Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

KML-Experten berichten

16th ICML 2021 Virtual

Kompetenznetz Maligne Lymphome

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Aggressive Lymphome

Offenlegung potentieller Interessenskonflikte

LymphomKompetenz KOMPAKT – ICML2021 wird in Kooperation mit vier unterstützenden Firmen durchgeführt.
Meine persönlichen Disclosures betreffen:

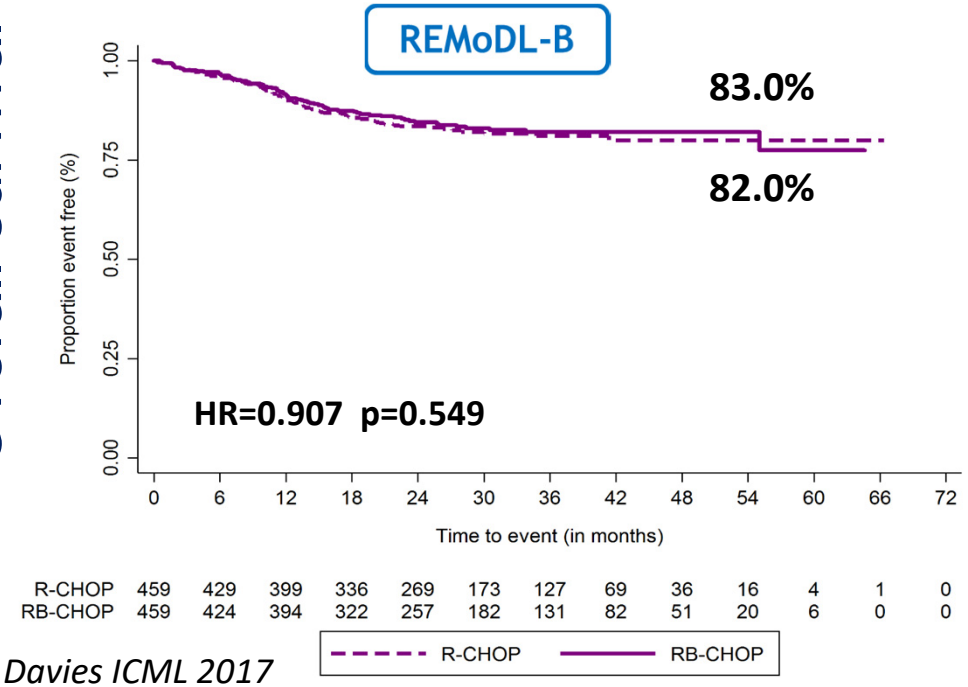
Anstellungsverhältnis, Führungsposition	Keine
Beratungs-/ Gutachtertätigkeit	Regeneron
Besitz von Geschäftsanteilen, Aktien oder Fonds	Keine
Patent, Urheberrecht, Verkaufslizenz	Patents for molecular subtyping of aggressive lymphoma
Honorare	AstraZeneca, BMS, Gilead
Finanzierung wissenschaftlicher Untersuchungen	Gilead (Reserach Award 2018)
Andere finanzielle Beziehungen	Keine
Immaterielle Interessenkonflikte	Keine

Kapitel 1

Erstlinientherapie

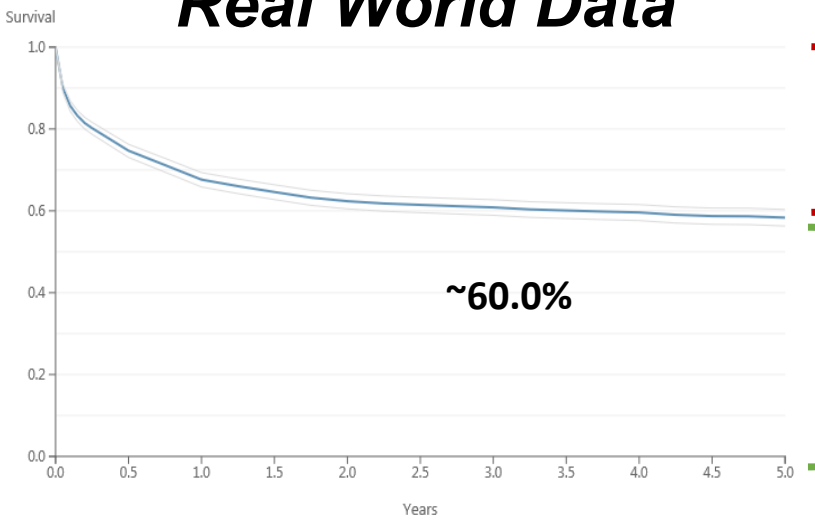
DLBCL – A Curable Disease – Trial vs. Real World

Overall survival



Davies ICML 2017

Real World Data



Haematological Malignancies research Network 2017

➔ R-CHOP is the established standard in 1st line.

