Beyond Chemo-immunotherapy in the treatment of B-cell Lymphomas

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Disclosures:

Advisory Board/Consultancy: BMS, Genentech, AbbVie, KiTE pharma, Celgene, Adaptive Biotechnology

Research funding: BMS, Merck, Celgene, MEI-Pharma

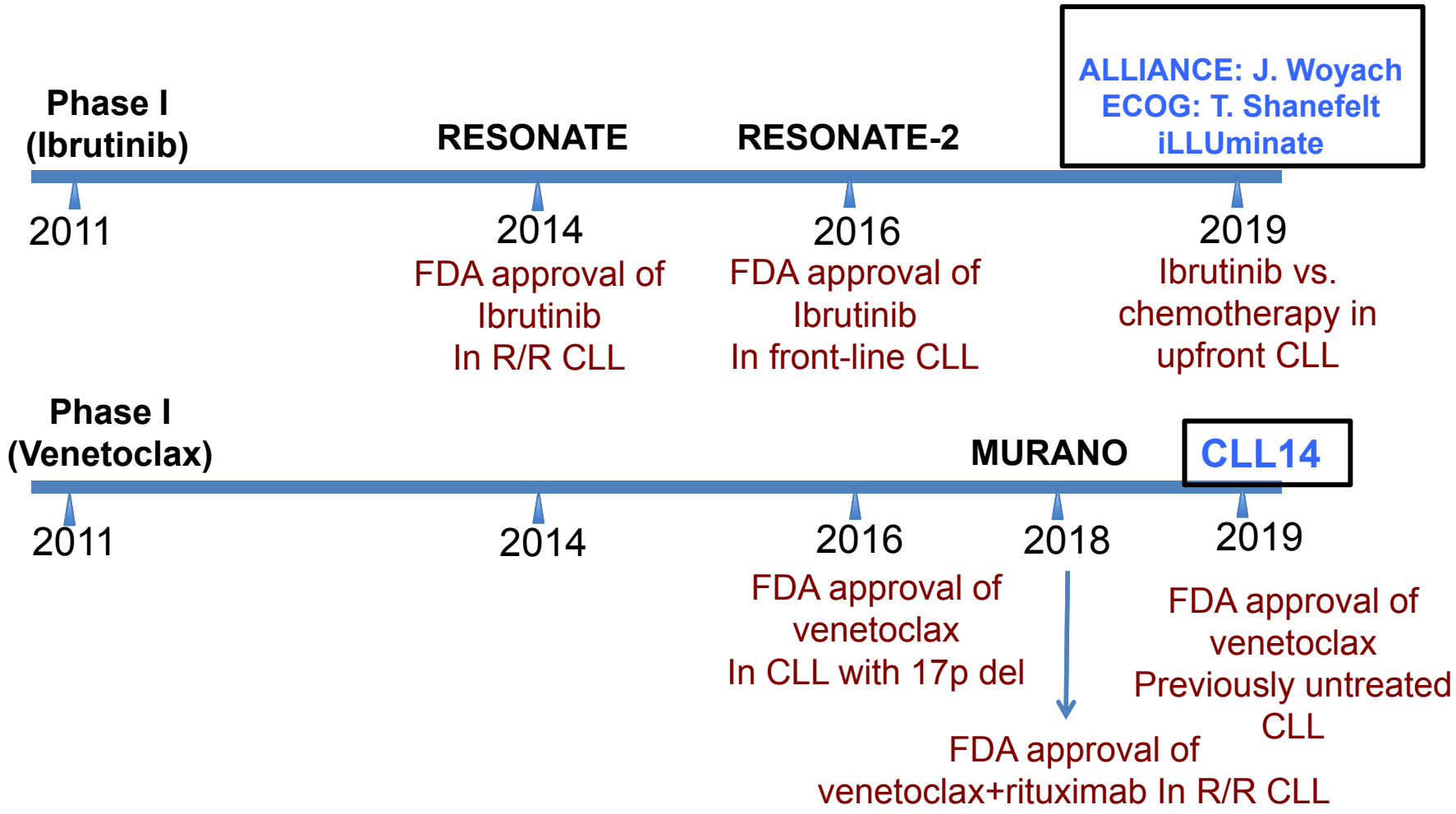
Off label Drug use: Acalibrutinib, Lenalidomide, Ibrutinib

FDA non-approved drugs: MOR-208, Anti-CD47 Ab, MEI-401

Highlights

- Updates in chronic lymphocytic leukemia
- Follicular lymphoma: treatment options
- Treatment approaches in Diffuse Large B-cell Lymphoma

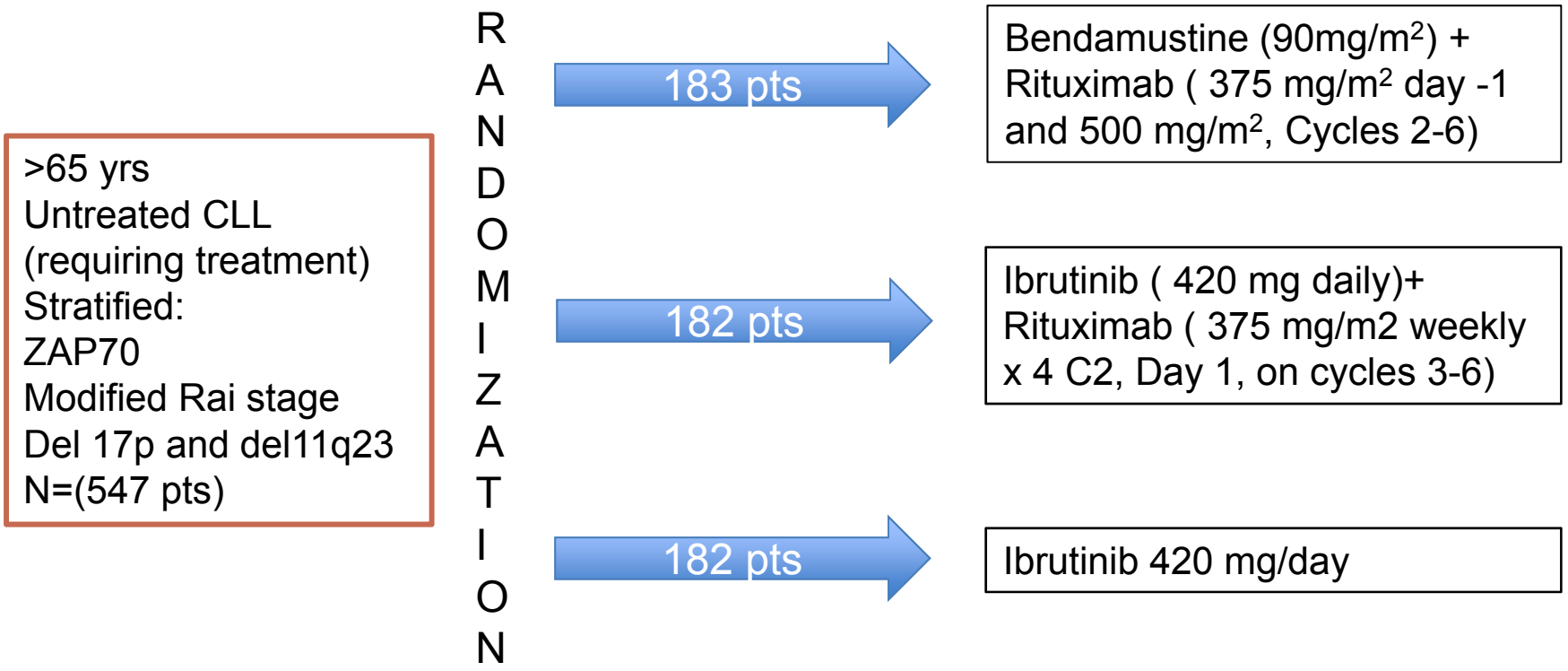
Chronic Lymphocytic Leukemia



Summary of practice changing clinical trials

Trials	Treatment arms	Response rates	PFS
CLL8	FCR vs. FC	87% vs. 83% (p=0.012)	65% vs. 45% (p<0.0001)
CLL10	FCR vs. BR	96% vs. 95%	41.7 vs. 55.2 months (p=0.0003)
CLL11	Obinutuzumab+ chlorambucil vs. Rituximab +chlorambucil vs. Chlorambucil	77.3% vs. 65.7% vs. 31.4%	26.7 vs. 11.1 vs. 16.3 months (p<0.001)
COMPLEMENT	Ofatumumab + chlorambucil vs. chlorambucil	82% vs. 69%	22.4 vs. 13.1 months (p< 0.0001)
RESONATE	Ibrutinib vs. Ofatumumab	63% vs. 4% (p<0.001)	NR vs. 8.1 months (p<0.001)
RESONATE 2	Ibrutinib vs. chlorambucil	86% vs. 35% (p<0.001)	NR vs. 18.9 months (p<0.001)

Ibrutinib Vs. Chemotherapy in Older patients with untreated CLL: ALLIANCE



Primary End point: progression free survival
Secondary end points: overall survival, response rates, QOL

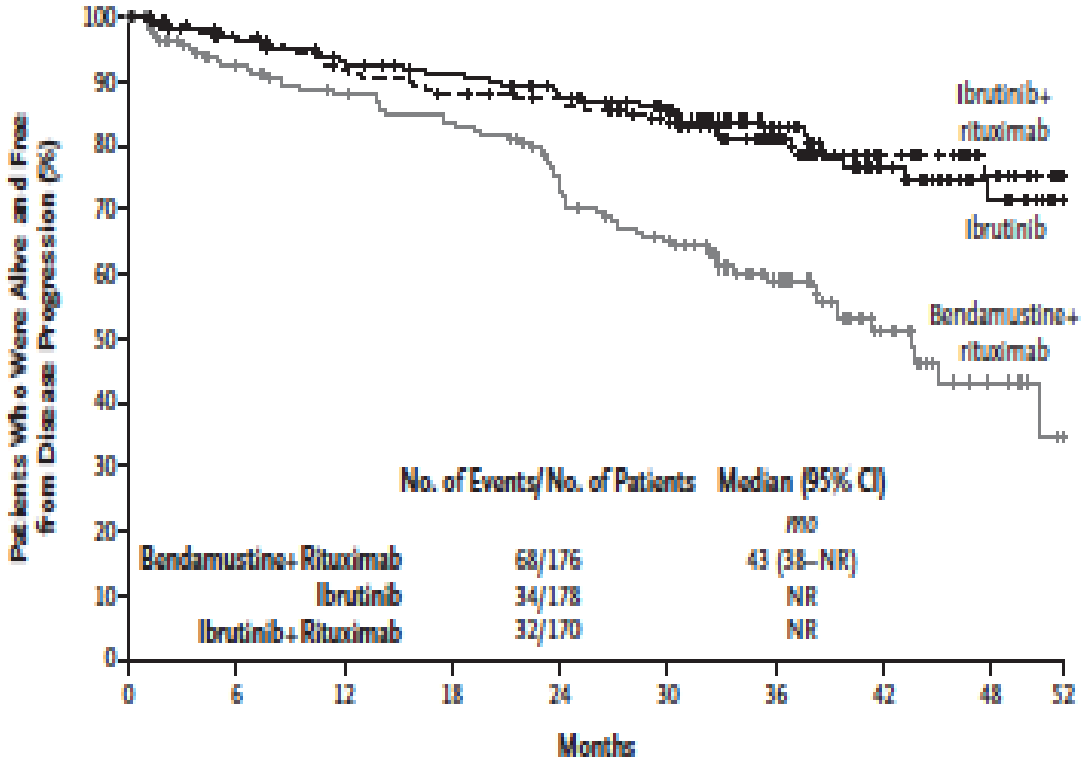
Woyach et al., NEJM 2018

Baseline Characteristics

Characteristics	Bendamustine+ Rituximab	Ibrutinib	Ibrutinib+ rituximab
Age (median)	70 yrs	71 yrs	71 yrs
Rai (high risk)%	54%	54%	54%
Del 17 p	8%	5%	6%
Del 11q	18%	19%	21%
Mutated TP53	9%	9%	12%
Complex karyotype	27%	24%	36%
Unmutated IgVH	58%	63%	61%

Woyach et al., NEJM 2018

Progression Free survival, Median Follow up: 38 months



No. at Risk										
Bendamustine+rituximab	176	140	129	122	103	88	57	26	11	0
Ibrutinib	178	165	154	147	136	120	78	45	22	0
Ibrutinib+rituximab	170	159	145	138	132	115	74	40	20	0

Woyach et al., NEJM 2018

Adverse events

AE (any grade)	BR	Ibrutinib	Ibrutinib+ rituximab
Hematological events	61%	41%	39%
HTN	14%	29%	34%
Atrial Fibrillation	3%	17%	14%
Death	1%	7%	7%

Conclusions:

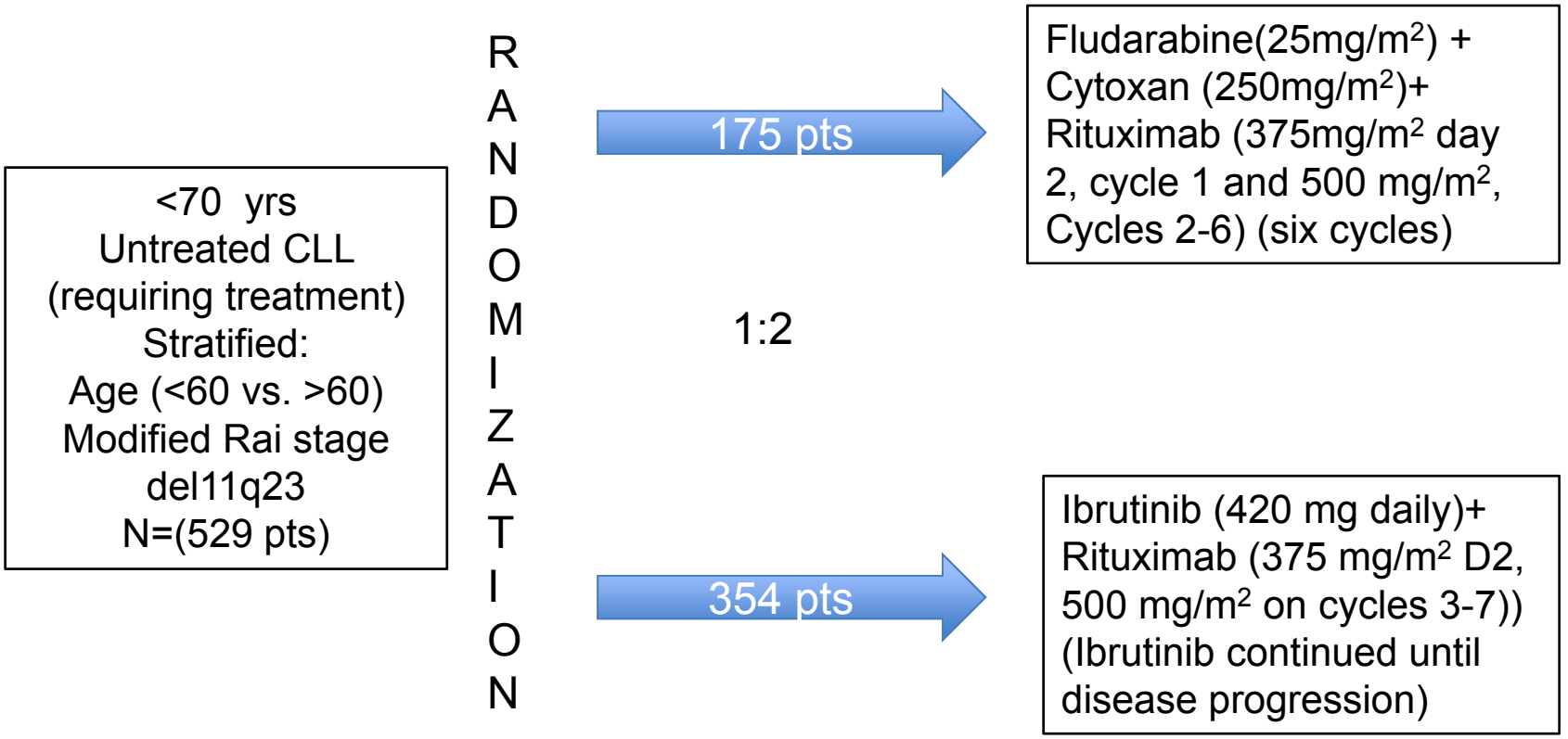
- Treatment with Ibrutinib was superior to Bendamustine and rituximab
- There was no significant difference between Ibrutinib vs. Ibrutinib and rituximab

