Hôpitaux Universitaires
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université
PARIS
DIDEROT
PARIS 7

SORBONNE PARIS CITÉ
RECHERCHE
ENSEIGNEMENT SUPÉRIEUR

Déficit immunitaire et « thérapies ciblées »

Michael Darmon
Réanimation médicale
Hôpital Saint-Louis, APHP
Université Paris-7 Paris-Diderot

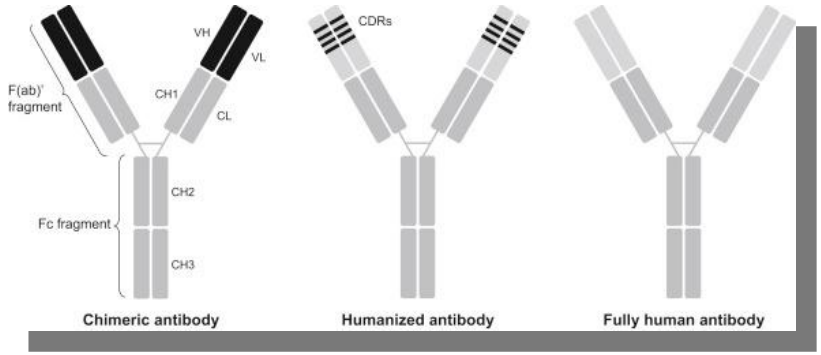
Vaste sujet

1- Biothérapies/Thérapies ciblées/ ’Biologics’

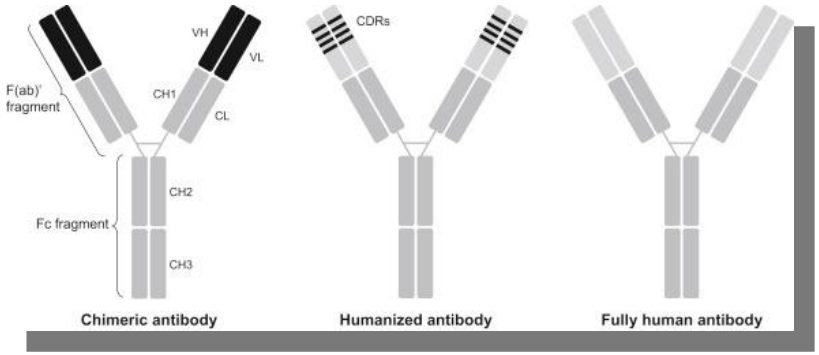
2- Immunothérapies

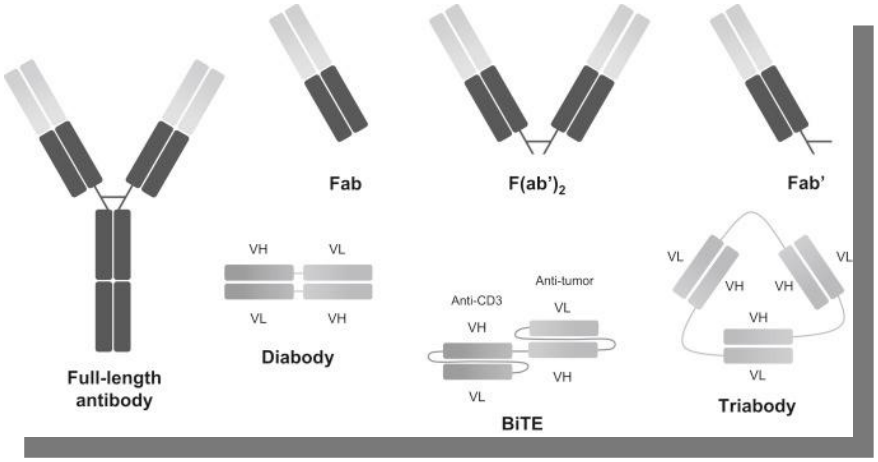
3- Ac Monoclonaux

Fragments FAB, Ac bispécifiques, BITE…



Place	Type	Exemples		
Préfixe	Aléatoire	-		
Systéme A	Systéme cible	t(u)=tumeur	l(i)= immun	c(i)=cardioV
Systéme B	Origine	u=humain	zu=humanisé	xi=chimérique
Suffixe	Type	mab = mAb = domaine variable des Ig		





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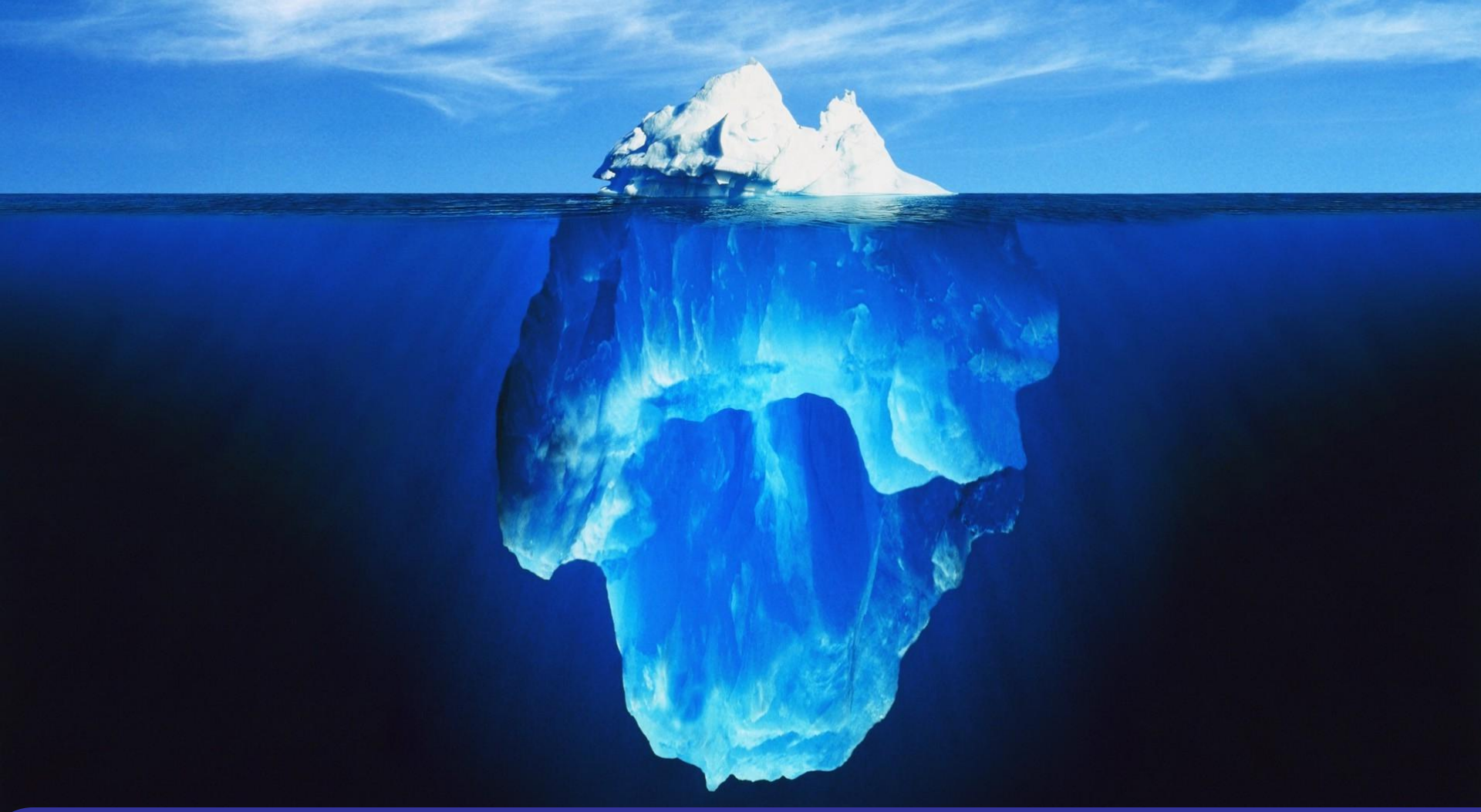


Complication des « biothérapies »

