

CLL: Treatment in the Novel Era

Treatment after failure of kinase inhibitors

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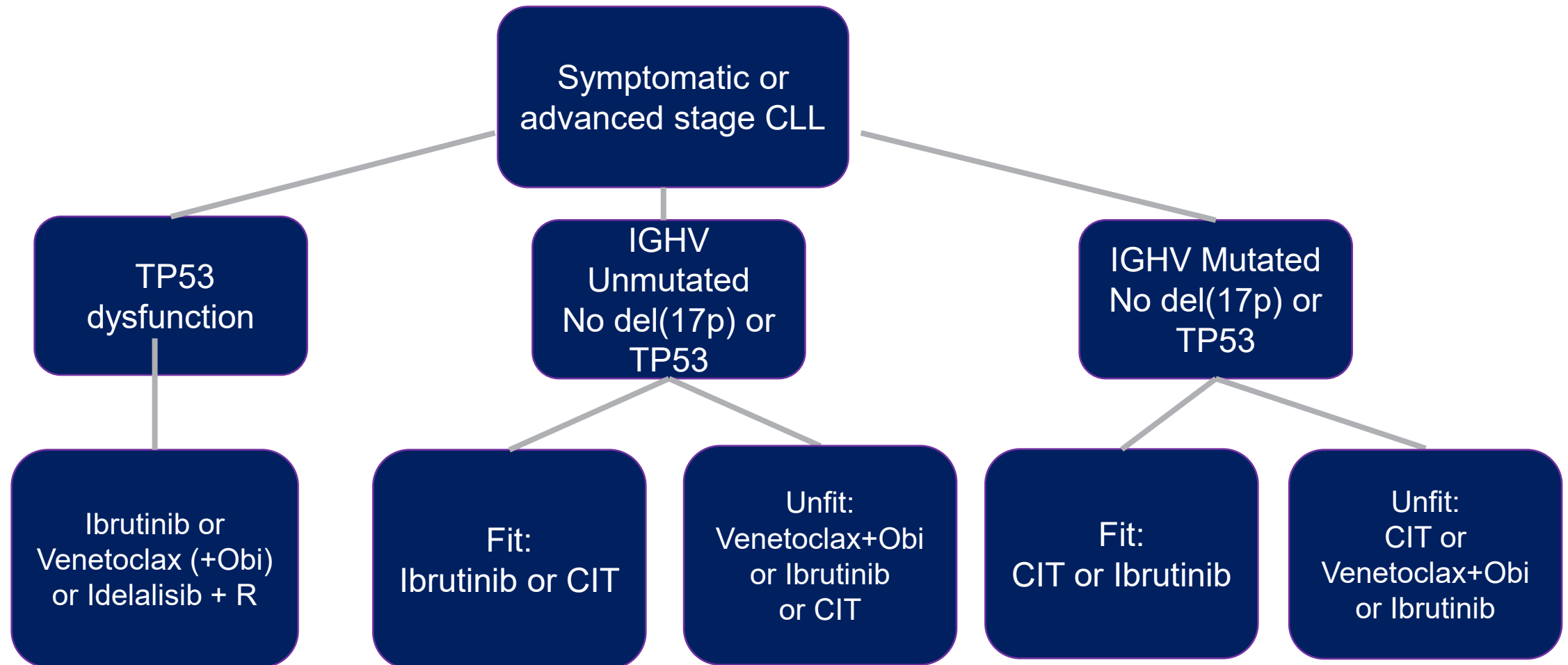


Disclosure of conflicts of interest

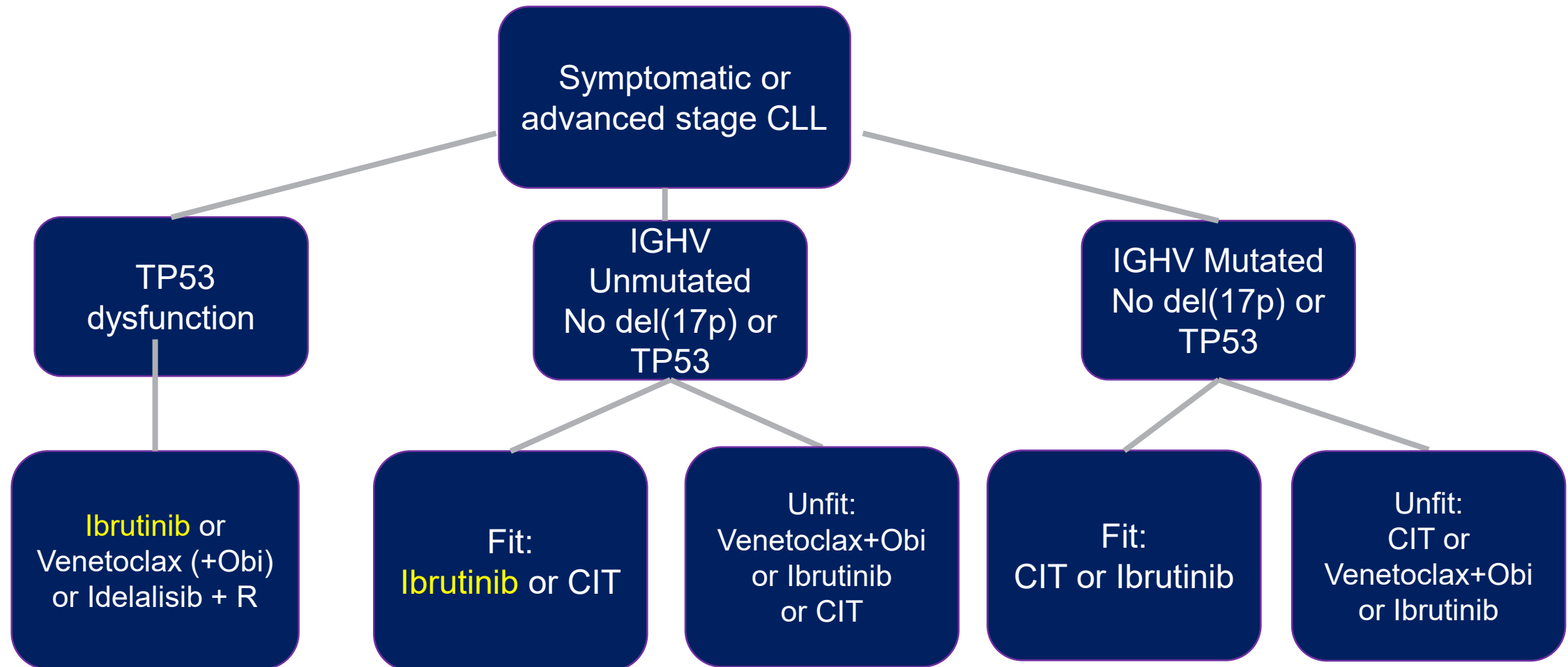
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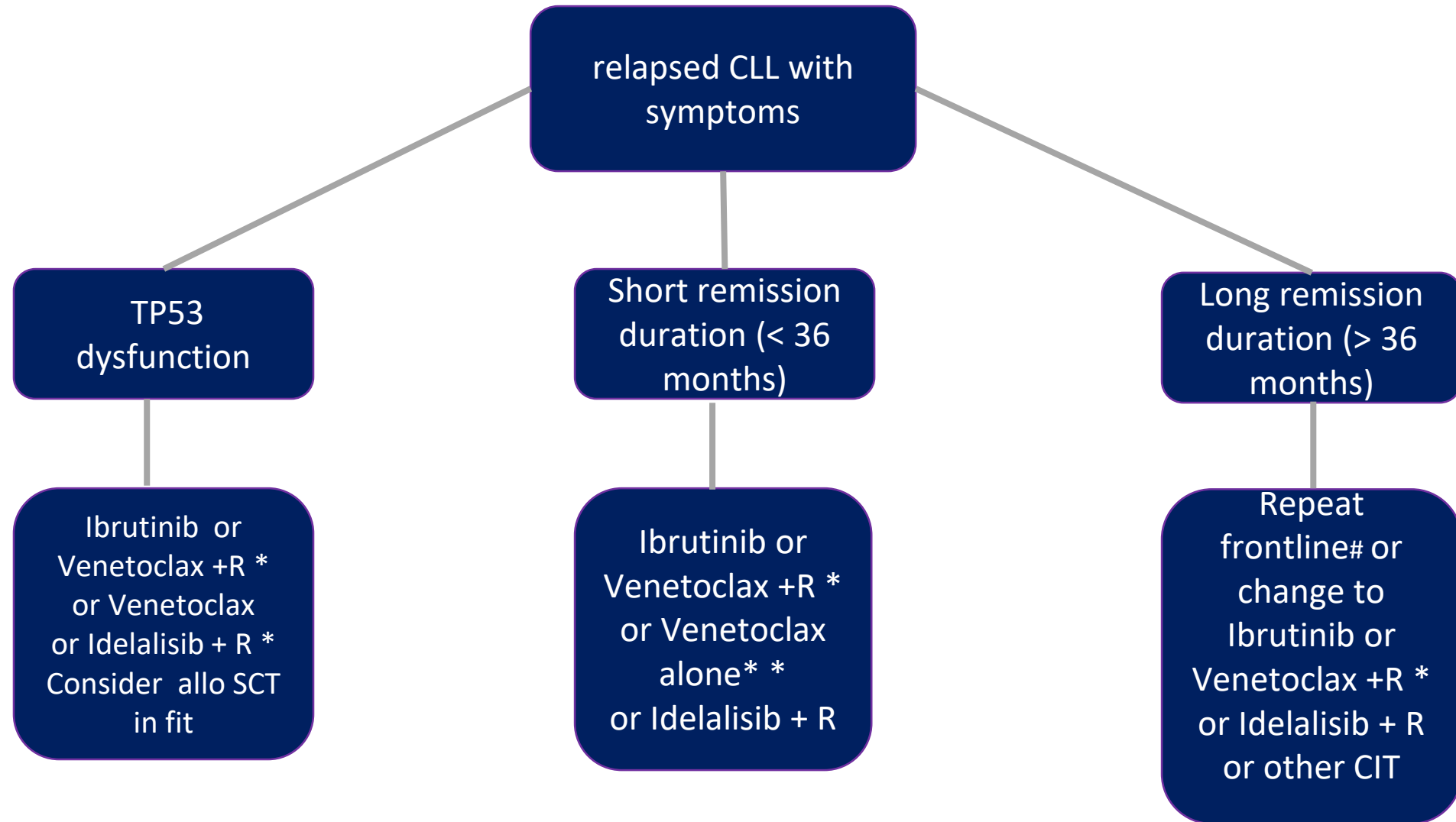
Treatment algorithm for 1st-line therapy of CLL / SLL



