Linfocitosis / Inversión de Formula
LLC – Linfomas

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Fundaleu

Linfocitosis

- **Linfocitosis** corresponde a ALC >4000 linfocitos/microL para adultos
- **Linfocitopenia** corresponde a ALC <1000 linfocitos/microL para adultos

- **Subpoblaciones de Linfocitos** – Las proporciones normales de linfocitos Normal T, Linfocitos B y natural killer (NK) en sangre periférica son:
  - T cells (CD3+) – 60 to 80 %
  - B cells (CD20+) – 10 to 20 %
  - NK cells (CD56+) – 5 to 10 %

- **Subpoblaciones de linfocitos T**– Las proporciones normales de linfocitos T en sangre periférica son :
  - Helper/inducer T cells (CD4+) – 60 to 70 %
  - Suppressor/cytotoxic T cells (CD8+) – 30 to 40 %

Linfocitosis - Causas

- **Cuadros virales** (Mononucleosis, HIV, CMV, Hepatitis mas comunes)
  - Rubeola, paperas, influenza
- Cuadro de Hipersensiblidad por drogas
- Asplenia (post-esplenectomía)
- Timoma
- **Linfocitosis policlonal B persistente**
  - Síndrome de linfocitosis policlonal B persitente (PPBL) sido descripta en mujeres jóvenes-adultas fumadoras

- **Clonales**
  - Linfocitosis B monoclonal
  - Leucemia Linfática Crónica
  - LGL leucemia a linfocitos grandes granulares T
  - Linfomas no Hodgkin (Folicular, Manto, Marginal/esplénico, tricoleucemia, síndrome de Sezary)
  - Leucemia Linfoblastica Aguda

Evaluación de Inversión de la formula en la practica clínica

Evaluar:	
	Si el paciente tiene leucocitosis
	Evaluar frotis !!
	Si son linfocitos maduros – sombras de Gumprecht?
	Evaluar adenopatías periféricas
	Evaluar otras citopenias
	Evaluar LDH como marcador de proliferación hematológica
	Podría realizar estudio de imágenes: ecografía o panTC
	No esta indicado el PET

Evaluación de Inversión de la formula en la practica clínica

La mayoría de los pacientes que evaluamos con inversión de la formula (sin leucocitosis, citopenias, adenopatías o síntomas B) son de causa benigna

Ante alguna sospecha de enfermedad hematológica estaría indicado la citometría de flujo (panel linfoproliferativo)

La biopsia de Medula Ósea ha perdido valor en la evaluación de la inversión de la formula

Podría optarse por control evolutivo si solo presenta inversión de la formula

Que pacientes requieren evaluación por citometría de flujo con Inversión de la formula

Indicado si:

- En forma urgente si hay sospecha leucemia aguda (células inmaduras – blastos)
- > 10.000 linfocitos/microL valores absolutos
- Linfocitosis progresiva
- Citopenias
- Esplenomegalia
- Adenopatías
- Ante la duda controlar

Diagnóstico hematológico mas frecuente: Leucemia Linfática Crónica (LLC)

- LLC: Más de 5 x 10^9 linfocitos/L (5000/uL)
- Citometría de Flujo:
  - Antígenos de superficie B (CD19, CD20^{débil} y CD23)
  - Expresión débil de Ig de superficie (IgM o IgD) con expresión de cadenas kappa o lambda
  - Co-expresión de CD5 (antígeno de superficie de Linfo T)

* Biopsia de Médula ósea no se requiere al diagnóstico pero si previo a comenzar el tratamiento

* La presencia de < de 5000/uL linfocitos B sin adenopatías se define hoy como linfocitosis B monoclonal (MBL)

J.G.Gribben. Blood, 14 January 2010. Volumen 115. Number 2.

This sentinel description of chronic lymphocytic leukemia (CLL) by William Dameshek is widely quoted in the literature. In this paper, which followed the identification of B lymphocytes in 1965, Dameshek provided a summary of the major pathologic and clinical features of the disease that manifest at different times during its progression. Although he lacked the modern molecular biology tools available today, Dameshek correctly described many aspects of CLL. He postulated that CLL lymphocytes are clonal (actually "neoplastic cells"), that they are immunologically incompetent, and that they have prolonged survival, leading to accumulation in the tissues. Although our understanding of CLL-associated immune suppression has extended since this article was published, this paper put forth hypotheses that were subsequently validated by others.

BLOOD *The Journal of Hematology*

APRIL, 1967 VOL. XXIX, NO. 4, PART II

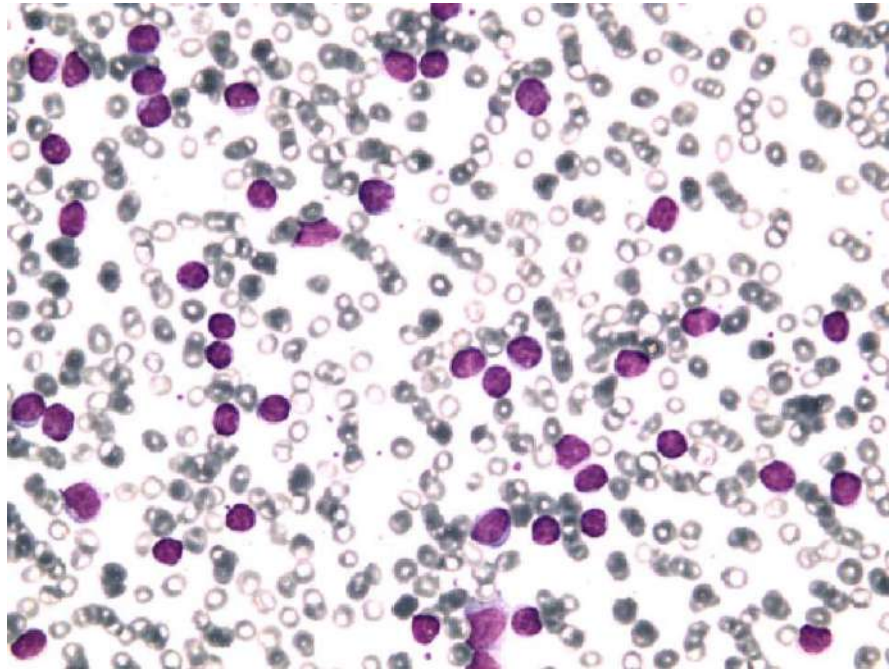
Special Article

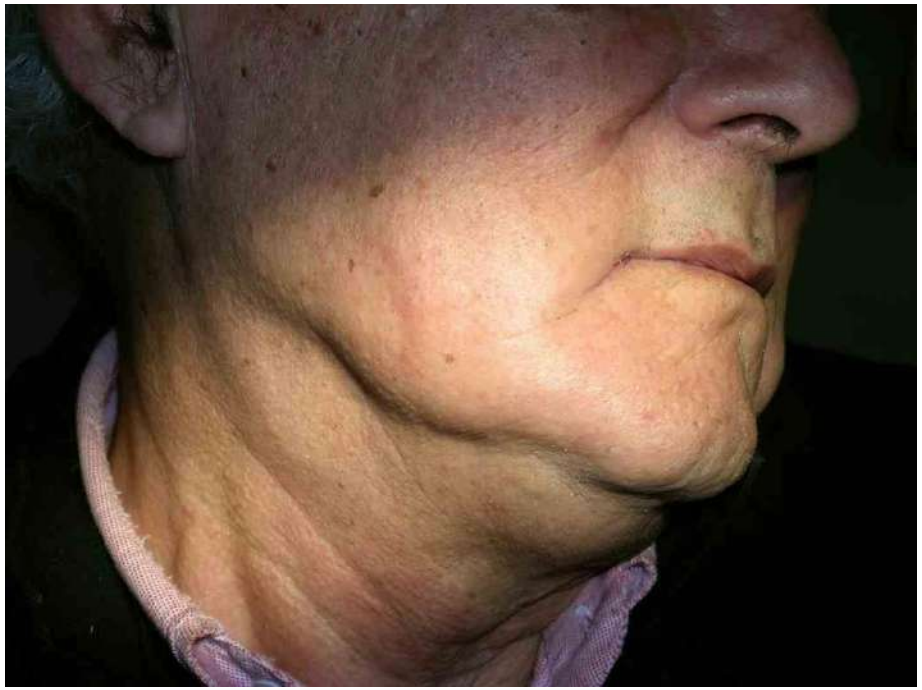
Chronic Lymphocytic Leukemia—an Accumulative Disease of Immunologically Incompetent Lymphocytes

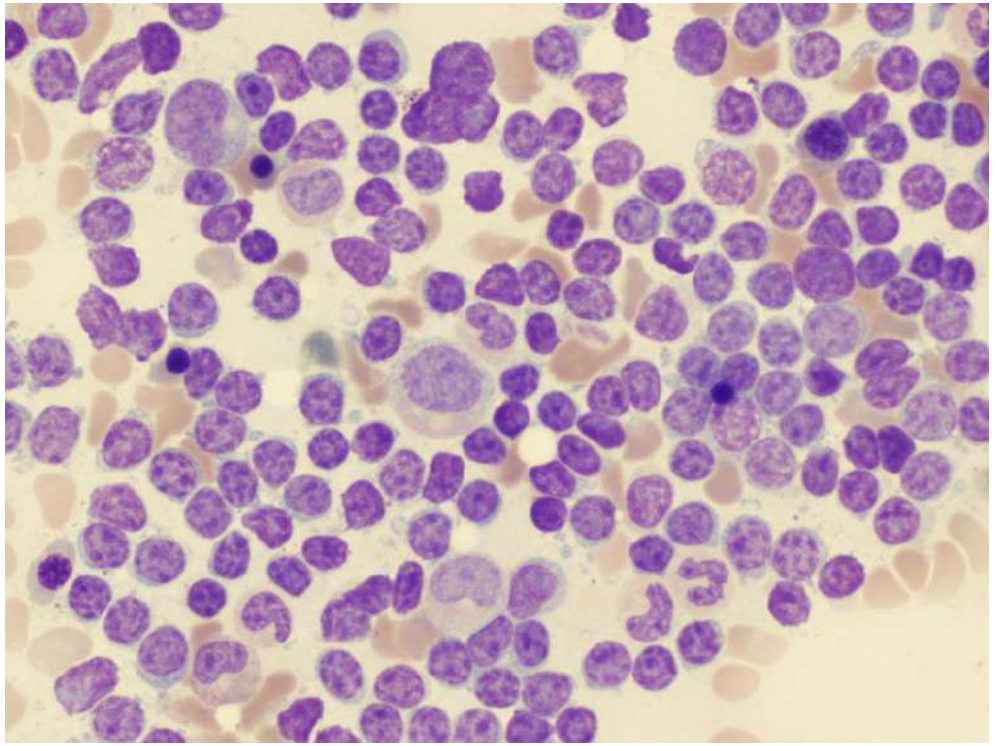
By WILLIAM DAMESHEK

OF THE VARIOUS FORMS of leukemia, the chronic lymphocytic variety is, in many ways, of unusual interest. This is due not only to its considerable clinical diversity, but also to the frequent presence of abnormal immune manifestations, including both immunologic incompetence and autoimmune disorders. Since the lymphocyte may be called the "central" immunocyte, the manifestations of disturbed immunity are not unexpected; in fact, we have classified chronic lymphocytic leukemia as one of the "immunoproliferative disorders."[1] As the disease progresses and the numbers of lymphocytes become enormously increased, both in the blood and the tissues, the various indications of both immunologic incompetence and of autoimmunity become more marked. Evidence has already been forthcoming that the small, "mature"-looking lymphocytes of the disease show indications of decreased functional capacity in vitro. The distinct possibility is therefore present that the indications of immunologic incompetence are due to the accumulation of immunologically incompetent lymphocytes.

Aspecto frecuente de Leucemia Linfática Crónica

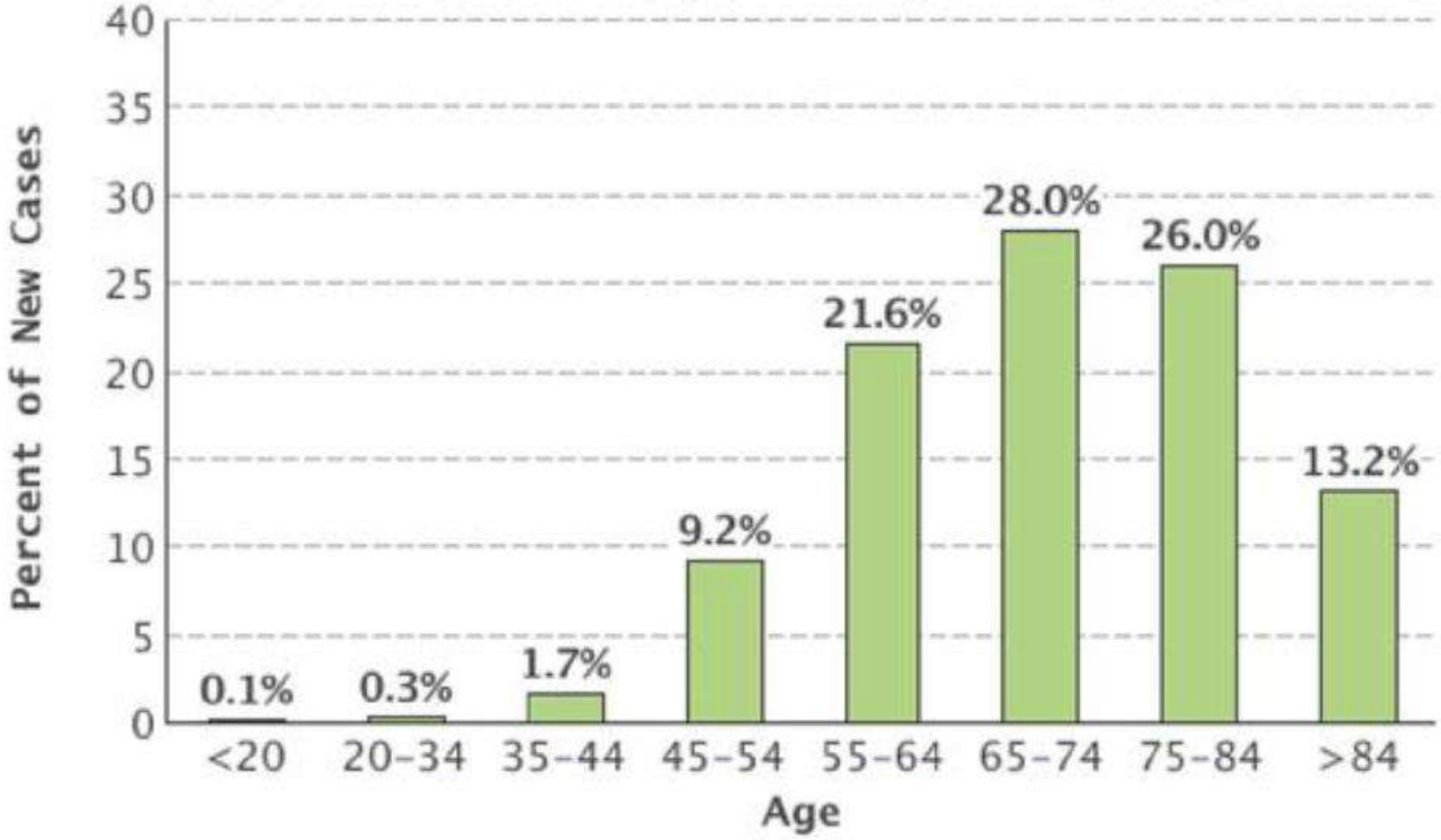






Compromiso de Medula Ósea

Mediana de edad de LLC: 72 años



Historia/antecedentes familiares

- First-degree relatives of CLL patients have elevated risks:
  - 8.5 fold risk of CLL
- Elevated risks of other LPDs
  - 1.9 fold risk of NHL
    - 4.0 fold risk of LPL/WM
    - 3.3 fold risk of Hairy Cell
    - 1.6 fold risk of FL

Goldin et al. Blood (2004) 104:1850
Goldin et al. Haematologica (2009) 94:647

CLL STAGING SYSTEMS

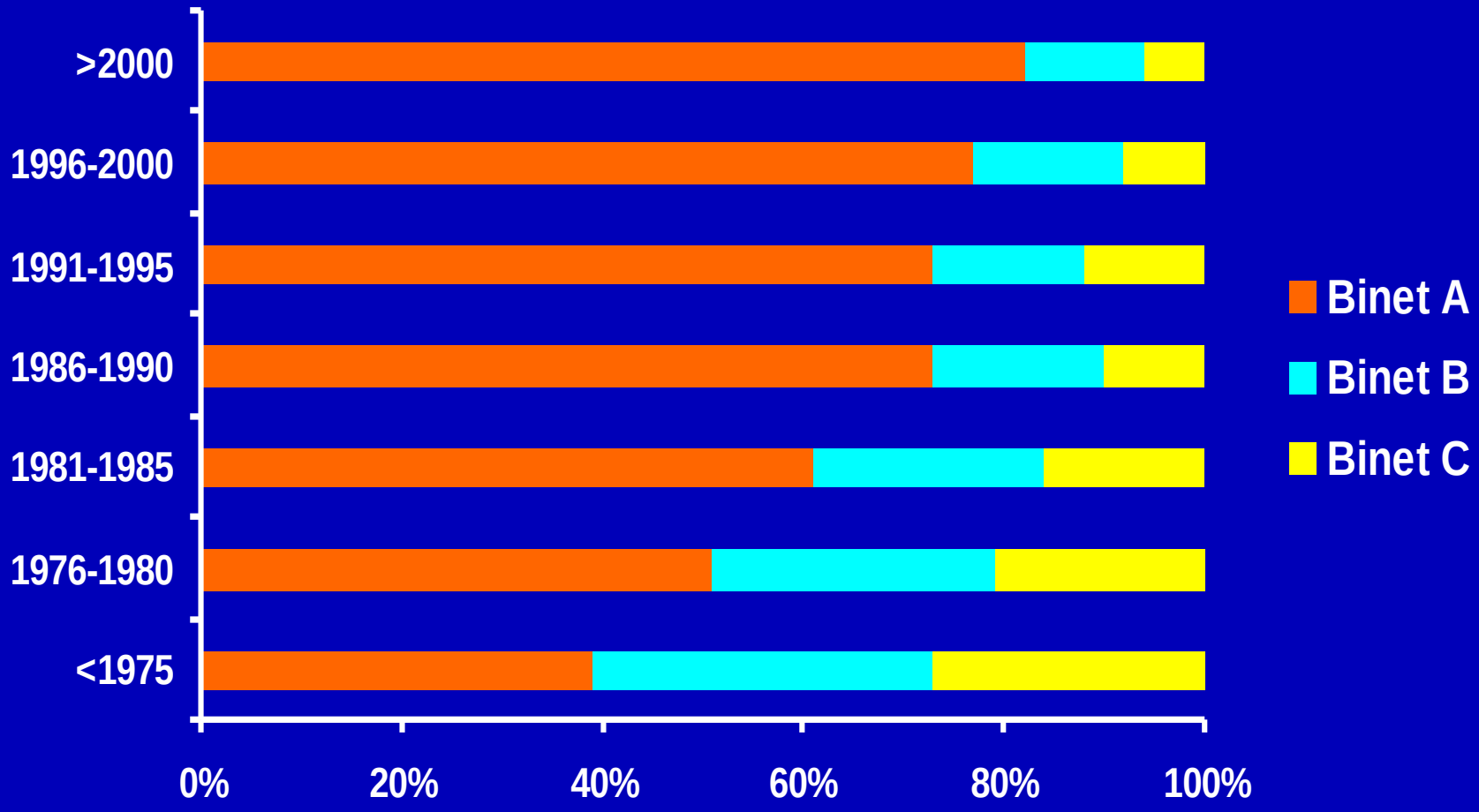
Rai System[a]

Stage	Description	Modified Risk Status
0	Lymphocytosis, lymphocytes in blood >15,000/mcL and >40% lymphocytes in the bone marrow	Low
I	Stage 0 with enlarged node(s)	Intermediate
II	Stage 0–I with splenomegaly, hepatomegaly, or both	Intermediate
III[c]	Stage 0–II with hemoglobin <11.0 g/dL or hematocrit <33%	High
IV[c]	Stage 0–III with platelets <100,000/mcL	High

Binet System[b]

Stage	Description
A	Hemoglobin ≥10 g/dL and Platelets ≥100,000/mm^3 and <3 enlarged areas
B	Hemoglobin ≥10 g/dL and Platelets ≥100,000/mm^3 and ≥3 enlarged areas
C[c]	Hemoglobin <10 g/dL and/or Platelets <100,000/mm^3 and any number of enlarged areas

Clinical stages at diagnosis over time (Barcelona series, n =1200)



Montserrat *Hematology* 2006

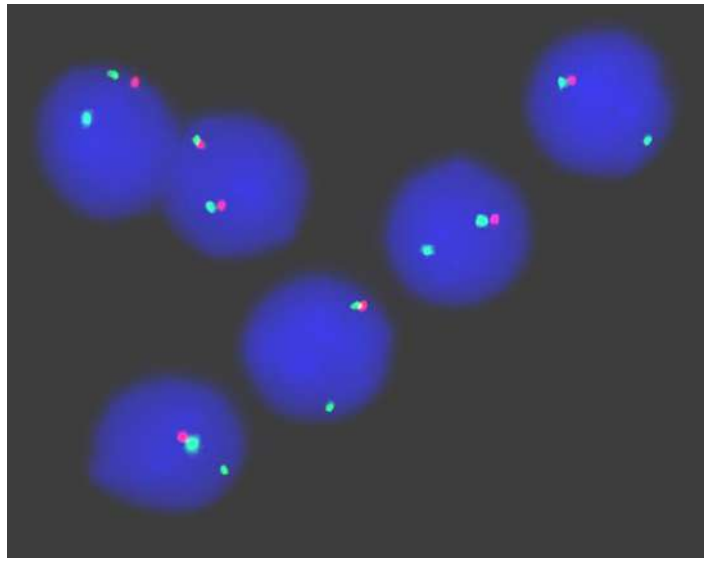
Treatment indications CLL – iwCLL 2018

- Marrow failure (progressive, hgb <10, plt <100k)
- Massive (≥6cm below costal margin) or progressive splenomegaly
- Massive (≥ 10 cm) or progressive lymphadenopathy
- Progressive lymphocytosis (doubling time < 6 months)
- Autoimmune cytopenias **not** responding to other treatment
- Organ-threatening disease
- Constitutional Symptoms which include any of the following:
  - Unintentional weight loss of 10% or more within 6 months
  - Significant fatigue
  - Fever >38º C for 2 weeks or more without evidence of infection
  - Night sweats >1 month without evidence of infection

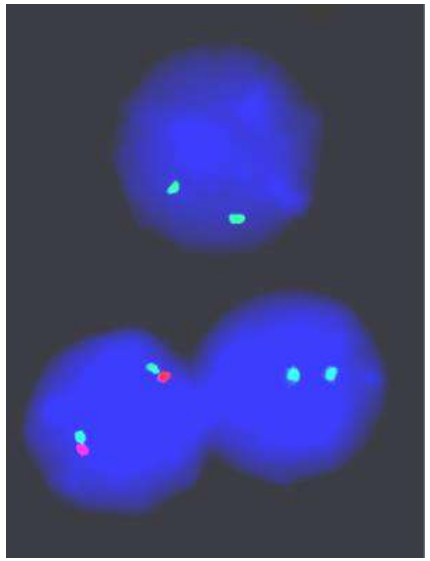
Hallek M et al, iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood. 2018; 131:2745-60

Fluorescencia in situ por hibridación (FISH) para detectar las alteraciones citogenéticas

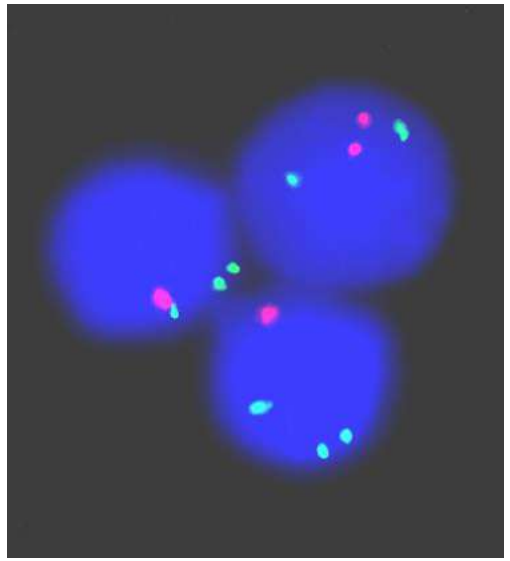
17p–



13q–



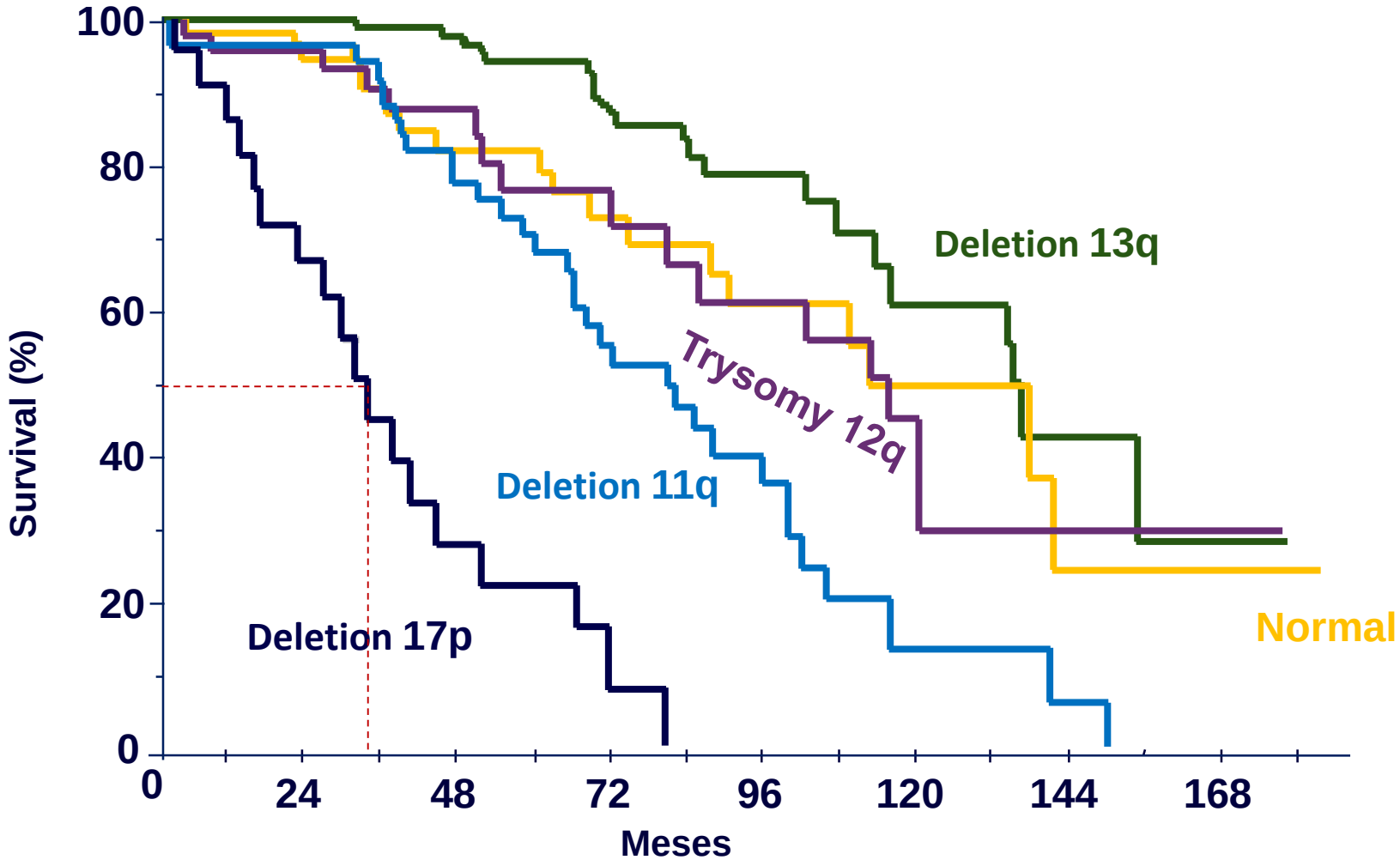
+12q



* Las guías de la iwCLL sugieren testear para alteraciones citogenéticas en la práctica habitual previo a comenzar tratamiento