Pourquoi tant d'incertitudes

1- Rythme d'une molécule apparue par mois

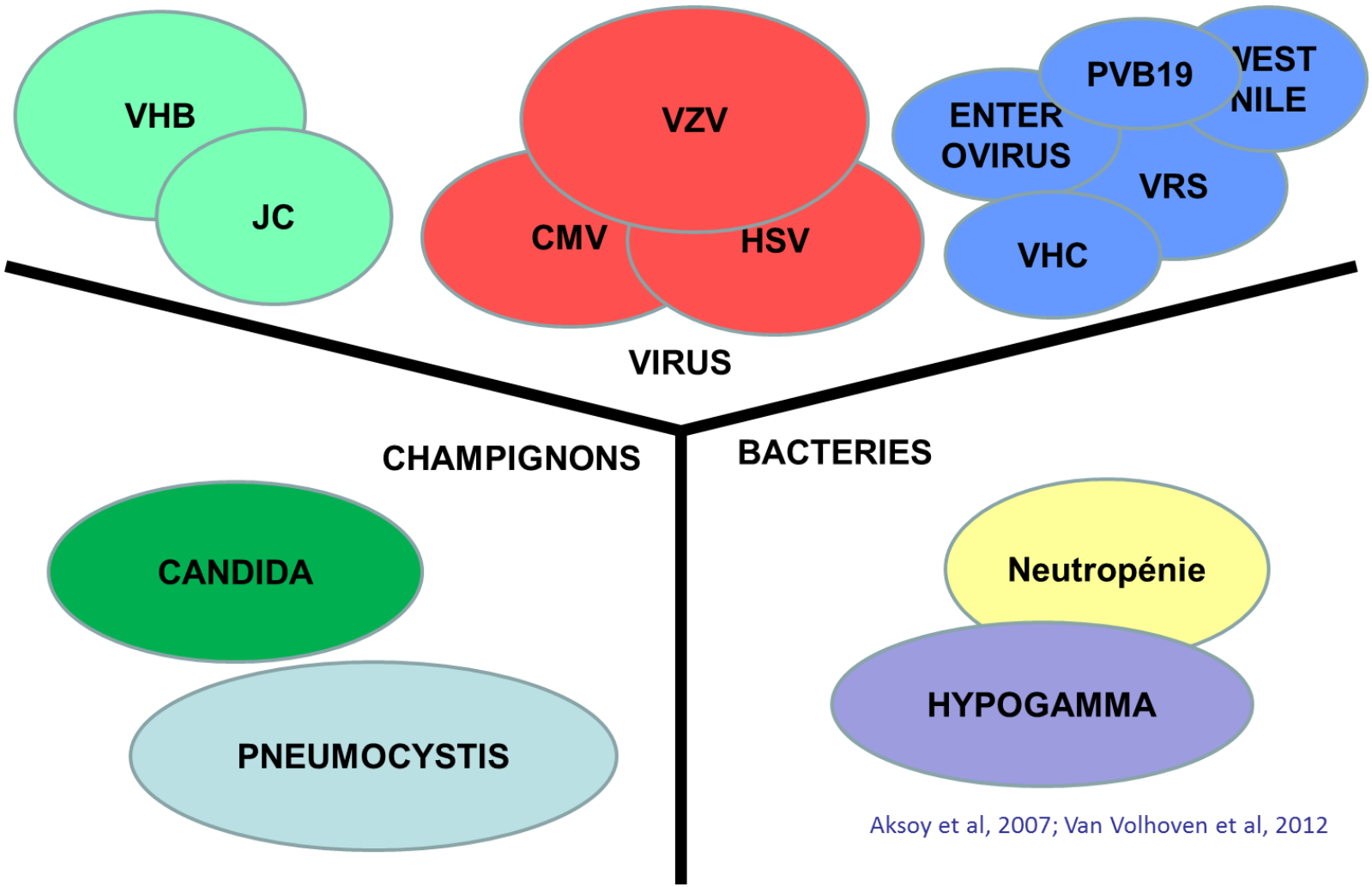
2- Identifier une modification des risques demande du temps

3- Rôle de l'immunodépression sous jacente

4- Certains risques concernent des pathologies rares

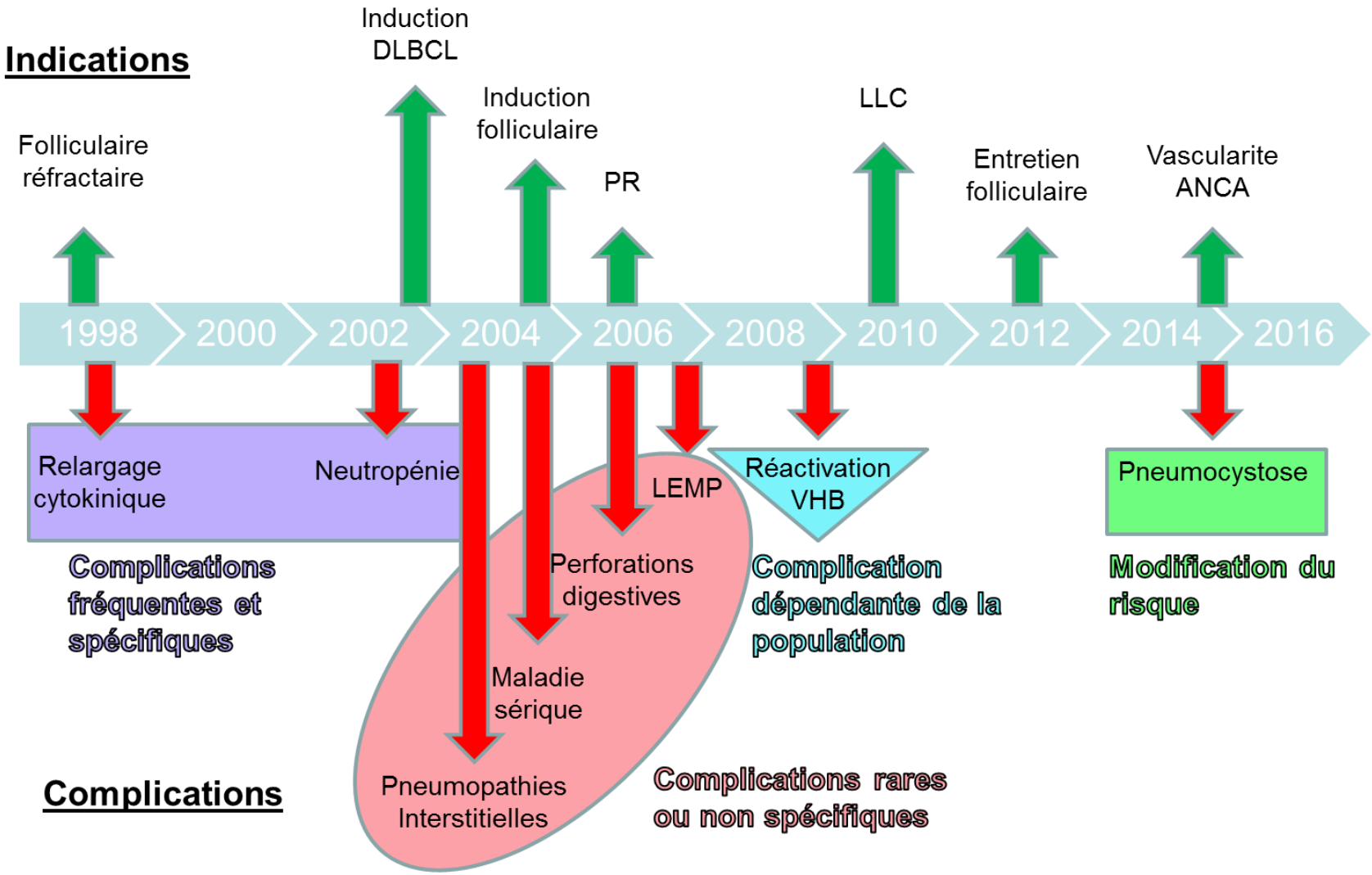
5- Passer de la suspicion à la certitude

Infections sous anti-CD20



Aksoy et al, 2007; Van Volhoven et al, 2012

20 ans aprés


Indications
Induction DLBCL
Induction folliculaire
LLC
Folliculaire réfractaire
PR
Entretien folliculaire
Vascularite ANCA
1998
2000
2002
2004
2006
2008
2010
2012
2014
2016
Relargage cytokinique
Neutropénie
LEMP
Réactivation VHB
Pneumocystose
Complications fréquentes et spécifiques
Perforations digestives
Complication dépendante de la population
Modification du risque
Maladie sérique
Complications
Pneumopathies Interstitielles
Complications rares ou non spécifiques

Review

ESCMID Study Group for Infections in Compromised Hosts (ESGICH) consensus document on the safety of targeted and biologic therapies: an infectious diseases perspective—cell surface receptors and associated signaling pathways

J. Aguilar-Company [1], M. Fernández-Ruiz [3,4], R. García-Campelo [5], A.C. Garrido-Castro [6], I. Ruiz-Camps [2,4,*]

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Narrative review

ESCMID Study Group for Infections in Compromised Hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective—immune checkpoint inhibitors, cell adhesion inhibitors, sphingosine 1–phosphate receptor modulators and proteasome inhibitors

G. Redelman-Sidi [1,*], O. Michielin [2], C. Cervera [5], C. Ribi [3], J.M. Aguado [6,7], M. Fernández-Ruiz [6,7], O. Manuel [4]

Review

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G. Redelman-Sidi [1,*], O. Michielin [2], C. Cervera [5], C. Ribi [3], J.M. Aguado [6,7], M. Fernández-Ruiz [6,7]

Revised manuscript (CLM-17-12786.R1) [for for AA publication]

Review paper

Title page

Complete title: ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an Infectious Diseases perspective (Intracellular signaling pathways: tyrosine kinase and mTOR inhibitors)

Review

ESCMID Study Group for Infections in Compromised Hosts (ESGICH) consensus document on the safety of targeted and biologic therapies: an infectiou associated s