Caveats:

- Treatment until progression
- Side effect profile, elderly patients
- Chronic (low grade) toxicities

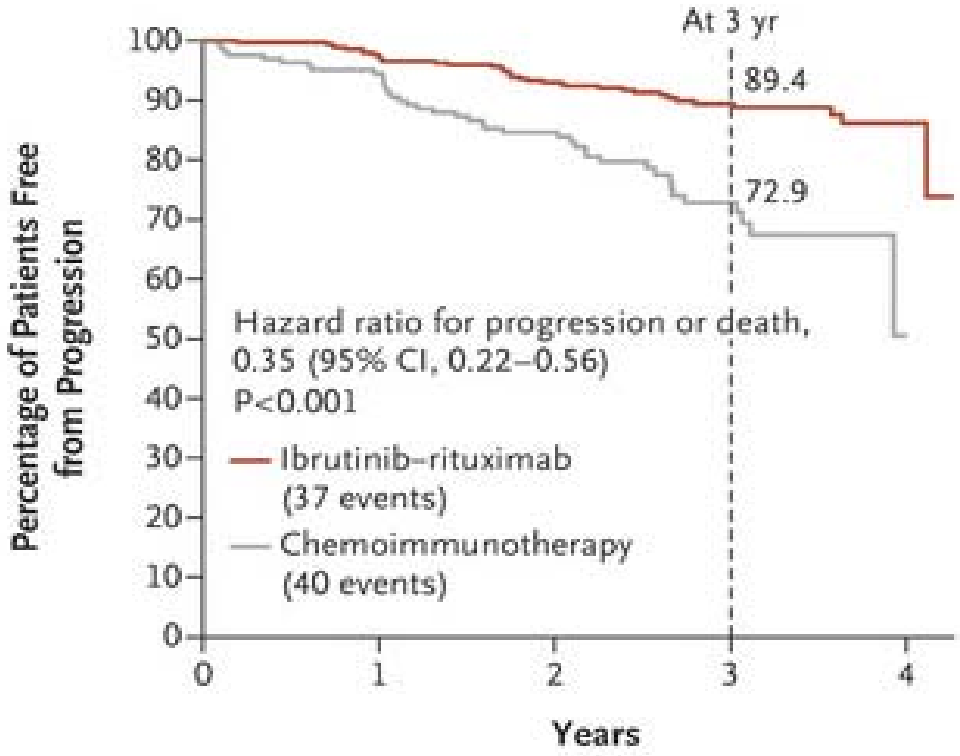
Woyach et al., NEJM 2018

Ibrutinib-Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia (ECOG)



Shanafelt., NEJM 2019; 381:432

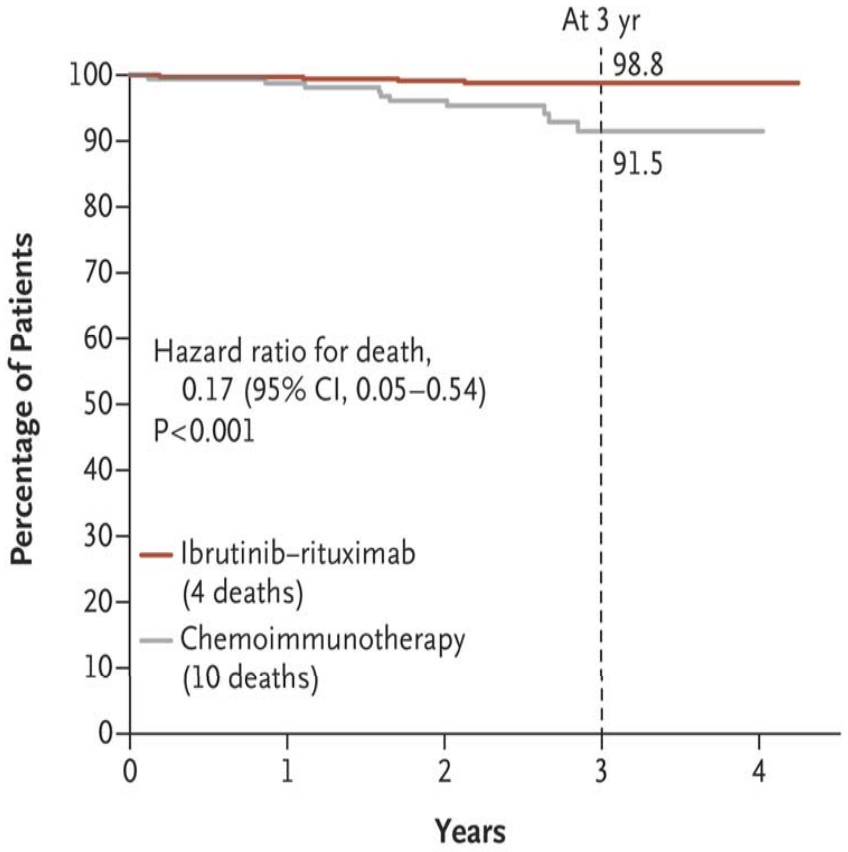
Progression Free Survival; Median Follow up: 33.6 months



No. at Risk					
Ibrutinib–rituximab	354	339	298	148	16
Chemoimmunotherapy	175	147	112	50	0

Shanafelt., NEJM 2019; 381:432

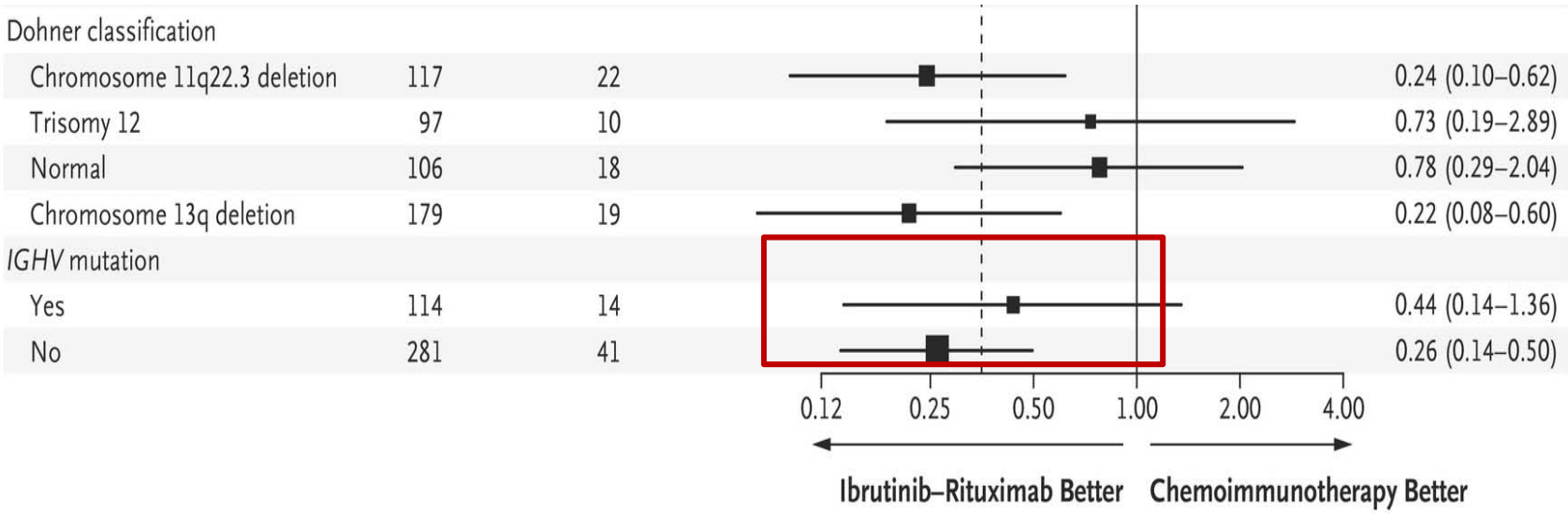
Overall Survival



No. at Risk

Ibrutinib–rituximab	354	347	318	166	18
Chemoimmunotherapy	175	155	130	58	1

Subgroup Analysis: Favor CIT over IR in IgVH mutated patients



Shanafelt., NEJM 2019; 381:432

Adverse events:

AE (any grade)	FCR	Ibrutinib+ rituximab
Hematological events (neutropenia)	44.9%	24.6%
HTN	8.2%	18.8%
Atrial Fibrillation	3.2%	7.4%
Neutropenic fever	20.3%	10.5%

Conclusions:

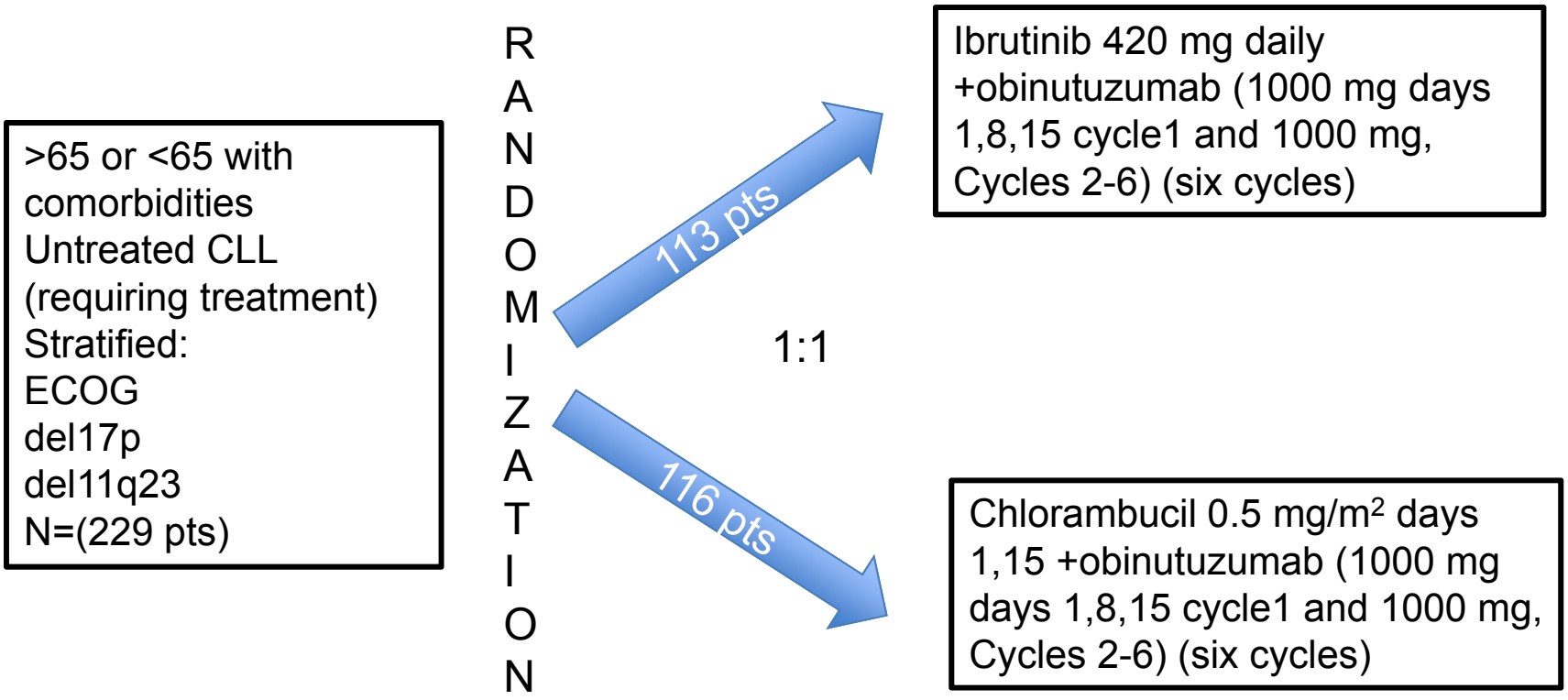
- Treatment with Ibrutinib + rituximab was superior (PFS and OS) to FCR in patients < 70 yrs
- No major benefit in patients with Unmutated IgVH

CAVEAT:

- Treatment until progression
- Clonal selection, drug resistance?

