“Chronic Lymphocytic Leukemia and Obinutuzumab Treatment”

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Disclosures

- Investigator in Clinical Trials: Roche, Pfeizer, MSD, Novartis, Libbs, Celgene, Abbvie e Janssen
- Advisory Board: Roche, Abbvie and Novartis

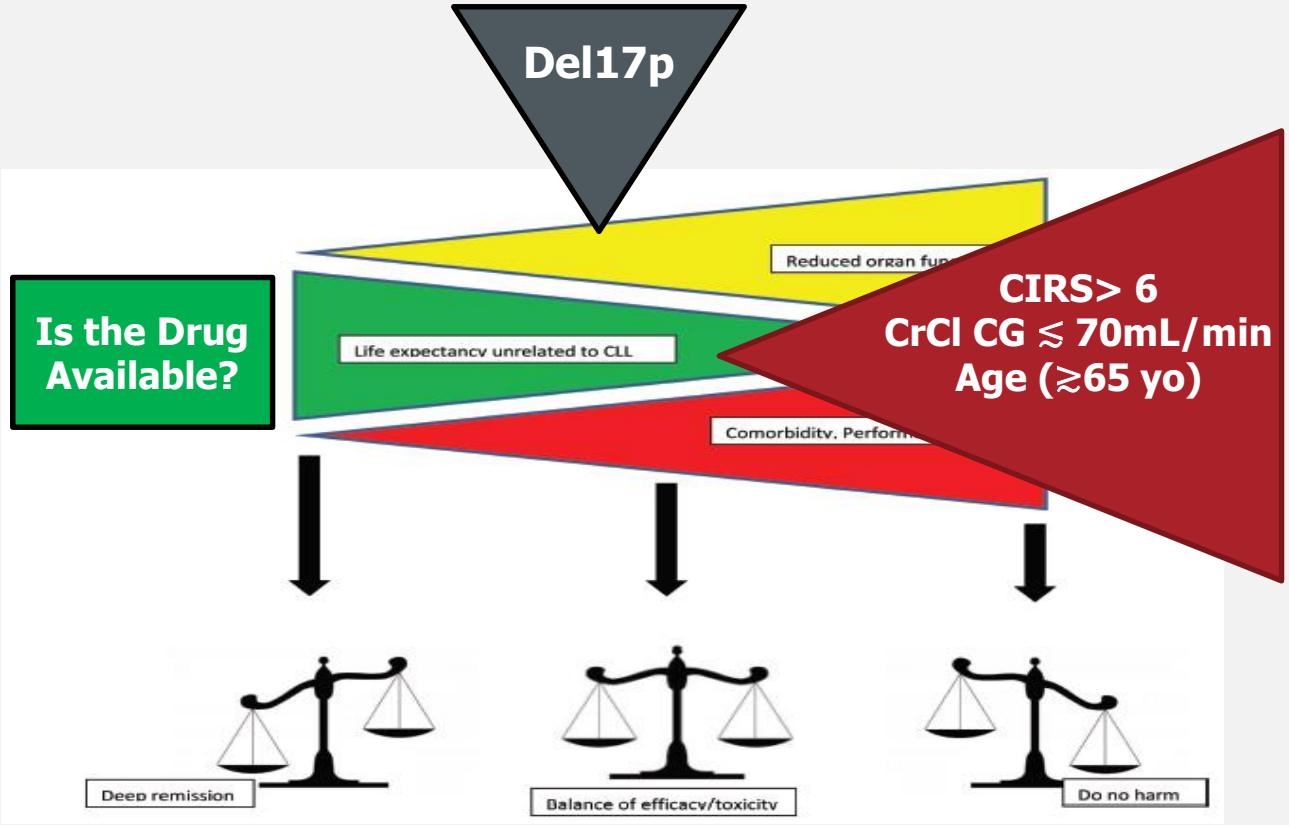
Chronic Lymphocytic Leukemia

Best first line treatment for 95 years old patients

Who?

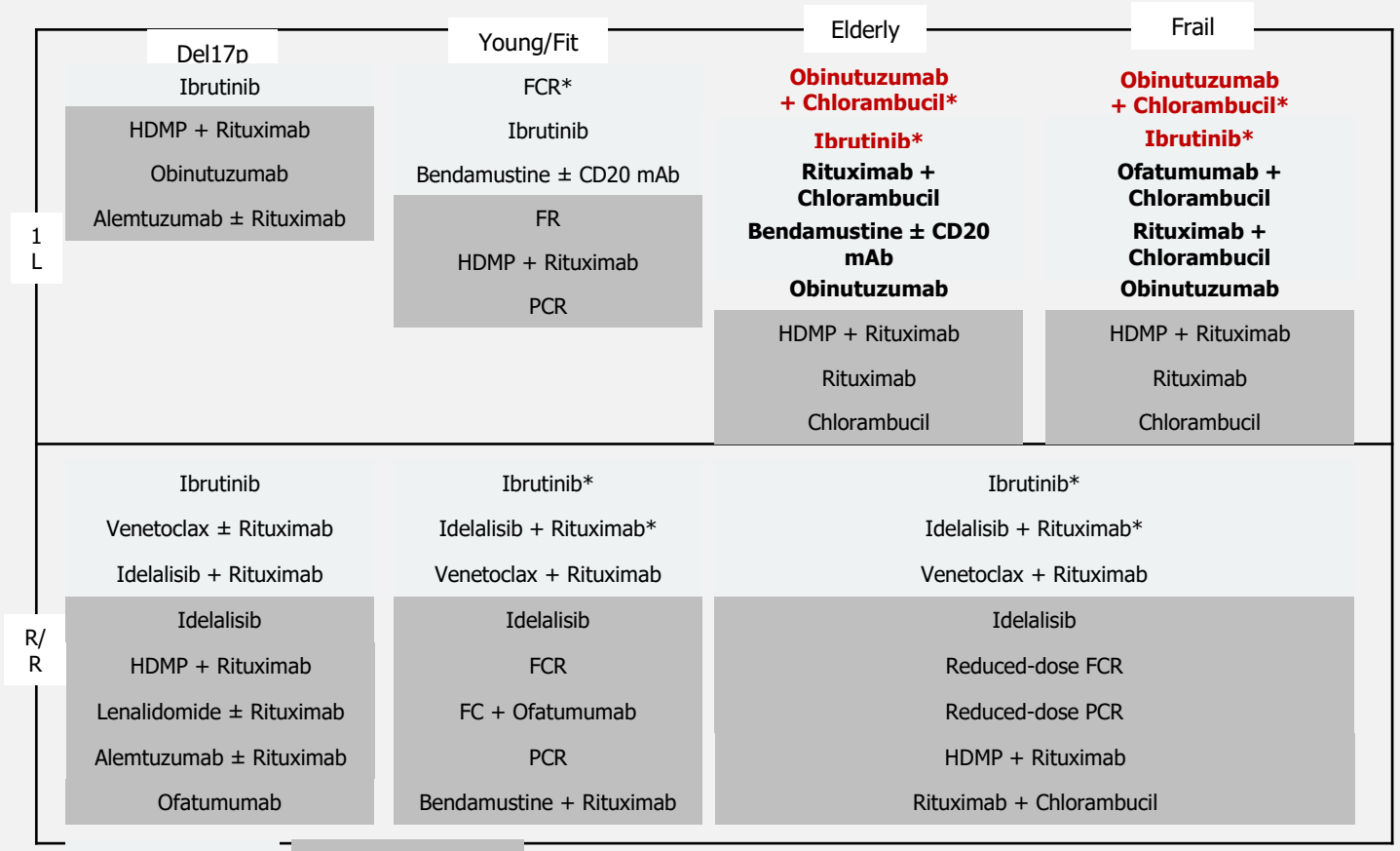
Disease?

