ASH 2020 LYMPHOMA HIGHLIGHTS

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Disclosures

- None

Objectives

- Diffuse Large B Cell Lymphoma
  - Improving frontline therapy in high-risk patients:
    - ZUMA-12 assessing CAR-T first line (Abstract 405)
  - R/R patients:
    - Epcoritamab bi-specific monoclonal antibody (Abstract 402)
    - Odronextamab bi-specific monoclonal antibody (Abstract 400)
- Follicular Lymphoma
  - R/R patients:
    - ZUMA-5 assessing CAR-T third line treatment (Abstract 700)
- Chronic Lymphocytic Leukemia
  - Frontline trials:
    - Importance of uMRD: Venetoclax and Obinotuzumab frontline CLL14 (Abstract 127)
    - Fixed duration treatment: Ibrutinib plus Venetoclax frontline (CAPTIVATE) study results (Abstract 123)
  - R/R trials:
    - Long-term outcomes of Ven-R (MURANO trial) (Abstract 125)

DIFFUSE LARGE B-CELL LYMPHOMA

STANDARD THERAPY OPTIONS

- Frontline therapy: R-CHOP
- Salvage therapy (R-GDP, R-ICE, R-DHAP) + ASCT in first relapse
- CAR-T cell Tx
  - An option for patients with lymphoma refractory to >=2 lines of therapy
- Novel agents
- Allogeneic transplant (rarely an option)
- Palliative single/multi-agent chemotherapy
- BiTE Tx
  - Investigational and holds promise!

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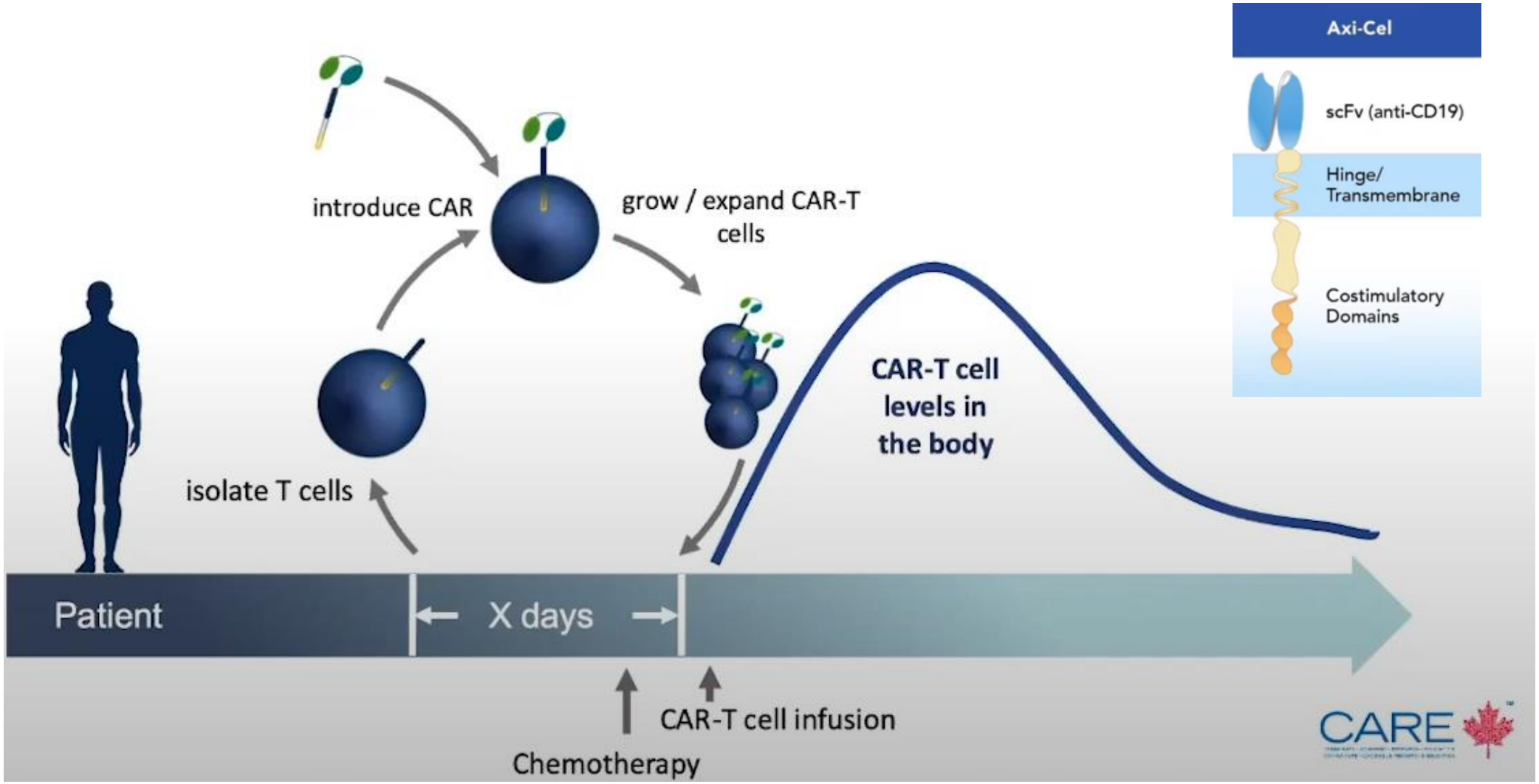
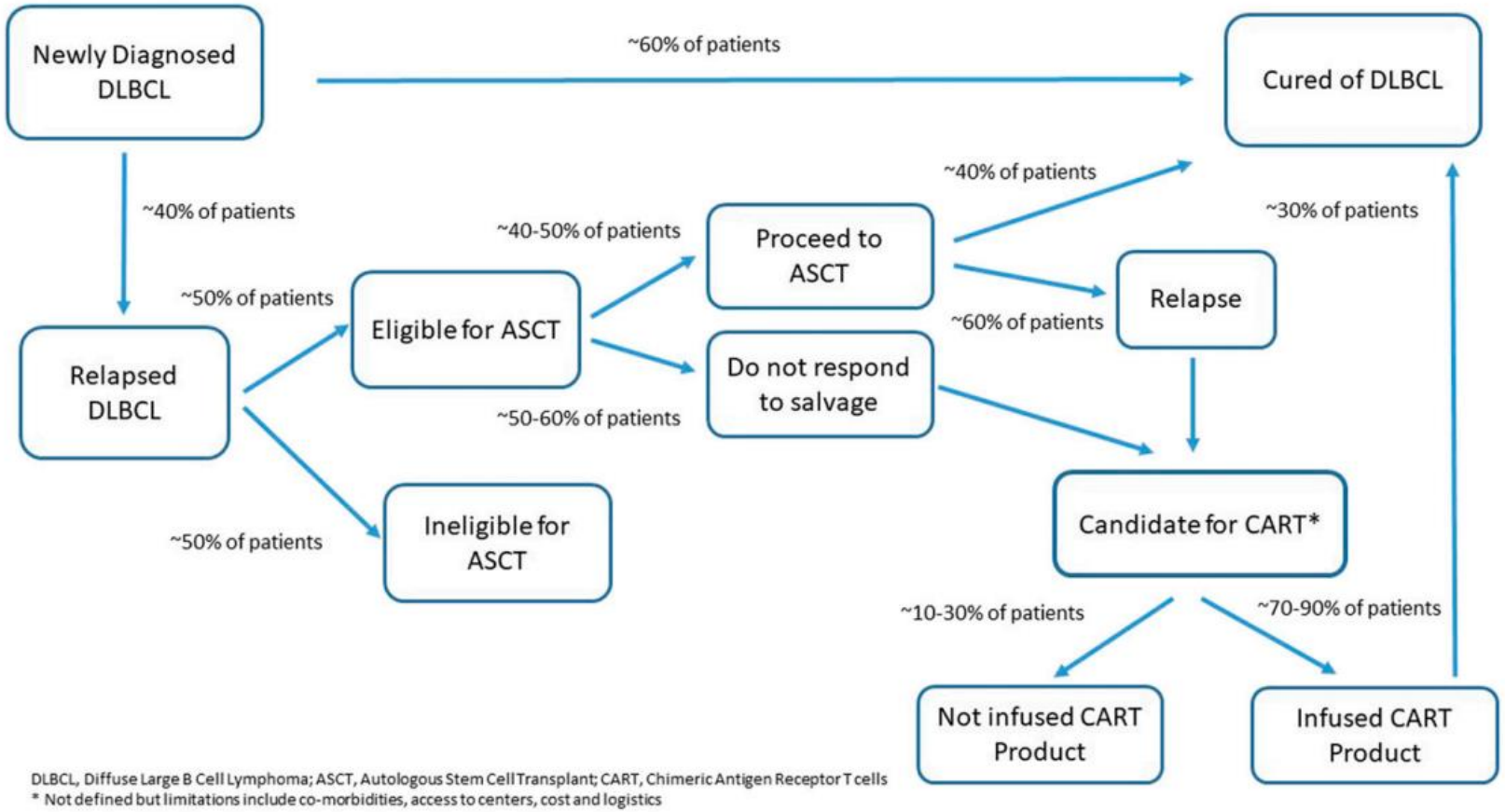
- Novel agents (polatuzumab, ibrutinib, lenalidomide, pembrolizumab)
- Allogeneic transplant (rarely an option)
- Palliative single/multi-agent chemotherapy
- **BiTE Tx**
  - Investigational and holds promise!

ENGINEERED CELL THERAPEUTICS



Aggressive lymphoma outcomes



DLBCL, Diffuse Large B Cell Lymphoma; ASCT, Autologous Stem Cell Transplant; CART, Chimeric Antigen Receptor T cells
* Not defined but limitations include co-morbidities, access to centers, cost and logistics

Figure 1. DLBCL. *Not defined, but limitations include comorbidities, access to centers, cost, and logistics.

Maddocks K. Novel targets in aggressive lymphoma. Heamatology Am Soc Hematol Educ Program. 2020 (1): 101-106

Gaps in knowledge

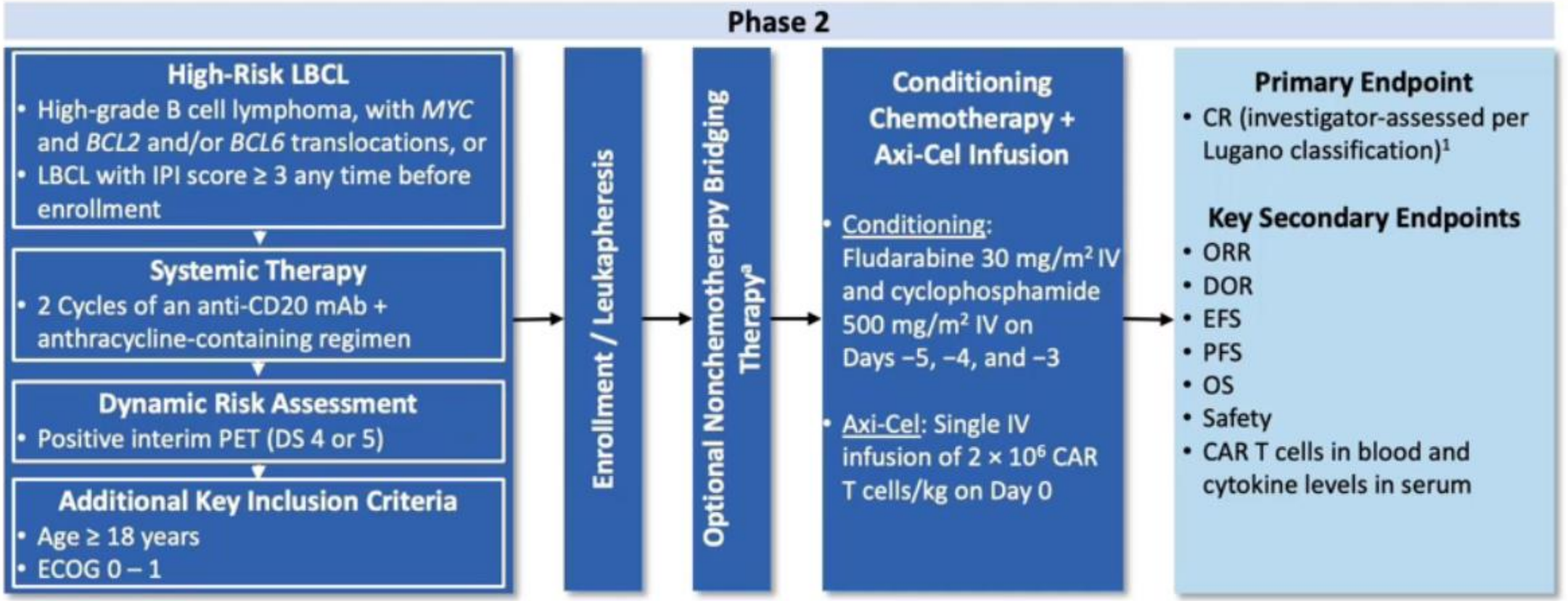
- Addition of novel therapies to RCHOP have shown no benefit
  - 2 studies ongoing:
    - POLLARIX Trial results pending (Polatuzumab + RCHP vs RCHOP)
    - Escalade Trial results pending (Acalabrutinib + R-CHOP vs RCHOP)
- Identify therapies for patients not candidates for ASCT or those that progress post CAR-T

Interim analysis of ZUMA-12: A Phase 2 Study of Axi-Cell as First-Line Therapy in Patients with High-Risk Large B Cell Lymphoma (Abstract 405)

- Patients with high-risk LBCL have poor outcomes
  - Early disease resistance after first-line rituximab-based chemoimmunotherapy confers a poor prognosis
- Axi-cel (autologous anti-CD19 CAR T cell therapy) is currently approved for patients with R/R LBCL after >=2 lines of systemic therapies
  - ZUMA-1 study: ORR 82% with a CR rate of 58%
  - Median of 51.1 months of follow-up, median OS was 25.8 months
  - 40% PFS at 27.1 months
- ZUMA-12 is a phase 2, multicenter, open-label, single-arm study of axi-cel as part of first line therapy in patients with high risk LBCL.

Neelapu et al. ASH 2020

ZUMA-12 Study Design



[a] Administered after leukapheresis and completed prior to initiating conditioning chemotherapy; PET-CT was required after bridging.

1. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068.

Axi-cel, axicabtagene ciloleucel; BCL, B cell lymphoma; CAR, chimeric antigen receptor; CR, complete response; CT, computed tomography; DLBCL, diffuse large B cell lymphoma; DOR, duration of response; DS, Deauville score; ECOG, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; IPI, International Prognostic Index; IV, intravenous; LBCL, large B cell lymphoma; mAb, monoclonal antibody; ORR, overall response rate; OS, overall survival; PET, positron-emission tomography; PFS, progression-free survival.