Shanafelt., NEJM 2019; 381:432

iLLUMINATE Study: Ibrutinib plus obinutuzumab vs. chlorambucil plus obinutuzumab in first line treatment of CLL: A phase 3 study



Primary End point: Progression Free survival
Secondary End points: OS, MRD, ORR, platelet and Hb improvement

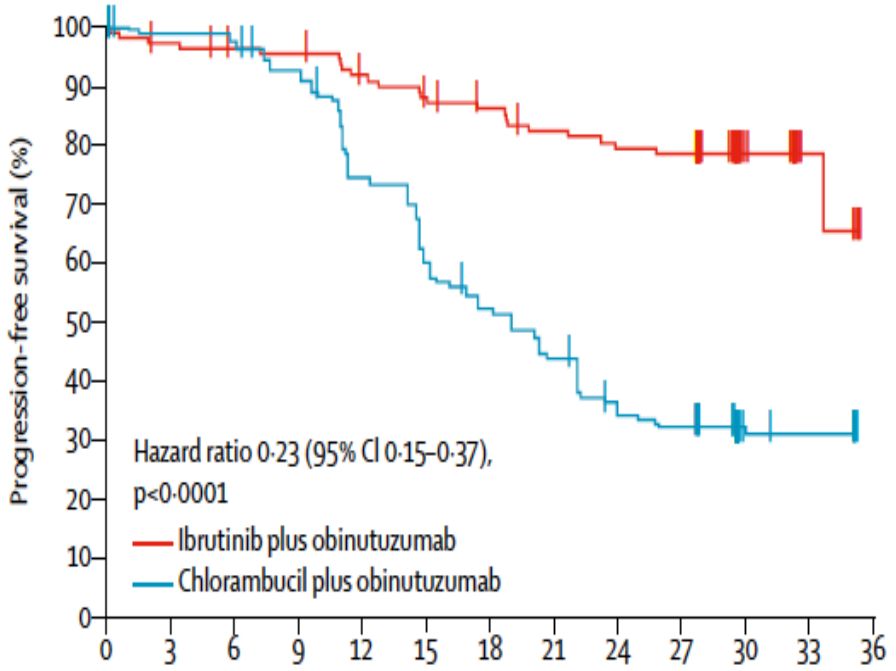
Moreno et al., Lancet Oncology 2019 20;43

Baseline Characteristics

Characteristic	Ibrutinib + Obinutuzumab	Chlorambucil + Obinutuzumab
Age (median)	70 yrs	72 yrs
Rai (high risk)%	53%	51%
Del 17 p	12%	16%
Del 11q	12%	19%
Mutated TP53	12%	15%
CIRS > 6	33%	31%
Unmutated IgVH	62%	53%

Moreno et al., Lancet Oncology 2019 20;43

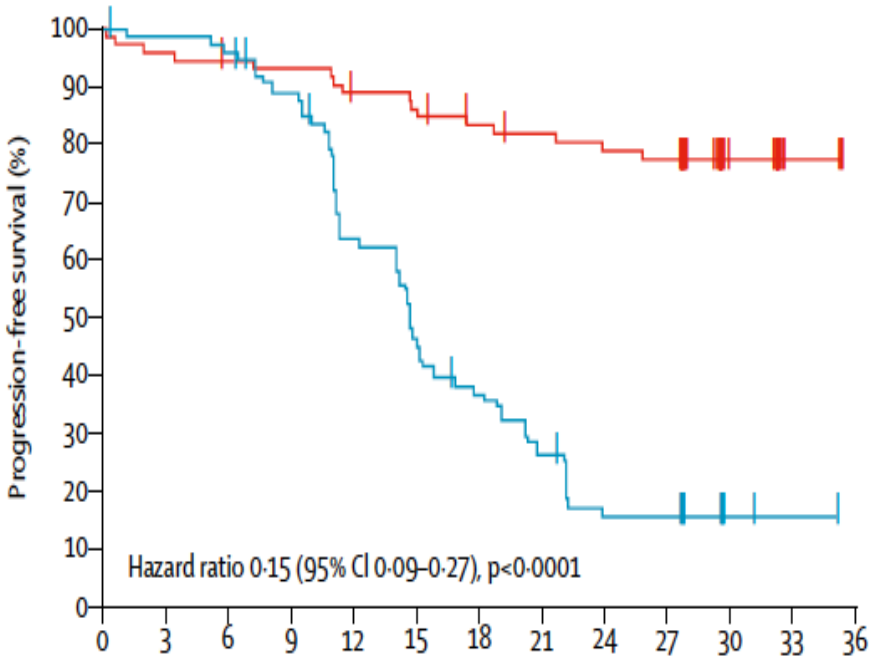
Progression Free survival: Median Follow up; 31.3 months



Number at risk (number censored)													
Ibrutinib plus obinutuzumab	113	109	106	105	99	94	90	85	82	81	28	6	0
	(0)	(1)	(3)	(3)	(5)	(6)	(8)	(9)	(9)	(9)	(62)	(84)	(89)
Chlorambucil plus obinutuzumab	116	111	109	102	81	67	56	47	35	33	6	5	0
	(0)	(4)	(4)	(6)	(7)	(7)	(8)	(8)	(10)	(10)	(36)	(37)	(42)

Moreno et al., Lancet Oncology 2019 20;43

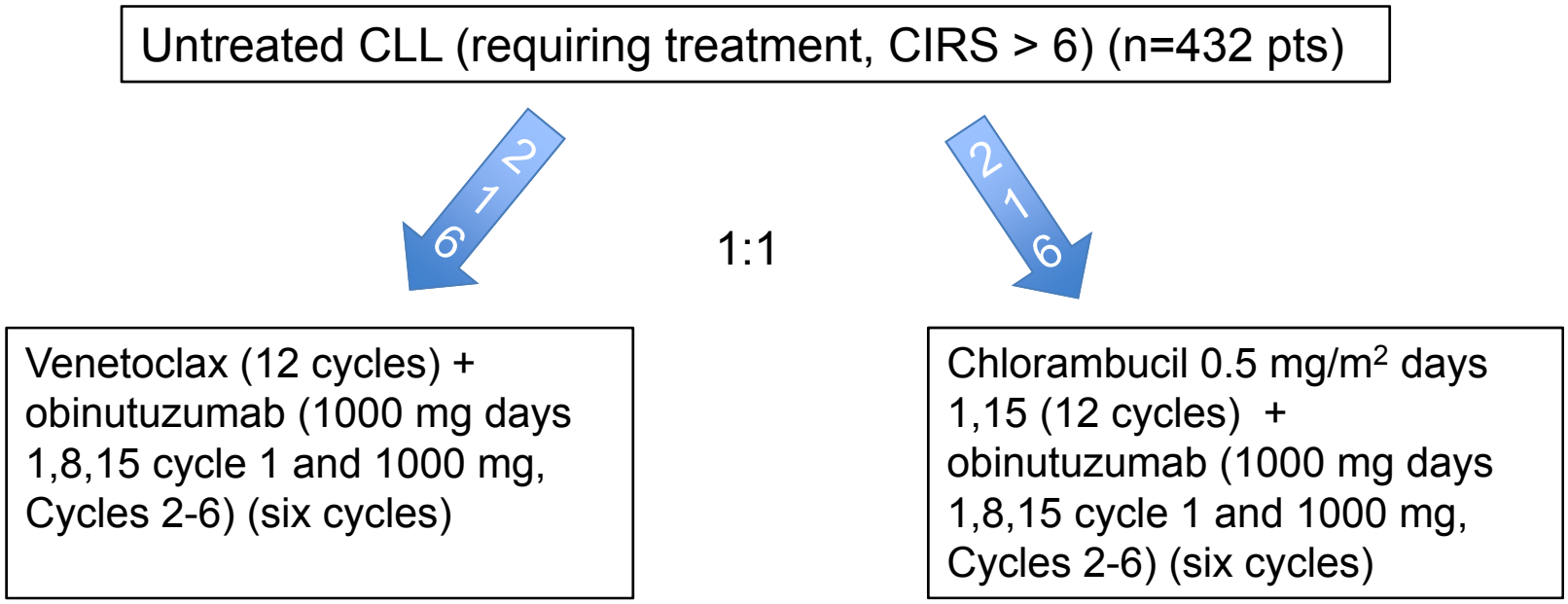
PFS in patients with high risk group (17p del, 11q, TP53)



Number at risk (number censored)													
Ibrutinib plus obinutuzumab	73	70	68	67	63	61	57	55	53	52	17	3	0
	(0)	(0)	(1)	(1)	(2)	(2)	(4)	(5)	(5)	(5)	(40)	(54)	(57)
Chlorambucil plus obinutuzumab	75	73	71	64	45	33	25	18	10	10	2	1	0
	(0)	(1)	(1)	(3)	(4)	(4)	(5)	(5)	(6)	(6)	(14)	(15)	(16)

Moreno et al., Lancet Oncology 2019 20;43

CLL 14: Venetoclax and obinutuzumab in patients with CLL and coexisting conditions



Primary End point: PFS
Secondary End points: MRD negativity, OS, ORR, EFS, duration of response, time to new anti-leukemic treatment

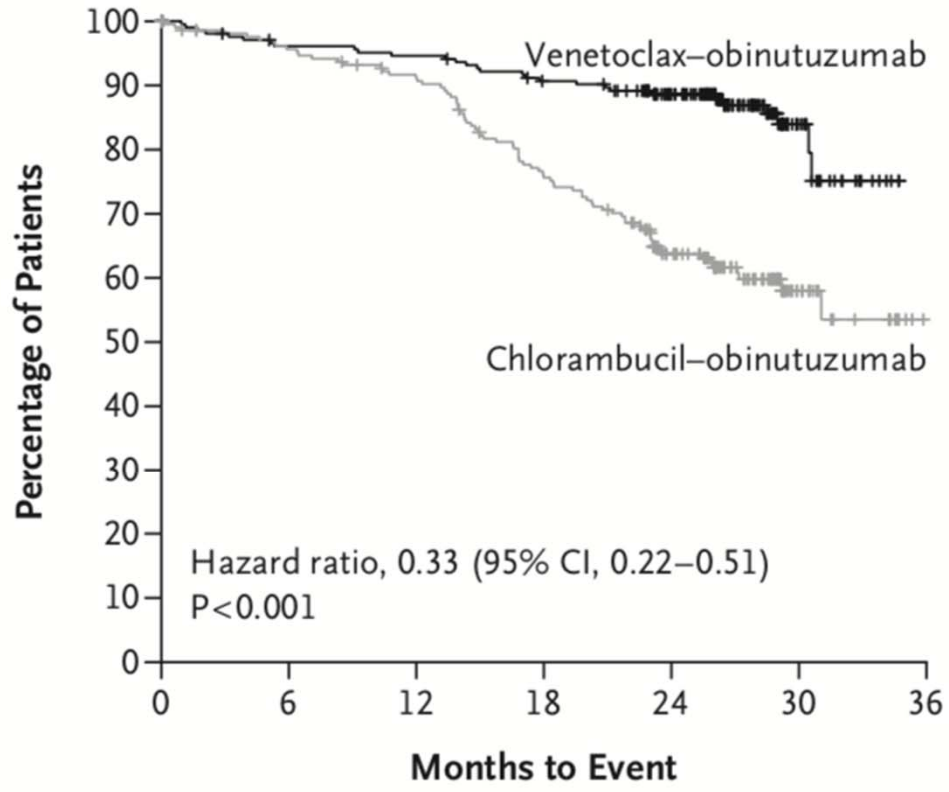
Fischer et al., NEJM 2019; 380: 2225

Baseline Characteristics

Characteristic	venetoclax + Obinutuzumab	Chlorambucil + Obinutuzumab
Age >75 yrs	33%	36%
Binet stage C	43%	42.6%
Del 17 p	8.5%	7.3%
Del 11q	18%	19.7%
Mutated TP53	11.1%	8.3%
CIRS > 6	86%	81.9%
Unmutated IgVH	60.5%	59.1%
TLS- high risk	22.2%	19.9%

Fischer et al., NEJM 2019; 380: 2225

Progression Free Survival: Median follow up, 28.1 months

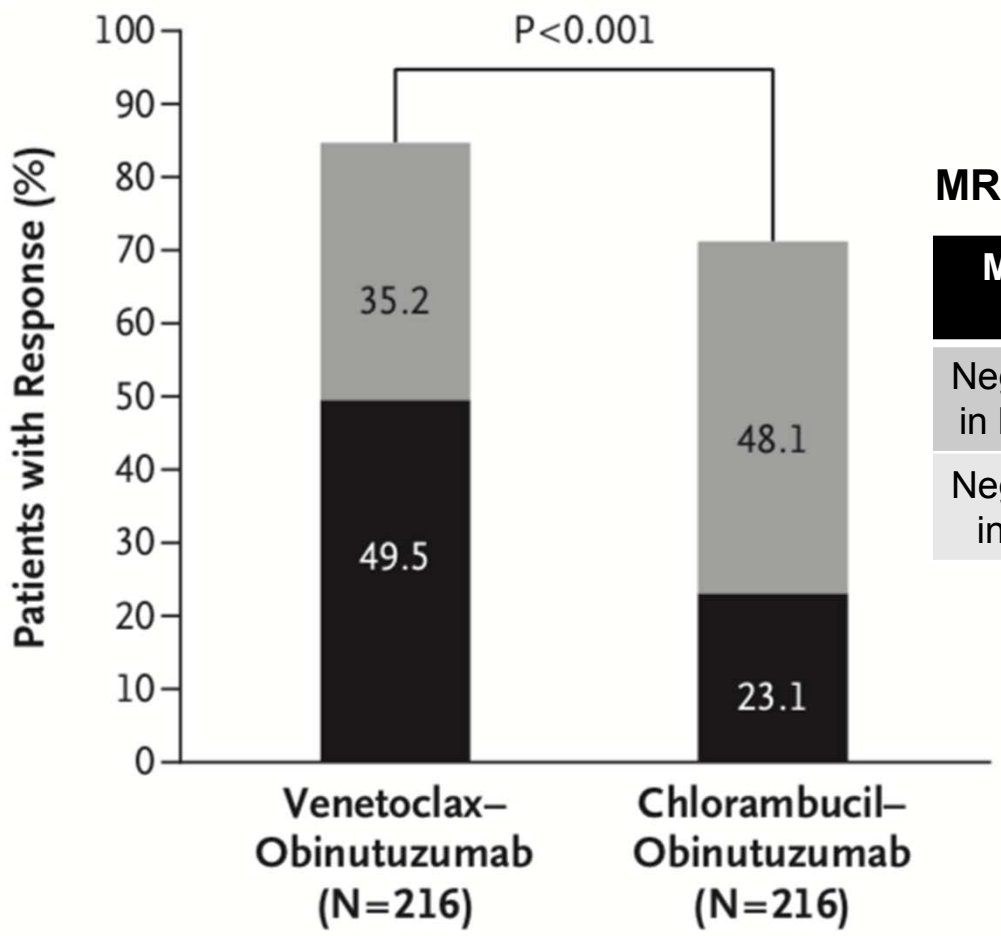


No. at Risk

Venetoclax–obinutuzumab	216	195	192	181	148	23	0
Chlorambucil–obinutuzumab	216	195	183	151	108	20	0

Fischer et al., NEJM 2019; 380: 2225

Overall Response rate and MRD status by treatment arm



MRD status

MRD	Ven+O	Chl+O
Negative in blood	75.1%	35.2%
Negative in BM	56.9%	17.1%

Partial response

Complete response

Fischer et al., NEJM 2019; 380: 2225

Adverse events

AE (grade 3 or 4)	Ven + O	Chl+O
Neutropenia	52.8%	42.1%
Thrombocytopenia	13.7%	15%
Infections	17.5%	15%
TLS syndrome	3 patients	5 patients

Conclusions:

- Venetoclax and obinutuzumab is associated with longer PFS compared with obinutuzumab and chlorambucil in newly diagnosed patients with CLL
- Fixed duration of treatment is attractive

Fischer et al., NEJM 2019; 380: 2225

ASCEND TRIAL: Acalibrutinib vs. Investigator's choice in Relapsed/refractory CLL

N=310 pts

Investigator's choice: Bendamustine + rituximab or Idelalisib + rituximab

No prior Ibrutinib

16% with 17p del, 27% with del 11q, 42% had advanced stage Rai

Primary end point: Progression Free Survival

At a median Follow up of 16.1 months, PFS was not reached in patients treated with acalibrutinib vs. 16.5 months with BR or Idelalisib+ rituximab

