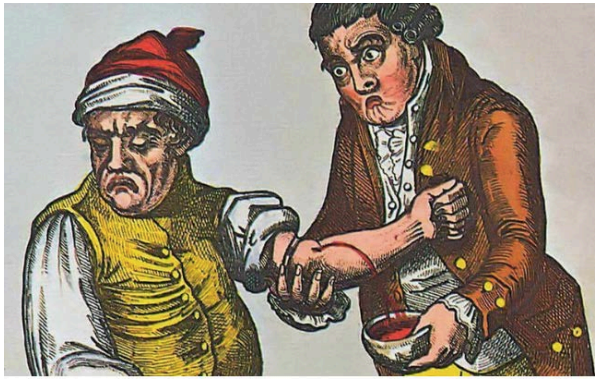
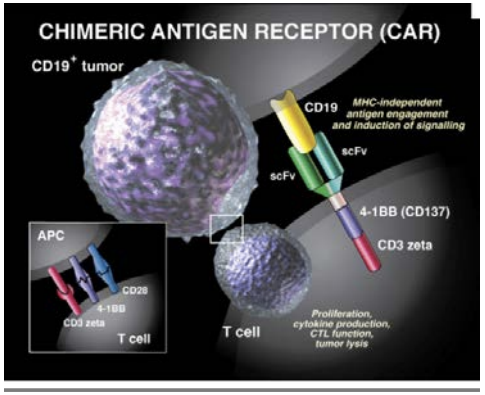
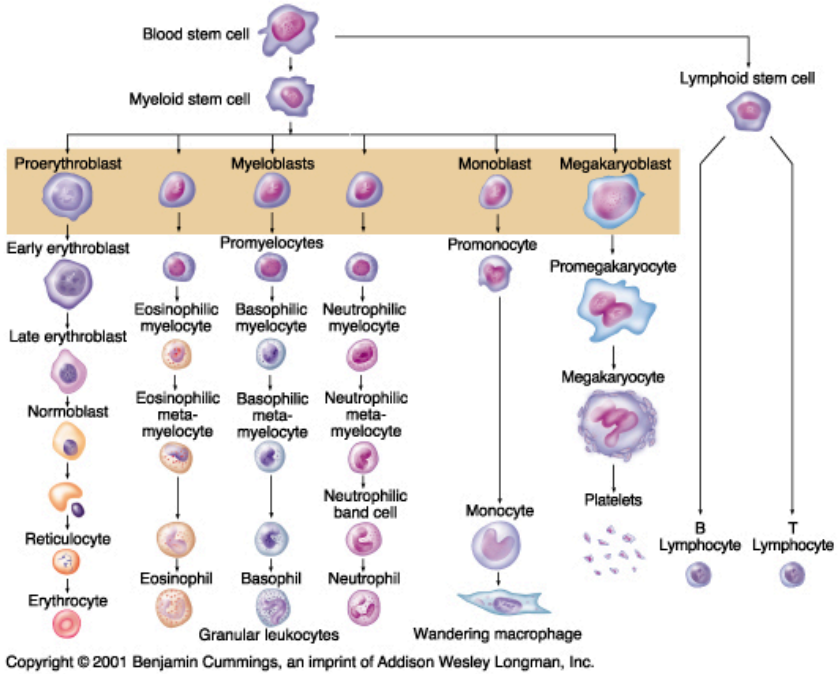
Evolution des traitements en hématologie

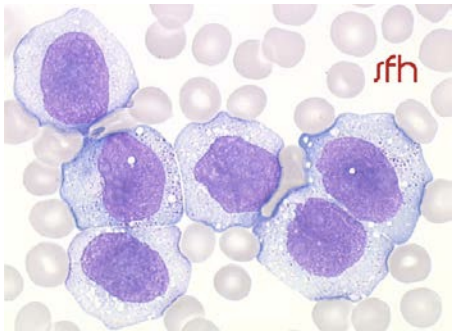


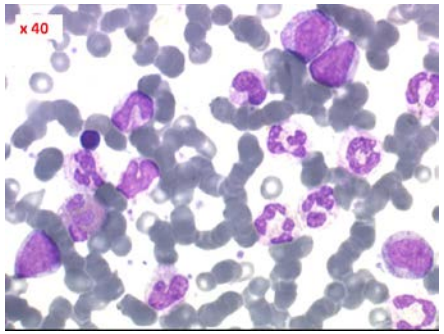


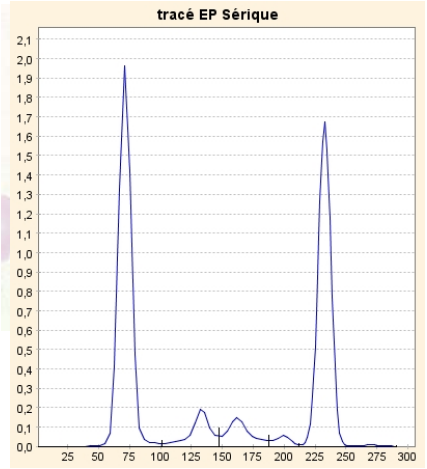
Maladies traitées en hématologie

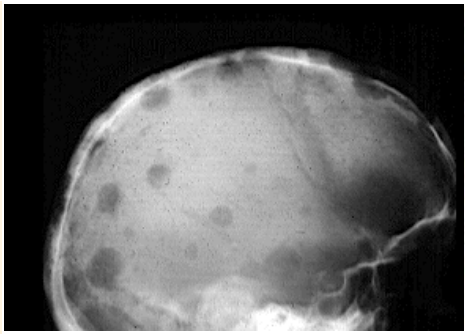
- Malignes:
  - Myéloïdes
    - Leucémies aigües
    - Syndrome myéloprolifératifs chroniques
      - Maladie de Vaquez
      - Thrombocytémie essentielle
      - Leucémies myéloïdes chroniques
      - Myélofibrose primitives
  - Lymphoïdes
    - Lymphomes
      - Maladie de Hodgkin
      - Lymphomes non-hodgkinien
    - Leucémie lymphoïde chronique
    - Myélomes



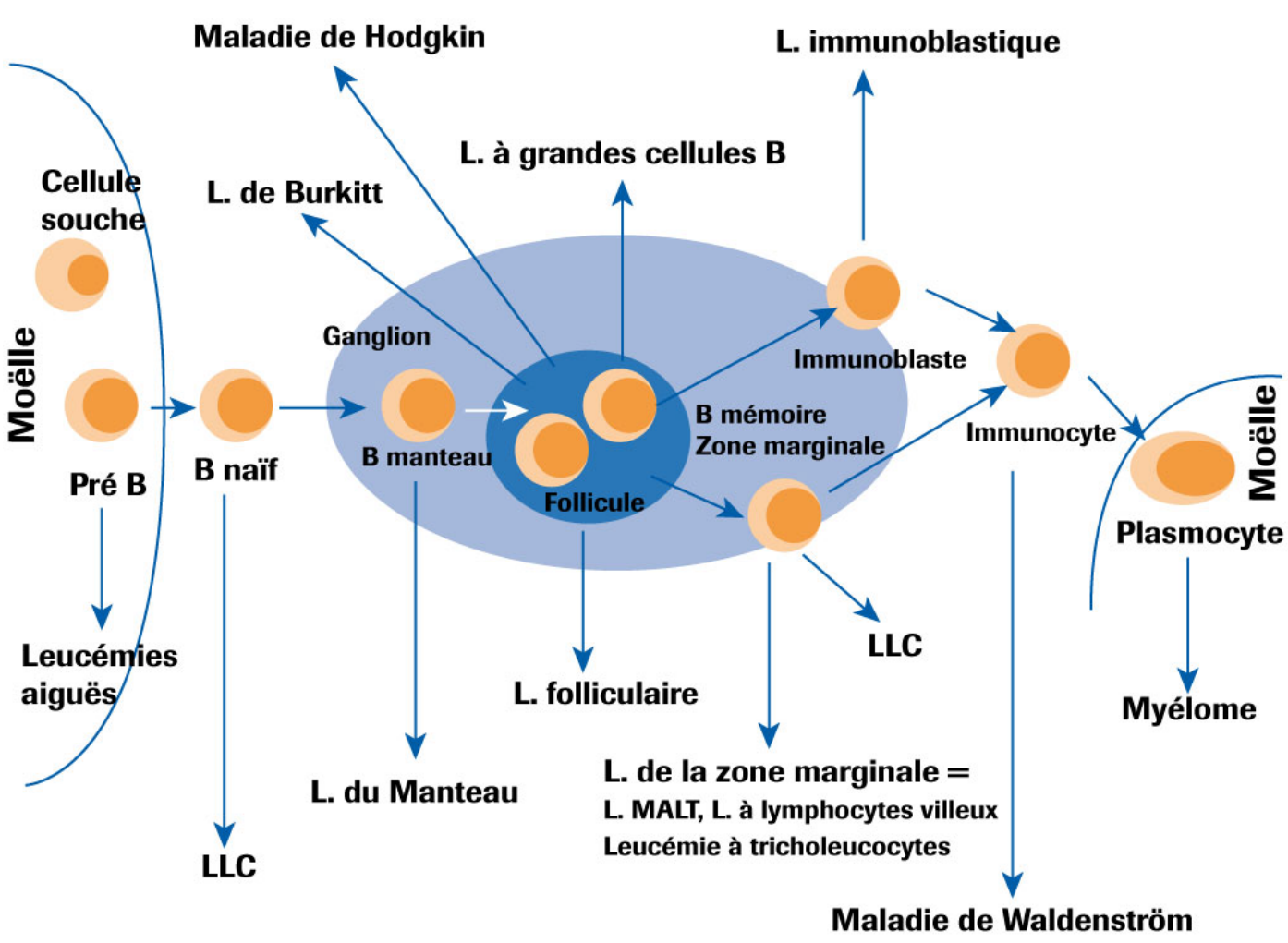


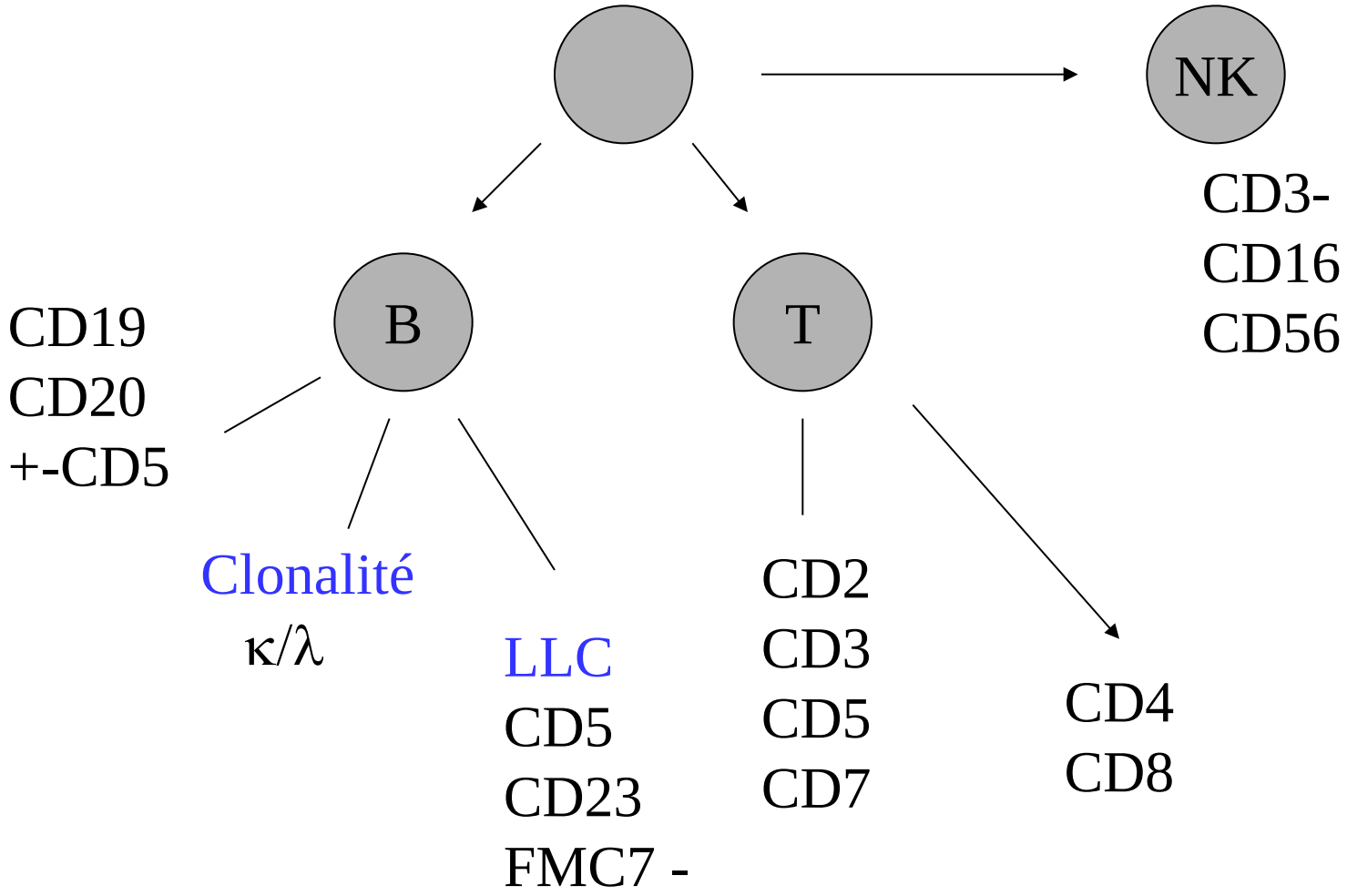






Type du lymphome fonction de la nature de la cellule responsable




NK
CD3-
CD16
CD56
B
T
CD19
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FMC7 -
CD2
CD3
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CD7
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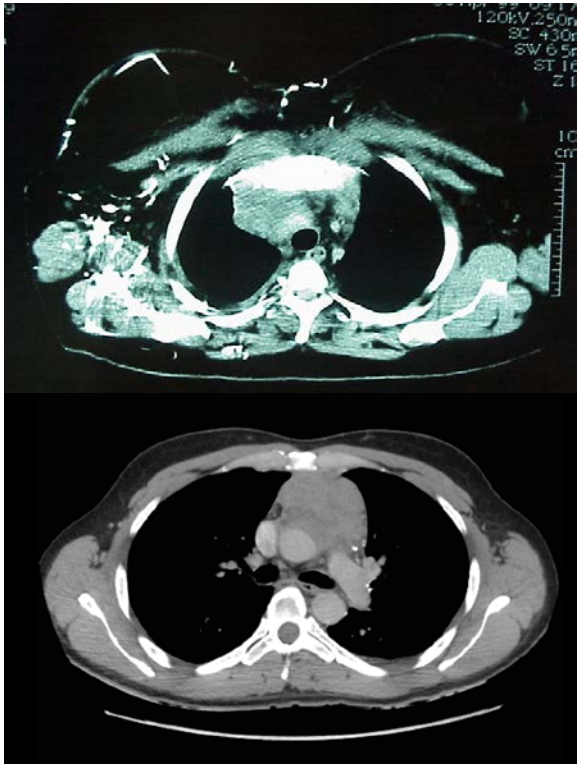
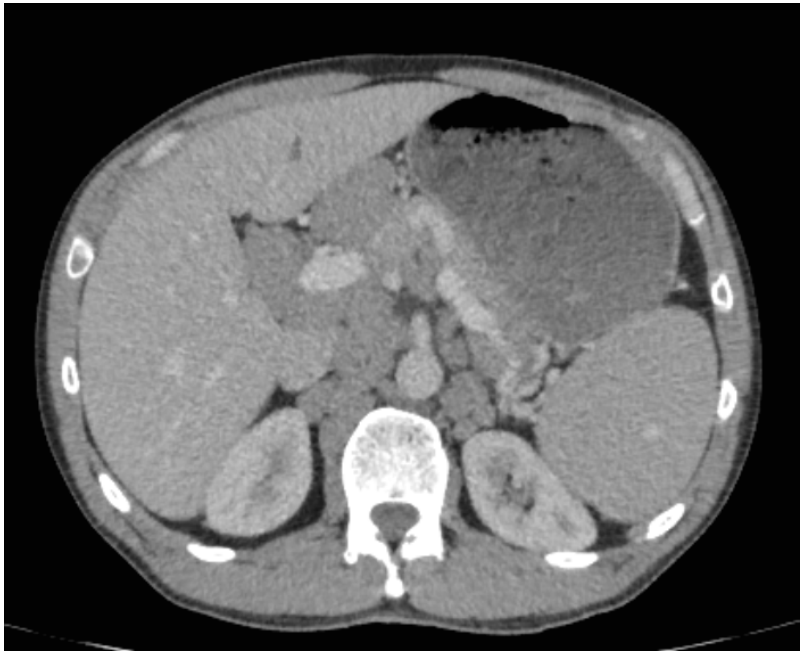
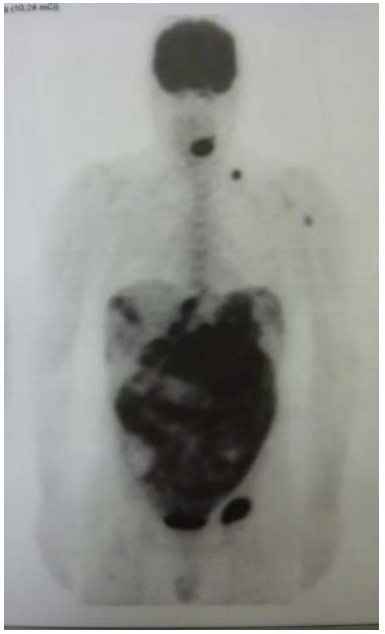
CD8





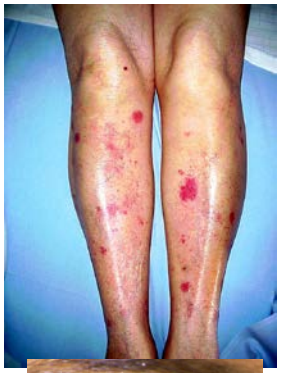
ETUDE PRE-POST THERAPEUTIQUE

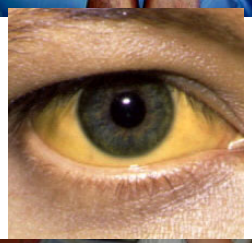
PRE THERAPEUTIQUE 20/08/2014

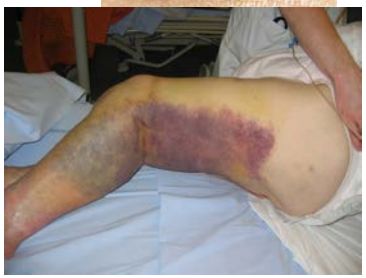


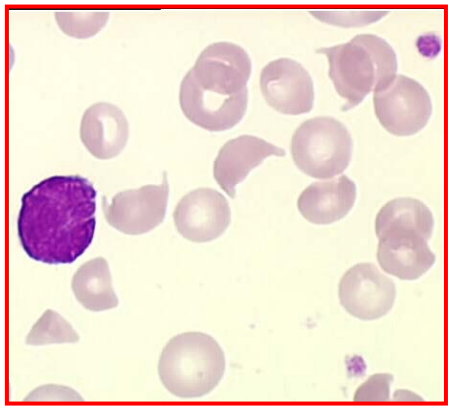
Maladies traitées en hématologie

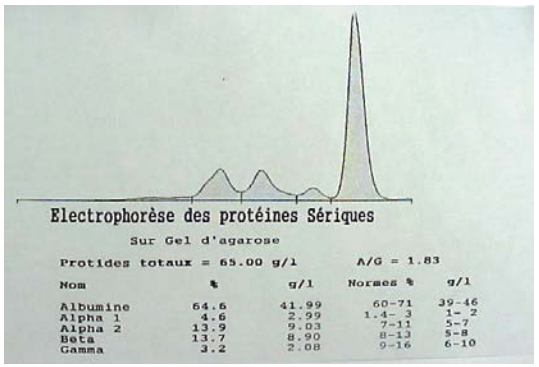
- Non malignes
  - Cytopénies auto-immunes et autres pathologies liées à des auto-anticorps
  - Microangiopathies thrombotiques
  - Déficits immunitaires
  - Maladies de dépôt d'immunoglobulines (amylose AL)

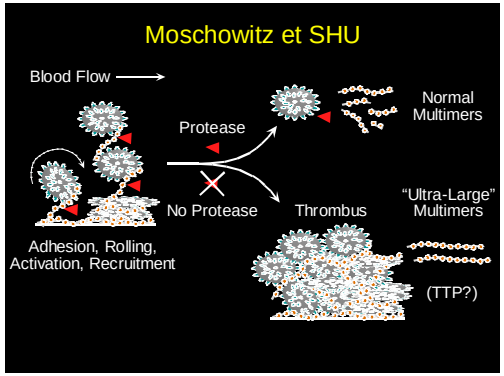


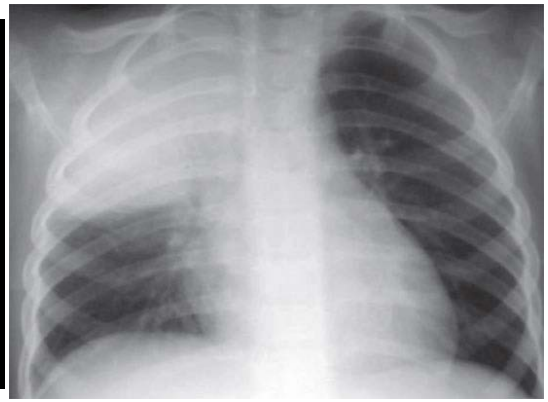






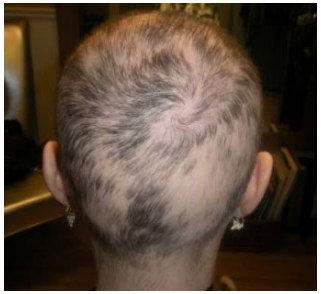


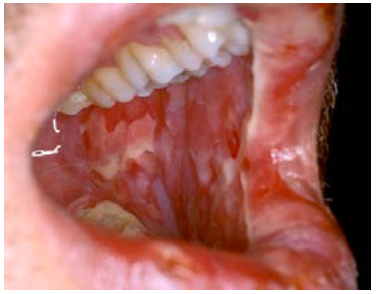




Chimiothérapies

- En général agissent sur les cellules en division en gênant la division cellulaire, pas de spécificité
- Actives sur toutes les cellules en division rapide :
  - Alopécie
  - Mucites
- Souvent émétisantes





- Toxicité multiples:
  - Baisse des cellules sanguines
  - Toxicité cardiaque, neurologique, pulmonaire etc…

- Mais guérissent ou donnent de longues rémissions dans un grand nombre de cancers hématologiques
  - 90% des maladies de Hodgkin localisées sont guéries par l'ABVD
  - 5 ans de rémission pour les leucémies lymphoïdes chroniques avec FCR

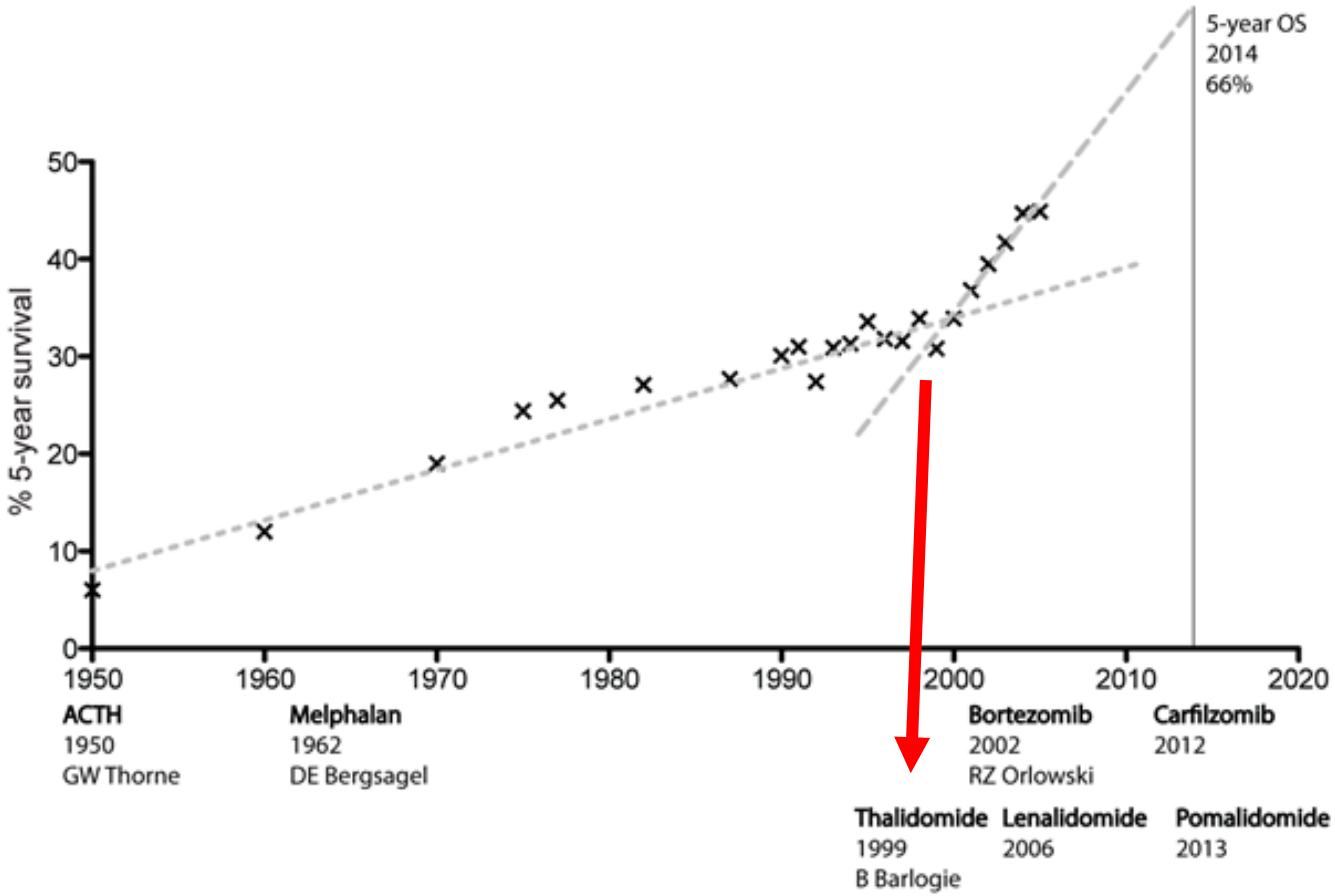
Chimiothérapies

- Plusieurs familles
  - Alkylants (endoxan, alkeran): ajoutent un groupe alkyle bloquant la réplication de l'ADN
  - Antimétabolites (methotrexate): prennent la place des bases purines ou pyrimidines ou inhibent leur synthése, bloquant la synthèse de l'ADN et la mitose
  - Alcaloïdes: poisons du fuseau qui bloquent la division cellulaire
  - Inhibiteurs de la topoisomérase: perturbent l'enroulement de l'ADN

