Please note, these are the actual video-recorded proceedings from the live CME event and may include the use of trade names and other raw, unedited content.

Diffuse Large B-Cell Lymphoma

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Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Genentech, Gilead Sciences Inc, Kite Pharma Inc, Nordic Nanovector, Pharmacyclics LLC, an AbbVie Company, Portola Pharmaceuticals Inc, Seattle Genetics
Contracted Research	Celgene Corporation

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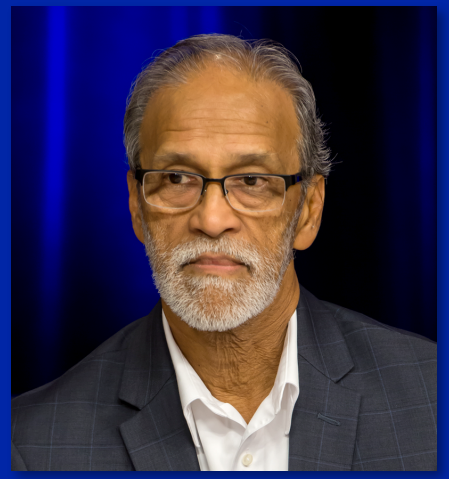
Case presentation: Dr Kumar



83-year-old man with DLBCL

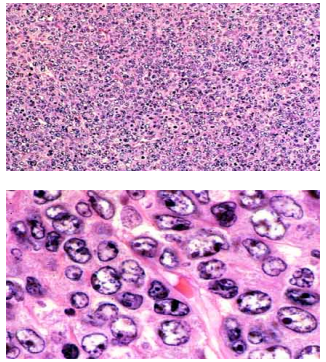
- Presented with fatigue and right testicular swelling
- Ultrasound of testicles: Severe right orchitis → radical right orchiectomy
- Pathology: DLBCL, nongerminal center type, involving spermatic cord but free resection margins
- PET scan negative for distant disease, no marrow involvement
- Brain MRI normal; cerebrospinal fluid showed no overt evidence of disease

Additional questions regarding the management of DLBCL

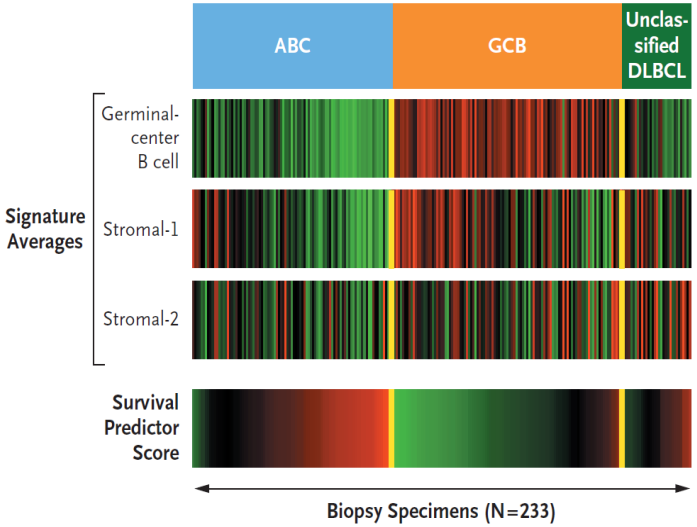
Dr Bessnow

DLBCL has multiple clinicopathologic subsets/heterogeneity

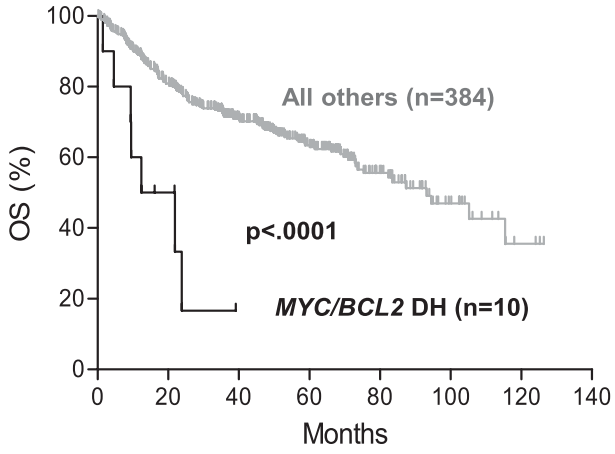
Histopathology



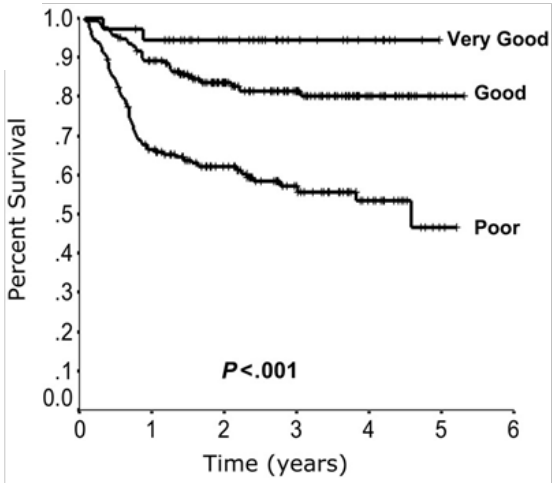
Cell-of-origin

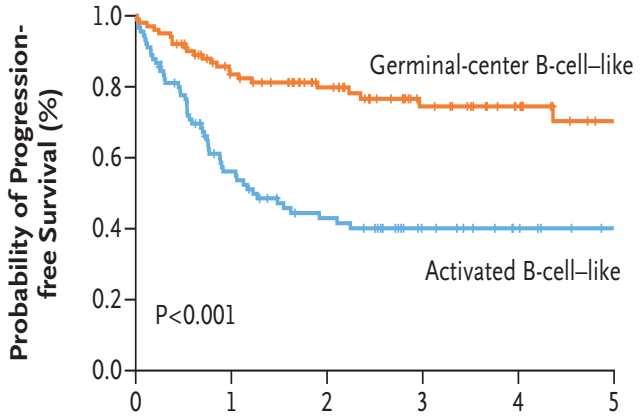


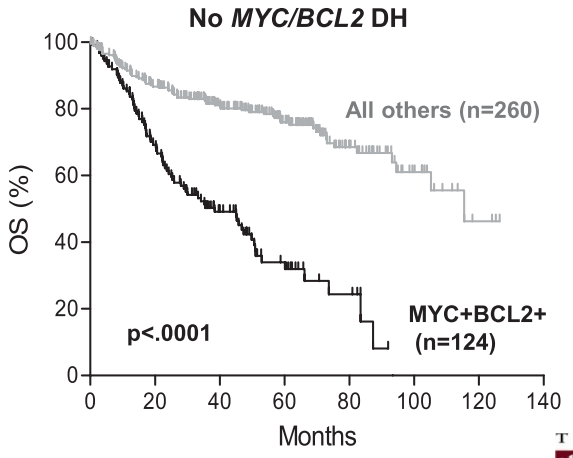
DHL, DEL, other



Clinical features/IPI







DHL = double-hit lymphoma;
DEL = double-expressor lymphoma

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Retrospective data identifies high-risk groups unlikely to be cured with R-CHOP

SUBSET	FREQ	R-CHOP		
		CR	PFS	OS
ABC DLBCL	30-50%	NR	2-yr 28%	2-yr 46%
Double-hit lymphoma	3-12%	40%	NR	<1yr
Dual expression of MYC, BCL2	21%	NR	5-yr 27%	5-yr 30%
Elderly DLBCL >60y	50%	70-80%	5-yr 50%	5-yr 58%
High IPI	45%	NR	4-yr 53%	4-yr 55%

Ref: Aukema Blood 2011; Hu Blood 2013; Oki 2014, Maurer 2014, Feugier 2005, Sehn 2005; Nowakowski 2014; Johnson JCO 2012.

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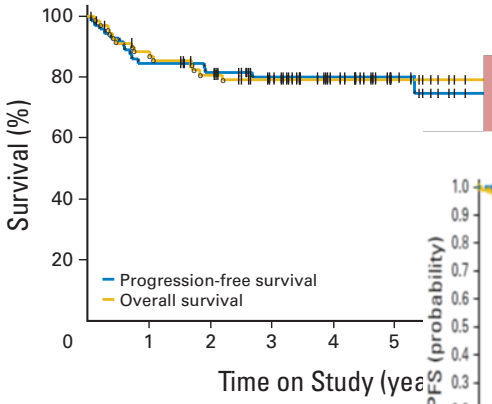
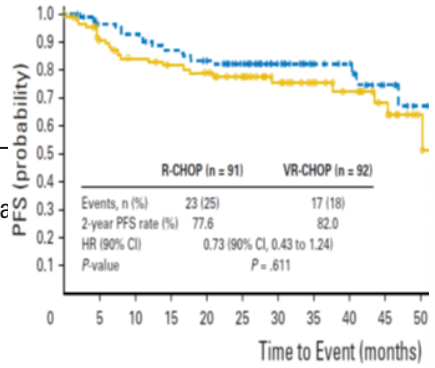
Can we move beyond R-CHOP?

