Kompetenznetz Maligne Lymphome

# Lymphom Kompetenz KOMPAKT

KML KONGRESSE

Expert:innen berichten zu Lymphomen & Leukämien

## 66th ASH Meeting 2024

## San Diego & virtuell

Kompetenznetz Maligne Lymphome

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**Prof. Dr. med. Barbara Eichhorst**
Klinik I für Innere Medizin | Uniklinik Köln

# Chronische lymphatische Leukämie (CLL)

# Offenlegung potentieller Interessenskonflikte

LymphomKompetenz KOMPAKT – ASH2024 wird in Kooperation mit sieben unterstützenden Firmen durchgeführt.
Meine persönlichen Disclosures betreffen:

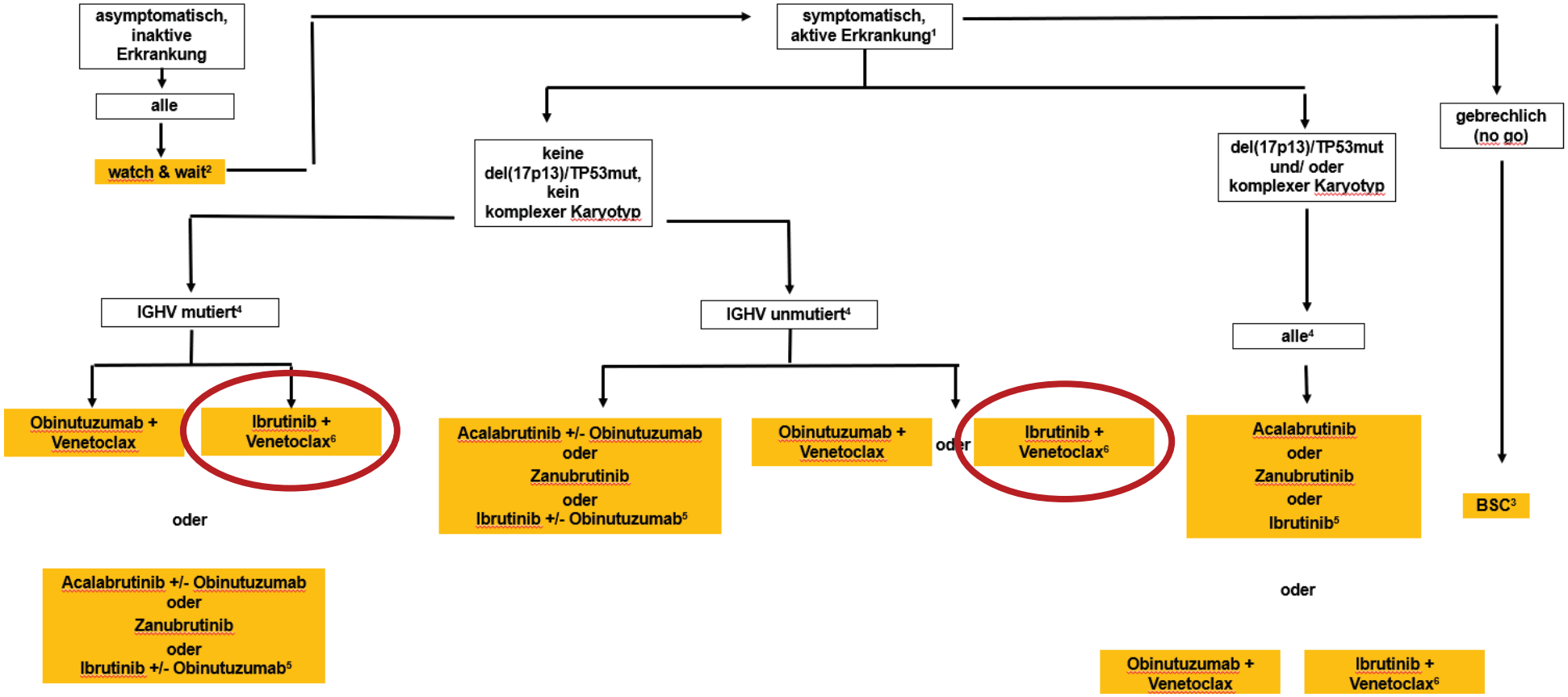
| | |
|---|---|
| **Anstellungsverhältnis, Führungsposition** | - |
| **Beratungs-/ Gutachtertätigkeit** | **Janssen, AbbVie, AstraZeneca, BeiGene, MSD, Lilly, Galapagos** |
| **Besitz von Geschäftsanteilen, Aktien oder Fonds** | - |
| **Patent, Urheberrecht, Verkaufslizenz** | - |
| **Honorare** | **Roche, AbbVie, BeiGene, AstraZeneca, MSD, Lilly** |
| **Finanzierung wissenschaftlicher Untersuchungen** | **Janssen, Roche, AbbVie, BeiGene, AstraZeneca** |
| **Andere finanzielle Beziehungen** | - |
| **Immaterielle Interessenkonflikte** | Leitung der DCLLSG |

# Kapitel 1

Erstlinientherapie der CLL mit Venetoclax + BTKi

# Erstlinientherapie der CLL

## Onkopediaguidelines nach Update 2024




Clemens-Martin Wendtner et al., Onkopedia (www.onkodeia.com) by Sep 2024

# AMPLIFY Studie: Acalabrutinib/Venetoclax vs Acalabrutinib/Venetoclax/Obinutuzumab vs FCR or BR

**1009 Fixed-Duration Acalabrutinib Plus Venetoclax with or without Obinutuzumab Versus Chemoimmunotherapy for First-Line Treatment of Chronic Lymphocytic Leukemia: Interim Analysis of the Multicenter, Open-Label, Randomized, Phase 3 AMPLIFY Trial**

