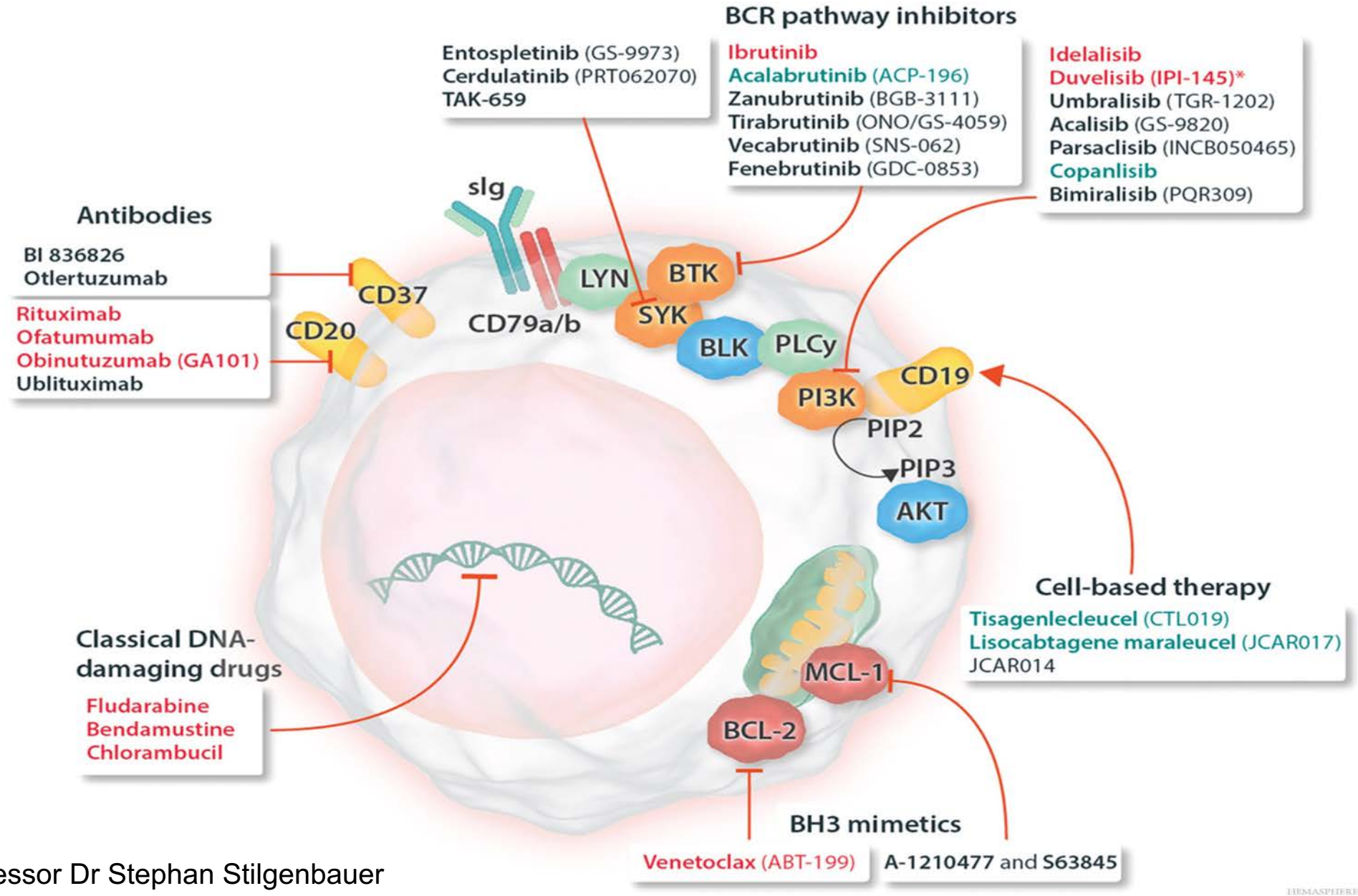
Upfront Management of CLL in Patients Who Are Older or Have Comorbidities

Stephan Stilgenbauer

From Biology to Therapy: New Treatment Options in CLL

Yosifov, Wolf, Stilgenbauer, Mertens. Hemashere (review) 2019



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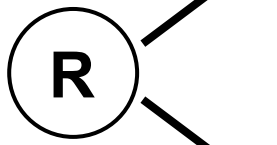
CLL14 Trial: untreated elderly/unfit CLL
Chlorambucil or Venetoclax + Obinutuzumab

Fischer et al. NEJM 2019

Untreated CLL
with "active disease"

<u>Median values of:</u>
Age 72 years
CIRS score 8
Creat. Clear. 66.4 ml/min



Chlorambucil + Obinutuzumab
(Clb + Obi), n=216

Venetoclax + Obinutuzumab
(Ven + Obi), n=216

- International phase-III trial, 196 centers, 21 countries
- Obinutuzumab: 1000 mg for six cycles in both arms
- Chlorambucil: 0.5 mg/kg, d 1+15, <u>12 cycles</u> of 28 days
- Venetoclax: ramp-up, then 400 mg/d, <u>12 cycles</u> of 28 days

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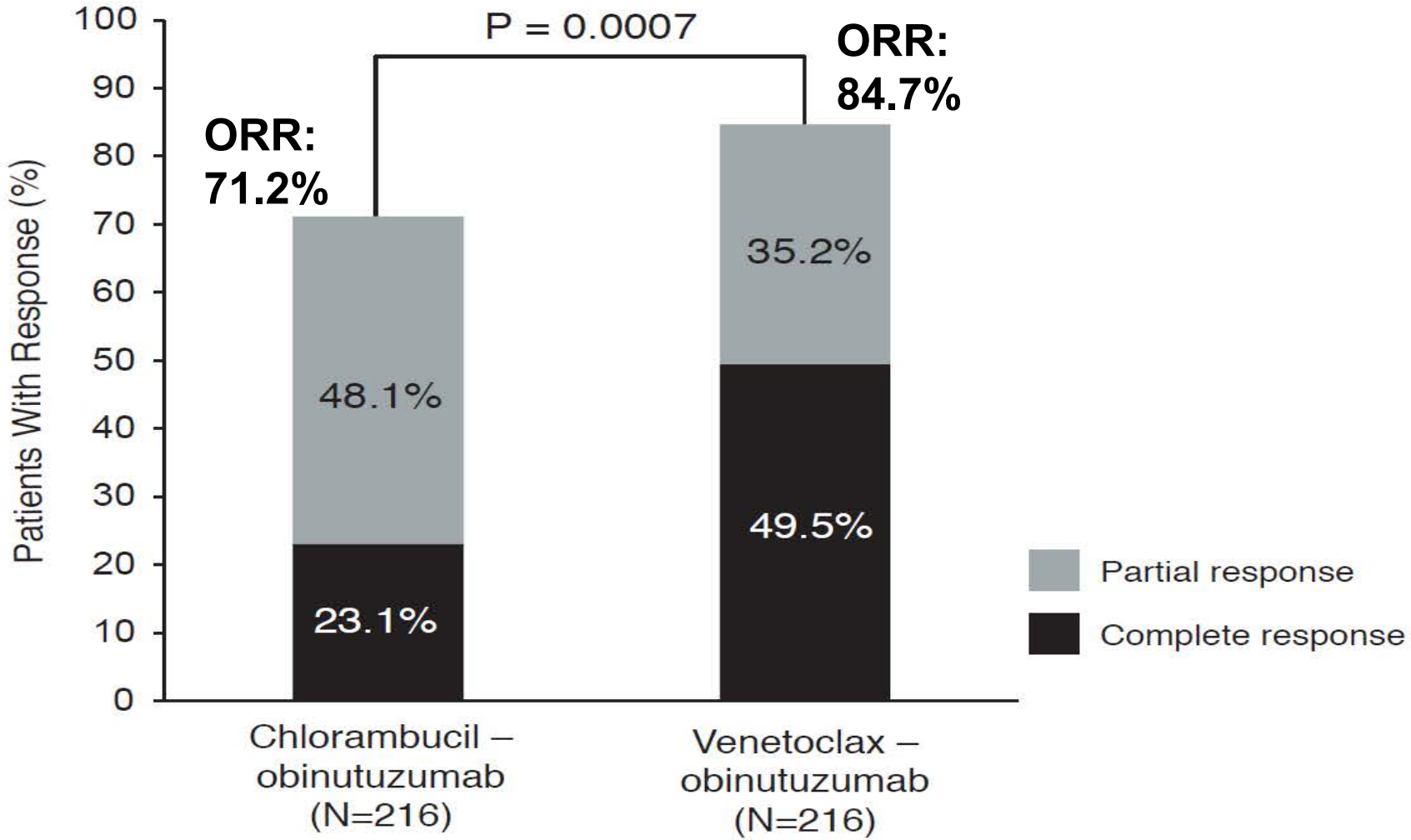
CLL14: untreated elderly/unfit CLL: Clinical Response

Fischer et al. NEJM 2019



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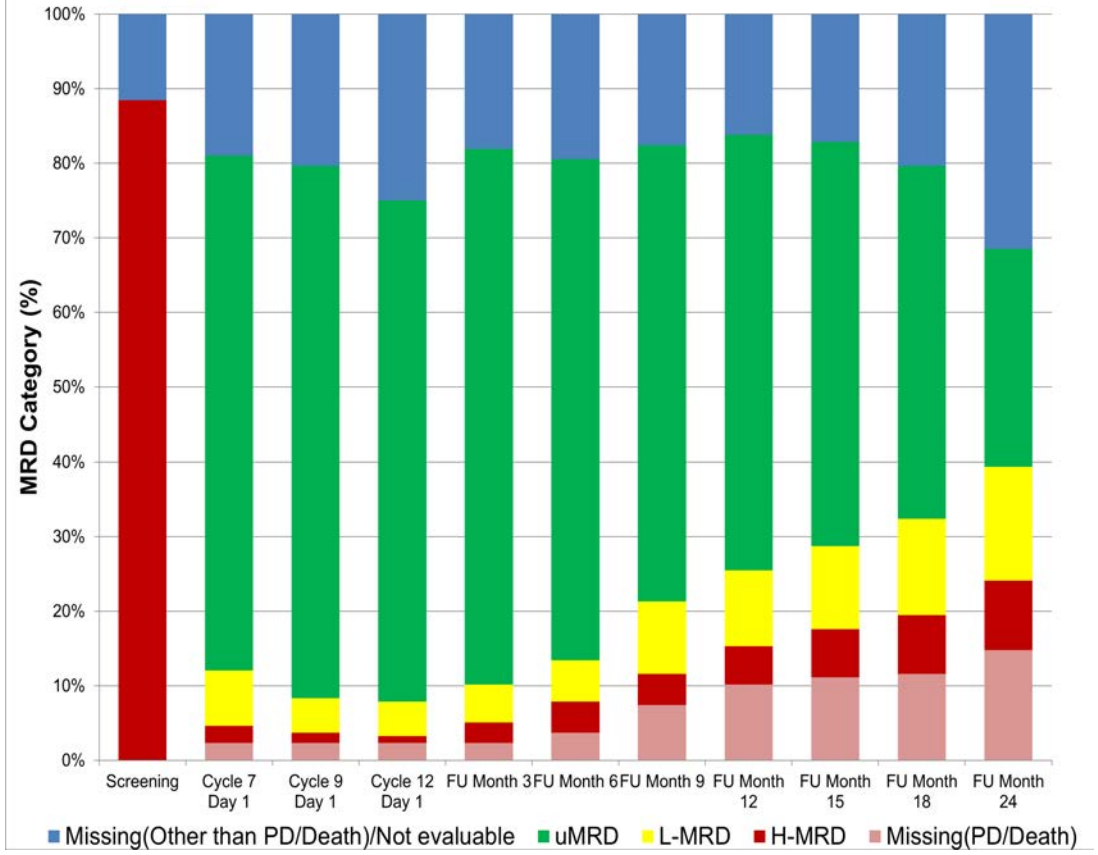
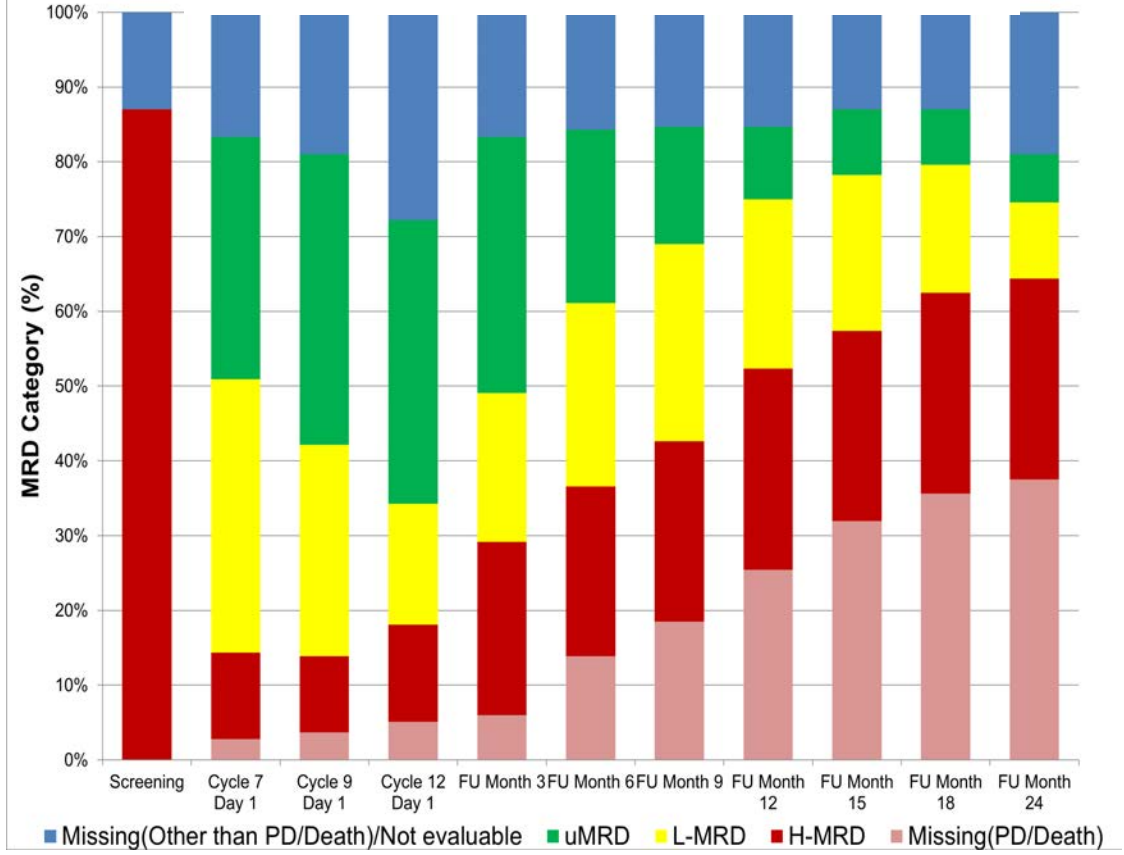
CLL14: untreated elderly/unfit CLL: MRD Response and Time Course

