First-Line Therapy for the Treatment of Diffuse Large B-Cell Lymphoma

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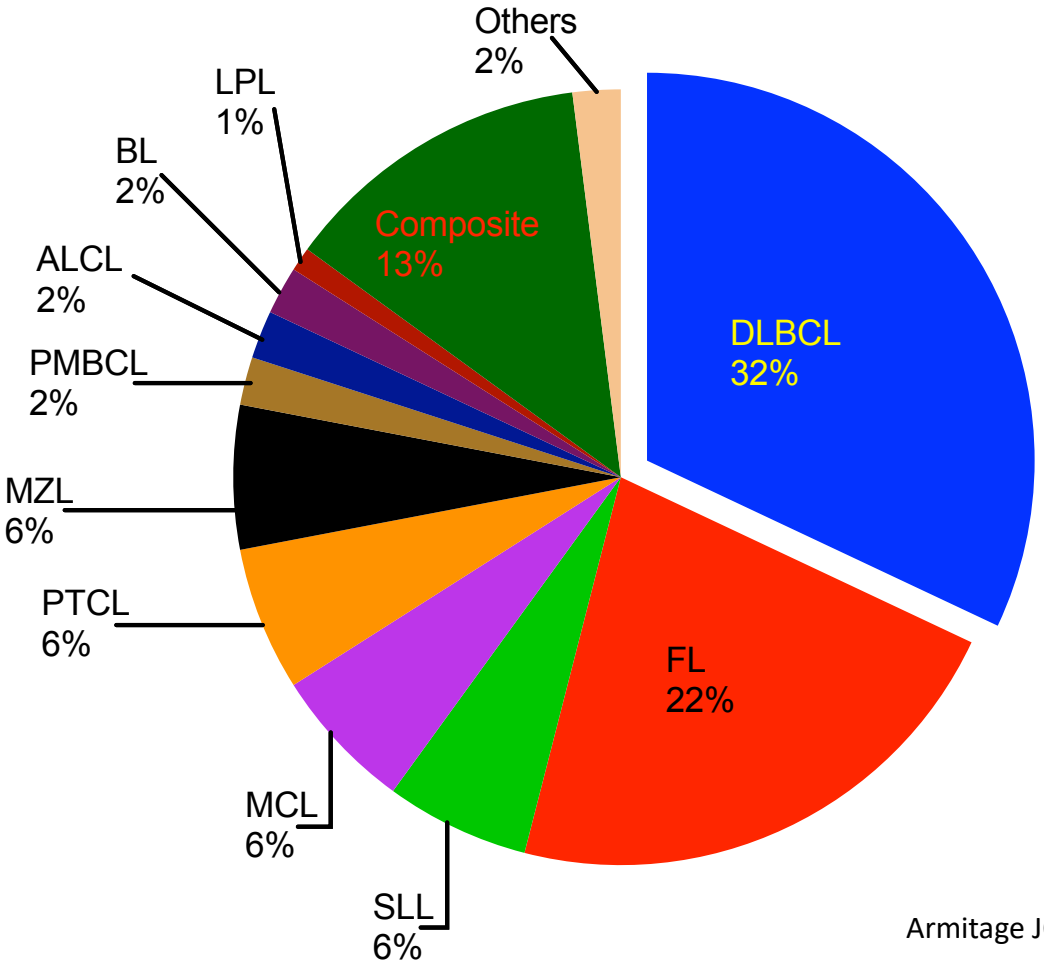
Disclosures

- Advisory Board
  - Genenta Science, ADC Therapeutics, Novartis, Servier, Roche
- Consultancy
  - Boehringer Ingelheim, Sanofi
- Honoraria
  - Amgen, Janssen Oncology, AstraZeneca, BMS, MSD, Takeda
- Research Support
  - Rhizen Pharmaceuticals