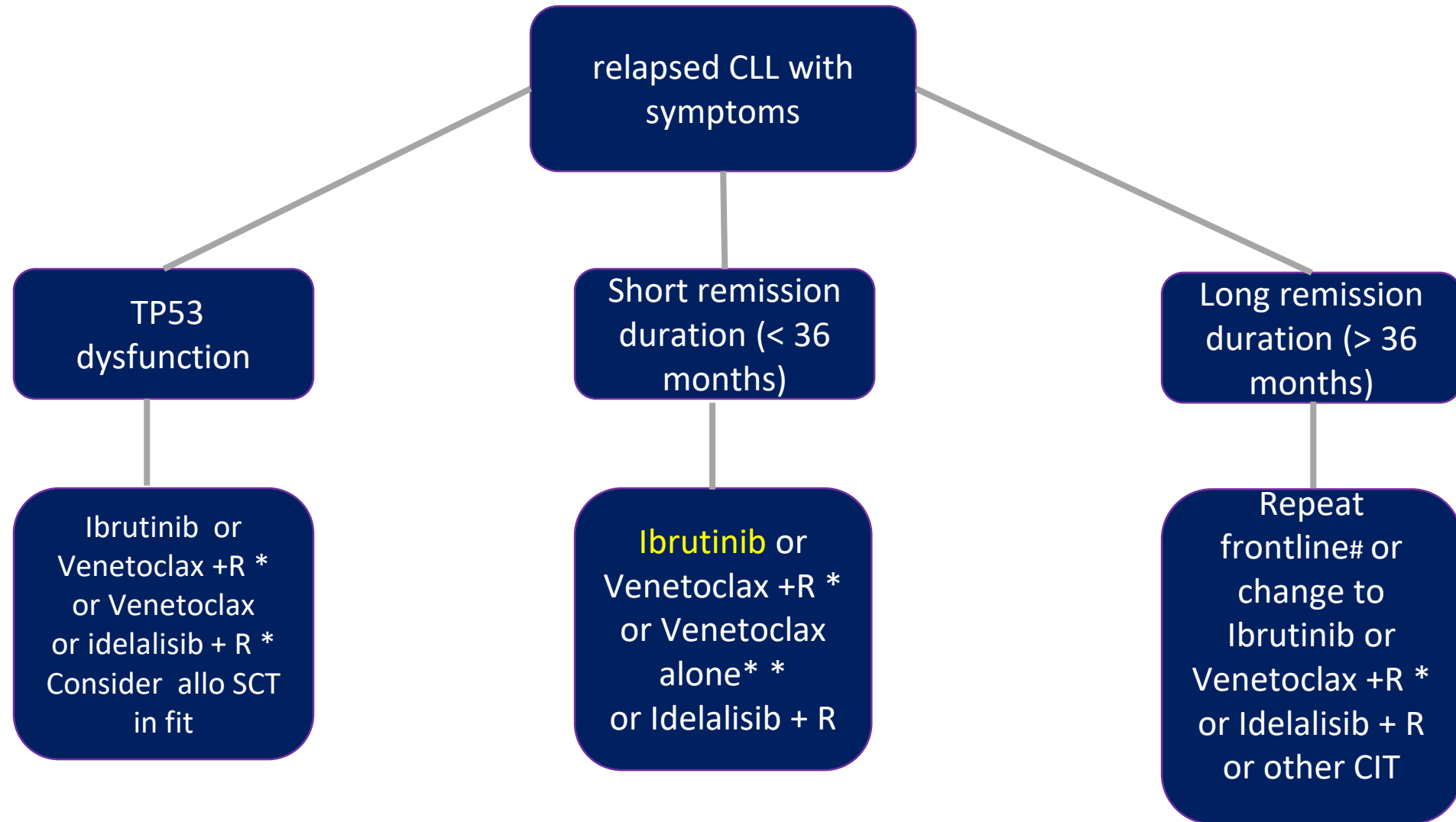
Treatment algorithm for 1st-line therapy of CLL / SLL



Treatment algorithm for treatment of rel/ref CLL / SLL



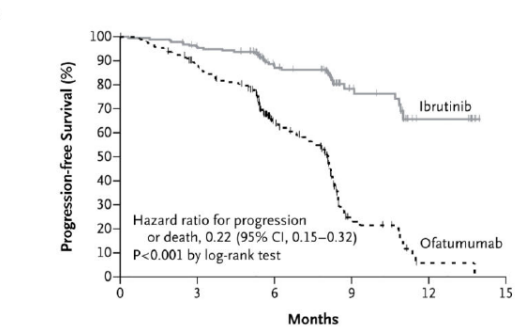
Treatment algorithm for treatment of rel/ref CLL / SLL



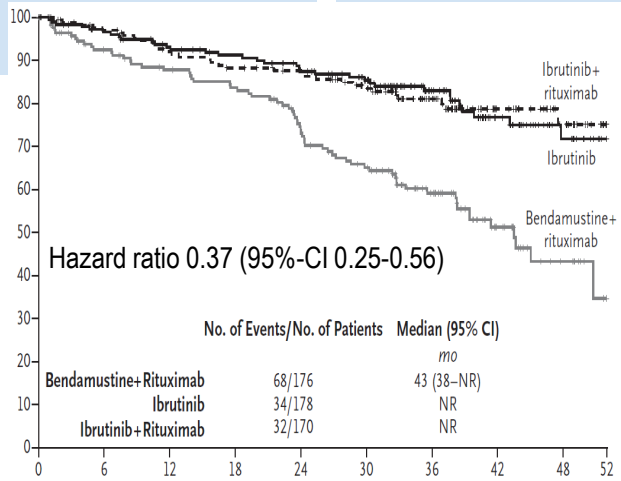
Changing use of novel agents for CLL

Past
BCR-I in very advanced disease (refractory and/or very high-risk)

Bulky disease ≥ 5 cm — no. (%) [§]	124 (64)
Interphase cytogenetic abnormalities — no. (%)	
Chromosome 11q22.3 deletion	63 (32)
Chromosome 17p13.1 deletion ¶	63 (32)
β_2 -microglobulin >3.5 mg/liter — no. (%)	153 (78)
Previous therapies	
Median no. (range)	3 (1–12)
≥ 3 — no. (%)	103 (53)

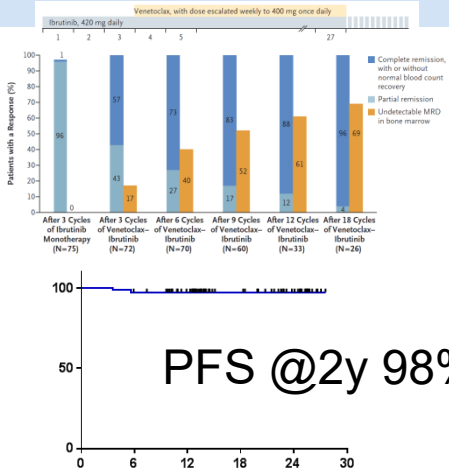


Yesterday
CLL with del17p/TP53mut
→ Ibrutinib 1st line
→ Venetoclax after failure of BCR-I
CLL refractory to CIT or early relapse (<3y)
→ Ibrutinib or Idelalisib+R