Which?



Adaptado de Tait Shanafelt. Hematology 2013:158-167.

NCCN CLL Treatment Landscape



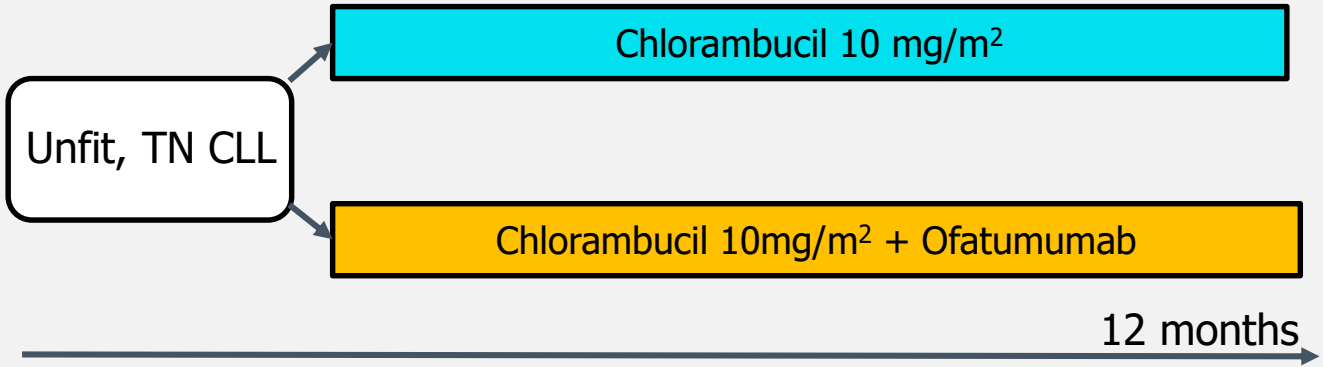
Adapted from NCCN v3.2018

Wierda et al. J Natl Compr Canc Netw 2017;15(3):293–311

Clinical Trials for Unfit Patients

Immuno-chemotherapy

COMPLEMENT1



447 patients

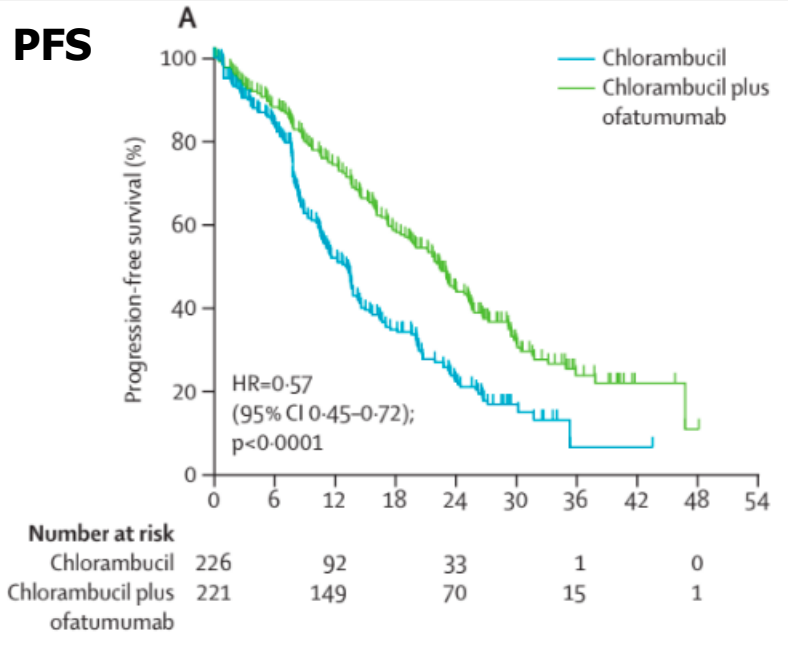
Endpoint: PFS

EA≥3 most common: neutropenia (26%) – O-Chlb

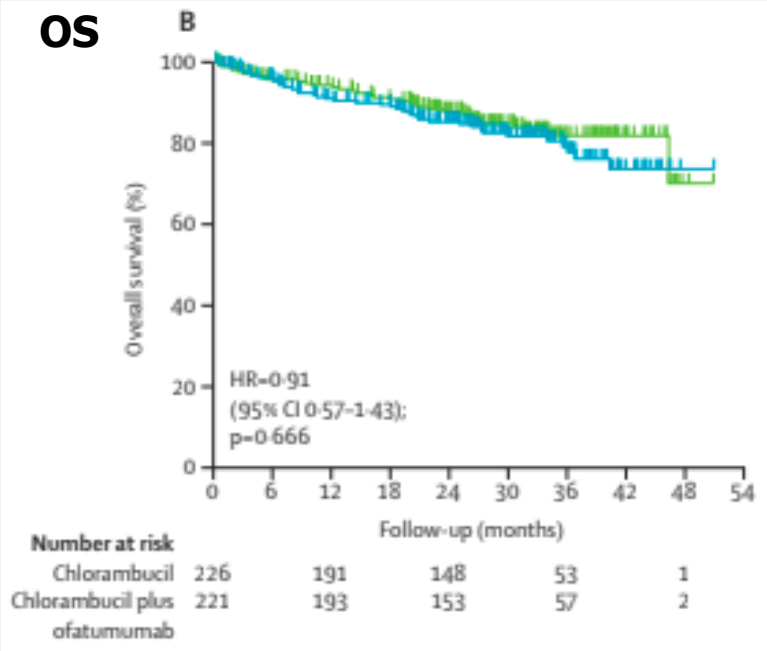
Hillmen P et al. The Lancet Vol 385 May 9, 2015

