Annual Steven Coutré CLL Memorial Lecture

Targeted Therapy for Initial Therapy of CLL

24th February 2024

Peter Hillmen

Disclosures – Peter Hillmen

Advisor/consultant

- Abbvie
- Astra Zeneca
- Beigene
- Gilead
- Janssen
- Novartis/GSK
- Pharmacyclics
- Roche

Research/trial support

- Abbvie
- Apellis
- Gilead
- Janssen
- Novartis/GSK
- Pharmacyclics
- Roche

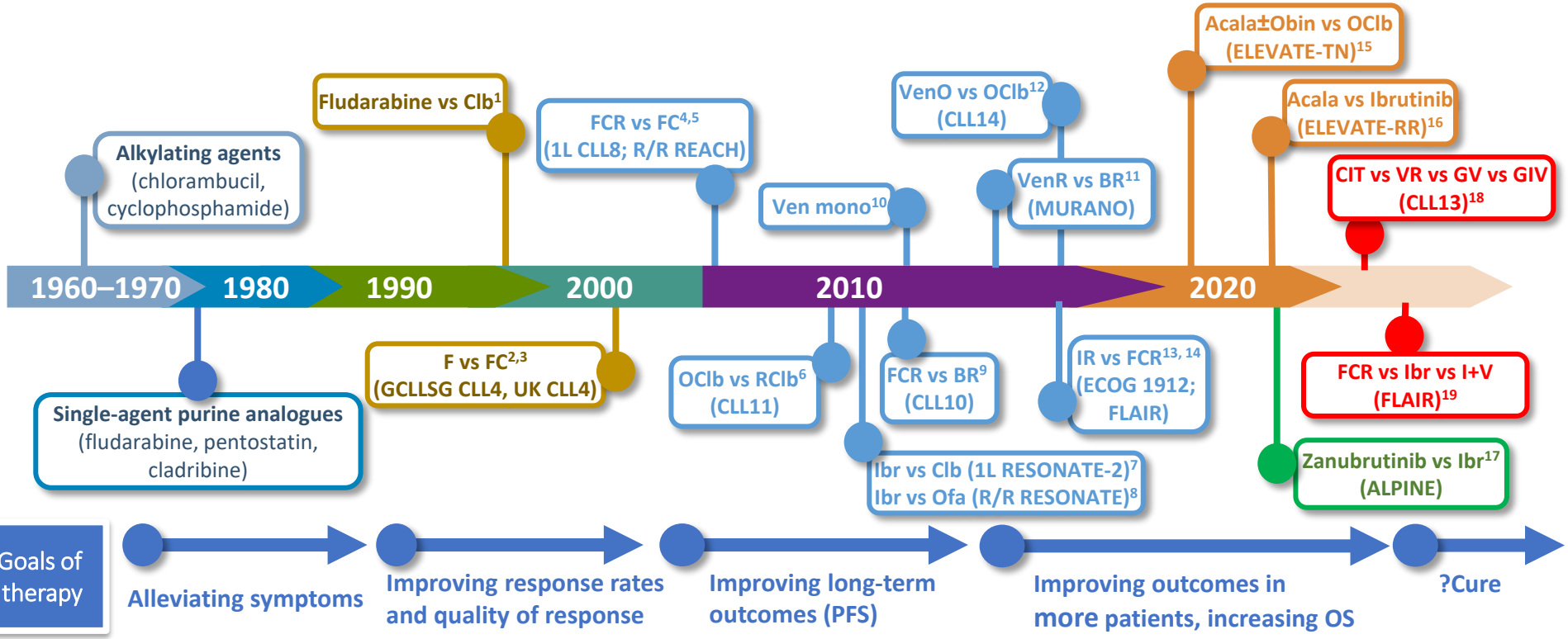
Employment

- Apellis Pharmaceuticals since May 2022

Presented with respect to work done in the University of Leeds and Leeds Teaching Hospitals

The views expressed are solely those of Peter Hillmen

Development of CLL Treatment over the last 60 years

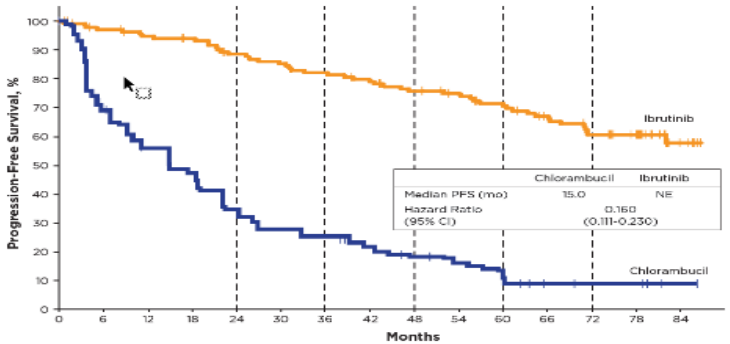


1. Rai KR, *et al. N Engl J Med* 2000; **343:**1750–1757; 2. Eichhorst BF, *et al. Blood* 2006; **114:**3382–3391; 3. Catovsky D, *et al. Lancet* 2007; **370:**230–239; 4. Hallek M, *et al. Lancet* 2010; **376:**1164–1174;
5. Robak T, *et al. J Clin Oncol* 2010; **8:**1756–1765; 6. Goede V, *et al. N Engl J Med* 2014; **370:**1101–1110; 7. Burger JA, *et al. N Engl J Med* 2015; **373:**2425–2437; 8. Byrd JC, *et al. N Engl J Med* 2014; **372:**213–223;
9. Eichhorst B, *et al. Lancet Oncol* 2016; **17:**928–942; 10. Roberts AW, *et al. N Engl J Med* 2016; **374:**311–322; 11. Seymour JF, *et al. N Engl J Med* 2018; **378:**1107–1120; 12. Fischer K, *et al. N Engl J Med* 2019; **380:**2225–2236;
13. Shanafelt TD, *et al. N Engl J Med* 2019; **381:**432–443; 14. Hillmen P, *et al. Lancet Oncology* 2023;**24:**535-552; 15. Sharman JP, *et al. Lancet* 2020; **379:**1278–1291; 16. Byrd JC *et al. J Clin Oncol* 2021;**39:**3441-3452;
17. Brown J *et al. N Engl J Med* 2023;**388:**319-332; 18. Eichhorst B *et al. N Engl J Med* 2023;**388:**1739-1754;19. Munir *et al. N Engl J Med* 2023 (online) .

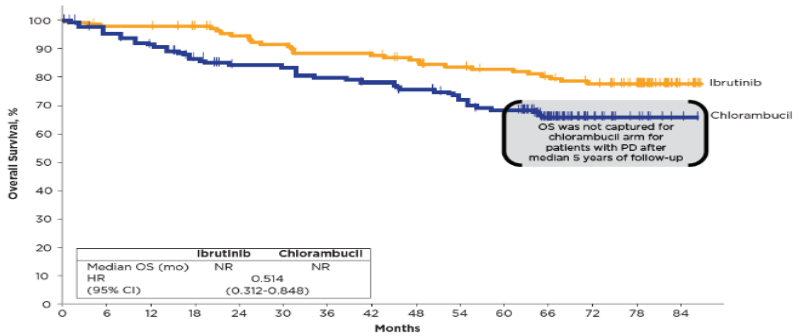
Phase III data supporting the use of continuous BTKi in the front-line setting of CLL compared to chlorambucil±obinutuzumab

RESONATE-2[1]

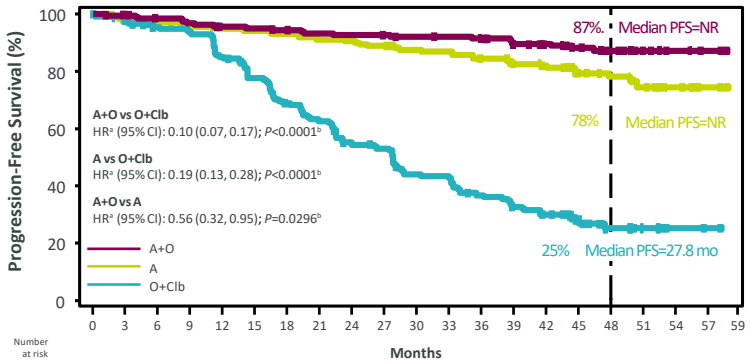
Progression free survival

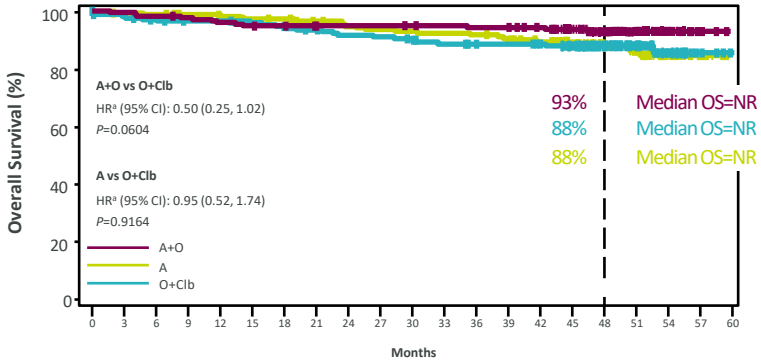


Overall Survival



ELEVATE-TN[2]

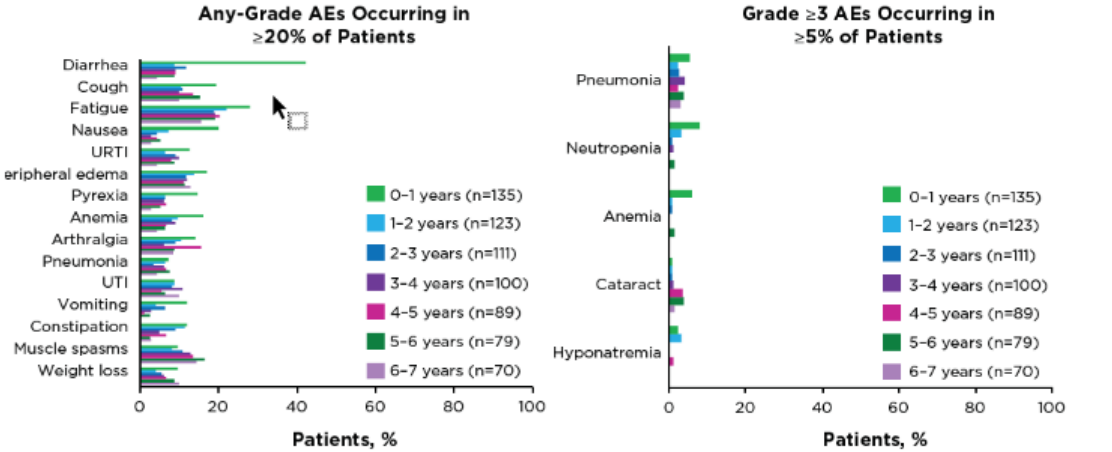




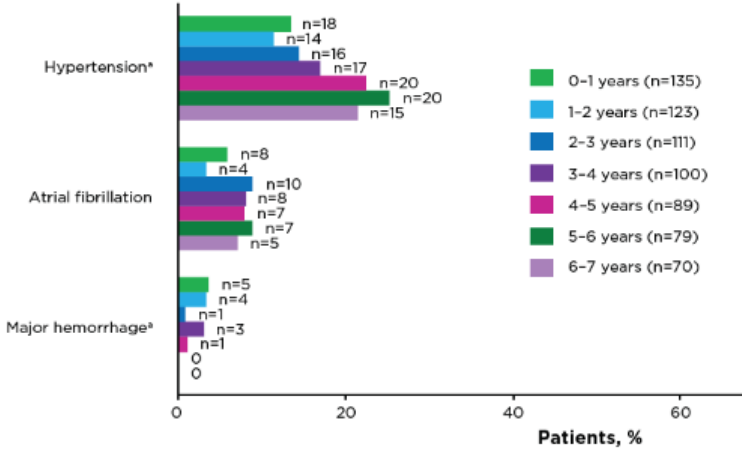
1. Ghia et al., EHA 2021; EP636 (poster presentation); 2. Sharman *et al.* Leukemia. 2022; 36(4): 1171–1175.

