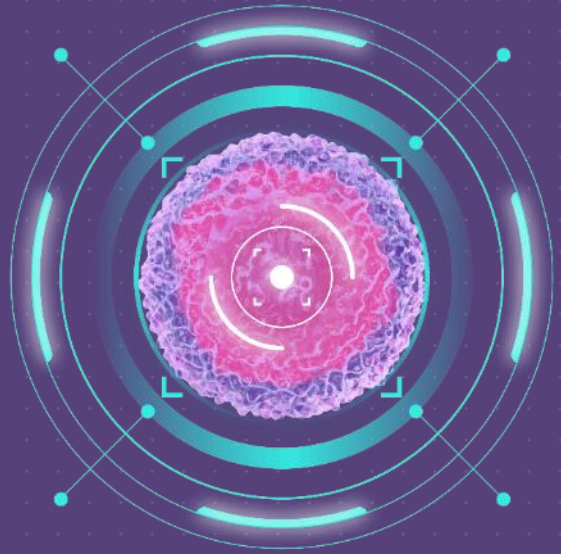
LymphomaHub

NEW CHEMOTHERAPY-FREE APPROACHES FOR THE TREATMENT OF LYMPHOID MALIGNANCIES



Scientific Education Support

Lymphoma Hub is delivered by Scientific Education Support (SES)

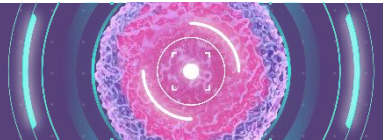
DLBCL – Chemotherapy-free Regimens Pros and Cons

Ulrich Jäger
Medizinische Universitsat Wien
Department of Internal Medicine
Division of Hematology & Hemostaseology

LymphomaHub

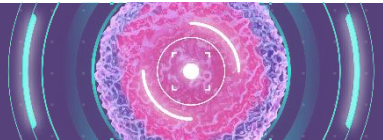
Disclosures - Ulrich Jäger, MD

Research support: (to institution)	Celgene, Emergent, Infinity, Janssen, Mundipharma, Roche, Novartis, Takeda-Millenium, True North Therapeutics
Consultant	Novartis, Roche, Abbvie, True North Therapeutics
Speakers Bureau	Roche
Honoraria	Abbvie, Amgen, AOP Orphan, Celgene, Emergent, Gilead, GSK, Janssen, Mundipharma, Novartis, Roche, Takeda-Millenium, True North Therapeutics
Scientific Advisory Board	Abbvie, Celgene, Gilead, Janssen, Millenium, Roche, Mundipharma, Novartis, True North Therapeutics



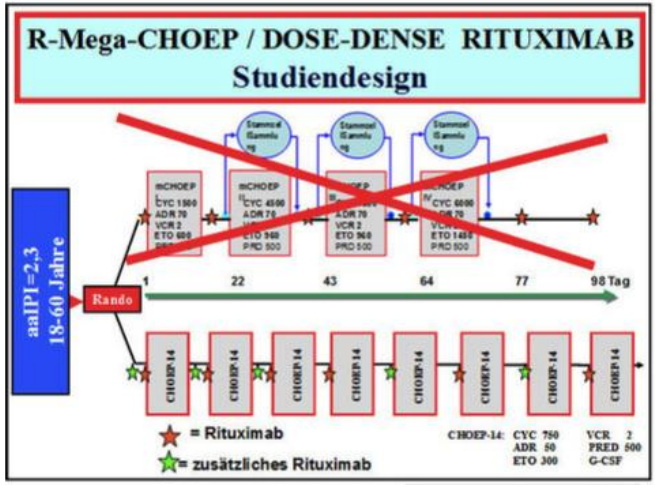
Considerations

- Chemo-combinations
- Antibody conjugated drugs
- True chemo-free
  - Induction, maintenance
  - Mono- or combination therapy
  - Cellular therapy (CAR-T)
- Prediction of response (precision approach)
  - Next-generation sequencing (NGS), biomarkers
  - Functional drug testing



Chemotherapy remains the backbone of first-line treatment of DLBCL

All major clinical evidence suggests that aggressive chemotherapy is mandatory...



…in the era of precision medicine...dreaming is allowed...

