Aggressive B-Cell Non-Hodgkin Lymphoma

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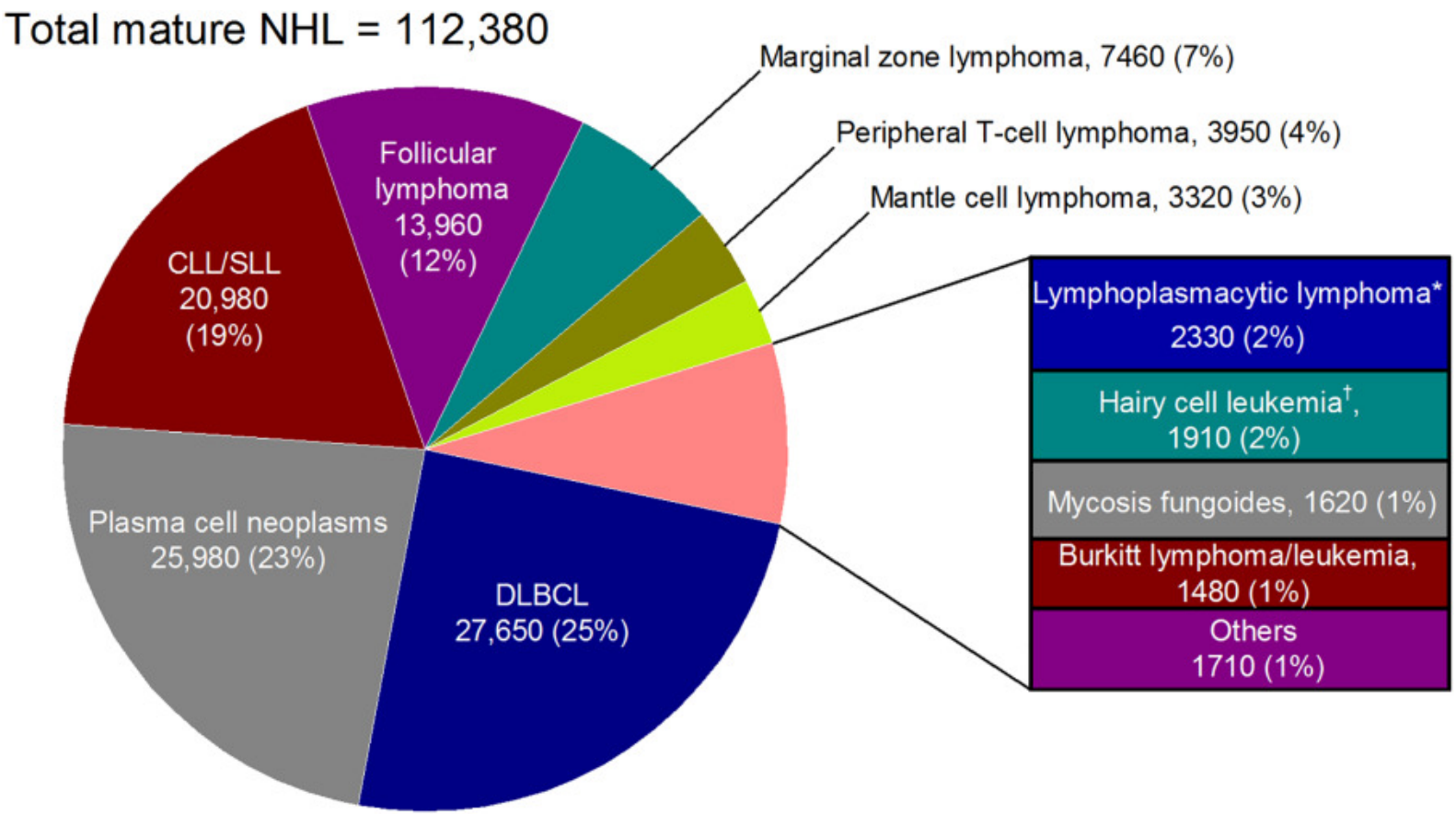
Topics

- Epidemiology, classification
- Clinical trials for DLBCL – design, endpoints, and lessons
- Diffuse Large B-Cell Lymphoma (DLBCL) and related entities
    - Limited stage
    - Advanced stage
    - Relapsed /refractory
  - Primary Mediastinal Large B-Cell Lymphoma (PMBCL)
  - High-Grade B-Cell Lymphoma (HGBCL) with MYC and BCL2 and/or BCL6 rearrangements = double hit
- Burkitt Lymphoma
- Mantle Cell Lymphoma

2016 NHL Incidence



DLBCL incidence: 7 per 100k

Table 1 WHO classification of mature large B-cell lymphoid neoplasms

Diffuse large B-cell lymphoma (DLBCL), NOS
– Germinal centre B-cell type[a]
– Activated B-cell type[a]
T-cell/histiocyte-rich large B-cell lymphoma
Primary DLBCL of the central nervous system (CNS)
EBV+ DLBCL, NOS[a]
EBV+ mucocutaneous ulcer[a]
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal/thymic large B-cell lymphoma
Intravascular large B-cell lymphoma
ALK+ large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
HHV8+ DLBCL, NOS[a]
Burkitt lymphoma
Burkitt-like lymphoma with 11q aberration[a]
High grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements[a]
High grade B-cell lymphoma, NOS[a]
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma
The provisional entities are listed in italics [a]Changes from the 2008 classification *NOS* not otherwise specified, *EBV* Epstein Barr virus

80% of DLBCL are "NOS"

Etiology

Increased Risk	Family history; genetic susceptibility loci (TNF/LTA; 6p25.3; 6p21.33; 2p23.3; 8q24-21) Viruses: EBV, HIV, HHV8, hepatitis B, hepatitis C Solid-organ transplantation B-cell–activating autoimmune disorders (SLE, Sjögren's syndrome, celiac disease) Immunodeficiency Increased body-mass index (in young adults) Agricultural pesticides Ionizing radiation
Decreased Risk	Allergies (including hay fever) Blood transfusion Alcohol consumption Vegetable consumption Sun exposure
No Significant Effect	Type 2 diabetes

Sehn NEJM 2021

Case 1- Limited Stage DLBCL

Case 1

- **40 yo M with history Hx Crohn's, on therapy**
    - Ustekinumab: IL-12 and IL-23 blocking MoAb
- PCP noticed a R axillary node, measuring 5 cm
- Core needle biopsy

DLBCL Pathology - Key testing

Question 1- Adequacy of sample for Dx? Morphology, clonality, other

Assay	Role	Notes
Flow	Clonality, cell surface markers	DLBCL can be flow negative
IHC	Biologic risk stratification	Hans criteria for Cell of Origin (COO) Double Expression of MYC >40% **and** BCL2 >50%
FISH	At Dx- MYC breakapart, then BCL2/6 if present	("Double hit" is now high-grade B-cell lymphoma)

Case 1 Biopsy: Pathologic findings

Flow cytometry: negative for abnormal B/T cell population

Morphology: Diffuse sheets of large atypical cells, background of small lymphocytes, histiocytes, rare plasma cells

IHC

- CD10+ (GCB subtype)
- MYC 5%
- Ki67 70%

FISH: BCL6 rearrangement (only)

Dx: Diffuse large B-cell lymphoma, NOS
GCB subtype

Case 1: Pretreatment evalution

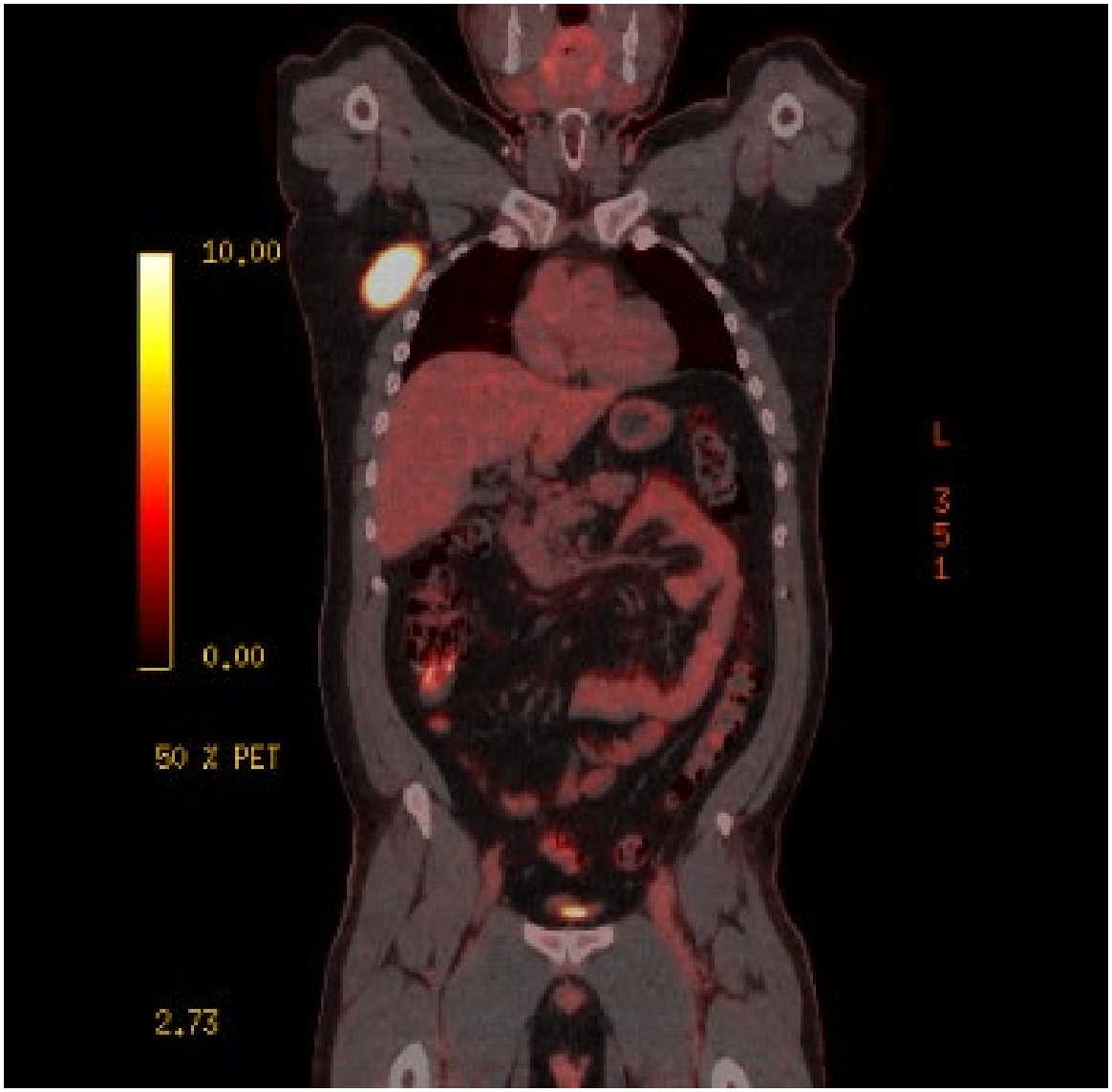
- Echo/MUGA (especially given HTN)
- Fertility evaluation and preference
- Laboratory workup (Hep B, HIV, LDH)
- Imaging and other staging
- Venous access

Case 1: PET-CT Staging

IMPRESSION:

1. Markedly FDG avid right axillary lymphadenopathy. Deauville 5.
2. No FDG PET evidence to suggest additional nodal nor extranodal involvement.