Fischer et al. NEJM 2019; Al-Sawaf et al. Lancet Onc 2020

Venetoclax + Obinutuzumab



Chlorambucil + Obinutuzumab



uMRD rate at 18month FU
Ven-Obi: 47.2%
Clb-Obi: 7.4%

uMRD $<10^{-4}$
L-MRD $10^{-4} < 10^{-2}$
H-MRD $\geq 10^{-2}$

Courtesy of Professor Dr Stephan Stilgenbauer

CLL14: untreated elderly/unfit CLL
Adverse Events

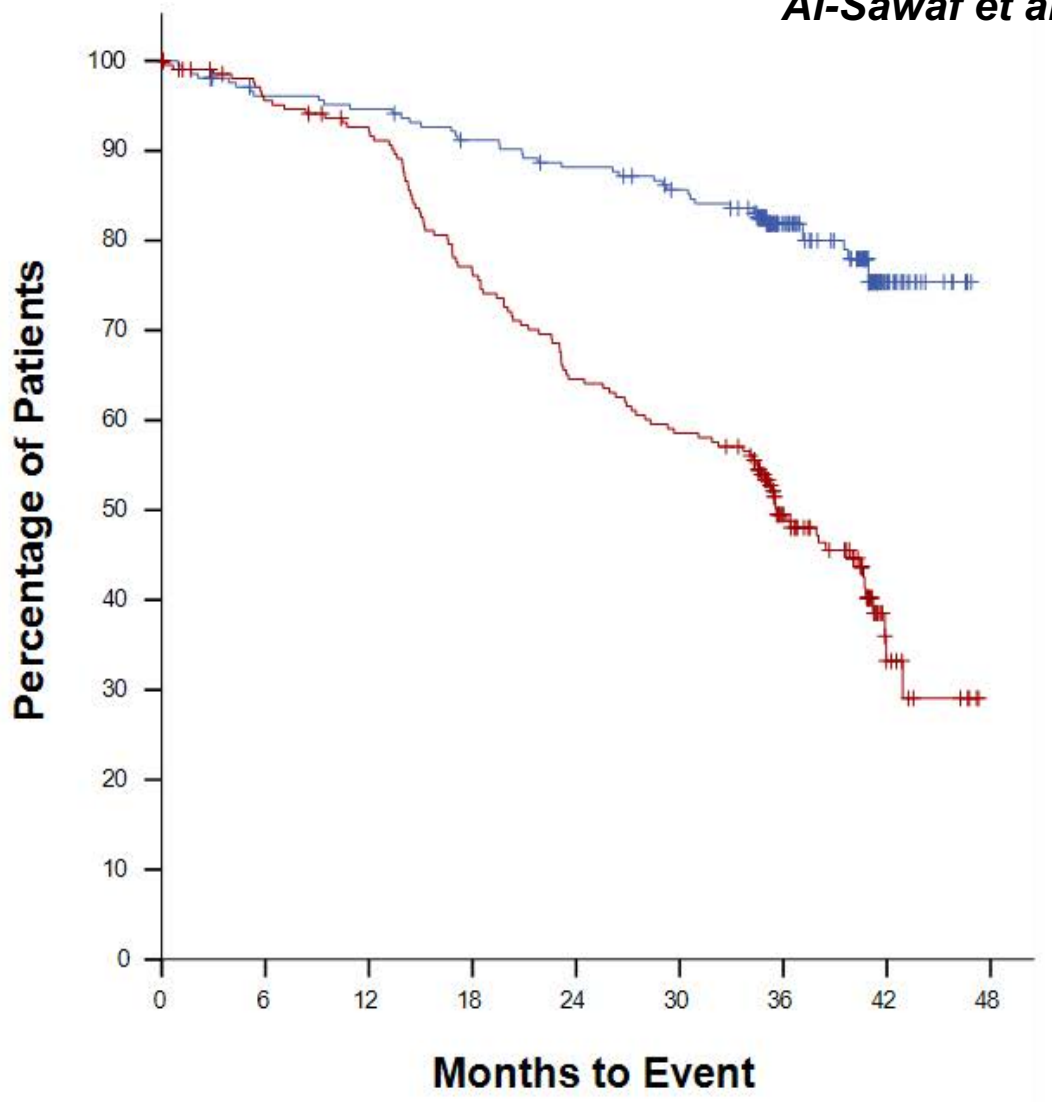
Fischer et al. NEJM 2019; Al-Sawaf et al. Lancet Onc 2020

	Venetoclax-obinutuzumab (N=212)		Chlorambucil-obinutuzumab (N=214)	
	During Treatment	**After Treatment**	**During Treatment**	**After Treatment**
Neutropenia	51.9%	4.0%	47.2%	1.9%
Thrombocytopenia	13.7%	0.5%	15.0%	0.0%
Anemia	7.5%	1.5%	6.1%	0.5%
Febrile neutropenia	4.2%	1.0%	3.3%	0.5%
Infusion-related reaction	9.0%	0.0%	9.8%	0.5%
Tumour lysis syndrome	1.4%	0.0%	3.3%	0.0%
Neoplasms	1.4%	6.4%	1.4%	1.9%

