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Indolent and Mantle Cell Lymphoma: Updating the Toolbox, Including and Beyond Anti-CD20 Antibodies

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Overview

- Current landscape of treatment options for iNHL and MCL
- Recently approved treatments/modalities
- Emerging/future therapies

Follicular lymphoma

Follicular Lymphoma

- 2nd most common non-Hodgkin lymphoma in The United States

- Prototype of low grade lymphomas
  Indolent course with median survival several decades
  Waxing and waning course with **inevitable relapse**
  Incurable

- Increases with age
  Median age 6th decade of life

25% of patients are <40 years

- Risk of transformation over time is 2-3% per year

GELF/NCCN Criteria for Treatment: High tumor burden vs. Low tumor burden

Lymph node/radiographic findings:

- Lymph nodes or tumor mass > 7cm
- Nodes > 3 cm in 3 distinct areas
- Symptoms related to organ compression, pleural effusion/ascites, splenic enlargement, renal/liver/bone involvement

- Biologic criteria:
  - Elevated LDH or B2M
  - Cytopenias due to marrow involvement
  - Lymphocytosis
- Symptoms
  - B symptoms, pruritus, depressed performance status
- Time-dependent criteria
  - Lymphoma progression over past 3 months

See Table 2 Smith ASH Ed Book 2013; Salles Int J Hematol 2012 96: 544

FL survival is improving for most patients

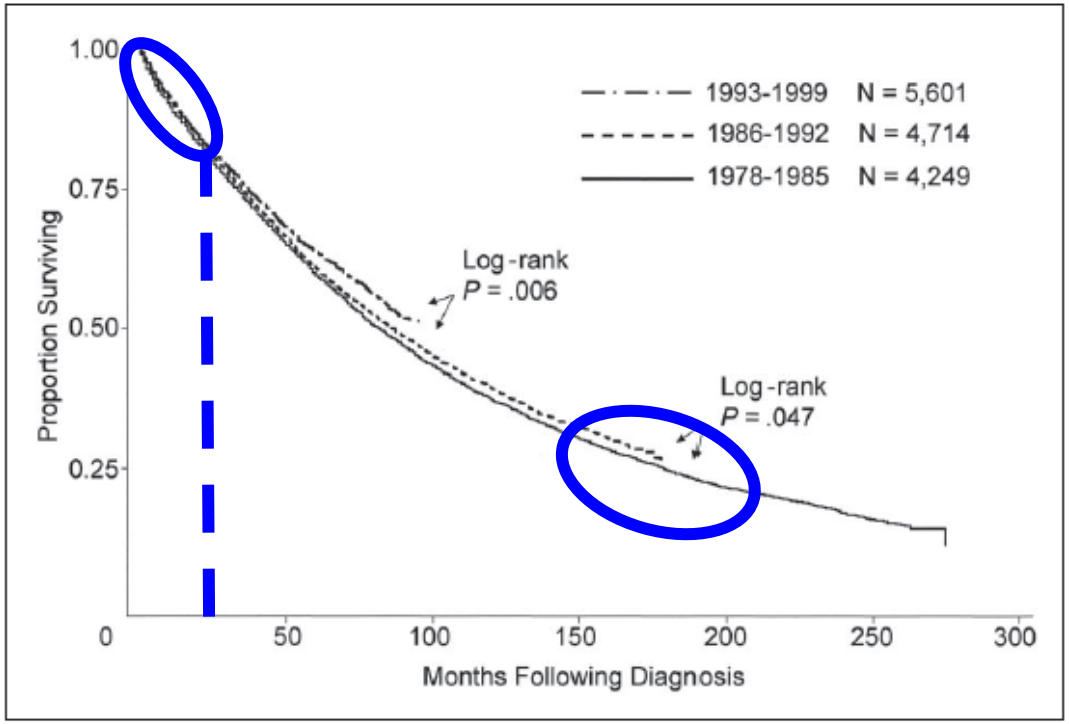

Fig 1. Kaplan-Meier survival curves of follicular lymphoma patients by diagnosis era (Surveillance, Epidemiology, and End Results–9; 1983 to 1999).

1990-1999

- **Relative 5-year survival 74%**
- **Relative 10-year survival 51%**

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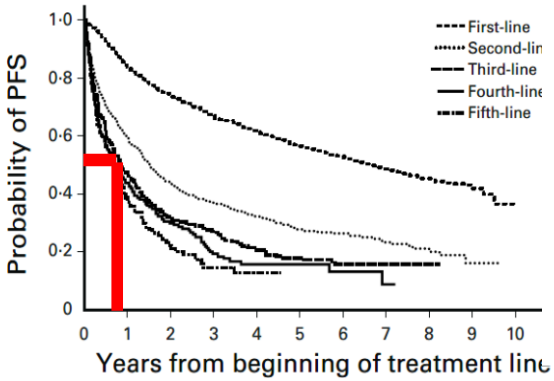
Swenson, et al., J Clin Oncol 23:5019-5026, 2005

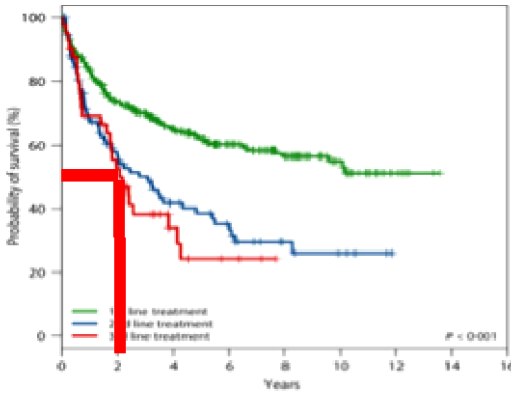
Follicular lymphoma snapshot: outcome after relapse

