How I Treat CLL in 2019

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Objectives

- To briefly discuss risk stratification in CLL and criteria to initiate therapy
- To discuss frontline therapy for CLL
  - Where we have come from
  - Where are we now
  - Where are we going

Treatment Indications

- Marrow failure (progressive, hgb <10, plt <100k)
- Massive (≥6 cm below costal margin), symptomatic, or progressive splenomegaly
- Massive (≥10 cm), symptomatic, or progressive lymphadenopathy
- Progressive lymphocytosis (doubling time <6 months)
- Autoimmune cytopenias NOT responding to other treatment
- Organ threatening disease
- Constitutional Symptoms

Hallek at al, Blood 2018

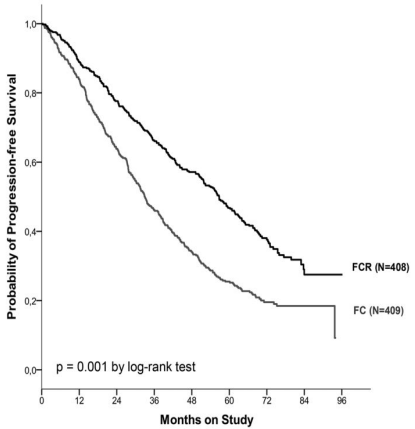
Pre-Therapy Testing

- Disease evaluation
  - CT scans can be considered
  - Bone marrow biopsy-especially if cytopenias present

- Molecular/genomic testing
  - IGVH mutational status
  - FISH-del13q, del17p, del11q, trisomy 12
    - Stimulated karyotype can be considered
  - TP53 mutation

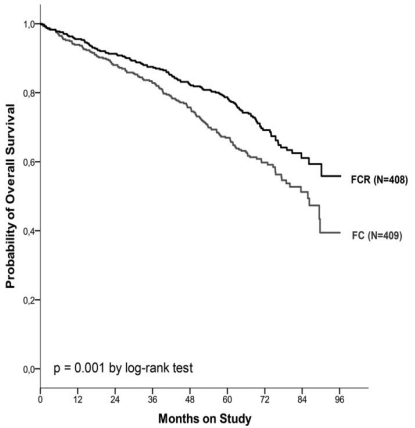
Where have we come from?
FCR is the Gold Standard—CLL8 Study

A



Number at risk	0	12	24	36	48	60	72	84	96
FCR	408	358	310	261	222	178	76	18	1
FC	409	232	236	167	119	86	39	13	0

B



Number at risk	0	12	24	36	48	60	72	84	96
FCR	408	384	363	342	318	290	134	41	2
FC	409	360	232	297	262	220	100	33	1

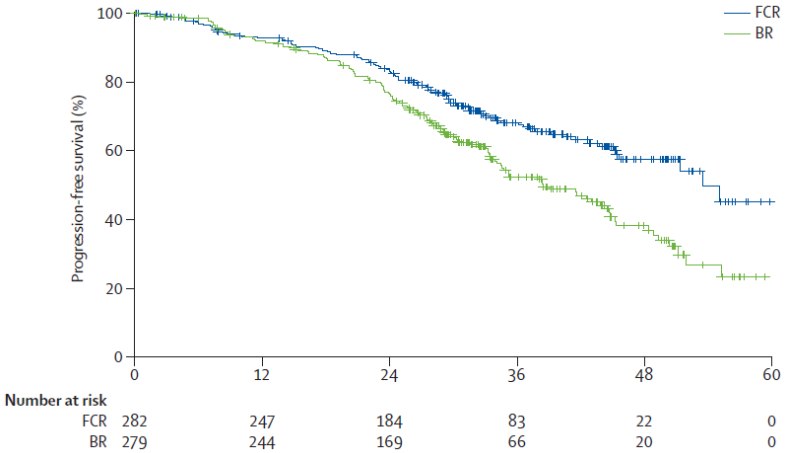
At 5.9 years

- Median PFS 56.8 mo vs 32.9 mo
- Median OS NR vs 86 mo

Fischer et al, Blood 2016

BR is inferior to FCR (except in older patients) CLL10 Trial

- Randomized untreated fit patients without del17p to FCR or BR
- PFS was shorter for BR vs FCR (41.7 vs 55.2, p=0.0003), **except for those age 65 and older**



Eichhorst et al., Lancet Hematology 2016

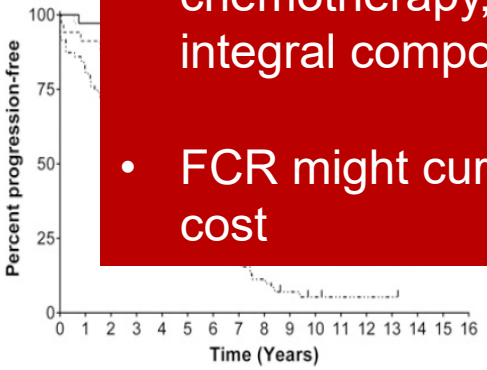
Long-Term FCR Data

- Two studies showing a plateau in relapse in IGHV mutated patients
- FISH

What Do These Data Tell Us?

