FCR

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Houston, Texas, USA

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ORIGINAL REPORT

Early Results of a Chemoimmunotherapy Regimen of Fludarabine, Cyclophosphamide, and Rituximab As Initial Therapy for Chronic Lymphocytic Leukemia

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ABSTRACT

Purpose

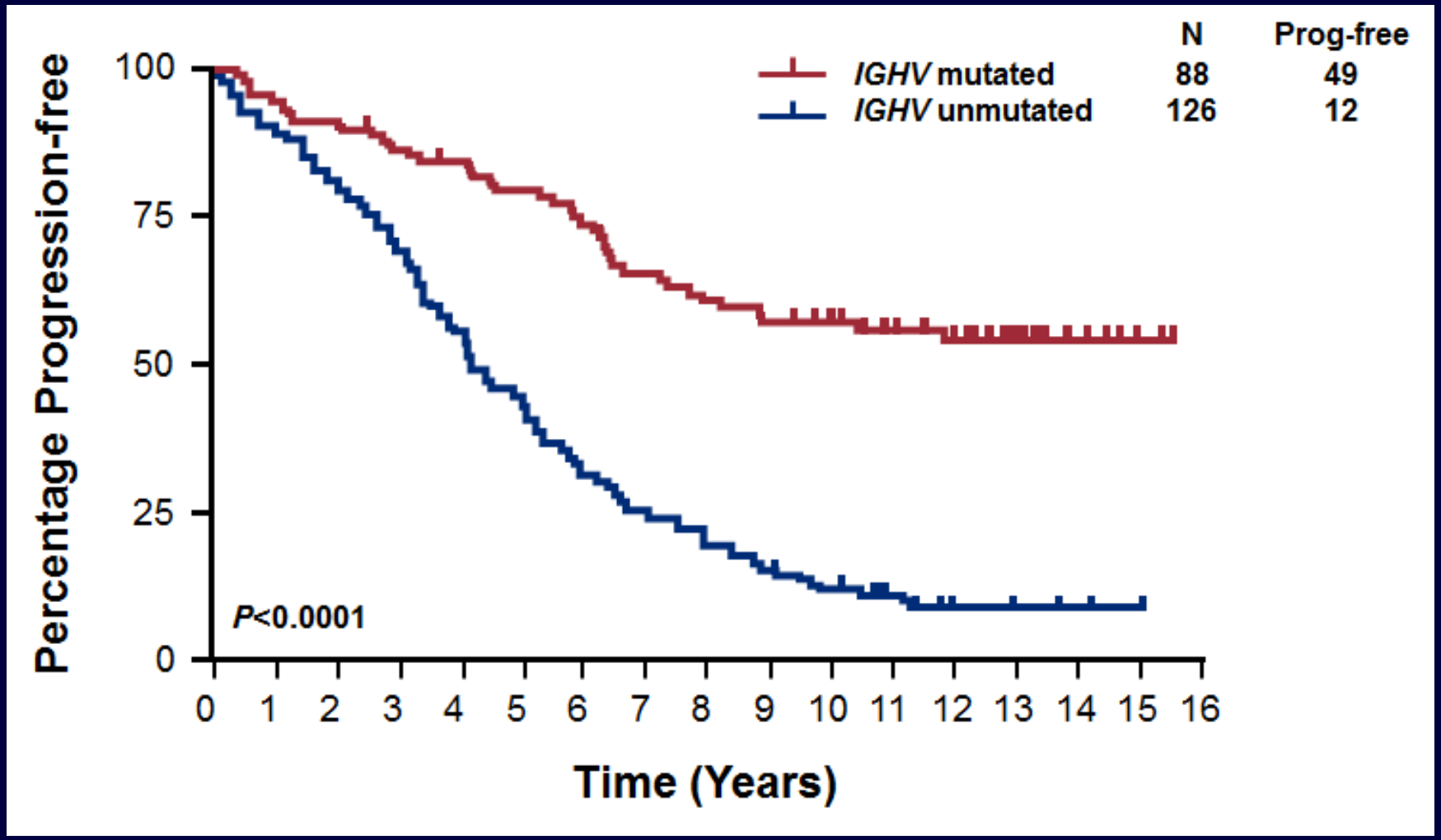
Fludarabine and cyclophosphamide (FC), which are active in treatment of chronic lymphocytic leukemia (CLL), are synergistic with the monoclonal antibody rituximab in vitro in lymphoma cell lines. A chemoimmunotherapy program consisting of fludarabine, cyclophosphamide, and rituximab (FCR) was developed with the goal of increasing the complete remission (CR) rate in previously untreated CLL patients to ≥ 50%.