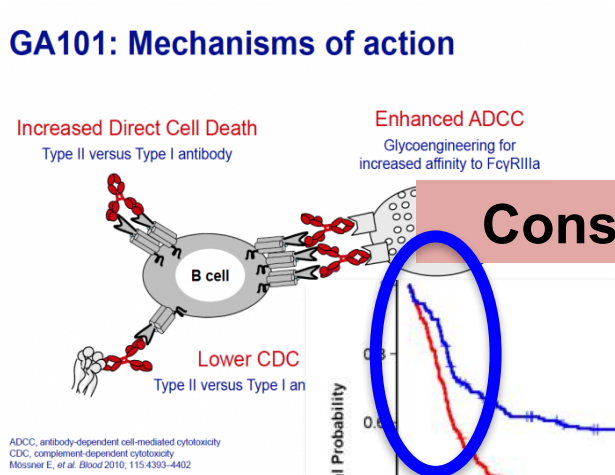
DA-EPOCH-R



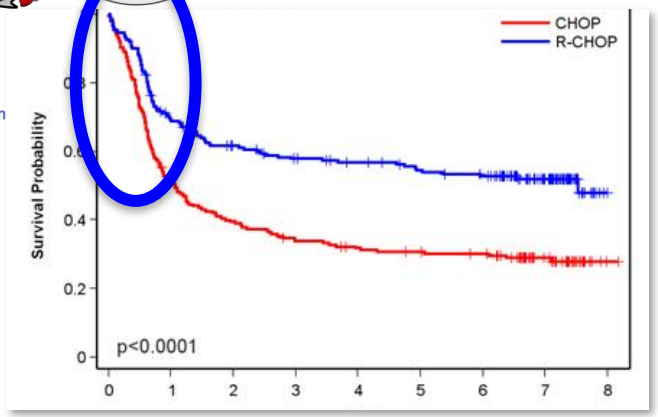
Add biologic agents



Obinutuzumab



Consolidation



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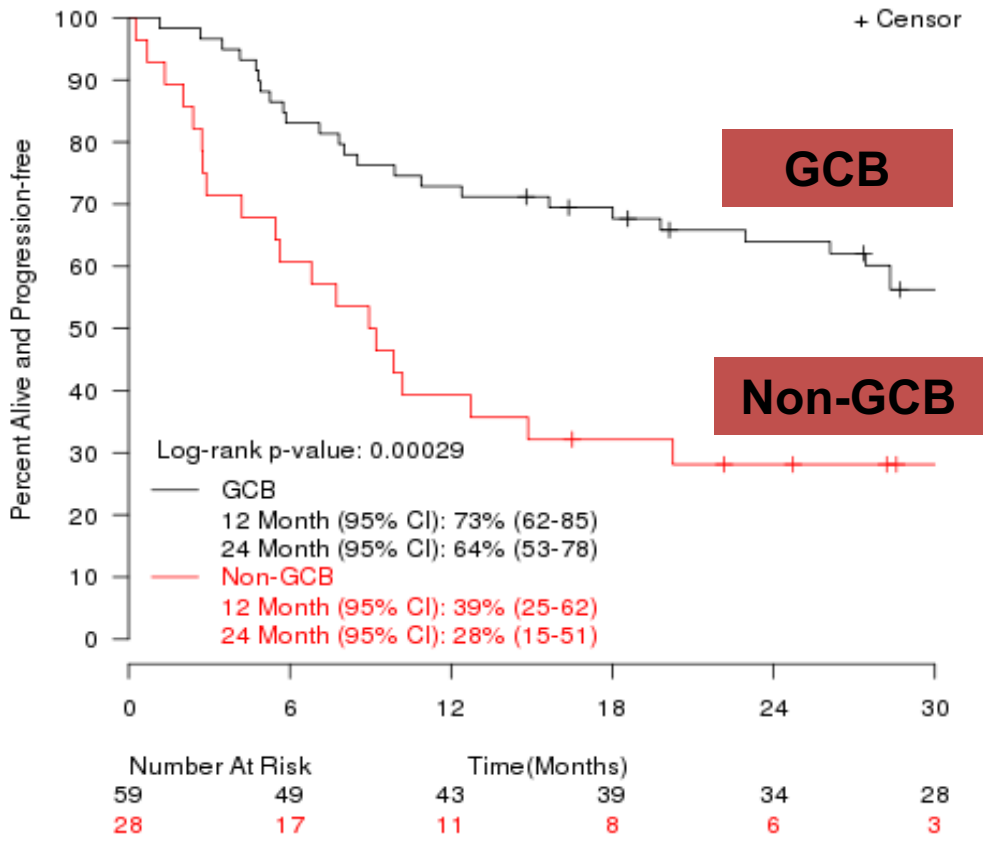
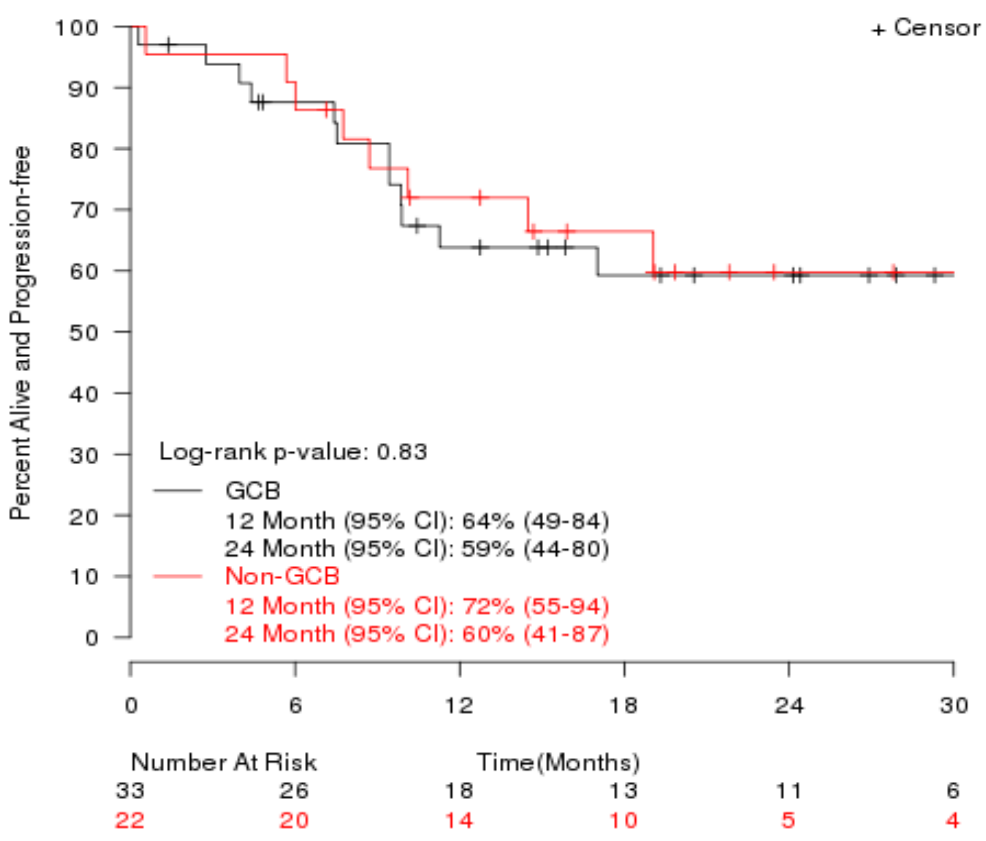
PFS by GCB vs. non-GCB Subtype* in R-CHOP Case-matched Control and R2-CHOP Patients

