

LAL e LAM : DAY

Stato dell'arte delle Leucemie Acute

ED. CENTRO

31 marzo 2026 Roma

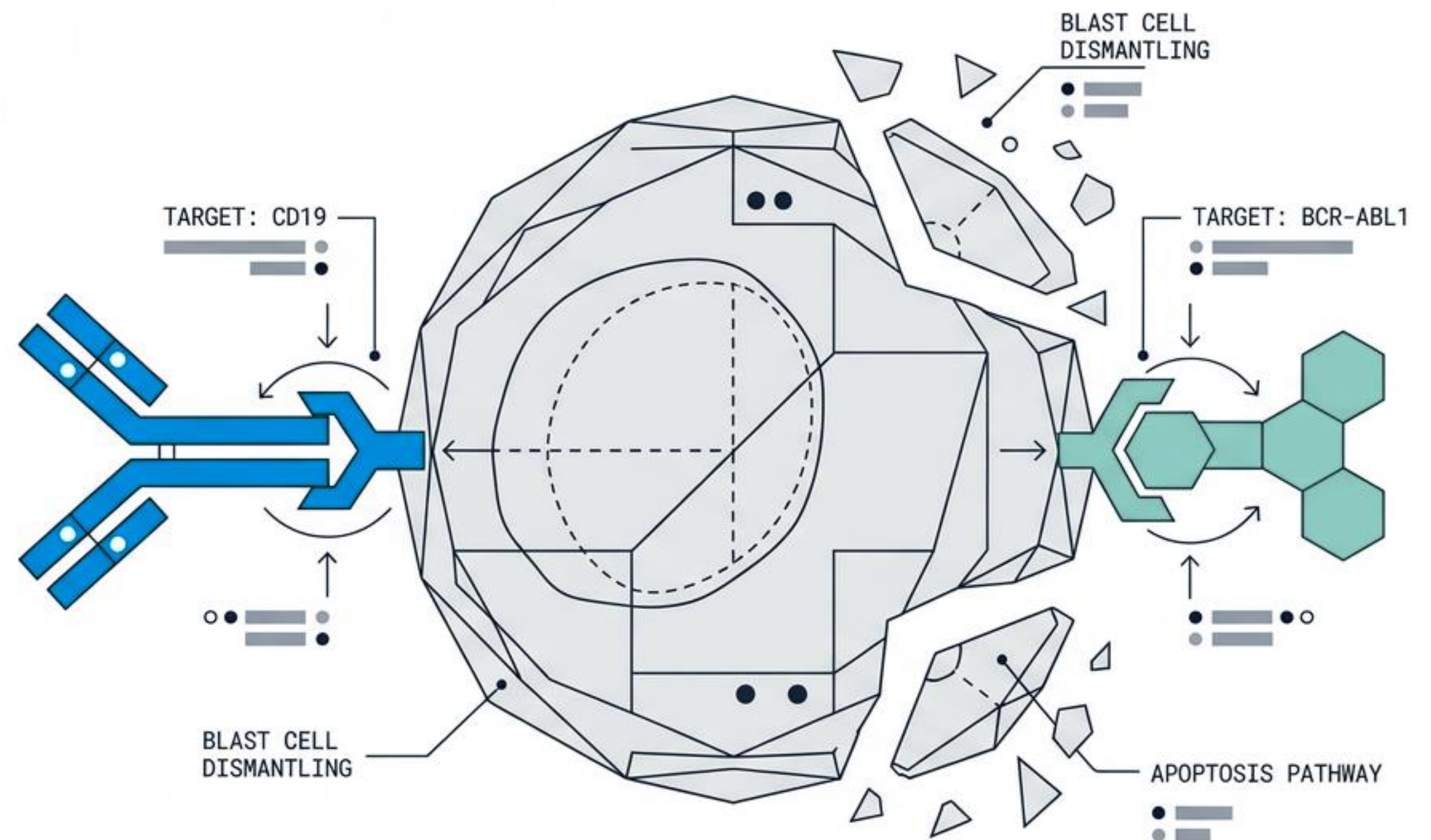
LEUCEMIA
LINFOBLASTICA ACUTA
(LLA) PH+
PAZIENTE UNFIT

IL CAMBIO DI
PARADIGMA

Ludovica Fucci

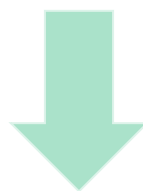


SAPIENZA
UNIVERSITÀ DI ROMA



DEFINIZIONE DI FITNESS

Valutazione delle comorbidità



Charlson Comorbidity Index

Comorbidity	Relative Weight Assignment
metastatic solid tumor	6
AIDS	6
moderate-to-severe liver disease	3
hemiplegia	2
moderate-to-severe renal failure	2
diabetes w/ end organ damage	2
neoplasia	2
leukemia/lymphoma	2
myocardial infarct	1
congestive heart failure	1
peripheral vascular disease	1
cerebrovascular disease	1
dementia	1
chronic pulmonary disease	1
connective tissue disease	1
ulcer disease	1
mild liver disease	1
Diabetes	1

