Annual Steven Coutre Chronic Lymphocytic Leukemia Memorial Lecture

Therapeutic Options in CLL in 2023: Choosing Wisely: Initial Therapy in CLL

Jennifer Woyach, MD
D Warren Brown Professor of Leukemia Research
The Ohio State University

The James

THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

Steven Coutre, MD

Objective

- To discuss the currently available standards for frontline CLL in the context of open questions in the field

What are the ongoing questions in frontline CLL?

- Is venetoclax/obin or continuous BTKi based therapy better?
- Are there patients who should be treated with CIT, and what is the best way to do this?
- What is the optimal fixed duration regimen in CLL?
- Should everyone receive a second generation BTKi?
- Is there a role for early therapy?

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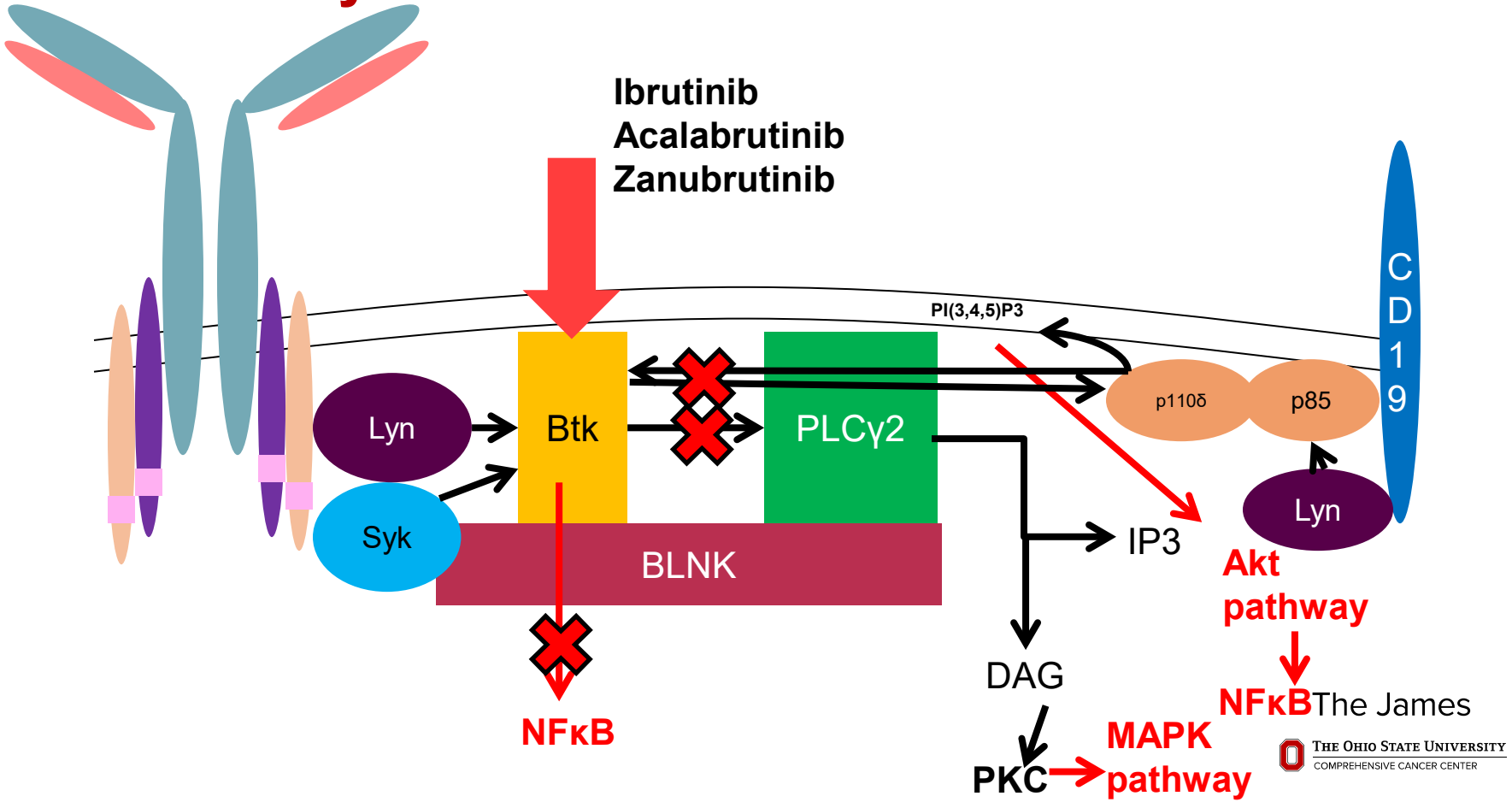
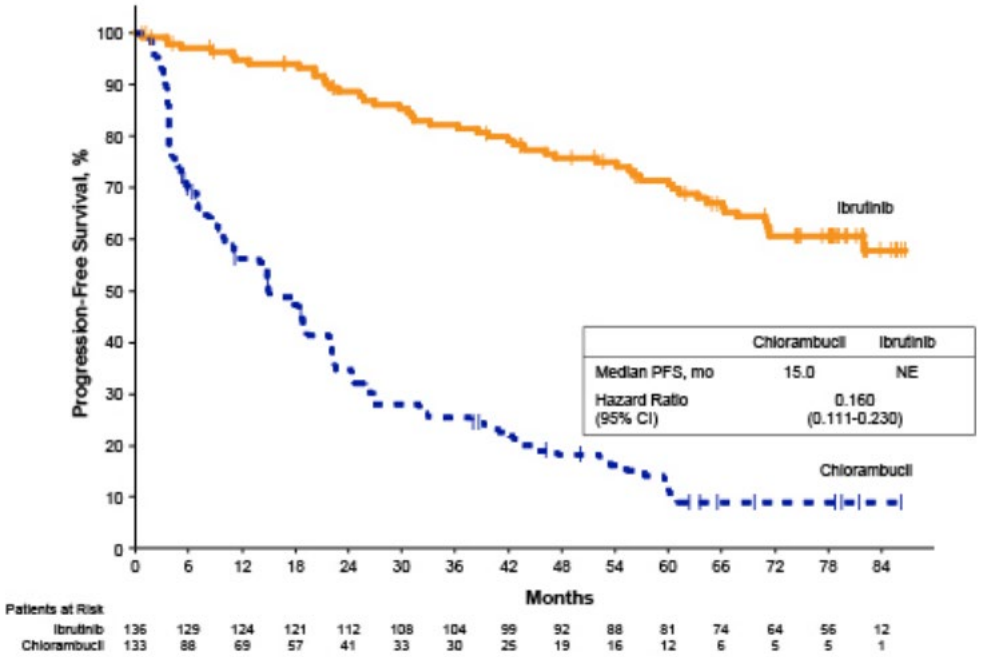
BCR Pathway and BTK Inhibition



Ibrutinib in Treatment-Naïve CLL: RESONATE 2



- Randomized untreated patients ≥65 to ibrutinib or chlorambucil
- 61% of patients progression-free at 6.5 years

Ghia et al, EHA 2021

DRIVE score 1

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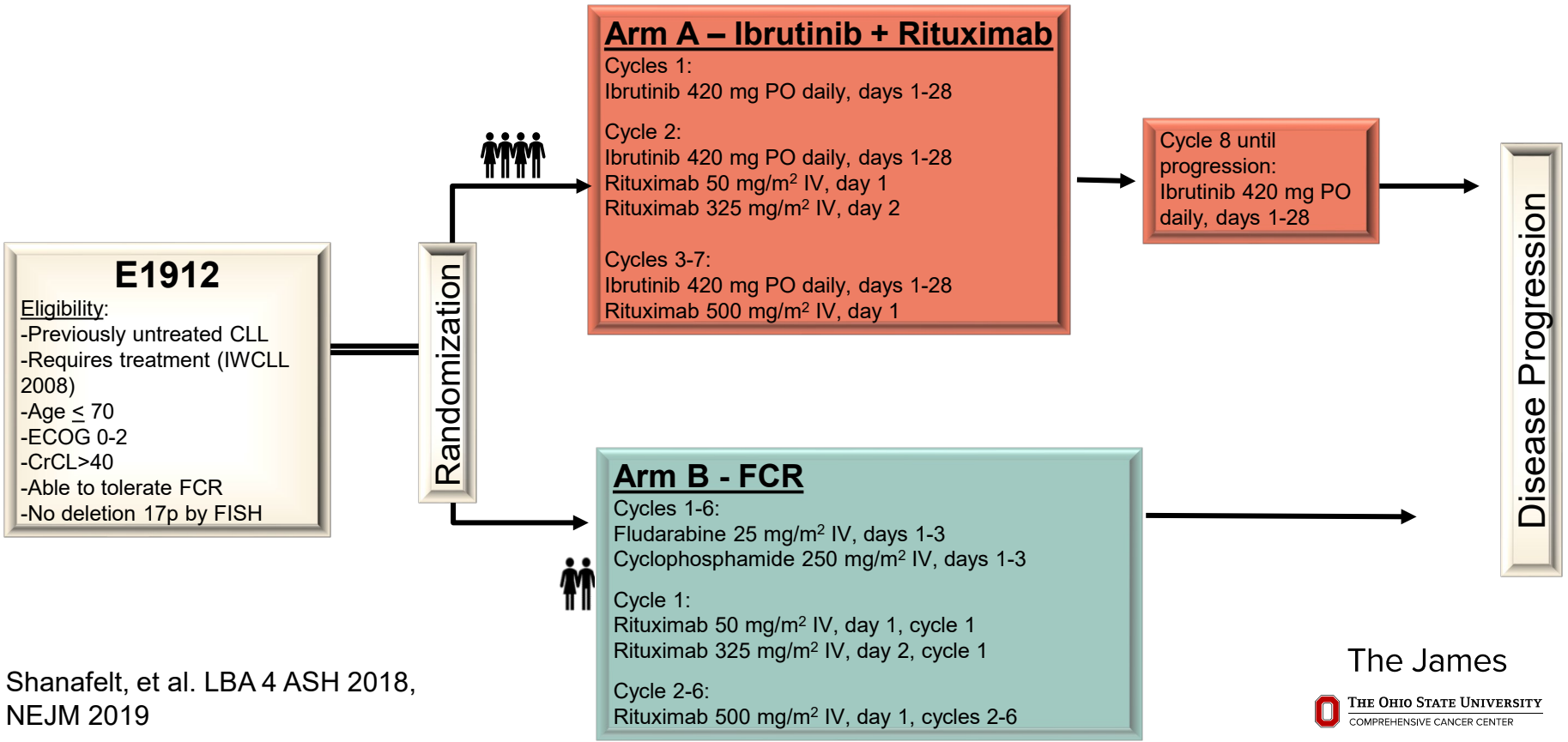
ECOG 1912 Study Design



Shanafelt, et al. LBA 4 ASH 2018, NEJM 2019

E1912 Patient Characteristics

Baseline characteristics		IR n=354	FCR n=175	Total
Median age (y)		58	57	58
Age ≥ 60		41.0%	40.0%	40.6%
Female		33.3%	31.4%	32.7%
ECOG = 0		63.8%	62.3%	63.3%
Rai stage 0		3.1%	5.1%	3.8%
Rai stage I-II		52.8%	53.7%	53.1%
Rai stage III-IV		44.1%	41.1%	43.1%
FISH	11q deletion	22.0%	22.3%	22.2%
	Trisomy 12	19.8%	15.4%	18.3%
	13q deletion	34.2%	33.1%	33.8
B2M >3.5 mg/L		51.9%	48.0%	50.6%
IGHV Unmutated*		75.0%	61.7%	71.1%