R-CHOP by COO



R2-CHOP by COO



Nowakowski JCO 2015

* As defined by Hans et al. Blood 2004

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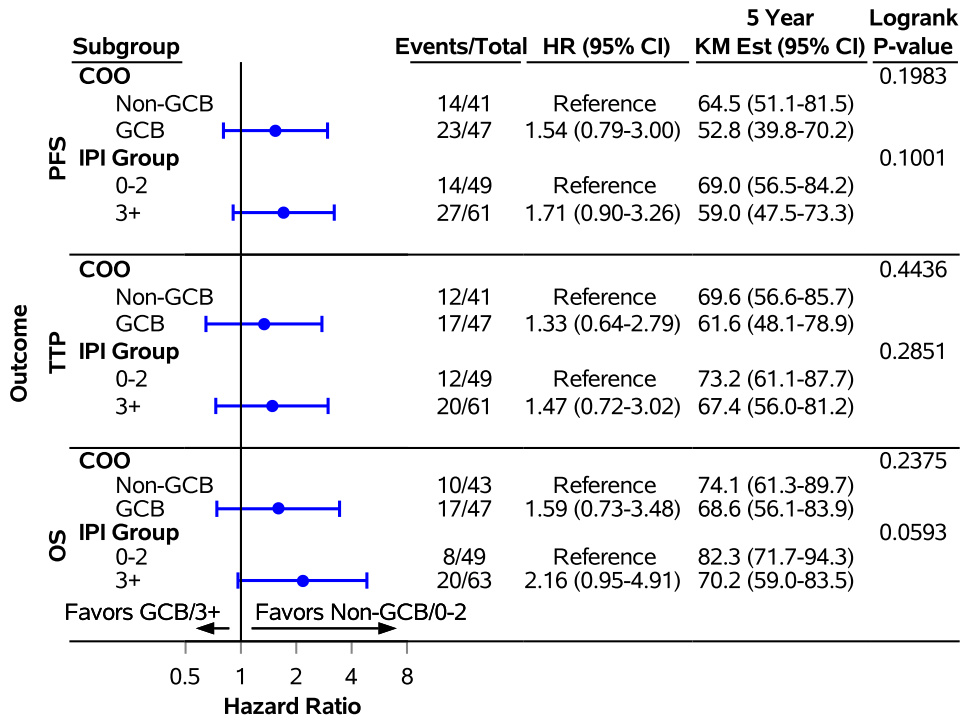
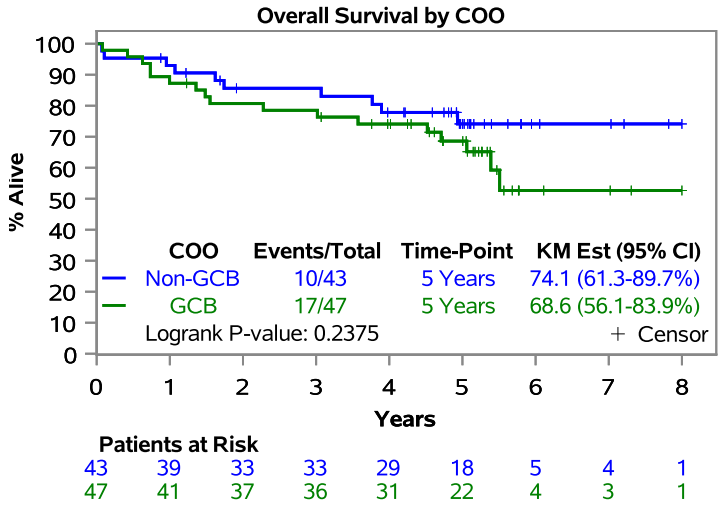
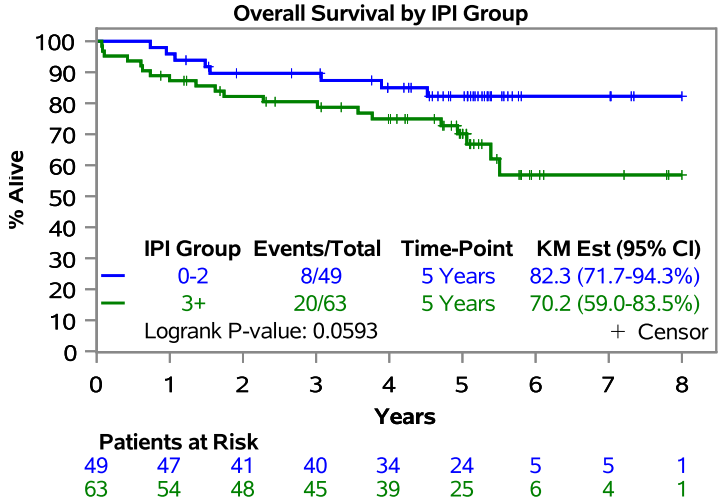
Updated and combined analysis of two phase 2 trials of lenalidomide plus R-CHOP in newly diagnosed non-GCB DLBCL







- 112 patients
- Median follow up 5.1y
- 5-yr PFS 63.5%
- 5-yr OS 75.4%
- AUTHORS' CONCLUSION: Addition of lenalidomide mitigates neg significance of non-GCB phenotype

Castellino Blood Ca J 2018

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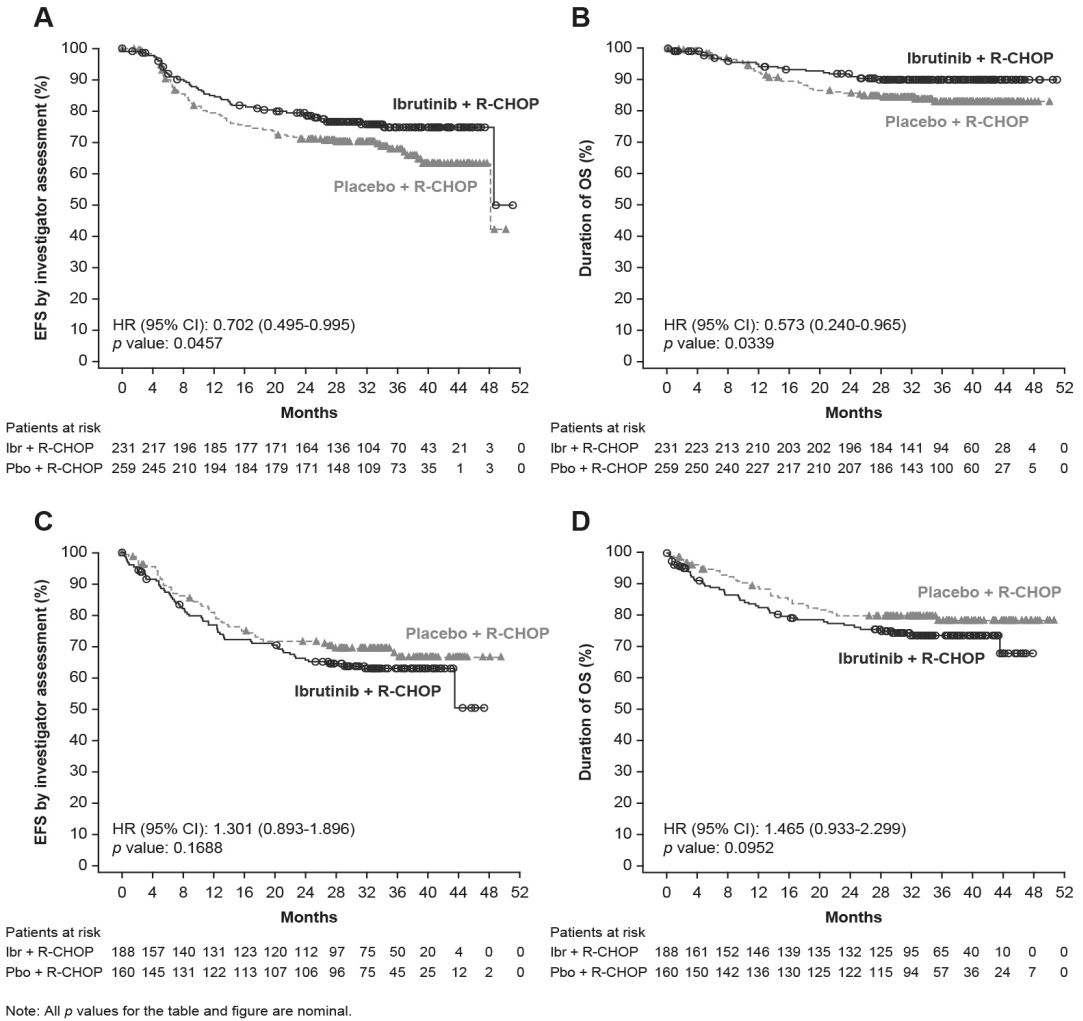
R-CHOP plus "X": still waiting for a winner

- R-CHOP +/- ibrutinib (PHOENIX) trial did not meet its endpoint in ITT group
- N=838 pts
- No diff in PFS, EFS, OS

BUT…impact of age?

