2021

Progetto Ematologia Romagna

LEUCEMIA LINFATICA CRONICA

Introduzione

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Kanti Roop Rai e Jacques-Louis Binet

STADIAZIONE

Stage		Definition
Binet system		
Binet A		Hb ≥100 g/l (6.21 mmol/l), platelets ≥100 × 10^9/l <3 involved lymphoid sites
Binet B		Hb ≥100 g/l (6.21 mmol/l), platelets ≥100 × 10^9/l ≥3 involved lymphoid sites
Binet C		Hb <100 g/l (6.21 mmol/l), platelets <100 × 10^9/l
Rai system		
Low-risk	Rai 0	Lymphocytosis >5 × 10^9/l
Intermediate-risk	Rai I Rai II	Lymphocytosis and lymphadenopathy Lymphocytosis and hepatomegaly and/or splenomegaly with/without lymphadenopathy
High-risk	Rai III	Lymphocytosis and Hb <110 g/l (6.83 mmol/l) with/without lymphadenopathy/organomegaly
	Rai IV	Lymphocytosis and platelets <100 × 10^9/l with/without lymphadenopathy/organomegaly

Sedi nodali coinvolte (alla palpazione):

- laterocervicale, ascellare, inguinale
- milza
- fegato

Rai KR. *Blood*, 1975; 46: 219-234 – Binet JL. Cancer, 1981; 48: 198-206 – Eichhorst B. *Ann Oncol*, 2021; 32: 23-33

PROCEDURE DIAGNOSTICHE E STADIATIVE

	Initial staging at diagnosis	Pre-treatment evaluation	Staging at the end of therapy	Follow-up	Relapse
History, physical examination and performance status	+	+	+	+	+
Complete blood count and differential	+	+	+	+	+
Serum chemistry including serum immunoglobulin and direct antiglobulin test	–	+	+	+	+
Cytogenetics (FISH) and molecular genetics for *TP53* mutation or *del(17p)*	(+)	+	–	–	+
IGHV mutational status	(+)	+	–	–	–
Marrow aspirate and biopsy	–	+	+	–	+
HBV, HCV, CMV and HIV serology	–	+	–		+
Radiological imaging (CT scan)	–	+	+		+

Modified from: Eichhorst B. *Ann Oncol*, 2021; 32: 23-33

FATTORI PROGNOSTICI E PREDITTIVI (1)

Biomarker	Method	Use	LoE, GoR
TP53 mutation or *del(17p)*	FISH and Sanger or NGS	Strongest prognostic and predictive relevance together with del(17p)	III, A
IGHV	Sanger or NGS	Strong prognostic evidence; predictive evidence for CIT	III, A
Complex karyotype	Chromosome banding	Possible prognostic and predictive relevance but not yet established prospectively	IV, C

Eichhorst B. *Ann Oncol*, 2021; 32: 23-33

FATTORI PROGNOSTICI E PREDITTIVI (2)

JOURNAL OF CLINICAL ONCOLOGY

CORRESPONDENCE

Prognostic or Predictive? It's Time to Get Back to Definitions!

- **Fattore prognostico**: caratteristica clinica o biologica misurabile che fornisce informazioni sul probabile *andamento della malattia in un paziente non trattato* (storia naturale). Aiuta ad identificare i pazienti ad alto rischio.
- **Fattore predittivo**: caratteristica clinica o biologica che fornisce informazioni sul probabile *beneficio di un trattamento*. Aiuta ad identificare i pazienti che possono beneficiare di *quel* trattamento.

Italiano A. *J Clin Oncol*, 2011; 29: 4718

CRITERI DI TRATTAMENTO

	General practice	Clinical trial
Treat with Rai stage 0	NGI*	RQ
Treat with Binet stage A	NGI*	RQ
Treat with Binet stage B or Rai stage I or II	Possible*	Possible*
Treat with Binet stage C or Rai stage III or IV†	Yes	Yes
Treatment of active/progressive disease	Yes	Yes
Treat without active/progressive disease	No	RQ

General practice is defined as the use of accepted treatment options for a CLL patient not enrolled on a clinical trial. Early therapy of CLL is generally not recommended outside of clinical trials; however, we recognize the need to conduct clinical trials testing the early use of novel agents.

RQ, research question.

*Treatment is indicated, if the disease is active

†Anemia and/or thrombocytopenia from CLL-unrelated causes should be excluded.