Today / Tomorrow
CLL patients with no longterm benefit of CIT
→ Ibrutinib 1st line
CLL patients unfit for intensive CIT
→ Venetoclax + Obi

Future
Venetoclax combinations duration either fixed or adapted to response
Venetoclax + Ab
Venetoclax + BCR-I
Venetoclax + BCR-I + AB
Novel novel agents



Byrd JC et al. Ibrutinib versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia N Engl J Med. 2014; 371: 213–223
Woyach JA et al. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. N Engl J Med. 2018; 379:2517-2528
Jain N et al. Ibrutinib and Venetoclax for First-Line Treatment of CLL. N Engl J Med. 2019; 380:2095-2103

Definition of failure of BCR-inhibitors in CLL

European LeukemiaNet Recommendations for the Management of Chronic Myeloid Leukemia (CML)

Response definitions for any TKI **first line**, and 2nd line in case of intolerance, all patients (CP, AP, and BC)

Time	Optimal response	Warning	Failure
Baseline		High risk Major route CCA/Ph+	
3 mos.	BCR-ABL ^{IS} ≤10%* Ph+ ≤35% (PCyR)	BCR-ABL ^{IS} >10%* Ph+ 36-95%	No CHR* Ph+ >95%
6 mos.	BCR-ABL ^{IS} <1%* Ph+ 0% (CCyR)	BCR-ABL ^{IS} 1-10%* Ph+ 1-35%	BCR-ABL ^{IS} >10%* Ph+ >35%
12 mos.	BCR-ABL ^{IS} ≤0.1%* (MMR)	BCR-ABL ^{IS} 0.1-1%*	BCR-ABL ^{IS} >1%* Ph+ >0%
Then, and at any time	MMR or better	CCA/Ph- (-7, or 7q-)	Loss of CHR Loss of CCyR Loss of MMR, confirmed** Mutations CCA/Ph+

*and/or **in 2 consecutive tests, of which one ≥1% IS: BCR-ABL on International Scale

- Insufficient response at a defined timepoint
- Relapse after response
- Mutations (predicting loss of response)

CLL

IWCLL 2018:

“Responses that should be considered clinically beneficial include CR and PR; all others (eg, stable disease, nonresponse, PD, death from any cause) should be rated as a treatment failure.” also PD @ 6m

Accepted for chemoimmunotherapy, less clear for continuous therapies with BCR-I due to initial lymphocytosis (PR-L, not PD!) and sometimes clinical improvement with persistent (therapy related) cytopenia or minor findings (e.g. splenomegaly).

General understanding failure of BCR-I includes:

- Progression under continuous treatment
- Side effects requiring permanent stopping of BCR-I

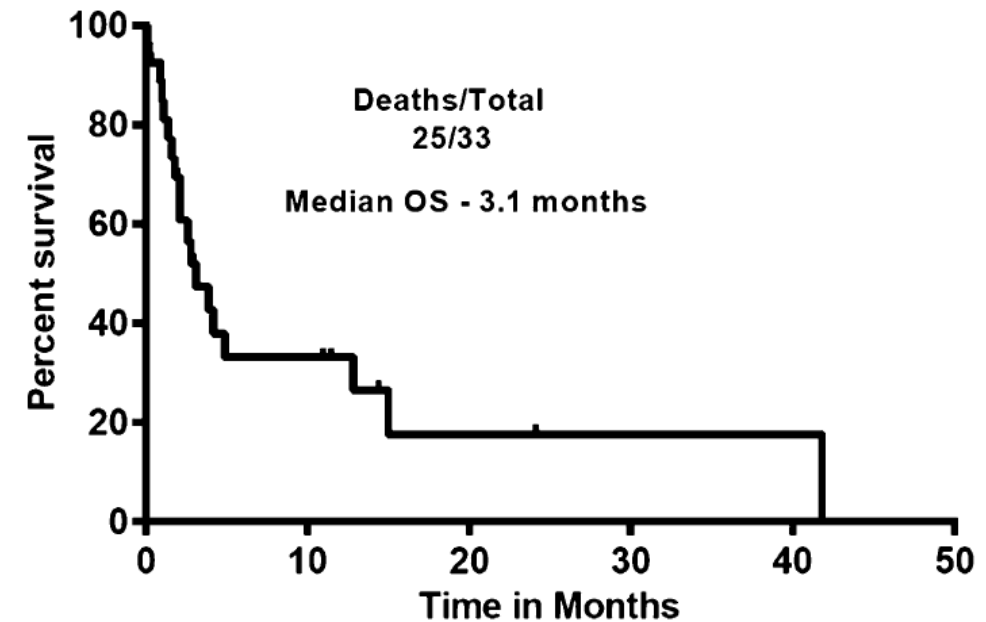
Discontinuation of Ibrutinib

MDACC, 33/127 patients treated in 4 clinical trial discontinued ibrutinib.

Reasons: Transformation (7), Progression (7), SCT (3), side effects (14), other (2)

Table 2. Characteristics of patients who discontinued ibrutinib

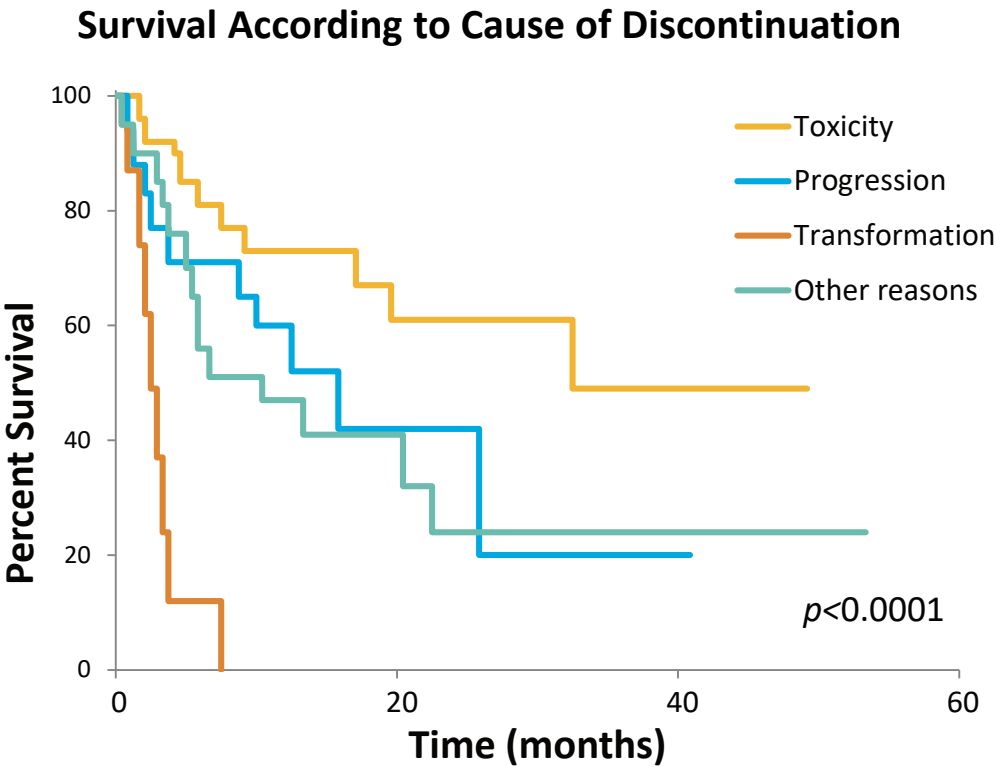
Characteristic	Category	Overall, N = 33
Age, years	Median (range)	61 (36-83)
White blood cell, K/ μ L	Median (range)	24 (2-323)
Rai stage, 3-4	Advanced	76%
CD38, >30%	High	52%
Zap-70 positive	By immunohistochemistry	70%
β 2 M, mg/L	≥ 4 mg/L	61%
IGHV mutation	Unmutated	94%
Fluorescence in situ hybridization category	del17p/del11q/others	58%/18%/24%
Karyotype	Complex	54%
Number of prior therapies	≥ 3	45%
Median number of prior therapies	Median (range)	2 (0-7)
Median time from diagnosis to ibrutinib, months	Median (range)	59 (8-150)



Historic data: 2010 – 2014. Poor-risk patients without any further options!

