Aggressive lymphoma
Nursing and Allied Providers Symposium

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Disclosures

Consulting advice:

Abbvie, Astellas, Astrazeneca, Bayer, Beigene, BMS, Calithera, Constellation, Eisai, Lilly, Epizyme, Genmab, Grail, Incyte, Janssen, Karyopharm, Merck, Mustang Bio, Pfizer, Roche/Genentech, Second Genome, Sutro, Caribou Biosciences

FDA approved and non-FDA approved drugs/indications will be discussed

Learning Objectives

Understand standard management of patients with aggressive lymphoma

Assess new data on emerging therapies in aggressive lymphoma

Topics

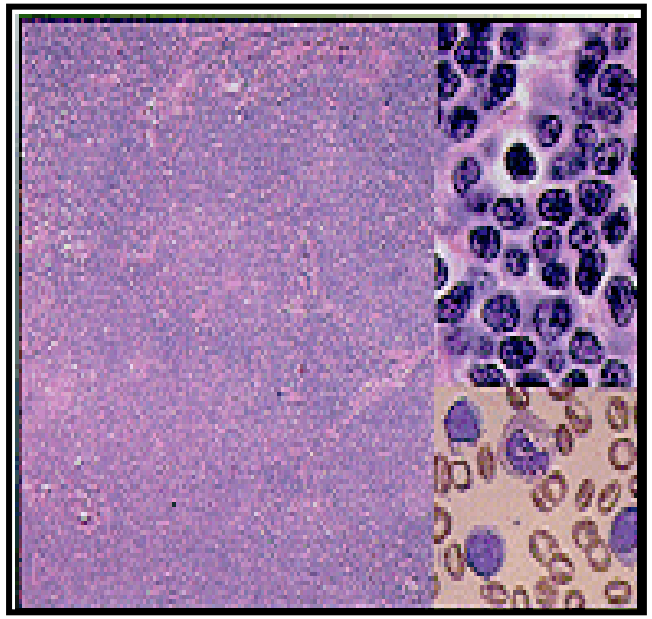
- Approach to lymphoma diagnosis
- General classification of aggressive lymphomas
- Diffuse large B cell lymphoma
- T cell lymphoma
- Mantle cell lymphoma

How does lymphoma present itself?

- Feel or see a mass (lymph nodes)
- Abnormal lab test or incidental finding on scan
  - Blood counts, chemistry, other
- Symptoms
  - Pain
  - Fatigue
  - Fever, weight loss
  - Location-related issue (e.g. bowel issue)

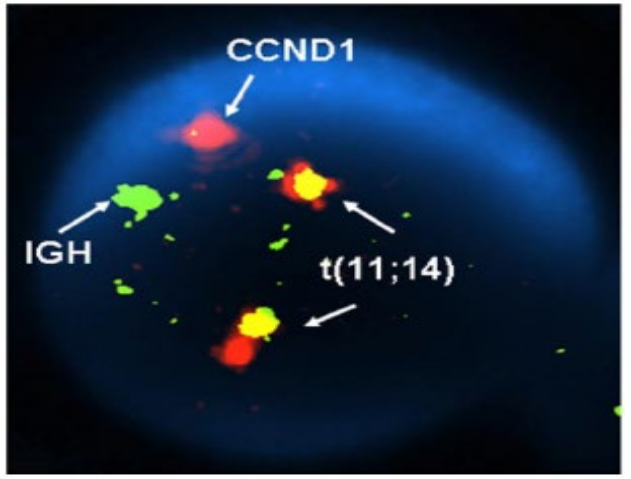
Making the diagnosis

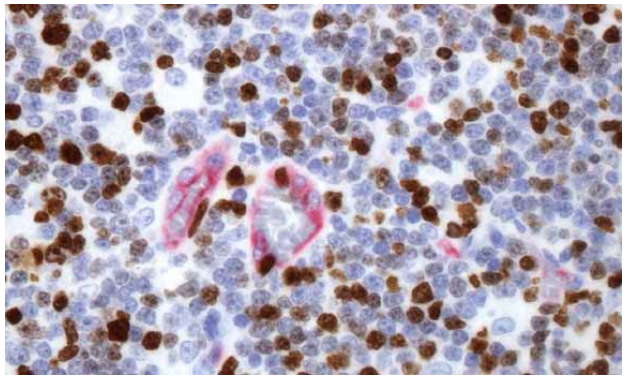
- Biopsy
  - Lymph node, bone marrow, other
  - Excisional, core needle, fine needle
  - More is better
- Sometimes appropriate to rebiopsy
- Pathology second opinions helpful



What does the pathologist do?

- Look at the material directly
  - Cell characteristics under the microscope
- Immunophenotype or “markers” (CD)
- Molecular studies
  - Clonality
  - Cytogenetics
  - Fluorescence in situ hybridization (FISH)





WHO Lymphoma Classification 2016

Table 1. 2016 WHO classification of mature lymphoid, histiocytic, and dendritic neoplasms

Mature B-cell neoplasms
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis*
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic B-cell lymphoma/leukemia, unclassifiable
Splenic diffuse red pulp small B-cell lymphoma
Hairy cell leukemia-variant
Lymphoplasmacytic lymphoma
Waldenström macroglobulinemia
Monoclonal gammopathy of undetermined significance (MGUS), IgM*
μ heavy-chain disease
γ heavy-chain disease
α heavy-chain disease
Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Monoclonal immunoglobulin deposition diseases*
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma
Pediatric nodal marginal zone lymphoma
Follicular lymphoma
In situ follicular neoplasia*
Duodenal-type follicular lymphoma*
Pediatric-type follicular lymphoma*
*Large B-cell lymphoma with IRF4 rearrangement**
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
In situ mantle cell neoplasia*
Diffuse large B-cell lymphoma (DLBCL), NOS
Germinal center B-cell type*
Activated B-cell type*
T-cell/histiocyte-rich large B-cell lymphoma
Primary DLBCL of the central nervous system (CNS)
Primary cutaneous DLBCL, leg type
EBV$^+$ DLBCL, NOS*
*EBV$^+$ mucocutaneous ulcer**
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**
Burkitt lymphoma
*Burkitt-like lymphoma with 11q aberration**
High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements*
High-grade B-cell lymphoma, NOS*
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma
Mature T and NK neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK-cell leukemia
Systemic EBV$^+$ T-cell lymphoma of childhood*
Hydroa vacciniforme–like lymphoproliferative disorder*
Adult T-cell leukemia/lymphoma
Extranodal NK-/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma

Table 1. (continued)

Monomorphic epitheliotropic intestinal T-cell lymphoma*
*Indolent T-cell lymphoproliferative disorder of the GI tract**
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphoma
*Primary cutaneous acral CD8$^+$ T-cell lymphoma**
*Primary cutaneous CD4$^+$ small/medium T-cell lymphoproliferative disorder**
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
*Follicular T-cell lymphoma**
*Nodal peripheral T-cell lymphoma with TFH phenotype**
Anaplastic large-cell lymphoma, ALK$^+$
Anaplastic large-cell lymphoma, ALK$^-$*
*Breast implant–associated anaplastic large-cell lymphoma**
Hodgkin lymphoma
Nodular lymphocyte predominant Hodgkin lymphoma
Classical Hodgkin lymphoma
Nodular sclerosis classical Hodgkin lymphoma
Lymphocyte-rich classical Hodgkin lymphoma
Mixed cellularity classical Hodgkin lymphoma
Lymphocyte-depleted classical Hodgkin lymphoma
Posttransplant lymphoproliferative disorders (PTLD)
Plasmacytic hyperplasia PTLD
Infectious mononucleosis PTLD
Florid follicular hyperplasia PTLD*
Polymorphic PTLD
Monomorphic PTLD (B- and T-/NK-cell types)
Classical Hodgkin lymphoma PTLD
Histiocytic and dendritic cell neoplasms
Histiocytic sarcoma
Langerhans cell histiocytosis
Langerhans cell sarcoma
Indeterminate dendritic cell tumor
Interdigitating dendritic cell sarcoma
Follicular dendritic cell sarcoma
Fibroblastic reticular cell tumor
Disseminated juvenile xanthogranuloma
Erdheim-Chester disease*