Background

- **FCR is standard treatment for younger fit patients with CLL**
  - **CR after 6 cycles 40-72%**
  - **Undetectable MRD @ 10^{-4} sensitivity (U-MRD4) in marrow after 6 cycles: 43-58%**
  - **3-5% risk of t-MDS/AML**
  - **IGHV-M : >55% PFS at >10 yrs**

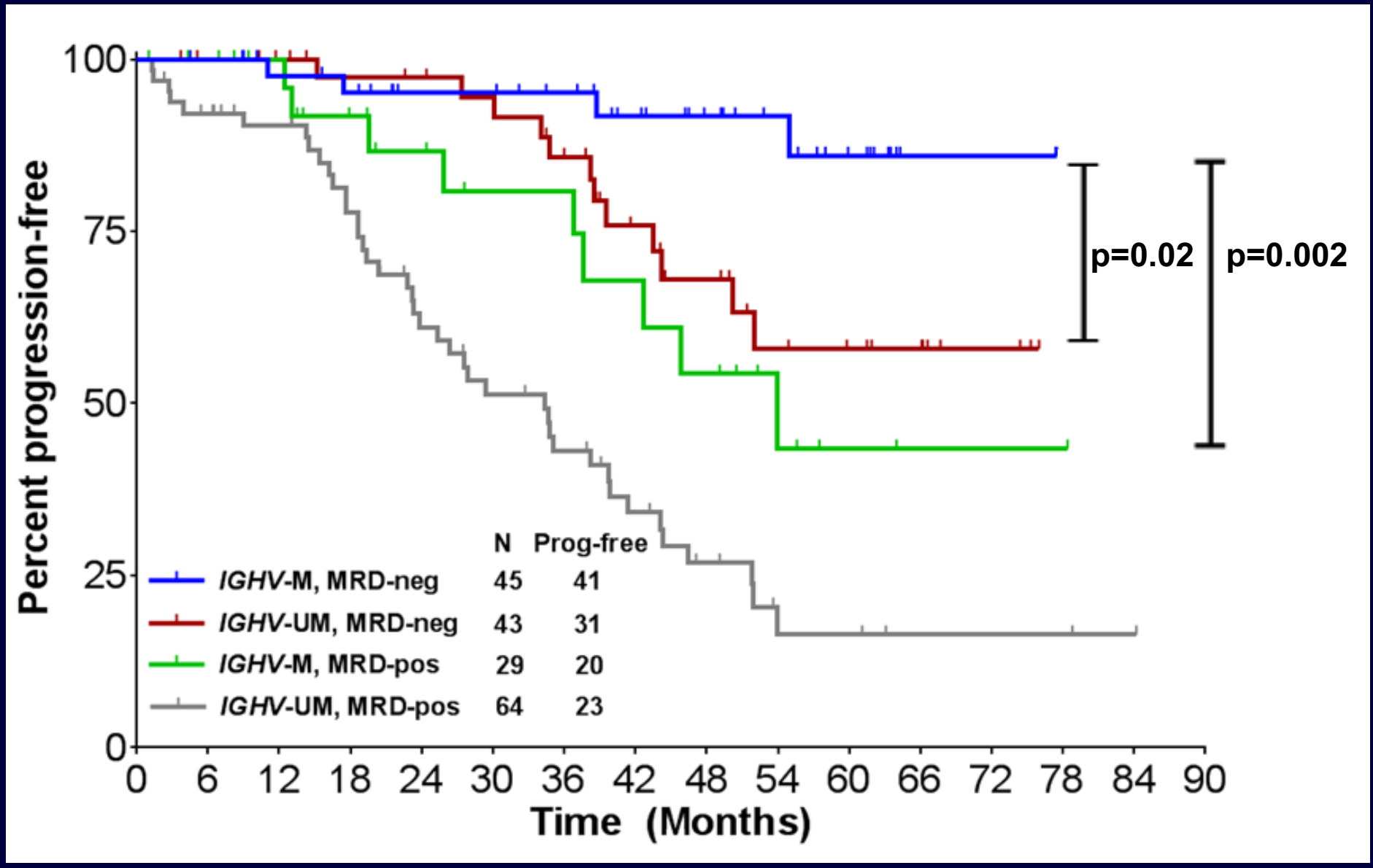
Keating, JCO 2005, Tam, Blood 2008, Thompson, Blood 2016, Strati, Blood 2014, Hallek, Lancet 2010, Bottcher, JCO 2012, Eichhorst, Lancet Onc 2016, Benjamini, Leuk Lymphoma 2015.

Favorable long-term PFS with Firstline FCR in *IGHV*-M Subgroup



Thompson et al. Blood. 2016;127(3):303-9.

