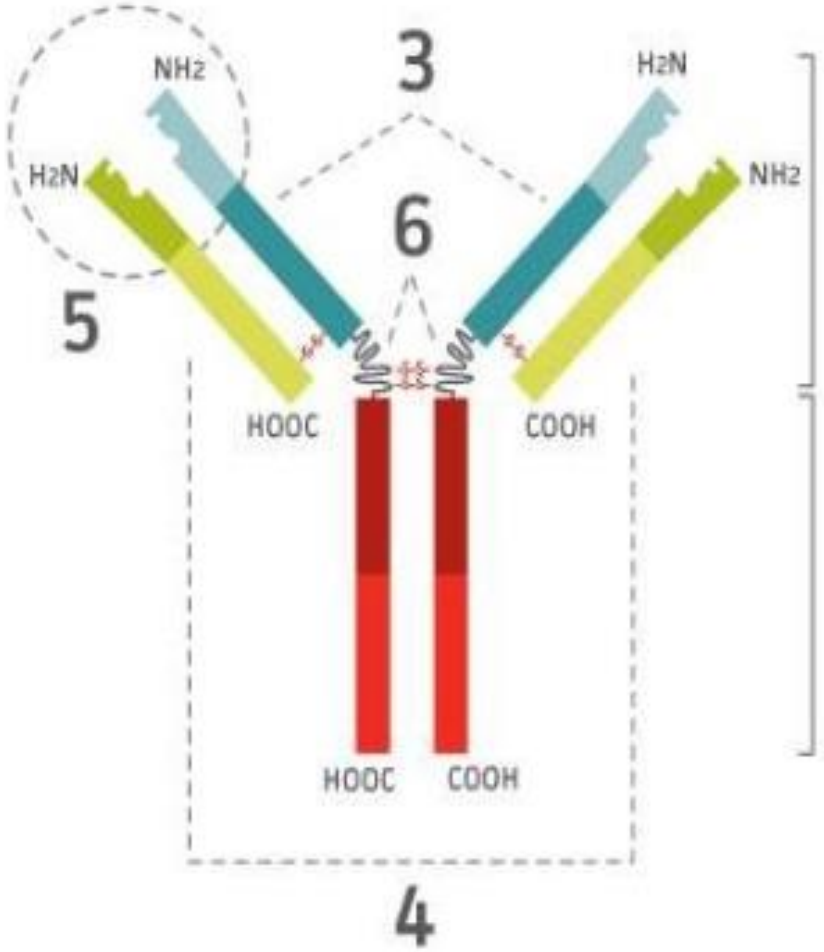
DEFINITION


Healthy Bone Marrow
Bone Marrow in Multiple Myeloma
Bone Marrow
White blood cell
(B-cell)
Foreign substance
(antigens)
Plasma cell
Normal
antibodies
DNA damage
Damaged
white blood cell
(B-cell)
Multiple Myeloma cell
M Proteins

PHYSIOPATHOLOGIE



Immunoglobulin structure



1 Fab region

2 Fc region

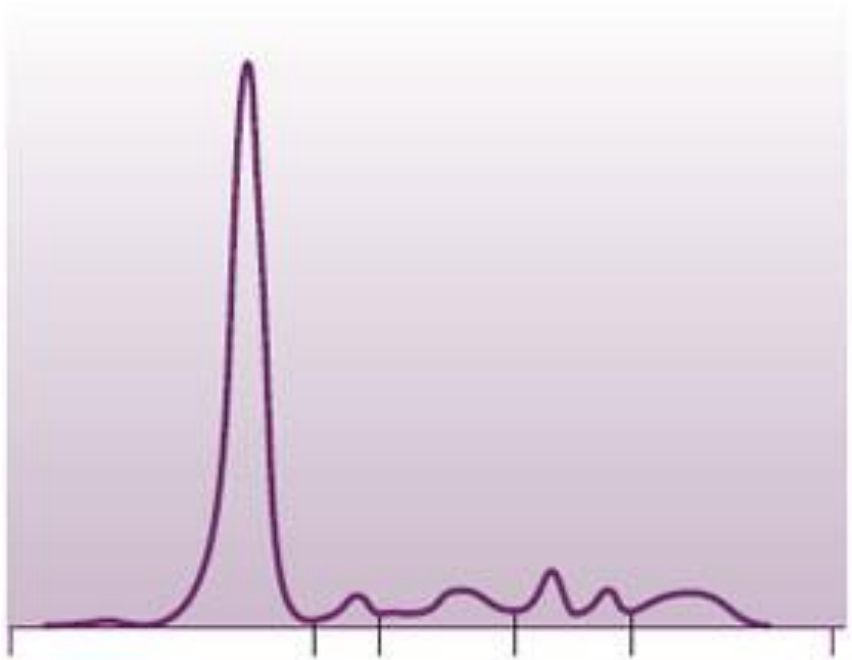
3 Heavy chain with one variable (V_H) domain followed by a constant domain (C_H1), a hinge region, and two more constant (C_H2 and C_H3) domains.

4 Light chain with one variable (V_L) and one constant (C_L) domain

5 Antigen binding site (paratope)

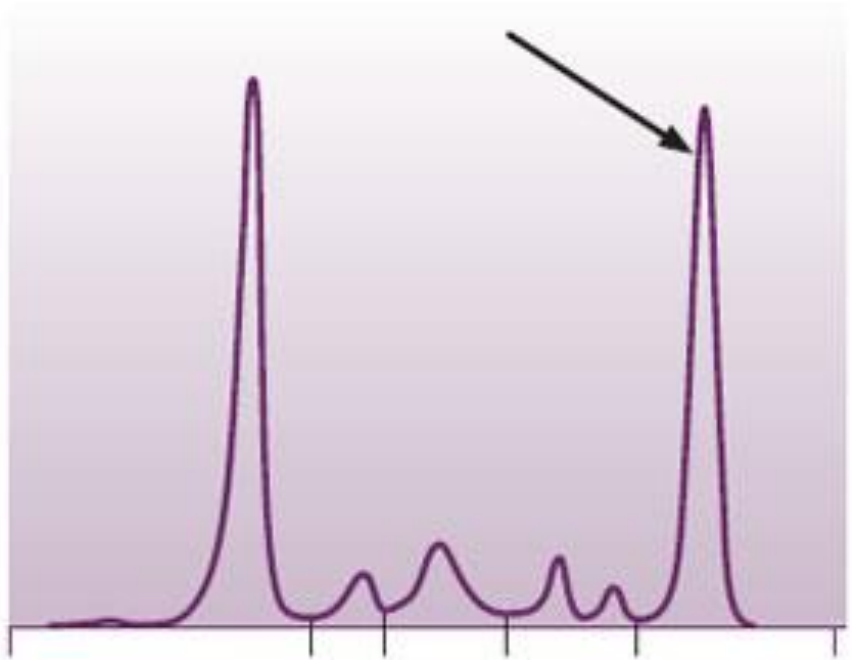
6 Hinge regions

PIC MONOCLONAL



A/G 2.32
T.P. : 7

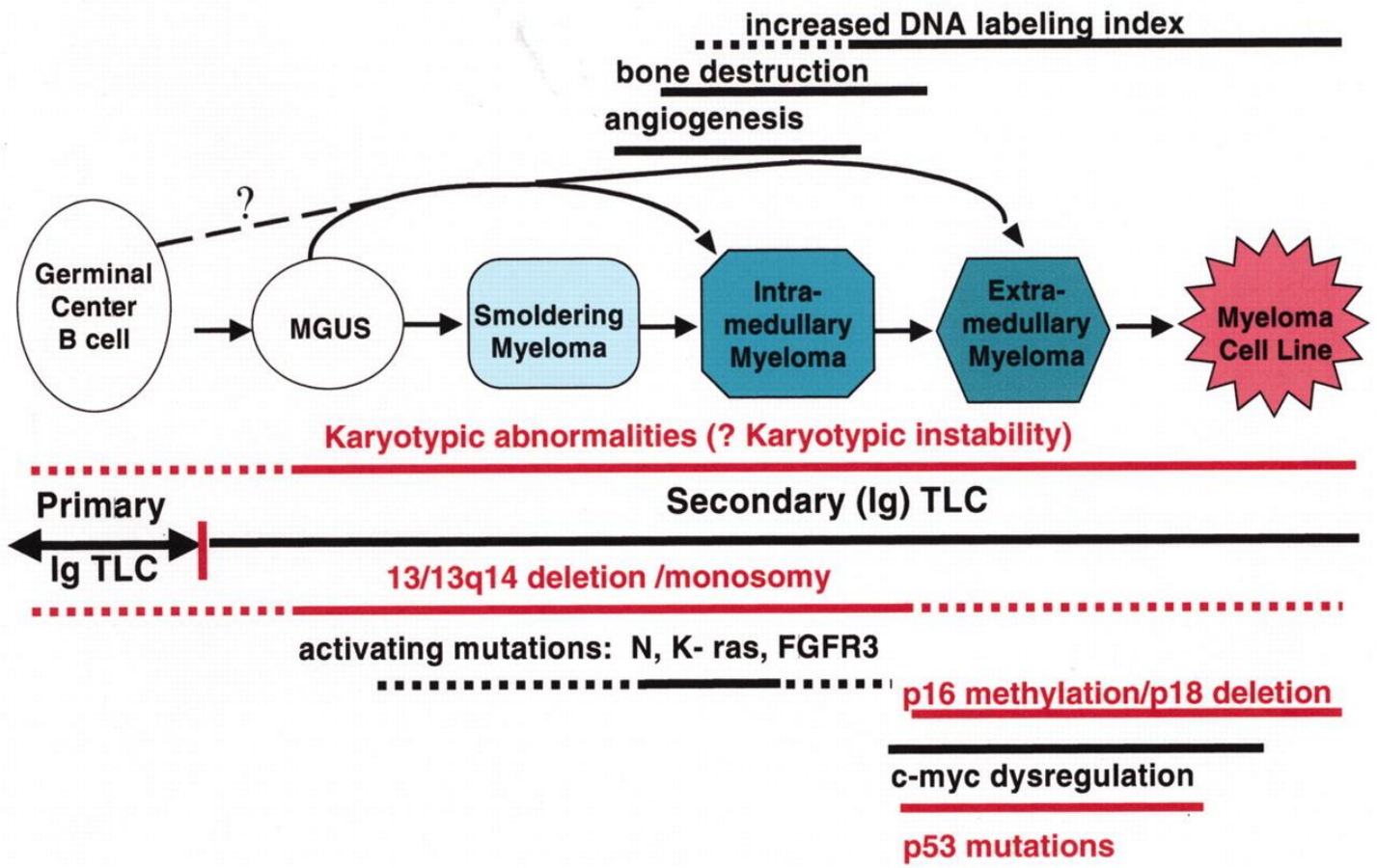
Fractions	%	Ref. %	g/dl	Ref. g/dl
Albumin	69.9	52.9–66.9	4.9	3.7–4.9
Alpha	3.5	3.0–5.8	0.2	0.2–0.4
Alpha 2	8.8	7.5–13.4	0.6	0.5–1.0
Beta	9.3	8.5–13.7	0.7	0.6–1.0
Gamma	8.5	8.8–19.2	0.6	0.6–1.4



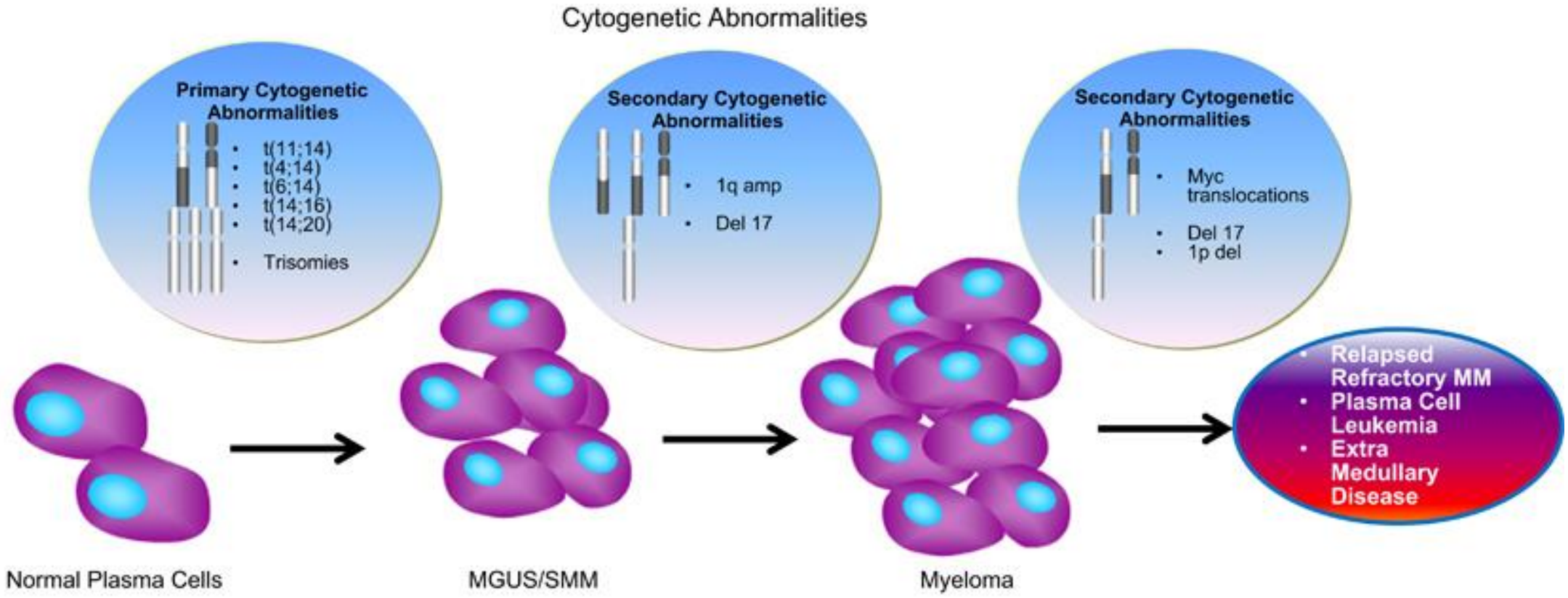
A/G 0.67
T.P. : 8.2

Fractions	%	Ref. %	g/dl	Ref. g/dl
Albumin	40.2	52.9–66.9	3.3 L	3.7–4.9
Alpha	4.8	3.0–5.8	0.4	0.2–0.4
Alpha 2	11.0	7.5–13.4	0.9	0.5–0.9
Beta	7.8	8.5–13.7	0.6	0.6–1.0
Gamma	36.2	8.8–19.2	3.0 H	0.6–1.4

PHYSIOPATHOLOGIE



PHYSIOPATHOLOGIE

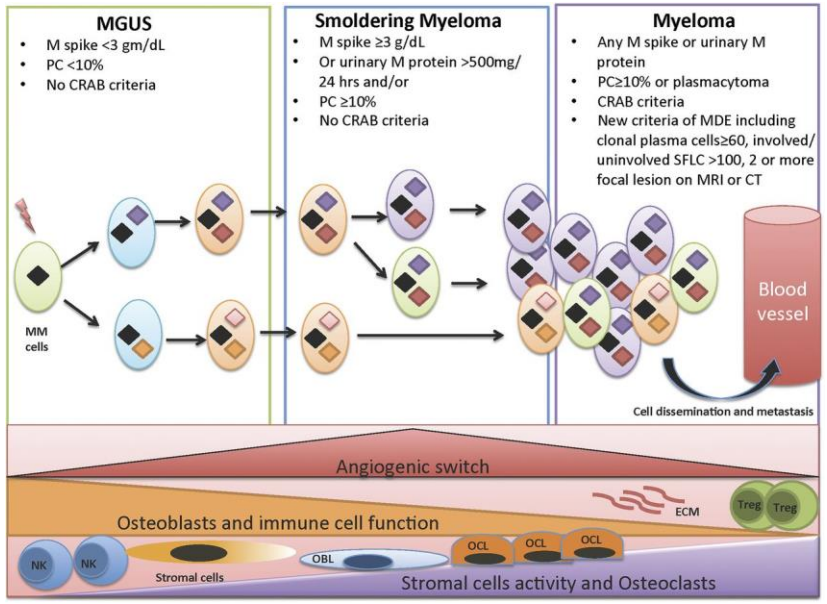


Trisomies, or any one IgH translocation, or combined trisomies and IgH translocations are associated with the establishment of the clone

Secondary Cytogenetic Abnormalities occur with progression; Del 17p, 1qamp, and t(4;14) associated with high risk of progression in SMM

Secondary Cytogenetic Abnormalities occur with progression; Del 17p, t(14;16) and t(14;20) associated with adverse prognosis in MM