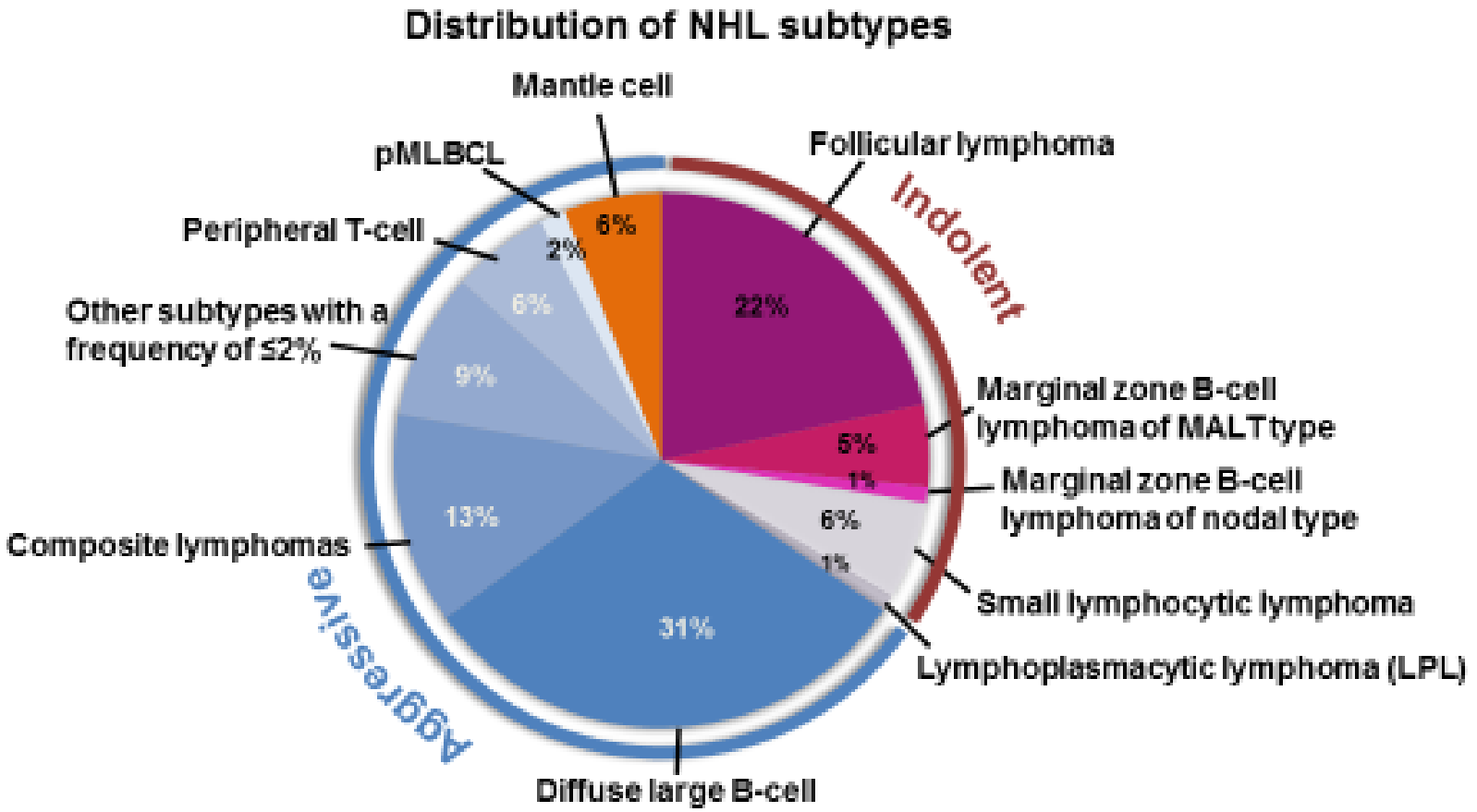
Provisional entities are listed in italics.
*Changes from the 2008 classification.

small population, but in others associated with a lymphocytosis.[4] Whereas in 2008 it was unknown whether MBL was a precursor of CLL, we now know that MBL precedes virtually all cases of **CLL/small lymphocytic lymphoma** (SLL).[5] The updated WHO will retain the current criteria for MBL, but will emphasize that "low-count" MBL, defined as a PB CLL count of $<0.5 \times 10^9$/L, must be distinguished from "high-count" MBL because low count MBL has significant differences from CLL, an extremely limited, if any, chance of progression, and, until new evidence is provided, does not require routine follow-up outside of standard medical care.[6,7] In contrast, high-count MBL requires routine/yearly follow-up, and has very similar phenotypic and genetic/molecular features as Rai stage 0 CLL, although immunoglobulin heavy chain variable region (IGHV)-mutated cases are more frequent in MBL.[8] Also impacting our diagnostic criteria, the revision will eliminate the option to diagnose CLL with $<5 \times 10^9$/L PB CLL cells in the absence of extramedullary

100 + entities

Swerdlow SH, Campo E, Pileri SA, et al. Blood. 2016 May 19;127(20):2375-90. doi: 10.1182/blood-2016-01-643569. Epub 2016 Mar 15. PMID: 26980727; PMCID: PMC4874220.

Less precision in practice



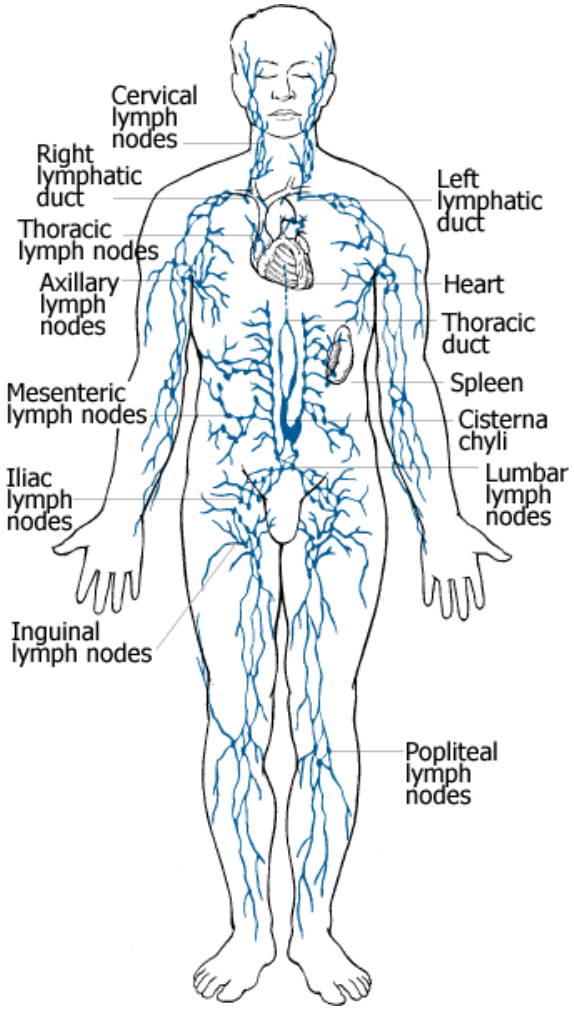
MALT, mucosa-associated lymphoid tissue pMLBCL, primary mediastinal large B-cell lymphoma

Armitage JO, et al. *J Clin Oncol.* 1998;16(8):2780-2795.

Staging tests

- Perhaps less important than in other tumors
- Physical examination
- Laboratory tests
- Bone marrow aspirate and biopsy (less important)
- Radiology tests (varies)
  - CT scan, PET scan, MRI
- Lumbar puncture – sometimes
- Other tests as appropriate (e.g. colonoscopy, eye exam)

Lymphoma staging



Most patients have stage III or IV

Less important than other cancers

NHL: Facts and Figures

Hematologic malignancies: Estimated U.S. new cases in 2010s

Type	Estimated New Cases
Lymphoma	**74,030**
Hodgkin's lymphoma	8,490
Non-Hodgkin lymphoma	**65,540**
Myeloma	**20,180**
Leukemia	**43,050**
Acute lymphocytic leukemia	5,330
Chronic lymphocytic leukemia	14,990
Acute myeloid leukemia	12,330
Chronic myeloid leukemia	4,870
Other leukemia	5,530

http://www.cancer.org/acs/groups/content/@nho/documents/document/acspc-024113.pdf

Non-Hodgkin Lymphoma

- Roughly 70,000 patients/year diagnosed in US
  - Incidence has tripled since 1980
- Prevalence over 300,000/year in US
  - Most common hematologic cancer, 5th overall
- 2 principal types account for 2/3 of patients
  - Survival of both has significantly improved over last 5-10 years (finally)
- Major challenges exist in trying to improve further

