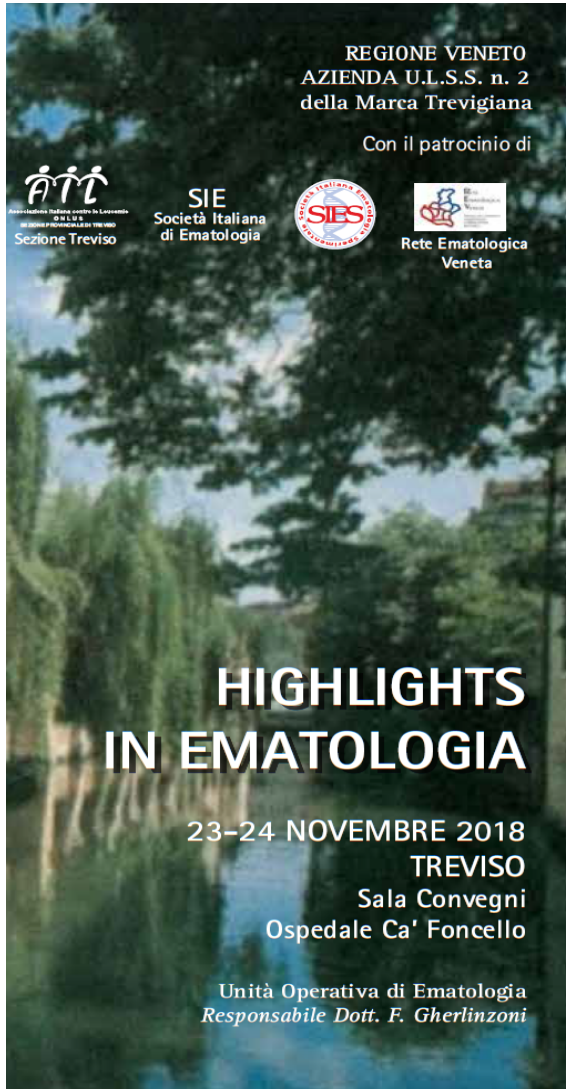

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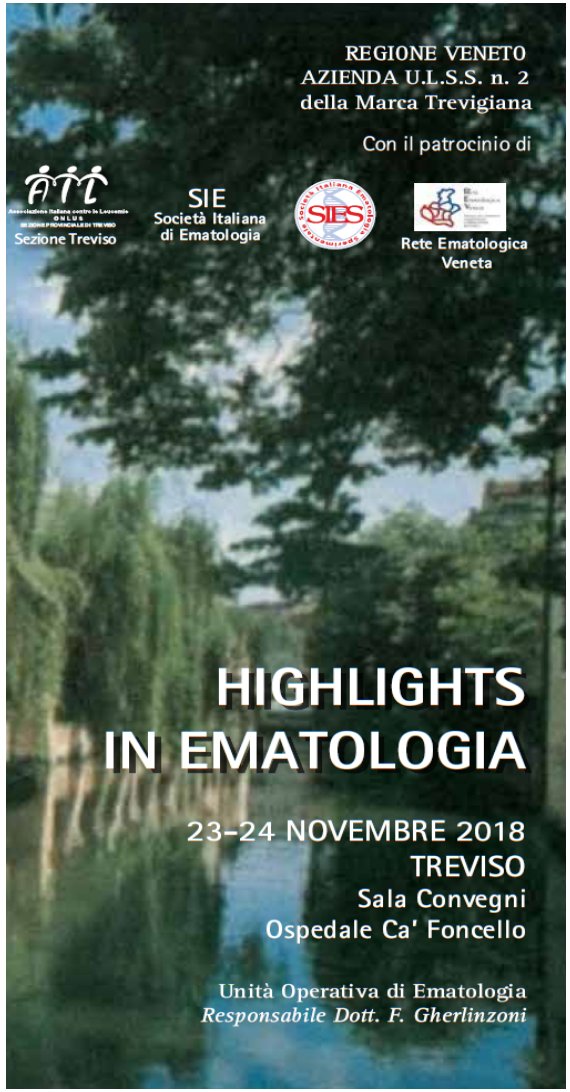
Università degli Studi di Ferrara

C'È ANCORA UN RUOLO PER LA CHEMIOIMMUNOTERAPIA NEL TRATTAMENTO DELLA LEUCEMIA LINFATICA CRONICA

Dr Maurizio Cavallari

UO di Ematologia e Centro Trapianti di Midollo Osseo
AOU Sant'Anna di Ferrara
Università degli Studi di Ferrara

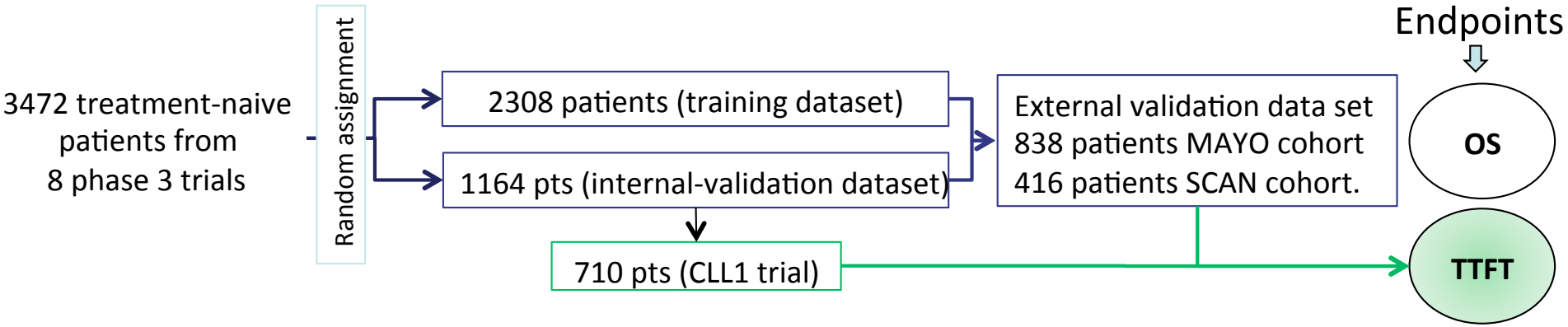


C'È ANCORA UN RUOLO PER LA CHEMIOIMMUNOTERAPIA NEL TRATTAMENTO DELLA LEUCEMIA LINFATICA CRONICA

- Prognostic/predictive markers
- Treatment
  - 1st line
  - Relapsed/Refractory (R/R)

Prognostic MARKERS: CLL-IPI

Comprehensive approach incorporating clinical, serum, genetic, and molecular markers into a single risk score



The International CLL-IPI working group, Lancet Oncol 17: 779-90

Overview on study datasets comprising the full analysis set:

few patients received chemoimmunotherapy

Country	Study ID	Randomized patients	Patients included in CLL-IPI analysis	First-line treatment (patients)	Recruitment period	Observation time (months) at time of analysis Median/mean (range)	Reference	Registration
France	CLL2007FMP	165	163[§]	FCR (82), FCCAM (83)	2007-2009	39·2 / 40·0 (39·9 – 48·8)	Leprêtre, *et al.* Blood 2012	NCT00564512
Germany	CLL1	710	710	HR F (93) HR W&W (96) LR W&W (521)	1997-2004	98·0 / 96·8 (0·4 – 166·9)	Bergmann, *et al.* (*submitted*)	NCT00262782
Germany	CLL4	362	348[$]	F (182) FC (180)	1999-2003	104·8 / 93·8 (0·0 – 151·3)	Eichhorst, *et al.* Blood 2006	ISRCTN75653261
Germany	CLL5	193	180[%§]	F (100) CLB (93)	2003-2006	67·2 / 63·9 (0·0 – 130·6)	Eichhorst, *et al.* Blood 2009	ISRCTN36294212
Germany	CLL8	817	785*	FC (409) FCR (408)	2003-2006	69·0 / 65·4 (0·0 – 96·4)	Hallek, *et al.* Lancet 2010	NCT00281918
Poland	PALG-CLL3	423	231[+]	FC (212) CC (211)	2004-2007	20·2 / 20·2 (1·0 – 45·3)	Robak, *et al.* JCO 2010	RNN/237/03/KE[#]
UK	LRF CLL4	777	777	F (196) FC (194) CLB (387)	1999-2004	90·4 / 92·9 (35·1 – 140·8)	Catovsky, *et al.* Lancet 2007	NCT58585610
US	E2997	278	278	F (137) FC (141)	1999-2005	88·0 / 85·1 (0·0 – 126·6)	Flinn, *et al.* JCO 2007	NCT00003764

The International CLL-IPI working group, Lancet Oncol 17: 779-90; supplementary material

Patient characteristics of the full analysis dataset and results of the univariate analyses for OS

	Patients (n=3472)	Median overall survival (months [95% CI])	5-year overall survival (95% CI)	10-year overall survival (95% CI)	log-rank p value	Hazard ratio (95% CI)	p value
Time between diagnosis and study entry					0·53		
≤1 year	2108 (62%)	97·6 (89·5–104·0)	67·6% (65·5–69·7)	41·5% (38·5–44·6)	..	1·00 (reference)	..
>1 year	1311 (38%)	90·7 (87·1–97·8)	68·6% (66·0–71·2)	38·1% (33·7–42·5)	..	1·03 (0·9–1·2)	0·53
Age					<0·0001		
≤65 years	2395 (69%)	124·0 (106·6–119·7)	74·0% (72·1–75·8)	46·9% (43·8–50·0)	..	1·00 (reference)	..
>65 years	1077 (31%)	87·0 (63·8–74·7)	54·9% (51·8–58·0)	26·4% (22·5–30·3)	..	1·9 (1·7–2·1)	<0·0001
Sex					<0·0001		
Female	1045 (30%)	124·0 (NE)	71·9% (69·0–74·7)	50·9% (46·6–55·1)	..	1·00 (reference)	..
Male	2427 (70%)	87·0 (83·6–90·9)	66·4% (64·4–68·3)	35·8% (32·8–38·7)	..	1·4 (1·2–1·6)	<0·0001
ECOG performance status					<0·0001		
0	1640 (63%)	144·7 (NE)	78·5% (76·4–80·5)	54·5% (50·9–58·0)	..	1·00 (reference)	..
1	858 (33%)	77·8 (73·7–84·5)	60·3% (56·8–63·7)	31·7% (26·5–36·9)	..	2·0 (1·8–2·3)	<0·0001
2 or 3	101 (4%)	58·6 (36·6–86·8)	49·0% (37·7–60·3)	26·2% (13·0–39·4)	..	2·9 (2·2–3·8)	<0·0001
B-symptoms*					<0·0001		
No	1615 (69%)	137·5 (NE)	79·7% (77·6–81·2)	57·2% (53·7–60·6)	..	1·00 (reference)	..
Yes	717 (31%)	89·7 (82·3–97·9)	69·2% (65·6–72·7)	32·4% (26·6–38·2)	..	1·7 (1·5–2·0)	<0·0001
Binet stage†					<0·0001		
A	992 (32%)	NR	83·7% (81·4–86·0)	63·1% (59·4–66·9)	..	1·00 (reference)	..
B	1260 (41%)	86·1 (83·1–91·5)	70·1% (67·4–72·7)	30·8% (25·9–35·8)	..	2·2 (1·9–2·5)	<0·0001
C	849 (27%)	68·9 (62·3–76·4)	54·9% (51·4–58·4)	25·9% (20·3–30·4)	..	3·0 (2·6–3·5)	<0·0001

