

An Evening with the Experts:

LYMPHOMA

Background and new paradigms in 2023

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Memorial Sloan Kettering
Cancer Center™

Objectives:

- 1) Why so many different lymphoma: navigating among various diseases with different prognoses and therapy?
- 2) New standard of care for patients with the main lymphoma subtypes (diffuse large B-cell, follicular, Hodgkin lymphoma)
- 3) What to expect from new drugs on the horizon: cellular therapies, bispecific antibodies, targeted therapies, ...

Objectives:

1) Why so many different lymphoma: navigating among various diseases with different prognoses and therapy?

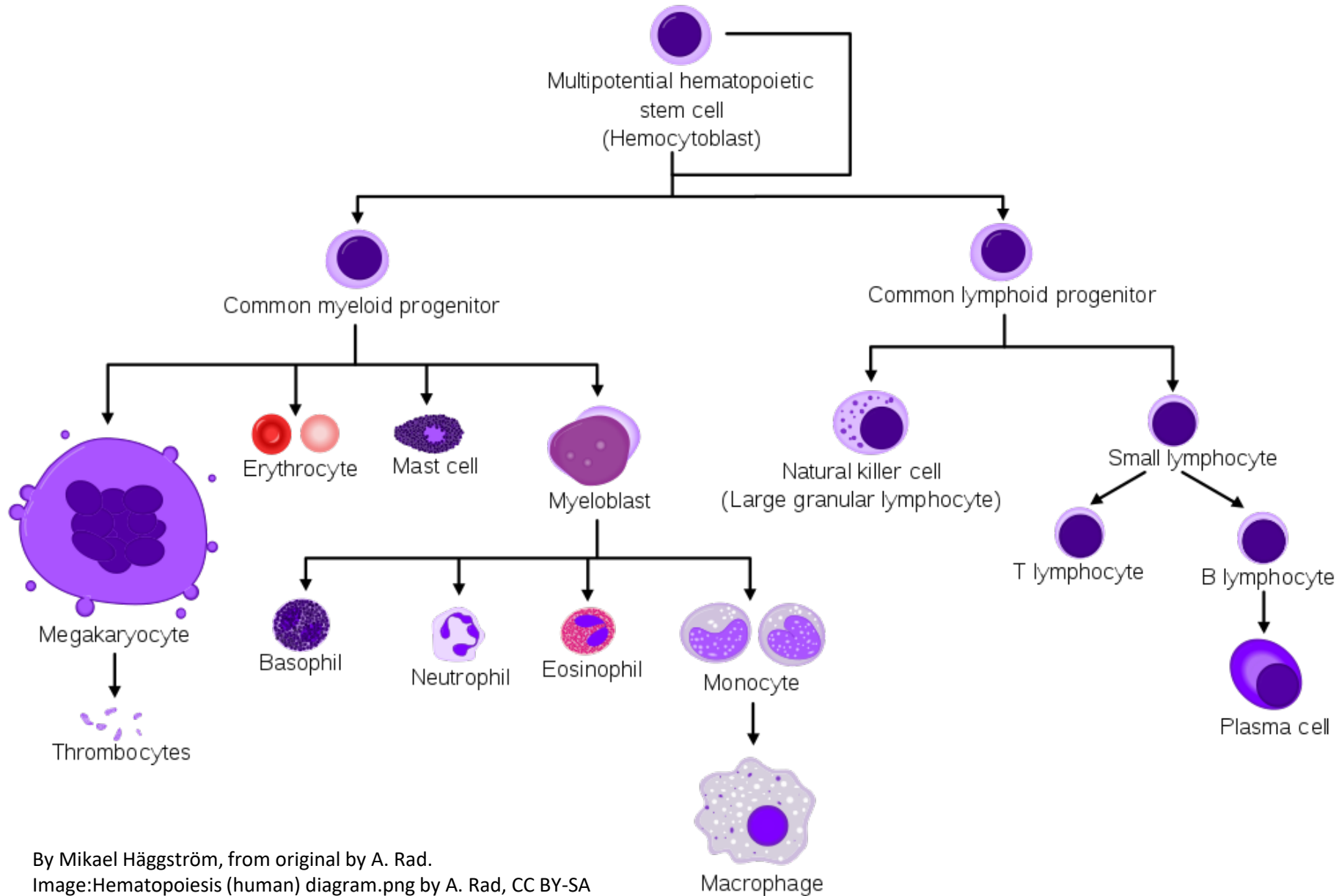
2) New standard of care for patients with the main lymphoma subtypes (diffuse large B-cell, follicular, Hodgkin lymphoma)

3) What to expect from new drugs on the horizon: cellular therapies, bispecific antibodies, targeted therapies, ...

What is Lymphoma?

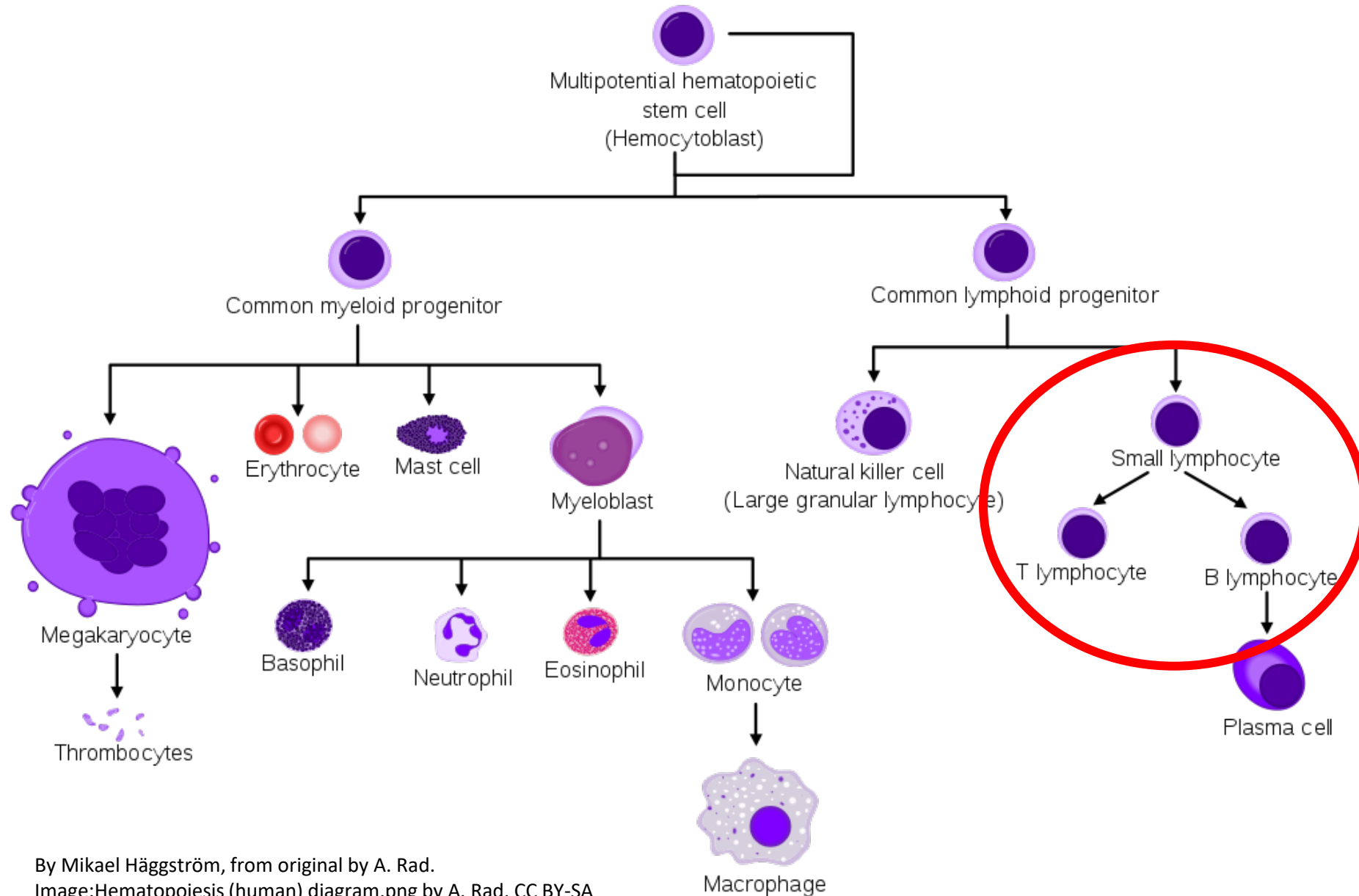
- **Cancer of cells of the immune system (lymphocytes)**
 - Lymphocytes are primarily found in lymph nodes, spleen, bone marrow, and thymus
 - But also in some epithelial and mucosal tissues
- They participate to the defense against infections (viruses and bacteria) but also react against anything “foreign” to our own body (tissue graft) and eventually against cancer
- **B lymphocytes (B cells):** involved in humoral immunity.
 - Make **antibodies** to help protect the body from bacteria and viruses.
- **T lymphocytes (T cells):** central role in cell-mediated immunity:
 - Helper, regulatory, or cytotoxic t-cells,
- **NK cells**

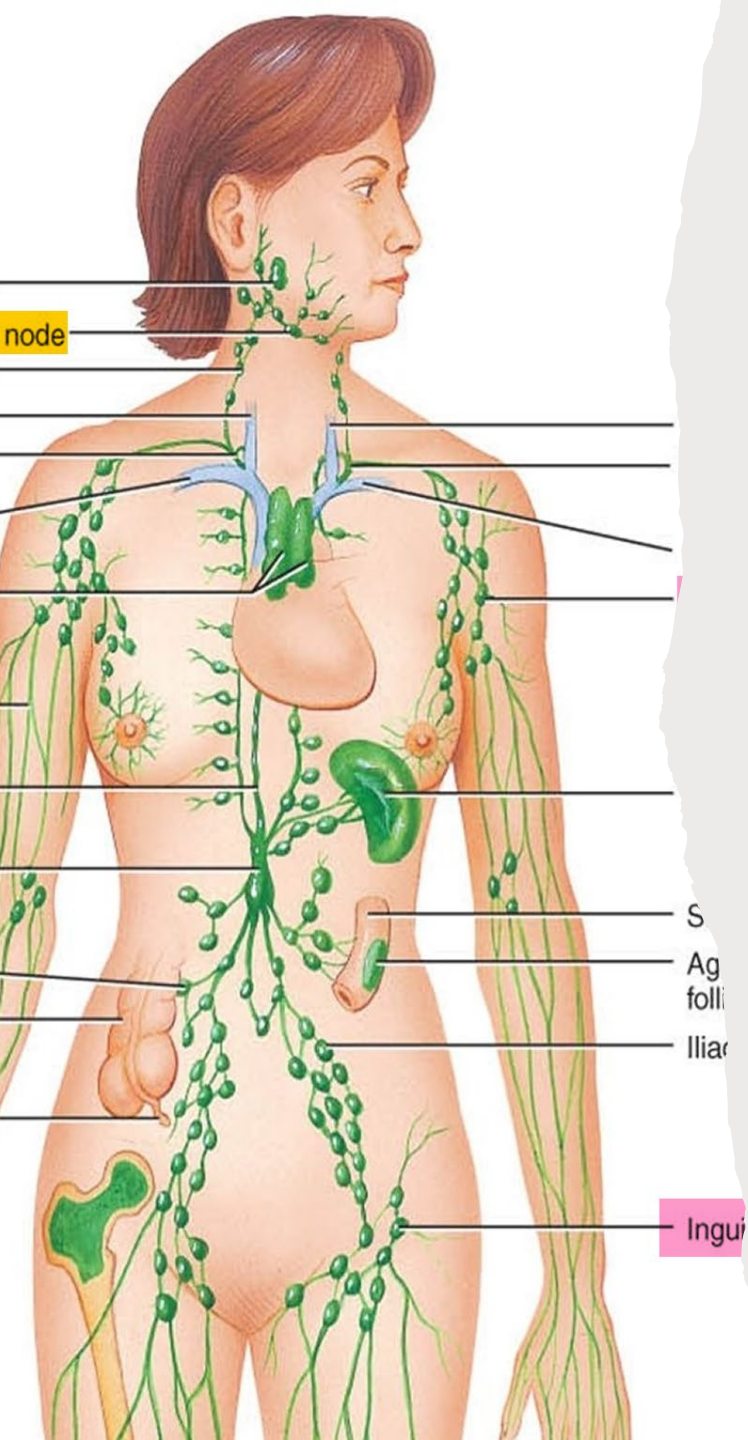
Blood cell manufacturing



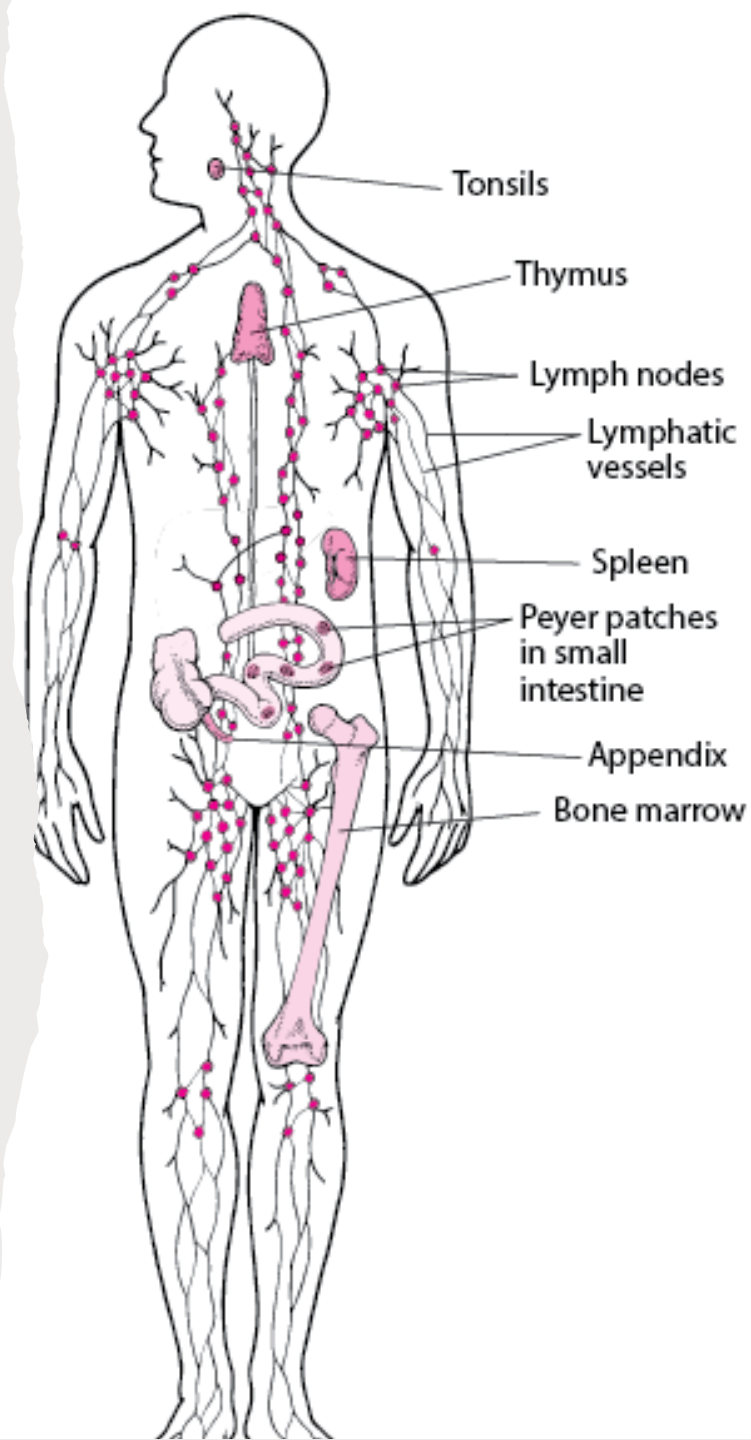
By Mikael Häggström, from original by A. Rad.
Image:Hematopoiesis (human) diagram.png by A. Rad, CC BY-SA
3.0, <https://commons.wikimedia.org/w/index.php?curid=7351905>

Blood cell manufacturing





- Lymphoid organs



Clinical Presentation of Lymphoma

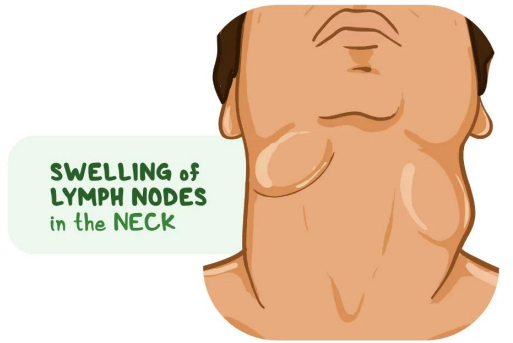
- Swollen lymph nodes
- Enlargement of spleen, liver
- Involvement of extra-nodal organs (skin, lung, GI tract, etc...)
- Biological abnormalities (blood counts, ...)