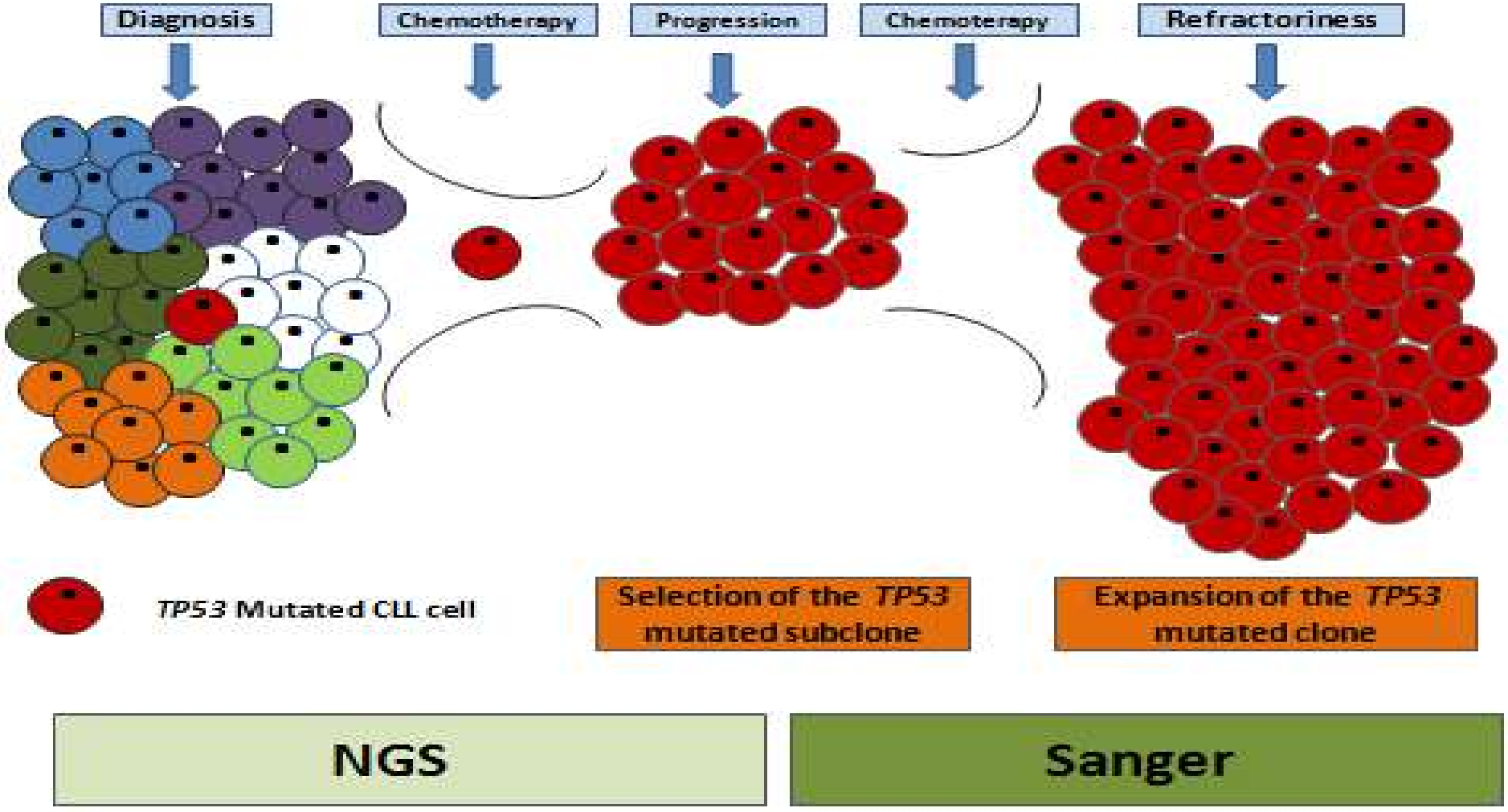
Hallek M, et al. Blood 2008; 111:5446–5456.

FISH - Cytogenetics



Döhner H, et al. N Engl J Med. 2000;343:1910-1916.

Clonal Evolution



IGHV: Estado mutacional de la región variable del gen de la cadena pesada de la inmunoglobulina

Non mutated U- CLL

- ⩾98% identity with the germinal line
- Usually defined as 98% or more sequence homology to the nearest germ line gene
- < 2% change in the nucleotidic change
- Aggresive clinical course

Mutated M-CLL

- <98% identity with the germinal line
- ≥2% change in the nucleotidic change
- Indolent clinical behavior

"borderline CLL" status: 97–97.9% identity with the germinal line

Leukemia. 2017;31:1477-81

IGHV: Overall Survival

Median OS: MUT 293 months vs UMUT 117 months
P = 0,001

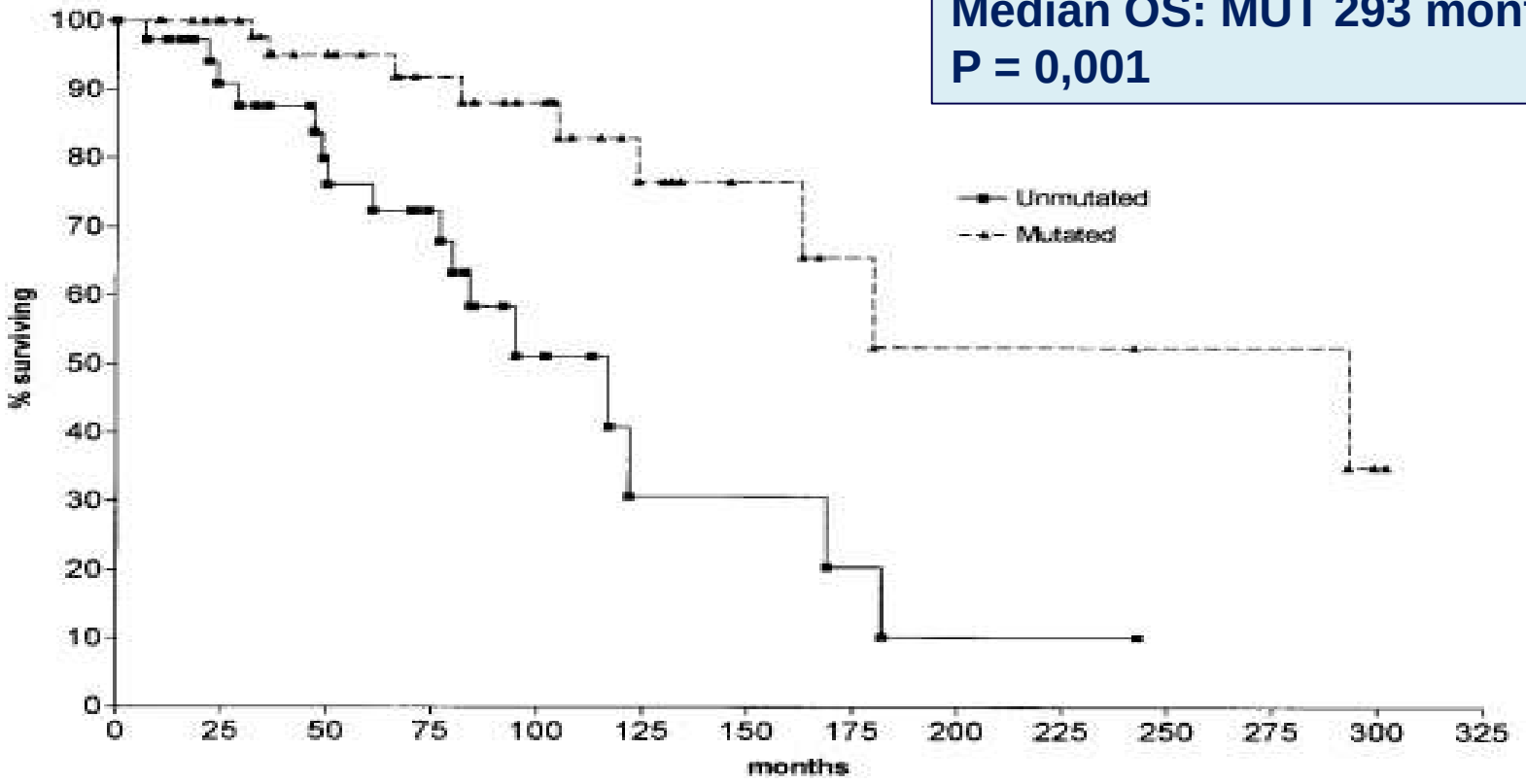
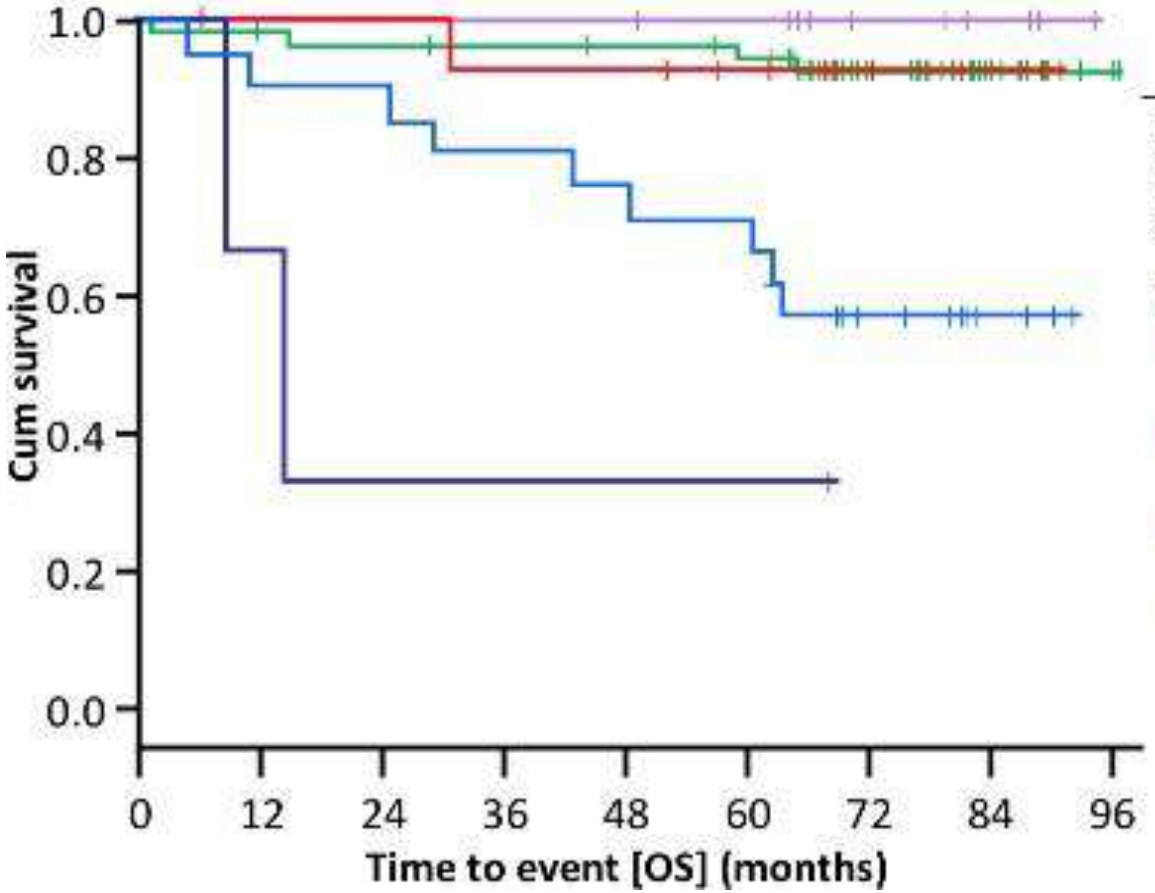


Fig 1. Kaplan-Meier survival curve comparing CLL patients with mutated and unmutated V_H genes. Median survival for unmutated CLL: 117 months; median survival for mutated CLL: 293 months. The difference is significant at the $P = .001$ level (log-rank test).

Hamblin TJ, et al. *Blood*. 1999;94:1848-1854

Survival after FCR Chemoimmunotherapy

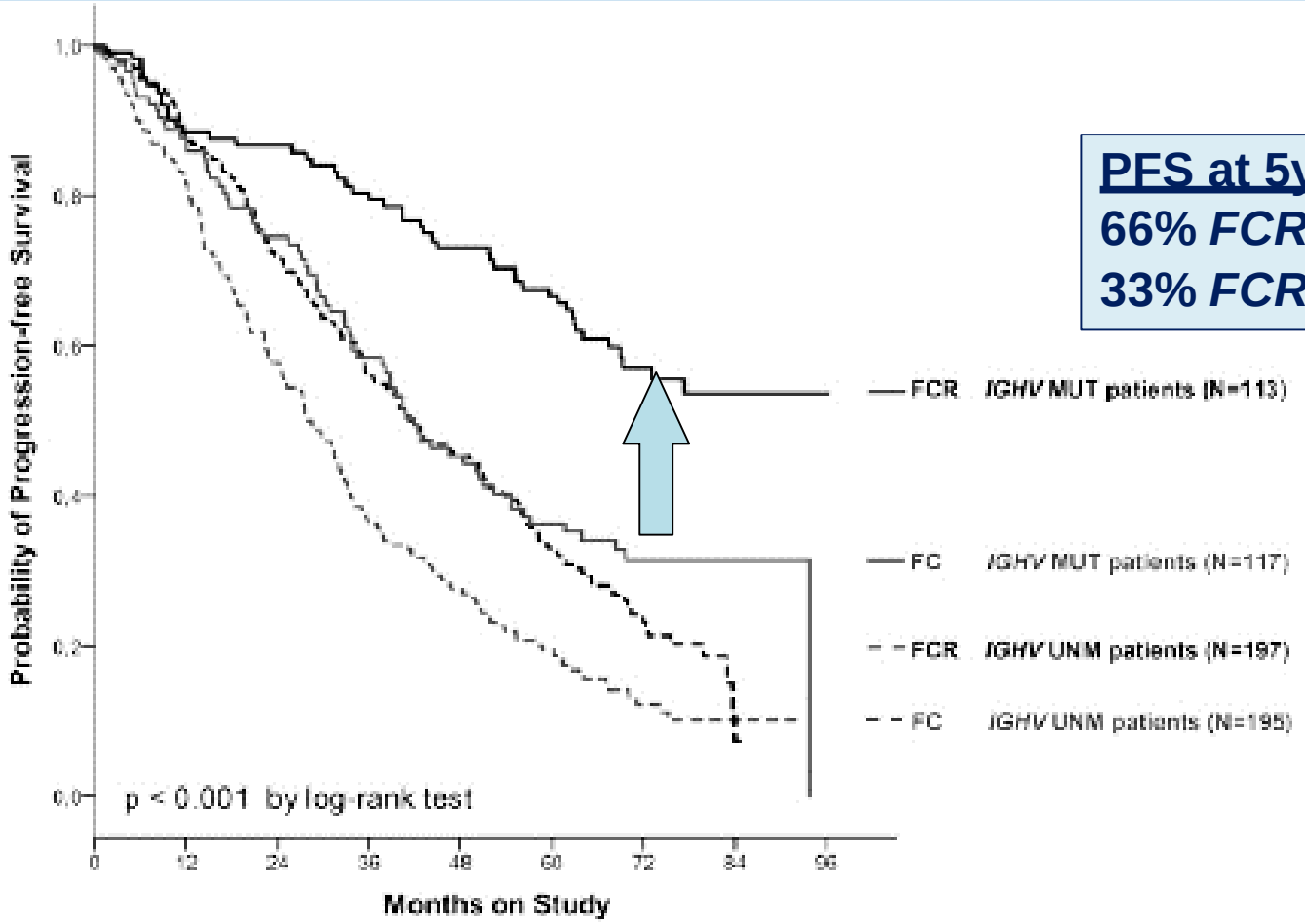


	N (%)	Pts alive, %	5-year OS, %
IGHV mutated patients*	107	85.0	66.6
+12q	10 (9.3)	100.0	100.0
13q–	58 (54.2)	93.1	94.6
11q–	15 (14.0)	93.3	92.9
Not**	21 (19.6)	57.1	71.4
17p–	3 (2.8)	33.3	33.3

Fischer K, et al. Blood, 2016; 127: 208–215

FCR: maximum benefit for IGHV mutated

FCR: limited benefit for IGHV unmutated



PFS at 5ys rate:

66% *FCR IGHV MUT*

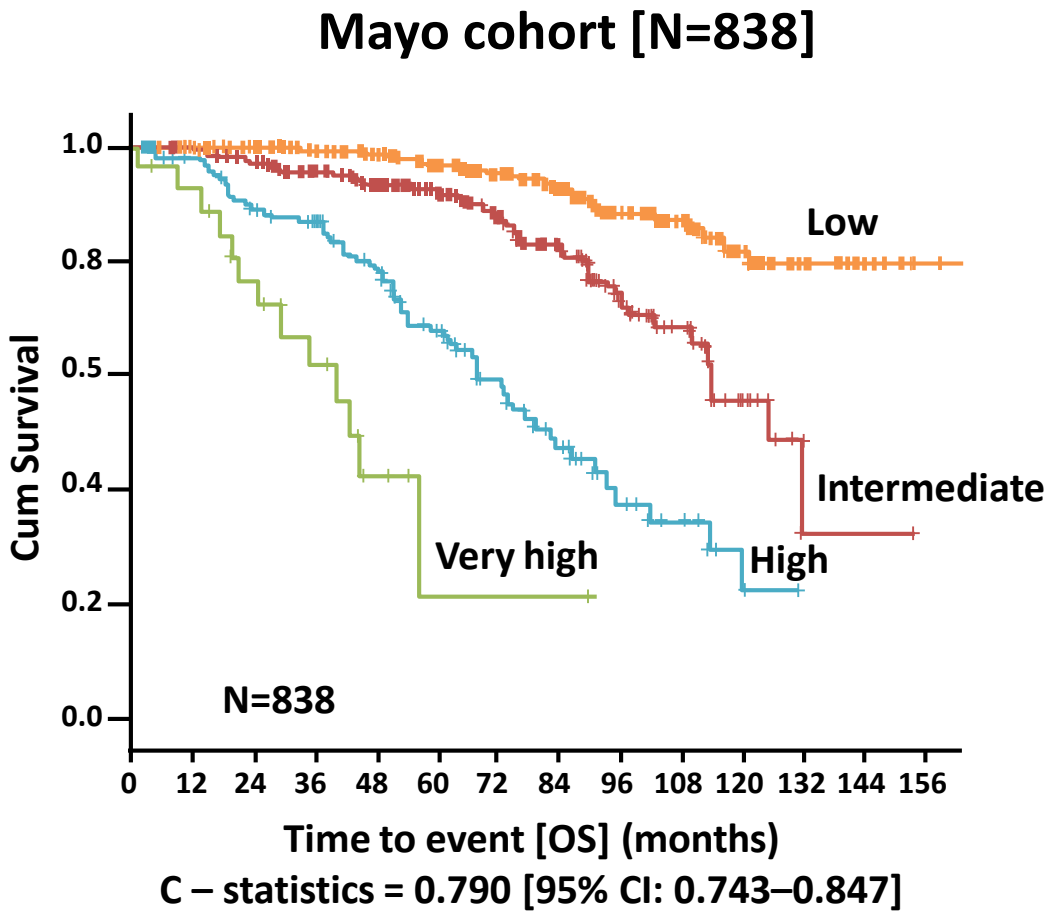
33% *FCR UNM*

Fischer K. Blood, 2016; 127

CLL-International Prognostic Index: CLL-IPI

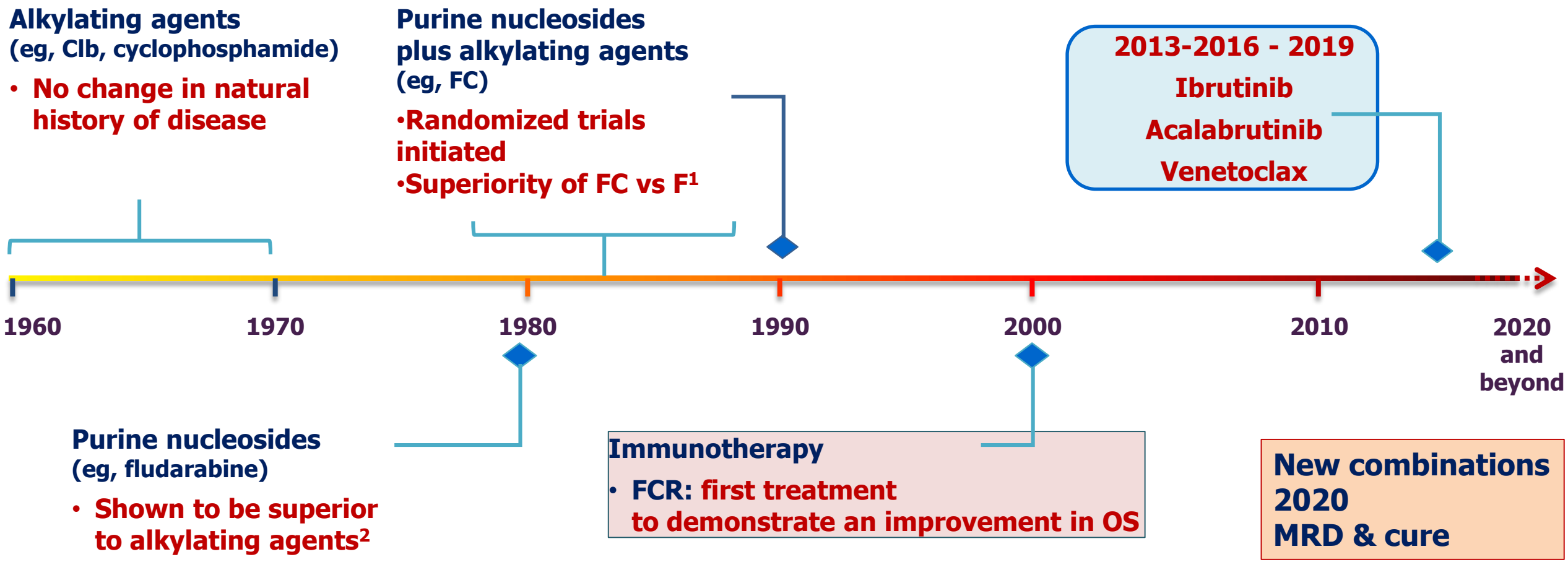
Variable	Adverse Factor	Grading
TP53/17p	Mutated/deleted	4
IGHV status	Unmutated	2
B2M	> 3.5 mg/dl	2
Clinical Stage	Binet B/C or Rai III/IV	2
Age	> 65 years	1
Prognostic score		0-10

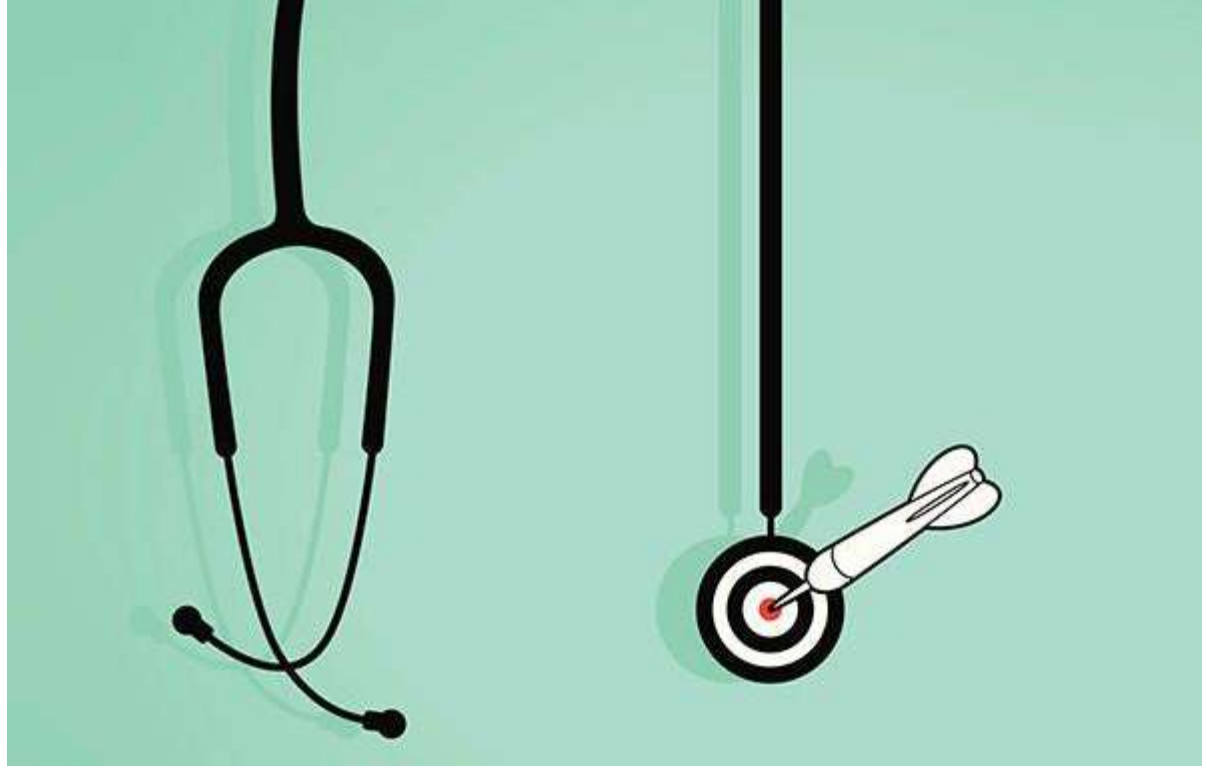
Risk group	Patients	5-year OS
Low	47%	94%
Intermediate	33%	91%
High	18%	68%
Very high	73%	21%

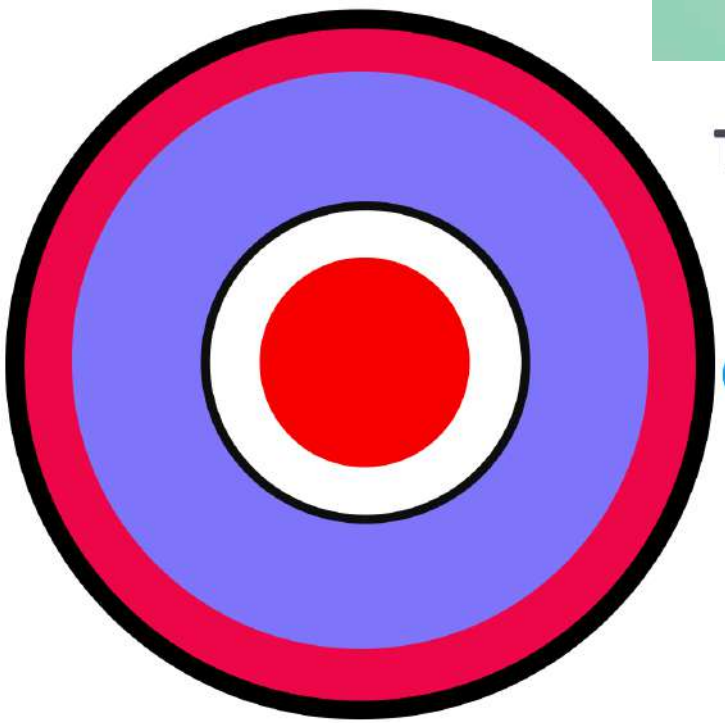


Kutsch N et al. ASCO Annual Meeting 2015. Abstract 7002.