Median survival for follicular lymphoma approaches 20 years, but…



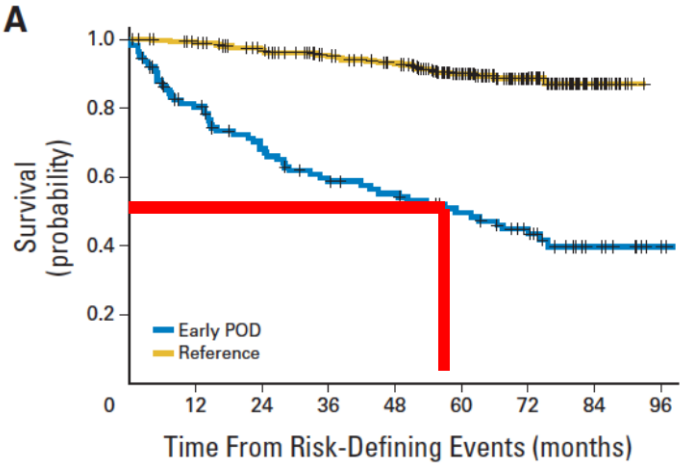
Link et al. *BJH*, 2018; 184: 660-63

PFS declines with each subsequent relapse



Rivas-Delgado et al. *BJH* 2018; 184: 753-59

OS declines with each subsequent relapse



Casulo J Clin Oncol. 2015 Aug 10;33(23):2516-22

Early relapse (POD24) predicts 5y OS of 50%

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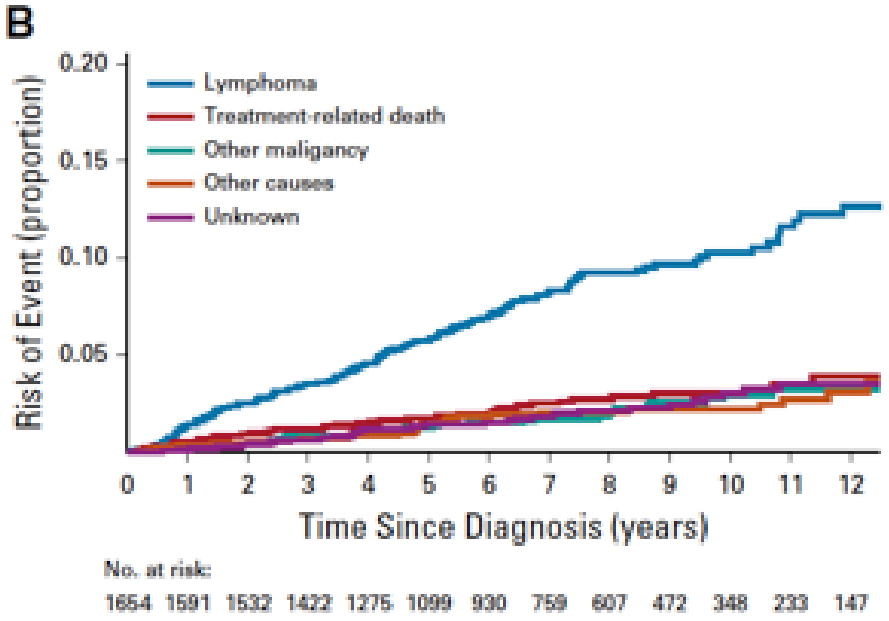
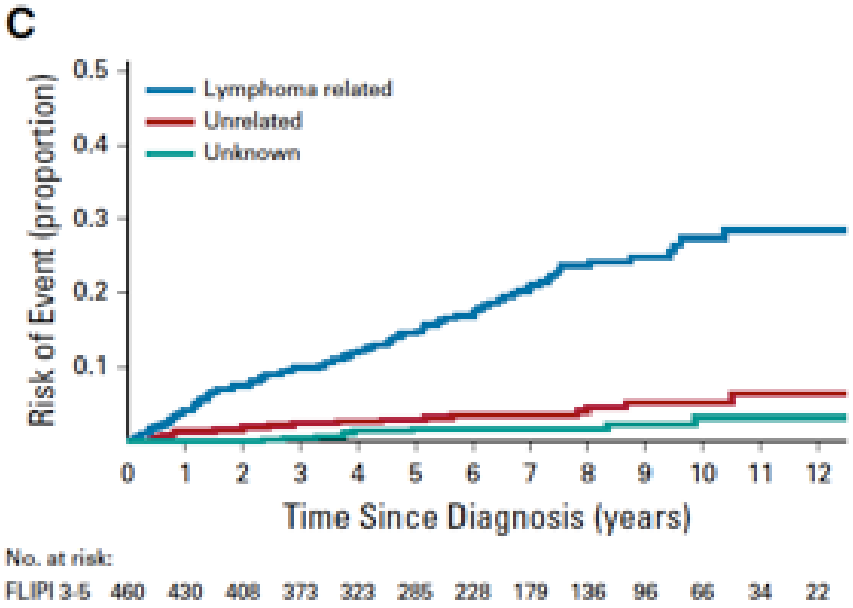
FL remains important cause of death



All patients



FLIPI 3-5

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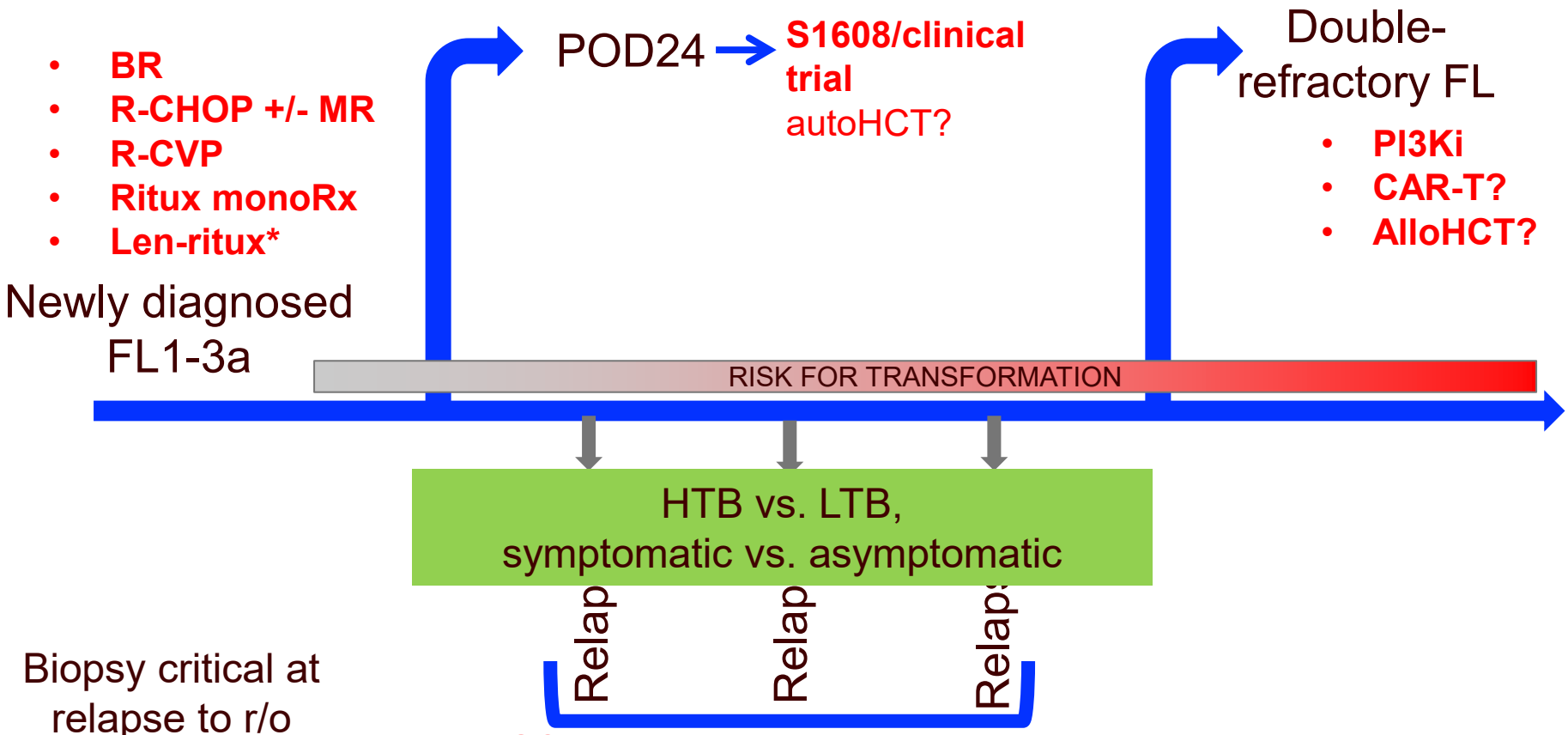
Sarkozy J Clin Oncol 2019 Jan 10;37(2):144-152

Relapsed follicular lymphoma: key considerations

- Wait until symptomatic
- No data on sequencing
- There are a number of options influenced by
  - Time to relapse
  - Likelihood of transformation
  - Prior therapy
- Toolbox includes:
  - Anti-CD20 monoclonal antibodies
  - PI3K inhibitors, EZH2 inhibitors, immunomodulatory agents
  - Stem cell transplant

FL: Clinical categories and treatment options



Biopsy critical at relapse to r/o transformation

- ASCT
- Benda + Obinu or Ritux
- Len-rituximab
- PI3Ki

- Radiation therapy Radioimmunotherapy
- Ritux monoRx
- Tazemetostat

*not approved
HTB = high tumor burden
LTB = low tumor burden
POD24 = early progression of disease w/i 24m of initial treatment

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March 2021: Axi-cel approved for r/r FL with ≥ 2 lines of therapy (ZUMA-5)

