UNIKLINIK KÖLN

DEUTSCHE STUDIENGRUPPE

KML SYMPOSIUM: CHRONISCHE LYMPHATISCHE LEUKÄMIE

Barbara Eichhorst

4. Oktober 2021

Potentielle Interessenskonflikte

Forschungsunterstützung:

Roche, Janssen, AbbVie, Gilead, BeiGene, AstraZeneca

Vortragstätigkeit:

Roche, Novartis, Gilead, Janssen, AbbVie, Celgene, Hexal, Adaptive Biotechnologies

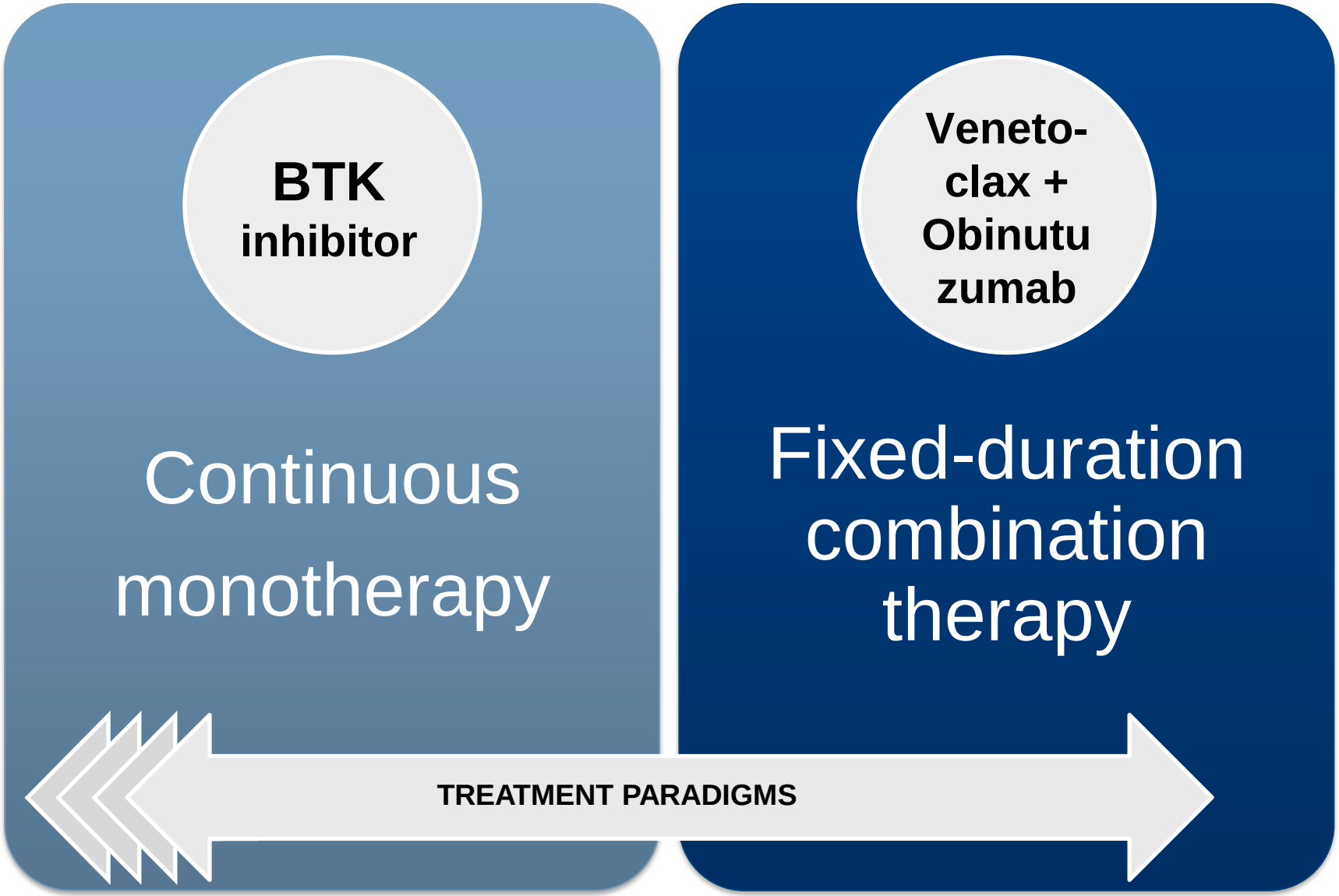
Beratertätigkeit:

Janssen, Roche, Novartis, AbbVie, Gilead, Celgene, ArQule, AstraZeneca, Oxford Biomedica, MSD

CLL first line treatment (updated August 2021)

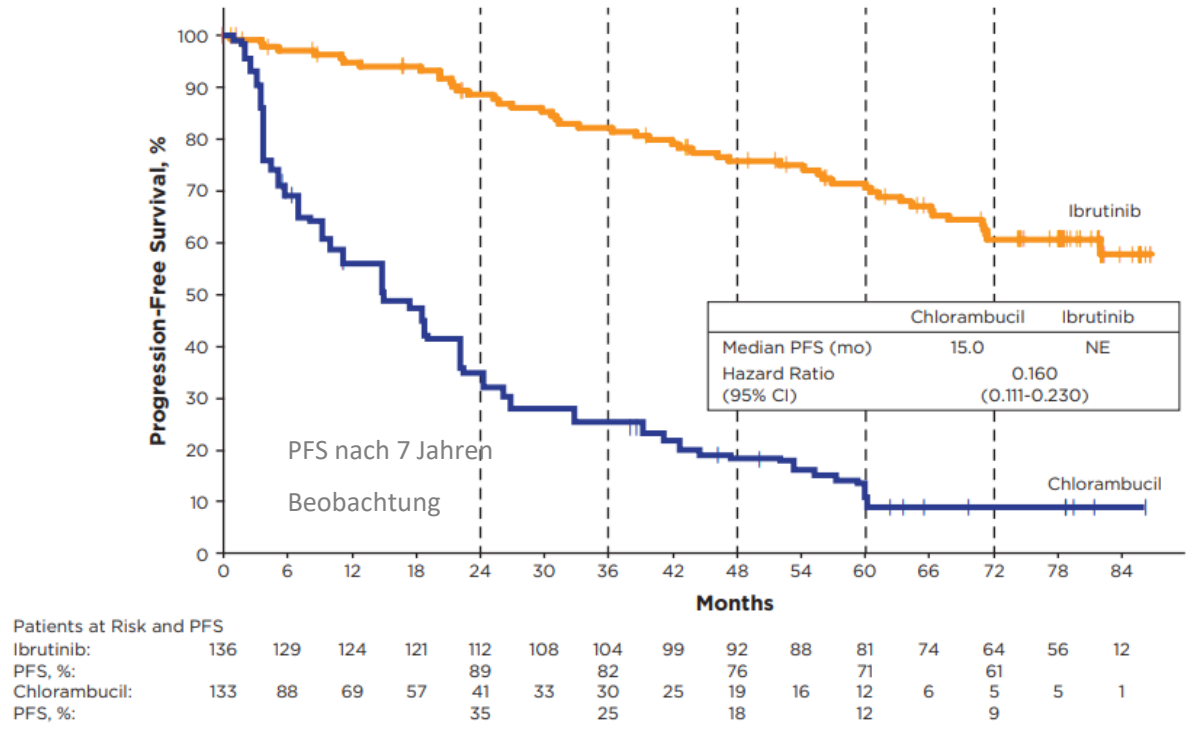
Stage	del(17p) or *TP53*mut	Fitness	IGHV	Therapy
Inactive disease, Binet A-B, Rai 0-II	Irrelevant	Irrelevant	Irrelevant	None
Active disease or Binet C or Rai III-IV	Yes	Irrelevant	Irrelevant	Ibrutinib/Acalabrutinib[1] or Venetoclax + Obinutuzumab or Idelalisib-Rituximab (if contraindications for other options)
	No	Go go	M	FCR (BR above 65 years) or Ibrutinib/Acalabrutinib[1] or Venetoclax + Obinutuzumab[2]
			U	Ibrutinib/Acalabrutinib[1] or FCR (BR above 65 years) or Venetoclax+Obinutuzumab
		Slow go	M	Venetoclax + Obinutuzumab or Ibrutinib/Acalabrutinib[1,2] or Chlorambucil-Obinutuzumab
			U	Venetoclax + Obinutuzumab or Ibrutinib/Acalabrutinib[1,2] + Chlorambucil-Obinutuzumab

1) Addition of obinutuzumab to acalabrutinib may be considered.
2) Consider and discuss with patient: Continuous vs fixed-duration therapy, specific side effects of drug classes (myelosuppression, infections, secondary malignancies for CIT; cardiac toxicity and bleeding for BTKi (Acalabrutinib < Ibrutinib); TLS and infections for Ven-Obi; autoimmune disease and opportunistic infections for Idelalisib.