Figure. Kaplan-Meier plot of EFS in < 65 years age group (A), OS in < 65 years age group (B), EFS in ≥ 65 years age group (C), and OS in ≥ 65 years age group (D)



Note: All *p* values for the table and figure are nominal.

Younes ASH 2018 Abstract 784 Monday, December 3, 2018: 3:30 PM
Ballroom 20A (San Diego Convention Center)

THE UNIVERSITY OF CHICAGO MEDICAL CENTER & BIOLOGICAL SCIENCES

Subset studies in newly diagnosed DLBCL

- 786 **Successful Treatment of *MYC* rearrangement Positive Large B Cell Lymphoma Patients with R-CHOP21 Plus Lenalidomide: Results of a Multicenter Phase II HOVON Trial** Monday, December 3, 2018: 4:00 PM Ballroom 20A (San Diego Convention Center) *Martine E.D. Chamuleau, MD, et al.*

- 782 **Venetoclax Plus Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone (R-CHOP) Improves Outcomes in BCL2-Positive First-Line Diffuse Large B-Cell Lymphoma (DLBCL): First Safety, Efficacy and Biomarker Analyses from the Phase II CAVALLI Study** Monday, December 3, 2018: 3:00 PM Ballroom 20A (San Diego Convention Center) *Franck Morschhauser, et al.*

- Godfrey J., **Lenalidomide plus dose-adjusted EPOCH-R in double hit and double expressing lymphoma**, Cancer 2018 (in press)

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RELAPSED/REFRACTORY DLBCL

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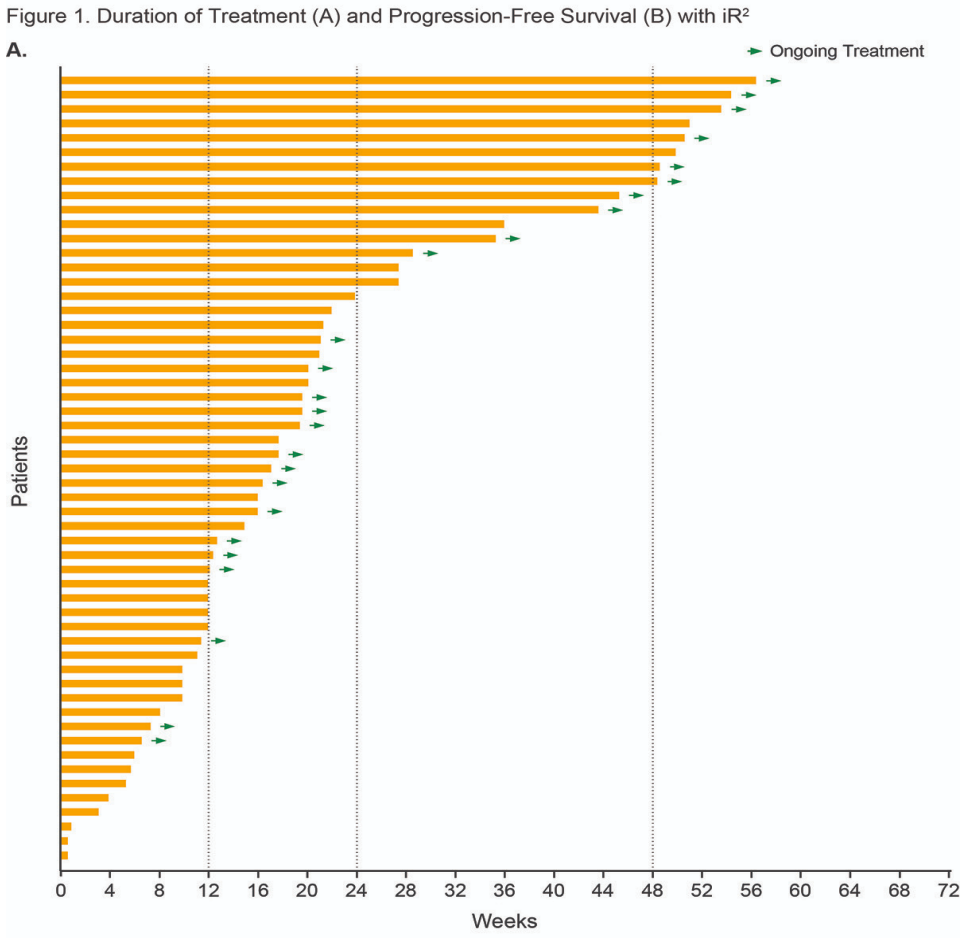
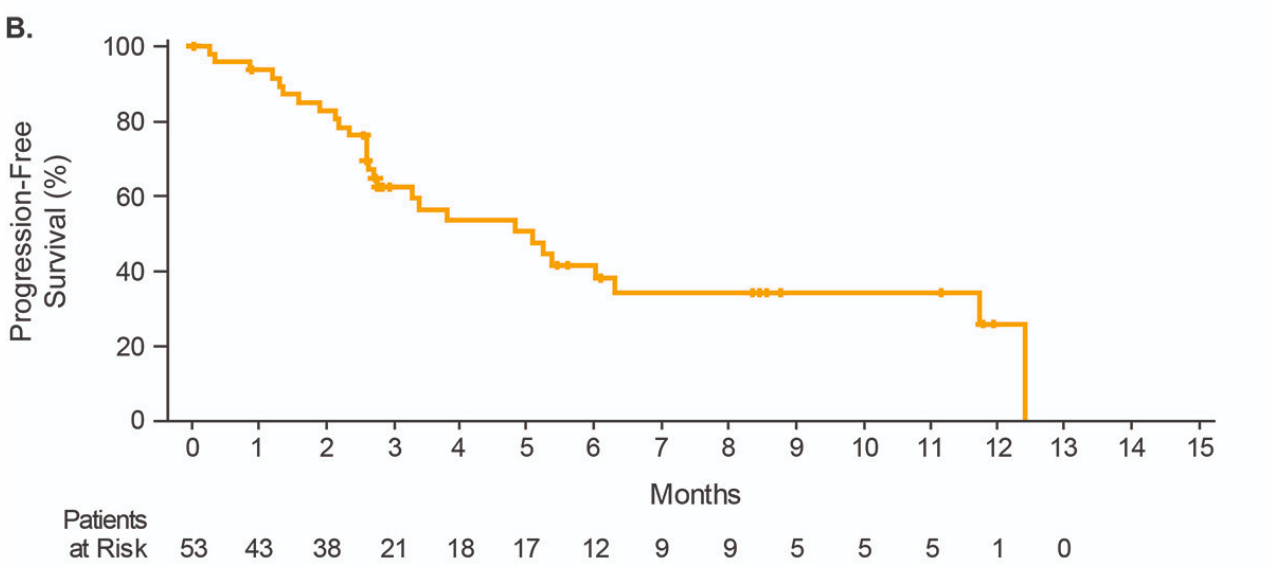
"IR^2" in rel/ref non-GCB DLBCL

