MANAGEMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

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Disclosures

- Consultant for AstraZeneca, BeiGene, Bristol-Myers Squibb, Celgene, Juno Therapeutics, Kite Pharma, and Pharmacyclics.

- On the Speakers Bureau for AstraZeneca, Janssen, and Pharmacyclics.

The off-label or investigational use of liso-cel, umbralisib, ublituximab, pirtobrutinib, zanubrutinib, and lisaftoclax will be discussed.

Objectives

- Epidemiology
- Diagnosis and workup
- Monoclonal B-lymphocytosis
- Prognostic markers
- Staging
- Treatment initiation guidelines
- Frontline therapeutic options updates
- Relapsed/refractory therapeutic options updates

Epidemiology

- Chronic lymphocytic leukemia (CLL) is a low grade leukemic lymphocytic lymphoma; small lymphocytic lymphoma (SLL) is a nodal form of the same disease
- CLL/SLL is the most common hematological malignancy in the Western world; incidence is ~5/100,000 persons per year in the US
- Median age at diagnosis ~72 years
- Male predominance
- Higher in Caucasians
- ~10% patients with a family history of some lymphoma
- Exact etiology is unknown

Muller-Hermlink HK, et al. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. World Health Organization Classification of Tumours: Pathology and Genetics of Tumours in Haematopoietic and Lymphoid Tissues. Lyon, France. IARC press, 2001: 195-6.

Diagnosis and workup

- Rule out masquerading other lymphoma
- History and physical examination; trend of CBCs; B symptoms (fever, night sweats, unexplained weight loss); severe fatigue
- Review CBC/differential, peripheral blood smear, flow cytometry/immunophenotyping: peripheral blood lymphocytosis with the presence of ≥5000 monoclonal B-cells/uL is required
  - CD5/19/23 positive by flow; CD20 dim
- Bone marrow biopsy and imaging typically not needed for diagnosis

Monoclonal B-lymphocytosis (MBL)

- Presence of monoclonal lymphocytosis but with <5000 B-cells/uL in the peripheral blood and no accompanying lymphadenopathy or organomegaly by physical examination or radiographical imaging, cytopenias or disease-related symptoms is defined as MBL

- Incidence in the US is 3%

- Progression to CLL/SLL can occur @ 1-2% per year

Prognostic markers

- Cytogenetics:
  - Del13q
  - Trisomy 12
  - Normal
  - Del11q
  - Del17p
  - Del6q
  - TP53 mutations
  - Notch1 mutations
  - SF3B1 mutations
  - Karyotype
- IGHV mutation status
- ZAP70
- CD38
- Lymphocyte doubling time (LDT)
- β2 microglobulin
- Stage of disease by Rai or Binet staging

Staging

Rai stage	Risk category	Clinical features
0	Low	Lymphocytosis alone
1	Intermediate	Lymphadenopathy
2	Intermediate	Hepato/splenomegaly
3	High	Anemia (<11g/dl)
4	High	Thrombocytopenia (<100,000/L)

Binet stage	Clinical features
A	HGB≥10 g/dl, platelets ≥100/L, <3 areas of lymphadenopathy/ organomegaly*
B	HGB≥10 g/dl, platelets ≥100/L, ≥3 areas of lymphadenopathy/ organomegaly*
C	Anemia (<10g/dl), thrombocytopenia (<100,000/L), or both

*nodal areas: cervical [head and neck], axillary, inguinal (including femoral lymph nodes), spleen, liver

Who needs treatment?

International workshop on CLL (iwCLL) guidelines for treatment initiation

- progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia
- massive (≥6cm below left subcostal margin), progressive, or symptomatic splenomegaly
- massive (≥10cm in longest diameter), progressive, or symptomatic lymphadenopathy
- progressive lymphocytosis with an increase of >50% over a 2 month period or LDT of <6 months
- autoimmune hemolytic anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy
- constitutional symptoms defined as ≥1 of the following:
  - (i) unintentional weight loss of ≥10% within the previous 6months
  - (ii) significant fatigue (ECOG PS ≥2;inability to work or perform usual activities)
  - (iii) fevers >100.5F or 38C for ≥2 weeks without other evidence of infection
  - (iv) night sweats for >1 month without evidence of infection

Hallek M, et al. Blood 2018. 131: 2745-2760

High risk, previously untreated CLL

- CLL12 trial
  - Ph3
  - Early stage (Binet A)
  - Double blind
  - Ibru vs. placebo

- EVOLVE CLL/SLL study
  - Ph3
  - Within 1 year of diagnosis
  - Early vs. delayed ven/obin

Table 1 The CLL-International Prognostic Index[30]

Prognostic factor	Points
Del17p on FISH or *TP53* mutation	4
Unmutated *IGHV* genes	2
Serum β2 microglobulin >3.5 mg/L	2
Rai stage I–IV	1
Age >65 years	1

Cumulative CLL-IPI score	Risk category	5-year TFS[a]
0–1	Low risk	78%
2–3	Intermediate risk	54%
4–6	High risk	32%
7–10	Very high risk	0%

FISH fluorescence in situ hybridization, *IGHV* immunoglobulin heavy chain gene, *TFS* treatment-free survival
[a]For the Mayo validation cohort

How to pick the right treatment?

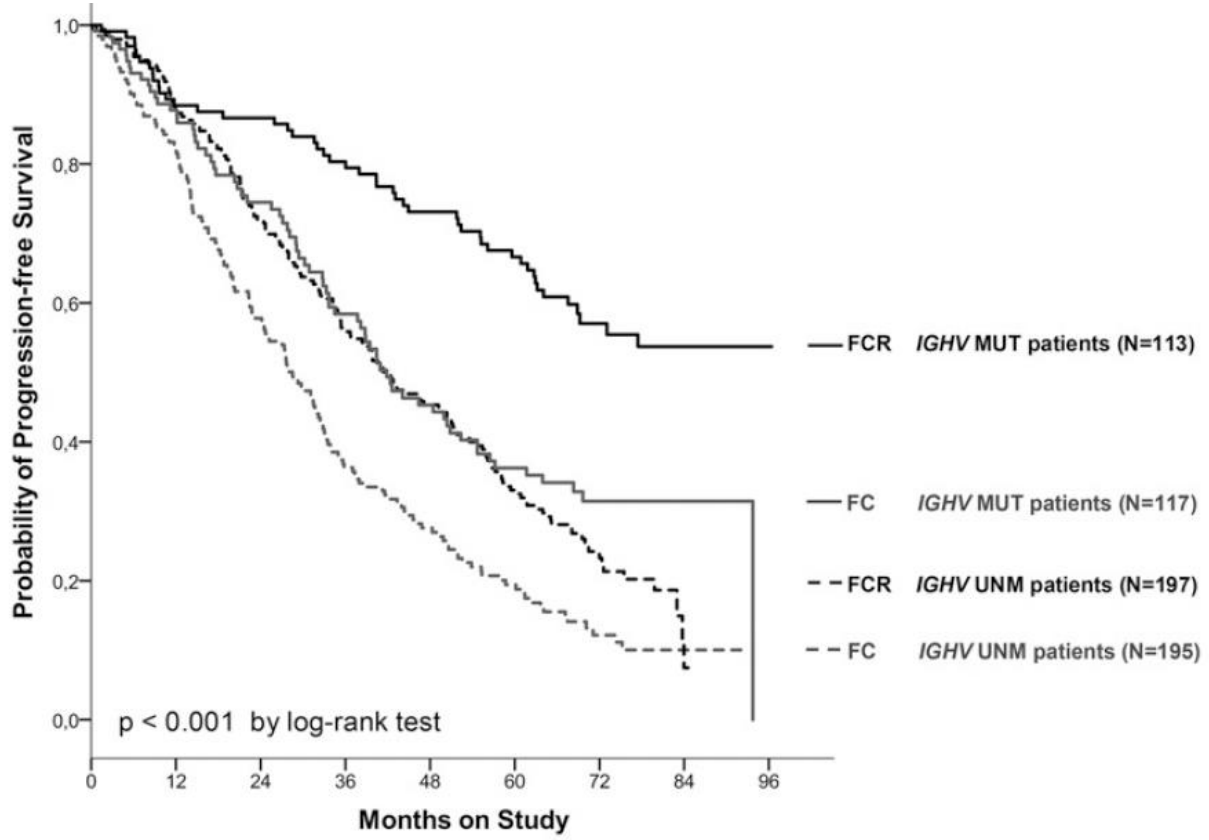
- Cytogenetic risk:
  - presence of del17p/TP53 mutation?
  - presence of unmutated IGHV?
- Stage of disease; lymphocyte doubling time and symptoms
  - Need for rapid debulking?
- Fitness of patient
  - Type of therapy
- Response to prior therapy

Frontline therapy

- Chemo-based treatment or not?
- Choice of novel targeted therapies?
- Single agent novel targeted therapy or combination?
- Fixed duration vs. MRD-based duration vs. indefinite treatment?

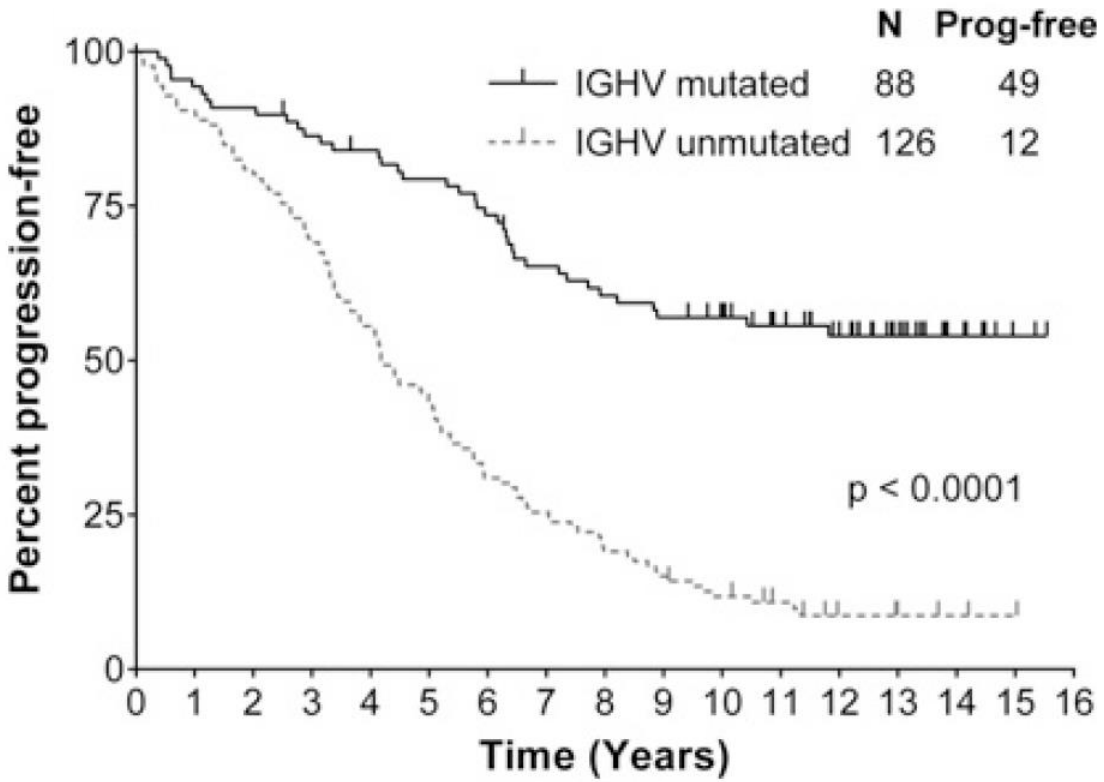
German CLL study group CLL8 study: FCR vs. FC

- Subgroup with exceptionally good outcome has right age/fitness, mutated IGHV genes and no del17p/del11q
- plateau after 4 yrs; MRD neg ≥10 yrs later – cure?



Eichhorst BF, et al. Hematol J 2006; 107: 885-91
Hallek M, et al. Lancet 2010; 376: 1164-74
Eichhorst B, et al. Blood 2014; 124: abs.19

MDACC FCR experience



Thompson et al., *Blood*, 2016

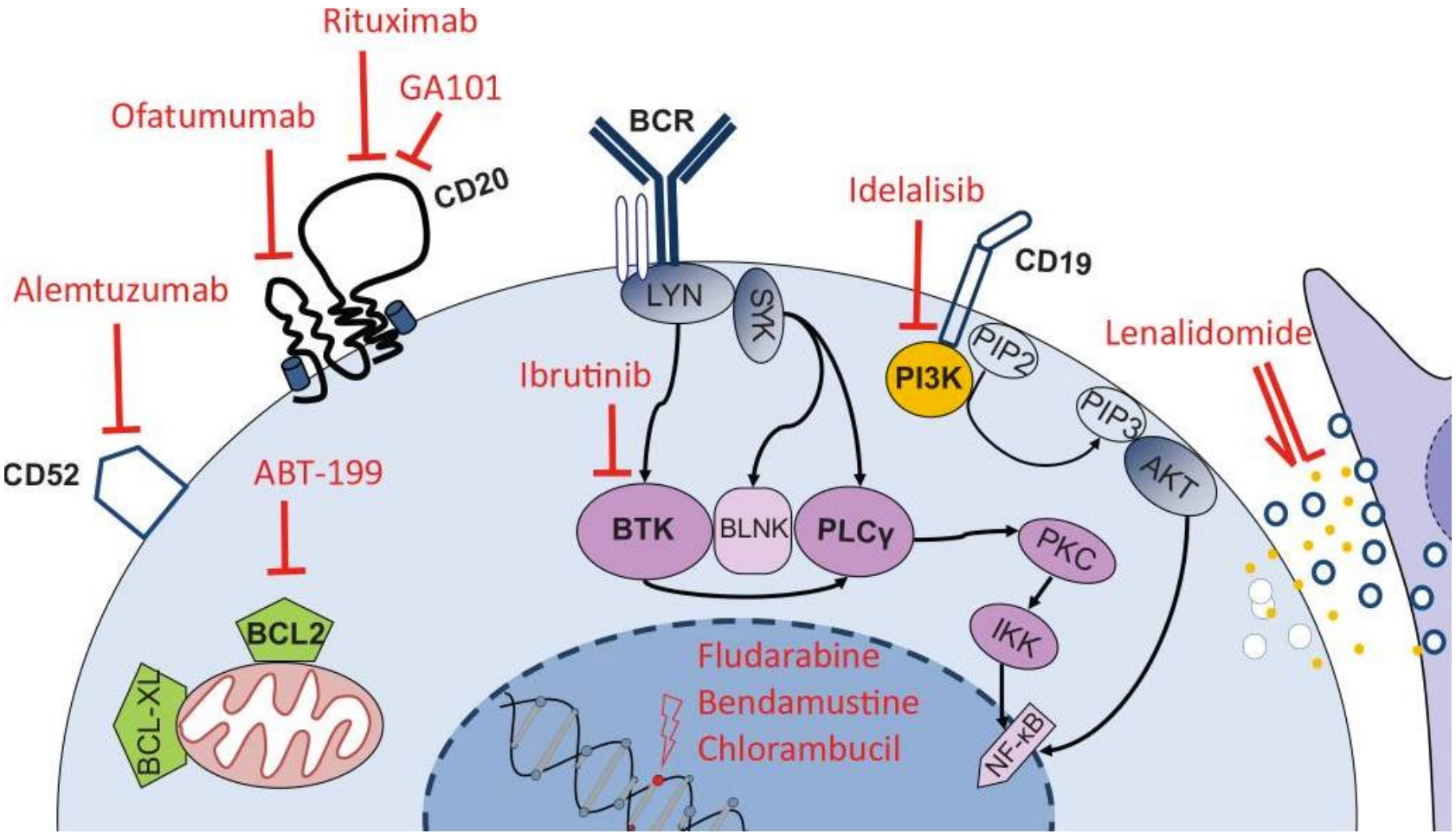
GCLLSG CLL10 trial: FCR vs. BR

- Phase 3 randomized trial, fit CLL patients (ages 33-81 yrs) with advanced stage disease, previously untreated, no 17p deletion
- N = 564; 6 cycles of either regimen; median followup 37.1 months