NGI, not generally indicated

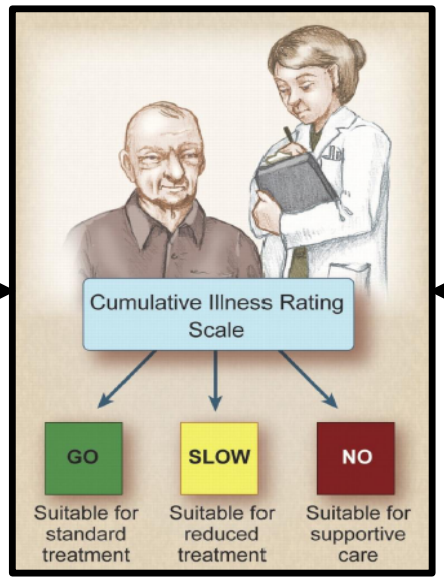
Hallek M. *Blood*, 2018; 131: 2745-2760

Valutare età e comorbilità, FISH, biologia molecolare

IGHV^{unmut}
***TP53*^{wt}, no del(17p)**

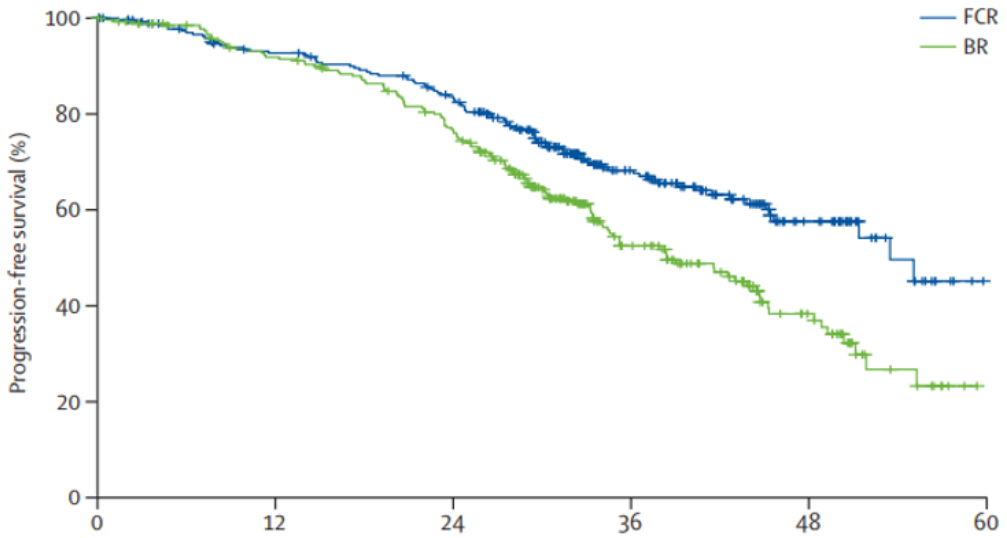
IGHV^{mut}
***TP53*^{wt}, no del(17p)**

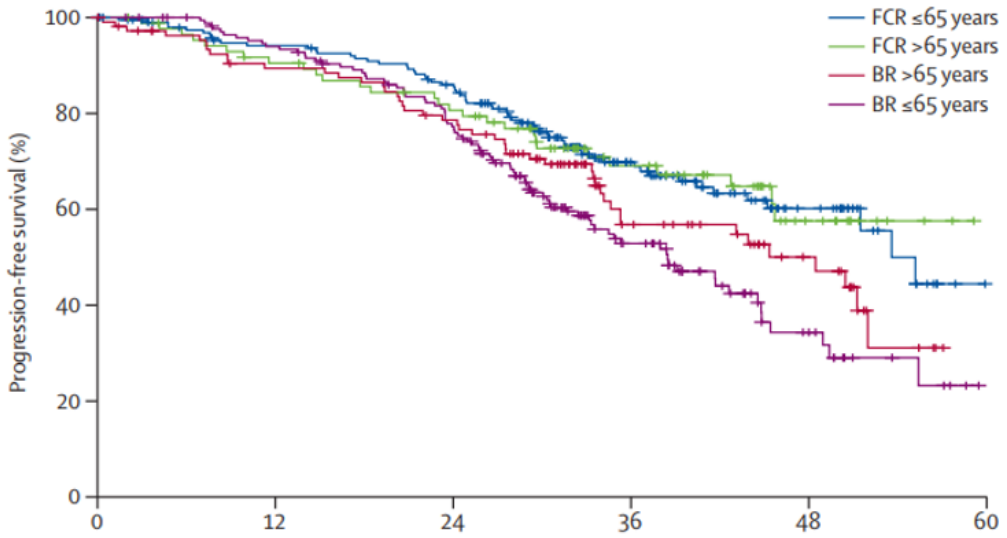
***TP53*^{mut} e/o del(17p)**



FCR *vs* BR

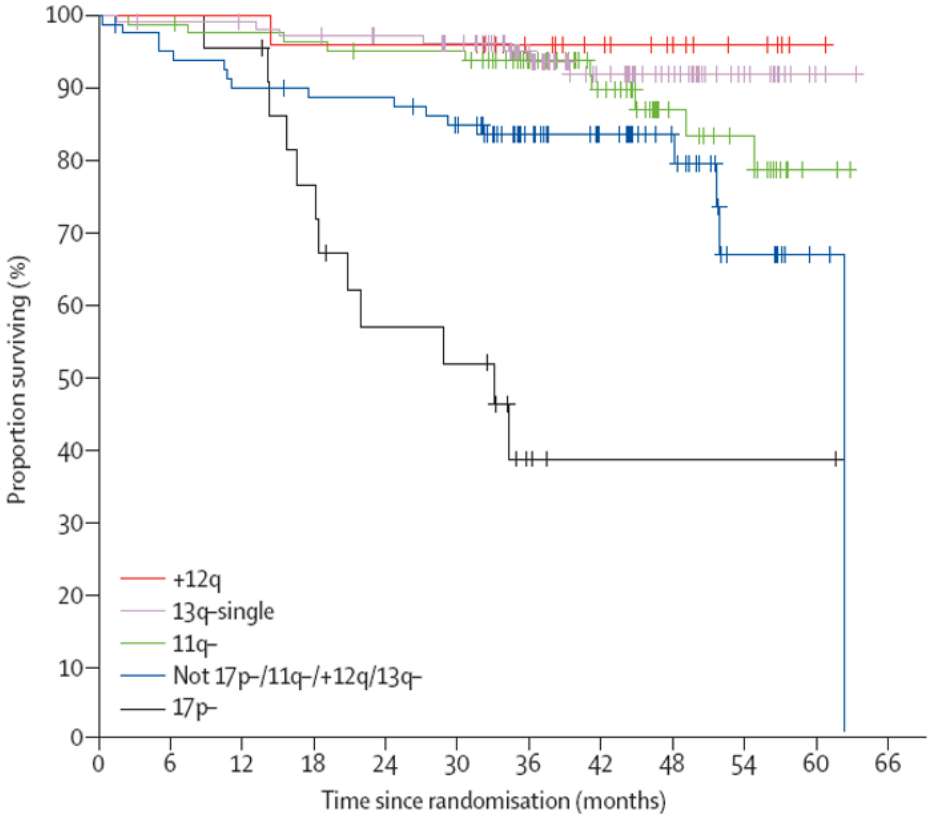
- La chemioimmunoterapia secondo schema FCR è il riferimento standard.
- La combinazione bendamustina + rituximab è utilizzabile nel paziente più anziano (> 65 anni) per la maggiore tollerabilità.



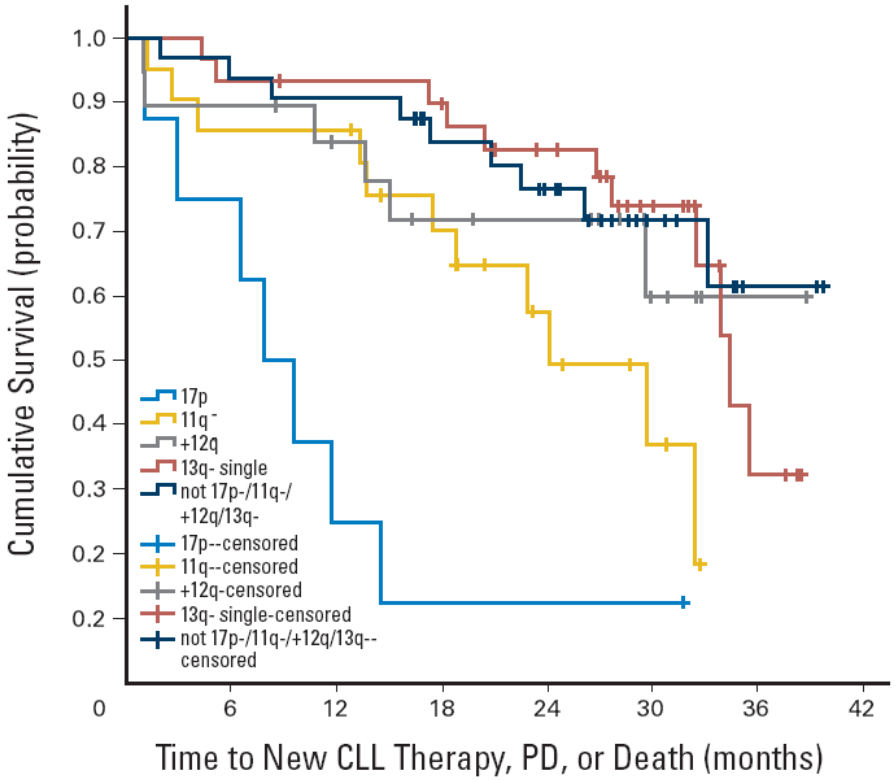


Eichhorst B. *Lancet Oncol*, 2016; 17: 928-942

VALORE PREDITTIVO DI *TP53*^{mut} E del(17p)



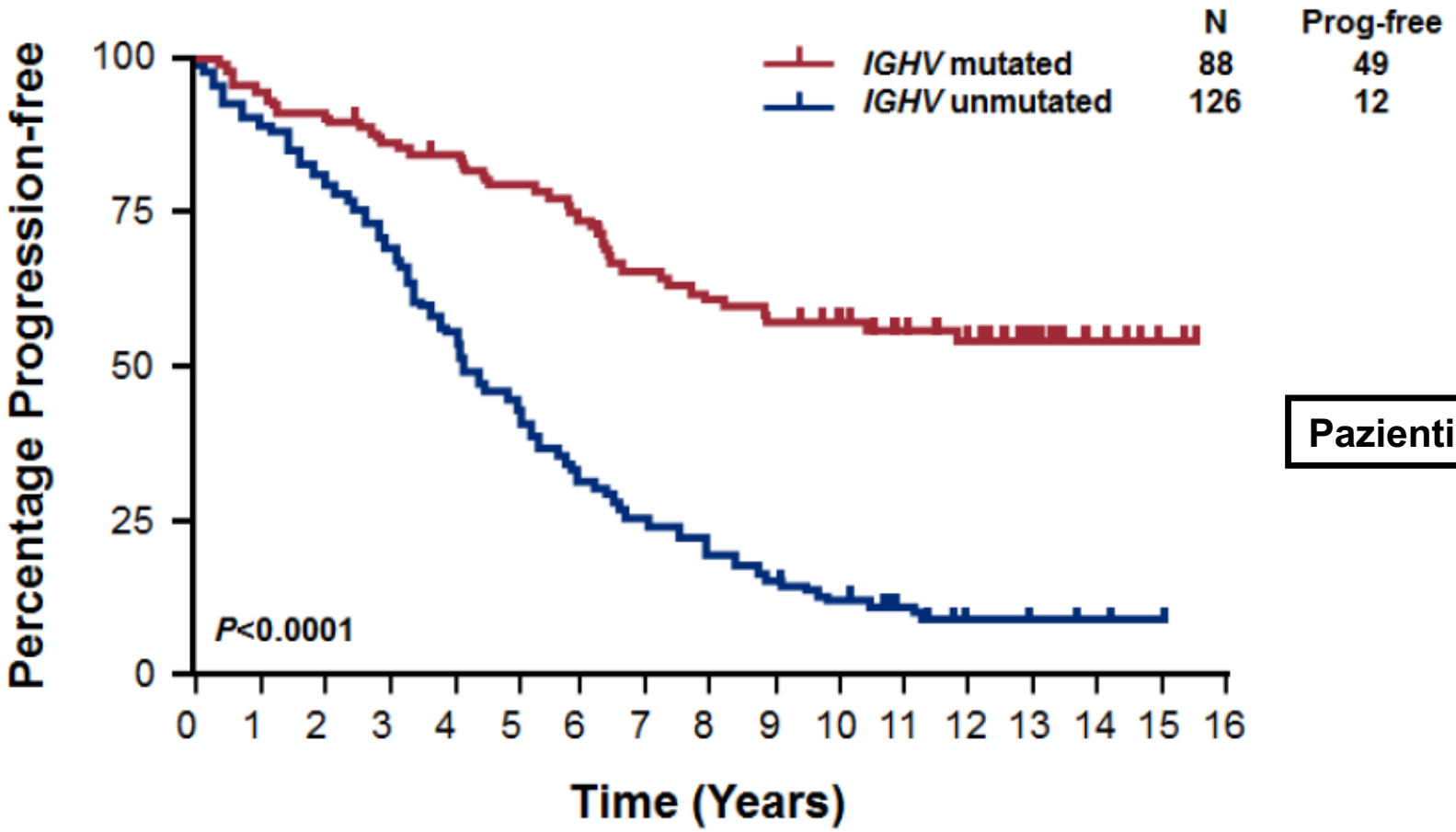
FCR



BR

Hallek M. *Lancet*, 2010; 376: 1164-1174 – Fischer K. *J Clin Oncol*, 2012; 30: 3209-3216