Patient Enrollment

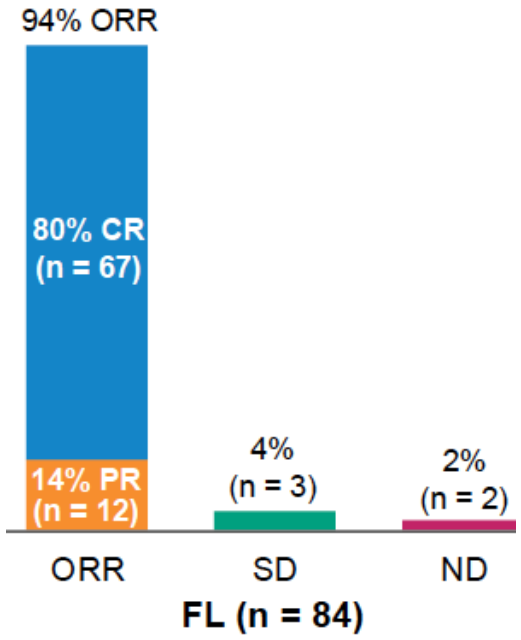
↓

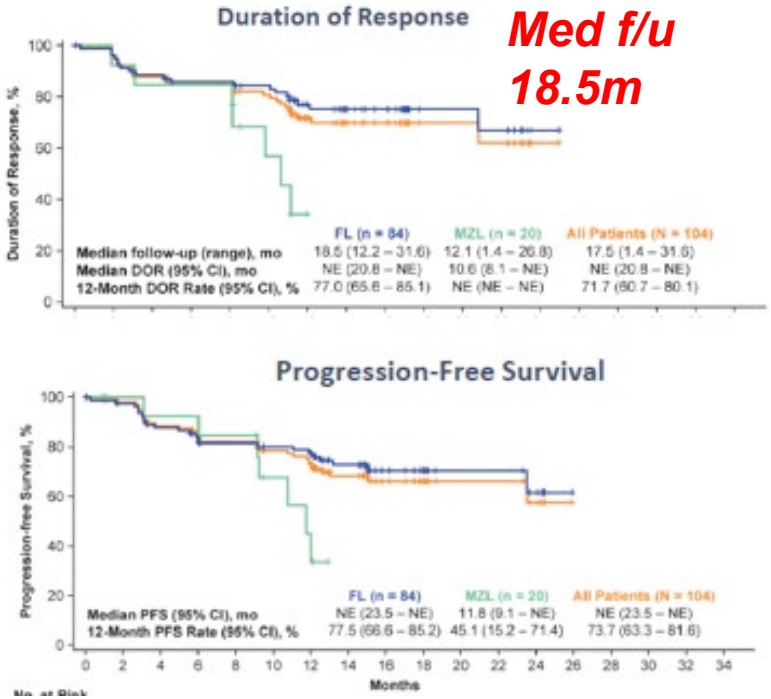
Flu/Cy conditioning

↓

Axi-cel 2 x 10^6/kg

Primary endpoint: ORR





Figures and data courtesy of Caron Jacobsen, MD from ASH 2020

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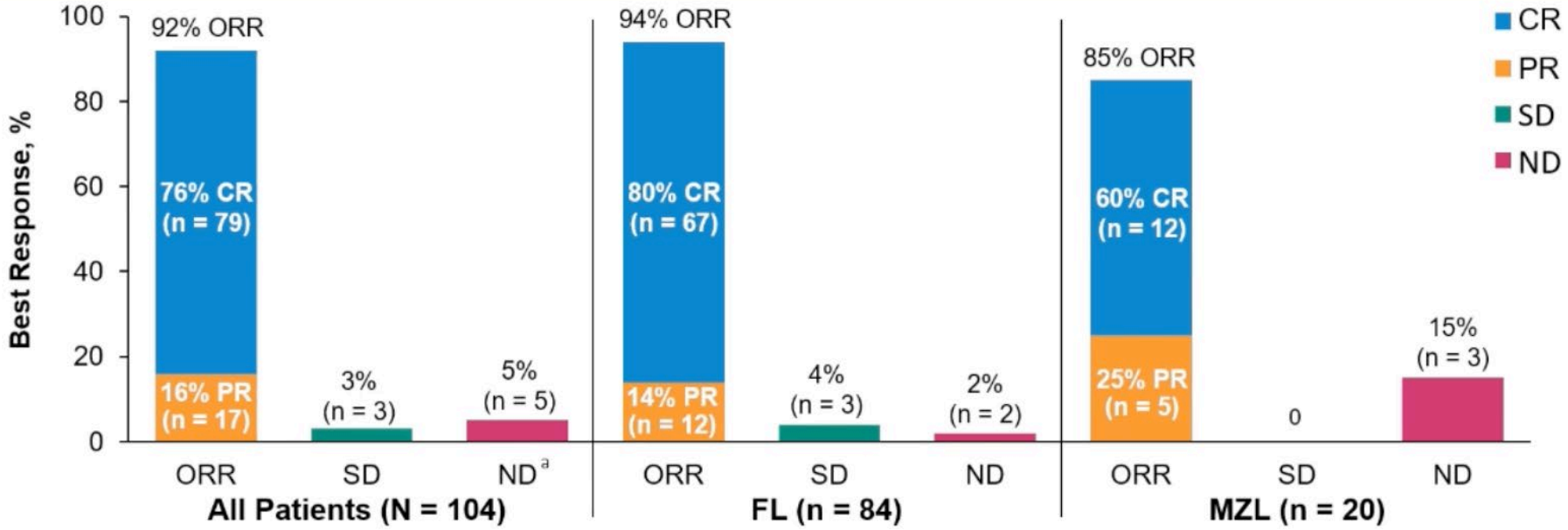
ZUMA-5: Response for FL and MZL

ORR by IRRC Assessment Was 92% (95% CI, 85 – 97); CR Rate Was 76% (95% CI, 67 – 84)



- The median time to first response was 1 month (range, 0.8 – 3.1)
- Among the 25 patients with FL who initially had a PR, 13 (52%) subsequently converted to a CR after a median of 2.2 months (range, 1.9 – 11.2)

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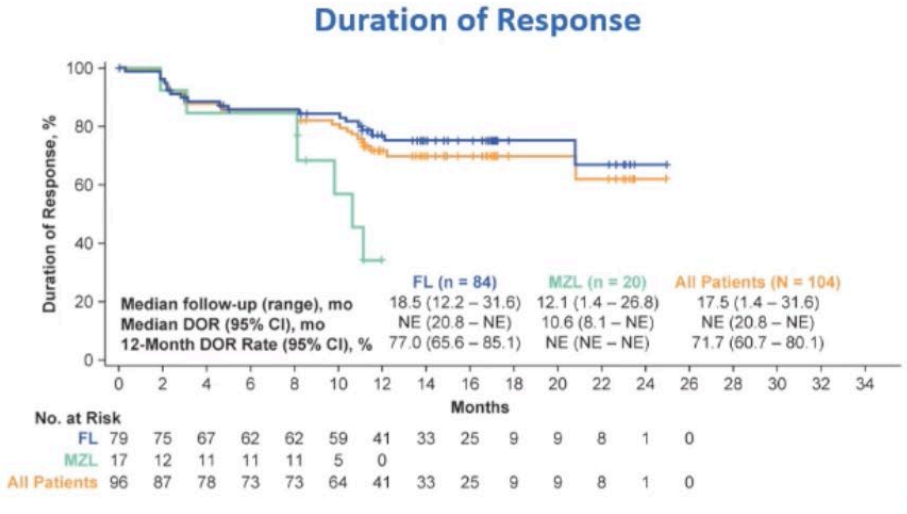
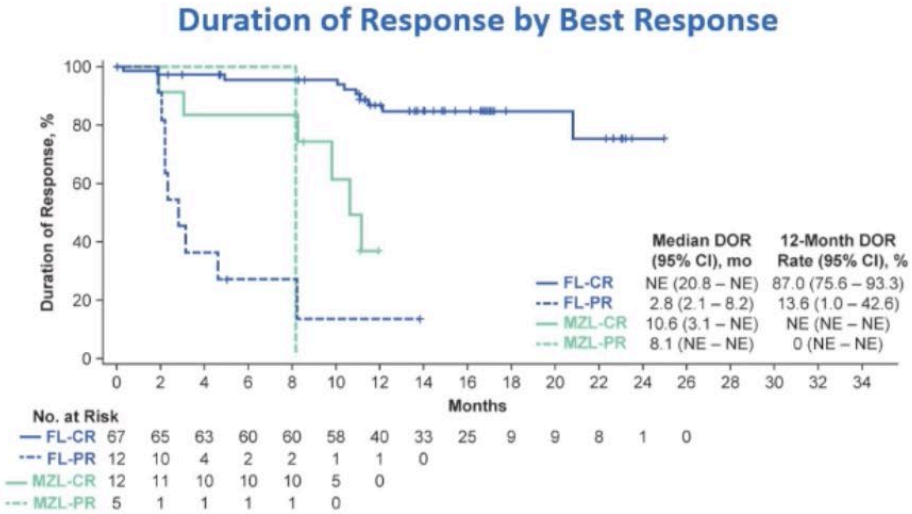
Jacobson ASH 2020 Abstract 700