*Tested in 437 (82%) patients

Shanafelt, et al. LBA 4 ASH 2018, NEJM 2019

Race NR

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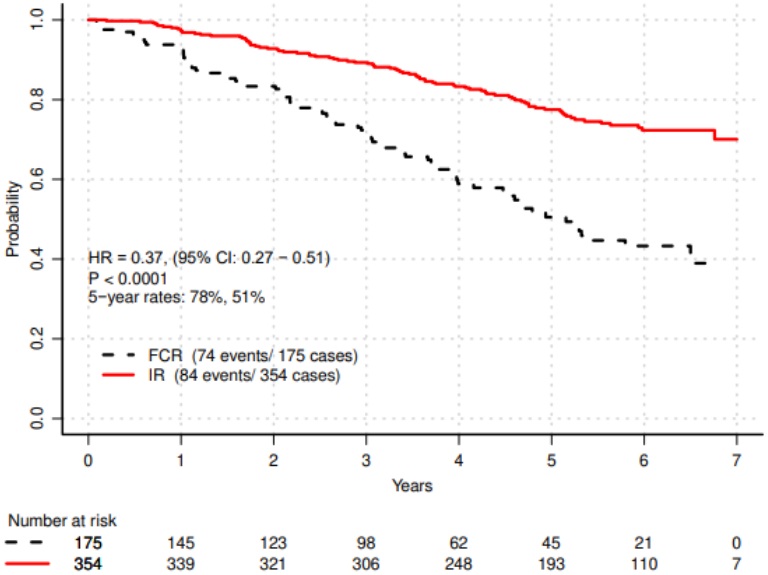
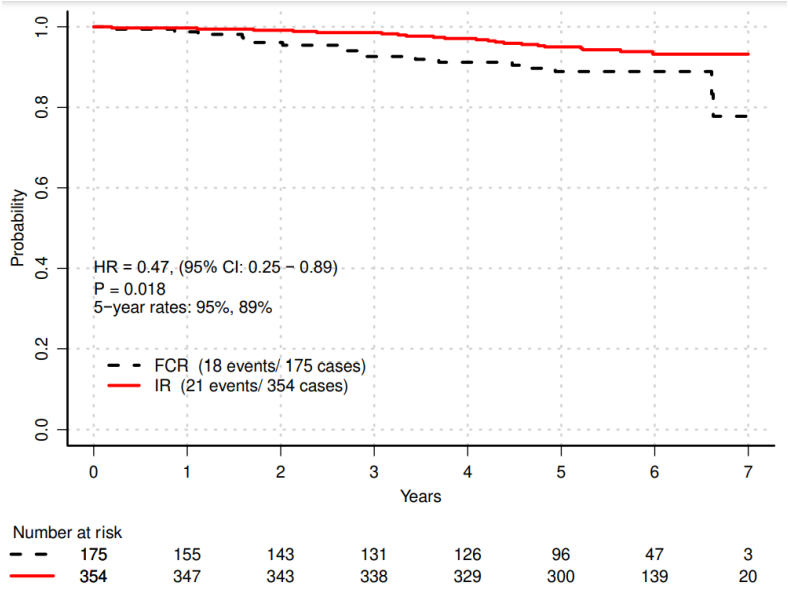
E1912 Progression Free Survival and Overall Survival

PFS



OS



5 yr PFS 78% vs 51%
5 yr OS 95% vs 89%

Shanafelt, et al, ASH 2019, abstract 33

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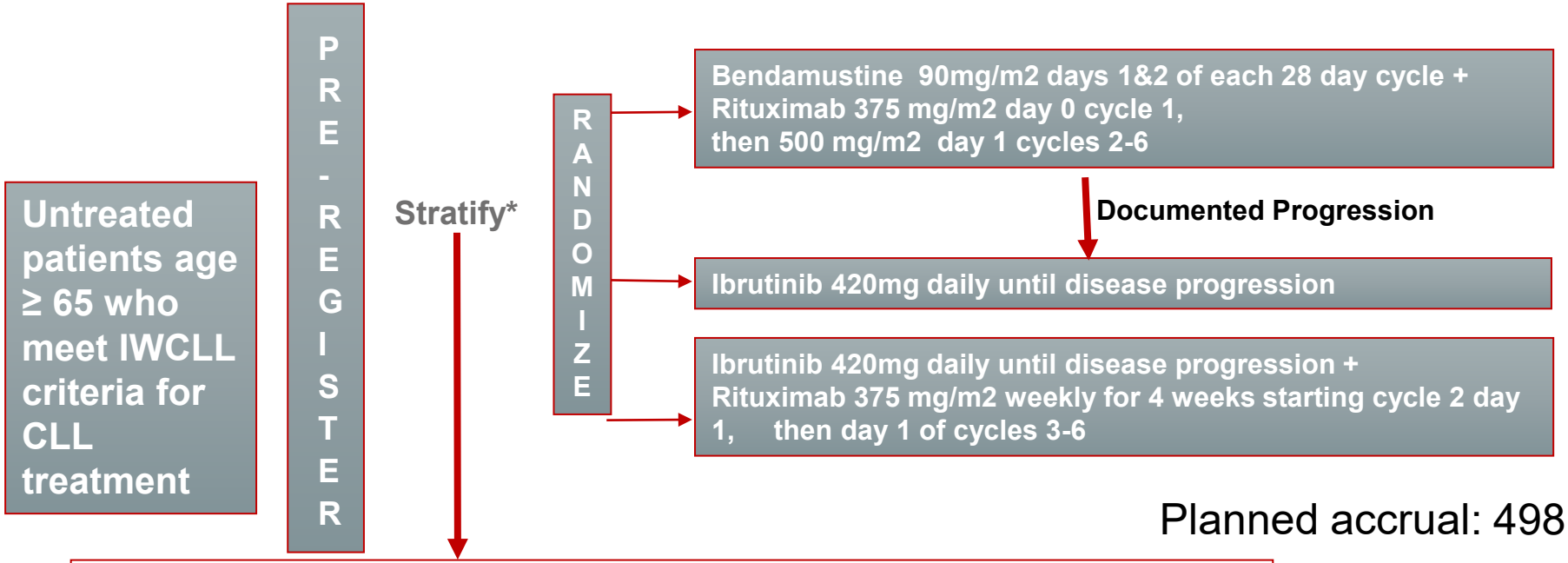
A041202 Schema



Planned accrual: 498

Stratification

- High risk vs intermediate risk Rai Stage
- Presence vs absence of del(11q22.3) or del(17p13.1) on FISH performed locally
- < 20% vs ≥ 20% Zap-70 methylation of CpG 3 performed centrally

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Patient Characteristics

Characteristic	Total N=547	BR N=183	Ibrutinib N=182	IR N=182
Age (years), median (range)	71 (65-89)	70 (65-86)	71 (65-89)	71 (65-86)
Male, %	67	65	68	69
ECOG 0-1, %	97	95	97	99
White blood cell count x10^3/μL, median (range)	82 (4-518)	92 (7-518)	79 (6-438)	70 (4-481)
FISH Characteristics, %				
Del (17p)	6	8	5	6
Del (11q)	19	18	19	21
TP53 mutation, %	10	9	9	12
Complex Karyotype, %	29	27	24	36
Zap-70 Unmethylated, %	53	52	53	53
IGVH unmutated*, %	61	58	63	61

*N= 360 total

DRIVE score 3

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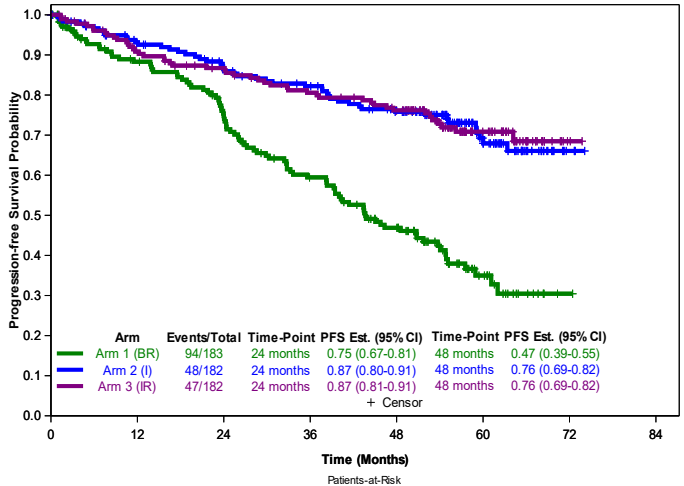
Woyach et al, NEJM 2018

A041202 Progression Free Survival and Overall Survival

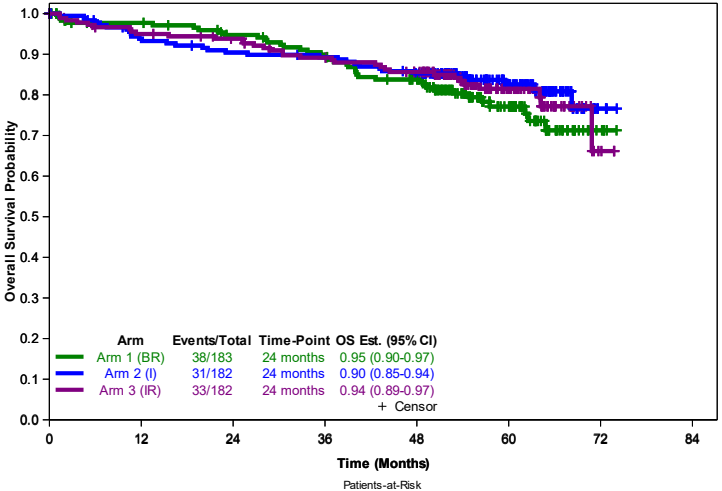


Pairwise Comparisons

I vs BR:
Hazard Ratio 0.36
95% CI: 0.26-0.52
P <0.0001

IR vs BR:
Hazard Ratio 0.36
95% CI: 0.25-0.51
P <0.0001

IR vs I:
Hazard Ratio 0.99
95% CI: 0.66-1.48
P = 0.96



Woyach et al, ASH 2021

Median Follow-up: 55 months

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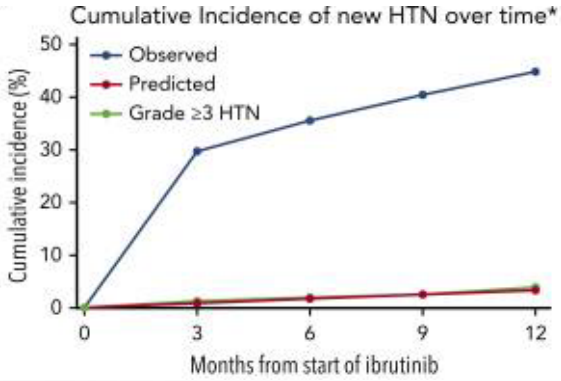
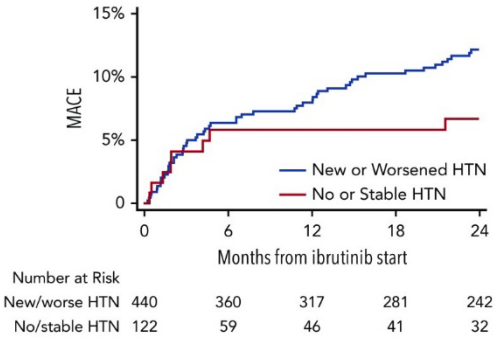
What is the down-side?

- Toxicity with ibrutinib leads to discontinuation rate 15-20% in trials, higher in real world experience
- Some adverse events (arthralgias) are not dangerous but can impact QOL
- Other adverse events (arrhythmias, HTN, bleeding) can be life-threatening

Median times to ibrutinib discontinuation stratified by toxicity	
Bleeding	8 months
Diarrhea	7.5 months
Atrial fibrillation	7 months
Infection	6 months
Arthralgia	5 months
Pneumonitis	4.5 months
Rash	3.5 months





Mato et al, Blood 2016; Dickerson et al, Blood 2019

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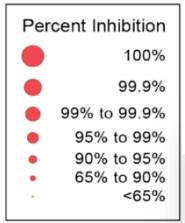
Arrhythmias with Ibrutinib

- **Atrial Fibrillation**
  - Analysis in 582 patients treated at Ohio State University
  - Estimated cumulative incidence of atrial fibrillation by time on treatment
    - 6 mo: 5.9%
    - 12 mo: 7.5%
    - 24 mo: 10.3%
  - Median time to onset of atrial fibrillation: 7.6 mo
  - Rate of atrial fibrillation increased ~4-fold with ibrutinib vs non-ibrutinib therapy (3.3 vs 0.84/100 person-year)

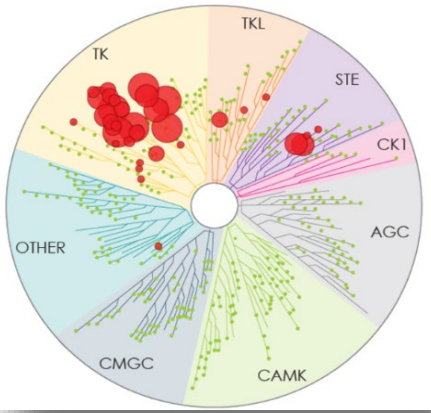
- **Ventricular arrhythmias**
  - Uncommon, but frequency increased vs general population (788 vs 200 to 400/100,000 person-year)
  - Long-term data with ibrutinib suggests about a 1% sudden death rate

Wiczer, et al. Blood Adv. 2017, Lampson et al. Blood 2017

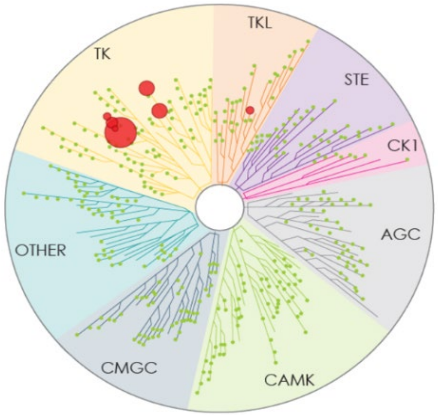
How are Next-Generation BTKi Different?