Courtesy of Professor Dr Stephan Stilgenbauer

CLL14: untreated elderly/unfit CLL
PFS by Treatment

Al-Sawaf et al. Lancet Onc 2020



Median PFS

Ven-Obi: not reached

Clb-Obi: 35.6 months

3-year PFS rate

Ven-Obi: 81.9%

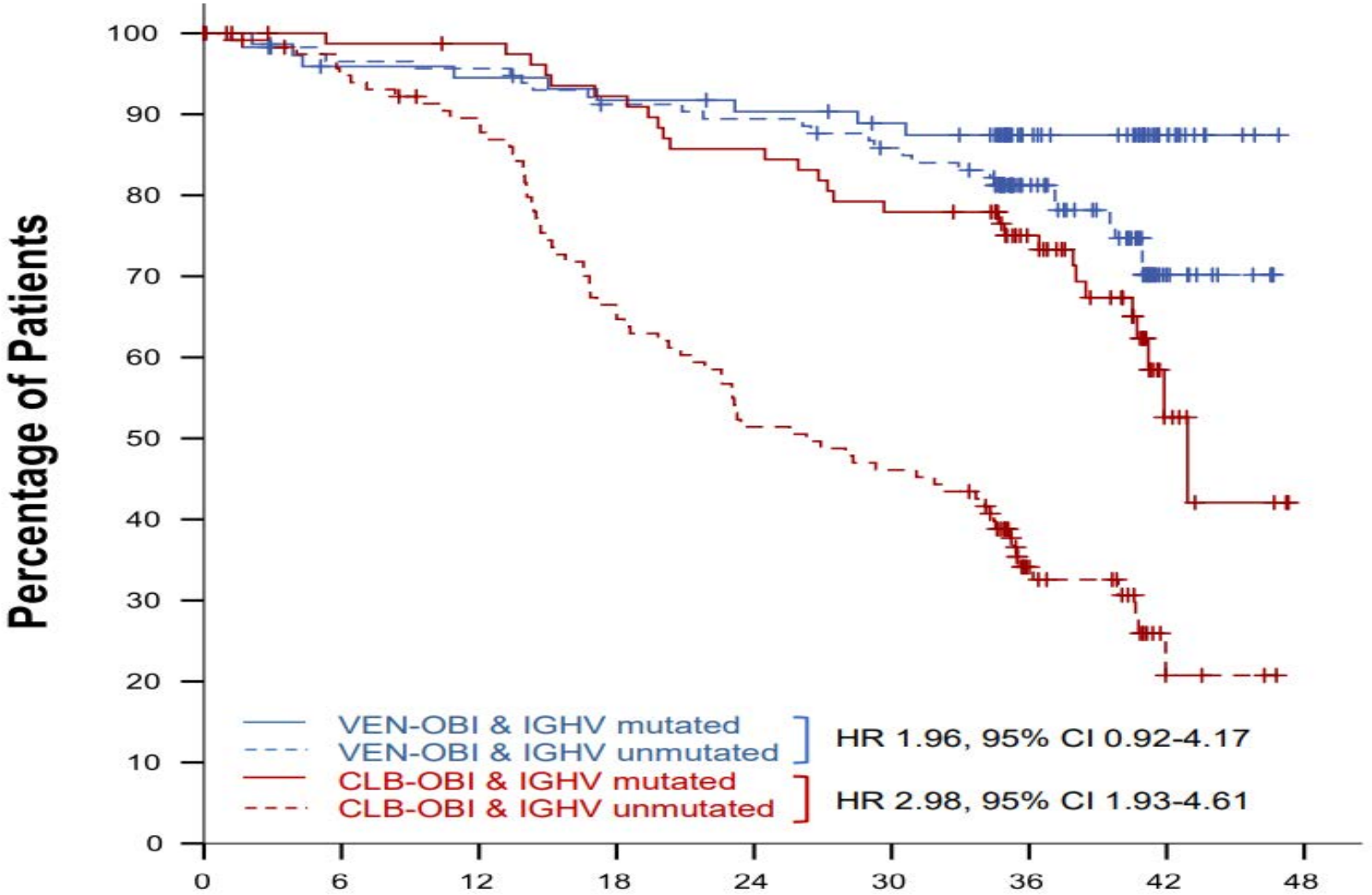
Clb-Obi:49.5%

HR 0.31, 95% CI [0.22-0.44], P<0.0001

Courtesy of Professor Dr Stephan Stilgenbauer

CLL14: untreated elderly/unfit CLL
PFS by IGHV and Treatment

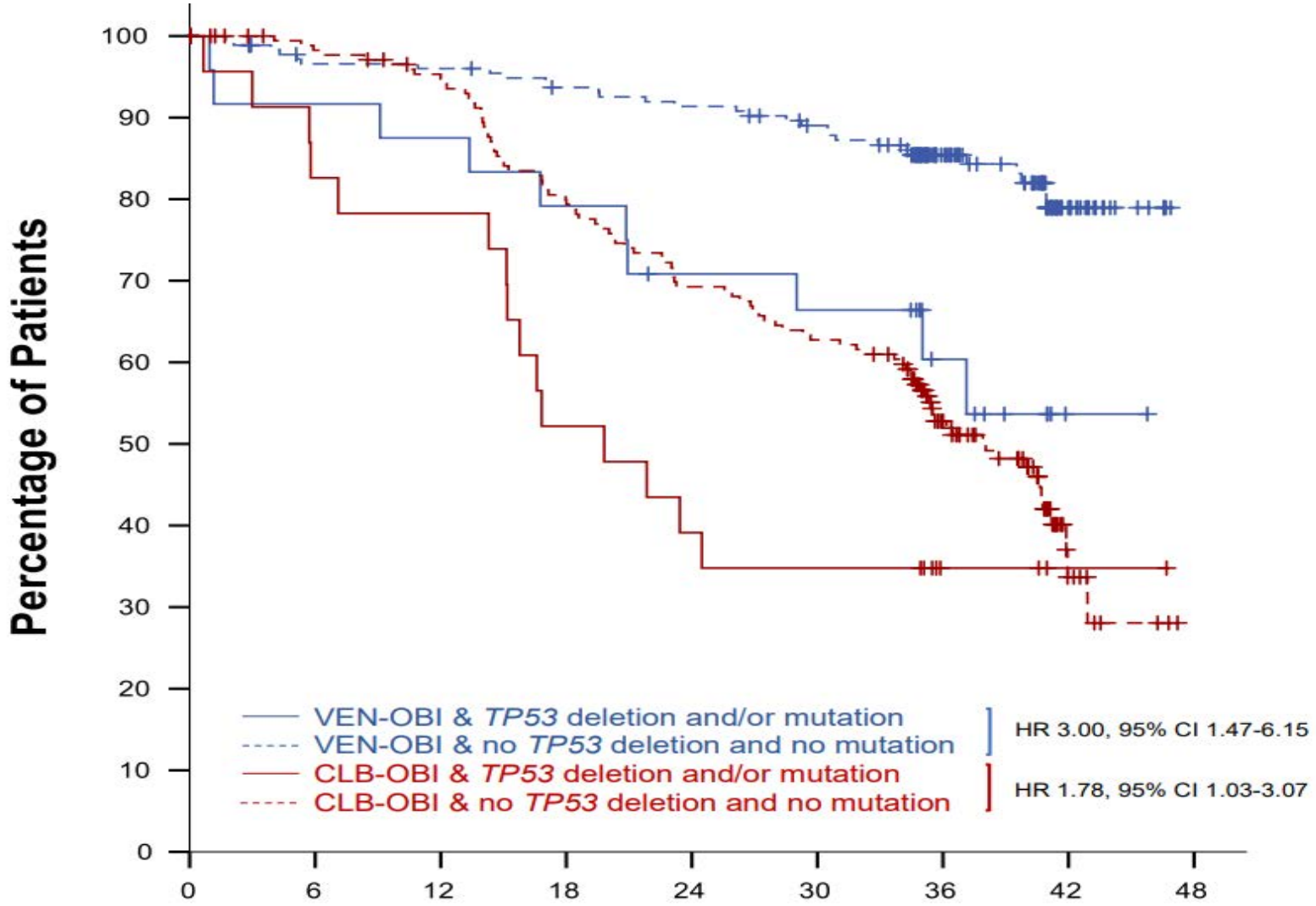
Tausch et al. Blood 2020; Al-Sawaf et al. Lancet Onc 2020



Courtesy of Professor Dr Stephan Stilgenbauer

CLL14: untreated elderly/unfit CLL
PFS by 17p- / *TP53* Mutation and Treatment

Tausch et al. Blood 2020; Al-Sawaf et al. Lancet Onc 2020



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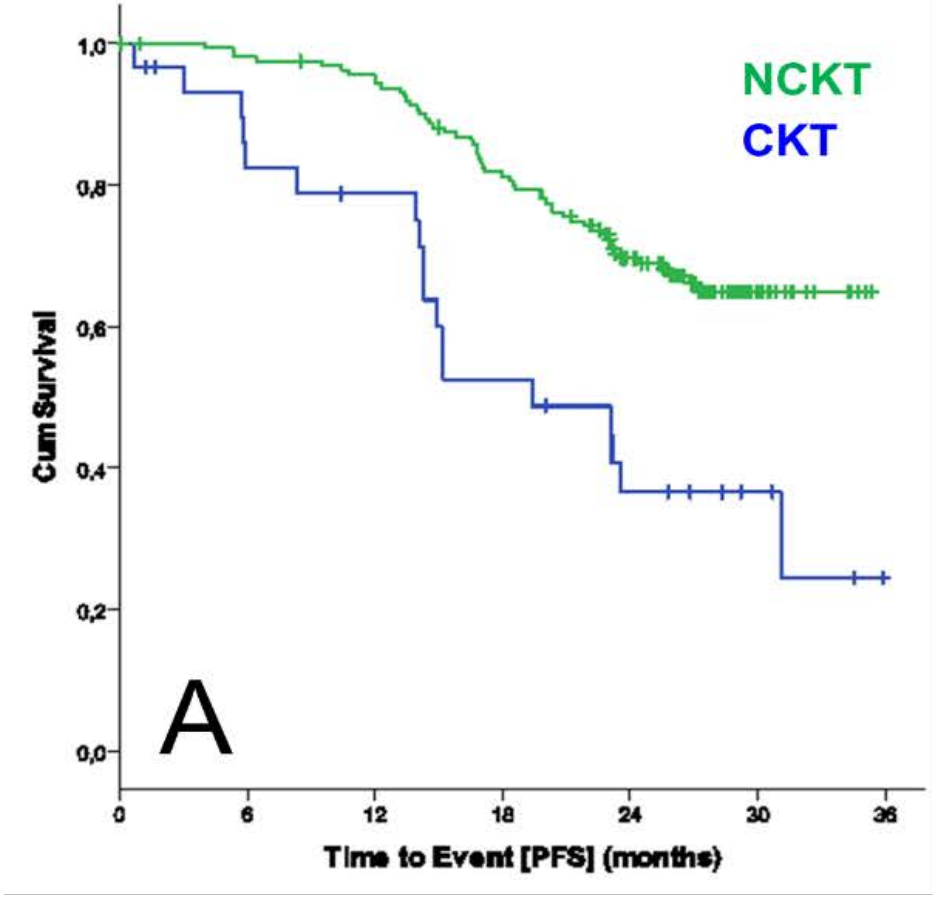
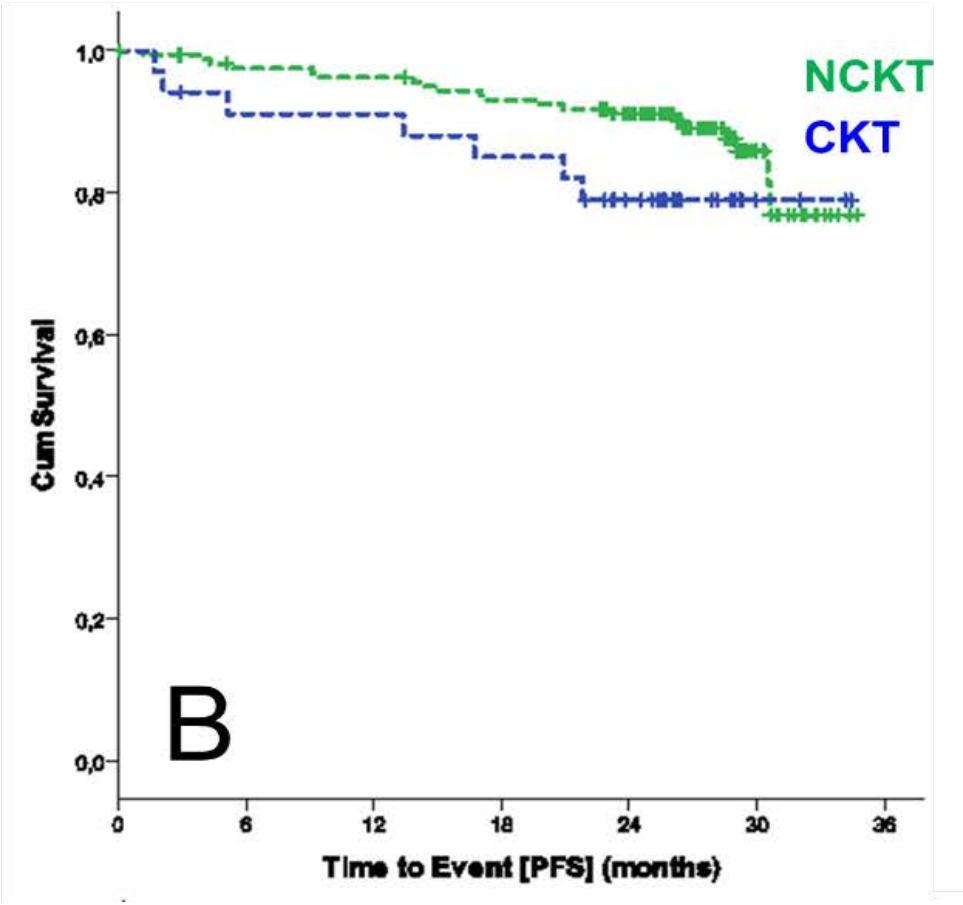
CLL14: untreated elderly/unfit CLL
PFS by Complex Karyotype and Treatment

Al-Sawaf et al. Blood 2020

Chlorambucil + Obinutuzumab



Venetoclax + Obinutuzumab



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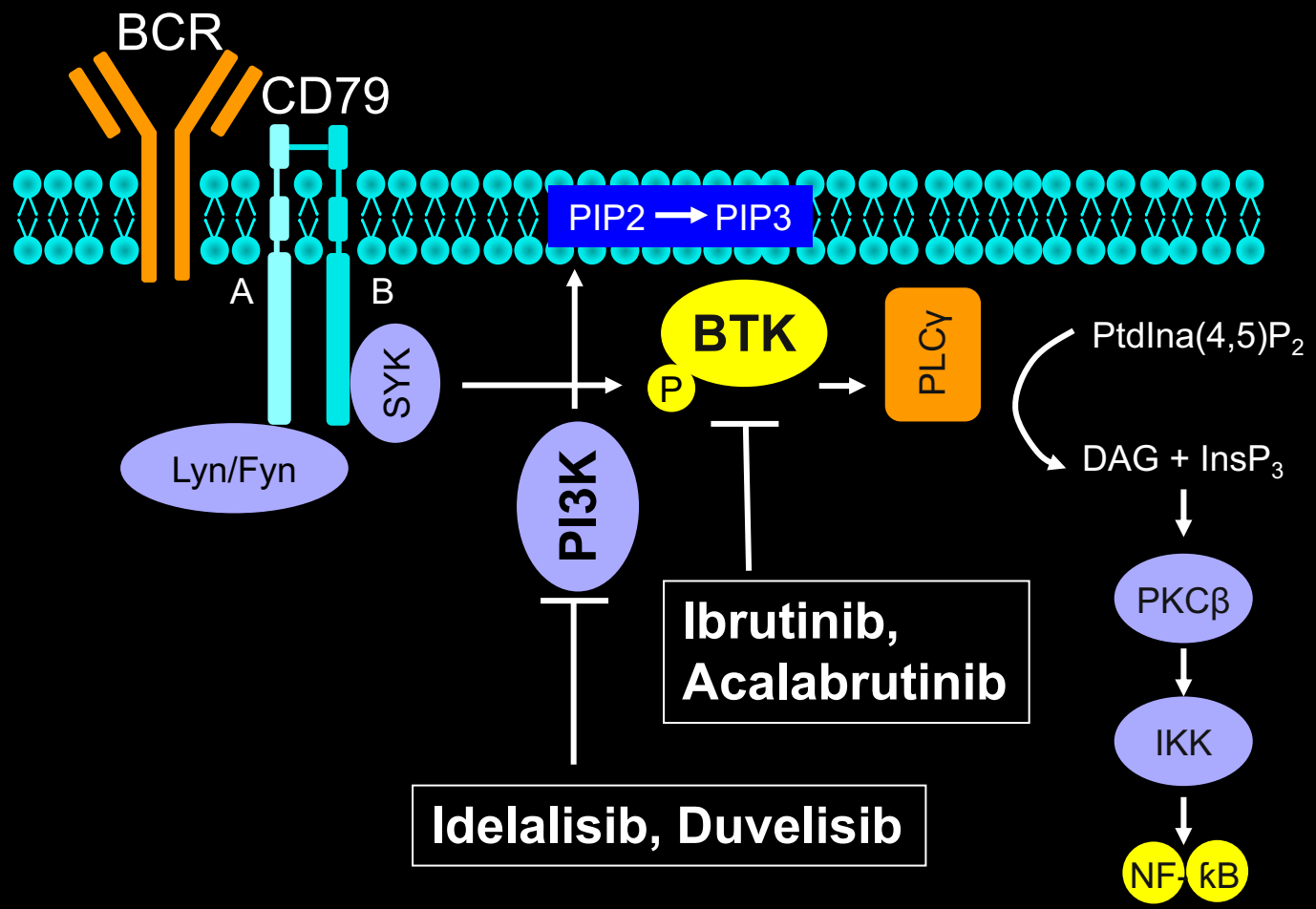
B-Cell Receptor Signaling Inhibition as Therapeutic Principle



