Curso Oncología Básica 2020
Instituto Nacional del Cáncer
Stgo, 30 de octubre 2020

Nuevas terapias en neoplasias hematológicas

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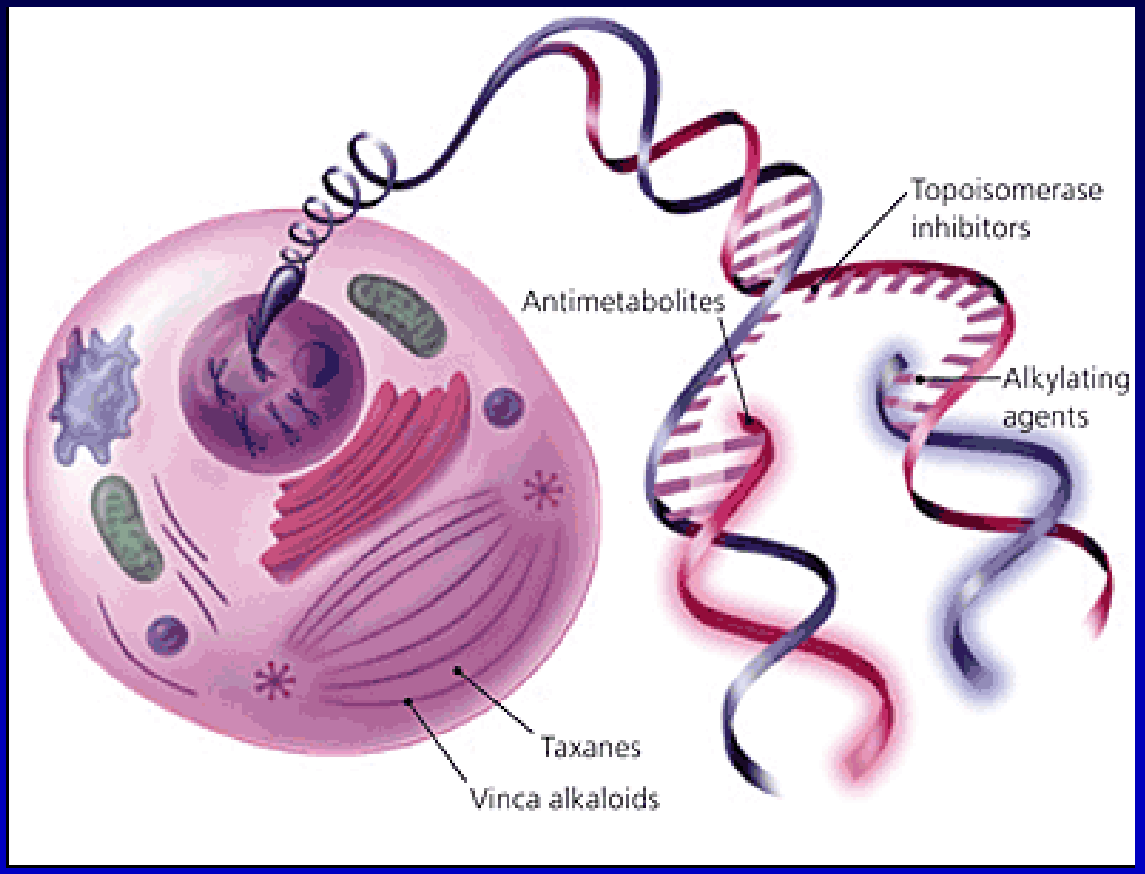
Terapia convencional



Genotoxicidad

Nuevos avances en tratamiento de neoplasias hematológicas:

- Inmunoterapia
- Tratamientos Target

Inmunoterapia en neoplasias hematológicas:

- El **trasplante de progenitores alogénico** es la forma mas antigua de inmunoterapia:
  - Por primera vez realizado en 1957
  - Efecto injerto vs tumor: potencial curativo de varias neoplasias hematológicas

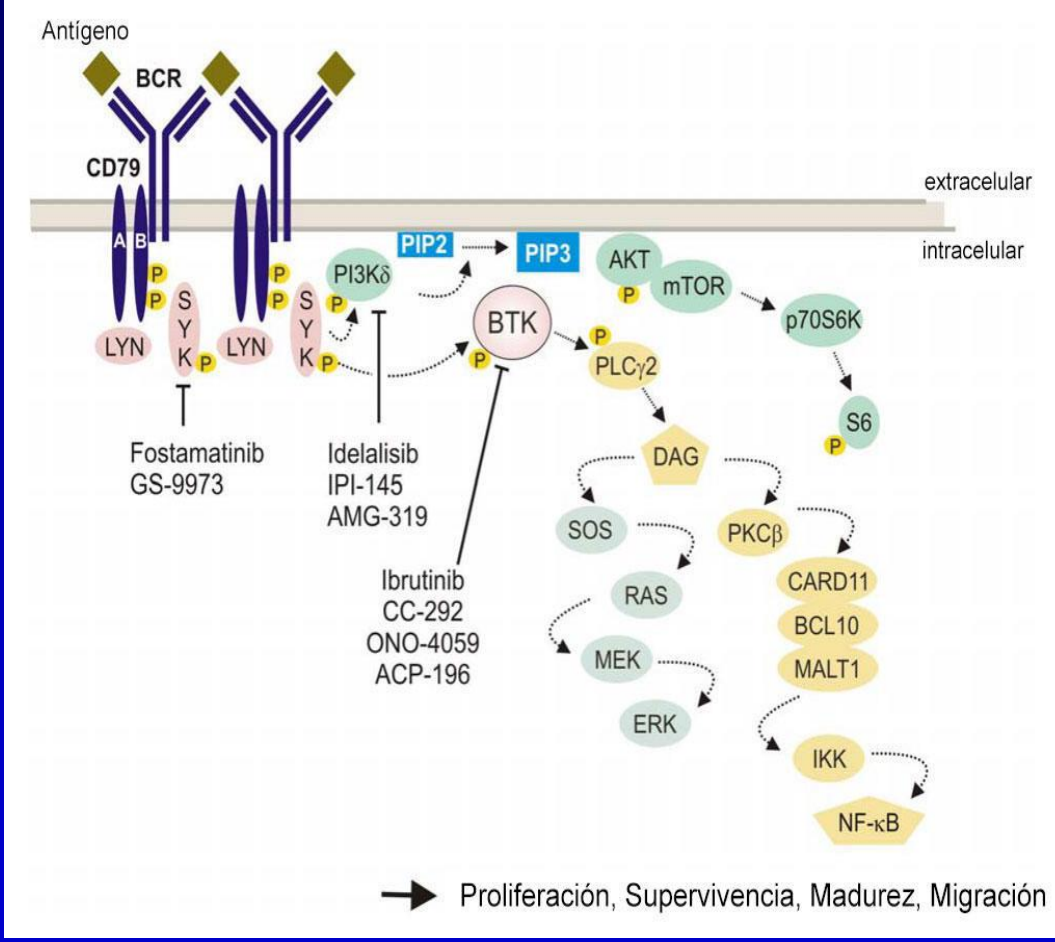
- **Nuevas terapias:**
  - Anticuerpos monoclonales
  - Inhibidores de Checkpoints inmunológicos.
  - Anticuerpos conjugados con drogas (ADC)
  - Anticuerpos bi específicos (BiTEs).
  - CART Cells

J Life Sci (Westlake Village). 2019 June ; 1(1): 46–52.

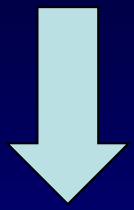
Terapia Target en neoplasias hematológicas:

- Usar moléculas pequeñas que inhiben de forma selectiva vías de señalización que participan en la génesis o mantención de la neoplasia:

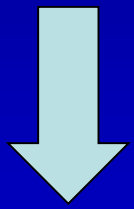
- Imatinib→ Quinasa BCR/ABL
- Ibrutinib→ Quinasa de Bruton (BTK)
- Idelalisib→ Fosfatidil inositol 3 quinasa
- Fostamatinib→ SYK quinasa



Quimioterapia



Terapias target
e
Inmunoterapia

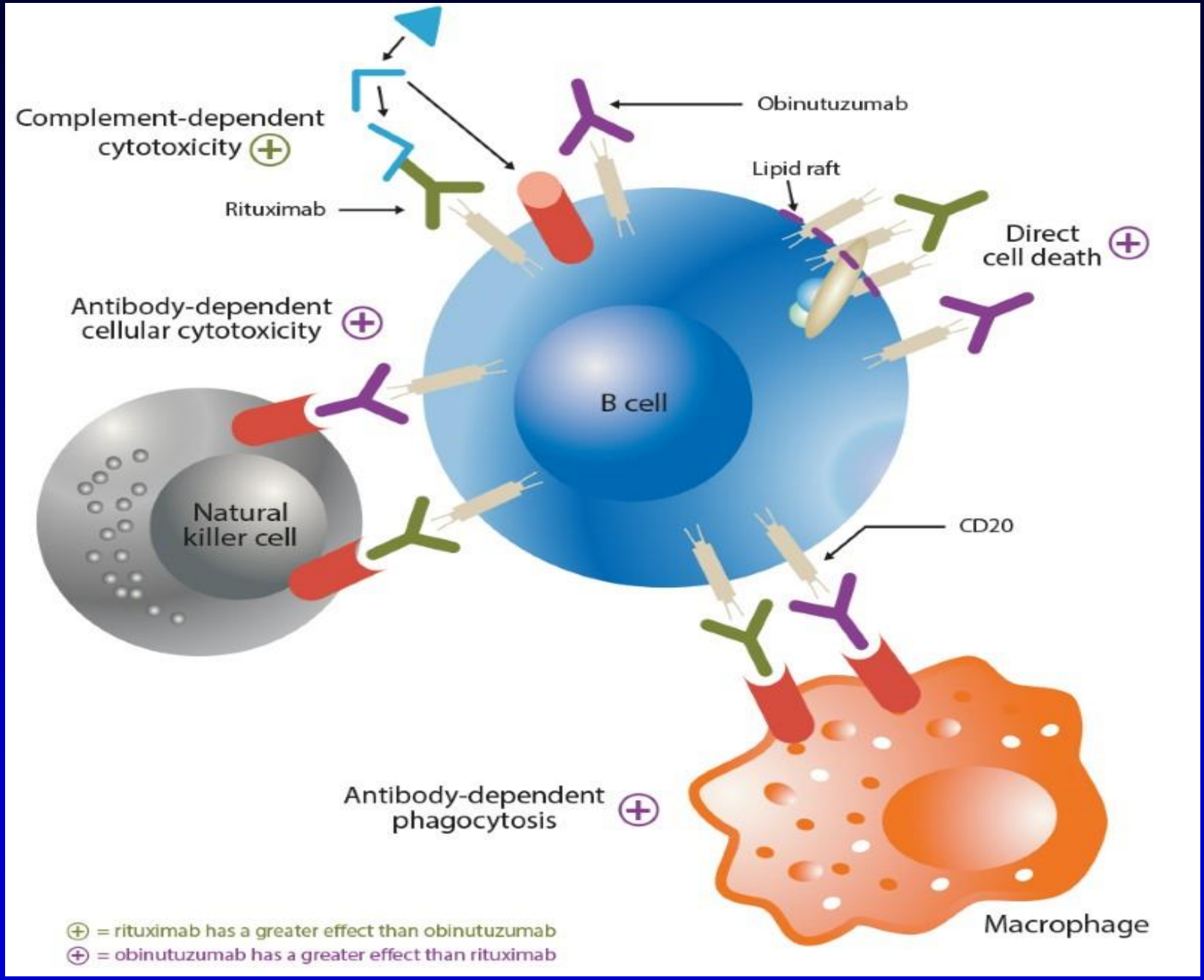


Terapias
personalizadas

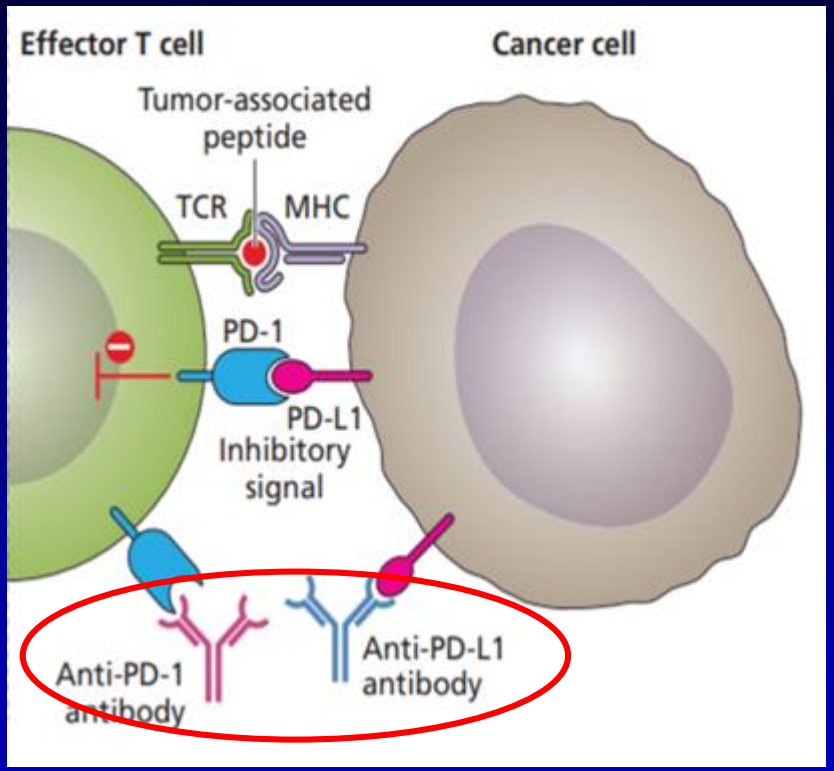
Anticuerpos monoclonales:

- **Ejercen su efecto a través de:**
- Citotoxicidad dependiente de complemento
- Citotoxicidad celular dependiente de anticuerpos
- Fagocitosis dependiente de anticuerpos
- Citotoxicidad directa

  - **Rituximab:** Ig contra CD20, primer Ig en ser aprobado por FDA
  - **Obinutuzumab:** Ig humanizado contra CD20, aumenta citotoxicidad directa y mediada por complemento.
  - **Daratumumab:** Ig anti CD38, aprobado para uso en mieloma múltiple
  - **Elotuzumab:** Ig anti SLAMF7 (glicoproteína de células de mieloma y NK). Citotoxicidad por anticuerpos y por células NK.


Complement-dependent cytotoxicity ⊕
Rituximab
Obinutuzumab
Lipid raft
Direct cell death ⊕
Antibody-dependent cellular cytotoxicity ⊕
B cell
Natural killer cell
CD20
Antibody-dependent phagocytosis ⊕
Macrophage
⊕ = rituximab has a greater effect than obinutuzumab
⊕ = obinutuzumab has a greater effect than rituximab

Inhibidores del Checkpoint:

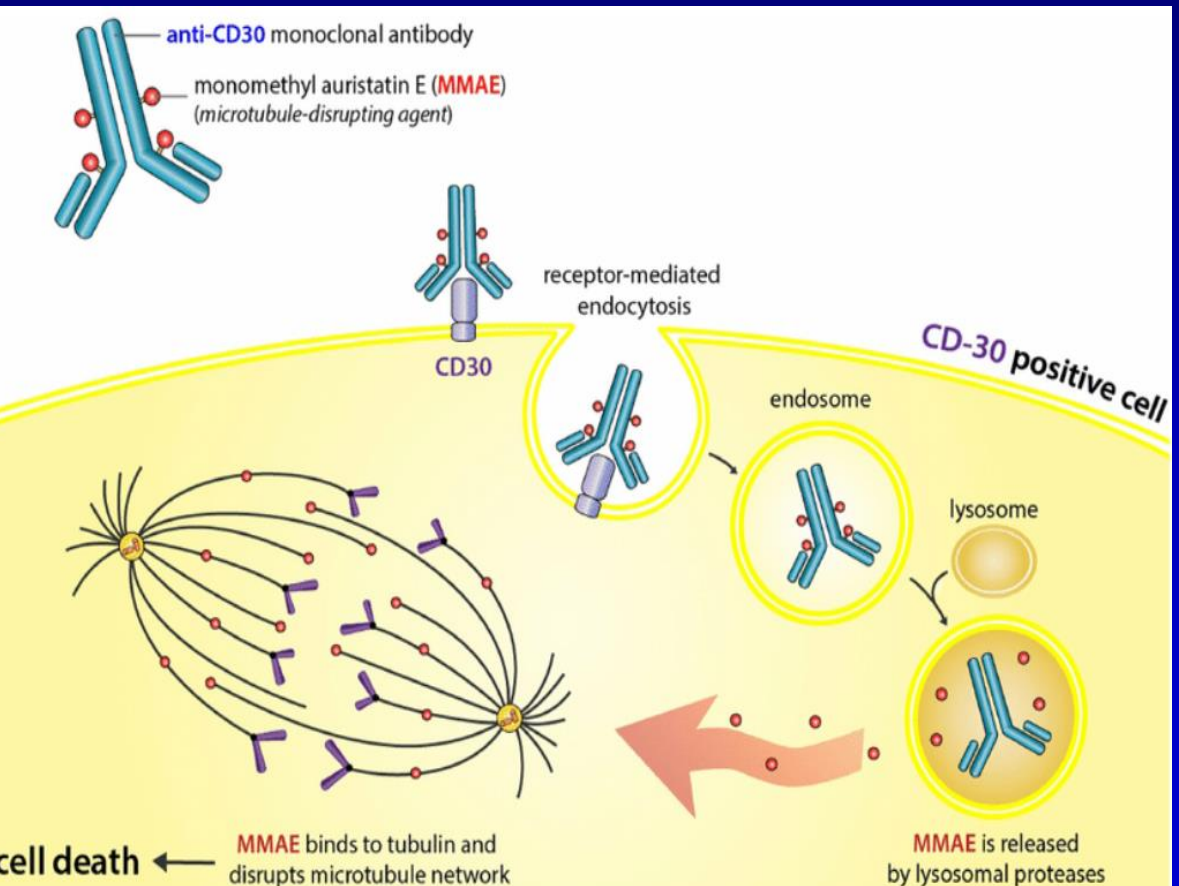


- **Moléculas "immune checkpoint“** inhiben la activación del LT una vez que reconoce el antígeno tumoral impidiendo acción del LT sobre la célula tumoral
  - PD-1 Ligando de célula tumoral es bloqueado por un anticuerpo anti PD1-L (Pembrolizumab)
  - PD1 es el receptores inhibitorio de LTc.
- **Linfoma de Hodgkin:**
  - Tiene alta expresión de PD-1 Ligando
  - Nivolumab y Pembrolizumab: aprobados para LH r/r (2016 y 2017)

ASH-SAP. Seventh edition. 2019

Anticuerpos conjugados con drogas (ACD):

- Se une una droga citotóxica al anticuerpo monoclonal
- Se utiliza el anticuerpo monoclonal para dirigir el citotóxico a una población celular determinada (y no para modular sistema inmune)



Brentuximab:

Ig monoclonal contra CD30 conjugado con monometil auristatina (MMAE), citotóxico que inhibe microtúbulos
Aprobado para tratamiento de linfoma de Hodgkin r/r 2011 y para consolidación posterior a TAMO en linfoma de Hodgkin de alto riesgo 2015

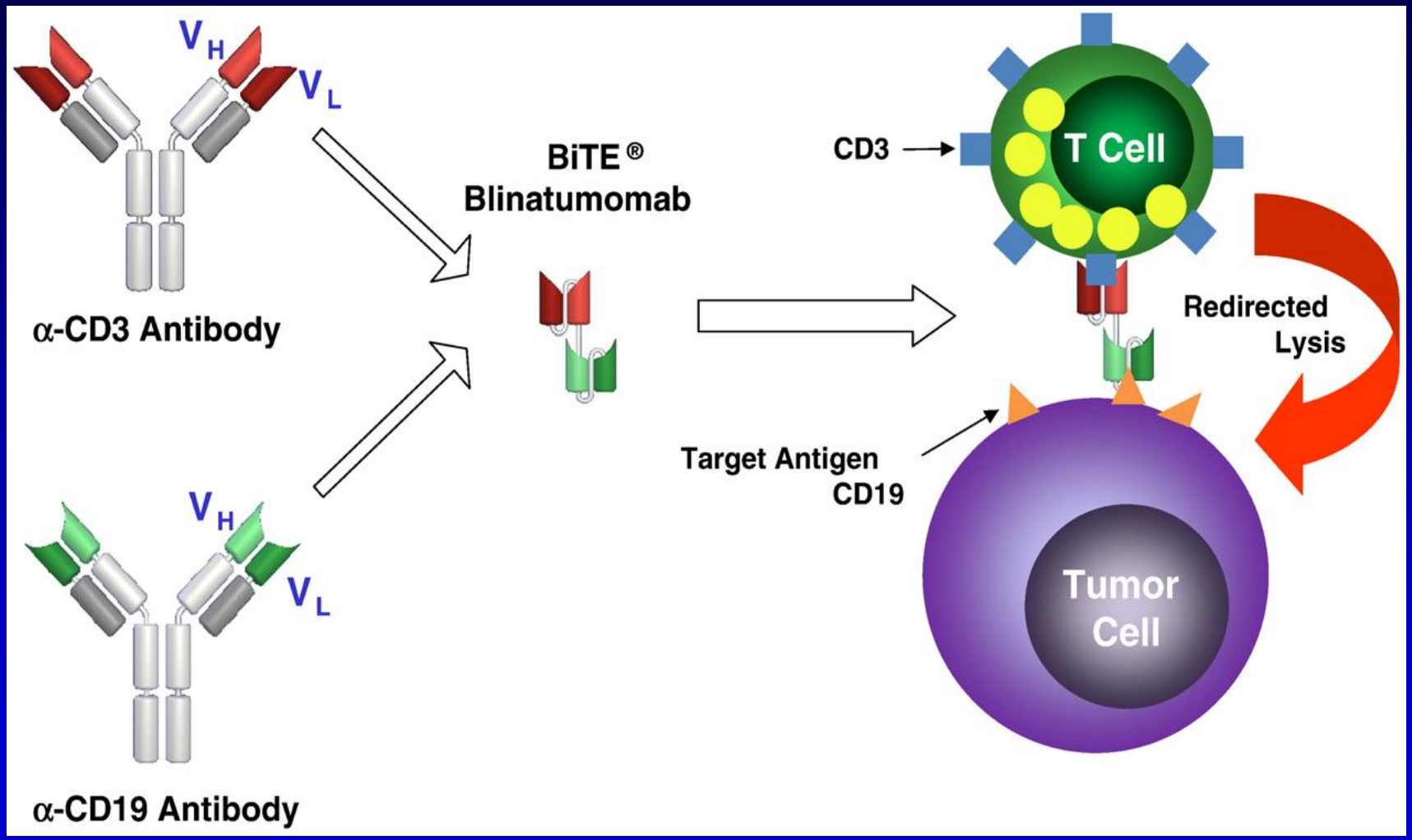
Collins et al. new therapies in t-cell Lymphoma. Lymphoma and Chronic Lymphocytic Leukemias 2014:4 1–8

Bispecific T cell engagers (BiTEs):

- Moléculas que contienen dos regiones variables de Ig, una dirigida contra CD3 y otra contra algún antígeno tumoral.
- Esto permite que se aproxime el linfocito T citotóxico con célula tumoral formando una sinapsis inmune que gatilla una respuesta inmune anti tumoral
- **Blinatumumab:**
  - Especificidad por CD3 y CD19
  - Uso en LLA Phi (-) refractaria y LDCGB refractario
- **En desarrollo:**
  - BiTEs contra CD33 en LMA
  - Biespecificos para CD16 de células NK y antígeno tumoral (BiKEs)

ASH-SAP. Seventh edition. 2019

Blinatumomab, es un anticuerpo biespecífico con una dual especificidad para CD19 y CD3

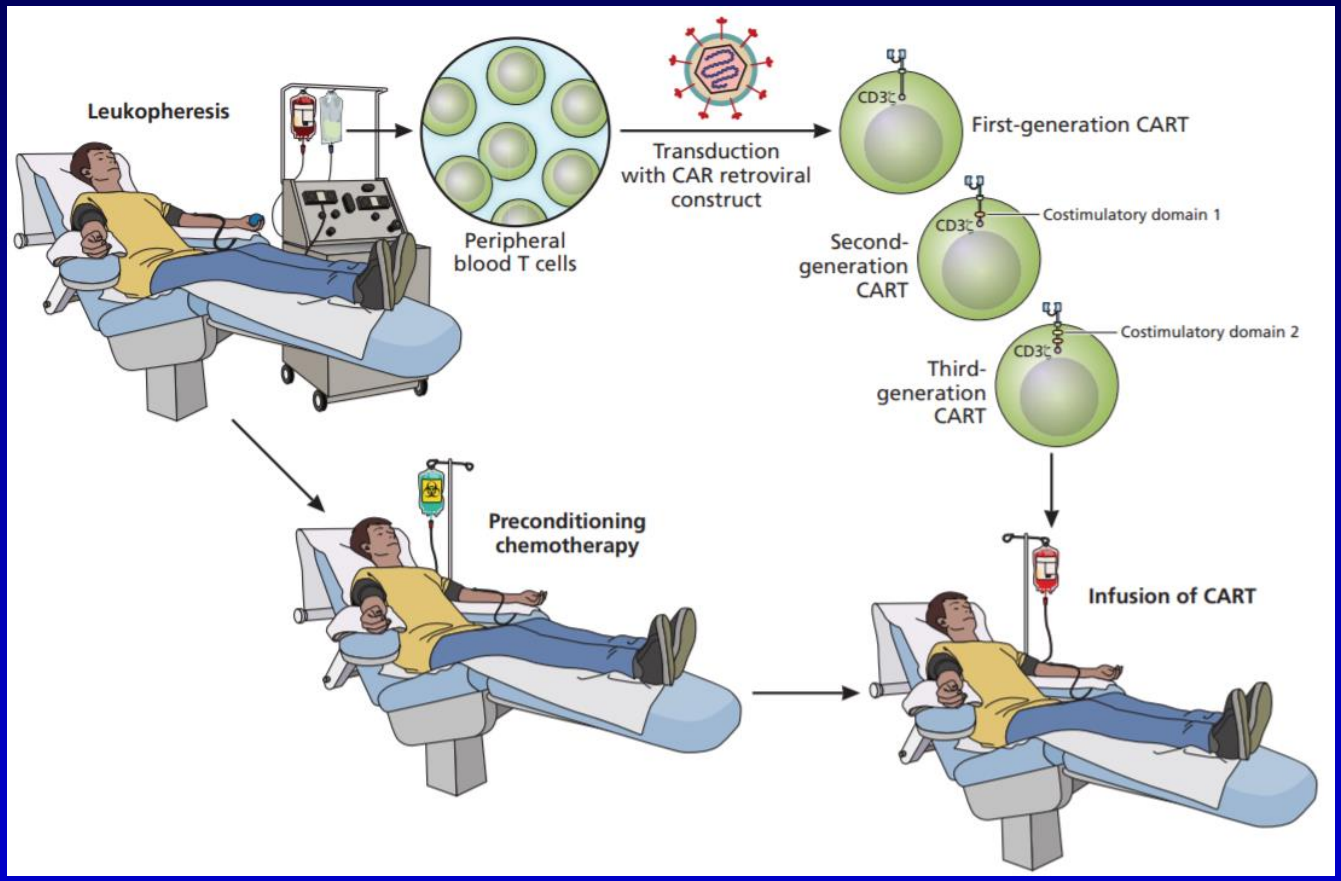


Nagorsen D, Baeuerle PA. Exp Cell Res. 2011 May 15;317(9):1255-60

CAR T- cell:

Linfocitos se cultivan con un retrovirus que incorpora un gen de receptor quimérico dirigido contra un antígeno tumoral especifico (CAR)

Linfocitos del paciente se extraen por aféresis



CART de 1°, 2° y 3° generación: Incorporan receptor quimérico y moléculas co-estimuladoras

CART se infunden en paciente y montan respuesta anti tumoral

ASH-SAP. Seventh edition. 2019

Leucemia Mieloide Aguda

- Es la forma mas frecuente de leucemia en el adulto, en USA 3-5 casos nuevos por 100.000 habitantes al año
- Su incidencia aumenta con la edad, en USA de 1.3 a 12.2 por 100.000 habitantes sobre los 65 años
- Sobre los 65 años la mortalidad a un año es muy elevada 70%
- Puede aparecer en pacientes con patología hematológica previa o exposición a drogas como inhibidores de topoisomerasa, alquilantes o radiación
- En la mayoría aparece de novo

