4th POSTGRADUATE

CLL Conference

Bologna
November 13-14
2023

Royal Hotel Carlton

President:
Pier Luigi Zinzani

4th Postgraduate CLL Conference
Bologna

Is there a place for the new version of Fludarabine-containing regimen?

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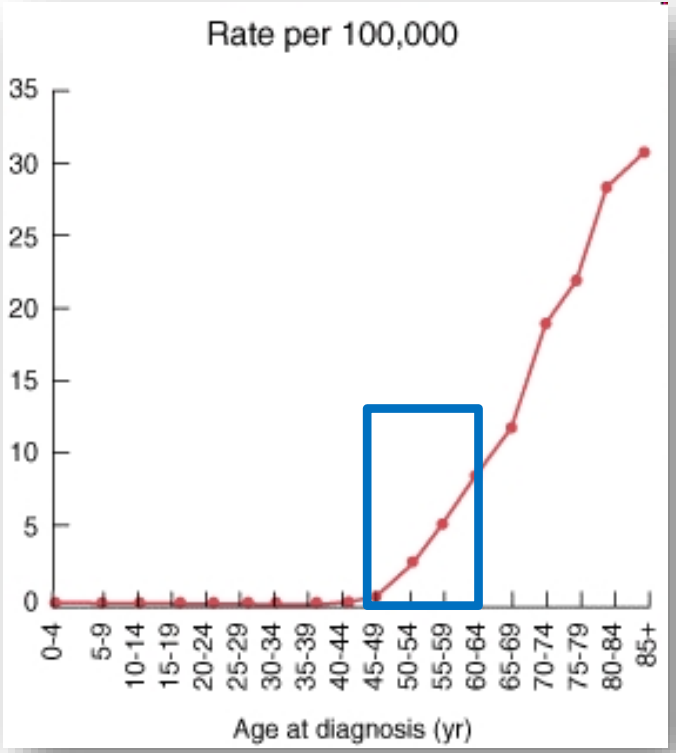
13 November, 2023

Disclosures of Matthew S. Davids, MD, MMSc

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie	✓		✓			✓	
Adaptive Biotechnologies			✓			✓	
Ascentage Pharma	✓		✓				
AstraZeneca	✓		✓			✓	
BeiGene			✓			✓	
Bristol-Myers Squibb			✓			✓	
Eli Lilly			✓			✓	
Genentech	✓		✓			✓	
Genmab			✓				
Janssen			✓			✓	
Merck			✓			✓	
Novartis	✓						
Nuvlaent			✓				
Research to Practice							✓ (Honoraria)
Secura Bio	✓		✓				
Takeda			✓			✓	
TG Therapeutics	✓		✓			✓	

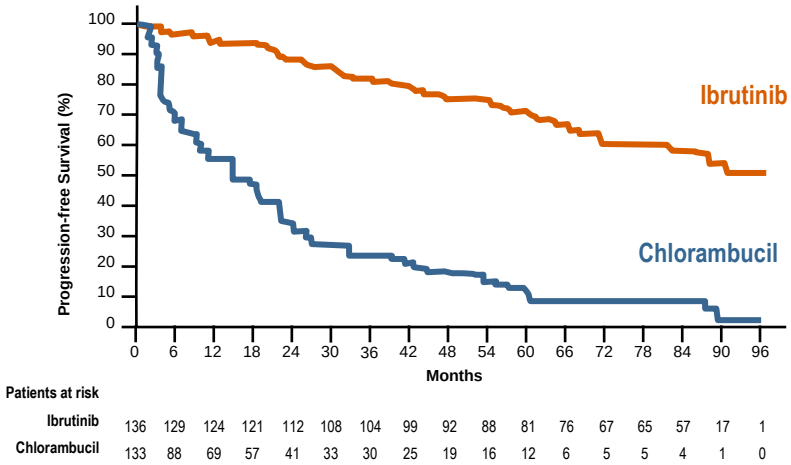
How can we provide our young, fit CLL patients with a normal lifespan?



US SEER Database, Accessed July 2021

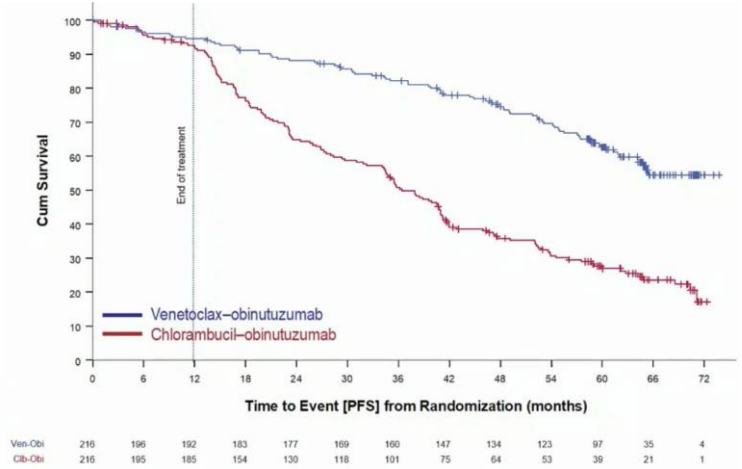
Very long-term follow-up is still not available for novel-agent only based approaches

