

Non-Hodgkin lymphoma

State of the art of treatment

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Disclosures for Stephen Ansell, MD, PhD

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Research Support/P.I.	PI – Seattle Genetics, BMS, Affimed, Regeneron, Pfizer clinical trials
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N/A = Not Applicable (no conflicts listed)

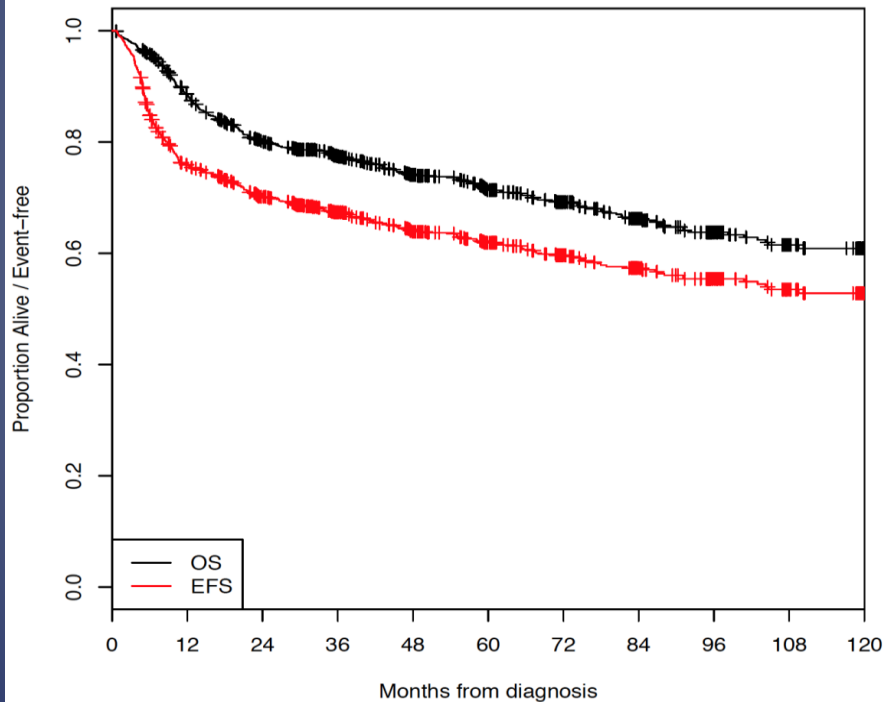
Lessons Learned So Far

- Improving on R-CHOP is proving difficult
- Immune Checkpoint Therapies are not as effective as expected
- CAR T-cell approaches look very promising

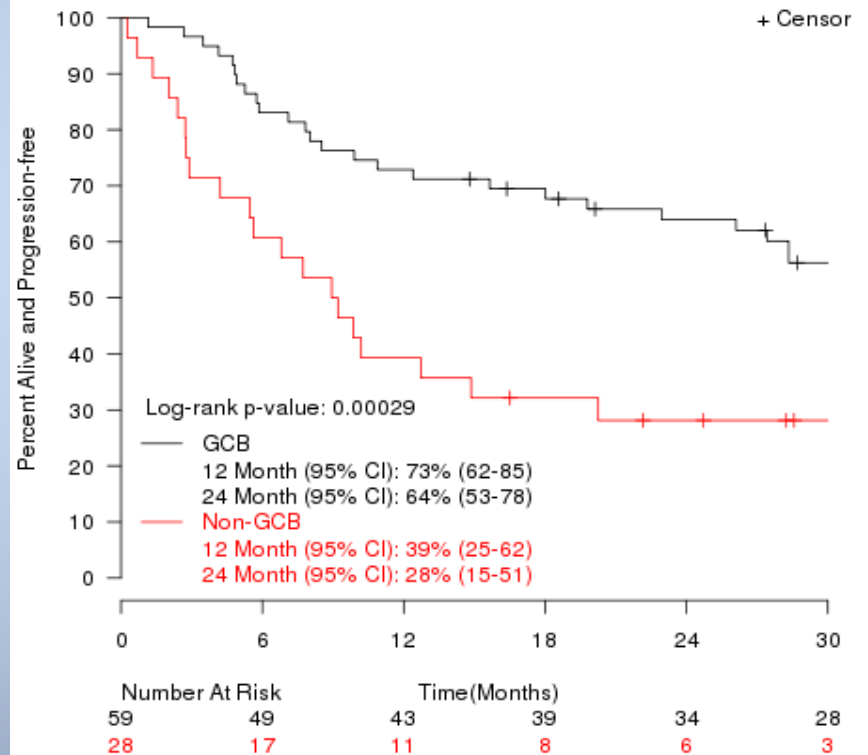
Diffuse Large B-cell Lymphoma

Historical Frontline Outcomes Based on R-CHOP

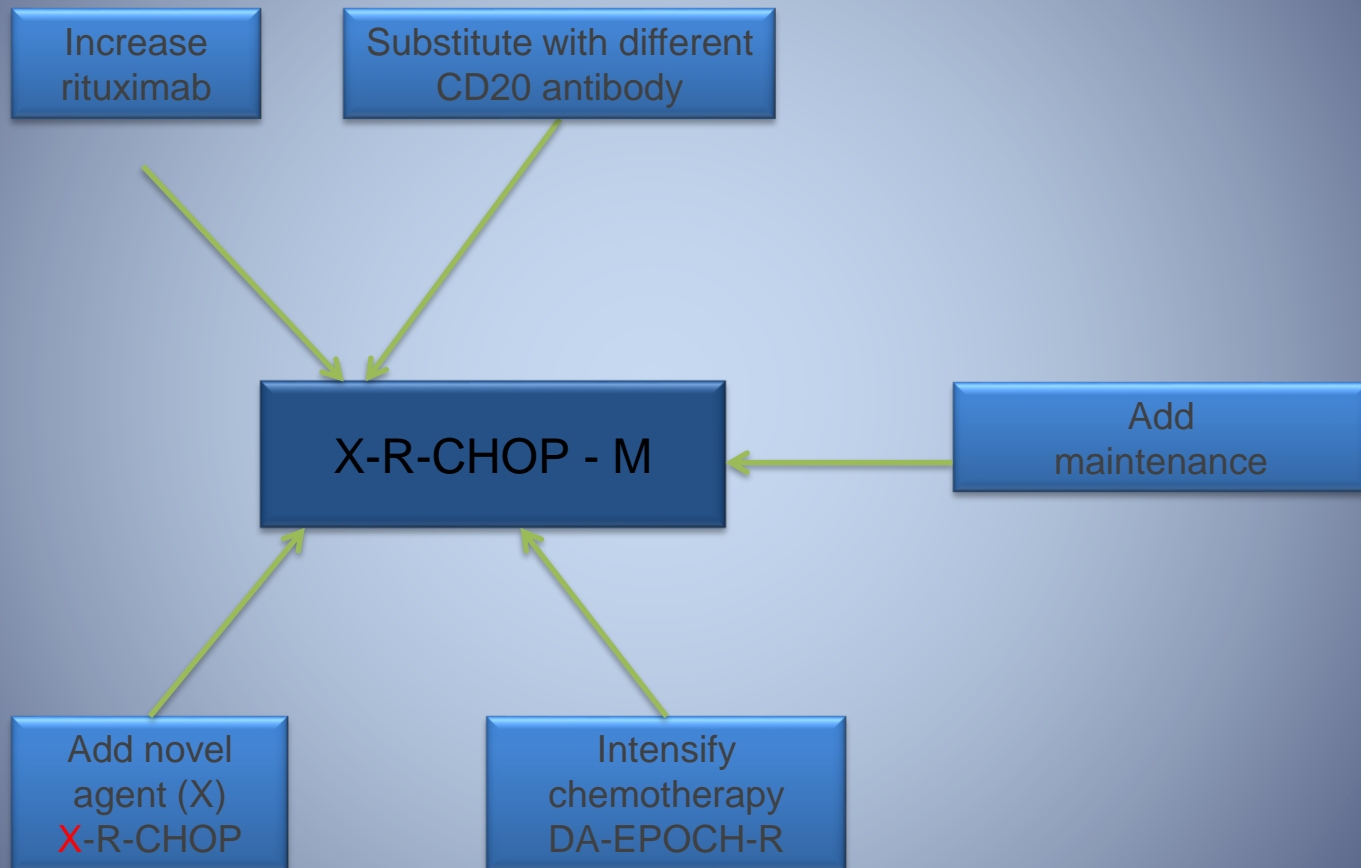
Outcomes in DLBCL Treated with R-CHOP Like Therapy
MER 2002–2012 (N=1039)



RCHOP: Progression-Free Survival by DLBCL Sub-Type



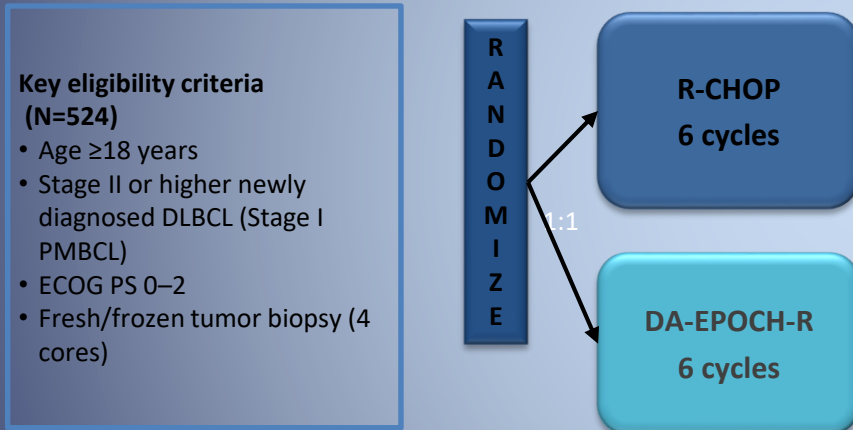
How can we improve on R-CHOP?