Relative Incidence of NHL Subtypes



Armitage JO et al, JCO 16: 2780-2795, 1998

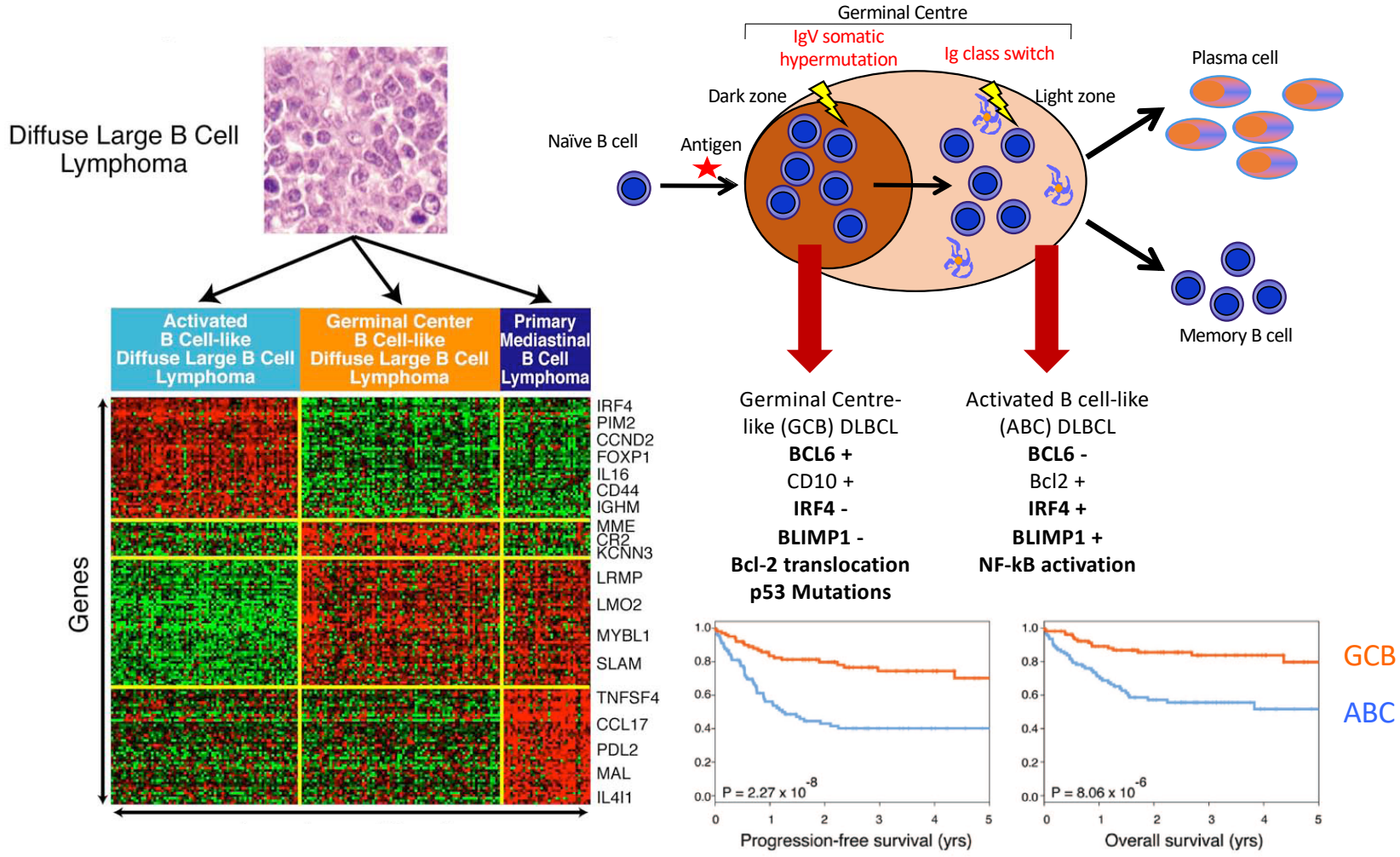
Diffuse Large B-cell Lymphoma

- *Heterogeneity* is the hallmark of DLBCL
- Morphologic, molecular, clinical

DLBCL Heterogeneity – WHO 2016

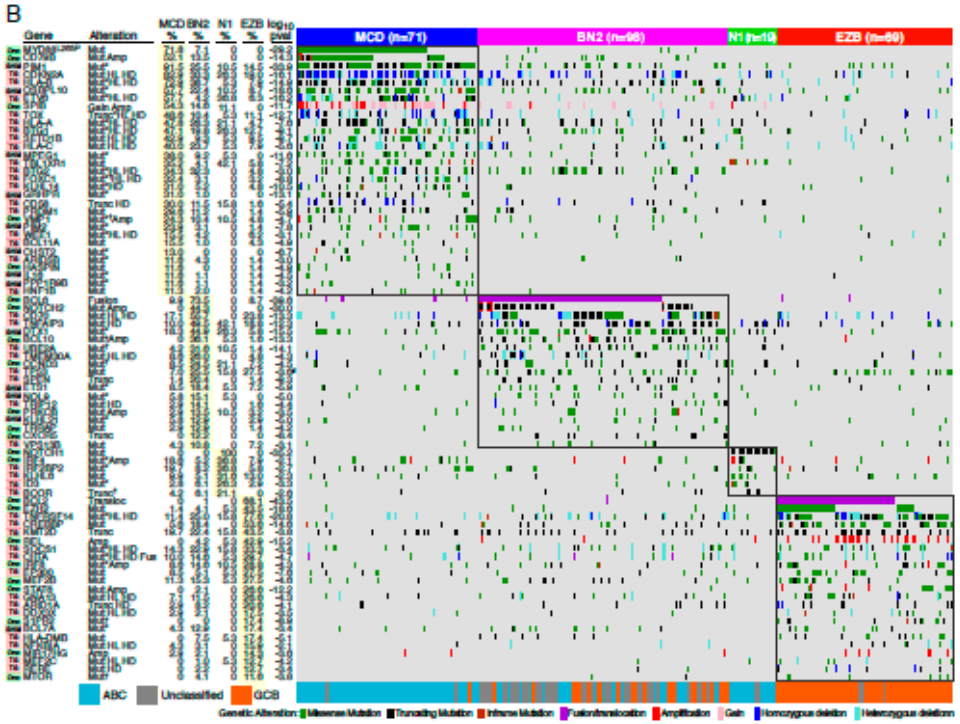
Entity/Category	Change
Diffuse large B-cell lymphoma (DLBCL), NOS • Germinal center B-cell type* • Activated B-cell type*	• Distinction of GCB vs ABC/non-GC type required with use of IHC algorithm acceptable, may affect therapy • Coexpression of MYC and BCL2 considered new prognostic marker (DEL)
T-cell/histiocyte-rich large B-cell lymphoma	-
Primary DLBCL of the CNS	-
Primary cutaneous DLBCL, leg type	-
EBV+ DLBCL, NOS*	Replaces EBV+ DLBCL of the elderly because it may occur in younger patients
DLBCL associated with chronic inflammation	-
Primary Mediastinal Large B-Cell Lymphoma	-
Plasmablastic Lymphoma	-
Primary effusion lymphoma	-
Intravascular Large B-Cell Lymphoma	-
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 translocations*	• New category for all DHL and THL
High-grade B-cell lymphoma, NOS*	• Cases lacking MYC and BCL2 or BCL6 translocations
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and cHL	-

DLBCL Tumor Heterogeneity - 2000

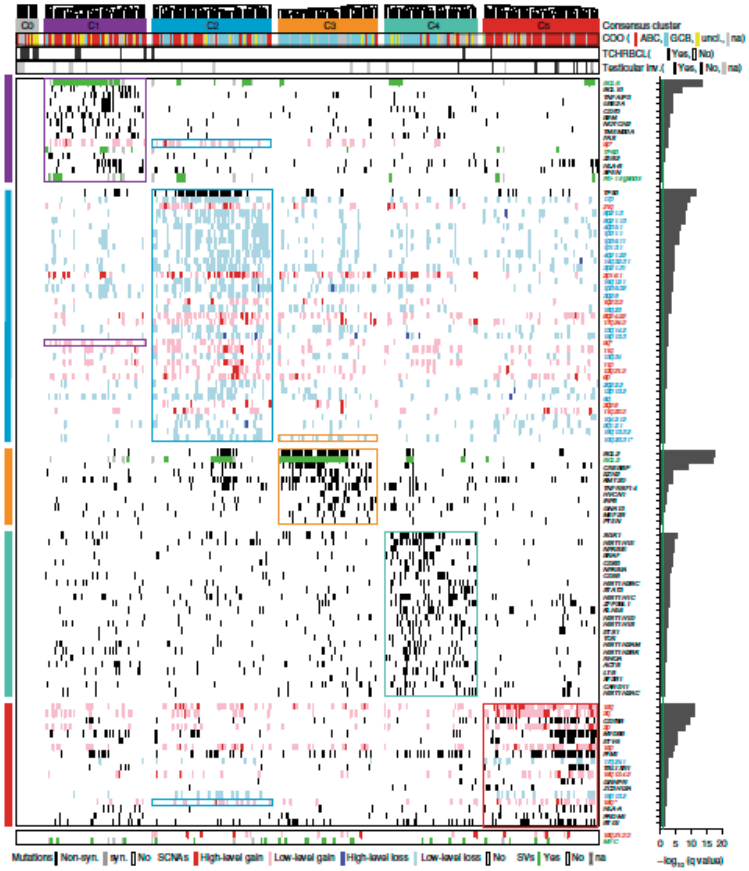


Alizadeh A et al, Nature 2000; Staudt LM, N Engl J Med 2003

DLBCL Tumor Heterogeneity - 2020

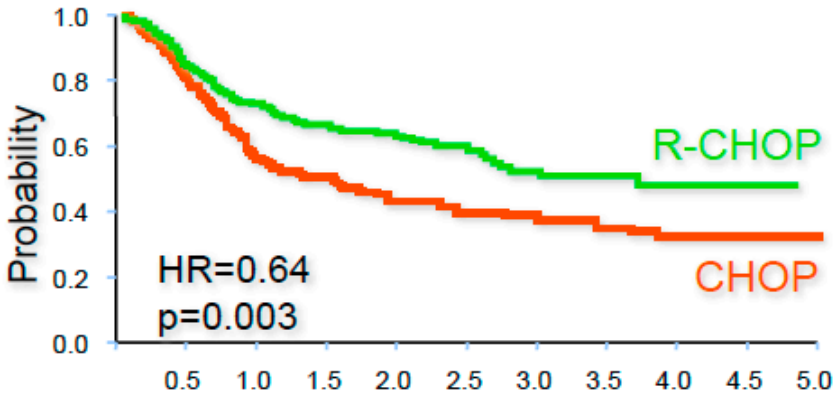


Schmitz R, et al. *N EnglJ Med.*2018;378:1396-407

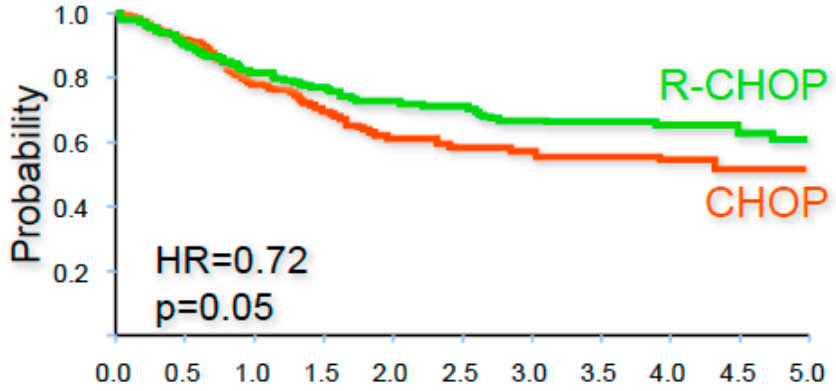


Chapuy, et al. *Nature Med.*2018;24:679-90

R-CHOP



Failure-Free Survival



Overall Survival

Coiffier et al N Engl J Med. 2002; Habermann et al J Clin Oncol 2006

First-Line Therapy for DLBCL

- R-CHOP-21 x 6 cycles for advanced-stage disease
- R-CHOP-21 x 3 - 4 cycles for early-stage disease