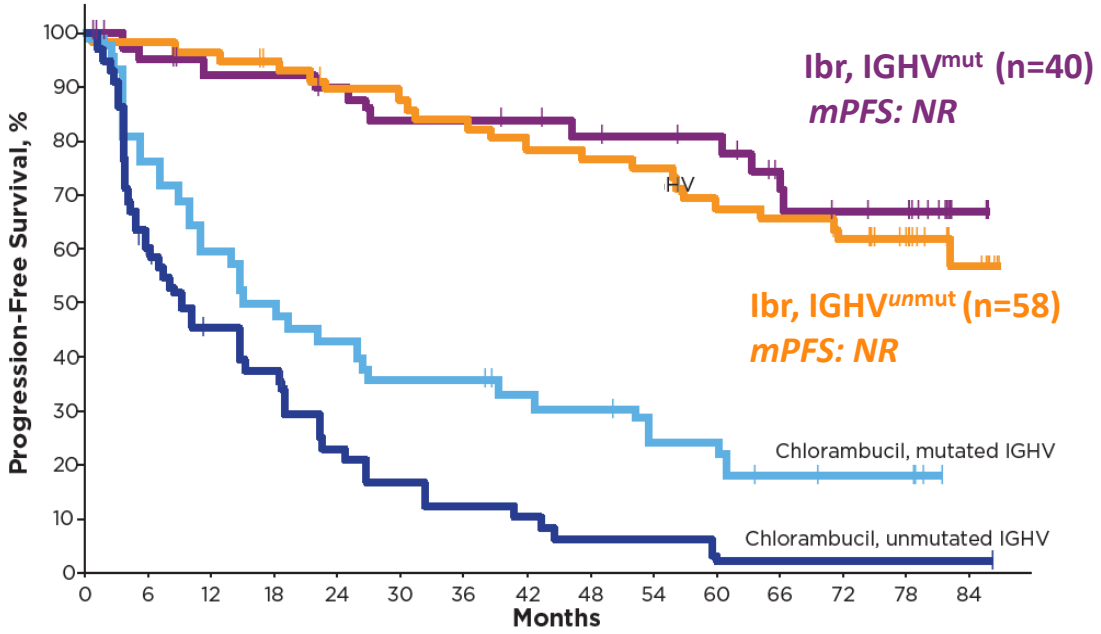

BTK inhibitor
Continuous monotherapy
Veneto-clax + Obinutu zumab
Fixed-duration combination therapy
TREATMENT PARADIGMS

BTK INHIBITOR IBRUTINIB VS CHEMO/-IMMUNTHERAPIE: PFS

RESONATE 2-STUDIE: ERSTLINIE IBRUTINIB VS CHLORAMBUCIL BEI ÄLTEREN PATIENTEN



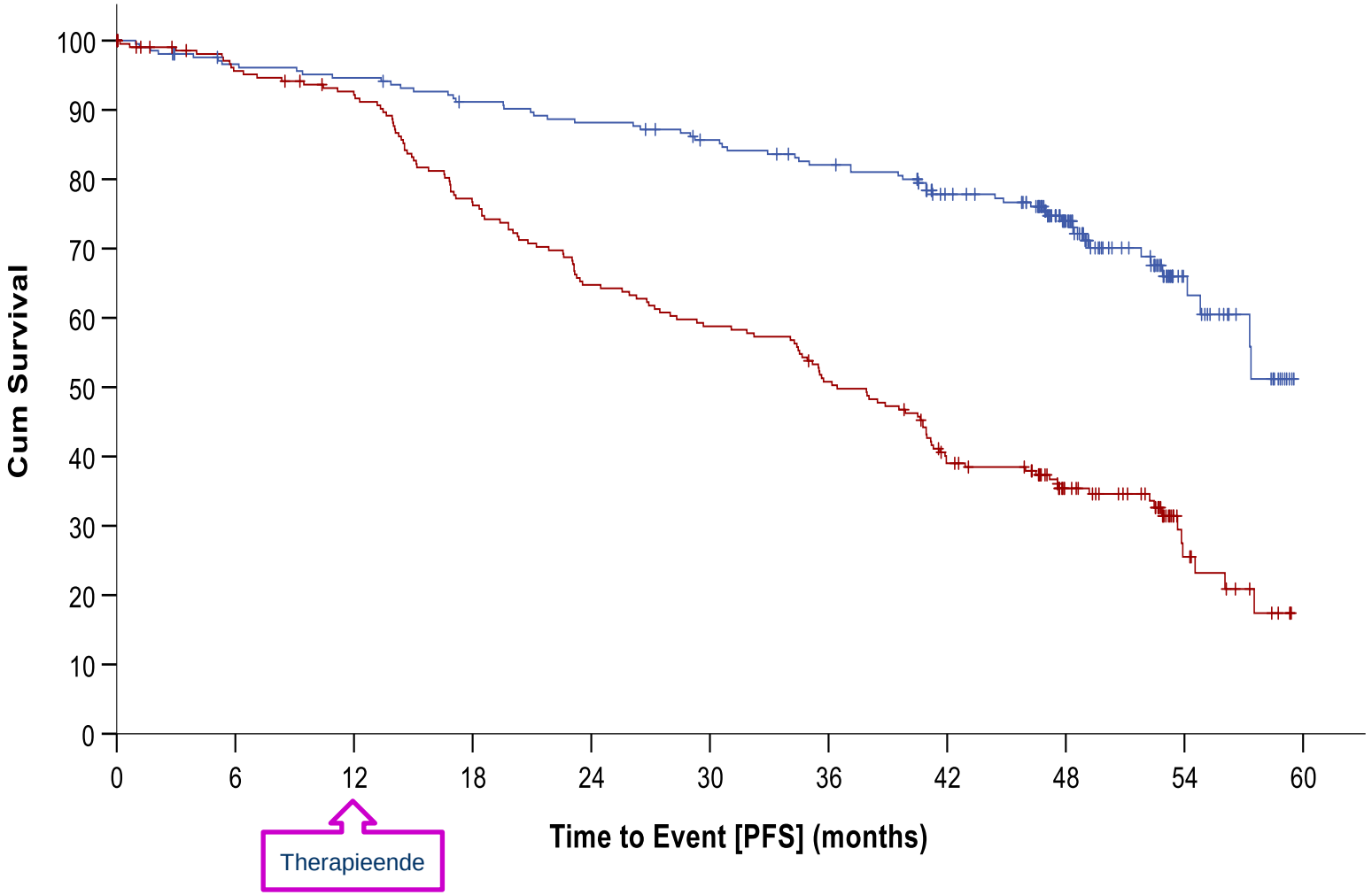
RESONATE 2-STUDIE: PFS NACH IGHV



Ghia P. et al., EHA 2021 Abstract EP 636

CLL14-STUDY: CLB+OBINUTUZUMAB VS. VENETOCLAX PLUS OBIN.