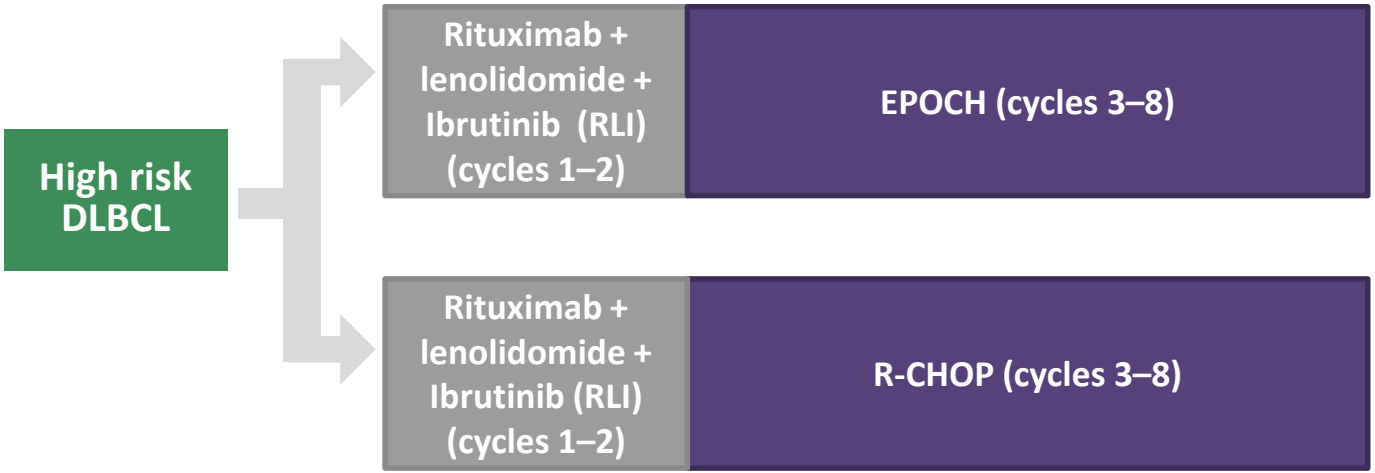
Images provided by the presenter

Improving R-CHOP: R-CHOP + X in first line

Drug			Trial name	Results
Induction X / R-CHOP				
Bevacizumab	**RA-CHOP**	DLBCL	**MAIN[1]**	**No benefit**
Bortezomib	**BorR-CHOP**	DLBCL	**ReMoDL-B[2]**	**No benefit 30-month PFS**
Ibrutinib	**IR-CHOP**	ABC DLBCL	**PHOENIX[3]**	**No benefit EFS.** ***ICML abstract #093***
Lenalidomide	**R^2-CHOP**	ABC DLBCL	**ROBUST[4]**	**PFS not superior vs R-CHOP** ***ICML abstract #005***
Venetoclax	**R-CHOP**	DLBCL	**CAVALLI[5]**	Phase Ib trial completed. Managable safety profile. ***ICML abstract #085***
Durvalumab	**R-CHOP (+/- lenalidomide)**	DLBCL (high risk)	**FUSION[6]**	Phase II, recruiting. Sep 2017: Partial Clinical Hold for Arm A. ***ICML abstract #087***
Maintenance R-CHOP + X				
Rituximab		DLBCL	**NHL13[7]**	**No benefit 3y EFS**
Enzastaurin		DLBCL	**PRELUDE[8]**	**No benefit 4y DFS**
Everolimus		DLBCL	**PILLAR-2[9]**	**No benefit 2y DFS**
Lenalidomide		DLBCL	**REMARC[10]**	**PFS benefit**

1.Seymour *et al*. *Haematologica.* 2014;99:1343–9; 2. Davies *et al. Lancet* Oncology. 2019;20:649–62; 3. Younes *et al*. *J Clin Oncol.* 2019 DOI: 10.1200/JCO.18.02403; 4. Celgene Reports First Quarter 2019 Operating and Financial Results. Celgene. Published April 25, 2019. https://bit.ly/2UX0RGZ; 5. Zelenetz *et al. Blood.* 2019 DOI: 10.1182/blood-2018-11-880526; 6. https://clinicaltrials.gov/ct2/show/NCT03003520; 7. Jaeger *et al. Haematologica.* 2015;100:955–63; 8. Crump *et al*. *J Clin Oncol.* 2016;34:2484-92; 9. Witzig *et al*. ASCO 2016. Abstract 7506; 10. Thieblemont *et al. J Clin Oncol.* 2017;35:2473–81

SMART START – non-randomised, parallel Phase II study



Primary endpoints:

- ORR after 2 cycles of RLI
- CR after 8 cycles of RLI and chemotherapy

Rituximab 375 mg/m^2 IV Day 1, ibrutinib 560 mg PO daily, and lenalidomide 25 mg PO Days 1–10 of 21 day cycles for 2 cycles, followed by 6 additional cycles of RLI with chemotherapy

CR, complete response; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; IV, intravenous; ORR, overall response rate; PO, orally; RLI, rituximab, lenolidomide and ibrutinib; R- CHOP, rituximab, prednisone, vincristine, cyclophosphamide, and doxorubicin

Westin J, *et al.* ASCO 2019. Abstract # 7508

SMART START – results

Outcome	RLI (n=58)	RLI + chemotherapy (n=49)
ORR	86%	NA
CR	36%	96%
PR	50%	4%
SD	7%	-
MR	5%	-
PD	2%	-

Adverse effect in ≥25% patients

- Nausea
- Peripheral sensory neuropathy
- Diarrhea
- Mucositis oral
- Anemia
- Thrombocytopenia
- Rash
- Neutropenia
- Dyspnea

ORR, overall response rate; CR, complete response; PR, partial response; SD, stable disease; MR, minor response; PD, progressive disease; RLI, rituximab, lenolidomide and ibrutinib;

Westin *et al.* ASCO 2019 abstract 7508;

Antibody-drug-conjugates in DLBCL

Product	Combination partner	Indication	Phase II	Results
Polatuzumab vedotin	Rituximab (or obinutuzumab)	R/R DLBCL	ROMULUS[1,2]	ORR: 54% mPFS: 5.6 months mDoR: 13.4 months
	Rituximab (or obinutuzumab) plus bendamustine	R/R DLBCL	NCT02257567[3,4]	CR: 40% mPFS: 6.7 months mOS: 11.8 months
Brentuximab vedotin	Rituximab	R/R DLBCL	NCT01421667[5]	ORR: 44% CR: 17% mPFS: 4 months mDoR: 5.6 months mDoR in CR pts: 16.6 months
	R-CHOP	DLBCL	NCT01925612[6]	ORR: 97% CR: 80%

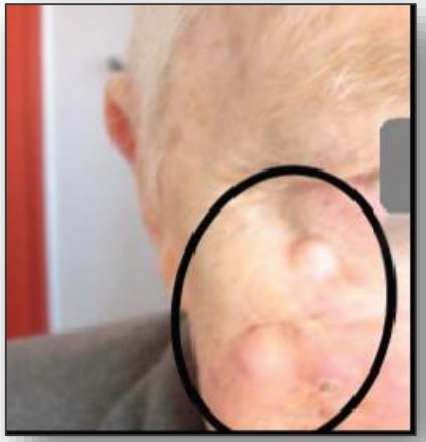
CR, complete response; DoR, duration of response; m, median; ORR, overall response rate; PFS, progression-free survival.