- Radiotherapy for bulky disease

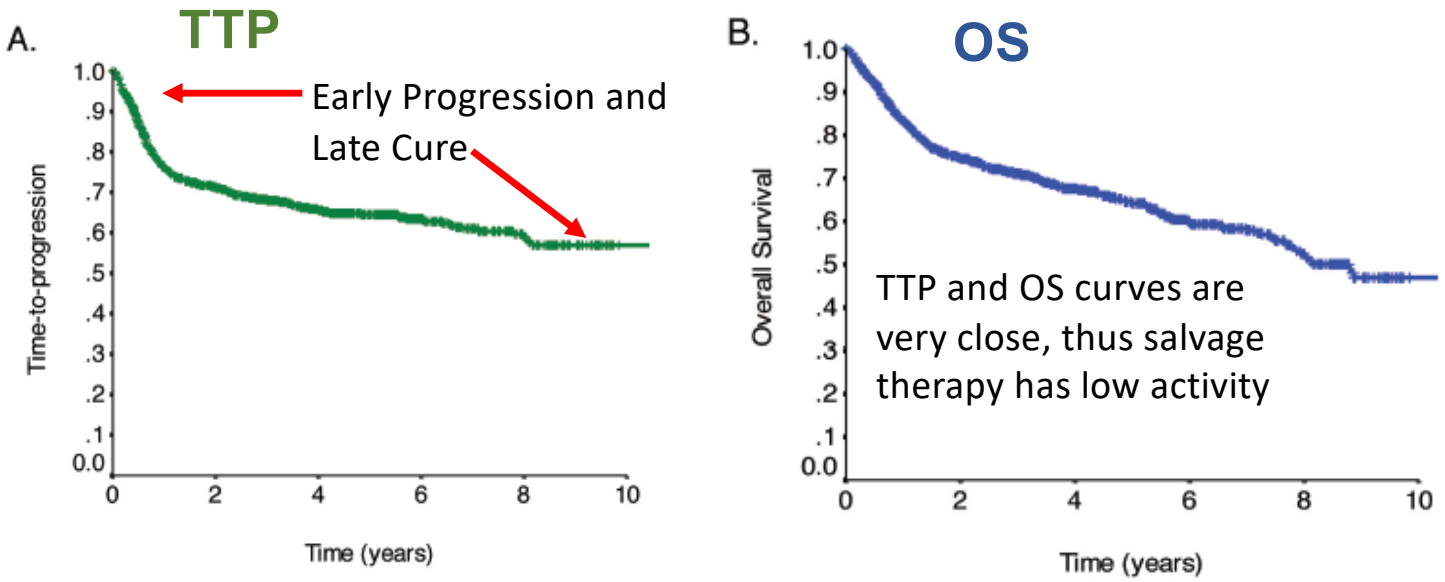
- Elderly patients (>70 yrs) require therapy and dose adjustment based on fitness status

First-Line Therapy for DLBCL

- 5-yr survival rates in the first-line setting range from 60% to 70%
- Up to 50% primary refractory / refractory / early relapse / late relapse

R-CHOP: International Standard of Care

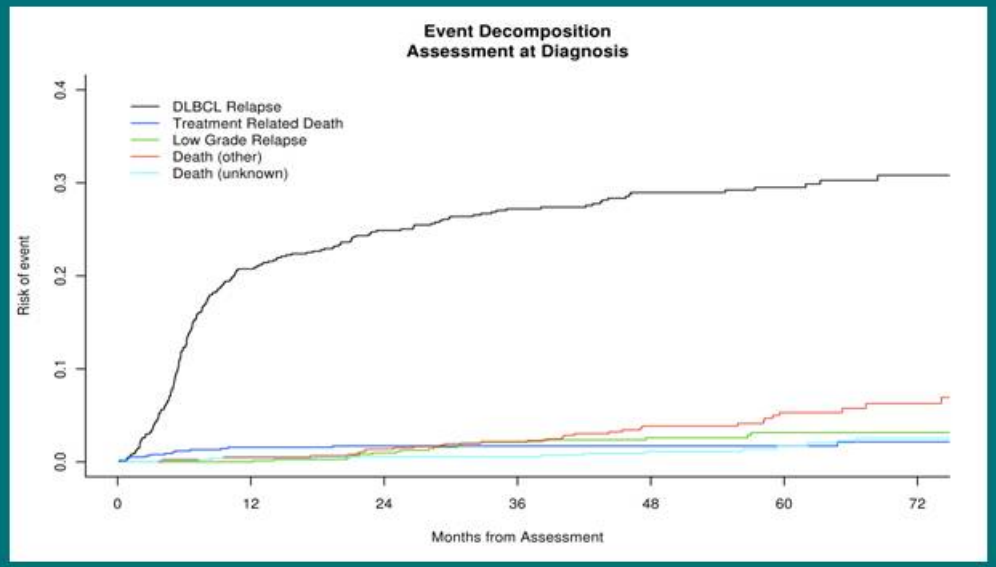
Patients with DLBCL treated with R-CHOP-21 at BCCA (n=1476)



BC Cancer Agency Database, Sehn, Hematology 2012

R-CHOP: International Standard of Care

Risk and Cause of Death in DLBCL Patients Mayo Clinic/U of Iowa Cohort (N=680)



Majority opf patients relapsing after R-CHOP will die from the disease

Most deaths in the first 2 years

Maurer, M, ASH 2012 Abstract 1540

How can we improve the treatment of DLBCL? New Drugs - New Biology

- New MoAbs (± CHOP)
- More chemotherapy
- COO-oriented therapy
  - New agents
  - New biology

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Comparison of FDA-approved anti-CD20 MoAb

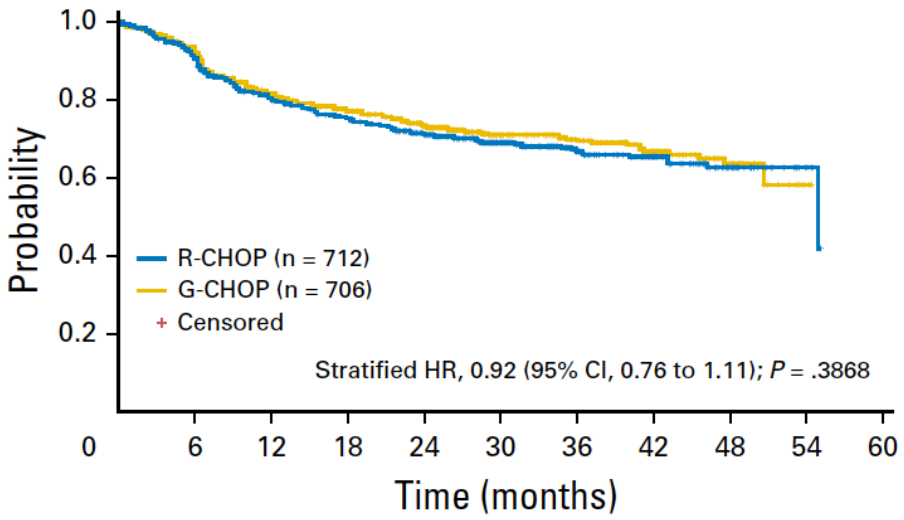
	Rituximab	Ofatumumab	Obinutuzumab
Type	I	I	II
Apoptosis	+	-/+	++
ADCC	++	+/-	+++
Complement Fixation	++	+++	+/-

Obinutuzumab or Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Previously Untreated Diffuse Large B-Cell Lymphoma

Umberto Vitolo, Marek Trněný, David Belada, John M. Burke, Angelo Michele Carella, Neil Chua, Pau Abrisqueta, Judit Demeter, Ian Flinn, Xiaonan Hong, Won Seog Kim, Antonio Pinto, Yuan-Kai Shi, Yoichi Tatsumi, Mikkel Z. Oestergaard, Michael Wenger, Günter Fingerle-Rowson, Olivier Catalani, Tina Nielsen, Maurizio Martelli, and Laurie H. Sehn