- Unintentional weight loss
- Night sweats
- Unexplained fevers

B-symptoms

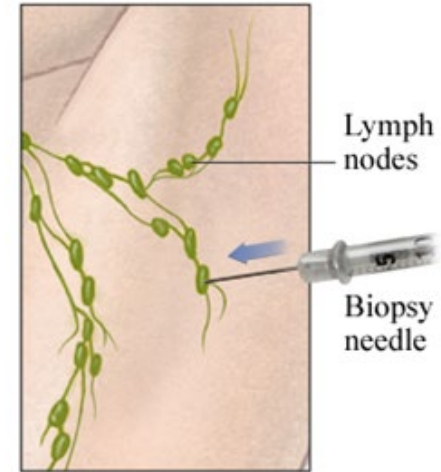
- Fatigue
- Pruritus (Hodgkin, T-cell)
- Skin Rashes

Non-specific

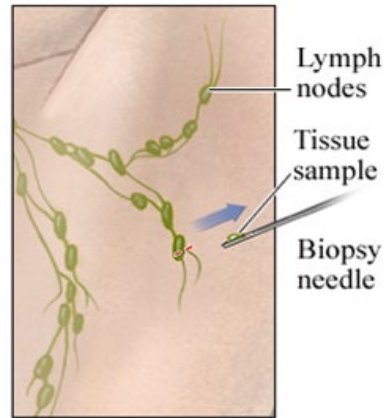


Diagnosis & Work up: Biopsy

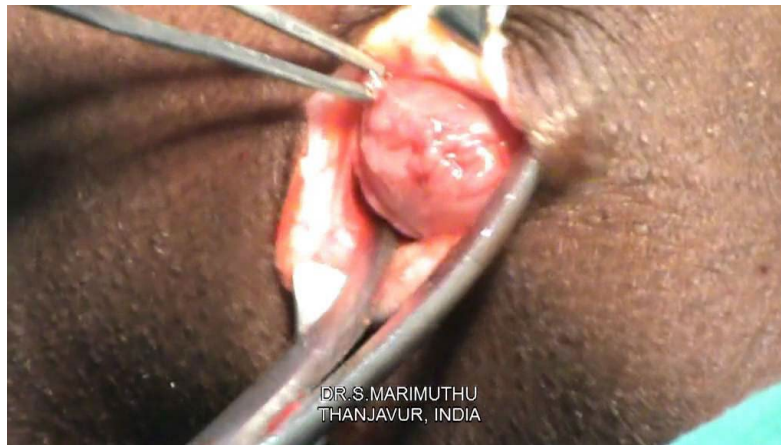
- Biopsy
 - Excisional biopsy
 - Core biopsy
 - FNA not preferred



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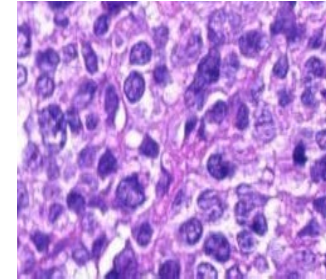
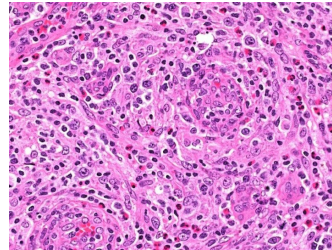
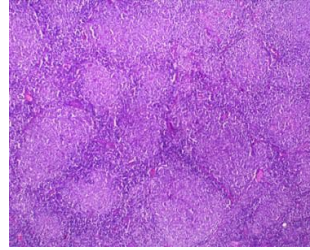


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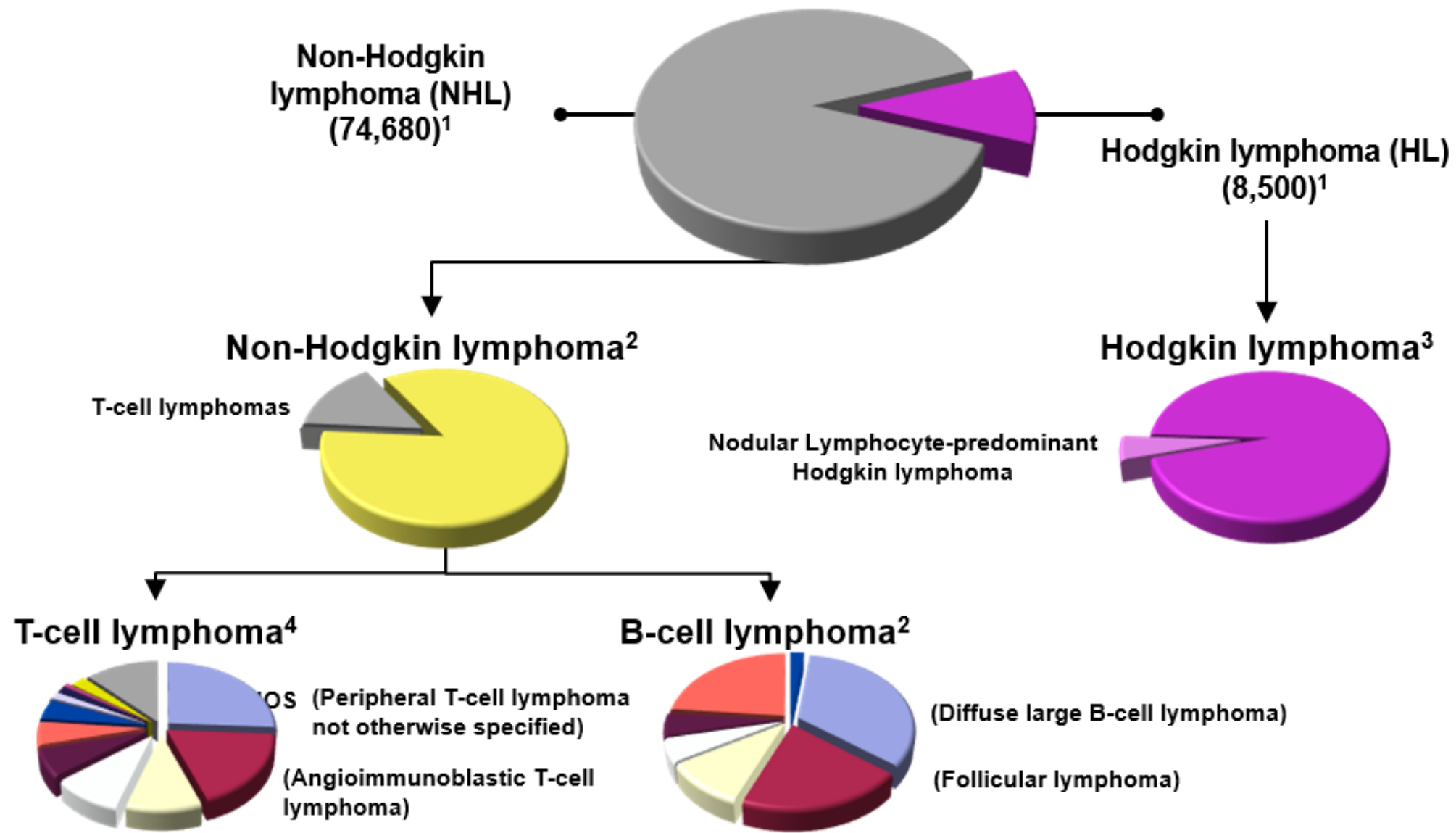
Many lymphoma entities...

- Non-Hodgkin lymphoma
 - B- cell lymphomas
 - T-cell lymphomas



- Hodgkin lymphoma
 - Reed-Sternberg cells

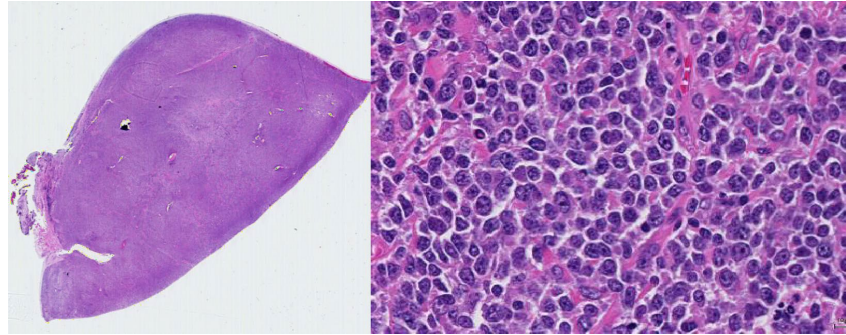




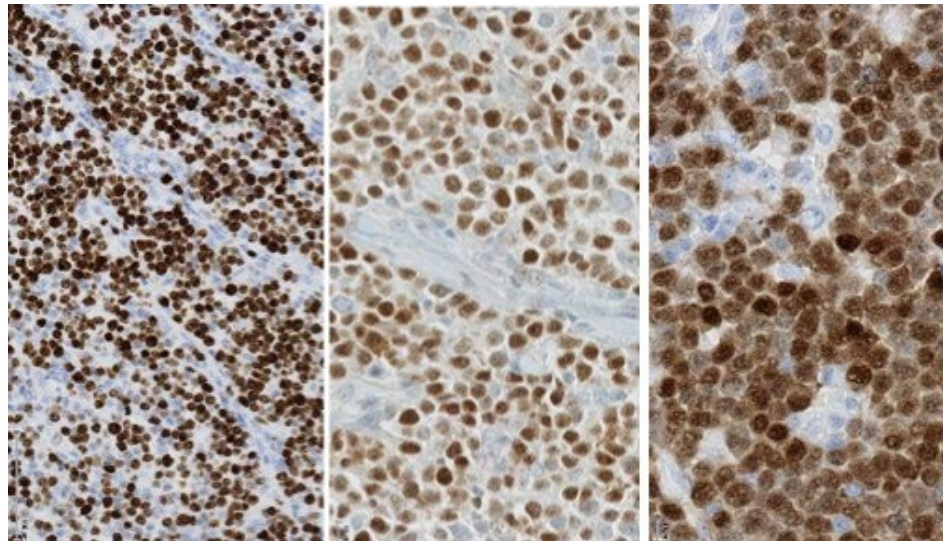
References: 1. American Cancer Society. *Cancer Facts & Figures 2018*. Atlanta, GA: American Cancer Society; 2018. 2. About Non-Hodgkin Lymphoma. American Cancer Society Web site. <https://www.cancer.org/cancer/non-hodgkin-lymphoma/about/types-of-non-hodgkin-lymphoma.html>. Updated March 24, 2017. Accessed January 15, 2018. 3. Küppers R. *Nat Rev Cancer*. 2009;9(1):15-27. 4. Vose J et al; International T-Cell Lymphoma Project. *J Clin Oncol*. 2008;26(25):4124-4130.

Tools to classify lymphoma entities... (1)

Morphology

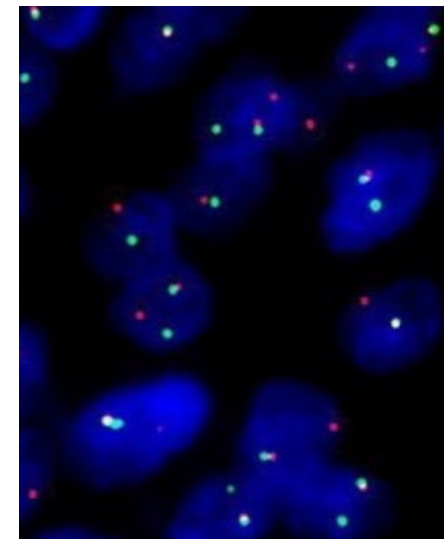


Immunohistochemistry



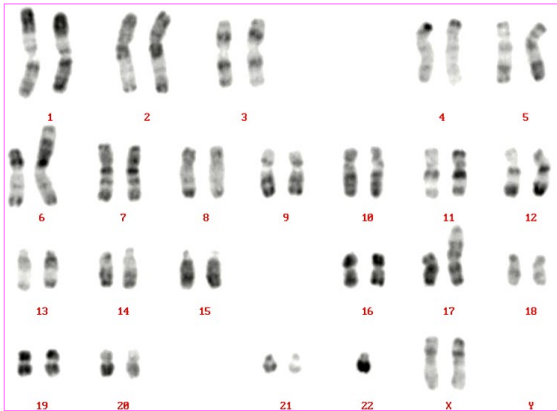
FISH

(fluorescence in situ hybridization)



Tools to classify/study lymphoma entities... (2)

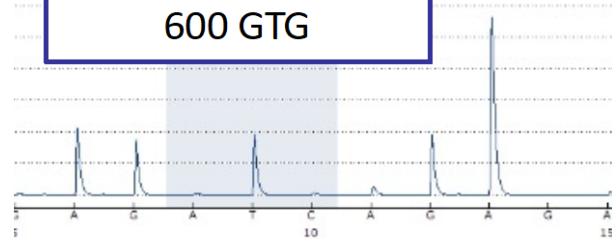
Chromosome abnormalities



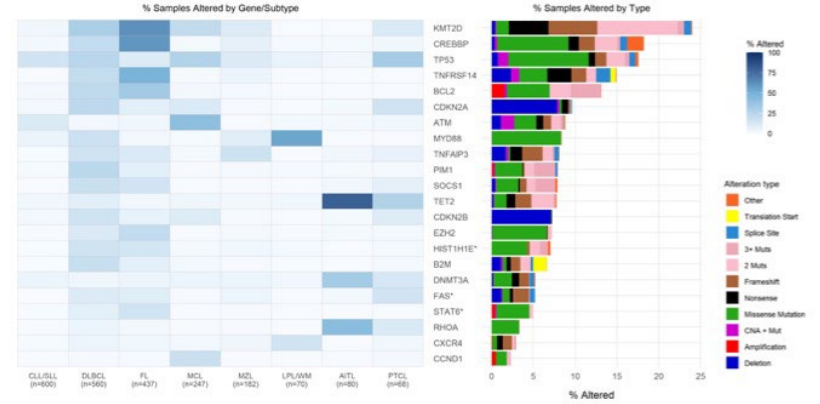
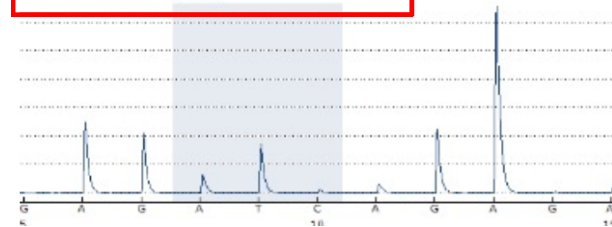
Mutation of genes



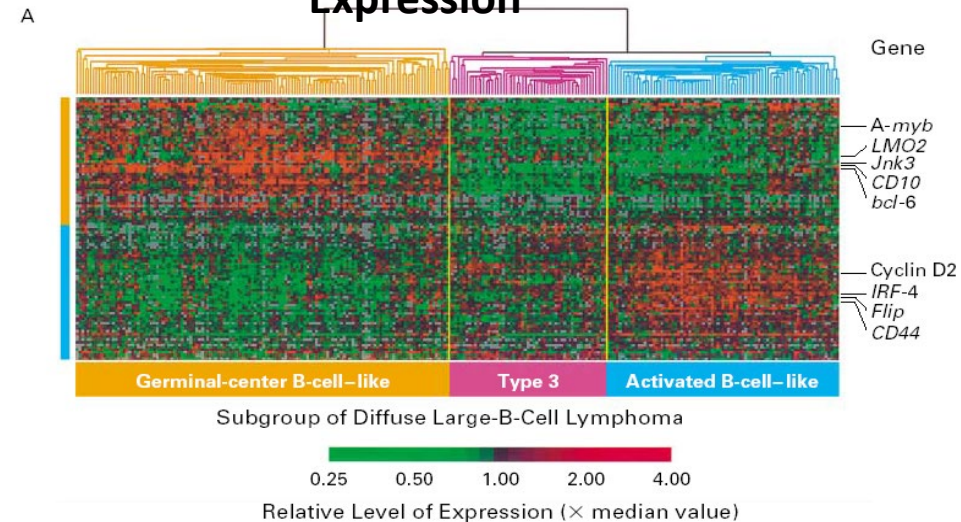
Wild-type sequence
600 GTG



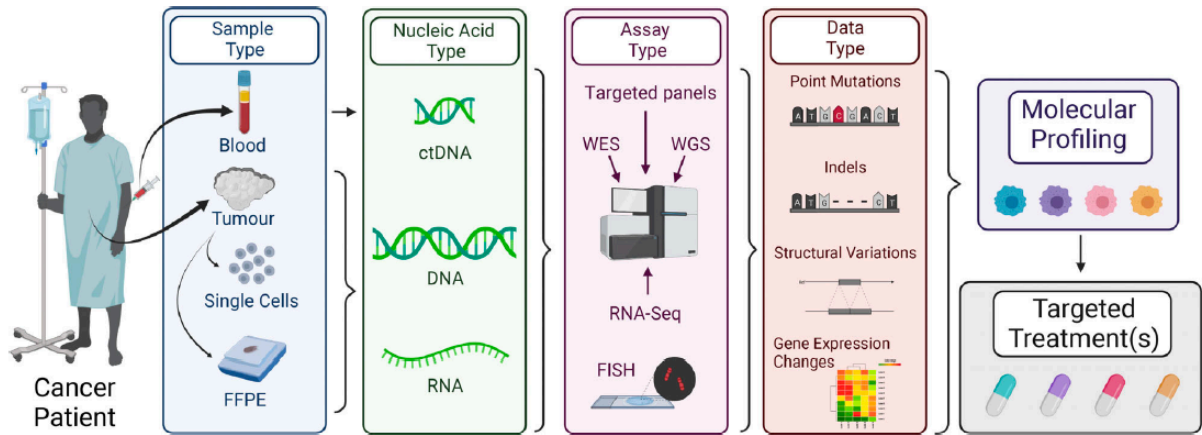
GTG>GAG
c.1799T>A (p.V600E)



Panel of Gene Expression



Tumor biology: mutations ...