RESONATE-2: AEs with up to 7 years of follow-up

Prevalence of most frequent AEs over time in ibrutinib-treated patients



AEs of clinical interest over time in patients treated with ibrutinib



66/79 patients (84%) had an AE that had a complete resolution following a dose hold of at least 7 days

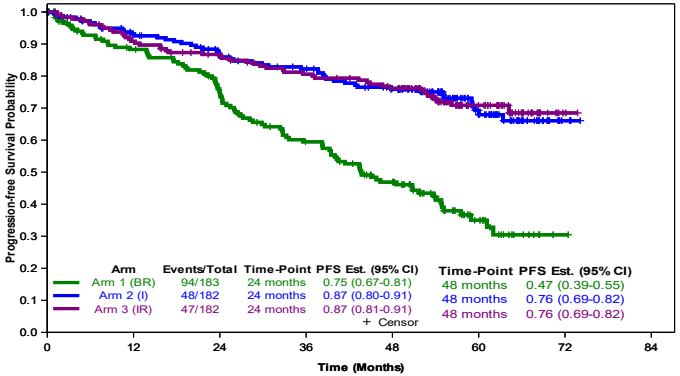
- 31 patients (23%) experienced AEs leading to dose reductions.
  - AEs occurring in >1 patient were thrombocytopenia (n=3), and anemia, arthralgia, diarrhea, fatigue, and palpitations (n=2, each).
- At current follow-up (up to 7 years), 31 patients (23%) experienced AEs as the primary cause of ibrutinib discontinuation.
  - AEs occurring in >1 patient were atrial fibrillation (n=5), pneumonia (n=3), and palpitations (n=2).

Ghia et al., EHA 2021; EP636 (poster presentation)

Phase III data supporting the use of continuous BTKi in the front-line setting of CLL compared to BR or FCR

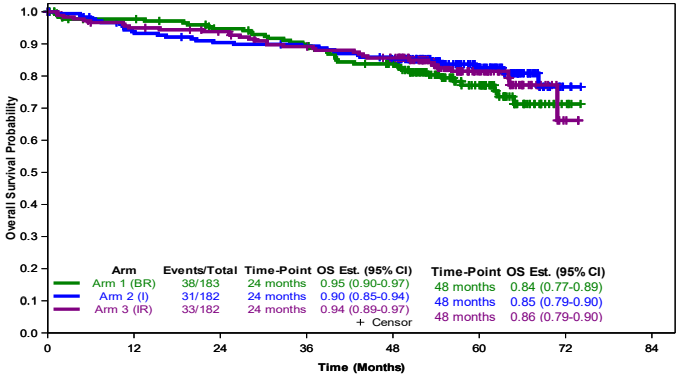
Alliance A041202[1]

Progression free survival

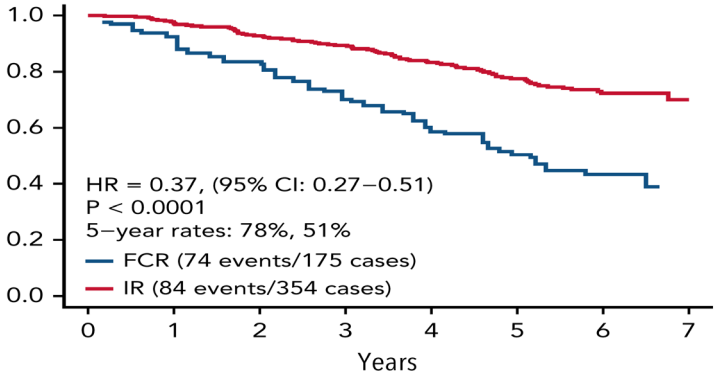


Median follow-up: 55 months

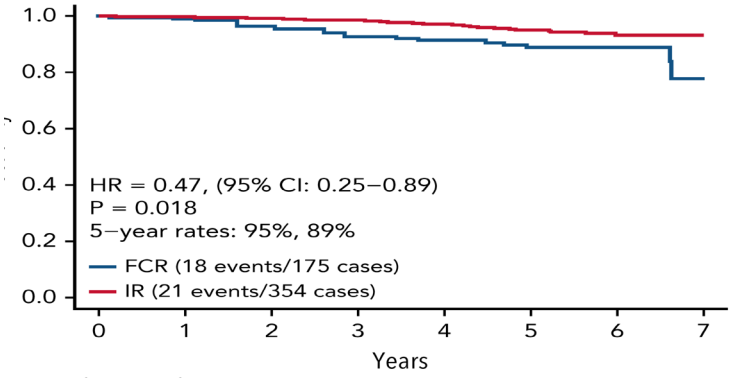
Overall Survival



ECOG 1912[2]



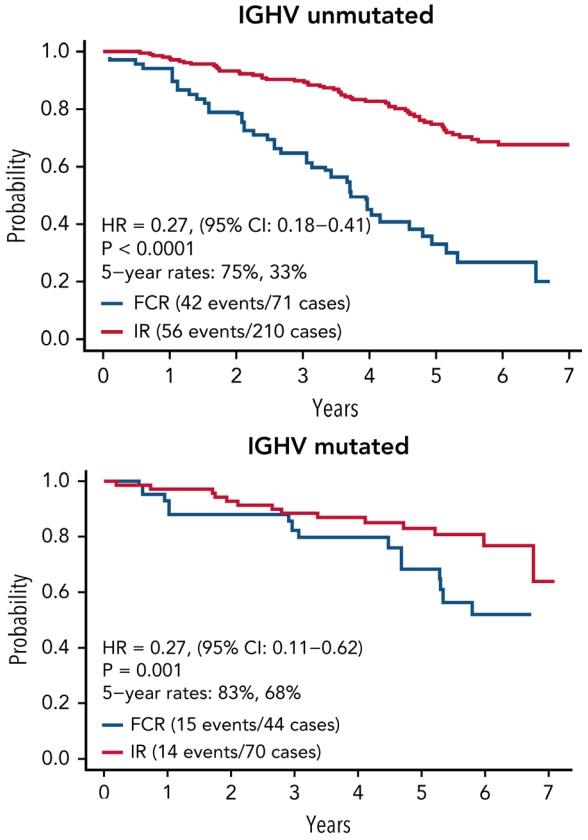
Median follow-up: 6 years



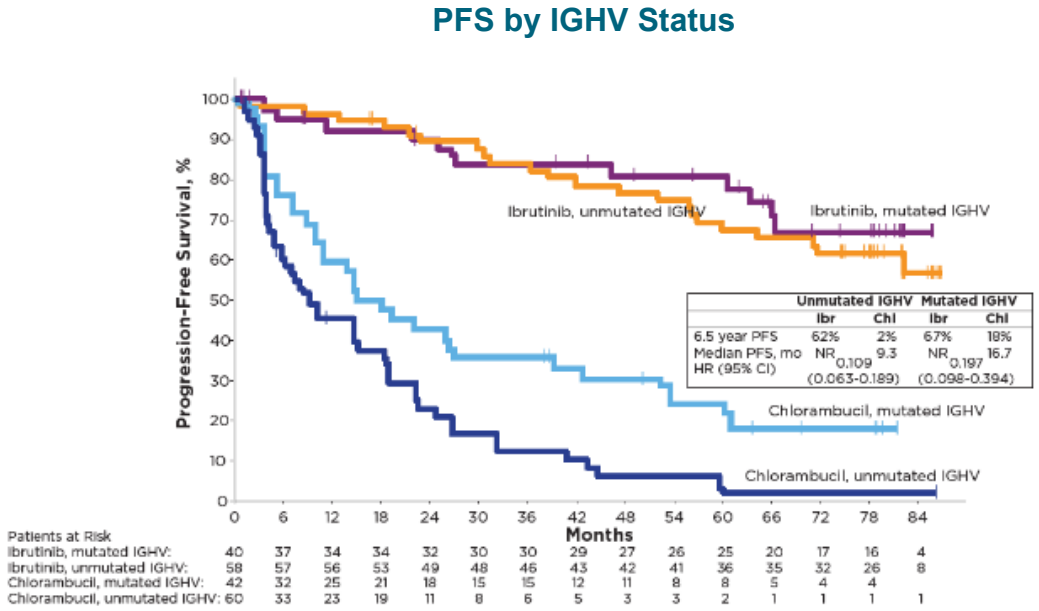
1. Woyach JA, *et al.* ASH 2021; 2. Shanafelt *et al.*, Blood 2022; 140:112-120.

PFS for continuous ibrutinib in V_H unmutated CLL

Ibrutinib+R vs FCR (ECOG1912)[1]



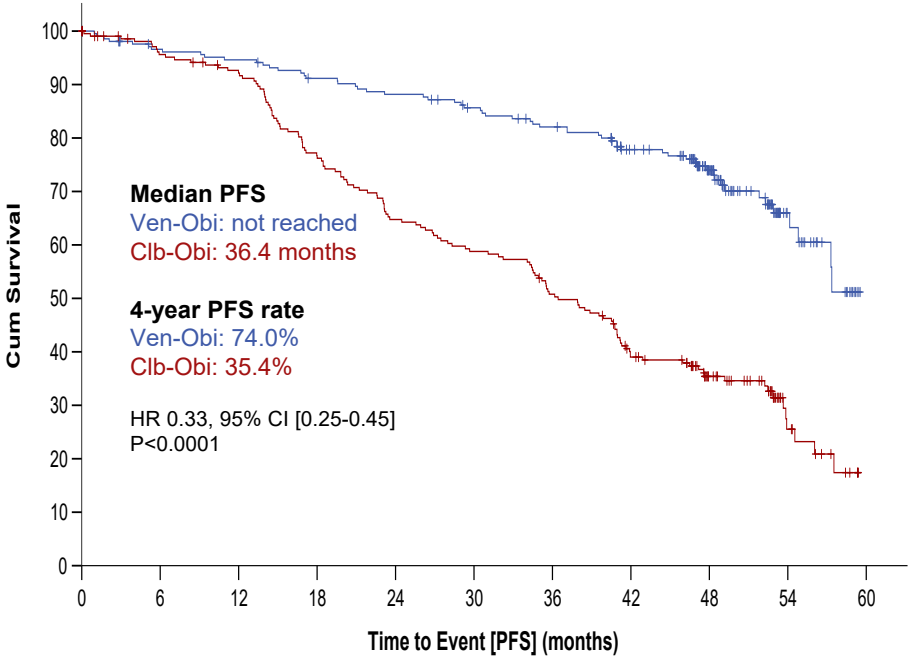
Ibrutinib vs chlorambucil (Resonate-2)[2]



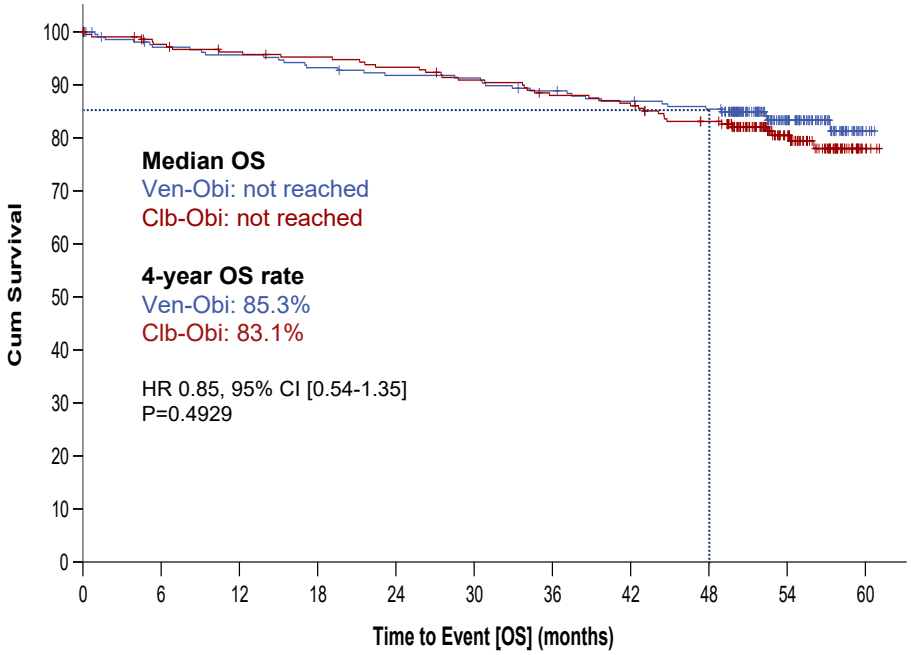
1. Shanafelt *et al*., Blood 2022; 140:112-120; 2. Ghia et al., EHA 2021; EP636 (poster presentation)

Phase III data supporting 12 months fixed duration of venetoclax +obin in front-line CLL compared to chlorambucil+obin (GCLL14)