Vitolo, JCO, 2017

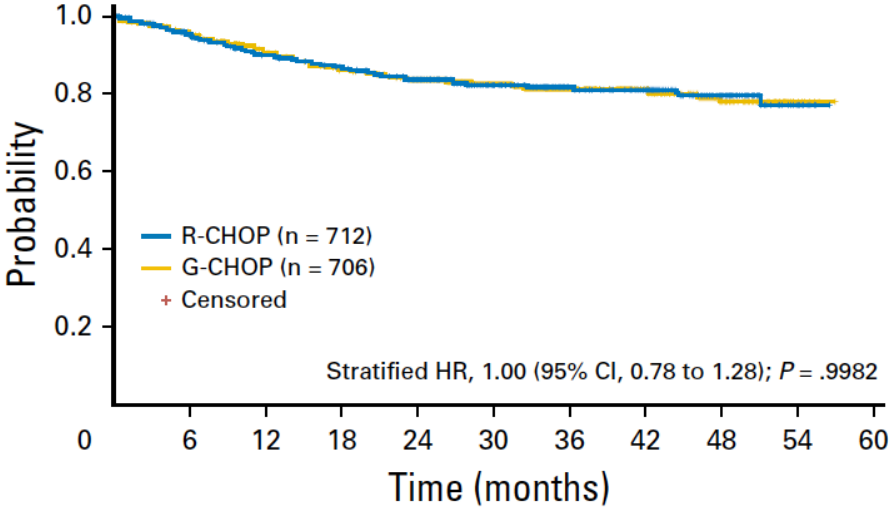
PFS



No. 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

OS



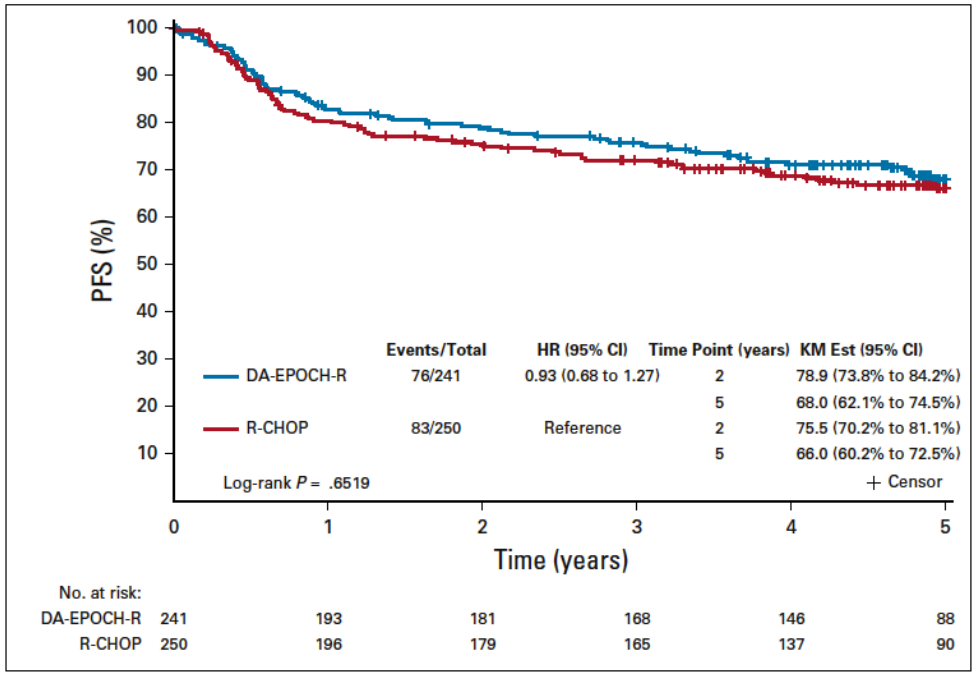
No. at risk:

R-CHOP	712	663	617	586	540	319	190	138	71	9
G-CHOP	706	659	616	582	552	316	201	138	67	8

How can we improve the treatment of DLBCL? New Drugs - New Biology

- New MoAbs (± CHOP)
- More chemotherapy
- COO-oriented therapy
  - New agents
  - New biology

Phase III Trial Alliance/CALGB 50303
R-CHOP *vs* DA-EPOCH-R



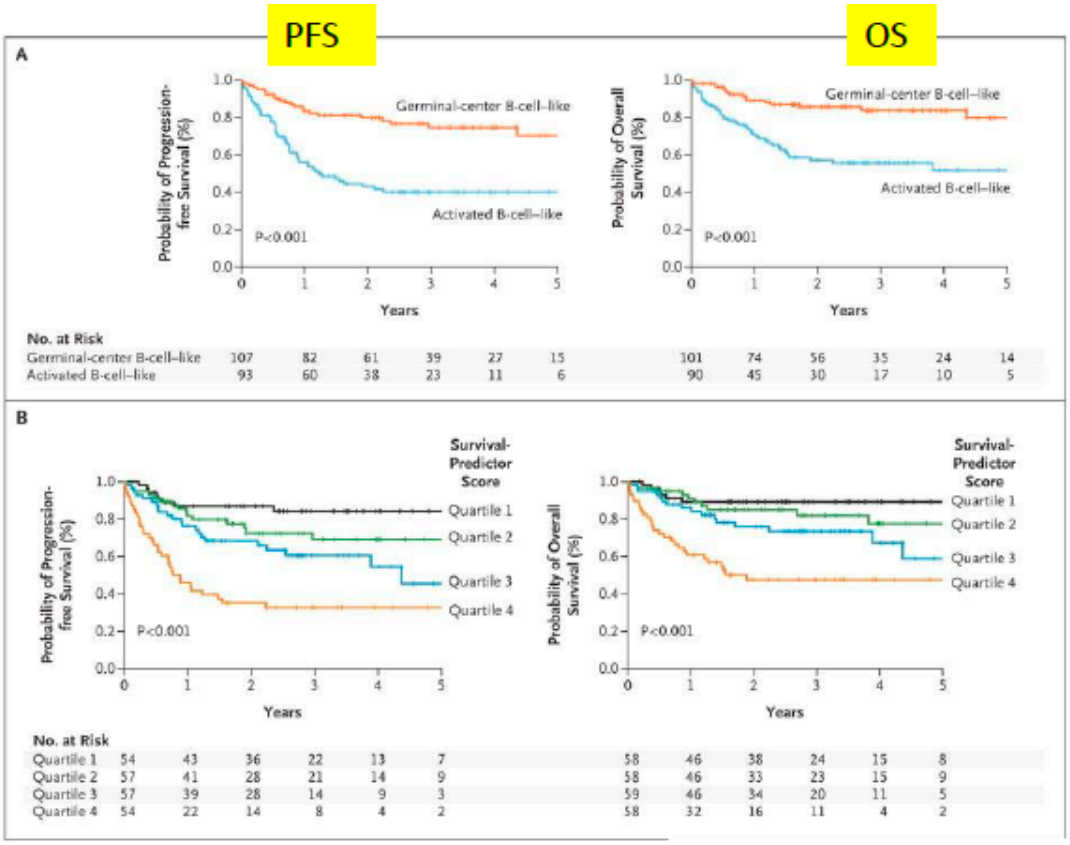
patient selection bias
IPI 0 to 1 (26%)
IPI 2 (37%)
IPI 3 (25%)
IPI 4 to 5 (12%)

Bartlett N.L. et al, J Clin Oncol 37:1790-1799.

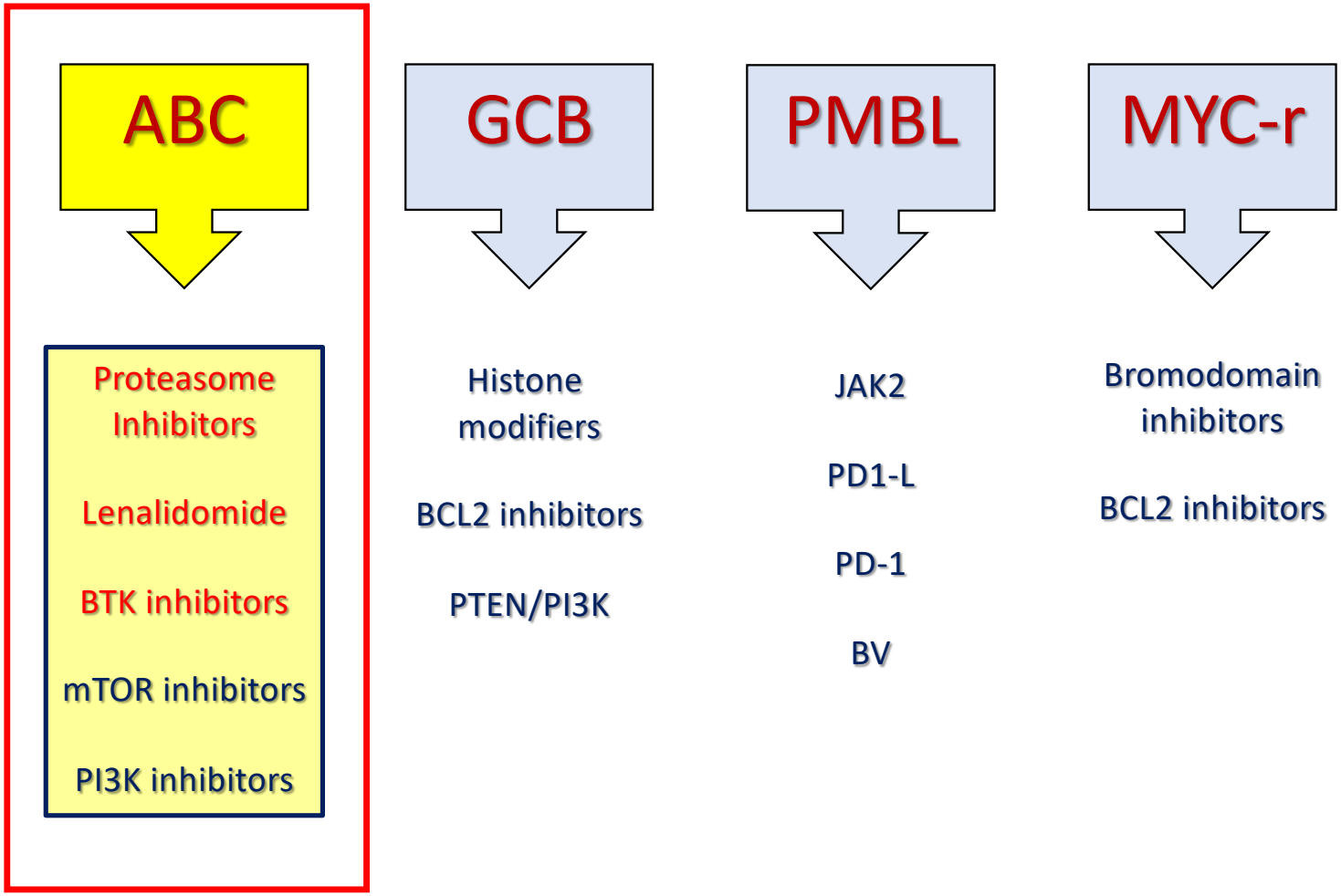
How can we improve the treatment of DLBCL? New Drugs - New Biology