Size- 5.2 x 4.6 cm



PET-CT Staging

- Detects *extranodal* sites better than CT
  - GI, head+neck, skin+soft tissue

- Can identify small but FDG avid nodes/spleen involvement

  - Stage migration and IPI shift

Case 1: Is BM Bx necessary in the PET era?

Some guidelines still say yes, but:

- BM Bx utilization in staging is decreasing in practice*
- PET-CT sensitivity high (meta-analysis: 88%)**
- Impact on Px debatable (e.g. marrow finds low-grade NHL)

Consider for:

- Key treatment decisions (stage/therapy change)
- Baseline cytopenias
- Uncertain PET result

*Bischin PMID 31993568
**Adams E J Nuc Med 2014

Limited Stage DLBCL: Short-course options

Regimen	Tested in	Downsides	Consider In (presenter opinion)
RCHOP x 3 + IFRT (Vs 8 CHOP) Miller NEJM 1998, Persky JCO 2008, Stephens JCO 2016	***Int-High grade NHL***	RT acute/late effects (40-46 Gy)	IPI risks present; elderly/frail with optimal XRT field
Options without XRT			
RCHOP-14 x 4-6 (vs with XRT) Lamy Blood 2018	***Lower risk DLBCL***; PET-CR after 4	q14 day RCHOP needs GCSF	**No IPI risks** + desire a brief treatment course
RCHOP-21 x 4 + 2 R (vs 6 RCHOP) Poeschel Lancet 2019	***Lowest risk DLBCL*** (stage 2 OK but no IPI risks)	May undertreat stage II? Extra 2 R needed?	**Lowest risk pts**/no IPI risks. Least toxic.
R-CHOP-21 x 4 (RCHOP x 3→ PET; **If neg**, 1 more) Persky SWOG S1001. Phase 2.	***All IPI / nonbulky***	Relies on PET; ?worse for non-GCB and DEL (low N)	**PET-3 negative** → stop after 4 RCHOP. Best in low biologic risk pts.

Case 1 follow-up: Treatment Course, and EOT PET

RCHOP x 4

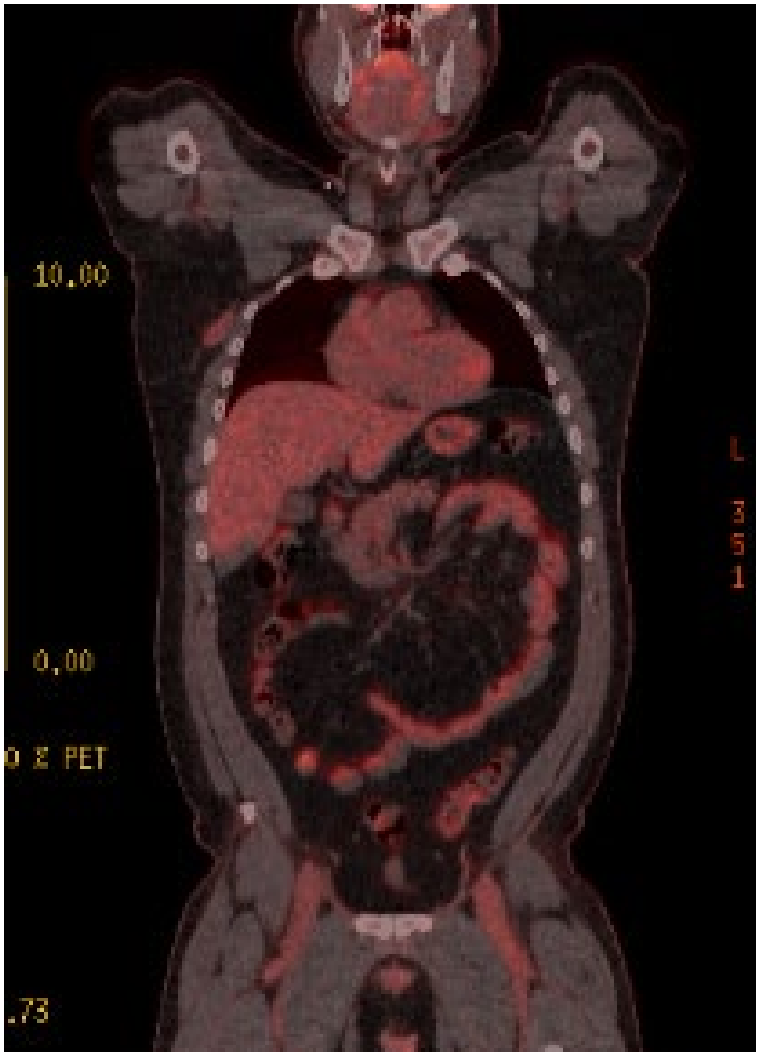
- prednisone side effects, mild sensory PN
- Mild neutropenia, anemia Hgb 12

End of Tx PET:

Deaville 3 CR (uptake > mediastinum but ≤ liver)

- remnant 2 cm node

Follow-up chest CT @ 3 mo.- stable



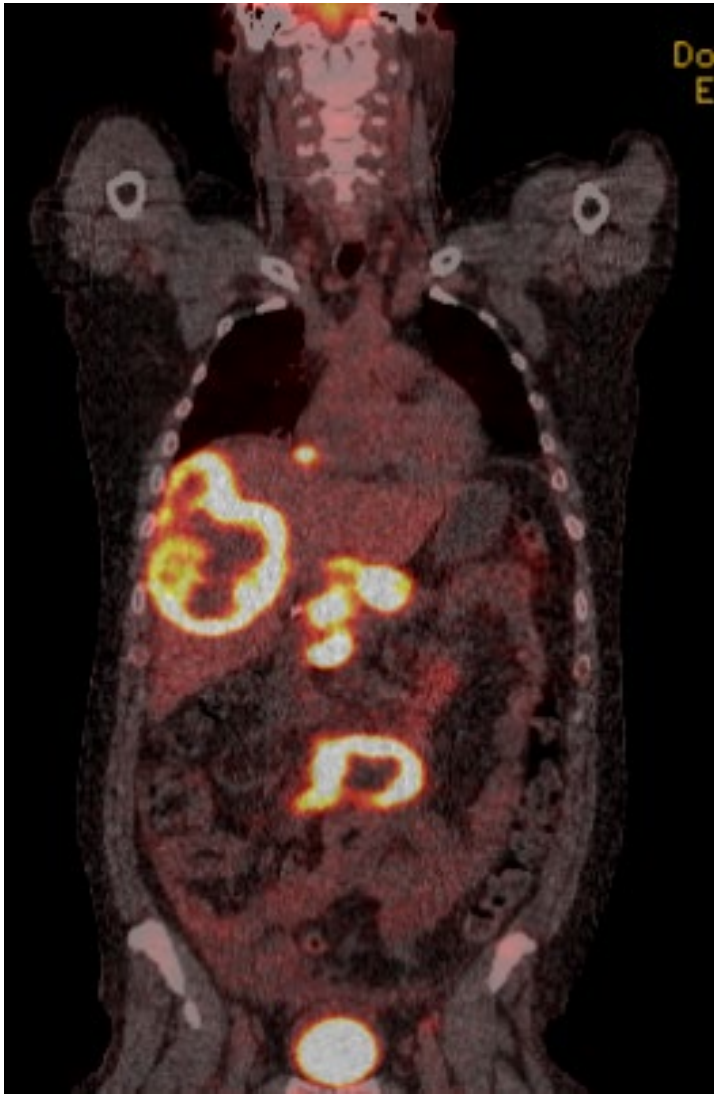
Case 2: Advanced stage DLBCL

52 M with sleep apnea, otherwise healthy

- 30 lb weight loss
- Acute right upper quadrant pain
- ED: D-dimer elevated, CT-PE negative for pulmonary embolism, but noted a mass in the liver

Case 2: PET-CT

- Large mesenteric mass/surrounding LAD, periportal LAD
- 3 large liver lesions
- Bone uptake - manubrium, sternum, and left iliac bone
- Ascites, pleural effusions



Case 2: Biopsy and labs

Liver core needle biopsy

- CD10 - /non-GCB DLBCL
- No MYC translocation
- No MYC IHC tested (depleted tissue)

