# What are the best combinations of therapies using targeted agents?

**Tuesday November 5, 2019**
**11:30 – 11:45**
**Royal Hotel Carlton Bologna**

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MD Anderson Cancer Center
Houston, Texas, USA

# iFCG Trial: Study Design

**iFCG 3 courses**

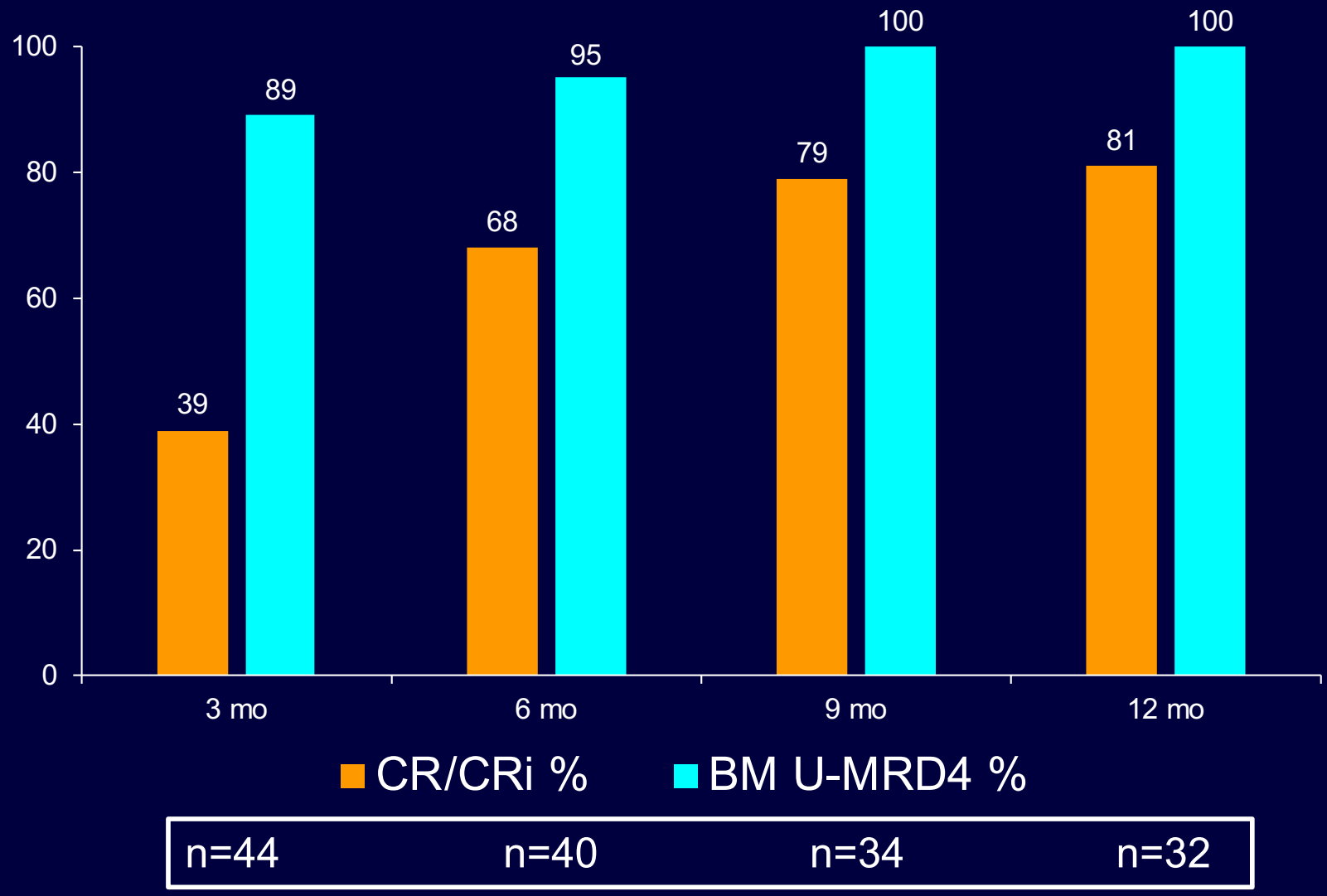
↓

**Ibrutinib for 9 courses (all pts)**
**+**
**Obinutuzumab for 3 courses (if CR/CRi with BM U-MRD4)**
**or**
**Obinutuzumab for 9 courses (if PR and/or BM $MRD^{pos}$)**

↓

**After 12 courses**
**BM U-MRD4 → stop ibrutinib**
**BM $MRD^{pos}$ → continue ibrutinib**

# Responses Improve with Time



# Responses in *IGHV*-M after C6

| Trial | Regimen | N | CT scan | CR / CRi % | BM U-MRD4 % |
|---|---|---|---|---|---|
| MDACC | FCR x6 | 88 | No | 83 | 51 |
| MDACC | FCR x6 | 82 | No | 66 | 56 |
| CLL8 | FCR x6 | 113 | No | 50 | 50 |
| CLL10 | FCR x6 | 123 | Yes | 39 | 62 |
| MDACC | iFCG x3 → iG x3 | 40 | Yes | 68 | 95 |

Keating, JCO 2005, Tam, Blood 2008, Thompson, Blood 2016, Strati, Blood 2014, Hallek, Lancet 2010, Eichhorst, Lancet Onc 2016, Personal communication Barbara Eichhorst, GCLLSG

# Conclusions

- iFCG induces high rate of BM U-MRD4 remission: 87% after 3 cycles
- All 32 patients reaching 1 yr had BM U-MRD4 and discontinued ibrutinib
- No pt had disease progression or MRD relapse
- Neutropenia and thrombocytopenia common during iFCG courses; neutropenia risk decreased with prophylactic G-CSF
- **Open question:** how do we choose between FCR versus novel agents for younger fit and IGHV mutated patients?