J. Brown, Dana Faber Cancer Institute Boston, US

# AMPLIFY -Studie

## Studiendesign

**TN CLL (N=867)**

**Key inclusion criteria**
- Age ≥18 years
- TN CLL requiring treatment per iwCLL 2018 criteria[1]
- Without del(17p) or *TP53*[a]
- ECOG PS ≤2

**Key exclusion criteria**
- CIRS-Geriatric >6
- Significant cardiovascular disease

**Stratification**
- Age (>65 vs ≤65 years)
- IGHV mutational status
- Rai stage (≥3 vs <3)
- Geographic region

AMPLIFY: randomized, multicenter, open-label, Ph 3 trial

RANDOMIZE 1:1:1

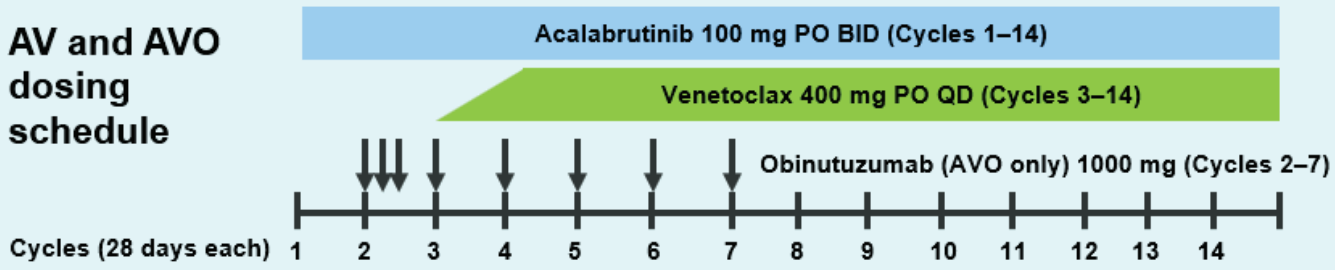
- AV (14 cycles)
- AVO (14 cycles)
- FCR/BR (6 cycles)

*Crossover not built into protocol*

**Primary endpoint**: IRC-assessed PFS (AV vs FCR/BR)

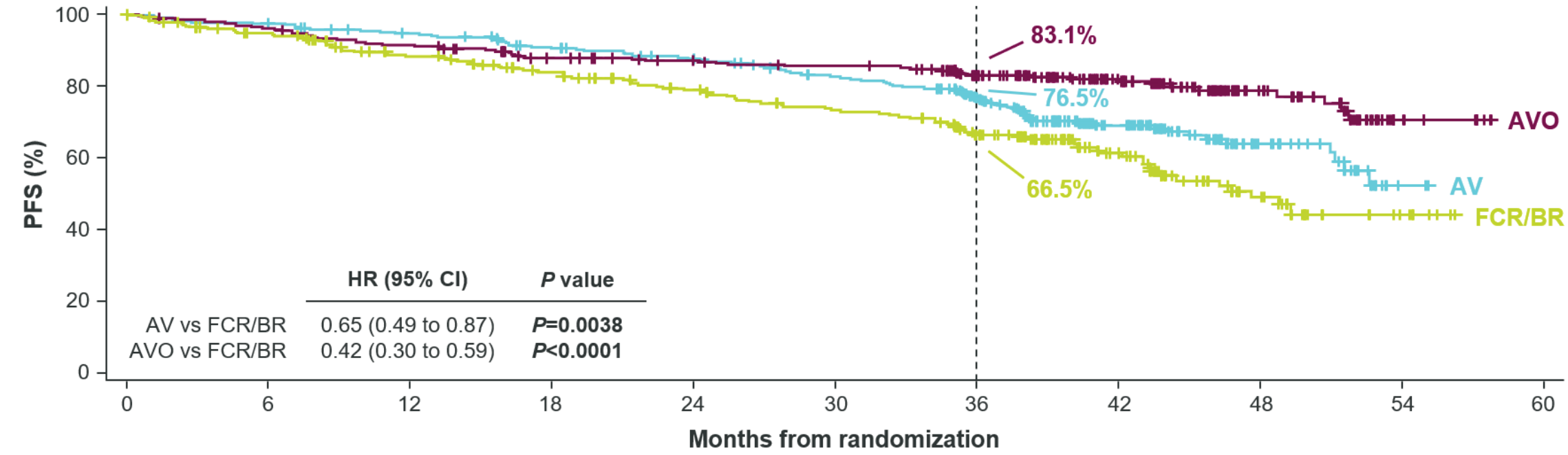
If primary endpoint met, secondary endpoints tested in fixed sequential hierarchy:
1) IRC-PFS (AVO vs FCR/BR)
2) uMRD (AV vs FCR/BR)
3) uMRD (AVO vs FCR/BR)
4) OS (AV vs FCR/BR)
5) OS (AVO vs FCR/BR)