Myélome: progrès en 40 ans

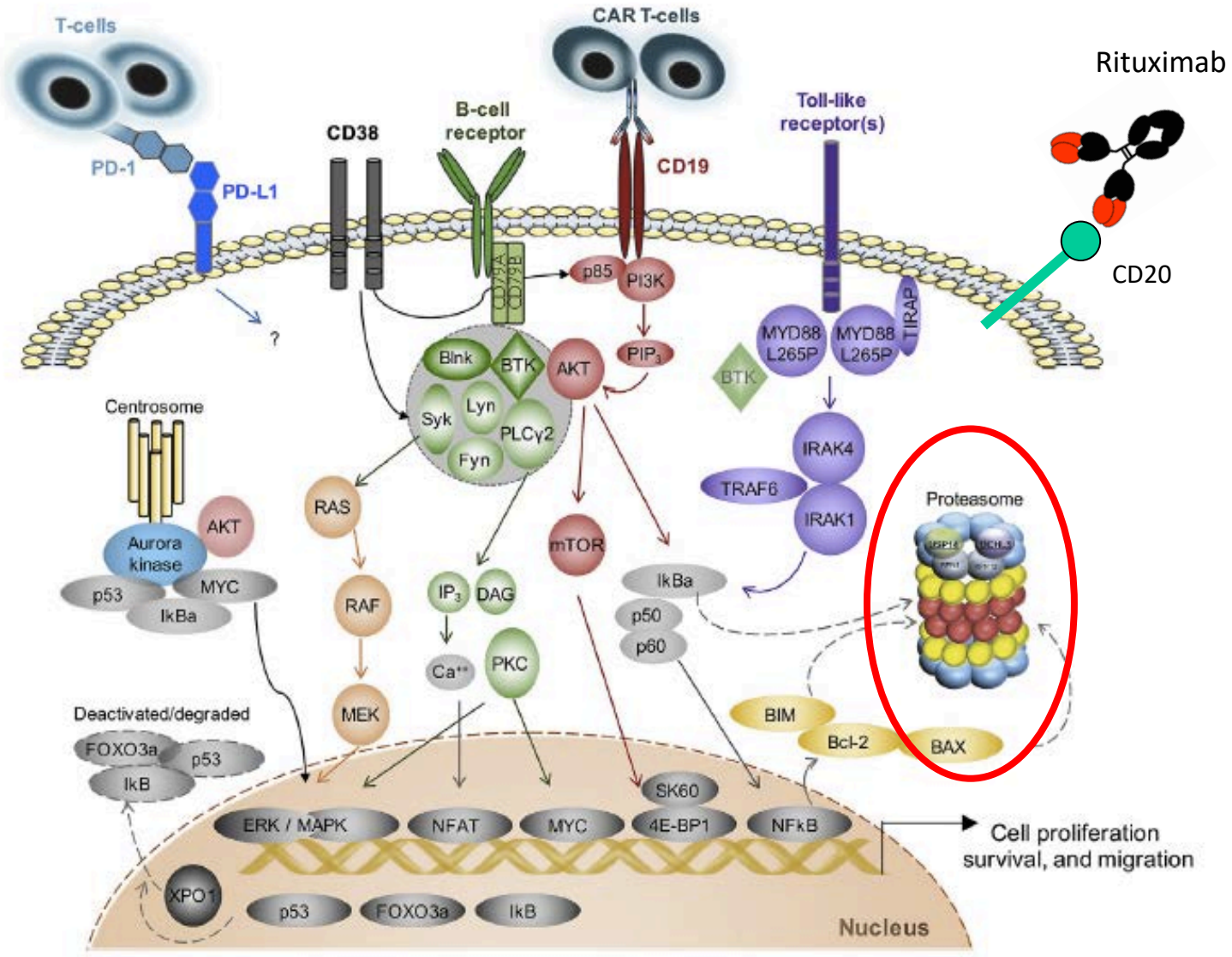
Improving 5-year survival in multiple myeloma.

Five-year survival rates from the SEER 1975-2010 database are plotted, with the introduction of active drugs noted on the bottom. A dramatic increased rate of improvement was noted for patients diagnosed from 1999 to 2005. If this trend has continued, the 5-year survival for a patient diagnosed in 2014 should be approximately 66%.

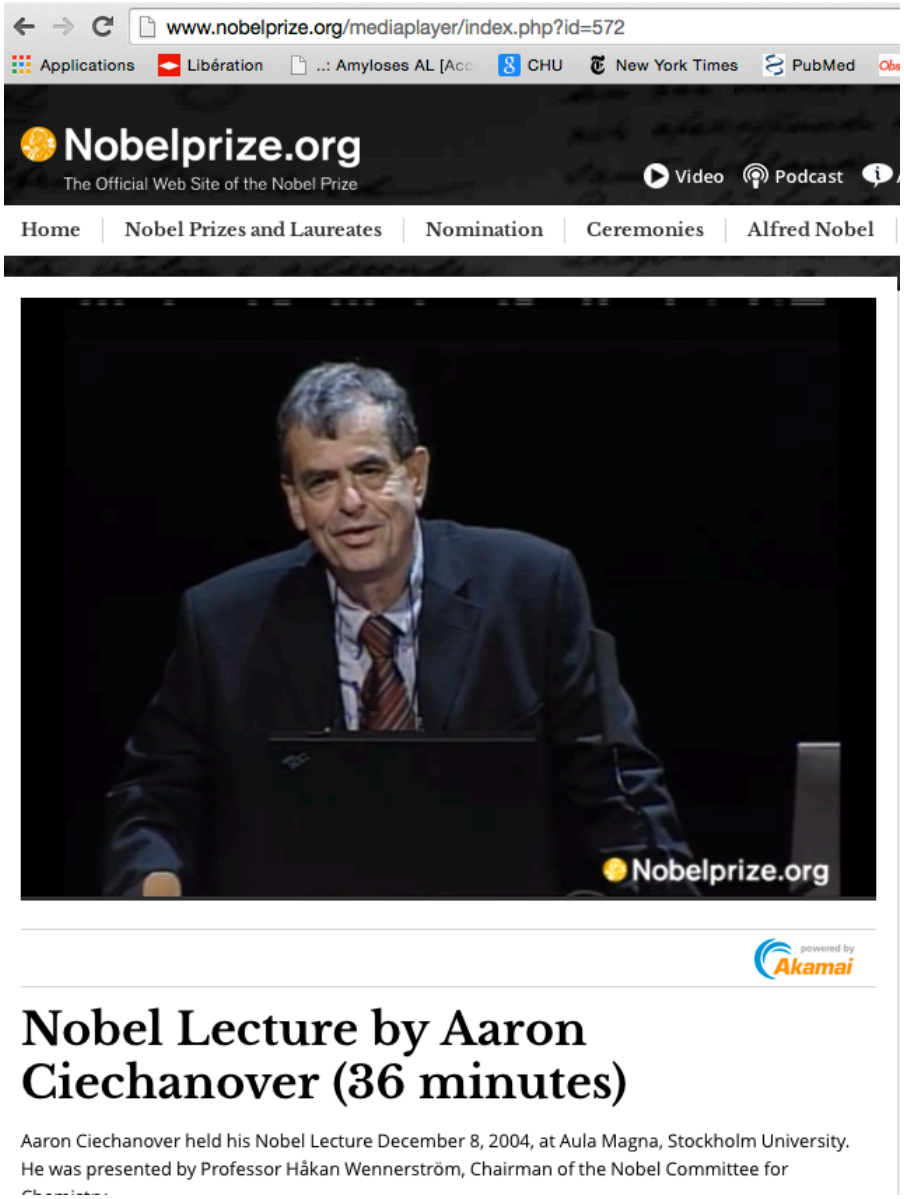


Expand

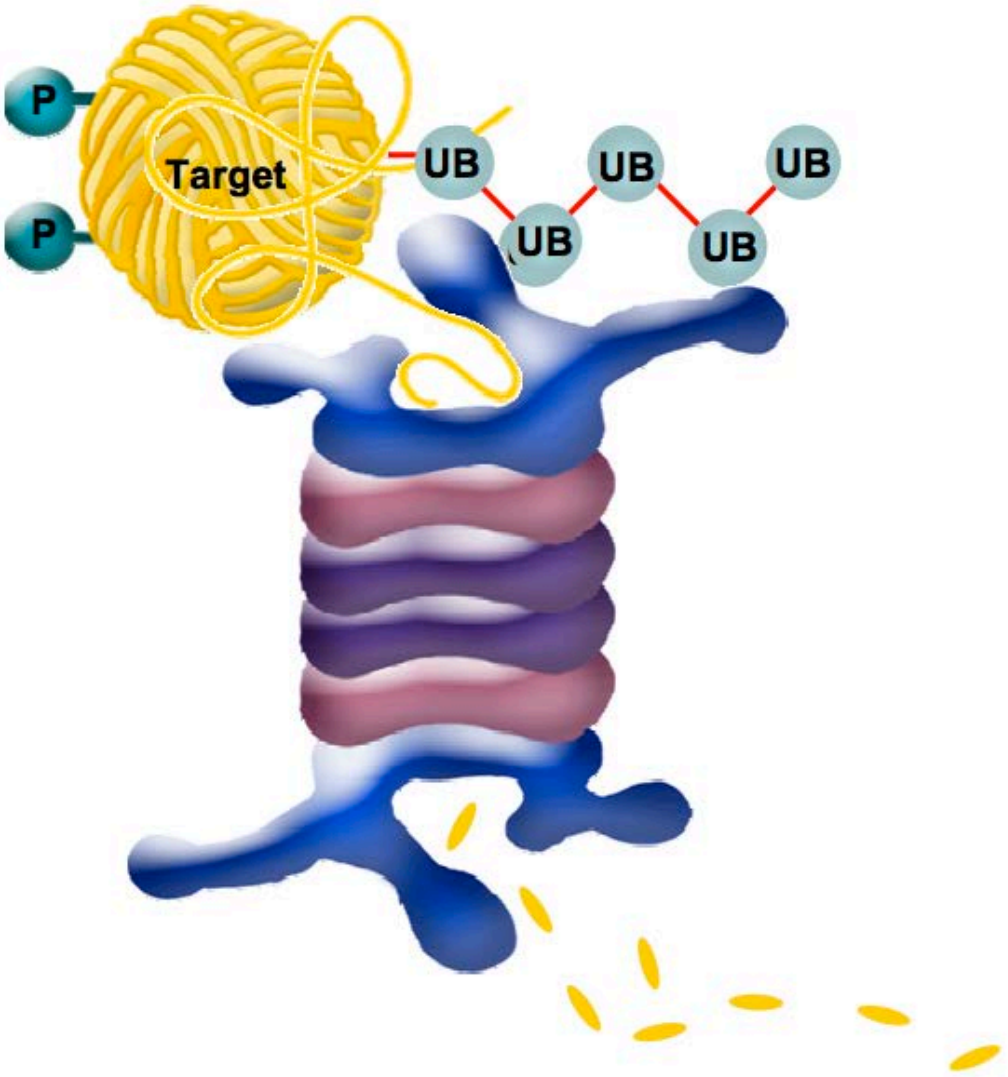
Biologie des cellules et des cancers



Inhibiteurs du protéasome



Inhibiteurs du protéasome



Inhibiteurs du protéasome

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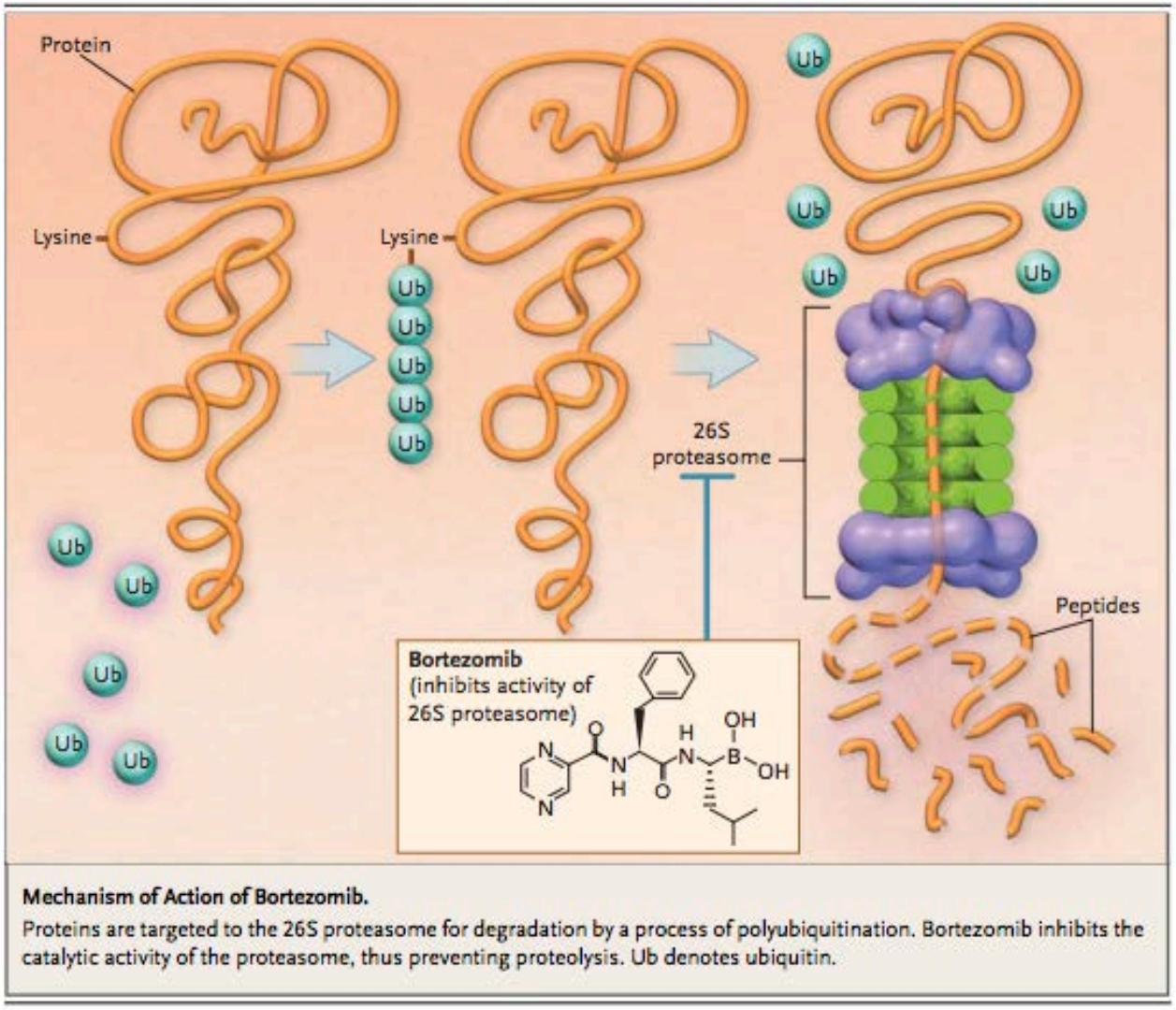
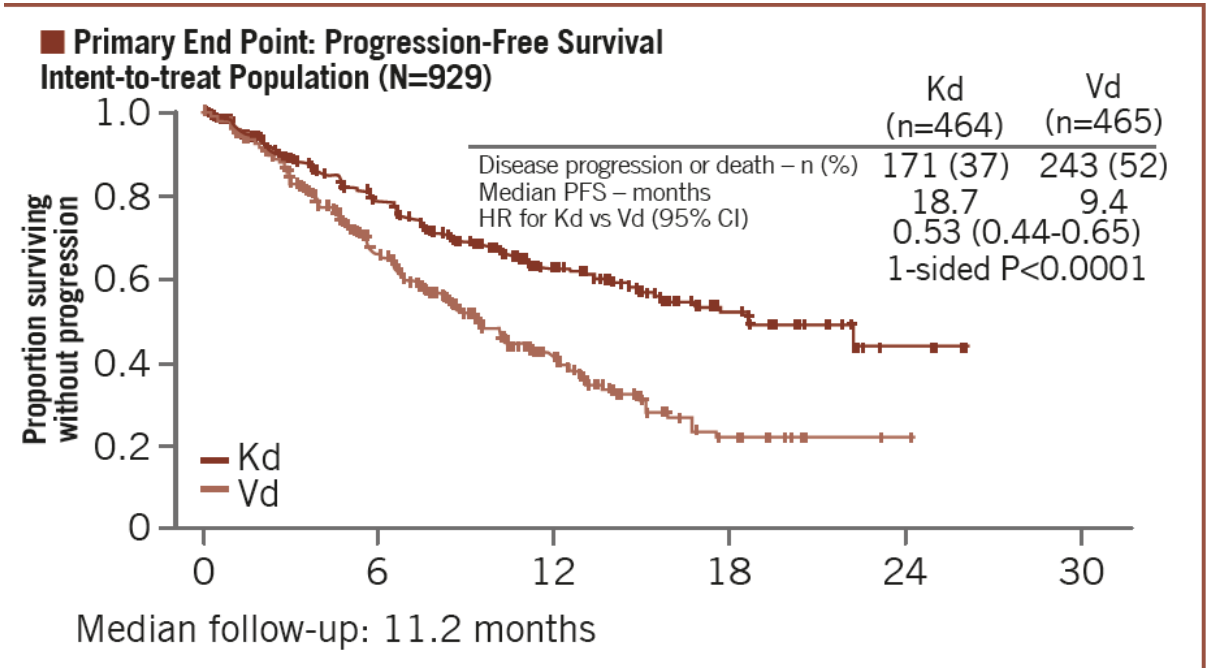


Mechanism of Action of Bortezomib.

Proteins are targeted to the 26S proteasome for degradation by a process of polyubiquitination. Bortezomib inhibits the catalytic activity of the proteasome, thus preventing proteolysis. Ub denotes ubiquitin.

Inhibiteurs du protéasome

- Bortezomib
- Ixazomid (oral)
- Carlfizomib



IMID

Thalidomide

IMID

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Correction Has Been Published

Antitumor Activity of Thalidomide in Refractory Multiple Myeloma

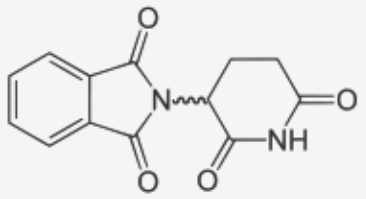
Seema Singhal, M.D., Jayesh Mehta, M.D., Raman Desikan, M.D., Dan Ayers, M.S., Paula Roberson, Ph.D., Paul Eddlemon, B.S., Nikhil Munshi, M.D., Elias Anaissie, M.D., Carla Wilson, M.D., Ph.D., Madhav Dhodapkar, M.D., Jerome Zeldis, M.D., David Siegel, M.D., Ph.D., John Crowley, Ph.D., and Bart Barlogie, M.D., Ph.D.

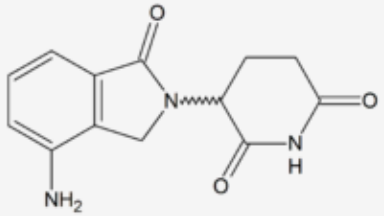
N Engl J Med 1999; 341:1565-1571 | November 18, 1999 | DOI: 10.1056/NEJM199911183412102

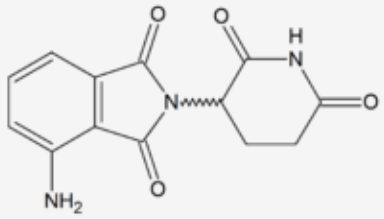
IMID

- 3 molécules très proches d'efficacité croissante
  - Thalidomide
    - Neurophaties, pas de cytopénie
  - Lenalidomide
    - Cytopénies, pas de neuropathies, éliminée par le rein
  - Pomalidomide
    - Cytopénies, pas de neuropathies, non éliminée par le rein

IMID

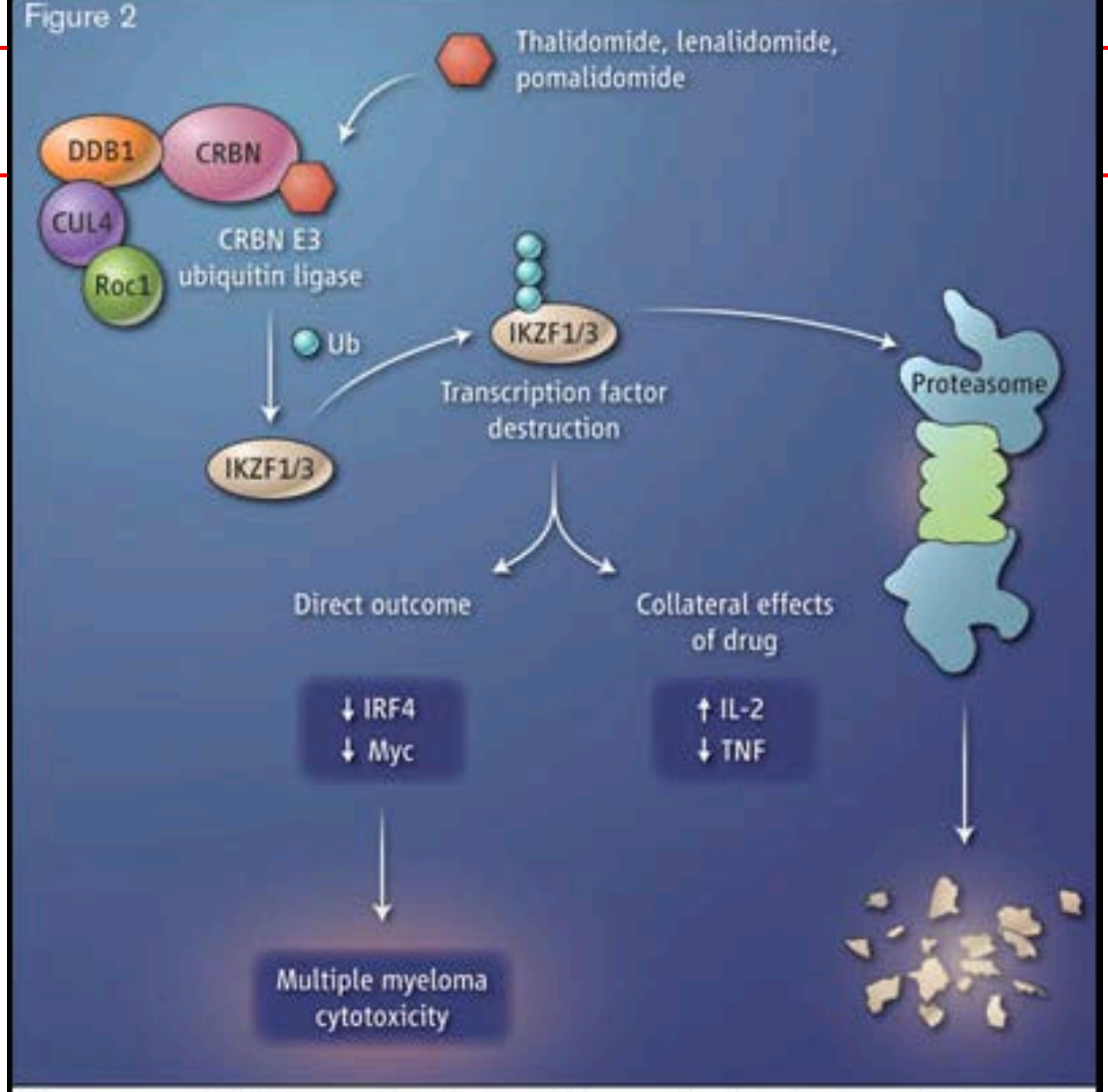
Thalidomide		
T_{max} [drug]	4 – 6 hours in subjects with MM.[14]	
Protein binding	55 – 65% [15]	
Metabolites	Hydrolized metabolites[15]	
Half-life [$t_{1/2}$]	5,5 – 7,6 hours[15]	

Lenalidomide		
T_{max} [drug]	0,6 – 1,5 hours in healthy subjects [16] 0,5 – 4 hours in subjects with MM [17]	
Protein binding	~30% [16]	
Metabolites	Has not yet been studied [16]	
Half-life [$t_{1/2}$]	3 hours in healthy subjects [16] 3,1 – 4,2 hours in subjects with MM [17]	

Pomalidomide		
T_{max} [drug]	0,5 – 8 hours [18]	
Protein binding	Unknown	
Metabolites	Unknown	
Half-life [$t_{1/2}$]	6,2 – 7,9 hours[18]	

IMID

Mécanisme d'action:



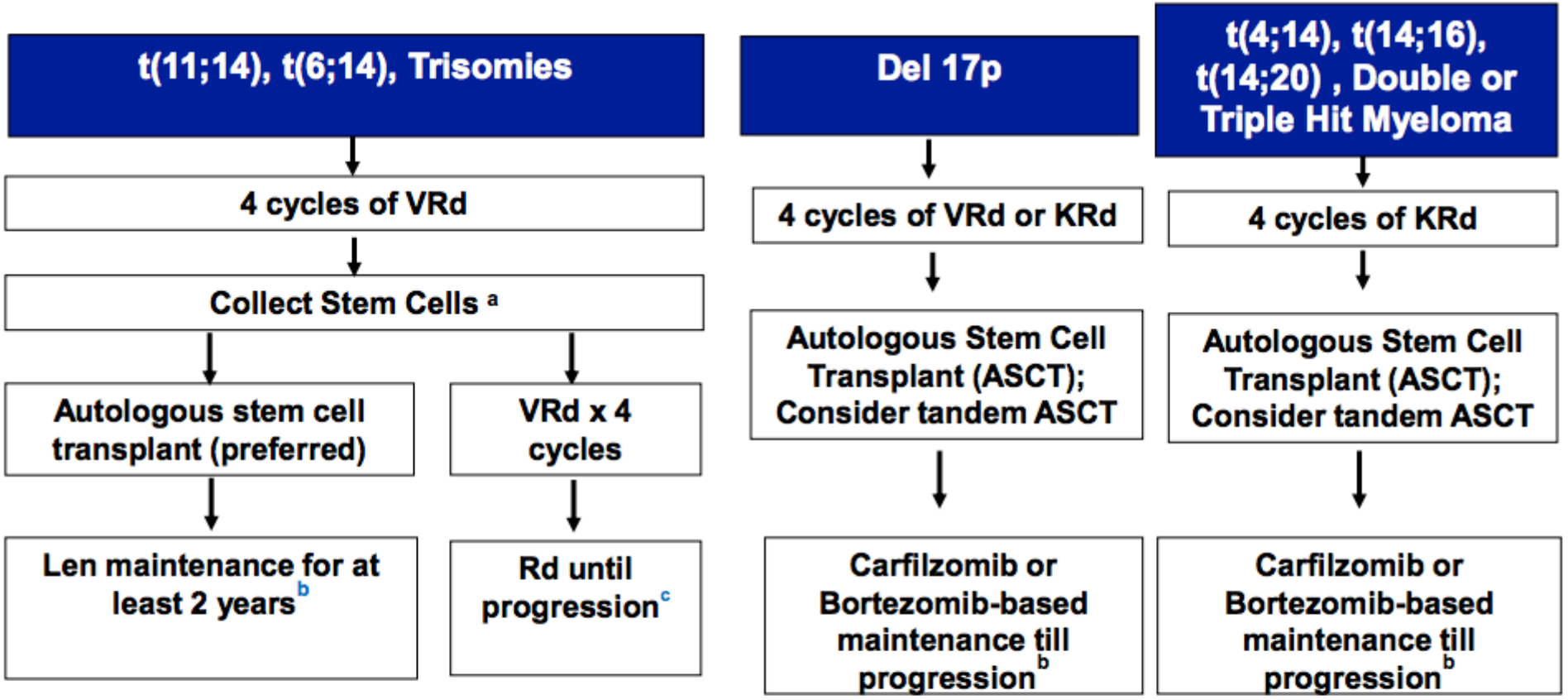
Immune modulators and myeloma. The small-molecule drugs thalidomide, lenalidomide, and pomalidomide bind to the protein cereblon (CRBN), which activates the enzymatic activity of the CRBN E3 ubiquitin ligase complex. The transcription factors Ikaros (IKZF1) and Aiolos (IKZF3) are modified with ubiquitin (Ub) molecules, targeting them for proteolysis. This alters the function of T cells and B cells, with a toxic outcome for multiple myeloma cells.