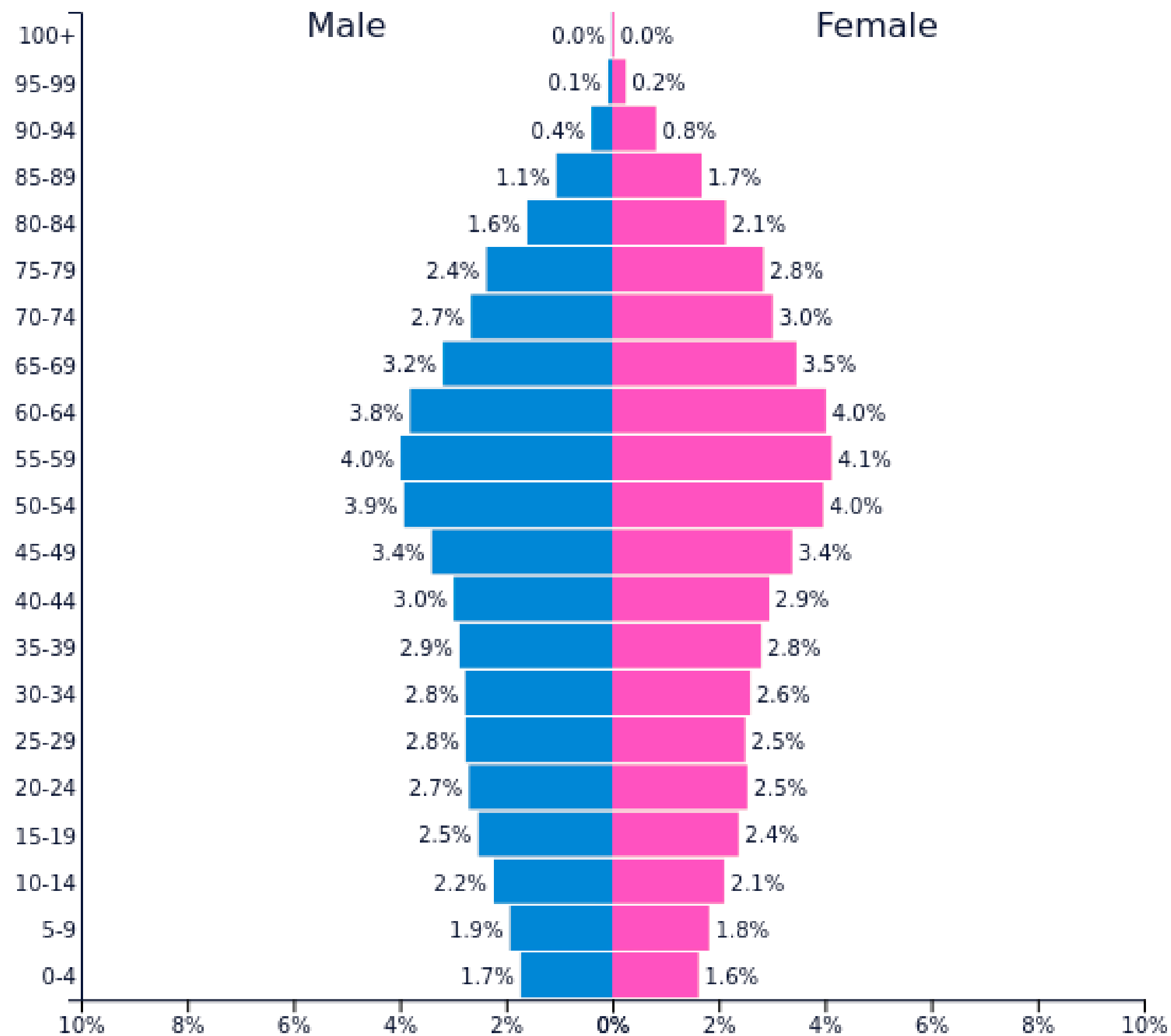
Valutazione geriatrica



Complete Geriatric Assessment

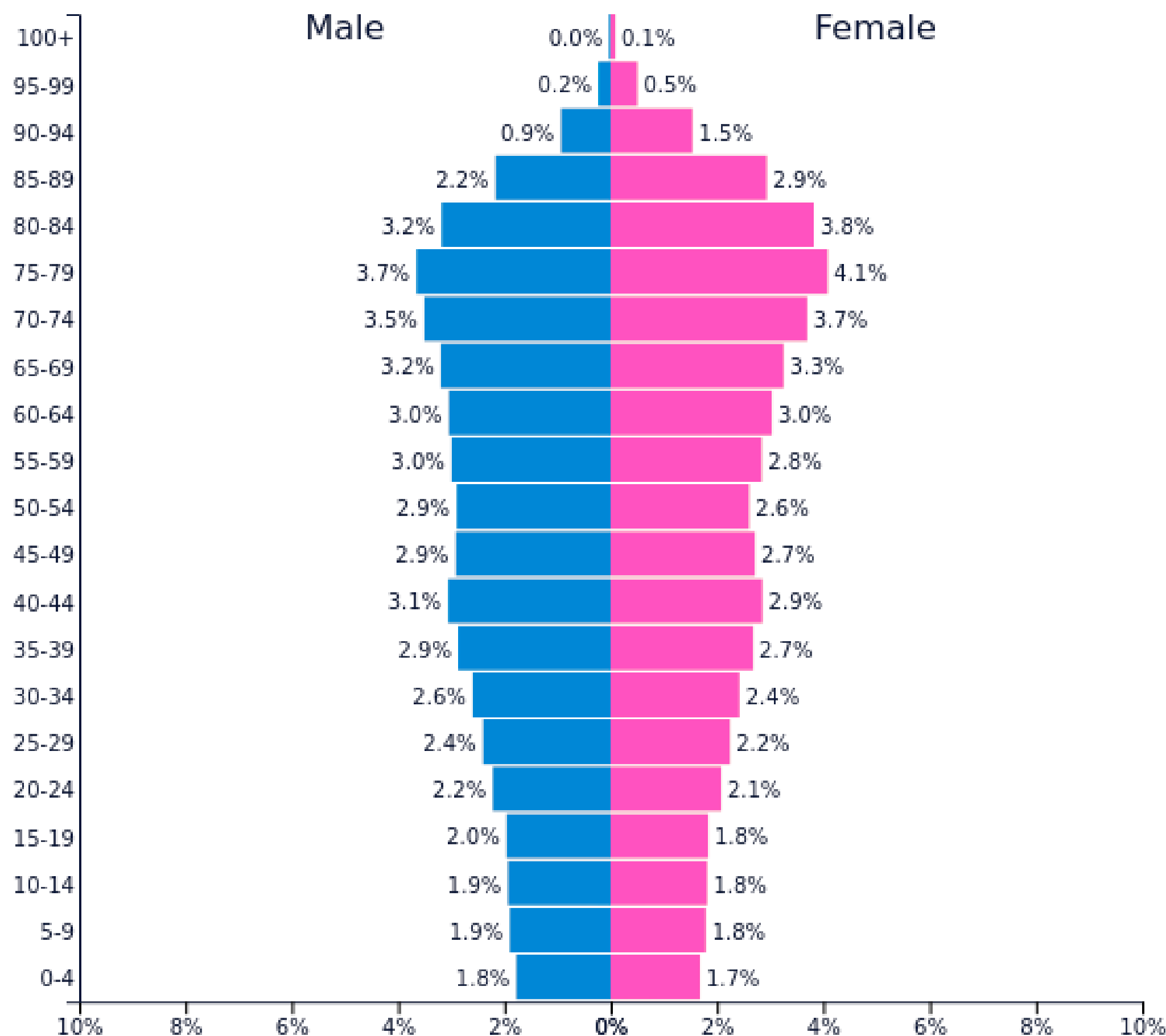
Geriatric domain	Measurement options
Function/physical performance	Activities of Daily Living
	Instrumental Activities of Daily Living
	History of falls
	Timed Up-and-Go
	Short Physical Performance Battery
	Handgrip testing
Comorbidity/pharmacy	Charlson Comorbidity Scale
	Cumulative Illness Scale–Geriatrics
	Comorbidity count and severity
	Medication Count
	Beers Criteria
Cognition	Mini-Mental Status Examination
	Blessed–Orientation–Memory Scale
	Short Portable Mental Status Questionnaire
	Montreal Cognitive Assessment
	Geriatric Depression Scale
Psychological status	Hospital Anxiety and Depression Scale
	Mini-Nutritional Assessment
Nutrition	Weight loss
	BMI
	Needs assessment of financial capabilities,
Social support	Transportation, and caregiver status
	Medical Outcomes Survey Social Support

SITUAZIONE ITALIANA



PopulationPyramid.net

Italy - 2026
Population: 58,926,166



PopulationPyramid.net

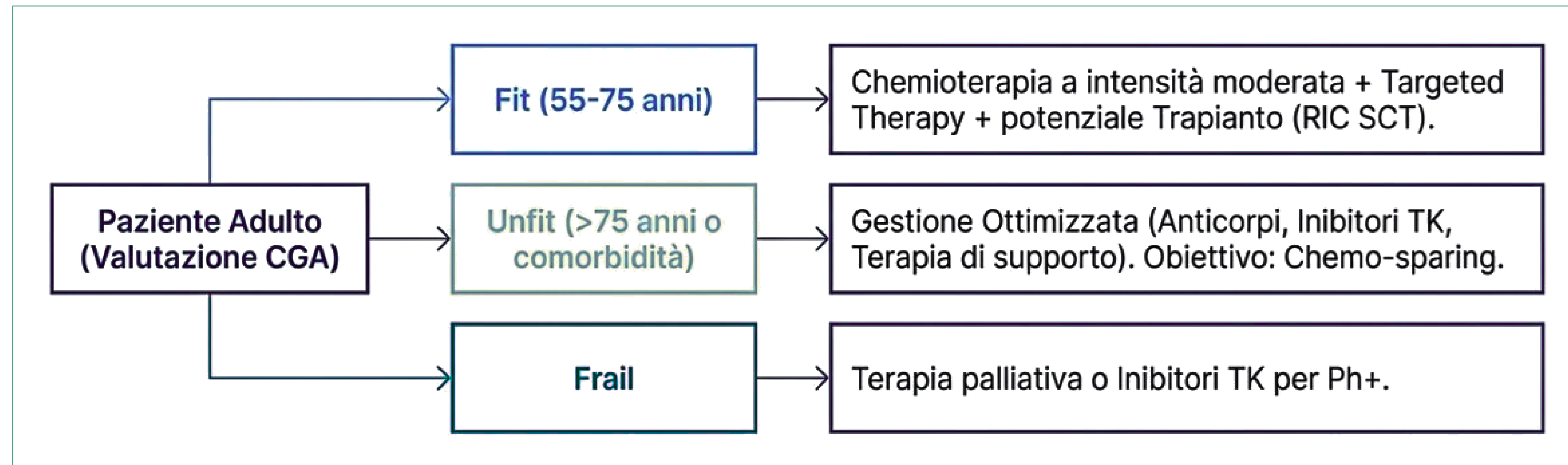
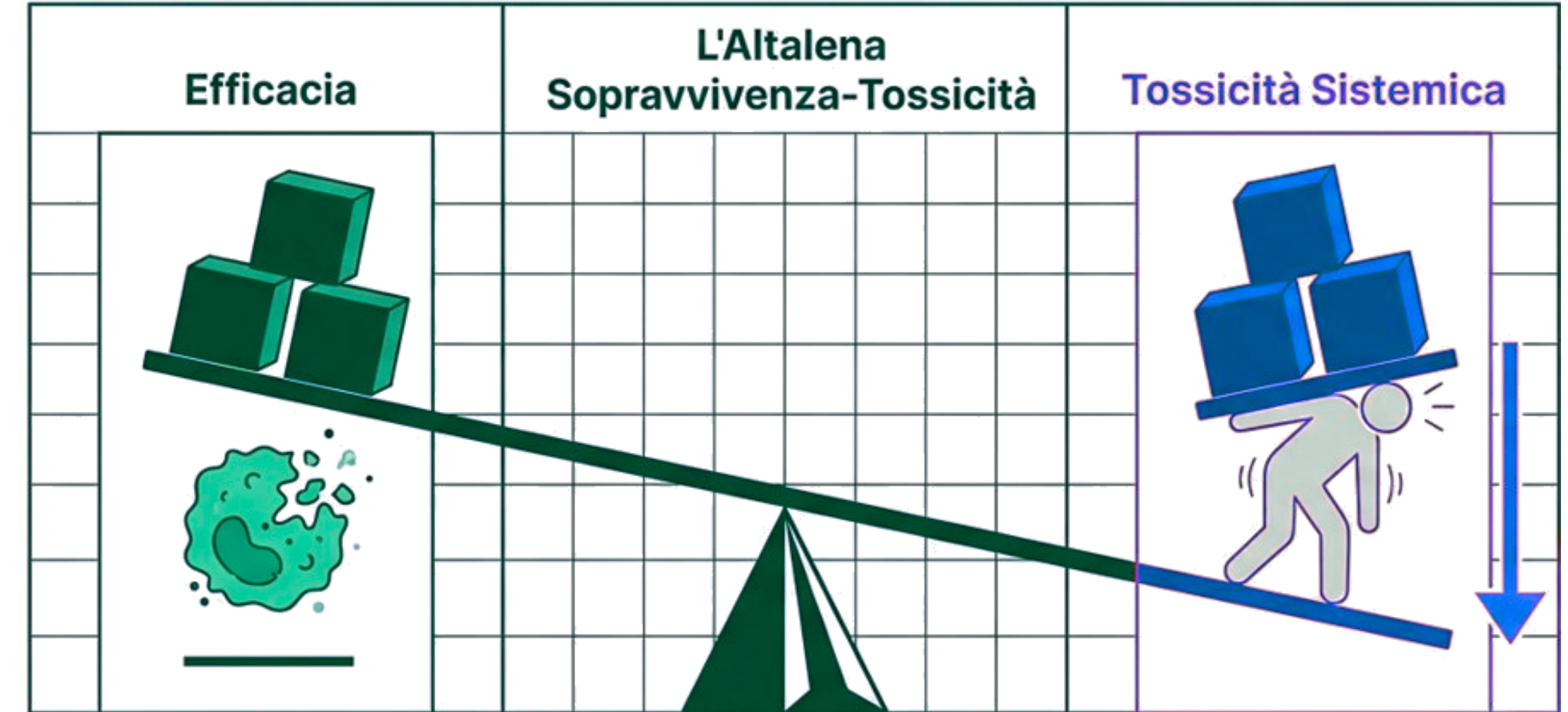
Italy - 2050
Population: 51,891,098

TRATTAMENTO UNFIT/ANZIANI

LLA Ph+ → sottogruppo genetico più frequente in LLA adulte, incidenza che aumenta con l'età.