U-MRD4 *IGHV*-M: Highly Favorable PFS after FCR



Thompson et al. Leukemia. 2018 Apr 17.

iFCG Trial Rationale

- **Higher U-MRD will improve PFS and OS**
  - Obinutuzumab: higher U-MRD than rituximab (CLL11)
  - Ibrutinib with CIT: higher U-MRD (HELIOS trial)
- **Reducing chemo may lower t-MDS/AML**
  - Number of FC cycles reduced from 6 to 3

Eligibility Criteria

- Previously untreated CLL/SLL meeting IWCLL treatment criteria
- ≥18 years
- *IGHV*-M
- No del(17p) or *TP53* mutation
- Adequate organ function
  - ANC >500/µL
  - platelets >50,000/µL
  - ALT and AST ≤2.5 x ULN
  - total bilirubin ≤1.5 x ULN
  - GFR ≥ 30 ml/min

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})

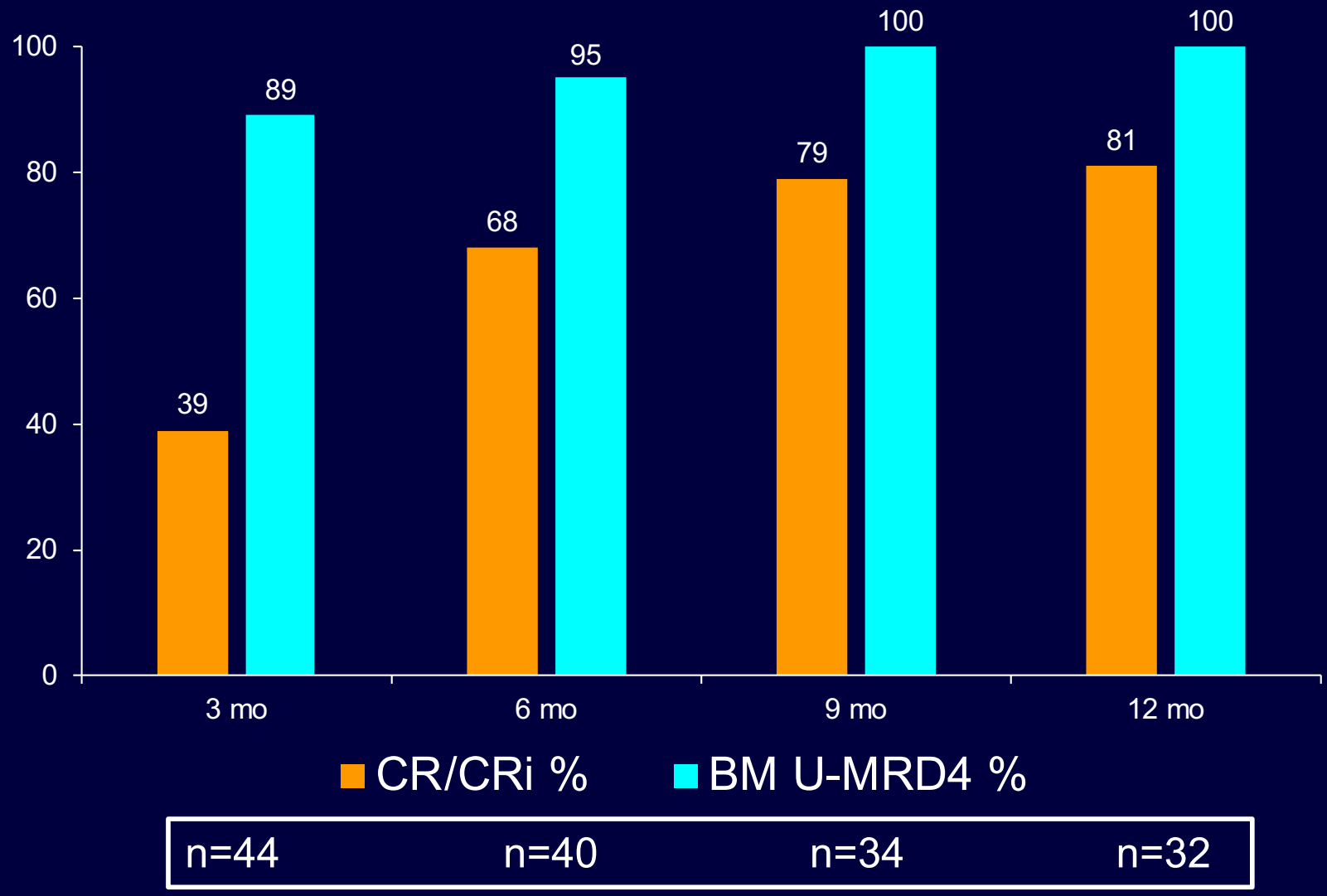
↓

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

Baseline Characteristics (N=45)

		n (%) or median [range]
Age, yrs		60 [25-71]
Gender, M		35 (78)
Rai stage	0 I-II III-IV	1 (2) 22 (49) 22 (49)
ALC, K/μL PLT, K/μL HGB, g/dL		52.9 [1.5-208] 120 [62-292] 11.9 [8.5-15.6]
B2M, mg/L		2.7 [1.3-8.1]
FISH	Del(13q) Trisomy 12 Negative Del(11q)	31 (69) 7 (16) 6 (13) 1 (2)
Cytogenetics (n=39)	Diploid	27 (69)
Mutations (n=39)	MYD88 SF3B1 NOTCH1 BIRC3	5 (13) 3 (8) 1 (3) 1 (3)