RESONATE-2: 8-year PFS



Barr et al., *Blood Advances*, 2022

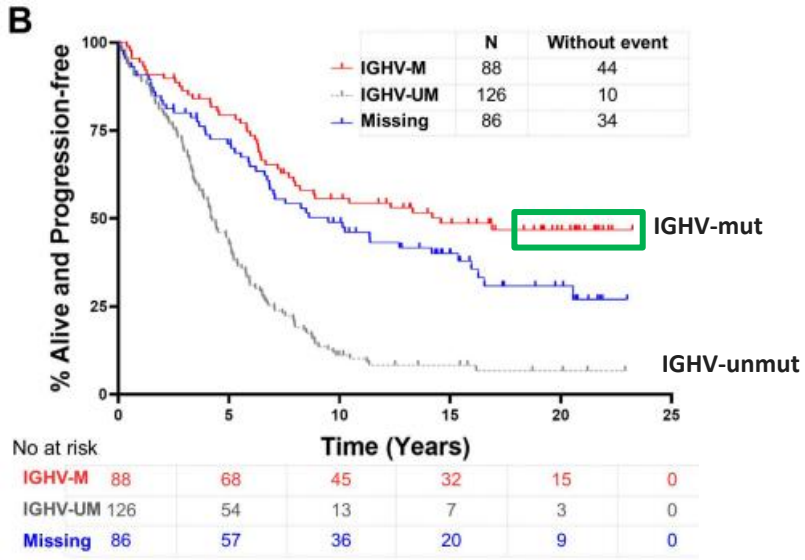
CLL14: 6-year PFS



Al-Sawaf et al., *ICML*, 2023

There is a precedent for functional cure in CLL with very long-term follow-up

FCR



Thompson et al., *Blood*, 2023

- **Secondary malignancies**
  - **32% overall including 6.3% MDS/AML**

- **Separate study of 797 CLL pts including WW:**
  - **36% with second cancers**
  - **<u>No difference</u> in WW vs treated**

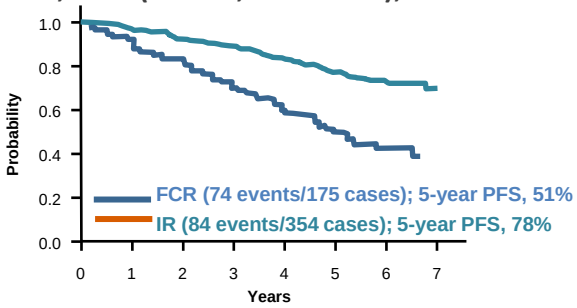
Falchi et al., *Ann Oncol*, 2016

Phase 3 Data of IR vs FCR

ECOG 1912 (US)[1]

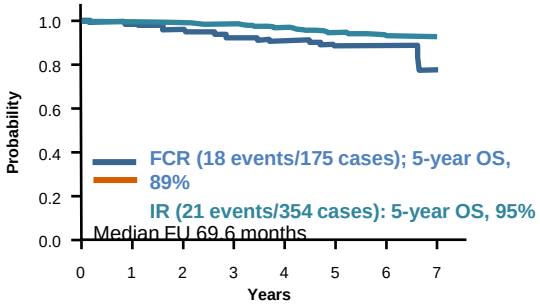
PFS

HR, 0.37 (95% CI, 0.27–0.51); *P* < 0.0001



OS

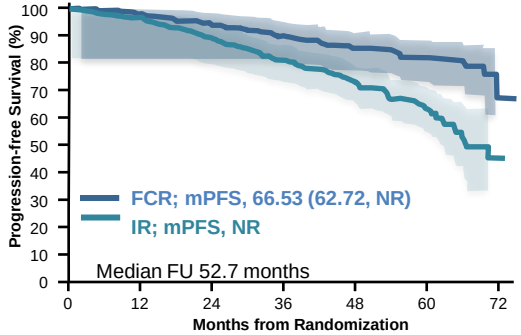
HR, 0.47 (95% CI, 0.25–0.89); *P* = 0.018



FLAIR (UK)[2]

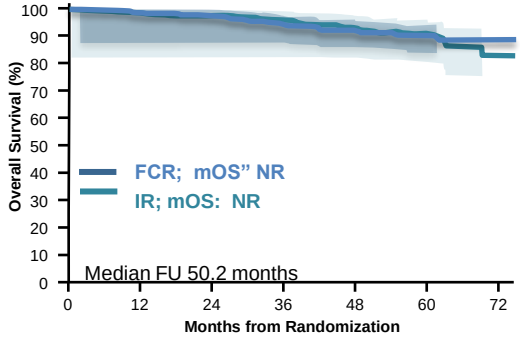
PFS

HR, 0.44 (95% CI, 0.32-0.60); *P* < 0.001



OS

HR, 1.01 (95% CI, 0.61-1.68); *P* = 0.9560



Shanafelt TD, et al. *Blood.* 2022;140(2):112-120. Hillmen, et al. *Blood.* 2021;138 (Supplement 1): 642.