- Ibrutinib plus lenalidomide and rituximab



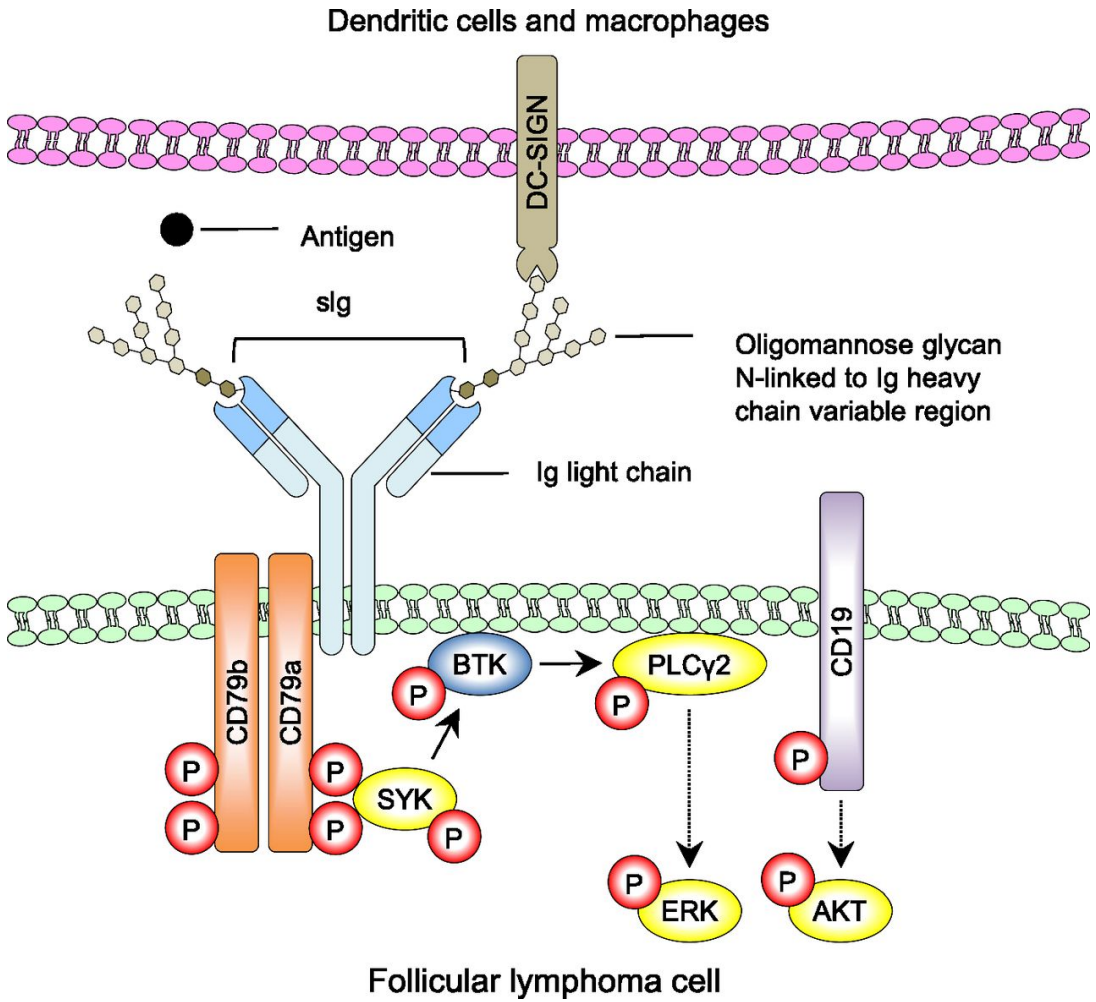


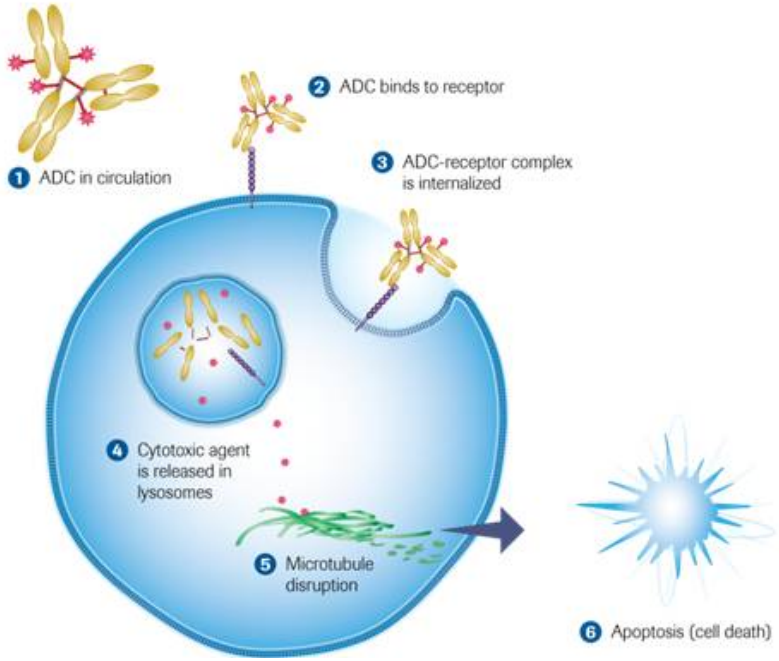
- N=55 pts
- Med age 63 y
- >50% refractory to last treatment
- ORR 50% with CR 30%
- Med DR 9m

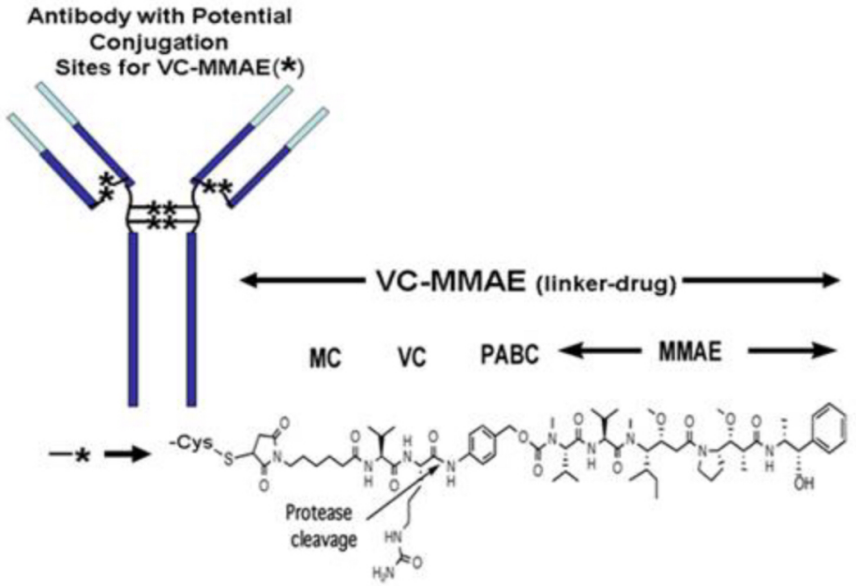
Ramachandren ASH 2018 Abstract 402 Sunday, December 2, 2018: 1:15 PM

THE UNIVERSITY OF CHICAGO MEDICAL CENTER & BIOLOGICAL SCIENCES

Targeting CD79B: Polatuzumab vedotin in B-cell lymphoma patients







Morschhauser et al, ASCO 2014
Strout. Blood 2015;126:1871-1872

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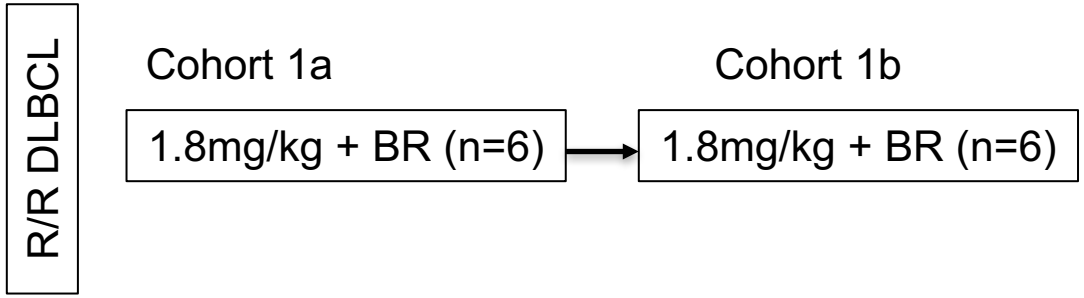
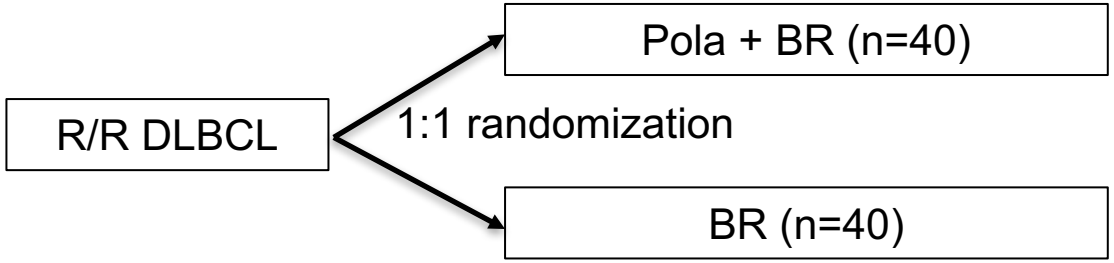
GO29365: Polatuzumab Vedotin, an Anti-CD79b Antibody-Drug Conjugate, in Combination with BR for R/R DLBCL or FL

