Recent Advances In The Treatment of DLBCL

Subtypes of Diffuse Large B-Cell Lymphoma In The 2017 WHO Classification

Morphology

- DLBCL-NOS
- T-Cell/histocyte rich
- Plasmablastic
- High grade NOS*

Genetics

- GCB
- ABC
- High grade with MYC and BCL2/BCL6*
- With IRF4 rearrangement

* No longer DLBCL

IHC

- ALK positive

Primary Site

- Mediastinal
- CNS
- Effusion
- Intravascular
- Skin

Other

- EBV positive
- EBV positive mucocutaneous ulcer
- With chronic inflammation
- Lymphomatoid granulomotosis
- HHV8 positive

DLBCL

WHO 5	ICC
Primary LBCL immune privileged sites	---
Lymphoid proliferation in immunodeficiency	EBV (+) polymorphic B-cell LPD
---	High grade LBCL with MYC & BCL-6 rearrangements
Transformation of Indolent B-cell lymphomas	---

We Are Probably At The Time To Focus New Classification Efforts On Identifying Subtypes Likely to Respond To A Specific Therapy

Primary Therapy

1) Don’t forget a trick to improve outcome in old/very ill patients

2) Finally, a better regimen for some patients

Pre-Phase Therapy In The Elderly And Unwell

- Done to allow work-up and reduce 1st cycle deaths
- Prednisone 100 mg/day x 5-7 +/- Vincristine 1mg
- 50% reduction in 1st cycle deaths

Ways To Have A Better Treatment Than CHOP-R

- Different regimen (ProMACE-CytoBOM, MACOP-B, M-BACOD, ACVBP)
- Increase dose intensity (CHOP-14)
- Prolonged infusion (EPOCH-R)
- Add or substitute another drug
- Adjuvant or consolidation therapy
- Maintenance therapy
- Pharmacogenomic driven therapy

Polatuzumab vedotin single agent activity in R/R DLBCL

ORR - 48%

CR - 25%

Substituting Polatuzumab Vedotin For Vincristine In CHOP-R For Primary Therapy Of Patients With DLBCL (NEJM 2022; 356:351-62)