- New MoAbs (± CHOP)
- More chemotherapy
- COO-oriented therapy
  - New agents
  - New biology

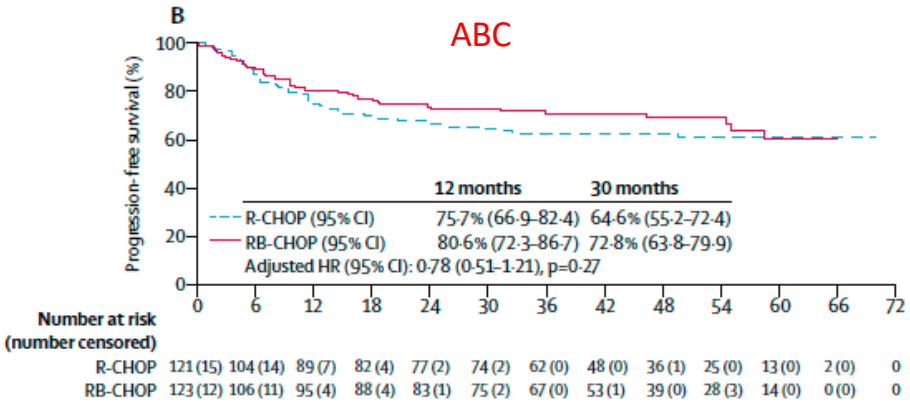
Gene-Expression Predictors in R-CHOP-Treated DLBCL



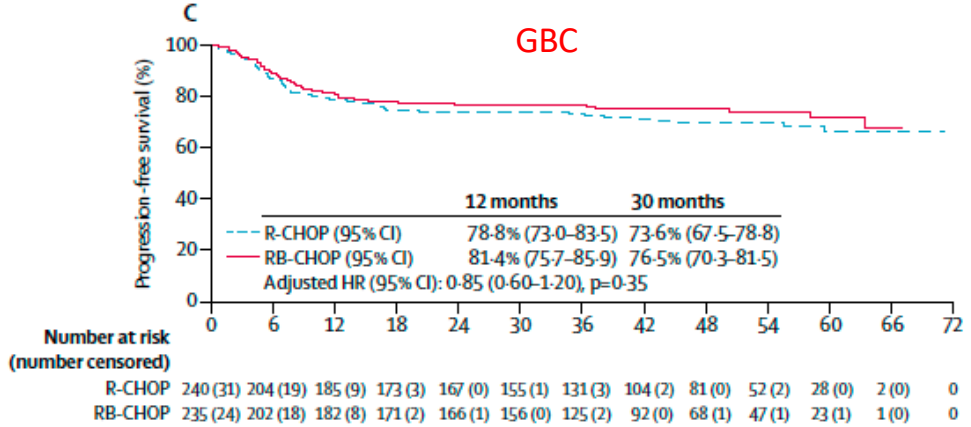
Lenz G et al. N Engl J Med 2008;359:2313-2323.


ABC
GCB
PMBL
MYC-r
Proteasome Inhibitors
Lenalidomide
BTK inhibitors
mTOR inhibitors
PI3K inhibitors
Histone modifiers
BCL2 inhibitors
PTEN/PI3K
JAK2
PD1-L
PD-1
BV
Bromodomain inhibitors
BCL2 inhibitors

ABC



GBC

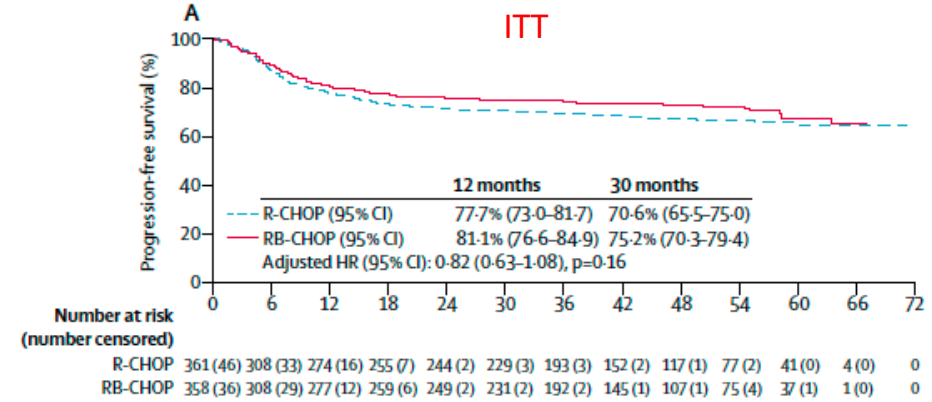


Gene-expression profiling of bortezomib added to standard chemoimmunotherapy for diffuse large B-cell lymphoma (REMoDL-B): an open-label, randomised, phase 3 trial

Andrew Davies, Thomas E Cummin, Sharon Barrans, Tom Maishman, Christoph Mamot, Urban Novak, Josh Caddy, Louise Stanton, Shamim Kazmi-Stokes, Andrew McMillan, Paul Fields, Christopher Pocock, Graham P Collins, Richard Stephens, Francesco Cucco, Alexandra Clipson, Chulin Sha, Reuben Tooze, Matthew A Care, Gareth Griffiths, Ming-Qing Du, David R Westhead, Catherine Burton, Peter W M Johnson