PFS after median observation time 52.4 months



Median PFS

Ven-Obi: not reached

Clb-Obi: 36.4 months

4-year PFS rate

Ven-Obi: 74.0%

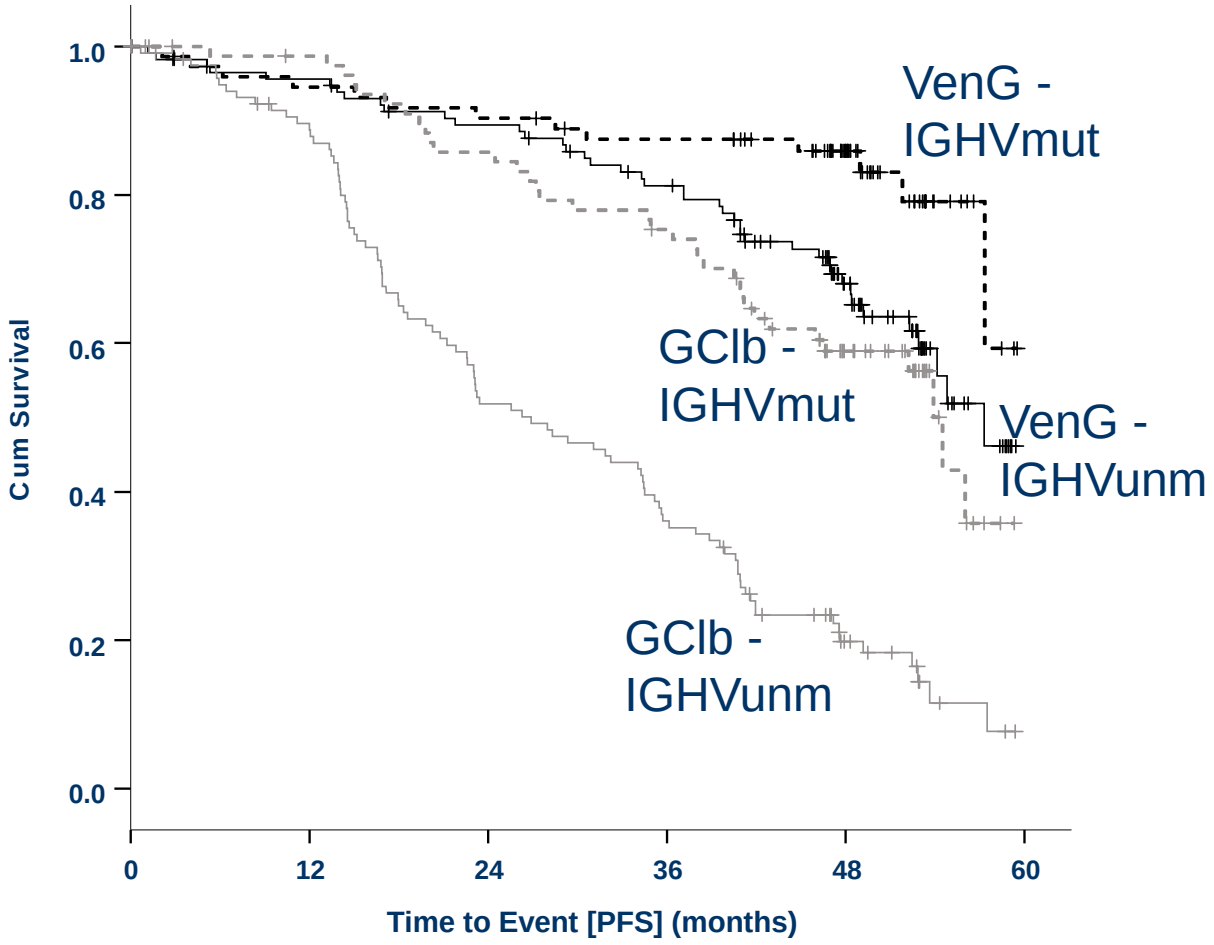
Clb-Obi: 35.4%

HR 0.33, 95% CI [0.25-0.45] **P<0.0001**

Al Sawaf O et al. Oral presentation. EHA 2021. Abstract 146

CLL14-STUDY: CLB+OBINUTUZUMAB VS. VENETOCLAX PLUS OBIN.

PFS according to IGHV Status



VenG vs. GClb in dependence of IGHV status

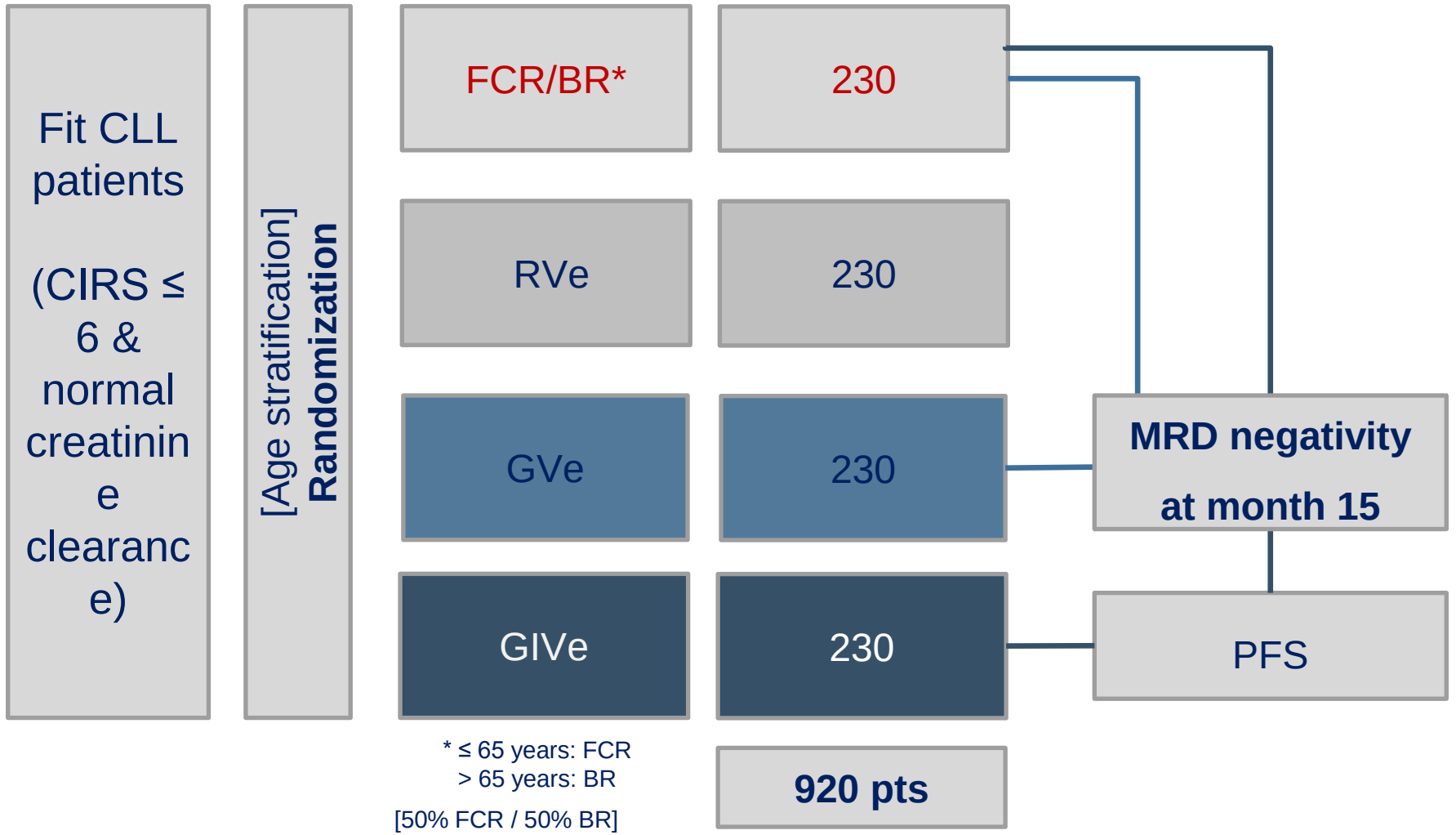
IGHVunm - VenG
IGHVunm - GClb
HR 0.25 (95%CI 0.17-0.37)