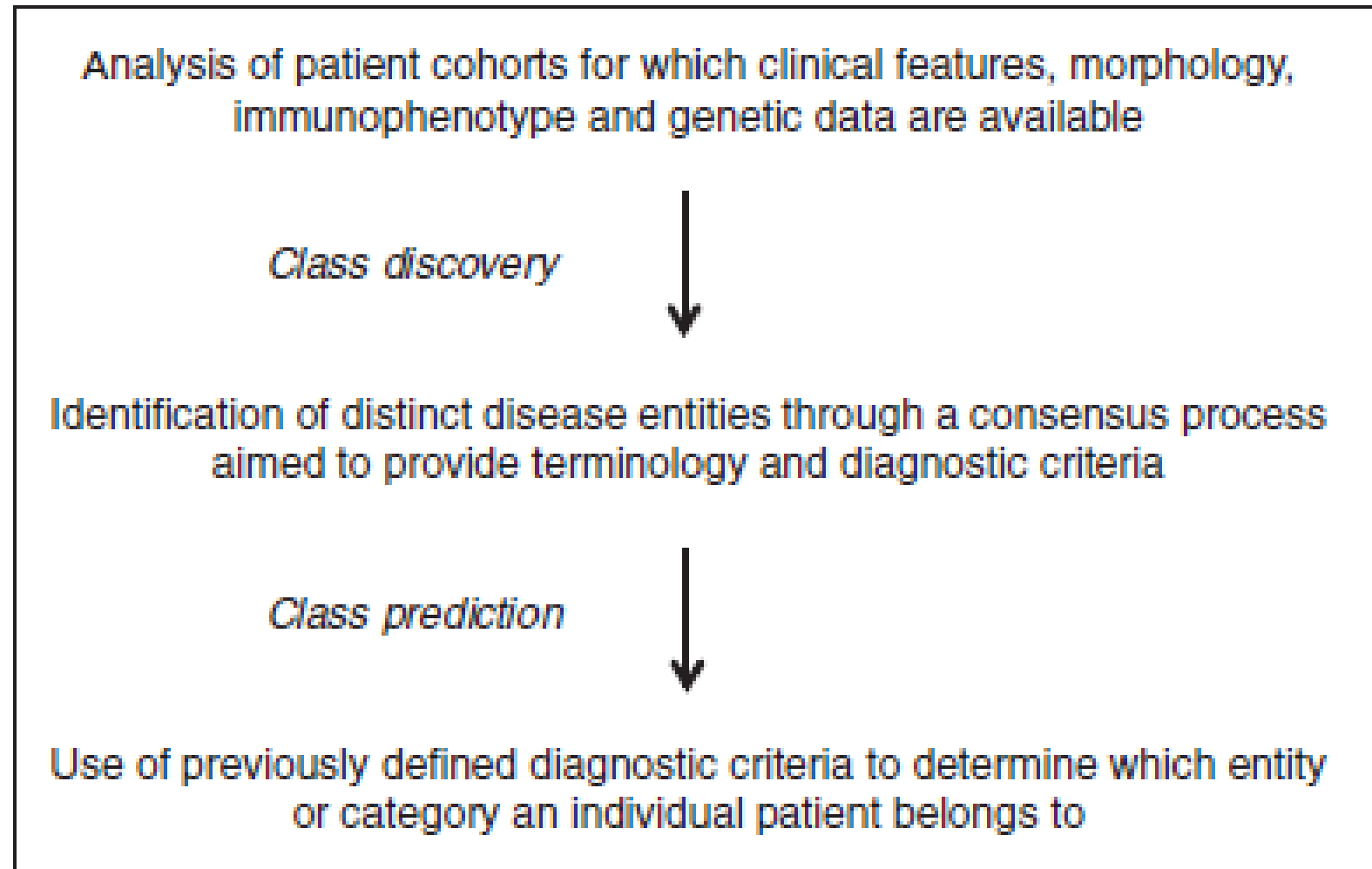
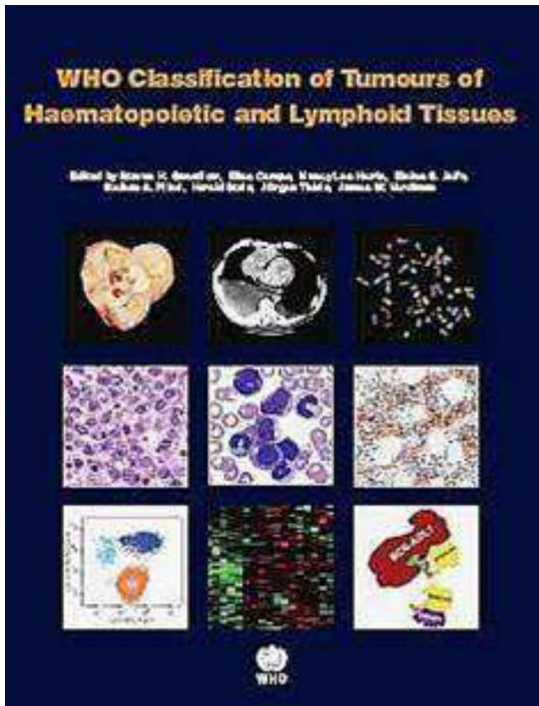


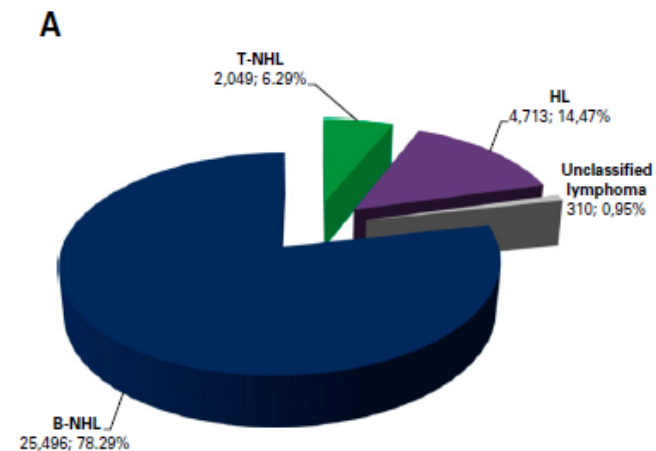
Figure 1. The classification process.

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

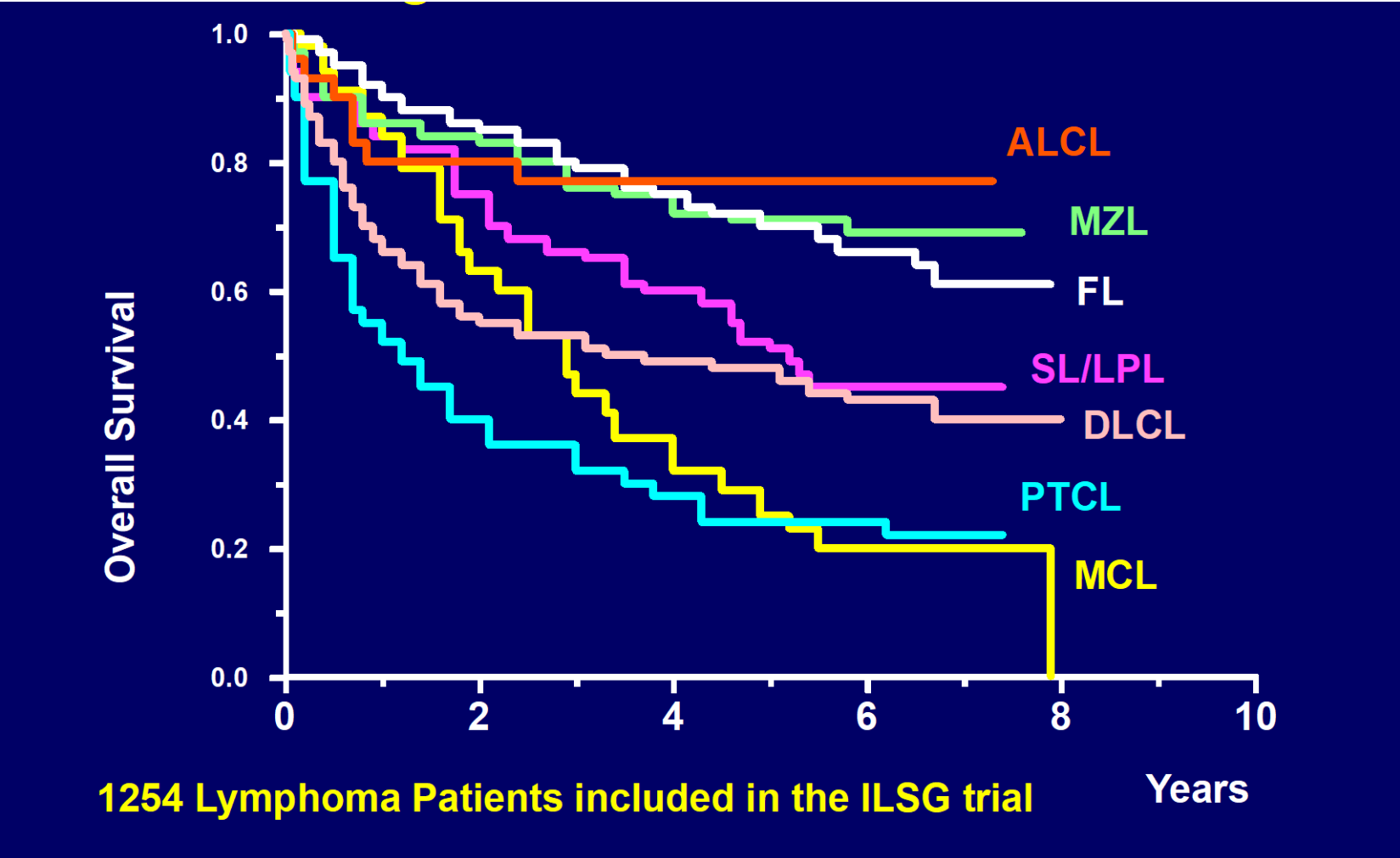
Mature B-cell neoplasms
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis*
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
<i>Splenic B-cell lymphoma/leukemia, unclassifiable</i>
<i>Splenic diffuse red pulp small B-cell lymphoma</i>
<i>Hairy cell leukemia-variant</i>
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
<i>Pediatric nodal marginal zone lymphoma</i>
Follicular lymphoma
In situ follicular neoplasia*
Duodenal-type follicular lymphoma*
Pediatric-type follicular lymphoma*
<i>Large B-cell lymphoma with IRF4 rearrangement*</i>
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*
<i>EBV⁺ mucocutaneous ulcer*</i>
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
<i>HHV8⁺ DLBCL, NOS*</i>
Burkitt lymphoma
<i>Burkitt-like lymphoma with 11q aberration*</i>
High-grade B-cell lymphoma, with <i>MYC</i> and <i>BCL2</i> and/or <i>BCL6</i> 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
<i>Chronic lymphoproliferative disorder of NK cells</i>
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

B-cell**T-cell****Table 1. (continued)**

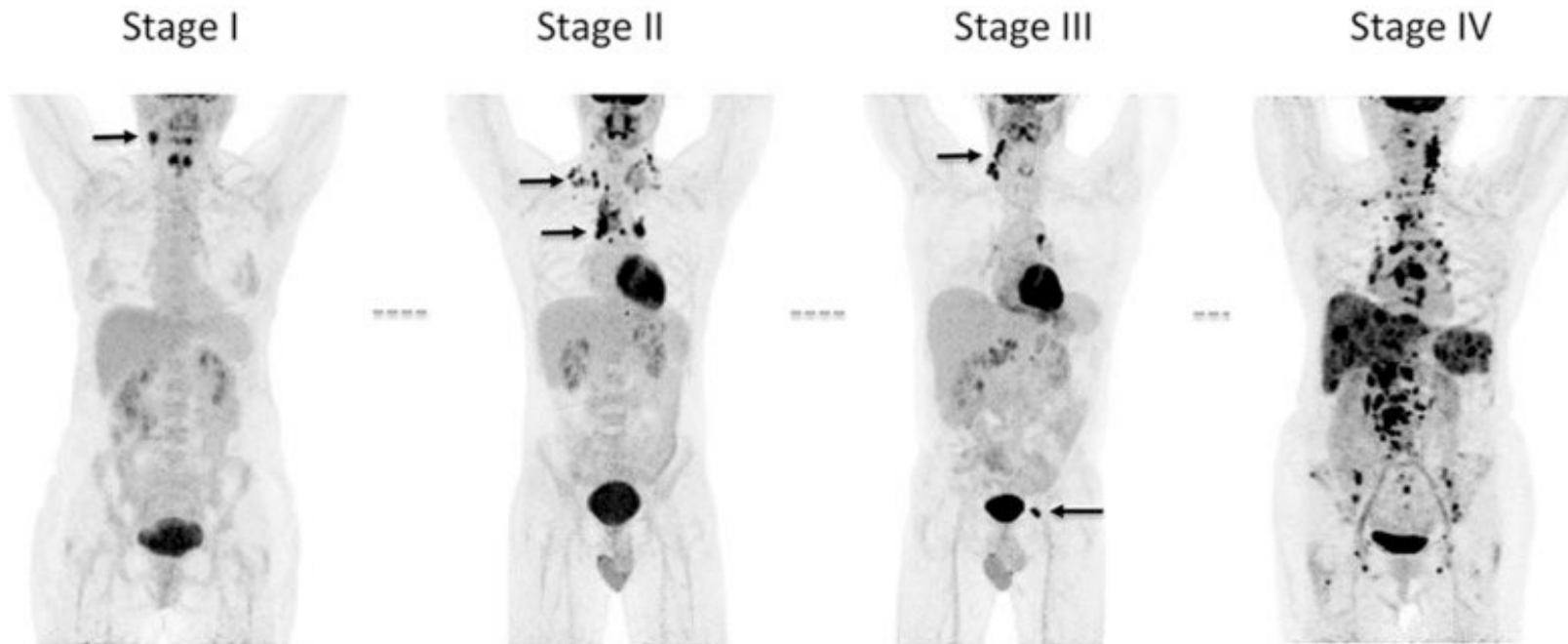
Monomorphic epitheliotropic intestinal T-cell lymphoma*
<i>Indolent T-cell lymphoproliferative disorder of the GI tract*</i>
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30 ⁺ T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous γδ T-cell lymphoma
<i>Primary cutaneous CD8⁺ aggressive epidermotropic cytotoxic T-cell lymphoma*</i>
<i>Primary cutaneous acral CD8⁺ T-cell lymphoma*</i>
<i>Primary cutaneous CD4⁺ small/medium T-cell lymphoproliferative disorder*</i>
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
<i>Follicular T-cell lymphoma*</i>
<i>Nodal peripheral T-cell lymphoma with TFH phenotype*</i>
Anaplastic large-cell lymphoma, ALK ⁺
Anaplastic large-cell lymphoma, ALK ⁻ *
<i>Breast implant-associated anaplastic large-cell lymphoma*</i>
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*

T-cell**Hodgkin****PTLD****Histiocytic/
Dendritic cell**

Different diseases, different prognosis, different treatments...