Treatment evolution in CLL



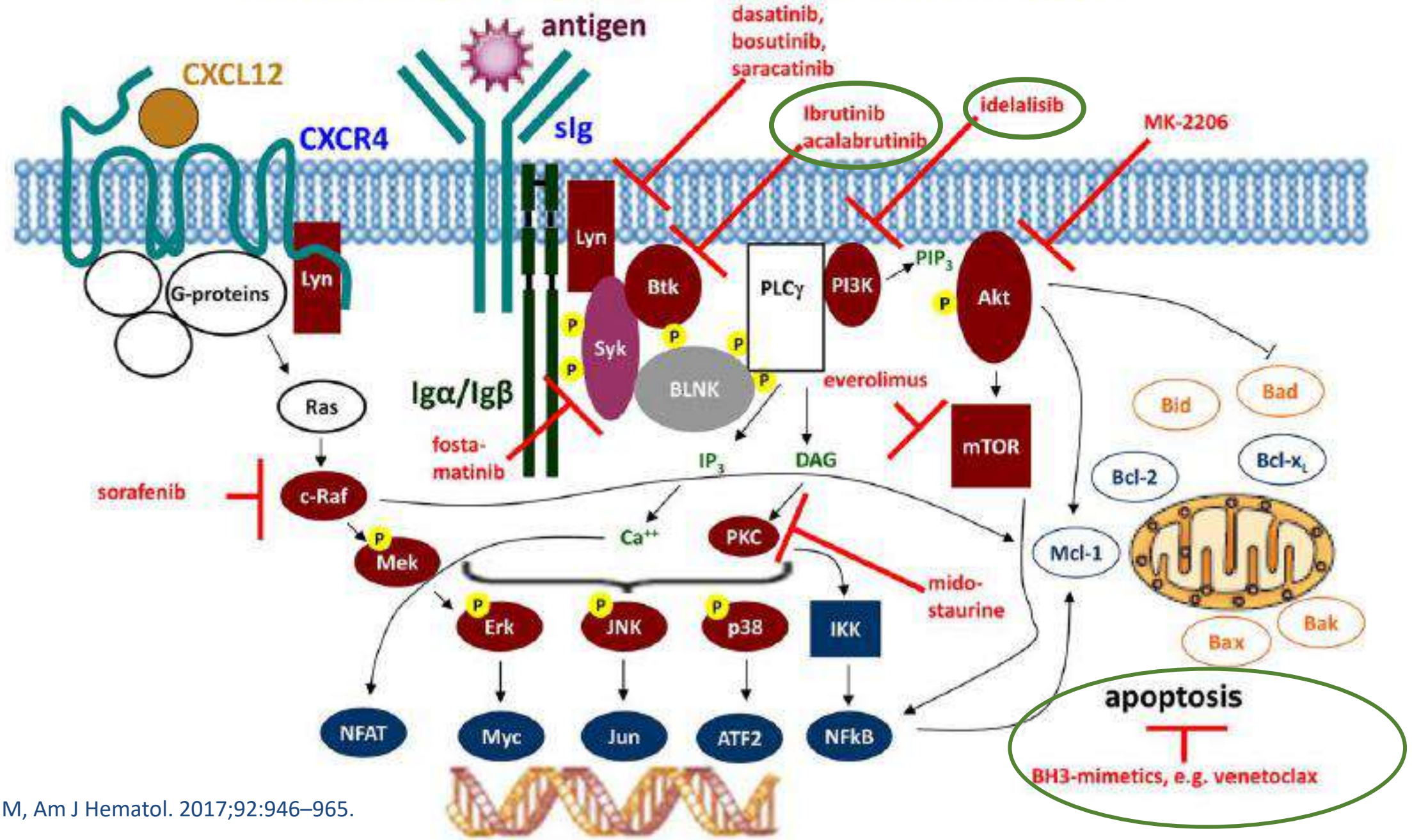




TARGETED THERAPY

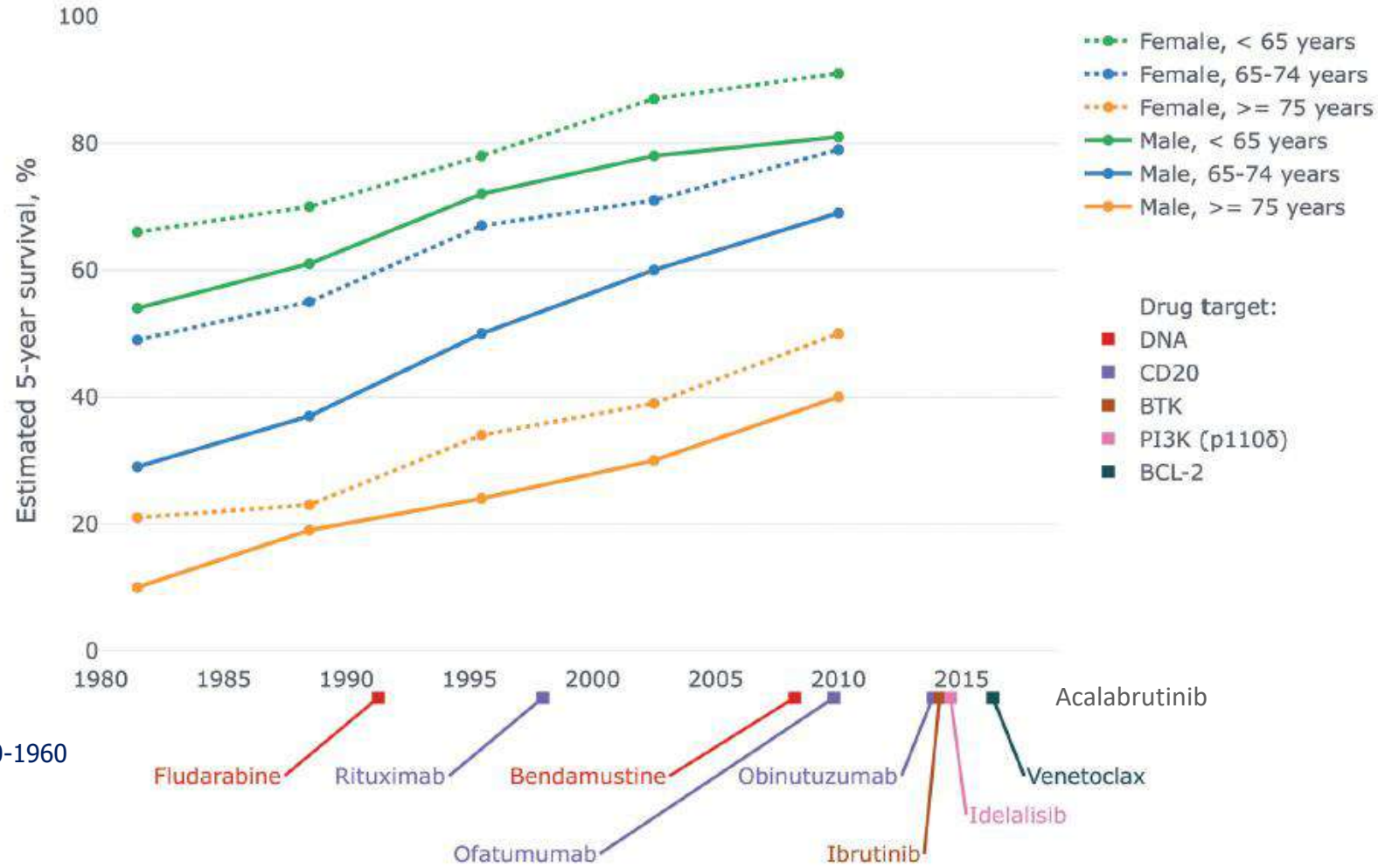
Avoids Normal
Cells & Goes Directly
to the Cancer Cells

Survival signaling in CLL: targets of novel agents



Hallek M, Am J Hematol. 2017;92:946–965.

Timeline of regulatory approval of major drugs for treatment of CLL paralleled by improving survival of CLL patients



Alkylating agents
(Clb, cyclophosphamide) 1950-1960

Adapted form Hemasphere 2019. Yosifov et al From Biology to Therapy: The CLL Success Story

The NEW ENGLAND JOURNAL of MEDICINE

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., Ian W. Flinn, M.D., Ph.D., Jan A. Burger, M.D., Ph.D., Kristie A. Blum, M.D., Barbara Grant, M.D., Jeff P. Sharman, M.D., Morton Coleman, M.D., William G. Wierda, M.D., Ph.D., Jeffrey A. Jones, M.D., M.P.H., Weiqiang Zhao, M.D., Ph.D., Nyla A. Heerema, Ph.D., Amy J. Johnson, Ph.D., Juthamas Sukbuntherng, Ph.D., Betty Y. Chang, Ph.D., Fong Clow, Sc.D., Eric Hedrick, M.D., Joseph J. Buggy, Ph.D., Danelle F. James, M.D., and Susan O'Brien, M.D.

Major Phase 3 Trials Support the Use of Targeted Agents in CLL

Ibrutunib

- ✓ **RESONATE-2**:superior PFS and OS vs Clb
- ✓ **iLLUMINATE**: superior PFS vs GClb
- ✓ **ALLIANCE:** superior PFS vs BR in older patients
- ✓ **ECOG 1912:** superior PFS and OS vs FCR in younger patients
- ✓ **FLAIR:** superior PFS vs FCR in younger patients
- ✓ **HELIOS:** superior PFS vs BR

Acalabrutinib

- ✓ **ELEVATE-TN**: superior PFS for acalabrutinib regimens vs GClb
- ✓ **ASCEND:** superior PFS vs Idelalisib/BR

Zanubrutinib

- ✓ **SEQUOIA**: superior PFS vs BR

Venetoclax

- ✓ **CLL14**: VenG superior to GClb in unfit patients
- ✓ **CLL13**: VenG superior to FCR/BR in fit patients
- ✓ **MURANO:** VenR superior to BR

Ibru + Ven

- ✓ **GLOW:** I+V superior PFS vs GClb

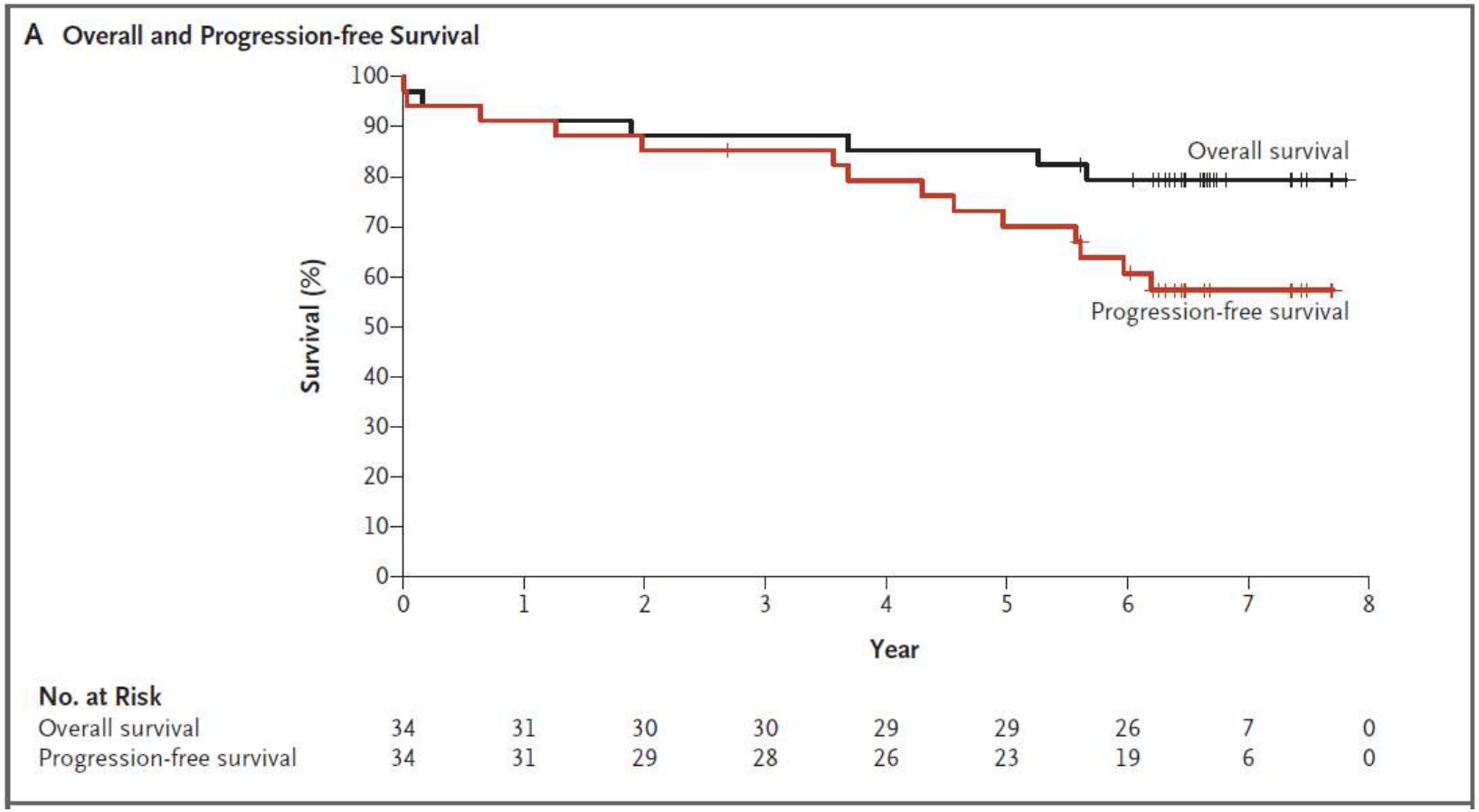
Continuous BTKi

FD BCL-2 inh combination

BTK and BCL-2 inh combination

Authors slide

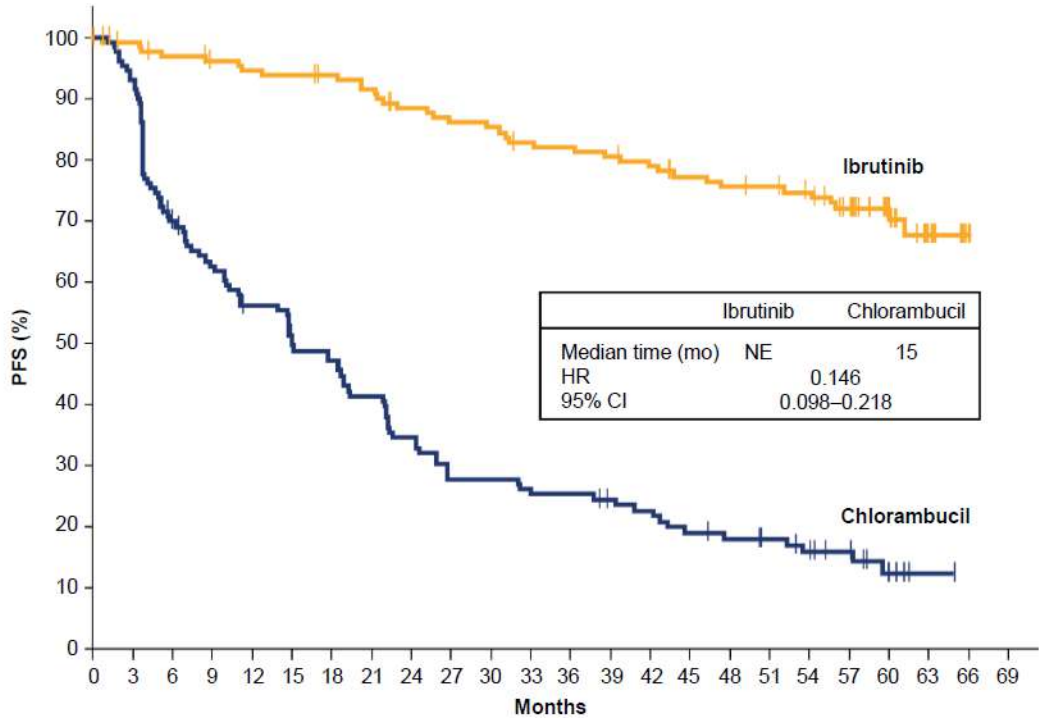
Ibrutinib for 1L treatment of CLL with 17p/TP53 aberration: OS and PFS

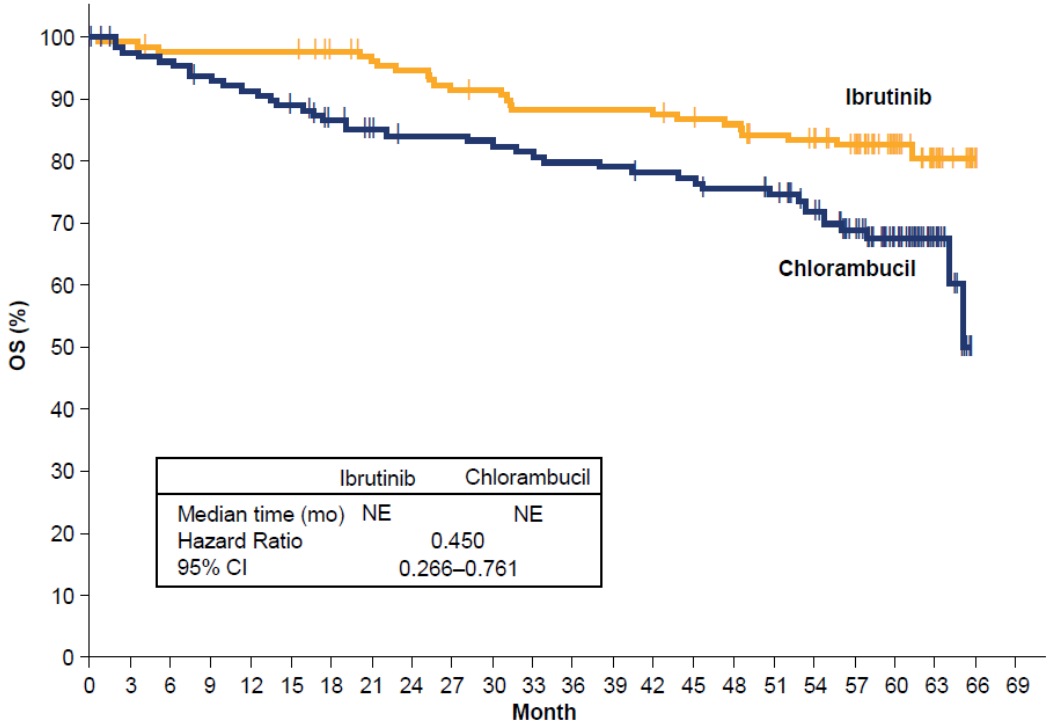


34 patients with chronic lymphocytic leukemia with TP53 alterations who were treated with ibrutinib as first-line therapy

Ahn IE, et al. N Engl J Med.2020; 383: 498-500.

RESONATE: PFS and OS Benefit of Ibrutinib vs Chlorambucil in First-Line CLL/SLL Continues with Long-Term Follow-Up





Improved OS for ibrutinib vs chlorambucil:
–5-year estimates: 83% vs 68%
–HR (95% CI): 0.450 (0.266–0.761)

Tedeschi A. EHA 2019.

Final 5-year results from a phase 3 study (HELIOS) of ibrutinib BR vs BR in patients with relapsed/refractory CLL

Figure 1. PFS for Ibrutinib Plus BR and Placebo Plus BR

Median PFS 65.1 months (n = 289) Ibr arm, vs 14.3 months placebo; n = 289; HR 0.229 [0.183-0.286]; *p* < 0.0001

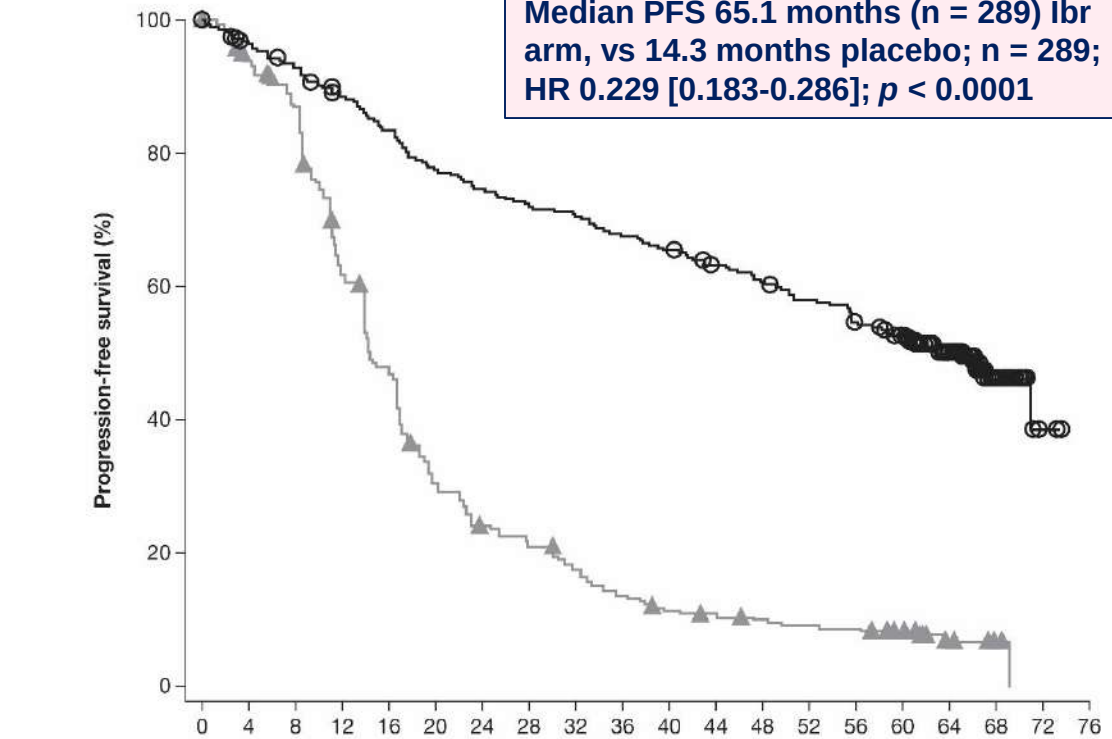
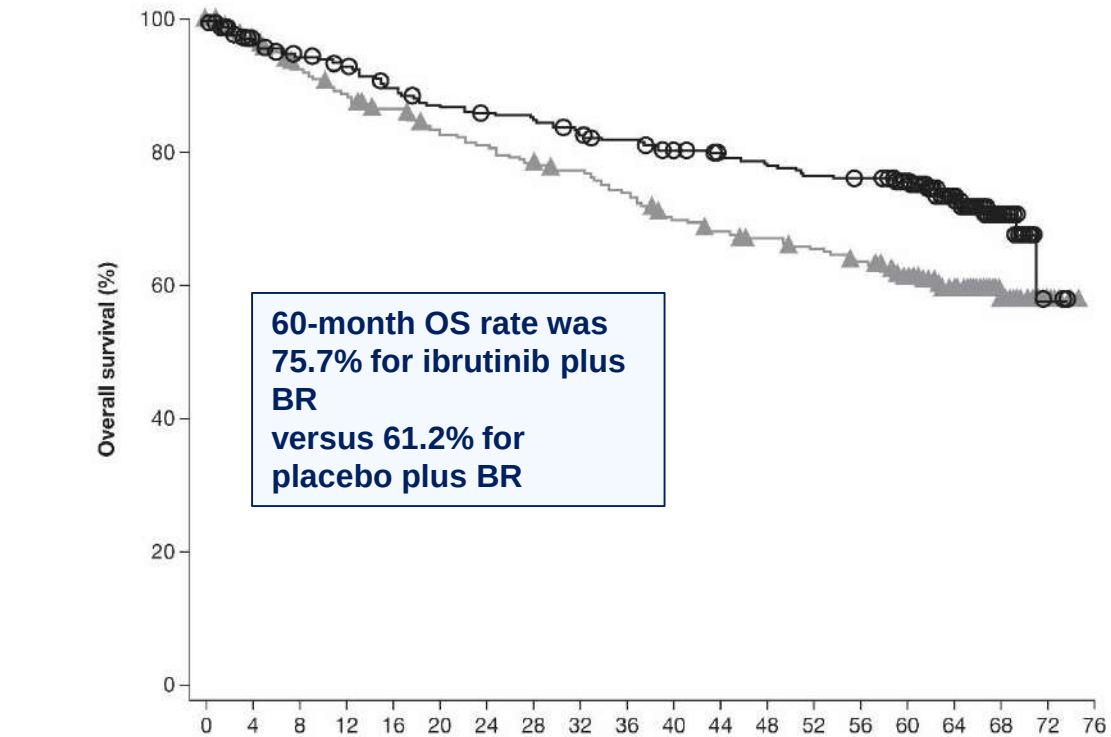


