Come riconoscere (e quali sono) i criteri per selezionare la strategia terapeutica ottimale per il paziente?

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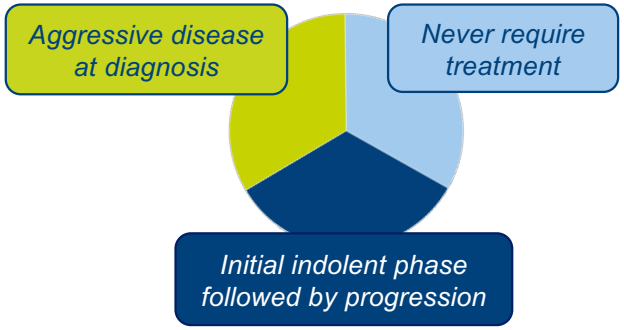
L'OTTIMIZZAZIONE DELLA
TERAPIA LEUCEMIA LINFATICA CRONICA:
UNA CONDIZIONE DINAMICA ED INNOVATIVA

12-13 APRILE 2022 BOLOGNA ROYAL HOTEL CARLTON

A.D. 1308 unipg
DIPARTIMENTO DI MEDICINA E CHIRURGIA

Treatment is not always required for CLL



Low risk
Binet group A
Rai stage 0

Intermediate risk
Binet group B
Rai stage I/II

High risk
Binet group C
Rai stage III/IV

+

Active, symptomatic disease

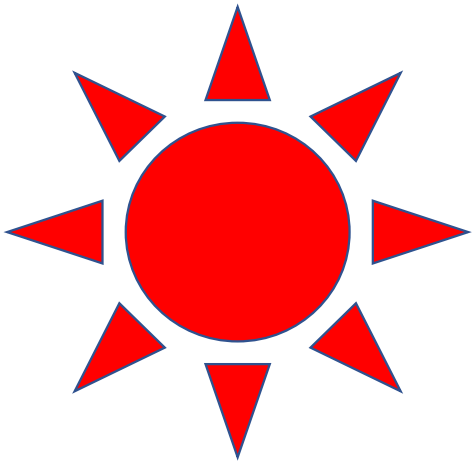
Defined as one or more of:[1,2]

- Significant B-symptoms[a]
- Symptoms or complications from lymphadenopathy, splenomegaly or hepatomegaly
- LDT <6 months[b]
- Autoimmune anaemia and/or thrombocytopenia poorly responsive to conventional therapy

→

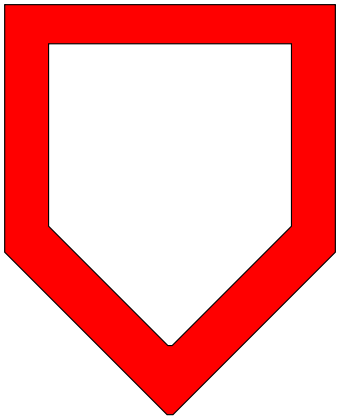
Initiate treatment

The armamentarium of treatments for CLL has expanded tremendously



CHEMOTHERAPIES

Non-specific inhibition of cell division

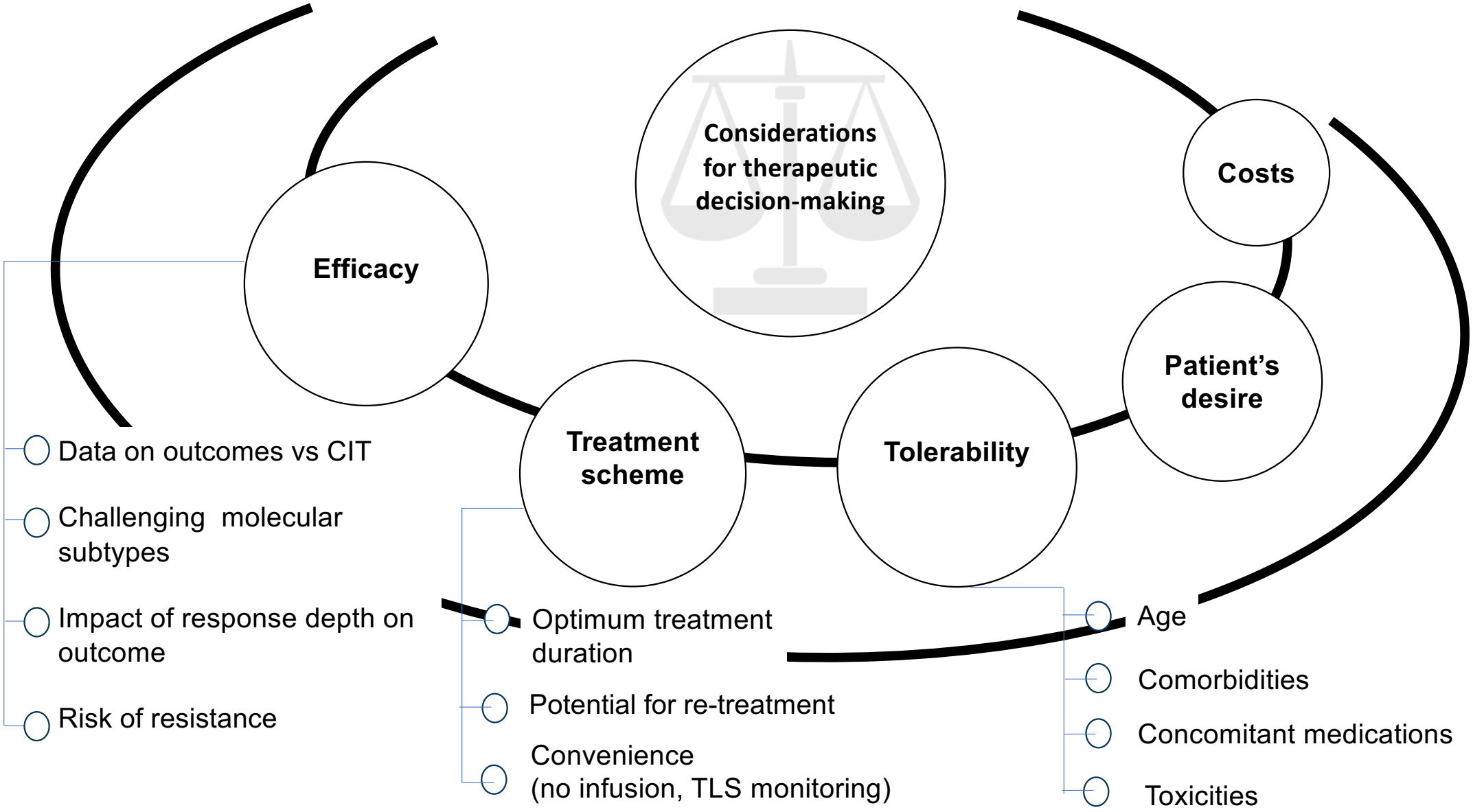


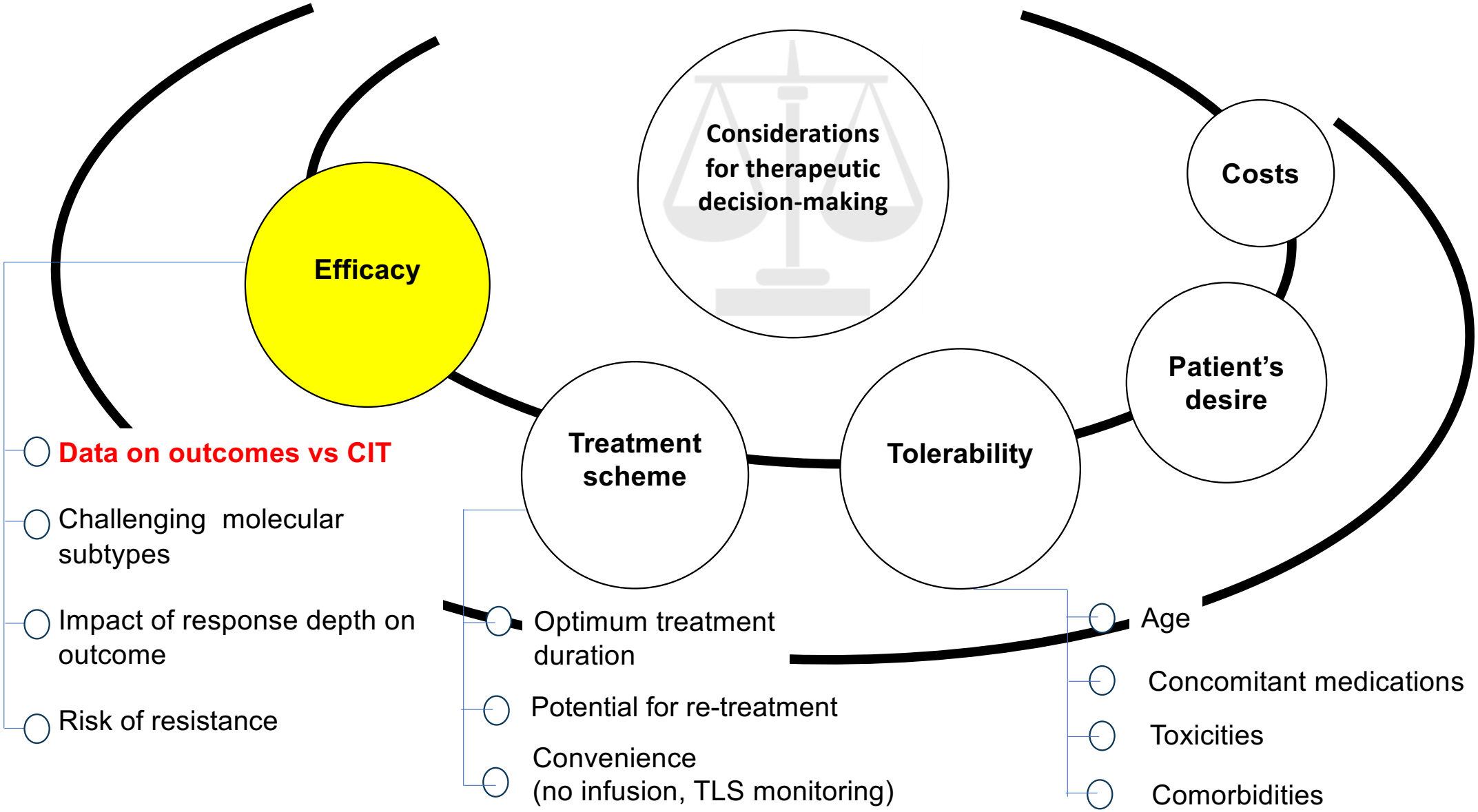
IMMUNOTHERAPIES

Help the immune system fight cancer by flagging cancer cells for destruction

TARGETED THERAPIES

Block distinct molecular pathways inside cancer cells


Considerations for therapeutic decision-making
Efficacy
Treatment scheme
Tolerability
Patient's desire
Costs
Data on outcomes vs CIT
Challenging molecular subtypes
Impact of response depth on outcome
Risk of resistance
Optimum treatment duration
Potential for re-treatment
Convenience (no infusion, TLS monitoring)
Age
Comorbidities
Concomitant medications
Toxicities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Convenience (no infusion, TLS monitoring)
Age
Concomitant medications
Toxicities
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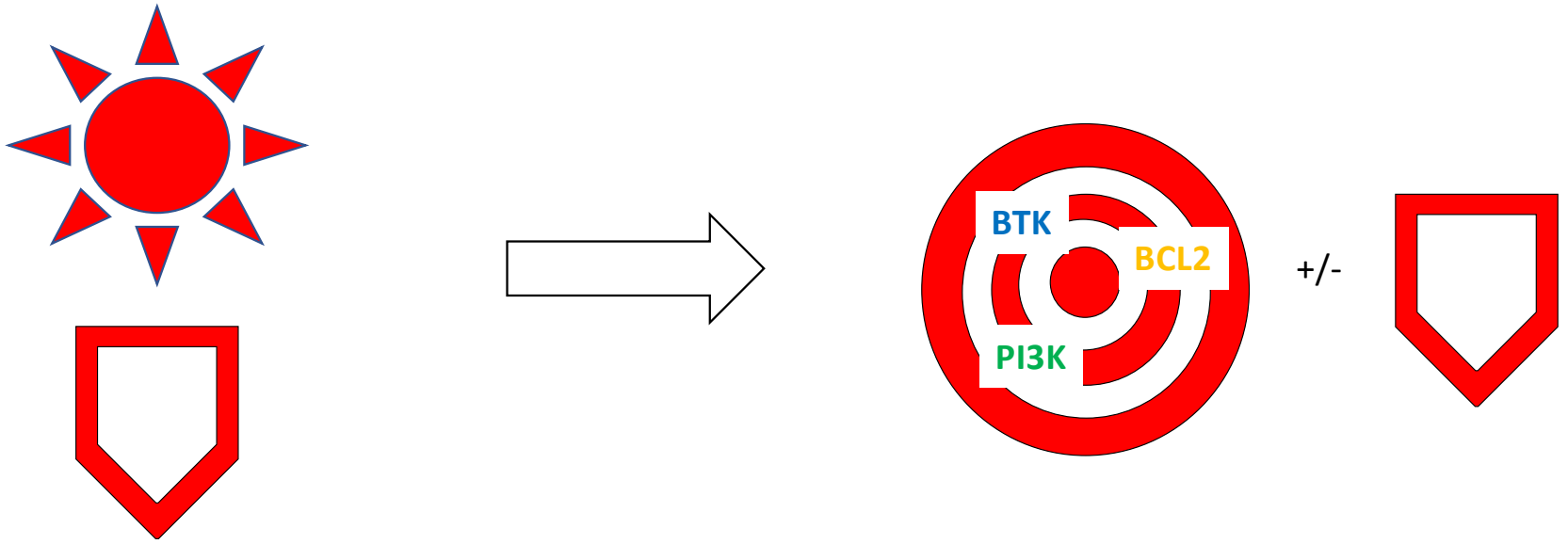
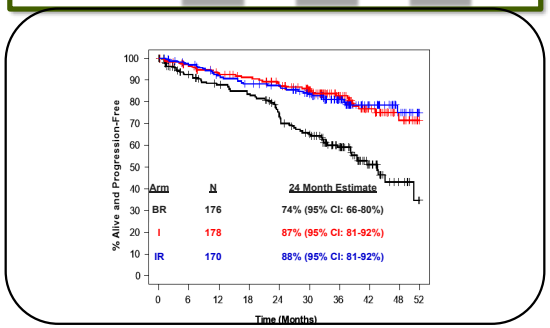
Novel agents have eclipsed chemoimmunotherapy as treatment for CLL in the vast majority of patients



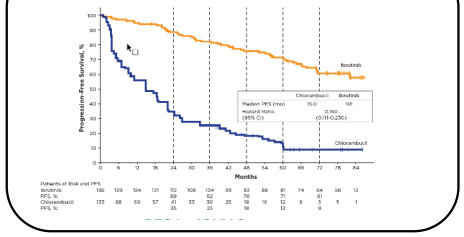
CHEMOIMMUNOTHERAPIES **TARGETED THERAPIES**

Targeted therapy outperform CIT in key phase 3 trials in first line CLL

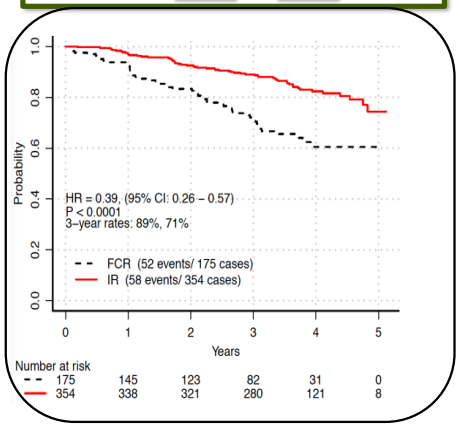
Alliance 202[1] Ibr vs IR vs BR



RESONATE-2[4] Ibr vs Clb



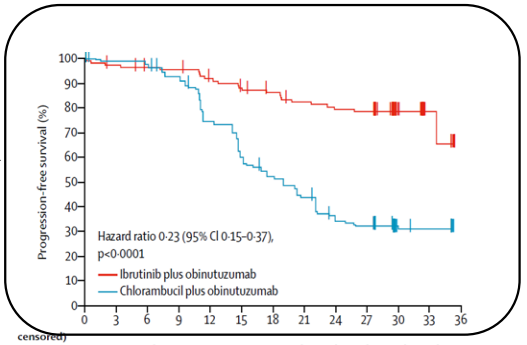
ECOG 1912[2,3] IR vs FCR

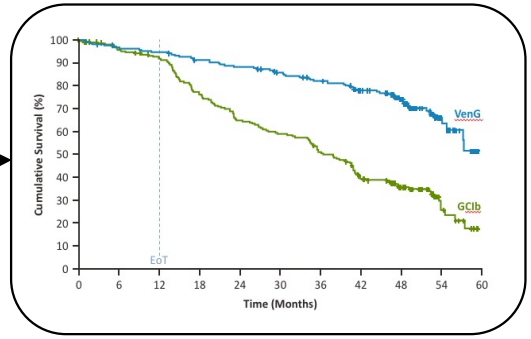


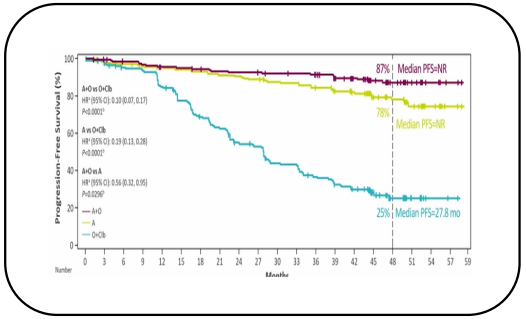
iLLUMINATE[5] IO vs OClb

CLL14[6] VenO vs OClb

ELEVATE TN[7] A vs AO vs OClb





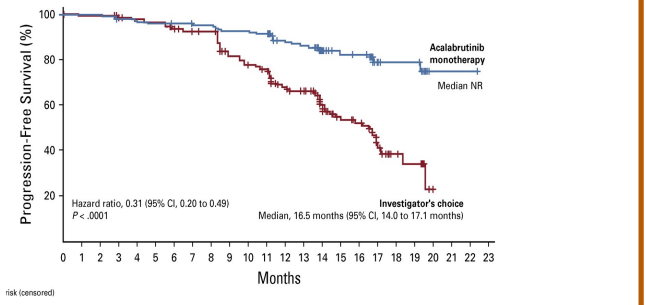


Fit → Unfit

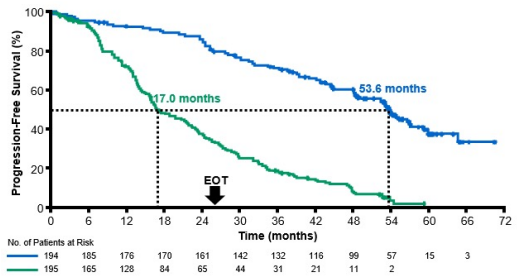
A, acalabrutinib; AO, acalabrutinib + obinutuzumab;
BR, bendamustine + rituximab; Clb, chlorambucil;
IO, ibrutinib + obinutuzumab; IR, ibrutinib + rituximab.