J. Aguilar-Comp
I. Ruiz-Camps [2]

Narrative review

ESCMID Stud
consensus do
therapies: an infectious diseases perspective—immune checkpoint inhibitors, cell adhesion inhibitors, sphingosine 1–phosphate receptor modulators and proteasome inhibitors

G. Redelman-Sidi [1,*], O. Michielin [2], C. Cervera [5], C. Ribi [3], J.M. Aguado [6,7], M. Fernández-Ruiz [6,7]

Narrative Review

ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (agents targeting lymphoid cells surface antigens [I]: CD19, CD20 and CD52)

M. Mikulska [1,*], S. Lanini [2], C. Gudiol [3], L. Drgona [4], G. Ippolito [2], M. Fernández-Ruiz [5,6], B. Salzberger [7]

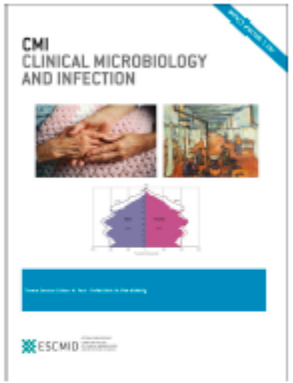
Revised manuscript (CLM-17-12786.R1) [for for AA publication]

Review paper

Title page

Complete title: ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an Infectious Diseases perspective (Intracellular signaling pathways: tyrosine kinase and mTOR inhibitors)

Accepted Manuscript



ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an Infectious Diseases perspective (Soluble immune effector molecules [II]: agents targeting interleukins, immunoglobulins and complement factors)

Kevin L. Winthrop, Xavier Mariette, Jose T. Silva, Esther Benamu, Leonard H. Calabrese, Alexandre Dumusc, Josef S. Smolen, José María Aguado, Mario Fernández-Ruiz

therapies: an infectious diseases perspective—immune checkpoint inhibitors, cell adhesion inhibitors, sphingosine 1–phosphate receptor modulators and proteasome inhibitors

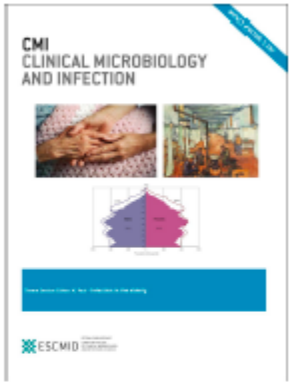
G. Redelman-Sidi [1,*], O. Michielin [2], C. Cervera [5], C. Ribi [3], J.M. Aguado [6,7], M. Fernández-Ruiz [6,7]

Revised manuscript (CLM-17-12786.R1) [for for AA publication]

Review paper

Title page

Complete title: ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an Infectious Diseases perspective (Intracellular signaling pathways: tyrosine kinase and mTOR inhibitors)



ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an Infectious Diseases perspective (Soluble immune effector molecules [II]: agents targeting interleukins, immunoglobulins and complement factors)

;ICH)

Kevin L. Winthrop, Xavier Mariette, Jose T. Silva, Esther Benamu, Leonard H. Calabrese, Alexandre Dumusc, Josef S. Smolen, José María Aguado, Mario Fernández-Ruiz

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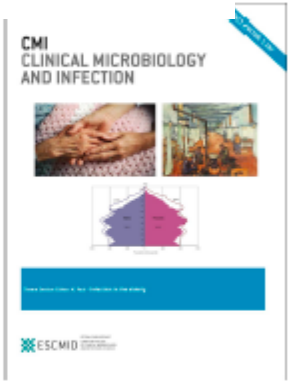
inhibit
modul

G. Redel
M. Fern



ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an Infectious Diseases perspective (Agents targeting lymphoid or myeloid cells surface antigens [II]: CD22, CD30, CD33, CD38, CD40, SLAMF-7 and CCR4)

Lubos Drgona, Carlota Gudiol, Simone Lanini, Bernd Salzberger, Giuseppe Ippolito, Małgorzata Mikulska

Complete title: ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an Infectious Diseases perspective (Intracellular signaling pathways: tyrosine kinase and mTOR inhibitors)

En pratique

Inhibiteurs des molécules de surface (VEGF/EGFR)

Risque de neutropénie (anti-VEGF) sinon données insuffisantes

Inhibiteurs de check-points/protéasome

Risque d'infection virale (anti-intégrines/Inh. Prot).

Anti-TK (Bruton, MEK, BRAF…)

On ne sais pas (hémopathie sous jacente)

Anti-CD…

30 (Brentux), 33 (Mylotarg),38 (Dara), 40(Lucatu),319(Elotu)… Virus (?)

Anti-TNF

BK et granulomatose. Autre?

ESGICH & ESGICH & al. Clin Microbiol Inf 2018

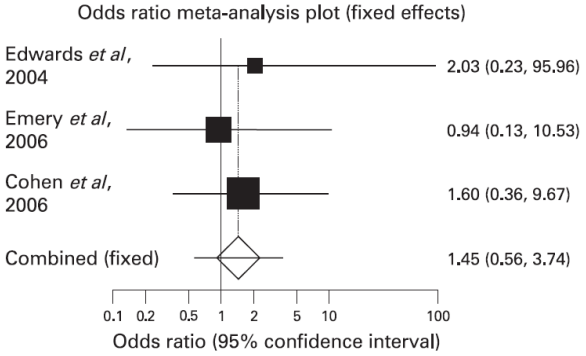
Risque estimé selon déficit attendu

Neutrophils / phagocytosis	T cells	B cells
AML / ALL MDS Aplastic anemia Chemotherapy	ALL, hairy cell leukemia HG Lymphoma Hodgkin Corticosteriods Chemotherapy (fludarabine) Cyclosporine, FK 506…	MM LG Lymphoma CLL Chemotherapy Corticosteriods
Bacteria Candida Aspergillus HSV	Pneumocystis CMV Virus-like Aspergillus	Encapsulated bacteria

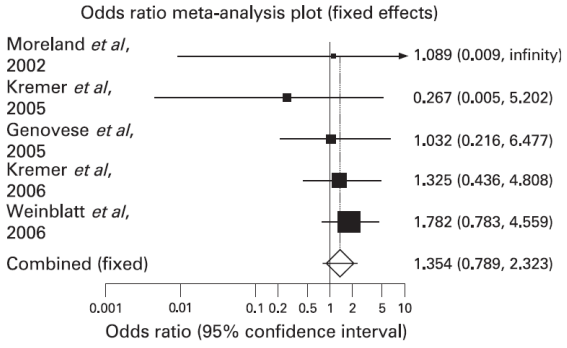
Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials

C Salliot, M Dougados, L Gossec

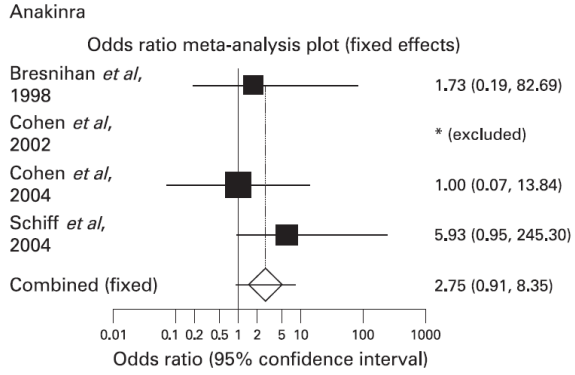
Rituximab



Abatacept



Anakinra



Ann Rheum Dis 2009;**68**:25–32. doi:10.1136/ard.2007.083188

Serious infection							
Abatacept	control	26 per 1000	25 per 1000 (11 to 58)	OR 0.97 (0.40 to 2.31)	2052 (5 studies)	⊕⊕⊕⊕ high	Not statistically significant
Adalimumab	control	26 per 1000	32 per 1000 (17 to 60)	OR 1.23 (0.65 to 2.40)	4847 (15 studies)	⊕⊕⊕◯ moderate[1]	Not statistically significant
Anakinra	control	26 per 1000	98 per 1000 (32 to 310)	OR 4.05 (1.22 to 16.84)	3436 (4 studies)	⊕⊕⊕◯ moderate[1]	14 (4 to 181)
Certolizumab pegol	control	26 per 1000	113 per 1000 (39 to 330)	OR 4.75 (1.52 to 18.45)	1683 (4 studies)	⊕⊕⊕⊕ high	12 (4 to 79)
Etanercept	control	26 per 1000	33 per 1000 (19 to 61)	OR 1.29 (0.72 to 2.45)	4630 (19 studies)	⊕⊕⊕◯ moderate[1]	Not statistically significant
Golimumab	control	26 per 1000	29 per 1000 (12 to 65)	OR 1.11 (0.45 to 2.59)	1334 (6 studies)	⊕⊕⊕◯ moderate[1]	Not statistically significant
Infliximab	control	26 per 1000	36 per 1000 (20 to 65)	OR 1.41 (0.75 to 2.62)	2652 (13 studies)	⊕⊕⊕◯ moderate[1]	Not statistically significant
Rituximab	control	26 per 1000	7 per 1000 (1 to 55)	OR 0.26 (0.03 to 2.16)	377 (2 studies)	⊕⊕◯◯ low[1,2]	Not statistically significant
Tocilizumab	control	26 per 1000	22 per 1000 (5 to 87)	OR 0.84 (0.20 to 3.56)	842 (3 studies)	⊕⊕⊕◯ moderate[1]	Not statistically significant
All nine biologics	control	26 per 1000	35 per 1000 (27 to 46)	OR 1.37 (1.04 to 1.82)	21,853 (70 studies)	⊕⊕⊕◯ moderate[1]	108 (50 to 989)