**AV and AVO dosing schedule**



# AMPLIFY -Studie

## Primärer Endpunkt: PFS

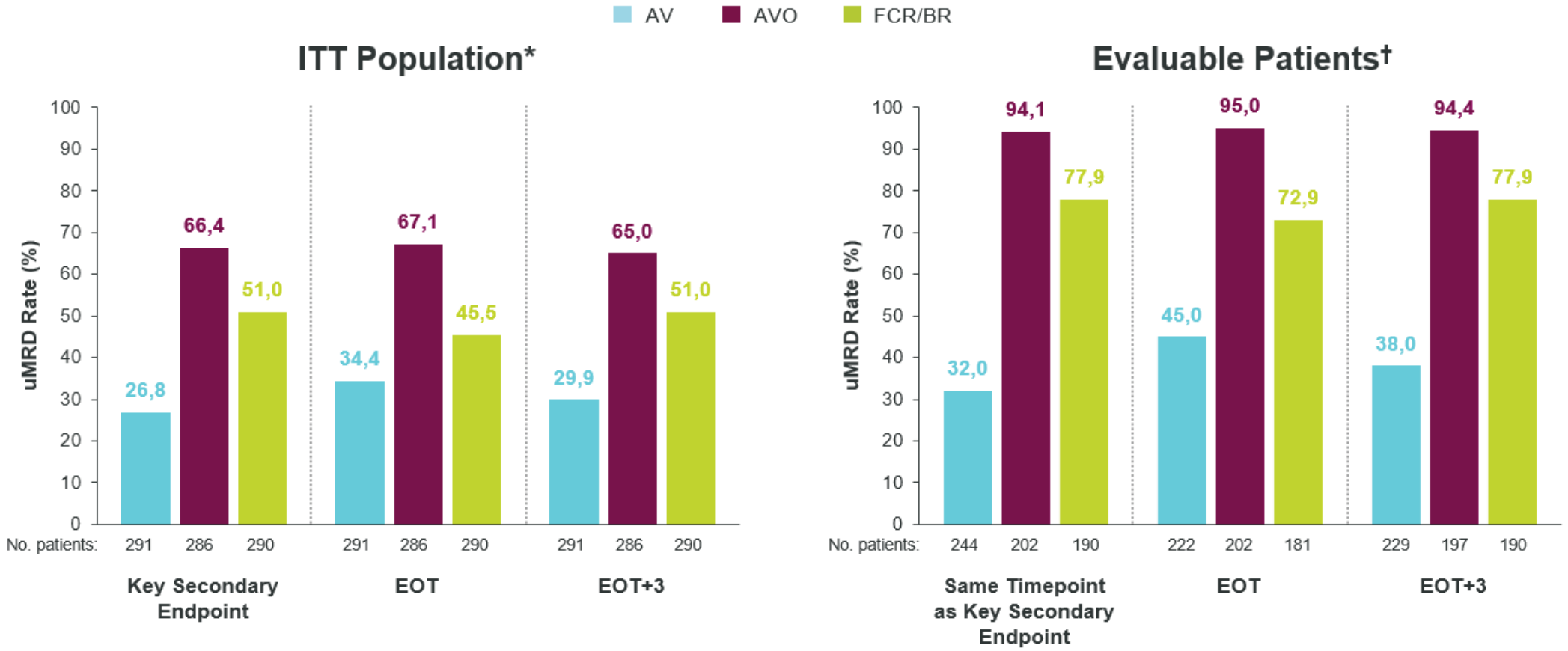



**Patients at risk**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| AV | 291 | 282 | 269 | 251 | 237 | 219 | 177 | 102 | 35 | 3 | 0 |
| AVO | 286 | 272 | 258 | 237 | 225 | 219 | 191 | 116 | 51 | 7 | 0 |
| FCR/BR | 290 | 236 | 208 | 189 | 170 | 154 | 127 | 66 | 28 | 6 | 0 |