Progression free survival



Overall Survival



Al-Sawaf et al., ASH 2020; abstract 127 (oral presentation)

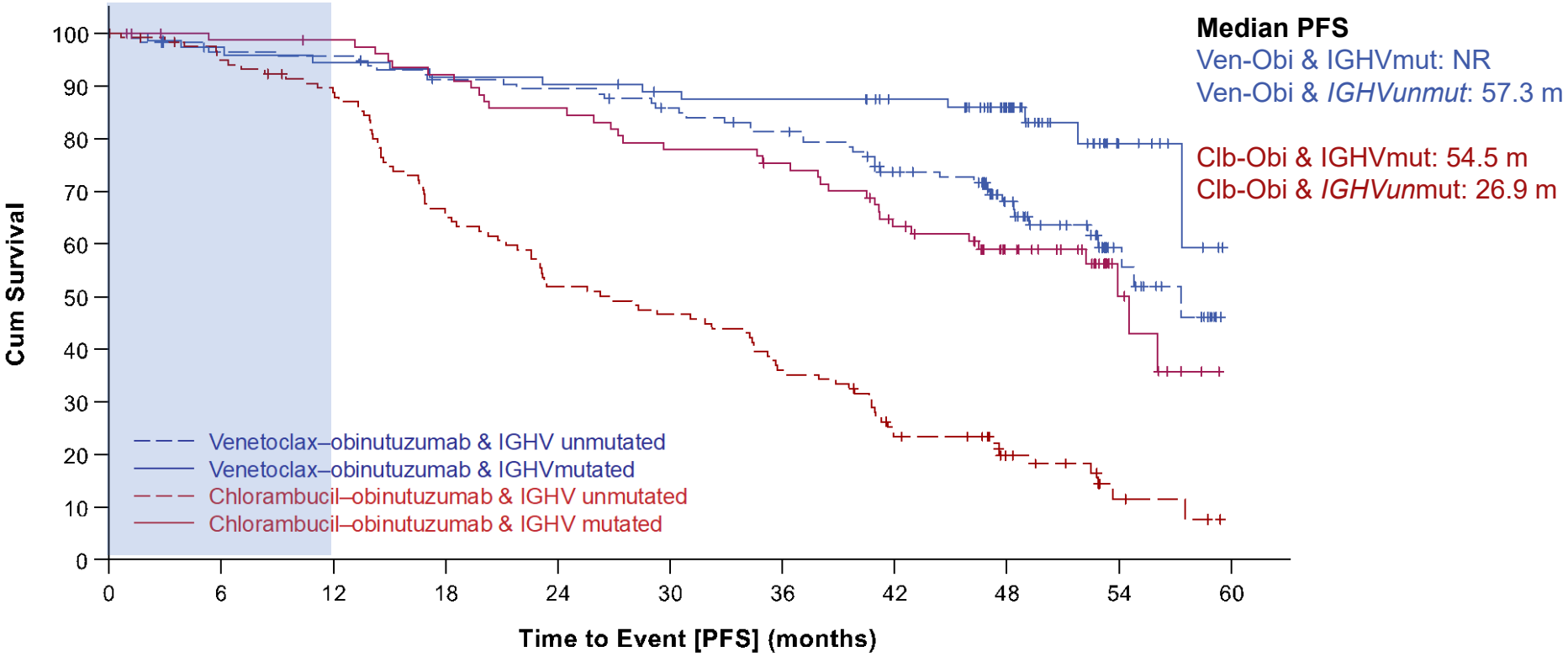
GCLLSG CLL14: Most frequent ≥ grade 3 adverse events

	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%
Leukopenia	2.4%	0.0%	4.7%	0.0%
Pneunomia	3.3%	3.0%	2.8%	1.4%
Infusion-related reaction	9.0%	0.0%	9.8%	0.5%
Tumour lysis syndrome	1.4%	0.0%	3.3%	0.0%

Al-Sawaf et al., EHA 2021; S146 (oral presentation)

GCLLSG CLL14: PROGRESSION-FREE SURVIVAL – IGHV status

Median observation time 52.4 months



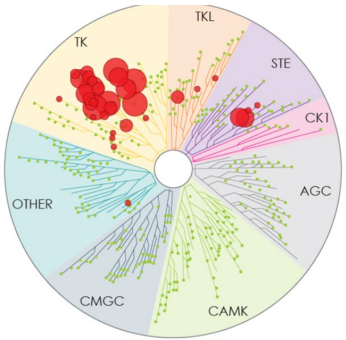
Al-Sawaf et al., EHA 2021; S146 (oral presentation)

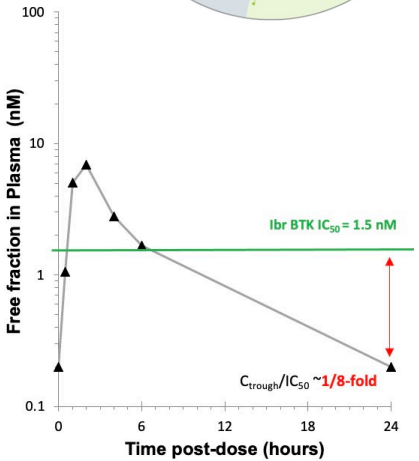
Pharmacokinetics and Selectivity of Ibrutinib, Acalabrutinib and Zanubrutinib

Whole Kinase Panel Selectivity Profiles

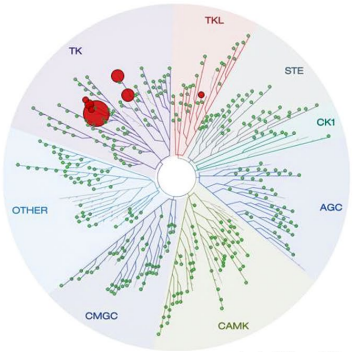
BTKi PK: Relative Time Spent Above IC_{50}

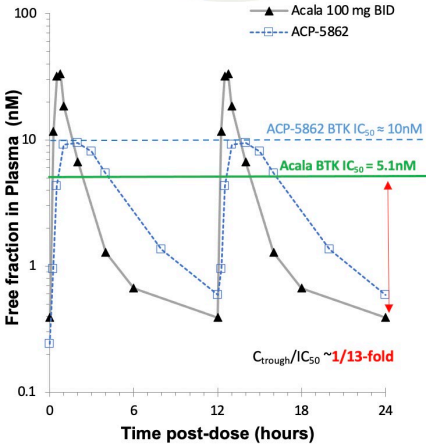
Ibrutinib 420 mg QD



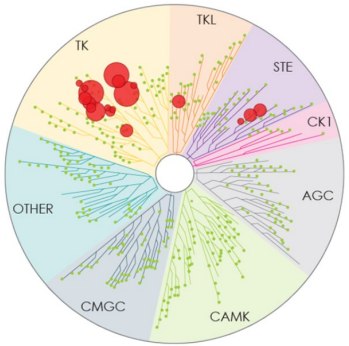


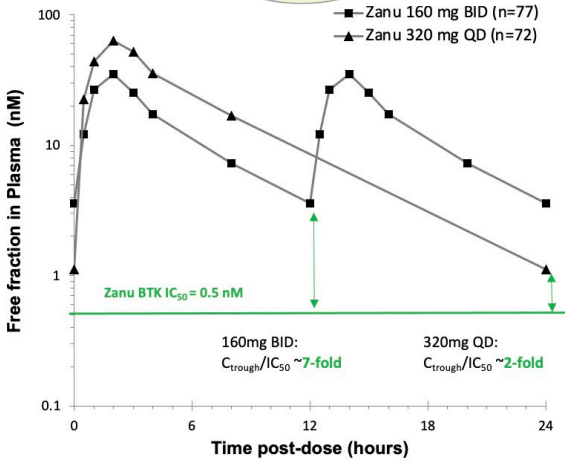
Acalabrutinib 100mg BD





Zanubrutinib 160mg BD





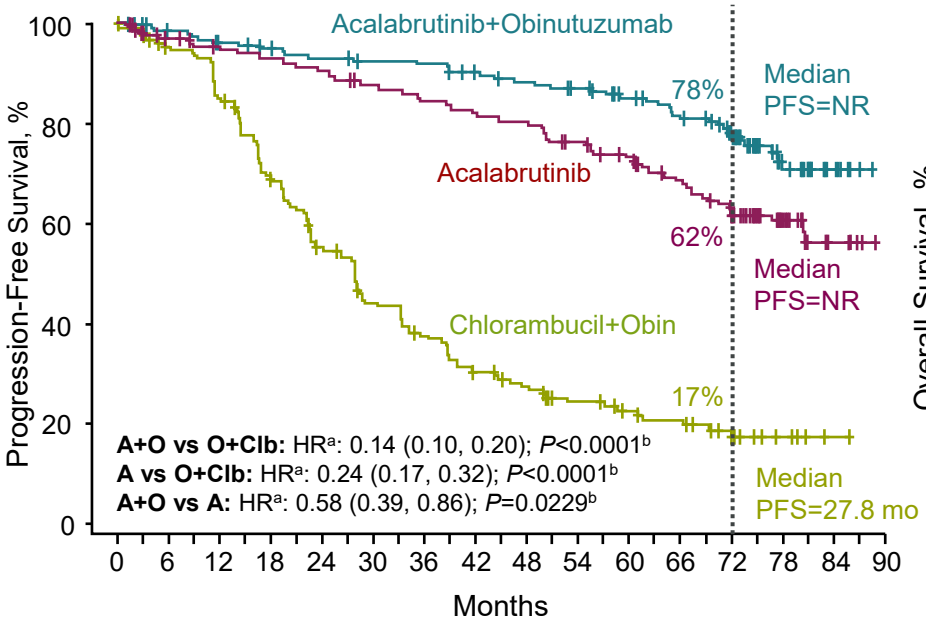
Note: These data are from 3 separate analyses. Limitations of cross-trial comparisons apply.

BTK potencies of zanubrutinib, ibrutinib and acalabrutinib (IC_{50}) were based on biochemical assays from Kaptein et al *Blood* 2018;132:1871. PK and plasma protein binding data were obtained from published work (Byrd et al. *NEJM* 2016;374:323-32. Advani et al *JCO* 2013;31:88-94. Zhou et al. *CPT: PSP* 2019;8:489-99. Edlund et al. *Clin Pharmacokinet* 2019;58:659-72. Ou et al. *Leuk Lymphoma* in press. Ibrutinib Clin Pharm and Biopharmaceutics Review; FDA 205552Org2s000. The concentration time profiles for ibrutinib major active metabolite (PCI-45227) at 560 mg are not available, thus not summarized here. It has been noted that PCI-45227 is ~15-fold less potent compared to the parent molecule.