Nei pazienti di età superiore ai 50 anni, almeno il 50% delle LLA di linea B è Ph+.

UNMET CLINICAL NEED

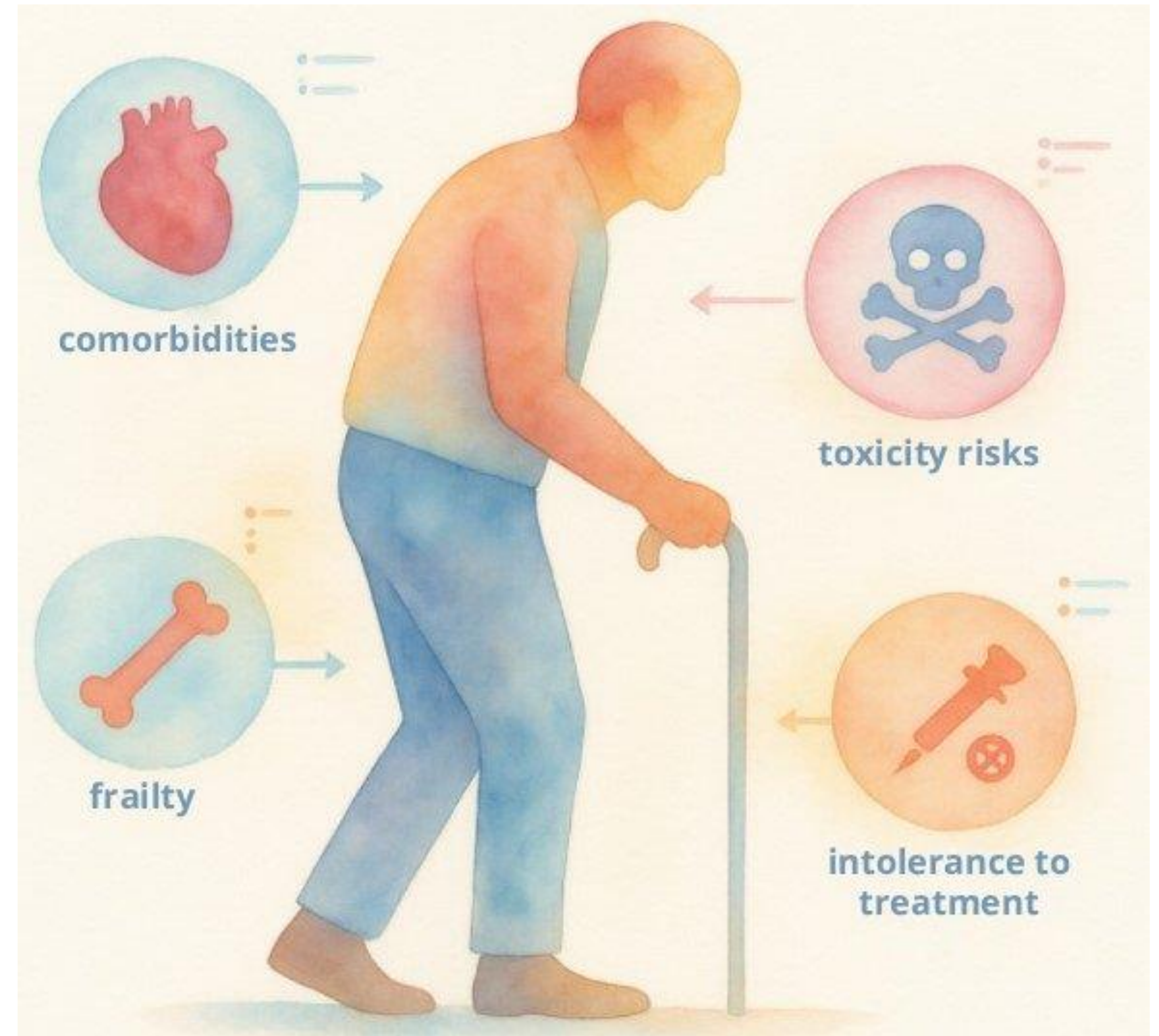


Algoritmo trattamento LAL paziente adulto

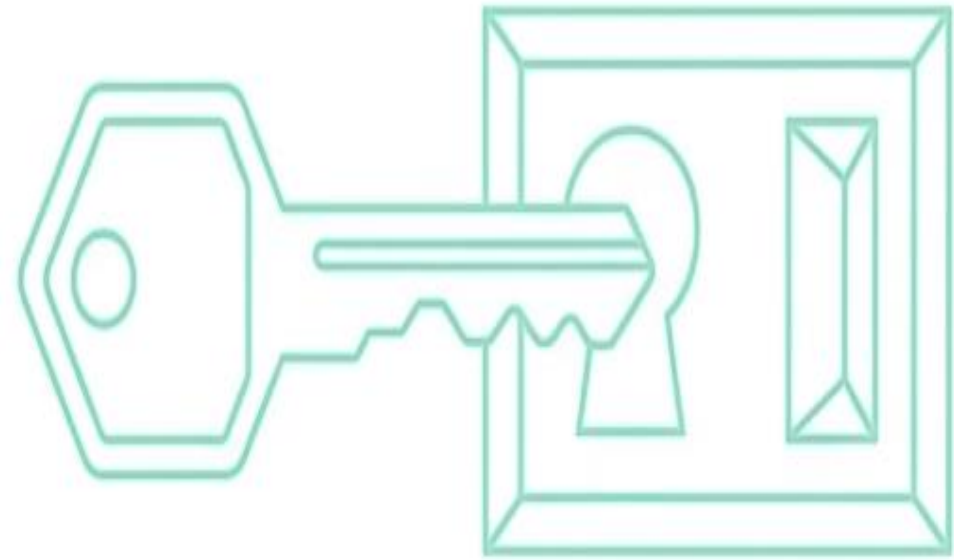
COMORBIDITA':

- DM tipo 2 in tp
- Ipertensione arteriosa in tp
- Ipertrofia prostatica benigna in tp
- Stenosi del canale vertebrale
- Sostituzione valvolare aortica (portatore di protesi meccanica) per stenosi valvolare nel 2009
- Fibrillazione atriale in tp anticoagulante
- Porpora di Schonlein-Henoch trattata con steroidi nel 2013
- Paresi periferica n. radiale destro nel 2017
- Protesizzazione anca bilaterale

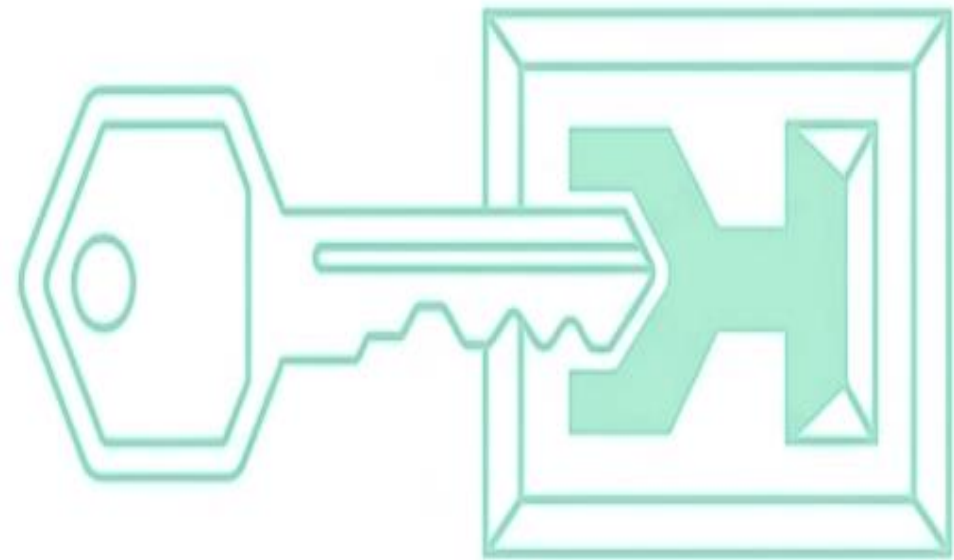
- Dicembre 2019 → DIAGNOSI LAL Ph+ → Imatinib + steroidi + profilassi IT (15 PL). CHR post-induzione, con persistenza MRD+.



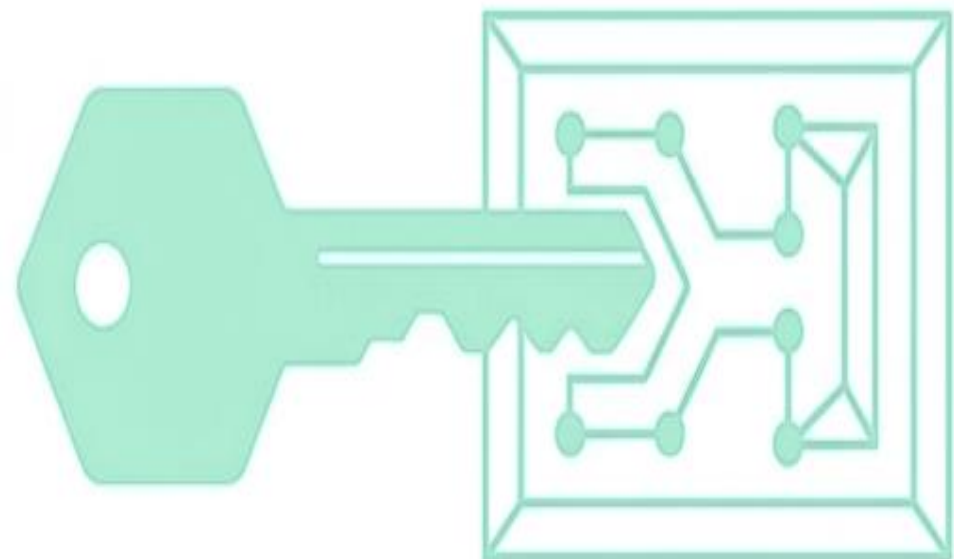
EVOLUZIONE DELL'INIBIZIONE *BCR::ABL1*



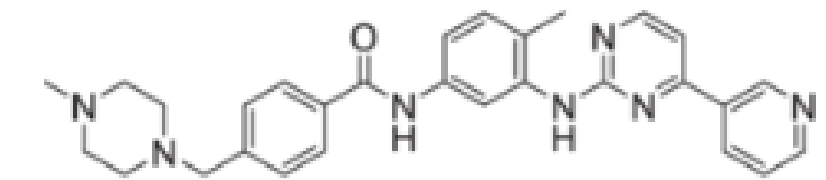
1° generazione (IMATINIB) → efficace ma vulnerabile a mutazioni che conferiscono resistenza;