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# Combined Ibrutinib and Venetoclax in Patients with Treatment-Naïve High-Risk Chronic Lymphocytic Leukemia (CLL)


Nitin Jain, Michael Keating, Philip Thompson, Alessandra Ferrajoli, Jan Burger, Gautam Borthakur, Koichi Takahashi, Zeev Estrov, Nathan Fowler, Tapan Kadia, Marina Konopleva, Yesid Alvarado, Musa Yilmaz, Courtney DiNardo, Prithviraj Bose, Maro Ohanian, Naveen Pemmaraju, Elias Jabbour, Koji Sasaki, Rashmi Kanagal-Shamanna, Keyur Patel, Jeffrey Jorgensen, Naveen Garg, Xuemei Wang, Katrina Sondermann, Nichole Cruz, Chongjuan Wei, Ana Ayala, William Plunkett, Hagop Kantarjian, Varsha Gandhi, William Wierda

Department of Leukemia, MDACC



ASH 2018, Abstract 186

# BCR vs. BCL2 Inhibitor

| | BCR Inhibitor (Ibrutinib) | BCL2 Inhibitor (Venetoclax) |
|---|---|---|
| Response | Blood ++<br>LN +++<br>Marrow + | Blood +++<br>LN ++<br>Marrow +++ |
| Lymphocytosis | +++ | - |
| CR in R/R CLL | 10% | 20-25% |
| AE profile | Atrial fibrillation, neutropenia, bleeding | TLS, neutropenia |

# Ibrutinib + Venetoclax

- Investigator-initiated phase II trial
- Patients with a previously untreated CLL/SLL with at least one high-risk feature:
  - Del(17p) or mutated *TP53*
  - Del(11q)
  - Unmutated *IGHV*
  - Age ≥65 yrs

# Treatment Schema

| | C1 | C2 | C3 | C4 ---> C27 |
|---|---|---|---|---|
| Ibrutinib | 420mg daily | 420mg daily | 420mg daily | 420mg daily |
| Venetoclax | - | - | - | 20mg daily x1 wk then;<br>50mg daily x1 wk then;<br>100mg daily x1 wk then;<br>200mg daily x1 wk then;<br>400mg daily continuous |

**Duration of Therapy**

- VEN: 24 cycles of combination
- IBR: 24 cycles of combination (stop if BM U-MRD4 at 24 cycle)
  (For BM MRD4 positive at 24 cycle: IBR continues until progression)

