10th EDITION

Highlights from EHA

Chronic Lymphocytic Leukemia

PROGRAMMA

Coordinamento Scientifico
Robin Foà

22-23 SETTEMBRE 2017
GRAND HOTEL BAGLIONI
FIRENZE

Paolo Ghia

(S461) CYTOGENETIC COMPLEXITY IN CHRONIC LYMPHOCYTIC LEUKEMIA: DEFINITIONS, ASSOCIATIONS WITH OTHER BIOMARKERS AND CLINICAL IMPACT; A RETROSPECTIVE STUDY ON BEHALF OF ERIC

Panagiotis Baliakas (Department of Immunology, Genetics and Pathology, Science for Life Laboratory,Uppsala University,Uppsala,Sweden)

Saturday 16:00 - 16:15

(S462) IS FCR THE TREATMENT OF CHOICE FOR IGHV MUTATED CLL WITHOUT POOR FISH CYTOGENETICS?

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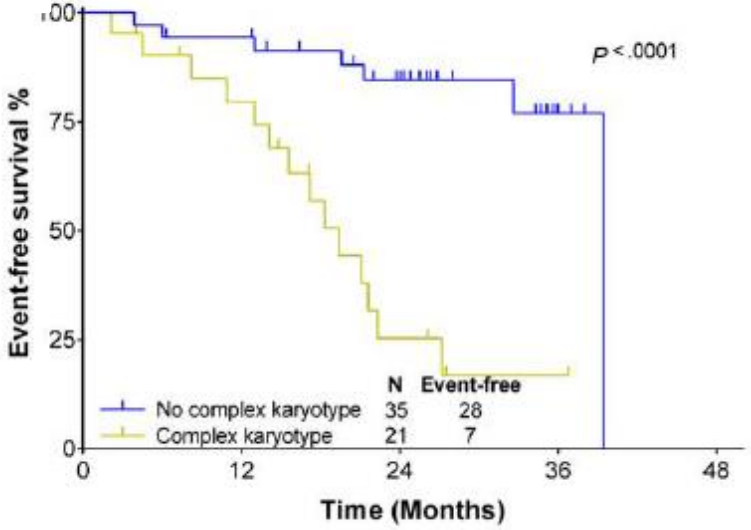
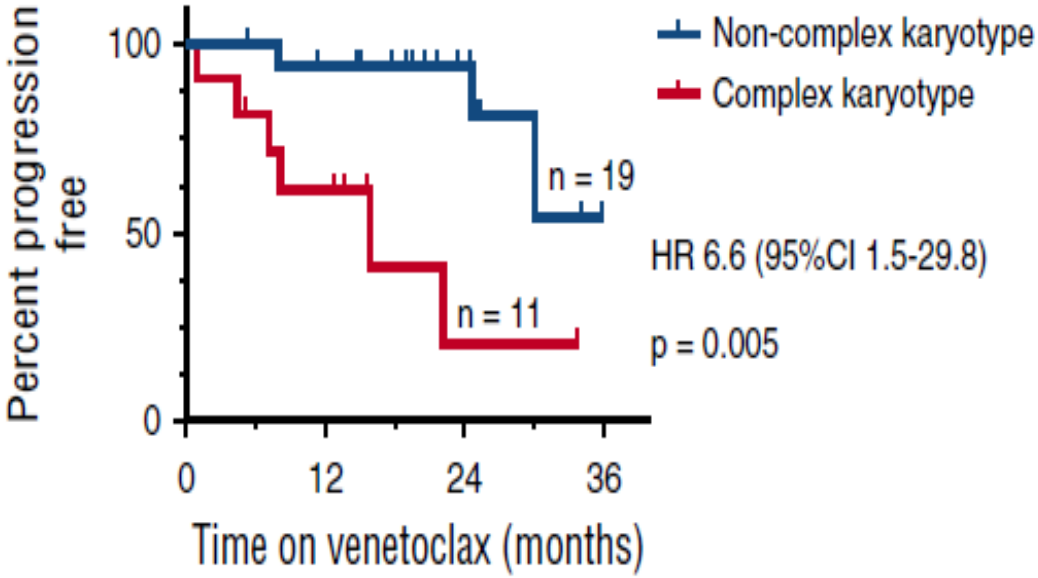
Peter Hillmen (The Leeds Teaching Hospitals, St. James Institute of Oncology,Leeds,United Kingdom)

Complex Karyotype: a novel predictive marker?





Complex karyotype superseded del(17p)

Thompson PA et al. Cancer 2015

Anderson MA et al. Blood 2017

Ibrutinib and Idela in R/R CLL *by CK status*

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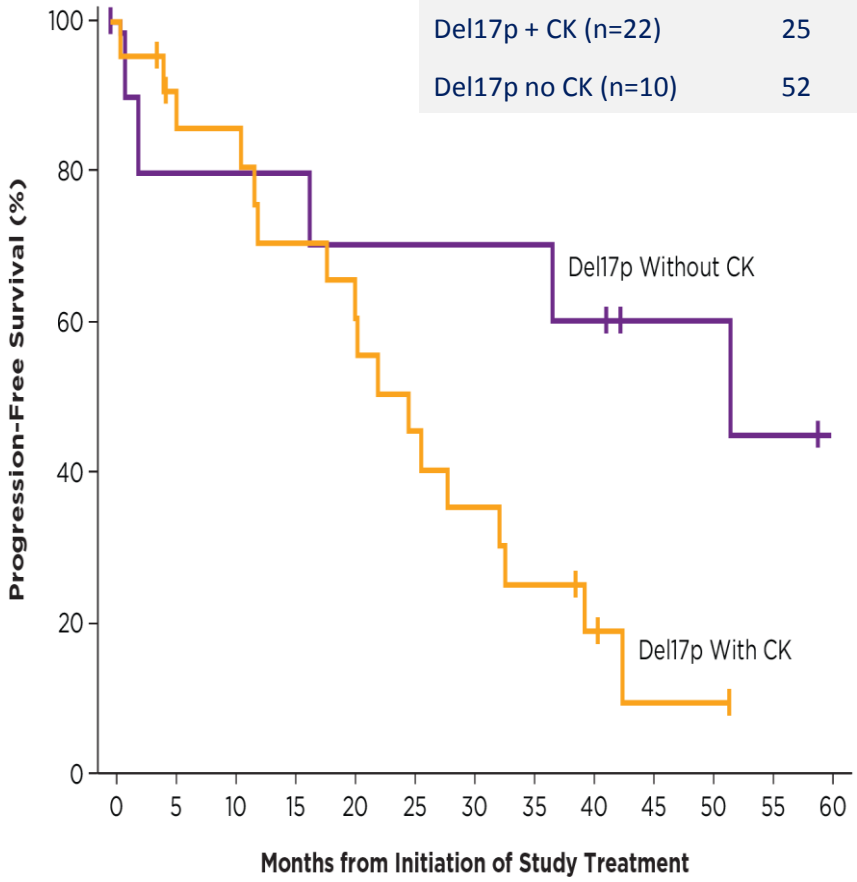
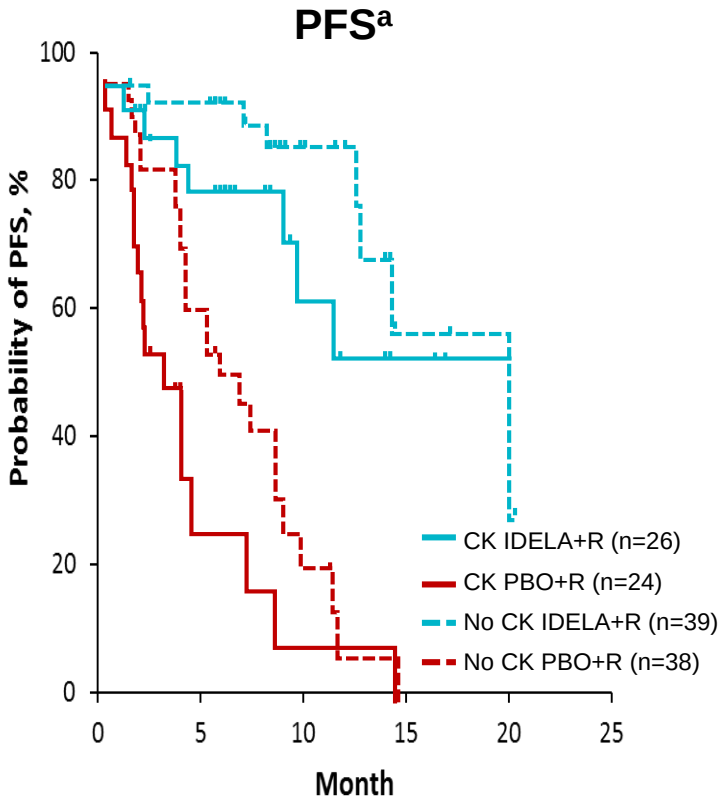
	Median PFS mo
Del17p + CK (n=22)	25
Del17p no CK (n=10)	52



CK, complex karyotype; NR, not reached.