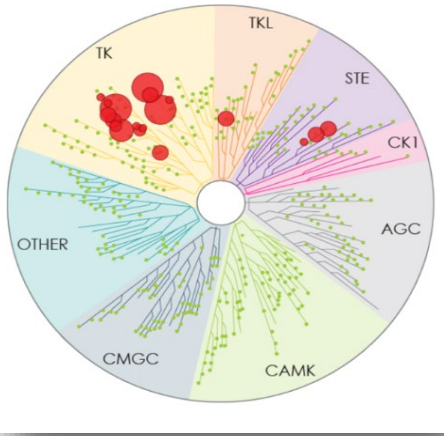
Ibrutinib



Acalabrutinib

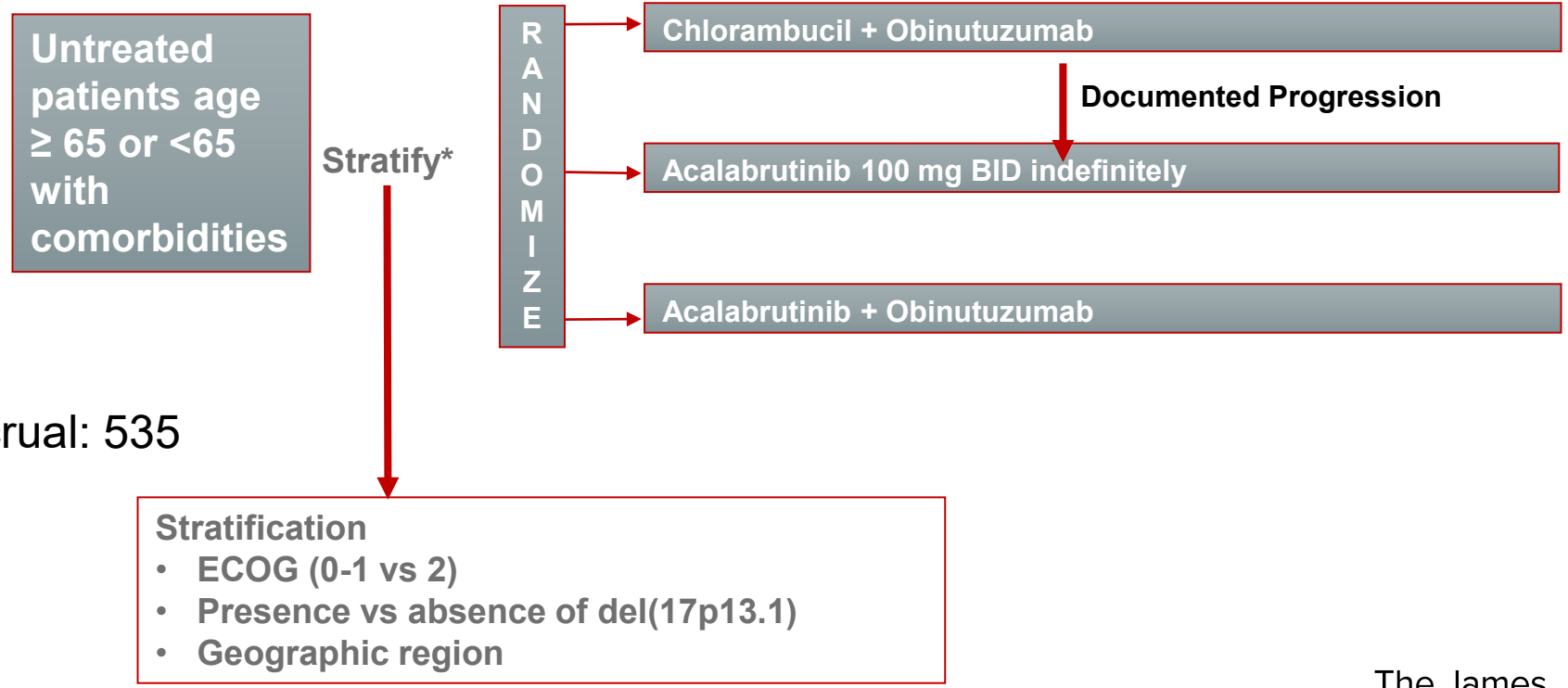


Zanubrutinib



Increased selectivity is expected to lead to improved tolerability

ELEVATE TN Study

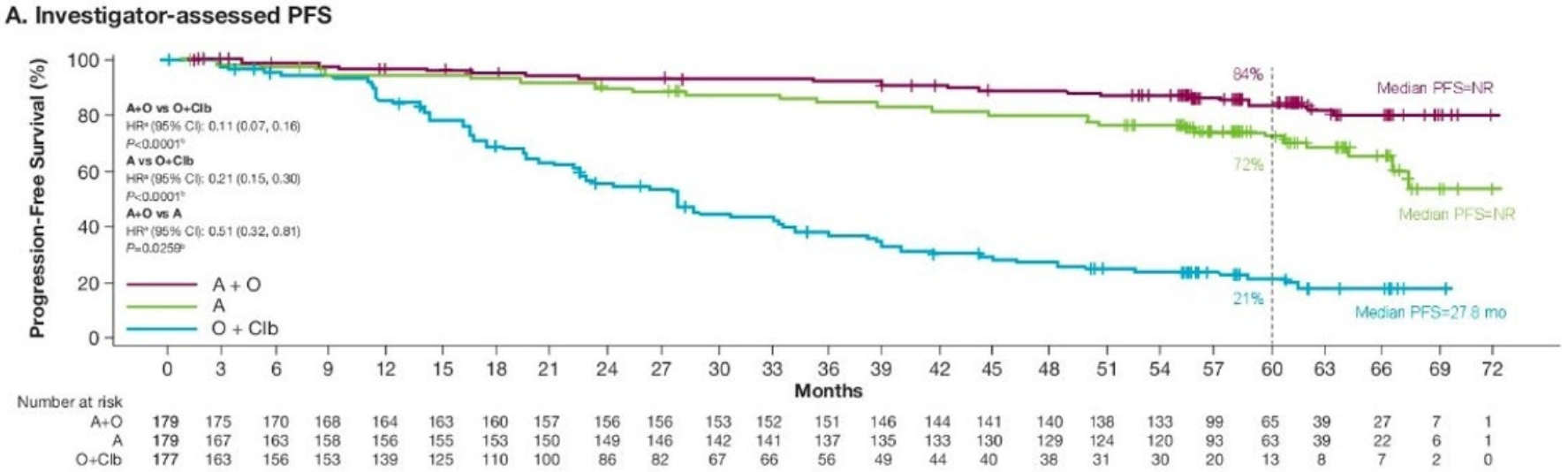


Accrual: 535

Sharman et al, Lancet 2020

DRIVE score 4

ELEVATE-TN Long-term Follow-up



5 year PFS:

A + O 84%
A 72%
Ch + O 21%

Sharman et al, ASCO 2022

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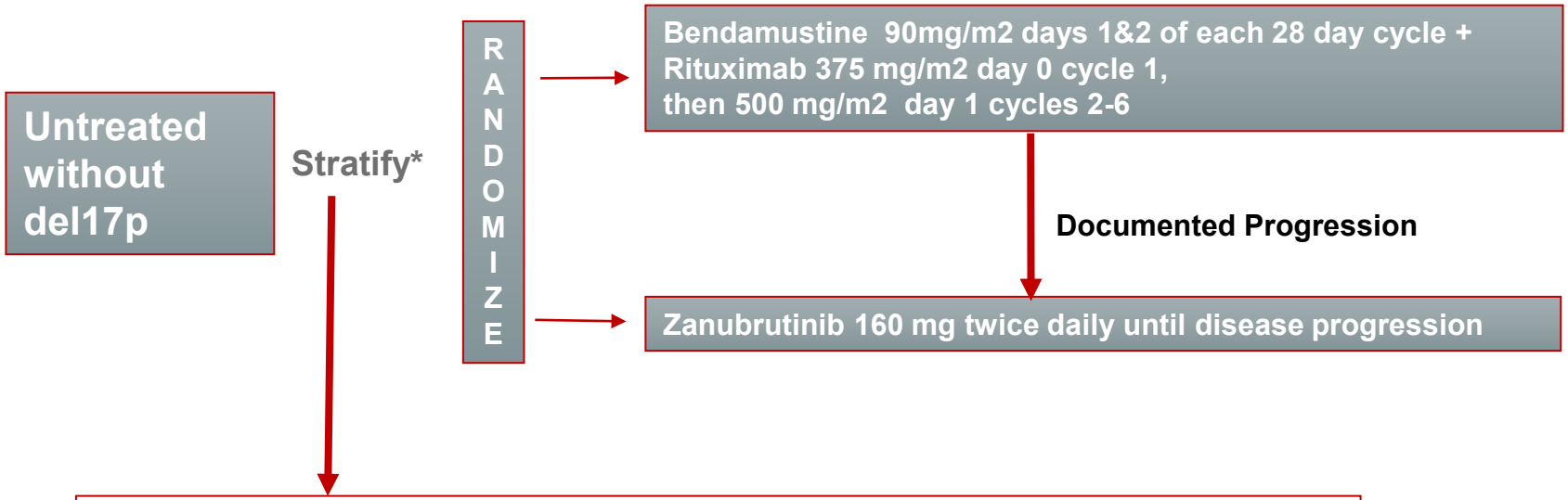
Sequoia Study



Stratification

- Age (<65 vs ≥65 years)
- Binet stage (C vs A/B)
- IGHV mutated vs unmutated
- Geographical region (North America vs Europe vs Asia-Pacific)

DRIVE score 0

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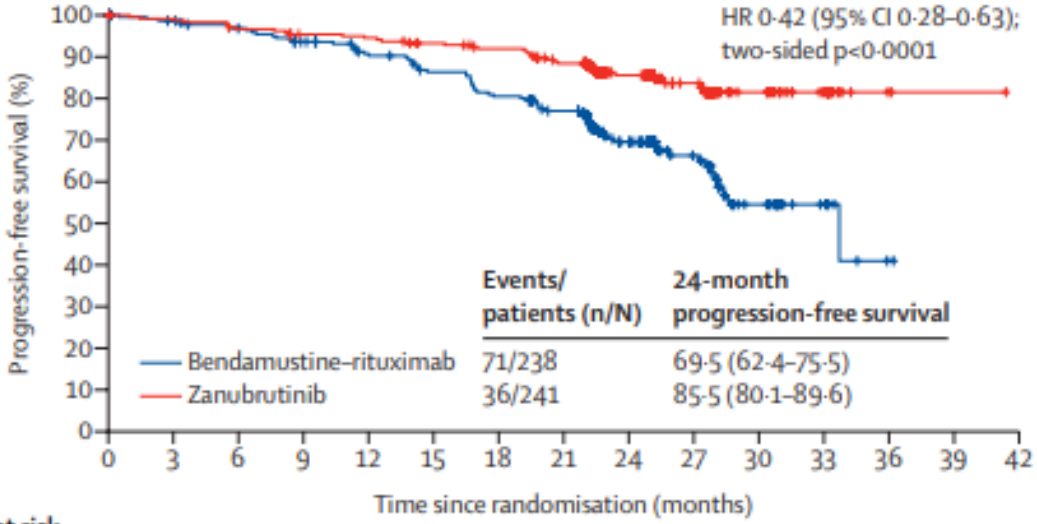
Sequoia Baseline Characteristics

Baseline characteristics		Zanu n=241	BR n=238
Median age (y)		70	70
Age ≥ 65		81%	81%
Female		37%	39%
ECOG = 0		46%	42%
Binet Stage A/B		71%	71%
Binet Stage C		29%	29%
TP53 mutated		6%	6%
FISH	11q deletion	18%	19%
	Trisomy 12	19%	21%
	13q deletion	56%	54%
B2M >3.5 mg/L		58%	57%
IGHV Unmutated		53%	52%

Sequoia PFS



Number at risk number censored)															
Bendamustine–rituximab	238 (0)	218 (17)	210 (21)	200 (24)	187 (30)	176 (33)	164 (33)	150 (40)	89 (89)	54 (121)	20 (148)	8 (160)	1 (166)	0 (167)	.. ..
Zanubrutinib	241 (0)	237 (2)	230 (3)	224 (6)	222 (6)	214 (11)	208 (14)	195 (19)	123 (86)	79 (128)	31 (174)	17 (188)	2 (203)	1 (205)	0 (205)