Labs

Alk phos 141, AST 41

LDH 813

CBC normal

IPI 3

IPI and NCCN – IPI

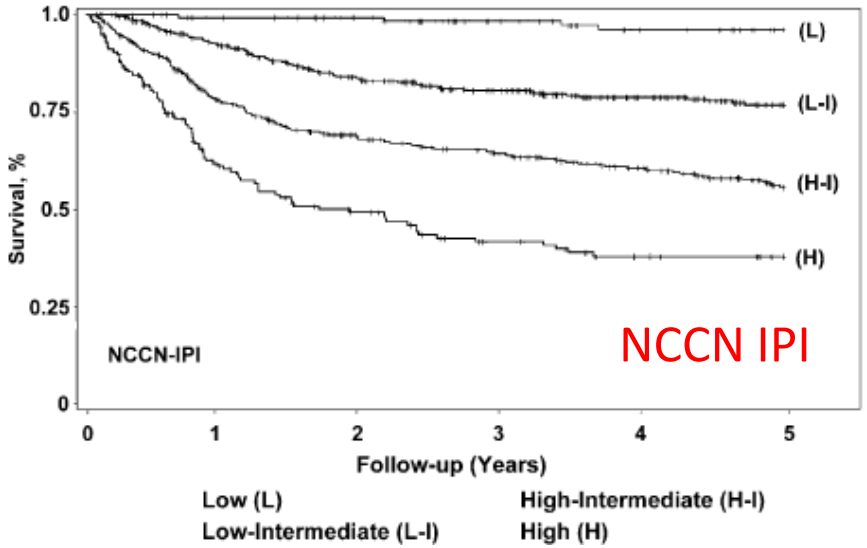
Table 3. The NCCN-IPI

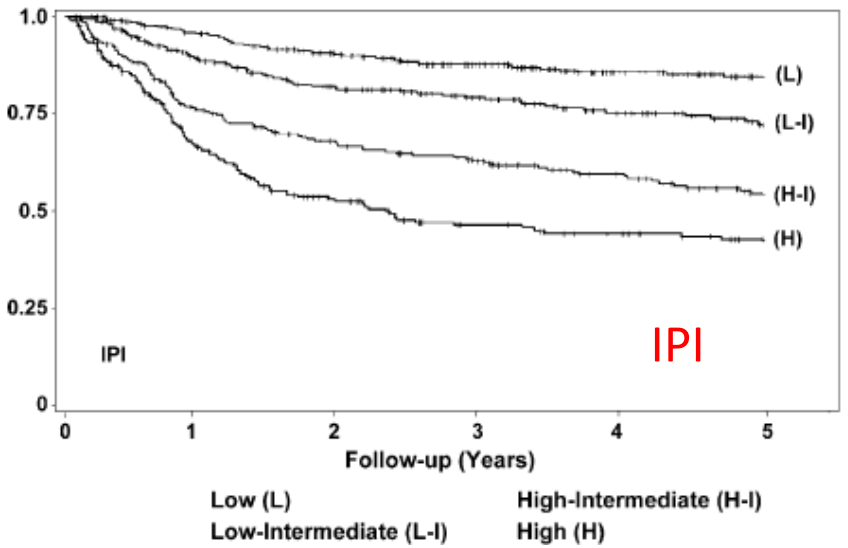
NCCN-IPI	Score
Age, y	
>40 to ≤60	1
>60 to ≤75	2
>75	3
LDH, normalized	
>1 to ≤3	1
>3	2
Ann Arbor stage III-IV	1
Extranodal disease*	1
Performance status ≥2	1

*Disease in bone marrow, CNS, liver/GI tract, or lung.

Benefits to NCCN IPI

- DLBCL pt specific
- High LDH elevations represented
- Slightly wider range/better discrimination of groups





Zhou *Blood* 2014

DLBCL and Cell of origin

- **Germinal Center (GCB)** most common
  - Germinal center genes upregulated (*BCL6* and *EZH2)*

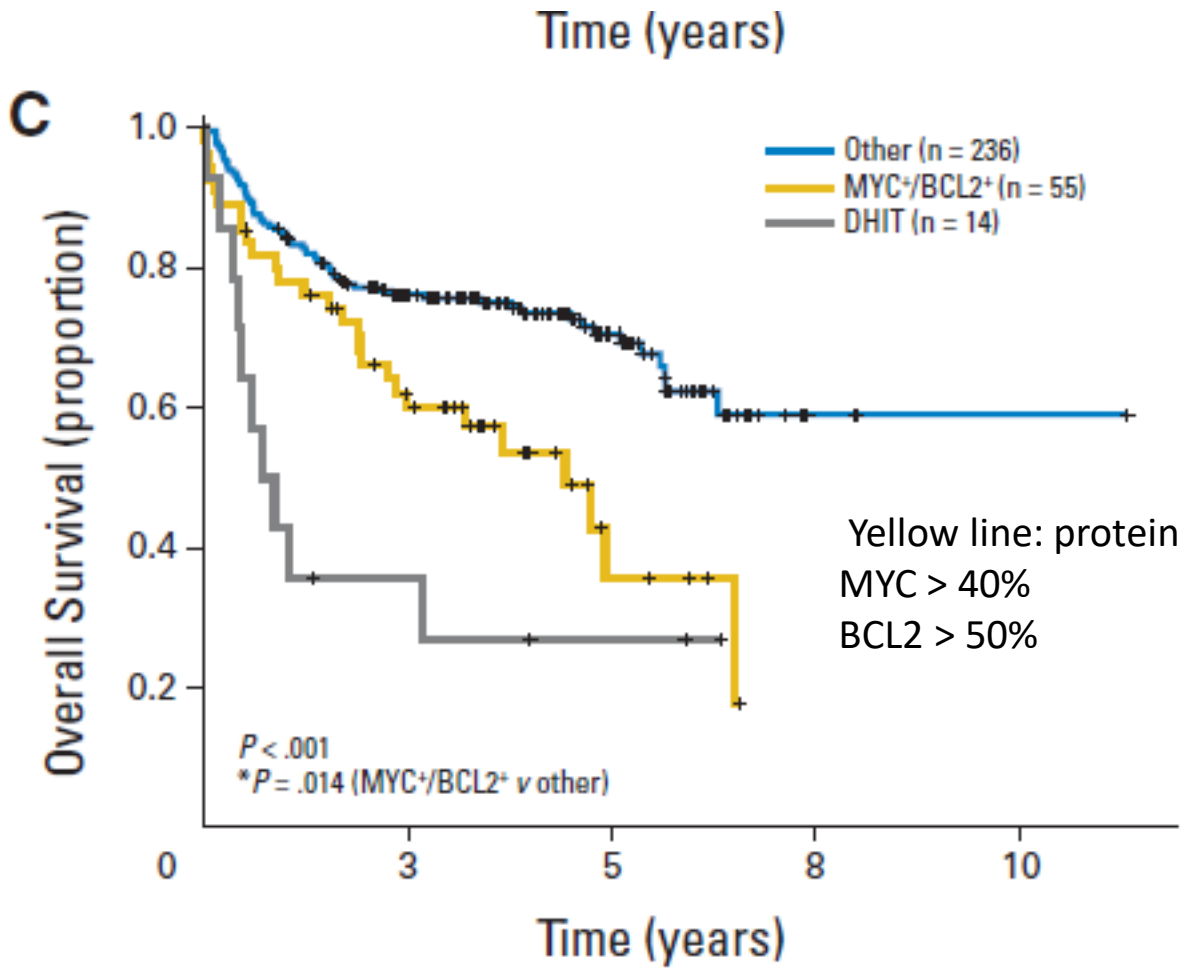
- **Activated B-cell Subtype (ABC):** <1/3 of cares
  - BCR signaling/ NFkB activation

Immunohistochemistry: 70-80% concordance with GEP
  - "Non-GCB" includes ABC and unclassifiable subtypes

Cell of origin is not yet proven to guide 1L treatment selection

MYC dysregulation: Double hit vs Protein Expression

Double expressor (protein) ≈ 30%
Double hit ≈ 10 %



Yellow line: protein overexpression
MYC > 40%
BCL2 > 50%

Johnson (BCCA) JCO 2012

DLBCL: How urgent is treatment?

Acute presentations → need urgent workup (partial list)

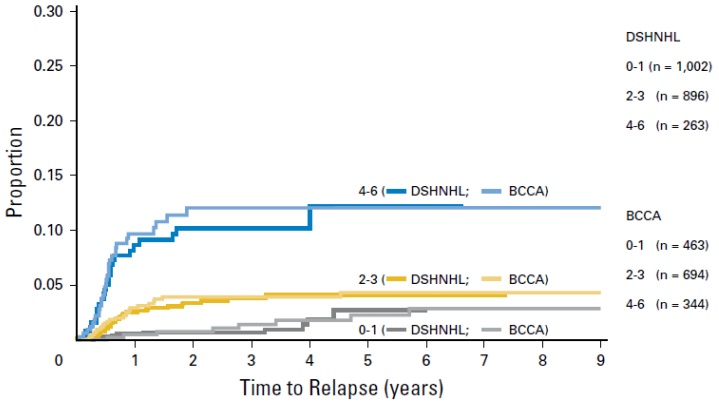
- Poor PS, disease-related or unclear
- Very high (3x or greater) LDH elevations
- Neurologic sxs/**compressive** effects
- Metabolic- lactic acidosis, hyperCa
- **TLS-** allopurinol (at least), repeat labs next day as outpt

Assessment of CNS Relapse Risk

- CNS IPI*:
  - Same as IPI plus kidney or adrenal involvement
  - Low (0-1) or intermediate (2-3) risk: defer LP
    - Risk of CNS relapse < 5%
  - **High (4-6) risk: evaluate further**
    - **Risk of CNS relapse > 10%**

Other risks

- HIV-associated
- Testicular DLBCL
- Breast DLBCL

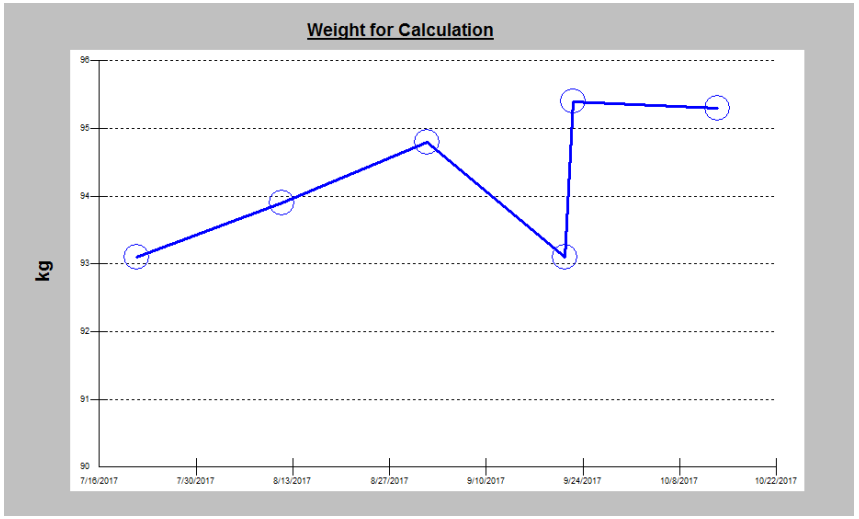


*Schmitz, et al. *J Clin Oncol*. 2016;34:3150-3156.
**Klanova Bood 2019

Case 2: Treatment Course, and EOT PET

Pembro-RCHOP x 6 (UW/FHCRC clinical trial)