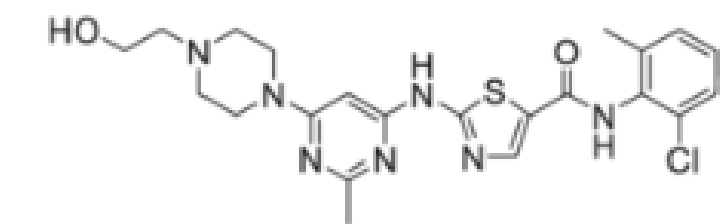
2° generazione (DASATINIB) → più potente ma inefficace sulla mutazione «gatekeeper» T315I;



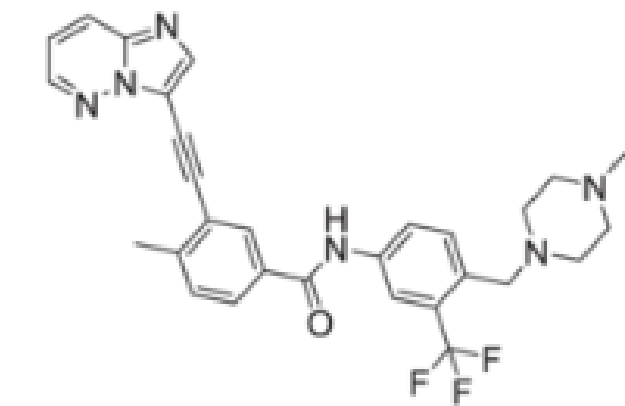
3° generazione (PONATINIB) → pan-inibitore attivo anche su mutazione T315I.



Imatinib



Dasatinib



Ponatinib

- Aprile 2020 → per MRD+ sostituisce Imatinib con Dasatinib + esegue trattamento sperimentale con infusione di cellule autologhe NK (IV cicli).

I principali effetti collaterali dei TKI

Imatinib AEs (% of patients)^b

Fluid retention (62%)^f
 Nausea (50%)
 Muscle cramps (49%)
 Musculoskeletal pain (47%)
 Diarrhea (45%)
 Rash (40%)
 Fatigue (39%)
 Headache (37%)
 Abdominal pain (37%)
 Joint pain (31%)
 Nasopharyngitis (31%)
 Hemorrhage (29%)
 Myalgia (24%)
 Vomiting (23%)
 URTI (21%)
 Cough (20%)

Dasatinib AEs (% of patients)^c

Fluid retention (38%)^g
 Diarrhea (22%)
 Headache (14%)
 Musculoskeletal pain (14%)
 Rash (14%)
 Abdominal pain (11%)
 Fatigue (11%)
 Nausea (10%)
 Pulmonary hypertension (5%)

Nilotinib AEs (% of patients)^d

Rash (38%)
 Headache (32%)
 Nasopharyngitis (27%)
 Fatigue (23%)
 Nausea (22%)
 Arthralgia (22%)
 Pruritus (21%)
 Constipation (20%)

Ponatinib AEs (% of patients)^e

Hypertension (68%)
 Rash (54%)
 Abdominal pain (49%)
 Fatigue/asthenia (39%)
 Headache (39%)
 Dry skin (39%)
 Constipation (37%)
 Arthralgia (26%)
 Nausea (23%)
 Pyrexia (23%)
 Myalgia (22%)

Note. AE = adverse event; URTI = upper respiratory tract infection. Information from Novartis (2015a); ARIAD Pharmaceuticals (2015); Bristol-Myers Squibb (2015); Novartis (2015b).

^aThis information is from the prescribing information for each product and is not based on head-to-head comparisons.

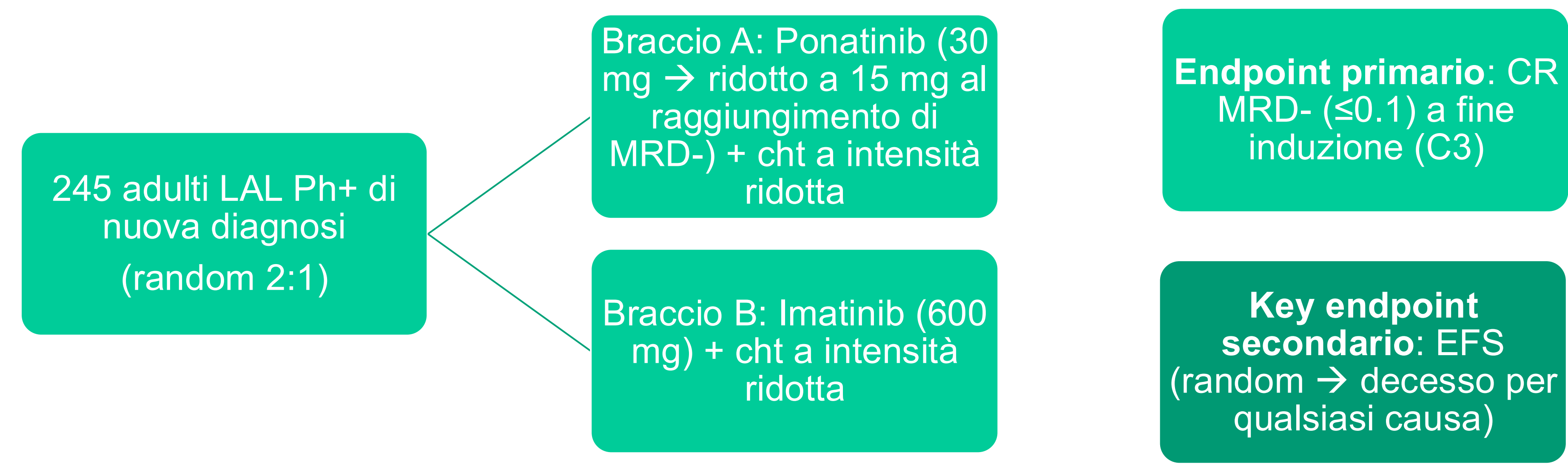
^bAmong newly diagnosed chronic phase chronic myeloid leukemia (CP-CML) patients (AEs occurring in ≥ 20% of patients); follow-up/treatment duration is not reported.

^cAmong newly diagnosed CP-CML patients (AEs occurring in ≥ 10% of patients); minimum 36-month follow-up.

^dAmong newly diagnosed CP-CML patients (AEs occurring in ≥ 20% of patients); median treatment duration: 48 months.

- Ottobre 2020 → ipertensione polmonare e versamento pleuro-pericardico correlati a Dasatinib → torna a Imatinib. Osservazione. CHR MRD+.
- Gennaio 2023 → incremento MRD + recidiva SNC → IT sino a sterilizzazione liquor + shift a Ponatinib + L-VAMP 1 ciclo con ottenimento CHR MRD-.

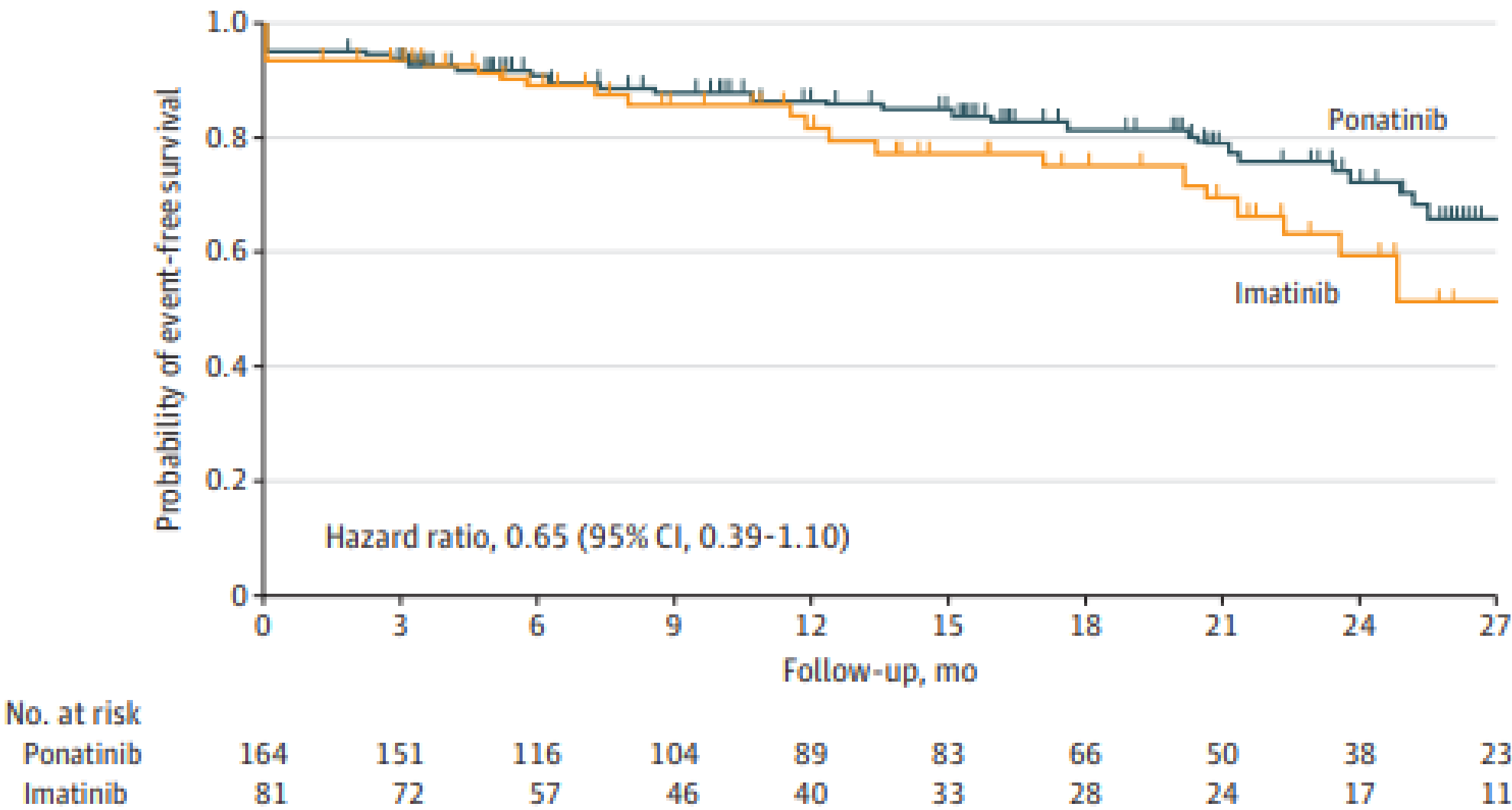
STUDIO PhALLCON IMATINIB VS PONATINIB IN 1°LINEA