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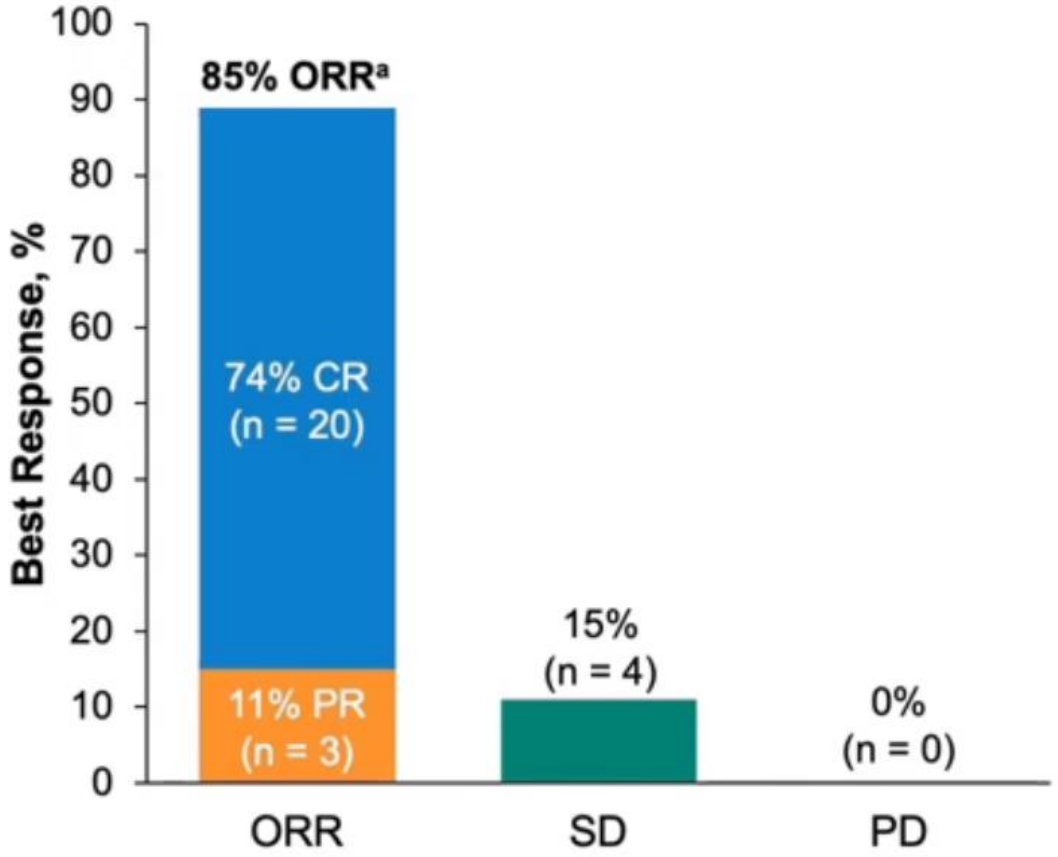
ORR Was 85% and CR Rate Was 74%



	Response Evaluable N = 27[b]
Median follow-up (range), months	9.3 (0.9 – 18.0)
Patients with ≥ 6-month follow-up, n (%)	19 (70)
Patients with ongoing response as of data cutoff	19 (70)
Median time to response (range), months	
Initial objective response	1.0 (0.9 – 3.1)
CR	1.0 (0.9 – 6.4)
Patients converted from PR / SD to CR, n (%)	5 (19)
PR to CR	4 (15)
SD to CR	1 (4)

[a] In the safety evaluable set (N = 32), the ORR was 88% and CR rate was 78%.
[b] Includes all treated patients with centrally confirmed disease type (double-/triple-hit lymphomas) or IPI score ≥ 3 who received ≥ 1×10^6 CAR T cells/kg and have ≥ 1 month of follow-up.
CAR, chimeric antigen receptor; CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

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CAR T Cell Toxicities

- Cytokine Release Syndrome (CRS)
- Neurological toxicity
  - Immune Effector Cell Associated Neurotoxicity Syndrome
- Prolonged cytopenias
- B-cell aplasia
- Hypogammaglobulinaemia

Study conclusions

- First study evaluating CAR T cell therapy in the first line setting in high risk LBCL patients.
- Patients had high ORR and CR rates (historic cohorts had CR rates has been less than 50%)
- New insights into response to treatment in patients exposed to fewer first line therapies:
  - Increased number of CCR7+CD45RA+T cells infused in ZUMA 12 as compared to ZUMA 1 and greater CAR T cell expansion in ZUMA 12 noted.
  - Suggesting improved T cell fitness in first line treatment
- The future:
  - Final analysis results (median follow-up only 9.5 months)
  - A head-to-head comparison of R-CHOP to CAR T in the first line setting
  - ZUMA-7 results (second line, transplant eligible)

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Bispecific T cell engagers

- Mosunetuzumab
  - 3 Phase I trials
  - 3 Phase I/II trials
- Gliofitamab
  - 6 Phase I trials
  - 1 Phase III trial
- Odronextamab
  - 2 Phase I trial
  - 1 Phase II trial
- Epcoritamab (subcutaneous)
  - 1 Phase I/II trial
- Plamotamab
  - 1 Phase I trial

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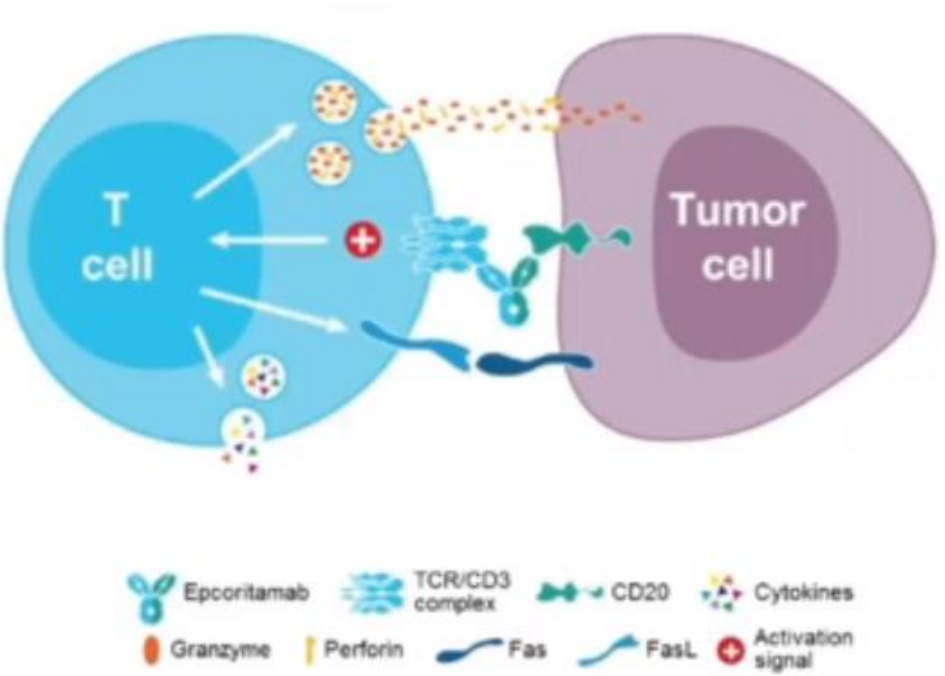
Subcutaneous Epcoritamab Induces Complete Responses with an Encouraging Safety Profile across Relapsed/Refractory B-Cell Non-Hodgkin Lymphoma subtypes, Including Patients with Prior CAR-T Therapy: Updated Dose Escalation Data (Abstract 402)

- Patients who relapse or become refractory to chemotherapy face poor outcomes as treatment options are limited by efficacy and toxicity
- Epcoritamab is a subcutaneously administered bispecific antibody that induces T-cell mediated killing of CD20-expressing tumors.
  - 1 mL subcutaneous injection
  - More gradual increase and lower peak in plasma cytokine levels compared with intravenous administration
  - Long plasma half-life
  - Favorable safety profile



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GCT3013-01: Phase I/II study design

Dose escalation*

Expansion part

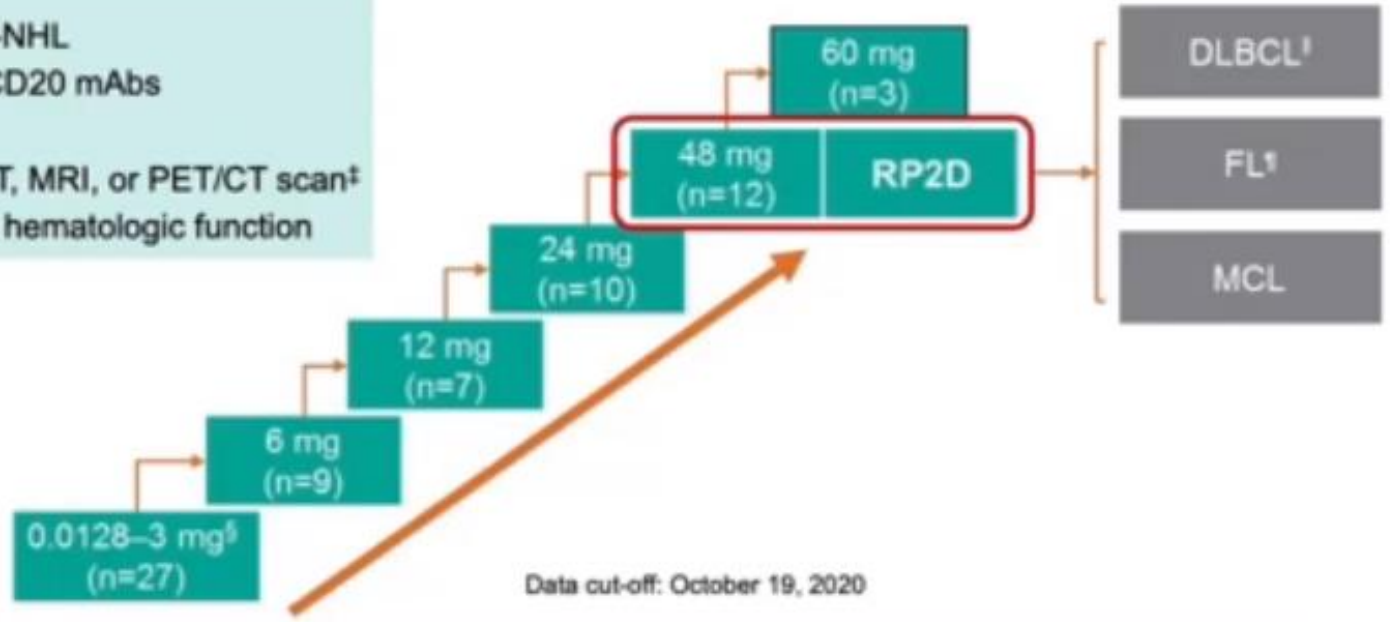
Flat-dose epcoritamab administered in 28-day cycles until disease progression or unacceptable toxicity

Objectives

Primary
- Maximum tolerated dose (MTD)
- Recommended Phase II dose (RP2D)

Secondary
- Safety/tolerability
- Anti-tumor activity

Inclusion criteria†
- Adults with R/R CD20+ B-NHL
- Prior treatment with anti-CD20 mAbs
- ECOG PS 0–2
- Measurable disease by CT, MRI, or PET/CT scan‡
- Adequate renal, liver, and hematologic function



RP2D determined to be 48 mg. Expansion part is enrolling

*Modified Bayesian optimal interval design consisting of accelerated and standard titration. Accelerated titration includes single-patient cohorts; up to 2 patients may be added (at the currently investigated dose) to obtain additional PK/PD biomarker data. †Patients previously treated with CAR-T cell therapy were allowed (protocol amended after study start). ‡CT or MRI scans: Weeks 6, 12, 18, 24, and every 12 weeks thereafter. PET scans not required in all patients. §Includes the following priming/final dose levels (mg): 0.004/0.0128, 0.0128/0.04, 0.04/0.12, 0.12/0.38, 0.04/0.76, 0.04/0.25/1.5, 0.04/0.5/3. ¶Includes patients with DLBCL or other aggressive histologies. ¶Includes FL or other indolent histologies

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Demographics and baseline characteristics

Characteristic	All histologies* (N=68)	DLBCL (n=46)	FL (n=12)
Median age, years (range)	68 (21–84)	68 (21–82)	73 (35–84)
Male, n (%)	45 (66)	30 (65)	8 (67)
Median time since most recent relapse or progression, months (range)	1.6 (0–88)	1.5 (0–88)	1.6 (1–17)
Prior lines of therapy, median (range)	3 (1–18)	3 (1–6)	5 (1–18)
Prior therapies, n (%)			
Anti-CD20 mAb	68 (100)	46 (100)	12 (100)
Anthracyclines	62 (91)	46 (100)	9 (75)
Alkylating agents	67 (99)	46 (100)	12 (100)
Autologous stem cell transplantation	7 (10)	5 (11)	1 (8)
CAR-T cell therapy	6 (9)	5 (11)	0 (0)
Refractory to, n (%)			
Most recent systemic therapy	59 (87)	42 (91)	10 (83)
Alkylating agents	56 (82)	40 (87)	9 (75)
CD20 mAbs	60 (88)	42 (91)	10 (83)
ECOG PS,† n (%)			
0	35 (52)	23 (50)	6 (50)
1	29 (43)	21 (46)	4 (33)
2	3 (4)	2 (4)	1 (8)

Patients were heavily pretreated; most patients were refractory to anti-CD20 therapy

*Includes 10 patients with MCL, marginal zone lymphoma, or small lymphocytic lymphoma. †One patient had ECOG PS 3, which was a protocol violation

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Patient disposition and exposure

	All histologies (N=68)	DLBCL (n=46)	FL (n=12)
Treatment ongoing, n (%)	17 (25)	11 (24)	5 (42)
Treatment discontinued due to, n (%)			
Disease progression	45 (66)	30 (65)	7 (58)
Adverse events*	1 (2)	1 (2)	–
Initiation of new treatment (SCT)	3 (4)	3 (7)	–
Other†	2 (2)	1 (2)	–
Median duration of exposure, weeks (range)	11 (0–56)	7 (0–52)	26 (13–56)
Median duration of follow-up, months (range)	10 (0–19)	7 (1–19)	12 (4–17)

At a median follow-up of 10 months, treatment is still ongoing in 25% of patients.
There were no discontinuations due to treatment-related adverse events

*Patient had COVID-19. Other includes death (n=1) and investigator/sponsor chose to discontinue treatment (n=1)

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Response by histology

Response*	DLBCL (n=46)		FL (n=12)		MCL‡
	12–60 mg (n=23)	48–60 mg† (n=12)	0.76–48 mg (n=11)	12–48 mg (n=5)	0.76–48 mg (n=4)
Evaluable patients, n	22§	11§	10‖	5	4**
ORR, n (%)¶	15 (68)	10 (91)	9 (90)††	4 (80)	2 (50)
CR	10 (46)	6 (55)	5 (50)	3 (60)	1 (25)
PR	5 (23)	4 (36)	4 (40)	1 (20)	1 (25)
Stable disease, n (%)	1 (5)	0	0	0	1 (25)
Progressive disease, n (%)	5 (23)	0	1 (10)	1 (20)	0

*Response assessments were based on Lugano 2014 response criteria by investigator assessment (modified response-evaluable population). †Includes 3 patients who received 60-mg dose before RP2D was determined. ‡1 patient had blastoid/pleomorphic MCL; 1 had unknown histology. §Excludes 1 patient who discontinued before first assessment due to COVID-19. ‖Excludes 1 patient who discontinued before first assessment due to post cardiac (CABG) surgery. ¶Response rates are based on number of evaluable patients (defined as patients with at least 1 post-baseline disease assessment or who died without a post-baseline disease assessment). **Includes 1 patient who died before assessment. ††9/10 patients had response evaluation by PET scans (not mandatory until recent protocol amendment)

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Study conclusions

- Epcoritamab is a novel, subcutaneously administered BiTE therapy.
- Epcoritamab shows a favorable safety profile
  - CRS events were Grade 1 and 2
- Epcoritamab showed efficacy in heavily pretreated patients including patients previously treated with CAR T therapy
  - In patients with DLBCL receiving >=48 mg dose, response was achieved in 10 of 11 patients.
- Next steps: Phase 2 expansion study to test the efficacy of epcoritamab

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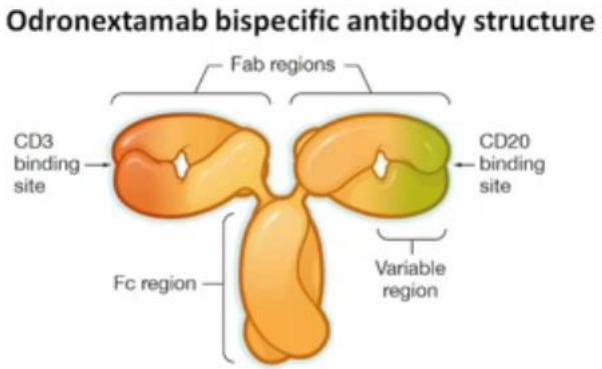
Odronextamab, a human CD20 x CD3 Bispecific Antibody, Induces Durable, Complete Responses in Patients with Highly Refractory B-Cell Non-Hodgkin Lymphoma, Including Patients Refractory to CAR T Therapy (Abstract 400)



