AT THE FOREFRONT
UChicago Medicine

Current Therapies in Aggressive B- and T-cell Lymphomas: An Update

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DISCLOSURES

Sonali M. Smith, MD

- I have the following relevant financial relationships to disclose:
  - Consultant for: Genentech/Roche, Celgene, TGTX, Karyopharm, Janssen, Bantam
  - Speaker's Bureau for: none
  - Stockholder in: none
  - Honoraria from: none
  - Employee of: none
  - Institutional research funding: Portola, Genentech, Acerta, Pharmacyclics, Celgene, Curis, BMS, TG Therapeutics, Merck, Forty-Seven, Novartis
- • I may discuss off label use and/or investigational use in my presentation. I will disclose when they are being discussed in an off-label manner.

Overview: new data and treatment options for aggressive lymphomas

DLBCL

Management of limited stage disease

DLBCL

Treatment options for rel/ref disease

MCL

Treatment options for rel/ref disease

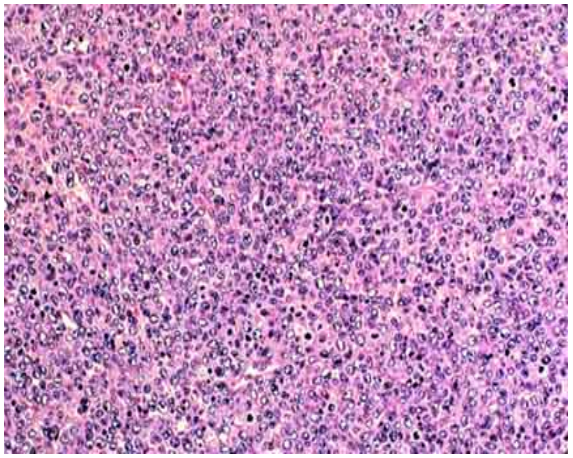
T cell lymphomas

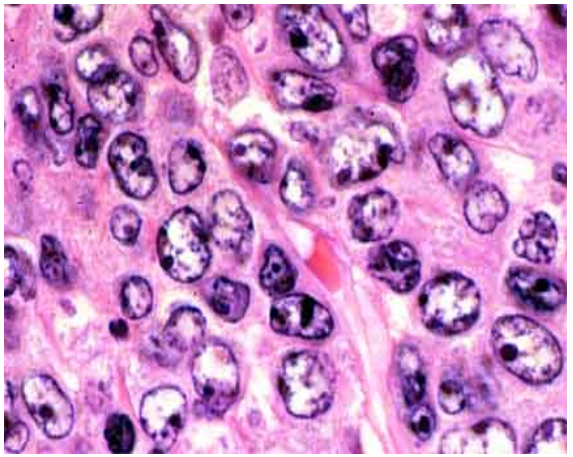
Role of ASCT in CR1 after BV-CHP

Diffuse Large B-cell Lymphoma

- Most common non-Hodgkin lymphoma
  - 40% of global NHL burden is DLBCL
  - Approximately 25-30K new cases per year in US
- All ages
  - Increases with age
- Both genders
- All races
- All socioeconomic classes
- Can manifest in nearly any organ or body part

Variable cure rate: 30-90%

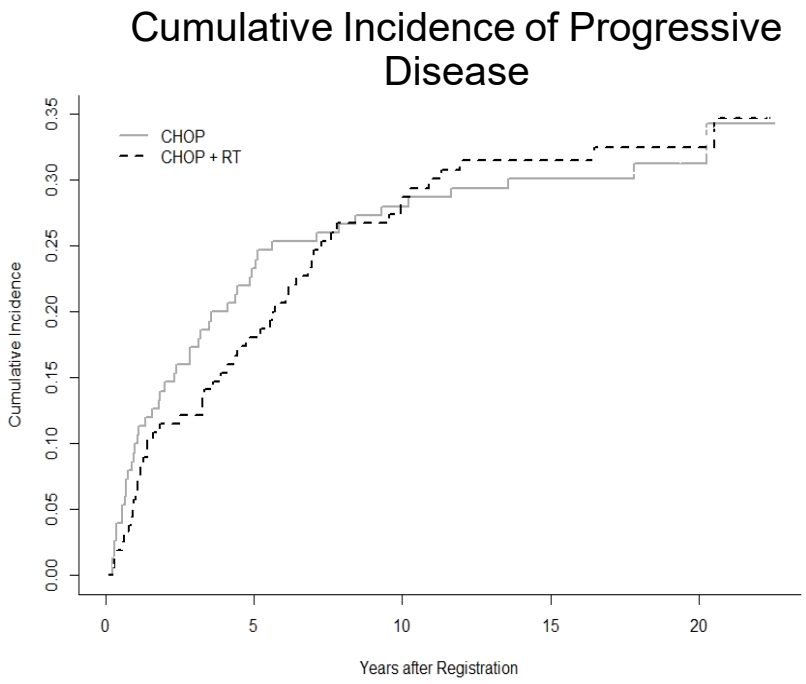




MANAGEMENT OF LIMITED STAGE DLBCL

Limited Stage Diffuse Large B-cell Lymphoma (DLBCL)

- About 25-30% of new DLBCL diagnosis
- SWOG S8736 - CHOP x 3 + radiation had superior PFS and OS compared to CHOP x 8
  - Difference disappeared by year 9 due to late relapses[1-3]
- Stage modified (Miller) IPI predicted outcome
  - Age > 60, Stage II (vs I), elevated LDH, WHO PS 2 (vs 0-1)



Stephens et al, JCO 2016

1. Miller et al, NEJM 1998. 2. Miller et al, ASH 2001, 724a. 3. Stephens et al, JCO 2016

Slide courtesy of Daniel Persky

Clinical Trials in Limited Stage DLBCL in the Rituximab Era

Trial	Design	Patients	PFS	OS
SWOG S0014 Persky, JCO 2008	Ph II: R-CHOPx3 + IFRT	Stage-modified IPI≥1 (n=60)	4-y: 88%	4-y: 92%
SWOG S0313 Persky, Blood 2015	Ph II: CHOPx3 + IFRT + RIT	Stage-modified IPI≥1 (n=46)	5-y: 82%	5-y: 87%
MINT Trial, Pfreundschuh, Lancet 2011	Ph III: CHOPx6 *v* R-CHOPx6 (+IFRT for stage I bulky)	≤60y; aaIPI=0, <7.5cm (n=101)	6-y: 90%	6-y: 95%
FLYER Trial Poeschel, ASH 2018	Ph III: R-CHOPx6 *v* R-CHOPx4+2R	≤60y; aaIPI=0, <7.5cm (N=588)	3-y: 94 *v* 96%	3-y: 98 *v* 99%
LYSA/GOELMS Lamy, Blood 2018	Ph III: PET-guided (PET-pos if >mediast) R-CHOPx4-6 *v* R-CHOPx4-6 + RT	Stage I/II, <7cm (n=319)	5-y EFS: 89 *v* 92%	5-y: 92 *v* 96%

Key Questions:

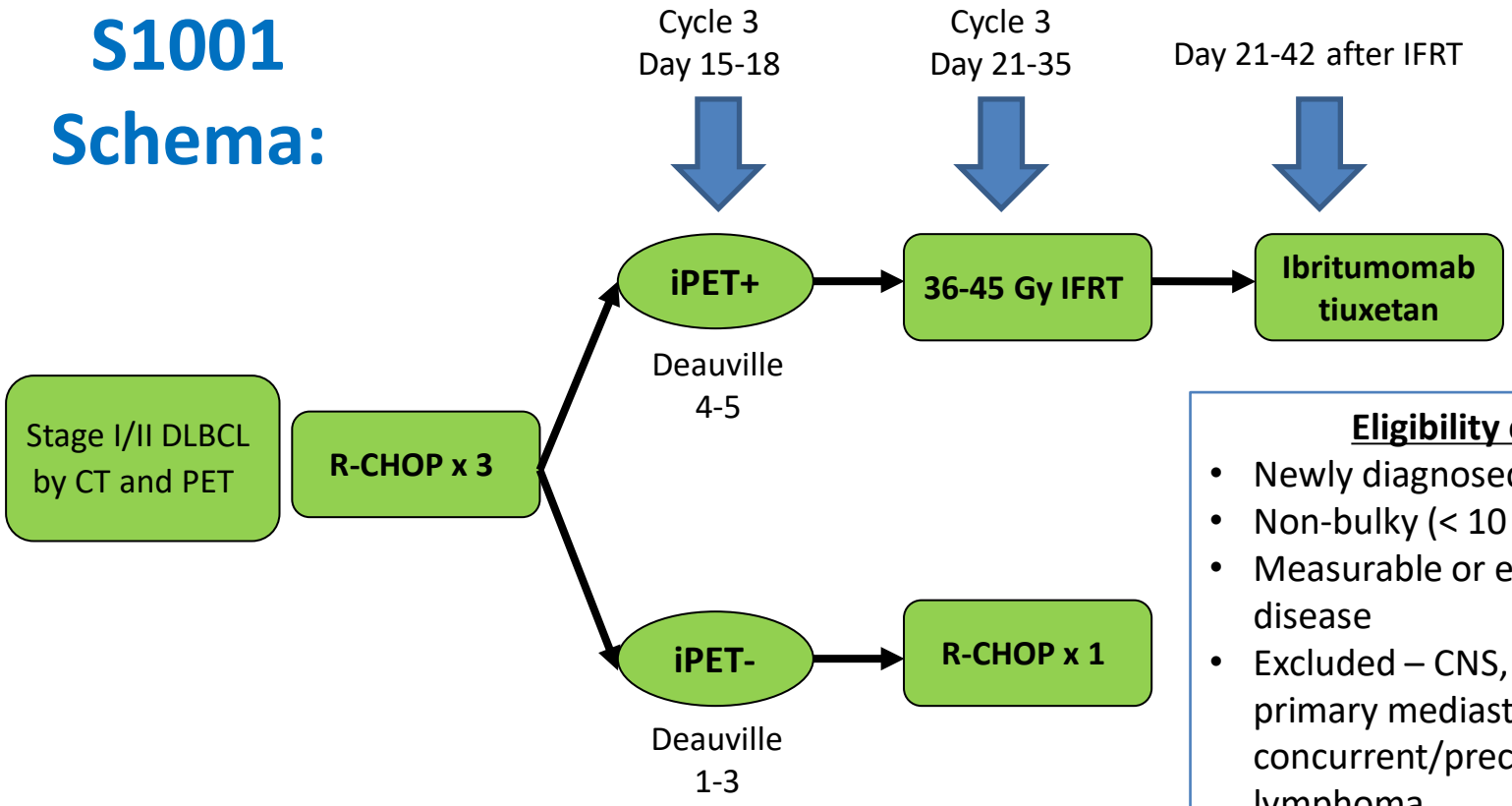
How much chemo is needed?

What is the role of radiation?

Does PET-adapted therapy maintain outcomes?

PET-Directed Therapy for Patients with Limited-Stage Diffuse Large B-Cell Lymphoma - Results of Intergroup NCTN Study S1001

S1001 Schema:



Eligibility criteria

- Newly diagnosed DLBCL
- Non-bulky (< 10 cm) stage I/II
- Measurable or evaluable disease
- Excluded – CNS, testicular, primary mediastinal, and concurrent/preceding indolent lymphoma

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Patient Characteristics: S1001

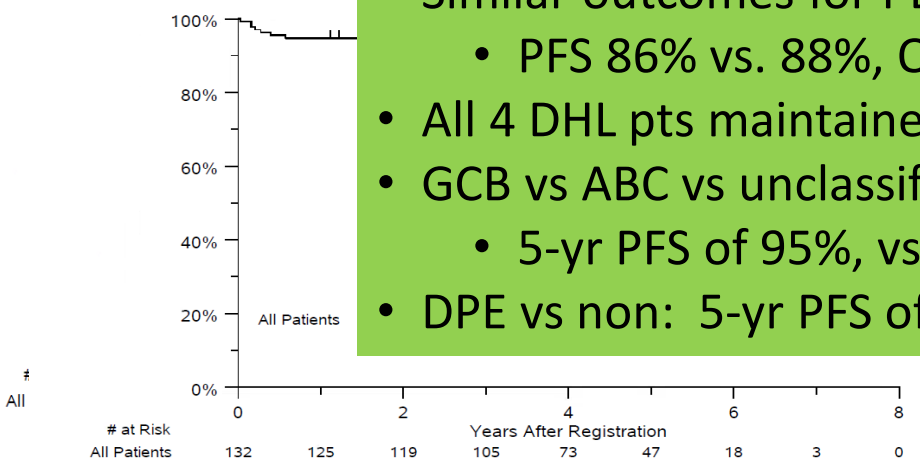
Patient Characteristic	S1001 (n=132)
Median Age (years, range)	62 (18-86)
Age > 60 years	71 (54%)
Male	70 (53%)
Performance status: 0 1 2	 89 (67%) 39 (30%) 4 (3%)
Stage I (rest stage II)	82 (62%)
Median largest diameter (cm, range)	3.5 (1.0 - 9.7 cm)
Extranodal involvement	57 (43%)
Head and Neck-only involvement	87 (66%)
Stage modified (Miller) IPI (smIPI) 0 1 2 3	 35 (27%) 55 (42%) 37 (28%) 5 (4%)

