Diffuse Large B cell Lymphoma

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Disclosures

- Consulting fees from Novartis
- Clinical Research supported by Novartis, Amgen, Celldex and Celgene
- Co-founder and equity holder of Cambium Medical Technologies & Cambium Oncology
- I will be discussing non-FDA approved indications during my presentation.

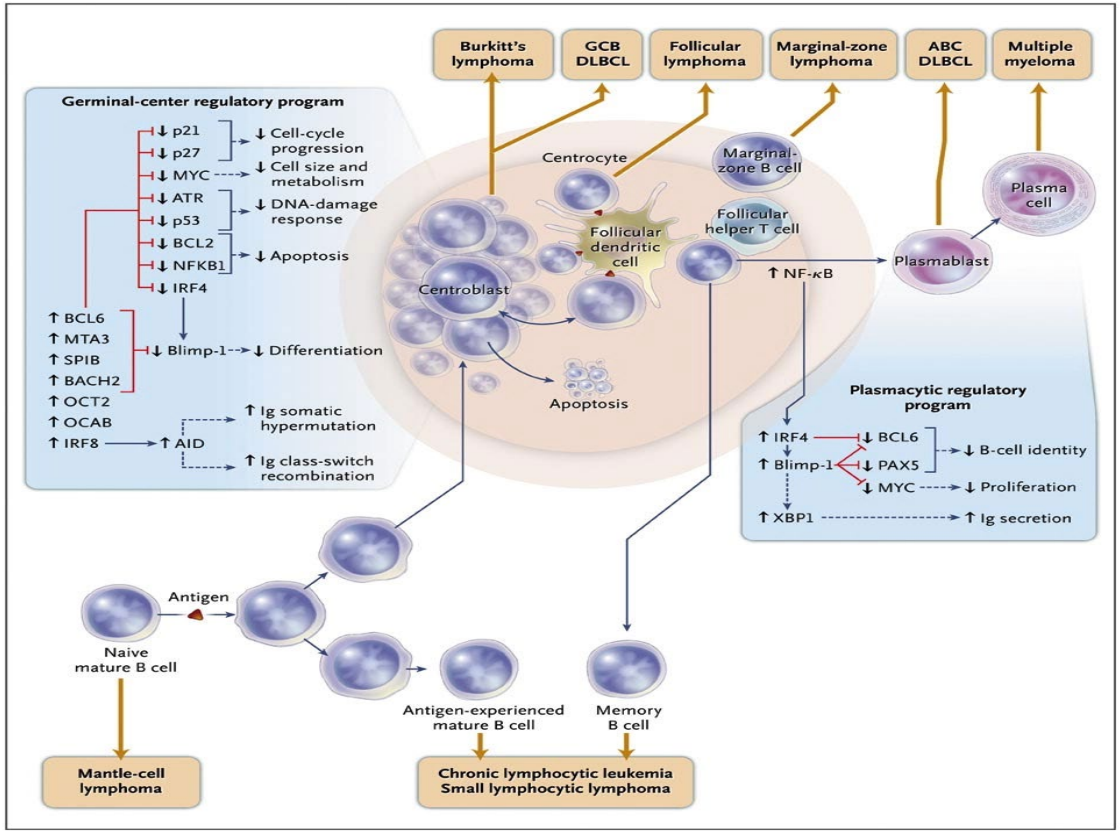
Outline of Talk

- DLBCL epidemiology
- Subsets of DLBCL
- Standard Therapies
- Management of Relapsed/Refractory Disease

DLBCL epidemiology

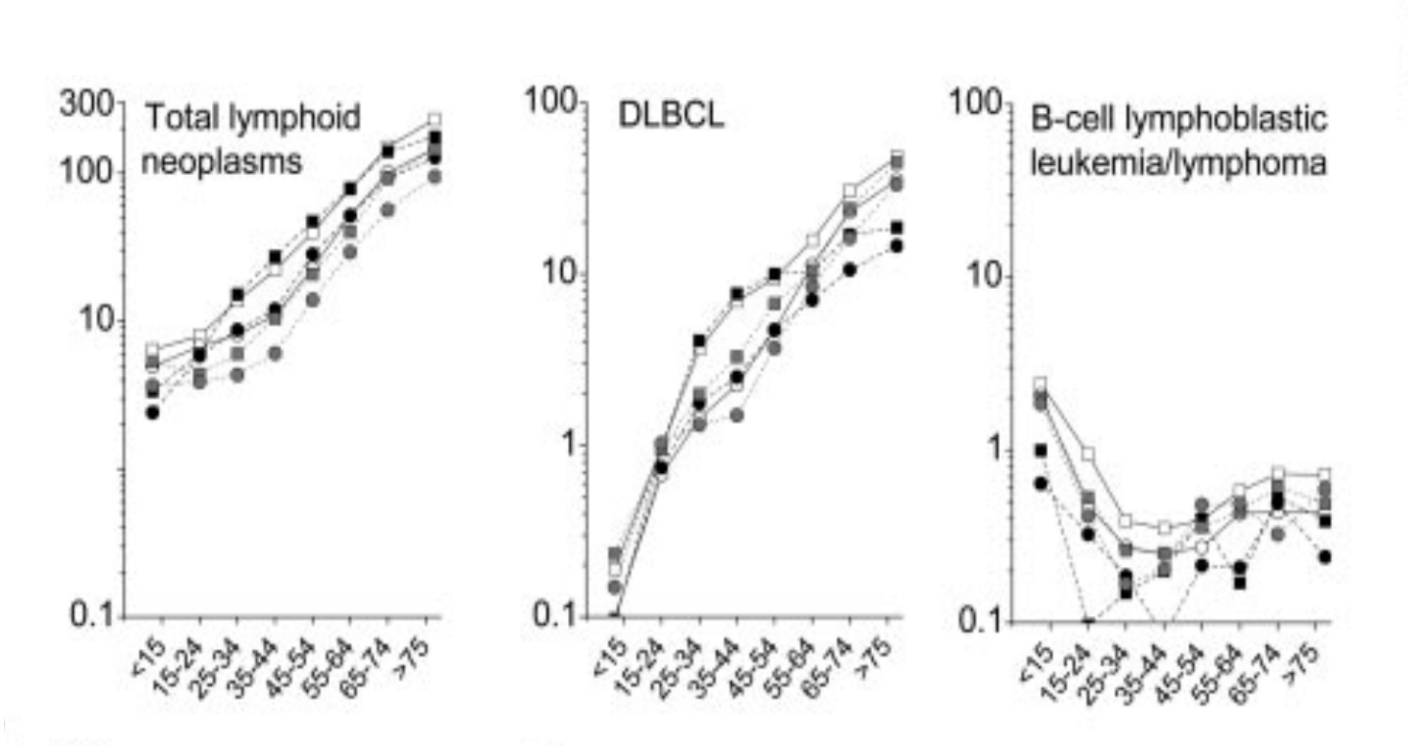
- Most common histologic subtype of non-Hodgkin lymphoma accounting for ~25% cases
- ~100,000 new cases word-wide with ~50,000 deaths/year.
- Arises from activated mature B cells resembling centroblasts or immunoblasts.
- Typically presents with a rapidly enlarging symptomatic nodal mass
- 60 percent of patients present with stage III or IV disease

Ontogeny of Lymphomagenesis



Lenz G, Staudt LM. N Engl J Med 2010;362:1417

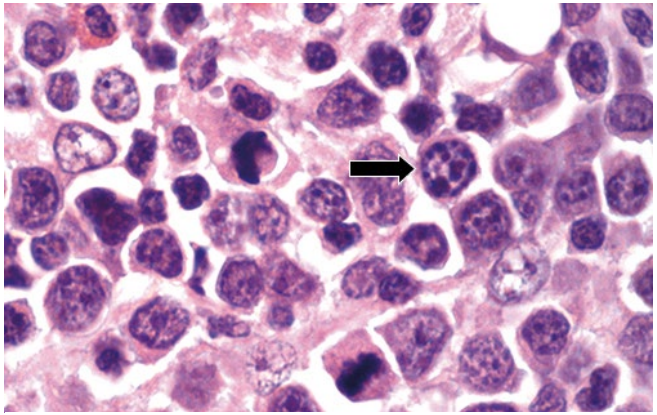
The incidence of DLBCL increases with age



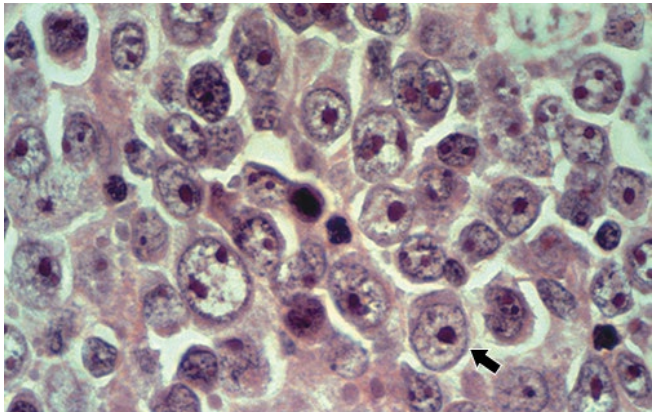
Morton, 2006. Blood **107:265**

Histological Appearance of DLBCL

Centroblast



Immunoblast



Sun T. Flow Cytometry, Immunohistochemistry, and Molecular Genetics for Hematologic Neoplasms