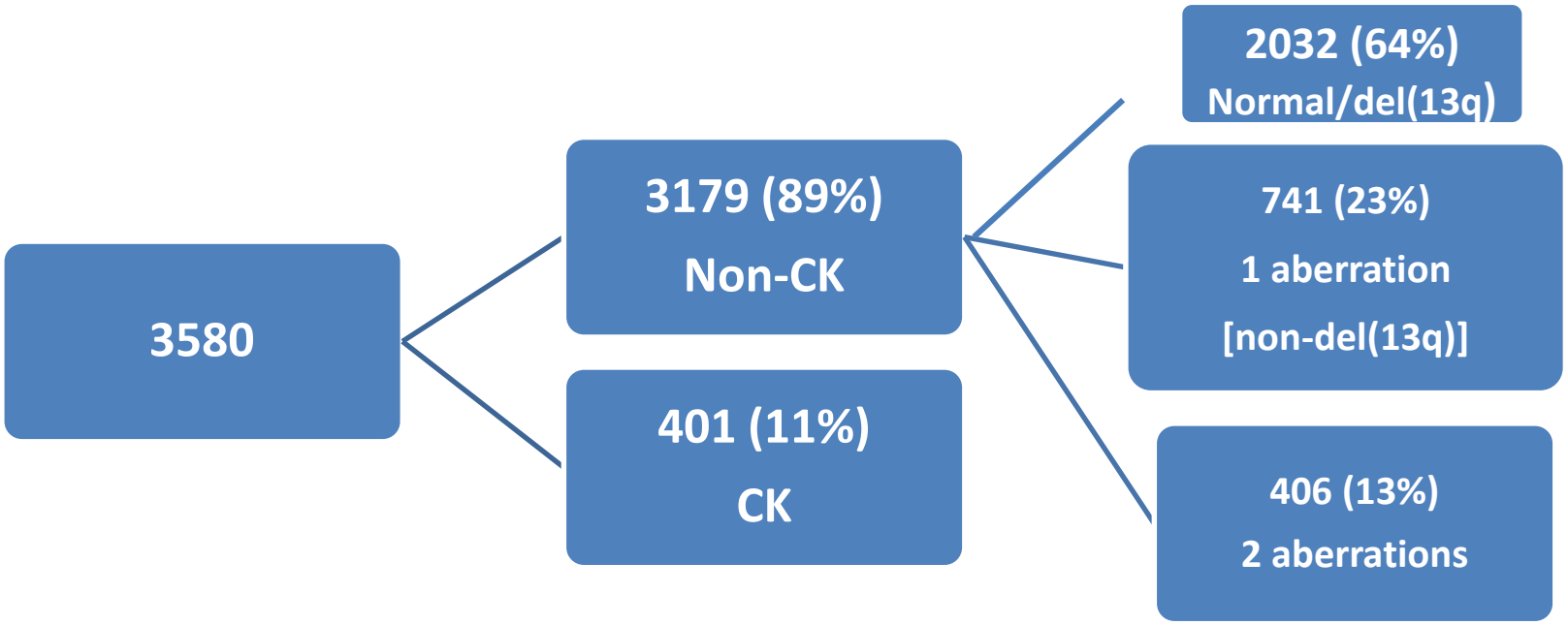


- ORR in patients treated with IDELA+R with CK was 80.8% (95% CI: 60.6, 93.4) vs 89.7% (95% CI: 75.8, 97.1) without CK
- OS HR for patients treated with IDELA+R with CK vs no CK was 1.97 (95% CI: 0.87, 4.48; p=0.10, unadjusted)

Jones J, et al. EHA 2016 (Abstract S429; oral presentation).

Kreuzer, iwCLL 2017, Presentation #410

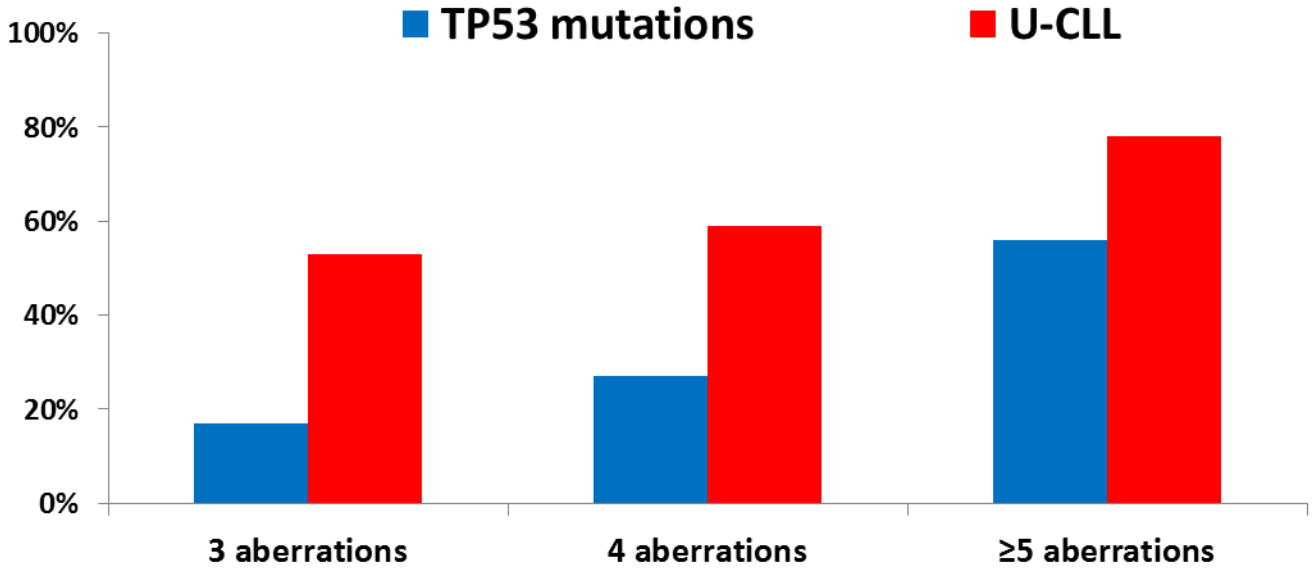
Dissecting CK in CLL



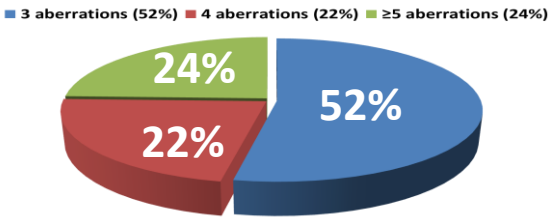
No difference in the detection rate of CK between different cell stimulation protocols

