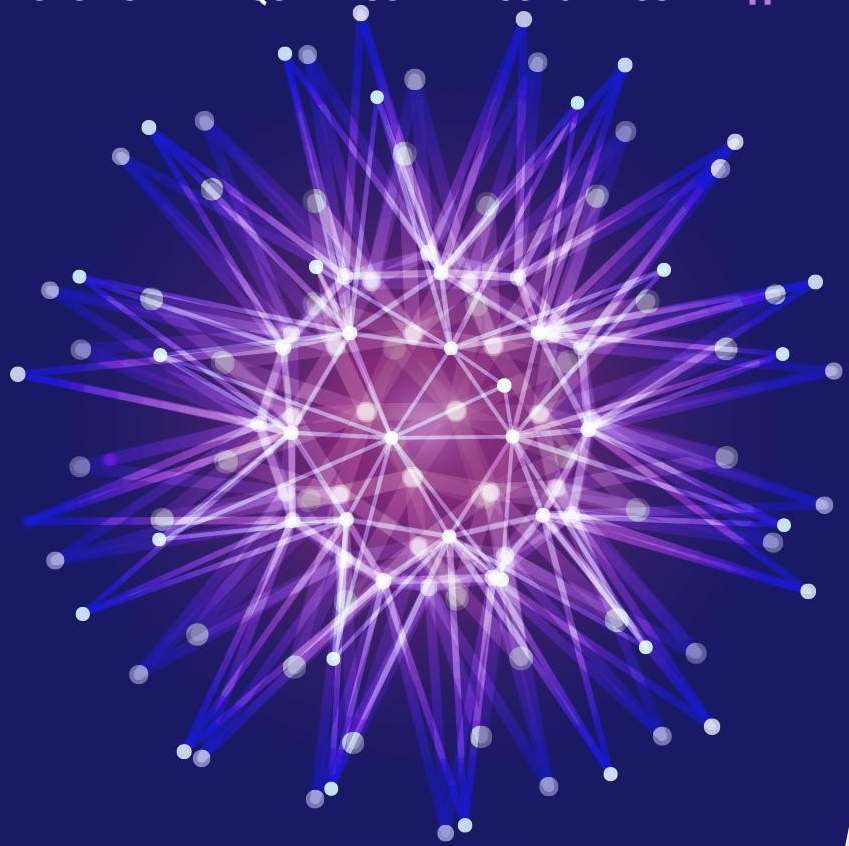
LEUCEMIA LINFATICA CRONICA MALATTIA SEMPRE PIÙ CRONICIZZATA: QUALI NUOVI PERCORSI DI CURA?

27/11/2020



Andrea Visentin
Ricercatore Università degli Studi di Padova

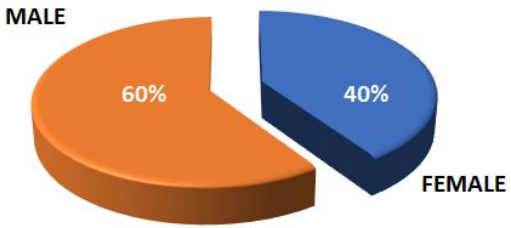
LLC: IL FUTURO E' GIA' QUI?

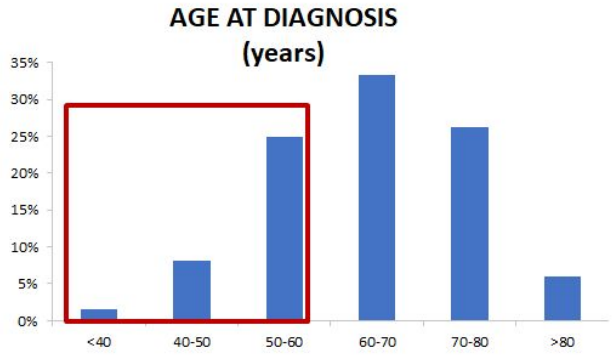
Andrea Visentin, MD PhD

LEUCEMIA LINFATICA CRONICA
MALATTIA SEMPRE PIÙ CRONICIZZATA:
QUALI NUOVI PERCORSI DI CURA?

Epidemiology – a rare tumor

- The incidence of CLL in Europe is 4.56 and 5.78 /100,000 people/yy for female and male, respectively.
- Median age at diagnosis 72 years, 77 at first treatment
- 1/3 of patient have less of 65 yy at diagnosis.

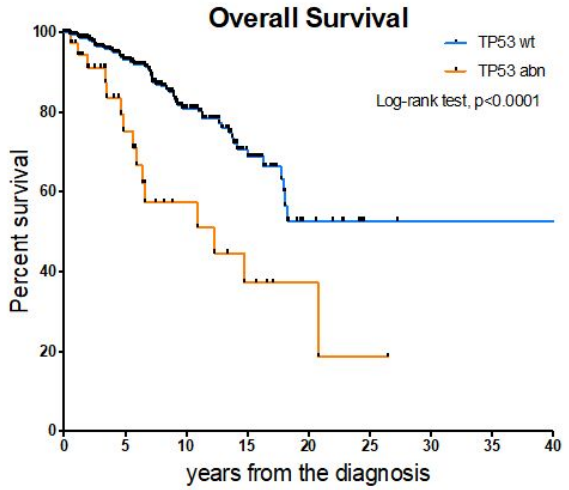


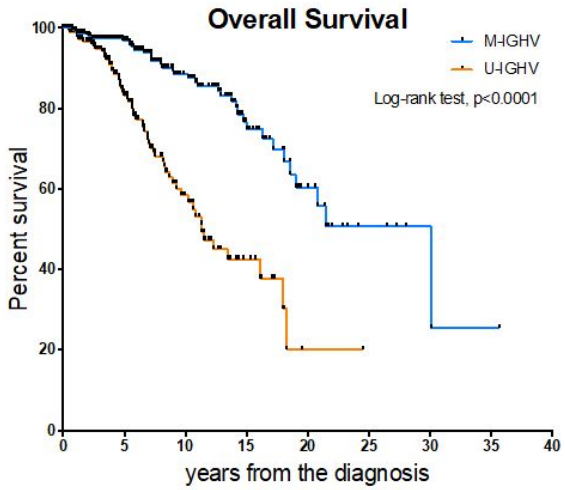


Visentin A, CLML 2015

CLL Database of Padua

- Almost 920 patients, 60% male, 73% Binet A, 49% >65yy at diagnosis
- After a median follow-up of 100 months 41% required at least a treatment