➔ Many all-comer trials failed their clinical endpoint.

How to Improve?

Urgent need to understand the clinical heterogeneity in DLBCL

Strategy 1

Identify high-risk DLBCL by clinical/radiographic makers

↓

Risk-adapted treatment

C. Thieblemont, Paris (017)

Strategy 2

Understand the molecular heterogeneity and identify actionable alterations

↓

Biological-informed treatment

M. Zhang, Shanghai (027)

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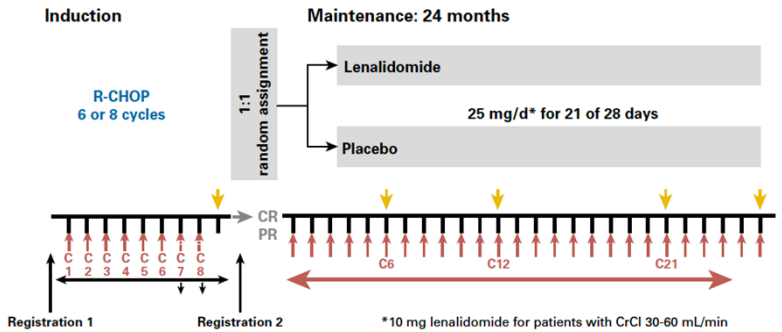
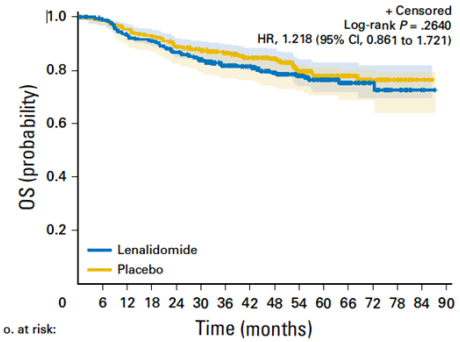
017 – Defining ulta-high-risk DLBCL patients prior to initial treatment based on an integrative host and disease prognostic score (from REMARC study)

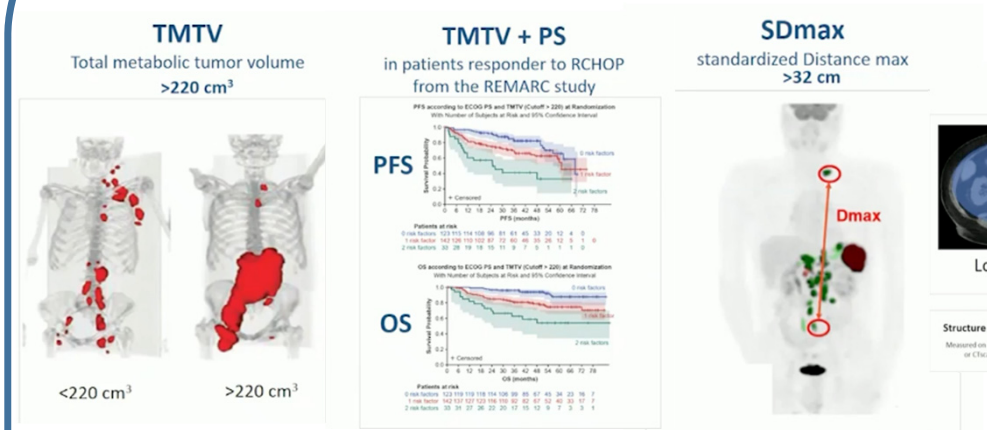
REMARC Trial





Thieblemont C et al JCO 2017

MVED²



Metabolic Volume ECOG Distance Density

0.57 (if ECOG PS ≥2) + 0.76 (if SDMAX > 32) +
0.70 (if LSAD > -90) + 0.59 (if TMTV>220)

Based on 4 baseline reproducible and easy parameters

3 risk- categories
Low-, intermediate-, and high-risk

Cottereau et al CCR 2016; Cercellino et al Blood 2020;
Cottereau et al Ann Oncol 2020; Deux et al ICML21, Abs #166

Thieblemont C ICML 2021

017 – Defining ulta-high-risk DLBCL patients prior to initial treatment based on an integrative host and disease prognostic score (from REMARC study)