ENTITES CLINIQUES



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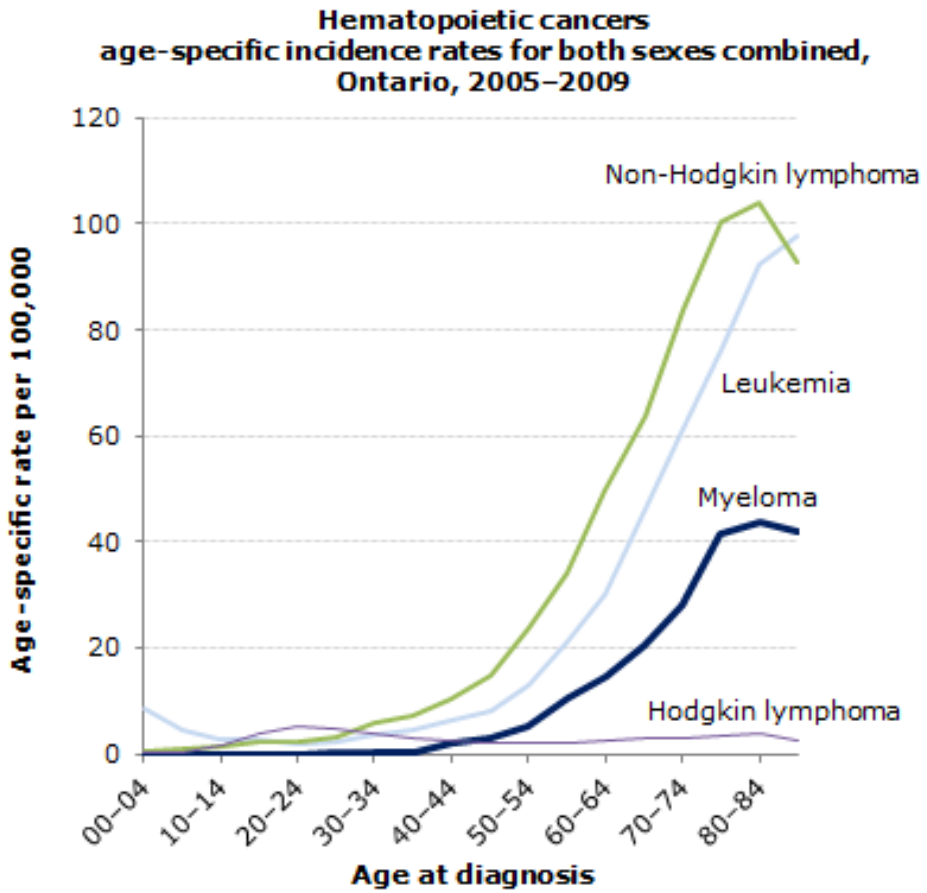
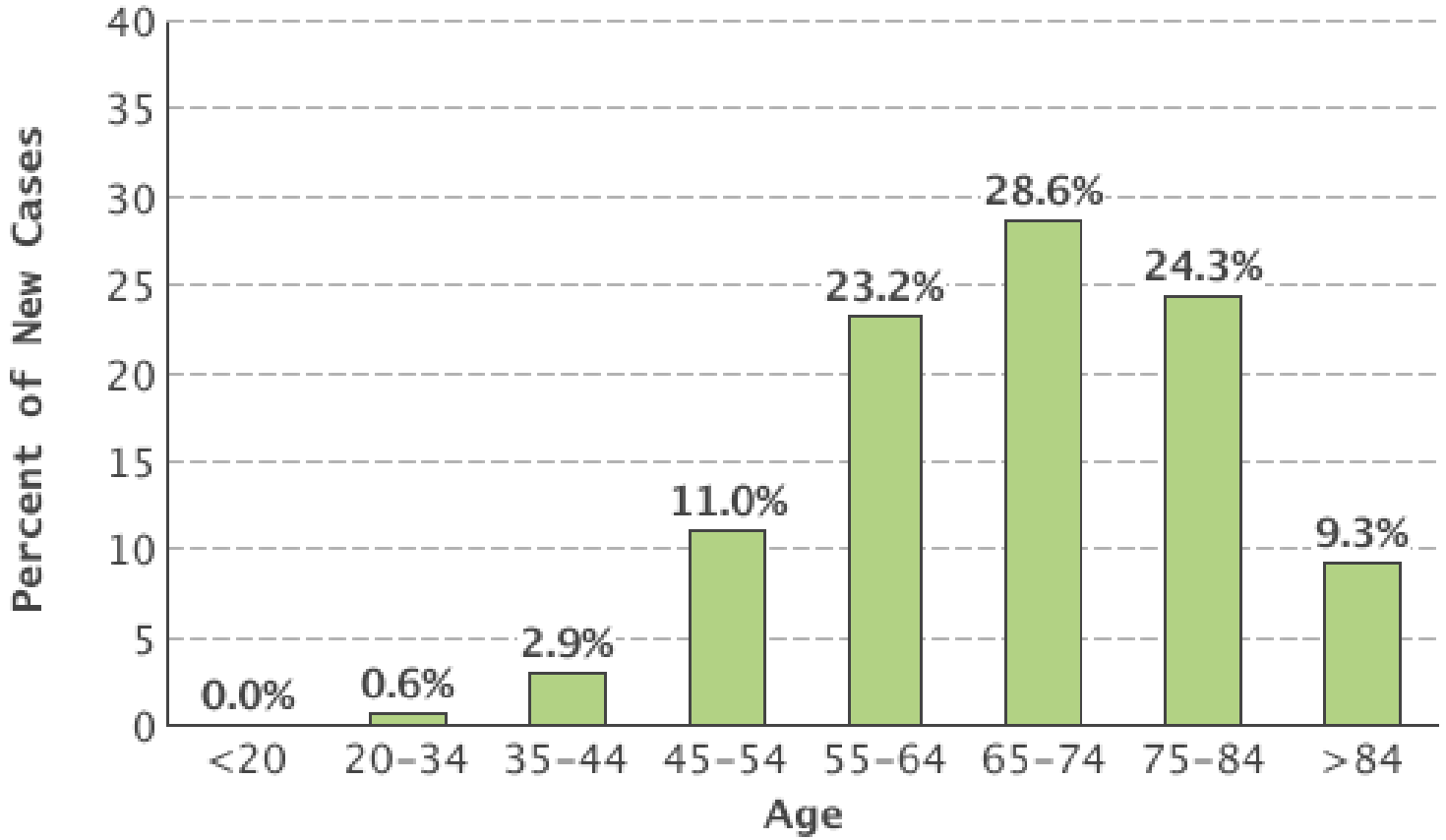
INCIDENCE

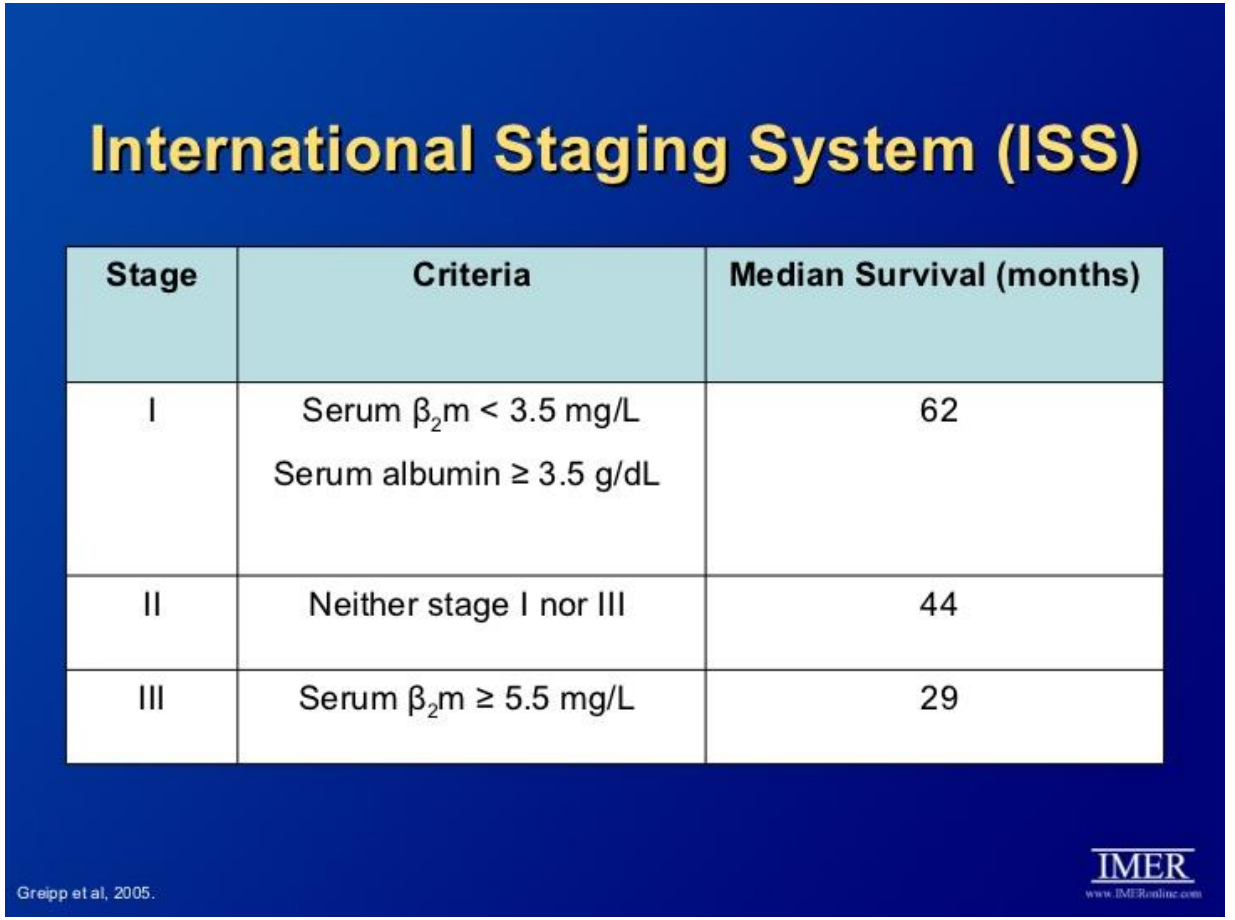


Source: Cancer Care Ontario (Ontario Cancer Registry, 2012)

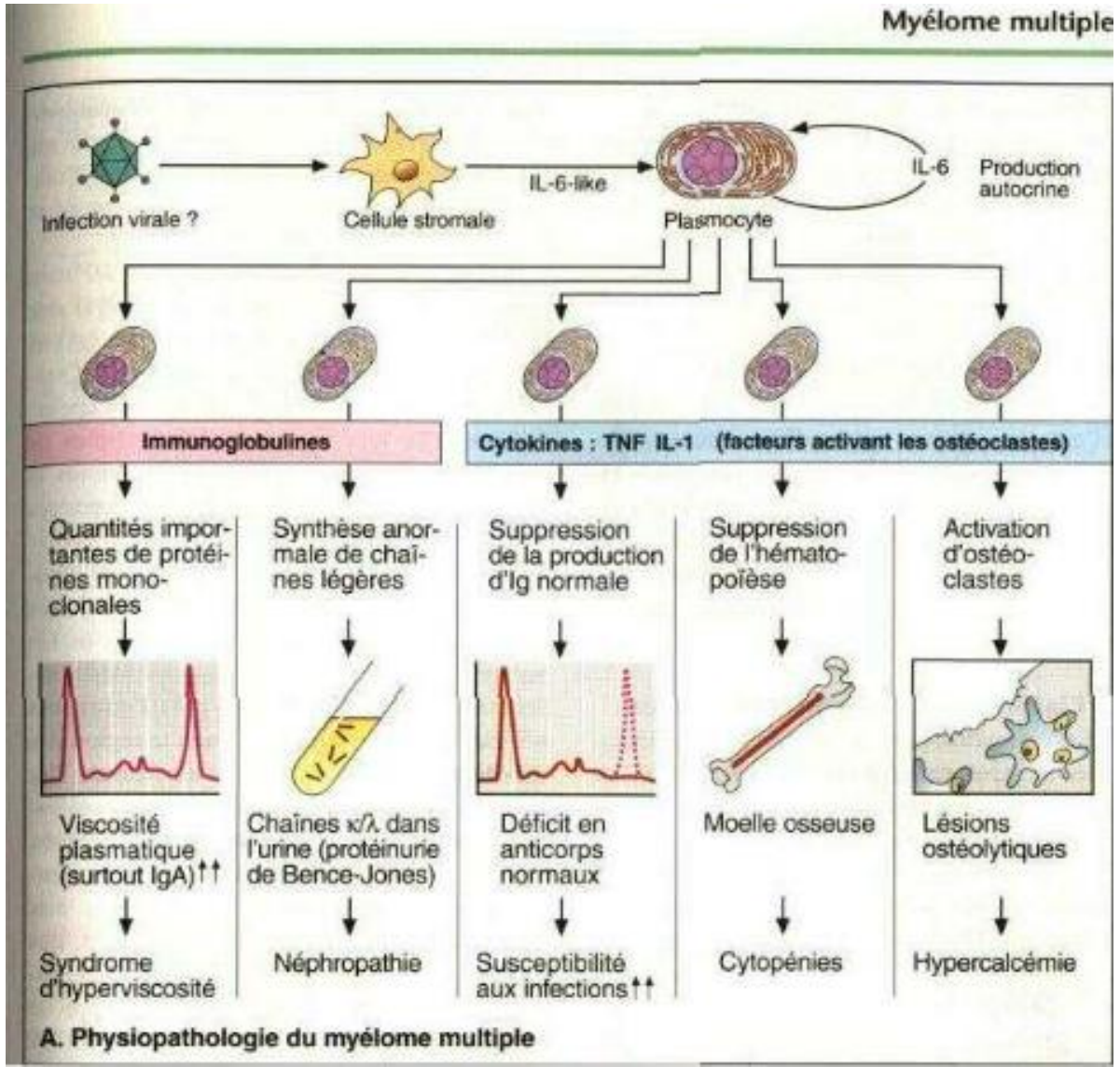
INCIDENCE


Percent of New Cases
40
35
30
25
20
15
10
5
0
0.0%
0.6%
2.9%
11.0%
23.2%
28.6%
24.3%
9.3%
<20
20–34
35–44
45–54
55–64
65–74
75–84
>84
Age

MYELOME MULTIPLE : PRONOSTIC



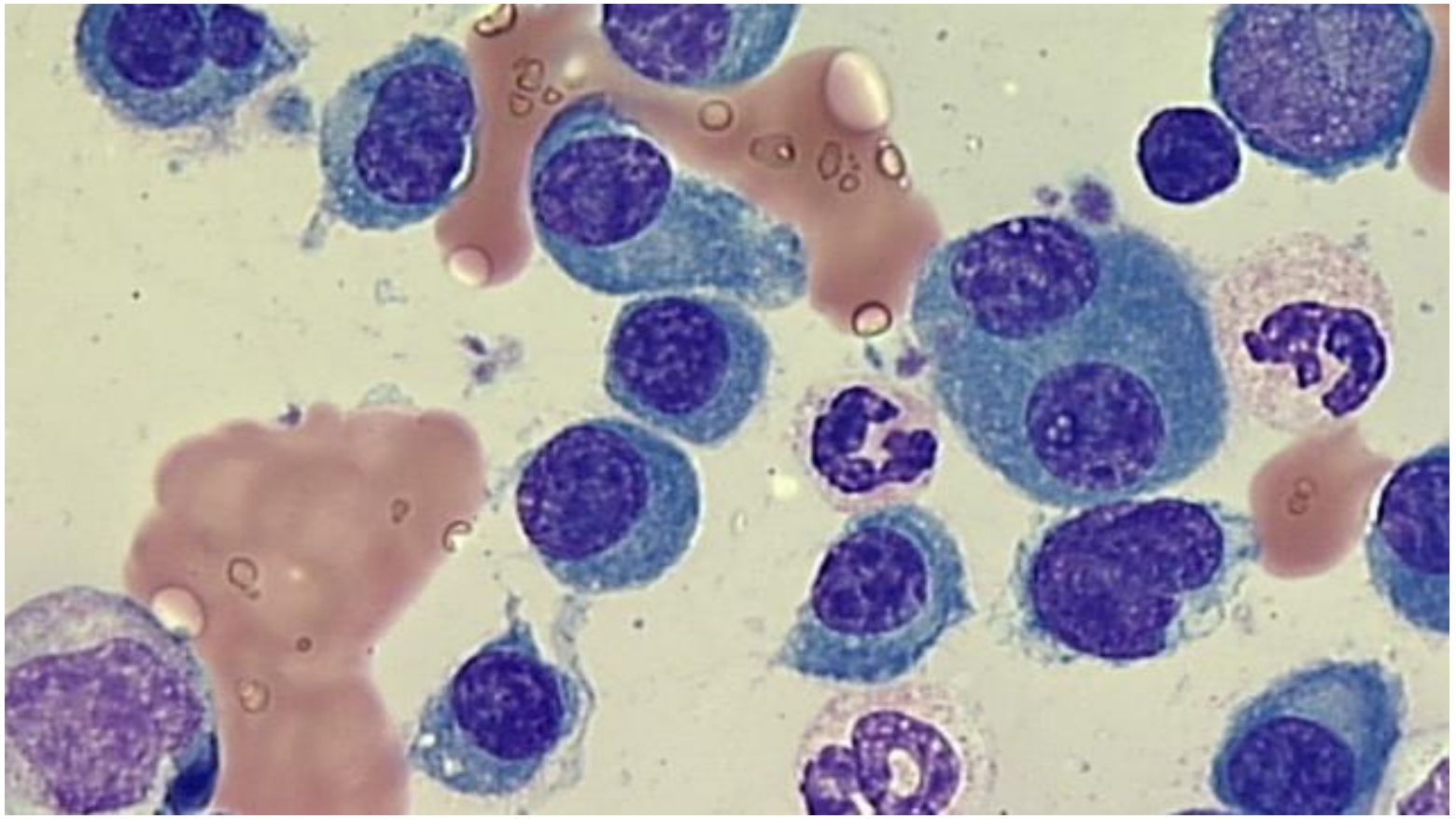
PHYSIOPATHOLOGIE

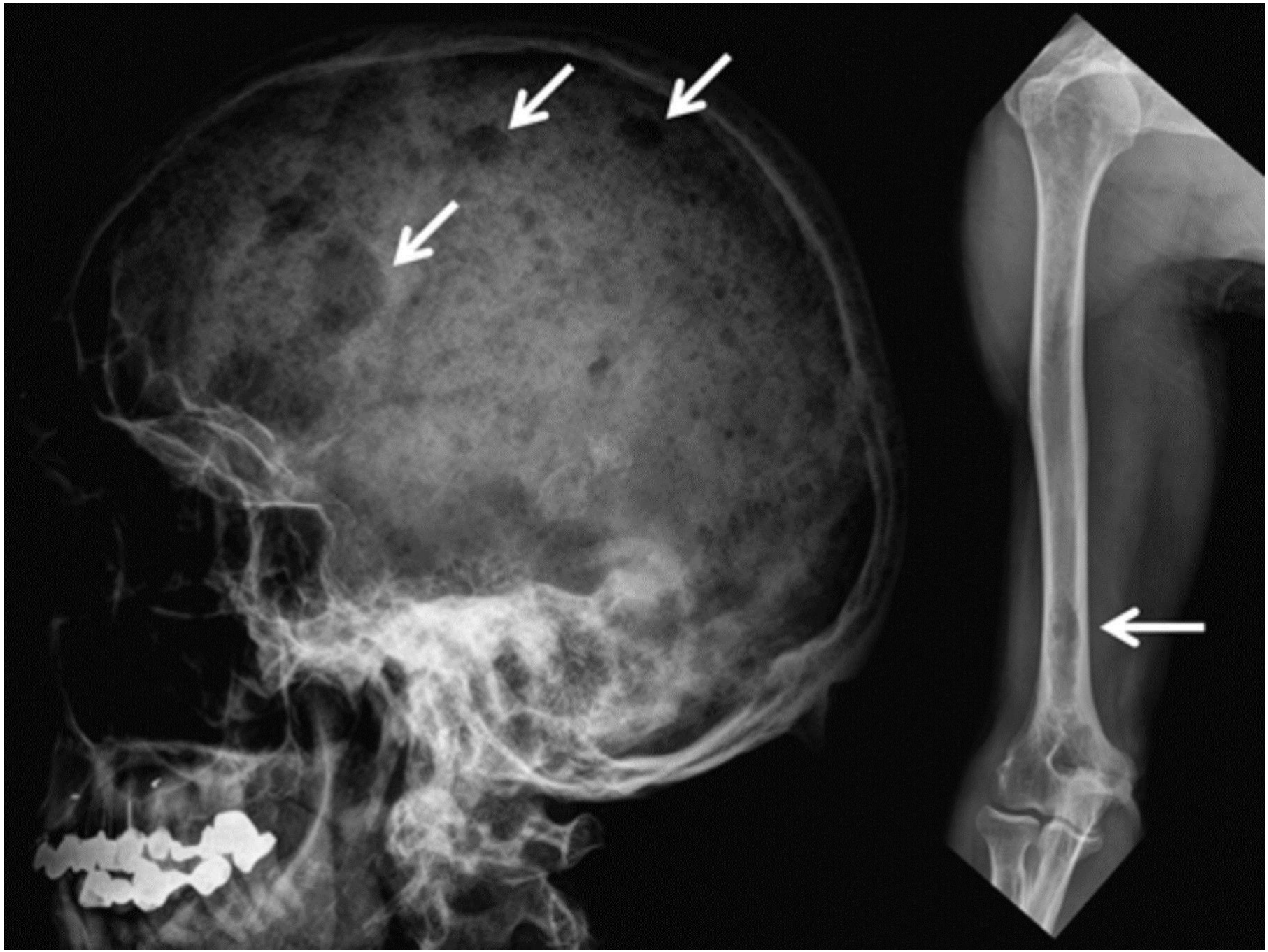


MYELOME MULTIPLE : DEFINITION

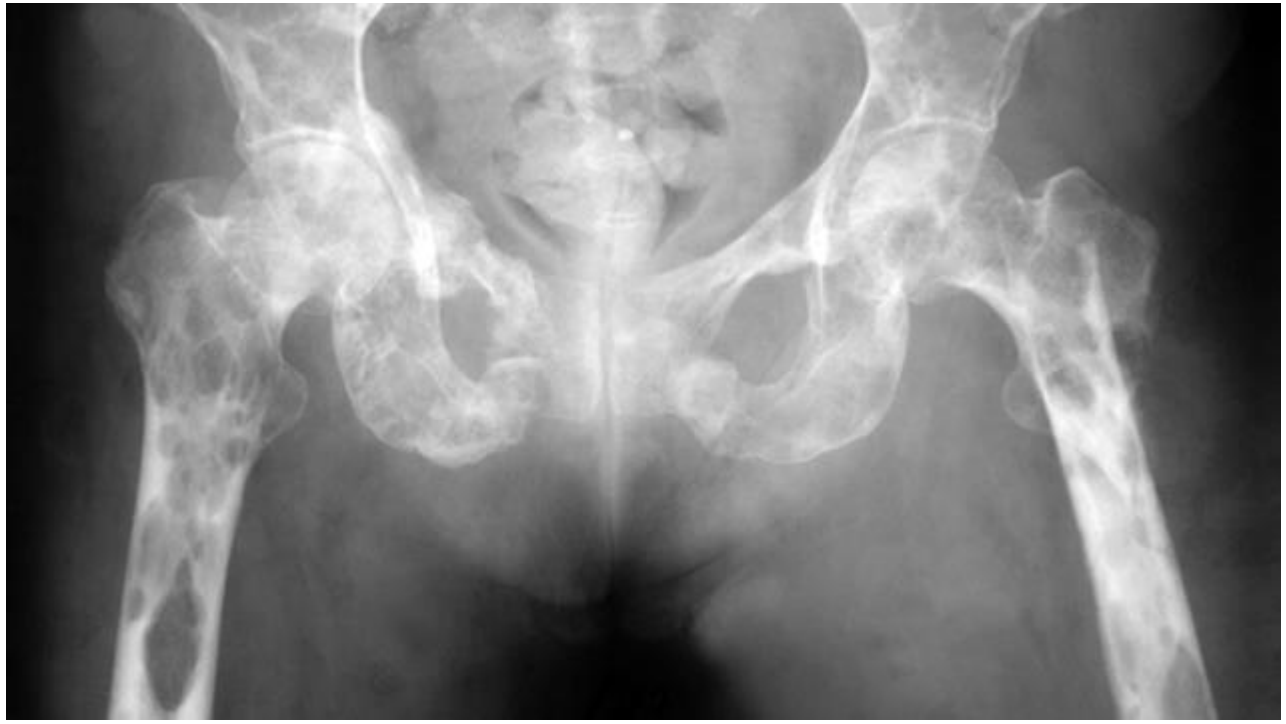
- Plasmocytose médullaire > 10 % ou biopsie osseuse ou extra médullaire diagnostique et
  - end organ damage
    - C : hypercalcémie
    - R : insuffisance rénale : cl créat < 40 ml/min
    - A : anémie : Hb < 10 gr/dl
    - B : atteinte osseuse
  - myeloma defining events
    - plasmocytose médullaire > 60 %
    - FLC ratio > 100 et free light chain > 100 mgr/l
    - > 1 lésion focale > 5 mm à la RMN