Responses Improve with Time



Responses in *IGHV*-M after C6

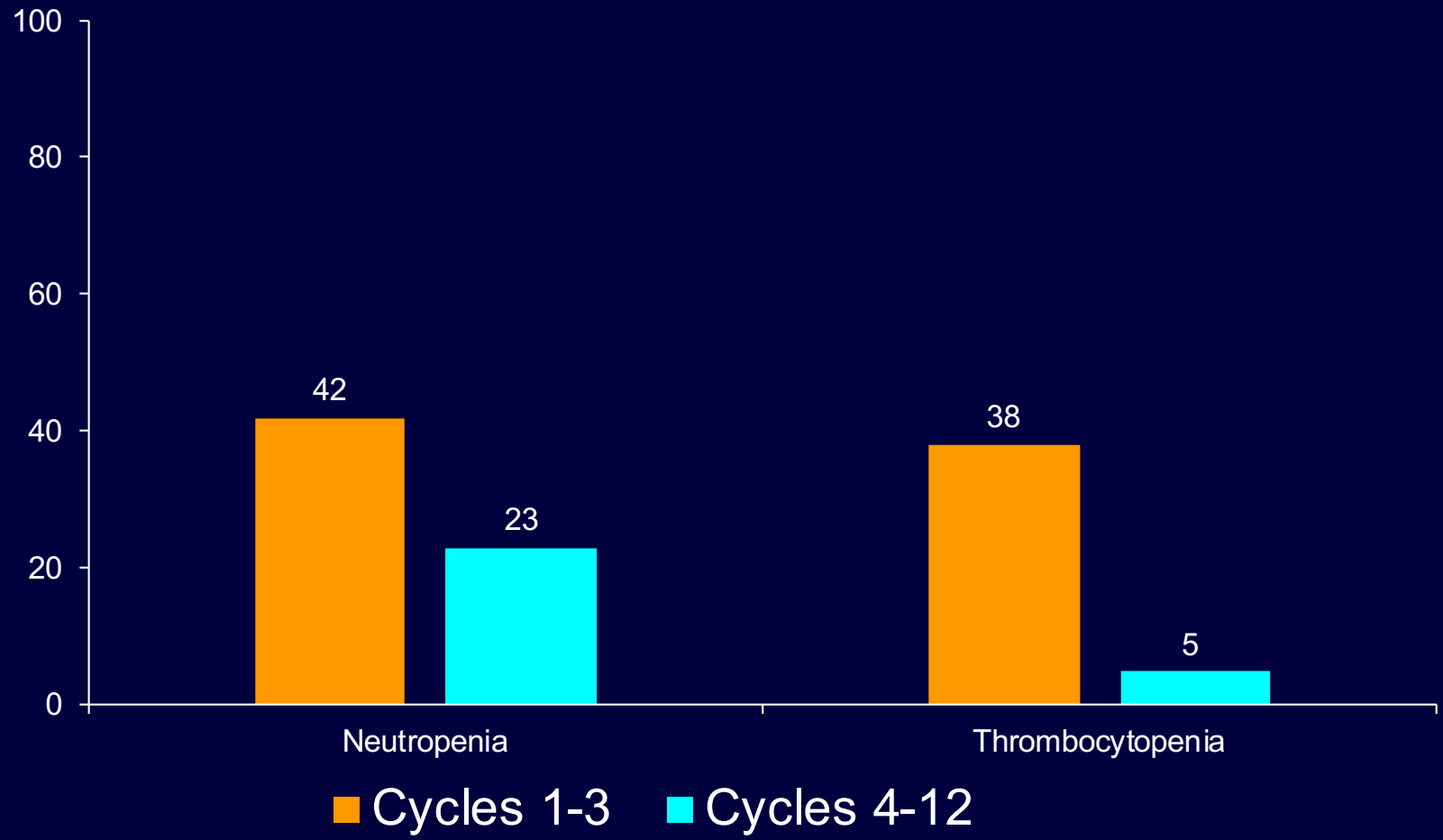
Trial	Regimen	N	CT scan	CR / CRi %	BM U-MRD4 %
MDACC	FCR x6	88	No	83	51
MDACC	FCR x6	82	No	66	56
CLL8	FCR x6	113	No	50	50
CLL10	FCR x6	123	Yes	39	62
MDACC	iFCG x3 → iG x3	40	Yes	68	95

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

Treatment Discontinuation at 1 Year

- 32 pts reached 1-yr follow-up
  - All 32 had BM U-MRD4 (26 CR/CRi, 6 PR) and discontinued ibrutinib
  - Median follow-up after stopping ibrutinib 13.6 months (range 1.4-20.7)
  - No pt had MRD or clinical relapse