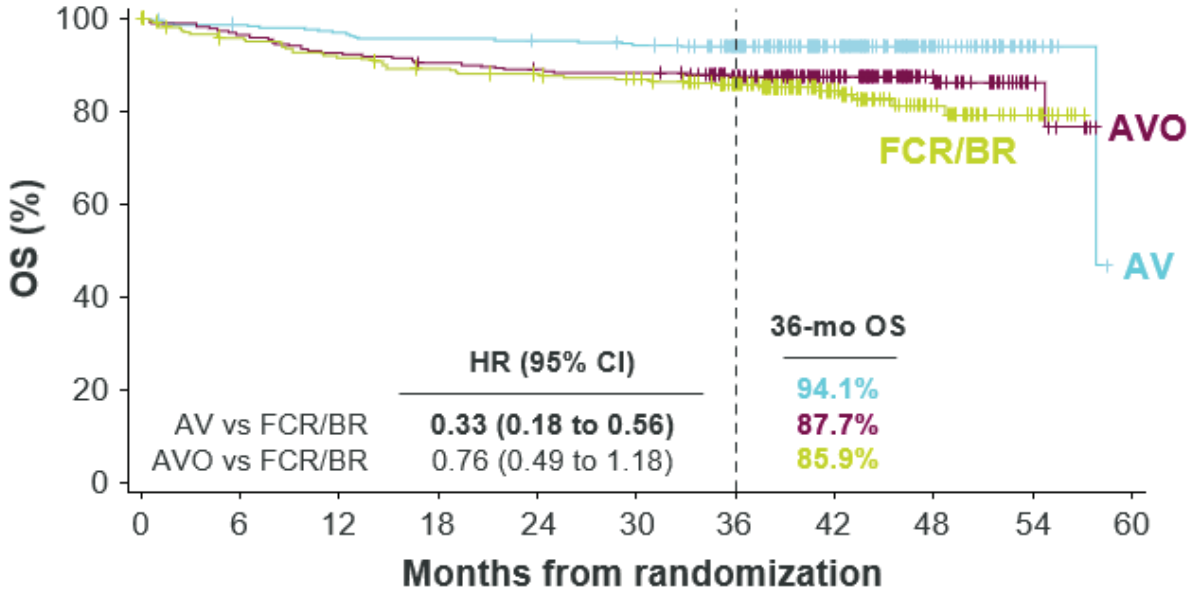
# AMPLIFY -Studie

## Minimal residual disease (MRD) nach Durchflusszytometrie



# AMPLIFY -Studie

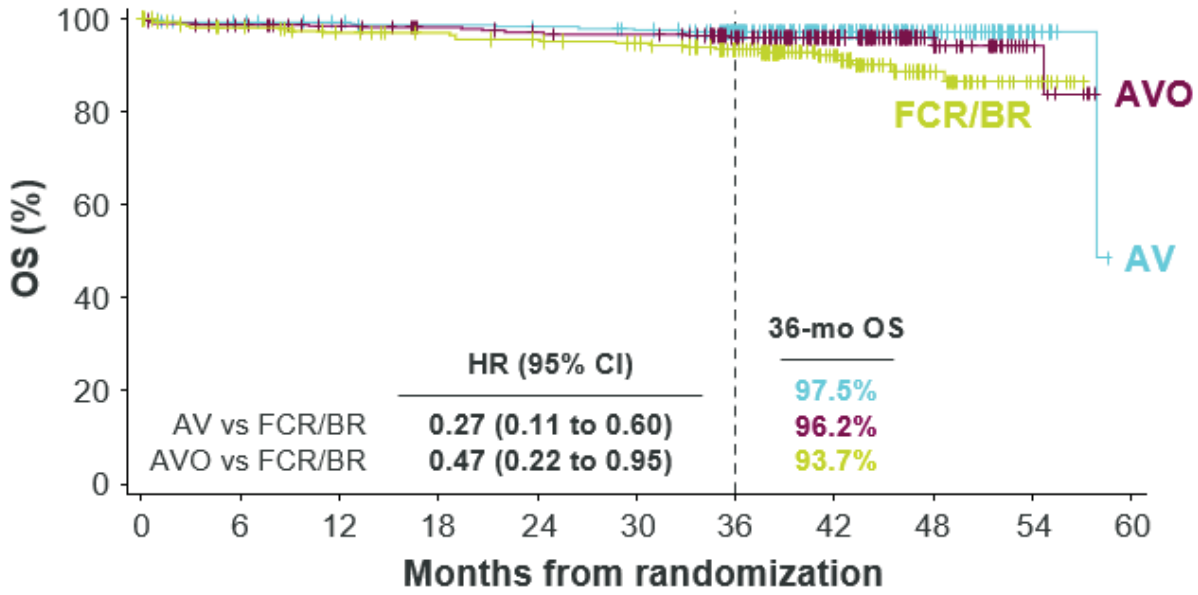
## With AV vs FCR/BR




**Patients at risk**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| AV | 291 | 286 | 281 | 277 | 275 | 270 | 233 | 142 | 58 | 10 | 0 |
| AVO | 286 | 276 | 265 | 257 | 252 | 250 | 223 | 143 | 64 | 10 | 0 |
| FCR/BR | 290 | 247 | 236 | 228 | 223 | 217 | 182 | 98 | 45 | 13 | 0 |

## With AV and AVO vs FCR/BR (COVID-19 Deaths Censored)




**Patients at risk**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| AV | 291 | 286 | 281 | 277 | 275 | 270 | 233 | 142 | 58 | 10 | 0 |
| AVO | 286 | 276 | 265 | 257 | 252 | 250 | 223 | 143 | 64 | 10 | 0 |
| FCR/BR | 290 | 247 | 236 | 228 | 223 | 217 | 182 | 98 | 45 | 13 | 0 |

**COVID-19 deaths: 10 (AV), 25 (AVO), 21 (FCR/BR)**

ITT population

# AMPLIFY -Studie

## Nebenwirkungen: alle

| | AV (n=291) | | AVO (n=284) | | FCR/BR (n=259) | |
|---|---|---|---|---|---|---|
| Preferred Term | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| Neutropenia | 90 (30.9) | 78 (26.8) | 114 (40.1) | 100 (35.2) | 99 (38.2) | 84 (32.4) |
| Diarrhea | 95 (32.6) | 5 (1.7) | 103 (36.3) | 4 (1.4) | 28 (10.8) | 1 (0.4) |
| Headache | 102 (35.1) | 4 (1.4) | 80 (28.2) | 1 (0.4) | 20 (7.7) | 1 (0.4) |
| Nausea | 43 (14.8) | 0 | 62 (21.8) | 2 (0.7) | 93 (35.9) | 0 |
| Infusion-related reaction | 0 | 0 | 56 (19.7) | 6 (2.1) | 85 (32.8) | 9 (3.5) |
| COVID-19 | 55 (18.9) | 8 (2.7) | 58 (20.4) | 19 (6.7) | 6 (2.3) | 4 (1.5) |
| Pyrexia | 17 (5.8) | 1 (0.3) | 44 (15.5) | 5 (1.8) | 47 (18.1) | 6 (2.3) |
| Contusion | 40 (13.7) | 0 | 44 (15.5) | 0 | 4 (1.5) | 0 |
| Neutrophil count decreased | 18 (6.2) | 16 (5.5) | 29 (10.2) | 29 (10.2) | 27 (10.4) | 22 (8.5) |
| Thrombocytopenia | 13 (4.5) | 4 (1.4) | 24 (8.5) | 17 (6.0) | 33 (12.7) | 22 (8.5) |
| COVID-19 pneumonia | 21 (7.2) | 16 (5.5) | 35 (12.3) | 33 (11.6) | 7 (2.7) | 7 (2.7) |
| Febrile neutropenia | 5 (1.7) | 5 (1.7) | 7 (2.5) | 7 (2.5) | 24 (9.3) | 24 (9.3) |
| Anemia | 20 (6.9) | 11 (3.8) | 13 (4.6) | 6 (2.1) | 25 (9.7) | 17 (6.6) |

