3rd POSTGRADUATE

CLL Conference

Bologna
November 14-15
2022

Royal Hotel Carlton

President:
Pier Luigi Zinzani

New version of Fludarabine-containing regimen

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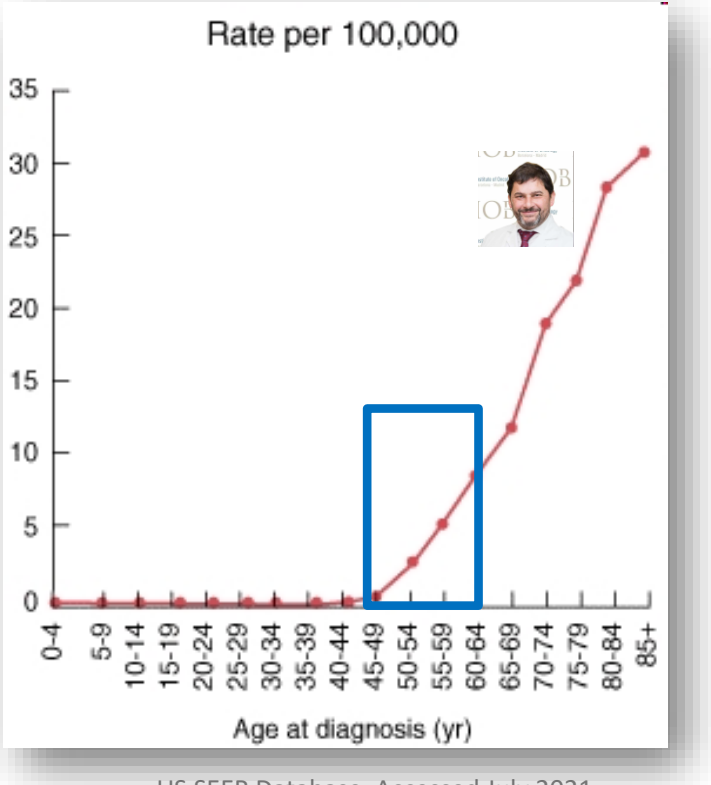
14 November, 2022

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	✓		✓			✓	
Janssen			✓			✓	
Merck			✓			✓	
Novartis	✓						
Ono Pharmaceuticals			✓				
Research to Practice							✓ (Honoraria)
Secura Bio	✓		✓				
Takeda			✓			✓	
TG Therapeutics	✓		✓			✓	

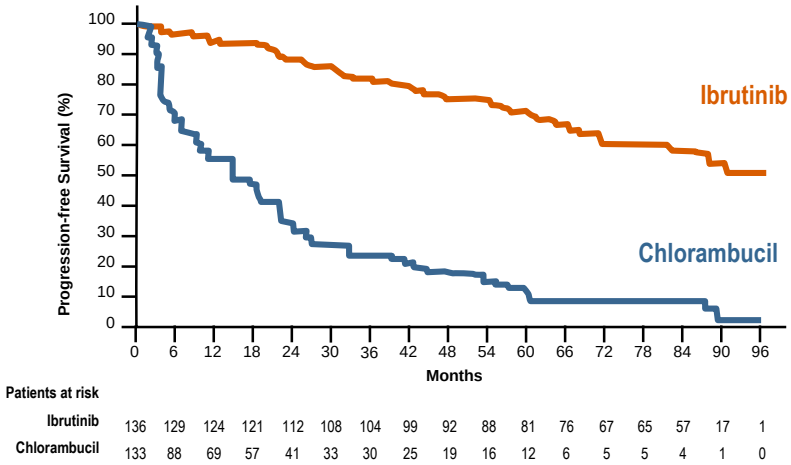
How can we provide our young, fit CLL patients with a normal lifespan?



US SEER Database, Accessed July 2021

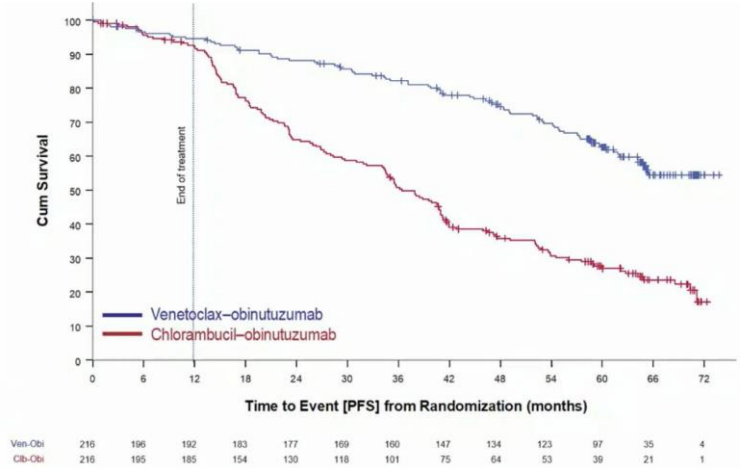
Very long-term follow-up is still not available for novel-agent only based approaches