COMPLEMENT1

PFS



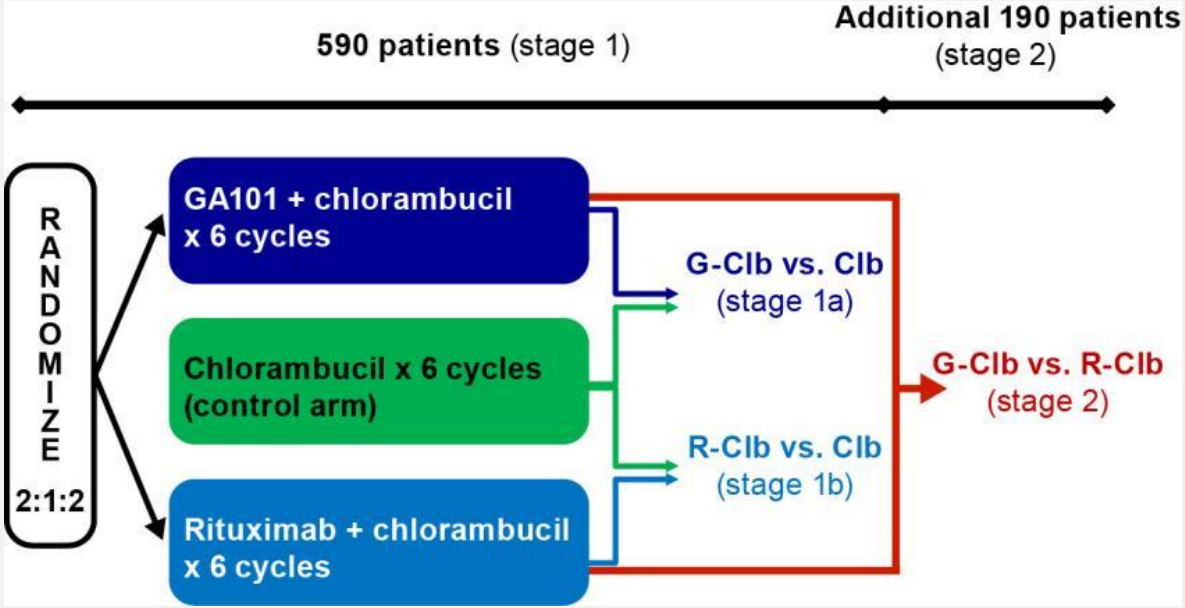
OS



Hillmen P et al. The Lancet Vol 385 May 9, 2015

(CLL11) Chlorambucil + Obinutuzumab: 781 patients

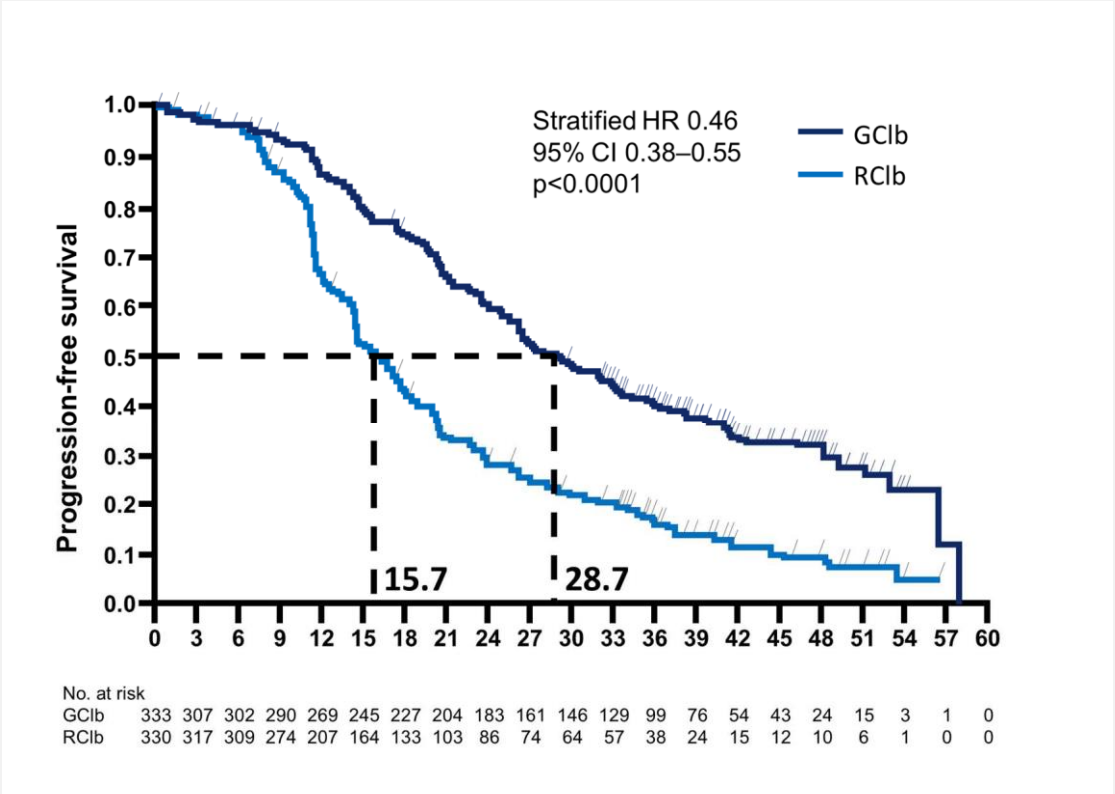
CLL, 1st Line with Comorbidities



Goede V, et al. N Engl J Med 2014; 370:1101–1110;