- Odronextamab is a CD20 x CD3 bispecific antibody:
  - Binds to CD3 on T cells and CD20 on malignant B cells, triggering T-cell-mediated cytotoxicity
  - Safety and efficacy data (Phase 1 study)

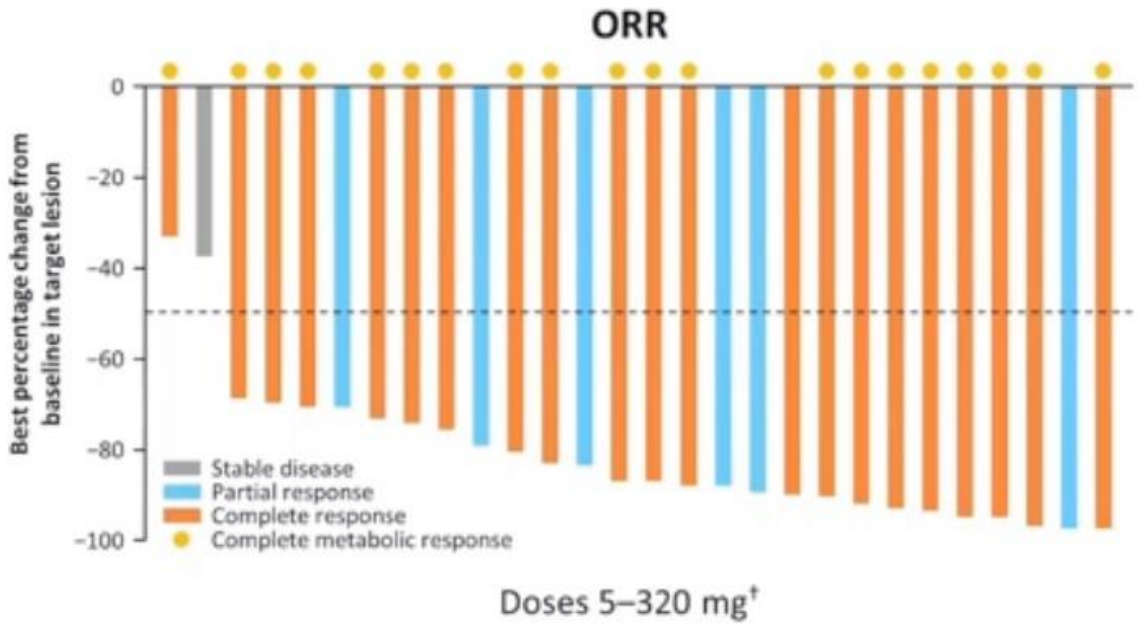
Bannerji et al. ASH 2020

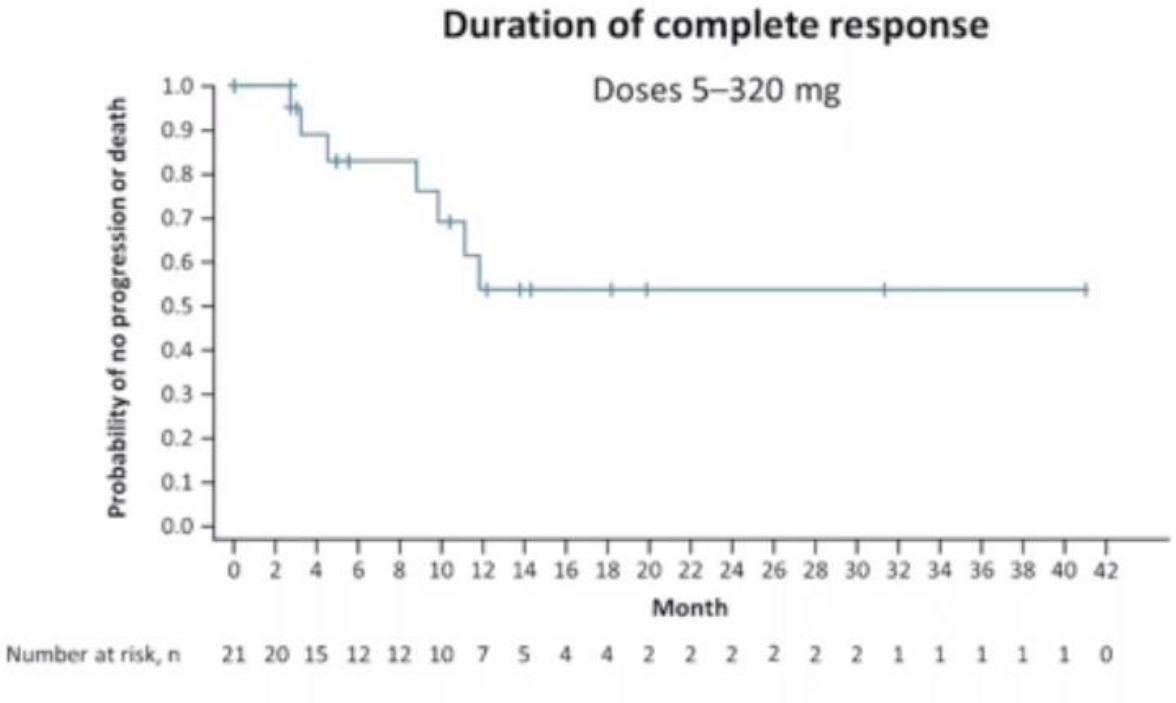
Odronextamab antitumor activity in R/R follicular lymphoma

ORR: **90%** (n=27/30); **CR rate**: **70%** (n=21/30)

CRs appear durable; median DoCR not reached

- **81%** of CRs were durable,* and are ongoing for up to **41 months**





Data cut-off: Oct 14, 2020.

Response per investigator assessment according to Lugano criteria. Median duration of follow up is 9 months (range, 1–44).

*Defined as a CR lasting at least 3 months; †Two patients with missing tumor assessments are not presented.

CR, complete response; DoCR, duration of complete response; ORR, objective response rate; R/R, relapsed/refractory.

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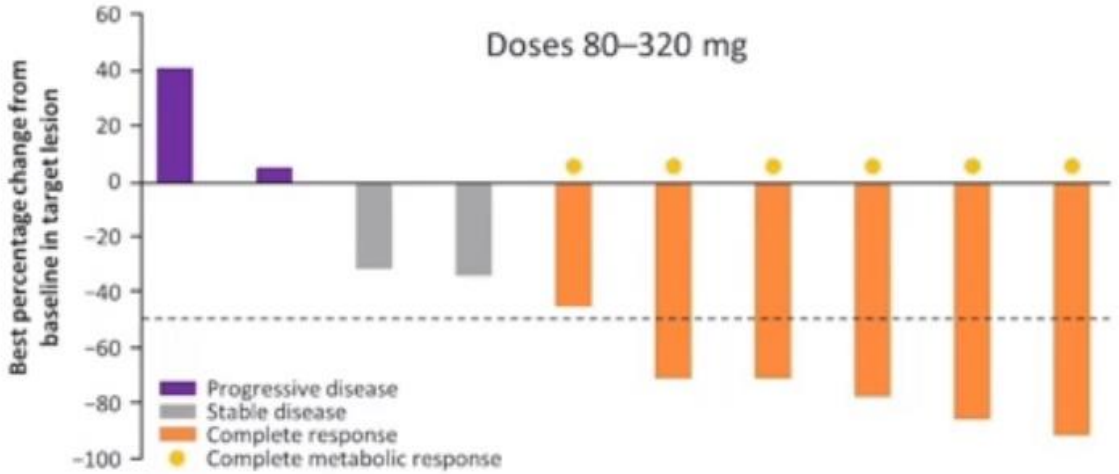
Odronextamab antitumor activity in R/R DLBCL: no prior CAR T

ORR: **55%** (n=6/11); **CR rate**: **55%** (n=6/11)

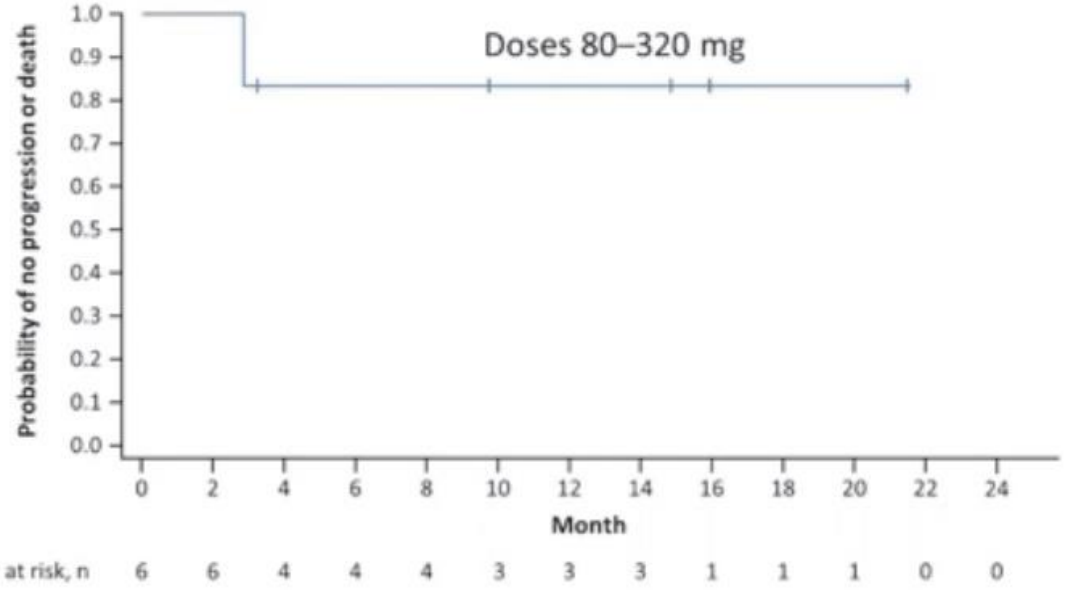
CRs appear durable; median DoCR not reached

- **83%** of CRs were durable,* and are ongoing for up to **21 months**

ORR



Duration of complete response



Data cut-off: Oct 14, 2020.

Response per investigator assessment according to Lugano criteria. Median duration of follow up is 6 months (range, 1–24).

*Defined as a CR lasting at least 3 months.

CAR T, chimeric antigen receptor T cell; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DoCR, duration of complete response; ORR, objective response rate; R/R, relapsed/refractory.

Bannerji et al. ASH 2020

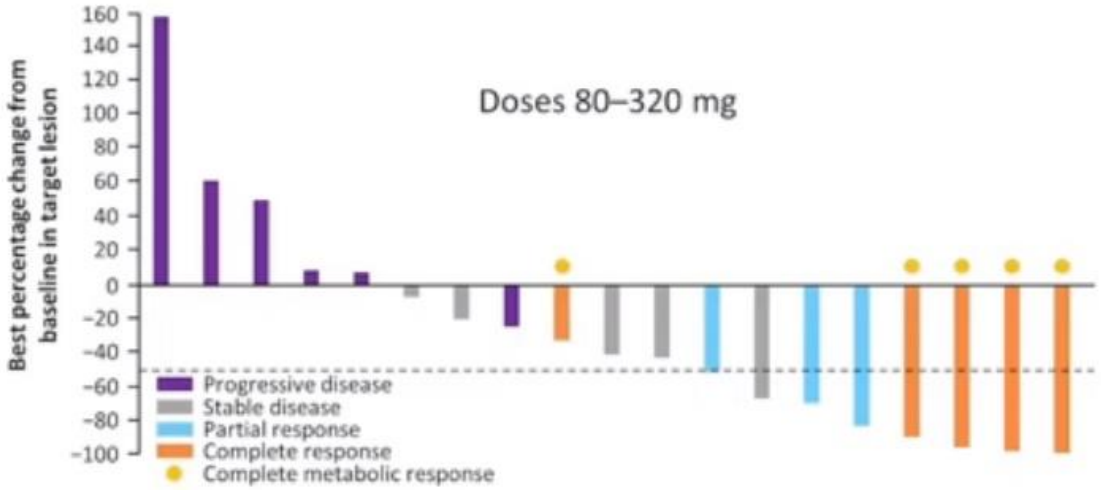
Odronextamab antitumor activity in R/R DLBCL: post-CAR T

ORR: **33%** (n=8/24); **CR rate**: **21%** (n=5/24)

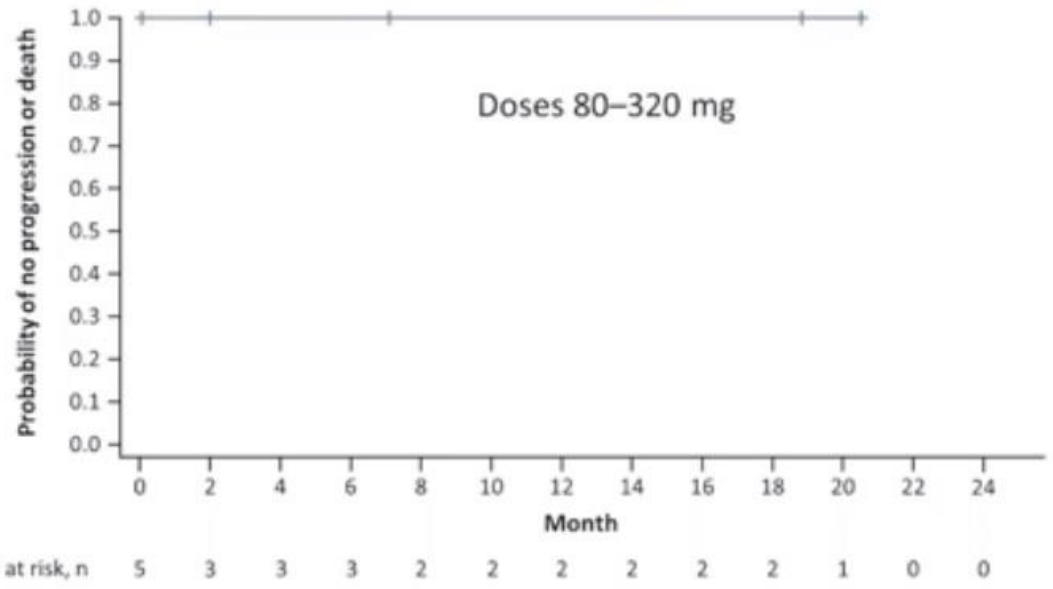
CRs appear durable; median DoCR not reached

- **100%** of CRs are ongoing,* for up to **20 months**

ORR



Duration of complete response



Data cut-off: Oct 14, 2020.

Response per investigator assessment according to Lugano criteria. Median duration of follow up is 3 months (range, 0–22).

*At time of last tumor assessment.

CAR T, chimeric antigen receptor T cell; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DoCR, duration of complete response; ORR, objective response rate; R/R, relapsed/refractory.

