
3rd POSTGRADUATE

CLL Conference

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President:
Pier Luigi Zinzani

HOW TO TREAT OLDER PATIENTS?

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Disclosures

	Research funding	Consultancy
BMS	✓	✓
Gilead	✓	✓
AstraZeneca	✓	✓
AbbVie	✓	✓
Roche	✓	✓
Janssen	✓	✓
Novartis	✓	✓
Takeda	✓	✓
TG Therapeutics		✓
Kite	✓	✓
Lilly		✓
BeiGene	✓	✓
Advantage		✓
Allogene		✓

No share ownership, patents or board membership

Outline

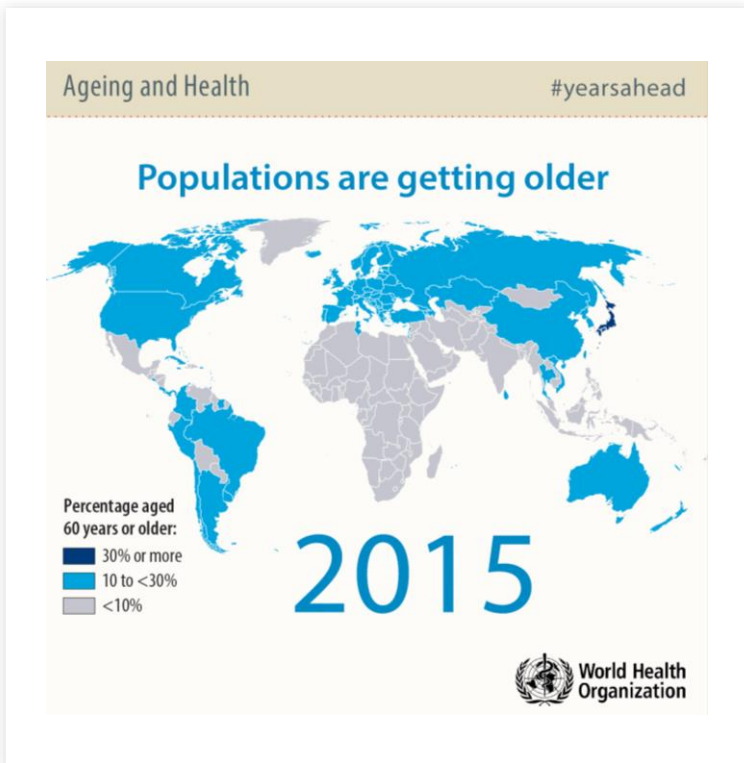
1. Impact of patient's age and fitness in CLL
2. Geriatric assessment
3. How to treat elderly CLL?



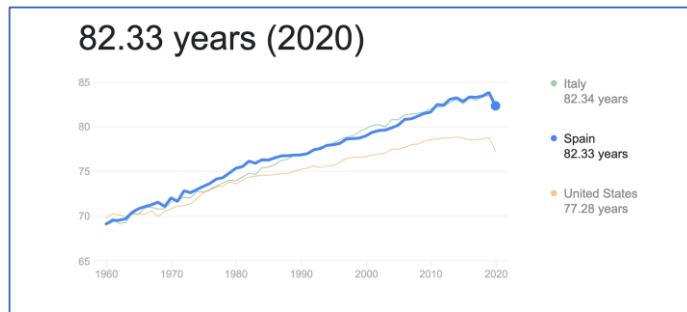
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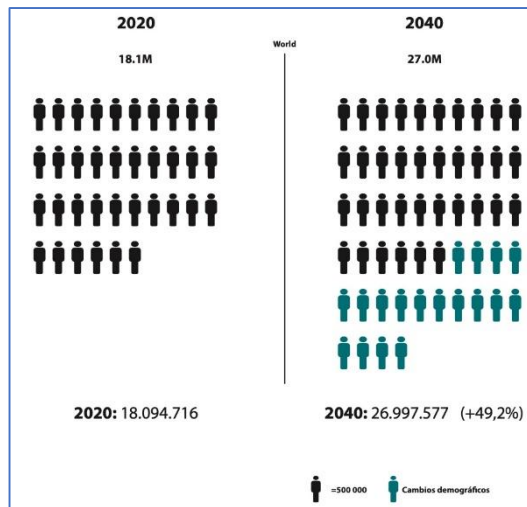