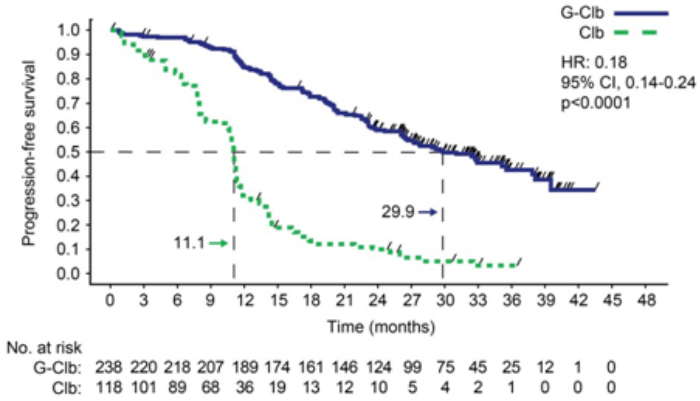
VALORE PREDITTIVO DI IGHV^{unmut}

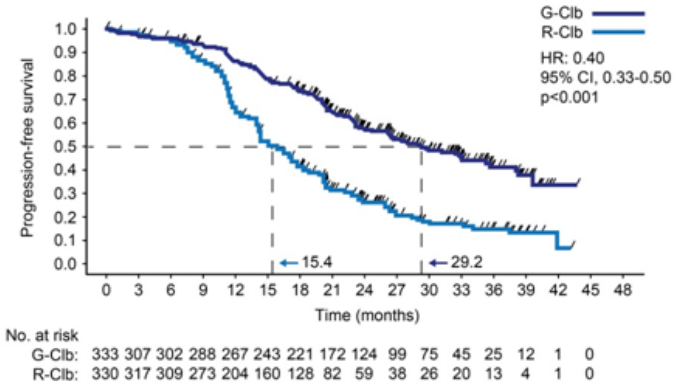


Pazienti trattati con FCR

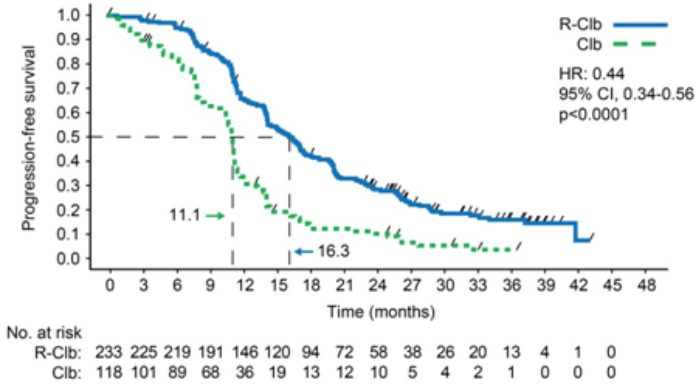
Thompson PA. *Blood*, 2016; 127: 303-309

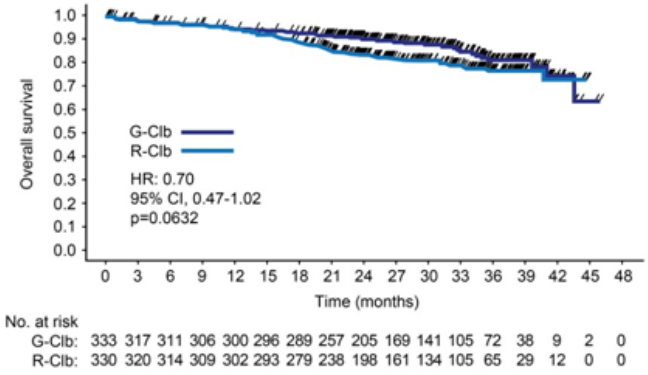
OBINUTUZUMAB-CLORAMBUCILE





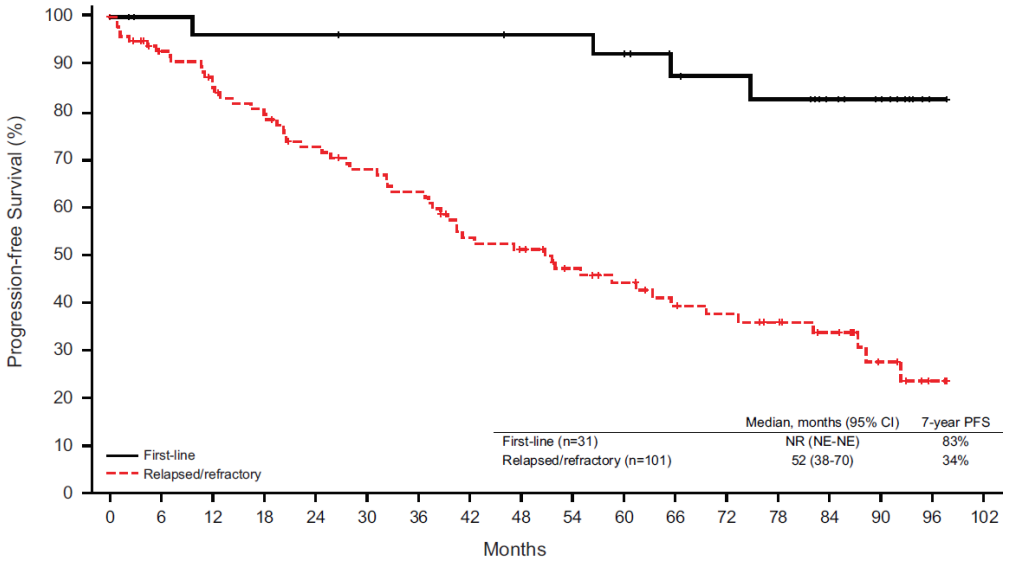
Età mediana: 71 anni
CIRS mediano: 8
Cl_{cr} mediana: 62 mL/min

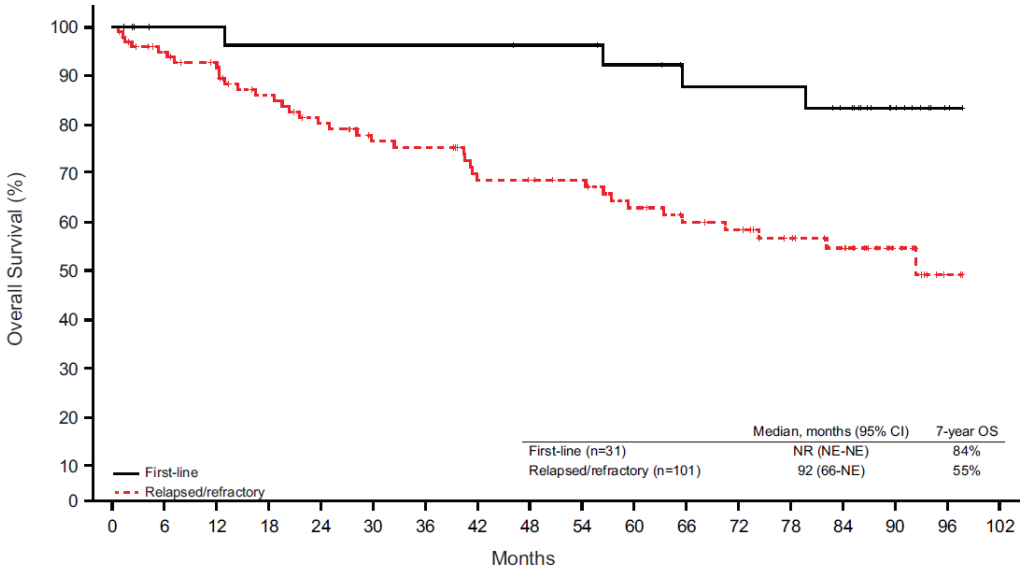




Goede V. *N Engl J Med*, 2014; 370: 1101-1110 – Goede V. *Leukemia*, 2015; 29: 1602-1604