Figure 2. OS for Ibrutinib Plus BR and Placebo Plus BR

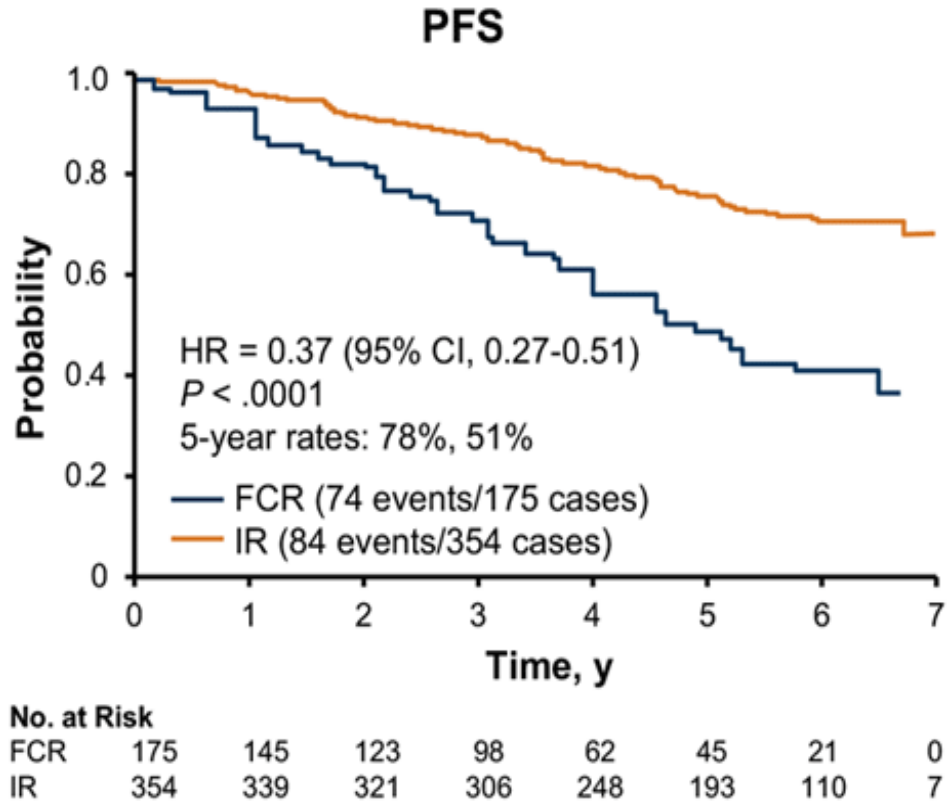
60-month OS rate was 75.7% for ibrutinib plus BR versus 61.2% for placebo plus BR

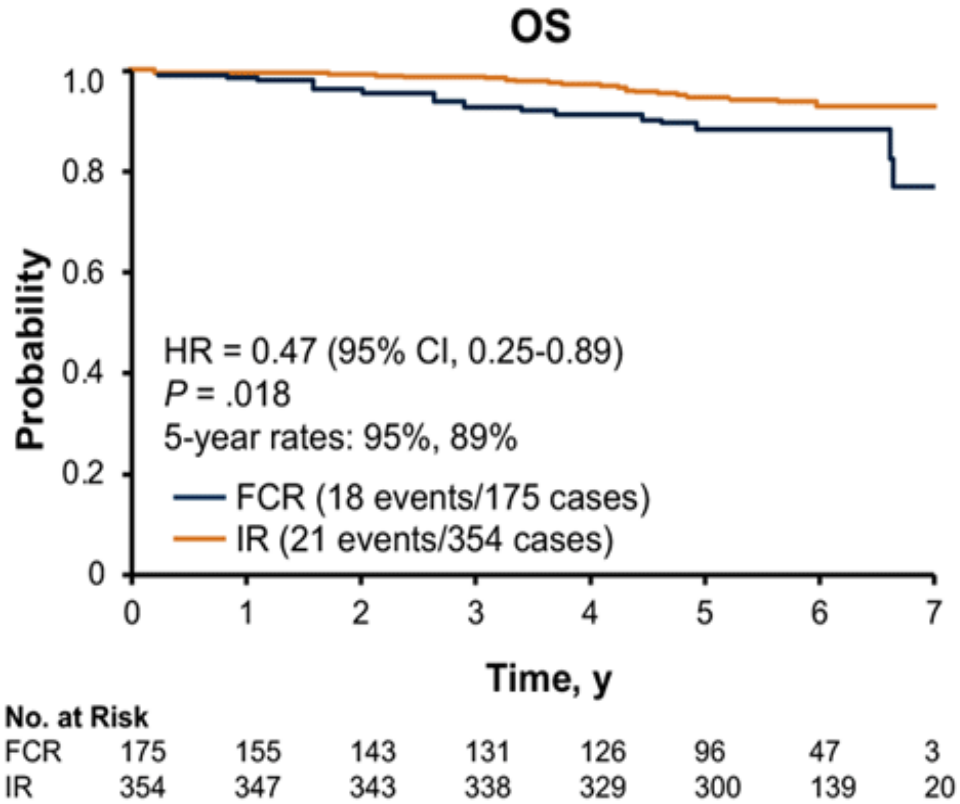


Graeme F., Cramer P, Pavlovsky MA, Hallek M et al. EHA. IWCLL 2019

ECOG 1912: Ibrutinib + Rituximab vs FCR
Inclusion of Patients Aged ≤70 Years

Median observation time: 70 months[1]





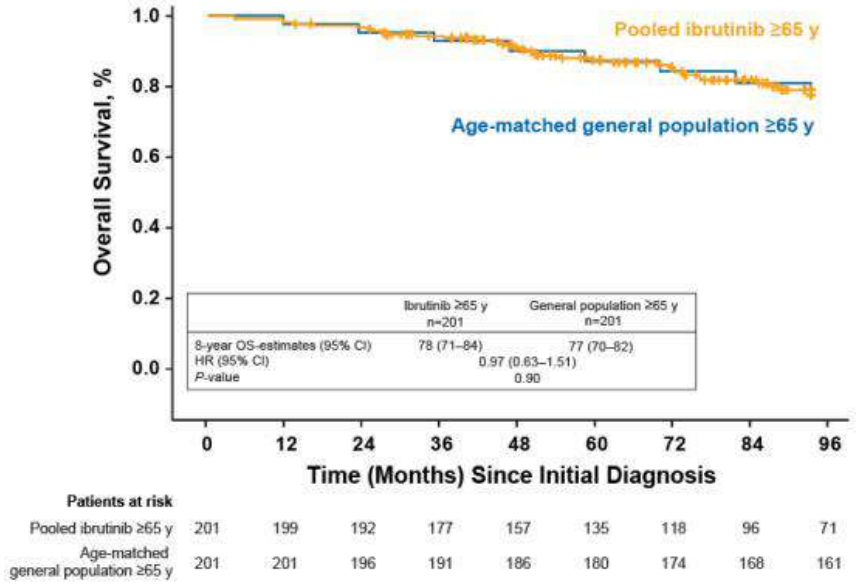
1. Shanafelt T et al. *Blood*. 2022;140:112-120.

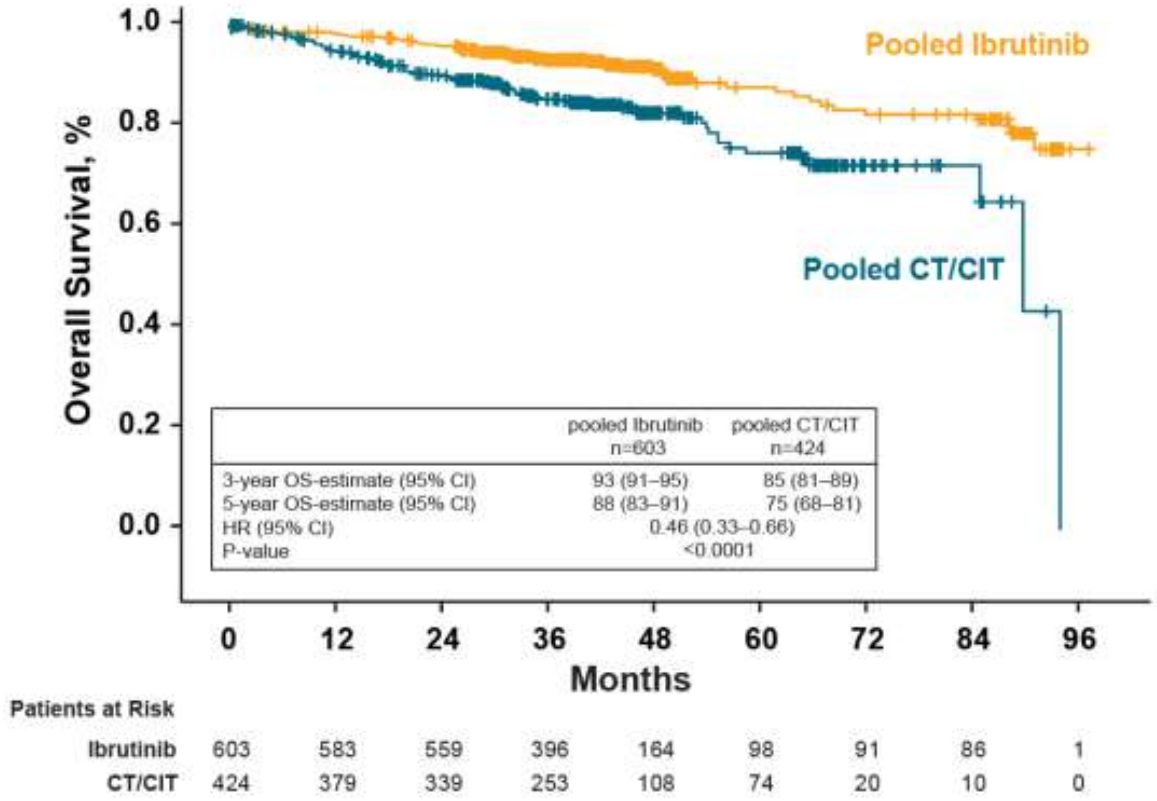
Initiating first line (1L) Ibrutinib in patients with CLL Improves OS outcomes to rates approximating an age-Matched population ≥65 years

Pooled analysis on OS Ibrutinib vs CT/CIT on 3 phase III trials (RESONATE-2, ECOG1912 e Illuminate)

603 1L Ibrutinib monoterapia (22,6%), Ibr + R (58,7%), Ibr + obi (18,7%)

424 CT/CIT [FCR (41,3%), Clb (31,4%), Clb+O (27,4%)





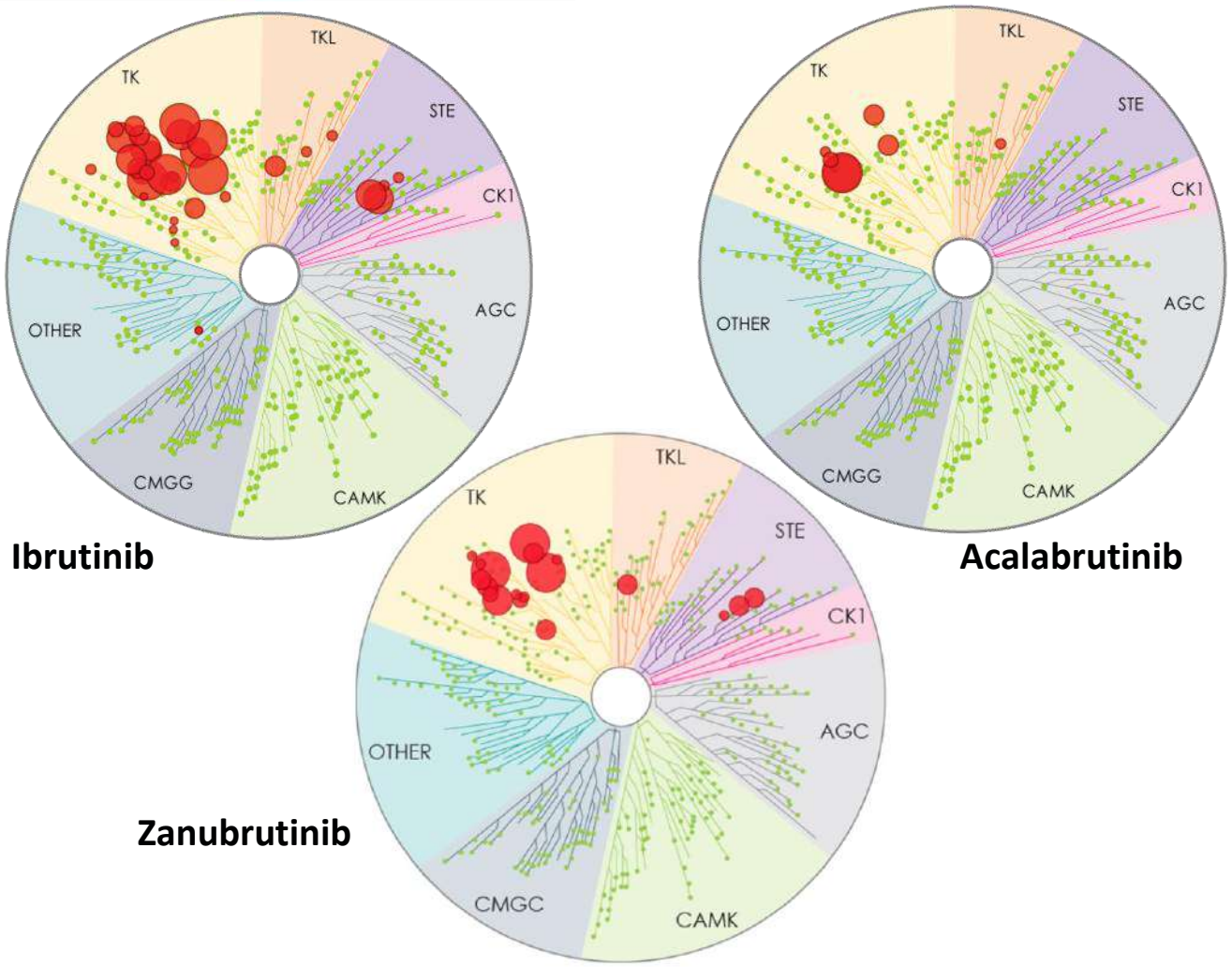
Ghia P, et al. ASH. 2022. Oral presentation #1809

Kinase Selectivity of BTK Inhibitors

Kinase	IC_{50}/EC_{50} (nM)		
	Ibrutinib	Acalabrutinib	Zanubrutinib
BTK	1.5	5.1	0.5
TEC	10	126	44
ITK	4.9	> 1000	50
BMX	0.8	46	1.4
EGFR	5.3	> 1000	21
ERBB4	3.4	16	6.9
JAK3	32	> 1000	1377
BLK	0.1	> 1000	2.5

Kinase Selectivity Profiling at 1 μmol/L (in vitro)

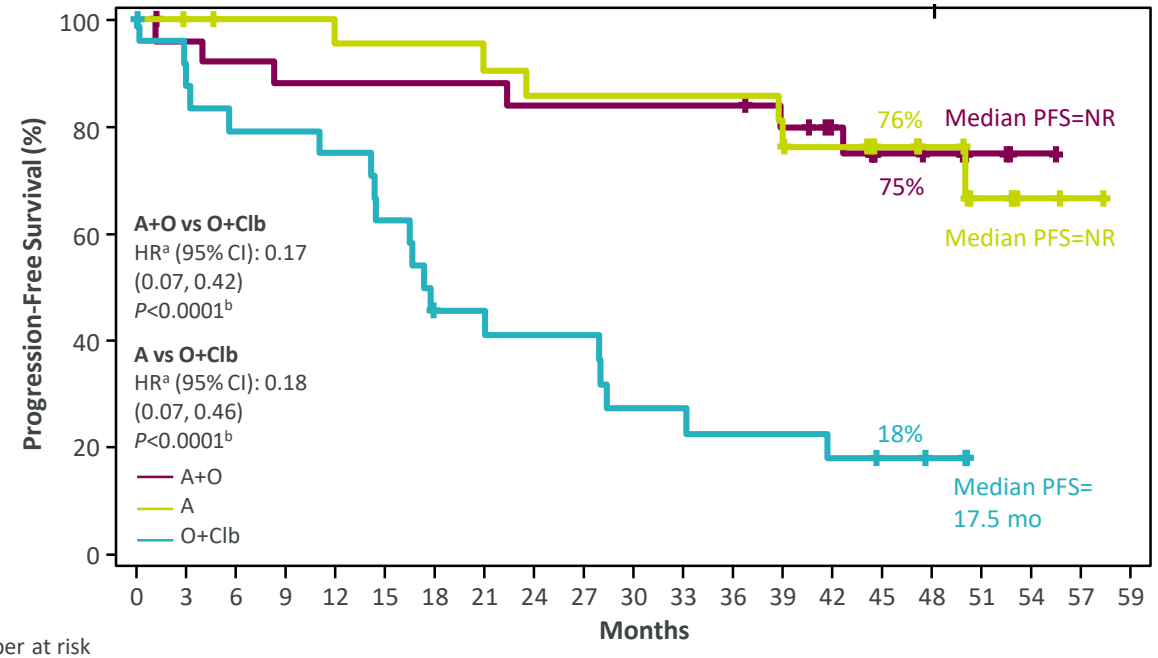
Larger red circles represent stronger inhibition



Kaptein. ASH 2018. Abstr 1871.

Investigator-assessed PFS in Patients With del(17p) and/or Mutated *TP53* OR Unmutated IGHV

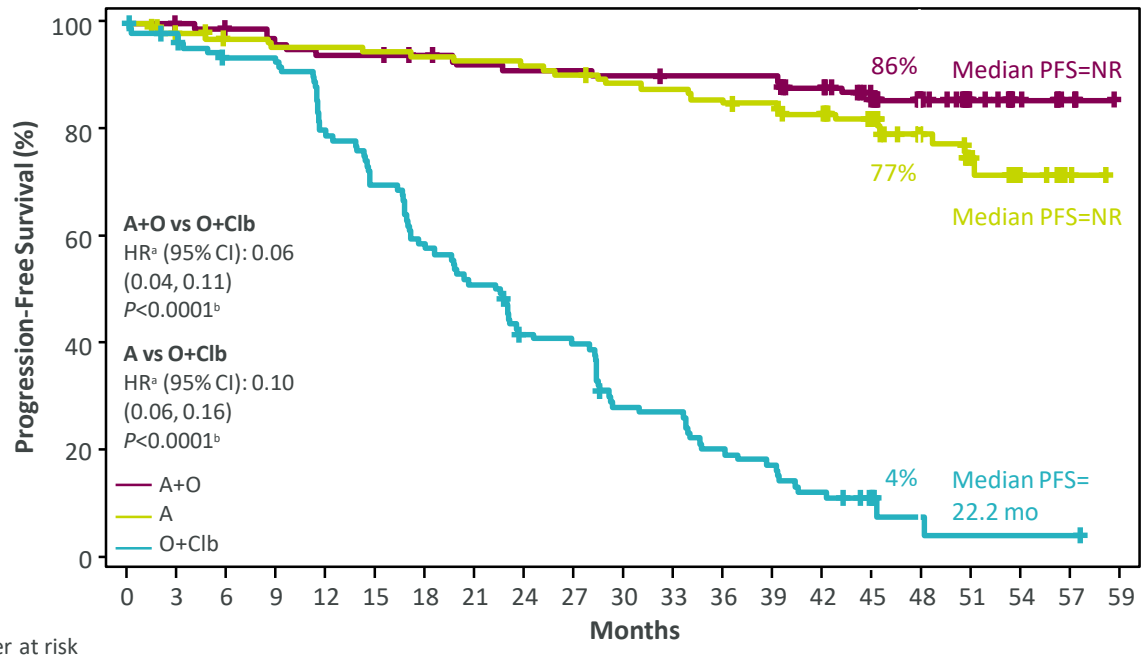
Del(17p) and/or Mutated *TP53*^1



Number at risk

A+O	25	24	23	22	22	22	22	22	21	21	21	21	21	19	16	9	8	3	1	0	0
A	23	22	21	21	20	20	20	19	18	18	18	18	18	15	15	11	9	5	2	1	0
O+Clb	25	21	19	19	18	15	10	9	9	9	6	6	5	5	4	3	2	0	0	0	0

Unmutated IGHV^2



Number at risk

A+O	103	102	100	97	95	95	94	92	91	91	90	89	89	84	78	47	35	17	7	1	0
A	119	112	109	107	107	106	105	104	103	101	98	97	93	89	84	52	38	22	11	1	0
O+Clb	116	105	101	99	85	75	62	55	43	41	28	27	19	14	11	2	1	1	1	1	0

[a]Hazard ratio was based on unstratified Cox-Proportional-Hazards model. [b]*P*-value was based on unstratified log-rank test.

A, acalabrutinib; CI, confidence interval; Clb, chlorambucil; HR, hazard ratio; IGHV, immunoglobulin heavy chain variable region; NR, not reached; O, obinutuzumab; PFS, progression-free survival.

1. Adapted from Sharman J et al. Poster presented at American Society of Clinical Oncology (ASCO) Annual Meeting: June 4-6, 2021, 7509 [REF-112426], 2. Adapted from Sharman J et al. Poster presented at American Society of Clinical Oncology (ASCO) Annual Meeting: June 4-6, 2021, 7509 Suppl. [REF-116086]

Sharman *et al.*, S148, EHA 2021.

The NEW ENGLAND JOURNAL of MEDICINE

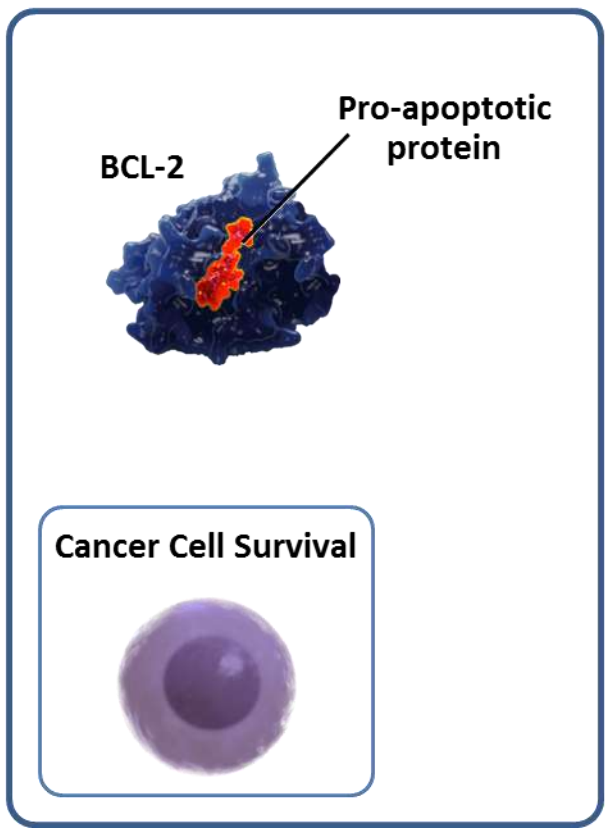
ORIGINAL ARTICLE

Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia

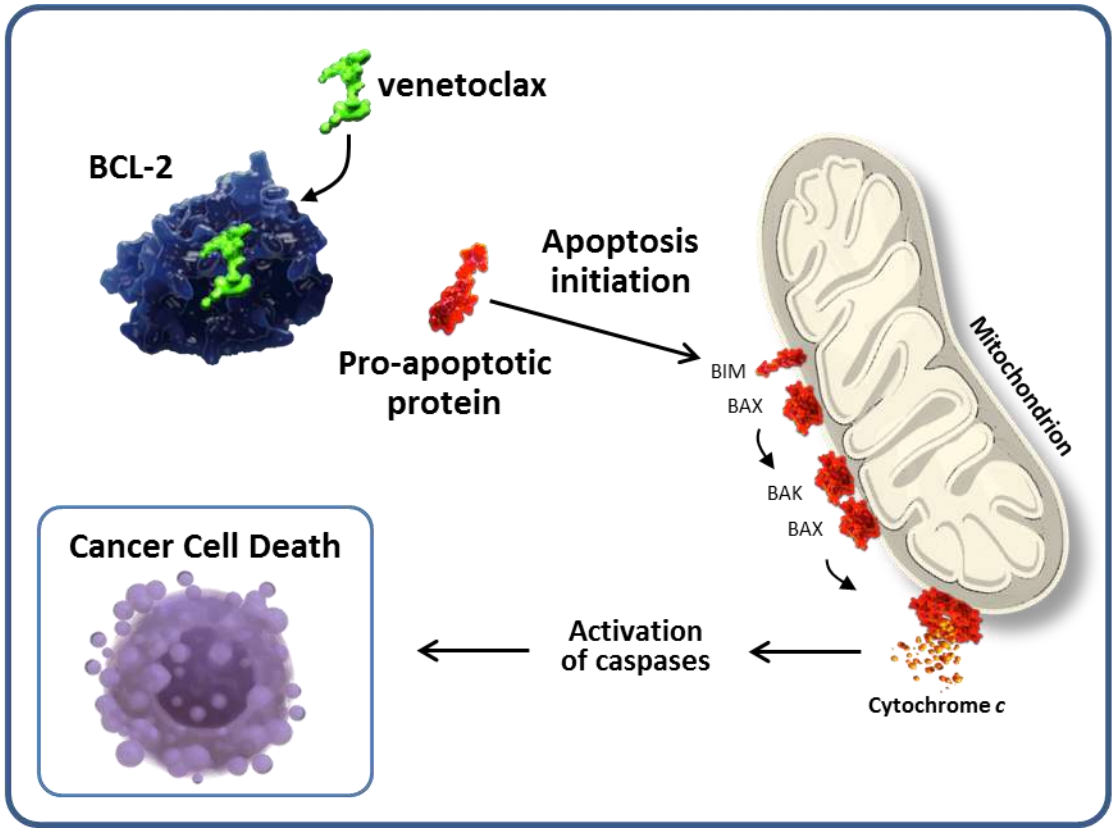
Andrew W. Roberts, M.B., B.S., Ph.D., Matthew S. Davids, M.D., John M. Pagel, M.D., Ph.D., Brad S. Kahl, M.D., Soham D. Puvvada, M.D., John F. Gerecitano, M.D., Ph.D., Thomas J. Kipps, M.D., Ph.D., Mary Ann Anderson, M.B., B.S., Jennifer R. Brown, M.D., Ph.D., Lori Gressick, B.S., Shekman Wong, Ph.D., Martin Dunbar, Dr.P.H., Ming Zhu, Ph.D., Monali B. Desai, M.D., M.P.H., Elisa Cerri, M.D., Sari Heitner Enschede, M.D., Rod A. Humerickhouse, M.D., Ph.D., William G. Wierda, M.D., Ph.D., and John F. Seymour, M.B., B.S., Ph.D.