MYELOME : CYTOLOGIE





LESIONS OSSEUSES

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PLAN

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blood® flashback 1968

In 1958, Blokhin et al reported the first experience with sarcolysin (melphalan) in multiple myeloma, which was followed by several case reports. However, the dose, treatment duration, and definition of response remained to be established. This article by Alexanian et al represents a seminal contribution in myeloma history, describing the role of melphalan in a series of 82 patients. The study established (1) the current dose and schedule of melphalan, (2) the efficacy of therapy (49% responses, including recovery of anemia), and (3) the value of M-protein levels for assessment of response and disease activity. The median survival was 34 months from diagnosis and 42 months from symptoms, with a difference of more than 30 months between responders and nonresponders.

Alexanian R, Bergsagel DE, Migliore PJ, Vaughn WK, Howe CD. Melphalan therapy for plasma cell myeloma. *Blood*. 1968;31(1):1-10.

BLOOD *The Journal of Hematology*
JANUARY, 1968 Vol. XXXI, No. 1

Melphalan Therapy for Plasma Cell Myeloma

By Raymond Alexanian, Daniel E. Bergsagel, Philip J. Migliore, William K. Vaughn and Clifton D. Howe

UNTIL RECENTLY, chemotherapy for multiple myeloma has been disappointing. Synthesis of 3-{p-[bis-(2-chloroethyl)amino]phenyl}L-alanine (melphalan) by Bergel and Stock[1] in 1953 and of the DL-form (sarcolysin) by Larionov et al.[2] in 1955 was followed in 1958 by the application of sarcolysin in plasma cell myeloma by Blokhin et al.[3] Numerous investigators have since used melphalan for myeloma patients, with objective improvement in 15[4] to 85 per cent.[5] This varied response rate reflects differences in patient selection, assumed duration of adequate treatment trial, and criteria used for evaluation of response.

This report documents the incidence of objective improvement and survival time in 82 consecutive patients with plasma cell myeloma treated with melphalan* at one institution during a 7-year period. Certain disease parameters, particularly the level of serum and urine myeloma protein, were examined in detail before and after institution of therapy in order to identify those features that provided more precise criteria for assessing the incidence, degree, and duration of clinical response.

Methods of Study

All patients with plasma cell myeloma treated with melphalan at The University of Texas M. D. Anderson Hospital and Tumor Institute between June 1, 1959 and December 1,

From the Departments of Medicine and Pathology, The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas 77025.

This work was supported by Grant CA 03195, and in part by Grants CA 06939 and PH 43-64-917 from the United States Public Health Service.

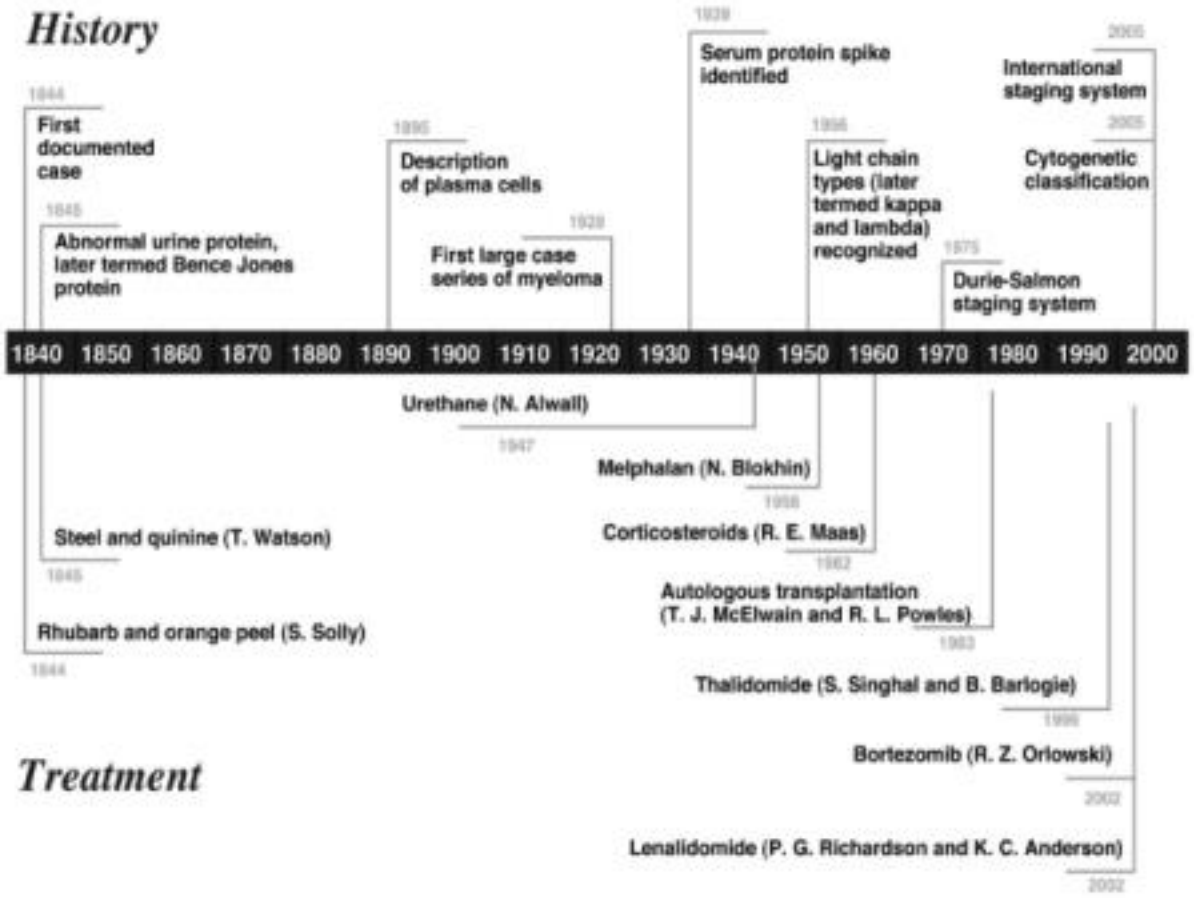
Raymond Alexanian, M.D.: *Associate Professor of Medicine, The University of Texas M. D. Anderson Hospital, Houston, Texas 77025.* Daniel E. Bergsagel, M.D.: *Chief of Medicine, Princess Margaret Hospital, Toronto, Canada.* Philip J. Migliore, M.D.: *Assistant Professor of Pathology, The University of Texas M. D. Anderson Hospital.* William K. Vaughn, M.S.: *Biostatistician, The University of Texas M. D. Anderson Hospital.* Clifton D. Howe, M.D.: *Head, Department of Medicine, The University of Texas M. D. Anderson Hospital.*

**Supplied by the Cancer Chemotherapy National Service Center and administered in a protocol study under the auspices of the Southwest Cancer Chemotherapy Study Group.*

▶The articles featured in the *Blood* Flashback series were selected and the commentaries written by the *Blood* Editors. Complete versions of all the articles in the series, commemorating the journal's 70th-anniversary year, can be found on the *Blood* Web site at www.bloodjournal.org/collection/blood-flashback.

DOI 10.1182/blood-2016-06-724054

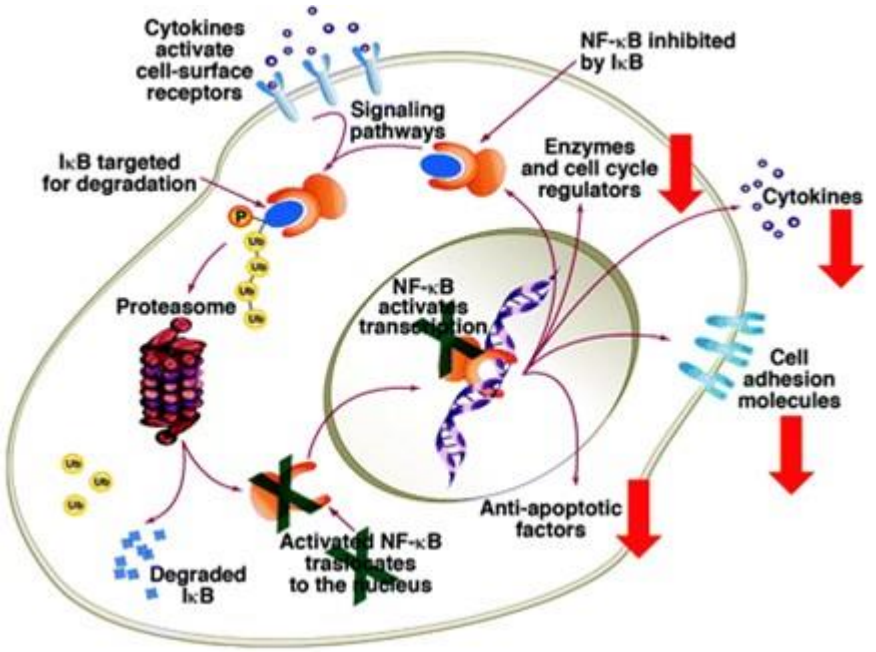
MYELOME MULTIPLE :TRAITEMENTS



MYELOME MULTIPLE : TRAITEMENTS ACTUELS

- Alkylants : melphalan, cyclophophamide
- Corticoïdes: prednisolone, dexamethasone
- Inhibiteurs du protéasome : bortézomib
- Imids : thalidomide, lenalidomide

INHIBITEURS DU PROTEASOME



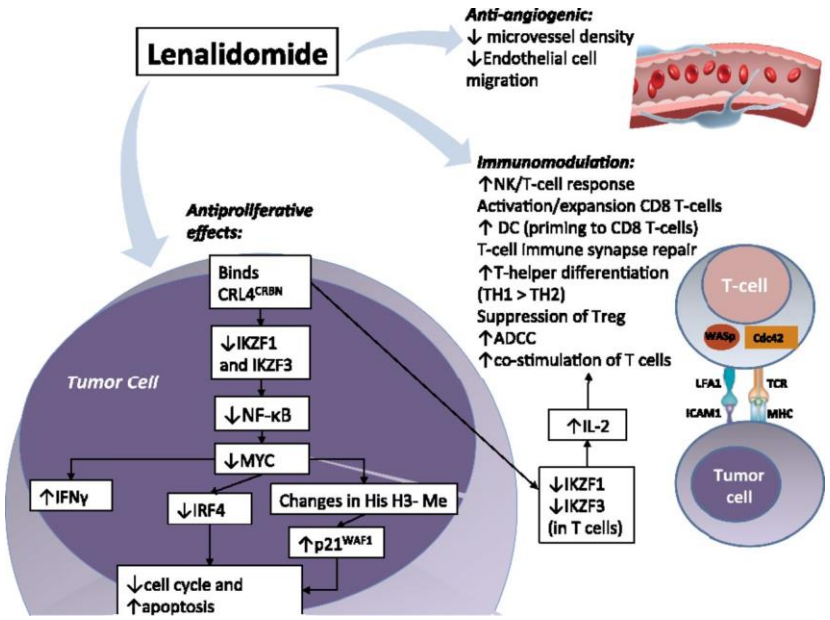
BORTEZOMIB : EFFETS SECONDAIRES

- Pancytopénies : thrombopénie
- Diarrhée
- Neuropathie périphérique et autonome

espacement hebdomadaire

administration sous cutanée

IMID : MODE D'ACTION



IMID : EFFETS SECONDAIRES

- Thalidomide

  somnolence
  constipation
  neuropathie
  tératogène
  thrombogène

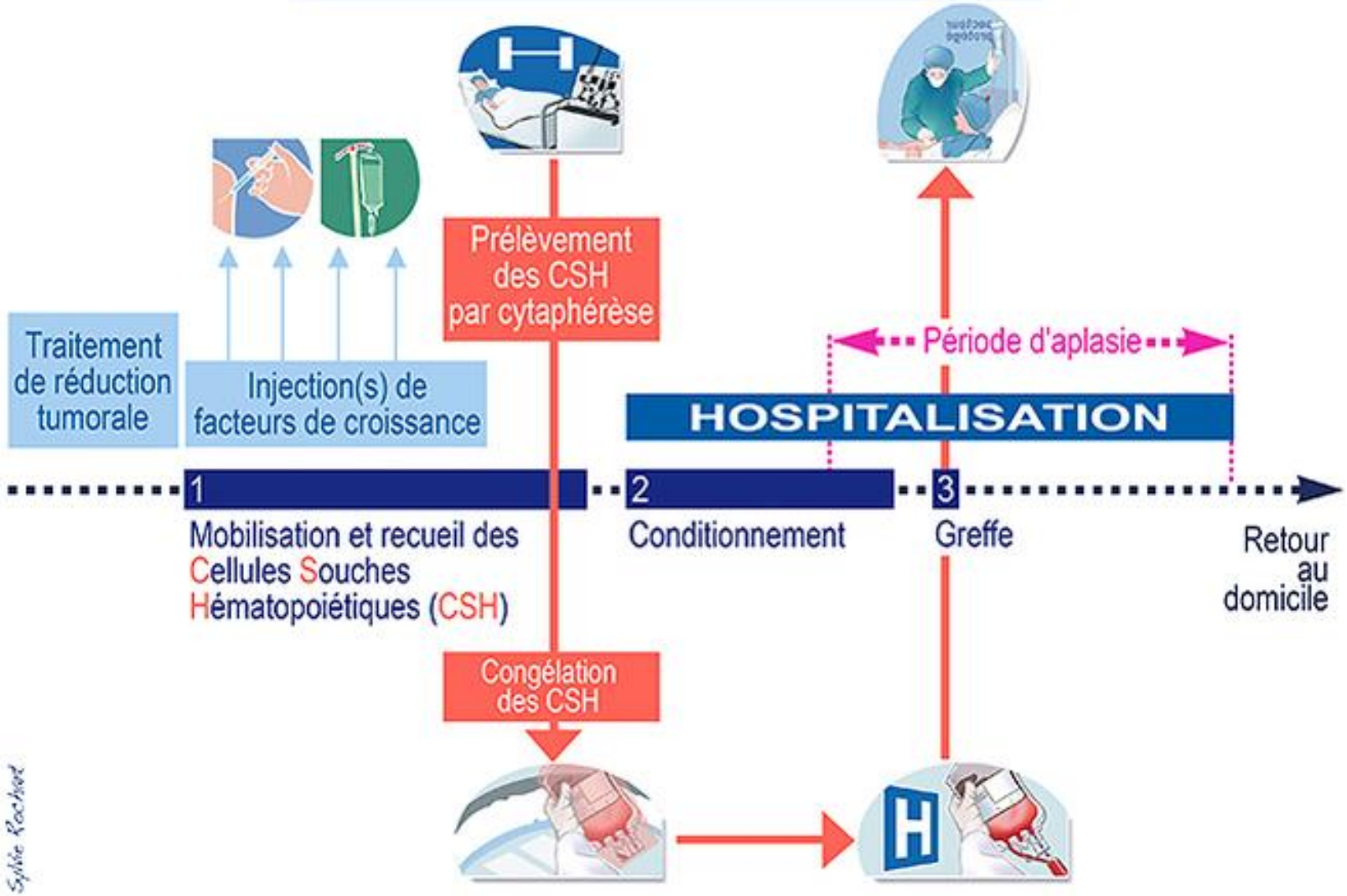
- Lénalidomide

  cytopénie
  diarrhée
  cutané
  tératogène
  thrombogène

TRAITEMENT PATIENT JEUNE

- Induction VTD : velcade, thalidomide, dexamethasone
- Greffe autologue : melphalan 200 mgr/m2
- Consolidation : 2 VTD
- Maintenance : revlimid 2 ans

Autogreffe de cellules souches périphériques



TRAITEMENT PATIENT JEUNE

- Induction VTD : velcade, thalidomide, dexamethasone
- Greffe autologue : melphalan 200 mgr/m2
- Consolidation : 2 VTD
- Maintenance : revlimid 2 ans

TRAITEMENT : PATIENT AGE

- MPT > MP
- **MPV** > MP
- MPR continu > MP
- **Len – dex** > MPT

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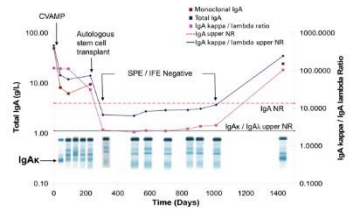
EVOLUTION


CVAMP
Autologous stem cell transplant
SPE / IFE Negative
Monoclonal IgA
Total IgA
IgA kappa / lambda ratio
IgA upper NR
IgA kappa / lambda upper NR
IgA NR
IgAκ / IgAλ upper NR
IgAκ
Total IgA (g/L)
IgA kappa / IgA lambda Ratio
Time (Days)
100.00
10.00
1.00
0.10
1000.0000
100.0000
10.0000
1.0000
0.1000
0
200
400
600
800
1000
1200
1400