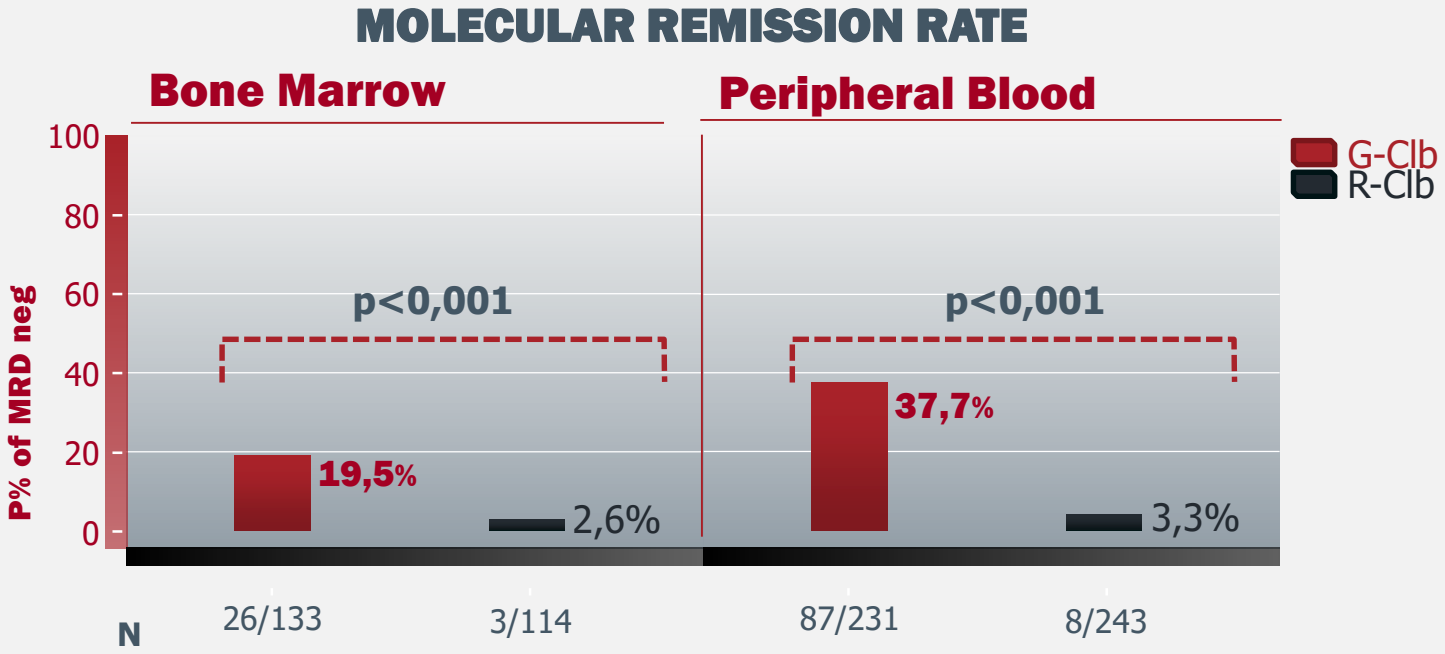
Update CLL11: 40 months FUP

Progression Free Survival: G-Clb > R-Clb



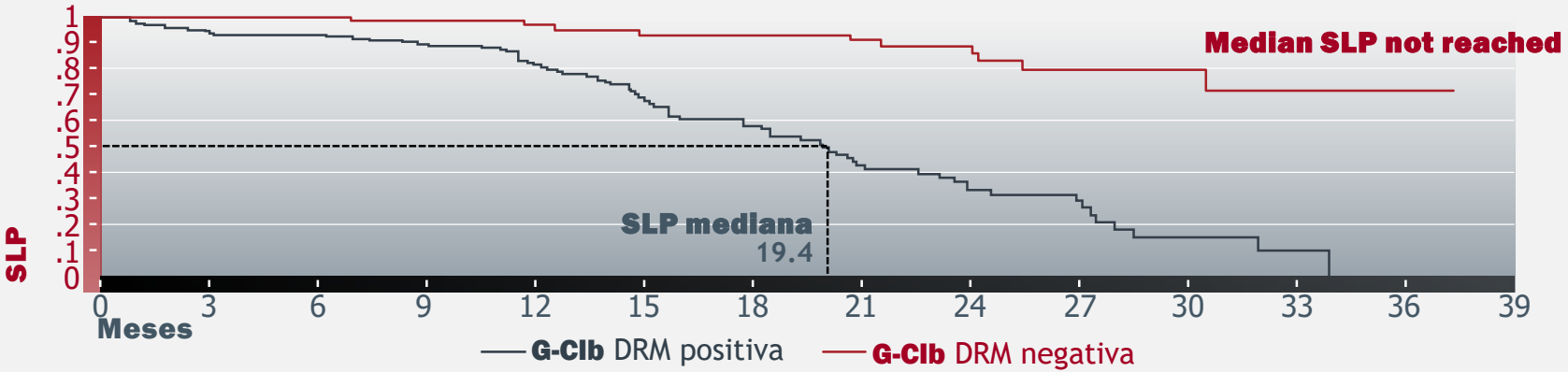
Goede et al., Blood 2015, 126:1733 (ASH Annual Meeting Abstract)

CLL11:
MRD AT THE END OF TREATMENT



Goede V, et al. N Engl J Med 2014; 370:1101–1110;
Hallek M, et al. Blood 2008; 111:5446–5456.
*DRM = Doença Residual Mínima

CLL11 :
PROGRESSION FREE SURVIVAL AND NEGATIVE MRD



Goede V, *et al*. N Engl J Med 2014; 370:1101–1110; Supplemental appendix.

Adverse Events

CLL11

CLL11 stage II: Grade ≥3 AEs

Incidence of grade ≥3 AEs with G-Clb vs R-Clb was higher owing to increased grade ≥3 IRRs

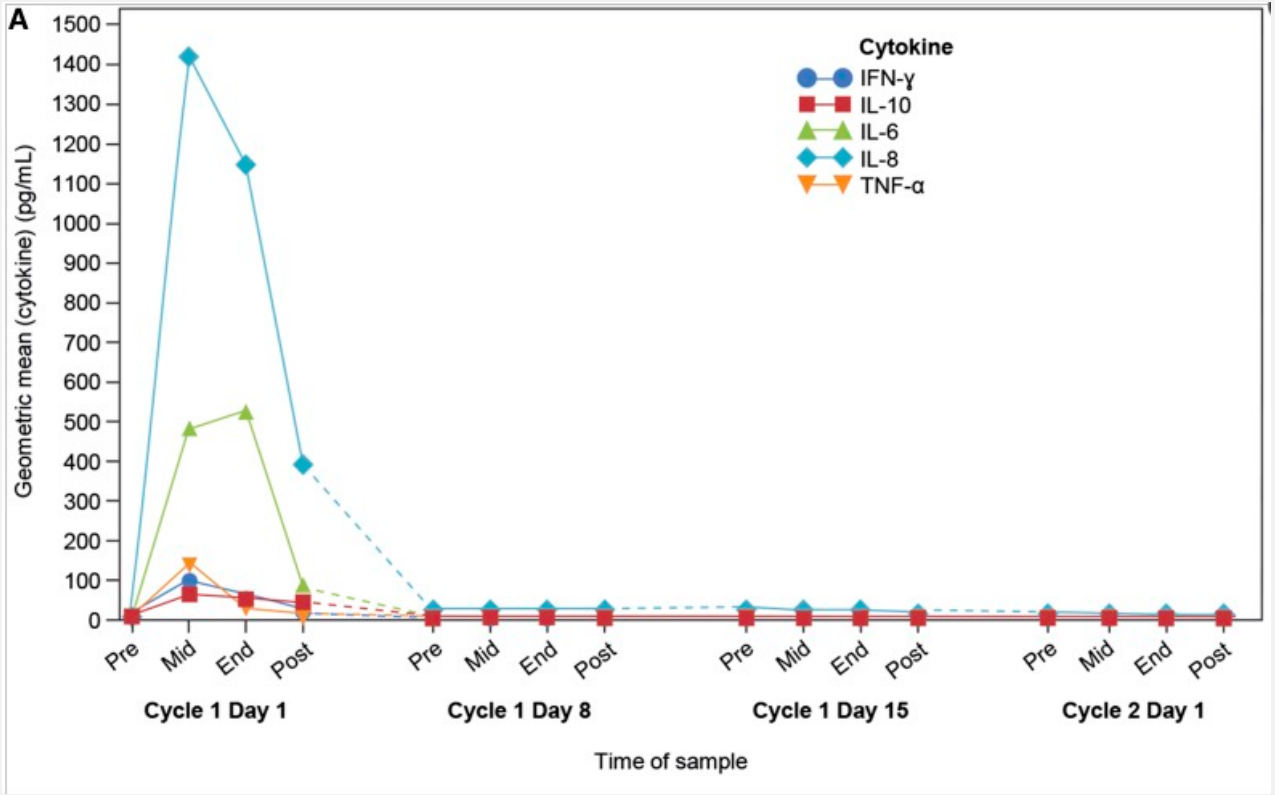
Patients, n (%)	R-Clb (n=321)	G-Clb (n=336)
Any grade ≥3 AE	186 (58)	239 (71)
IRRs	13(4)	67 (20)
Neutropenia	91 (28)	111 (33)
Infections	46 (14)	41(12)
Thrombocytopenia	10 (3)	35 (10)

- All grade ≥3 AEs occurring until the **May 2013 clinical cut-off** in ≥5% of patients are shown
- There were no deaths attributed to IRRs, neutropenia or thrombocytopenia. There were two deaths from infection in the R-Clb arm (both pneumonia) and two in the G-Clb arm (septic shock, pulmonary sepsis)

Five patients who were randomised to R-Clb received one infusion of GAZYVA in error and are included in the safety population for G-Clb and not R-Clb
Patients who received no treatment are excluded from the safety population (G-Clb=2; R-Clb=4)
AE, adverse event; Clb, chlorambucil; CLL, chronic lymphocytic leukaemia;
G-Clb, GAZYVA + Clb; IRR, infusion-related reaction; R-Clb, MabThera + Clb