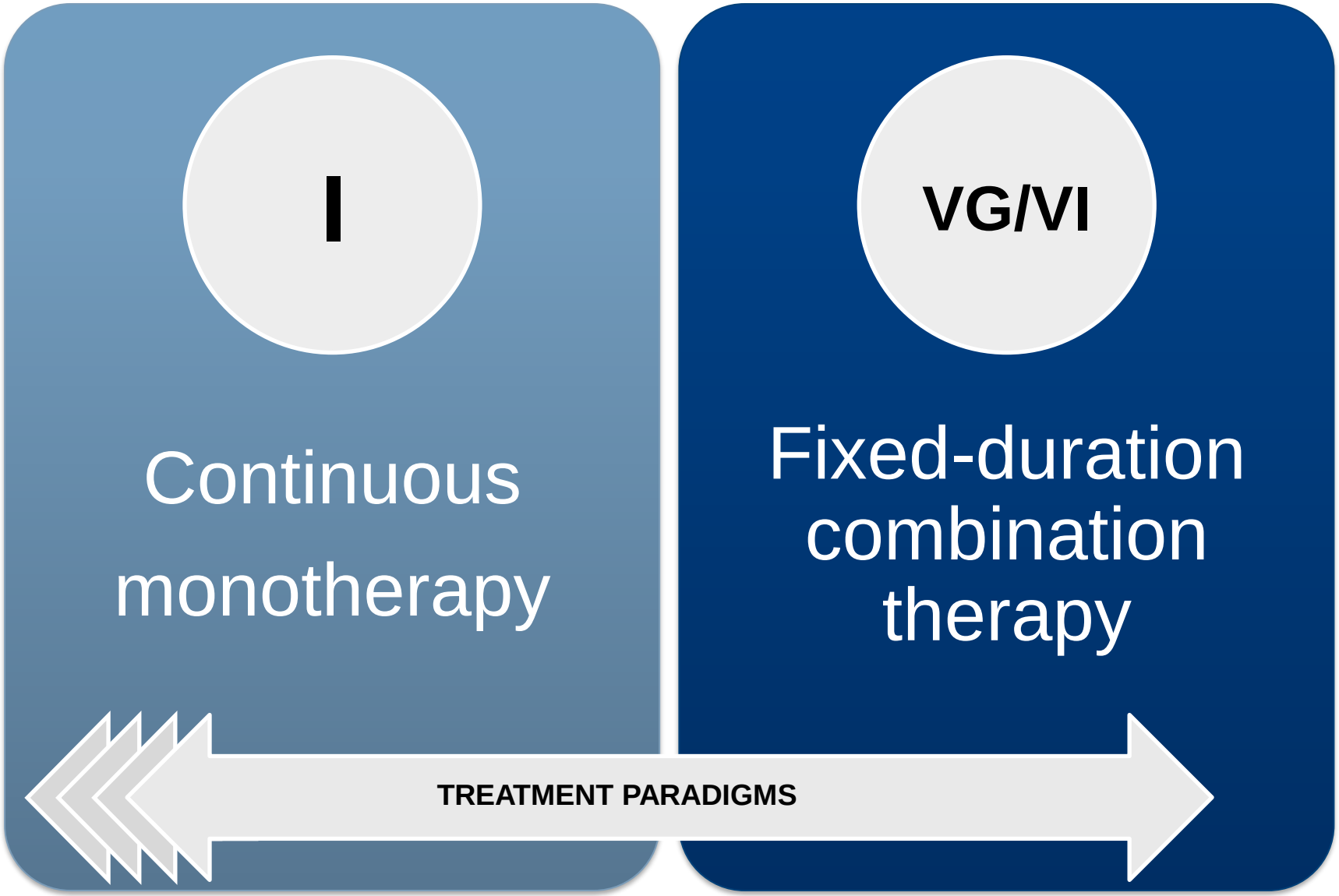
IGHVmut - VenG
IGHVmut - GClb
HR 0.36 (95%CI 0.19-0.68)

Al Sawaf O et al. Oral presentation. EHA 2021. Abstract 146

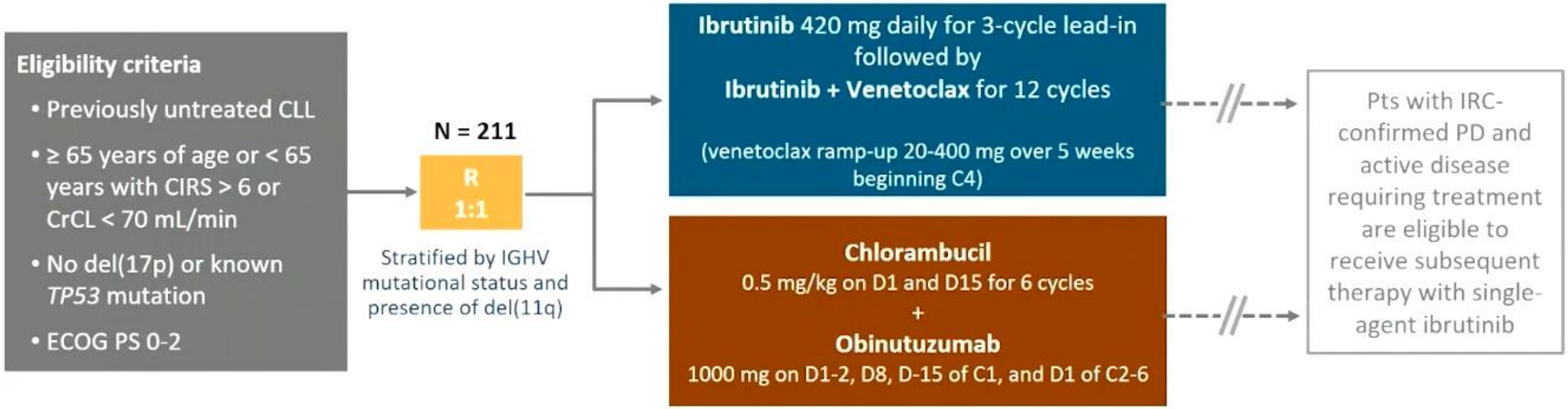
Fit Patients: GAIA Study/CLL13

Standard chemoimmunotherapy vs. ABT-199 + R vs. ABT-199 + G vs. ABT-199 + I + G




I
Continuous monotherapy
VG/VI
Fixed-duration combination therapy
TREATMENT PARADIGMS

