

How to treat "Old, Old" patients

Francesca R Mauro

Dipartimento di Medicina Traslazionale e di Precisione

Università Sapienza, Roma

LEUCEMIA LINFATICA CRONICA:

L'INNOVATIVITÀ TERAPEUTICA
ED ALTRE...



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DICHIARAZIONE

Francesca R Mauro

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Abbvie	x				x	x	
Beigene						x	
Takeda	x				x	x	



CLASSIFICATION OF ELDERLY POPULATION

Classified into

1. Young old (60 to less than 75 years)
2. Old (75 years to less than 85 years)
3. Oldest old (85 years and above)
4. Frail elderly (above 60 years with cognitive impairment or a disability)



Median age at CLL diagnosis= 72 years

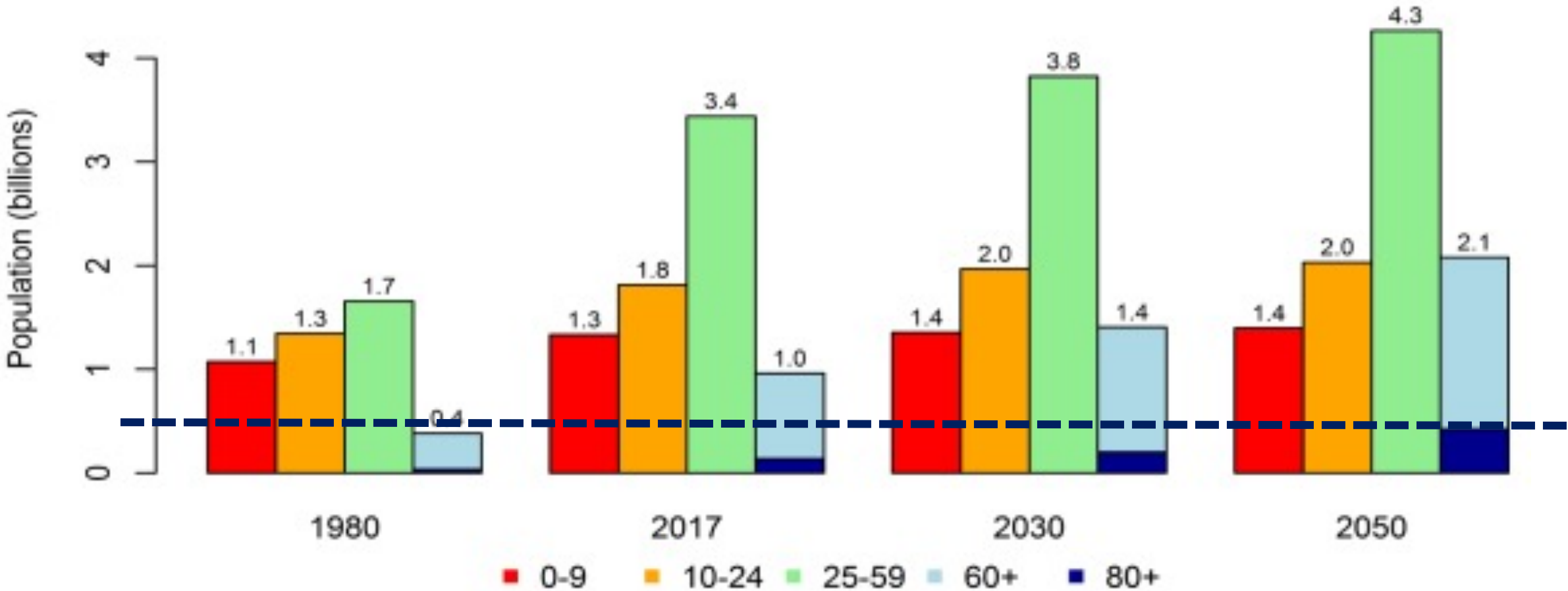
≥ 80 years old → 20% of CLL pts,

NCI. Cancer stat facts: leukemia—CLL; 2019

Expected increase in the age and social changes

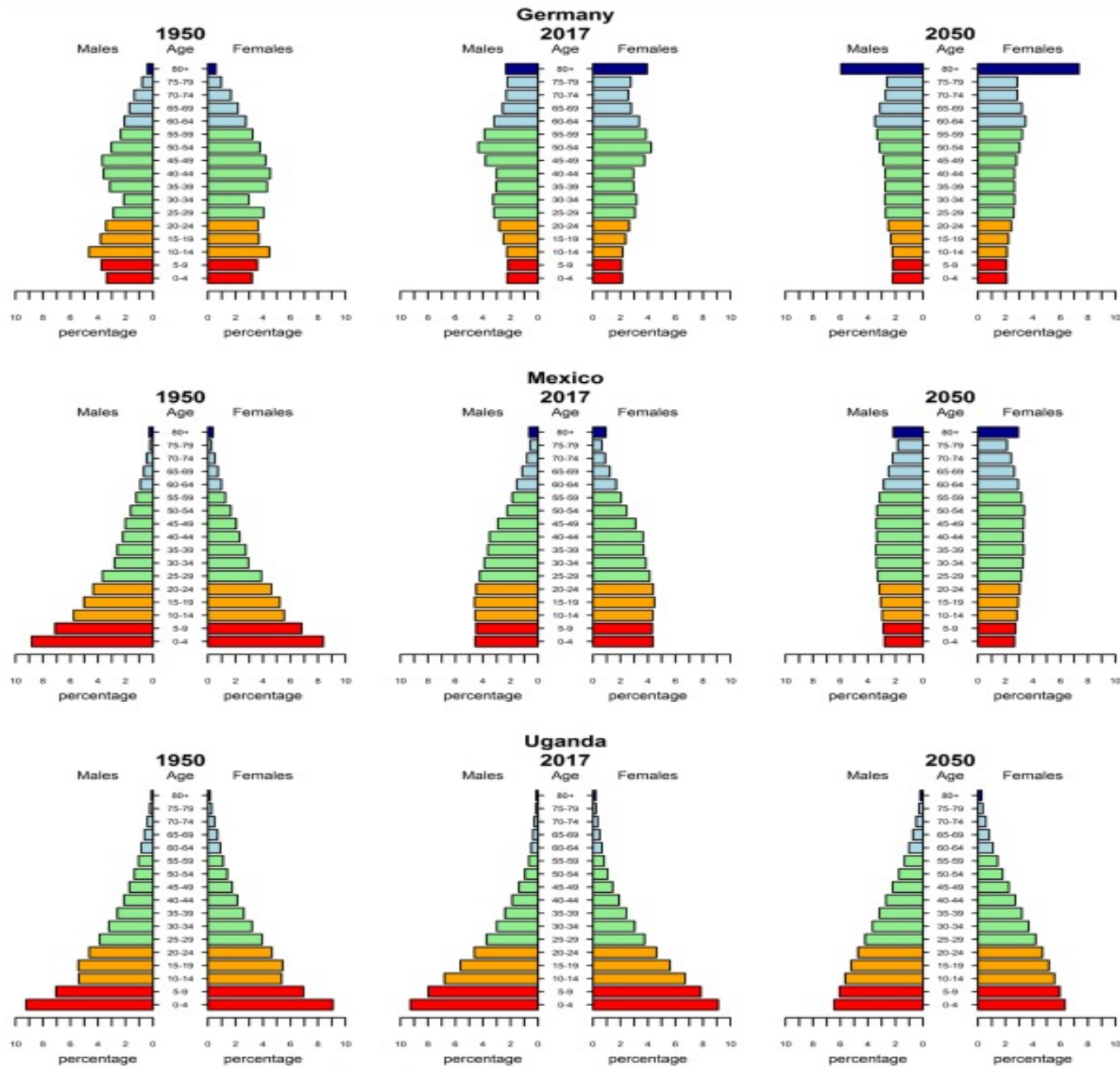


CHANGES IN THE AGE OF THE WORLD POPULATION



Data source: United Nations (2017). World Population Prospects: the 2017 Revision.