RESONATE-2: 8-year PFS



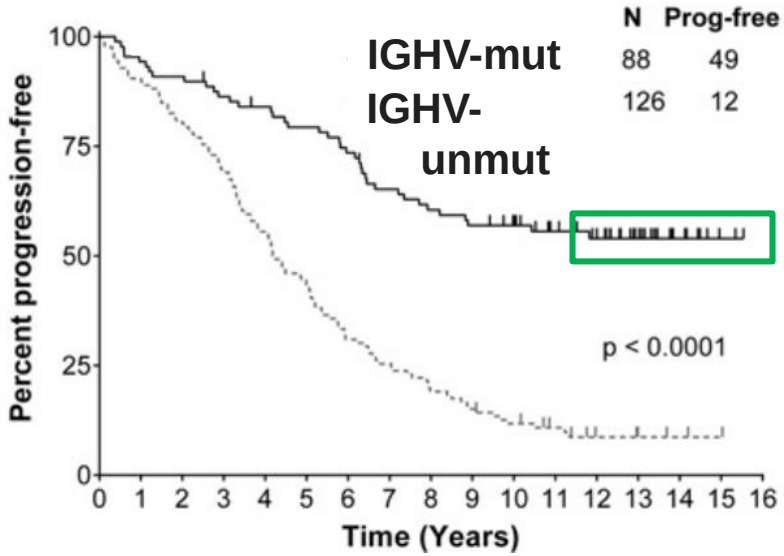
Barr et al., *Blood Advances*, 2022

CLL14: 5-year PFS



Al Sawaf et al., *EHA Annual Meeting*, 2022

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



Thompson et al., *Blood*, 2016

- Secondary malignancies
  - Solid tumors (21% [~1/2 NMSC])
  - RT (8%)
  - Other Hematologic (6%)
- Separate study of 797 CLL pts including WW:
  - 36% with second cancers
  - No difference in WW vs treated

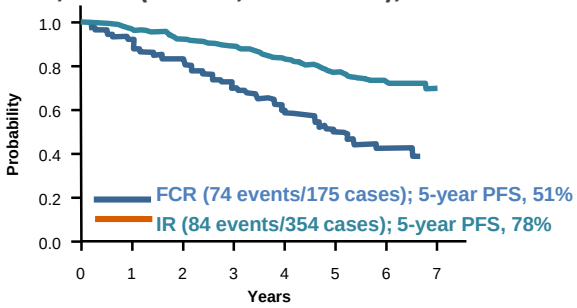
Falchi et al., *Ann Oncol*, 2016

Phase 3 Data of IR vs FCR

ECOG 1912 (US)[1]

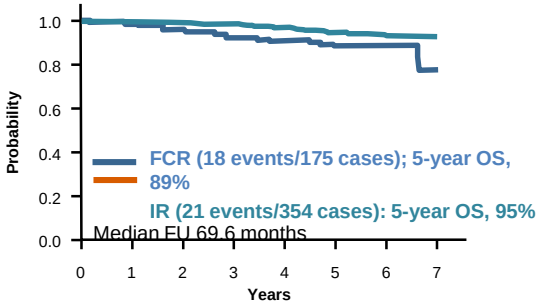
PFS

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

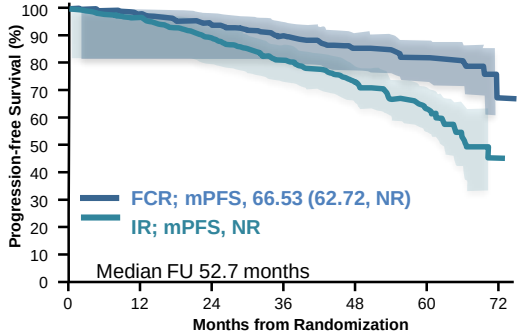


Shanafelt TD, et al. *Blood.* 2022;140(2):112-120.