1. Woyach JA, *et al. N Engl J Med* 2018; **379:**2517–2528 (incl. suppl.); 2. Shanafelt TD, *et al. N Engl J Med* 2019; **381:**432–443 (incl. suppl);
3. Shanafelt TD, *et al.* ASH 2019; Abstract 33 (Oral); 4. Burger JA, *et al. N Engl J Med* 2015; **373:**2425–2437; 5. Moreno C, *et al. Lancet Oncol* 2019; **20:**43–56;
6. Fischer K, *et al. N Engl J Med* 2019; **380:**2225–2236 (incl. suppl); 7. Sharman JP, *et al. Lancet* 2020; **396:**1278–1291.

Patients with relapsed/refractory CLL have multiple treatment options with targeted agents

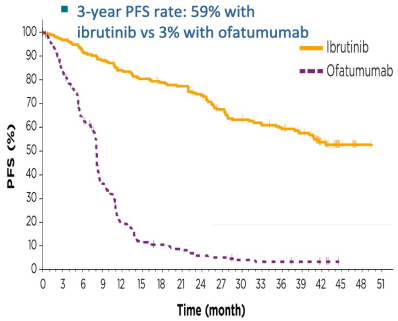


ASCEND[3,4] **Acala** vs **IdR/BR**



MURANO[5] **VenR** vs **BR**

- BTK inhibitors have proven track record of providing durable remission and are generally well tolerated
- In the case of ibrutinib intolerance, prospective data support tolerability of acalabrutinib
- Time-limited therapy with venetoclax in combination with rituximab outperforms chemotherapy with both PFS and OS benefit
- Though effective, currently available PI3K inhibitors are limited by toxicity profile



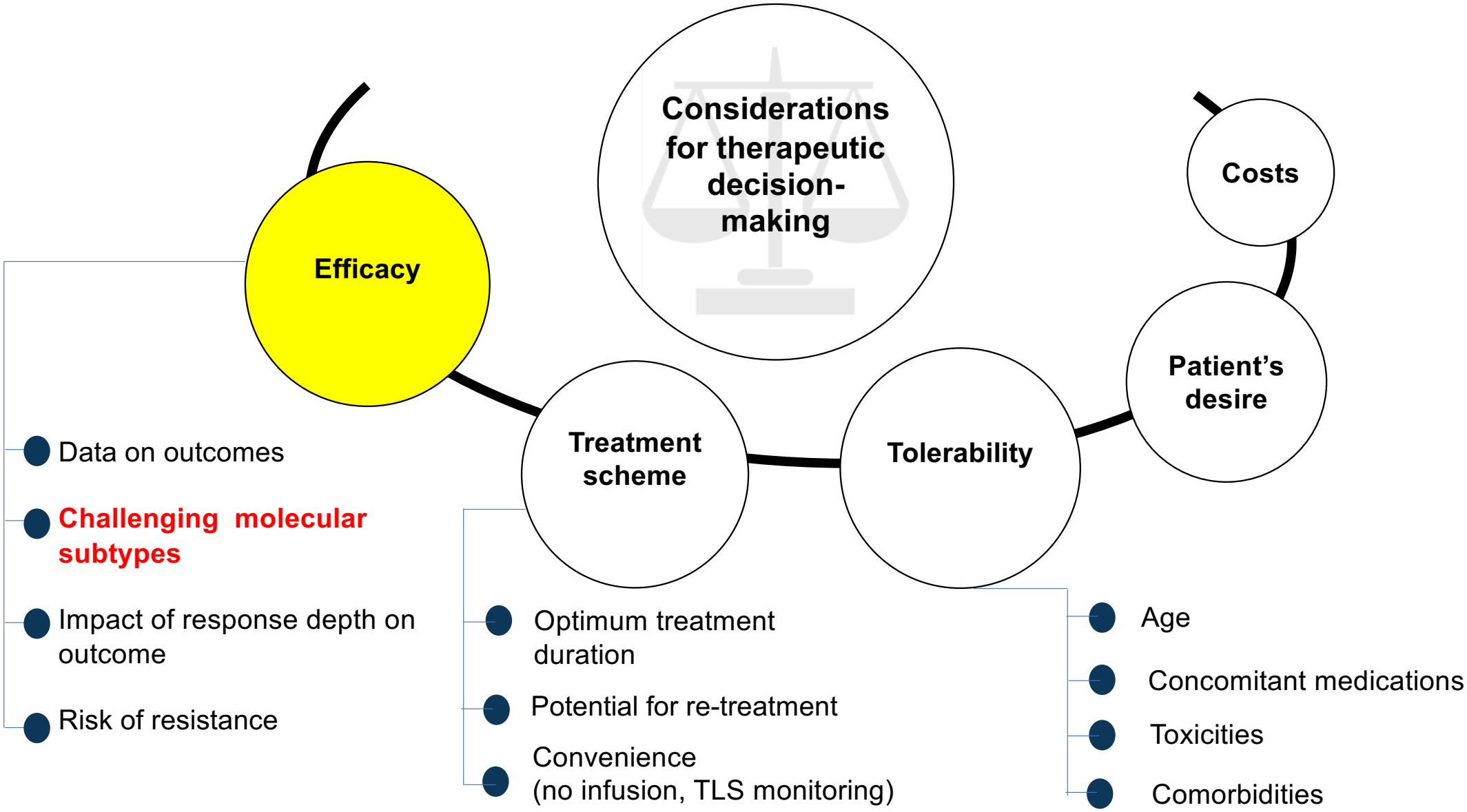
RESONATE[1,2] **I** vs **Ofa**

1 — 2 — 3

Median prior lines of therapy (experimental arm)

IdR, idelalisib + rituximab; Ofa, ofatumumab; VenR, venetoclax + rituximab.

1. Byrd JC, *et al. N Engl J Med* 2014; **371:**213–223; 2. Munir T, *et al. Am J Hematol* 2019; **94:**1353–1363 (incl. suppl.); 3. Ghia P, *et al. J Clin Oncol* 2020; **38:**2849–2861; 4. Ghia P, *et al.* ASH 2020; Abstract 3140 (Poster); 5. Seymour JF, *et al. N Engl J Med* 2018; **378:**1107–1120 (incl. suppl.).


Considerations for therapeutic decision-making
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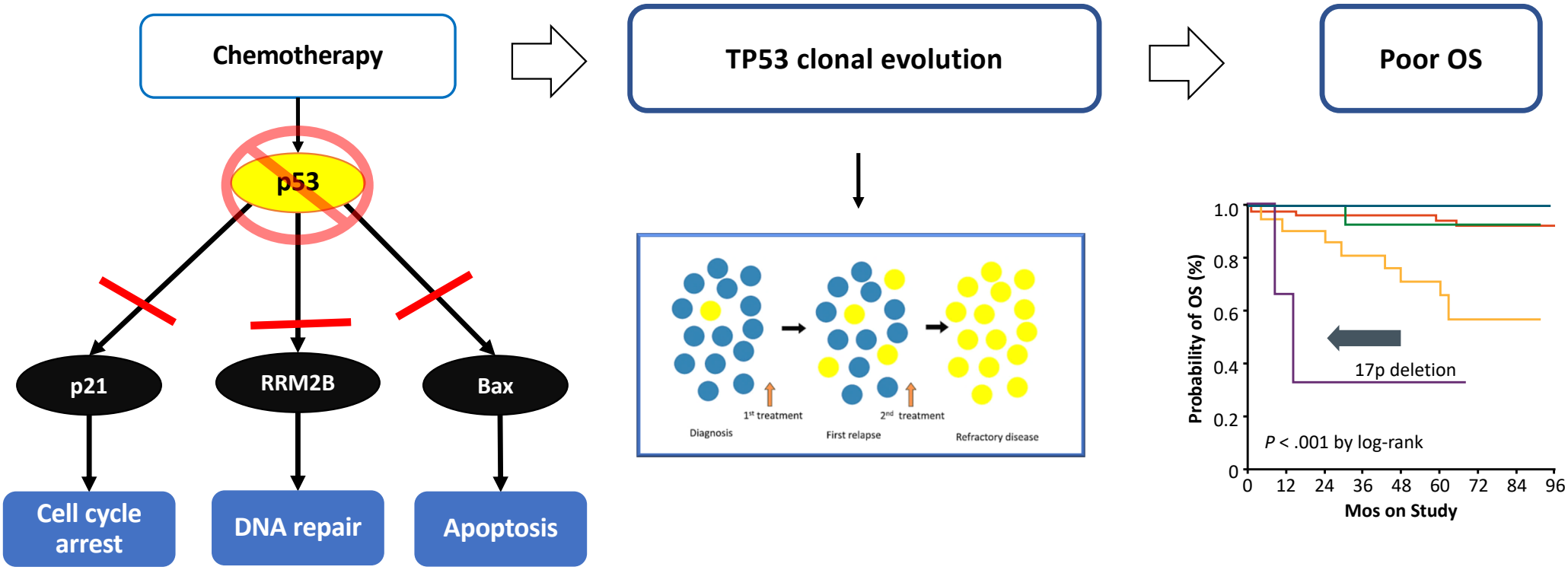
Risk of resistance
Optimum treatment duration
Potential for re-treatment
Convenience (no infusion, TLS monitoring)
Age
Concomitant medications
Toxicities
Comorbidities

TP53 aberrations lead to resistance, clonal selection and poor outcomes with chemoimmunotherapy

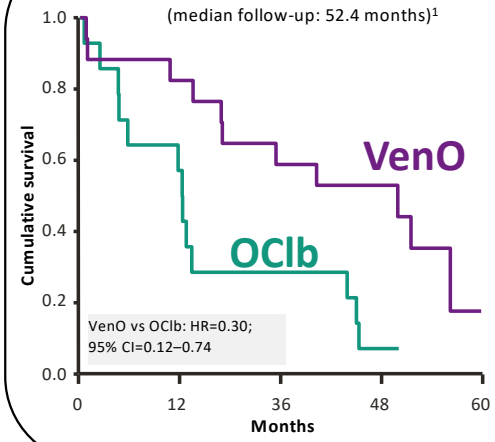


Trbusek M & Malcikova J. *Adv Exp Med Biol* 2013; 792:109–131.
Hanahan D & Weinberg RA. *Cell* 2000; 100:57–70.
Dearden C. CLonal selection: survival of the fittest? Blood. 2014
Landau D et al. Nature 2015; 526(7574):525-30

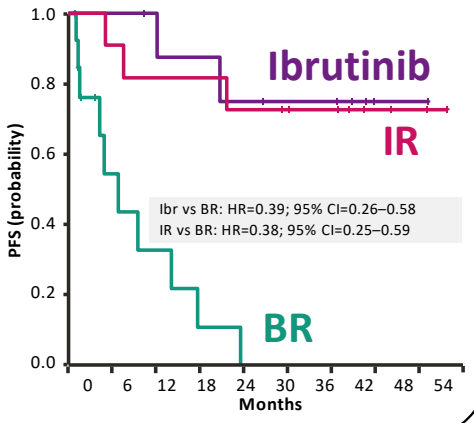
Targeted agents improve outcomes vs CIT in CLL with del(17p)/*TP53*^{mut}

1L

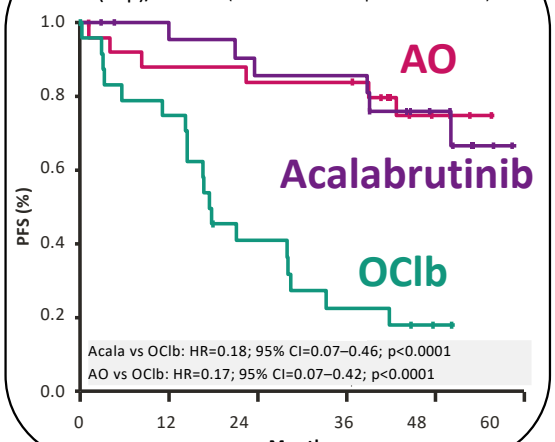
CLL14 : PFS in patients with del(17p)
(median follow-up: 52.4 months)[1]



Alliance : PFS in patients with del(17p) (median follow-up: 38 months)[3]



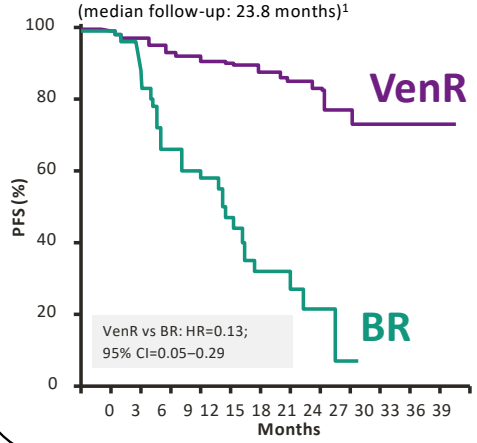
ELEVATE TN : PFS in patients with del(17p)/*TP53*^{mut} (median follow-up: 46.9 months)[4]



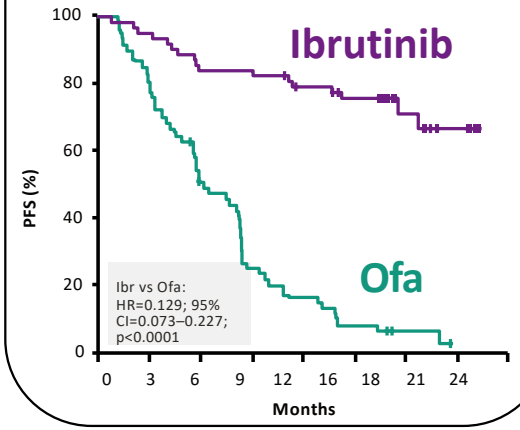
1. Tausch E, *et al.* EHA 2021; Abstract S144 (Oral);
2. Tausch E, *et al.* EHA 2021. Abstract S146;
3. Woyach JA, *et al. N Engl J Med* 2018; **379:**2517–2528);
4. Sharman JP, *et al.* EHA 2021; Abstract S148 (Oral);
5. Moreno C, *et al. Lancet Oncol* 2019; **20:**43–56;

R/R

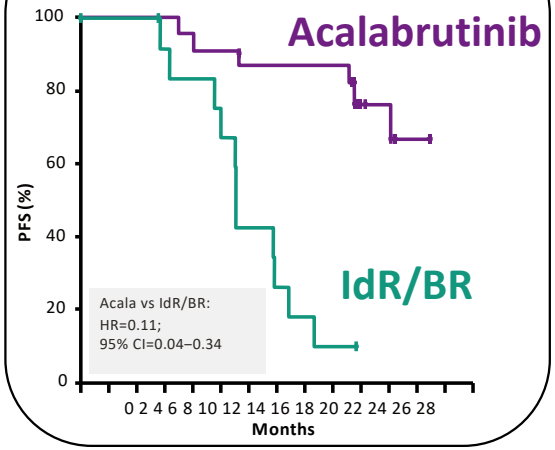
MURANO: PFS in patients with del(17p)
(median follow-up: 23.8 months)[1]



RESONATE: PFS in patients with del(17p)
(median follow-up: 19 months)[3]



ASCEND: PFS in patients with del(17p)/*TP53*^{mut}
(median follow-up: 22.0 months)[4]

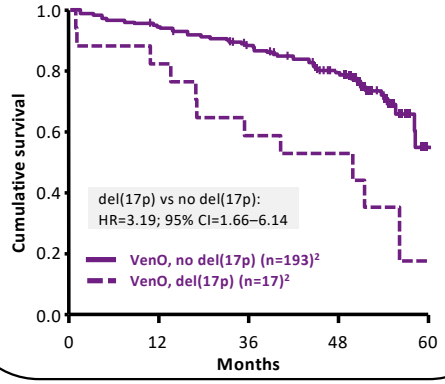


1. Seymour JF, *et al. N Engl J Med* 2018;;
2. Venclyxto® (venetoclax) SmPC; June 2021 update (accessed July 2021);
3. Brown JR, *et al. Leukemia* 2018; **32**:83–91 (incl. suppl.)
; 4. Ghia P, *et al.* ASH 2020; Abstract 3140 (Poster).