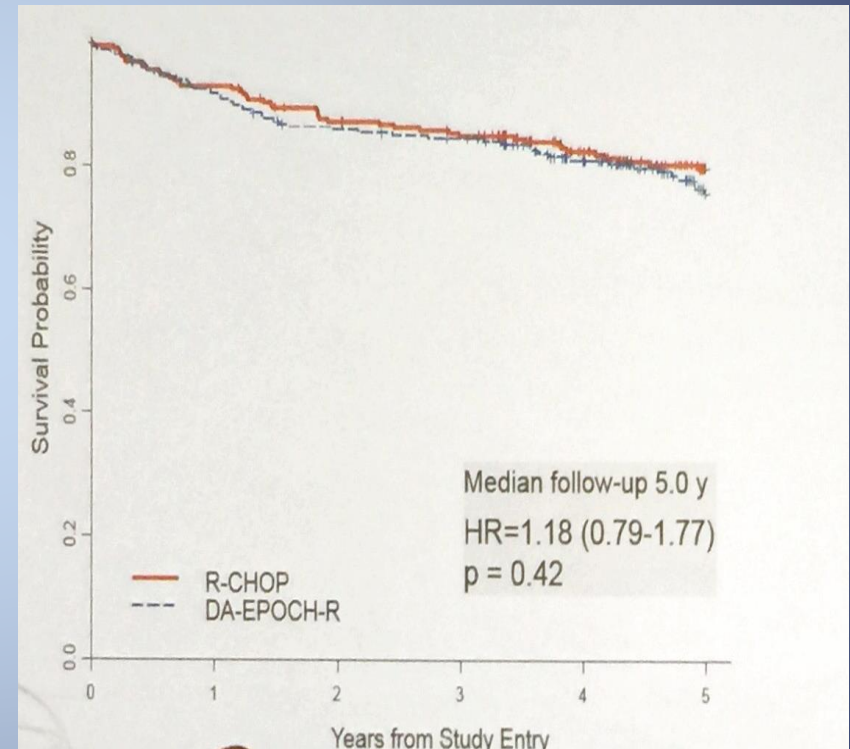
1. Intensify Therapy –

Phase III study of R-CHOP vs DA-EPOCH-R

Study schema



Event-free survival



2. Add maintenance therapy – Everolimus - PILLAR-2

Study design: Adjuvant everolimus

Disease-free survival

Patients

- Age ≥ 18 years
- Stage 2 bulky disease, stage 3, or stage 4 DLBCL
- Poor risk (IPI, 3-5)
- First-line therapy with R-chemo (5-8 cycles)
- PET confirmed CR to first-line R-chemo
- ECOG PS 0-2

Randomization (1:1)

N=742

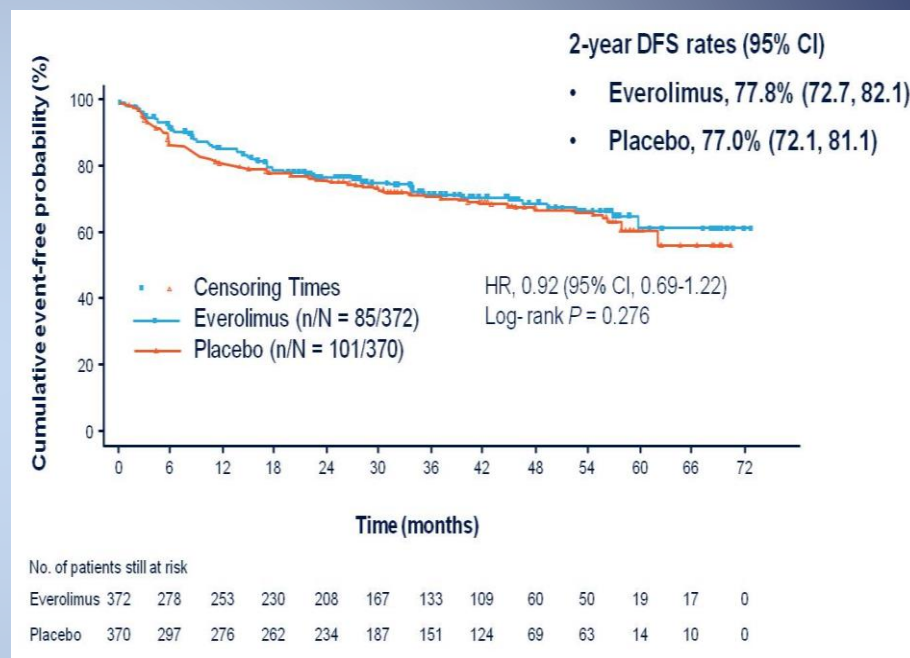
Everolimus
10 mg PO daily
for 1 year
N=372

Placebo
PO daily
for 1 year
N=370

Stratification by R-chemo

- R-CHOP, n=725
- R-EPOCH, n=17

Treatment for 1 year or until disease relapse, unacceptable toxicity, death, or discontinuation of other reason



End points

Primary

- Disease-free survival (DFS): time from randomization to recurrence or death due to any cause

Secondary

- Overall Survival (OS): time from randomization to death due to any cause
- Lymphoma-specific survival (LSS): time from randomization to death due to lymphoma
- Safety

Exploratory

- DFS and OS by subgroups: IPI (3 vs 4+5); Gender (male vs female); Age (<65 vs ≥ 65 years); Tumor type (GCB vs non-GCB vs other); Race (Caucasian vs Asian vs other)