http://apps.who.int/iris/bitstream/10665/186466/1/9789240694873_spa.pdf



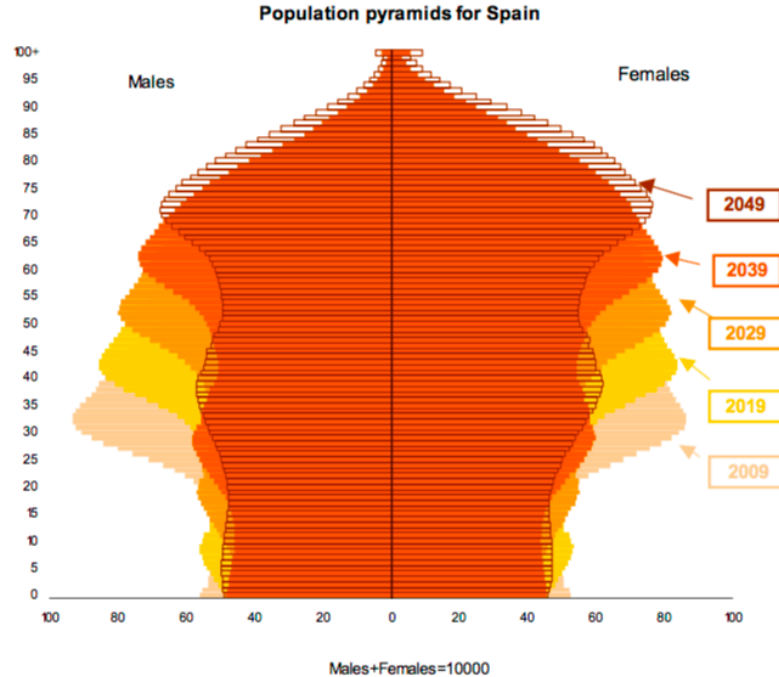
Source: data.worldbank.org



Cancer incidence: 49,2%
50% > 65 yrs
GLOBOCAN

https://gco.iarc.fr/tomorrow/en/dataviz/isotype?age_start=0&single_unit=500000

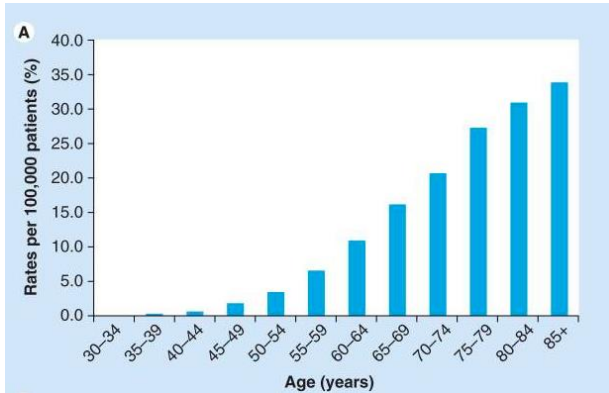
Spanish population pyramid



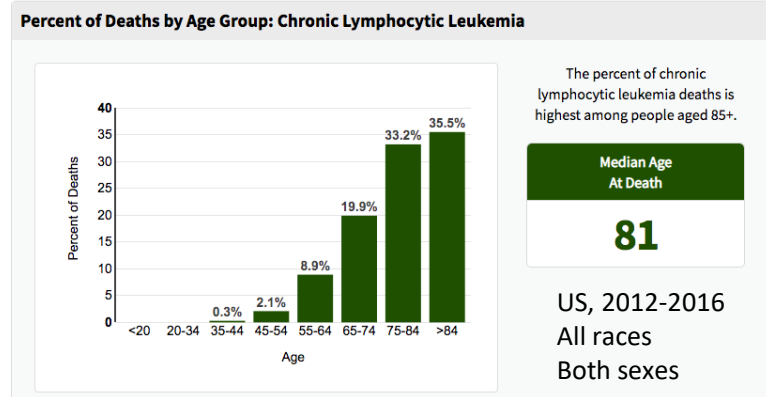
Data Source: Long-Term Population Projection http://www.ine.es/en/prensa/np587_en.pdf

Population and CLL trends in aging

- Median age, 72 y-o
- Incidence 37.9 cases/100.000/year > 85 years
- Increasing life expectancy



Gribben JG. *Expert Rev Anticancer Ther.* 2010



Data Source: <https://seer.cancer.gov/statfacts/html/amyl.html>

Impact of patients' age and fitness

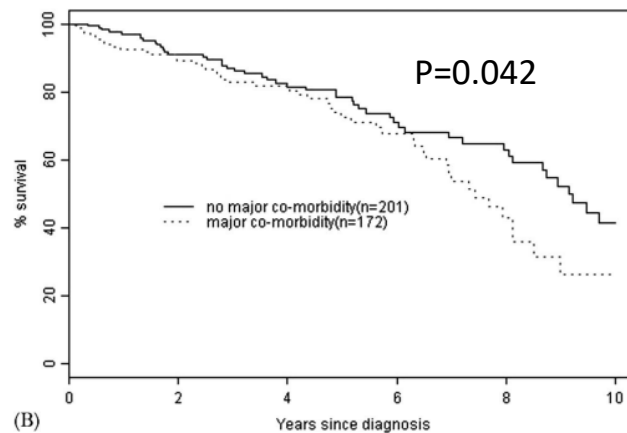
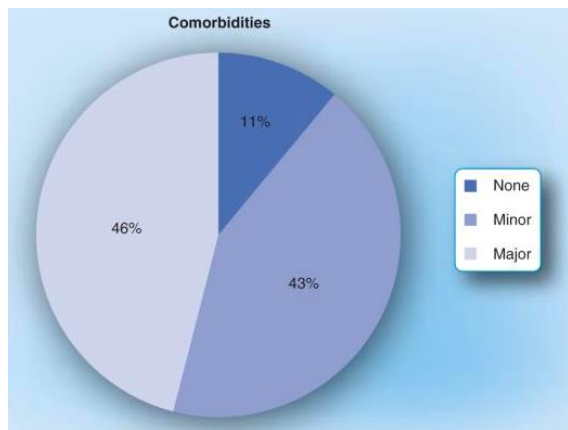
- OS shorter than age-matched populations (except > 75 yo in early stages) (*Shanafeld T et al, Cancer 2010*)
- Elderly patients (>70 years) with CLL (*Baumann T et al., Haematologica 2014*)
 - Higher advanced disease
 - Treated less frequently
- Pharmacokinetic changes in older patients
 - Renal function and tolerability to fludarabine (*Dauids MS et al, Blood 2017*)
- Polypharmacy
 - 84% patients with cancer receiving > 5 medications (*Nightingale G et al, JCO 2015*)
- Elderly traditionally underrepresented in clinical trials

Impact of patients' age and fitness

Age linked to life expectancy →
Influences treatment paradigm

Patient Age, Years	Additional Years of Life Expectancy	
	Men	Women
65	19.2	21.7
70	15.4	17.4
75	11.8	13.6
80	8.7	10.1
85	6.2	7.3

According to U.S. Social Security data.



