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INVESTIGATING MOLECULAR PATHWAYS RATIONALLY OVER CONVENTIONAL TREATMENT FOR DIFFUSE LARGE B-CELL LYMPHOMA: IMPROVE DLBCL

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DLBCL, diffuse large B-cell lymphoma

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THE EVOLUTION OF FRONT-LINE THERAPIES FOR DLBCL

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- Despite years of effort, front-line treatment for DLBCL has largely remained R-CHOP
- Increased understanding of molecular subtypes of DLBCL has lead to recognition of at least two major classifications: **GC and ABC subtypes**
- Large phase 3 trials have attempted to escalate therapy (dose-adjusted R-EPOCH) or introduce newer anti-CD20 monoclonal antibodies to improve outcomes
- Additionally, novel agents such as bortezomib, lenalidomide and ibrutinib have been added into treatment with R-CHOP with the goal of preferentially improving outcomes of the higher-risk (ABC) subtype
- Recently, new molecular techniques have further sub-classified GC and ABC DLBCL into clusters of patients with unique and reproducible disease biology. These approaches represent an opportunity to **explore rational molecularly targeted therapies for DLBCL** in the front-line setting

ABC, activated B-cell; DLBCL, diffuse large B-cell lymphoma; GC, germinal center; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-EPOCH, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin

RECENT PHASE 3 TRIALS IN FRONTLINE DLBCL

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Phase 3 Trial	Subgroup	Lead-in R-CHOP?	Outcome (PFS/EFS)	Author Conclusions/Additional Information
GOYA[1] R-CHOP vs. G-CHOP (N=1,418)	All	–	Negative	• Obinutuzumab not superior to rituximab for DLBCL
Alliance/CALGB 50303[2] R-CHOP vs. DA-EPOCH-R (N=524)	All	–	Negative	• Selection bias, resulting in enrolment of patients with more indolent disease
PHOENIX[3] R-CHOP ± ibrutinib (N=838)	Non-GC by Hans	–	Negative	• Toxicity of combination preferentially impaired outcomes of older patients • Subgroup imprecise
ROBUST[4] R-CHOP ± lenalidomide (N=570)	ABC by GEP	–	Negative	• Subgroup imprecise
REMoDL-B[5] R-CHOP ± bortezomib (N=1,128)	Stratified by GEP	Allowed	Negative	• Subgroup imprecise

ABC, activated B-cell; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; G-CHOP, obinutuzumab plus CHOP; GEP, gene expression profiling; N, number; non-GC, non-germinal center; PFS, progression-free survival; R-CHOP, rituximab plus CHOP

1. Vitolo U, et al. J Clin Oncol. 2017;35(31):3529-3537; 2. Bartlett NL, et al. J Clin Oncol. 2019; PMID 30939090 [Epub ahead of print]; 3. Younes A, et al. J Clin Oncol. 2019;37(15):1285-1295; 4. Celgene Reports First Quarter 2019 Operating and Financial Results. April 25, 2019; 5. Davies A, et al. Lancet Oncol. 2019;20(5):649-662

RECENT INTEGRATED GENOMIC APPROACHES TO SUBCLASSIFY DLBCL INDEPENDENTLY IDENTIFY SIMILAR SUBGROUPS

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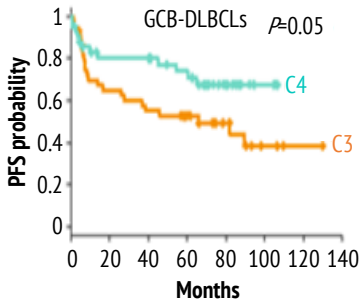
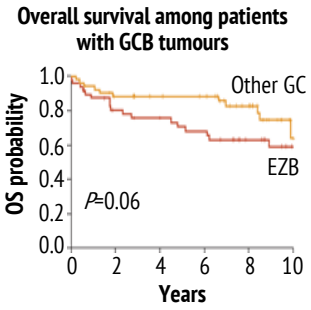
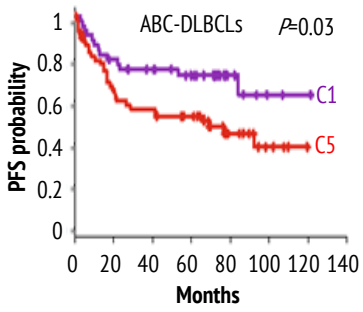
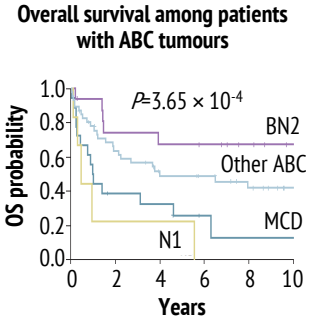
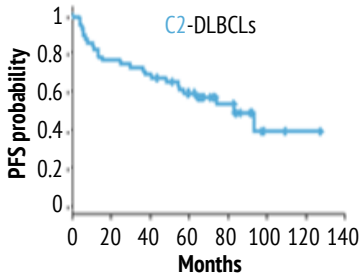
COO	Risk	Chapuy & Shipp[1]		Schmitz & Staudt[2]		Possible Agent
Germinal Center	Lower Risk	**Cluster 4** Histone mutations JAK/STAT and PI3K signalling NF-κB mutations		**Other GC**		**PI3K or JAK inhibitor**
	Higher Risk	**Cluster 3** Bcl-2 translocations EZH2 mutations PI3K signalling		**EZB** Bcl-2 translocations EZH2 mutations		**Bcl-2 and/or EZH2 inhibitor** **PI3K inhibitor**
ABC	Lower Risk	**Cluster 1** Immune evasion NOTCH2/NF-κB mutation Bcl-6 translocations MYD88$^{non\text{-}L265P}$ mutation		**BN2** Immune evasion NOTCH2/NF-κB mutation Bcl-6 alterations		**Proteasome inhibitor** **Checkpoint inhibitor**
	Higher Risk	**Cluster 5** CD79B, MYD88^{L265P} mutation 18q gains Bcl-2/MALT-1 expression		**N1** NOTCH1 mutations **MCD** CD79B, MYD88^{L265P}		**Btk inhibitor**
Other	Higher Risk	**Cluster 2** Inactivation of p53, CDKN2A loss				**Tissue-agnostic treatment**