Persky J Clin Oncol 2020 Jul 13;JCO2000999

S1001: PFS and OS

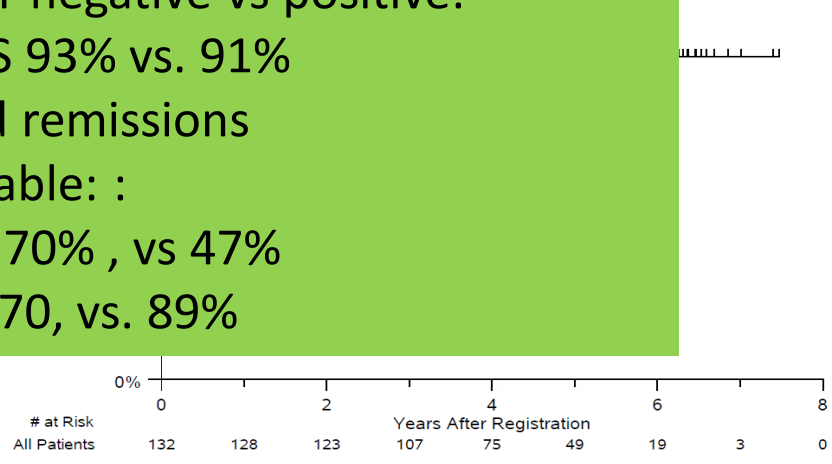
Results: Median follow up 4.5 yrs (range 1.1 – 7.5 yrs)

Progression-free Survival



5-year estimate 87%

Overall Survival



5-year estimate 90%

- Similar outcomes for PET negative vs positive:
  - PFS 86% vs. 88%, OS 93% vs. 91%
- All 4 DHL pts maintained remissions
- GCB vs ABC vs unclassifiable: :
  - 5-yr PFS of 95%, vs. 70% , vs 47%
- DPE vs non: 5-yr PFS of 70, vs. 89%

SWOG CANCER RESEARCH NETWORK

NCI National Clinical Trials Network NCI Community Oncology Research Program

Persky J Clin Oncol 2020 Jul 13;JCO2000999

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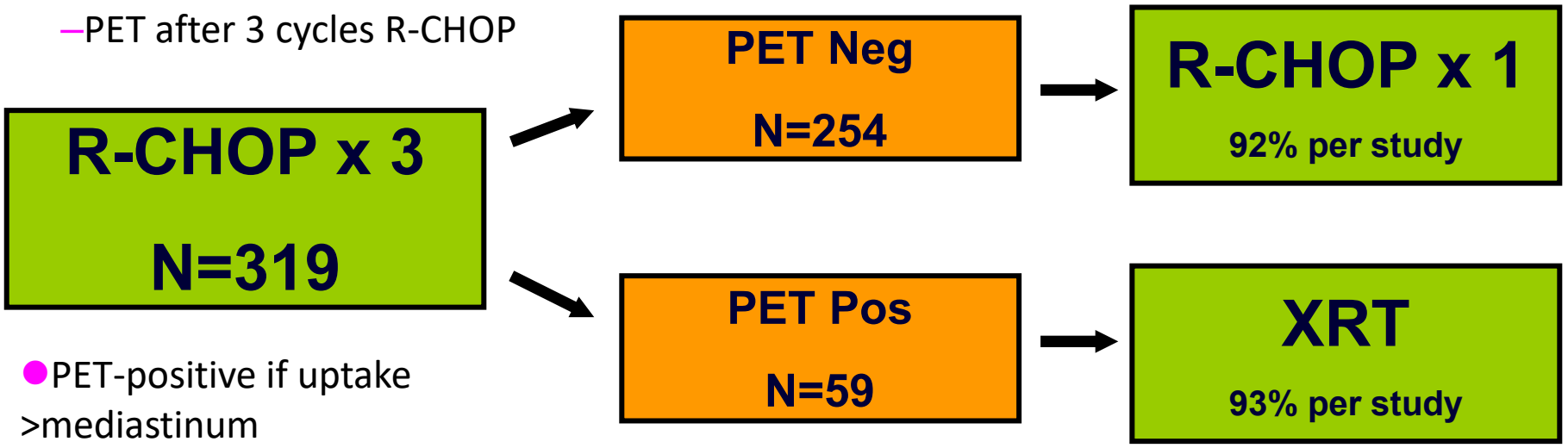
BCA: Long-term outcomes of PET-adapted treatment in limited stage DLBCL

- Age ≥ 16 years
- Newly diagnosed confirmed DLBCL
- Between Mar 2005 and Feb 2019
- Limited stage (Stage I/II, non-bulky <10cm, no B-symptoms, radiation encompassable)
- PET after 3 cycles R-CHOP



- PET-positive if uptake >mediastinum
  - 2005-2013: IHP guidelines
  - 2014-2019: Deauville criteria (D3-5 positive)
- Staging PET scans recommended since 2011

Sehn Blood (2019) 134 (Supplement_1): 401.

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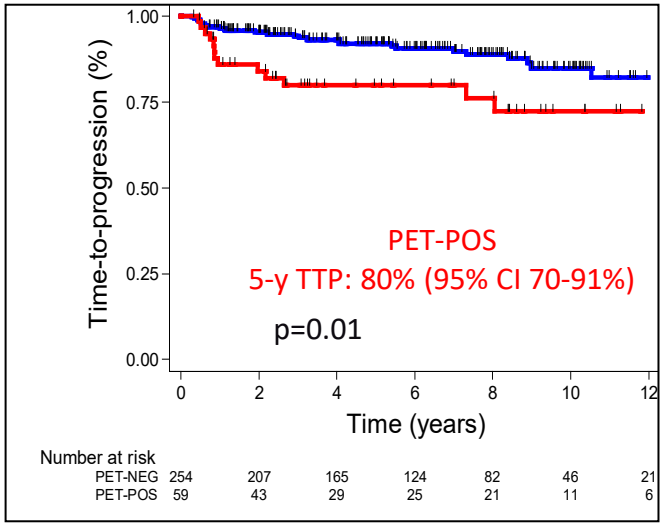
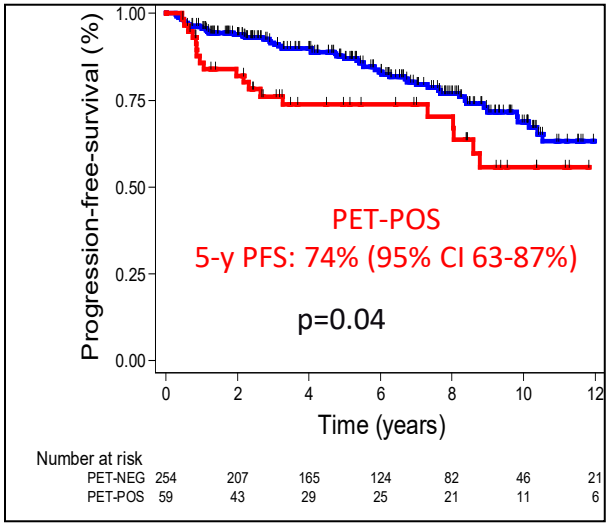
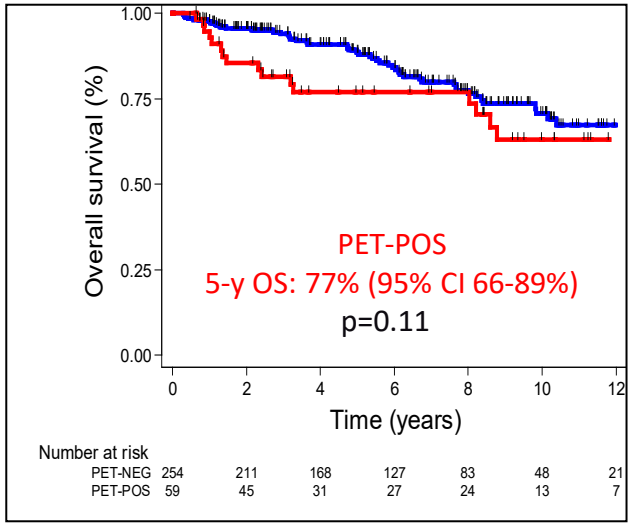
Outcomes According to PET Status (n=313)







MVA: Only Age > 60 y (p=0.002) and PET positivity (p=0.018) significant

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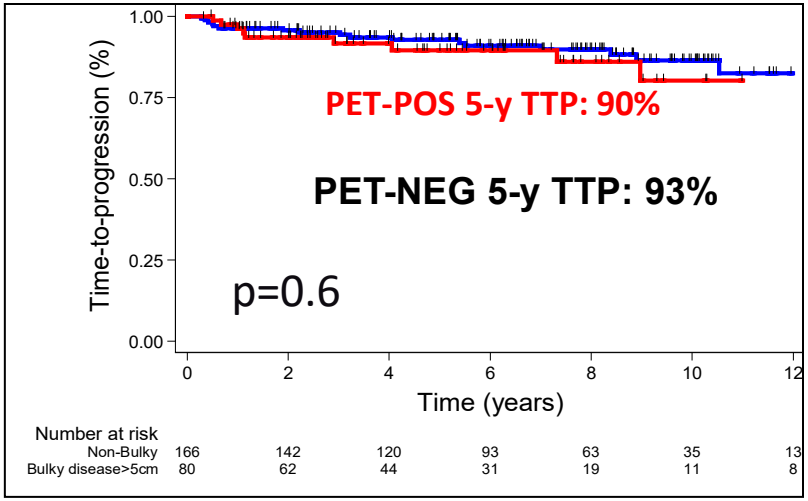
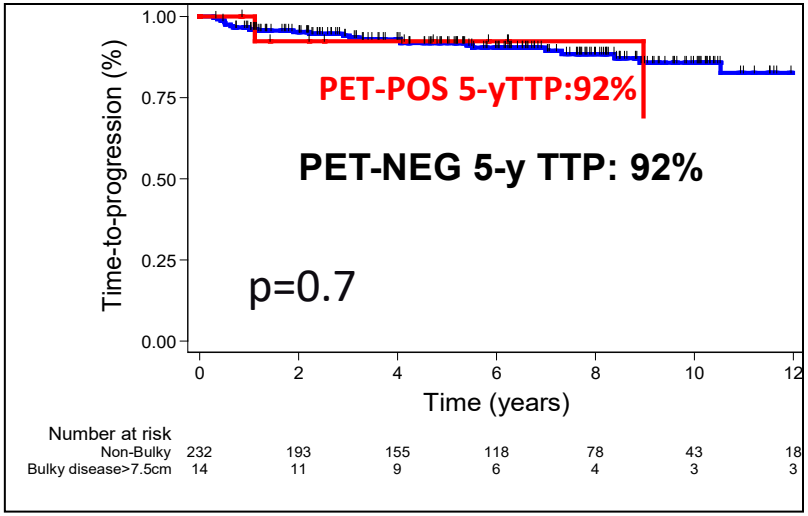
Time-to-Progression in PET-Negative Patients According to Bulk of Disease

Bulk defined as ≥5cm



Bulk defined as ≥7.5 cm



Sehn Blood (2019) 134 (Supplement_1): 401.