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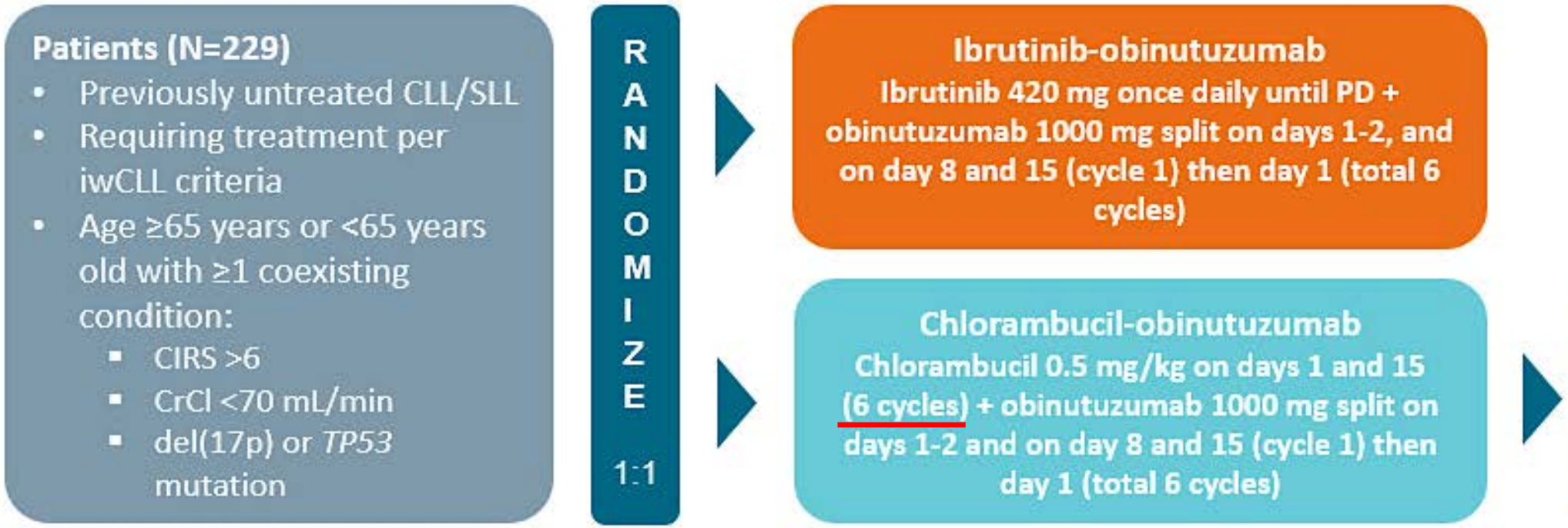
iLLUMINATE: untreated elderly/unfit CLL
Obinutuzumab plus Ibrutinib or Chlorambucil

Moreno et al. Lancet Oncol 2019



Stratification: del(17p) vs. del(11q) vs. neither del(17p) or del(11q); ECOG 2 vs 0-1

Cross over allowed upon PD

Primary end point

- PFS by IRC assessment

Secondary end points include

- PFS by IRC in high-risk population
- Rate of undetectable MRD
- ORR
- OS
- Infusion-related reactions
- Safety

Courtesy of Professor Dr Stephan Stilgenbauer

iLLUMINATE: untreated elderly/unfit CLL
Adverse Events

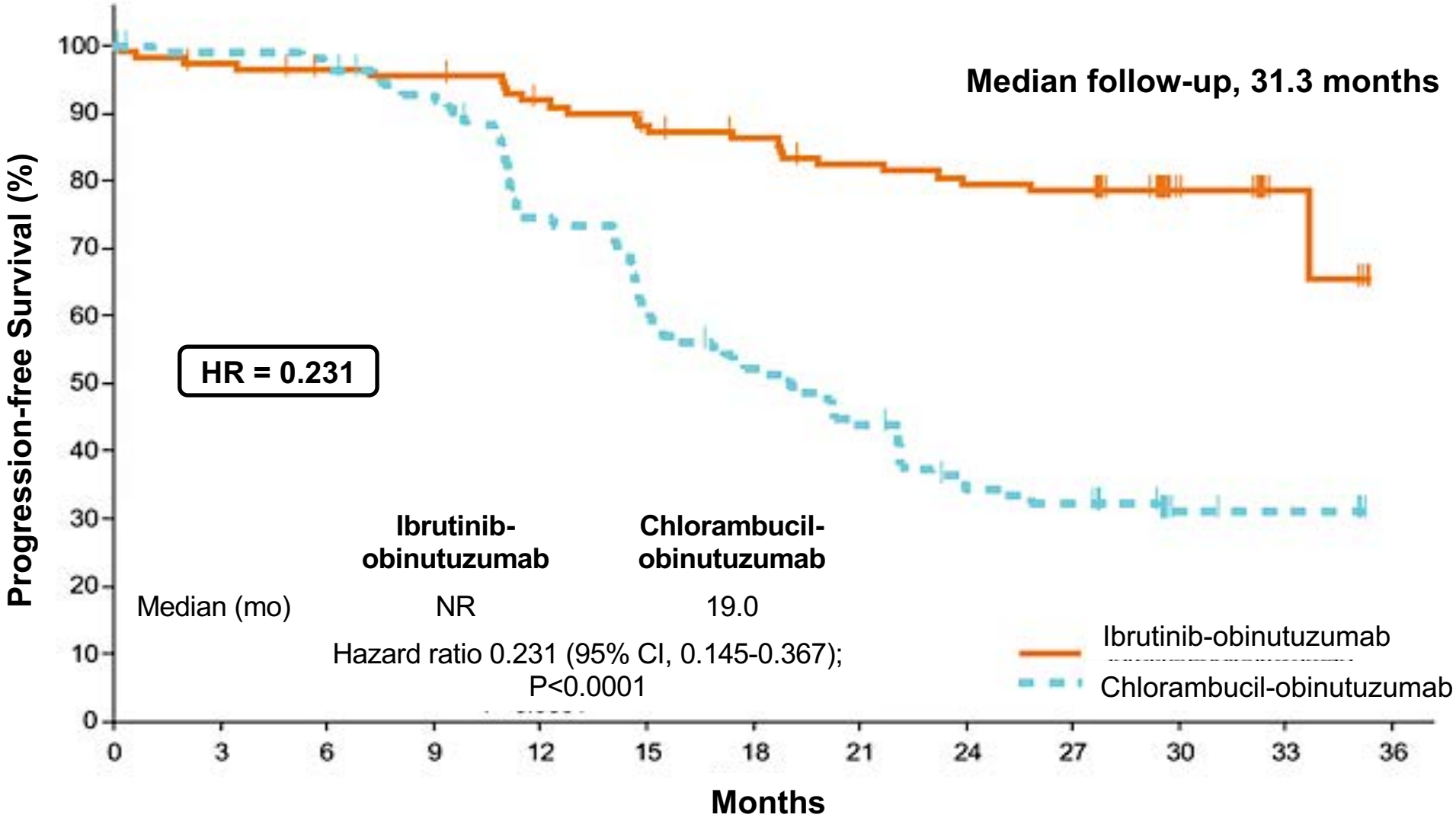
Moreno et al. Lancet Oncol 2019

	Ibrutinib-obinutuzumab N=113		Chlorambucil-obinutuzumab N=115	
	First 6 months	AE period[b]	First 6 months	AE period[b]
Median duration of treatment, months (range)	—	29.3 (0.10–36.6)	—	5.1 (0.03–6.7)
Most common grade ≥3 AEs[a]				
Any	54 %	77 %	71 %	72 %
Neutropenia	28 %	36 %	46 %	46 %
Thrombocytopenia	18 %	19 %	10 %	10 %
Pneumonia	4 %	7 %	3 %	4 %
Atrial fibrillation	3 %	5 %	0 %	0 %
Febrile neutropenia	3 %	4 %	6 %	6 %
Anemia	3 %	4 %	8 %	8 %
Hypertension	1 %	4 %	3 %	3 %
Neutrophil count decreased	3 %	4 %	0 %	0 %
Infusion-related reaction	2 %	2 %	8 %	8 %

Courtesy of Professor Dr Stephan Stilgenbauer

iLLUMINATE: untreated elderly/unfit CLL
Primary Endpoint: PFS

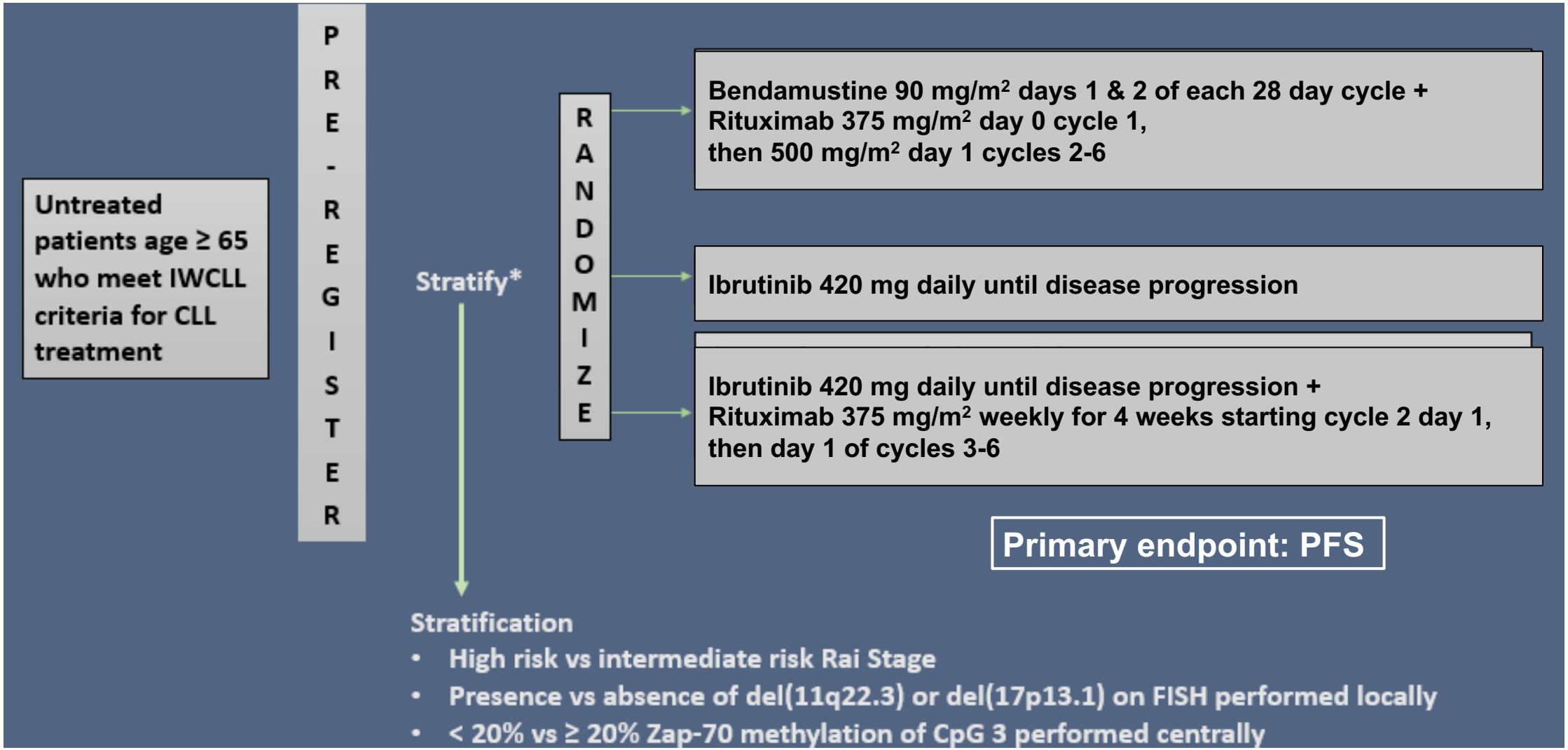
Moreno et al. Lancet Oncol 2019



Courtesy of Professor Dr Stephan Stilgenbauer

ALLIANCE A041202: untreated older CLL Patients Ibrutinib +/- Rituximab compared with BR