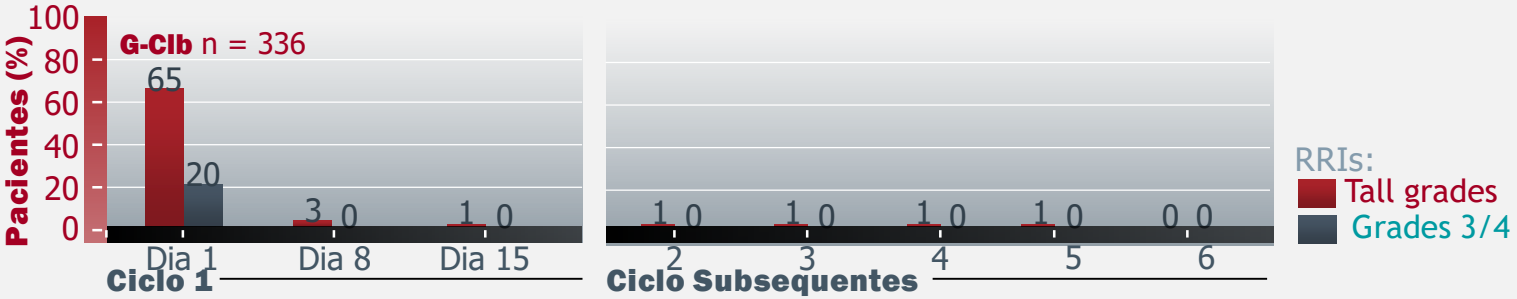
Goede V, et al. N Engl J Med 2014;370:1101–1110

Cytokine release and IRR: CLL pts treated with Obinutuzumab



Freeman et al. Blood . 2015 Dec 10; 126(24): 2646–2649

CLL11 :
MOST COMUM ADVERSE EVENT IS INFUSIONAL REACTION



Atention to the first cycle: IRR grades 3 and 4 → Day 1

To reduce the IRR: pre-medication, debulking

Goede V, et al. N Engl J Med 2014; 370:1101–1110;S upplemental appendix.

R-Bendamustine

R- Benda, Untreated CLL, Phase II Trial, German Chronic Lymphocytic Leukemia Study Group

Rituximab 375 mg/m2 C1 Rituximab 500 mg/m2 C2-C 6

Benda **90** mg/m2 D1-2, C1-C6

6 cycles

117 patients fit and unfit

Primary endpoint: Overall response

Fisher K et al. J Clin Oncol 2012; 30:3209-3216.

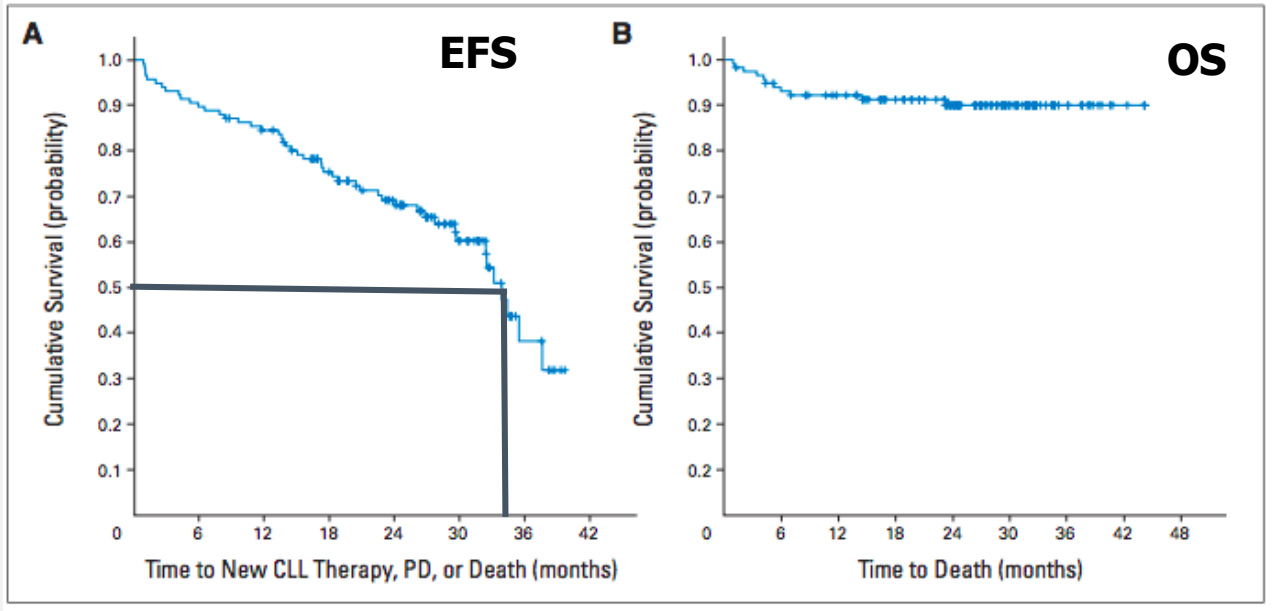
R- Benda, Untreated CLL, Phase II Trial, German Chronic Lymphocytic Leukemia Study Group

- Median age **64 years** (max 78 yrs)
- **1/4 population: 70 years or older**
- **1/3 had a creatinine clearance ≲70 mL/min**

Fisher K et al. J Clin Oncol 2012; 30:3209-3216.

R-Benda, efficacy

- ORR: 80%, CR 21%
- MRD in PB: 57.8%
- MRD in BM: 29.2%



Fisher K et al. J Clin Oncol 2012; 30:3209-3216.

R- Benda, Untreated CLL, Phase II Trial, German Chronic Lymphocytic Leukemia Study Group

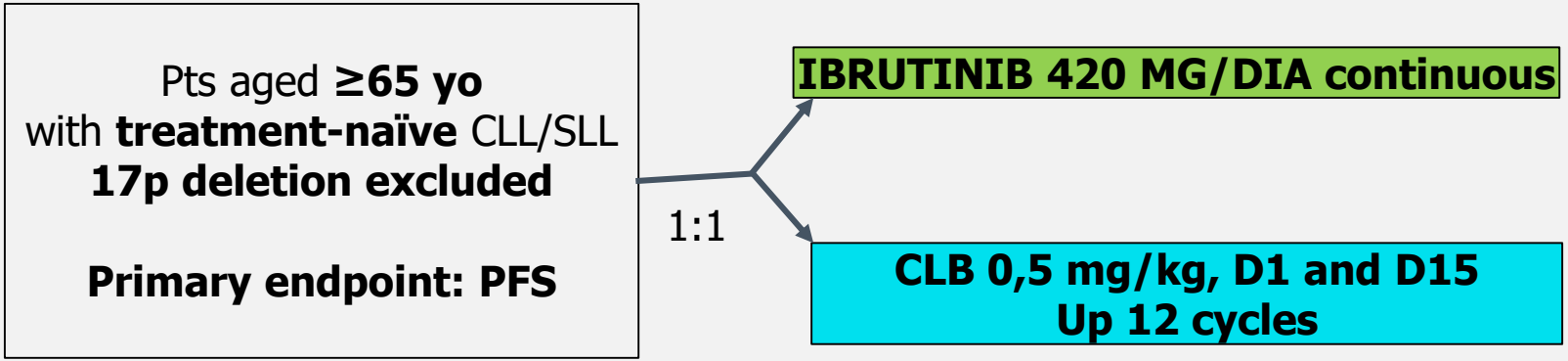
- **The most common adverse events were hematologic toxicities**
- **1/4 was not able to complete the full six cycles**
- **62.4% treatment was delayed between 1 and 28 days**
- **1/2 decreased the dose due to hematologic toxicity**
- 72,6 % used infectious prophylaxis
- 21,4% were treated with G-CSF

Fisher K et al. J Clin Oncol 2012; 30:3209-3216.