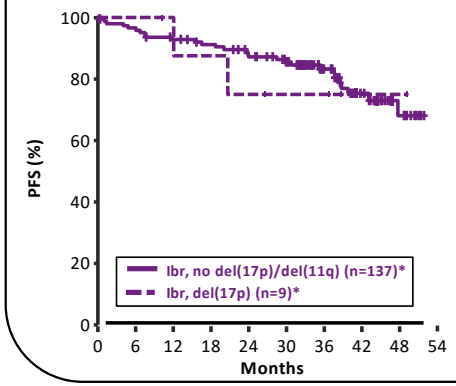
TP53 aberrations continue to be an adverse prognostic factor, but these patients do much better in the modern era of targeted therapies

1L

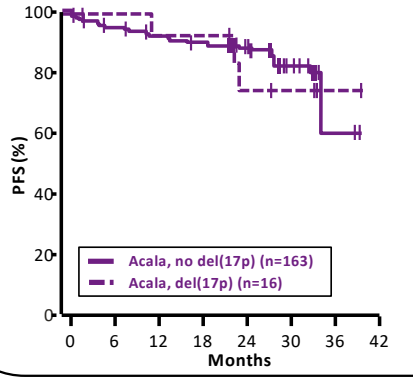
CLL14: PFS with VenO by del(17p) status
(median follow-up: 52.4 months)[1]



Alliance 202: PFS with Ibr by del(17p) status
(median follow-up: 38 months)[3]

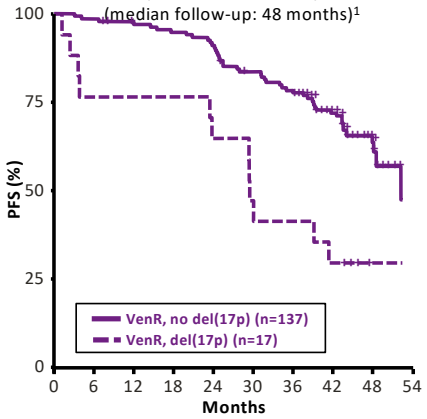


ELEVATE TN: PFS with Acala by del(17p) status
(median follow-up: 28.3 months)[4]

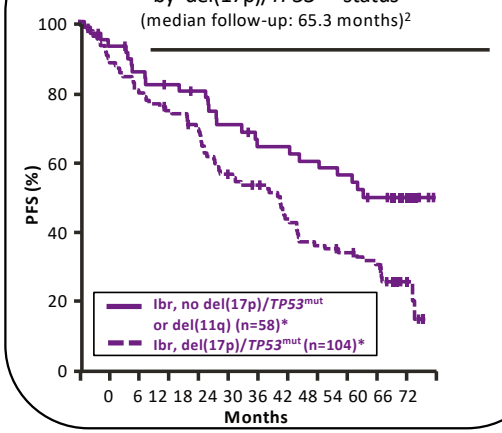


R/R

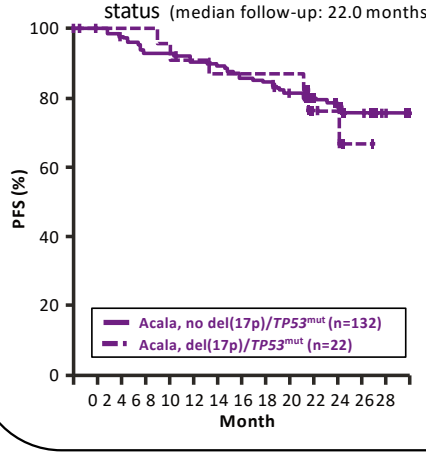
MURANO: PFS with VenR by del(17p) (aCGH assessment)
(median follow-up: 48 months)[1]



RESONATE: PFS with Ibr by del(17p)/*TP53*^{mut} status
(median follow-up: 65.3 months)[2]



ASCEND: PFS with Acala by del(17p)/*TP53*^{mut} status (median follow-up: 22.0 months)[3]

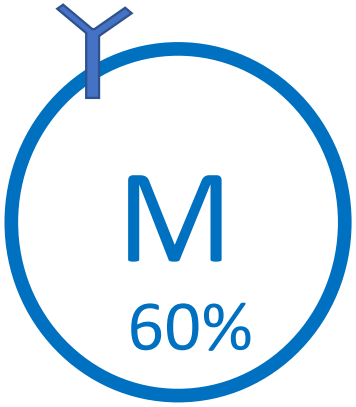


1. Kater AP, *et al. J Clin Oncol* 2020; **34:**4042–4054 (incl. suppl.);
2. Munir T, *et al. Am J Hematol* 2019; **94:**1353–1363 (incl. suppl.); 3. Ghia P, *et al.* ASH 2020; Abstract 3140 (Poster).

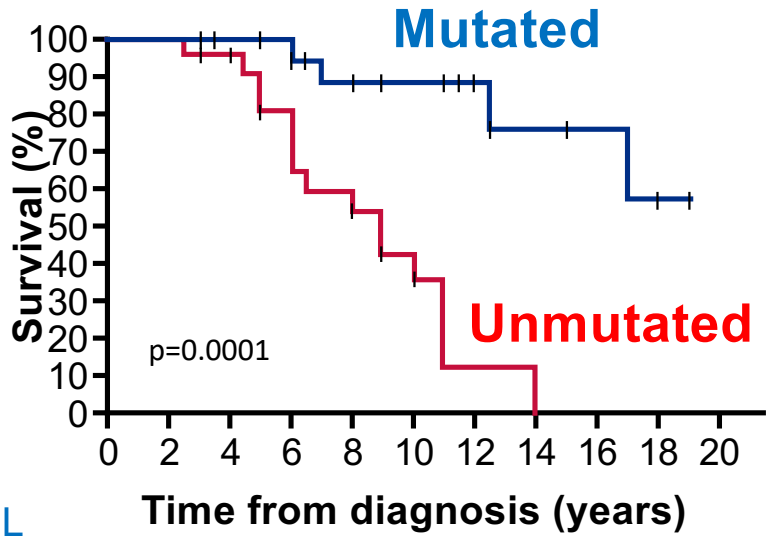
* mPFS NR for no del(17p)/*TP53*^{mut} or del(11q), mPFS 40.6 months for del(17p)/*TP53*^{mut}.
aCGH, array comparative genomic hybridization.

Impact of IGHV mutation status: biological and clinical differences

- Active, treatment-resistant disease[2,3]
- Faster clonal expansion, and shorter survival with chemo-based therapy[2,3]
- Higher genetic instability and higher risk of unfavorable genetic mutations[1,2]



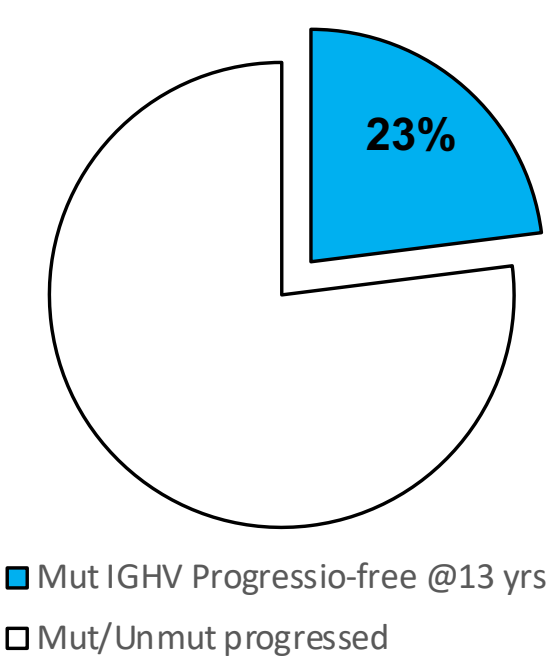
- Indolent disease[2–4]
- Stable/slow expansion of CLL clones[2–4]
- Lower degree of clonal evolution



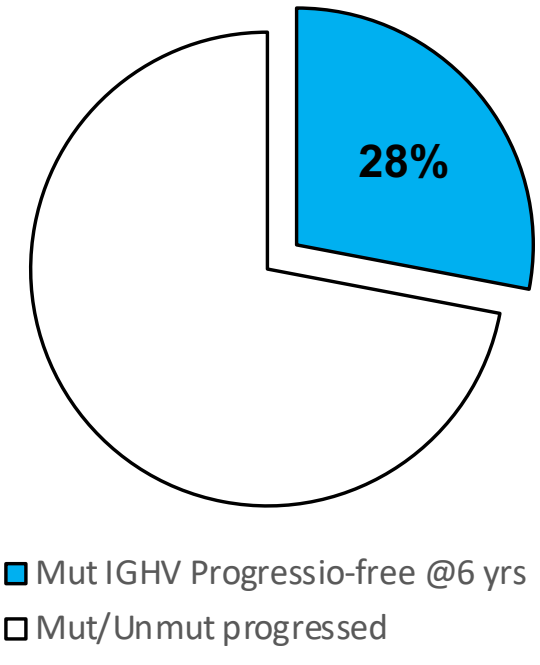
Damle RN, *et al. Blood* 1999.
Stilgenbauer S, *et al. Blood* 2014.
Fabbri and Dalla-Favera, Nature Reviews Cancer, 2016

First-line FCR induces long-term remissions in IGHV mutated patients

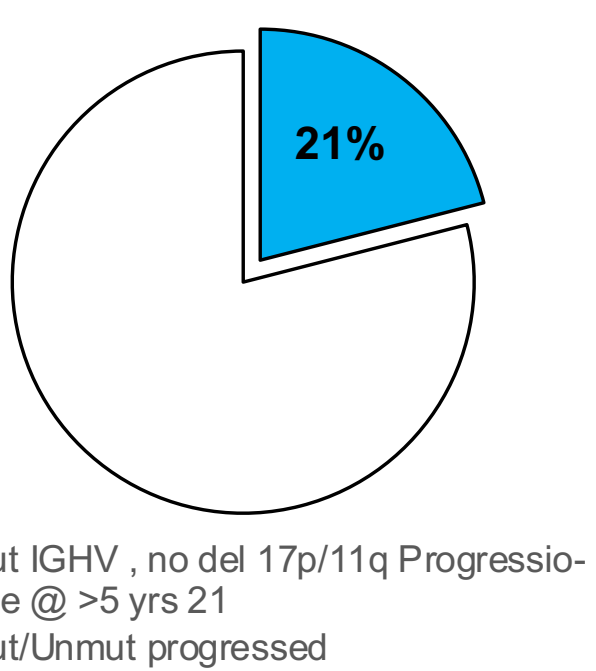
Thompson et al., Blood 2016



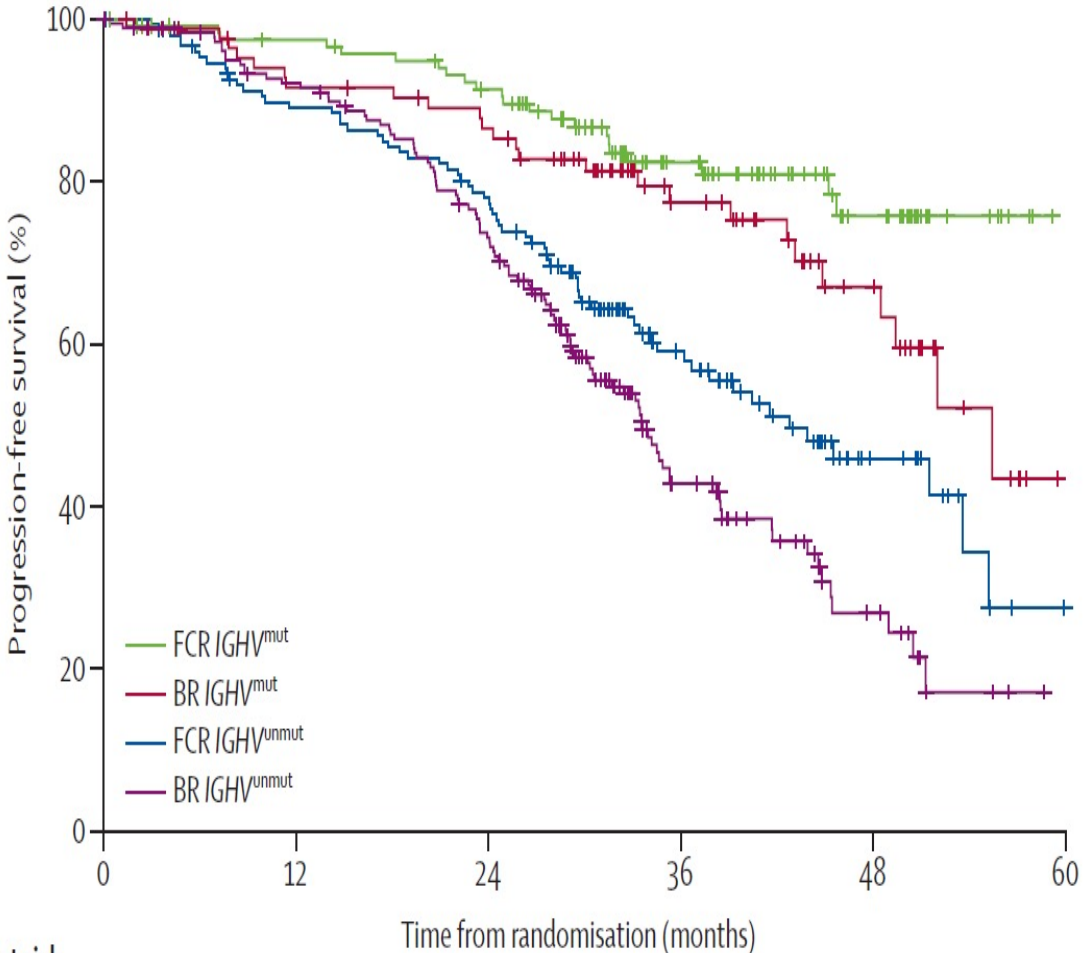
Fisher et al. Blood 2016



Rossi et al., Blood 2015



Unmutated *IGHV* is associated with a higher risk of progression after first-line chemoimmunotherapy



FCR **MUT** IGHV

FCR **UNMUT** IGHV

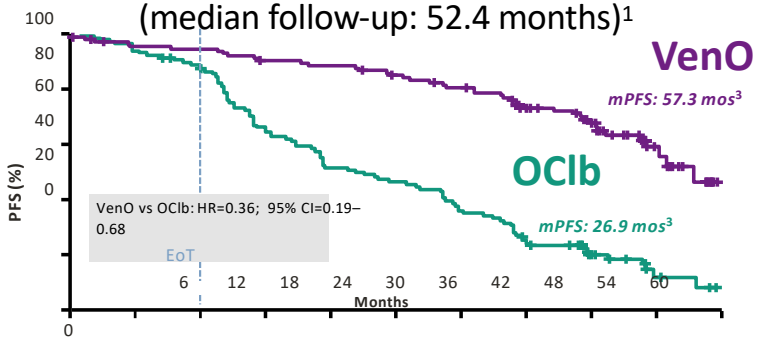
BR **MUT** IGHV

BR **UNMUT** IGHV

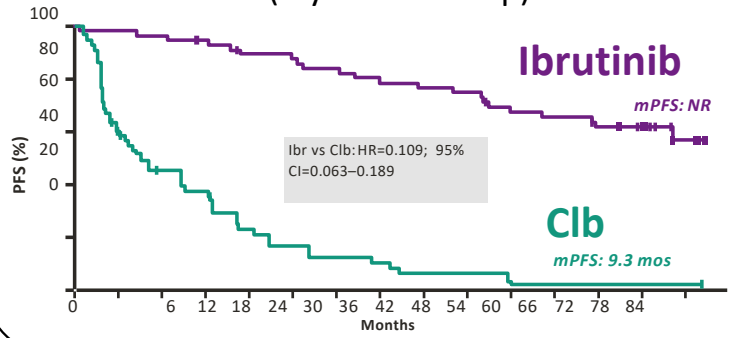
Eichhorst B, et al. Lancet Oncol 2016; 17(7): 928-42.

Improved outcomes with targeted agents vs CIT/chemotherapy in 1L patients with <u>unmutated IGHV</u>

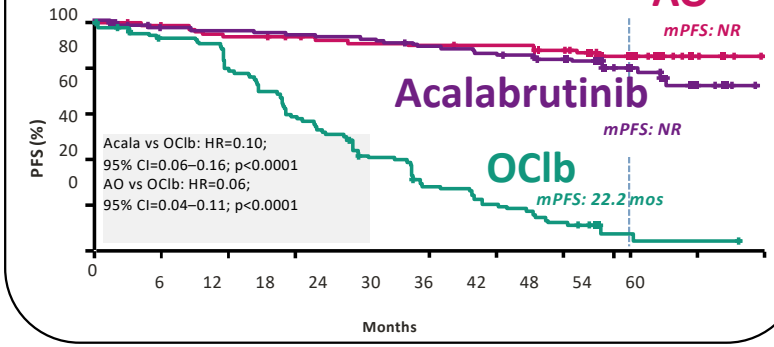
CLL14: PFS in patients with IGHV^{unmut} (median follow-up: 52.4 months)[1]



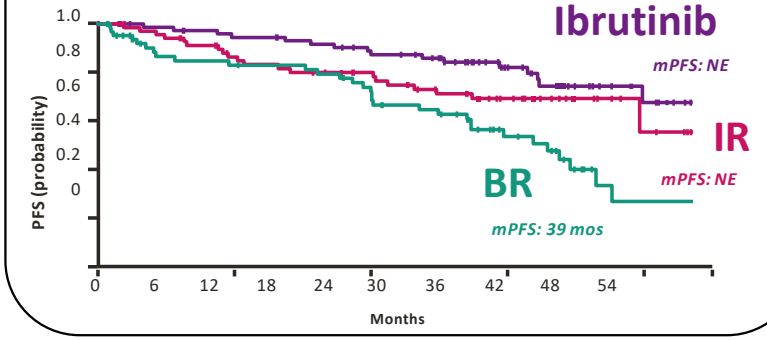
RESONATE-2: PFS in patients with IGHV^{unmut} (7-year follow-up)[2]



ELEVATE TN: PFS in patients with IGHV^{unmut} (median follow-up: 46.9 months)[4]



Alliance 202: PFS in patients with IGHV^{unmut} (median follow-up: 38 months)[6]

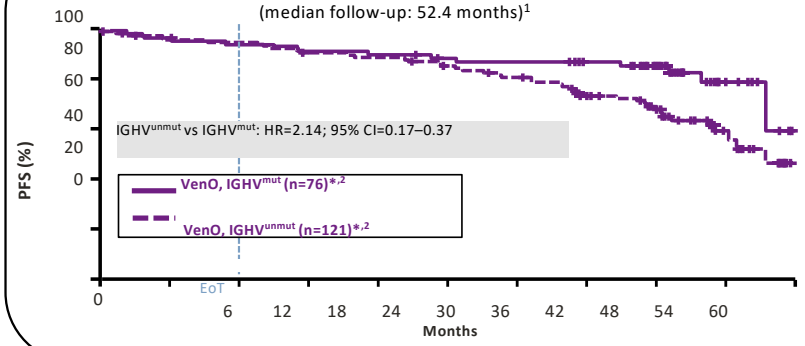


1. Tausch E, *et al.* EHA 2021; Abstract S144 (Oral); 2. Tausch E, *et al.* EHA 2021. Abstract S144; 3. Al-Sawaf O, *et al.* EHA 2021; Abstract S146 (Oral); 4. Sharman JP, *et al.* EHA 2021; Abstract S148 (Oral); 5. Ghia P, *et al.* EHA 2021; Abstract EP636 (Poster); 6. Woyach JA, *et al. N Engl J Med* 2018; **379**:2517–2528 (incl. appendix).