NEJM 2015

Venetcolax: Inhibidor del BCL2 Proteina anti-Apoptotica



BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins.[1-3]

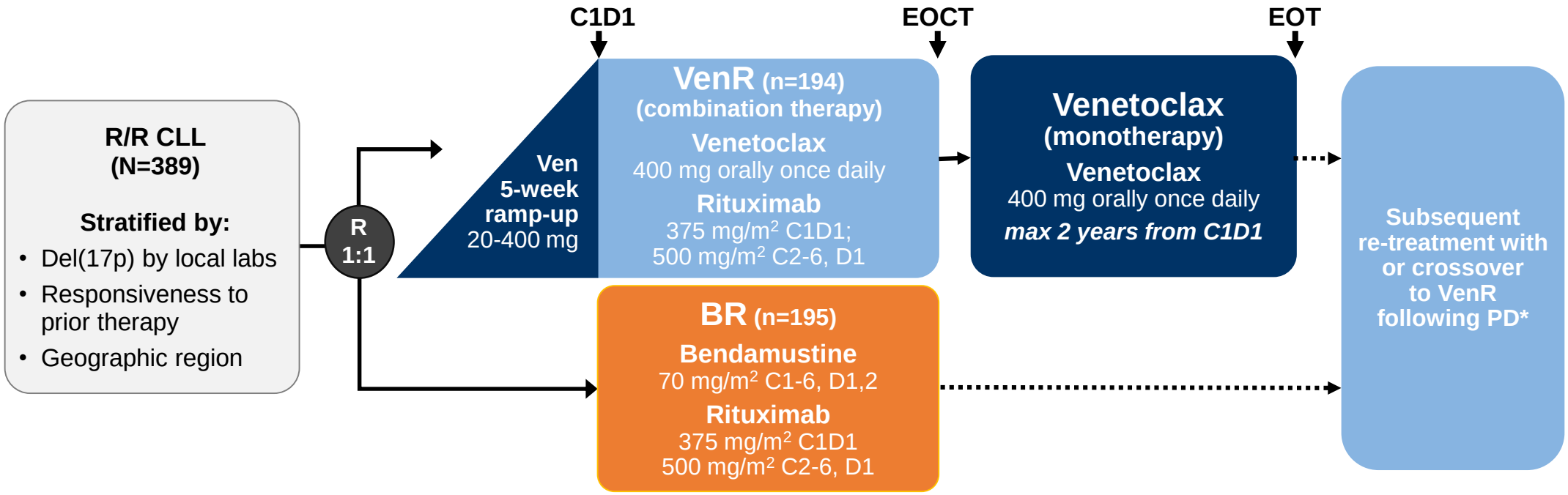


Venetoclax binds selectively to BCL-2, freeing pro-apoptotic proteins that initiate programmed cell death (apoptosis).[4-6]

1. Leverson JD, et al. *Sci Transl Med* 2015; 7:279ra40. 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. Brander et al. European 21st Congress Hematologic Association 2016. June 9-12 2016. Poster P223

MURANO Study (NCT02005471)

- Global, phase 3, open-label, randomized study[1]



- At 48 months of follow-up, deep responses with uMRD were associated with favorable PFS[2]

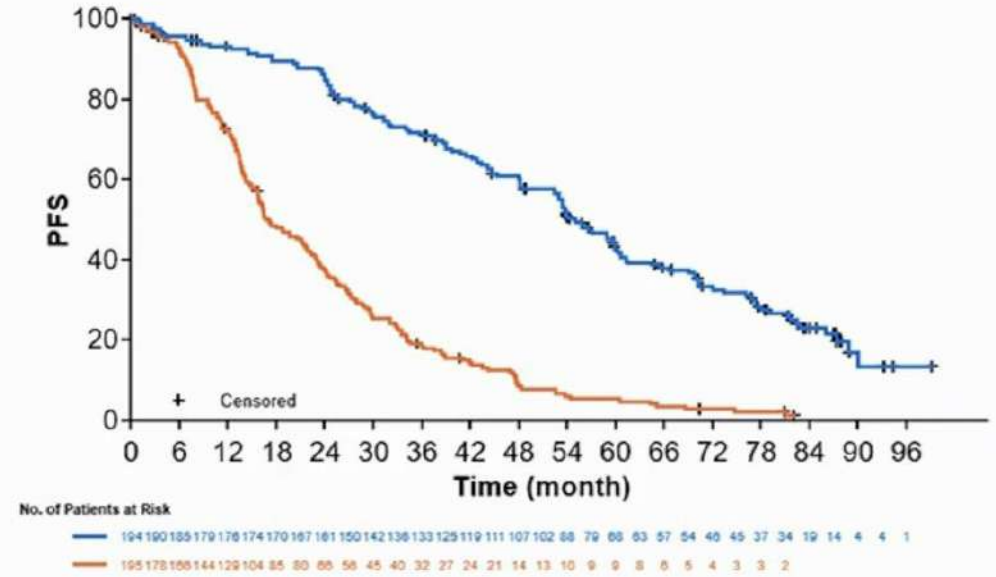
*Investigator-assessed PD according to IWCLL criteria.

C = cycle; D = day; EOCT = end of combination treatment; EOT = end of treatment; VenR = venetoclax-rituximab

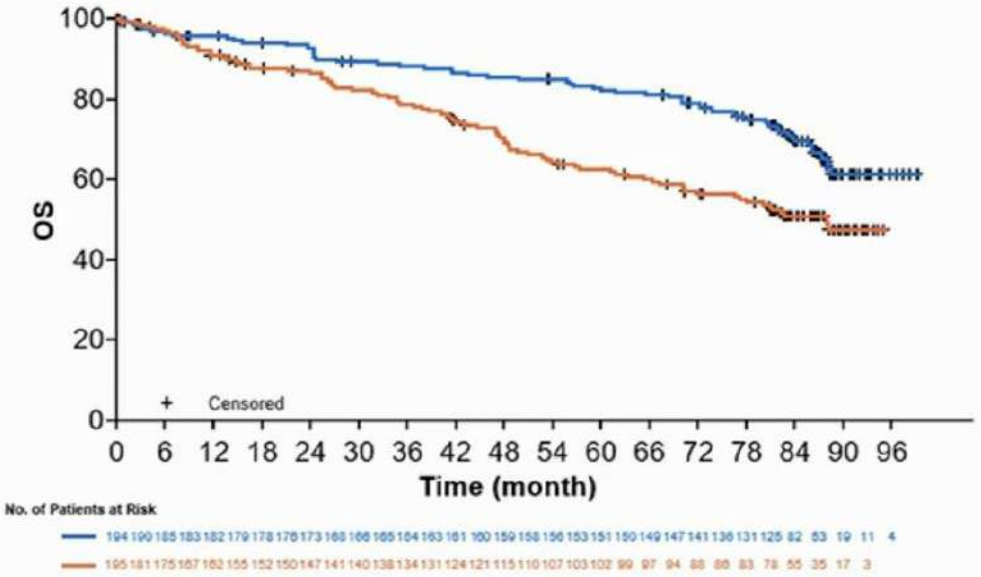
1. Seymour JF et al. *N Engl J Med*. 2018;378(12):1107-20. 2. Kater AP et al. *J Clin Oncol*. 2020;38(34):4042-54.

PFS and OS with VenR over BR were sustained at 7 years

	Median PFS (95% CI), months	HR* (95% CI)	7-year PFS (%)
VenR (n=194)	54.7 (52.3–59.9)	0.23 (0.18–0.29) Stratified P-value <0.0001†	23.0
BR (n=195)	17.0 (15.5–21.7)		NE



	Median OS (95% CI), months	HR‡ (95% CI)	7-year OS (%)
VenR (n=194)	NE	0.53 (0.37–0.74) Stratified P-value <0.0002†	69.6
BR (n=195)	87.8 (70.1–NE)		51.0

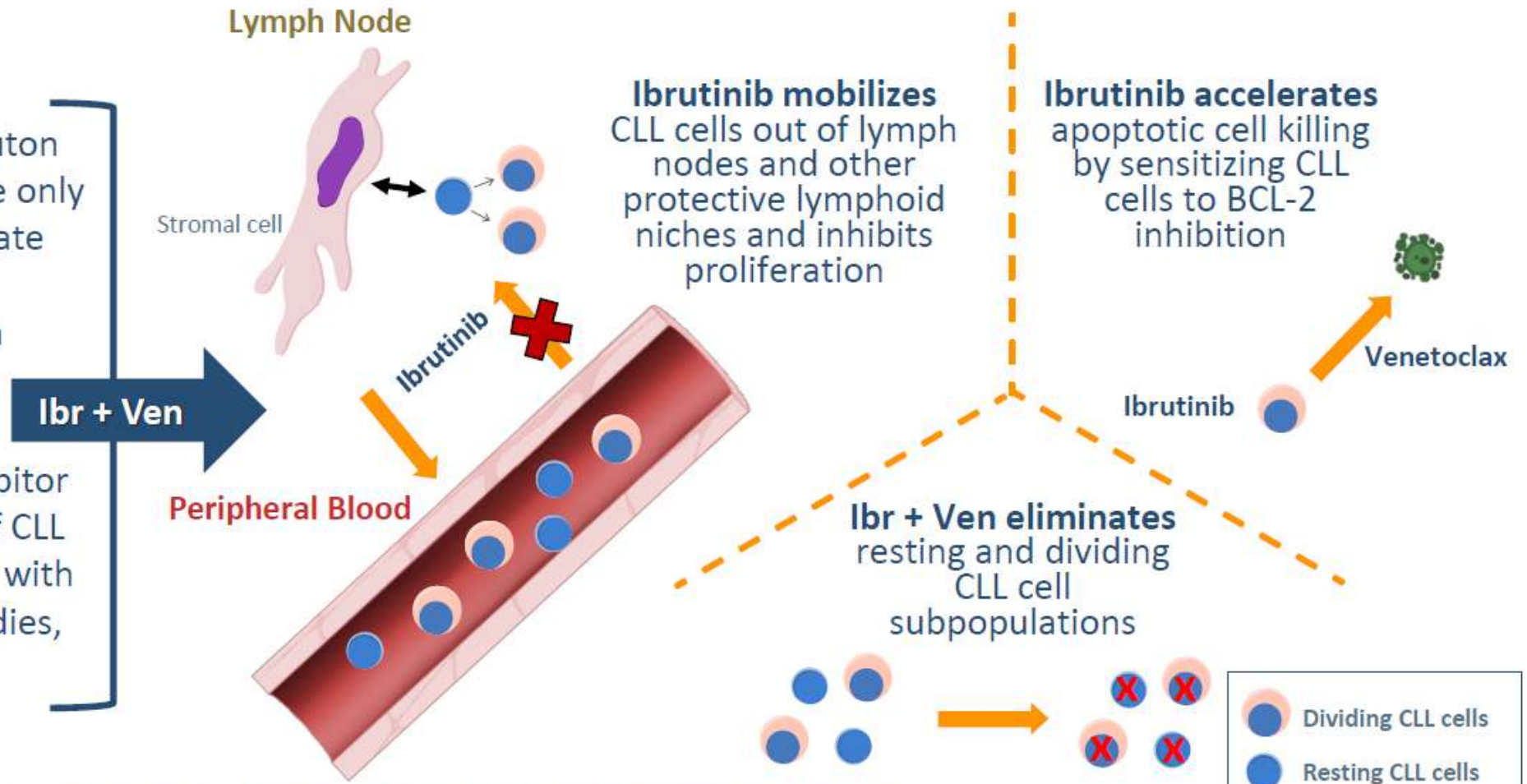


- Median follow up for efficacy (range) was 86.8 months (0.3–99.2) for VenR and 84.4 months (0.0−95.0) for BR
- No new safety signals were identified since the 5-year data cut,[1] with all patients outside of the AE reporting window§

Seymour J. ICML 2023. # 156

Rationale: Ibrutinib and Venetoclax Have Distinct and Complementary Modes of Action That Work Synergistically[1-3]

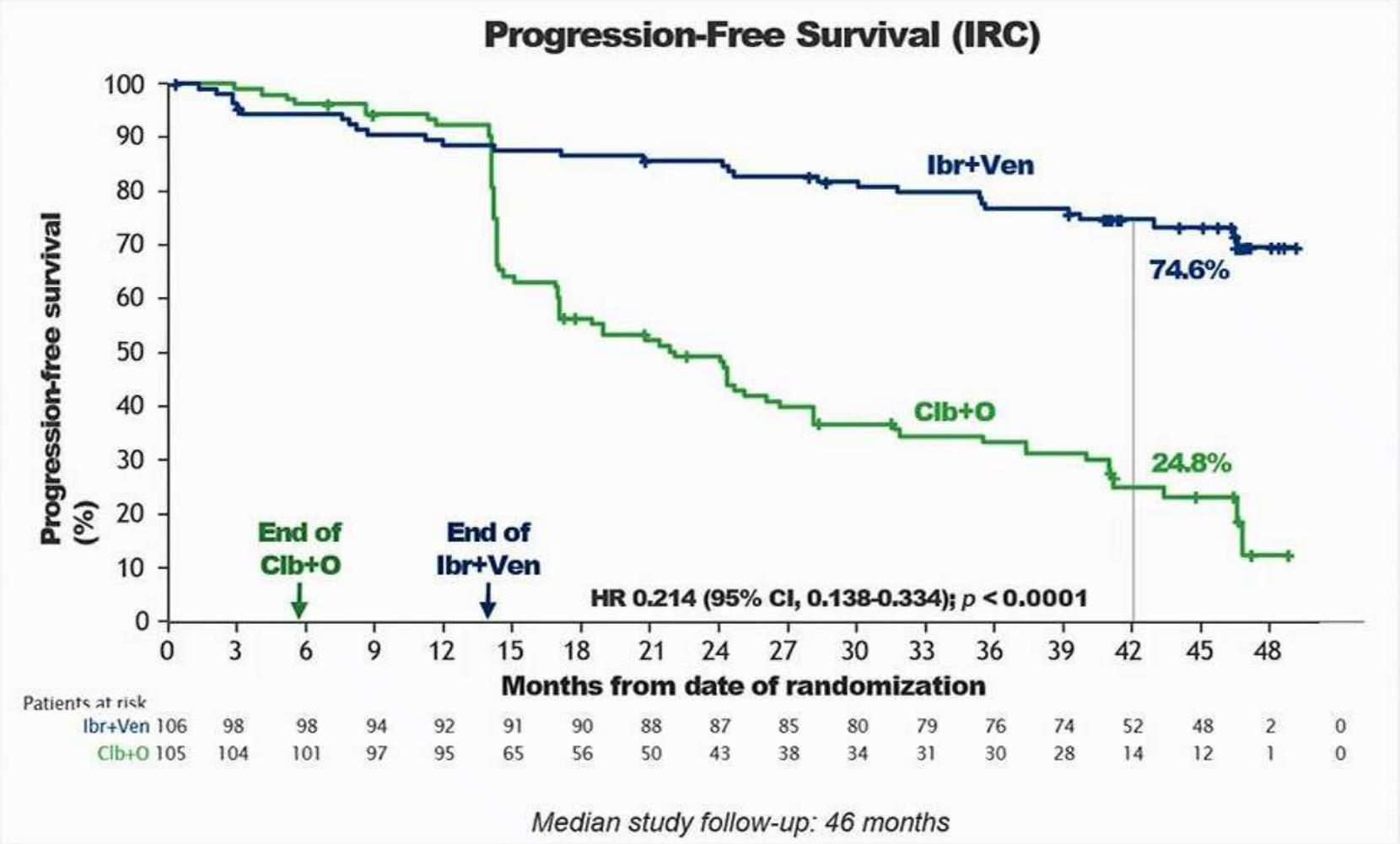
- Ibrutinib, a once-daily oral Bruton tyrosine kinase inhibitor, is the only targeted therapy to demonstrate significant OS benefit in randomized phase 3 studies in first-line CLL[4,5]
- Venetoclax, an oral BCL-2 inhibitor approved for the treatment of CLL as a single agent or combined with anti-CD20 monoclonal antibodies, achieves high rates of uMRD[6]



CLL, chronic lymphocytic leukemia; Ibr, ibrutinib; OS, overall survival; uMRD, undetectable minimal residual disease; Ven, venetoclax.

1. Lu P et al. *Blood Cancer J.* 2021;11:39. 2. Deng J et al. *Leukemia.* 2017;31:2075-2084. 3. Cervantes-Gomez F et al. *Clin Cancer Res.* 2015;21:3705-3715. 4. Burger JA et al. *Leukemia.* 2020;34:787-798. 5. Shanafelt T et al. *N Engl J Med.* 2019;381:432-443. 6. VENCLEXTA (venetoclax tablets) [package insert]. South San Francisco, CA: Genentech USA Inc; 2021.

GLOW: Progression-Free Survival by IRC Remained Superior For Ibr+Ven Versus Clb+O With 4 Years of Study Follow-up

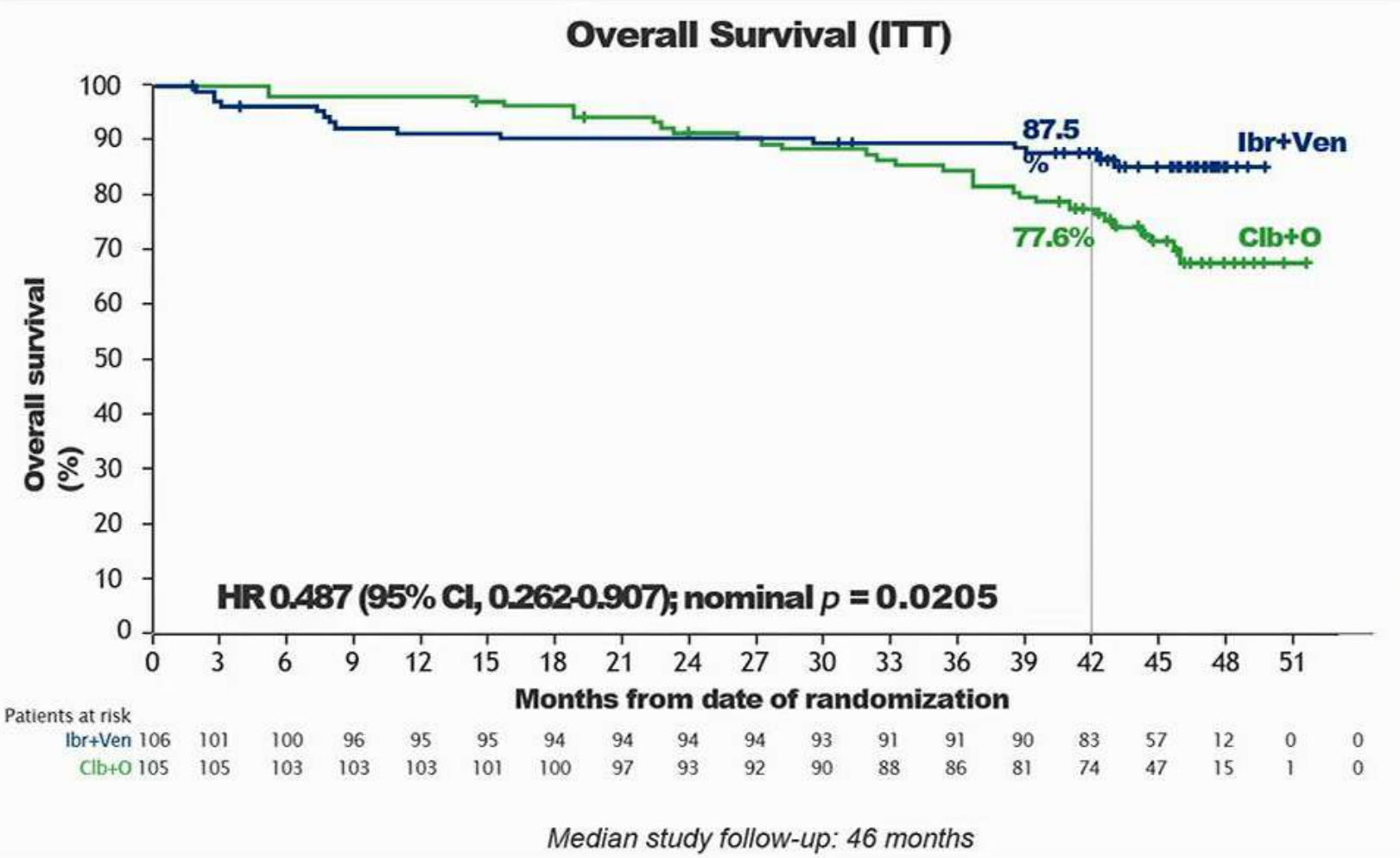


- **Ibr+Ven reduced the risk of progression or death by 79%** versus Clb+O
  - HR 0.214 (95% CI, 0.138-0.334); $p < 0.0001$
- Estimated 3.5-year PFS rates:
  - **74.6%** for Ibr+Ven
  - **24.8%** for Clb+O

uMRD rates at EOT+3 were 54.7% for Ibr+Ven and 39.0% for Clb+O

Niemann C, et al. ASH. 2022. Oral presentation # 93

GLOW: Ibr+Ven Improved Overall Survival Versus Clb+O With 4 Years of Study Follow-up



Median study follow-up: 46 months

- In the Clb+O arm, 39/41 patients requiring subsequent treatment received a BTKi or venetoclax
- The majority of deaths in the Clb+O arm occurred while off any treatment
- More infection-related deaths were seen in the Clb+O arm

Causes of Death

n (%)	Ibr+Ven (N = 106)	Clb+O (N = 105)
PD	1 (0.9)	2 (1.9)
Infections	4 (3.8)	11 (10.5)
Other[a]	10 (9.4)	17 (16.2)
TOTAL	**15 (14.2)**	**30 (28.6)**

[a]Cause and number (Ibr+Ven arm, Clb+O arm) of "other" deaths: general/unknown (4, 5), cardiac (2, 4), central nervous system (2, 3), neoplasm (1, 3), euthanasia (1

ITT, intent to treat; BTKi, Bruton's tyrosine kinase inhibitor; PD, progressive disease; HR hazard ratio; CI, confidence interval.

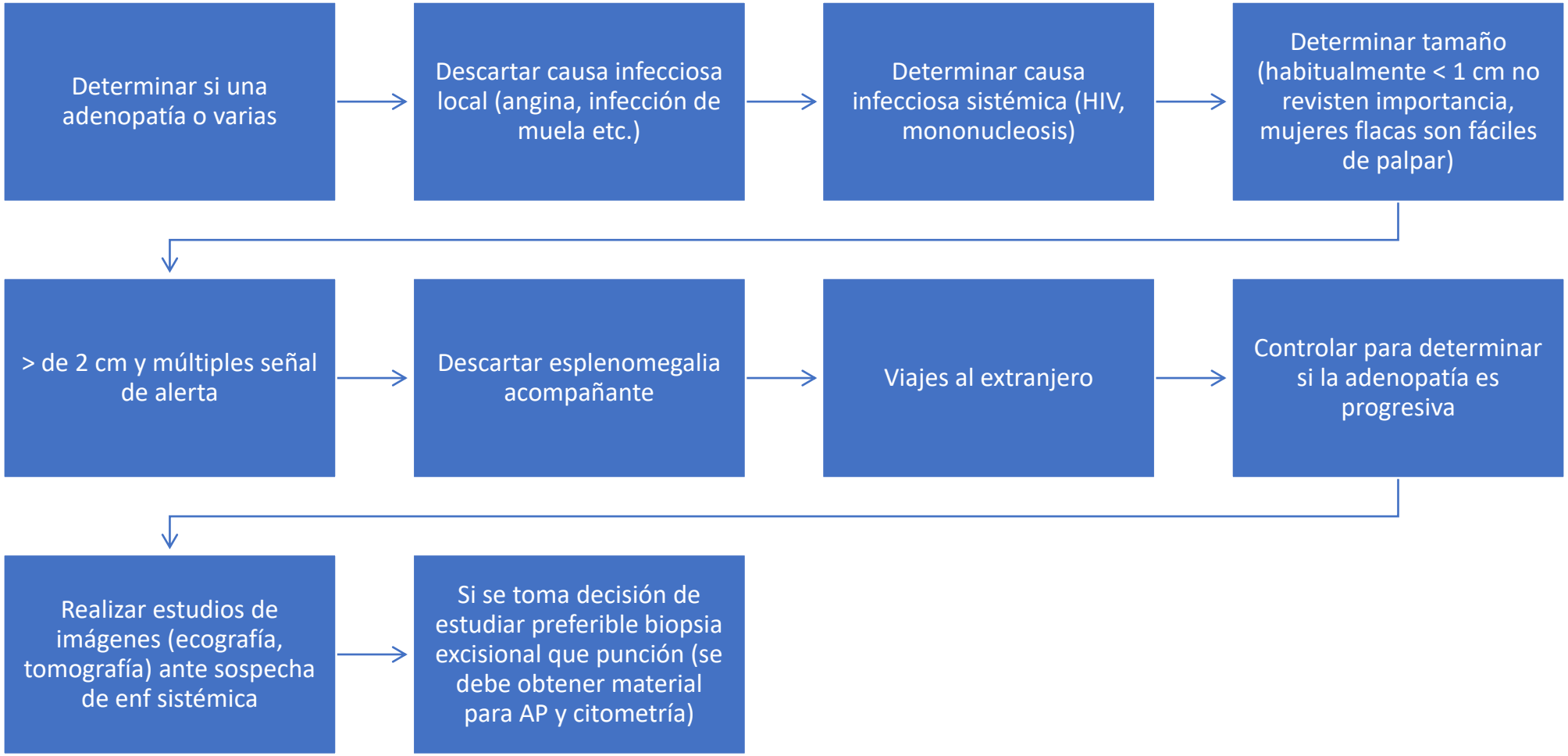
Niemann C, et al. ASH. 2022. Oral presentation # 93

Evaluación del paciente con adenopatía periférica (dilema diagnostico)

- Determinar si una adenopatía o varias, descatar esplenomegalia acompañante
- Descartar causa infecciosa local (angina, infección de muela etc.)
- Determinar causa infecciosa sistémica (HIV, mononucleosis)
- Determinar tamaño (habitualmente < 1 cm no revisten importancia, mujeres flacas son fáciles de palpar)
- > de 2 cm y múltiples adenopatías señal de alerta!!