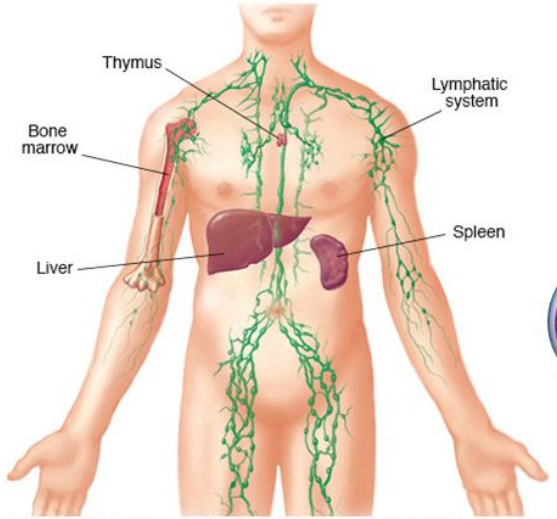


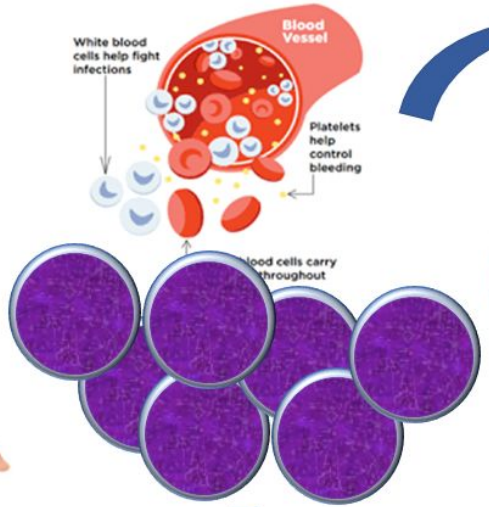


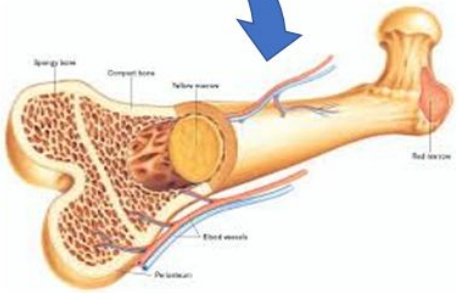
Visentin A, Eu J Cancer 2016

Tumor load of CLL

1 lymphocytosis



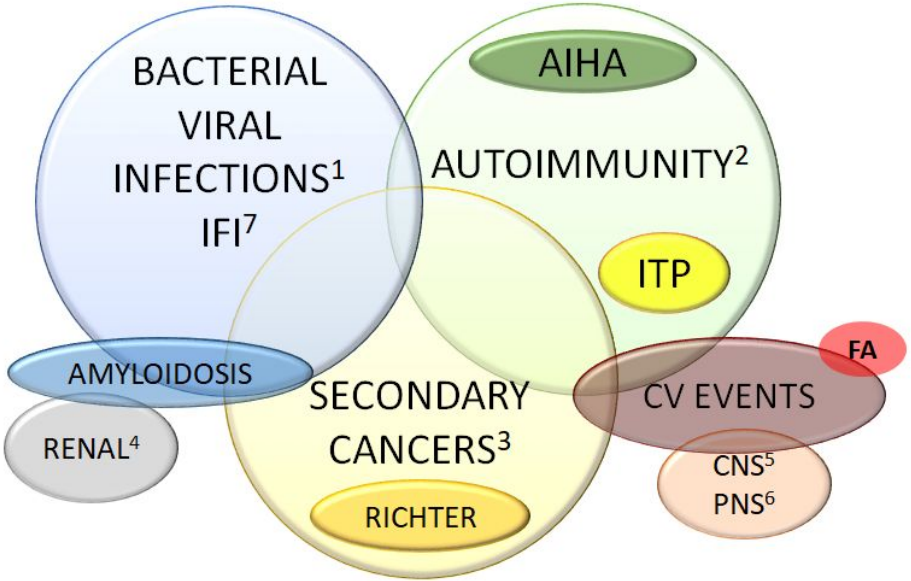




4 anemia
5 thromobocytopenia

2 lymphadenopathy
3 splenomegaly - hepatomegaly

Common complications in CLL



1 Visentin A, Haematologica 2015; 2 Stilgenbauer, ASCO 2015; 3 Visentin A, Eu j Cancer 2016; 4 Strati P, Haematologica 2015; 5 Lopez da Silva R., CLML 2012; 6 Briani C Haematologica 2016; 7 Visentin A, Hematol Oncol 2016.

INDICATIONS TO TREATMENT

- La linfocitosi da sola è raramente un'indicazione alla terapia. Il doubling time all'epoca dei BCRi sta perdendo di significato nell'indicazione alla terapia.

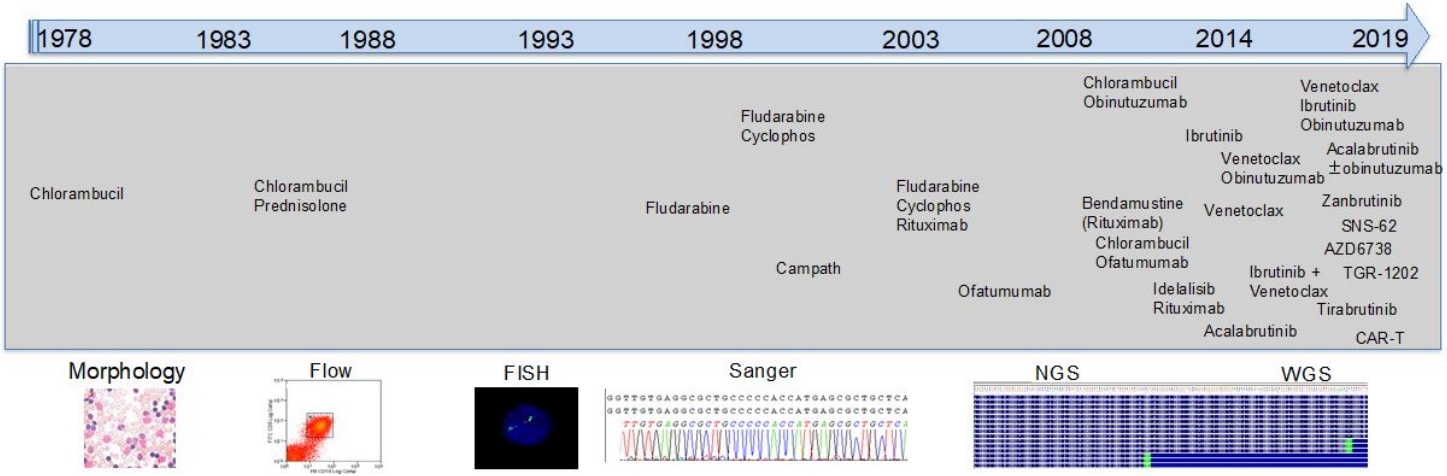
Per definire LLC in fase attiva deve essere presente almeno uno dei successivi:

- Progressiva insufficienza midollare dimostrata da comparsa o peggioramento di anemia e/o trombocitopenia, non causata da fenomeni autoimmuni.
- Anemia e/o trombocitopenia autoimmune resistente alla terapia immunosoppressiva.
- Splenomegalia massiva (>6 cm dall'arcata costale o progressiva o sintomatica) o epatomegalia
- Linfoadenopatia massiva >10 cm, progressiva o sintomatica
- Linfocitosi progressiva con LDT < 6 mesi (per linfocitosi>30.000/∝L).
- Sintomi sistemici legati alla malattia:
  - Perdita del 10% del peso negli ultimi 6 mesi.
  - Profonda astenia (ECOG 2).
  - Febbre ≥ 38°C che dura da almeno 15 giorni in assenza di infezione evidente o sospetta, di altra malattia neoplastica o autoimmune.

Sudorazione notturna profusa in assenza di altra patologia che la giustifichi, per >1 mese senza evidenza di infezione.