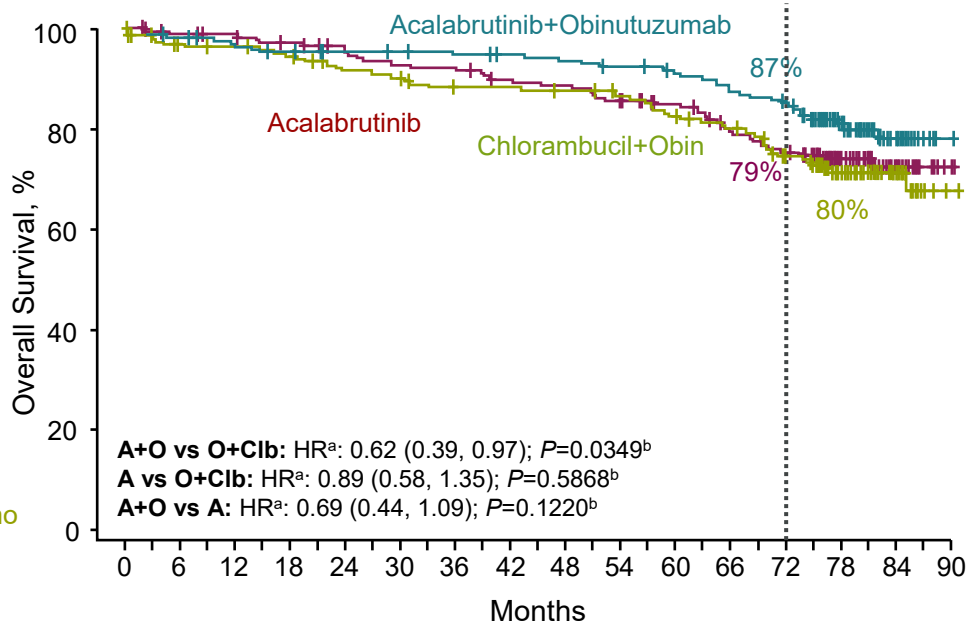
ELEVATE-TN 6 year update at ASH 2023

Acalabrutinib±Obinutuzumab vs Chlorambucil+Obinutuzumab

Progression-Free Survival



Overall Survival



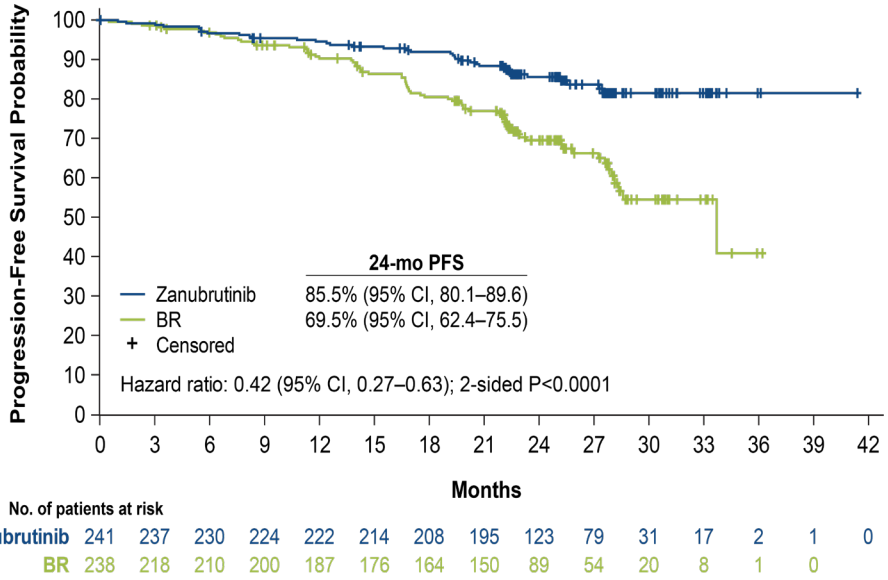
[a]Hazard ratio based on stratified Cox proportional-hazards model.
[b]*P*-value based on stratified log-rank test.

Sharman *et al*, Leukemia, 2022 Apr;36(4):1171-1175; Sharman *et al*, ASH 2023, Abst 636.

SEQUOIA: RESULTS OF A PHASE 3 RANDOMIZED STUDY OF ZANUBRUTINIB VERSUS BENDAMUSTINE + RITUXIMAB IN PATIENTS WITH TREATMENT-NAIVE CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

Constantine S. Tam, Krzysztof Giannopoulos, Wojciech Jurczak, Martin Šimkovič, Mazyar Shadman, Anders Österborg, Luca Laurenti, Patricia Walker, Stephen Opat, Henry Chan, Hanna Ciepluch, Richard Greil, Monica Tani, Marek Trněný, Danielle M. Brander, Ian W. Flinn, Sebastian Grosicki, Emma Verner, Jennifer R. Brown, Brad S. Kahl, Paolo Ghia, Jianyong Li, Tian Tian, Lei Zhou, Carol Marimpietri, Jason C. Paik, Aileen Cohen, Jane Huang, Tadeusz Robak, and Peter Hillmen

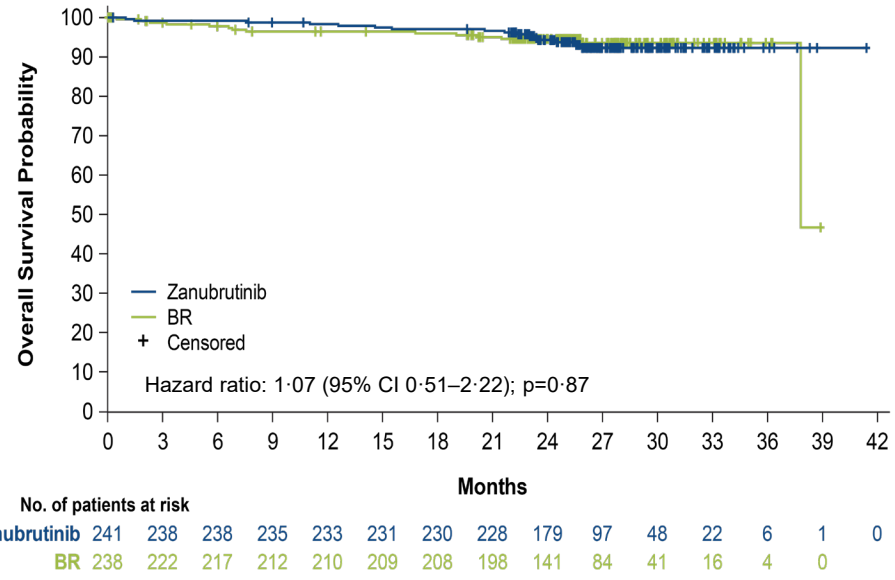
Progression-Free Survival Per IRC Assessment



No. of patients at risk

Zanubrutinib	241	237	230	224	222	214	208	195	123	79	31	17	2	1	0
BR	238	218	210	200	187	176	164	150	89	54	20	8	1	0	

Overall Survival



No. of patients at risk

Zanubrutinib	241	238	238	235	233	231	230	228	179	97	48	22	6	1	0
BR	238	222	217	212	210	209	208	198	141	84	41	16	4	0	

Tam *et al*, Lancet Oncol. 2022 Aug;23(8):1031-1043.

First-line venetoclax combinations in CLL: 4-year follow-up from the phase 3 GAIA/CLL13 trial

Moritz Fürstenau, Matthias Ritgen, Sandra Robrecht, Julia von Tresckow, Can Zhang, Anke Schilhabel, Michael Gregor, Patrick Thornton, Philipp B. Staber, Tamar Tadmor, Vesa Lindström, Gunnar Juliusson, Ann Janssens, Mark-David Levin, Caspar da Cunha-Bang, Christof Schneider, Neta Goldschmidt, Elisabeth Vandenberghe, Davide Rossi, Rudolf Benz, Daniel Heintel, Christian B Poulsen, Ilse Christiansen, Henrik Frederiksen, Lisbeth Enggaard, Eduardus FM Posthuma, Djamila E Issa, Hein PJ Visser, Mar Bellido, Nadine Kutsch, Jan Dürig, Alexander Stehle, Matthias Vöhringer, Sebastian Böttcher, Clemens Schulte, Florian Simon, Maria Fink, Kirsten Fischer, Emily Holmes, Karl-Anton Kreuzer, Matthias Ritgen, Monika Brüggemann, Eugen Tausch, Stephan Stilgenbauer, Michael Hallek, Arnon P Kater, Carsten U Niemann, Barbara Eichhorst

65th ASH annual meeting | December 9-12, 2023 | San Diego, USA

Study Design - GAIA/CLL13

Key patient characteristics

Randomized patients (=ITT population): **n= 926**

Median age:	**61 years** (range: 27-84)
Median CIRS score:	**2** (range: 0-7)
Unmutated IGHV:	**56%** of all patients
Complex karyotype:	**17%** of all patients

Follow-up analysis (data cut-off: 01/2023)

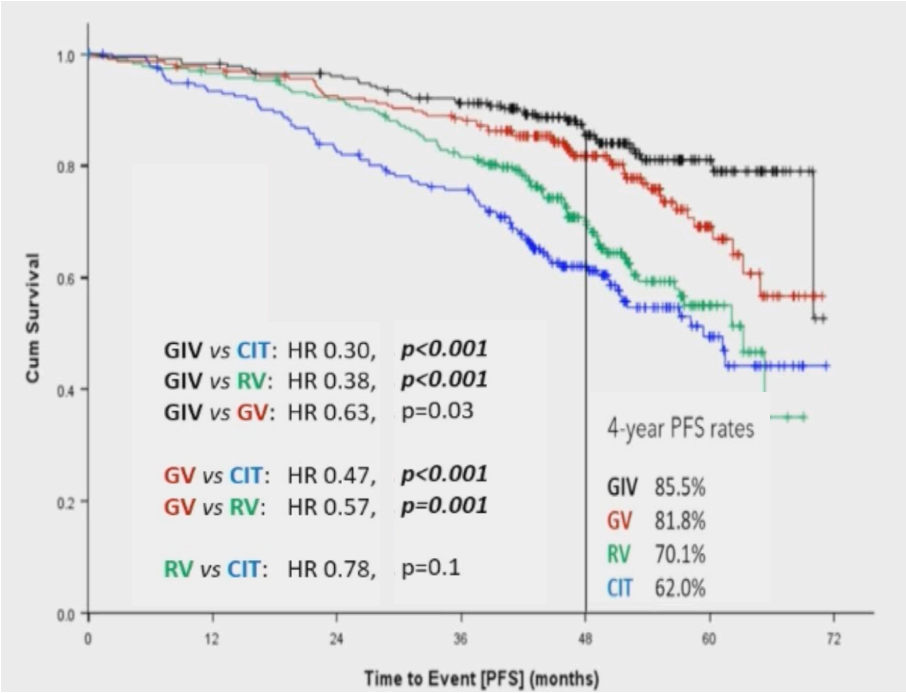
Median observation time
50.7 months (IQR: 44.6-57.9)

Median observation time after end of treatment
40.7 months (IQR: 34.5-47.9)

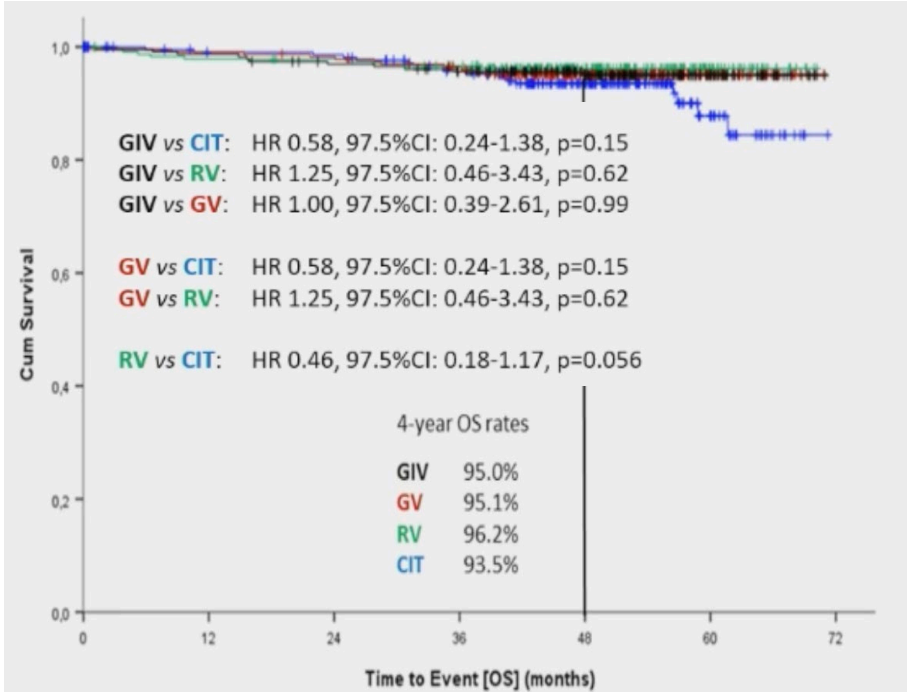
Fürstenau *et al.*, ASH 2023; abstract 635 (oral presentation)

GAIA/CLL13 Trial: Four-year follow-up ASH 2023

Progression free survival



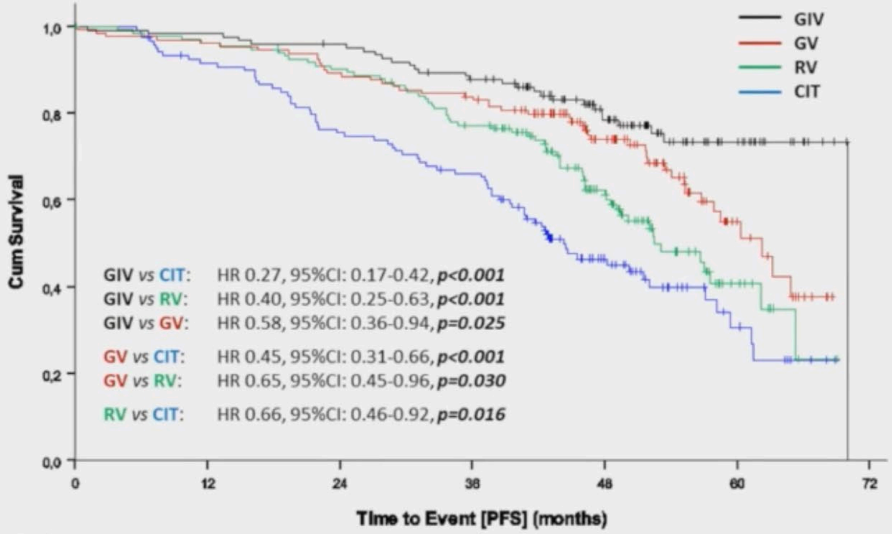
Overall Survival



Fürstenau *et al.*, ASH 2023; abstract 635 (oral presentation)