From Stewart KA. How thalidomide works against cancer. Science. 2014;343:256-257. Reprinted with permission from AAAS.

MAYO CLINIC

mSMART – Off-Study

Transplant Eligible



[a] *If age >65 or > 4 cycles of VRd, consider mobilization with G-CSF plus cytoxan or plerixafor*

[b] *Duration based on tolerance; consider risks and benefits for treatment beyond 3 years*

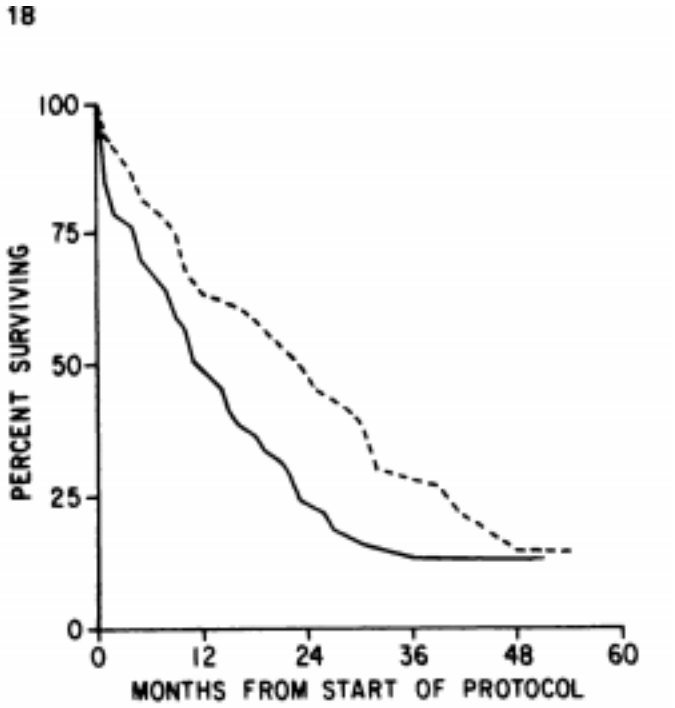
c Continuing Rd for patients responding to Rd and with low toxicities

Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110; Mikhael et al. Mayo Clin Proc 2013;88:360-376. v14 //last reviewed May 2018

Myélome: progrès en 40 ans

Tohoku J. exp. Med., 1975, 116, 317-325

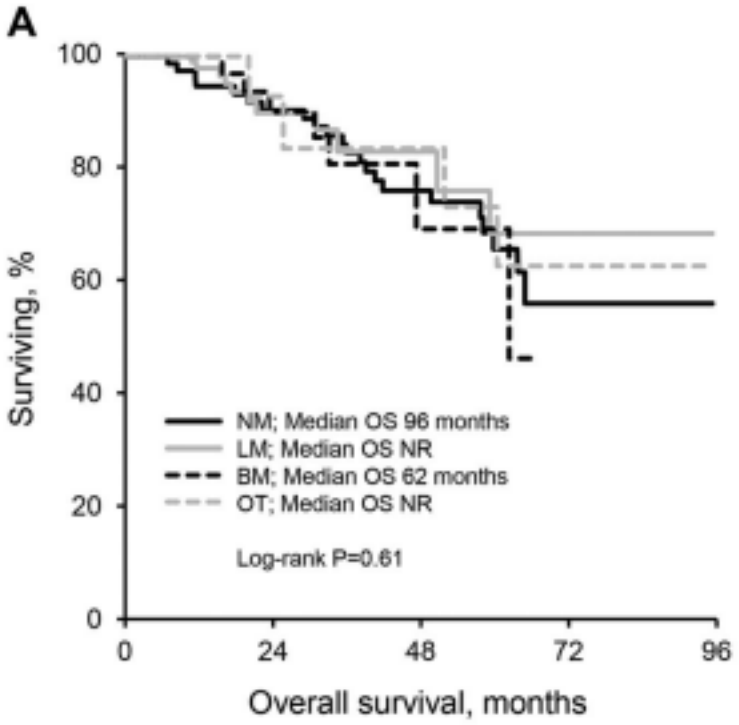
Treatment of Multiple Myeloma and Macroglobulinemia Waldenström: A Long-Term Follow-Up Study



Blood Cancer Journal

Blood Cancer J. 2018 Nov; 8(11): 106.
Published online 2018 Nov 8. doi: [10.1038/s41408-018-0147-7]
PMCID: PMC6224498
PMID: 30409963

Bortezomib, lenalidomide, and dexamethasone (VRd) followed by autologous stem cell transplant for multiple myeloma



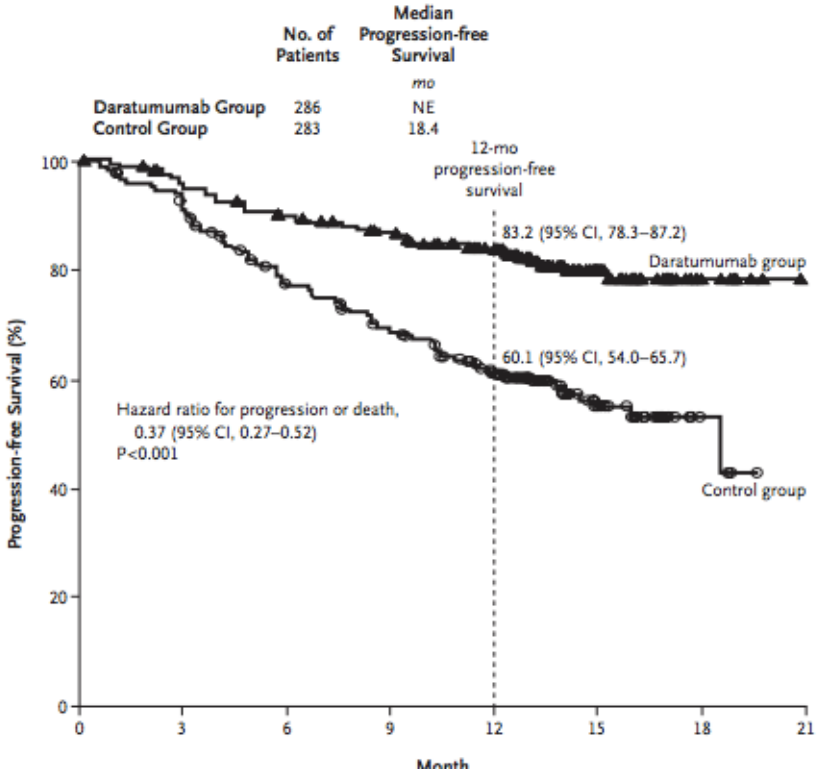
2016: daratumumab

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 6, 2016 VOL. 375 NO. 14

Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma

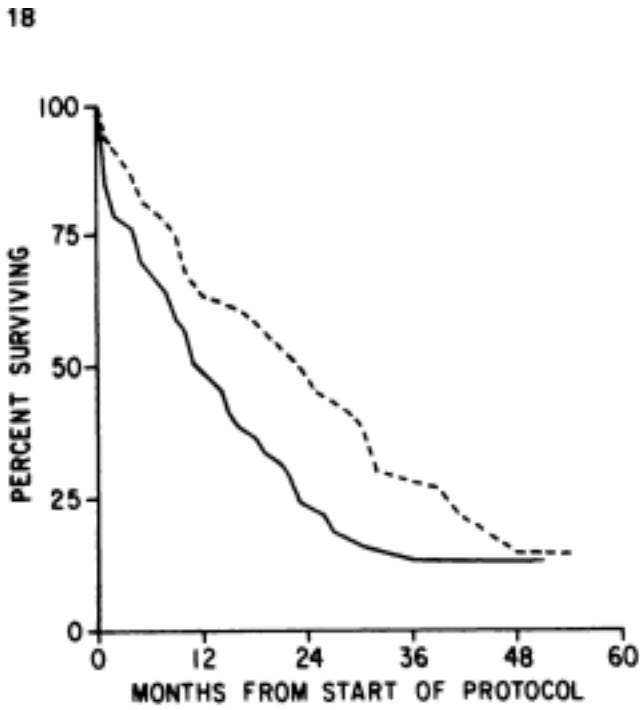
M.A. Dimopoulos, A. Oriol, H. Nahi, J. San-Miguel, N.J. Bahlis, S.Z. Usmani, N. Rabin, R.Z. Orlowski, M. Komarnicki, K. Suzuki, T. Plesner, S.-S. Yoon, D. Ben Yehuda, P.G. Richardson, H. Goldschmidt, D. Reece, S. Lisby, N.Z. Khokhar, L. O'Rourke, C. Chiu, X. Qin, M. Guckert, T. Ahmadi, and P. Moreau, for the POLLUX Investigators*



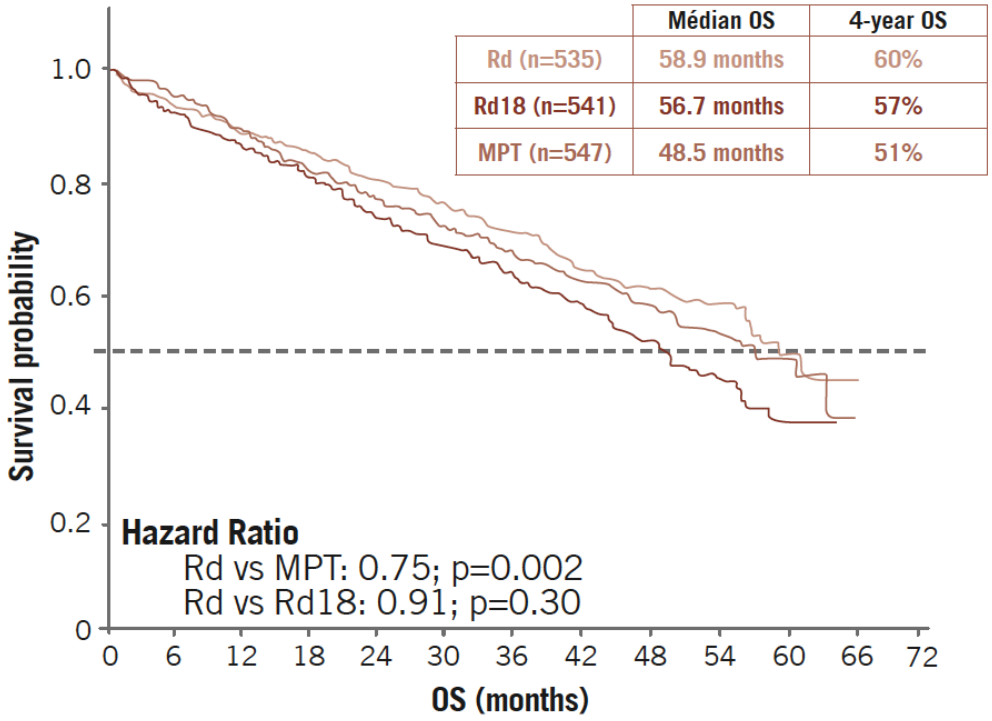
Myélome: progrès en 40 ans

Tohoku J. exp. Med., 1975, 116, 317–325

Treatment of Multiple Myeloma and Macroglobulinemia Waldenström: A Long-Term Follow-Up Study



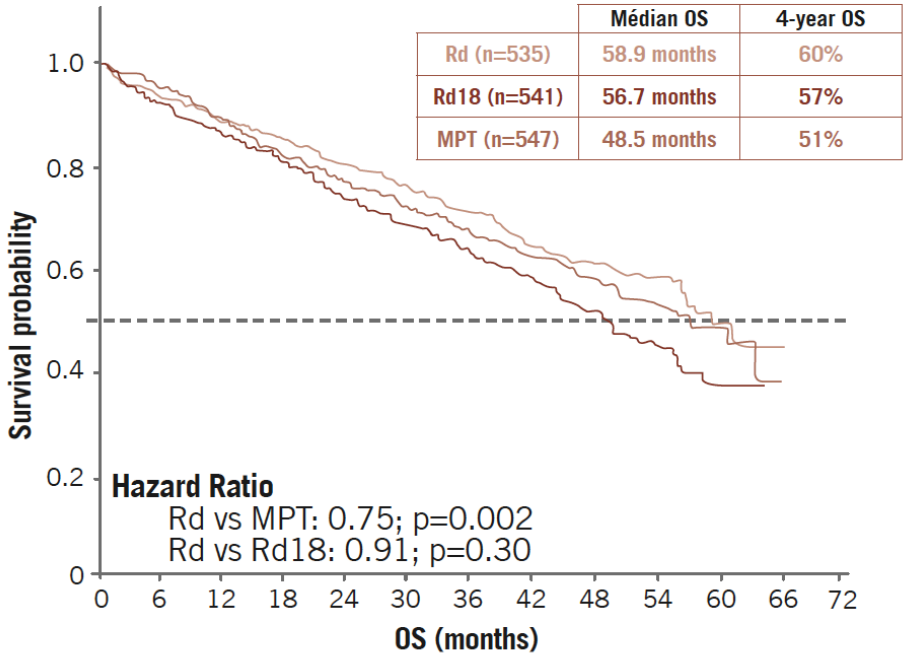
FIRST Trial: Overall survival
Median follow-up of 45.5 months as of 3 March 2014
697 deaths (43% of ITT)



Myélome: progrès en 40 ans

FIRST Trial: Overall survival
Median follow-up of 45.5 months as of 3 March 2014
697 deaths (43% of ITT)

	Médian OS	4-year OS
Rd (n=535)	58.9 months	60%
Rd18 (n=541)	56.7 months	57%
MPT (n=547)	48.5 months	51%



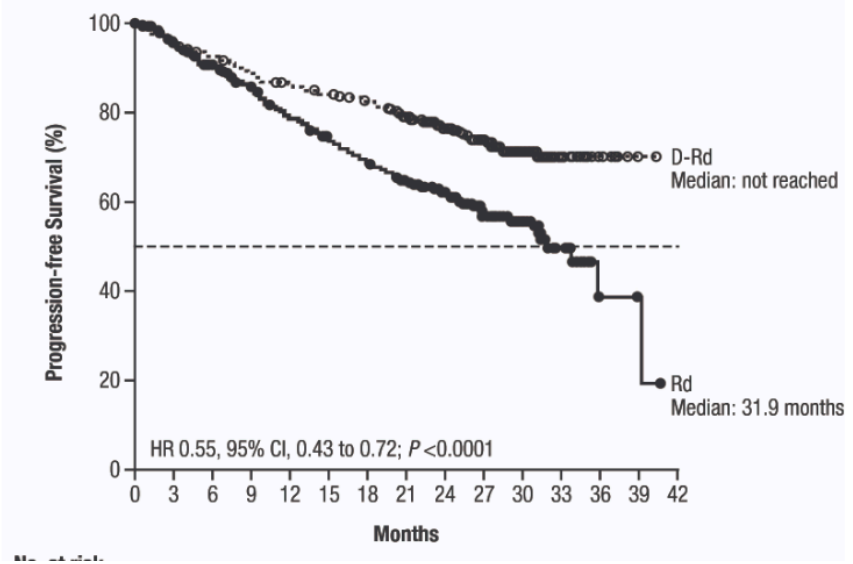
Late-Breaking Abstracts Session

Program: General Sessions
Hematology Disease Topics & Pathways:
Biological Processes

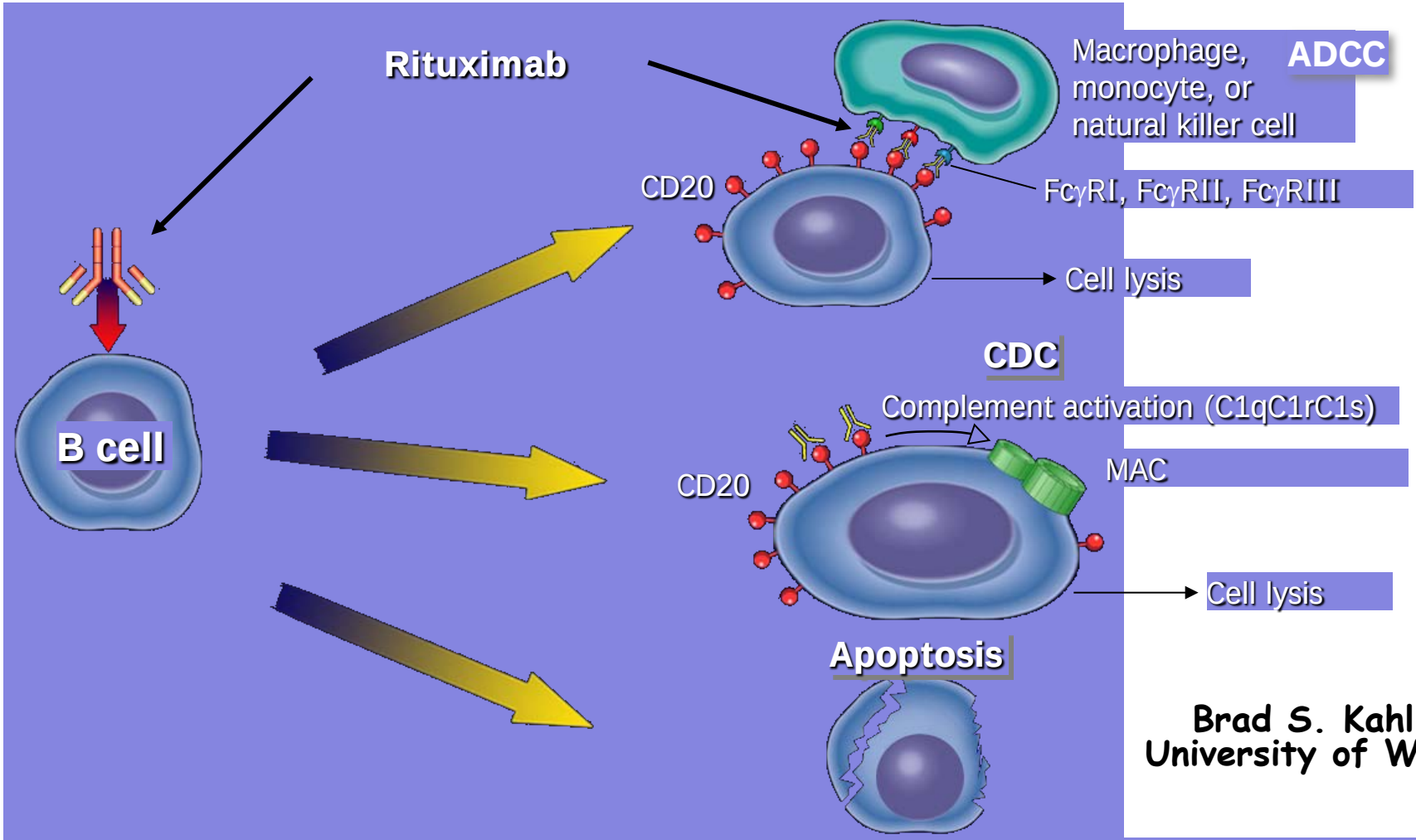
Tuesday, December 4, 2018: 7:30 AM-9:15 AM
Hall AB (San Diego Convention Center)

LBA-2 Phase 3 Randomized Study of Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) in Patients with Newly Diagnosed Multiple Myeloma (NDMM) Ineligible for Transplant (MAIA)

Figure: Progression-free survival for patients with NDMM ineligible for transplant treated with D-Rd or Rd in MAIA

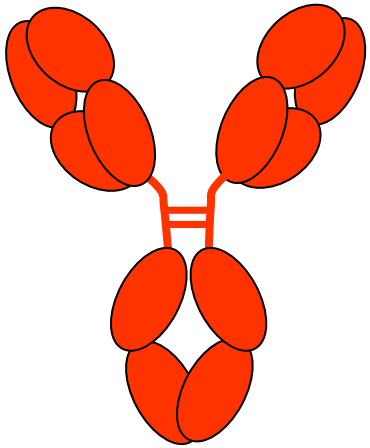


Anticorps monoclonaux: exemple Rituximab

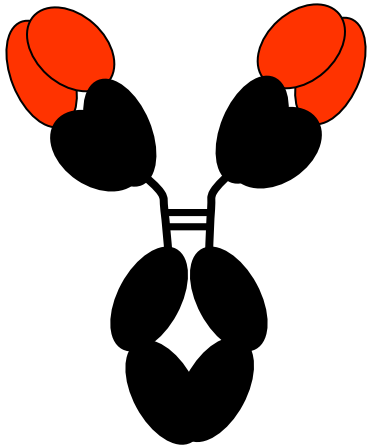


Anderson et al. *Biochem Soc Trans*. 1997;25:705; Golay et al. *Blood*. 2000;95:3900; Reff et al. *Blood*. 1994;83:435; Clynes et al. *Nat Med*. 2000;6:443; Shan et al. *Cancer Immunol Immunother*. 2000;48:673; Silverman et al. *Arthritis Rheum*. 2003;48:1484.

Evolution des AC monoclonaux

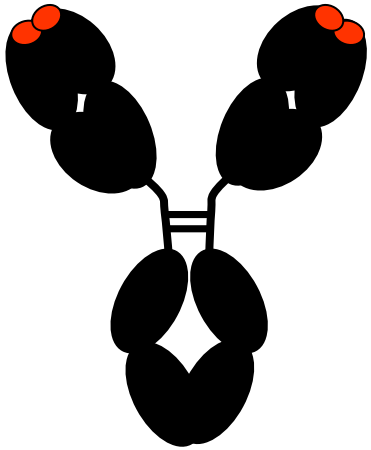


Acm murins
1975



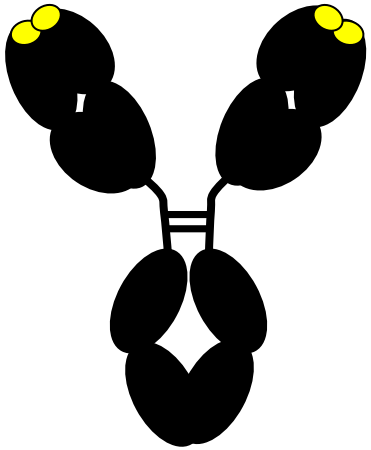
Acm chimériques
1984

Rituximab,



Acm humanisés
1988-1991

Bevacizumab



Acm intégralement humains
1994-1999

Souris transgéniques

Efficacité dans les lymphomes

The NEW ENGLAND JOURNAL of MEDICINE

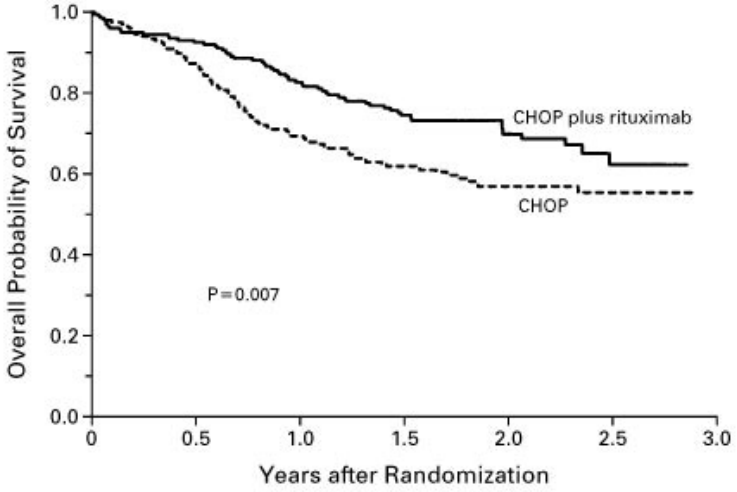
HOME | ARTICLES & MULTIMEDIA | ISSUES | SPECIALTIES & TOPICS | FOR AUTHORS | CME

ORIGINAL ARTICLE

CHOP Chemotherapy plus Rituximab Compared with CHOP Alone in Elderly Patients with Diffuse Large-B-Cell Lymphoma

Bertrand Coiffier, M.D., Eric Lepage, M.D., Ph.D., Josette Brière, M.D., Raoul Herbrecht, M.D., Hervé Tilly, M.D., Reda Bouabdallah, M.D., Pierre Morel, M.D., Eric Van Den Neste, M.D., Gilles Salles, M.D., Ph.D., Philippe Gaulard, M.D., Felix Reyes, M.D., Pierre Lederlin, Pierre Lederlin, Ph.D., and Christian Gisselbrecht, M.D.