G3-4 Hematological Toxicity Most Common in First 3 Courses



Risk of G3-4 neutropenia during C1-3 after prophylactic G-CSF = 27%

Pertinent Non-Hem Toxicities

- Infusion related reactions
  - All grades 42%, G3-4, 4%
- Atrial fibrillation: 11%
- G3-4 transaminitis : 13%

Infectious Complications (N=45)

Infections (G3-4)	**n (%)**
– Neutropenic fever	5 (14)
• PJP PNA (n=1)	
• Culture negative (n=4)	
– Pneumonia (non-neutropenic)	2 (6)
– Cellulitis	2 (6)
– Pulmonary MAC infection	1 (3)
– Acute cholecystitis	1 (3)
– Colitis	1 (3)

- **After institution of prophylactic G-CSF, no pt had neutropenic fever**
- **No pt had invasive fungal infection**

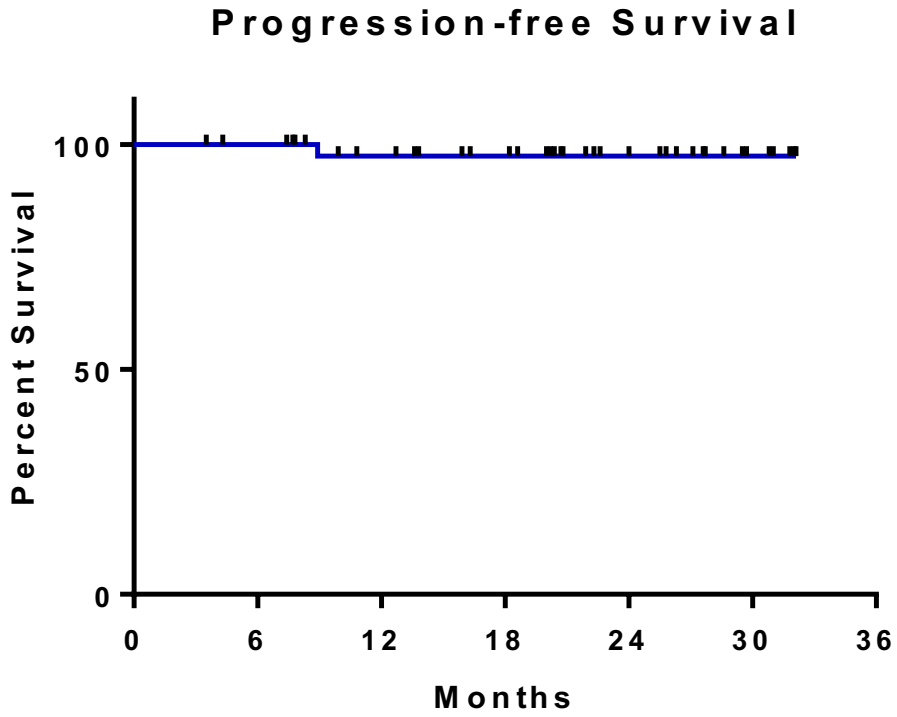
Dose Reductions (N=45)

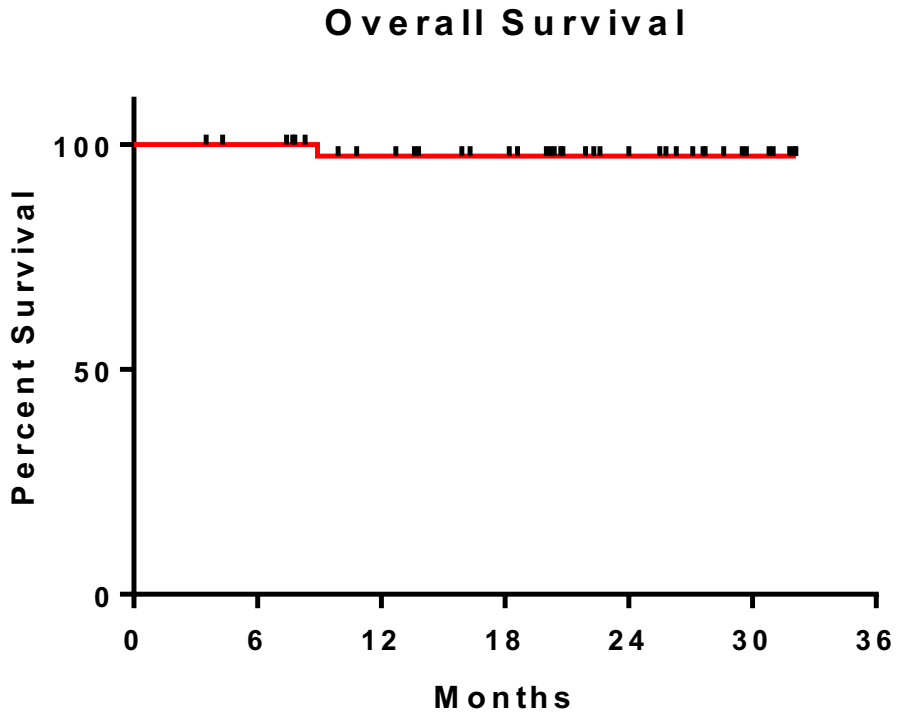
- FC: 43%
  - After institution of prophylactic G-CSF = 13%
- Ibrutinib: 41%
- Most common reason for dose reduction: myelosuppression