ZUMA-5: Duration of response for FL and MZL

Duration of Response





Median f/u 17.5m
All 151 pts received intended treatment

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ZUMA-5: CRS and ICANS for FL and MZL

Parameter	FL (n = 124)	MZL (n = 22)	All Patients (N = 146)
CRS, n (%)[a]			
Any grade	97 (78)	22 (100)	119 (82)
Grade ≥ 3	8 (6)	2 (9)	10 (7)
Most common symptoms of any grade, n/n (%)			
Pyrexia	94/97 (97)	20/22 (91)	114/119 (96)
Hypotension	39/97 (40)	10/22 (45)	49/119 (41)
Median time to onset (range), days	4 (1 – 15)	4 (1 – 9)	4 (1 – 15)
Median duration of events (range), days	6 (1 – 27)	6 (2 – 14)	6 (1 – 27)
Patients with resolved events, n/n (%)	96/97 (99)[b]	22/22 (100)	118/119 (99)[b]
Neurologic events, n (%)[a]			
Any grade	70 (56)	17 (77)	87 (60)
Grade ≥ 3	19 (15)	9 (41)	28 (19)
Most common events of any grade, n/n (%)			
Tremor	36/70 (51)	9/17 (53)	45/87 (52)
Confusional state	28/70 (40)	7/17 (41)	35/87 (40)
Median time to onset (range), days	7 (1 – 177)	7 (3 – 19)	7 (1 – 177)
Median duration of events (range), days	14 (1 – 452)	10 (2 – 81)	14 (1 – 452)
Patients with resolved events, n/n (%)	67/70 (96)	14/17 (82)	81/87 (93)

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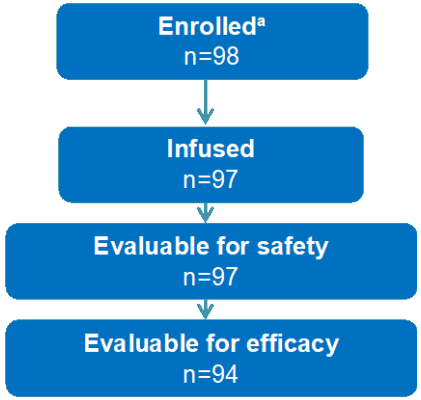
ELARA: Tisa-cel in r/r FL



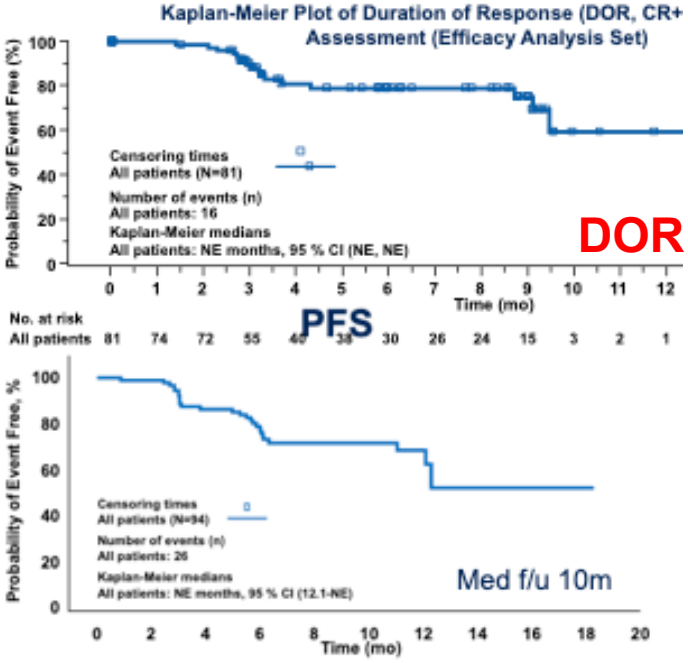
Vast majority of patients received cellular product

Lymphodepleting therapy could be Flu/Cy or bendamustine

18% of patients received tisagenlecleucel infusion in outpatient setting

Response Rate, %	Patients Evaluable for Efficacy[b] (n=94)
CR	66.0[b]
PR	20.2
ORR (CR+PR)	86.2

Primary endpoint: CR



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Schuster ASCO 2021 Abstract 7508: Efficacy and safety of tisagenlecleucel (Tisa-cel) in adult patients (Pts) with relapsed/refractory follicular lymphoma (r/r FL): Primary analysis of the phase 2 Elara trial

ELARA: phase 2 international trial of tisa-cel in FL (n=98)

Adverse Events, n (%)	Treated Patients N=97
Any AE (all grade)	92 (94.8)
AEs suspected to be drug-related	71 (73.2)
Any SAE	37 (38.1)
Suspected to be drug-related	26 (26.8)
Any grade 3/4 AE	68 (70.1)
Suspected to be drug-related	37 (38.1)
Death	3 (3.1)
Deaths due to study indication	3 (3.1)
Deaths within 30 days post infusion	0

	Treated Patients N=97	
AESI (within 8 weeks of infusion)	All grades, %	Grade ≥3, %
Cytokine release syndrome[a]	48.5	0
Serious neurological adverse reactions	9.3	1.0
Infections	18.6	4.1
Tumor lysis syndrome	1.0	0
Prolonged depletion of B cells/ agammaglobulinemia	9.3	0
Hematologic disorders including cytopenias		
Neutropenia[b,c]	28.9	24.7
Anemia[b]	22.7	12.4
Thrombocytopenia[b]	15.5	8.2

Promising safety profile

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Fowler ASH 2020 abstract 1149

Comparing cytokine release syndrome and neurotoxicity

	All grades	≥ Gr 3
ELARA		
CRS	48.5%	0%
NT/ICANS	9.3%	1%
Time to onset	8 days	
ZUMA-5		
CRS	78%	6%
NT/ICANS	56%	15%
Time to onset	4 days	

In ELARA trial:
Most CRS (75%) and all neurotoxicity (100%) occurred in patients with bulky disease

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Key patient characteristics in ELARA and ZUMA-5 trials

ELARA

	All Patients (N=97)
Median age (range), y	57.0 (29-73)
≥65 y, n (%)	24 (24.7)
ECOG PS, n (%)	
0	56 (57.7)
1	37 (38.1)
Bulky disease at study entry,[c] n (%)	63 (64.9)
Median no. of prior therapies (range)	4 (2-13)
POD24 from first anti-CD20 mAb-containing therapy,[d] n (%)	58 (59.8)
Refractory to ≥2 regimens,[f] n (%)	74 (76.3)
Prior therapy	
Anti-CD20 mAb and alkylating agents,[h] n (%)	63 (64.9)
PI3K inhibitors, n (%)	20 (20.6)
Lenalidomide and rituximab, n (%)	16 (16.5)

ZUMA-5

Characteristic	FL (n = 124)
Median age (range), years	60 (34 – 79)
≥ 65 years, n (%)	38 (31)
Male, n (%)	
ECOG 1, n (%)	46 (37)
Stage III-IV disease, n (%)	106 (85)
≥ 3 FLIPI, n (%)	54 (44)
High tumor bulk (GELF criteria), n (%)[a]	64 (52)
Median no. of prior therapies (range)	3 (1 – 10)[b]
≥ 3, n (%)	78 (63)
Refractory disease, n (%)[c]	84 (68)
POD24 from first anti-CD20 mAb-containing therapy, n (%)[d]	68 (55)
Prior autologous SCT, n (%)	30 (24)

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Predictors of Response and Toxicity

Dana-Farber Cancer Institute

The Jimmy Fund

PRE-TREATMENT POST-TREATMENT

PATIENT

T-CELLS

TUMOR

Improved Response

- Low tumor burden, low LDH
- Low pretreatment inflammatory markers
- Absence of medical comorbidities
- Lack of need for bridging therapy

- Proportion of CCR7+ and other early memory T-cells in the CAR product
- Faster doubling time *in vitro*
- Higher CAR T-cell peak to tumor burden ratio

- Absence of CD58 mutations
- Low tumor MDSCs
- High TILs
- Absence of MYC overexpression

Increased Toxicity

- High tumor burden, pretreatment LDH
- High pretreatment inflammatory markers
- ? High pretreatment monocyte levels

- High peak CAR T-cell levels
- High peak cytokine levels
- Markers of DIC (including fibrinogen levels)
- Early CRS

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Slide courtesy of Caron Jacobsen, MD

Which indolent lymphoma patients should be considered for CAR-T?