Outcomes observed with targeted agents in 1L patients by IGHV status

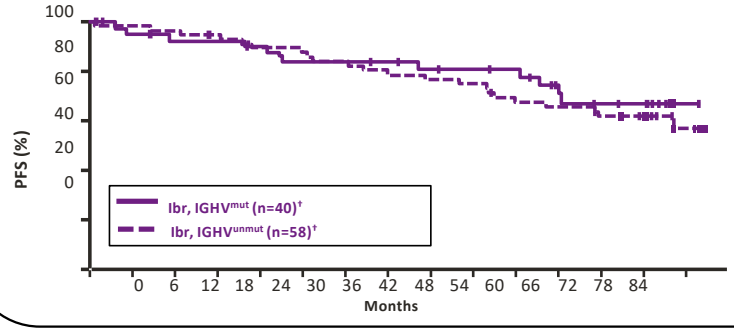
CLL14: PFS with VenO by IGHV status

(median follow-up: 52.4 months)[1]



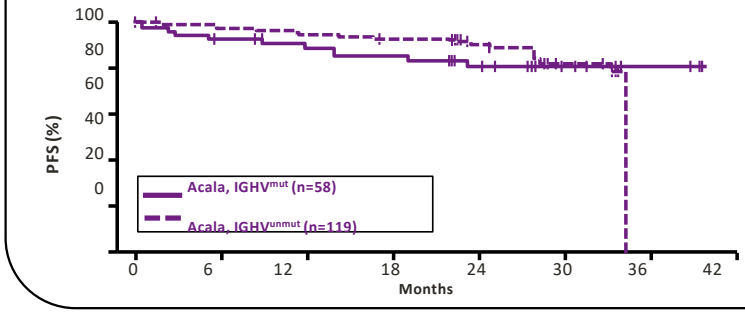
RESONATE-2: PFS with Ibr by IGHV status

(7-year follow-up)[4]



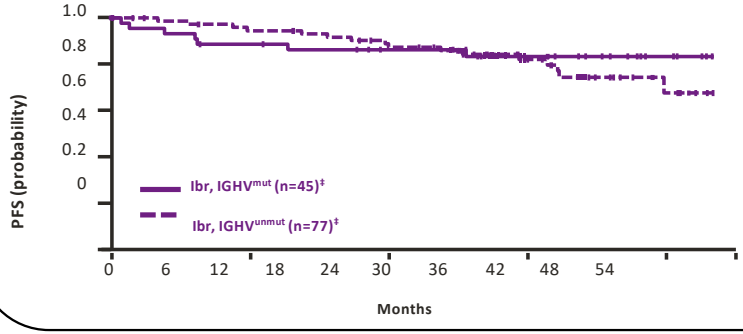
ELEVATE TN: PFS with Acala by IGHV status

(median follow-up: 28.3 months)[3]



Alliance 202: PFS with Ibr by IGHV status

(median follow-up: 38 months)[5]



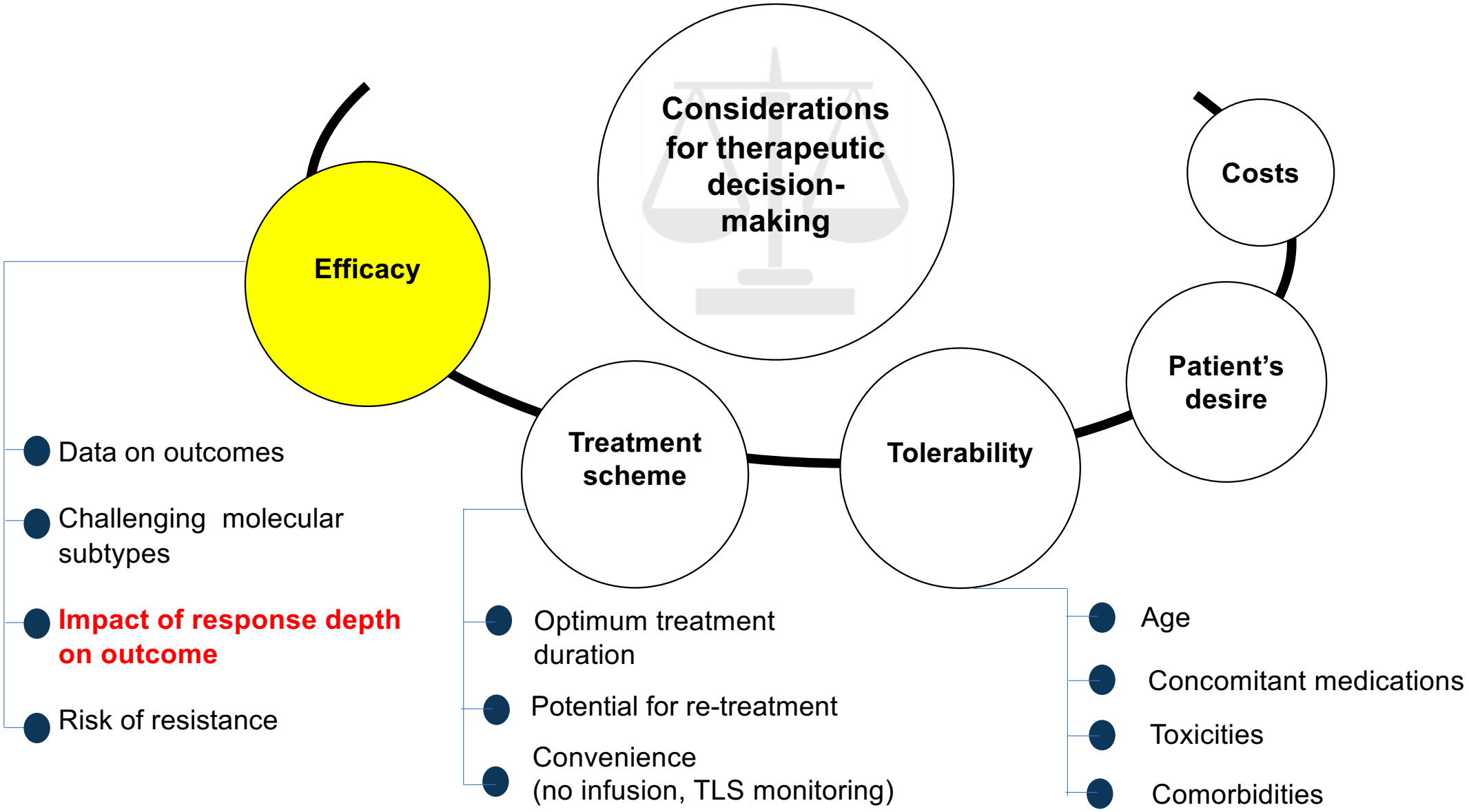
* mPFS NR for IGHV^{mut}, mPFS 57.3 months for IGHV^{unmut}; † mPFS NR in all arms;
‡ mPFS NE in all arms.

1. Tausch E, *et al.* EHA 2021; Abstract S144 (Oral); 2. Tausch E, *et al.* EHA 2021. Abstract S144; 3. Sharman JP, *et al. Lancet* 2020; **396**:1278–1291;
4. Ghia P, *et al.* EHA 2021; Abstract EP636 (Poster); 5. Woyach JA, *et al. N Engl J Med* 2018; **379**:2517–2528 (incl. appendix); 6. Al-Sawaf O, *et al.* EHA 2021; Abstract S146 (Oral).

Defining the place for chemoimmunotherapy in CLL

- Ideal FCR candidates
  - Young
  - Fit
  - *TP53* intact
  - *IGHV* mutated

- For patients who are “ideal FCR candidates”, BR is not an ideal substitute
- BR may play a limited role in 2022 in older, *TP53* intact, *IGHV* mutated patients, but there are many other choices to consider
- Short- and long-term toxicities should be discussed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Optimum treatment duration
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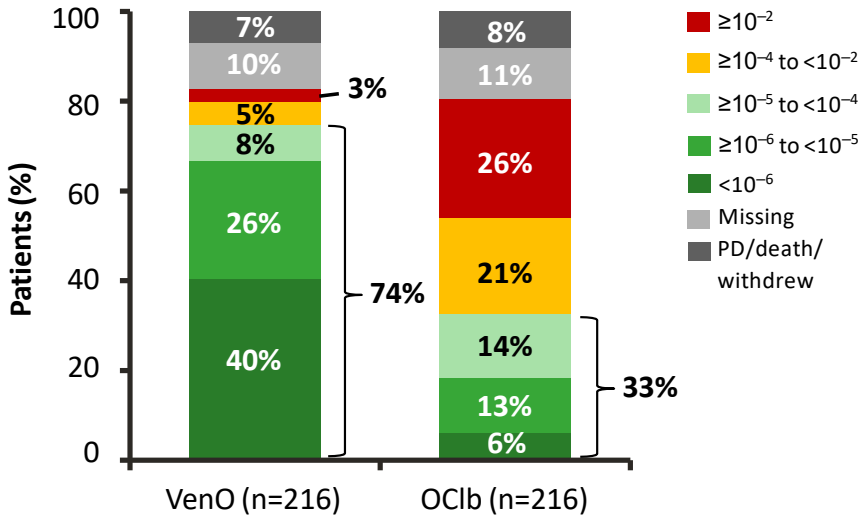
Convenience (no infusion, TLS monitoring)
Age
Concomitant medications
Toxicities
Comorbidities

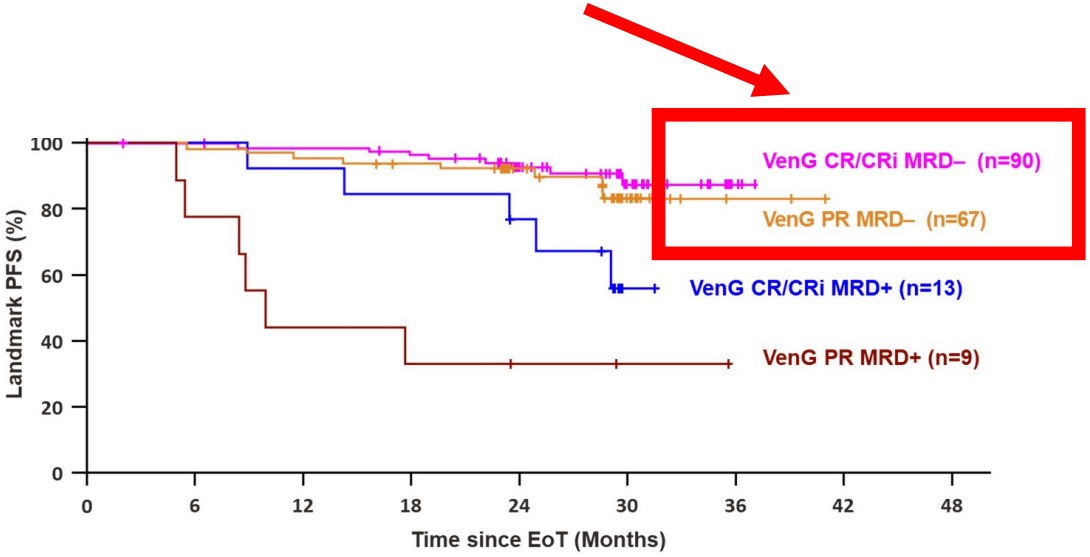
uMRD is a key goal of fixed-duration targeted treatment regimens: the CLL 14 study

CLL14: Phase 3 trial of VenO vs OClb in previously untreated patients with CLL (N=432)[1,3]

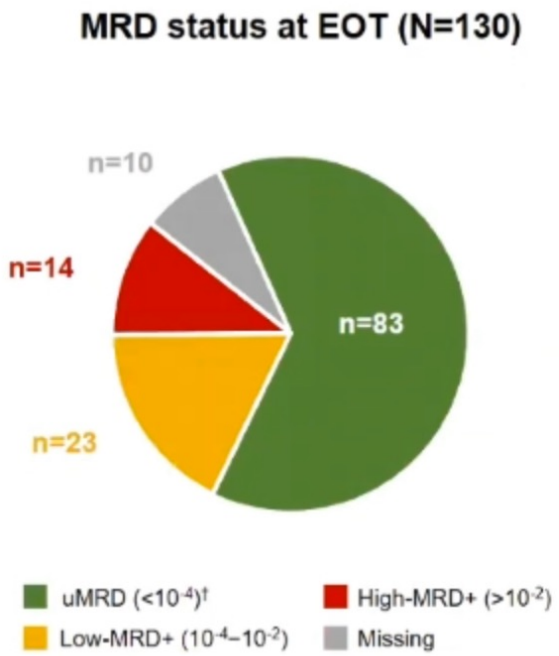
PB MRD response by NGS* 3 months after EoT

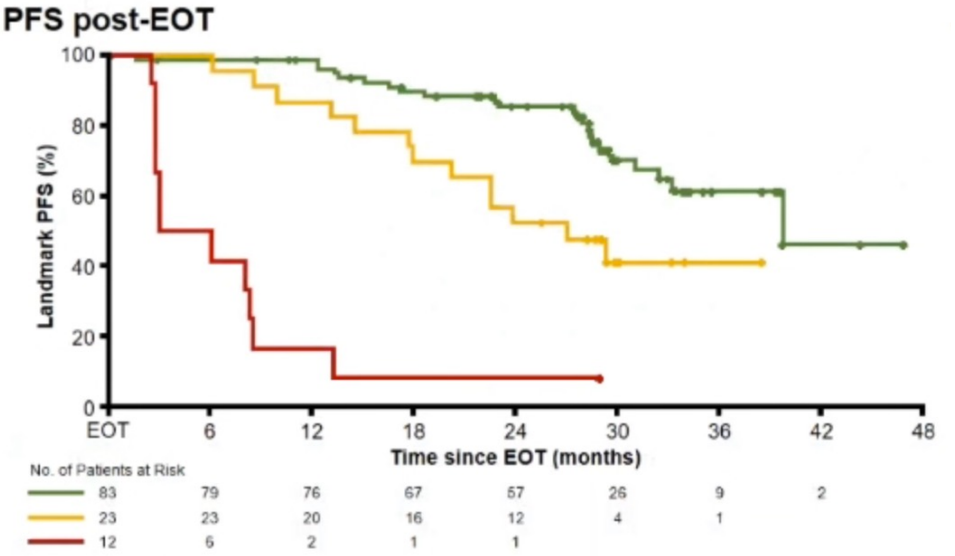


Patients in PR have a similar outcome as patients with CR when uMRD levels are achieved



High uMRD rates predicting longer PFS in the MURANO trial





*uMRD <1 CLL cell/10,000 leukocytes, + censored

CI, confidence interval; EOT, end of treatment; NE, not evaluable; NS, not significant; OS, overall survival; PFS, progr

C1D1 — EOT

Approx. 24 mo

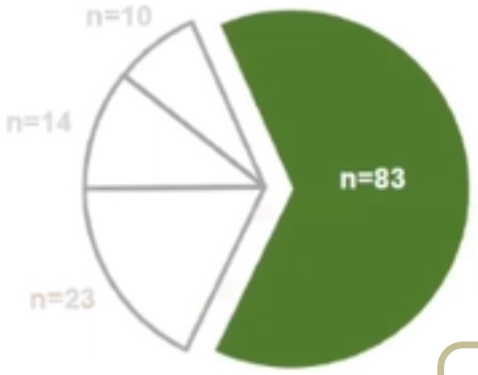
N=130; †uMRD <1 CLL cell/10,000 leukocytes

*Investigator-assessed PD according to International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria

C, cycle; D, day; CLL, chronic lymphocytic leukemia; EOT, end of treatment; mo, months; PD, progressive disease; (u)MRD, (undetectable) minimal residual disease; Ven, venetoclax

Long delay between EOT and MRD conversion observed

MRD status at EOT (N=130)



Time from EOT to MRD Conversion

32 (38.6%)
Remained uMRD

28 (33.7%)
MRD conversion no PD

4 (4.8%)
PD without MRD conversion

19 (22.9%)
MRD conversion with PD

C1D1 — EOT — MRD conversion

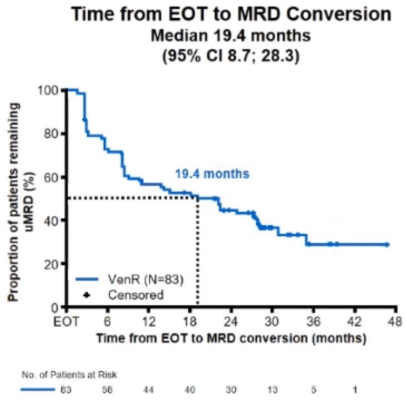
Approx. 24 mo

MEDIAN TIME TO CONVERSION **19 mo**

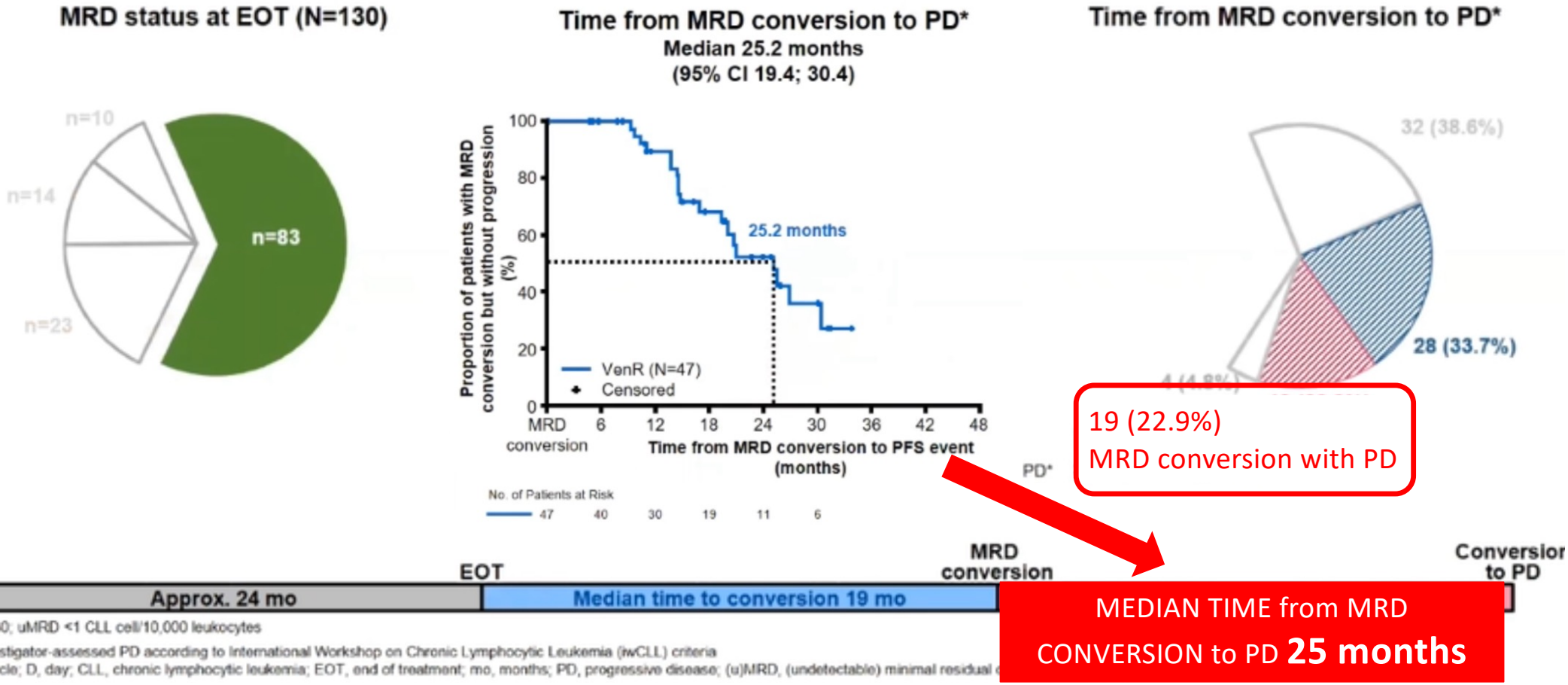
N=130; uMRD <1 CLL cell/10,000 leukocytes