Sing et al. Cochrane Reviews 2011

Rheumatology International
https://doi.org/10.1007/s00296-018-4041-1

Rheumatology
INTERNATIONAL

SYSTEMATIC REVIEW

Efficacy and safety of interleukin-1 antagonists in rheumatoid arthritis: a systematic review and meta-analysis

Shekoufeh Nikfar[1,2] · Parisa Saiyarsarai[1] · Bereket Molla Tigabu[1,3] · Mohammad Abdollahi[2,4]

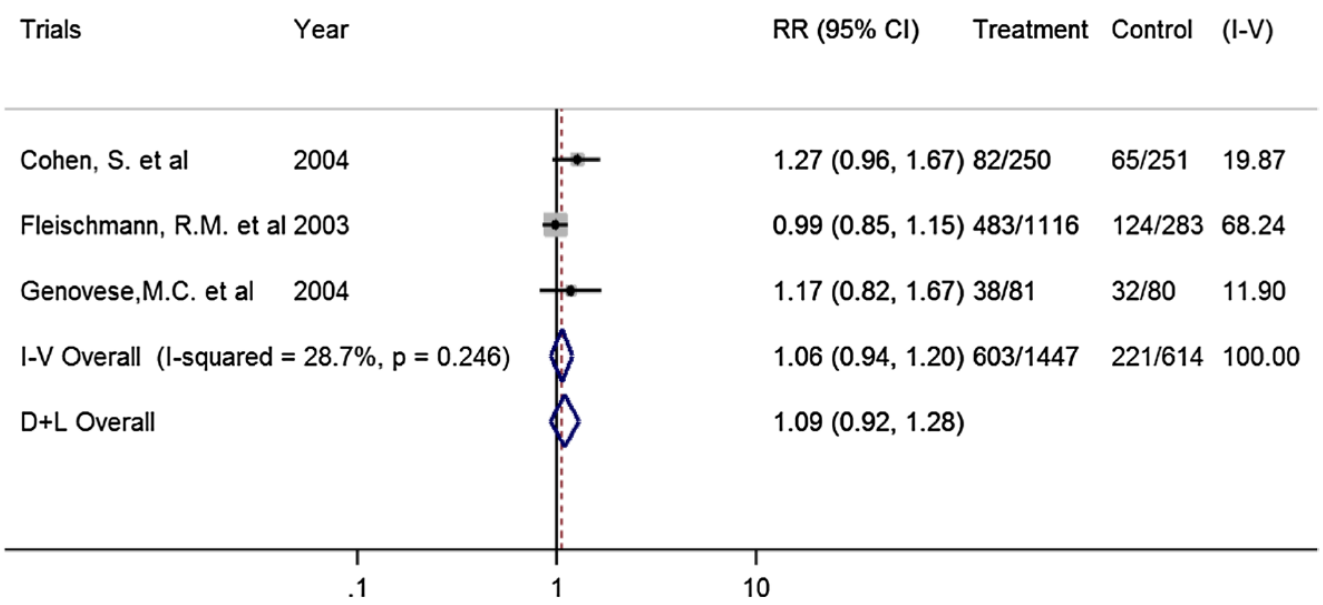


Fig. 11 Infections after 24 weeks of treatment

Peu de certitudes

NATURE MEDICINE, VOLUME 2, NUMBER 5, MAY 1996

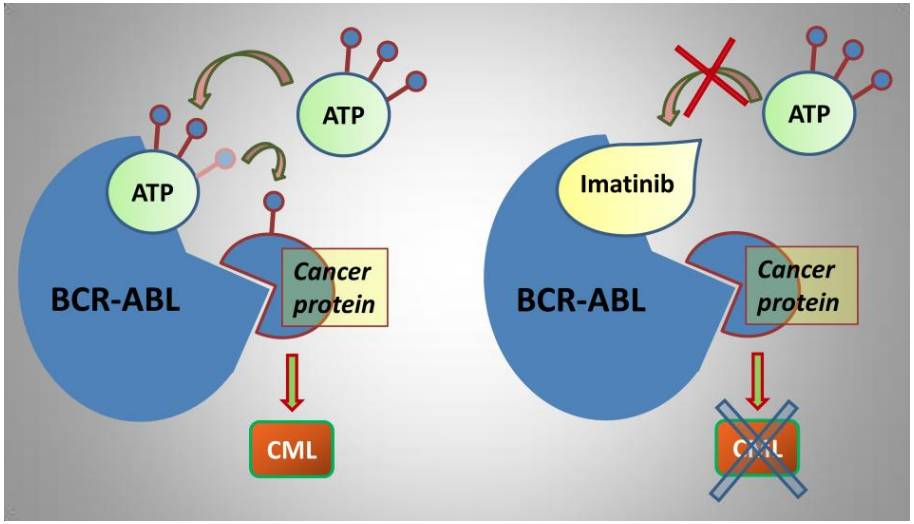
Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells

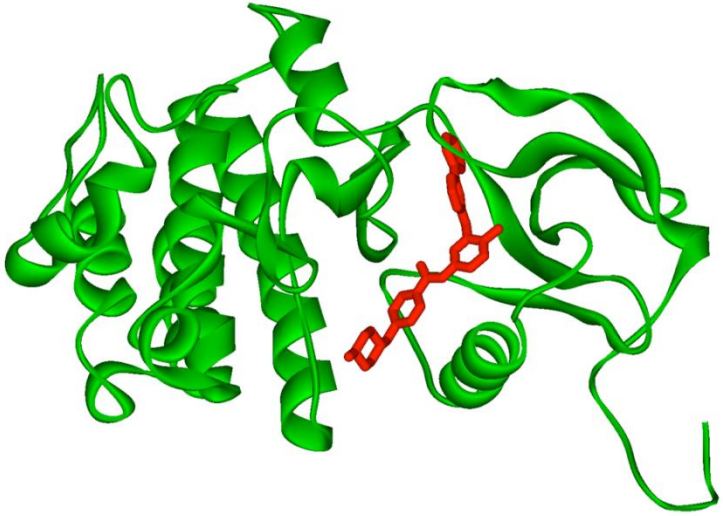
BRIAN J. DRUKER[1], SHU TAMURA[1], ELISABETH BUCHDUNGER[2], SAYURI OHNO[1], GERALD M. SEGAL[1], SHANE FANNING[1], JÜRG ZIMMERMANN[2] & NICHOLAS B. LYDON[2]

[1]*Division of Hematology and Medical Oncology, Oregon Health Sciences University, 3181 S.W. Sam Jackson Park Road, Portland, Oregon, USA*

[2]*Ciba Pharmaceuticals Division, Oncology Research Department, Ciba-Geigy Limited, CH-4002, Basel, Switzerland*

Correspondence should be addressed to B.J.D.