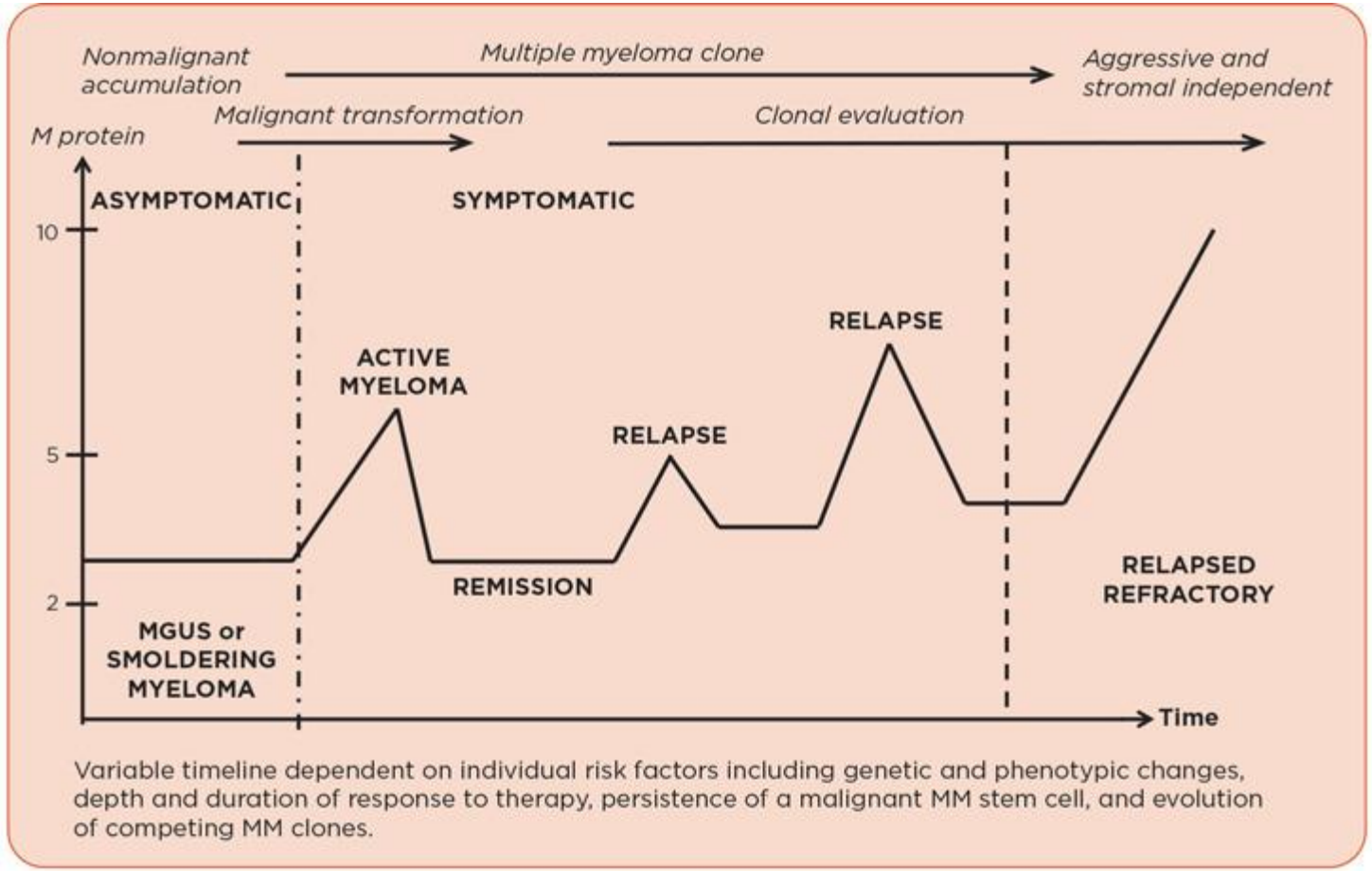


Figure 2. Multiple myeloma disease trajectory characterized by malignant transformation; serial cycles of response, remission, and relapse in the presence of treatment; and clonal evolution with diminished depth and duration of response over time. Information from Agarwal & Ghobrial (2013), Borrello (2012), Durie et al. (2003), Keats et al. (2012).

RECHUTE

Rechute clinique

- **Un ou plusieurs de ces critères :**
  - Apparition d'un nouveau plasmocytome dans les tissus mous ou de lésions osseuses à l'imagerie
  - Augmentation de la taille des plasmocytomes existants ou des lésions osseuses> 50 % (et d'au moins 1 cm)
  - Hypercalcémie
  - Baisse de l'hémoglobine (telle que définie au diagnostic)
  - Dysfonction rénale (*de novo* ou récurrente)
  - Hyperviscosité nécessitant une intervention thérapeutique

Rechute biologique

- Un doublement du composant monoclonal lors de deux mesures consécutives dans un intervalle < 2 mois avec pour valeur de référence 0,5 g/dL,

  OU

- Lors de 2 mesures consécutives, de toute augmentation :
  - du taux sérique de protéine monoclonale ≥ 1 g/dL, ou
  - de la protéine monoclonale urinaire ≥ 500 mg/24h, ou
  - des chaines légéres libres ≥ 20 mg/dL (et un ratio anormal de
  - chaines légéres libres) ou augmentation de 25%

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NOUVEAUX TRAITEMENTS

- Imids : pomalidomide
- Inhibiteurs du protéasomes : carfilzomib, ixazomib
- Anticorps monoclonaux : daratumumab, elotuzumab
- HDAC inhibiteurs : panobinostat
- Anticorps anti-PD1

NOUVEAUX TRAITEMENTS

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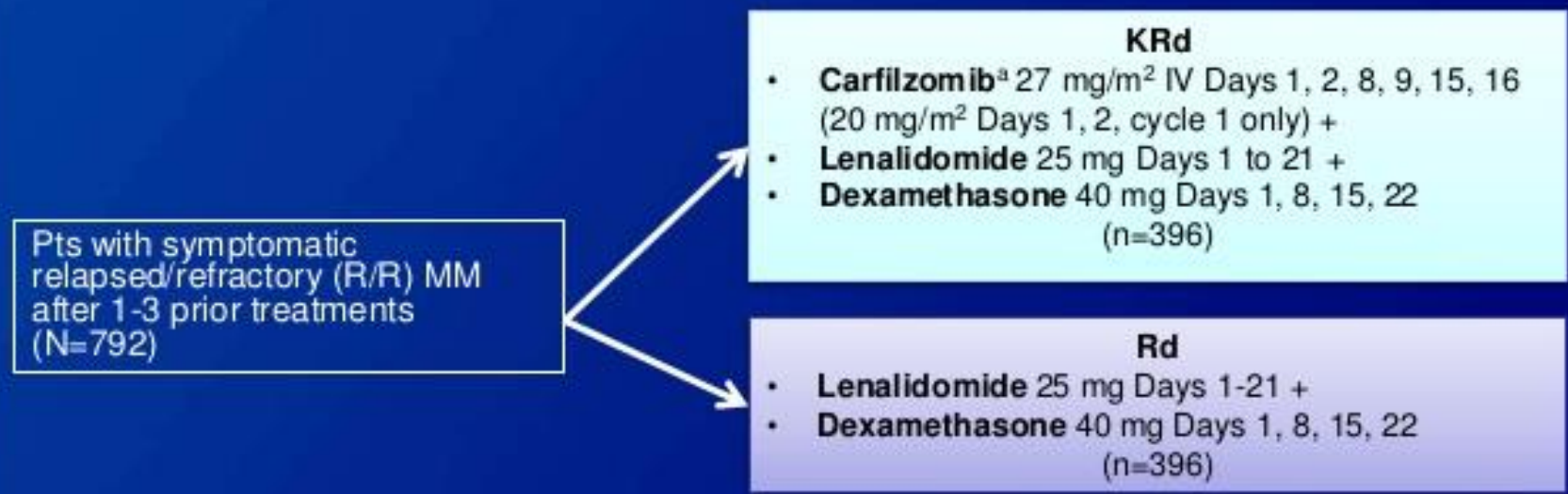
Reg. No.: 1C 111/58 (NC)
Kyprolis®
(carfilzomib) for Injection
60 mg/vial
Single-use vial.
Discard unused portion.
For Intravenous Administration Only.
℞ only
AD9964
Kyprolis®
(carfilzomib) for Injection
60 mg/vial

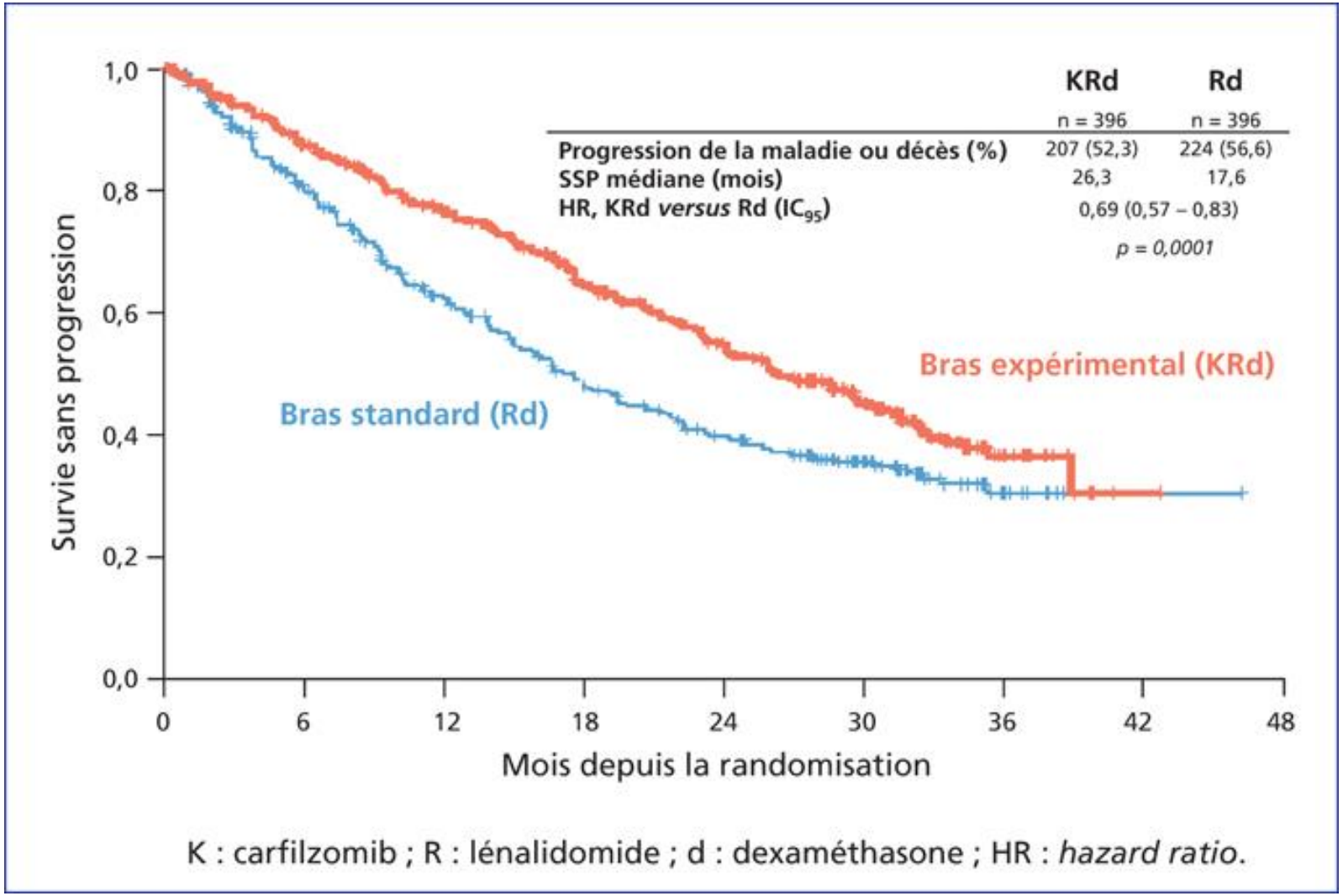
Phase III ASPIRE: Lenalidomide/Dexamethasone ± Carfilzomib in R/R MM

- Randomized, open-label, multicenter phase III trial
  - Stratified by β2MG, prior bortezomib, and prior lenalidomide



[a]After cycle 12, carfilzomib given on Days 1, 2, 15, 16. After cycle 18, carfilzomib discontinued.
Stewart et al, 2015.

KRd : ETUDE ASPIRE



K : carfilzomib ; R : lénalidomide ; d : dexaméthasone ; HR : *hazard ratio*.

KRD : ETUDE ASPIRE

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)

* Adverse events reported in at least 25% of patients in either treatment group are listed. Other adverse events of particular clinical relevance are also listed. The safety population included all patients who received at least one dose of a study drug.

† The category of acute renal failure included (in descending order of frequency) acute renal failure, renal failure, renal impairment, azotemia, oliguria, anuria, toxic nephropathy, and prerenal failure.

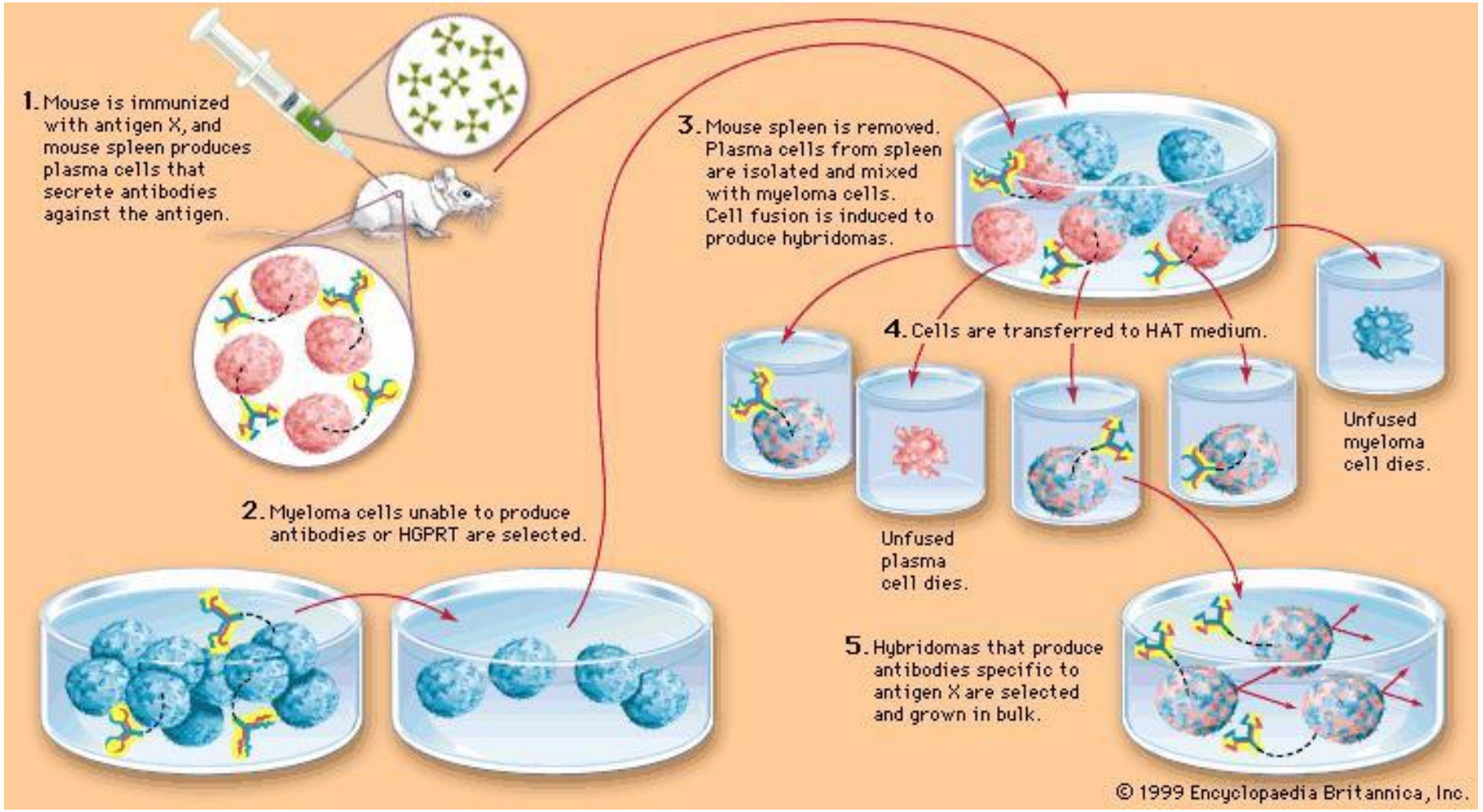
‡ The category of cardiac failure included (in descending order of frequency) cardiac failure, congestive cardiac failure, pulmonary edema, hepatic congestion, cardiopulmonary failure, acute pulmonary edema, acute cardiac failure, and right ventricular failure.

§ The category of ischemic heart disease included (in descending order of frequency) angina pectoris, myocardial infarction, acute myocardial infarction, an increased serum creatine kinase level, coronary artery disease, myocardial ischemia, coronary artery occlusion, an increased troponin level, an increased level of troponin T, an acute coronary syndrome, abnormal results on a cardiac stress test, cardiomyopathy stress, unstable angina, coronary-artery stenosis, an abnormal ST-T segment on electrocardiography, and an abnormal T wave on electrocardiography.

NOUVEAUX TRAITEMENTS

- Imids : pomalidomide
- Inhibiteurs du protéasomes : carfilzomib, ixazomib
- Anticorps monoclonaux : daratumumab, elotuzumab
- HDAC inhibiteurs : panobinostat
- Anticorps anti-PD1