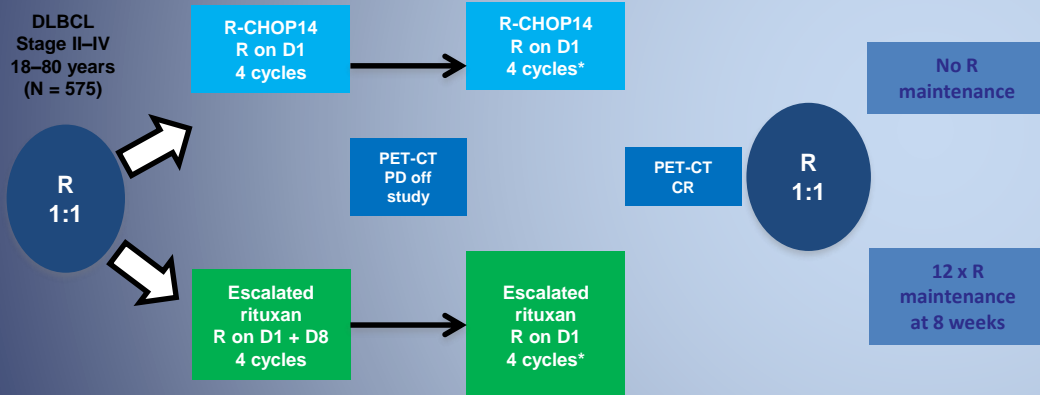


NORDIC LYMPHOMA GROUP

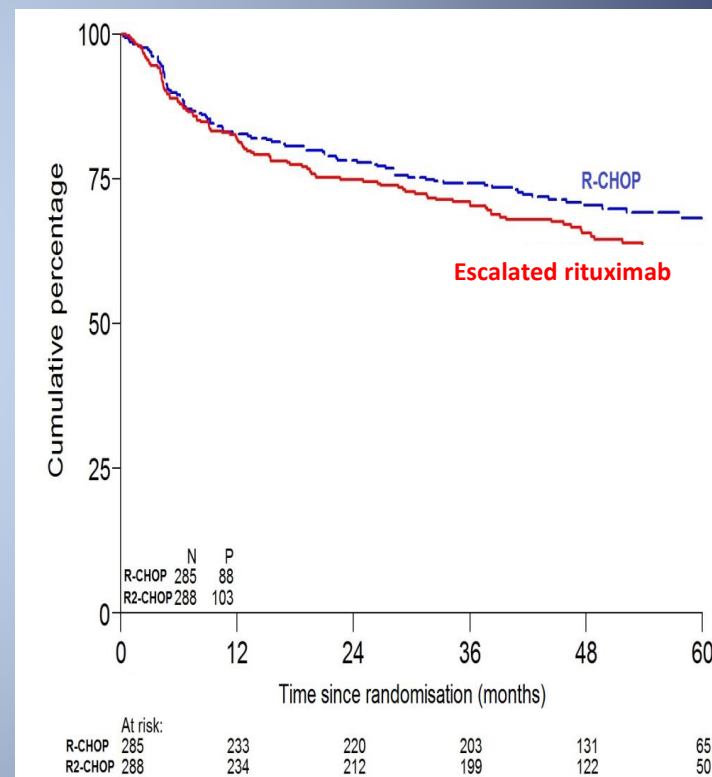
3. Increase Rituximab dosing

HOVON Trial

Study design



PFS



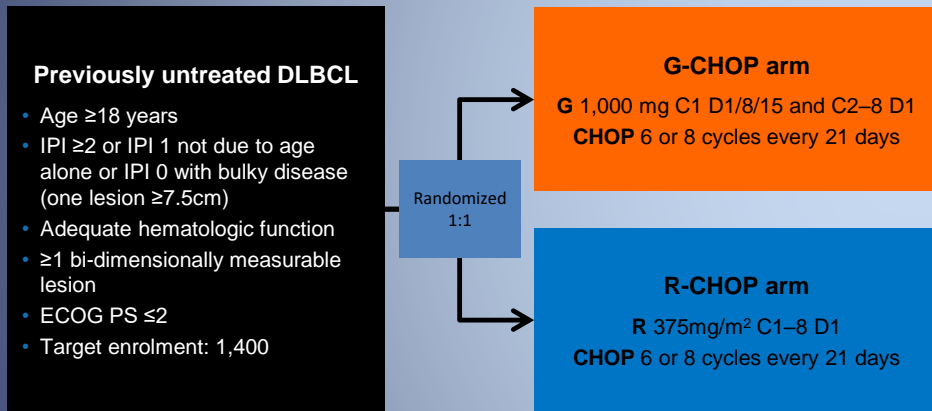
Median follow up 52.7 months

4. Use a different anti-CD20 antibody

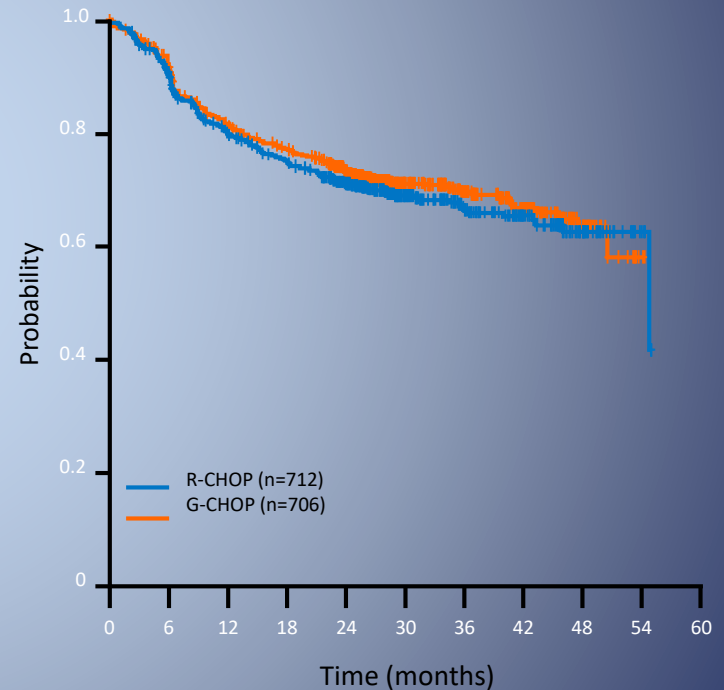
GOYA study

International, open-label, randomized, Phase III study in 1L DLBCL patients

- Scientific support from the Fondazione Italiana Linfomi



Kaplan–Meier plot of investigator-assessed PFS by treatment arm (primary endpoint)



No. of patients at risk

R-CHOP	712	616	527	488	413	227	142	96	41	6
G-CHOP	706	622	540	502	425	240	158	102	39	2

	6	12	18	24	30	36	42	48	54	60
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- Number of CHOP cycles pre-planned in advance for all patients at each site
- Randomization stratification factors:
 - Planned number of CHOP cycles
 - IPI
 - Geographic region

5. Add New Drugs to RCHOP

XR-CHOP

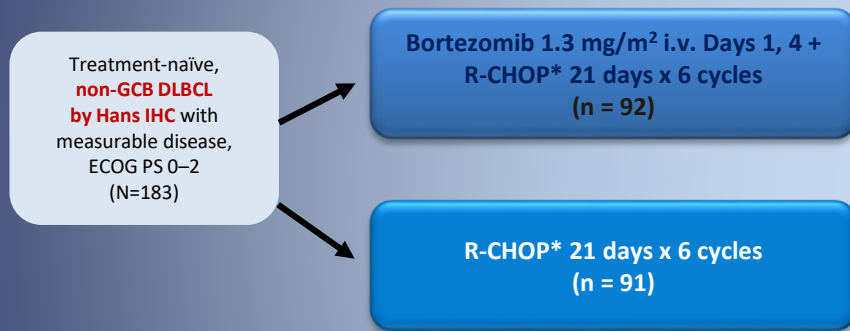
- What X?
- Bortezomib: Bor-RCHOP (Phase III – Pyramid/ReModel)
- Ibrutinib: IR-CHOP (Phase III - Phoenix)
- Everolimus: EveR-CHOP (Phase Ib)
- Lenalidomide: R2-CHOP (Phase III – Robust, Intergroup)

5. Add Bortezomib to RCHOP

PYRAMID: Non-GCB DLBCL

Study design

Prospective randomized, open-label, Phase II study

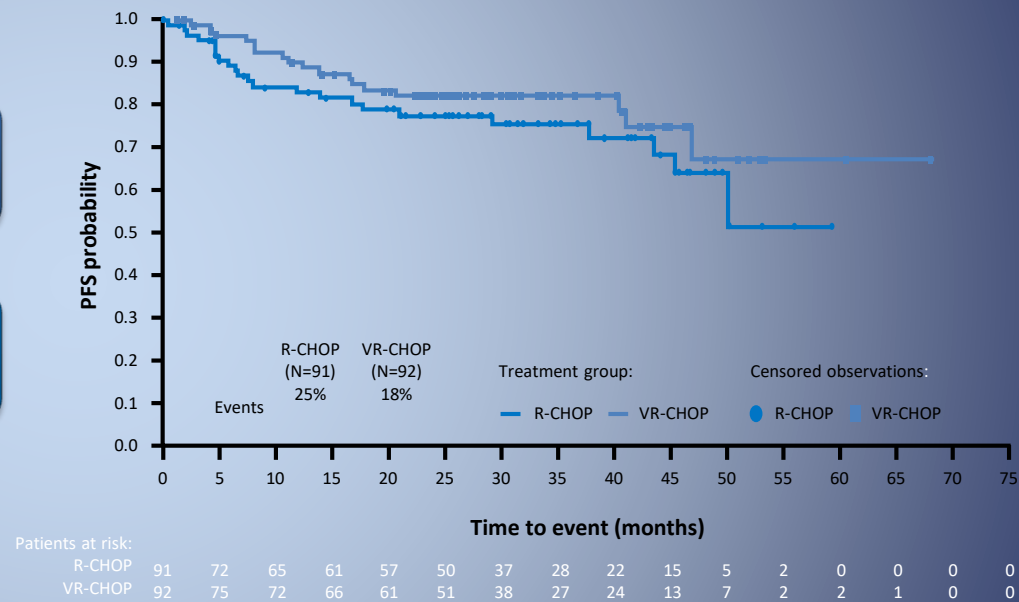


Limits:

- Patient selection in the PYRAMID trial may have played a role → R-CHOP alone produced better outcomes than expected
- IHC based on Hans algorithm

VR-CHOP, bortezomib, rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone.

PFS



- **2-year PFS: 78% R-CHOP vs 82% VR-CHOP**
 - **HR (95% CI): 0.73 (0.43–1.24); p=0.611**

Leonard JP, et al. Blood 2015;126:811a.
(Updated data presented in oral presentation at ASH annual meeting)