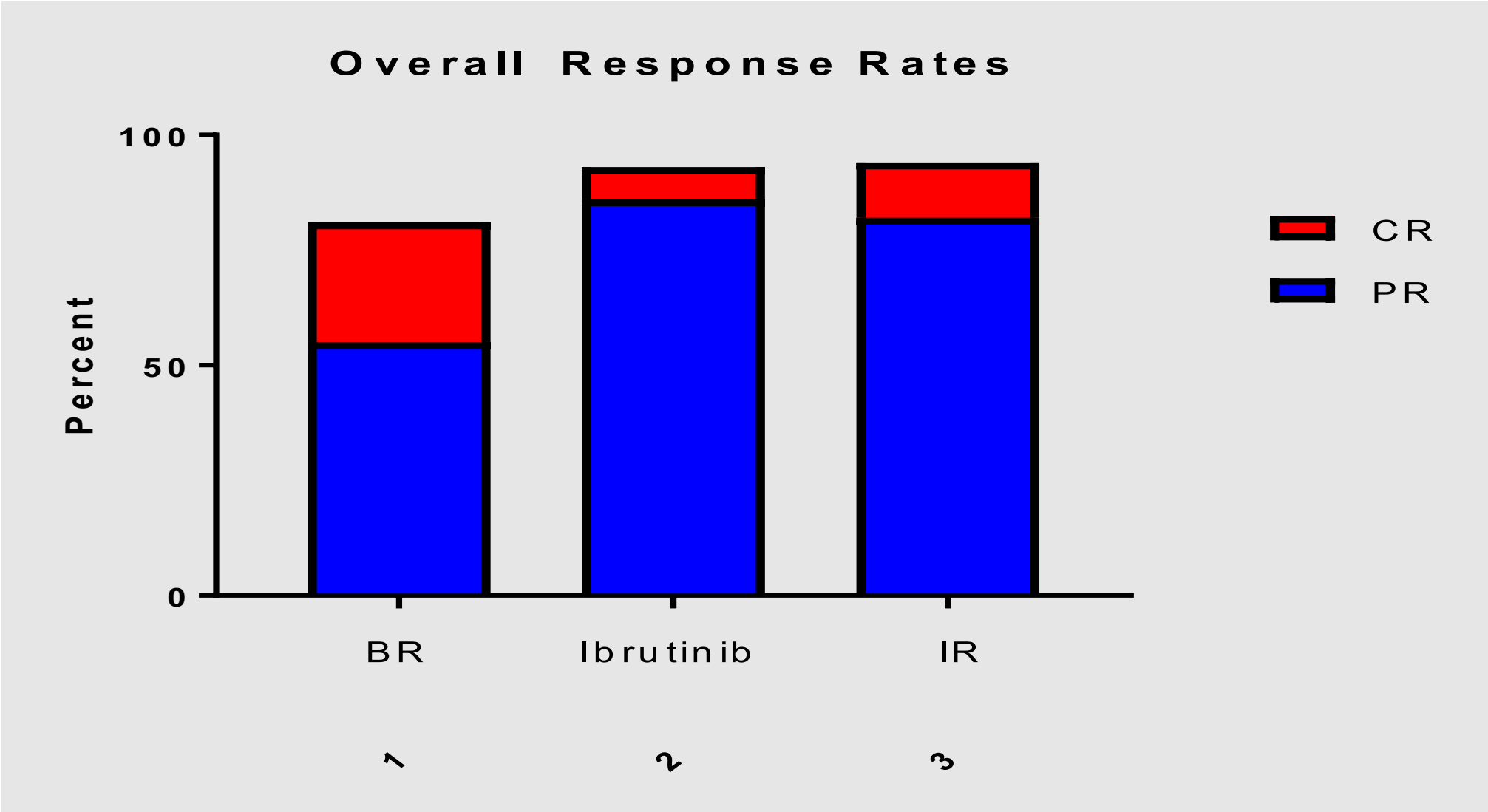
Woyach et al. N Engl J Med 2018



Courtesy of Professor Dr Stephan Stilgenbauer

ALLIANCE A041202: untreated older CLL Patients Response

Woyach et al. N Engl J Med 2018



Courtesy of Professor Dr Stephan Stilgenbauer

ALLIANCE A041202: untreated older CLL Patients Adverse Events

Woyach et al. N Engl J Med 2018

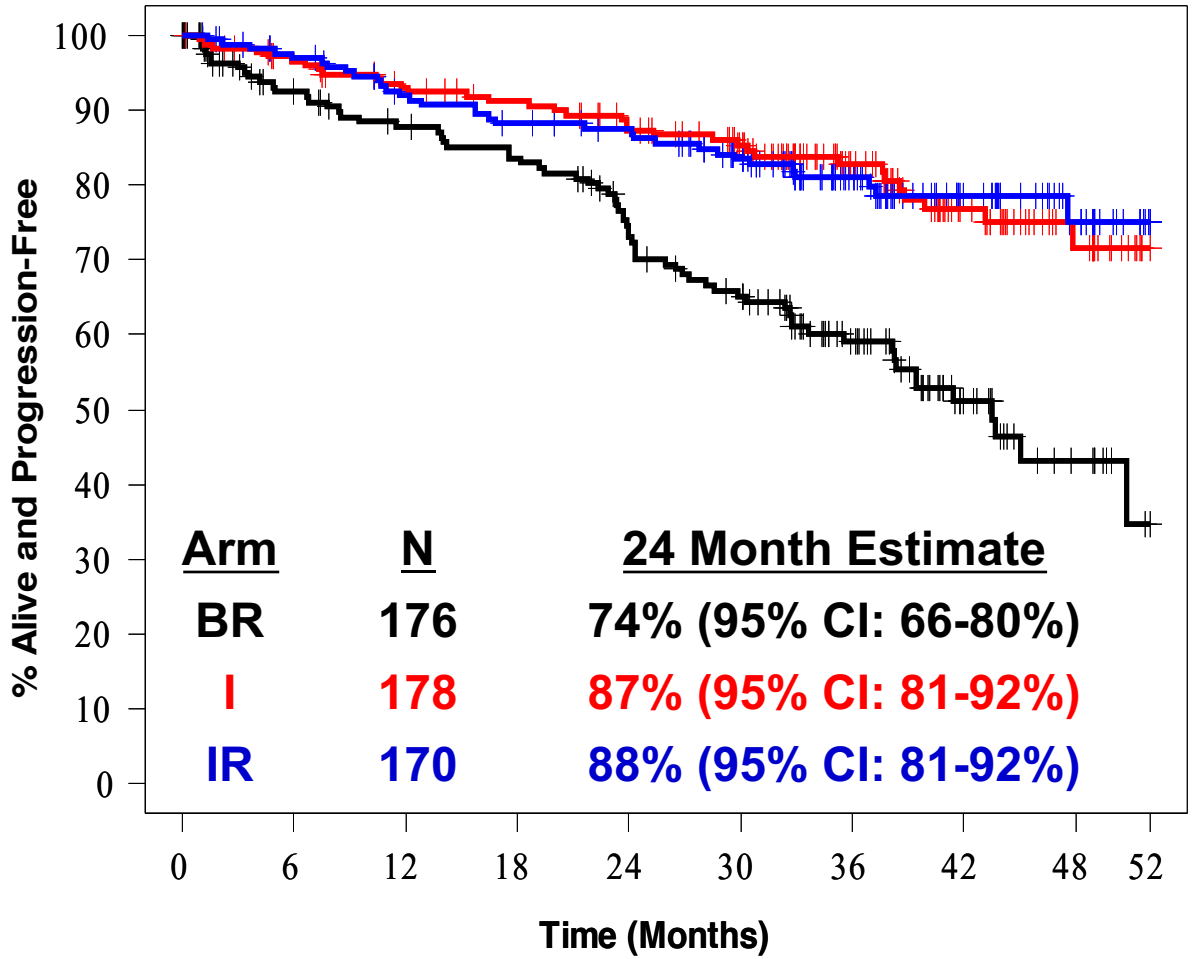
Grade 3- 5 adverse events during treatment + 30 days, excl. crossover (Median time on treatment: BR 6 months, I and IR: 32 months)

Adverse event	BR (n=176)	Ibrutinib (n=180)	IR (n=181)	P-value
Hematologic, no (%)	**107 (61)**	**74 (41)**	**70 (38)**	**<0.001**
Anemia	22 (13)	21 (12)	11 (6)	0.09
Neutropenia	71 (40)	27 (15)	39 (22)	<0.001
Thrombocytopenia	26 (15)	12 (7)	9 (5)	0.08
Non-hematol., no (%)	**111 (63)**	**133 (74)**	**134 (74)**	**0.04**
Bleeding	0	3 (2)	5 (3)	0.46
Infections	26 (15)	37 (21)	37 (20)	0.62
Febrile neutropenia	13 (7)	3 (2)	1 (1)	<0.001
Atrial fibrillation	5 (3)	17 (9)	10 (6)	0.05
Hypertension	25 (14)	53 (29)	61 (34)	<0.001

Courtesy of Professor Dr Stephan Stilgenbauer

ALLIANCE A041202: untreated older CLL Patients
Primary Endpoint: PFS

Woyach et al. N Engl J Med 2018



Pairwise comparisons

I vs BR
HR: 0.39 (95% CI: 0.26-0.58)
(1-sided p value <0.001)

IR vs BR
HR: 0.38 (95% CI: 0.25-0.59)
(1-sided p value <0.001)

IR vs I
HR: 1.00 (95% CI: 0.62-1.62)
(1-sided p value 0.49)

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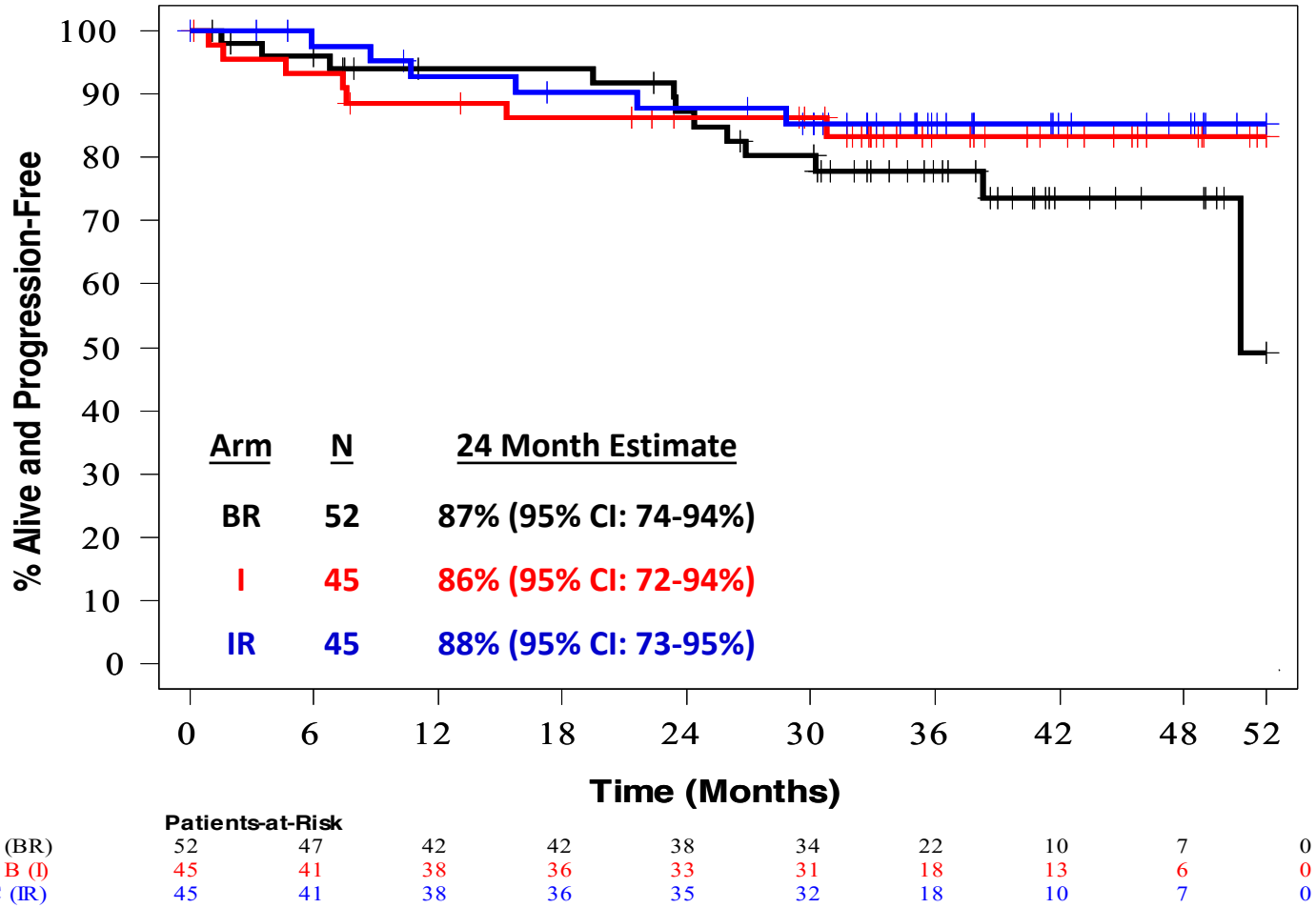
ALLIANCE A041202: untreated older CLL Patients
Primary Endpoint: PFS