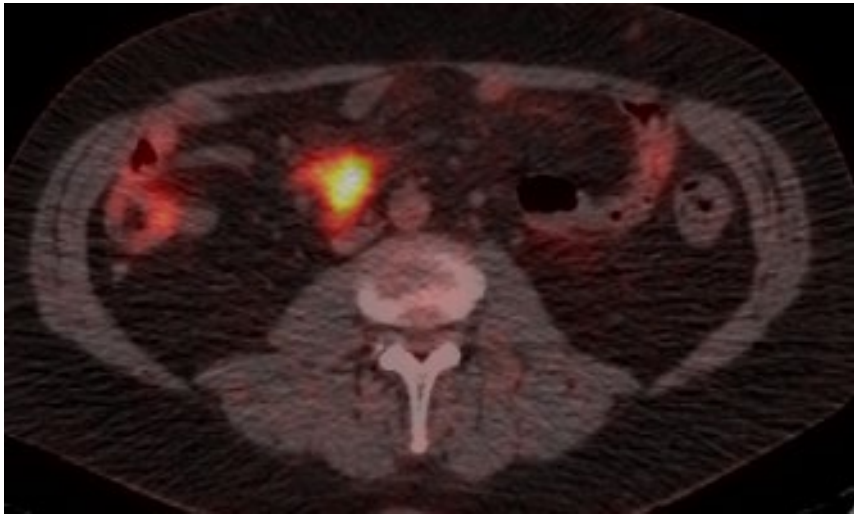
- LDH down, weight up
- Neuropathy



End of treatment PET

1. New hypermetabolic mesenteric mass

2. Focal increased metabolic activity in the sigmoid colon ? lymphomatous involvement.



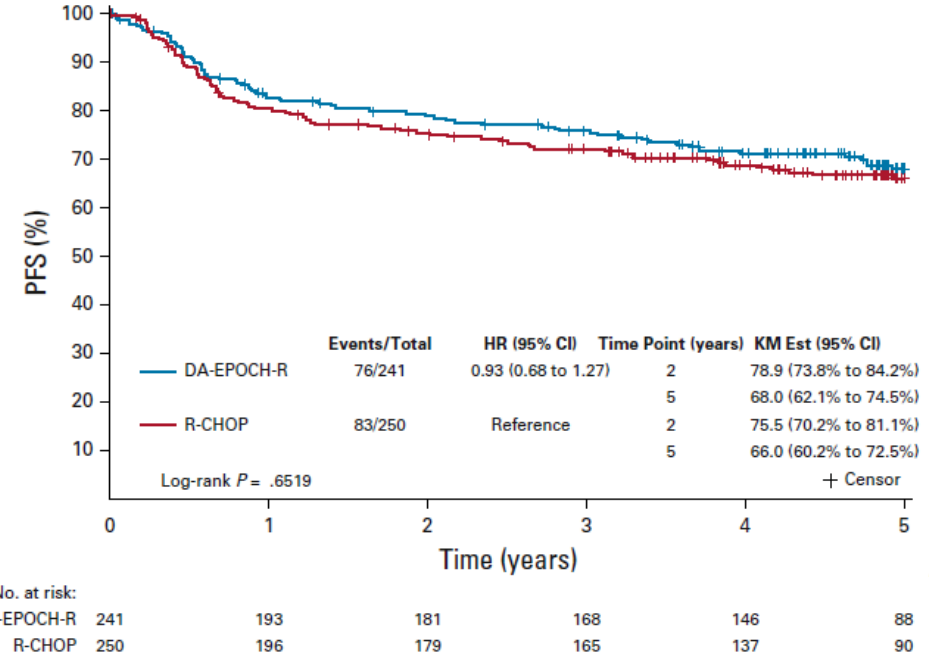
(other FDG-avid sites resolved, including liver)

Deauville score 5

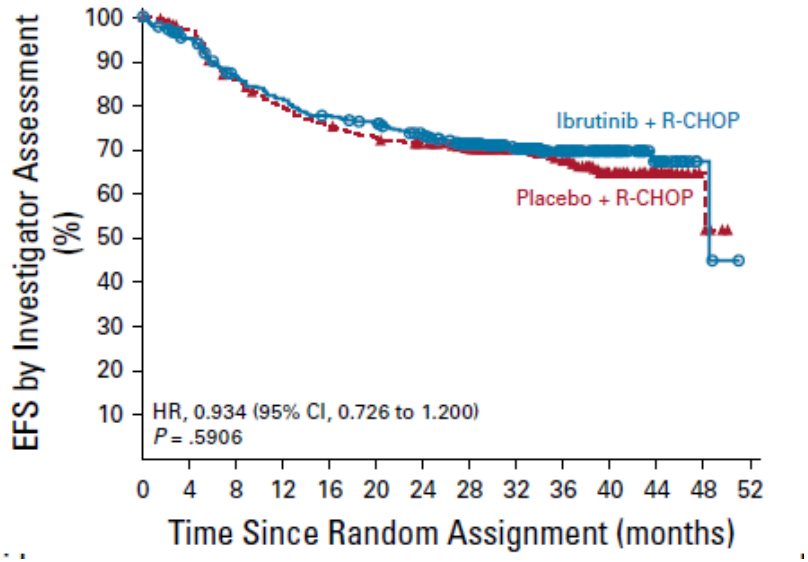
BIOPSY: MESENTERIC FAT NECROSIS

Remains in CR 4 years later

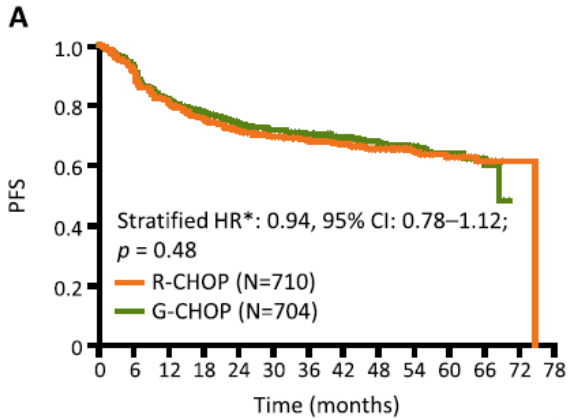
Randomized trials vs RCHOP in DLBCL- “typical” outcomes



DA-EPOCH+R vs RCHOP
Bartlett JCO 2019

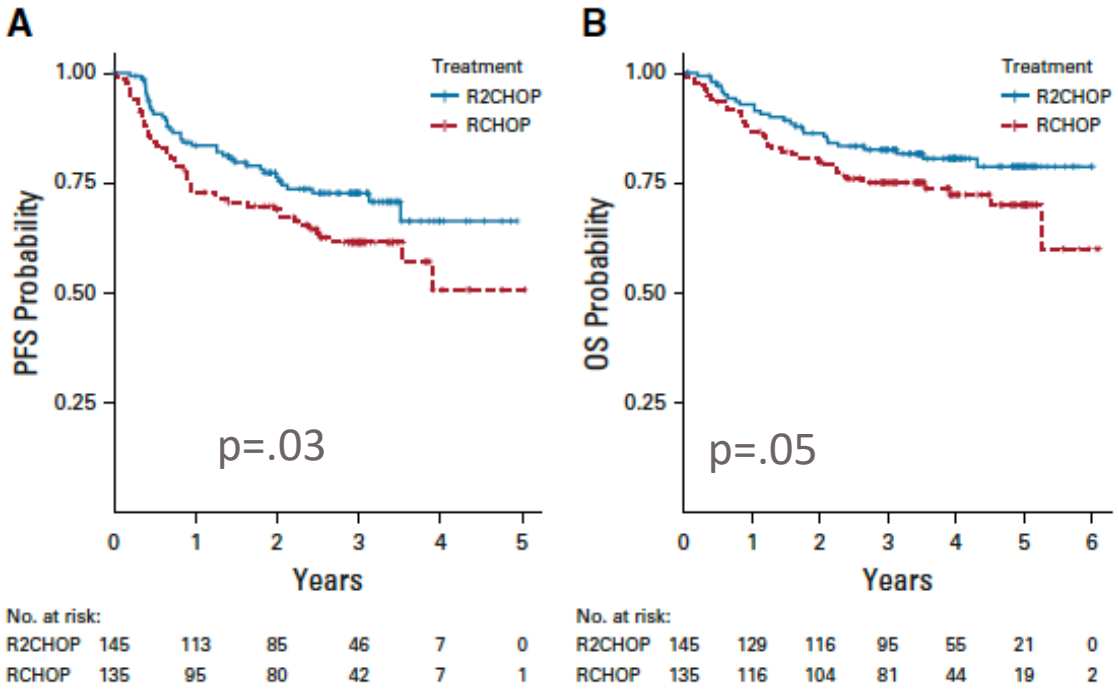


RCHOP ibrutinib vs RCHOP
Younes JCO 2019



GCHOP vS RCHOP
Sehn J Hem Onc 2020

A positive trial? E1412: Len+ RCHOP vs RCHOP



- Wide CI's/small N
  - One-sided P: "signal seeking study"
- Combo arm more toxic: diarrhea, anemia, F+N, low plts
- Randomized phase 3 in ABC DLBCL (*same author + JCO issue*)- negative

Nowakowski JCO 2021

Why can't RCHOP be beat?