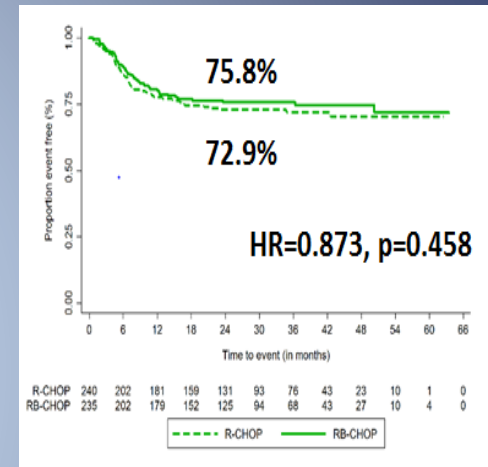
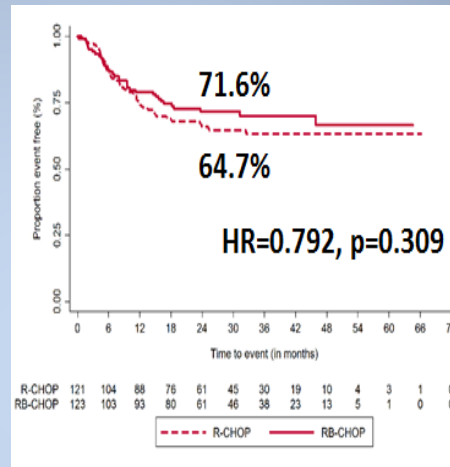
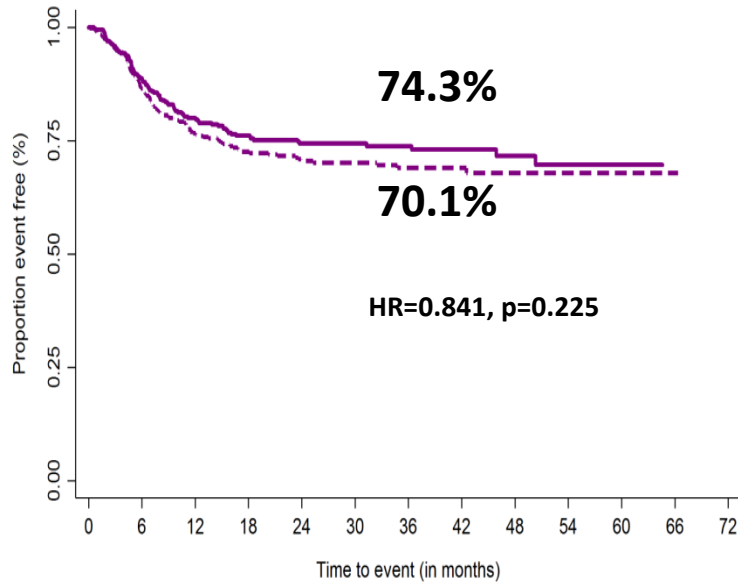
5. Add Bortezomib to RCHOP

REMoDL-B Trial

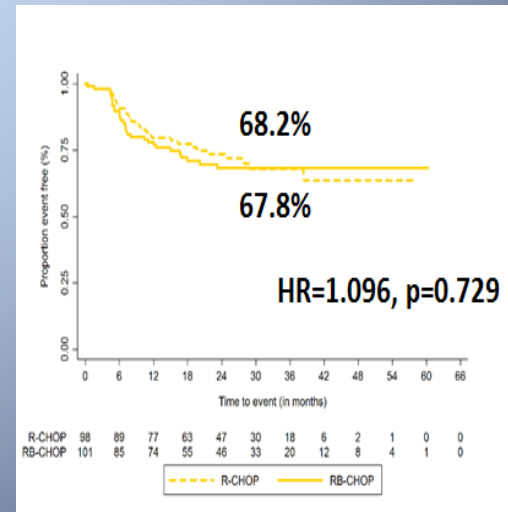
ITT population: GCB + ABC patients N=719

ABC: N=244

GCB: N=475

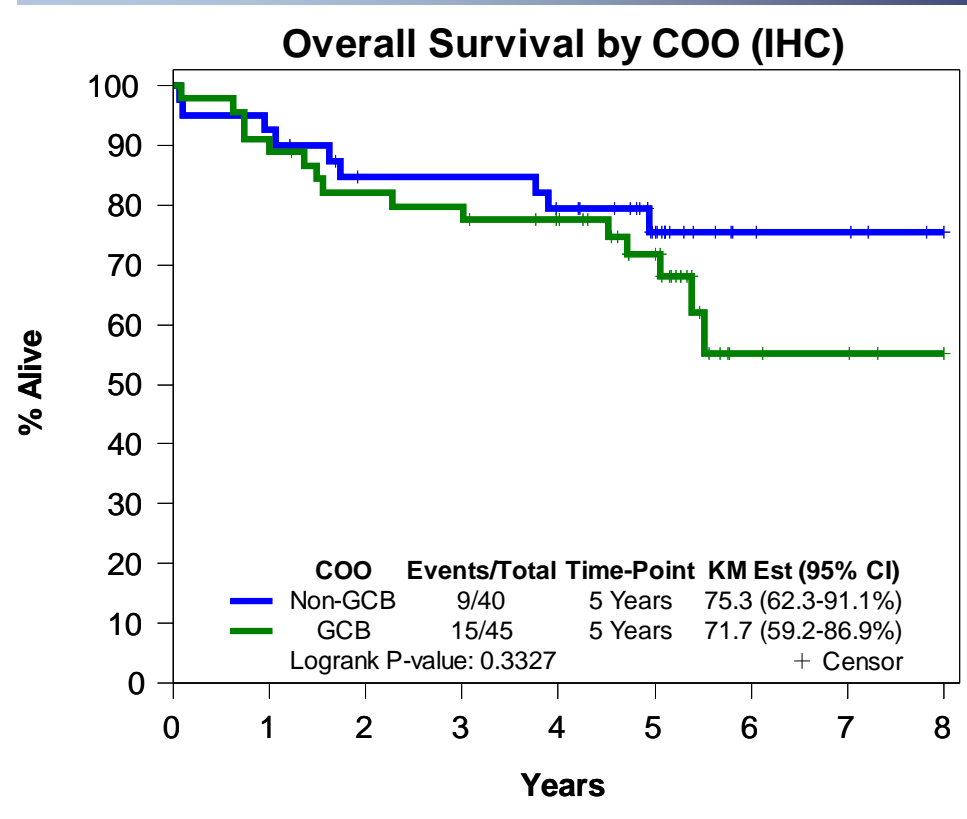
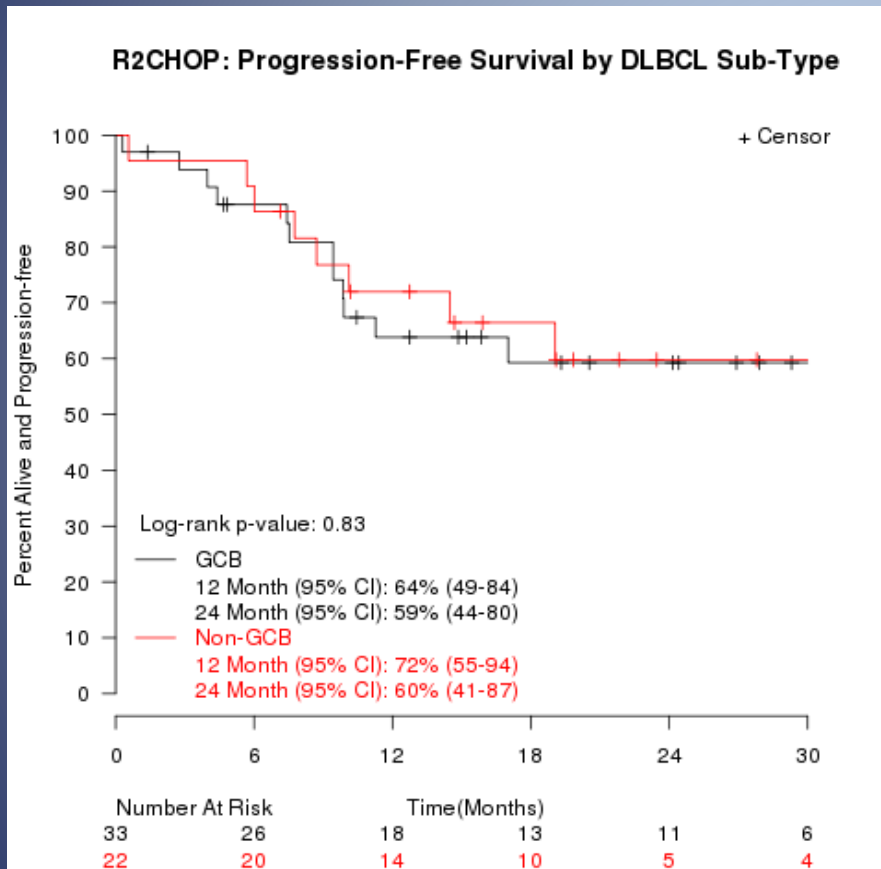