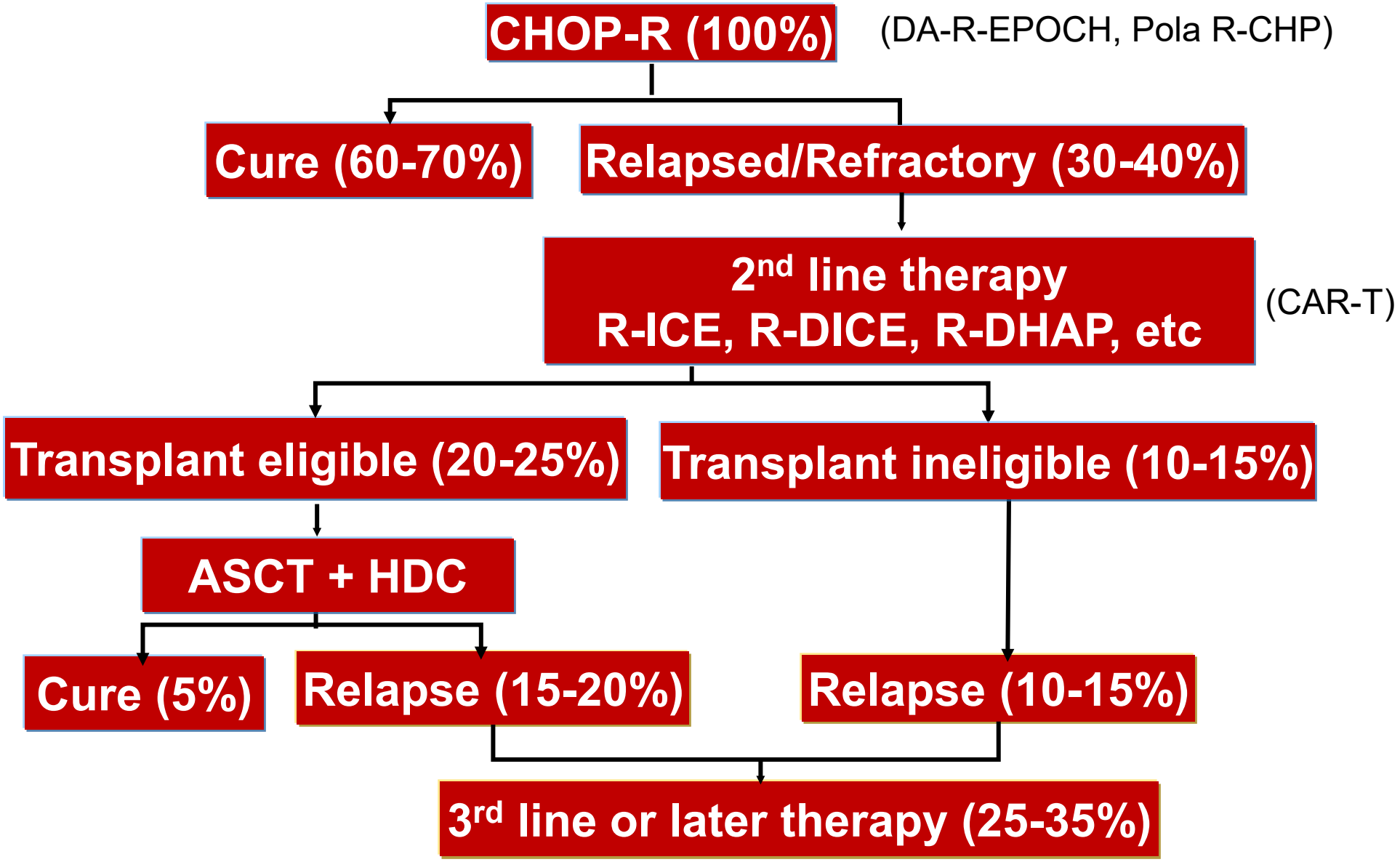
Case Presentation

- A 65 year old male with a history of hypertension and hypercholesterolemia presents with a 2 week history of cervical mass. He has a 30 pack year smoking history. Feels well.
- Exam shows bilateral cervical lymph nodes, firm, 2 cm range.
- CBC normal, LDH and chemistries normal
- Excisional biopsy shows diffuse large B cell lymphoma
- Does he need treatment? If so, what are goals of therapy?

Diffuse large B cell lymphoma

- Median age 60, usually with advanced stage disease
  - LAN, extranodal disease, symptoms
- Practical objective of treatment – cure (70%)
- Reasonably good clinical prognostic tools
- Most patients have been treated same first line (R-CHOP chemoimmunotherapy)
- Unmet need – more cures, reduce toxicity
- Who should we treat differently?
- If refractory to second-line therapy, prognosis less favorable

Treatment algorithm for DLBCL



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- Exam shows bilateral cervical LN, firm, 2 cm range.
- CBC normal, LDH and chemistries normal
- Excisional biopsy shows diffuse large B cell lymphoma
- What is his prognosis?

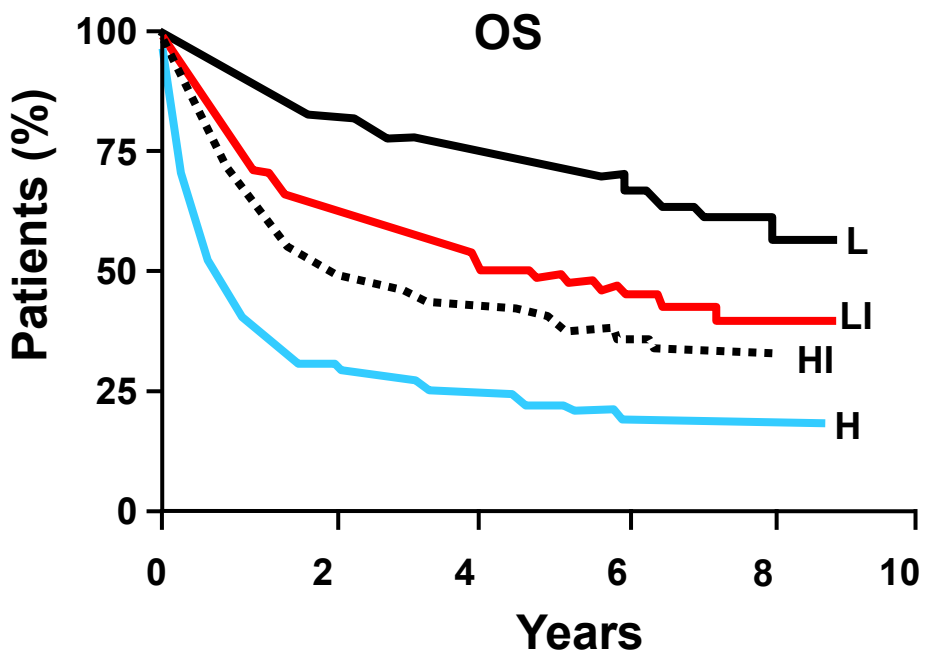
International Prognostic Index (IPI) in aggressive NHL

Prognostic factors (APLES)

- **A**ge >60 years
- **P**erformance status >1
- **L**DH >1× normal
- **E**xtranodal sites >1
- **S**tage III or IV

OR

Risk Category	Factors
Low (L)	0 or 1
Low intermediate (LI)	2
High intermediate (HI)	3
High (H)	4 or 5



International NHL Prognostic Factors Project. *N Engl J Med.* 1993;329:987.
Armitage. *CA Cancer J Clin.* 2005;55:368.

What does the physician need or want to know when approaching a new DLBCL patient?

- **Clinical features**
  - **International Prognostic Index**
  - **Primary mediastinal (R-EPOCH)**
  - **CNS, testicular (variations of rx)**
- **Pathological and molecular features**
  - **Bone marrow involvement (variations of rx)**
  - **Double hit (FISH) > Double protein (R-EPOCH chemoimmunotherapy)**
  - **Cell of origin (Germinal Center/Activated B Cell)**

Comparison of CHOP-R and EPOCH-R

R-CHOP

Rituximab 375 mg/m^2 d1
Cyclophosphamide 750 mg/m2 d1
Doxorubicin 50 mg/m^2 d1
Vincristine 1.4 mg/m^2 (2 mg cap) d1
Prednisone 40 mg/m^2 d1-5

q3w × 6

DA*-R-EPOCH

Rituximab 375 mg/m^2 d1
Etoposide 50 mg/m^2/d CI d1-4*
Doxorubicin 10 mg/m^2/d CI d1-4*
Vincristine 0.4 mg/m^2/d CI d1-4
Cyclophosphamide 750 mg/m^2 d5*
Prednisone 60 mg/m^2 bid d1-4
G-CSF 5 µg/kg d6-ANC recovery