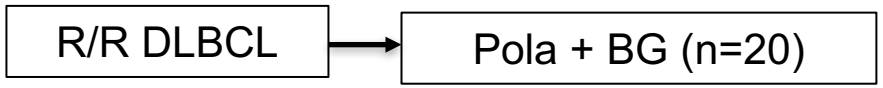
Ph Ib safety run-in: Pola + BR or BG



Ph II randomization: Pola + BR versus BR



Ph II expansion: Pola + BR



Primary endpoints

- **Phase Ib:** Percentage of Participants with Adverse Events
- **Phase II:** Percentage of Participants with Complete Response (CR)

Sehn LH et al. *Proc ASH* 2018;Abstract 1683

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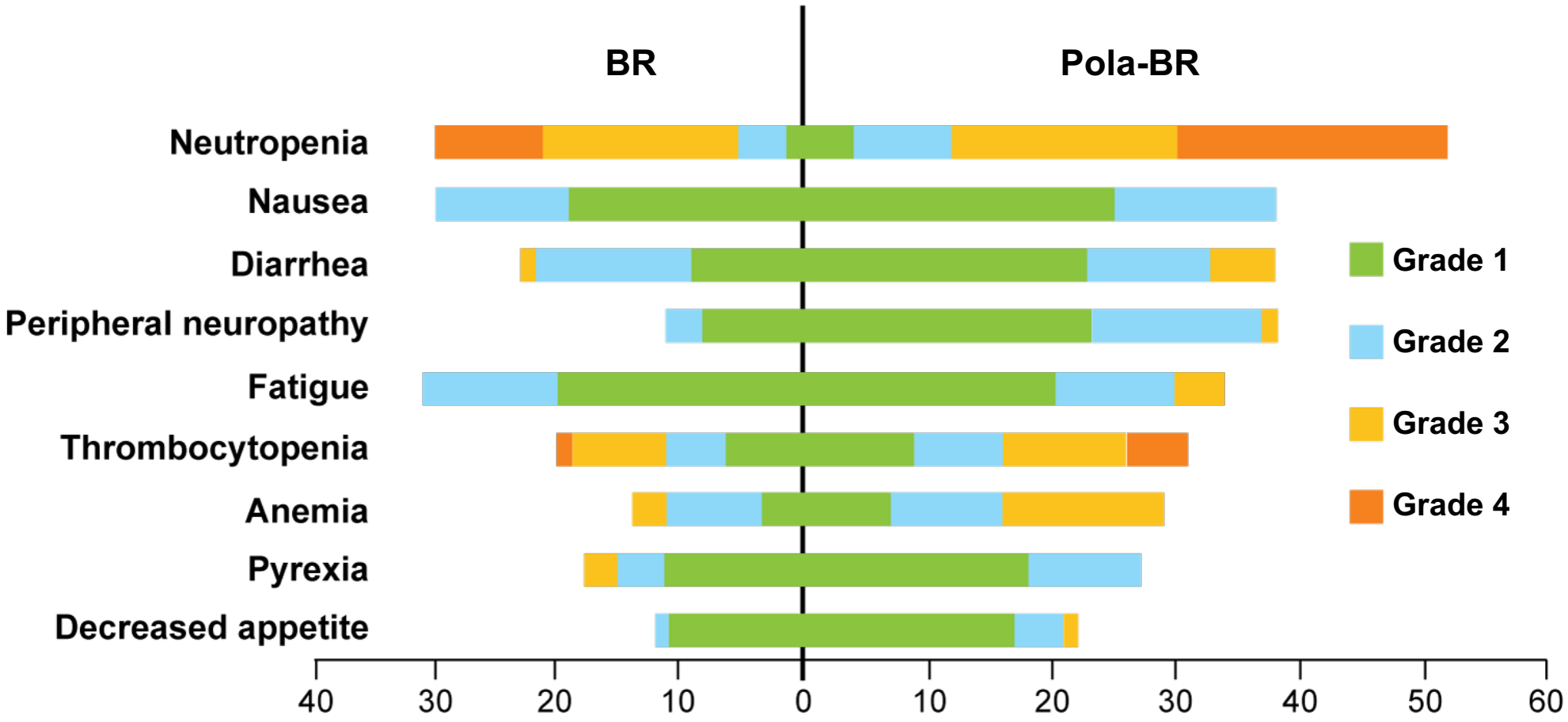
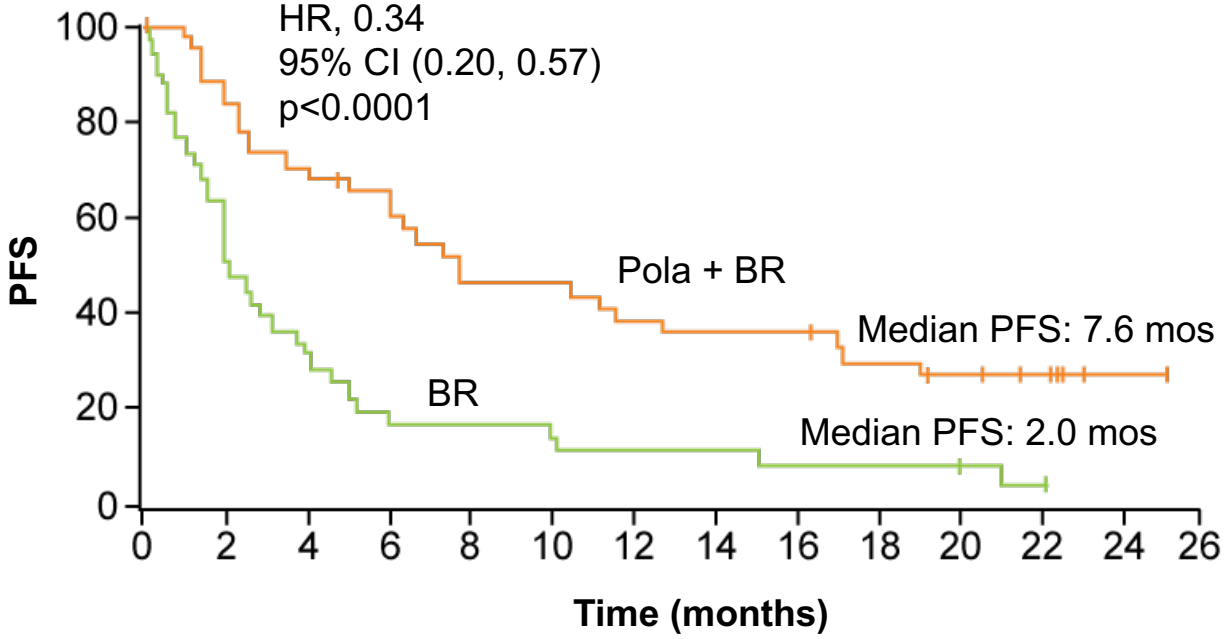
GO29365: Safety Results of Polatuzumab Vedotin in Combination with BR for R/R DLBCL or FL