Kombination BTK Inhibitor Ibrutinib + Bcl2 Inhibitor Venetoclax

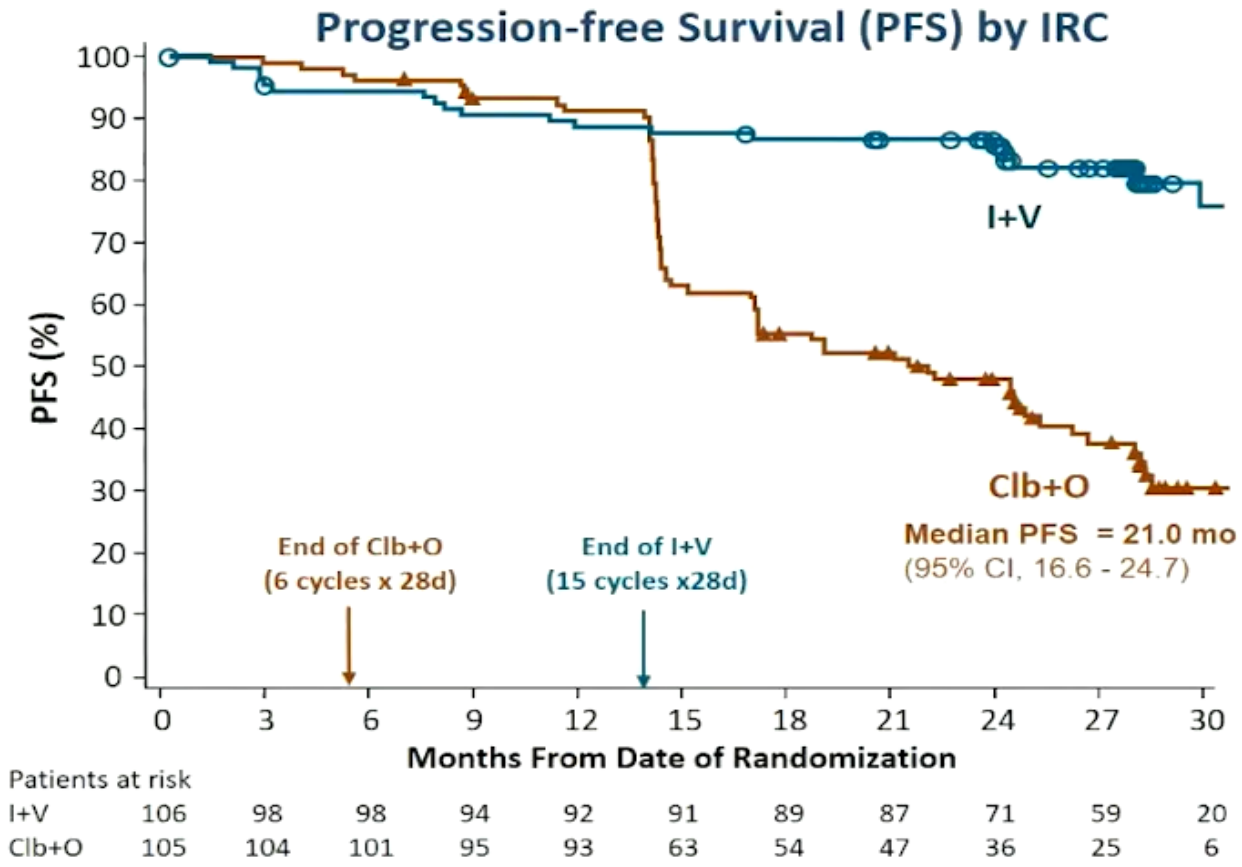


Primary end point: Progression-free survival by independent review committee (IRC)

- 71 PFS events to detect an effect size with an HR = 0.5 (80% power at a 2-sided significance level of 0.05)

Kater et al. , EHA 2021. Abstract LBA 1902

Glow-Studie (IV vs. ClbObin): PFS nach 27.7 Monaten



Kater et al. , EHA 2021. Abstract LBA 1902

CLL17

A PROSPECTIVE, RANDOMIZED, OPEN-LABEL, MULTICENTRE PHASE-III TRIAL OF **IBRUTINIB** VERSUS **VENETOCLAX PLUS OBINUTUZUMAB** VERSUS **IBRUTINIB PLUS VENETOCLAX** FOR PATIENTS WITH PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKAEMIA

Patients with previously untreated CLL

Incl. fit and unfit patients
Incl. patients with del17p/TP53 mut

1:1:1 Randomization

Stratification according to fitness, del17p/TP53, IGHV

Ibrutinib

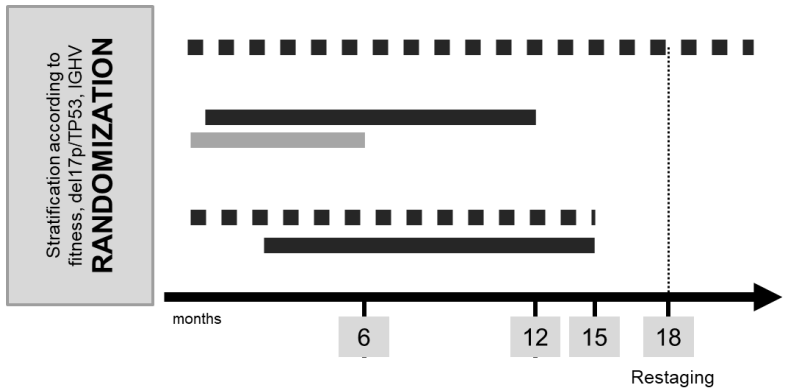
Venetoclax Obinutuzumab

Venetoclax Ibrutinib

897 patients

Primary endpoint:
Progression-free survival

TREATMENT SCHEDULE



Ibrutinib d1 420 mg po daily until PD or intolerance

Venetoclax 400 mg po daily (c1 d22 – c12 d28)
Obinutuzumab 1000 mg iv (c1 d1(2)/8/15, c 2-6 d1)

Ibrutinib 420 mg po daily (c1 d1 – c15 d28)
Venetoclax 400 mg po daily (c4 d1 – c15 d28)

TIMELINES

Start of recruitment	Q4/2020
Expected end of recruitment	Q4/2023
End of study	Q1/2027

DEUTSCHE STUDIENGRUPPE CLL

Nordic CLL Study Group

cancer trials ireland

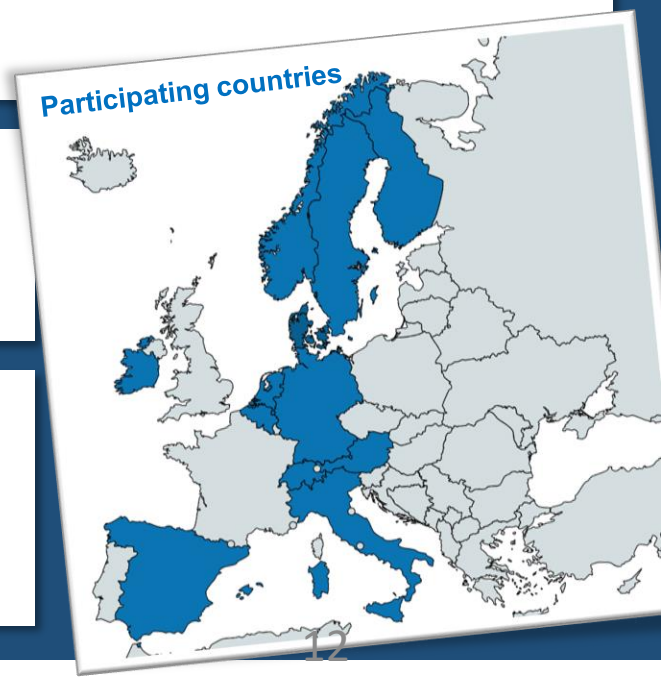
The Israeli CLL Association (ICLLA)
CLL
The Israeli CLL Study Group (ICLLSG)