q3w × 6

*

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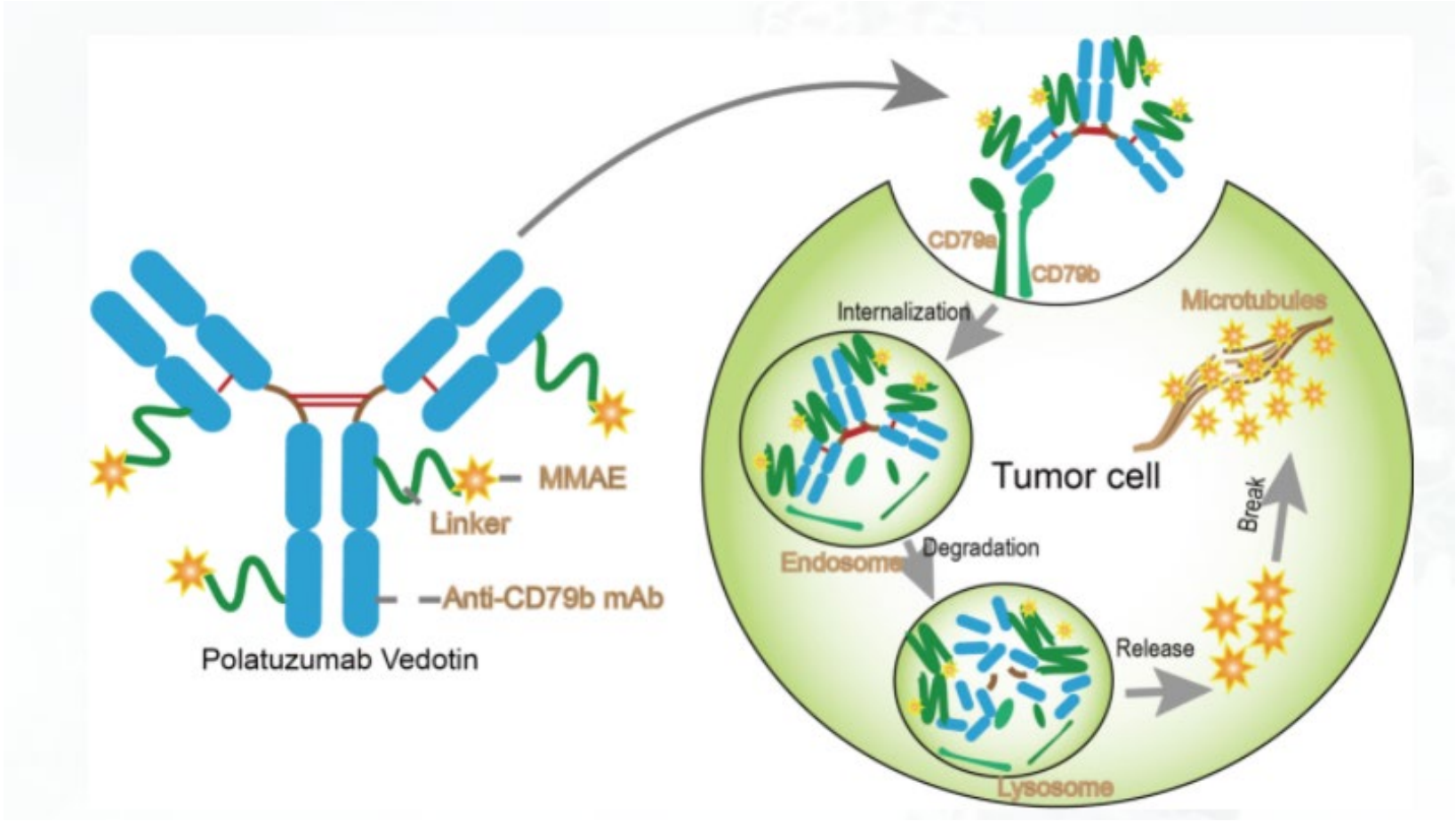
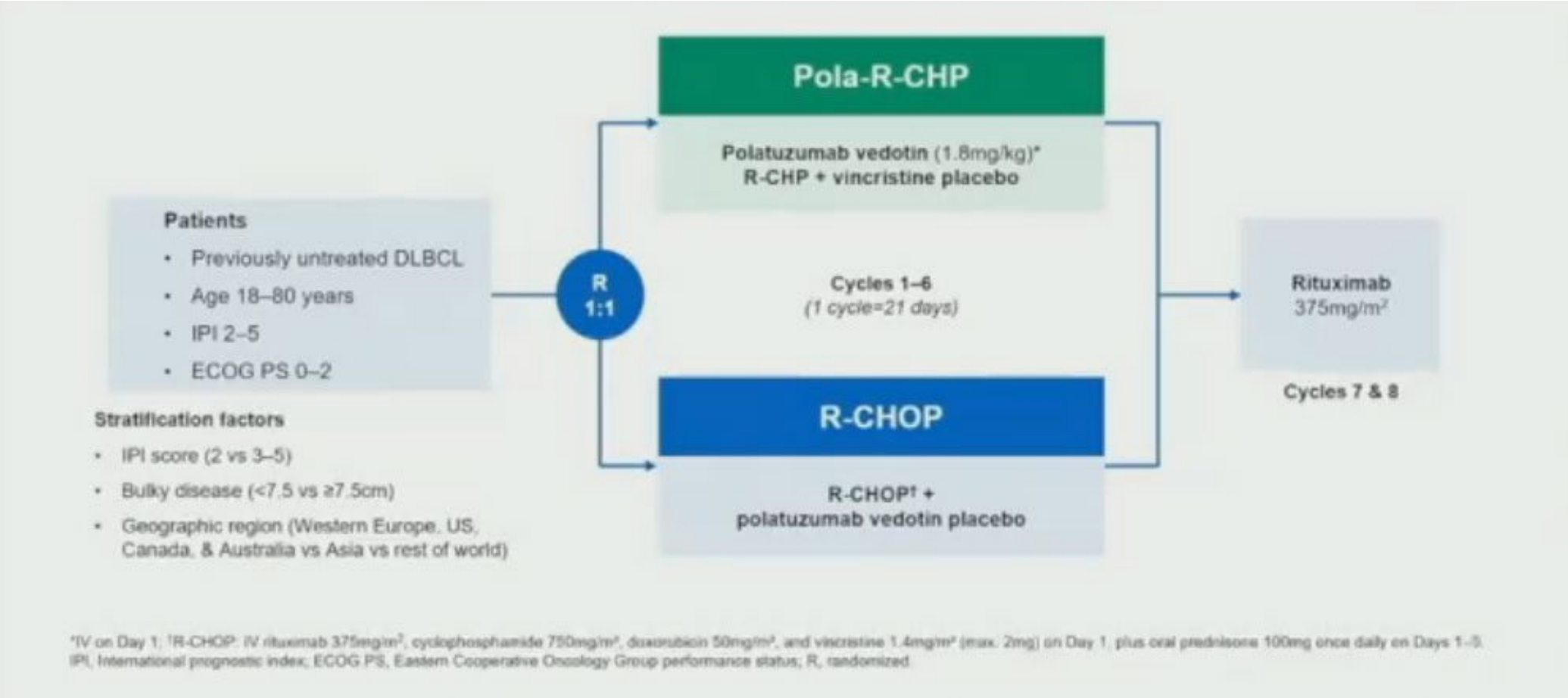
Polatuzumab vedotin (anti-CD79b antibody drug conjugate)



https://www.creativebiolabs.net/polatuzumab-vedotin-overview.htm

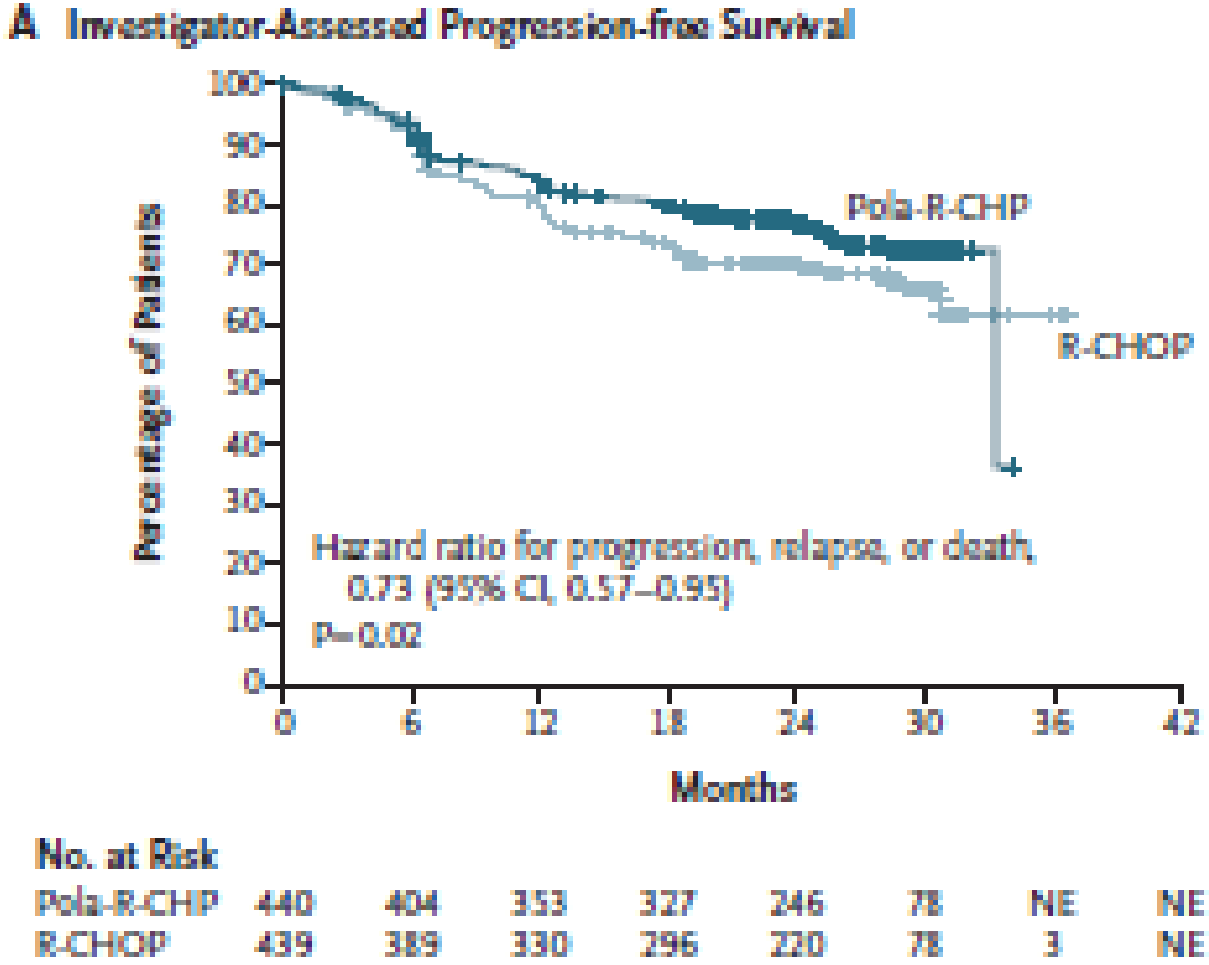
R-CHOP vs Polatuzumab-R-CHP in DLBCL (IPI 2-5)

Tilly et al, NEJM 2021



R-CHOP vs Polatuzumab-R-CHP in DLBCL - PFS

Tilly et al, NEJM 2021



24 mo PFS:
76.7% Pola-R-CHP
70.2% R-CHOP

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- Exam shows bilateral cervical LN, firm, 2 cm range.
- CBC normal, LDH and chemistries normal
- He goes into a PET negative CR after R-CHOP
- How do you follow him?