**Primary endpoint: CR/CRi**

# Eligibility Criteria

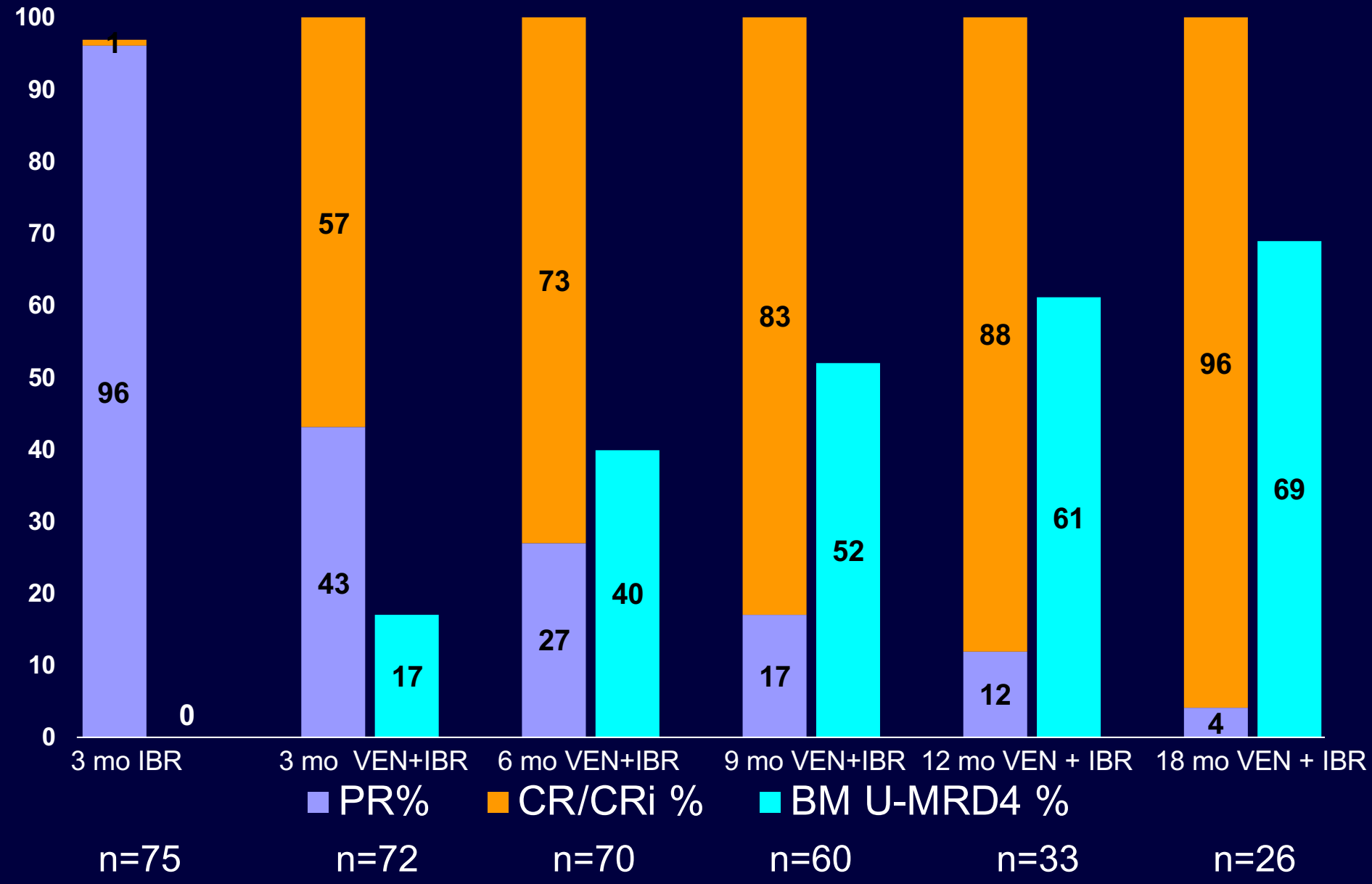
- Previously untreated high-risk CLL/SLL, meeting 2008 IWCLL treatment criteria
- ≥18 years
- Adequate organ function:
  - GFR >50 ml/min
  - ALT and AST ≤3.0 x ULN
  - Total bilirubin ≤1.5 x ULN
  - Platelets >20 K/μL

# Trial Status

- 80 pts enrolled July 2016 – June 2018
- 75 pts initiated combination
  - 5 pts off study during ibrutinib monotherapy
- Median follow-up 14.8 (5.6-27.5) months