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Study conclusions

- Odronextamab, a novel CD20 x CD3 bispecific antibody
- Durable, CR achieved in heavily pretreated patients with FL and DLBCL
  - R/R FL: 70% CR, 81% CRs are durable and ongoing for up to 41 months
  - R/R DLBCL no prior CAR T: 55% CR; 84% of CRs are durable and are ongoing for up to 21 months
  - R/R DLBCL post CAR-T: 21% CR; 100% of CRs are ongoing, for up to 20 months
- Acceptable risk profile
  - CRS, ICANS-like events (highest grade 3)
- Next steps: Phase 2 trial in R/R NHL

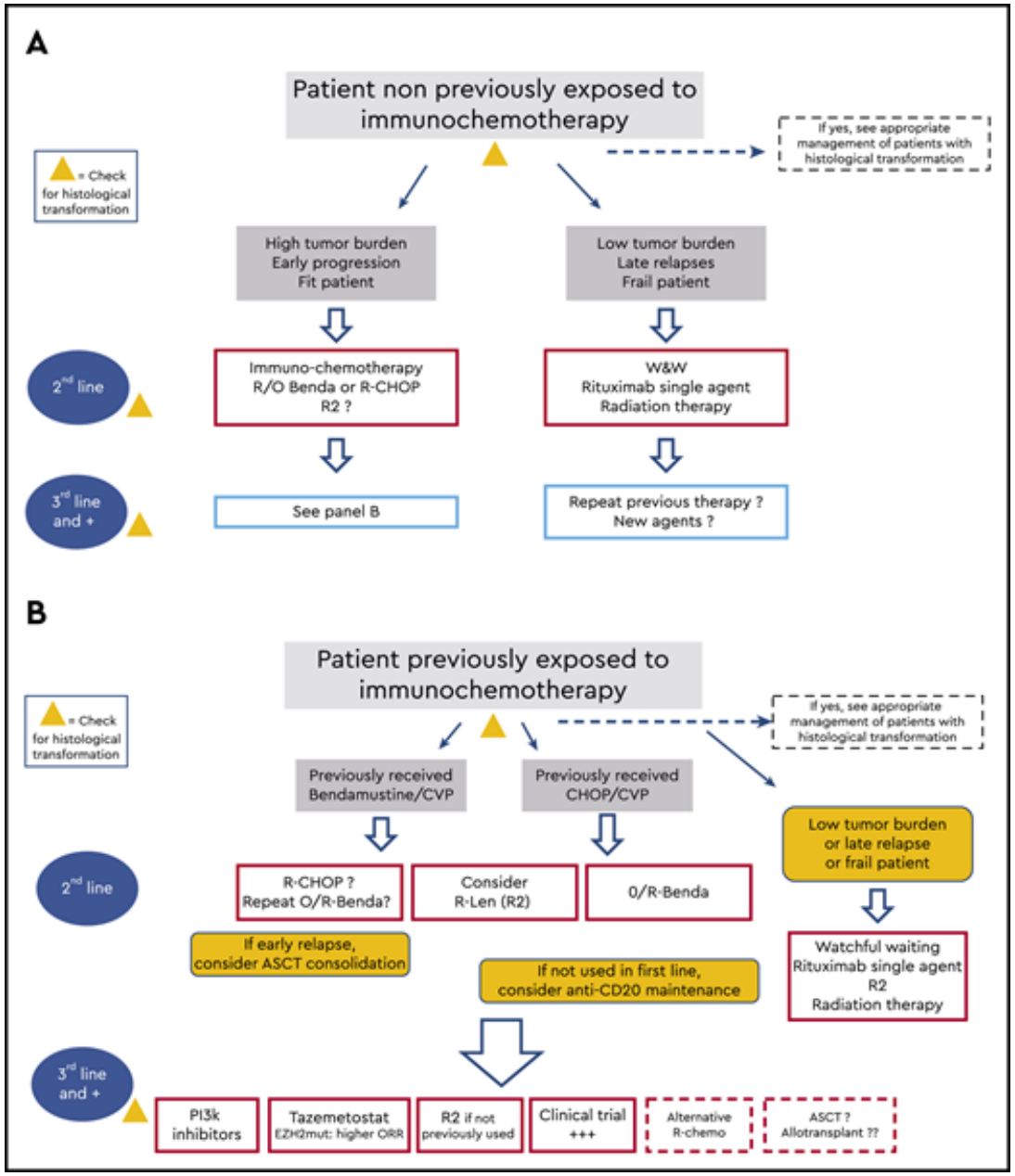
FOLLICULAR LYMPHOMA

Frontline and relapsed setting

- Bendamustine and rituximab
  - PFS 69.5 months (STIL)
- BR + maintenance rituximab
  - 3 year PFS 74% v 58% (maintenance v no maintenance)
- RELAPSED SETTING
  - Benda naïve: Benda
  - If treated with BR as first line:
    - Retreat with R-chemo
    - Autologous stem cell transplant
    - CAR T cell tx
    - BiTE tx
    - BTKis, Revlimid, PI_3K inhibitors

R/R FL

- Idelalisib (Median PFS 11 months)
- Duvelisib (Median PFS 10 months)
- Copanlisib (Median PFS 13 months)
- Bispecific antibodies:
  - Mosunetuzumab
  - Glofitamab



Salles G. How do I sequence therapy for follicular lymphoma? Hematology Am Soc Hematol Educ Program (2020): 287-294

Primary Analysis of ZUMA-5: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma (iNHL) (Abstract 700)

- Patients with FL and MZL frequently relapse with standard treatment
- FL after >=2 lines of therapy, CR rates are low and median duration of response is in the span of 1 year
- ZUMA-5 is a multicenter, single arm, Phase 2 study of axi-cel in patients with R/R iNHL (FL (Grades 1 -3a) or MZL(nodal or extranodal)) after >=2 lines of therapy

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ZUMA-5 Study Design

Phase 2 (N = 151 enrolled)

R/R iNHL	N = 146 Treated (124 FL, 22 MZL)

Key Eligibility Criteria

- R/R FL (Grades 1 – 3a) or MZL (nodal or extranodal)[a]
- ≥ 2 Prior lines of therapy—must have included an anti-CD20 mAb combined with an alkylating agent[b]

Conditioning Regimen

- Fludarabine 30 mg/m^2 IV and cyclophosphamide 500 mg/m^2 IV on Days −5, −4, −3

Axi-Cel: 2 × 10^6 CAR+ cells/kg

Primary Endpoint

- ORR (IRRC-assessed per the Lugano classification[1])

Key Secondary Endpoints

- CR rate (IRRC-assessed)
- Investigator-assessed ORR[1]
- DOR, PFS, OS
- AEs
- CAR T cell and cytokine levels

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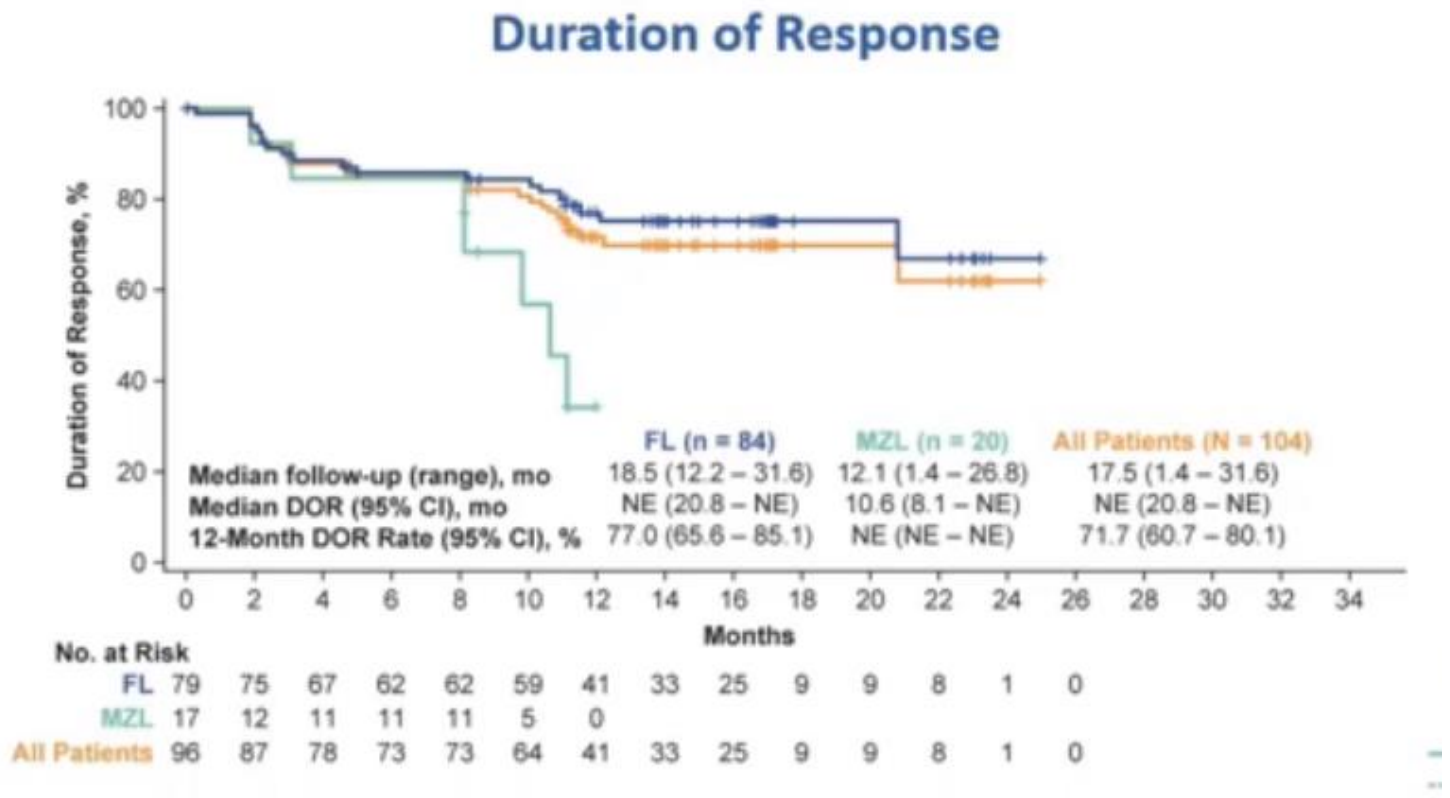
ZUMA-5 Results

iNHLs ORR 92% (CR 76%)
FL ORR 94% (80% CR)
MZL ORR 85% (CR 60%)
ORR was comparable across POD24, FLIPI, GELF, refractory status and prior lines of therapy.



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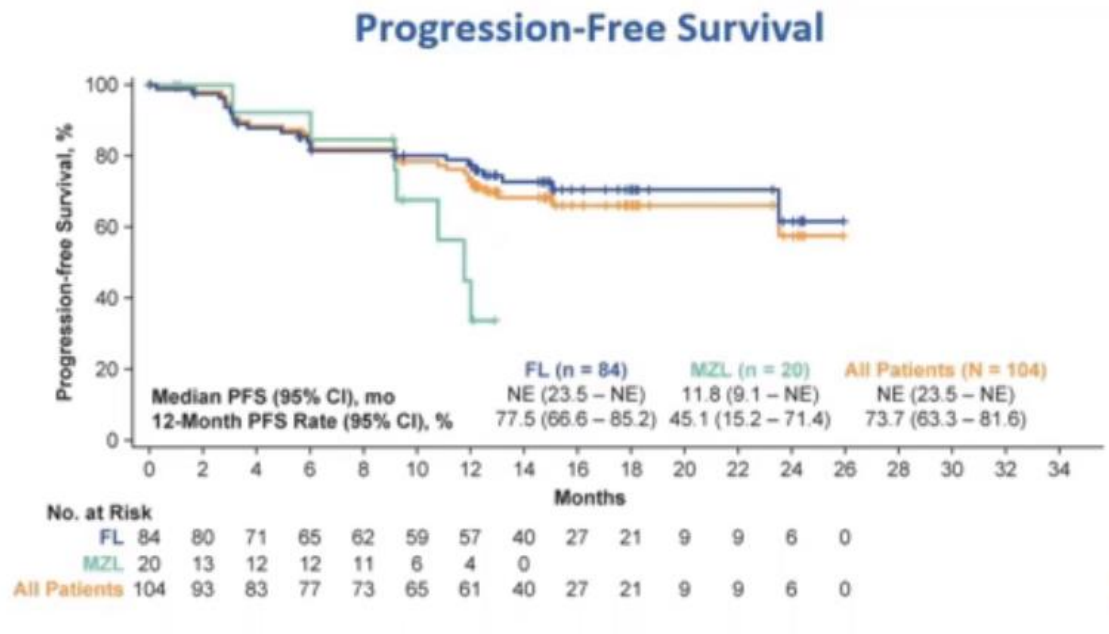
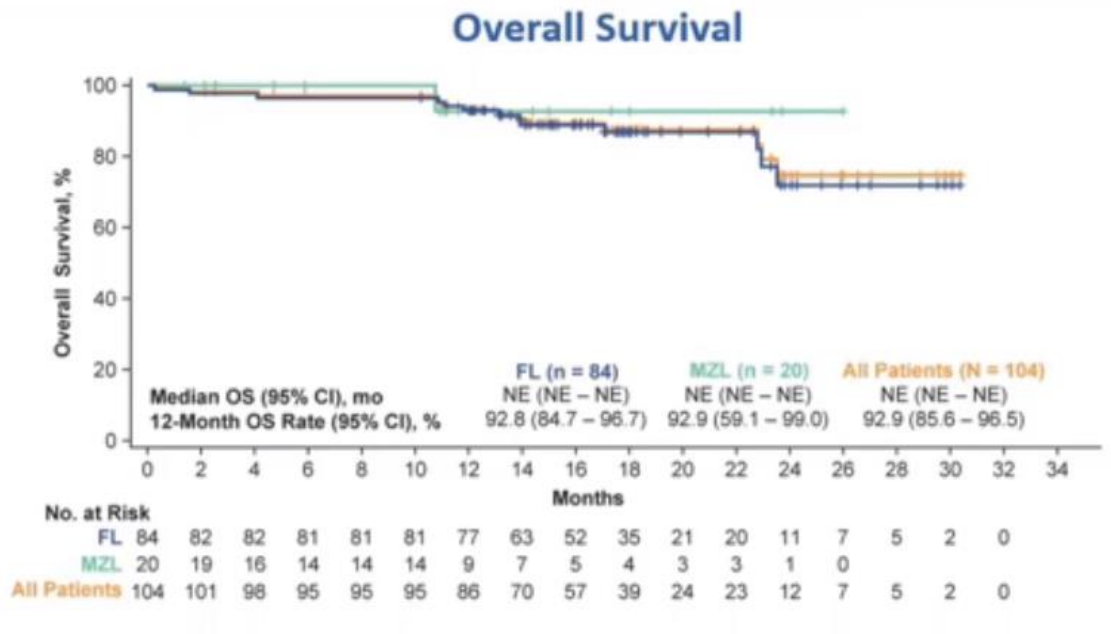
ZUMA-5 Results (continued)





Grade >=3 CRS occurred in 7% of patients with iNHL (6% FL, 9% MZL)

Grade >=3 Neurologic events occurred in 19% of patients with iNHL (15% in FL, 41% in MZL)

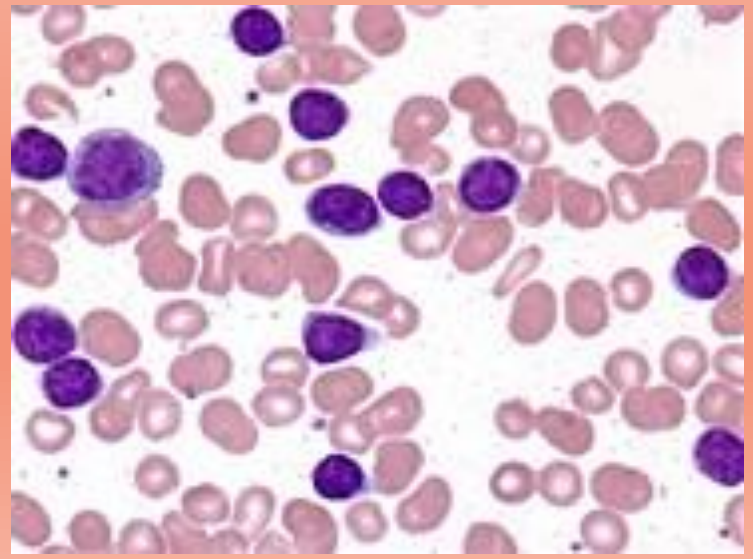
Jacobson et al. ASH 2020

Study Conclusions

- Axi-cel is safe and effective for the treatment of indolent lymphoma
- ORR and CR rates are better than in DLBCL
- Durability of response: 64% of FL patients with ongoing responses
- Next steps:
  - Can CAR T treatment potentially cure Follicular Lymphoma? (long term data needed)
  - At what stage should this therapy be used in the future?
    - POD 24 group
    - Relapsed/refractory group