1. Morschhauser *et al. Lancet Haematol.* 2019 DOI: 10.1016/S2352-3026(19)30026-2; 2. https://clinicaltrials.gov/ct2/show/NCT01691898; 3. Sehn *et al.* ASH 2018. Abstract #7507; 4. https://clinicaltrials.gov/ct2/show/NCT02257567; 5. Jacobsen *et al. Blood.* 2015;125:1394–1402; 6. Bartlett *et al.* ASCO 2015. Abstract #8506

Chemo-free treatment options beyond first line

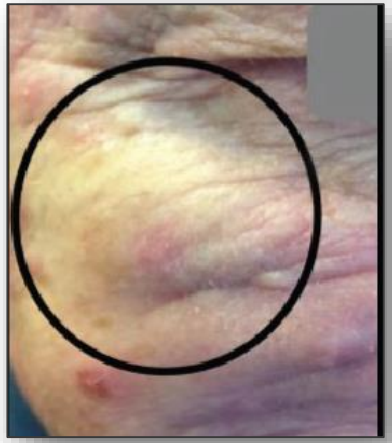
Diffuse large B-cell lymphoma (*MYD88^{mut}*)

Ibrutinib treatment Day 0



Drug name	Rank	RBF	P-value
Cisplatin	1	0.504	2.34e−06
Ibrutinib	**2**	**0.661**	**0.000477**
Ixazomib	3	0.797	0.00915
Oxaliplatin	4	0.807	0.00666
Vinblastine Sulfate	5	0.829	0.0174
EPZ−5676	6	0.836	0.0162

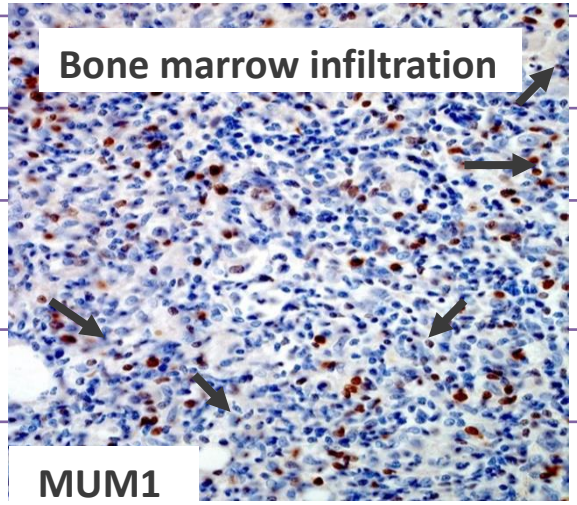
Ibrutinib treatment Day 26



Images provided by Ulrich Jäger

Case report: DLBCL elderly – relapsed
Pat. G. B., 80 yrs, Architect

Date	Diagnosis	Response/ Relapse	Duration (mo)
2002	DLBCL, CD20+, CS IIA (abdominal, splenomegaly; IPI: 2 [LDH, age > 60])	1st CR 12/2002	48
03/ 2006	1st relapse: T-cell rich DLBCL, CD20+, CS IVA (BM, lumbar spine); IPI: 3; cardiac comorbidity: NSTEMI, pacemaker	2nd CR 12/2006	27
07/ 2008	2nd relapse: TCR-DLBCL, CD20-; CS IVA (BM), PET +	No response	
12/ 2008	Still BM infiltration with bc16+, mum-1 + DLBCL		



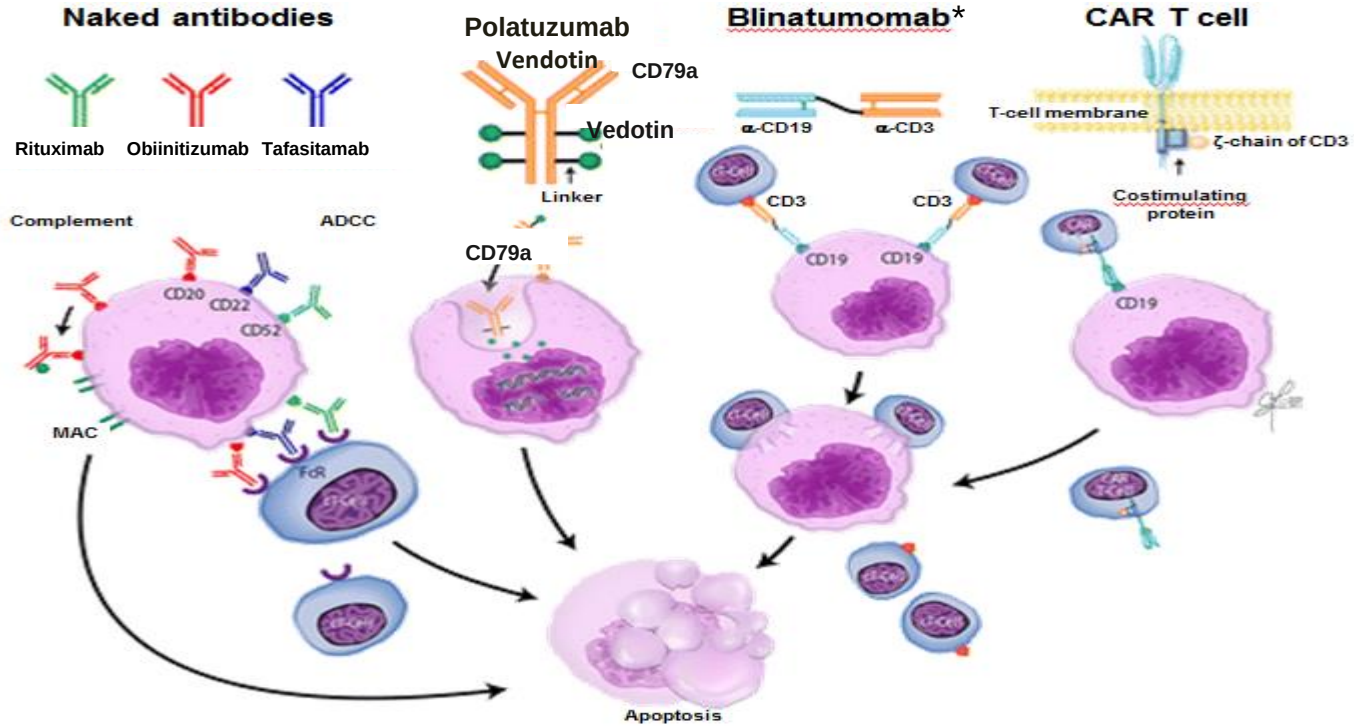
BEAM, carmustine, etoposide, cytarabine & melphalan; BM, bone marrow; CR, complete response; CS, clinical stage; NSTEMI, non-ST-elevation myocardial infarction; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine & prednisone; R-ICE, rituximab, ifosfamide, carboplatin & etoposide