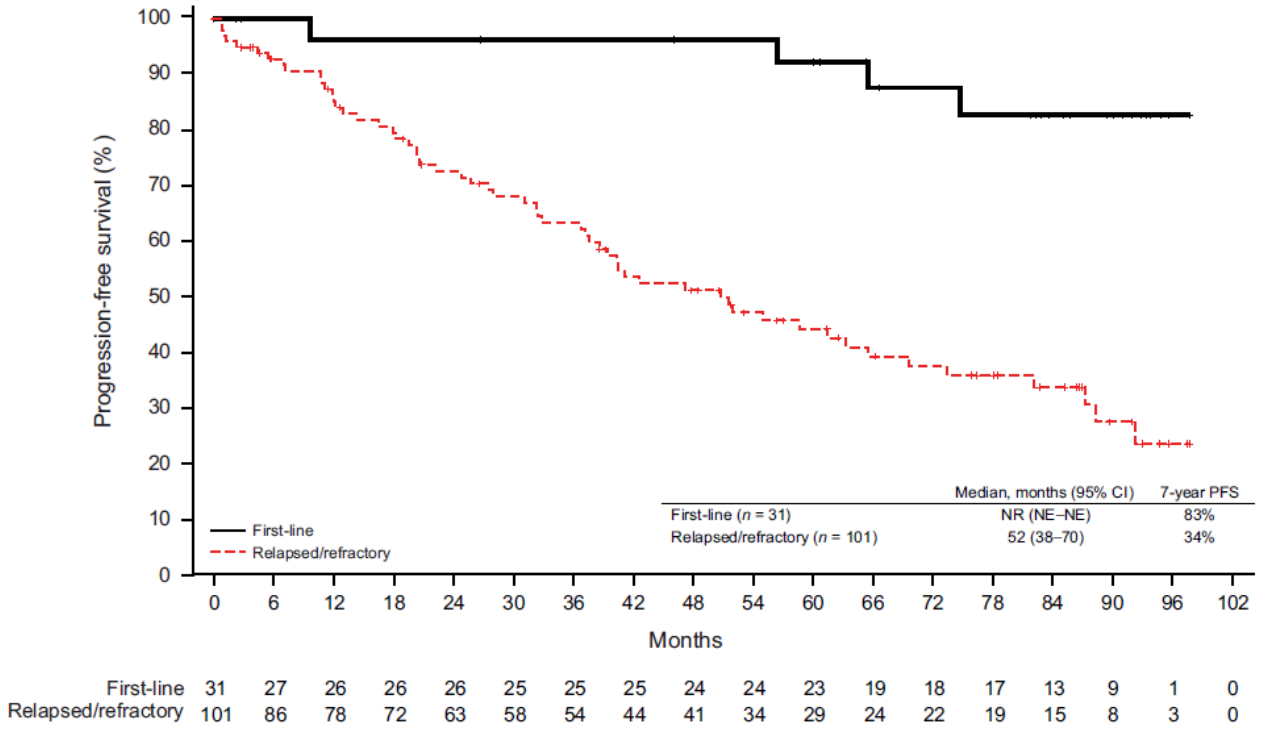
	FCR	BR	P-value
ORR	95%	96%	1.0
CR	40%	31%	0.034 [higher MRD negative CRs in FCR arm]
Median PFS	55.2 months	41.7 months	0.001 [better in <65 years old]
OS at 3 years	91%	92%	0.897
Severe neutropenia	84%	59%	<0.001
Severe infections	39%	25%	0.001 [especially in older pts]

Eichhorst B, et al. Lancet Oncol 2016; 17: 928-42

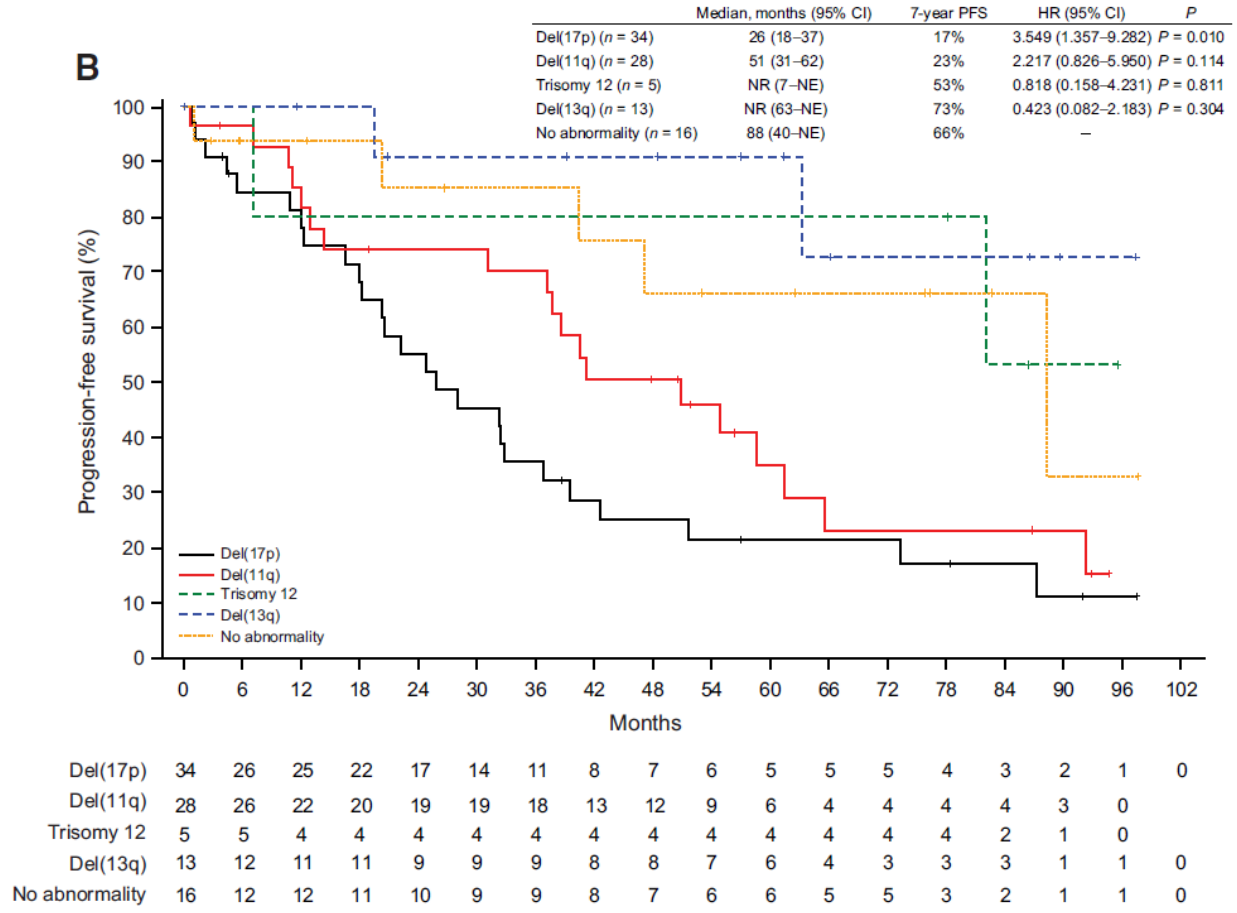
Targeted therapy



Ibrutinib 8-year followup: Pivotal Ph1b/2 PCYC 1102 trial

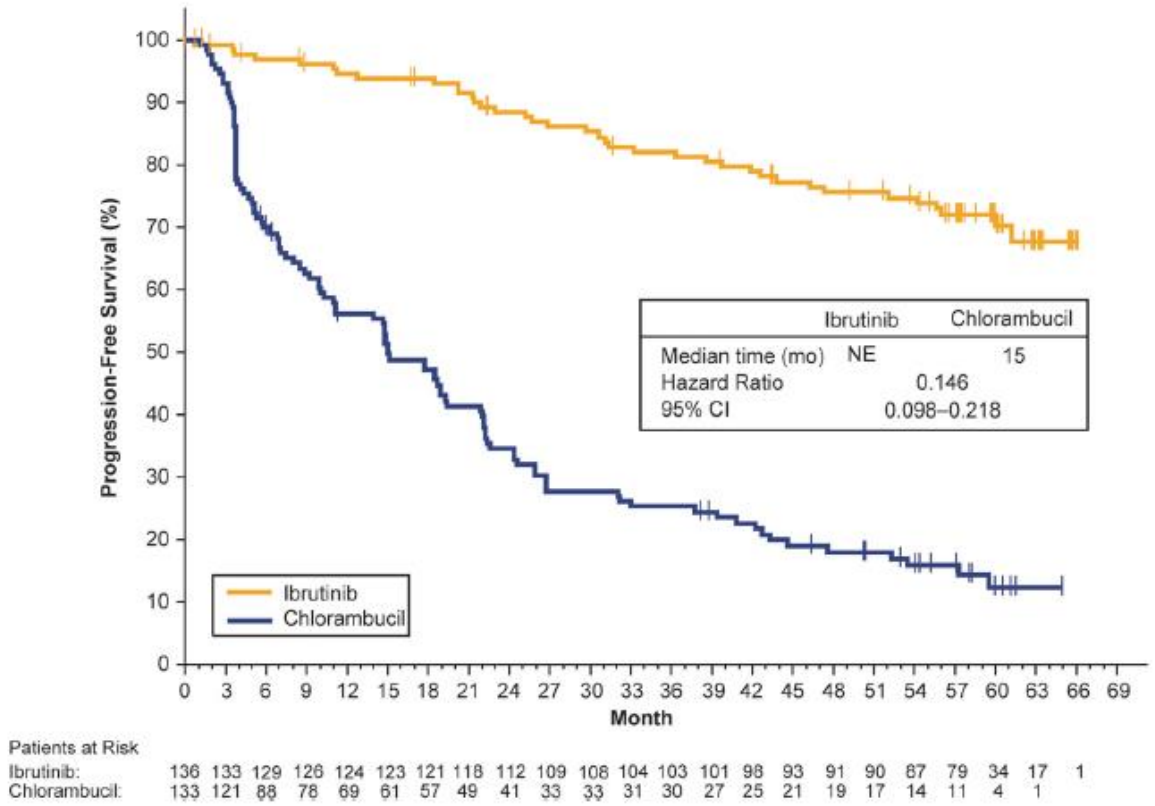


N= 132; frontline n =31, age >/= 65 yrs; rel/ref n = 101



Byrd J, et al. Clin Cancer Res 2020; 26: 3918-27

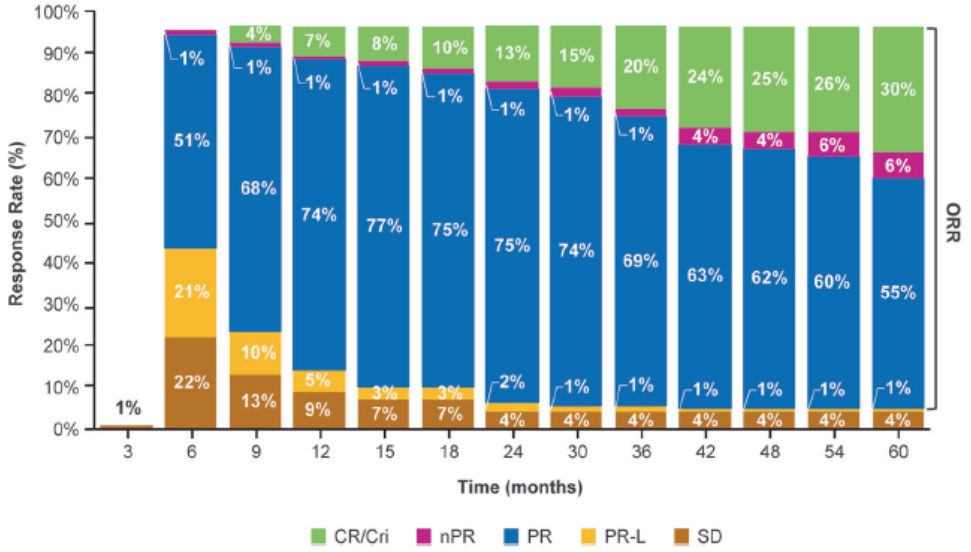
Ibrutinib 5 yr update: RESONATE 2 Ph3 trial