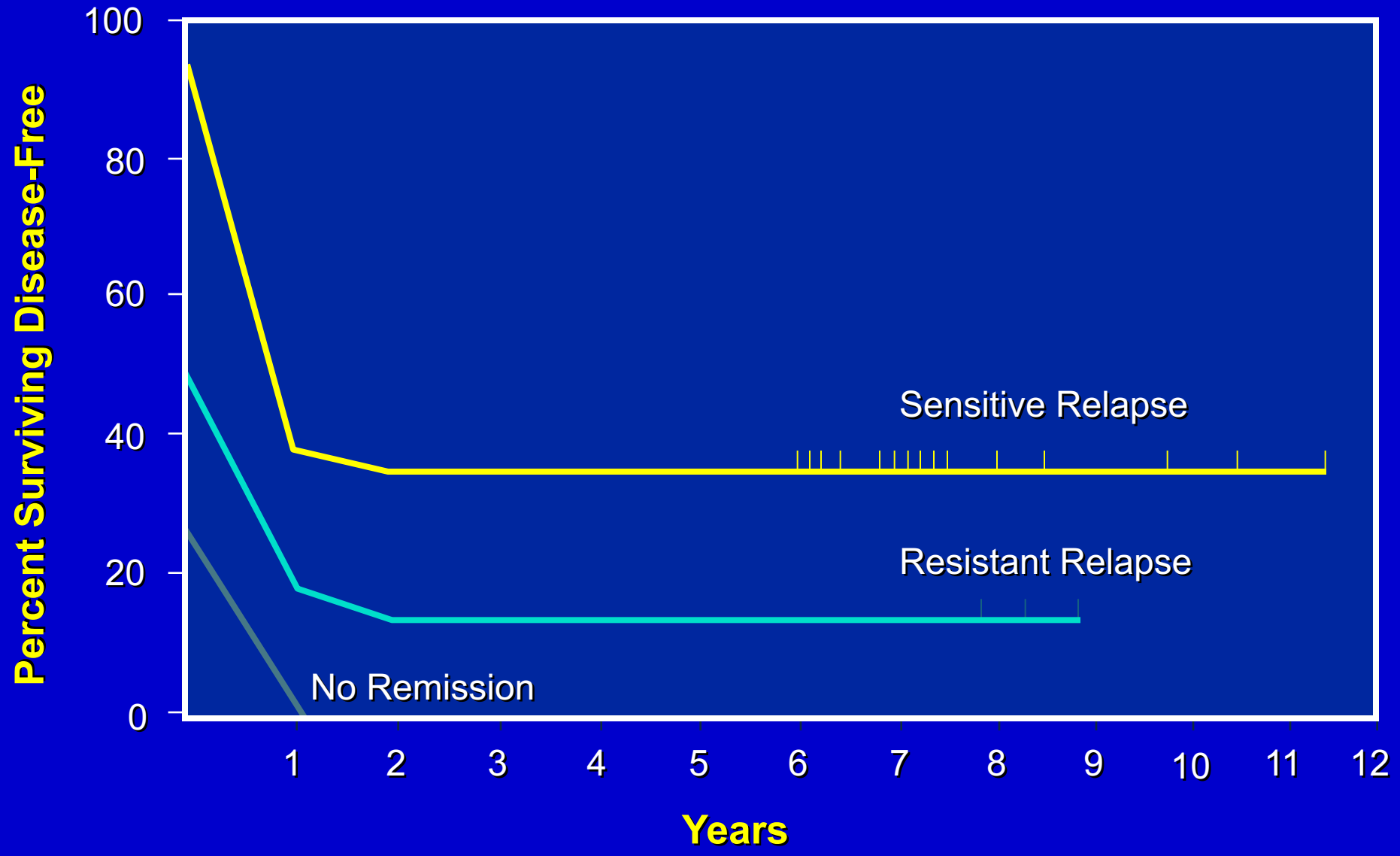
- 879 patients
- Overall PFS was 77% (Pola-R-CHP) and 70% (CHOP-R)
- Benefit was primarily in patients > 60 years of age, those with ABC subtype, and those with higher IPI scores

Outcome By Subgroups (2 year PFS)

Group	Pola-R-CHP	R-CHOP
age > 60	78%	70%
Male	76%	66%
IPI 3-5	75%	65%
ABC genetic subtype	84%	59%

Curing Patients Who Fail Primary Treatment

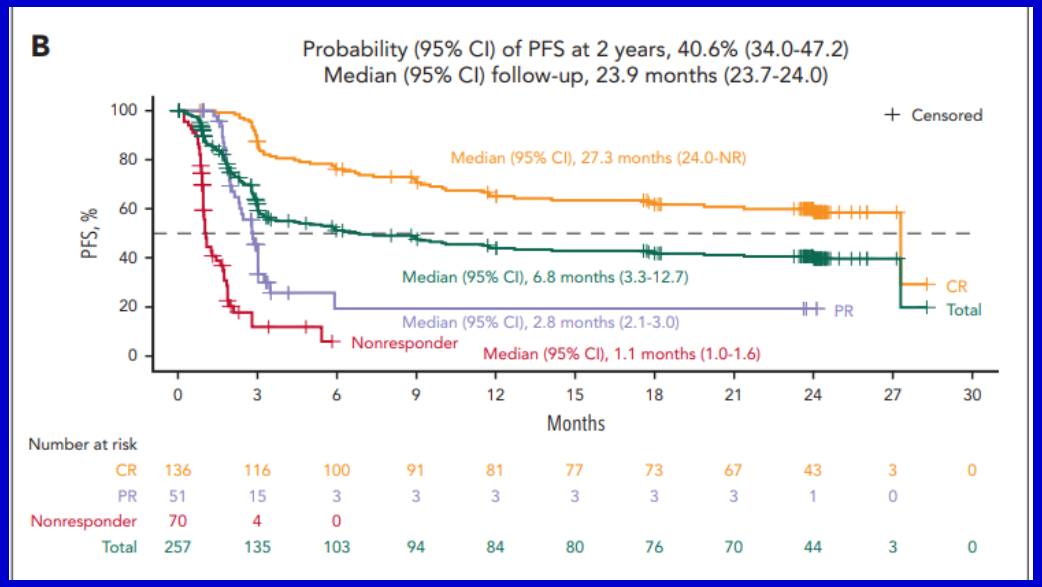
- Autologous Transplant
- CAR-T Cell Therapy
- Bispecific Antibodies
- VIPOR Regimen