Common Adverse events (all grades): headache (22%), neutropenia (19%), diarrhea (18%), cough (15%)

Conclusion: Acalibrutinib monotherapy significantly improves PFS, has a better safety profile in patients with R/R CLL

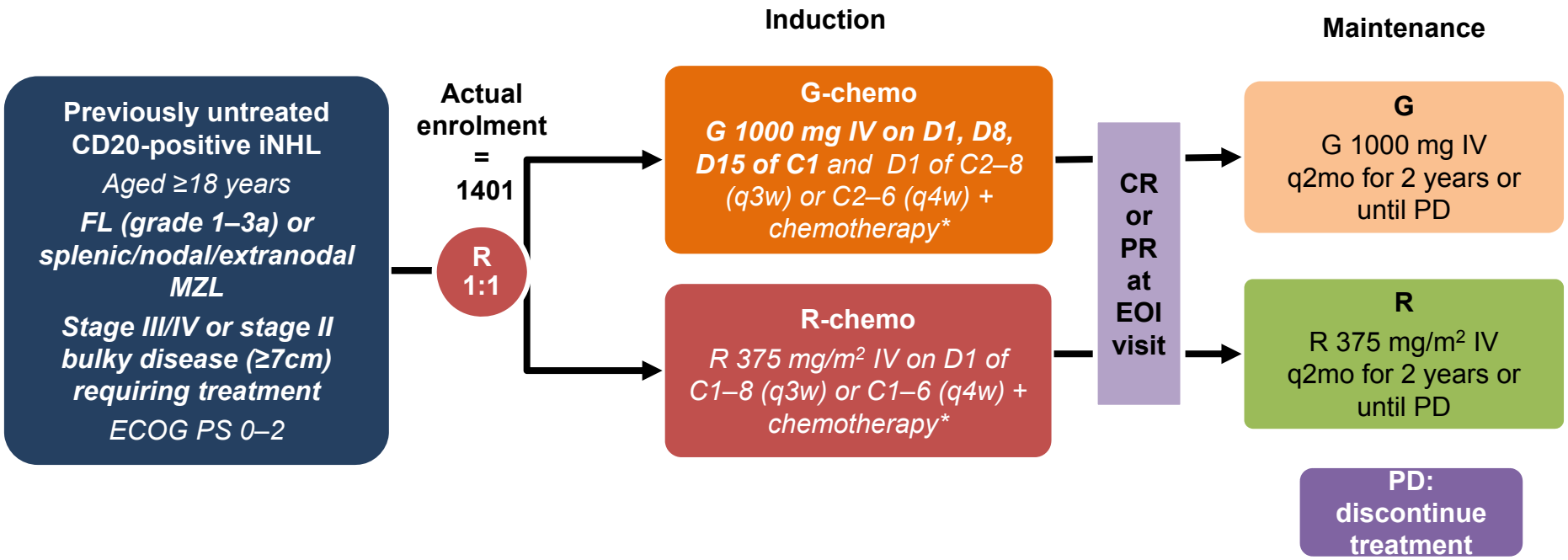
Case:

- 59 YO patient diagnosed with CLL, del 13q, Unmutated IgVH, diagnosed in 2016. Now with progressive lymphocytosis (89K ALC), thrombocytopenia (Platelets: 82 K) and progressive symptomatic splenomegaly. No comorbidities. Repeat FISH reveals del 13q. What is your treatment of choice?

1. Ibrutinib+Rituximab
2. Ibrutinib+obinutuzumab
3. FCR
4. Venetoclax+ Obinutuzumab
5. BR
6. Ibrutinib
7. Obinutuzumab

Updates in the treatment of relapsed/ refractory Follicular Lymphoma

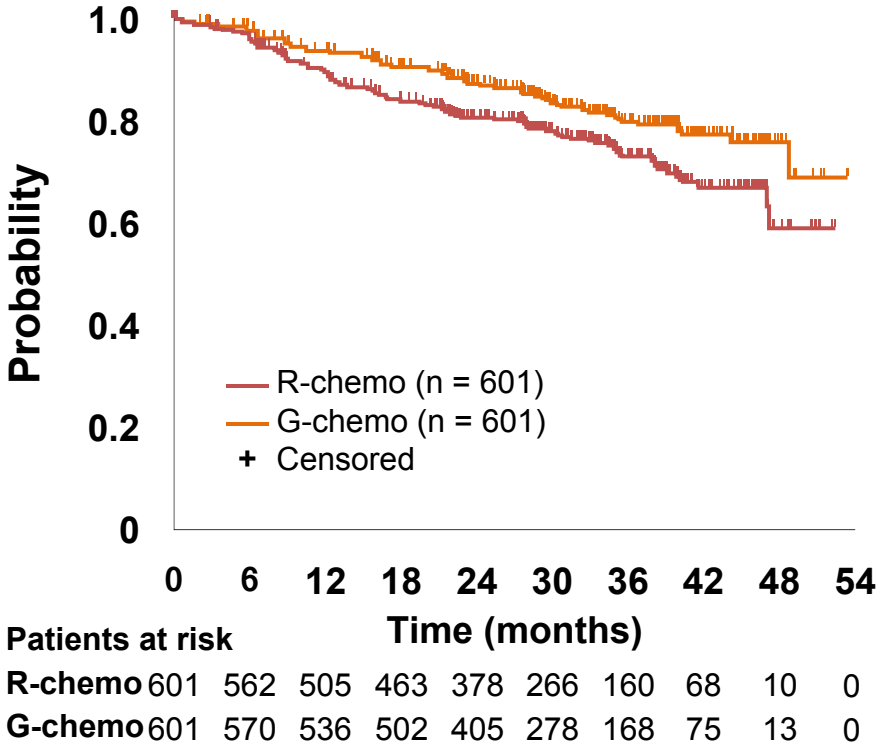
Obinutuzumab-based Induction and Maintenance in patients with previously untreated Follicular Lymphoma: Randomized Phase 3 GALLIUM study



Marcus et al., NEJM 2017: 377

Improved PFS with obinutuzumab based chemotherapy compared with rituximab and chemotherapy in indolent Lymphoma

Kaplan-Meier plot of INV-assessed PFS in FL by treatment arm



PFS (Investigator Assessed)		
	R-chemo n = 601	G-chemo n = 601
Pts with event, n (%)	144 (24.0)	101 (16.8)
3-year PFS, % (95% CI)	73.3 (68.8–77.2)	80.0 (75.9–83.6)
Median PFS, mos (95% CI)	NE (47.1–NE)	NE (NE–NE)

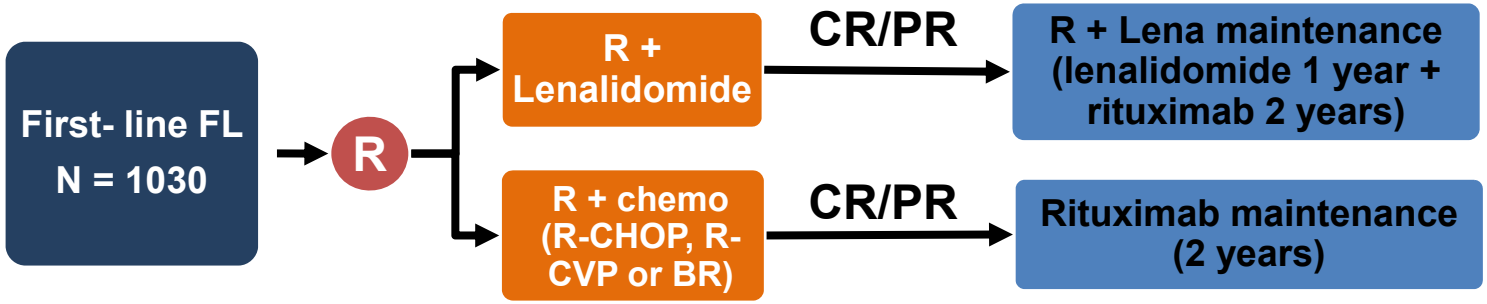
HR = 0.66 (95% CI, 0.51–0.85)
Stratified *P*=0.001

Median follow-up = 34.5 months

Marcus et al., NEJM 2017: 377

Lenalidomide and rituximab in indolent NHL as frontline therapy compared with Immunochemotherapy

RELEVANCE: International study



Primary End point: Progression Free survival

Morschhauser F et al. *N Engl J Med.* 2018;379

Baseline characteristics

Characteristic	R + Lena (n = 513)	R-Chemo (n = 517)
Median age, yrs (range)	59 (30–89)	59 (23–83)
>70 yrs, n (%)	80 (16)	78 (15)
Male, n (%)	251 (49)	251 (49)
ECOG PS, n (%)		
0	341 (66)	345 (67)
1	157 (31)	157 (30)
2	13 (3)	14 (3)
Ann Arbor stage, n (%)		
I/II	30 (6)	40 (8)
III/IV	483 (94)	477 (92)

Characteristic, n (%)	R + Lena (n = 513)	R-Chemo (n = 517)
Bulky disease (>7 cm)	218 (42)	199 (38)
FLIPI score: risk		
Low (0/1)	77 (15)	76 (15)
Intermediate (2)	183 (36)	191 (37)
High (3–5)	253 (49)	250 (48)
B-symptoms	141 (27)	134 (26)
FL grade		
1 or 2	437 (85)	443 (86)
3a	65 (13)	63 (12)
LDH (>ULN)	156 (30)	137 (26)

Morschhauser F et al. *N Engl J Med.* 2018;379

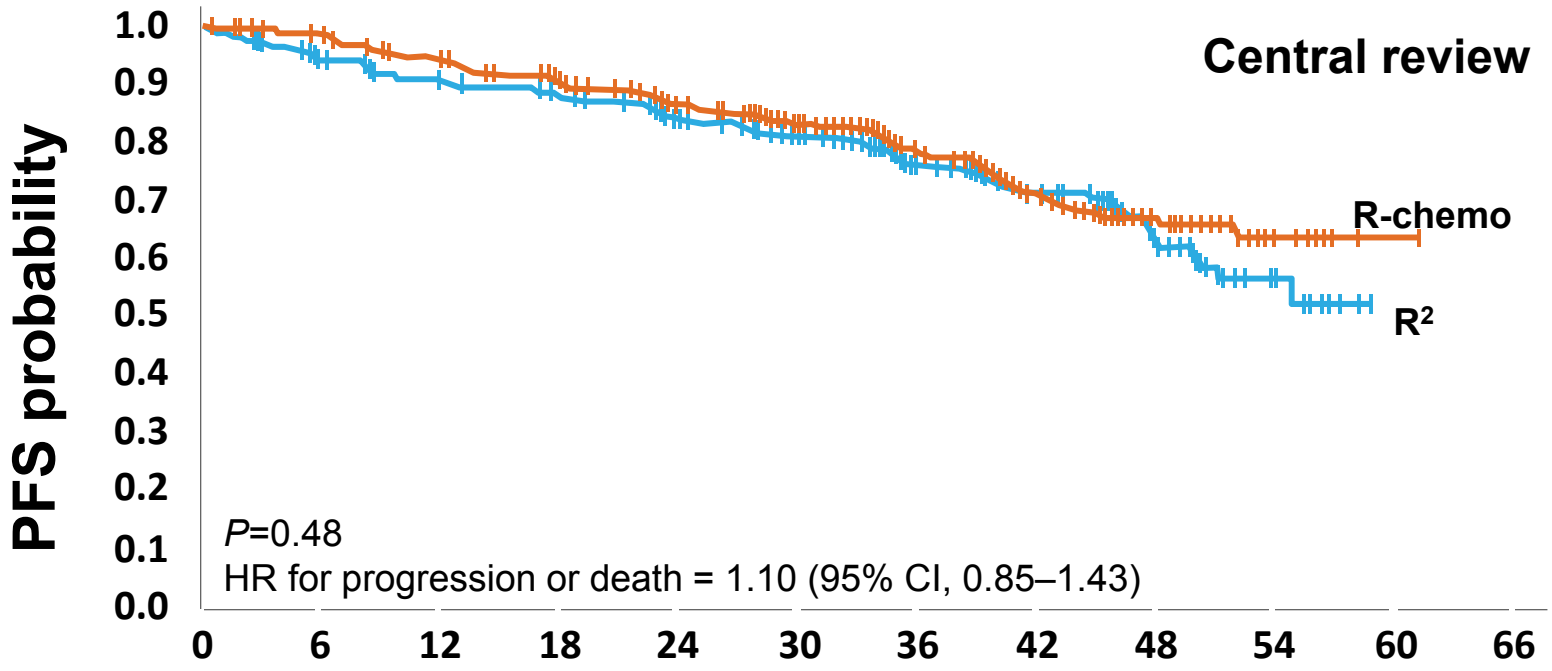
Efficacy

Outcome	R = Lena (n = 513)	R-Chemo (n = 517)
CR/CRu at 120 wks, %	48	53
Best CR/CRu (at any time), %	59	67
Best ORR, %	84	89
3-year DoR, %	77	74
Events, n (%)	119 (23)	111 (21)
3-year PFS, % (95% CI)	77 (72–80)	78 (74–82)
HR = 1.10 (95% CI, 0.85–1.43), *P*=0.48		
3-year OS (immature), %	94 (91–96)	94 (91–96)
HR = 1.16 (95% CI, 0.72–1.86)		

Prespecified subgroup analysis of interim PFS showed similar outcomes in both treatment arms.