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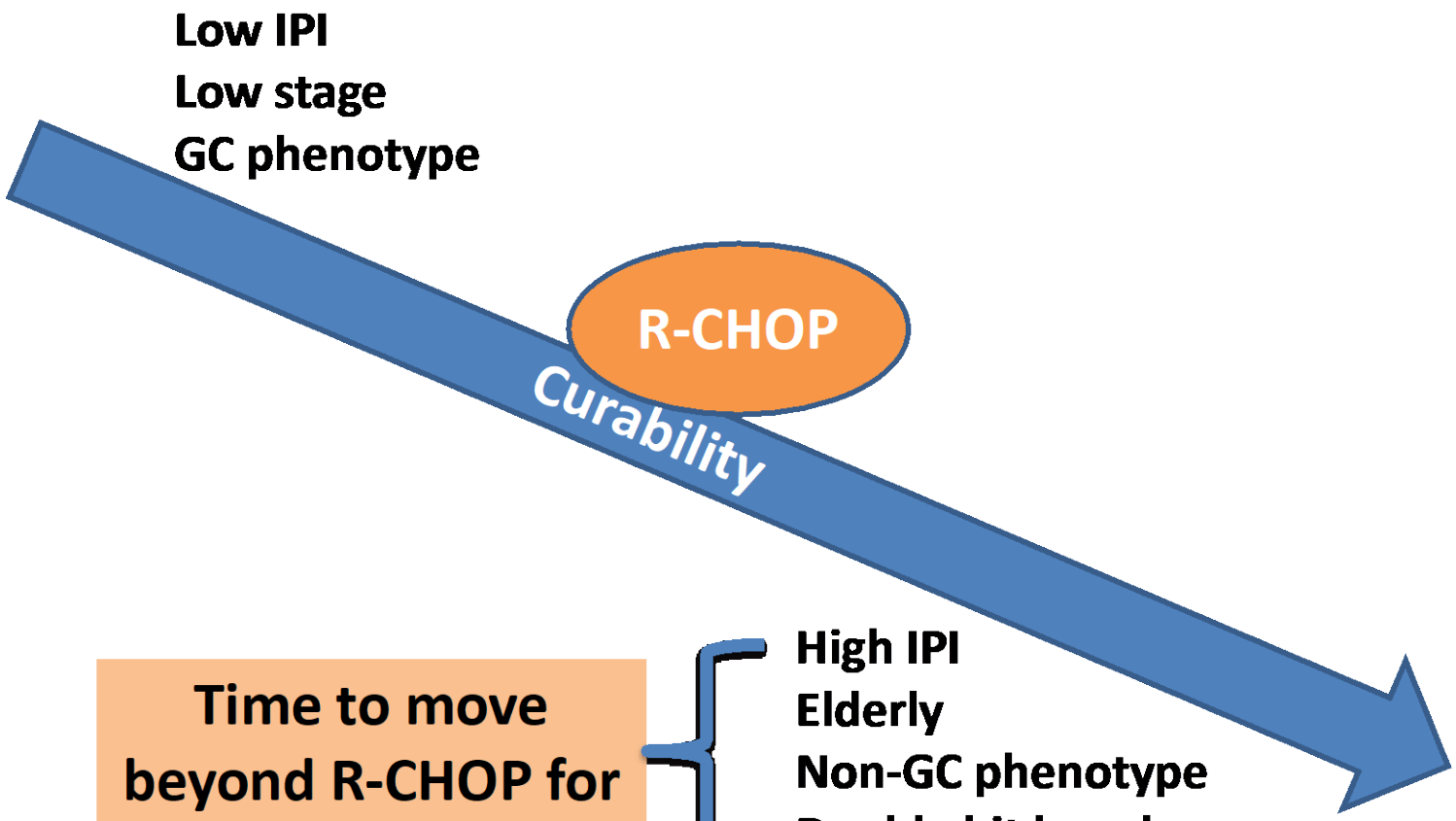
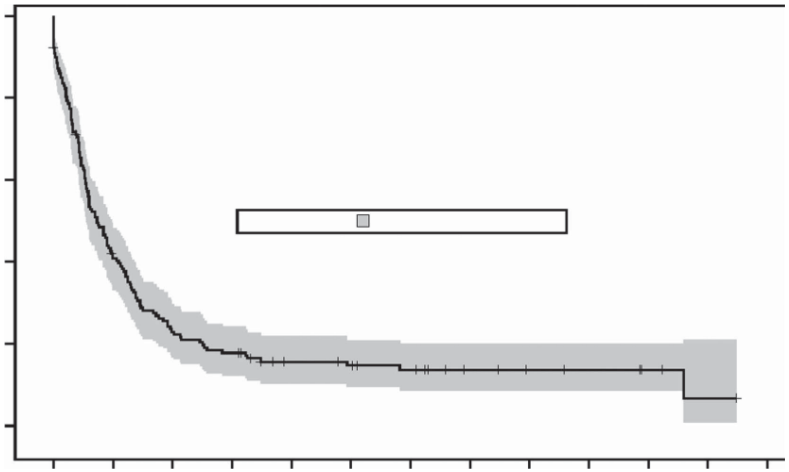
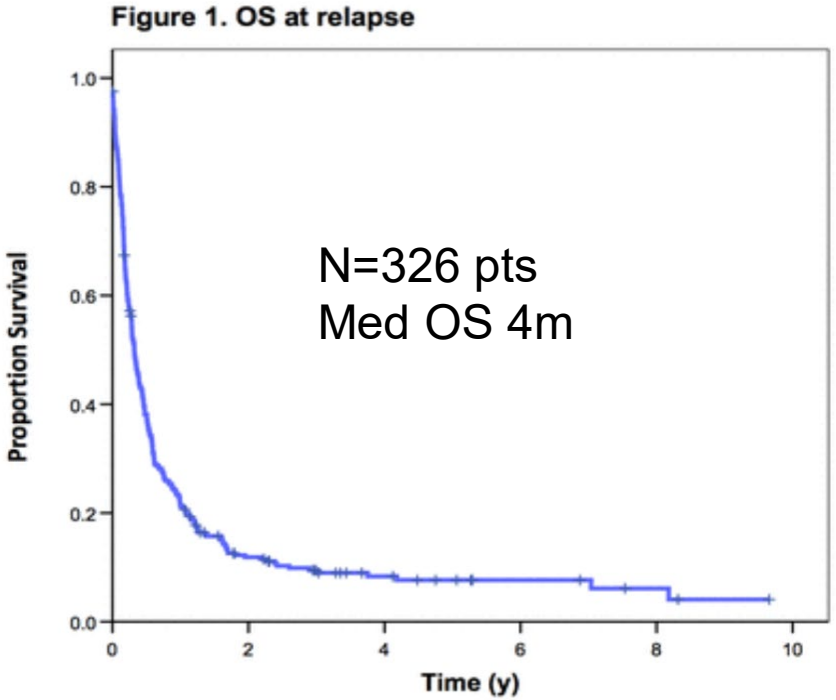
DIFFUSE LARGE B-CELL LYMPHOMA: RELAPSED/REFRACTORY DISEASE

Many subsets of DLBCL are not cured with R-CHOP



If transplant is not an option…

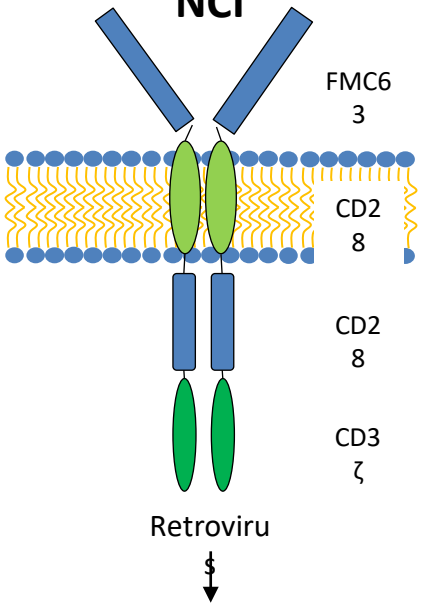




Van den Neste Bone Marrow Transplantation (2016) 51, 51–57
Kansara ASH 2014

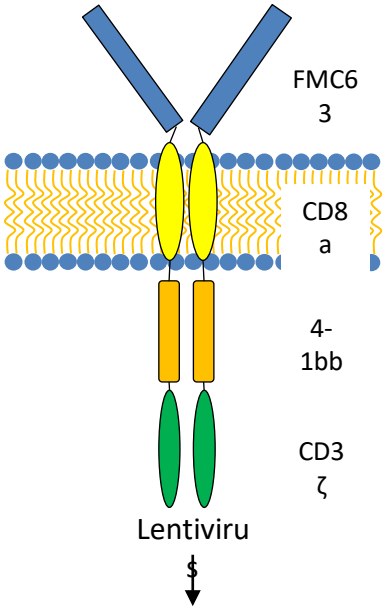
Two Anti-CD19 CAR T-cell Constructs are Currently FDA Approved as 3rd Line Therapy for R/R DLBCL

Axicabtagene ciloleucel (*aka* Axi-cel; Yescarta)
NCI



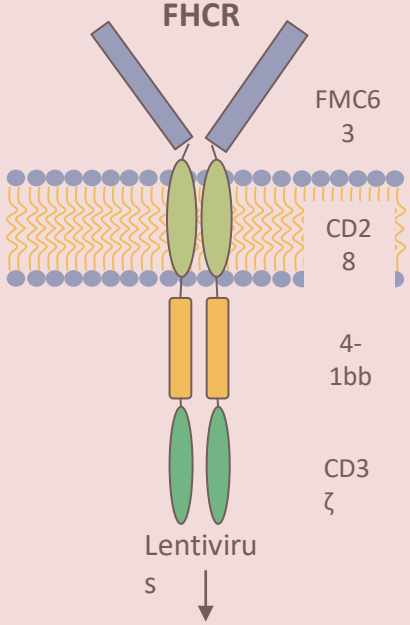
Kite Pharma - Gilead
KTE-C19

Tisagenlecleucel (*aka* Kymriah)
UPenn



Novartis
CTL-019

Lisocabtagene maraleucel
(*aka* Liso-cel)
FHCR



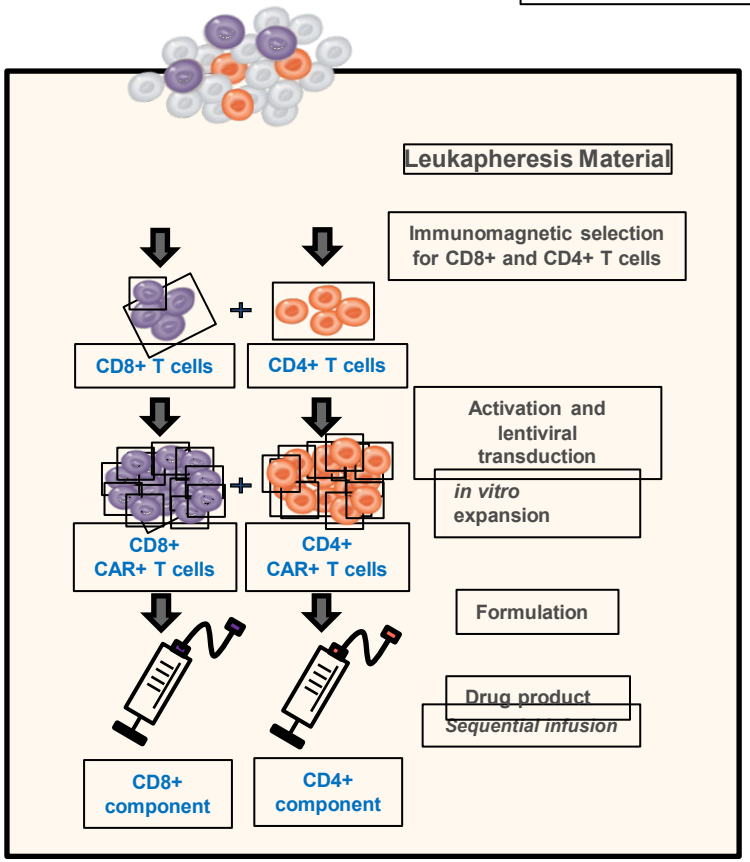
Juno Therapeutics - Celgene
JCAR 017

[1] Adapted from: van der Stegen SJ et al. Nat Rev Drug Discov. 2015 Jul;14(7):499-509.

Lisocabtagene maraleucel (liso-cel; JCAR017) Differs from Current CAR T-cell Products

CD19-Directed, Defined Composition, 4-1BB CAR T Cell Product

Apheresis product undergoes a T-cell selection step (*vs* unselected mononuclear cells for Axi-cel, Tisagenlecleucel)



CD8+ and CD4+ CAR+ T cell components are administered separately at equal target doses of CD8+ and CD4+ CAR+ T cells

The defined composition of liso-cel results in:

- Consistent administered CD8+ and CD4+ CAR+ T cell dose
- Low variability in the CD8+/CD4+ ratio

Dose and ratio of CD8+ and CD4+ CAR+ T cells may influence the incidence and severity of CRS and neurological events

Abramson Blood (2019) 134 (Supplement_1): 241.

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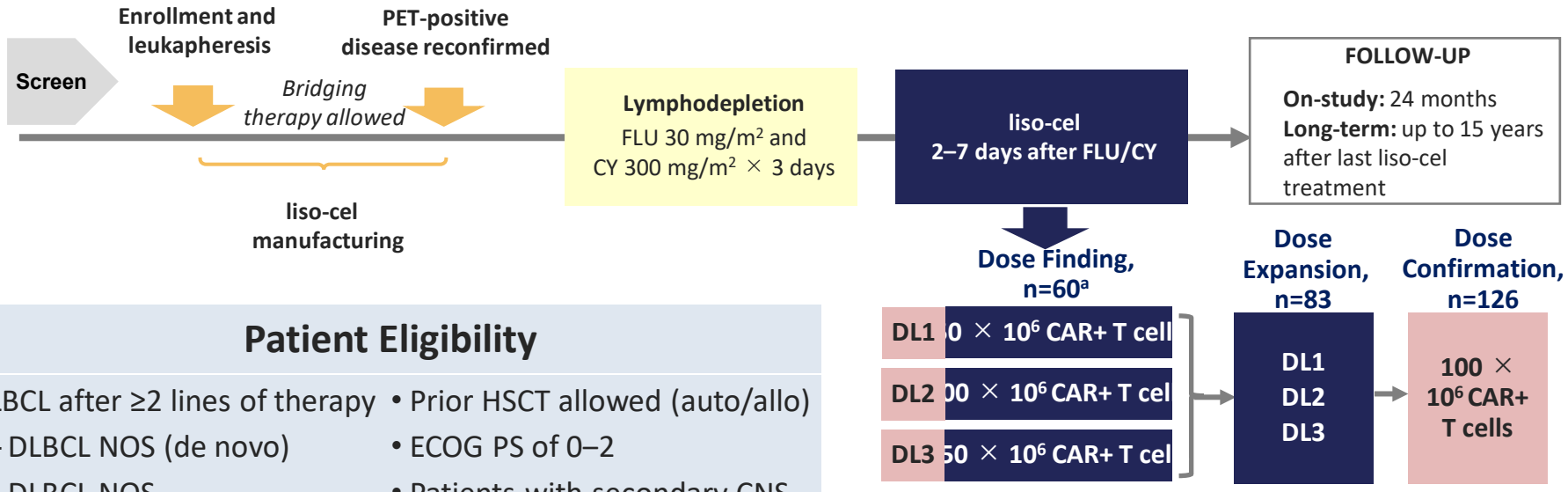
241: Pivotal Safety and Efficacy Results From TRANSCEND NHL 001, a Multicenter Phase 1 Study of lisocabtagene maraleucel (liso-cel) in Relapsed/Refractory (R/R) DLBCL (Abramson et al)



Patient Eligibility

- LBCL after ≥2 lines of therapy
  - DLBCL NOS (de novo)
  - DLBCL NOS (transformed from FL, CLL, MZL, or other)
  - HGBCL (double/triple hit)
  - PMBCL
  - FL3B
- Prior HSCT allowed (auto/allo)
- ECOG PS of 0–2
- Patients with secondary CNS lymphoma were eligible
- CrCl >30 mL/min/1.73 m²
- LVEF ≥40%
- No lower threshold for ALC, ANC, platelets, or hemoglobin

End Points

Primary

- Adverse events, ORR by IRC

Secondary

- CR rate by IRC, duration of response, PFS, OS, PK

Abramson Blood (2019) 134 (Supplement_1): 241.