FLAIR (UK)[2]

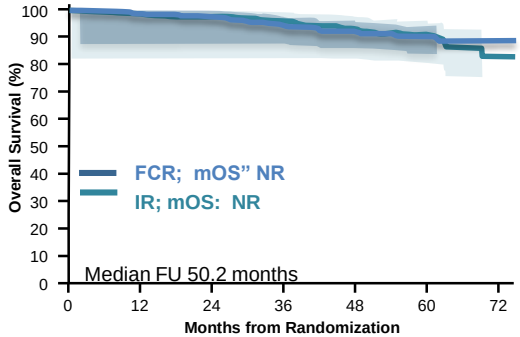
PFS

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



OS

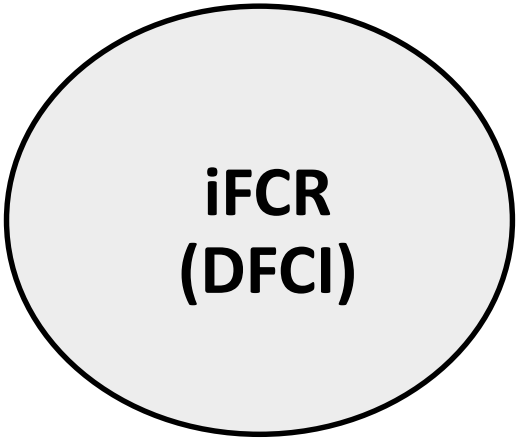
HR, 1.01 (95% CI, 0.61-1.68); *P* = 0.9560

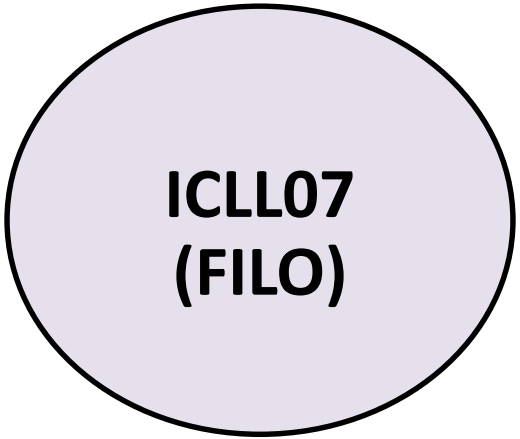


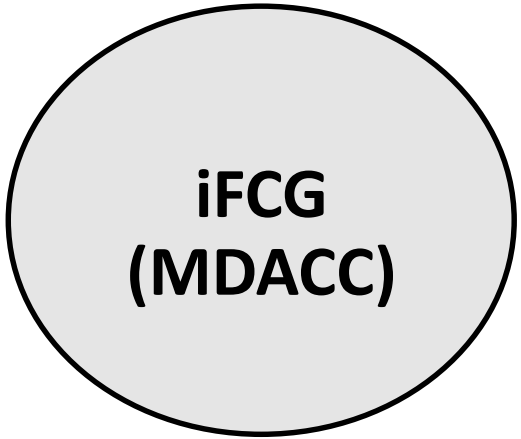
Hillmen, et al. *Blood.* 2021;138 (Supplement 1): 642

Why choose?

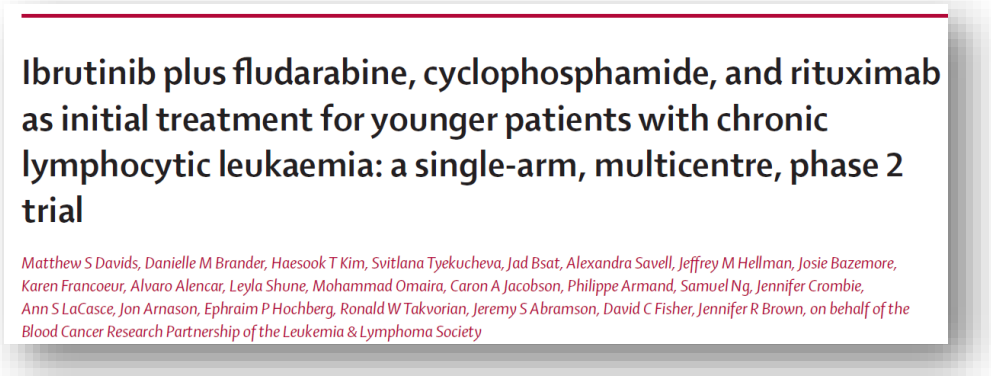
3 ongoing phase 2 studies are exploring ibrutinib + FC + CD20