Unc.: N=199



Median follow-up of surviving patients: 28.4 months

Adding Lenalidomide to R-CHOP may overcome the poor outcome of ABC type

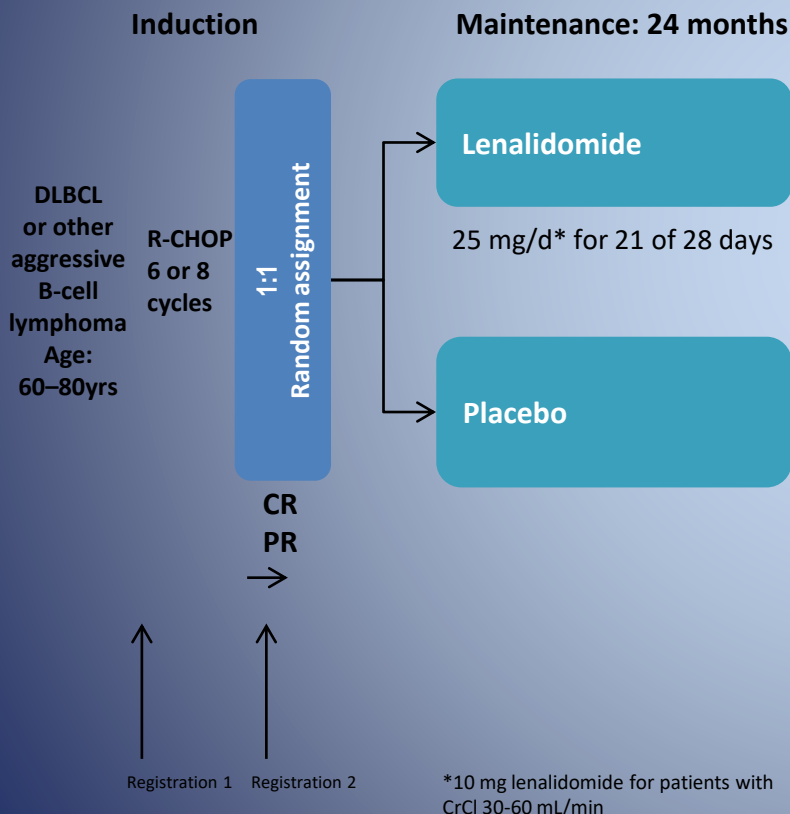


Randomized trial completed – awaiting results

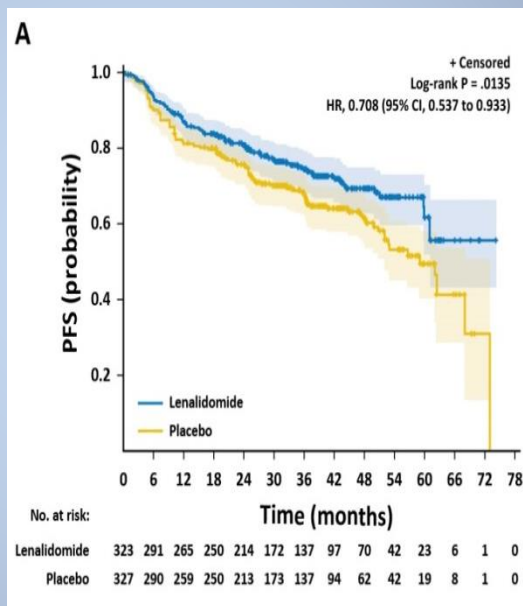
*As defined by Hans et al. Blood 2004;103:275–282.

Adding Lenalidomide Maintenance therapy may improve outcome in DLBCL – REMARC

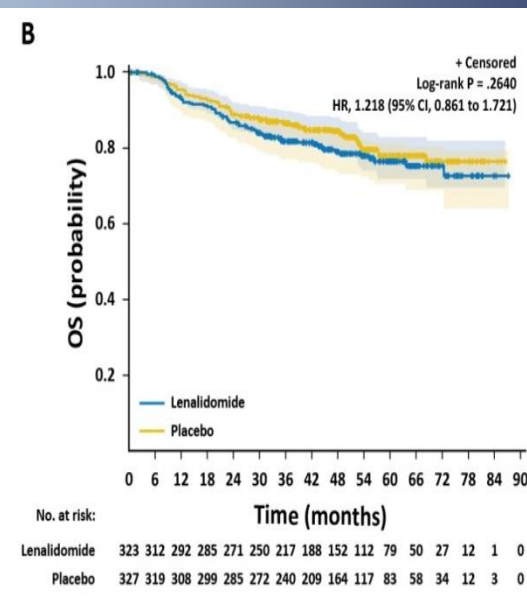
Study design



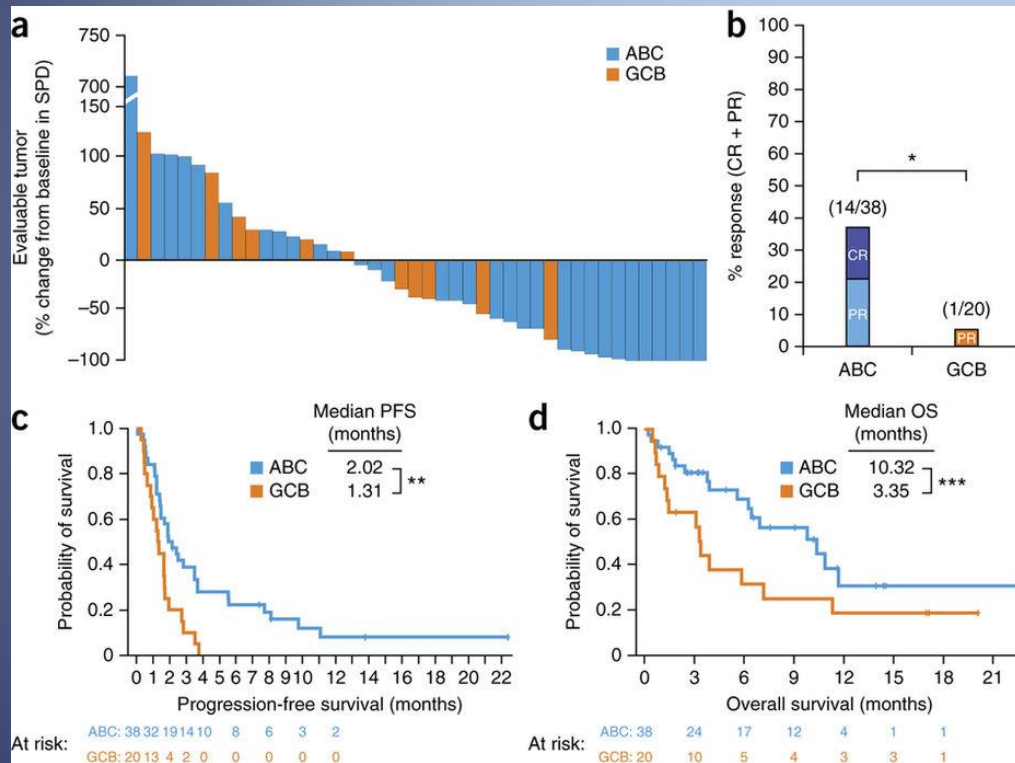
PFS



OS



Adding Ibrutinib to R-CHOP may overcome the poor outcome of ABC type



Phase Ib trial of ibrutinib + RCHOP

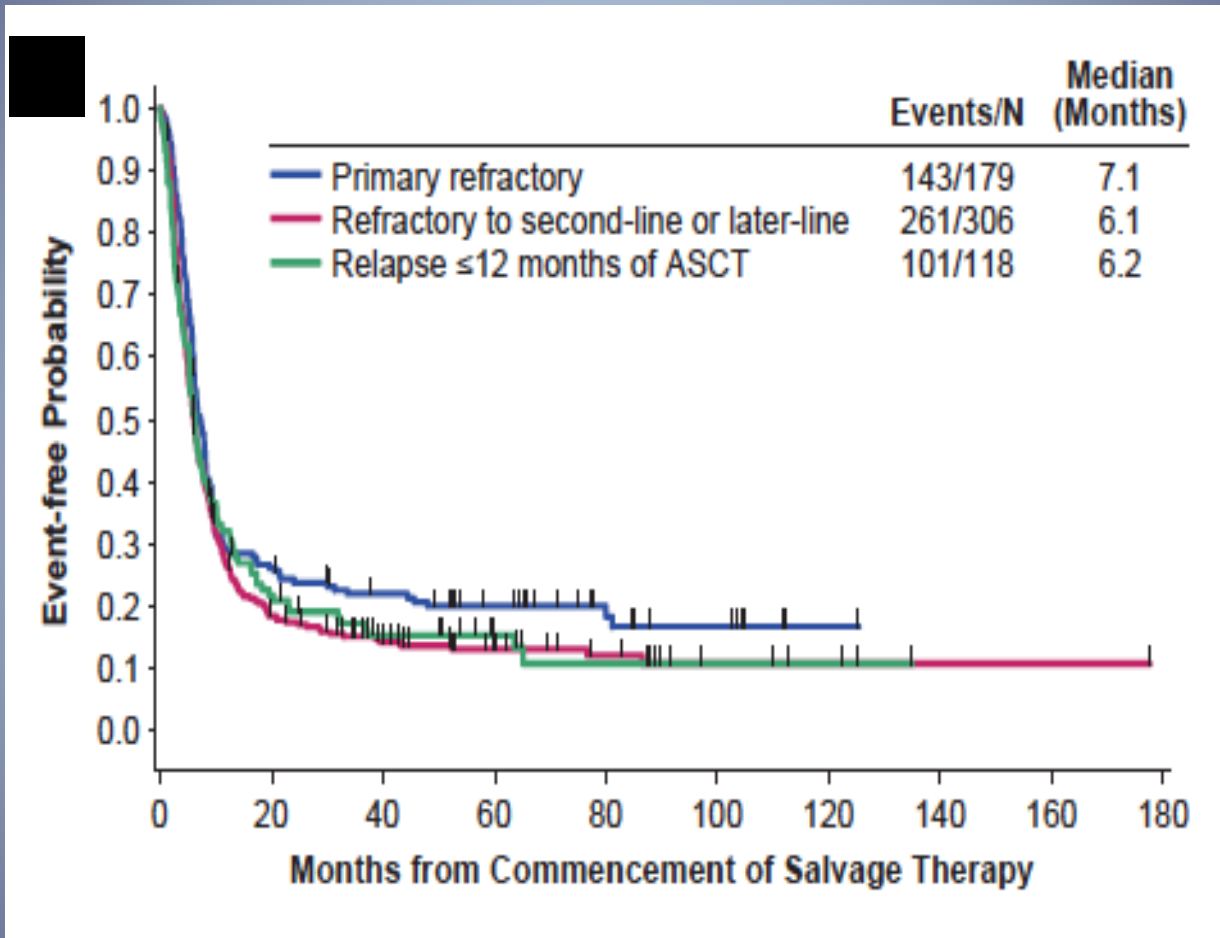
- 33 patients
- Combination was well tolerated
- ORR – 91%
- CR rate – 70%
- No clear difference by COO
- Randomized trial completed – “did not meet the primary endpoint of EFS in patients with non-GCB subtype of DLBCL, including ABC subtype of DLBCL”.