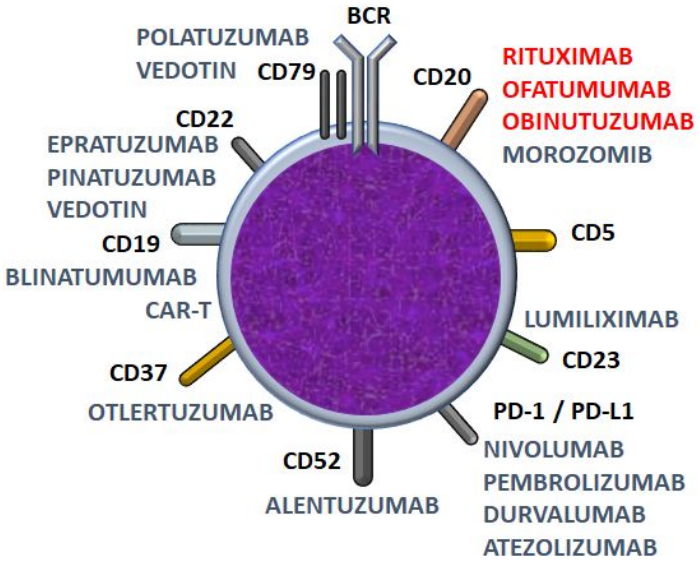
PDTA REV 2018

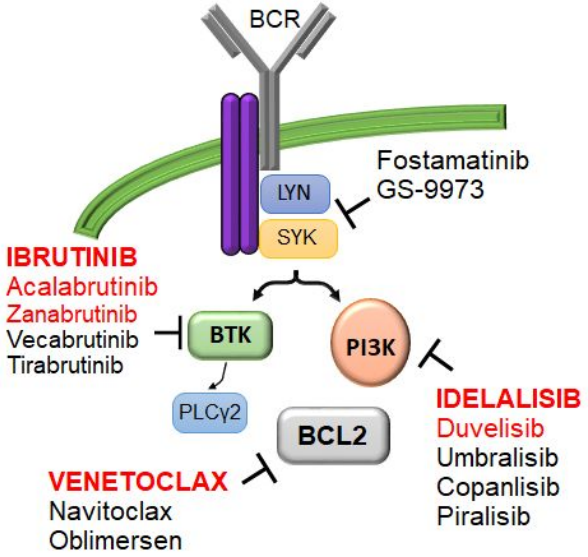
Evolution of CLL treatment



Peter Hillman, ERIC meeting 2019

New targets – New drugs for CLL Treatment



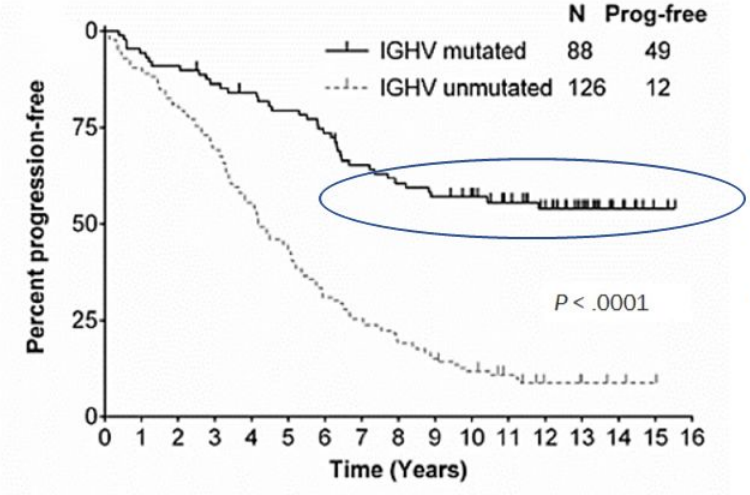


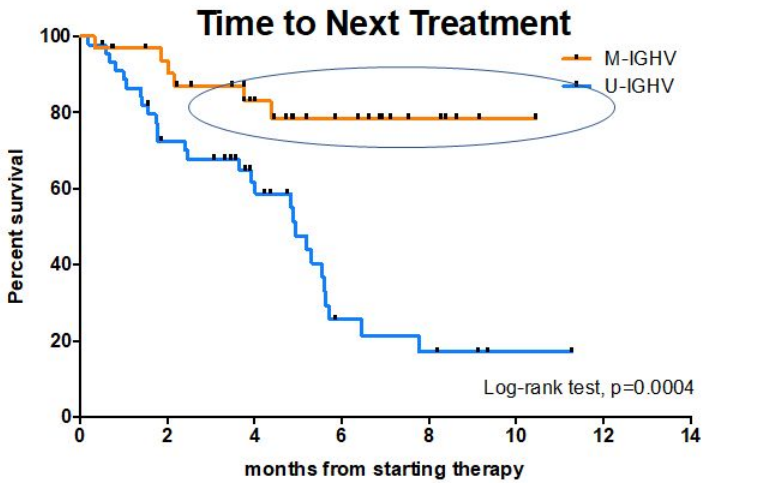
MILESTONES OF CLL MANAGEMENT

1. Which patients should received chemoimmunotherapy?

Impact of IGHV status on the PFS after chemo

- The curve of M-IGHV patients reaches a PFS plateau.
- Someone relapse, but 80% of patients do not require other therapy after FCR



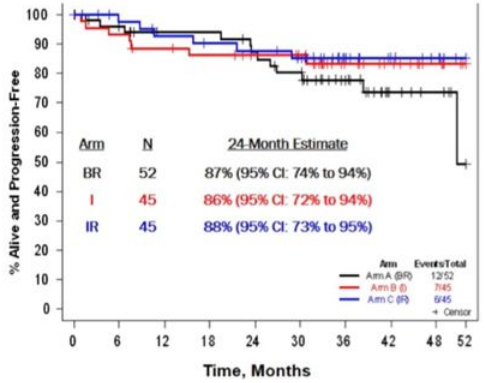


Thompson P, Blood 2016; Visentin A, Clinical lymphoma myeloma & leukemia2019

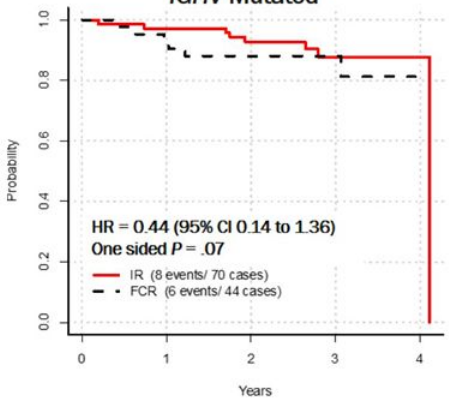
1L Ibrutinib vs Chemo in M-IGHV patients

- Chemo (FCR, BR or G-CHL) was superimposable to ibrutinib in treatment naive M-IGHV patients;
- Chemoimmunotherapy should be chosen based on age and comorbidities.

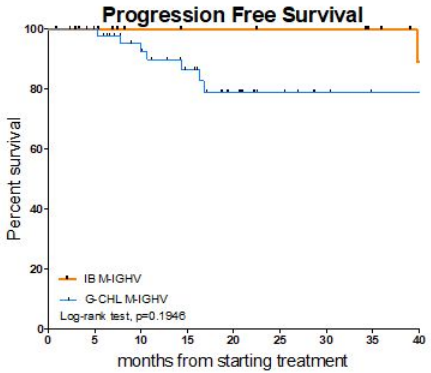
ALLIANCE
IB vs R-IB vs BR



ECOG-ECRIN E1912
R-IB vs FCR
***IGHV* Mutated**



CLL CAMPUS
G-CHL vs IB



Woyach J, NEJM 2018; Shanafelt T, NEJM 2018, Visentin A, in preparation

Is chemoimmunotherapy dead in CLL? NO

1. Only as 1st line treatment;
2. Only for low-risk patients (M-IGHV no 11q$^-$ no TP53 disruption);
3. FCR or G-CLB/BR depending on age, creatinine clearance, comorbidities.

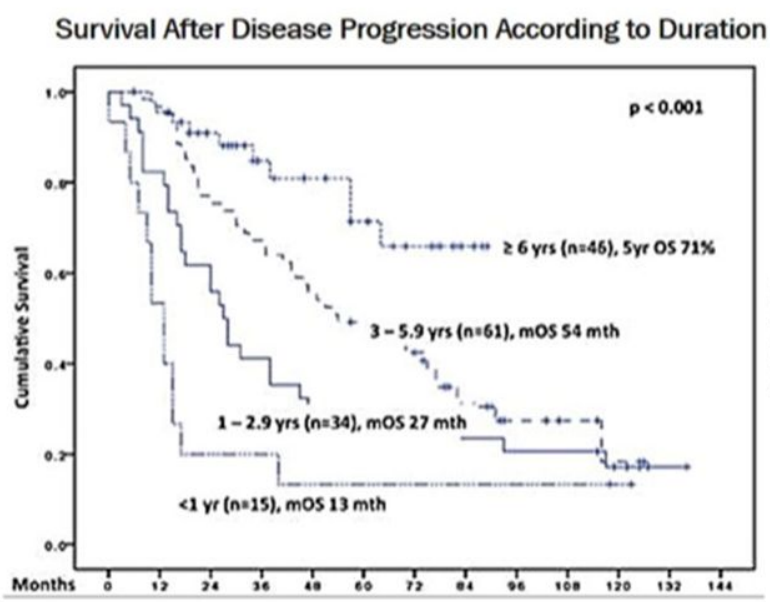
PDTA REV 2018

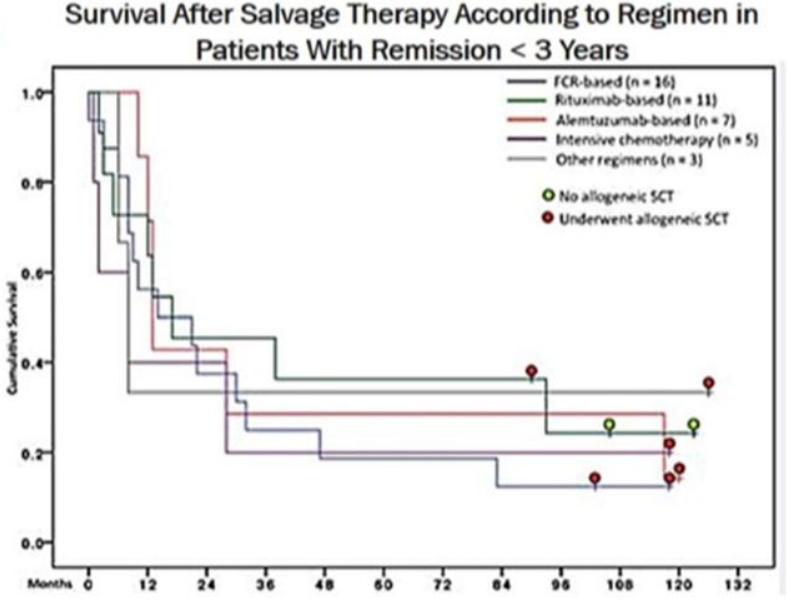
MILESTONES OF CLL MANAGEMENT

1. Which patients should received chemoimmunotherapy?

2. BTK inhibitor, ibrutinib, for relapsed/refractory patients

SURVIVAL AFTER FCR





Tam CS, et al. *Blood*. 2014;124:3059-3064.