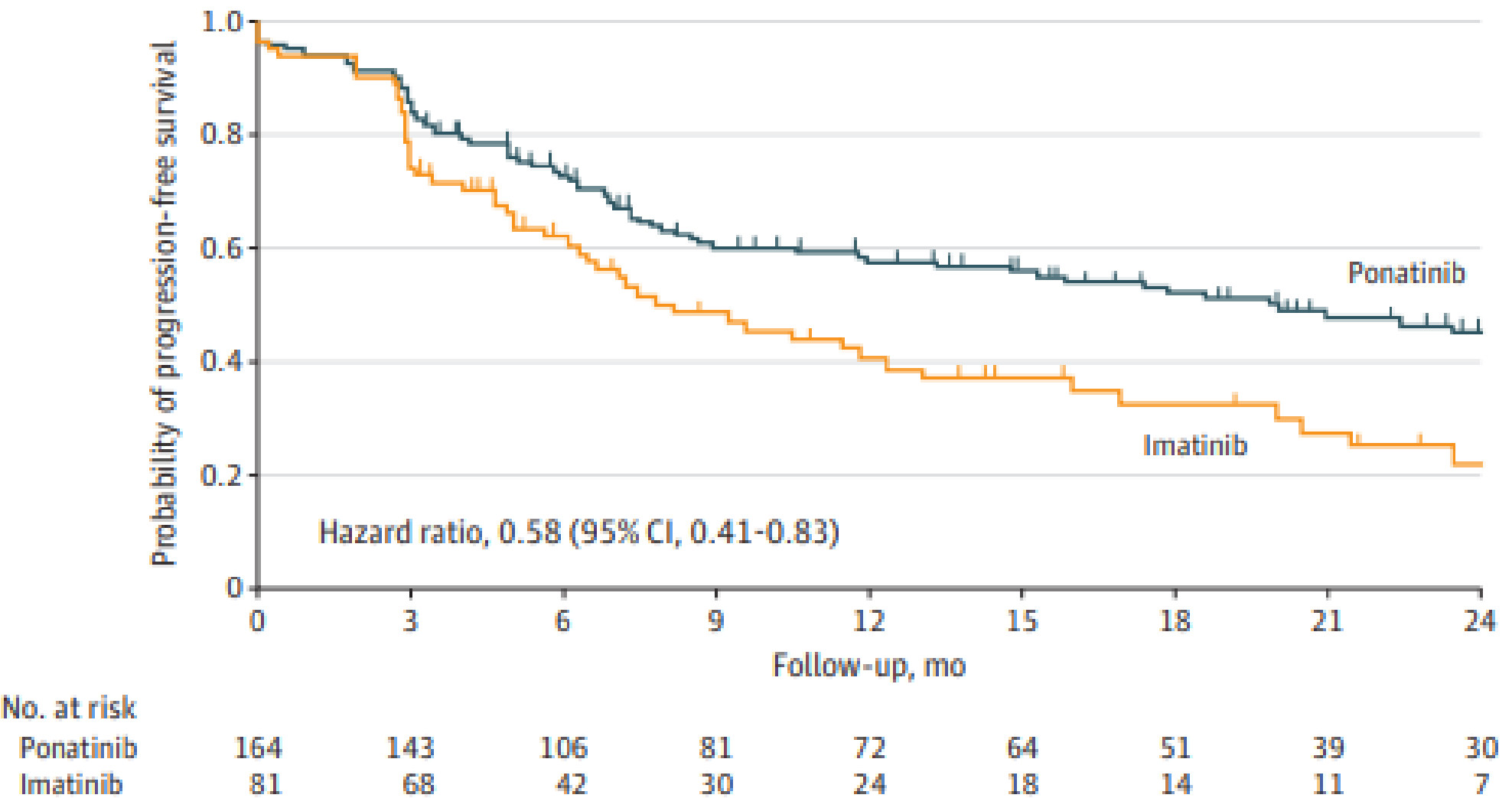
Outcomes	Ponatinib (n = 154)	Imatinib (n = 78)	Risk difference (95% CI)	Relative risk (95% CI)	P value
Primary end point: MRD-negative complete remission at end of induction, No. (%) ^b	53 (34.4)	13 (16.7)	0.18 (0.06-0.29)	2.06 (1.19-3.56) ^c	.002 ^c
MRD negativity (MR4) at end of induction, No. (%)	61 (43.0) ^d	15 (22.1) ^d	0.21 (0.08-0.34)	1.94 (1.19-3.17) ^c	.002 ^c
Duration of MRD-negative complete remission	n = 53	n = 13			
Loss-of-response events, No. (%)	9 (17.0)	6 (46.2)			
Duration, median (95% CI), mo	NE (16.6-NE)	18.0 (8.4-27.8)	NA	NA	