- Viajes al extranjero
- Controlar para determinar si la adenopatía es progresiva
- Realizar estudios de imágenes (ecografía, tomografía) ante sospecha de enf sistémica
- Si se toma decisión de estudiar preferible biopsia excisional que punción (se debe obtener material para AP y citometría)

Evaluación del paciente con adenopatía periférica (dilema diagnostico)



Evaluación del paciente con adenopatía periférica (dilema diagnostico)

- En una serie pacientes con ganglios <1 cm^2 ninguno tuvo cáncer como parado con:
- 8 % cáncer entre 1 -2 .25 cm^2
- 38 % cáncer con ganglios y >2 .25 cm^2 *

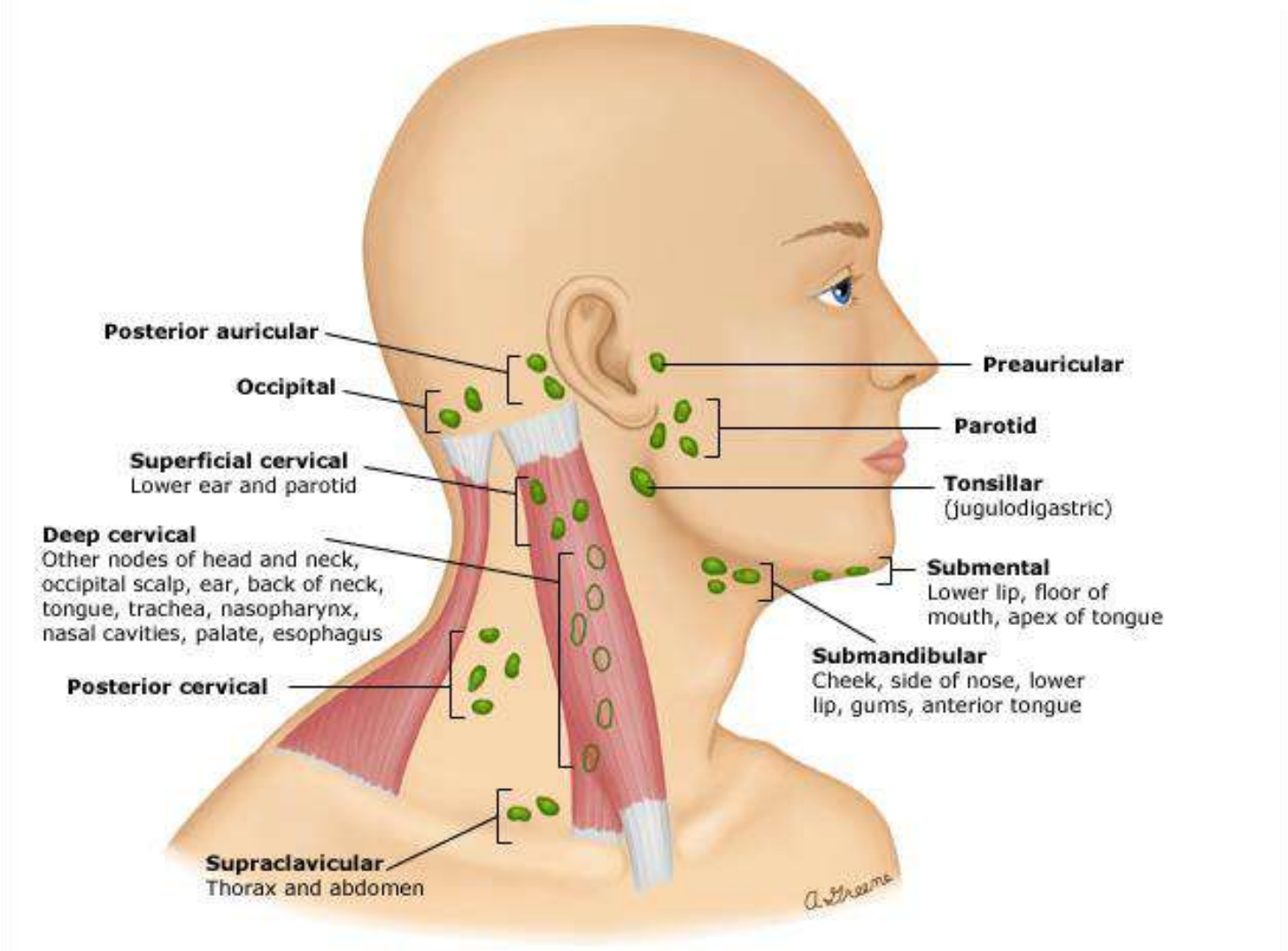
Consistencia

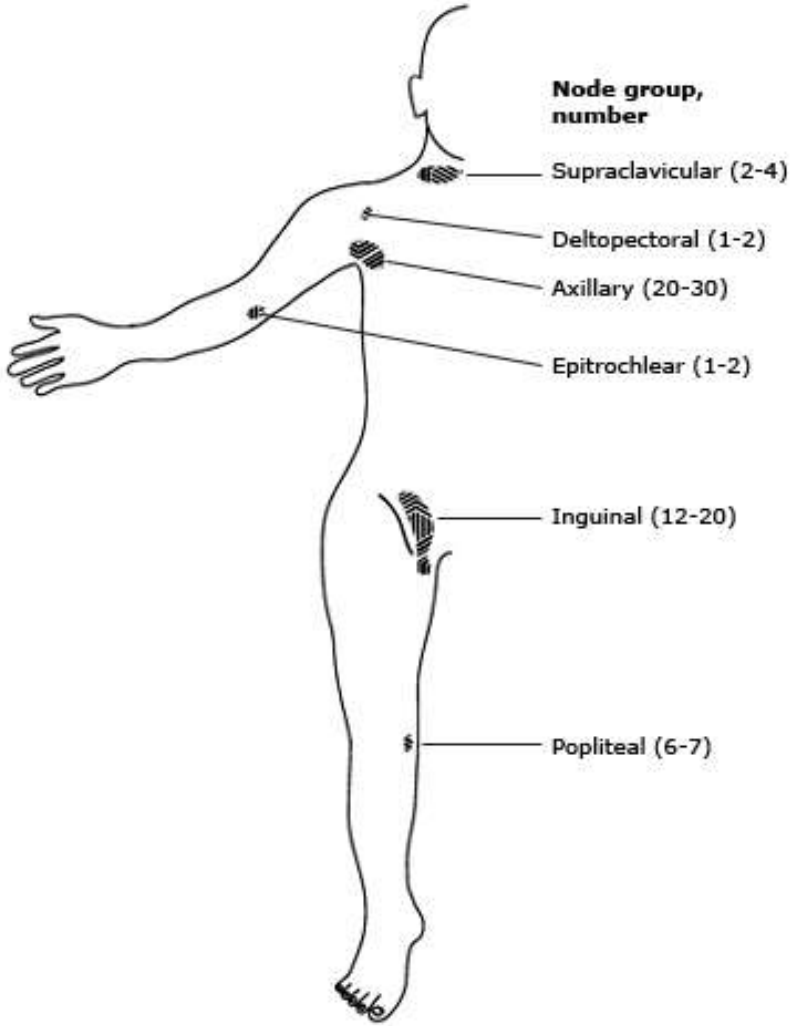
- Duro pétreo
- Elásticos firmes
- Blandos grandes

- Si la sospecha es alta de síndrome linfoproliferativo se puede solicitar panTC o PET

* Pangalis GA et al.Semin Oncol. 1993;20(6):570.

Adenopatías periféricas





Adenopatías: localización

Lymph node groups: Location, lymphatic drainage and selected differential diagnosis*

Location	Lymphatic drainage	Causes
Submandibular	Tongue, submaxillary gland, lips and mouth, conjunctivae	Infections of head, neck, sinuses, ears, eyes, scalp, pharynx
Submental	Lower lip, floor of mouth, tip of tongue, skin of cheek	Mononucleosis syndromes, Epstein-Barr virus, cytomegalovirus, toxoplasmosiss
Jugular	Tongue, tonsil, pinna, parotid	Pharyngitis organisms, rubella
Posterior cervical	Scalp and neck, skin of arms and pectorals, thorax, cervical and axillary nodes	Mononucleosis syndromes, Epstein-Barr virus, tuberculosis, lymphoma, head and neck malignancy
Suboccipital	Scalp and head	Local infection
Postauricular	External auditory meatus, pinna, scalp	Local infection
Preauricular	Eyelids and conjunctivae, temporal region, portions of the auricle and external ear canal	Local infection
Right supraclavicular node	Mediastinum, lungs, esophagus	Lung, retroperitoneal, or esophageal cancer; lymphoma; bacterial or fungal infection
Left supraclavicular node	Thorax, abdomen (via thoracic duct)	Gastrointestinal, abdominal, thoracic, or retroperitoneal cancer; lymphoma; bacterial or fungal infection
Axillary	Arm, thoracic wall, breast	Infections, cat-scratch disease, lymphoma, breast cancer, silicone implants, brucellosis, melanoma
Epitrochlear	Ulnar aspect of forearm and hand	Infections, lymphoma, sarcoidosis, tularemia, secondary syphilis
Inguinal	Penis, scrotum, vulva, vagina, perineum, gluteal region, lower abdominal wall, lower anal canal	Infections of the leg or foot, STIs (eg, herpes simplex virus, gonococcal infection, syphilis, chancroid, granuloma inguinale, lymphogranuloma venereum), lymphoma, pelvic malignancy, bubonic plague

STIs: sexually transmitted infections.

* This is a partial list and not meant to be all-inclusive.

Causas de adenopatías periféricas

Cause	Examples
Infections	
Bacterial	
▪ Localized	Streptococcal pharyngitis; skin infections; tularemia; plague; cat scratch disease; diphtheria; chancroid; rat bite fever; early Lyme disease; early (primary) syphilis
▪ Generalized	Brucellosis; leptospirosis; lymphogranuloma venereum; typhoid fever; secondary syphilis
Viral	Human immunodeficiency virus; Epstein-Barr virus; herpes simplex virus; cytomegalovirus; mumps; measles; rubella; hepatitis B; dengue fever
Mycobacterial	*Mycobacterium tuberculosis*; atypical mycobacteria
Fungal	Histoplasmosis; coccidioidomycosis; cryptococcosis
Protozoal	Toxoplasmosis; leishmaniasis
Cancer	Squamous cell cancer of the head and neck; metastatic skin cancer (face and scalp); metastatic cancer from another site; lymphoma; leukemia
Lymphoproliferative	Angioimmunoblastic lymphadenopathy with dysproteinemia
	Autoimmune lymphoproliferative disease
	Rosai-Dorfman disease
	Hemophagocytic lymphohistiocytosis
Immunologic	Serum sickness; drug reactions (phenytoin); IgG4-related disease
Endocrine	Primary adrenal insufficiency (Addison's disease)
Miscellaneous	Sarcoidosis; lipid storage diseases; amyloidosis; histiocytosis; chronic granulomatous diseases; Castleman disease; Kikuchi disease; Kawasaki disease; inflammatory pseudotumor; systemic lupus erythematosus; rheumatoid arthritis; Still's disease; dermatomyositis; eosinophilic granulomatosis with polyangiitis (Churg-Strauss)

Causas no malignas

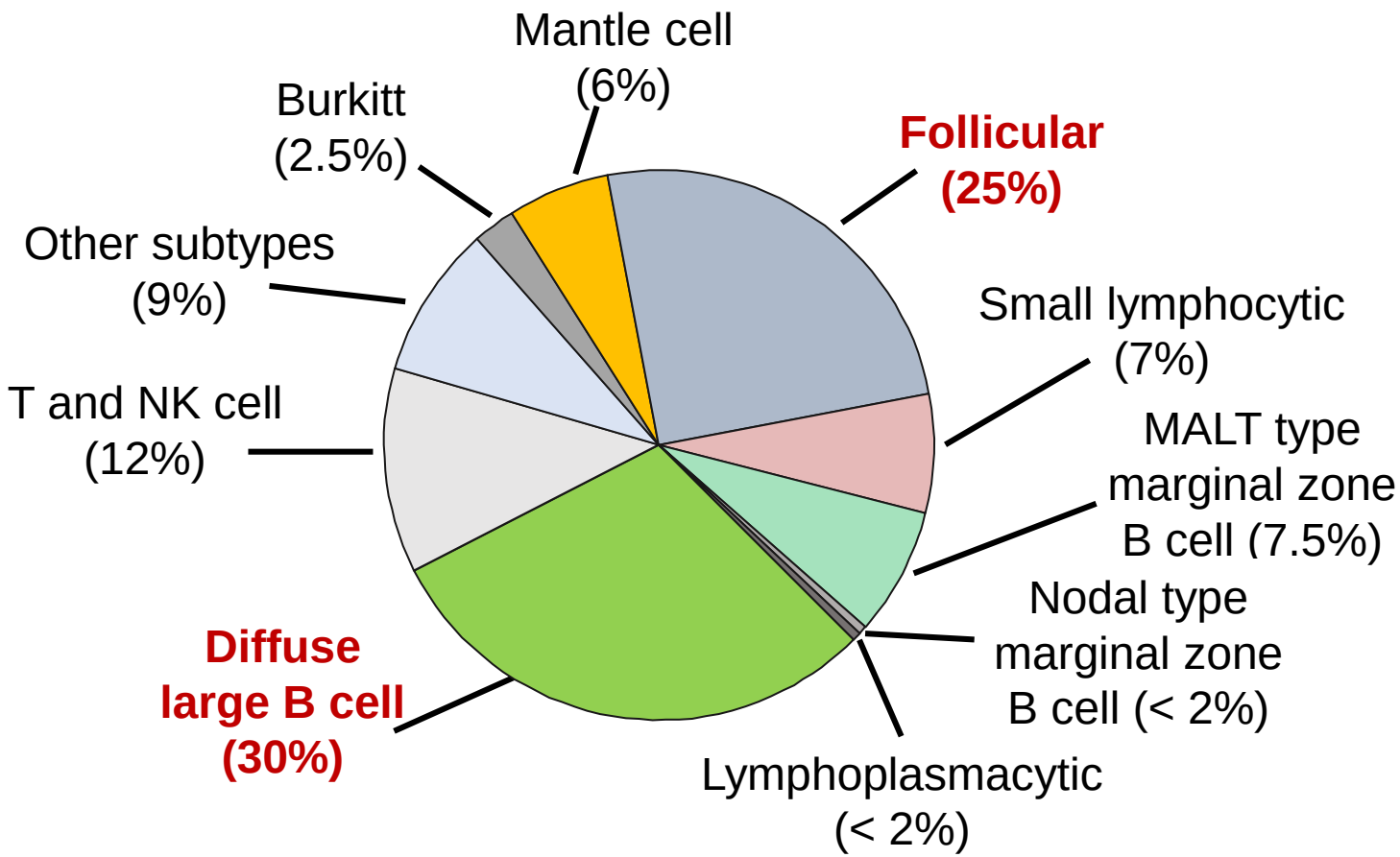
- **Infecciosas** (HIV, mononucleosis, micobacterias etc)
- **Medicamentosa –** Fenitoina puede causar adenopatías generalizadas
- **Lupus eritematoso sitemico** – pueden presentar adenopatías el 50 % de los pacientes con LES
- **Sarcoidosis** – mas frecuentemente ocurre en pulmón hasta un 30% presentan manifestaciones extratorácicas
- **Enfermedad de Castleman**– hiperplasia angiofolicular
- **Enfermedad de Kikuchi** mas frecuentemente en mujeres jóvenes caracterizada por adenopatías cervicales
- **Enfermedad de Kawasaki** – es una forma infrecuente de vasculitis ocurre en niños
- **Enfermedad de Rosai-Dorfman** – es una condición caracterizada por adenopatías debido a acumulación de histiocitos en los ganglios usualmente cervicales

Clasificación histórica de Linfomas

1832	Hodgkin	A report of seven lymphoma cases
1966	Rappaport	Rappaport Classification
1974	Lukes–Collins	Lukes–Collins Classification
1978	Lennert	Keil Classification
1982	National Cancer Institute	Working Formulation of Non-Hodgkin Lymphoma
1988	Stansfeld et al.	Updated Keil Classification
1994	Harris et al.	REAL Classification
2001	Jaffe et al.	2001 WHO Classification
2008	Swerdlow et al.	2008 WHO Classification

REAL, Revised European-American Classification of Lymphoid Neoplasms; *WHO*, World Health Organization.

Non Hodgkin's Lymphoma: Incidence



Lichtman. Williams Hematology, 7th edition. 2006;1408.

Clasificación WHO Linfoma de Hodgkin

TABLE 56.7 **Hodgkin Lymphoma**

- Nodular lymphocyte-predominant Hodgkin lymphoma
- Classic Hodgkin lymphoma
  - Nodular sclerosis classic Hodgkin lymphoma
  - Lymphocyte-rich classic Hodgkin lymphoma
  - Mixed cellularity classic Hodgkin lymphoma
  - Lymphocyte-depleted classic Hodgkin lymphoma

5 entidades

Clasificación WHO Neoplasias B maduras

- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- Splenic lymphoma/leukemia, unclassifiable
- Splenic diffuse red pulp small B-cell lymphoma
- Hairy cell leukemia variant
- Lymphoplasmacytic lymphoma
- Waldenström macroglobulinemia
- Heavy chain diseases
  - μHeavy chain disease
  - γHeavy chain disease
  - αHeavy chain disease
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extraosseous plasmacytoma
- Extranodal marginal zone lymphoma of MALT lymphoma
- Nodal marginal zone lymphoma
- Pediatric nodal marginal zone lymphoma
- Follicular lymphoma
- Pediatric follicular lymphoma
- Primary cutaneous follicle center lymphoma

36 entidades

- Mantle cell lymphoma
- DLBCL, NOS
- T-cell/histiocyte–rich large B-cell lymphoma
- Primary DLBCL of the CNS
- Primary cutaneous DLBCL, leg type
- EBV-positive DLBCL of the elderly
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK-positive large B-cell lymphoma
- Plasmablastic lymphoma
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
- Primary effusion lymphoma
- Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classic Hodgkin lymphoma

Clasificación WHO Neoplasias maduras T y NK

TABLE 56.10 World Health Organization Classification of Mature T-Cell and Natural Killer Cell Neoplasms

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- Chronic lymphoproliferative disorder of NK cells
- Aggressive NK-cell leukemia
- Systemic EBV-positive T-cell lymphoproliferative disease of childhood
- Hydroa vacciniforme-like lymphoma
- Adult T-cell leukemia/lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous $CD30^-$ T-cell lymphoproliferative disorders
- Lymphomatoid papulosis
- Primary cutaneous anaplastic large-cell lymphoma
- Primary cutaneous T-cell lymphoma
- Primary cutaneous aggressive epidermotropic $CD8^+$ cytotoxic T-cell lymphoma
- Primary cutaneous small/medium $CD4^+$ T-cell lymphoma
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large-cell lymphoma, ALK-positive
- Anaplastic large-cell lymphoma, ALK-negative

23 entidades

Total = 64 entidades (Linfomas B, T y Hodgkin)

WHO 2022 5th. ICC 2022

CLASIFICACIONES ACTUALES BASADAS EN :
CLÍNICA ,MORFOLOGÍA , FENOTIPO Y GENOTIPO

The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee

Elias Campo,[1] Elaine S. Jaffe,[2] James R. Cook,[3] Leticia Quintanilla-Martinez,[4] Steven H. Swerdlow,[5] Kenneth C. Anderson,[6] Pierre Brousset,[7] Lorenzo Cerroni,[8] Laurence de Leval,[9] Stefan Dirnhofer,[10] Ahmet Dogan,[11] Andrew L. Feldman,[12] Falko Fend,[4] Jonathan W. Friedberg,[13] Philippe Gaulard,[14,15] Paolo Ghia,[16] Steven M. Horwitz,[17] Rebecca L. King,[12] Gilles Salles,[17] Jesus San-Miguel,[18] John F. Seymour,[19] Steven P. Treon,[6] Julie M. Vose,[20] Emanuele Zucca,[21] Ranjana Advani,[22] Stephen Ansell,[23] Wing-Yan Au,[24] Carlos Barrionuevo,[25] Leif Bergsagel,[26] Wing C. Chan,[27] Jeffrey I. Cohen,[28] Francesco d'Amore,[29] Andrew Davies,[30] Brunangelo Falini,[31] Irene M. Ghobrial,[6,32] John R. Goodlad,[33] John G. Gribben,[34] Eric D. Hsi,[35] Brad S. Kahl,[36] Won-Seog Kim,[37] Shaji Kumar,[23] Ann S. LaCasce,[6] Camille Laurent,[7] Georg Lenz,[38] John P. Leonard,[39] Michael P. Link,[40] Armando Lopez-Guillermo,[41] Maria Victoria Mateos,[42] Elizabeth Macintyre,[43] Ari M. Melnick,[44] Franck Morschhauser,[45] Shigeo Nakamura,[46] Marina Narbaitz,[47] Astrid Pavlovsky,[48] Stefano A. Pileri,[49] Miguel Piris,[50] Barbara Pro,[51] Vincent Rajkumar,[12] Steven T. Rosen,[52] Birgitta Sander,[53] Laurie Sehn,[54] Margaret A. Shipp,[6] Sonali M. Smith,[55] Louis M. Staudt,[56] Catherine Thieblemont,[57,58] Thomas Tousseyn,[59] Wyndham H. Wilson,[56] Tadashi Yoshino,[60] Pier-Luigi Zinzani,[61] Martin Dreyling,[62] David W. Scott,[54] Jane N. Winter,[63] and Andrew D. Zelenetz[17,64]

Blodd; 15 september 2022. Volume 140,

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms

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Leukemia; 2022

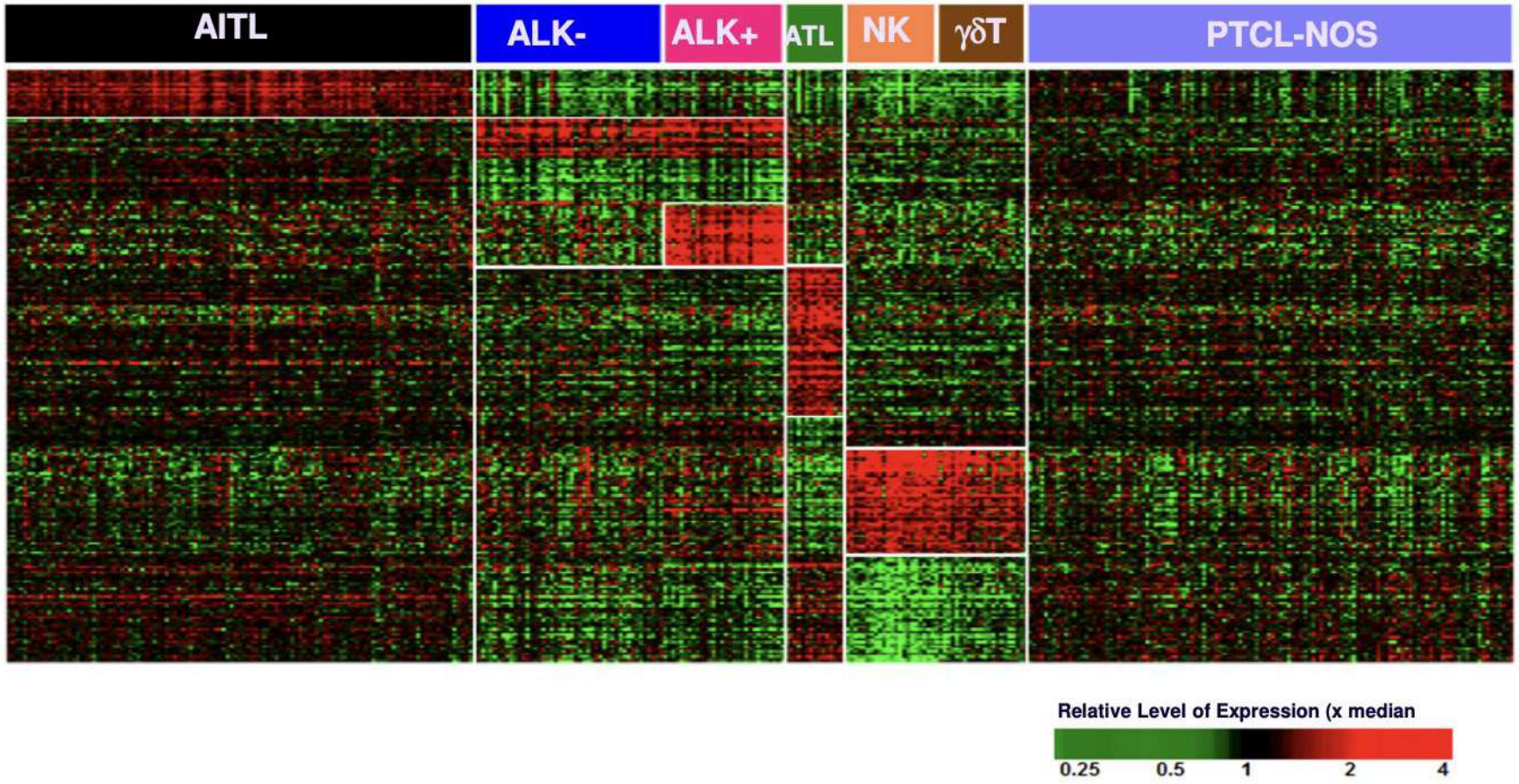
Individual evaluation of each case by experts in haematopathology