# AMPLIFY -Studie

## Nebenwirkungen: von speziellem Interesse

| | AV (n=291) | | AVO (n=284) | | FCR/BR (n=259) | |
|---|---|---|---|---|---|---|
| | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| Any ECI | 222 (76.3) | 136 (46.7) | 242 (85.2) | 188 (66.2) | 185 (71.4) | 141 (54.4) |
| Cardiac events | 27 (9.3) | 5 (1.7) | 34 (12.0) | 7 (2.5) | 9 (3.5) | 3 (1.2) |
| Atrial fibrillation | 2 (0.7) | 1 (0.3) | 6 (2.1) | 2 (0.7) | 2 (0.8) | 2 (0.8) |
| Ventricular tachyarrhythmias[a] | 2 (0.7) | 0 | 3 (1.1) | 0 | 0 | 0 |
| Hypertension | 12 (4.1) | 8 (2.7) | 11 (3.9) | 6 (2.1) | 7 (2.7) | 2 (0.8) |
| Hemorrhage | 94 (32.3) | 3 (1.0) | 86 (30.3) | 6 (2.1) | 11 (4.2) | 1 (0.4) |
| Major hemorrhage | 3 (1.0) | 3 (1.0) | 8 (2.8) | 6 (2.1) | 2 (0.8) | 1 (0.4) |
| Neutropenia (any)[b] | 108 (37.1) | 94 (32.3) | 143 (50.4) | 131 (46.1) | 132 (51.0) | 112 (43.2) |
| Infections (any) | 148 (50.9) | 36 (12.4) | 153 (53.9) | 67 (23.6) | 82 (31.7) | 26 (10.0) |
| Second primary malignancies | 15 (5.2) | 5 (1.7) | 12 (4.2) | 5 (1.8) | 2 (0.8) | 0 |
| Excl. non-melanoma skin | 8 (2.7) | 5 (1.7) | 7 (2.5) | 4 (1.4) | 1 (0.4) | 0 |
| Tumor lysis syndrome | 1 (0.3) | 1 (0.3) | 1 (0.4) | 1 (0.4) | 8 (3.1) | 8 (3.1) |

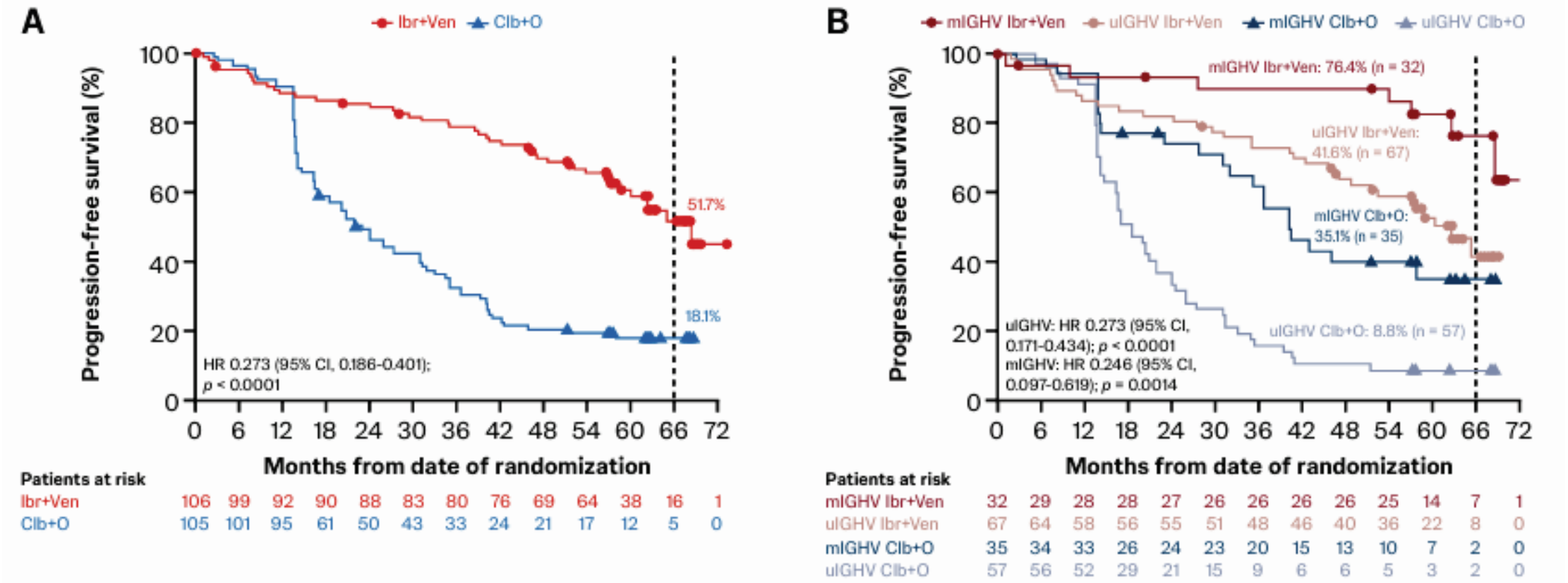
# GLOW Phase III Studie: Ibrutinib + Venetoclax bei älteren Patienten

**1871:First-Line Ibrutinib Plus Venetoclax Vs Chlorambucil Plus Obinutuzumab in Elderly or Comorbid Patients (Pts) with Chronic Lymphocytic Leukemia (CLL): Glow Study 64-Month Follow-up (FU) and Adverse Event (AE)-Free Progression-Free Survival (PFS) Analysis**

C. Niemann, Kopenhagen, Dänemark

# GLOW-Studie: Ibrutinib + Venetoclax

## PFS nach 67 Monaten FU



# Kapitel 2

Rezidivtherapie der CLL:

Herausforderung doppelt refraktäre Patienten und Pirtobrutinib

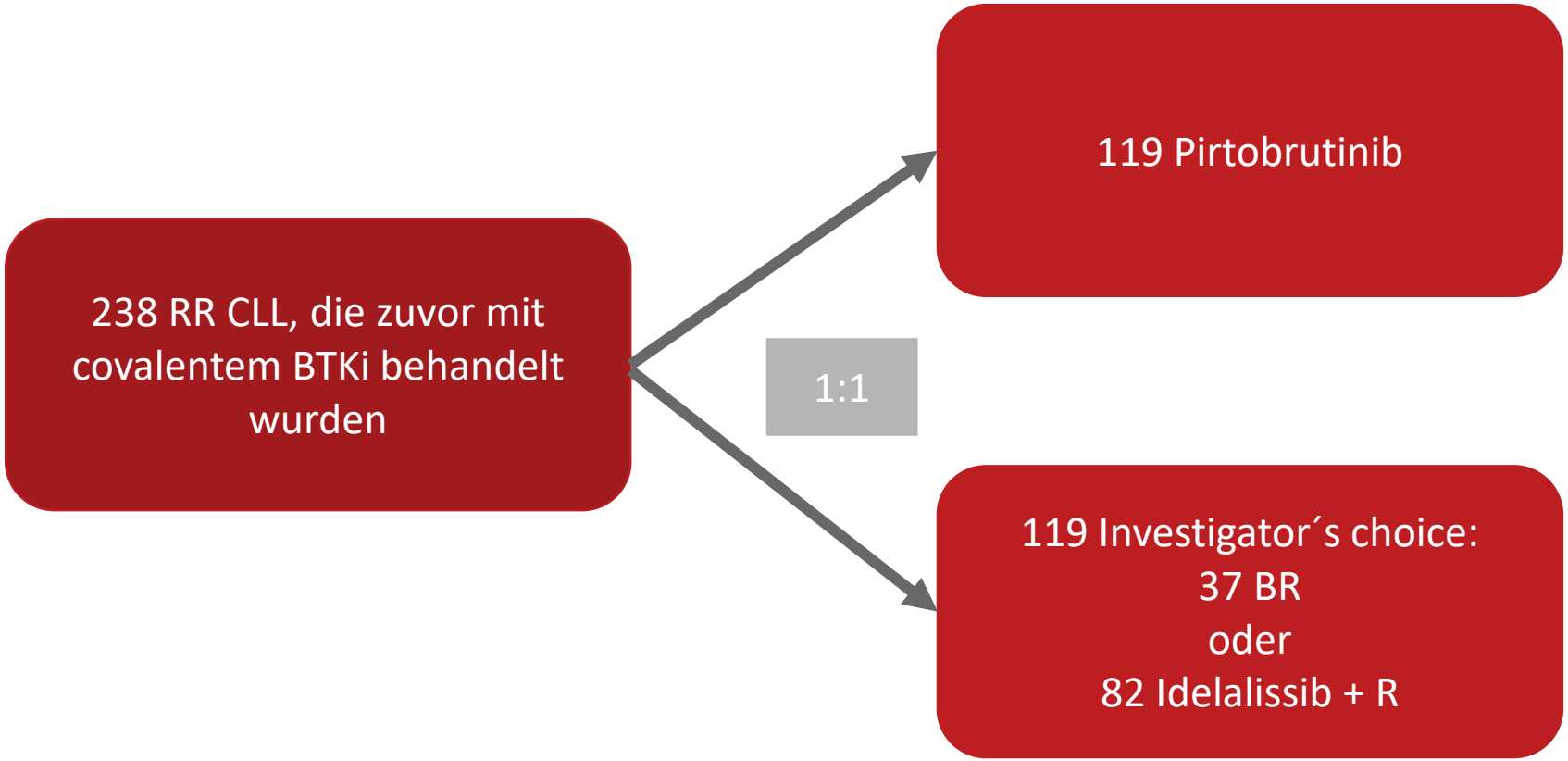
# BRUIN CLL-321 Phase III Studie zu Pirtobrutinib in R/R CLL

**886 BRUIN CLL-321: Randomized Phase III Trial of Pirtobrutinib Versus Idelalisib Plus Rituximab (IdelaR) or Bendamustine Plus Rituximab (BR) in BTK Inhibitor Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma**

J. Sharman, Eugene, Oregon

# BRUIN-Studie: Pirtobrutinib vs Investigators Choice in RR CLL

**Studiendesign**



# BRUIN-Studie: Pirtobrutinib vs Investigators Choice in RR CLL

## Ergbnisse

| Analyse/Endpunkt | HR (Pirtobrutinib vs. IC) |
|---|---|
| **PFS** | |
| **IRC-assessiertes PFS (11,6 Monate Follow-up)** | 0,55 (95% KI: 0,38-0,78; p=0,0007) |
| **Investigator-assessiertes PFS** | 0,42 (95% KI: 0,29-0,62; p<0,0001) |
| **Subgruppenanalyse für IRC-assessiertes PFS** | |
| **- Vorherige Venetoclax-Behandlung** | 0,54 (95% KI: 0.33-0.86) |
| **- Komplexer Karyotyp** | 0,34 (95% KI: 0,21-0,56) |
| **- TP53-Mutation und/oder del(17p)** | 0,52 (95% KI: 0,33-0,84) |
| **TTNT und OS** | |
| **TTNT** | 0,38 (95% KI: 0,25-0,56) |
| **OS** | Durchschnittliches OS nicht erreicht |