Oral Target Therapy

Ibrutinib

Resonate-2 ™



Burger et al. N Engl J Med 2015;373:2425-37
Tedeschhi et al. Blood 2017; 126:495;

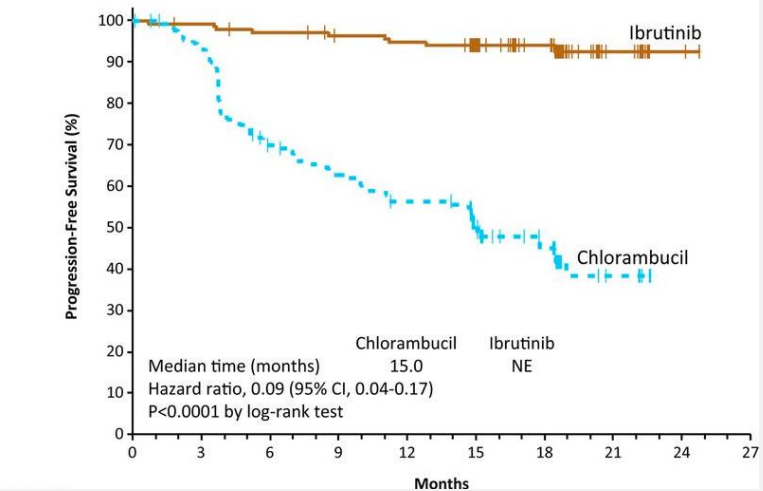
Resonate-2 ™

- 269 pts enrolled
- Median age: 73 years (70% ≥70 years)
- Baseline characteristics were balanced between arms:
  - 69% had comorbidities at baseline including CIRS score >6, reduced creatinine clearance, or ECOG status of 2.

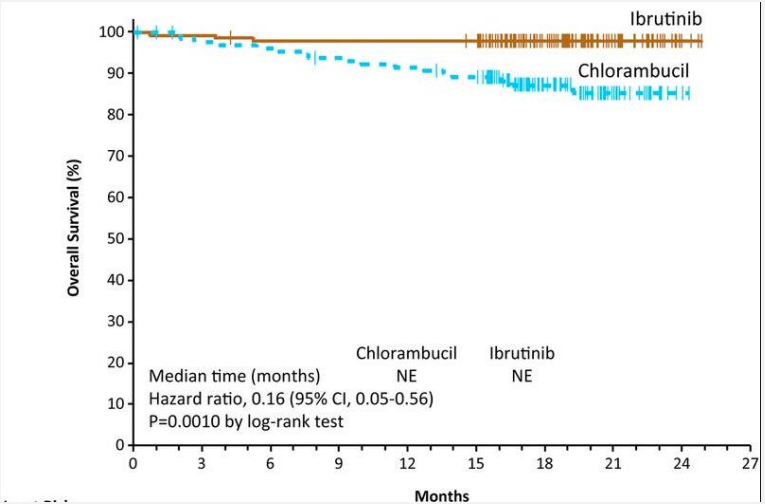
Burger et al. N Engl J Med 2015;373:2425-37
Tedeschhi et al. Blood 2017; 126:495;

Resonate-2 ™: 3-year Follow up

PFS



SG



Tedeschhi et al. Blood 2017; 126:495;

Adverse Events: 3-year Follow up

Prevalence of Most Common* G≥3 AEs Over Time on Ibrutinib Arm				
Adverse Event, n(%)	**0-1Year (N=135)**	**1-2 Years (N=123)**	**2-3 Years (N=111)**	**3-4 Years (N=47)**
Neutropenia	11 (8)	4 (3)	1 (1)	0
Pneumonia	7 (5)	3 (2)	4 (4)	0
Infections	**23 (17)**	**9 (7)**	**10 (9)**	**0**
Bleeding	4 (3)	4 (3)	1 (1)	0
Atrial Fibrillation	**2 (1)**	**0**	**4 (4)**	**0**
Hypertension	6 (4)	2 (2)	0	0
Thrombocytopenia	3 (2)	2 (2)	0	1 (2)
Diarrhea	5 (4)	0	1 (1)	0

*> 5 % of patients

Tedeschhi et al. Blood 2015 126:495

Long Term AE with Ibrutinib **(Warning and Precautions)**

- **Hemorrhage:**
  - **Major bleeding** in up to **6%** of patients, **minor up to 50%**
  - **At risk: use of antiplatelet or anticoagulant therapies**
  - Consider the benefit-risk of withholding Ibrutinib for at least 3 to 7 days pre- and postsurgery depending upon the type of surgery and the risk of bleeding.
- **Infections** - 14% to 29% of patients.
- **Cytopenias** (Grades 3 or 4)
  - neutropenia (range, 13% to 29%),
  - thrombocytopenia (range, 5% to 17%),

https://www.imbruvica.com/prescribing-information

Long Term AE with Ibrutinib (Warning and Precautions)

- **Hypertension**
  - Hypertension (range, 6% to 17%), median time to onset of 4.6 months (range, 0.03 to 22 months).
- **Atrial Fibrillation**
  - Atrial fibrillation and atrial flutter (range, 6% to 9%)
  - **Pts at risk: hypertension, acute infections, and a previous history of atrial fibrillation**.

https://www.imbruvica.com/prescribing-information

Cross-Trial

Ibrutinib vs Chemotherapy

Robak et al. Blood 2017 130:1750

Cross-Trial

IBRUTINIB

RESONATE-2

IMMUNO-CHEMOTHERAPY

Phase III Trials
(Fit and Unfit)

FCR – CLL8
FCR – CLL10
BR- CLL10
G-Clb – CLL11
R-Cbl – CLL11
Ofa-Clb – COMPLEMENT1

Robak et al. Blood 2017 130:1750

Cross-Trial: Population

Unfit: *
Fit: *

Population	RESONATE-2 Ibrutinib N=136 *	CLL10 BR N=279 *	CLL10 FCR N=282 *	CLL8 FCR N=408 *	CLL11 G-CLB N=333 *	CLL11 R-Clb N=330 *	COMPLEMENT-1 Ofa-Clb N= 221 *
Median age	73 (65-89)	61 (54-69)	62 (55-67)	61 (30-80)	74 (39-89)	73 (40-90)	69 (35-92)
Median CIRS	5	2	2	1	8	8	9
Unmutated IGHV	43%	68%	55%	63%	62%	61%	57%
Del(17p)	Excluded	Excluded	Excluded	7%	7%	7%	5%