Jacobson et al. ASH 2020

CHRONIC LYMPHOCYTIC LEUKEMIA



CLL-IPI for Prognosis

1) TP53 status (no abnormalities v/s del[17p] or TP53 mutation or both)
2) IGHV mutational status (mutated v/s unmutated)
3) Serum β2-microglobulin concentration (≤3.5 mg/L v/s >3.5 mg/L)
4) Clinical stage (Binet A or Rai 0 v/s Binet B–C or Rai I–IV)
5) Age (≤65 years v/s >65 years)

Risk Group	CLL-IPI risk score
Low-risk	0-1
Intermediate-risk	2-3
High-risk	4-6
Very High-risk	7-10

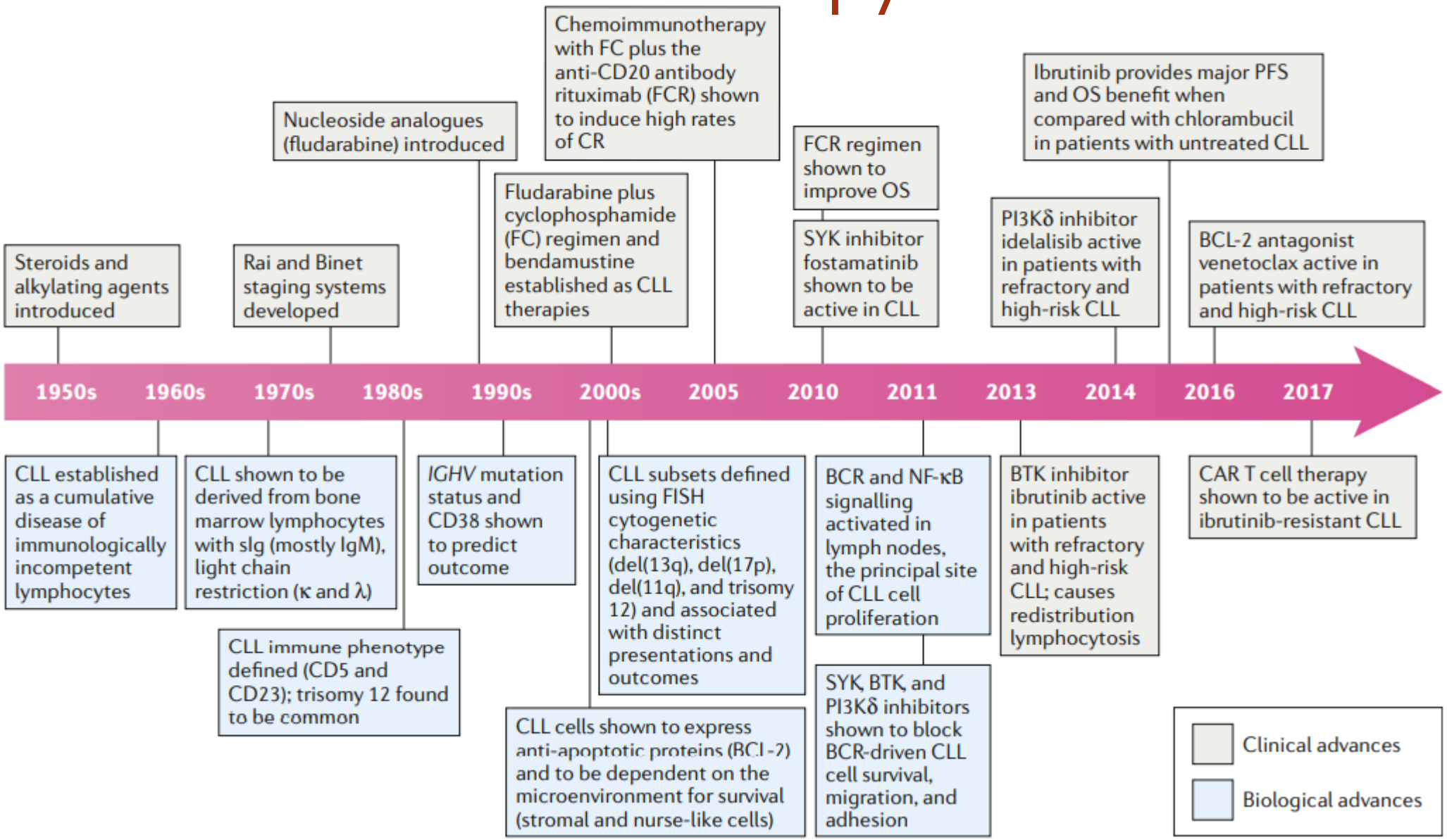
Lancet Oncol. 2016;S1470-2045:30029-8

OS of Untreated Patients based on CLL-IPI

	CLL-IPI risk score	Patients	Median overall survival (months [95% CI])	5-year overall survival (95% CI)	10-year overall survival (95% CI)	Comparisons	Hazard ratio (95% CI)
Training dataset		1214					
Low	0–1	341 (28%)	NR	93·2% (90·5–96·0)	79·0% (71·8–86·3)	..	..
Intermediate	2–3	474 (39%)	105 (96–119)	79·3% (75·5–83·2)	39·2% (31·0–47·4)	vs 0–1	3·5 (2·5–4·8)
High	4–6	337 (28%)	75 (68–82)	63·3% (57·9–68·8)	21·9% (14·2–29·6)	vs 2–3	1·9 (1·5–2·3)
Very high	7–10	62 (5%)	29 (18–40)	23·3% (12·5–34·1)	3·5%* (NE)	vs 4–6	3·6 (2·6–4·8)
Internal-validation dataset		585					
Low	0–1	186 (32%)	NR	90·7% (86·4–95·1)	86·5% (80·5–92·4)	..	..
Intermediate	2–3	200 (34%)	104 (84–123)	79·8% (73·9–85·8)	40·1% (29·3–50·9)	vs 0–1	4·6 (2·8–7·4)
High	4–6	147 (25%)	63 (51–73)	52·8% (44·5–61·1)	16·1% (6·7–25·4)	vs 2–3	2·2 (1·6–3·0)
Very high	7–10	52 (9%)	31 (20–39)	18·6% (7·5–29·7)	0%† (NE)	vs 4–6	2·6 (1·8–3·7)

Lancet Oncol. 2016;S1470-2045:30029-8

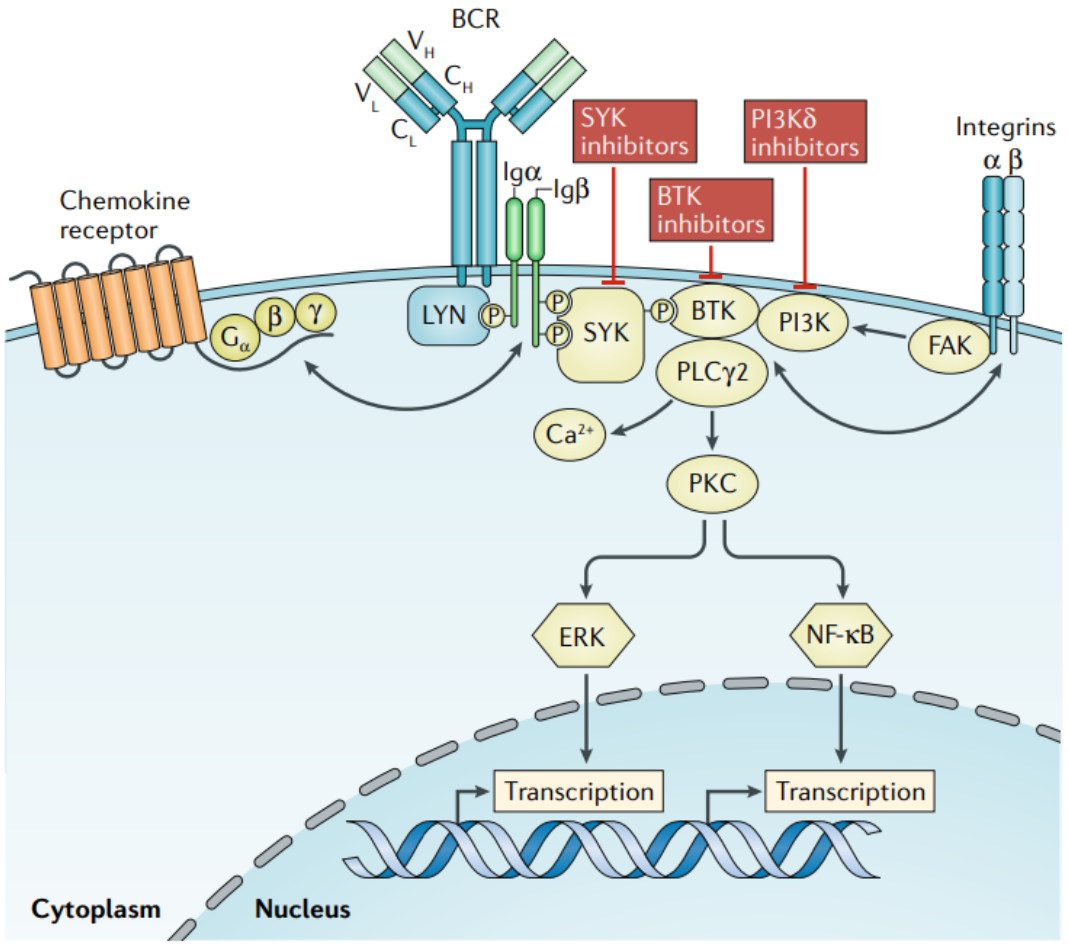
The Evolution of CLL Therapy



Burger et al. Nat Rev Clin Oncol. 2018 15 (8): 510-527

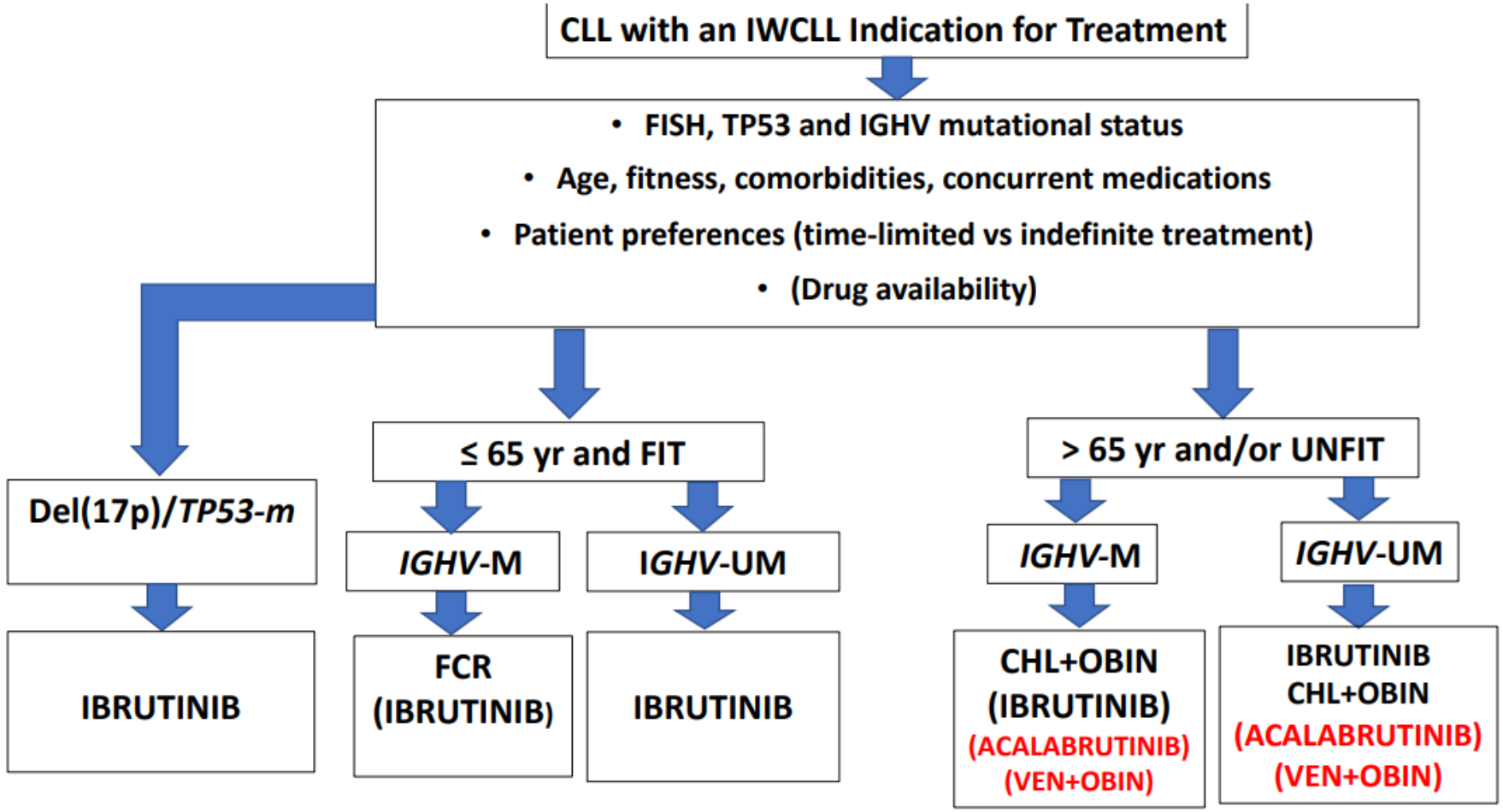
Targeted Agents in CLL

- Idelalisib – PI3K inhibitior
- Ibrutinib – BTK inhibitor
- Venetoclax – BCL2 inhibitor



Burger et al. Nat Rev Clin Oncol. 2018 15 (8): 510-527

Algorithm for CLL Treatment



Frontline Treatment Data

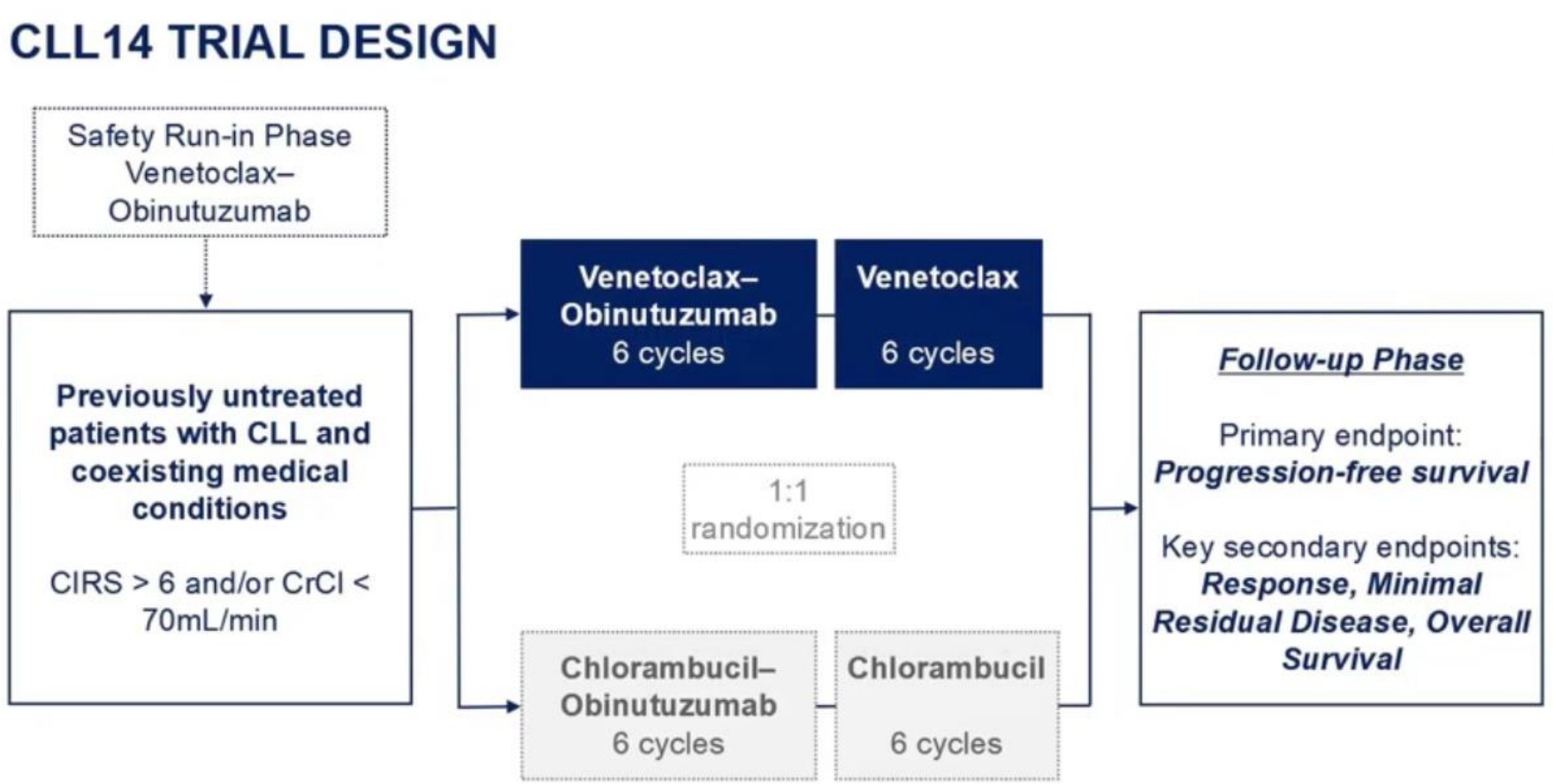
- Chlor – Ob
  - Median PFS 27 months
  - TTNT 48 months
- FCR
  - Median PFS 52 months
  - < 65, IGHV mutation, negative 17p del