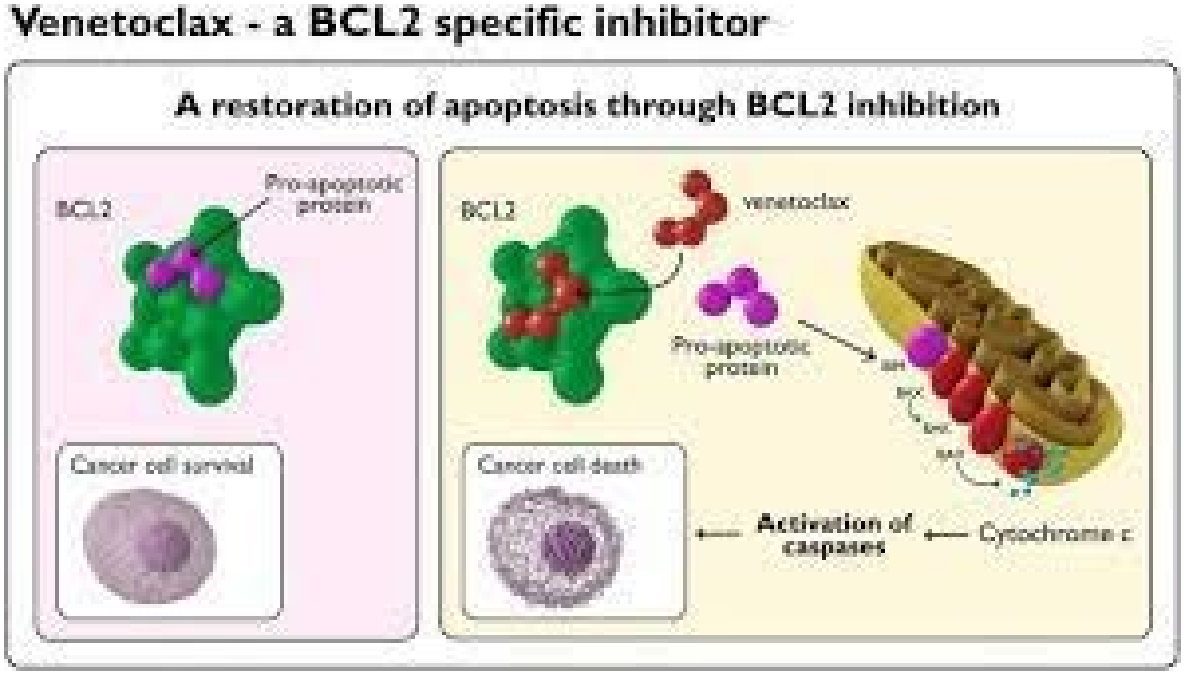
DRIVE score 1

Tam et al, Lancet Oncol 2022

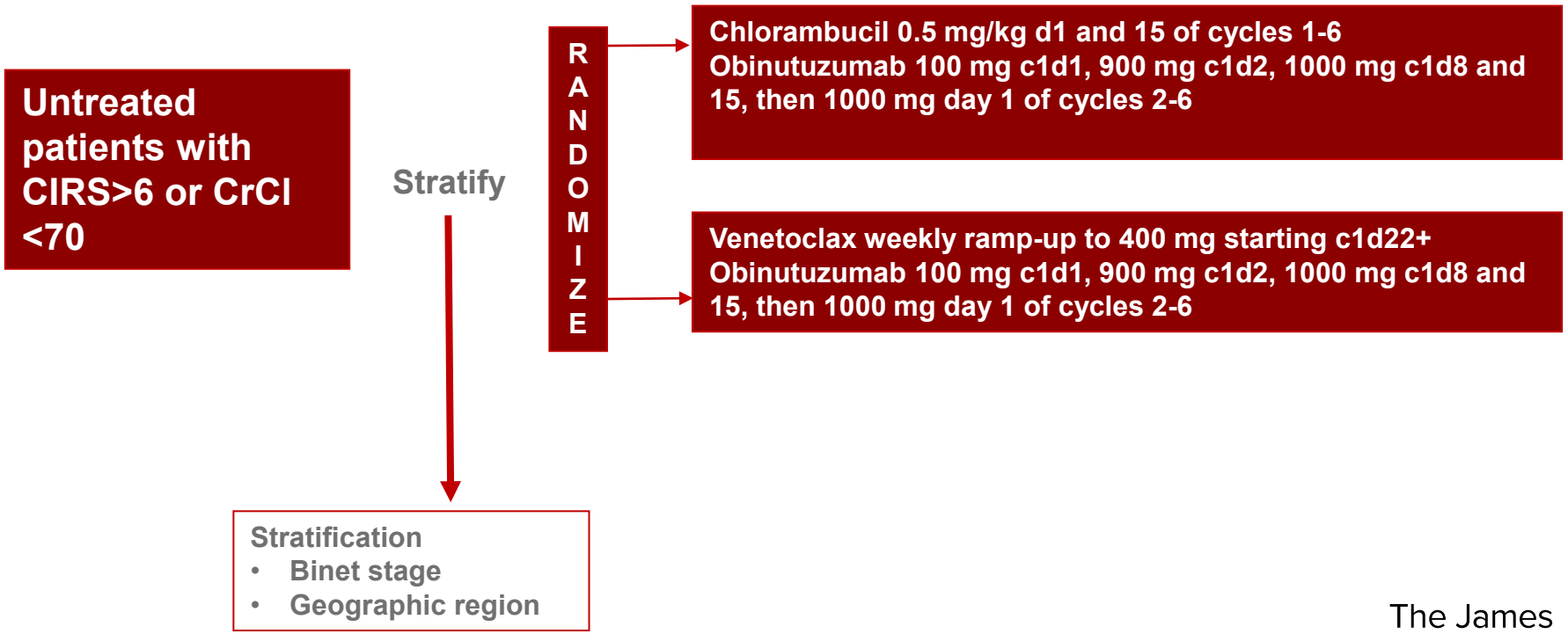
What do these data tell us?

- Ibrutinib is more effective than chemoimmunotherapy in the treatment of CLL
- Ibrutinib may be more toxic in older patients than in younger
- The addition of rituximab to ibrutinib does not improve PFS.
- Acalabrutinib and zanubrutinib also show excellent results with better safety profiles
- Acalabrutinib may combine better with anti-CD20 ab than ibrutinib

BCL2 inhibition in CLL: Venetoclax



CLL14 Study Design



Fischer, NEJM 2019

Patient Characteristics

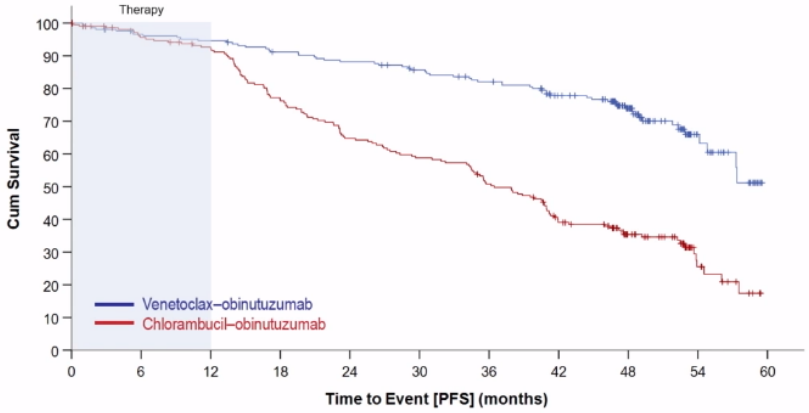
Characteristic	VO N=216	ChO N=216
Age (years), median (range)	72 (41-89)	72 (41-89)
Male, %	67.6	66.2
CIRS-G score >6	86.1	81.9
FISH Characteristics, %		
Del (17p)	8.5	7.3
Del (11q) without del(17p)	18	19.7
TP53 mutation, %	11.1	8.3
IGVH unmutated, %	60.5	59.1

DRIVE score 3

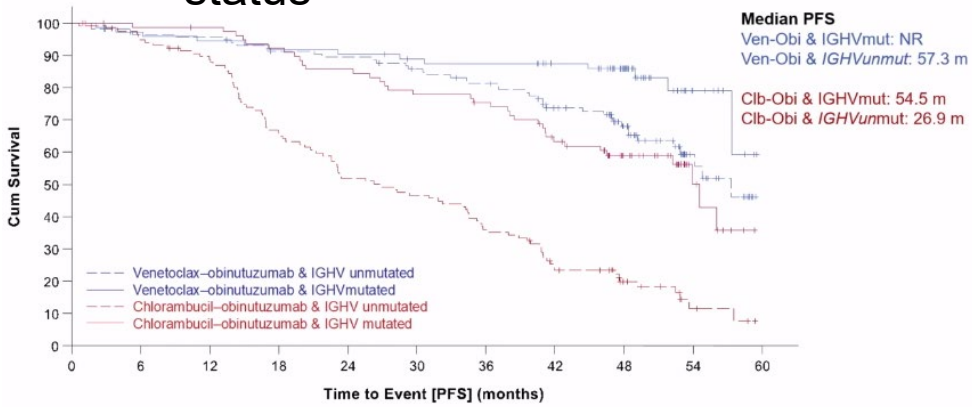
Fischer, NEJM 2019

Long-term update from CLL14

PFS



PFS by IGHV status

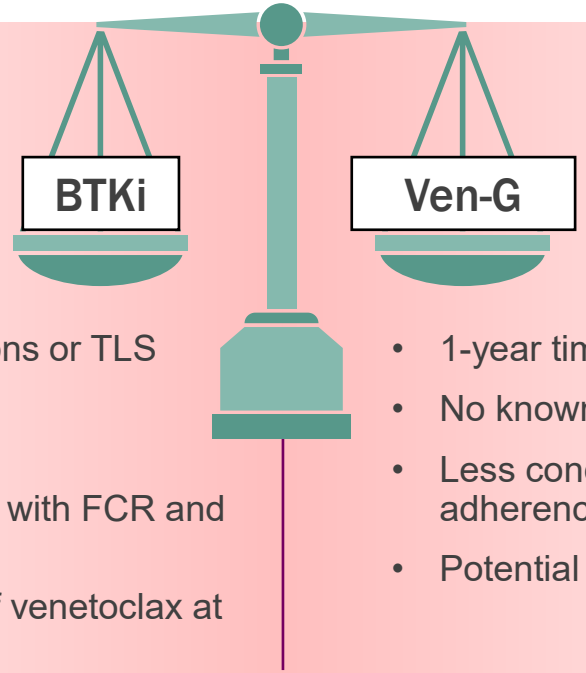


Al-Sawaf et al, EHA 2021

What does this trial tell us?

- Venetoclax + obinutuzumab is more effective than chlorambucil + obinutuzumab
- At 4 years, PFS for VO is similar to what is reported for BTKi
- Long term results will be critical to determine efficacy of this fixed duration regimen vs indefinite regimens

BTKi vs Ven/Obin in TN CLL: Factors to Consider



- Convenience (no infusions or TLS monitoring)
- Long-term efficacy data
- Phase 3 data compared with FCR and BR (ibrutinib)
- More data for efficacy of venetoclax at time of progression

- 1-year time-limited therapy
- No known cardiac or bleeding risks
- Less concern with long-term adherence
- Potential for cost-savings

ıes

Is venetoclax/obin or continuous BTKi based therapy better?

- Efficacy differences—unknown. CLL17 will definitively answer this question. Long-term follow-up from current studies will be helpful
- Cost differences—likely favors venetoclax/obin
- Safety differences—short term probably favors venetoclax, but long-term unknown
- My approach: Assuming relatively equivalent efficacy, comes down to patient preference on therapy duration, willingness for upfront visit intensity. I prioritize ven/obin for IGHV mutated and BTKi for patients with TP53 abnormalities

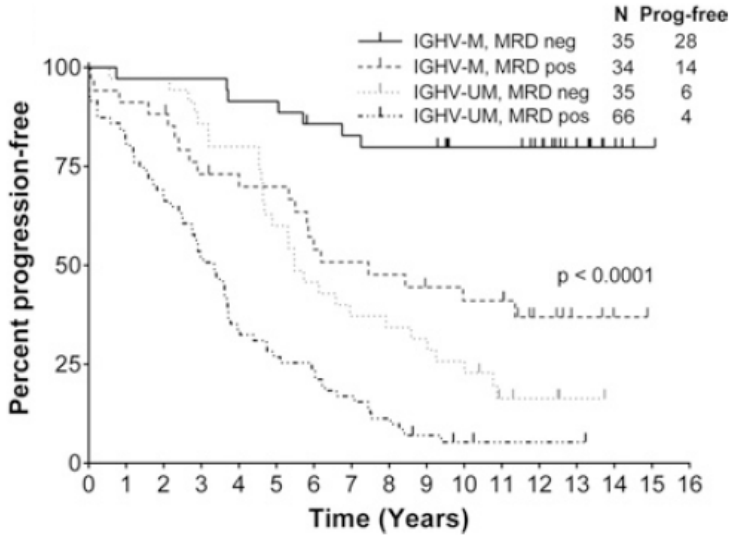
What are the ongoing questions in frontline CLL?

- Is venetoclax/obin or continuous BTKi based therapy more effective?
- **Are there patients who should be treated with CIT, and what is the best way to do this?**
- What is the optimal fixed duration regimen in CLL?
- Should everyone receive a second generation BTKi?
- Is there a role for early therapy?