IBRUTINIB IN PRIMA LINEA *vs* LINEE SUCCESSIVE



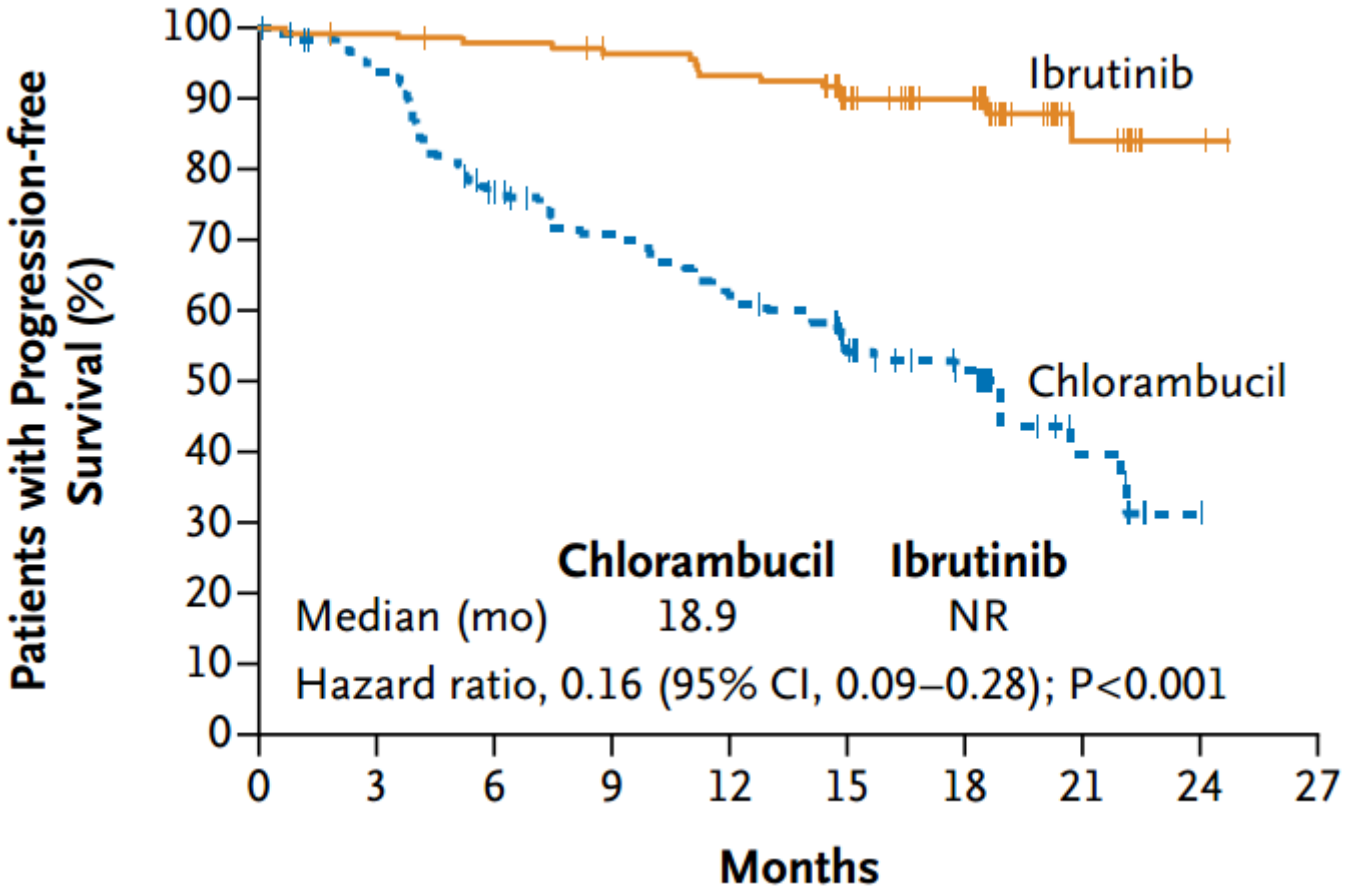


Pazienti in 1ª linea

Età mediana: 71 anni (100% > 65 anni, 74% ≥ 70 anni)
del(17p): 6%
IGHV^{unmut}: 48%

Byrd JC. *Blood*, 2015; 125: 2497-2506 – O'Brien S. *Blood*, 2018; 131: 1910-1919 – Byrd JC. *Clin Cancer Res*, 2020; 26: 3918-3927

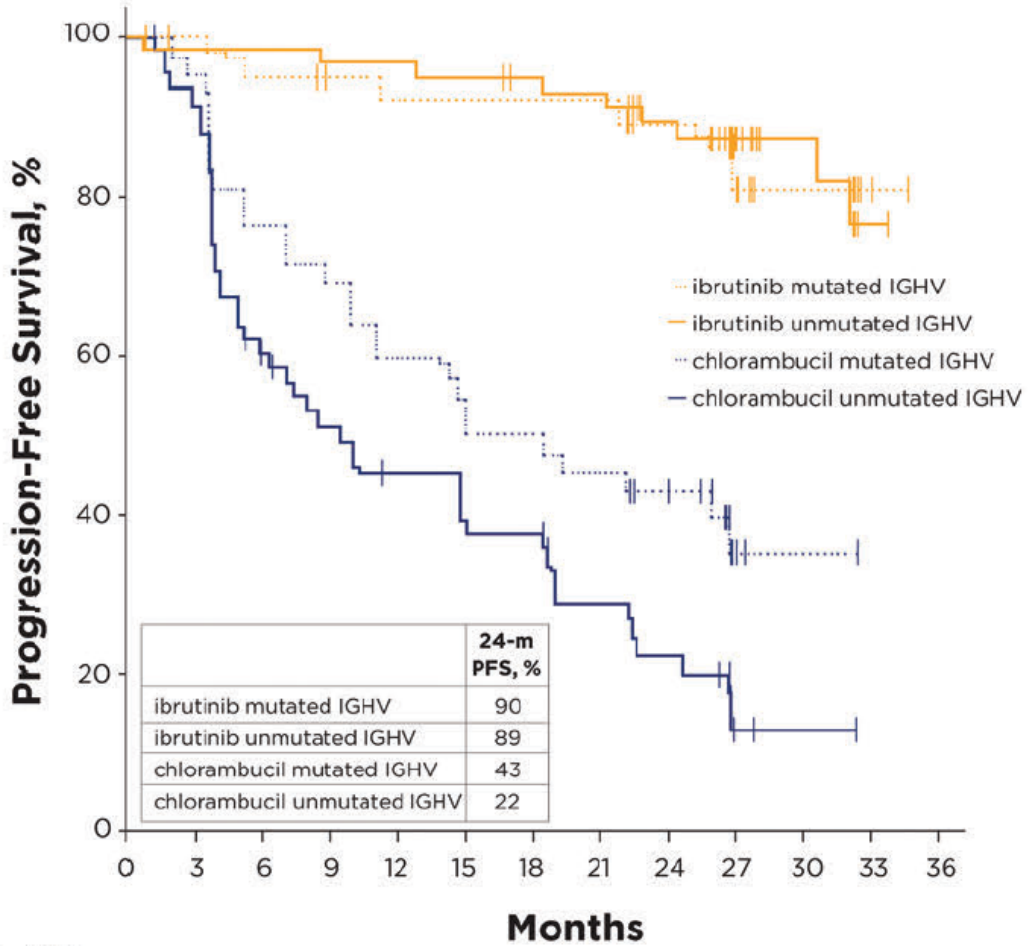
IBRUTINIB *vs* CLORAMBUCILE (1)



Età mediana: 71 anni
CIRS > 6: 32%

Burger JA. *N Engl J Med*, 2015; 373: 2425-2437

IBRUTINIB *vs* CLORAMBUCILE (2)

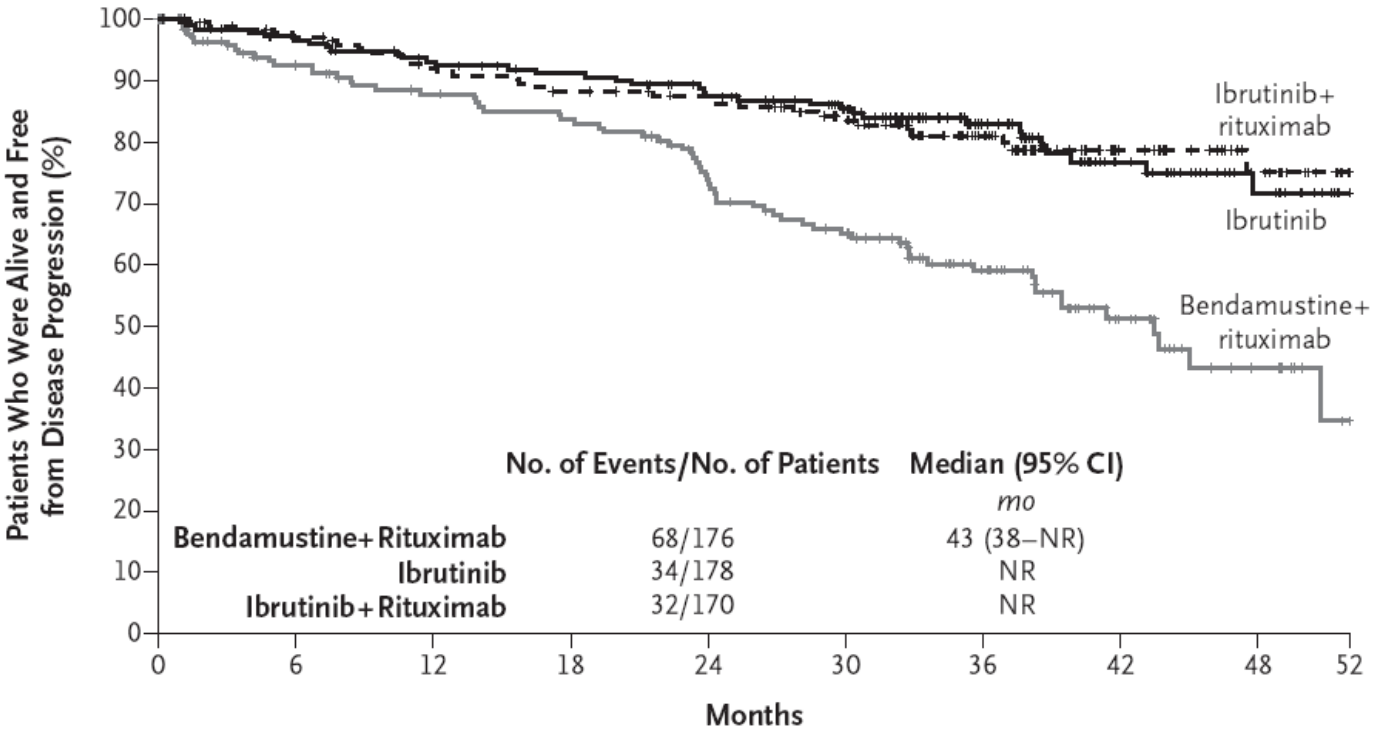


	24-m PFS, %
ibrutinib mutated IGHV	90
ibrutinib unmutated IGHV	89
chlorambucil mutated IGHV	43
chlorambucil unmutated IGHV	22

L'utilizzo di ibrutinib riduce la differenza di sopravvivenza tra pazienti IGHV^{mut} e IGHV^{unmut}.