N= 269, age 65 yrs or older

	With del(11q)		Without del(11q)	
	Ibr	Chl	Ibr	Chl
60 mo PFS	79%	0	67%	18%
Median PFS, mo	NE	9	NE	18
HR (95% CI)	0.034 (0.010, 0.108)		0.205 (0.132, 0.318)	

	Unmutated IGHV		Mutated IGHV	
	Ibr	Chl	Ibr	Chl
60 mo PFS	67%	6%	81%	24%
Median PFS, mo	NE	9	NE	17
HR (95% CI)	0.105 (0.058, 0.190)		0.153 (0.067, 0.349)	



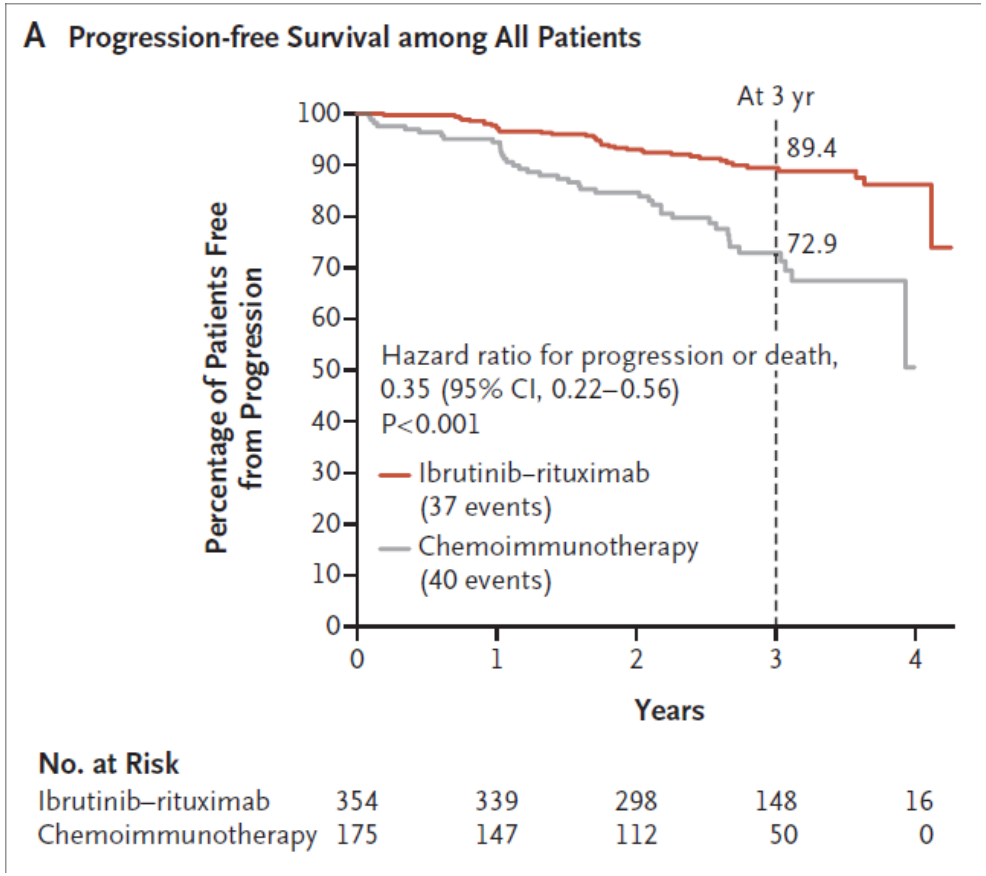
Burger JA, et al. Leukemia 2020; 34: 787-98

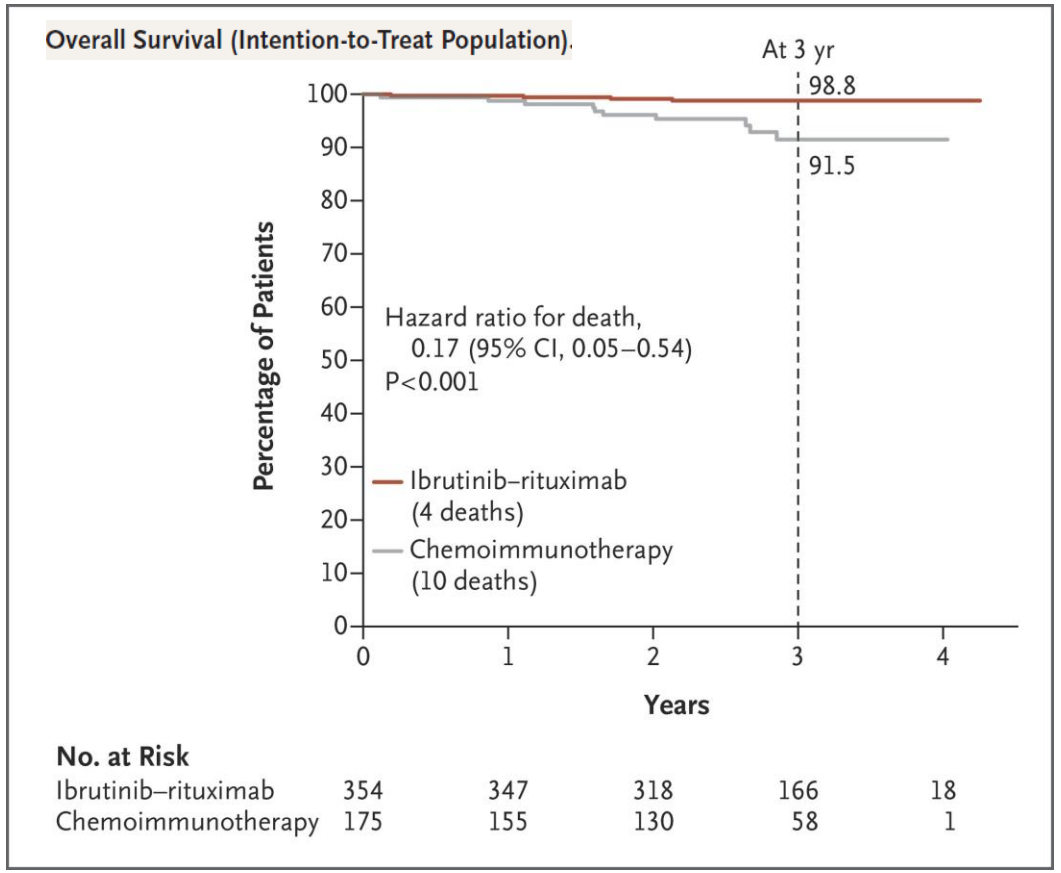
Other FDA approved targeted therapies

- Acalabrutinib – covalent BTKi
- Venetoclax – BCL2i
- Idelalisib – PI3Kδi (further trials halted due to toxicities)
- Duvelisib - PI3Kδ and γ inhibitor
- Rituximab, ofatumumab, obinutuzumab – CD20 MAbs

E1912 trial: ibru-R vs. FCR

- Ph3 trial with 2:1 randomization
- Age 70 yrs or less; no del17p/TP53 mutation patients
- N= 529



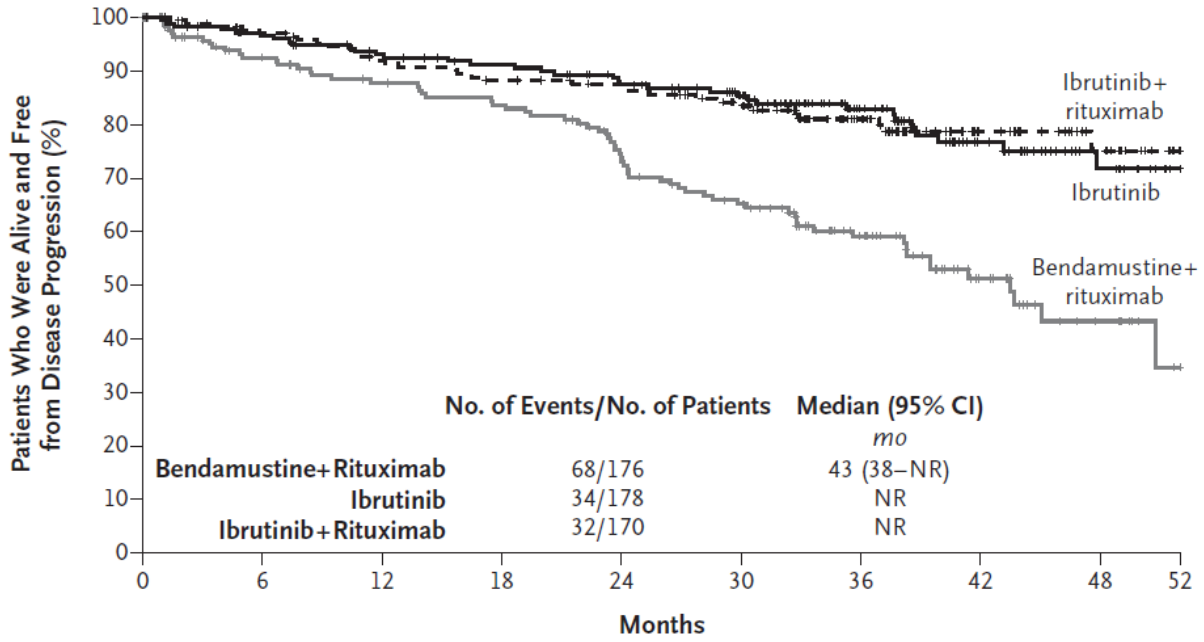


Shanafelt TD et al. N Engl J Med 2019;381:432-443

Alliance A041202 trial: ibru vs. ibru-R vs. BR

- Ph3 trial with 1:1:1 randomization
- Age 65 yrs and above
- N = 547

A Primary Analysis



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

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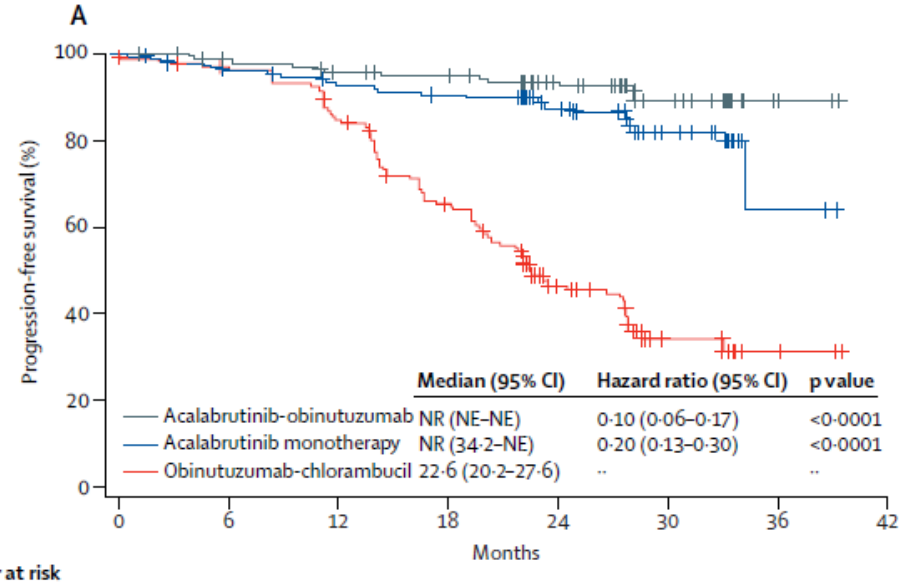
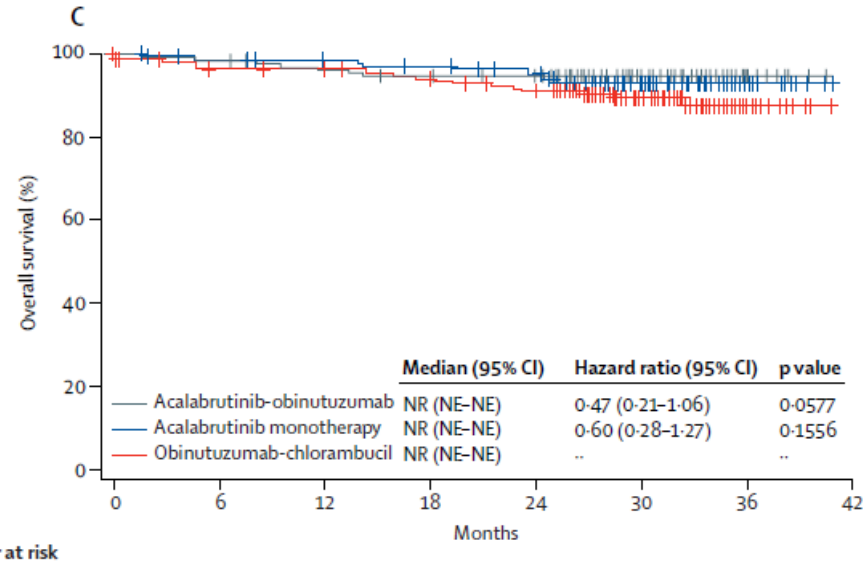
Woyach JA, et al. N Engl J Med 2018; 379: 2517-28

ELEVATE TN trial: acala vs. acala-G vs. clb-G

- Ph3 trial with 1:1:1 randomization
- Age 65 yrs and above (or younger with comorbidities)
- N = 535



Number at risk (number censored)														
Acalabrutinib-obinutuzumab	179 (0)	176 (3)	170 (7)	168 (7)	163 (9)	160 (11)	159 (11)	155 (13)	109 (58)	104 (63)	46 (119)	41 (124)	4 (161)	2 (163)
Acalabrutinib monotherapy	179 (0)	166 (9)	161 (11)	157 (13)	153 (14)	150 (14)	148 (15)	147 (15)	103 (56)	94 (64)	43 (112)	40 (115)	4 (149)	3 (150)
Obinutuzumab-chlorambucil	177 (0)	162 (12)	157 (15)	151 (15)	136 (16)	113 (19)	102 (20)	86 (21)	46 (49)	41 (52)	13 (72)	13 (72)	3 (81)	2 (82)