Efficacy – PFS

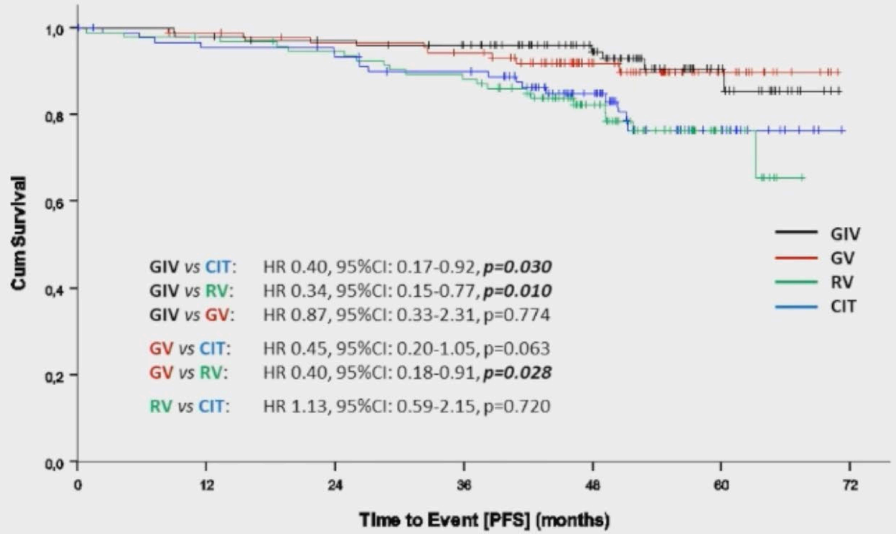
PFS, patients with unmutated IGHV



Pts at risk

CIT	131	108	89	77	34	9
RV	134	128	119	100	56	10
GV	130	125	116	108	67	15
GIV	123	121	117	105	65	24

PFS, patients with mutated IGHV



Pts at risk

CIT	95	86	83	78	50	15
RV	95	92	88	82	47	11
GV	89	87	83	80	48	15
GIV	101	99	95	90	60	20

Fürstenau *et al.*, ASH 2023; abstract 635 (oral presentation)

Ibrutinib Plus Venetoclax with MRD-Directed Duration of Treatment Is Superior to FCR and Is a New Standard of Care for Previously Untreated CLL: Report of the Phase III UK NCRI Flair Study

Peter Hillmen, David Cairns, Adrian Bloor, David Allsup, Kate Cwynarski, Andrew Pettitt, Shankara Paneesha, Christopher Fox, Toby Eyre, Francesco Forconi, Nagah Elmusharaf, Ben Kennedy, John Gribben, Nicholas Pemberton, Oonagh Sheehy, Gavin Preston, Anna Schuh, Dena Howard, Anna Hockaday, Sharon Jackson, Natasha Greatorex, Sean Girvan, Sue Bell, Julia M Brown, Nichola Webster, Surita Dalal, Ruth de Tute, Andrew Rawstron, Piers EM Patten, Talha Munir
on behalf of the NCRI CLL Subgroup.

Abstract No: 631, Oral Presentation, ASH Annual Meeting
Sunday, December 10th 2023

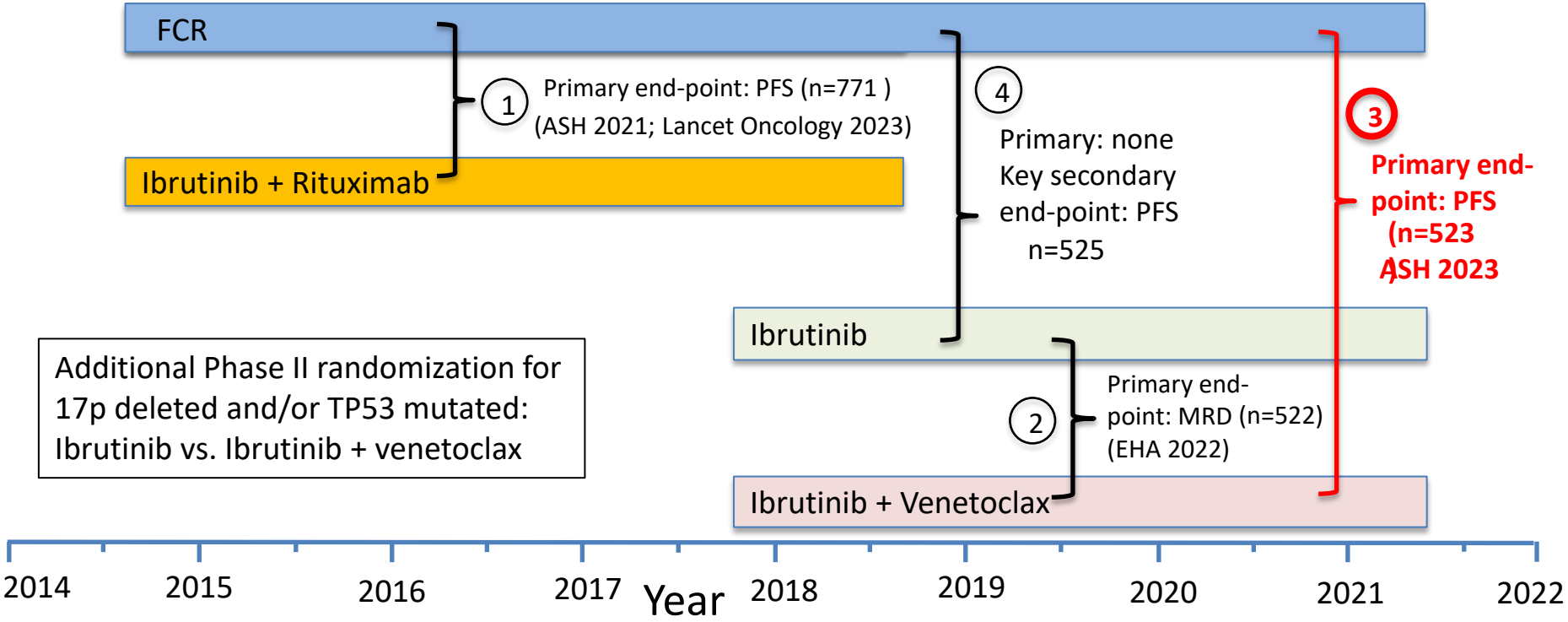
National Cancer Research Institute

CANCER RESEARCH UK

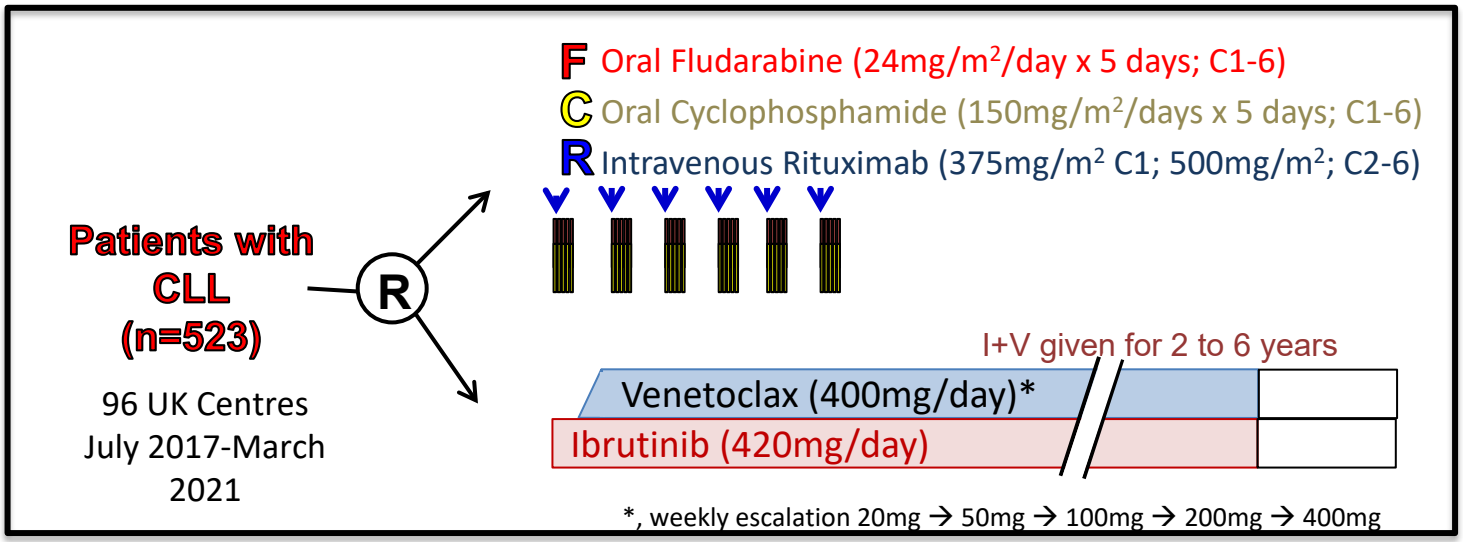
ctru University of Leeds

LEEDS CLINICAL TRIALS UNIT

Adaptive design of Flair



Flair FCR vs I+V: Trial design



Primary end-point:
To assess whether I+V is superior to FCR in terms of PFS

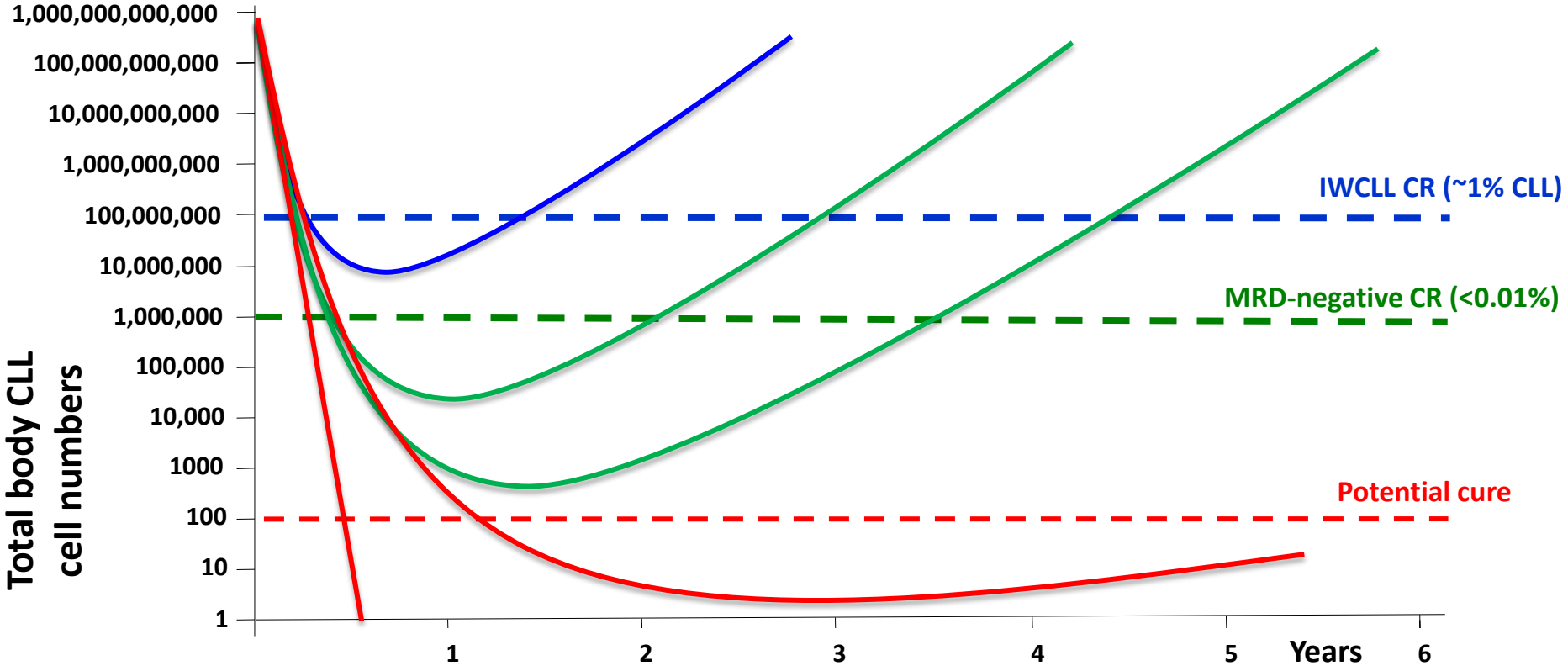
Key secondary end-points:
Overall survival
Response incl. MRD
Safety and toxicity