Diagnostic value of somatic mutations in mature small B-cell lymphoid neoplasms

Hairy Cell Leukemia	***BRAF* V600E**	**79-100% HCL** 4% Plasma cell myeloma 3% NHL (Other BRAF mut)
HCL-v **HCLc IGHV4-34**	***MAP2K1***	**50% HCLv** **50% HCLc IGHV4-34** 0% HCL BRAFmut
Waldenström M/LPL	***MYD88* L265P**	**90% WM** 29% DLBCL-ABC 6% MZL 3% CLL

Tiacci et al NEJM 2011 Ngo Nature 2011; Puente Nature 2011;
Xi L et al Blood 2012; Xu et al ASH 2011; Hunter Z et al ASH 2011;Waterfall Nat Genet 2014

Gene expression profiling allows reclassification of 14% of PTCL, NOS as AITL

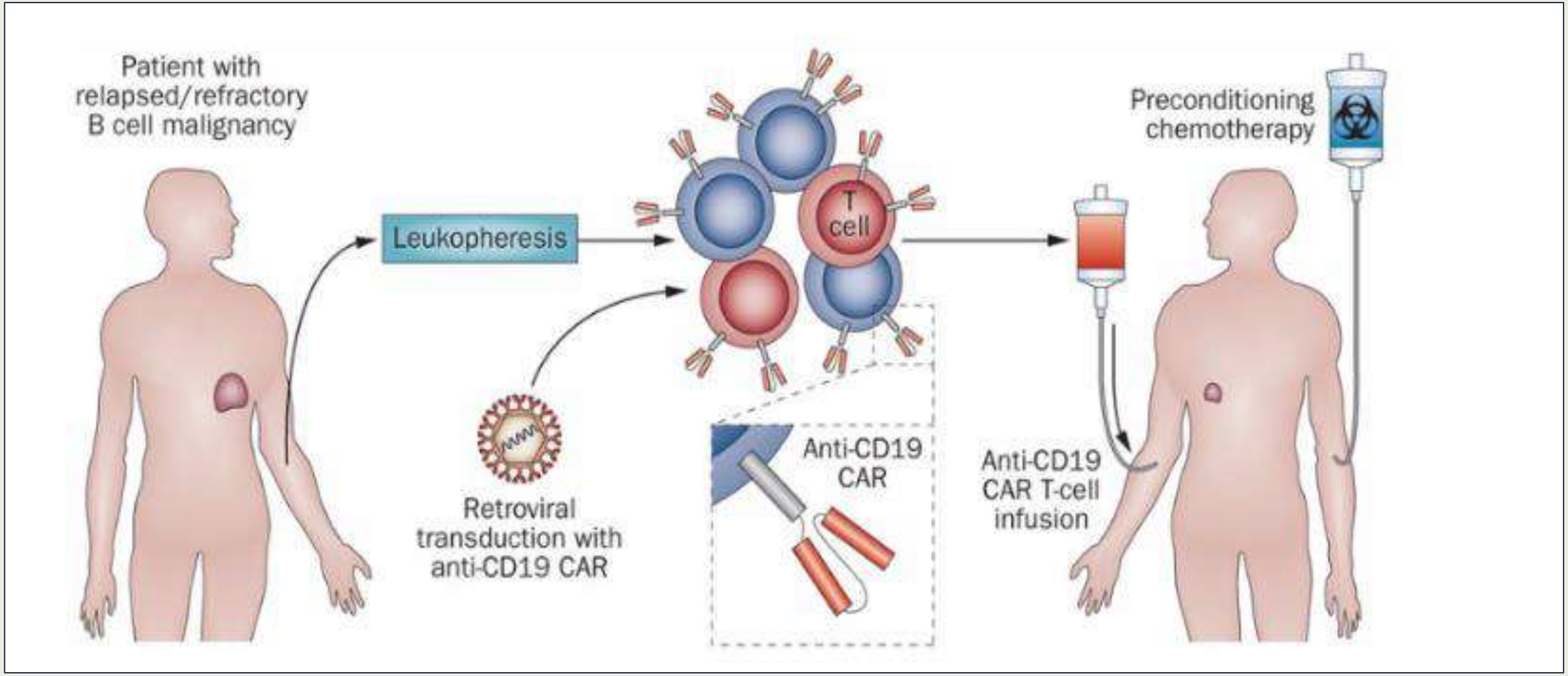


Gene expression signatures of PTCL ; Iqbal et al. *Blood 2014*

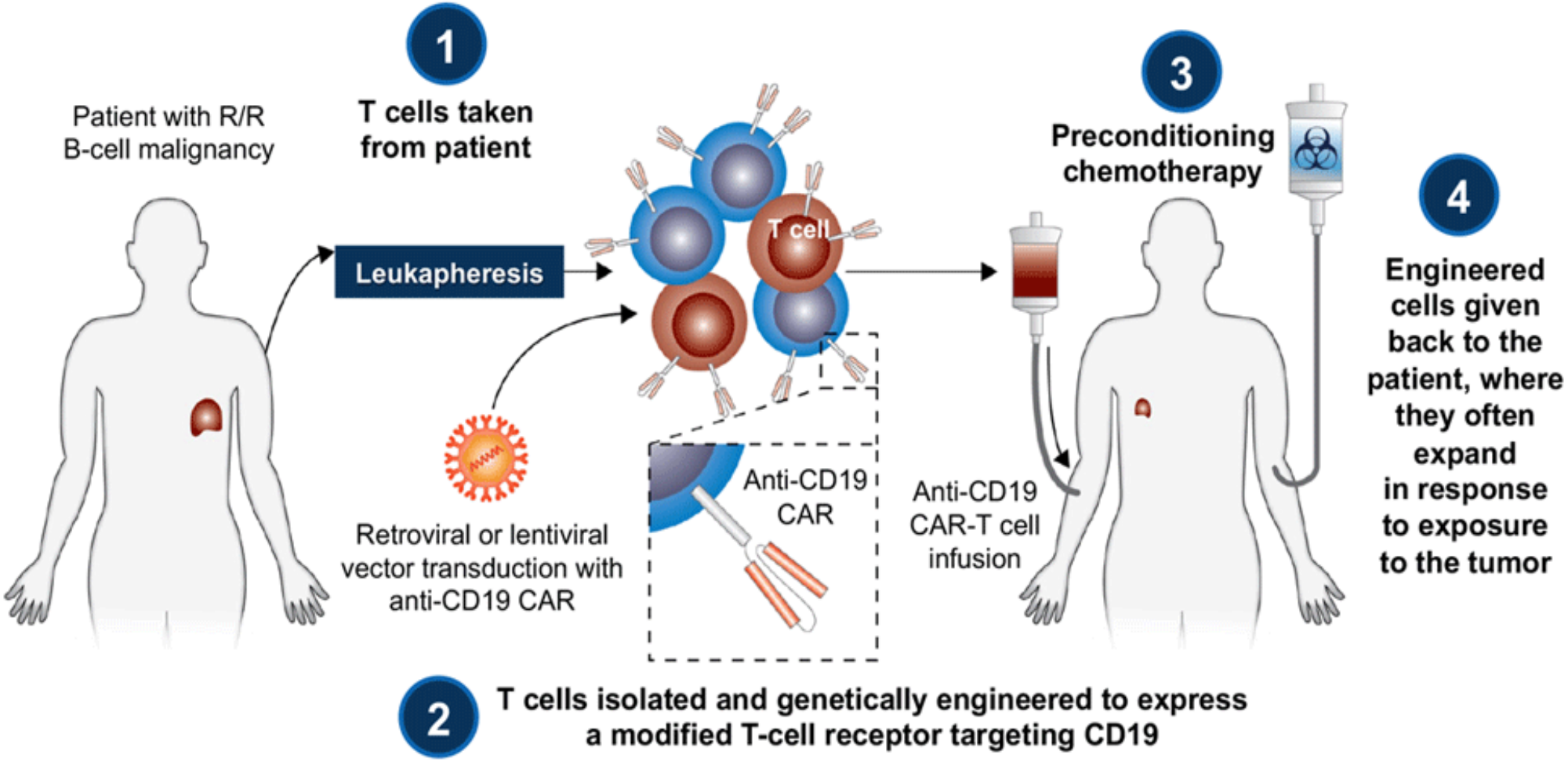
Terapias celulares

Lifnomas – LLC – Mieloma Multiple – Leucemia Linfoblastica

Terapias celulares: CARTs

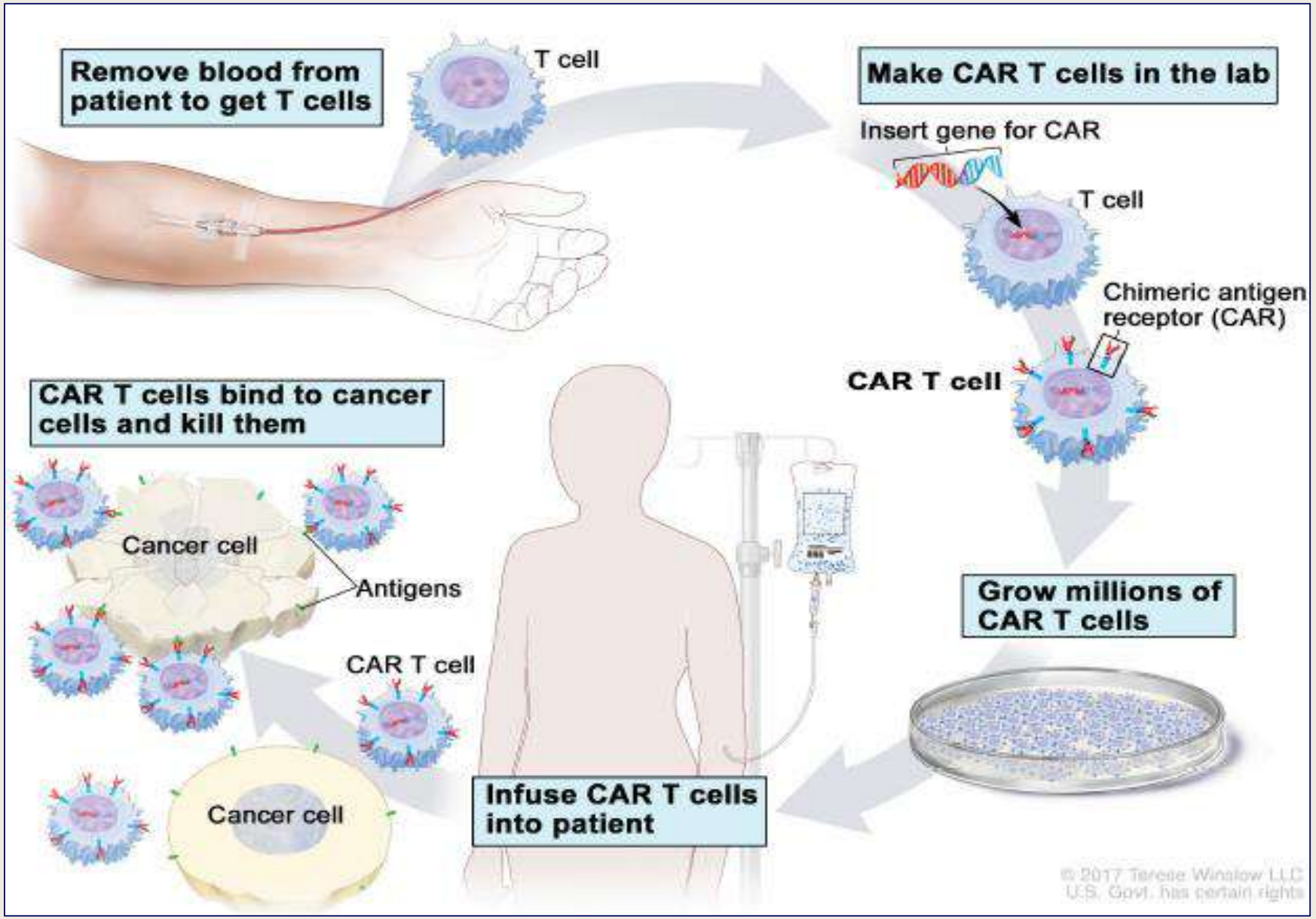


Overview of CAR-T Cell Therapy[1,2]

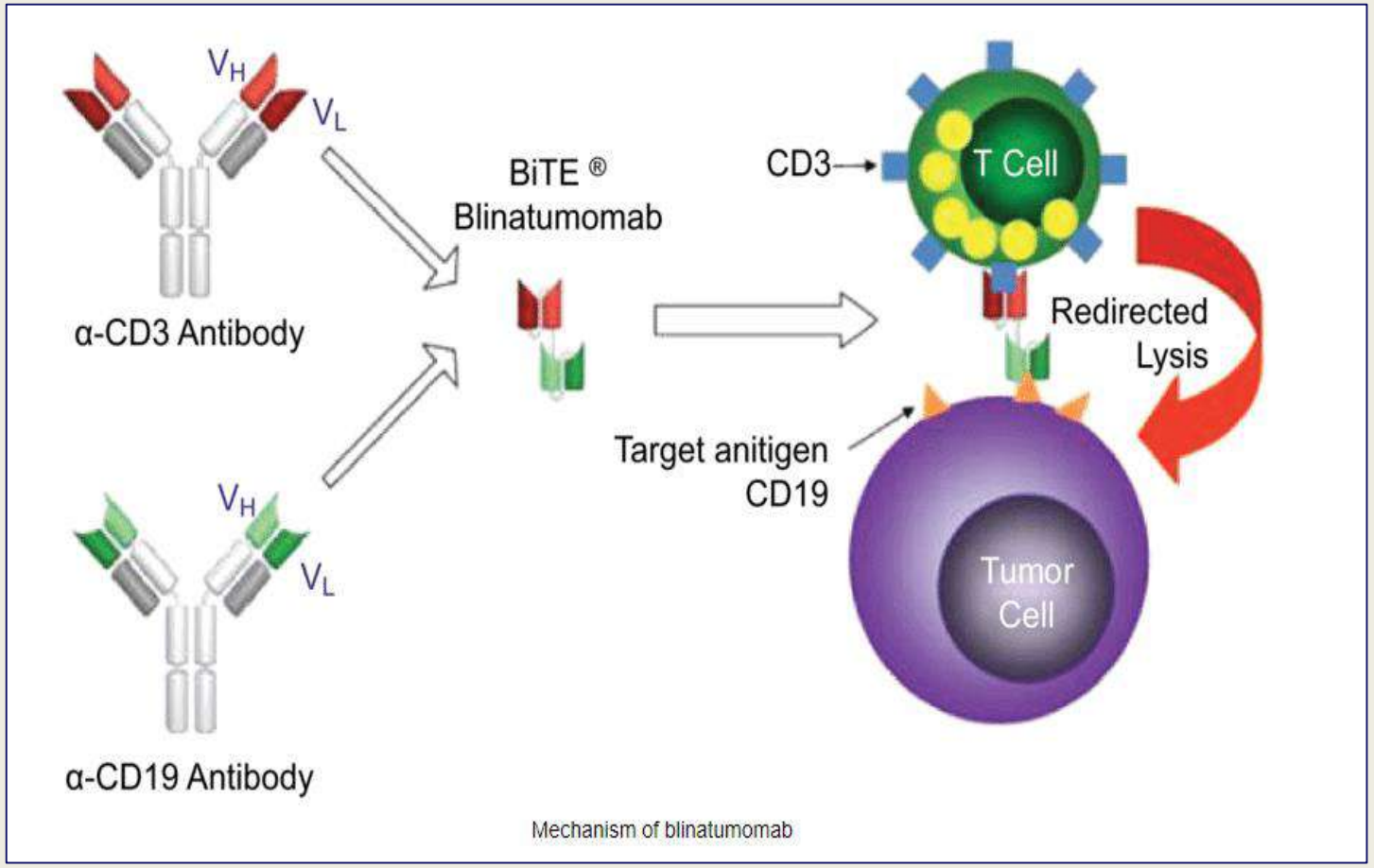


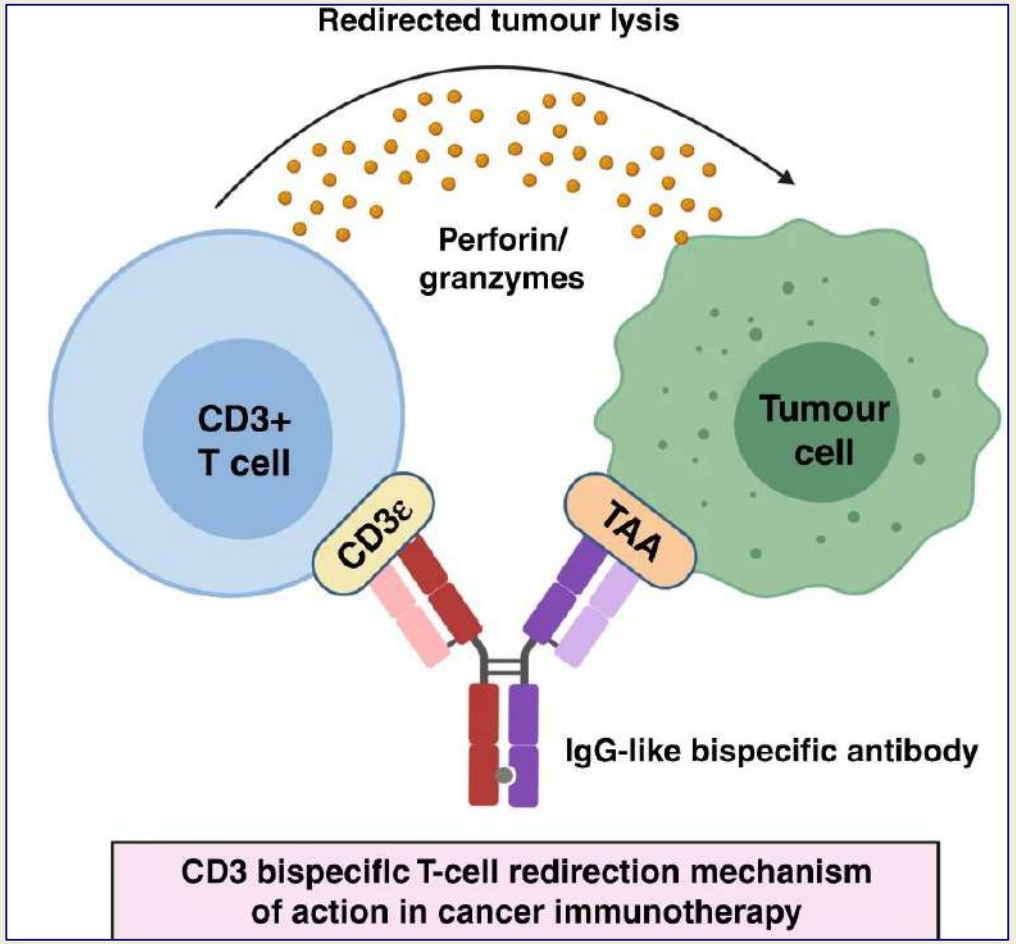
1. https://labiotech.eu/immuno-oncology-history-car-t-nyt/. 2. Levine BL. *Cancer Gene Ther*. 2015;22:79-84.

Terapias celulares: CARTs

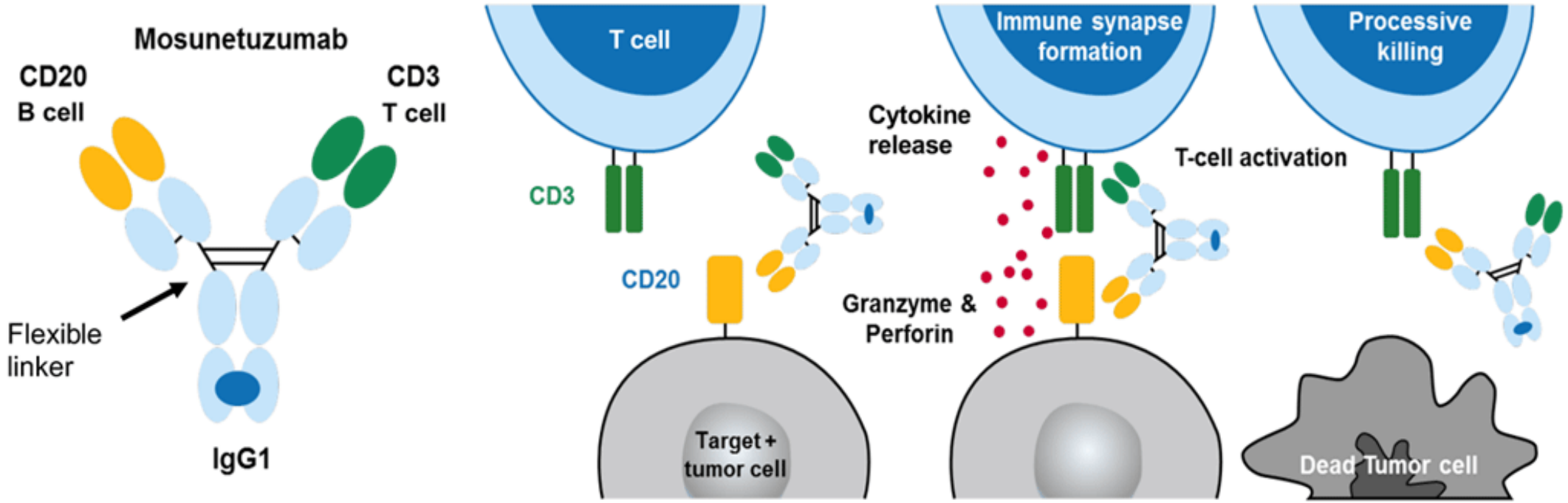


Mecanismo de Acción de los Bites





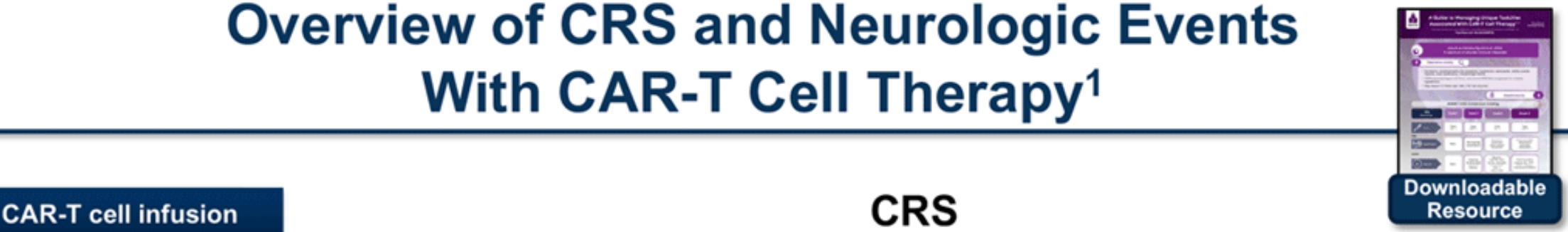
The Mechanisms of T-Cell Dependent Bispecific Antibodies[1]

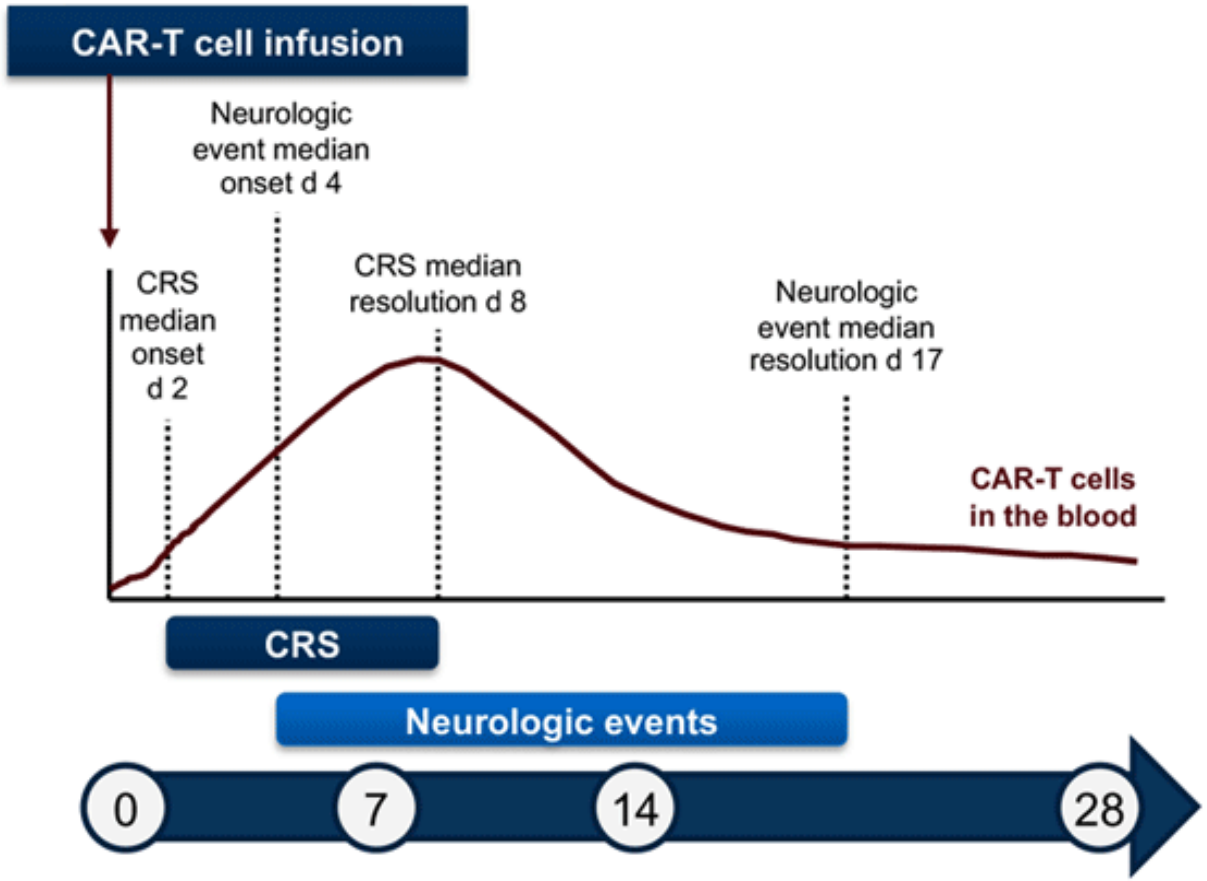


Redirects cytotoxicity of endogenous T cells against malignant B cells by simultaneously binding to CD3 on T cells and a tumor-associated antigen on B cells[1]