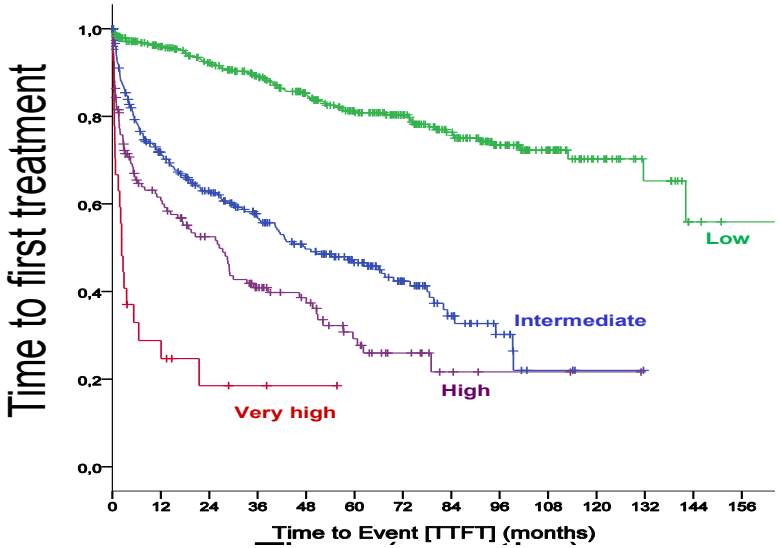
The International CLL-IPI working group, Lancet Oncol 17: 779-90

Prognostic markers: CLL-IPI

Comprehensive approach incorporating clinical, serum, genetic, and molecular markers into a single risk score: CLL-IPI

Time to first treatment

Variable	Adverse factor	Coeff.	HR	Grading
***TP53* (17p)**	deleted and/or mutated	**1.442**	**4.2**	**4**
***IGHV* status**	Unmutated	**0.941**	**2.6**	**2**
B2M, mg/L	> 3.5	**0.665**	**2.0**	**2**
Clinical stage	Binet B/C **or** Rai I-IV	**0.499**	**1.6**	**1**
Age	> 65 years	**0.555**	**1.7**	**1**
Prognostic Score				**0 – 10**



The International CLL-IPI working group, Lancet Oncol 17: 779-90

Prognostic markers: they can be used to estimate outcome irrespective of the treatment

Overall survival

CLL IPI

Useful in a selected patient population

- Chemo +/--- CIT
- Relatively young patients (>65 years: 31%)
- Relatively adv stage (Binet B/C: 68%)
- ECOG PS 0-1

Variable	Adverse factor	Coeff.	HR	Grading
***TP53* (17p)**	deleted and/or mutated	**1.442**	**4.2**	**4**
***IGHV* status**	Unmutated	**0.941**	**2.6**	**2**
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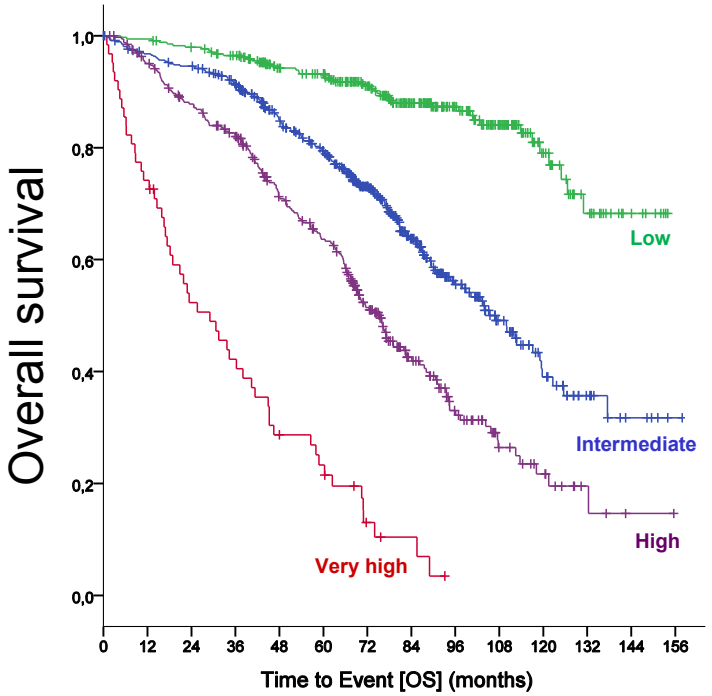
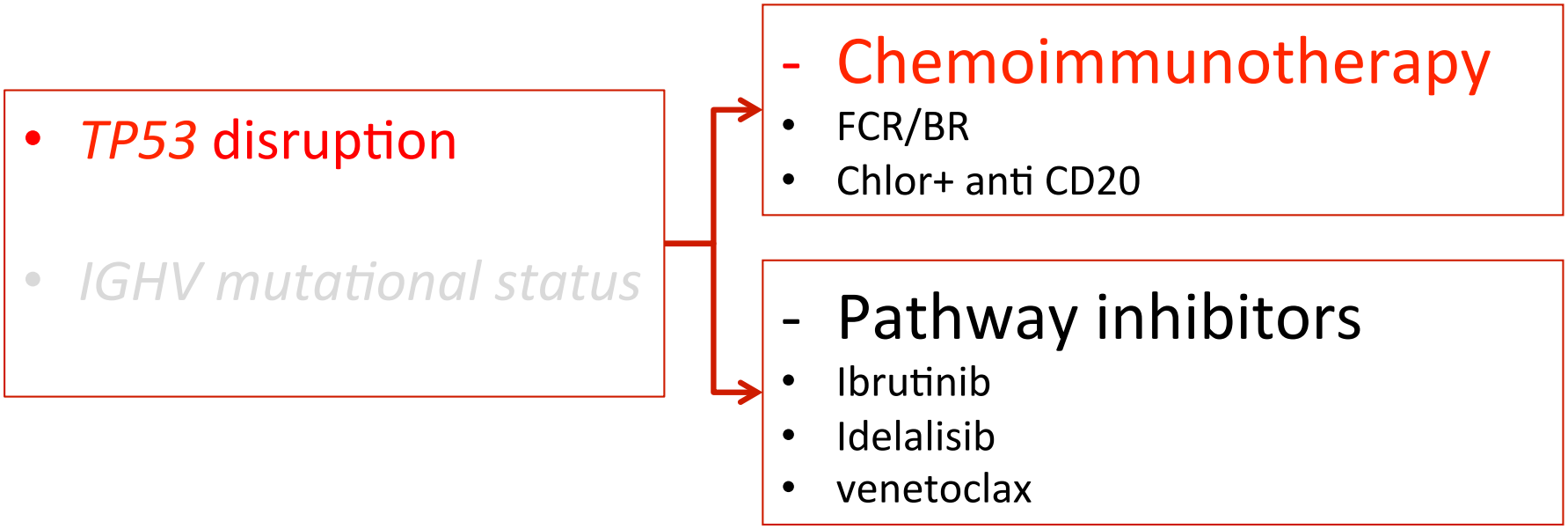
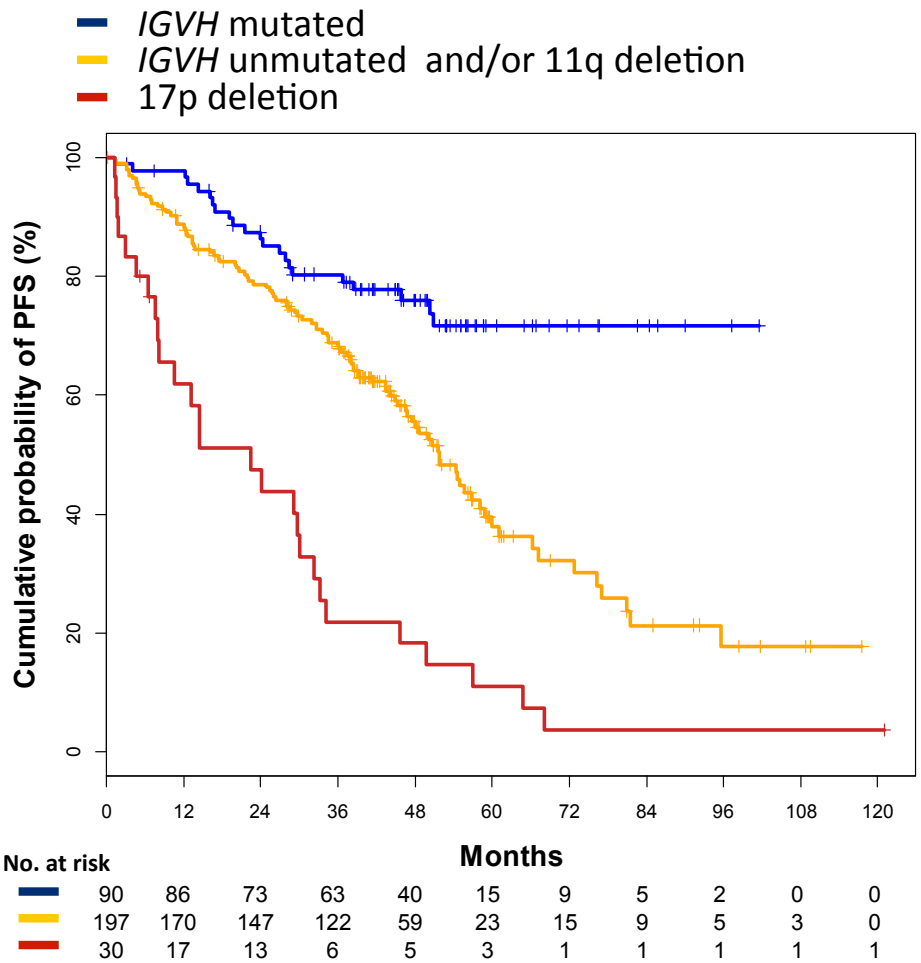
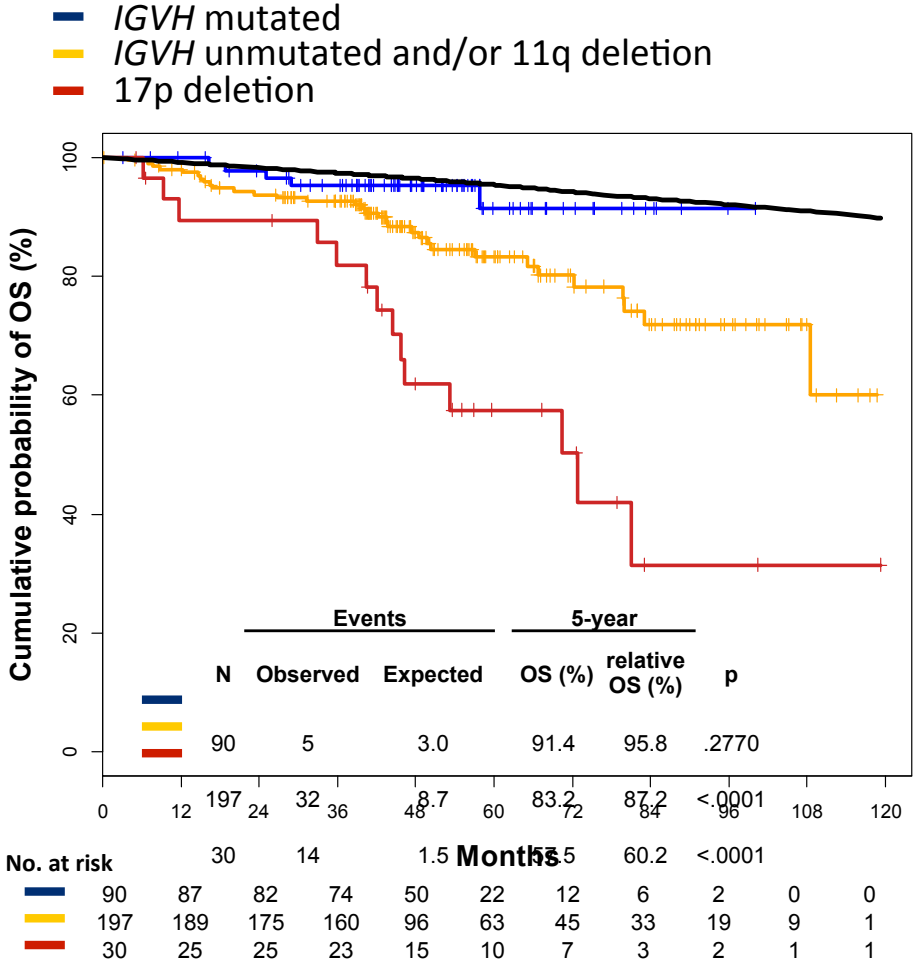