Discontinuation of Ibrutinib real world data

Reason for discontinuation (n=90)	Median time to discontinuation (Months)	Median OS (Months)
Intolerance (n=29; 32%)	16	33
Progression (n=19; 21%)	22.3	16
Transformation (n=9; 10%)	13.2	2.3
Miscellaneous (n=28; 31%)	10.4	11



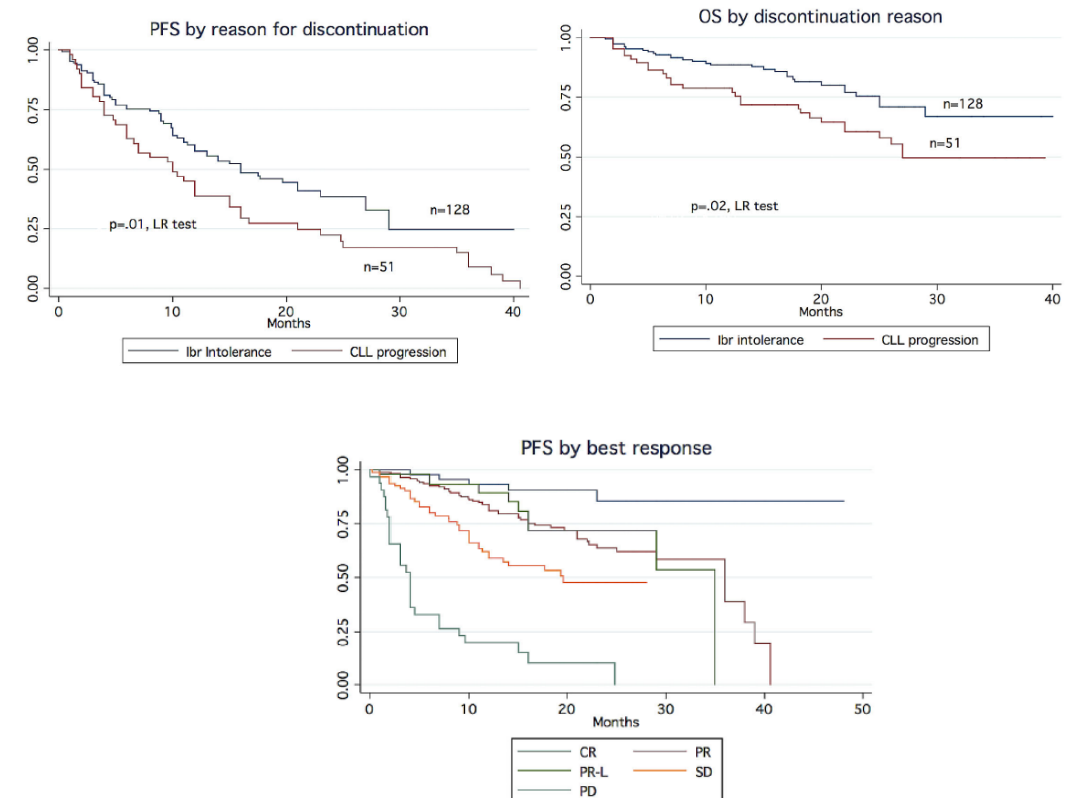
Survival was associated with the reason for discontinuation; patients who had toxicity had better survival compared with those who had progressive CLL or disease transformation.

Discontinuation of Ibrutinib real world data

- Connect® Chronic Lymphocytic Leukemia Registry in US (2014-2016).
- 621 ibrutinib-treated patients. Ø FU 17 months.
- **42% of patients discontinued ibrutinib (Ø 7 months).**

Reason for ibrutinib discontinuation	Ibrutinib in front-line (n=19)	Ibrutinib in relapse (n=231)
Toxicity	63.1% (n=12)	50.2% (n=116)
CLL progression	15.8% (n=3)	20.9% (n=49)
Other/unrelated death	5.3% (n=1)	12.1% (n=28)
Physician's or patient's preference	10.5% (n=2)	6.7% (n=15)
RT DLBCL	5.3% (n=1)	4.6% (n=10)
Stem cell transplantation/CAR T-cell	0	3.3% (n=8)
Financial concerns	0	0.8% (n=2)
Secondary malignancy	0	0.8% (n=2)
RT Hodgkin lymphoma	0	0.4% (n=1)

CLL: chronic lymphocytic leukemia; RT DLBCL: Richter transformation to diffuse large B-cell lymphoma; CAR T-cell: chimeric antigen receptor T-cell; RT: Richter transformation.



Discontinuation of Ibrutinib real world data

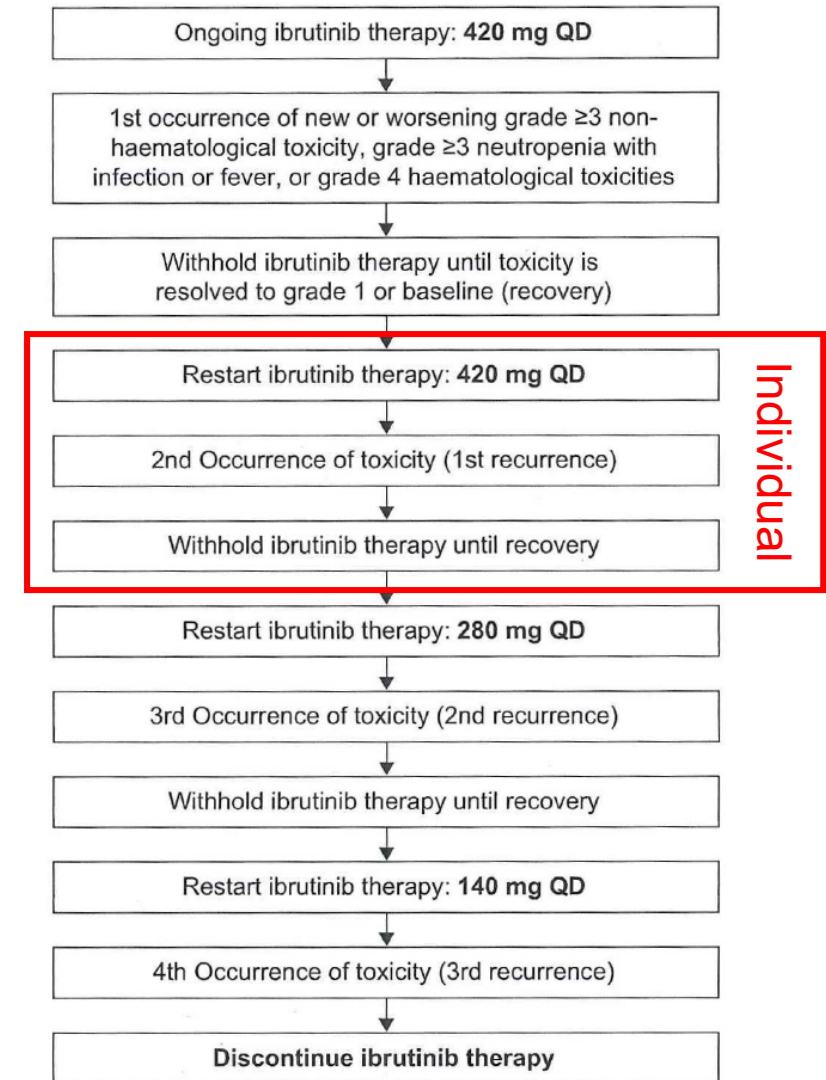
- **Reasons for stopping ibrutinib due to toxicity:**

- Front-line treatment:
 - arthralgia (42%),
 - atrial fibrillation (25%),
 - rash (17%).
- R/R patients:
 - atrial fibrillation (12%),
 - infection (11%),
 - pneumonitis (10%),
 - bleeding (9%),
 - diarrhea (7%).

How was
the management of toxicities?