Morschhauser F et al. *N Engl J Med.* 2018;379

PFS with chemo-free regimen (R^2) vs. standard R-chemo: RELEVANCE

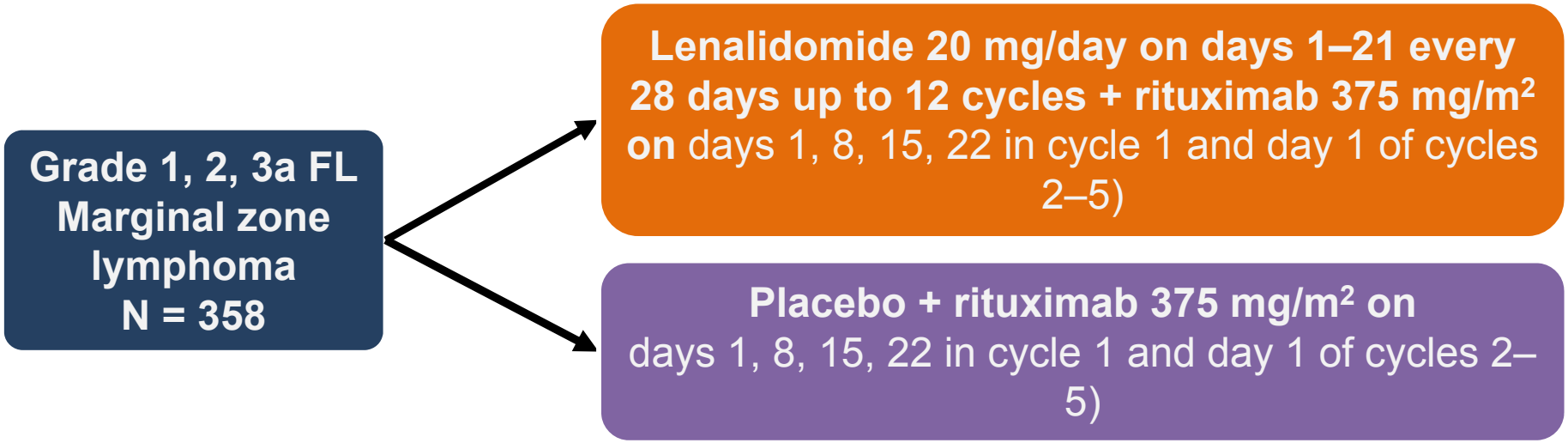


No. of patients at risk

R^2	513	435	409	393	364	282	174	107	49	13	0	0
R-chemo	517	474	446	417	387	287	175	109	51	14	1	0

Morschhauser F et al. *N Engl J Med.* 2018;379

Phase 3, multicenter, double blind, randomized study of lenalidomide and rituximab in relapsed indolent FL (AUGMENT)



Primary endpoint: Progression-free survival

Secondary endpoints: CR, ORR, safety, time to next anti-lymphoma treatment

Leonard JP et al. JCO 2019; 37

AUGMENT: Patient Population

Characteristic, n (%)	R² (n = 178)	R-Placebo (n = 180)
Median age, yrs (range)	64 (26–86)	62 (35–88)
▪ Age ≥60 yrs	108 (61)	106 (59)
▪ Age ≥65 yrs	82 (46)	73 (41)
ECOG PS 1/2*	62 (35)	52 (29)
BM involvement, n involved/performed (%)	33/106 (31)	31/111 (28)
Ann Arbor stage III or IV at entry	137 (77)	124 (69)
Bulky disease†	45 (25)	49 (27)
High tumor burden by GELF	97 (54)	86 (48)
FL/MZL	147 (83)/ 31 (17)	148 (82)/ 32 (18)
LDH > ULN	43 (24)	39 (22)
B symptoms	16 (9)	12 (7)
FLIPI score‡		
▪ 0/1	52 (29)	67 (37)
▪ 2	55 (31)	58 (32)
▪ 3–5	69 (39)	54 (30)

Characteristic, n (%)	R² (n = 178)	R-Placebo (n = 180)
No. of prior systemic antilymphoma regimens		
▪ 1	102 (57)	97 (54)
▪ 2	31 (17)	42 (23)
▪ ≥ 3	45 (25)	41 (23)
Prior rituximab	152 (85)	150 (83)
Prior rituximab-chemotherapy regimen	130 (73)	129 (72)
≤2 yrs since last antilymphoma therapy	89 (50)	92 (51)
Relapse		
▪ ≤2 yrs since diagnosis	56 (31)	61 (34)
▪ ≤2 yrs since initial therapy	66 (37)	75 (42)
Refractory to last regimen§	30 (17)	26 (14)

Leonard JP et al. JCO 2019; 37

Median follow-up; 28.3 months

Outcome	R^2 (n = 178)	R-Placebo (n = 180)	HR (95% CI)	*P* Value
Median PFS by IRC, mos (95% CI)	39.4 (22.9–NE)	14.1 (11.4–16.7)	0.46 (0.34–0.62)	<0.0001
Median PFS by investigator, mos (95% CI)	25.3 (21.2–NE)	14.3 (12.4–17.7)	0.51 (0.38–0.69)	<0.0001
ORR by IRC, % ▪ **CR** ▪ **PR**	78 34 44	53 18 35	—	<0.0001
ORR by investigator, % ▪ **CR** ▪ **PR**	79 32 47	59 21 39	—	<0.0001
Median DoR, mos (95% CI)	36.6 (22.9–NR)	21.7 (12.8–27.6)	0.53 (0.36–0.79)	0.0015
Median OS, mos ▪ **2-yr OS, % (95% CI)**	NR 93 (87–96)	NR 87 (81–92)	0.61 (0.33–1.13)	NR
Median OS in patients with FL, mos ▪ **2-yr OS, % (95% CI)**	**NR** **95 (90–98)**	**NR** **86 (79–91)**	**0.45 (0.22–0.91)**	**0.02**

Leonard JP et al. JCO 2019; 37

AUGMENT: Safety

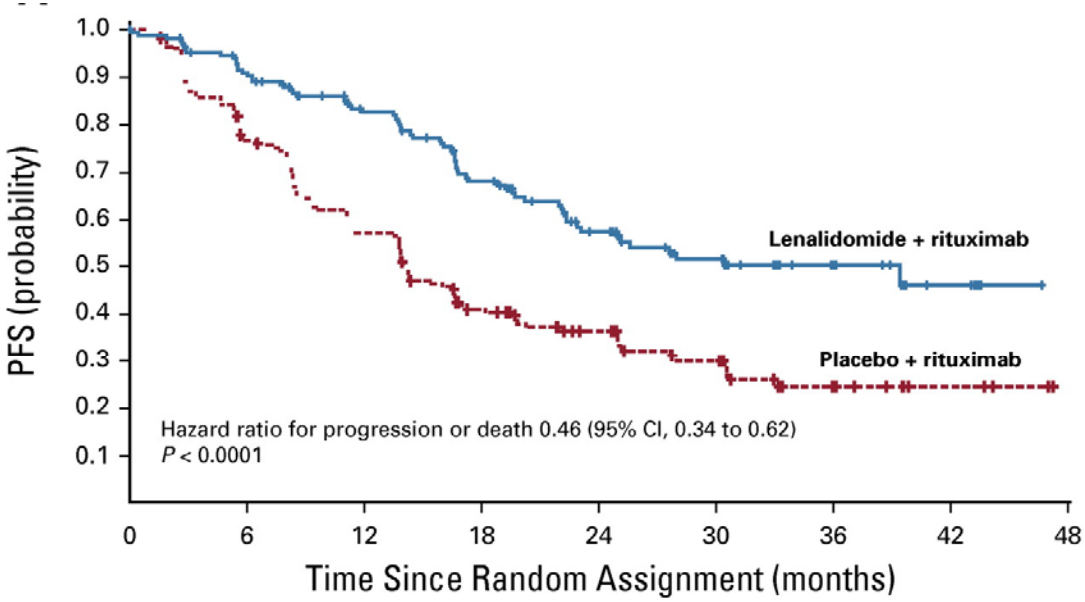
AEs of Special Interest, n (%)	R^2 (n = 176)	R-Placebo (n = 180)
All secondary primary malignancies	6 (3)	10 (6)
▪ **Hematologic malignancies**	1 (1)	2 (1)
▪ **Sold tumor**	2 (1)	6 (3)
▪ **Noninvasive**	3 (2)	3 (2)
Venous thromboembolism AEs	6 (3)	3 (2)
Arterial thromboembolism AEs	1 (1)	4 (2)
Mixed thromboembolism AEs	3 (2)	1 (1)

- Treatment-emergent AEs more common with R^2 included infections, neutropenia, cutaneous reactions, constipation, leukopenia, anemia, thrombocytopenia, and tumor flare

- Histologic transformation occurred in 1% with R^2 vs 6% with R-placebo.

Leonard JP et al. JCO 2019; 37

AUGMENT: Results



No. at risk:									
Lenalidomide + rituximab	178	148	124	91	59	39	20	7	0
Placebo + rituximab	180	132	92	58	40	26	10	4	0

Improved PFS with Lenalidomide and rituximab in patients who received one prior therapy for indolent NHL compared with rituximab.

Lenalidomide and rituximab is an FDA approved therapy for relapsed/refractory indolent NHL

Leonard JP et al. JCO 2019; 37

Comparing across PI3K inhibitors in FL

	Idelalisib	Copanlisib	Duvelisib
Number of pts	125	142	129
Route	oral	Intravenous	Oral
Overall Response	56%	59%	46%
Complete Response	9.6%	12%	5%
m PFS	11 months	11.2 months	9.9 months
Side effect profile	Diarrhea (colitis) Transaminitis Pneumonitis	Hyperglycemia HTN	Diarrhea, Cytopenias, Infections

The PI3Kδ Inhibitor ME-401 ± Rituximab in Relapsed/Refractory (R/R) Follicular Lymphoma (FL), Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL)

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Study Design

Dose Escalation	**FL, CLL/SLL** • 60, 120, 180 mg • Once daily continuously in 28-day cycles	**Completed** • Adaptive 6+6 CRM design • No DLTs in 56-day DLT window • MTD not defined
ME-401 + Rituximab	**FL, CLL/SLL, MZL, DLBCL** • 60 mg qd x2 cycles then intermittent dosing cycles ≥3 • Rituximab 375 mg/m^2 weekly x4 then x1 in cycles 3-6	**Completed**
Monotherapy Expansion	**FL, CLL/SLL** • 60 mg qd x2 cycles then intermittent dosing cycles ≥3	**Enrolling**

- Age ≥18
- ECOG performance status 0-2
- Failure of ≥1 prior therapy or ≥2 prior in DLBCL
- No prior PI3Ki therapy

- ME-401 dose modification for toxicity
  - Initially by reducing daily dose
  - Recently by switching to intermittent dosing
- PJP prophylaxis

Intermittent **Dosing Schedule**

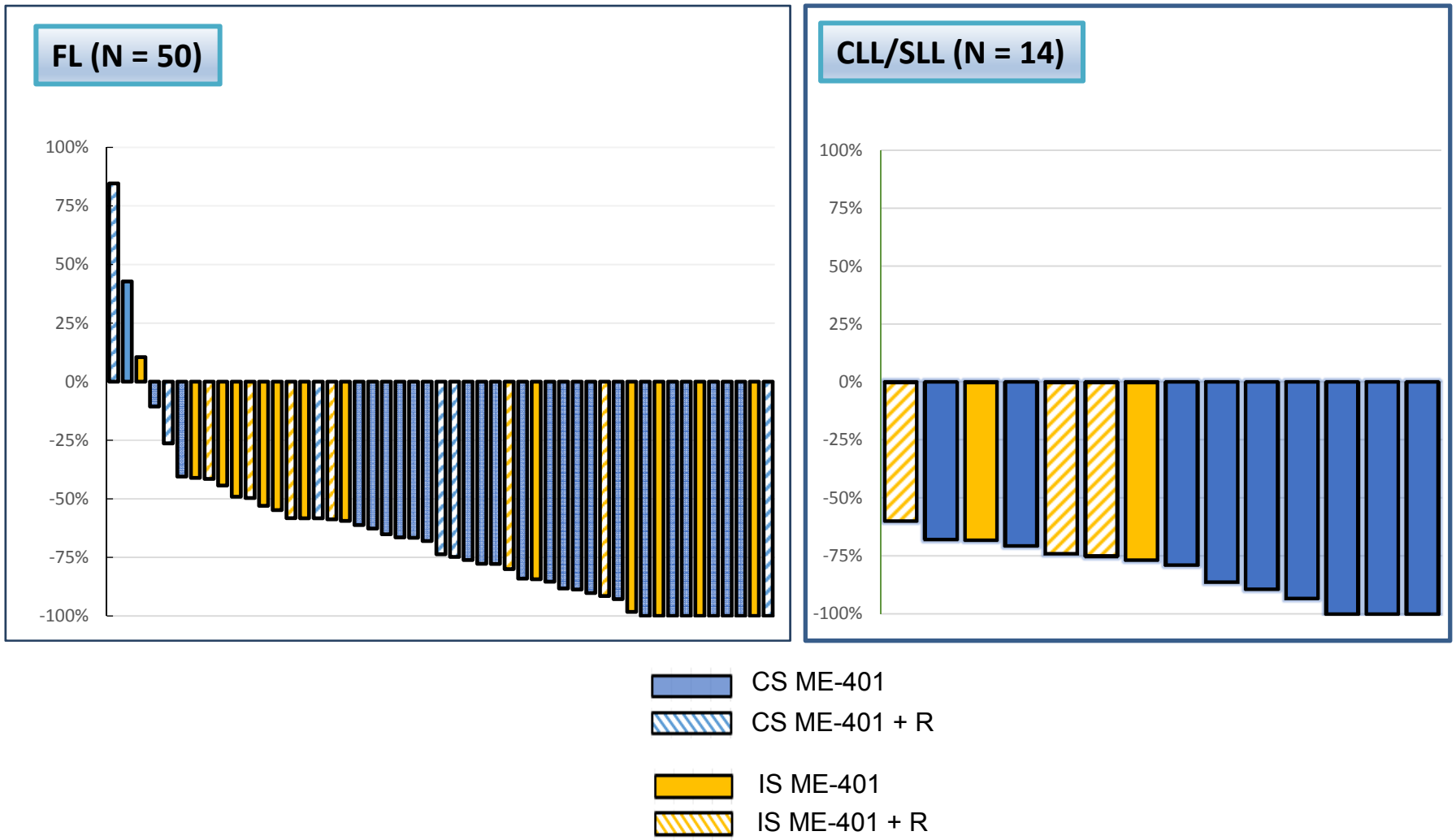
- Continuous dosing schedule (CS) resulted in grade 3 diarrhea/colitis and skin rash in ~1/3rd of patients
- Likely due to on-target inhibition of Tregs
- Intermittent dosing (IS) might allow Treg repopulation without loss of tumor control
- IS beginning in Cycle 3
  - Most responses observed by end of Cycle 2
  - Drug-related AEs typically occur in later cycles
- Patients could be reverted to daily dosing if loss of tumor control on IS

Overall Response Rate

Evaluable Patients	FL (N = 50)	CLL/SLL (N = 14)	Total (N = 64)
All groups	40 (80%)	14 (100%)	54 (83%)
By treatment arm ME-401 monotherapy ME-401 + rituximab	30/38 (79%) 10/12 (83%)	11/11 (100%) 3/3 (100%)	41/49 (84%) 13/15 (87%)
By schedule IS group CS group	15/20 (75%) 25/30 (83%)	5/5 (100%) 9/9 (100%)	20/25 (80%) 34/39 (87%)