Predictive markers: they can be used to anticipate the efficacy of a particular therapy



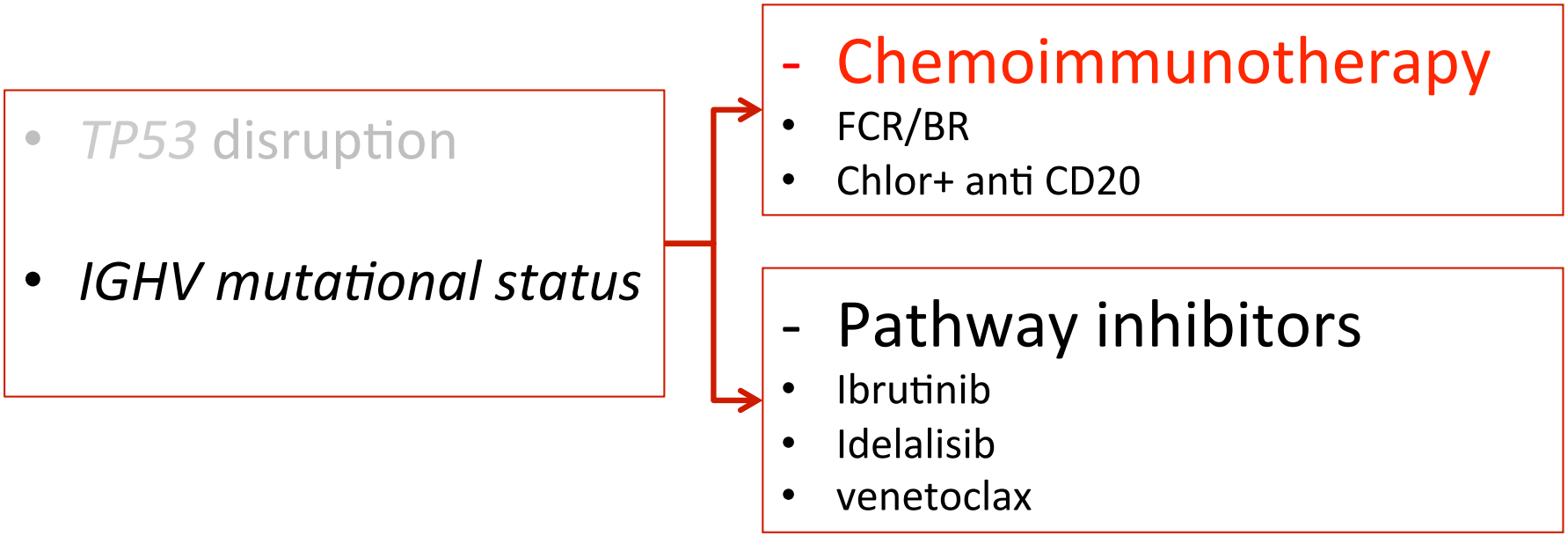
PFS and OS after FCR: role of *IGHV* mutational status, 11q- and 17p- as prognostic factors: A **real-world** multicentre retrospective analysis of patients treated with FCR





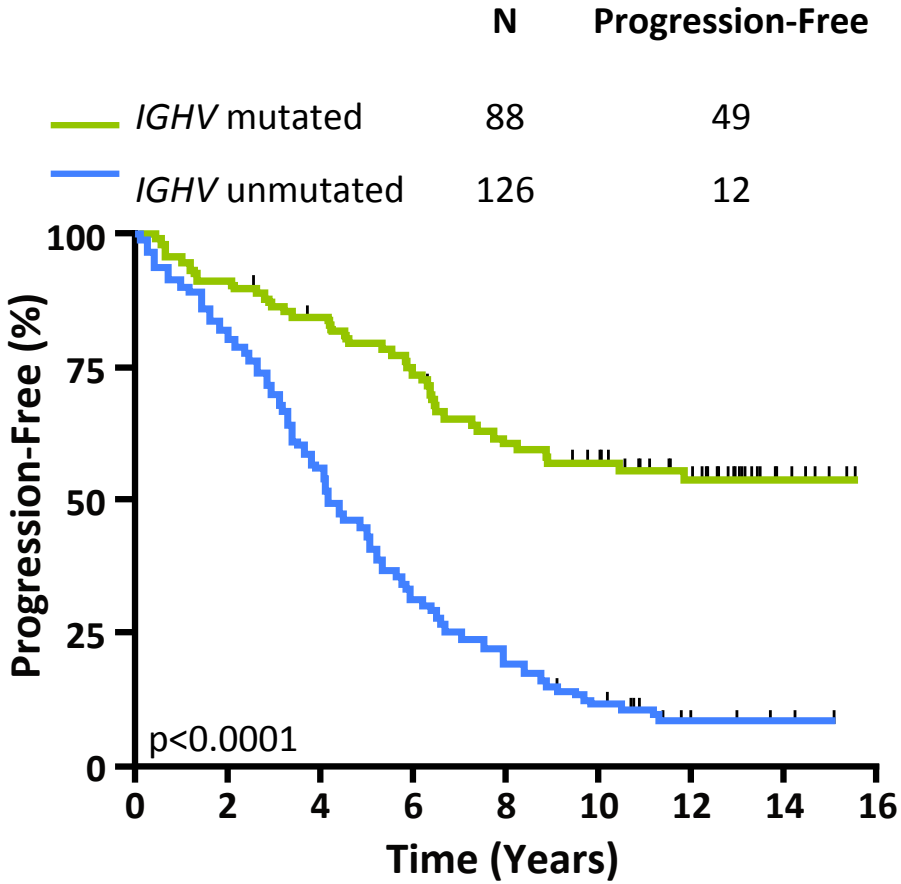
Rossi et al, Blood 2015

Predictive markers: they can be used to anticipate the efficacy of a particular therapy



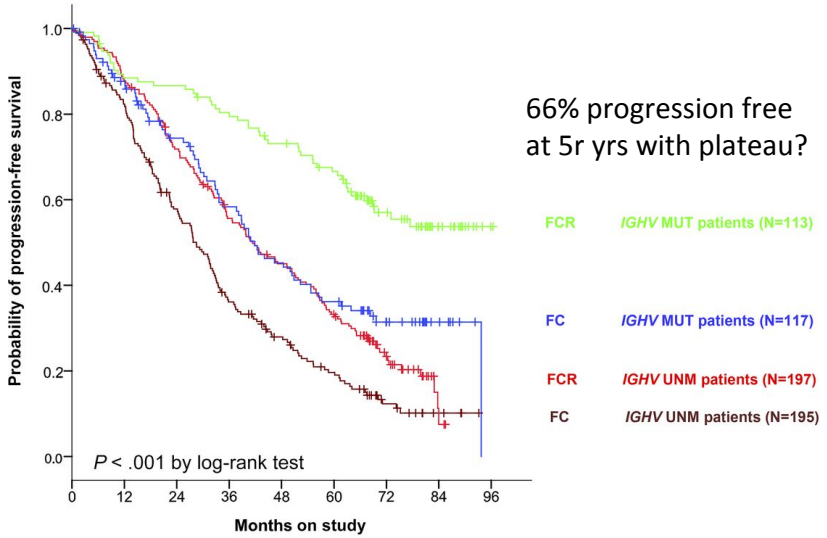
IGHV mutational status is a strong predictor of PFS:

Long term PFS at >10 years with FCR (MDACC)



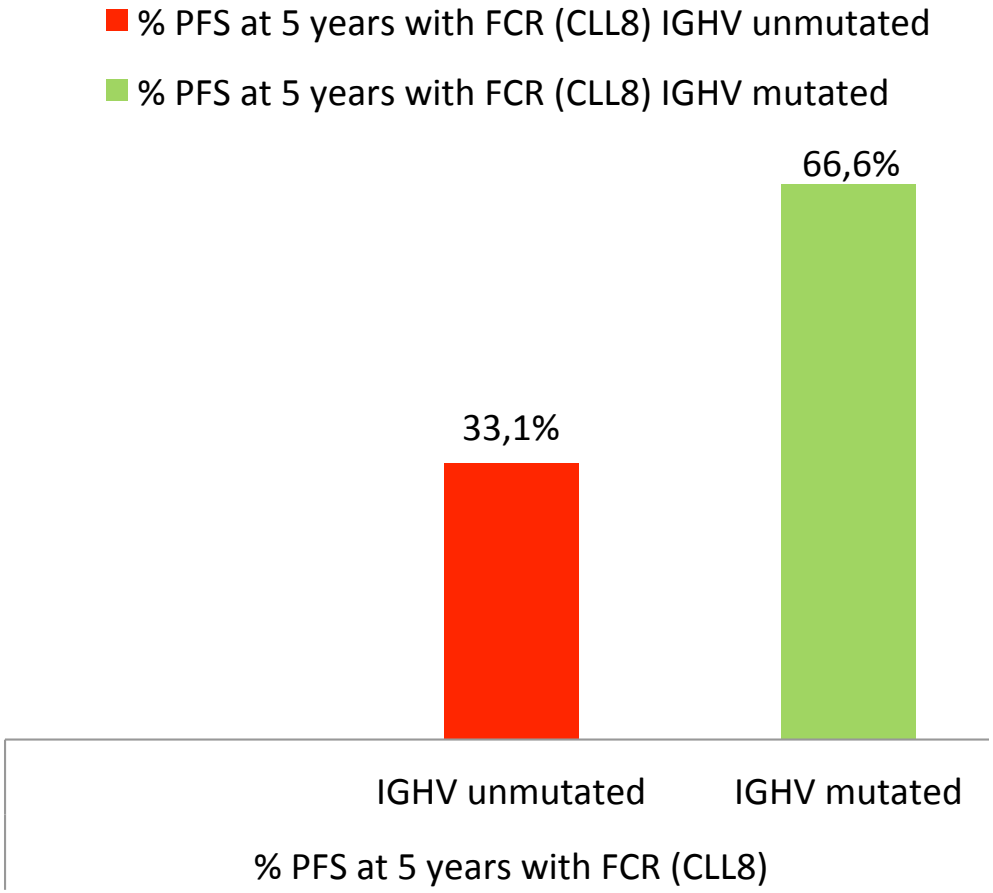
Thompson PA et al, Blood 2016; 127:303-9

IGHV mutational status is a strong predictor of PFS:
Long term PFS with FCR (GCLLSG – CLL8)