HYBRIDOME


1. Mouse is immunized with antigen X, and mouse spleen produces plasma cells that secrete antibodies against the antigen.
2. Myeloma cells unable to produce antibodies or HGPRT are selected.
3. Mouse spleen is removed. Plasma cells from spleen are isolated and mixed with myeloma cells. Cell fusion is induced to produce hybridomas.
4. Cells are transferred to HAT medium.
Unfused myeloma cell dies.
Unfused plasma cell dies.
5. Hybridomas that produce antibodies specific to antigen X are selected and grown in bulk.
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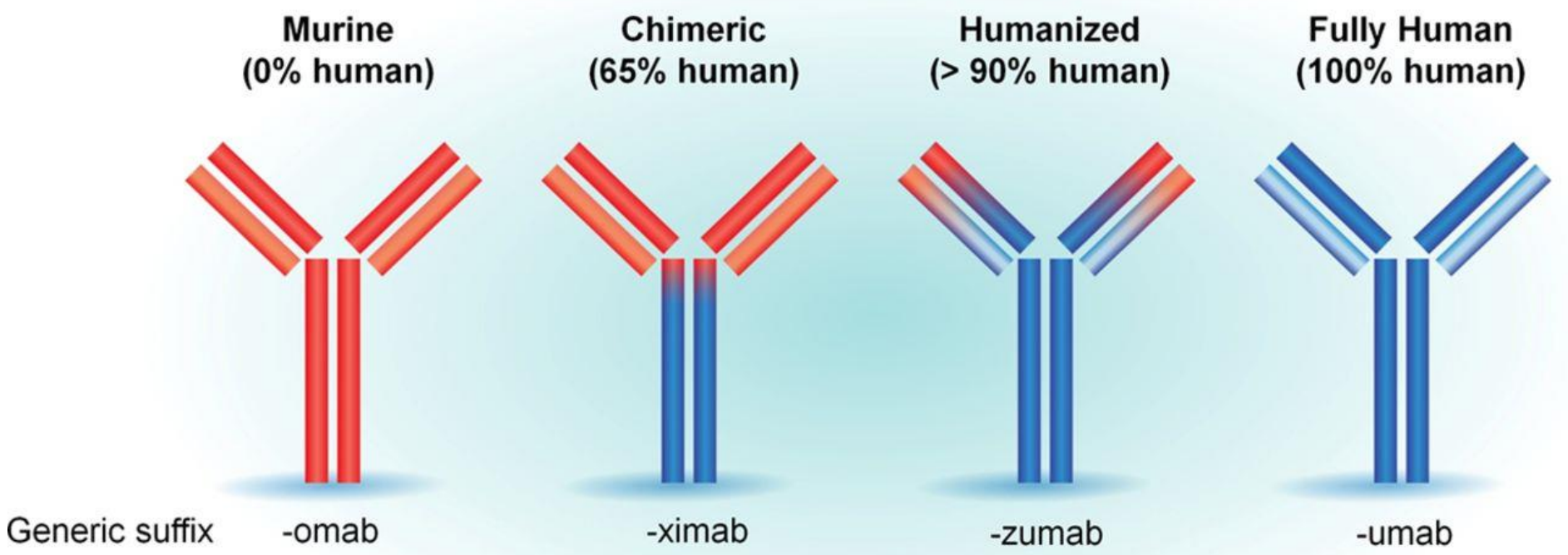
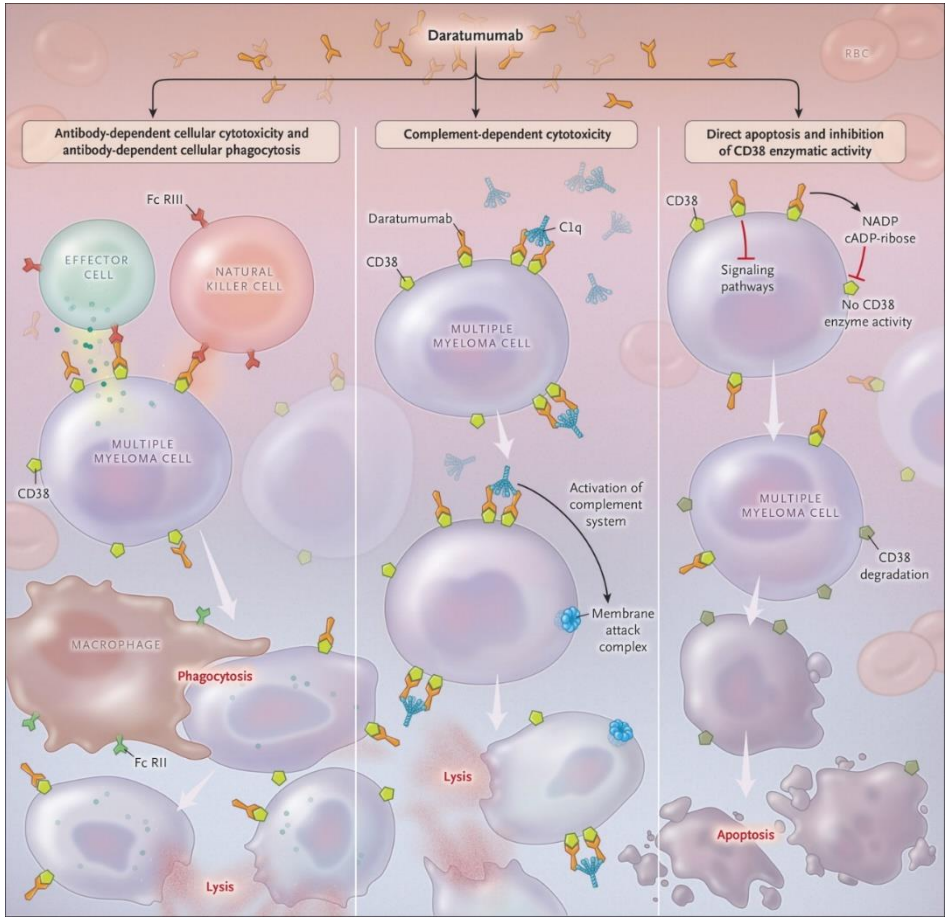
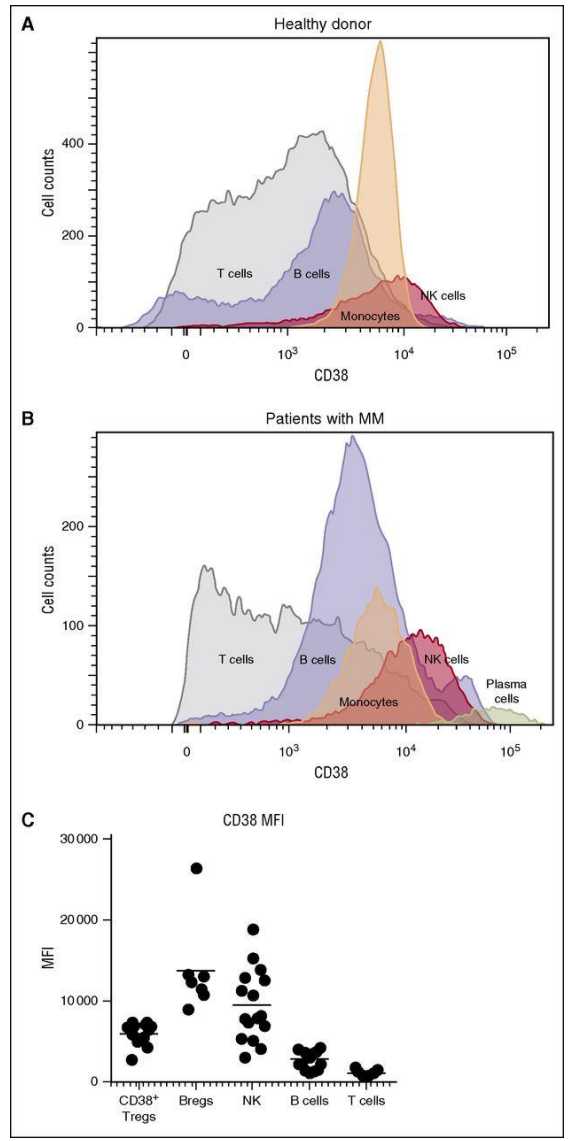
ANTICORPS MONOCLONAUX

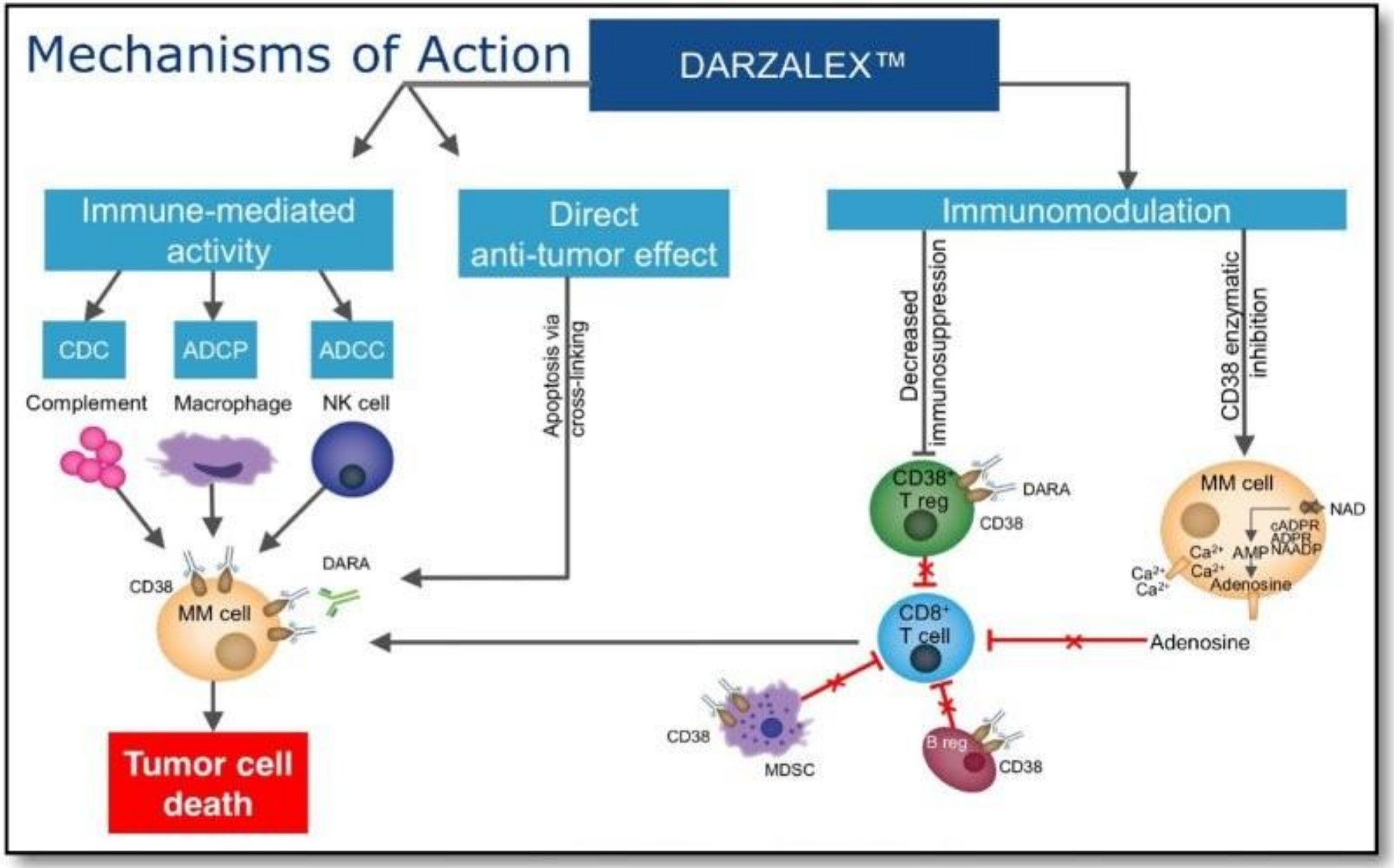



DARZALEX™
(daratumumab)
Injection
400 mg/20 mL
(20 mg/mL)
For Intravenous Infusion Only
Janssen
NDC 57894-502-20
Rx only
DARZALEX™
(daratumumab)
Injection
400 mg/20 mL
(20 mg/mL)
For Intravenous Infusion Only
Dilute Before Use
Single-Dose Only. Discard Unused Portion
Janssen
NDC 57894-502-20 Rx Only
DARZALEX™
(daratumumab)
Injection
400 mg/20 mL
(20 mg/mL)
For Intravenous Infusion Only

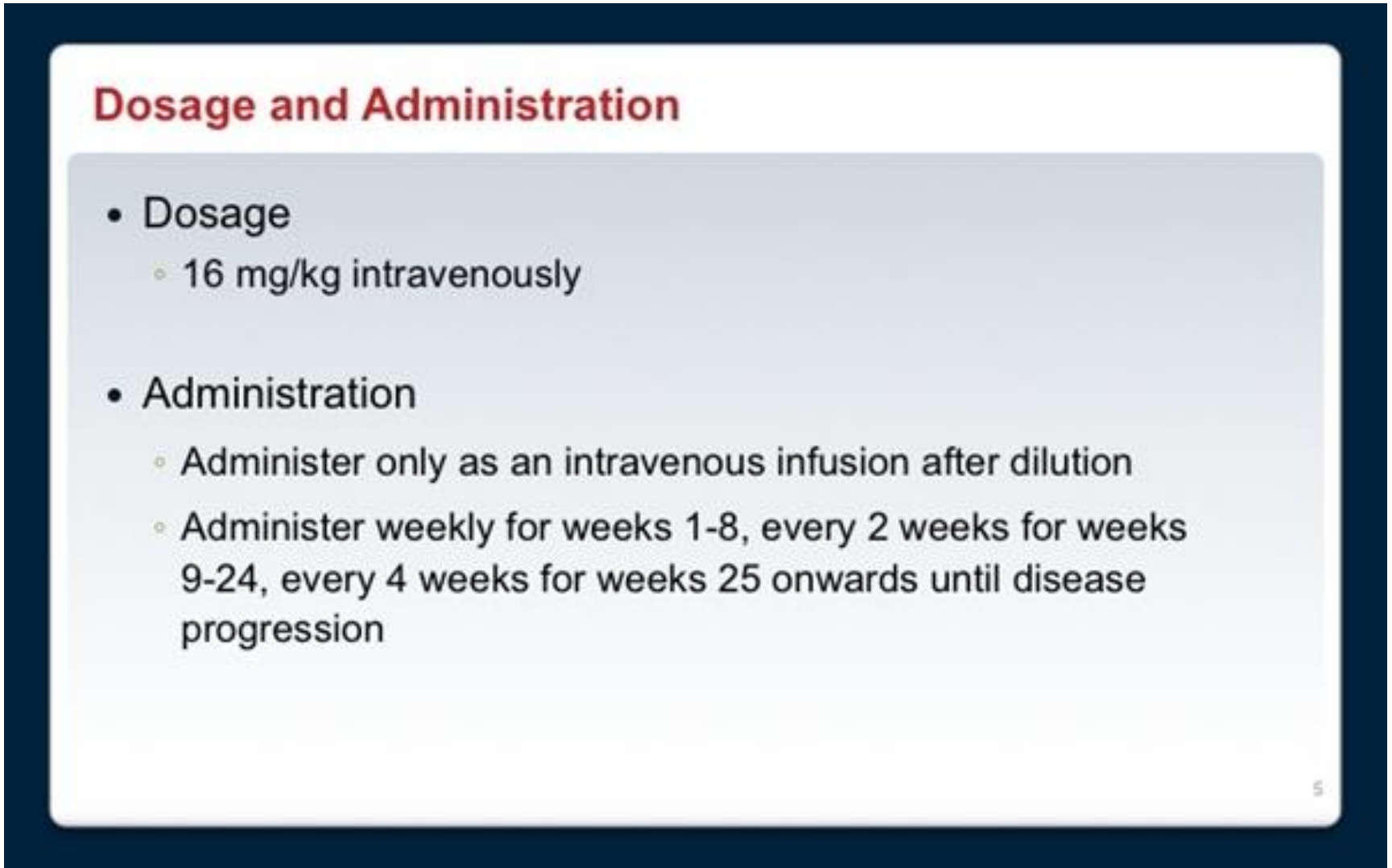
DARATUMUMAB



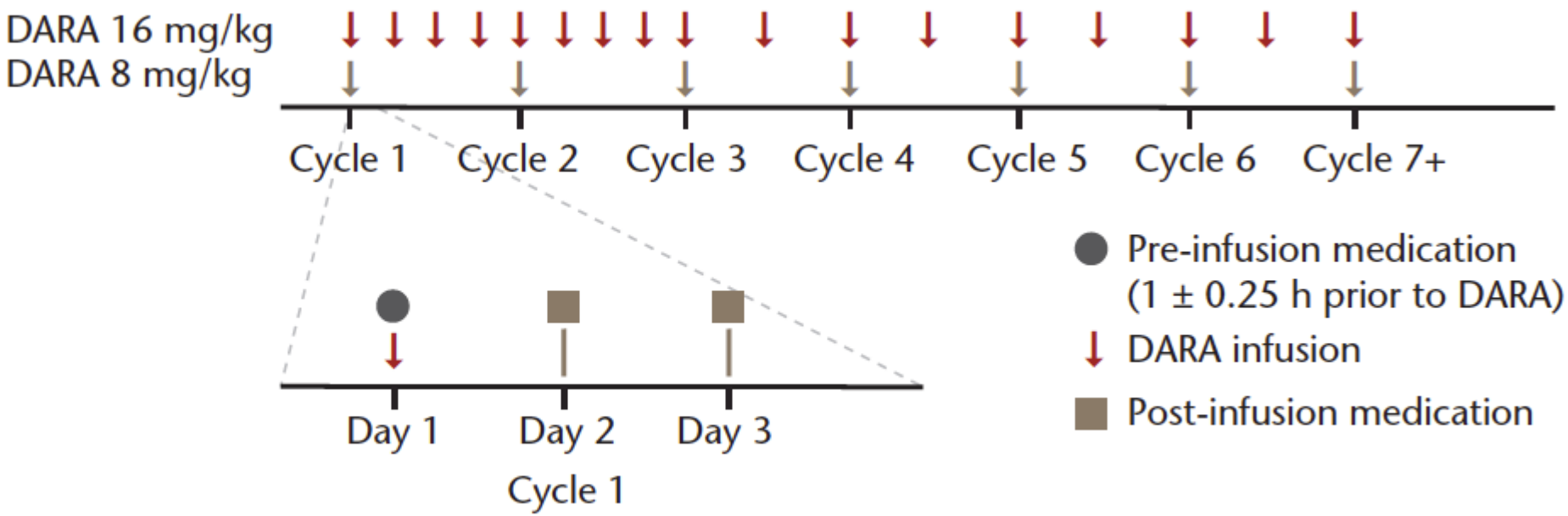

A
Healthy donor
Cell counts
400
200
0
T cells
B cells
NK cells
Monocytes
0
10^3
10^4
10^5
CD38
B
Patients with MM
Cell counts
200
100
0
T cells
B cells
NK cells
Plasma cells
Monocytes
0
10^3
10^4
10^5
CD38
C
CD38 MFI
MFI
30 000
20 000
10 000
0
CD38+ Tregs
Bregs
NK
B cells
T cells


Mechanisms of Action
DARZALEX™
Immune-mediated activity
Direct anti-tumor effect
Immunomodulation
CDC
ADCP
ADCC
Complement
Macrophage
NK cell
Apoptosis via cross-linking
Decreased immunosuppression
CD38 enzymatic inhibition
CD38
DARA
MM cell
Tumor cell death
CD38+ T reg
DARA
CD38
MM cell
NAD
cADPR
ADPR
NAADP
Ca2+
AMP
Adenosine
CD8+ T cell
Adenosine
CD38
MDSC
B reg
CD38

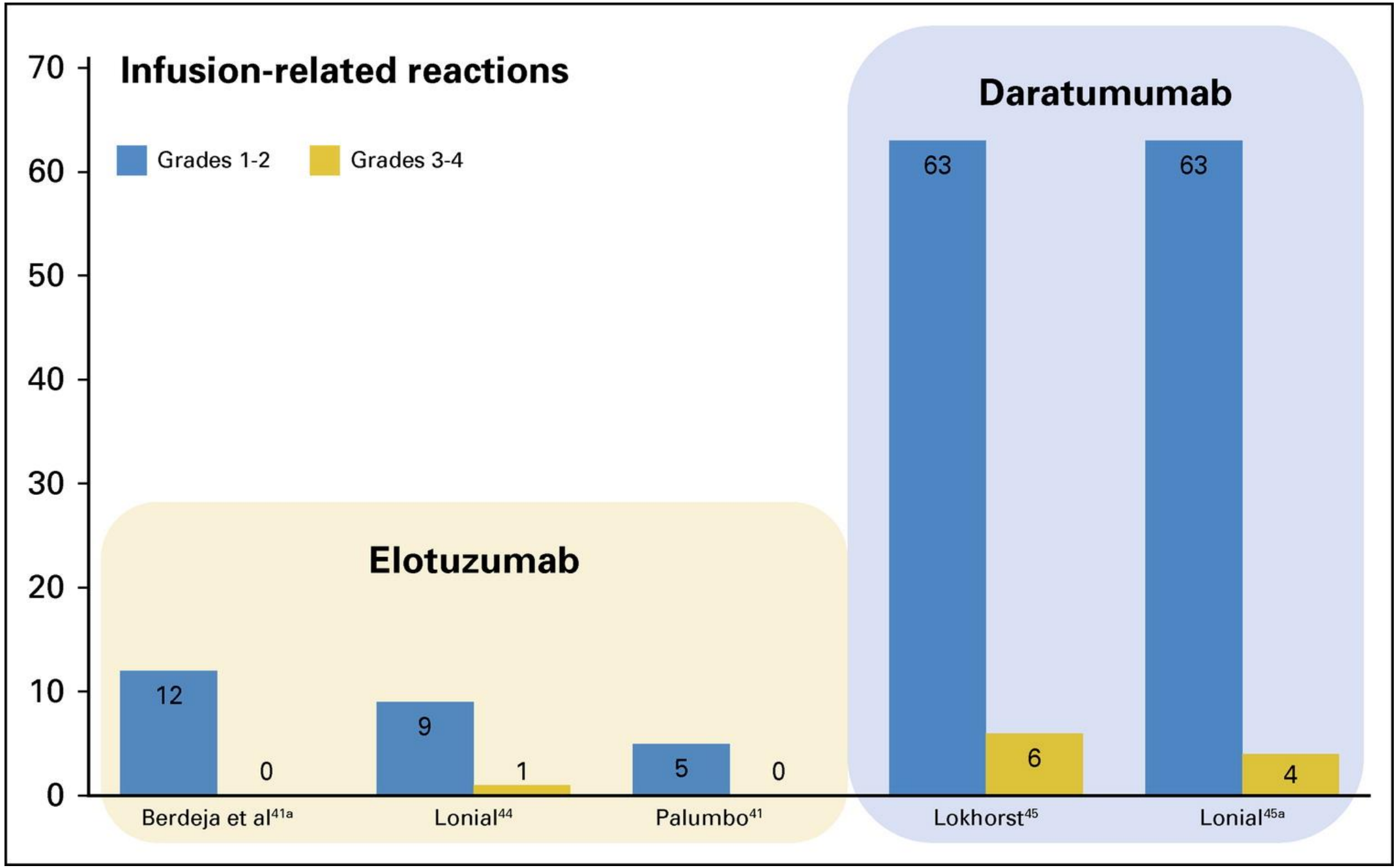
DARATUMUMAB : ADMINISTRATION



Study design



DARA = daratumumab


Infusion-related reactions
Grades 1-2
Grades 3-4
70
60
50
40
30
20
10
0
Elotuzumab
Daratumumab
12
0
9
1
5
0
63
6
63
4
Berdeja et al[41a]
Lonial[44]
Palumbo[41]
Lokhorst[45]
Lonial[45a]