Patient Disposition

- Of the 45 pts enrolled, 4 off study
  - New onset CHF (n=1)
    - 26-yr-old in course 9 (receiving iG). Developed new onset CHF. No prior cardiac history. Started weight loss supplement few days prior to symptoms. Died from worsening CHF. ? Ibrutinib-related
  - Pulmonary MAC infection (n=1)
  - G3 IRR, G4 thrombocytopenia (n=1)
  - Consent withdrawal (n=1)

Overall Survival for All Pts (N=45)



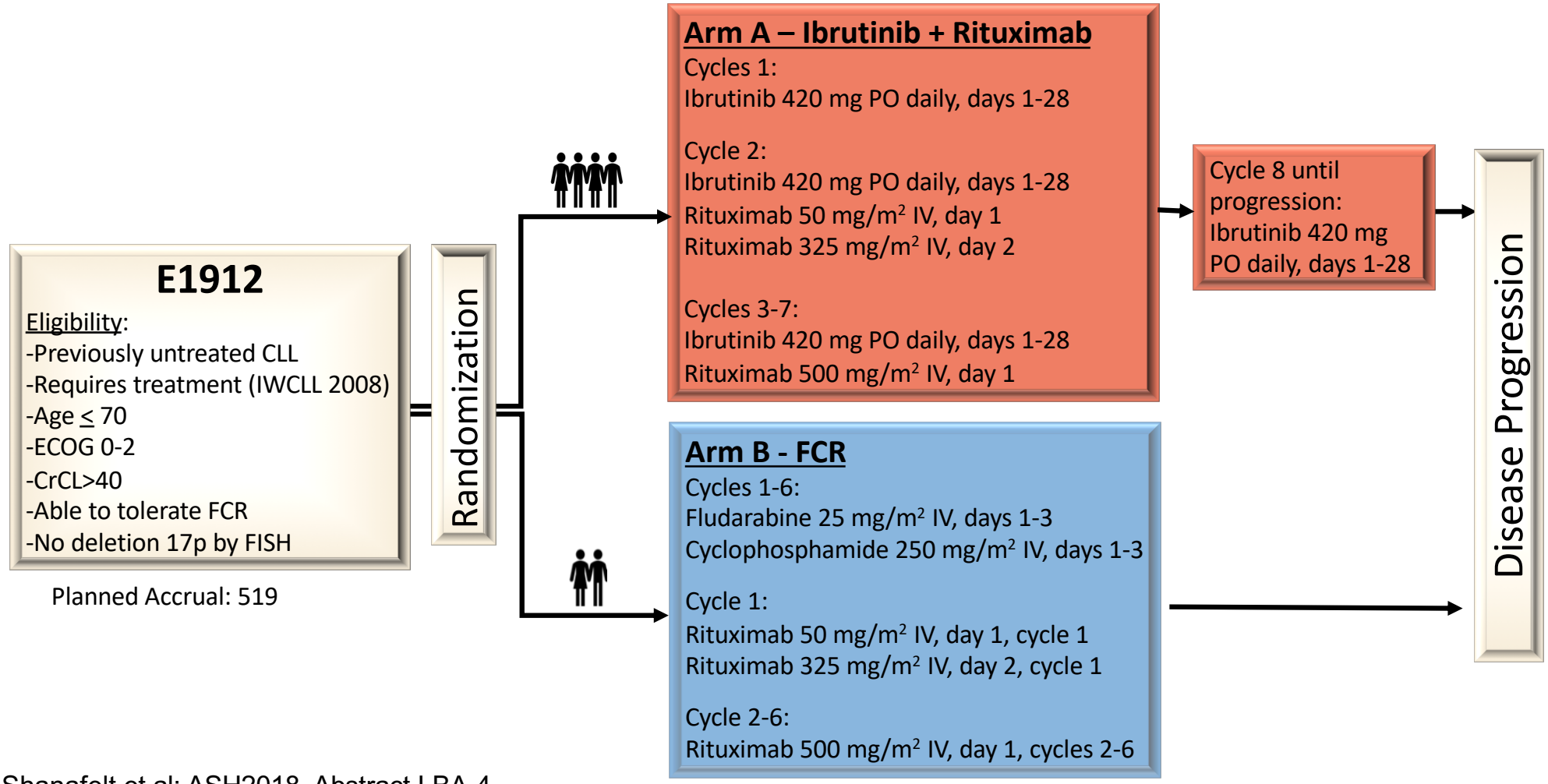