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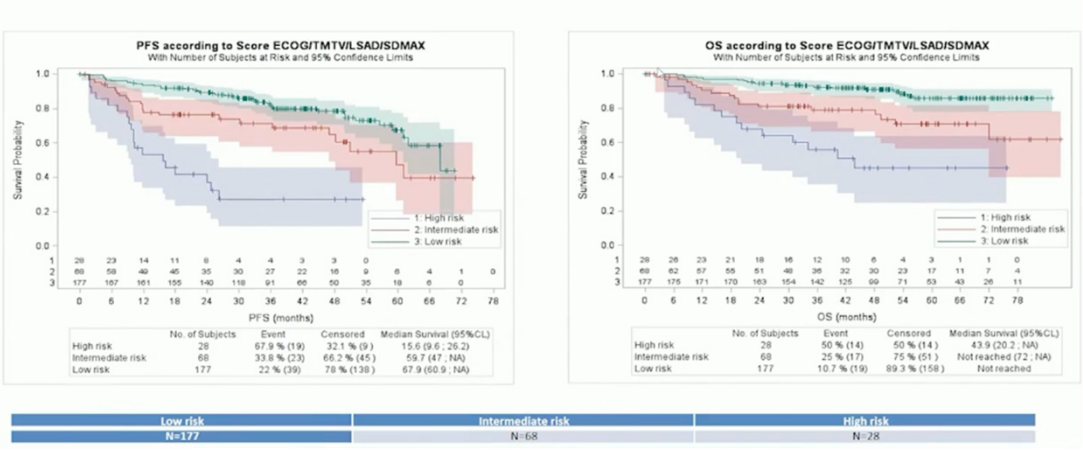
Patient characteristics

Risk categories	Low n=177 (65%)	Intermediate n=68 (25%)	High n=28 (10%)	p
Sex Male	101 (57%)	41 (60%)	**22 (60%)**	0,089
Age >=70 years	62 (35%)	10 (50%)	**10 (36%)**	0,093
Stage III-IV	157 (89%)	64 (94%)	**25 (89%)**	0,092
ExtraNodal >=2	8 (4,5%)	48 (70%°	**25 (89%)**	**<0,001**
Bone Marrow involved	19 (11%)	17 (25%)	**12 (43%)**	**<0,001**
Elevated LDH	95 (54%)	49 (72%)	**22(78%)**	**0,002**
NCCN IPI low Int High-Int High	63 (36%) 93 (52%) 13 (7,3%)	7 (10%) 44 (65%) 13 (19%)	**0 (0%)** **18 (64%)** **10 (36%)**	**<0,001**
ABC profile	41 (23%)	10 (15%)	**13 (46%)**	**0.046**

Outcome



- Adipose tissue alteration as an independent prognostic factor (biology of tumor vs. host)
- Upfront radiographic score that may discriminate ultra-high-risk DLBCL patients, even R-CHOP responder

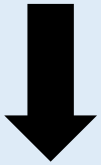
Thieblemont C ICML 2021

How to Improve?

Urgent need to understand the clinical heterogeneity in DLBCL

Strategy 1

Identify high-risk DLBCL by clinical/radiographic makers

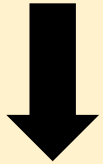


Risk-adapted treatment

C. Thieblemont, Paris (017)

Strategy 2

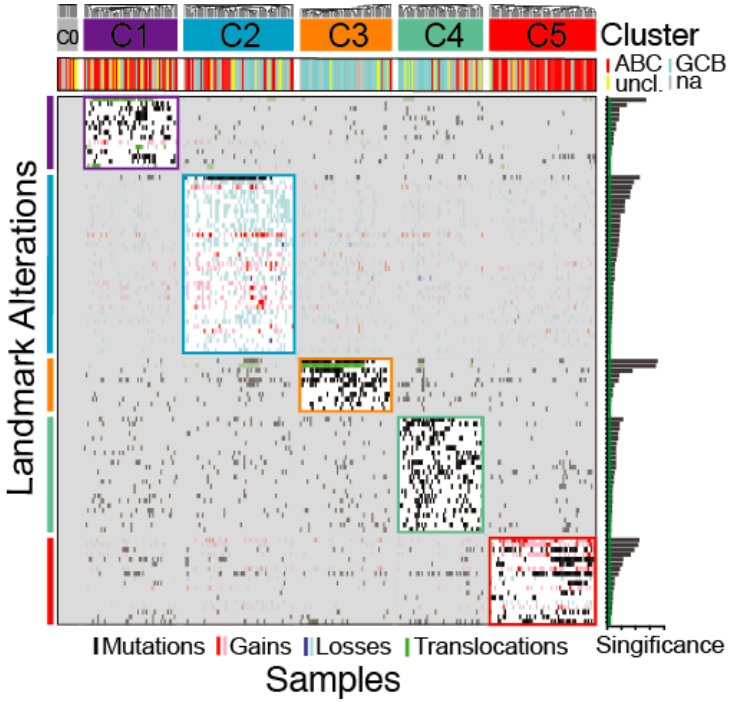
Understand the molecular heterogeneity and identify actionable alterations