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Baseline Characteristics

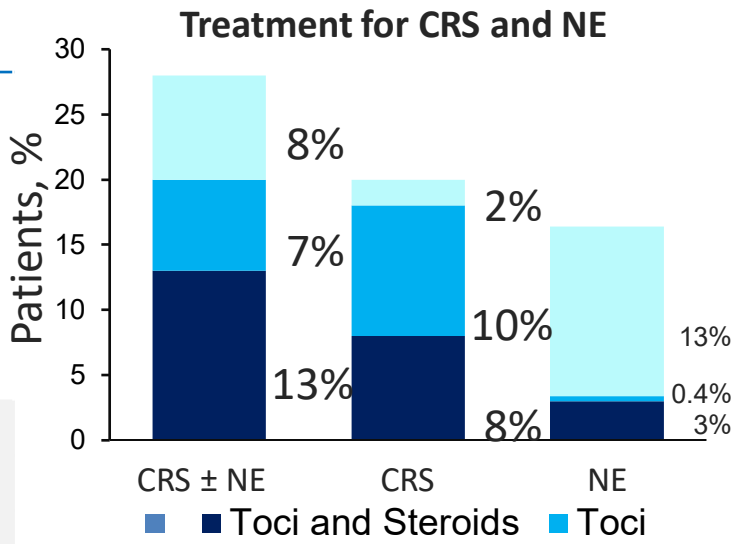
Characteristic	All liso-cel–Treated Patients (N=269)
Age, median (range), years	63 (18–86)
% ≥65	42
% ≥75	10
% **NHL subtypes**	
DLBCL NOS	51
Transformed from FL / other indolent lymphomas	22 / 7
HGBCL[a] / PMBCL / FL3B	13/ 16 / 1
% **Secondary CNS lymphoma**	3
% **ECOG PS of 0–1 / 2 at screening**	99 / 1
% **High disease burden**	38
% **Creatinine clearance >30 to <60 mL/min**	19
% **LVEF ≥40% to <50%**	5
Prior systemic therapies, median (range)	3 (1–8)
% ≥4 prior therapies	26
% **Received prior HSCT**	35
Autologous / allogeneic HSCT	33/3
% Chemotherapy-refractory	67
% **Never achieved CR with prior therapy**	44
% **Received bridging therapy**	59

89% of patients had high-risk features known to portend a shortened overall survival

- HGBCL/double/triple hit lymphoma
- ECOG PS of 2
- Primary refractory disease
- Refractory to second-line or later therapy
- No prior ASCT
- Never achieved CR

Patient Incidence and Management of CRS and NE

	All liso-cel–Treated Patients (N=269)
CRS	
Any grade, n (%)	113 (42)
Grade 3, n (%)	4 (1)
Grade 4, n (%)	2 (1)
Time to onset, median (range), days	5 (1–14)
Time to resolution, median (range), days	5 (1–17)
NE	
Any grade, n (%)	80 (30)
Grade 3, n (%)	23 (9)
Grade 4, n (%)	4 (1)
Time to onset, median (range), days	9 (1–66)
Time to resolution, median (range), days	11 (1–86)
ICU admissions,n (%)	19 (7)
For CRS and/or NE	12 (4)
Other reasons	7 (3)



- 3% of patients received vasopressors for CRS or NE
- 2 patients received other anti-inflammatory/anticytokine agents

CRS and NE were reversible

- 1 patient had an unresolved NE (grade 1 tremor) at data cutoff
- 8 patients had ongoing CRS/NE at time of death from other reasons

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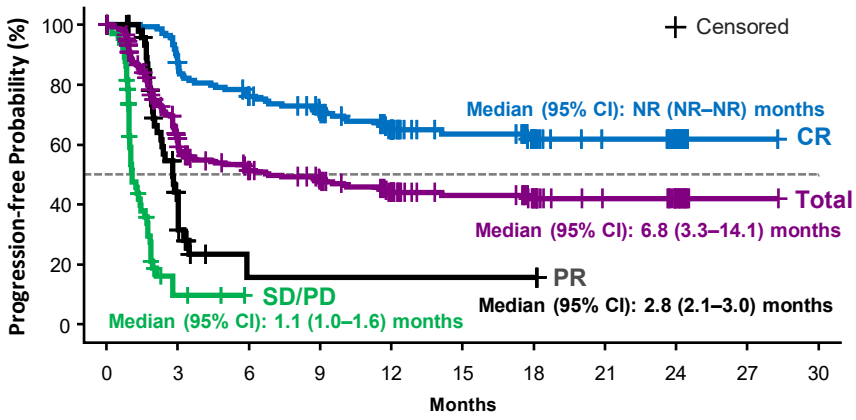
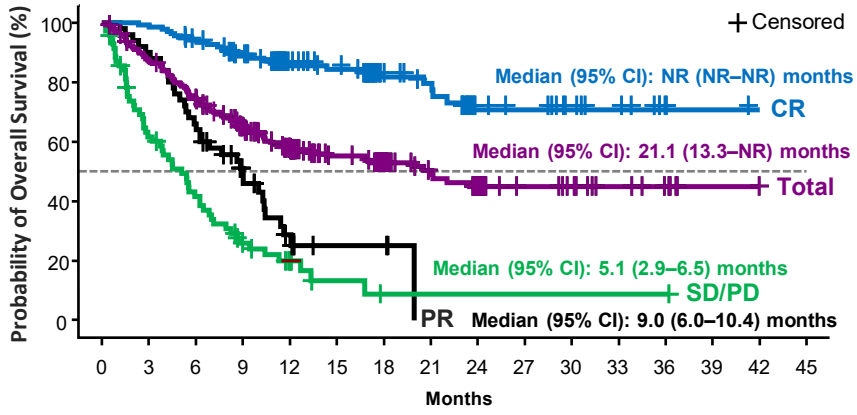
PFS and OS by Objective Response

PFS Median Follow-up (95% CI): 12.3 (12.0–17.5) Months



CR	136	116	98	85	63	45	31	23	14	1	0
PR	50	14	2	2	2	2	2	0			
SD/PD	70	3	0								
Total	256	133	100	87	65	47	33	23	14	1	0

OS Median Follow-up (95% CI): 17.6 (13.5–18.0) Months



CR	136	135	128	113	94	68	48	36	26	16	13	8	5	1	0
PR	50	45	33	20	8	3	3	0							
SD/PD	70	41	27	14	7	3	1	1	1	1	1	1	1	0	
Total	256	221	188	147	109	74	52	37	27	17	14	9	6	1	0

6-month PFS (95% CI), %	
All patients	51.4 (44.6–57.7)
Patients with BOR of CR	76.1 (67.9–82.4)
12-month PFS (95% CI), %	
All patients	44.1 (37.3–50.7)
Patients with BOR of CR	65.1 (56.1–72.7)

6-month OS (95% CI), %	
All patients	74.7 (68.9–79.6)
Patients with BOR of CR	94.1 (88.6–97.0)
12-month OS (95% CI), %	
All patients	57.9 (51.3–63.8)
Patients with BOR of CR	85.5 (78.2–90.5)

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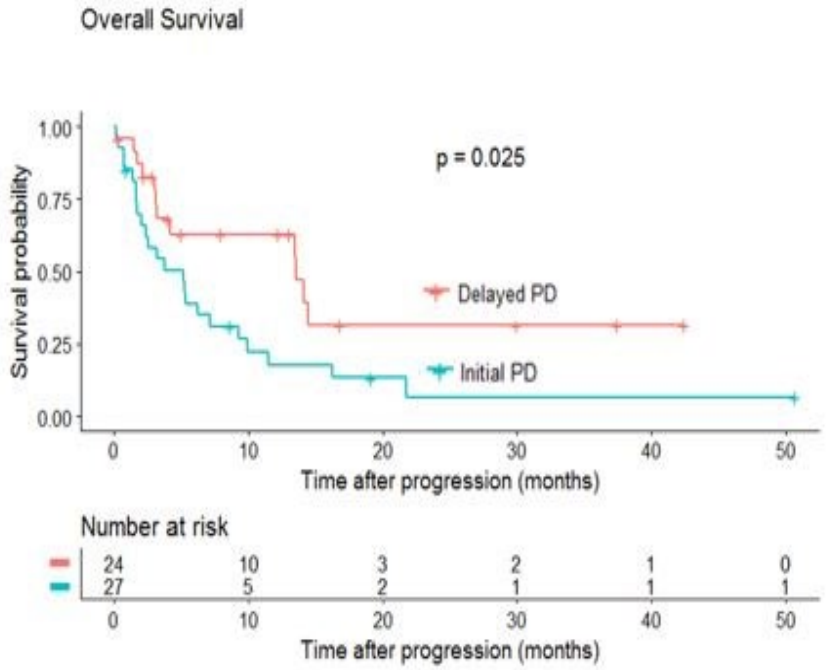
If CAR-T doesn't work…



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. 13.6m

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

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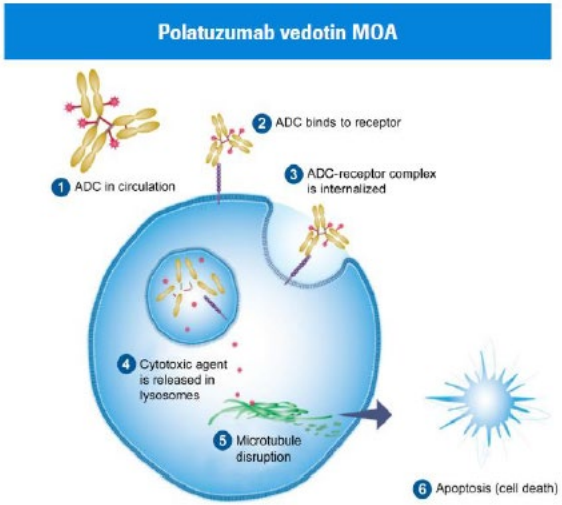
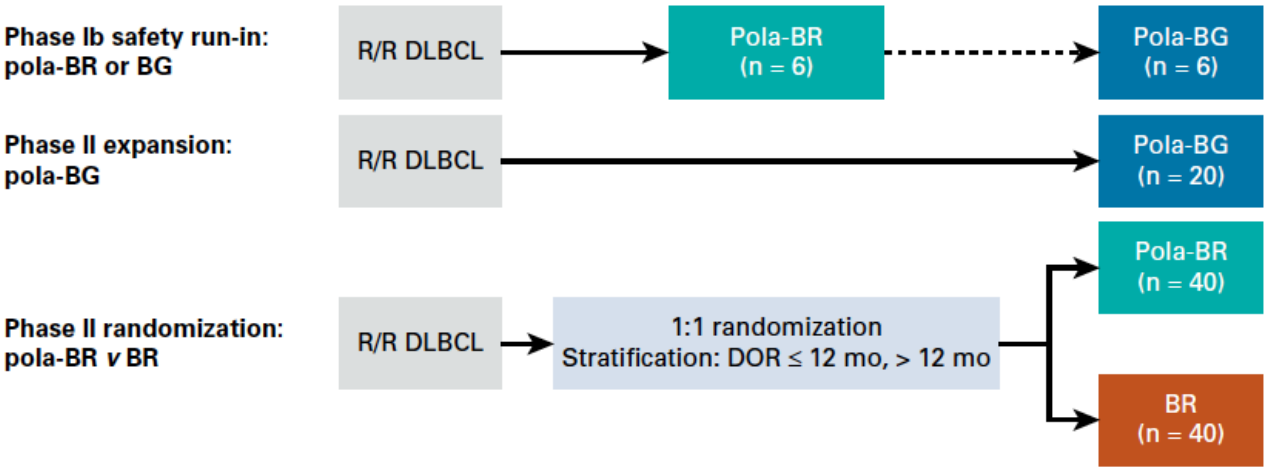
No standard of care—goal is palliation

- ***Clinical trials***
- Chemoimmunotherapy
  - Gemcitabine-based regimens
  - Pola-BR
- Non-chemotherapy options
  - Selinexor
  - Tafasitamab-lenalidomide (FDA-approved 7/31/2020)
  - *Ibrutinib (preferential activity in non-GC DLBCL)**
  - *Len/rituximab (preferential activity in non-GC DLBCL)**
- Best supportive care