Why choose?

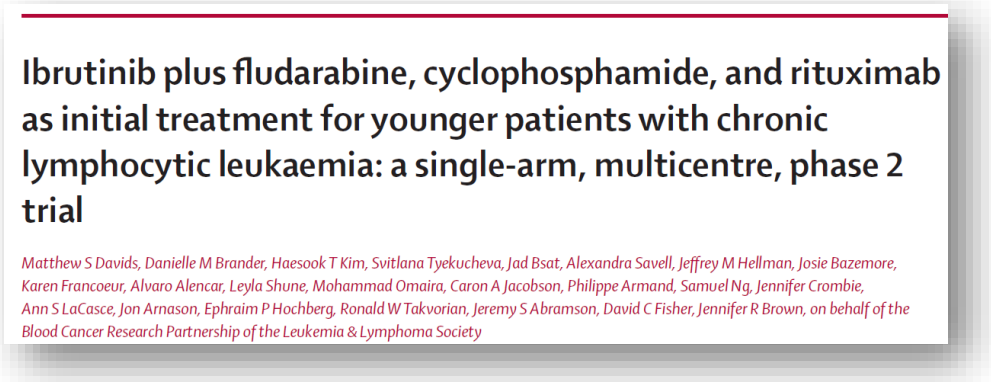
3 ongoing phase 2 studies are exploring ibrutinib + FC + CD20

iFCR (DFCI)

ICLL07 (FILO)

iFCG (MDACC)

iFCR trial



Ibrutinib plus fludarabine, cyclophosphamide, and rituximab as initial treatment for younger patients with chronic lymphocytic leukaemia: a single-arm, multicentre, phase 2 trial

Matthew S Davids, Danielle M Brander, Haesook T Kim, Svitlana Tyekucheva, Jad Bsat, Alexandra Savell, Jeffrey M Hellman, Josie Bazemore, Karen Francoeur, Alvaro Alencar, Leyla Shune, Mohammad Omaira, Caron A Jacobson, Philippe Armand, Samuel Ng, Jennifer Crombie, Ann S LaCasce, Jon Arnason, Ephraim P Hochberg, Ronald W Takvorian, Jeremy S Abramson, David C Fisher, Jennifer R Brown, on behalf of the Blood Cancer Research Partnership of the Leukemia & Lymphoma Society

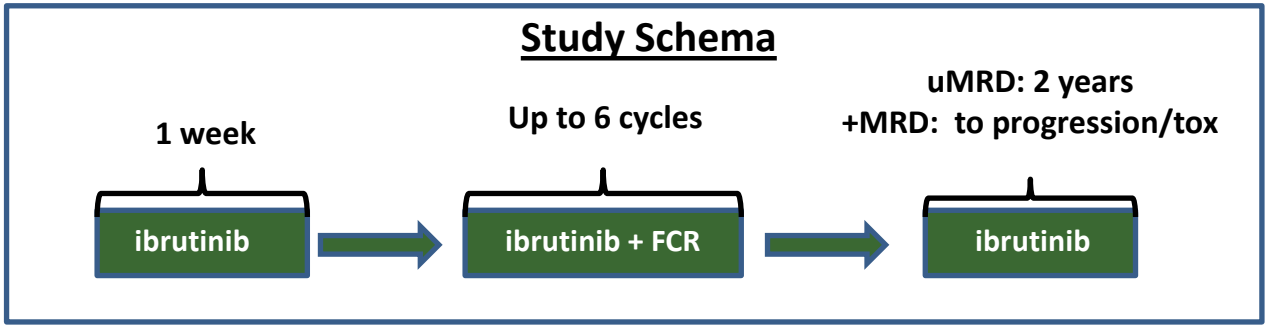
- N=85 patients enrolled at 7 US sites between 10/2014 and 4/2018
- Median age at enrollment: 55 years (range 38-65)
- FISH

del(17p)	del(11q)	Trisomy 12	del(13q)	Normal
n=4/83 (5%)	n=17/83 (20%)	n=14/83 (17%)	n=45/83 (54%)	n=14/82 (17%)

- Complex karyotype: 14/83 (17%), including 4/83 (5%) with del(17p) and 10/83 (12%) without
- *IGHV*: 46/79 (58%) unmutated
- Somatic Mutations: *TP53* mutated n=3, *NOTCH1* mutated n=5