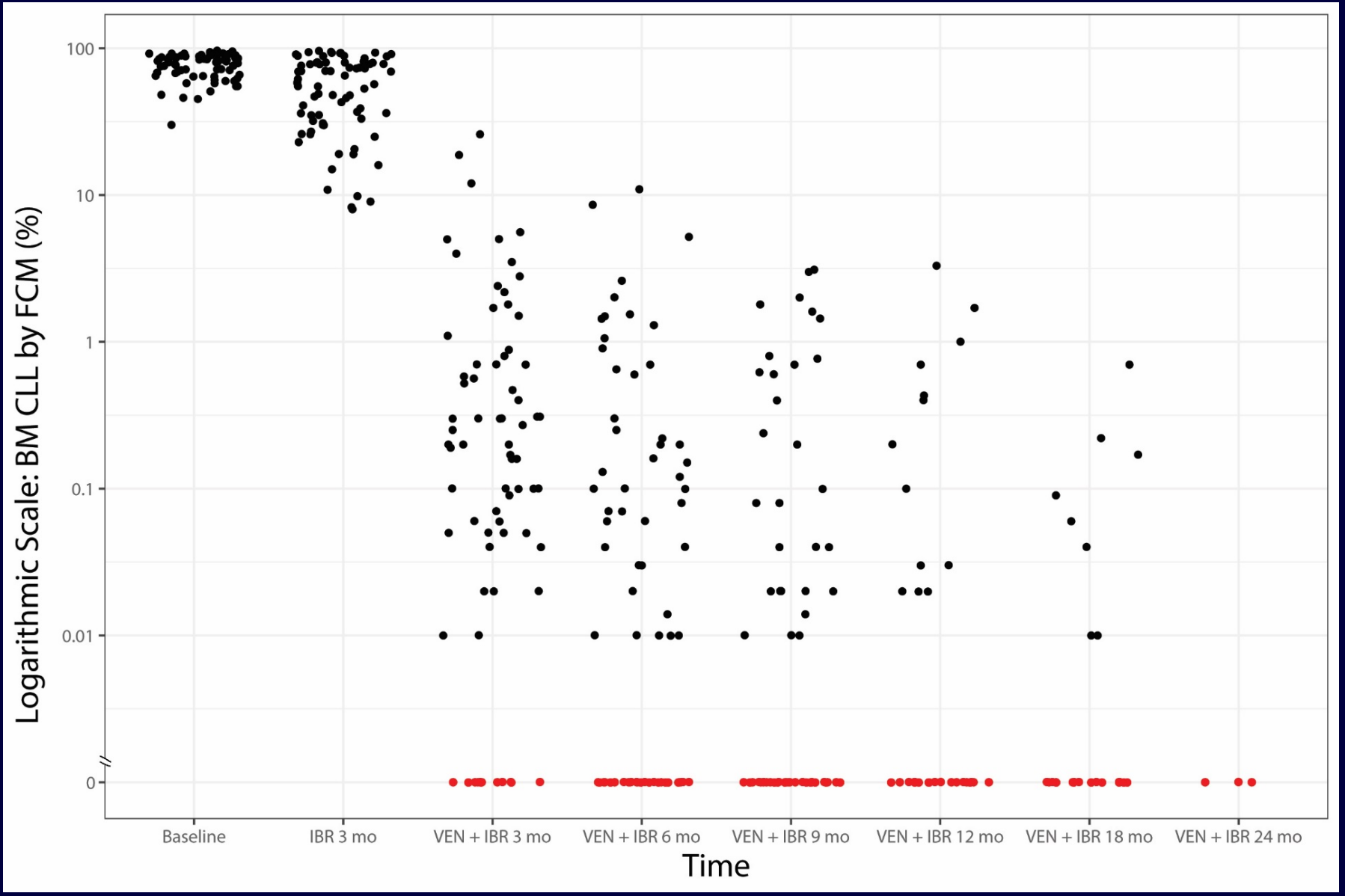
Ven + Ibr in TN CLL, ASH 2018, Abs 186

# Responses Improve with Ongoing Therapy

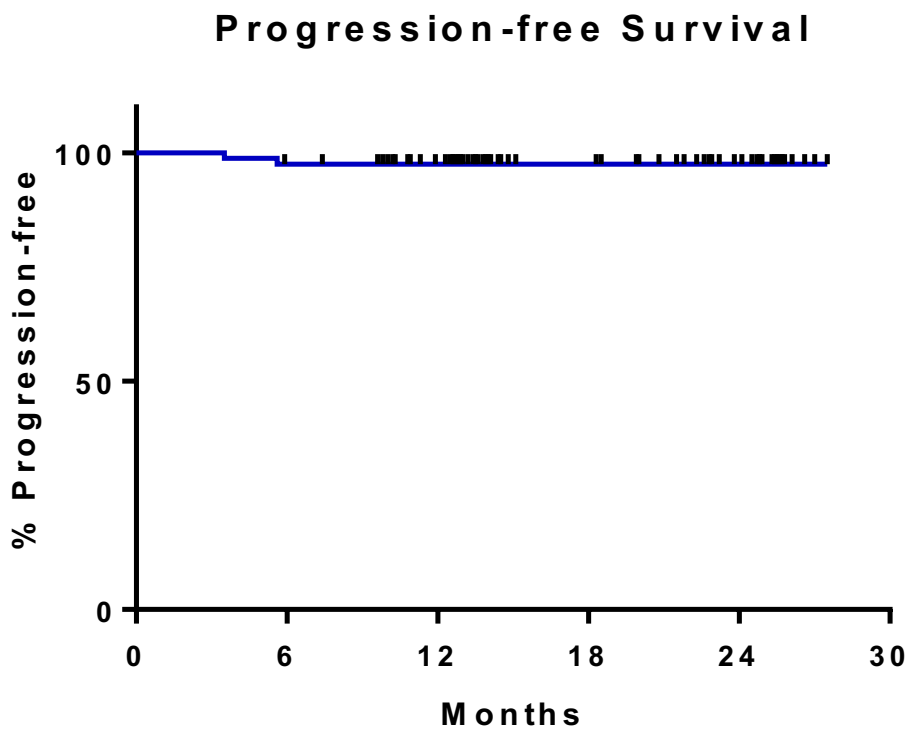


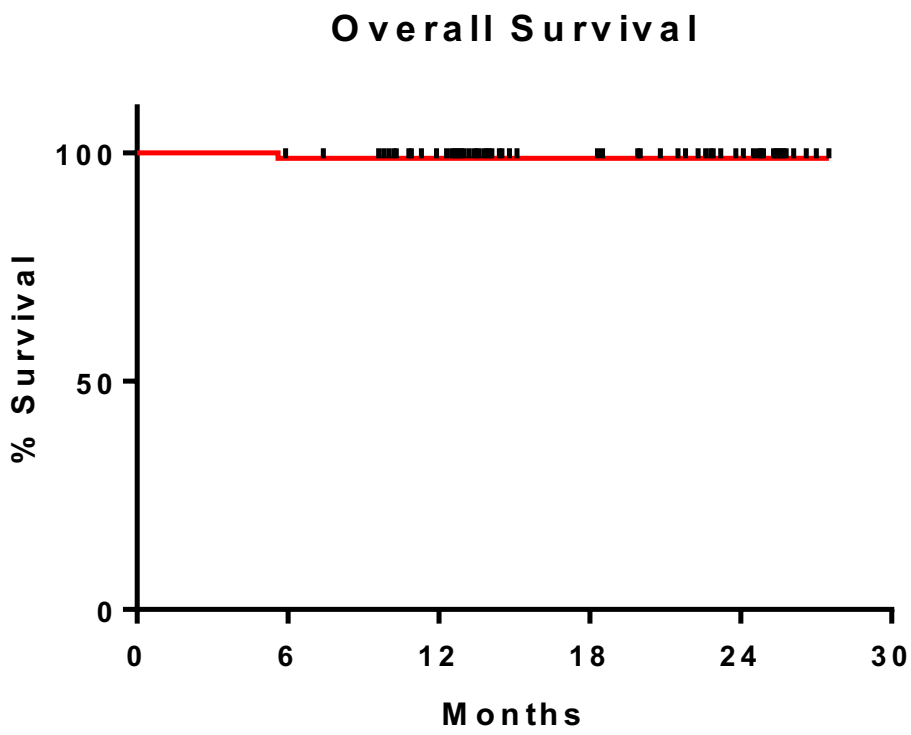
Ven + Ibr in TN CLL, ASH 2018, Abs 186

# Venetoclax Leads to Rapid Reduction in CLL Bone Marrow Disease



# PFS and OS for all Pts (N=80)



# Conclusions

- Combined venetoclax and ibrutinib is an effective, safe, and chemotherapy-free oral regimen for pts with high-risk previously untreated CLL
- 80% high-risk and 48% medium-risk pts had down-grading of TLS risk category with ibrutinib
- Responses improve with ongoing therapy
  - At 12 mo combo: 88% CR/CRi, 61% BM U-MRD4
  - At 18 mo combo: 96% CR/CRi, 69% BM U-MRD4

# Randomized trial of ibrutinib versus ibrutinib plus rituximab in patients with chronic lymphocytic leukemia (CLL)

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THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

# Study Design

- **Relapsed/Refractory** (n=179)
- **Treatment naïve** with 17p del or TP53 mutated (n=27)

**Stratification factors**
- ECOG PS (0-1 vs. 2)
- High-risk cytogenetic abnormalities (del17p, TP53 mutation, del11q)

**Ibrutinib (n=102)**

Ibrutinib 420 MG daily until disease progression/death/side effects

**Ibrutinib + rituximab (n=104)**

Ibrutinib 420 MG daily plus rituximab (375 mg/m$^2$ weekly x 4, then monthly for cycles 2-6)