STUDIO PhALLCON IMATINIB VS PONATINIB IN 1°LINEA

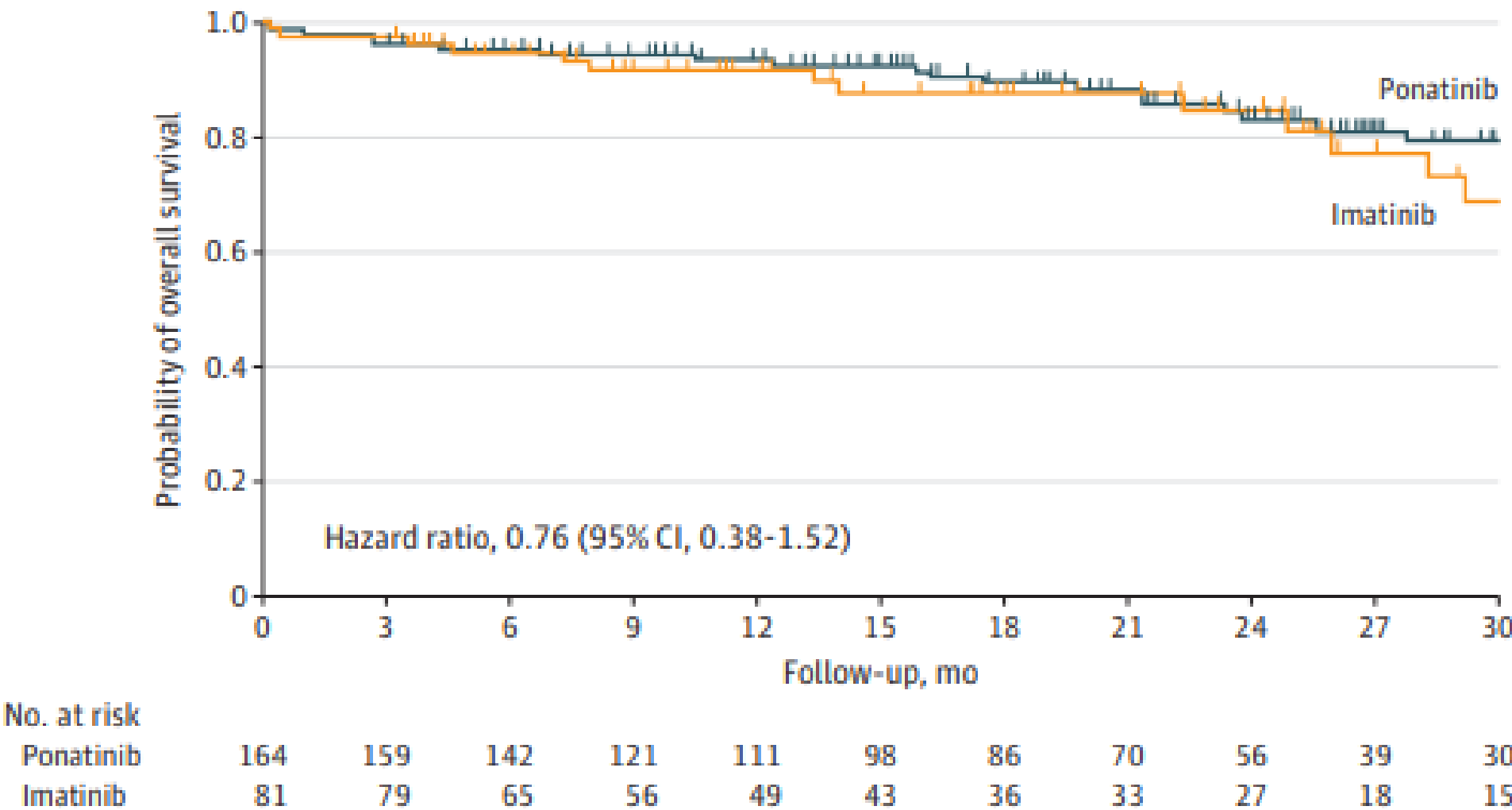
A Event-free survival



B Progression-free survival



C Overall survival



STUDIO PhALLCON IMATINIB VS PONATINIB IN 1°LINEA

	No. (%)			
Adverse events	Ponatinib (n = 163)		Imatinib (n = 81)	
Treatment-emergent adverse events ^a				
Any	162 (99.4)		80 (98.8)	
Serious	97 (59.5)		45 (55.6)	
Grade 3-4	139 (85.3)		71 (87.7)	
Grade 5	8 (4.9)		4 (4.9)	
Treatment-related adverse events ^a				
Any	141 (86.5)		67 (82.7)	
Serious	34 (20.9)		16 (19.8)	
Grade 3-4	107 (65.6)		48 (59.3)	
Grade 5	0		1 (1.2)	
Adverse events of special interest	Any grade	Grade 3-4	Any grade	Grade 3-4
Adjudicated arterial occlusive events ^b				
Any	4 (2.5)	2 (1.2)	1 (1.2)	0
Cardiovascular events	2 (1.2)	2 (1.2)	0	0
Cerebrovascular events	1 (0.6)	0	1 (1.2)	0
Peripheral vascular events	1 (0.6)	0	0	0
Adjudicated venous thromboembolic events ^b				
Any	19 (11.7)	6 (3.7)	10 (12.3)	1 (1.2)
Peripherally inserted central catheter line or central venous catheter related	8 (4.9)	NA	6 (7.4)	NA
Deep vein thrombosis	13 (8.0)	5 (3.1)	9 (11.1)	0
Superficial vein thrombosis	5 (3.1)	0	0	0
Pulmonary embolism	2 (1.2)	1 (0.6)	1 (1.2)	1 (1.2)

Abbreviation: NA, not available.

^a Higher grades indicate more serious adverse events. The sum of values for the serious and grade 3, 4, or 5 adverse event categories does not sum to the value in the “any” category because individual patients could have had events in multiple categories.

^b Arterial occlusive events and venous thromboembolic events were reviewed based on an adjudication charter written before the start of the study by an

independent cardiovascular end point adjudication committee comprising experts with experience and training appropriate for reviews of the cardiovascular end points. The committee adjudicated all arterial occlusive and venous thromboembolic events reported by the study sites (ie, initial diagnoses, laboratory values, results of procedures, and hospital discharge summaries).

STUDIO INCB84344-201: APPROCCIO CHEMO-FREE

Ponatinib + steroidi in prima linea per pazienti LAL Ph+ unfit o > 60 anni (44 pazienti, età mediana a diagnosi 66.5 aa).

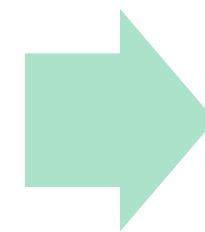
ENDPOINT PRIMARIO

1. Remissione completa con risposta ematologica (CHR) a 6 mesi, definita come:
 - ✓ Blasti midollari $\leq 5\%$,
 - ✓ No blasti in SVP,
 - ✓ No malattia extramidollare.

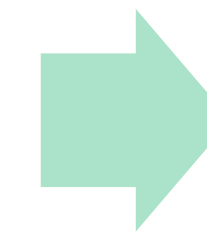
ENDPOINT SECONDARI

1. CHR a 6, 12, 24, 36 e 48 sett.,
2. CCyR a 6, 12, 24, 36 e 48 sett. e durata,
3. CMR e MMR (BCR-ABL1/ABL1 $\leq 0,01$ e $\leq 0,10$) a 12, 24, 36 e 48 sett. e durata,
4. EFS → tempo dall'arruolamento a qualsiasi evento (mancato raggiungimento della CHR alla settimana 6, interruzione del trattamento, perdita della CHR o decesso per qualsiasi causa),
5. OS calcolata → tempo dall'arruolamento al decesso per qualsiasi causa.

Prefase steroidea
(PDN 40-60
mg/mq/die) per 7-14
giorni



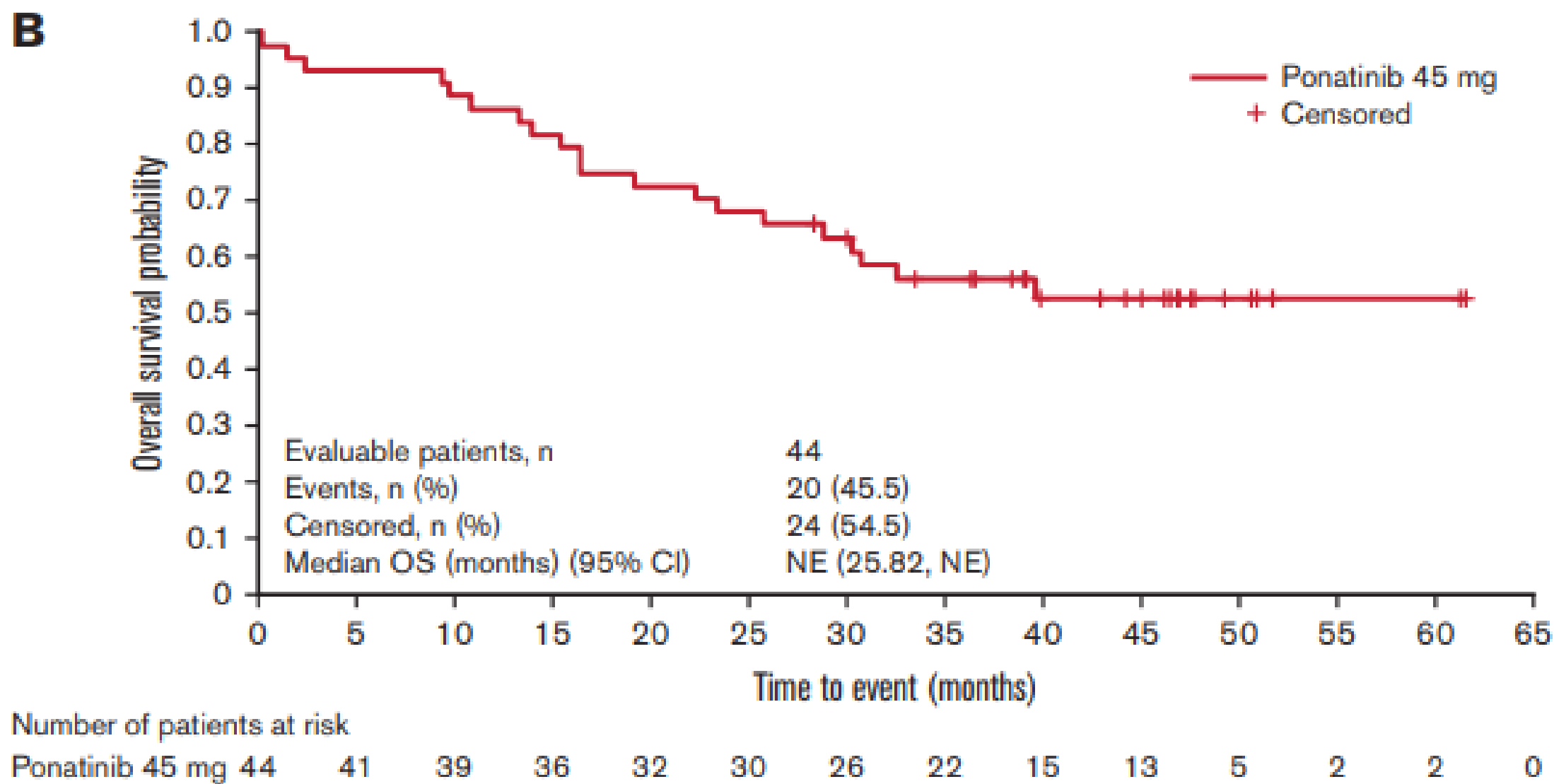
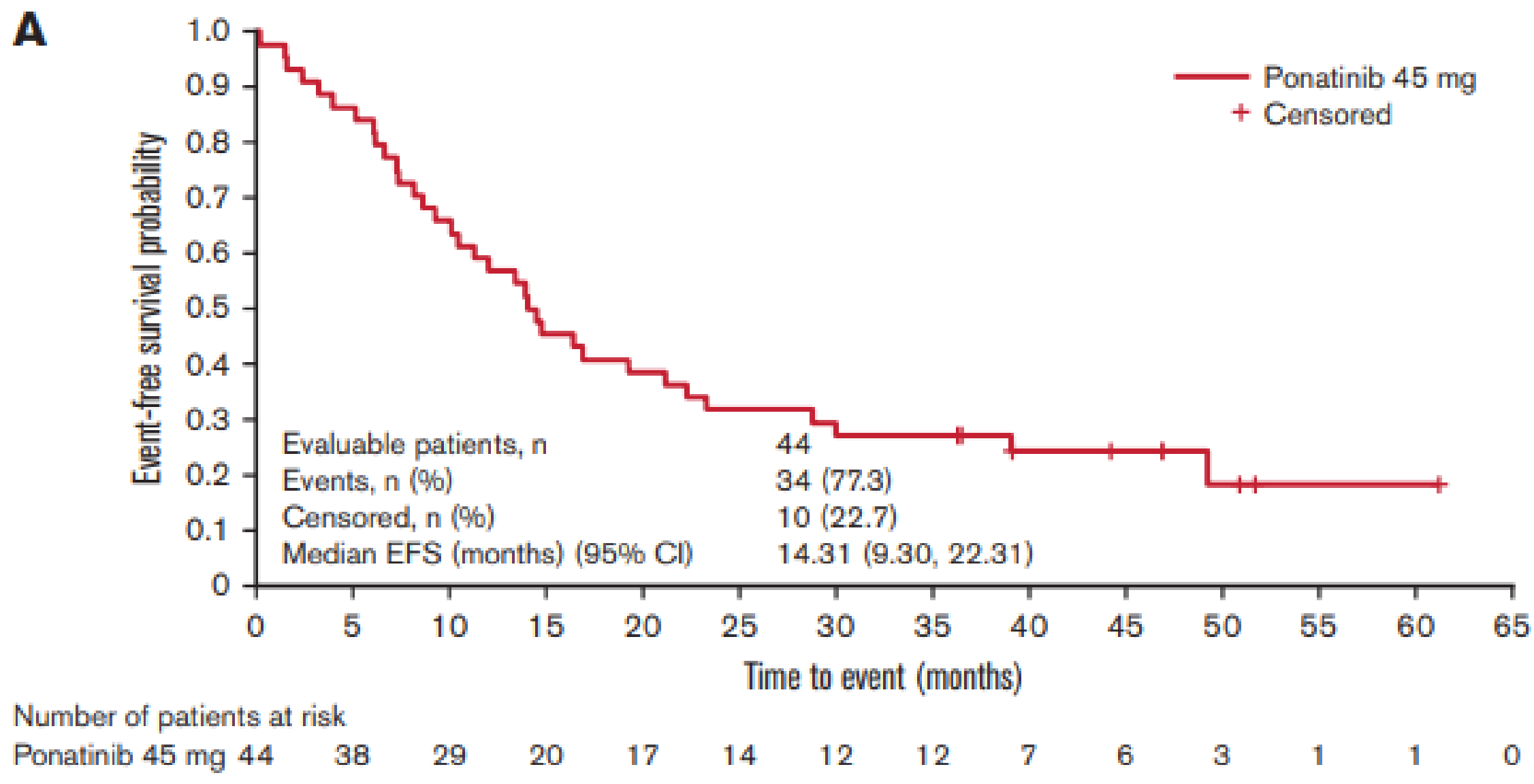
Ponatinib 45 mg/die
per 8 cicli (6 sett/ciclo)
+ PDN 60 mg/mq/die
da G+1 a G+29 e
profilassi IT