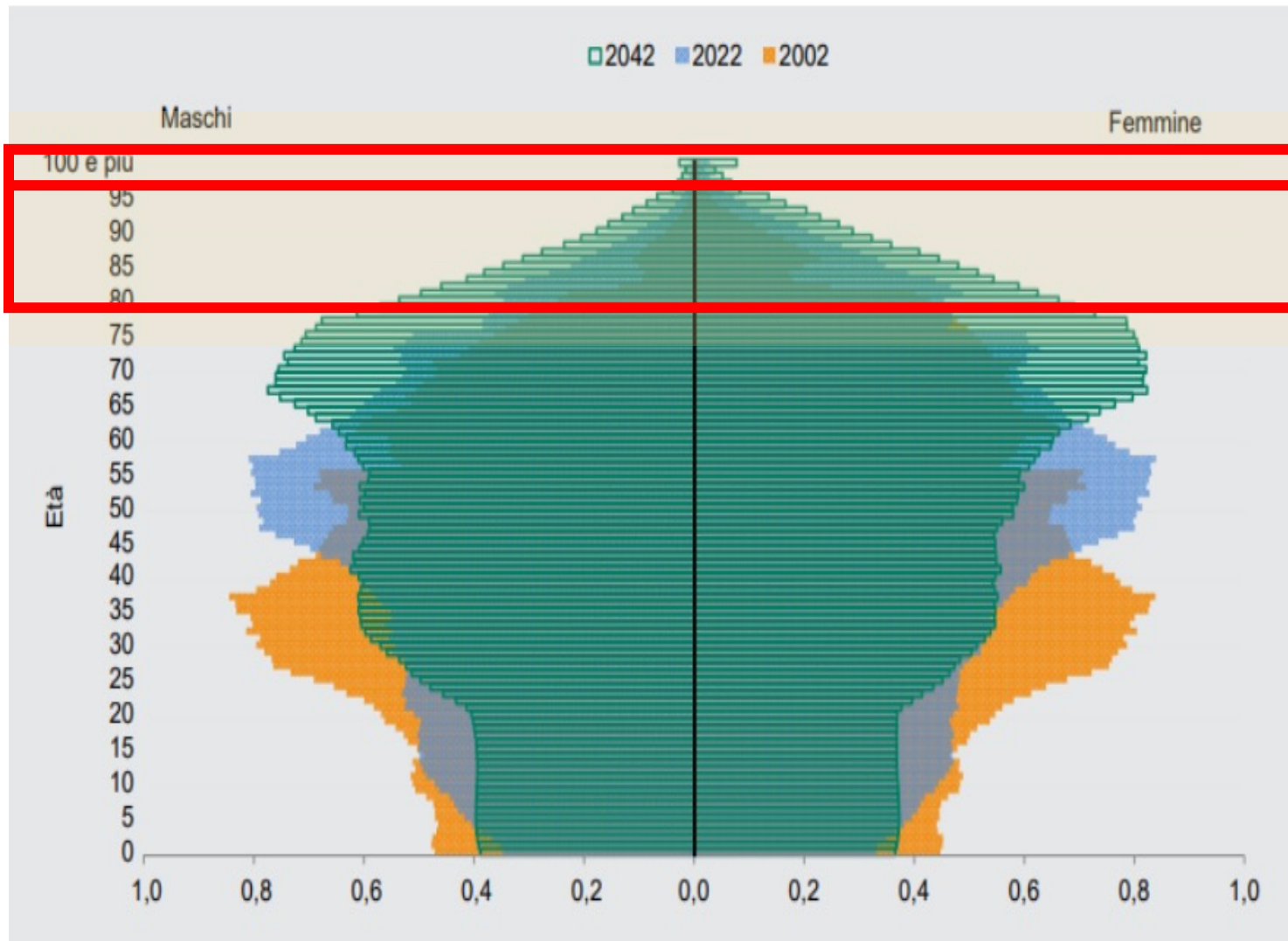




Data source: United Nations (2017). World Population Prospects: the 2017 Revision.



Come saremo nel 2042 in Italia? Gli anziani nel 2042



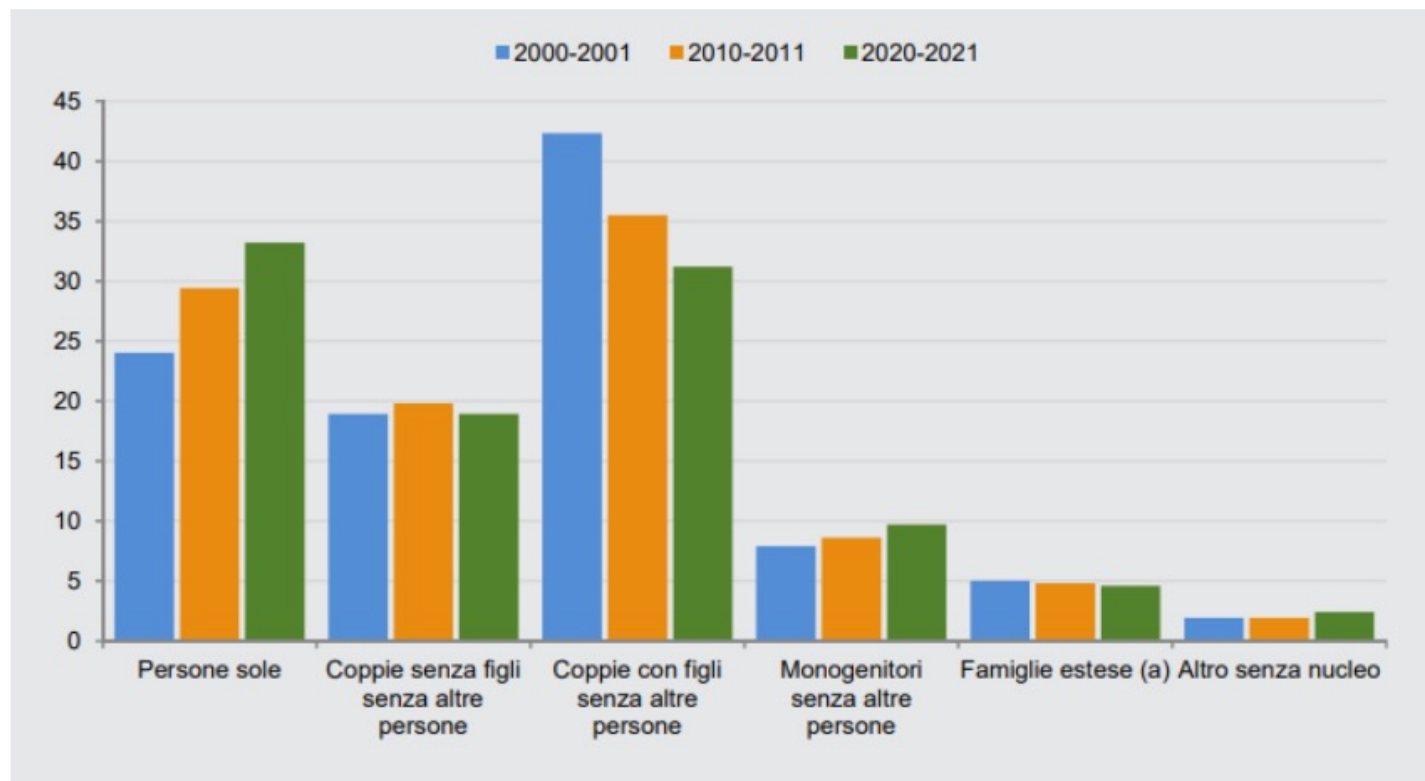
In the next 20 years, expected:

≥ 80 yrs people \rightarrow 4,500.000

and ...

100 yrs people \rightarrow 400.000

EXPECTED CHANGES IN THE FAMILY STRUCTURE: ITALY



Fonte: Istat, Indagine Aspetti della vita quotidiana

(a) Famiglie con due o più nuclei e famiglie con un nucleo con altre persone.