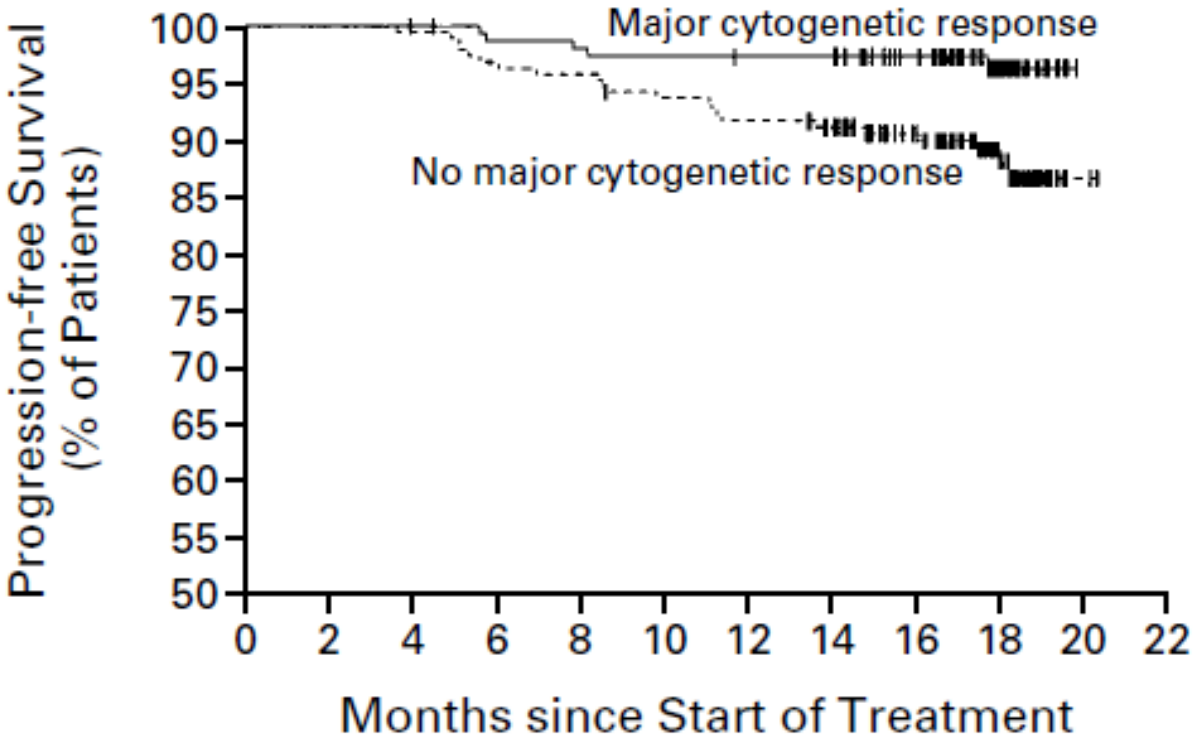




VOLUME 346 FEBRUARY 28, 2002 NUMBER 9

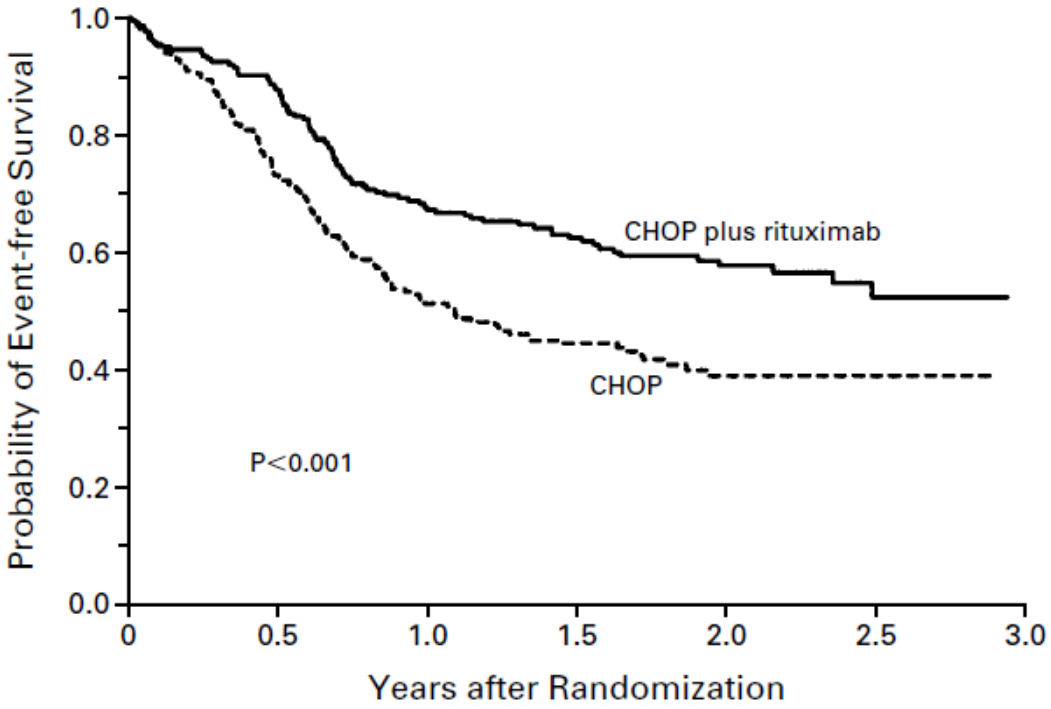
HEMATOLOGIC AND CYTOGENETIC RESPONSES TO IMATINIB MESYLATE IN CHRONIC MYELOGENOUS LEUKEMIA

HAGOP KANTARJIAN, M.D., CHARLES SAWYERS, M.D., ANDREAS HOCHHAUS, M.D., FRANCOIS GUILHOT, M.D., CHARLES SCHIFFER, M.D., CARLO GAMBACORTI-PASSERINI, M.D., DIETGER NIEDERWIESER, M.D., DEBRA RESTA, R.N., RENAUD CAPDEVILLE, M.D., ULRIKE ZOELLNER, M.Sc., MOSHE TALPAZ, M.D., AND BRIAN DRUKER, M.D., FOR THE INTERNATIONAL STI571 CML STUDY GROUP*



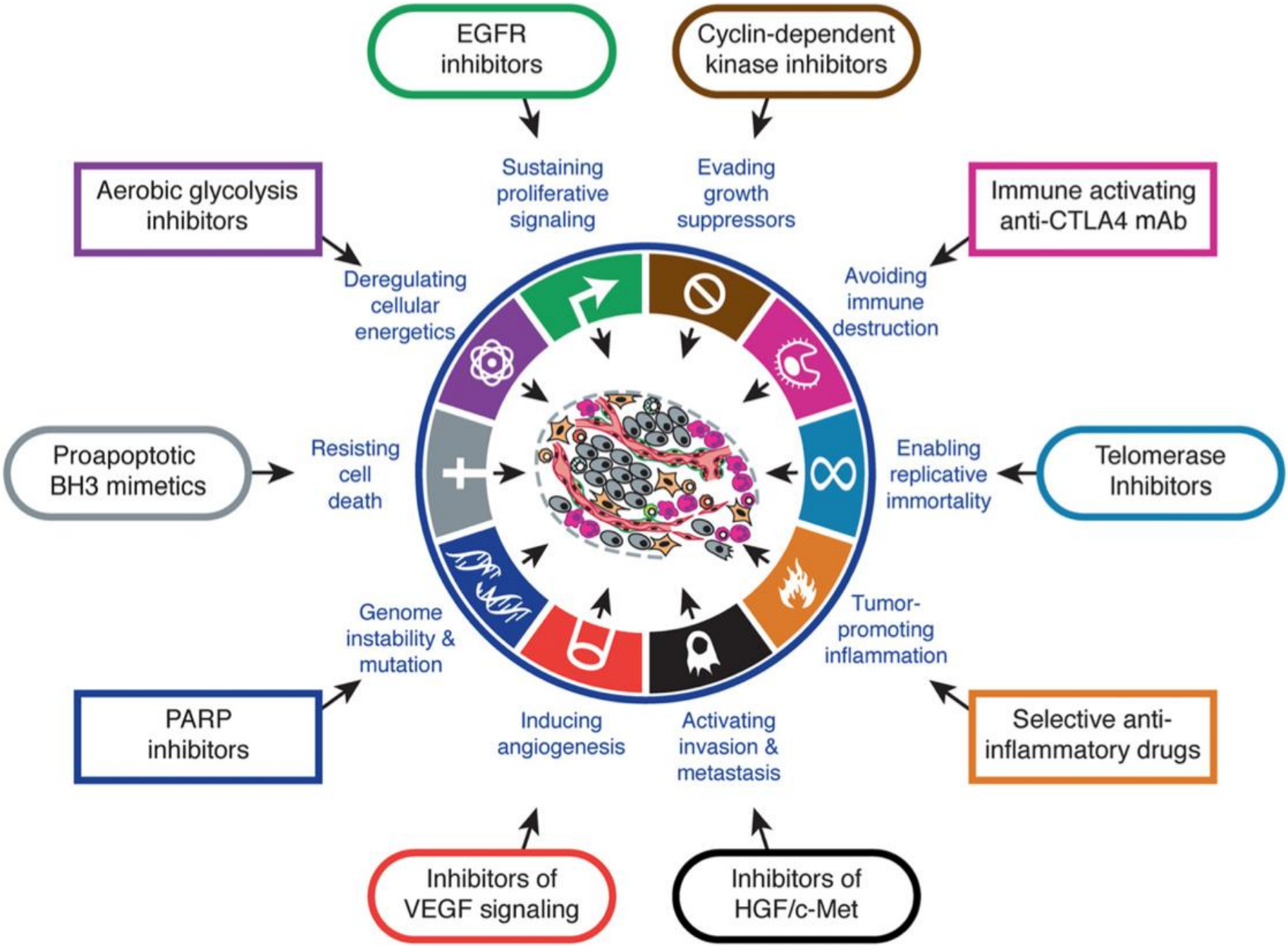
CHOP CHEMOTHERAPY PLUS RITUXIMAB COMPARED WITH CHOP ALONE IN ELDERLY PATIENTS WITH DIFFUSE LARGE-B-CELL LYMPHOMA

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., AND CHRISTIAN GISSELBRECHT, M.D.



NO. AT RISK						
CHOP plus rituximab	202	177	137	108	63	19
CHOP	197	144	101	72	42	17

Figure 1. Event-free Survival among 399 Patients Assigned to Chemotherapy with Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP) or with CHOP plus Rituximab.