Fase di estensione
con proseguo
Ponatinib se beneficio.
Riduzioni di dose
valutate in base a AEs.

STUDIO INCB84344-201: APPROCCIO CHEMO-FREE

Response	Week 6	Week 12	Week 24	Week 36	Week 48
CHR, n (%)	40 (90.9)	37 (84.1)	38 (86.4)*	29 (65.9)	25 (56.8)
CCyR, n (%)	21 (47.7)	19 (43.2)	24 (54.5)*	16 (36.4)	15 (34.1)
CMR, n (%)	21 (47.7)	21 (47.7)	18 (40.9)	18 (40.9)	16 (36.4)
MMR, n (%)	15 (34.1)	11 (25.0)	14 (31.8)*	8 (18.2)	6 (13.6)



Necessità di consolidamento della risposta ottenuta.

STUDIO INCB84344-201: APPROCCIO CHEMO-FREE

TEAEs occurring in ≥ 5% patients, n (%)	Any grade	Grade ≥ 3
Any TEAE	41 (93.2)	32 (72.7)
Cardiac disorders	13 (29.5)	8 (18.2)
Acute coronary syndrome	3 (6.8)	3 (6.8)
Atrial fibrillation	3 (6.8)	2 (4.5)
Gastrointestinal disorders	15 (34.1)	3 (6.8)
Constipation	4 (9.1)	0 (0.0)
Diarrhea	3 (6.8)	0 (0.0)
Dyspepsia	3 (6.8)	0 (0.0)
Hemorrhoids	3 (6.8)	0 (0.0)
General disorders	18 (40.9)	4 (9.1)
Asthenia	10 (22.7)	1 (2.3)
Pyrexia	5 (11.4)	1 (2.3)
Chest pain	4 (9.1)	0 (0.0)
Edema peripheral	3 (6.8)	0 (0.0)
Laboratory investigations	14 (31.8)	6 (13.6)
Alanine aminotransferase increased	7 (15.9)	1 (2.3)
γ-glutamyltransferase increased	7 (15.9)	3 (6.8)
Lipase increased	4 (9.1)	1 (2.3)
Amylase increased	3 (6.8)	0 (0.0)
Blood alkaline phosphatase increased	3 (6.8)	0 (0.0)
Metabolism and nutrition disorders	13 (29.5)	3 (6.8)
Hyperglycemia	4 (9.1)	1 (2.3)
Decreased appetite	3 (6.8)	0 (0.0)
Musculoskeletal and connective tissue disorders	18 (40.9)	1 (2.3)
Pain in extremity	4 (9.1)	0 (0.0)
Myalgia	3 (6.8)	0 (0.0)
Nervous system disorders	11 (25.0)	2 (4.5)
Headache	6 (13.6)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders	8 (18.2)	2 (4.5)
Cough	4 (9.1)	0 (0.0)
Skin and subcutaneous tissue disorders	26 (59.1)	9 (20.5)
Rash	16 (36.4)	2 (4.5)
Erythema	7 (15.9)	2 (4.5)
Skin exfoliation	3 (6.8)	3 (6.8)
Skin ulcer	3 (6.8)	1 (2.3)
Surgical and medical procedures	3 (6.8)	0 (0.0)
Astringent therapy	3 (6.8)	0 (0.0)
Vascular disorders	12 (27.3)	7 (15.9)
Hypertension	5 (11.4)	3 (6.8)

Nello studio **INCB84344-201** nel 43,2% dei casi si è resa necessaria una riduzione della dose a causa di eventi avversi, prevalentemente cardiovascolari o vascolari (27-29%).

PONATINIB: STEP-DOWN APPROACH

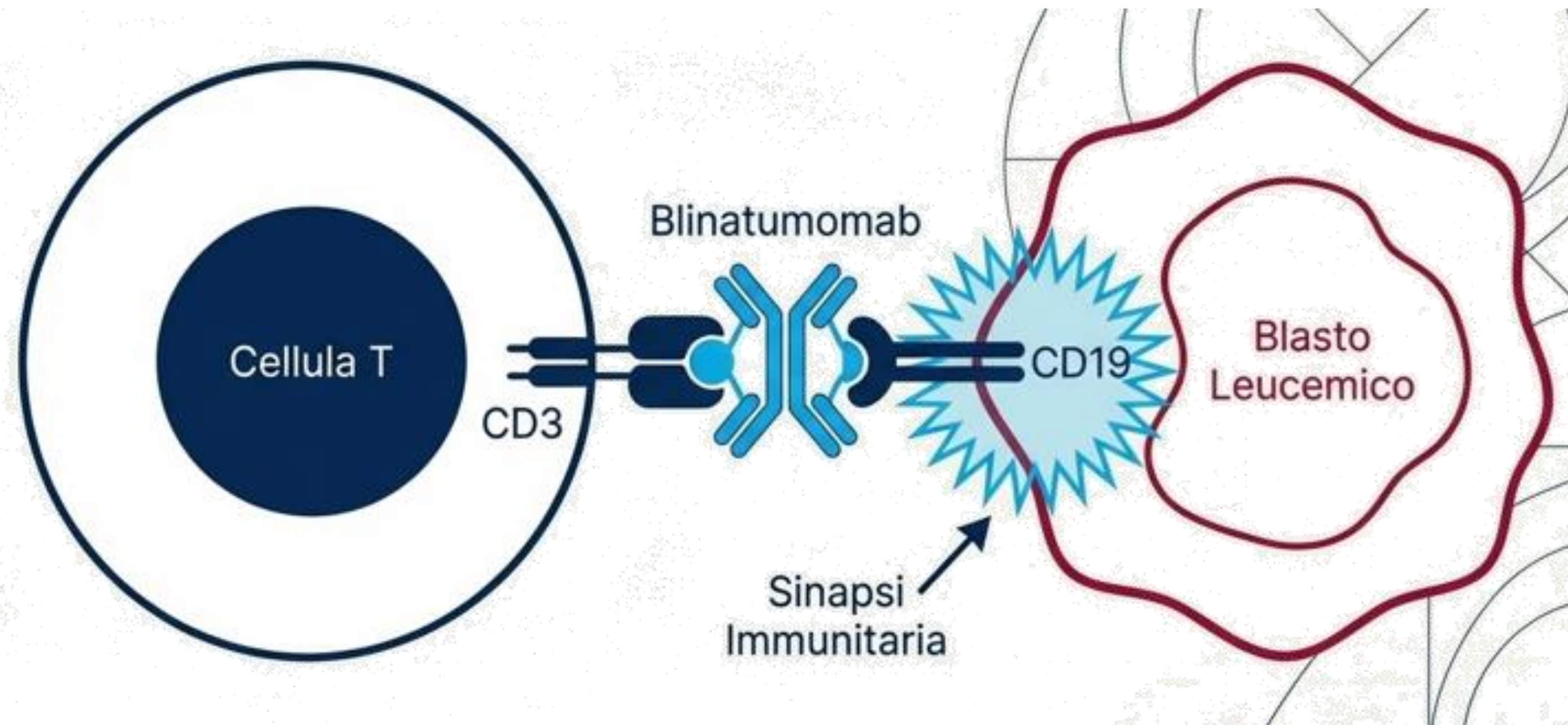
Approccio iniziale (sec. comorbidità) 45–30 mg/die

Raggiungimento MRD- (CMR)

De-escalation a 15 mg/die (mantenimento)

- Aprile 2023 (dopo soli 3 mesi) → per comparsa di flutter atriale correlato a Ponatinib. Shift a Imatinib, osservazione con ri-positivizzazione MRD.