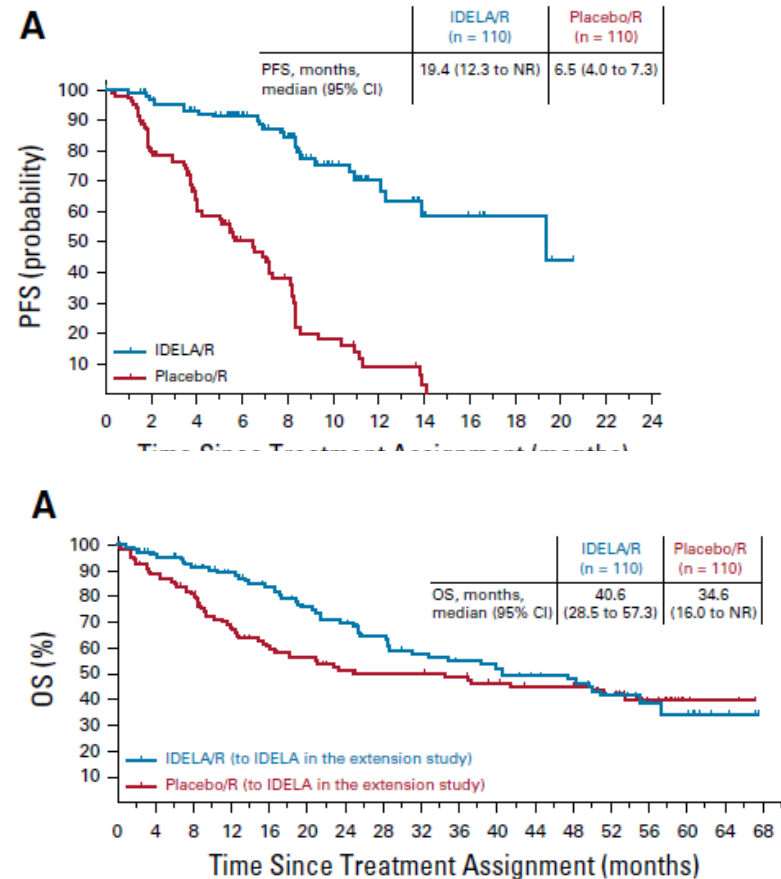
Management of toxicities of ibrutinib

- **Most patients will have some toxicities!**
- Check co-medications
(drug-interactions → CYP3A4)
- Identify patients with high-risk for specific toxicities
e.g. cardiac disease → risk for atrial fibrillation,
anticoagulation or antiaggregation,
immunodeficiency and risk for infections.
- Inform about potential toxicities
(e.g. early onset diarrhea, arthralgia, cytopenias).
- Symptomatic treatment of mild toxicities.
- Dose reductions are frequently required.
(without impact on outcome!)

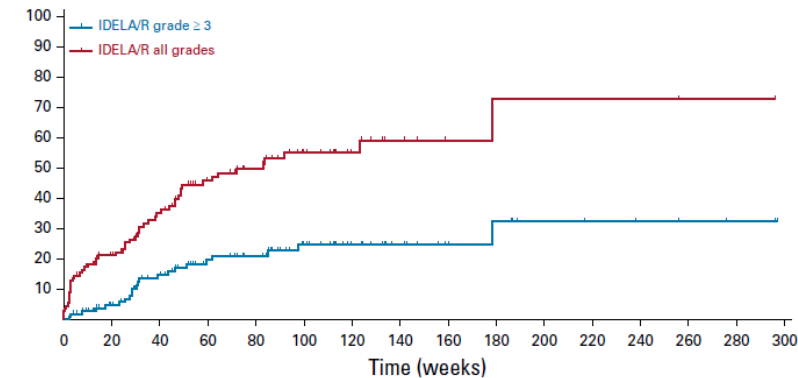


Intolerance of BCR-I: Idelalisib

- Phase-III Idela+R vs, placebo+R
- Longterm results



Cumulative Rate of Diarrhea/Colitis



Immunologic side effects mostly during first 2 years (diarrhea/colitis, hepatitis, pneumonitis)
Increased rate of infections during follow-up
After 1 year 58% of patients on idelalisib,
after 2 years 29% of patients on idelalisib.

Sharman JP et al. Final Results of a Randomized, Phase III Study of Rituximab With or Without Idelalisib Followed by Open-Label Idelalisib in Patients With Relapsed Chronic Lymphocytic Leukemia).

J Clin Oncol 2019; 37:1391-1402.

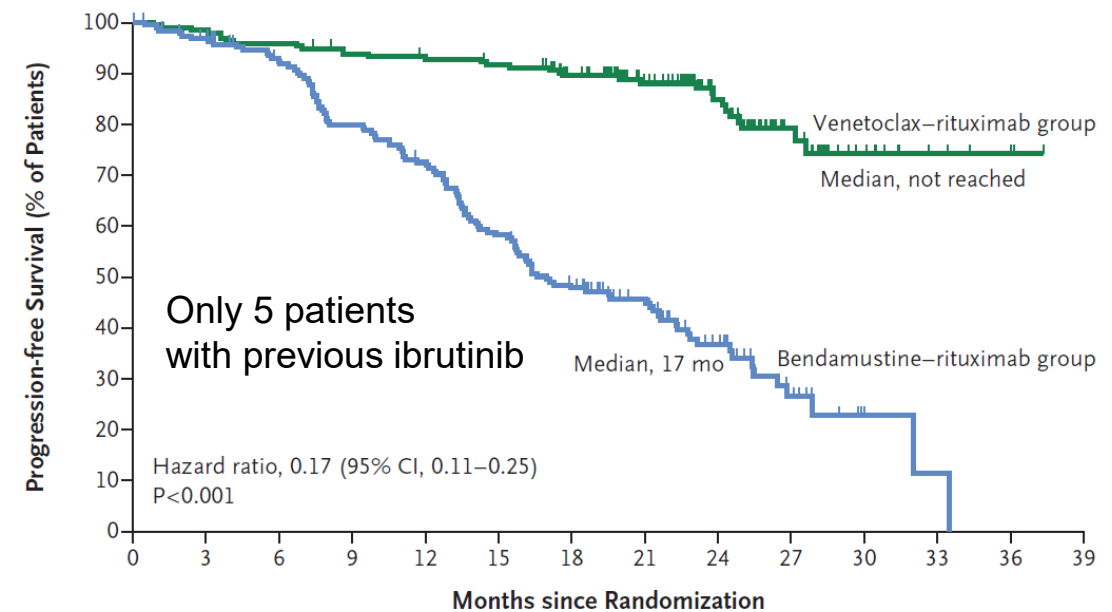
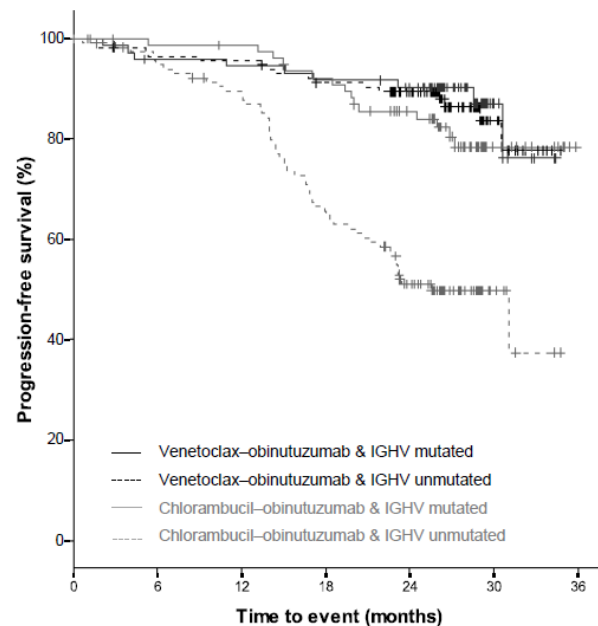
Coutré SE et al. Management of adverse events associated with idelalisib treatment: expert panel opinion. Leukemia & Lymphoma 56:10, 2779-2786

Watch and wait:

- Patients with response to BCR-I may not need any treatment after stopping!
- Consider: previous therapies,
 length of therapy with BCR-I,
 quality of response,
 type and severity of toxicity,
 patient's wish.
- Some patients will have a symptomatic relapse within weeks, therefore plan further treatment.
- Some patients will be without any treatment for several months ((1-2 years))

Chemoimmunotherapy?

- Can be considered in patients with favourable risk factors for response to CIT (no del17p, no TP53 mutation, mutated IgHV) after first-line ibrutinib or minimal previous exposition to CIT.



Treatment Options in Intolerance of BCR-I

BCR-I after intolerance of previous BCR-I:

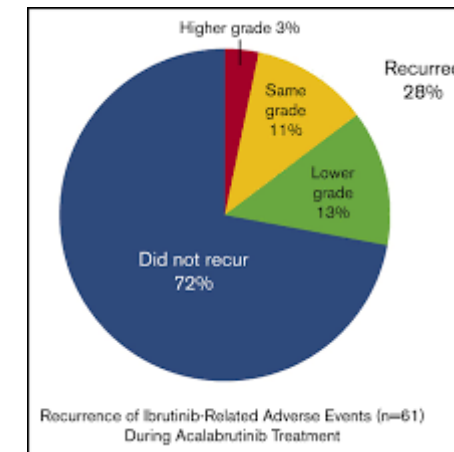
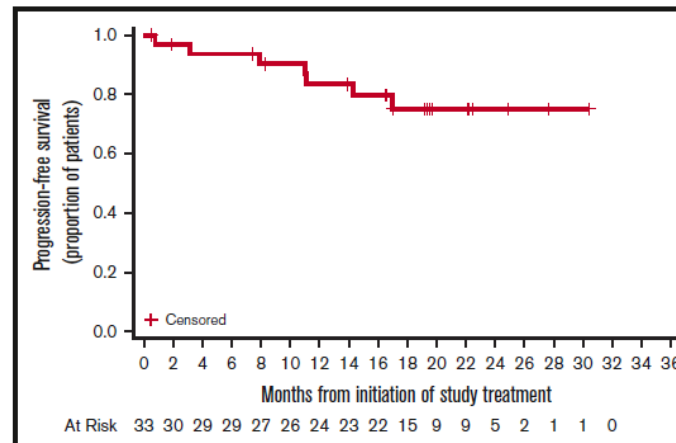
- Some patients with lower grade toxicity or reversible risk factors (e.g. stop of anticoagulation) may accept **same agent** for a second time, often at a lower dose.
- **Same class of BCR-I** (e.g. BTK-I: acalabrutinib, PI3K-I: Duvelisib, both not available in Europe)

Phase-II, 33 patients,
median 4 prior therapies

Table 3. Investigator-assessed responses in treated patients (N = 33)

Best response	n (%)
CR (bone marrow confirmed)	1 (3.0)
PR	19 (57.6)
PRL	5 (15.2)
Stable disease	6 (18.2)
ORR (\geq PR)	20 (60.6)
95% CI*	42.1-77.1
ORR (\geq PRL)	25 (75.8)
95% CI*	57.7-88.9

*95% exact binomial confidence interval (CI).