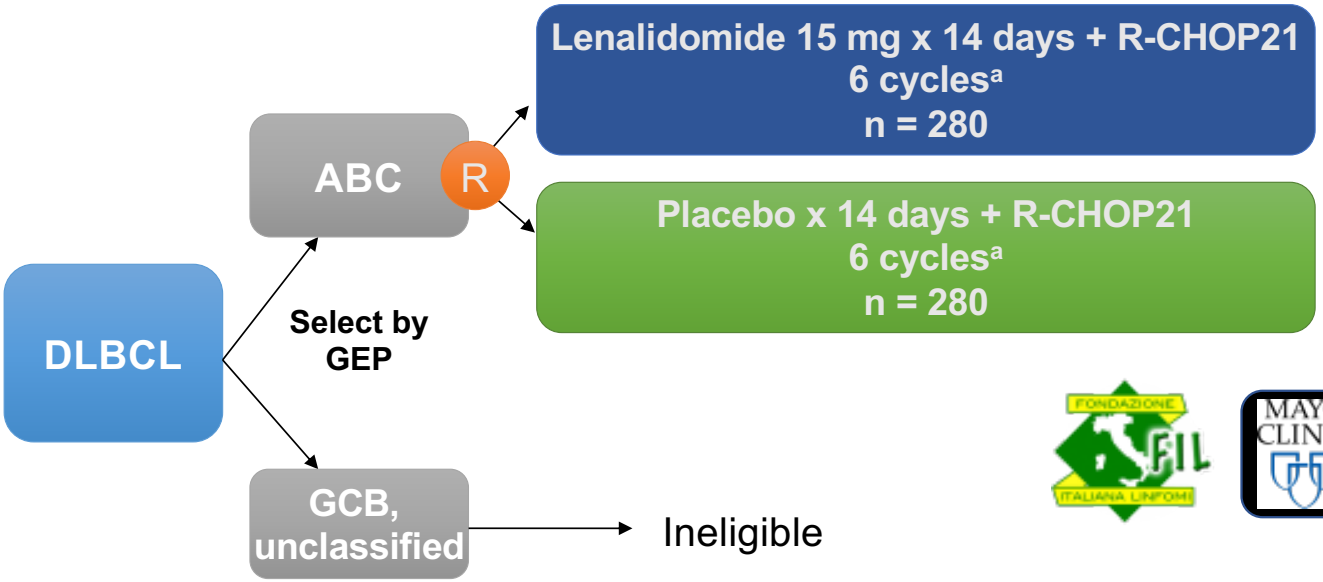
Lancet Oncol, 20_649, 2019

ITT



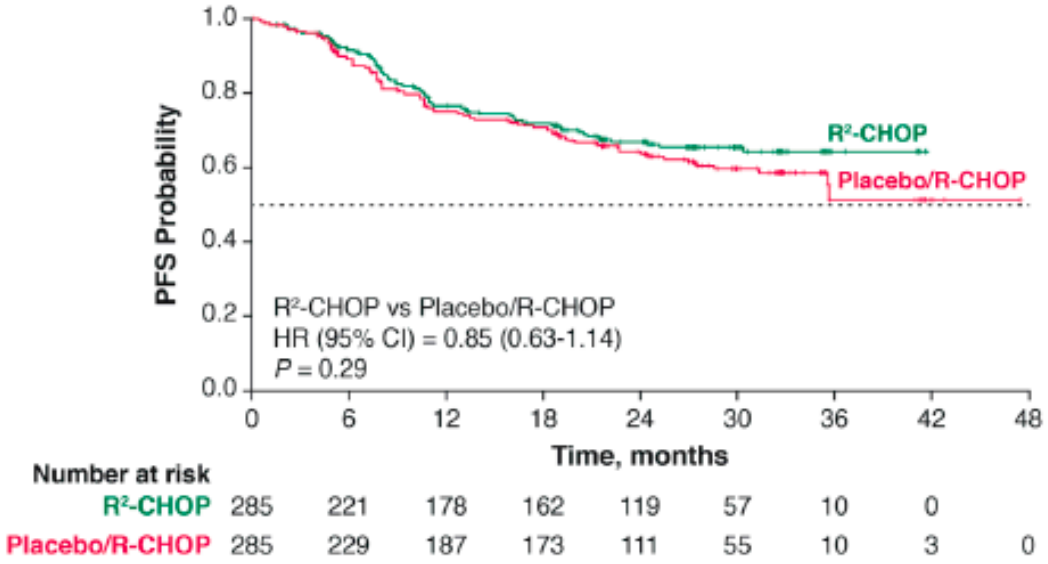
ROBUST study design: COO categorization made on Nanostring

Team leader: FIL and Mayo Clinic.
PIs: U. Vitolo, T. Witzig.
Writing committee: U. Vitolo, A. Chiappella, M. Spina, T. Witzig, G. Nowakowski.

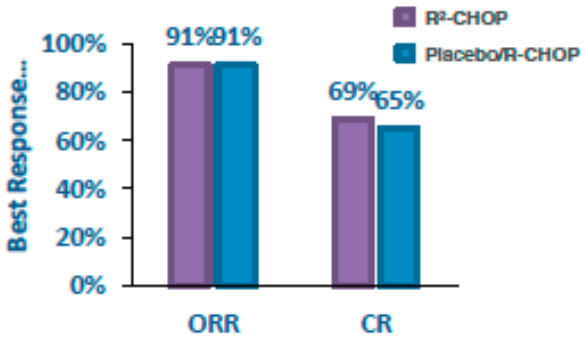


- Newly diagnosed ABC DLBCL; IPI ≥ 2; ECOG PS ≤ 2; age 18–80 years
- Primary endpoint = PFS; N = 560
- 90% power to detect 60% difference in PFS (control median PFS estimate = 24 months)

ROBUST Trial: PFS



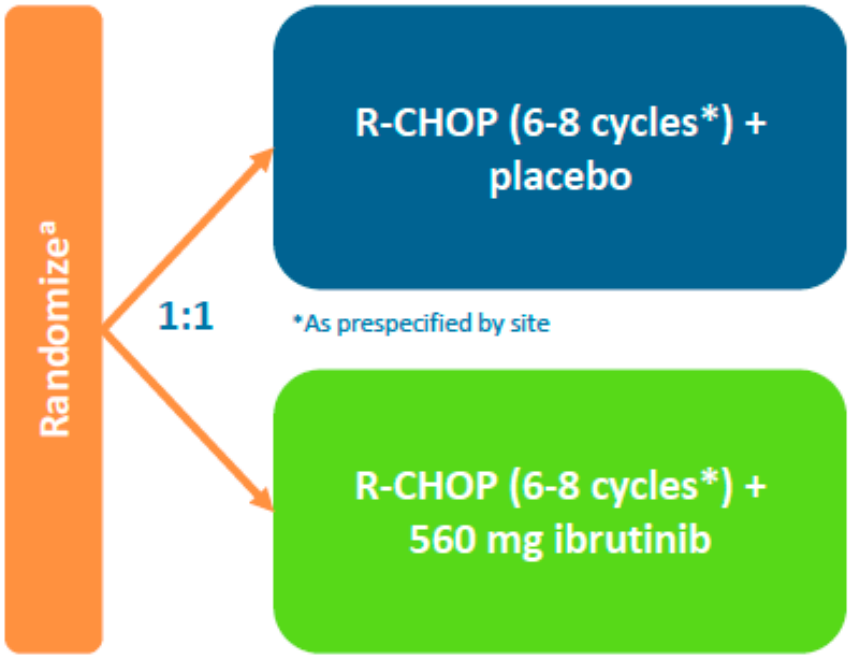
PFS Rates	R²-CHOP (n = 285)	Placebo/R-CHOP (n = 285)
1-y	77%	75%
2-y	67%	64%



- At a median follow-up of 27.1 mo (range, 0-47), the primary endpoint of PFS was not met (medians not reached)
- ORR and CR rates were high in both arms
- **Median time from diagnosis to treatment was 31 days for each arm**

Data cut-off 15Mar2019.
Complete response (CR) was assessed by 2014 IWG criteria with CT-PET (Cheson et al. *J Clin Oncol.* 2014;32:3059-3068).

PHOENIX Phase III Randomized Trial



*Stratified by R-IPI, region, and number of prespecified treatment cycles (6 vs 8 cycles).
- Prophylactic antibiotics and G-CSF were not mandated but were permitted at the investigator's discretion per local or other standard guidelines