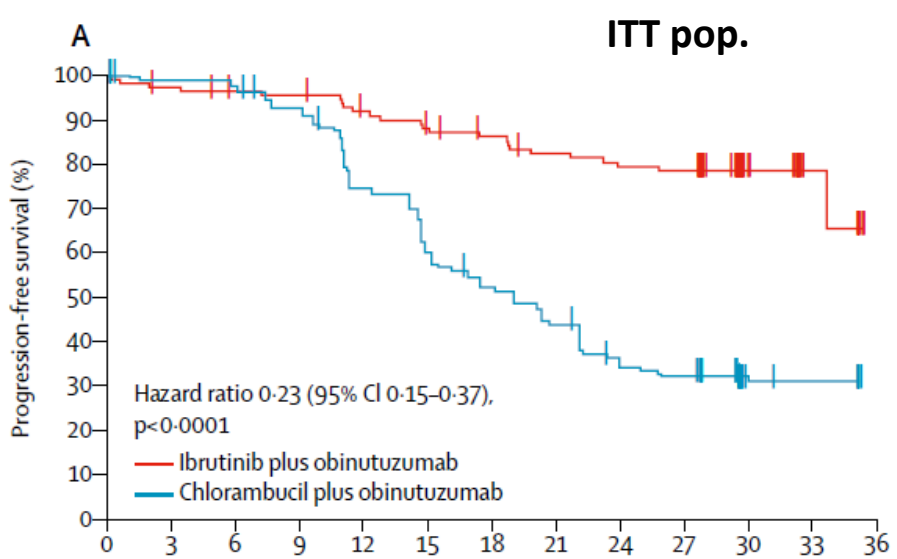
Number at risk (number censored)														
Acalabrutinib-obinutuzumab	179 (0)	178 (0)	176 (0)	173 (2)	170 (2)	168 (2)	167 (3)	165 (5)	164 (6)	122 (48)	75 (95)	47 (123)	15 (155)	3 (167)
Acalabrutinib monotherapy	179 (0)	175 (3)	173 (4)	171 (6)	169 (7)	167 (7)	166 (8)	163 (10)	159 (11)	119 (49)	77 (91)	49 (119)	19 (149)	5 (163)
Obinutuzumab-chlorambucil	177 (0)	168 (6)	165 (7)	163 (8)	163 (8)	160 (10)	158 (10)	154 (12)	150 (13)	111 (51)	70 (91)	44 (116)	17 (143)	4 (156)

City of Hope.

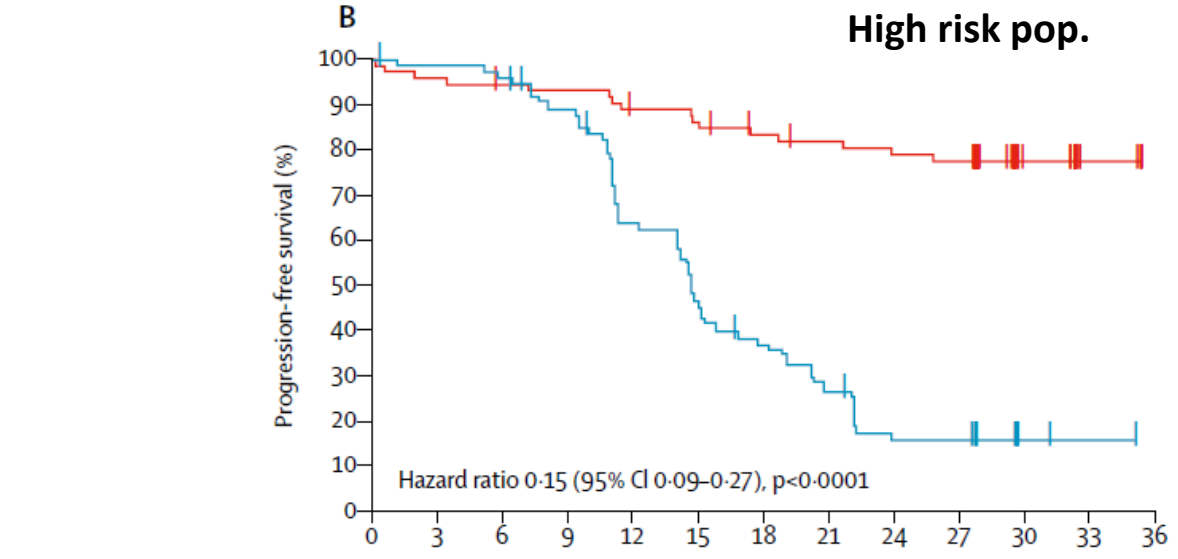
Sharman J, et al. Lancet 2020; 395: 1278-91

iLLUMUNATE: ibru-G vs. clb-G

- Ph3 trial with 1:1 randomization
- Age 65 yrs and above OR younger with comorbidities
- N = 229



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)

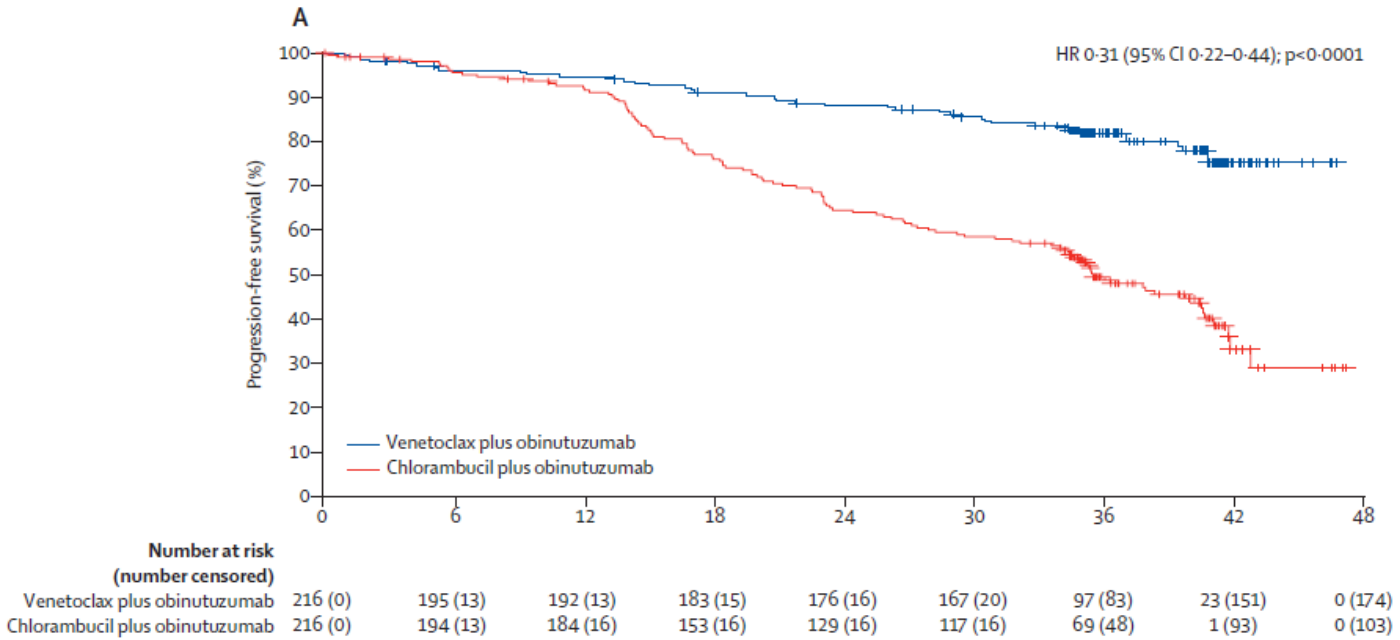


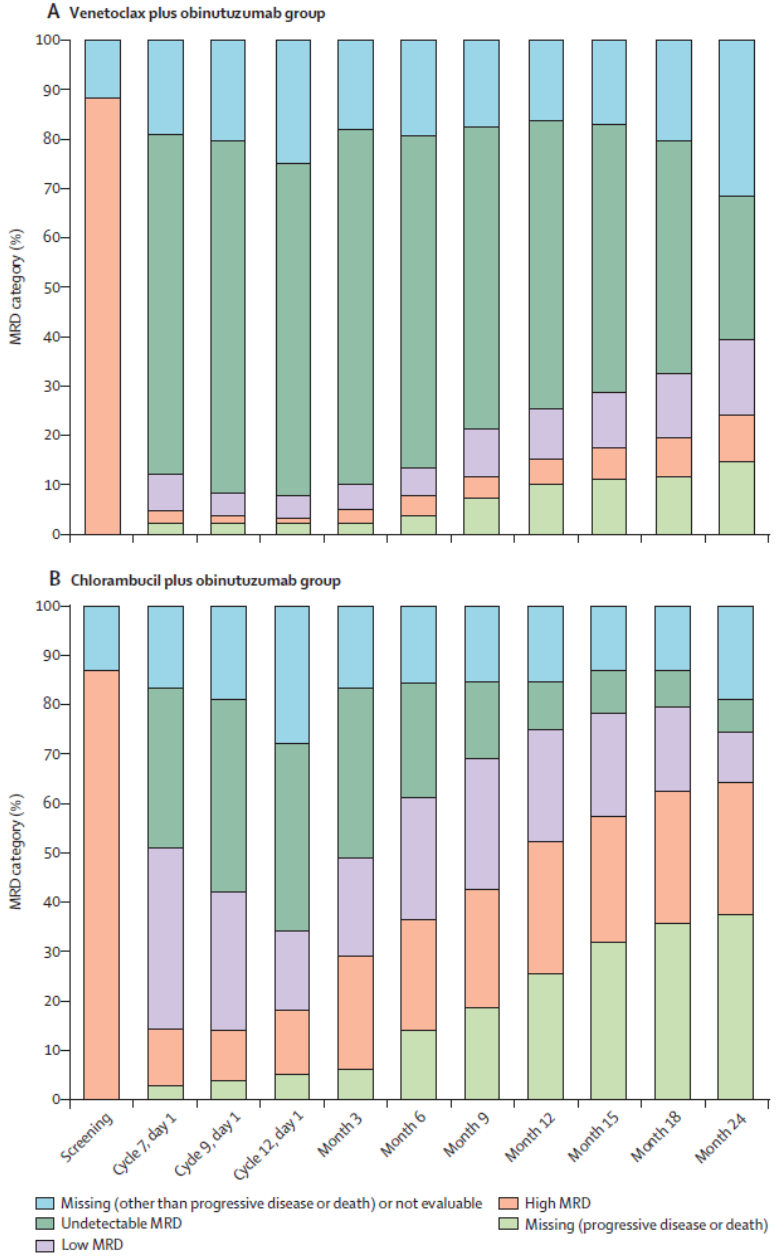
Number at risk (number censored)													
Ibrutinib plus obinutuzumab	73	70	68	67	63	61	57	55	53	52	17	3	0
	(0)	(0)	(1)	(1)	(2)	(2)	(4)	(5)	(5)	(5)	(40)	(54)	(57)
Chlorambucil plus obinutuzumab	75	73	71	64	45	33	25	18	10	10	2	1	0
	(0)	(1)	(1)	(3)	(4)	(4)	(5)	(5)	(6)	(6)	(14)	(15)	(16)

Moreno C, et al. Lancet Oncol 2019; 21: 1188-1200

CLL14 trial: ven-G vs. clb-G

- Ph3 with 1:1 randomization
- Age 18 yrs and above AND with comorbidities
- N = 432



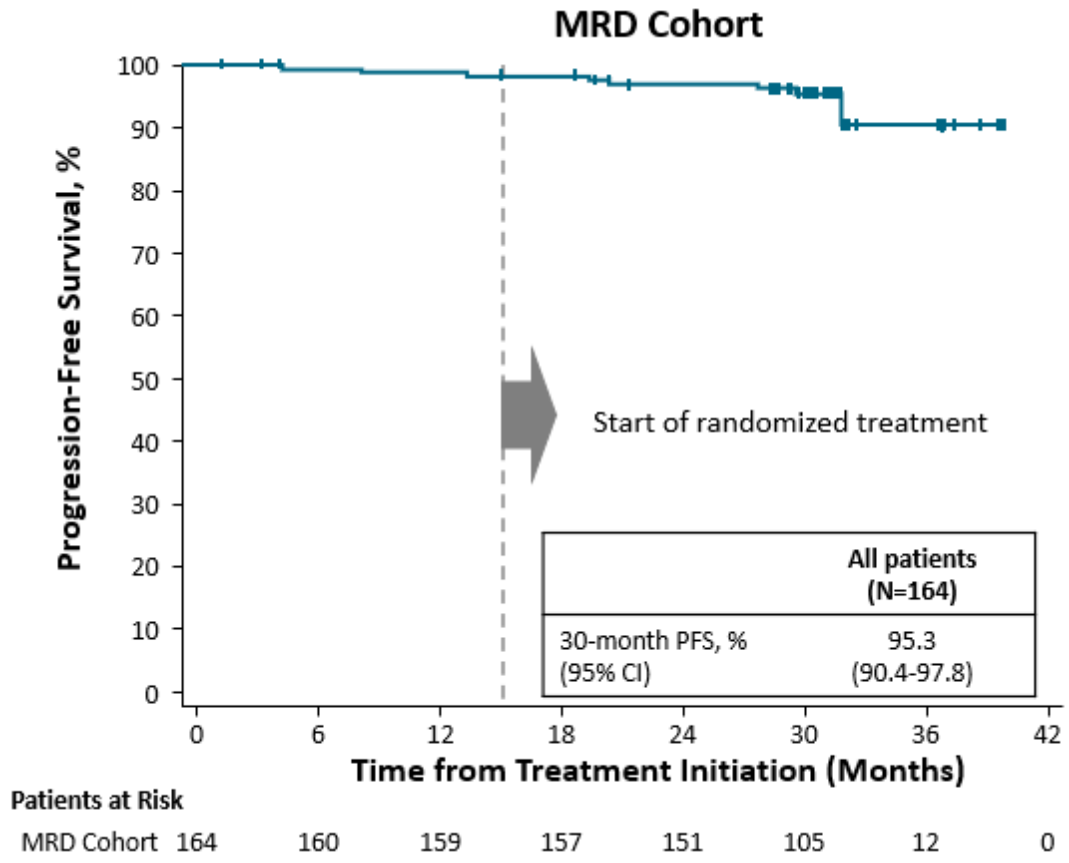


Al-Sawaf O, et al. Lancet Oncol 2020; 21: 1188-1200

Combinations of targeted therapies - frontline

- CAPTIVATE ibru+ven trial – MRD and fixed duration cohorts
- MDACC ibru + ven trial – frontline and rel/ref patients
- IVO trial - OSU
- AVO trial – DFCI
- AVO trial - OSU
- BOVen trial
- GLOW Ph3 ibru + ven vs. clb + obin trial (older pts)
- ECOG Ph3 iO vs. iVO trial (younger pts) – accrual completed
- Alliance Ph3 iO vs. iVO trial (older pts) - ongoing