- Ibrutinib
  - Burger et al, 2015 (RESONATE 2)
    - Ibrutinib vs chlorambucil (2 year OS 98% vs 85%)
    - 42% discontinuation rate at 5 years due to adverse events.
  - Shanefelt et al. 2018
    - IR vs FCR (2 year PFS 89% vs 73%)
    - Favours IR for unmutated IGHV
  - Woyach et al., 2018
    - I vs IR vs BR (2-year PFS 87% v 88% v 74%)
    - Ritux addition offered no benefit
  - ELEVATE TN
    - Acalabrutinib + G vs A vs Chlo O (PFS at 24 months 93% vs 87% vs 47%)

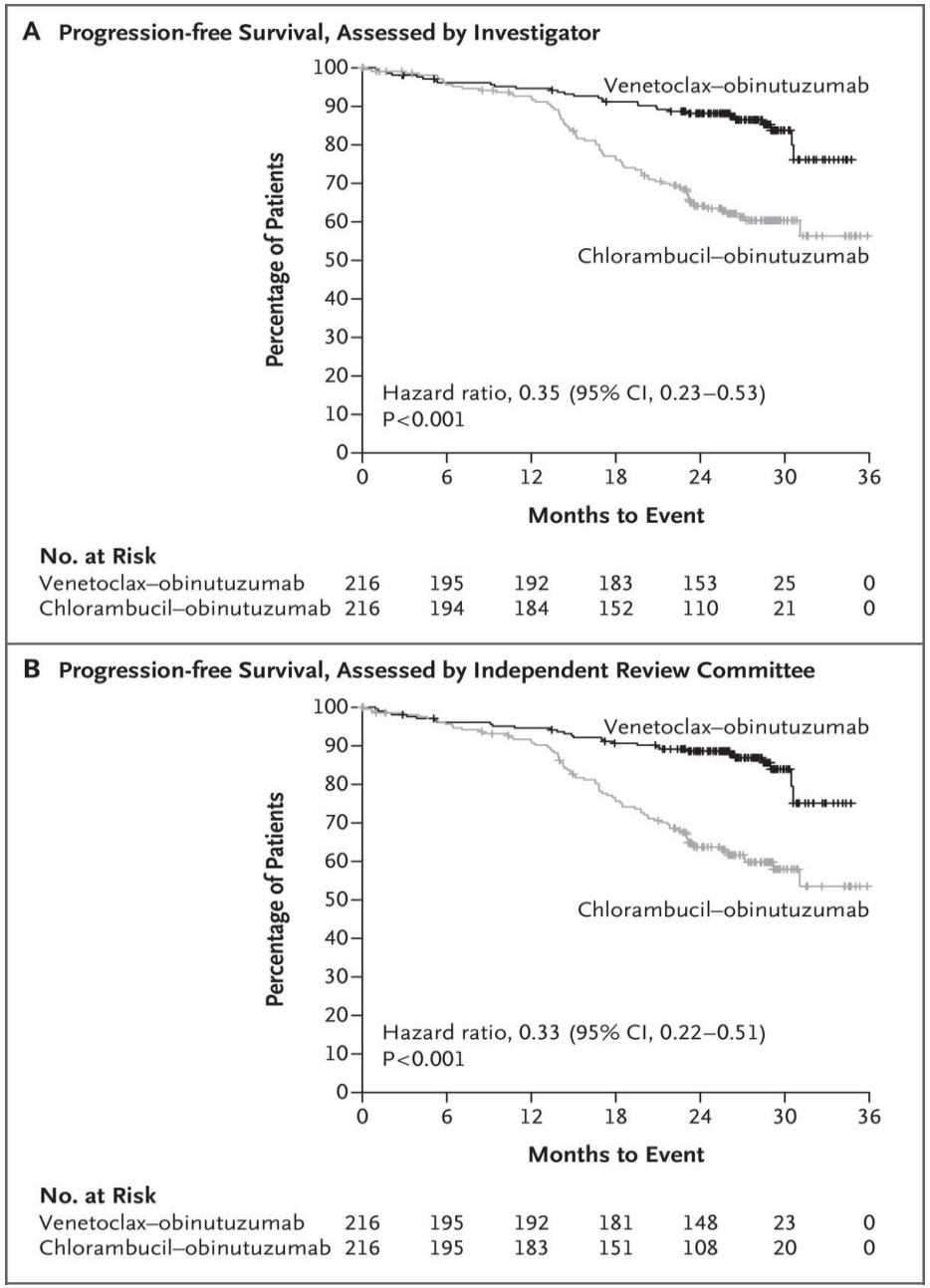
Knowledge gaps in frontline treatment

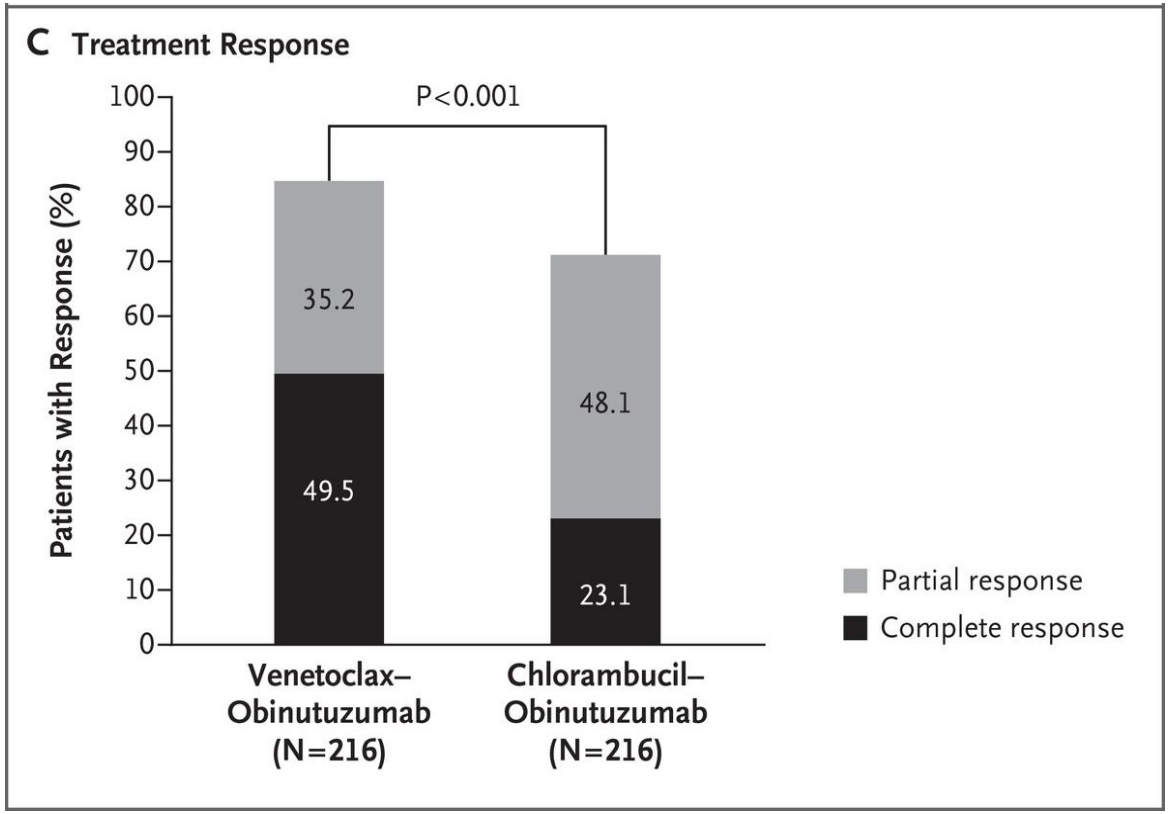
- Utility of Minimal Residual Disease status
- Ibrutinib is an indefinite treatment regimen:
  - Hope for fixed duration treatments

CLL14 – First upfront Venetoclax trial



Fischer et al. Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. NEJM 2019. 380 (23): 2225 – 2236



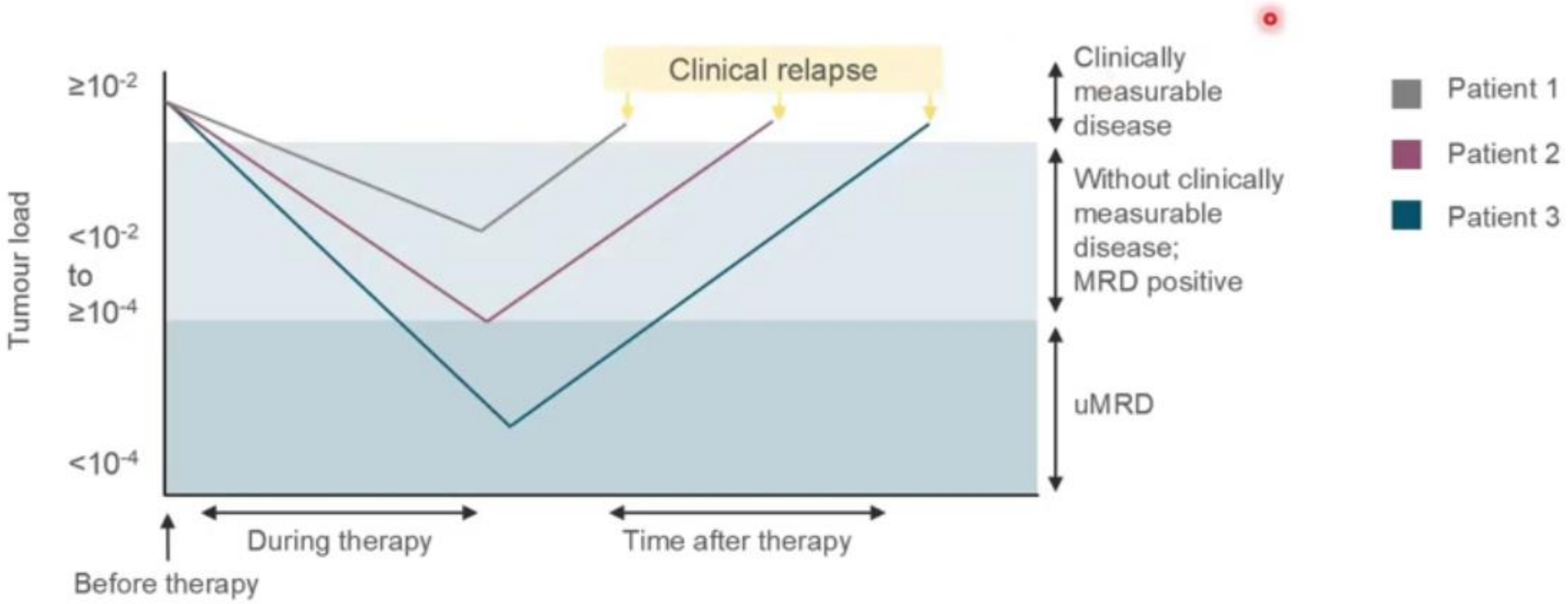


PFS at 36 months: 82% vs 50%

Fischer et al. Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. NEJM 2019. 380 (23): 2225 – 2236