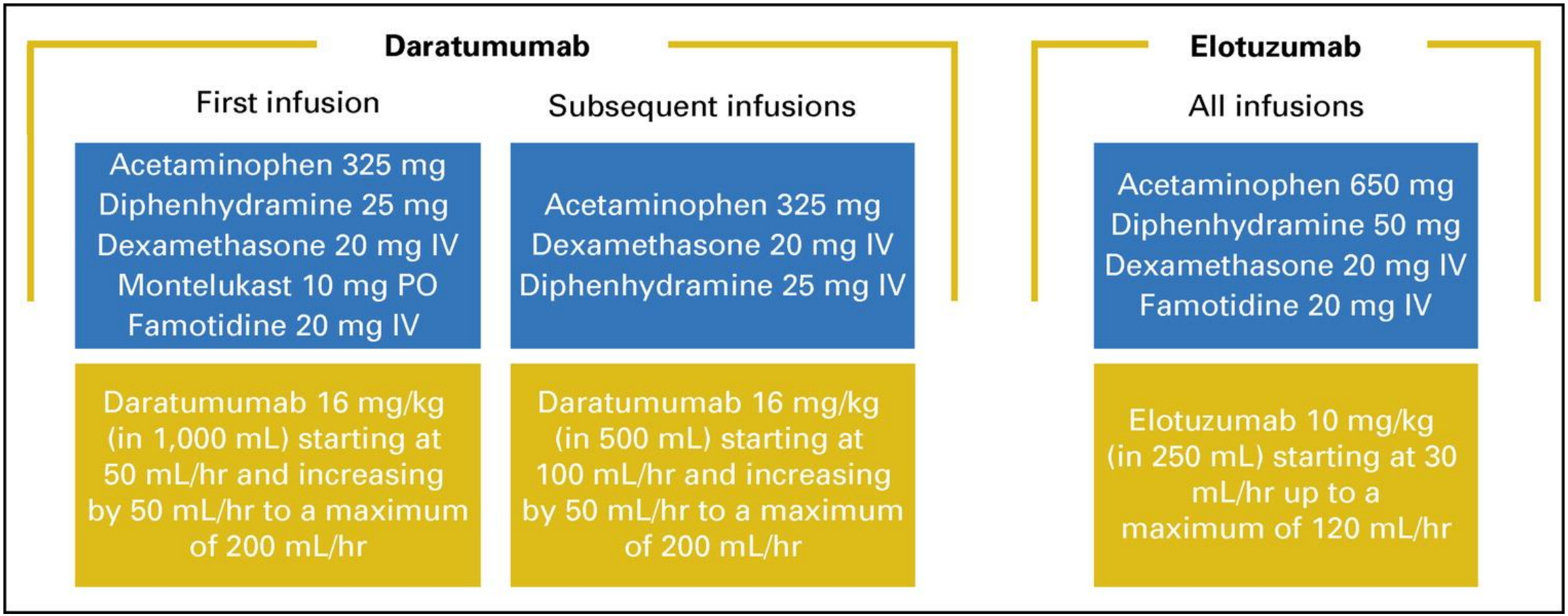

Daratumumab
First infusion
Acetaminophen 325 mg
Diphenhydramine 25 mg
Dexamethasone 20 mg IV
Montelukast 10 mg PO
Famotidine 20 mg IV
Daratumumab 16 mg/kg (in 1,000 mL) starting at 50 mL/hr and increasing by 50 mL/hr to a maximum of 200 mL/hr
Subsequent infusions
Acetaminophen 325 mg
Dexamethasone 20 mg IV
Diphenhydramine 25 mg IV
Daratumumab 16 mg/kg (in 500 mL) starting at 100 mL/hr and increasing by 50 mL/hr to a maximum of 200 mL/hr
Elotuzumab
All infusions
Acetaminophen 650 mg
Diphenhydramine 50 mg
Dexamethasone 20 mg IV
Famotidine 20 mg IV
Elotuzumab 10 mg/kg (in 250 mL) starting at 30 mL/hr up to a maximum of 120 mL/hr

Table 1. Recommendations for the management of grade 1 or 2 IRRs

IRR	Action
Grade 1 or 2	The infusion should be paused. When the patient's condition is stable, infusion may be restarted at the investigator's discretion. Upon restart, the infusion rate should be half of that employed before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion.
Grade 2 or higher event of laryngeal edema Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from onset	Patient must be withdrawn from treatment

IRR = infusion-related reaction

Table 2. Recommendations for the management of grade ≥3 IRRs

IRR	Action
Grade 3 or higher	Infusion must be stopped and the patient must be observed carefully until resolution of the IRR
If the intensity of the IRR remains at grade 3 or 4 after 2 hours	Patient must be withdrawn from treatment
If the intensity of the IRR decreases to grade 1 or 2 within 2 hours	Infusion may be restarted at the investigator's discretion. Upon restart, the infusion rate should be half of that employed before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion.
If the intensity of the IRR returns to grade 3 or 4 after restart of the infusion	The procedure described above may be repeated at the investigator's discretion
If the intensity of the IRR increases to grade 3 or 4 for a third time	Patient must be withdrawn from treatment

IRR = infusion-related reaction

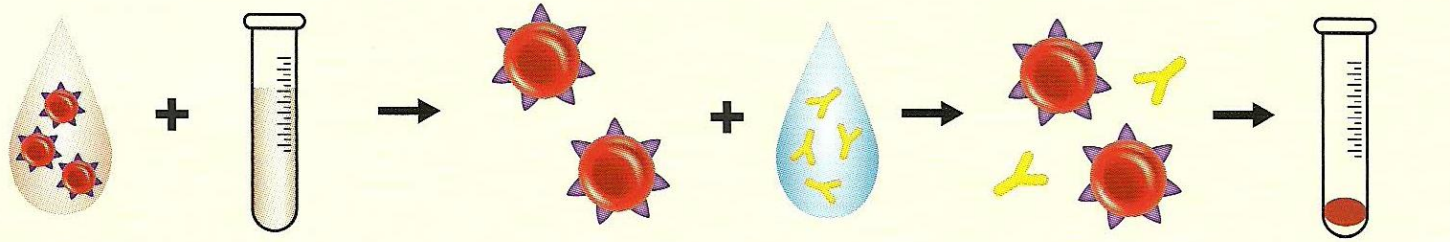
Daratumumab

Additional Points

- Infusion reactions experienced by 48% of patients; most were grade 1/2 and > 90% occurred during first treatment cycle
  - 9% had reaction after first dose (5% with second infusion, 4% with subsequent infusions)
  - Premedication regimen -- to be completed 60 min before infusion; includes corticosteroid, acetaminophen, diphenhydramine
    - Postinfusion and day 2 corticosteroid needed
  - Start first infusion early in the day
- Patients need herpes zoster prophylaxis
- Can interfere with serologic testing
  - RBCs should be typed and crossed before first infusion
  - Elotuzumab and daratumumab may interfere with SPEP/IFX measures
    - Applicable in patients with CR and PD

Darzalex® PI 2015.

Test de Coombs indirect négatif typique



GR du panel

Sérum du patient ne contenant pas d'anticorps contre les antigènes mineurs

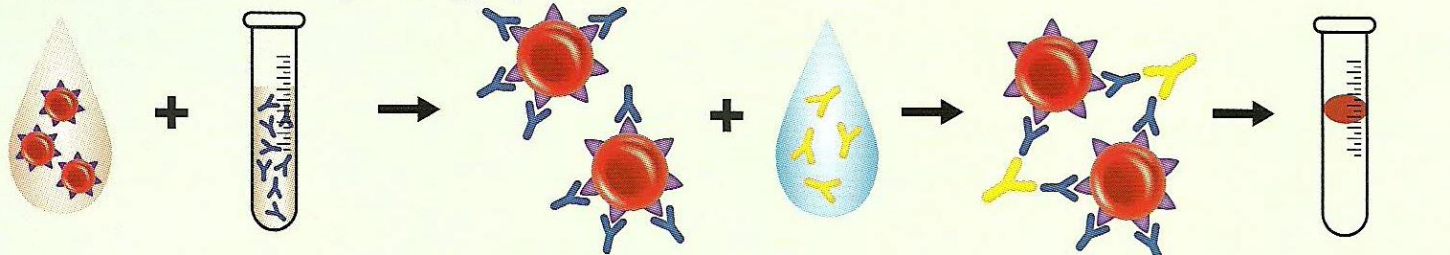
Les anticorps du patient ne se lient pas aux antigènes à la surface des GR du panel

Réactif de Coombs

Pas d'agglutination

Test de Coombs indirect négatif

Test de Coombs indirect positif typique



GR du panel

Sérum du patient contenant des anticorps contre les antigènes mineurs

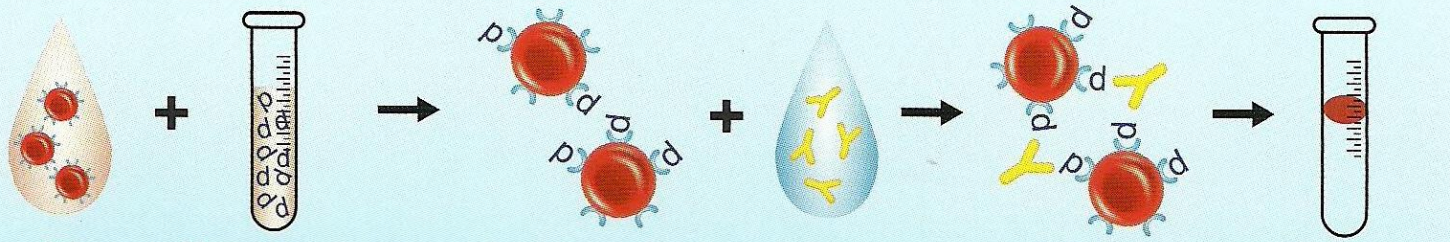
Les anticorps du patient se lient aux antigènes à la surface des GR du panel