**Total = 206**

**Primary end point**: 2-year PFS

**Secondary end points**: ORR, safety and tolerability

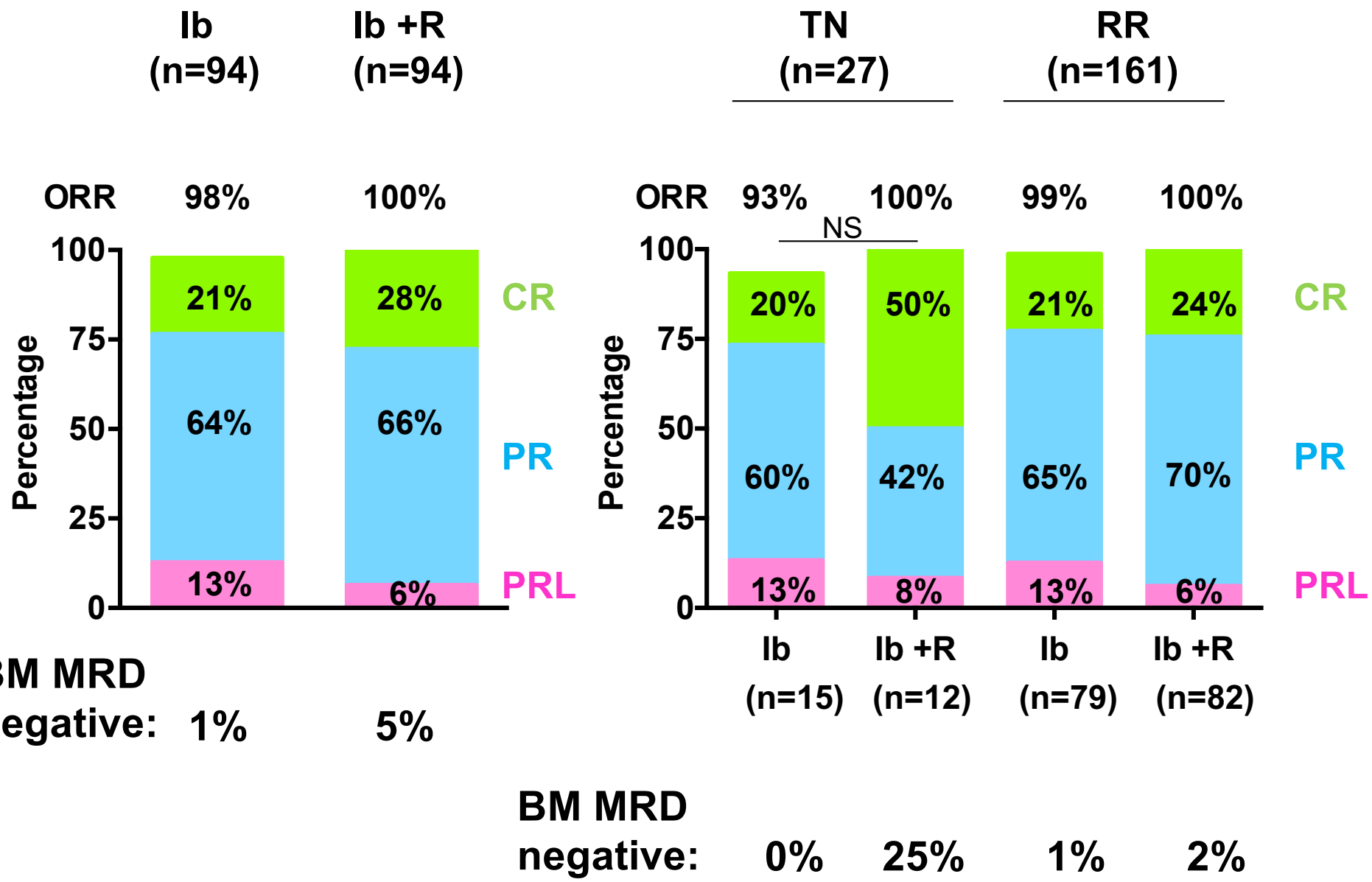
# Patient Characteristics

| Characteristics | Ibrutinib n (% or range) | Ibrutinib + rituximab n (% or range) |
|---|---|---|
| Median age, years (range) | 64 (44 -83) | 65 (42 -81) |
| **Cytogenetic abnormalities** | | |
| **17p del** | **26 (25.5)** | **30 (28.8)** |
| **11q del** | **26 (25.5)** | **15 (14.4)** |
| Trisomy 12 | 11 (10.8) | 16 (15.4) |
| 13q del | 22 (21.6) | 23 (22.1) |
| **TP53 mutatated** | **29 (28.4)** | **21 (20.2)** |
| **Unmutated *IGHV*** | **60 (58.8)** | **62 (59.6)** |
| **ZAP-70 Positive** | 63 (61.8) | 60 (60.6) |
| **CD38 Positive** | 50 (49.0) | 50 (48.1) |
| **RAI stage** | | |
| 0 | 11 (10.8) | 5 (4.8) |
| I-II | 54 (52.9) | 57 (54.8) |
| III-IV | 37 (36.5) | 42 (40.4) |