**not FDA-approved*

Pola-BR: anti CD79b ADC plus BR





- Primary endpoint CR rate at EOT
- Med f/u 22.3 months

Sehn *Journal of Clinical Oncology* 36, no. 15_suppl (May 20, 2018) 7507-7507.
Figure courtesy of Roche.com

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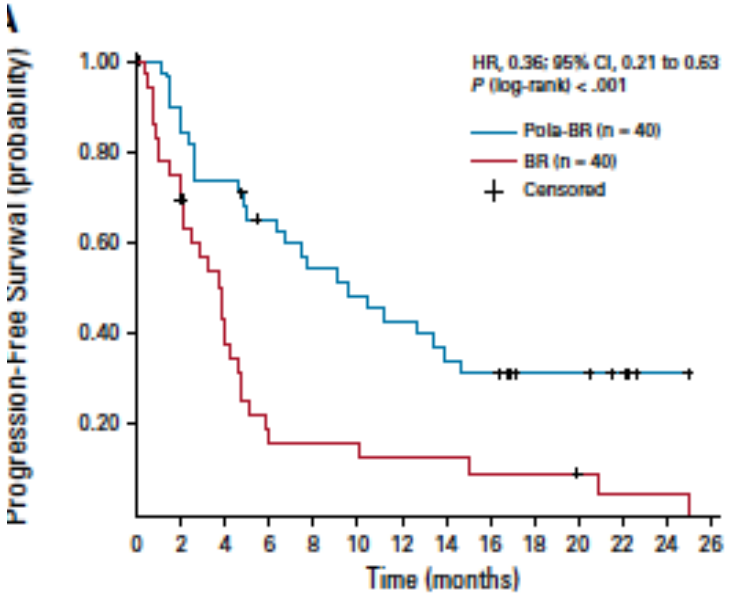
RP2: Pola-BR vs. BR

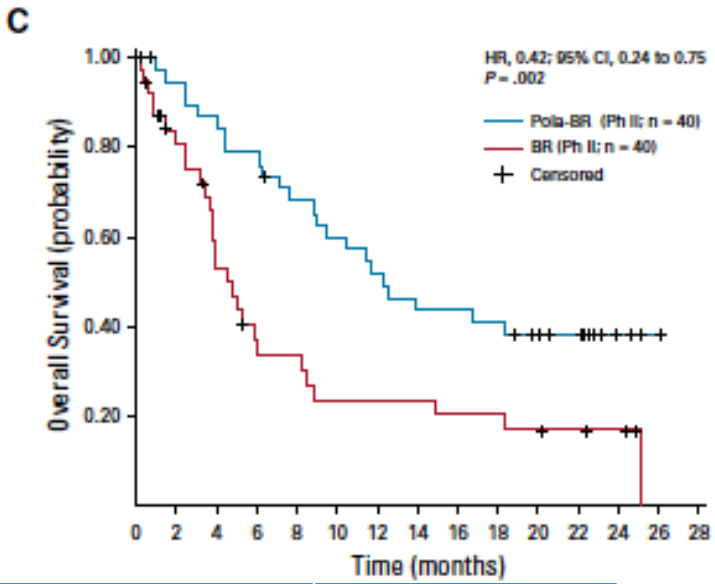
	Pola-BR (n=40)	BR (n=40)
Median age	67y (33-86)	71y (30-84)
Male	70%	62.5%
PS 0-1	83%	78%
ABC-DLBCL	48%	48%
GCB-DLBCL	38%	43%
Med prior Rx	2 (1-7)	2 (1-5)
Ref to last Rx	75%	85%
DOR to last Rx $\leq$ 12 m	45%	48%

Main reasons for transplant ineligibility include advanced age and insufficient response to prior salvage therapy

Sehn *Journal of Clinical Oncology* 36, no. 15_suppl (May 20, 2018) 7507-7507.

Pola-BR vs. BR Results





	Pola-BR (n=40)	BR (n=40)
EOT Response % (ORR/CR)	45/40	18/18
Best response % (ORR/CR)	63/50	25/23
Med DR	12.6	7.7m
Med PFS	9.5m	3.7m
Med OS	12.4m	4.7m

Sehn *Journal of Clinical Oncology* 36, no. 15_suppl (May 20, 2018) 7507-7507.

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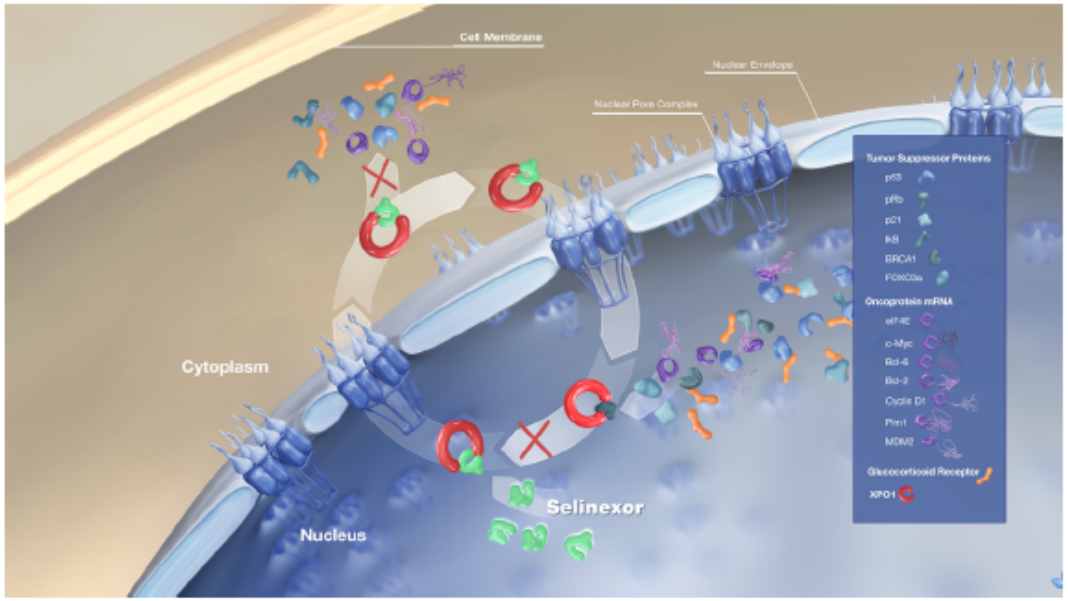
Selinexor: oral XPO1 inhibitor

Selinexor: Mechanism of Action



Exportin 1 (XPO1 or CRM1) mediates the nuclear export of proteins, mRNAs, rRNAs, snRNAs and impacts

- **Tumor suppressor proteins** (p53, IκB, FOXO etc.)
- **eIF4E** (Translational initiation factor) bound oncogenic mRNAs (c-Myc, Bcl-xL, cyclins etc.)

Selinexor is an oral selective **XPO1** inhibitor; preclinical data support that XPO1 inhibition:

- Reactivates multiple TSPs relevant to NHL, (p53, p21, IκB, FOXO etc.)
- Disrupts localization of eIF4e (overexpressed in most B-cell lymphomas[1]
- Reduces c-Myc, Bcl-2, and Bcl-6 levels[2-3]

1. Kodali 2011 2. Kuruvilla 2014 3. Schmidt 2013

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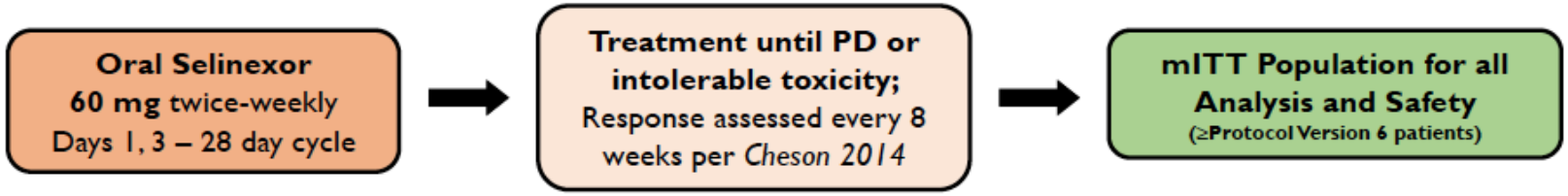
SADAL: Phase 2b trial of selinexor monotherapy



Objectives:

- **Primary Endpoint**: Overall response rate (ORR): Independent Central Radiological Review (ICRR); Lugano Classification (2014)
- **Secondary Endpoints**: Duration of response (DOR), Overall survival (OS), Safety

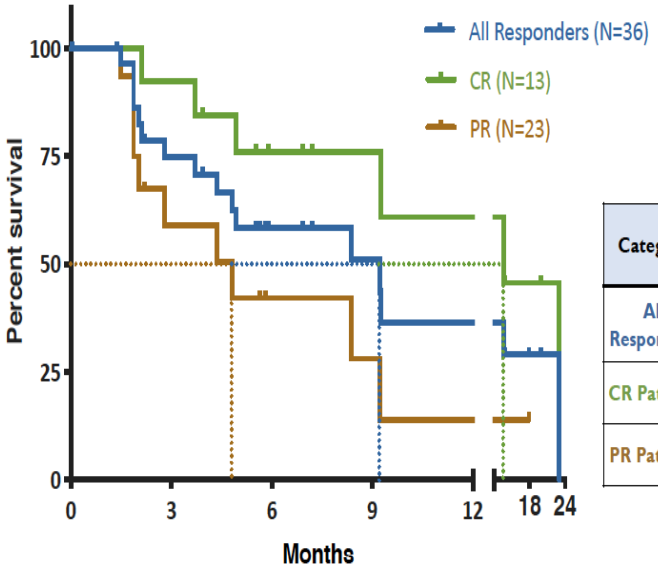
Modified Intent to Treat (mITT) Population: All patients who were randomized to the **60 mg Arm**

Characteristic	N
Enrolled* as of April 3, 2019	**127**
Median Age, Years (Range)	**67** (35–87)
Males (%) : Females (%)	**75** (59%) : **52** (41%)
Median Years from DLBCL Diagnosis (Range)	**2.6 yrs** (<1–26.2)
De novo DLBCL : Transformed DLBCL : Unknown	**96** (76%) : **30** (24%) : **1** (<1%)
GCB Subtype : Non-GCB Subtype : Unclassified	**59** GCB : **63** Non-GCB : **5** Unclassified
Median Prior Treatment Regimens (Range)	**2 (1–6)**
Prior Transplantation	39 (31%)

Kalakonda ICML 2019

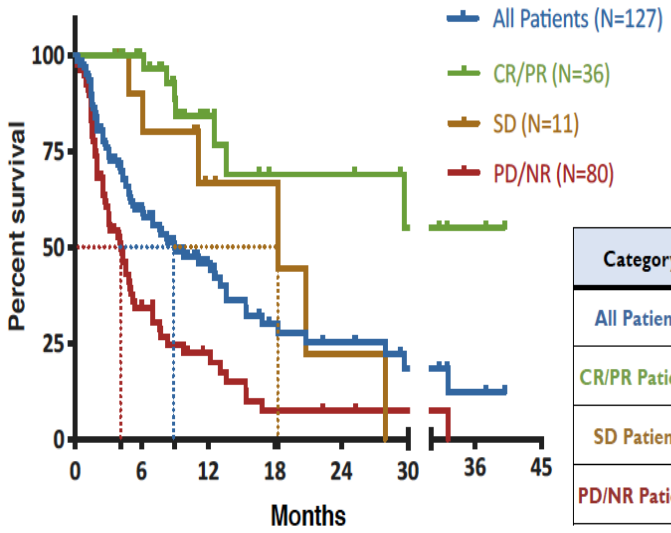
SADAL: Results

Duration of response



Category	Median DOR (months)	95% CI
All Responders	9.2	(4.8 – 23.0)
CR Patients	13.5	(9.3 – 23.0)
PR Patients	4.8	(2.0 – NE)

Overall survival



Category	Median OS (months)	95% CI
All Patients	9.0	(6.2 – 13.7)
CR/PR Patients	Not Reached	(13.7 – NE)
SD Patients	18.3	(11.1 – 28.0)
PD/NR Patients	4.1	(3.0 – 5.2)

Median follow-up of 11 months

- Selinexor dosing is 60mg BIW with 17% stopping due to A/Es
- ORR 29% (CR 13%)
- Median DOR 9.3 months and for CR 23 months
- Main toxicities: asthenia, nausea, weight loss, cytopenias