Davids et al, *Lancet Haem*, 2019

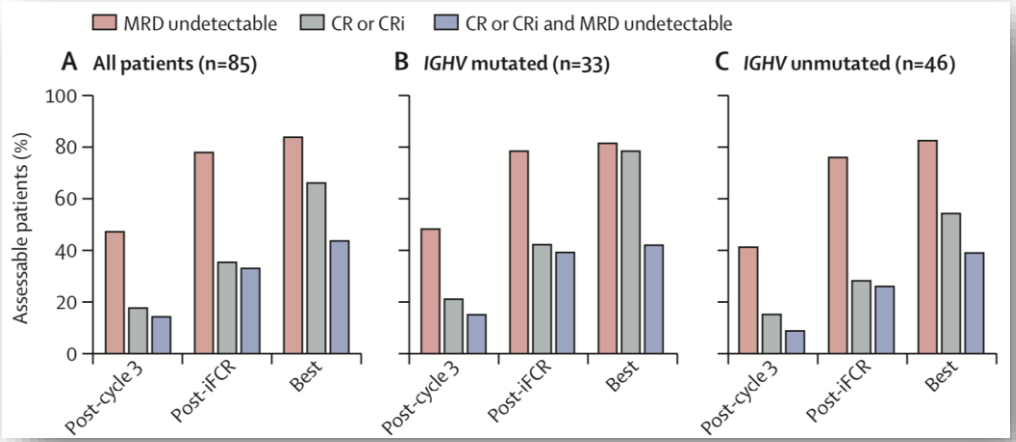
Phase 2 study of iFCR as initial therapy for younger CLL patients



- Ibrutinib dosed at 420 mg daily
- FCR dosed as per standard of care
- Retreatment with ibrutinib allowed in patients who relapse
- Toxicity assessments by CTCAE v4.03 and iwCLL hematologic criteria
- Response evaluations: after 3 cycles, 2 months after final FCR, then every 6 months
- Pegfilgrastim, PJP, and HSV/VZV prophylaxis mandatory for all patients

iFCR: Initial Efficacy and Safety Results

- Median follow-up at initial report 16.5 months (IQR 10.6–34.1)
- ***Primary Endpoint:*** CR with BM-uMRD 2 months after the last cycle of iFCR was achieved by 28/85 (33%, 95% CI 0·23–0·44)
- **Best BM-uMRD rate by ITT:** 84%, higher than any prior CIT or NA regimen for initial CLL therapy



Hematologic Toxicity:
- Neutropenia (62% all grade; 35% Gr 3-4)
- Thrombocytopenia (74% all grade; 32% Gr 3-4)
- Anemia (49% all grade; 11% Gr 3)

SAEs:
- Febrile neutropenia (9.4% (8/85))
- Atrial fibrillation (3.5% (3/85))
- *Pneumocystis jiroveci* pneumonia (2.4% (2/85), 1 on prophy, 1 off)
- 2º malignancies, all skin (7%, 6/85: 4 BCC, 1 each SCC and melanoma)
- Sudden death, presumed cardiac, 17 mo. into ibrut maint (1.2%, 1/85)

Davids et al, *Lancet Haem*, 2019

iFCR: Updated Safety Analysis

- Median follow-up now 63 mo. (6.8-95.8)

	Grade, N					Total, N (%)
	1	2	3	4	5	
Sudden cardiac death (during 2Y I-M)	0	0	0	0	1	1 (1)
Atrial fibrillation	4	1	2	0	0	7 (8)
Hypertension	6	14	6	0	0	26 (31)
Bruising	43	6	0	0	0	49 (58)
Hematoma	1	0	0	0	0	1 (1)
Febrile neutropenia	0	0	9	1	0	10 (12)
Second malignancy or hematologic disorder*	3	4	1	3	0	11 (13)

*** Second malignancy or hematologic disorder**

- Most commonly skin cancer: basal cell carcinoma (n=5), squamous cell carcinoma (n=1), malignant melanoma (n=1)

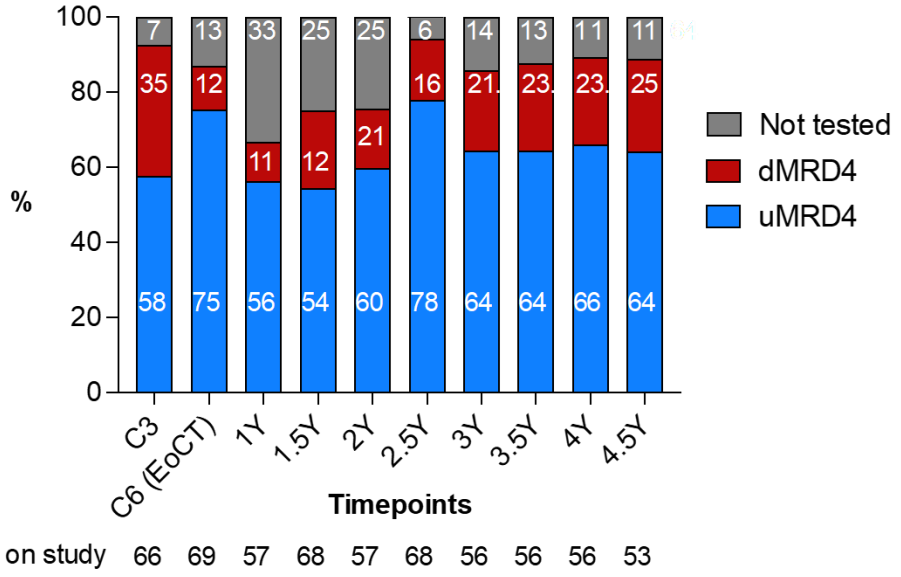
- Other conditions: hemophagocytic lymphohistiocytosis (n=1), myelodysplastic syndrome (MDS; n=2), aplastic anemia (n=1)
  - MDS: both patients had low-grade MDS, one patient started eltrombopag, the other on observation
  - Aplastic anemia: off study, pursued allogeneic stem cell transplant