Barr PM. *Haematologica*, 2018; 103: 1502-1510

IBRUTINIB ± RITUXIMAB *vs* BR



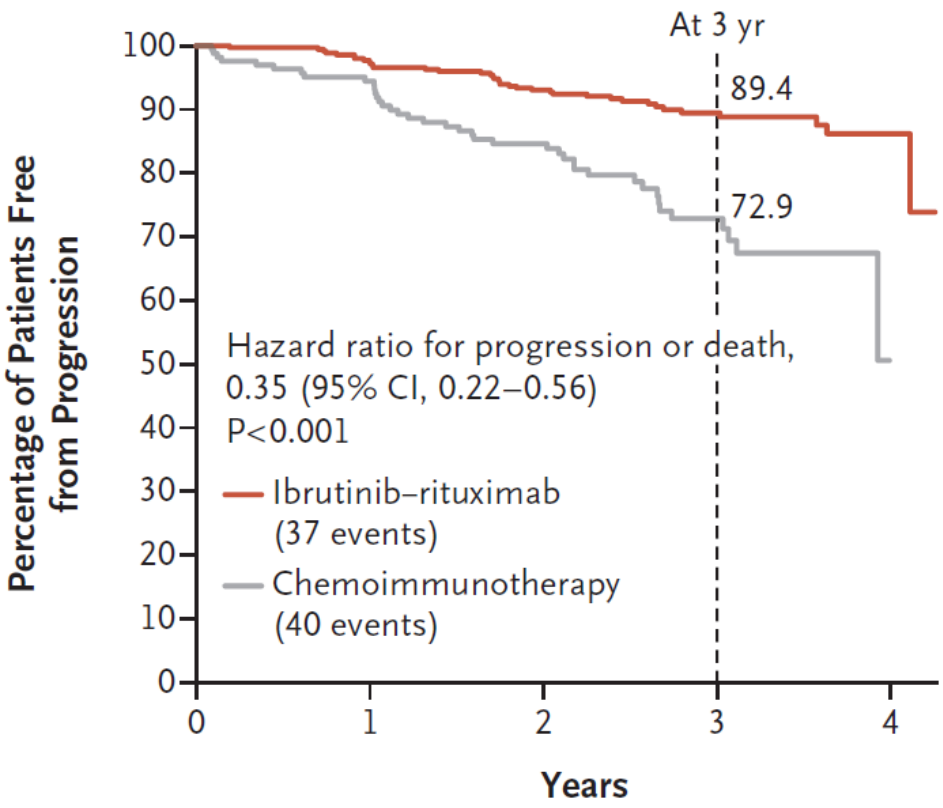
Età mediana: 71 anni

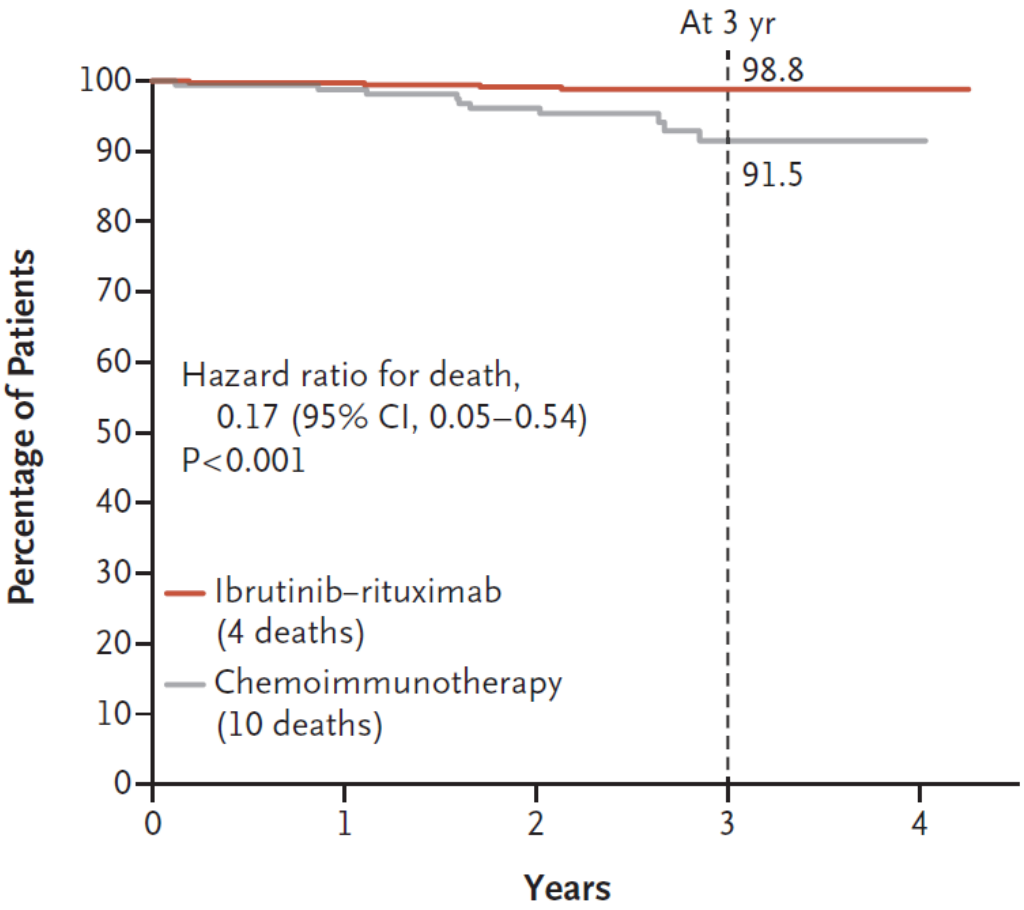
No. at Risk

Bendamustine+rituximab	176	140	129	122	103	88	57	26	11	0
Ibrutinib	178	165	154	147	136	120	78	45	22	0
Ibrutinib+rituximab	170	159	145	138	132	115	74	40	20	0

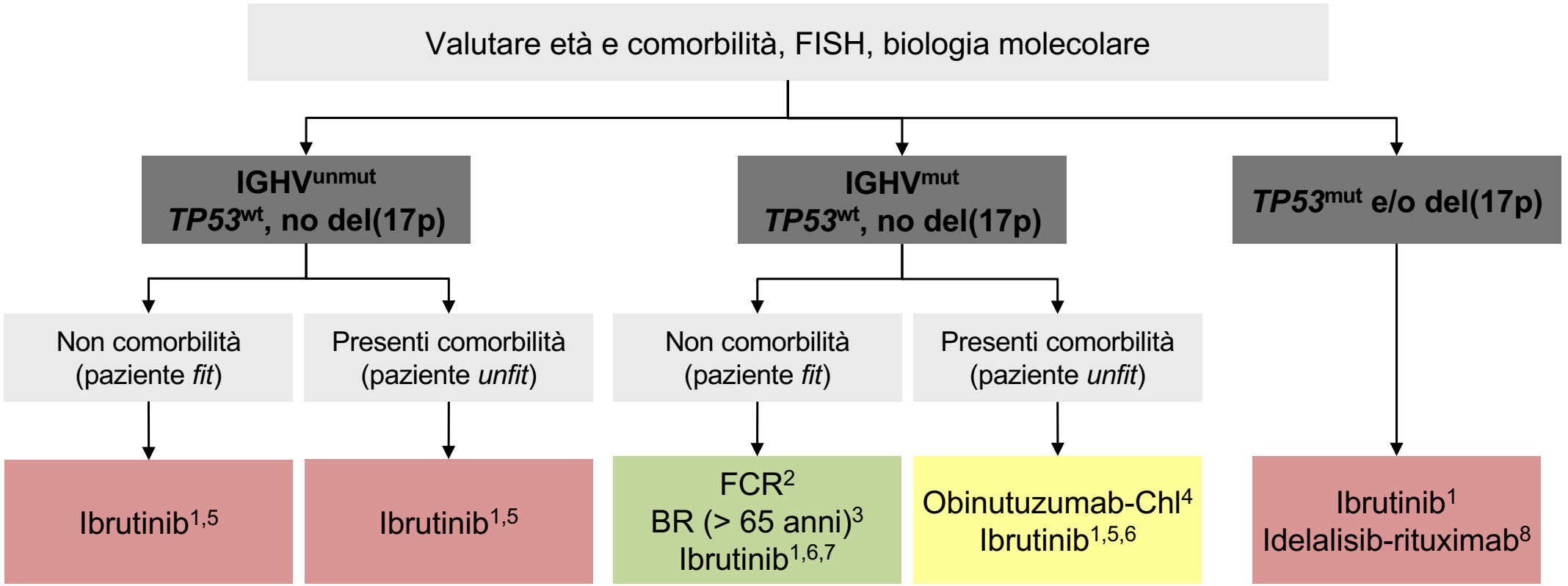
Woyach JA. *N Engl J Med*, 2018; 379: 2517-2528