- Chemoimmunotherapy is superior to chemotherapy, establishing rituximab as an integral component of CLL treatment
- FCR might cure some patients, but not without cost

4.7%



Papillary thyroid cancer	2
Esophageal adenocarcinoma	1
Merkel cell tumor	1
Brain tumor	1
Colorectal cancer	1
Other	3

Thompson et al, Blood 2016

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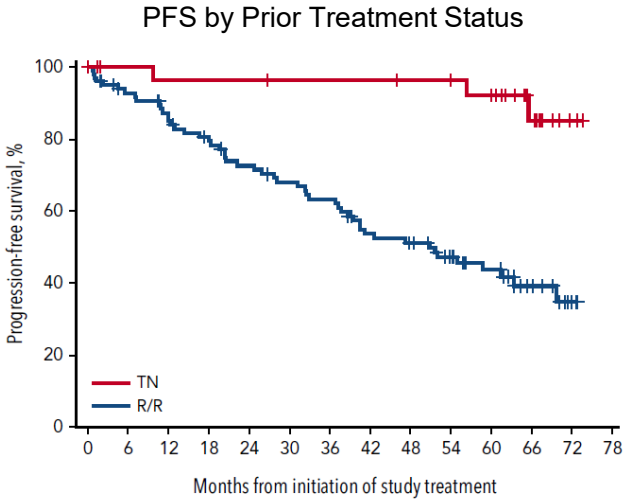
Where are we now?
Ibrutinib in Treatment-Naïve Patients (n=31)

- ORR 89% (95% CI: 81.3-94.4)
- CR rate 29% (R/R =10%)
- Median PFS not reached
- Estimated 5-year PFS is 92%
- 55% remain on treatment



O'Brien et al., Blood 2018

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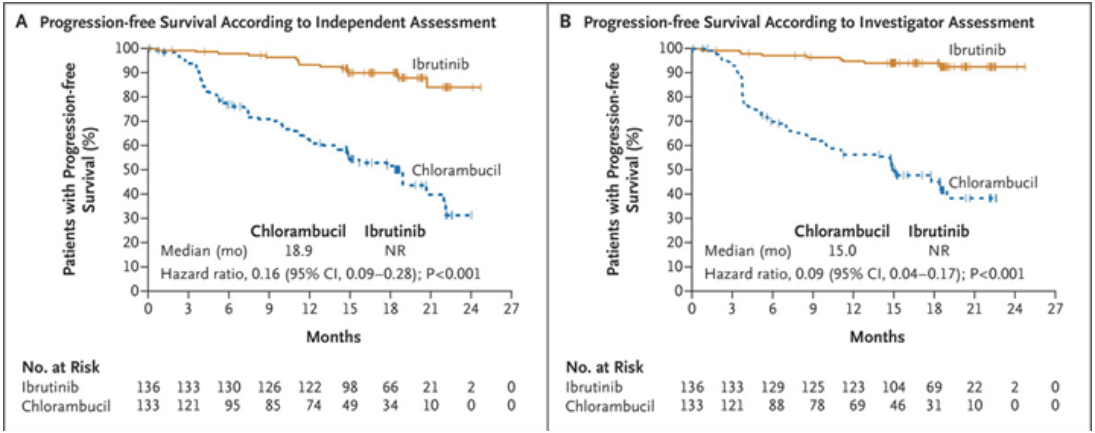
Ibrutinib in Treatment-Naïve CLL: RESONATE 2



- Randomized untreated patients ≥65 to ibrutinib or chlorambucil (0.5 mg/kg D1 and D15 x12 cycles)
- Median follow-up 18.4 months
- 84% lower risk of progression or death with ibrutinib
- 89% of patients progression-free at 2 years