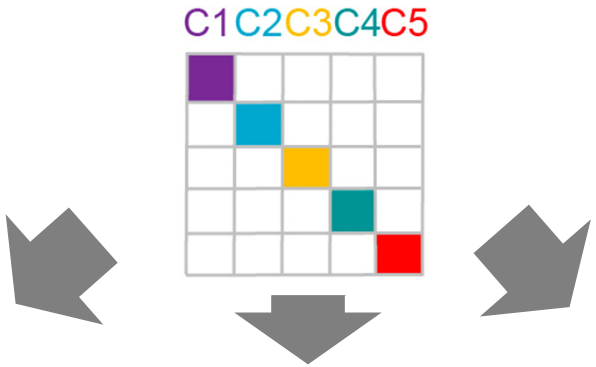


Biological-informed treatment

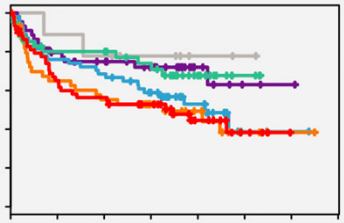
M. Zhang, Shanghai (027)

Genetically Distinct DLBCL Subtypes

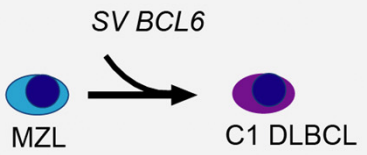




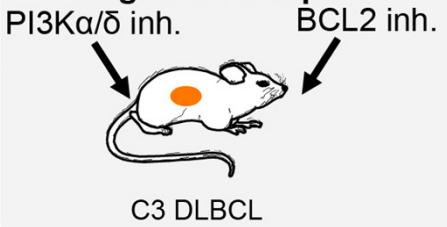
Outcome Prediction



Novel Insight into Lymphomagenesis



Combination of Targeted Therapies



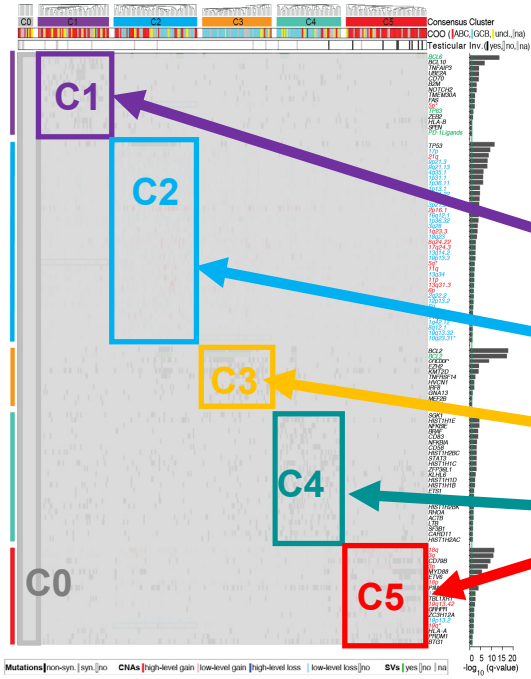
➔ Genetically-defined DLBCL subsets (C1-C5) predict different outcomes, provide novel insights into lymphomagenesis and suggest certain combinations of targeted therapies.

Chapuy et al. Nat Med 2018

Bojarczuk and Chapuy. EHA Educational 2019

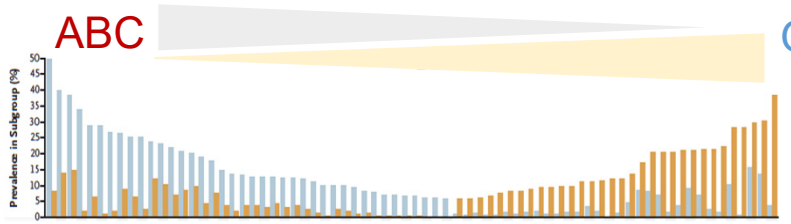
Genetic DLBCL Classifications

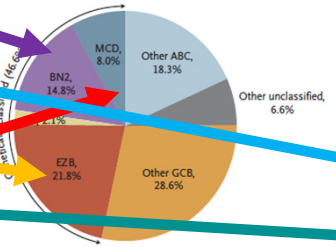
C1-C5 DLBCLs



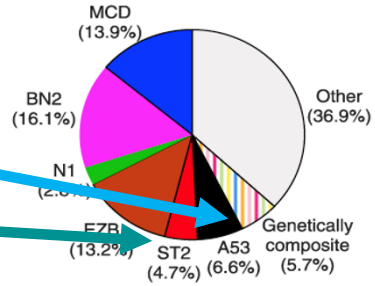
Chapuy, Stewart, Dunford, et al. *Nat. Med.* 2018