Ibrutinib+venetoclax: CAPTIVATE Ph2 trial – MRD cohort



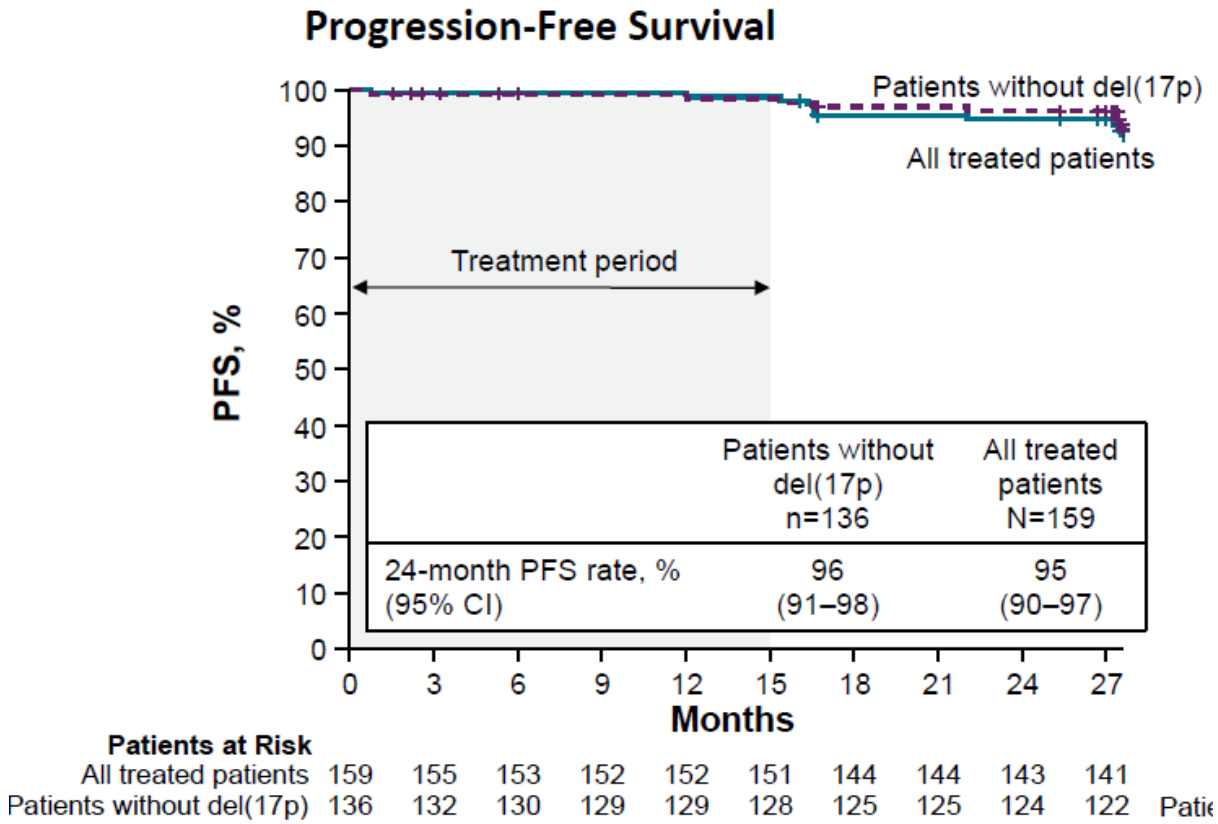
- Median follow-up on study: 31.3 months
  - Median follow-up post-randomization: 16.6 months
- 30-month PFS rates were > 95% across all randomized arms

	Confirmed uMRD		uMRD Not Confirmed	
	Placebo (n = 43)	Ibrutinib (n = 43)	Ibrutinib (n = 31)	Ibrutinib + Venetoclax (n = 32)
30-month PFS (95% CI)	95.3 (82.7, 98.8)	100.0 (100, 100)	95.2 (70.7, 99.3)	96.7 (78.6, 99.5)

Wierda W, et al. ASH annual meeting 2020

Ibru + ven: CAPTIVATE Ph2 trial – FD cohort

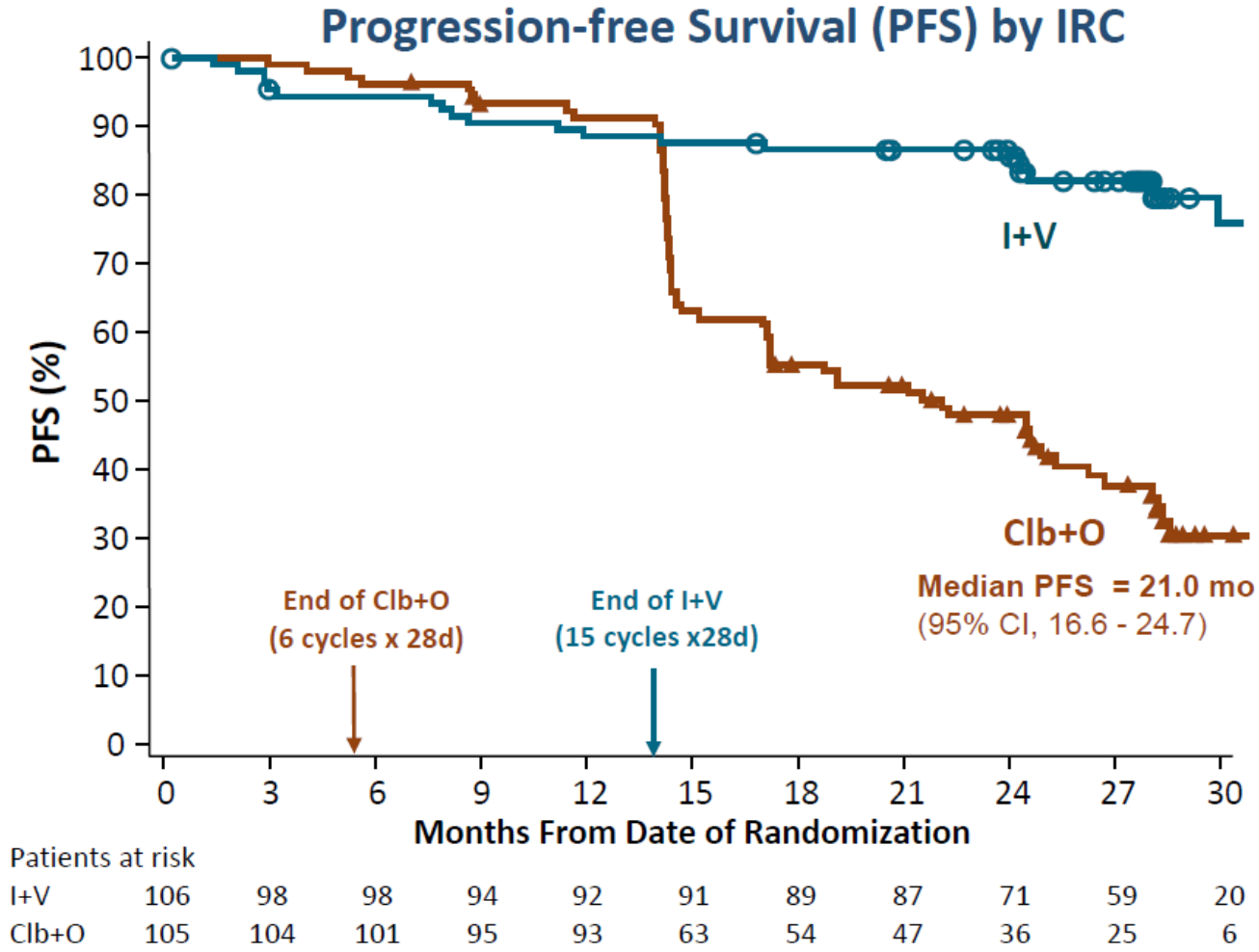
Median follow-up: 27.9 months (range, 0.8–33.2)



- 3 cycles of ibru lead in followed by ven ramp up and combination therapy for 12 cycles
- Primary endpoint met: CR/Cri rate of 56% with similarly high rates overall and in patients with high risk features of disease
- High rates of uMRD
- 2-yr PFS and OS rates >95%
- Estimated 2-yr PFS rates 93% in unmutated IGHV pts and 97% in mutated IGHV

Wierda W, et al. 19th iwCLL2021 (virtual) meeting

GLOW Ph3 trial: ibru+ven vs. clb-G



- With a median follow-up of 27.7 months, IRC-assessed PFS for VenI was superior to OClb
- VenI reduced the risk of progression or death by 78% vs OClb
- PFS by INV assessment was consistent with IRC
- Rates of uMRD were significantly higher for VenI, particularly BM uMRD, which was 3 times higher vs OClb

Kater AP, *et al.* EHA annual meeting 2021

Personal thought: Choice between BTKi and venG as frontline therapy

Favors BTKi:

- Longer follow-up data with ibrutinib
- Use of newer BTKi improves toxicity profile
- High ORR with ven after BTKi vs less data on the reverse
- Intense early monitoring needed with ven

Favors VenG:

- High CR and undetectable MRD
- Fewer long term side effects
- Time-limited therapy, ?avoid selection pressure for resistance
- Less cost?

Adverse event considerations

- BTKi:
  - Atrial fibrillation
  - Hemorrhage
  - Arthralgias
  - HTN
  - Rash
  - Infections
- Ven:
  - Tumor lysis syndrome
  - Infections

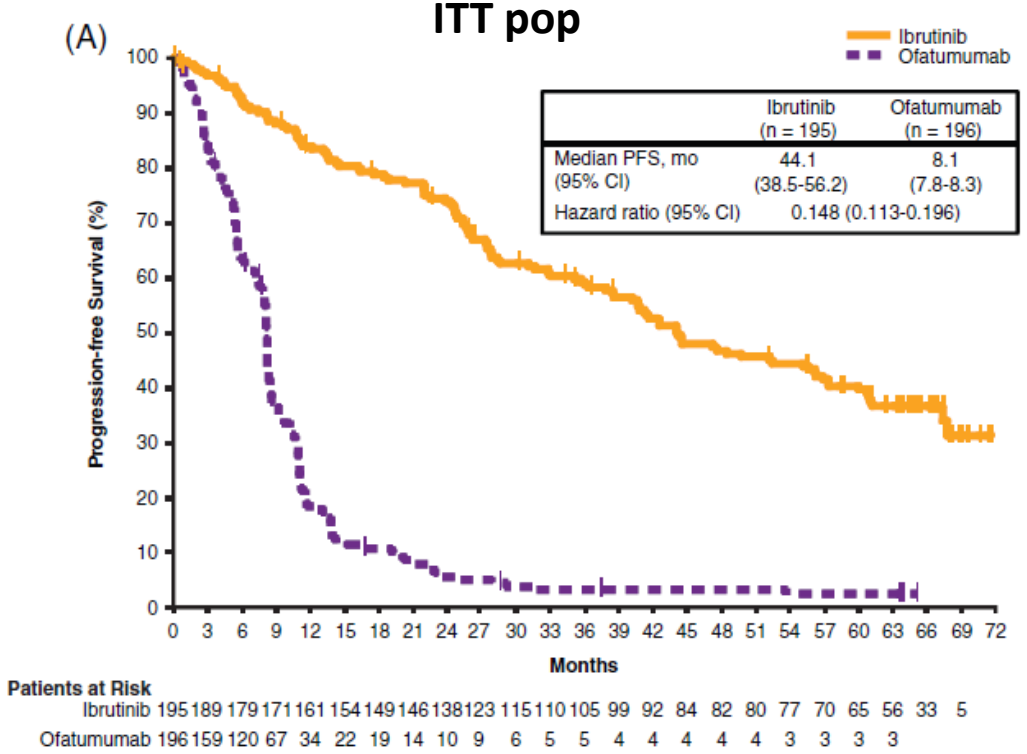
Relapsed/refractory therapy

- Chemo-based treatment or not?
- Choice of novel targeted therapies?
- Single agent novel targeted therapy or combination?
- Fixed duration vs. MRD-based duration vs. indefinite treatment?