Gribben JG. *Expert Rev Anticancer Ther.* 2010

Thurmes et al, *Leukemia & Lymphoma* 2008

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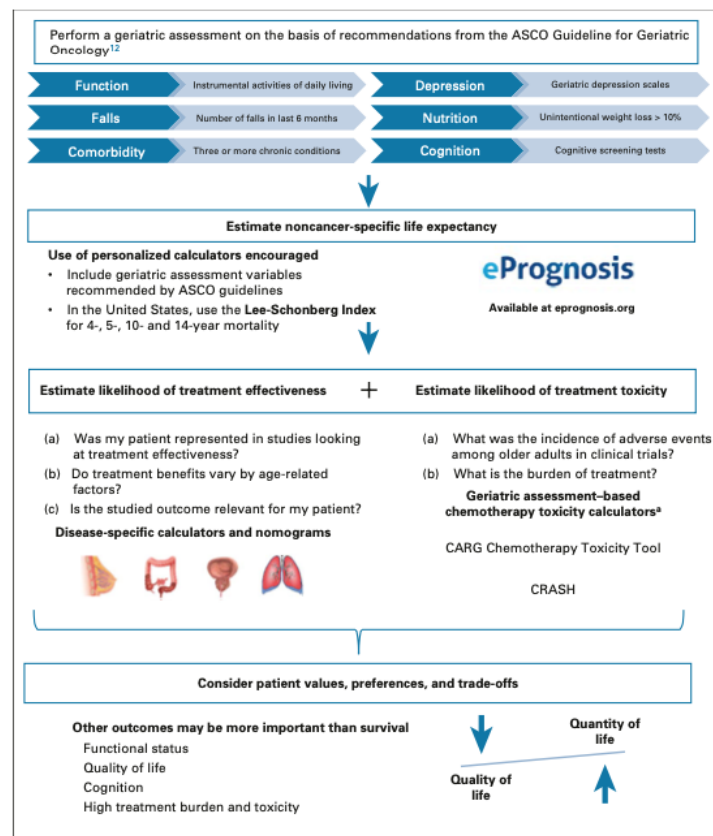


Comprehensive Geriatric Assessment

Decision Making in Older Adults With Cancer

Journal of Clinical Oncology*
An American Society of Clinical Oncology Journal

DuMontier C, Loh KP, Soto-Perez-de-Celis E, Dale W.
Decision Making in Older Adults With Cancer. J Clin Oncol.
2021 Jul 1;39(19):2164-2174. doi: 10.1200/JCO.21.00165.
Epub 2021 May 27. PMID: 34043434; PMCID:
PMC8260915.



Framework for decision making in older adults with cancer. aCurrent toxicity calculators exist for chemotherapy only. For surgical risks, consider the ACS NSQIP Surgical Risk Calculator, which to include outcomes for older adults. **ACS**: American College of Surgeons; **CARG**: Cancer and Aging Research Group; **CRASH**: Chemotherapy Risk Assessment Scale for High-Age Patients; **NSQIP**: National Surgical Quality Improvement Program.

Comorbidities assessment tools

- Different tools: CIRS, ECOG PS, Karnofsky PS
- CIRS commonly used in trials (*Linn et al, J Am Geriatr Soc 1968*)
- CIRS does not correlate well with PS
- No comorbidity score prospectively validated in CLL

Clinical eye useful but overlook some frail patients

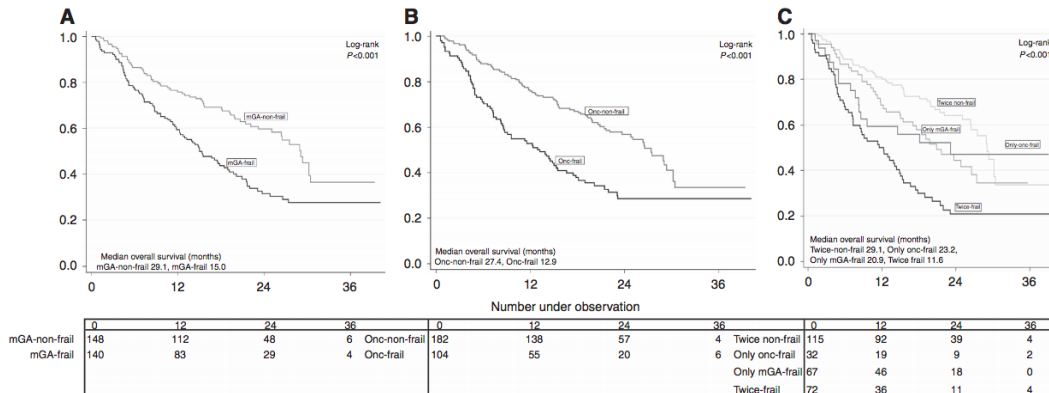


Figure 1. Kaplan Meier curves of overall survival (months) according to (A) mGA-non-frail/mGA frail, (B) onc-non-frail/onc-frail (C) both frailty classifications combined.

- 307 cancer patients (solid and hem)
- Median age 77 y (70 - 95)
- 67 (23%) patients classified as fragile by mGA-frail, but considered fit by clinical eye

Kirkhus L, et al. *Br J Cancer*. 2017; 117(4): 470–477.