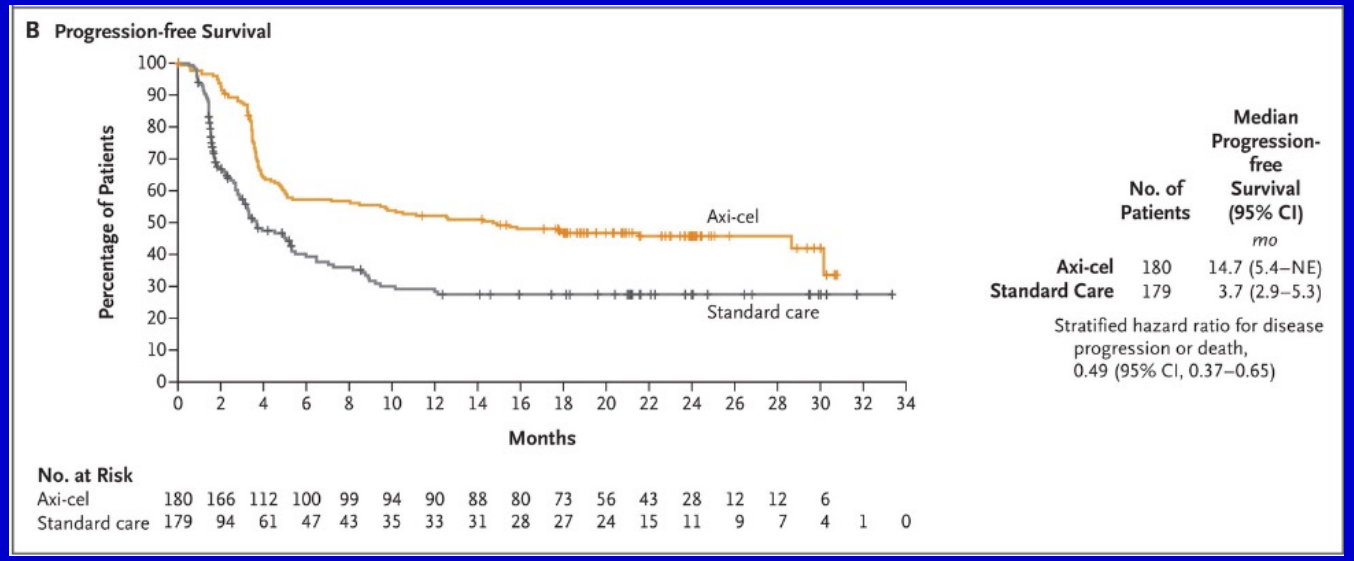
New England Journal of Medicine 316:1493-1498, 1987