Surveillance CT scans are a source of anxiety and fear for lymphoma survivors

- 70 survivors of curable adult aggressive lymphoma (median 4.9 years from dx)
- 37% met criteria for clinically significant anxiety
- Despite representing a largely cured population, in qualitative interviews patients reported fear of recurrence as a major concern and considerable anxiety around the time of a follow-up imaging scan
- Strategies to minimize follow-up imaging and to improve doctor–patient communication should be prospectively evaluated to address these clinically significant issues

Thompson CA, Charlson ME, Schenkein E, et al . Ann Oncol. 2010 Nov;21(11):2262-2266.

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Routine imaging for diffuse large B-cell lymphoma (DLBCL) in first complete remission does not improve post-treatment survival: A Danish–Swedish population-based study

- 2 cohorts, Danish (n=525, routine imaging) and Swedish (n=696, no routine imaging) patients with DLBCL in first remission
- Similar OS

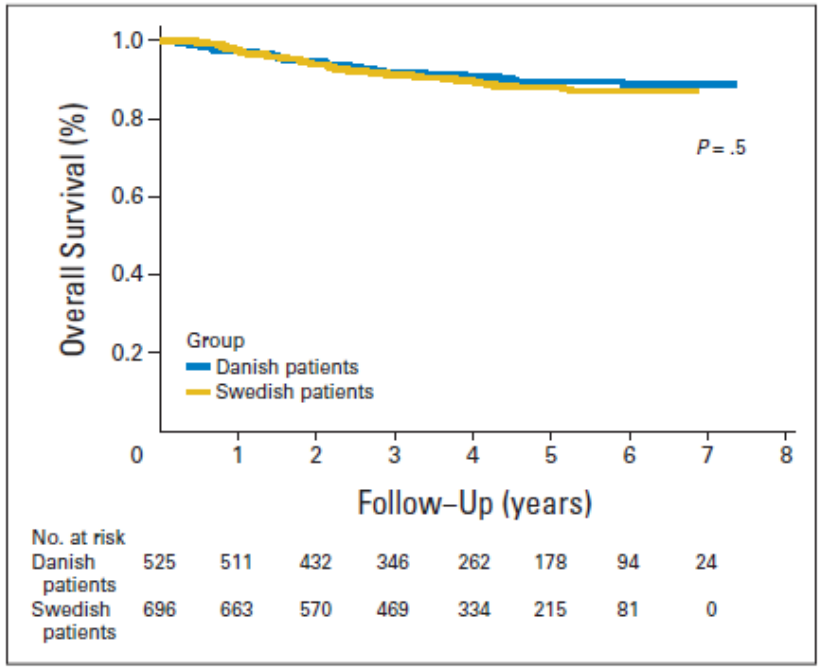

Fig 1. Post-treatment survival of 1,221 Danish and Swedish patients with diffuse large B-cell lymphoma in first complete remission.

El-Ghalaly et al, J Clin Oncol. 2015 Dec 1;33(34):3993-8.

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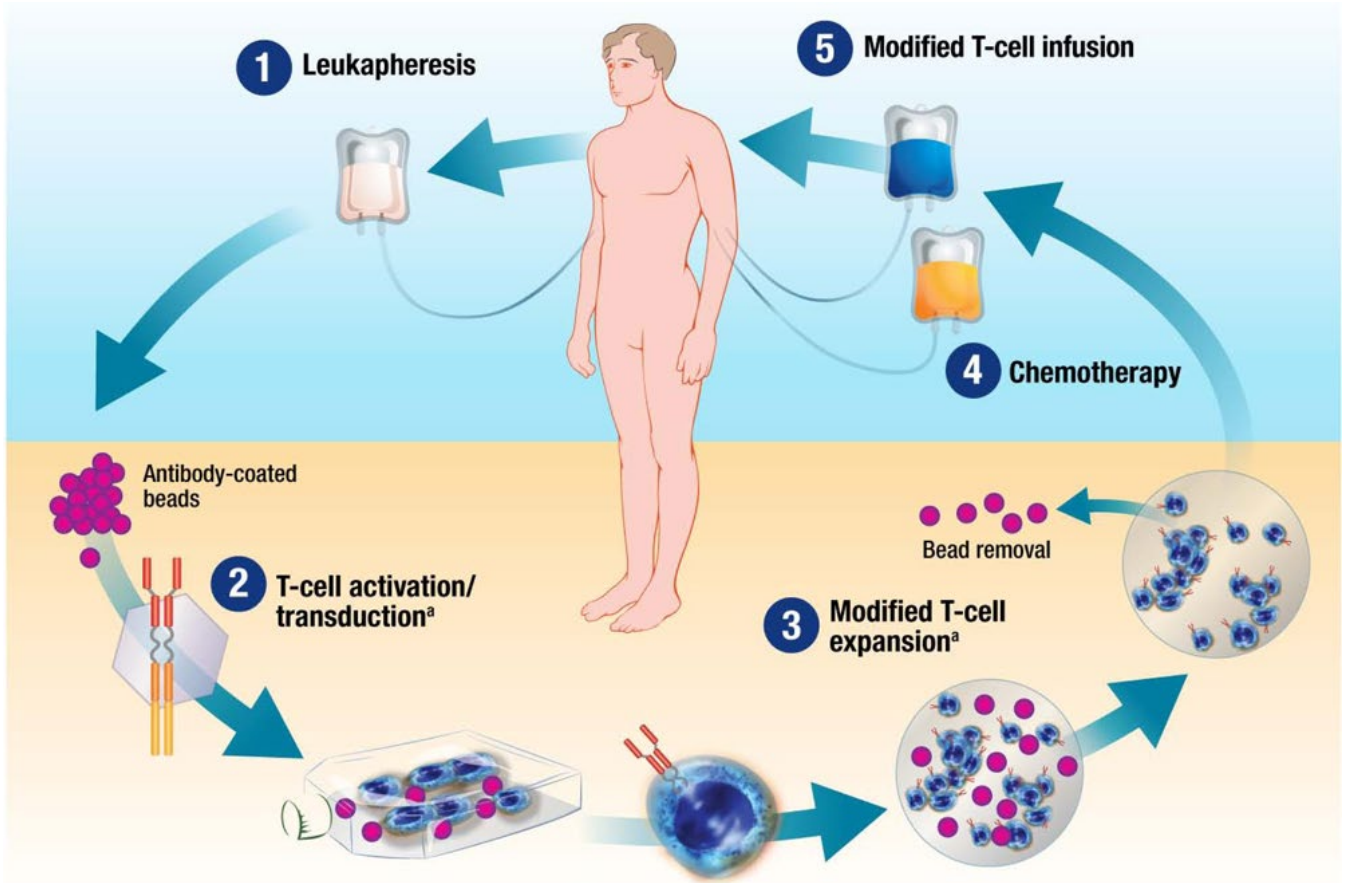
- Exam shows bilateral cervical LN, firm, 2 cm range.
- CBC normal, LDH and chemistries normal
- Excisional biopsy shows diffuse large B cell lymphoma
- He receives R-CHOP and relapses 8 months later
- What is his prognosis?