MCD/BN2/EZB/N1/ST2/A53/Other DLBCLs





Schmitz, Wright, Huang, Johnson, et al. *NEJM* 2018



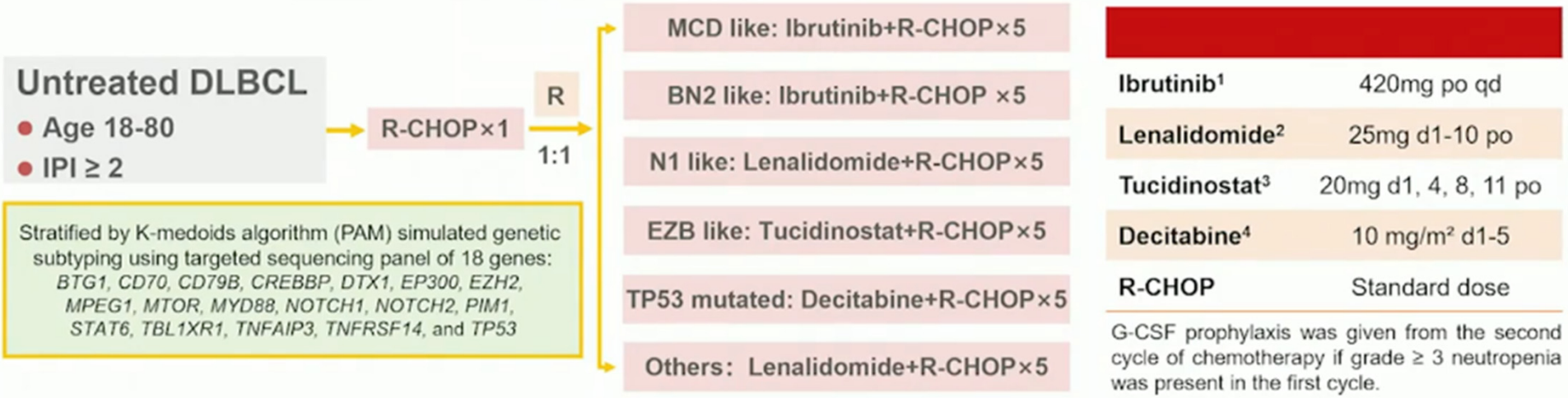
Wright et al. *Cancer Cell* 2020

➔ DLBCL is genetically heterogeneous disease with at least 5 genetic subtypes.

➔ Field of very active research and therefore this represents a moving target.

026 – Genetic Subtype Guided Rituximab-based Immunochemotherapy Improves Outcome in Newly diagnosed DLBCL: First Report of a Randomized Phase 2 Study

- The study started from **July, 2019**.
- All patients were treated with ONE cycle of standard R-CHOP immediately at diagnosis.
- Patients were randomly assigned 1:1 and stratified by genetic subtype.
- Using targeted sequencing and FISH for BCL2, MYC translocation and BCL6 fusion to classify patients into six genetic subtypes MCD like, BN2 like, N1 like, EZB like, according to **NEJM classification (2018)**, *TP53* mutation, and others.



Ibrutinib[1]	420mg po qd
Lenalidomide[2]	25mg d1-10 po
Tucidinostat[3]	20mg d1, 4, 8, 11 po
Decitabine[4]	10 mg/m² d1-5
R-CHOP	Standard dose

G-CSF prophylaxis was given from the second cycle of chemotherapy if grade ≥ 3 neutropenia was present in the first cycle.

1. *Younes et al., J Clin Oncol* 2019. 2. *Nowakowski et al., J Clin Oncol* 2021. 3. *Zhang et al., Clin Epigenet* 2020. 4. *Zhang et al.*, ICML 2019 abstract (NCT02951728)

Muchen Zhang, Shanghai, China

026 – Genetic Subtype Guided Rituximab-based Immunochemotherapy Improves Outcome in Newly diagnosed DLBCL: First Report of a Randomized Phase 2 Study

- **Primary end point:** CR rate
- **Secondary end point:** PFS, OS, ORR and safety
- **Key Eligible Criteria:** de novo DLBLC, age 18-80, IPI>=2, ECOG>=2, EF>50%
- **Patient characteristics:**

	Total (n=128)	R-CHOP-X (n=64)	R-CHOP (n=64)
Age (year): Median (range)	64 (25-74)	64 (29-74)	64.5 (25-74)
Gender-Male: n (%)	67 (52)	32 (50)	35 (55)
Stage III-IV: n (%)	99 (77)	47 (73)	52 (81)
Elevated LDH: n (%)	102 (80)	53 (83)	49 (77)
Extranodal sites ≥ 2: n (%)	66 (52)	33 (52)	33 (52)
ECOG performance status 0-1: n (%)	106 (83)	54 (84)	52 (81)
IPI 3-5: n (%)	83 (65)	42 (66)	41 (64)

- Baseline characteristics were comparable between arms
- High risk population: 65% of IPI ≥ 3, 77% of advanced stage