Durability of Response After CAR-T Cell Therapy For R/R DLBCL

Lisocabtagene maraleucel



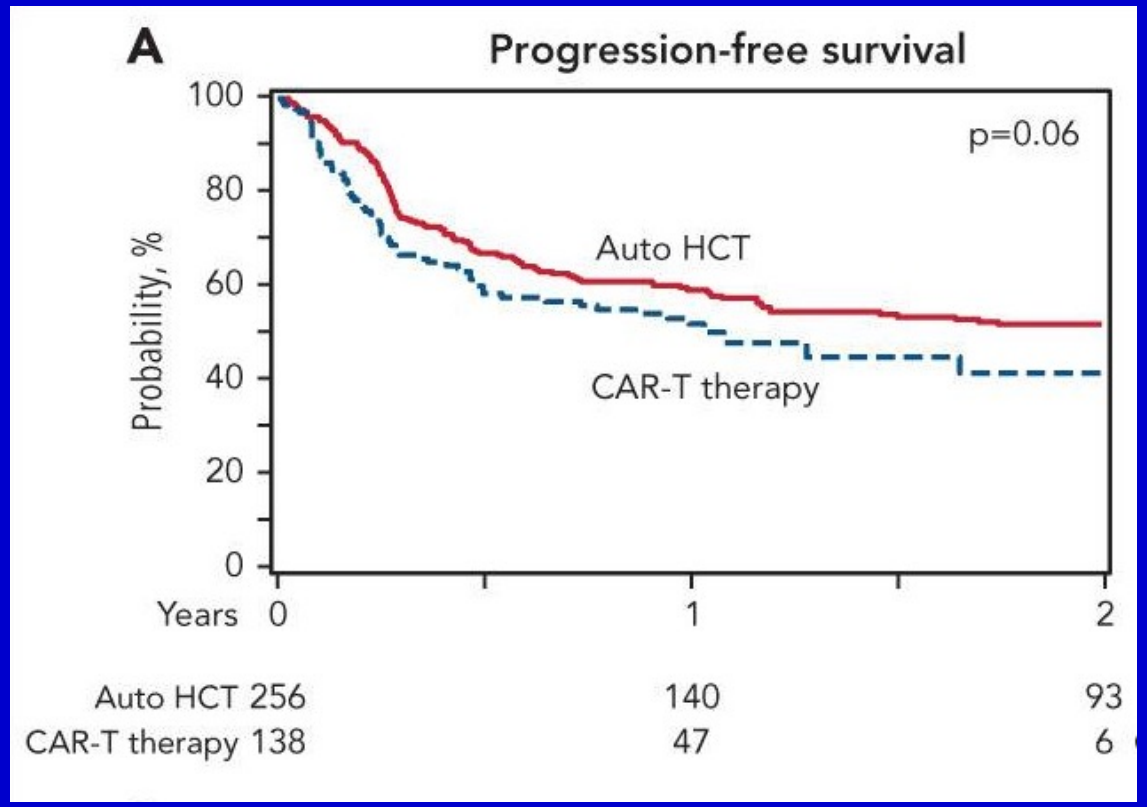
Axicabtagene ciloleucel