2040:

39% single-member families

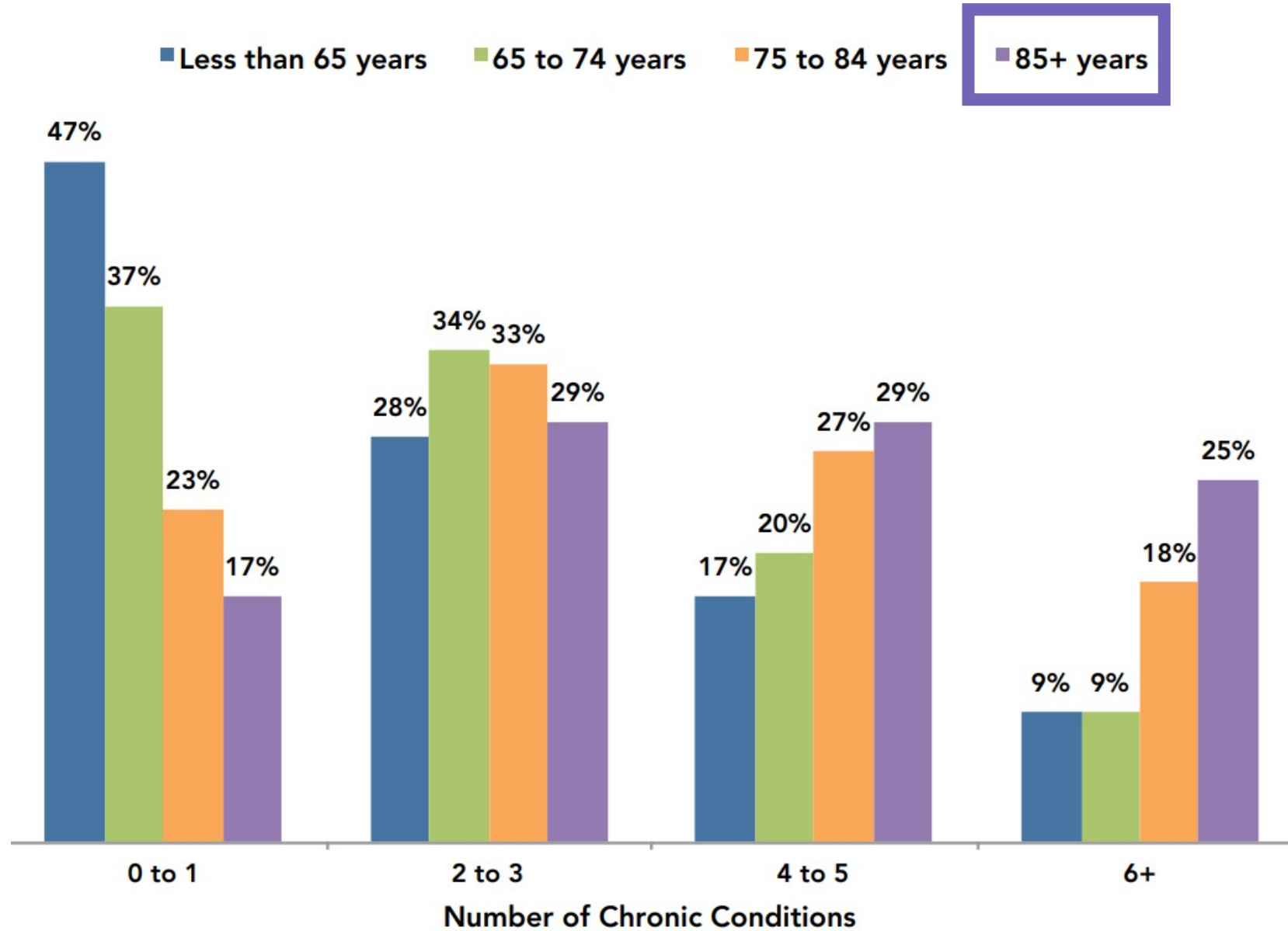
11.3% childless parents

Istat, Indagine Aspetti della vita quotidiana (a) Famiglie con due o più nuclei e famiglie con un nucleo con altre persone.

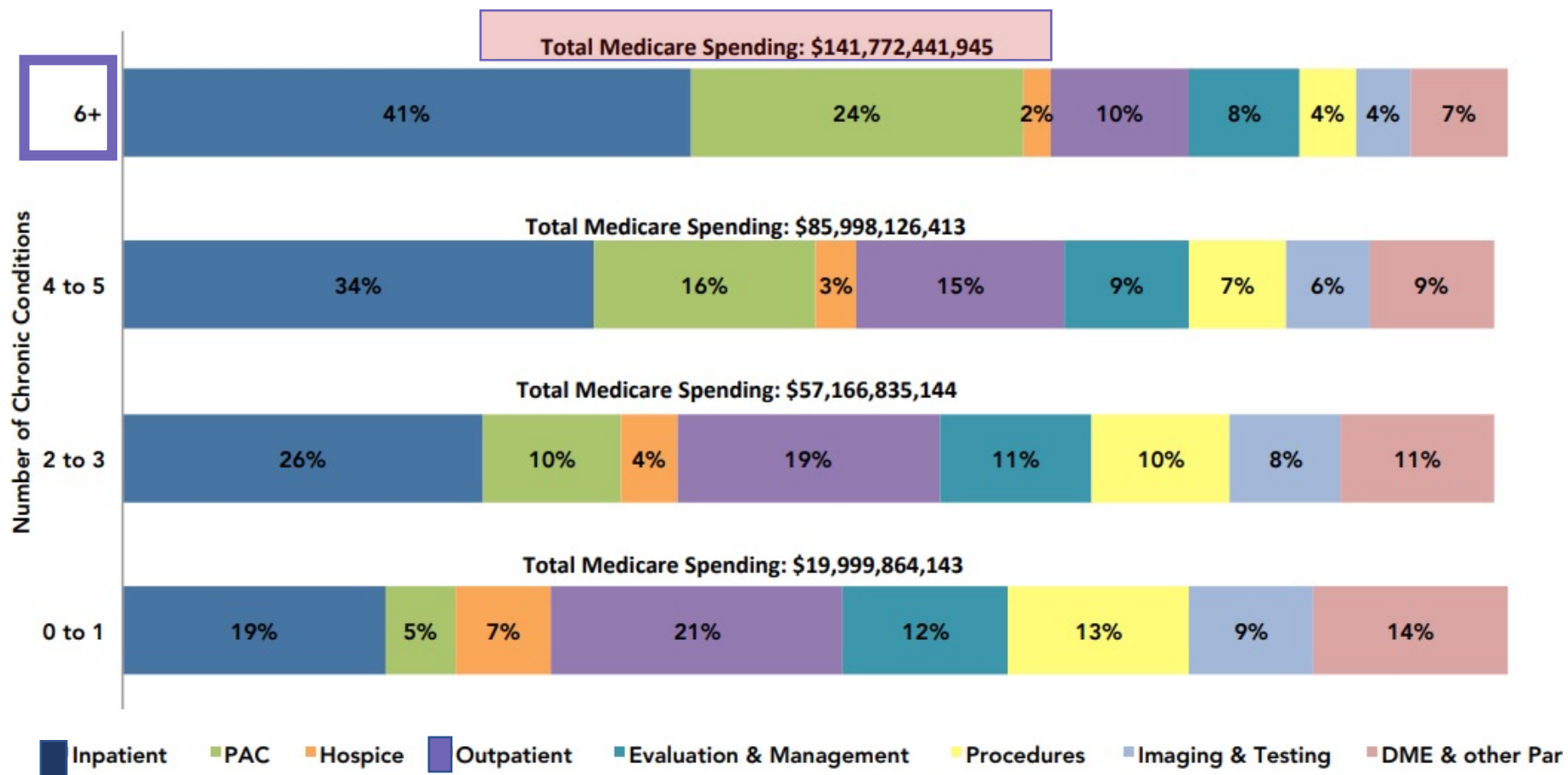
The prevalence of comorbidities increases with age