Mecanismos de acción

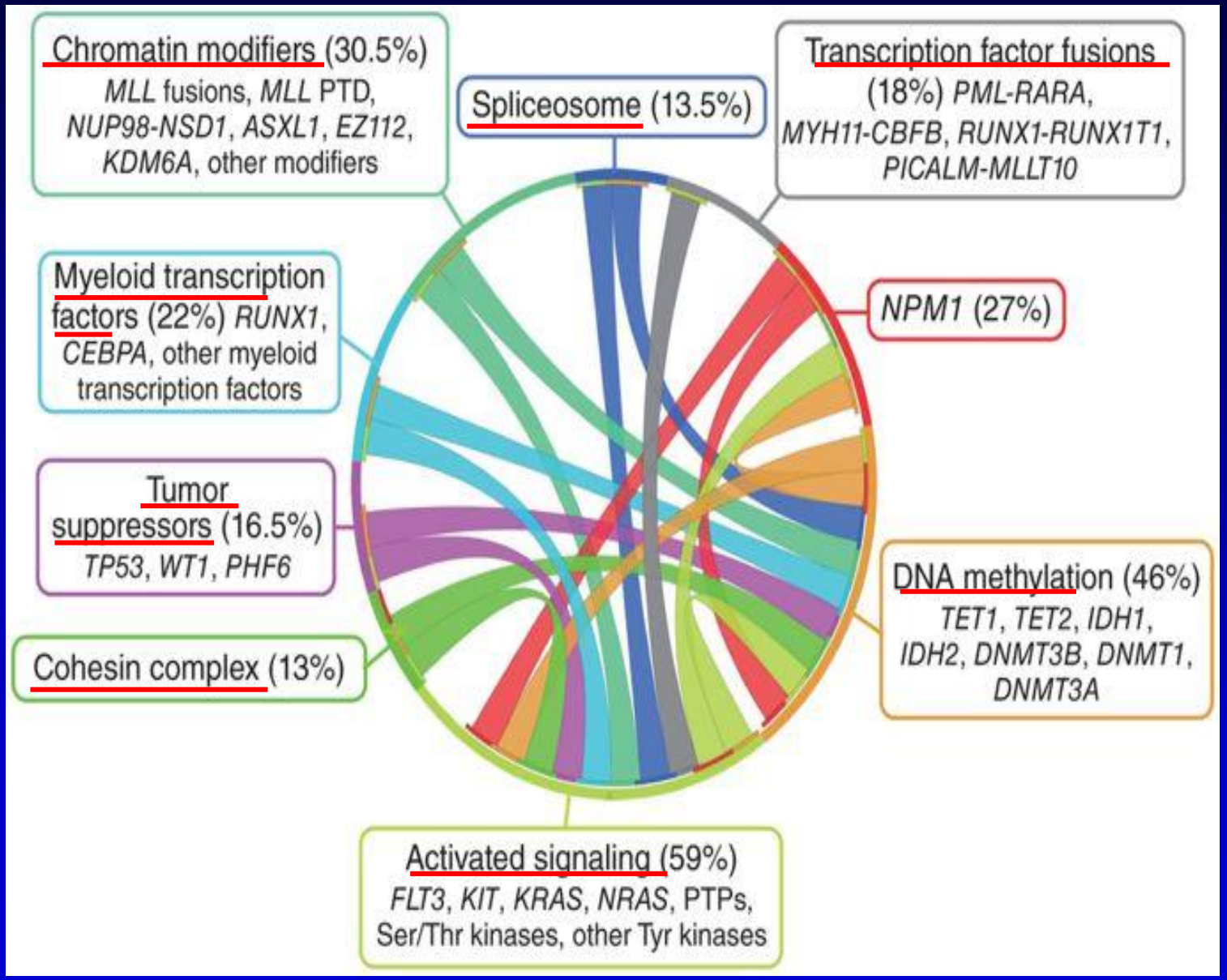
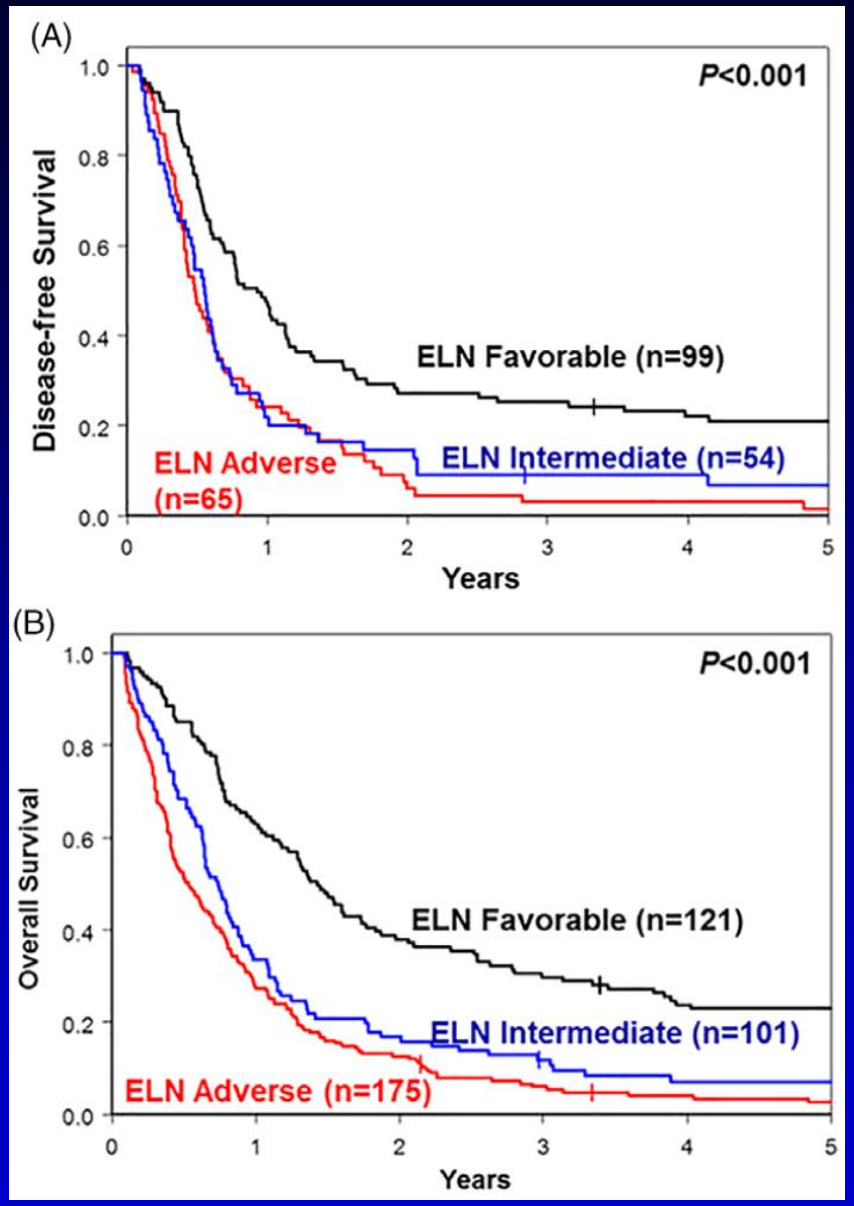


TABLE 2 2017 ELN risk stratification by genetics

Risk category*	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} = allelic ratio < 0.5
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high} = allelic ratio > 0.5
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype monosomal karyotype
	Wild-type *NPM1* and *FLT3*-ITD^{high†}
	Mutated *RUNX1*
	Mutated *ASXL1*
	Mutated *TP53*



Am J Hematol. 2018;93:1267–1291.

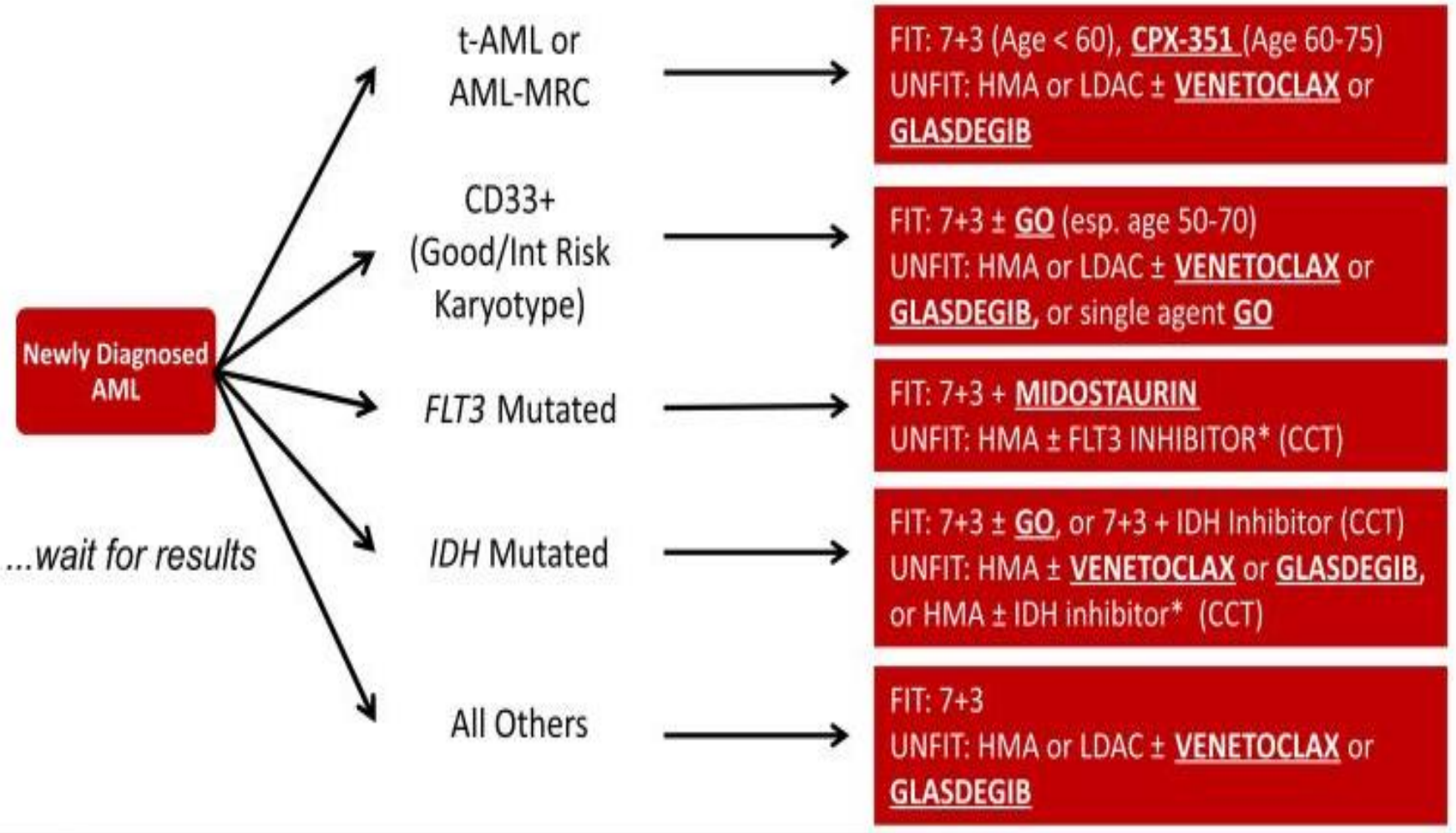
Leucemia mieloide aguda en primera línea:

- Terapia estándar:
  - QT de inducción: 3+7 o FLAG-Ida
  - **ASOCIADO a un tercer agente TARGET**

- Terapia estándar en paciente no fit:
  - **Hipometilantes + inhibidor de Bcl-2**
  - **Inhibidor de Bcl-2 + QT estándar abreviada**

Am J Hematol. 2018;93:1267–1291.

AML Induction Therapy – A More Complicated Landscape



CCT= current clinical trial; *=off label

Aplicaciones clínicas de la biología molecular

- Mutación FLT3: agregar inhibidor de FLT3 (Midostaurina, Sorafebib, quizartinib), considerar TPH alogénico
- IDH 1 y 2 agregar un inhibidor de IDH Enasidenib en IDH 2, Ivosidenib en IDH1
- Mutación MNP1 en diploide sensible a Citarabina
- Mutación TP53: Considerar Decitabina por 10 días + otro (GO o Venetoclax) y referir a TPH

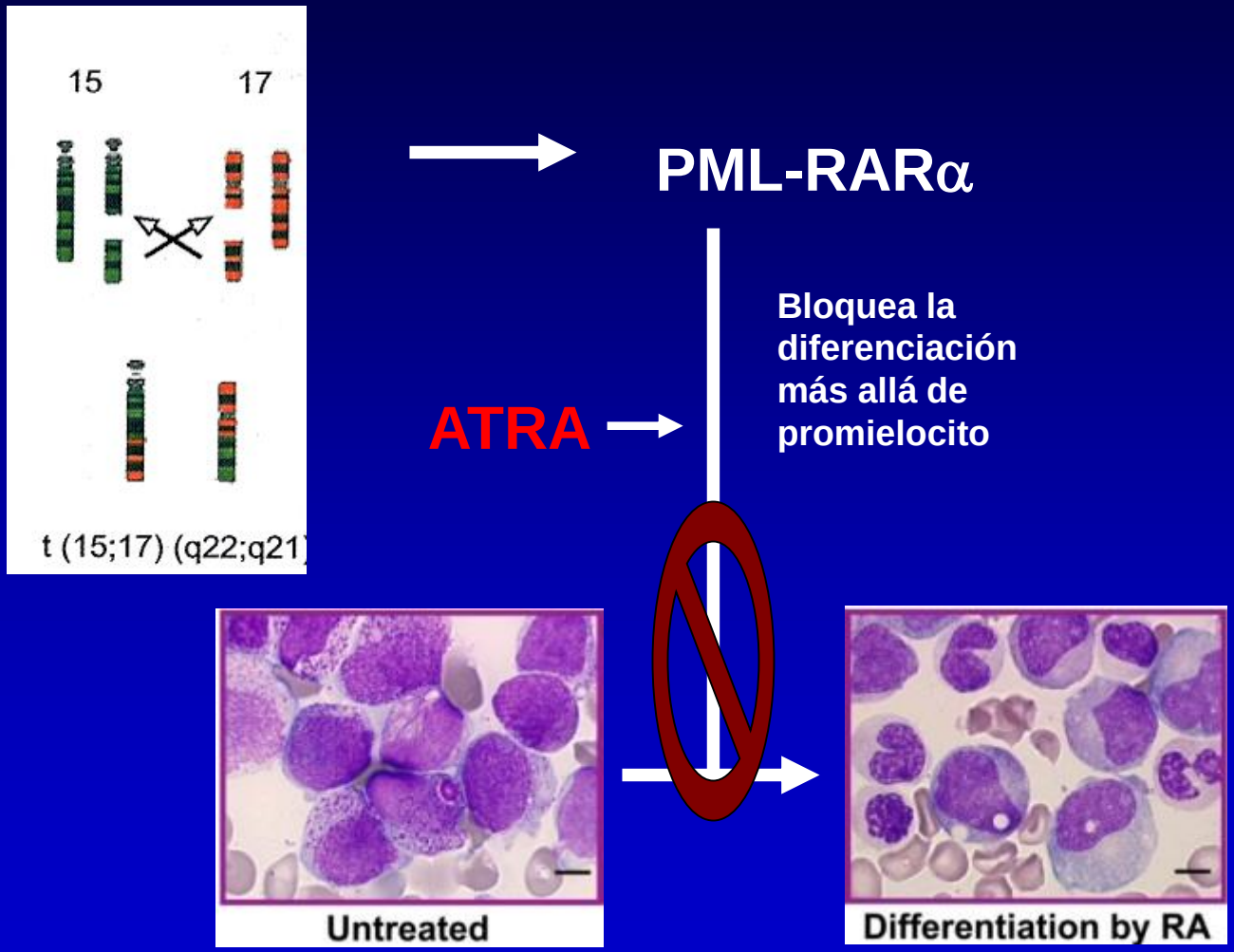
LMA secundaria:

- Entidad de pobre pronostico, bajas tasas de RC y OS
- Asociado a cariotipos complejos, TP53 mutado y exposición a QT

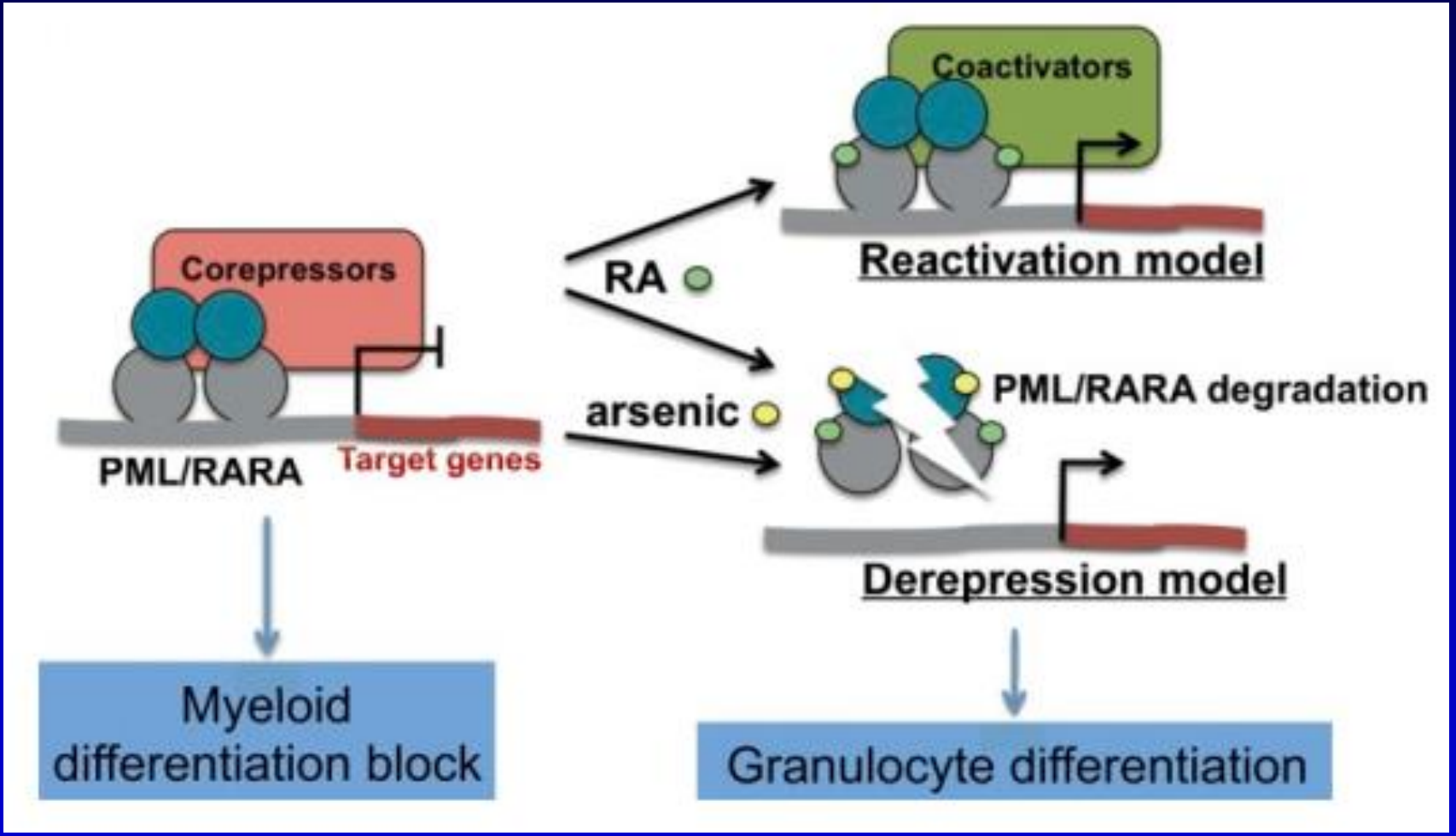
- **Venetoclax:**
  - Inhibidor oral de proteína anti apoptótica Bcl-2
  - Bcl-2 responsable de resistencia a QT en LMA
  - Buenos resultados en LMA en > 65 años con citogenética de riesgo intermedio o adverso:
    - Venetoclax + HMA: CR + CR i 66% y OS media de 18 meses
    - Venetoclax + citarabina dosis bajas: CR + CR i 62% y OS media 12 meses
  - En estudio: Venetoclax + 3 + 7 o FLAG- Ida

Am J Hematol. 2018;93:1267–1291.

Leucemia promielocítica

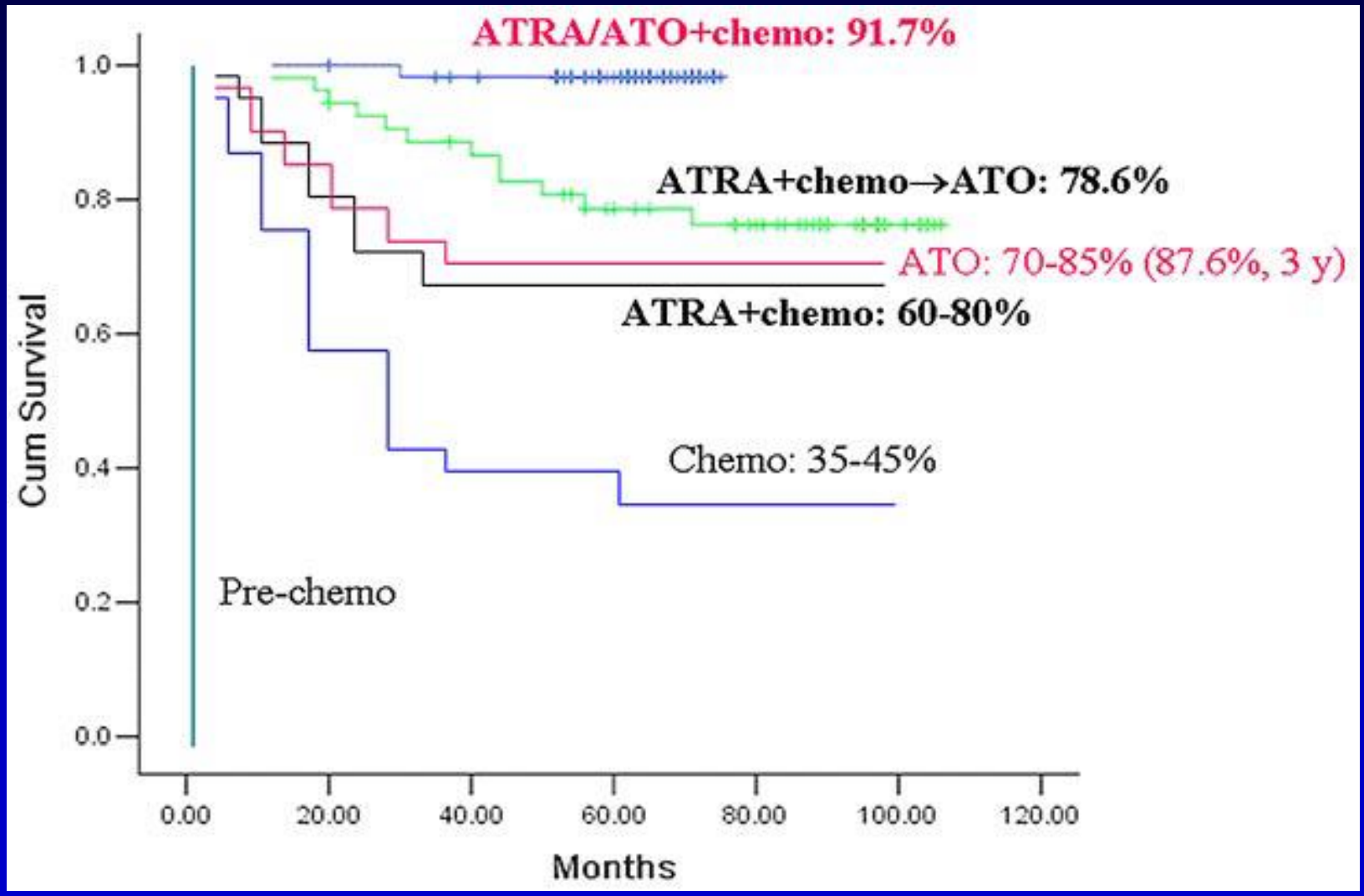


ATRA y Trioxido de arsénico en el tratamiento de la LPMA



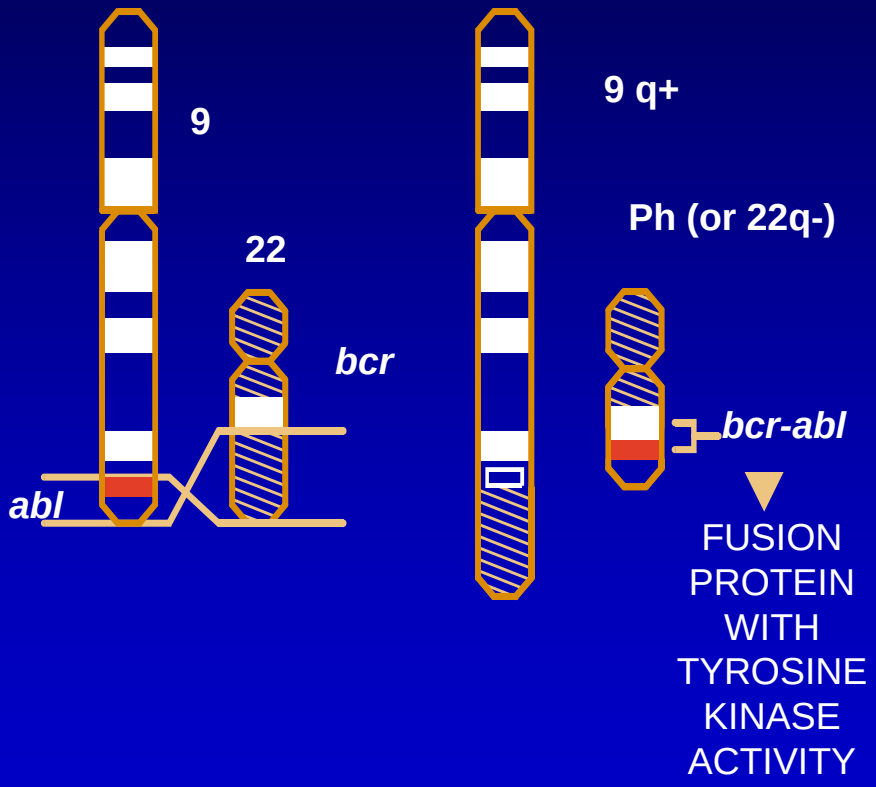
de Thé H, Le Bras M, Lallemand-Breitenbach V - J. Cell Biol. (2012