Robak et al. Blood 2017 130:1750

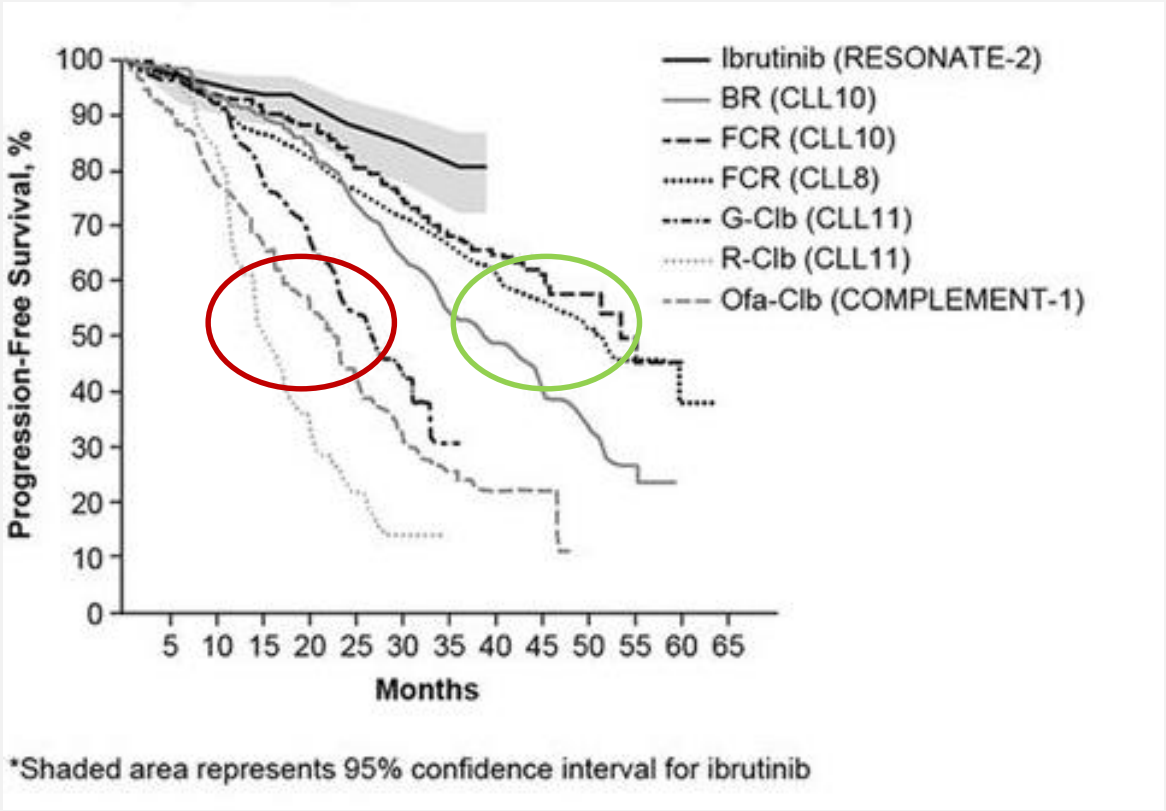
Cross-Trial: Safety

Population	RESONATE-2 Ibrutinib N=136	CLL8 FCR N=408	CLL10 BR N=279	CLL10 FCR N=282	CLL11 G-CLB N=333	CLL11 R-Clb N=330	COMPLEMENT-1 Ofa-Clb N= 221
Overall Grade≥3 AE	73%	76%	84%	94%	70%	55%	50%
Infection Grade≥3	**25%**	**25%**	**27%**	**40%**	**12%**	**14%**	**9%**
≤ 65 yrs			27%	36%			
> 65 yrs			25%	48%			
Anemia Grade≥3	9%	5%	10%	14%	4%	4%	5%
Neutropenia Grade≥3	12%	34%	59%	84%	33%	28%	26%
Thrombocytopenia Grade≥3	4%	7%	14%	22%	10%	3%	5%

*Median treatment duration was approximated using the median number and length of cycles; mean number of cycles reported for CLL8 FCR. **Grade 3-4 AEs reported for CLL8 FCR. †Data collected only for CLL10. ‡FCR N=193, BR N=171. §FCR N=86, BR N=107.