HOVON

GELLC Grupo Español de Leucemia Linfocítica Crónica

fondazione GIMEMA FRANCO MANDELLI

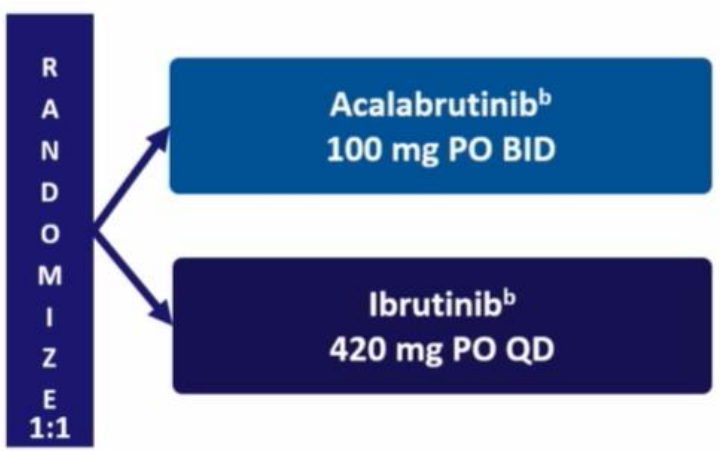
SAKK

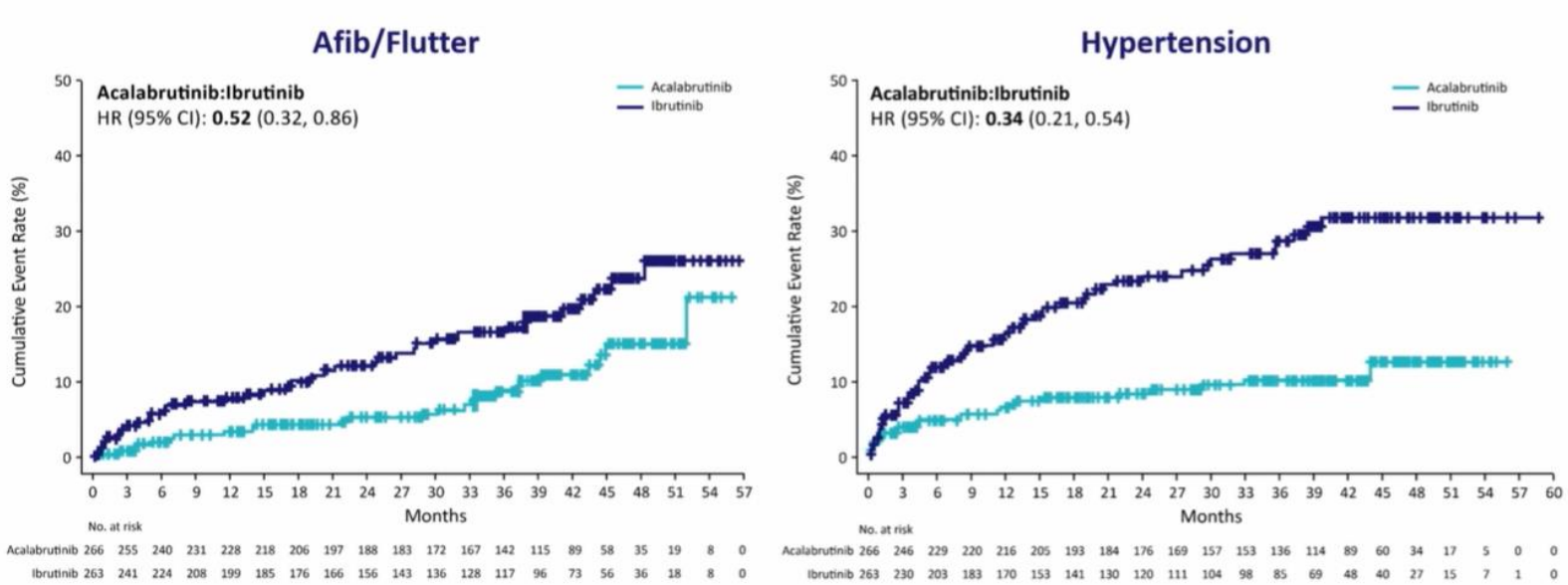


BTK Inhibitoren Ibrutinib vs Acalabrutinib

Welche Rolle spielt das unterschiedliche Nebenwirkungsspektrum?

Direkter Vergleich Acalabrutinib vs. Ibrutinib: ELEVATE RR - Studie

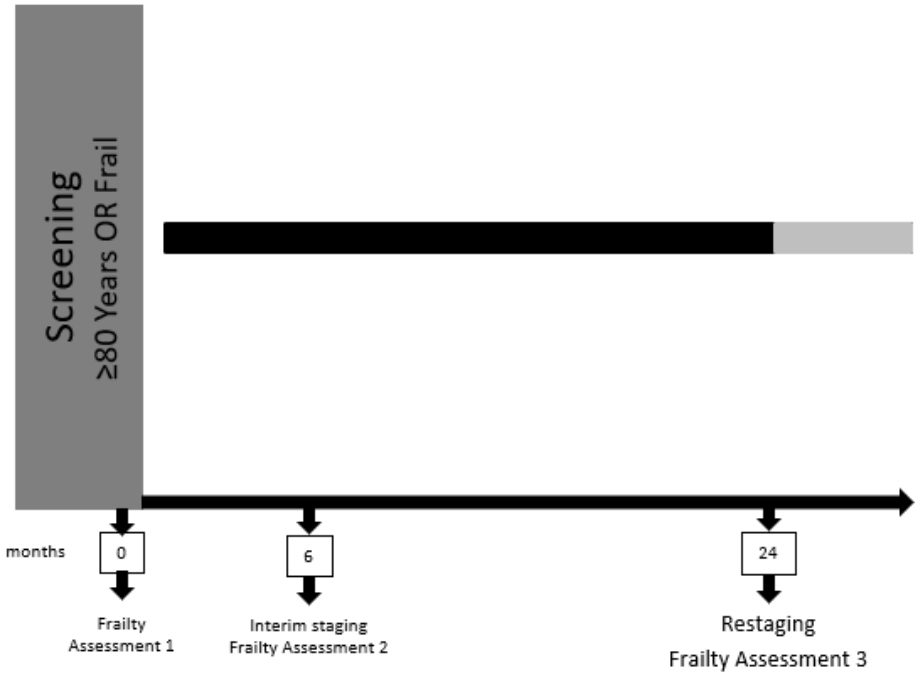




Hillmen P et al. Oral presentation. EHA 2021. Abstract S145

CLL-FRAIL STUDY

- Prospective, multicenter, single-arm phase-II study
- **50** eligible patients to be included in 20 sites in Germany and Austria
- Target population:
  - Pts very old (≥80y) AND/OR frail patients
  - treatment-naive or relapsed/ refractory CLL (prior line)



Acalabrutinib 100mg p.o BID until PD

Initial response assessment:

Cycle 7 day 1

Final Restaging:

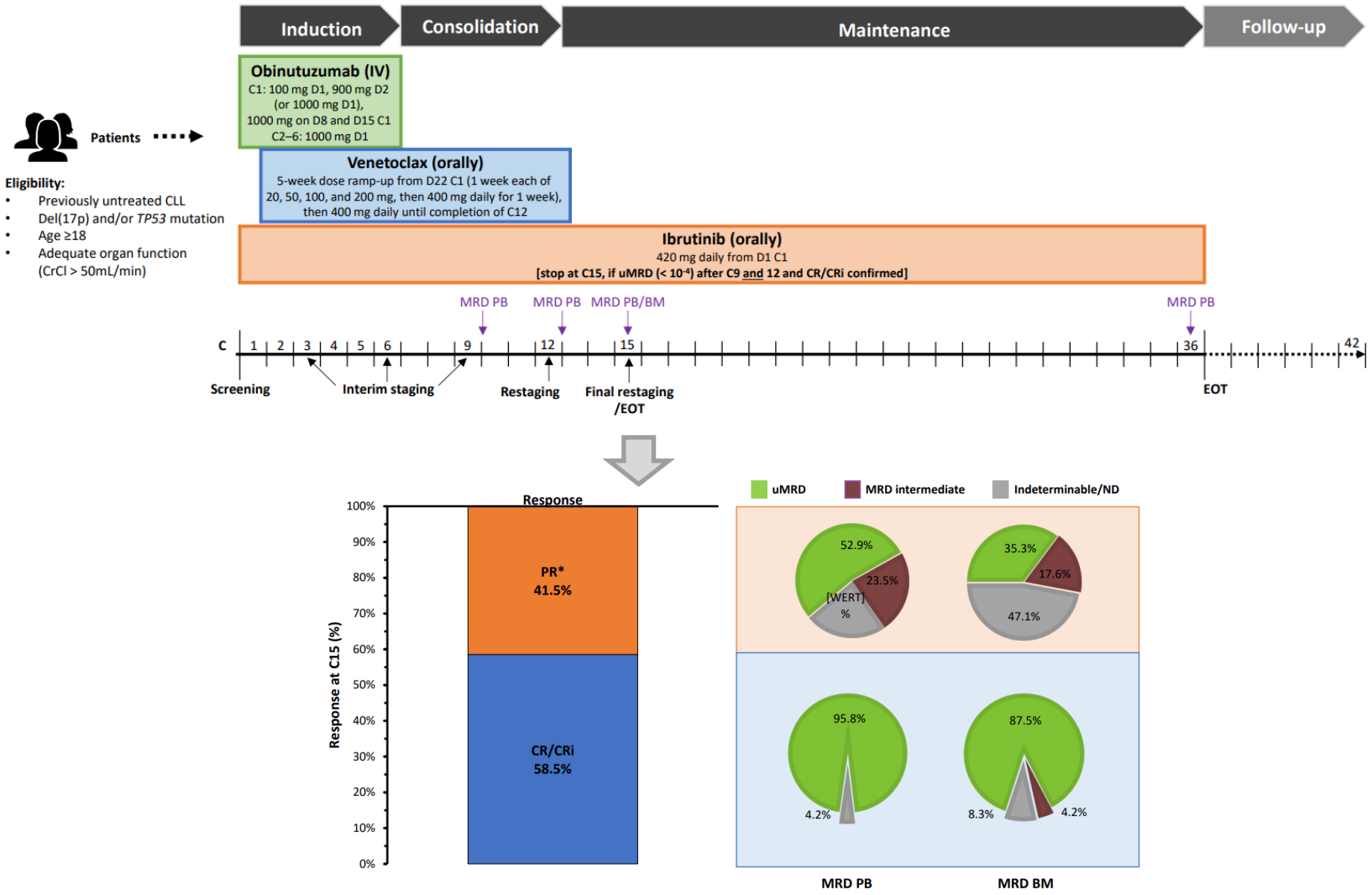
Cycle 25 day 1

Stellenwert von Triplekombinationen ?