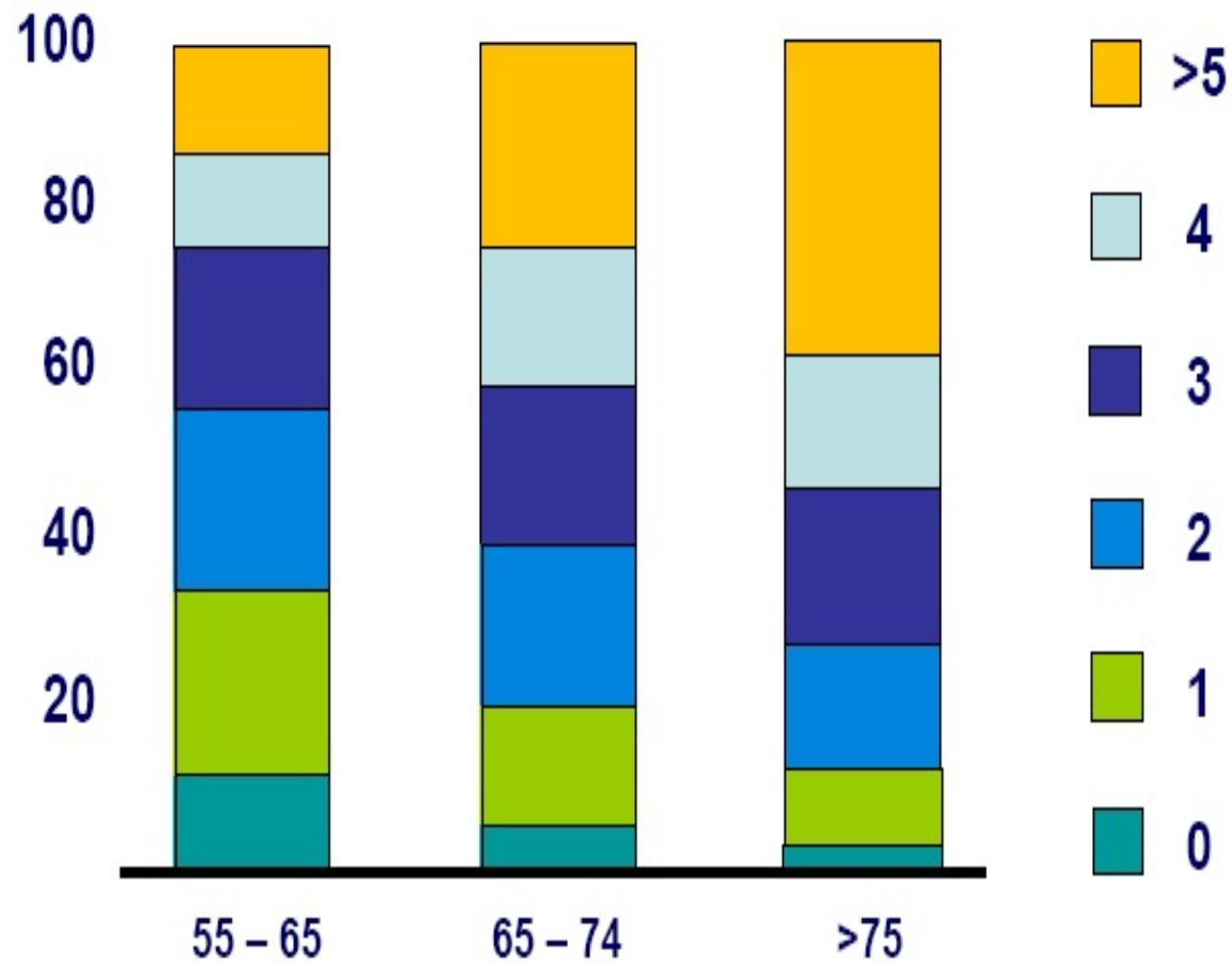


% OF MEDICARE BENEFICIARIES BY NUMBER OF CHRONIC CONDITIONS AND AGE



PER CAPITA MEDICARE SPENDING FOR MEDICARE FFS BENEFICIARIES BY NUMBER OF CHRONIC CONDITIONS: 2010





**the majority patients with CLL aged >75 years
 → ≥5 comorbidities**

Thurmes et al. Leuk and Lymphoma 2008

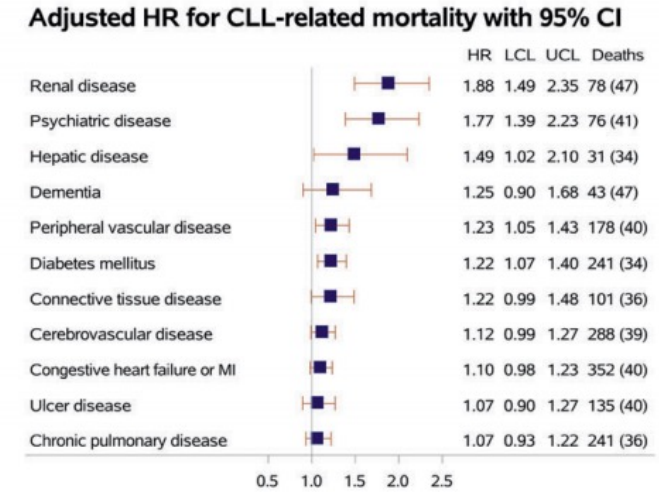
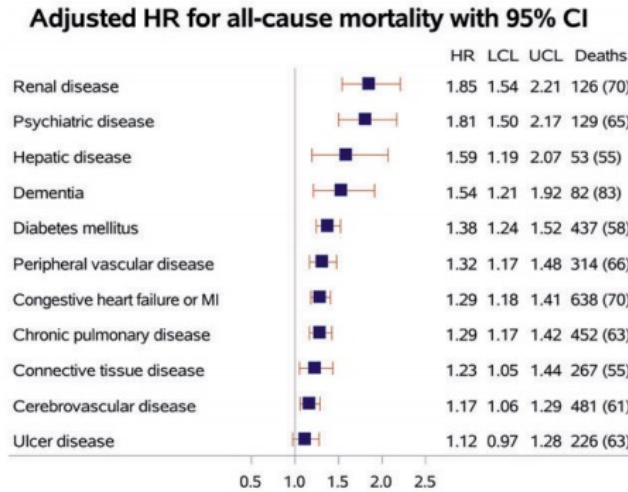
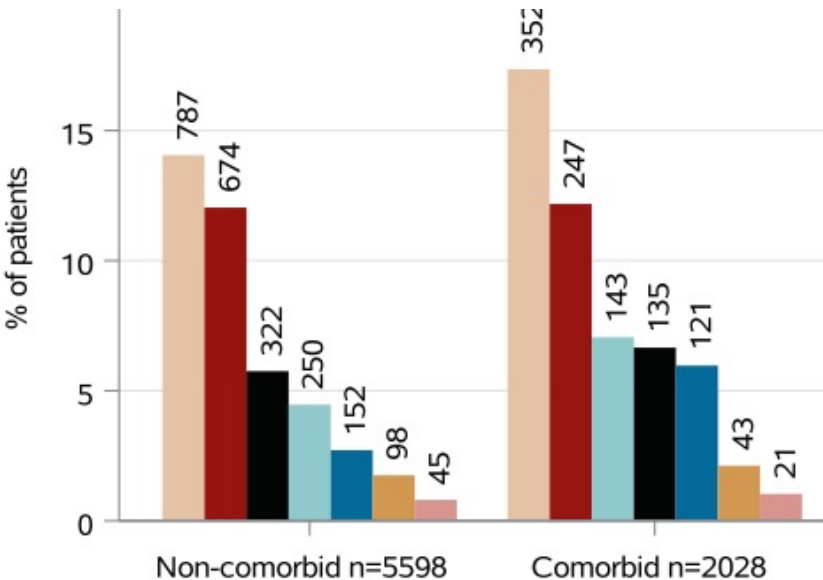


INCREASING PREVALENCE OF CLL WITH AN ESTIMATED FUTURE RISE: A NATIONWIDE POPULATION-BASED STUDY

Danish, nation-wide registers, **9170 consecutive CLL patients** diagnosed in 1997–2018, median follow-up 5.0 yrs

All comorbidities individually associated with increased all-cause and CLL-related mortality

Renal disease psychiatric disease carrying the highest impact



Most common cause of mortality: infections

Mortality due to CVD increased with the number of comorbidities

Rotbain et al, Leukemia 2021





Increase in the proportion
of elderly patients with CLL with
.... comorbidities
.....polypharmacy
.....need for hospitalization

.....without a family caregiver, from
•single-member families
•childless families