Case report: DLBCL elderly – relapsed
Pat. G. B., 80 yrs, Architect

Date	Diagnosis	Bone marrow infiltration	Response/ Relapse	Duration (mo)
2002	DLBCL, CD20+, CS IIA (abdominal, splenomegaly; IPI: 2 [LDH, age > 60])		1st CR 12/2002	48
03/ 2006	1st relapse: T-cell rich DLBCL, CD20+, CS IVA (BM, lumbar spine); IPI: 3; cardiac comorbidity: NSTEMI, pacemaker		2nd CR 12/2006	27
07/ 2008	2nd relapse: TCR-DLBCL, CD20-; CS IVA (BM), PET +		No response	
12/ 2008	Still BM infiltration with bc16+, mum-1 + DLBCL	MUM1		
01/ 2009	Still BM infiltration with bc16+, mum-1 + DLBCL	Salvage treatment with lenalidomide (25mg – 21d/8 day off courses)	3rd CR 3/2009 (BM biopsy, PET neg)	9+
01/ 2010		Maintenance with 10mg lenalidomide	3rd CCR	14 (died: pulmonary embolism)

BEAM, carmustine, etoposide, cytarabine & melphalan; BM, bone marrow; CR, complete response; CS, clinical stage; NSTEMI, non-ST-elevation myocardial infarction; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine & prednisone; R-ICE, rituximab, ifosfamide, carboplatin & etoposide

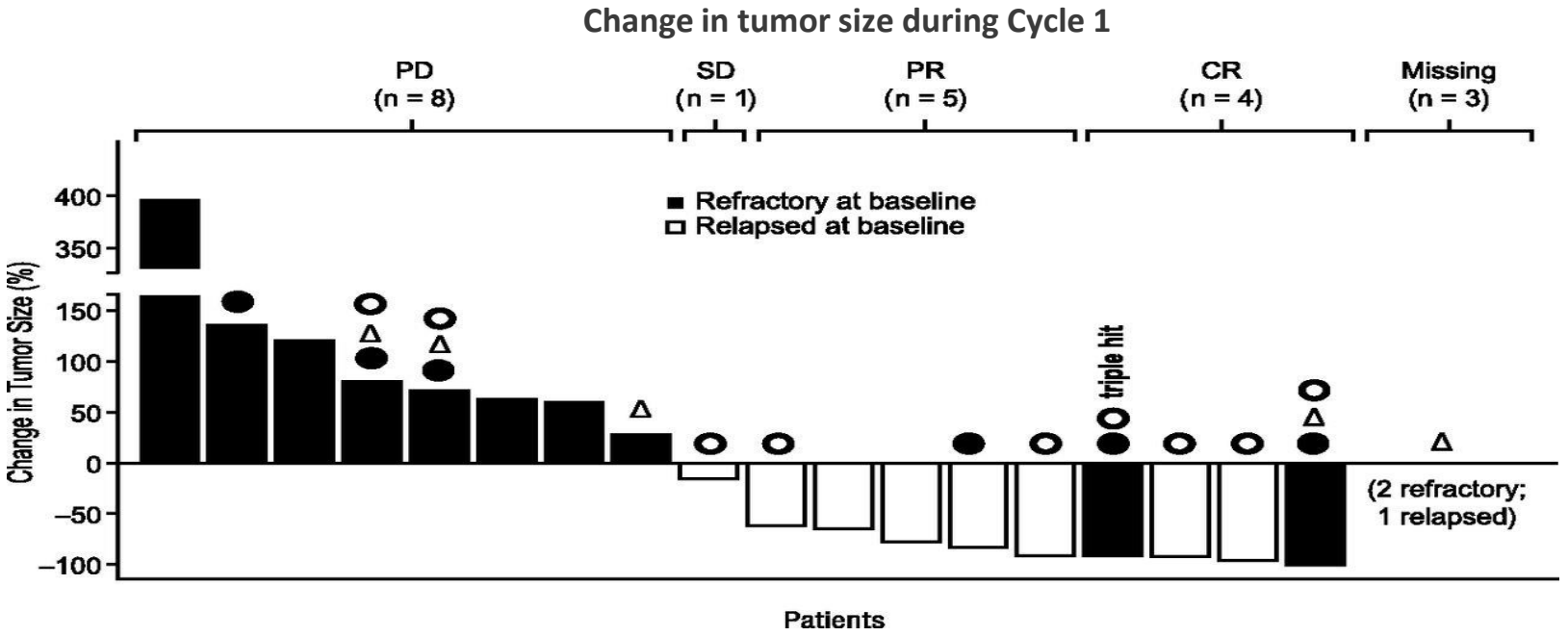
Treating R/R B-NHL with antibody driven approaches



B-NHL, b-cell non-Hodgkin lymphoma; R/R, relapsed/refractory

Courtesy: Max Topp, Würzburg

Activity of blinatumomab in DLBCL



● patients who had previous ASCT
Δ patients with bulky disease (diameter >7.5 cm) at baseline
○ patients with transformed disease at baseline

Overall response rates (n=25):
4 CR, 5 PR = 36%)

ASCT, autologous stem cell transplantation ; CR, complete response; DLBCL, diffuse large b-cell lymphoma; PR, partial response; SD, stable disease