Woyach et al. N Engl J Med 2018

IGHV Mutated Subgroup



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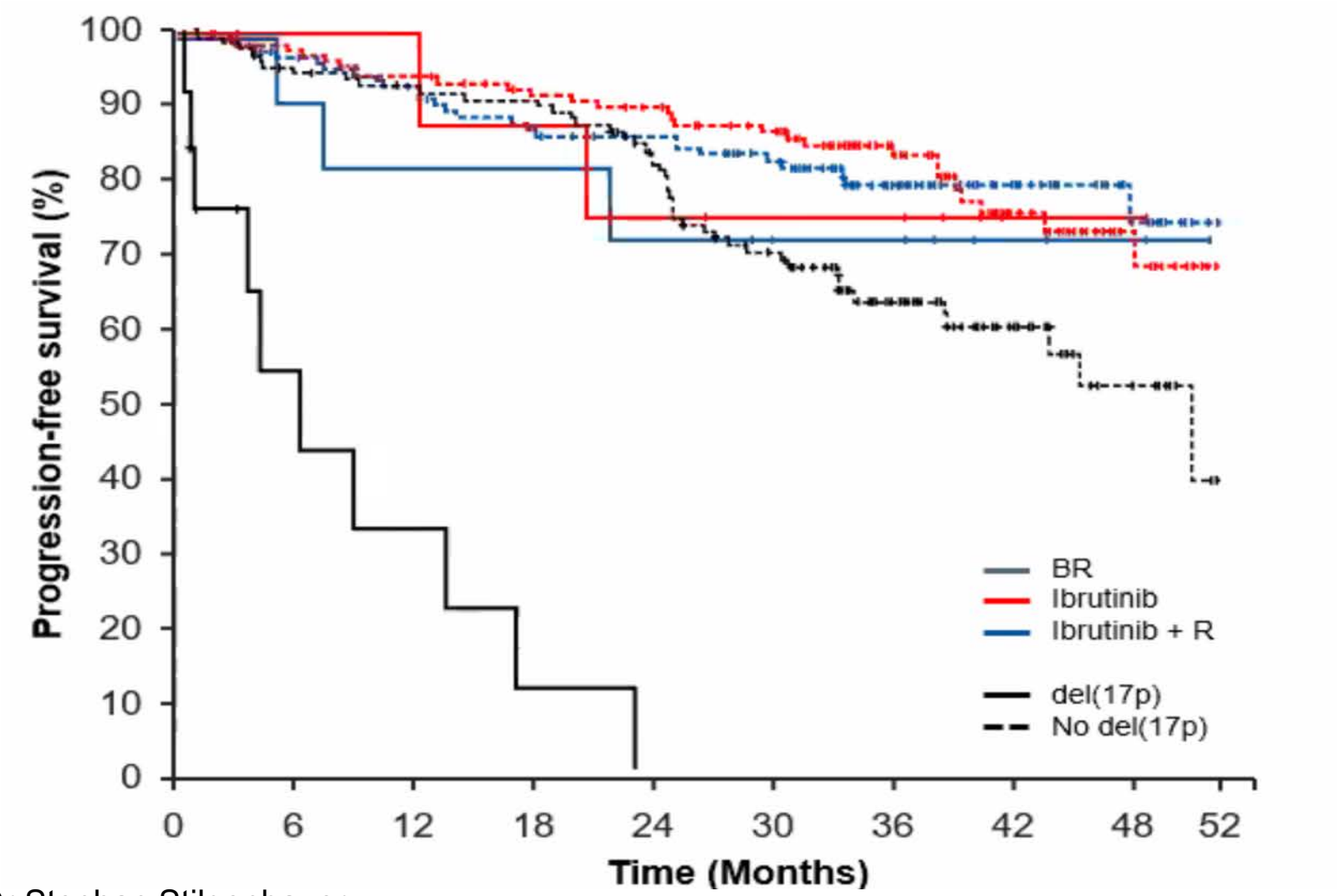
ALLIANCE A041202: untreated older CLL Patients
Primary Endpoint: PFS

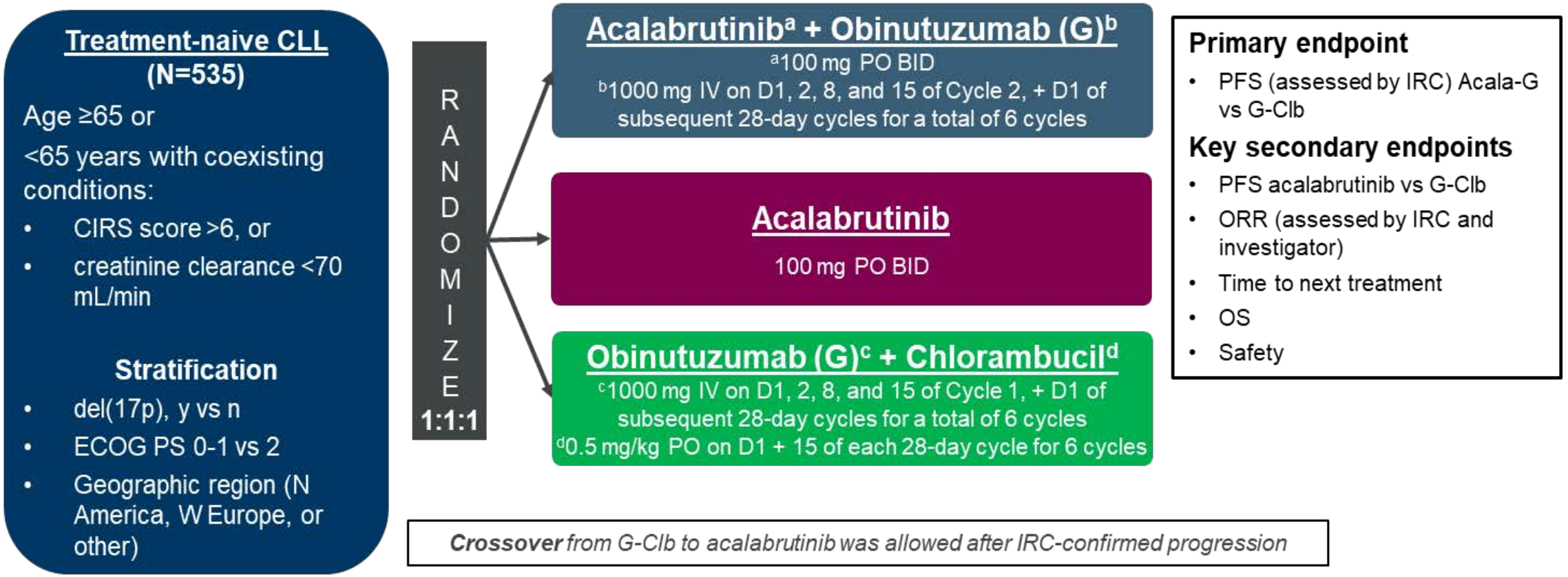
Woyach et al. N Engl J Med 2018, ASH 2018



Courtesy of Professor Dr Stephan Stilgenbauer

ELEVATE-TN: untreated older CLL Patients Acalabrutinib +/- Obinutuzumab compared with Obinutuzumab+Chlorambucil

Sharman et al. Lancet 2020



Courtesy of Professor Dr Stephan Stilgenbauer

ELEVATE-TN: untreated older CLL Patients Acalabrutinib +/- Obinutuzumab compared with Obinutuzumab+Chlorambucil

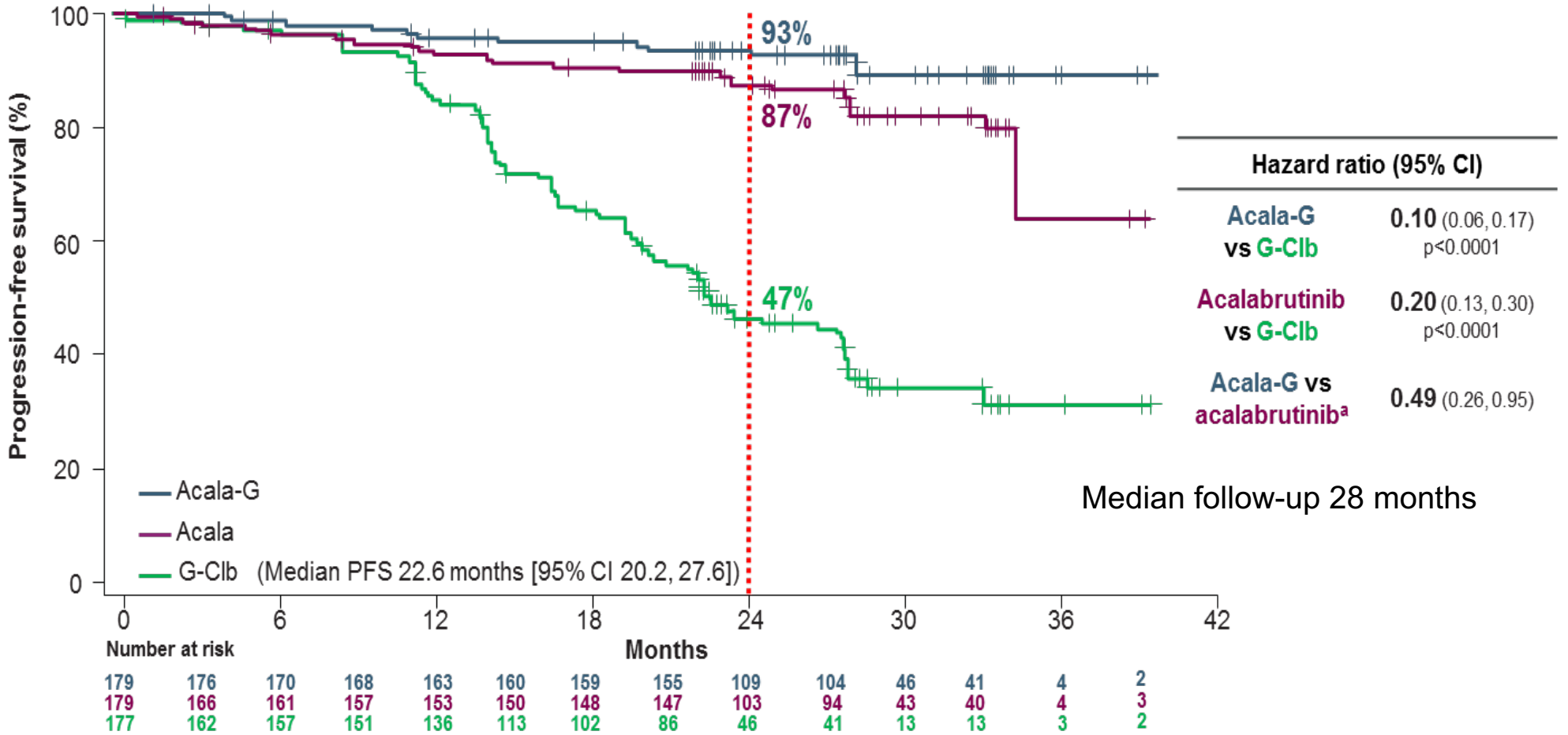
Sharman et al. Lancet 2020

AEs, n (%)	Acala-G N=178		Acalabrutinb N=179		G-Clb N=169	
	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
Headache	71 (39.9)	2 (1.1)	66 (36.9)	2 (1.1)	20 (11.8)	0
Diarrhea	69 (38.8)	8 (4.5)	62 (34.6)	1 (0.6)	36 (21.3)	3 (1.8)
Neutropenia	56 (31.5)	53 (29.8)	19 (10.6)	17 (9.5)	76 (45.0)	70 (41.4)
Fatigue	50 (28.1)	3 (1.7)	33 (18.4)	2 (1.1)	29 (17.2)	1 (0.6)
Contusion	42 (23.6)	0	27 (15.1)	0	7 (4.1)	7 (4.1)
Arthralgia	39 (21.9)	2 (1.1)	28 (15.6)	1 (0.6)	8 (4.7)	2 (1.2)
Cough	39 (21.9)	0	33 (18.4)	1 (0.6)	15 (8.9)	0
URTI	38 (21.3)	4 (2.2)	33 (18.4)	0	14 (8.3)	1 (0.6)
Nausea	36 (20.2)	0	40 (22.3)	0	53 (31.4)	0
Dizziness	32 (18.0)	0	21 (11.7)	0	10 (5.9)	0
IRR	24 (13.5)	4 (2.2)	0	0	67 (39.6)	9 (5.3)
Pyrexia	23 (12.9)	0	12 (6.7)	1 (0.6)	35 (20.7)	1 (0.6)

Courtesy of Professor Dr Stephan Stilgenbauer

ELEVATE-TN: untreated older CLL Patients Acalabrutinib +/- Obinutuzumab compared with Obinutuzumab+Chlorambucil