.....with a comorbid family caregiver

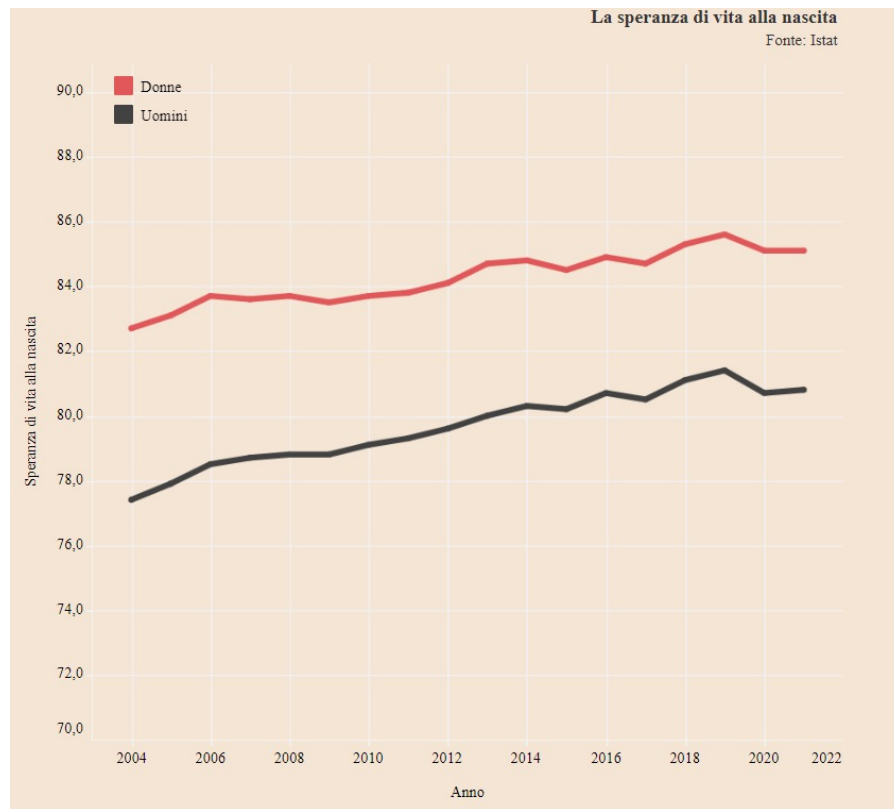
What is the goal of treatment for
old/oldest patients with CLL?



The goal of therapy in all patients including those with CLL:
to maintain at least the same life expectancy as in a healthy subject

And, possibly.....

without significantly modifying the quality of life with respect to that expected for the chronological age

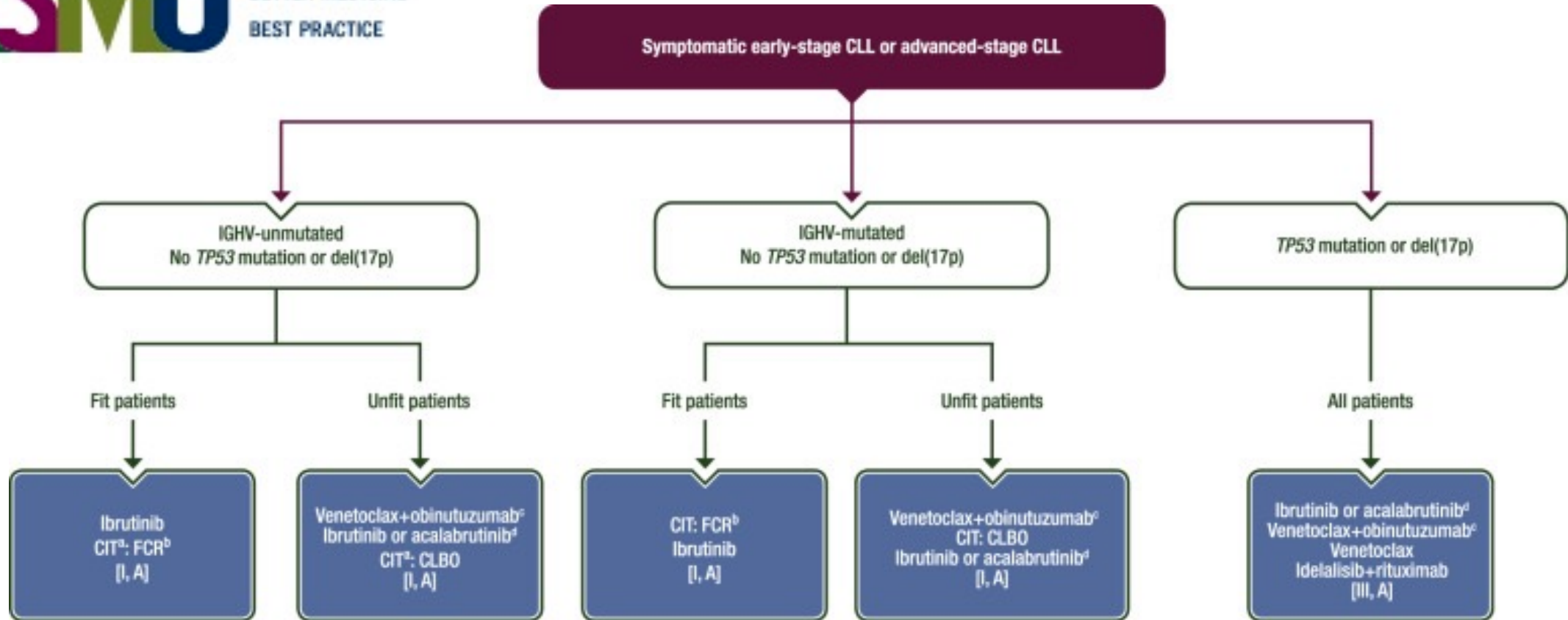


Life expectancy in Italy:

WOMEN= 84,7 yrs

MEN= 80,1 yrs

Oldest old (85 years and above)



What therapeutic guidelines for the optimal treatment choice in old/oldest patients with CLL?

OLDER PATIENTS ARE UNDER-REPRESENTED IN CLINICAL TRIALS

Trial	Schedule	Med age	Age range	No pts >80 yrs
RESONATE-2	IBR	72	65–90	ND
ILLUMINATE	IBR-G	70	66–75	ND
ALLIANCE	IBR/IBR-R	71	65–89	ND
GIMEMA CLL 1114	IBR-R	73	37–88	ND
CLL14	VEN-G	72	67–77	ND
GLOW	VEN-IBR	71	47–93	ND