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

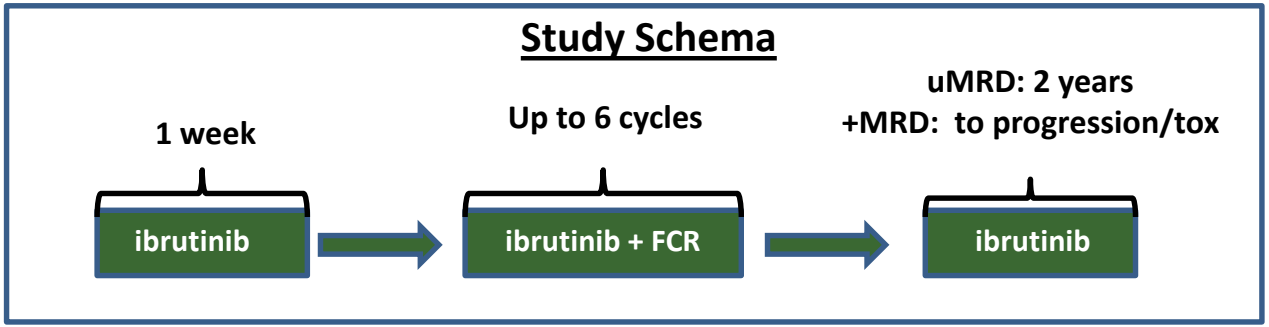
- N=85 patients enrolled at 7 US sites between 10/2014 and 4/2018
- Median age at enrollment: 55 years (range 38-65)
- FISH

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

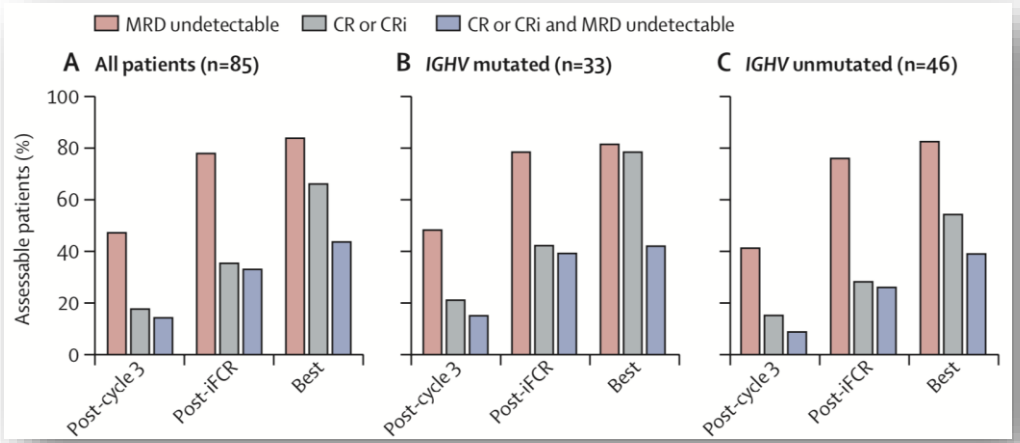
Phase 2 study of iFCR as initial therapy for younger CLL patients



- 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 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 40.3 mo. (3.1-76)

Selected non-hematologic tox in >25% of pts:

Toxicity	Grade 1-2	Grade 3	Grade 4
Nausea	62 (73%)	1 (1%)	0
Bruising	46 (54%)	0	0
Arthralgia	33 (39%)	0	0
Diarrhea	32 (38%)	3 (4%)	0
Constipation	30 (35%)	0	0
Cough	30 (35%)	0	0
Hyponatremia	29 (34%)	1 (1%)	1 (1%)
URI	28 (33%)	0	0
Acneiform rash	27 (32%)	1 (1%)	0
Increased AST	26 (31%)	2 (2%)	2 (2%)
Myalgia	23 (27%)	0	0
Headache	22 (26%)	0	0
Hypertension	19 (22%)	4 (5%)	0

Hematologic Toxicity:

- Neutropenia (40% Gr 3-4, up from 35% from previous report)
- Thrombocytopenia (32% Gr 3-4, unchanged from previous report)
- Anemia (11% Gr 3, unchanged from previous report)