# Kapitel 3

Behandlung des alten/gebrechlicheren Patienten

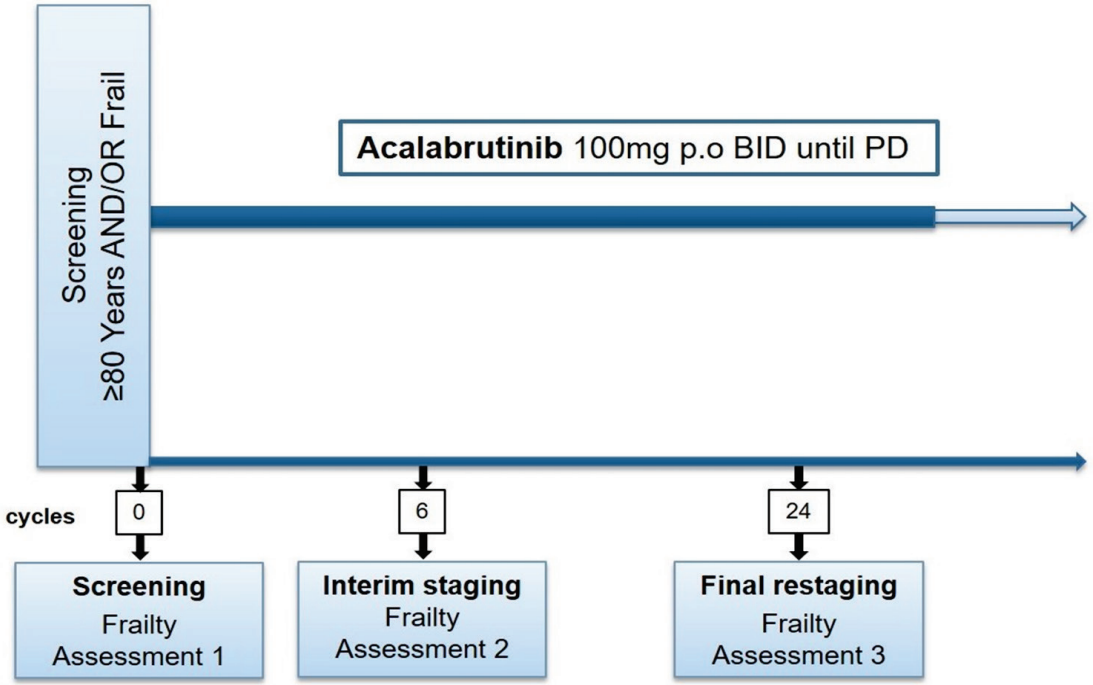
# FRAIL-Studie: Behandlung des alten/gebrechlichen Patienten

**4618 Efficacy and Safety of Acalabrutinib Treatment in Very Old (≥80y) and/or Frail Patients with Chronic Lymphocytic Leukemia (CLL) – Primary Endpoint Analysis of the Phase II CLL-Frail Trial**

F. Simon, Köln

# FRAIL-Studie: Acalabrutinib bei alten/gebrechlichen Patienten

## Studiendesign und Patientencharcteristika




| | |
|---|---|
| **Total (ITT), N** | **53** |
| **Total (Safety population), n** | **52** |
| **Total (FAS), n** | **46** |
| **Median observation time** | **17.7 months** |
| Ongoing treatment, n | 34 (65%) |
| Reasons for discontinuation, n (%) | 18 |
| Adverse event | 10 (56%) |
| Death | 5 (28%) |
| Withdrawn consent | 3 (17%) |
| Median age (range) | 81 (54-91) |
| Frail | 25 (48%) |
| Treatment-naïve | 36 (68%) |
| Median CIRS (range) | 9 (2-18) |
| Pre-existing cardiac comorbidities | 31 (58%) |
| Pre-existing hypertension | 45 (85%) |

# FRAIL-Studie: Acalabrutinib bei alten/gebrechlichen Patienten

## Wirksamkeit

PFS nach 12 Monaten: 87.5%
OS nach 12 Monaten: 91.9%

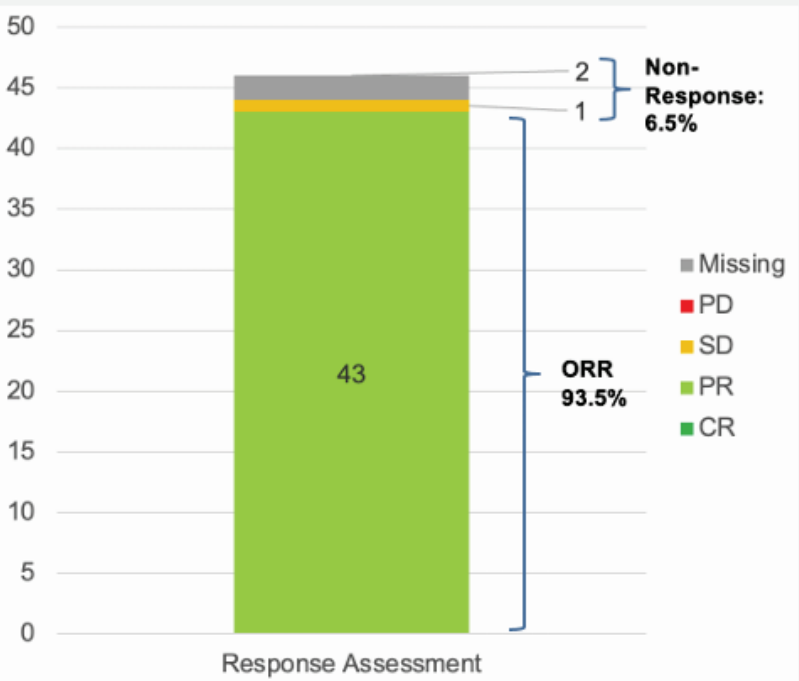
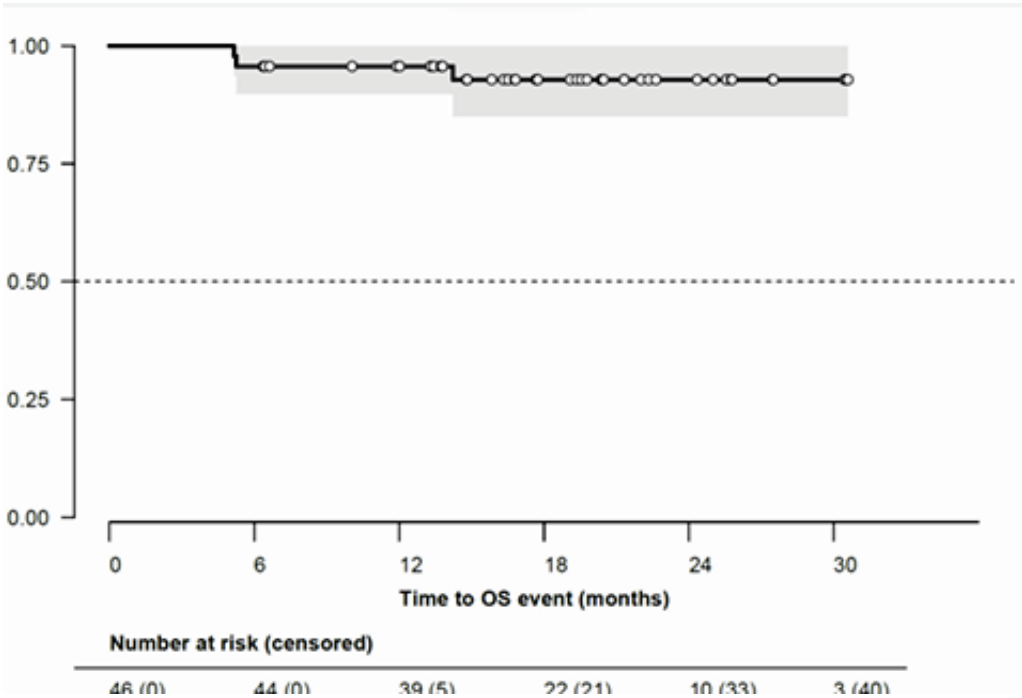