No Richter's syndrome observed to date

Ahn et al, ICML, 2023

iFCR: Updated Efficacy Analysis

- MRD assessment using multi-color flow cytometry
- 69 patients had serial MRD data (more frequent PB data than BM data)
- Patients who were off study or did not reach the timepoints were considered unevaluable.
- **At 4.5Y, 64% of evaluable patients maintained PB-uMRD4.**
- NGS-based MRD assessment is ongoing.

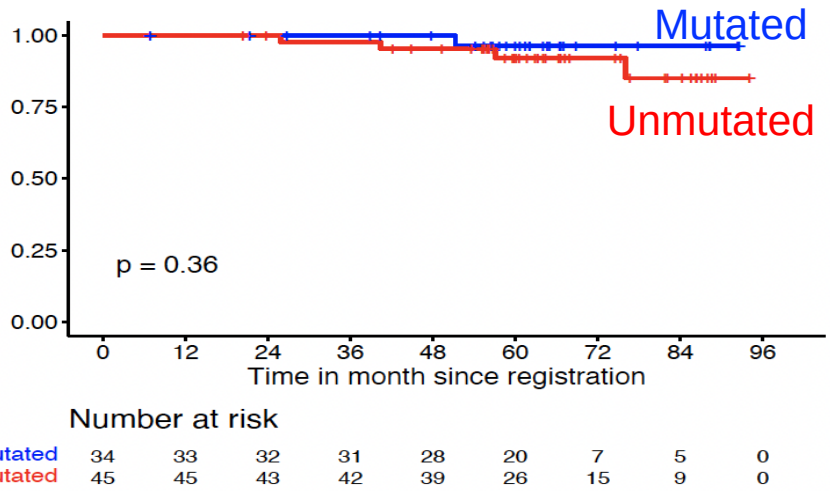


Ahn et al, ICML, 2023

iFCR: Updated Survival Data

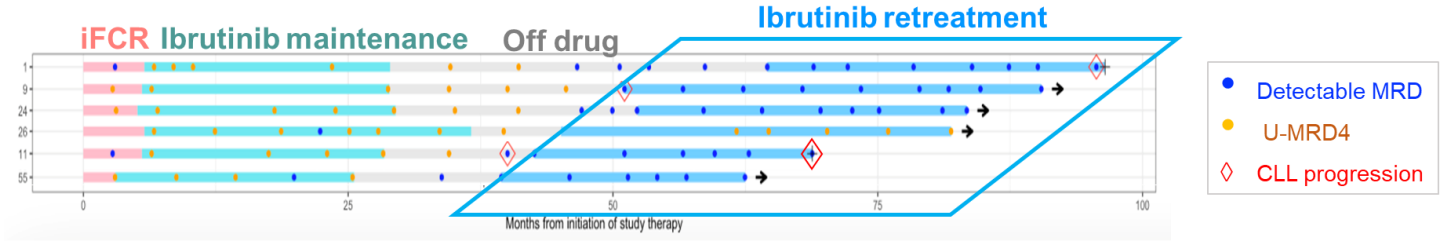
- Median follow-up of 63 months (range 6.8-95.8)
- 5 CLL progression and 1 death
- 5-year OS: 99% (95% CI 96-100%)
- 5-year PFS: 94% (95% CI 89-100%)
- No significant PFS difference based on IGHV status

PFS by IGHV mutation status



Ahn et al, ICML, 2023

iFCR: Re-treatment with ibrutinib can be effective

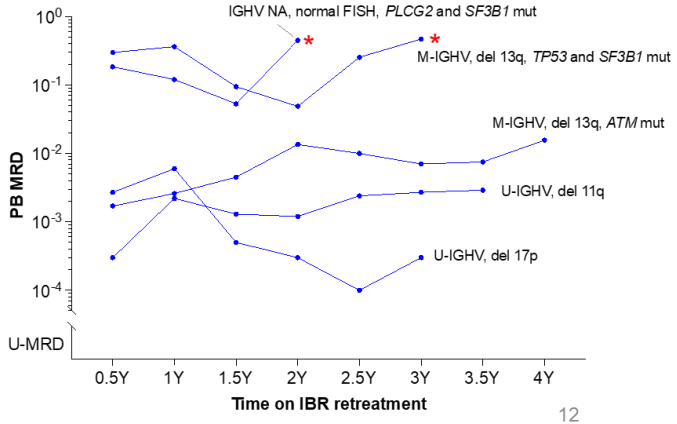


6 patients received IBR retreatment

- All had MRD conversion, 2 had CLL progression
- Median time on retreatment: 34 months

Outcome

- 4 of 6 patients responded to retreatment (3 PR, 1 unconfirmed CR)
- 2 had stable disease → CLL progression at 32 & 23 months on retreatment
- MRD growth stabilized but was not eradicated during retreatment.