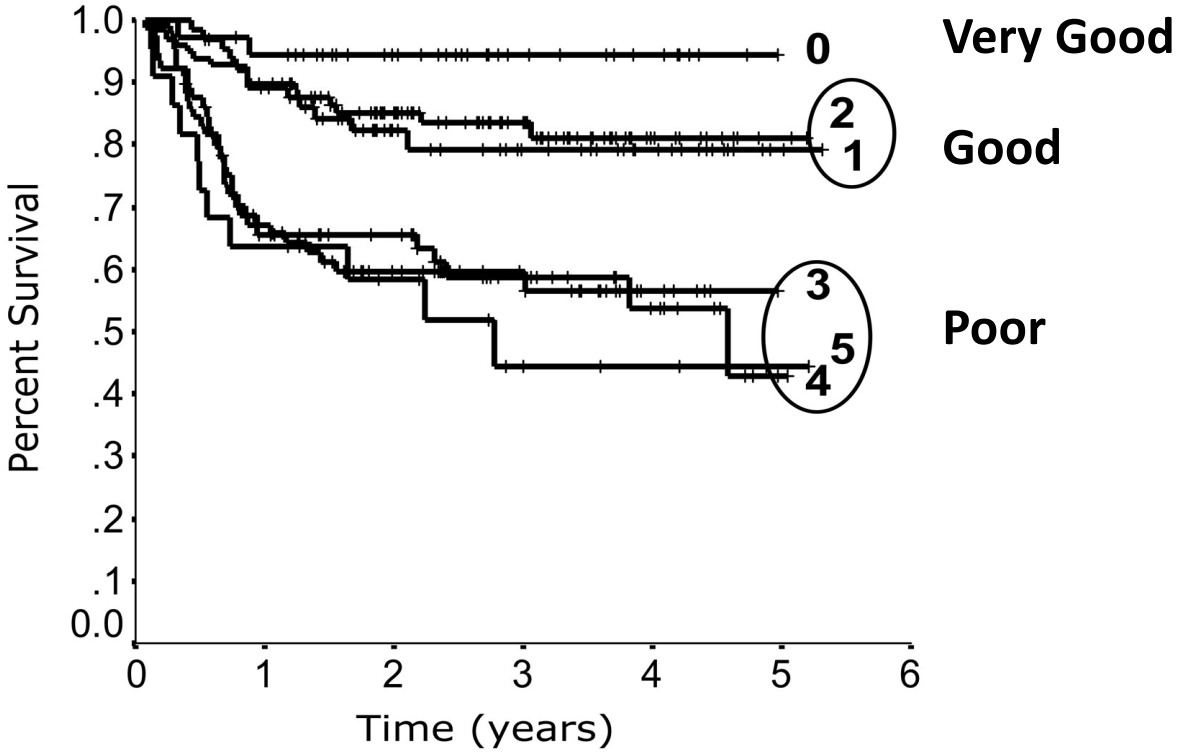
Revised International Prognostic Index (IPI) Score

IPI factors	
Age greater than 60 years	51%
PS greater than 2	41%
Elevated LDH	55%
More than 1 extra-nodal site	34%
Stage III/IV	59%

	# IPI factors	% Patients	4-yr PFS, %	4-yr OS, %
Very good	0	10	94	94
Good	1, 2	45	80	79
Poor	3, 4, 5	45	53	55

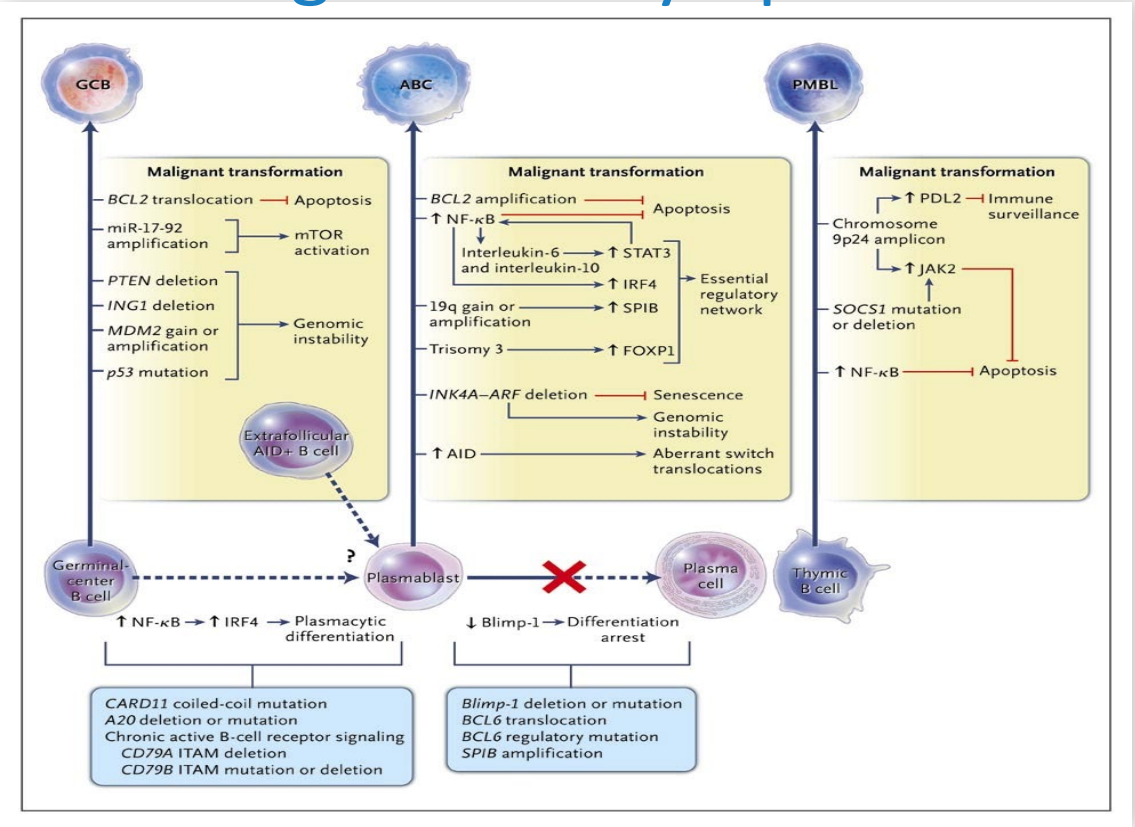
Sehn Blood 2007 109:1857-1861

Survival based upon the Revised IPI



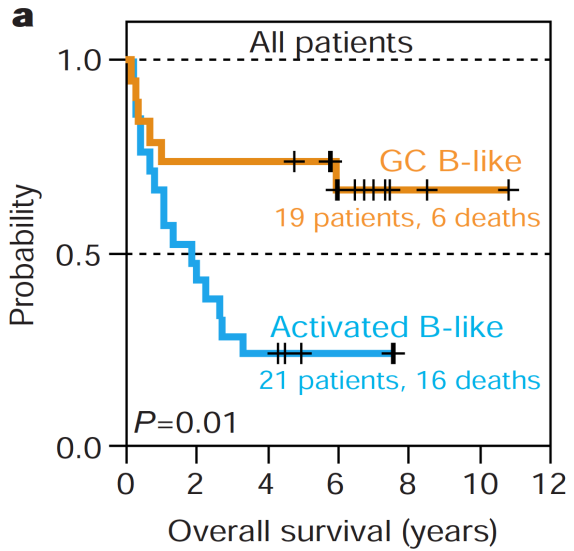
Sehn Blood 2007 109:1857

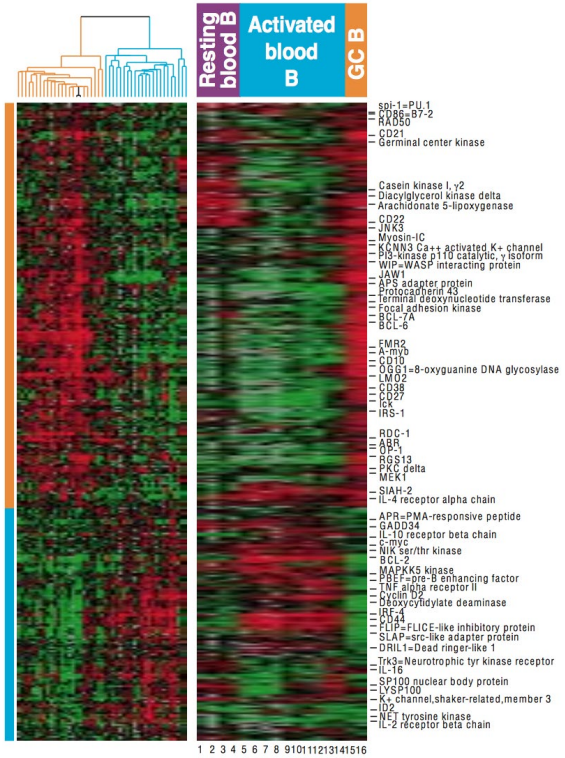
Oncogenic Pathways for Three Subtypes of Diffuse Large-B-Cell Lymphoma



Lenz G, Staudt LM. N Engl J Med 2010;362:1417-1429.