Key Inclusion Criteria:

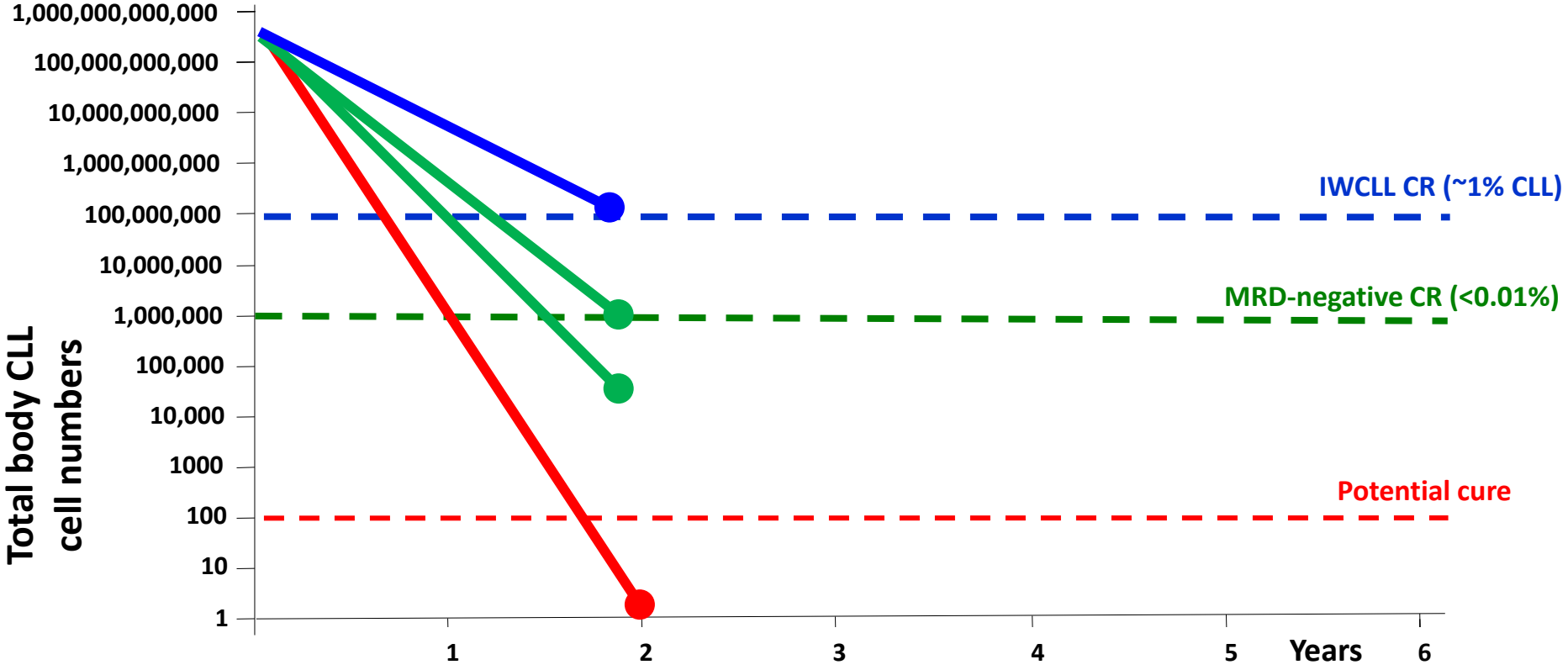
- Previously untreated CLL requiring therapy by IWCLL criteria
- Considered fit for FCR
- ≤75 years old

Key Exclusion Criteria:
Prior therapy for CLL; History of Richter's transformation; >20% TP53 deletion by FISH; Concomitant warfarin (or equivalent) Symptomatic cardiac failure or angina

Measurable residual disease in CLL and “cure”



Individual patient sensitivity to I+V is variable



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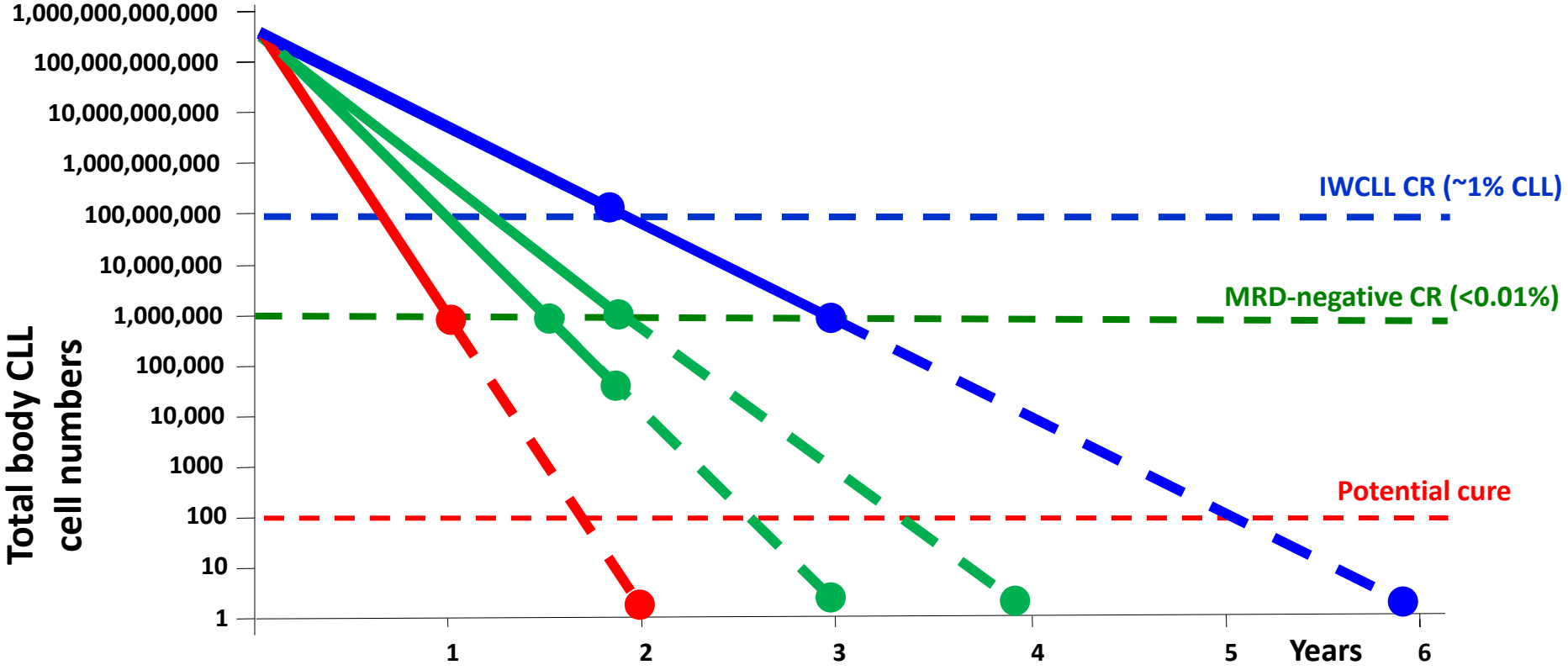
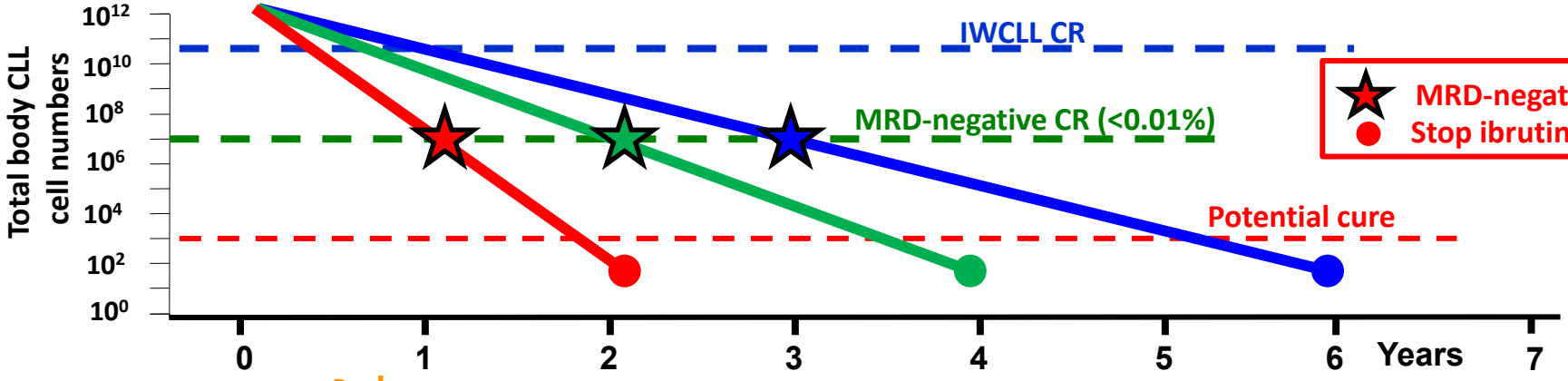
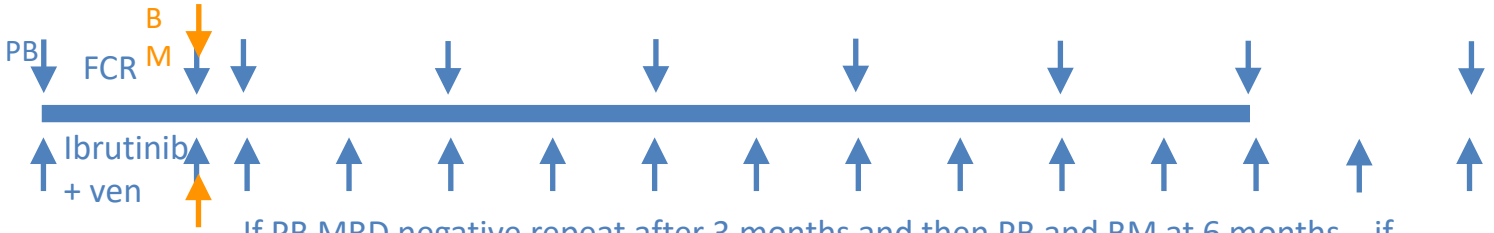
MRD-guided duration of I+V in FLAIR



Stopping rules for ibrutinib + venetoclax in Flair



Testing schedule
(Central lab, MRD flow, MRD negative <1 CLL cell in 10^4)



If PB MRD negative repeat after 3 months and then PB and BM at 6 months – if all MRD negative then first PB MRD negative result is time to MRD negativity

Defining treatment duration
2 to 6 years Ibrutinib or both ibr+venetoclax
Double time after MRD negative

Restart ibrutinib + venetoclax if becomes MRD positive prior to Year 6

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Flair FCR vs I+V: Baseline Characteristics

		FCR (n=263)	Ibrutinib+venetoclax (n=260)	Total (n=523)
Age	Median (yr)	62	62	62
	>65 years	82 (31.2%)	81 (31.2%)	163 (31.2%)
Gender	Male	187 (71.1%)	186 (71.5%)	373 (71.3%)
Binet stage	Prog A or B	152 (57.8%)	151 (58.1%)	303 (57.9%)
	C	111 (42.2%)	109 (41.9%)	220 (42.1%)
Duration of CLL prior to randomisation	Median (mo)	33.7	37.9	35.8
B symptoms	Yes	121 (46.5%)	128 (49.2%)	249 (47.9%)

Flair FCR vs I+V: Prognostic markers

		FCR (n=263)	Ibrutinib+venetoclax (n=260)	Total (n=523)*
IGHV	Mutated (excl subset 2)	79 (30%)	92 (35.8%)	171 (32.7%)
	Unmutated (excl subset 2)	139 (52.8%)	124 (47.7%)	*261* (49.9%)
	Ig Stereotype Subset 2	13 (4.9%)	13 (5%)	26 (5%)
	Not available	32 (12.2%)	31 (11.9%)	63 (12%)
FISH Hierarchy	17p deletion*	0 (0%)	1 (0.4%)	1 (0.2%)
	11q deletion	50 (19%)	45 (17.3%)	95 (18.2%)
	Trisomy 12	29 (11%)	57 (21.9%)	86 (16.4%)
	Normal	69 (26.2%)	52 (20%)	121 (23.1%)
	13q deletion	100 (38%)	87 (33.5%)	187 (35.8%)
	Failed/incomplete	15 (5.7%)	18 (6.9%)	33 (6.3%)

* Patients with >20% 17p deleted cells were excluded.