1. Highest-risk patients are often *excluded* from trials:
   - ECOG >1 or 2 exclusionary; part of IPI
   - Prephase treatment not allowed
   - Hospitalized patients/those needing urgent RCHOP can't accrue

→ *Effect size assumptions don't apply to the actual population enrolled*

2. Current biologic risk stratification hasn't "panned out" and/or subsets get too small

Current and future RCHOP-based trials

Randomized phase 3

- RCH-P with polatuzumab (Polarix): Fully accrued, data soon
- RCHOP + Enzastaurin (ENGINE): Fully accrued, maturing
- RCHOP+ tafasitamab /lenalidomide: accruing
- RCHOP + acalabrutinib for non-GCB: accruing
- RCHOP + epcoritamab (CD20/3 bispecific): starting this year

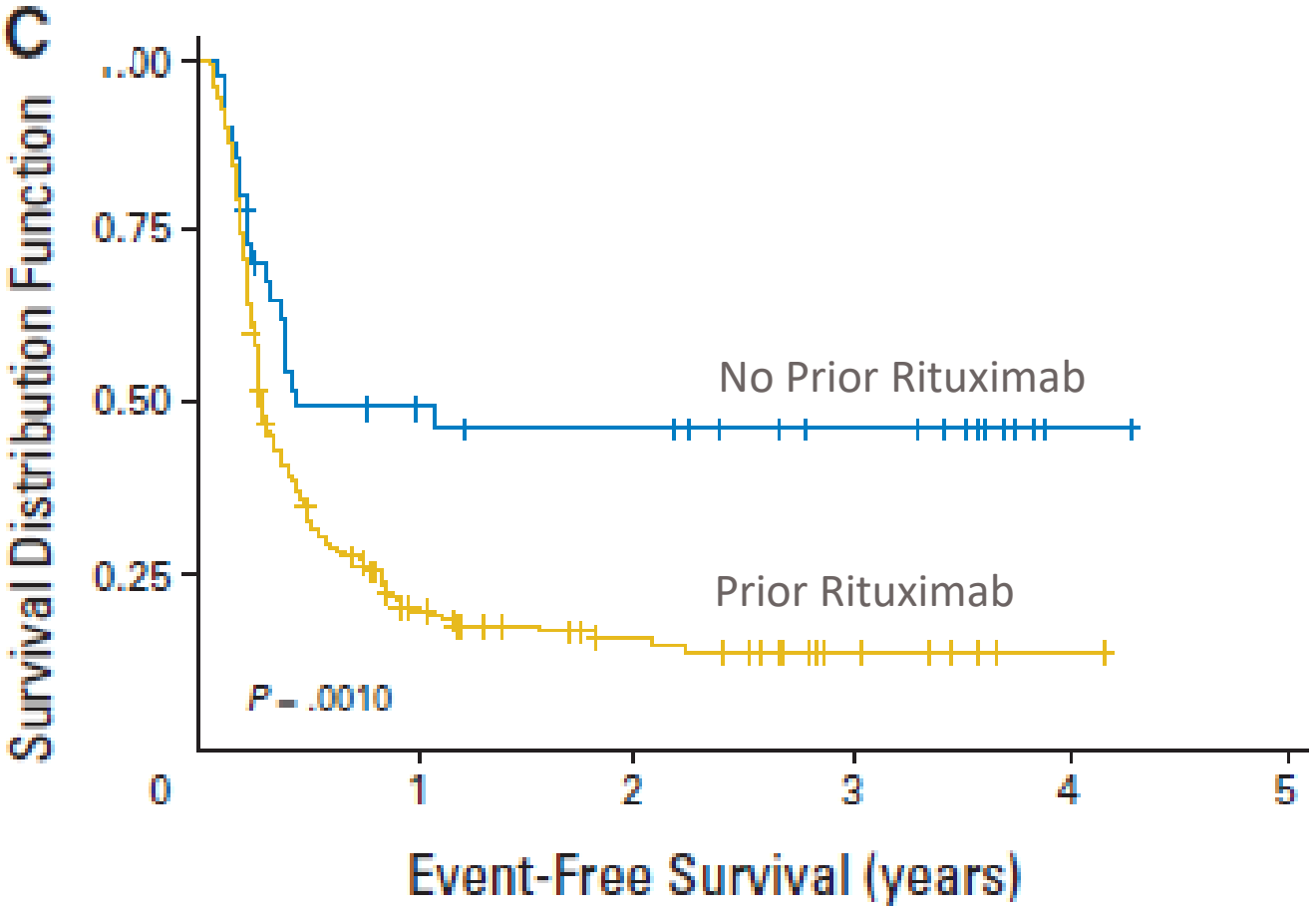
Nonrandomized trials: Checkpoint blockade+ RCHOP –several ongoing trials

"Window" trials: prephase treatment e.g. PD-1 inhibitor or targeted Tx→ PET→ RCHOP

Case 3- Relapsed/Refractory DLBCL

- 69 yo stage IV GCB DLBCL, non-DEL
- RCHOP x 6→ PR, observed
- Within 8 months of RCHOP, PET progression, Bx→ DLBCL

Poor salvage outcomes for early relapse post-RCHOP



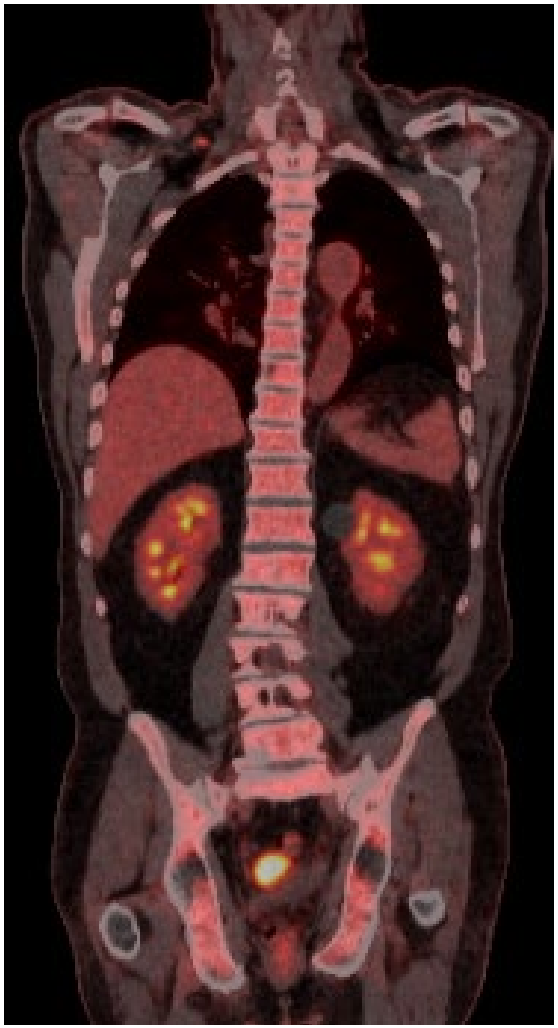
Gisselbrecht C, *et al. J Clin Oncol.* 2010;28:4184–4190

Case 3- Relapsed/Refractory DLBCL

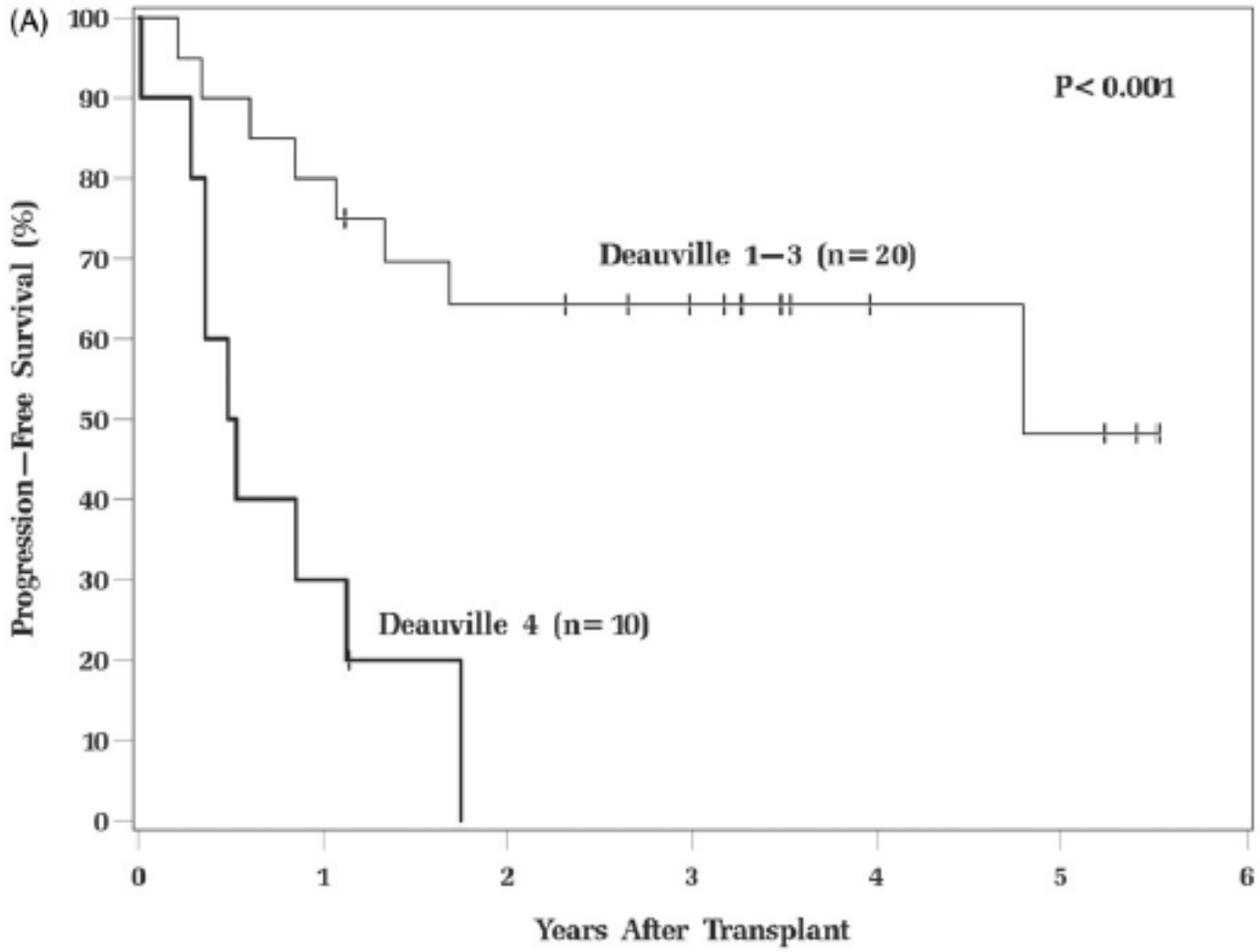
- Fit patient, early relapse: **RICE x 3**

- PET-CT:

Interval significant improvement compared to 2/8/2018, still with residual metabolic small right supraclavicular lymph node. No evidence of new lesion. Deauville score 4.