Baliakas et al, EHA 2017, oral presentation

Dissecting CK in CLL

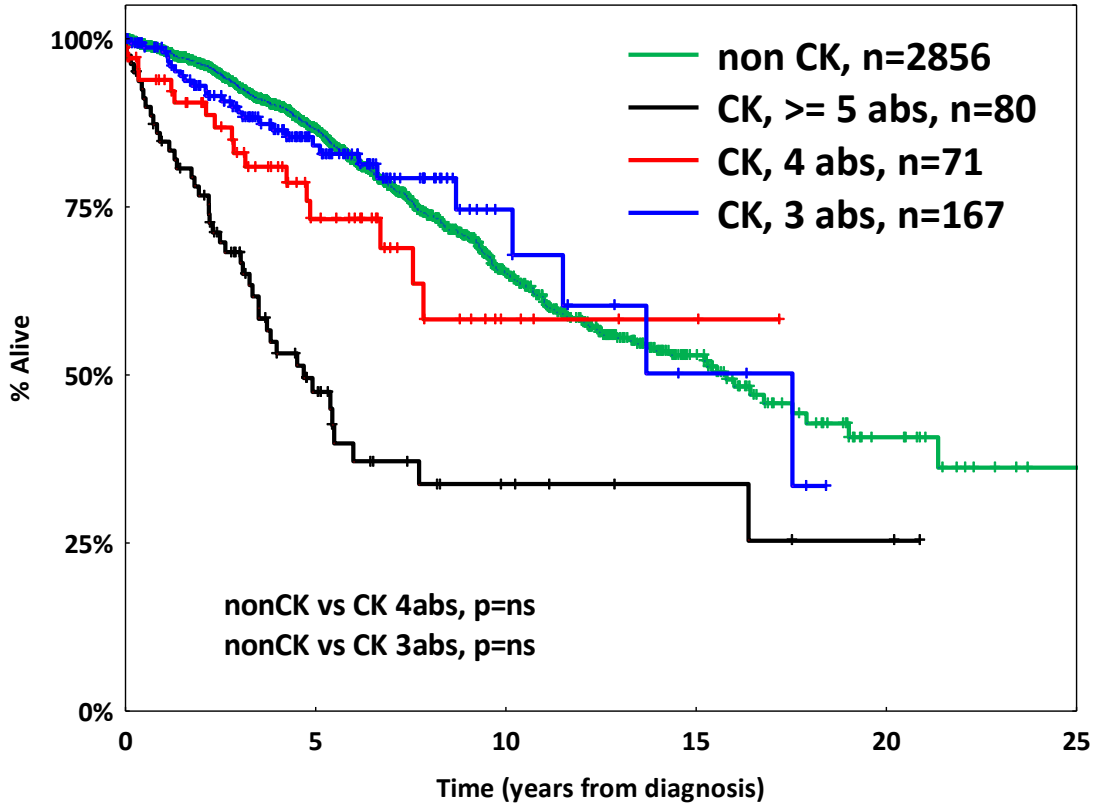


5 abs vs 4 abs: p<0.05
5abs vs 3 abs: p<0.05
4abs vs 3abs: p=ns



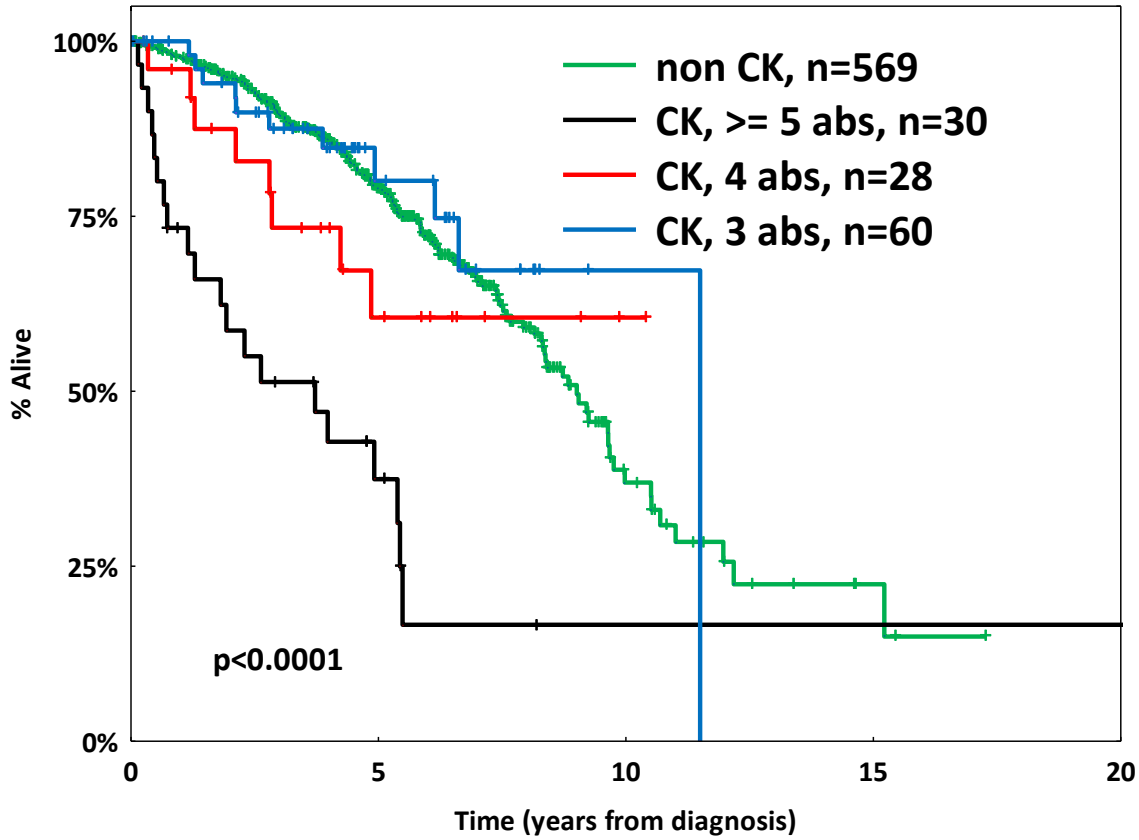
Baliakas et al, EHA 2017, oral presentation

You need 5 or more aberrations to be bad



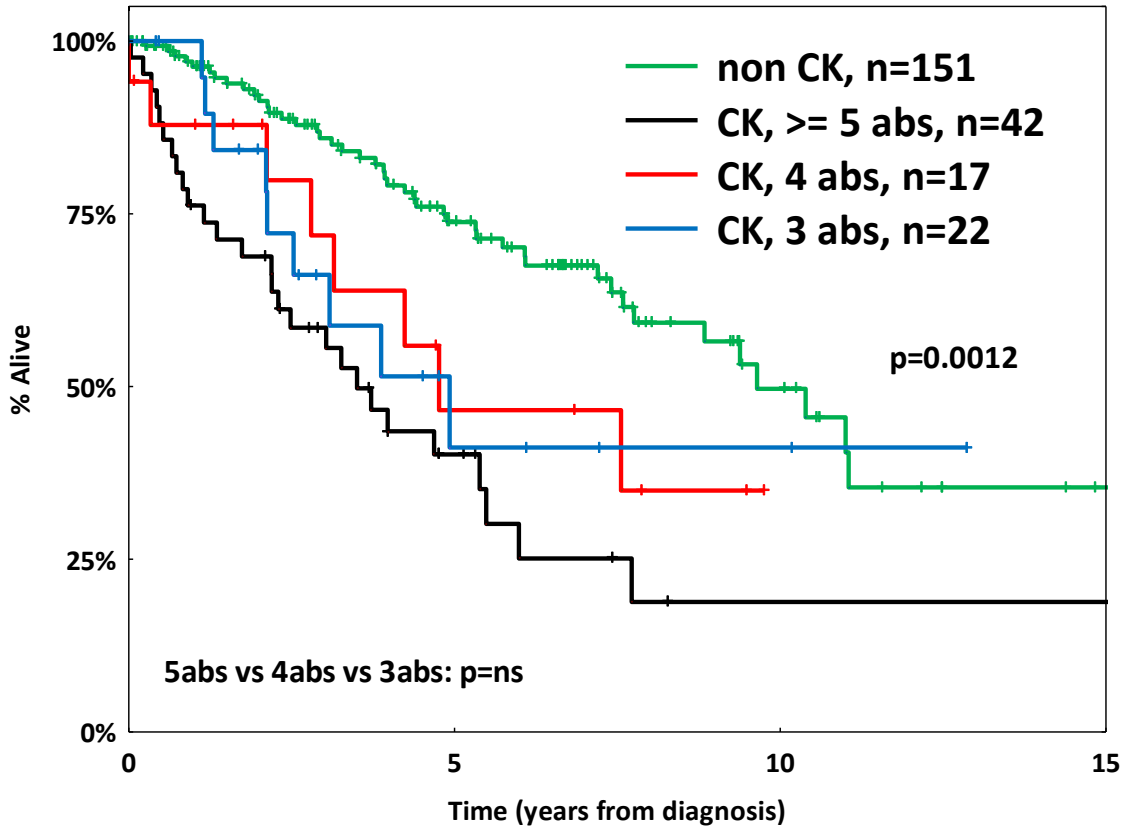
Baliakas et al, EHA 2017, oral presentation