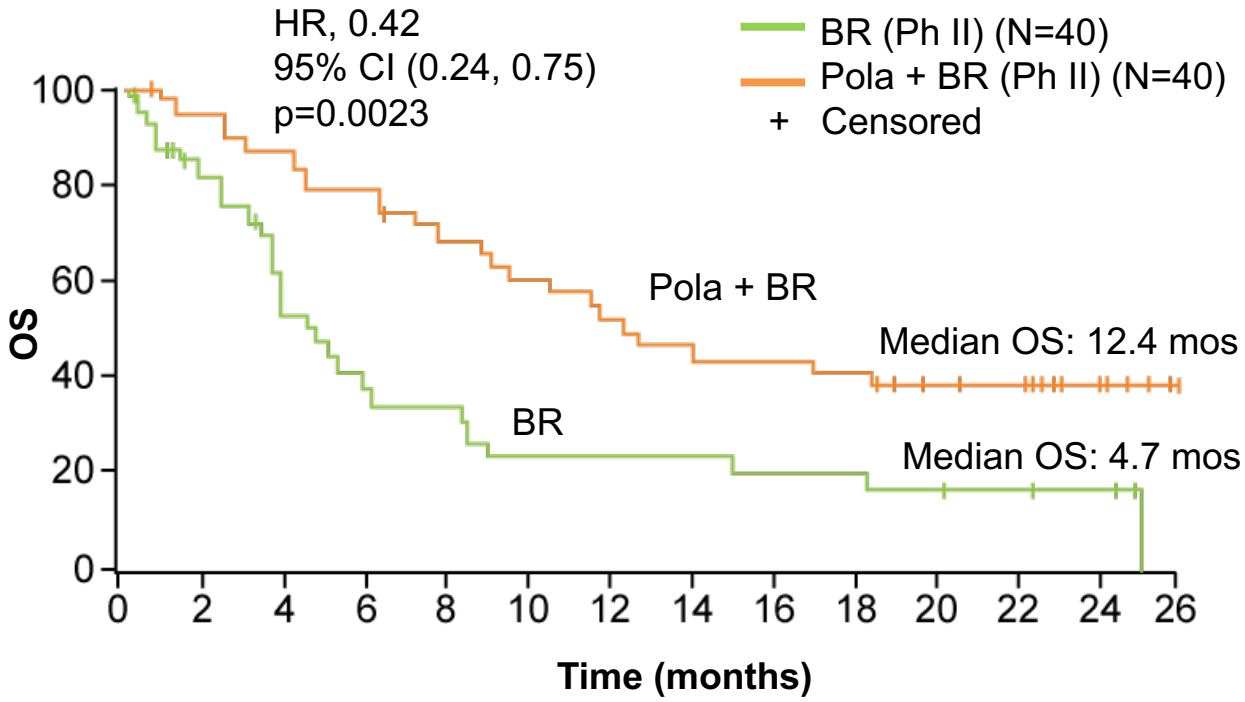


Sehn LH et al. *Proc ASCO* 2018;Abstract 7507

THE UNIVERSITY OF CHICAGO MEDICAL CENTER & BIOLOGICAL SCIENCES

GO29365: Updated Phase II Trial Results of Polatuzumab Vedotin in Combination with BR for R/R DLBCL or FL





- Overall response rates for pola + BR and BR were 45% and 18%, respectively
- Updated follow-up suggests that durable responses could be possible; responses of >20 months have been observed with pola + BR or pola + BG
- Updated safety results are similar to those previously described with no new safety signals identified

Sehn LH et al. *Proc ASH* 2018;Abstract 1683

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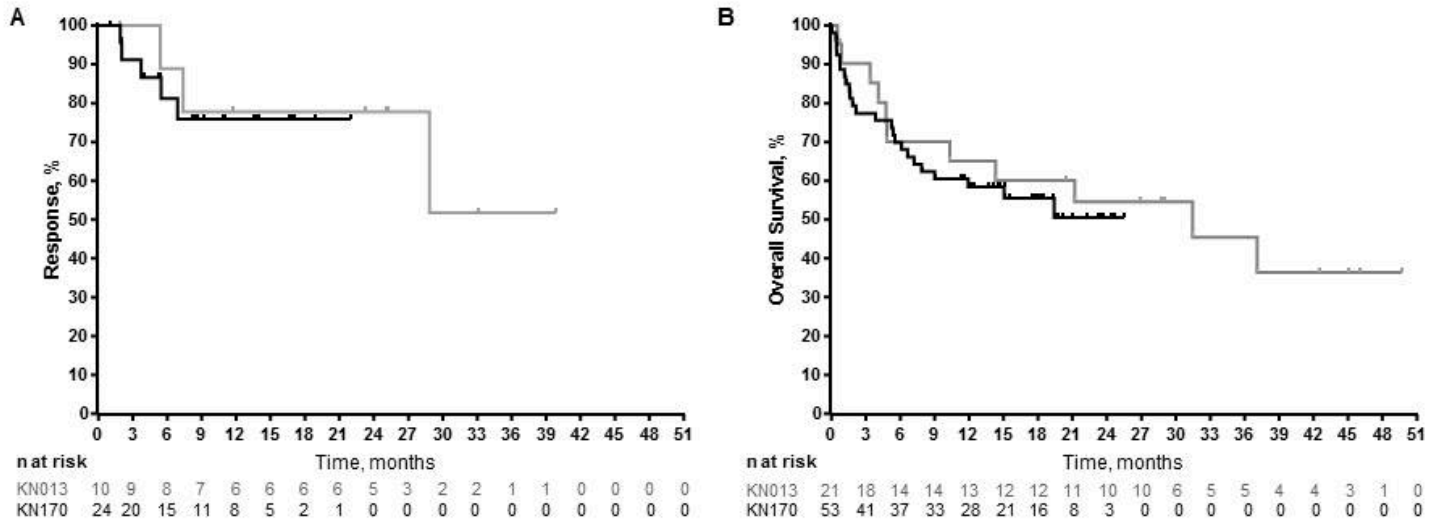
PD-1 inhibitors in rel/ref PMBCL

Pembrolizumab in Patients with Relapsed or Refractory Primary Mediastinal Large B-Cell Lymphoma (PMBCL): Data from the KEYNOTE-013 and KEYNOTE-170 Studies

- N=74 pts
- Med 3 prior lines of treatment
- 50% were transplant ineligible due to chemoref disease
- Med DoR not reached in either group (>29 m in KN013 and >12m in KN170)

Figure. Duration of response and overall survival in patients with rrPMBCL treated with pembrolizumab



Armand ASH 2018 Abstract 228 Saturday, December 1, 2018: 5:15 PM
Pacific Ballroom 20 (Marriott Marquis San Diego Marina)

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Where do PD-1 inhibitors fit in DLBCL?

- No role for PD-1 inhibition after autologous stem cell transplant
  - Chen ASH 2018 Abstract 706 Monday, December 3, 2018: 11:15 AM Grand Hall B (Manchester Grand Hyatt San Diego)

- Checkpoint inhibition may re-sensitize patients to chemotherapy
  - Carreau ASH Abstract 93 Saturday, December 1, 2018: 10:00 AM Pacific Ballroom 20 (Marriott Marquis San Diego Marina)

- PD-1 alterations only occur in a subset of DLBCL patients (approximately 30%) and are associated with a “T-cell inflamed” phenotype
  - Kline ASH Abstract 673 Monday, December 3, 2018: 10:30 AM Pacific Ballroom 15 (Marriott Marquis San Diego Marina)

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CAR-T IN DLBCL: ONE YEAR LATER…

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Summary of Pivotal CAR-T Trials in R/R DLBCL

	JULIET (N=93)	TRANSCEND-NHL-001 (N=102)	ZUMA-1 (N=108)
Agent	Tisagenlecleucel	Lisocabtagene maraleucel	Axicabtagene ciloleucel
Median prior therapies (range)	3 (1-6)	3 (1-8)	NR (1-5+)
ORR	52%	75%	82%
CR	40%	55%	58%

Borchmann P et al. Proc EHA 2018;Abstract S799; Abramson JS et al. Proc ASCO 2018;Abstract 7505; Locke FL et al. Proc ASCO 2018;Abstract 3003; Locke FL et al. Proc ASCO 2018;Abstract 3039

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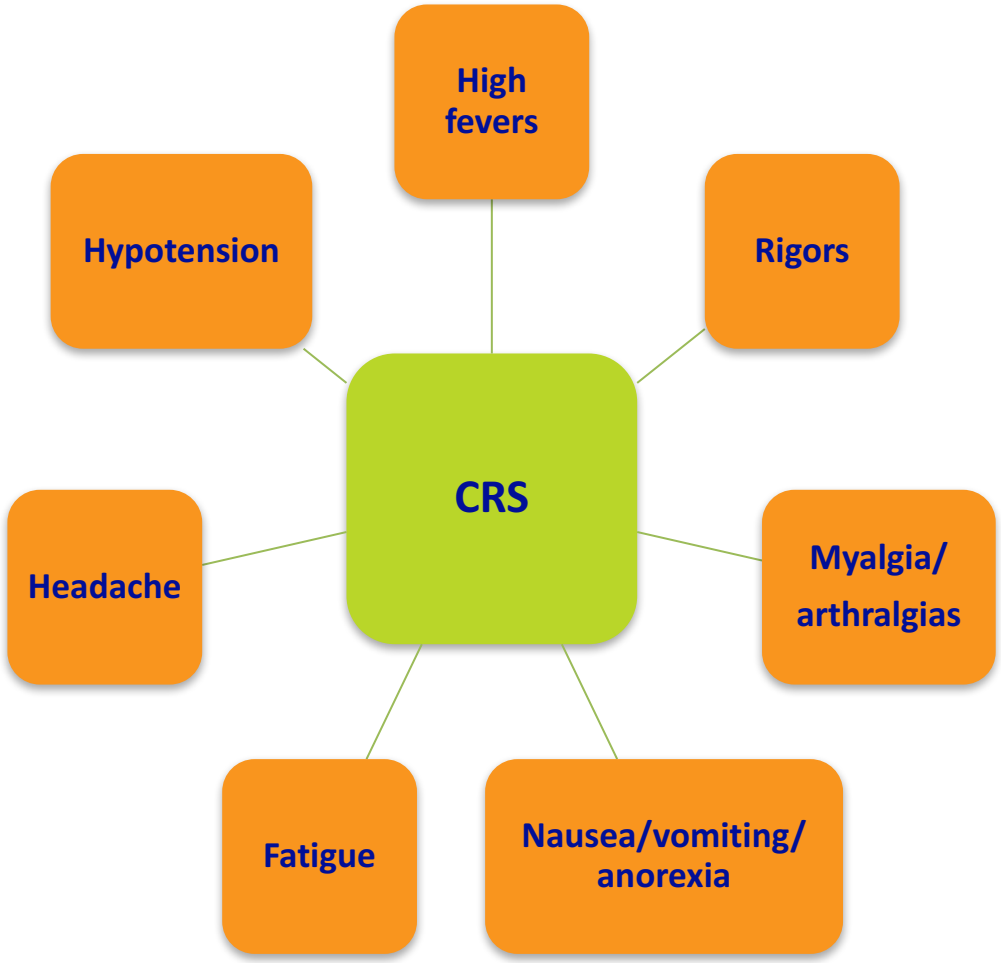
Cytokine Release Syndrome (CRS) and Neurotoxicity in Key Pivotal CAR-T Trials