Wilson et al. Nat Med. 2015 Aug;21(8):922-6.

Younes et al. Lancet Oncol. 2014 Aug;15(9):1019-26.

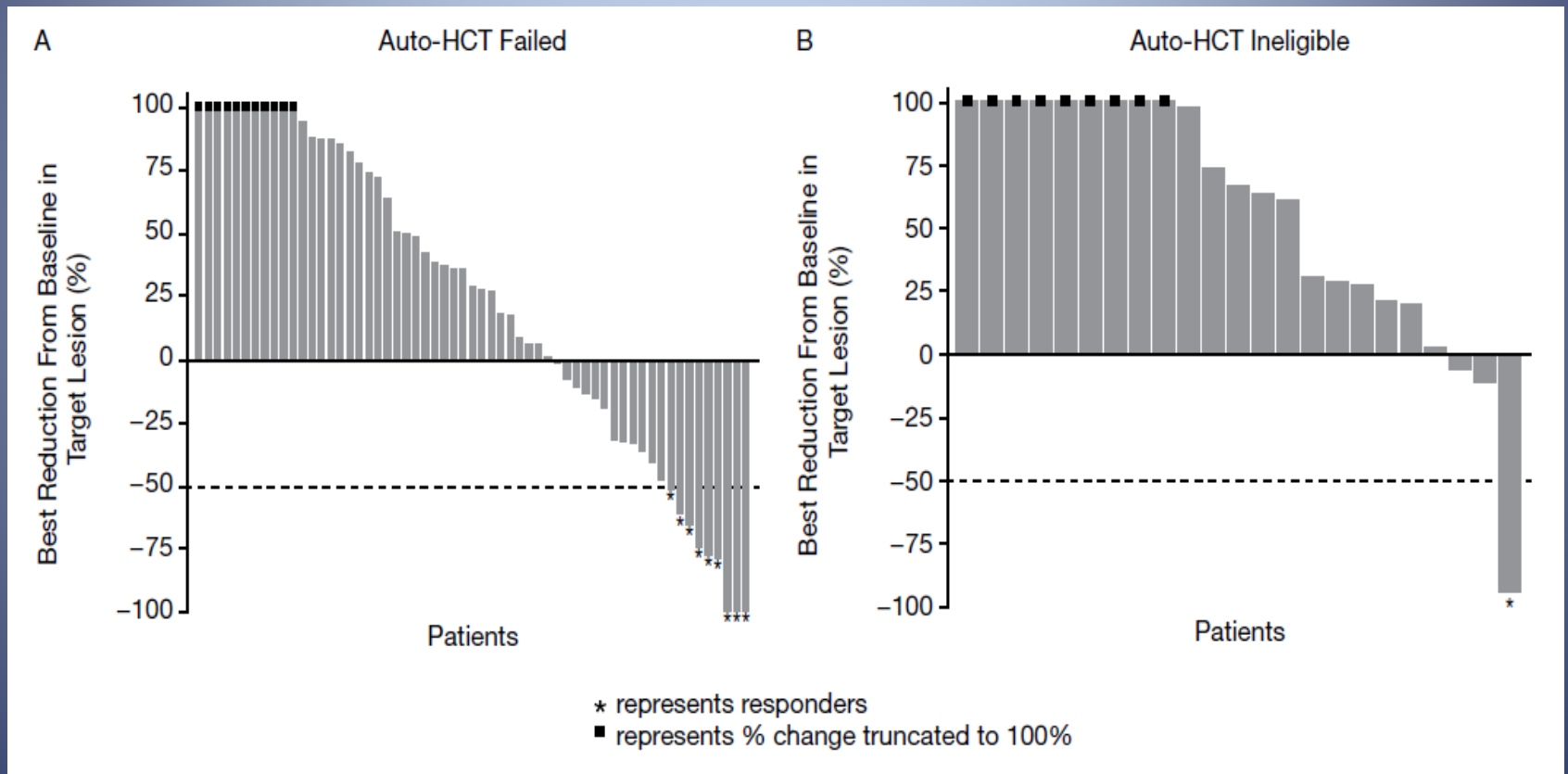
Overall Survival in Refractory DLBCL:

Historical Outcomes data – SCHOLAR-1

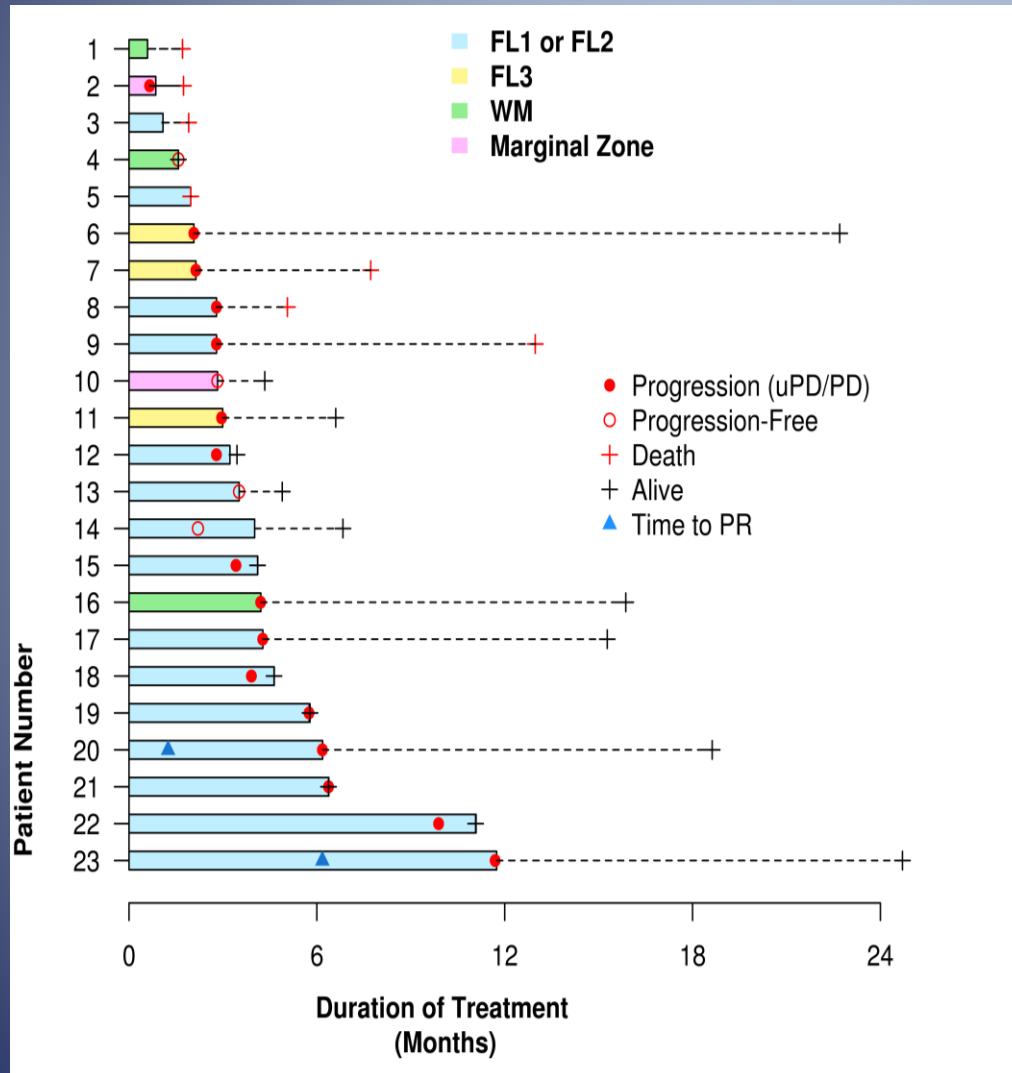


- N = 636
- ORR = 26%; CR rate = 7%
- Median OS = 6.3 months

Immune checkpoint therapy (Nivolumab) is not very effective in de novo DLBCL



Modest ORR in Indolent lymphoma patients receiving pembrolizumab.