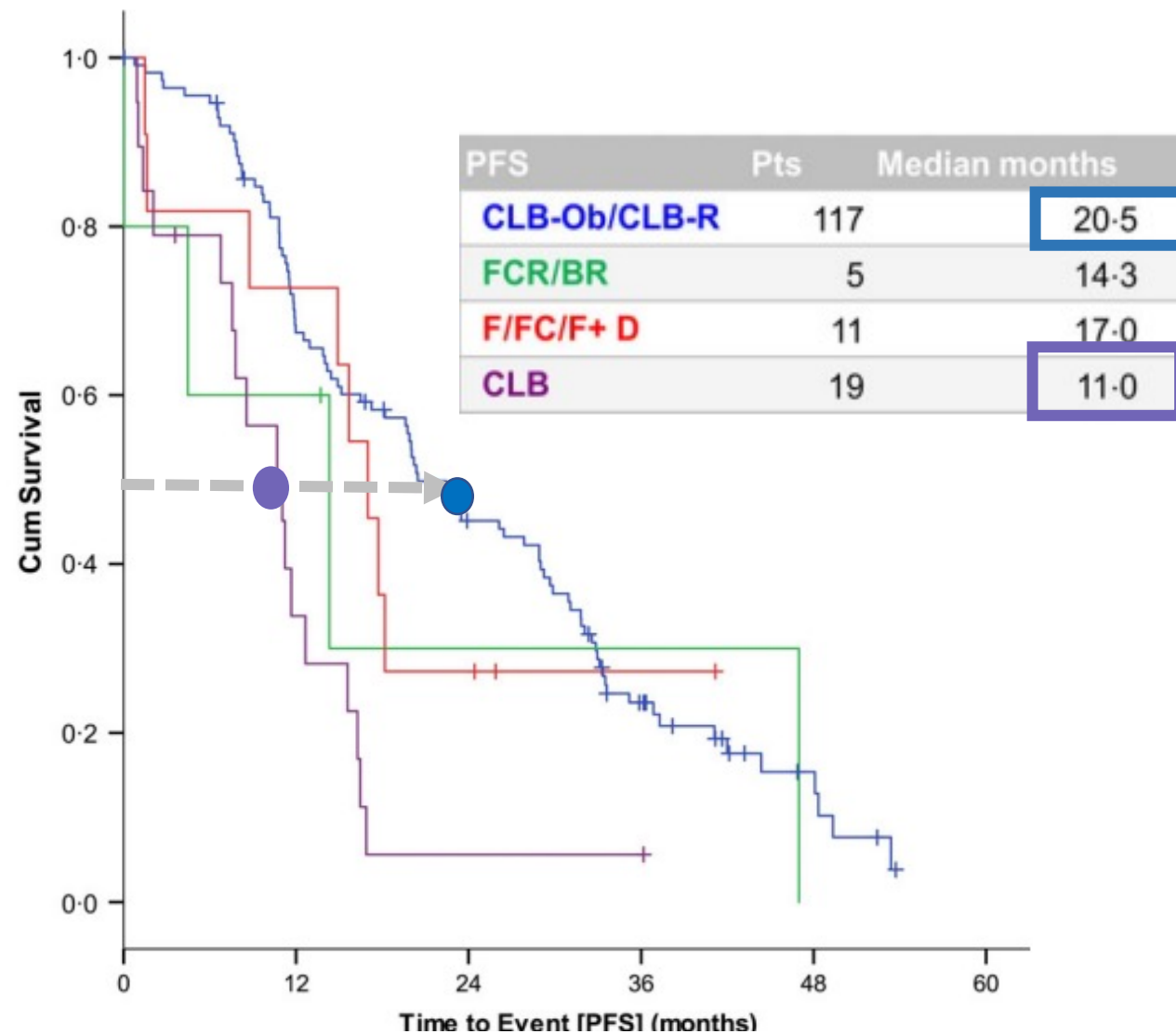
- Older patients are under-represented in clinical trials
- Their outcomes not described in therapeutic clinical trials, making it difficult to assess the safety and efficacy of some regimens
- Retrospective studies



OUTCOME OF CLL PATIENTS AGED 80 YEARS OR OLDER TREATED WITH CT/CIT

Retrospective - 7 GSG trials		
Patients	N=152	
Comorbidities	Med Age	82 (80–90)
	Med CIRS	8 (0–18)
	• Heart	50.3%
	• Blood pressure	73.8%
	• Renal	52.4%
	• Musculoskeletal	50.3%
	• Endocrine/metabolic	48.3%
	• Neurological/ Psychiatric	37%
IGHV	68.7%	
Del17p	16%	

Hematologic toxicity 43%
Severe infections 13%



Al Sawaf et al. BJH, 2017



IBRUTINIB IN VERY ELDERLY PATIENTS WITH R/R CLL: A RW STUDY OF 71 PATIENTS TREATED IN FRANCE: A FILO GROUP STUDY

Study design	Retrospective RWE trial- France early access program	
Patients	71 R/R patients with active CLL Age > 71 yrs Median age 79,3 (75-89.9) Age > 80 yrs: 39.4%	
Comorbidities	hypertension	39%
	cardiologic	29% (AF 13%)
	Renal insuff	31%
Anti aggregant/ anticoagulant		42%
No prior treatments		3 (1-9)
Binet stage C		68%
Del(17p)/TP53^{mut}		19%
Treatment	Ibrutinib single agent	

Toxicity profile	Hematologic	15.5%
	Infections	10.5%
	Bleeding	19%
	Cardiac	7%
	Diarrhea	24%
	Myalgia/arthralgia	20%
Dose reduction		52%
Discontinuation		32.4%
12 month-PR rate		76%
12 month- PFS		77%
12 month-OS		91%
The only factor impacting PFS		Prior arteritis/ myocardial ischemia

Ibrutinib effective in very elderly patients
Elderly require adequate toxicity management with dose reductions

Michallet et al., AJH 2017



IBRUTINIB IN PATIENTS OVER 80 YEARS OLD WITH CLL: A MULTICENTER ITALIAN COHORT

Multicenter, retrospective enrolling 60 consecutive patients with TN or R/R CLL, ≥80 years old treated with ibrutinib in clinical practice. Median observation: 27 months

Patients' and CLL characteristics

Patients' and CLL characteristics	Patients (n = 60)
Median age, y (range)	81 (80-87)
Male, n (%)	33 (55)
Female, n (%)	27 (45)
Total CIRS score > 6, n (%)	46 (76.6)
Concomitant cardioactive therapies, n (%)	
At least 1 cardioactive drug	44 (73.3)
>2 cardioactive drugs	18 (10.8)
Antihypertensive drugs	38 (63.3)
Anticoagulants	3 (5)
Lipid-lowering drugs	10 (16.7)
Antiplatelets drugs	21 (35)
IGHV mutational status, n (%)	
Mutated	24 (40)
Unmutated	32 (53.3)
Deletion in 17p	20 (33.3)
TP53 mutational status, n (%)	
Mutated	19 (31.7)

Adverse events

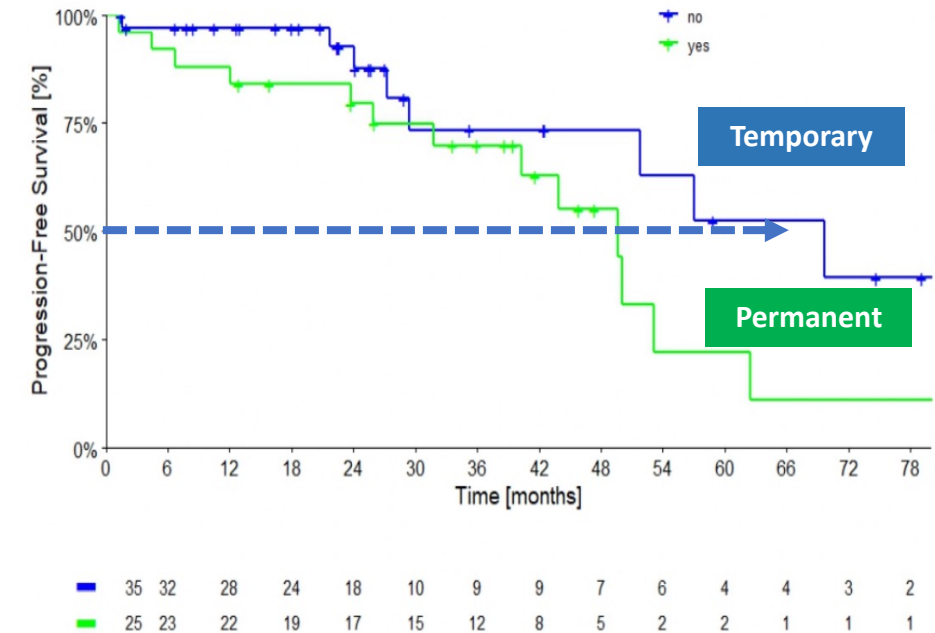
Gr.≥3 infections	21%
CDV events	32%
AF @ 24 mos	16%
HTN@ 24 mos	16%
Acute coronary syndrome	5%
Gr.≤2 bleeding events	37%
TD due to AEs:	23%.

No relationship between concomitant cardiovascular risk factors or previous events and the development of HTN or AF

Echocardiographic LA measurement identified patients at higher risk of developing AF.