Complex karyotype aggravates outcomes in IG-unmutated CLL



Baliakas et al, EHA 2017, oral presentation

Complex karyotype aggravates outcomes in CLL with *TP53*abs



Baliakas et al, EHA 2017, oral presentation

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Long-term remissions with FCR in first-line CLL

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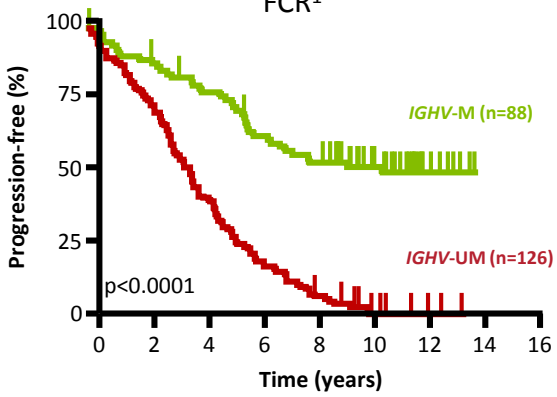
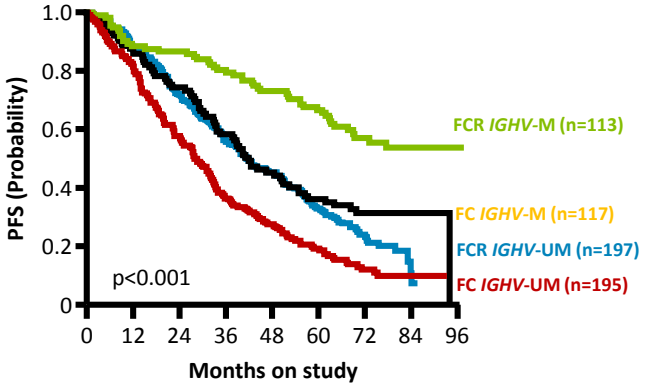
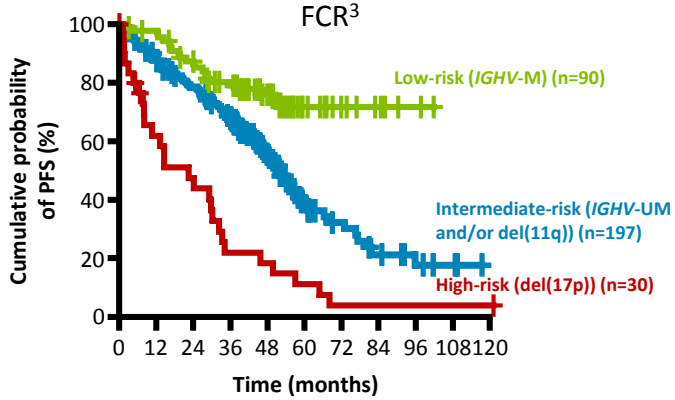
FCR300: Retrospective analysis of 300 CLL patients treated with 1L FCR[1]



CLL8: Phase 3 randomized trial of FCR vs FC in 1L CLL[2]



Italian retrospective analysis: 404 CLL patients treated with 1L FCR[3]



IGHV-M, IGHV-mutated; IGHV-UM, IGHV-unmutated.

1. Thompson PA, et al. Blood 2016; 127:303–309;
2. Fischer K, et al. Blood 2016; 127:208–215;
3. Rossi D, et al. Blood 2015; 126:1921–1924.

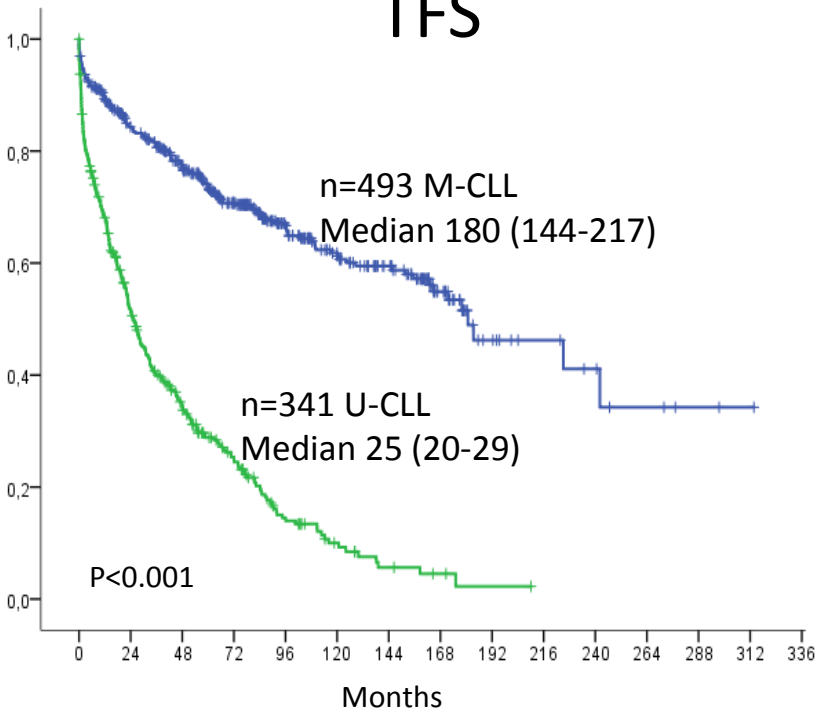
Objectives

To evaluate the outcome of M-CLL patients without poor FISH cytogenetics in relation to the type of therapy

- 834 CLL patients from 3 European Institutions (Italy, Spain, Sweden)
- M-CLL: n= 493 (165 patients required therapy)
- U-CLL: n= 341 (272 patients required therapy)