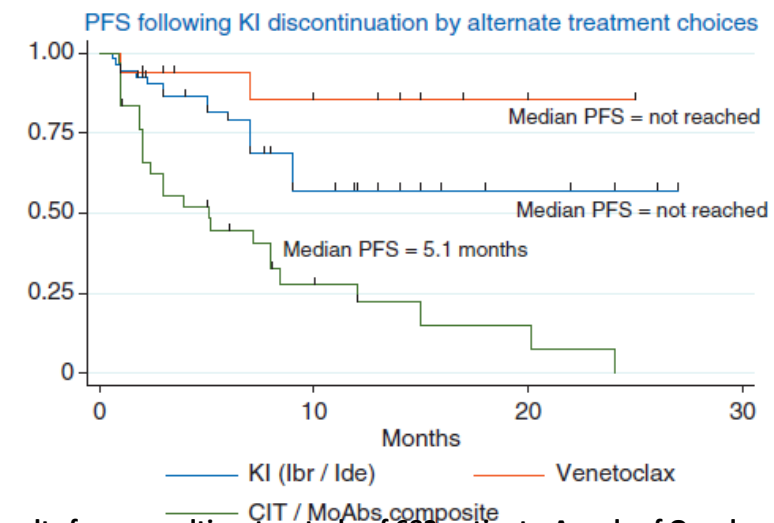
- **Change of BCR-I** (ibrutinib \leftrightarrow idelalisib) ?

Venetoclax vs. BCR-I:

- Retrospective “real world” data (683 patients, 258 stopped ibrutinib, 58 stopped idelalisib):

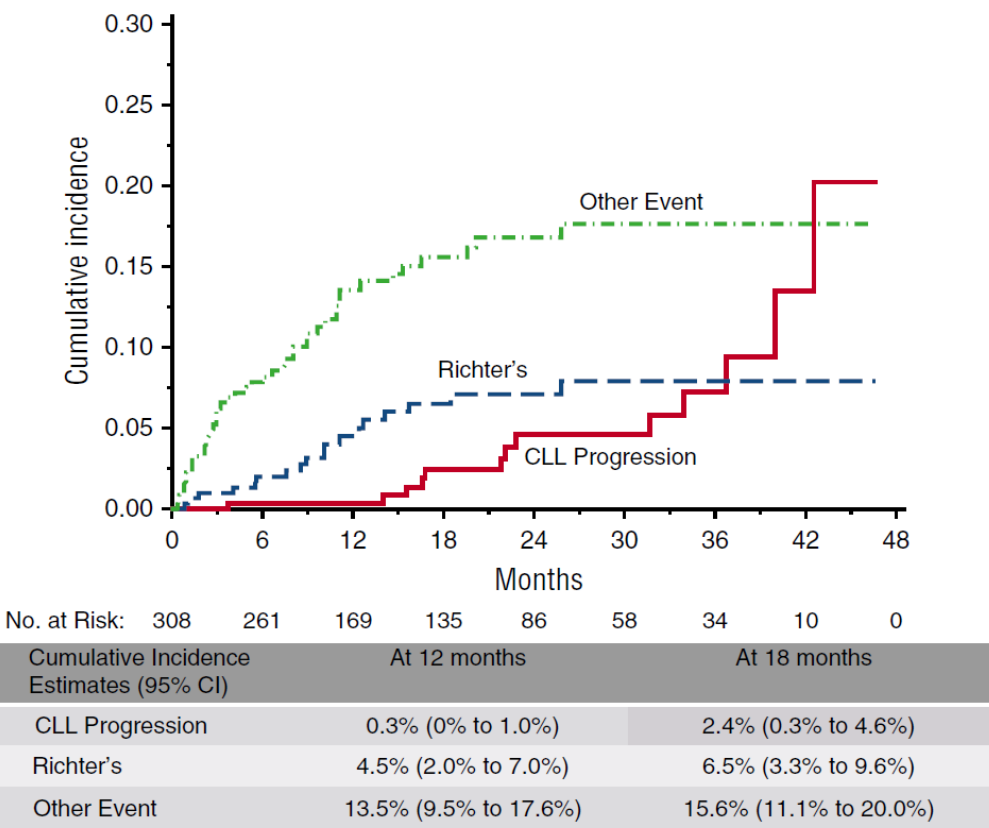
	Ibrutinib → idelalisib	Idelalisib → ibrutinib	Kinase inhibitor → venetoclax
ORR (%)	46	75	74
CR (%)	0	5	32
PR/PR with lymphocytosis (%)	46	70	42
Stable disease (%)	39	15	16
Progressive disease (%)	15	10	10

- Ibrutinib → idelalisib with lower response
- Idelalisib → ibrutinib with lower CR rate
- Both with shorter PFS
- CIT poor in r/r CLL failing BCR-I



Failure of BCR-I due to progressive disease

“Because most patients will not attain a complete response, and many will have circulating leukemia cells for long periods of time, determining which patients are indeed relapsing can be a challenge.”

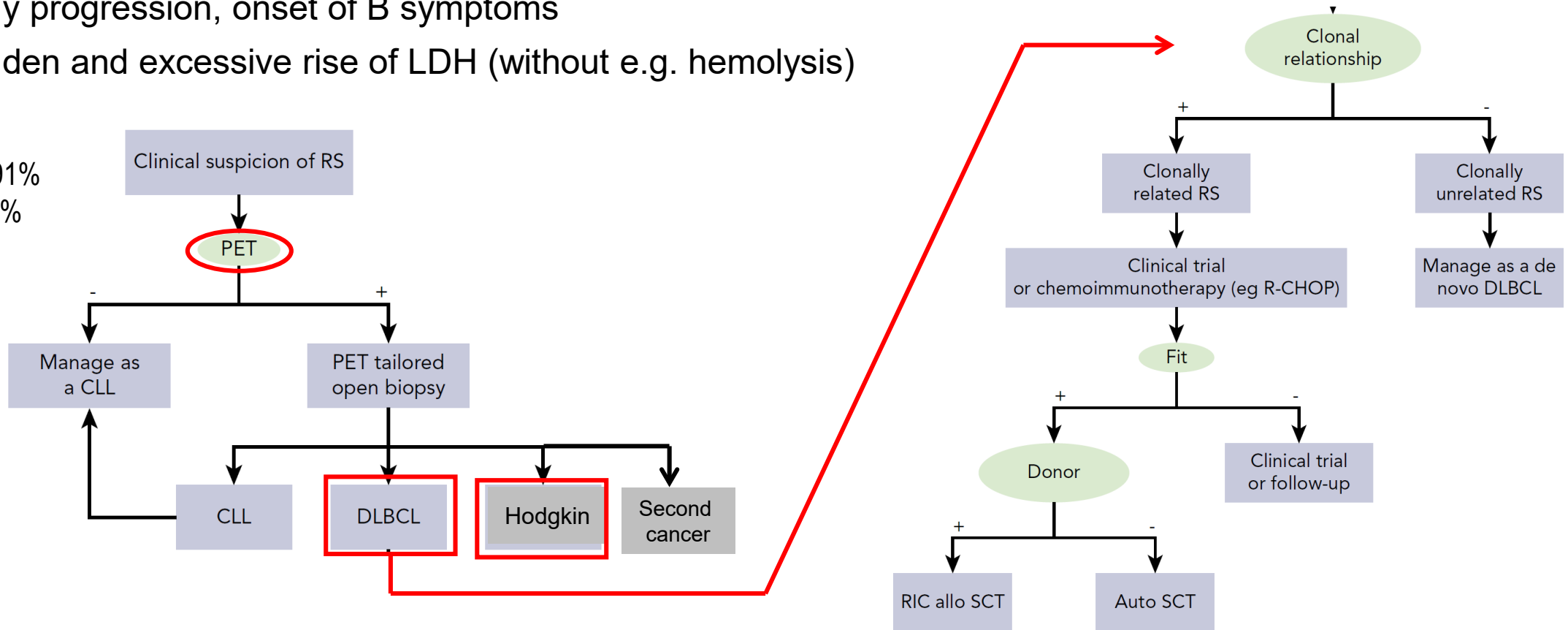


Evaluation of suspected transformation in CLL:

When to suspect transformation of CLL

- Asymmetric growth of lymph nodes or fast growth of bulky disease (e.g. abdominal)
- Early progression, onset of B symptoms
- Sudden and excessive rise of LDH (without e.g. hemolysis)

Sensitivity 91%
Specificity 80%
PPV 53%
NPV 97%



- **Hodgkin:** treat according to stage and fitness of the patient (“ABVD”)

■ Table 1. Published studies reporting outcomes in Richter’s syndrome diffuse large B-cell lymphoma specific cohorts.