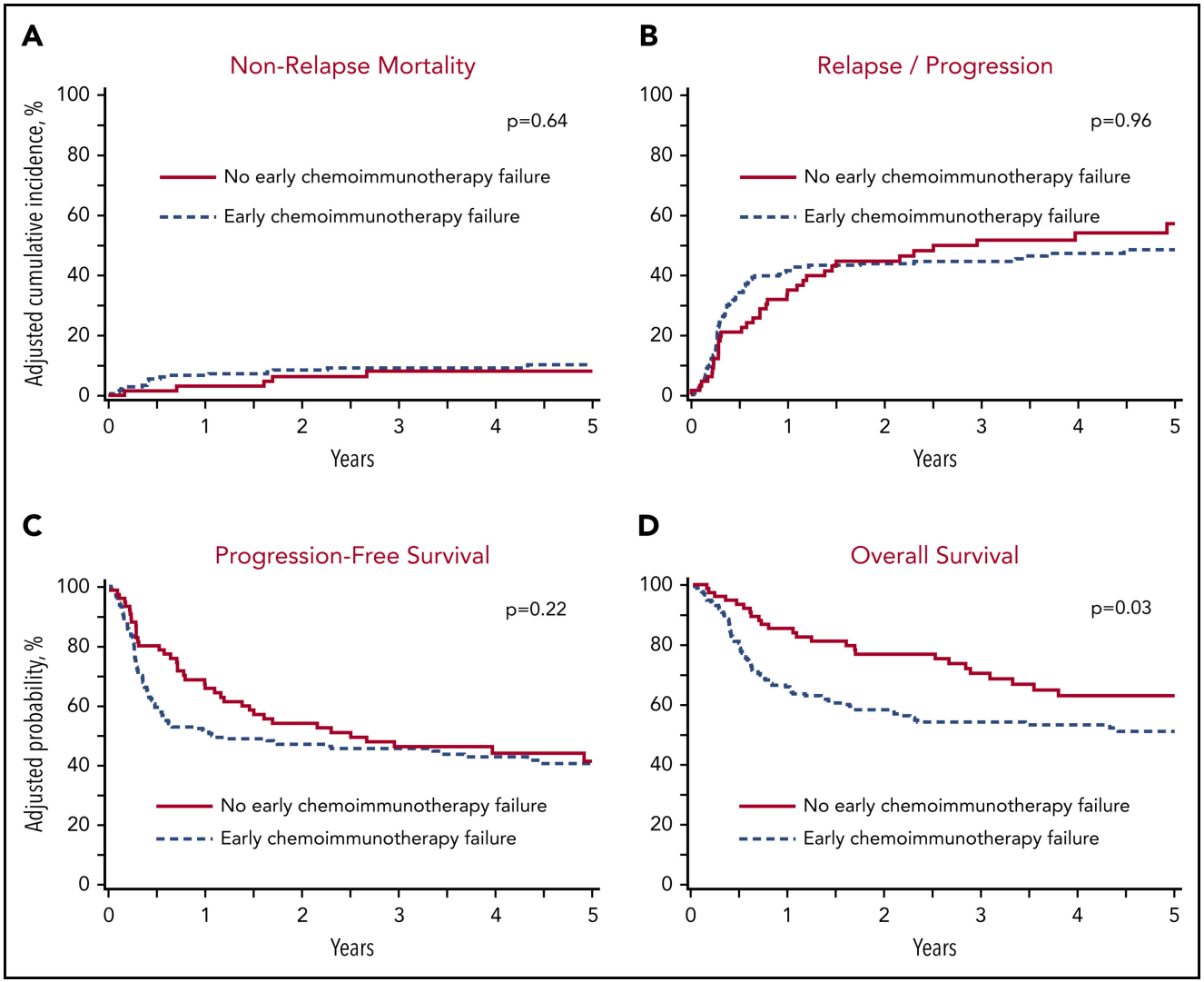


Pre-ASCT PET and outcomes with transplant: PFS



A good PR vs a bad PR…

CIBMTR: Patients transplanted with PET PR



Shah et al, Blood 2021

Case 3- Relapsed/Refractory DLBCL

- BEAM Auto
- Radiation (R supraclavicular field) to 30 Gy
- 5 months later- growing axillary node, DLBCL
- CD19- directed Car T-cell therapy (on trial)

Priorities in Treating Relapsed DLBCL

1. Recognize high risk pts

   - Relapse < 1 yr after start of RCHOP, high secondary IPI, MYC rearrangements

2. Establish treatment goal (curative vs palliative)
   - **Curative** "Plan A" remains ASCT*, with *quick reflex* to CAR T-cell therapy
     - Biopsy early /often (antigen expression, certainty of plan)
   - **Palliative** goal- several approvals since 2020

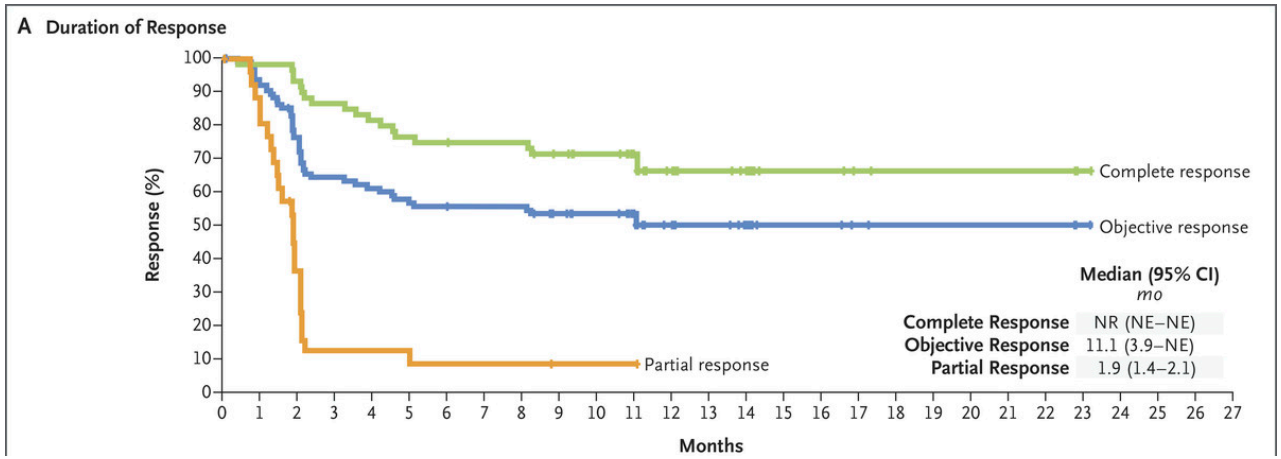
*May change soon

CD19 Car T-cell therapies

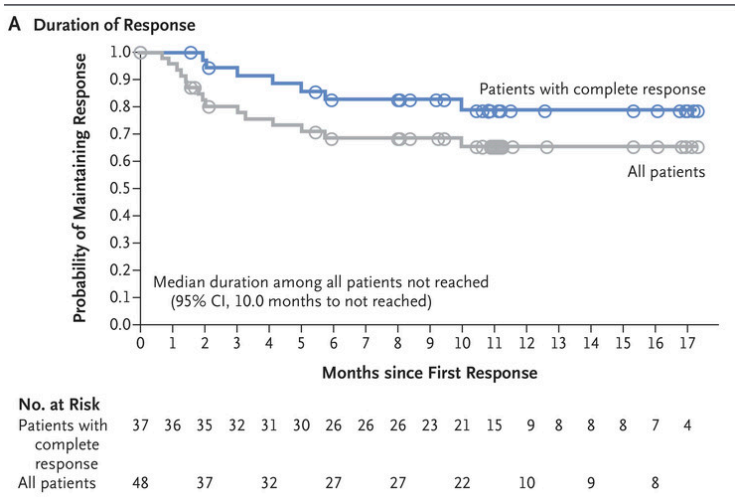
Approved for relapsed/ref DLBCL after ≥2 Tx:

- Axicabtagene ciloleucel (Yescarta): Kite, Oct 2017
- Tisagenlecleucel (Kymriah): Novartis, May 2018
- Lisocabtagene maraleucel (Breyanzi) BMS/Juno, Feb 2021

CD19 CAR T: Complete responses are durable



Axi-cel



Tisagenlecleucel

Axi-cel: Neelapu SS et al. N Engl J Med 2017;377:2531-2544.
Tisagen: SJ Schuster et al. N Engl J Med 2019;380:45-56.

Ongoing Phase III CAR vs. Auto Trials

ZUMA-7

- Pts randomized to axi-cel (no bridging allowed) vs. platinum salvage, and responding patients receive HDT + ASCT.
- Primary endpoint: EFS (n=350)