IBRUTINIB + RITUXIMAB *vs* FCR





Shanafelt TD. *N Engl J Med*, 2019; 381: 432-443

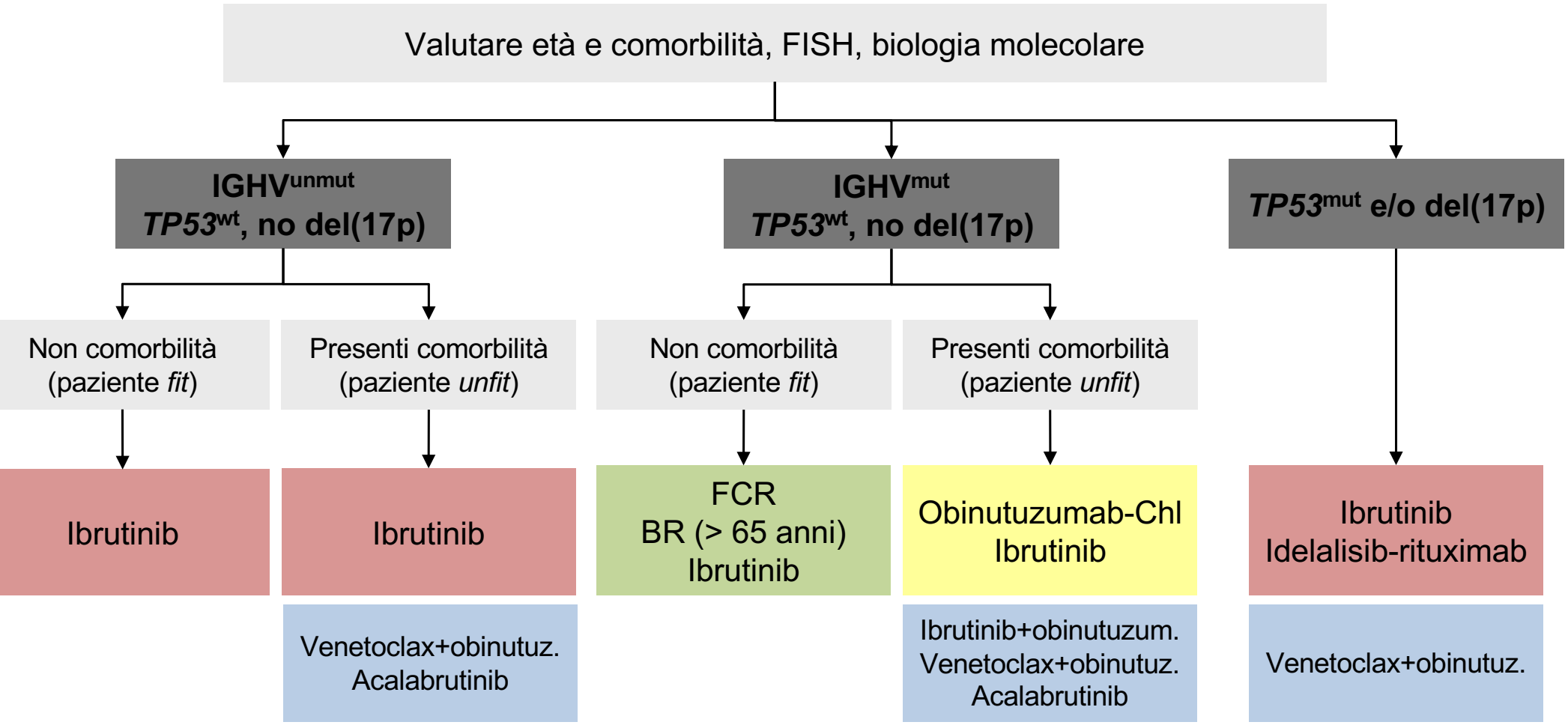


1. Byrd JC. *Clin Cancer Res*, 2020; 26: 3918-3927
2. Hallek M. *Lancet*, 2010; 376: 1164-1174
3. Fischer K. *J Clin Oncol*, 2012; 30: 3209-3216
4. Goede V. *Leukemia*, 2015; 29: 1602-1604
5. Burger JA. *N Engl J Med*, 2015; 373: 2425-2437
6. Woyach JA. *N Engl J Med*, 2018; 379: 2517-2528
7. Shanafelt TD. *N Engl J Med*, 2019; 381: 432-443
8. Furman RR. *N Engl J Med*, 2014; 370: 997-1007

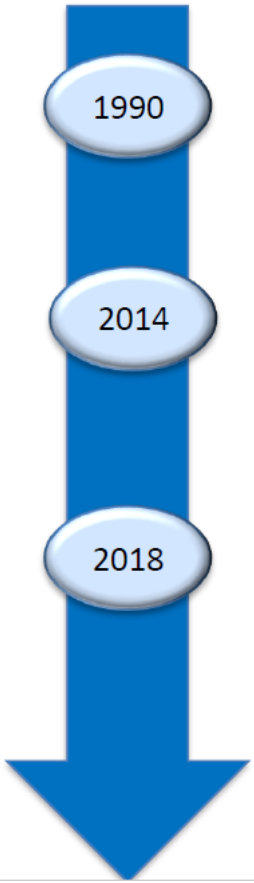
NUOVE COMBINAZIONI PER LA PRIMA LINEA (fase 3)

Studio	Fase	Caratteristiche	Trattamento	Pz.	ORR	CR	PFS	OS
CLL-14[1]	3	Età mediana: 72 aa CIRS mediano: 8 Cl_{cr}: 66,4 mL/min *TP53*^{mut}/del17p: 14% IGHV^{unmut}: 60%	Venetoclax + obinutuzumab	216	85%	50%	NR	NR
			Clorambucile + obinutuzumab	216	71%	23%	35,6 m	NR
ILLUMINATE[2]	3	Età mediana: 71 aa CIRS mediano: 4 Cl_{cr}: ~ 71 mL/min Alto rischio: 65%	Ibrutinib + obinutuzumab	113	88%	19%	NR	NR
			Clorambucile + obinutuzumab	116	73%	8%	19,0 m	NR
ELEVATE-TN[3]	3	Età mediana: 70 aa Alto rischio: 69% Altissimo rischio: 12% del17p: 9% *TP53*^{mut}: 11% IGHV^{unmut}: 63%	Acalabrutinib + obinutuzumab	179	94%	13%	NR	NR
			Acalabrutinib	179	86%	1%	NR	NR
			Clorambucile + obinutuzumab	177	79%	5%	22,6 m	NR

1. Fischer K. *N Engl J Med*, 2019; 380: 2225-2236
2. Moreno C. *Lancet Oncol*, 2019; 20: 43-56
3. Sharman JP. *Lancet*, 2020; 395: 1278-1291

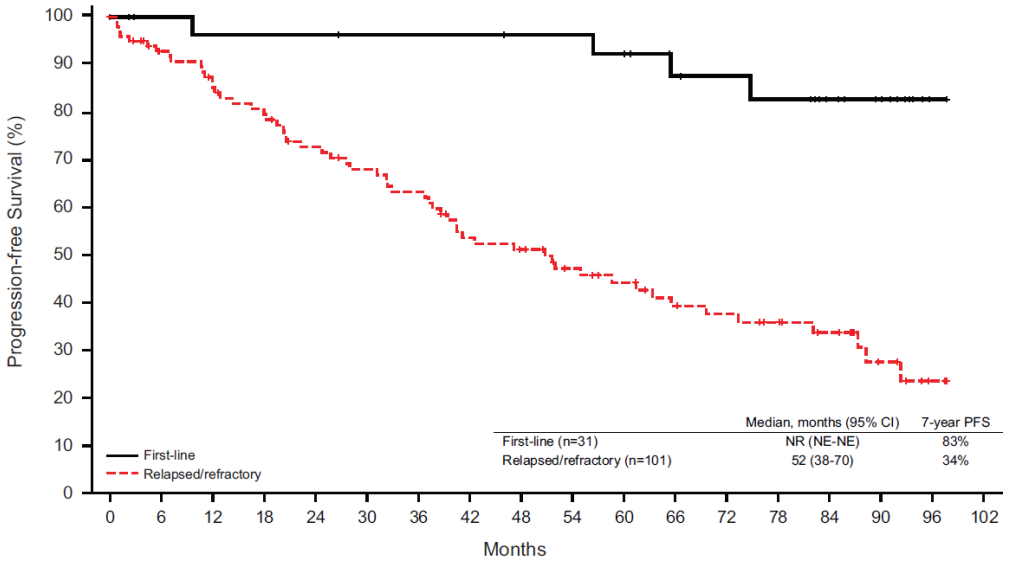

Valutare età e comorbilità, FISH, biologia molecolare
IGHV^unmut TP53^wt, no del(17p)
IGHV^mut TP53^wt, no del(17p)
TP53^mut e/o del(17p)
Non comorbilità (paziente fit)
Presenti comorbilità (paziente unfit)
Non comorbilità (paziente fit)
Presenti comorbilità (paziente unfit)
Ibrutinib
Ibrutinib
Venetoclax+obinutuz.
Acalabrutinib
FCR
BR (> 65 anni)
Ibrutinib
Obinutuzumab-Chl
Ibrutinib
Ibrutinib+obinutuzum.
Venetoclax+obinutuz.
Acalabrutinib
Ibrutinib
Idelalisib-rituximab
Venetoclax+obinutuz.