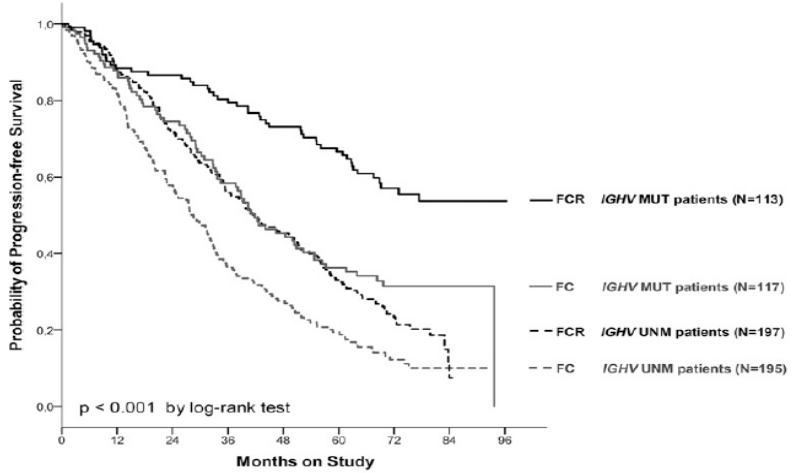
Long-Term FCR Data

- Two studies showing a plateau in relapse in IGHV mutated patients
- FISH panel data not available

MD Anderson Cohort



GCLLSG CLL8



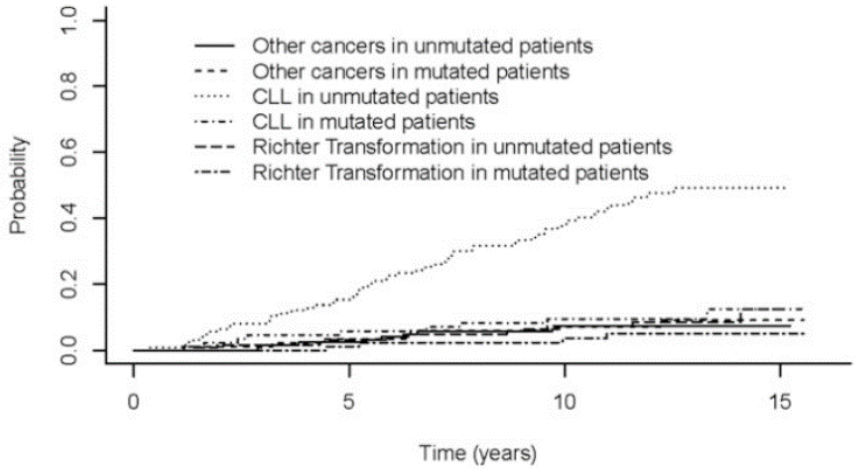
Thompson et al, Blood 2016; Fischer et al., Blood 2016

Long-Term FCR Toxicities

Cancer	Number
Secondary hematologic	
AML/myelodysplasia	14
Myeloproliferative disorder, unclassified	1
T-acute lymphoblastic leukemia	1
Mature T-cell lymphoproliferative disorders	3
RT	
Diffuse large B-cell lymphoma	20
Hodgkin lymphoma	3
Burkitt lymphoma	1
Solid tumors	
Non-melanoma skin cancer	28
Prostate	9
Breast cancer	4
Melanoma	4
Lung cancer	3
Ovarian cancer	3
Renal cell carcinoma	3
Papillary thyroid cancer	2
Esophageal adenocarcinoma	1
Merkel cell tumor	1
Brain tumor	1
Colorectal cancer	1
Other	3

4.7%

Cumulative Incidence of Death



Thompson et al, Blood 2016

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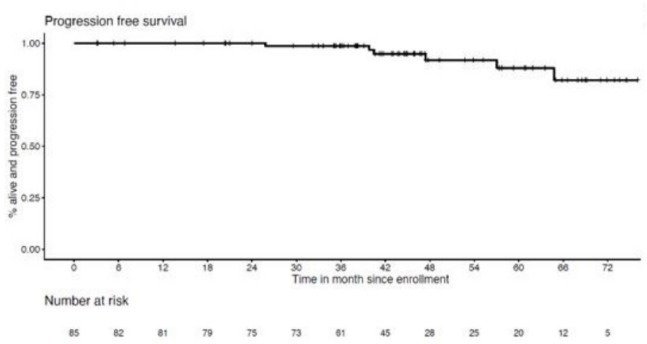
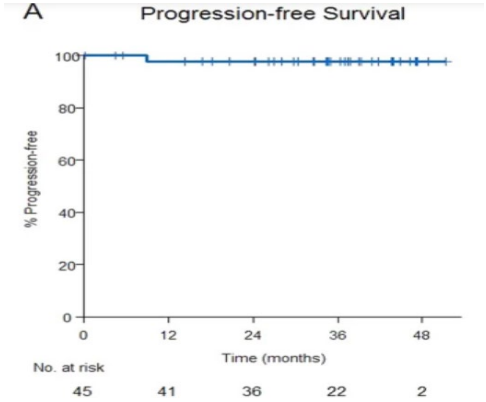
Abbreviated FCR + BTKi



- iFCR (6 cycles)
- Median f/u 40.3 mo, CR with uMRD marrow 55% (uMRD marrow 84%)
- 40 month PFS 97%
- 2 MDS



- iFCG (3 cycles)
- All mutated IGHV and no TP53
- Median f/u 41.3 mo, CR 69%, uMRD marrow 98%
- 36 month PFS 98%
- 1 MDS

Davids et al, ASH 2021
Jain et al, Leukemia 2021

Are there patients who should be treated with CIT, and what is the best way to do this?

- Only young, fit patients with IGVH mutated CLL and without high risk genomic abnormalities should be considered for FCR due to the high chance of cure (but ven-based regimens also look great; follow-up from CLL13 trial will help)
- FCR + ibrutinib and FCG + ibrutinib in clinical trials with excellent results
- My approach: No chemotherapy

What are the ongoing questions in frontline CLL?

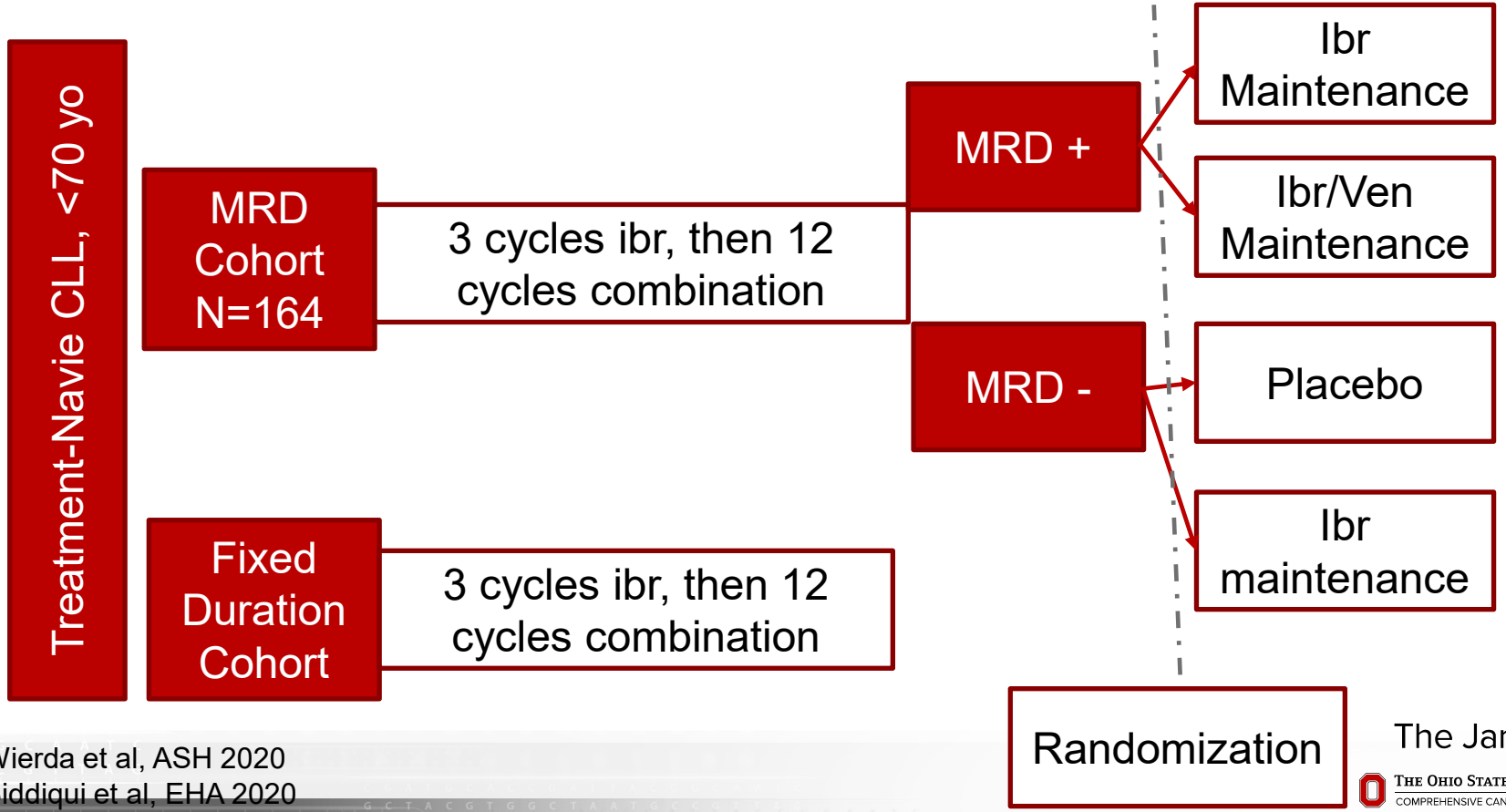
- Is venetoclax/obin or continuous BTKi based therapy more effective?
- Are there patients who should be treated with CIT, and what is the best way to do this?
- **What is the optimal fixed duration regimen in CLL?**
- Should everyone receive a second generation BTKi?
- Is there a role for early therapy?

What is the optimal time-limited regimen in CLL?

- Venetoclax/Obinutuzumab
- Venetoclax/Ibrutinib
- Venetoclax/Ibrutinib/Obinutuzumab
- Venetoclax/Acalabrutinib
- Venetoclax/Acalabrutinib/Obinutuzumab
- Venetoclax/Zanubrutinib
- Venetoclax/Zanubrutinib/Obinutuzumab

- Also, should they be fixed duration or MRD-guided??

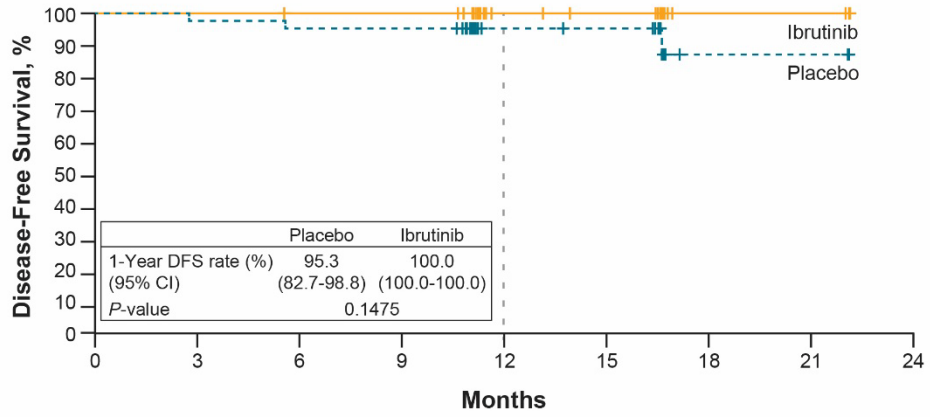
Phase 2 CAPTIVATE



Wierda et al, ASH 2020
Siddiqui et al, EHA 2020

Phase 2 CAPTIVATE MRD Cohort

Figure. DFS by Randomized Treatment Arm in Confirmed uMRD Group[a]



Patients at Risk

Placebo	43	42	41	41	22	21	3	3	0
Ibrutinib	43	43	42	42	25	23	5	5	0

[a]The 3 DFS events in placebo arm were disease progression in 2 patients and MRD relapse in 1 patient.