Evolución del tratamiento de la LPMA

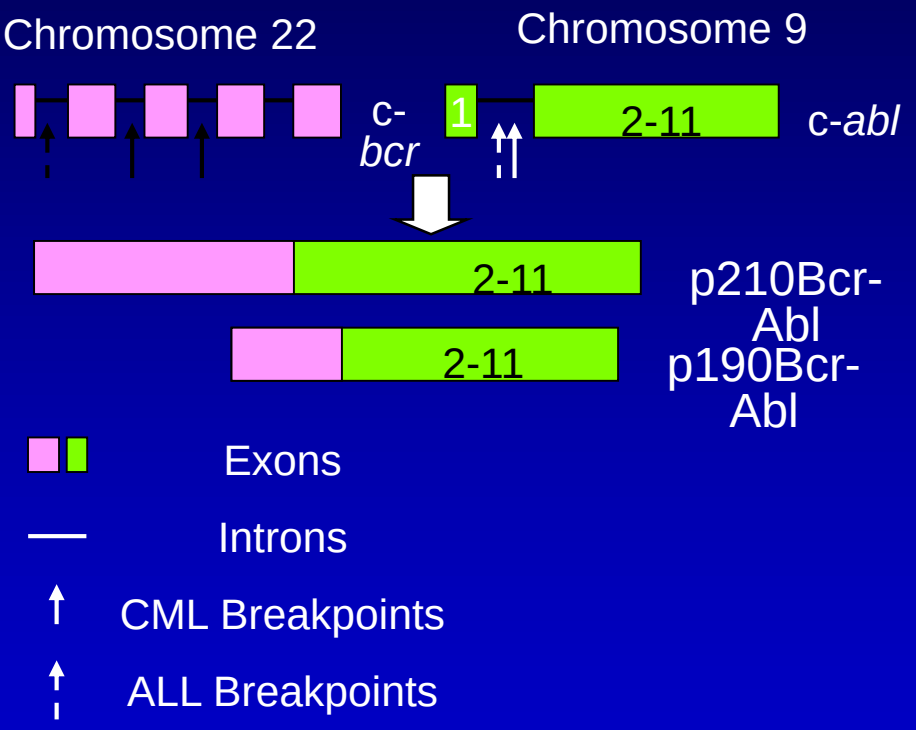


Blood. 2011;117(24):6425-6437

Leucemia Mieloide Crónica



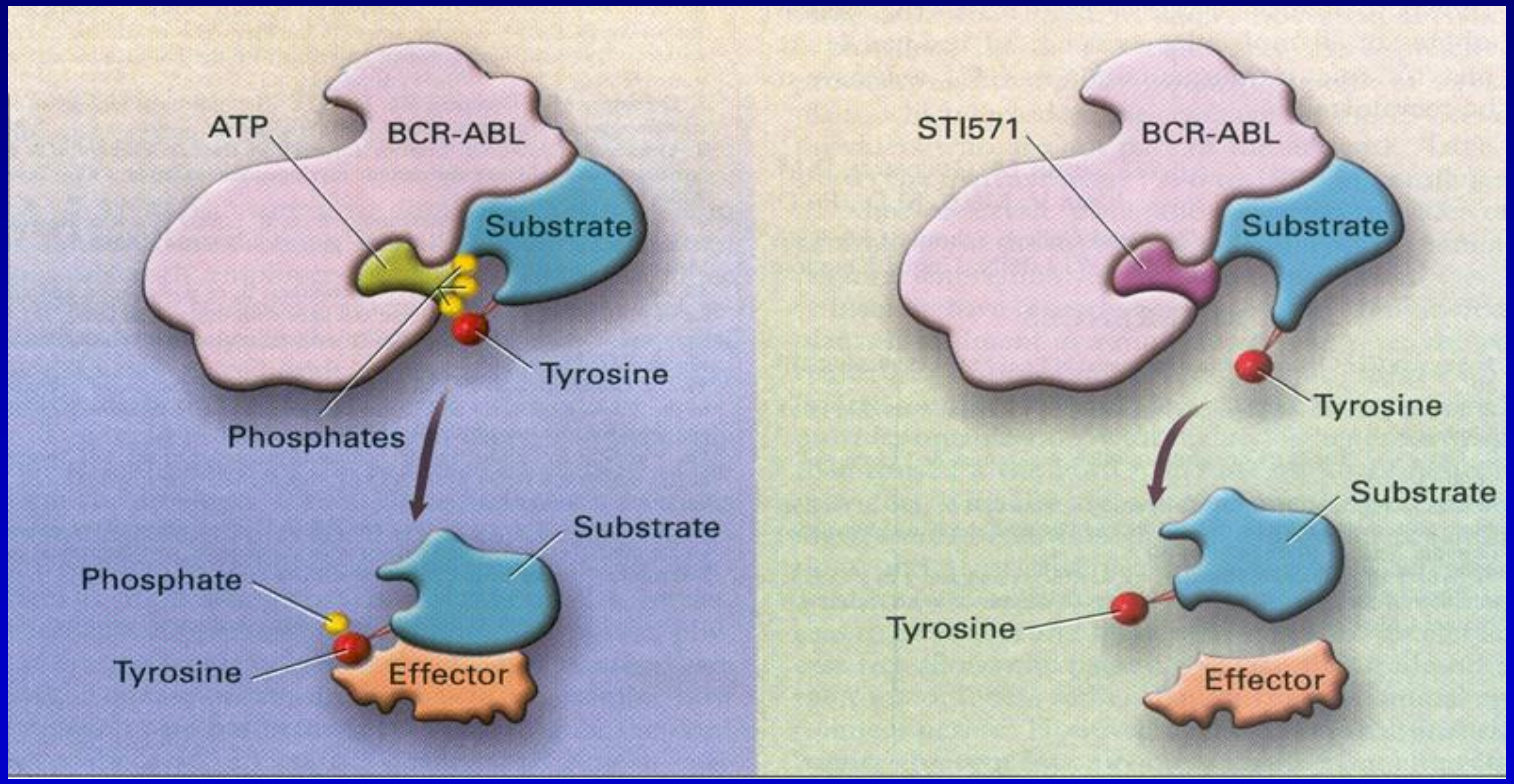
t(9;22) translocation



bcr-abl gene structure

Mecanismo de acción de Imatinib

- Inhibe competitivamente el sitio de unión del ATP en la quinasa ABL



Goldman JM, Melo JV. *N Engl J Med.* 2001;344:1084-1086.

Original Article

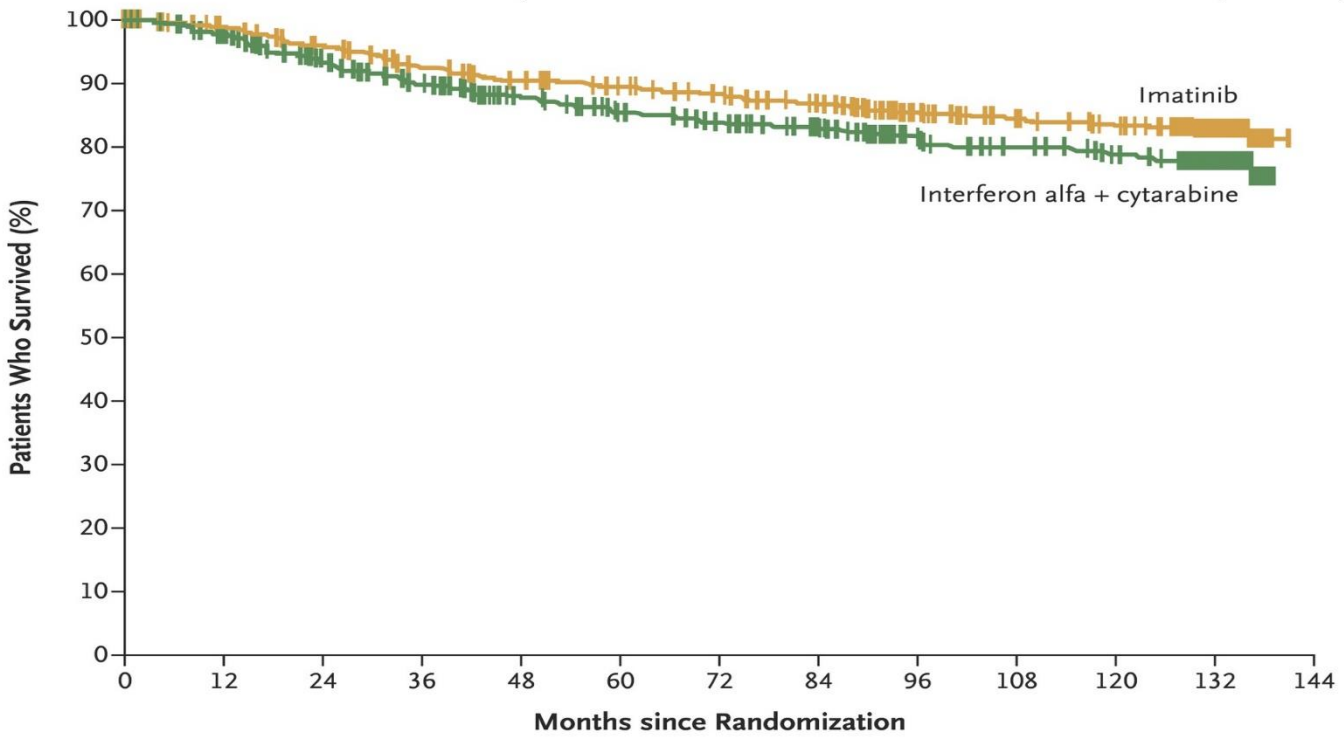
Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia

Andreas Hochhaus, M.D., Richard A. Larson, M.D., François Guilhot, M.D., Jerald P. Radich, M.D., Susan Branford, Ph.D., Timothy P. Hughes, M.D., Michele Baccarani, M.D., Michael W. Deininger, M.D., Ph.D., Francisco Cervantes, M.D., Satoko Fujihara, Ph.D., Christine-Elke Ortmann, M.Sc., Hans D. Menssen, M.D., Hagop Kantarjian, M.D., Stephen G. O'Brien, M.D., Ph.D., Brian J. Druker, M.D., for the IRIS Investigators

N Engl J Med
Volume 376(10):917-927
March 9, 2017

The NEW ENGLAND JOURNAL of MEDICINE

Kaplan–Meier Estimated Overall Survival Rates at 10 Years in the Intention-to-Treat Population.



No. at Risk								
Imatinib	553	542	492	461	430	368	250	0
Interferon alfa + cytarabine	553	512	441	388	358	299	199	0
No. of Deaths								
Imatinib	0	6	41	57	71	82	88	89
Interferon alfa + cytarabine	0	12	52	73	83	96	104	105

Hochhaus A et al. N Engl J Med ;376:917-927

The NEW ENGLAND JOURNAL of MEDICINE

American Society of Hematology Self-Assessment Program, Seventh Edition, 2019

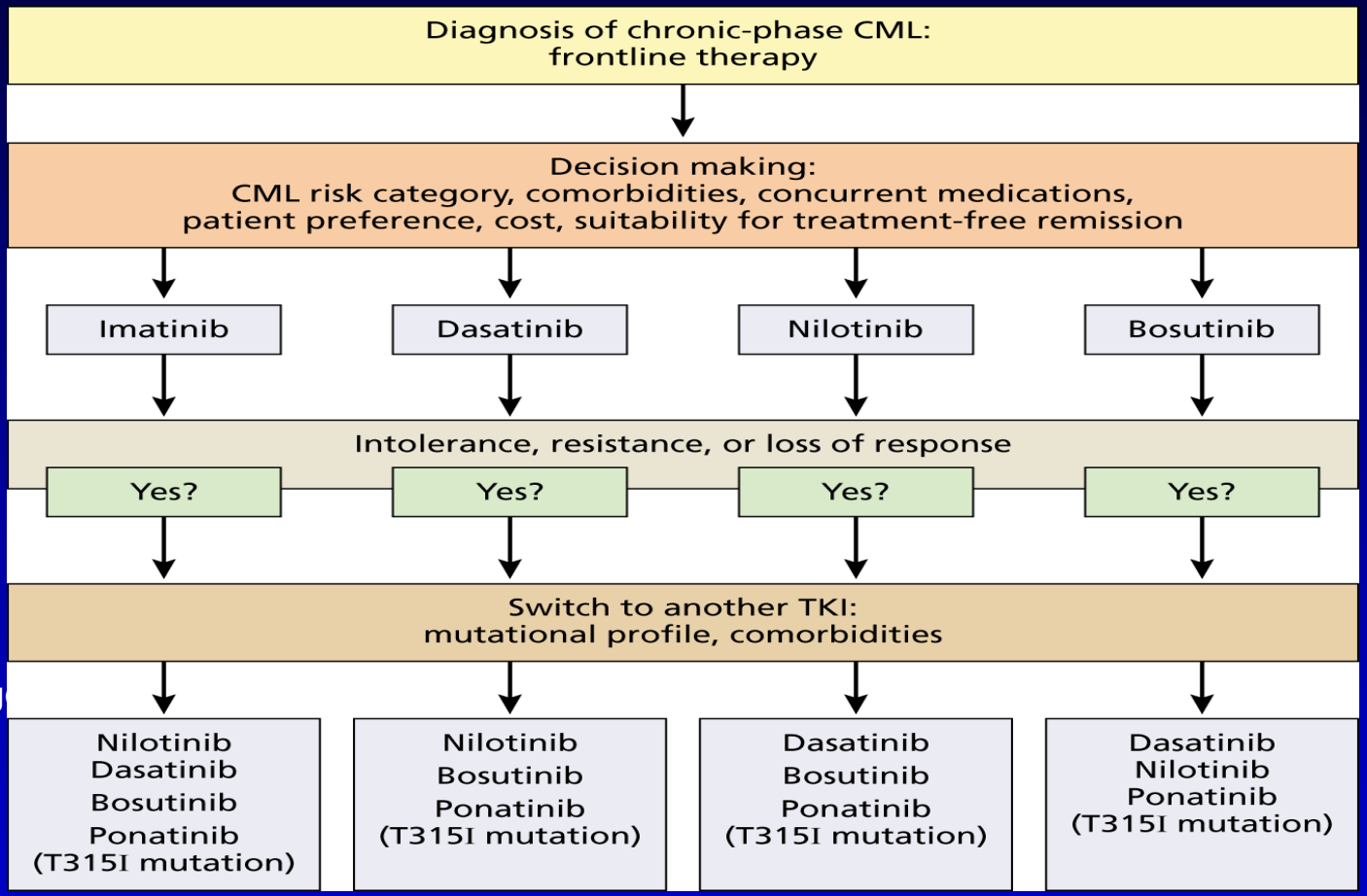
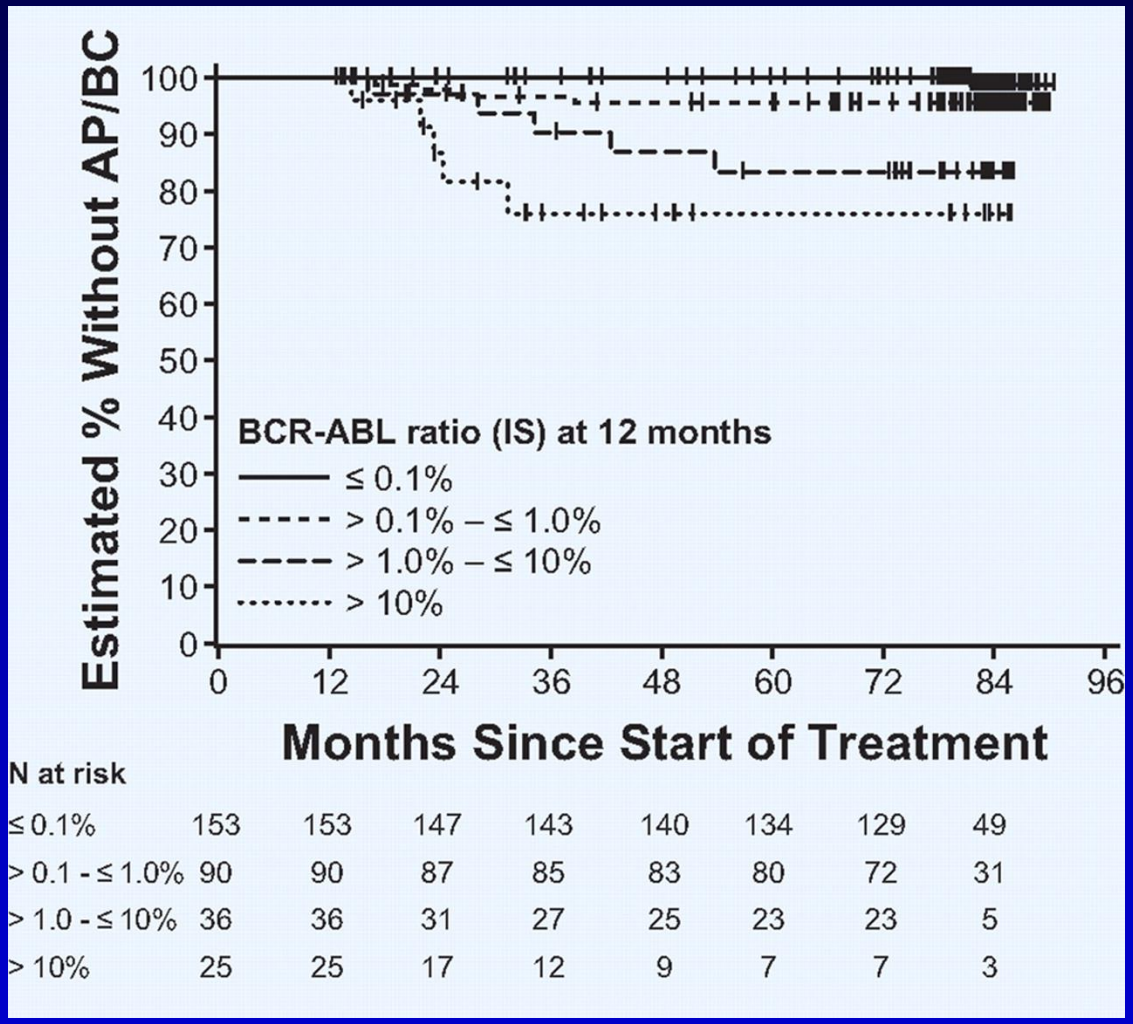


Figure Leg

A proposed algorithm for CML treatment.

Decision-making for CML treatment in the first- and second-line is shown. Patients with disease that is resistant to primary treatment with imatinib should be treated with dasatinib, nilotinib, or bosutinib in the second-line setting based upon mutational screening results and comorbidity assessment. Patients with disease that is resistant to primary treatment with dasatinib, nilotinib, or bosutinib can be treated with an alternate TKI (other than imatinib) in the second-line setting. Ponatinib is a treatment option for patients with a T315I mutation and, as indicated on the label, for patients for whom no other TKI is indicated. However, caution should be exercised when selecting next-line therapy in patients failing first-line, second-generation TKI therapy if they are fully adherent to therapy, but are resistant without evidence of TKD mutations. Studies support that this is a group of patients who are at increased risk for failing a second-line, second-generation TKI and earlier consideration for ponatinib may be warranted. Omacetaxine is a treatment option for patients with disease that is resistant and/or intolerant to 2 or more TKIs.

Importancia de la profundidad de respuesta en LMC



N at risk								
≤ 0.1%	153	153	147	143	140	134	129	49
> 0.1 - ≤ 1.0%	90	90	87	85	83	80	72	31
> 1.0 - ≤ 10%	36	36	31	27	25	23	23	5
> 10%	25	25	17	12	9	7	7	3

Schiffer, C. A. Blood 2010;116:3686-3687

Discontinuación ITK:

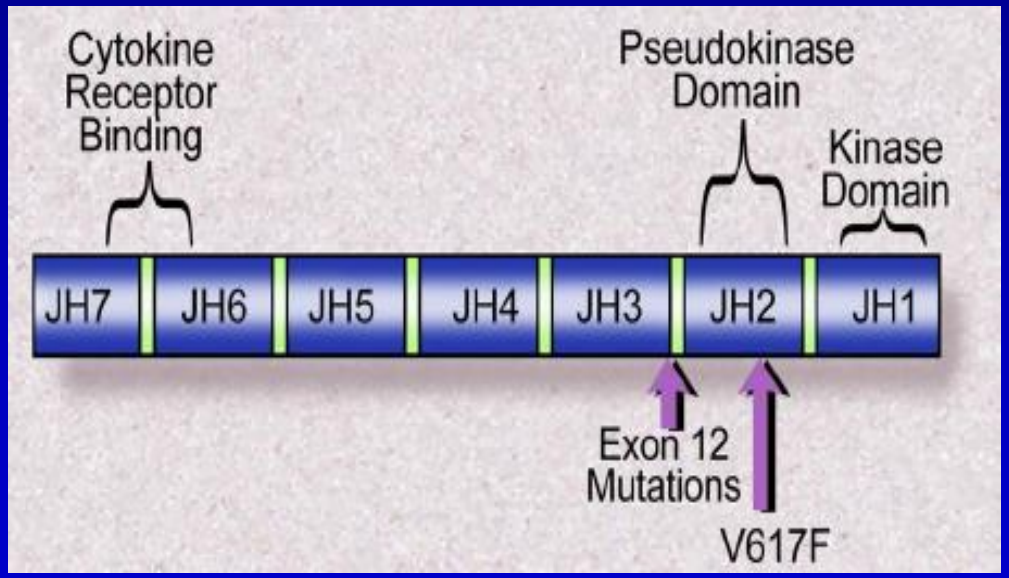
TABLE 7 Requirements for TKI discontinuation in clinical practice

Parameter	Discontinuation of TKI	
	Yes	No
Sokal risk	Low-intermediate	High
BCR-ABL1 transcripts	Quantifiable (e13a2 or e14a2)	Not quantifiable
CML stage	Chronic	Accelerated/blast phase
Response to first TKI	Optimal	Failure
Duration of all TKIs therapy	>6-8 y	<3 y
Depth of molecular response	CMR (MR4.5)	Less than MR4
Duration of molecular response	>3+ y	<3 y
Monitoring availability	Ideal (every 2 mo in years 1-2)	Poor; non-compliant

Am J Hematol. 2020;9 5:691–709

PV, TE, MFI

- Mutación JAK2: cambio nucleotido 1849 del exón 12 resulta en la sustitución valina por fenilalanina en el codón 617 (JAK2 V617F).
- PV: >95%
- TE – MFI: 50 - 60%



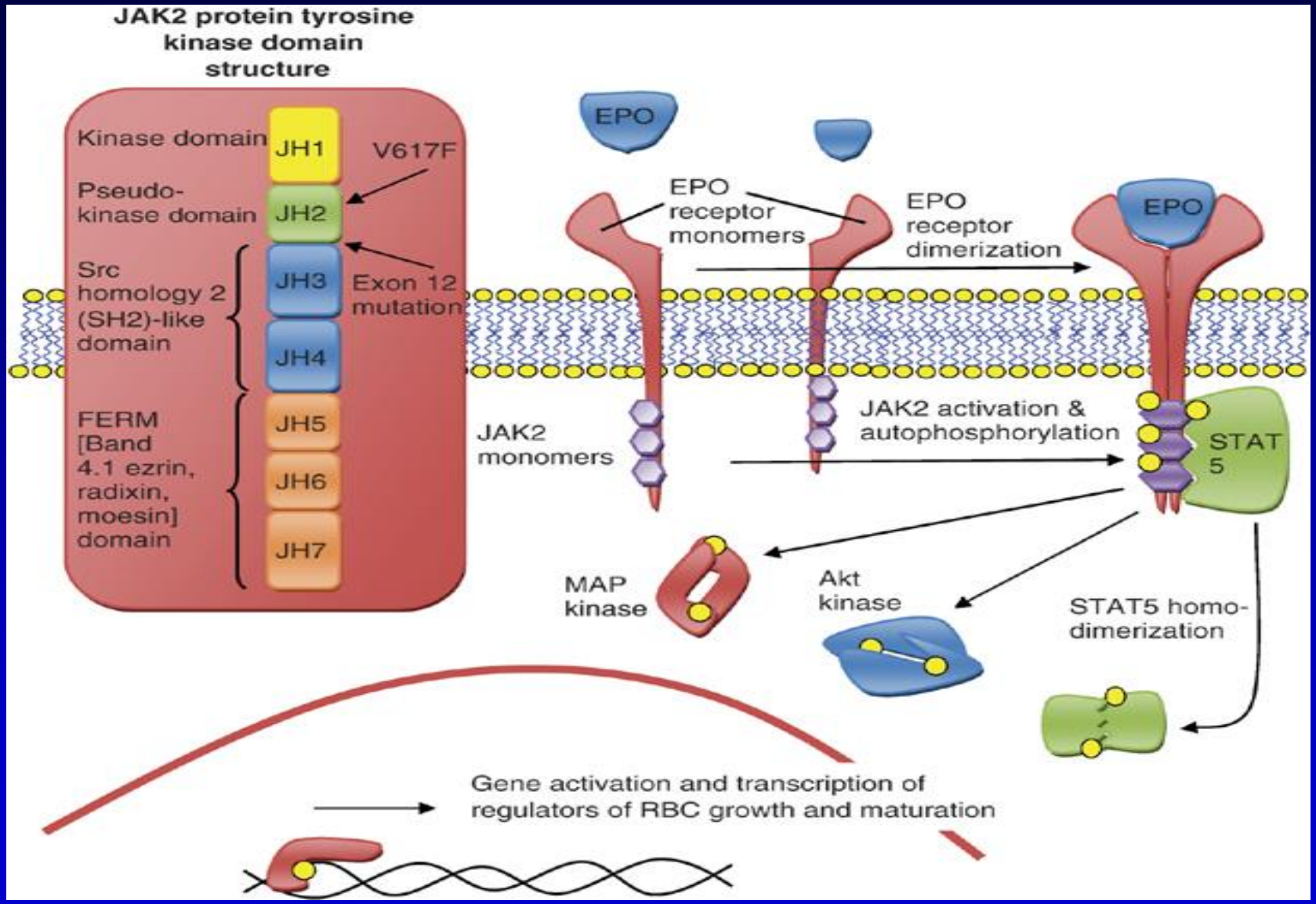
Base genética:

- **Mutaciones driver mas frecuentes en PV, TE y MF**:
  - JAK2 V617F
  - JAK2 exón 12
  - CALR
  - cMPL

Table 18-2 Somatic mutations seen in patients with ET, PV, and MF

Gene name	Mutation effect	PV (%)	ET (%)	MF (%)
JAK2 (V617F)	JAK/STAT signaling	95–97	50–60	50–60
JAK2 exon 12	JAK/STAT signaling	1–2	0	0
CALR	JAK/STAT signaling	0	25	30
MPL	JAK/STAT signaling	0	3–5	5–10
CBL	JAK/STAT signaling	Rare	Rare	5–10
SH2B3/LNK	JAK/STAT signaling	1–2	3–6	3–6
ASXL1	Epigenetic modification	2	2–5	10–35
EZH2	Epigenetic modification	1–2	1–2	7–10
IDH1/2	Epigenetic modification	1–2	1–2	5–6
DNMT3A	Epigenetic modification	5–10	1–5	8–12
TET2	Epigenetic modification	10–20	5	10–20
SF3B1	mRNA splicing	2	2	5
SRSF2	mRNA splicing	Rare	Rare	5–17
U2AF1	mRNA splicing	Rare	Rare	16
ZRSR2	mRNA splicing	Rare	Rare	1
TP53	DNA repair	Rare	Rare	Rare

JAK2 V617F


JAK2 protein tyrosine kinase domain structure
Kinase domain
JH1
V617F
Pseudo-kinase domain
JH2
Src homology 2 (SH2)-like domain
JH3
Exon 12 mutation
JH4
FERM [Band 4.1 ezrin, radixin, moesin] domain
JH5
JH6
JH7
EPO
EPO receptor monomers
EPO receptor dimerization
EPO
JAK2 monomers
JAK2 activation & autophosphorylation
STAT 5
MAP kinase
Akt kinase
STAT5 homo-dimerization
Gene activation and transcription of regulators of RBC growth and maturation

Ruxolitinib en MF de riesgo bajo o intermedio -1:

- LTS COMFORT I y II
- OS 5.3 vs 3.8 años.
- ¿Posible rol modificador de enfermedad? ¿uso precoz?
- Beneficio independiente de estado mutacional de JAK2

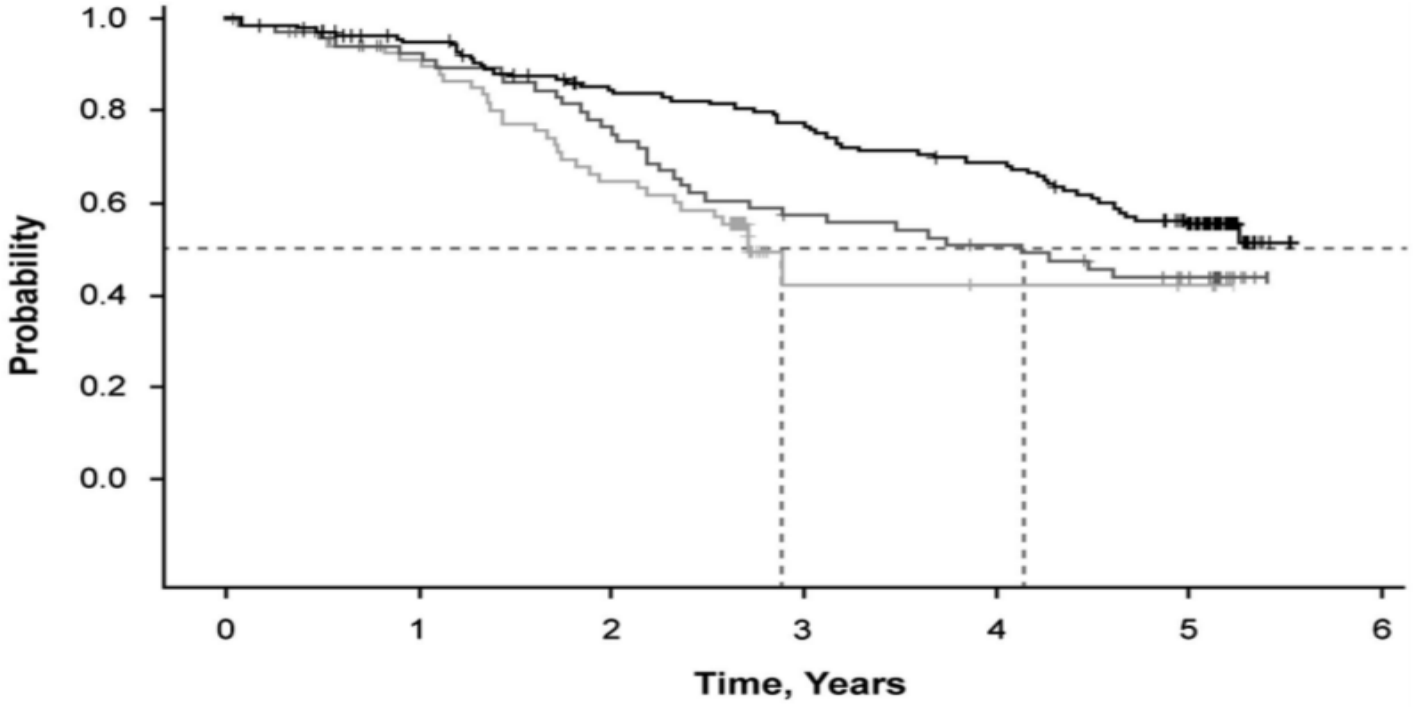
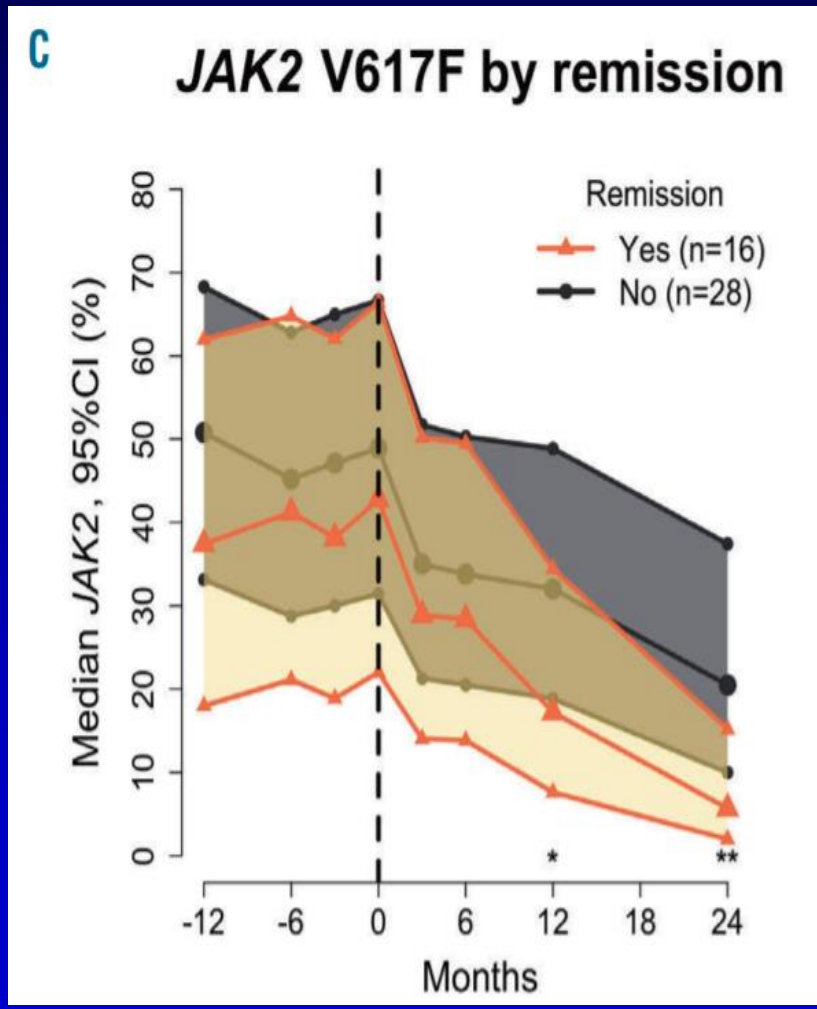


Figure 4. Kaplan–Meier analysis of OS by ITT analysis and RPSFT corrected for crossover from the BAT arm.