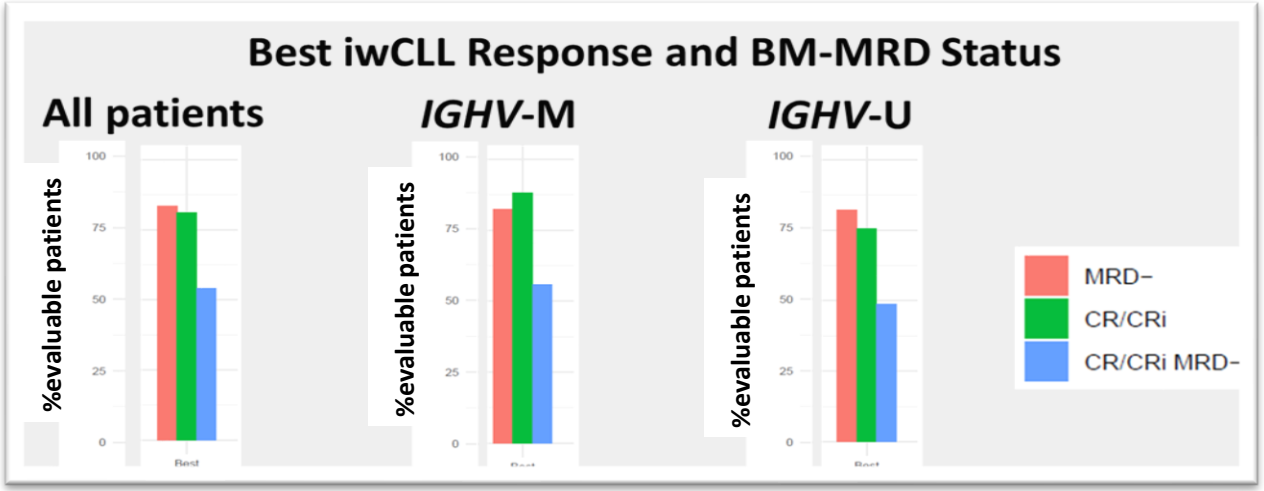
Additional SAEs:

- Febrile neutropenia (12% (10/85), up from 9% previously)
- Afib (8% (7/85) up from 3.5% previously)
- 3 pts with COVID-19 infection after vaccination while off tx (all recovered)
- 2 pts developed MDS, both now in CR for CLL and MDS after allo transplant

No Richter's syndrome observed to date

Davids et al, *ASH Annual Meeting*, 2021

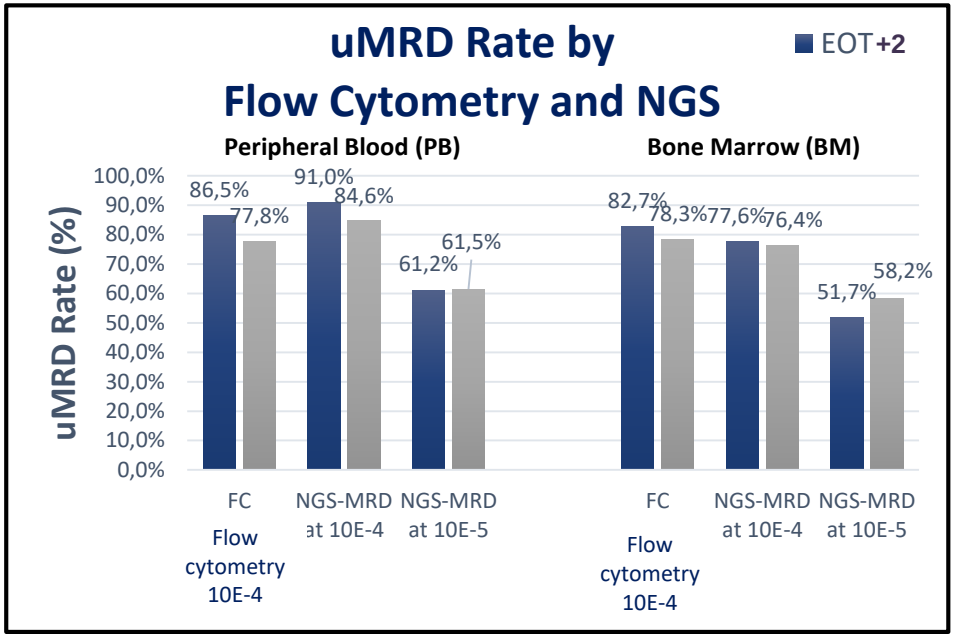
iFCR: Updated Efficacy Analysis



- Best rate of CR with BM-uMRD by ITT increased to 55% with ibrutinib maintenance
- CR rate deepened with ibrutinib maintenance from 34% 2 mo. post-FCR to 81% as best rate
  - IGHV-M: 41% 2 mo. post-FCR to 88% as best rate
  - IGHV-U: 28% 2 mo. post-FCR to 76% as best rate
- Best rate of BM-uMRD by ITT remained at 84%
- Best BM MRD-negative by ITT: 91% in the 81 patients with wildtype *TP53*