Molecular profiling is more useful to prognosticate survival than histological sub-classification of DLBCL



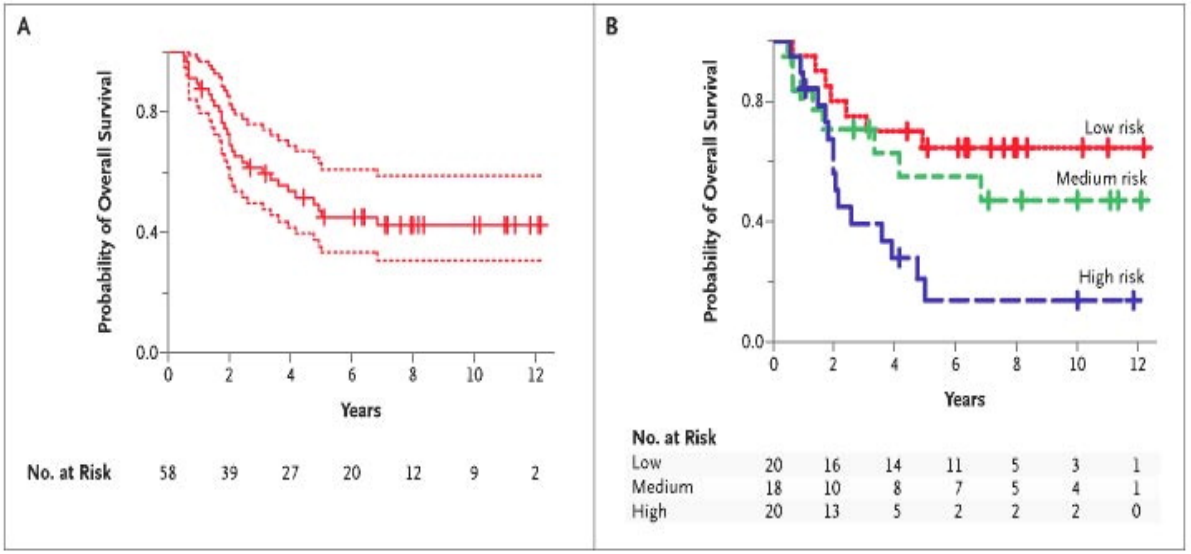


Alizadeh Nature 2000. 403:503

Untreated lymphoma patients, 17,856 cDNA clones on this microarray

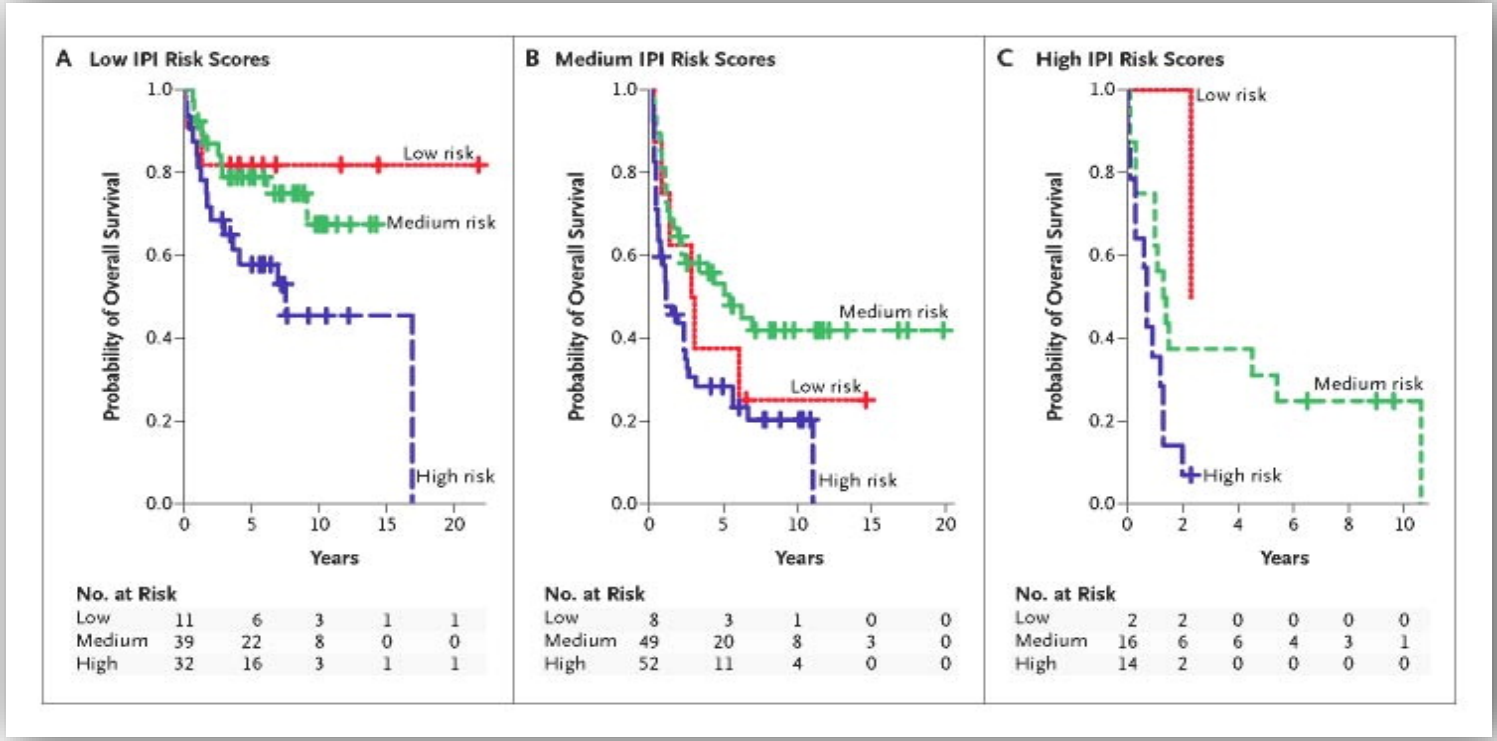
A six-gene model that predicts survival in DLBCL

Germinal-center B-cell signature (***LMO2*** and ***BCL6***): ↑expression= **↑better survival**
Lymph-node signature (***FN1***): ↑expression= **↑better survival**
Activated B-cell signature (***BCL2, CCND2, SCYA3***): ↑expression= **↓survival**



Lossos IS et al. N Engl J Med 2004;350:1828

Six-gene model adds to the prognostic power of the IPI in predicting survival in DLBCL patients



Lossos IS et al. N Engl J Med 2004;350:1828.

DLBCL Treatment Landscape

DLBCL is the most common lymphoma in the United States with

- 30% of patients relapse after receiving first-line treatment
- 10% of patients have refractory disease

SOC for relapsed/refractory patients is high dose chemotherapy followed by auto-SCT

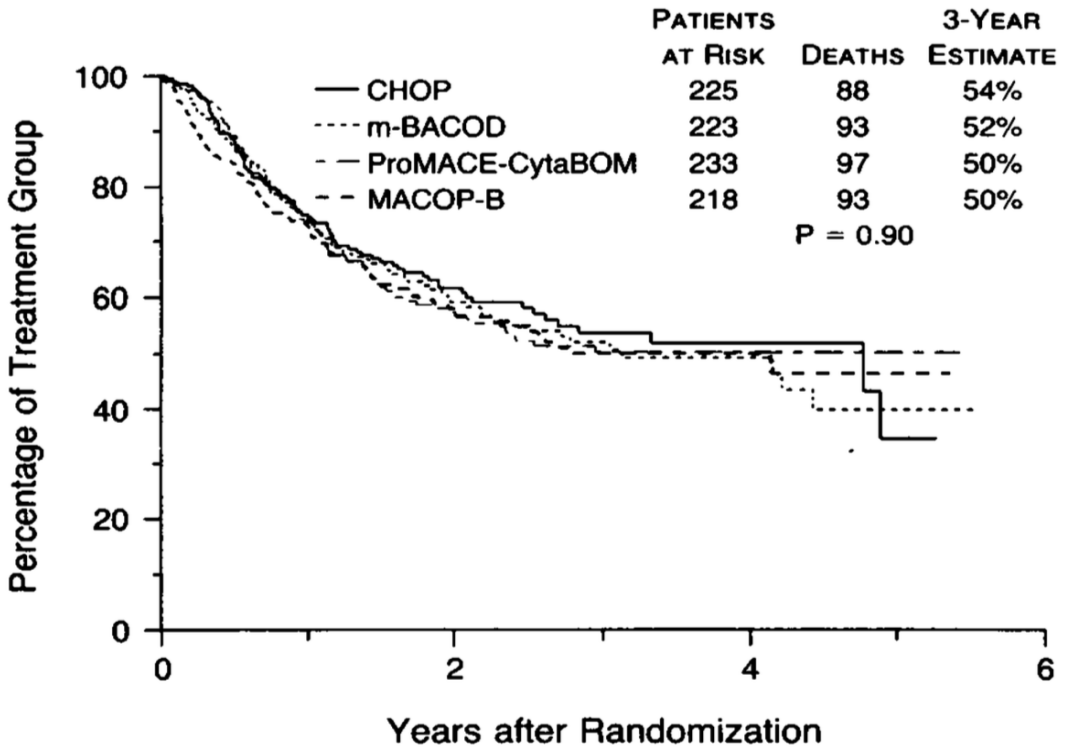
- Only about a quarter of these patients can receive a transplant