ORR: 88.3%

PFS by treatment discontinuation



Temporary drug withholding, <30 days → median PFS: 69.7 months
Permanent drug interruptions → median PFS: 49.7 (p=0.079)

Reda et al. Blood Adv. 2023

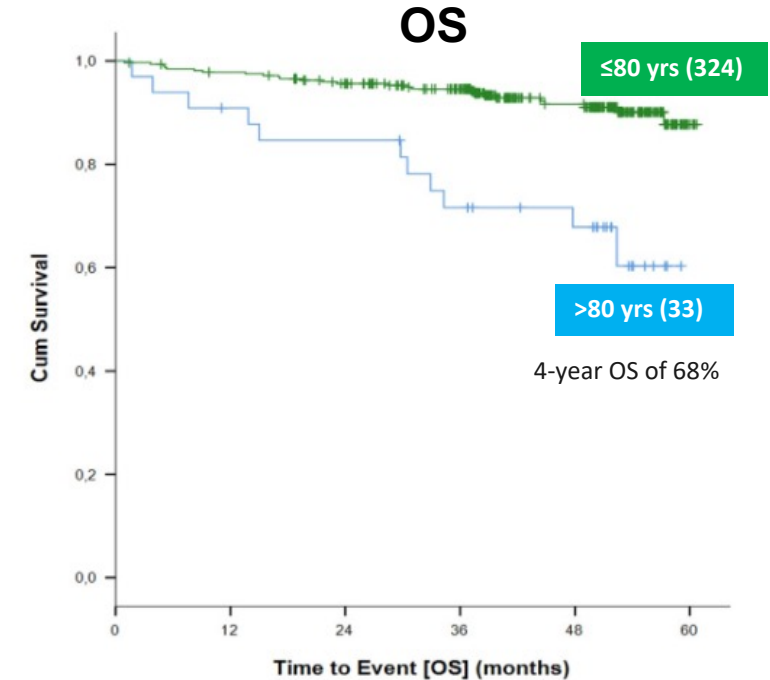
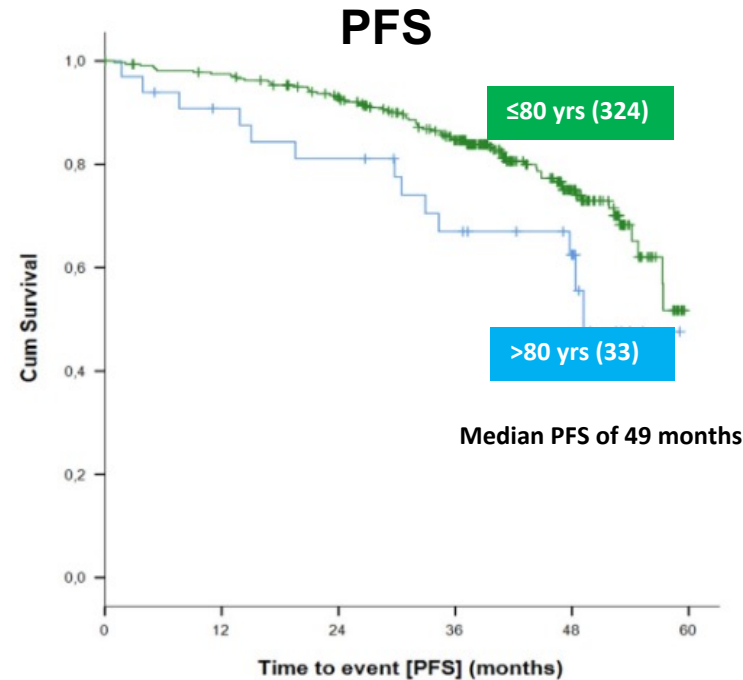


POOLED ANALYSIS OF FIRST-LINE TREATMENT WITH TARGETED AGENTS IN PATIENTS WITH CLL AGED 80 YEARS AND OLDER

Table 1: Patient characteristics

Baseline Characteristics	Total
All patients, N	33
Age (years)	33
Mean [SD]	82.7 [2.7]
Median	82.0
IQR	81.0-84.5
Range	80-89
Gender, N (%)	33
Female	15 (45.5)
Male	18 (54.5)
ECOG performance status (categorical), N (%)	33
0-1	31 (93.9)
> 1	2 (6.1)
Binet stage, N (%)	33
A	3 (9.1)
B	10 (30.3)
C	20 (60.6)
Constitutional symptoms, N (%)	33
No	21 (63.6)
Yes	12 (36.4)
Total CIRS score (categorical), N (%)	31
≤ 6	9 (29.0)
> 6	22 (71.0)
Missing information	2 (6.1)
Creatinine clearance (mL/min) (categorical), N (%)	33
< 50	19 (57.6)
≥ 50	14 (42.4)
< 70	30 (90.9)
≥ 70	3 (9.1)
Genetic aberration, type according to hierarchical model, N (%)	33
del(17p)	2 (6.1)
del(11q)	5 (15.2)
Trisomy 12	6 (18.2)
No del(17p)/ del(11q)/ trisomy12/ del(13q)	8 (24.2)
del(13q) alone	12 (36.4)
IGHV mutational status, N (%)	32
Unmutated	18 (56.3)
Mutated	14 (43.7)
Missing information	1 (3.0)
CLL-IPI risk group, N (%)	29
Low	0 (0.0)
Intermediate	9 (31.0)
High	17 (58.8)
Very high	3 (10.3)
Missing information	4 (12.1)

- 33 patients with CLL, ≥80 years old
- GVe: 82% ; GIVe: 6%; bendamustine + ibrutinib + obinutuzumab/ofatumumab: 12%.
- ORR 73% (CR 36%; PB-uMRD 73%)
- AEs cause of death in 5 cases
- 48% discontinued treatment prematurely.



CONCLUSIONS:

Targeted agents feasible and effective in ≥80-year-old pts with CLL
 Comparable survival to an age- and sex-matched population.

Simon et al. 2021 ASH



Do age, has an impact on outcomes of patients with CLL treated with targeted agents?



Cox proportional regression hazards model of factor on PFS, EFS, OS, Tox-DTD, and PDR

	PFS		EFS		OS		Tox-DTD		PDR	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age	0.82 (0.57-1.18)	.296	0.83 (0.59-1.15)	.254	0.85 (0.54-1.35)	.496	0.91 (0.53-1.54)	.722	0.73 (0.45-1.18)	.201
ECOG-PS	2.43 (1.72-3.42)	<.001	2.63 (1.92-3.61)	<.001	3.90 (2.61-5.85)	<.001	3.30 (2.09-5.20)	<.001	1.52 (0.91-2.55)	.112
CIRS6	1.48 (1.02-2.15)	.037	1.44 (1.03-2.00)	.033	1.01 (0.63-1.62)	.964	1.33 (0.80-2.21)	.270	1.12 (0.70-1.81)	.638
CIRS3 ⁺	0.79 (0.52-1.19)	.261	1.03 (0.71-1.48)	.894	0.95 (0.58-1.56)	.844	1.54 (0.94-2.51)	.084	1.72 (1.08-2.75)	.024
CCI	1.10 (0.71-1.72)	.662	1.19 (0.79-1.78)	.416	1.37 (0.75-2.52)	.306	1.53 (0.72-3.25)	.268	3.88 (1.50-10.06)	.005
Neutropenia	1.70 (1.09-2.67)	.020	1.51 (1.001-2.27)	.049	1.72 (1.01-2.91)	.044	1.83 (1.04-3.22)	.038	1.08 (0.57-2.02)	.814
CYP3A4	1.07 (0.66-1.76)	.780	1.26 (0.82-1.94)	.285	1.09 (0.59-2.03)	.784	1.15 (0.59-2.25)	.670	2.05 (1.24-3.41)	.005
del(17p) and/or <i>TP53</i> ^{mut}	2.19 (1.57-3.04)	<.001	1.78 (1.32-2.40)	<.001	2.06 (1.35-3.15)	<.001	1.59 (0.98-2.57)	.059	0.94 (0.60-1.48)	.800
Lines of previous Tx	1.85 (1.17-2.95)	.009	1.65 (1.10-2.48)	.015	2.73 (1.33-5.60)	.006	1.80 (0.97-3.34)	.064	1.32 (0.79-2.22)	.289