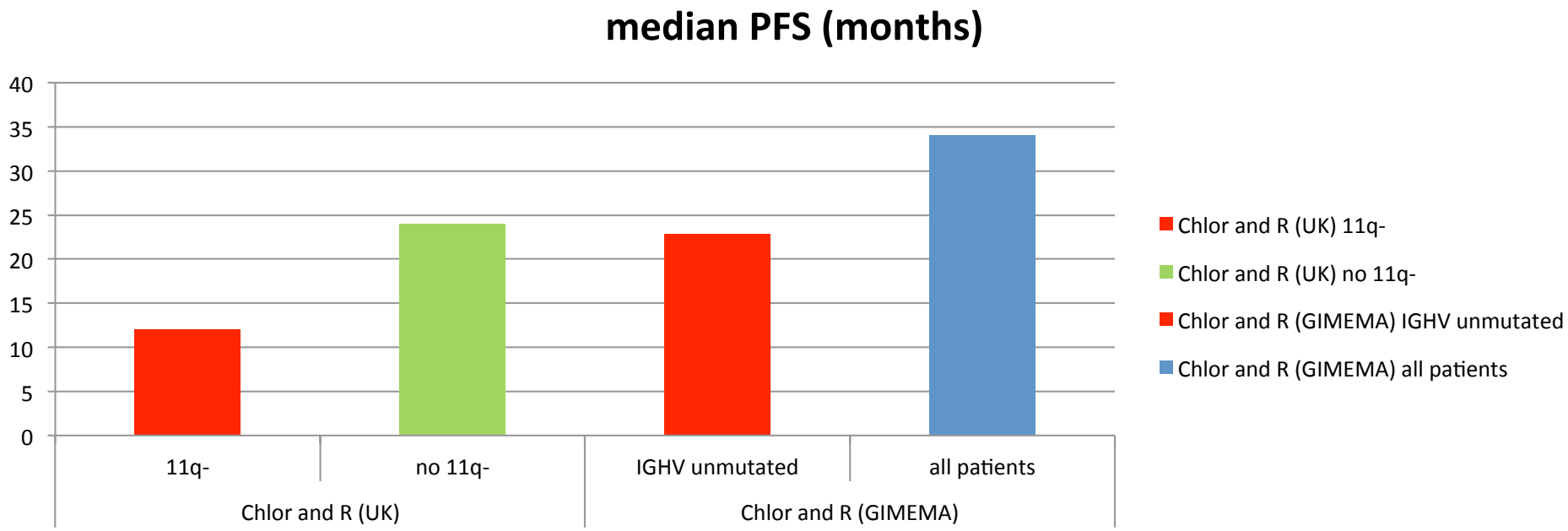
Number at risk	0	12	24	36	48	60	72	84	96
FCR *IGHV* MUT	113	99	97	89	80	71	37	15	1
FC *IGHV* MUT	117	96	75	58	45	36	21	7	0
FCR *IGHV* UNM	197	173	140	106	85	61	25	2	0
FC *IGHV* UNM	195	153	105	65	45	30	12	4	0

Fischer K et al. Blood. 2016;127(2):208-215



Adverse prognostic factors with chlorambucil and rituximab (phase II studies)

Median PFS (elderly/unfit)

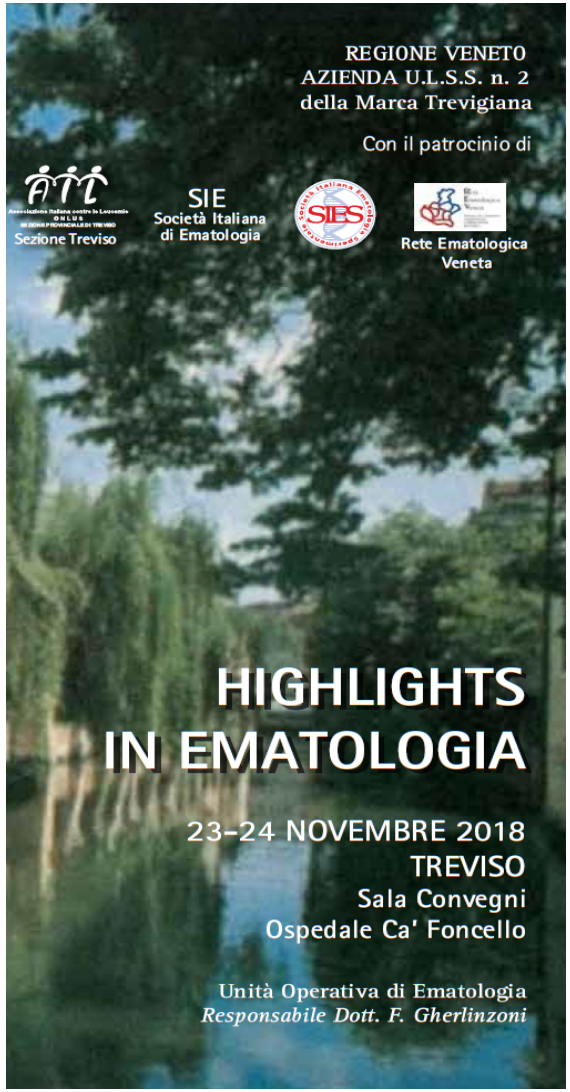


1. Hillmen P et al, J Clin Oncol. 2014 Apr 20;32(12):1236-41
2. Foà R et al. Am J Hematol. 2014 May;89(5):480-6

Predictive factors with chemoimmunotherapy in clinical trials (genetics)

	FCR		BR		Chlor + anti CD20	
	PFS	Survival	PFS	Survival	PFS	Survival
17p-/*TP53* mutations	yes	yes	yes	unknown	yes	unknown
IGHV unmutated	yes	Yes (CLL8)	yes	unknown	yes	unknown

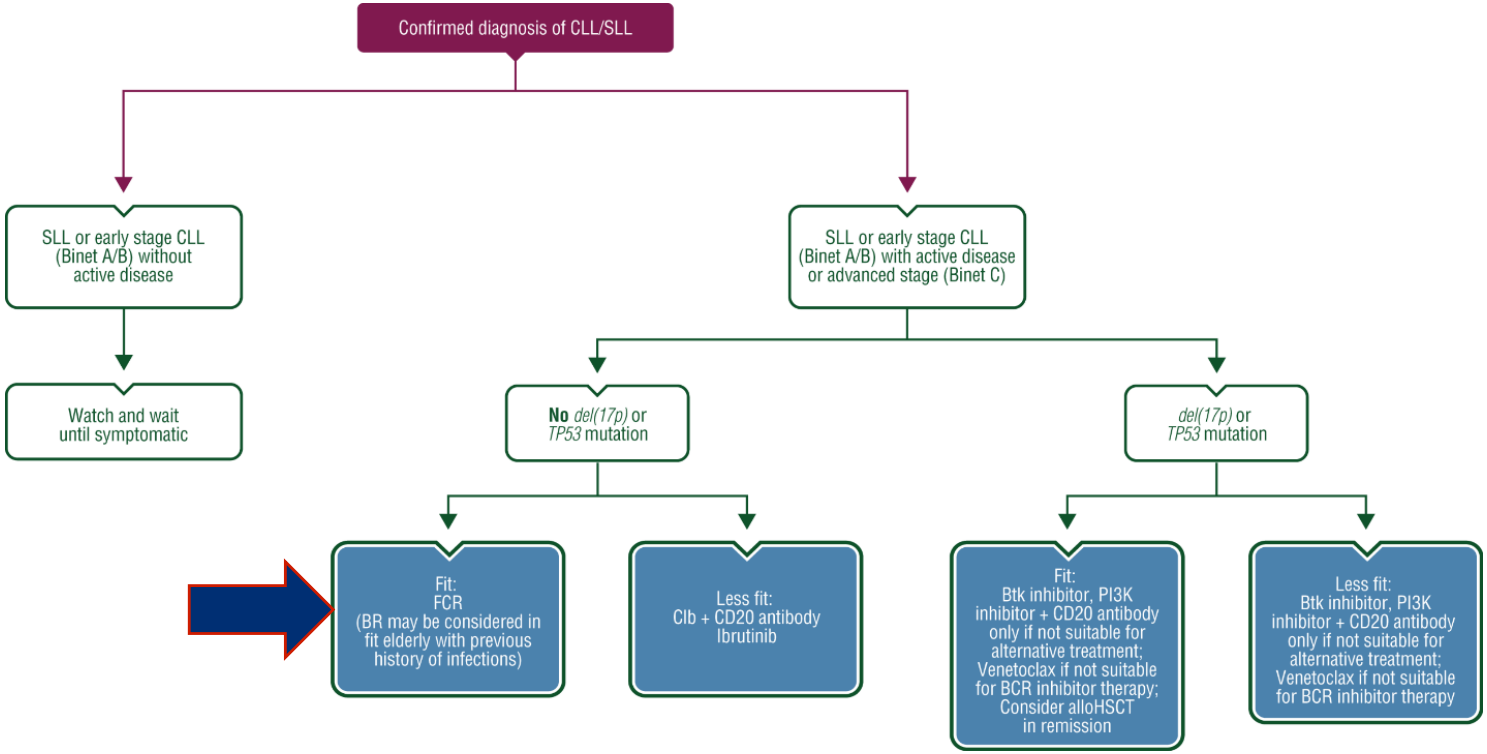
Stilgenbauer S et al. Blood. 2014;123:3247-3254; Rossi et al, Blood 2015; Fischer K et al. J Clin Oncol 2012; 30:3209-3216; Herling et al, Blood. 2016;128(3):395-404; Fischer K et al. Blood. 2016;127(2):208-215
Eichhorst et al Lancet Oncol 2016;17:928-42, Hillmen P et al, J Clin Oncol. 2014 Apr 20;32(12):1236-41; Foà R et al. Am J Hematol. 2014 May;89(5):480-6;



C'È ANCORA UN RUOLO PER LA CHEMIOIMMUNOTERAPIA NEL TRATTAMENTO DELLA LEUCEMIA LINFATICA CRONICA

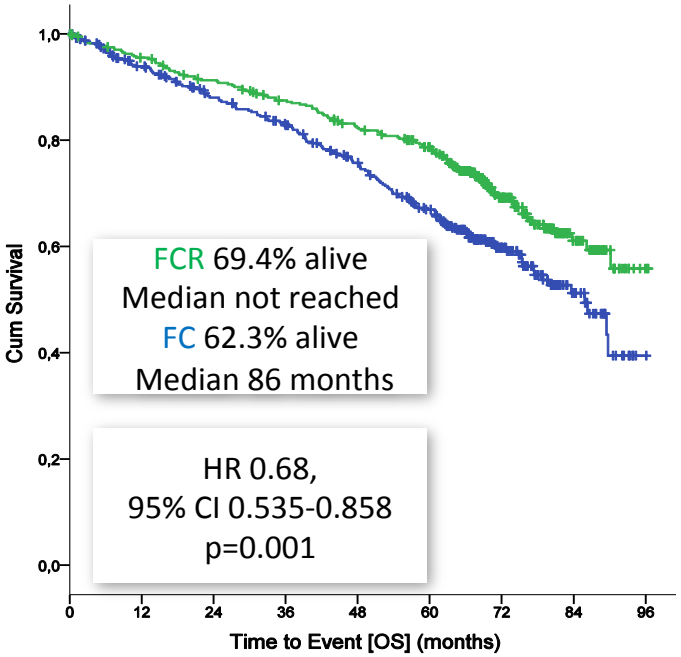
- Prognostic/predictive markers
- Treatment
  - 1st line
  - Relapsed/Refractory (R/R)

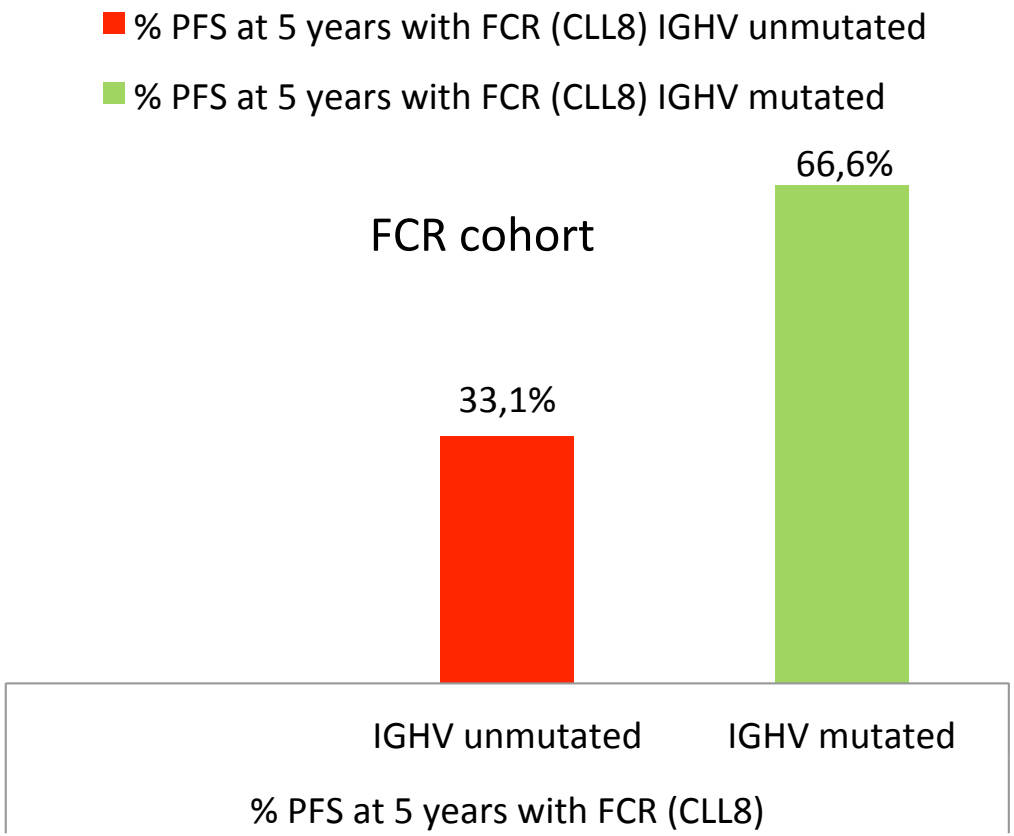
esmo.org/Guidelines/Haematological-Malignancies