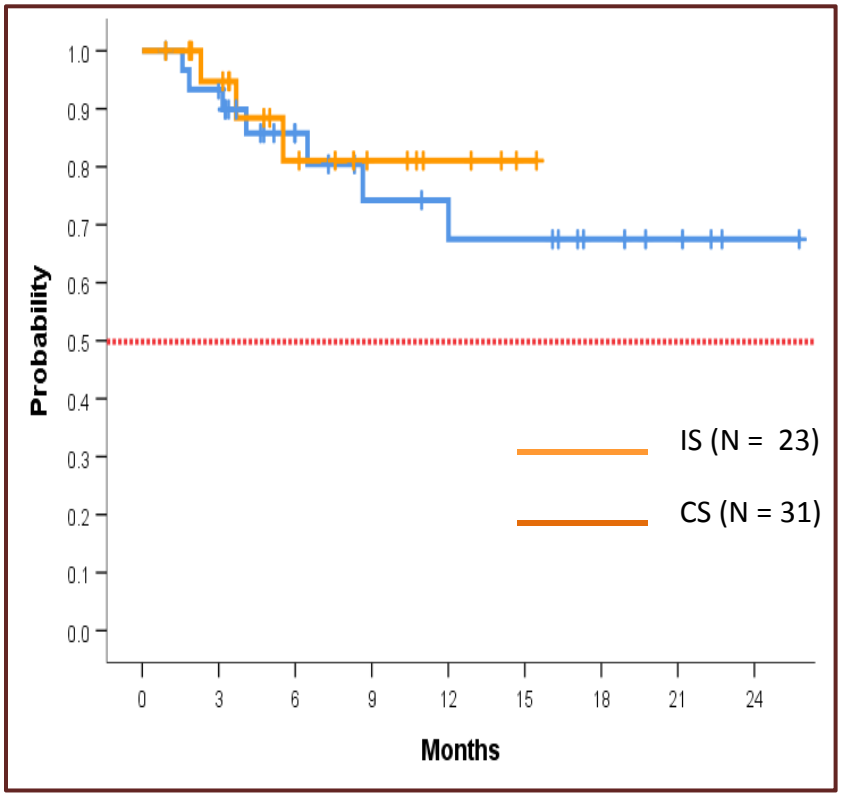
Disease assessment at end of Cycle 2, 6 and then every 6 months. Lugano criteria for FL and iw-CLL for CLL/SLL

Best Change From Baseline of Measurable Lesions

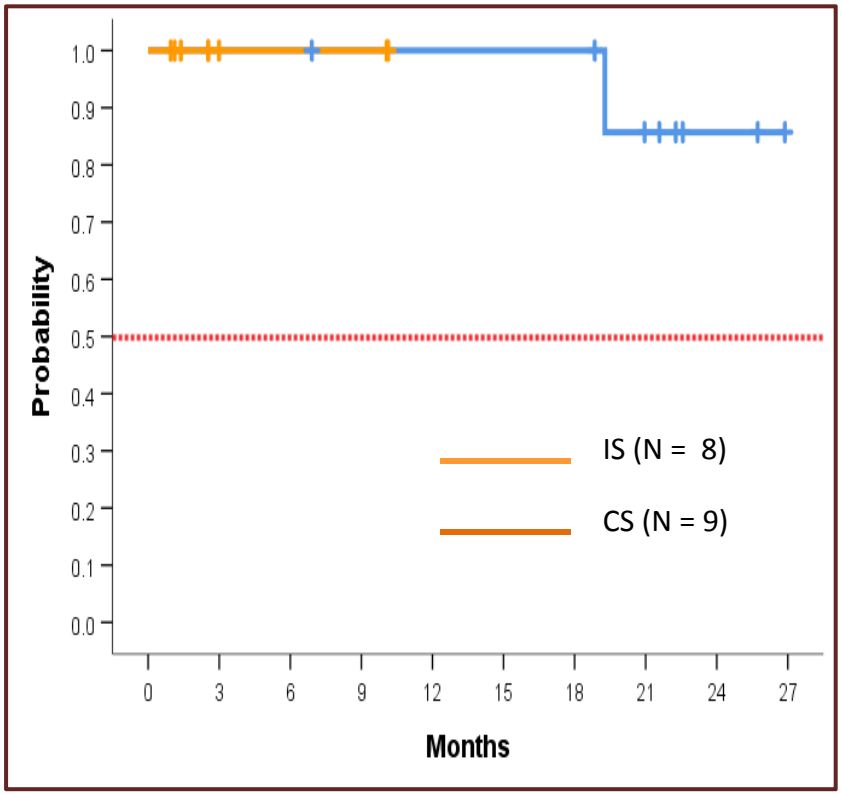


Progression-Free Survival

FL (N = 54)



CLL/SLL (N = 17)

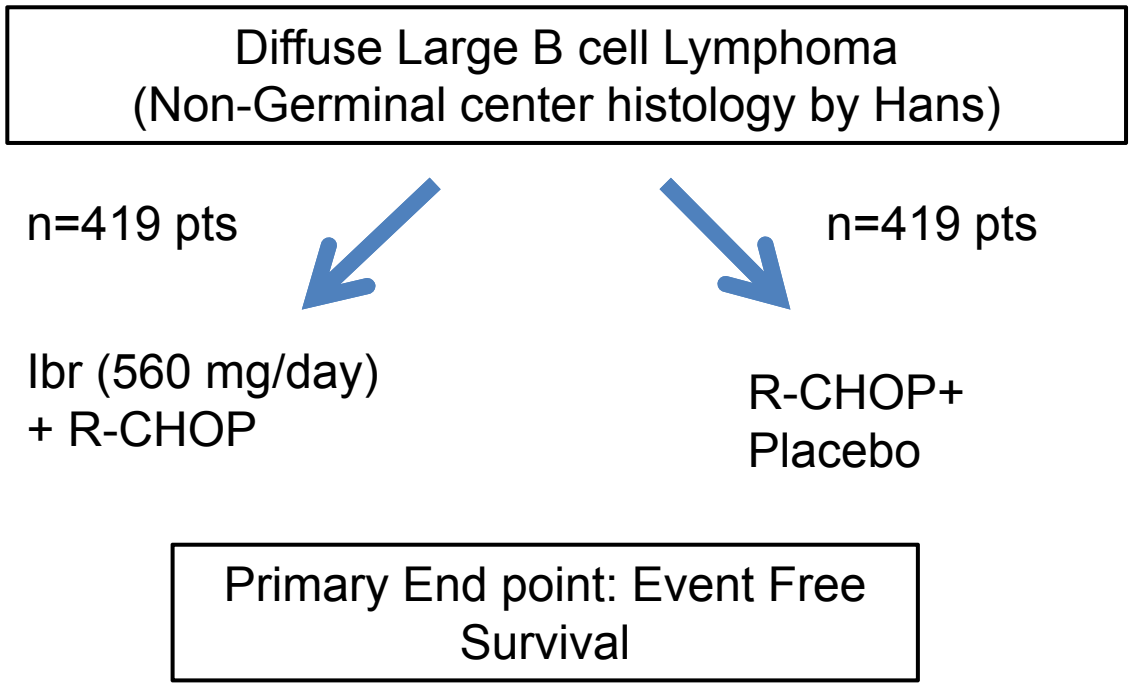


Adverse Events of Special Interest: FL + CLL/SLL (N=71)

AESI	All Grades		Grade 3	
	CS Group (N = 40)	IS Group (N = 31)	CS Group (N = 40)	IS Group (N = 31)
Diarrhea/colitis	17 (42.5%)	15 (48.7%)	8 (20.0%)	3 (9.7%)
Rash, all types	15 (37.5%)	5 (16.1%)	4 (10.0%)	0
ALT/AST increased	10 (25.0%)	7 (22.6%)	3 (7.5%)	1 (3.2%)
Mucositis	7 (17.5%)	1 (3.2%)	1 (2.5%)	0
Pneumonia/Pneumonitis	5 (12.5%)	1 (3.2%)	5 (12.5%)	1 (3.2%)

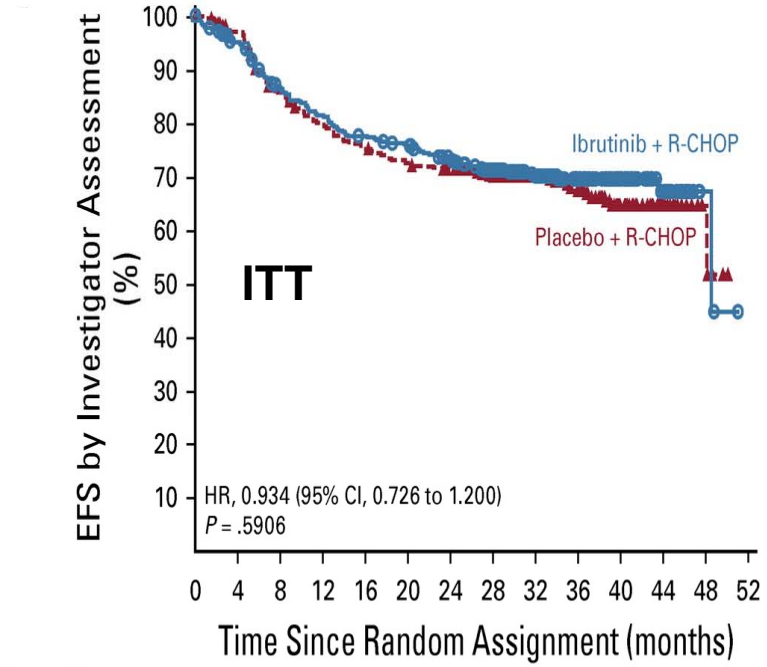
Treatment updates in Diffuse Large B-cell Lymphoma

PHOENIX: Randomized Phase III Trial of Ibrutinib and Rituximab plus Cyclophosphamide, doxorubicin, vincristine and prednisone in Non-Germinal Center B-cell Diffuse Large B cell Lymphoma



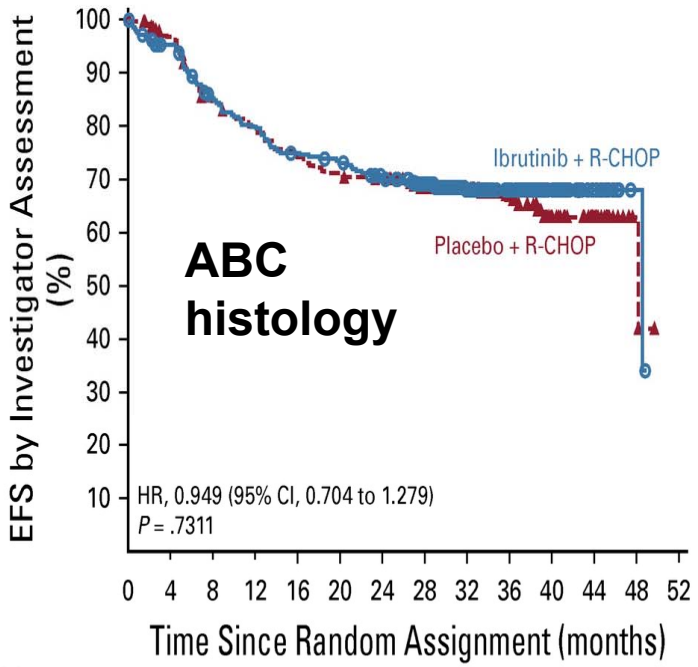
Younes A, JCO 2019;37(15)

Progression Free Survival of patients receiving IR-CHOP compared with R-CHOP



No. at risk:

Ibrutinib + R-CHOP	419	374	336	316	300	291	276	233	179	120	63	25	3	0
Placebo + R-CHOP	419	390	341	316	297	286	277	244	184	118	60	33	5	0

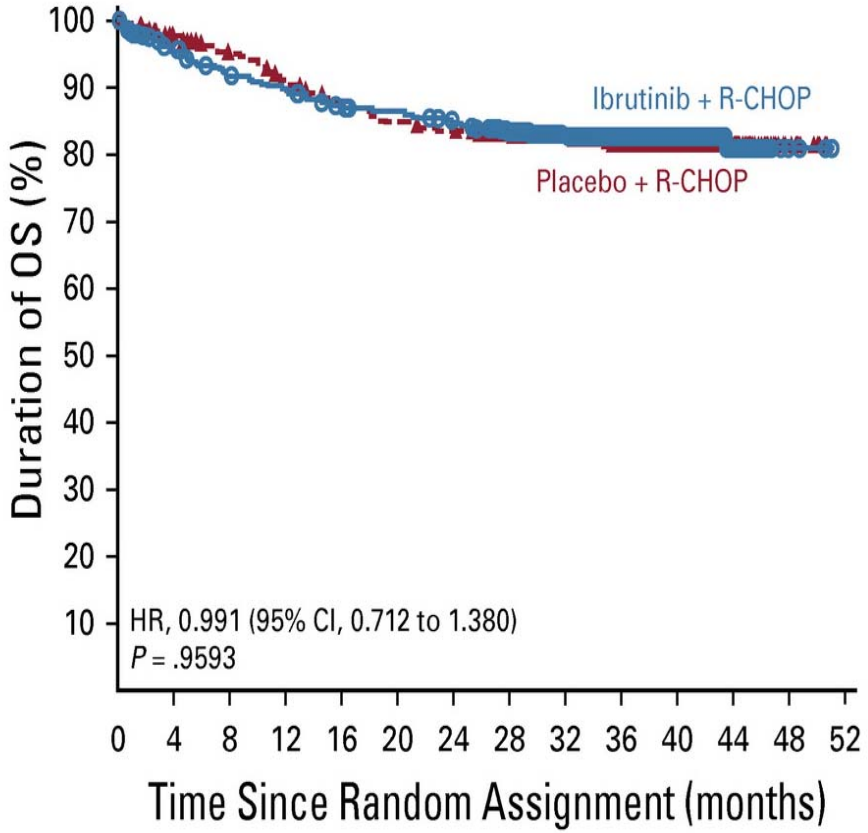


No. at risk:

Ibrutinib + R-CHOP	285	256	225	211	197	191	181	149	111	77	39	15	2	0
Placebo + R-CHOP	282	260	225	212	196	188	183	160	125	78	41	25	3	0

Younes A, JCO 2019;37(15)