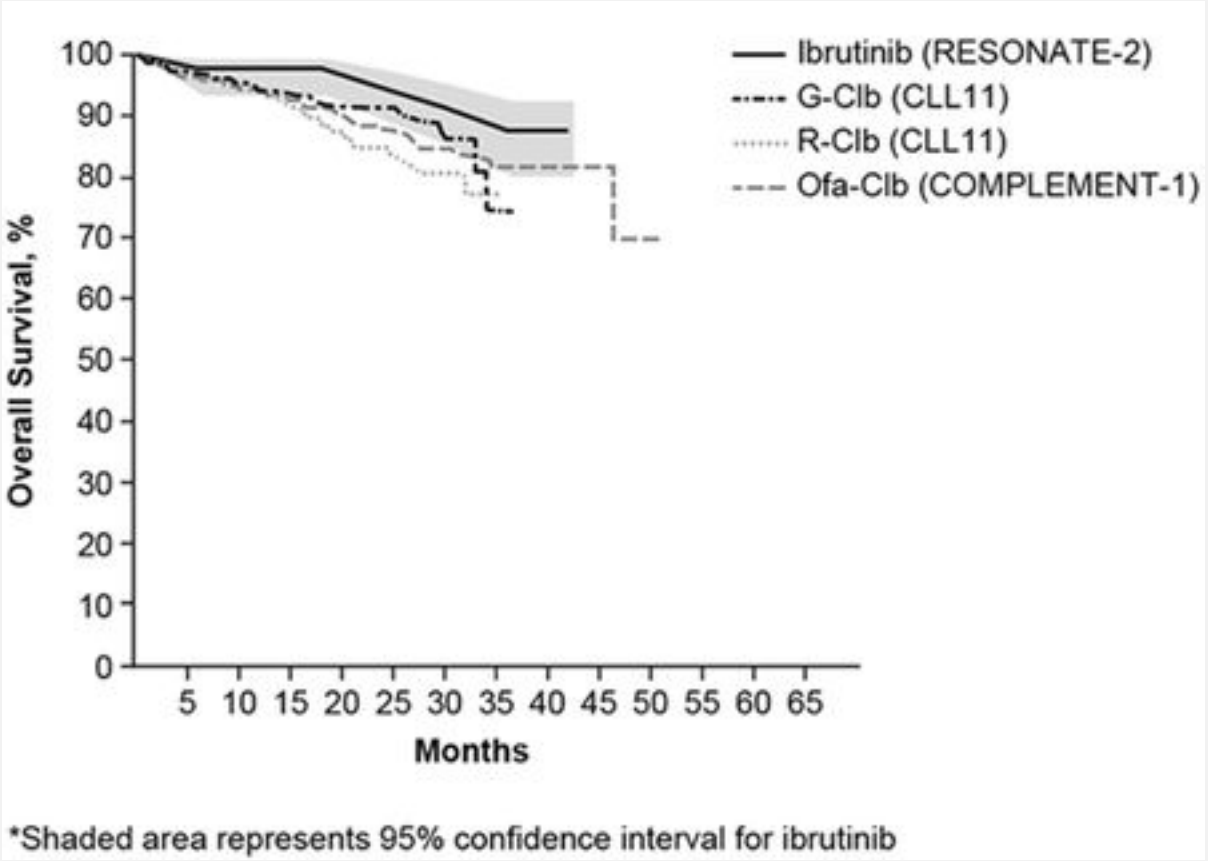
Robak et al. Blood 2017 130:1750

Cross-Trial: PFS



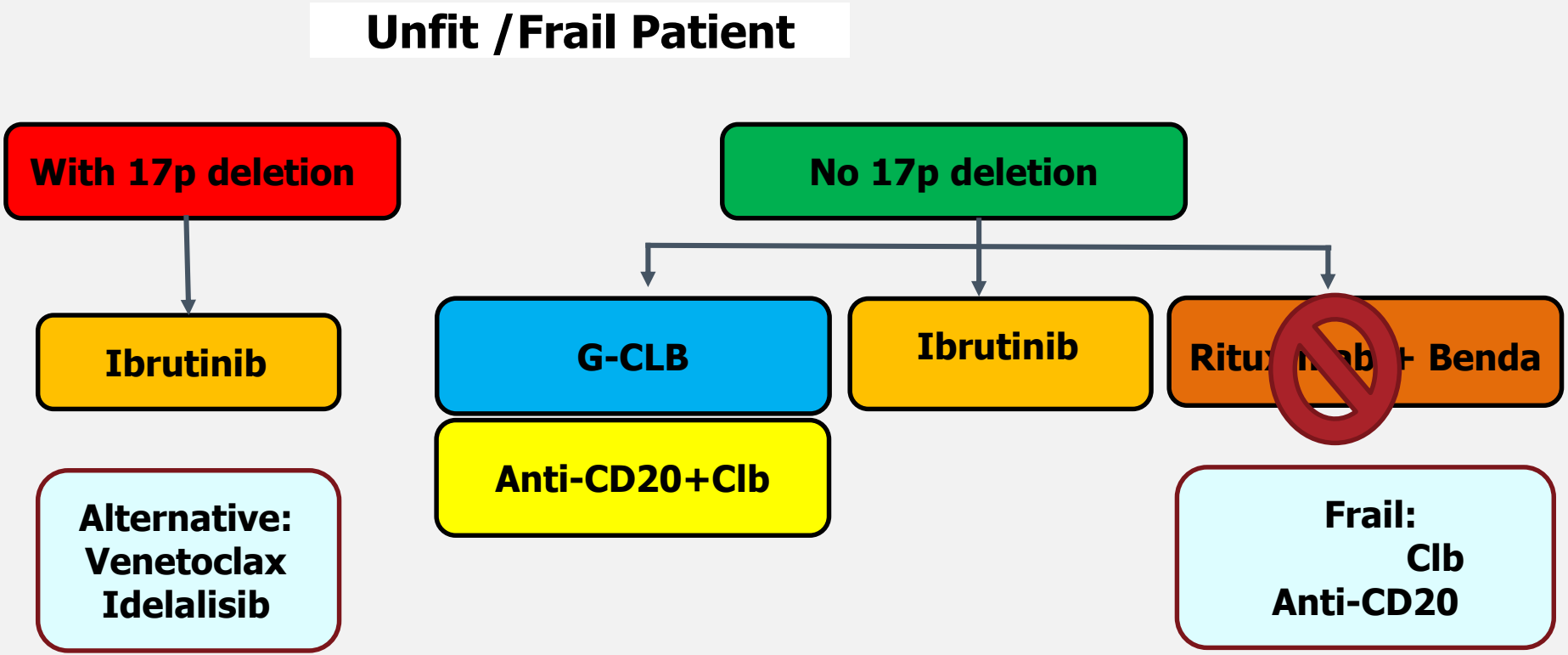
Robak et al. Blood 2017 130:1750

Cross-Trial: OS



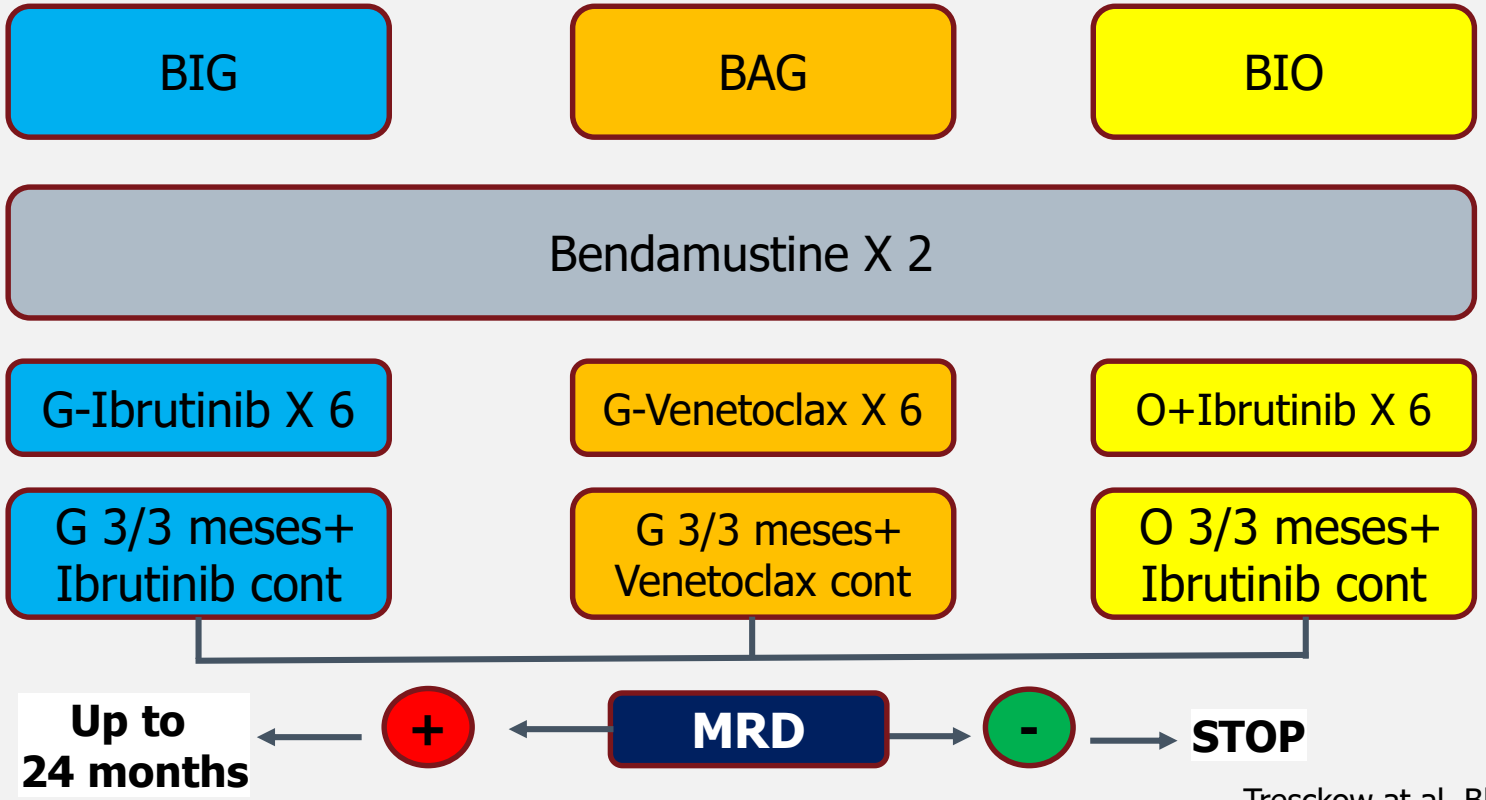
Robak et al. Blood 2017 130:1750

How to treat a 95 years old patient?



Adaptado de ESMO (http://www.esmo.org, acessed in Feb 2018;
NCCN (www.nccn.org, acessed in Feb 2018; Rev Bras Hematol Hemoter 2016;38:346-57

MRD based therapy



G: Obinutuzumab, **O**: Ofatumumab

Tresckow at al. Blood 2015 126:4151

Cramer et al. Blood 2016 128:2044

Cramer et al. Blood 2017 130:494

Conclusions

- Single continuous oral agents are effective and have low toxicity.
  - Problems: long term adverse events, high cost
- Chlb-obinutuzumab treatment: effective, many patients achieve MRD neg and stop treatment.
  - Problems: acute toxicity (IRR) and cytopenias
- Bendamustine is effective but associated with high rates of hematologic toxicity
- Phase III trials and long term follow up are necessary
- **Recognizing patient's fitness and disease status is mandatory before chosing the treatment**

Jain et al. Blood 2017 130:495
Stilgenbauer et al. Blood 2017 130:4309
Flinn et al. Blood 2017 130:430