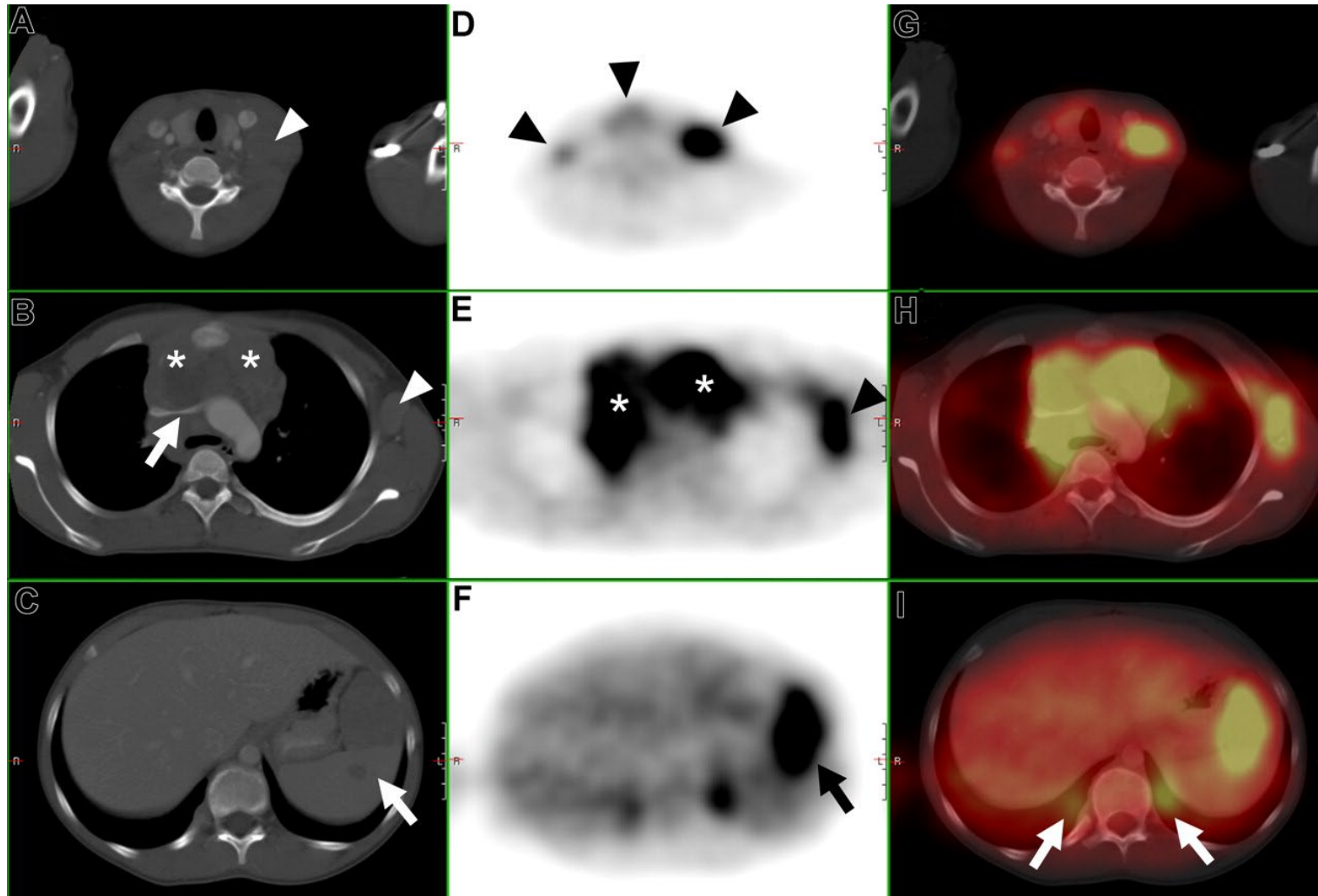


Staging of lymphoma



Tarek Christoffer El-Galaly, MD, DMSc, Lars Christian Gormsen, MD, PhD, Martin Hutchings, MD, PhD
PET/CT for Staging; Past, Present, and Future. *Seminars Nuc Med*, vol 48(1):4-16, 2018
<https://doi.org/10.1053/j.semnuclmed.2017.09.001>

CT, FDG-PET, and FDG-PET/CT fusion



Thomas C. Kwee et al. Blood 2008;111:504-516

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Prognostic scores

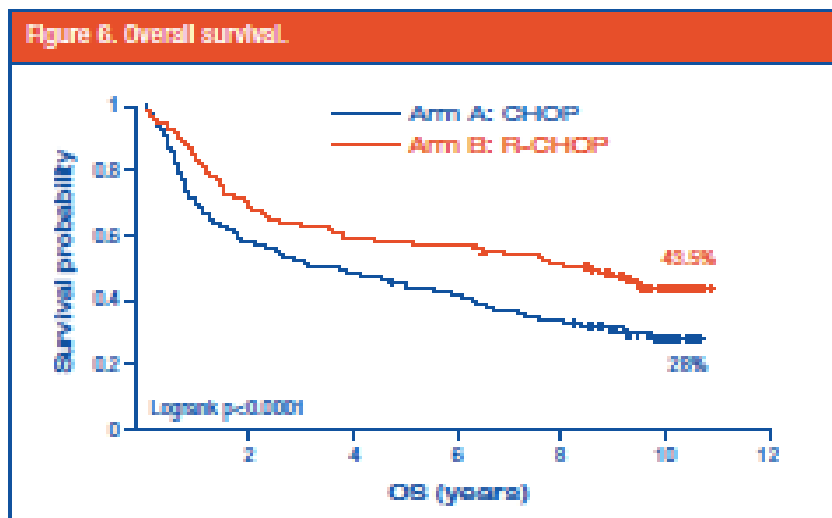
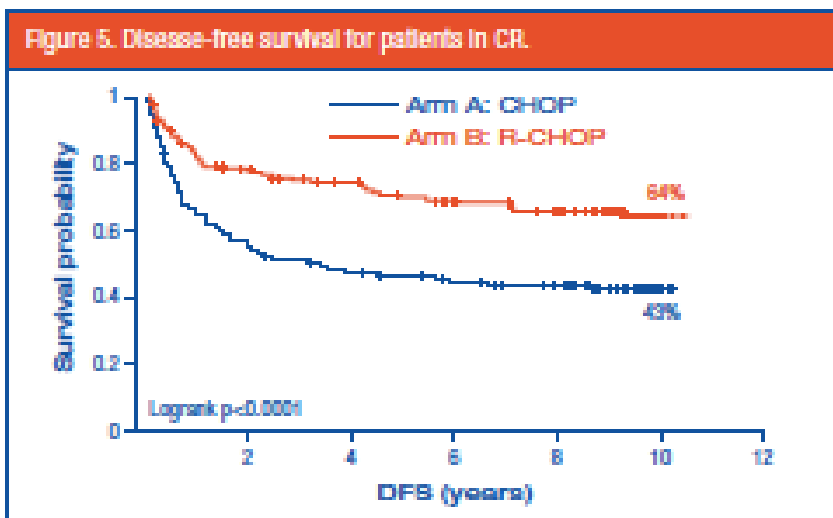
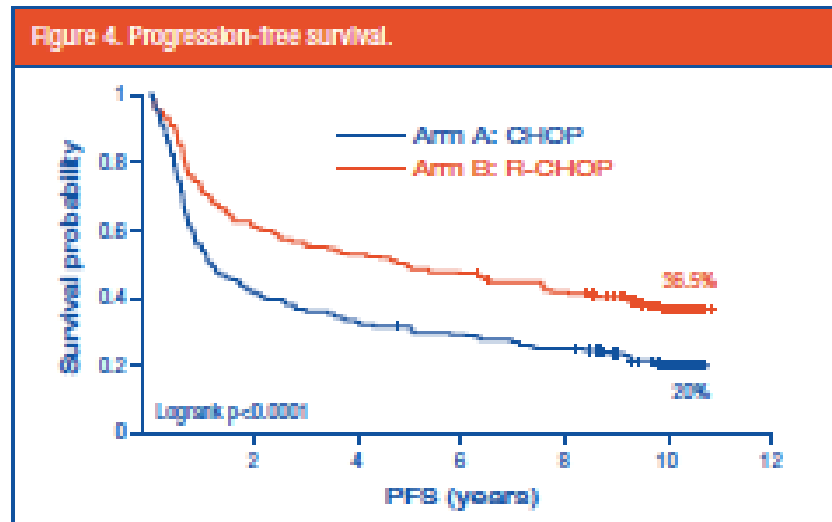
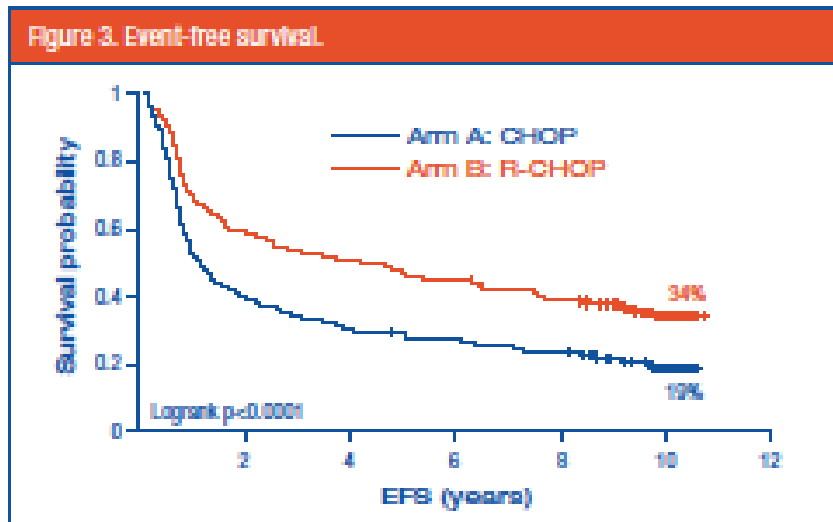
- **Predict overall and progression-free survival of NHL based on risk factors**
- **International Prognostic Score (IPI)**
 - One point is assigned for each of these risk factors:
 - age >60 years;
 - stage III or IV disease;
 - elevated serum LDH;
 - Eastern Cooperative Oncology Group (ECOG) performance status of >1
 - Extranodal sites >1
- aalPI NHL (stage, LDH, ECOG PS)
- Others: FLIPI1/2 (FL), MIPI (MCL), IPS (HL), PIT (T-cell)

Progressively replaced by biology

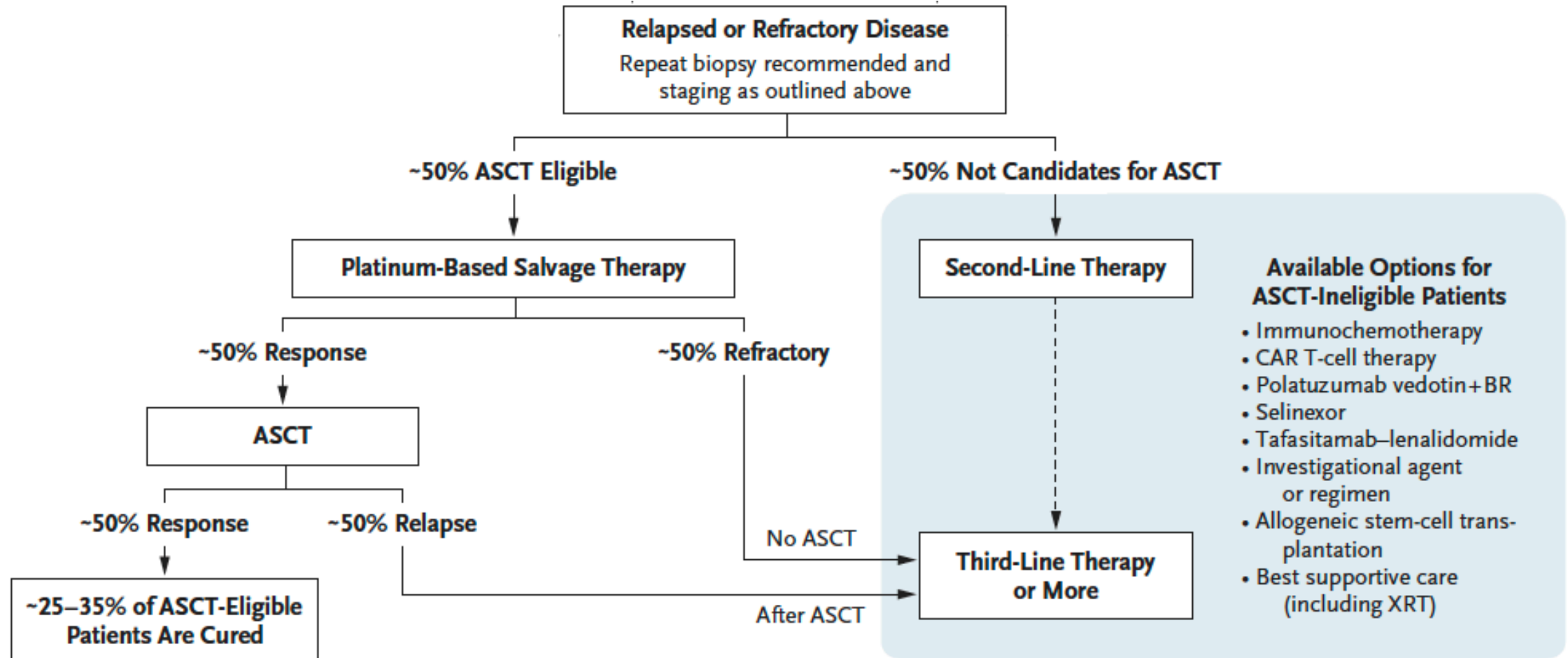
Diffuse large B-cell lymphoma treatments: After diagnosis

- Chemotherapy: combination chemo-immunotherapy
 - R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone)
4 or 6 cycles
 - R-da-EPOCH (Rituximab, Etoposide, Prednisone, Cyclophosphamide, Doxorubicin)
- Radiation Consolidation

Rituximab-CHOP 98-5 GELA study: 10 years follow-up



Relapsed DLBCL Treatment algorithm in 2021



ORIGINAL ARTICLE

Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma

F.L. Locke, D.B. Miklos, C.A. Jacobson, M.-A. Perales, M.-J. Kersten, O.O. Oluwole, A. Ghobadi, A.P. Rapoport, J. McGuirk, J.M. Pagel, J. Muñoz, U. Farooq, T. van Meerten, P.M. Reagan, A. Sureda, I.W. Flinn, P. Vandenberghe, K.W. Song, M. Dickinson, M.C. Minnema, P.A. Riedell, L.A. Leslie, S. Chaganti, Y. Yang, S. Filosto, J. Shah, M. Schupp, C. To, P. Cheng, L.I. Gordon, and J.R. Westin, for All ZUMA-7 Investigators and Contributing Kite Members*

ORIGINAL ARTICLE

Second-Line Tisagenlecleucel or Standard Care in Aggressive B-Cell Lymphoma

M.R. Bishop, M. Dickinson, D. Purtil, P. Barba, A. Santoro, N. Hamad, K. Kato, A. Sureda, R. Greil, C. Thieblemont, F. Morschhauser, M. Janz, I. Flinn, W. Rabitsch, Y.-L. Kwong, M.J. Kersten, M.C. Minnema, H. Holte, E.H.L. Chan, J. Martinez-Lopez, A.M.S. Müller, R.T. Maziarz, J.P. McGuirk, E. Bachy, S. Le Gouill, M. Dreyling, H. Harigae, D. Bond, C. Andreadis, P. McSweeney, M. Kharfan-Dabaja, S. Newsome, E. Degtyarev, R. Awasthi, C. del Corral, G. Andreola, A. Masood, S.J. Schuster, U. Jäger, P. Borchmann, and J.R. Westin