Höchstrisiko-CLL mit *TP53* Mutation und del(17p)

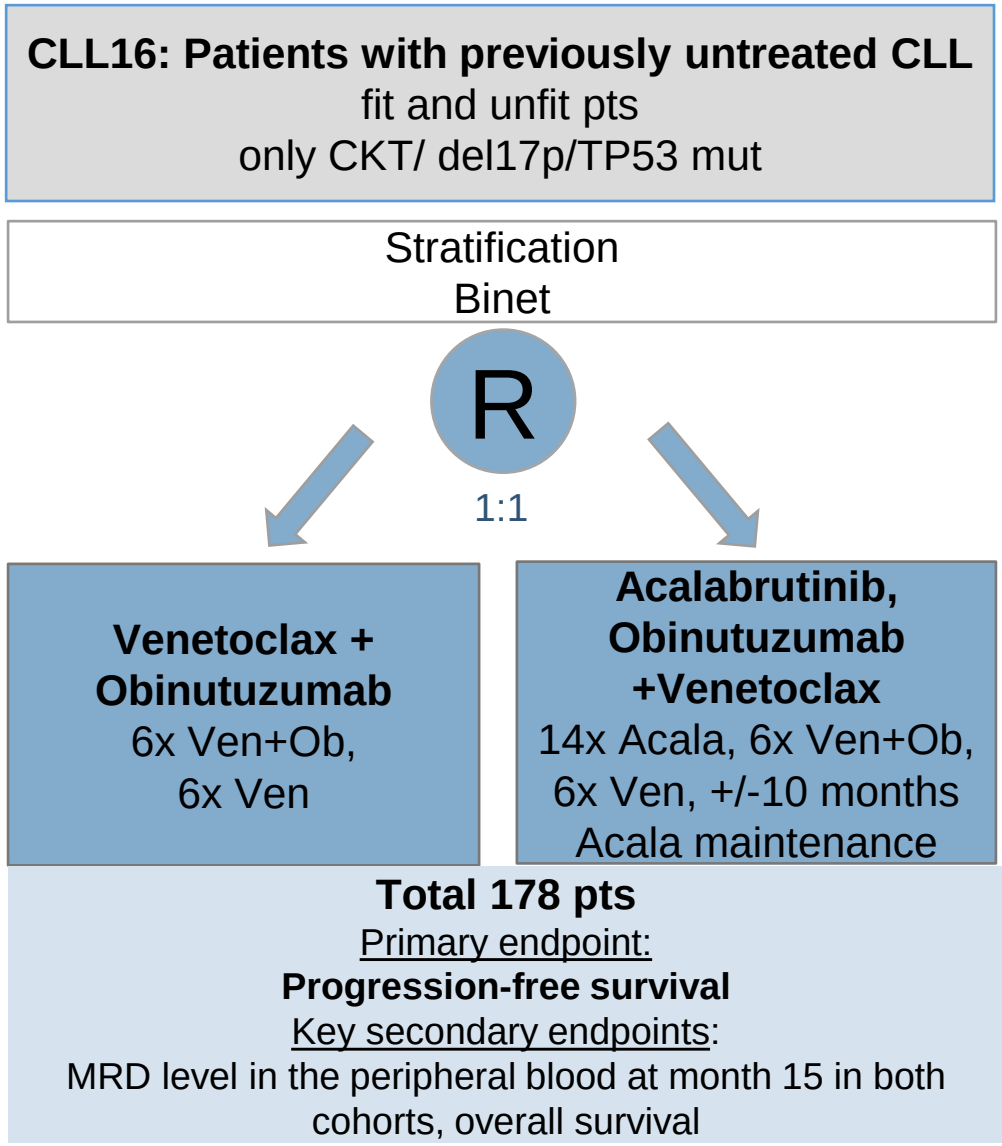
Rezidivierte CLL

CLL2 GIVE STUDY OF THE GCLLSG:
Evaluating triple combination in high risk CLL



Huber H.,.....Stilgenbauer S.: Oral presentation. EHA 2020, submmitted

CLL 16 STUDY OF THE GCLLSG:
Evaluating time limited combination therapies in high risk CLL