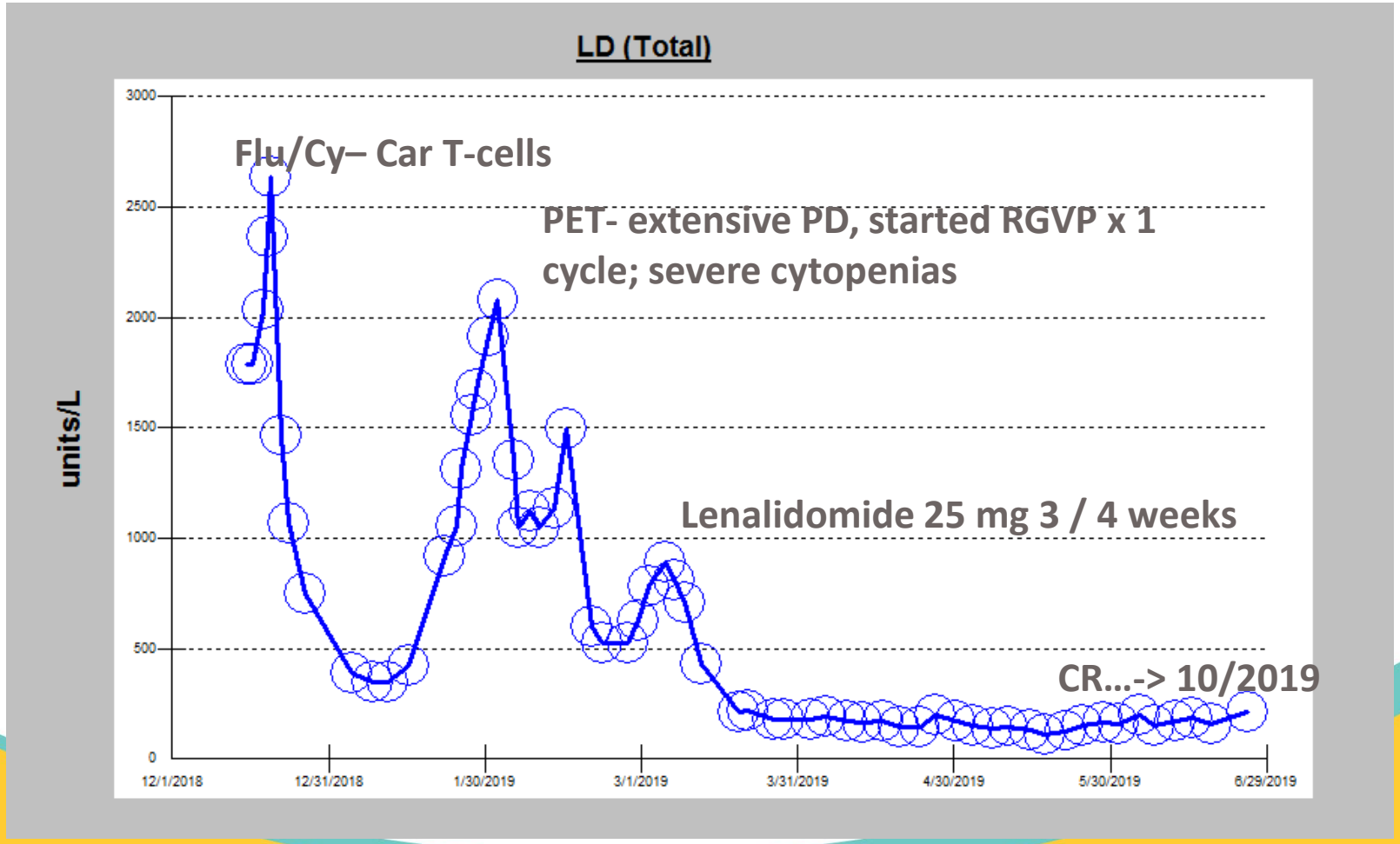
TRANSFORM

- Pts randomized to liso-cel (with optional bridging) vs. platinum salvage, and responding patients receive HDT + ASCT.
- Primary endpoint: EFS (n=182)

BELINDA

- Pts randomized to tisa-cel (with optional bridging) vs. platinum salvage x 2-3 cycles), and responding patients receive HDT + ASCT.
- Primary endpoint: EFS (n=318)

Case 3- R/R DLBCL, now with failure of CAR T-cells



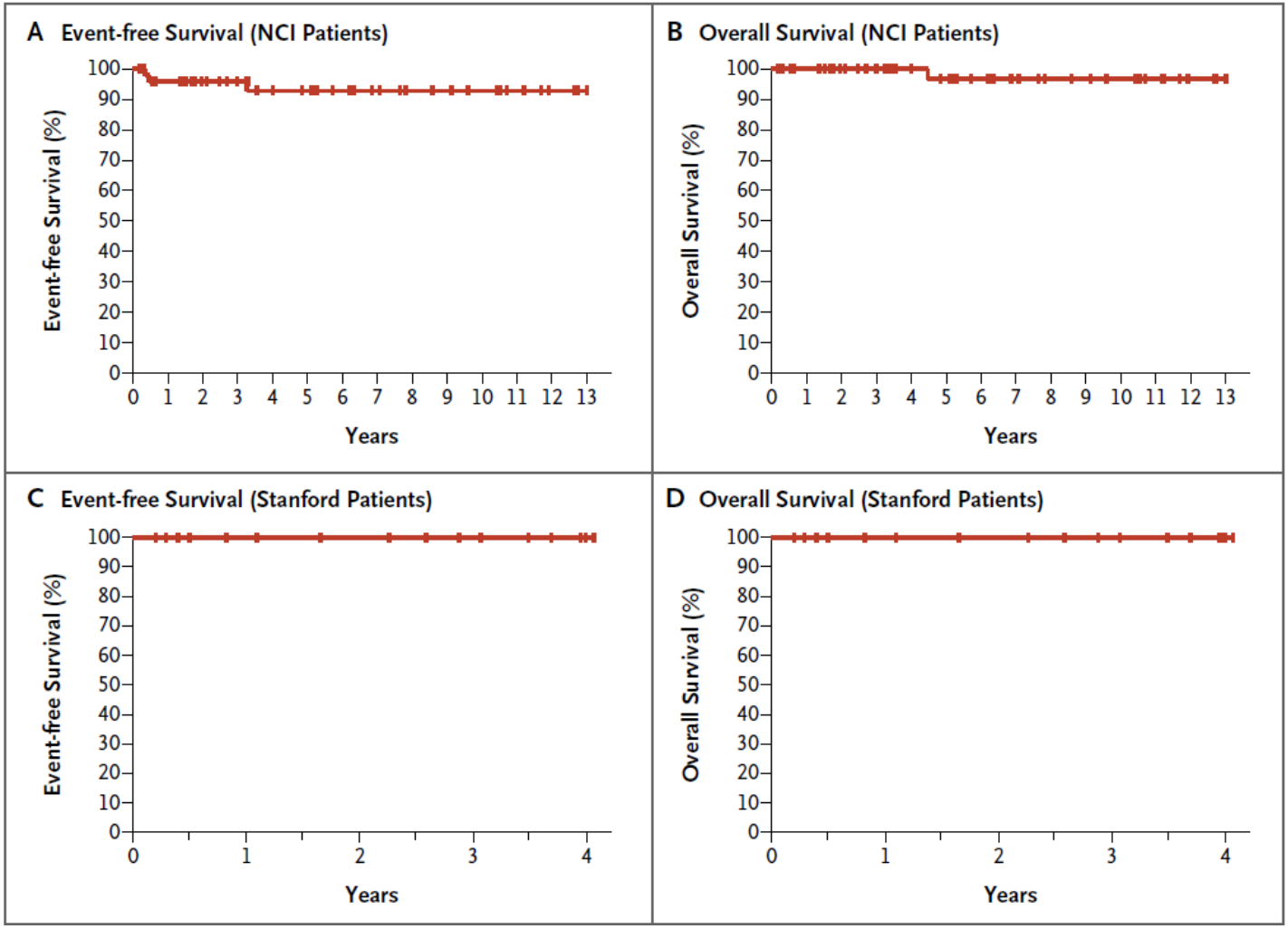
Recent Approvals in R/R DLBCL

Drug	Mechanism	Study population: relevance	Notes
Polatuzumab + BR Sehn JCO 2020	Chemo + CD79 ADC: MMAE payload	Most pt refractory to prior Tx	Infection problems, neuropathy PFS < 1yr, lower in post-marketing data.
Selinexor Kalakonda Lancet Haem 2020	Small molecule, targeting nuclear export	Excluded *recent* refractory pts	Nausea, ; low ORR and <3 mo PFS; restricted population
Tafasitamab + Lenalidomide Salles Lancet Onc 2020	CD19 MoAb + immunomodulator	50% had received only 1 prior line	Small trial, 43% CR rate, IO/non-chemo option.
Loncastuximab Tesirine 4/23/21 FDA approval, LOTIS-2	CD19 ADC: PBD payload	2 prior lines required + mostly refractory	48% ORR/24% CR. Cytopenias, GGT elevation, volume overload

DA-EPOCH-R for PMBCL: Without XRT

NCI:
N = 51
Prospective

Stanford:
N = 16
Retrospective



Dunleavy, *et al*. *New Engl J Med*. 2013;368:1408-1416.

R-CHOP for PMBCL: With or Without XRT

UNFOLDER: 2 x 2 design: RCHOP 14 vs RCHOP 21, RT vs none

- N=131 PMBCL

- RT vs **No RT** comparison (not powered)

PFS: 95% vs **90%** (p=.25)
OS: 98% vs **96% (p=0.64)**

- **No impact of dose density** (q14 vs q21) on EFS, PFS nor OS.

- **PET-guided therapy** (omit RT for negative EOT PET)- TBD (IELSG 37 trial)

"Unfolder" trial analysis. Held EHA 2021, Abstract S230

High-Grade B-Cell Lymphoma

- **Represent <10%** of aggressive B-cell lymphomas

2 subcategories:

- ***With MYC* and *BCL2* and/or *BCL6* rearrangements**
  - Gene rearrangements by FISH/cytogenetics
  - Copy-number alterations/protein expression don't count
- **Not otherwise specified**
  - Similar to entity previously called BCLU or Burkitt-like but lacking translocations

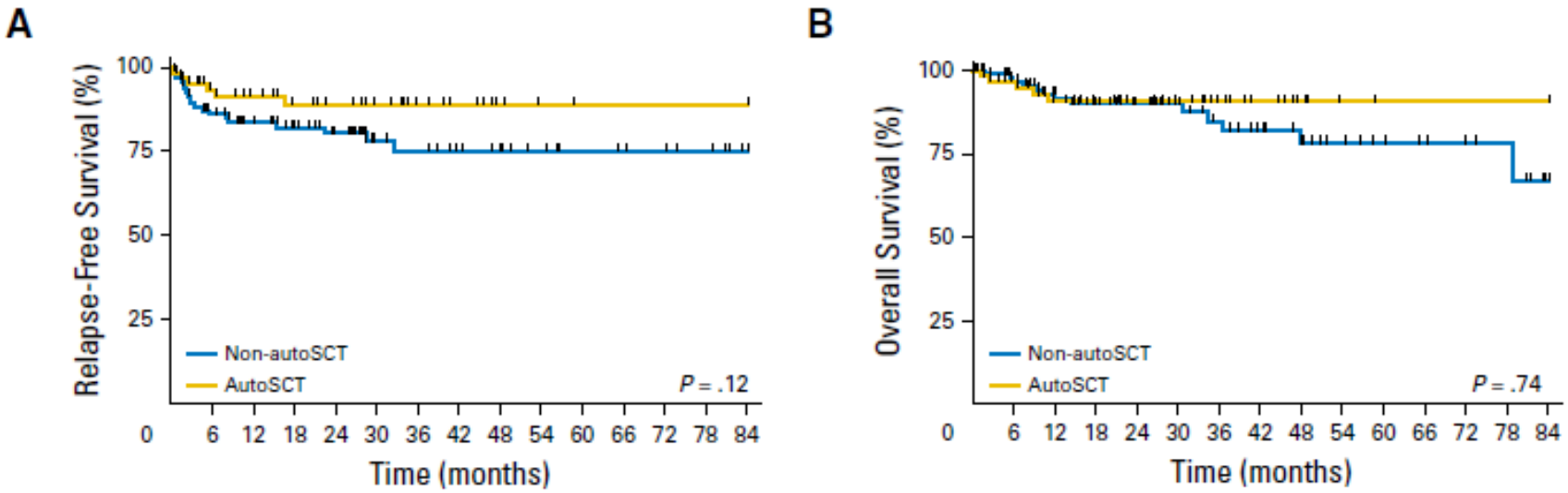
Swerdlow, *et al*. *Blood.* 2016; 127(20):2375-2390.