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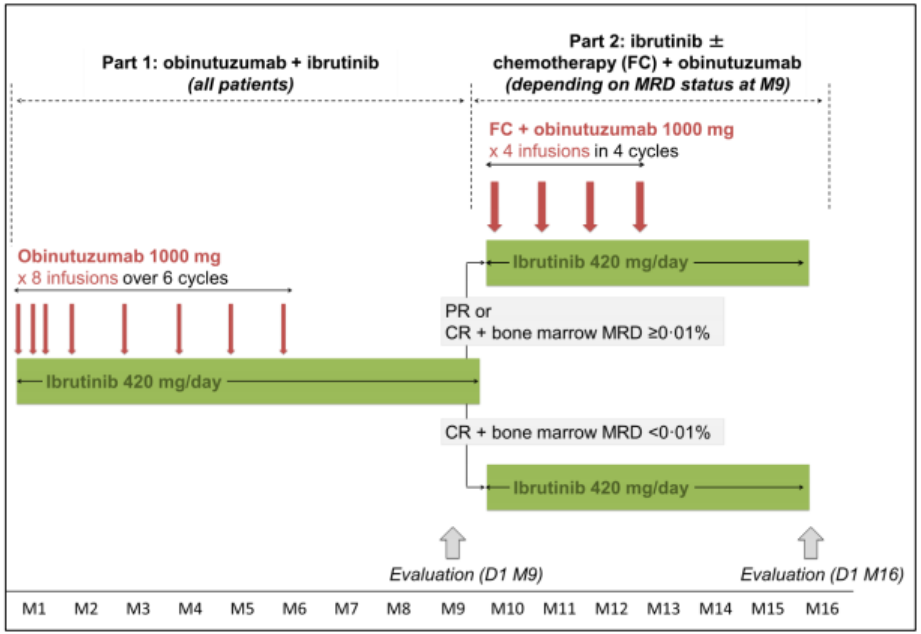
Ahn et al, ICML, 2023

Phase 2 ICLL07 FILO Study



- N=135
- Median age 62 (range 52-66)
- 56% U-IGHV
- Del(17p) excluded
- 10 pts had CR + BM-uMRD in part 1
- 115 patients received iFCO

Michallet et al, *Lancet Haem*, 2019

Phase 2 ICLL07 FILO Study: Safety

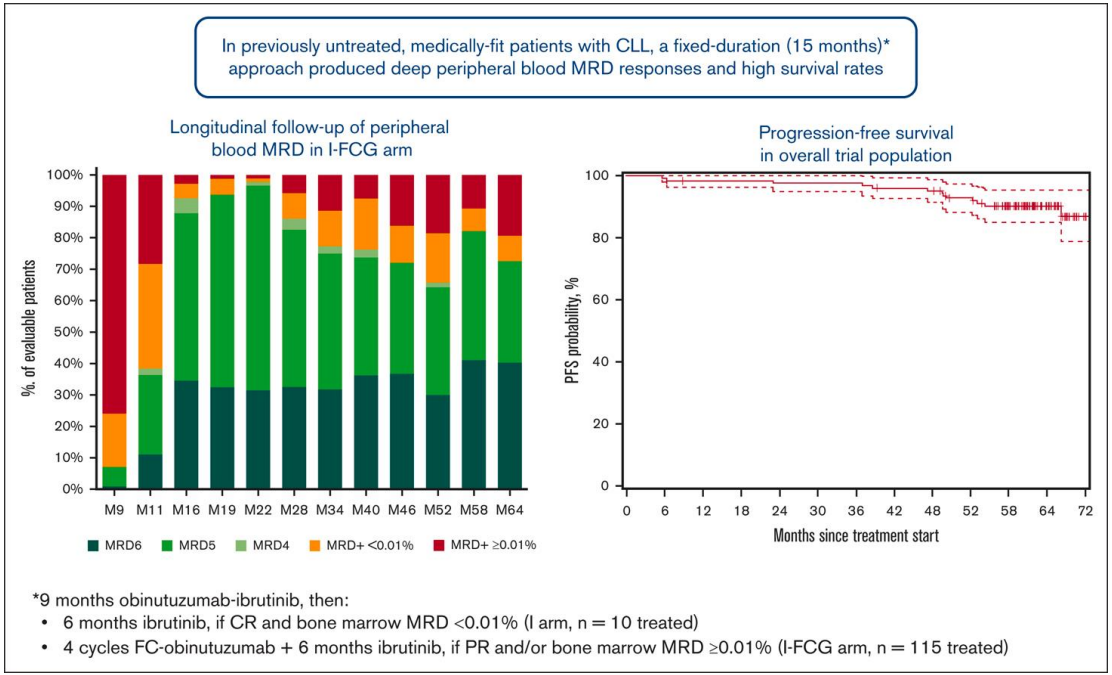
	Induction phase (n=133)			MRD-guided phase (n=125)		
	Grade 1 and 2 events	Grade 3 events	Grade 4 events	Grade 1 and 2 events	Grade 3 events	Grade 4 events
Haematological adverse events						
Thrombocytopenia	45 (34%)	22 (17%)	20 (15%)	43 (33%)	10 (8%)	9 (7%)
Neutropenia	14 (11%)	17 (13%)	15 (11%)	15 (12%)	20 (15%)	11 (8%)
Anaemia	26 (20%)	5 (4%)	2 (2%)	34 (26%)	3 (2%)	3 (2%)
Febrile neutropenia	..	2 (2%)	..	..	2 (2%)	2 (2%)
Non-haematological adverse events						
Gastrointestinal disorders	14 (11%)	4 (3%)	-	62 (48%)	10 (8%)	3 (2%)
Cardiac events	..	..	3 (2%)	..	..	3 (2%)
Infusion-related reactions	83 (62%)	7 (5%)	4 (3%)	..	..	..
Tissue disorders	13 (10%)	..	..	..	..	..
Hepatobiliary disorders	13 (10%)	..	..	..	..	..