Figure 2: ORR for the FAS was 93.5% (95% CI: 0.82 – 0.97, p<0.001). ORR in the ITT population was 81.1% with 9 missing response assessments.

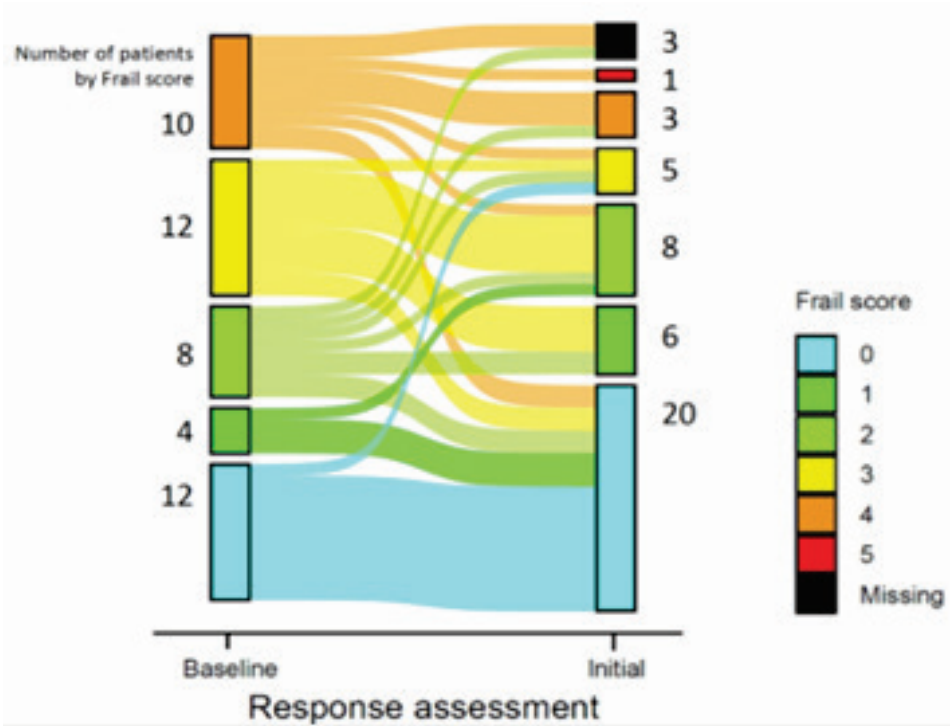


# FRAIL-Studie: Acalabrutinib bei alten/gebrechlichen Patienten

## Sicherheit und Verträglichkeit

| | All grades | Grade ≥3 |
|---|---|---|
| **AEs** | **52 (100)** | **33 (63.5)** |
| COVID-19 | 19 (36.5) | 3 (5.8) |
| Haematoma | 19 (36.5) | 0 |
| Diarrhoea | 12 (23.1) | 1 (1.9) |
| Anemia | 9 (17.3) | 6 (11.5) |
| Constipation | 9 (17.3) | 0 |
| Headache | 9 (17.3) | 0 |
| Fatigue | 8 (15.4) | 0 |
| Oedema | 8 (15.4) | |
| Contusion | 7 (13.5) | 0 |
| Thrombocytopenia | 6 (11.5) | 1 (1.9) |
| Vertigo | 6 (11.5) | 0 |
| Dehydration | 6 (11.5) | 1 (1.9) |
| Rash | 6 (11.5) | 2 (3.8) |
| Cardiac failure | 4 (7.7) | 3 (5.8) |
| Palpitations | 4 (7.7) | 0 |

Frailscore im Verlauf



# Zusammenfassung | Take-Home-Messages

**Erstlinientherapie der CLL:**

Zulassung Kombination Acalabrutinib + Venetoclax als Alternative zu Ibrutinib + Venetoclax 2025 erwartet.

(Anmerkungen: AV evtl geringere Effektivität als IV, aber Beurteilung durch Rekrutierung in der Pandemie bei COVID19-Todesfällen beeinträchtigt.)

IV bei älteren Patienten mit anhaltend gutem Outcome.

**Rezidivtherapie der CLL:**

Zulassung nicht-covalent bindender BTKi Pirtobrutinib 2025 erwartet

**Behandlung alter/gebrechlicher Patienten mit CLL:**

BTKi Acalabrutinib wirksam und gut verträglich

Die Kurzpräsentationen sind online unter

**www.lymphome.de/ash2024**

Für den Inhalt verantwortlich:

Prof. Dr. med. Barbara Eichhorst

Uniklinik Köln

Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

KML KONGRESSE

Expert:innen berichten zu Lymphomen & Leukämien

Das Informationsprojekt wird unterstützt von den Firmen:

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Lilly

Diese hatten keinen Einfluss auf die Inhalte.