Study agents	Year reported	Phase	Studied patients	Total no. enrolled (no. RS)	ORR (RS specific)	CR (RS specific)	PFS in months (median)	OS in months (median)
HyperCVXD 59	2001	II	RS	29 (29)	41%	38%	NR	10
FACPGM 60	2002	II	RS, PLL, NHL	22 (15)	5%	5%	NR	2.2
OFAR1 61	2008	I–II	FR-CLL, RS	50 (20)	50%	20%	NR	6 month OS: 59%
OFAR2 51	2013	I–II	R/R-CLL, RS	102 (35)	39%	6.50%	NR	6.6
RCHOP 62	2014	II	R/R CLL, RS	60 (15)	67%	7%	10	21
OCHOP 18	2016	II	RS	37 (37)	46%	27%	6.2	11.4
REPOCH 63	2018	Retrospective	RS	46 (46)	39%	NR	3.5	5.9

Recommendation:
Followed by allo SCT.

Due to poor response and fitness rarely done.

Option autologous SCT.

- **Use of new strategies warranted:**
- Novel agents, combination of novel agents
- Combination of chemoimmunotherapy and novel agents
- CAR-T cells
- Inclusion in clinical trials whenever possible.

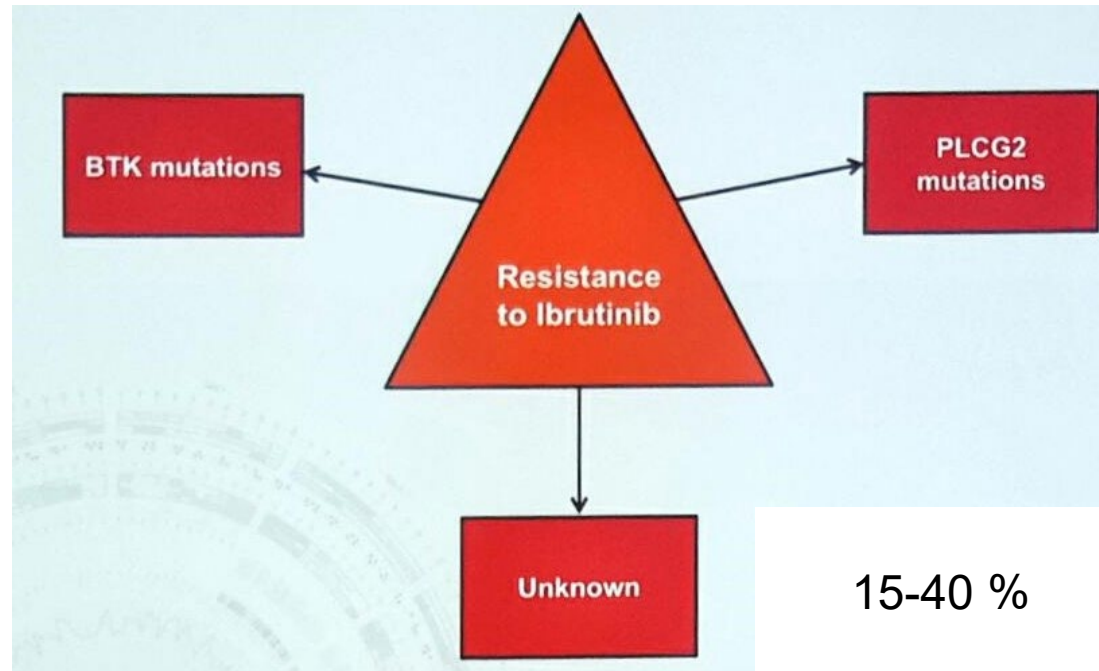
CLL: Progress und Transformation

Ursula Vehling-Kaiser, Landshut, D
Michael Hallek, Köln, D

V635	Resistenzentwicklung unter BTKi und BCL2i Stephan Stilgenbauer, Homburg, D	15:45
V636	Diagnostisches und therapeutisches Vorgehen bei (Verdacht auf) Richter-Transformation Alexander Egle, Salzburg, A	16:15
V637	CAR-T-Zelltherapie für Patienten mit CLL Peter Dreger, Heidelberg, D	16:45

Molecular mechanisms of resistance to ibrutinib

50% - 80%



5 -10%

15-40 %

- BTK C481S mutation cannot be inhibited by BTK inhibitors with covalent binding (ibrutinib, acalabrutinib) novel non covalent inhibitors (other binding site) may be active.
- Downstream mutations of PLC γ 2 induce resistance to other BCR-I.
- Laboratory testing for mutations is not standardized.

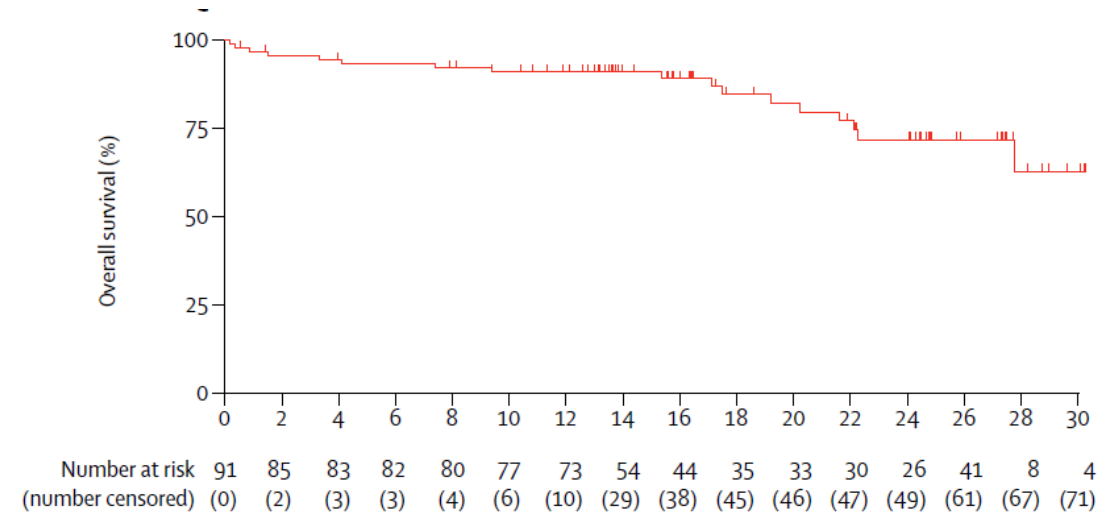
Treatment of CLL resistant to BCR-I (Ibrutinib)

- Venetoclax monotherapy after Ibrutinib failure (PD not intolerance)
- Phase-II, multicenter, US, 2014 – 2016, 91 patients median 4 previous therapies.

	Main cohort (n=43)	Expansion cohort (n=48)	All patients (n=91)
Overall response	30 (70%, 54–83)	29 (60%, 43–72)	59 (65%, 53–74)
Complete response or complete response with incomplete bone marrow recovery	4 (9%)	4 (8%)	8 (9%)
Nodular partial response	2 (5%)	1 (2%)	3 (3%)
Partial response	24 (56%)	24 (48%)	48 (52%)
Stable disease	8 (19%)	14 (29%)	22 (24%)
Disease progression	1* (2%)	4* (8%)	5 (5%)
Discontinued before response assessment	4 (9%)	2 (4%)	6 (7%)

Data are n (%) or n (%; 95% CI). *Patients who discontinued because of progression.