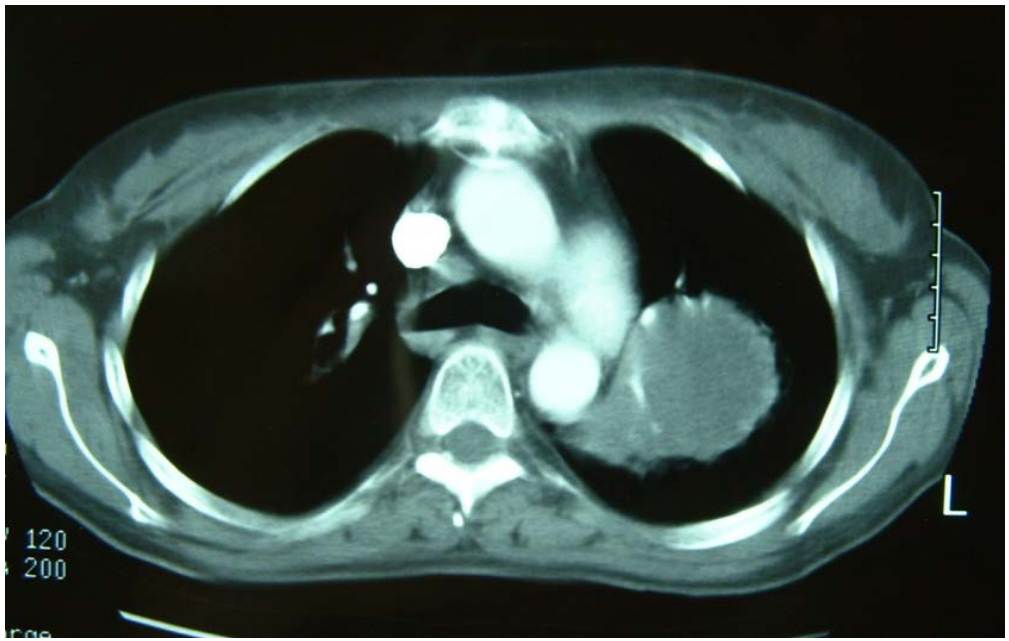
N Engl J Med 2002; 346:235-242 | January 24, 2002 | DOI: 10.1056/NEJMoa011795

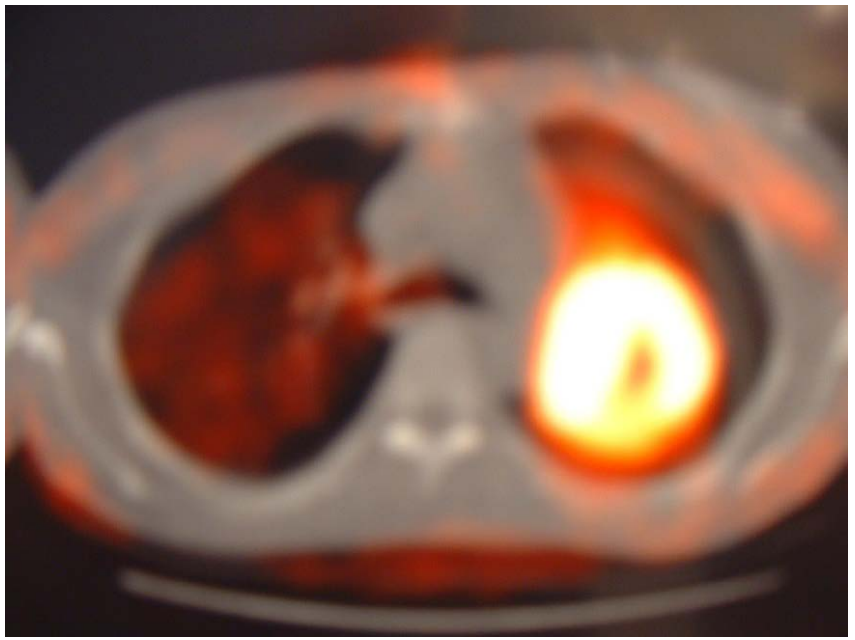


No. at Risk

CHOP plus rituximab	202	187	167	118	64	21
CHOP	197	171	136	96	58	16

Patiente transplanté cardiaque, lymphome B lié à l' EBV





Fin de la chimio dans certains lymphomes ?

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Example: "Heart attack" AND "Los Angeles"
Search for studies: Search
Advanced Search | Help | Studies by Topic | Glossary

Now Available for Public Comment: Notice of Proposed Rulemaking (NPRM) for FDAAA 801 and NIH Draft Reporting Policy for NIH-Funded Trials

Find Studies | About Clinical Studies | Submit Studies | Resources | About This Site

Home > Find Studies > Search Results > Study Record Detail

Text Size

Trial record **9 of 92** for: revlimid rituximab

◂ Previous Study | Return to List | Next Study ▸

A Phase 3 Open Label Randomized Study to Compare the Efficacy and Safety of Rituximab Plus Lenalidomide (CC-5013) Versus Rituximab Plus Chemotherapy Followed by Rituximab in Subjects With Previously Untreated Follicular Lymphoma (RELEVANCE)

This study is currently recruiting participants. (see Contacts and Locations)
Verified July 2012 by The Lymphoma Academic Research Organisation

ClinicalTrials.gov Identifier:
NCT01650701

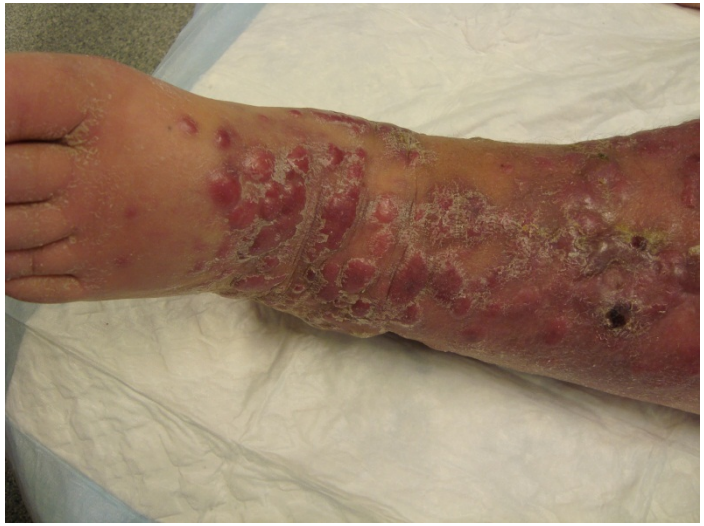
The NEW ENGLAND JOURNAL of MEDICINE

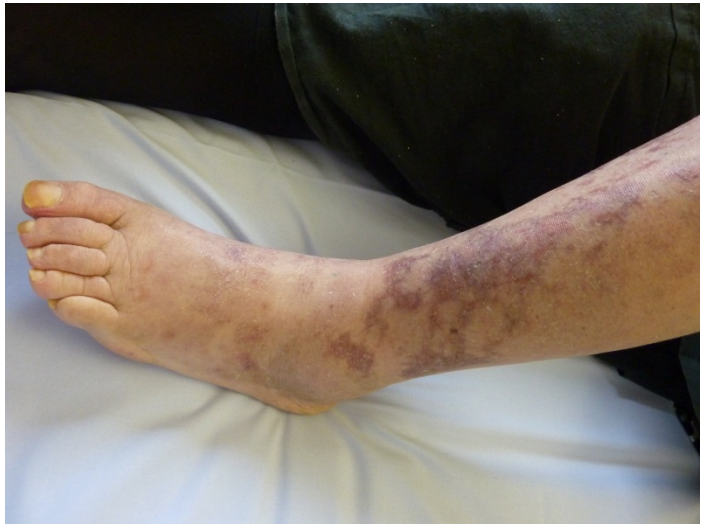
ORIGINAL ARTICLE

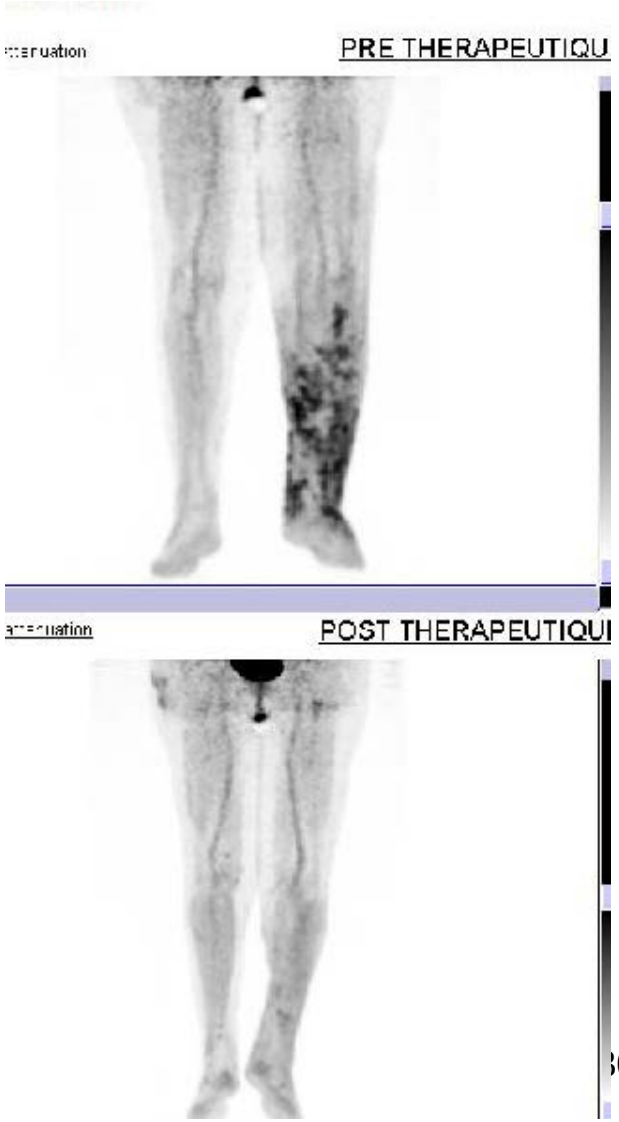
Lenalidomide plus Rituximab as Initial Treatment for Mantle-Cell Lymphoma

N ENGL J MED 373;19 NEJM.ORG NOVEMBER 5, 2015

LNH EBV: association HDAC et gancyclovir





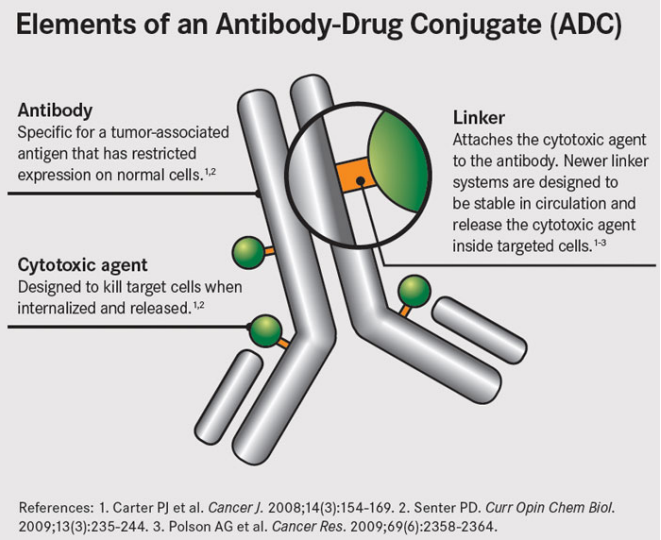


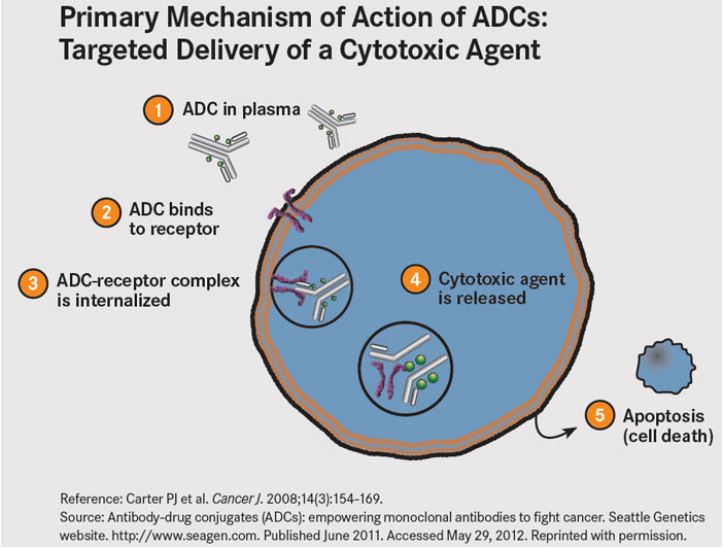
Efficacité dans les pathologies auto-immunes

- Liées à des auto-anticorps
  - AHAI et PTI
  - Sd de Moschowitz
  - Maladies des agglutinines froides
  - Cryoglobulines mixtes
  - Maladies bulleuses de la peau
  - Hémophilies acquises

- Autres
  - Polyarthrite rhumatoïde
  - Lupus

Anticorps conjugués





- Anti CD 30 + auristatine : maladie de Hodgkin, certains lymphomes

- Anti-CD22 + auristatine: leucémie aigüe lymphoblastique

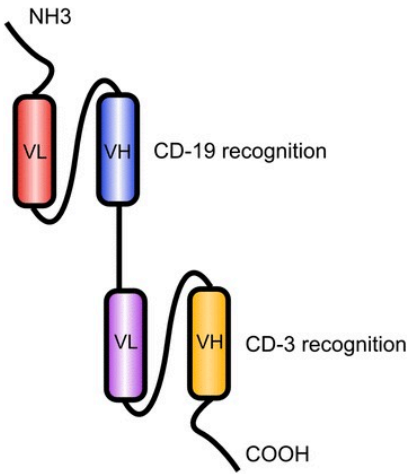
- Anti-CD20 et isotope radioactif: lymphome B

-Anti CD33 et isotope radioactif: leucémie aigüe myéloïde

-Limoges: anticorps conjugués avec Plomb radioactif

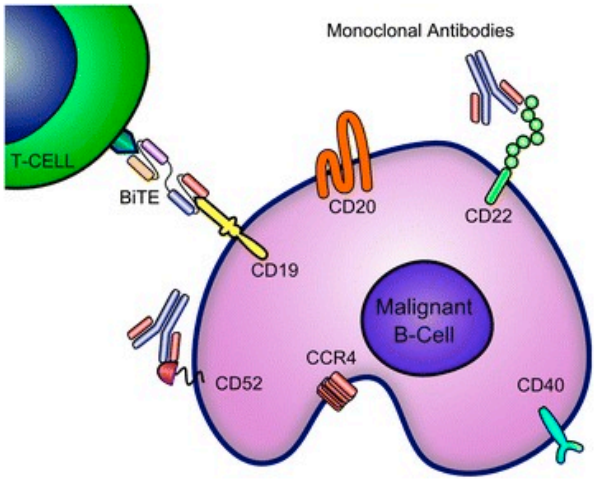
Anticorps bi-spécifiques

Figure 3



The bispecific T-cell engager blinatumomab targeting CD-19. Abbreviations: VL: variable region light chain; VH: variable region heavy chain.

Figure 1



Lymphoma cell surface targets for immunotherapy. Abbreviations: BiTE, Bispecific T-cell Engager; CCR4, C-C Chemokine Receptor Type 4.

Anticorps bi-spécifiques

blood

Prepublished online October 19, 2015;
doi:10.1182/blood-2015-06-649111 originally published online
October 19, 2015

Long-term survival and T-Cell kinetics in adult patients with relapsed/refractory B-precursor acute lymphoblastic leukemia who achieved minimal residual disease response following treatment with Anti-CD19 BiTE® antibody construct blinatumomab

Gerhard Zugmaier, Nicola Gökbuget, Matthias Klinger, Andreas Viardot, Matthias Stelljes, Svenja Neumann, Heinz-A. Horst, Reinhard Marks, Christoph Faul, Helmut Diedrich, Albrecht Reichle, Monika Brüggemann, Chris Holland, Margit Schmidt, Hermann Einsele, Ralf C. Bargou and Max S. Topp

Patiente de 71 ans, rechute de LAL

16/08/2017
11:20
Définitive
170269752

envahissement massif par une population blastique homogène : rapport N/C très élevé, taille moyenne en majorité, chromatine d'allure lymphoblastique, pas de grains cytoplasmiques

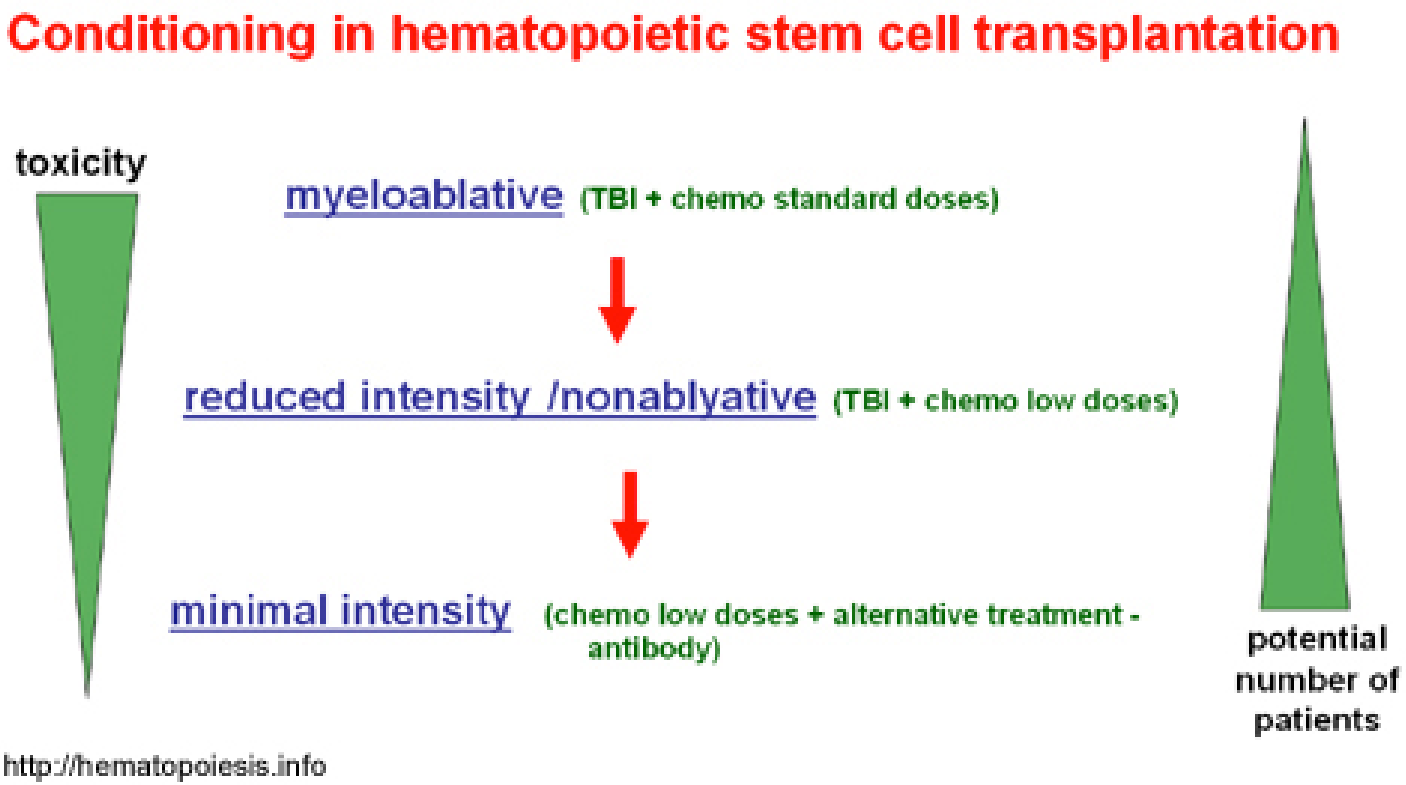
Rechute, envahissement blastique massif

Traitement par Blinatunomab

23/10/2017
11:15
Définitive
170346111

Sternum	
Normale	
Facile	
Normale	
5.0	1.5
4.5	4.5
25.0	4.5
26.5	16.5
61.0	1.0
2.5	30.5
	8.0
	0.5
	Normaux
	Frottis de bonne richesse. Hypoplasie de la lignée granuleuse Pas d'excès de blastes.
	Aspect cytologique compatible avec une rémission cytologique : oas

Progrès dans les allogreffes



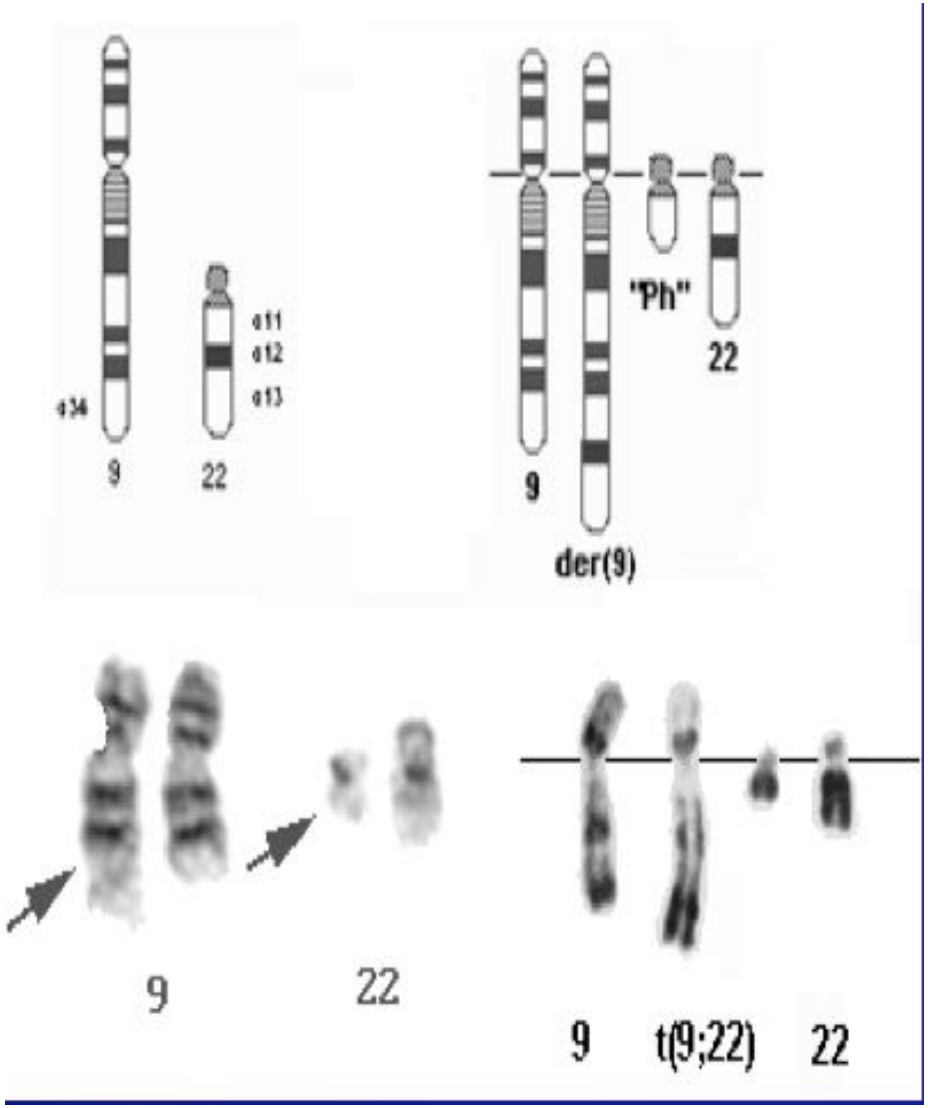
1 chance sur 4 d'être HLA compatible avec un frère ou une soeur