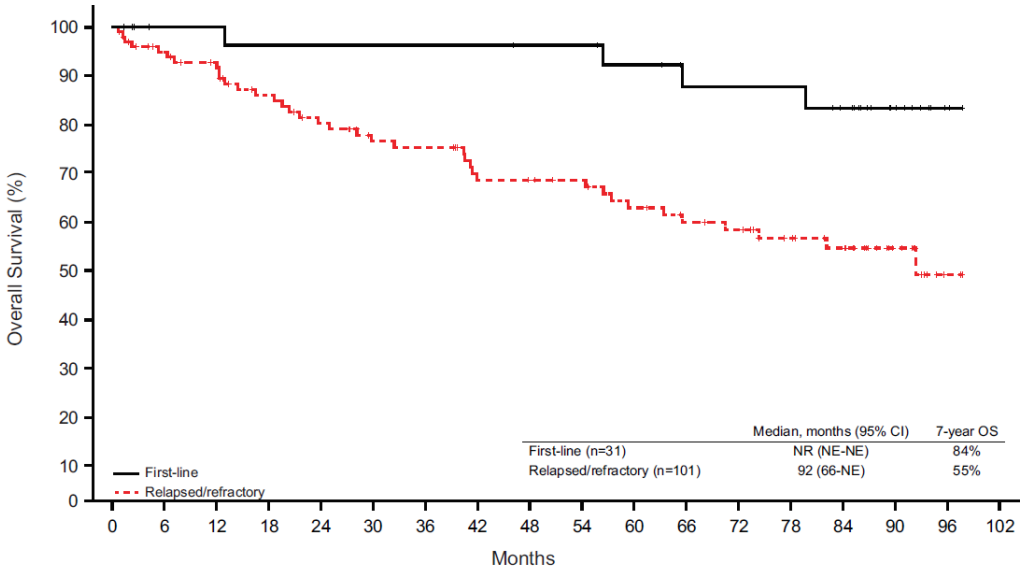
I PARADIGMI DI TRATTAMENTO ALLA RICADUTA



Fixed Duration Therapy	Chemoimmunotherapy
Continuous Therapy	**BCR pathway inhibitors** **Venetoclax**
Fixed Duration Therapy	**Venetoclax + rituximab**

IBRUTINIB IN PRIMA LINEA *vs* LINEE SUCCESSIVE





Pazienti in ≥ 2ª linea

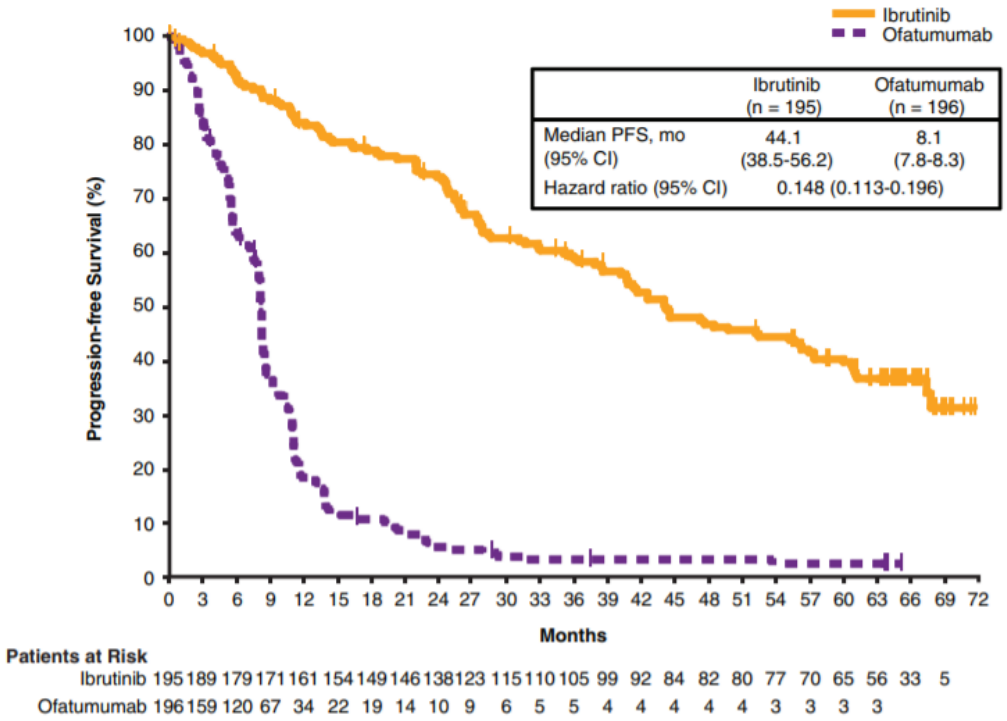
Età mediana: 64 anni (*range* 37-82)

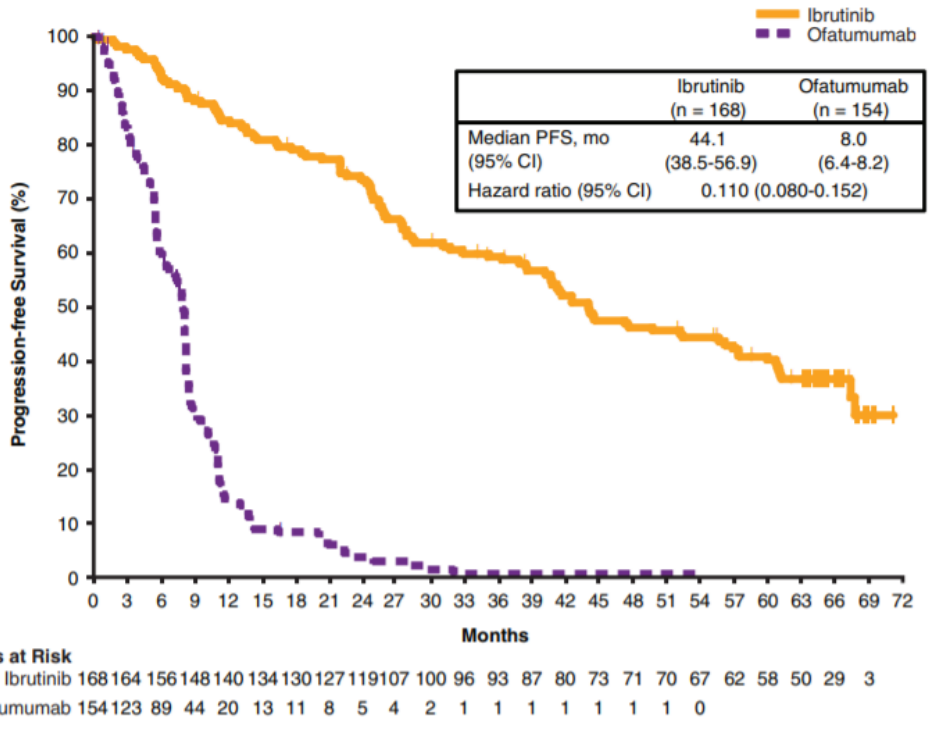
del(17p): 34%

IGHV^{unmut}: 78%

Byrd JC. *Blood*, 2015; 125: 2497-2506 – O'Brien S. *Blood*, 2018; 131: 1910-1919 – Byrd JC. *Clin Cancer Res*, 2020; 26: 3918-3927

IBRUTINIB *vs* OFATUMUMAB ALLA RICADUTA

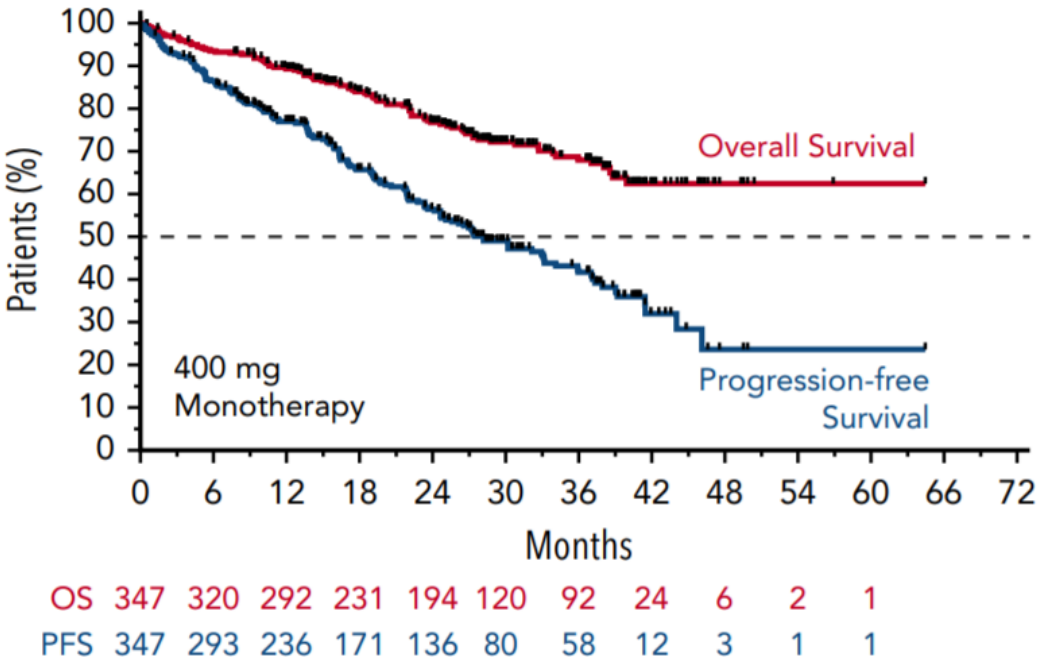


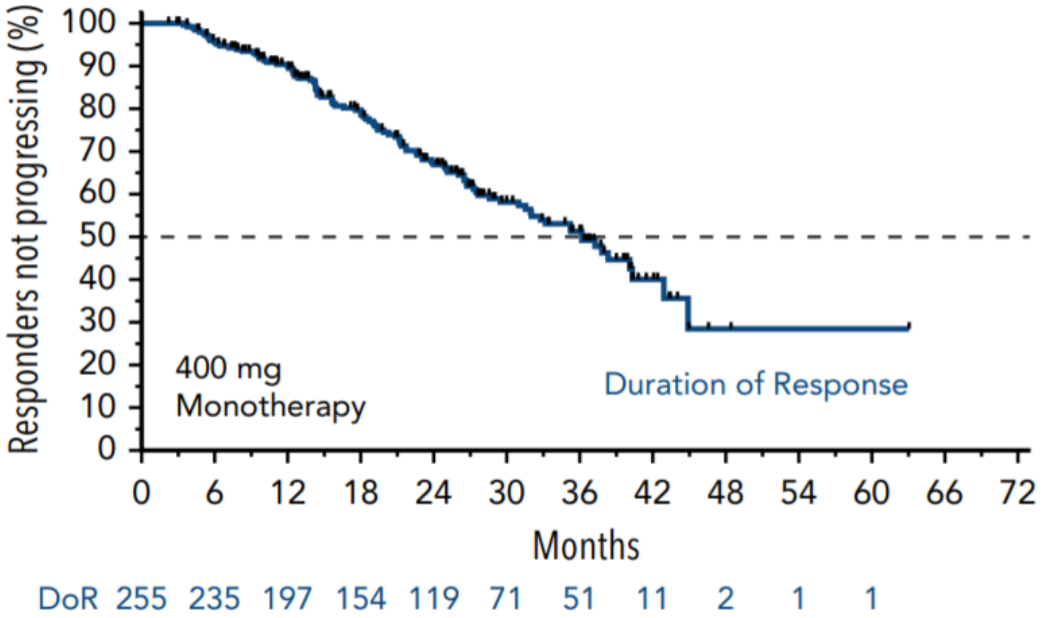


Byrd JC. *N Engl J Med*, 2014; 371: 213-223 – Munir T. *Am J Hematol*, 2019; 94: 1353-1363