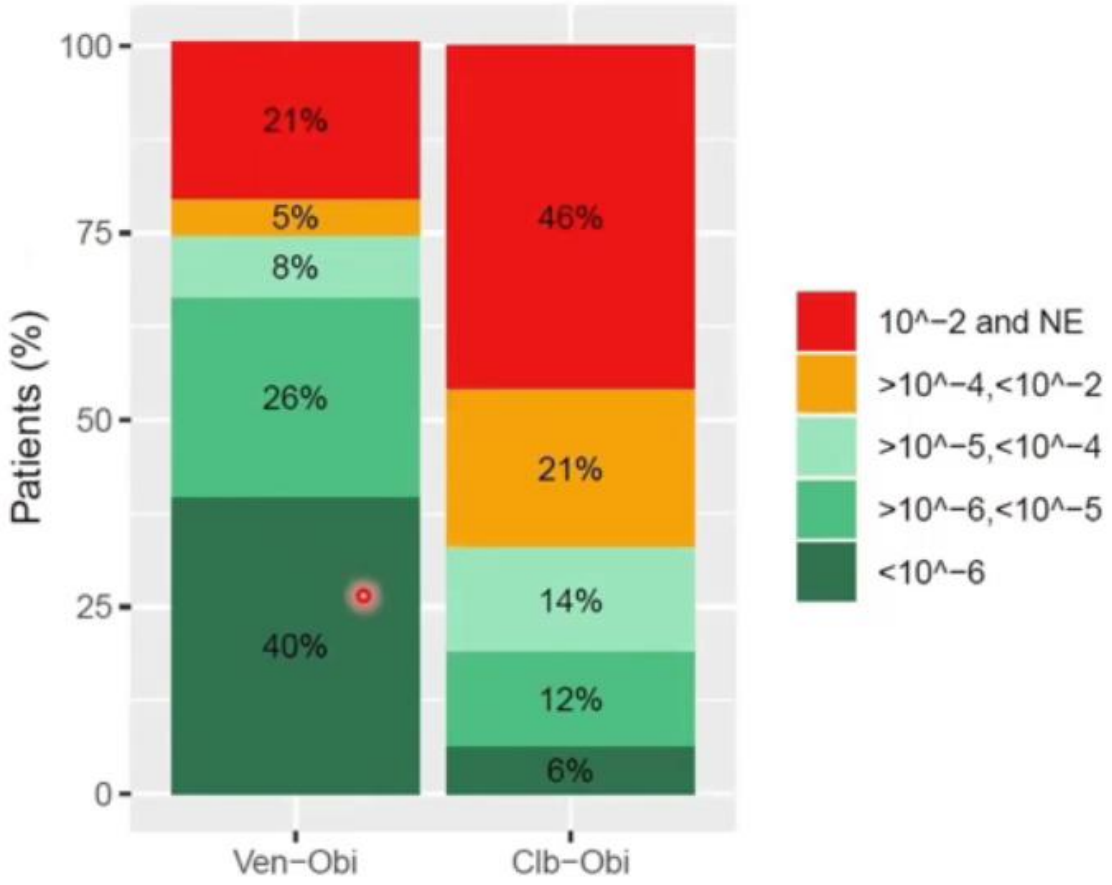
Minimal Residual Disease significance

- uMRD is a key goal of fixed-duration treatment regimens



Bottcher et al. Heatol Oncol Clin North Am. 2013. 27 (2): 267-88

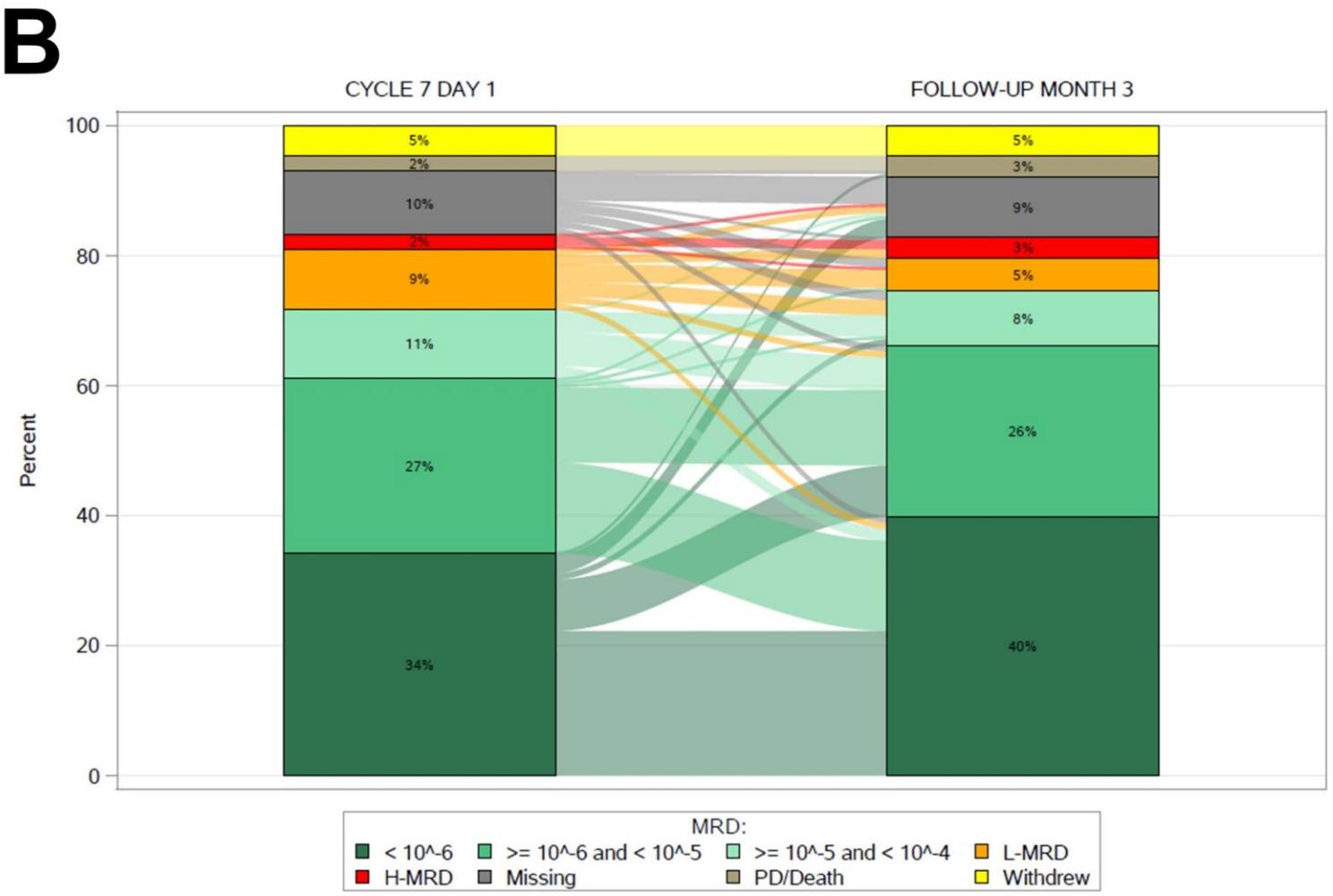
Clonal Dynamics after Venetoclax-Obinutuzumab Therapy: Novel Insights from the Randomized, Phase 3 CLL 14 Trial MRD results (CLL14 Abstract 127)



The CLL14 trial demonstrated very high rates of uMRD *after* **12 cycles of Venetoclax-Obinutuzumab**.

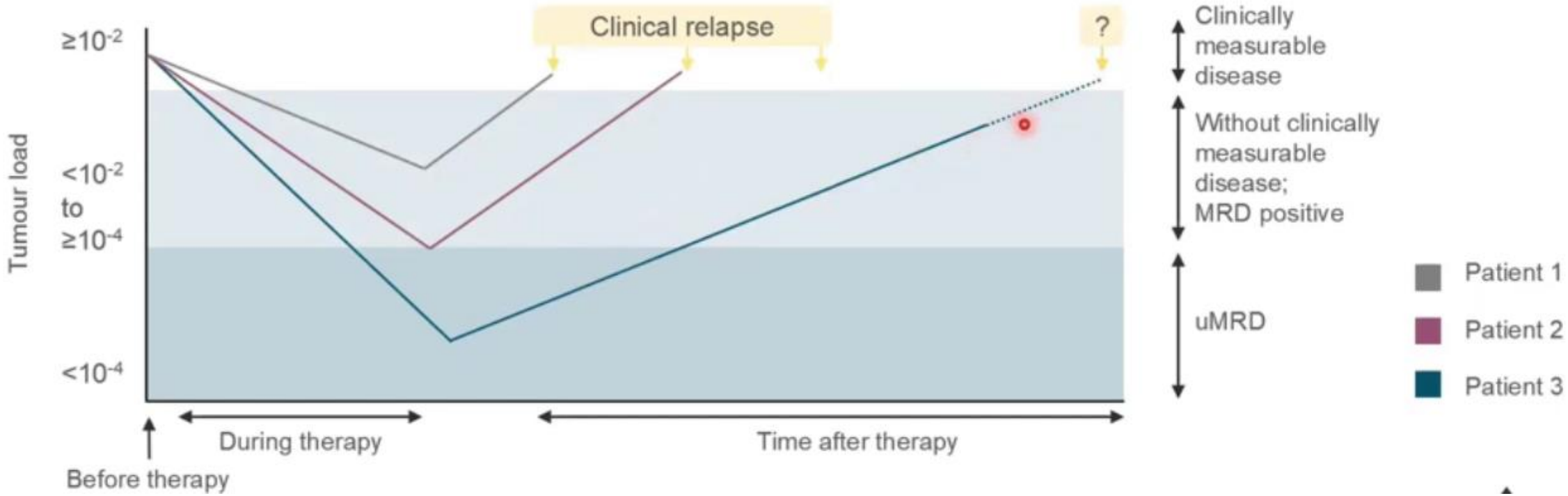
Al-Sawaf et al. ASH 2020.

MRD response deepened with continuation of Venetoclax treatment



Al-Sawaf et al. ASH 2020.

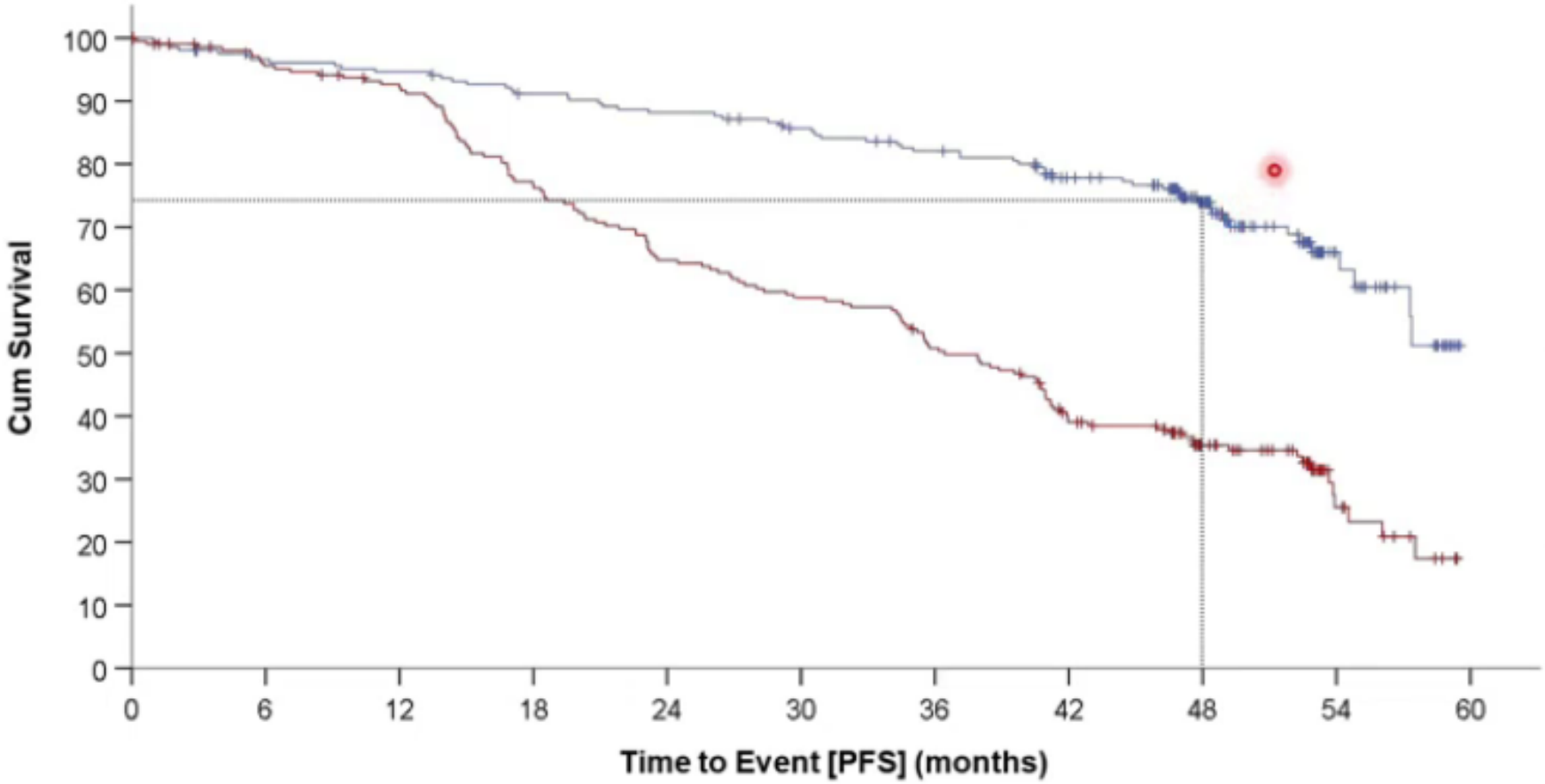
Deeper MRD modulates time after therapy



Al-Sawaf et al. ASH 2020.

4-YEAR FOLLOW-UP: PROGRESSION-FREE SURVIVAL

Median observation time 52.4 months



Median PFS

Ven-Obi: not reached

Clb-Obi: 36.4 months

4-year PFS rate

Ven-Obi: 74.0%

Clb-Obi: 35.4%

HR 0.33, 95% CI [0.25-0.45]

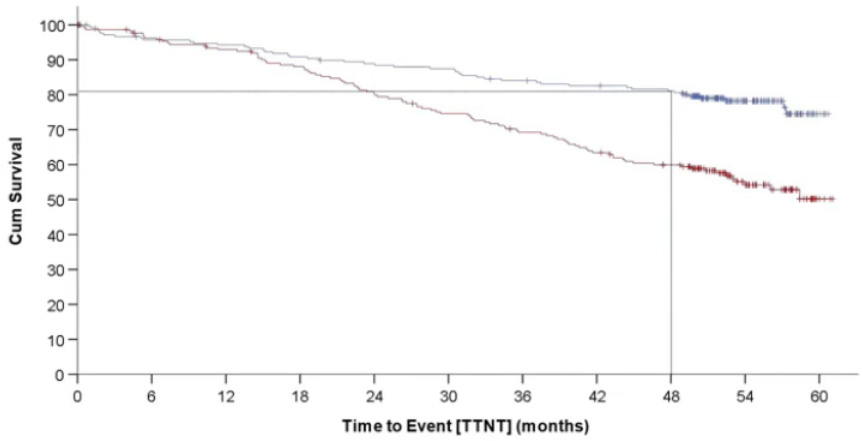
P<0.0001

Al-Sawaf et al. ASH 2020.

4-year Follow-up

4-YEAR FOLLOW-UP: TIME TO NEXT TREATMENT

Median observation time 52.4 months



Median TTNT
Ven-Obi: not reached
Clb-Obi: not reached

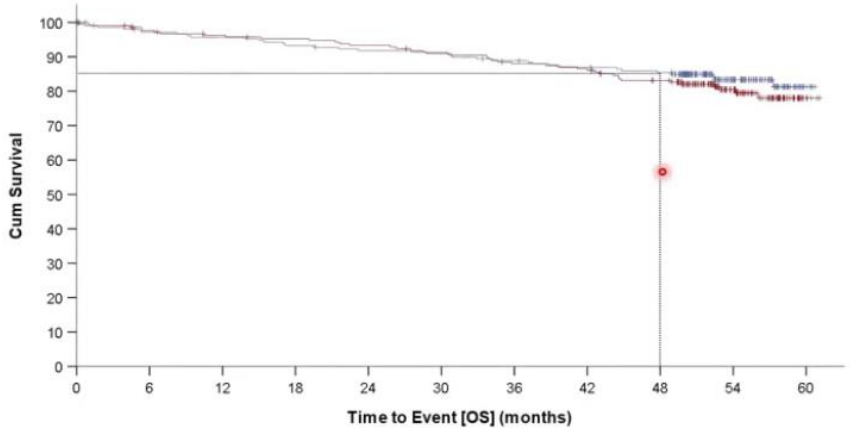
4-year TTNT rate
Ven-Obi: 81.08%
Clb-Obi: 59.9%

Next anti-leukemic therapy:
Ven-Obi: 35 PDs – 17 NLT
Clb-Obi: 122 PDs – 70 NLT

HR 0.46, 95% CI [0.32-0.65]
P<0.0001

4-YEAR FOLLOW-UP: OVERALL SURVIVAL

Median observation time 52.4 months



Median OS
Ven-Obi: not reached
Clb-Obi: not reached

4-year OS rate
Ven-Obi: 85.3%
Clb-Obi: 83.1%

HR 0.85, 95% CI [0.54-1.35]
P=0.4929

Al-Sawaf et al. ASH 2020.

Study Conclusions

- Clonal growth was lower after Ven-Obi indicating more effective MRD eradication with Ven-Obi
- **Sustained PFS benefit due to deeper MRD status** with 4-year PFS rate of 74% for Ven-Obi patients vs 35% for Chlor-Obi

Al-Sawaf et al. ASH 2020.

Ibrutinib Plus Venetoclax for First-Line Treatment of CLL/SLL: 1-Year Disease-Free Survival (DFS) Results From the MRD Cohort of the Phase 2 CAPTIVATE Study (Abstract 123)

- Ibrutinib and venetoclax have synergistic and complementary antitumor activity and act via mobilization and clearance of CLL cells leading to deep responses.
- CAPTIVATE is an international phase 2 study evaluating first line treatment with 12 cycles of combined ibrutinib + venetoclax

Wierda et al. ASH 2020

Patients (N=164)
- Previously untreated CLL/SLL
- Active disease requiring treatment per iwCLL criteria[1]
- Age <70 years
- ECOG PS 0–1

Ibrutinib lead-in
Ibrutinib 420 mg once daily
(3 cycles[a])

Ibrutinib + Venetoclax
Ibrutinib 420 mg once daily + venetoclax ramp-up to 400 mg once daily
(12 cycles[a])

MRD-guided randomization
Stratified by IGHV mutation status

Confirmed uMRD
Randomize 1:1 (double-blind)
- Placebo
- Ibrutinib

uMRD not confirmed
Randomize 1:1 (open-label)
- Ibrutinib
- Ibrutinib + Venetoclax

- **Confirmed undetectable MRD (uMRD):** defined as having uMRD ($<10^{-4}$ by 8-color flow cytometry) serially over at least 3 cycles, and undetectable MRD in both PB and BM
- **uMRD Not Confirmed:** Defined as having detectable MRD or uMRD not confirmed serially or not confirmed in both PB and BM
- **Primary endpoint:** 1-year DFS rate in patients with Confirmed undetectable MRD (uMRD) randomized to placebo vs ibrutinib
  - DFS rate: proportion of patients who remain free of MRD relapse ($\geq 10^{-2}$ confirmed on 2 separate occasions), and without disease progression or death
- **Key secondary endpoints:** rates of uMRD, response, PFS, TLS risk reduction, and safety

DFS, disease-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; TLS, tumor lysis syndrome.