Réactif de Coombs

Agglutination

Test de Coombs indirect positif

Test de Coombs indirect typique chez un patient traité par daratumumab



GR du panel

Sérum du patient contenant du daratumumab

Le daratumumab se lie aux CD38 à la surface des GR

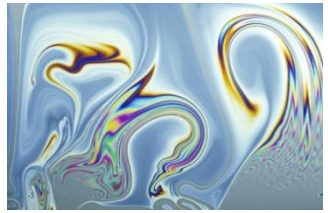
Réactif de Coombs

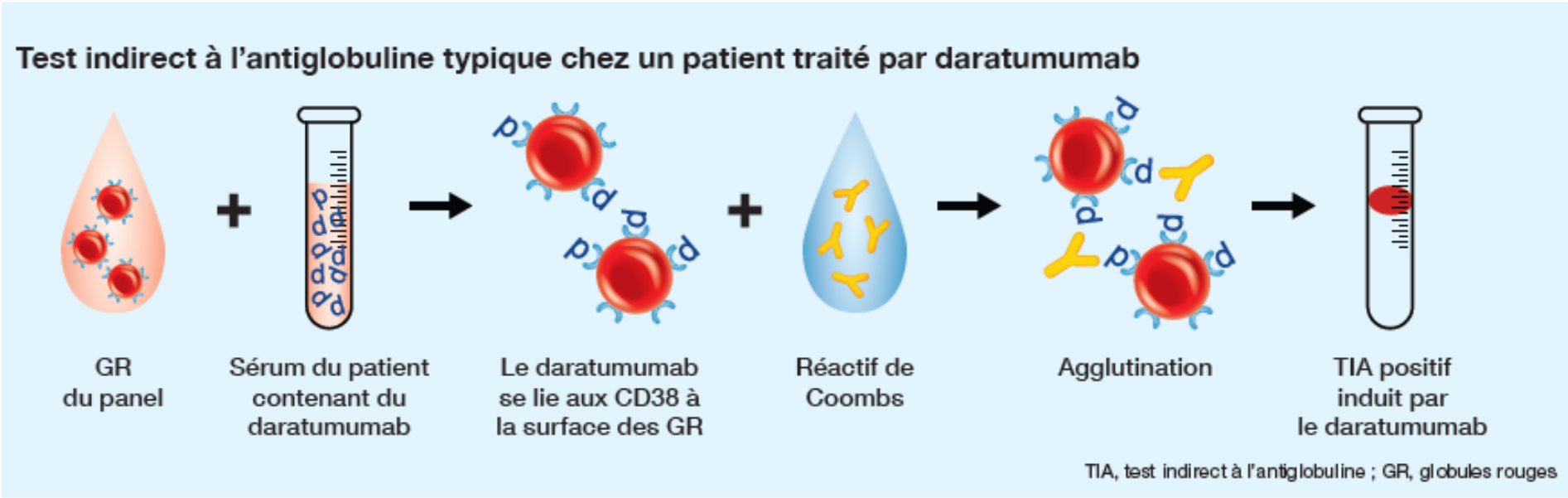
Agglutination

Résultat faussement positif du test de Coombs indirect

GR, globules rouges

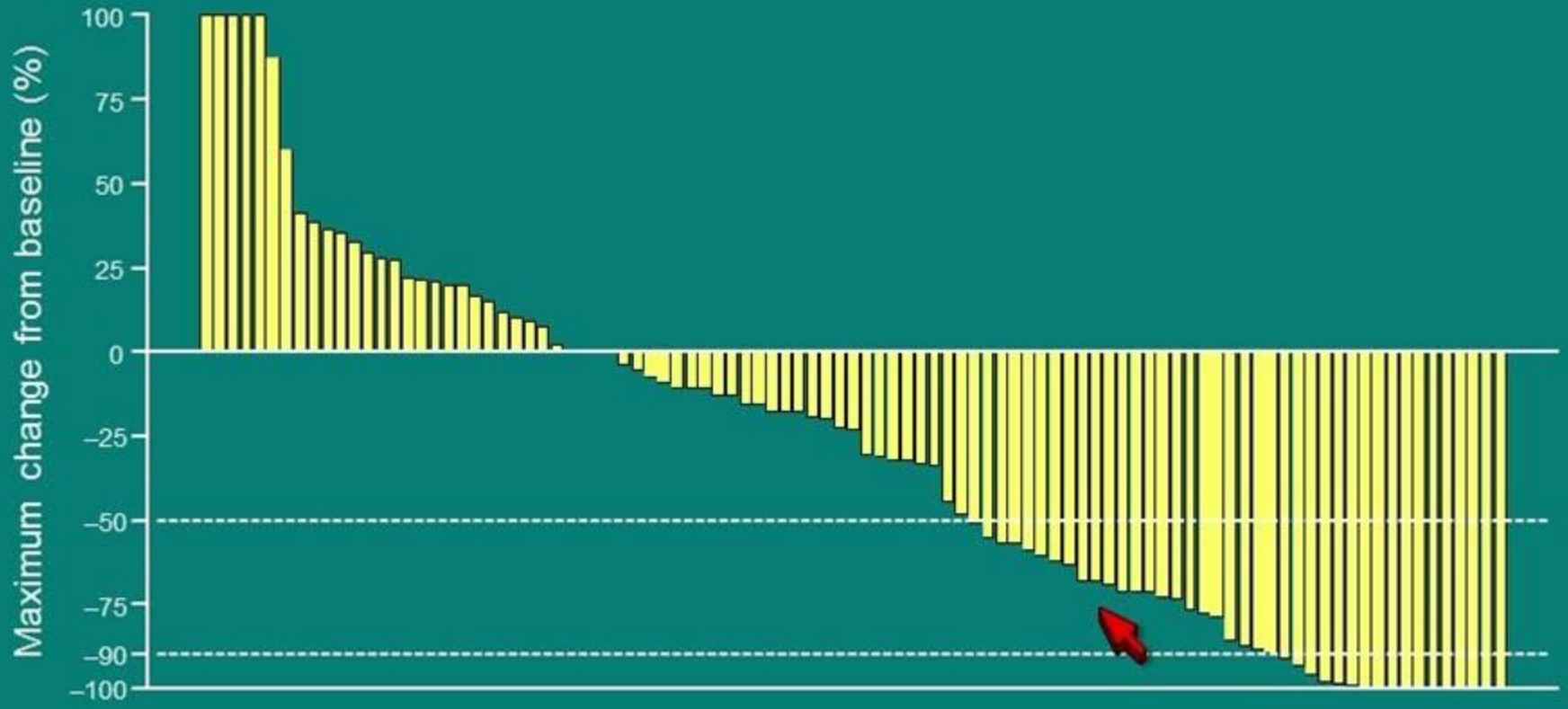
Interférences biologiques





Chari et al, ASH 2015

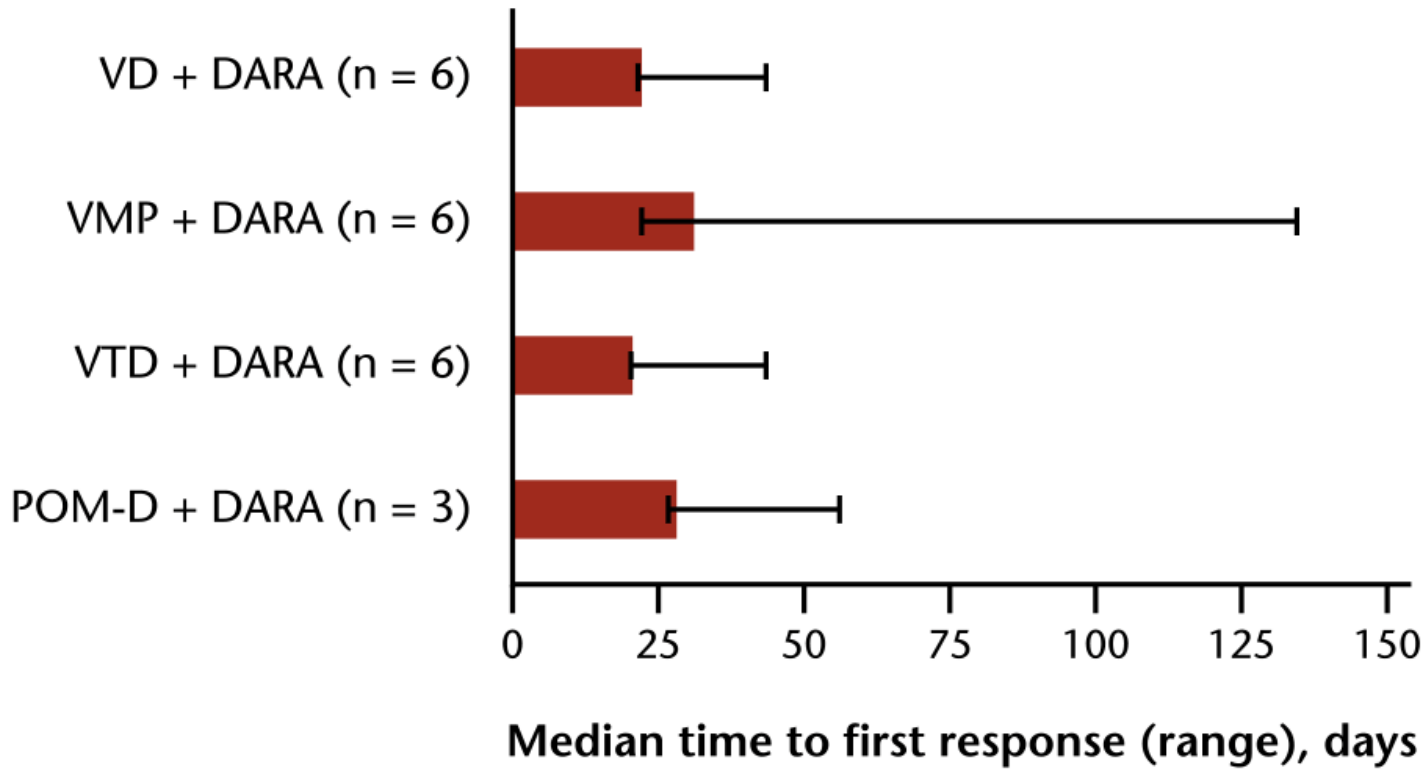
Change in Paraprotein From Baseline



The majority of patients had reductions in paraprotein from baseline

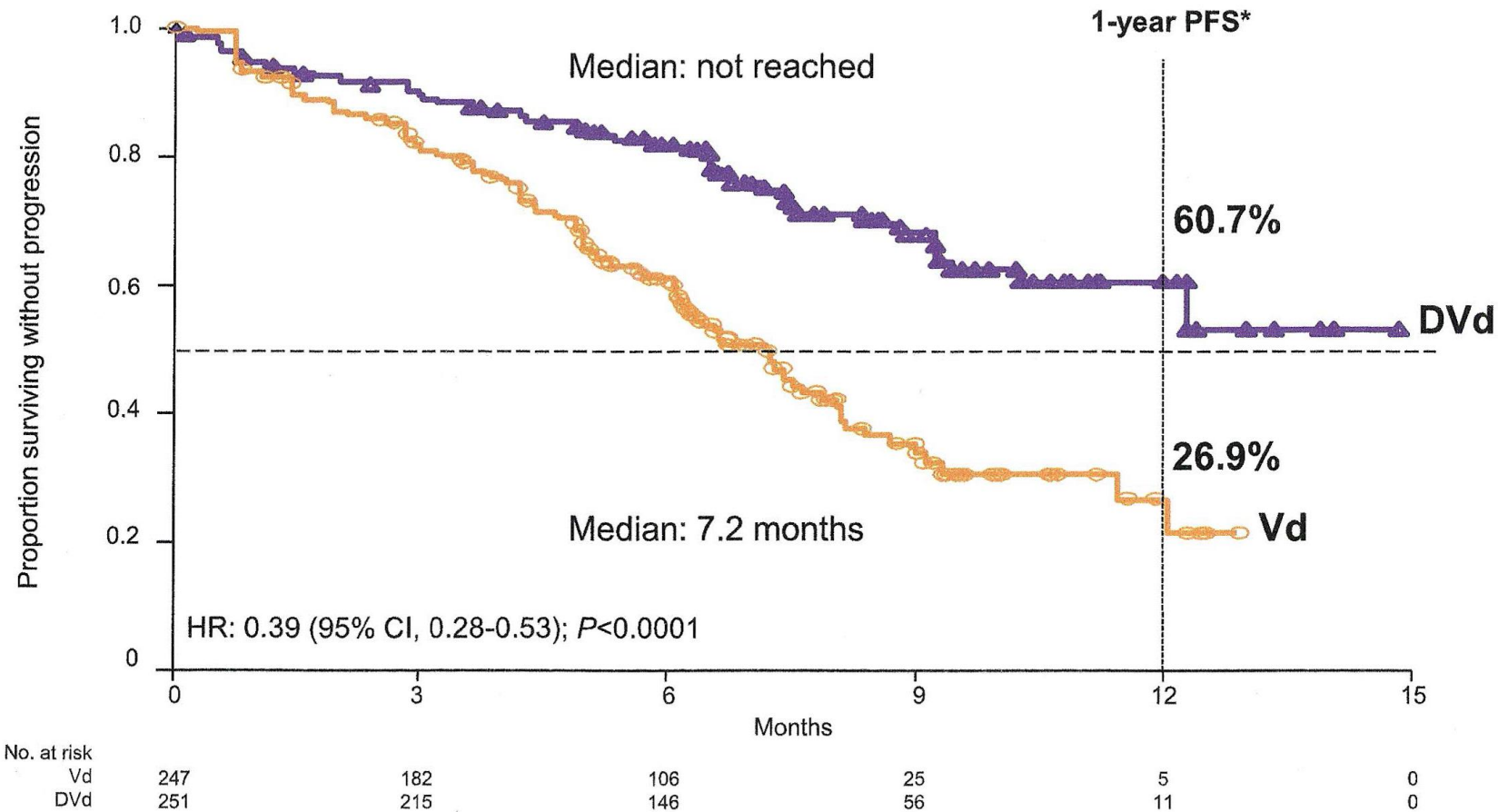
- 40 patients (38%) had reductions >50%
- 17 patients (16%) had reductions >90%

Figure 2. Median time to first response



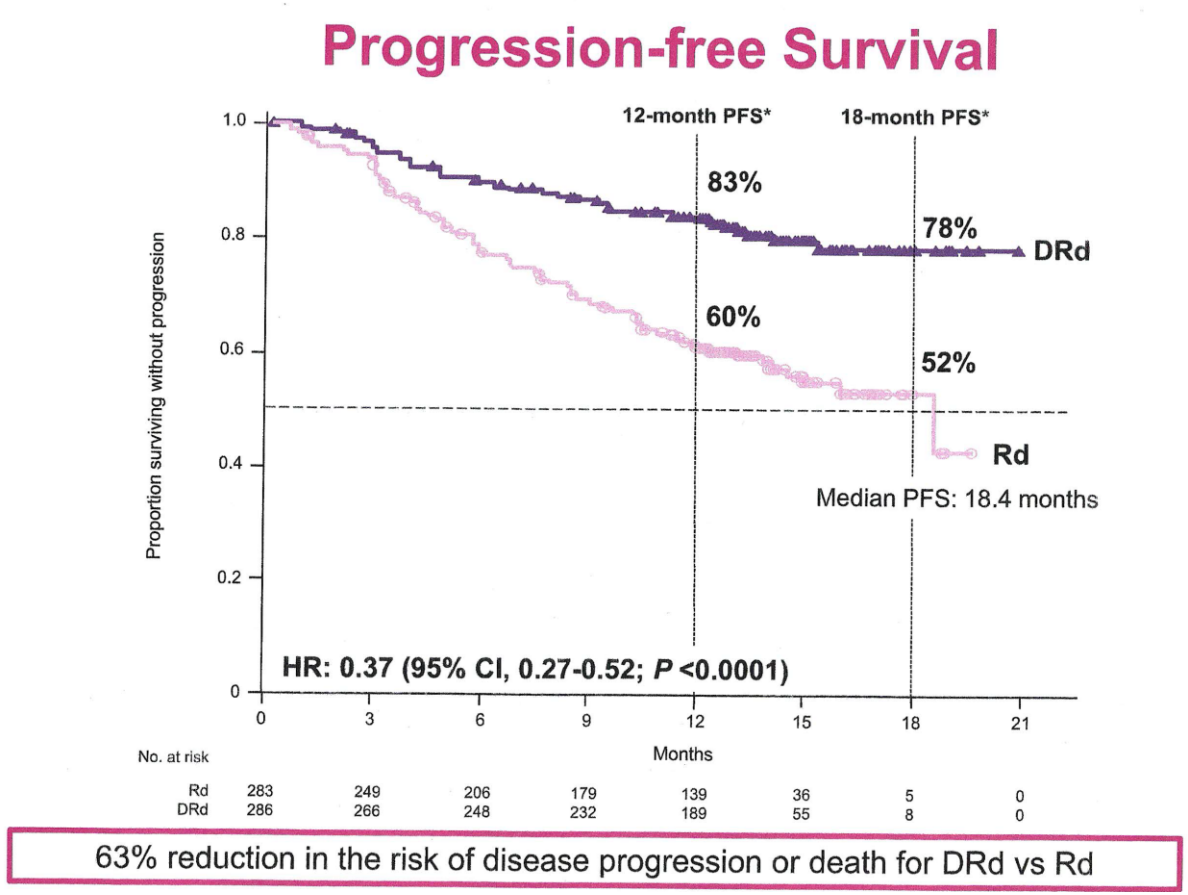
DARA = daratumumab; POM-D = pomalidomide, dexamethasone; VD = bortezomib, dexamethasone; VMP = bortezomib, melphalan, prednisone; VTD = bortezomib, thalidomide, dexamethasone

Progression-free Survival



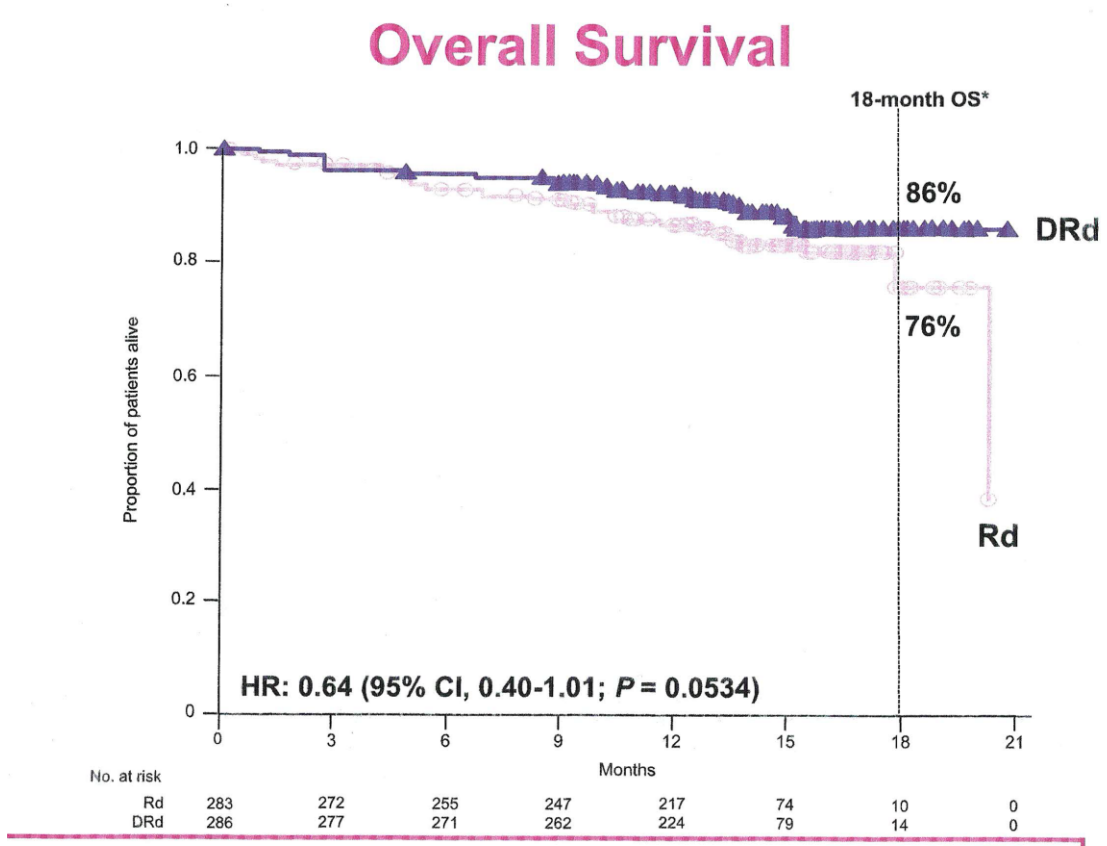
61% reduction in the risk of disease progression or death for DVd vs Vd

DARA LEN DEX (POLLUX)



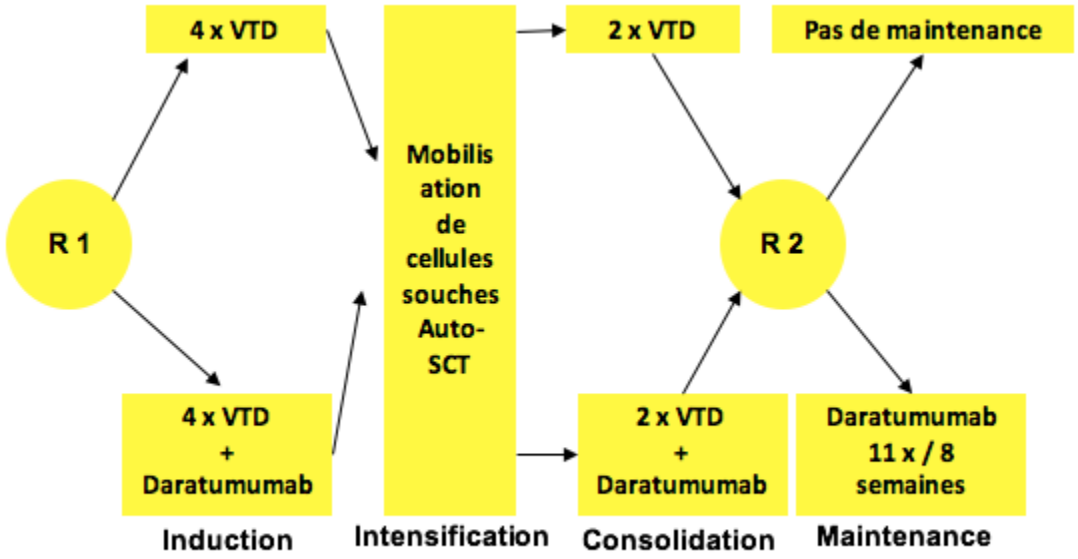
63% reduction in the risk of disease progression or death for DRd vs Rd

DARA LEN DEXA : POLLUX



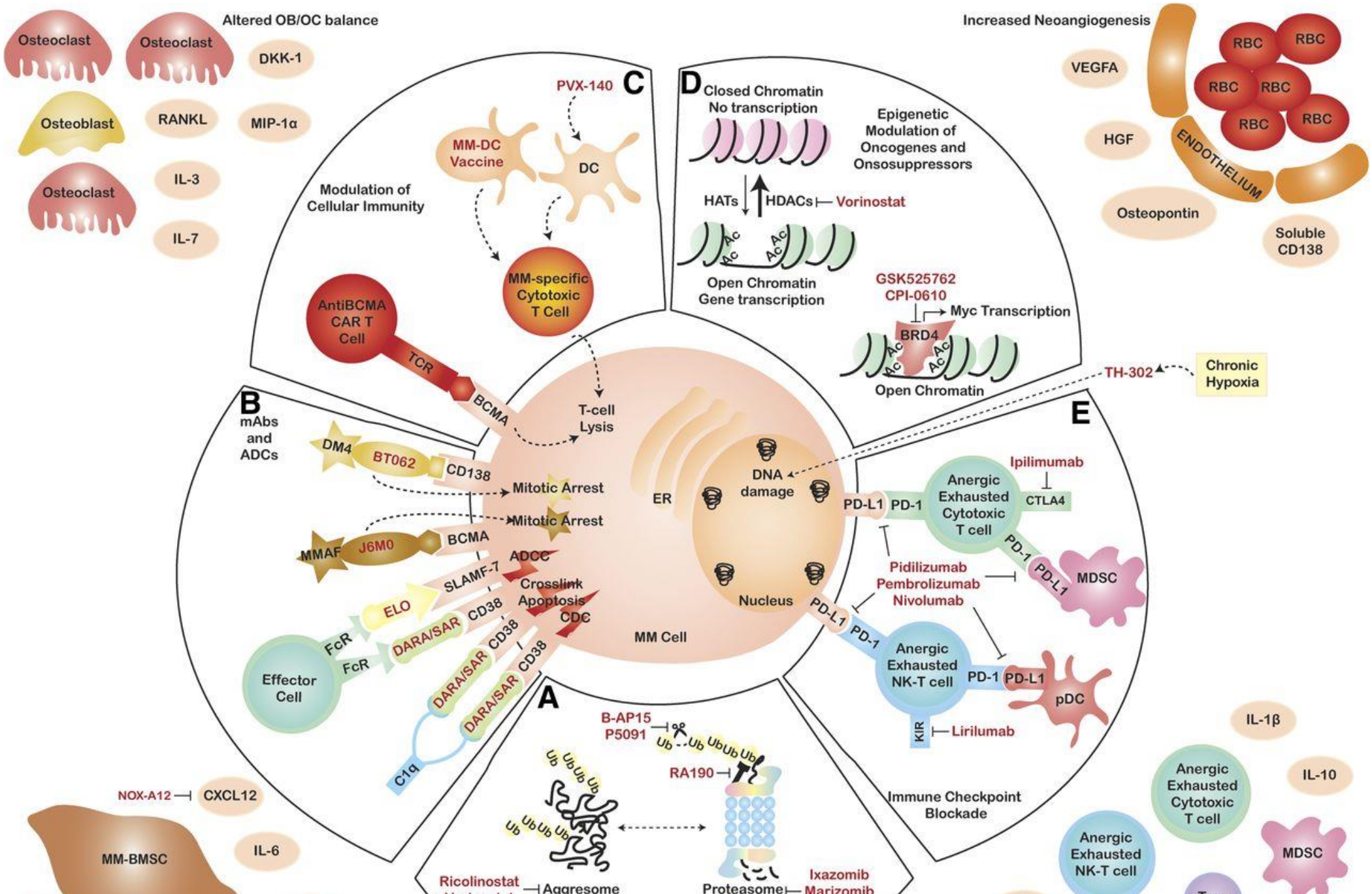
18-month overall survival: 86% in DRd versus 76% in Rd