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Prognostic/predictive factors in older pts with CLL

CLL-IPI validated in older patients (> 70 y)
(Lancet Oncol 2016; 17:779)

Some biomarkers lose prognostic power with advancing age

(Shanafeld et al, Cancer 2010)

- IgHV status not predicting OS at age > 75

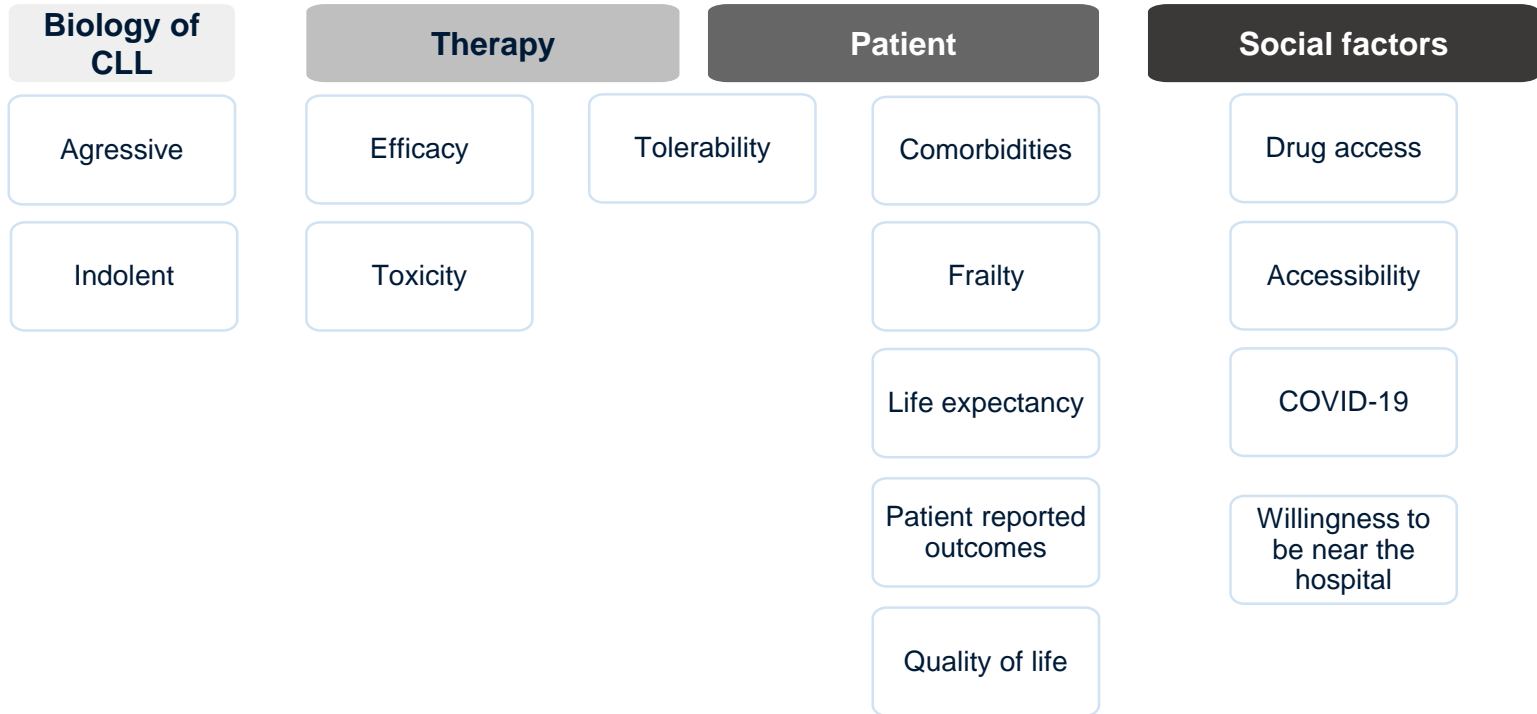
Increased incidence of TP53 aberrations in elderly CLL?
(Truger et al, Br J Haematol 2015)

Del(17p) or TP53 mutation retain their predictive value in older CLL

(Shanafeld et al, Cancer 2010; Bosch F et al, JCO 2009)

Genomic aging (clonal hematopoiesis)?

Treatment decision in elderly CLL



Does CIT still have a role in elderly CLL?

- FCR tolerated only in selected older patients
 - 11% of CLL8 study > 70 yrs (low CIRS, normal CrCl)
 - Prolonged neutropenia (stem-cell exhaustion)
 - Increased risk of SPM in older pts (*Maurer et al, Leukemia 2016*)
- Chl + Obinutuzumab considered standard in unfit (CIRS > 6 and/or CrCl < 70 mL/min) until recently
 - Median PFS at 3 yrs: 41%
- Targeted therapies equal or superior to CIT in all trials

CLL13 (Gaia): Benefit of VenO vs. CIT

Category	Subgroup	N	VenO			CIT			Hazard ratio	95% CI
			N	Events	36-month PFS rate (%)	N	Events	36-month PFS rate (%)		
All		926	229	33	87.7	229	67	75.5		
Binet stage at screening	A	246	60	6	89.4	61	12	79.5	0.46	0.17 – 1.22
	B	349	90	13	88.7	85	25	79.1	0.44	0.23 – 0.87
	C	331	79	14	85.3	83	30	68.8	0.39	0.21 – 0.73
Age groups (years)	≤65	597	147	21	88.2	150	34	83.7	0.54	0.31 – 0.93
	>65	329	82	12	86.6	79	33	61.6	0.29	0.15 – 0.55