Patients with refractory DLBCL have a poor prognosis

- Low rate of response to salvage therapy (CR 8%; PR 18%)[1]
- Short survival (median OS 4 to 6 months)[1-2]

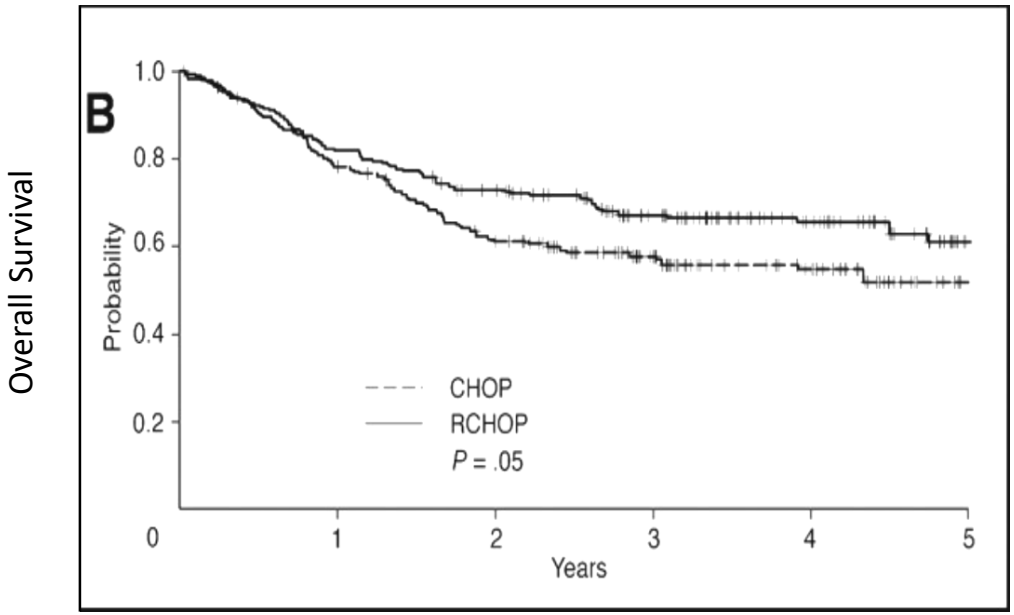
1. Crump M, et al. *Blood.* 2017;130(16):1800-1808.
2. Van den Neste E, et al. *BMT*. 2016;51:51-57.

No combination chemotherapy regimen proved superior to CHOP in 1993



Fisher NEJM 1993 328:1002.

Rituximab-CHOP is superior to CHOP alone in older patients with diffuse large B-cell lymphoma



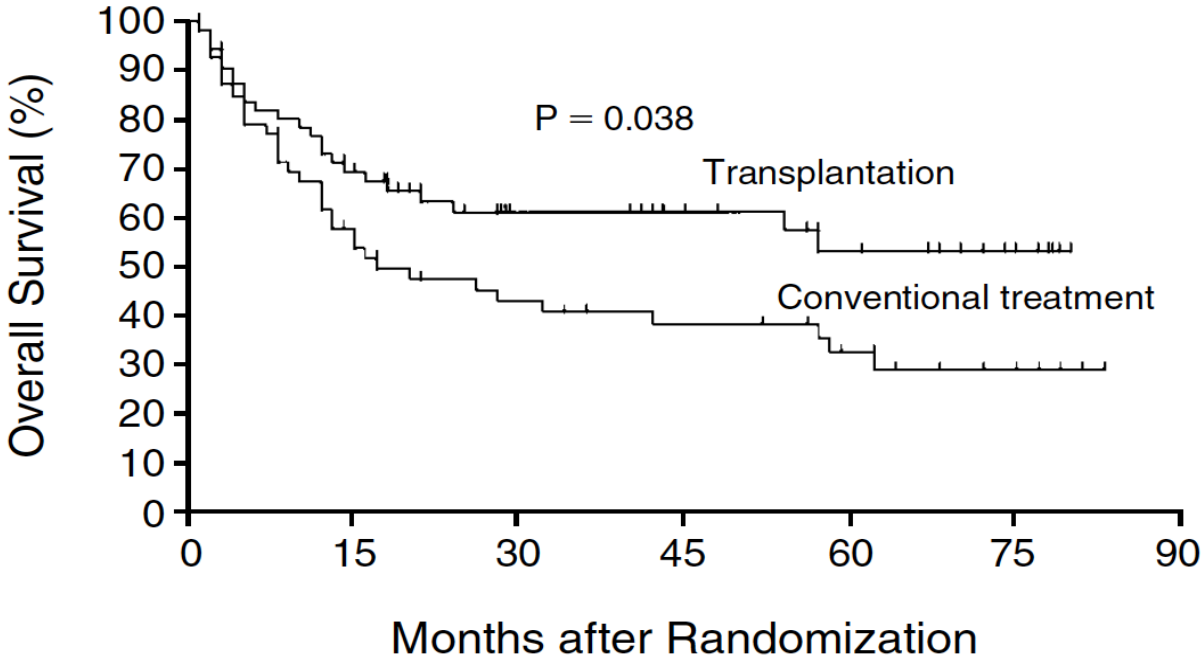
Habermann TM, JCO 2006

DA-EPOCH-R combination is not superior to RCHOP in 2016: CALGB/Alliance 50303

- Pts with stage II or higher newly diagnosed DLBCL, age ≥ 18 years, HIV negative
- No difference in EFS or OS between R-CHOP and DA-EPOCH-R with hazard ratio of 1.02 and p=0.89, median follow-up of 4.9 years
- DA-EPOCH-R showed increased toxicity consistent with higher dose-intensity but not increased grade 5 toxicity.
- More patients on DA-EPOCH-R did not complete treatment

Wilson, 2016. ASH abstract #469

Auto-transplant yields better overall survival for relapsed DLBCL in the pre-Rituximab era

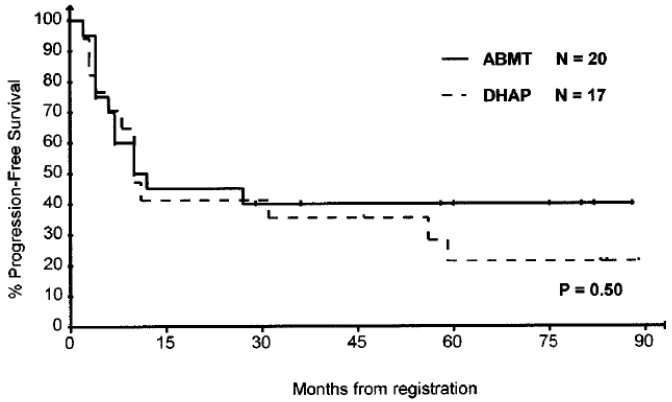


Philip NEJM 1995;333:1540

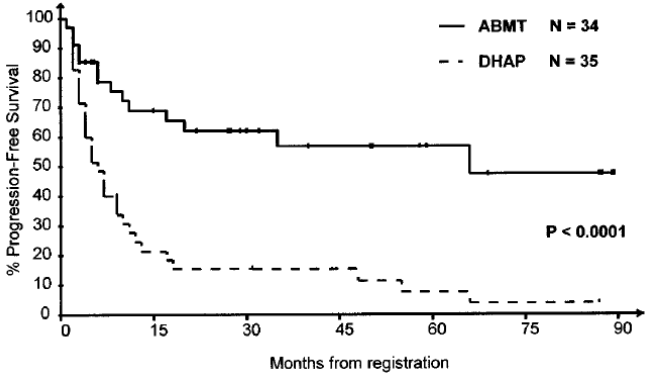
The benefit of auto-transplant in the Parma study was among subjects with a high IPI score at relapse

Age adj. IPI= clinical stage (3 or 4), high LHD, and poor PS (ECOG PS≥2)

Low IPI (0)



High IPI (1-3)



Blay Blood 1998;92:3562

Early auto-transplant yielded better overall survival for poor-risk DLBCL in the pre-Rituximab era