Sharman et al. Lancet 2020



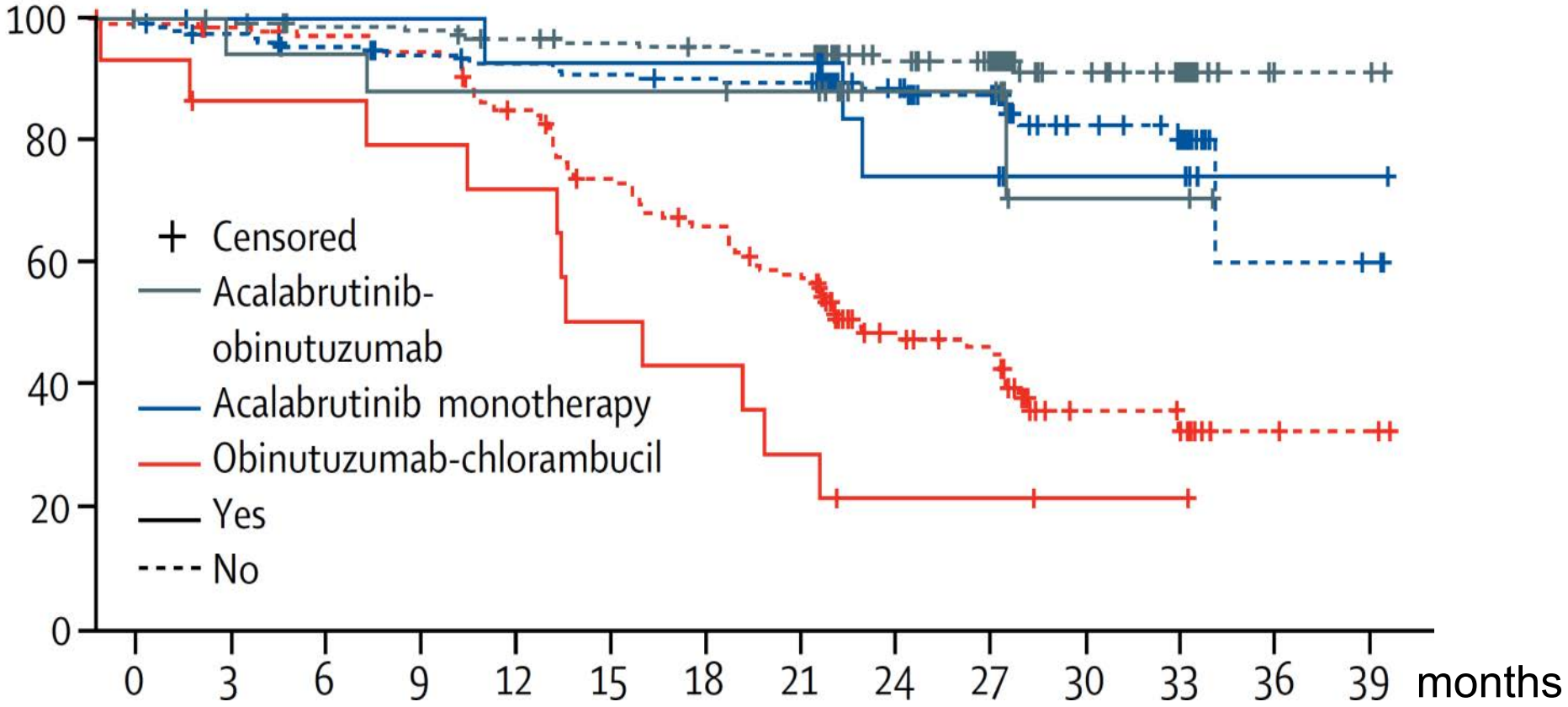
Median follow-up 28 months

Courtesy of Professor Dr Stephan Stilgenbauer

ELEVATE-TN: untreated older CLL Patients Acalabrutinib +/- Obinutuzumab compared with Obinutuzumab+Chlorambucil

Sharman et al. Lancet 2020

PFS: 17p- Subgroup



Courtesy of Professor Dr Stephan Stilgenbauer

Upfront Management of CLL in Patients Who Are Older or Have Comorbidities

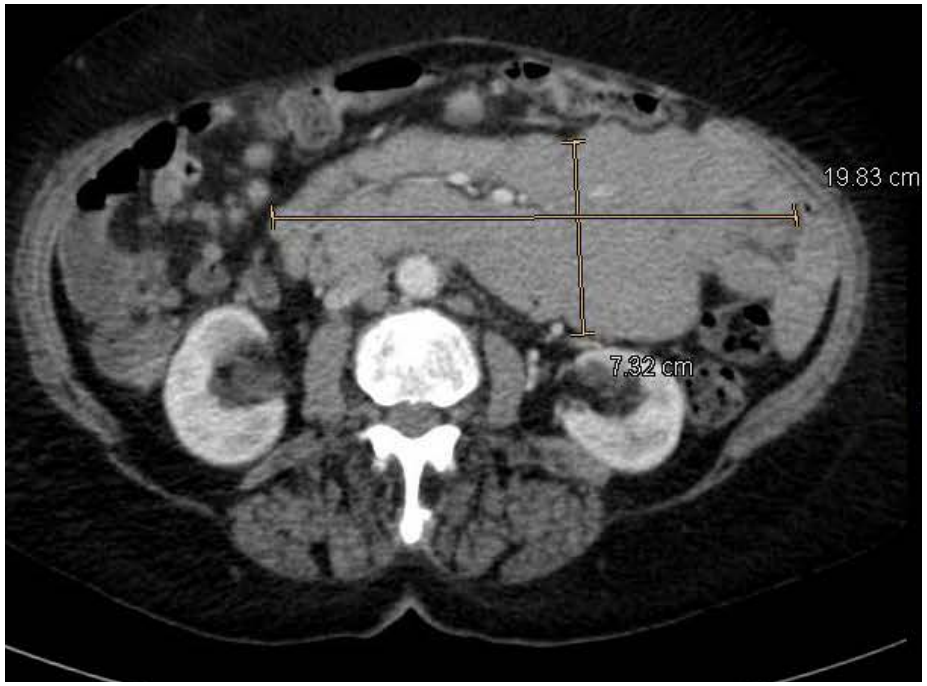
- PFS improvement with targeted therapy, i.e. venetoclax + obinutuzumab, ibrutinib and acalabrutinib (+/- CD20 antibody) over chemoimmunotherapy
- PFS appears similar for all targeted approaches in cross trial comparison
- Benefit most pronounced in CLL with unmutated IGHV
- Outcome of 17p-/*TP53*^{mut} CLL still inferior with all targeted therapy approaches but much improved over chemoimmunotherapy
- Choice of BCL2 or BTK targeting agent largely based on tolerability:
  - Patient preference (treatment duration and monitoring)
  - Coexisting conditions (hypertension, cardiovascular and renal disease)
  - Concomitant medication (anticoagulants, antiplatelets, CYP3A interaction)

Courtesy of Professor Dr Stephan Stilgenbauer

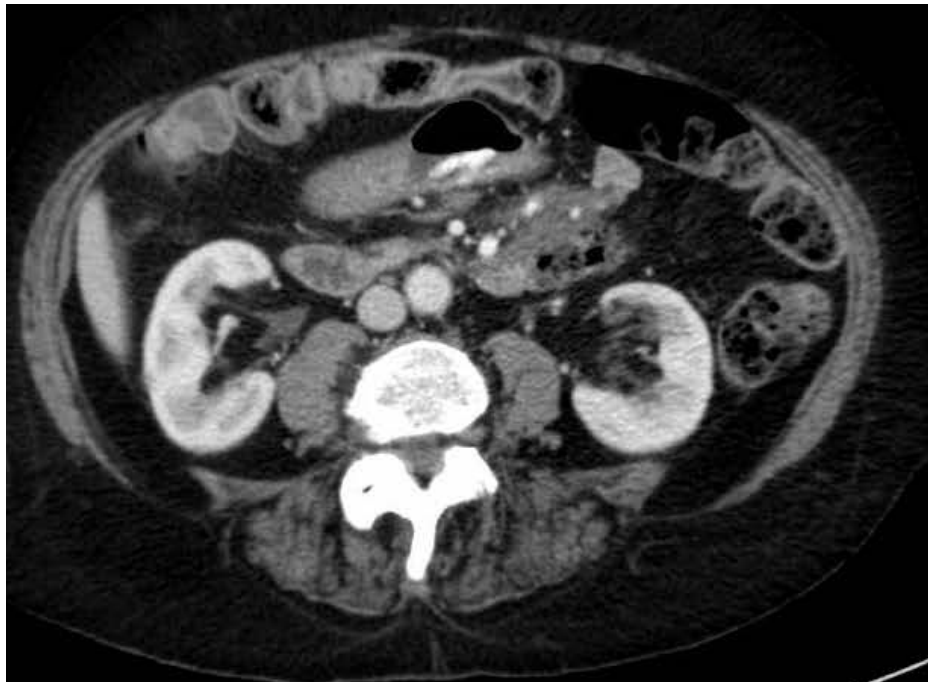
Novel Therapy: Selective BCL2 Targeting Small Molecule Inhibitor Venetoclax (ABT-199)

Case report:
76 year-old female, 17p- CLL, 3 prior lines, refractory

Baseline CT staging:



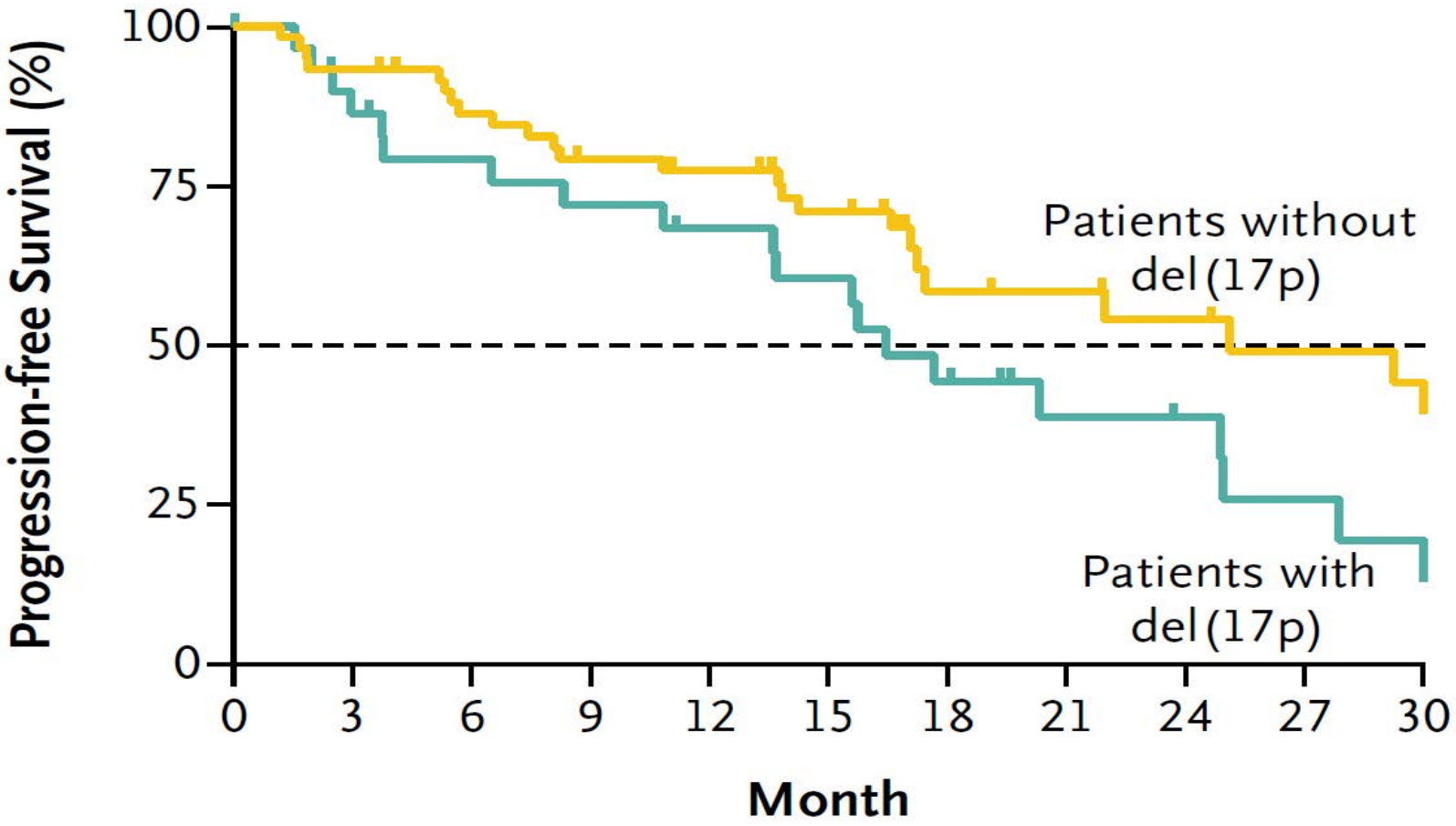
Month 3 on therapy:



Courtesy of Professor Dr Stephan Stilgenbauer

Venetoclax (ABT-199) First in Human Trial

Roberts et al., NEJM 2016; Anderson et al., Blood 2017



Factors associated with failure (n=67): F-refract., complex karyotype

CLL14: untreated elderly/unfit CLL: MRD Response

Fischer et al. NEJM 2019

	Obi-Ven	Obi-Clb	*P* value
Number of patients, N	216	216	
Peripheral blood			
Negative ($<10^{-4}$)	76 %	35 %	< 0.001
Negative ($<10^{-4}$) in CR	42 %	14 %	< 0.001
Bone marrow			
Negative ($<10^{-4}$)	57 %	17 %	< 0.001
Negative ($<10^{-4}$) in CR	34 %	11 %	< 0.001