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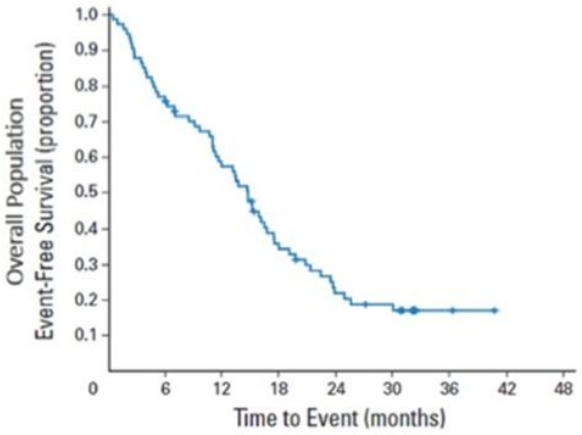
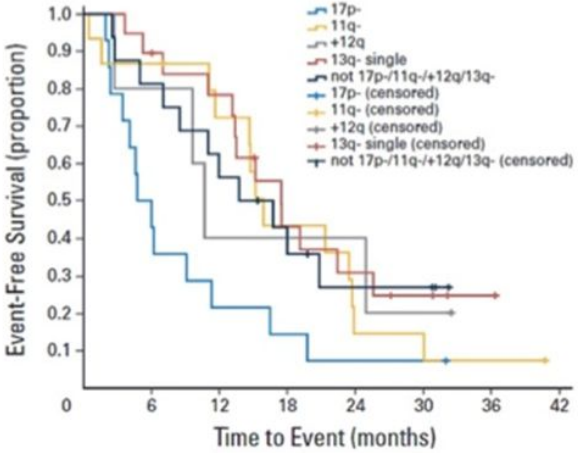
MILESTONES OF CLL MANAGEMENT

- GCLLSG phase 2 study (n = 78) of salvage BR (81% post fludarabine-based therapy)
- Acceptable EFS in the overall population, shorter in del(17p) patients

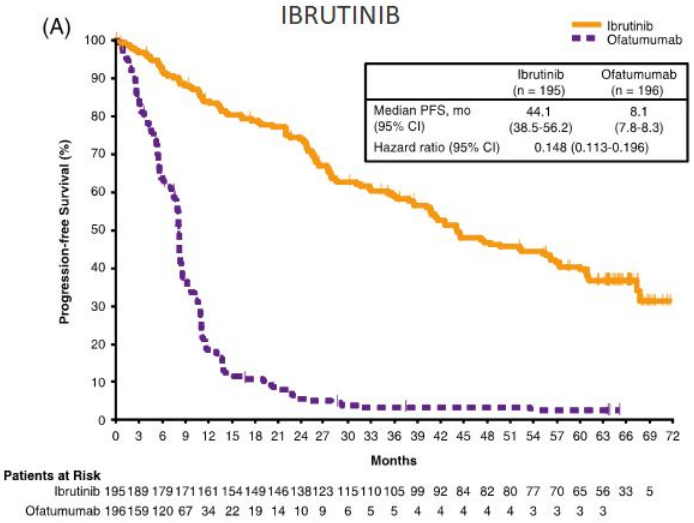


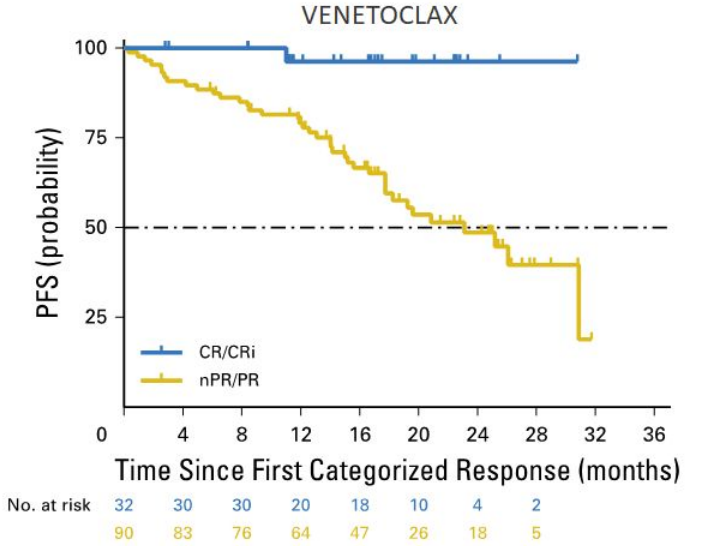


Fischer K, et al. *J Clin Oncol*. 2011;29:3559-3566.

IBRUTINIB AND VENETOCLAX IN RELAPSED CLL

- Ibrutinib, an oral BTK inhibitor, and venetoclax, an oral BCL2 inhibitor, are highly active in relapsed patients with TP53 disruption (deletion and mutation)

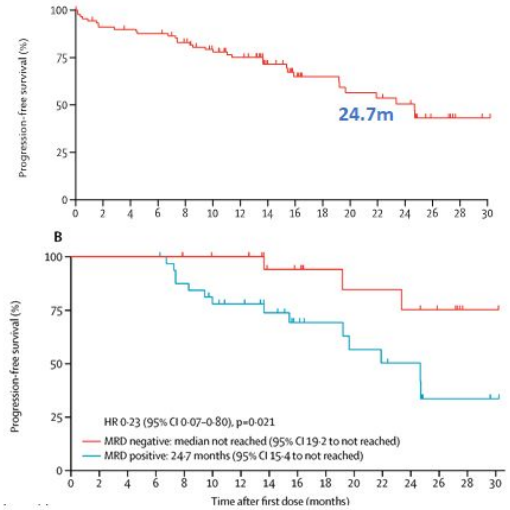




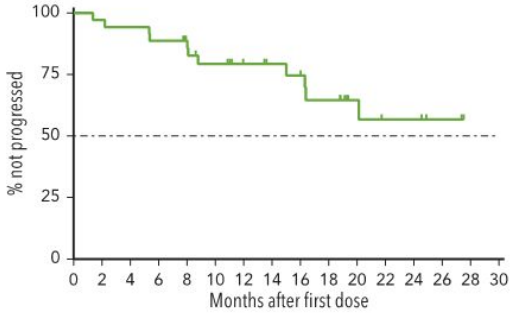
Munhir T AJH 2019; Stilgenbauer S, JCO 2018

VENETOCLAX after BCRi

- 91pts patients R/R after **IBRUTINIB**
- 47% 17p-, 29% high-risk TLS, median of 4 previous therapies
- 65% ORR, 9% CR, 26% MRD- pb



- 36 pts patients R/R after **IDELALISIB**
- 31% 17p-, 25% high-risk TLS
- median of 3 previous therapies
- 67% ORR, 8 % CR, 22% MRD- pb

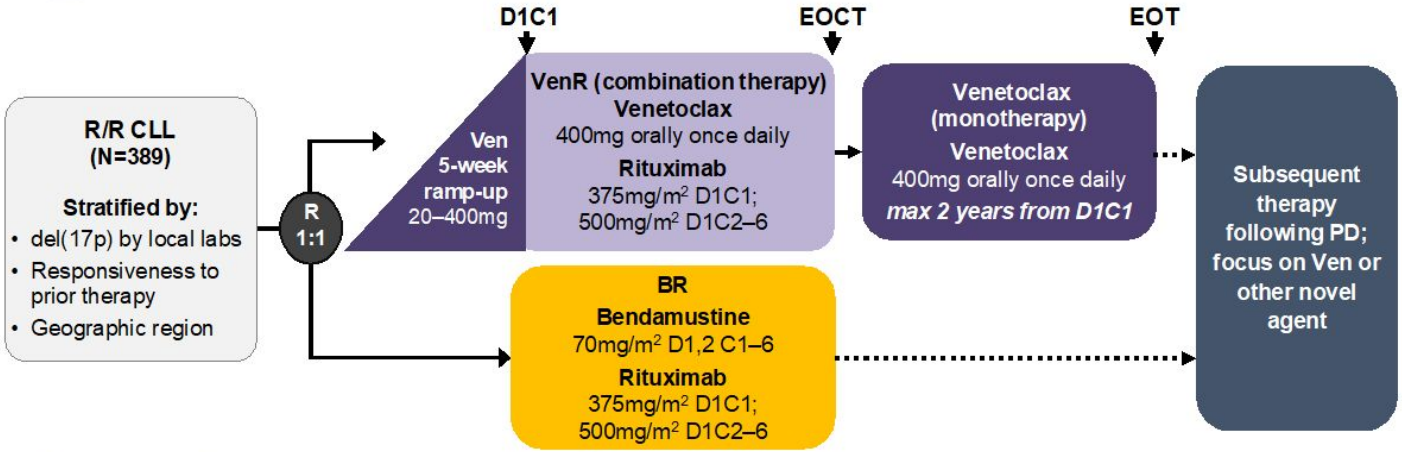


Jones, Lancet Oncology 2017; Coutre S, Blood 2018

MILESTONES OF CLL MANAGEMENT

1. Which patients should received chemoimmunotherapy?
2. BTK inhibitor, ibrutinib, for relapsed/refractory patients
3. Fixed duration therapy with venetoclax-rituximab

MURANO TRIAL, VenR vs BR



- **Primary endpoint:** investigator-assessed PFS
- **Secondary endpoint:** rates of clearance of MRD
- Clinical response and MRD* in PB during Ven monotherapy and follow-up visits were assessed every 3 months for 3 years, then every 6 months thereafter, or until PD

*Undetectable MRD defined as <1 CLL cell/10,000 leukocytes, determined by ASO-PCR or flow cytometry per iwCLL recommendations for reporting of MRD.
BR, bendamustine–rituximab; D1C1, day 1, cycle 1; D1C2-6, day 1, cycles 2-6; EOCT, end of combination treatment; EOT, end of treatment; MRD, minimal residual disease; PB, peripheral blood; PD, progressive disease/disease progression; R, randomization; R/R, relapsed/refractory VenR, venetoclax–rituximab