No patient had disease progression or MRD relapse

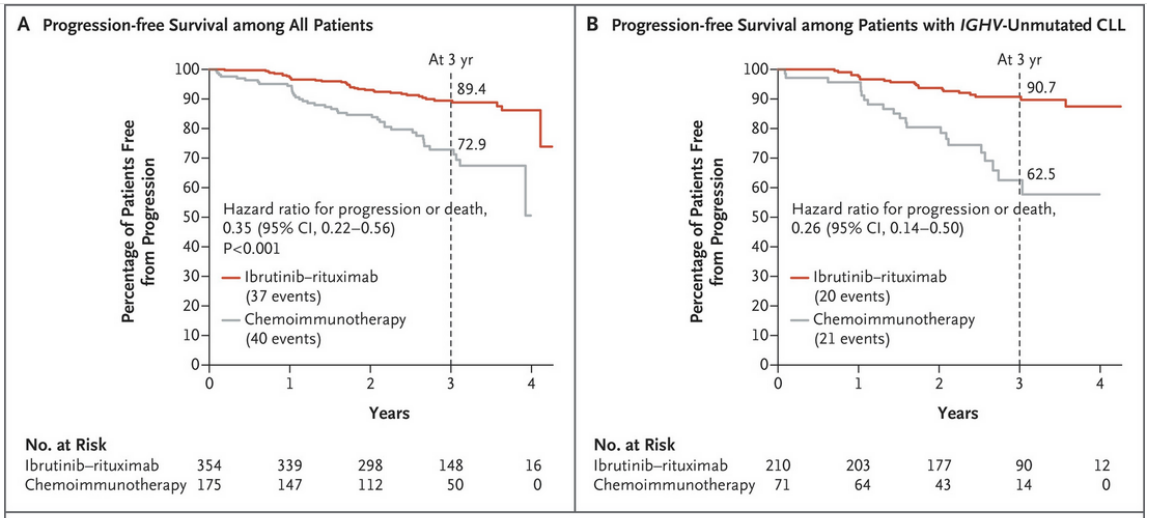
Conclusions

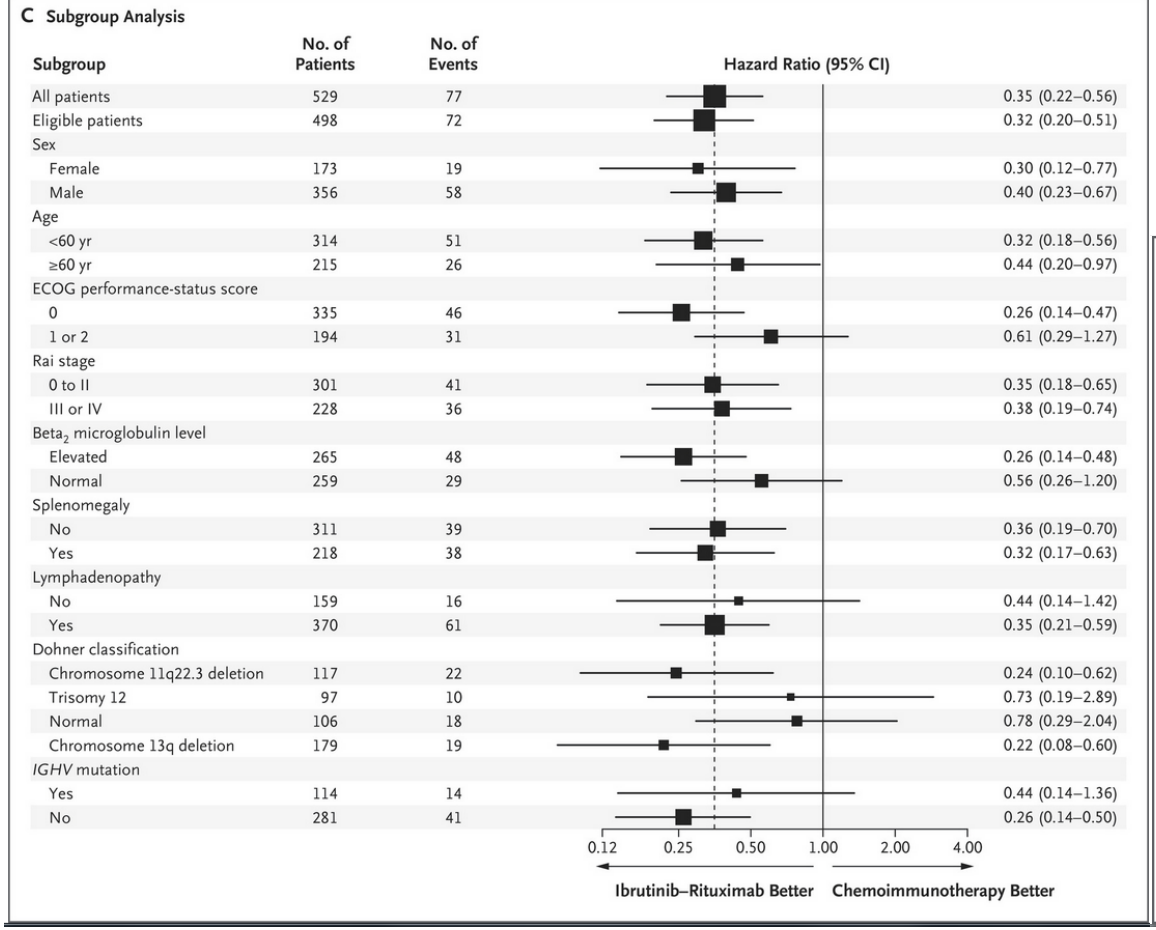
- iFCG induces high rate of BM U-MRD4 remission: 87% after 3 cycles
- All 32 patients reaching 1 yr had BM U-MRD4 and discontinued ibrutinib
- No pt had disease progression or MRD relapse
- Neutropenia and thrombocytopenia common during iFCG courses; neutropenia risk decreased with prophylactic G-CSF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