- Patient identification is key!
  - The vast majority of patients with FL do well without aggressive treatments
  - **Disease characteristics**:
    - early POD, double refractory, multiple prior regimens with sequentially shorter PFS
  - **Patient characteristics**:
    - No upper age limit, adequate cardiac/renal/pulmonary/neurologic reserve
  - Bulky disease and need for bridging therapy are poor prognostic factors
- No clear difference between axi-cel and tisa-cel in terms of efficacy in FL
- Marginal zone lymphoma needs more data

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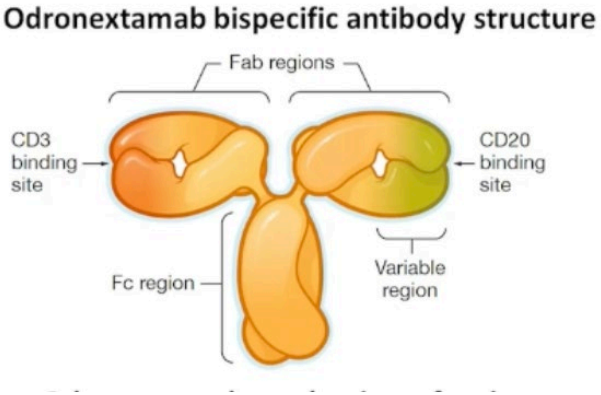
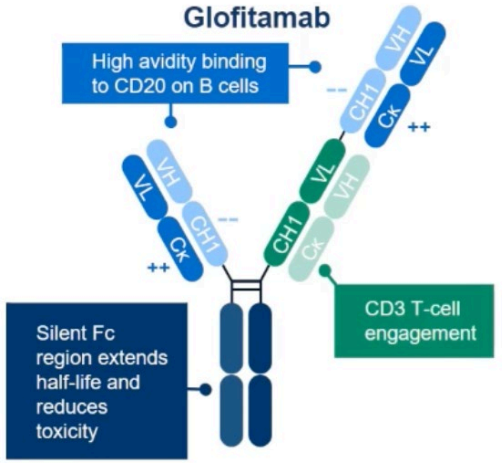
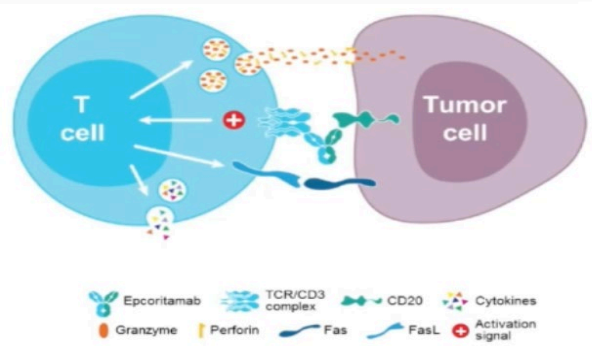
Very short follow up so far: is this a cure??

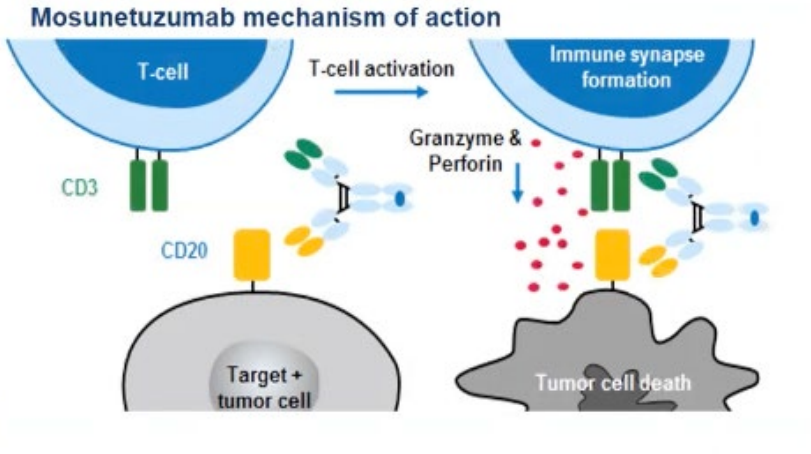
Emerging class of agents: bispecific antibodies







Distinct CD20 epitope



Olszewski ASH 2020 #401
Matasar ASH 2020 #2096
Philips ASH 2020 #1184

REGN1979 Bannerji ASH 2020 #400;
Glofitamab Hutchings ASH 2020 #403
Epcoritamab Hutchings ASH 2020 #402

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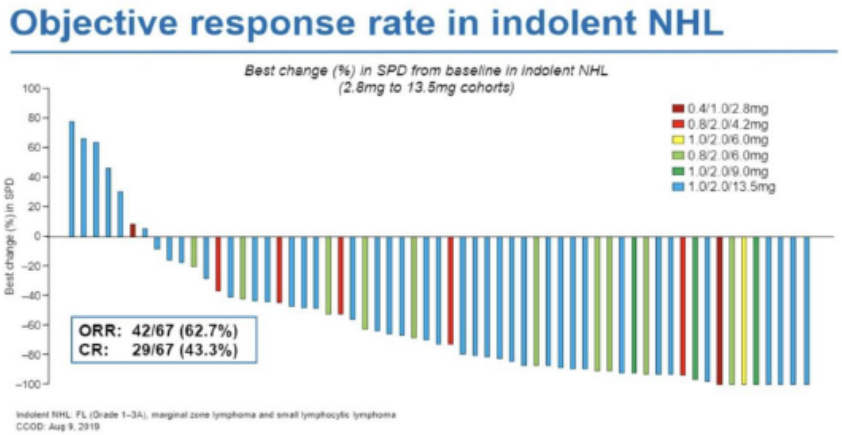
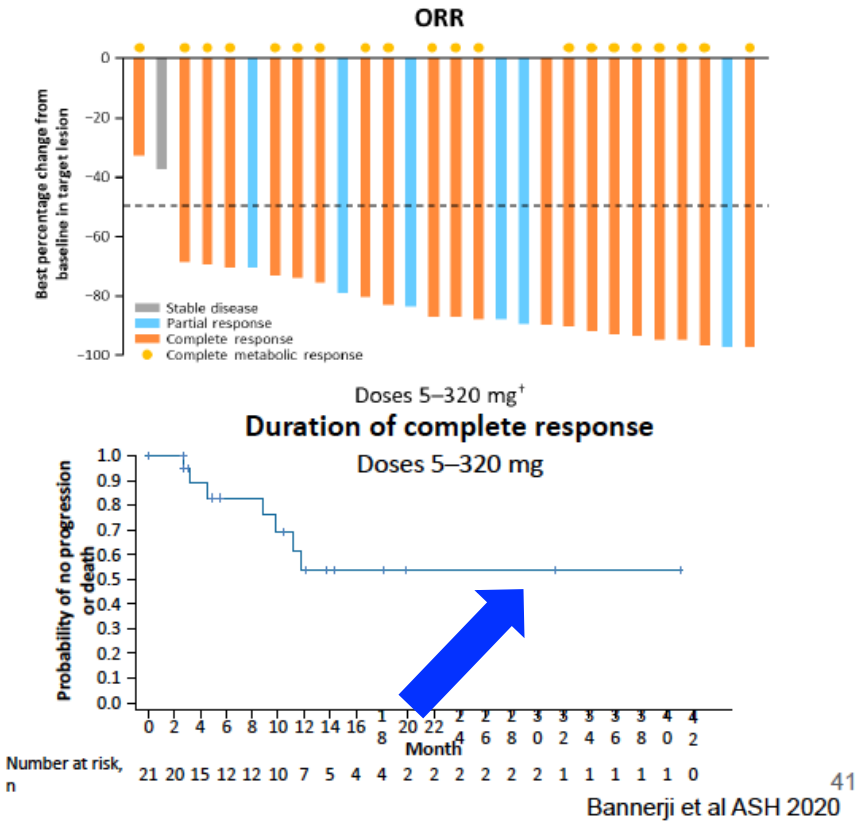
Bispecific antibodies in indolent lymphomas