- Confirmed uMRD 30 month PFS
  - 95.3% placebo
  - 100% ibrutinib
- Without confirmed uMRD 30 month PFS
  - 95.2% ibrutinib
  - 96.7% ibr/ven

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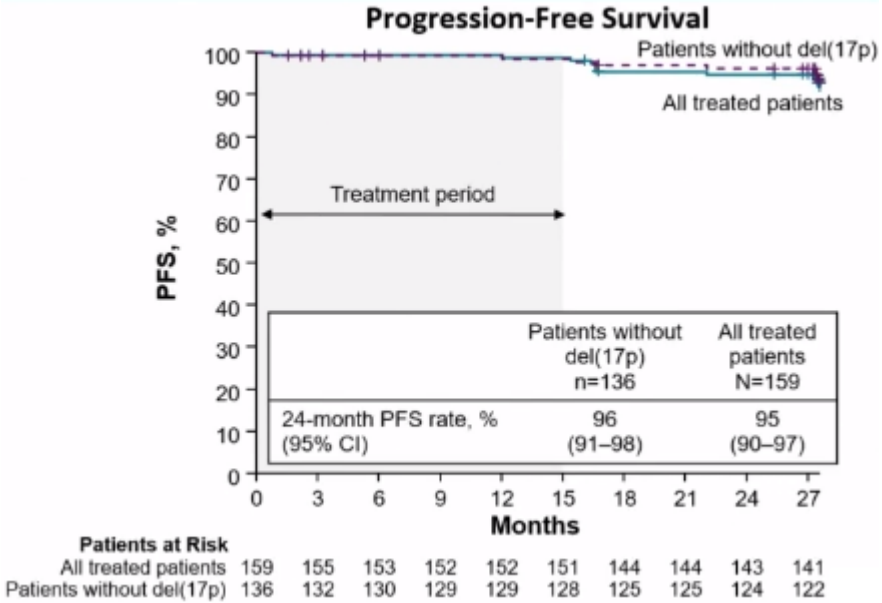
Ibrutinib/Venetoclax Fixed Duration: CAPTIVATE

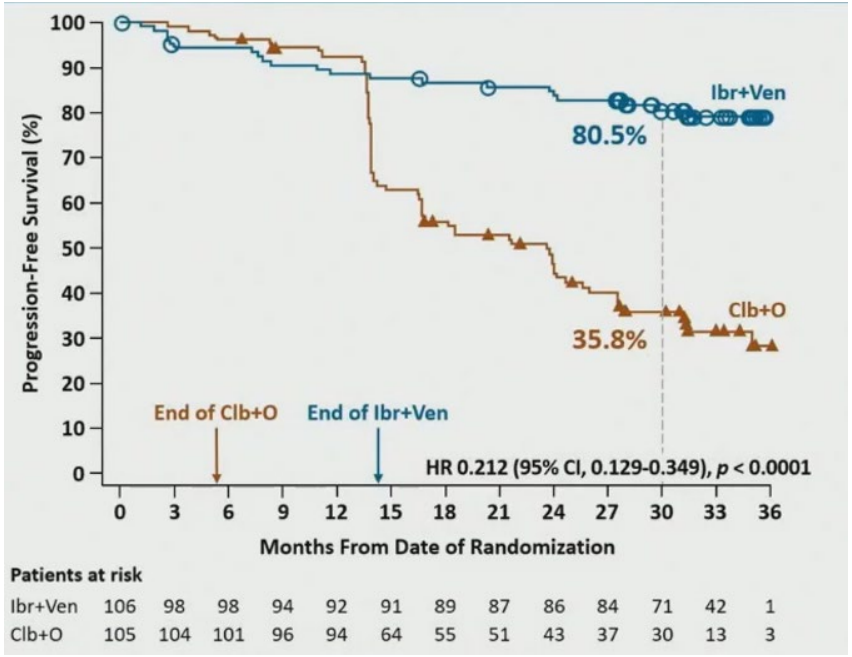
Characteristic	All treated patients N=159
Median age, years (range)	60 (33–71)
Male, n (%)	106 (67)
Rai stage III/IV disease, n (%)	44 (28)
High-risk features, n (%)	
Unmutated IGHV	89 (56)
del(17p)/*TP53* mutation	27 (17)
del(17p)	20 (13)
del(11q)[a]	28 (18)
Complex karyotype[b]	31 (19)
Any cytopenia, n (%)	54 (34)
ANC ≤1.5 × 10^9/L	13 (8)
Hemoglobin ≤11 g/dL	37 (23)
Platelets ≤100 × 10^9/L	21 (13)
Lymph node diameter ≥5 cm, n (%)	48 (30)
Median ALC × 10^9/L (range)	70 (1–503)
ALC ≥25 × 10^9/L, n (%)	120 (75)



Allan et al, EHA 2021

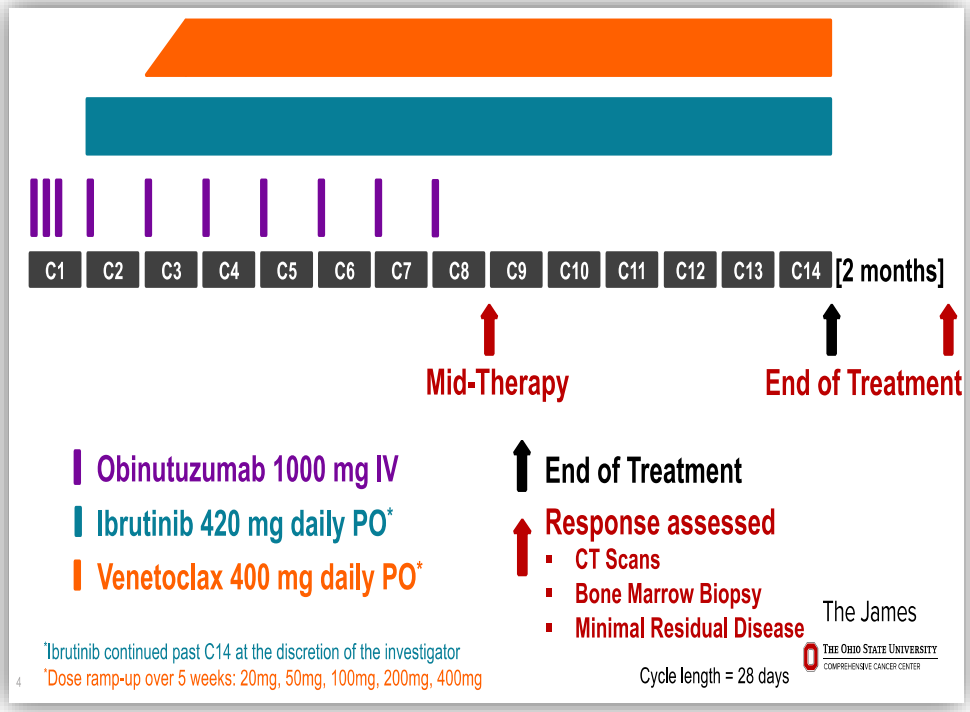
Ibrutinib/Venetoclax Fixed Duration: GLOW

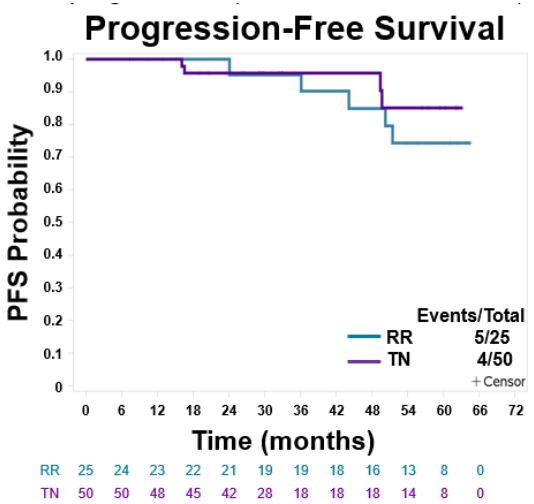
Characteristic	I+V (N = 106)	Clb+O (N = 105)
Age, median (range), years	71.0 (47, 93)	71.0 (57, 88)
≥ 75 years, %	33.0	35.2
Male, %	55.7	60.0
ECOG PS 1-2, %	67.0	62.9
CIRS score, median (IQR)	9 (6-12)	8 (5-10)
> 6, %	**69.8**	**58.1**
CrCl, median (range) mL/min	66.5 (34.0, 168.1)	63.2 (32.3, 180.9)
Rai Stage III-IV, %	57.3	52.5
Bulky Disease ≥5cm, %	39.0	36.2
Elevated LDH, %	**33.0**	**48.6**
Mutated *IGHV*[a], %	25.5	25.7
Unmutated *IGHV*[a], %	51.9	51.4
Del(11q), %	18.9	17.1
TP53 mutation, %	6.6	1.9



Munir et al, ASH 2021; Kater et al NEJM Evidence 2022

Ibrutinib/Venetoclax/Obinutuzumab Phase 2





Rogers et al, ASCO 2022

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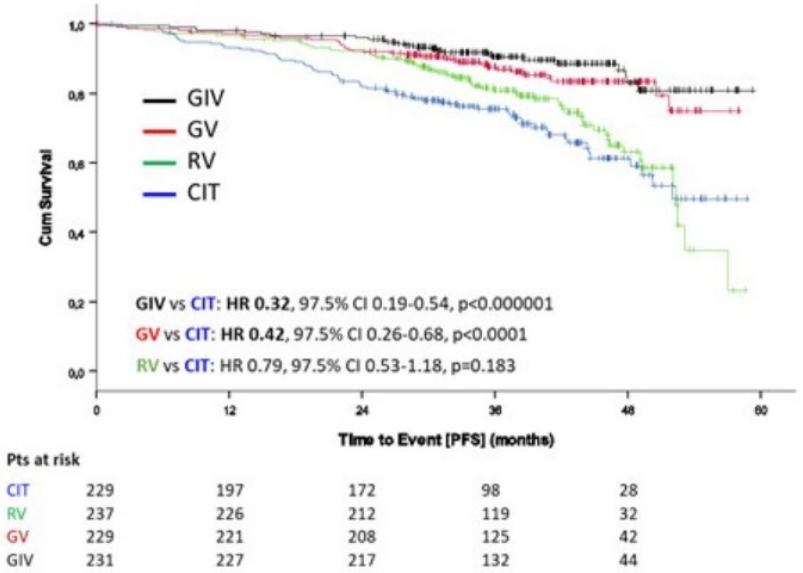
Ibrutinib/Venetoclax/Obinutuzumab Phase 3

- GAIA/CLL13 Study
- CIT vs VR vs VO vs IVO
- Median follow-up 38.8 months



Eichhorst et al, EHA 2022

What is the Optimal Time-Limited Regimen in CLL

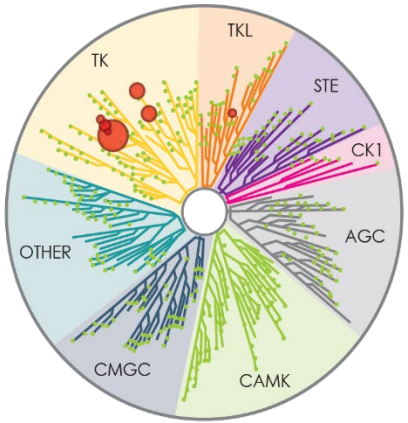
- Second generation combinations: AVO, ZV, ZVO all showing excellent early efficacy, may have improved safety
- Adding obinutuzumab adds some toxicity, studies will need to clarify the role of this
- Several ongoing and planned studies will compare BTK/BCL2 regimens to Ven/Obin

- My thoughts: BTK/BCL2 combos are appealing for patients with intermediate/?high risk disease, but long-term data are needed before switching practice from ven/obin

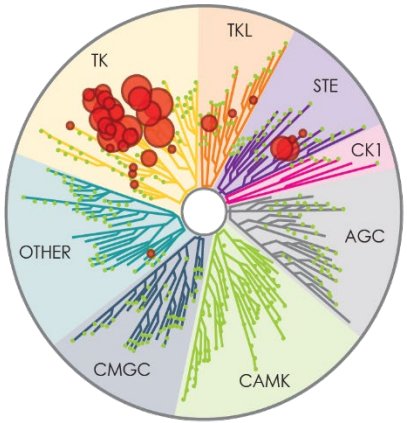
What are the ongoing questions in frontline CLL?

- Is venetoclax/obin or continuous BTKi based therapy more effective?
- Are there patients who should be treated with CIT, and what is the best way to do this?
- What is the optimal fixed duration regimen in CLL?
- **Should everyone receive a second generation BTKi?**
- Is there a role for early therapy?