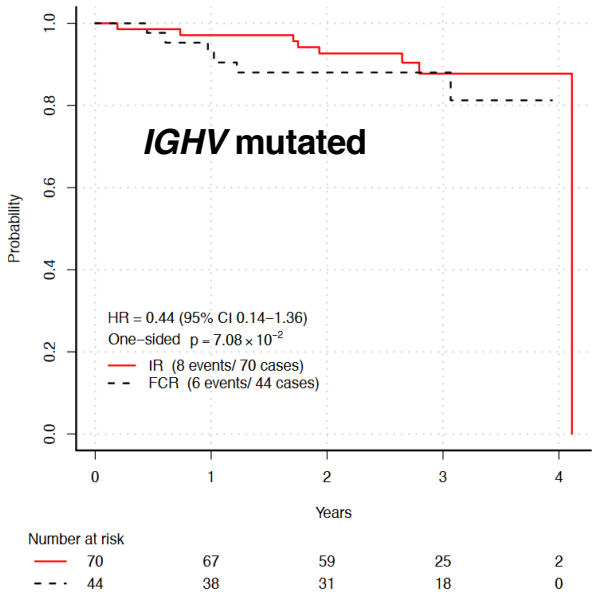
Study design

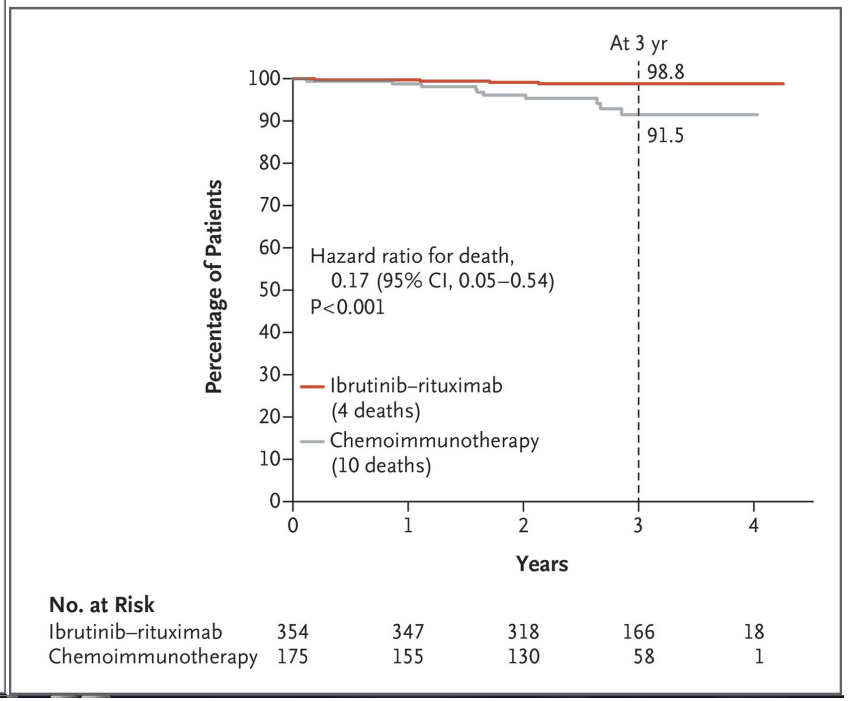


Shanafelt et al; ASH2018, Abstract LBA-4









Shanafelt et al; NEJM 381(5):432-443, 08-2019

Thank-
you!

Dept. of Leukemia, MDACC

Questions? jaburger@mdanderson.org