Mosunetuzumab



Schuster et al ASH 2019

Odronextamab (REGN1979)



Bannerji et al ASH 2020

Dana-Farber Cancer Institute

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Slide courtesy of Caron Jacobson, MD

Mantle cell lymphoma

Mantle Cell Lymphoma

- 6% of all NHL cases
- Median age: 58 years; M:F ratio: 3:1
- Diagnosis:
  - Genetic hallmark: *t(11;14)*
  - CD20+CD5+
- **Incurable**
- Typically advanced stage
  - B symptoms: < 50% cases
  - 90% extranodal involvement: BM, blood, liver, GI
  - Generalized adenopathy: 70% to 90%
  - CNS involvement at relapse: 4% to 22% (↑ with blastoid)
- Survival is improving
  - Older literature would cite 3-5 years

Lichtman MA. *Williams Hematology, 7th Ed*. The McGraw-Hill Companies; 2006.

MCL is a heterogeneous disease

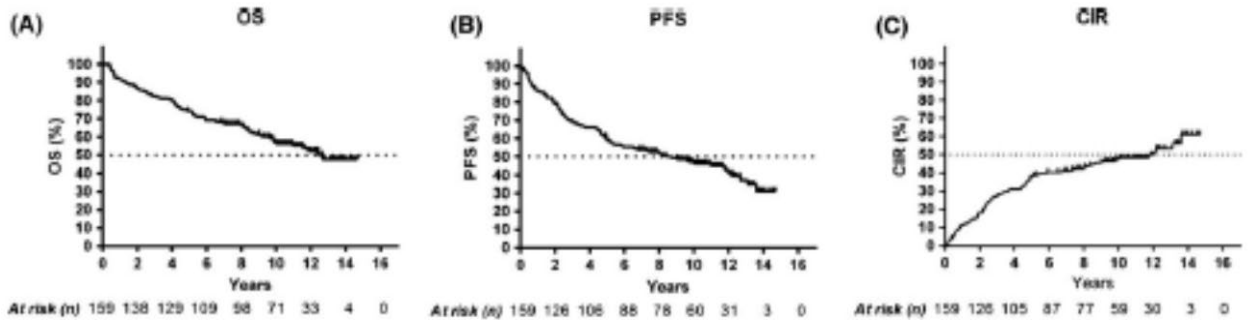
- Morphologic variants
  - Classical
  - Blastoid
- Clinical variants
  - “indolent” MCL
- Mantle cell IPI (MIPI)
- P53 status is increasingly important
- Treatment is often based on
  - Age
  - Comorbidities (i.e. “fit” vs. “not fit”)

Induction → **Consolidation** → **+/-Maintenance**

Mantle cell lymphoma: initial treatment approach

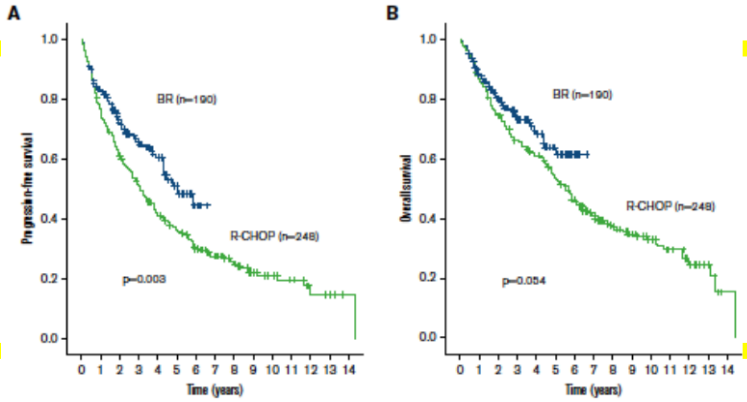
INDUCTION **CONSOLIDATION** **MAINTENANCE**

YOUNG/FIT



15-year f/u of Nordic MCL2: excellent outcomes but continuous relapse

OLDER/UNFIT



3-yr PFS 77% and OS 82% in younger patients with BR

R x 2-3y

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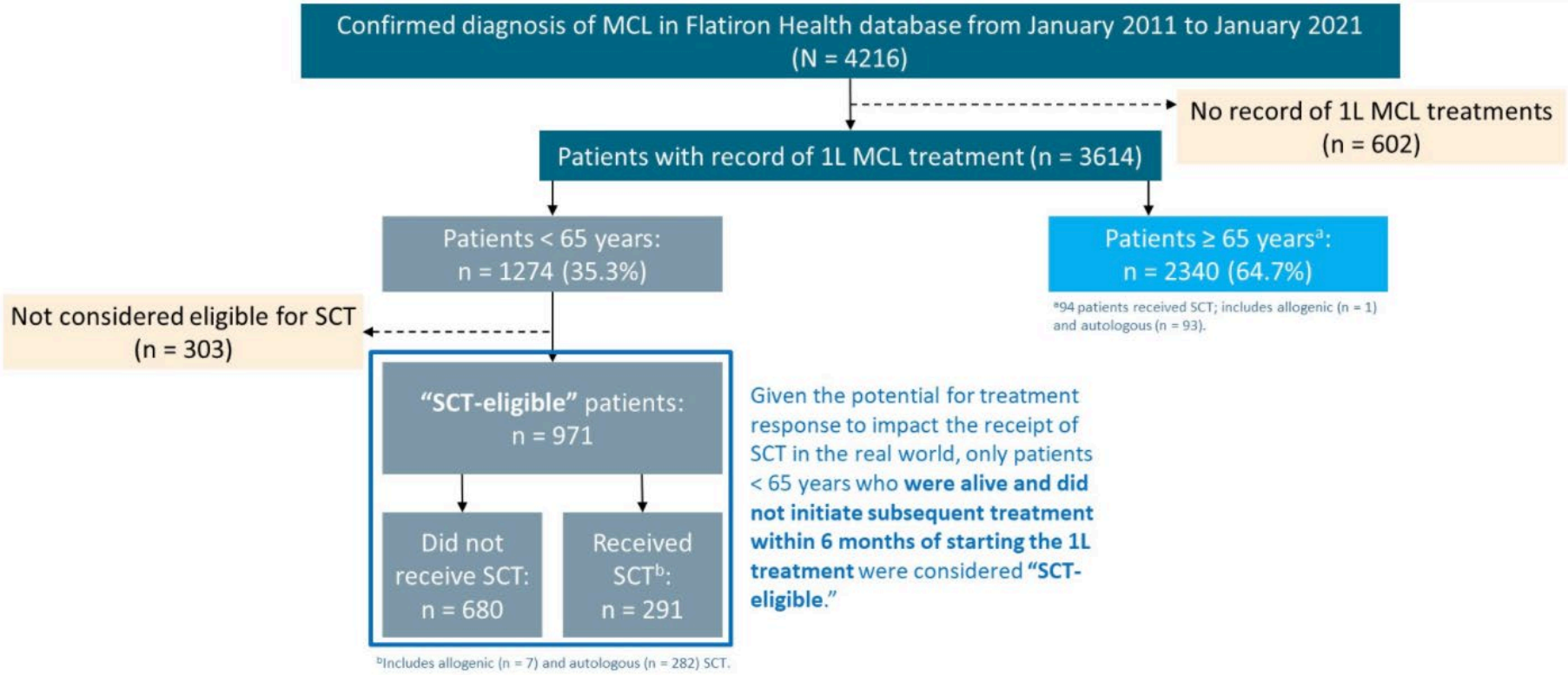
Eskelund Br J Haematol 2016 Nov;175(3):410-418;
Villa Blood Adv 2020 Aug 11;4(15):3486-3494

Does the real-world experience match the data?