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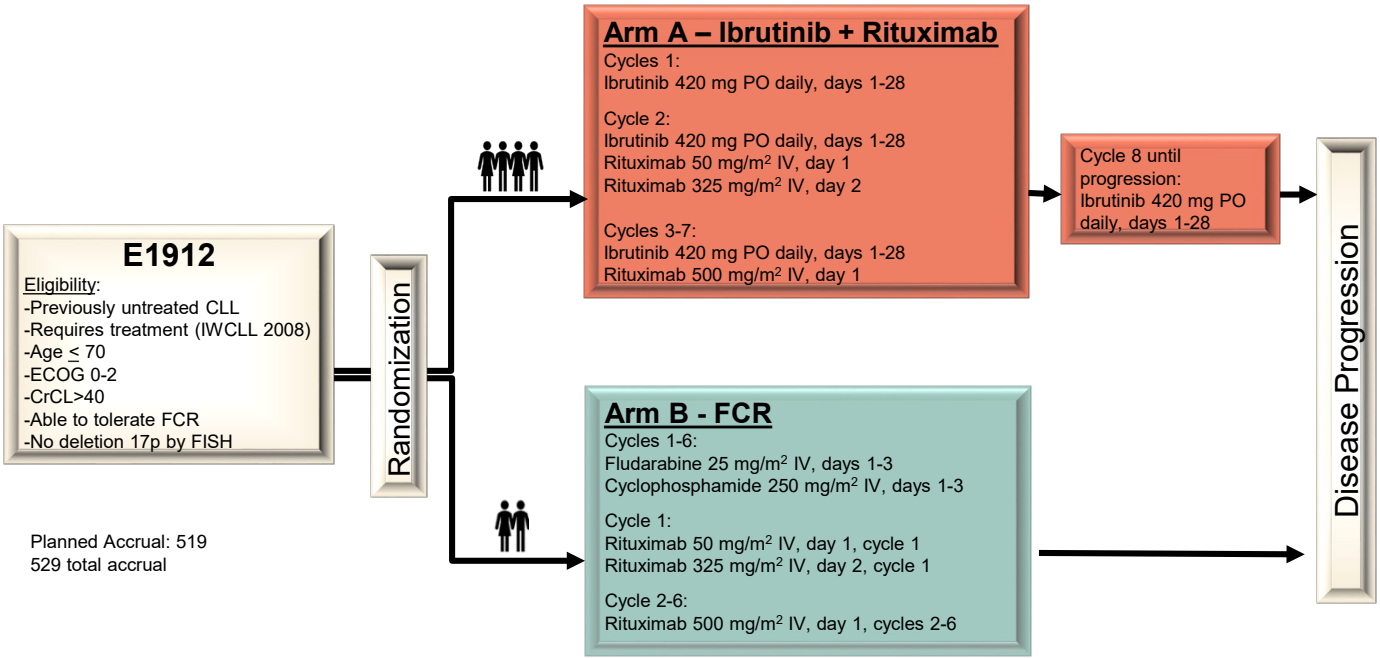
Burger et al, N Engl J Med 2015

ECOG 1912 Study Design



Planned Accrual: 519
529 total accrual

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Shanafelt, et al. LBA 4 ASH 2018

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

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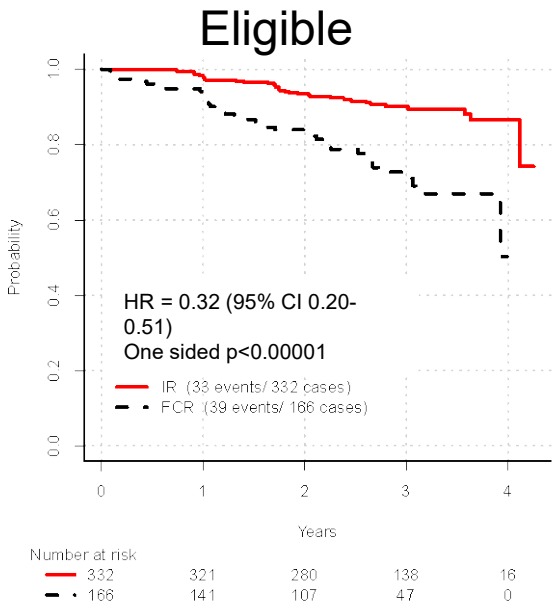
Shanafelt, et al. LBA 4 ASH 2018