Kalakonda ICML 2019

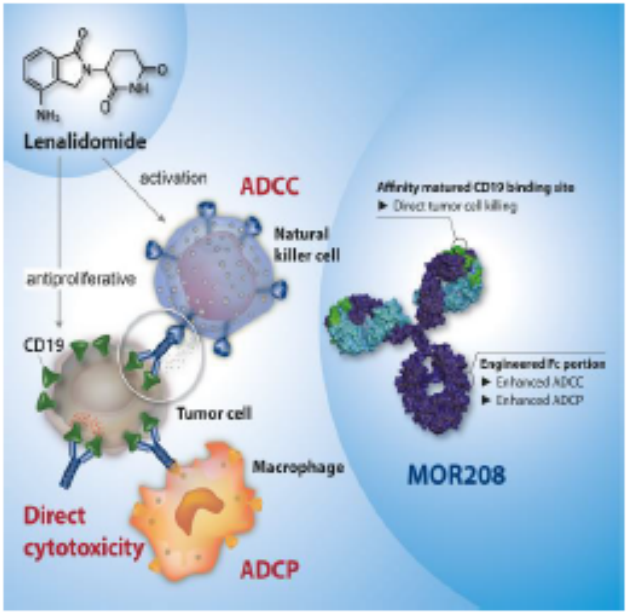
Tafasitamab MOA

MOR208
Fc-enhanced, anti-CD19 mAb

+

Lenalidomide

- ADCC ↑
- ADCP ↑
- Direct Cell Death
- Encouraging single agent activity in NHL patients with long DoR in R/R DLBCL



- T and NK Cell Activation/Expansion
- Direct Cell Death
- Demonstrated activity as an anti-lymphoma agent, alone or in combination
- Approved for treatment of MCL and FL/MZL

Potentiation of activity by combining Tafasitamab & LEN in vivo and in vitro

Salles et al. ICML 2019. #124.
Hortonet al., 2008; Awanet al., 2010; Richter et al., 2013; MorphoSys data on file; Wu et al., 2008; Lapalombella et al., 2008; Zhang et al., 2013, Wiernik et al., 2008; Witzig et al., 2011; Czuczman et al., 2017; Jurczak et al, 2018

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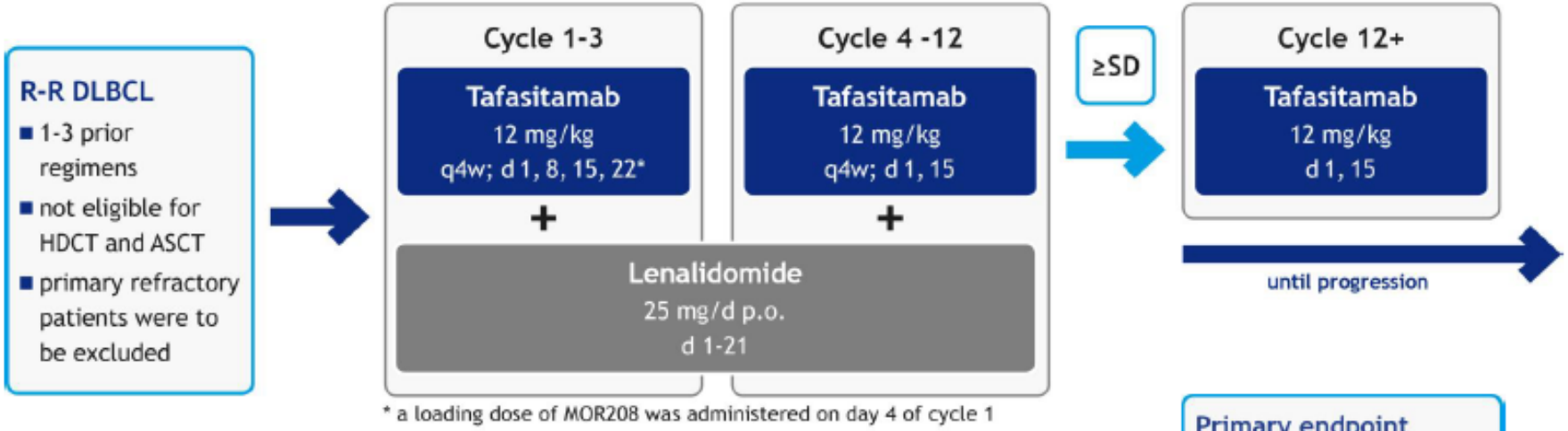
L-MIND: Study Design



* a loading dose of MOR208 was administered on day 4 of cycle 1

- Sample size suitable to detect ≥15% absolute increase in ORR for Tafasitamab/LEN combination vs. LEN monotherapy at 85% power, 2-sided alpha of 5%
- Mature Data: Primary Endpoint Analysis with data cut-off 30 Nov 2018; minimum Follow-Up 12 months, median Follow-Up 17.3 months

-Primary refractory DLBCL was defined as no response to or progression/relapse during or within 6 months of frontline therapy.
-Response assessment (Cheson 2007 Criteria) was after cycles 2, 4, 6, 9 and 12, thereafter every 3 cycles.
-ASCT, autologous stem cell transplant; HDCT, high-dose chemotherapy; SD, stable disease, p.o., per os.

Primary endpoint
- ORR (Central read)

Secondary endpoints
- PFS
- DoR
- OS
- Safety of the Tafasitamab + LEN combination
- Exploratory and biomarker-based analyses

- Salles et al. ICML 2019. #124.

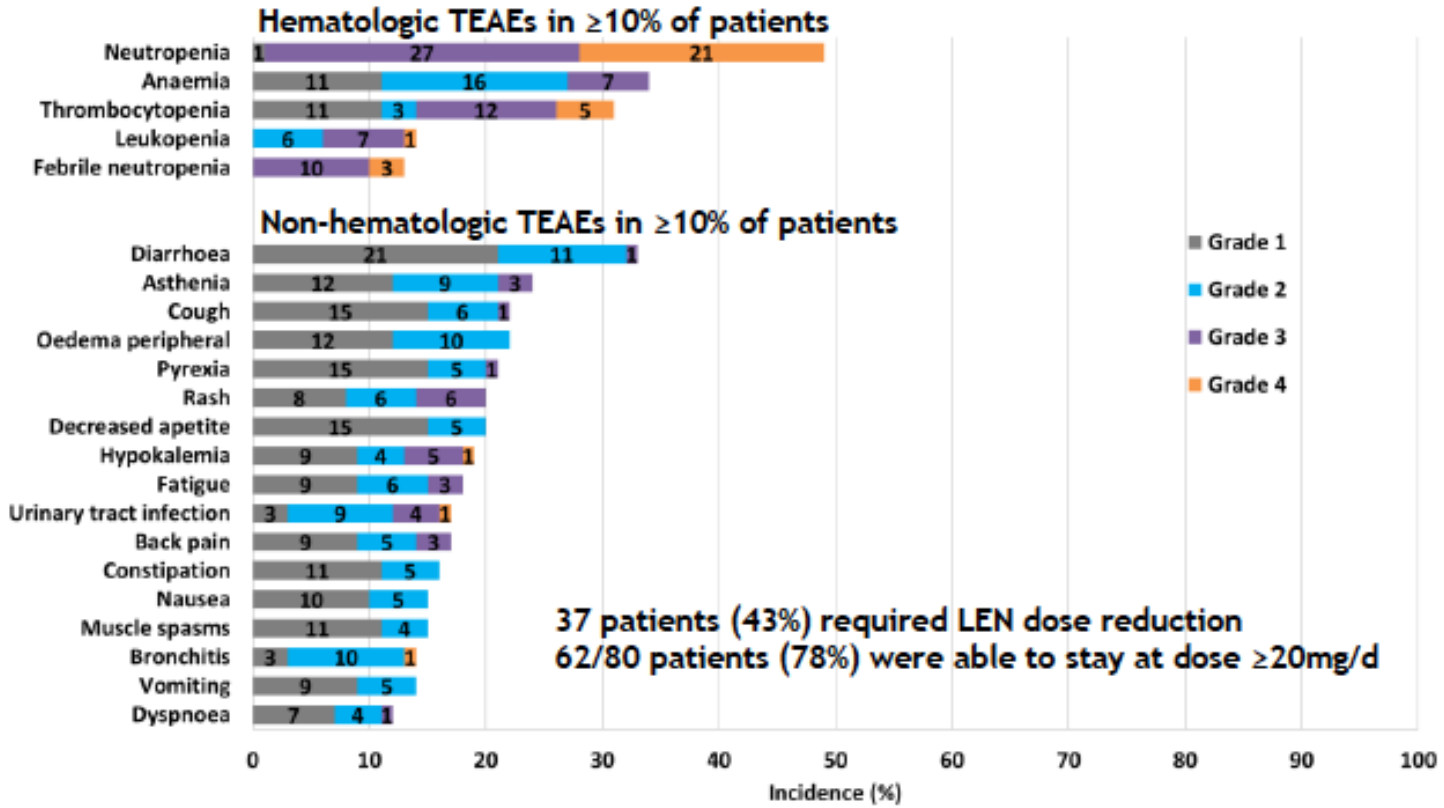
L-MIND: Baseline Characteristics

Characteristic	Specification	n=81 (%)
Sex	Male Female	44 (54) 37 (46)
Age [years]*	median (range)	72 (41-86)
Risk (IPI)*	0-2 3-5	40 (49) 41 (51)
Ann Arbor Stage*	I-II III-IV	20 (25) 61 (75)
Elevated LDH*	Yes No	45 (56) 36 (44)
Prior Lines*	median 1 2 3 4	2 40 (49) 35 (43) 5 (6) 1(1)
Primary Refractory	Yes No	15 (18) 66 (82)
Refractory to last prior therapy*	Yes No	36 (44) 45 (56)
Prior SCT	Yes No	9 (11) 72 (89)
Cell of Origin (Centrally assessed - Hans algorithm)	GCB Non-GCB Unknown	37 (46) 20 (25) 24 (30)

*at study entry

- Salles et al. ICML 2019. #124.

L-MIND: Treatment-Emergent AEs



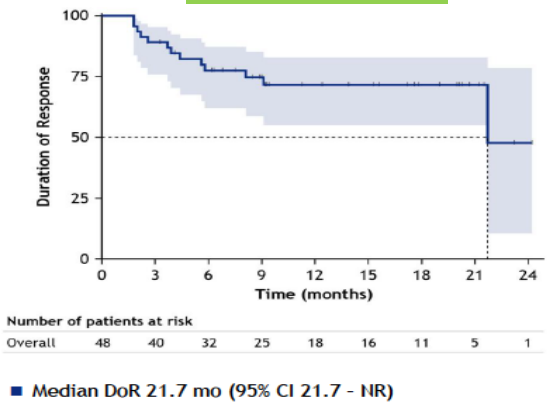
- 5 infusion-related reactions in 5 patients (6%) were reported for Tafasitamab (all grade 1)
- Treatment-related SAEs occurred in 15 (18.5%) patients (primarily infections [10%] or neutropenic fever [5%])
- 4 treatment-emergent deaths (sudden death, respiratory failure, cerebrovascular accident, PML) were reported as unrelated to study drugs

N=81. TEAEs, treatment-emergent adverse events, numbers represent % patients

- Salles et al. ICML 2019. #124.

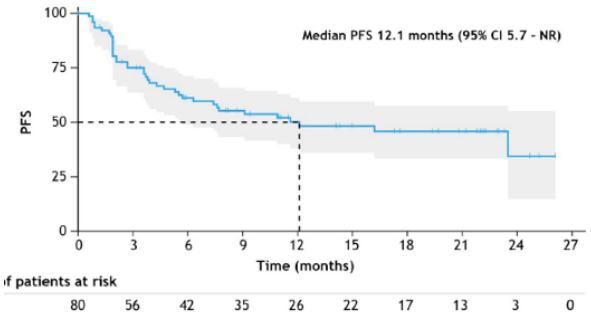
L-MIND: Efficacy

DR



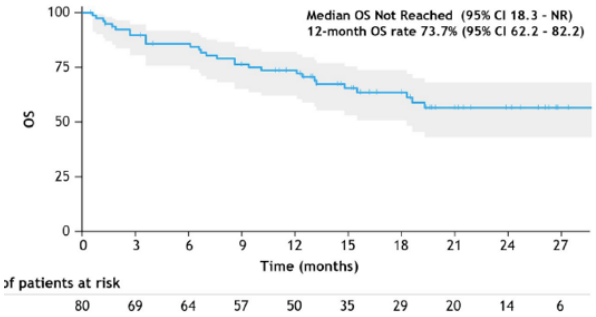
■ Median DoR 21.7 mo (95% CI 21.7 - NR)

PFS



Median Follow-up Time 17.3 months
39 PFS events recorded
28 patients still ongoing with study treatment

OS



Median Follow-up Time: 19.6 months
29 deaths recorded

<u>Key Outcomes</u>:

ORR 60%**

CR 42.9%

Med DR 21.7m

Med PFS 12.1m

12m OS 73.7%

Salles et al. ICML 2019. #124; Lancet Oncology 2020.