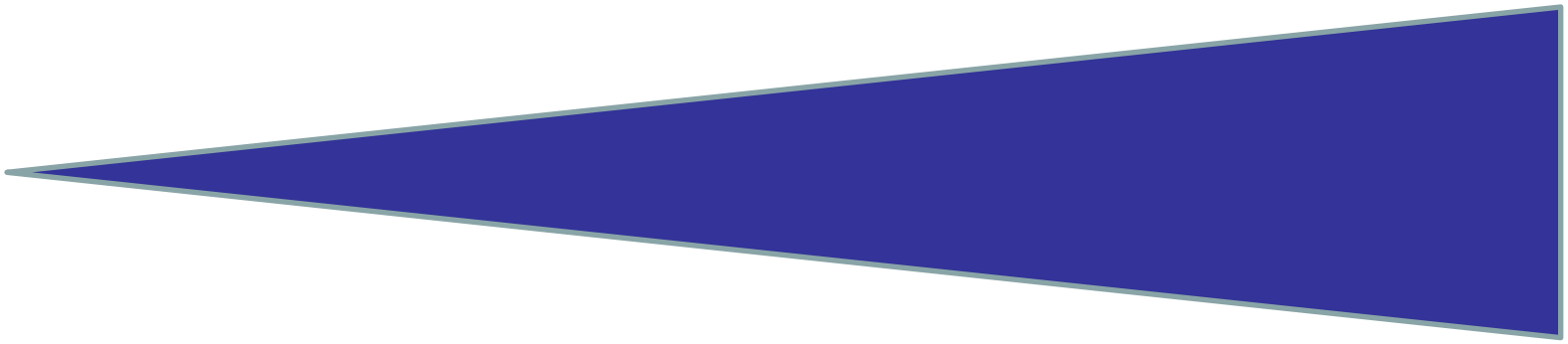

EGFR inhibitors
Cyclin-dependent kinase inhibitors
Sustaining proliferative signaling
Evading growth suppressors
Aerobic glycolysis inhibitors
Immune activating anti-CTLA4 mAb
Deregulating cellular energetics
Avoiding immune destruction
Proapoptotic BH3 mimetics
Resisting cell death
Enabling replicative immortality
Telomerase Inhibitors
Genome instability & mutation
Tumor-promoting inflammation
PARP inhibitors
Inducing angiogenesis
Activating invasion & metastasis
Selective anti-inflammatory drugs
Inhibitors of VEGF signaling
Inhibitors of HGF/c-Met

Ma classification sous-corticale

Anti-TNF
mycobactéries

Anti-CD20
Neutropénie
LEMP

Anti-CD52

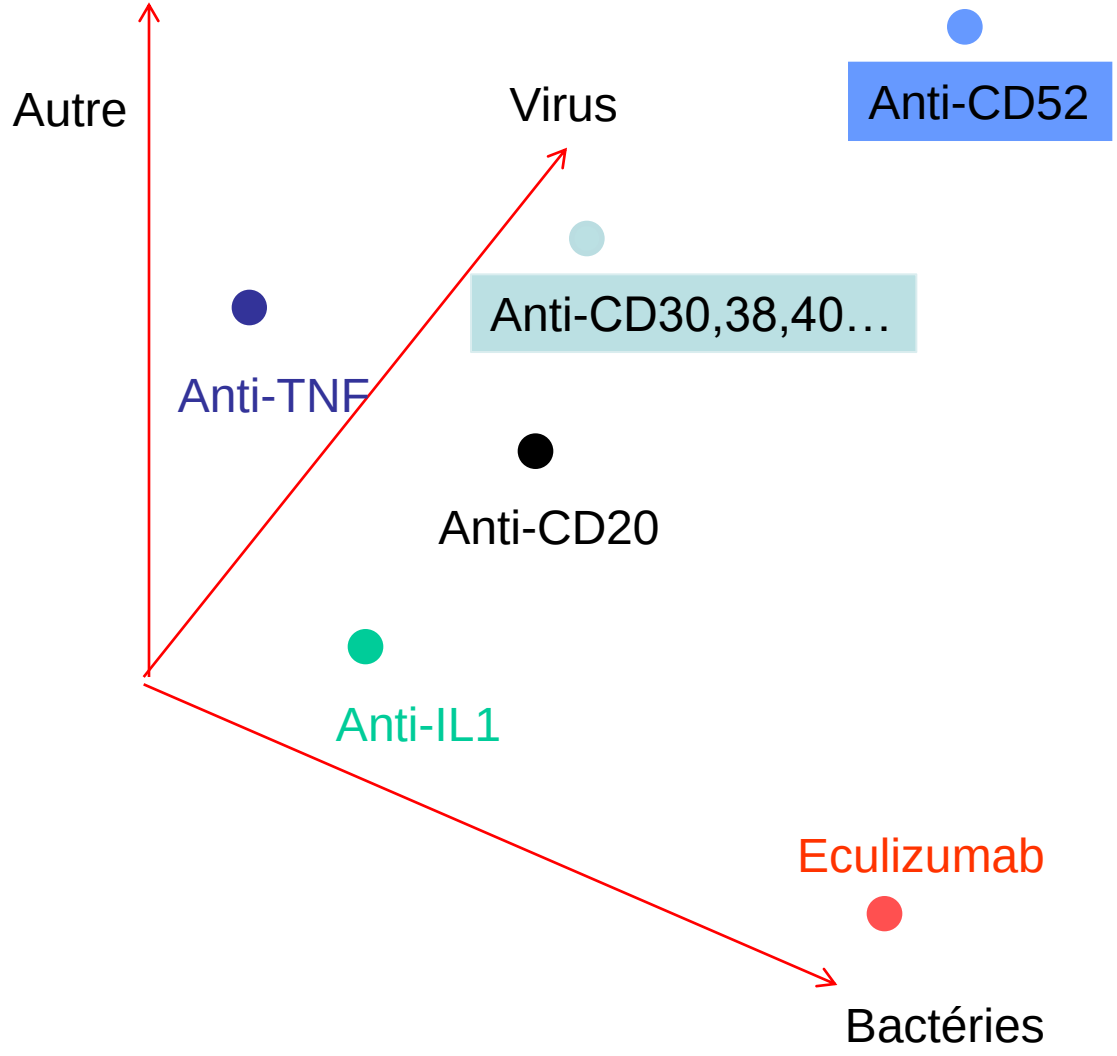


Modification
du risque

Immunodépression

AIDS-like

Ma classification sous-corticale



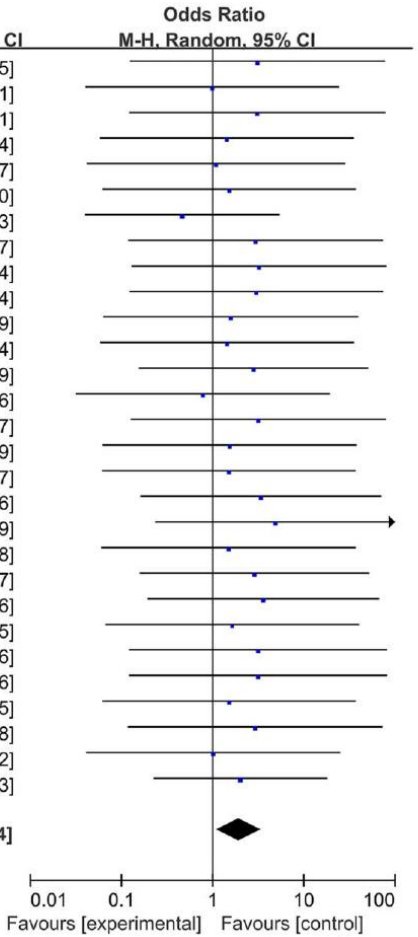
BMJ Open

Risk of tuberculosis in patients treated with TNF-α antagonists: a systematic review and meta-analysis of randomised controlled trials

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Baranauskaite 2012	1	57	0	58	3.1%	3.11 [0.12, 77.85]
Barker 2011	1	653	0	215	3.2%	0.99 [0.04, 24.41]
Braun 2002	1	35	0	35	3.1%	3.09 [0.12, 78.41]
Breedveld 2006	1	542	0	257	3.2%	1.43 [0.06, 35.14]
Chen 2009	1	35	0	12	3.1%	1.09 [0.04, 28.47]
Colombel 2010	1	338	0	170	3.2%	1.52 [0.06, 37.40]
Couriel 2009	1	29	2	28	5.4%	0.46 [0.04, 5.43]
Ho-Yong KIM 2007	1	65	0	63	3.1%	2.95 [0.12, 73.87]
Judson 2014	1	55	0	58	3.1%	3.22 [0.13, 80.74]
Kavanaugh 2013	1	515	0	517	3.2%	3.02 [0.12, 74.24]
Kennedy 2014	1	85	0	44	3.1%	1.58 [0.06, 39.59]
Keystone 2004	1	419	0	200	3.2%	1.44 [0.06, 35.44]
Keystone 2008	5	783	0	199	3.9%	2.82 [0.16, 51.19]
Maini 1999	1	340	0	88	3.2%	0.78 [0.03, 19.36]
Nam 2014	1	55	0	57	3.1%	3.17 [0.13, 79.37]
Reich 2012	1	117	0	59	3.2%	1.53 [0.06, 38.19]
Rutgeerts 2005	1	243	0	121	3.2%	1.50 [0.06, 37.17]
Schiff 2008	2	165	0	110	3.5%	3.38 [0.16, 71.06]
Schiff 2014	2	328	0	318	3.5%	4.88 [0.23, 101.99]
Sieper 2014	1	106	0	52	3.2%	1.49 [0.06, 37.28]
Smolen 2009	5	492	0	127	3.9%	2.88 [0.16, 52.37]
St Clair 2004	4	751	0	298	3.8%	3.59 [0.19, 66.96]
Suzuki 2014	1	177	0	96	3.2%	1.64 [0.07, 40.65]
Tam 2012	1	20	0	20	3.1%	3.15 [0.12, 82.16]
Van Den Bosch 2002	1	20	0	20	3.1%	3.15 [0.12, 82.16]
van der Heijde 2007	1	454	0	228	3.2%	1.51 [0.06, 37.25]
van Vollenhoven 2011	1	79	0	76	3.2%	2.92 [0.12, 72.88]
Wenzel 2009	1	233	0	78	3.2%	1.01 [0.04, 25.12]
Westhovens 2006	4	721	1	363	6.8%	2.02 [0.22, 18.13]
Total (95% CI)		**7912**		**3967**	**100.0%**	**1.94 [1.10, 3.44]**
Total events	45		3			