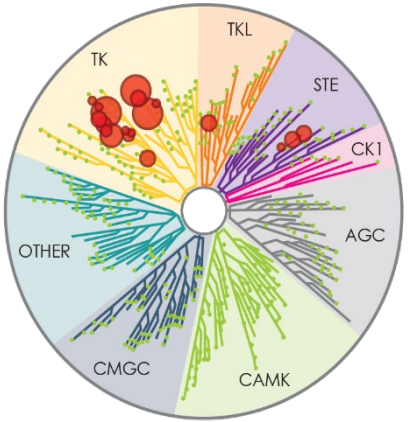
Acalabrutinib and Zanabrutinib are much more specific than Ibrutinib



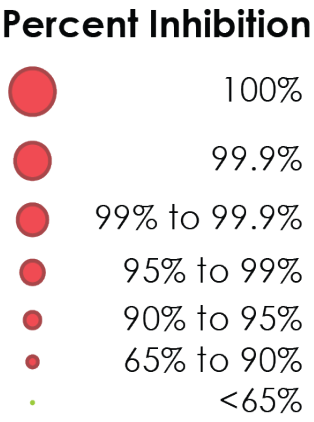
Acalabrutinib



Ibrutinib



Zanubrutinib



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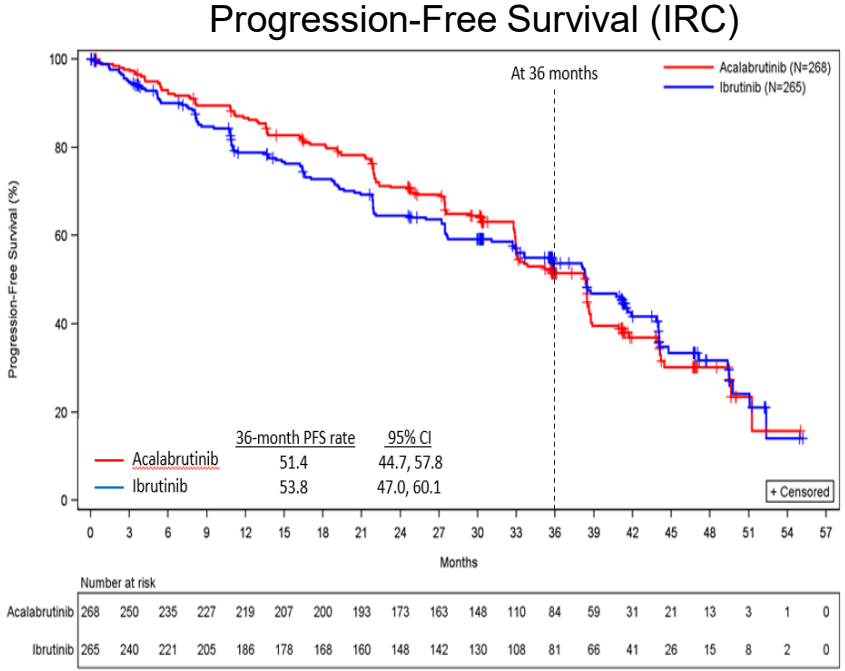
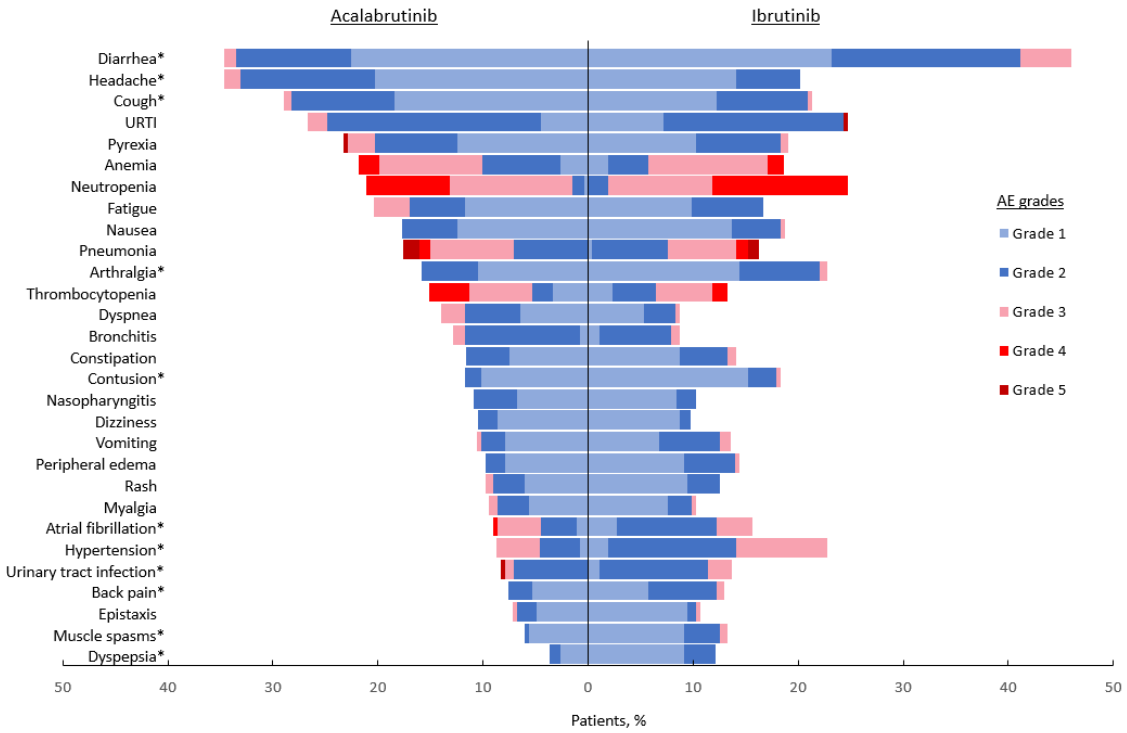
Ibrutinib vs Acalabrutinib (not frontline)

- 533 high risk R/R patients randomized to acalabrutinib vs ibrutinib
- Primary endpoint non-inferiority of acalabrutinib in terms of PFS
- Secondary endpoints (hierarchical): a fib, grade 3+ infection, Richter's, OS



Byrd et al, ASCO 2021

ELEVATE R/R Adverse Events



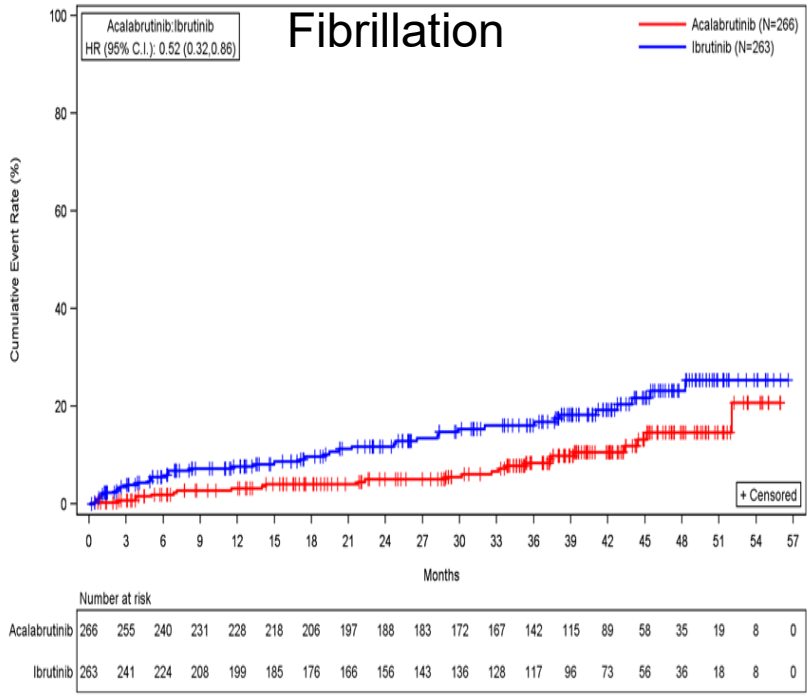
Key Toxicities

- Arthralgias: 16% vs 23%
- Diarrhea: 35% vs 46%
- Bleeding: 38% vs 51% for minor, major no different
- HTN: 9% vs 23%
- Atrial fibrillation: 16% vs 9%

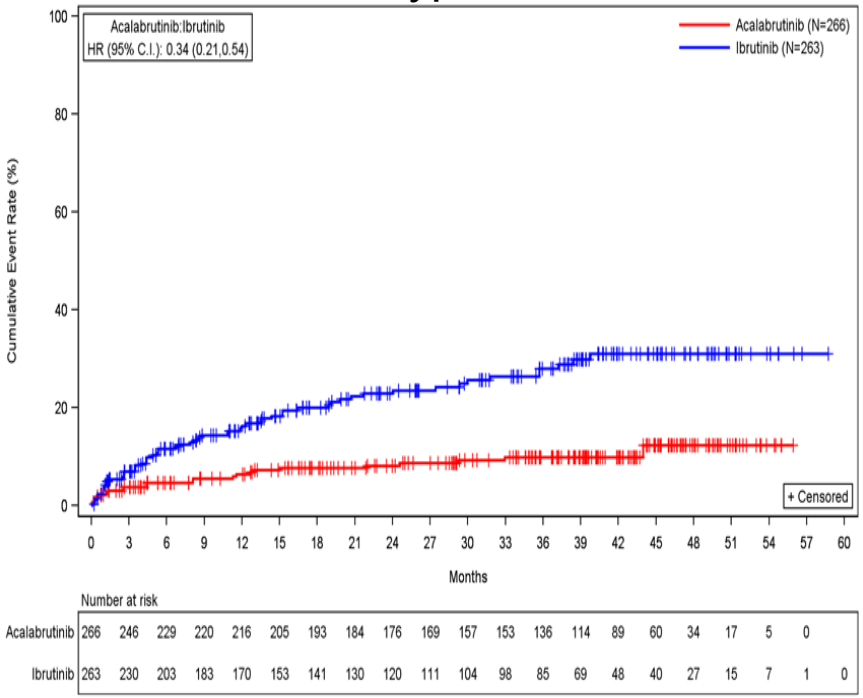
Byrd et al, ASCO 2021

Cumulative Incidence of Cardiac Events

Atrial Fibrillation



Hypertension



Byrd et al, ASCO 2021

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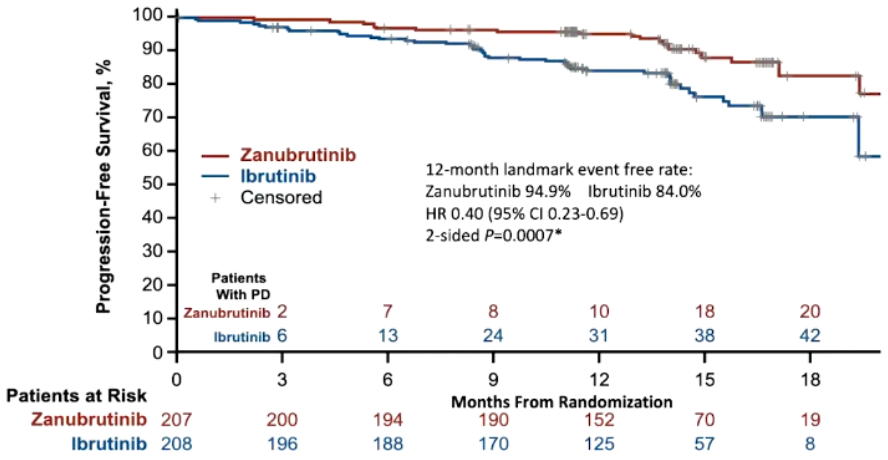
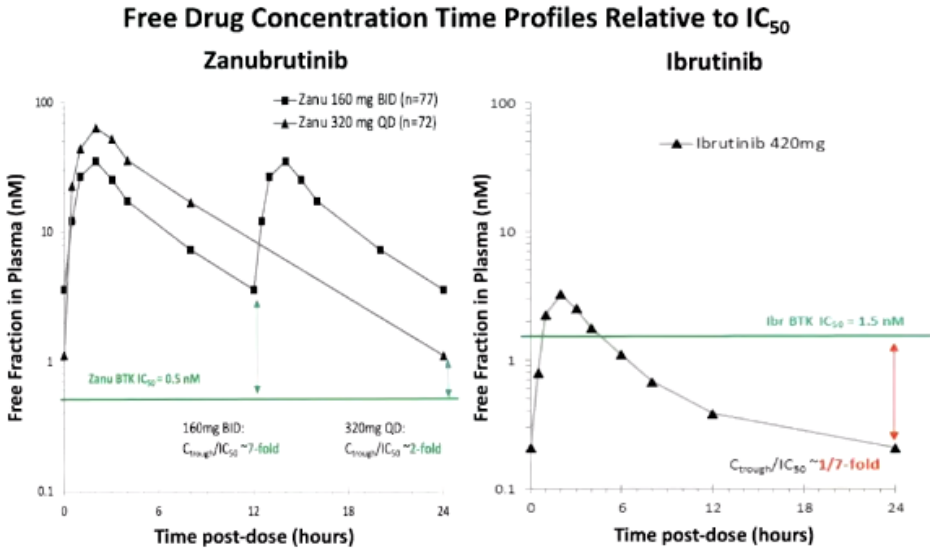
Zanubrutinib vs Ibrutinib (not frontline)





- 652 patients
- Primary endpoint ORR
- Atrial fibrillation 10.1% vs 2.5%

Hillmen et al, EHA 2021

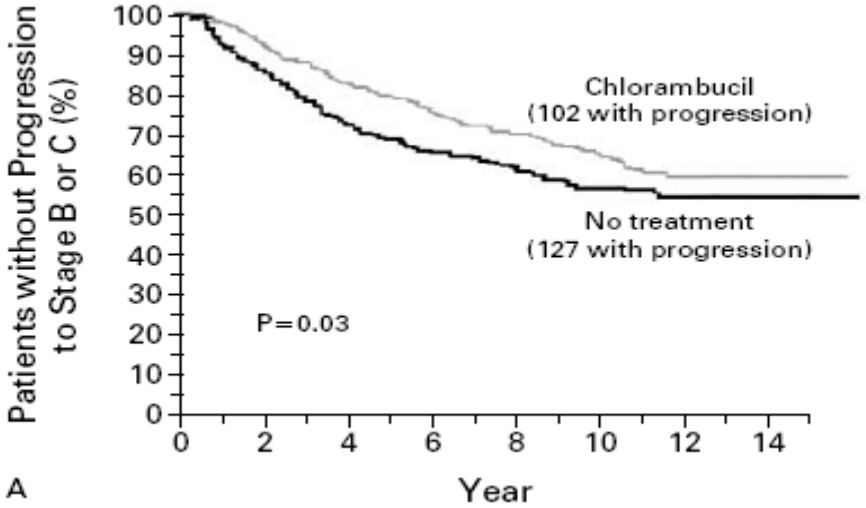
Should all patients receive a second generation BTKi?