Data are n (%) of patients. Grade 1 and 2 adverse events in ≥10% of patients and all grade 3 and 4 adverse events are shown. Three deaths occurred: one sudden death at month 8; one accidental fall at month 7; one death due to Hodgkin lymphoma Epstein Barr virus-associated haemophagocytosis syndrome at month 23.

Michallet et al, *Lancet Haem*, 2019

Phase 2 ICLL07 FILO Study: Efficacy

- Primary endpoint: 62% achieved CR with BM-uMRD after 15 mo. treatment



- Median follow-up 63 mo.
- PB uMRD (10-4) at mo. 64 was 80.6%, with no difference based on IGHV status
- 4 yr PFS/OS: 95.5%, 96.2%

Michallet et al, *Blood Adv*, 2023

Phase 2 iFCG Study

iFCG 3 courses

↓

Ibrutinib 9 courses (all pts)
+
Obinutuzumab 3 courses (CR/CRi with BM U-MRD4)
or
Obinutuzumab 9 courses (PR or BM MRD^{pos})

↓

After 12 courses
BM U-MRD4 → stop ibrutinib
BM MRD^{pos} → continue ibrutinib

- N=45
- Median age 60 (range 25-71)
- 100% Mutated IGHV
- Del(17p) excluded
- After 3 courses of iFCG:
  - 17 pts with CR with BM-uMRD
  - 27 pts with PR and/or BM-dMRD

Antiviral prophylaxis with acyclovir / valacyclovir required, PJP prophylaxis optional
Prophylactic G-CSF optional in the early part of the trial (later required)

Jain et al, *Leukemia*, 2021

Phase 2 iFCG Study: Safety

- Grade 3/4 Hematologic AEs:
  - Neutropenia (60%)
  - Thrombocytopenia (40%)
- Neutropenic fever in 13%
- 1 pt developed MDS

Table 2 Non-hematologic adverse events in all 45 patients[a].

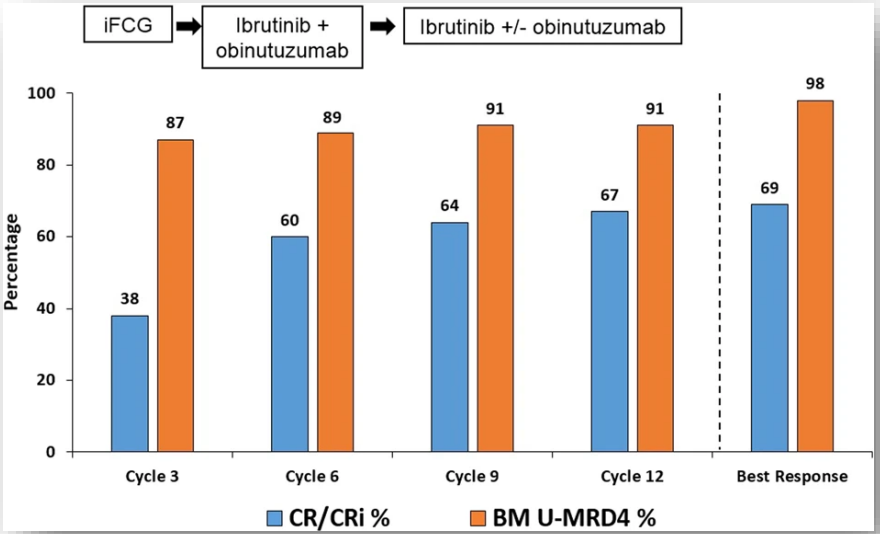
Event	No. of patients (%)	
	Any grade	Grade 3 or higher
Nausea/vomiting	26 (58)	0
Easy bruising	25 (56)	0
Infusion-related reactions	20 (44)	2 (4)
Skin rash	16 (36)	0
Arthralgia	16 (36)	1 (2)
Atrial fibrillation	5 (11)	2 (4)
Diarrhea	5 (11)	0
Myalgia	5 (11)	0
Gastroesophageal reflux disease	5 (11)	0
Taste changes	5 (11)	0
Fatigue	4 (9)	0
Dry skin	3 (7)	0
Nail changes	3 (7)	0
Constipation	3 (7)	0