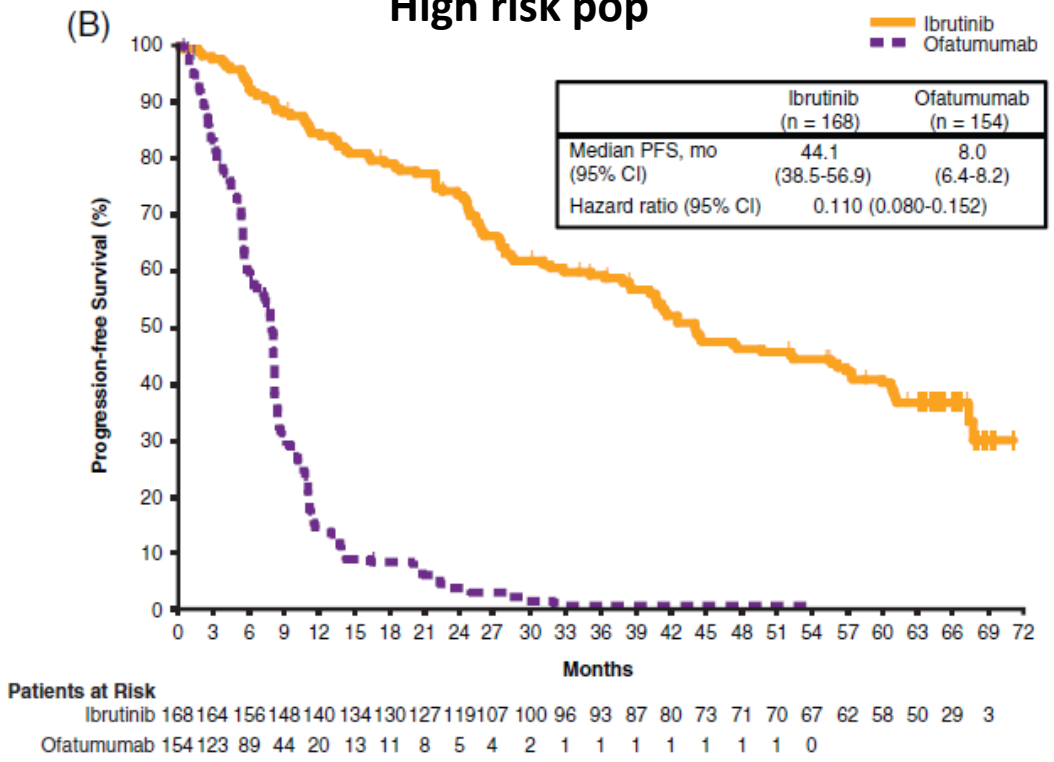
RESONATE Ph3 trial: ibru vs. ofa

- Ph3 trial with 1:1 randomization
- N = 391

ITT pop



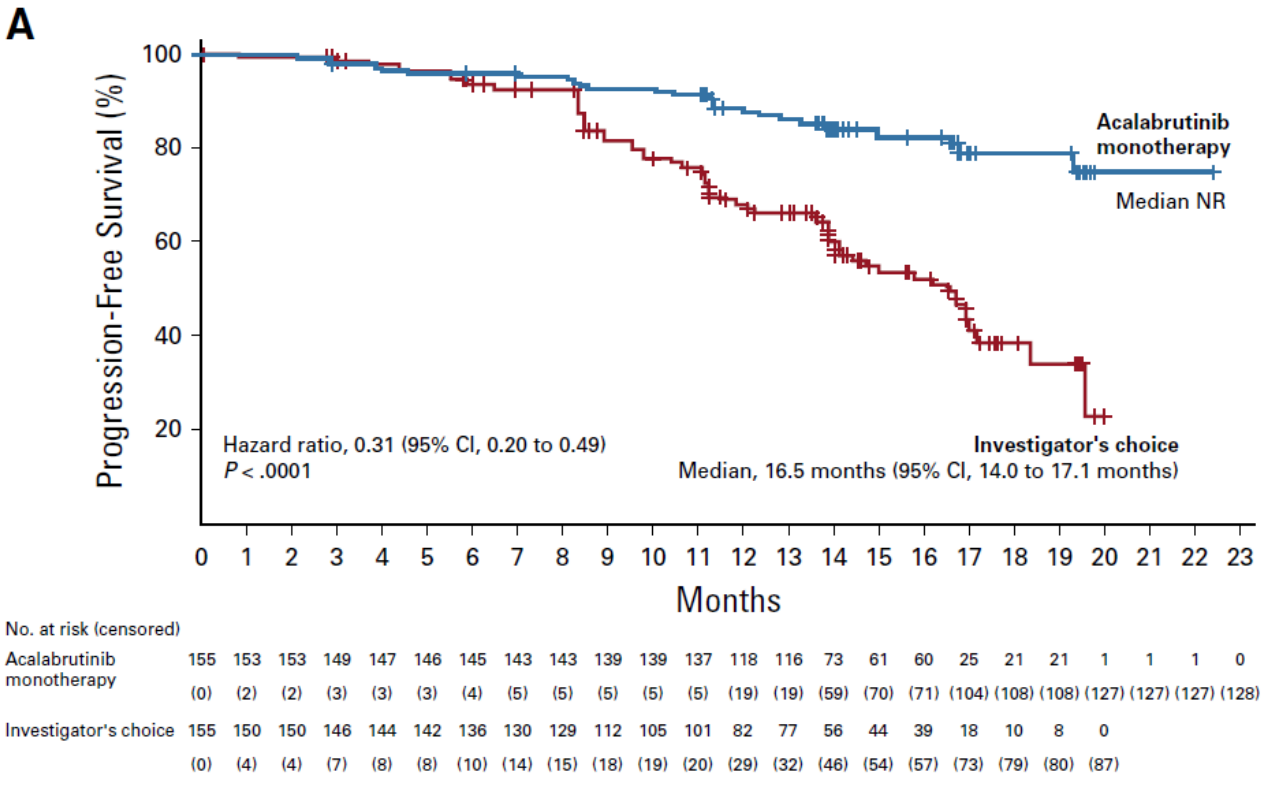
High risk pop

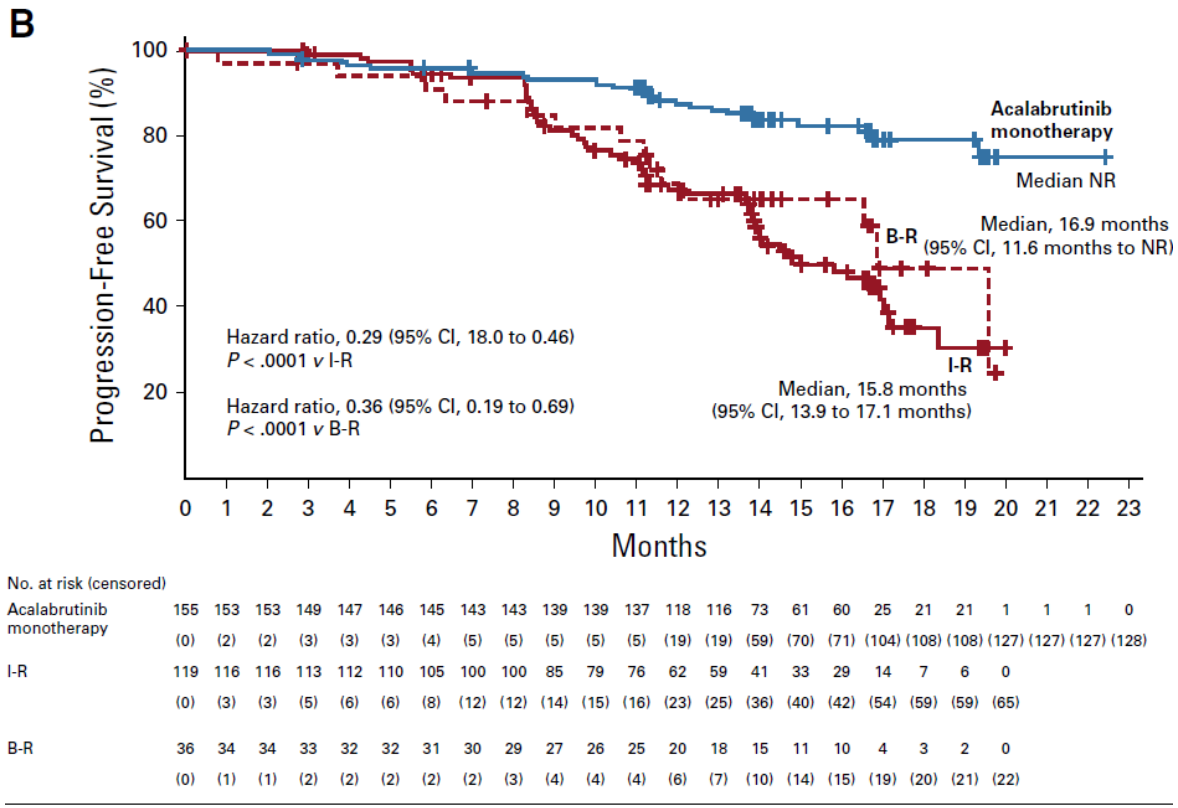


Munir T, et al. Am J Hematol 2019; 94: 1353-63

ASCEND Ph3 trial: acala vs. investigator's choice of idela-R or BR

- Ph3 trial randomized 1:1
- N = 310





Ghia P, et al. J Clin Oncol 2020; 38: 2849-61

ELEVATE-RR: acala vs. ibru

CL-006 (ELEVATE-RR)

A Phase 3 St

Key Inclusion Criteria
- At least 1 of the follo
  - Presence of 17
    laboratory

Stratification
- Presence or Abse
- ECOG 2 vs </=1
- Number of prior t
  (1-3 vs > 4)

Primary Endpoint

Secondary Endpoints

OS
Superiority[b]?

Events of Clinical Interest

Events, n (%)	Any grade		Grade ≥3	
	Acalabrutinib (n=266)	Ibrutinib (n=263)	Acalabrutinib (n=266)	Ibrutinib (n=263)
Cardiac events	64 (24.1)	79 (30.0)	23 (8.6)	25 (9.5)
Atrial fibrillation[a]*	25 (9.4)	**42 (16.0)**	13 (4.9)	10 (3.8)
Ventricular arrhythmias[b]	0	3 (1.1)	0	1 (0.4)
Bleeding events*	101 (38.0)	**135 (51.3)**	10 (3.8)	12 (4.6)
Major bleeding events[c]	12 (4.5)	14 (5.3)	10 (3.8)	12 (4.6)
Hypertension[d]*	25 (9.4)	**61 (23.2)**	11 (4.1)	**24 (9.1)**
Infections[e]	208 (78.2)	214 (81.4)	82 (30.8)	79 (30.0)
ILD/pneumonitis*	7 (2.6)	**17 (6.5)**	1 (0.4)	2 (0.8)
SPMs excluding NMSC	24 (9.0)	20 (7.6)	16 (6.0)	14 (5.3)

Higher incidence indicated in **bold yellow** for terms with statistical differences.
*Two-sided P-value for event comparisons <0.05 without multiplicity adjustment.

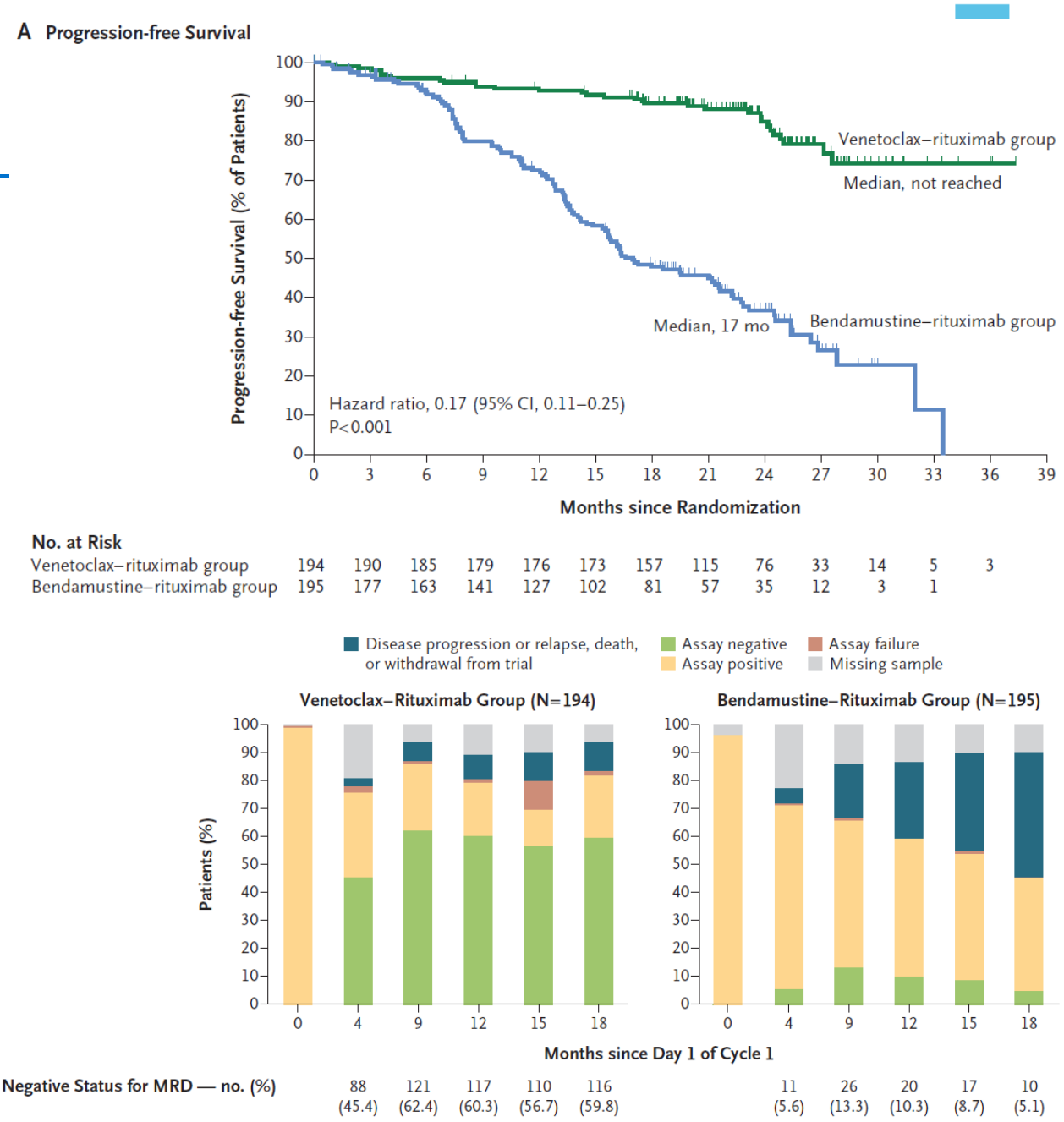
Median follow-up: 40.9 months (range, 0.0–59.1).
CI, confidence interval; IRC, independent review committee; PFS, progression-free survival.