Overall Survival

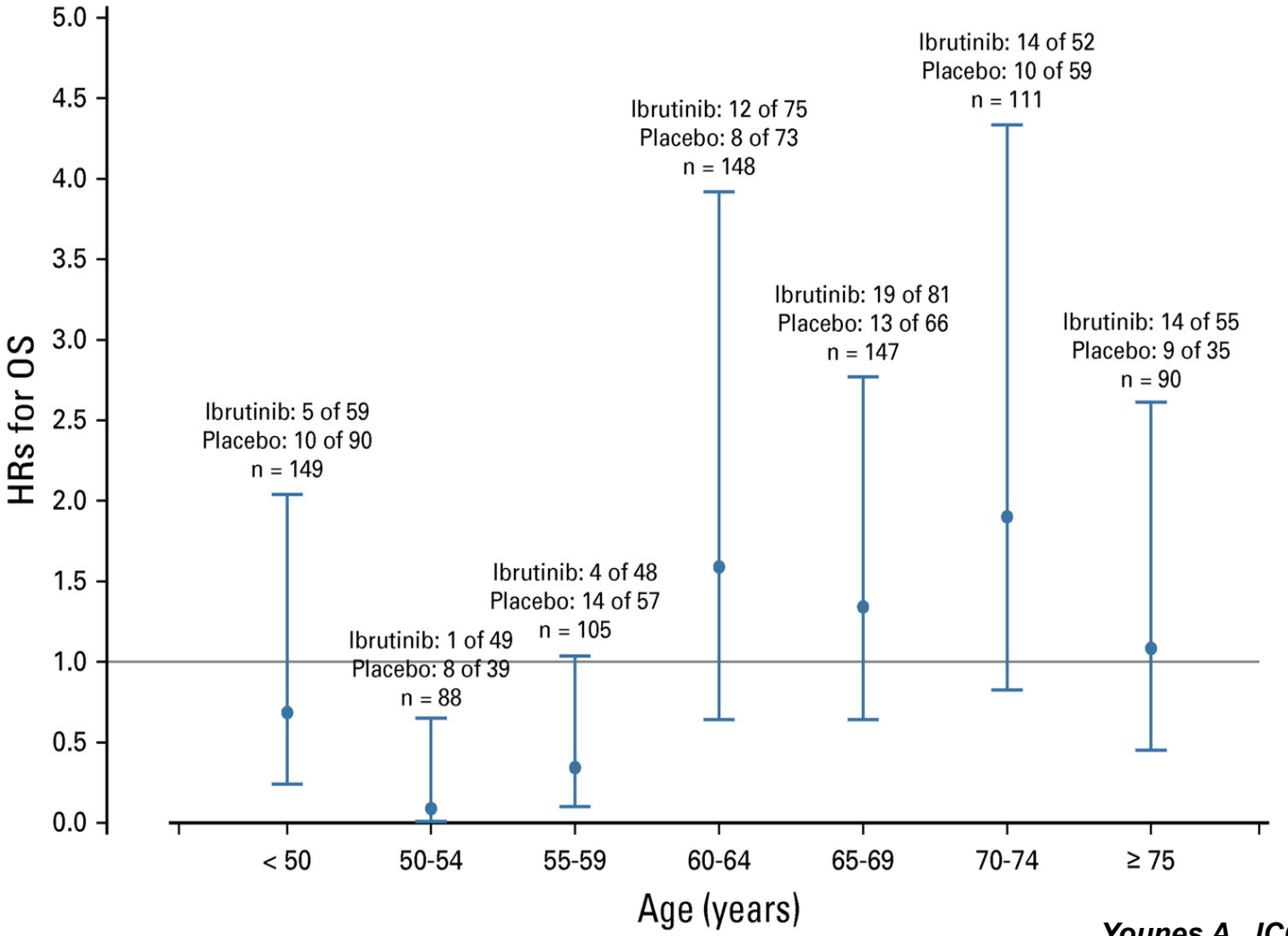


No. at risk:

Ibrutinib + R-CHOP	419	384	365	356	342	337	328	309	236	159	100	38	4	0
Placebo + R-CHOP	419	400	382	363	347	335	329	301	237	157	99	51	12	0

Younes A, JCO 2019;37(15)

?Benefit of Ibrutinib with R-CHOP by age



Younes A, JCO 2019;37(15)

ROBUST: Randomized Phase III Trial of lenalidomide and Rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone in activated B-cell Diffuse Large B cell Lymphoma

Diffuse Large B cell Lymphoma (ABC histology)
N=570 patients

Median follow up:
27.1 months

Lenalidomide (15 mg/day, days 1-14) + R-CHOP

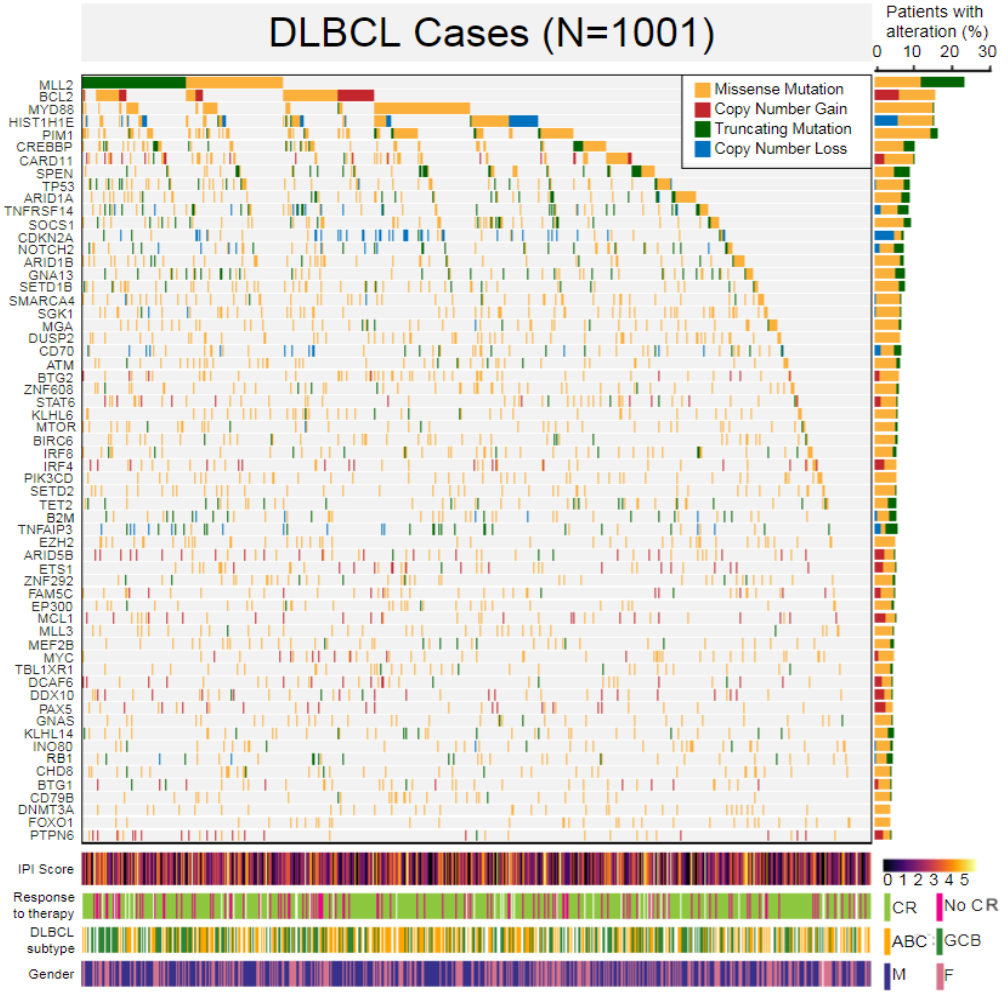
R-CHOP+ Placebo

Primary End point: Progression Free survival

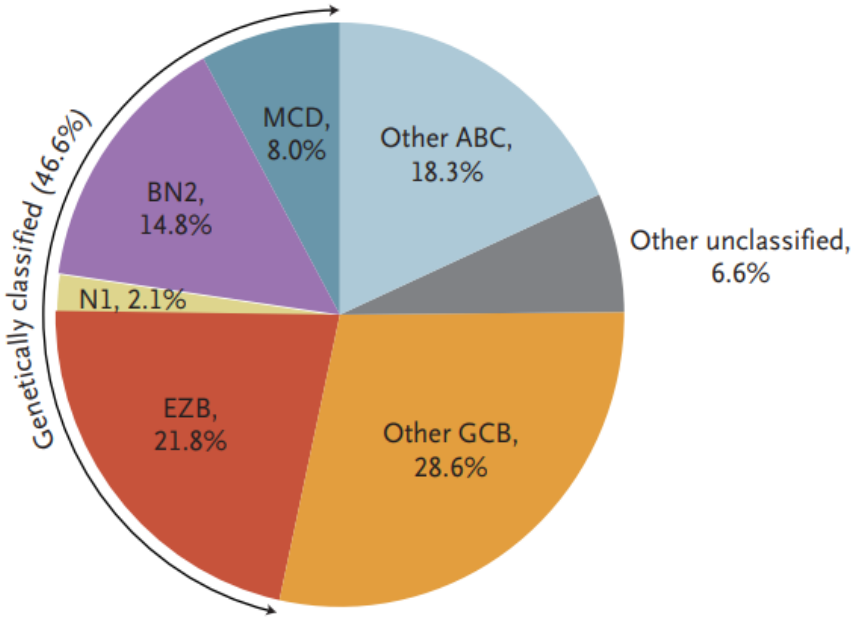
	Len-R-CHOP	R-CHOP+ placebo
ORR	91%	91%
Complete response	69%	65%
Overall survival	79%	80%

Evolving genetics of DLBCL

- 27 of 150 driver genes newly-described in DLBCL (dave et al., Cell 2017)
- Comprehensive model for risk stratification
- ~36% of DLBCL show alteration suggesting therapeutic sensitivity



Evolving genetics of DLBCL



574 DLBCL samples (staudt.L et al., NEJM 2017)

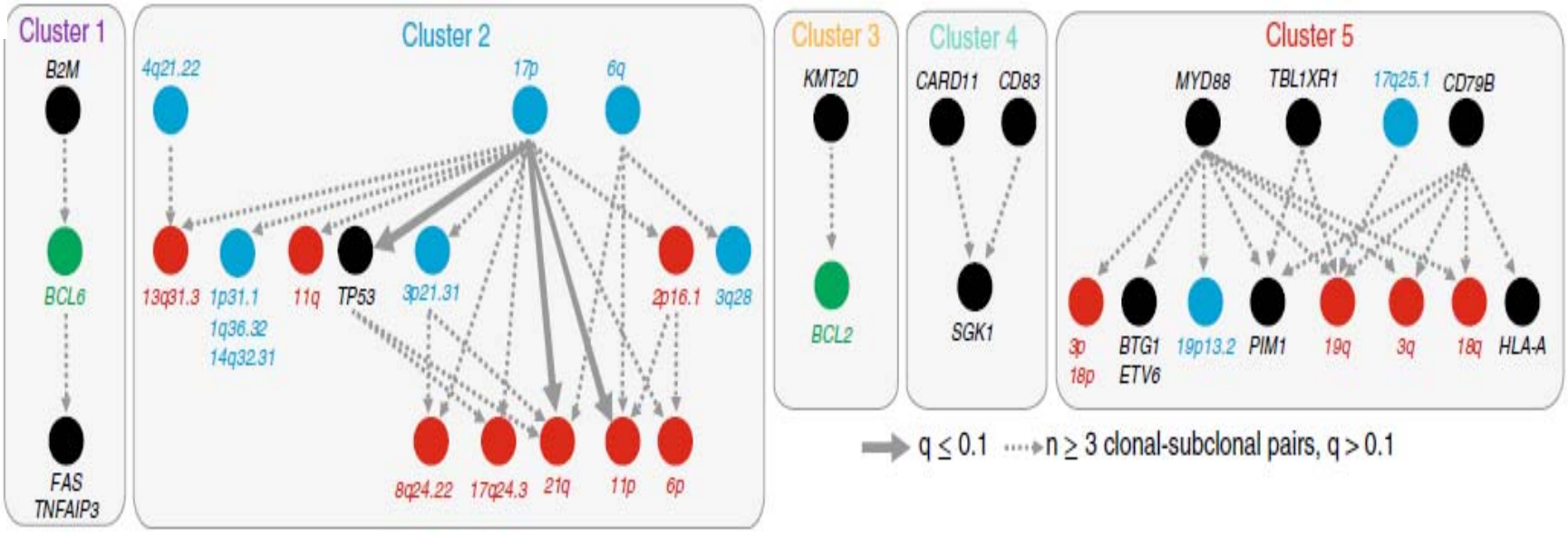
- Exome, transcriptome sequencing
- Array-based CAN
- Targeted amplicon resequencing of 372 genes

Subgroups

- MCD (MYD88 + CD79B)
- BN2 (BCL6 + NOTCH2)
- N1 (NOTCH1)
- EZB (EZH2 + BCL2)

BN2 and EZB	Favorable survival
MCD and N1	Inferior outcomes
MCD and BN2	“Chronic active” BCR signaling

Evolving genetics of DLBCL

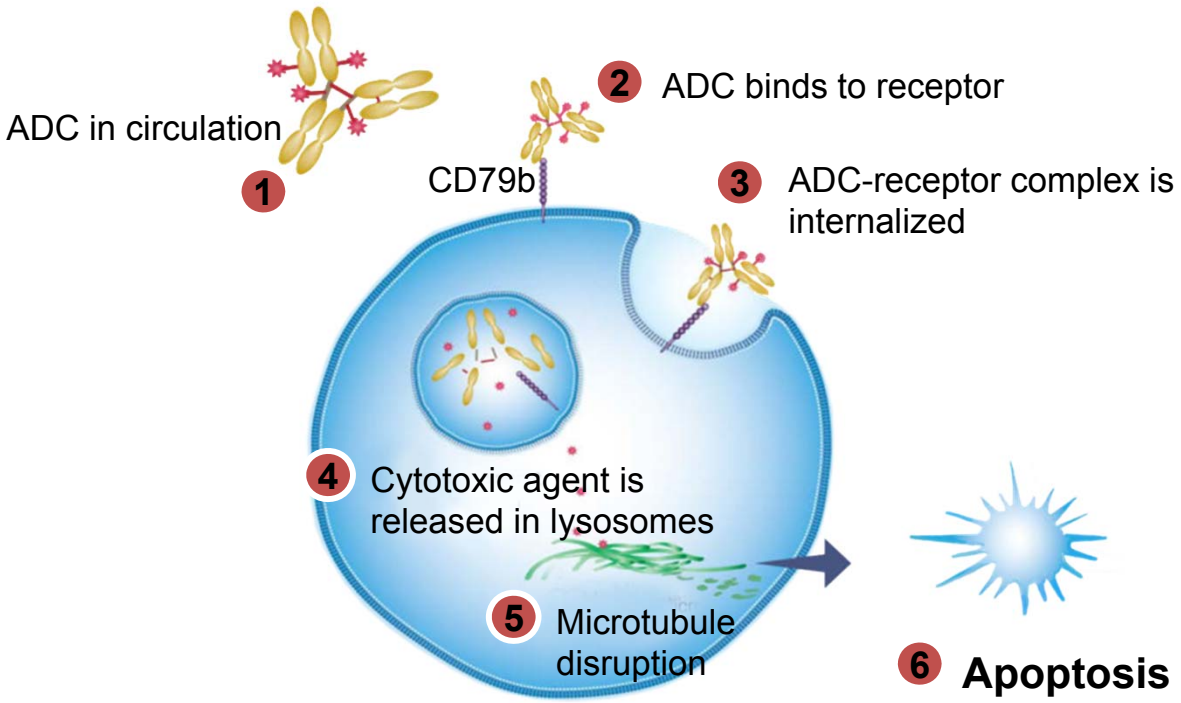


Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5
ABC (non-L265 MYD88)	GCB+ABC	GCB	GCB	ABC
NFKB, BCL6, NOTCH2	TP53	BCL2, EZH2, PI3K	Immune evasion signature	CD79B, MYD88 L265P
NOTCH inhibitors or PD1 pathway inhibitors	No rational therapies	BCL2,PI3k and EZH2 inhibitors	JAK/STAT and BRAF/MEK1 blockade	Inhibition of BCR/TLR signaling