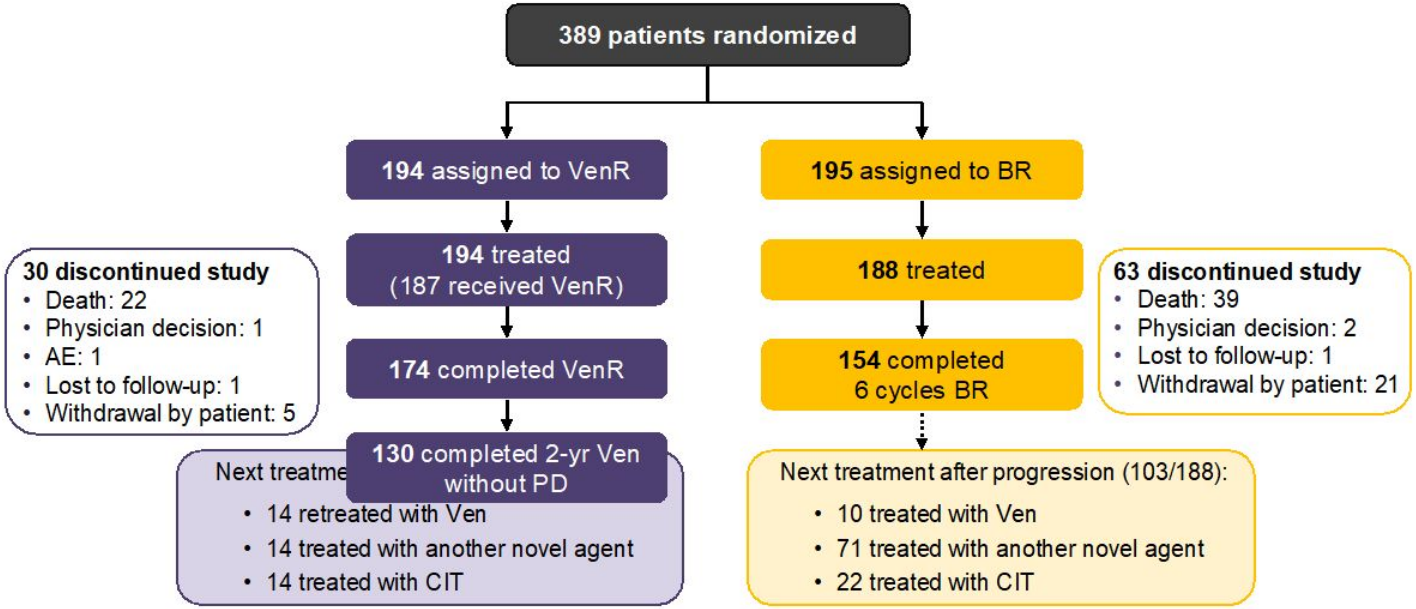
Seymour. ASH 2019. Abstr 355.

MURANO TRIAL, VenR vs BR

	VenR (n=194)	BR (n=195)
Median age, years (range)	65 (28–83)	66 (22–85)
Patients with lymphocyte count ≥25 x 10^9/L, n (%)	129 (66.5)	134 (68.7)
del(17p) and/or deleterious mutations in *TP53*, n/N (%)*	72/178 (40.4)	75/170 (44.1)
Number of prior therapies, n (%)		
1	111 (57.2)	117 (60.0)
2	58 (29.9)	43 (22.1)
3	23 (11.0)	35 (17.9)
>3	2 (1.0)	0
Prior therapies, n (%)		
Alkylating agent	185 (95.4)	182 (93.3)
Bendamustine	4 (2.1)	5 (2.6)
Purine analog	158 (81.4)	157 (80.5)
Anti-CD20 antibody	148 (76.3)	153 (78.5)
B-cell receptor pathway inhibitors	3 (1.5)	5 (2.6)

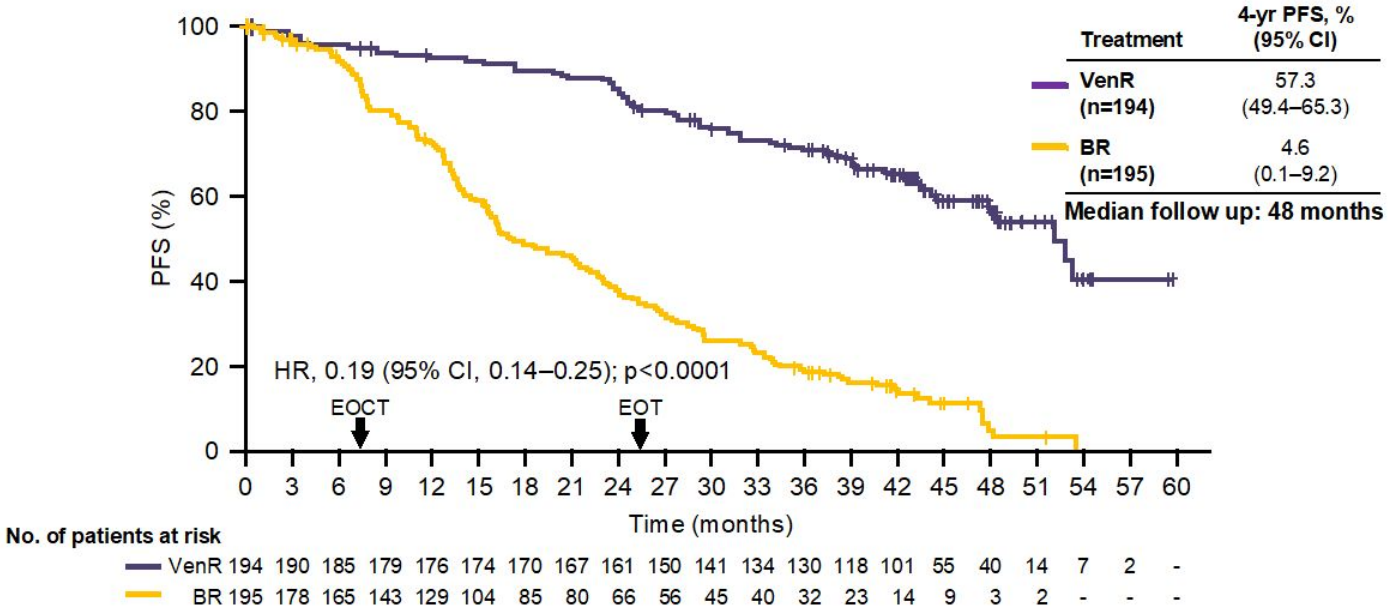
Seymour. ASH 2019. Abstr 355.

MURANO TRIAL, Venetoclax-rituximab



Kater A, JCO 2020

MURANO TRIAL, VenR vs BR 4-years follow-up

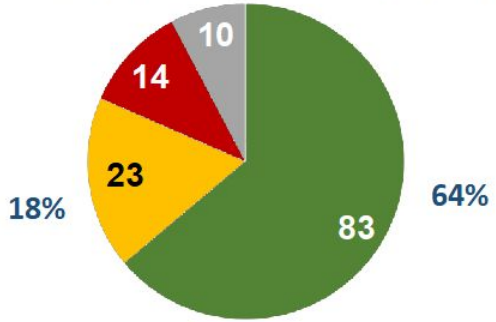


Kater A, JCO 2020

MURANO TRIAL, MRD AFTER 24 MONTHS

- In total, 130/194 patients completed 2 years of Ven therapy
- With a median 22 months off therapy (range 1–25 months), **35 progression events had occurred in 130 patients who completed 2 years of Ven**

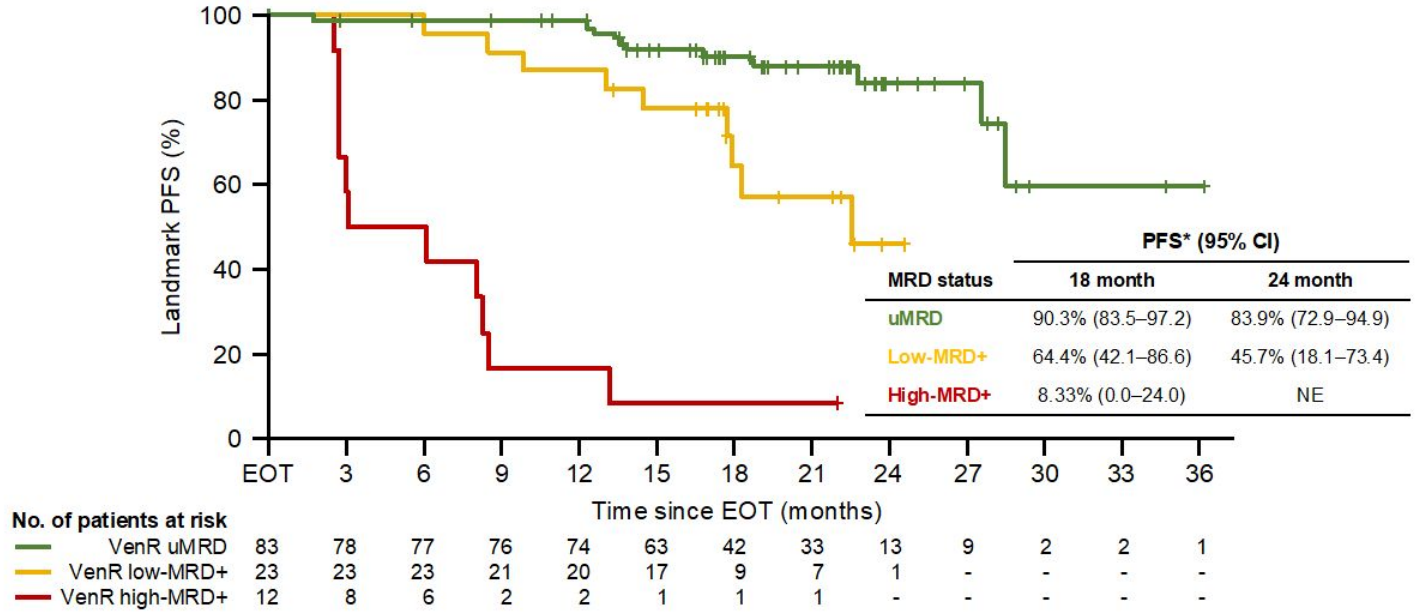
MRD status at EOT (month 24; n=130)