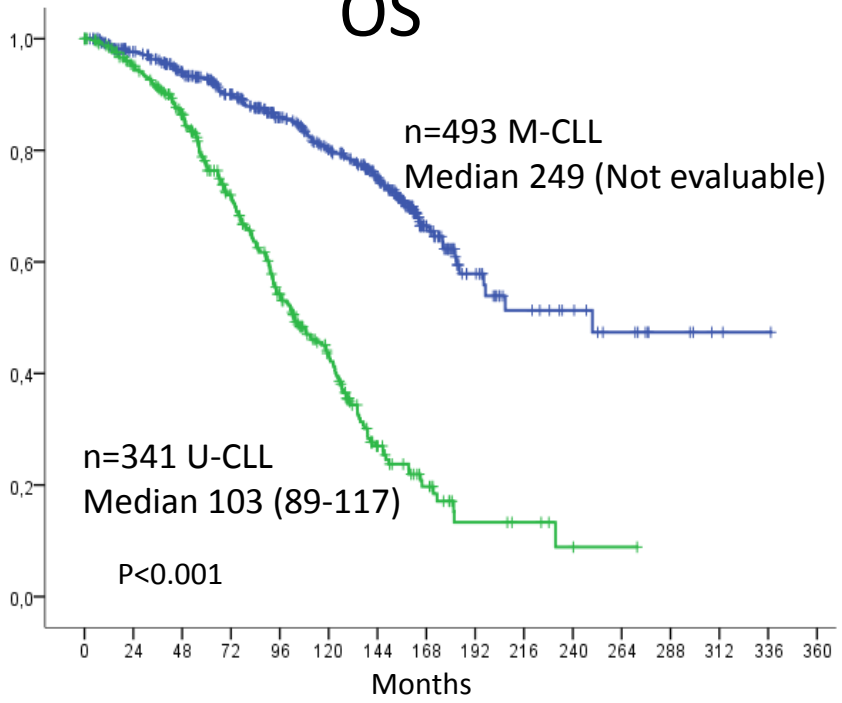
TFS and OS: mutated vs unmutated CLL

TFS



5yr-TFS was 73% (CI, 71-75) for M-CLL and 28% (CI, 26-30) for U-CLL

OS



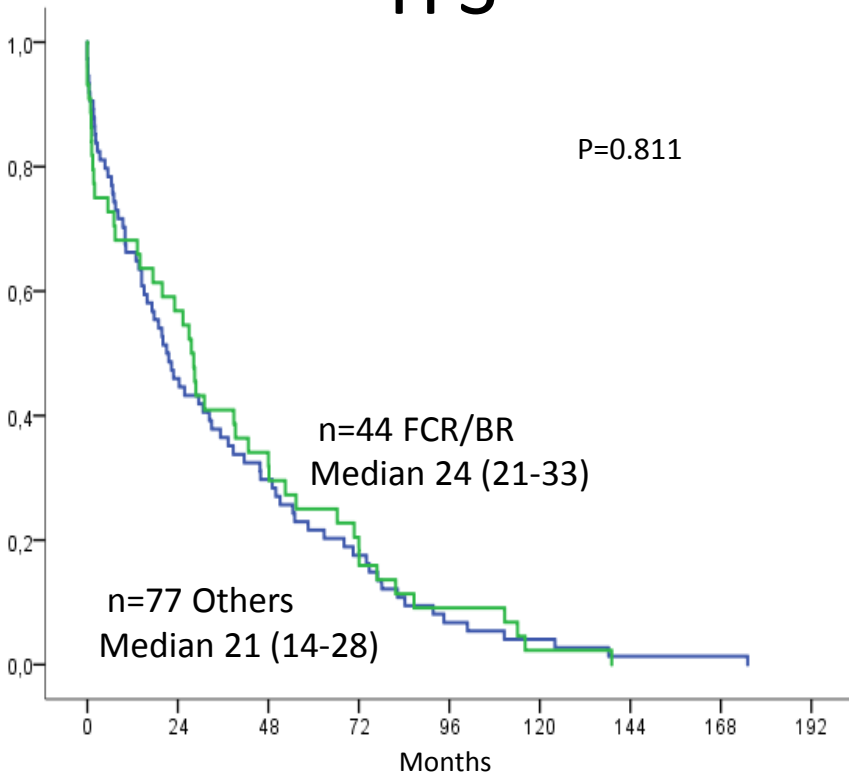
5-yr OS was 92% (CI, 90-93) for M-CLL and 77% (CI, 75-79) for U-CLL

The median duration of response to first therapy was 28 months (95% CI 24-32 months) in M-CLL vs 18 months (95% CI 16-20) in U-CLL (p<0.001)

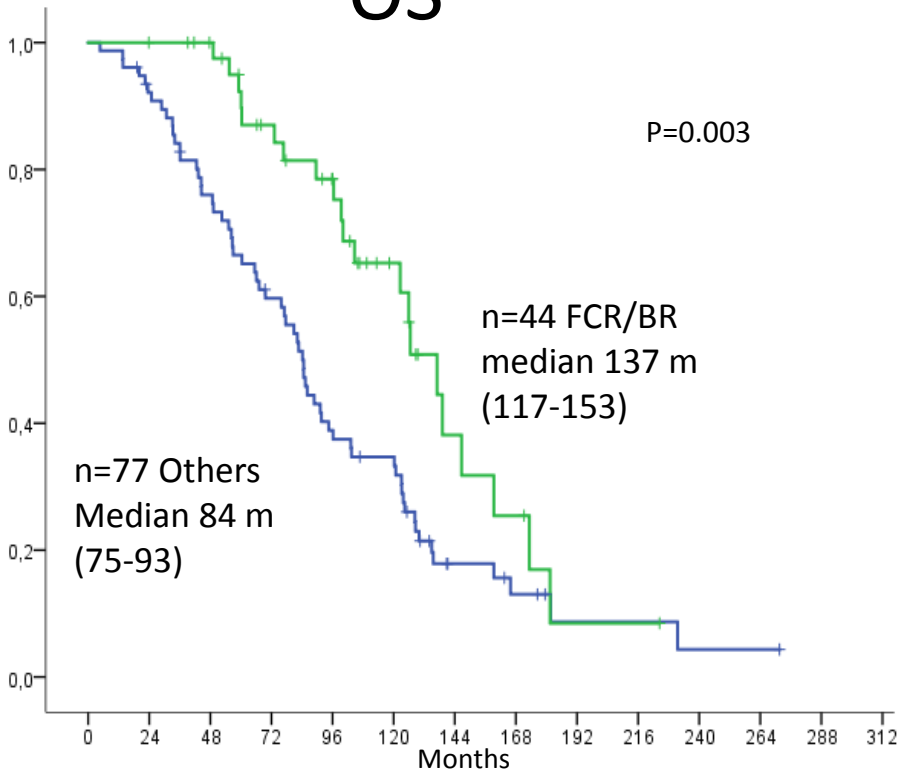
Cuellar-García et al, EHA 2017 oral presentation

Outcome according to type of therapy in unmutated CLL

TFS



OS

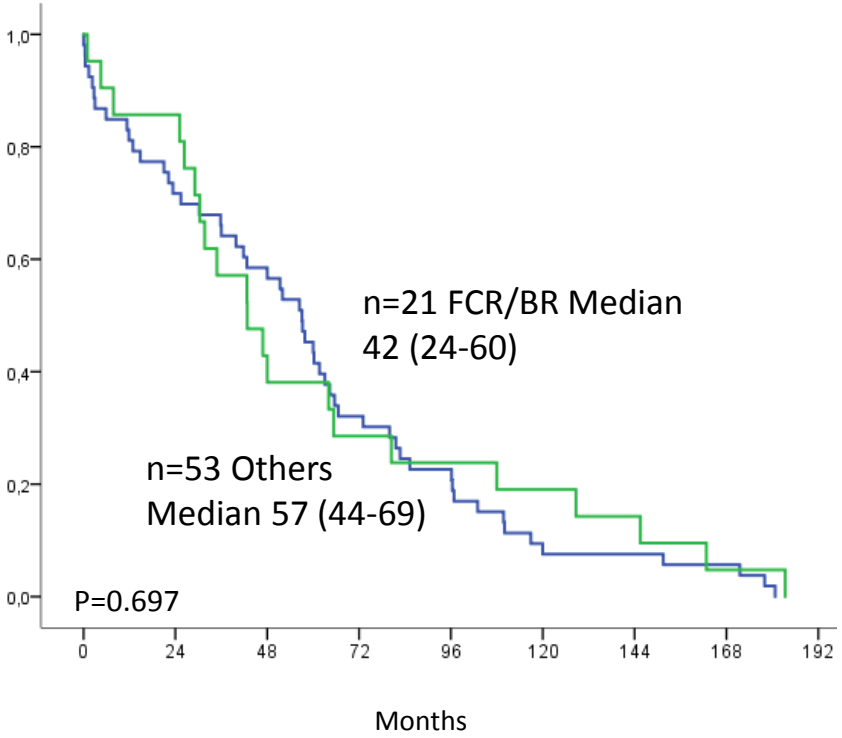


Patients treated with small molecules and allogeneic SCT were excluded from this analysis

Cuellar-García et al, EHA 2017 oral presentation

Outcome according to type of therapy in mutated CLL without poor cytogenetics

TFS



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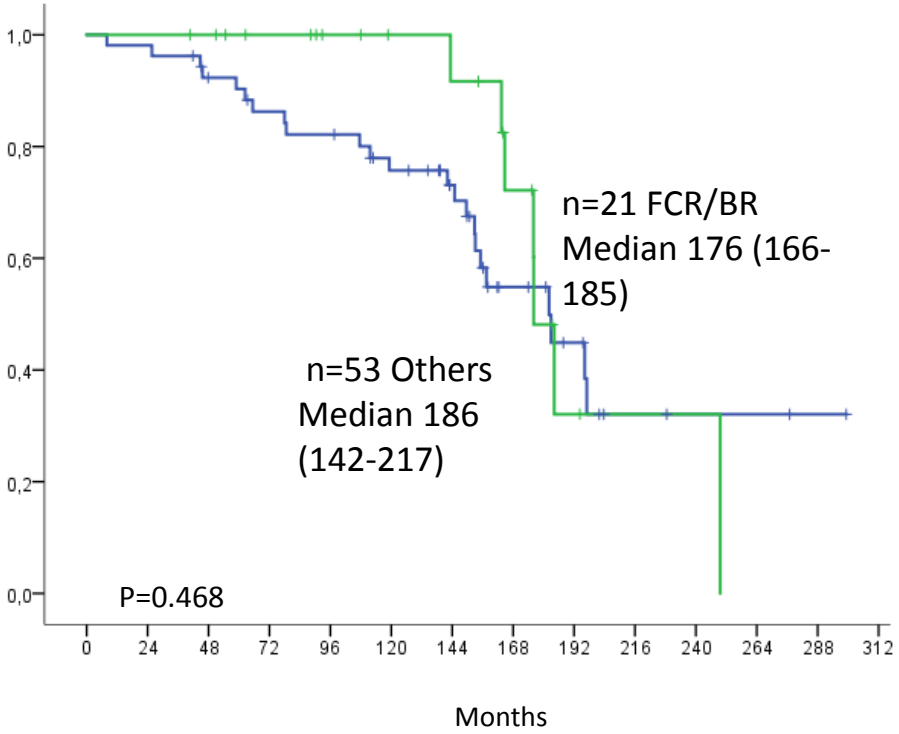