From: Appendix 4: Chronic lymphocytic leukaemia: eUpdate published online 27 June 2017 (www.esmo.org/Guidelines/Haematological-Malignancies)
Ann Oncol. 2017;28(suppl_4):iv149-iv152. doi:10.1093/annonc/mdx242

Long term follow-up (median 5,9 y) of the GCLLSG – CLL8 study: *PFS and unmutated IGHV*

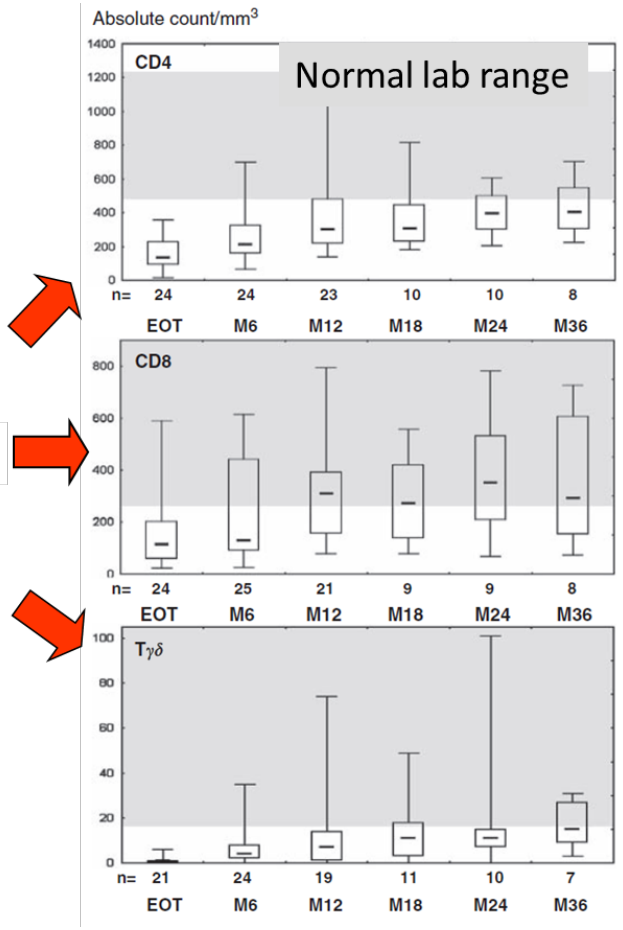




Fischer K et al. Blood. 2016;127:208-215

Immune recovery after fludarabine–cyclophosphamide–rituximab treatment in CLL

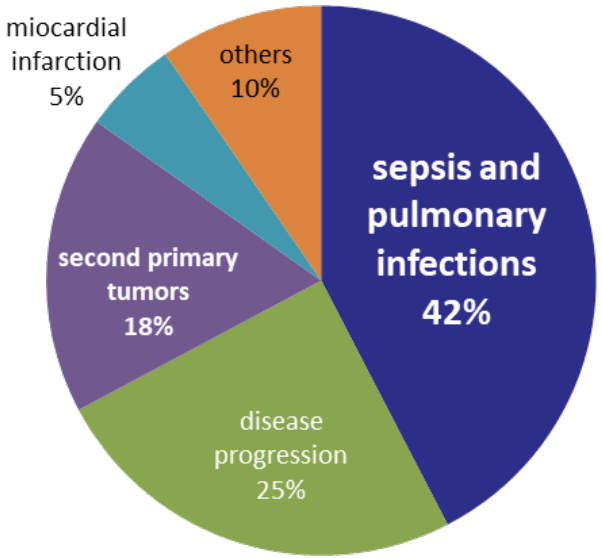
sustained depletion of all T-cells



Ysebaert L et al, Leukemia 2010 24: 1310–1316

Causes of death after FCR in the CLL8 trial

FCR arm (n.125 events / 408 patients; 5,9 yrs median f.u.)



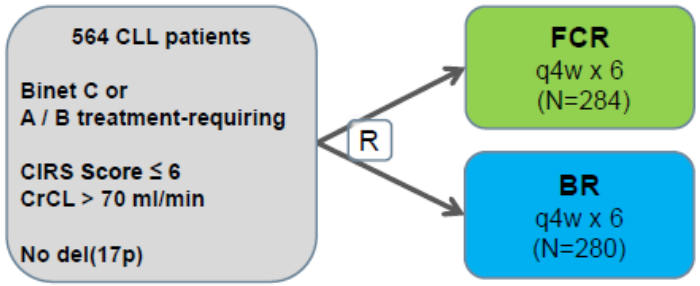
Median time to onset (months) after last dose of study treatment	
sepsis and pulmonary infections	46
second primary tumors	27

Fischer K et al. Blood. 2016;127(2):208-215

FCR vs BR in Previously Untreated and Physically Fit Patients with CLL: Final Analysis of the GCLLSG- CLL10 Study (17p- excluded per protocol)

- Study hypotheses
  - 1. BR non-inferior to FCR in terms of PFS
  - 2. BR potentially better tolerability compared to FCR
- Assumptions*:
- PFS @ 2 yearss
  - under FCR: 75%
  - under BR: > 67,5% for non-inferiority (7.5% difference or less)
  - → Complete 95% CI of the HR [λ BR/FCR] has to be < 1.388

Study Design

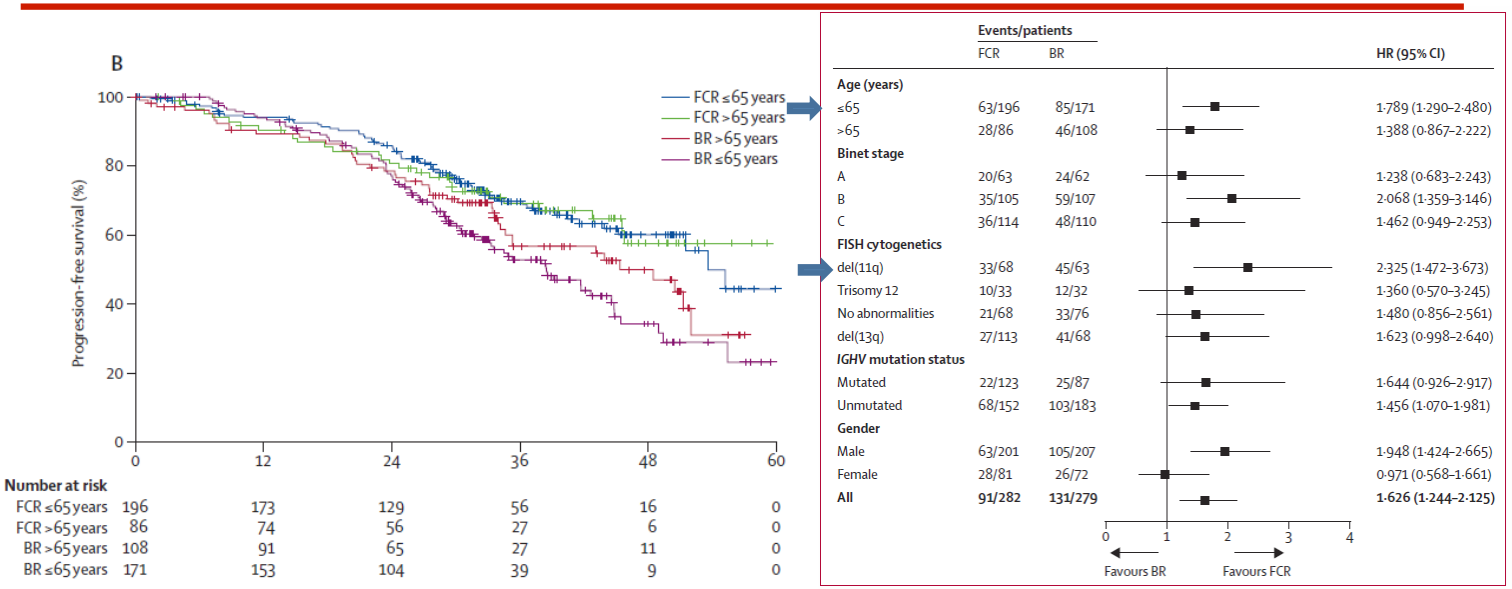


Median observation time for all patients: 37,1 (0-59,9) m

Baseline patient characteristics	FCR n=284	BR n=280	p value
Med. age	61	62,1	0,131
Age > 65	30,5%	38,7%	0,042
Age ≥ 70	14%	22%	0.020
Male	71,3%	74,2%	0,45
Median time since diagnosis (m)	21,6	24,6	0,846
ECOG PS 0	64,1%	64,1%	0,194
Med. CIRS	2	2	0,489
Binet A	22,3%	22,2%	
Binet B	37,3%	38,4%	0,846
Binet C	40,4%	39,4%	
IGHV unmutated	55,3%	67,8%	0,003
11q deletion	24,1%	22,6%	0,691
Trisomy 12	12,4%	12,2%	1
13q deletion	55%	52,7%	0,612
s-TK (U/l) > 10.0	72,8%	72,6%	1
s-β2m (mg/l) > 3.5	30,9%	38,1%	0,086