Status off-therapy, n (%)	uMRD ($<10^{-4}$) n=83	Low-MRD+ (10^{-4}–10^{-2}) n=23	High-MRD+ ($>10^{-2}$) n=14	Unknown n=10

Kater A, JCO 2020

MURANO TRIAL, IMPACT OF MRD ON PFS



MRD status	PFS* (95% CI) 18 month	24 month
uMRD	90.3% (83.5–97.2)	83.9% (72.9–94.9)
Low-MRD+	64.4% (42.1–86.6)	45.7% (18.1–73.4)
High-MRD+	8.33% (0.0–24.0)	NE

Kater A, JCO 2020

MURANO, safety by venetoclax treatment

- Severe neutropenia are common during the ramp-up phase but infections are rare events.

G-CSF →

Grade 3/4 TEAEs With ≥ 2% Difference Between Arms, n (%)	VenR Combination (n = 194)	Ven Monotherapy (n = 171)
Neutropenia	106 (54.6)	20 (11.7)
Anemia	16 (8.2)	5 (2.9)
Thrombocytopenia	9 (4.6)	3 (1.8)
→ Febrile neutropenia	7 (3.6)	0
Pneumonia	8 (4.1)	2 (1.2)
Infusion-related reaction	4 (2.1)	0
TLS/Clinical TLS	6 (3.1)/1 (0.5)	0/0
Hyperglycemia	4 (2.1)	0
Hypogammaglobulinemia	3 (1.5)	1 (0.6)

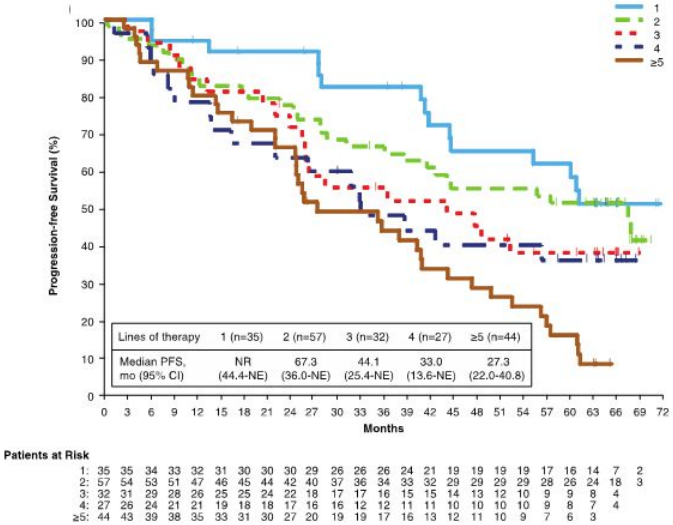
Kater A, JCO 2020

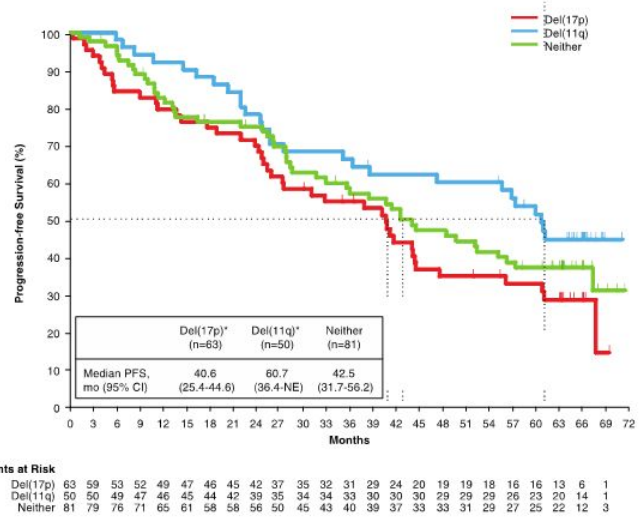
MILESTONES OF CLL MANAGEMENT

1. Which patients should received chemoimmunotherapy?
2. BTK and BCL2 inhibitors for relapsed/refractory patients
3. Fixed duration therapy with venetoclax-based treatment
4. Which patients should receive continuous vs fixed therapy

RESONATE: ibrutinib phase 3 trial, sub-analysis

- Early treatment with ibrutinib is associated with a better outcome.
- Patients with 11q- expercienced the best results.

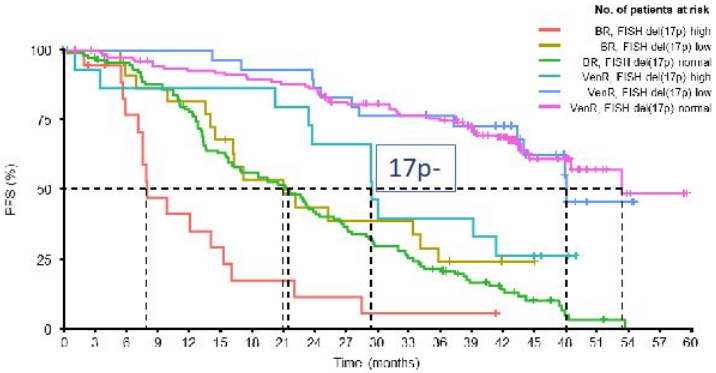




Munhir T AJH 2019; Stilgenbauer S, JCO 2018

MURANO: venetoclax phase 3 trial, sub-analysis

- Progression free survival is shorter for 17p-
- MRD neg patients had a better survival
- M-IGHV patients without 17p- have the higher likelihood to achieved MRD-



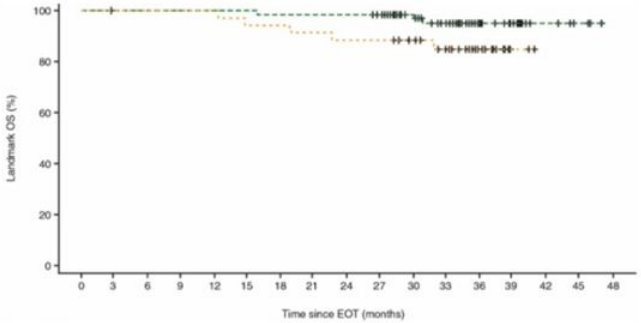


Table 1: MRD conversion and PD status according to pts' genetic profile status.

	del(17p) n (%)		GC (≥3 CNV) n (%)		IGVH n (%)	
	Yes BEP; n=4	No BEP; n=54	Yes BEP; n=18	No BEP; n=40	unmut BEP; n=56	mut BEP; n=23
Sustained uMRD	0 (0)	21 (39)	5 (28)	16 (40)	20 (36)	10 (44)
Conversion to MRD (no PD)	0 (0)	21 (39)	5 (28)	16 (40)	15 (27)	12 (52)
Conversion with subsequent PD	4 (100)	12 (22)	8 (44)	8 (20)	21 (37)	1 (4)

BEP, biomarker evaluable population; CNV, copy number variations; del(17p), chromosome 17p deletion; GC, genomic complexity; IGHV, immunoglobulin heavy chain variable region; MRD, minimal residual disease; mut, mutated; uMRD, undetectable minimal residual disease; unmut, unmutated; PD, progressive disease; pts, patients.