Articles

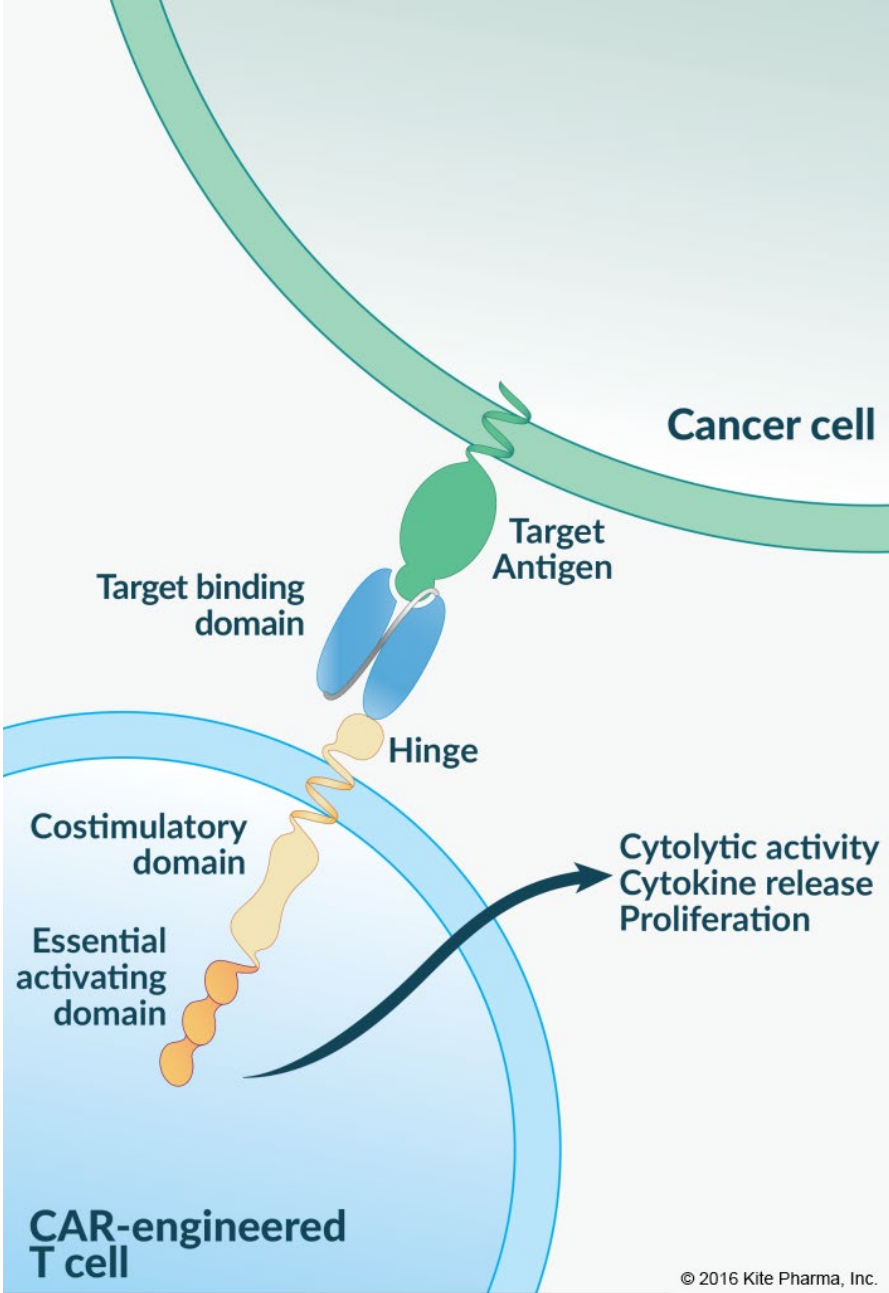


Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial

Manali Kamdar, Scott R Solomon, Jon Arnason, Patrick B Johnston, Bertram Glass, Veronika Bachanova, Sami Ibrahim, Stephan Mielke, Pim Mutsaers, Francisco Hernandez-Ilizaliturri, Koji Izutsu, Franck Morschhauser, Matthew Lunning, David G Maloney, Alessandro Crotta, Sandrine Montheard, Alessandro Previtall, Lara Stepan, Ken Ogasawara, Timothy Mack*, Jeremy S Abramson, for the TRANSFORM Investigators†

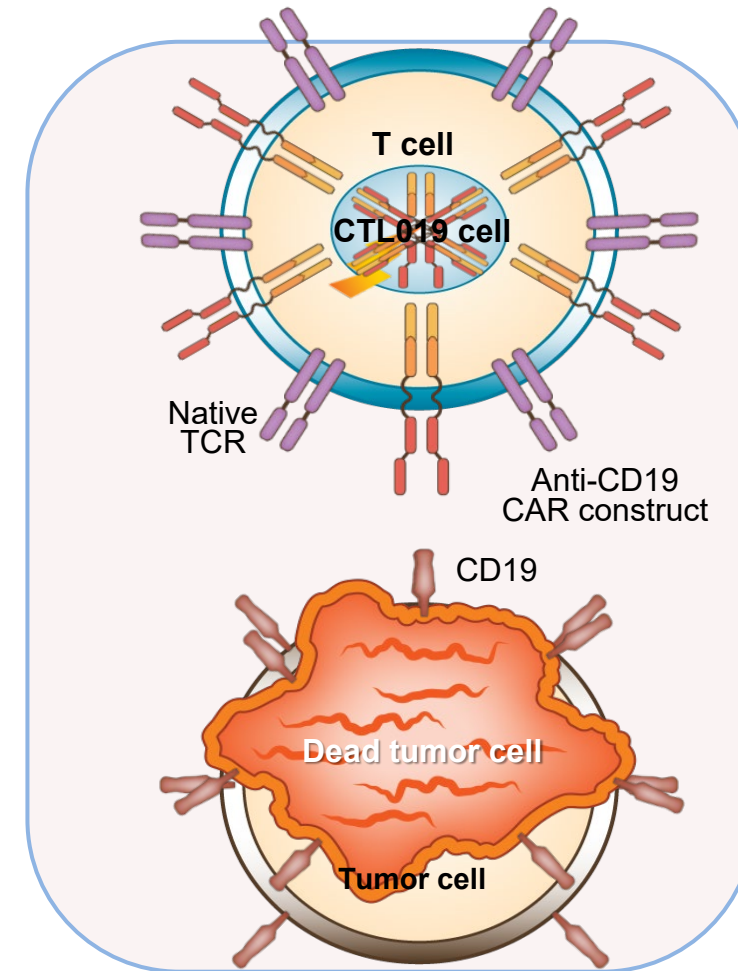
- Locke FL et al, N Engl J Med. 2022 Feb 17;386(7):640-654 ; Bishop MR et al, N Engl J Med. 2022 Feb 17;386(7):629-639. ; Kamdar M et al, Lancet. 2022 Jun 18;399(10343):2294-2308.

Chimeric Antigen Receptor T-cell (CAR T or CAR T-cell)



How do CAR T cells work ?

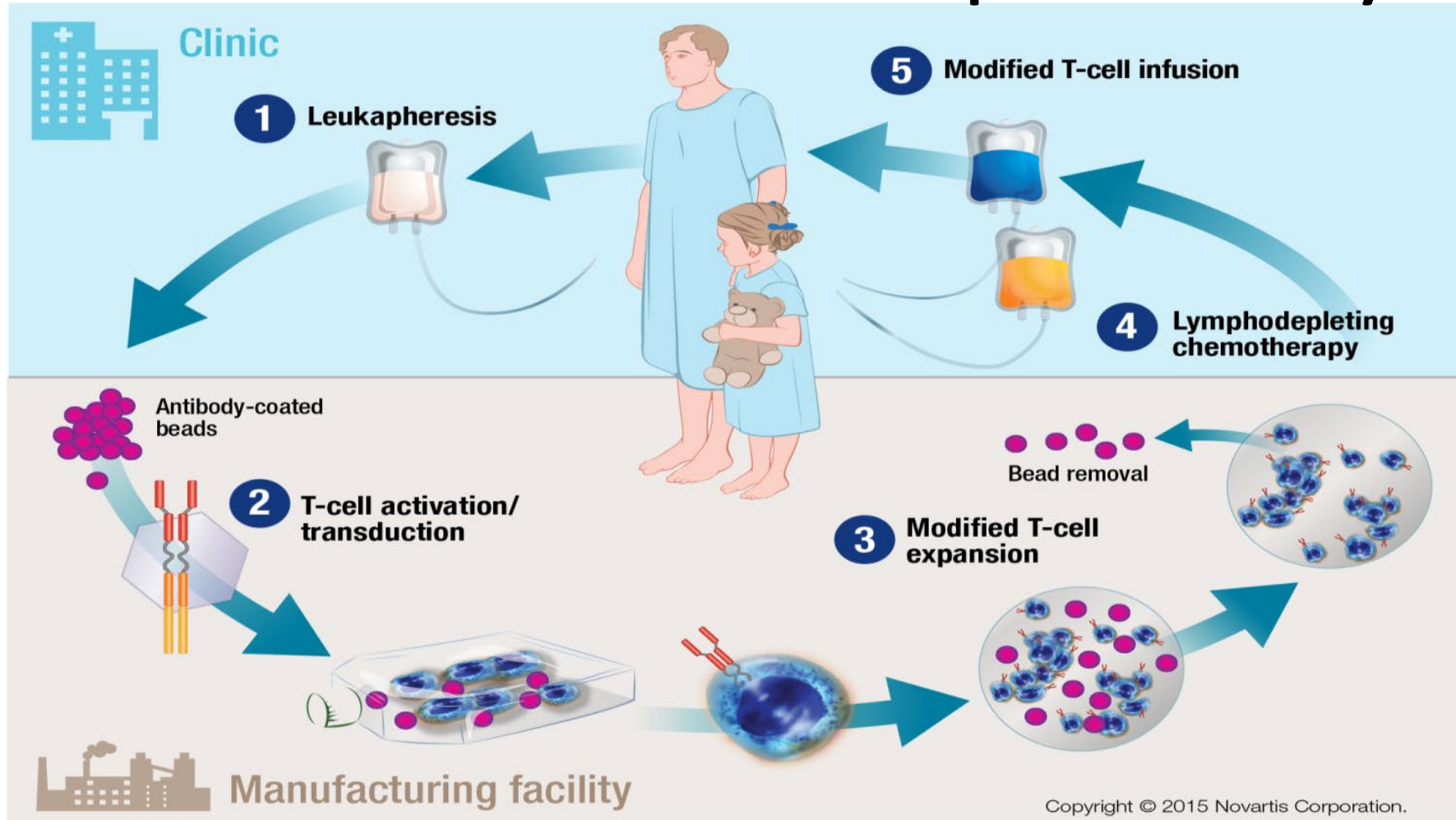
- Gene transfer technology is used to stably express CARs on T cells^{1,2}
 - Novel antigen specificity
- CAR-T cells can thus be directed against any tumor cell that expresses the CD19 surface antigen^{1,3}
- CAR-T cell – therapy takes advantage of the cytotoxic potential of T cells, thereby killing tumor cells in an antigen-dependent manner^{1,3}
- Persistent CAR-T cells consist of both effector (cytotoxic) and central memory T cells³



CAR-T cells, chimeric antigen receptor T-cells; CD19, cluster of differentiation 19; TCR, T-cell receptor.

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.

CAR-T: How does it work practically?

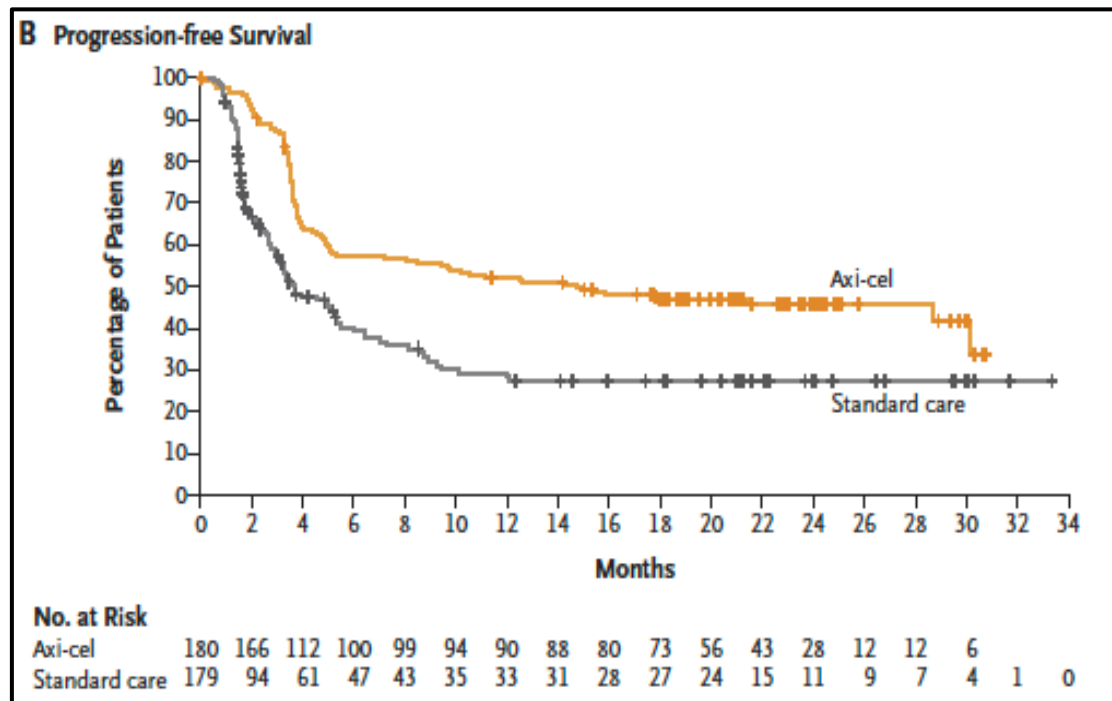


CAR T cell side effects

- **Cytokine release syndrome (CRS)**
- **Neurologic Toxicity**
- B-cell aplasia
 - Hypogammaglobulinemia
 - Infections
- Myelosuppression
- GI symptoms
- Hypersensitivity reactions

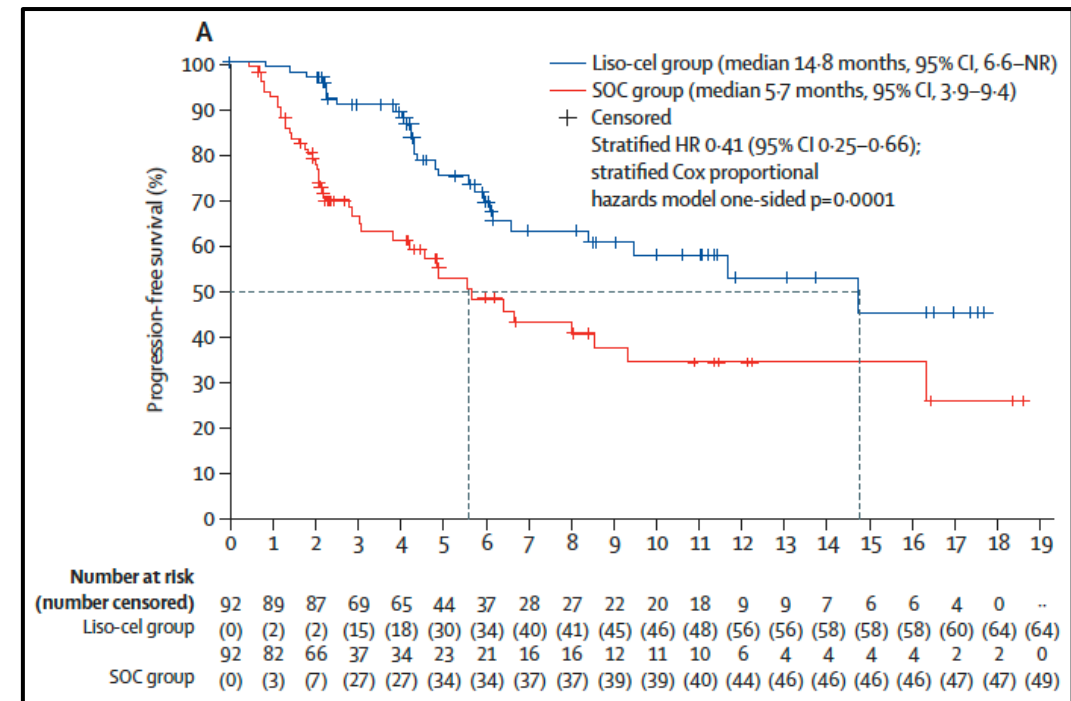
CAR T already replaces ASCT in patients with DLBCL and early relapse