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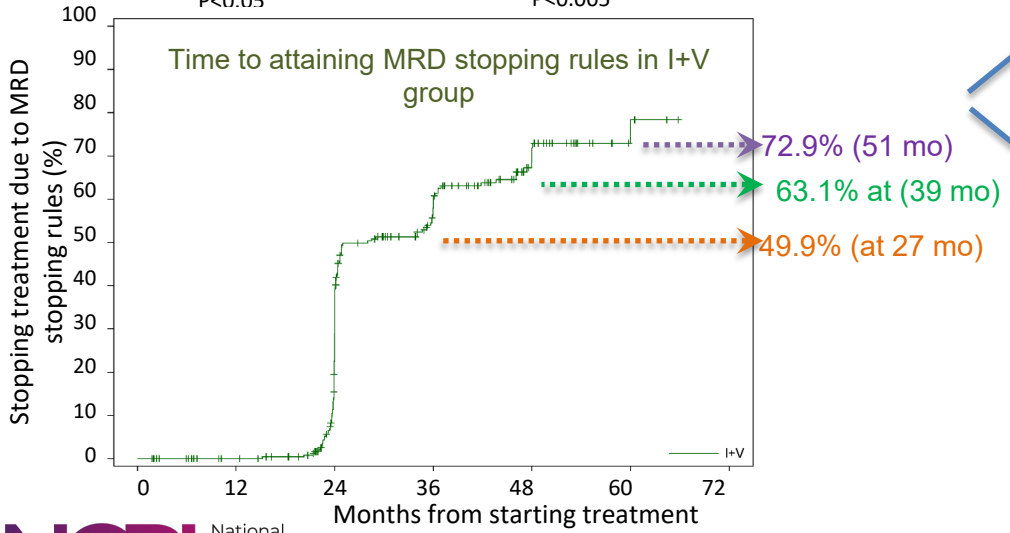
Flair iwCLL response and MRD stopping rules

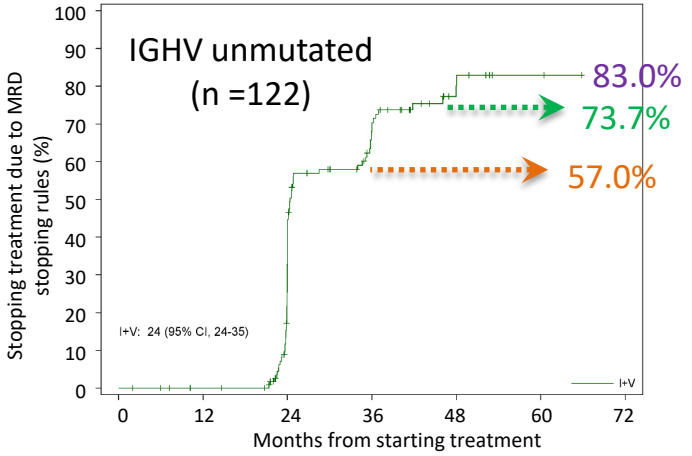
iwCLL Responses

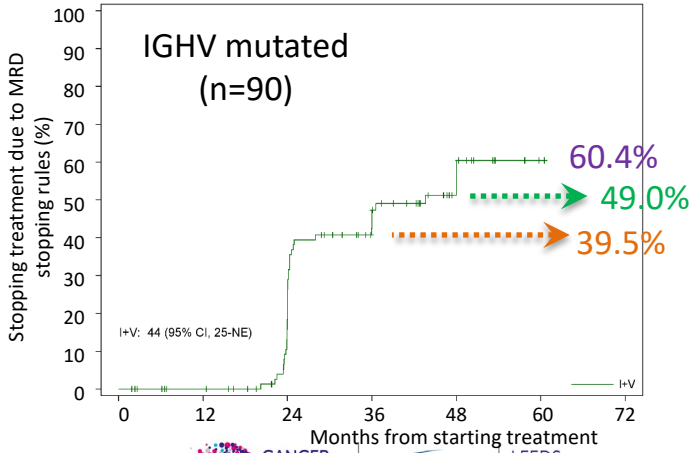
	Complete Response/CRi		Overall Response		BM uMRD
	9 months	Anytime	9 months	Anytime	Anytime
FCR	**49%**	**71.5%**	**76.4%**	**83.7%**	**40.3%**
I+V	**59.2%**	**92.3%**	**86.5%**	**95.4%**	**61.9%**

Odds ratio: 1.51 P<0.05

Odds ratio: 2.0 P<0.005







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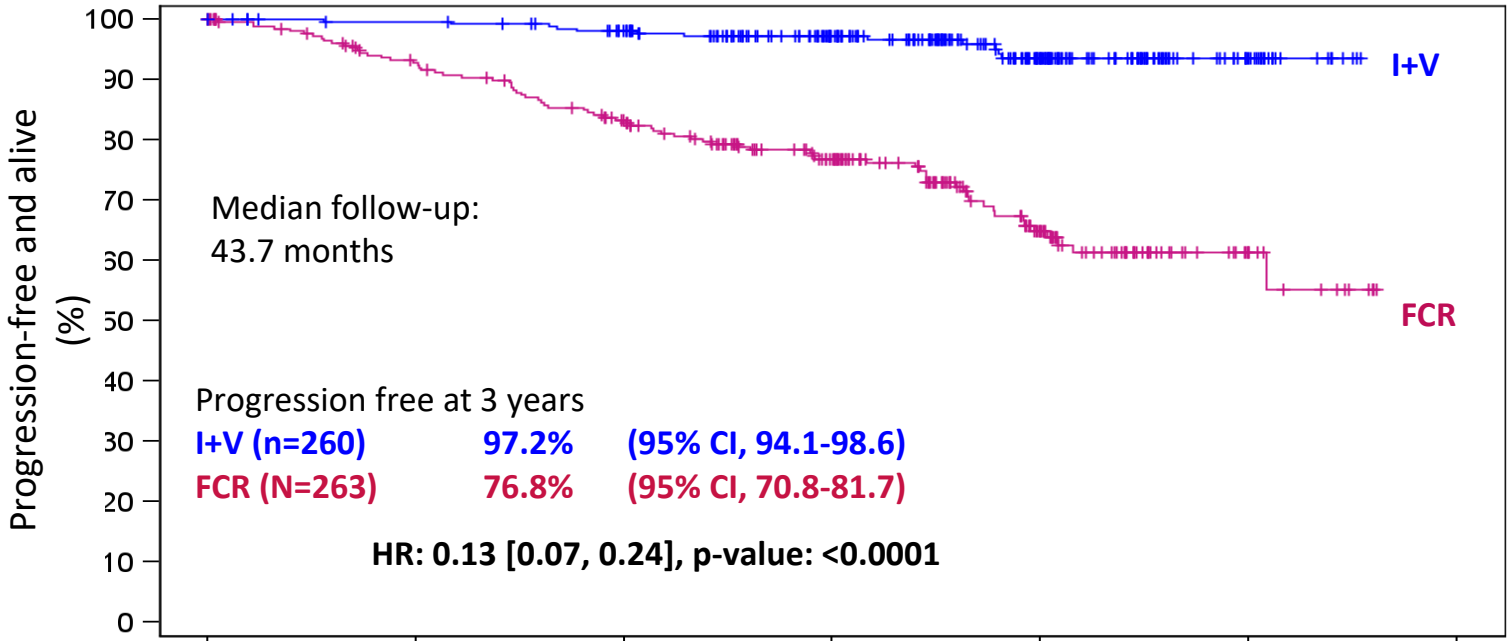
Flair Primary end-point: PFS for FCR versus I+V



No. at risk						
I+V	260	253	239	183	99	21	0
FCR	263	227	194	145	68	12	0

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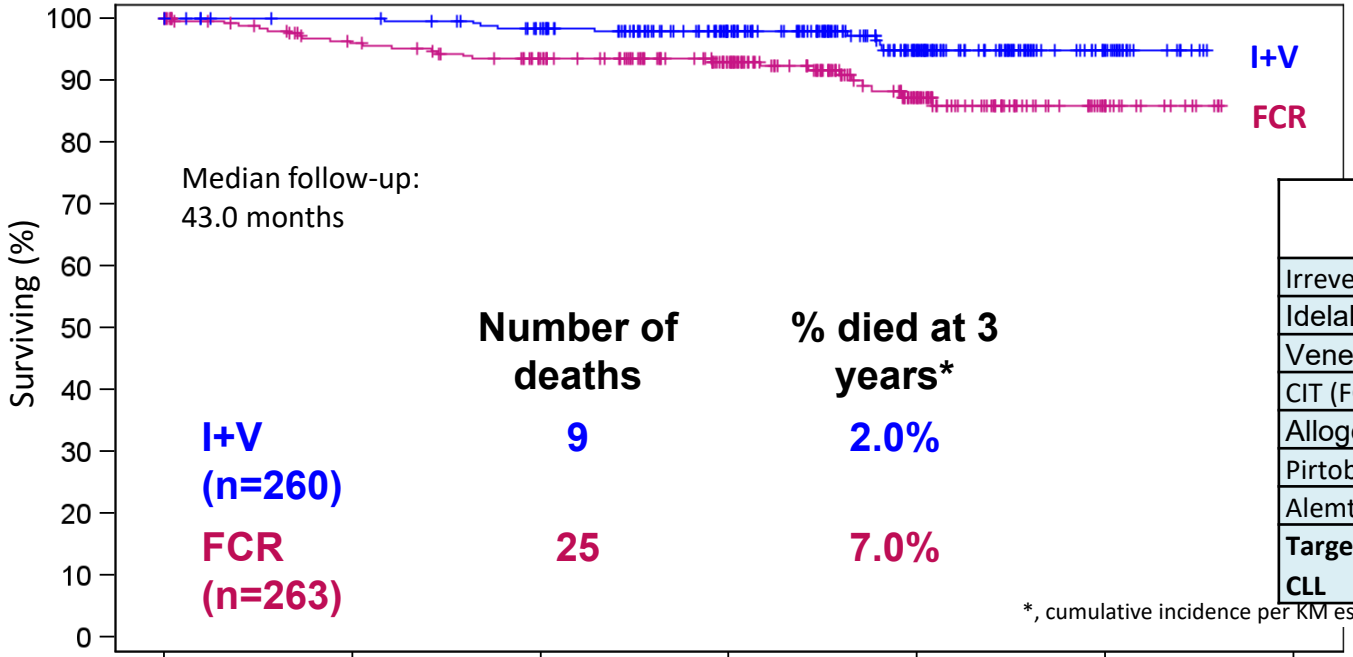
Flair Overall Survival in FCR versus I+V



Treatment after progression

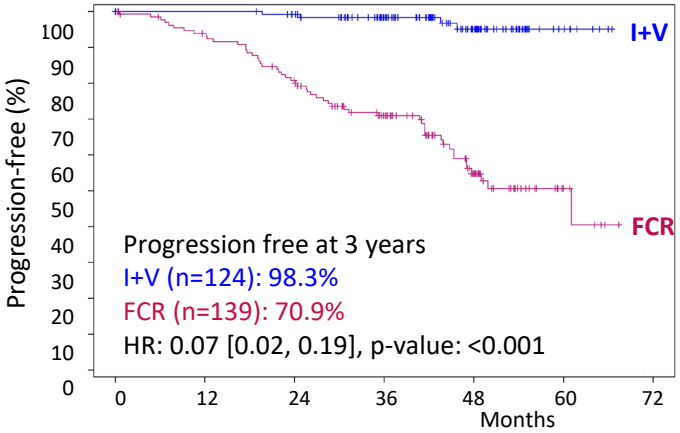
	FCR (n=42)	I+V (n=5)
Irreversible BTKi	23	2
Idelalisib + R	1	0
Venetoclax + R	11	0
CIT (FCR/BR/ChlR)	6	1
Allogeneic SCT	1	0
Pirtobrutinib	0	1
Alemtuzumab	0	1
Targeted therapy for CLL	**35/42 (83%)**	**3/5 (60%)**