Viardot A, *et al. Blood.* 2016;127:1410–6

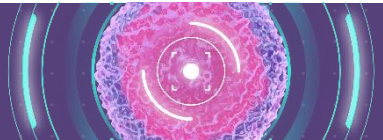
Slide courtesy of Max Topp, Würzburg

Bispecific antibody trials in R/R B-NHL

Modality and specificity	Name	Disease setting	Development stage
Dual affinity re-targeting (DART®) anti-CD19/CD3	Duvortuxizumab	R/R B-NHL	Phase I
Bispecific anti-CD19/CD3 tandem diabody (TandAb®)	AFM11	R/R B-NHL	Phase I
Bispecific native format anti-CD20/CD3	REGN1979	R/R B-NHL + CLL	Phase I
Bispecific next generation anti-CD20/CD3 (2:1 format)	CD3xCD20 TCB	R/R B-NHL	Phase I
Bispecific native format anti-CD20/CD3	Mosenutuzumab	R/R B-NHL	Phase I + II
Bispecific T-cell engaging (BITE®)	Blinatumomab	R/R B-NHL	Phase I + II

B-NHL, b-cell non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; R/R, relapsed/refractory

Courtesy: Max Topp, Würzburg



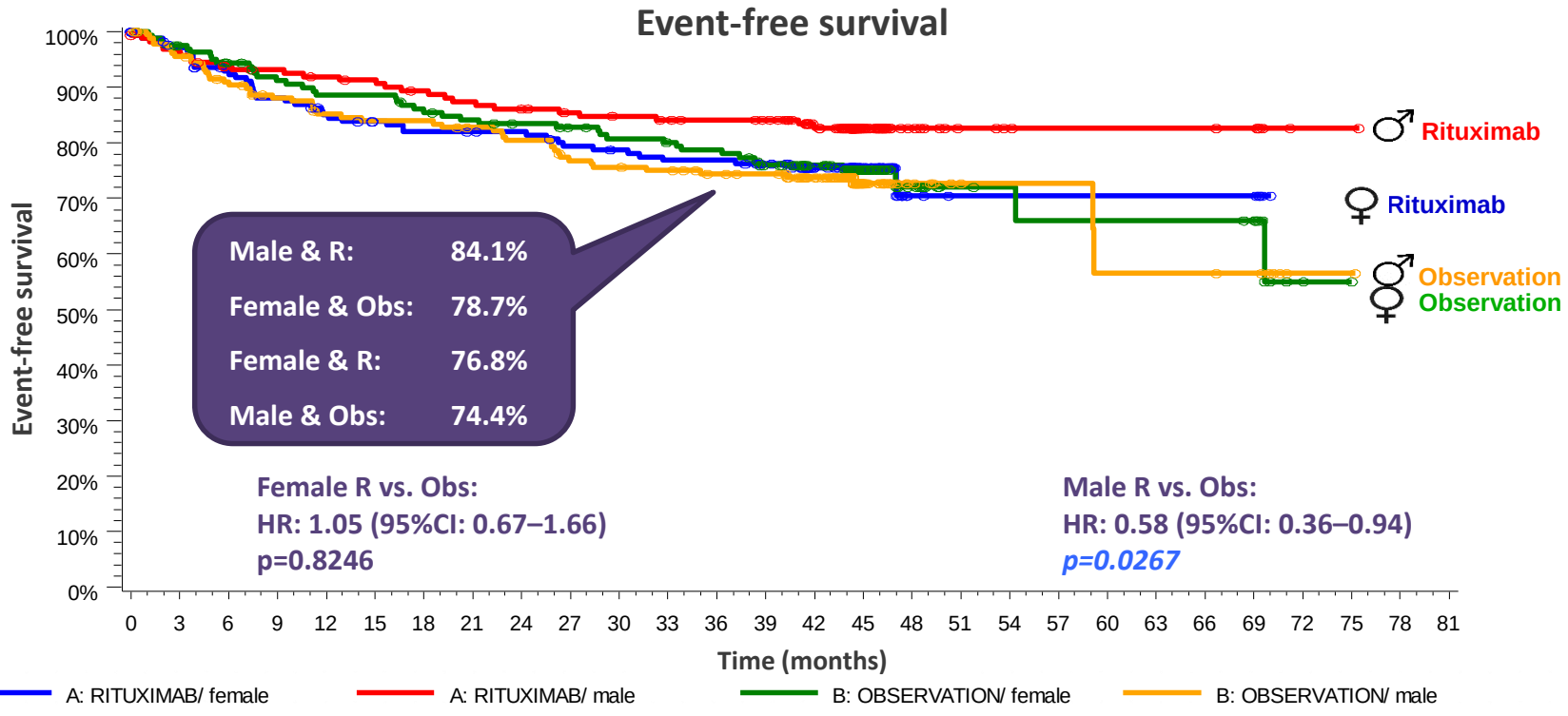
True ‘chemo-free’ therapy in R/R DLBCL

Agent	Studies	Endpoint	ORR/CR	References
Ibrutinib	Phase 1/2, 80 DLBCL	ORR	37% in ABC, 5% in GCB; 80% in MYD88mut	Wilson WH *et al. Nat Med* 2015[1]
Ibrutinib + Nivolumab	Multicenter Phase 1/2a, 45 DLBCL included	ORR	36%	Younes A *et al. Lancet Haematol* 2019[2]
Lenalidomide	Multicenter, Phase 2/3, 102 DLBCL	ORR	27.5%	Czuczman MS *et al. Clin Cancer Res* 2017[3]
Lenallidomide + Obinutuzumab	Phase 1b/2, 77 DLBCL included	ORR	35.2% / 16.9%	Morschhauser F *et al. Blood* 2016[4]
EZH2 inhibitor (tazemetostat)	Multicenter, Phase 2, 95 DLBCL included	ORR	40% in DLBCL with *EZH2* gene mutation; 18% in DLBCL with wt *EZH2*	Morschhauser F *et al. ICML* 2017[5]
Blinatumomab	Phase 2, 21 DLBCL	ORR	43% / 19%	Viardot A *et al. Blood* 2016[6]
Pembrolizumab	Phase 1/2, 8 DLBCL	Safety	25% (1 CR, 1 PR, 6 PD)	Chong E *et al.* Blood 2017[7]
Obinutuzumab + venetoclax	AGMT NHL15B	ORR	NA	Recruiting[8]
Tafasitamab (MOR208) + lenalidomide	L-MIND	ORR	58%	Maddocks *et al*. ASCO 2019[9]
CAR-T cells	ZUMA-1, JULIET, TRANSCEND	ORR	52–83% / 40–58%	Locke FL *et al. Lancet* Oncol 2019[10] Schuster S *et al*. NEJM 2019[11] Abramson J *et al*. *J Clin Oncol* 2018[12]