Zuma-7 – Progression Free Survival
Axi-cel > ASCT



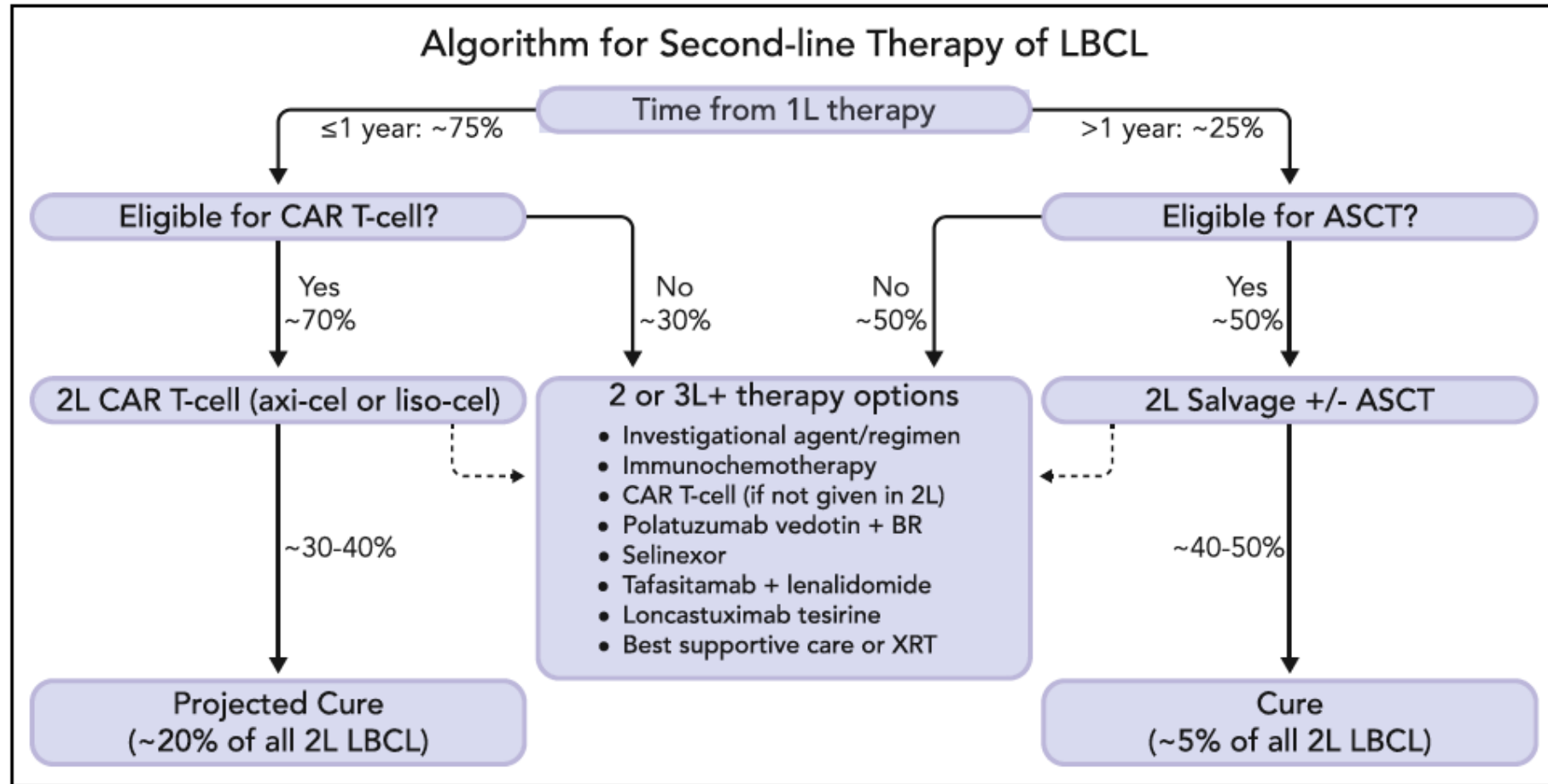
Locke F et al, NEJM 2021

Transform – Progression Free Survival
Liso-cel > ASCT



Kamdar M et al, Lancet 2022

Relapsed DLBCL: Treatment algorithm in 2022

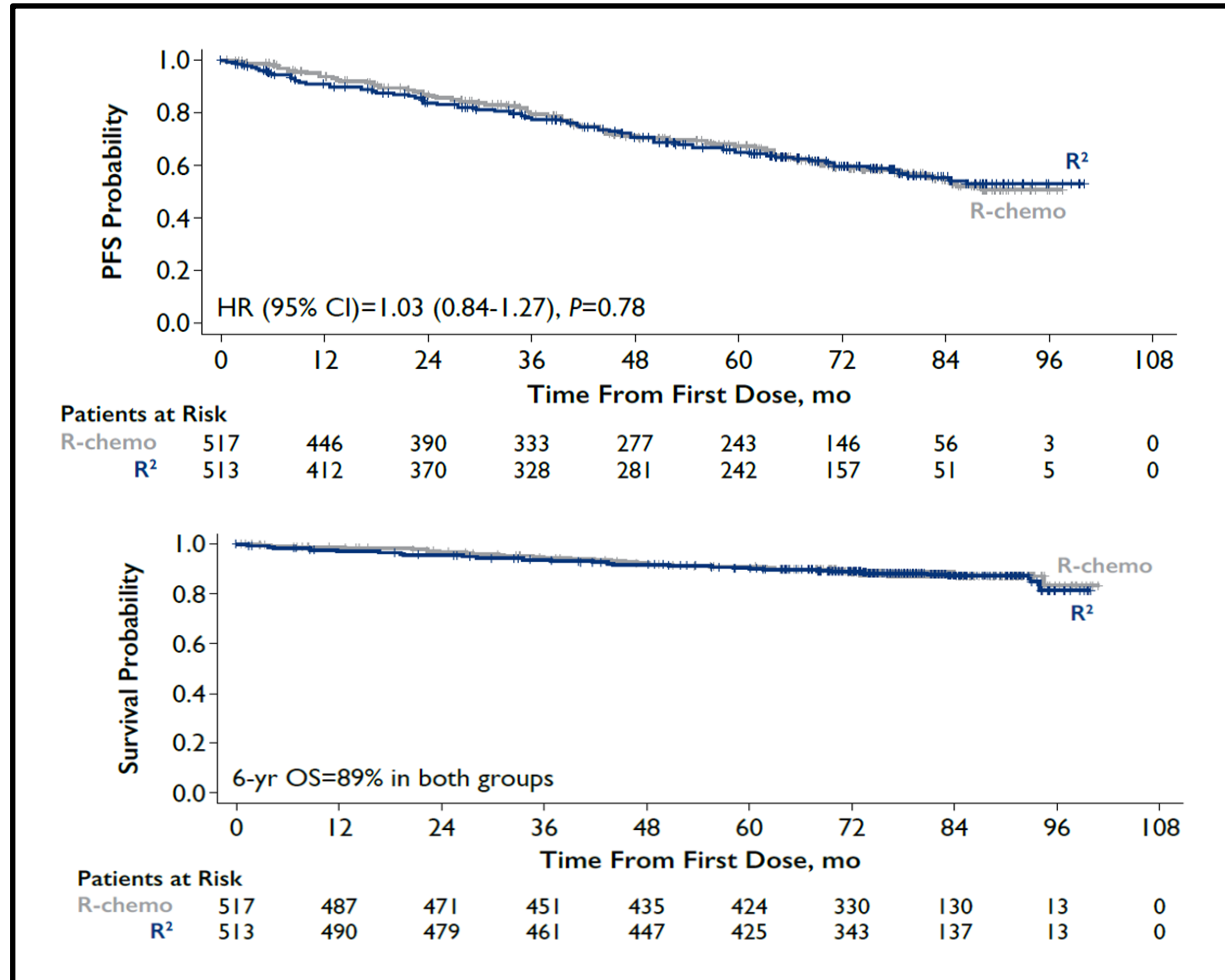


Follicular Lymphoma Treatment : 1st line :

- Observation +++
- Rituximab single agent
- Immuno-chemotherapy:
 - Rituximab or obinutuzumab + Chemo
 - (O=obinutuzumab=G=Gazyva)
 - R/G-CHOP, R/G-bendamustine; R/G-CVP
- +/- Rituximab/Obinutuzumab maintenance
- Rituximab / lenalidomide (Revlimid) – R2
- Radiation
 - Boom Boom (2GY x2)

Moving away from chemotherapy in the first line setting?

Rituximab-Lenalidomide:



Gr 3-4 neutropenia and febrile neutropenia

- more frequent with R-chemo

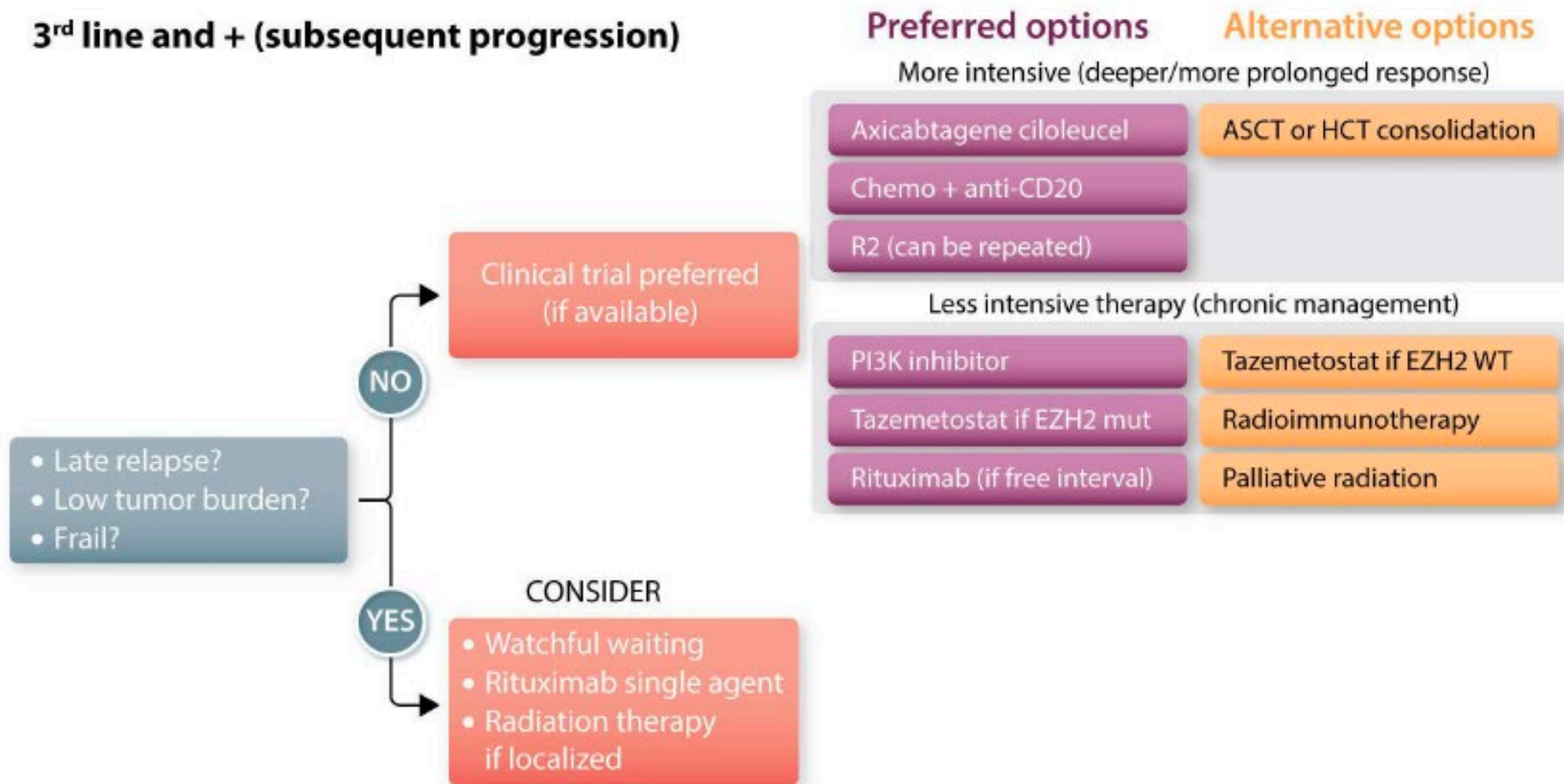
Gr 3-4 Cutaneous reactions

- More frequent with R-Len

One of the “preferred options” in NCCN guidelines

Options at later lines (3+)

3rd line and + (subsequent progression)



Always rule out histological transformation - new biopsy recommended

FOLLICULAR LYMPHOMA

53 years old patient

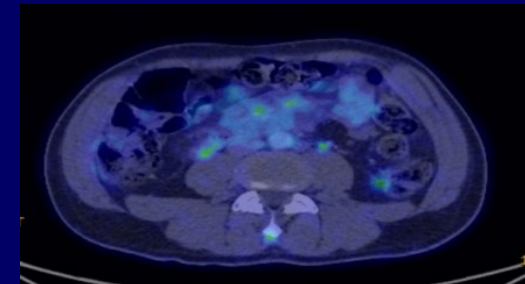
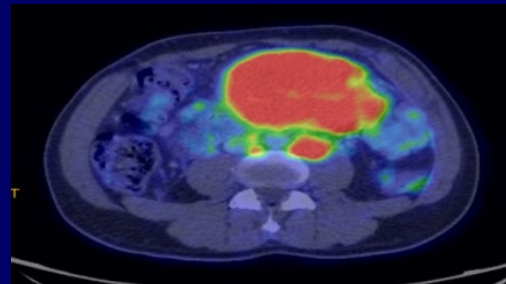
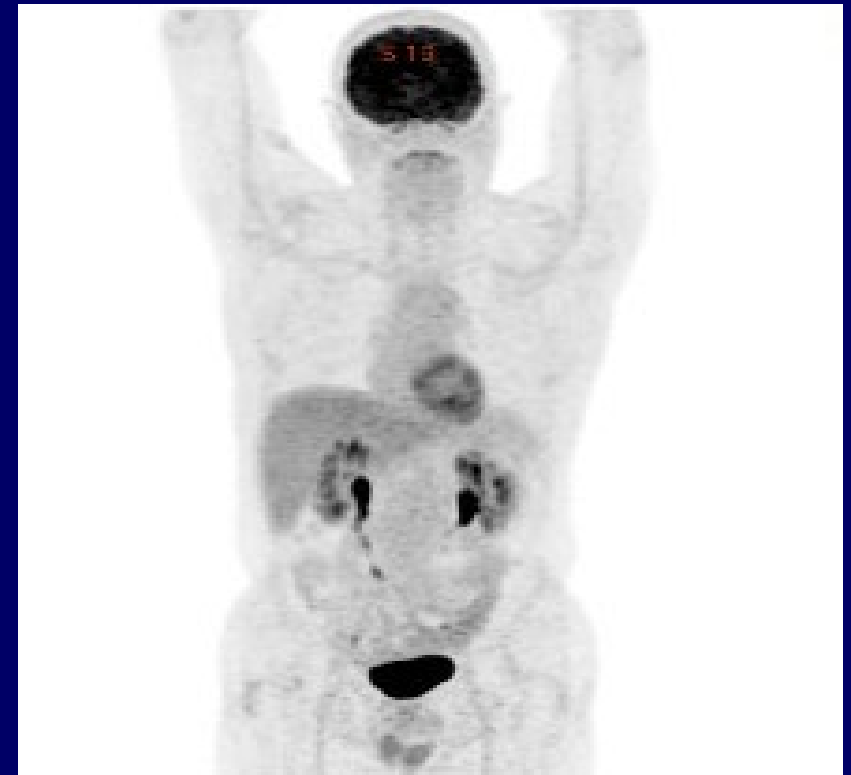
Resistant to 4 lines of subsequent Tx:

- R-CHOP x 6
- R-DHAOx + I
- Obinu + LEN
- Benda + Obinu

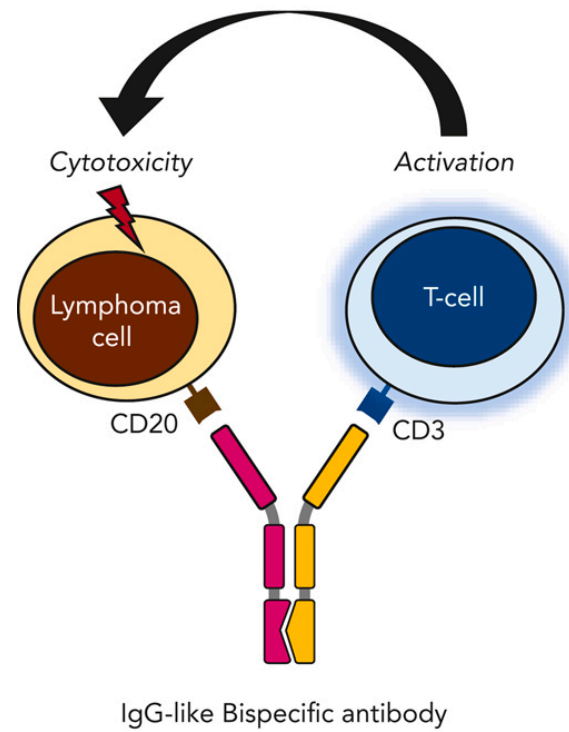
Before CAR-T



3 months post CAR-T



Bispecific antibodies



T-cell lymphoma treatments

- 1st Line
 - CHO(E)P, BV-CHP*, clinical trial
 - Cyclophosphamide, doxorubicin, vincristine, (etoposide), prednisone
 - Brentuximab vedotin + cyclophosphamide, doxorubicin, prednisone
 - Possibly auto-SCT for eligible patients who achieve remission
- Relapsed/refractory
 - Clinical trial
 - Brentuximab vedotin (for CD30+)
 - HDAC inhibitors (romidepsin)
 - Chemotherapy
 - Allogeneic stem cell transplant

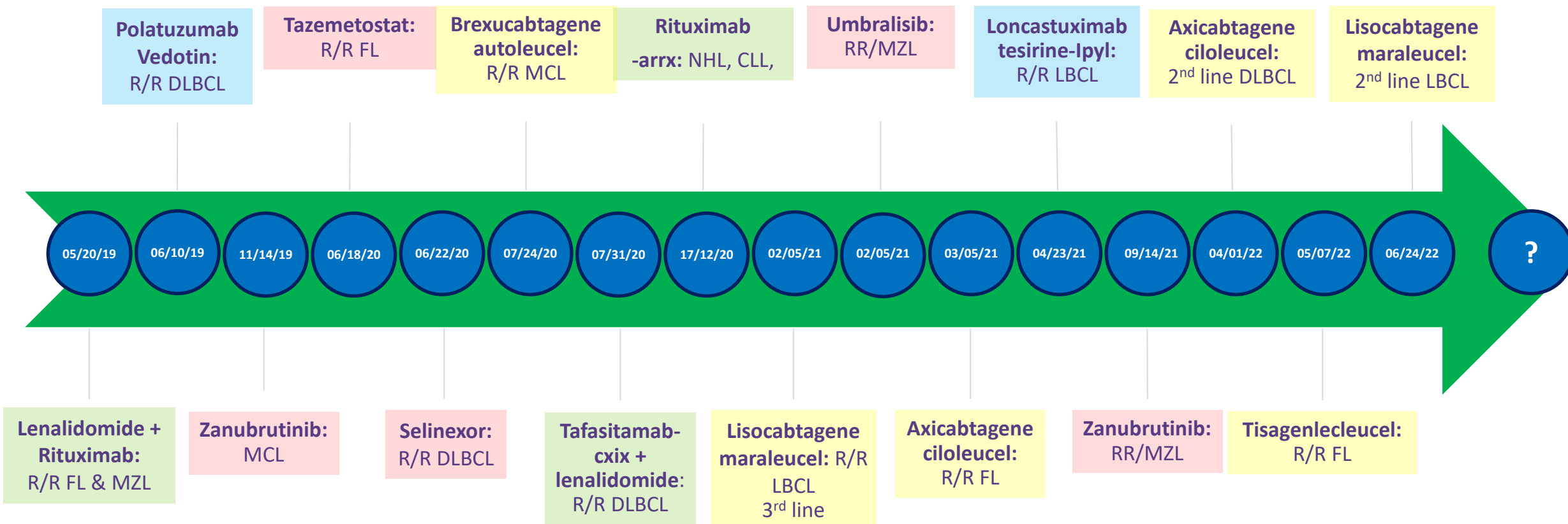
Hodgkin Lymphoma Treatment

- ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) or AVD + BV (Brentuximab Vedotin)
- BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, procarbazine)
- Second line: High dose therapy → auto SCT
 - Brentuximab or Brentuximab + Nivolumab
 - ICE (ifosfamide, carboplatin, etoposide)
 - Pembrolizumab + GVD*
- Radiation therapy

Objectives:

- 1) Why so many different lymphoma: navigating among various diseases with different prognoses and therapy?
- 2) New standard of care for patients with the main lymphoma subtypes (diffuse large B-cell, follicular, Hodgkin lymphoma)
- 3) What to expect from new drugs on the horizon: cellular therapies, bispecific antibodies, targeted therapies, ...