1. Sun LL et al. *Sci Transl Med.* 2015;7:287ra70.

Overview of CRS and Neurologic Events With CAR-T Cell Therapy[1]





CRS

Common	Serious
• Fever • Hypotension • Tachycardia • Hypoxia • Chills	• Atrial fibrillation • Ventricular tachycardia • Cardiac arrest • Cardiac failure • Renal insufficiency • Capillary leak syndrome • Hypotension • Hypoxia • HLH/MAS

Neurologic Events

Common	Serious
• Encephalopathy • Tremor • Dizziness • Delirium • Confusion • Agitation	• Seizures • Leukoencephalopathy • Cerebral edema • Aphasia • Obtundation

1. Jacobson C et al. *Oncologist*. 2020;25:e138-e146.

Epcoritamab with rituximab + lenalidomide (R^2) provides durable responses in high-risk follicular lymphoma, regardless of POD24 status

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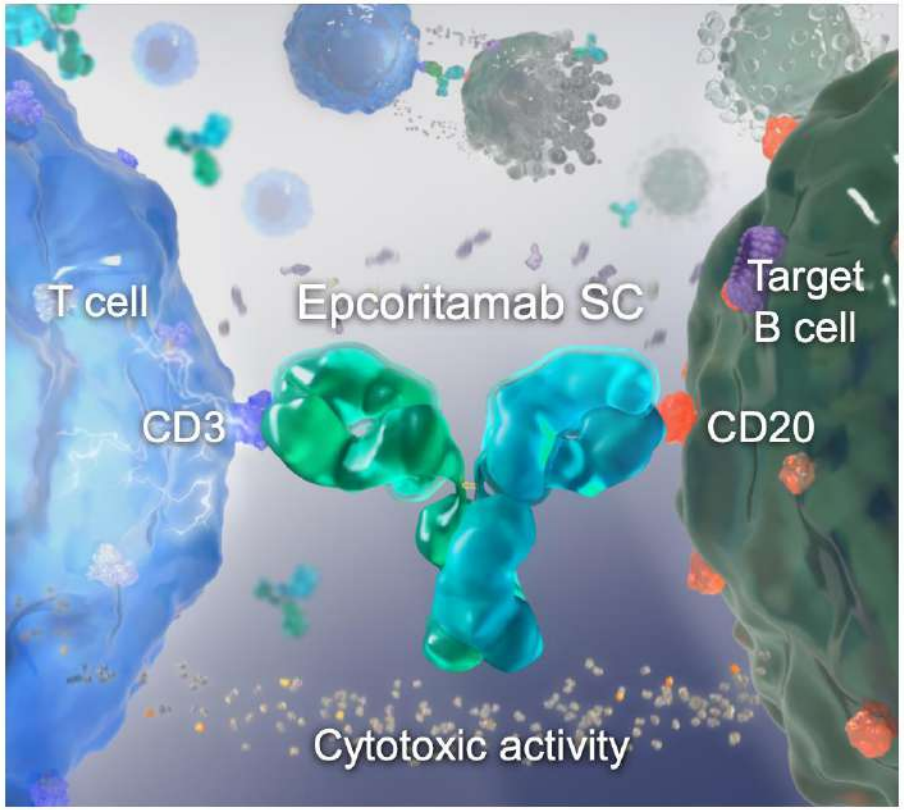
Epcoritamab SC

- Epcoritamab is a subcutaneously (SC) administered CD3xCD20 bispecific antibody developed using the DuoBody® platform[1-4]
- Single-agent epcoritamab SC has demonstrated deep and durable responses with manageable safety in the EPCORE NHL-1 trial[4]
- Based on these data, epcoritamab SC is approved by the US FDA for the treatment of adults with relapsed or refractory (R/R) DLBCL, NOS, including DLBCL arising from indolent lymphoma, and HGBCL after ≥2L systemic therapy[5]
- Epcoritamab SC + R² is being assessed in the ongoing EPCORE NHL-2 trial (NCT04663347)
- Epcoritamab SC + R² have nonoverlapping modes of action[1,6]
- The immunomodulatory properties of lenalidomide may increase the therapeutic potential of epcoritamab SC[1,6]



1. Engelberts PJ, et al. *EBioMedicine*. 2020;52:102625. **2.** van der Horst HJ, et al. *Blood Cancer J*. 2021;11:38. **3.** Hutchings M, et al. *Lancet*. 2021;398:1157-69. **4.** Thieblemont C, et al. *J Clin Oncol*. 2023;41:2238-47. **5.** EPKINLY [prescribing information]. Plainsboro, NJ: Genmab US, Inc.; 2023. **6.** Chiu CW, et al. AACR 2021. Abstract 1574.

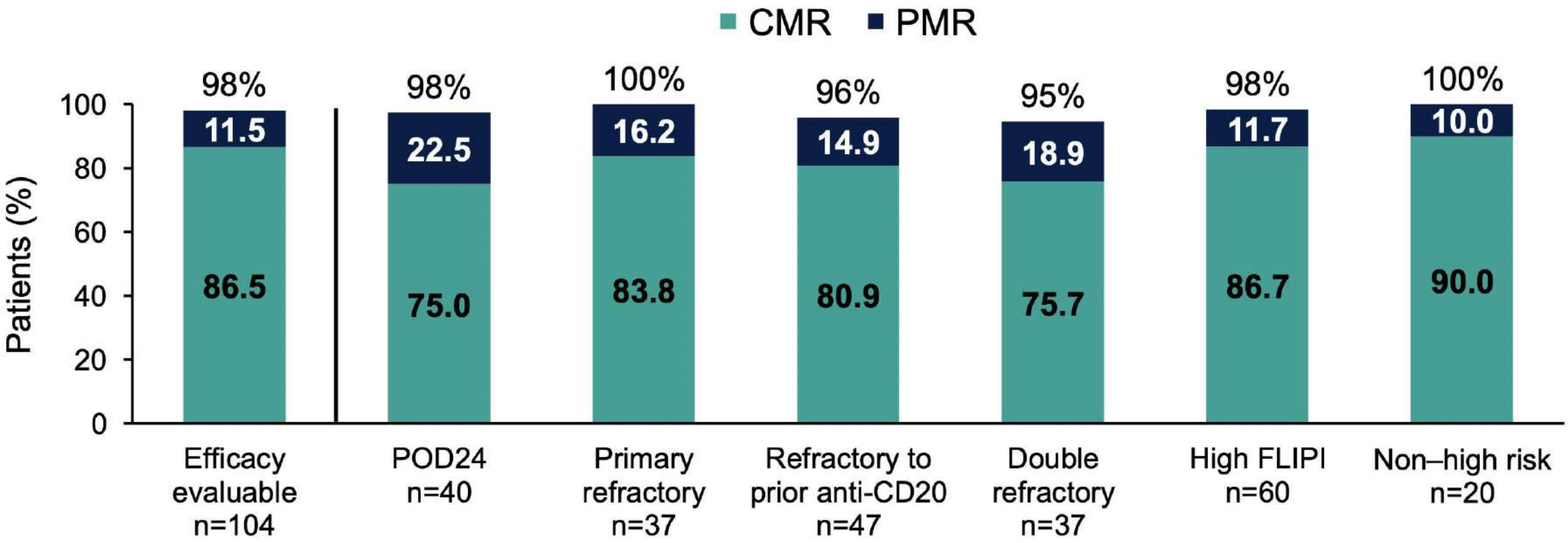
Antitumor Activity With Epcoritamab SC + R²

Response[a]	Efficacy Evaluable for Epcoritamab SC + R² n=104
Overall response	**98%**
CMR	87%
PMR	12%
Stable disease	1%
Progressive disease	1%

Data cutoff: January 31, 2023. Median follow-up: 11.4 mo (range, 2.1–22.1). [a]Based on modified response-evaluable population, defined as patients with ≥1 target lesion at baseline and ≥1 postbaseline response evaluation and patients who died within 60 d of first dose.

High overall response and CMR rates observed with epcoritamab SC + R²

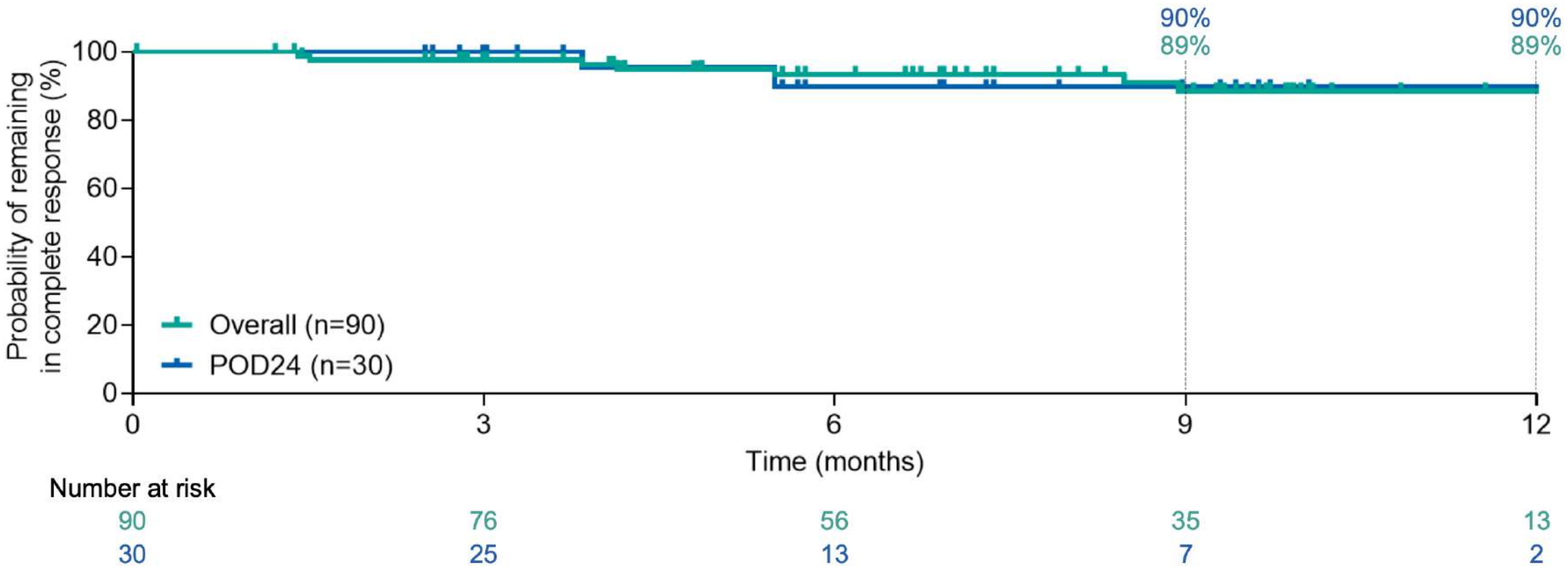
Antitumor Activity in Subgroups



High overall response and CMR rates regardless of subgroup

Data cutoff: January 31, 2023. Median follow-up: 11.4 mo (range, 2.1–22.1). Definitions for all subgroups available in Study Design and Patient Disposition.

Duration of Complete Response – Overall and POD24



Epcoritamab SC + R² led to durable complete responses, including in POD24 patients

DoCR is among complete responders in response-evaluable set. The 9-mo/12-mo DoCR estimates for POD24 2L (n=18) and POD24 3L+ (n=12) are 85%/85% and 100%/100%, respectively. Median follow-up for overall population: 11.4 mo (range, 2.1–22.1). Median follow-up for POD24: 9.5 mo (range, 2.4+ to 19.4). Median follow-up for POD24 2L: 9.2 mo (range, 3.0–19.4). Median follow-up for POD24 3L+: 9.5 mo (range, 2.4+ to 16.7). Percentages are Kaplan–Meier estimates.

Conclusions

- Linfocitosis determinar si es aislada o no y otros hallazgos relevantes de laboratorio (leucocitosis, esplenomegalia, citopenias), examen físico, síntomas
- De ser inversión de la formula aislada controlar evolutivamente cada 3-6 meses inicialmente (luego en forma anual)
- Citometria de flujo ante sospecha de neoplasia hematológica
- Adenopatías ver tamaño otras localizaciones y si son adenopatías múltiples o progresivas y se descartan causas infecciosas optaría por biopsia excisional
- Estudio de imágenes (TC o PET) ante sospecha de neoplasia o síndrome linfoproliferativo
- De ser necesario biopsia con AP y Citometria de Flujo (panel linfoproliferativo)
- Siempre ante la duda es importante el control evolutivo
- Evitar alarmar al paciente !!!

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GRACIAS

Treatment Characteristics: Cost

- Cost of targeted agents markedly greater than traditional CIT

Average Wholesale Cost in U.S. [§]		
	1 Month	1 yr
Ibrutinib	$15,522	$182,664
Venetoclax	$14,049*	$157,571
Obinutuzumab (6 cycles)	$62,888	
FCR (6 cycles)	$45,420	

Shanafelt et al., J Oncol Pract. 2015 May;11(3):252-8; Jain et al., Blood 2015;126:871; Hilal et al. Curr Hematol Malignancy Report 2018; 13:327-243

[§]Prices vary dependent on country affordability

Estadios Tempranos
Tratamiento vs Observación

LLC indolente: Clorambucilo vs Observación hasta progresión

- 1535 paciente: LLC Binet A no tratados (abarca 2 períodos)

<u>1980-1985: 609 pacientes Randomizados</u>
Clorambucilo 0.1 mg/kg/d vs observación

158 / 308 pacientes asignados a observación fueron tratados

→ *Mediana seguimiento 11 años*

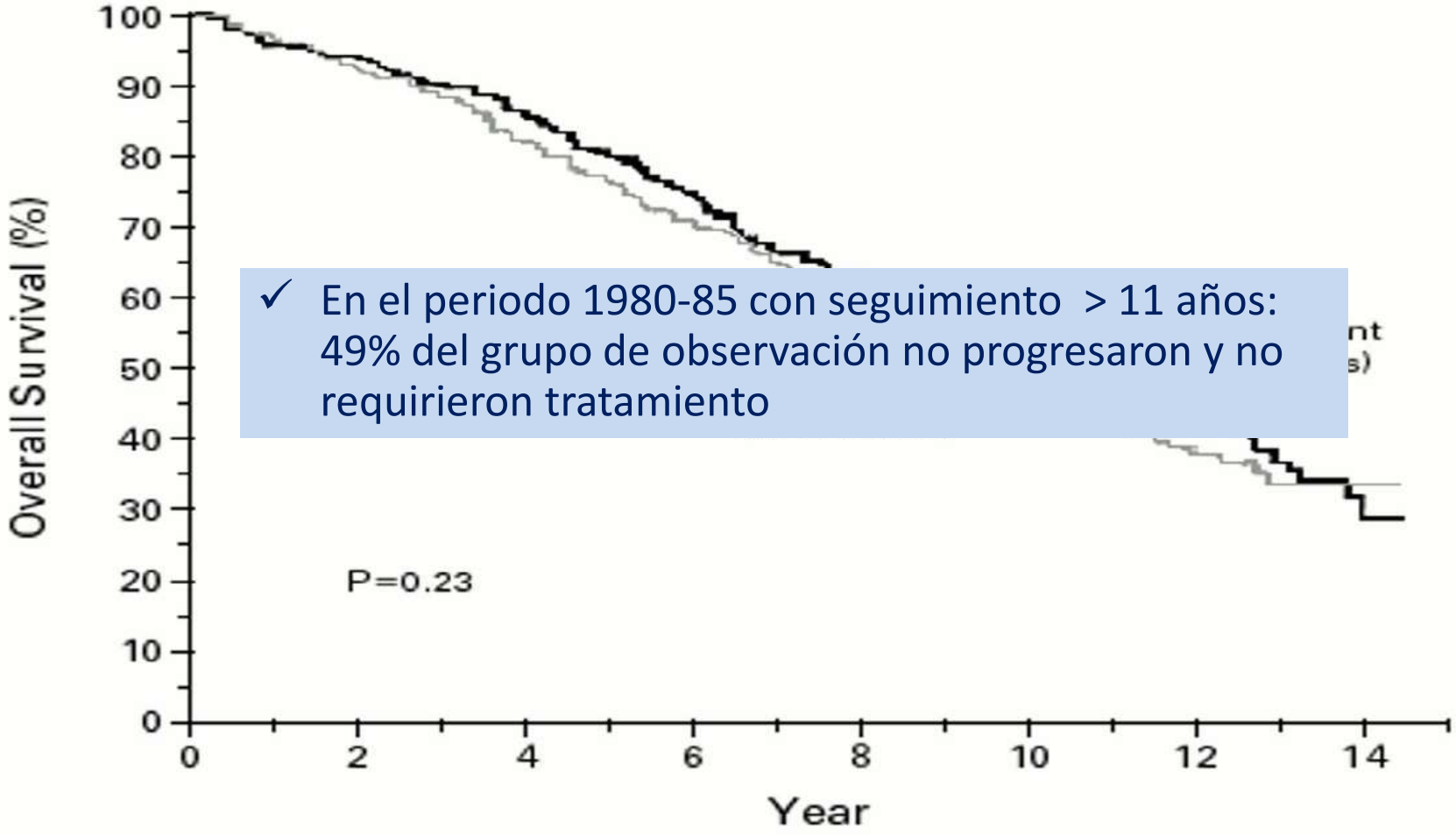
<u>1985-1990: 926 pacientes Randomizados</u>
Clorambucilo 0.3 mg/kg. + pred. 40 mg/m^2 por 5 d vs observacion

187 / 466 pacientes asignados a observación fueron tratados

→ *Mediana seguimiento 6 años*

Sobrevida Global

G. Dighiero et al. NEJM May 21,1998



- ✓ En el periodo 1980-85 con seguimiento > 11 años: 49% del grupo de observación no progresaron y no requirieron tratamiento

No. at Risk															
Chlorambucil	301	296	283	277	264	246	230	205	191	179	132	86	54	26	2
No treatment	308	291	284	266	247	230	213	196	179	159	114	70	39	17	7

G. Dighiero et al. NEJM May 21, 1998

STUDY DESIGN

DEUTSCHE STUDIENGRUPPE

Key eligibility:

- Binet A
- Asymptomatic
- Treatment-naive

RISK STRATIFICATION

LOW
N=152

INTERM.
N=273

HIGH
N=82

VERY HIGH
N=8

RANDOMIZATION 1:1

WATCH & WAIT N=152

IBRUTINIB N=182

PLACEBO N=181

420 [mg/d] until **symptomatic** PD

Median observation time is 31.0 months

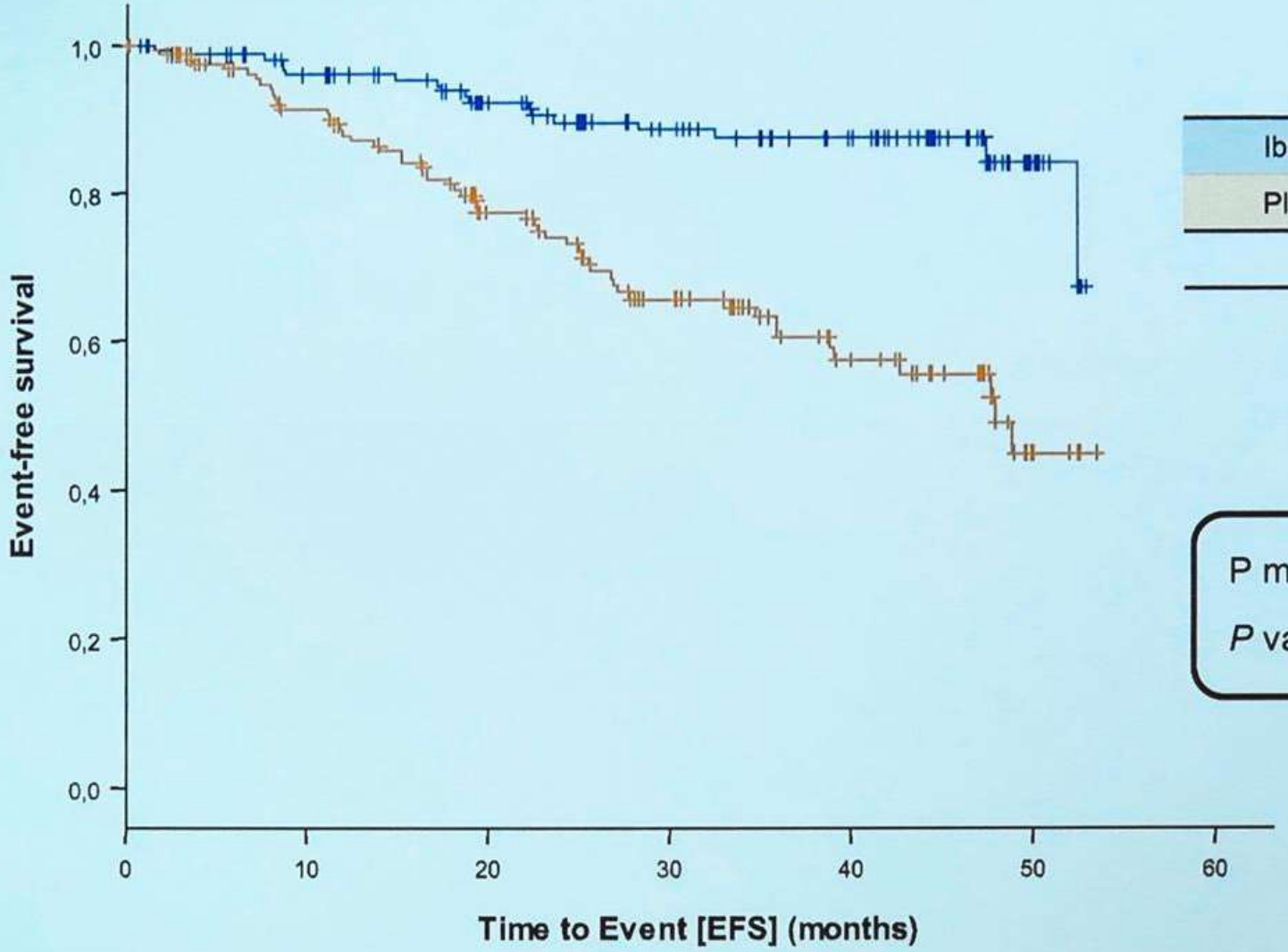
FPI
APR-2014

LPI
FEB-2019

PRIMARY EFS ENDPOINT ANALYSIS

Time to symptomatic progression, CLL treatment and/or death

DEUTSCHE STUDIENGRUPPE

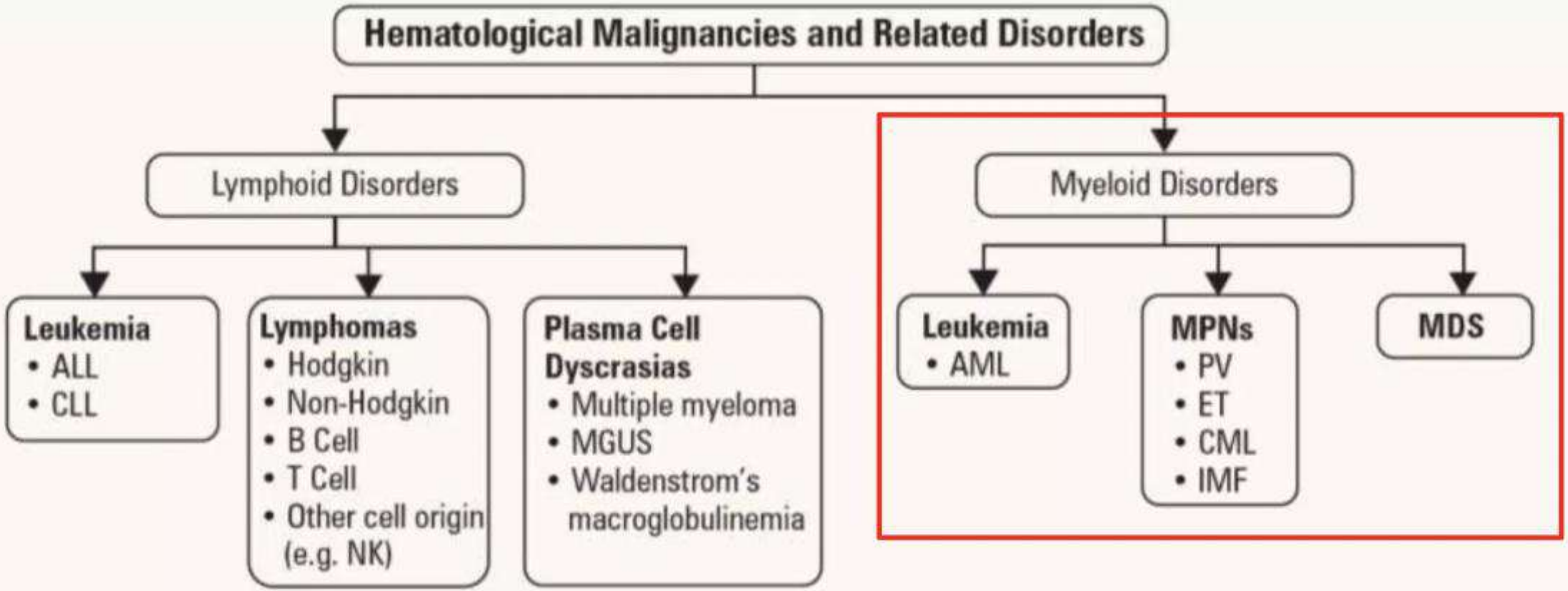


	total	events	N	%
Ibrutinib	182	18	164	90.1
Placebo	181	55	126	69.9
	363	73	290	79.9

P $median_{EFS}$ 47.8 vs. NR

P value <0.0001; HR 0.248

Hematological malignancies



ALL = acute lymphocytic leukemia; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; ET = essential thrombocythemia; IMF = idiopathic myelofibrosis; MDS = myelodysplastic syndromes; MGUS = monoclonal gammopathy of unknown significance; MPN = myeloproliferative neoplasms; PV = polycythemia vera

Hematopoiesis