ABC, activated B cell-like; CR, complete response; EZH2, enhancer of zeste homolog 2; GCB, germinal center B cell-like; ORR, overall response rate

1. Wilson *et al. Nat Med*. 2015;21:922–6; 2. Younes *et al. Lancet Haematol.* 2019 DOI: 10.1016/S2352-3026(18)30217-5; 3. Czuczman *et al. Clin Cancer Res.* 2017;23:4127–37; 4. Morschhauser *et al, Blood*. 2016;128:4202; 5. Morschhauser *et al*. *J Clin Oncol.* 2017:34: 15 suppl; 6. Viardot A *et al. Blood*. 2016;127:1410–6; 7. Chong *et al. Blood.* 2017;130:4121; 8. https://clinicaltrials.gov/ct2/show/NCT02987400; 9. Maddocs *et al*. ASCO poster 7521, 2019; 10. Locke FL *et al*. *Lancet Oncol*. 2019;20:31–42; 11. Schuster SJ *et al*. *N Engl J Med*. 2019;380: 45–56; 12. Abramson J *et al. J Clin Oncol.* 2018;36:7505.

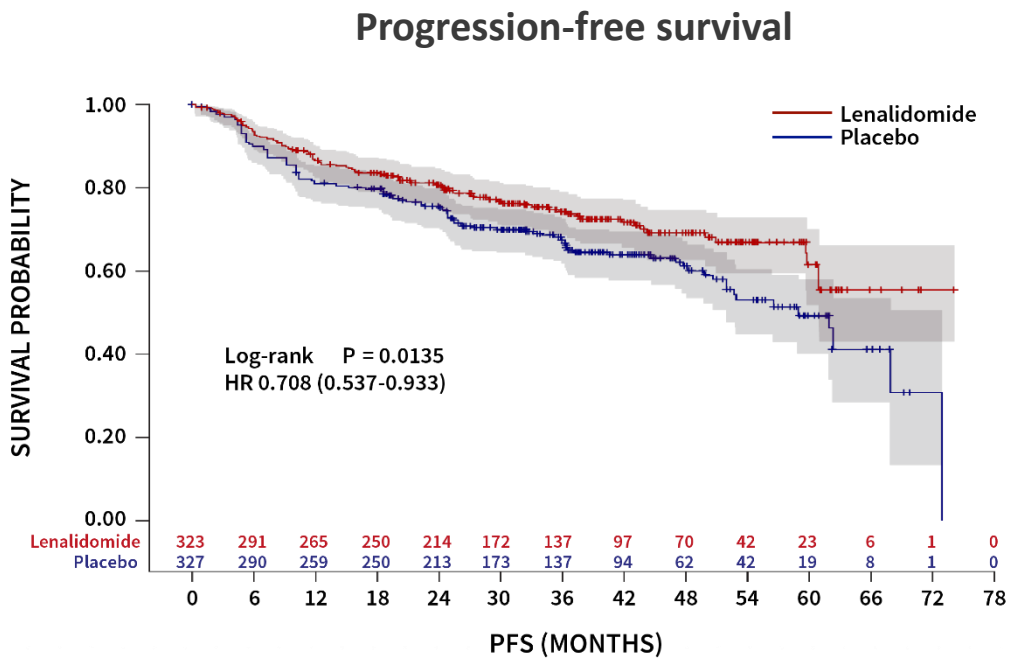
Male patients benefit from R-maintenance



Obs, observation; R, rituximab

Jaeger U *et al. Haematologica*. 2015;100:955–63

REMARC: Progression-free survival (central review)



- At a median follow-up of 40 months, median PFS was not reached for lenalidomide and 58.8 months for placebo

PFS, progression-free survival

Thieblemont *et al. J Clin Oncol.* 2017;35:2473–81

CAR-T cell treatment in R/R setting

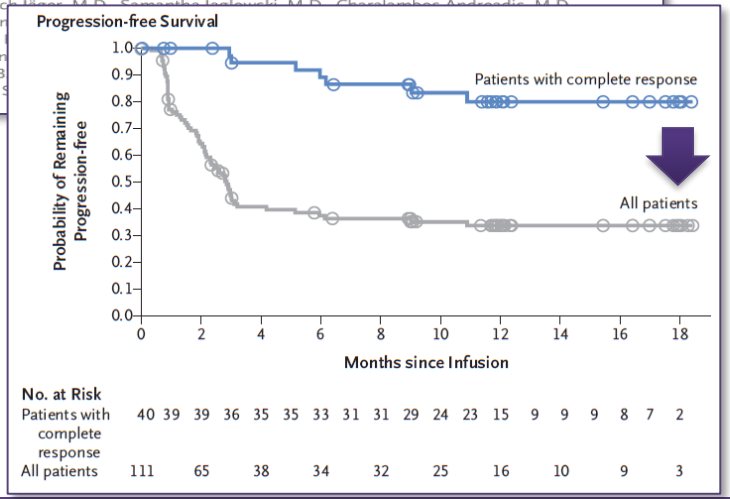
Long-term outcome of patients with R/R DLBCL after CD-19 CAR-T cell therapy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma

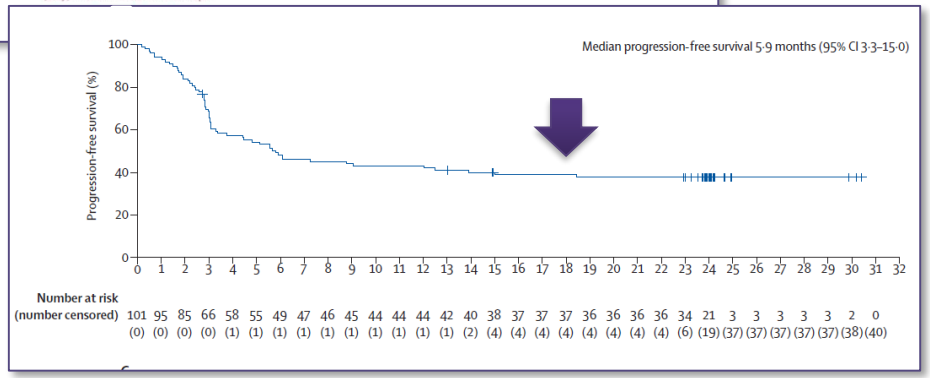
Stephen J. Schuster, M.D., Michael R. Bishop, M.D., Constantine S. Tam, M.D., Edmund K. Waller, M.D., Ph.D., Peter Borchmann, M.D., Joseph P. McGuirk, D.O., Ulrich Jäger, M.D., Samantha Jaglowski, M.D., Charalambos Andreadis, M.D., Jason S. John Lida B Gilles S



Articles

Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial

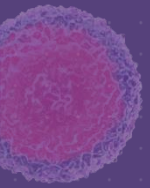
Frederick L Locke*, Armin Ghobadi, Caron A Jacobson, David B Miklos, Lazaros J Lekakis, Olalekan O Oluwole, Yi Lin, Ira Braunschweig, Brian T Hill, John M Timmerman, Abhinav Deol, Patrick M Reagan, Patrick Stiff, Ian W Flinn, Umar Farooq, Andre Goy, Peter A McSweeney, Javier Munoz, Tanya Siddiqi, Julio C Chavez, Alex F Herrera, Nancy L Bartlett, Jeffrey S Wiezorek, Lynn Navale, Allen Xue, Yizhou Jiang, Adrian Bot, John M Rossi, Jenny J Kim, William Y Go, Sattva S Neelapu*

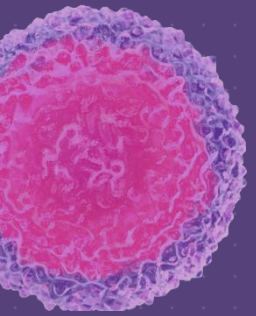


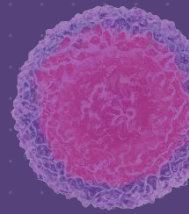
18 months PFS ≈ 40%

CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; PFS, progression-free survival

1. Schuster SJ, *et al. N Eng J Med,* 2019; 380:45-56; 2. Locke FL *et al. Lancet Oncol.* 2019;20:31–42



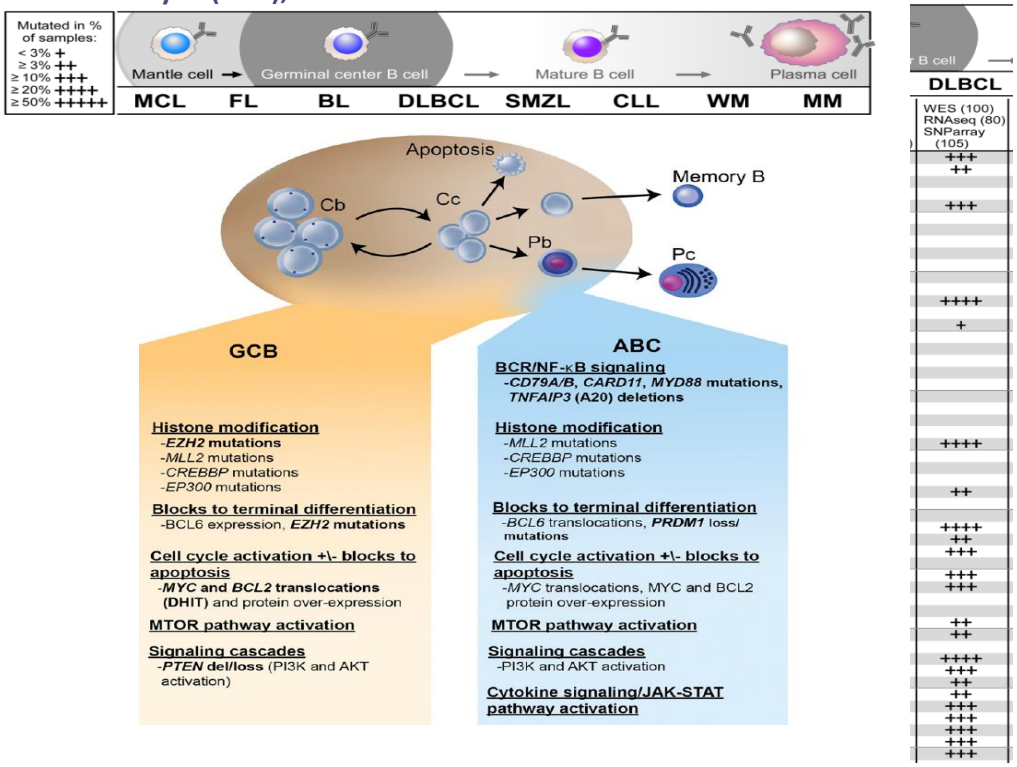




Predicting response

Predicting response: Defining subgroups

Genetic analysis (NGS), Biomarkers[1,2]



Genetic subgroups[3]