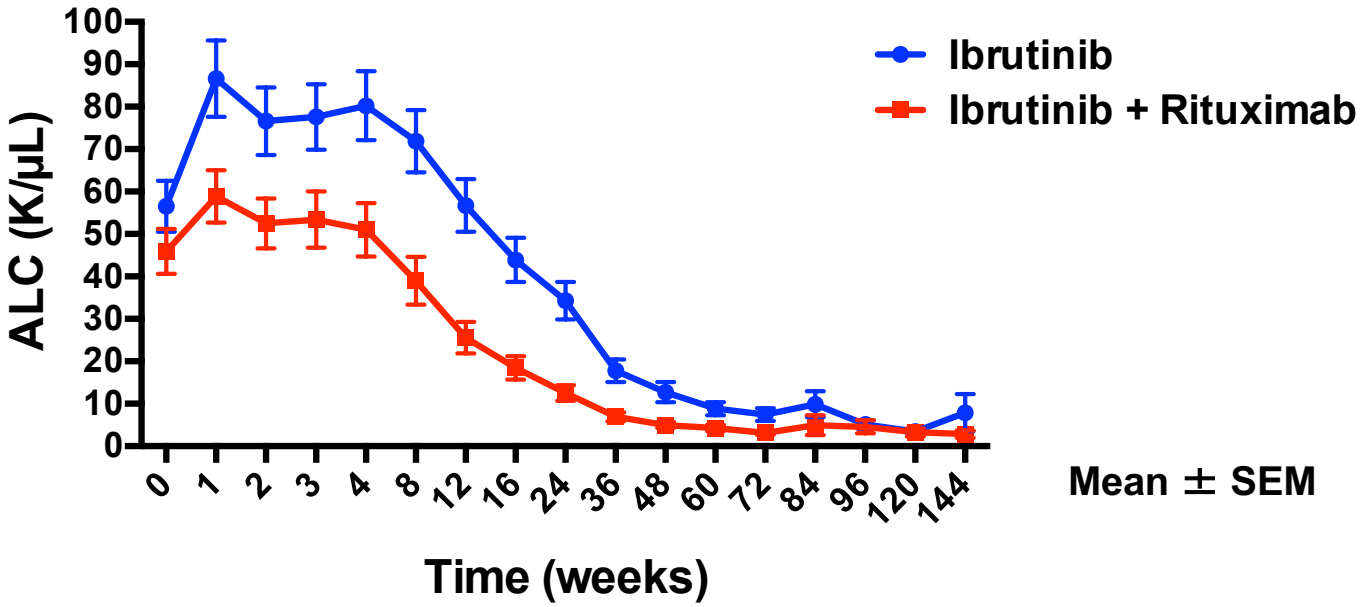
# Patient Characteristics

| Characteristics | Ibrutinib median (range) | Ibrutinib + rituximab median (range) |
|---|---|---|
| **Lines of prior therapies, n (freq. %)** | | |
| **0** | 15 (14.7) | 12 (11.5) |
| **1-2** | 66 (64.7) | 76 (73.1) |
| **3** | 10 (9.8) | 7 (6.7) |
| **≥4** | 11 (10.8) | 9 (8.6) |
| **WBC (K/µL)** | 41.6 (2.8 – 361.8) | 36.8 (1.2 – 321.4) |
| **ALC (K/µL)** | 29.6 (0.5 – 350.9) | 29.5 (0.5 – 292.4) |
| **Hemoglobin (g/dL)** | 12.6 (8.0 -17.0) | 12.4 (7.3 – 16.3) |
| **Platelets (K/µL)** | 122 (30 – 368) | 127 (24 – 465) |
| **β2 microglobulin (mg/L)** | 3.7 (1.3 – 13.1) | 3.7 (1.4 – 11.9) |

# Best Response



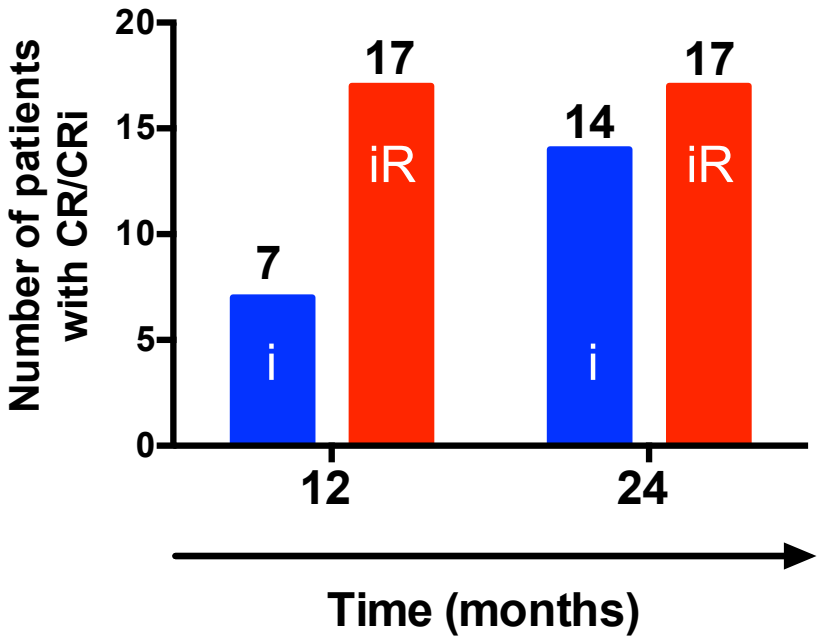
# Trended absolute lymphocyte counts (ALC)



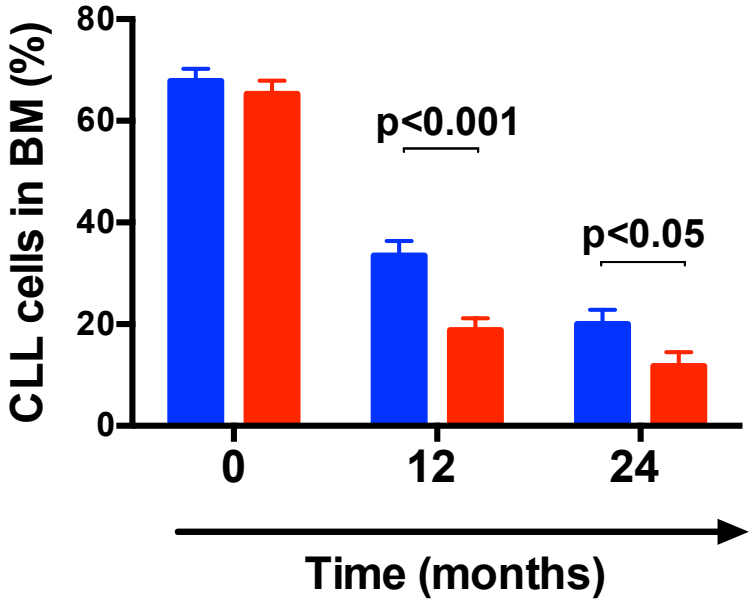

| | ibrutinib | ibrutinib + R | p value |
|---|---|---|---|
| **Time to ALC normalization in months (range)** | 8.9 (0.2 – 29.9) | 3.0 (0.2 – 29.9) | <0.001 |