Key eligibility criteria

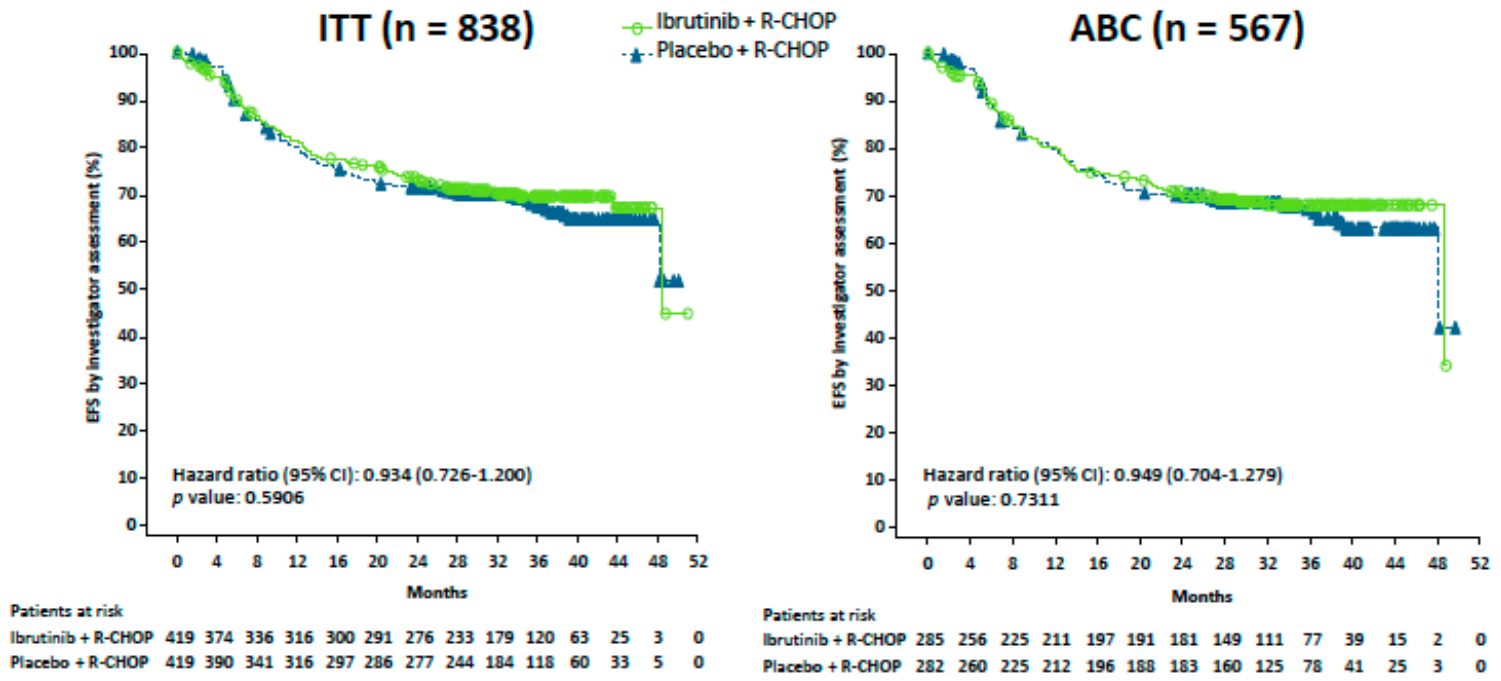
- Untreated non-GCB DLBCL
  - Determined by Hans-based IHC at a central laboratory
  - Retrospectively analyzed for ABC subtype using GEP
- Stage II to IV measureable disease
- R-IPI ≥ 1
- ECOG performance status ≤ 2

End points

- Primary end point: EFS† in ITT (non-GCB) and ABC subgroup
- Secondary end points: PFS, CR rate, OS, safety
  - Response assessed per Revised Response Criteria for Malignant Lymphoma[1]

†EFS: time from randomization to PD, relapse from CR, initiation of subsequent disease-specific therapy for PET-positive or biopsy-proven residual disease after ≥ 6 cycles of R-CHOP, or any-cause death.

PHOENIX Trial – EFS (Primary End Point)



- Overall response (89.3% vs 93.1%) and CR rates (67.3% vs 68.0%) were similar in the ibrutinib + R-CHOP and placebo + R-CHOP arms in the ITT population
- CNS progression was observed: 10 (2.4%) vs 16 (3.8%) patients in the ibrutinib + R-CHOP and placebo + R-CHOP arms

17Younes A et al JCO 2019

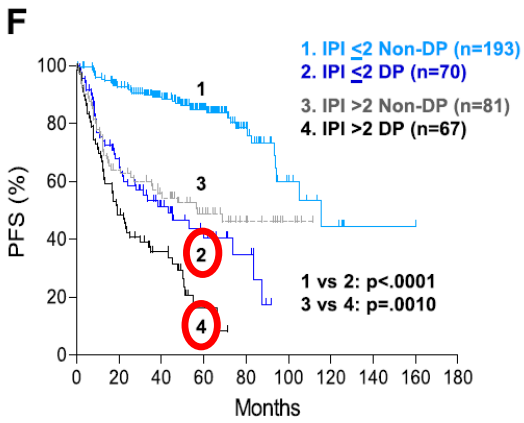
New Biology - Biomarkers for High-Risk DLBCL

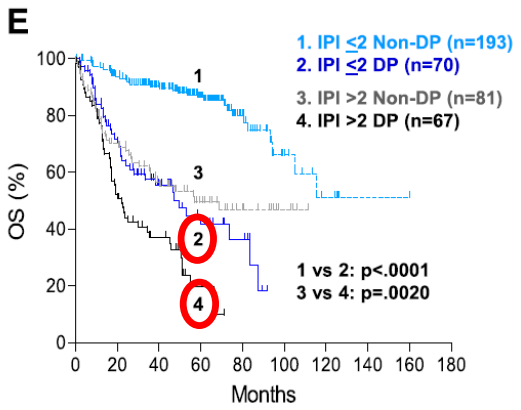
Biomarkers	High-low Risk Group	Therapeutic Target Identification
MYC (40%), BCL2 (50%), BCL6 (50%) expression by IHC	YES	YES
FISH for MYC/BCL2/BCL6 translocations del17p, p53mut	YES	NO
COO (ABC vs GCB) by Nanostring	YES	YES
MRD analysis by DNA-seq of blood/marrow V(D)J	YES	NO
Targeted resequencing of oncogenic driver genes	YES	YES