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RELAPSED/REFRACTORY MCL

Zanubrutinib monotherapy in rel/ref MCL

Rel/ref MCL → Zanubrutinib 160mg BID

Primary endpoint: ORR

- *Second generation BTKi*
- *Lower off-target inhibitory activity on other kinases (ITK, JAK3, EGFR)*

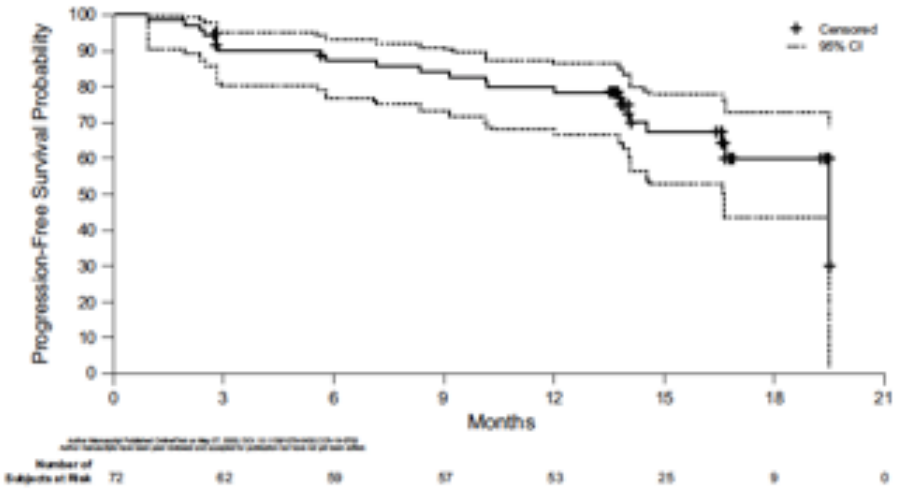
	N=86
Male	67 (77.9)
Chinese	86 (100)
Med age	60.5y (34-75y)
≥ 65 y	22 (25.6)
Refractory disease	45 (52.3)
TP53-mutated (n=54)	15 (27.8)

No new TEAEs
Less HTN, a.fib, bleeding

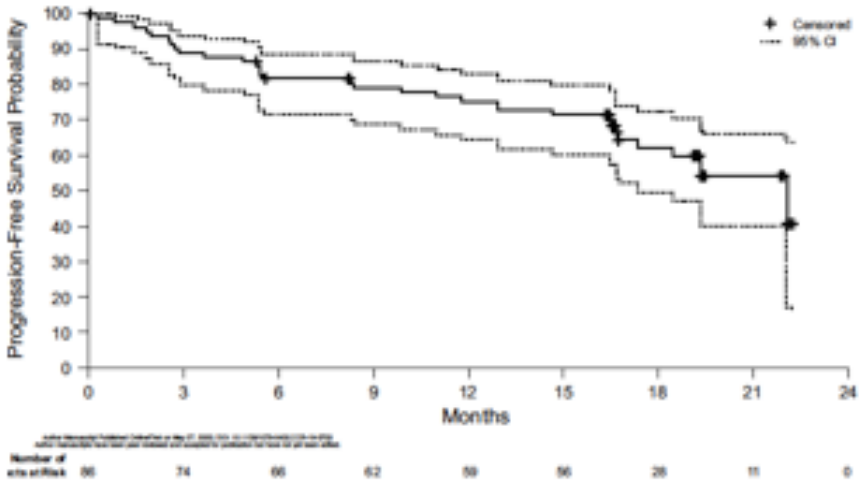
Song Clin Cancer Res 2020 May 27;clincanres.3703.2019 doi: 10.1158/1078-0432.CCR-19-3703.

Zanu monotherapy in rel/ref MCL

Duration of response



Progression-free survival



- ORR 84%
- CR 69%
- Med DR 19.5m
- Med PFS 22.1m
- EFS at 12m 76%

Song Clin Cancer Res 2020 May 27;clincanres.3703.2019 doi: 10.1158/1078-0432.CCR-19-3703.

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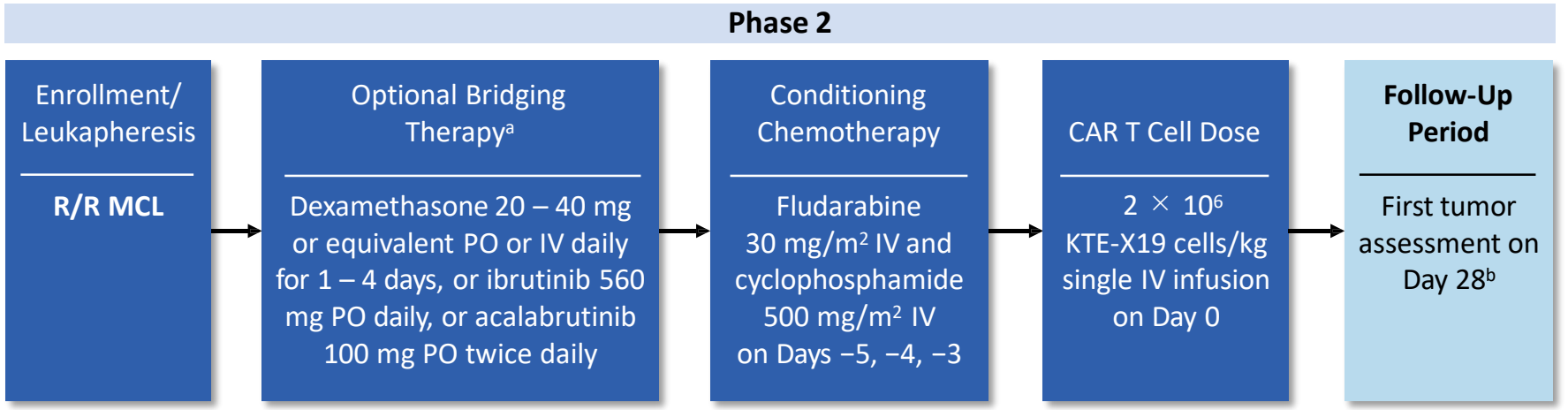
CAR-T in rel/ref MCL: ZUMA-2



- R/R MCL defined as
  - Disease progression after last regimen or
  - Failure to exhibit a CR or PR to the last regimen
- 1 – 5 Prior therapies that must have included
  - An anthracycline- or bendamustine-containing chemotherapy and
  - Anti-CD20 monoclonal antibody therapy and
  - Ibrutinib or acalabrutinib

[a] Administered after leukapheresis and completed ≤ 5 days before initiating conditioning chemotherapy; PET-CT was required post-bridging.
[b] Bone marrow biopsy was done at screening and if positive, not done, or indeterminate, a biopsy was needed to confirm CR.
AE, adverse event; CAR, chimeric antigen receptor, DOR, duration of response; EQ-5D, European Quality of Life-5 Dimensions; IRRC, Independent Radiology Review Committee; IWG, International Working Group; MCL, mantle cell lymphoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, oral; R/R, relapsed/refractory.
1. Cheson BD, et al. *J Clin Oncol.* 2014;32:3059-3068. 2. Cheson BD, et al. *J Clin Oncol.* 2007;25:579-586.

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

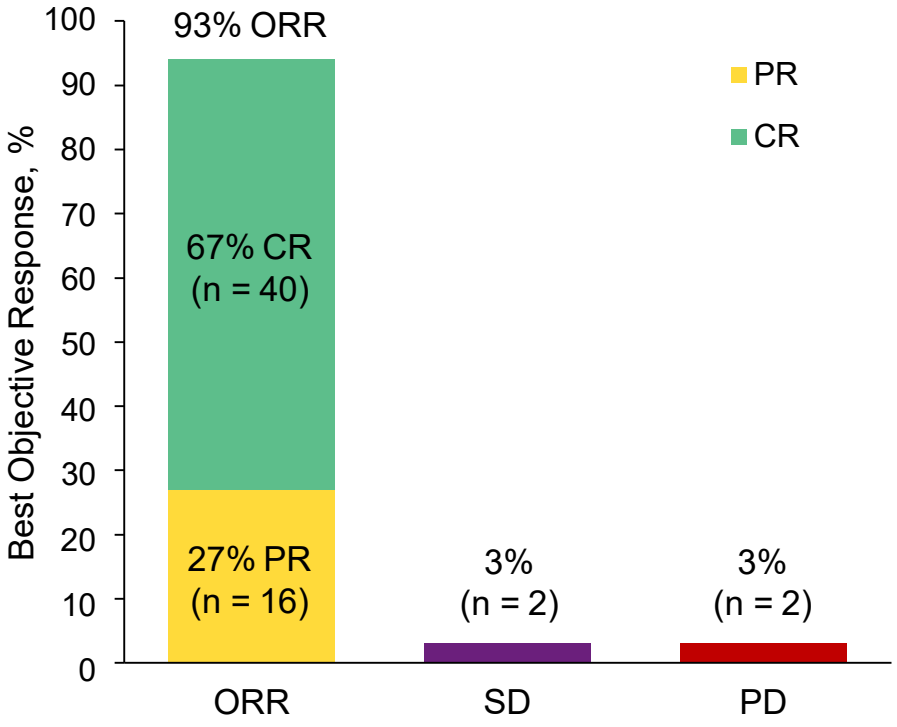
Baseline Disease Characteristics

Characteristic	N = 68
Median age (range), years	65 (38 – 79)
≥ 65 years, n (%)	39 (57)
Male, n (%)	57 (84)
Stage IV disease, n (%)	58 (85)
ECOG 0/1, n (%)	100 (100)
Intermediate/high-risk MIPI, n (%)	38 (56)
Ki-67 proliferation index ≥ 50%, n/n (%)[a]	34/49 (69)
TP53 mutation, n/n (%)	6/36 (17)
Bone marrow involvement, n (%)	37 (54)
Extranodal disease, n (%)[b]	38 (56)
MCL morphology, n (%)[c]	
Classical	40 (59)
Pleomorphic	4 (6)
Blastoid	17 (25)

[a] Ki-67 data were available for 49 patients at diagnosis. [b] Excludes bone marrow and splenic involvement. [C] Morphology was unknown for 10 patients.
BTKi, Bruton tyrosine kinase inhibitor; ECOG, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; MIPI, Mantle Cell Lymphoma International Prognostic Index.

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

ORR by IRRC Assessment Was 93% (95% CI, 84 – 98) and CR Rate Was 67% (95% CI, 53 – 78)



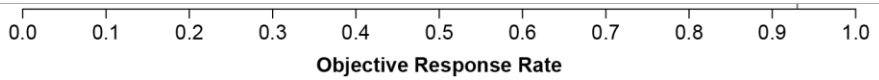
	Efficacy-Evaluable N = 60
Median follow-up (range), mo	12.3 (7.0 – 32.3)
Patients with ≥ 24 mo follow-up, n (%)	28 (47)
Median time to response (range), mo	
Initial response	1.0 (0.8 – 3.1)
CR	3.0 (0.9 – 9.3)
Patients converted from PR/SD to CR, n (%)	24 (40)
PR to CR	21 (35)
SD to CR	3 (5)

Investigator-assessed ORR in N = 60 was 88% (CR rate 70%), with 95% and 90% concordance between IRRC- and investigator-assessed ORR and CR rate, respectively. IRRC-assessed ORR in ITT (N = 74) was 85% (CR Rate 59%).
CR, complete response; IRRC, Independent Radiology Review Committee; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

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

ORR Was Consistent Across Key Subgroups

	Evaluable Patients	Responding Patients	ORR (95% CI)
Overall	60	56	0.93 (0.84, 0.98)
Age			
< 65 Years	28	26	0.93 (0.76, 0.99)
≥ 65 Years	32	30	0.94 (0.79, 0.99)
MCL morphology			
Classical MCL	35	32	0.91 (0.77, 0.98)
Pleomorphic	4	4	1.00 (0.40, 1.00)
Blastoid	14	13	0.93 (0.66, 1.00)
Ki-67 index			
< 50%	14	14	1.00 (0.77, 1.00)
≥ 50%	32	30	0.94 (0.79, 0.99)
Disease stage			
I-II	2	2	1.00 (0.16, 1.00)
III-IV	58	54	0.93 (0.83, 0.98)
Simplified MIPI			
Low risk	25	23	0.92 (0.74, 0.99)
Intermediate/high risk	33	31	0.94 (0.80, 0.99)
Steroid use for AE management			
Yes	35	33	0.94 (0.81, 0.99)
No	25	23	0.92 (0.74, 0.99)
Tocilizumab use			
Yes	42	40	0.95 (0.84, 0.99)
No	18	16	0.89 (0.65, 0.99)
Bridging therapy use			
Yes	21	19	0.90 (0.70, 0.99)
No	39	37	0.95 (0.83, 0.99)



- The median DOR has not been reached after a median follow-up of 12.3 months
  - 57% of all patients and 78% of patients with a CR remain in remission
- The first 28 patients treated had a median follow-up of 27.0 months (range, 25.3 – 32.3)

CR, complete response; MCL, mantle cell lymphoma; MIPI, MCL International Prognostic Index; ORR, objective response rate.