VENETOCLAX (AGENTE SINGOLO)

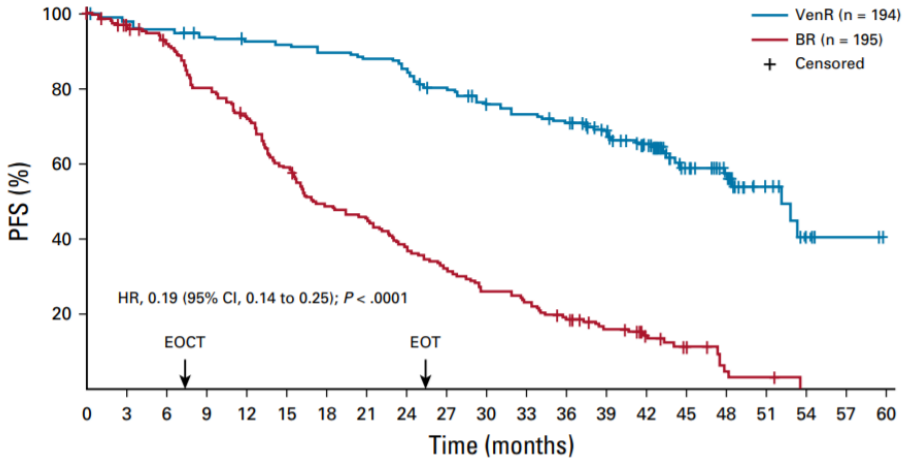
Analisi di 4 studi di fase 1-2 con venetoclax in monoterapia (347 pazienti)

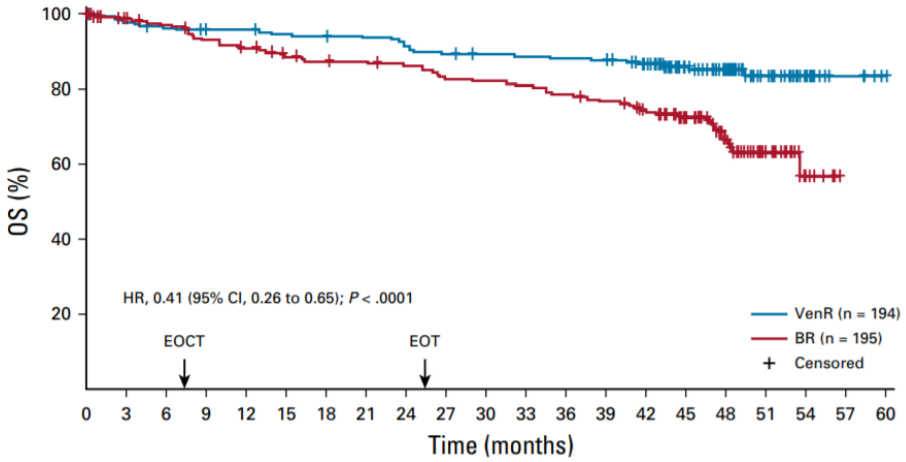


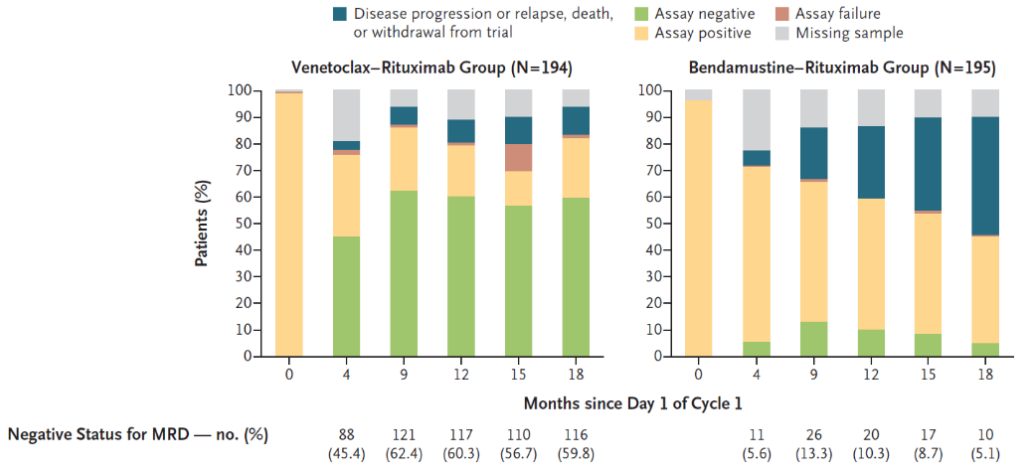


Roberts AW. *N Engl J Med*, 2016; 374: 311-322 – Coutre S. *Blood*, 2018; 131: 1704-1711
Jones JA. *Lancet Oncol*, 2018; 19: 65-75 – Stilgenbauer S. *J Clin Oncol*, 2018; 36: 1973-1980 – Roberts AW. *Blood*, 2019; 134: 111-122

VENETOCLAX + RITUXIMAB *vs* BR







Negative Status for MRD — no. (%)	88 (45.4)	121 (62.4)	117 (60.3)	110 (56.7)	116 (59.8)	11 (5.6)	26 (13.3)	20 (10.3)	17 (8.7)	10 (5.1)

Seymour JF. *N Engl J Med*, 2018; 378: 1107-1120
Kater AP. *J Clin Oncol*, 2020; 38: 4042-4054

I PARADIGMI DI TRATTAMENTO ALLA RICADUTA

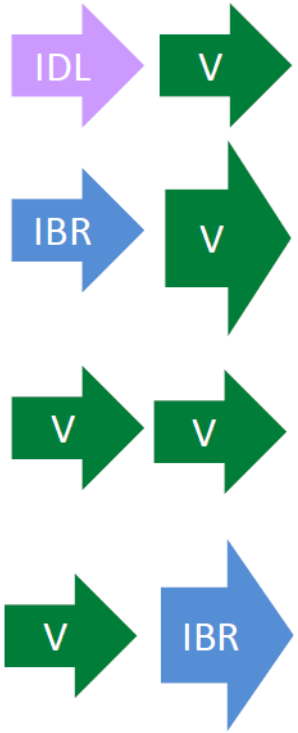
Trattamento continuo
Inibitori BCR

- **Sopravvivenza (PFS)**: superiore rispetto a chemioimmunoterapia. Manca confronto diretto con venetoclax.
- **Controllo della malattia a lungo termine**: adeguato.
- **Risposte**: prevalentemente parziali, mantenute nel tempo finché la terapia viene continuata.
- Basso rischio di sindrome da lisi tumorale.
- **Eventi avversi**: possibile causa di discontinuazione.
- ***Compliance* del paziente**: problema per una terapia continua.

Trattamento a durata fissa
Venetoclax + rituximab

- **Sopravvivenza (PFS)**: superiore rispetto a chemioimmunoterapia. Manca confronto diretto con ibrutinib.
- **Risposte**: risposte profonde, talora negativizzazione MRD, con sospensione del trattamento.
- **Eventi avversi**: maggiore rischio di sindrome da lisi tumorale e neutropenia.
- **Minore durata di trattamento**: migliore *compliance* del paziente, minore esposizione a farmaci, minore tasso di resistenza indotta dal trattamento, possibilità di ritrattamento alla progressione.

COME IMPIEGARE IN SEQUENZA I NUOVI FARMACI?



Patients	N	ORR	PFS	References
VEN naïve	36	67%	Med: 25 months	Coutre et al. Blood. 2018
	91	65%	Med: 24.7 months	Jones et al. Lancet Oncol. 2017
	191 67	BCRi naive 85% BCRi exposed. 64%	24 months: 79% 24 months: 71%	Kater et al. EHA 2020
VEN exposed	V 3 VR 11	3/3 6/11 55%	DOR: 7-27 months	Brander et al., ASH 2018 Seymour et al., ASH 2019
BCRi naïve	23	91%	Med: 34 months	Lin er al. Blood 2020
BCRi naïve	44	84%	Med: 32 months	Mato et al. Clin Canc Res 2020
BCRi exposed	30	53%	Intoler.: NR Refract.: Med=4 months	