City of Hope

Byrd J, et al. ASCO annual mtg 2021

MURANO Ph3 trial: ven-R vs. BR

- phase 3 trial with 1:1 randomization
- N = 389 individuals
- 5-yr update (ASH2020):
  - median PFS with ven-R was 53.6 months, compared with 17.0 months with BR;
  - OS rates for VR and BR were 82.1% and 62.2%, respectively;
  - 3-yr post–EOT survival estimates for patients with uMRD and MRD were 95% and 85%, respectively.
  - Of the participants with uMRD, 32 did not have PD at EOT and remained with uMRD at 5 years; a total of 4 pts had PD, and 47 experienced MRD conversion over a median of 19.4 months - PD developed in 19 patients over a median period of 25.2 months. Increased risk of MRD conversion and PD correlated with the baseline presence of del(17p), genomic complexity, and unmutated *IGVH*.



City of Hope.

Seymour J, et al. N Engl J Med 2018; 378: 1107-20

Combinations of targeted therapies – rel/ref

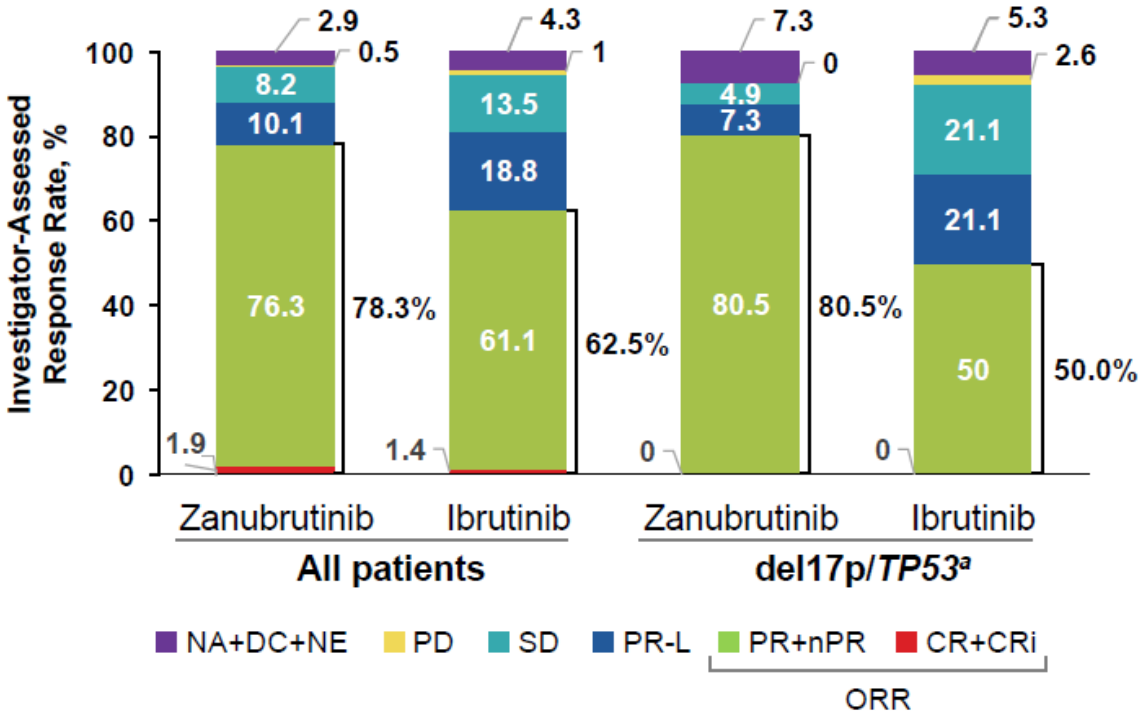
- CLARITY ibru + ven trial
- Ibru + ven Stanford/COH trial

Novel therapeutics

- Zanubrutinib (covalent BTKi)
- LOXO305/pirtobrutinib (non-covalent BTKi)
- APG2575/lisaftoclax (BCL2i)
- Umbralisib/ublituximab (U2)
- Liso-cel CAR T cell therapy

Zanubrutinib: ALPINE Ph3 trial of zanu vs. ibru (interim analysis)

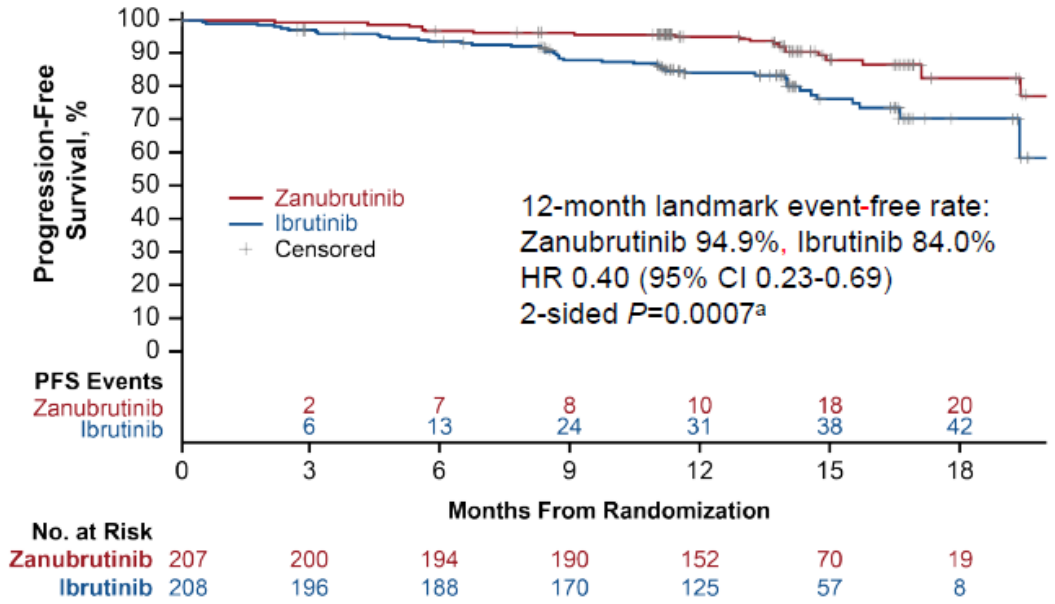
ORR



[a]In patients with del17p, ORR was zanubrutinib 83.3% and ibrutinib 53.8%.

ORR was significantly[b] higher with zanubrutinib vs ibrutinib

PFS

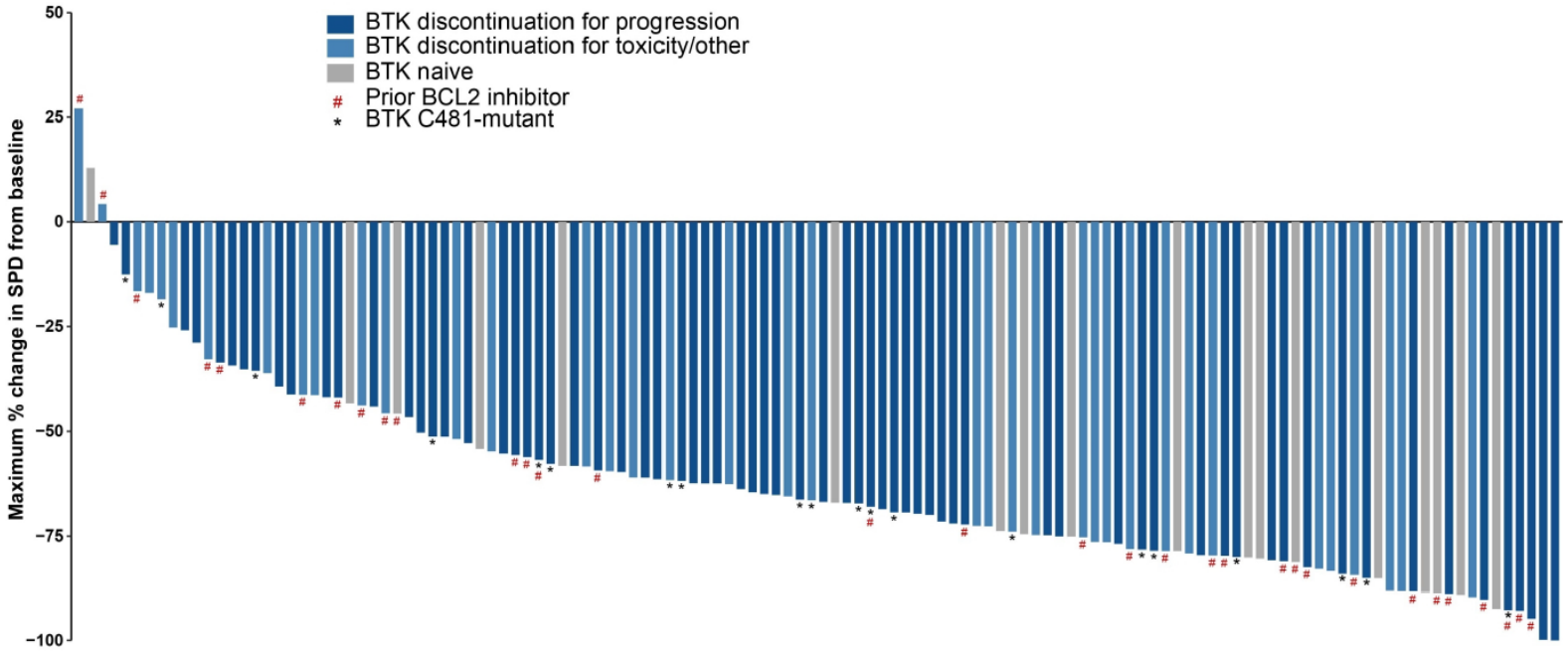


12-month overall survival rates were:
Zanubrutinib 97.0% (11 deaths) and ibrutinib 92.7% (19 deaths)
HR 0.54 (95% CI 0.25-1.16) 2-sided *P*=0.1081[c]

Hillmen P, et al. 19th iwCLL2021 (virtual) meeting

Pirtobrutinib: BRUIN Ph1/2 trial; oral

Characteristics	n=170
Median age, years (range)	69 (36-88)
Female, n (%)	61 (36)
Male, n (%)	109 (64)
ECOG PS, n (%)	
0	87 (51)
1	69 (41)
2	13 (8)
Median number prior lines of systemic therapy (range)	3 (1-11)
BTK pre-treated	4 (1-11)
Prior therapy, n (%)	
BTK inhibitor	**146 (86)**
Chemotherapy	140 (82)
Anti-CD20 antibody	153 (90)
BCL2 inhibitor	**57 (34)**
PI3K inhibitor	**36 (21)**
Lenalidomide	14 (8)
Autologous stem cell transplant	0
Allogeneic stem cell transplant	3 (2)
CAR-T	10 (6)
Reason discontinued any prior BTKi, n (%)	
Progressive disease	**98 (67)**
Toxicity/other	**48 (33)**



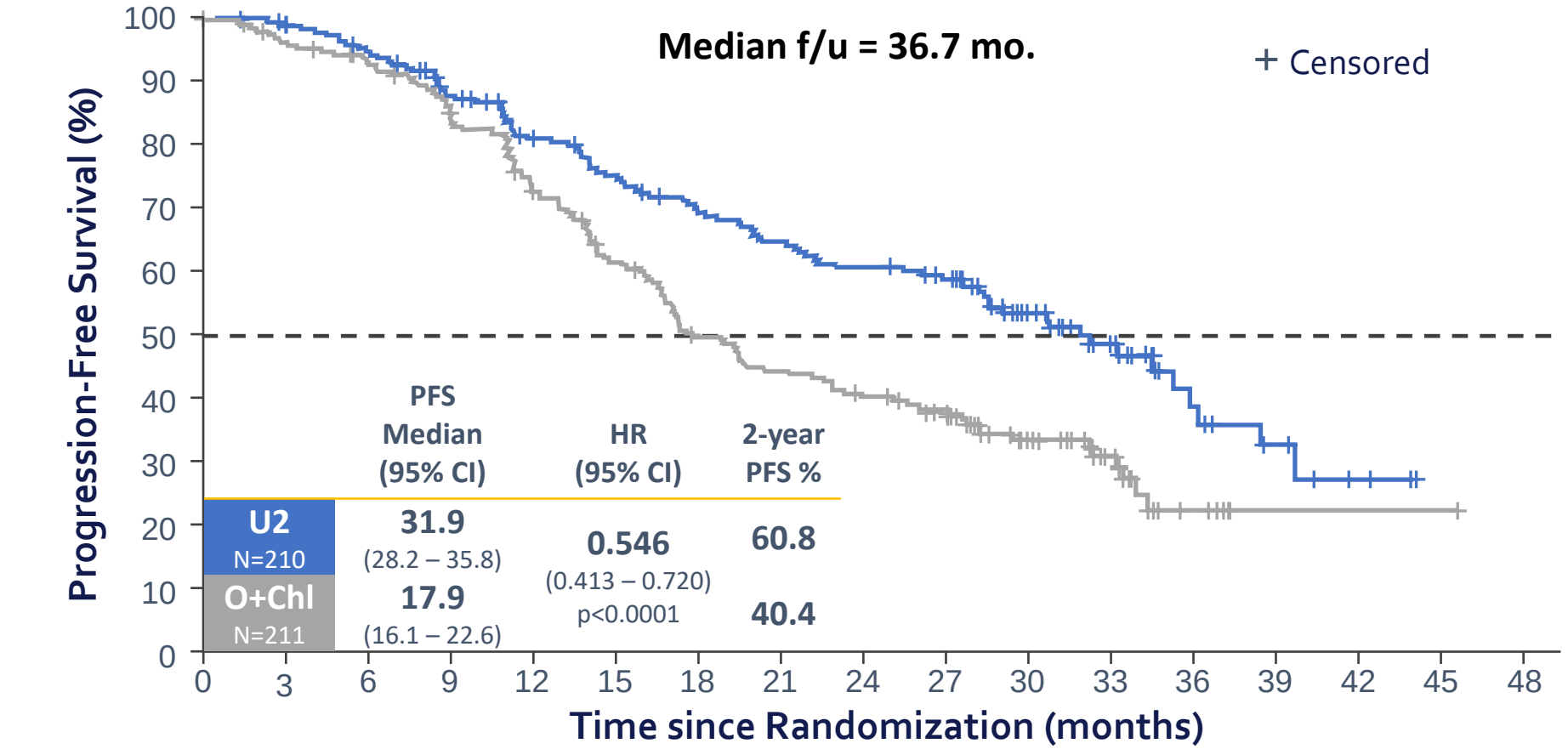
Mato A, et al. Lancet 2021; 397: 892-901
Jurczak W, et al. 19th iwCLL2021 (virtual) meeting

Lisaftoclax: first-in-human Ph1 trial; oral

- N = 36
- The most common treatment-related AEs, occurring in more than 15% of patients, were fatigue (27.8%), neutropenia (22.2%), diarrhea (19.4%), and anemia (16.7%).
- The most common AEs of grade 3 or higher included neutropenia (13.9%), nausea (5.6%), and platelet count decrease (5.6%).
- Among the 15 patients with CLL/SLL, the median duration of treatment was 9 cycles (range, 5-24 cycles). A partial response was seen in 12 patients (80%) with CLL/SLL; no CRs occurred in this group of patients. The median time to response was 2 cycles (range, 2-8 cycles) in this cohort.