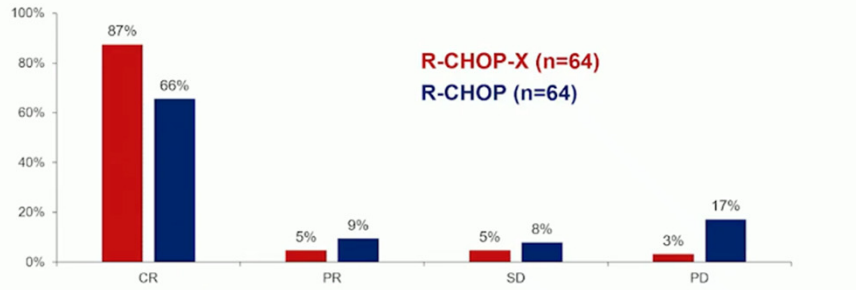
Muchen Zhang, Shanghai, China

026 – Genetic Subtype Guided Rituximab-based Immunochemotherapy Improves Outcome in Newly diagnosed DLBCL: First Report of a Randomized Phase 2 Study

Molecular Characteristics

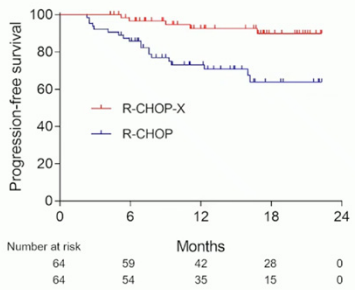
		Total (n=128)	R-CHOP-X (n=64)	R-CHOP (n=64)
Cell of origin: n (%)	GCB	48 (38)	28 (42)	21 (33)
	Non-GCB	80 (62)	37 (58)	43 (67)
MYC/BCL2 double expression: n (%)	DE	46 (36)	24 (38)	22 (34)
	Non-DE	82 (64)	42 (63)	44 (66)
Genetic subtype: n (%)	MCD like	26 (20)	13 (20)	13 (20)
	BN2 like	23 (18)	11 (17)	12 (19)
	N1 like	5 (4)	3 (5)	2 (3)
	EZB like	3 (2)	1 (2)	2 (3)
	TP53 mutation	21 (16)	11 (17)	10 (16)
	Others	50 (39)	25 (39)	25 (39)

Primary end point : CR-rate



	R-CHOP-X	R-CHOP	P value
CRR, % (95%CI)	87 (79-96)	66 (54-78)	0.003

Secondary end point : PFS-rate



Median follow-up 16.1 months

	R-CHOP-X	R-CHOP
1-year PFS (95%CI)	93% (81%-97%)	73% (60%-83%)

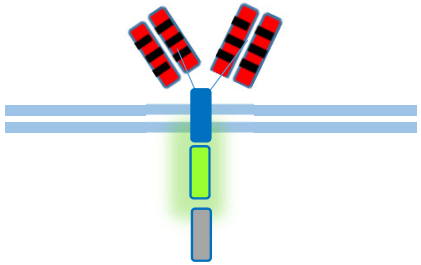
- Molecular-informed, randomized phase II trial that met the primary end point
- Increased CR, mainly due to MCD, BN2 and A53
- *Caveat:* Small study, selection bias (fit young pat that benefited from ibrutinib)

Muchen Zhang, Shanghai, China

Kapitel 2

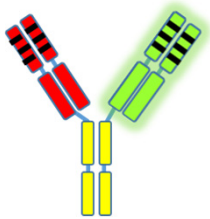
Refraktäre und Rezidivierte DLBCL

What is new?



CARTs

Le Gouill S, Nantes (084)



bispecific antibodies

Carlo-Stella C, Milan (015)

Hutchings M, Copenhagen (016)

084 - First results of DLBCL patients treated with CAR-T cells and enrolled in DESCAR-T registry, a French real-life database for CAR-T cells in hematologic malignancies.