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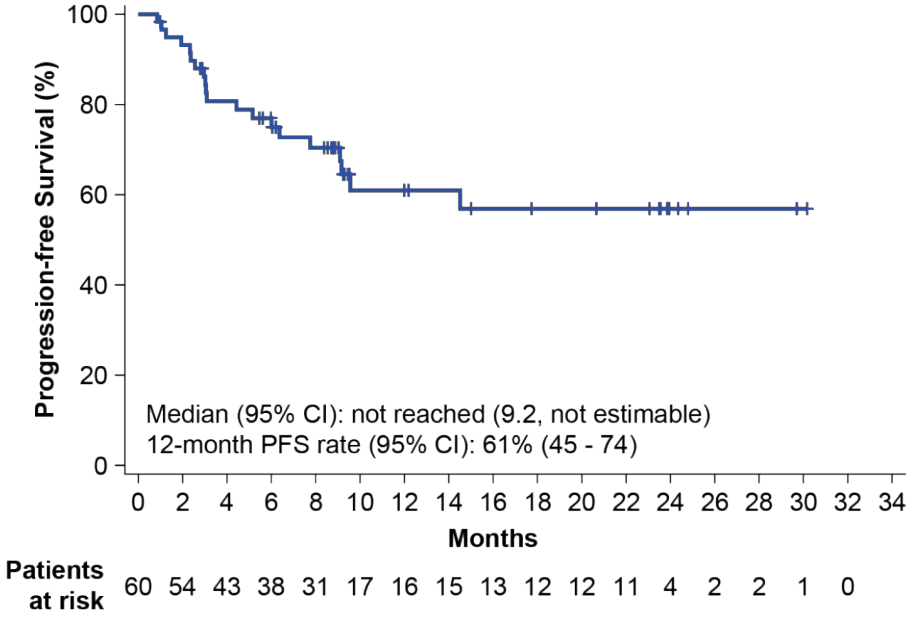
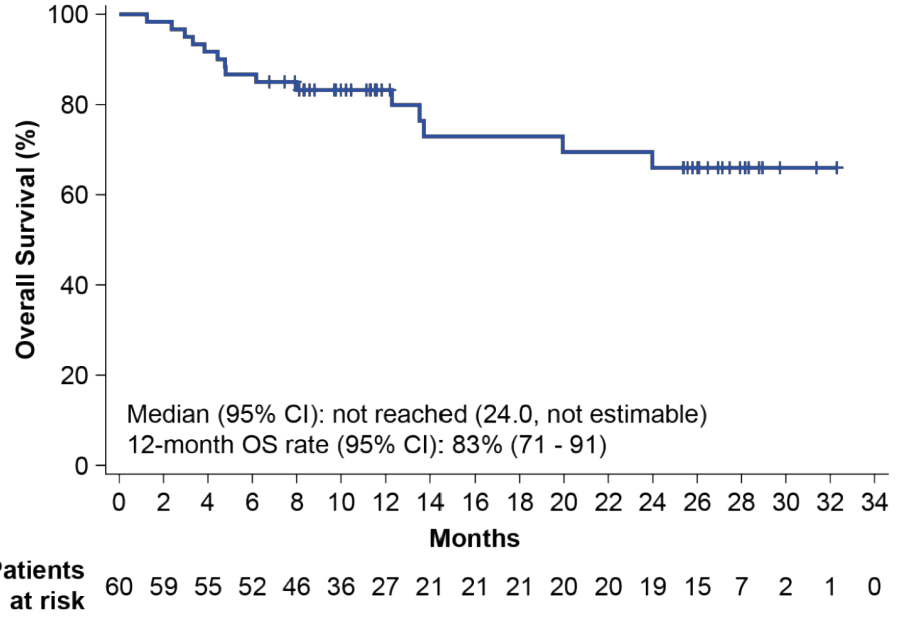
Progression-Free Survival and Overall Survival

- Median PFS and median OS were not reached after a median follow-up of 12.3 months





OS, overall survival; PFS, progression-free survival.

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Cytokine Release Syndrome

- No Grade 5 CRS occurred

Parameter	N = 68
CRS, n (%)[a]	
Any grade	62 (91)
Grade ≥ 3	10 (15)
Most common any grade symptoms of CRS, n (%)	
Pyrexia	62 (91)
Hypotension	35 (51)
Hypoxia	23 (34)
AE management, n (%)	
Tocilizumab	40 (59)
Corticosteroids	15 (22)
Median time to onset (range), days	2 (1 – 13)
Median duration of events, days	11
Patients with resolved events, n (%)	62/62 (100)

[a] CRS was graded per Lee DW, et al. *Blood*. 2014;124:188-195. Individual symptoms of CRS were graded per National Cancer Institute's Common Terminology Criteria for Adverse Events, v 4.03.
AE, adverse event; CRS, cytokine release syndrome.

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

Neurologic Events

Parameter	N = 68
Neurologic events, n (%)[a]	
Any grade	43 (63)
Grade ≥ 3	21 (31)
Most common any grade symptoms, n (%)	
Tremor	24 (35)
Encephalopathy	21 (31)
Confusional state	14 (21)
AE management, n (%)	
Tocilizumab	18 (26)
Corticosteroids	26 (38)
Median time to onset (range), days	7 (1 – 32)
Median duration of events, days	12
Patients with resolved events, n (%)	37/43 (86)[b]

- No Grade 5 neurologic events occurred
- One patient had Grade 4 cerebral edema confirmed by MRI of the brain
  - The patient was intubated and treated with aggressive multimodality therapies including tociluzumab, siltuximab, high-dose steroids, intrathecal Ara C plus dexamethasone, mannitol, ventriculostomy and IV ATG[c]
  - The neurotoxicities fully resolved and the patient remains in CR 24 months later
  - This is the first reported use of ATG in treating CAR T cell-related toxicities

[a] Neurologic events were graded per National Cancer Institute's Common Terminology Criteria for Adverse Events, v 4.03. [b] Four patients had ongoing neurologic events at data cutoff: Grade 1 tremor (n = 3), Grade 2 concentration impairment (n = 1), and Grade 1 dysesthesia (n = 1). Two patients died from unrelated AEs (organizing pneumonia and staphylococcal bacteremia) prior to the resolution of the neurologic events. [c] Rabbit ATG.
AE, adverse event; ALT, alanine aminotransferase; ATG, anti-thymocyte globulin; CRS, cytokine release syndrome; IV, intravenous.

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

Conclusions

- KTE-X19, in a single infusion, demonstrates high rates of durable responses in R/R MCL
  - The 93% ORR, which includes a 67% CR rate, is the highest reported rate of disease response in patients with prior BTKi failure
  - Of the initial 28 patients treated, 43% are in remission after ≥ 2 years of follow-up
- The safety profile is consistent with that reported in prior studies of anti-CD19 CAR T cell therapies in aggressive NHL
  - No deaths due to CRS or neurologic events; most symptoms occurred early and were generally reversible
- The efficacy, reliable and rapid manufacturing, and manageable toxicities identify an important and promising role for KTE-X19 in treating patients with R/R MCL who have an urgent unmet medical need

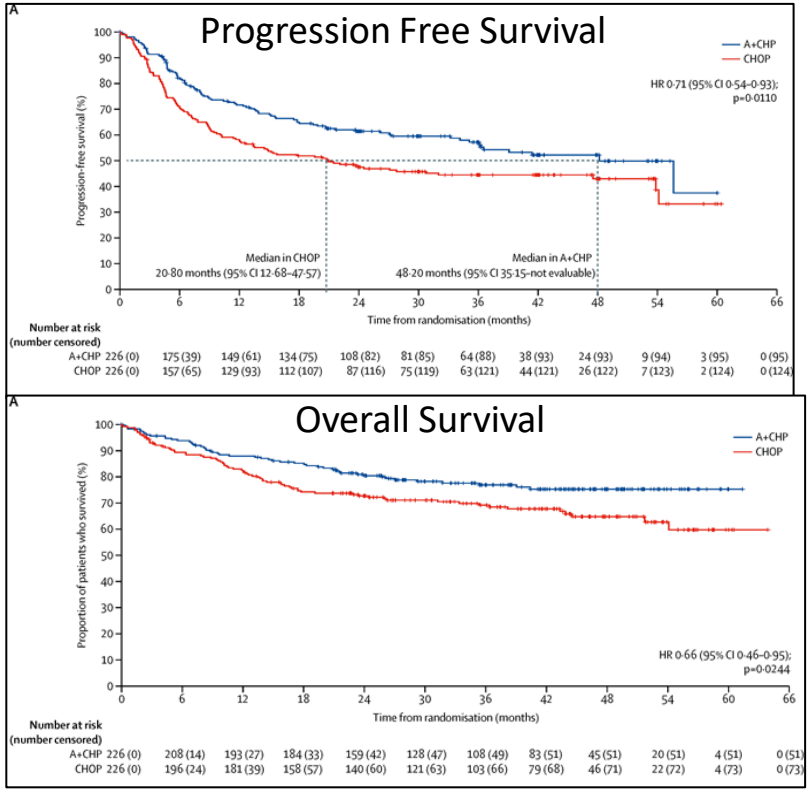
BTKi, Bruton tyrosine kinase inhibitor; CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphoma; ORR, objective response rate; R/R, relapsed/refractory.

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

T-CELL LYMPHOMAS: ROLE OF CONSOLIDATIVE ASCT AFTER BV-CHP

ECHELON-2: BV-CHP vs CHOP

- BV-CHP improves PFS (HR 0.71)
  - 3 year PFS: BV-CHP: 57% vs. CHOP: 44%
  - 34% reduction in risk of death
- Difference was most pronounced in ALCL
  - Less pronounced with AITL (HR 0.87) or PTCL (HR 0.83)
- BV approved in combination with chemotherapy for frontline use in CD30+ PTCL
- **19% patients underwent a consolidative autologous transplant in CR**



Horwitz Lancet 2019

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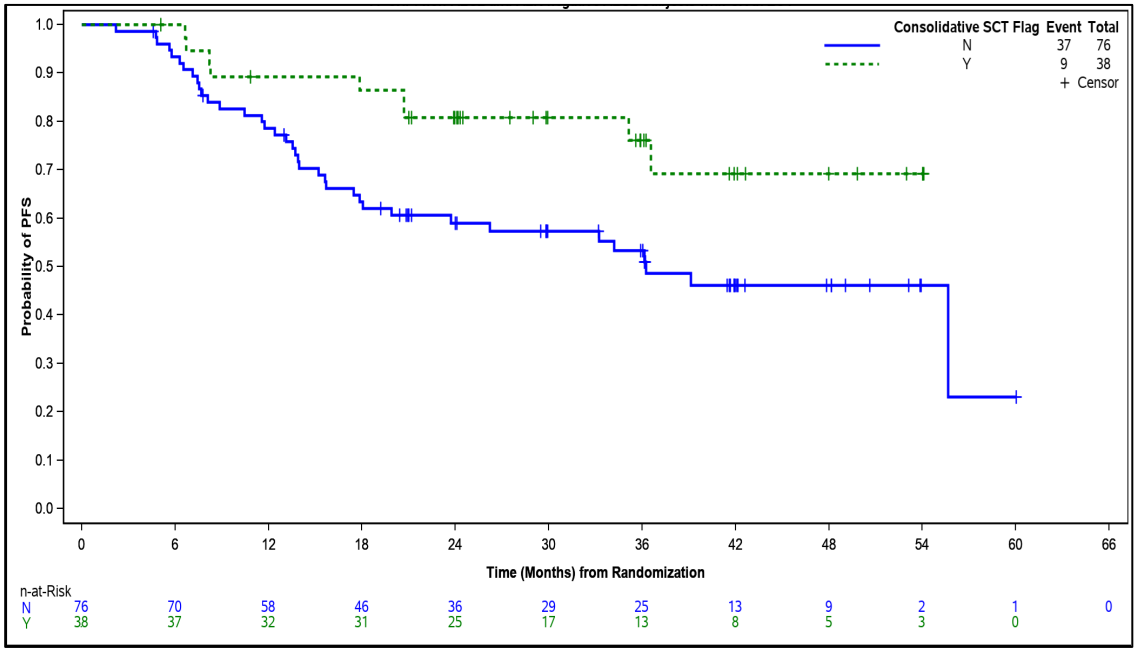
Treatment of Patients with CD30+ Peripheral T-Cell Lymphomas (ECHELON-2):

The use of consolidative SCT was infrequent in Asian countries, suggesting regional practice differences.

Numerical PFS estimates favor the use of consolidative SCT in patients with PCTL in a CR at EOT after frontline BV+CHP.

	ALK– sALCL N=76		Non-sALCL N=38		Combined N=114	
	SCT (n=27)	No SCT (n=49)	SCT (n=11)	No SCT (n=27)	SCT[a] (n=38)	No SCT (n=76)
Estimated PFS at 3 years, % (95% CI)	80.4 (59.1, 91.4)	56.9 (40.6, 70.3)	70.1 (32.3, 89.5)	46.7 (26.7, 64.4)	76.1 (56.9, 87.6)	53.3 (40.7, 64.3)
Univariate, HR (95% CI)	0.49 (0.19, 1.27)		0.36 (0.10, 1.26)		0.38 (0.18, 0.82)	
Multivariate, HR (95% CI) adjusting for:						
Age[b]	0.54 (0.20, 1.45)		0.32 (0.09, 1.15)		0.39 (0.18, 0.86)	
Region[c]	0.47 (0.18,1.22)		0.37 (0.10, 1.33)		0.38 (0.18, 0.82)	
Age[b] + Region[c]	0.52 (0.19, 1.41)		0.32 (0.09, 1.19)		0.39 (0.18, 0.86)	
Median follow-up[d], mos (95% CI)	29.9 (24.2, 36.1)	41.6 (29.8, 42.0)	49.8 (21.2, 54.0)	42.6 (29.5, 53.9)	35.9 (24.5, 41.9)	41.6 (33.2, 42.1)



Savage Blood (2019) 134 (Supplement_1): 464.

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Overview: new data and treatment options for aggressive lymphomas

DLBCL

Management of limited stage disease

DLBCL

Treatment options for rel/ref disease

MCL

Treatment options for rel/ref disease

T cell lymphomas

Role of ASCT in CR1 after BV-CHP

Fourteen new treatments approved in 2019-2020 for lymphomas!

Questions?

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