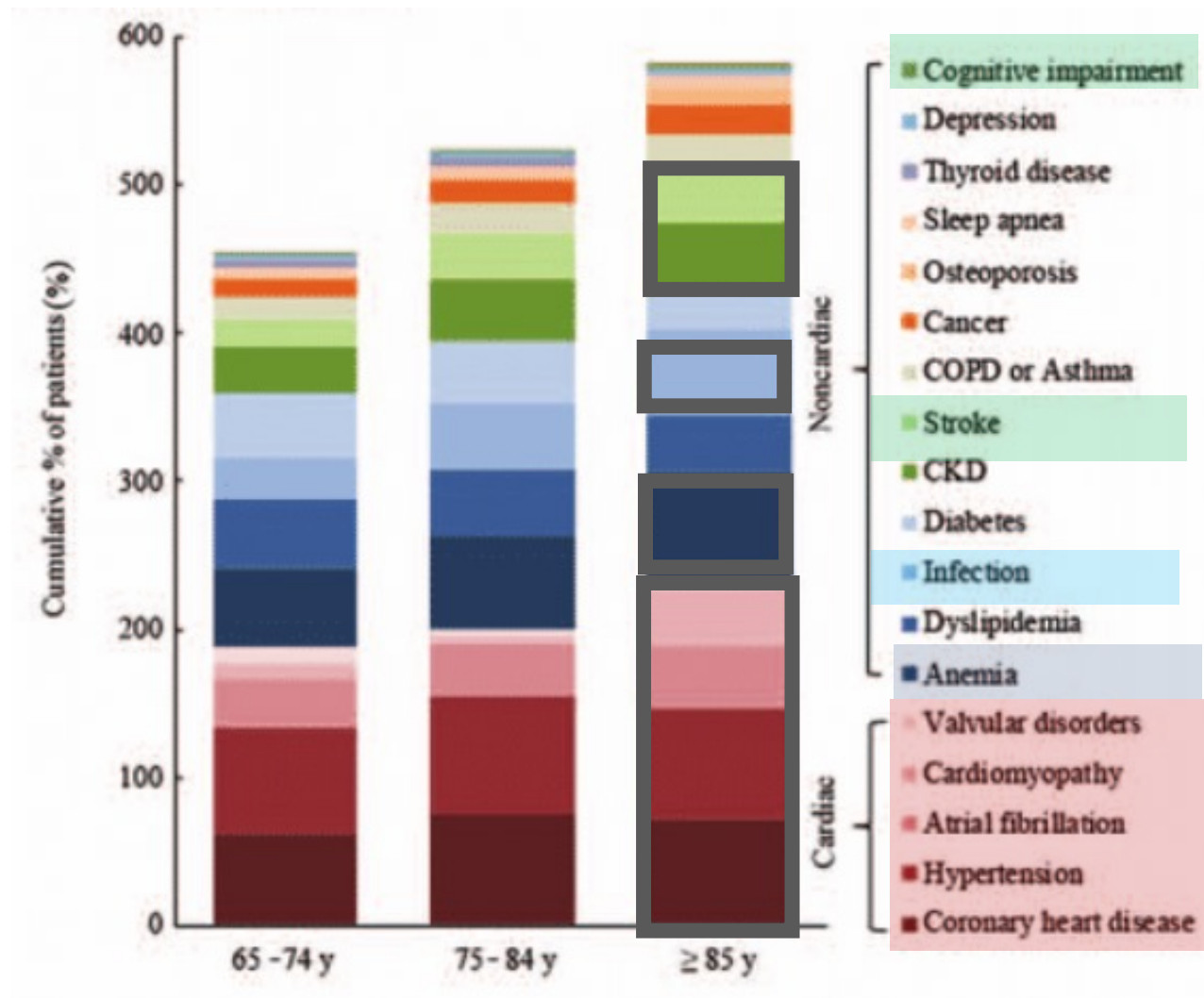
Tedeschi et al. Blood Adv 2022



What impact do comorbidities of older patients have on the choice of targeted agents?



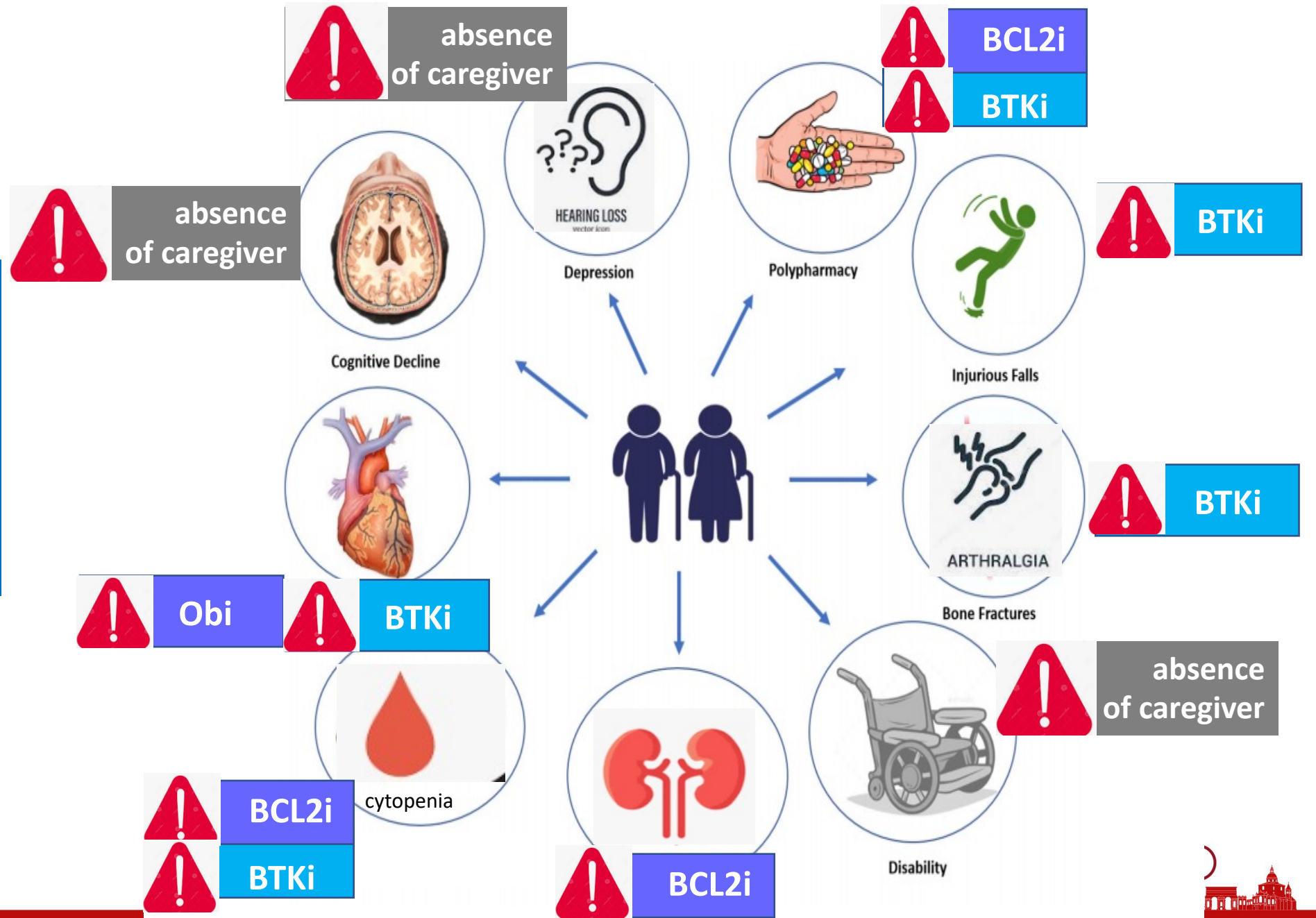
Type of comorbidities by age



Meng-Xi Yang et al., CMJ 2019



comorbidities and the presence of a caregiver can greatly influence treatment choice



How to treat "Old, Old" patients with CLL- Conclusions

- The proportion of old, old patients with CLL will increase in the next years.
- Comorbidities influence treatment decisions and outcomes
- Old, old patients are under-represented in clinical trials making it difficult to assess the appropriateness of treatment regimens in the elderly population.
- The treatment choice is complex and should be individualized on the basis of:
 - comorbidities
 - polypharmacy
 - availability of a caregiver
 - life expectancy