Possibilité récente de prendre les membres de la famille à moitié compatibles

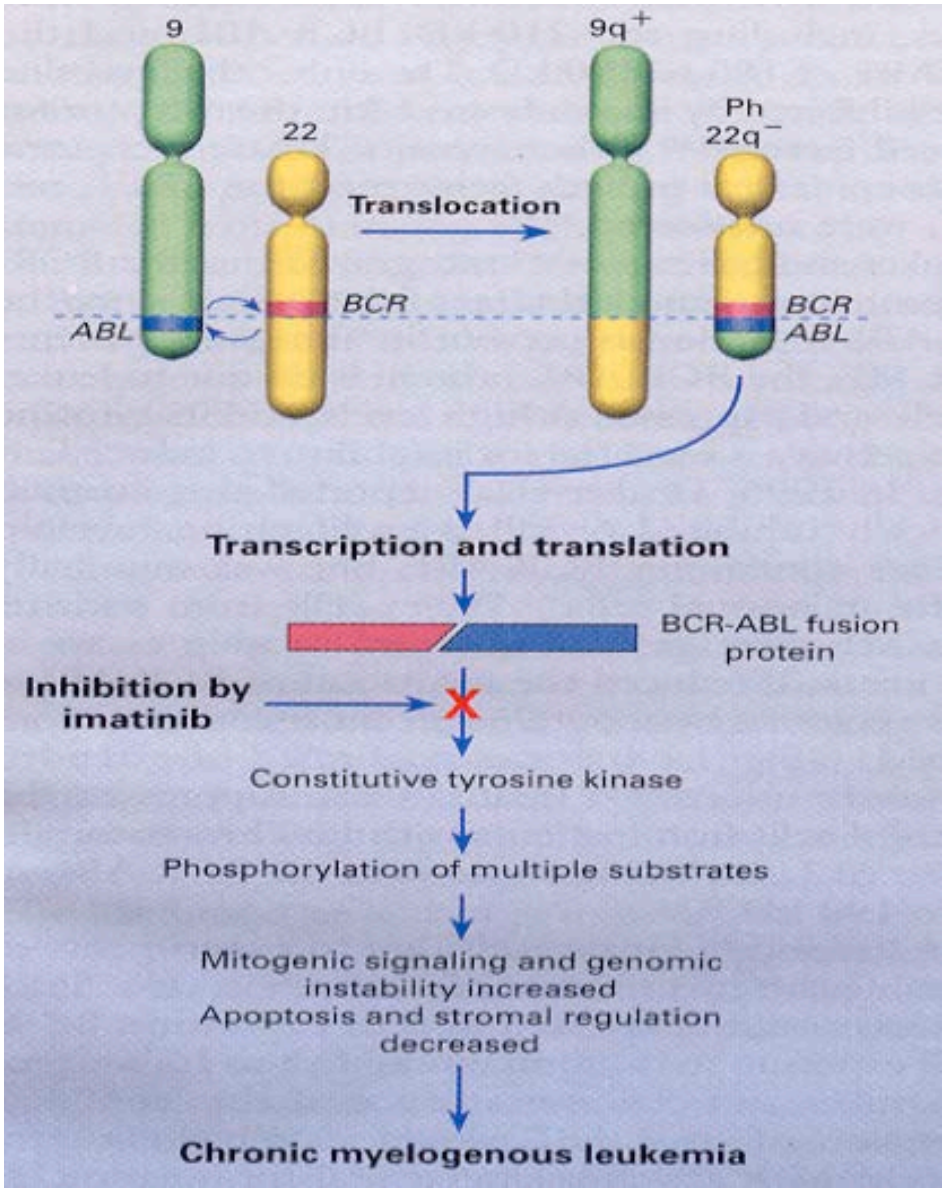
Parents et enfants tous compatibles, frère et soeur: 3 chances sur 4

Greffes haplo-identiques

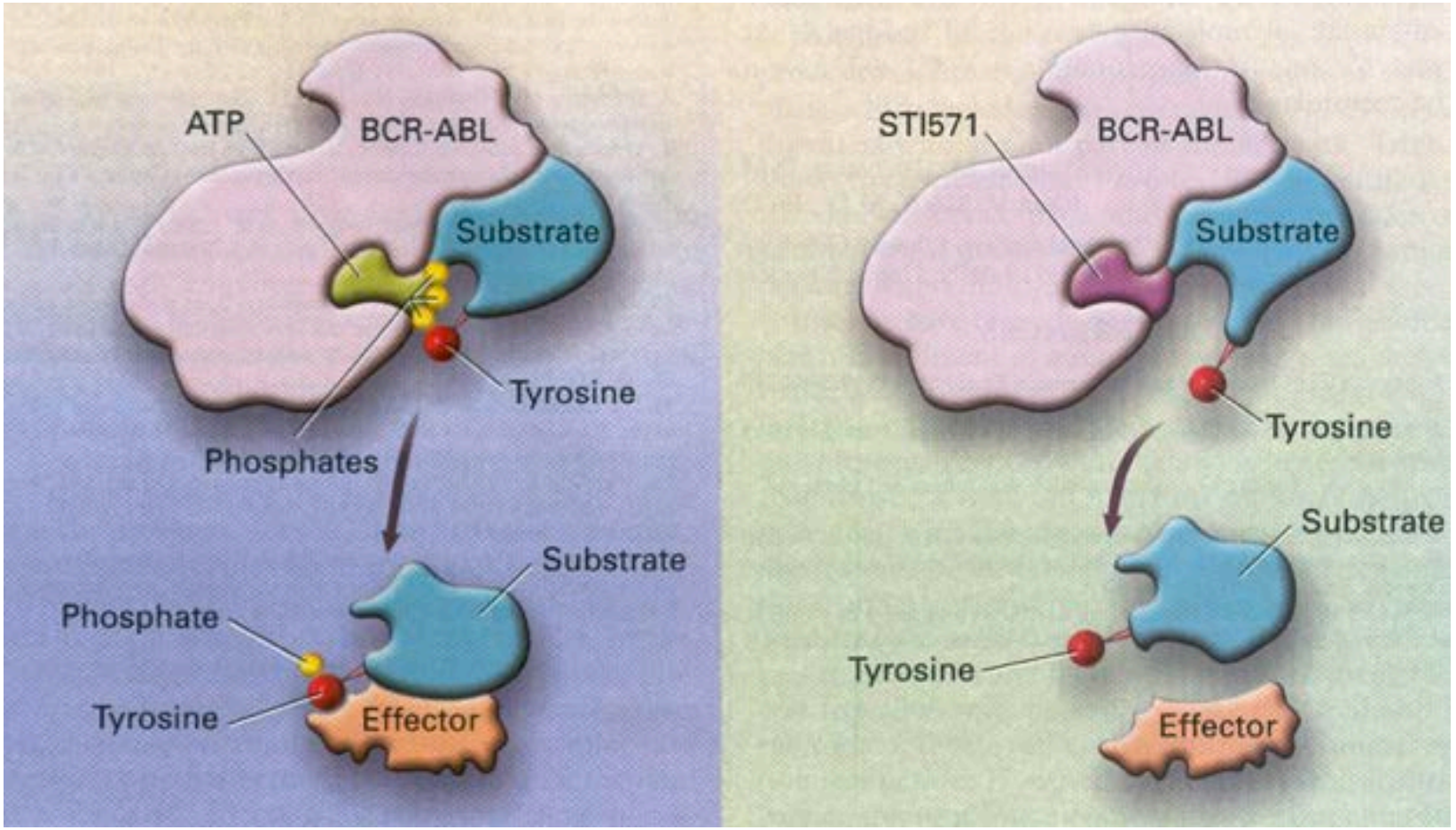
Inhibiteurs de thyrosine kinase: LMC



Inhibiteurs de thyrosine kinase: LMC



Inhibiteurs de thyrosine kinase: LMC

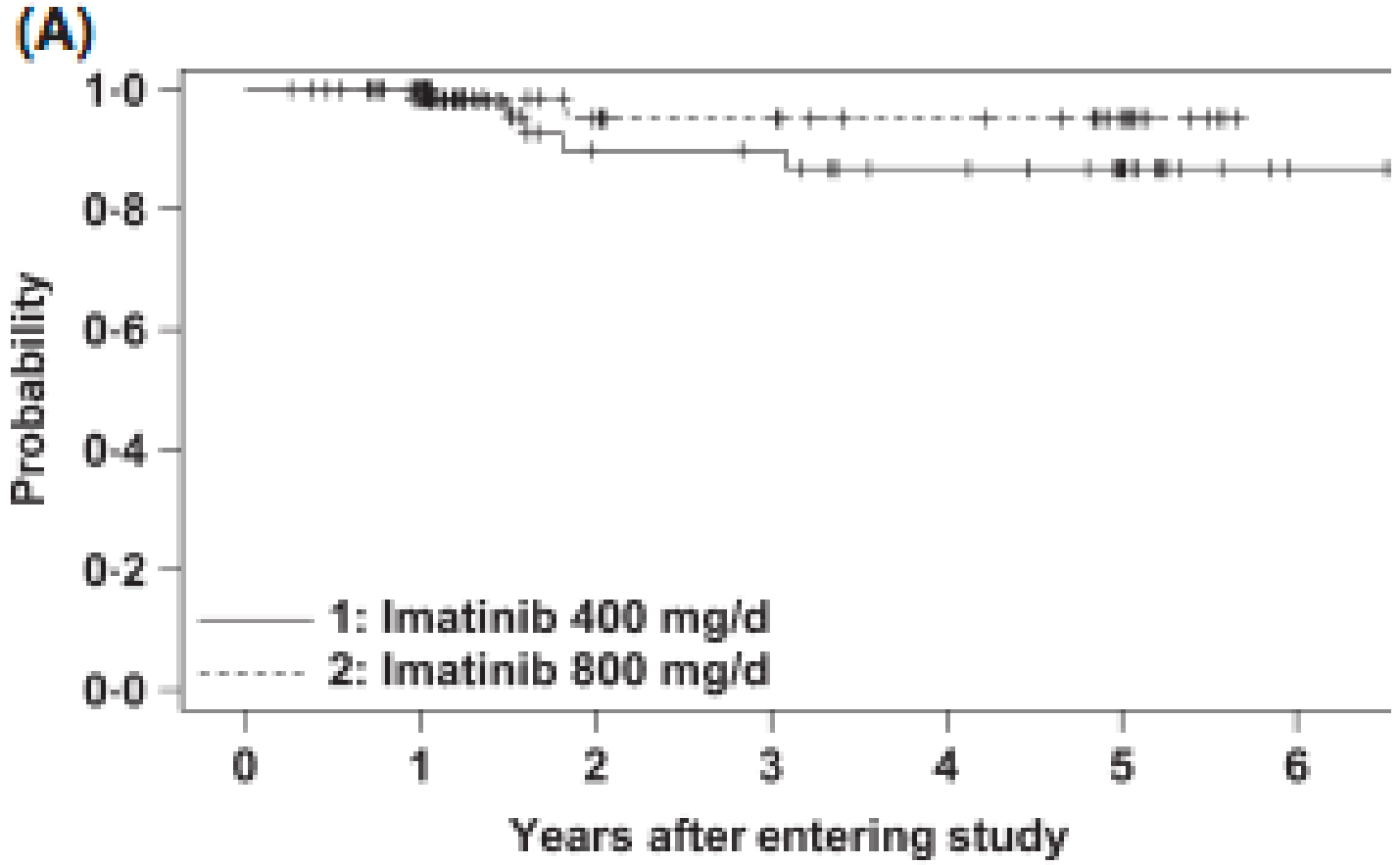


Inhibiteurs de thyrosine kinase: LMC

CML - prognosis En 2002

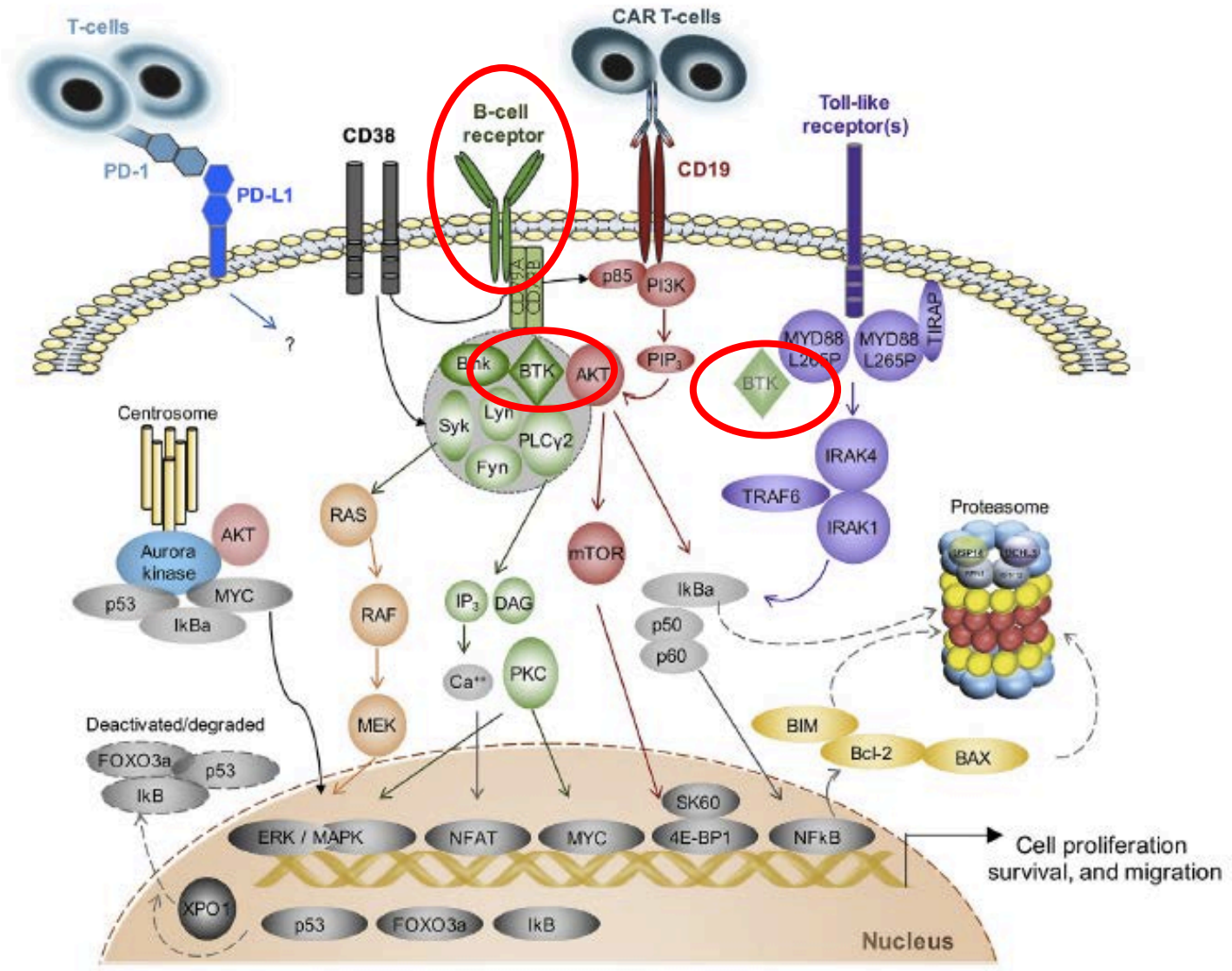
- Median survival 3.5 yrs (range 2-8 yrs)
- Interferon + chemotherapy :6 years
- Transplant : 5+ years
- imatinib mesylate ?

Inhibiteurs de thyrosine kinase: LMC

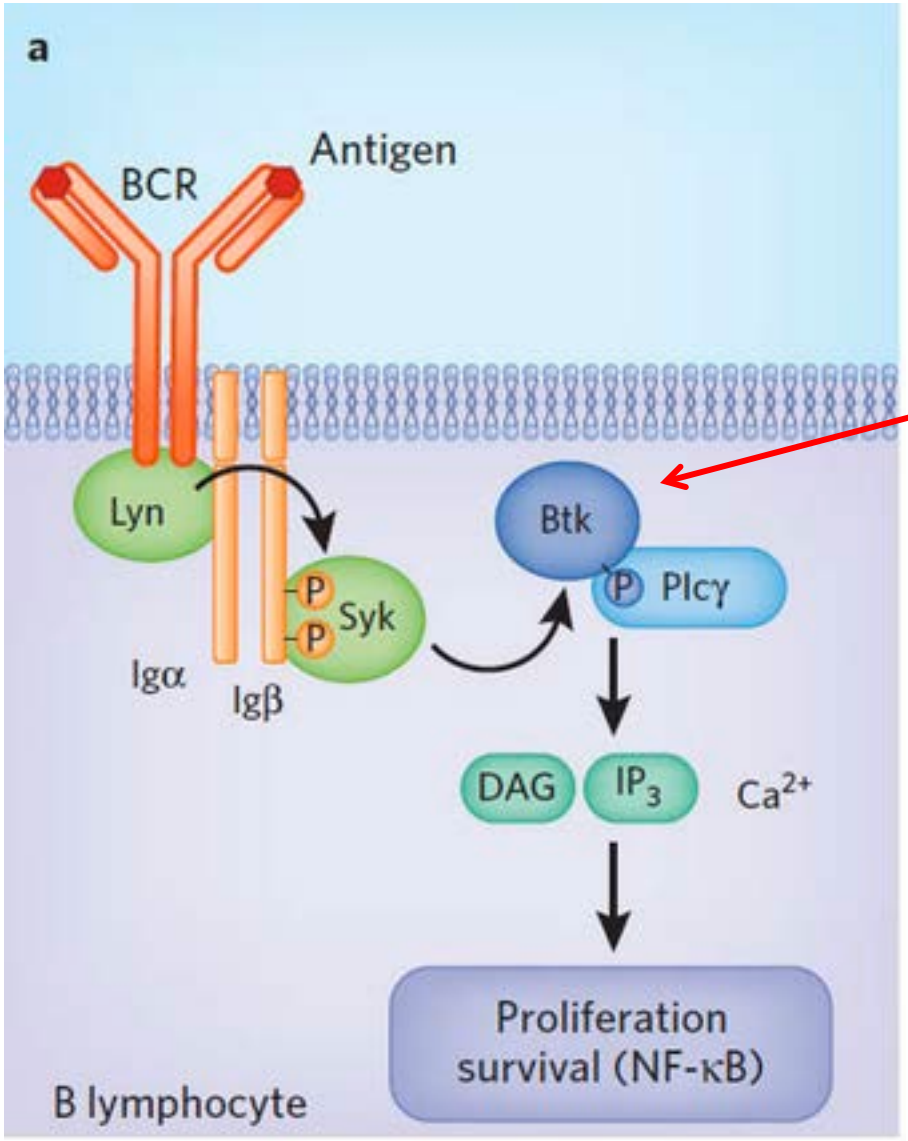


Survie avec Glivec

Inhibiteurs de la voie du récepteur B

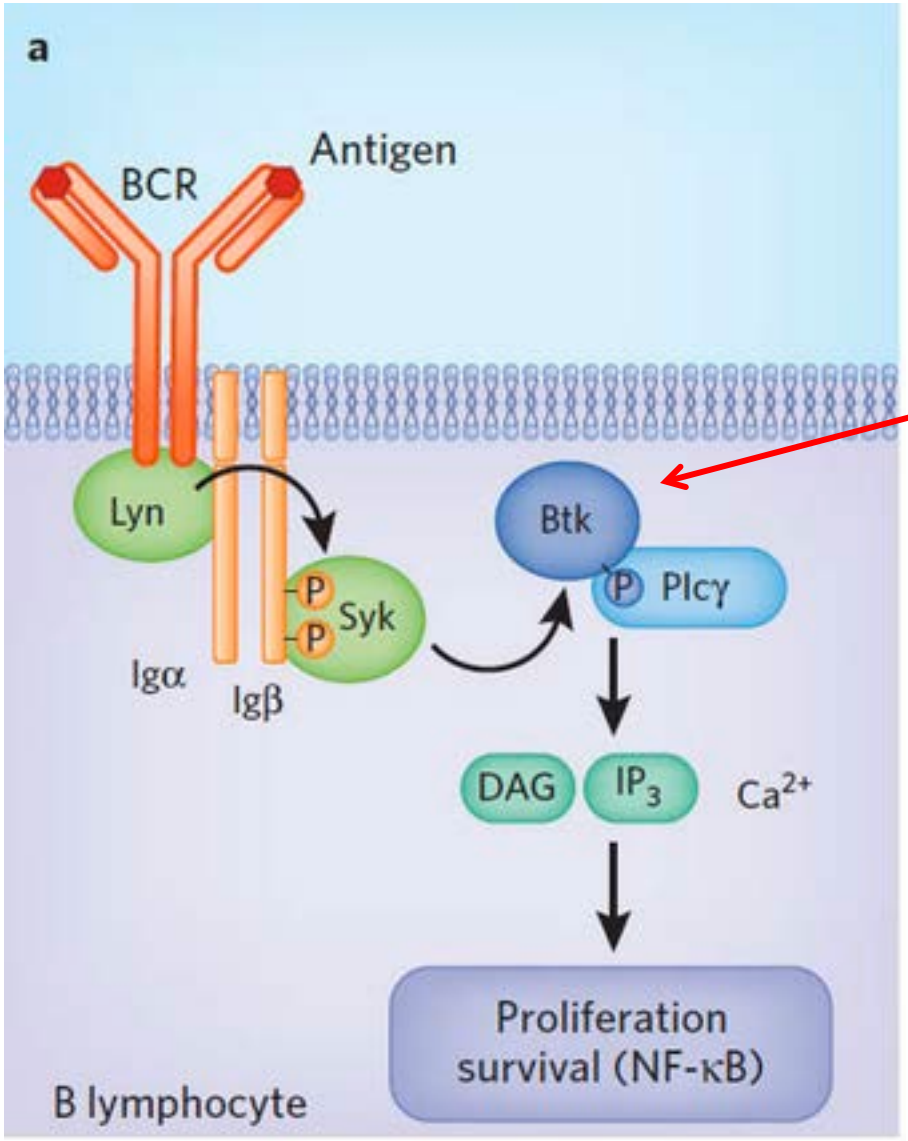


Inhibiteurs de la voie du BCR



Mutation de BTK: déficit Immunitaire humoral: Maladie de Bruton, absence de Lymphocyte B

Inhibiteurs de la voie du BCR



Inhibiteur de BTK:
Actif +++ sur les
proliférations B

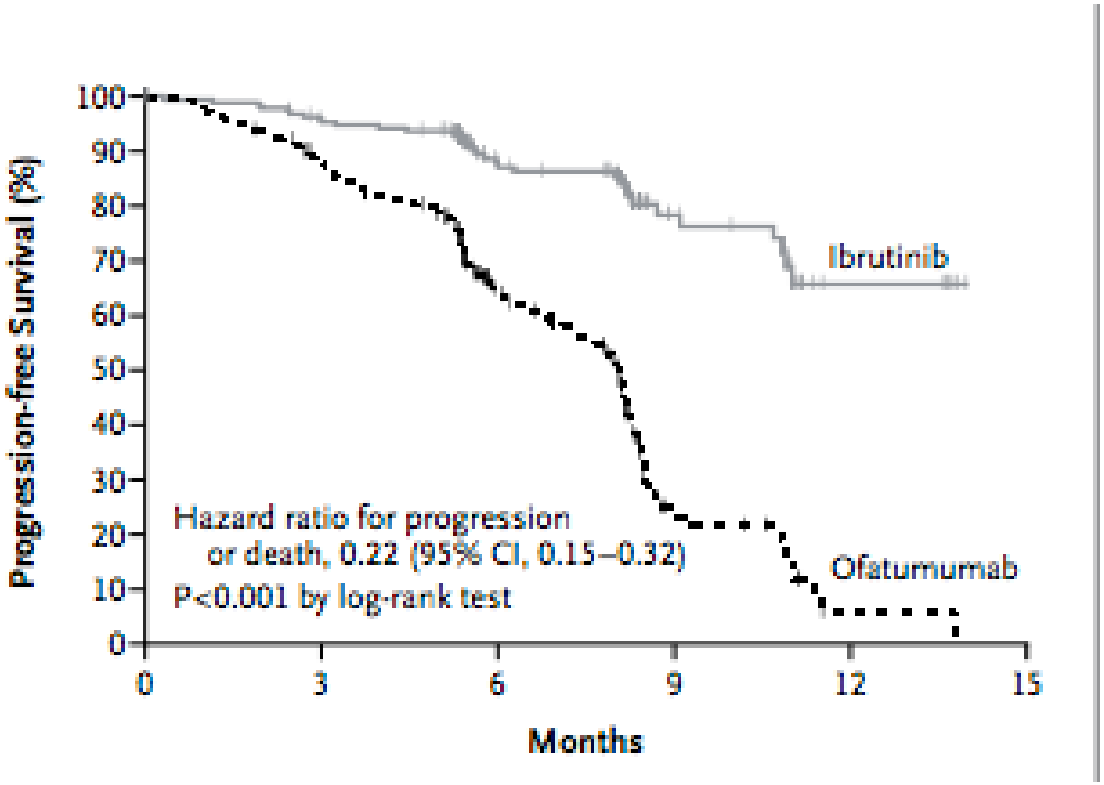
Ibrutinib dans les LLC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ibrutinib versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia

A



Ibrutinib dans les LLC

LBA-4 A Randomized Phase III Study of Ibrutinib (PCI-32765)-Based Therapy Vs. Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL): A Trial of the ECOG-ACRIN Cancer Research Group (E1912)

529 patients

Figure 1. Progression-Free Survival (all randomized)

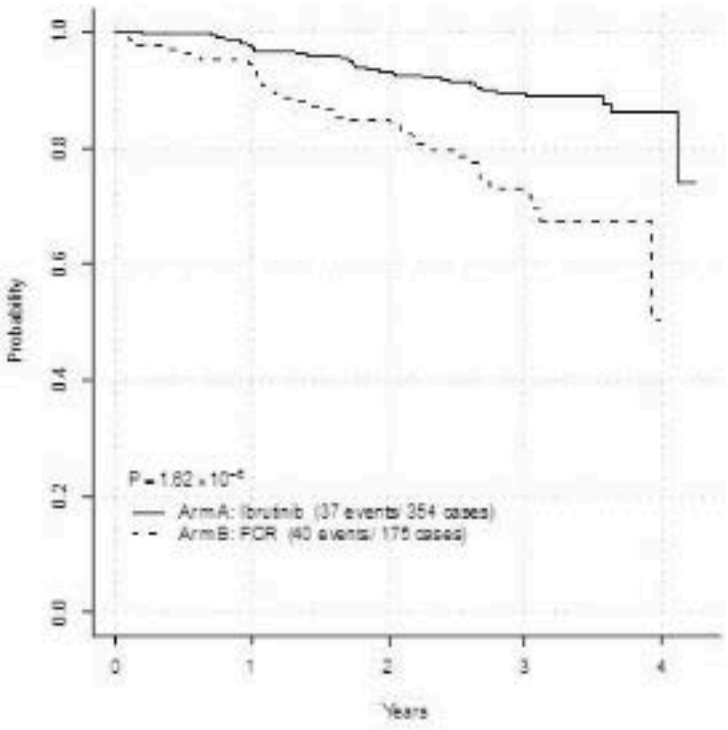
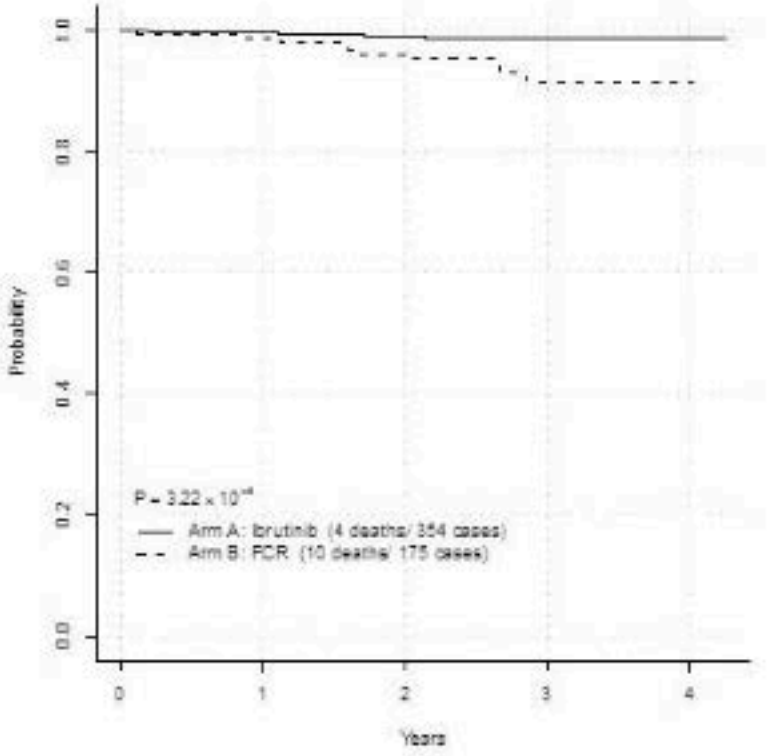


Figure 1B. Overall Survival (all randomized)



Homme de 70 ans

Il a été fait chez lui le diagnostic de lymphome B à grandes cellules CD20+ sur une biopsie sus claviculaire en juin 2009. Il avait à ce moment là une polyadénopathie coelio-mésentériques et médiastinale avec un épanchement bilatéral. Il a été traité par R-CHOP 8 cycles jusqu'à début 2010. Il y a une efficacité partielle et il persistait des adénopathies visibles au pet scan à la fin des 8 cycles. Un traitement par IFOSFAMIDE-VP16 et CISPLATINE associé au RITUXIMAB a été débuté en mars 2010, il a eu 3 cycles qui ont permis une régression partielle du lymphome et qui sont accompagnés de cytopénies profondes. Il a ensuite été placé sous ENDOXAN oral qu'il a poursuivi pendant 2 ans avec une maladie peu évolutive.