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Martin ASCO 2020

Real-world (rw) results: mantle cell lymphoma (n=3600)

- BR was most commonly used 1L treatment
  - Only one-third of pts < 65 received cytarabine-containing regimen
  - Only 23% underwent SCT

- Med rwTTNT was 28m in pts <65y and 22m in pts ≥ 65y
  - Worse than reported in trials

- Despite lower use of SCT, there was no clear rwTTNT or rwOS benefit among SCT-eligible patients

Implication for clinical trial development!!

Martin ASCO 2020

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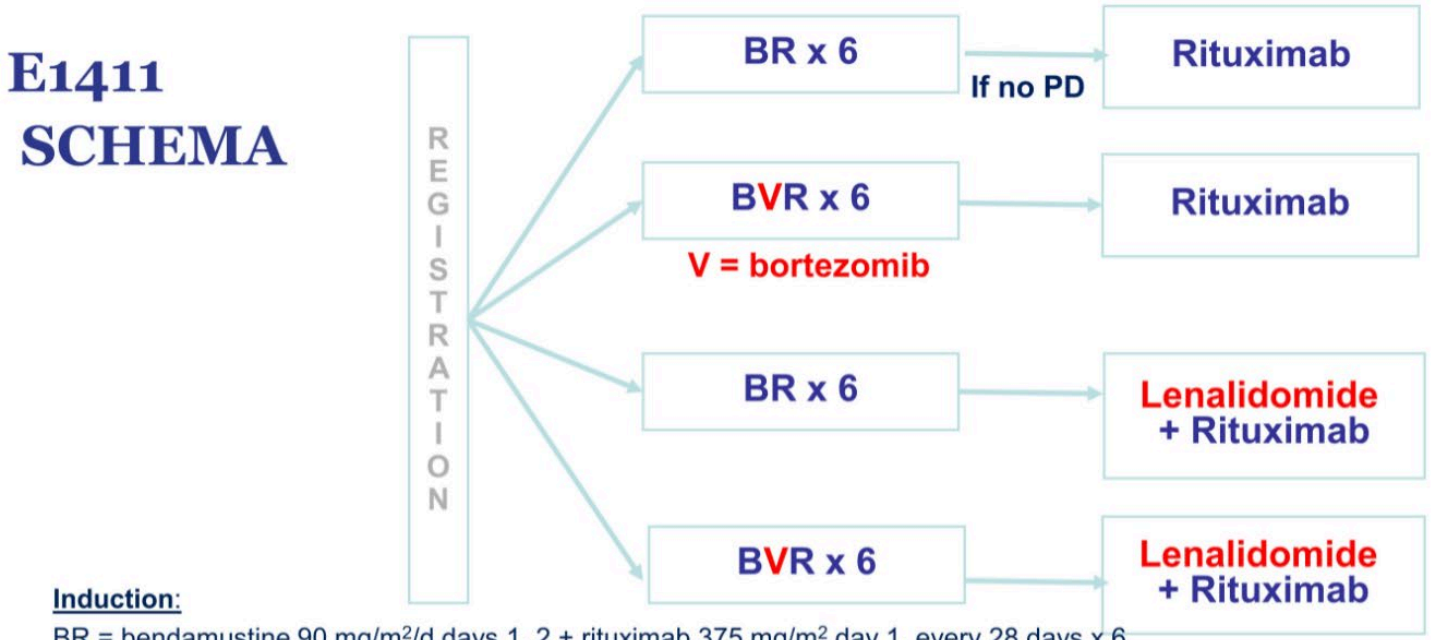
BR as a backbone for new regimens: ECOG-ACRIN E1411



Induction:

BR = bendamustine 90 mg/m^2/d days 1, 2 + rituximab 375 mg/m^2 day 1, every 28 days x 6

BVR = BR + bortezomib 1.3 mg/m^2 days 1, 4, 8, 11 (later amended to 1.6 mg/m^2 days 1, 8), IV or SQ

Consolidation:

Rituximab 375 mg/m^2 every 8 weeks x 12 doses ± Lenalidomide 15 mg/d 21/28 days x 24 cycles

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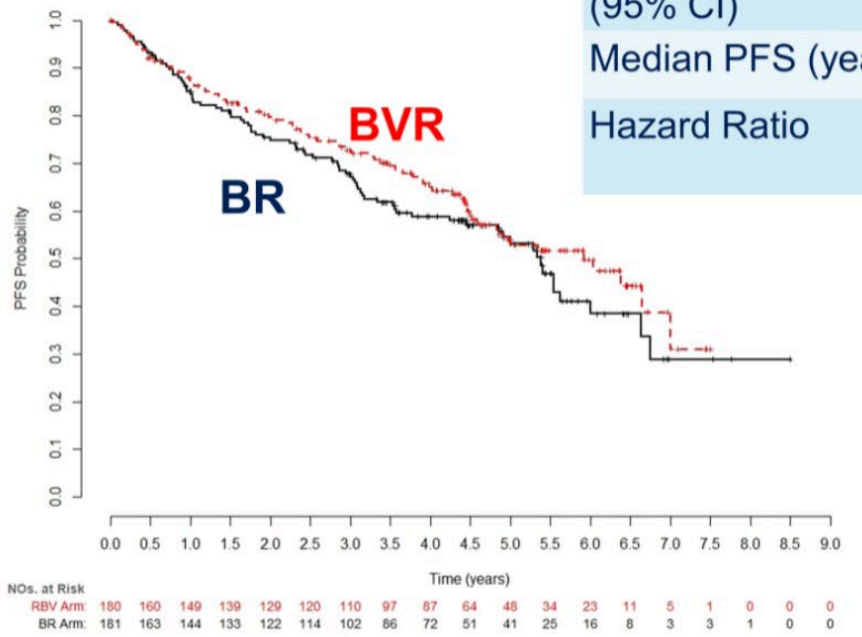
Addition of bortezomib to BR does not improve outcomes

PFS: BR vs BVR



	BR	BVR
2 year PFS % (95% CI)	74.8% (68.6-81.6)	79.7% (73.9-85.9)
Median PFS (years)	5.4	5.9
Hazard Ratio	0.83 (0.60 -1.15)	

No difference by MIPI or age

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Smith M ASCO 2021

Treatment approach in rel/ref MCL

- No data on sequencing
- List of options:
  - BTK inhibitors
  - Lenalidomide-rituximab
  - Venetoclax
  - Chemoimmunotherapy (if long duration of response to prior treatment)
  - Bortezomib-based treatment

Ven-len/ritux trial ongoing (Philips ASCO 2021)

- Potential role of delayed autoHCT
- Allogeneic HCT
- CAR-T * ~~(not yet FDA-approved)~~ APPROVED!