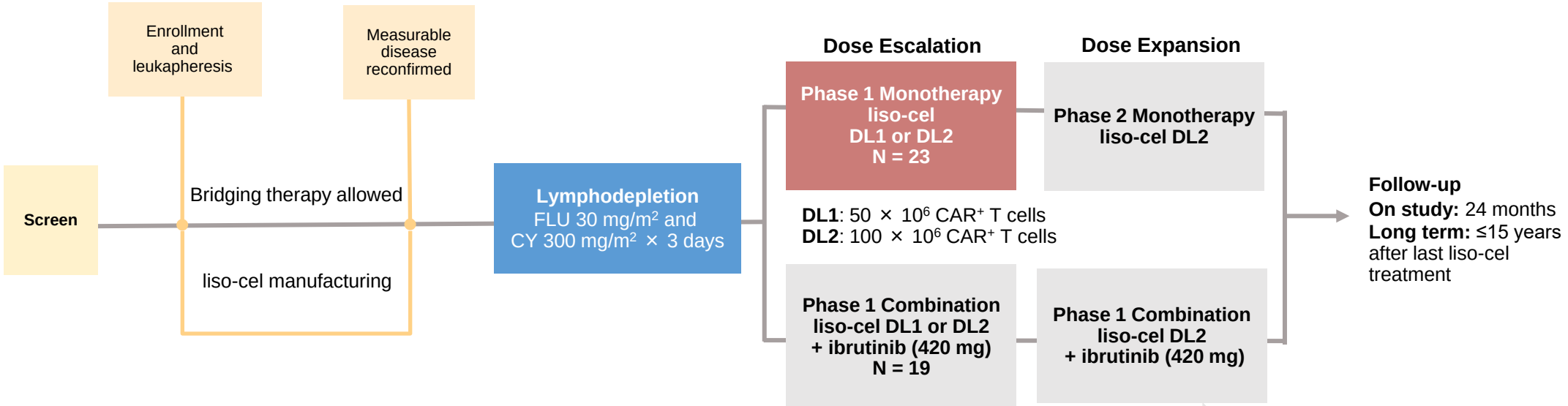
Ailawadhi S, et al. 19th iwCLL2021 (virtual) meeting

Umbralisib/ublituximab (U2): UNITY Ph3 trial of U2 vs. clb-G



Jurczak W, et al. 19th iwCLL2021 (virtual) meeting

CAR-T cell therapy: TRANSCEND-CLL004 trial



Key eligibility (monotherapy cohort):

- R/R CLL/SLL
- Ineligible for BTKi or prior BTKi failure
- High-risk disease: ≥2 prior therapies failed
- Standard-risk disease: ≥3 prior therapies failed
- ECOG PS of 0—1

Key eligibility (ibrutinib combination cohort):

- R/R CLL/SLL, and
- Progressing on ibrutinib at enrollment, ***or***
- High-risk features[c] and received ibrutinib for ≥6 months with less than a CR, ***or***
- *BTK* or *PLCγ2* mutations, ***or***
- Prior ibrutinib with no contraindication to reinitiating ibrutinib

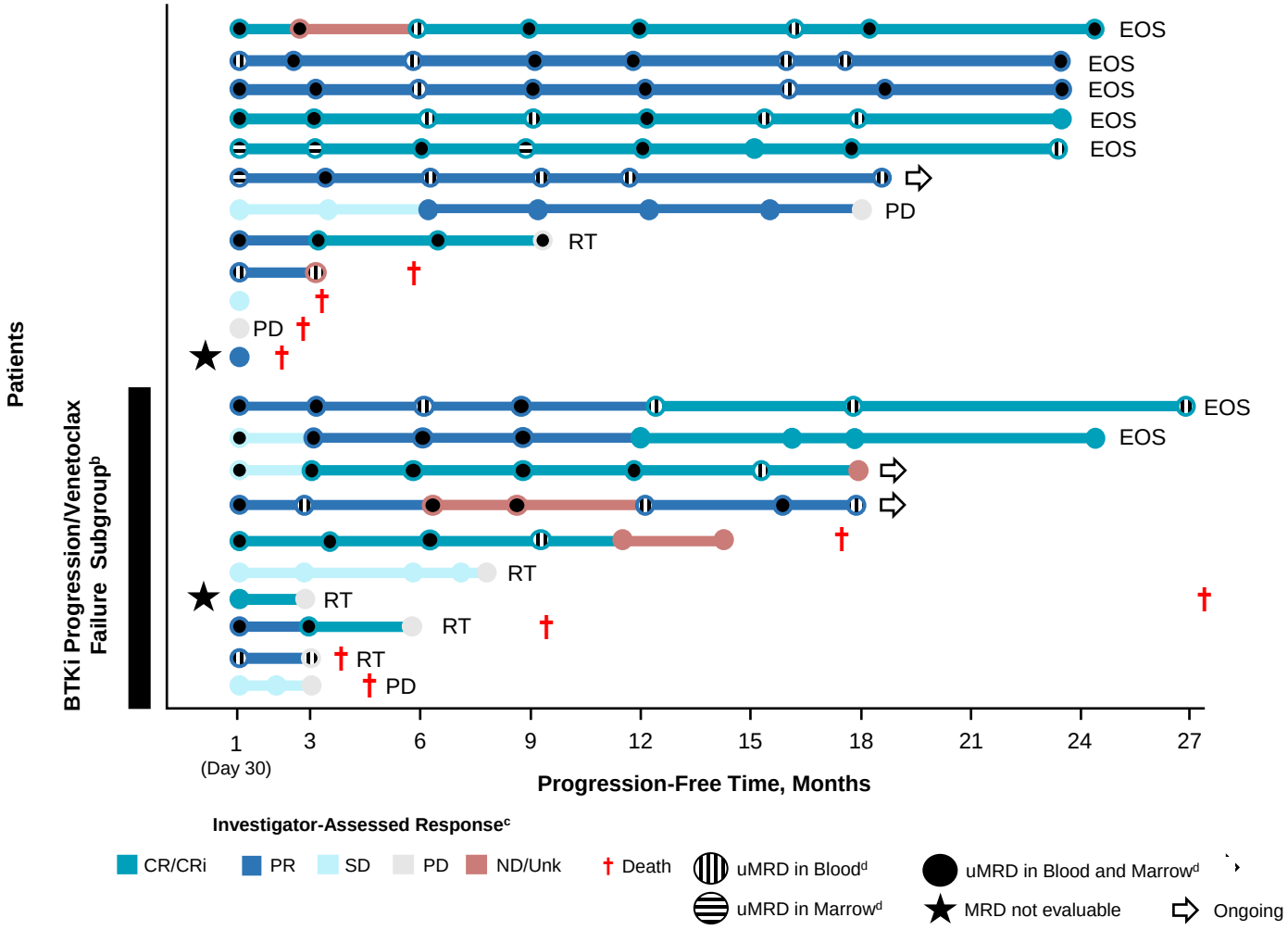
Siddiqi T, et al. Virtual ASH annual meeting 2020
Wierda WG, et al. 19th iwCLL2021 (virtual) meeting

Toxicity: CRS and NE

Parameter	Monotherapy cohort (n=23)	Ibrutinib combination cohort (n=23)
Cytokine release syndrome (CRS)		
All-grade CRS, n (%)	17 (74)	18 (78)
Median time to CRS onset, days (range)	3 (1–10)	7 (1—13)
Median duration of CRS, days (range)	12 (2–50)	5.5 (3—13)
Grade 3 CRS,[a] n (%)	**2 (9)**	**1 (4)**
Neurological events (NEs)		
All-grade NEs, n (%)	9 (39)	7 (30)
Median time to NE onset, days (range)	4 (2–21)	9 (5—13)
Median duration of NE, days (range)	20.5 (6–50)	7 (1—10)
Grade ≥3 NEs,[b] n (%)	**5 (22)**	**4 (17)**

Siddiqi T, et al. Virtual ASH annual meeting 2020
Wierda WG, et al. 19th iwCLL2021 (virtual) meeting

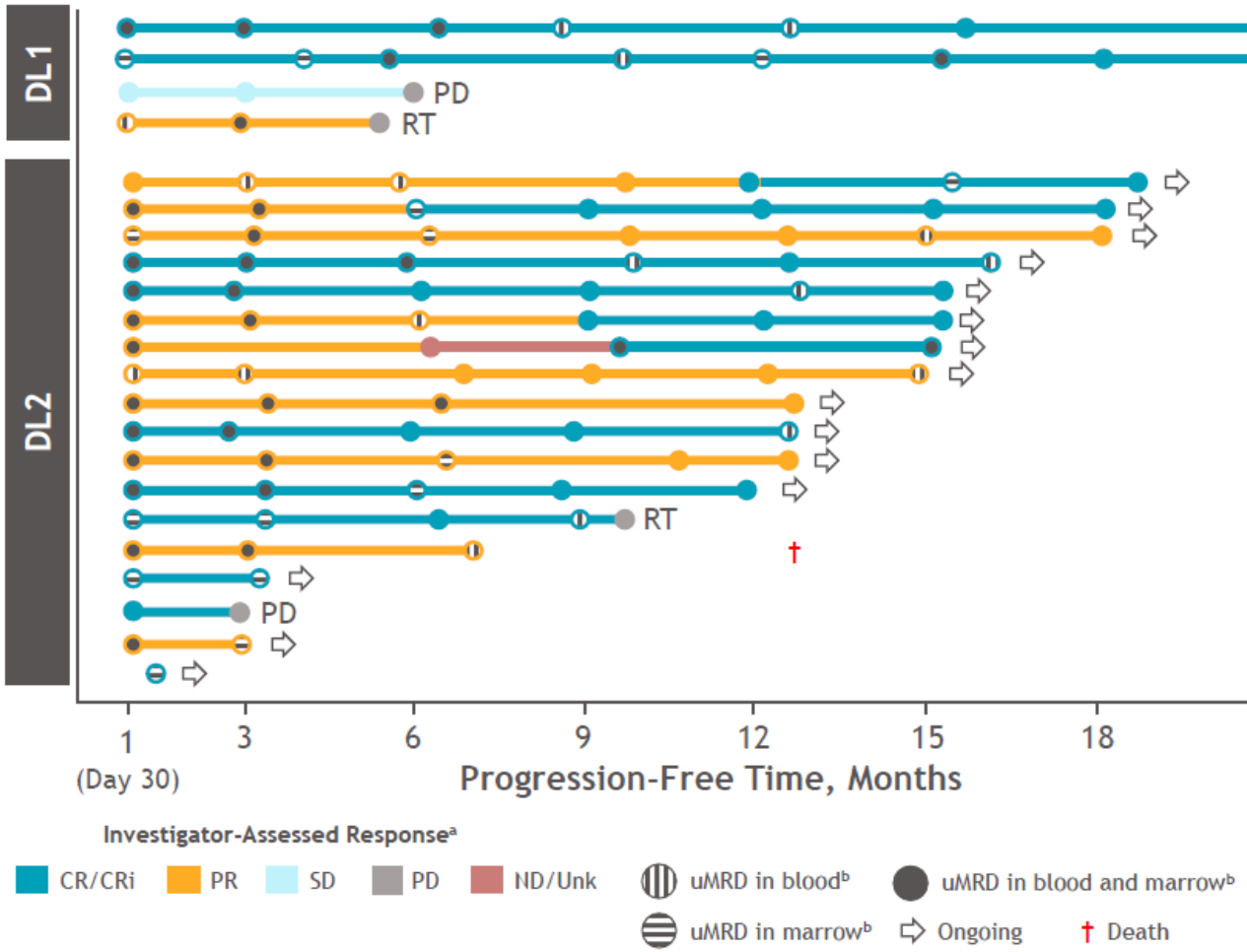
Monotherapy cohort responses: 2-year followup



- ORR was 82% (CR/CRi, 46%; PR, 36%), with 68% (n = 15/22)[a] of patients achieving a rapid response within 30 days
- 27% (n = 6/22) of patients had a deepening of response
- Response was durable. At 12 months, 50% (n = 11/22) were in response and only 2 of these responders progressed beyond 12 months
- Four of the 15 patients with uMRD (blood) response (CR or PR) have progressed, with 3 due to Richter transformation (RT)
- The subgroup also demonstrated rapid and durable responses
- Four of 6 progression events in the subgroup were due to RT

Siddiqi T, et al. Virtual ASH annual meeting 2020

Ibrutinib combination cohort responses: 10-month followup



- All responders (n = 21/22) achieved a response by Day 30 after liso-cel
- Among 18 patients with ≥6 months of follow-up, 83% (n = 15/18) maintained or improved response from Day 30
- Two patients achieved a response, but later progressed due to Richter transformation (RT)
- Patients receiving DL2 will be followed for 48 months
- One patient died due to complications from COVID-19

Wierda WG, et al. 19th iwCLL2021 (virtual) meeting

Overall Conclusions

- Explosion of novel therapies for CLL in recent years, including monoclonal antibodies (like obinutuzumab), small molecule inhibitors of various kinases (like BTK and PI3K) and the antiapoptotic pathway (especially Bcl2), and CD19-specific CAR-T cells
- These novel, non-chemotherapeutic agents seem to have done away with the need for standard chemoimmunotherapy in CLL
- Combination studies are underway to improve outcomes further and possibly find a cure

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