Kater A, JCO 2020; Seymour ASH 2020

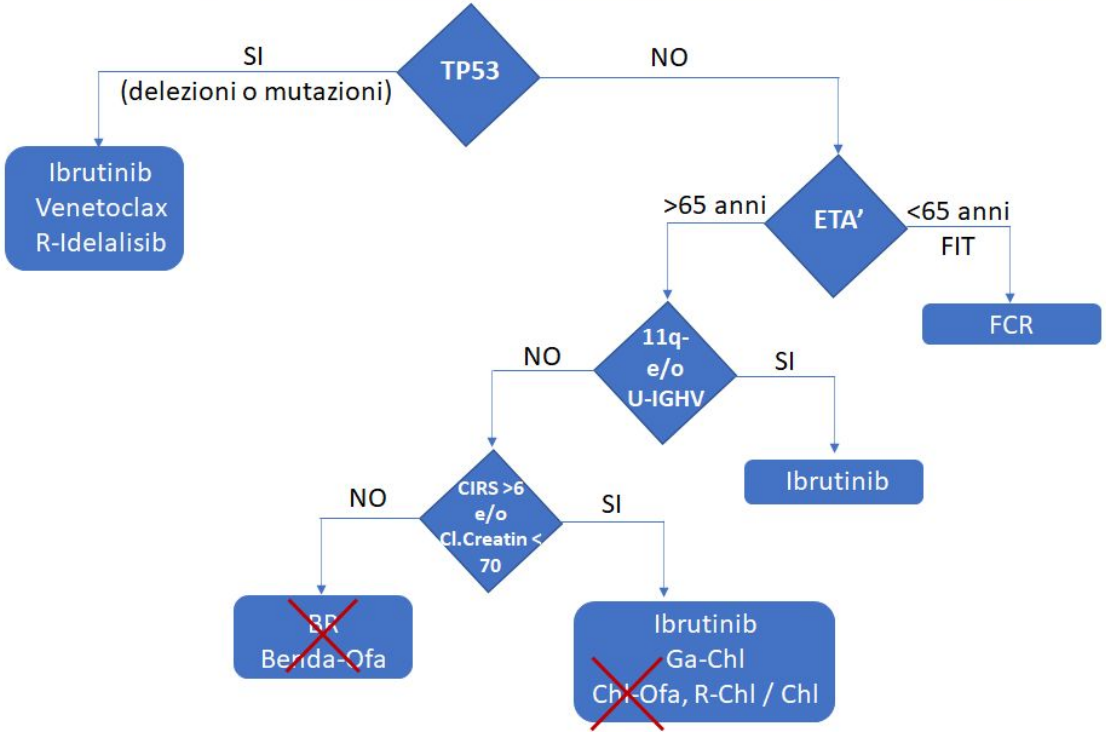
In the next future....

- ACALABRUTINIB: for ibrutinib intollerant patients and maybe as first-line therapy in combination with obinutuzumab.

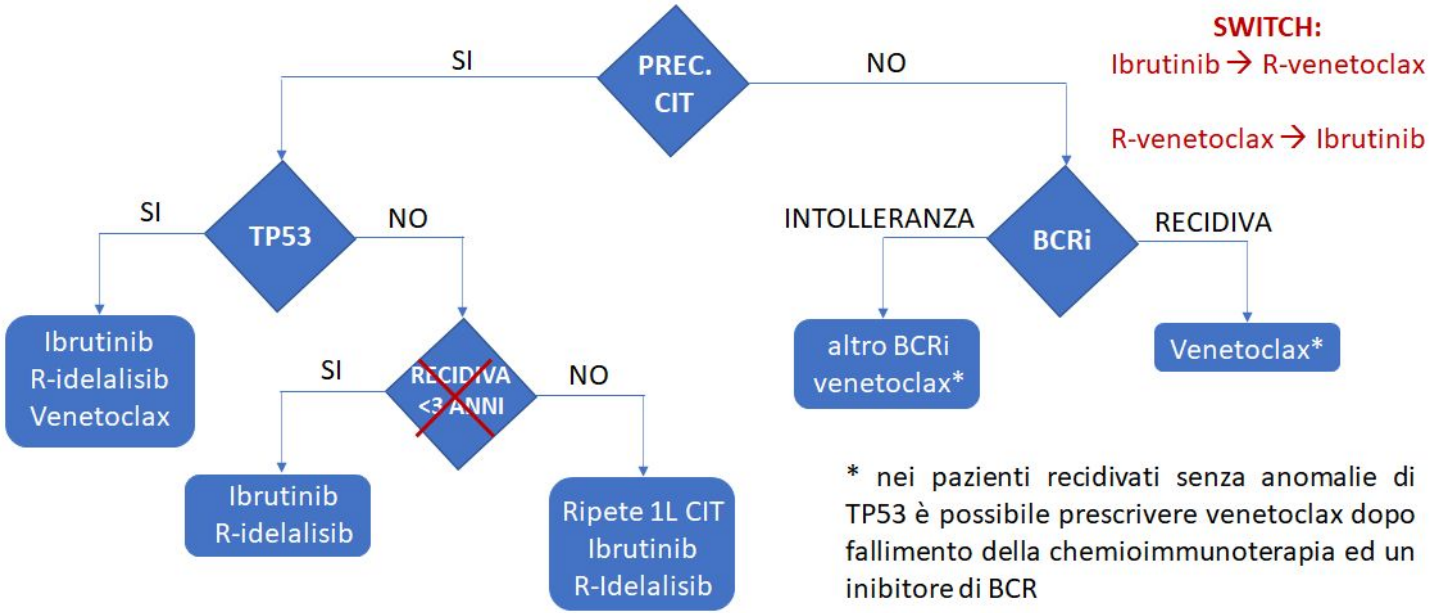
- VENETOCLAX-OBINUTUZUMAB: 12 months first-line treatment.

- ZANUBRUTINIB
- UMBRALISIB
- CAR-T

PDTA REV 2018 – 1L CLL



PDTA REV 2018 – R/R



* nei pazienti recidivati senza anomalie di TP53 è possibile prescrivere venetoclax dopo fallimento della chemioimmunoterapia ed un inibitore di BCR

In the next future....

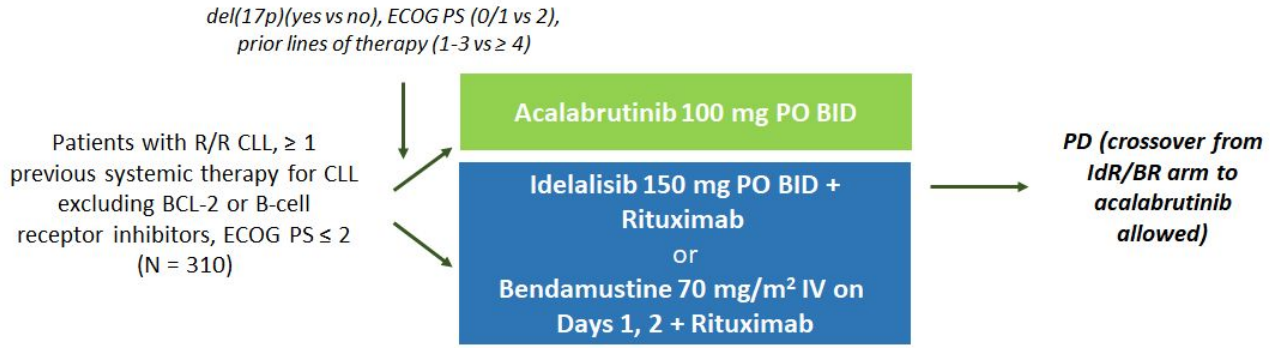
GRAZIE PER L'ATTENZIONE

LEUCEMIA LINFATICA CRONICA
MALATTIA SEMPRE PIÙ CRONICIZZATA: QUALI NUOVI PERCORSI DI CURA?

MOTORE SANITÀ
Innovazione Sostenibile

ASCEND: Trial Design

- International, randomized, open-label phase III trial

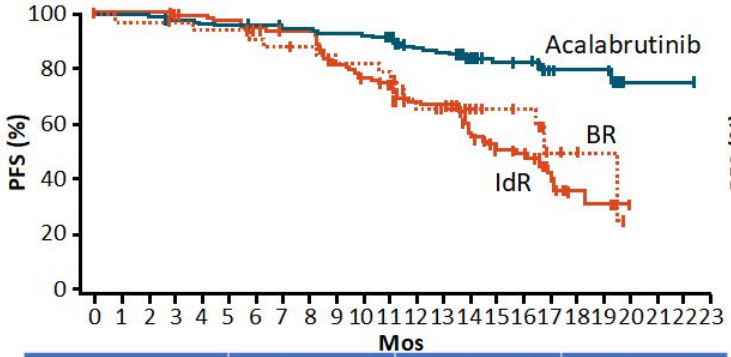


- Primary endpoints: PFS per IRC
- Secondary endpoints: ORR, DoR, PFS per investigator, OS
- Interim analysis planned after ≈79 PFS events

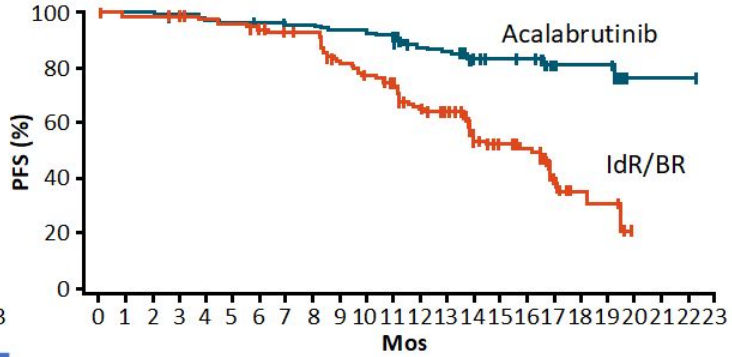
Ghia P, JCO 2020

ASCEND: PFS by treatment and high-risk status

- Acalabrutinib improved PFS of R/R patients than BR or R-idelalisib.