Double Expressor Lymphoma or p53mut R-CHOP

Myc+BCL2+

Hu S., Blood 2013



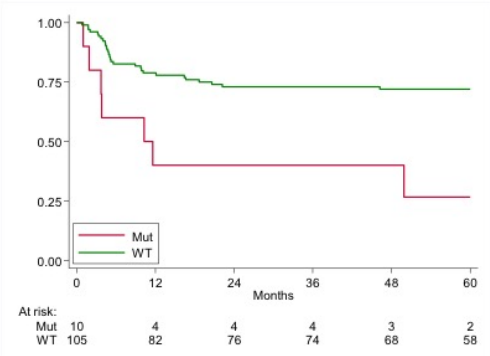


Mutated p53

5-yr FFS 27% mut

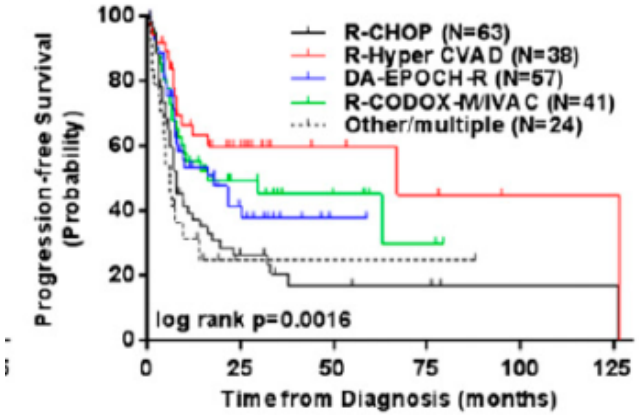
5-yr FFS 72% unmut

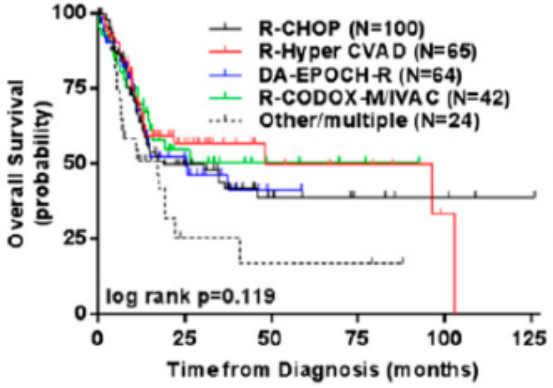
Chiappella A., EHA 2018



Double Hit - Chemo

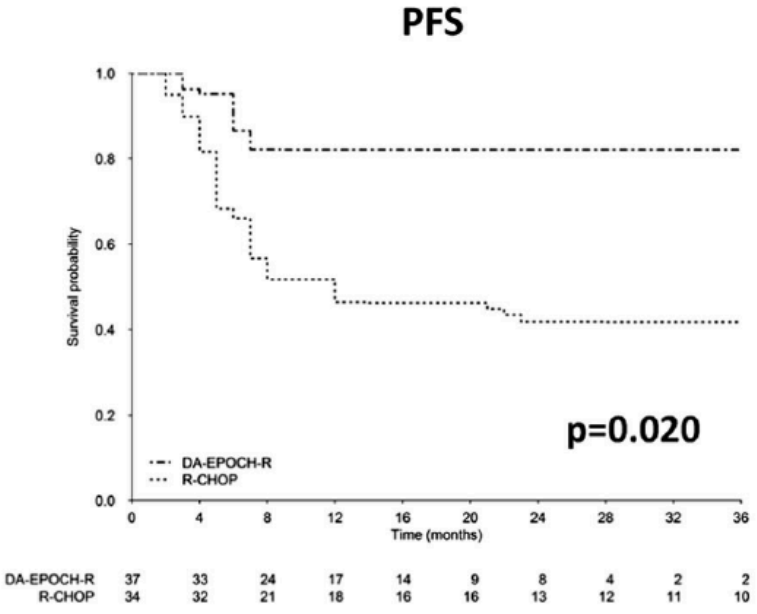
N=311 DH/TH (FISH)
Retrospective

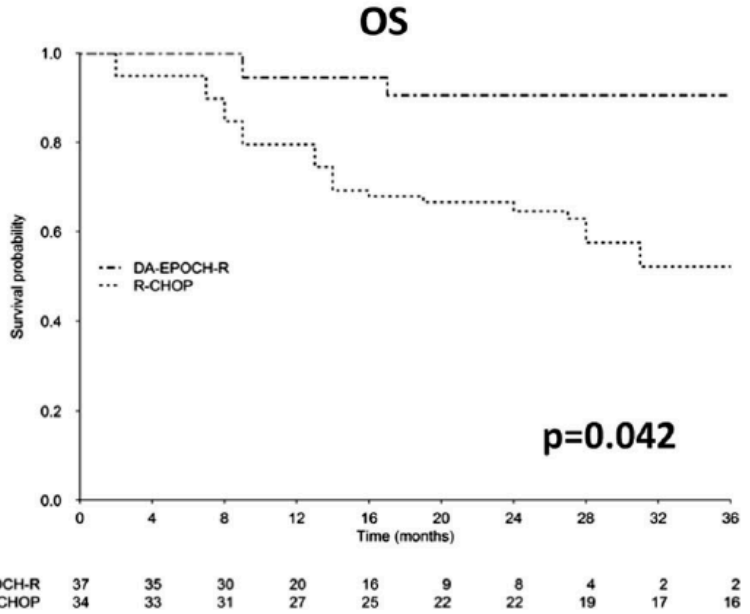




Petrich AM Blood 2014

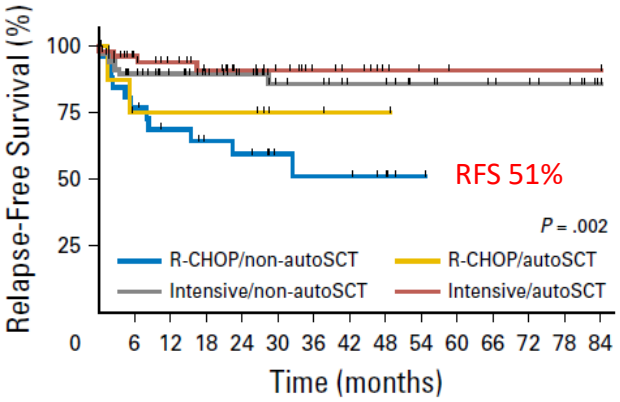
DA-EPOCH-R in DH/DE <65 yrs

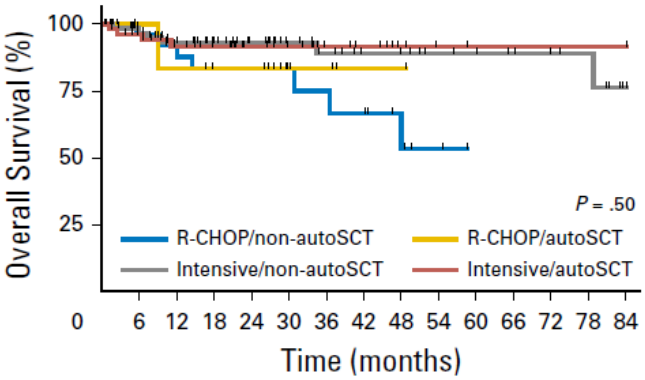




Dodero et al., Leukemia, 2019

Double Hit - ASCT



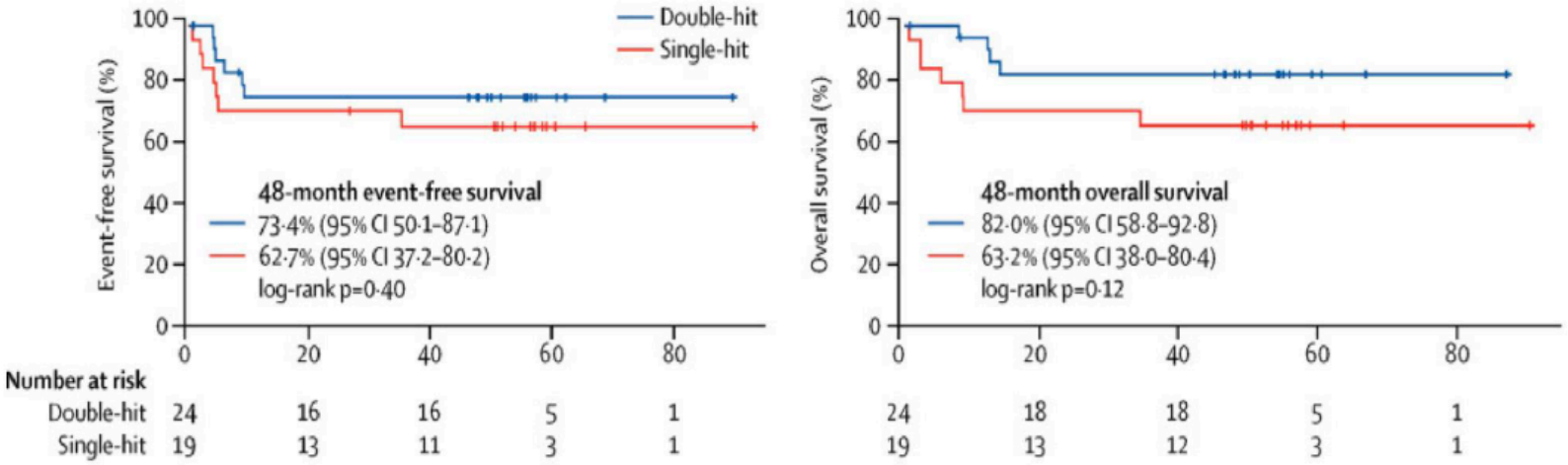


R-CHOP: non-autoSCT << autoSCT

Intensified chemo: non-autoSCT = autoSCT

Landsburg DJ JCO 2017

Myc Translocation – Prospective Study



Dunleavy et al, Lancet Hematology, 2018

Risk Factors for CNS Relapse

CNS-IPI

1 point for:

Age, y > 60

LDH > normal

ECOG Performance status >1

Ann Arbor stage III -IV

Extranodal disease >1

Kidney and/or adrenal gland involvement

Three distinct risk groups: low (L, 0-1 pt), intermediate (I, 2-3 pts), high (H, 4-5-6 pts).

Schmitz N et al, JCO 2016

Histologic subtype	Histologic subtype-specific risk factors	Approximate CNS relapse risk
DLBCL	CNS-IPI ≥ 4[6]	10% at 2 y
	or involvement of breast,[17] testis,[18] uterus,[19] epidural,[20,21] kidney/ adrenals[6,16]	Varies by site
	MYC/BCL2 DE DLBCL, particularly if ABC subtype[22]	10% at 2 y (15% if ABC COO)
	CD5$^+$ DLBCL[23]	12.7% at 2 y
	Intravascular large B-cell lymphoma[24]	25% at 3 y
	IgM-secreting DLBCL[25]	41% cumulative incidence (7 of 17)
HGBL with *MYC* and *BCL2* and/or *BCL6* rearrangements[26]		13% at 3 y
MCL	Blastoid histology or Ki-67 ≥ 30%[27]	25.4% at 2 y
PTCL (PTCL-NOS, AITL, ALCL)	>1 extranodal site, skin or gastrointestinal involvement[28]	~10% at 2 y
ALK$^+$ ALCL	>1 extranodal site[29]	1-y 15%

Chin CK and Cheah CY, Blood 2017

Prophylaxys of CNS Relapse

- IT vs IV

- MTX 3 g/sqm, IV, 2 – 3 cycles

Conclusions

- R-CHOP remains the standard of care for DLBCL
- New treatments for specific subsets (DHL, DEL, ABC-DE, PD-L1-expressing lymphoma, …)
- New agents will emerge from a better understanding of DLBCL biology
  - Cell surface ag, immune modulators, signaling pathway, IMIDs, epigenetic modifiers
- More predictive endpoints than PET (MRD, CAPP-SEQ)
- Well-designed clinical trials (single agents and combinations)