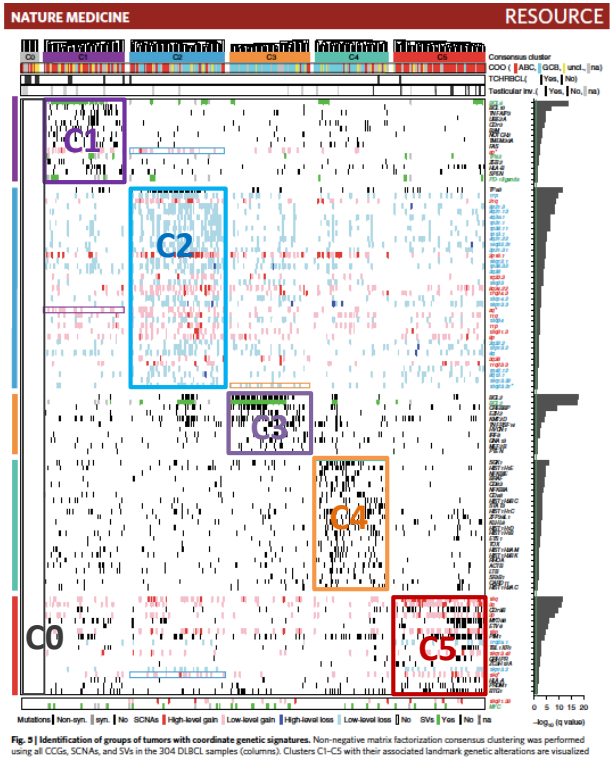


Fig. 5 | Identification of groups of tumors with coordinate genetic signatures. Non-negative matrix factorization consensus clustering was performed using all CCGs, SCNAs, and SVs in the 304 DLBCL samples (columns). Clusters C1–C5 with their associated landmark genetic alterations are visualized

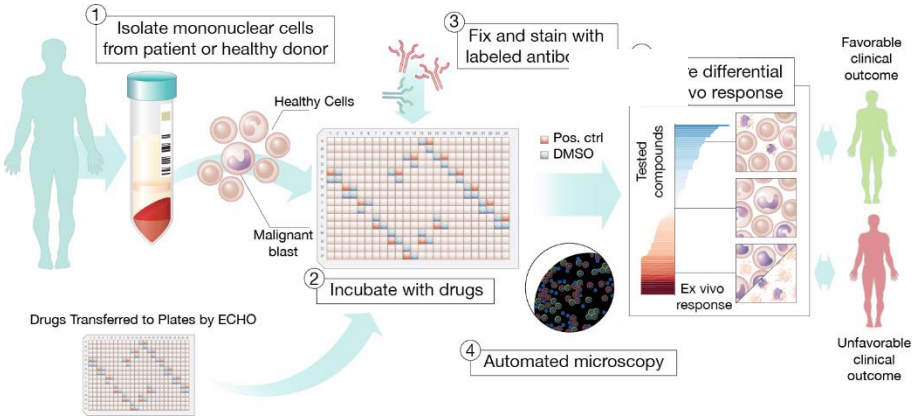
Figures adapted from: 1. Sehn LH & Gascoyne RD. *Blood.* 2015;125:22–32; 2. Gruber M and Wu CJ. *Semin Hematol*. 2014;51:177–87; 3. Chapuy B *et al*. *Nat Medicine.* 2018: 24: 679–90

Predicting response – Defining subgroups

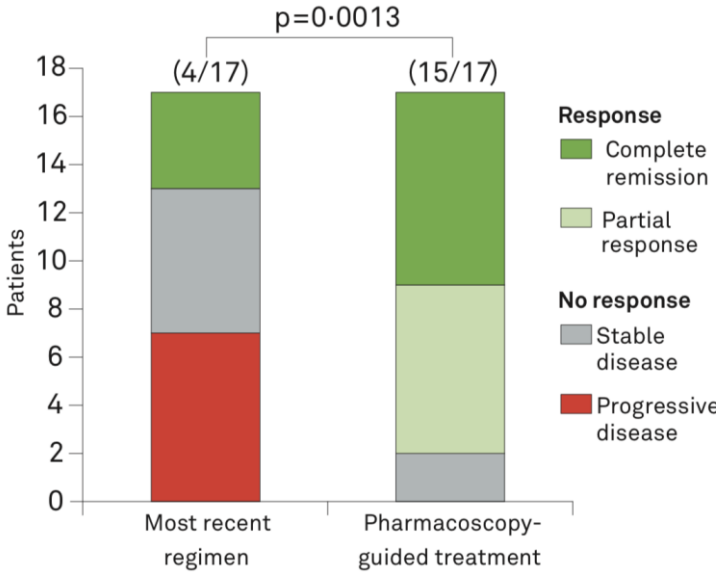
Functional drug testing

Image-based ex-vivo drug screening for patients with aggressive haematological malignancies: interim results from a single-arm, open-label, pilot study

Berend Snijder*, Gregory I Vladimer*, Nikolaus Krall, Katsuhiro Miura, Ann-Sofie Schmolke, Christoph Kornauth, Oscar Lopez de la Fuente, Hye-Soo Choi, Emiel van der Kouwe, Sinan Gültekin, Lukas Kazianka, Johannes W Bigenzahn, Gregor Hoermann, Nicole Prutsch, Olaf Merkel, Anna Ringler, Monika Sabler, Georg Jeryczynski, Marius E Mayerhoefer, Ingrid Simonitsch-Klupp, Katharina Ocko, Franz Felberbauer‡, Leonhard Müllauer, Gerald W Prager, Belgin Korkmaz, Lukas Kenner, Wolfgang R Sperr, Robert Kralovics, Heinz Gisslinger, Peter Valent, Stefan Kubicek, Ulrich Jäger, Philipp B Staber†, Giulio Superti-Furga†



Overall response rate: from 24% to 88%



Odds ratio: 24.38 [95% CI 3.99–125.4]

11/17 patients with R/R B-cell malignancies:

- 6 DLBCL; 3 B-LBL/ALL; 1 PMBL; 1 FL G3A

DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; G, Grade; PMBCL, primary mediastinal large B-cell lymphoma; R/R, relapsed/refractory

Snijder B *et al. Lancet Haematol.* 2017;4:e595–e606

Chemotherapy-free treatment of DLBCL: options for further development
PRECISION APPROACH

Establish PREDICTORS for chemo-free single agent or combination Tx

Study COMBINATIONS of chemo-free Tx with conventional CTx

Develop NOVEL, more active small molecules/ antibodies/ cellular immuno Tx


Round table
discussion

Thank you