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Cuellar-García et al, EHA 2017 oral presentation

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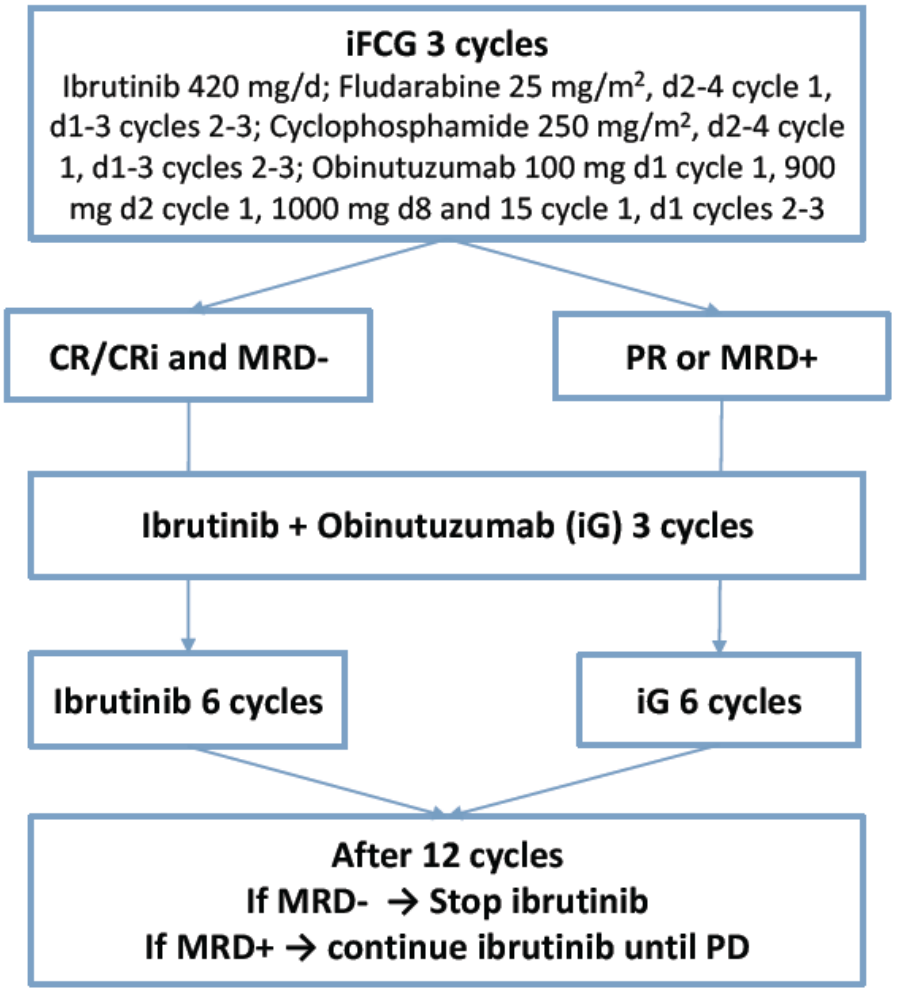
Phase 2 Study of Ibrutinib, FC, and Obinutuzumab (iFCG) for Previously Untreated Patients With CLL With Mutated *IGVH* and Non-Del(17p)

Key eligibility criteria

- Previously untreated CLL/SLL*
- Age ≥18 years
- *IGVH* mutation
- No del(17p) or *TP53* mutation
- Adequate organ function

Primary endpoint: % CR/CRi and BM MRD-negative after 3 cycles of iFCG

- Blood, marrow and CT scans q3 months during first year, then q6 months
- Any lymph node >1.5 cm on CT: PR
- MRD assessed by 4-color flow in BM (sensitivity 10^{-4})
- 29 patients initiated treatment
  - 24 completed 3 cycles of iFCG
- Median follow-up of 8.3 months



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Efficacy (N=24)	3 Months		Best Response	
	n/N (%)	BM MRD neg, n/N (%)	n/N (%)	BM MRD neg, n/N (%)
ORR	24/24 (100)	20/24 (83)	24/24 (100)	All neg.
CR/CRi	10/24 (42)	All neg.	18/24 (75)	All neg.
PR	14/24 (58)	10/14 (71)	6/24 (25)	All neg.

- BM MRD- after 3 cycles: iFCG 83% vs FCR 26%
- Responses improve over time
  - 89% MRD- and 74% CR/CRi at 6 months
  - 100% MRD- and 77% CR/CRi at 9 months
  - 100% MRD- and 67% CR/CRi at 12 months

Jain et al EHA 2017 oral presentation

- **iFCG induces high rate of MRD- remission in BM (83% after 3 cycles)**
- **All patients (n=9) who reached the 1-year time point were BM MRD- and have discontinued ibrutinib per study design**
- **Common AEs during iFCG therapy were neutropenia and thrombocytopenia**

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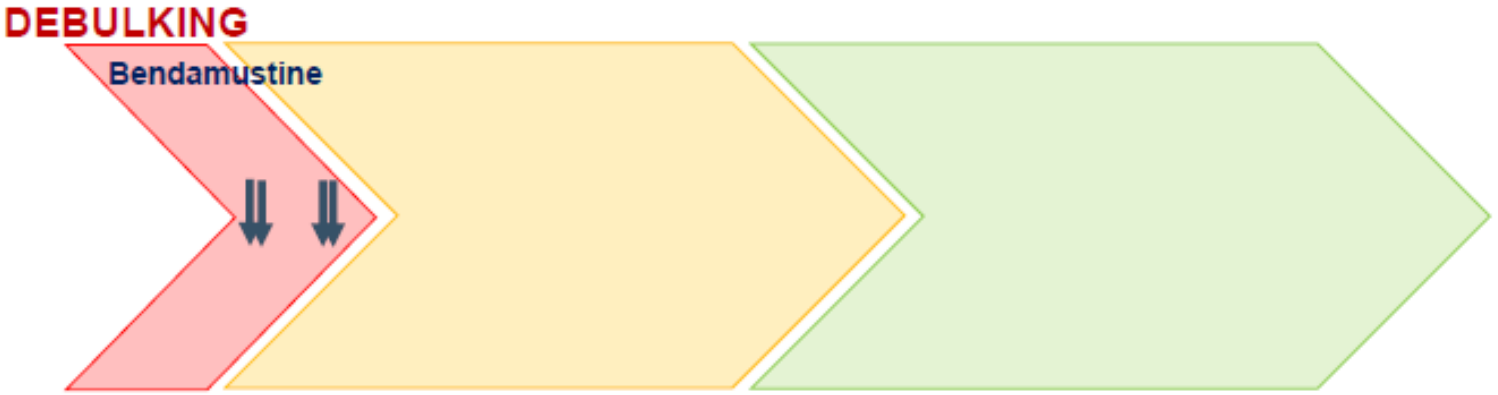
CLL2-BAG:

Bendamustine, ABT-199 (venetoclax), GA101 (obinutuzumab)



DEBULKING: Bendamustine (2 cycles with a duration of 28 days)

should be omitted in case of:

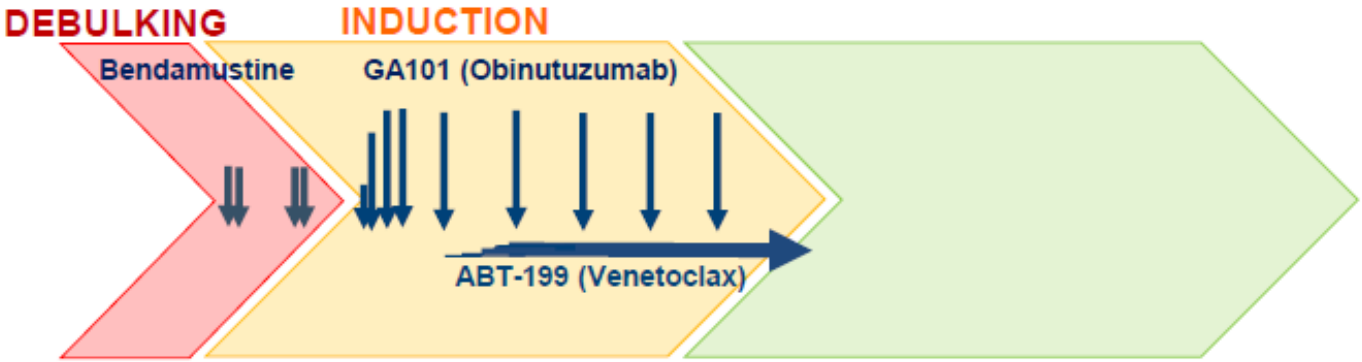
- **contraindications for the usage of bendamustine**, e.g. known hypersensitivity to bendamustine, refractoriness to bendamustine or chemotherapy-induced bone marrow damage) **or**
- **if not necessary due to low tumour burden** (ALC ≤ 25.000/µl and absence of bulky disease with lymph nodes ≤5 cm in the longest diameter)

Bendamustine:	cycles 1-2:	days 1 & 2:	70 mg/m² i.v.

Phase 2 CLL2-Bag Trial of Sequential Bendamustine (B), Obinutuzumab (G), and Venetoclax (A) in CLL

CLL2-BAG:

Bendamustine, ABT-199 (venetoclax), GA101 (obinutuzumab)



INDUCTION: Obinutuzumab & Venetoclax (6 cycles with a duration of 28 days)

Obinutuzumab (GA101):	cycle 1:	day 1:	100 mg i.v.
		day 1 (or 2):	900 mg i.v.
		days 8 & 15:	1000 mg i.v.
	cycles 2-6:	day 1:	1000 mg i.v.
Venetoclax (ABT-199):	cycle 2:	days 1-7:	20 mg p.o.
		days 8-14:	50 mg p.o.
		days 5-21:	100 mg p.o.
		days 22-28:	200 mg p.o.
	cycles 3-6:	days 1-28:	400 mg p.o.

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Phase 2 CLL2-Bag Trial of Sequential Bendamustine (B), Obinutuzumab (G), and Venetoclax (A) in CLL

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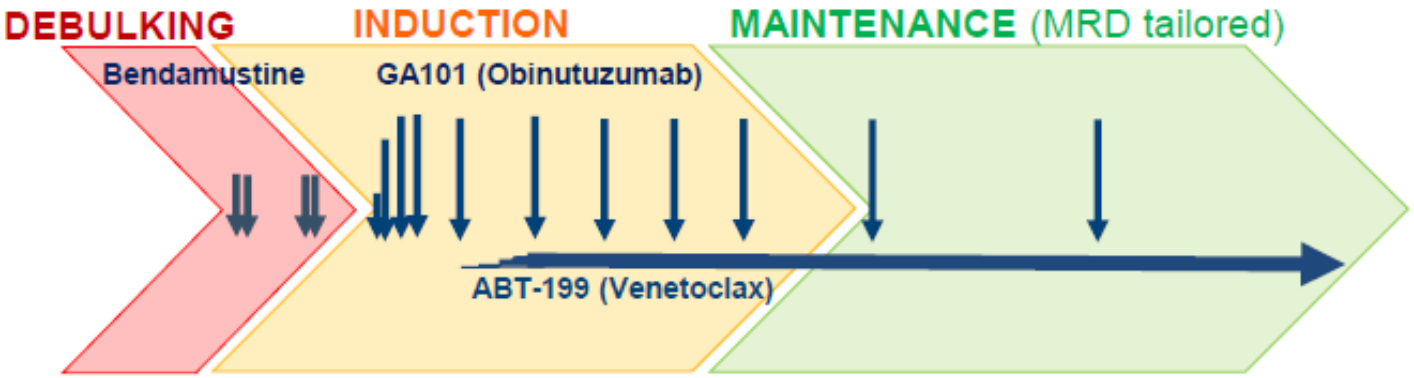
Bendamustine, ABT-199 (venetoclax), GA101 (obinutuzumab)



MAINTENANCE: Obinutuzumab & Venetoclax (2-8 cycles with a duration of 84 days)

will be continued until (whichever occurs first):

- three months after **achievement of (clinical) CR/CRi and MRD negativity** (confirmed by 2 measurements)
- completion of **24 months of maintenance** (8 cycles each with a duration of 84 calendar days)
- progression of CLL or start of new CLL treatment, or
- unacceptable toxicity.

Obinutuzumab (GA101):	cycles 1-8:	day 1:	1000 mg i.v.
Venetoclax (ABT-199):	cycles 1-8:	day 1-84:	400 mg p.o.

Cramer et al EHA 2017 oral presentation

Phase 2 CLL2-Bag Trial of Sequential Bendamustine (B), Obinutuzumab (G), and Venetoclax (A) in CLL

	all patients (n=63)	treatment-naïve (n=34)	relapsed/refractory (n=29)
Responses			
- **CR**	**5 pts (8%)**	3 (9%)	2 (7%)
- **unconfirmed/clinical CR/CRi***	**20 pts (32%)**	14 (41%)	6 (21%)
- **PR**	**35 pts (56%)**	17 (50%)	18 (62%)
- **SD**	**-**	-	-
- **Progression**	**3 pts (5%)**	-	3 (10%)
Overall response rate	**60 pts (95%)**	**34 (100%)**	**26 (90%)**

*) missing CT scan and/or bone marrow biopsy

	all patients (n=63)	treatment-naïve (n=34)	relapsed/refractory (n=29)
MRD in peripheral blood			
- **negative** ($< 10^{-4}$)	**55 pts (87%)**	31 (91%)	24 (83%)
- **intermediate** ($\geq 10^{-4}$ and $< 10^{-2}$)	**2 pts (3%)**	2 (6%)	-
- **positive** ($\geq 10^{-2}$)	**4 pts (6%)**	1 (3%)	3 (10%)
- missing	2 pts (3%)	-	2 (7%)
MRD in bone marrow			
- **negative** ($< 10^{-4}$)	**8 pts (13%)**	4 (12%)	4 (14%)
- **intermediate** ($\geq 10^{-4}$ and $< 10^{-2}$)	-	-	-
- **positive** ($\geq 10^{-2}$)	-	-	-
- missing	55 pts (87%)	30 (88%)	25 (86%)

Cramer et al EHA 2017 oral presentation

Authors' conclusions

Bendamustine, followed by obinutuzumab and venetoclax does not lead to cumulative or unexpected toxicity.

Only one laboratory TLS occurred with venetoclax in this sequential regimen.

At the end of induction, **overall response rate was 95%.**

87% of patients were MRD negative in peripheral blood at the end of induction.