Eichhorst B, et al. EHA 2022. Abstract LB2365

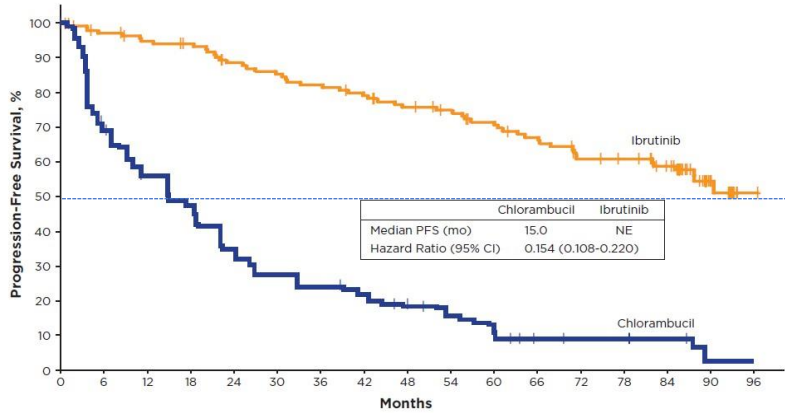
TREATMENT	TRIAL	Median age	Median CIRS	N=	CR	uMRD	PFS (3 years)	PFS (3 years) UM-IGHV	Benefit in OS
CLB + Obinu	CLL11 ^{1,2}	74	8	333	21%	30%	40%	30%	Yes
CLB + Rituxi	CLL11 ^{1,2}	73	8	330	7%	3%	20%	20%	
Ibrutinib	Resonate-2 ³	70	4/5	136	18%	-	80%	70%	Yes
Ibrutinib	Alliance* ⁴	70	-	182	7%	1%	85%	70%	No
Ibru + Rituxi	Alliance* ⁴	71	-	182	12%	4%	80%	70%	
Benda + R	Alliance* ⁴	71	-	182	26%	8%	60%	50%	
Acalabrutinib + O	Elevate ⁵	70		179	13%		93%	80%	Yes
Acalabrutinib	Elevate ⁵	71		179	1%		87%	80%	
CLB + Obinu	Elevate ⁵	70		177	5%		47%	20%	
Ven + Obinu	CLL14 ⁶	71	8	216	50%	42%	75%	80%	No
CLB + Obinu	CLL14 ⁶	72	9	216	23%	14%	55%	30%	
I + V	Glow	71	9	106	38.7%	52%	85% (2 yr)	-	No
CLB + Obinu	Glow	71	8	105	11.4%	17%	47% (2 yrs)	-	

¹Goede et al, NEJM 2014; ²Goede et al, Blood 2015; ³Barr et al, Haematologica 2018; ⁴Woyach et al, NEJM 2018; ⁵Sharman et al, Lancet 2020; ⁶Fischer et al, NEJM 2019; ⁷Kater et al, EHA 2021

RESONATE-2: PFS

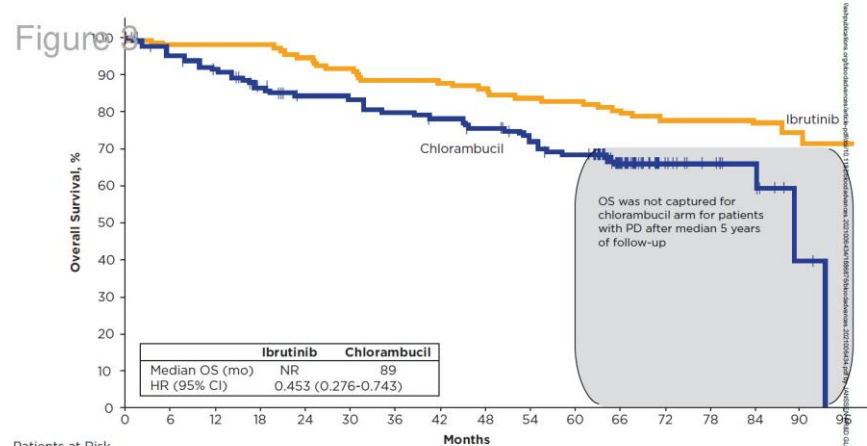
Ibrutinib vs. CLB

Resonate-2 PFS
 (median follow-up: 8 years)²



Patients at Risk	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96
Ibrutinib:	136	129	124	121	112	108	104	99	92	88	81	76	67	65	57	17	1
Chlorambucil:	133	88	69	57	41	33	30	25	19	16	12	6	5	5	4	1	0

Resonate-2: OS



Patients at Risk	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96
Ibrutinib:	136	131	131	127	121	117	113	112	107	101	98	95	91	89	86	27	1
Chlorambucil:	133	124	116	106	98	97	93	90	86	79	74	50	20	13	10	2	0

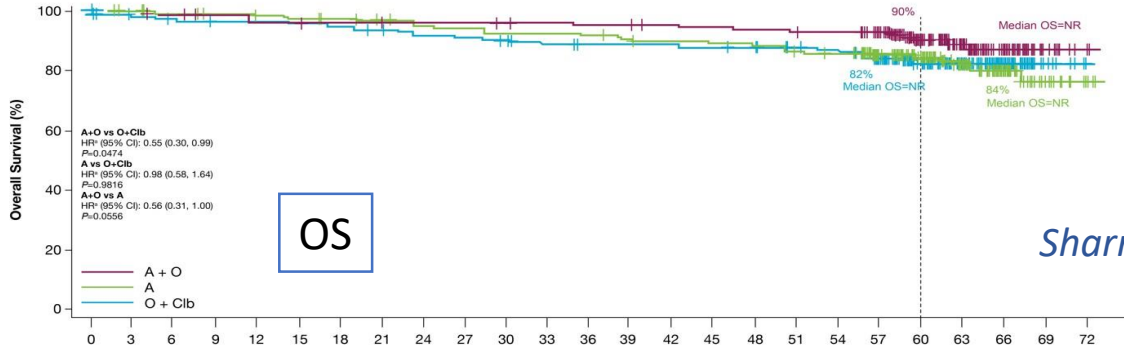
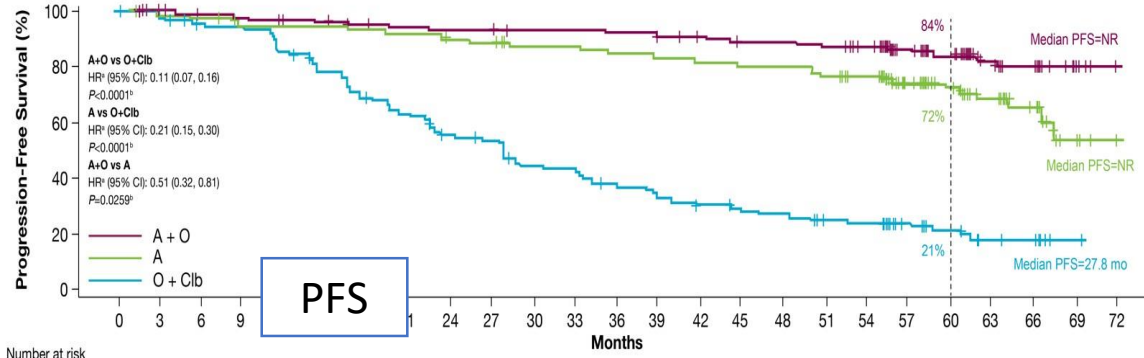
Burger JA, et al. *N Engl J Med* 2015; **373**:2425–2437; 2. Burger JA, et al. *Leukemia* 2020; **34**:787–798