Il a été à nouveau progressif sur un pet scan fait en octobre 011 et il a été démarré un traitement par R-DHAC à ½ puis à ¼ de dose. Il a eu 6 cycles, jusqu'en novembre 2012 avec à nouveau une maladie qui répondait partiellement au traitement et des épisodes d'aplasie fébrile. En mai 2013 il a été noté une progression clinique et sur le scanner. Il a eu un traitement par R-mini-CHOP qui a été poursuivit jusqu'en janvier 2014. Il n'a pas eu de chimiothérapie depuis avec une progression lente de son lymphome. Actuellement il a des masses palpables en sous cutanée avec une masse du creux sus claviculaire qui fait 8 cm, une masse du flanc droit qui fait 7 cm et 2 masses au niveau des omoplates de 8 et 9 cm. Il a des adénopathies axillaires bilatérales entre 3 et 6 cm, une adénopathie inguinale droite de 7 cm. Il a 2 masses au dessus des yeux qui font 5 cm et une polyadénopathie jugulocarotidienne. Il n'a pas de splénomégalie. Son poids est à 92 kg pour 1,75 m, sa tension est à 13/8 ce jour. A noter qu'il a un site qui doit être fonctionnel en place.

Je lui fais ce jour un bilan sanguin et une cytoponction des masses tumorales avec une cytométrie de flux.

Je suis un peu étonné par l'évolution de ce lymphome qui n'est pas celle d'un lymphome agressif mais plus d'un lymphome de bas grade.

PROPRIETES CD45/STRUCTURE		
Représente :		99
Marqueur :		CD2
Pourcentage de positivité		4
ETUDE DES MARQUEURS DE DIFFERENCIATION, POPULATION D'INTERET A		
Population d'intérêt :		lymphocytes T
Mode de sélection :		CD45 fort CD3+
Représente :		4
Marqueur :		CD4
Pourcentage de positivité		22
Marqueur :		CD8
Pourcentage de positivité		78
Rapport CD4/CD8	↓	0.28
ETUDE DES MARQUEURS DE DIFFERENCIATION, POPULATION D'INTERET B		
Population d'intérêt :		Cellules B
Mode de sélection :		CD19+/CD45+
Représente :		96
Marqueur :		chaîne Kappa de surface
Pourcentage de positivité		99.9
Intensité		Fort
Marqueur :		Chaine Lambda de surface
Pourcentage de positivité		0.1
Marqueur :		CD5
Pourcentage de positivité		100
Marqueur :		CD20
Pourcentage de positivité		100
Intensité		Médium
Marqueur :		FMC7
Pourcentage de positivité		29
Marqueur :		CD23
Pourcentage de positivité		1
Marqueur :		CD79b
Pourcentage de positivité		8
Intensité		Faible
Marqueur :		CD38
Pourcentage de positivité		97

ETUDE DE L'HYPEREXPRESSION DE LA CYCLINE D1, CONCLUSION		
Conclusion		Présence d'une hyperexpression de la cycline D1 détectable sur gel après coloration au Bet.
NON CONFORMITES (IMMUNOLOGIE)		
Marqueur :		CD43
Pourcentage de positivité		98
Score de MATUTES :		2
MATUTES cytologie :		Cellules de lymphome du manteau
Rapport Kappa/Lambda	↑	999.00

tumorales lymphocytaires de taille moyenne à cytoplasme légèrement basophile,
atine lache, évocateur d'un lymphome du manteau.
manteau

de 70 ans

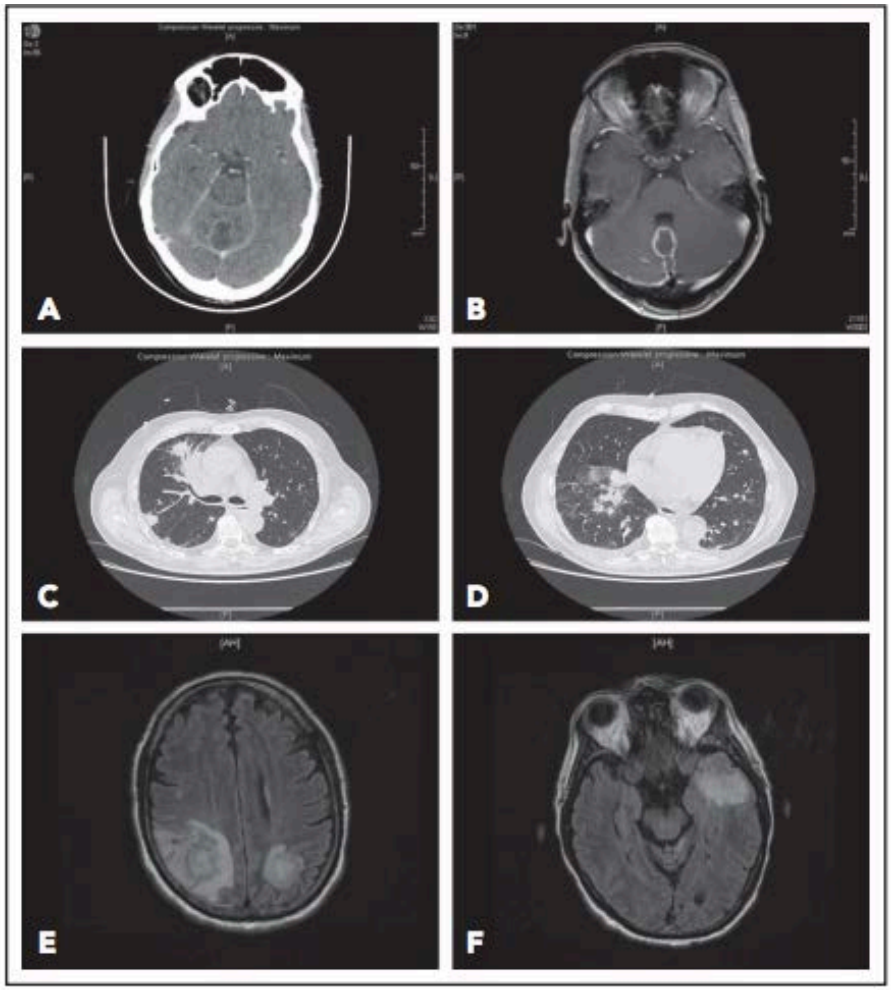
Traitement par Ibrutinib,
4 cps par jour
Disparition de l'ensemble des masses tumorales en 1 mois

RC persistante 2 ans après

Early-onset invasive aspergillosis and other fungal infections in patients treated with ibrutinib

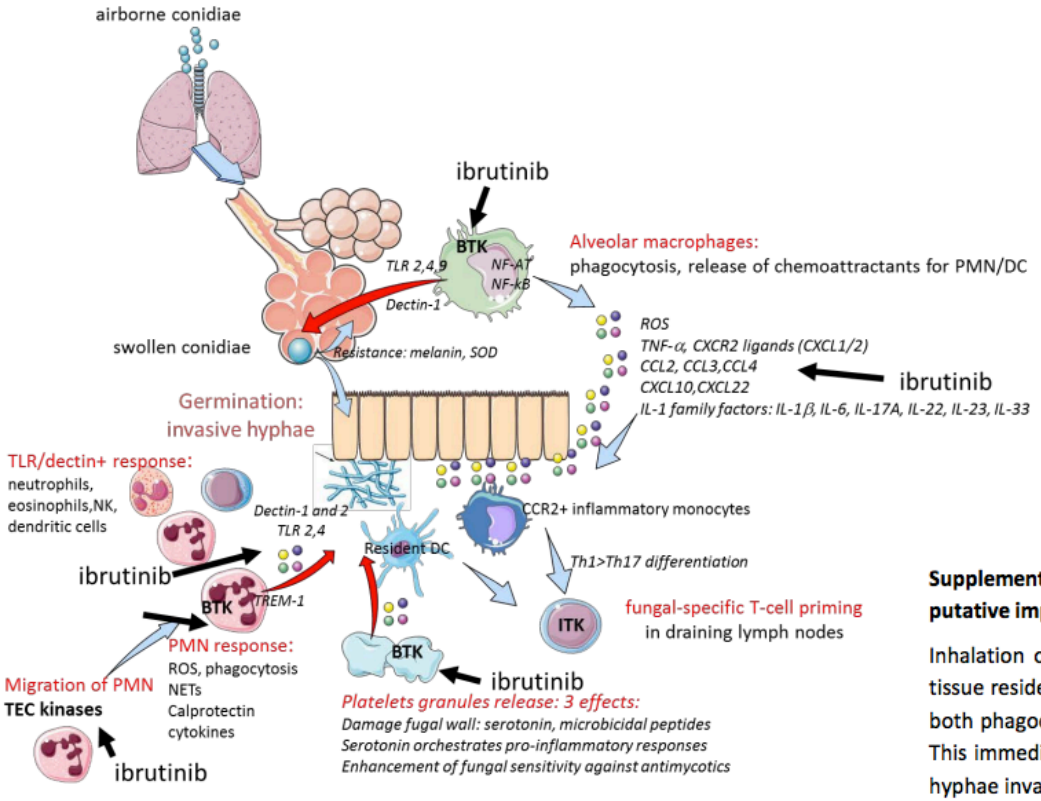
David Ghez,[1] Anne Calleja,[2] Caroline Protin,[3] Marine Baron,[4] Marie-Pierre Ledoux,[5] Gandhi Damaj,[6] Mathieu Dupont,[7] Brigitte Dreyfus,[8] Emmanuelle Ferrant,[9] Charles Herbaux,[10] Kamel Laribi,[11] Ronan Le Calloch,[12] Marion Malphettes,[13] Franciane Paul,[14] Laetitia Souchet,[4] Malgorzata Truchan-Graczyk,[15] Karen Delavigne,[16] Caroline Dartigeas,[17] and Loïc Ysebaert,[3] on behalf on the French Innovative Leukemia Organization (FILO) CLL group

blood® 26 APRIL 2018 | VOLUME 131, NUMBER 17 **1955**



KEY POINTS

- **Ibrutinib may be associated with invasive fungal infections especially IA.**
- **Most infections usually occur during the first months of treatment, often in patients with other risk factors for fungal infections.**

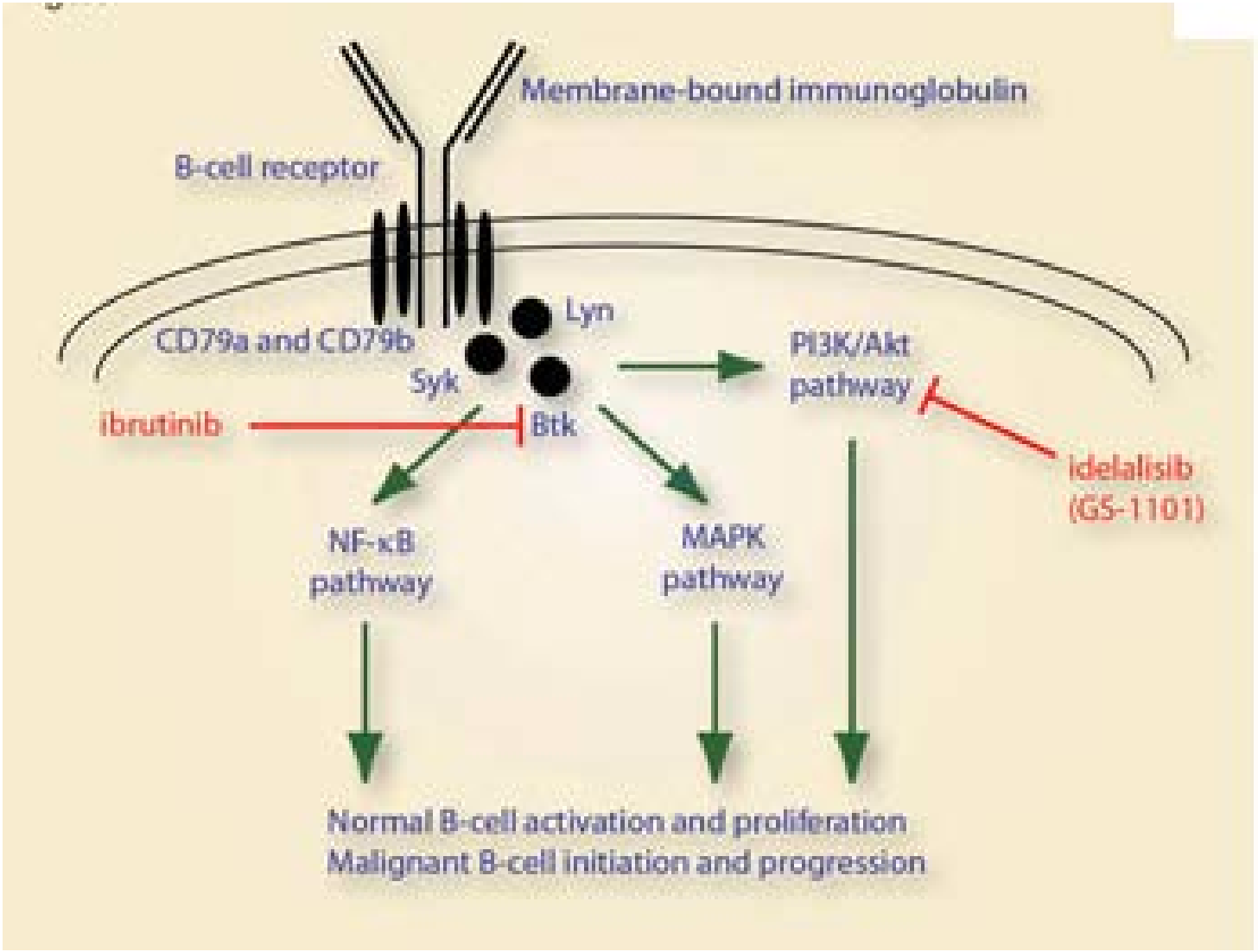


Supplementary Figure 1: Orchestrated immune responses against aspergillosis and putative impact of ibrutinib.

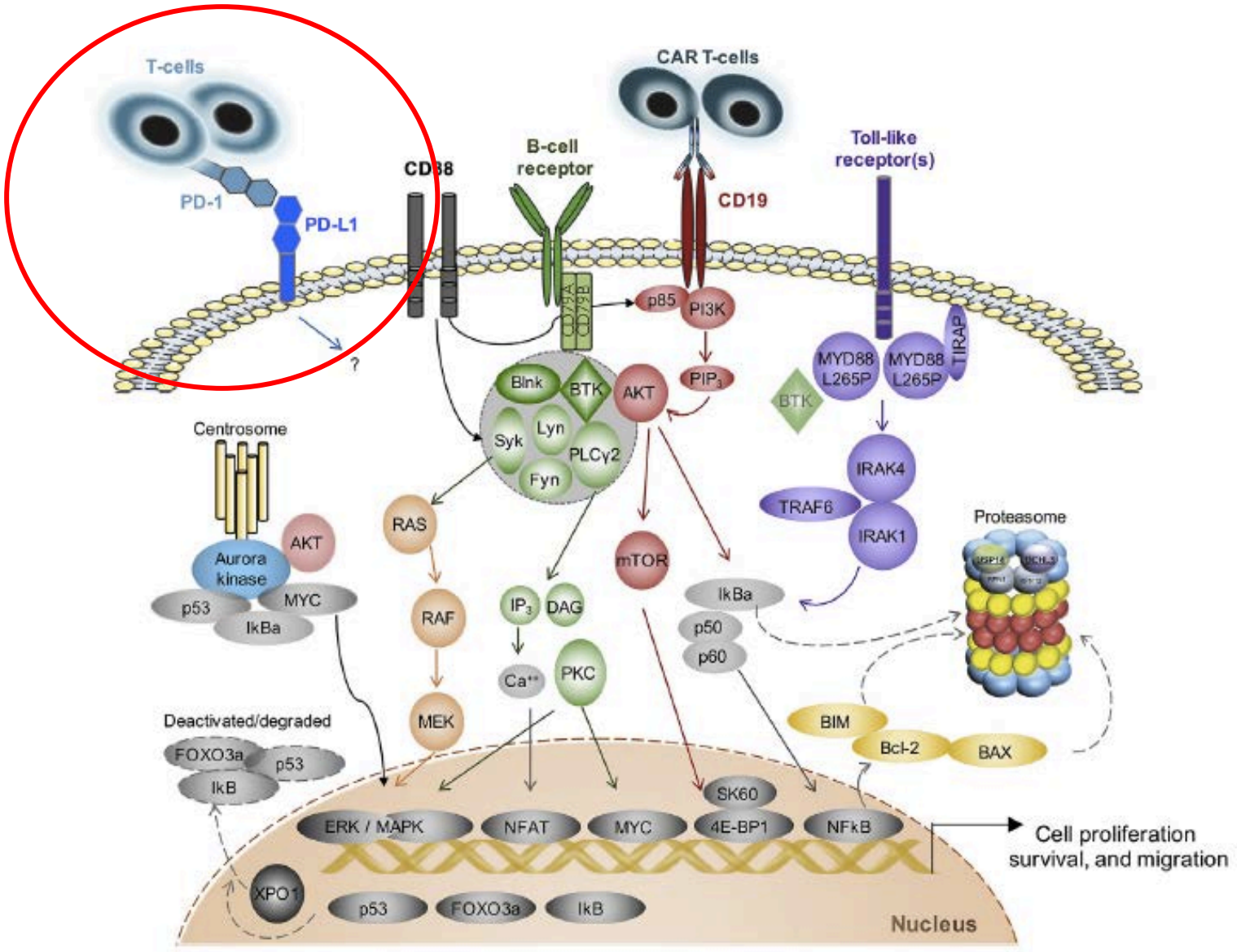
Inhalation of fungal conidiae leads to their initial recognition by lung epithelial cells and tissue resident innate immune cells (alveolar macrophages, dendritic cells) which are able to both phagocytose and release fungicidal products to block germination of swollen conidiae. This immediate response orchestrates neutrophil recruitment, a key step in the blockade of hyphae invasion (so-called *invasive aspergillosis*). It is followed by a second wave of immuno-infiltration by TLR2-4 and Dectin 1-2 expressing cells (including monocytes, plasmocytic dendritic cells, NK cells, eosinophils). Platelets also participate to this innate response by releasing soluble factors that can inhibit aspergillus growth. Ibrutinib is a targeted inhibitor of Btk, Tec, Itk, which first blocks TLR9-mediated signaling in alveolar macrophages (leading to reduced phagocytosis, conidia clearance and chemoattractants release) then limits recruitment of neutrophils (but also their release of cytokines and NETs formation upon TLR2/4 and TREM-1 stimulation respectively). Ibrutinib also perturbs platelet functions (aggregation but also degranulation). Corticosteroids enhance immuno-suppressive effects of ibrutinib, and may increase the risk of hyphae dissemination to brain. We are thankful to Servier medical art (http://www.servier.com) for figure graphics.

CCL: C-C motif ligand, CCR: C-C chemokine receptor, CXCL: C-X-C motif ligand, DC: dendritic cells, IL: interleukin, NETs: neutrophils extra-cellular traps, NF-AT: nuclear factor of activated T cells, NF-κB: nuclear factor-kappa B, PMN: polymorphonuclear neutrophils, ROS: reactive oxygen species, SOD: superoxyde dismutase, TLR: toll-like receptor.

Autre inhibiteur: idealisib



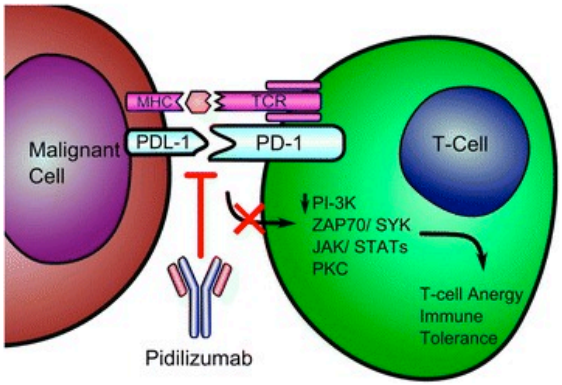
Immunothérapie: Anti-PD1



Immunothérapie: Anti-PD1

- Ne plus cibler la tumeur mais la rendre accessible par les cellules T cytotoxiques

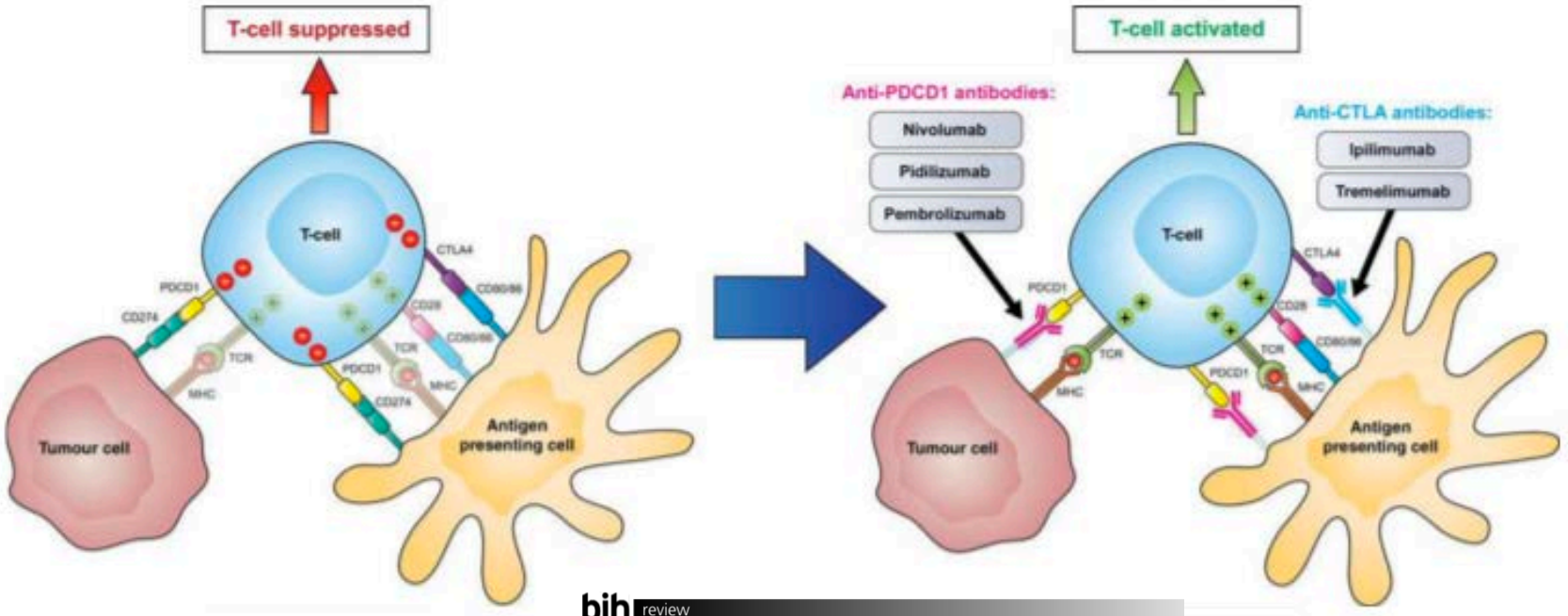
Figure 2



Mechanism of pidilizumab, which increases T cell activation and cytokine release by inhibiting co-inhibitory signaling up-regulated by tumors. Abbreviations: MHC Major Histocompatibility Complex; TCR, T-cell Receptor; PDL-1, Programmed Death Ligand 1; PD-1, Programmed Cell Death Protein 1.