Novel drugs

Abstract	First author	Title
S772	Nastoupil	Phase 1 Study of Ublituximab, TGR-1202, and Ibrutinib in R/R CLL and NHL
S773	Hamlin	Phase 2 Study of Cerdulatinib in R/R B Cell Malignancies

Phase 1 Study of Ublituximab, TGR-1202, and Ibrutinib in R/R CLL and NHL

Key eligibility criteria
- R/R NHL, CLL
- ≥1 prior therapy (treatment-naïve CLL/SLL allowed)
- ECOG PS 0-2
- Richter's transformation or refractory to prior PI3K or BTK inhibitors allowed

3+3 Dose Escalation:
Ublituximab 900 mg: day 1, 8, 15 of cycle 1, day 1 of cycles 2-6, cycle 9, and cycle 12 +
TGR-1202: 400, 600, 800 mg qd
Ibrutinib 420 mg (CLL/SLL) or 560 mg (NHL) qd

Primary objectives:
safety and MTD
Secondary objectives:
efficacy (ORR, TTR, DOR, PFS)

Patient Characteristics		(N=38)
Median age, years (range)		65 (32-85)
Male / female, n		29 / 9
Histology, n	CLL/SLL	20
	FL	6
	DLBCL	6
	MCL	4
	MZL	2
ECOG PS 0 / 1 / 2, n		14 / 21 / 3
Median prior treatments, n (range)		3 (0-6)*
≥3 prior therapies, %		55
Refractory to prior therapy, %		34
Refractory to rituximab, %		39

*3 patients with CLL were treatment-naïve, all others were R/R to prior therapy.

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- Median time on study 11.1 months
- 81% of patients on study > 6 months

Best Overall Response	n	CR, n	PR, n	ORR, n (%)
CLL/SLL	19	6	13	19 (100)
MZL	2	1	1	2 (100)
MCL	4	2	2	4 (100)
FL	5	1	3	4 (80)
DLBCL	6	0	1	1 (17)
Total	**36**	**10**	**20**	**30 (83)**

- All 3 treatment-naïve patients with CLL achieved PR

Phase 2 Study of Cerdulatinib in R/R B Cell Malignancies:

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Key eligibility criteria
- Patients with R/R CLL/SLL, R/R iNHL, or relapsed DLBCL, MCL, or transformed FL

Cerdulatinib BID: 30 mg and 35 mg dosing was evaluated

Primary aim: safety and activity of cerdulatinib in B-cell malignancies

Response, n/N (%)	CLL/SLL	FL
PR	10/13 (77)	3/6 (50)

Most Common AEs, %	N=37
Diarrhea	27
Fatigue	27
Nausea	24
Most Common Grade ≥3 AEs, %	
Infection	14
Abdominal pain	8
Hypertension	8

3 patients at 35 mg BID dose had SAEs – 2 grade 5 infections, 1 grade 3 pancreatitis

• Starting dose reduced to 30 mg BID and a PK monitoring and dose reduction strategy was implemented

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(S461) CYTOGENETIC COMPLEXITY IN CHRONIC LYMPHOCYTIC LEUKEMIA: DEFINITIONS, ASSOCIATIONS WITH OTHER BIOMARKERS AND CLINICAL IMPACT; A RETROSPECTIVE STUDY ON BEHALF OF ERIC

Panagiotis Baliakas (Department of Immunology, Genetics and Pathology, Science for Life Laboratory,Uppsala University,Uppsala,Sweden)

Saturday 16:00 - 16:15

(S462) IS FCR THE TREATMENT OF CHOICE FOR IGHV MUTATED CLL WITHOUT POOR FISH CYTOGENETICS?

Carolina Cuéllar-García (Department of Hematology,Hospital Santa Creu i Sant Pau,Barcelona,Spain)

Saturday 16:15 - 16:30

(S463) IBRUTINIB, FLUDARABINE, CYCLOPHOSPHAMIDE, AND OBINUTUZUMAB (GA101) (IFCG) FOR PREVIOUSLY UNTREATED PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) WITH MUTATED IGHV AND NON-DEL(17P)

Nitin Jain (Leukemia,MD Anderson Cancer Center,Houston,United States)

Saturday 16:30 - 16:45

(S464) BENDAMUSTINE (B), FOLLOWED BY OBINUTUZUMAB (G, GA101) AND VENETOCLAX (A, ABT-199) IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): CLL2-BAG PHASE-II-TRIAL OF THE GERMAN CLL STUDY GROUP (GCLLSG)

Paula Cramer (Department I of Internal Medicine and German CLL Study Group,University Hospital Cologne,Cologne,Germany)

Saturday 16:45 - 17:00

(S465) SAFETY RESULTS OF TERMINATED PHASE 2 STUDY OF IDELALISIB PLUS RITUXIMAB IN TREATMENT NAÏVE CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) WITH DEL(17P)

Peter Hillmen (The Leeds Teaching Hospitals, St. James Institute of Oncology,Leeds,United Kingdom)

Terminated Phase 2 Study of Idelalisib and Rituximab in TN CLL With Del(17p)

n (%)	Idelalisib + Rituximab		
	Age <65 y n=41	Age ≥65 y n=61	Total N=102
Any adverse event (AE)	40 (98)	61 (100)	101 (99)
≥ Grade 3 AEs	35 (85)	47 (77)	82 (80)
Serious AEs	19 (46)	27 (44)	46 (45)
AEs leading to study drug interruption	31 (76)	40 (66)	71 (70)
AEs leading to study drug discontinuation	12 (29)	16 (26)	28 (28)
AEs leading to death	1 (2)	3 (5)	4 (4)

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Terminated Phase 2 Study of Idelalisib and Rituximab in TN CLL With Del(17p)

Treatment-emergent Adverse Events of Interest	Idelalisib + Rituximab		
n (%)	Age <65 y n=41	Age ≥65 y n=61	Total N=102
Grade ≥3 diarrhea/colitis	7 (17)	9 (15)	16 (16)
Grade ≥3 febrile neutropenia	1 (2)	4 (7)	5 (5)
Any Grade pneumonitis	3 (7)	2 (3)	5 (5)

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Terminated Phase 2 Study of Idelalisib and Rituximab in TN CLL With Del(17p)

n (%)	Idelalisib + Rituximab		
	Age <65 y n=41	Age ≥65 y n=61	Total N=102
Grade ≥3 infections*	9 (22)	10 (16)	19 (19)
Lower respiratory tract and lung infections	4 (10)	3 (5)	7 (7)
Sepsis	0	3 (5)	3 (3)
Abdominal and gastrointestinal infections	2 (5)	0	2 (2)
Influenza viral infections	1 (2)	1 (2)	2 (2)
Pseudomonal infections	0	2 (3)	2 (2)
Urinary tract infections	2 (5)	0	2 (2)
Bacterial infections	0	1 (2)	1 (1)
Candida infections	0	1 (2)	1 (1)
Clostridia infections	0	1 (2)	1 (1)
Fungal infections	0	1 (2)	1 (1)
Streptococcal infections	0	1 (2)	1 (1)
Upper respiratory tract infections	1 (2)	0	1 (1)
Any Grade Cytomegalovirus (CMV) infections†	2 (5)	3 (5)	5 (5)
Any Grade Pneumocystis infections/pneumonia‡	1 (2)	2 (3)	3 (3)

*Includes Grade ≥3 CMV and PJP infections; †All 5 patients with CMV were IgG positive at Screening and 2 were IgM positive; ‡None on prophylaxis.

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Terminated Phase 2 Study of Idelalisib and Rituximab in TN CLL With Del(17p)

Abnormalities, n (%)	Idelalisib + Rituximab			
	Age <65 y n=41	Age ≥65 y n=61	Total N=102	
	Grade ≥3	Grade ≥3	Any Grade	Grade ≥3
Hematologic				
Neutropenia	14 (34)	24 (39)	68 (67)	38 (37)
Anemia	2 (5)	2 (3)	28 (28)	4 (4)
Thrombocytopenia	0 (0)	5 (8)	29 (28)	5 (5)
Transaminases				
ALT and/or AST increased*	18 (44)	24 (39)	81 (79)	42 (41)

* <65 y vs ≥65 y, p-value = 0.58.

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Authors' conclusions

- In front-line CLL, IDELA plus rituximab treatment resulted in a similar pattern of AEs to that seen in relapsed CLL studies with similar duration of therapy
  - However, the frequency of Grade ≥3 ALT/AST was increased compared to the relapsed setting
- There was no significant effect of age on the risk of either ALT/AST elevations or diarrhoea/colitis
- There was a trend toward higher risk of Grade ≥3 ALT/AST elevation in patients with IGHV mutation
- The occurrence of CMV and PJP infections is consistent with current IDELA labelling and speaks to the potential benefit of risk mitigation through PJP prophylaxis and CMV monitoring during treatment

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THE END
THANK YOU FOR THE ATTENTION
PROGRAMMA
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