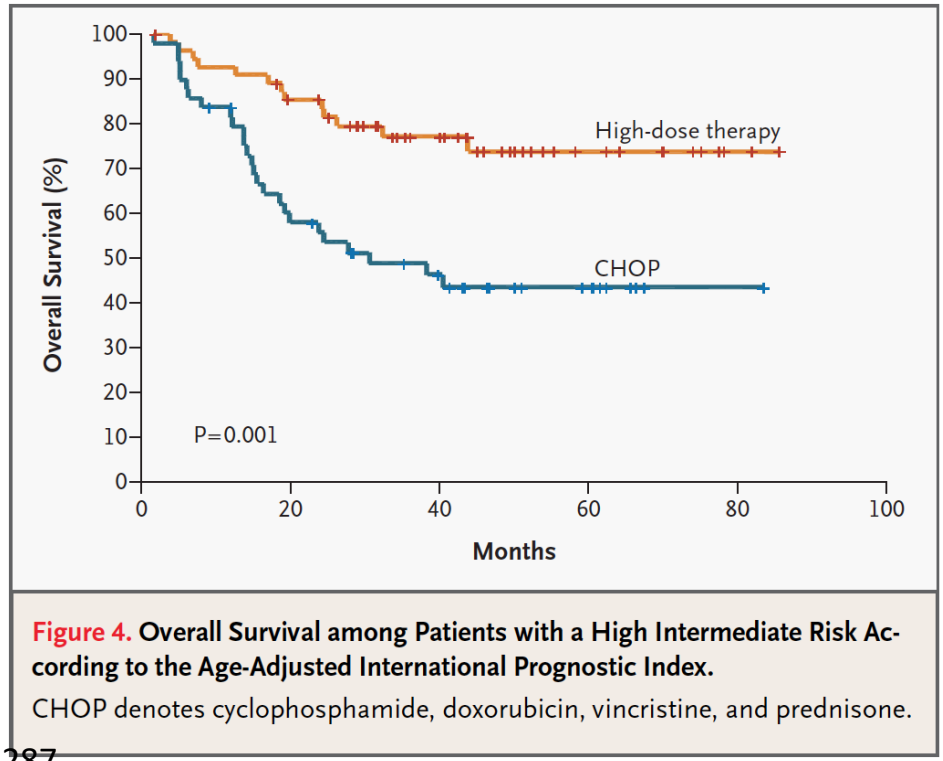


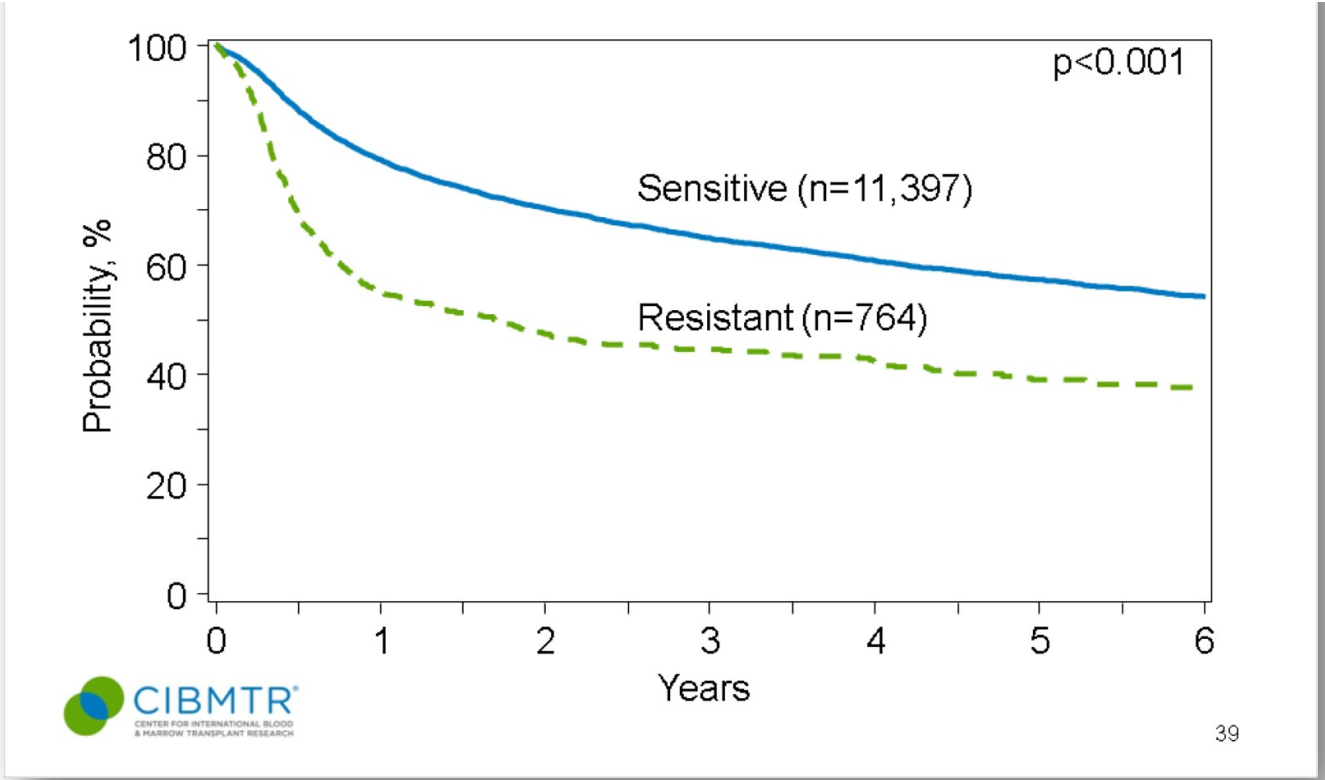
Figure 4. Overall Survival among Patients with a High Intermediate Risk According to the Age-Adjusted International Prognostic Index.

CHOP denotes cyclophosphamide, doxorubicin, vincristine, and prednisone.

IPI score 4 or 5

Milipied NEJM 2004. 350:1287

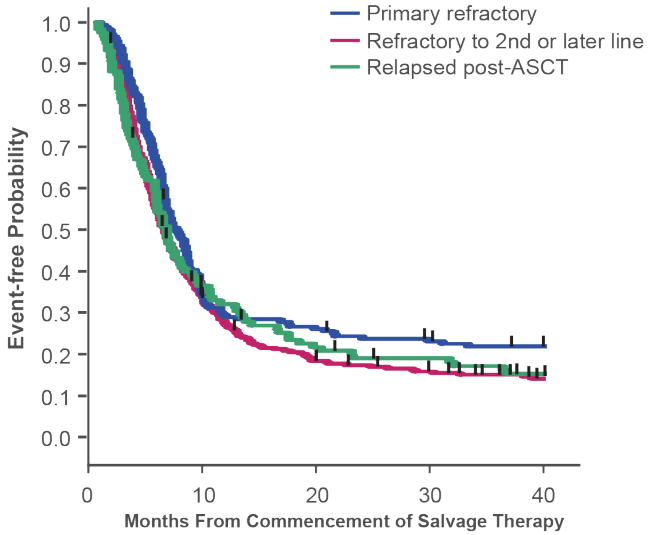
Survival after auto-transplant for DLBCL 2004-2014



SCHOLAR-1 demonstrated poor survival in patients with relapsed/refractory DLBCL

SCHOLAR-1 Patient Response Rate to Chemotherapy	
Measurement (n/N)	**Integrated Response Rate (n=636)**
Number of patients evaluated for response	529
Response rate, % (95% CI)	26% (22,31)
- Complete Response Rate	**8% (4,15)**
- Partial Response Rate	**18% (13,23)**

Adapted with permission from the American Society of Hematology.



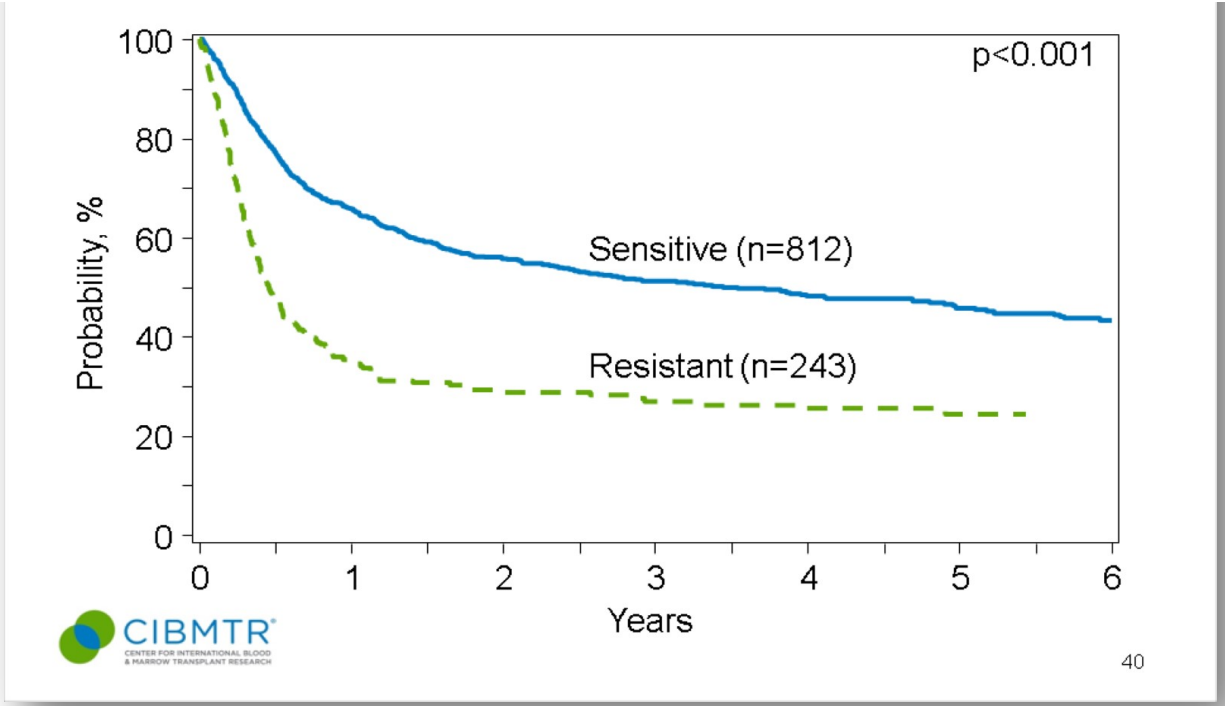
Median overall survival was 6.6 months in the SCHOLAR-1 meta-analysis of patients with r/r DLBCL who were primary refractory, chemorefractory, or who relapsed <= 1 year post ASCT

Crump M et al. *Blood*. 2017.