Heterogeneity: Tau² = 0.00; Chi² = 3.79, df = 28 (P = 1.00); I² = 0%

Test for overall effect: Z = 2.28 (P = 0.02)

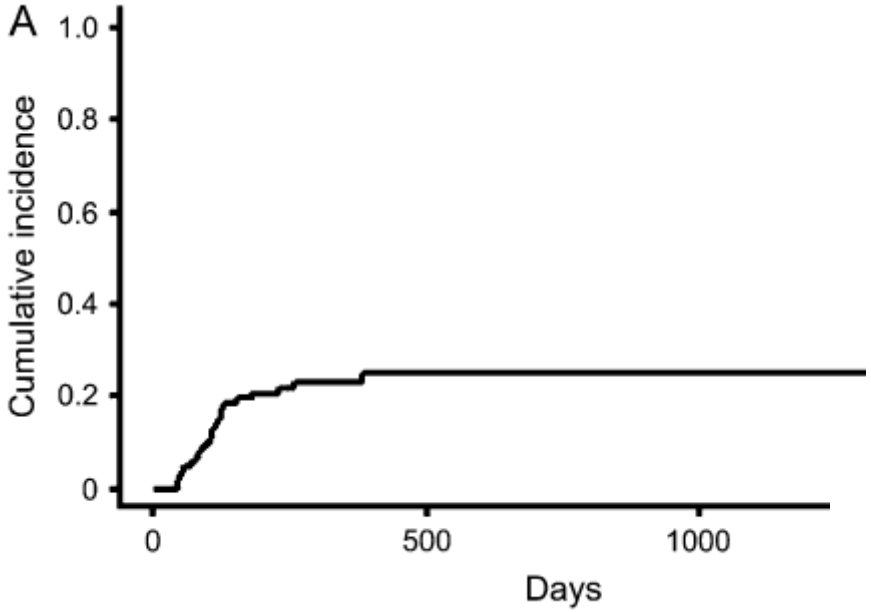


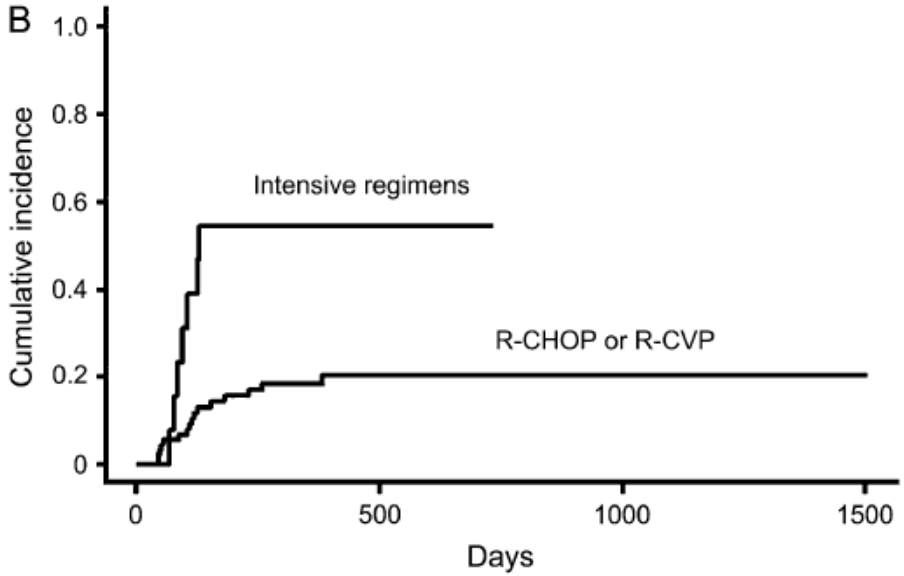
Zhang Z, *et al*. *BMJ Open* 2017;**7**:e012567. doi:10.1136/bmjopen-2016-012567

A high incidence of late-onset neutropenia following rituximab-containing chemotherapy as a primary treatment of CD20-positive B-cell lymphoma: a single-institution study

E. Nitta[1†], K. Izutsu[1†], T. Sato[1], Y. Ota[3], K. Takeuchi[4], A. Kamijo[2], K. Takahashi[2], K. Oshima[1], Y. Kanda[1], S. Chiba[1], T. Motokura[1] & M. Kurokawa[1*]

Ann Oncol 2007





Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project

Kenneth R. Carson,[1] Andrew M. Evens,[2,3] Elizabeth A. Richey,[2] Thomas M. Habermann,[4] Daniele Focosi,[5] John F. Seymour,[6] Jacob Laubach,[7] Susie D. Bawn,[8] Leo I. Gordon,[2,3] Jane N. Winter,[2,3] Richard R. Furman,[9] Julie M. Vose,[10] Andrew D. Zelenetz,[9,11] Ronac Mamtani,[9] Dennis W. Raisch,[12] Gary W. Dorshimer,[13] Steven T. Rosen,[2,3] Kenji Muro,[14] Numa R. Gottardi-Littell,[15] Robert L. Talley,[16] Oliver Sartor,[17] David Green,[2,3] Eugene O. Major,[18] and Charles L. Bennett[2,3,19]

BLOOD, 14 MAY 2009 • VOLUME 113, NUMBER 20

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Progressive Multifocal Leukoencephalopathy in a Patient Treated with Natalizumab

Annette Langer-Gould, M.D., Scott W. Atlas, M.D., Ari J. Green, M.D., Andrew W. Bollen, M.D., and Daniel Pelletier, M.D.