Barr et al., *Blood Advances* 2022

Barr et al, *Blood Advances* 2022

ELEVATE TRIAL: 4 yr FU

A + O vs. A vs. CLB + O



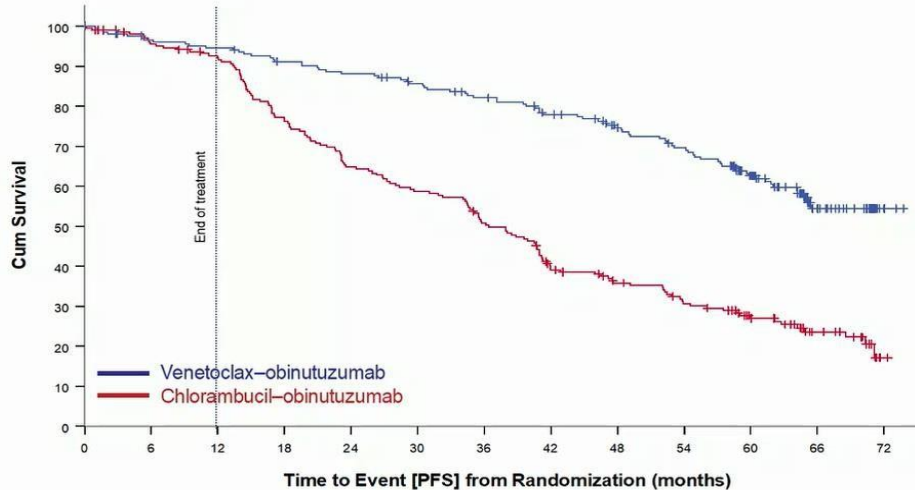
Sharman et al, Leukemia 2022

CLL14 STUDY

V+O vs. CLB + O

PROGRESSION-FREE SURVIVAL

Median observation time 65.4 months



Ven-Obi	216	196	192	183	177	169	160	147	134	123	97	35	4
Clb-Obi	216	195	185	154	130	118	101	75	64	53	39	21	1