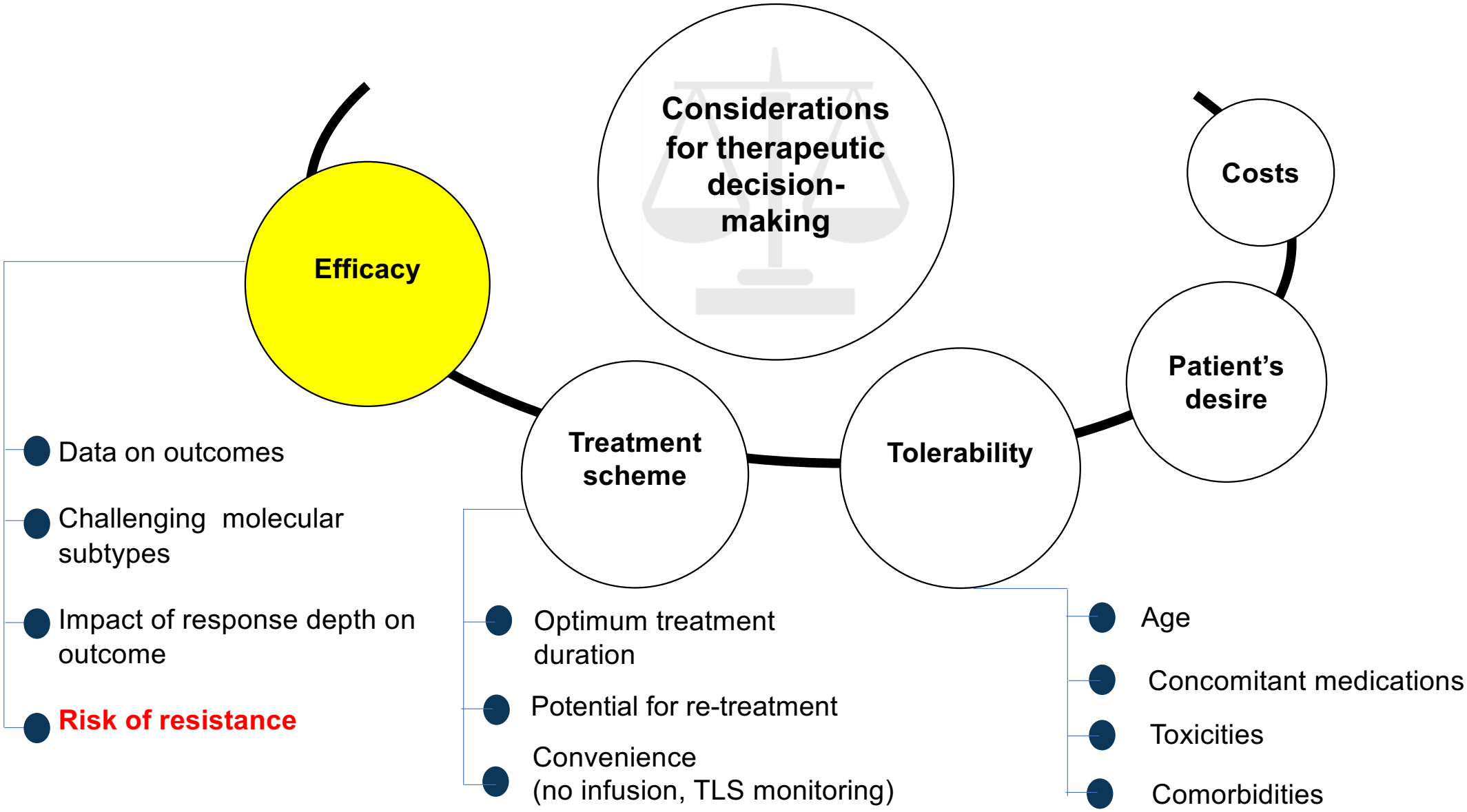
*Investigator-assessed PD according to International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria

C, cycle; D, day; CLL, chronic lymphocytic leukemia; EOT, end of treatment; mo, months; PD, progressive disease; (u)MRD, (undetectable) minimal residual disease;



Long delay between MRD conversion and clinical PD observed

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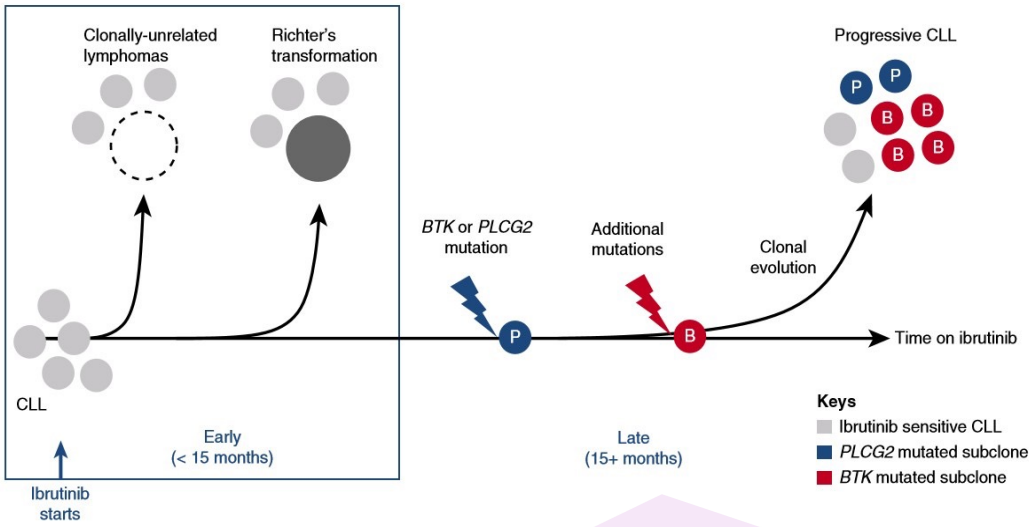
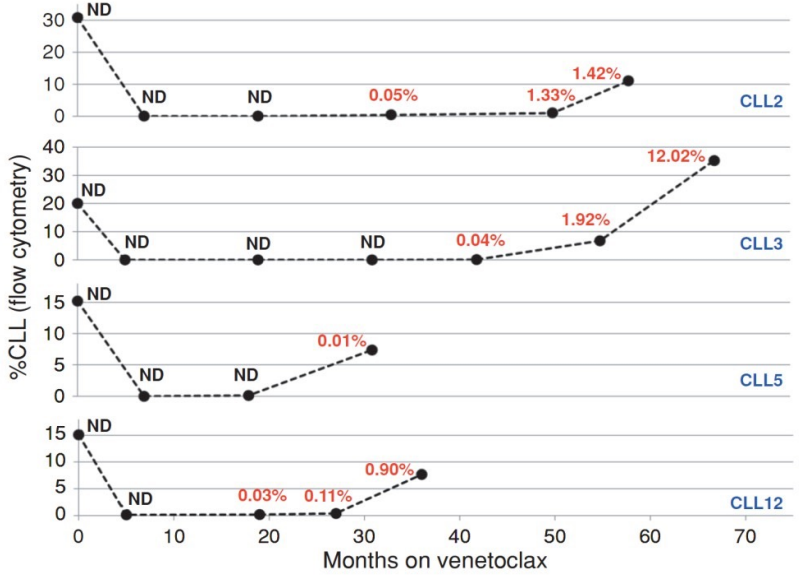
Resistance to targeted therapies: Continuous monotherapy treatment

Molecular patterns of ibrutinib-resistant disease[1]



BTK/PLCγ2 resistance mutations: preceded PD by **≤15.4 months** (median **8 months**)[1]

Acquired resistance mutations in *BCL2* to venetoclax monotherapy (n=4)*,[2]



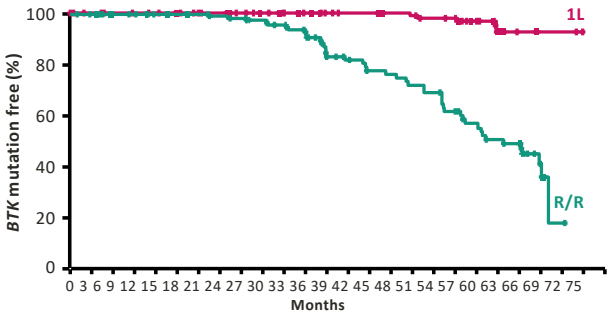
BCL2 G101V mutations: preceded PD by **≤25 months** (median **32 months** on venetoclax)[2]

* CLL burden measured by multiparameter flow cytometry in serial BM aspirates from 4 patients from initiation of venetoclax until the clinical diagnosis of PD. The VAF of *BCL2* p.G101V in BM samples measured by droplet digital PCR is overlaid; *BCL2* p.G101V VAF is indicated in red.
BM, bone marrow; ND, not detected; PLCγ2, phospholipase C gamma 2; VAF, variant allele frequency.

1. Ahn IE, *et al. Blood* 2017; **129:**1469–1479; 2. Blombery P, *et al. Cancer Disov* 2019; **9:**342–353.

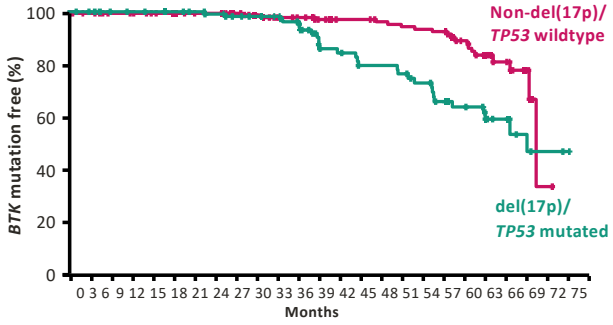
BTK mutations occur more frequently in patients with del(17p)/*TP53*^{mut} treated with ibrutinib

Freedom from *BTK* mutation in patients with del(17p)/*TP53*^{mut}: 1L vs R/R



	1L (n=238)	R/R (n=150)
Median time to detection (95% CI)	NR (NE–NE)	61 (53–67)
3-year mutation-free estimates (95% CI)	100 (100–100)	83 (74–90)
HR (95% CI)	0.069 (0.027–0.175)	
p value	<0.001	

Freedom from *BTK* mutation in all patients: With vs without del(17p)/*TP53*^{mut}

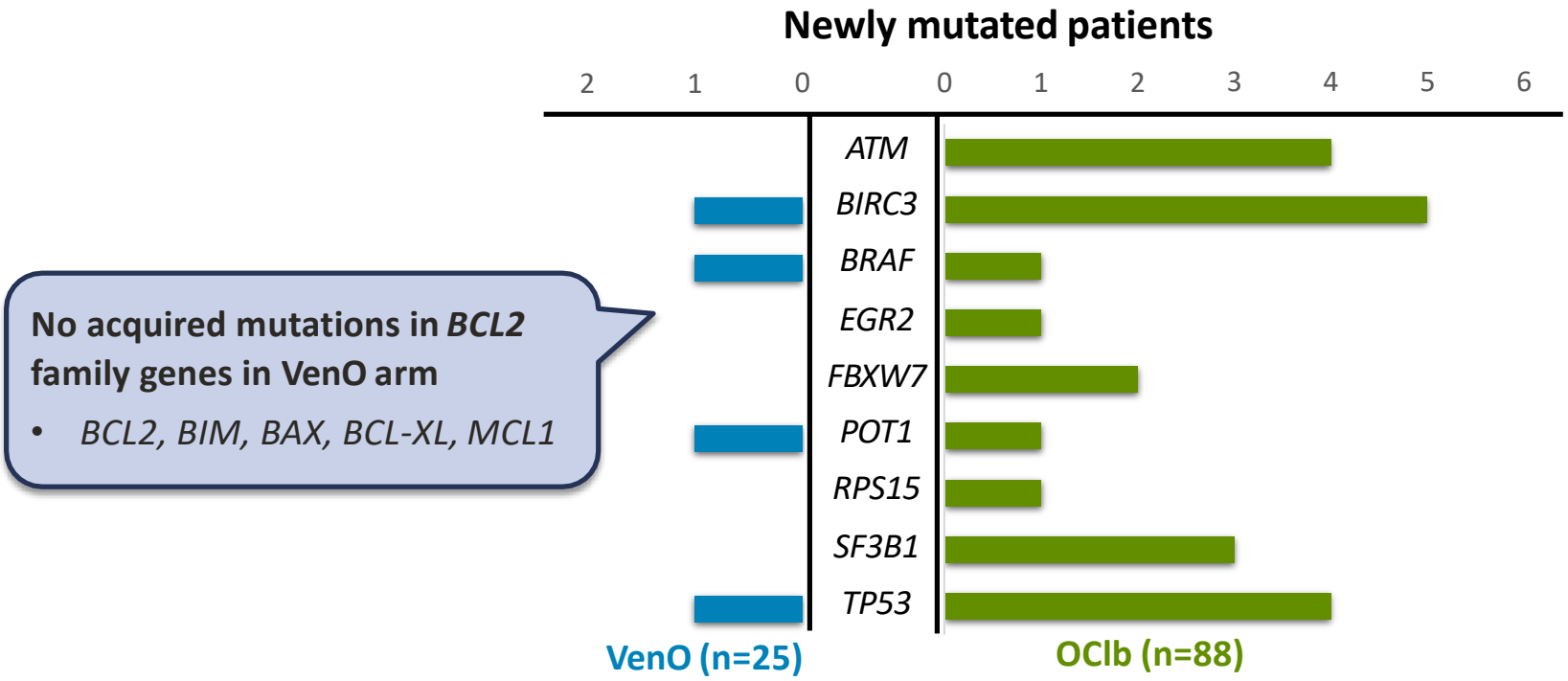


	del(17p)/*TP53*^{mut} (n=149)	Non-del(17p)/*TP53*^{mut} (n=237)
Median time to detection (95% CI)	66 (60–NE)	67 (66–NE)
3-year mutation-free estimates (95% CI)	86 (76–92)	98 (94–99)
HR (95% CI)	0.350 (0.197–0.621)	
p value	<0.001	

Pooled analysis of *BTK* and *PLCG* mutations in 5 ibrutinib trials (N=338)
1L: RESONATE-2, iLLUMINATE, NCT01500733; R/R: RESONATE, RESONATE-17

Wiestner A, *et al.* ASH 2020; Abstract 2225 (Poster).

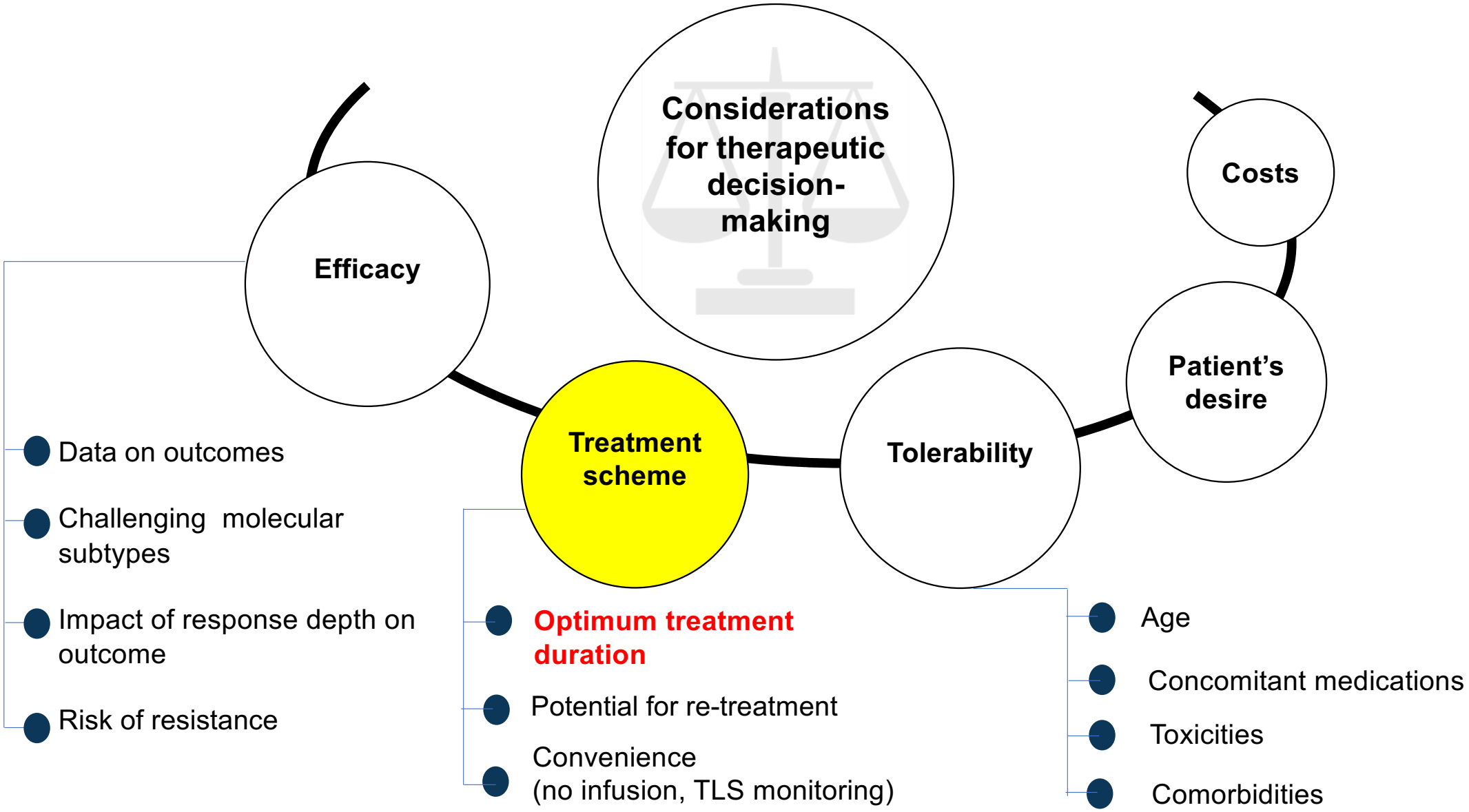
No acquired *BCL2* resistance mutations with fixed-duration venetoclax therapy



CLL14: Acquired mutations in previously untreated CLL patients after 12 cycles of VenO or OClb

VenO, venetoclax + obinutuzumab; OClb, obinutuzumab + chlorambucil.