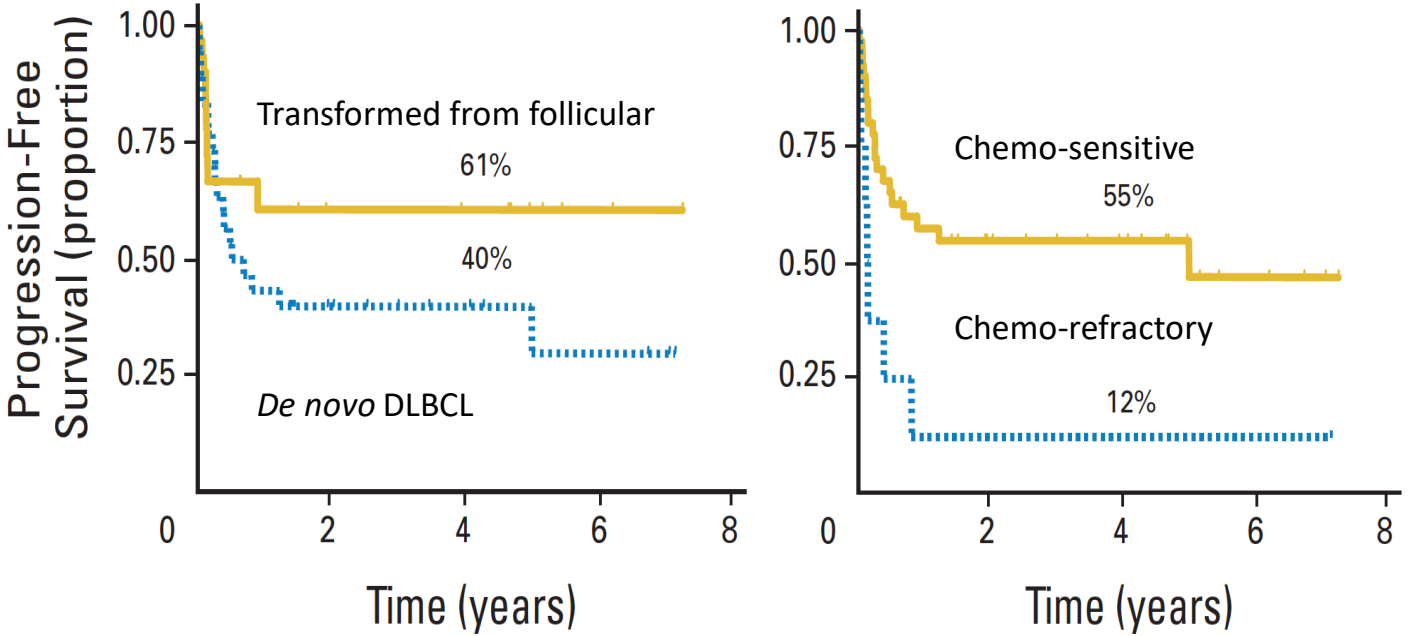
Current strategies to manage relapsed DLBCL

1. Allo-transplant
2. Ibrutinib
3. Revlimid
4. Venatoclax
5. Novel T cell Therapy

Survival after allo-transplant for DLBCL with HLA-matching sibling 2004-2014

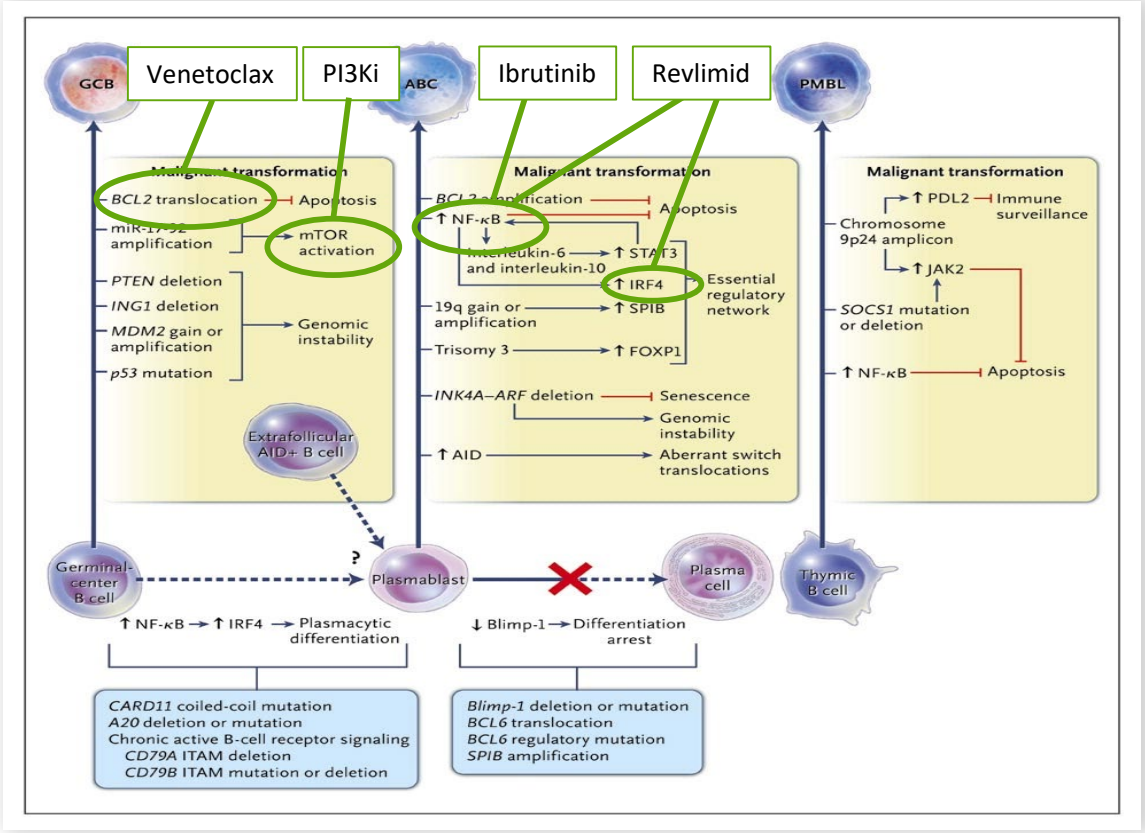


Alemtuzumab-based allo-transplantation with DLI: ineffective in refractory DLBCL



Thomson, 2009. J Clin Oncol 27:426-432.

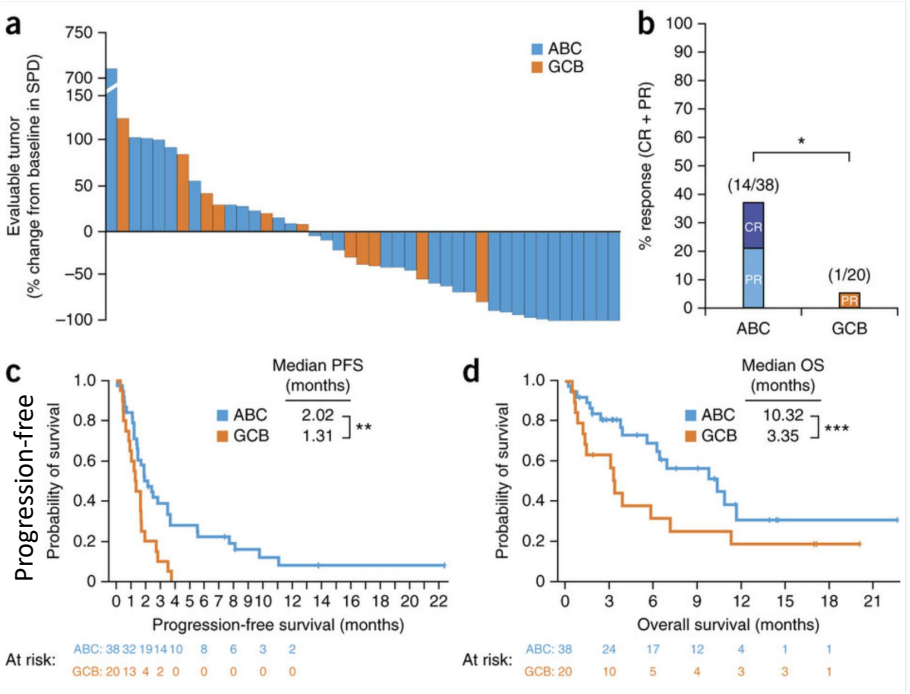
Oncogenic Pathways for Three Subtypes of Diffuse Large-B-Cell Lymphoma.



Lenz G, Staudt LM. N Engl J Med 2010;362:1417

Ibrutinib is effective in ABC-type relapsed/refractory DLBCL

BCR-dependent route to ABC DLBCL also includes tumors without mutations in the BCR, as 67% of ibrutinib responders had wild-type *CD79A* and *CD79B*.