Eichhorst et al., ASH 2014, Abstract # 19

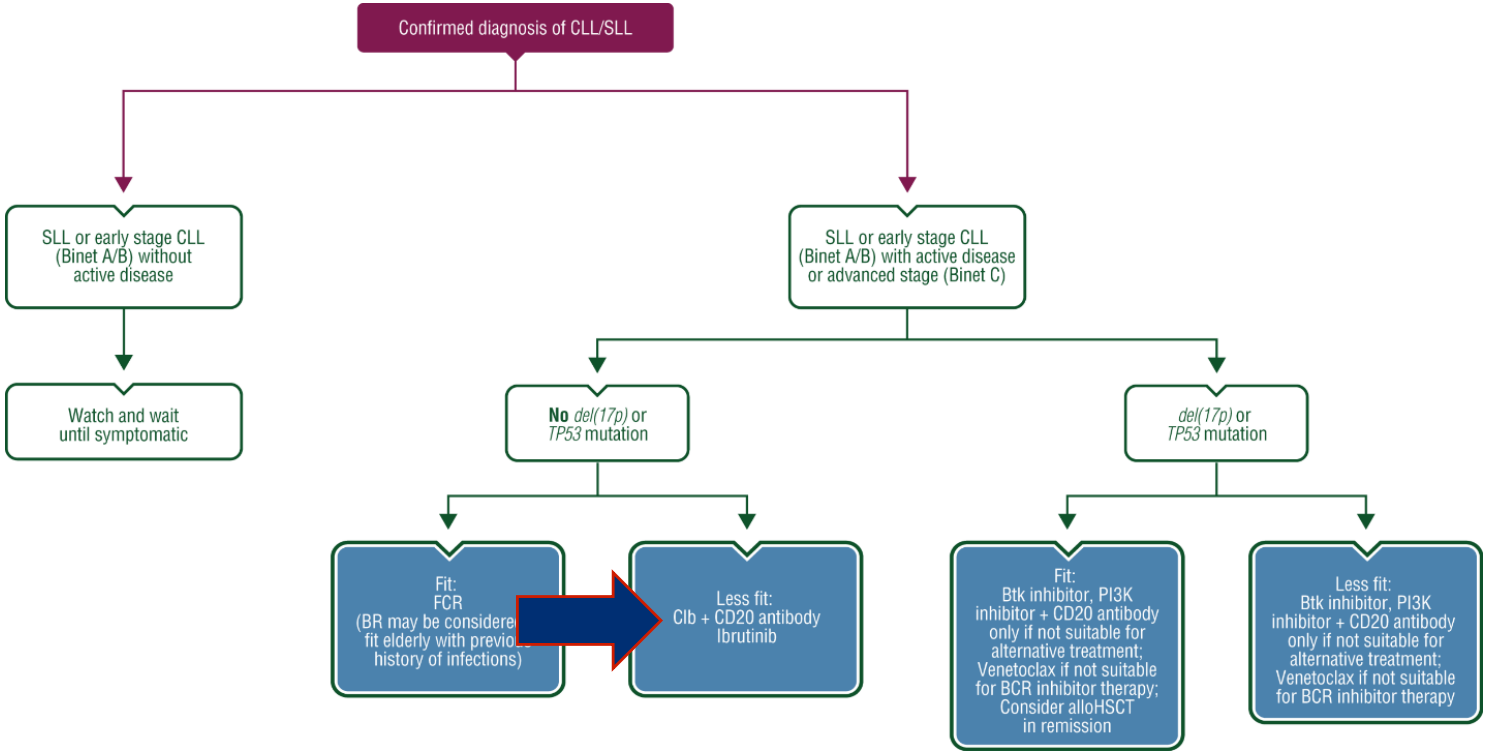
PFS according to risk groups in the CLL10 study:



- FCR better than BR in the total population
- FCR better than BR in patients with IGHV unmutated and in patients with 11q-
- Median PFS in the BR arm in pst with unmutated IGHV: 34 months
- NO difference in the patients >65 years (post-hoc analysis)

Eichhorst et al Lancet Oncol 2016;17:928-42

esmo.org/Guidelines/Haematological-Malignancies



From: Appendix 4: Chronic lymphocytic leukaemia: eUpdate published online 27 June 2017 (www.esmo.org/Guidelines/Haematological-Malignancies)

Ann Oncol. 2017;28(suppl_4):iv149-iv152. doi:10.1093/annonc/mdx242

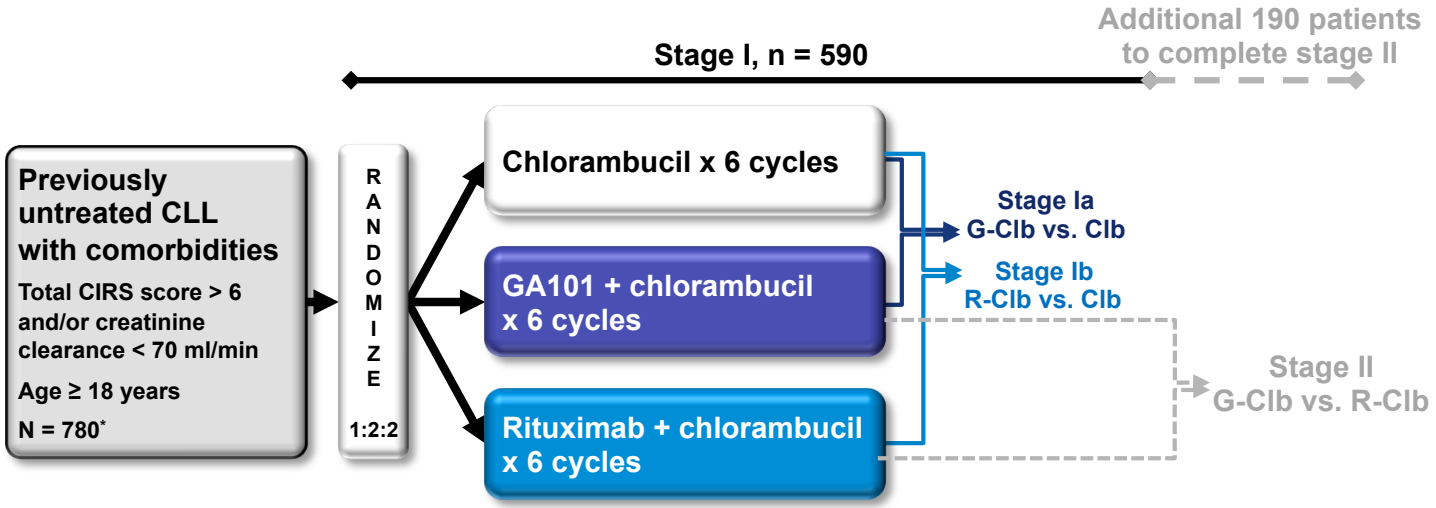
Elderly CLL

Efficacy of chlorambucil + Rituximab as first line treatment

	No. of patients	Median age	Total dose of Chlor	%CR/CRi	Median PFS (months)
	100	70	420 mg/ sqm	10	23,5
	85	70	448 mg/ sqm	19	34,7
	233	73	6 mg / Kg	8,3	15,7

UK: Hillmen P, JCO, Mar 17. [Epub ahead of print] 2014
Italy: Foà R on behalf of the GIMEMA group: Am J Hematol. 2014;89: 480-6
CLL11: Goede V, on behalf of CCLLSG: N Engl J Med. 2014;370:1101-10

CLL11 Phase III: Study design



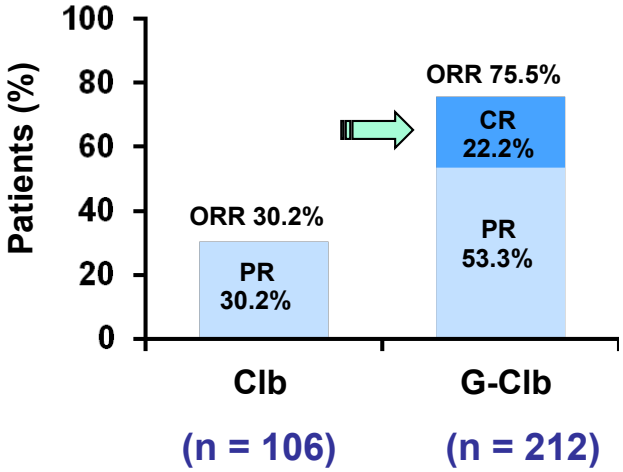
GA101: 1,000 mg Days 1, 8, and 15 Cycle 1; Day 1 Cycles 2–6, every 28 days

Rituximab: 375 mg/m^2 Day 1 Cycle 1, 500 mg/m^2 Day 1 Cycles 2–6, every 28 days

Clb: 0.5 mg/kg Day 1 and Day 15 Cycle 1–6, every 28 days

Goede V, *et al. J Clin Oncol* 2013: 31 suppl: Abstract 7004 (presentation update).
www.clinicaltrials.gov NCT01010061.

CLL11 stage Ia: Investigator-assessed end-of-treatment response



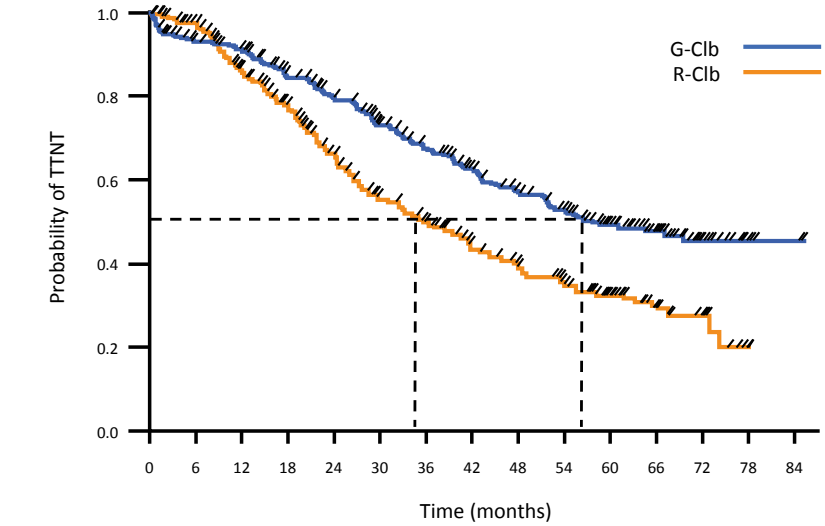
	Patients, n (%)[1]	
End of treatment ORR	**30.2**	**75.5**
CR[a]	**0**	**22.2**
PR[b]	**30.2**	**53.3**
SD	**21.7**	**4.7**
PD	**25.5**	**3.8**
Not evaluable	**22.6**	**16.0**

- End of treatment response is defined as the first assessment occurring > 56 days after the end of treatment
- Response assessed by iwCLL criteria[2]

[a] incudes CRi = CR with incomplete hematologic recovery; [b] includes nPR = nodular partial response; PD = progressive disease; SD = stable disease.

1. Adapted from Goede V, *et al. J Clin Oncol* 2013: 31 suppl: Abstract 7004 (presentation update).
2. Hallek M, *et al. Blood* 2008; 111:5446–5456.

TTNT: G-Clb vs R-Clb



Goede et al; EHA 2018 abs S151 https://learningcenter.ehaweb.org/eha/2018/stockholm/215923/

	G-Clb n=333	R-Clb n=330
Patients with events, n (%)	136 (40.8)	174 (52.7)
5-year TTNT, % (95% CI)	49 (42–55)	32 (25–38)
Median TTNT, months	56.4	34.9
HR (95% CI), p-value	0.58 (0.46–0.73), p<0.0001	

Median observation time: 59.4 months

First line treatment in CLL: data from pivotal randomized trials

Fit patients

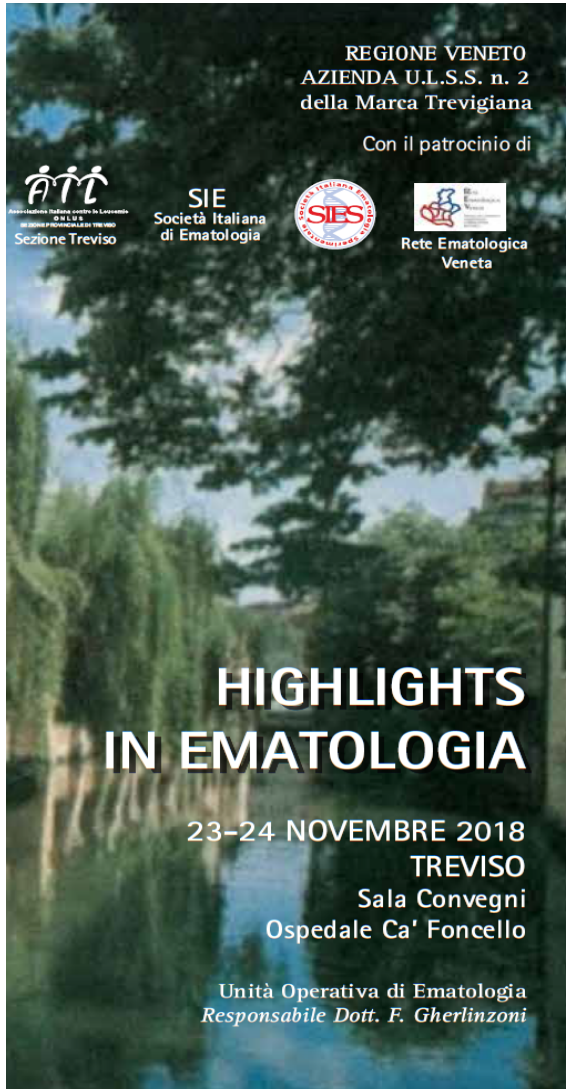
- FCR prolongs survival vs FC
- FCR prolongs PFS vs BR, not in >65 y.o. patients (post-hoc analysis)