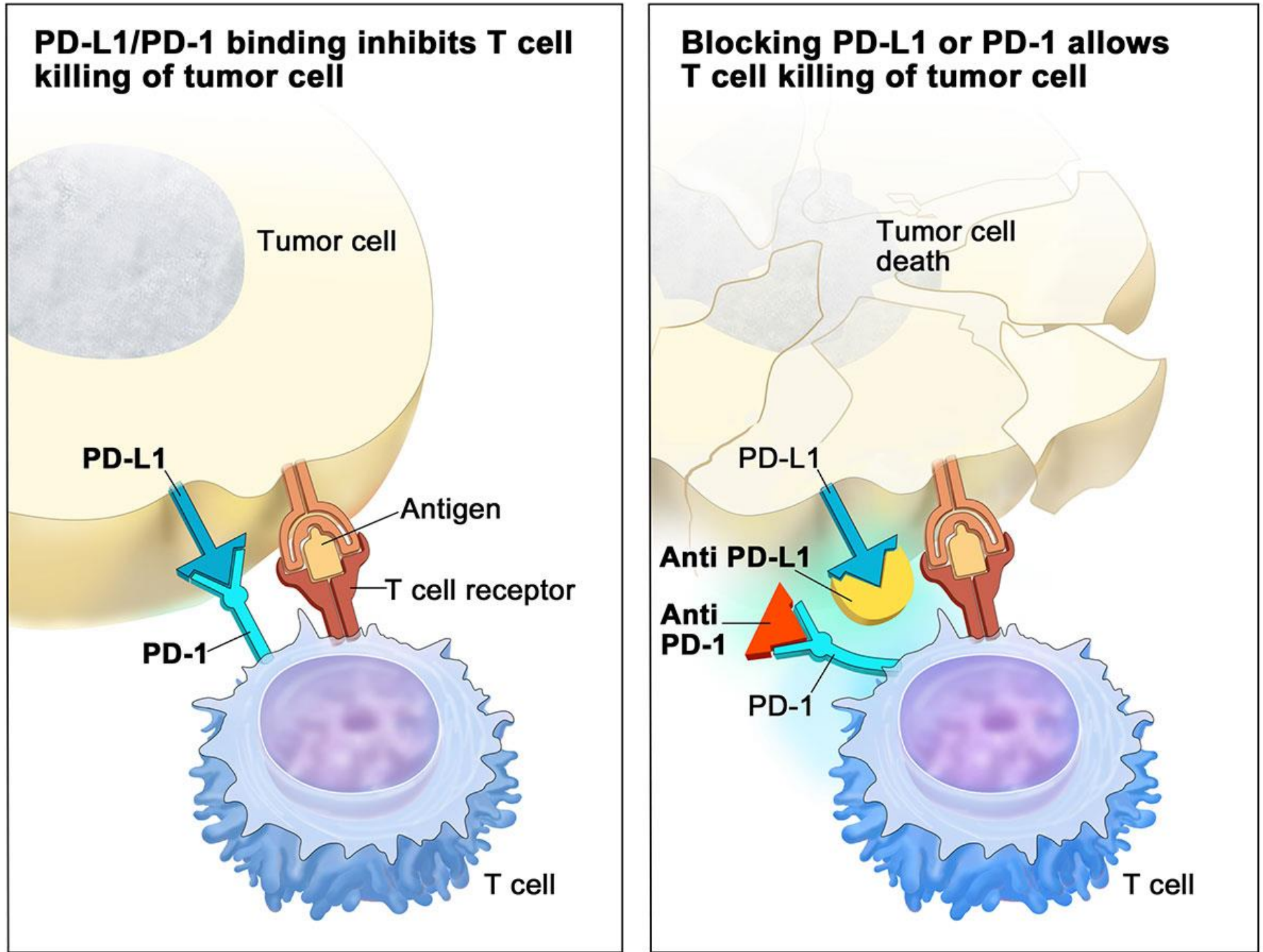
DARATUMUMAB 1°LIGNE : CASSIOPEE



daratumumab combinations

combo	patients	ORR (%)
bortezomib and dexamethasone (bor/dex)	newly diagnosed, SCT eligible	100
bortezomib, thalidomide, and dexamethasone (BTD)	newly diagnosed, SCT eligible	100
bortezomib, melphalan, and prednisone (BMP)	newly diagnosed, not transplant eligible	100
pomalidomide and dexamethasone (pom/dex)	2 line failures	50


Altered OB/OC balance
Osteoclast
Osteoclast
Osteoblast
Osteoclast
DKK-1
RANKL
MIP-1α
IL-3
IL-7
Increased Neoangiogenesis
VEGFA
HGF
Osteopontin
RBC
RBC
RBC
RBC
RBC
ENDOTHELIUM
Soluble CD138
C
PVX-140
MM-DC Vaccine
DC
Modulation of Cellular Immunity
MM-specific Cytotoxic T Cell
AntiBCMA CAR T Cell
TCR
BCMA
T-cell Lysis
D
Closed Chromatin
No transcription
Epigenetic Modulation of Oncogenes and Onsosuppressors
HATs
HDACs
Vorinostat
Ac
Open Chromatin
Gene transcription
GSK525762
CPI-0610
Myc Transcription
BRD4
Open Chromatin
TH-302
Chronic Hypoxia
B
mAbs and ADCs
DM4
BT062
CD138
Mitotic Arrest
Mitotic Arrest
MMAF
J6M0
BCMA
ADCC
SLAMF-7
ELO
FcR
DARA/SAR
CD38
Crosslink Apoptosis
CDC
Effector Cell
C1q
ER
DNA damage
Nucleus
MM Cell
E
Ipilimumab
CTLA4
Anergic Exhausted Cytotoxic T cell
PD-L1
PD-1
MDSC
Pidilizumab
Pembrolizumab
Nivolumab
Anergic Exhausted NK-T cell
KIR
Lirilumab
pDC
Immune Checkpoint Blockade
A
B-AP15
P5091
Ub
RA190
Ricolinostat
Aggresome
Proteasome
Ixazomib
Marizomib
NOX-A12
CXCL12
IL-6
MM-BMSC
IL-1β
IL-10
Anergic Exhausted Cytotoxic T cell
Anergic Exhausted NK-T cell
MDSC


PD-L1/PD-1 binding inhibits T cell killing of tumor cell
Tumor cell
PD-L1
Antigen
T cell receptor
PD-1
T cell
Blocking PD-L1 or PD-1 allows T cell killing of tumor cell
Tumor cell death
PD-L1
Anti PD-L1
Anti PD-1
PD-1
T cell

Are IMiDs and PD-1 Inhibitors Synergistic in Multiple Myeloma?

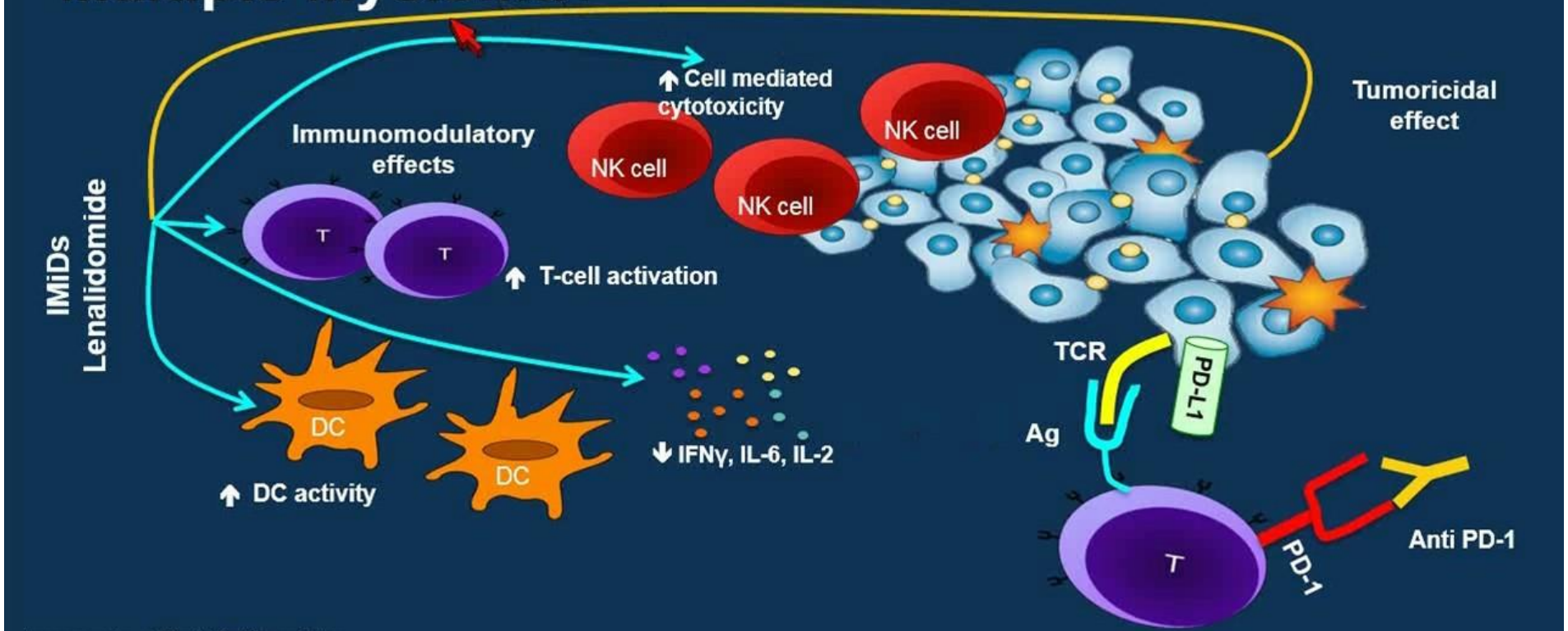


Image courtesy of Paula Rodríguez-Otero

Pembrolizumab in Combination With Lenalidomide and Low-Dose Dexamethasone for Relapsed/Refractory Multiple Myeloma: Final Efficacy and Safety Analysis

Maria-Victoria Mateos,[1] Robert Orlowski,[2] David Siegel,[3] Donna Reece,[4] Philippe Moreau,[5] Enrique Ocio,[1] Jatin Shah,[2] Paula Rodriguez-Otero,[6] Nikhil Munshi,[7] David Avigan,[8] Rad Ghori,[9] Patricia Marinello,[9] Jesus San Miguel[6]

[1]Complejo Asistencial Universitario de Salamanca/IBSAL, Salamanca, Spain; [2]The University of Texas, MD Anderson Cancer Center, Houston, TX, USA; [3]Hackensack University Medical Center, Hackensack, NJ, USA; [4]Princess Margaret Cancer Centre, Toronto, ON, Canada; [5]University Hospital Hotel-Dieu, Nantes, France; [6]Clínica Universidad de Navarra, Pamplona, Spain; [7]Dana-Farber Cancer Institute, Boston, MA; [8]Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA, USA; [9]Merck & Co, Inc, Kenilworth, NJ, USA

ASCO ANNUAL MEETING '16

Pembrolizumab + Pomalidomide/ Dexamethasone in R/R MM: Efficacy

Outcome, %	Evaluable Pts (N = 27)	Double Refractory (n = 20)	High-Risk Cytogenetics (n = 12)
ORR	60	55	50
▪ sCR	4	0	0
▪ CR	0	0	0
▪ VGPR	15	10	8
▪ PR	41	45	42
SD	30	30	42
PD	10	15	8

- M-protein or FLC reduction from baseline of up to 85%
- Durable responses; median time to best response: 2 mos (range 1-9)
- Median PFS, OS not reached with short 7.4-mo follow-up

Badros AZ, et al. ASH 2015. Abstract 506.

Slide credit: clinicaloptions.com

Table 2 Selected Adverse Events

Agent, Patients (N), and Study [Reference]	Nivolumab N = 296[7]		Pembrolizumab N = 135[65]		MPDL3280A N = 171[a][49]		BMS-936559 N = 207[17]		MEDI4736 10 mg/kg q2wk N = 346[19]		MSB-0010718C N = 28[67]	Ipilimumab N = 131[68]	
Adverse Event	**Any Gr**	**Gr 3/4**	**Any Gr**	**Gr 3/4**	**Any Gr**	**Gr 3/4**	**Any Gr**	**Gr 3/4**	**Any Gr**	**Gr 3/4**	**Any Gr**	**Any Gr**	**Gr 3/4**
Pneumonitis	3%	1%	4%	0%	NR	0%	NR	NR	1%	0%	NR	NR	NR
Diarrhea	11%	1%	20%	1%	26%	1%	9%	0%	5%	0%	10.7%	32.8%	5.3%
Colitis	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	7.6%	5.3%
Rash	12%	0%	21%	2%	18%	1%	7%	0%	0%	< 1%	NR	19.1%	0.8%
Pruritus	9%	< 1%	21%	1%	NR	NR	6%	0%	0%	< 1%	NR	24.4%	0%
Vitiligo	3%	0%	9%	0%	NR	NR	2%	0%	NR	NR	NR	2.3%	0%
ALT elevation	4%	1%	8%	0%	NR	3%	1%	0%	4%	1%	NR	1.5%	0%
AST elevation	3%	1%	10%	1%	NR	NR	NR	NR	4%	1%	10.7%	0.8%	0%
Infusion reaction/hypersensitivity	3%	< 1%	NR	NR	NR	NR	11%	< 1%	NR	NR	NR	NR	NR
Fatigue	NR	NR	30%	1%	43%	4%	NR	NR	13%	1%	35.7%	42%	6.9%
Hyperthyroidism/hypothyroidism	3%	< 1%	8%	1%	NR	NR	3%	0%	3%	< 1%	NR	1.5%	0%

[a]Regardless of attribution.

ALT = alanine transaminase; AST = aspartate transaminase; Gr = grade; NR = not reported.

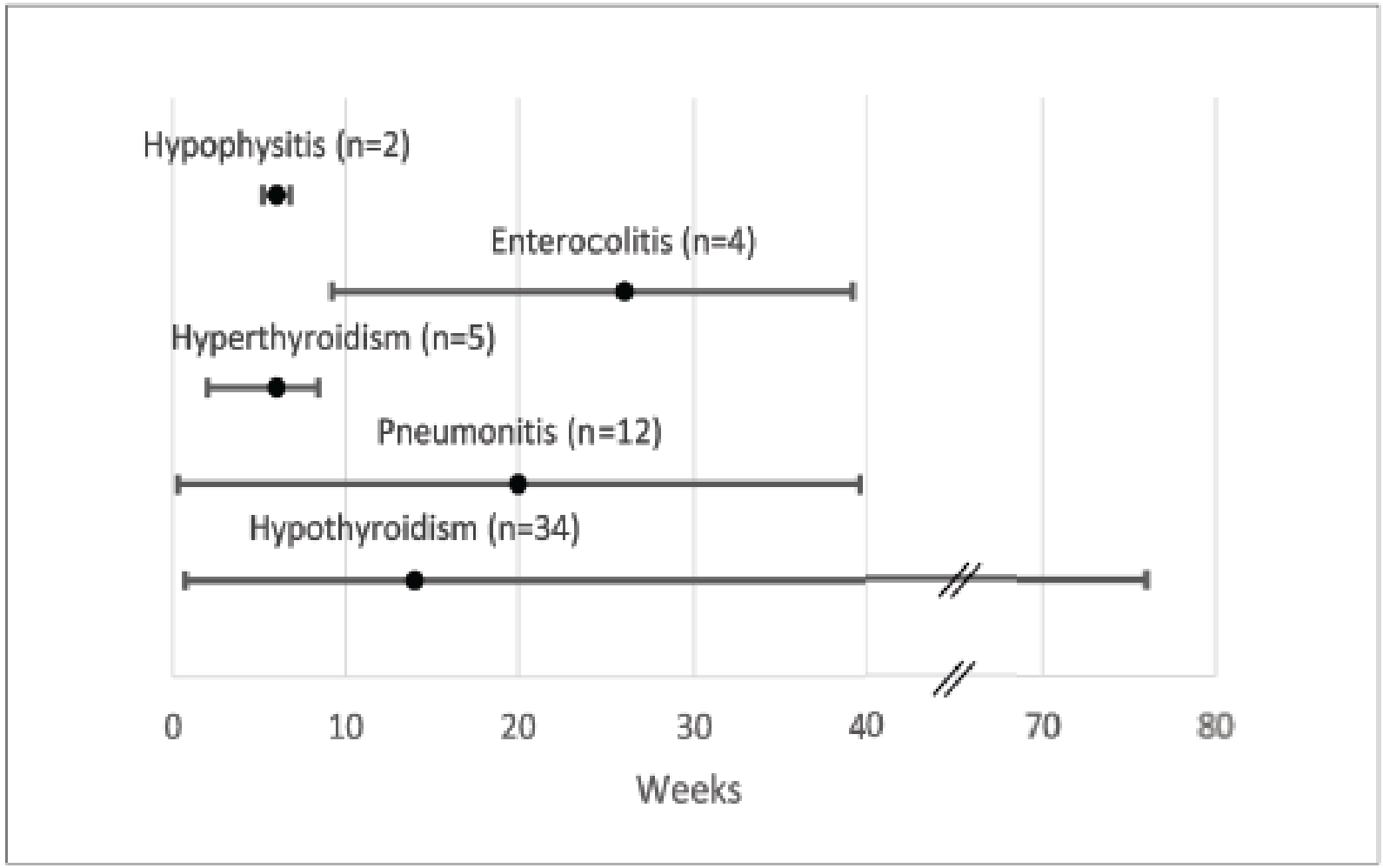
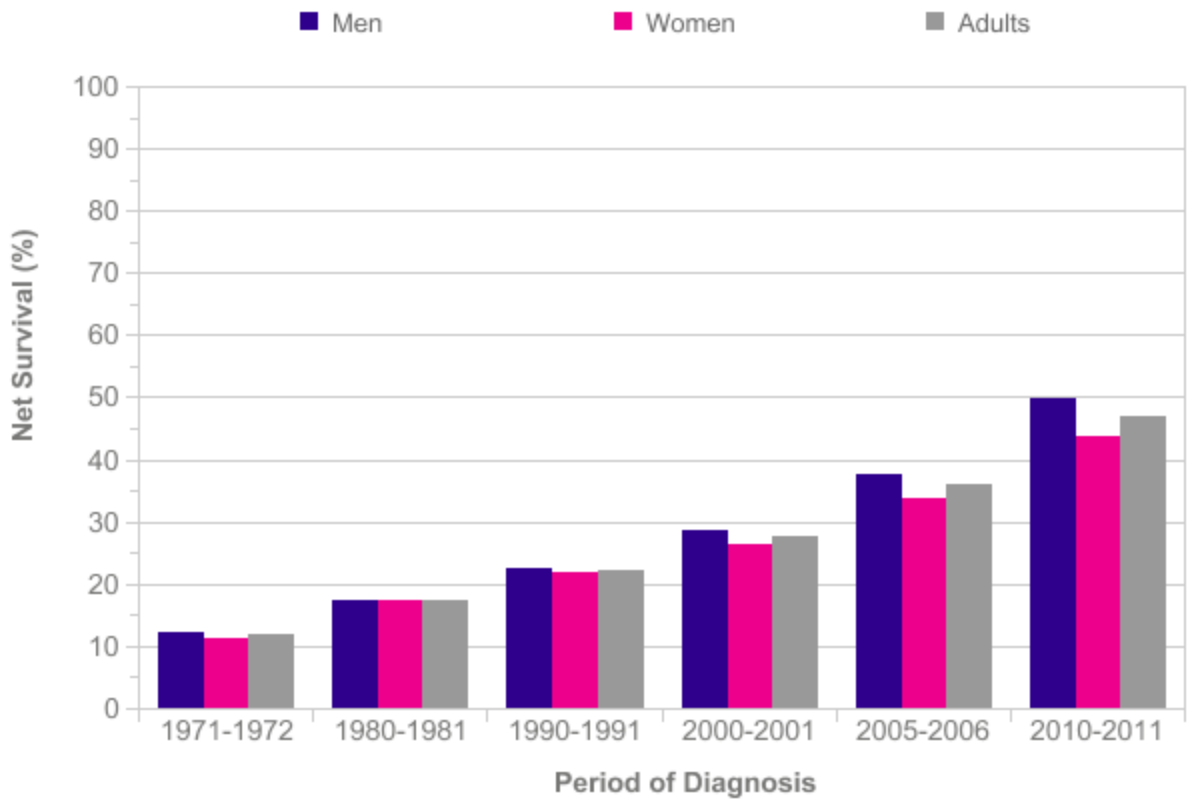


Figure 1: Time After Initiation of Therapy to Onset of Various Immune-Mediated Adverse Events In 411 Patients With Advanced Melanoma Who Received Pembrolizumab—Circles represent median; bars signify ranges. Data are from pembrolizumab prescribing information.[39]

TRAITEMENTS ADJUVANTS

- Antibiotiques
- Vaccinations
- Facteurs de croissance : érythropoïétine
  G-CSF
- Biphosphonates, calcium, vitamine D
- Radiothérapie
- Kyphoplastie
- Anticoagulants
- Antidouleurs
- ….

MYELOME : SURVIE



CONCLUSIONS

- Maladie de la personne âgée
- Maladie mortelle
- Maladie chronique
- Nouvelles thérapeutiques ciblées
- Allongement de la survie
- Coût!!