High-Grade B-Cell Lymphoma

- Aggressive clinical presentation; higher risk of EN and CNS involvement
  - No clear standard of treatment but RCHOP associated w/poor outcomes
  - Consider intensive immunochemotherapy regimens, such as DA-EPOCH-R
  - No randomized trial showing benefit; retrospective data conflict

HGBCL in CR1: Role of Auto SCT

- 159 patients with DHL who achieved CR1
- Compared outcomes by initial regimen and use of stem cell transplant vs observation in CR1
- Median f/u = 26.5 months (range, 0.2-114.6)



Landsburg, Cassaday *et al*. *J Clin Oncol*. 2017

DLBCL and HGBCL: Summary

- **Still RCHOP for DLBCL** (including variants and tFL)
  - 4 cycles without RT for low-IPI limited stage dz/PET negative
  - DEL status (MYC/BCL IHC+) portends inferior outcome
  - CNS-IPI – useful in CNS relapse risk evalution, but how to treat?
- **DLBCL early treatment failure = bad**
  - ASCT standard for fit+ chemosensitive relapse, but this may change soon
  - Car T-cell therapy is a high priority for chemorefractory DLBCL
  - Several recent drug approvals
- **"Non-RCHOP diseases"**:
  - da-EPOCH-R (no planned RT) for PMBCL, though R-CHOP is likely acceptable for most
  - Trial or intensified Tx (EPOCH, HyperCVAD) *generally recommended* for HGBCL

Burkitt Lymphoma

Subtypes

- Endemic (African)
- Sporadic (non-endemic)
- Immunodeficiency-associated

Starry sky pattern
FISH: t8;14 or other MYC rearrangement

Presentation (Sporadic)

- Rapidly growing /bulky mass, high lDH
- Distal ileum, cecum, other GI sites; EN sites

Van Gogh- The Starry Night 1889
→
ASH image bank:
Timothy C Carll, MD; Girish Venkataraman, MD, MBBS

Burkitt Lymphoma

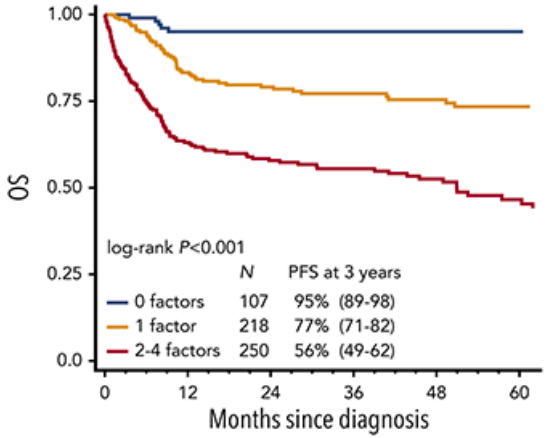
Burkitt Lymphoma in the Modern Era: Real World Outcomes and Prognostication

641 untreated adult patients with Burkitt lymphoma (across 30 US centers)

- Median age 47 years
- HIV+ status in 22%
- ECOG performance status 2-4 in 22%
- LDH >3x upper limit of normal in 39%
- CNS involvement in 19%

Prognosis

- BL-IPI
  - Factors: age ≥ 40, ECOG ≥ 2, LDH > 3× ULN, CNS+
  - 3-year OS **96, 76, and 59%** (0, 1 and 2+ factors)



Treatment Standards

- Rituximab +
  - Magrath (CODOX-M/IVAC); HyperCVAD+ Mtx/ara-C; da- EPOCH
  - No randomized trials yet
  - HyperCVAD+R may have higher TRM

Olszewski JCO 2021
Evens Bloos 2021

Mantle Cell Lymphoma

- Affects patients in their mid-60s
- M:F ratio 4:1
- Typically present in advanced stage
  - 90% have extranodal disease (Bone marrow, blood, GI)
- B symptoms, elevated LDH in about 1/3 or fewer
- Variable clinical course; generally considered incurable
- MIPI = Mantle Cell International Prognostic Score
  - Age, LDH, WBC, performance status, and Ki-67

Mantle Cell Lymphoma

- **Fit/younger:** Induction chemotherapy then ASCT
  - **Goal**: Prolonged remission, esp. for low-MIPI
  - **Various induction regimens**
    - BR; ara-C HyperCVAD; NORDIC, etc.
    - Role of transplant esp for MRD negative (EA4151)

- **Older/infirm:** BR or VR-CAP. RCHOP? Len + R?
  - R maintenance?

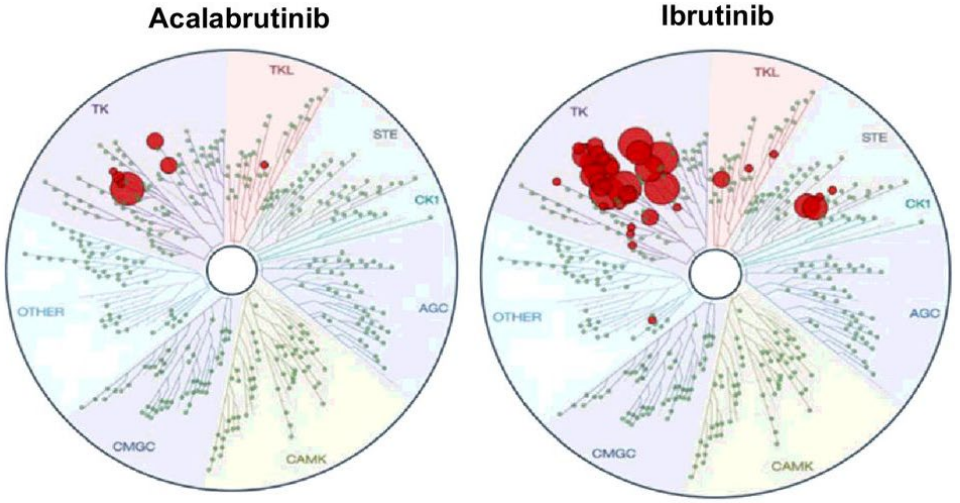
BTK Inhibitors for Relapsed MCL

Approved agents

1- Ibrutinib approved first, longest “track record”

2- Acalabrutinib

3- Zanubrutinib



Herman Clin Cancer Res 2017

Selection

Drug interactions, side effects, cost?

No comparative studies in r/r Mantle Cell Lymphoma (yet)

NON-MCL data: Rates of Notable Adverse Events, by BTK

	ELEVATE RR relapsed high-risk CLL Byrd, ASCO 2021 abs.		**ALPINE** (relapsed CLL) Hillmen, EHA 2021 abs.		**ASPEN (Waldenstrom)** Tam, Blood 2020		**Pooled review** (B-cell malignancies) Sawalha Onc Targets Ther 2020		
Event (%)	Ibr	Acala	Ibr	Zanu	Ibr	Zanu	Ibr	Acala	Zanu
A. Fib any grade	**16.0**	9.4	**10.1**	2.5	**15**	2	**11**	2	2
Bleeding serious / gr 3	**4.6**	3.8	**3.9**	2.9	**0.5** (rate)	0.3 (rate)	**5**	3	3
HTN gr 3	**9.1**	4.1	10.6	**10.8**	**0.8** (rate)	0.3 (rate)	**5**	<3	3
Diarrhea gr 3	**4.9**	1.1	**-**	-	1	**3**	**4**	2	1
Stop drug due to AE	**21.4**	14.7	**13.0**	7.8	**9**	4	**10**	6	10

Differences in follow-up, study design/ lack of blinding, and abstract-only detail must be considered at this time.

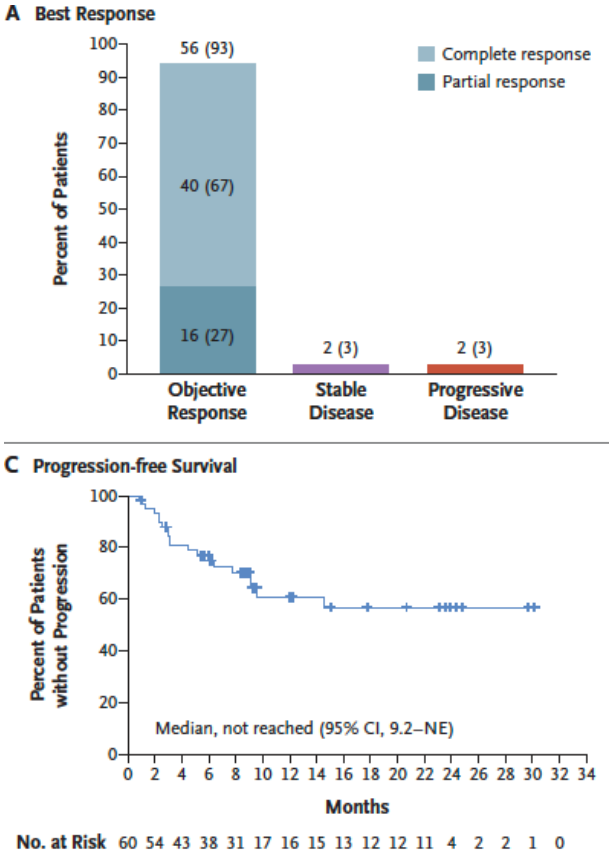
CD19 CAR T-cell: Brexucabtagene (Tecartus)

- **ORR 93%, CR 67%**
- 12 month PFS 61%, OS 83%

Toxicities:

- 15% Cytokine release syndrome, grade 3 or higher (occurs early)
- 31% Neurotoxicity grade 3 or higher (occurs days later)

When to use? Approved for "relapsed or refractory MCL in adults"- e.g. irrespective of prior BTK –I, other tx.



Wang NEJM 2020

Thank you

FRED HUTCH

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