E1912 Progression Free Survival



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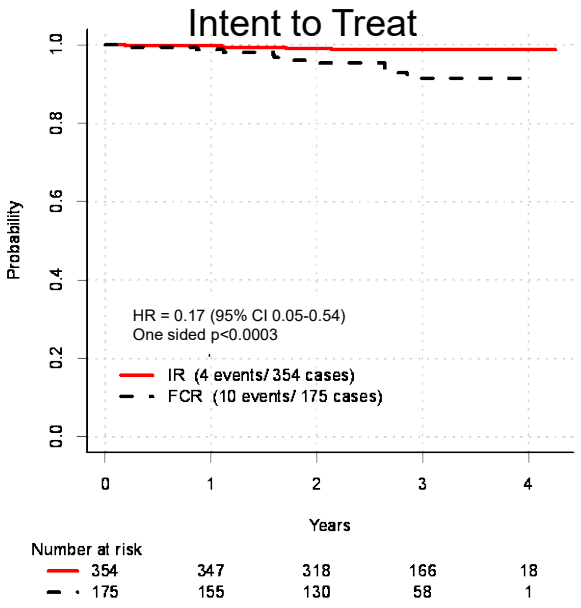
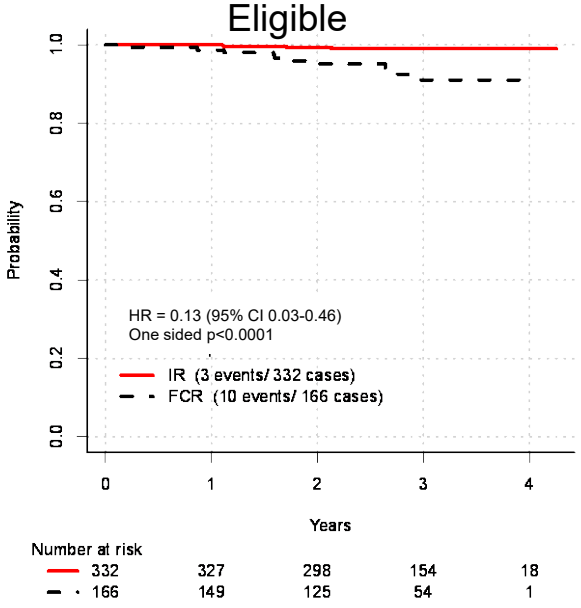
E1912 Overall Survival





Shanafelt, et al. LBA 4 ASH 2018

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E1912 Grade 3-5 Treatment Related Adverse Events Throughout Observation

Adverse event	IR (%) N= 352	FCR (%) N=158	p value
Neutropenia	22.7%	43.7%	<0.001
Anemia	2.6%	12.0%	<0.001
Thrombocytopenia	2.9%	13.9%	<0.001
Any Infection	7.1%	19.0%	<0.001
Infection	5.4%	8.2%	0.24
Neutropenic fever	2.3%	15.8%	<0.001
Atrial fibrillation	2.9%	0.0%	**0.04**
Bleeding	1.1%	0.0%	0.32
Hypertension	7.4%	1.9%	**0.01**
Diarrhea	2.6%	0.6%	0.19
Any Grade 3 or higher AE	**58.5%**	**72.1%**	**P=0.004**

Shanafelt, et al. LBA 4 ASH 2018

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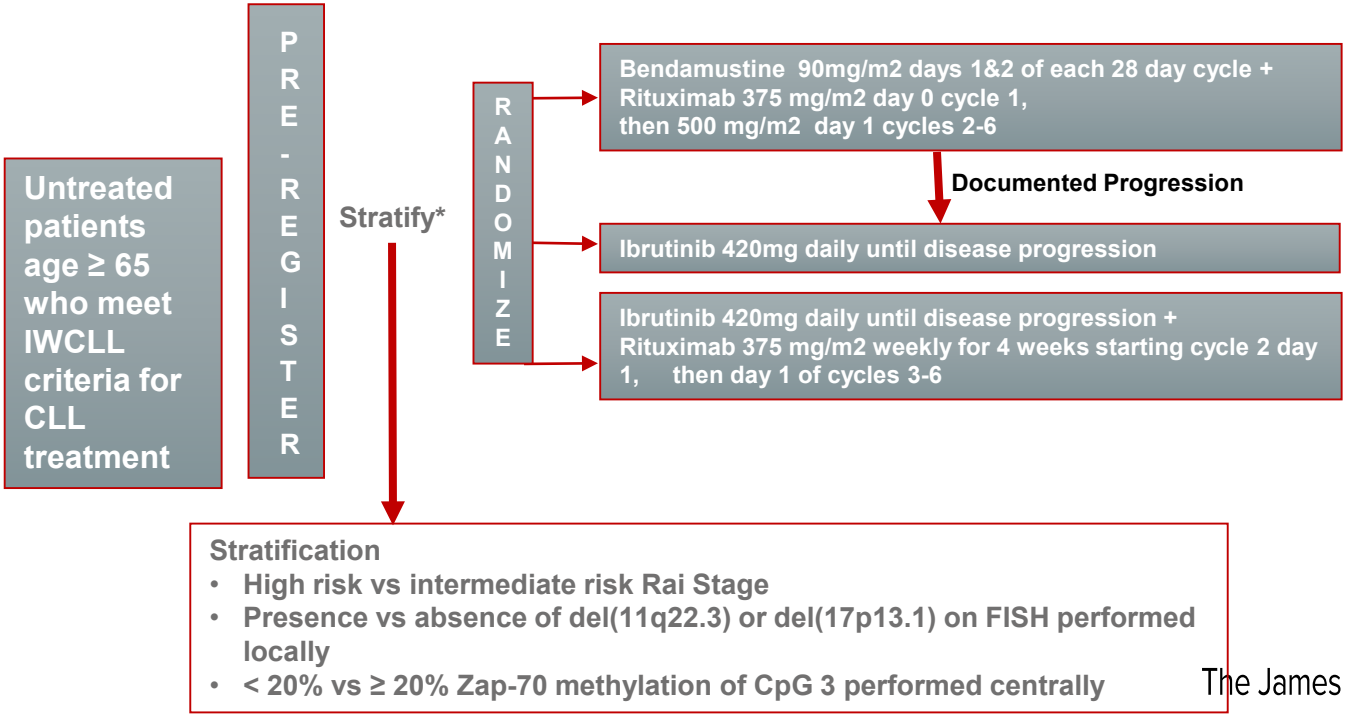
A041202 Schema