# Time to CR and BM response

## CR/CRi




## % CLL cells in BM

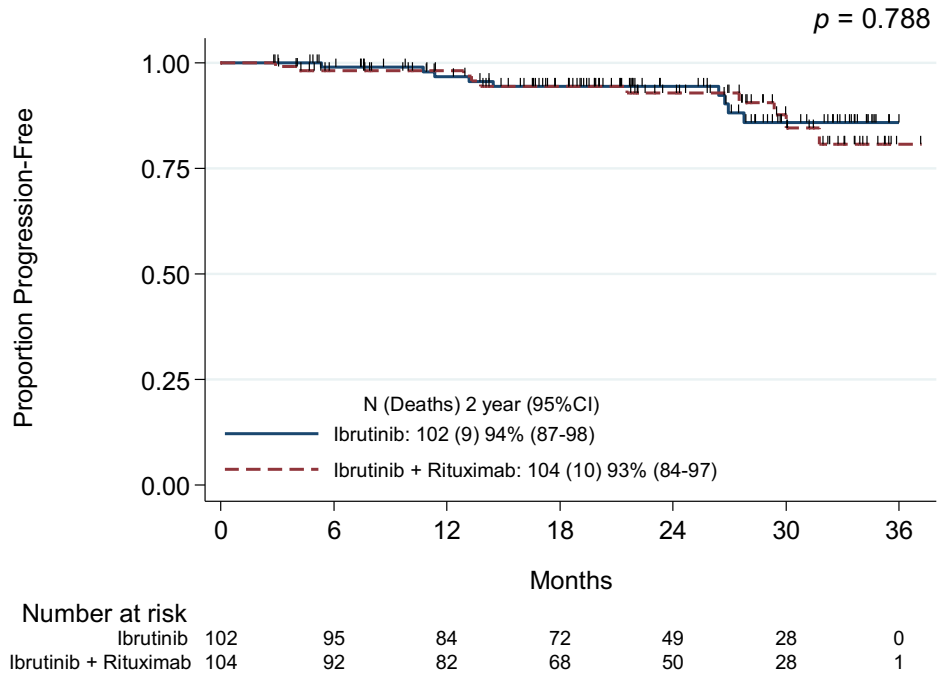



Ibrutinib (i)

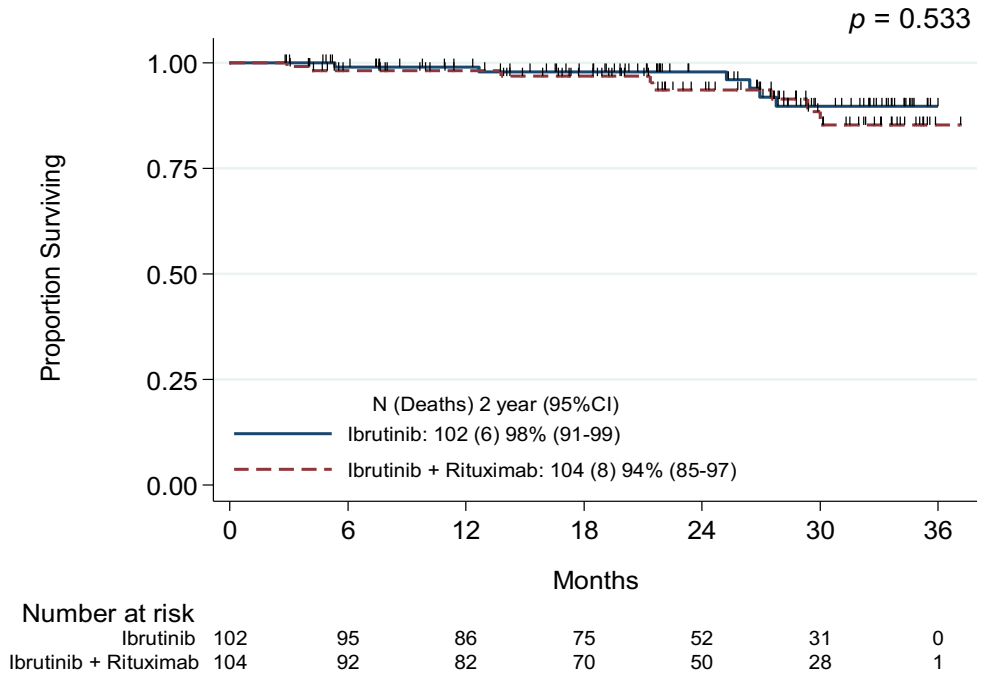
Ibrutinib+rituximab (iR)

| | Ibrutinib | Ibrutinib +R | p value |
|---|---|---|---|
| **Time to CR/Cri** in months (range) | **21.1** (10.5 – 33.1) | **11.5** (4.8 – 23.7) | 0.032 |

# PFS




# OS




| | Ibrutinib (n=102) | Ibrutinib +R (n=104) |
|---|---|---|
| Follow-up in months (range) | **25.2 (2.7 – 35.9)** | **22.7 (2.8 – 37.1)** |

**No difference in PFS and OS for patients receiving ibrutinib versus ibrutinib plus rituximab**

# Conclusions

- iFCG is a good combination for younger IGHV mutated CLL pt, concern: secondary MDS/AML risk not known
- Ibrutinib and venetoclax is highly effective, most patients achieve MRD-negative remission. Problem: short FU, long-term efficacy and toxicity not know. Not feasible in most countries.
- BTKi plus CD20 mAbs: no added survival benefit from anti-CD20, but faster and deeper remission, especially in treatment-naïve CLL: ideal combo for limited-duration therapy?
- At this time, single agent ibrutinib or venetoclax (+/-CD20 mAbs) remain standard-of-care therapy for higher-risk or RR CLL

# BGB trial proposal for CLL frontline therapy