Tausch E, *et al.* EHA 2021; oral presentation S144.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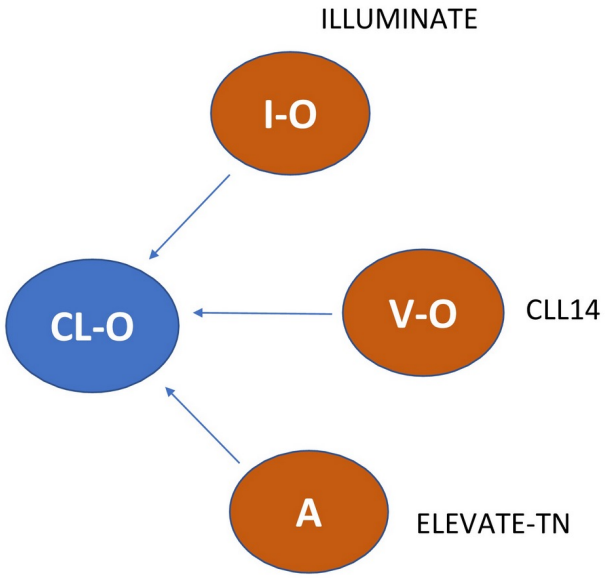
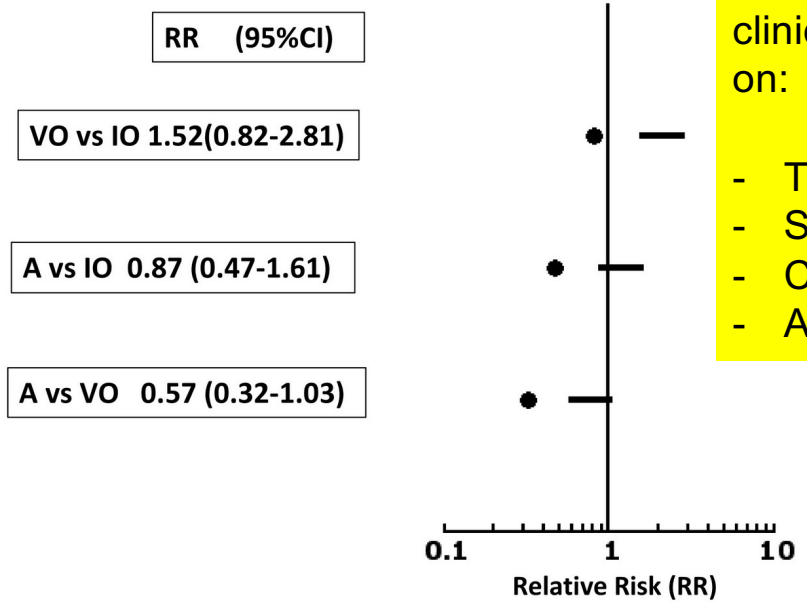
Lack of significant difference in PFS for time-limited and continuous therapy in a network meta-analysis





IO, Ibrutinitib-Obinutuzumab
A, Acalabrutinib
VO, Venetoclax-Obinutuzumab
CL-O, Chlorambucil-Obinutuzumab

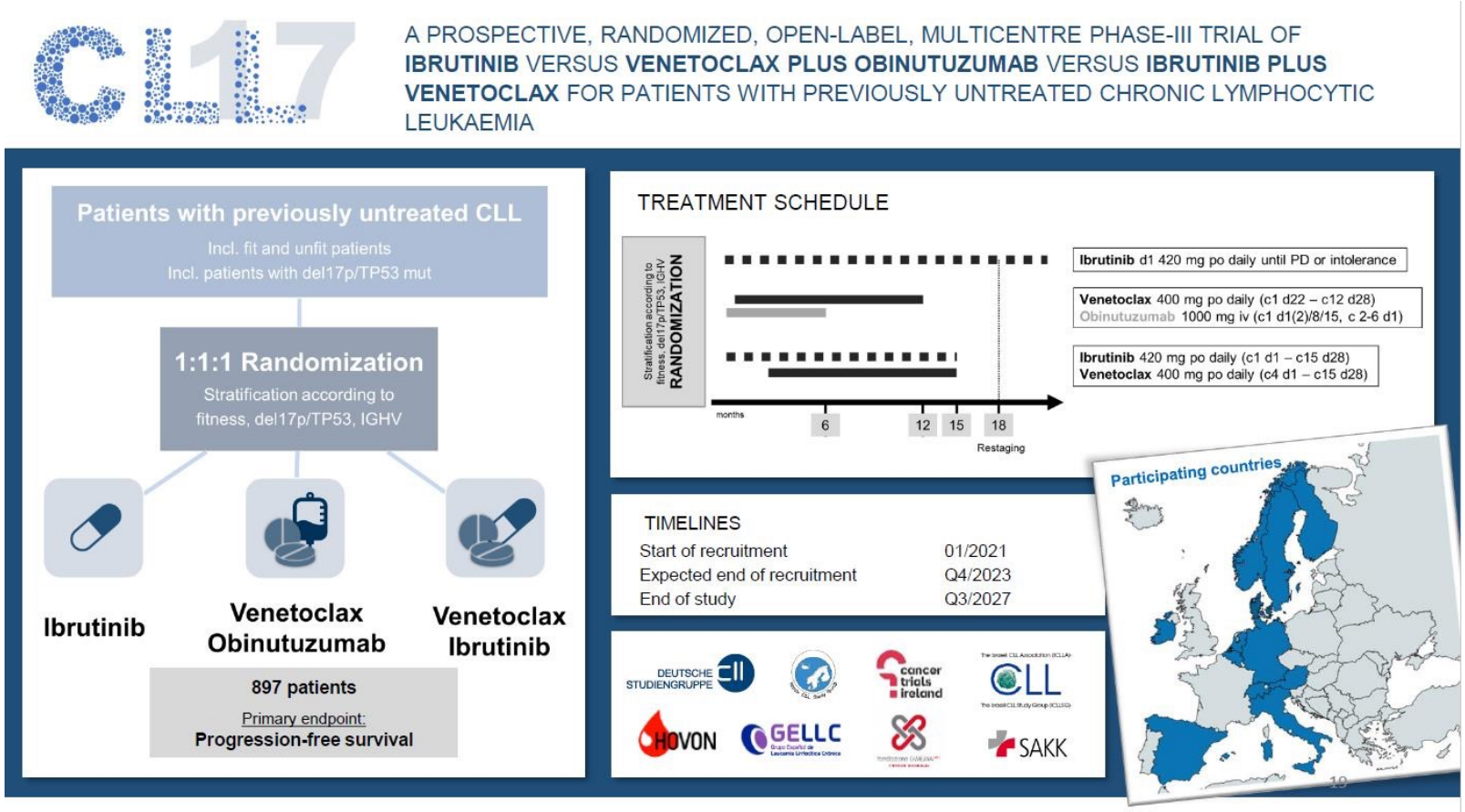
Upper limit of 95% CI for RR crossing 1.0 indicates no statistical difference among different regimens.
Relative Risks (RRs) are represented in the forester plot in logarithmic scale.

Treatment selection in routine clinical practice should be based on:

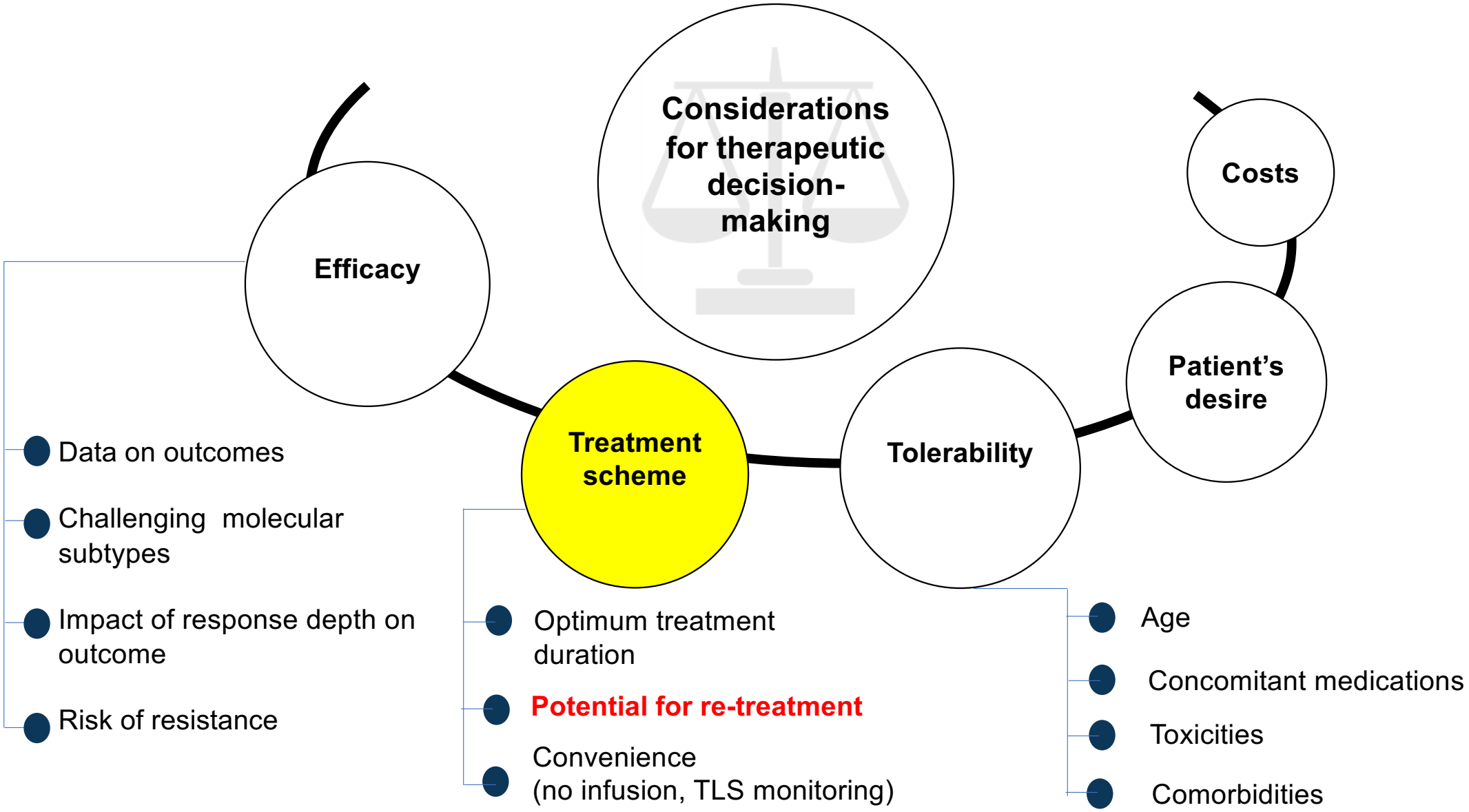
- Treatment objectives
- Safety
- Costs
- Availability

Molica et al. ASH 2020 abstract 3152

The discussion will be addressed in the CLL17 trial by the German Study Group



but we will need a couple of years until we have the answers on this trial!!!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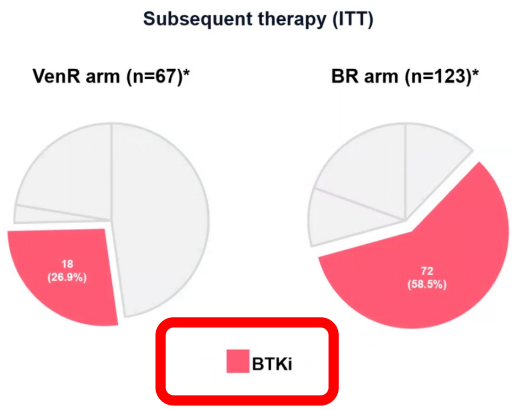
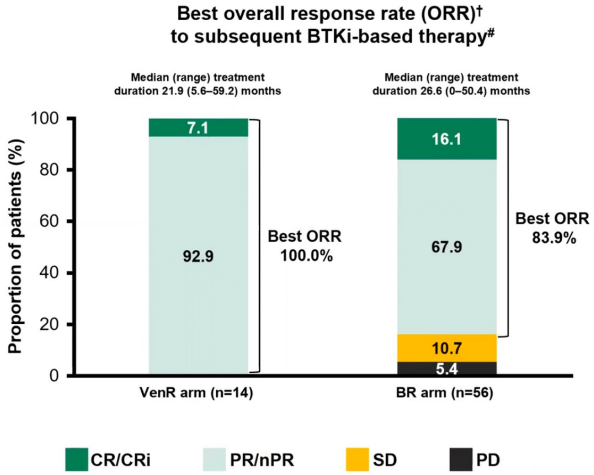
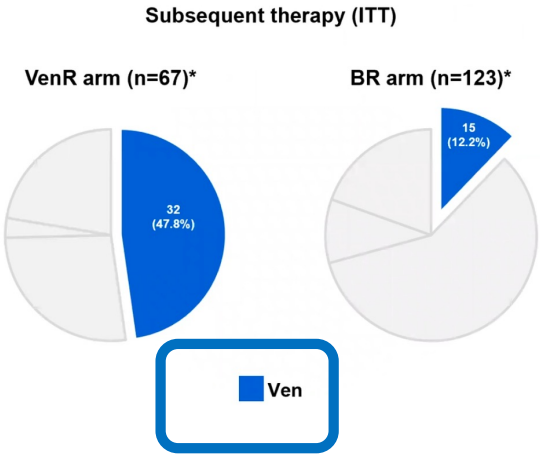
High response rates to subsequent therapy in the MURANO trial

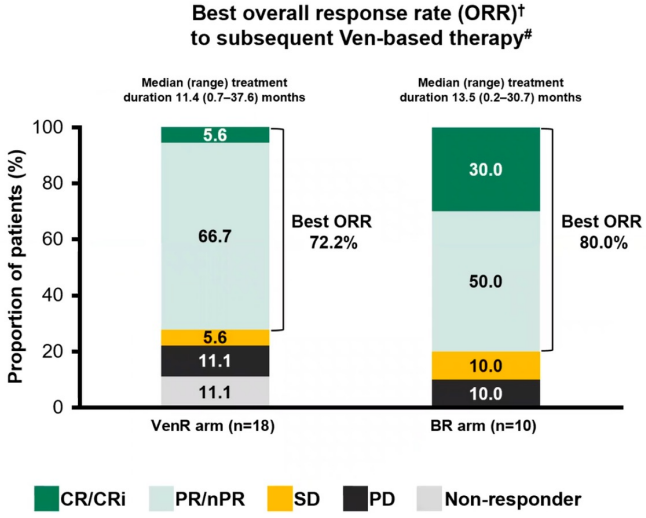




VenR → BTKi

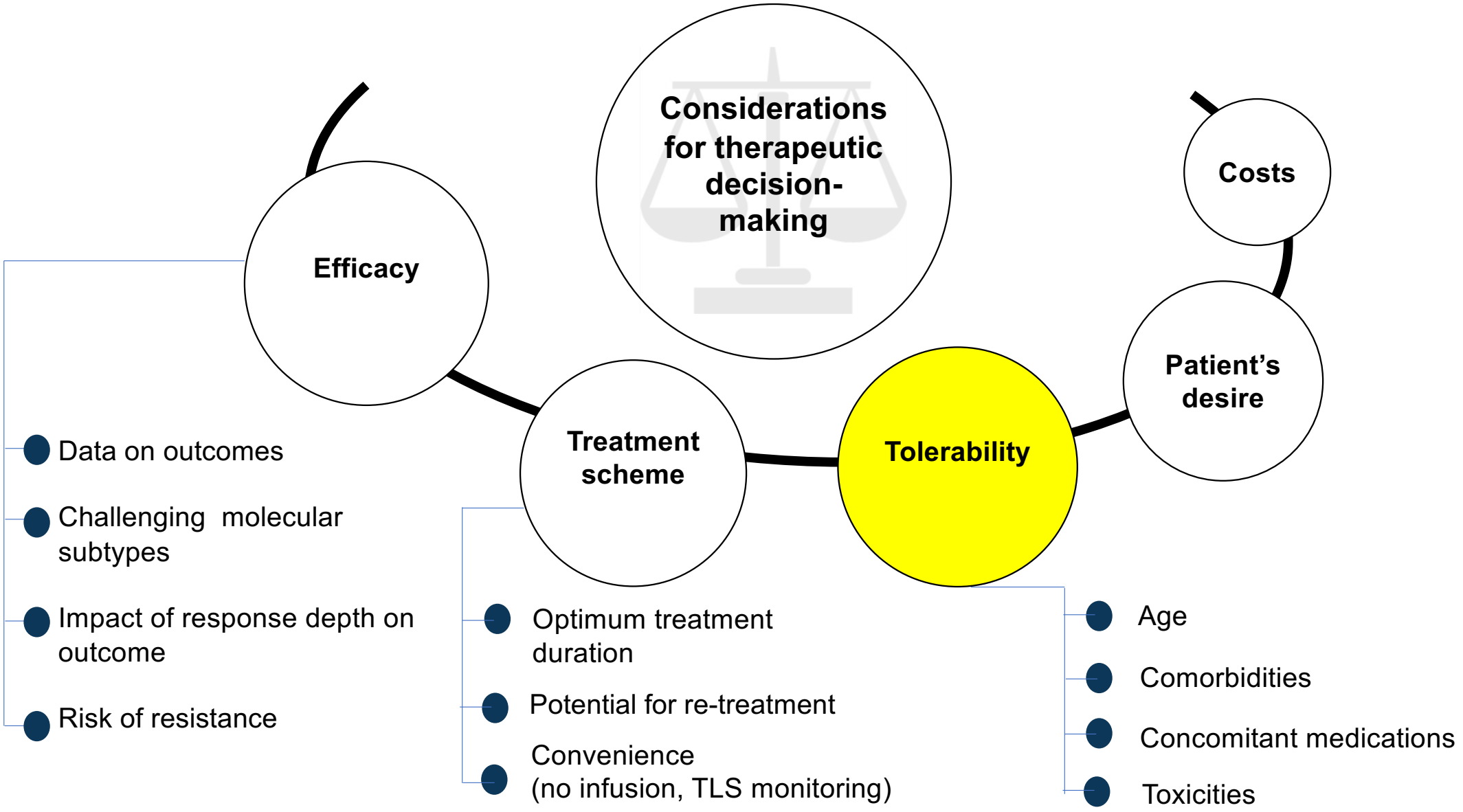
14/14





VenR → Ven

13/18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The age of a patient is linked to life expectancy, which in turn may determine the treatment paradigm