Planned accrual: 498
Total accrual 547

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

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Woyach et al, NEJM 2019

Primary Endpoint: Progression Free Survival
Eligible Patient Population

Arm	N	24 Month Estimate
BR	176	74% (95% CI: 66-80%)
I	178	87% (95% CI: 81-92%)
IR	170	88% (95% CI: 81-92%)

Pairwise Comparisons

I vs BR:
Hazard Ratio 0.39
95% CI: 0.26-0.58
(1-sided P-value <0.001)

IR vs BR:
Hazard Ratio 0.38
95% CI: 0.25-0.59
(1-sided P-value <0.001)

IR vs I:
Hazard Ratio 1.00
95% CI: 0.62-1.62
(1-sided P-value 0.49)

Patients-at-Risk

176	140	129	122	103	88	57	26	11	0
178	165	154	147	136	120	78	45	22	0
170	159	145	138	132	115	74	40	20	0

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Woyach et al, NEJM 2019

Overall Survival
Intention-to-Treat Patient Population

Arm	N	24 Month Estimate
BR	183	95% (95% CI: 91-98%)
I	183	90% (95% CI: 85-94%)
IR	182	94% (95% CI: 89-97%)

Median Follow-up: 38 months

Patients-at-Risk

183	166	163	160	153	143	98	53	23	1
182	175	166	161	156	146	100	62	26	1
182	172	169	165	161	147	100	55	24	1

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Grade 3, 4, or 5 Adverse Events
During treatment or follow-up (excluding crossover)

Ac	lue
All Hematolo	01
Anemia	9
Neutropeni	01
Thrombocy	08
All Non-hem	4
Bleeding	6
Infections	2
Febrile neut	01
Atrial fibrill	5
Hypertensio	01
Unexplaine	4

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

- Deat
- Deaths during active treatment + 30 days, up to 6 cycles: 2 (1%), 3 (2%), 6 (3%)

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Woyach et al, NEJM 2019

Where are we going?
What are the ongoing questions in frontline CLL?