Interferón alfa recombinante + Ruxolitinib:

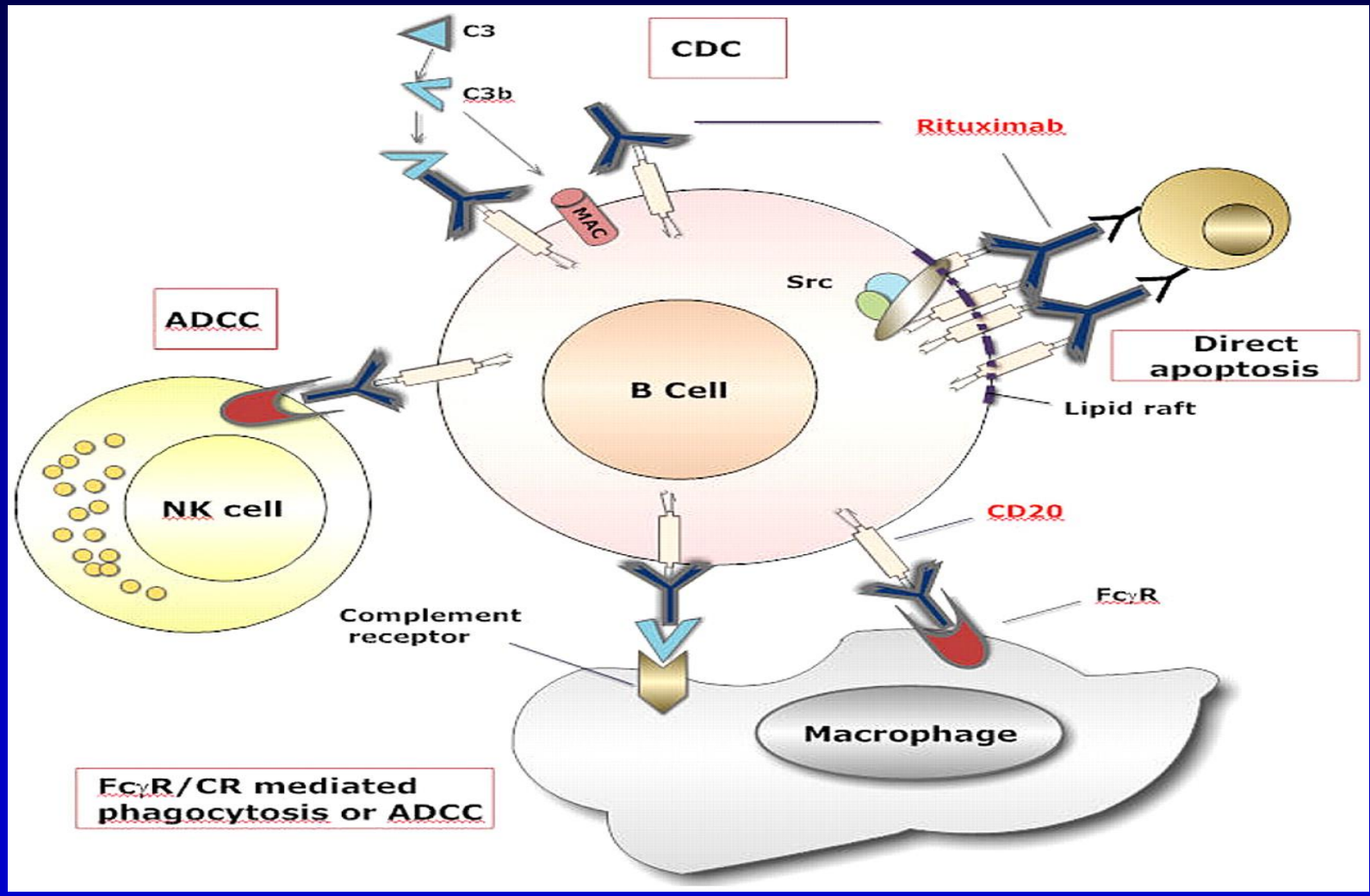
- Efecto sinérgico:
  - Ruxolitinib: para tratar síntomas constitucionales y esplenomegalia
  - INF alfa: para afectar stem cells
- Estudio fase II en PV y MF:



Haematologica 2020 Volume 105(9):2262-2272

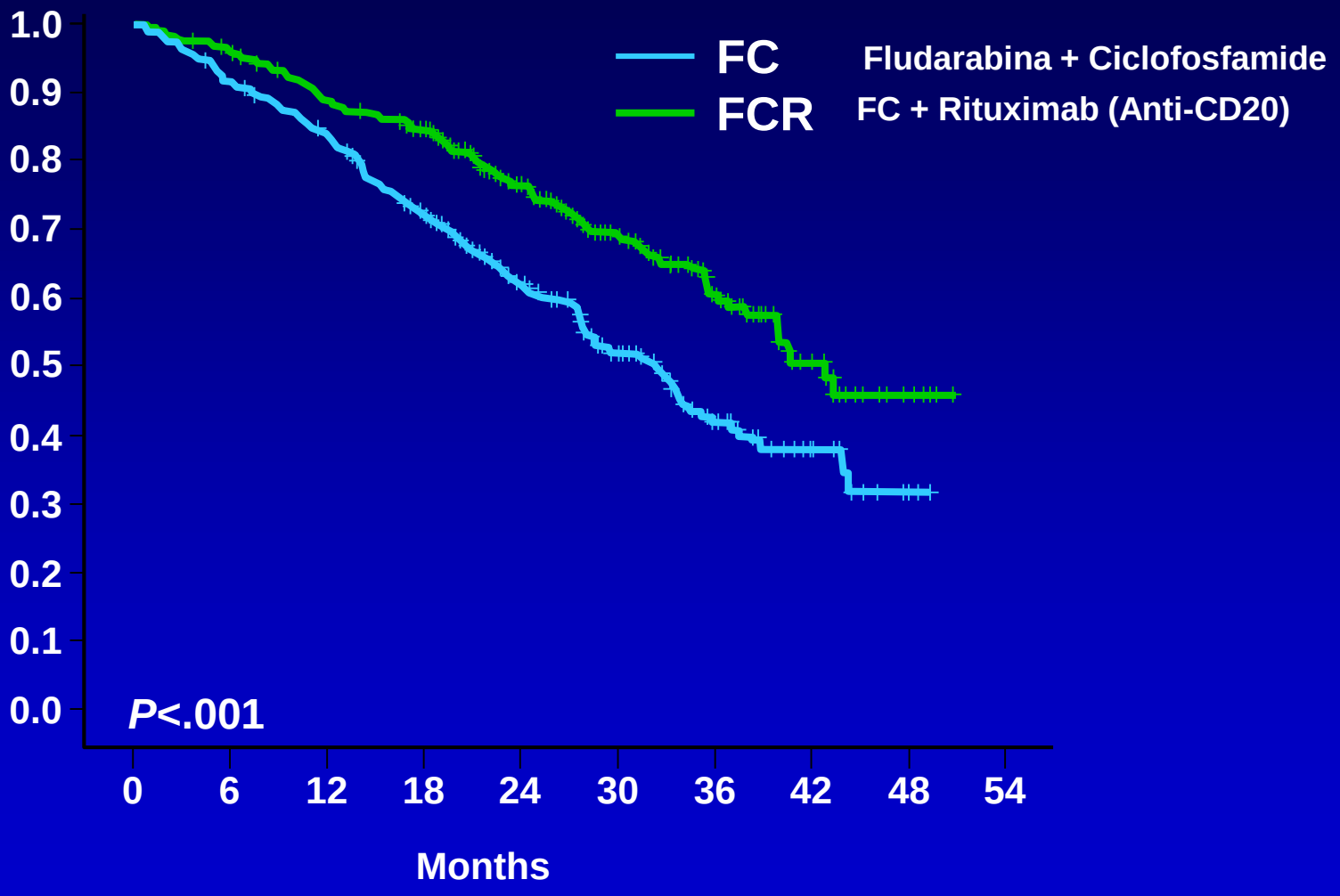
Avances en neoplasia linfoides

Rituximab
Anticuerpo anti CD 20



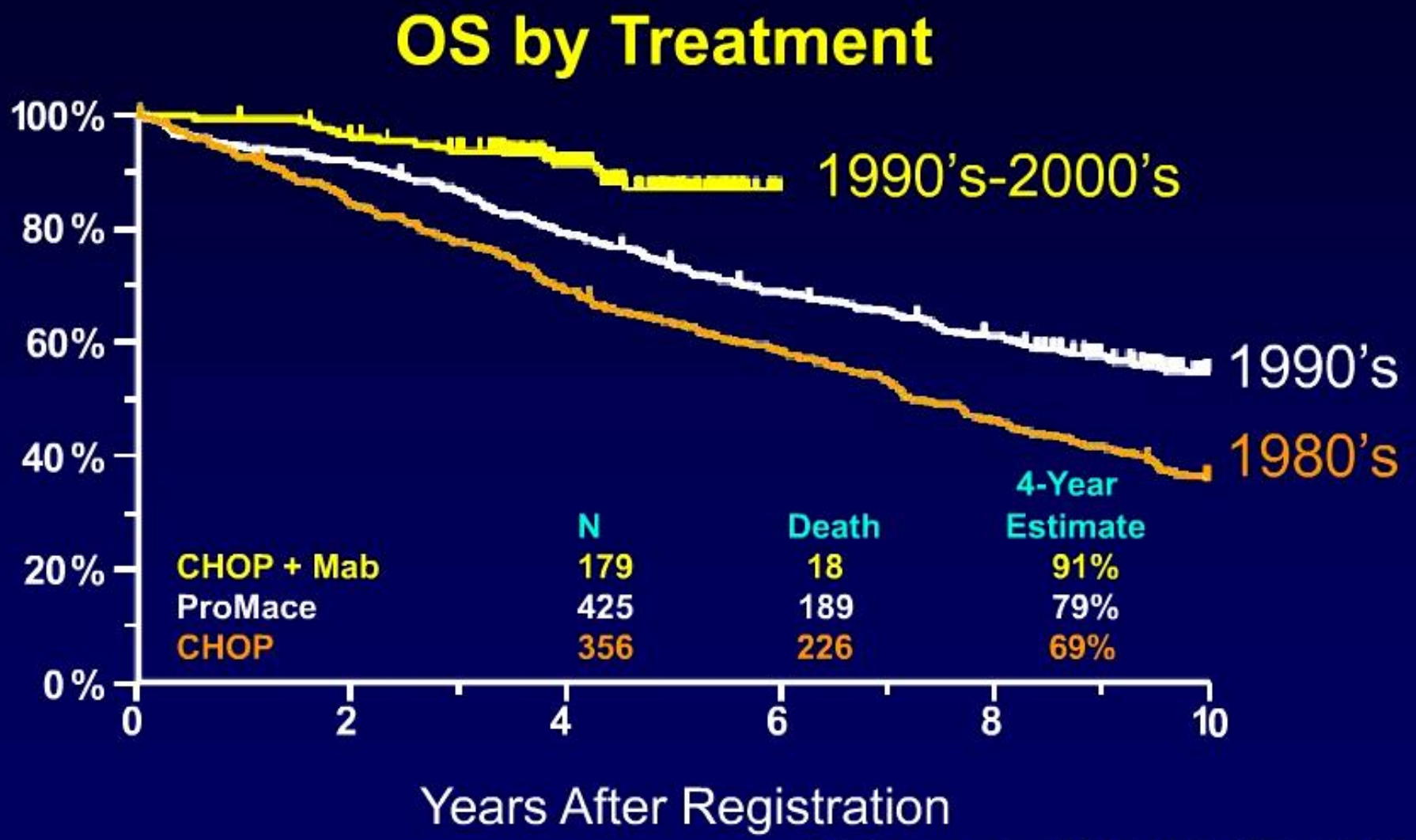
Jaglowski, S. M. et al. Blood 2010;116:3705-3714

CLL8: Progression-Free Survival (PFS)



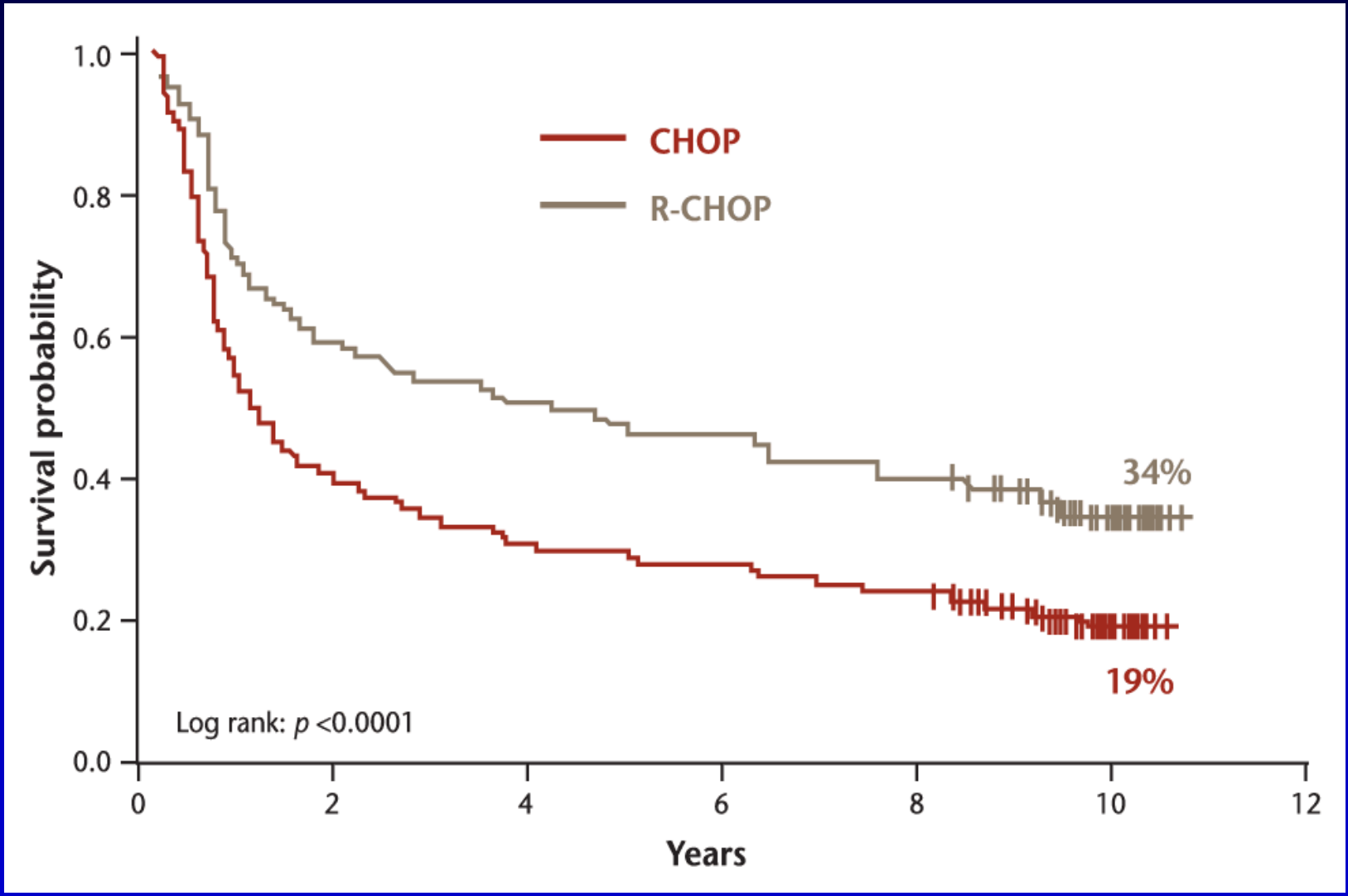
Hallek M, et al. *Blood*. 2009;114: Abstract 535.

Impact of anti-CD20 therapy on Follicular NHL: Updated SWOG data

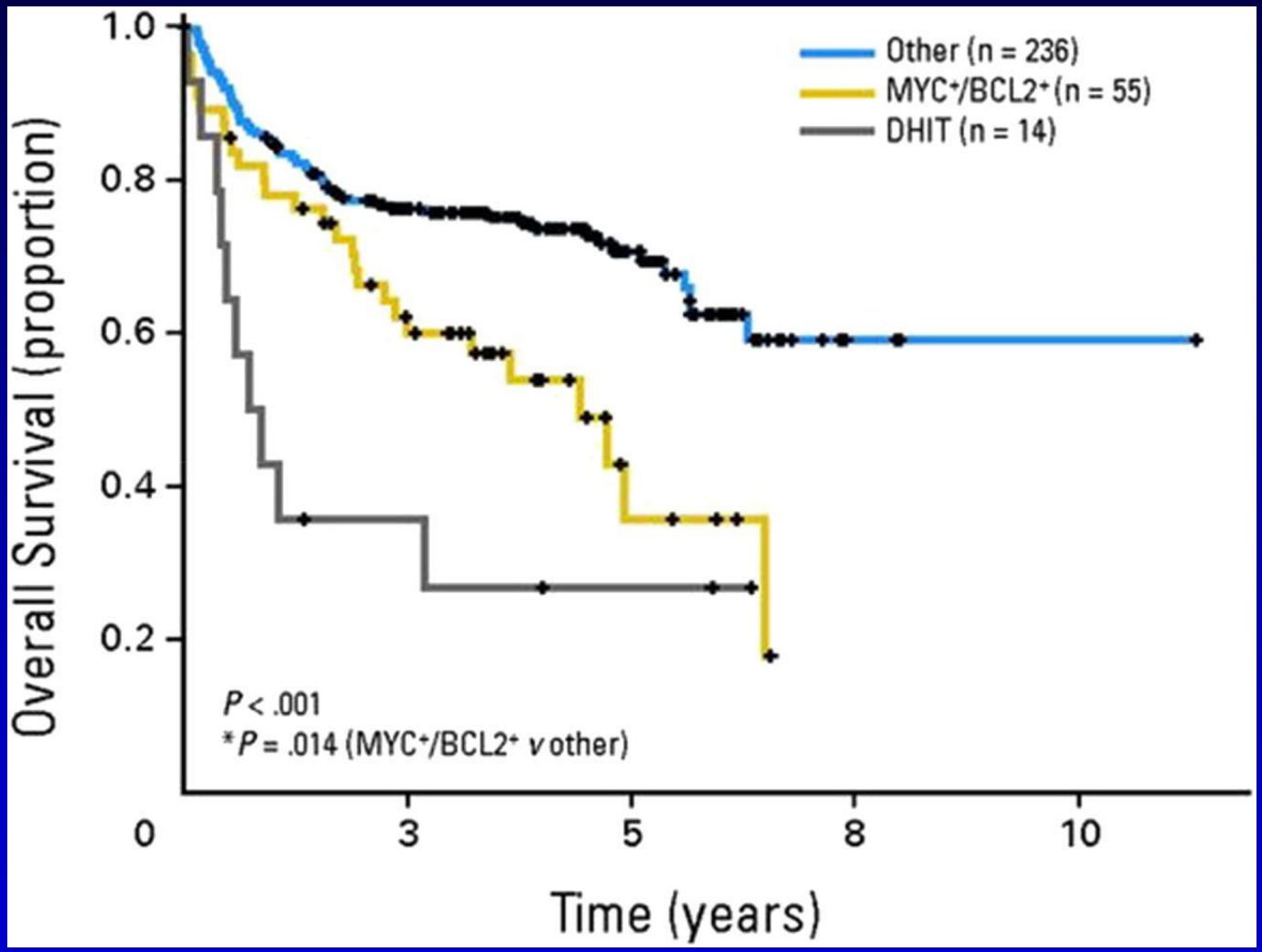


Fisher et al, JCO 23:8447, 2005

CHOP vs R-CHOP en DLBCL (GELA LNH 98.5)

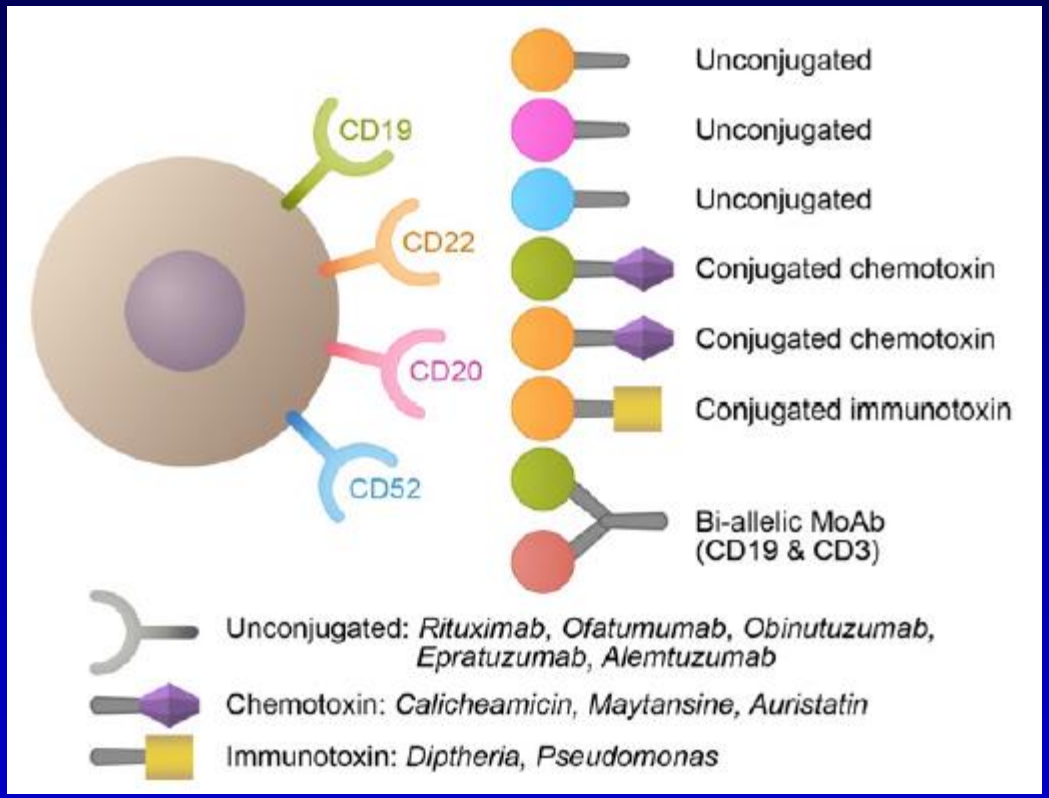


OS of patients with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone according to the presence of concurrent expression of MYC and BCL2 proteins (MYC+/BCL2+) or the presence of concurrent M...