	Acala (n = 155)	IdR (n = 118)	BR (n = 36)
mPFS, mos	NR	15.8	16.9
HR (95% CI) vs IdR	0.29 (0.18-0.46); P < .0001		
HR (95% CI) vs BR	0.36 (0.18-0.69); P < .0001		
1-yr PFS rate, %	88	68	69



	Acala (n = 135)	IdR/BR (n = 137)
mPFS, mos	NR	16.2
HR (95% CI)	0.27 (0.17-0.44); P < .0001	
1-yr PFS rate, %	88	66

Ghia P, JCO 2020

ASCEND: safety

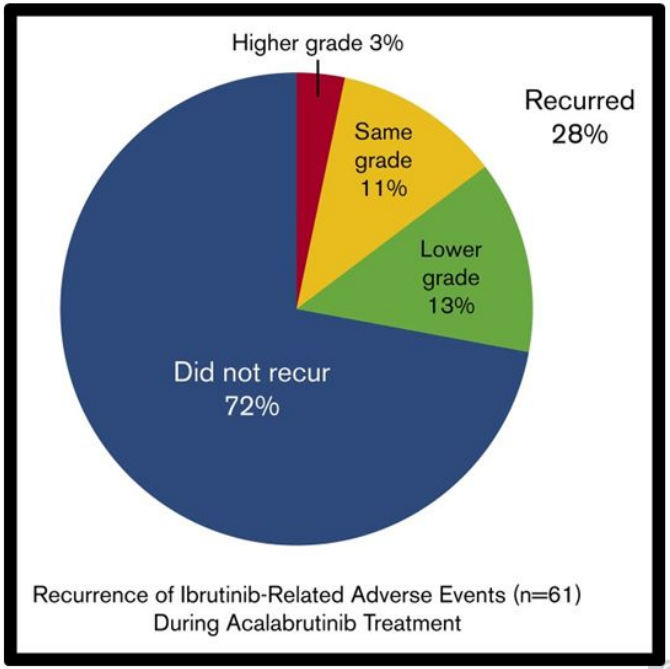
- A NEW kind of adverse event to manage, headache!

Most Common AEs, n (%)	Acalabrutinib (n = 154)		IdR (n = 118)		BR (n = 35)	
	Any	Grade ≥ 3	Any	Grade ≥ 3	Any	Grade ≥ 3
Headache	34 (22)	1 (1)	7 (6)	0	0	0
Neutropenia	30 (19)	24 (16)	53 (45)	47 (40)	12 (34)	11 (31)
Diarrhea	28 (18)	2 (1)	55 (47)	28 (24)	5 (14)	0
Anemia	23 (15)	18 (12)	11 (9)	8 (7)	4 (11)	3 (9)
Cough	23 (15)	0	18 (15)	1 (1)	2 (6)	0
Pyrexia	19 (12)	1 (1)	21 (18)	8 (7)	6 (17)	1 (3)
Fatigue	15 (10)	2 (1)	10 (8)	0	8 (23)	1 (3)
Nausea	11 (7)	0	15 (13)	1 (1)	7 (20)	0
IRR	0	0	9 (8)	2 (2)	8 (23)	1 (3)
AEs of clinical interest for acalabrutinib						
Atrial fibrillation	8 (5)	2 (1)	4 (3)	1 (1)	1 (3)	1 (3)
Bleeding	40 (26)	3 (2)	9 (8)	3 (3)	2 (6)	1 (3)
Hypertension	5 (3)	3 (2)	5 (4)	1 (1)	0	0
SPM (no NMSC)	10 (6)	5 (3)	3 (3)	0	1 (3)	1 (3)

Ghia P, JCO 2020

Acalabrutinib in Ibrutinib-Intolerant

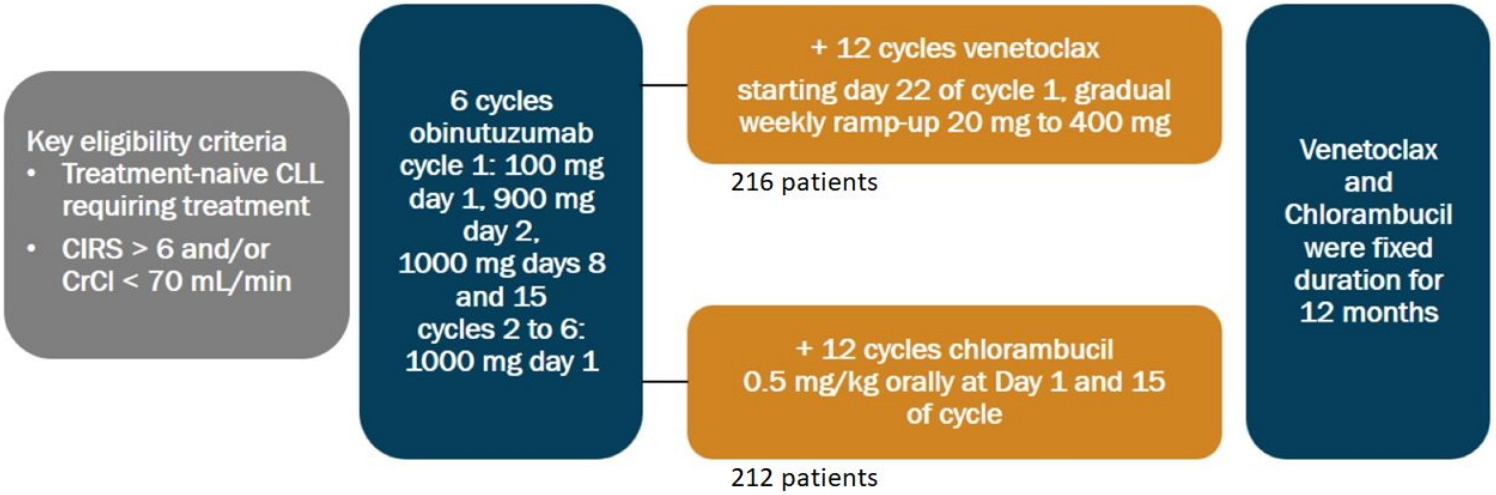
- Phase I/II ACE-CL-001 Trial
- Among 33 patients, 23 remained on acalabrutinib
- No acalabrutinib dose reductions occurred
- Of 61 ibrutinib-related AEs, 72% did not recur and 13% recurred at a lower grade with acalabrutinib
- ORR was 76%
- Median PFS not reached; 1-yr PFS rate was 83.4%



Awan. Blood Adv. 2019;3:1553.

Slide credit: clinicaloptions.com

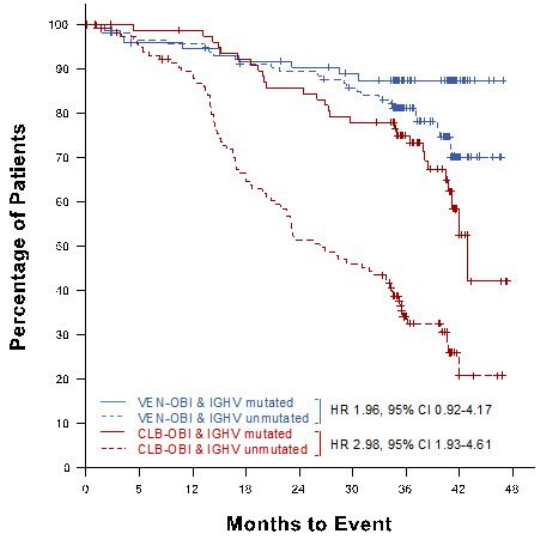
Phase III CLL14, G-venetoclax vs G-clb

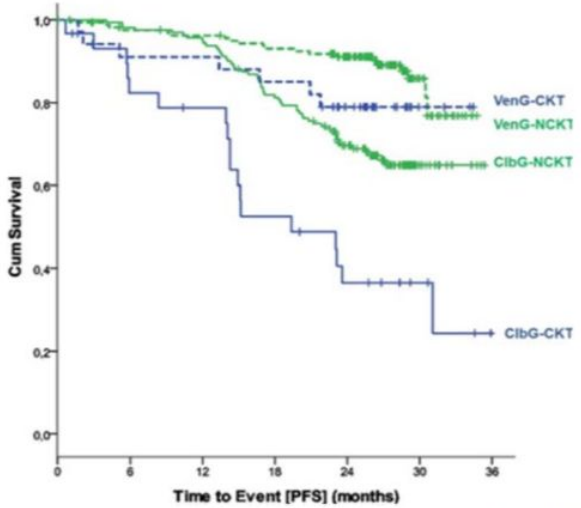


Fischer K, NEJM 2019

Phase III CLL14, PFS by IGHV status and CK

- After a median follow-up of 39 months, G-Ven improves PFS and TTNT but not OS.
- At 15 months the rate of uMRD by ASO-PCR was 76% vs 35%.
- G-venetoclax overcomes the adverse prognosis of U-IGHV (HR 0.23) and CK (HR 0.23).





Al-sawaf O, Lancet 2020