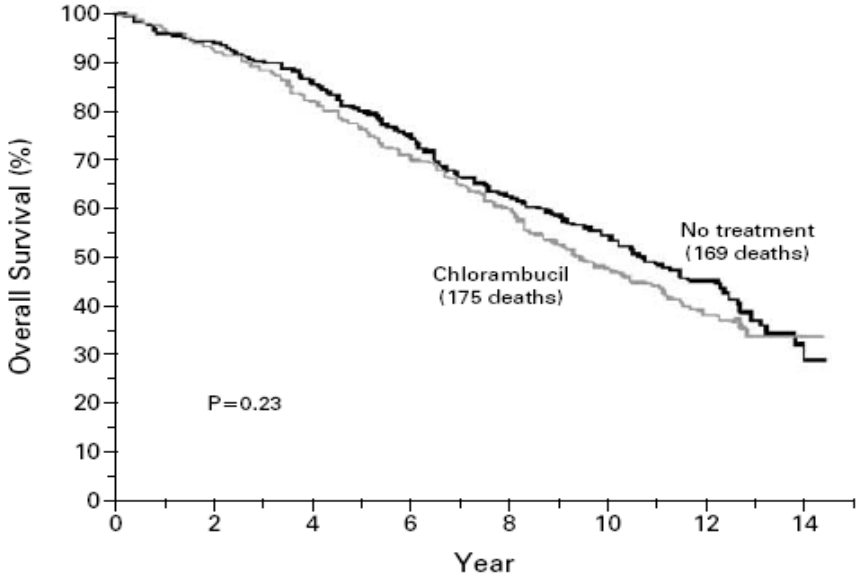
- Safety data favors second generation BTKi
- Twice daily dosing of second generation BTKi may limit compliance/efficacy in the real world setting
- NCCN guidelines favor second generation BTKi

What are the ongoing questions in frontline CLL?

- Is venetoclax/obin or continuous BTKi based therapy more effective?
- Are there patients who should be treated with CIT, and what is the best way to do this?
- What is the optimal fixed duration regimen in CLL?
- Should everyone receive a second generation BTKi?
- **Is there a role for early therapy?**

Is There a Role for Early Therapy?

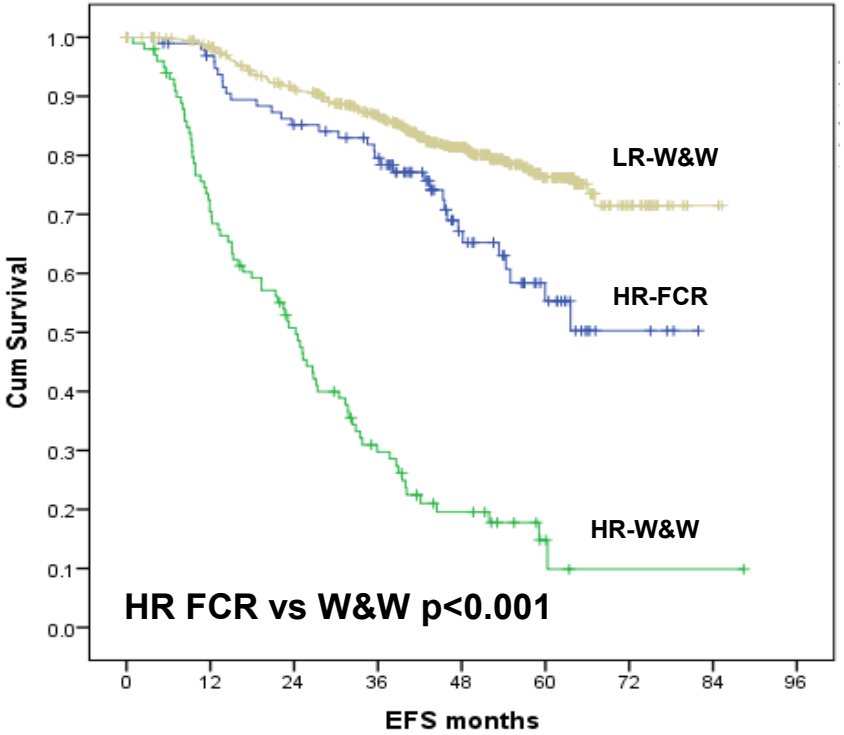




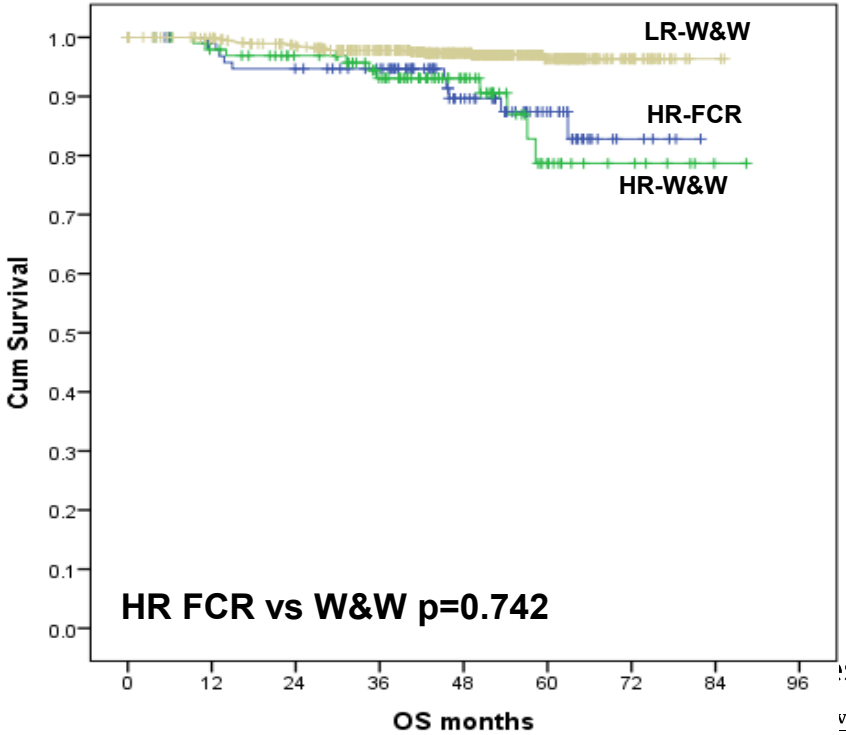
Dighiero, et al. *NEJM* 1998

Is There a Role for Early Treatment: CIT Era

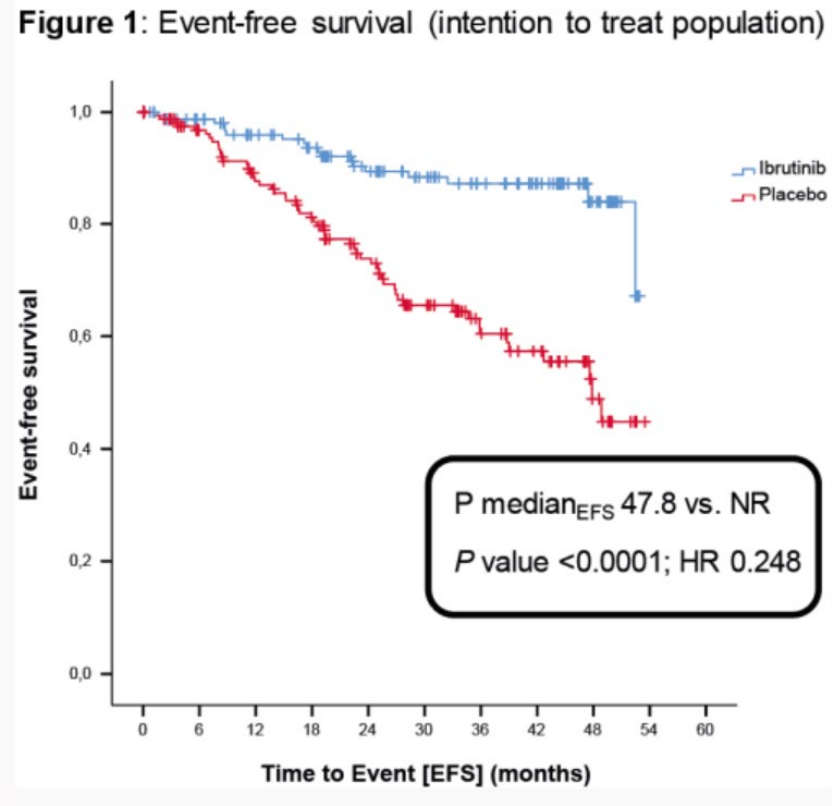
Event Free Survival



Overall Survival



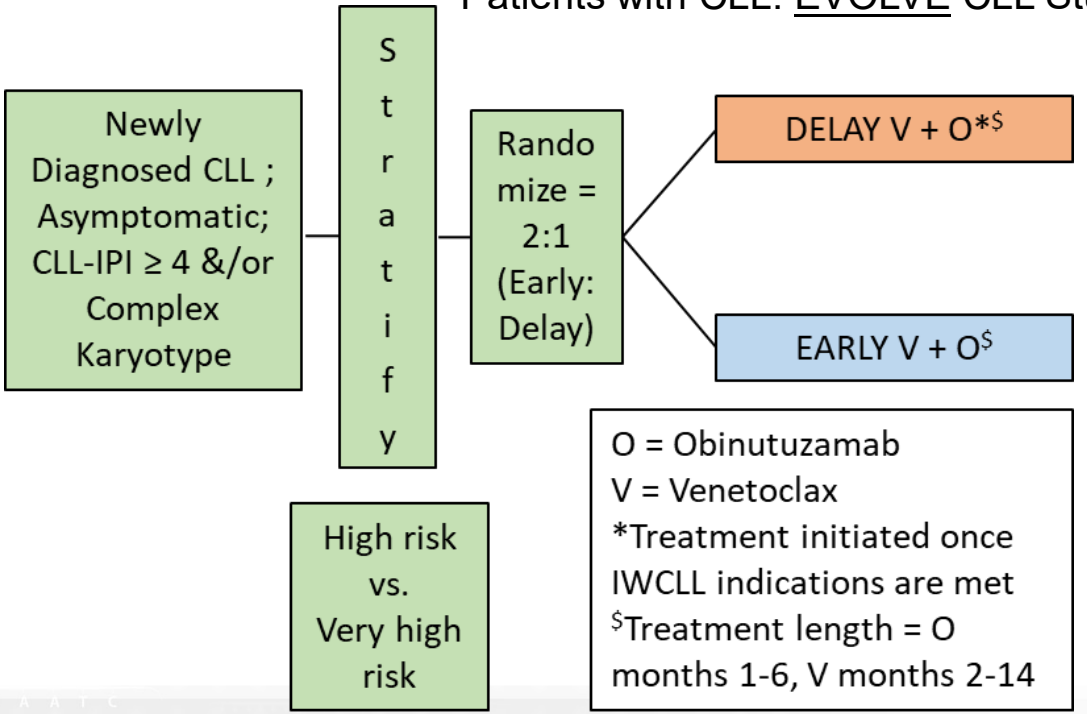
CLL 12 Event Free Survival



Langerbeins et al, EHA 2019

NCTN Early Intervention Study S1925

Randomized, Phase III Study of Early Intervention with Venetoclax and Obinutuzumab versus DeLayed Therapy with VEnetoclax and Obinutuzumab in Newly Diagnosed Asymptomatic High-Risk Patients with CLL: EVOLVE CLL Study



- Primary endpoint = OS
- Goal = Improve 6-yr OS from 60% to 80%
- N = 247 patients
- Secondary endpoints =
  - Safety, ORR, DOR, PFS, TTNT, MRD, QOL, resistance

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So where are we going in frontline CLL?

- Long-term follow-up of E1912 and FLAIR will be critical to determine how best to manage young IGHV mutated patients
- Combinations of targeted therapies are promising, with multiple ongoing and planned studies to answer key questions
- Acalabrutinib and Zanabrutinib are more tolerable and as effective than ibrutinib
- Whether some patients may benefit from early therapy remains to be seen, but is an attractive concept for high risk patients

Final Conclusions

- Ibrutinib and now venetoclax, acalabrutinib, and zanubrutinib have changed the paradigm of CLL therapy, and most patients with CLL should never receive chemotherapy

- Although our current treatments are effective, there remain many open questions

- Prospective clinical trials remain extremely important to help determine the optimal frontline treatments for our patients with CLL

Jennifer.Woyach@osumc.edu CLL.osu.edu

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