Andrew Davies Hematology 2017;2017:284-294

Nuevos blancos en neoplasias linfoides



Therapy	Description
CD20	
Rituximab	When added to conventional chemotherapy has been shown to improve survival in younger adults
Ofatumumab	Binds to a different epitope than rituximab, which may allow it to overcome rituximab-resistant disease
Obinutuzumab	Novel glycoengineered type II CD20 monoclonal antibody superior to rituximab and ofatumumab in the induction of direct cell death.
CD19	
SAR3419	Conjugated to a synthetic maytansinoid that is release intracellularly after antigen internalization
SGN-CD19A	Humanized anti-CD19 monoclonal antibody conjugated to the microtubule-disrupting agent. On internalization, it binds to tubulin and induces G2/M arrest and apoptosis
Blinatumomab	Bispecific antibody that redirects cytotoxic T cells to cells that express CD19
CD22	
Epratuzumab	Studied as part of combination therapy in adults and children with modest activity
Epratuzumab-SN38	Antibody conjugated to a topoisomerase I inhibitor to enhance cell killing potential
Inotuzumab ozogamicin	Antibody conjugated to the cytotoxin calicheamicin
Moxetumomab	Antibody conjugated to bacterial or plant toxin
CD52	
Alemtuzumab	Antibody that has only displayed little activity in B- and T-cell disease

Blood.2015;125(26):4010-4016

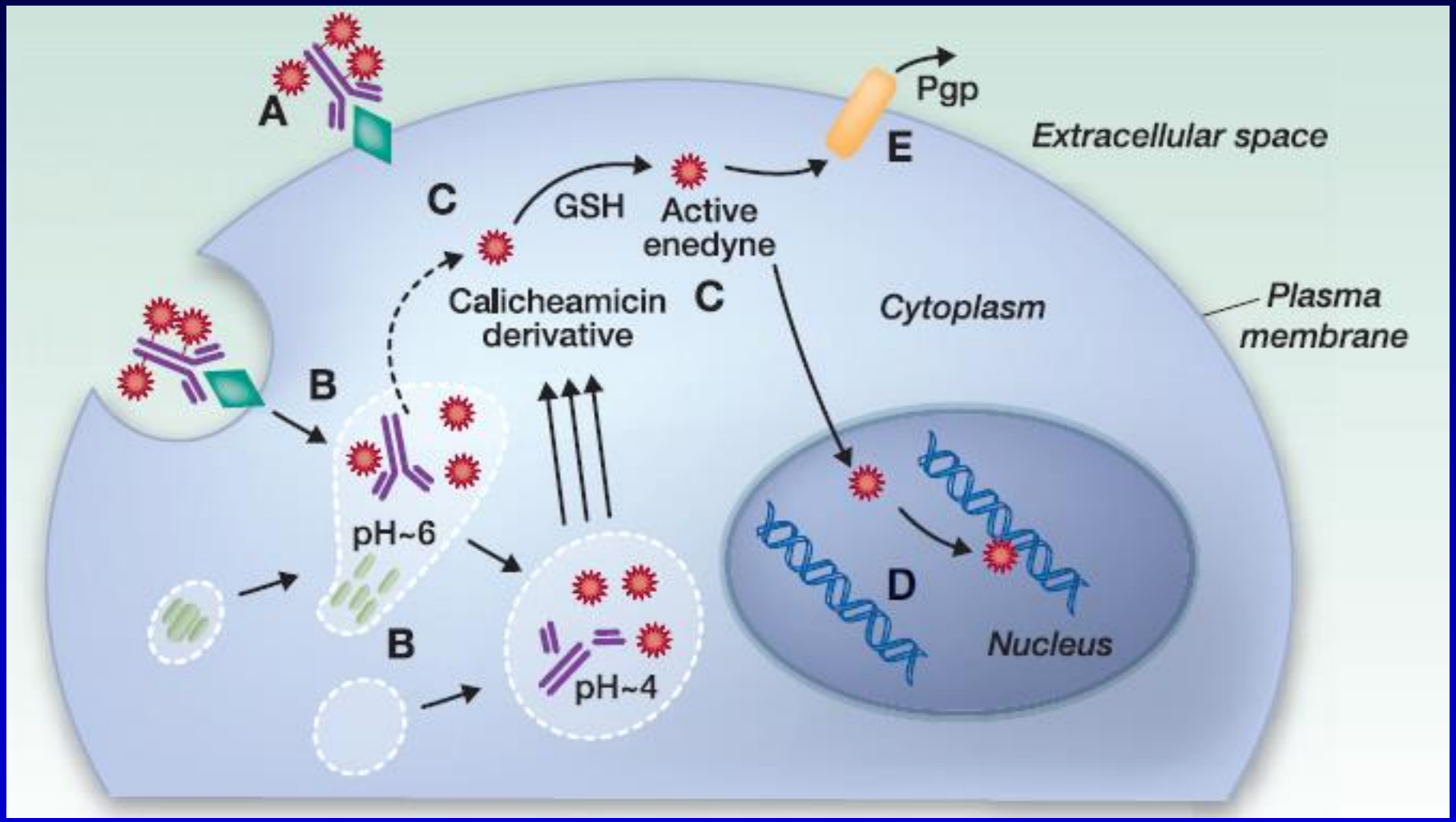
Tratamiento de LLA:

- 20% de pacientes tienen enfermedad primariamente refractaria
- 40-60% de adultos con LLA recidivan
- Sobrevida a 5 años de LLA: 75% en adultos jóvenes y 25% en mayores.

- Primeria línea:
  - Phi (-): HyperCVAD, GRAALL (Cy, VCR, Doxo, Dexa, L-Asp, MTX, ARA-C, 6-MP)
  - Phi (+): HyperCVAD + inhibidores de ITK
  - 2020: libre de QT: Dasa + Inotuzumab- Ozogamicina (anti CD22)
- Recidivado / refractario:
  - Inotuzumab o blinatumumab (bi-especifico) → elección.
  - Quimioterapia de rescate basada en citarabina.

ASH-SAP. Seventh edition. 2019

Inotuzumab Ozogamicin
Mecanismo de acción: anti CD22



Clin Cancer Res; 17(20) October 15, 2011

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia

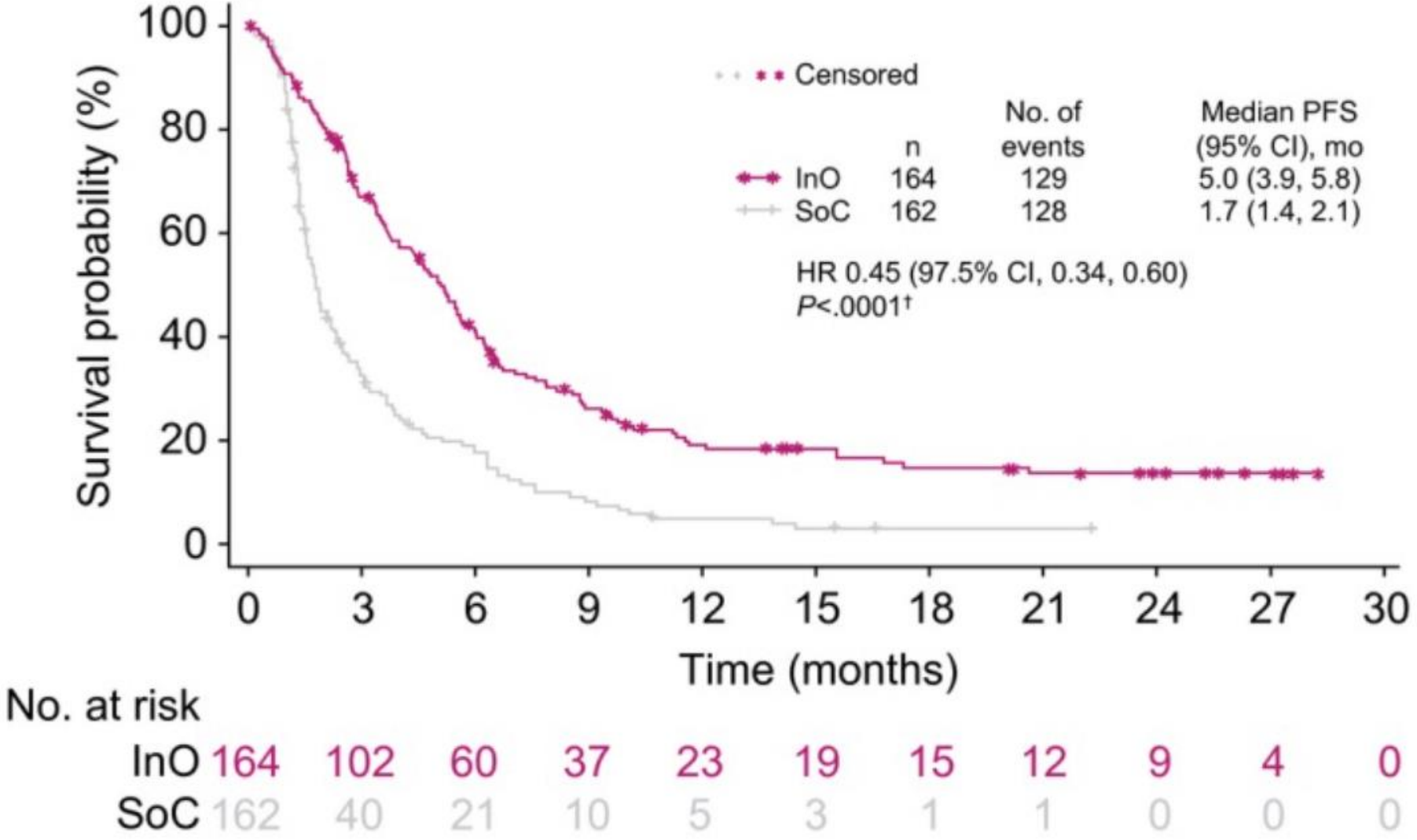
Hagop M. Kantarjian, M.D., Daniel J. DeAngelo, M.D., Ph.D., Matthias Stelljes, M.D., Giovanni Martinelli, M.D., Michaela Liedtke, M.D., Wendy Stock, M.D., Nicola Gökbuget, M.D., Susan O'Brien, M.D., Kongming Wang, Ph.D., Tao Wang, Ph.D., M. Luisa Paccagnella, Ph.D., Barbara Sleight, M.D., Erik Vandendries, M.D., Ph.D., and Anjali S. Advani, M.D.

Original Article

Inotuzumab Ozogamicin Versus Standard of Care in Relapsed or Refractory Acute Lymphoblastic Leukemia: Final Report and Long-Term Survival Follow-Up From the Randomized, Phase 3 INO-VATE Study

Hagop M. Kantarjian, MD [1]; Daniel J. DeAngelo, MD[2]; Matthias Stelljes, MD[3]; Michaela Liedtke, MD[4]; Wendy Stock, MD[5]; Nicola Gökbuget, MD[6]; Susan M. O'Brien, MD[7]; Elias Jabbour, MD [1]; Tao Wang, PhD[8]; Jane Liang White, ScD[8]; Barbara Sleight, MD[8]; Erik Vandendries, MD[9]; and Anjali S. Advani, MD[10]

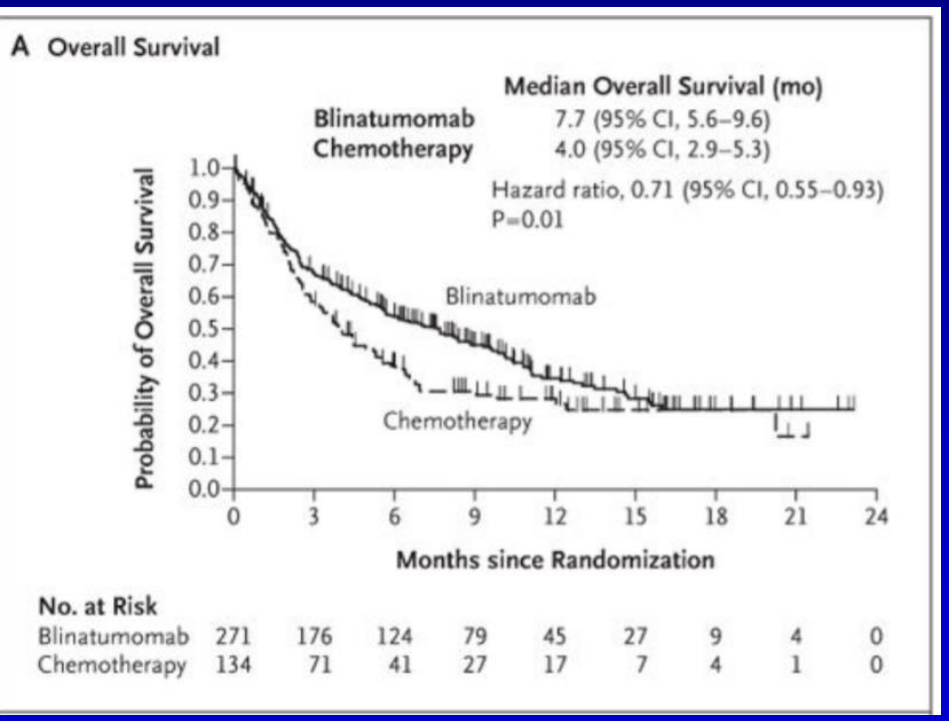
Cancer. 2019 Jul 15; 125(14): 2474–2487.

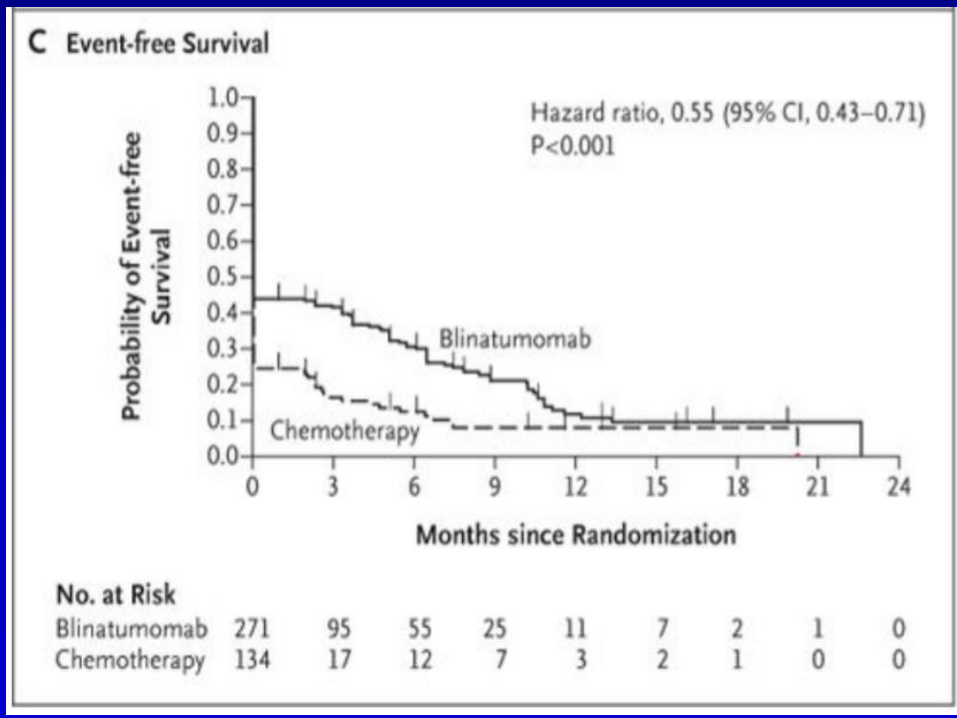


2-year OS rates of 22.8% and 10.0%

Blinatumumab: Bispecifc T-cell Engager (BiTE®): LLA recidivada refractaria

- RCT fase 3: Blinatumumab vs QT estándar
- CR: 44 vs 25%
- OS: 7.7 vs 4 m
- Toxicidad G3-4 menor (87 vs 92%)





N Engl J Med. 2017 March 02; 376(9): 836–847.

Leucemia linfoblástica aguda:

- **Inmunoterapia en primera línea en pacientes mayores****

- **Asociado a QT de intensidad reducida:**
  - Inotuzumab Ozogamicina + mini Hyper-CVAD
- **Posterior a QT de primera línea en pacientes con MRD positiva:**
  - Blinatumumab logra negativizar MRD
  - Interesante en pacientes no candidatos a trasplante

** uso no aprobado por FDA, solo en contexto de ensayos clínicos.

ASH-SAP. Seventh edition. 2019

Original Article

Dasatinib–Blinatumomab for Ph-Positive Acute Lymphoblastic Leukemia in Adults

Robin Foà, M.D., Renato Bassan, M.D., Antonella Vitale, M.D., Loredana Elia, M.D., Alfonso Piciocchi, M.S., Maria-Cristina Puzzolo, Ph.D., Martina Canichella, M.D., Piera Viero, M.D., Felicetto Ferrara, M.D., Monia Lunghi, M.D., Francesco Fabbiano, M.D., Massimiliano Bonifacio, M.D., Nicola Fracchiolla, M.D., Paolo Di Bartolomeo, M.D., Alessandra Mancino, M.S., Maria-Stefania De Propris, Ph.D., Marco Vignetti, M.D., Anna Guarini, Ph.D., Alessandro Rambaldi, M.D., Sabina Chiaretti, M.D., Ph.D., for the GIMEMA Investigators

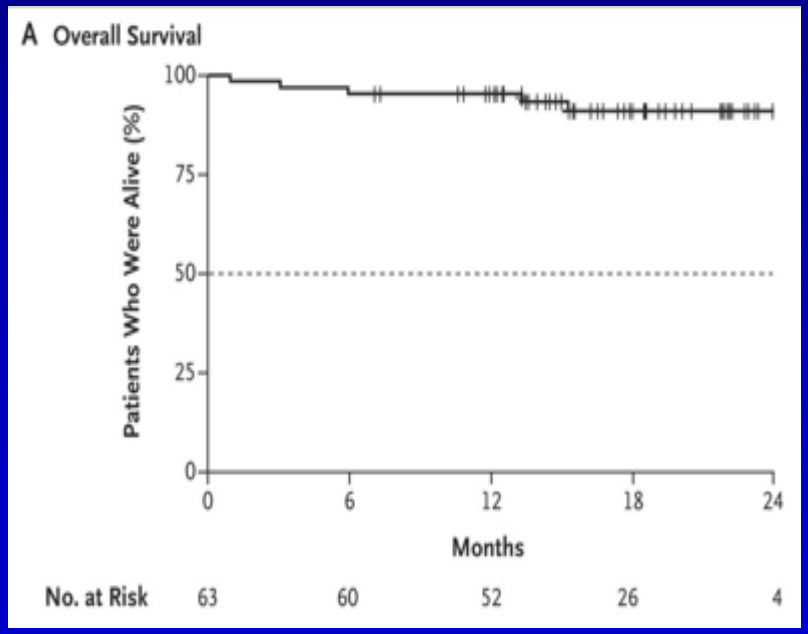
Blinatumumab: bi-especifico CD3 y CD19

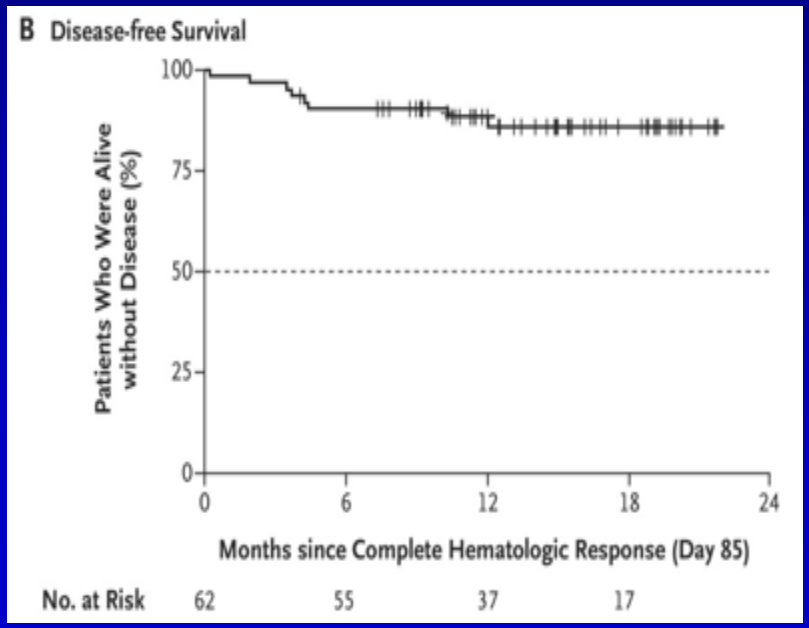
N Engl J Med
Volume 383(17):1613-1623
October 22, 2020

The NEW ENGLAND JOURNAL of MEDICINE

Study Overview

- In patients who have acute lymphoblastic leukemia with tumor cells that bear the Philadelphia chromosome, traditional therapy is not very effective.
- The use of the ABL kinase inhibitor dasatinib to achieve remission, followed by the bifunctional antibody blinatumomab (which has both anti-CD3 and anti-CD19 specificity as maintenance therapy), **led to complete remission in 98% of the patients.**

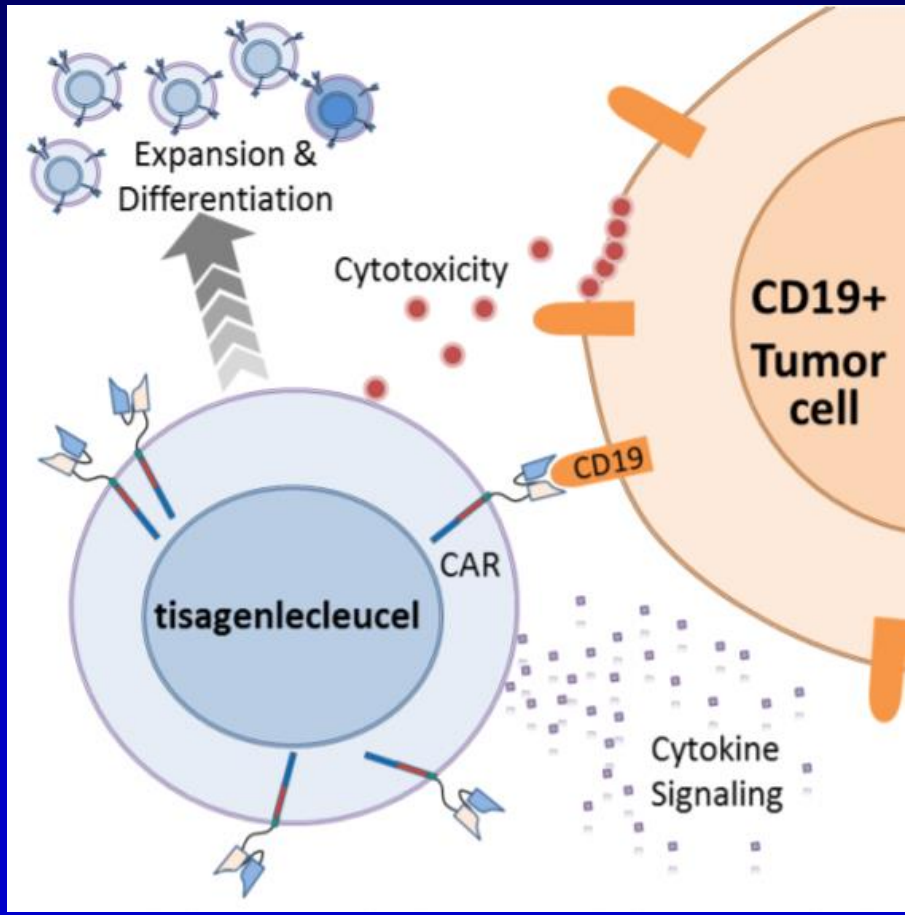




The NEW ENGLAND JOURNAL of MEDICINE

CAR-T (chimeric antigen recept or T): Tisagenlecleucel

- Linfocitos T autólogos dirigidos genéticamente contra células CD19 (+)
- Aprobado por FDA para < 25 años con LLA-B r/r
- Riesgo de CRS (~ 100%) y neurotoxicidad grave
- Requiere tratamiento con Tocilizumab (anti IL-6)
- Estudios pequeños: **CR > 80%, PFS y OS media de 13 y 6 meses**
- **Altas tasas de MRD (-)**



CART dirigidas contra CD19:

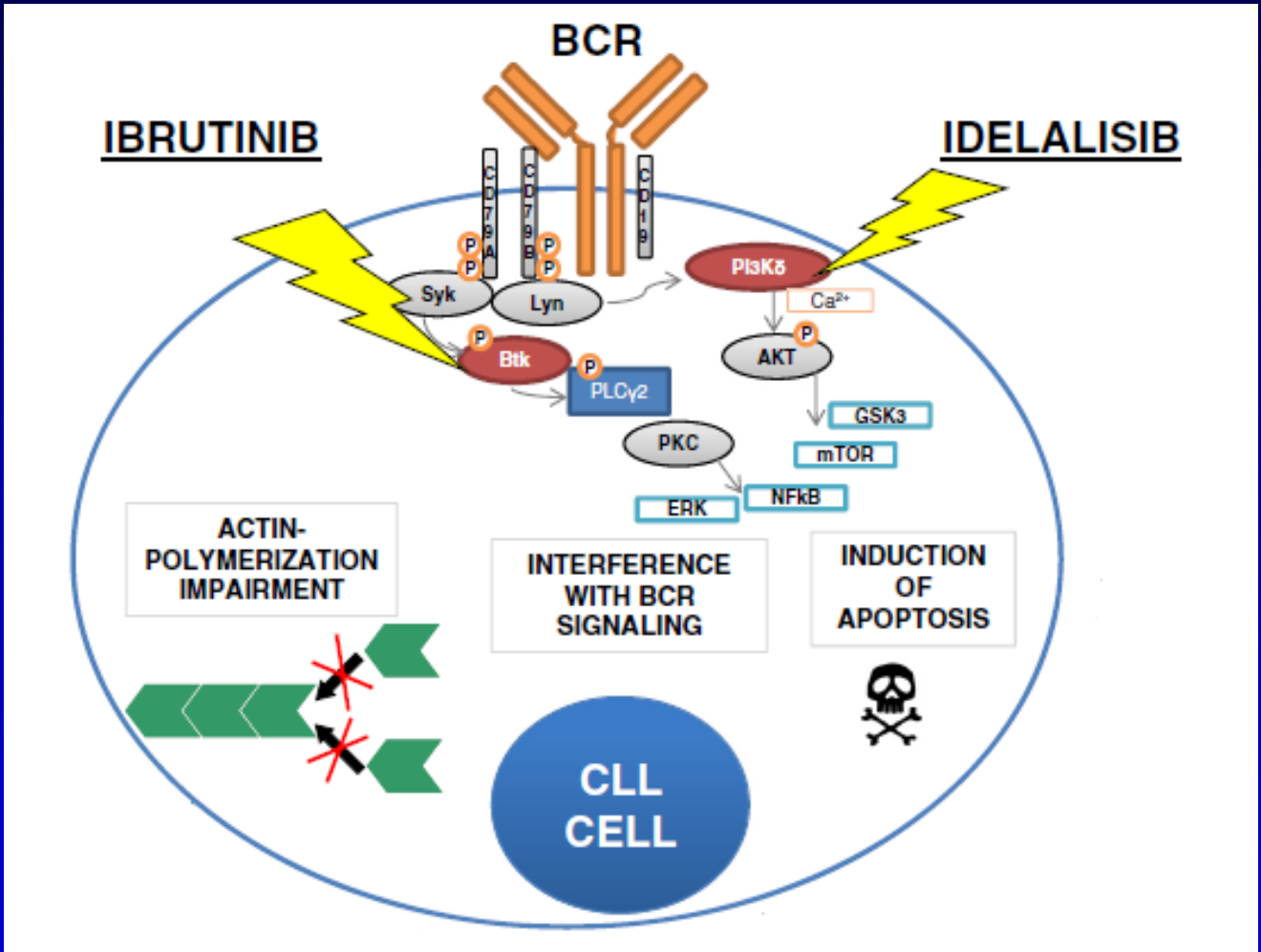
- **Estudio fase I:**
- 43 pacientes reciben CART (axicabtagene ciloleucel)
  - 28 LDCGB o PMBCL (19 refractarios a QT y 6 recidiva post TAMO)
  - 8 linfomas B de bajo grado
  - 7 LLC
- **Respuestas completas sostenida por > 3 años en el 51% de pacientes**

- Respuestas de larga duración con escasos efectos adversos a largo plazo → tratamiento de elección en LDCGB r/r

J Clin Oncol. 2020 Oct 6;JCO2001467.