Overview of B-cell lymphoma drug approvals, 2019 – 6/2022



Other New Treatment Options for Patients with B-cell Lymphoma

1. Monoclonal antibodies:
 - New anti-CD20 (ofatumomab, obinutuzumab, ublituximab, ..), tafasitamab
 - Antibody drug conjugates
 - Bi-specific Abs +++

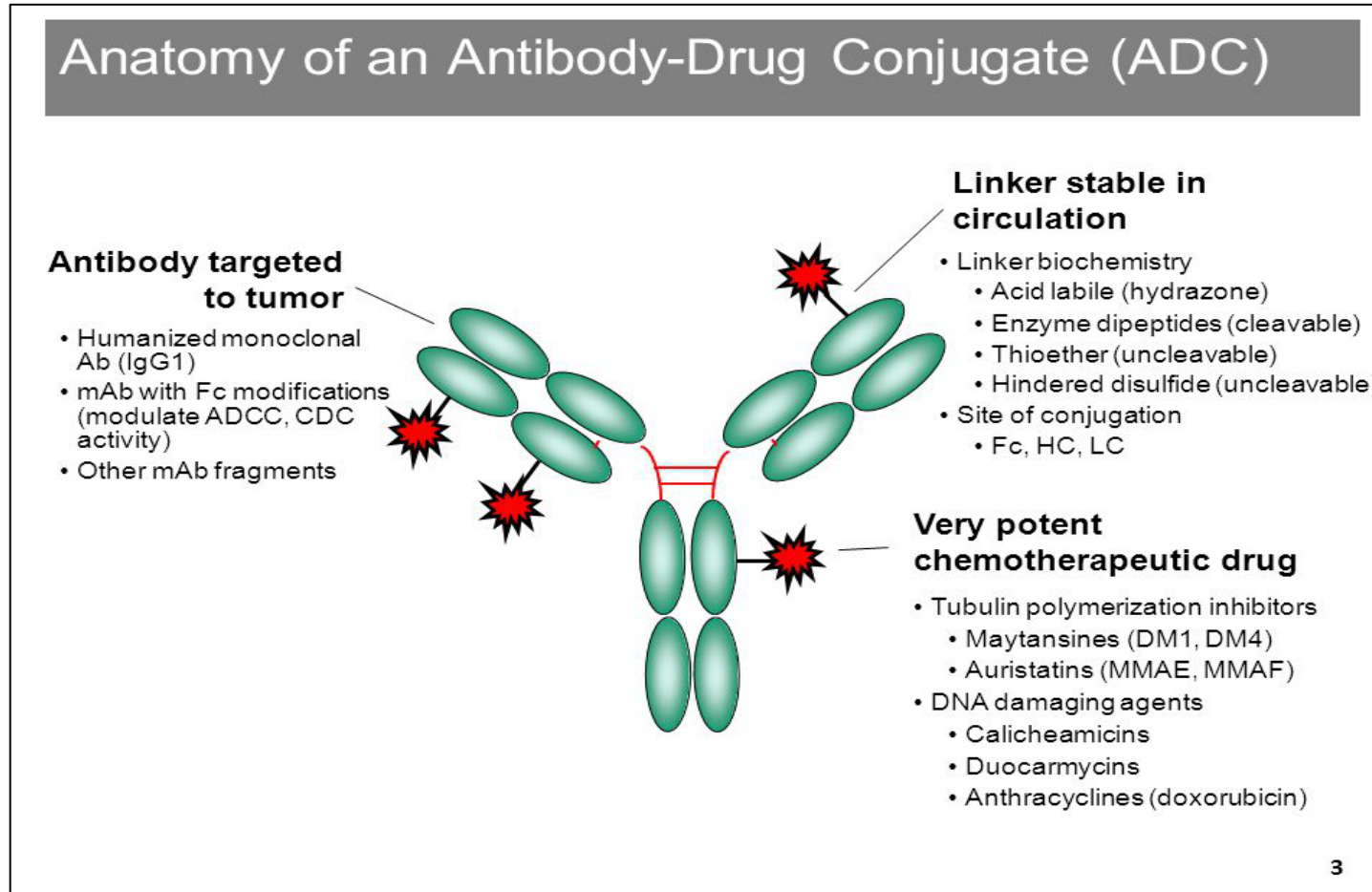
2. Improving rituximab efficacy with other agents:
 - Imids (lenalidomide) and Cellmods, anti-PD1, anti-CD47, ...

3. Kinase inhibitors:
 - PI3ki: Idelalisib, copanlisib, duvelisib, umbralisib (and Co...) ;
 - BTKi: ibrutinib (and Co)

4. Targeted agents:
 - cell survival: venetoclax, mTORi
 - epigenetic: HDACi (vorinostat), EZH2i (tazemetostat)

5. Cellular therapy (CAR-T): axi-cel, tisa-cel and liso-cel,... and others !

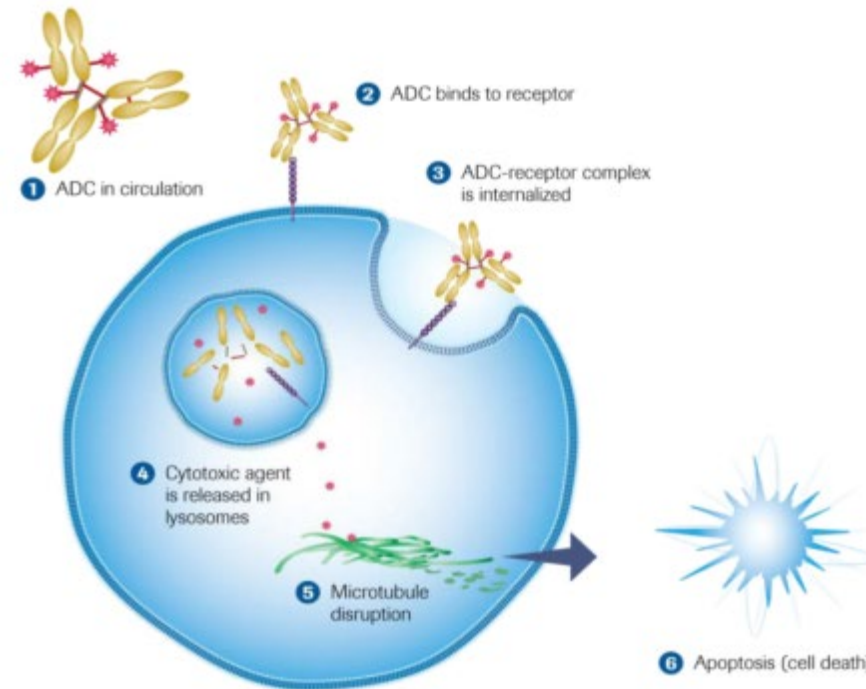
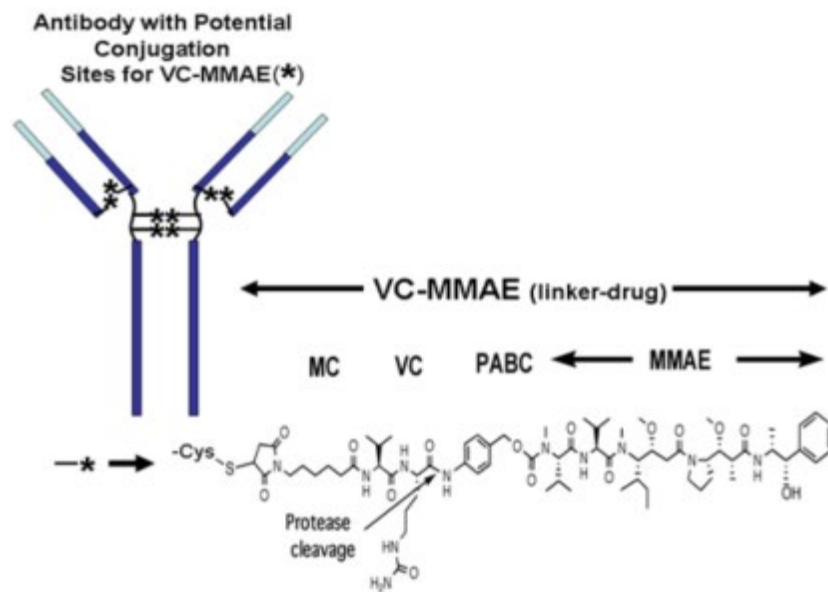
Antibody-Drug Conjugates (ADC)



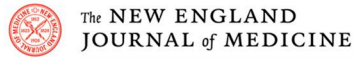
- Cytotoxic agent selected as the payload kills target cells after internalization and release inside the targeted cells.
- Stability of the linker has considerable impact on the toxicities that are then exerted by the payload.

Polatuzumab Vedotin (CD79b-ADC)

- Antibody drug conjugates (ADC) consisting of the microtubule inhibitor monomethyl auristatin E (MMAE) conjugated to CD79b monoclonal antibodies via a protease-cleavable peptide linker
- CD79b is expressed by most B-cell hematologic malignancies



Diffuse large B-cell Lymphoma: the Polarix study



ORIGINAL ARTICLE

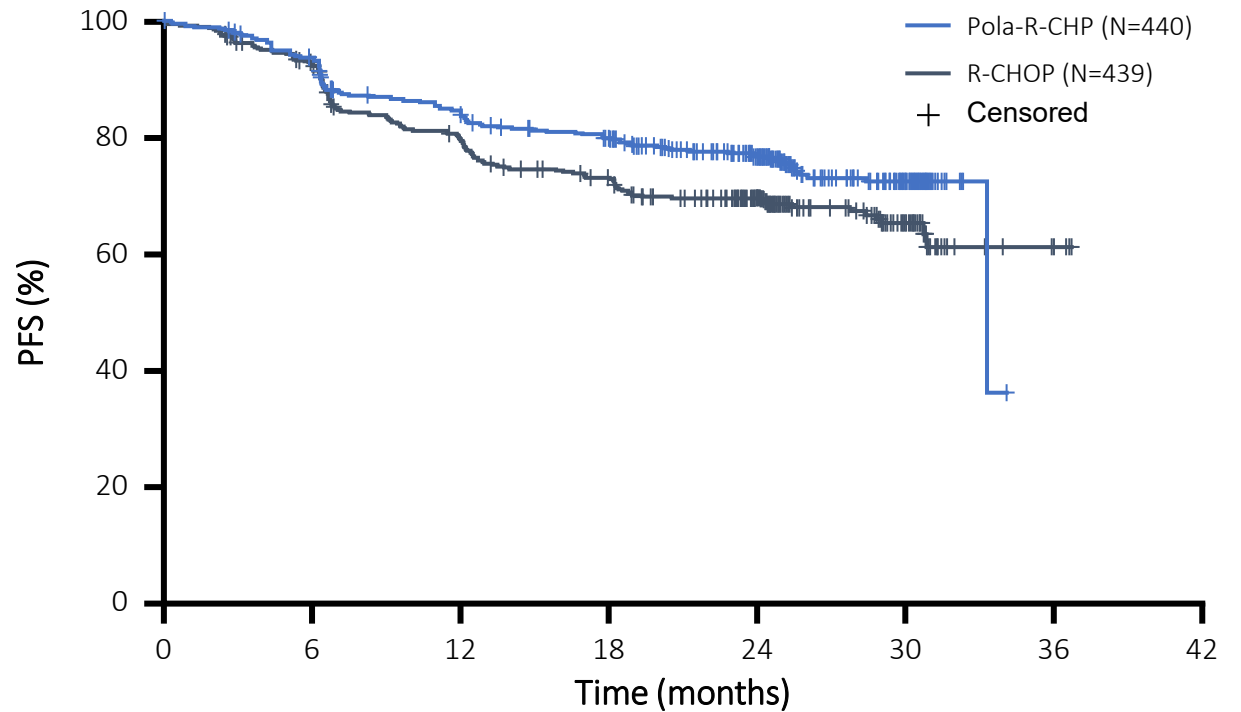
Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma

H. Tilly, F. Morschhauser, L.H. Sehn, J.W. Friedberg, M. Trneny, J.P. Sharman, C. Herbaux, J.M. Burke, M. Matasar, S. Rai, K. Izutsu, N. Mehta-Shah, L. Oberic, A. Chauchet, W. Jurczak, Y. Song, R. Greil, L. Mykhalska, J.M. Bergua-Burgues, M.C. Cheung, A. Pinto, H.-J. Shin, G. Haggood, E. Munhoz, P. Abrisqueta, J.-P. Gau, J. Hirata, Y. Jiang, M. Yan, C. Lee, C.R. Flowers, and G. Salles

Slightly more febrile neutropenia
(14% versus 8%)