Chimeric Antigen Receptor (CAR)-T cell therapy



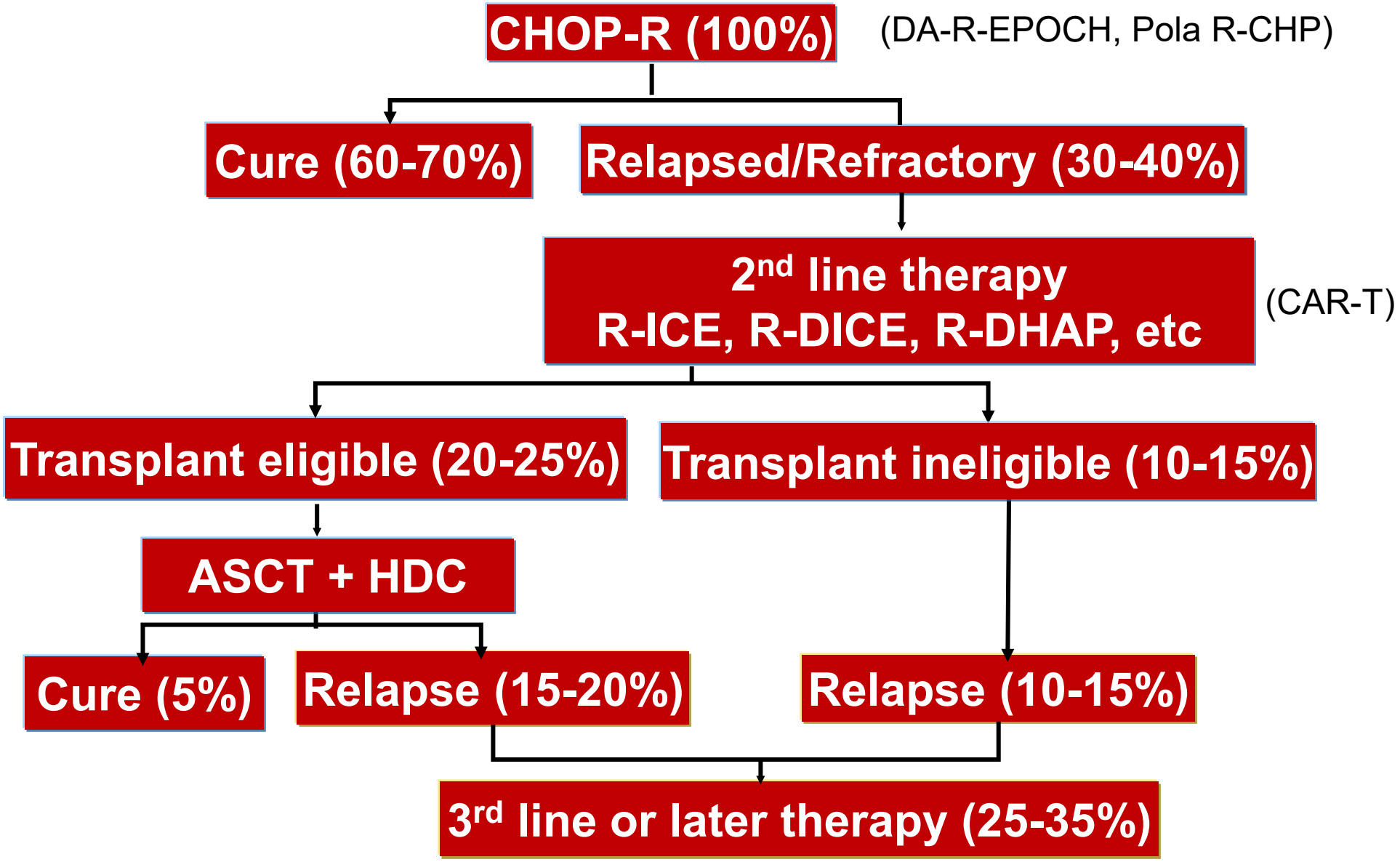
Summary of second line CAR-T studies

Randomized trials of CAR T-cells vs. SOC in 2nd line transplant-eligible DLBCL with primary refractory disease or relapse within 1 year of 1st line therapy

	ZUMA-7	TRANSFORM	BELINDA
CAR T-cell	Axicabtagene Ciloleucel	Lisocabtagene Maraleucel	Tisagenlecleucel
n	359	184	322
% infused in CAR arm	94%	98%	96%
Median EFS	8.3 mo vs. 2 mo	10.1 mo vs. 2.3 mo	3 mo vs. 3 mo
Hazard ratio	0.398 (*P*<*0*.0001)	0.349; (*P* < 0.0001)	1.07 (*P*=0.69)
Median follow-up	25 months	6 months	10 months
CR rate	65% vs 32%	66% vs 39%	28% vs 28%
Grade ≥3 CRS/NT	6% / 21%	1% / 4%	5% / 3%
	Locke, et al. Abstract 2	Kamdar, et al. Abstract 91	Bishop, et al. Abstract LBA-6

Toby Eyre

Treatment algorithm for DLBCL



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- Exam shows bilateral cervical LN, firm, 2 cm range.
- CBC normal, LDH and chemistries normal
- Excisional biopsy shows diffuse large B cell lymphoma
- He receives R-CHOP and relapses 16 months later
- His disease does not respond to second line R-ICE chemoimmunotherapy
- What is his prognosis?

3 approved CAR-T for recurrent DLBCL patients

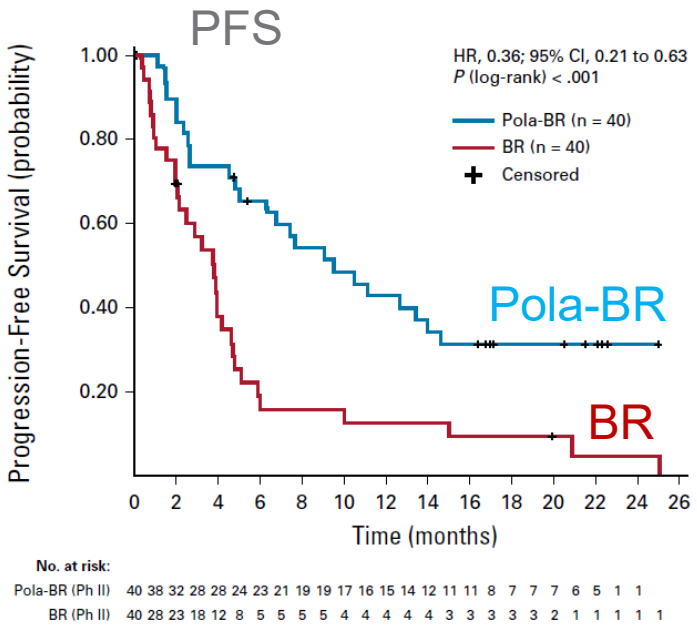
	ZUMA-1[1,2]	JULIET[3,4]	TRANSCEND CORE[5]
Product	**Axi-cel**	**Tisa-cel**	**Liso-cel**
# pheresed	111	165	344
# treated	101	111	269 (294*)
ORR (%)	82	54	73
CR (%)	54	40	53
6m ORR (%)	41	37	NR
mOS	25.8m	11.1m	21.1m

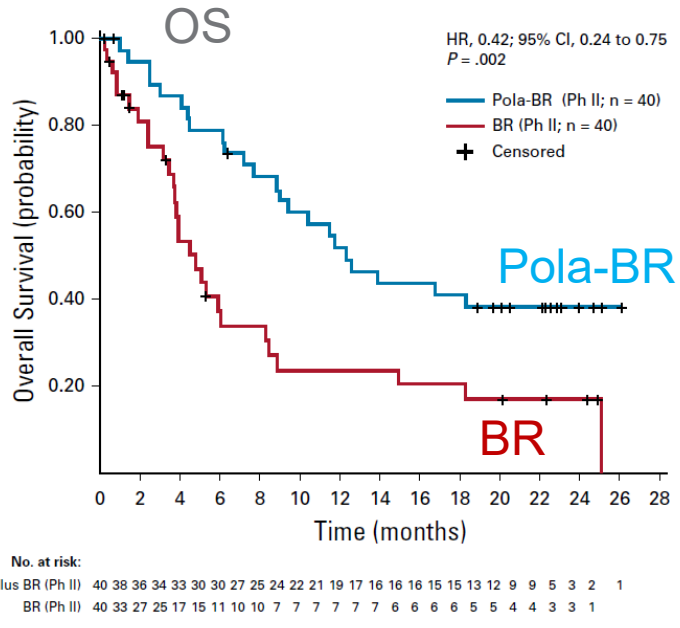
1. Jacobson, et al. *Blood*. 2020;136 (Supplement 1): 40–42. 2. Locke FL, et al. *Lancet Oncol*. 2019;20(1):31-42. 3.Schuster S, et al. *N Engl J Med*. 2019;380(1):45-56.
4. Maziarz RT, et al. *Blood Adv*. 2020;4(4):629-637. 5. Abramson JS, et al. *Lancet*. 2020;396(10254):839-852.

Initial clinical trial data with CAR-T cells

- Studies are generally non-comparative, single arm
- Time in preparing the T cells creates some biases
- Significant responses have been seen (some extending several years) in ALL, CLL and NHL of various types with refractory disease
- Toxicity (cytokine release) involving transient mental status changes/encephalopathy and ICU stays can occur
- ORR about 60-70%, CR about 30% (tend to be more durable)
- About 1/3 non-respond, 1/3 short response, 1/3 longer response
- Cytopenias, immunoglobulin depletion occur

Bendamustine-Rituximab (BR) ± Polatuzumab Vedotin in Relapsed DLBCL: Randomized Phase 2
CR 40% vs 17.5%