Leucemia Linfática Crónica
Blancos moleculares

Ibrutinib: bloqueo de BTK



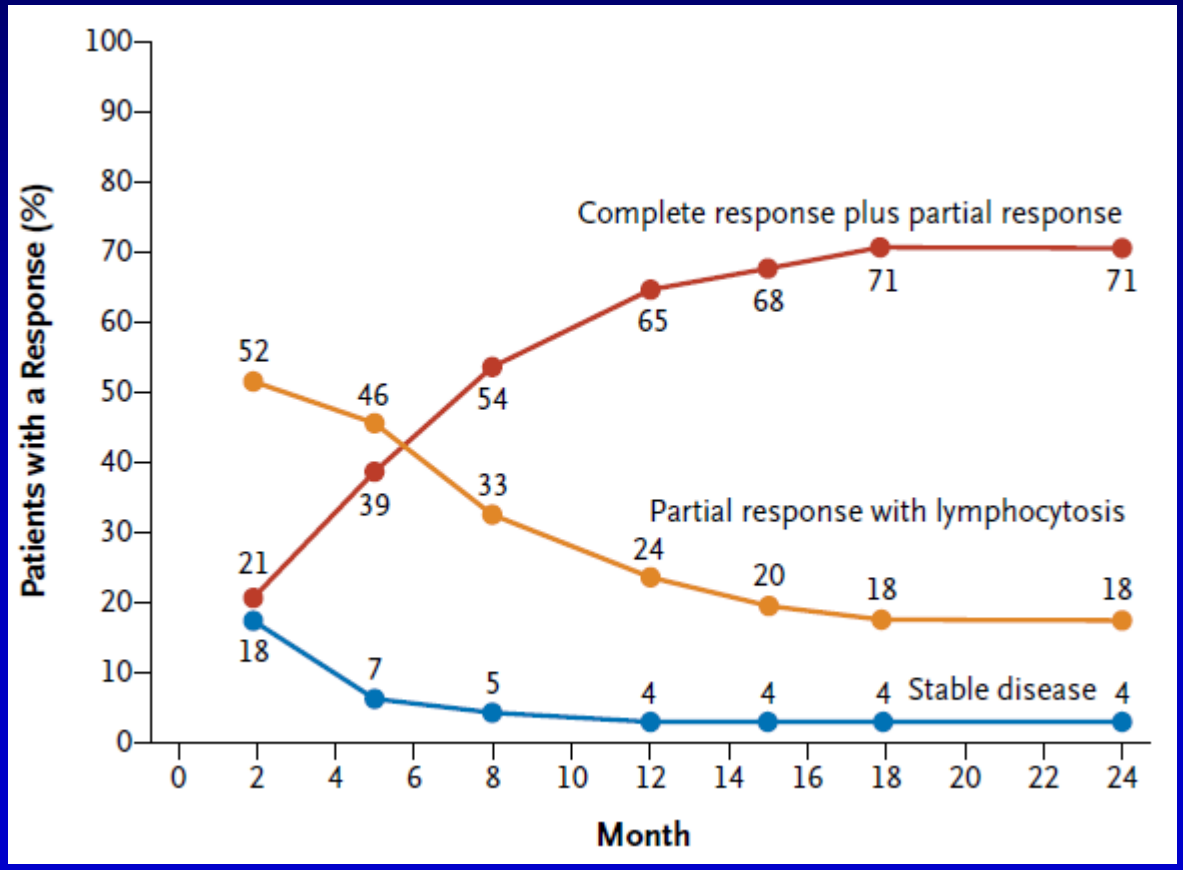
Idelalisib: Bloqueo fosfatidil inositol 3 quinasa

Maffei et al. Journal of Hematology & Oncology (2015) 8:60

ORIGINAL ARTICLE

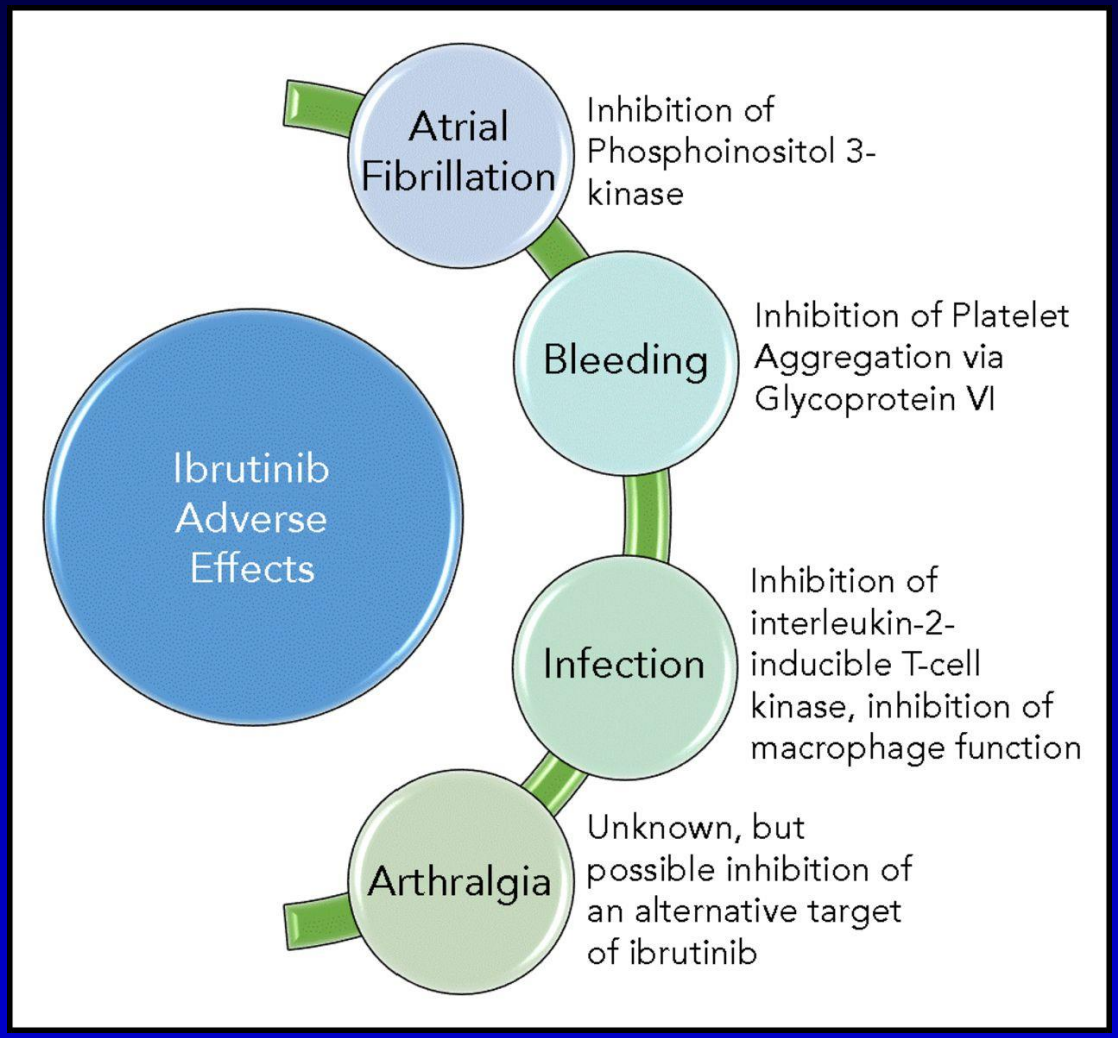
Targeting BTK with Ibrutinib in Relapsed Chronic Lymphocytic Leukemia

John C. Byrd, M.D., Richard R. Furman, M.D., Steven E. Coutre, M.D.,



N Engl J Med. 2013 Jul 4;369(1):32-42.

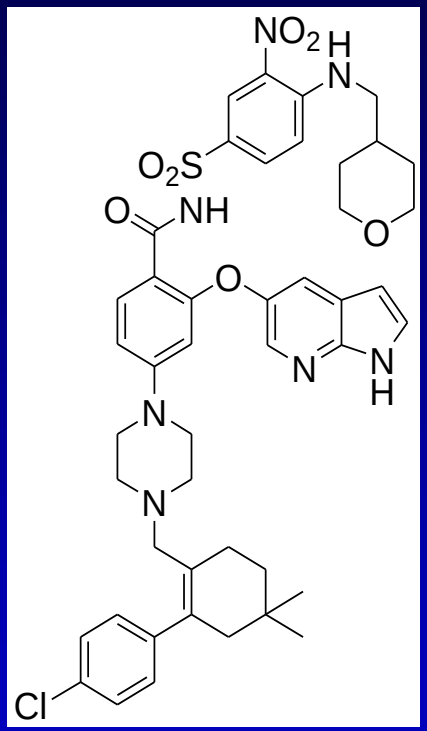
Proposed mechanisms for ibrutinib-related adverse events.



Deborah M. Stephens, and John C. Byrd
Blood 2019;133:1298-1307

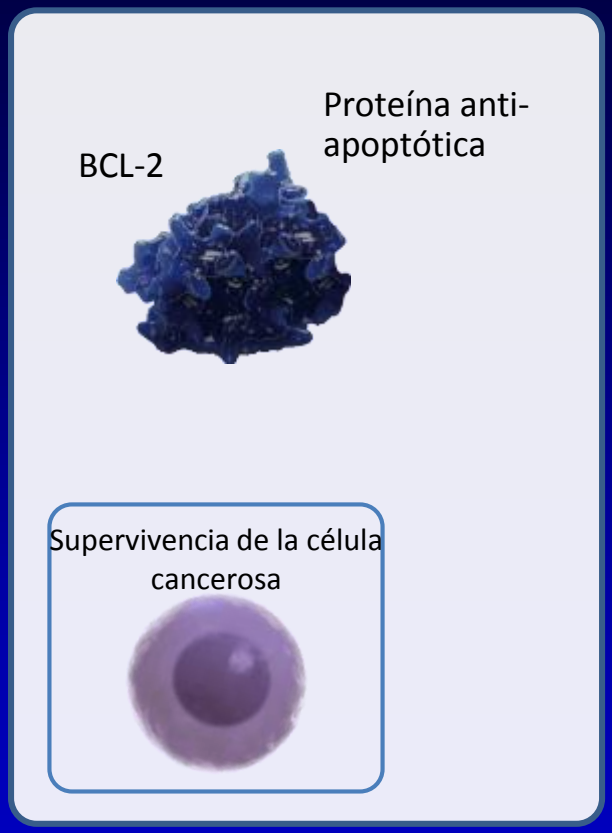
Venetoclax: Descripción General

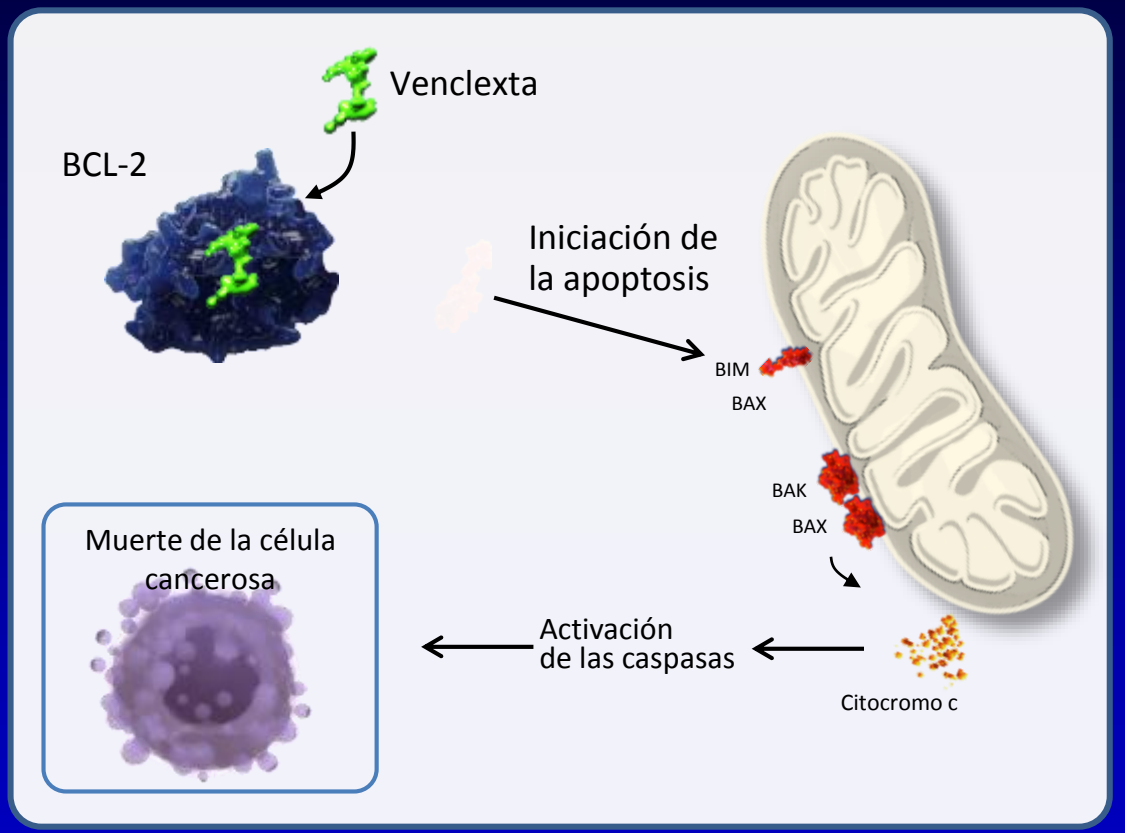
- Inhibidor selectivo y potente de BCL-2 (proteína de linfoma de células B - 2)
- Primer agente en su clase
- Una molécula pequeña, de administración por vía oral en tabletas de liberación inmediata de 10, 50, y 100 mg
- Administración una vez al día
  - Dosis gradual en primeras 4 semanas (20mg, 50mg, 100mg, 200mg)
  - Dosis de 400mg a partir de 5ta semana, hasta progresión de la enfermedad o toxicidad inaceptable



venetoclax

Restauración de la apoptosis a través de la inhibición de BCL-2





La sobreexpresión de BCL-2 permite a las células cancerosas evitar la apoptosis secuestrando las proteínas proapoptóticas.[1-3]

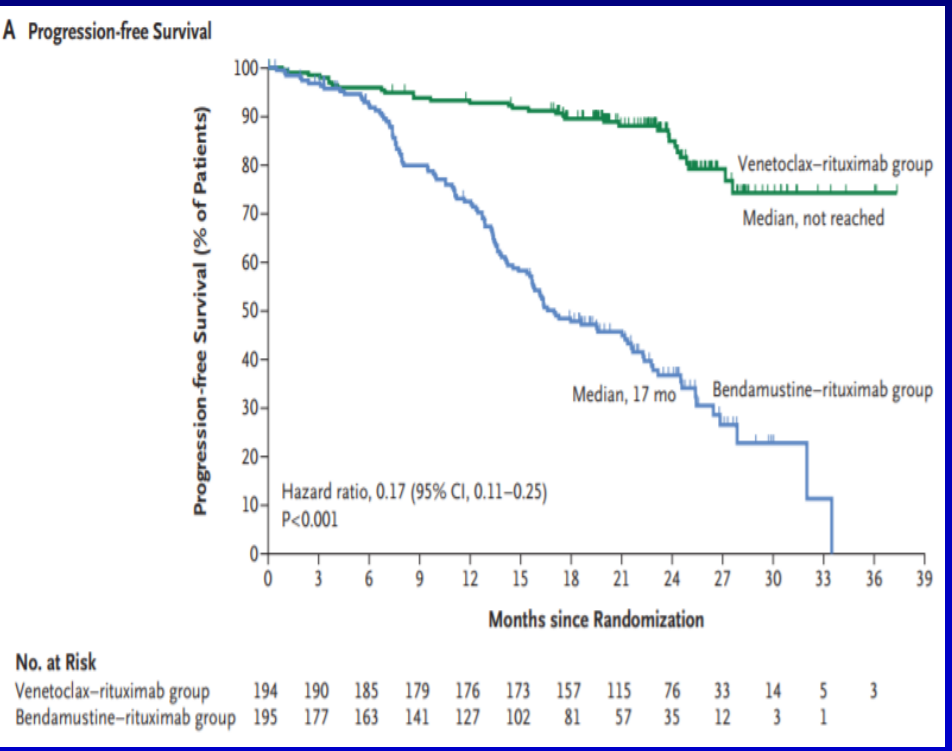
Venclexta se une selectivamente al BCL-2, liberando las proteínas proapoptóticas que inician la muerte celular programada (apoptosis).[4-6]

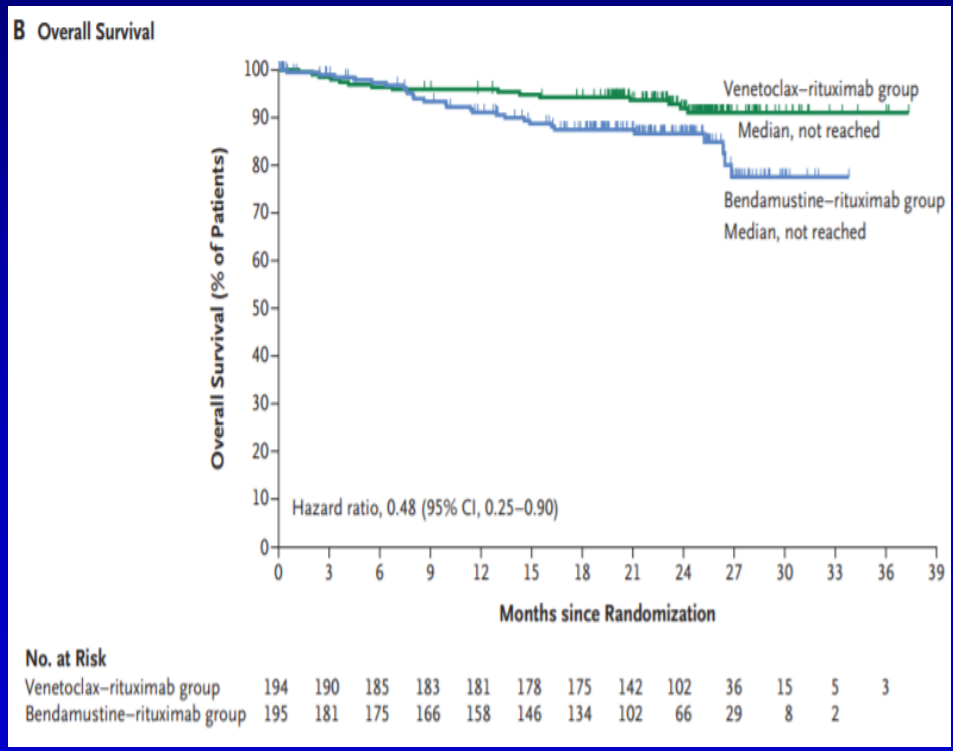
1. Leverson JD, et al. *Cancer*. 2015;7(279). 2. Czabotar, et al. *Nature Reviews* 2014;15:49-63. 3. Plati J, Bucur O, Khosravi-Far R. *Integr Biol (Camb)* 2011;3:279–296. 4. Certo M, et al. *Cancer Cell*. 2006;9(5):351-65. 5. Souers AJ, et al. *Nat Med*. 2013;19(2):202-8. 6. Del Gaizo Moore V et al. *J Clin Invest*. 2007;117(1):112-21.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

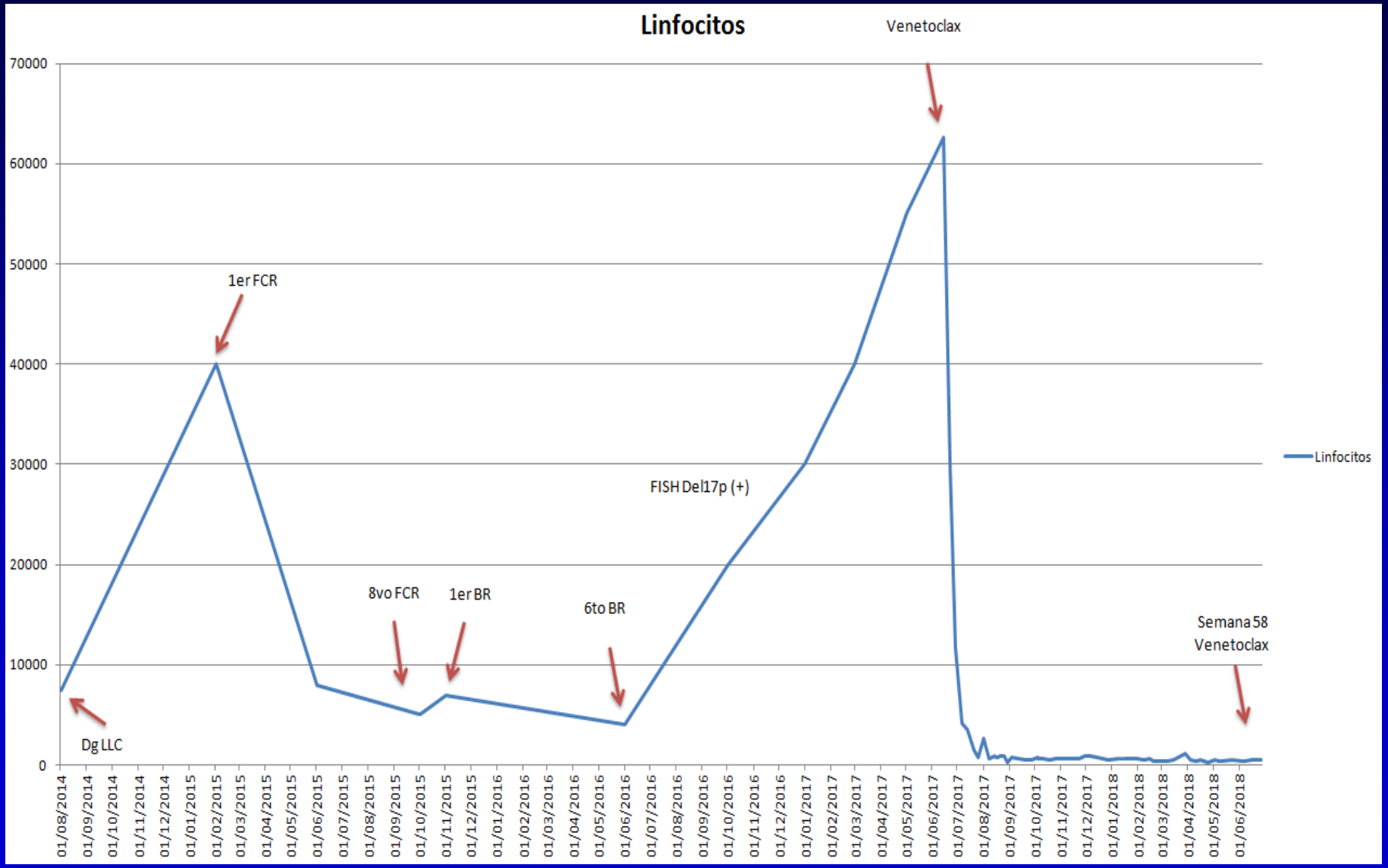
Venetoclax–Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia





- *NEJM med 378;12 nejm.org March 22, 2018*

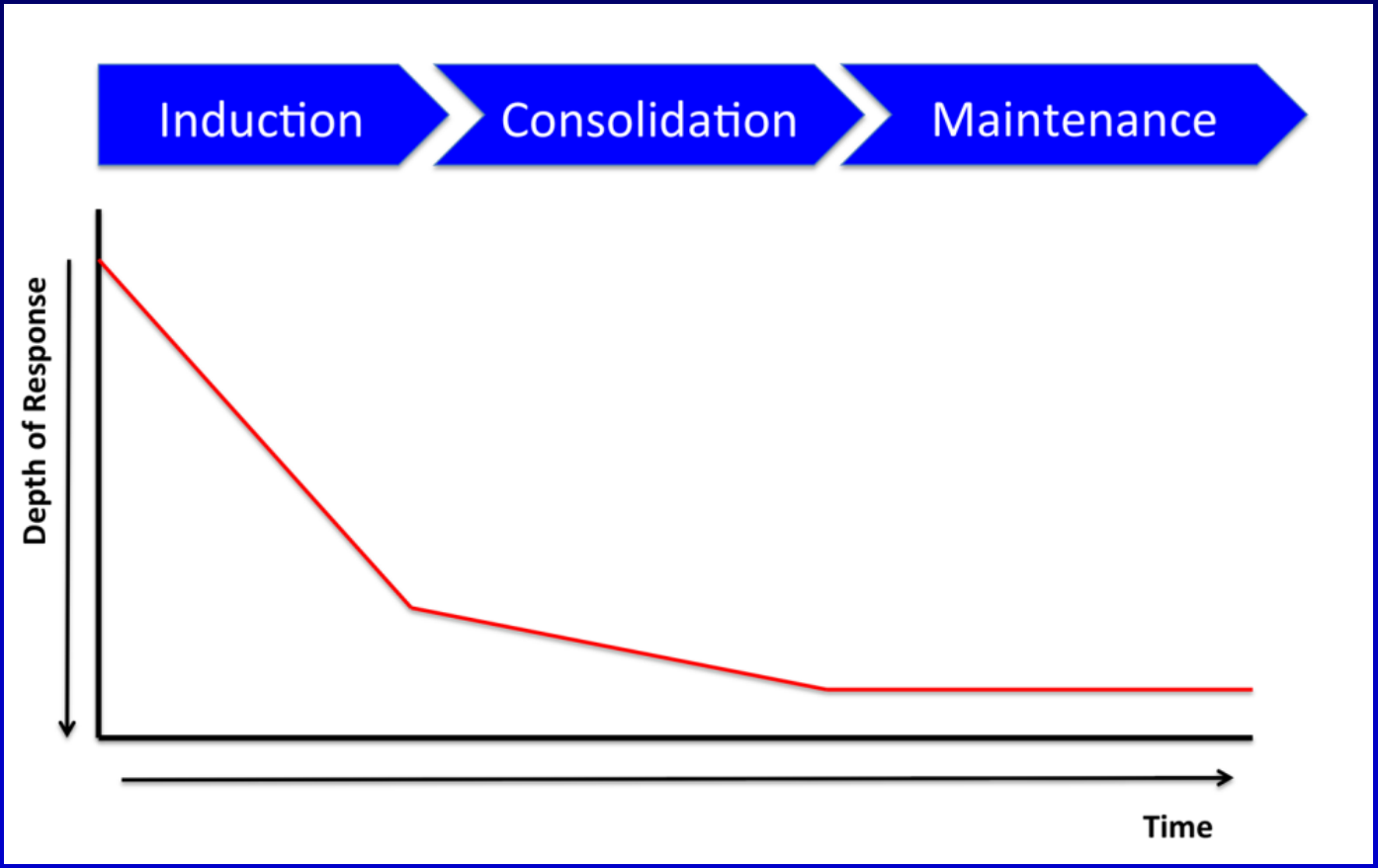
Hombre 72 años, LLC,
FCR - BR – VENETOCLAX. HCUCH 2018



Avances en Mieloma Múltiple

Nuevas estrategias terapéuticas en el tratamiento del MM

Inducción → TAMO → Consolidación →Mantención

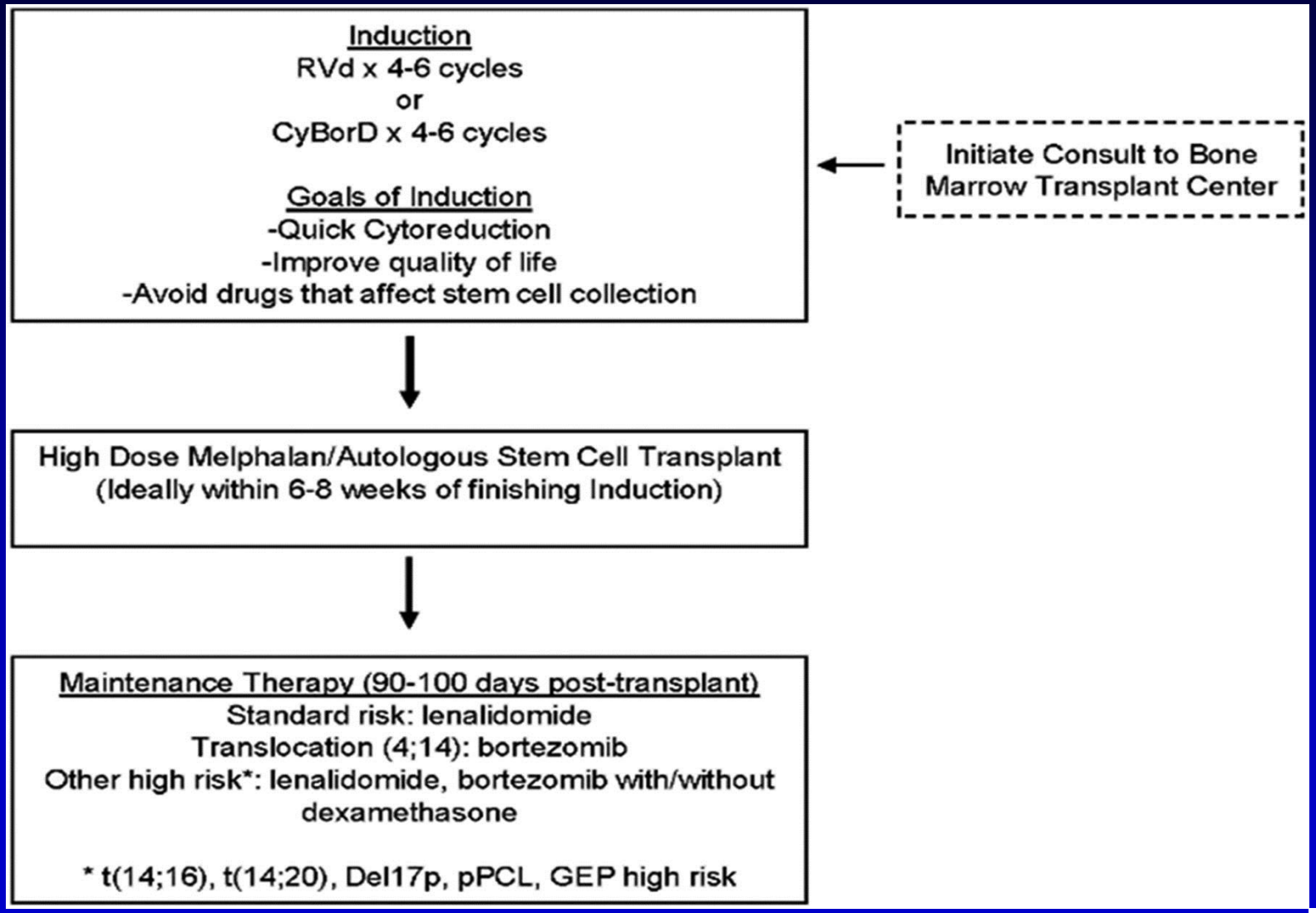


Nuevos blancos y drogas en el tratamiento del Mieloma Múltiple

- Inhibidores de proteosoma
  - Bortezomib
  - Carfilzomib
  - Ixazomib (oral)
- Drogas Inmunomoduladoras
  - Talidomida
  - Lenalidomida
  - Pomalidomida
- Anticuerpos
  - Elotuzumab (anti CS1 /SLAMF7)
  - Daratumumab

Se incluye drogas aprobadas o en estudios clínicos fase II-III

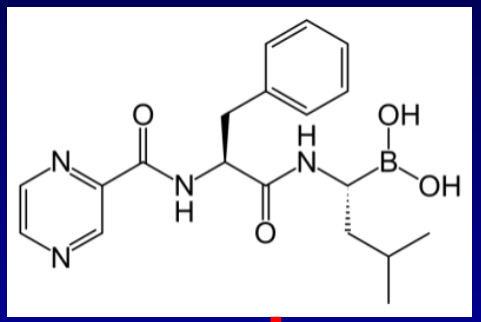
Approach to transplant-eligible newly diagnosed MM. pPCL, primary plasma cell leukemia.