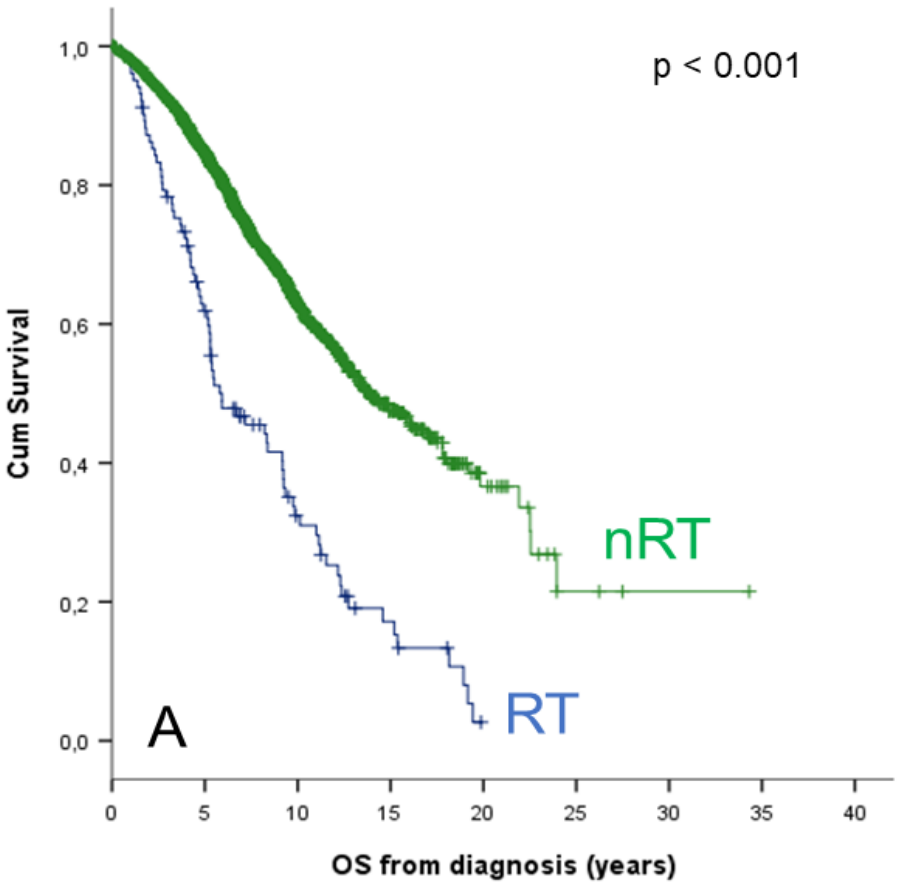
Worst case scenario

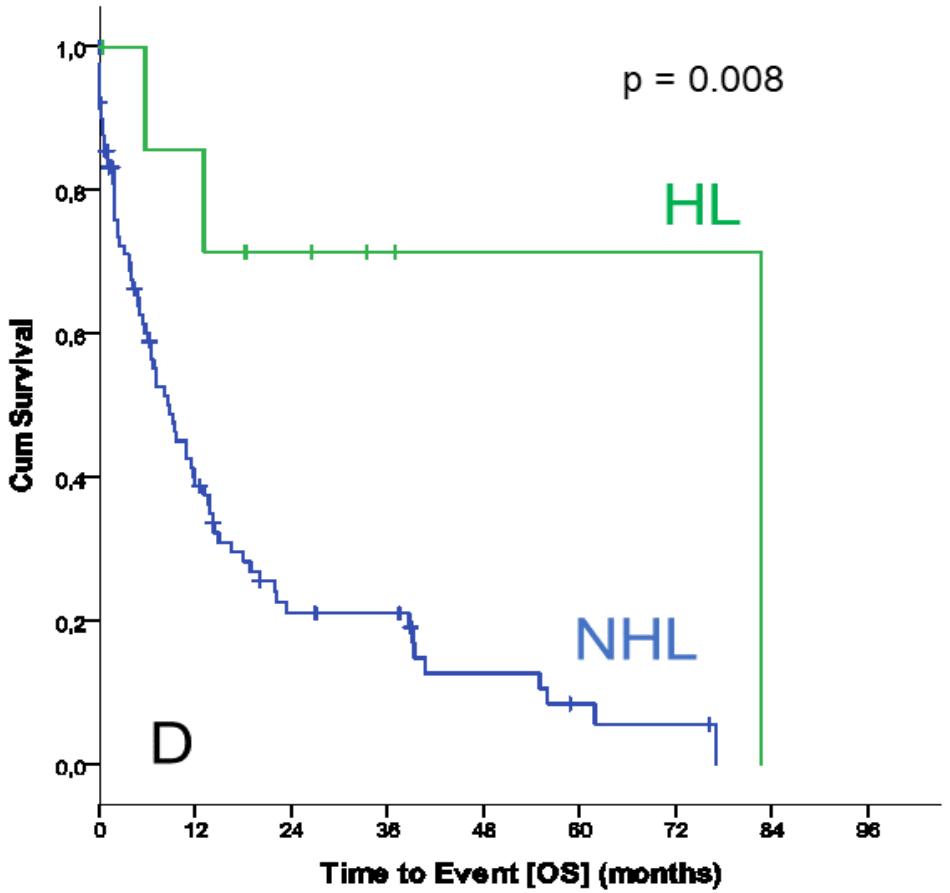
Richter Transformation:

DLBCL

Hodgkin Lymphom

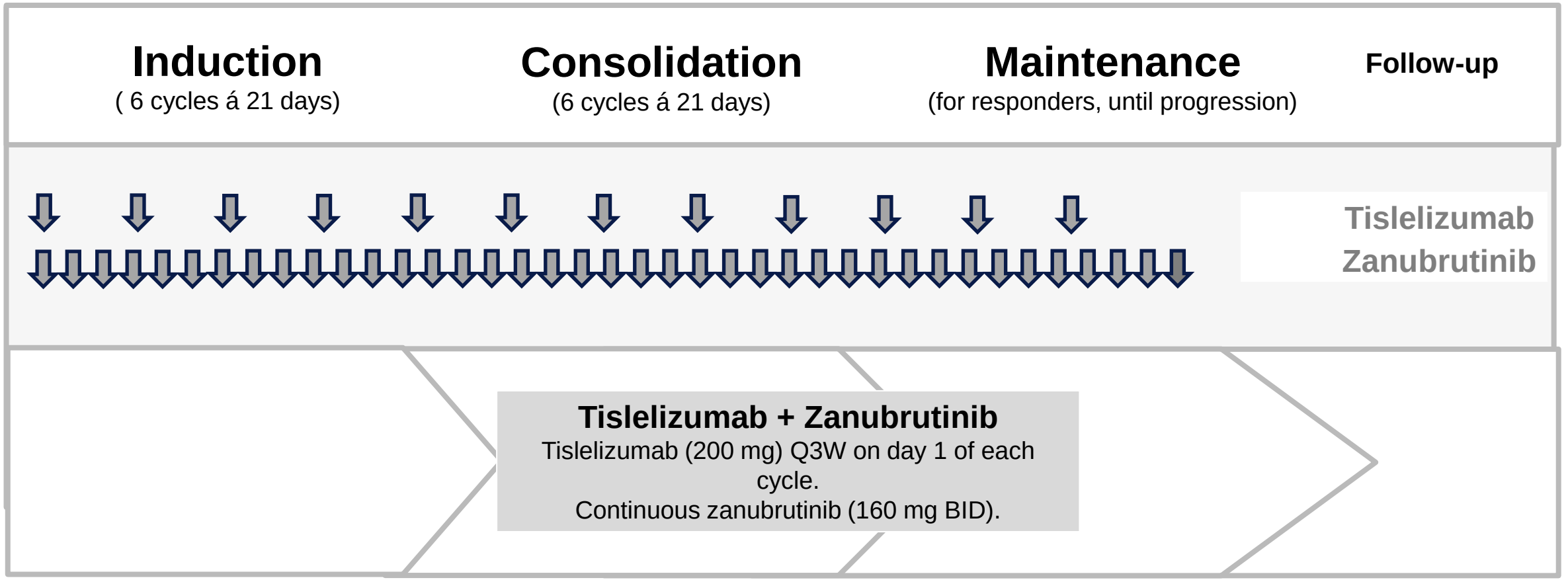
Worst case scenario RT: Pooled analysis of the GCLLSG





Al Sawaf et al. , Leukemia 2020

RT1-Studie der DCLLSG



DCLLSG Clinical Trials Juni 2021

DEUTSCHE STUDIENGRUPPE

Planned

CLL16
Treatment naive High Risk
Venetoclax-Obinutuzumab vs
Acalabrutinib-Venetoclax-
Obinutuzumab
Q4/2021

CLL LOXO
Pirtobrutinib vs
Pirtobrutinib+Venetoclax for
relapsed CLL

CLL ReVenG
Venetoclax-Obinutuzumab
retreatment for relapsed CLL
Q4/2021

CLL Y1-TOSO
Anti-FCμR CAR-T cells in CLL
Q2/2022

Recruiting

CLL17
Treatment Naive
Ibrutinib vs Venetoclax-
Obinutuzumab vs Ibrutinib-
Venetoclax

CLL-Frail
Very old or frail
Acalabrutinib

CLL2-BZAG
Relapse
Benda Debulking, Obi-Ven-
anubrutinib Induction, Obi-Ven-Z
Maintenance

CLL2-BAG
Relapse
Benda Debulking,Obi-Ven-
ZAnunrutinib Induction, Obi-Ven-Z
Maintenance

CLL-RT1
Richter's Transformation
Zanubutinib plus Tislelizumab

Follow-up

CLL12
Risk of Early Progression
Ibru vs. Placebo
Low Risk Watch&Wait

CLL13
Go Go
FCR/BR vs Ven-R vs Ven-Obi vs Ven-
Obi-Ibru

CLL14
Slow Go
Ven-Obi vs CLB-Obi

CLL2-BAAG
Relapse
Benda Debulking, Obi-Ven-
calabrutinib Induction, Obi-Ven-A
Maintenance

CLL2-GIVe
High Risk
17p(del)+ TP53 mut:
Ven-Obi-Ibru

CLL2-BCG
Relapse 17pdel, TP53mut
Benda Debulking,Idela+Obi
Induction, Idela+Obi Maintenance

CLLR 3
Relapse
Max. 3 Pretreatments
Induction: Benda-Obinutuzumab
Obi- Maintenance

International trials in cooperation with collaborative/academic partners in other countries

GCLLSG Registry
All patients with CLL, SLL, B-PLL, T-PLL, LGL, Richter's Syndrome, HCL


Moritz Fürstenau
Timo Kuchheuser
Christina Rhein
Angelina Glatt
Florian Simon
Adam
Jörn H.
Anna Fink
Janina Stumpf
Can Zhang
Michael Hallek
Kirsten Fischer
Olga Korf
Gabriele Kranz
Sandra Robrecht
Clemens Wendtner
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Paula Cramer
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Gabriele Strache
Lisa Engel
Florian

Thank you!