TABLE 2. Additional Expected Life Years According to Age and Sex

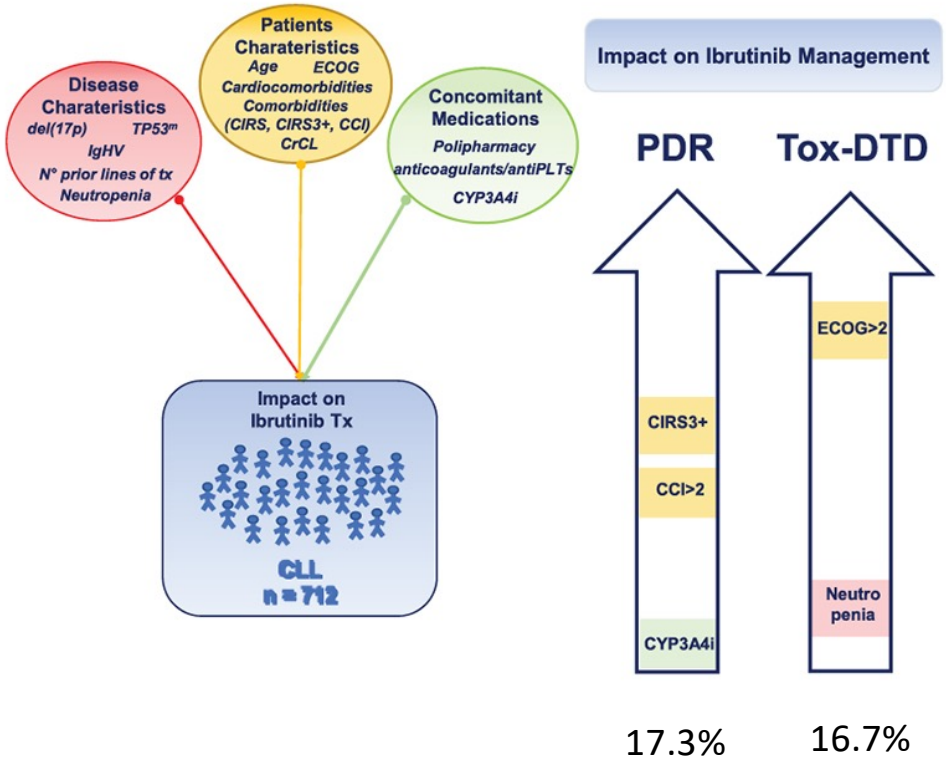
Patient Age, Years	Additional Years of Life Expectancy	
	Men	Women
65	19.2	21.7
70	15.4	17.4
75	11.8	13.6
80	8.7	10.1
85	6.2	7.3

According to U.S. Social Security data.

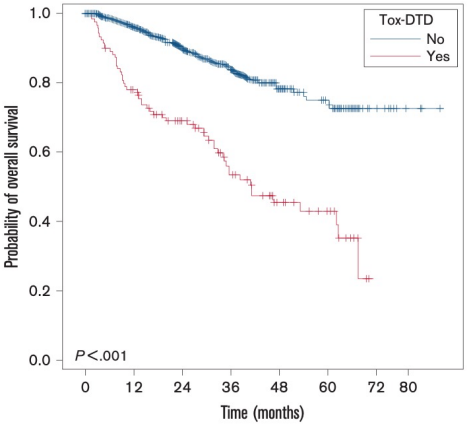
Avoid excessive treatment-related toxicity may be most appropriate in an older patient who has severe comorbid conditions that limit life expectancy

Jain et al. ASCO EDUCATIONAL BOOK 2018

Not age per se, but age-related conditions, may affect ibrutinib management



- Presence of a severe comorbidity was significantly associated with PDR (not translating into worse outcomes)
- CYP3A4 inhibitors use correlated with an increased risk of PDR.
- ECOG-PS and neutropenia resulted as the most accurate predictors of treatment feasibility (negatively affecting OS)



PDR: permanent dose reduction
Tox-DTD: definitive treatment discontinuation owing to toxicity

Tedeschi et al. Do age, fitness, and concomitant medications influence management and outcomes of patients with CLL treated with ibrutinib? Blood Adv 2021

Coexisting conditions and concomitant medications do not affect venetoclax management

221 relapsed/refractory patients

Venetoclax dosing and discontinuations

	Rate, % (proportion)
Achieved 400 mg daily	100% (221/221)
Maintained 400 mg daily	39.8% (88/221)
Required dose reduction at least once	21.7% (48/221)
Permanently maintained lower dosage after ≥1 dose reduction	70.8% (34/48)
Permanently reduced dosage	**21.7%** (48/221)
Required interruption at least once	31.2% (69/221)
Definitively discontinued due to toxicity after ≥1 dose interruption	11.6% (8/69)
Interrupted for ≥ 7 days	20.8% (46/221)
Definitively discontinued due to toxicity after ≥1 dose interruption ≥7 days	13% (6/46)
Definitively discontinued due to toxicity	5.9% (13/221)

PDR

Main reasons:
- ❑ Ven-induced cytopenia (53.8%)
- ❑ drug-to-drug interference (10.4%)
- ❑ infections (8.3%)

Reasons for tx discontinuations

Venetoclax definitive discontinuation on 221 pts	
All reasons	**85 (38.5%)**
CLL progression	38 (17.2%)
Richter transformation	20 (9%)
Toxicity	13 **5.9%**
Allo transplant	8 (3.6%)
Secondary malignancies	3 (1.4%)
Other reasons	3 (1.4%)

Tox-DTD

- ❑ **m time**: 2.3 mo (range 0.1-12.2 mo)
- ❑ **Main reasons**: infections (53.8%) cytopenia (30.8%)

Not influenced by: fitness parameter, age, concomitant medication, baseline neutropenia, or impaired renal function

None of the parameters generally considered for treatment choice should rule the decision process with this agent

Adverse Events of BTK vs BCL2 inhibitors

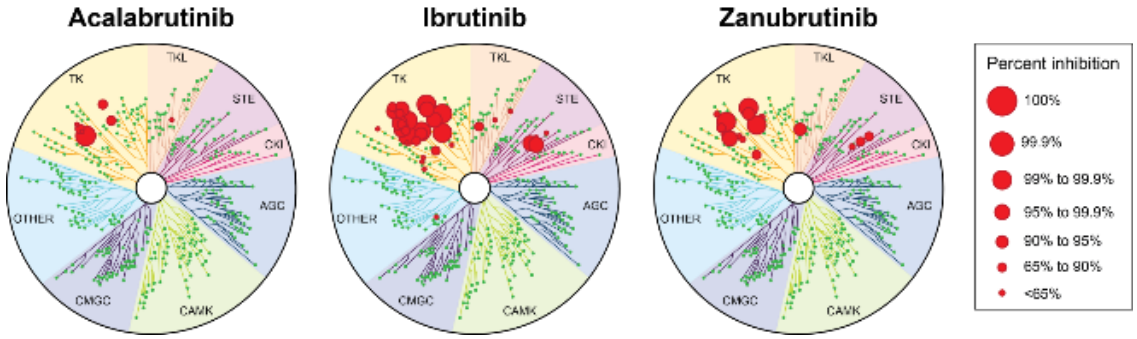
VENETOCLAX

- **Neutropenia**
  - Transient and manageable
  - Grade III/IV neutropenia in 37% of patients, predominantly in the rst 3-6 months of therapy;
  - GCS-F treatment and occasional dose interruptions are effective in the majority of cases
  - febrile neutropenia (4-5%)
  - Grade III/IV infections and infestations (18%)
- **Tumour Lysis Syndrome**
  - Warrant careful prophylaxis and monitoring,
  - Often laboratory TLS (Hyperphosphatemia)
  - Can be prevented or mitigated in the majority of cases (dose ramp-up, TLS prophylaxis, surveillance program, rare dose interruptions)
- **Diarrea**

IBRUTINIB

- **Toxicity is the most common reason for cessation**
  - May compromise the potential durable disease control of ibrutinib
  - 41% of patients discontinued therapy at a median of seven months
  - 63% of terminations in TN and 50% of R/R patients
  - Young TN patients 14% of cessation median F-U of 45 months
  - Older, heavily pre-treated and comorbid patients more likely to discontinue due to toxicity
  - Higher CIRS associated with a higher rate of cessation
- Most common adverse effects accounting for termination:
  - **Arthralgia,** data on the management are lacking
  - **Atrial Fibrillation** (10% of patients over 36 months)
  - **Rash**
  - **Infection**
  - **Bleeding** (50% pts, typically minor, major in 9%)
  - **Diarrhea**
- Increase the risk of sudden cardiac death and ventricular arhythmias. (2-4% HELIOS and ALLIANCE trial)

Differences in overall kinase selectivity have been observed among BTKis



Kinase	Acalabrutinib	Ibrutinib	Zanubrutinib
BTK[a]	5.1 ± 1.0	1.5 ± 0.2	0.5 ± 0.0
TEC[b]	126 ± 11	10 ± 12	44 ± 19
ITK[a]	>1000	4.9 ± 1.2	50 ± 5
TXK[c]	368 ± 141	2.0 ± 0.3	2.2 ± 0.6
BMX[c]	46 ± 12	0.8 ± 0.1	1.4 ± 0.4
EGFR[c]	>1000	5.3 ± 1.3	21 ± 1
ERBB2[c]	~1000	6.4 ± 1.8	88 ± 26
ERBB4[c]	16 ± 5	3.4 ± 1.4	6.9 ± 0.6
BLK[c]	>1000	0.1 ± 0.0	2.5 ± 0.4
JAK3[c]	>1000	32 ± 15	>1000

*Profiling of BTKi interactions with kinases having Cys in same position as Cys481 of BTK**

Mild effects of Acalbrutinib on TEC

No effects of Acalbrutinib on ITK

No effects of Acalbrutinib on EGFR

(10 times lower affinity than Ibrutinib)

Kinase	Acalabrutinib	Ibrutinib	Zanubrutinib
BLK	>1000	0.1 ± 0.0	2.5 ± 0.4
FGR	>1000	3.3 ± 1.1	101 ± 20
FYN	>1000	29 ± 0	755 ± 15
HCK	>1000	29 ± 0	>1000
LCK	>1000	6.3 ± 1.3	147 ± 13
LYN	>1000	20 ± 1	668 ± 127
SRC	>1000	19 ± 1	504 ± 37
YES1	>1000	4.1 ± 0.2	420 ± 143

Profiling of BTKis on Src family kinases†

<10-fold selectivity versus BTK

>10- to <100-fold selectivity versus BTK

>100-fold selectivity versus BTK

No effects of Acalbrutinib on SRC family kinases

Figures from Kaptein et al. Blood. 2018;132(Suppl 1):1871. *Values are mean ± SD, and are from: aIMAP assay, bLanthaScreen assay, cZ'-LYTE assay
†Values are mean ± SD and are from Z'-LYTE assay. 1. Kaptein et al. Blood 2018;132(Suppl 1):1871; 2. Barf et al. J Pharmacol Exp Ther 2017;363(2):240–252; 3. Estupiñán et al. Front Cell Dev Biol 2021;9:630942
AE, adverse event; BTK, Bruton tyrosine kinase; BTKi, BTK inhibitor; CV, cardiovascular; Cys, cysteine; HTN, hypertension; VF, ventricular fibrillation

Acalabrutinib vs ibrutinib: incidence of events of clinical interest in the Elevate R/R trial

Statistically significant reduction in any grade atrial fibrillation rates, lower incidence of bleeding events, hypertension, interstitial lung disease/pneumonitis

	Any grade		Grade ≥3	
Events, n (%)	**Acalabrutinib (n=266)**	**Ibrutinib (n=263)**	**Acalabrutinib (n=266)**	**Ibrutinib (n=263)**
Cardiac events	64 (24.1)	79 (30.0)	23 (8.6)	25 (9.5)
Atrial fibrillation[a]*	25 (9.4)	**42 (16.0)**	13 (4.9)	10 (3.8)
Ventricular arrythmias[b]	0	3 (1.1)	0	1 (0.4)
Bleeding events*	101 (38.0)	**135 (51.3)**	10 (3.8)	12 (4.6)
Major bleeding events[c]	12 (4.5)	14 (5.3)	10 (3.8)	12 (4.6)
Hypertension[d]*	25 (9.4)	**61 (23.2)**	11 (4.1)	**24 (9.1)**
Infections[e]	208 (78.2)	214 (81.4)	82 (30.8)	79 (30.0)
ILD/pneumonitis*	7 (2.6)	**17 (6.5)**	1 (0.4)	2 (0.8)
SPMs excluding NMSC	24 (9.0)	20 (7.6)	16 (6.0)	14 (5.3)

Higher incidence indicated in **bold** for terms with statistical differences.
*Two-sided *P*-value for event comparisons <0.05 without multiplicity adjustment.
[a]Includes events with preferred terms atrial fibrillation and atrial flutter. [b]Includes events with preferred terms torsade de pointes, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation, ventricular flutter, ventricular tachyarrhythmia, and ventricular tachycardia. [c]Defined as any hemorrhagic event that was serious, grade ≥3 in severity, or a central nervous system hemorrhage (any severity grade).[d]Included events with the preferred terms of hypertension, blood pressure increased, and blood pressure systolic increased. [e]Most common grade ≥3 infections were pneumonia (acalabrutinib, 10.5%; ibrutinib, 8.7%), sepsis (1.5% vs 2.7%, respectively), and UTI (1.1% vs 2.3%).
ILD = interstitial lung disease; NMSC = nonmelanoma skin cancer; SPMs = second primary malignancies; UTI = urinary tract infection.

Byrd JC et al. Poster Presented at: ASCO Virtual Annual Meeting; June 4-8, 2021.

Acalabrutinib vs ibrutinib: incidence of Most common AE's (any grade ≥ 15%) in the Elevate R/R trial

PROS

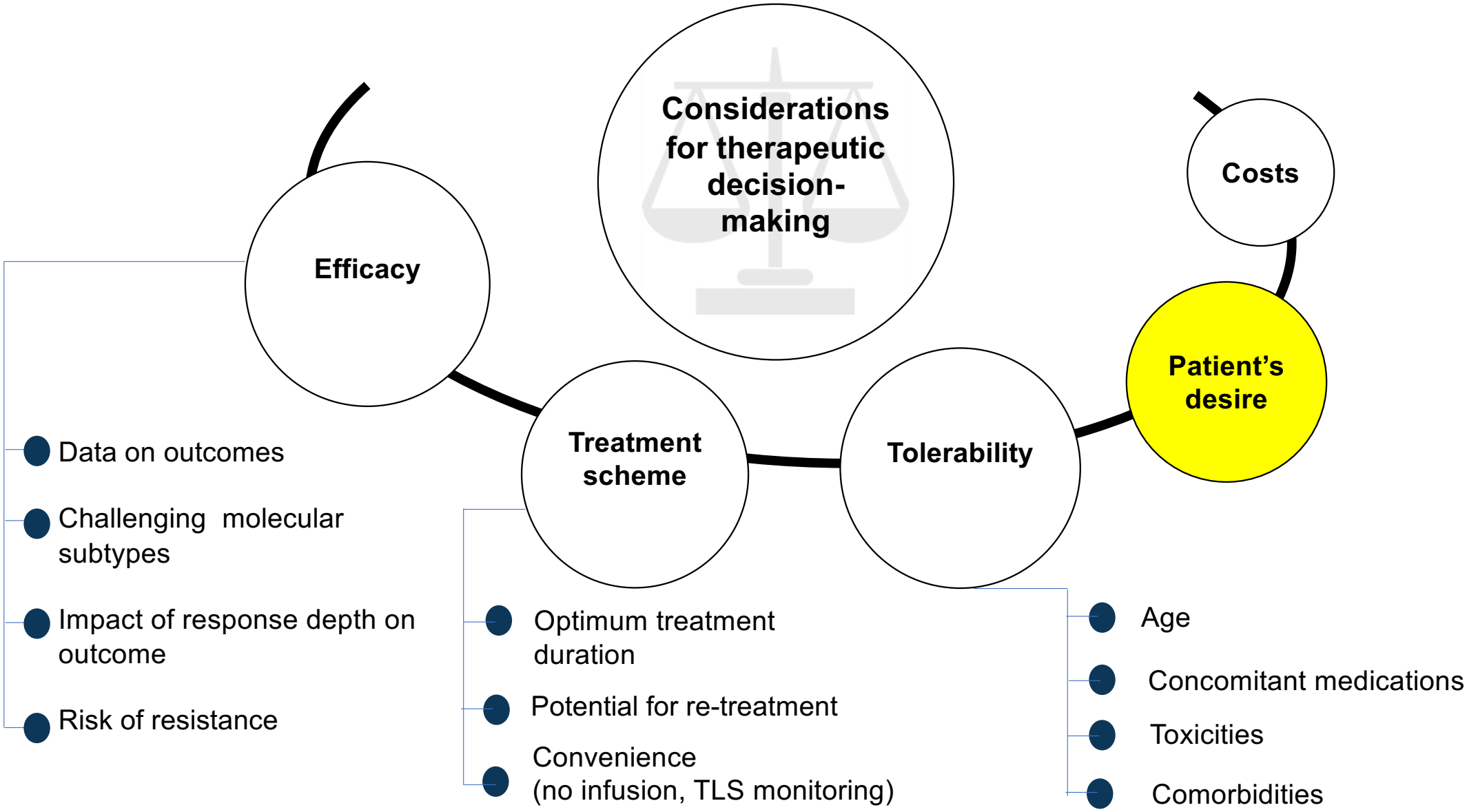
Any grade diarrhea, arthralgia, hypertensio, contusion, and atrial fibrillation occurred less frequently with acalabrutinib vs ibrutinib