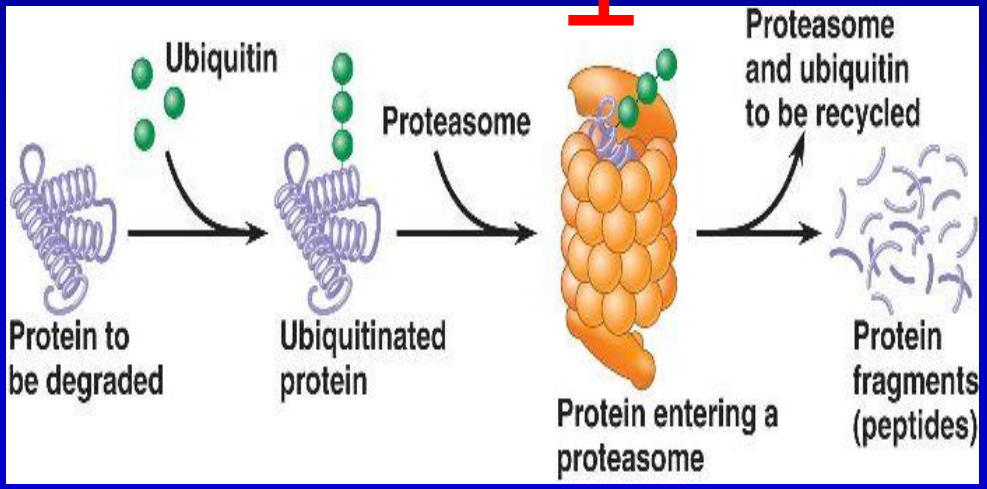


Saad Z. Usmani, and Eric Seifter Hematology 2018;2018:97-102

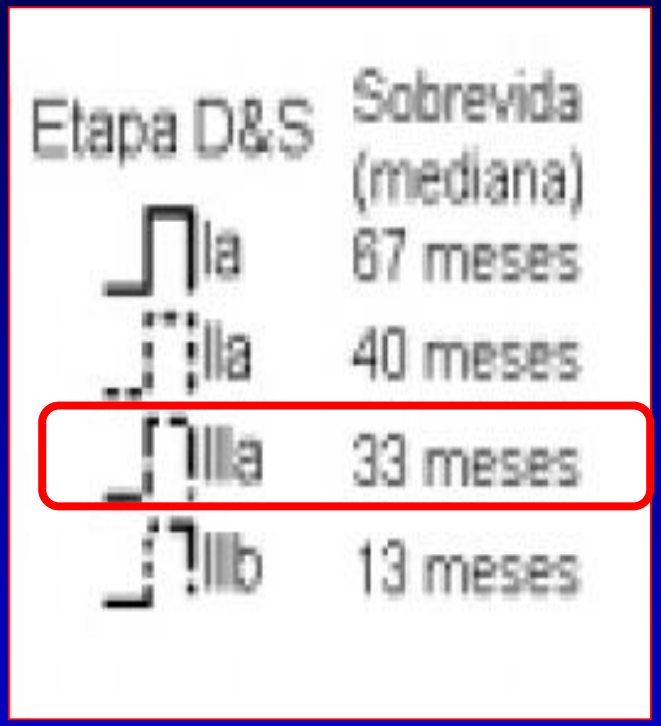
Bortezomib: un inhibidor del proteosoma

Proteínas mal plegadas y paraproteína no son ubiquitinizadas ni destruidas por proteosoma y su acumulación es toxica para la célula





What happened in 10 years in University of Chile Hospital?

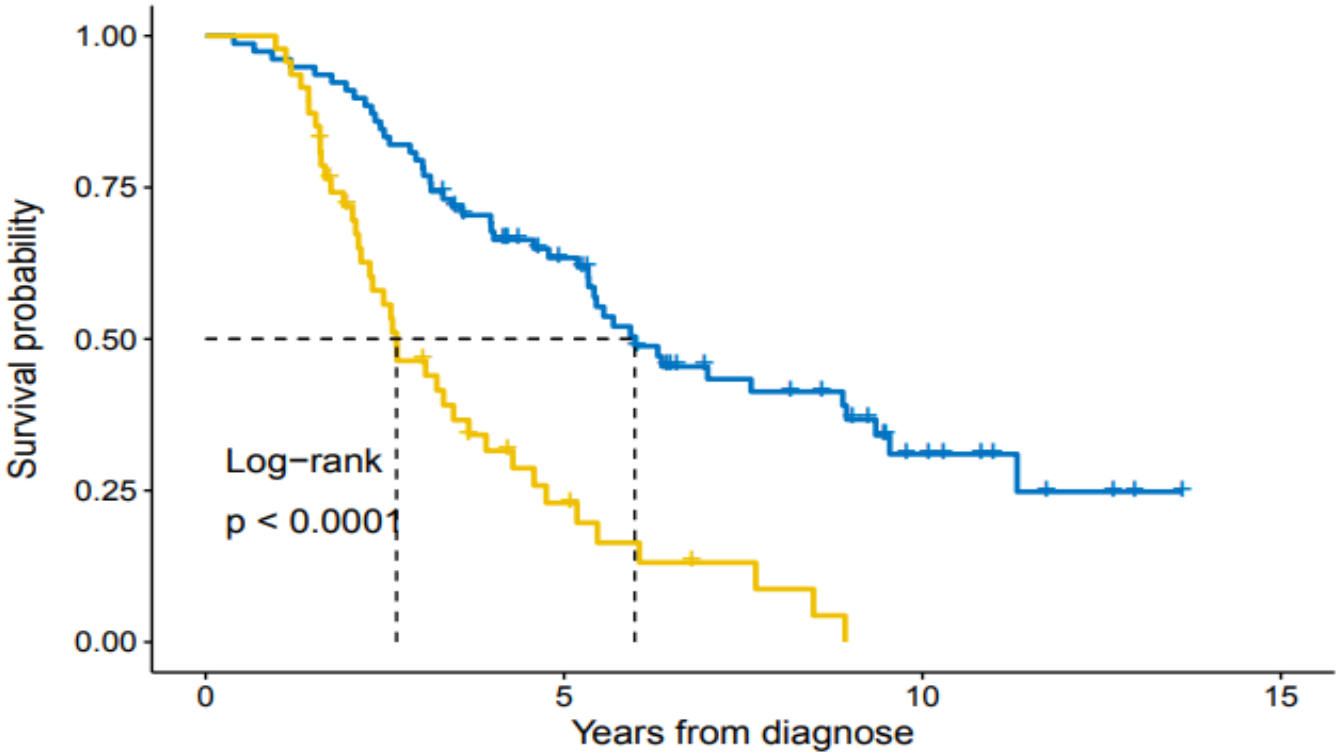


Median Survival (Months)

III a: 66

El uso de inhibidores del proteosoma implico un aumento en la sobrevida en pacientes del HCUCH en los últimos 10 años

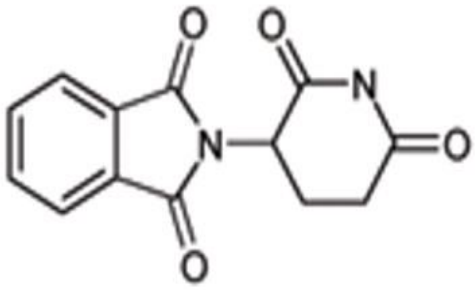
Probabilidad de sobrevida en 2 hospitales de la Región Metropolitana



-Azul: con utilización de nuevos tratamientos para mieloma

IMIDs

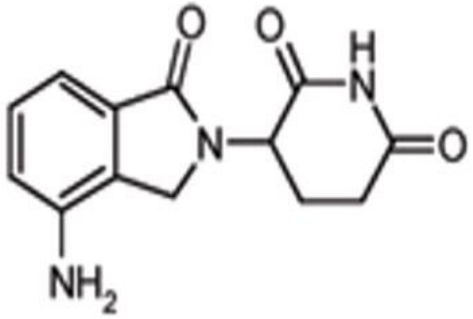
Talidomida, Lenalidomida, Pomalidomida



Thalidomide

100-200 mg/d

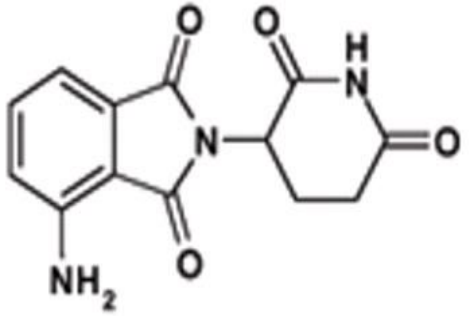
Neuropathy
Constipation
Sedation
DVT



Lenalidomide

15-25 mg/d

Myelosuppression
Skin rash
DVT

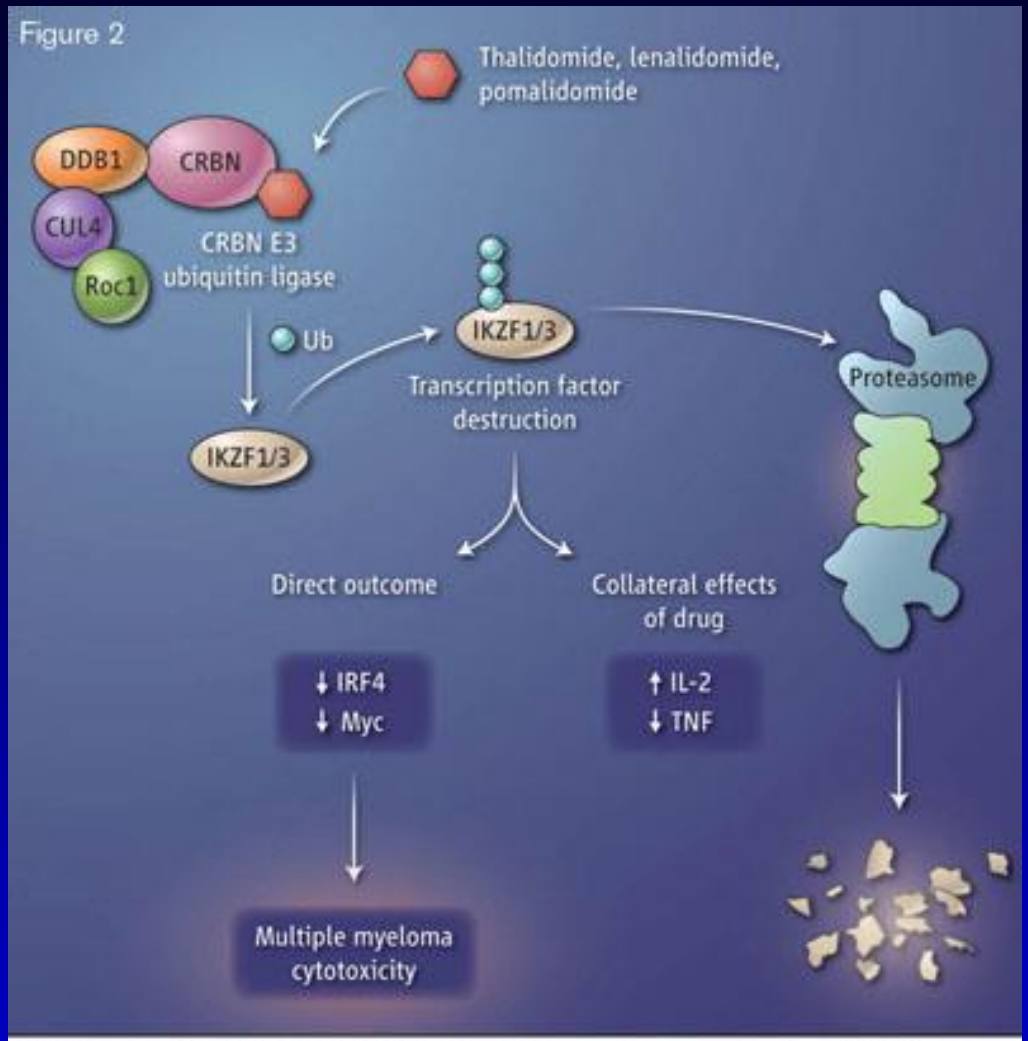


Pomalidomide

1-4 mg/d

Myelosuppression
Fatigue
Neuropathy

Hematology 2009



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.

Inmunoterapia en mieloma:

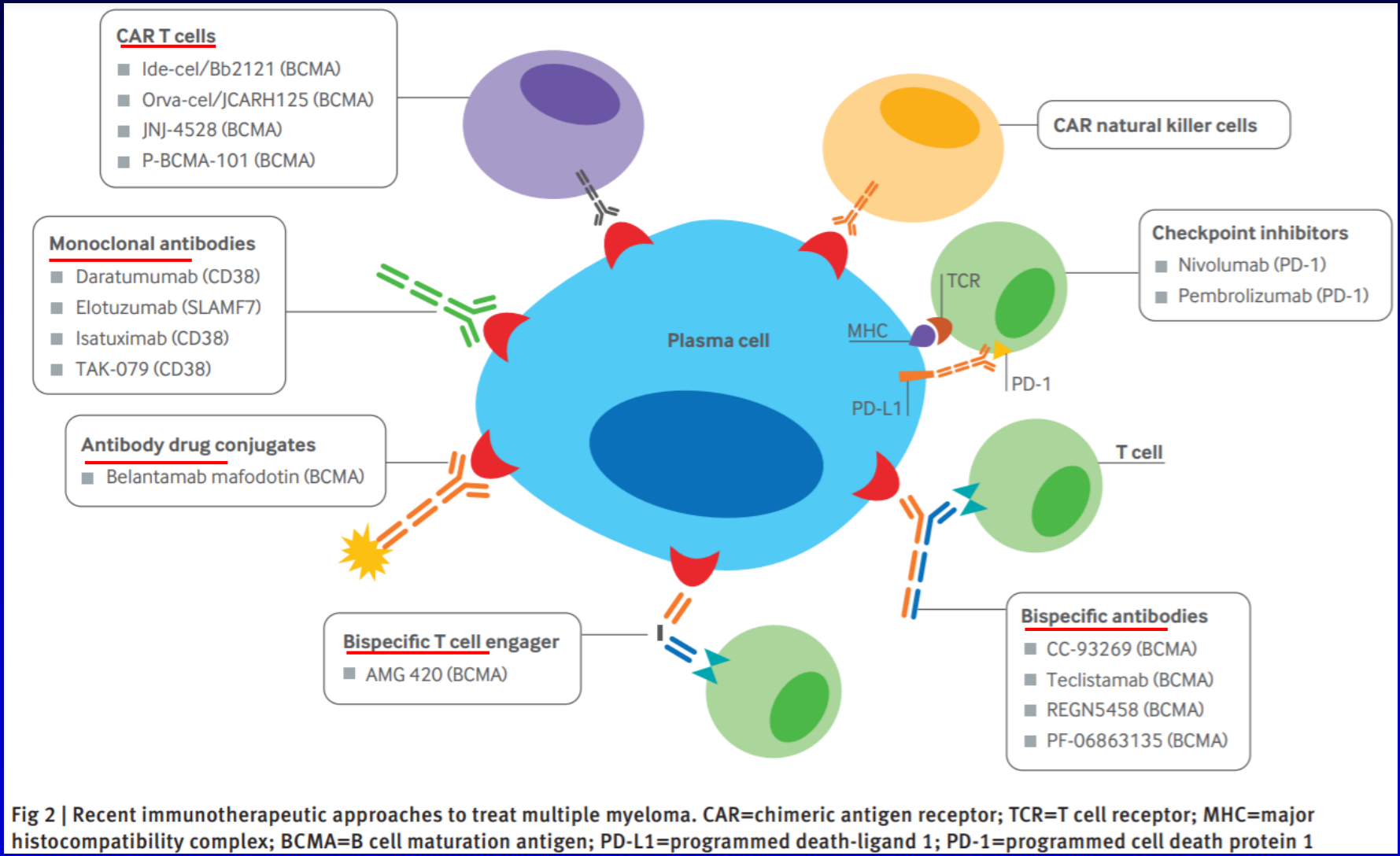
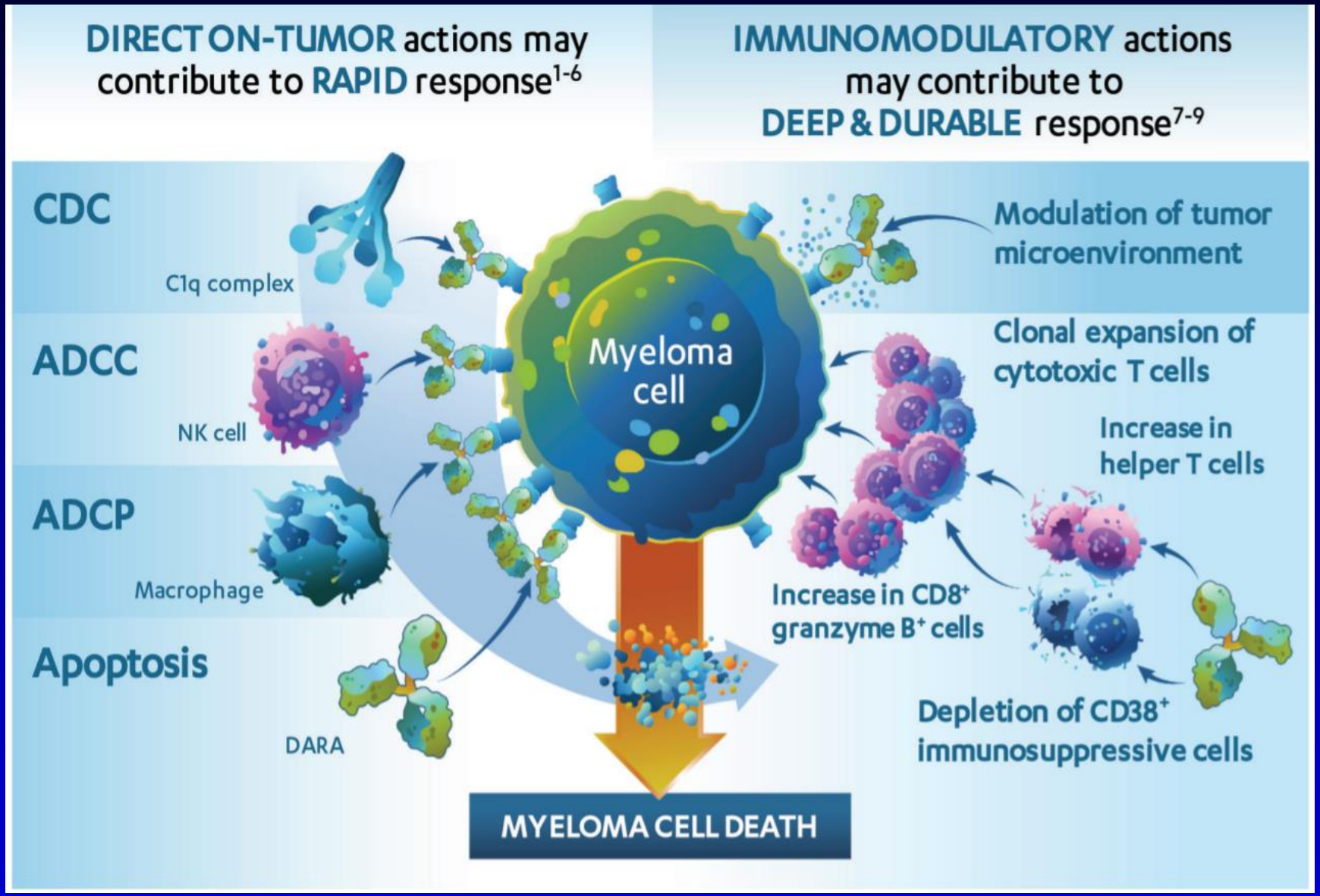


Fig 2 | Recent immunotherapeutic approaches to treat multiple myeloma. CAR=chimeric antigen receptor; TCR=T cell receptor; MHC=major histocompatibility complex; BCMA=B cell maturation antigen; PD-L1=programmed death-ligand 1; PD-1=programmed cell death protein 1

- *Emerging immunotherapies in multiple myeloma. BMJ 2020;370:m3176*



- *Emerging immunotherapies in multiple myeloma. BMJ 2020;370:m3176*

Original Article

Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma

Meletios A. Dimopoulos, M.D., Albert Oriol, M.D., Hareth Nahi, M.D., Jesus San-Miguel, M.D., Nizar J. Bahlis, M.D., Saad Z. Usmani, M.D., Neil Rabin, M.B., B.S., Ph.D., Robert Z. Orlowski, M.D., Mieczyslaw Komarnicki, M.D., Kenshi Suzuki, M.D., Torben Plesner, M.D., Sung-Soo Yoon, M.D., Dina Ben Yehuda, M.D., Paul G. Richardson, M.D., Hartmut Goldschmidt, M.D., Donna Reece, M.D., Steen Lisby, M.D., Nushmia Z. Khokhar, M.D., Lisa O'Rourke, M.S.N., Christopher Chiu, Ph.D., Xiang Qin, M.S., Mary Guckert, M.S.N., Tahamtan Ahmadi, M.D., Philippe Moreau, M.D., for the POLLUX Investigators

N Engl J Med
Volume 375(14):1319-1331
October 6, 2016

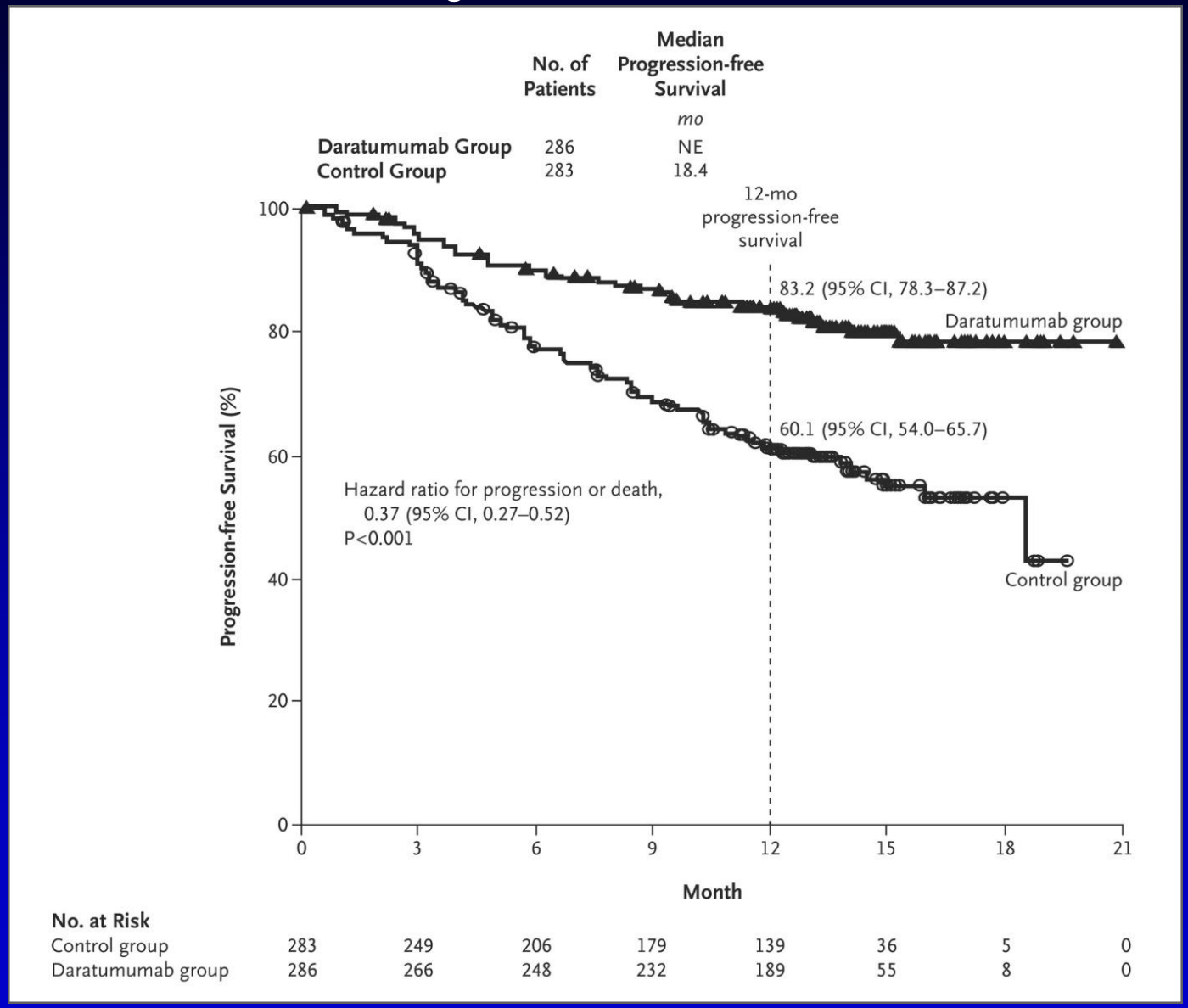
The NEW ENGLAND JOURNAL of MEDICINE

Study Overview

- The addition of daratumumab to lenalidomide and dexamethasone resulted in superior response rate and progression-free survival, as compared with lenalidomide and dexamethasone alone, at a cost of more frequent neutropenia and infusion reactions.

The NEW ENGLAND JOURNAL of MEDICINE

Progression-free Survival.



Dimopoulos MA et al. N Engl J Med 2016;375:1319-1331

Conclusions

- The addition of daratumumab to lenalidomide and dexamethasone significantly lengthened progression-free survival among patients with relapsed or refractory multiple myeloma.
- Daratumumab was associated with infusion-related reactions and a higher rate of neutropenia than the control therapy.