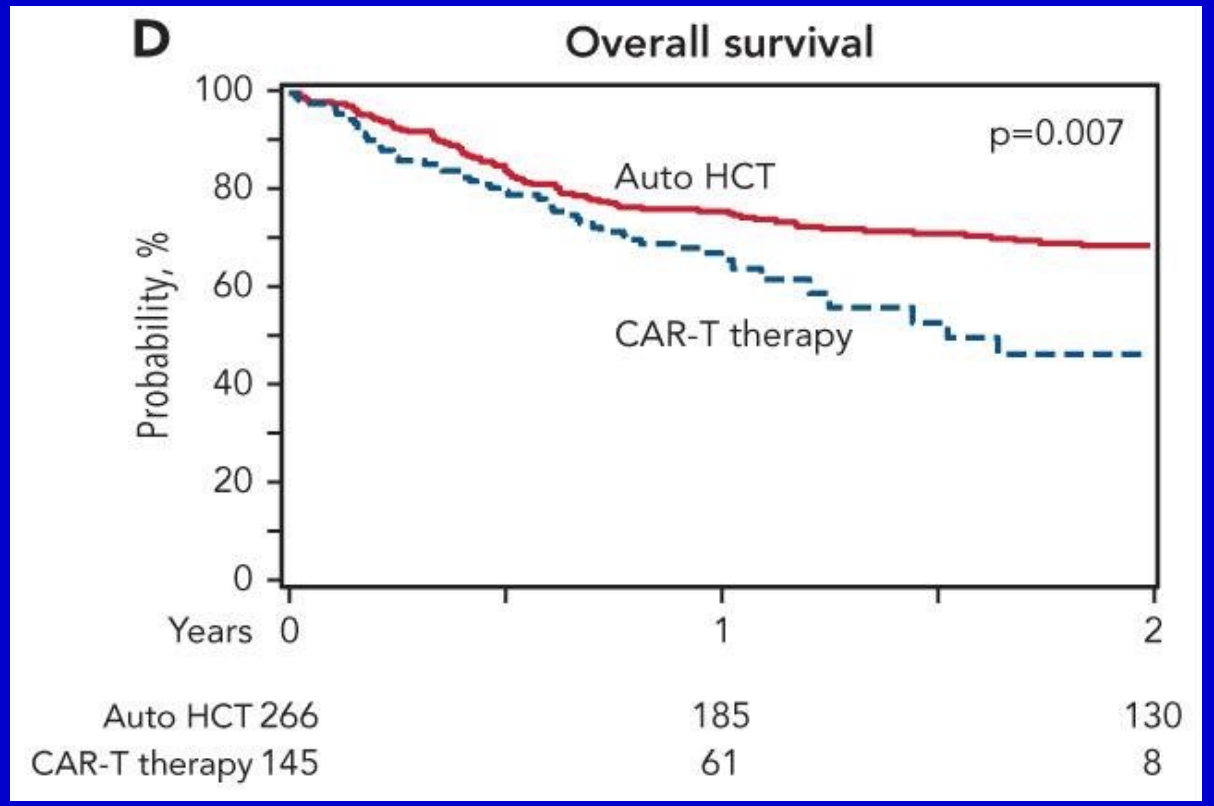


Blood 2024; 143: 404-416

NEJM 2022; 386:640-654

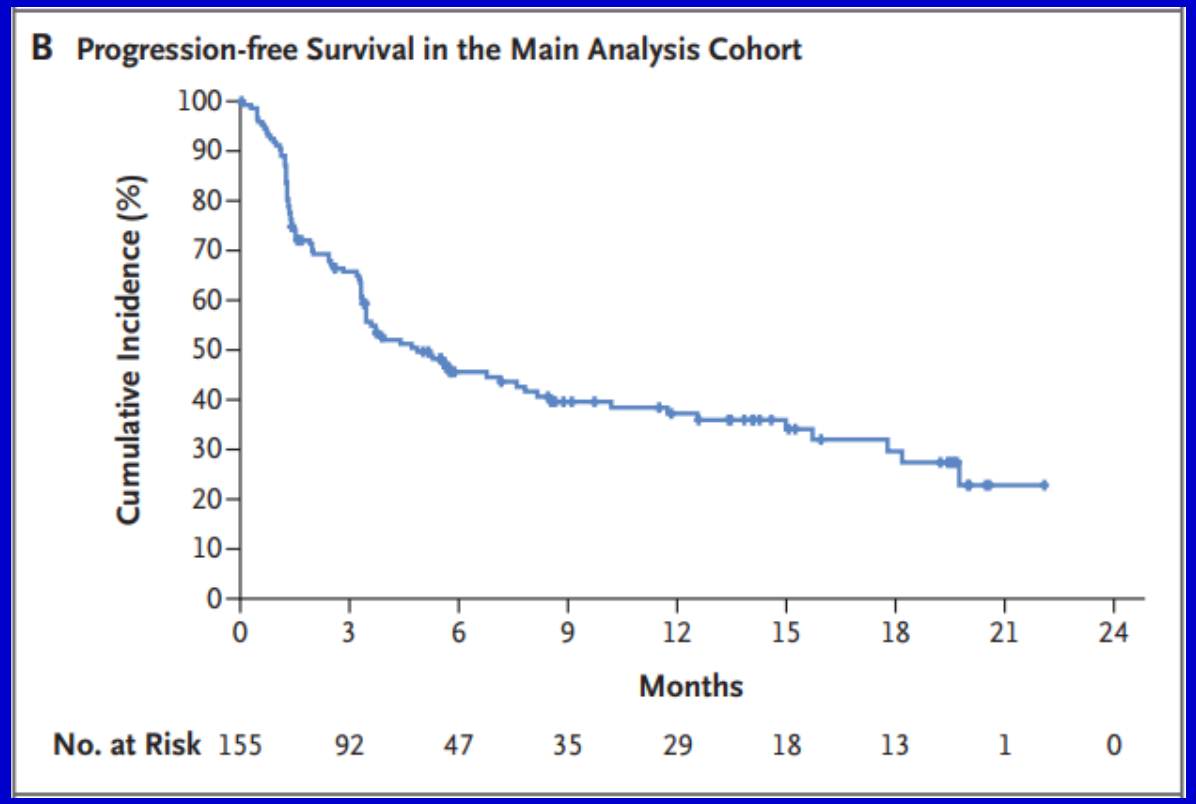
Autotransplant vs CAR-T Therapy For Relapsed DLBCL In PR