Unfit and/or >65

- Ibrutinib prolongs survival over chlormabucil despite crossover in patients >65 years
- Obinutuzumab added to Chlor prolongs PFS, TTNT and OS vs Rituximab + Chlor

Fischer K et al. Blood. 2016;127(2):208-215; Barr PM et al. Haematologica. 2018;103(9):1502-1510; Eichhorst B et al, Lancet Oncol. 2016 Jul;17(7):928-942; Goede V et al. N Engl J Med. 2014 Mar 20;370(12):1101-10;

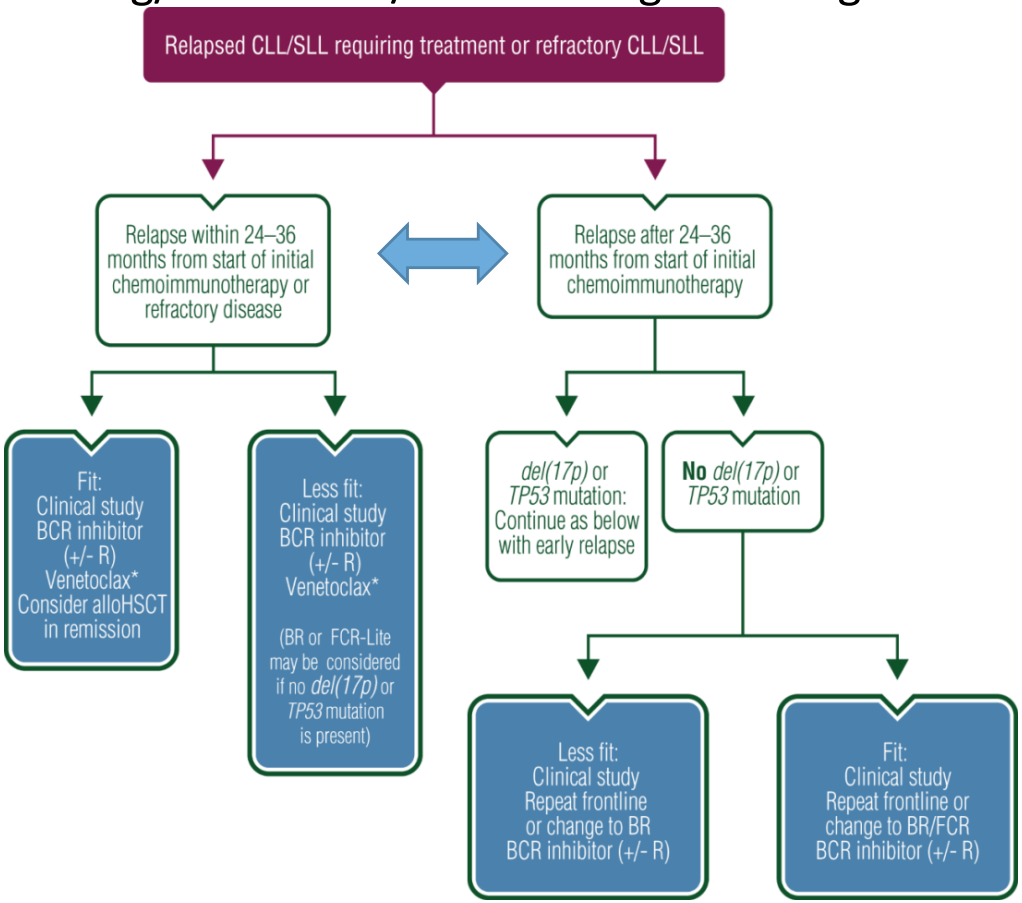
Goede et al; EHA 2018 abs S151 https://learningcenter.ehaweb.org/eha/2018/stockholm/215923/



C'È ANCORA UN RUOLO PER LA CHEMIOIMMUNOTERAPIA NEL TRATTAMENTO DELLA LEUCEMIA LINFATICA CRONICA

- Prognostic/predictive markers
- Treatment
  - 1st line
  - Relapsed/Refractory (R/R)

esmo.org/Guidelines/Haematological-Malignancies

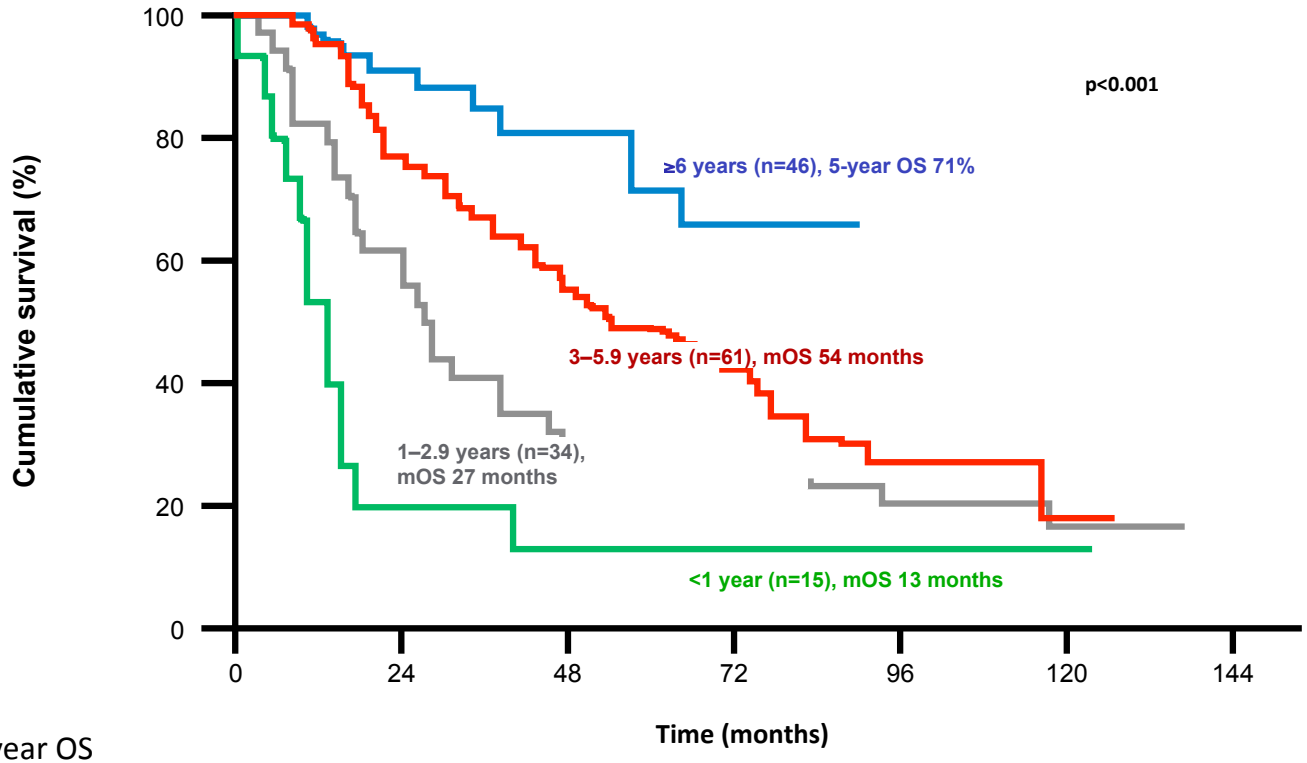


From: Appendix 4: Chronic lymphocytic leukaemia: eUpdate published online 27 June 2017 (www.esmo.org/Guidelines/Haematological-Malignancies)
Ann Oncol. 2017;28(suppl_4):iv149-iv152. doi:10.1093/annonc/mdx242

Survival is short in patients who relapse early

32% of patients relapse ≤ 3 years after FCR, median OS 2.5 years

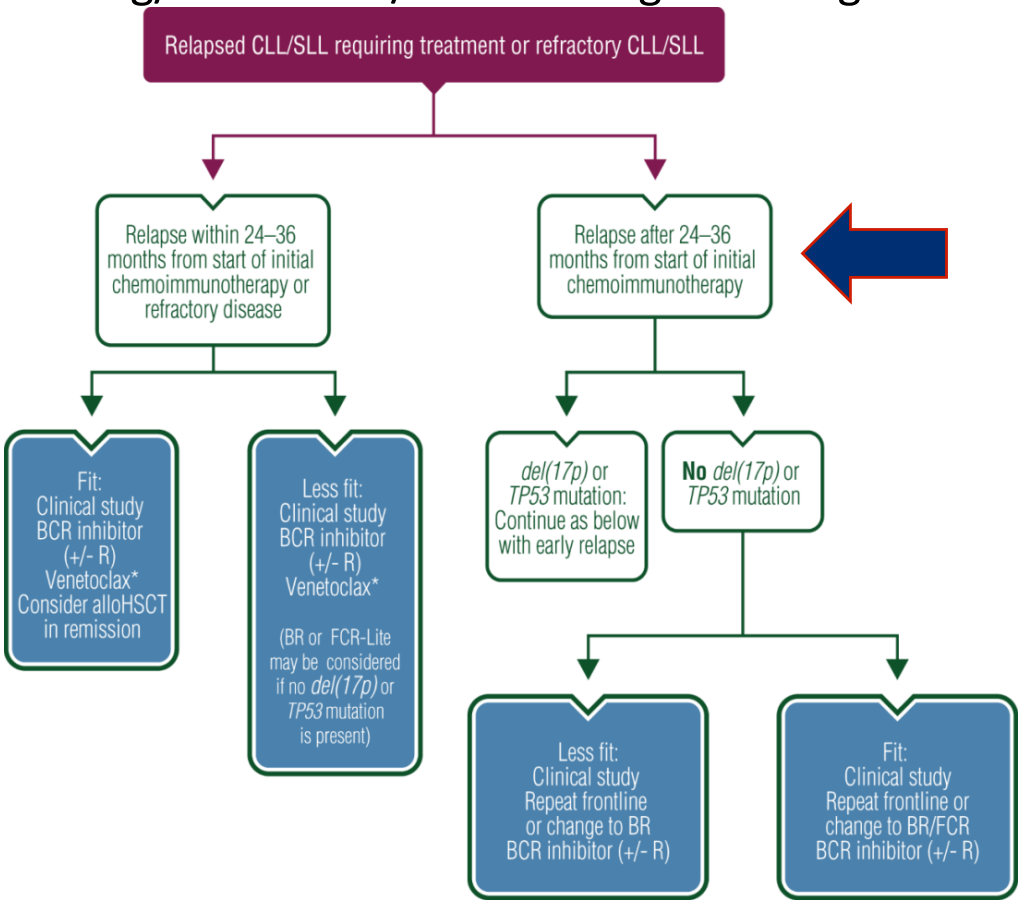
Phase II study of 156 patients who progressed after first-line FCR



[a] 5-year OS
mOS: median OS; OS: overall survival

Tam CS, *et al. Blood* 2014 124:3059–3064.

esmo.org/Guidelines/Haematological-Malignancies



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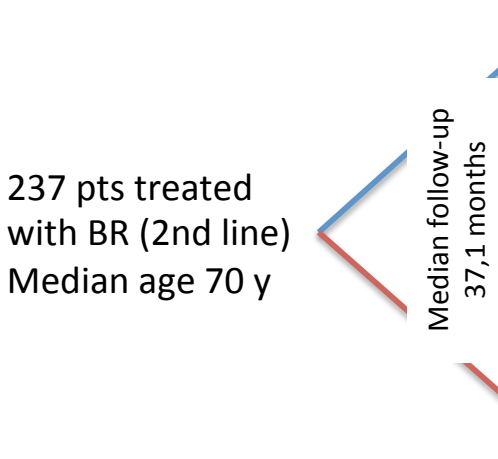
Is there a role for chemoimmunotherapy as first salvage treatment in CLL? Efficacy of Bendamustine and rituximab in a real-world patient population