The NEW ENGLAND JOURNAL of MEDICINE

Original Article

Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma

María-Victoria Mateos, M.D., Meletios A. Dimopoulos, M.D., Michele Cavo, M.D., Kenshi Suzuki, M.D., Andrzej Jakubowiak, M.D., Stefan Knop, M.D., Chantal Doyen, M.D., Paulo Lucio, M.D., Zsolt Nagy, M.D., Polina Kaplan, M.D., Ludek Pour, M.D., Mark Cook, M.D., Sebastian Grosicki, M.D., Andre Crepaldi, M.D., Anna M. Liberati, M.D., Philip Campbell, M.D., Tatiana Shelekhova, M.D., Sung-Soo Yoon, M.D., Genadi Iosava, Ph.D., Tomoaki Fujisaki, M.D., Mamta Garg, M.D., Christopher Chiu, Ph.D., Jianping Wang, Ph.D., Robin Carson, M.D., Wendy Crist, B.A., William Deraedt, M.Sc., Huong Nguyen, M.D., Ming Qi, M.D., Jesus San-Miguel, M.D., for the ALCYONE Trial Investigators

N Engl J Med
Volume 378(6):518-528
February 8, 2018

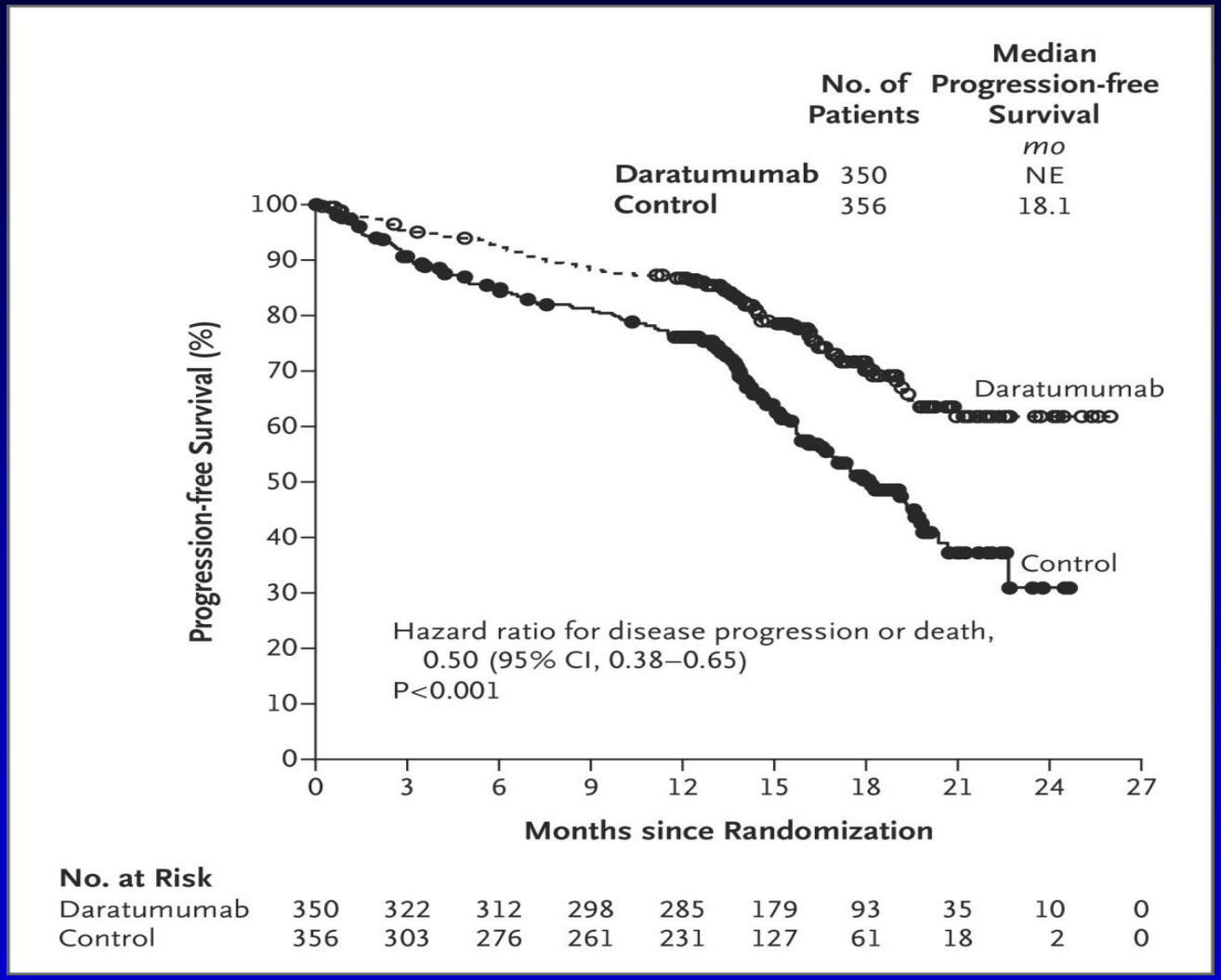
The NEW ENGLAND JOURNAL of MEDICINE

Study Overview

- In patients with newly diagnosed multiple myeloma who were ineligible for stem-cell transplantation, the addition of daratumumab to bortezomib, melphalan, and prednisone increased progression-free survival and the response rate at the cost of an increase in infections.

The NEW ENGLAND JOURNAL of MEDICINE

Progression-free Survival.



Mateos M-V et al. N Engl J Med 2018;378:518-528

The NEW ENGLAND JOURNAL of MEDICINE

Conclusions

- Among patients with newly diagnosed multiple myeloma who were ineligible for stem-cell transplantation, daratumumab combined with bortezomib, melphalan, and prednisone resulted in a lower risk of disease progression or death than the same regimen without daratumumab.
- The daratumumab-containing regimen was associated with more grade 3 or 4 infections.

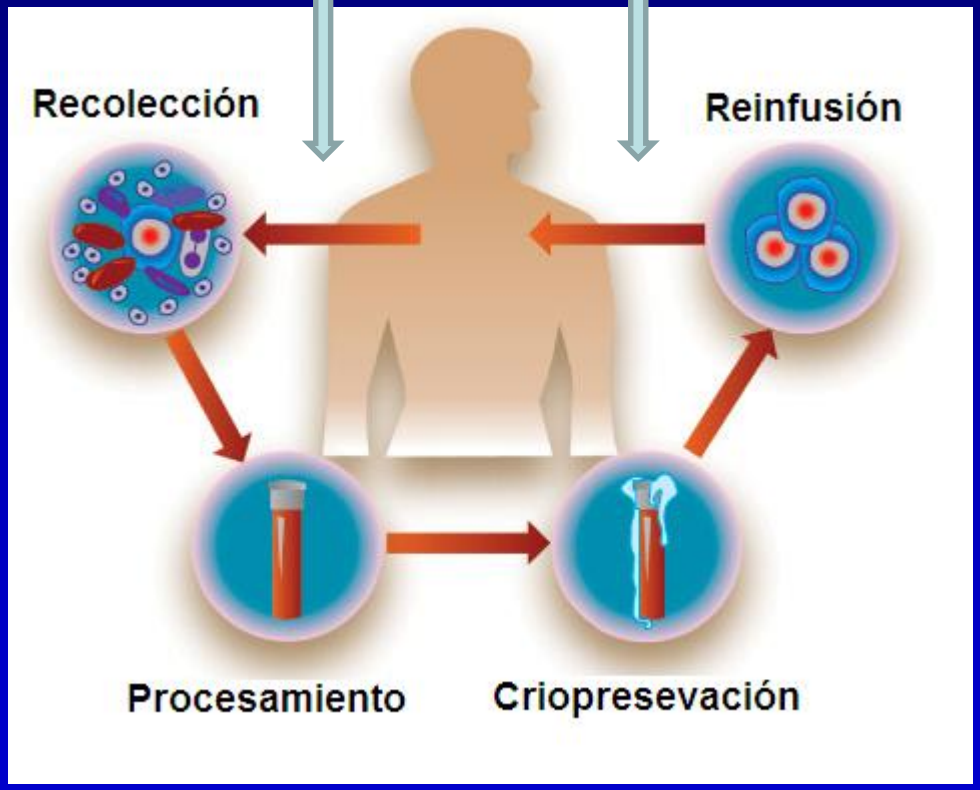
The NEW ENGLAND JOURNAL of MEDICINE

Trasplante Autólogo de Médula Ósea (TAMO)

QMT Inducción

QMT Movilización

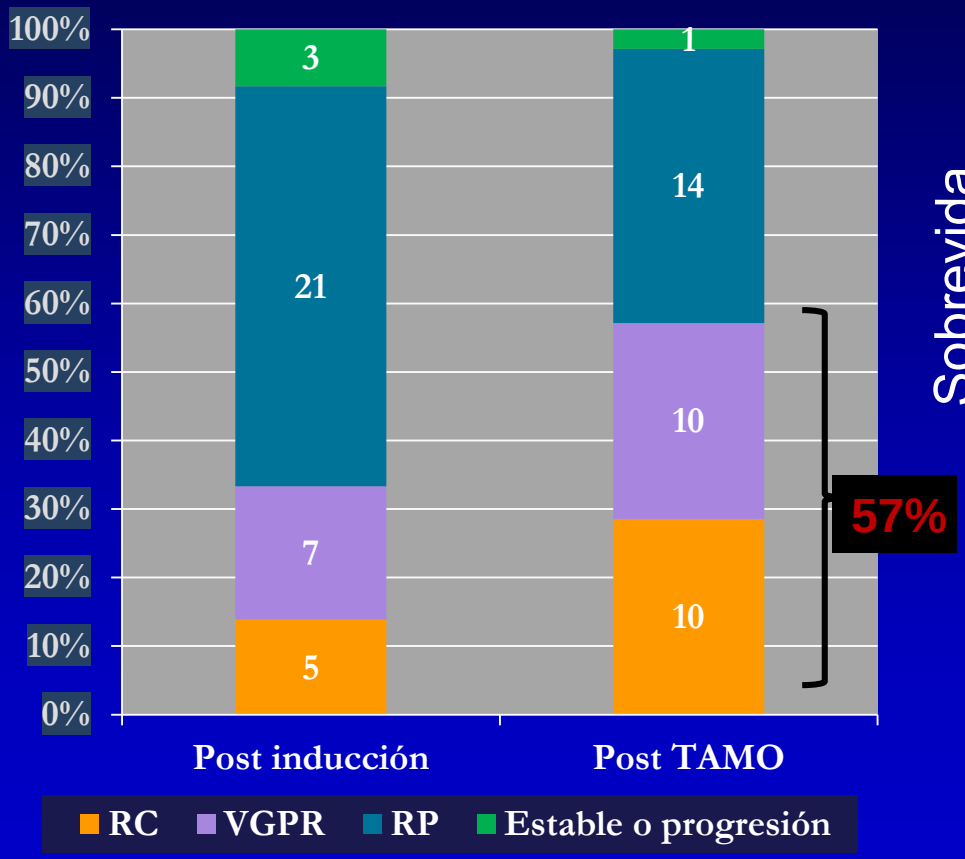
QMT Mieloablativa

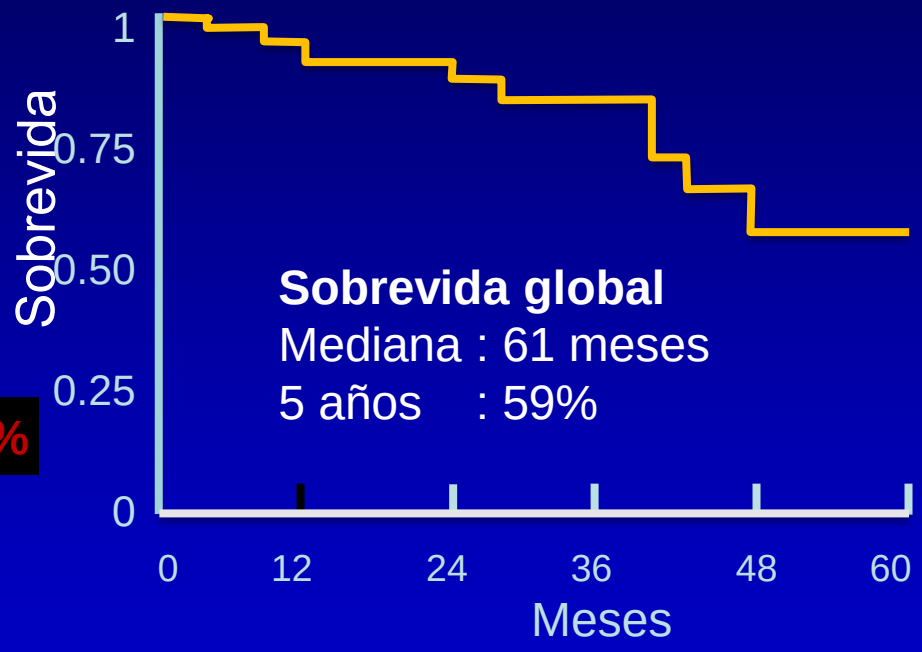


Trasplante Autólogo

Experiencia HCUCh

n:36





Conte G, Araos D, Alfaro J, González N, Aravena P, Torres C, Figueroa G. Trasplante autólogo de médula ósea en MM. Experiencia 1994-2008 en el HCUCH. XVI Congreso Chileno de Hematología. 24-27 Septiembre 2008. Coquimbo

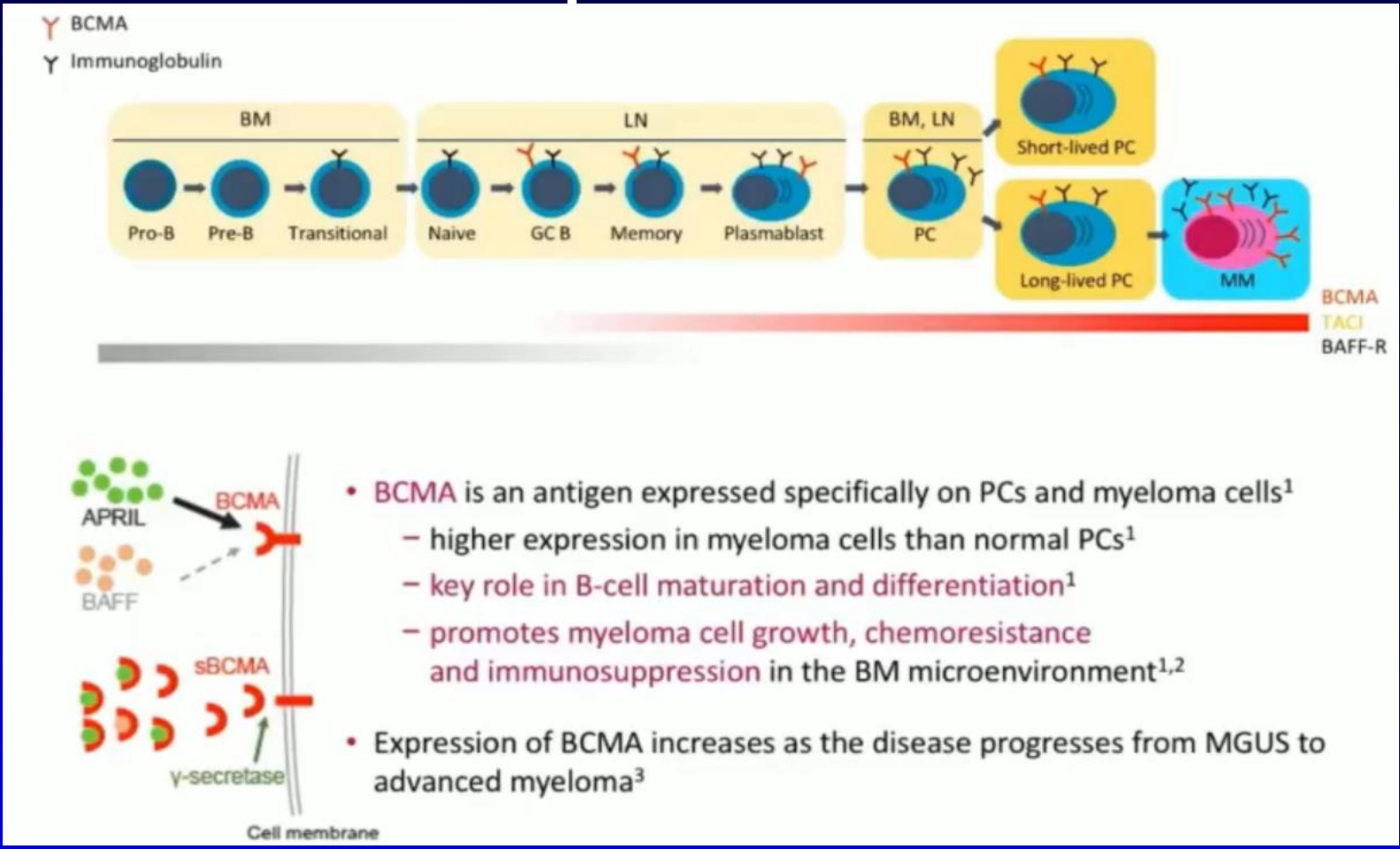
Personalized therapy in multiple myeloma according to patient age and vulnerability: a report of the European Myeloma Network (EMN)

Risk factors
• Age over 75 years • Mild, moderate or severe frailty: patients needing help for household tasks and personal care* • Comorbidities: cardiac dysfunction pulmonary dysfunction hepatic dysfunction renal dysfunction

GO-GO	*MODERATE-GO*	*SLOW-GO*
No risk factors ↓ DOSE LEVEL 0	At least one risk factor ↓ DOSE LEVEL −1	At least one risk factor plus occurrence of grade 3-4 non-hematologic AE ↓ DOSE LEVEL −2

Blood 2011-06-358812

Inmunoterapia en Mieloma Múltiple: BCMA

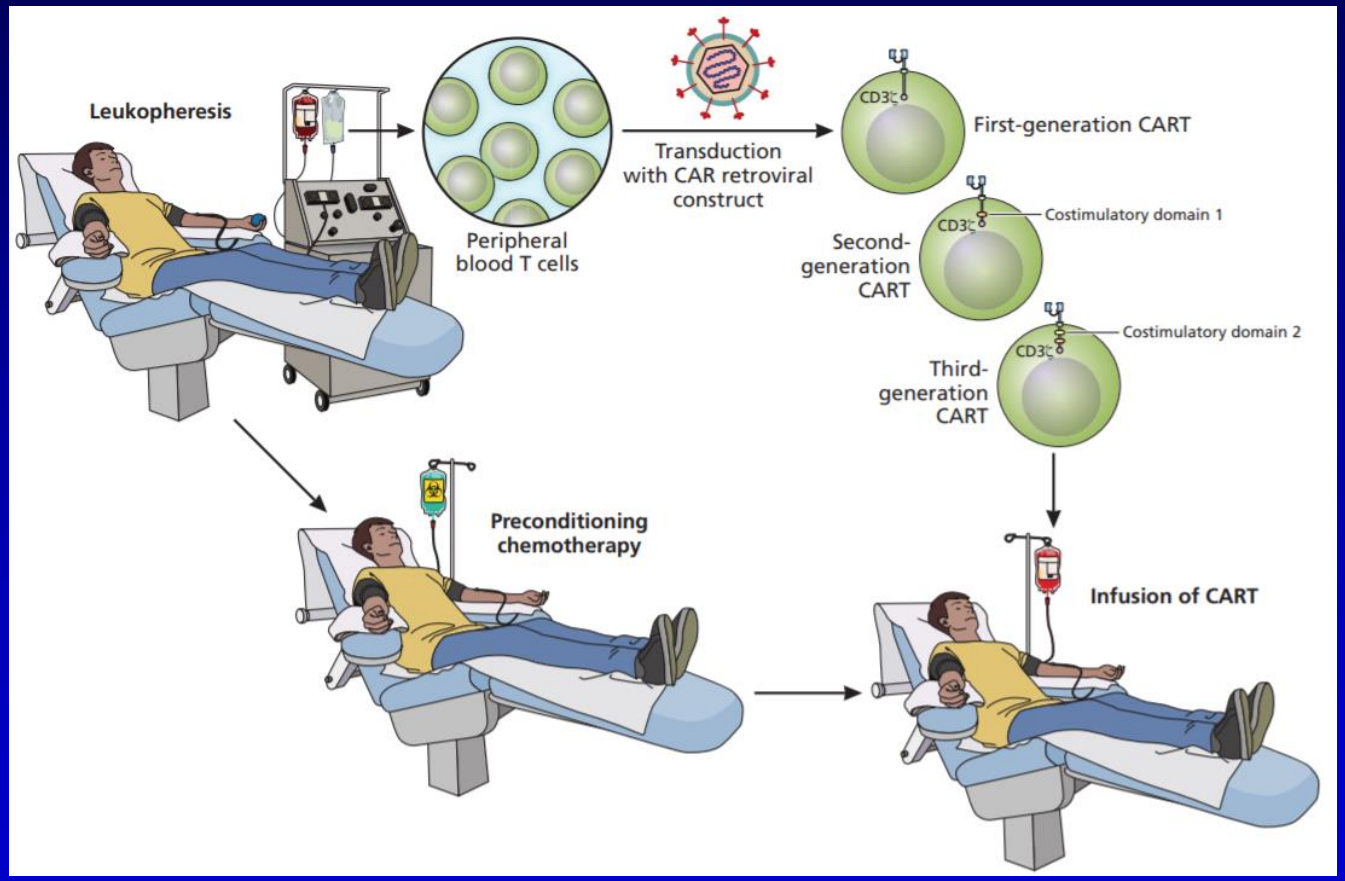


Target de tratamientos inmunológicos en mieloma: Ac conjugados con drogas, BITEs y CART- Cells

CAR T- cell dirigidos a BCMA:

Linfocitos se cultivan con retrovirus que incorpora DNA que codifica para un receptor quimérico dirigido contra un antígeno tumoral especifico (CAR)

Linfocitos del paciente se extraen por aféresis



CART de 1°, 2° y 3° generación: Incorporan receptor quimérico y moléculas co-estimuladoras

CART se infunden en paciente y montan respuesta anti tumoral

ASH-SAP. Seventh edition. 2019

Terapias dirigidas a BCMA:
10 estudios en curso

Table 2 | Summary of major multicenter clinical trials investigating multiple myeloma treatments*

Treatment agent, trial (No of participants)	Treatment type	Median No of prior lines of treatment	Dose range	Overall response rate (%)	Median progression free survival (months)	Cytokine release syndrome (%), any grade (grades 3-5)	Neurotoxicity (%), any grade (grades 3-5)
Bb2121 (ide-cel),[99] KarMMa (n=128)	CAR T cell	6	150-450×10^6 cells	73	8.8	84 (6)	18 (3)
JCARH125 (orva-cel),[100 101] EVOLVE (n=62)	CAR T cell	6	300-600×10^6 cells	92	Not reached	89 (3)	13 (3)
LCAR-B38M,[102-105] LEGEND-2 (n=57)	CAR T cell	3	0.07-2.1×10^6 cells/kg	88	19.9	90 (7)	2
JNJ-4528,[106 107] CARTITUDE-1 (n=29)	CAR T cell	5	0.52-0.89×10^6 cells/kg	100	Not reached	93 (7)	10 (3)
P-BCMA-101,[108] PRIME (n=19)	CAR T cell	6	50-1143×10^6 cells	63 (100†)	9.5	10 (0)	5 (5)
AMG 420[109] (n=42)	Bispecific antibody (BiTE)	3.5	0.2-800 µg/day, week infusions every 6 weeks, 10 cycles	31 (70‡)	Not reached	38 (2)	7 (7)
CC-93269[110] (n=30)	Bispecific antibody	5	0.15-10 mg weekly for 3 cycles, biweekly for 3 cycles then monthly	43 (89§)	Not reached	77 (3)	0
Teclistamab[111] (n=78)	Bispecific antibody (DuoBody)	6	0.3-720 µg/kg weekly	31 (67¶)	Not reached	56 (0)	8 (3)
Belantamab mafodotin,[112] DREAMM-2 (n=196)	Antibody drug conjugate	7	2.5 mg/kg every 3 weeks	31	2.9	Not applicable	Not applicable
		6	3.4 mg/kg every 3 weeks	34	4.9	Not applicable	Not applicable
Belantamab mafodotin and bortezomib,[113] DREAMM-6 (n=18)	Antibody drug conjugate	3	2.5 mg/kg every 3 weeks	78	Not reached	Not applicable	Not applicable

BiTE=bispecific T cell engager.
*This list is not comprehensive.
†P-BCMA-101 overall response rate at highest reported dose of 857×10^6 cells for 3 patients.
‡AMG 420 overall response rate at maximum tolerated dose of 400 µg/day for 10 patients.
§CC-93269 overall response rate at highest reported dose of 10 mg for 9 patients.
¶Teclistamab overall response rate at highest reported dose of 270 µg/kg for 12 patients.

- *Emerging immunotherapies in multiple myeloma. BMJ 2020;370:m3176*

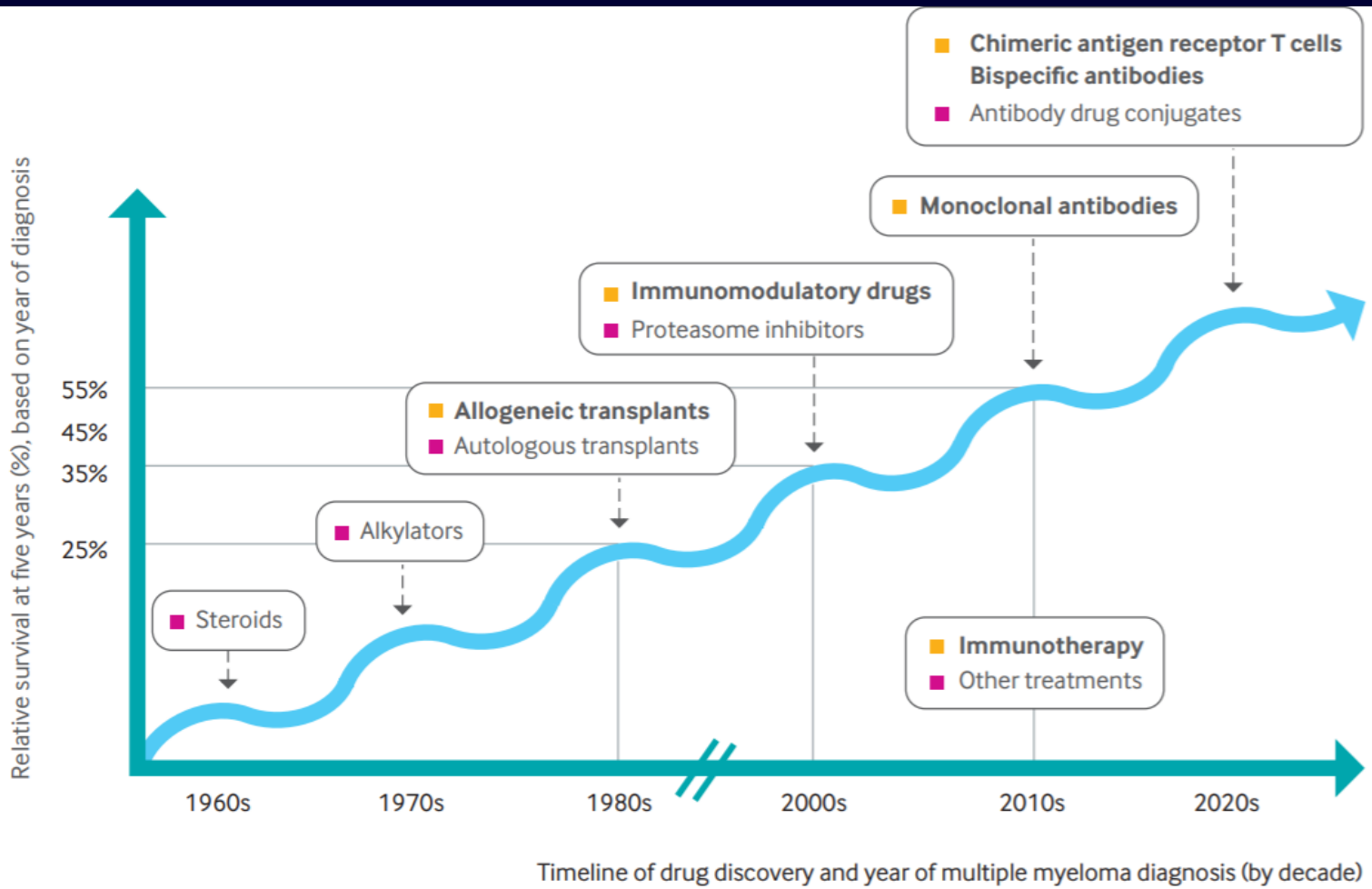


Fig 1 | Multiple myeloma treatments—timeline of drug discovery and five year relative survival (using data from the Surveillance, Epidemiology, and Ends Results program).[6] Data for year of diagnosis and relative survival are: 1975, 26.5% (observed); 1980, 26.0% (observed); 1985, 27.4% (observed); 1990, 29.9% (observed); 1995, 33.5% (observed); 2000, 34.6% (observed); 2005, 47.1% (observed); 2010, 53.6% (observed); 2015, 55.3% (modelled)

- *Emerging immunotherapies in multiple myeloma. BMJ 2020;370:m3176*

CONCLUSION

Desde una fase en que el tratamiento de neoplasias hematológicas utilizaba la quimioterapia y anticuerpos monoclonales, se ha modificado a una etapa con diferentes mecanismos de acción de anticuerpos, sumado a terapias dirigidas a alteraciones moleculares especificas. Esto ha significado una mejor calidad de vida, con mayor PFS y OS.

La asociación de anticuerpos con la terapia molecular de precisión nos llevara a dejar de lado la quimioterapia convencional

El futuro esta en aumentar la inmunidad antitumoral e ir paulatinamente disminuyendo la toxicidad de la quimioterapia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