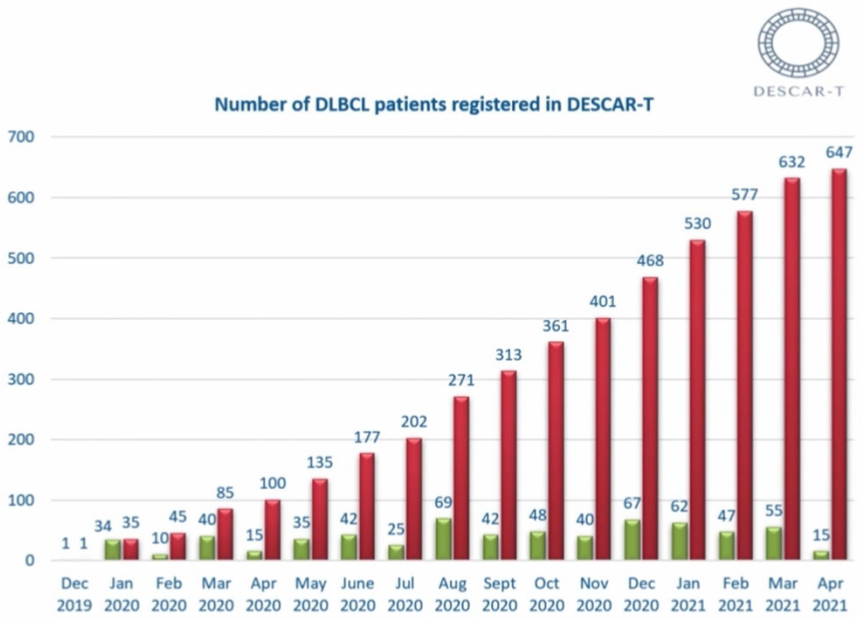
RESULTS: INCLUSIONS

Date: 12/04/2021

23 sites are qualified for CAR-T cells therapy and DESCAR-T

19 enrolling sites

Number of enrolled patients :
N = 647 DLBCL



- Large registry, real world data
- Collect for at least 15 years
- Preliminary analysis,
  - ➔ CAR T-cells are feasible
  - ➔ No new toxicity and/or safety signal,
  - ➔ but….

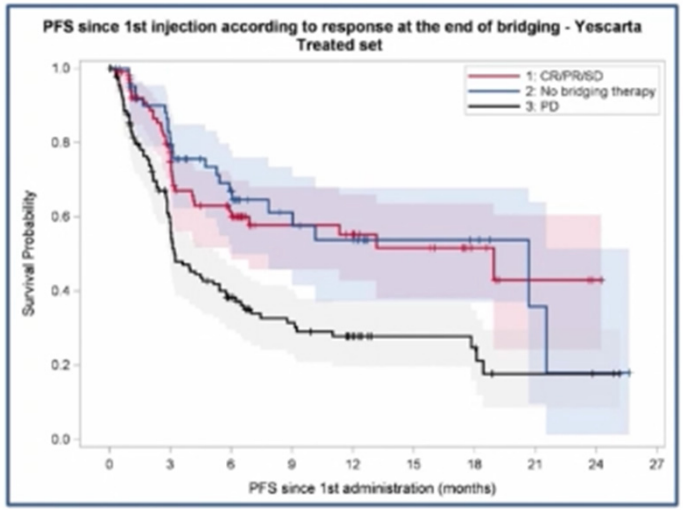
Steven Le Gouill et al., ICML 2021

084 - First results of DLBCL patients treated with CAR-T cells and enrolled in DESCAR-T registry, a French real-life database for CAR-T cells in hematologic malignancies.

Axi-cel

PFS at 6 months#:

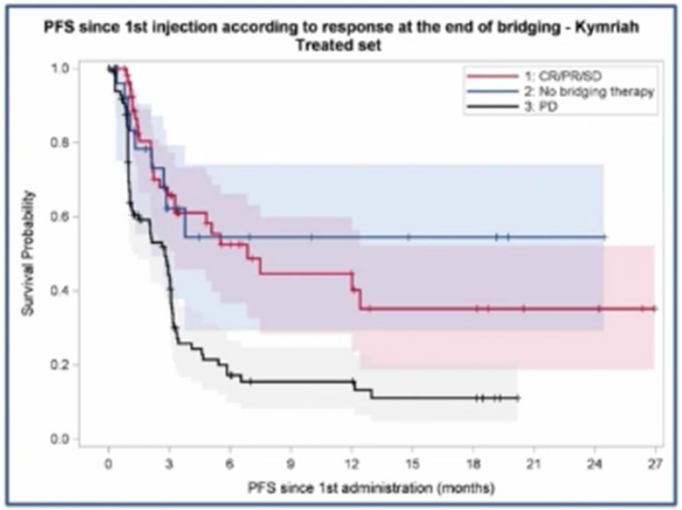
- CR/PR/SD = 61.4% [50– 71] (n=116)
- No bridging = 66.9% [52.5 – 77.9] (n=75)
- PD = 38.2% [29.5 – 46.9] (n=139)



Tisa-cel

PFS at 6 months * :

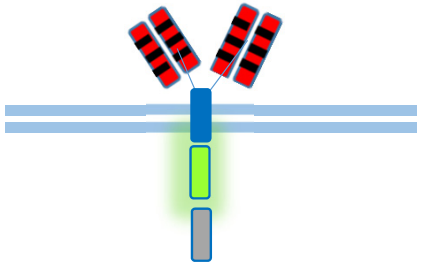
- CR/PR/SD = 52.5% [36.7 – 66] (n=57)
- No Bridging = 54.4% [29.2 – 74.1] (n=34)
- PD = 17.1% [9.7 – 26.4] (n=100)



➔ Remission before CAR T-cell reinfusion matters

Steven Le Gouill et al., ICML 2021

What is new?