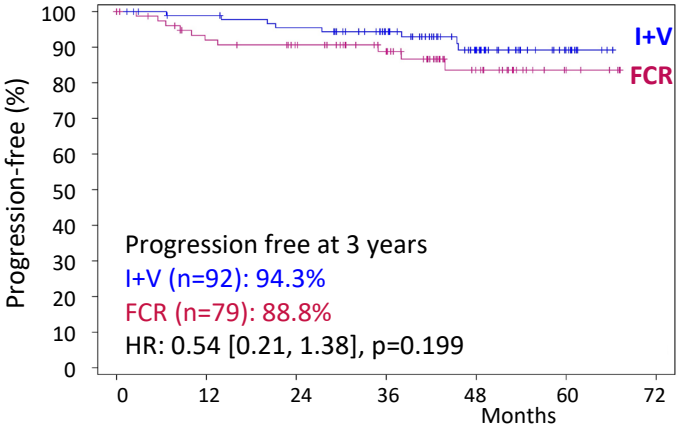
Flair Outcome by IGHV mutation status

IGHV unmutated (excl. Subset 2)

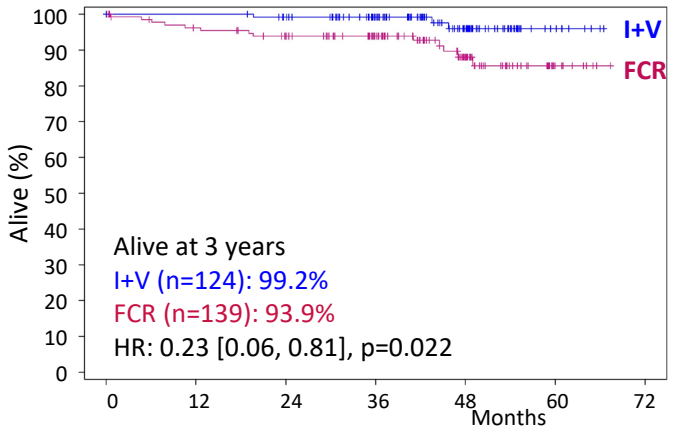
IGHV mutated (excl. Subset 2)

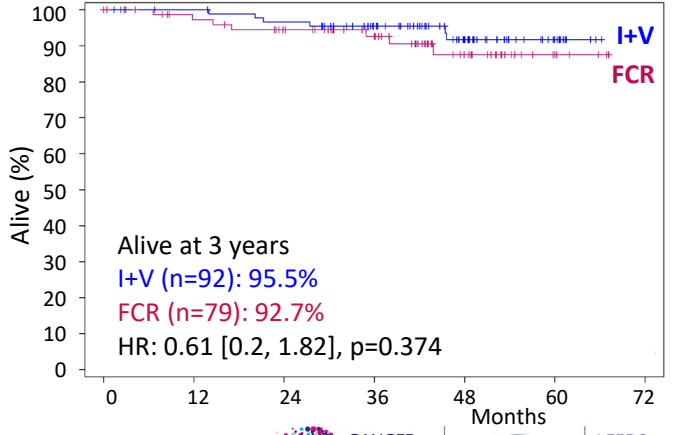
Progression Free Survival





Overall Survival





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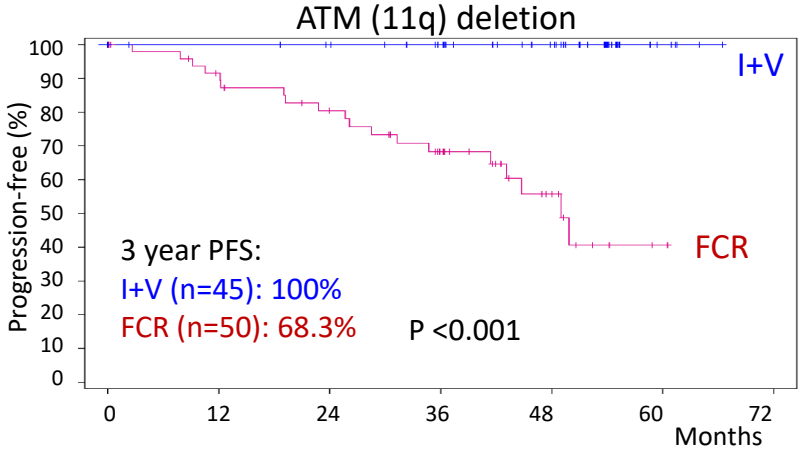
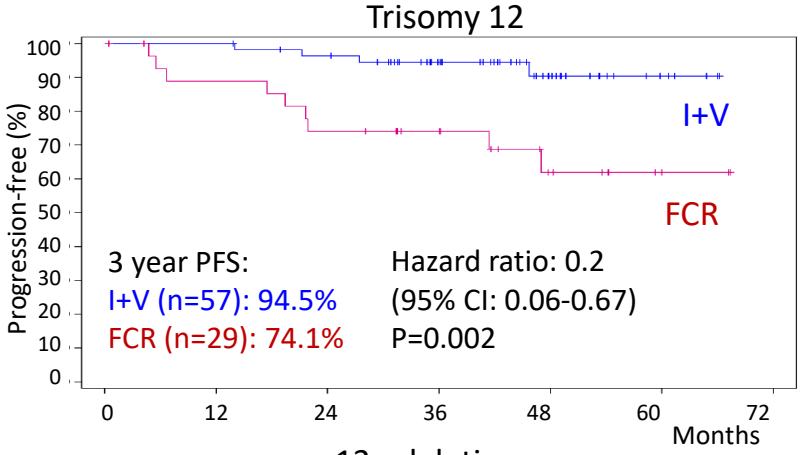
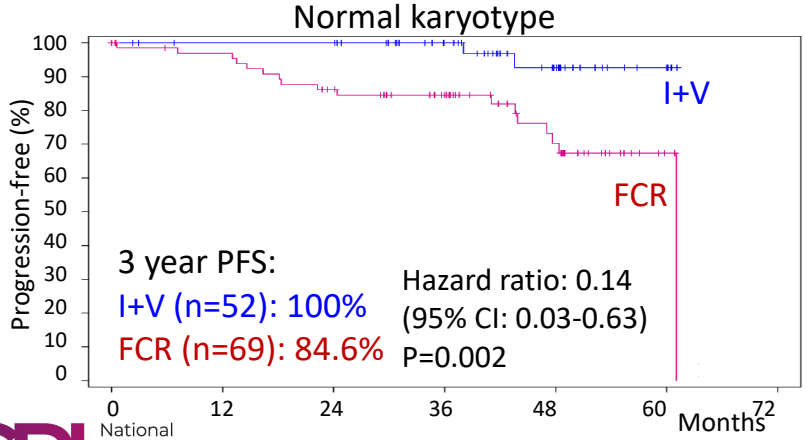
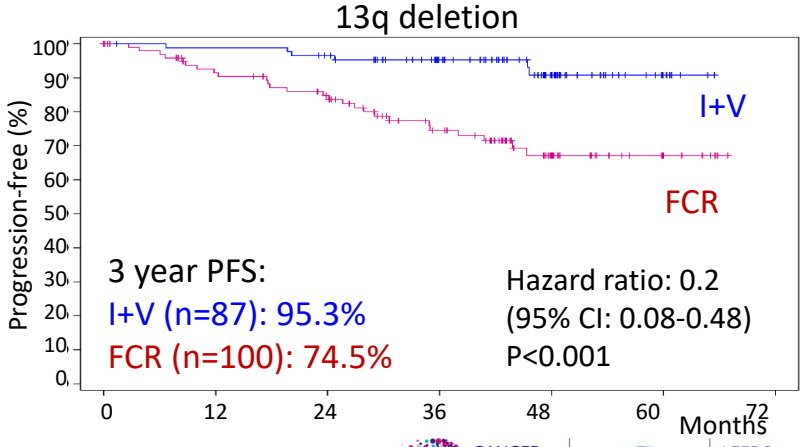
Flair FCR vs I+V: PFS hierarchical FISH abnormality









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Flair Serious Adverse Events & malignancies

SAEs, by MedDRA System organ class

	Number of participants reporting ≥1 SAE	
	FCR (n=239)	I+V (n=252)
Infections and infestations	45 (18.8%)	56 (22.2%)
Blood and lymphatic system disorders	**74 (31%)**	**13 (5.2%)**
Cardiac disorders	**1 (0.4%)**	**27 (10.7%)**
Gastrointestinal disorders	19 (7.9%)	9 (3.6%)
General disorders and administration site conditions	**12 (5%)**	**4 (1.6%)**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	5 (2.1%)	6 (2.4%)
Metabolism and nutrition disorders	**0 (0%)**	**10 (4%)**
Respiratory, thoracic and mediastinal disorders	6 (2.5%)	4 (1.6%)
Musculoskeletal and connective tissue disorders	3 (1.3%)	6 (2.4%)
Skin and subcutaneous tissue disorders	5 (2.1%)	4 (1.6%)
Nervous system disorders	2 (0.8%)	5 (2%)
Eye disorders	**0 (0%)**	**6 (2.4%)**

Secondary malignancies (SM)

	FCR	I+V
Incidence rate of cancers per 100 person-years (95% CIs)	**5.4** (5.11, 5.68)	**2.6** (2.40, 2.79)
BCC/SCC	16	13
MDS/AML	8	1
Lymphoma	5	3
Prostate/urological	5	1
Lung	3	0
GI	3	1
Breast	1	1
Melanoma	1	1
Myeloma	1	0
Endocrine	0	1
Other	5	2
Total patients*	**39**	**17**

*, some patients had more than one SM

Flair Safety and Toxicity: Deaths

- 31 deaths have occurred in the safety population. 23 from FCR participants and 8 from I+V.
- 7 deaths have been assessed as related to treatment (6 FCR; 1 I+V)
- 13 deaths were related to SAEs or SUSARs (8 FCR; 5 I+V)
- 2 of the 3 cardiac deaths in the I+V arm occurred after treatment was completed (35 days and 411 days later)

	FCR	I+V
Infection	7	1
Sudden/Cardiac	2	3
COVID-19	2	2
Richter's transformation	2	1
Non-haem malignancy	2	1
Allogeneic SCT – infection	1	0
Allogeneic SCT – GvHD	1	0
Disease progression	1	0
Hemorrhage	1	0
Lymphoma	1	0
Treatment related MDS/BMF	3	0
Total:	**23**	**8**

Flair Conclusion: MRD guided I+V versus FCR

- Ibrutinib plus venetoclax (I+V) significantly improved responses, progression free and overall survival compared to FCR in fit patients with previously untreated CLL
- More patients achieve an MRD negative remission with I+V than FCR
  - the majority of I+V patients achieve the MRD stopping criteria
- PFS better in IGHV unmutated, 11q deleted, Trisomy 12 and 13q deleted CLL amongst other sub-groups
- I+V was well tolerated with no unexpected toxicities
- The excellent results seen with I+V indicate that directing the duration of therapy according to individual MRD response maximizes outcomes

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Chronic Lymphocytic Leukemia Therapy Guided by Measurable Residual Disease

T. Munir, D.A. Cairns, A. Bloor, D. Allsup, K. Cwynarski, A. Pettitt, S. Paneesha, C.P. Fox, T.A. Eyre, F. Forconi, N. Elmusharaf, B. Kennedy, J. Gribben, N. Pemberton, O. Sheehy, G. Preston, A. Schuh, R. Walewska, L. Duley, D. Howard, A. Hockaday, S. Jackson, N. Greatorex, S. Girvan, S. Bell, J.M. Brown, N. Webster, S. Dalal, R. de Tute, A. Rawstron, P.E.M. Patten, and P. Hillmen, for the National Cancer Research Institute Chronic Lymphocytic Leukemia Subgroup*

N Engl J Med; 2024 Jan 25;390(4):326-337.

Conclusions

Current Advances:

- Huge progressive in the treatment of CLL over the last 10-15 years
  - Targeting the pathophysiology of CLL
- Chemotherapy replaced by targeted agents for all patients
  - Single agent targeted therapy leading to prolonged remissions
  - Managing toxicities critical
  - Combinations allow time limited therapy

Advances in the near future:

- Treatment stratified for IGHV mutated versus unmutated
- MRD guided therapy

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Flair Trial Management Group

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UK CLL Trials Biobank

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