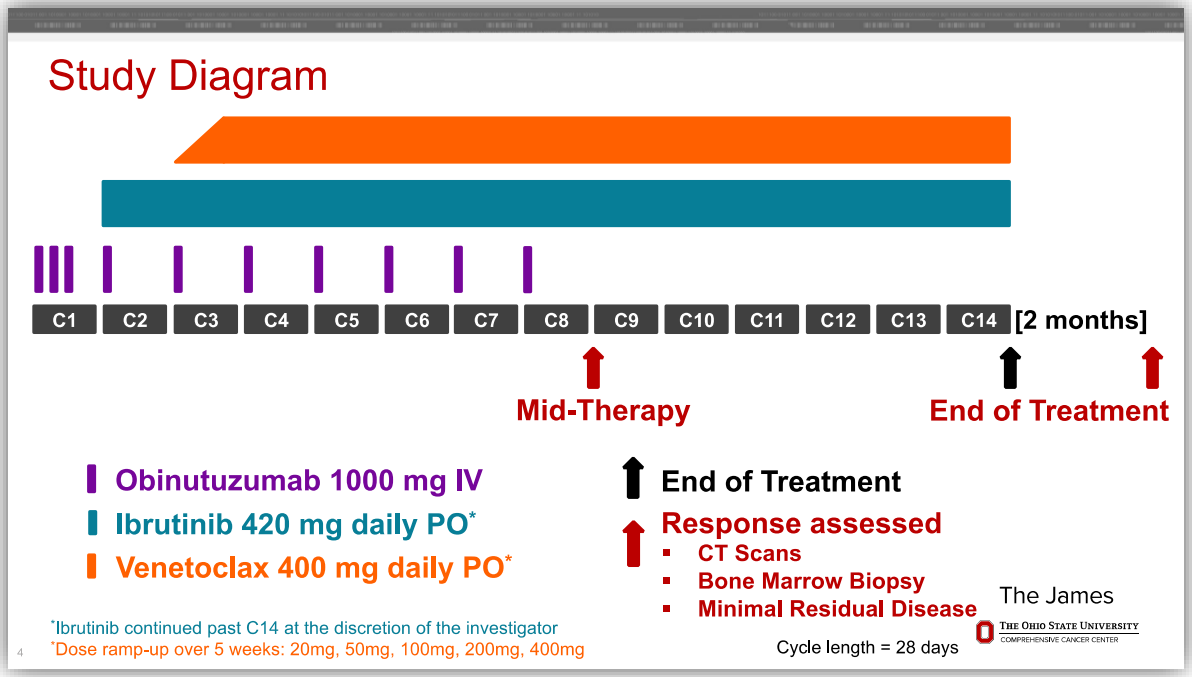
- Should anyone still be treated with chemoimmunotherapy?
- Can we improve on the efficacy and safety of ibrutinib by combination, time-limited therapy?
- Can we improve the safety of ibrutinib by using a different BTKi?

Should anyone still be treated with chemoimmunotherapy?

- Young, fit, IGHV mutated patients may be cured with FCR
  - Long-term follow up from ECOG study will help
  - Current trials of abbreviated FCR with targeted therapy might have a role

- Unfit patients with good risk disease may benefit from chlorambucil/obinutuzumab

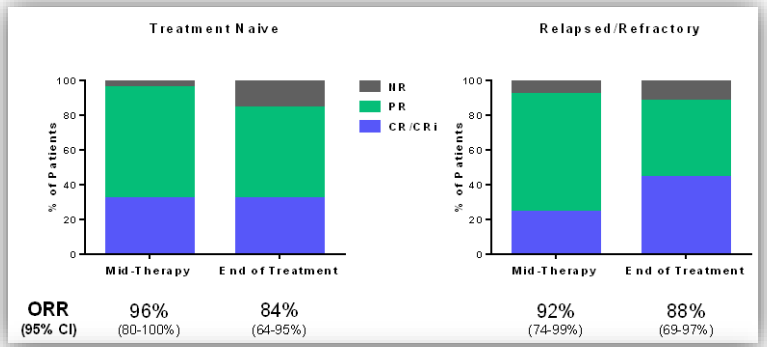
Can we improve on the efficacy and safety of ibrutinib through combination, time-limited therapy?

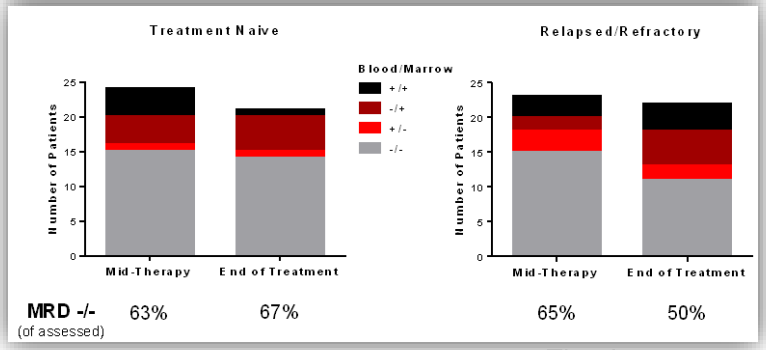


Rogers et al, ASH 2018

Obinutuzumab plus Venetoclax plus Ibrutinib Responses

- 50 total patients
- Mid-Therapy Responses:
  - TN: 8 CR/CRi, 16 PR
  - RR: 6 CR/CRi, 17 PR
- End of Treatment Responses:
  - TN: 8 CR/CRi, 13 PR
  - RR: 11 CR/CRi, 11 PR
- **Rate of MRD (-) CR:**
  - **TN: 28% (95% CI: 12-49%)**
  - **RR: 28% (95% CI: 12-49%)**