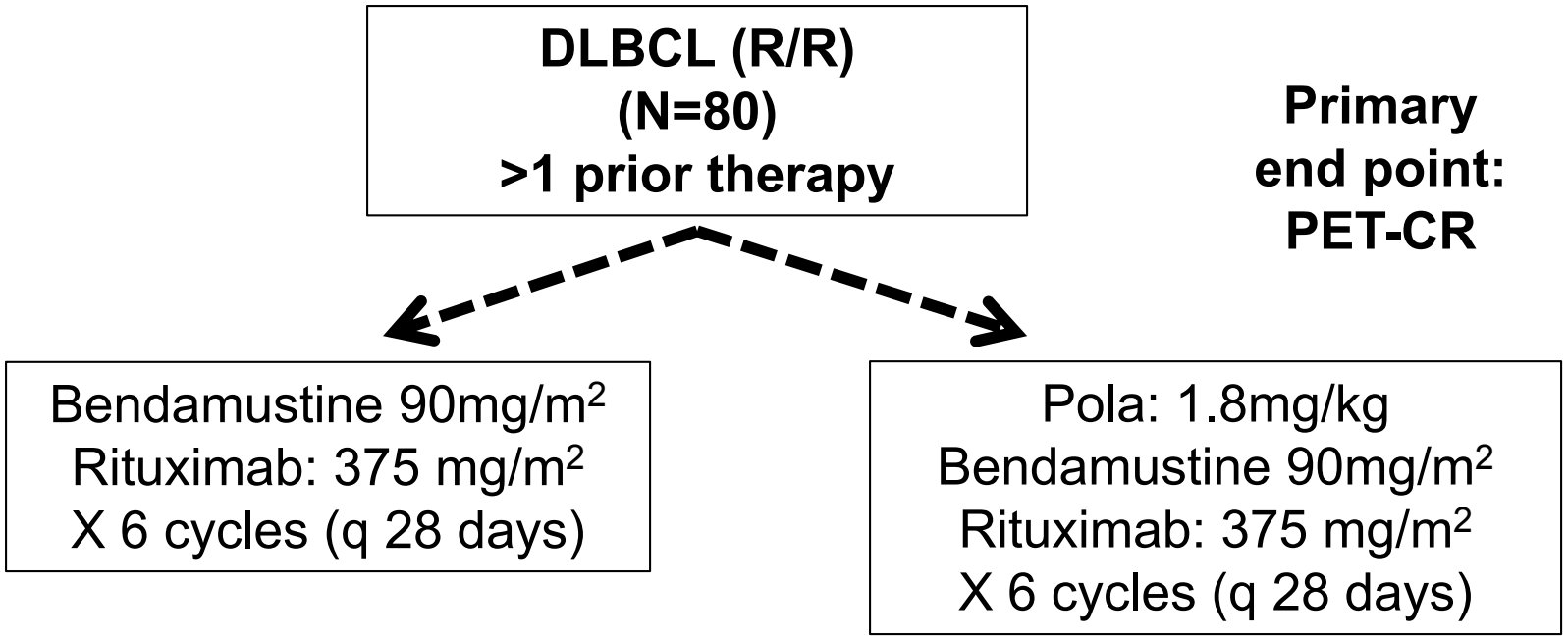
Chapuy/Shipp, Nature Medicine 2018

Polatuzumab vedotin: anti-CD79b drug conjugate

Polatuzumab vedotin
is composed of a cd79b-specific monoclonal antibody conjugated to a cytotoxin (MMAE) , via a stable linker



Randomized phase 2 trial of polatuzumab with bendamustine and rituximab in relapsed/refractory DLBCL



Efficacy: ITT

	BR (40 pts)	Pola+ BR (40 pts)	
PET-CR	15%	40%	
median PFS	2 months	6.7 months	P<0.0001
median OS	4.7 months	11.8 months	P=0.0008

Pola-BR is now an FDA approved combination therapy for relapsed DLBCL

POLARIX: Phase 3 study comparing R-CHOP to Pola- R-CHP
Anticipate completion of accrual by December 2019

CD47 blockade by 5F9 and rituximab in Non-Hodgkin's Lymphoma

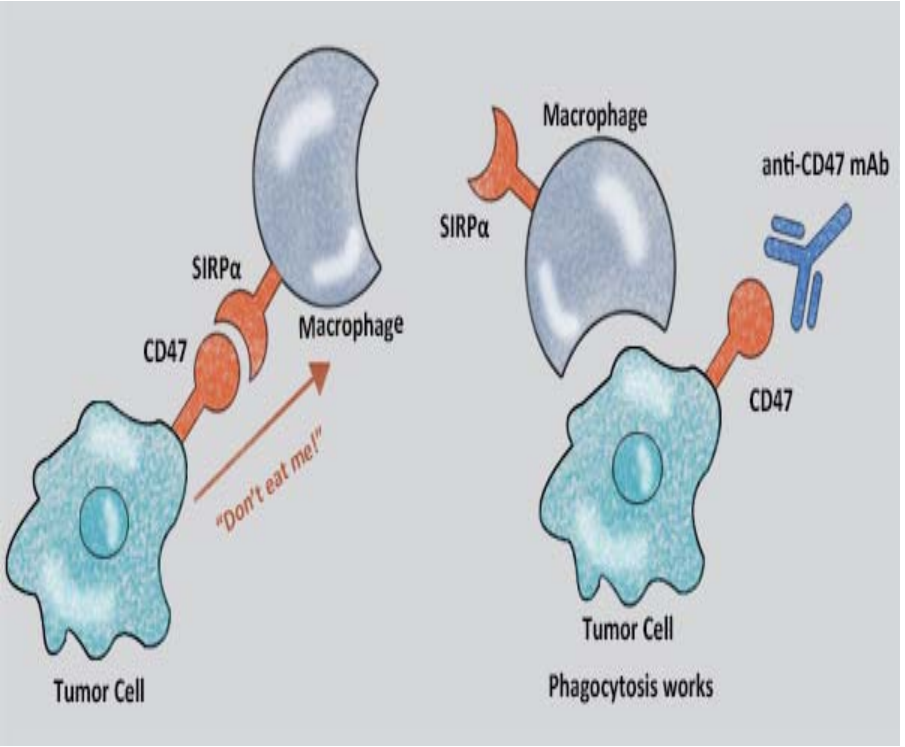
Phase Ib study in patients with DLBCL, FL

n=22 pts

Median number of prior therapies were 4, and pts were refractory to rituximab

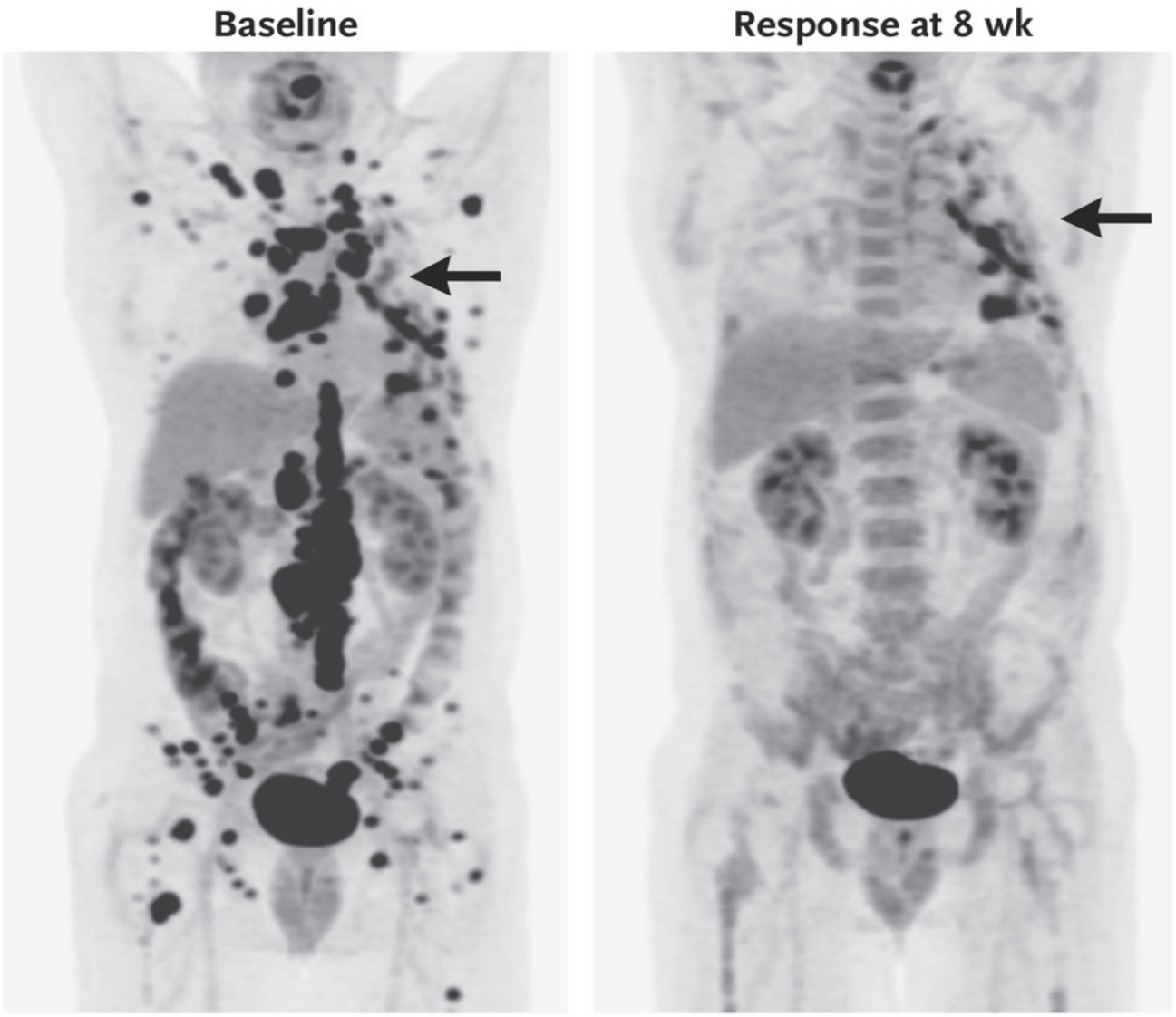
ORR: 50%, CR:36%

Anemia is an expected on target effect: CD47 blockade accelerates the elimination of aging red cells and is related to unmasking of the phagocytic signals on aging red cells.



Advani R et al. NEJM 2018;379

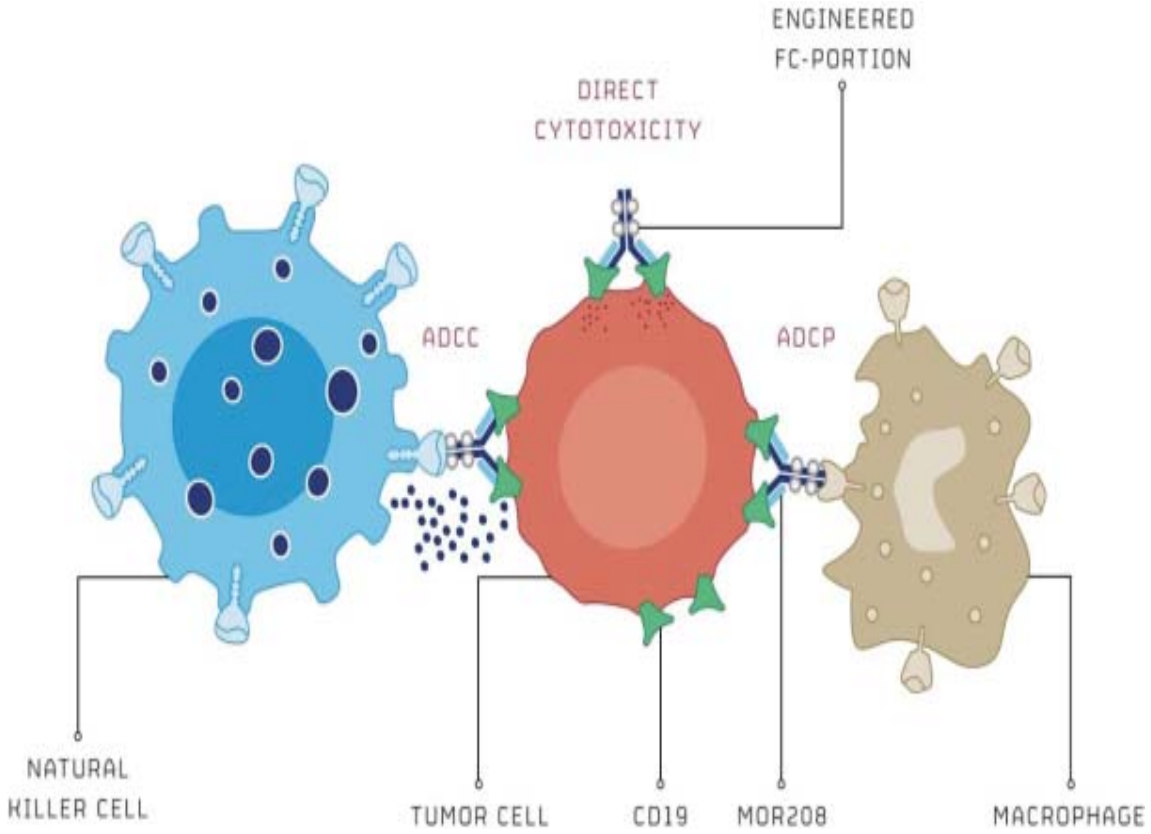
Complete Response in Male Patient with DLBCL



Advani R et al. NEJM 2018;379

L-MIND: Phase II study of Lenalidomide and MOR208 (tafasitamab) in Relapsed/refractory DLBCL

MOR208- Fc-enhanced, humanized, anti-CD19 monoclonal antibody



Maddocks K et al. JCO 2019;#7521

L-MIND: Phase II study of Lenalidomide and MOR208 (tafasitamab) in Relapsed/refractory DLBCL

Relapsed/Refractory DLBCL (> 1 line of therapy, ineligible for transplantation)

MOR208: weekly cycles 1-3 and q 2 weeks cycles 4-12 (until progression) + Lenalidomide 20 mg days 1-21 (12 cycles)

Primary End point: Overall response rate (n=81)

Treatment related SAE's: Infections (10%), neutropenic fever (5%)

Overall response rate: 58%, Complete response: 32%

Median PFS: 16.2 months, OS was not reached

MOR208+Lenalidomide has a breakthrough therapy designation

Maddocks K et al. JCO 2019;#7521

SUMMARY
Beyond Chemo-immunotherapy…….

- B-cell Lymphoma (Non-Hodgkin) is a heterogeneous malignancy with multiple targets
- The treatment approach to B- cell Lymphoma has changed over the past decade
- As more therapies become available, envision a WHO classification based on the target prominently expressed or anticipated response to therapy
- Future directions: discovering novel targeted agents, minimize side effects, curb duration of therapy by combining drugs

Thank you

QUESTIONS?