	Any grade		Grade ≥3	
Events, n (%)	**Acalabrutinib (n=266)**	**Ibrutinib (n=263)**	**Acalabrutinib (n=266)**	**Ibrutinib (n=263)**
Diarrhea[a,b]	92 (34.6)	**121 (46.0)**	3 (1.1)	**13 (4.9)**
Headache[a,b]	**92 (34.6)**	53 (20.2)	**4 (1.5)**	0
Cough[a]	**77 (28.9)**	56 (21.3)	2 (0.8)	1 (0.4)
URTI	71 (26.7)	65 (24.7)	5 (1.9)	1 (0.4)
Neutropenia	56 (21.1)	65 (24.7)	52 (19.5)	60 (22.8)
Pyrexia	62 (23.3)	50 (19.0)	8 (3.0)	2 (0.8)
Arthralgia[a]	42 (15.8)	**60 (22.8)**	0	2 (0.8)
Hypertension[a,b]	23 (8.6)	**60 (22.8)**	11 (4.1)	**23 (8.7)**
Anemia	58 (21.8)	49 (18.6)	31 (11.7)	34 (12.9)
Fatigue[b]	54 (20.3)	44 (16.7)	**9 (3.4)**	0
Nausea	47 (17.7)	49 (18.6)	0	1 (0.4)
Contusion[a]	31 (11.7)	**48 (18.3)**	0	1 (0.4)
Pneumonia	47 (17.7)	43 (16.3)	28 (10.5)	23 (8.7)
Atrial fibrillation[a]	24 (9.0)	**41 (15.6)**	12 (4.5)	9 (3.4)
Thrombocytopenia	40 (15.0)	35 (13.3)	26 (9.8)	18 (6.8)

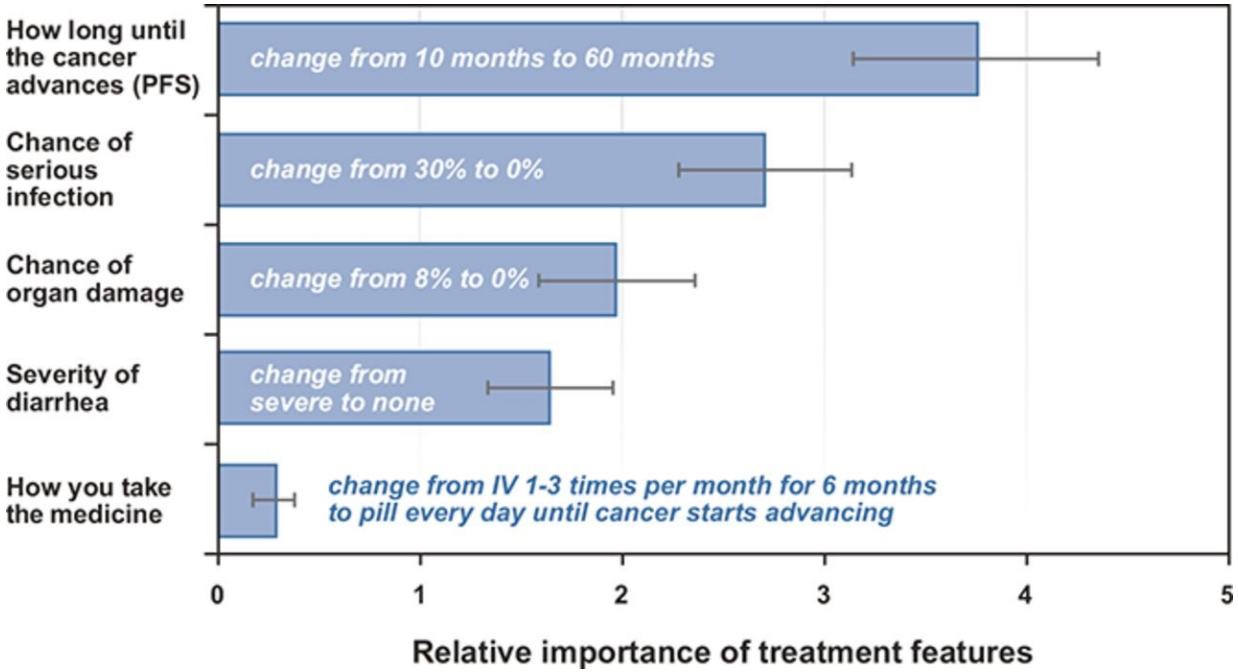
CONS

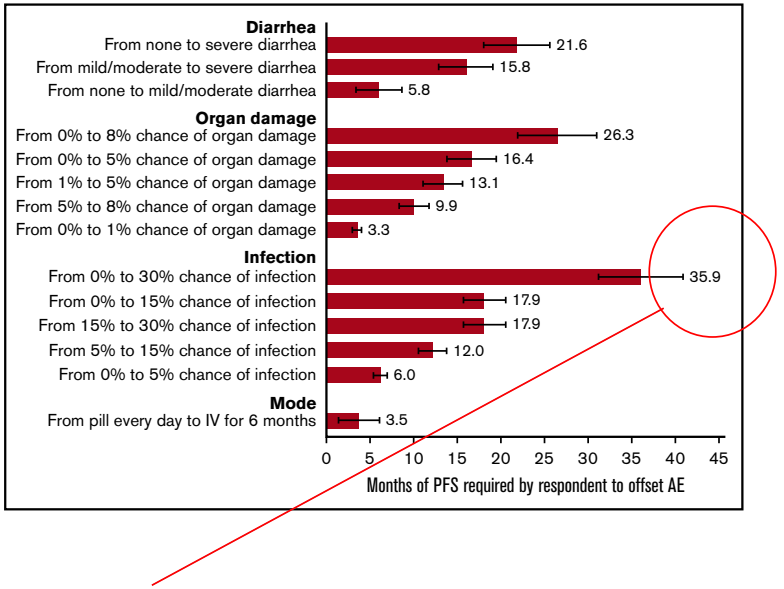
Headache, cough and fatigue occurred more frequently with acalabrutinib vs ibrutinib

Higher incidence in **bold** for terms with statistical differences.
[a]Based on Barnard's exact test, two-sided *P*-value <0.05 without multiplicity adjustment for any grade events. [b]Based on Barnard's exact test, two-sided *P*-value <0.05 without multiplicity adjustment for grade ≥3 events.
AE = adverse event; URTI = upper respiratory tract infection.
Byrd JC et al. Poster Presented at: ASCO Virtual Annual Meeting; June 4-8, 2021.


Considerations for therapeutic decision-making
Efficacy
Treatment scheme
Tolerability
Patient's desire
Costs
Data on outcomes
Challenging molecular subtypes
Impact of response depth on outcome
Risk of resistance
Optimum treatment duration
Potential for re-treatment
Convenience (no infusion, TLS monitoring)
Age
Concomitant medications
Toxicities
Comorbidities

Patients' priorities in selecting treatments: CLL patients value higher PFS





On average, 36 additional months of PFS would compensate respondents for an increase in the risk of serious infection from 0% to 30%.

Carol Mansfield et al., Blood Adv, 2017

CLL Patients' Preferences Towards Therapies: the Italian Experience (CHOICE Study)

Cross-sectional multicenter observational study

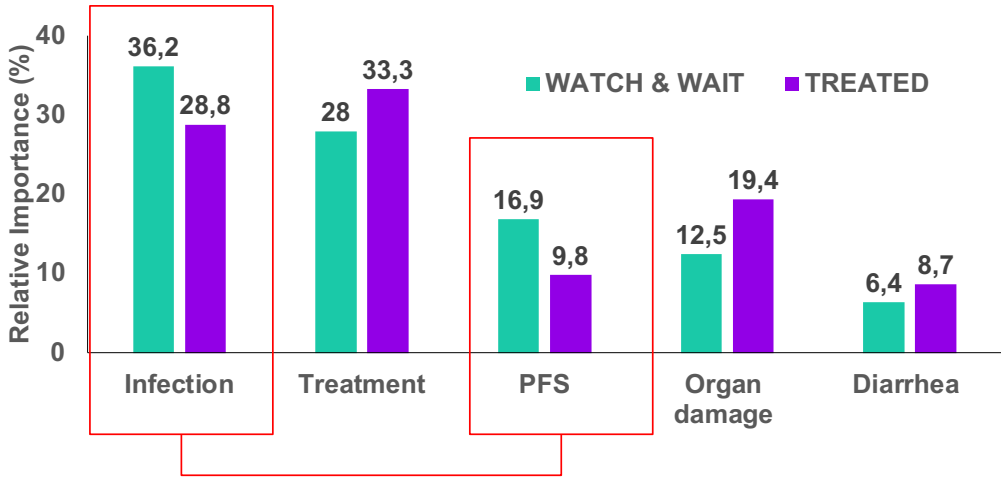
401 patients: 199 W&W and 198 Treated pts, 16 Italian centers

During the 1st wave of the COVID-19 pandemic in Italy (From February to July 2020)

Discrete Choice Experiment questionnaire

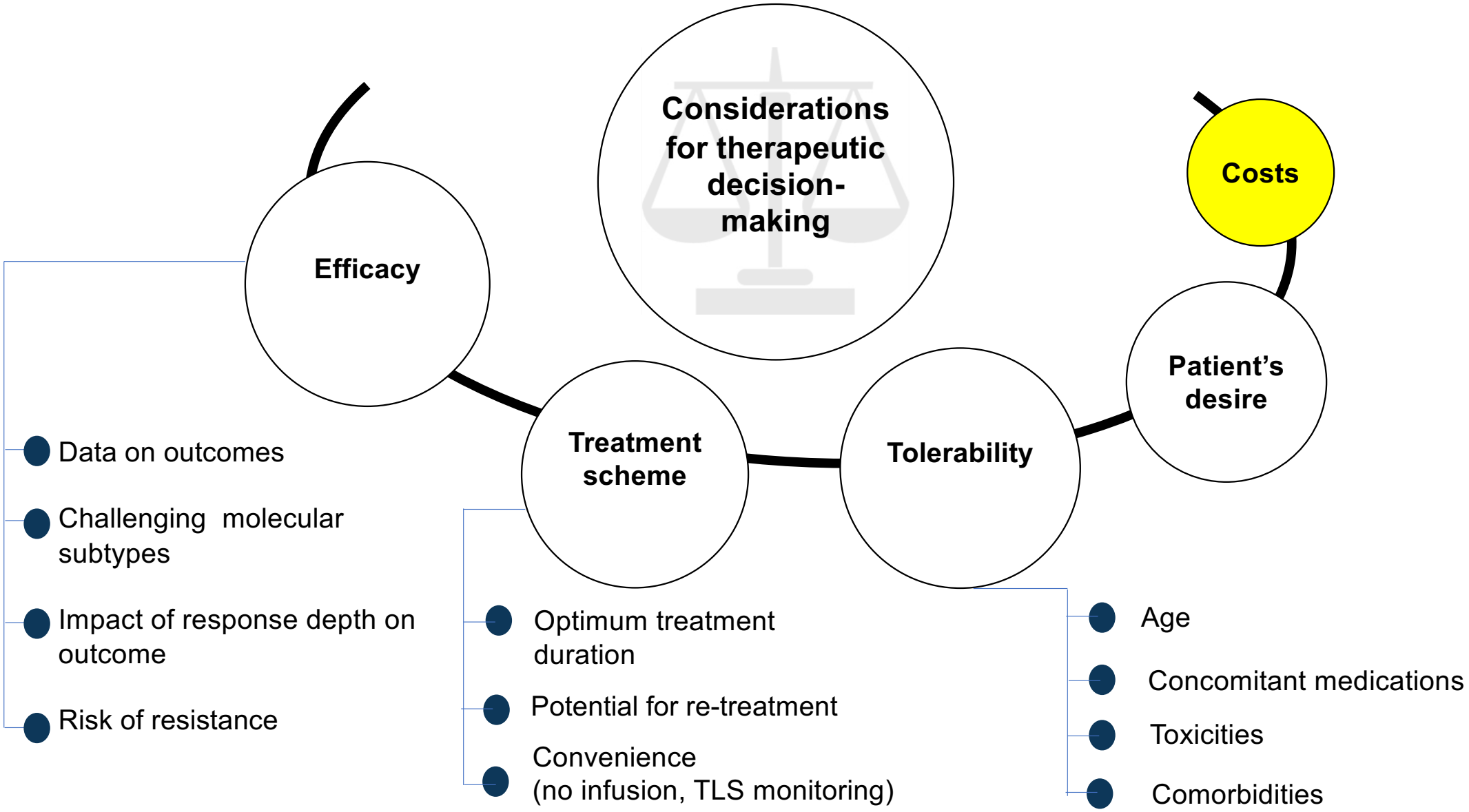
	Pazienti Naïve	Pazienti Trattati
Variabili	Livelli	Livelli
Durata e schema di terapia	•Oral until progression •IV 6 months •Oral 6 months + IV 6 months •Oral 12 months + IV 6 months	•Oral until progression •IV 6 months •Oral 24 months + IV 6 months •Oral until progression + IV 6 months
PFS	•24 months •36 months •48 months •60 months	•18 months •24 months •60 months
Possibile incidenza di Infezioni	•10% •15% •30%	•10% •15% •30%
Possibile incidenza di Diarrea	•5% •10%	•5% •15%
Possibile incidenza di Danno D'organo	•1% •6% •10%	•1% •6% •10%

In the CHOICE study patients had more concerns about possible infections



In contrast to previously published DCEs where PFS was the most important attribute

The limitation in hospital access during the 1st wave and the overall need of personal protection (masks usage) and social distancing might have influenced patients' responses


Considerations for therapeutic decision-making
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Treatment scheme
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Age
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Toxicities
Comorbidities

Analisi di costo-terapia nel trattamento della leucemia linfatica cronica recidivata/refrattaria : Venetoclax-Rituximab vs Ibrutinib

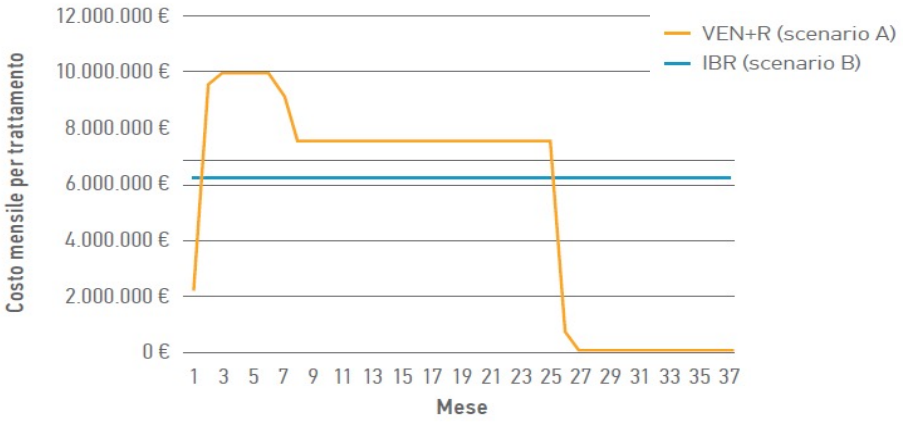
La terapia con Venetoclax-Rituximab genera un risparmio economico rispetto a Ibrutinib pari a circa 31.000€ per paziente

Cicli	Ramp-up	1-6	da 7 - 24	da 24 - 37	Totale Costo Ex-Factory/pz
Costo/Ciclo VenR	-	9.139,37 €	6.919,03 €	-	**196.546,61 €**
Costo/ciclo Ven	3.329,79 €	6.919,03 €	6.919,03 €	-	183.224,57 €
Costo/ciclo R	-	2.220,34 €	-	-	13.322,04 €
Costo/Ciclo Ibrutinib	-	6.147,03 €	6.147,03 €	6.147,03 €	**227.440,18 €**

Prezzo Ex-Factory

Costo per paziente della terapia VEN+R nell'orizzonte temporale di 37 mesi, considerando i costi di ritrattamento per progressione (scenario A)	Costo per paziente VEN in 37 mesi	183.224,57 €
	Costo per paziente R in 37 mesi	13.322,04 €
	Costo per paziente IBR	7.670,09 €
	Costo-terapia per paziente con VEN+ R (incluso ritrattamento con IBR) in 37 mesi	**204.216,70 €**
Costo per paziente della terapia con IBR nell'orizzonte temporale di 37 mesi (scenario B)		**227.440,18 €**

Curve costo-terapia rappresentanti il costo mensile dei due trattamenti, VEN+R (scenario A) e IBR (scenario B), per una popolazione teorica di **1.000 pazienti**



Dal risparmio generato nell'arco temporale di 37 mesi con l'utilizzo della terapia VenR su 1000 pazienti, considerando anche i costi di ritrattamento per progressione della malattia, è possibile trattare **114 pazienti in più**[1]

VenR= Venclyxto+rituximab; Ven= Venclyxto; R= Rituximab

Rigolin et al. Analisi di costo-terapia nel trattamento della leucemia linfatica cronica recidivata/refrattaria.Clinico Economics.Vol.14.2019

Conclusions

- Novel agents have eclipsed chemoimmunotherapy as treatment for CLL in the vast majority of patients (especially high risk patients)
- CIT (FCR) reserved to a limited number of patients
- Continuous versus time-limited treatment discussions are long discussions now and should be individualized to particular patients and their comorbidities
- Besides efficacy, treatment selection in routine clinical practice should be based on safety, treatment objectives and costs

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ASSOCIAZIONE UMBRA
PER LO STUDIO E LA
TERAPIA DELLE
LEUCEMIE E LINFOMI

COMITATO PER
LA VITA
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