Median PFS

Ven-Obi: not reached
Clb-Obi: 36.4 months

5-year PFS rate

Ven-Obi: 62.6%
Clb-Obi: 27.0%

HR 0.35, 95% CI [0.26-0.46]
P<0.0001

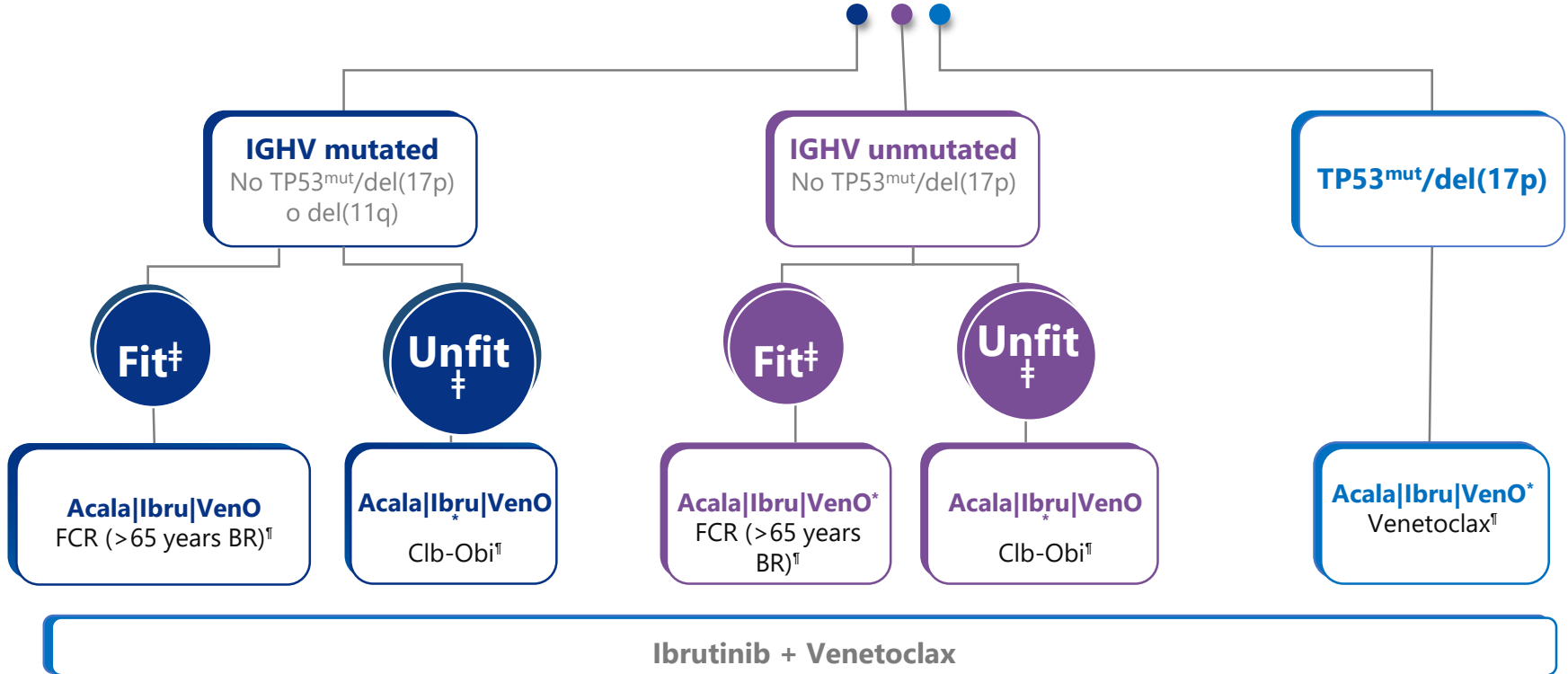
Al-Sawaf et al, EHA 2022

Aes of interest for elderly CLL

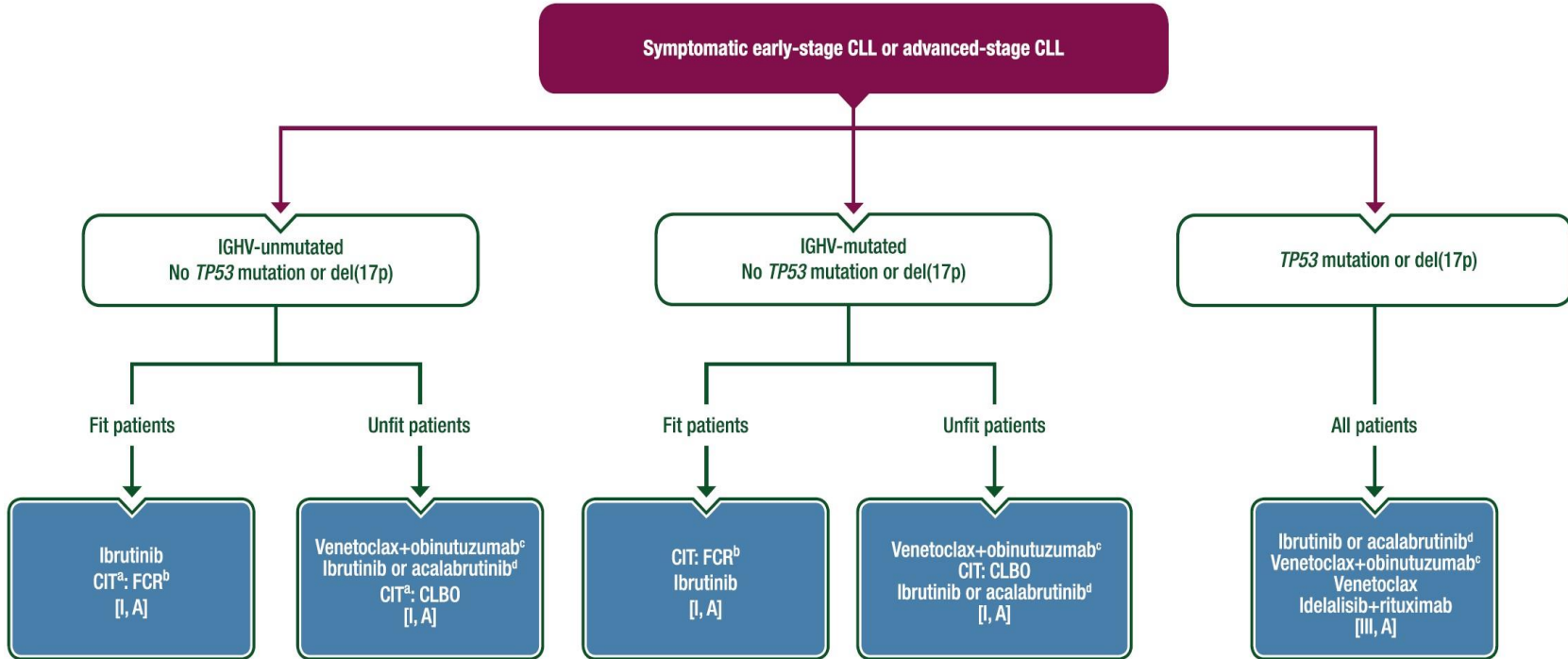
- Atrial fibrillation
 - Increased in patients with CLL
 - Shanafeld et al, Blood 2017
 - Ibrutinib: AFib up to 16% with longer FU (vs. 3-9% with second generation BTKi)
 - Higher risk of bleeding with anticoagulants & BTKi
- Tumor Lysis Syndrome
 - Increased risk with impaired renal function

CLL 1^oL
(active)
Clinical trial

<https://www.gellc.es/>



Guidelines ESMO 2021 (1L)



NCCN CLL Guidelines



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 1.2021

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

[NCCN Guidelines Index](#)

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SUGGESTED TREATMENT REGIMENS^{a,b,c,d} CLL/SLL without del(17p)/TP53 mutation (alphabetical by category)