- 23 patients
- ORR in follicular patients – 11% (2/18)
- ORR in WM/MZL patients – 40% (2/5 - MR)
- 11 patients had stable disease

Anti-CD19 CAR T Products in Clinical Development

	Axicabtagene Ciloleucel (KTE-C19, Yescarta)	Tisagenlecleucel (CTL019, Kymriah)	Lisocabtagene maraleucel (JCAR017)
Company	KITE	Novartis	Celgene/Juno
Binding Domain (All Murine ScFv)	FMC63	FMC63	FMC63
Indications	DLBCL, TFL PMBCL, MCL, ALL, CLL	NHL, ALL, CLL	Adult NHL, Pediatric ALL, CLL
Spacer Domain	CD28	CD8 α	IgG4 hinge
Transmembrane Domain	CD28	CD8 α	CD28
Stimulatory Domain	CD28-CD3 ζ	4-1BB-CD3 ζ	4-1BB-CD3 ζ
Starting Cell Population Selection	None	None	CD4+ and CD8+
Final CD4/CD8 ratio	Variable	Variable	1:1
Ablation Technology	None	None	EGFRt
Viral Vector	Gamma retrovirus	Lentivirus	Lentivirus

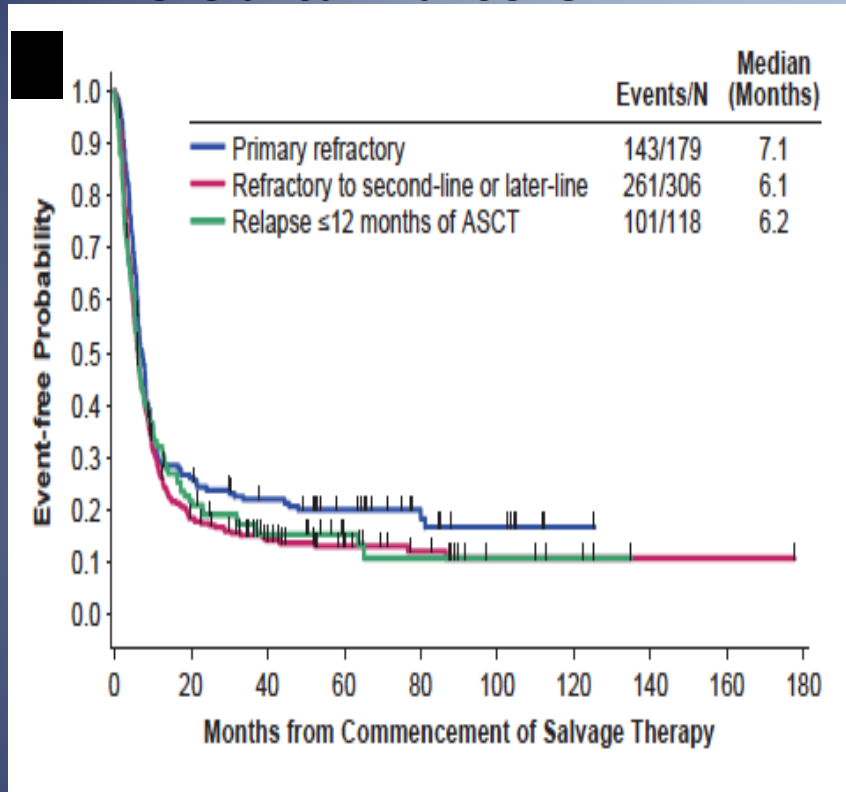
CD19 CAR T NHL Trial Data

	ZUMA-1 (Kite)	JULIET (Novartis)	Transcend (Juno)
Source	Phase 2 Primary Analysis ASH 2017	Phase 2 Interim Analysis ASH 2017	Phase 1 Interim Analysis ASH 2017
Enrollment	111 enrolled; 101 dosed	160 enrolled; 99 dosed (81 evaluable for response)	140 enrolled; 108 dosed (4 pending)
Population	<ul style="list-style-type: none"> • 78% refractory; 0% relapsed • 22% post ASCT • 16% TFL; 8% PMCBCL 	<ul style="list-style-type: none"> • 41% refractory; 59% relapsed • 47% post ASCT • 19% TFL; 0% PMBCL 	<ul style="list-style-type: none"> • 67% refractory; 24% relapsed • 40% post ASCT • 21% TFL; 0% PMBCL
Efficacy	<ul style="list-style-type: none"> • ORR: 82%; 54% CR • ITT ORR: 75%; 50% CR • Ongoing: 42%; 40% CR • Median follow-up 15.4 m 	<ul style="list-style-type: none"> • ORR: 53%; 40% CR • ITT ORR: 27%; 20% CR • Ongoing: 37%; 30% CR • Median follow-up 6 m 	<ul style="list-style-type: none"> • ORR: 74%; 52% CR • ITT ORR: 55%; 38% CR • Ongoing: 47%; 42% CR • Median follow-up 6 m
Safety*	<ul style="list-style-type: none"> • G3+ CRS 13% • G3+ NE 28% • G5 AE 3% 	<ul style="list-style-type: none"> • G3+ CRS 23% • G3+ NE 12% • G5 AE X% 	<ul style="list-style-type: none"> • G3+ CRS 1% • G3+ NE 15% • G5 AE 4%

* Different grading scales are used to assess CRS, neurotoxicity across trials.

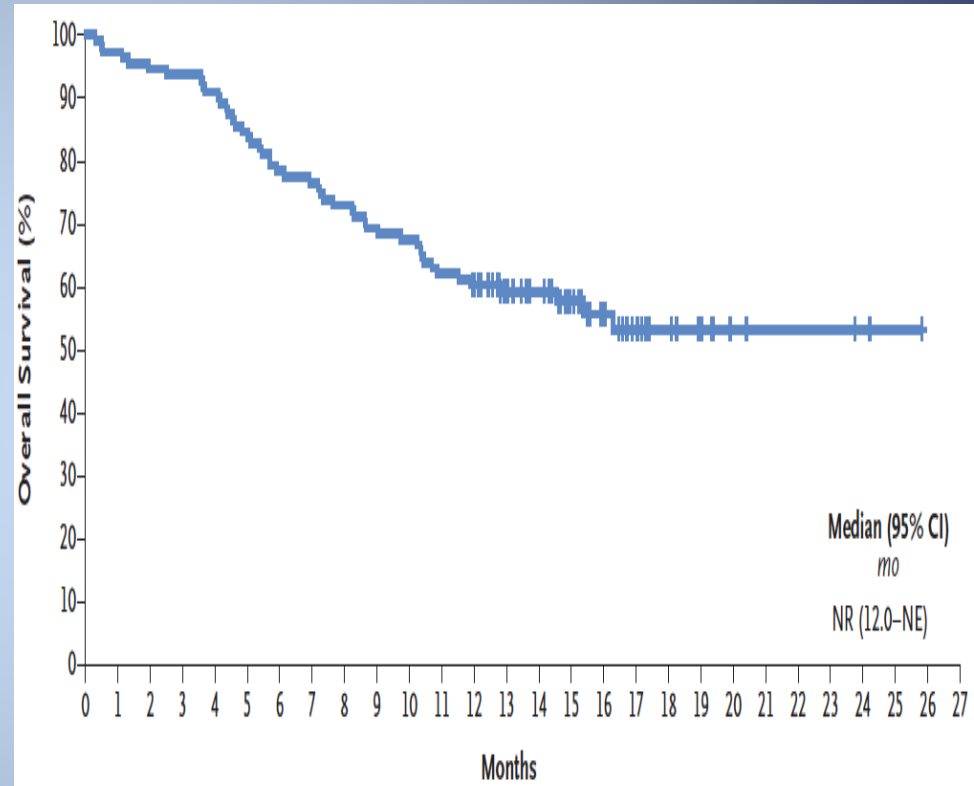
Outcomes in refractory DLBCL: Historical vs. KTE-C19