ABC, activated B-cell; C, cluster; COO, cell-of-origin; DLBCL, diffuse large B-cell lymphoma; GC, germinal center; GCB, germinal center B-cell; OS, overall survival; PFS, progression-free survival

1. Chapuy B, et al. Nat Med. 2018;24:679-690; 2. Schmitz R, et al. N Engl J Med. 2018;378:1396-1407

PROPOSAL FOR FRONT-LINE TREATMENT: INVESTIGATING MOLECULAR PATHWAYS RATIONALLY OVER CONVENTIONAL TREATMENT FOR DIFFUSE LARGE B-CELL LYMPHOMA: IMPROVE DLBCL

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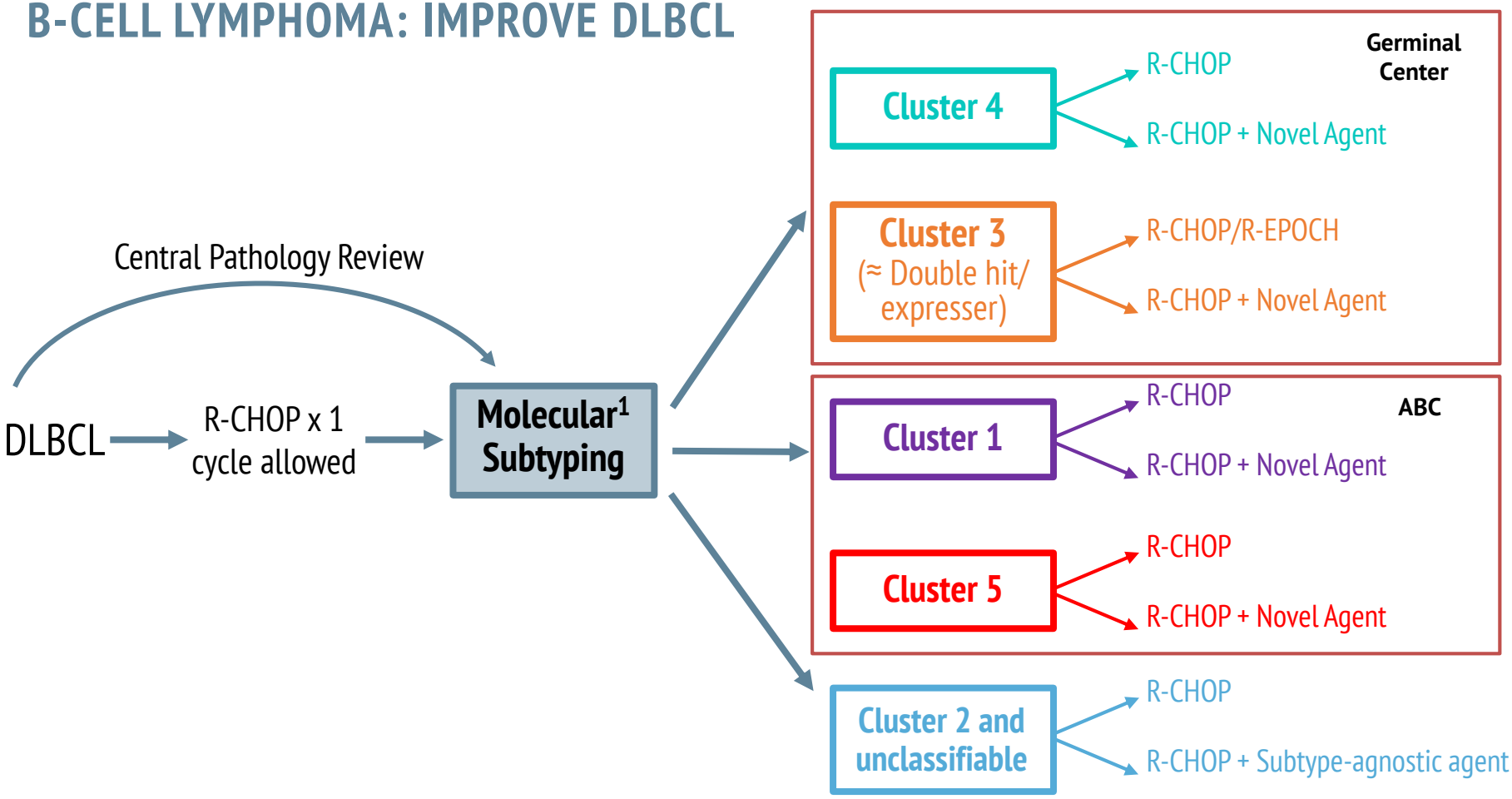

DLBCL, diffuse large B-cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-EPOCH, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin

1. Chapuy B, et al. Nat Med. 2018;24:679-690

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