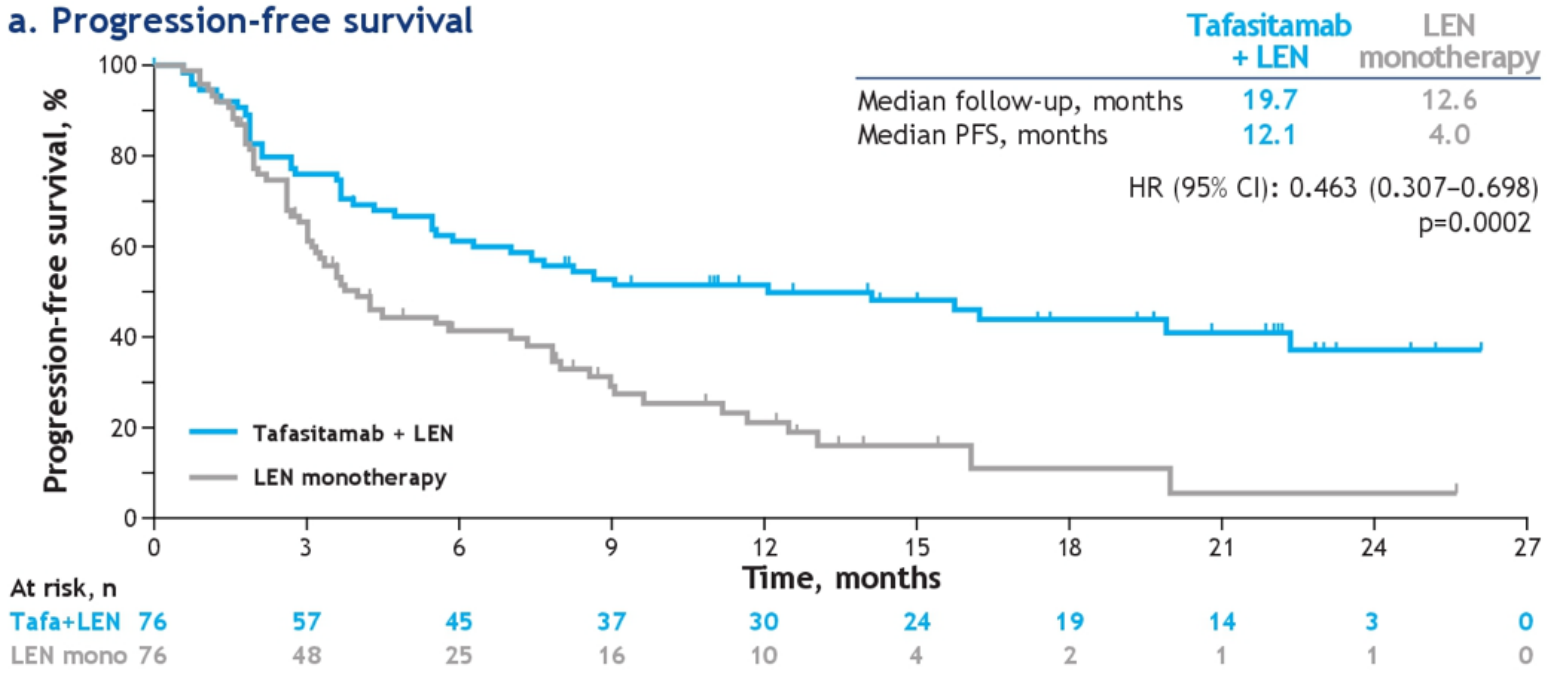




FDA approval 2019: +BR for relapsed/refractory DLBCL, >2 prior therapies

Sehn LH et al J Clin Oncol. 2020 Jan 10;38(2):155-165.

Tafasitamab/Lenalidomide (RE-MIND) compared to matched Len alone in recurrent DLBCL pts
ORR 67.1 vs 34.2%



Nowakowski GS, et al. ASCO 2020 (abstr 8020).

Selinexor

- Selective inhibitor of nuclear export (SINE), blocks XPO1
- Phase 2 SADAL study (preprint *Lancet* 2020)
- DLBCL (including tFL), 2-5 prior therapies (N=127)
- Selinexor oral 60 mg days 1 and 3 weekly
- ORR 28%, CR 12%
- Responses in both GCB and non-GCB (Hans)
- Common grade 3-4 AE cytopenias, fatigue, hyponatremia, nausea
- Median response duration 9.3 months

Kalakonda et al,Lancet Haematol. 2020 Jul;7(7):e511-e522.

Loncastuximab Tesirine in DLBCL

- Humanized anti-CD19 antibody conjugated to a PBD dimer toxin
- Administered IV every 3 weeks up to 1 year, then q 12 weeks
- N=145 subjects
- ORR 48.3%, CR rate 24.8%, PFS about 6 months
- Most common toxicities liver enzymes, cytopenias, fatigue
  - Edema also noted in 20% of patients

Caimi et al, ASH 2020

T cell lymphoma

CHOP or CHOEP chemoimmunotherapy standard of care (cures 30-40%)

Brentuximab vedotin if CD30+

Consideration of stem cell transplant in first remission

Various approaches and novel agents in relapsed setting

Cutaneous subtypes receive a number of skin-directed therapies before systemic treatment

Case Presentation

- A 65 year old male with a history of hypertension and hypercholesterolemia presents with a 2 week history of cervical mass. He has a 30 pack year smoking history. Feels well.
- Exam shows bilateral cervical LN, firm, 2 cm range.
- CBC normal, LDH and chemistries normal
- Excisional biopsy shows mantle cell lymphoma
- What is his prognosis?

Mantle cell lymphoma (MCL)

More common in older men

Median survival 5-10 years, more intense therapy longer remission

Watch and wait is an option for asymptomatic patients

Typically B-R based therapy for older patients

Often more intensive with SCT for younger patients

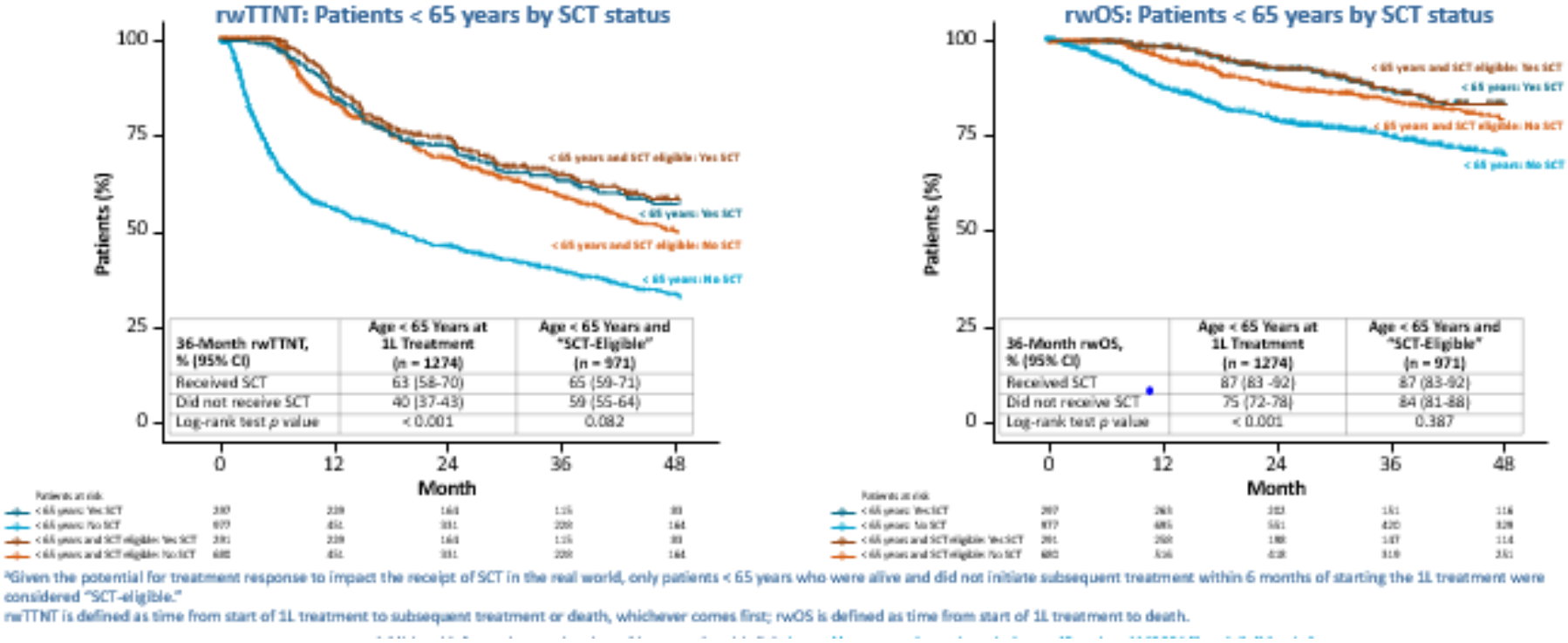
Benefit with rituximab maintenance

Bruton's Tyrosine Kinase Inhibitors (BTKi) often used now as second line

CAR-T recently approved

“Real world” data on 1274 MCL pts < 65yo SCT vs no SCT

- In the “SCT-eligible”[a] cohort (N = 971), 36-month rwTTNT was comparable for patients with SCT (65 [95%CI 59-71]) compared with those who did not receive SCT (59% [95% CI, 55-64])



[a]Given the potential for treatment response to impact the receipt of SCT in the real world, only patients < 65 years who were alive and did not initiate subsequent treatment within 6 months of starting the 1L treatment were considered “SCT-eligible.”

rwTTNT is defined as time from start of 1L treatment to subsequent treatment or death, whichever comes first; rwOS is defined as time from start of 1L treatment to death.