Overall survival: SCHOLAR-1



- N = 636
- ORR = 26%; CR rate = 7%
- Median OS = 6.3 months

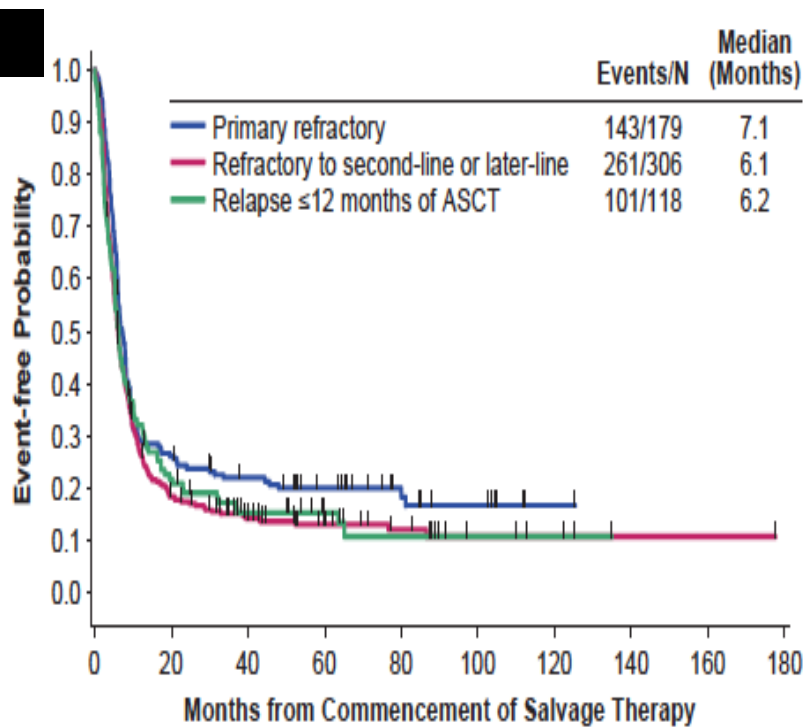
Overall survival: KTE-C19



- N = 108
- ORR = 82%; CR rate = 58%
- Median OS = >18 months

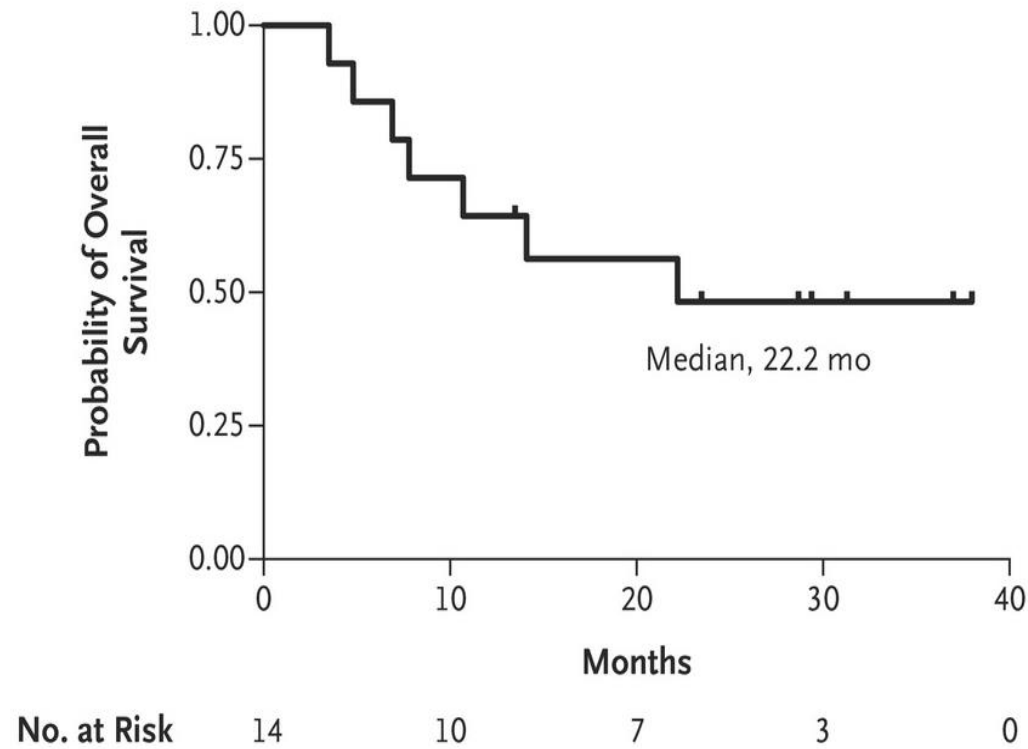
Outcomes in refractory DLBCL: Historical vs. CTL019

Overall survival: SCHOLAR-1



- N = 636
- ORR = 26%; CR rate = 7%
- Median OS = 6.3 months

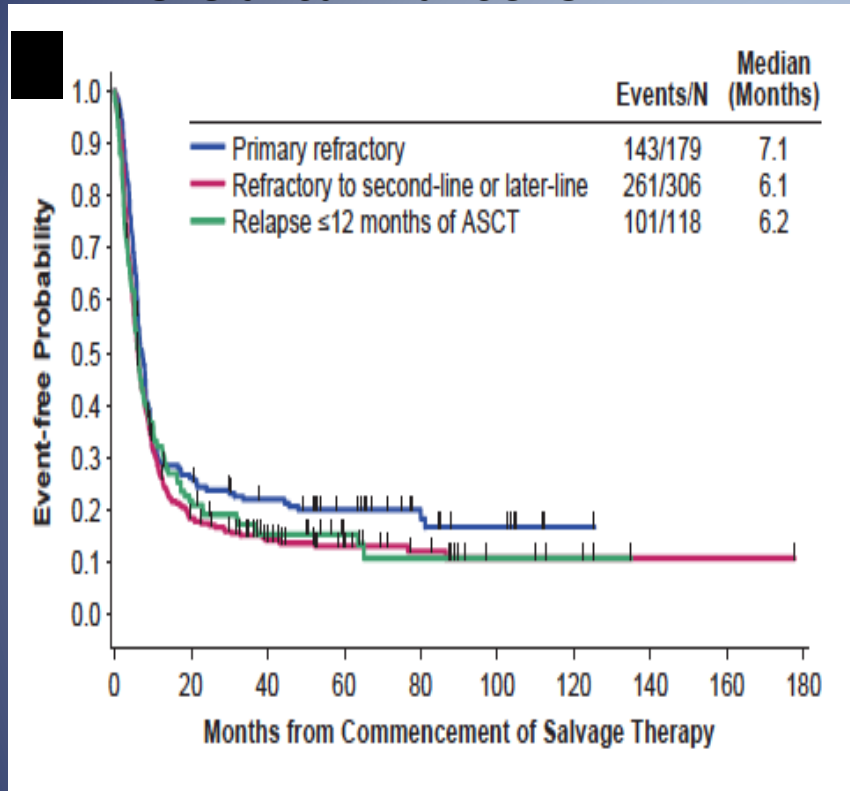
Overall survival: CTL019



- N = 28
- ORR = 53%; CR rate = 40%
- Median OS = 22.2 months

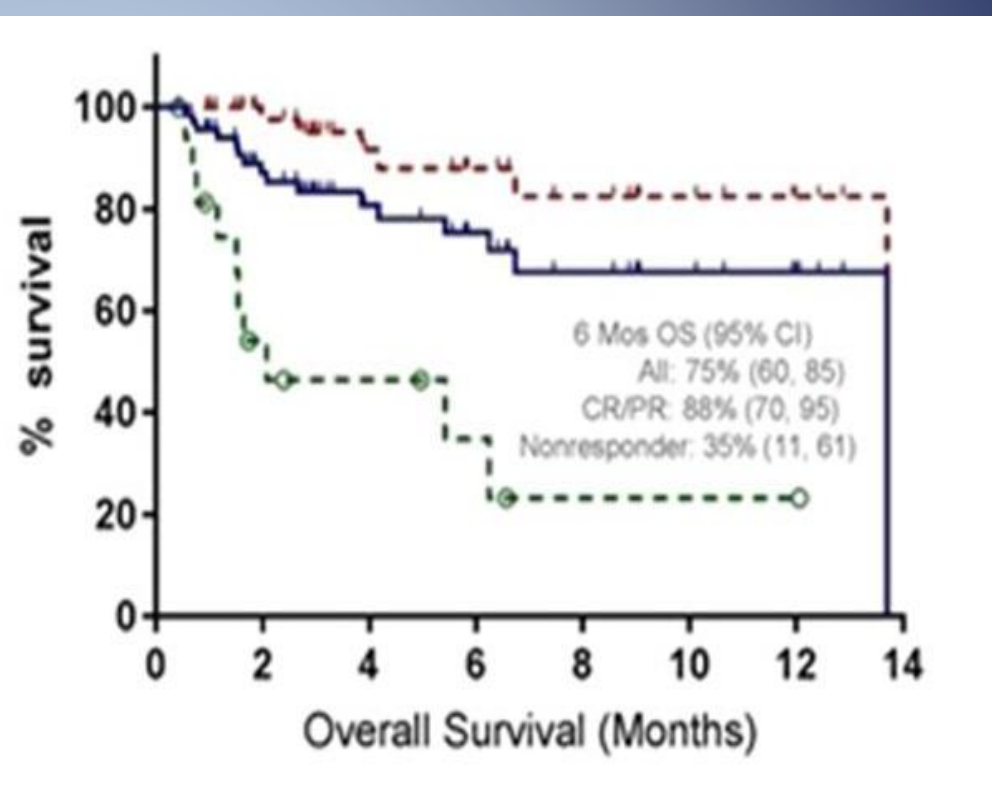
Outcomes in refractory DLBCL: Historical vs. JCAR017

Overall survival: SCHOLAR-1



- N = 636
- ORR = 26%; CR rate = 7%
- Median OS = 6.3 months

Overall survival: JCAR017



- N = 68
- ORR = 75%; CR rate = 53%
- Median OS = 13.7 months

State of the Landscape in Lymphoma

- The 'bar' is high in DLBCL and it is difficult to improve in unselected patients
- Novel agents in combination with RCHOP look somewhat promising
- Immune checkpoint blockade may not be effective in most lymphomas
- CAR T-cell results look very encouraging