Wilson Nature Medicine 21, 922–926 (2015)

Lenalidomide + R-CHOP Overcomes Negative Prognostic Impact of Non–GCB DLBCL: Phase II

R-CHOP -21

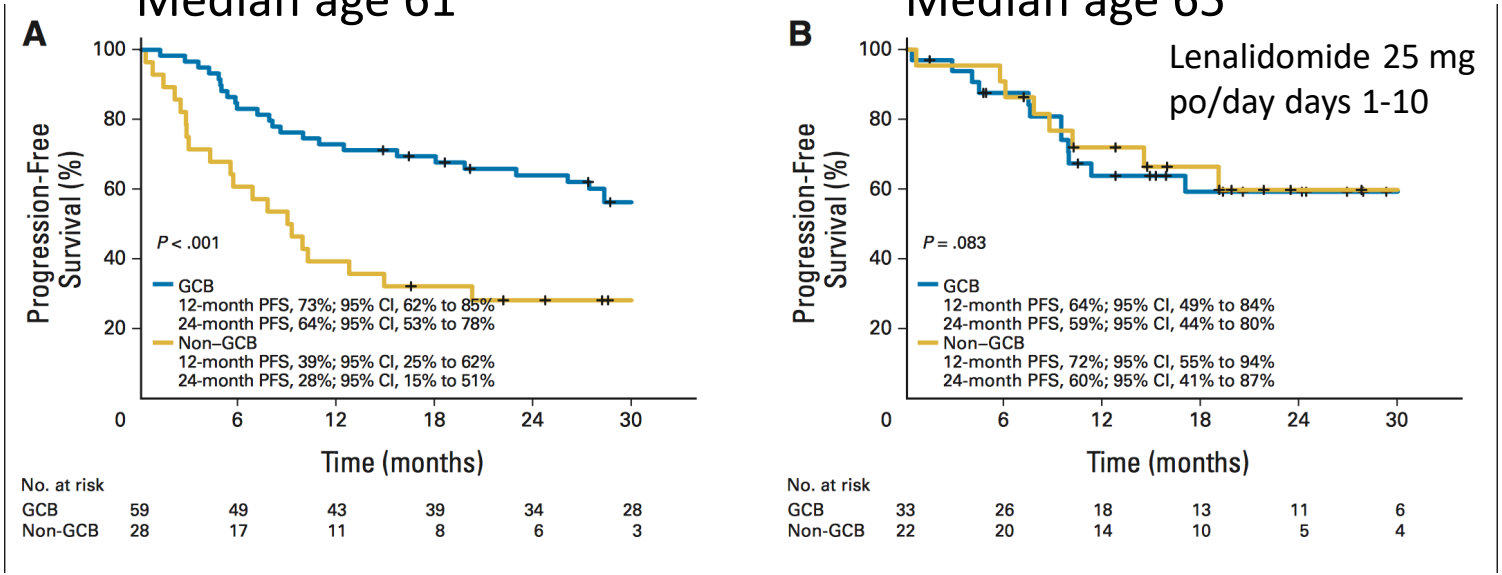
87 contemporaneous patients

Median age 61

R^2-CHOP- 21

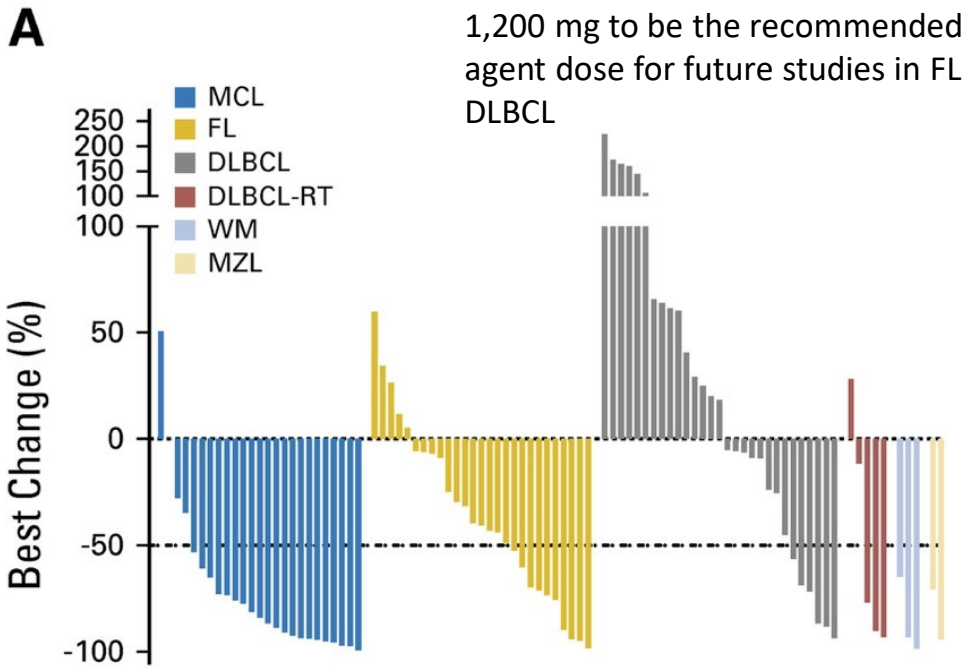
65 study patients

Median age 65



Nowakoski J Clin Oncol 33:251-257

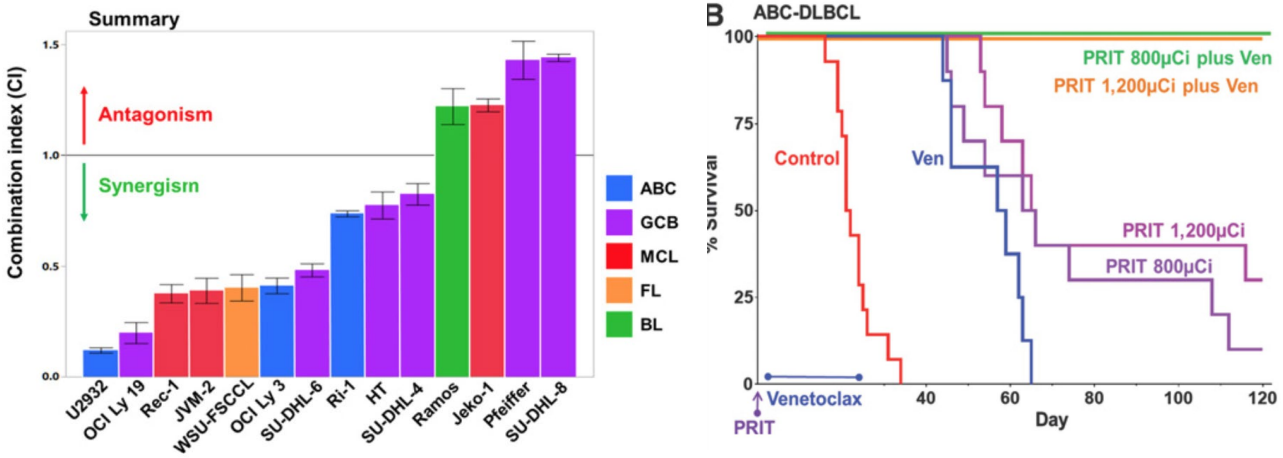
Phase I First-in-Human Study of Venetoclax in Patients With Relapsed or Refractory Non-Hodgkin Lymphoma



1,200 mg to be the recommended single-agent dose for future studies in FL and DLBCL

Davids 2017 JCO 35:826-833.

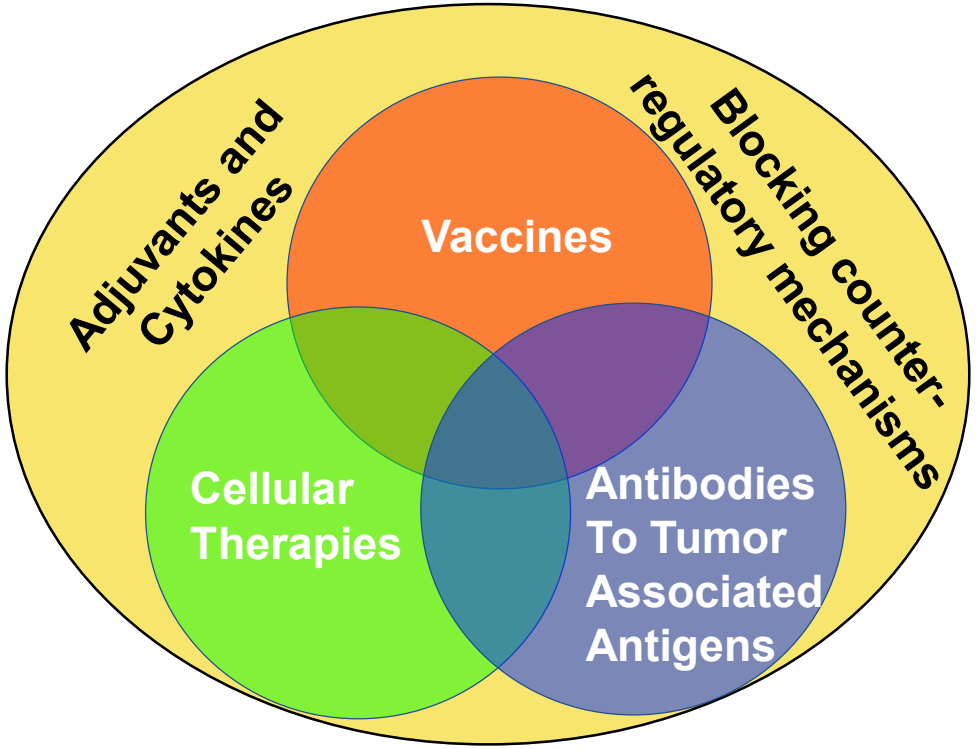
Venetoclax Synergizes with Radiotherapy for Treatment of B-cell Lymphomas