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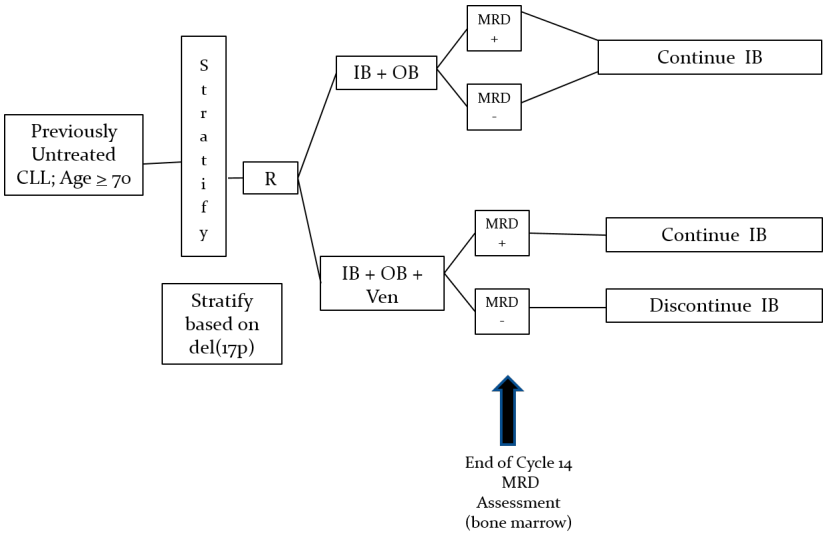
Rogers et al, ASH 2018

A041702: Randomized phase 3 study of first-line ibrutinib/obinutuzumab vs ibrutinib/venetoclax/obinutuzumab in patients ≥70



- Primary objective is to compare the PFS
- Eligibility:
  - CLL/SLL with no prior treatments
  - Indication for treatment
  - Age ≥70

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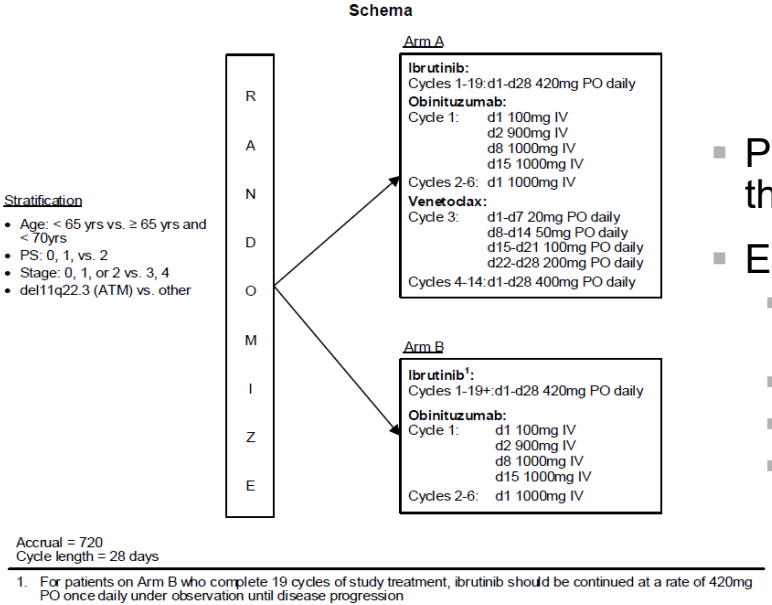
EA9161: Randomized phase 3 study of venetoclax + ibrutinib/obinutuzumab vs ibrutinib/obinutuzumab in untreated younger patients with CLL



- Primary objective is to compare the PFS
- Eligibility:
  - CLL/SLL with no prior treatments
  - Indication for treatment
  - Age ≥18 and <70
  - No deletion 17p13

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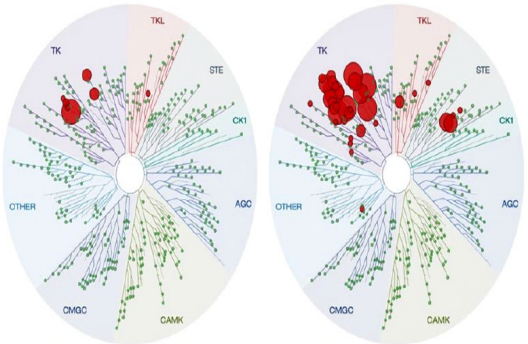
Can we Improve Safety by Using a Different BTK inhibitor?