Davids et al, *ASH Annual Meeting*, 2021

iFCR: Updated MRD Analysis with NGS data



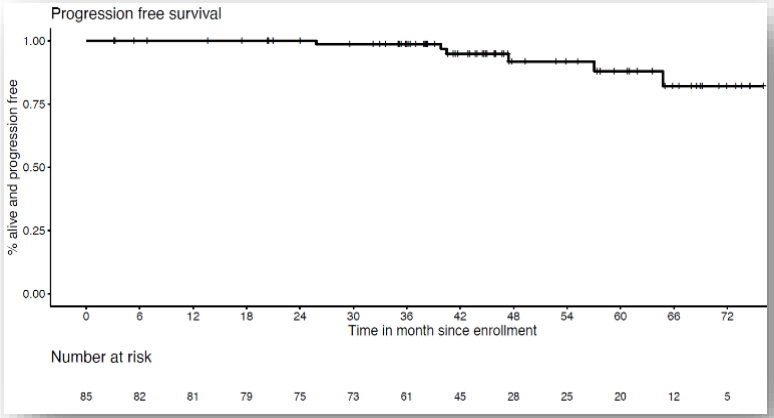
- **NGS-MRD data at 10^{-6} limited due to low number of total cells counted:**
  - Of 52 patients with paired EOT + 2 mo. flow/NGS samples from PB: 18/52 (35%) negative by flow at 10^{-4} were detectable at 10^{-6} by NGS
  - 22/44 (50%) patients with paired BM samples were negative by flow at 10^{-4} and detectable at 10^{-6} by NGS
  - At end of ibrutinib maintenance (24 mo. post FCR), 17/40 (43%) patients with paired BM samples were negative by flow at 10^{-4} and detectable at 10^{-6} by NGS

Davids et al, *ASH Annual Meeting*, 2021

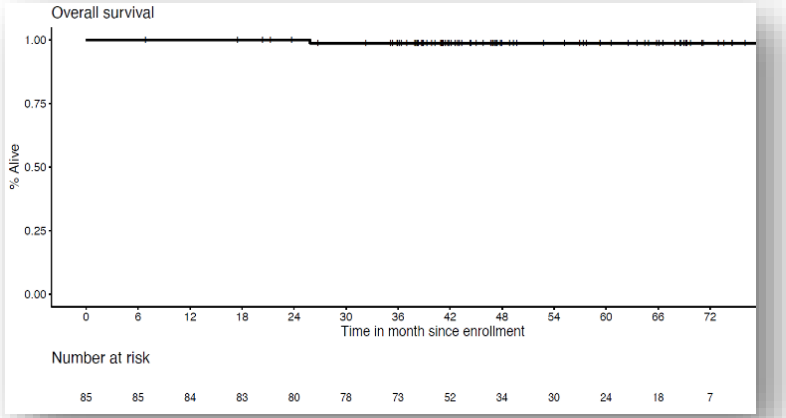
iFCR: Updated survival analyses

- Median follow-up 40.3 mo. (3.1-76)

PFS-1 (97% at median follow-up)



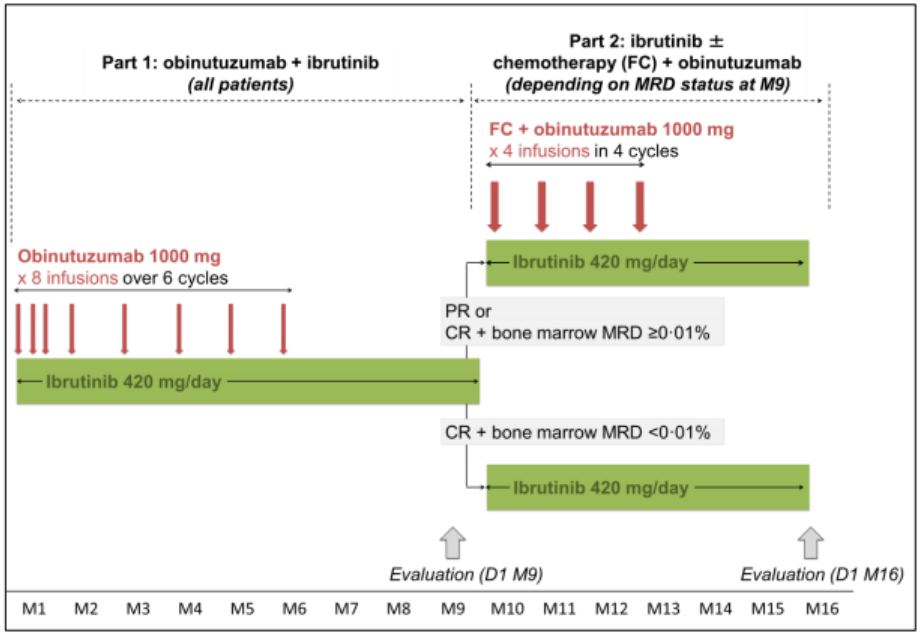
OS (99% at median follow-up)