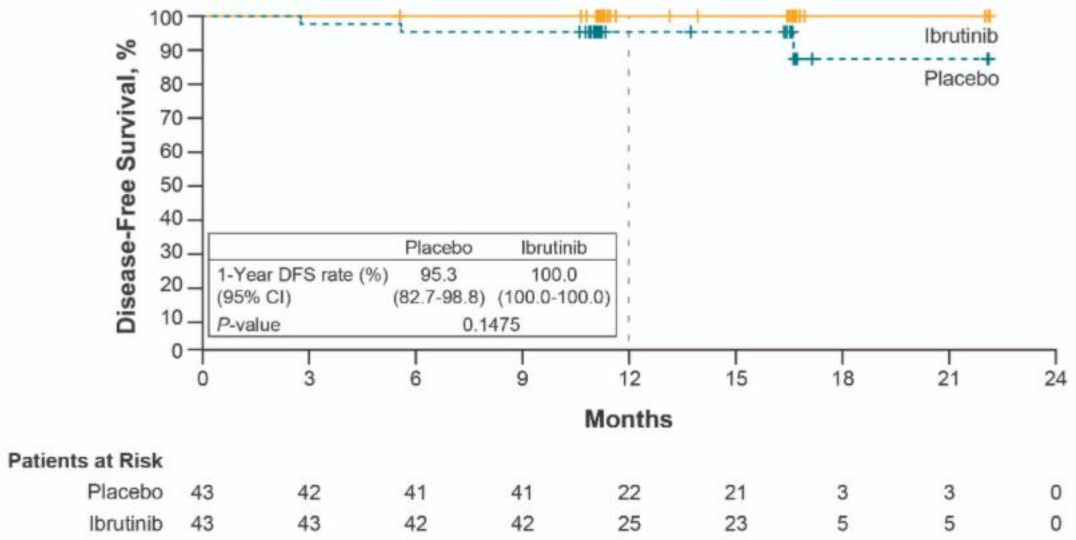
[a]1 cycle = 28 days. 1. Hallek M et al. *Blood*. 2008;111:5446-5456.

ASH 2020, CAPTIVATE-MRD; Wierda et al.

Wierda et al. ASH 2020

Disease Free Survival

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.

Table. PFS Rates by Randomized Treatment Arms

	30-Month PFS Rate % (95% CI)
Pts with Confirmed uMRD	
Placebo (n=43)	95.3 (82.7–98.8)
Ibr (n=43)	100.0 (100.0–100.0)
Pts without Confirmed uMRD	
Ibr (n=31)	95.2 (70.7–99.3)
Ibr + Ven (n=32)	96.7 (78.6–99.5)

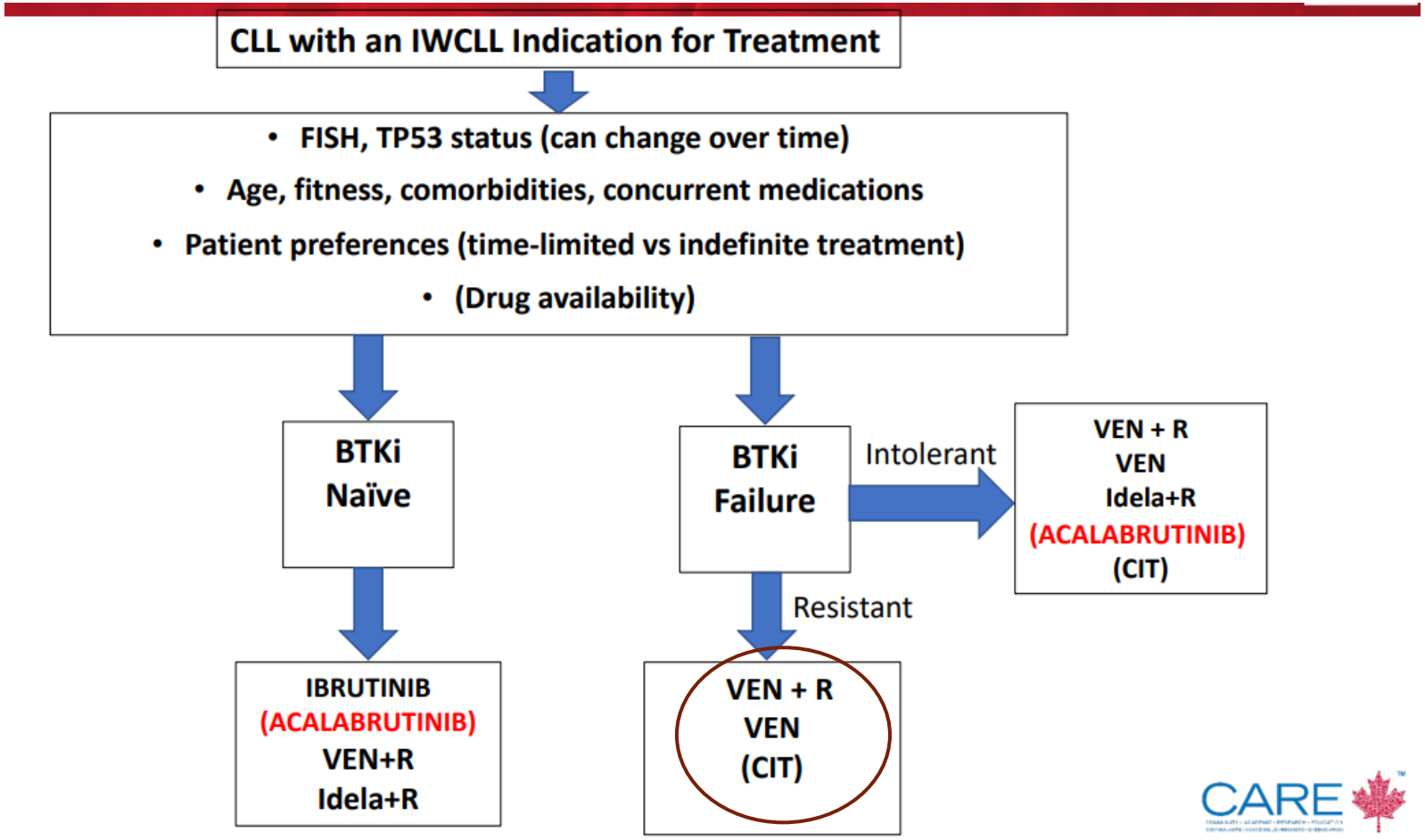
Wierda et al. ASH 2020

Study Conclusions

- 1-year DFS of 95% in patients with uMRD randomized to placebo after 12 cycles of ibrutinib + venetoclax **supports a fixed-duration treatment approach** and treatment discontinuation for those with uMRD.
- **Excellent combination option: 30-month PFS rates of > 95% across all treatment arms compare favorably to other first line fixed duration regimens** including FCR (3 year PFS 73%) and venetoclax + obinotuzumab (3 year PFS 82%)
- Ibrutinib + venetoclax provides highly concordant deep MRD remissions in BM (72%) and PB (75%) in first line CLL.
- No new safety signals emerged
- Need additional data (early data)

Wierda et al. ASH 2020

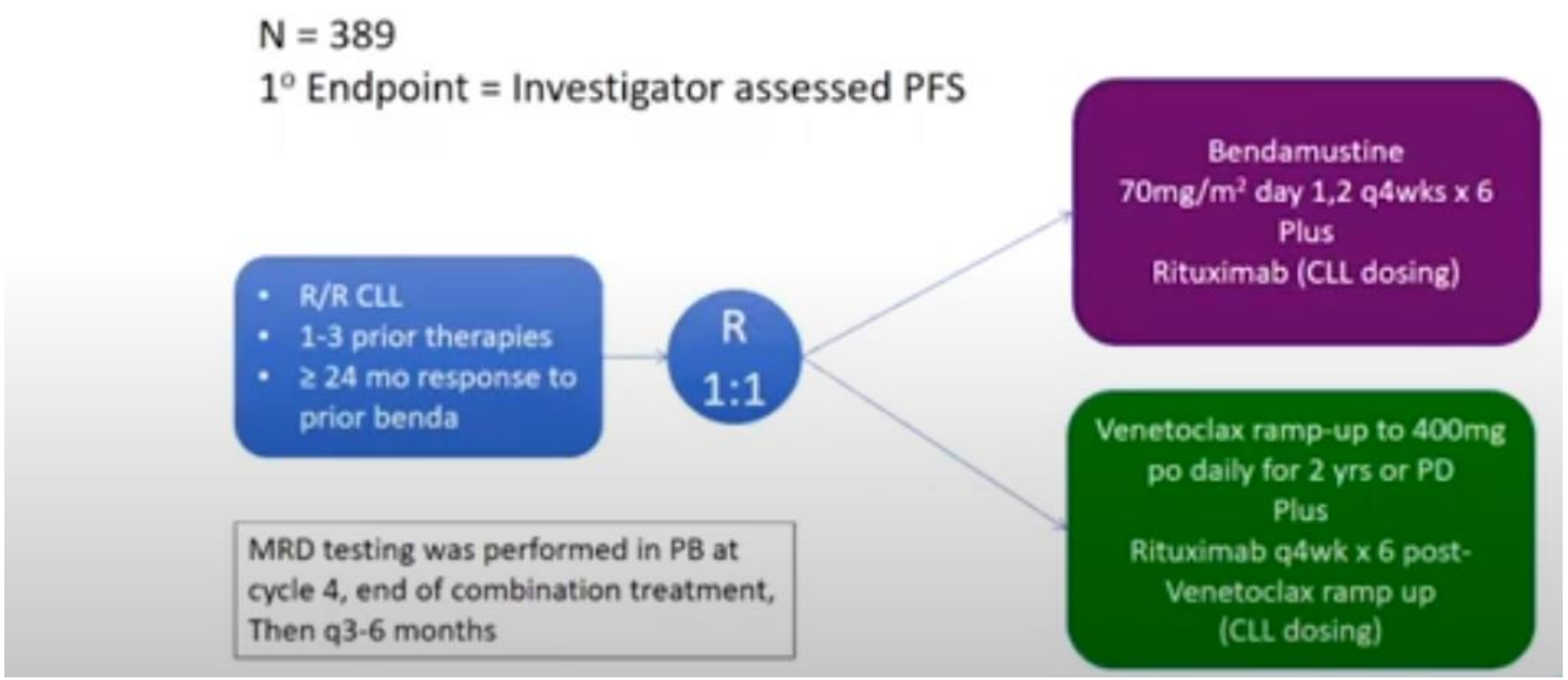
RELAPSED/REFRACTORY CLL TREATMENT ALGORITHM



Knowledge gaps in R/R CLL setting

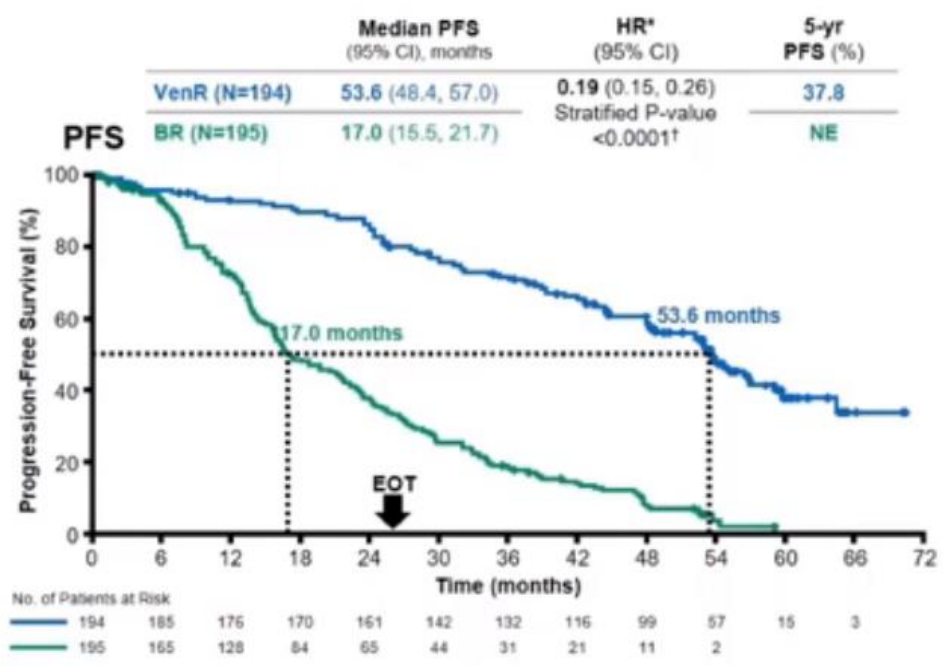
- Managing ibrutinib resistance
  - LOXO-305 in ibrutinib resistant patients (Abstract 542)
- Long-term outcomes of Ven-R in R/R setting

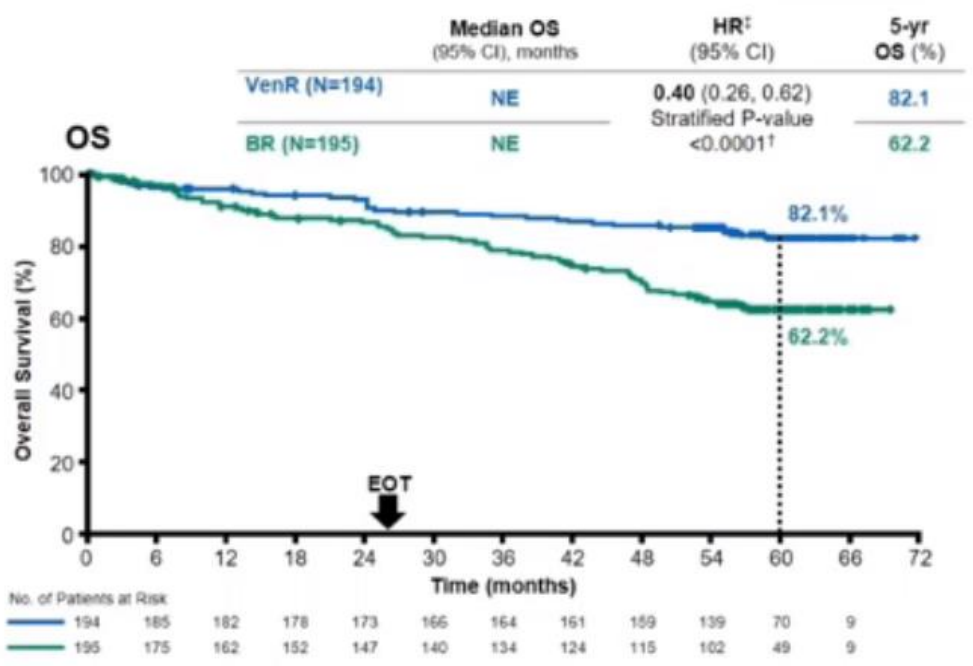
5-year analysis of MURANO Study Demonstrates Enduring uMRD in a Subset of Relapsed/Refractory Chronic Lymphocytic Leukemia (R/R CLL) Pts Following Fixed-Duration VenR Therapy (Abstract 125)



Kater et al. ASH 2020

VenR v BR (R/R CLL)





Kater et al. ASH 2020

Future Questions in CLL

- Head to head trial of ibrutinib vs acalabrutinib
  - CLL 17
- Use of MRD testing in CLL patients

Conclusions

- ASH 2020 highlights that treatment options for lymphoma are growing
- CAR-T and BiTE treatment are coming to the forefront for many aggressive and indolent NHL.
- For CLL, role of MRD and novel frontline combination treatment combinations are being explored
- In ibrutinib resistant patients, VenR shows excellent long-term efficacy and safety data.

Thank you!