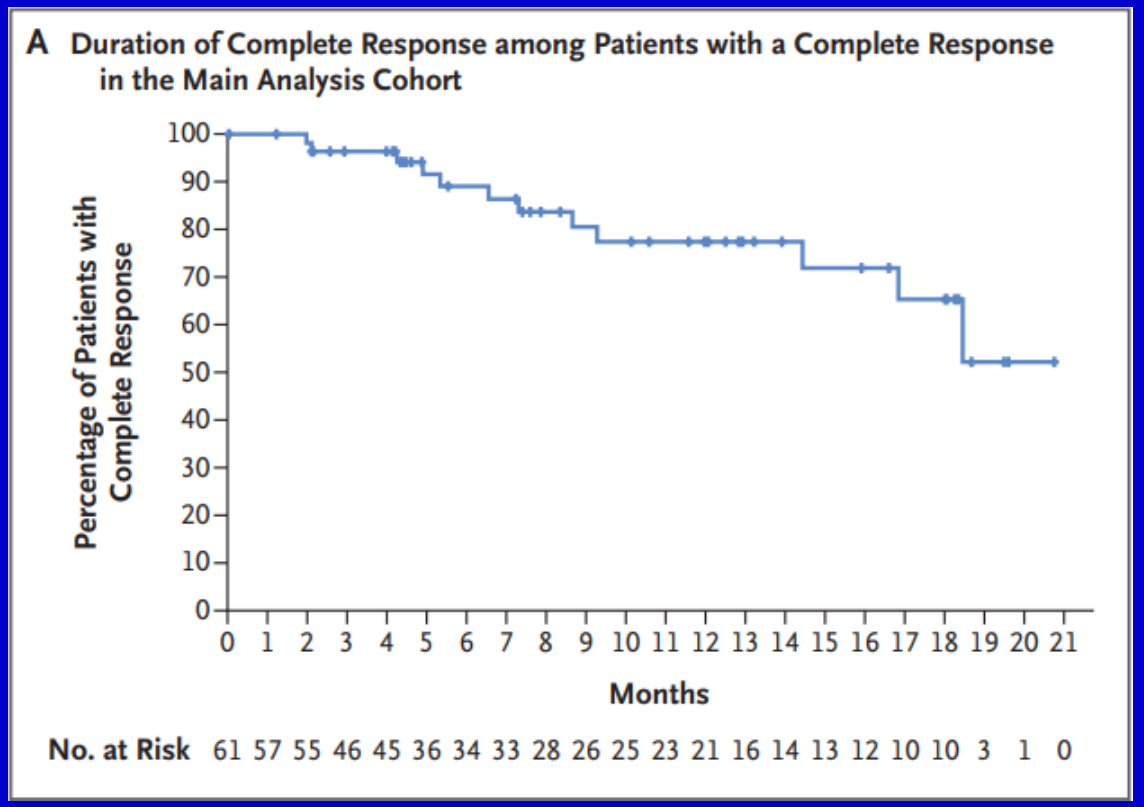




Blood 2022, 139: 1330-1339

The Bi-Specific Antibody Glofitamab In R/R DLBCL





NEJM 2022; 3878: 2220-2231

ViPOR Combination Targeted Therapy To Cure Relapsed DLBCL

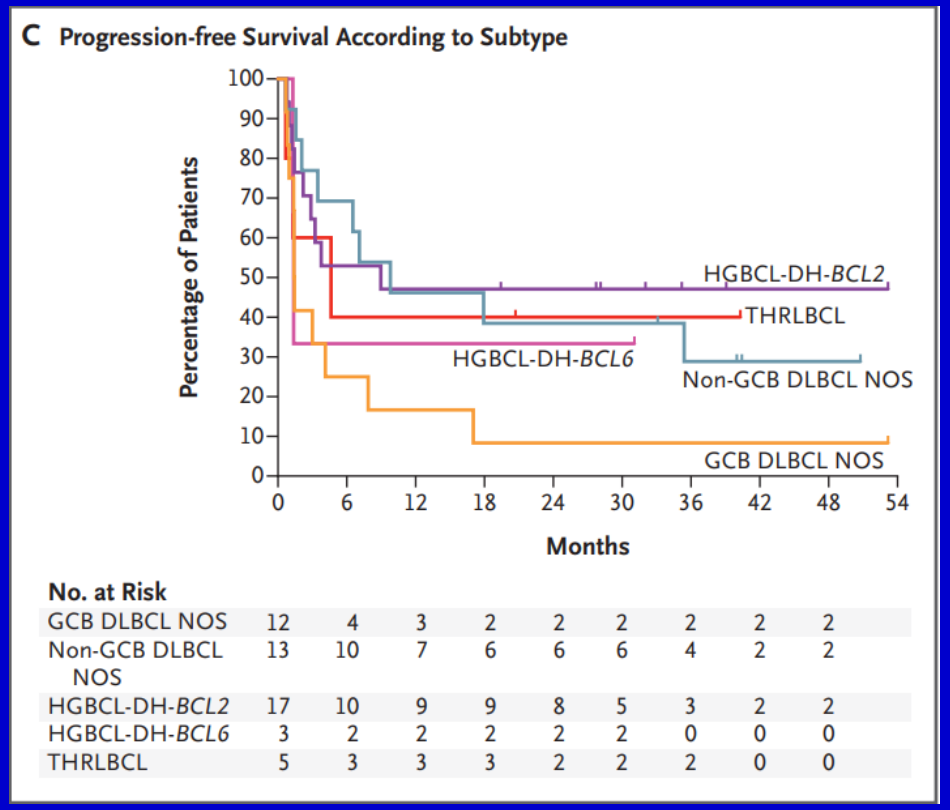
(venetoclax, ibrutinib, prednisone, obinutuzumab,lenalidomide)

CR by Subgroup

GCB-NOS– 0%

nonGCB – 62%

HG-DH – 53%



NEJM 2024;390:2143-2155

Will ctDNA Replace PET Scans For Treatment Response Assessment In DLBCL?

Test	Sensitivity
CLONO-seq	~10^{-4}
CAPP-seq	~10^{-5}
Phase-seq	~10^{-6}

Using ctDNA To:

1) Predict prognosis before therapy

2) Predict outcome after 1 or 2 treatment cycles

3) EOT testing to identify cured patients

4) Monitor for relapse

Treatment Outcome By EOT ctDNA Using Phase-seq

	2 year PFS (Roschewski, et al.)	2 year OS (Sworder, et al.)
EOT PET/CT:		
CR	90%	86%
noCR	66%	50%
EOT ctDNA:		
Undetectable	98%	94%
Detectable	33%	37%
EOT PET/CT positive:		
ctDNA undetectable	100%	
ctDNA detectable	0%	

Diffuse Large B-Cell Lymphoma

ELSEVIER

The Lancet

Volume 305, Issue 7901, 1 February 1975, Pages 248-250

ADVANCED DIFFUSE HISTIOCYTIC LYMPHOMA, A POTENTIALLY CURABLE DISEASE: RESULTS WITH COMBINATION CHEMOTHERAPY

VincentT. Devita JR., GeorgeP. Canellos, Bruce Chabner, Philip Schein [1], SusanP. Hubbard, RobertC. Young