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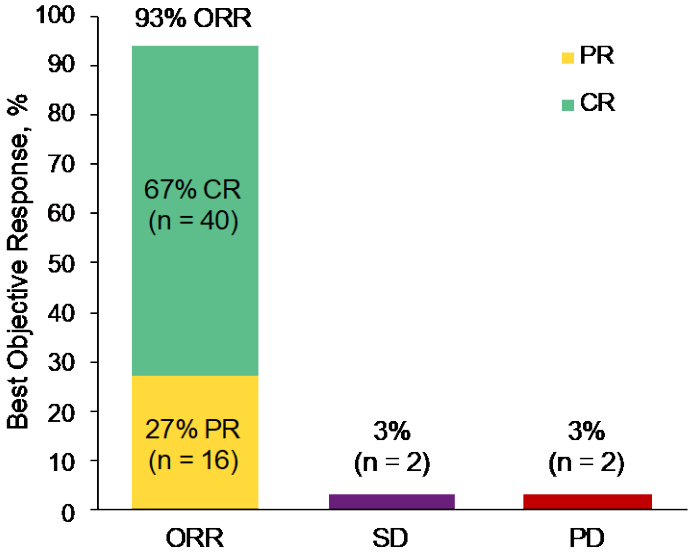
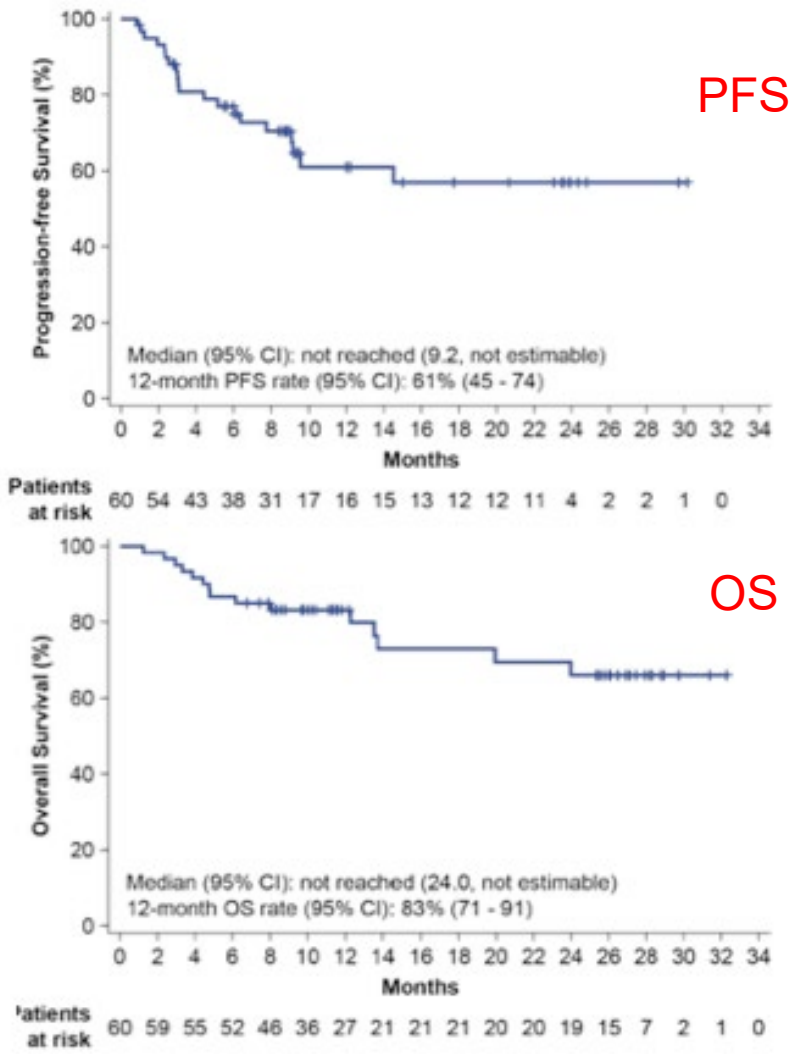
Modified from NCCN.org

ZUMA-2: CAR-T in rel/ref MCL

Key patient features:

- N=74 enrolled patients
- Med age 65 y
- Ki-67 ≥ 50% 69%
- TP53 mut 17%
- Blastoid 25%





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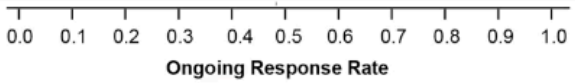
Wang N Engl J Med 2020; 382:1331-1342

ZUMA-2: ASH 2020 multicenter phase 2 trial of KTE-X19 in r/r MCL (N=60)

Ongoing Response Rate Was Consistent Across Adverse Prognostic Subgroups

	Evaluable Patients	Responding Patients	Ongoing Response Rate (95% CI)
Overall	60	29	0.48 (0.35 – 0.62)
Age at baseline			
< 65 Years	28	12	0.43 (0.24 – 0.63)
≥ 65 Years	32	17	0.53 (0.35 – 0.71)
Sex			
Male	51	25	0.49 (0.35 – 0.63)
Female	9	4	0.44 (0.14 – 0.79)
Morphological characteristics			
Classical	35	16	0.46 (0.29 – 0.63)
Pleomorphic	4	3	0.75 (0.19 – 0.99)
Blastoid	14	5	0.36 (0.13 – 0.65)
Ki-67 proliferation index			
≥ 30%	40	21	0.53 (0.36 – 0.68)
≥ 50%	34	19	0.56 (0.38 – 0.73)
Disease stage			
I-II	2	1	0.50 (0.01 – 0.99)
III-IV	58	28	0.48 (0.35 – 0.62)
s-MIPI score			
Low risk	25	11	0.44 (0.24 – 0.65)
Intermediate or high risk	33	16	0.48 (0.31 – 0.66)
***TP53* mutation**			
Mutation detected	6	3	0.50 (0.12 – 0.88)
Mutation undetected	30	17	0.57 (0.37 – 0.75)



s-MIPI, simplified Mantle Cell Lymphoma International Prognostic Index.

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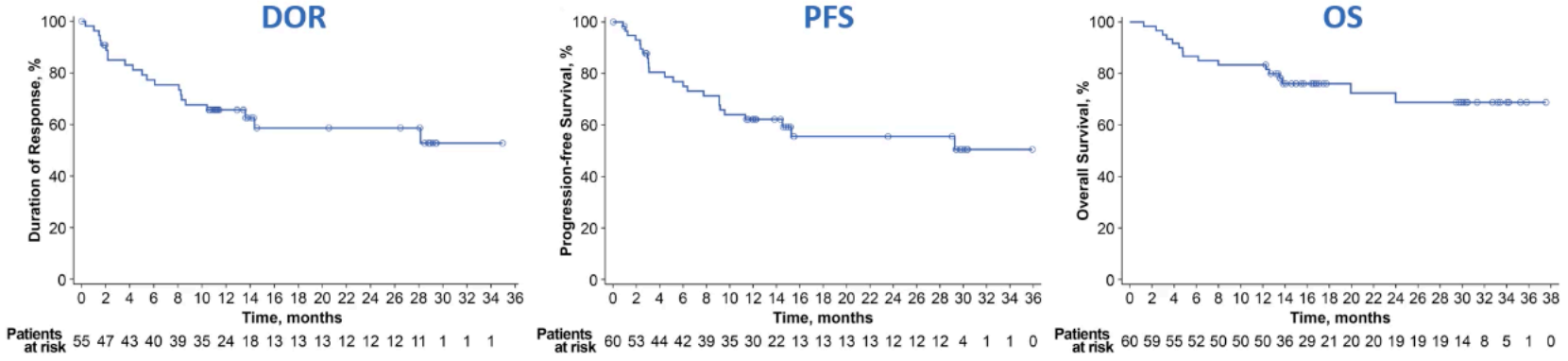
ZUMA-2: ASH 2020 multicenter phase 2 trial of KTE-X19 in r/r MCL (N=60)

Duration of Response, Progression-Free Survival, and Overall Survival

- The medians for DOR, PFS, and OS were not reached after a median follow-up of 17.5 months



	DOR		PFS		OS	
	Median (95% CI), mo	15-Mo Rate (95% CI), %	Median (95% CI), mo	15-Mo Rate (95% CI), %	Median (95% CI), mo	15-Mo Rate (95% CI), %
Evaluable pts (N = 60)	NR (14 – NE)[a]	59 (43 – 72)[a]	NR (10 – NE)	59 (45 – 71)	NR (NE – NE)	76 (63 – 85)
Pts in CR (n = 40)	NR (14 – NE)	70 (49 – 83)	NR (15 – NE)	75 (57 – 87)	NR (NE – NE)	92 (76 – 97)
Pts in PR (n = 15)	2 (1 – 4)	24 (6 – 49)	3 (2 – 5)	24 (6 – 49)	13 (3 – NE)	47 (21 – 69)

[a] Of 55 total responding patients.
CR, complete response; DOR, duration of response; NE, not evaluable; NR, not reached; PFS, progression-free survival; PR, partial response; pts, patients; OS, overall survival.

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Take home points: indolent and mantle cell lymphomas

- Toolbox is growing (!)
- Advent of cellular therapy for indolent lymphomas
  - Patient selection is critical
- Watch for bispecifics in indolent lymphomas
- New regimens for MCL on the horizon

Thank You

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