Immunothérapie: Anti-PD1

- Ne plus cibler la tumeur mais la rendre accessible par les cellules T cytotoxiques



bjh review

Immune checkpoint inhibition in lymphoid disease

Toby A. Eyre and Graham P. Collins

Department of Haematology, Oxford University Hospitals NHS Trust, Oxford, UK

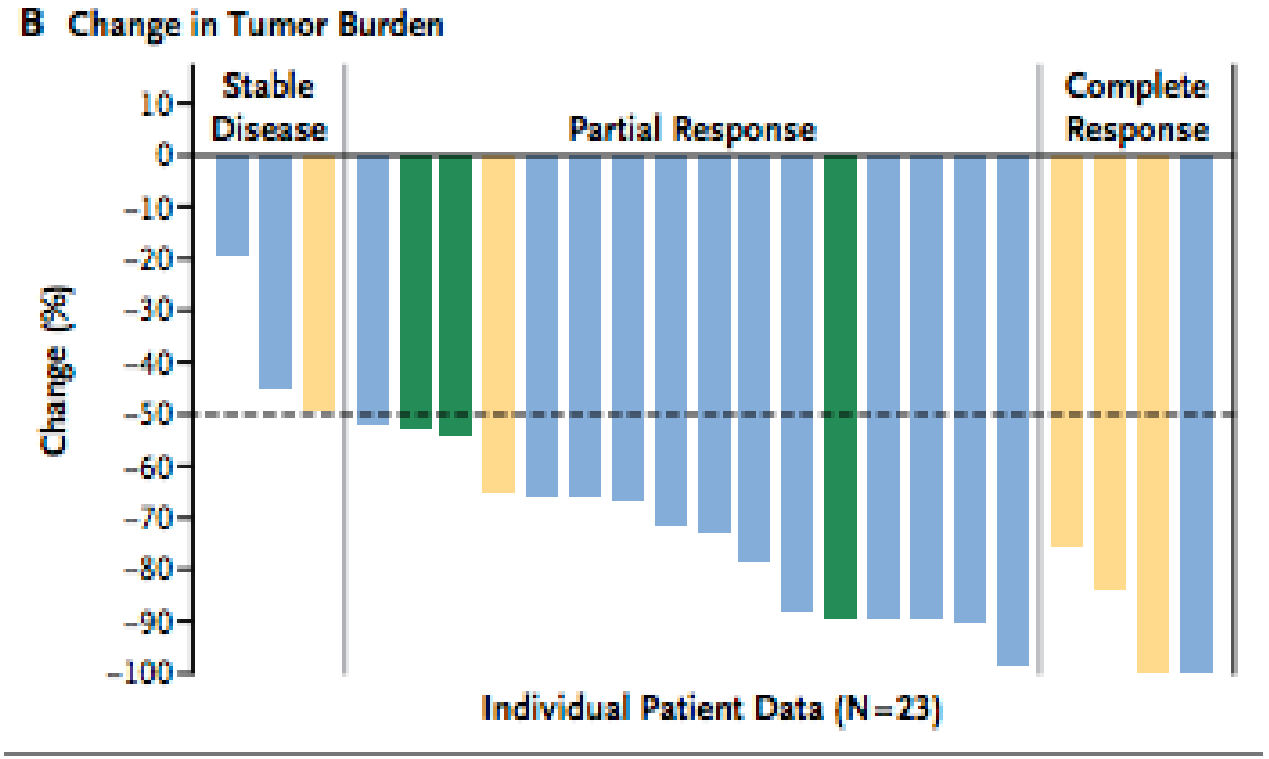
Immunothérapie: Anti-PD1

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 22, 2015 VOL. 372 NO. 4

PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma

Stephen M. Ansell, M.D., Ph.D., Alexander M. Lesokhin, M.D., Ivan Borrello, M.D., Ahmad Halwani, M.D., Emma C. Scott, M.D., Martin Gutierrez, M.D., Stephen J. Schuster, M.D., Michael M. Millenson, M.D., Deepika Cattry, M.S., Gordon J. Freeman, Ph.D., Scott J. Rodig, M.D., Ph.D., Bjoern Chapuy, M.D., Ph.D., Azra H. Ligon, Ph.D., Lili Zhu, M.S., Joseph F. Grosso, Ph.D., Su Young Kim, M.D., Ph.D., John M. Timmerman, M.D., Margaret A. Shipp, M.D., and Philippe Armand, M.D., Ph.D.



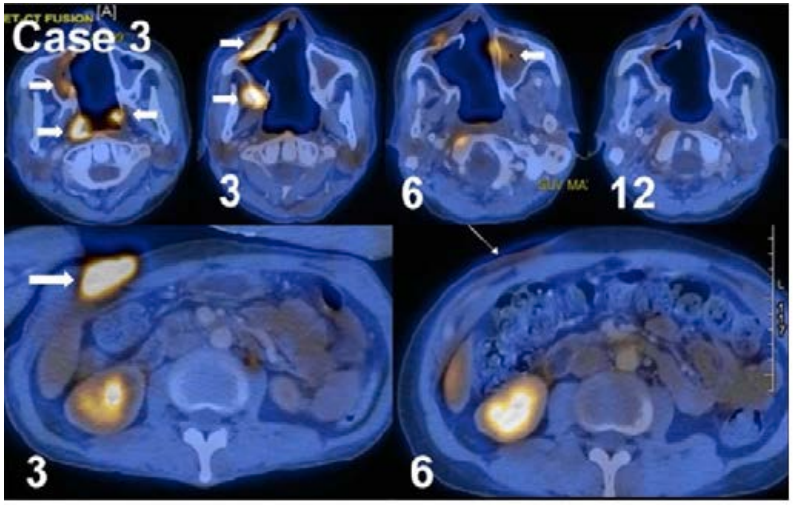
Lymphomes NK: anti-PD1

BLOOD, 27 APRIL 2017 • VOLUME 129, NUMBER 17

LYMPHOID NEOPLASIA

PD1 blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing L-asparaginase

Yok-Lam Kwong,[1] Thomas S. Y. Chan,[1] Daryl Tan,[2,3] Seok Jin Kim,[4] Li-Mei Poon,[5] Benjamin Mow,[6] Pek-Lan Khong,[7] Florence Loong,[8] Rex Au-Yeung,[8] Jabed Iqbal,[9] Colin Phipps,[2,3] and Eric Tse[1]



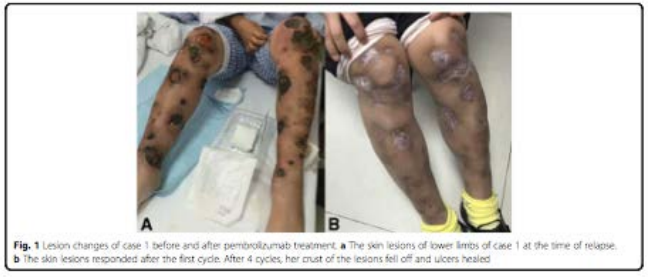
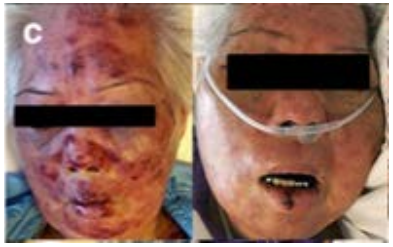


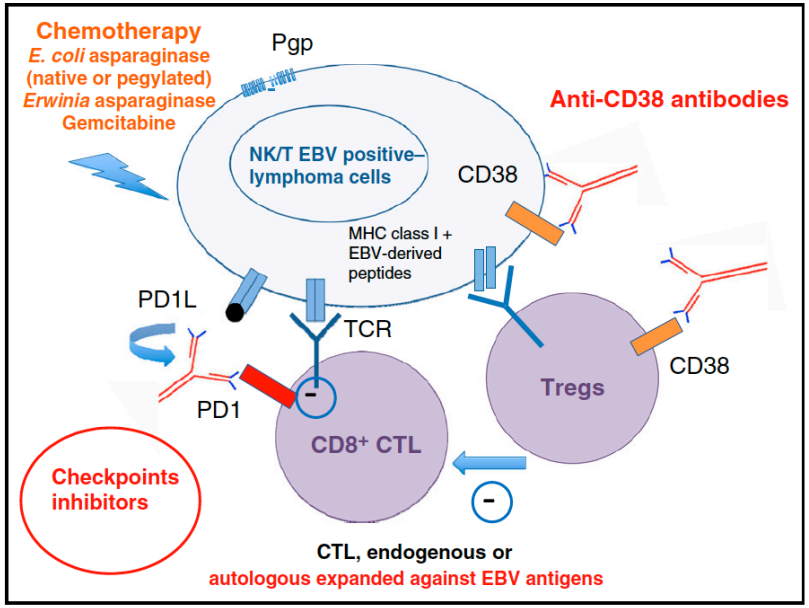
Fig. 1 Lesion changes of case 1 before and after pembrolizumab treatment. a The skin lesions of lower limbs of case 1 at the time of relapse. b The skin lesions responded after the first cycle. After 4 cycles, her crust of the lesions fell off and ulcers healed



Comment on Kwong et al, page 2437

A major turning point in NK/T-cell lymphoma?

Arnaud Jaccard[1] and Olivier Hermine[2] [1]CENTRE HOSPITALIER UNIVERSITAIRE LIMOGES; [2]ASSISTANCE PUBLIQUE - HÔPITAUX DE PARIS



Coûts ?

The NEW ENGLAND JOURNAL of MEDICINE

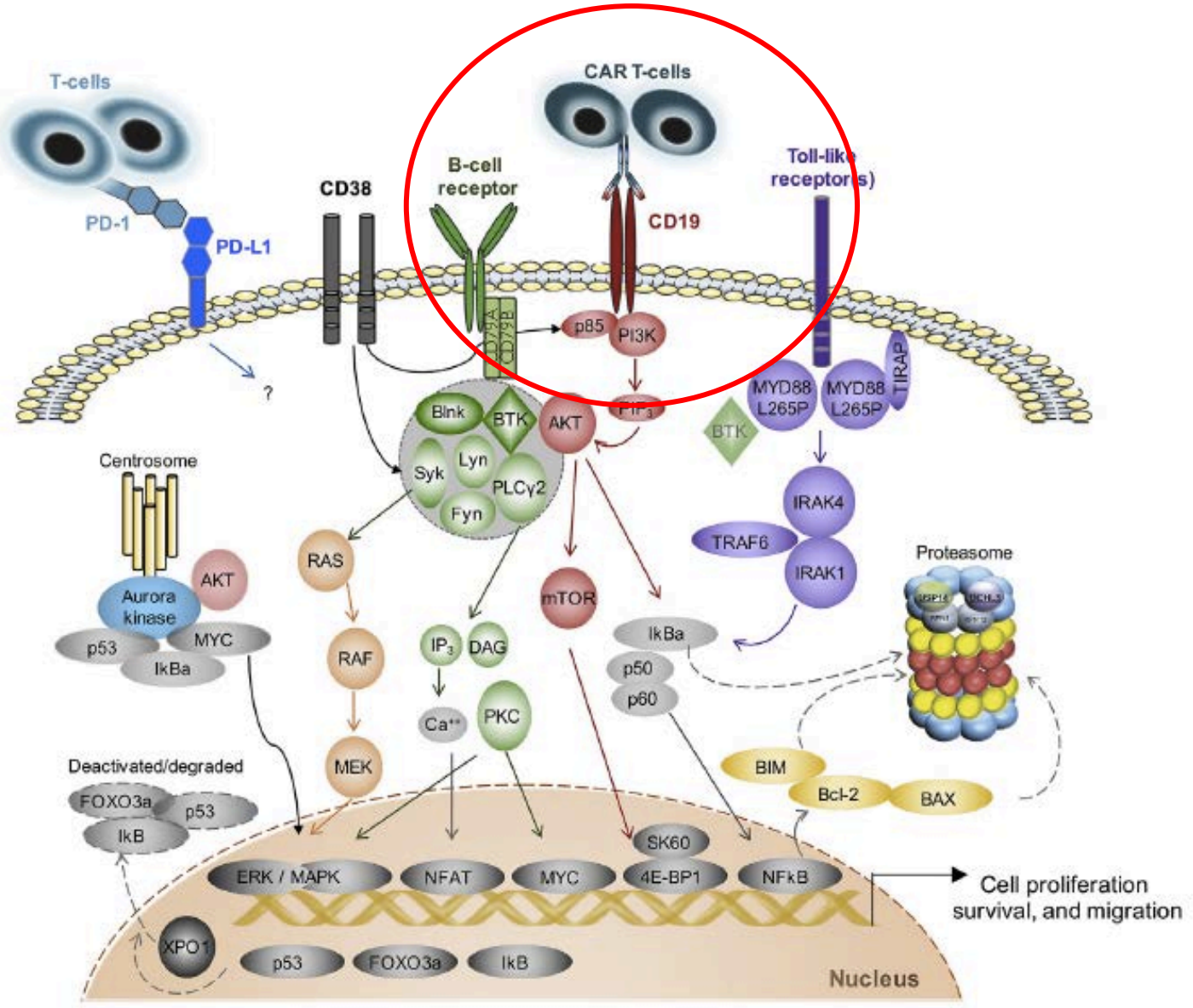
New Math on Drug Cost-Effectiveness

Peter B. Bach, M.D., M.A.P.P.

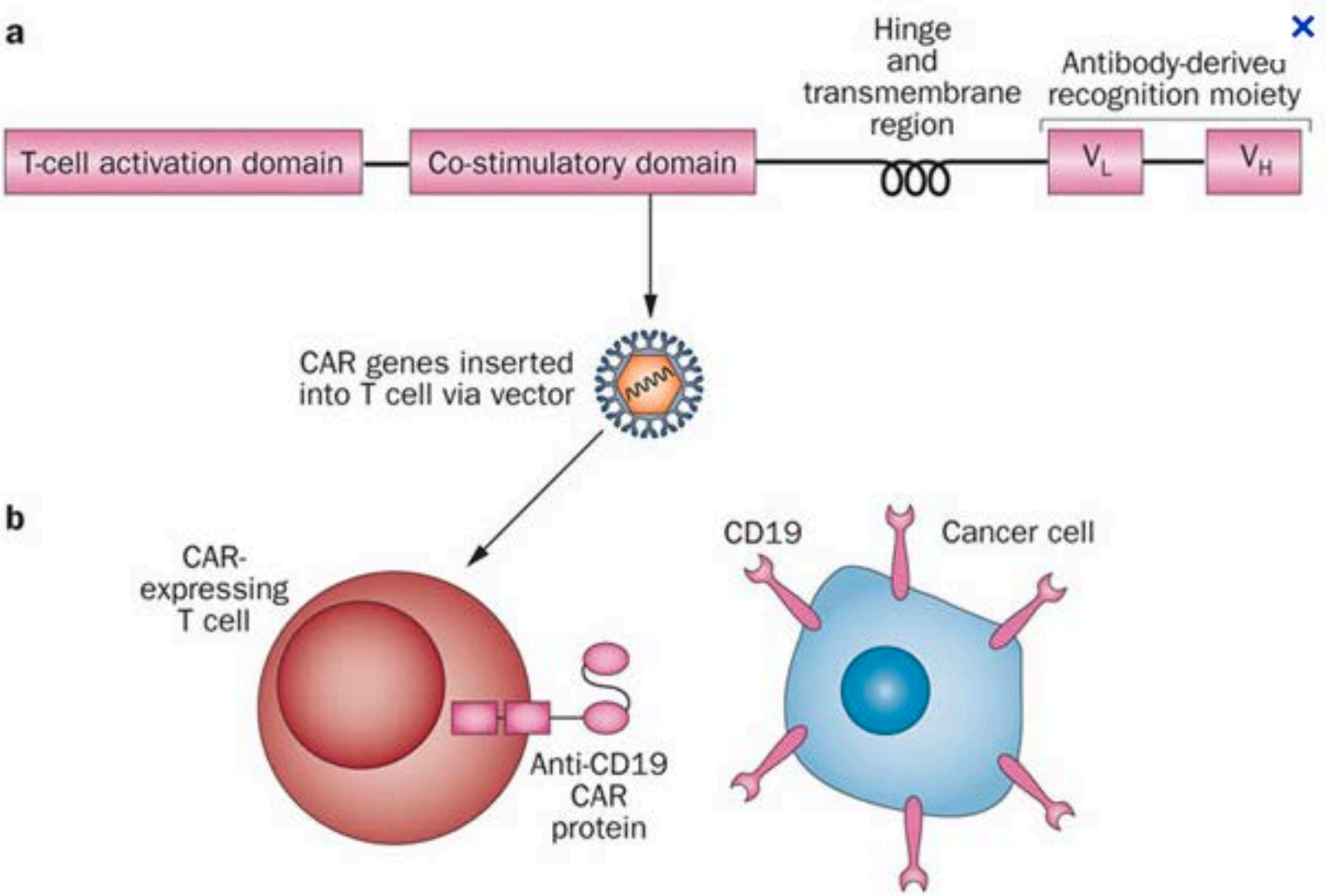
Nowadays, the reality of exorbitant drug pricing overshadows even the most exceptional stories of drug efficacy.

The rate of introduction of new and expensive drugs has accelerated; the pace of conversion to generics is slowing; the prices of many generics are rising; and expensive drugs are now being introduced for conditions that affect millions of people rather than thousands.

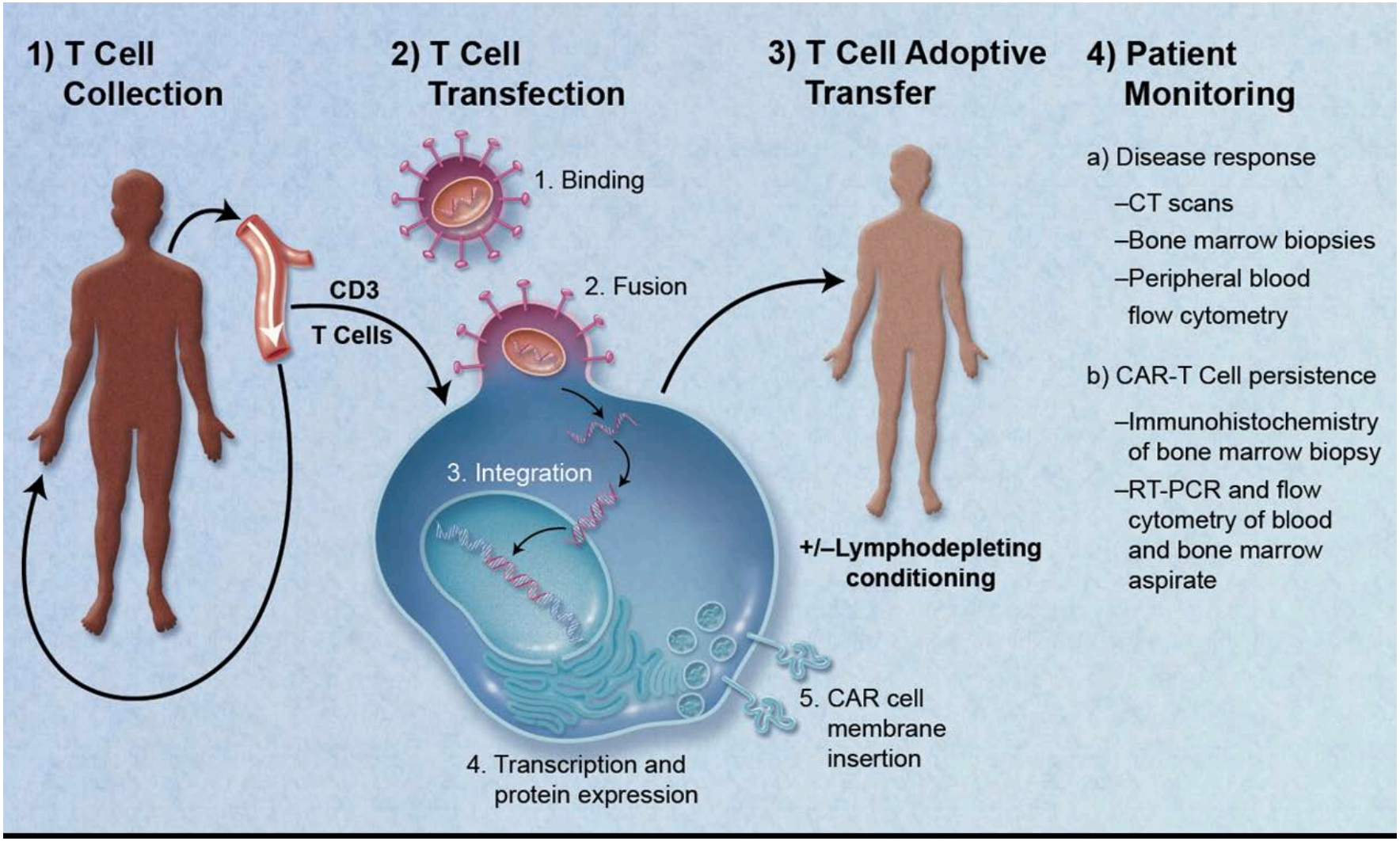
Chimeric antigen receptor t-cell (CAR)



Chimeric antigen receptor t-cell (CAR)



Chimeric antigen receptor t-cell (CAR)



In Girl's Last Hope, Altered Immune Cells Beat Leukemia

By DENISE GRADY DEC. 9, 2012

Emma Whitehead, with her mother, Kari. Last spring, Emma was near death from acute lymphoblastic leukemia but is now in remission after an experimental treatment at the Children's Hospital of Philadelphia.
Jeff Swensen for The New York Times

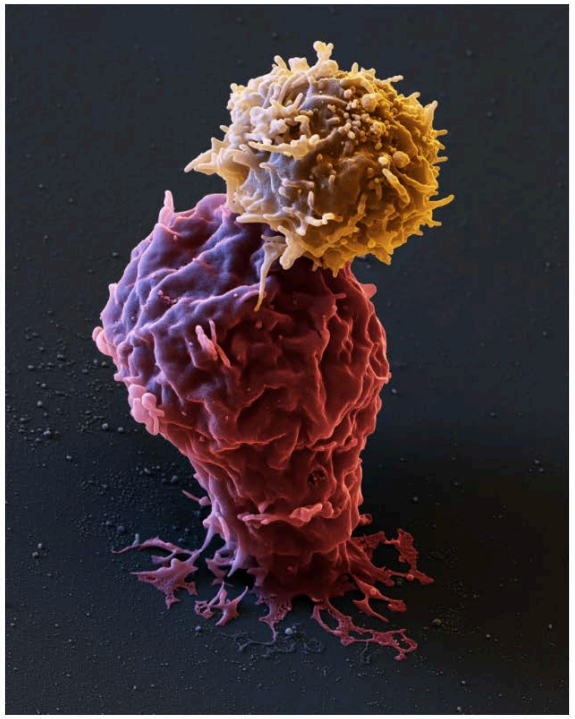
RELATED COVERAGE

An Experimental Treatment for Le
DEC. 9, 2012

Immune System, Loaded With Rer
cells, Vanquishes Cancer SEPT. 12, 20

The New York Times

Breakthrough Leukemia Treatment Backfires in a Rare Case



A sign that the treatment is working is that the patient becomes terribly ill, with raging fevers and chills . Its medical name is cytokine-release syndrome, or cytokine storm, The storm can also flood the lungs and cause perilous drops in blood pressure — effects that nearly killed Emma.

Steroids sometimes ease the reaction, but they did not help Emma. Her temperature hit 105. She wound up on a ventilator, unconscious and swollen almost beyond recognition, surrounded by friends and family who had come to say goodbye.

But at the 11th hour, a battery of blood tests gave the researchers a clue as to what might help save Emma: her level of one of the cytokines, interleukin-6 or IL-6, had shot up a thousandfold. Doctors had never seen such a spike before and thought it might be what was making her so sick.

Dr. June knew that a drug could lower IL-6 — his daughter takes it for rheumatoid arthritis. It had never been used for a crisis like Emma's, but there was little to lose. Her oncologist, ordered the drug. The response, he said, was "amazing."

Within hours, Emma began to stabilize. She woke up a week later, on May 2, the day she turned 7; the intensive-care staff sang "Happy Birthday."

Since then, the research team has used the same drug, tocilizumab, in several other patients.