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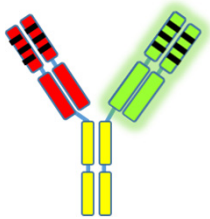


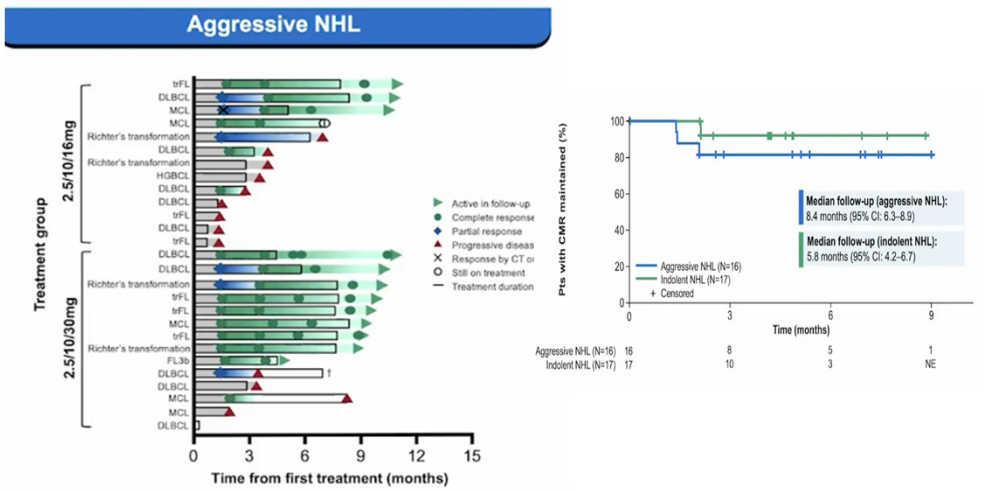
bispecific antibodies

Carlo-Stella C, Milan (015)

Hutchings M, Copenhagen (016)

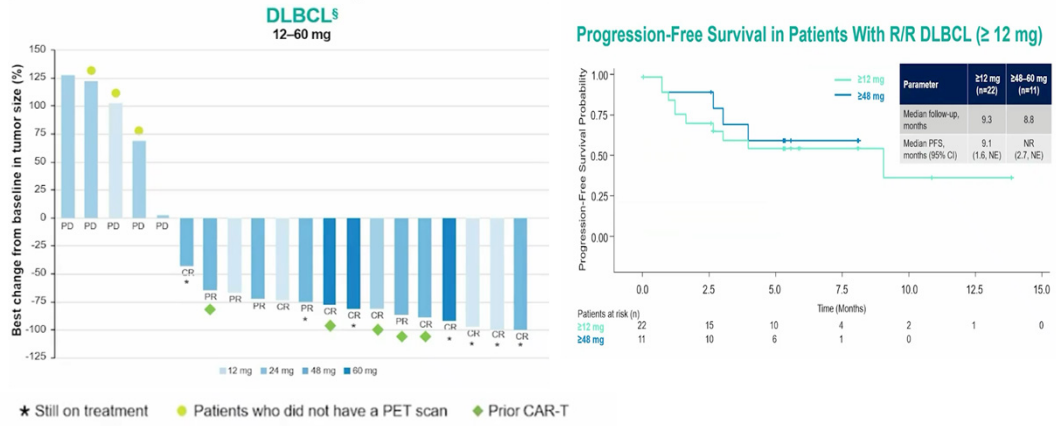
CD20 x CD3 Bispecfic Antibodies

Glofitamab



Carlo-Stella C, Milan (015)

Epcoritamab



Hutchings M, Copenhagen (016)

- ➔ Updates of previously reported very promising early safety and efficacy signals
- ➔ Optimized dosing (SUD) and application (after naked CD20, s.c.) make them BiMabs feasible
- ➔ Active post-CAR T-cells at different CD20 expression levels
- ➔ *Caveat:* at this point small studies with selection bias; longer follow-up needed

Zusammenfassung

Erstlinie DLBCL

- Identifikation von Hochrisiko-Patient:innen, z.B. neue radiomics Strategie (Fettgewebssignaturen)
- Biologisch-stratifizierten Therapieansätzen sind durchführbar

➔ **R-CHOP (like) bleibt Standard**

Refraktäre und rezidivierte DLBCL

- CAR-T Zell Ansätze sind durchführbar, sicher und in der Breite angekommen
- Remissionsstatus vor Re-infusion scheint wichtig und unterstreicht die Rolle von Brückentherapien
- Bispezifiche Antikörper zeigen ein vielversprechendes Sicherheits- und Effektivitätssignal

Haben Sie Fragen zu diesem Thema?

Schreiben Sie uns!

icml2021@lymphome.de

Die Kurzpräsentationen sind online unter

www.lymphome.de/icml2021

Für den Inhalt verantwortlich:

Prof. Dr. med. Björn Chapuy

Klinik für Hämatologie und Medizinische Onkologie | Universitätsmedizin Göttingen

Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

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