- One death on study due to presumed cardiac etiology 17 mo. into ibrutinib maintenance
- 13 pts who discontinued ibrutinib have had recurrent BM-MRD (including 5 with clinical progression of CLL)
- 7 restarted ibrutinib and all 7 responded with PR
- Median time on re-treatment is 12.8 mo. (range 4.2-26.2)

Davids et al, *ASH Annual Meeting*, 2021

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

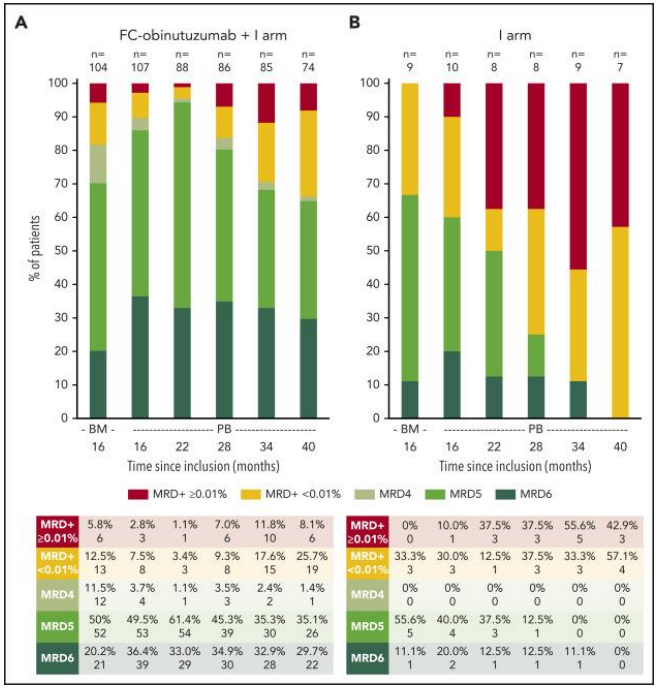
	Induction phase (n=133)			MRD-guided phase (n=125)		
	Grade 1 and 2 events	Grade 3 events	Grade 4 events	Grade 1 and 2 events	Grade 3 events	Grade 4 events
Haematological adverse events						
Thrombocytopenia	45 (34%)	22 (17%)	20 (15%)	43 (33%)	10 (8%)	9 (7%)
Neutropenia	14 (11%)	17 (13%)	15 (11%)	15 (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%)	..	..	..	..	..

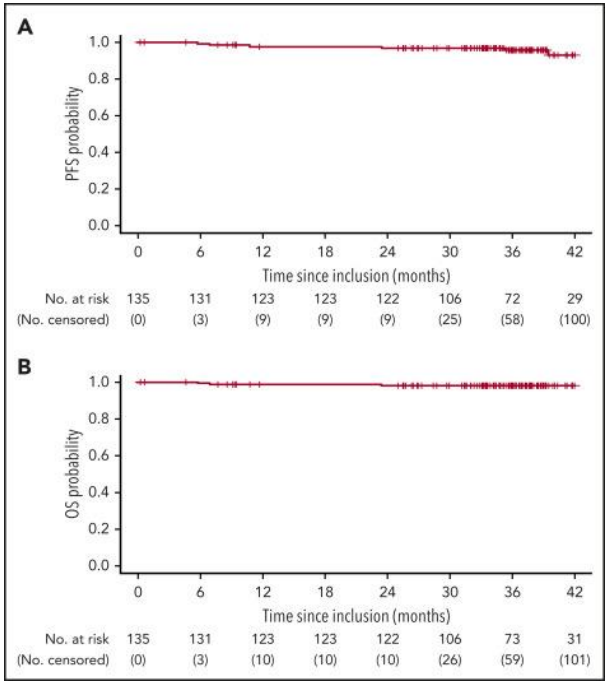
Data are n (%) of patients. Grade 1 and 2 adverse events in ≥10% of patients and all grade 3 and 4 adverse events are shown. Three deaths occurred: one sudden death at month 8; one accidental fall at month 7; one death due to Hodgkin lymphoma Epstein Barr virus-associated haemophagocytosis syndrome at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





Michallet et al, *Blood*, 2021

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].