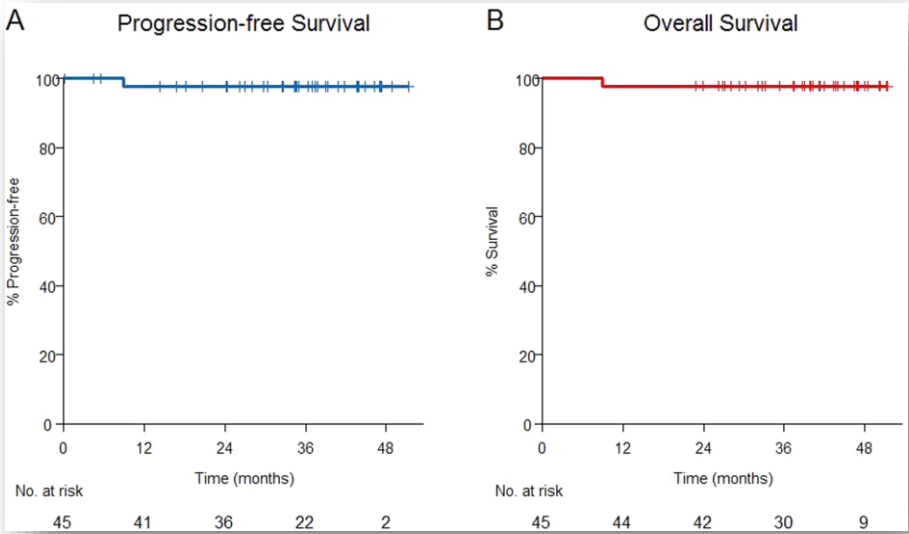
[a]Shown are adverse events at least possibly related to the study drugs and reported in at least 5% of the patients.

Jain et al, *Leukemia*, 2021

Phase 2 iFCG Study: Efficacy

Primary Endpoint: After three cycles of iFCG, 17/45 (38%, 90% CI 26–53%) patients achieved CR/CRi with BM U-MRD



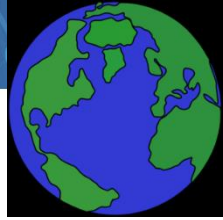


Jain et al, *Leukemia*, 2021

Summary of major studies of ibrutinib + FC + CD20

	iFCR-DFCI[1]	ICLL07-FILO[2]	iFCG-MDACC[3]
N	85	135	45
Median age (yrs, range)	55 (38-65)	62 (52-66)	60 (25-71)
IGHV unmutated	58%	56%	0%
TP53 aberrancy	5%	0%	0%
Median follow-up (mo.)	63	63	41.3
CR with BM-UMRD	33% (6 mo tx)	62% (15 mo tx)	38% (3 mo tx)
Best BM-UMRD	84% (91% in *TP53* wildtype)	79%	98%
5/4/3-year PFS / OS	94% / 99%	95.7% / 97.7%	98% / 98%
tMDS	2.4%	1.5%	2.2%

[1]Davids et al, *Lancet Haem*, 2019 and Ahn et al., *ICML*, 2023 [2]Michallet et al, *Lancet Haem*, 2019 and *Blood Adv*, 2023 [3]Jain et al, *Leukemia*, 2021



Selected ongoing Phase 3 frontline CLL trials

- **CLL13/GAIA**: FCR/BR vs. VR, vs. VO, vs. IVO (n=920)
- **UK NCRI FLAIR**: FCR vs. I vs. IV (vs. IR) (n=1,522)
- **Alliance A041702**: IO vs. IVO (older pts, n=454)
- **ECOG EA9161**: IO vs. IVO (younger pts, n=720)
- **ACE-CL-311:** AVO vs. AV vs. FCR/BR (n=780)
- **CLL17**: I vs. IV vs. VO (all comers, n=882)
- **MAJIC:** AV vs. VO (all comers, n=750)
-

Conclusioni

- **Continuous and time-limited novel agent only frontline regimens do not yet have very long-term follow-up, and their curative potential is currently unknown**
- **FCR remains the only conventional time-limited therapy with demonstrated curative potential with very long-term follow-up (now 20 years!)**
- **Three recent phase 2 studies combining ibrutinib with FC plus anti-CD20 have shown consistent results, with deep responses and reasonable tolerability in young, fit patients (iFCR, ICLL07, iFCG)**
- **Longer term follow-up is needed to better understand PFS/OS, rates of secondary cancers**
- **These data should not be extrapolated to the broader, more typical older CLL population**
- **This new approach cannot be considered standard of care without future comparative studies**


Grazie!