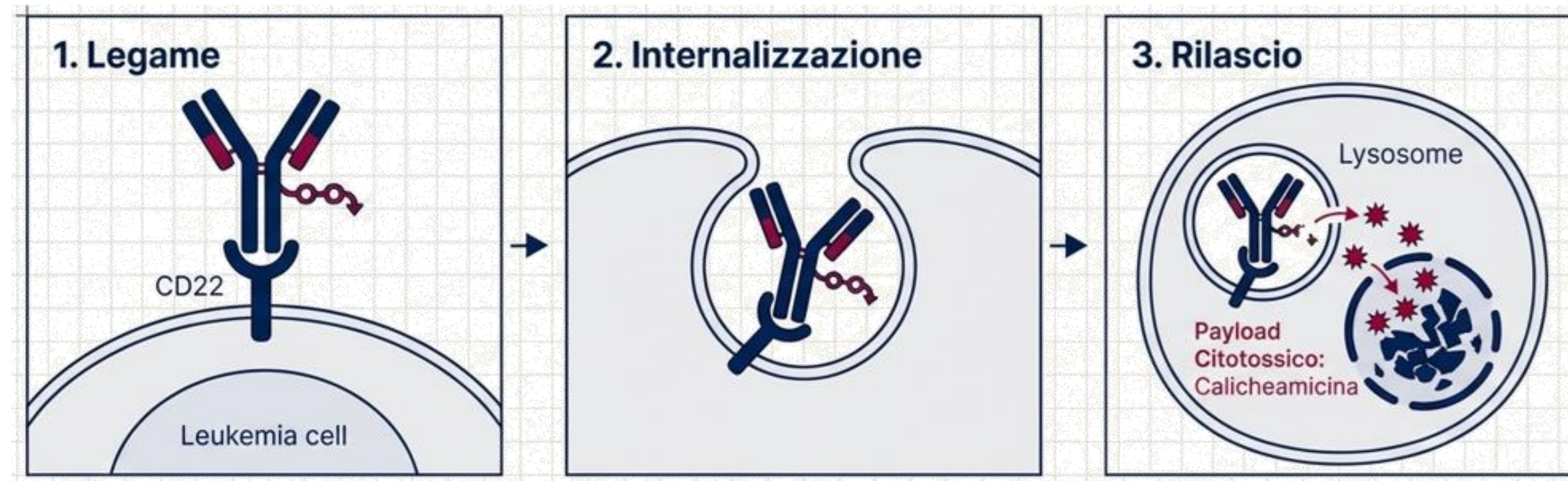
LA SINERGIA TKI + IMMUNOTERAPIA



Study	Treatment	N	Med Age	% CMR	SCT %	Relapses	% OS (x-Year)
SWOG1318 (US) [72]	Dasatinib + 3 Blina	24	73	63 (12/19)	5	8: 3 with T315I	75 (3-yr)
D-ALBA (Italy) [73]	Dasatinib + 2 Blina	63	54	75 (2 mons blina)	48	9: 4 CNS, 6 with T315I	80.7 (4-yr)
MDACC (US) [74]	Ponatinib + 5 Blina	84	50	78 PCR, 95 NGS	2	10: 5 CNS, 1 ph -ve	89 (4-yr)
ALL2820 (Italy) [75]	Ponatinib + 2-5 Blina	151	57	73	12	4: 1 CNS, 1 ph -ve	94.9 (1-yr)

N.B.: Approccio non percorribile in caso di CNS+.

INOTUZUMAB OZOGAMICIN: IL CAVALLO DI TROIA CD22+



Recruiting ⓘ

Study of Chemotherapy-Free Induction Regimen for Ph+ Acute Lymphoblastic Leukemia With Inotuzumab Ozogamicin (InO)

ClinicalTrials.gov ID ⓘ NCT04747912

Sponsor ⓘ University of Chicago

Information provided by ⓘ University of Chicago (Responsible Party)

Last Update Posted ⓘ 2025-03-07

Active, not recruiting ⓘ

Inotuzumab Ozogamicin in Treating Patients With B-cell Acute Lymphocytic Leukemia With Positive Minimal Residual Disease

ClinicalTrials.gov ID ⓘ NCT03441061

Sponsor ⓘ M.D. Anderson Cancer Center

Information provided by ⓘ M.D. Anderson Cancer Center (Responsible Party)

Last Update Posted ⓘ 2026-02-17

Unknown status ⓘ

Verified ⓘ 2021-12 by Gruppo Italiano Malattie EMatologiche dell'Adulto

Last known status was: Recruiting

Feasibility and Effectiveness of Inotuzumab Ozogamicin in B-Cell Acute Lymphoblastic Leukemia (ALL2418)

ClinicalTrials.gov ID ⓘ NCT03610438

Sponsor ⓘ Gruppo Italiano Malattie EMatologiche dell'Adulto

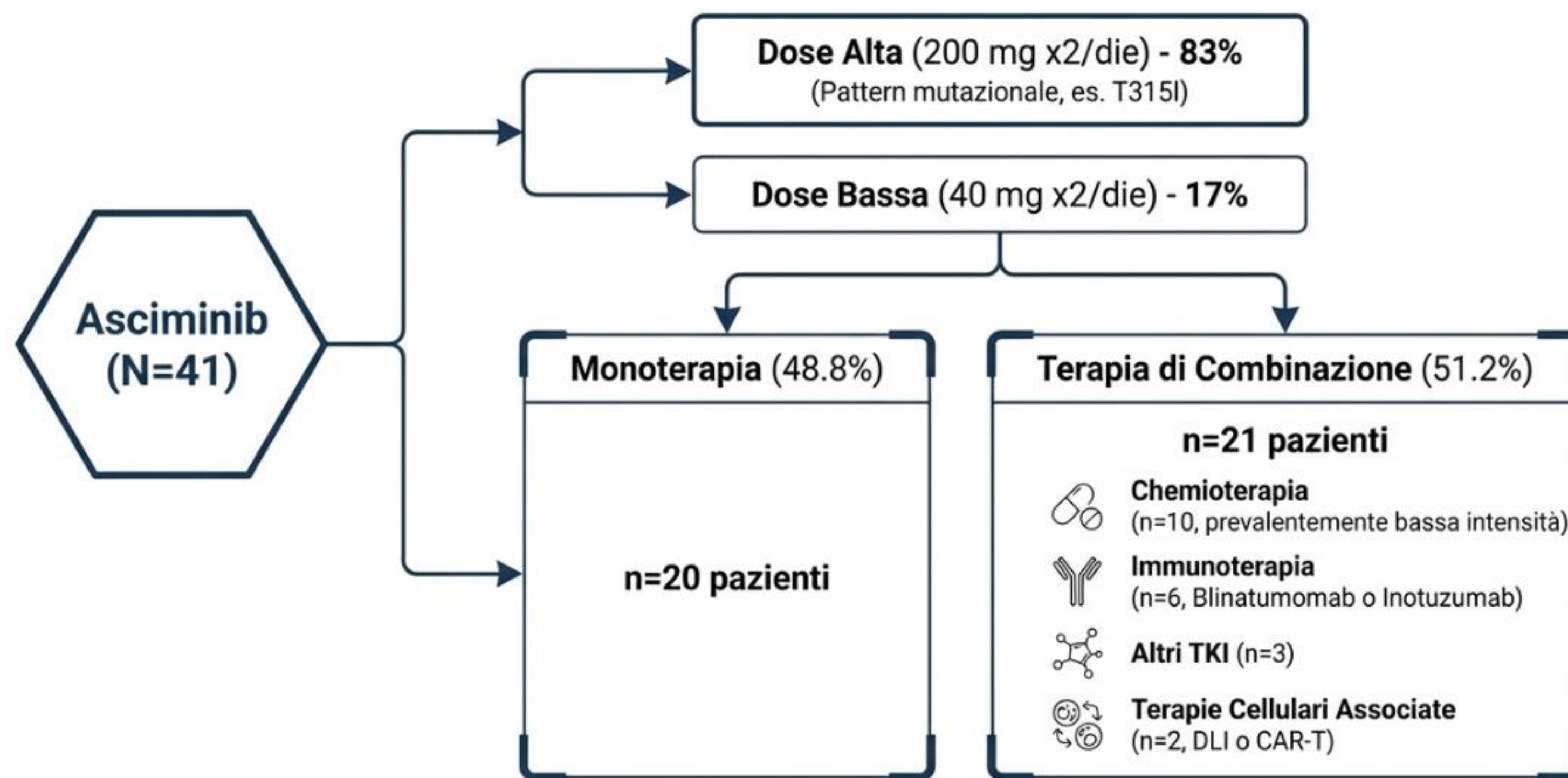
Information provided by ⓘ Gruppo Italiano Malattie EMatologiche dell'Adulto (Responsible Party)

Last Update Posted ⓘ 2022-01-04

- Luglio 2023 → recidiva midollare → Inotuzumab Ozogamicin con ottenimento CHR MRD- a Novembre 2023. Prosegue Imatinib e osservazione.
- Marzo 2024 → ri-positivizzazione MRD. Prosegue Imatinib e osservazione.

ASCIMINIB IN LAL PH+ R/R

Pazienti con età mediana pari a 56 aa e con una mediana di linee precedenti di terapia pari a 3.
93% avevano fallito terapia con Ponatinib, 77% presentavano mutazioni TKD pre-esistenti (più della metà T315I).



83% ha ottenuto CHR (88% in monoterapia vs 79% in combinazione) di cui il 57% anche MRD- con un profilo di sicurezza favorevole (AEs perlopiù citopenie di grado 3-4).

- Marzo 2025 → incremento MRD → Asciminib ad uso compassionevole inschema combinato con Imatinib → mantenimento di CHR MRD+.
- Febbraio 2026 → recidiva SNC → IT sino a sterilizzazione liquor, sospeso Asciminib, prosegue Imatinib e osservazione. Mantiene CHR MRD+.

CONCLUSIONI

1. Necessità di una valutazione multidimensionale (oltre l'età anagrafica);
2. Definizione dell'obiettivo terapeutico nel paziente unfit/anziano: cura o controllo cronico?
3. La «safety» come endpoint di rilevanza soprattutto nell'unfit/anziano;
4. Ottimizzazione della dose: l'approccio «Step-Down» nella pratica clinica;
5. Integrazione precoce dell'Immunoterapia e rimodulazione dosaggi TKI;
6. Il problema del santuario SNC;
7. Terapia con TKI di combinazione vs sequenziale: approcci per riduzione insorgenza di cloni resistenti?

Grazie per l'attenzione.