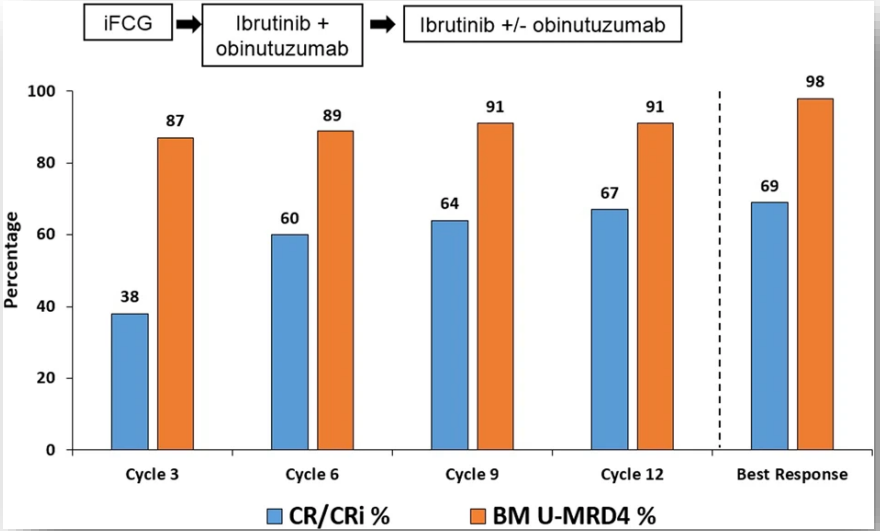
Event	No. of patients (%)	
	Any grade	Grade 3 or higher
Nausea/vomiting	26 (58)	0
Easy bruising	25 (56)	0
Infusion-related reactions	20 (44)	2 (4)
Skin rash	16 (36)	0
Arthralgia	16 (36)	1 (2)
Atrial fibrillation	5 (11)	2 (4)
Diarrhea	5 (11)	0
Myalgia	5 (11)	0
Gastroesophageal reflux disease	5 (11)	0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

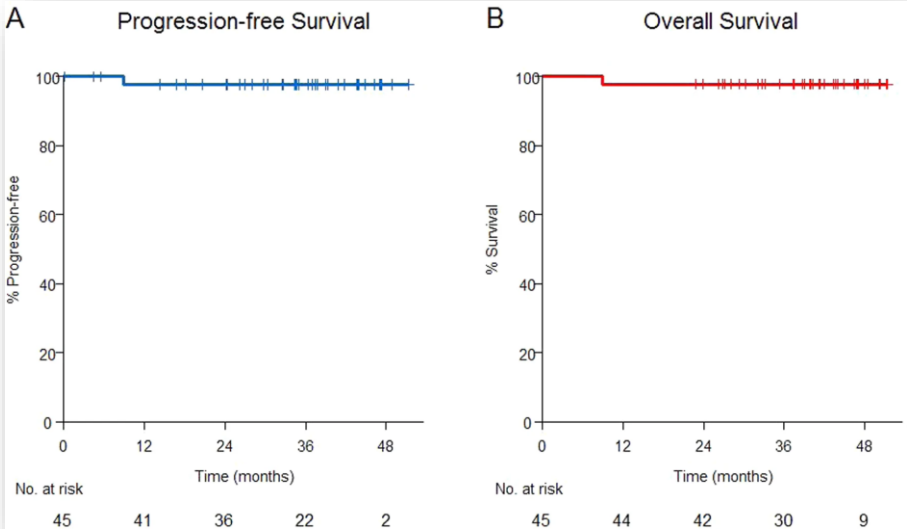
[a]Shown are adverse events at least possibly related to the study drugs and reported in at least 5% of the patients.

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



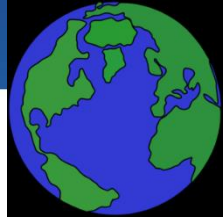


Jain et al, *Leukemia*, 2021

Summary of major studies of ibrutinib + FC + CD20 (n=265)

	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.)	40.3	36.7	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%
3-year PFS / OS	97% / 99%	95.7% / 97.7%	98% / 98%
tMDS	2.4%	0%	2.2%

[1]Davids et al, *Lancet Haem*, 2019 and *ASH*, 2021 [2]Michallet et al, *Lancet Haem*, 2019 and *Blood*, 2021 [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)
-

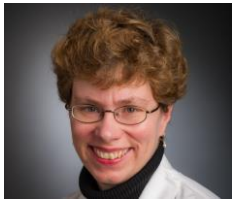
Conclusioni

- **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**
- **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**

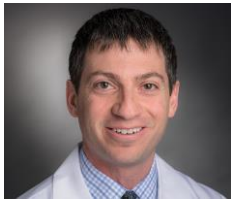
Dana-Farber Cancer Institute

Harvard Medical School

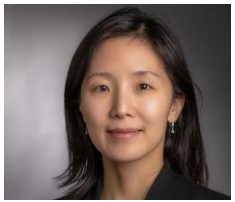
DFCI CLL Center



Jennifer Brown, MD, PhD



Matthew Davids, MD, MMSc



Inhye Ahn, MD

Catherine Wu, MD

We hope to welcome you to Boston next fall!