PubMed car-t cell

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Kalaitsidou M et al. Immunotherapy. (2015)

CAR T-cell therapy for pancreatic cancer.
DeSelm CJ et al. J Surg Oncol. (2017)

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Chimeric antigen receptor t-cell (CAR)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia

RESULTS

A total of 30 children and adults received CTL019. Complete remission was achieved in 27 patients (90%), including 2 patients with blinatumomab-refractory disease and 15 who had undergone stem-cell transplantation. CTL019 cells prolif-

895 Updated Analysis of the Efficacy and Safety of Tisagenlecleucel in Pediatric and Young Adult Patients with Relapsed/Refractory (r/r) Acute Lymphoblastic Leukemia

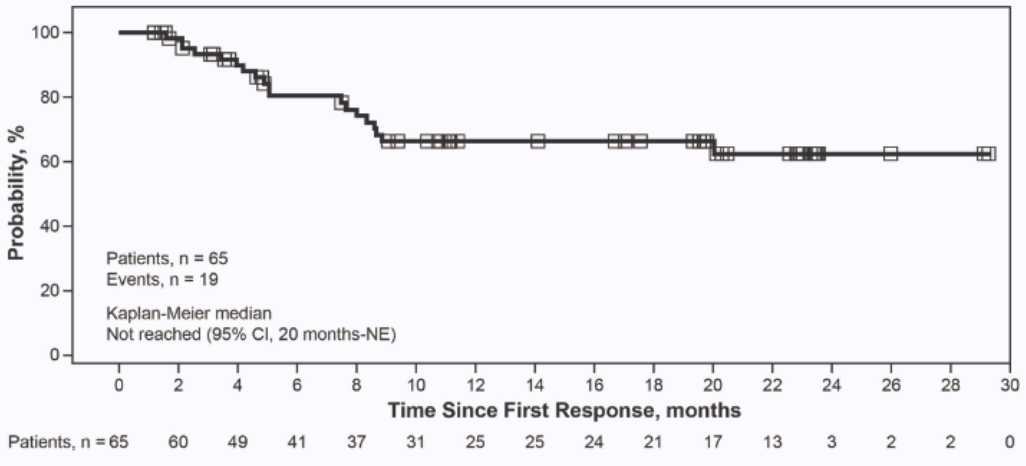
Program: Oral and Poster Abstracts
Type: Oral
Session: 612. Acute Lymphoblastic Leukemia: Clinical Studies: Improving Outcomes with Cellular Therapy
Hematology Disease Topics & Pathways:
Biological, Therapies, CAR-Ts

As of April 13, 2018, 113 pts were screened and 97 enrolled. There were 8 manufacturing failures (8%) and 10 pts (10%) were not infused due to death or adverse events (AEs).

	Patients (N = 79)	
	n (%)	95% CI, %
ORR	65 (82)	72-90
CR	49 (62)	
CRi	16 (20)	
Probability of relapse-free survival, %[a]		
12 Months	66	52-77
18 Months	66	52-77
Probability of overall survival, %		
12 Months	76	65-85
18 Months	70	58-79

[a] Among responding patients (n = 65).

Kaplan-Meier Plot of Duration of Remission Censoring SCT (by IRC assessment; full analysis set)



CAR T Cells and Other Cellular Therapies for Multiple Myeloma: 2018 Update

Adam D. Cohen, MD

PRACTICAL APPLICATIONS

- **Despite improved outcomes with novel agents, most patients with myeloma eventually develop drug resistance and succumb to their disease.**
- **Cellular therapies provide the potential to overcome drug resistance and induce durable remissions with a single treatment.**
- **BCMA-specific CAR T cells have shown promising clinical activity, including a high proportion of complete responses, in patients with highly refractory myeloma.**
- **BCMA CAR T cells can cause cytokine release syndrome and neurotoxicity, similar to CD19 CAR T cells, without unexpected off-target or off-tumor toxicities noted to date.**
- **Many CAR T and other cellular therapy trials for myeloma are opening in 2018, which will allow for greater availability of these approaches to patients.**

TABLE 1. Selected CAR T-Cell Targets and Trials for Myeloma*

Antigen	Trial Site, Company	Accrual	Identifier/Reference	Comments
BCMA	National Cancer Institute	Completed (26 patients)	NCT02215967[42,43]	First-in-human, CD28 domain, Cy/Flu conditioning; 13 of 16 (81%) ORR at highest dose
	University of Pennsylvania, Novartis	Completed (24 patients' data reported)	NCT02546167[44]	4-1BB domain; 6 of 10 (60%) ORR at high dose with Cy conditioning
	Multisite phase I, Bluebird	Ongoing (21 patients' data reported)	NCT02658929[45]	bb2121 construct, 4-1BB domain, Cy/Flu; 17 of 18 (94%) ORR at higher doses
	Multisite phase II, Bluebird	Ongoing	NCT03361748	bb2121 registration study, 94 patients
	Multisite phase I, Bluebird	Ongoing	NCT03274219	bb21217 product (same as bb2121 but enriched for memory T cells)
	Multisite phase I/II, Nanjing Legend	Ongoing (19 patients' data reported)	NCT03090659[46]	Binds two BCMA epitopes; Cy conditioning; less-treated population; 19 of 19 (100%) ORR
	Memorial Sloan Kettering/Juno	Ongoing (6 patients' data reported)	NCT03070327[47]	2 of 2 responded at higher dose with Cy/Flu; includes cohort with lenalidomide
	Fred Hutchinson, Juno	Ongoing	NCT03338972	Defined CD4/CD8 ratio in final CAR T product
	Multisite phase I/II, Juno	Ongoing	NCT03430011	JCARH125 construct, Flu/Cy
	Multisite phase I, Poseida	Ongoing	NCT03288493	Transposon-based construct[48]
	Multisite phase I, Kite	Ongoing	NCT03318861	KITE-585 construct, Flu/Cy
	Multiple hospital sites in China	Ongoing	NCT03322735 NCT03093168 NCT03380039 NCT02954445 NCT03302403	Small phase I/pilot studies
	Multisite phase I/II, Autolus Limited	Ongoing	NCT03287804	Novel CAR expressing APRIL to target BCMA and TACI
	Virginia Cancer Specialists, Cartesian Therapeutics	Ongoing	NCT03448978	Product contains $CD8^+$ cells only
CD19	University of Pennsylvania, Novartis	Completed (10 patients)	NCT02135406[49,50]	CD19 CAR T + salvage autoSCT. Targeting CD19+ myeloma precursor cells.
	Soochow University, China	Ongoing (10 patients reported)	NCT03196414[51]	CD19 CAR T + BCMA CAR T
			NCT03455972	Includes pilot of upfront CAR T cells + auto-SCT for high-risk MM
	General Hospital of PLA, China	Completed (5 patients)	NCT01886976	4 of 5 with stable disease for 3–7 months;

J Hematol Oncol. 2018 Oct 22;11(1):128. doi: 10.1186/s13045-018-0672-7.

Anti-BCMA CAR-T cells for treatment of plasma cell dyscrasia: case report on POEMS syndrome and multiple myeloma.

Xu J[1,2], Wang Q[1,2], Xu H[1,2], Gu C[3], Jiang L[1,2], Wang J[1,2], Wang D[1,2], Xu B[1,2], Mao X[1,2], Wang J[1,2], Wang Z[1,2], Xiao Y[1,2], Zhang Y[1,2], Li C[4,5], Zhou J[6,7].

⊕ Author information

Hematol Oncol. 2018 Nov 14. doi: 10.1002/hon.2568. [Epub ahead of print]

The Acceleration of CAR-T therapy in Non-Hodgkin Lymphoma.

Munshi PN[1], Ujjani C[2].

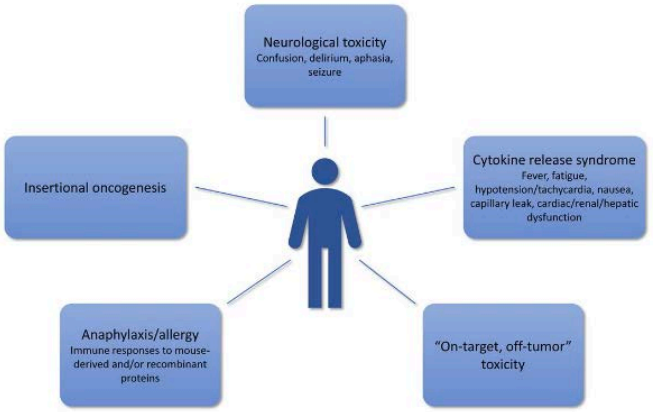


Figure 1. Depicted potential toxicities following CAR-T cell therapy. Adapted from Bonifant C, et al [34].

Table 1. CAR-T Therapies in Aggressive B-cell Lymphomas

Institution	NIH/NCI [26-28]	UPENN [29,30]	FHCRC [31,32]
Study/Sponsor	ZUMA 1/Kite-Gilead Axicabtagene ciloleucel	JULIET/Novartis Tisagenlecleucel	TRANSCEND/Juno-Celgene Core CD4:CD8 = 1:1 Lisocabtagene maraleucel
scFV Clone	CD19/CD3zeta/ CD28 FMC63	CD19/CD3zeta/ 4-1BB FMC63	CD19/CD3zeta/ 4-1BB FMC63
scFV Origin	Murine	Murine	Murine
Cell Population	PBMC	PBMC	CD4+ and CD8+ T cells
Gene Transfer System	Retrovirus	Lentivirus	Lentivirus
Lymphoma subtypes	DLBCL/PMBCL/TFL	DLBCL/TFL	DLBCL/TFL/FL Gr 3B
Conditioning Therapy	Cyclophosphamide/ Fludarabine	Cyclophosphamide/ Fludarabine or Bendamustine	Cyclophosphamide/ Fludarabine
Number of patients	108	111	102
CRS All Grades	93%	58%	37%
CRS Grade ≥ 3	13%	22%	1%
Neurotoxicity All Grades	65%	21%	23%
Neurotoxicity Grade ≥ 3	31%	12%	13%
Best ORR	82%	52% out of n=93	80% out of n=73
Best CR rate	58%	40% out of n=93	59% out of n=73
Durable ORR	42% at 12 months	34% at 12 months	47% at 6 months
Durable CR rate	40%	29%	41%

Zhonghua Xue Ye Xue Za Zhi. 2018 Oct 14;39(10):862-865. doi: 10.3760/cma.j.issn.0253-2727.2018.10.015.

[Efficacy and safety of reduced dose of PD-1 inhibitor combined with CD19-CAR-T on B-cell non-Hodgkin lymphoma patients with high expression of PD-1 in peripheral blood].

[Article in Chinese]

Wang J, Deng Q, Jiang YY, Zhang R, Zhu HB, Meng JX, Zhao MF, Li YM.

Disruption of *TET2* promotes the therapeutic efficacy of CD19–targeted T cells

14 JUNE 2018 | VOL 558 | NATURE | 307

RESEARCH LETTER

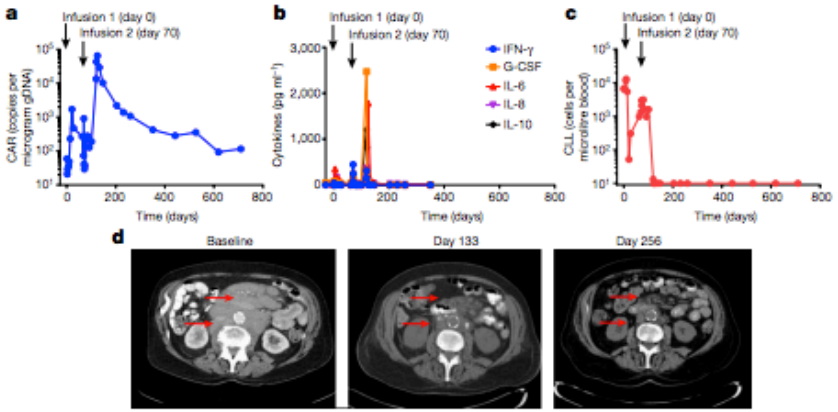


Fig. 1 | Evaluation of clinical responses following adoptive transfer of CAR T cells in a patient with CLL. a, In vivo expansion and persistence of CAR T cells. **b**, Longitudinal measurements of serum cytokines before and after CAR T cell infusions. **c**, Total number of circulating B-CLL cells before and after CTL019 therapy. **d**, Sequential CT imaging of chemotherapy-refractory lymphadenopathy. Red arrows indicate masses that were progressively reduced following the second CAR T cell infusion.

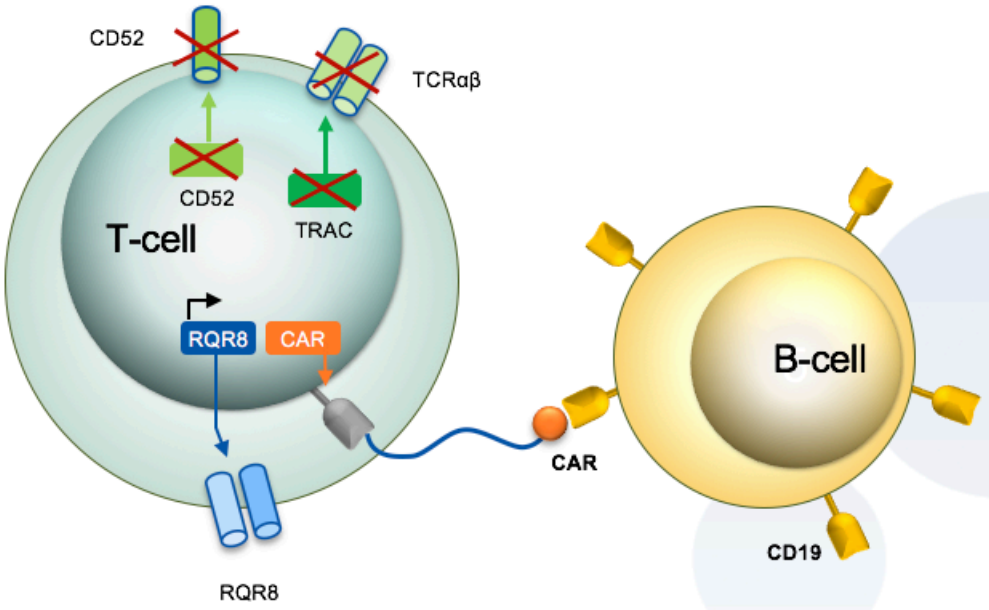
Unexpectedly, at the peak of the response, 94% of CAR T cells originated from a single clone in which lentiviral vector-mediated insertion of the CAR transgene disrupted the TET2 gene. Further analysis revealed a hypomorphic mutation in this patient's second TET2 allele. TET2-disrupted CAR T cells exhibited an epigenetic profile consistent with altered T cell differentiation and, at the peak of expansion, displayed a central memory phenotype.

These findings suggest that the progeny of a single CAR T cell induced leukaemia remission and that TET2 modification may be useful for improving immunotherapies.

CAR T allogéniques

UCART 19

- Premiers CAR T-cells allogéniques
- « Off-the-shelf »
- CAR : anti-CD19 scFv – CD3ζ – 4-1BB
- RQR8 (CD20 mimotope) : système suicide
- Knock-out par TALEN®
  (transcription activator-like effector nuclease)
  - TRAC
    - Pour prévenir la réaction du greffon contre l'hôte (GVH)
  - CD52
    - Pour permettre l'utilisation de l'alemtuzumab à visée de lymphodéplétion



D'après la communication orale de R. Benjamin, Abstract #896, ASH 2018

SEARCH

The New York Times

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CVS Will Offer Next-Day Delivery of Prescription Drugs

If You Te… Ligamen… Likely to… Years

HEALTH

F.D.A. Approves First Gene-Altering Leukemia Treatment, Costing $475,000

By DENISE GRADY AUG. 30, 2017

A technician working with human cells belonging to cancer patients at Novartis Pharmaceuticals in Morris Plains, N.J. The Food and Drug Administration on Wednesday approved Novartis's gene therapy for leukemia, the first-ever treatment that alters a patient's own cells to fight cancer.

Brent Stirton/Novartis Pharmaceuticals Corp., via Associated Press

RELATED COVERAGE

Setting the Body's 'Serial Killers' Loose on Cancer AUG. 1, 2016

Immune System, Loaded With Remade T-cells, Vanquishes Cancer SEPT. 12, 2011

A Breakthrough Against Leukemia Using Altered T-Cells DEC. 9, 2012

F.D.A. Panel Recommends Approval for Gene-Altering Leukemia Treatment JULY 12, 2017

Companies Rush to Develop 'Utterly Transformative' Gene Therapies JULY 23, 2017

Ils sont indiqués dans le traitement du lymphome B à grande cellule chez l'adulte. Kymriah peut être également utilisé dans le traitement de la leucémie aigue lymphoblastique B (LAL-B) chez l'enfant et le jeune adulte âgés de moins de 25 ans.

Apport d'internet

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

. . . And a Diagnostic Test Was Performed

N Engl J Med 2005; 353:2089-2090 | November 10, 2005 | DOI: 10.1056/NEJM200511103531923

To the Editor:

At a recent case conference with a distinguished visiting professor, a fellow in allergy and immunology presented the case of an infant with diarrhea; an unusual rash ("alligator skin"); multiple immunologic abnormalities, including low T-cell function; tissue eosinophilia (of the gastric mucosa) as well as peripheral eosinophilia; and an apparent X-linked genetic pattern (several male relatives died in infancy). The attending physicians and house staff discussed several diagnostic possibilities, but no consensus was reached. Finally, the visiting professor asked the fellow if she had made a diagnosis, and she reported that she had indeed and mentioned a rare syndrome known as IPEX (immunodeficiency, polyendocrinopathy, enteropathy, X-linked). It appeared to fit the case, and everyone seemed satisfied. (Several weeks later, genetic testing on the baby revealed a mutation in the *FOXP3* gene, confirming the diagnosis.)

"How did you make that diagnosis?" asked the professor. Came the reply, "Well, I had the skin-biopsy report, and I had a chart of the immunologic tests. So I entered the salient features into Google, and it popped right up."

"William Osler," I offered, "must be turning over in his grave. You googled the diagnosis?"

Google

Web Résultats **1 - 10** sur un total d'environ **23** pour **polyneuropathie ostéocondensation**. (**0,28** secondes)

Maladie de Waldenström

... le syndrome de Schnitzler (urticaire chronique, **ostéocondensation** et IgM **...** La **polyneuropathie** touche typiquement un sujet de la soixantaine, **...**

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La maladie de Kahler ou myélome multiple des os

Plus exceptionnellement ont été décrites des formes avec **ostéocondensation**. **...** Le syndrome POEMS [**Polyneuropathie**, Organomégalie (foie et rate surtout), **...**

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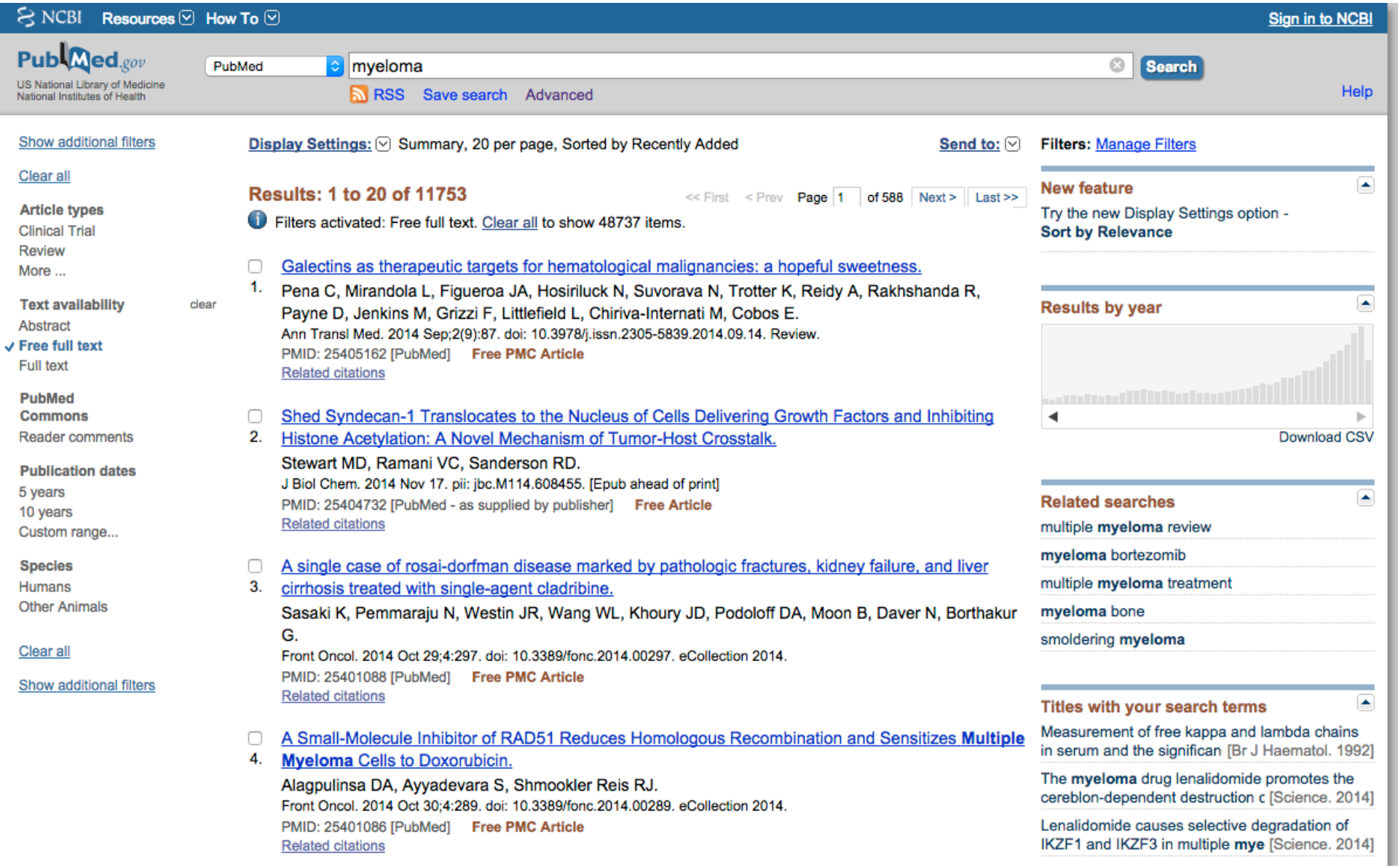

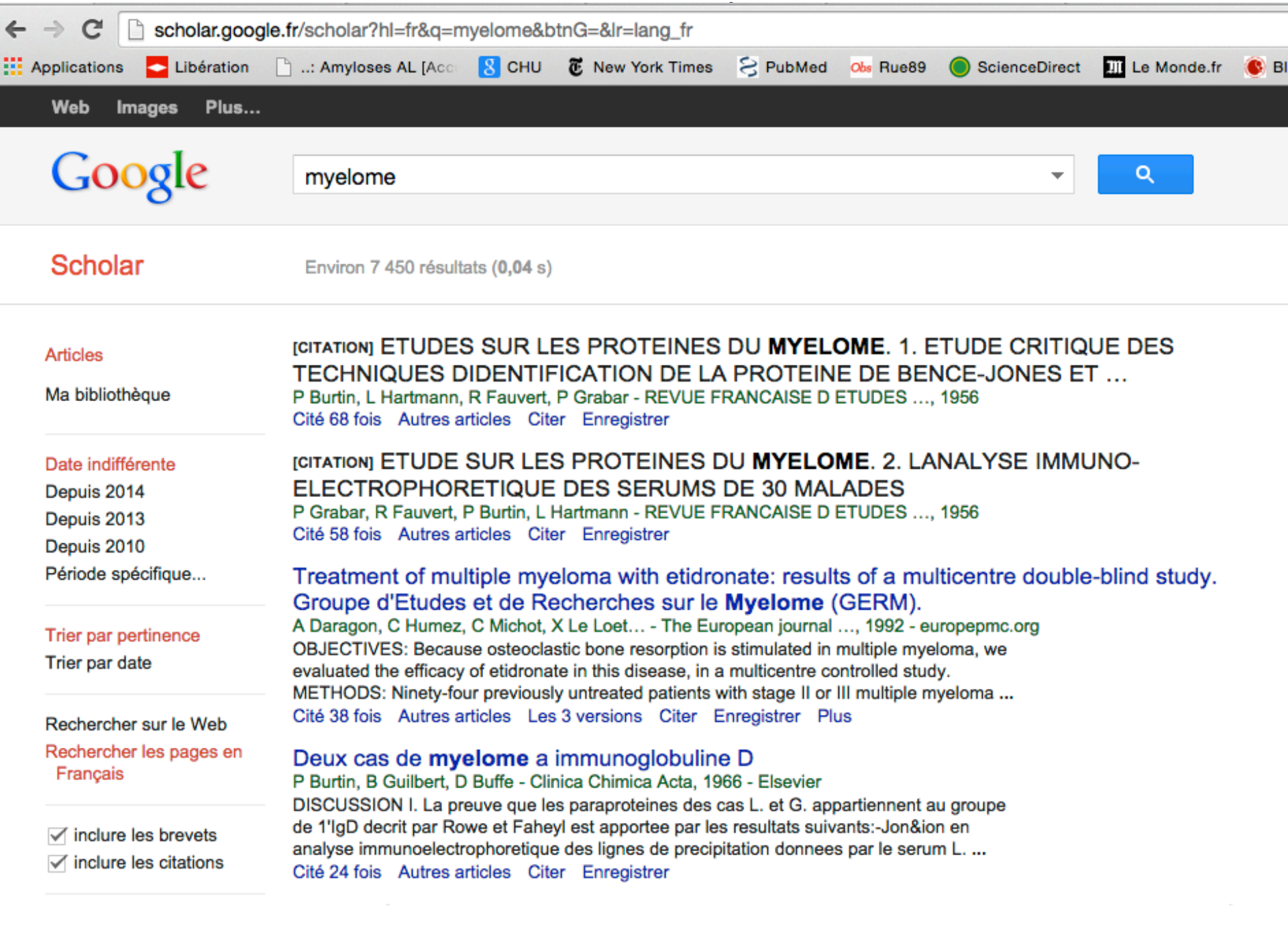
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OBJECTIVES: Because osteoclastic bone resorption is stimulated in multiple myeloma, we evaluated the efficacy of etidronate in this disease, in a multicentre controlled study.
METHODS: Ninety-four previously untreated patients with stage II or III multiple myeloma ...
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P Burtin, B Guilbert, D Buffe - Clinica Chimica Acta, 1966 - Elsevier
DISCUSSION I. La preuve que les paraproteines des cas L. et G. appartiennent au groupe de 1'IgD decrit par Rowe et Faheyl est apportee par les resultats suivants:-Jon&ion en analyse immunoelectrophoretique des lignes de precipitation donnees par le serum L. ...
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