- Acalabrutinib is more selective for BTK with less off-target kinase inhibition compared with ibrutinib in vitro

Acalabrutinib **Ibrutinib**



Kinase Selectivity Profiling at 1 μM

Larger red circles represent stronger inhibition

Kinase Inhibition Average IC_{50} (nM)

Kinase	Acalabrutinib	Ibrutinib
BTK	5.1	1.5
TEC	126.0	10
ITK	>1000	4.9
BMX	46	0.8
TXK	368	2.0
EGFR	>1000	5.3
ERBB2	~1000	6.4
ERBB4	16	3.4
BLK	>1000	0.1
JAK3	>1000	32

Byrd JC, et al. ASH 201

Phase 1b/2 study Acalabrutinib in TN CLL

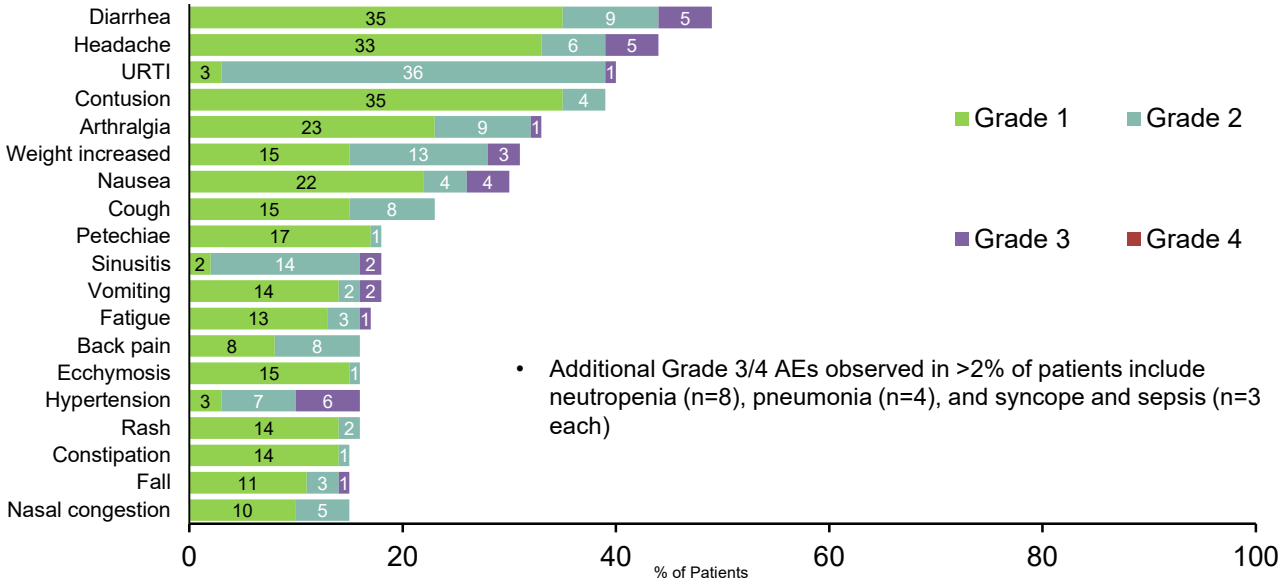
- At the median time on study of 42 months, 89% of patients remain on study treatment

Characteristics	N=99
Time on study, median (range), mo	42 (1-48)
Remain on acalabrutinib, n (%)	88 (89)
Discontinued acalabrutinib, n (%)	11 (11)
Disease progression[a]	2 (2)
Adverse event[b]	5 (5)
Pregnancy	1 (1)
Withdrawal of consent	2 (2)
Other[c]	1 (1)

- [a] Richter transformation occurred in 1 patient.
- [b] Adverse events leading to discontinuation were secondary malignancies (angiosarcoma, glioblastoma multiforme, small cell lung cancer; 1 patient each), sepsis (Grade 4; 1 patient) and urinary tract infection (Grade 3; 1 patient)
- [c] Initiation of subsequent cancer therapy (venetoclax).

Byrd et al, ASH 2018

Acalabrutinib Most Common Adverse Events



- Additional Grade 3/4 AEs observed in >2% of patients include neutropenia (n=8), pneumonia (n=4), and syncope and sepsis (n=3 each)

Byrd et al, ASH 2018

Adverse Events of Special Interest

- Atri
- Bru
  - C
  - C
- Hyp
- Infe

What Do These Data Tell Us?

- Long-term follow-up of E1912 will be critical to determine how best to manage young IGHV mutated patients
- Combinations of targeted therapies appear promising, and new intergroup studies will allow the opportunity to determine whether they are better than ibrutinib
- Acalabrutinib may be more tolerable than ibrutinib, but head to head comparison will be helpful

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Conclusions

- Ibrutinib has changed the paradigm of CLL therapy, and many patients with CLL will never receive chemotherapy
- Although our current treatments are effective, there remain areas in need of improvement
- Prospective clinical trials remain extremely important to help determine the optimal frontline treatments for our patients with CLL

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