Efficacy of bendamustine and rituximab as first salvage treatment in CLL and indirect comparison with ibrutinib: a GIMEMA, ERIC and UK CLL FORUM study



Multivariable analysis

Parameters	P	Hazard Ratio	95% C.I.	
17p- vs others	0.0004	2.92	1.631	5.296
IGVH mut/unmut	0.0299	0.53	0.299	0.94
Others vs Binet C	0.0192	0.536	0.319	0.903

Parameters	P	Hazard Ratio	95% C.I.	
Stage A-B vs C	0,0276	0,547	0,320	0,935
CR+PR vs NR	0.0001	0.344	0.198	0.595

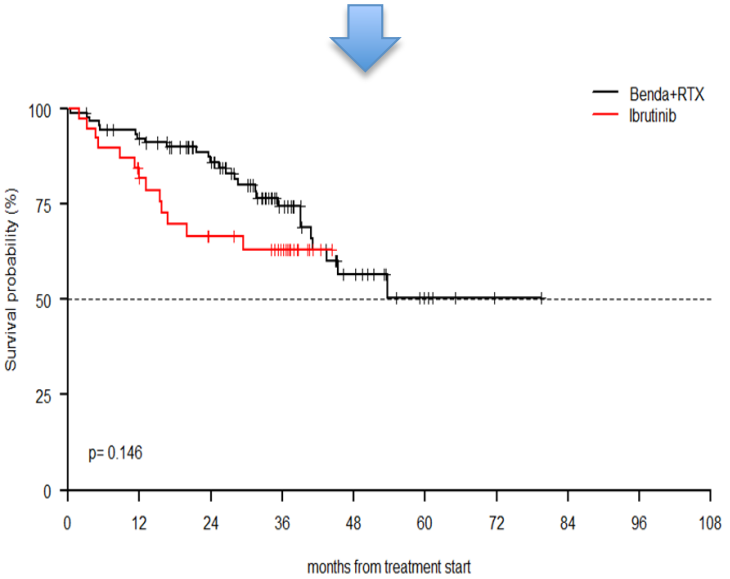
Cuneo A et a. Haematologica. 2018 Jul;103(7):1209-1217

Is there a role for chemoimmunotherapy as first salvage treatment in CLL? Indirect comparison of BR and ibrutinib in a real-world population

Baseline characteristics of the BR and the ibrutinib cohorts (UK + NPP GIMEMA) in patients treated with chemoimmunotherapy in first line

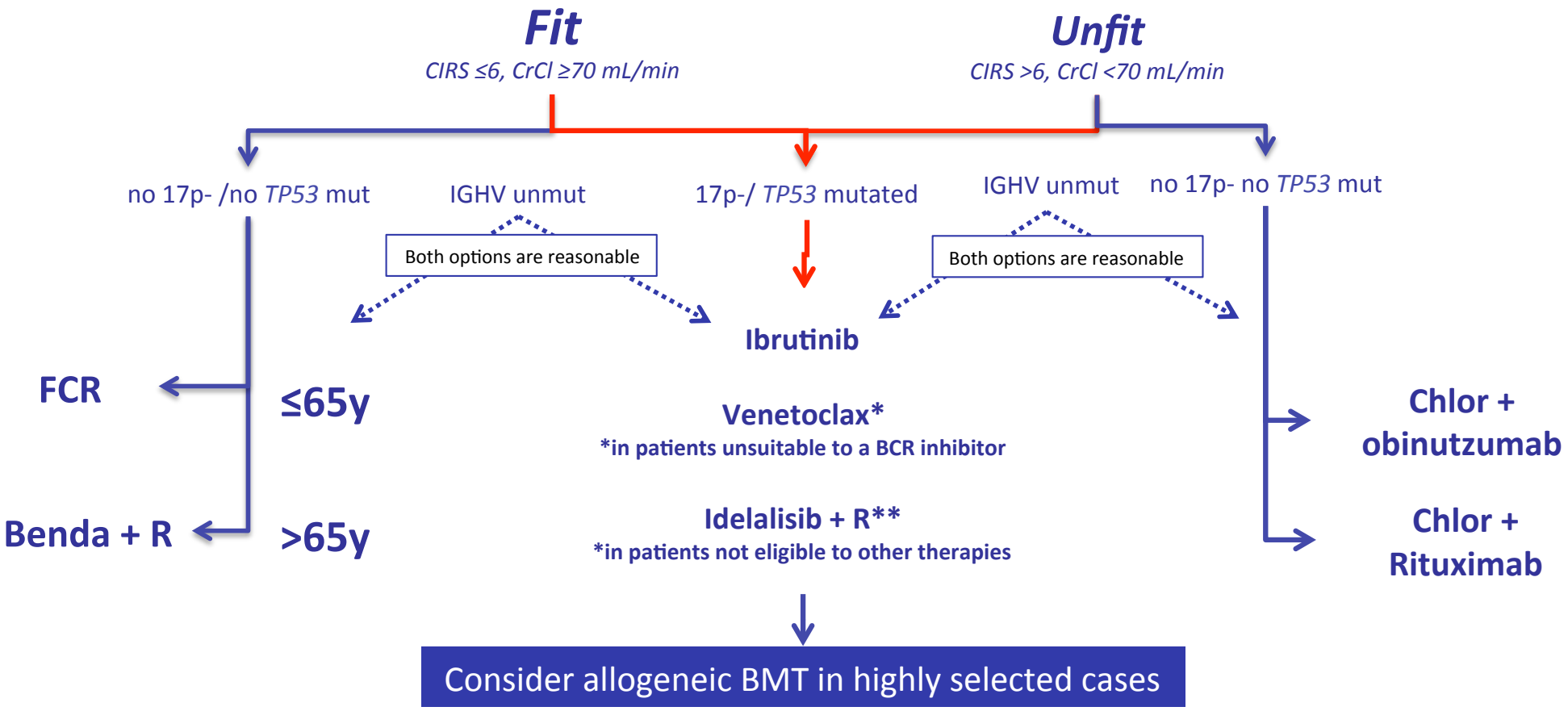
Variable	BR (n=137)	Ibrutinib (n=71)	p
Median age years (range)	68.2 (39.4-84.6)	67.1 (27.5-85.3)	0.603
Age years (%) ≤65/>65	39 (34.5)/74 (65.5)	27 (38.6)/43 (61.4)	0.691
Gender (%) M/F	91 (66.4)/46 (33.6)	45 (63.4)/ 26 (36.6)	0.777
ECOG PS (%) 0-1/≥2	113 (91.9)/10 (8.1)	57 (82.6)/ 12 (17.4)	0.090
Months between 1st line and 2nd line			
median (range)	30.60 (0.40, 79.40)	19.40 (1.80, 77.60)	0.001
n. <36/≥36 (%)	81 (59.1)/56 (40.9)	54 (76.1)/17 (23.9)	0.023
Response to 1st line treatment (%) no/yes	28 (20.4)/109 (79.6)	8 (15.1)/45 (84.9)	0.524
IGHV (%)mutated/unmutated	17 (19.5)/70 (80.5)	8 (32.0)/17 (68.0)	0.295
17p- (%) yes/no	16 (14.8)/92 (85.2)	22 (36.1)/39 (63.9)	0.003

OS in 39 patients treated second-line with ibrutinib and in 92 patients treated with second line BR.
All patients had intact 17p and received CIT front-line



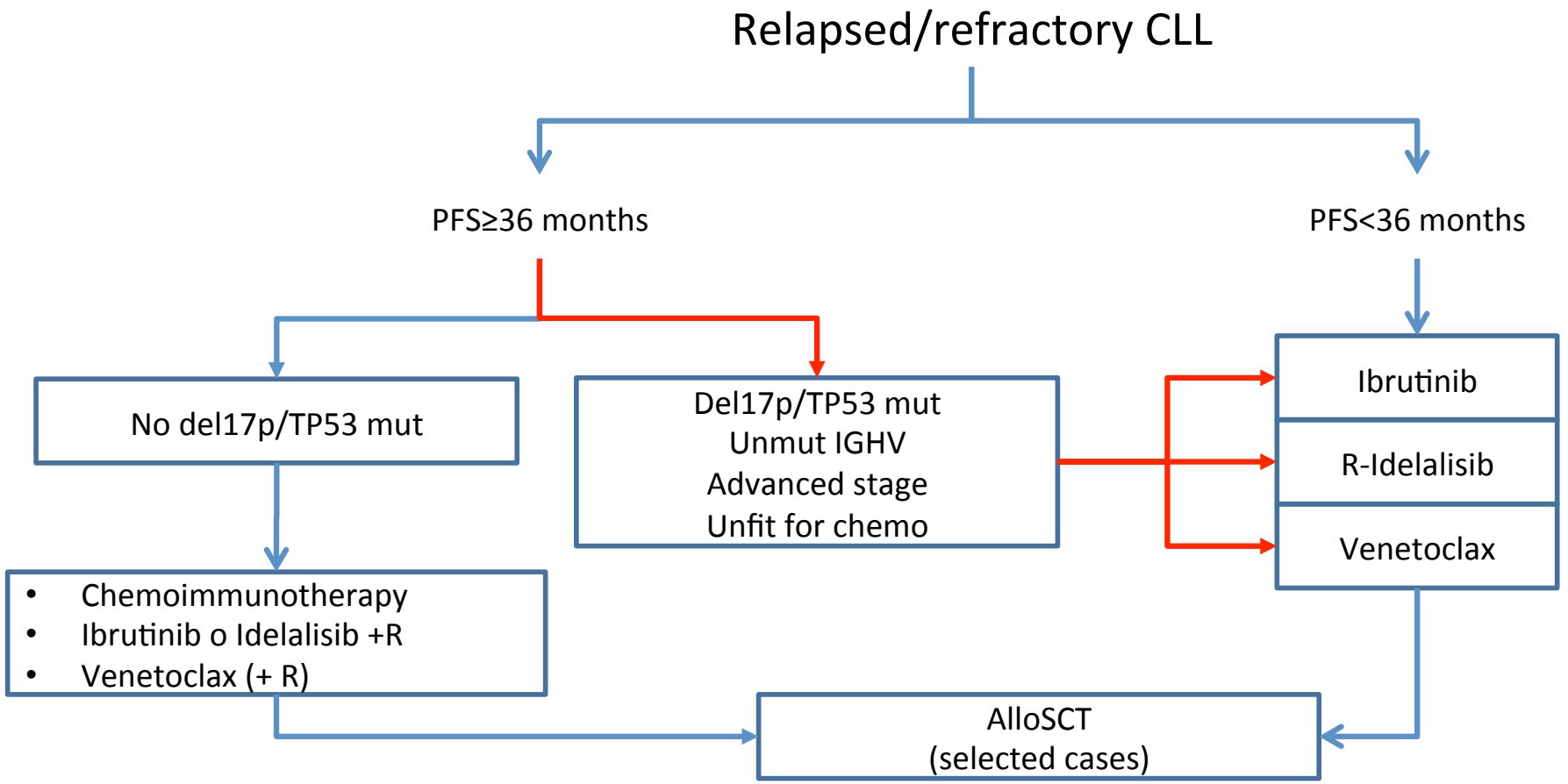
Cuneo A et a. Haematologica. 2018 Jul;103(7):1209-1217

Principal options for first line treatment of CLL



Cuneo A. personal view, Nov 2018

Principal options for relapsed/refractory CLL



Cuneo A. personal view, Nov 2018