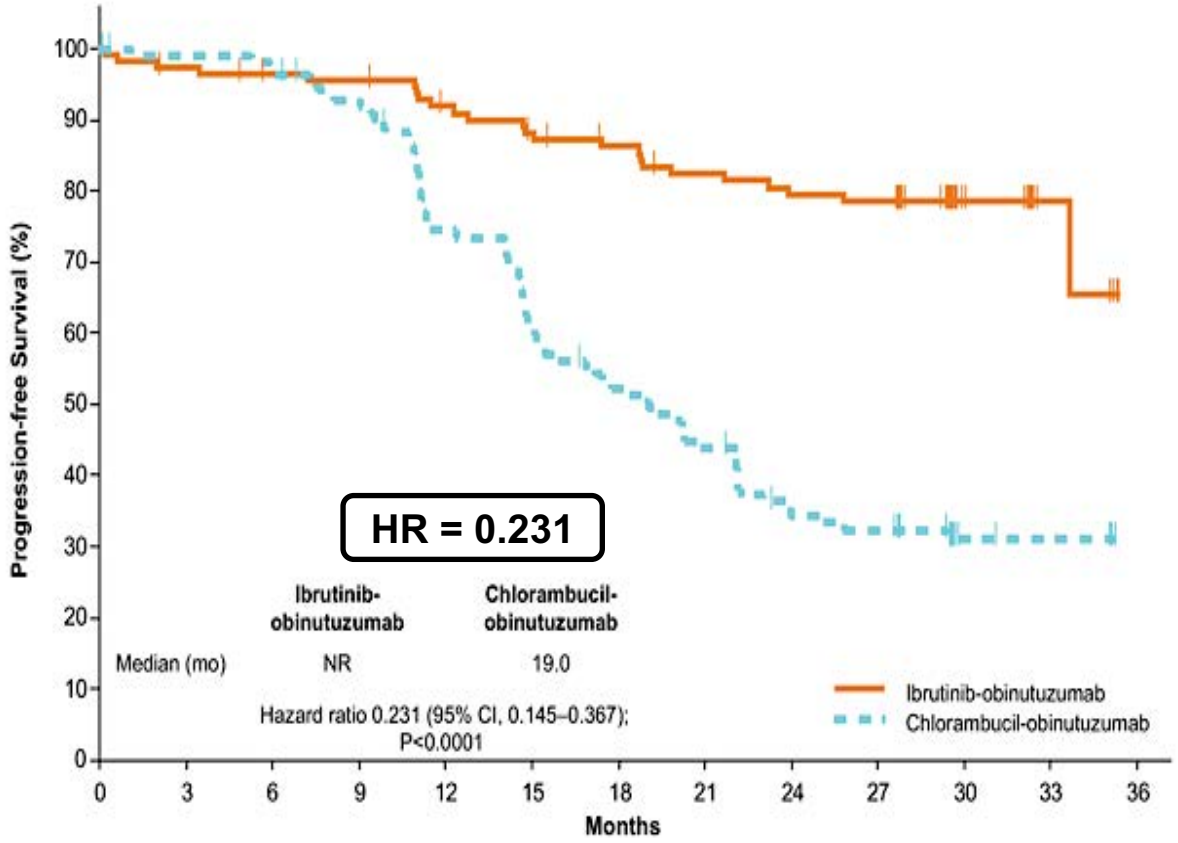
Courtesy of Professor Dr Stephan Stilgenbauer

iLLUMINATE: untreated elderly/unfit CLL
Primary Endpoint: PFS

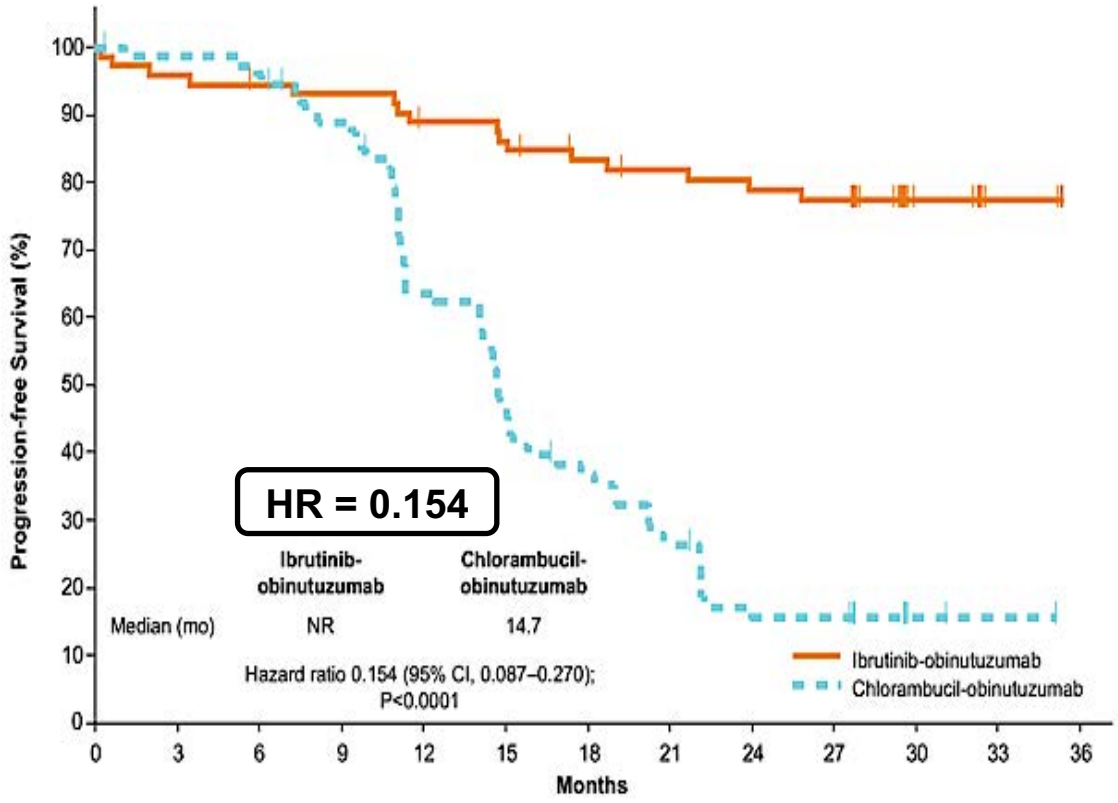
Moreno et al. Lancet Oncol 2019

ITT (IRC)

Median follow-up, 31.3 months



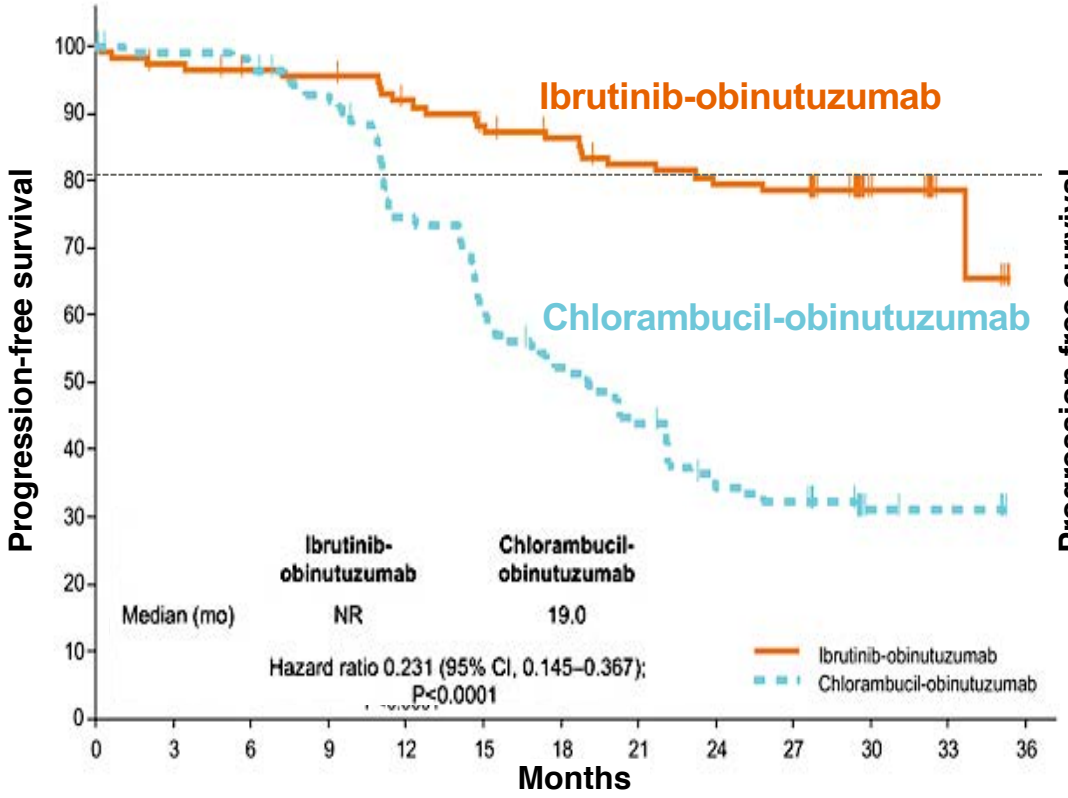
High Risk Population (ulGHV, del(11q), del(17p) and/or TP53 mutation)

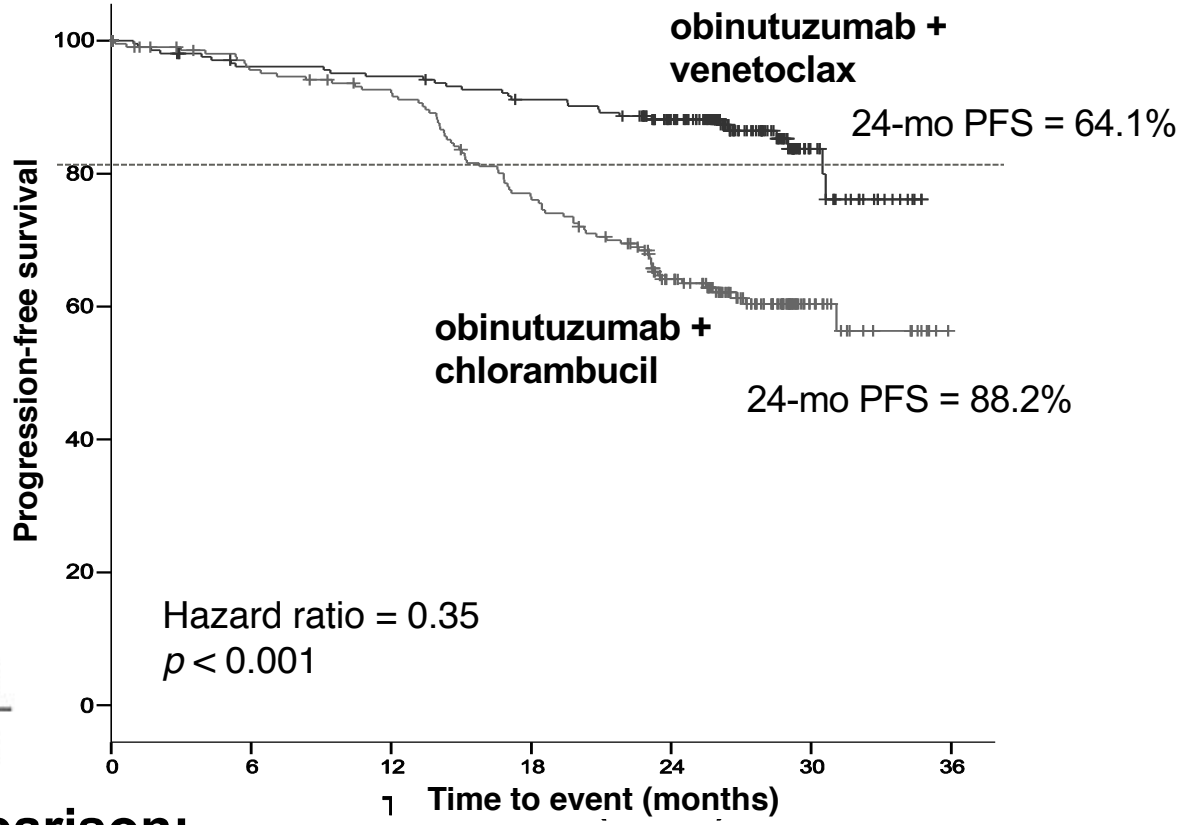


Courtesy of Professor Dr Stephan Stilgenbauer

Elderly CLL Patients with Comorbidity: Comparison of iLLUMINATE and CLL14

Moreno et al. Lancet Oncol 2018; Fischer et al. NEJM 2019





<u>Despite all caveats of cross-trial comparison:</u>

Similar outcome of experimental arms and difference of obi-clb arms (different schedules: 6 vs. 12 cycles)

Courtesy of Professor Dr Stephan Stilgenbauer