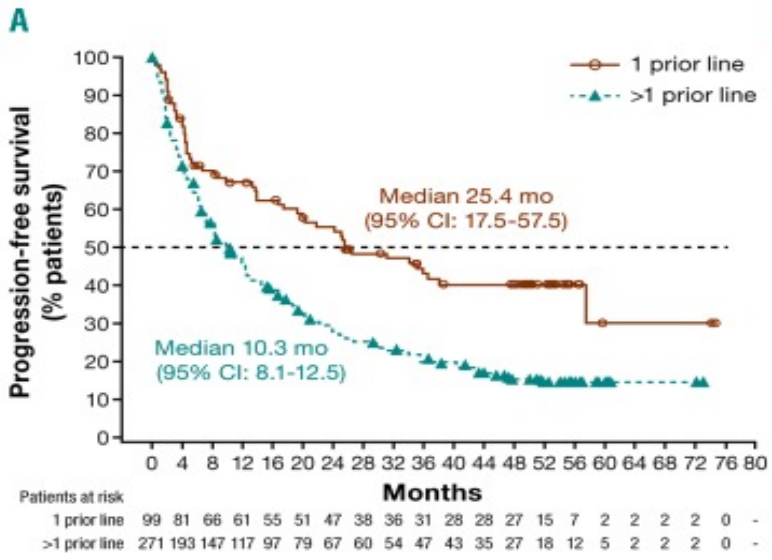
Martin et al, ASCO 2021

Evaluation of relapsed MCL patients and treatment options

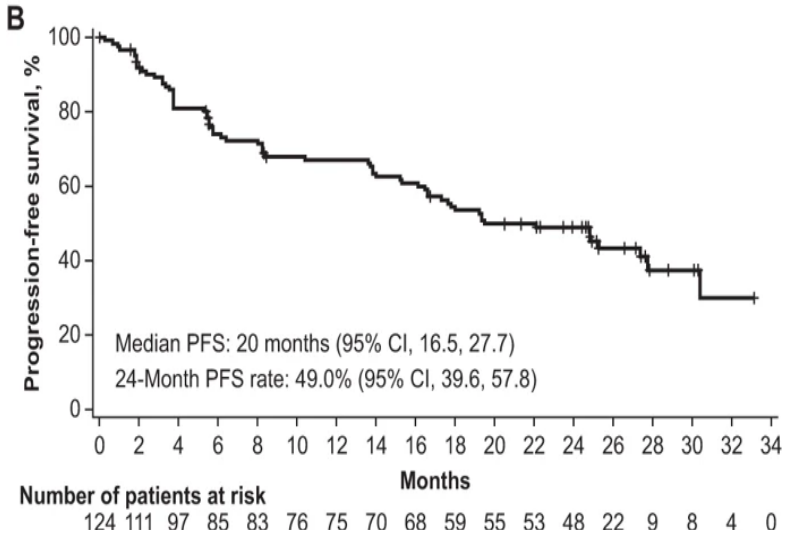
- Need to consider duration of remission, patient situation, disease status
- Treatment options
  - BTK Inhibitors: Ibrutinib, Acalabrutinib, Zanubrutinib
  - Lenalidomide (+/- rituximab)
  - CAR-T: Brexucabtagene autoleucel
  - Bortezomib
  - Bendamustine - rituximab
  - Lenalidomide – rituximab
  - Venetoclax?
- Investigational agents

Outcomes for BTK Inhibitors are comparable though toxicities may differ

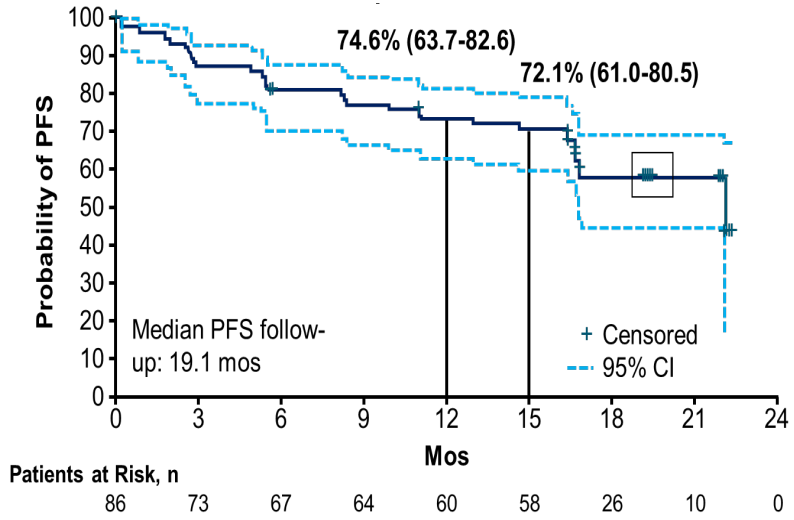
Ibrutinib



Acalabrutinib

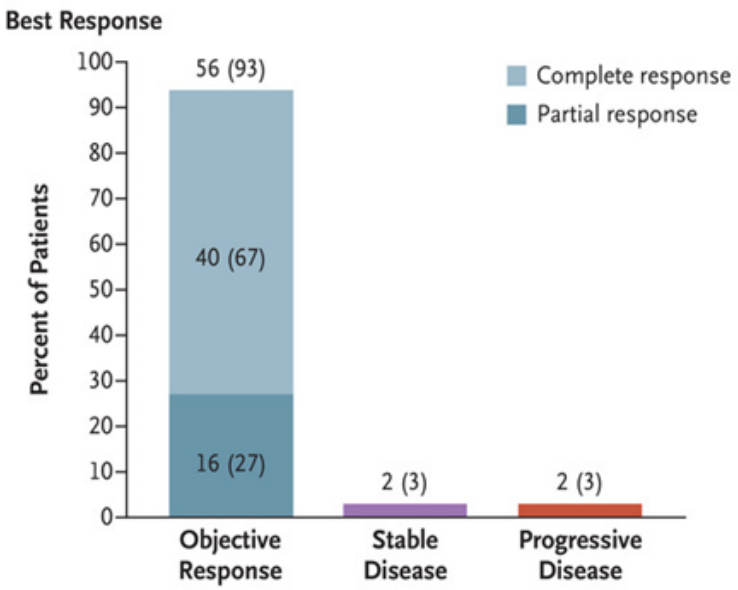


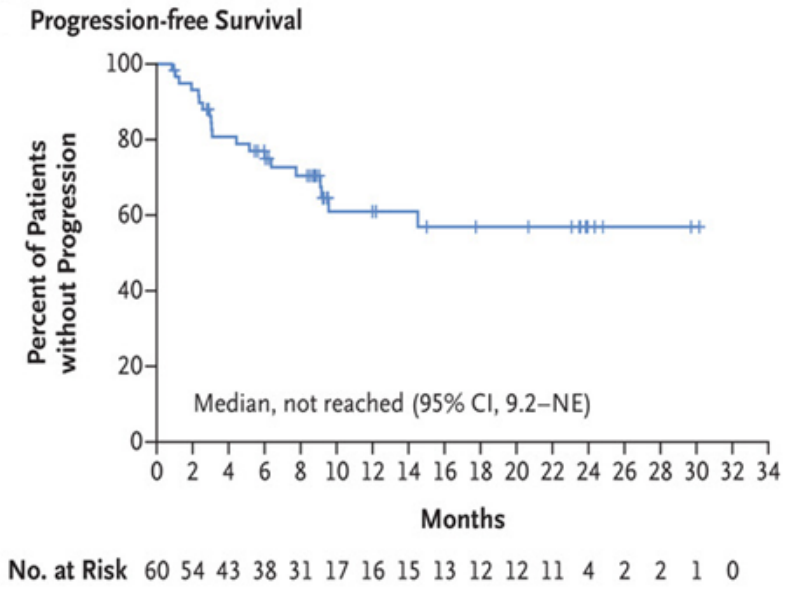
Zanubrutinib

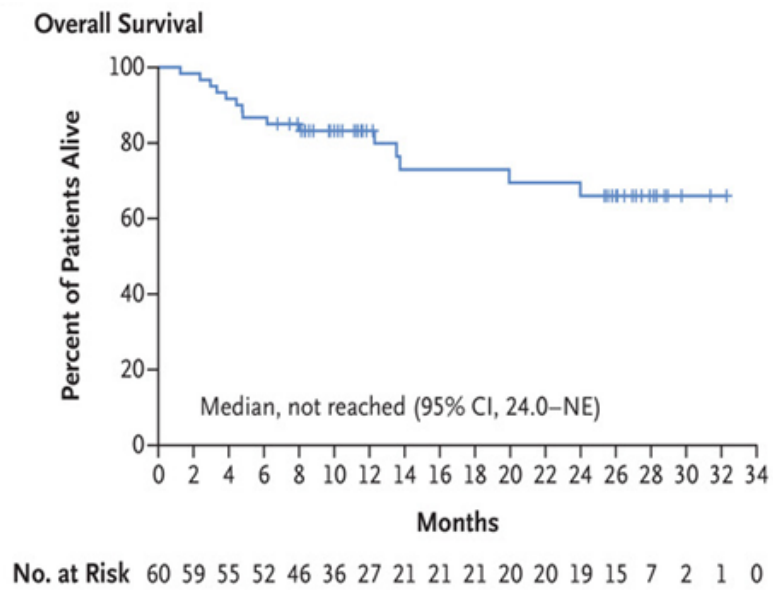


Rule, et al. *Haematologica*. 2019; 104(5): e211–e214. doi: 10.3324/haematol.2018.205229. Wang, et al. *Leukemia*. 2019;33:2762–2766. doi.org/10.1038/s41375-019-0575-9. Song. 15th ICML 2019. Abstr 015. https://doi.org/10.1002/hon.15_2629.

Brexucabtagene Autoleucel (CAR-T) in recurrent MCL







Wang et al, N Engl J Med. 2020 Apr 2;382(14):1331-1342.

Key take home points

- Accurate diagnosis essential
- Focus on goals of therapy
  - Cure vs long term management
- Quality of life issues particularly important in chronic lymphoma setting for long-term or palliative management
- New agents including CAR-T offer new options
- Consider clinical trial participation