N ENGL J MED 353;4 WWW.NEJM.ORG JULY 28, 2005

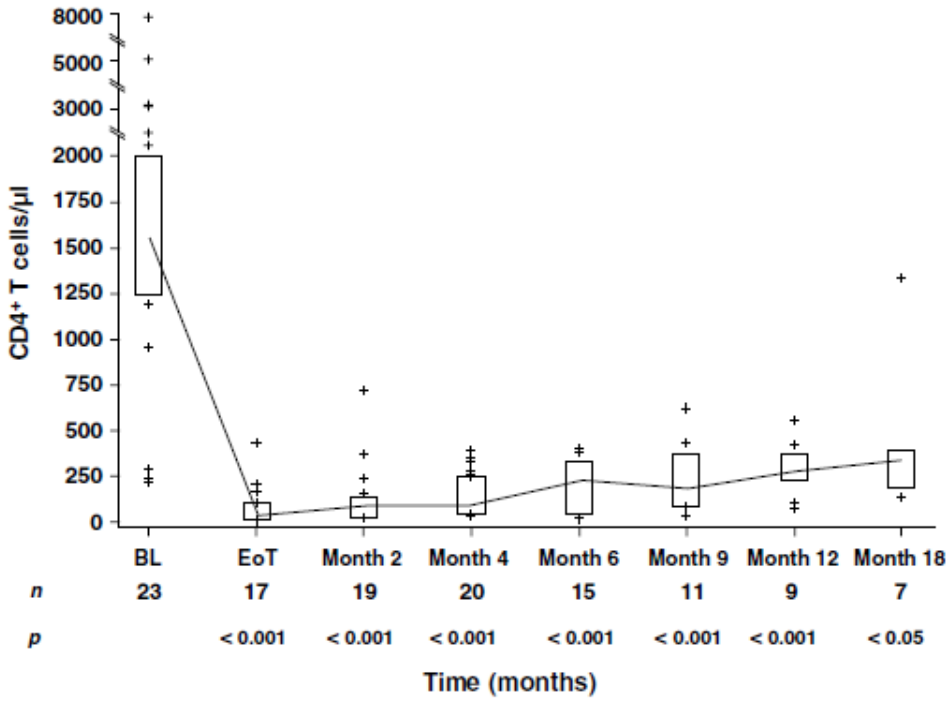
Leukemia (2004) 18, 484–490

www.nature.com/leu

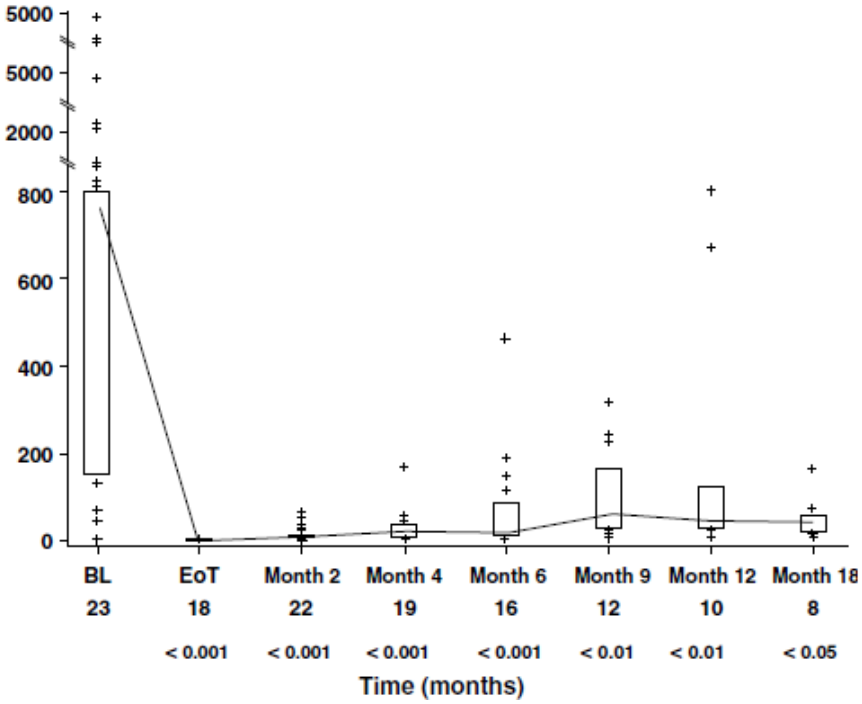
Cellular immune reconstitution after subcutaneous alemtuzumab (anti-CD52 monoclonal antibody, CAMPATH-1H) treatment as first-line therapy for B-cell chronic lymphocytic leukaemia

J Lundin[1], A Porwit-MacDonald[1], ED Rossmann[1], C Karlsson[1], P Edman[1,2,3], MR Rezvany[1,2,3], E Kimby[4], A Österborg[1,2,3] and H Mellstedt[1,2,3]

CD4+



CD19+ / CD5-



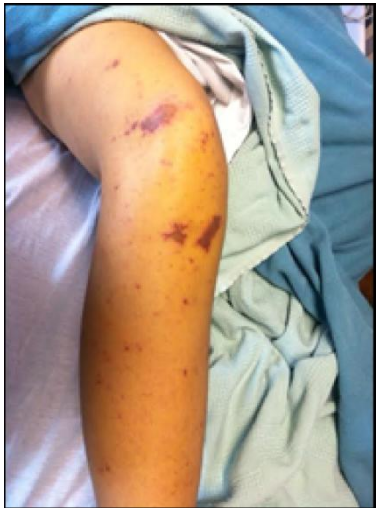
The Oncologist
Regulatory Issues: FDA

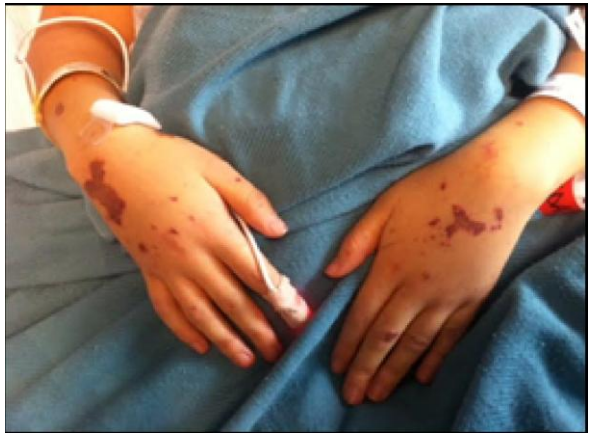
FDA Report: Eculizumab (Soliris®) for the Treatment of Patients with Paroxysmal Nocturnal Hemoglobinuria

Table 4. Adverse reactions occurring in ≥5% of patients in the TRIUMPH study

Reaction	Eculizumab (n = 43), n (%)	Placebo (n = 44), n (%)
Headache	19 (44)	12 (27)
Nasopharyngitis	10 (23)	8 (18)
Back pain	8 (19)	4 (9)
Nausea	7 (16)	5 (11)
Fatigue	5 (12)	1 (2)
Cough	5 (12)	4 (9)
Herpes simplex infections	3 (7)	0
Sinusitis	3 (7)	0
Respiratory tract infection	3 (7)	1 (2)
Constipation	3 (7)	2 (5)
Myalgia	3 (7)	1 (2)
Pain in extremity	3 (7)	1 (2)
Influenza-like illness	2 (5)	1 (2)

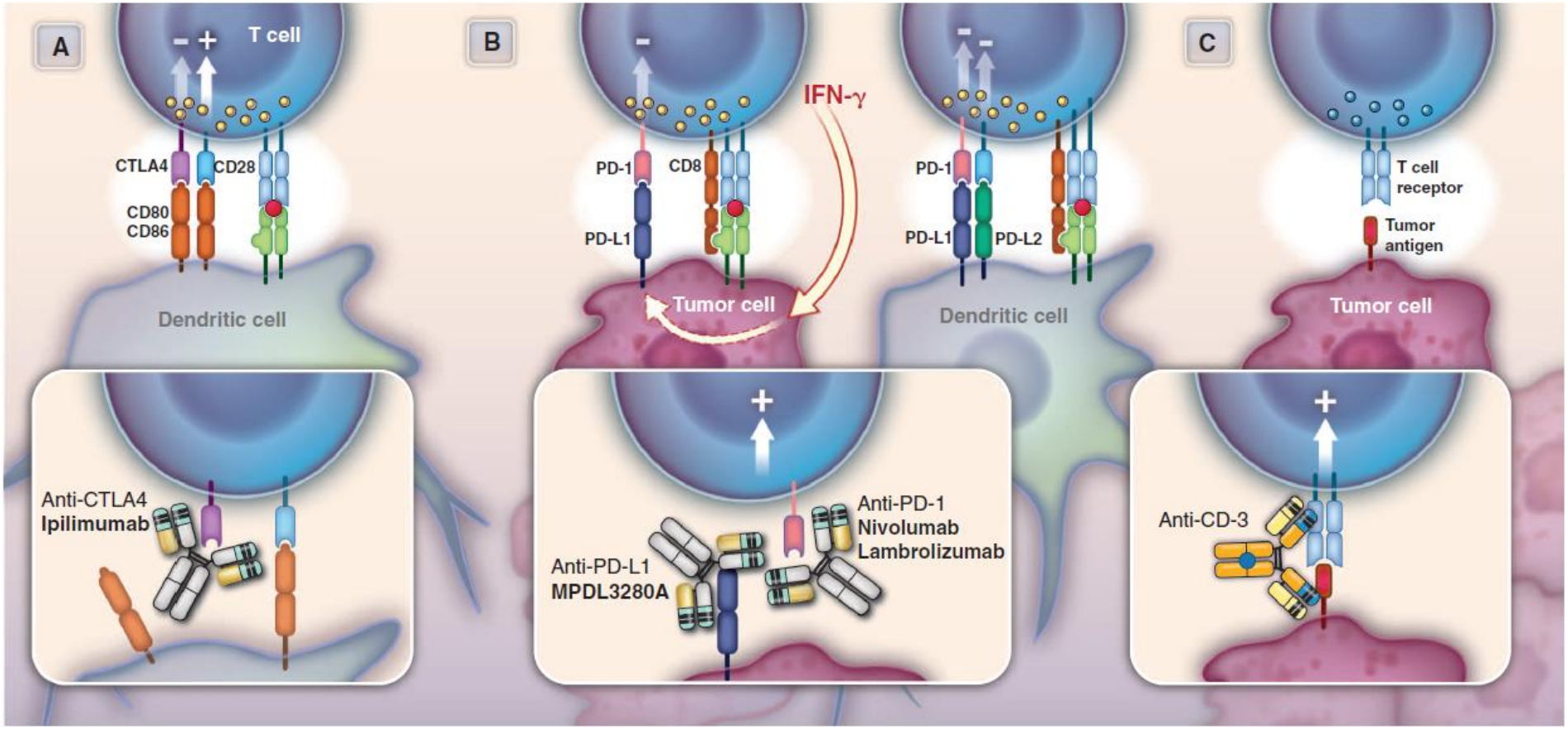
Abbreviation: TRIUMPH, A Hemoglobin Stabilization in Transfusion Reduction Efficacy and Safety Clinical Investigation, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Using Eculizumab and Paroxysmal Nocturnal Hemoglobinuria Patients.





3 cas d'infection à Méningocoque
Estimation du sur-risque
1000 à 10000x (!)

Double blocage et double cible



Slivkovski et al. Science 2013

Trois messages clés

- Majeure partie des thérapie: risque infectieux augmenté
- Tout patient sous « biothérapie » est à risque
- Garder un bon carnet d'adresse et être vigilant