Grade 3/4 AEs	JULIET	TRANSCEND NHL 001	ZUMA-1
CRS	22%	1%	12%
Neurologic	12%	13%	29%



Borchmann P et al. Proc EHA 2018;Abstract S799; Abramson JS et al. Proc ASCO 2018;Abstract 7505; Locke FL et al. Proc ASCO 2018;Abstract 3003

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"Real-world" Axi-cel

Table 1. Patient characteristics and outcomes: comparison between ZUMA-1 (Neelapu and Locke et al. NEJM 2017) and commercial standard of care axi-cel treatment at 17 US centers.

	ZUMA-1	This Study
N infused pts	108	165
% meeting ZUMA-1 eligibility criteria	100%	51%
Age, median (range)	58 (23-76)	59 (21 – 82)
ECOG 0 or 1	100%	84%
Prior autologous transplant	23%	31%
DLBCL including HGBCL, not tFL or PMBCL	78%	61%
ORR/CR	82%/58% (Best)	79%/50% (Day 30)
Grade 3 or higher toxicity	CRS 13%/NEs 31%	CRS 7%/NEs 31%

- Seventeen US academic centers
- N=165 with 78% pts completing axi-cel infusion
- Grade 3 CRS in 7%
- Grade 3 NE in 31%
- ORR at Day 30 in 112 evaluable pts was 79% with 50% CR
- PFS and OS data to be presented

Nastoupil ASH 2018 Abstract 91 Saturday, December 1, 2018: 9:30 AM
Pacific Ballroom 20 (Marriott Marquis San Diego Marina)

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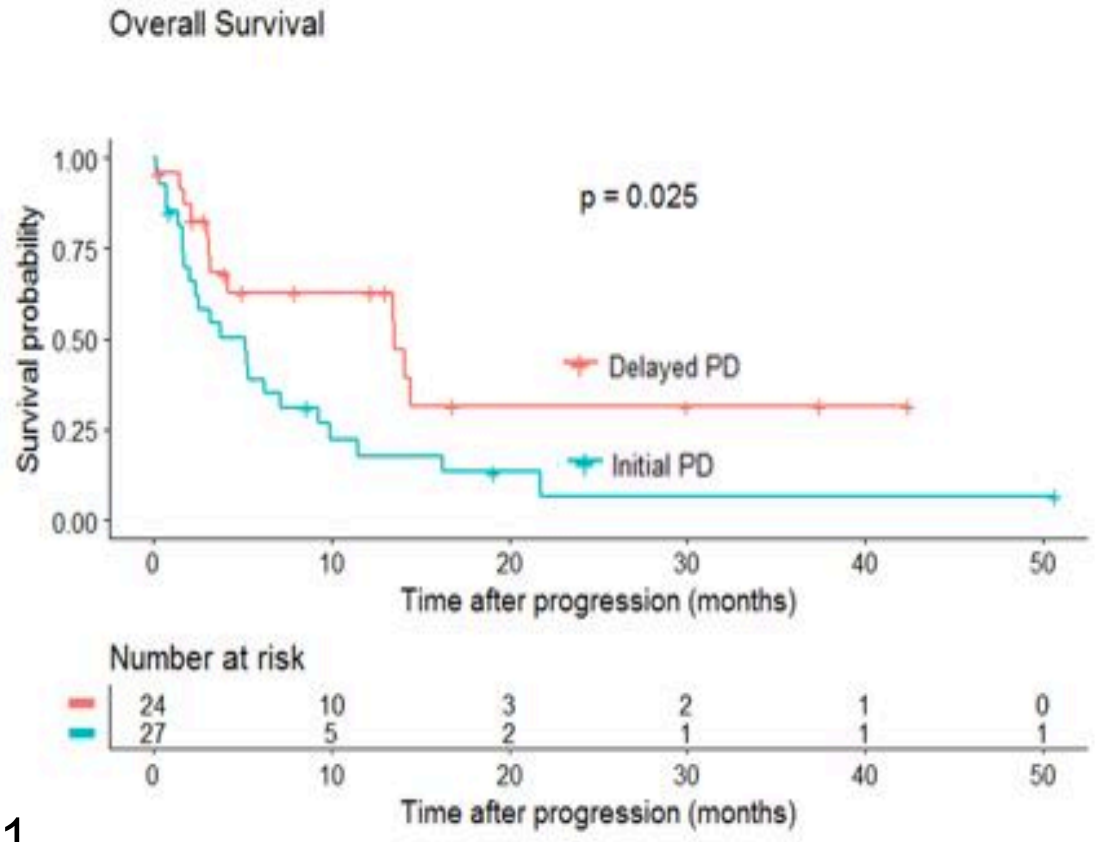
“Real-world” Axi-cel

- N=73 evaluable patients
- At 4m median f/u, best ORR and CRR was 64% and 41% among those treated.
- Predictors of poor outcome:
  - Poor PS, tumor bulk, high IPI, baseline CRP, prior ibrutinib
- 96% all-grade CRS, 17% grade 3-4 CRS

AUTHORS’ CONCLUSION: “The ORR and CR rate are lower than the 82% and 54% reported on ZUMA-1. This may reflect inclusion of sicker patients with a poorer PS, and/or with different histologies (ie transformation from non-FL). Outcomes were significantly worse in high risk lymphomas, reflected by IPI, PS, tumor bulk, and baseline CRP. Rates of CRS and NT were similar to ZUMA-1”

Jacobson ASH 2018 Abstract 92 Saturday, December 1, 2018: 9:45 AM
Pacific Ballroom 20 (Marriott Marquis San Diego Marina)

If CAR-T doesn't work…



Characteristic	Total (N=51)	Initial PD (N=27)	Delayed PD (N=24)
Gender			
Female	17 (33.3%)	8 (29.6%)	9 (37.5%)
Male	34 (66.7%)	19 (70.4%)	15 (62.5%)
Histology			
HGBCL	11 (21.6%)	3 (11.1%)	8 (33.3%)
DLBCL	29 (56.9%)	18 (66.7%)	11 (45.8%)
PMBCL	3 (5.9%)	2 (7.4%)	1 (4.2%)
tFL	8 (15.7%)	4 (14.8%)	4 (16.7%)
Median age (range)	60 (26-75)	60 (29-70)	59 (26-75)
Additional therapy after progression	39 (76.5%)	17 (63.0%)	22 (91.7%)
Next line of therapy			
Allogeneic Transplant	1 (2.6%)	0 (0.0%)	1 (4.5%)
CAR T	14 (35.9%)	6 (35.3%)	8 (36.4%)
Chemotherapy	7 (17.9%)	5 (29.4%)	2 (9.1%)
Immunotherapy	3 (7.7%)	1 (5.9%)	2 (9.1%)
Intrathecal	1 (2.6%)	0 (0.0%)	1 (4.5%)
Radiation	3 (7.7%)	1 (5.9%)	2 (9.1%)
Targeted	10 (25.6%)	4 (23.5%)	6 (27.3%)
Next treatment on clinical trial	5 (9.8%)	3 (11.1%)	2 (8.3%)
Allogeneic transplant after progression	4 (7.8%)	1 (3.7%)	3 (12.5%)

- N=51
- Initial progression did worse than delayed progression
  - Med OS 5.1 m vs. 13.6 m

Chow ASH Abstract 94 Saturday, December 1, 2018: 10:15 AM
Pacific Ballroom 20 (Marriott Marquis San Diego Marina)

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