Table 2: Response with venetoclax monotherapy as assessed by the investigator



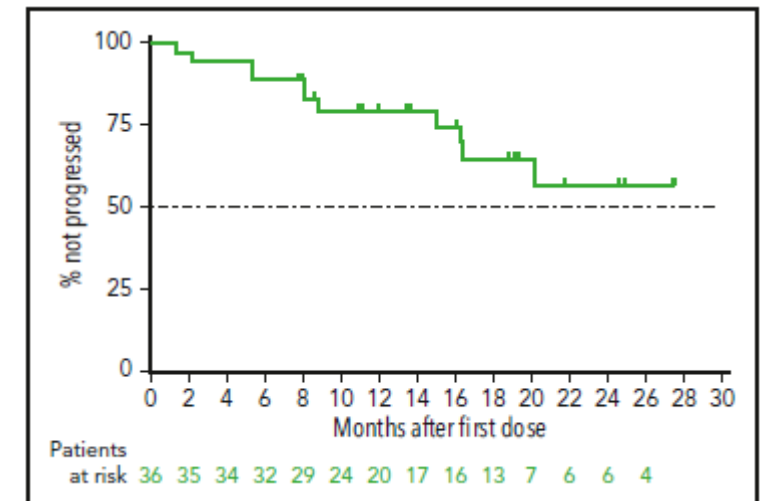
- Today less pretreated patients.
- Results probably better with addition of monoclonal ab.
- Not satisfactory for younger patients.

Treatment of CLL resistant to BCR-I (Idelalisib)

- Venetoclax monotherapy after Idelalisib + R / Idelalisib failure (PD not intolerance)
- Phase-II, multicenter, US, 2014 – 2016, 36 patients, median 3 previous therapies (10 ibrutinib).

Table 2. Best objective response with venetoclax monotherapy, as assessed by the investigator

	Patients who received idelalisib as the last prior BCRi		
	Main cohort (n = 21)	Expansion cohort (n = 15)	All patients (N = 36)
Time on venetoclax, median (range), months	20 (1-29)	10 (2-16)	14 (1-29)
ORR	14 (67)	10 (67)	24 (67)
CR/Cri	2 (10)/1 (5)	0/0	2 (6)/1 (3)
nPR	0	0	0
PR	11 (52)	10 (67)	21 (58)
SD	6 (29)	4 (27)	10 (28)
PD	1 (5)	1 (7)	2* (6)



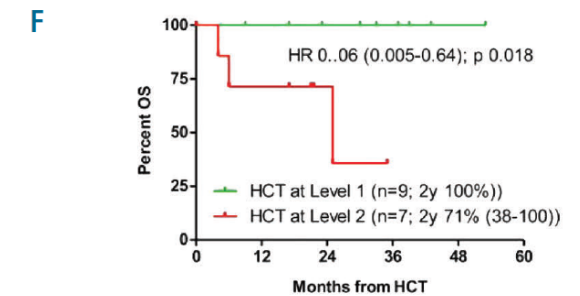
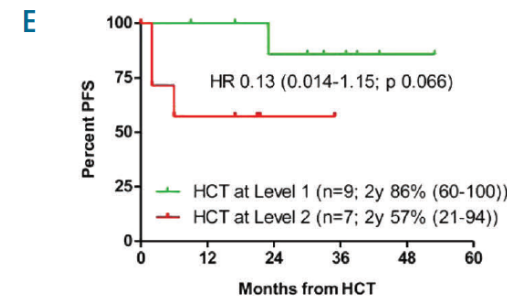
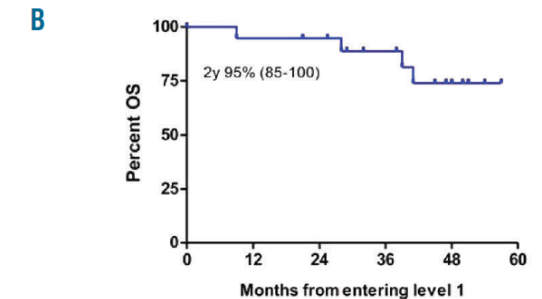
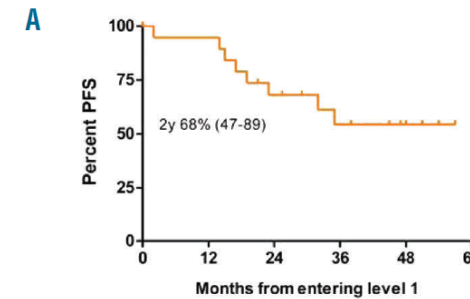
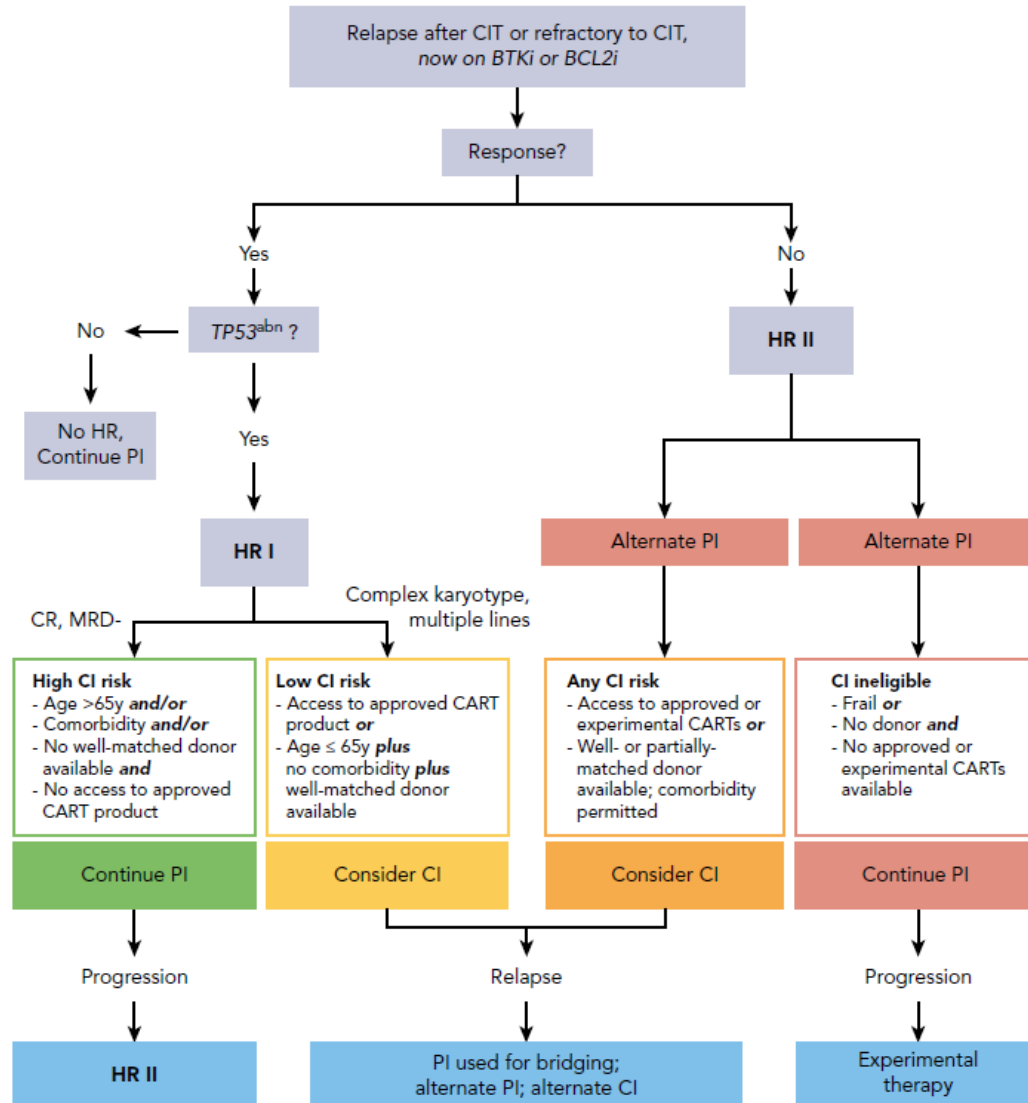
OS @ 1 y 94%.

- Today less pretreated patients.
- Results probably better with addition of monoclonal ab.
- Not satisfactory for younger patients.

Allogeneic Stem Cell Transplantation in CLL

Decision tree for therapy of chemoimmunotherapy-resistant untransformed CLL according to the revised high-risk concept.

Allo SCT in Heidelberg



Allogeneic SCT is still a valid option for fit CLL patients with very-high-risk disease or refractory to BCR-I, who are unlikely to have longterm benefit from a bcl2-inhibitor.

Dreger P et al. High-risk chronic lymphocytic leukemia in the era of pathway inhibitors: integrating molecular and cellular therapies . *Blood* 2018; 132.:892-902

Hoffmann A et al. Allogeneic transplantation in high-risk chronic lymphocytic leukemia: a single-center, intent-to-treat analysis . *Haematologica* 2019; 104: e305.

My treatment algorithm for CLL after failure of BCR-I