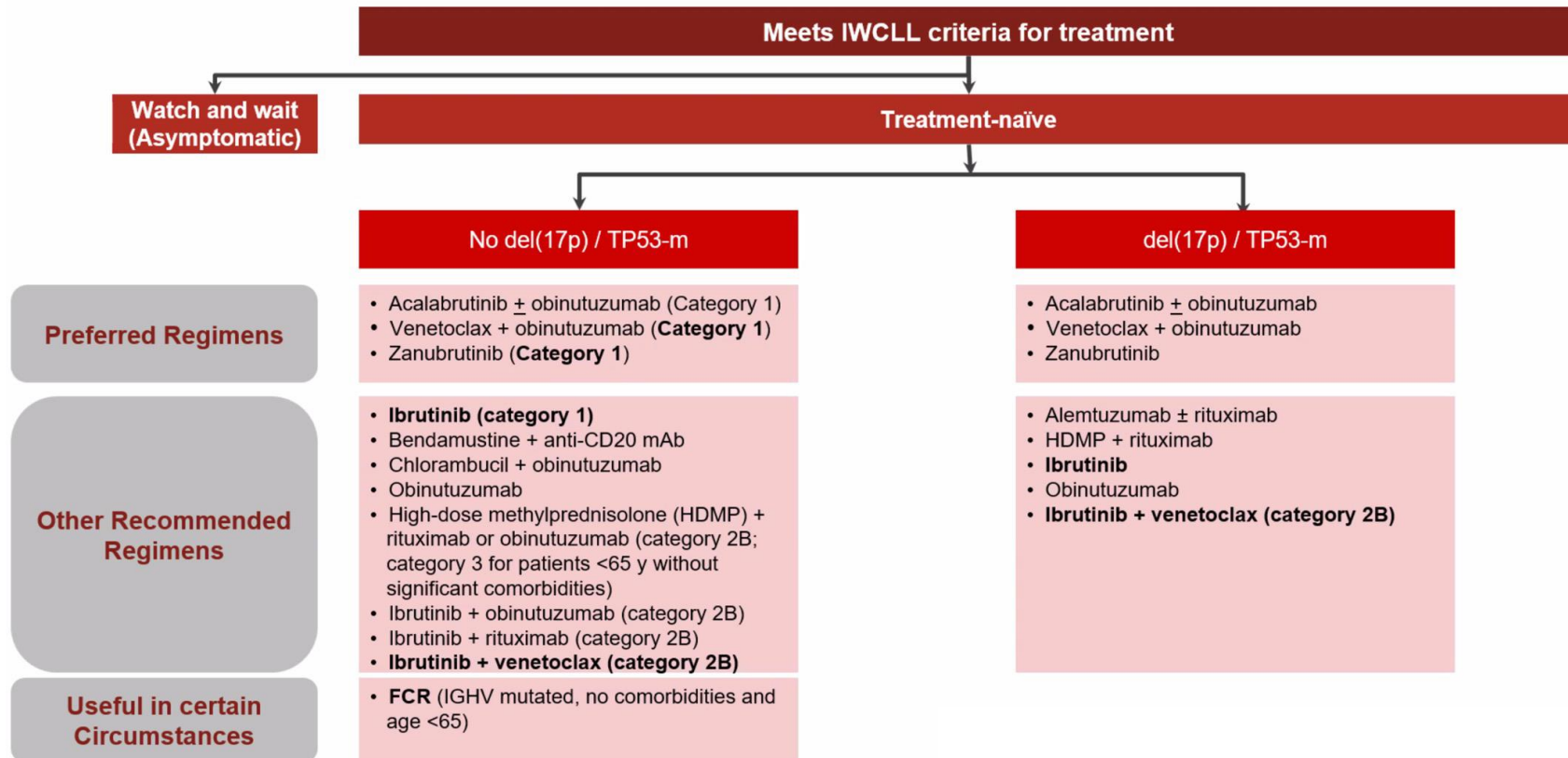
FIRST-LINE THERAPY ^e		
	<u>Preferred regimens</u>	<u>Other recommended regimens</u>
Frail patient with significant comorbidity (not able to tolerate purine analogs) <u>OR</u> Patients aged ≥65 y and younger patients with significant comorbidities (creatinine clearance [CrCl] <70 mL/min)	<ul style="list-style-type: none"> • Acalabrutinib^f ± obinutuzumab (category 1) • Ibrutinib^f (category 1) • Venetoclax^{f,g} + obinutuzumab (category 1) 	<ul style="list-style-type: none"> • Bendamustine (70 mg/m² in cycle 1 with escalation to 90 mg/m² if tolerated) + anti-CD20 monoclonal antibody^{d,h} (not recommended for frail patients) • Chlorambucil + obinutuzumab • High-dose methylprednisolone (HDMP) + rituximab (category 2B) • Ibrutinib^f + obinutuzumab (category 2B) • Obinutuzumab (category 2B) • Chlorambucil (category 3) • Rituximab (category 3)
Patients aged <65 y without significant comorbidities	<ul style="list-style-type: none"> • Acalabrutinib^f ± obinutuzumab (category 1) • Ibrutinib^f (category 1) • Venetoclax^{f,g} + obinutuzumab 	<ul style="list-style-type: none"> • Bendamustine + anti-CD20 monoclonal antibody^{d,h,i} • FCR (fludarabine,^j cyclophosphamide, rituximab)^{i,k} (preferred for patients with <i>IGHV</i>-mutated CLL) • FR (fludarabine^j + rituximab)^{k,l} • HDMP + rituximab (category 2B) • Ibrutinib^f + rituximab (category 2B) • PCR (pentostatin, cyclophosphamide, rituximab) (category 3)

POST FIRST-LINE CHEMOIMMUNOTHERAPY MAINTENANCE THERAPY

Other recommended regimen

- Consider lenalidomide for high-risk patients (blood MRD ≥10⁻² or ≥10⁻⁴ and <10⁻² with unmutated *IGHV*)^m after first-line therapy

1L CLL Treatment Algorithm (US, NCCN Guidelines, Version 1.2023)



SUMMARY

Comorbidity is common and prognostically relevant in elderly patients

Geriatric assessment should be part of the personalized therapeutic approach in CLL

Enormous progress in the treatment of elderly CLL with newer treatments

Choice of treatment → individualized according to disease and patient's characteristics (still a role for oral alkylating agents!)

Funding



Instituto
de Salud
Carlos III



PERIS 2016
2020

Pla estratègic de recerca
i innovació en salut