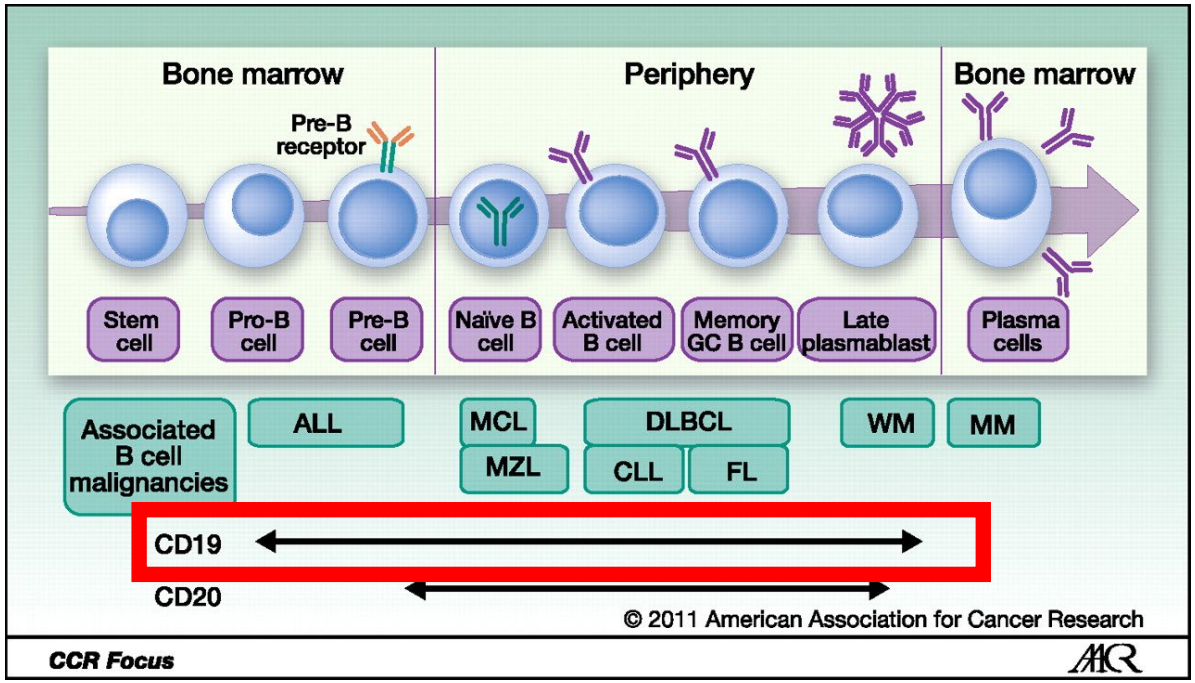
PRIT=radio-immuno therapy using a two-step "pretargeted" system directed against the CD20 antigen

O'Steen Cancer Res: 77: 3885–93

Can Immunological Modalities to Treat Cancer overcome chemotherapy-resistant DLBCL?



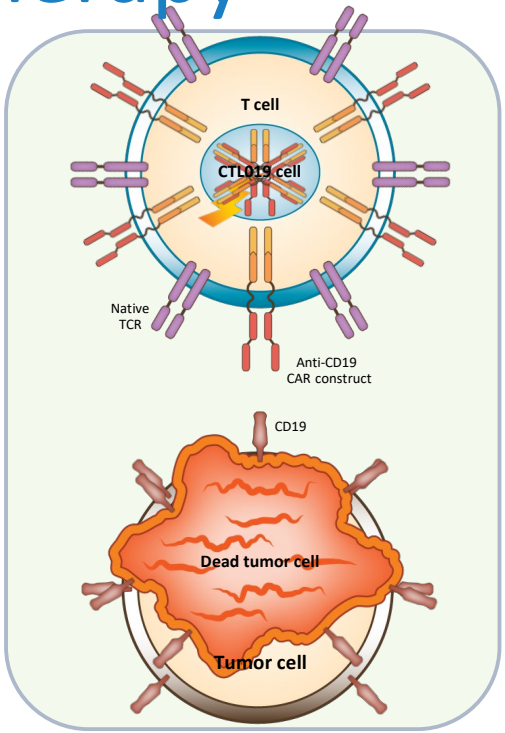
CD19 is an attractive target for B cell malignancies



Blanc, V et al., Clinical Cancer Research, Volume 17 , Issue 20

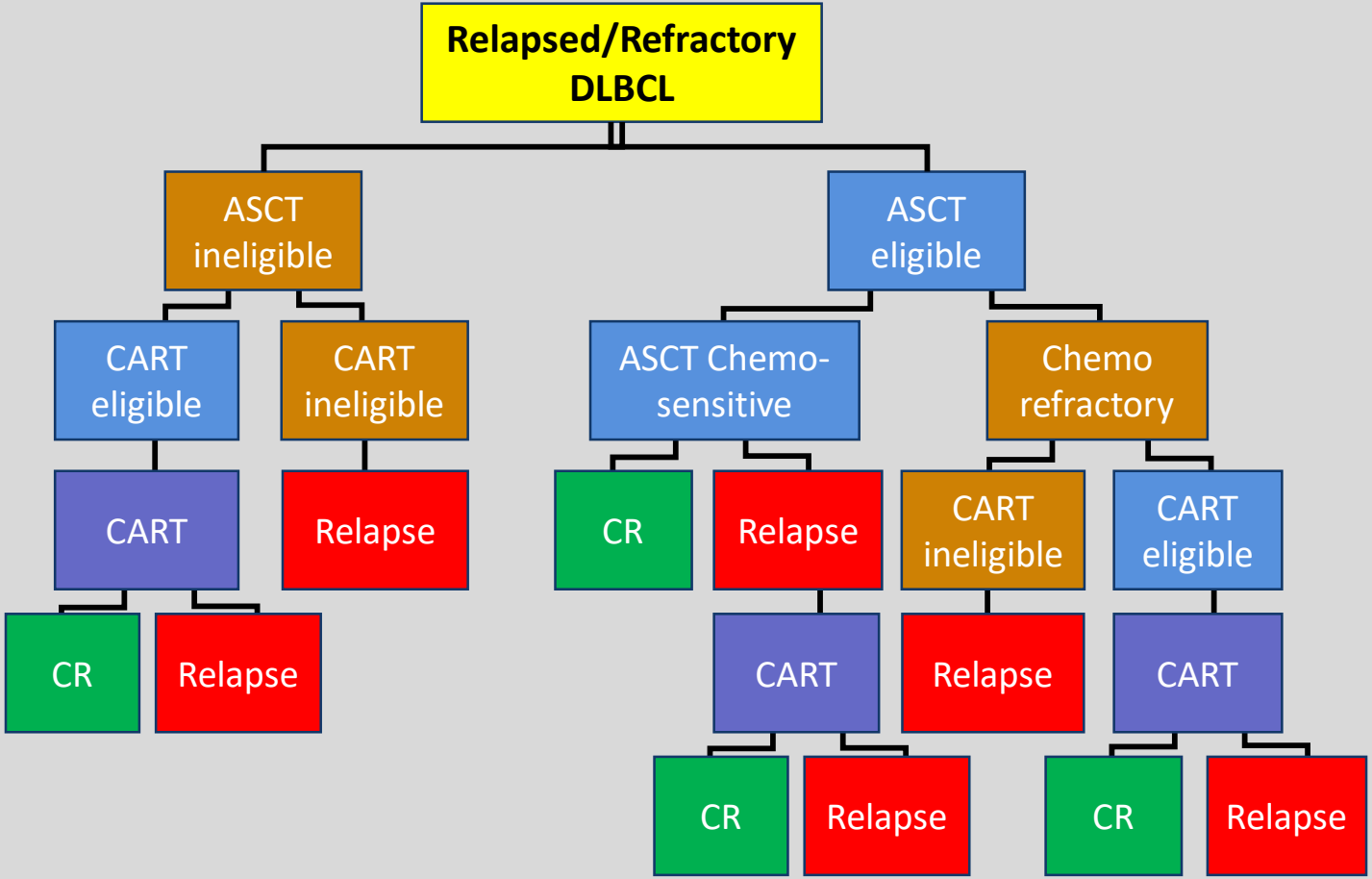
Chimeric Antigen Receptor (CAR) T cell therapy

- Gene transfer technology stably expresses CARs on T cells[1,2]
- CAR T cell therapy takes advantage of the cytotoxic potential of T cells, killing tumor cells in an *antigen-dependent* manner[1,3]
- Persistent CAR T cells consist of both effector (cytotoxic) and central memory T cells[3]
- **T cells are *non-cross resistant* to chemotherapy**



1.Milone MC, et al. *Mol Ther.* 2009;17:1453-1464.
2.Hollyman D, et al. *J Immunother.* 2009;32:169-180.
3.Kalos M, et al. *Sci Transl Med.* 2011;3:95ra73.

Treatment algorithm for relapsed/refractory DLBCL



CART in DLBCL to be discussed tomorrow!

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