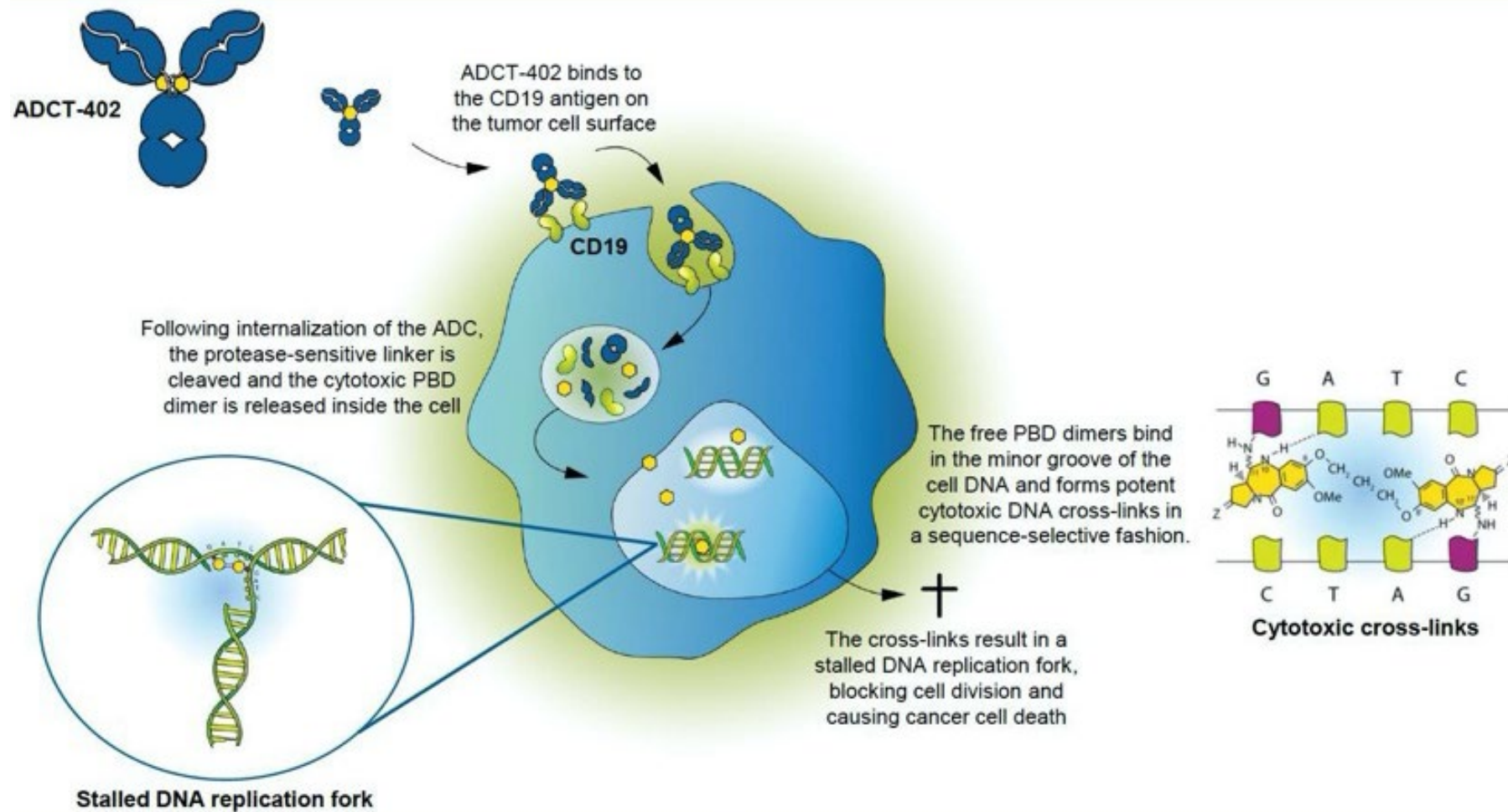
Same rate of neuropathy

Same Quality of Life scales

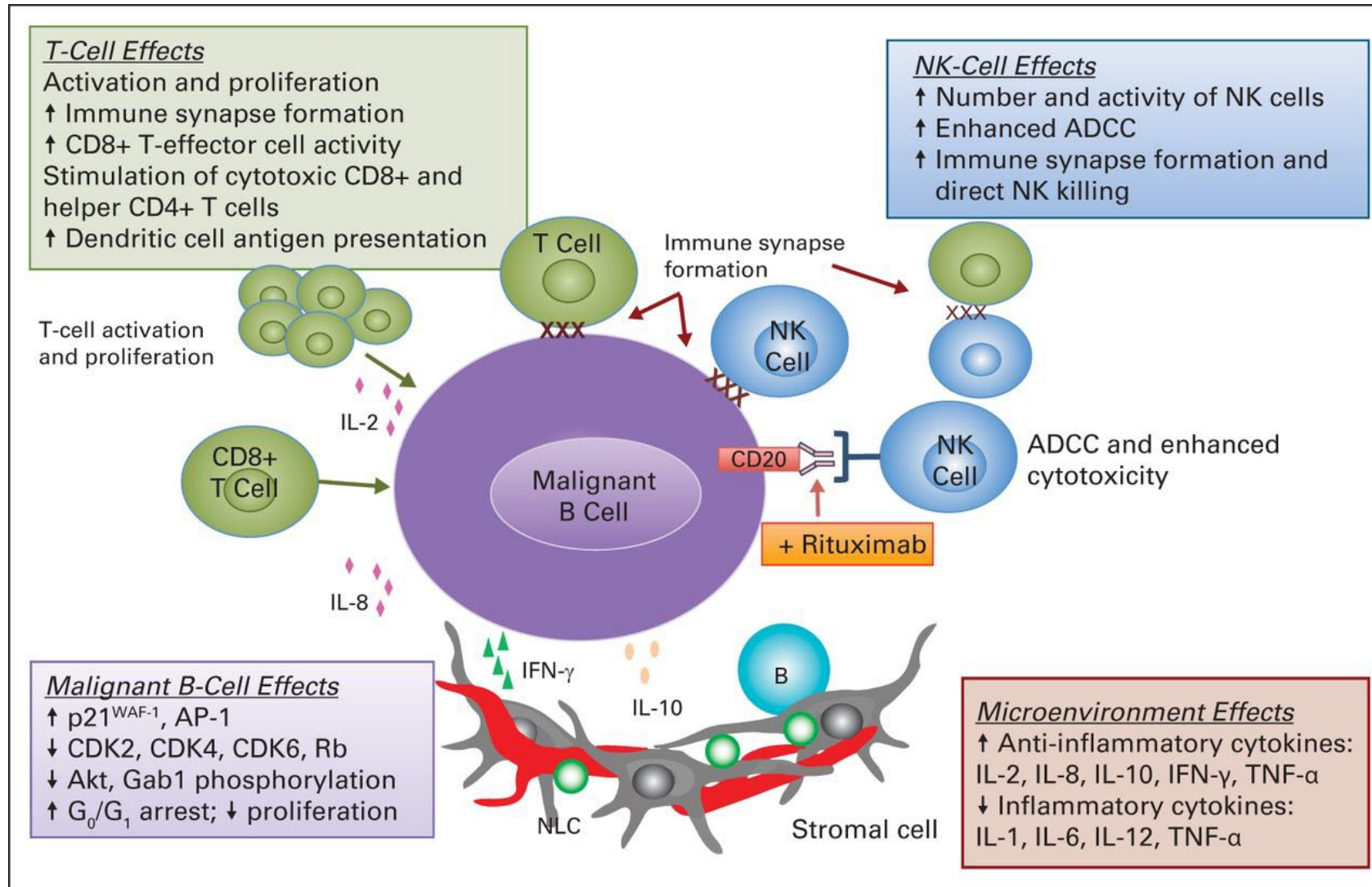


No difference in overall survival (yet?)

Loncastuximab tesirine

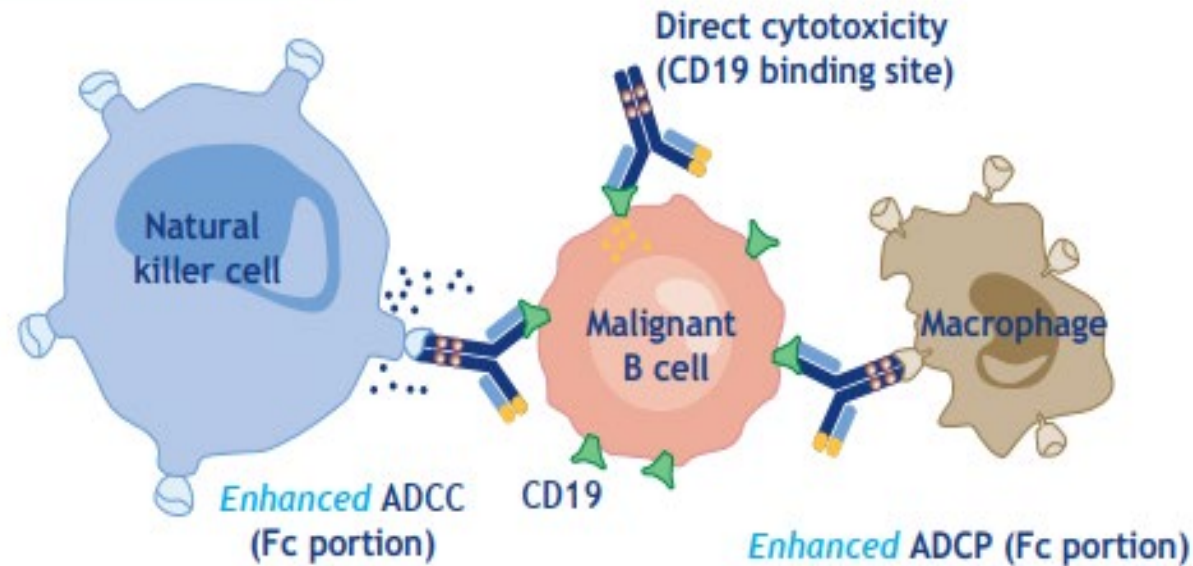
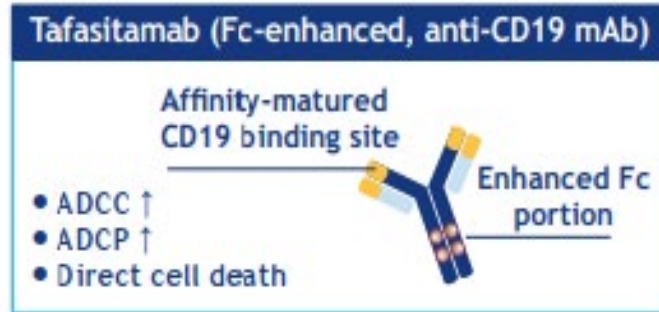


Mechanisms of action of lenalidomide in lymphoma cells and the nodal microenvironment

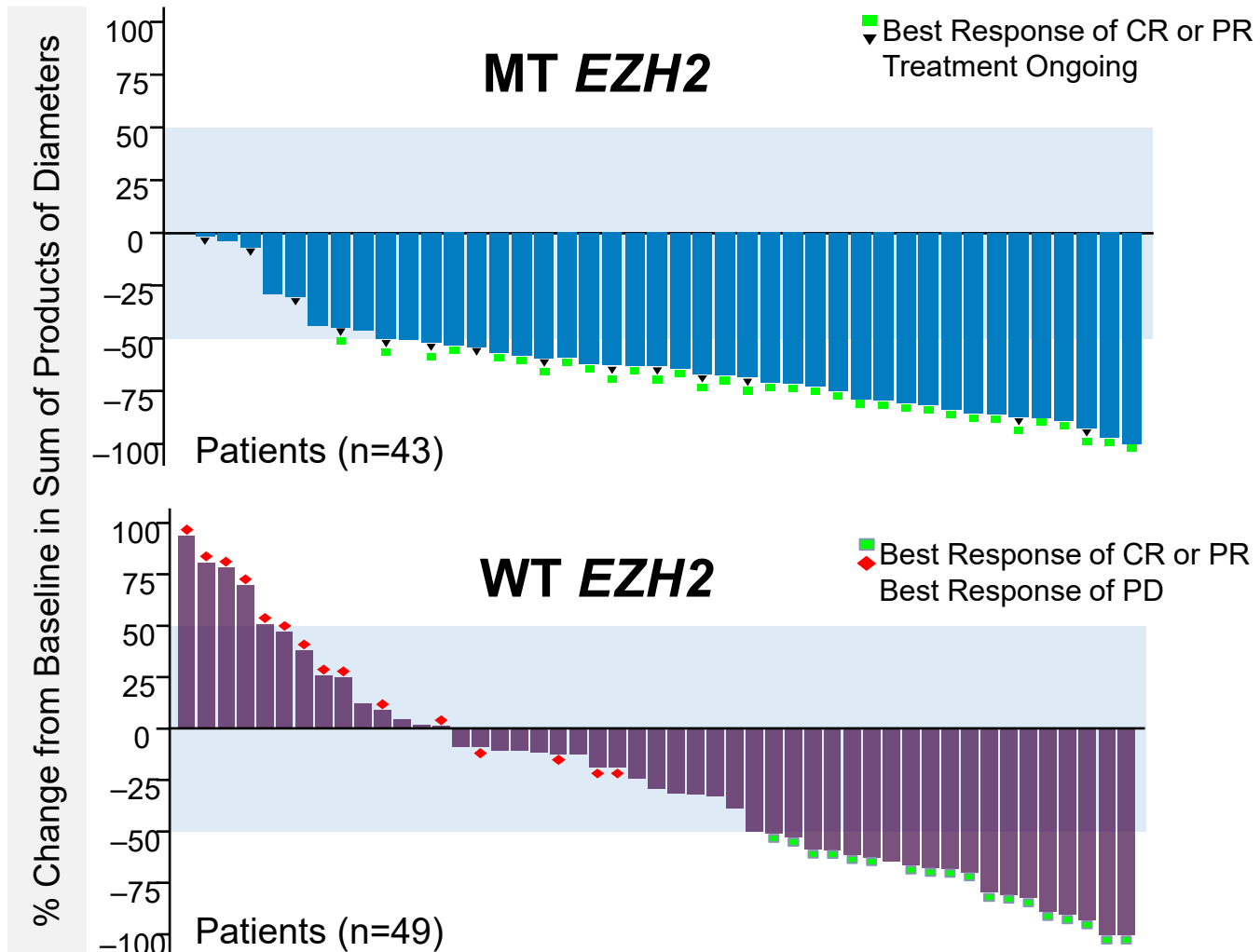
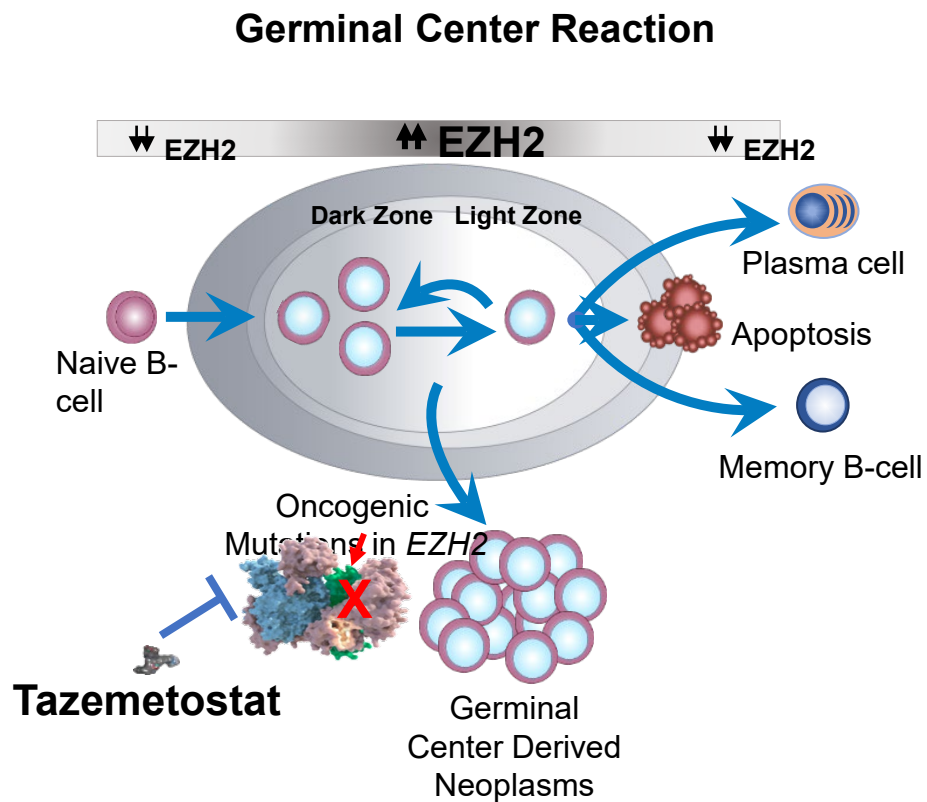


Tafasitamab a humanized and engineered anti-CD19 Ab

Previously known as XmAb5574, then MOR208

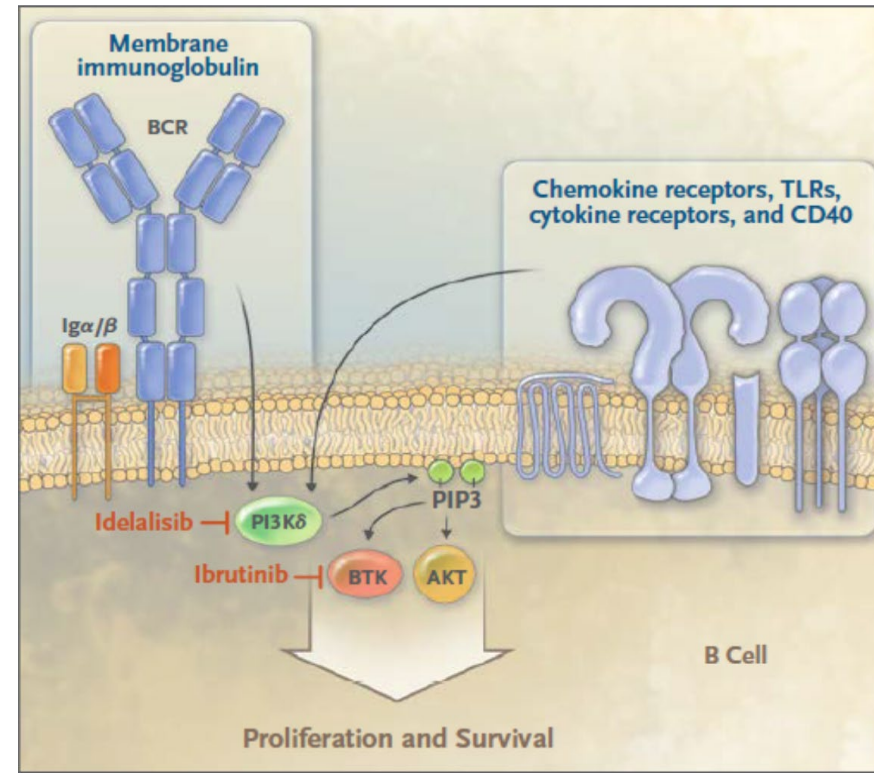


Targeting the epigenetic



Targeted small molecules

- PI3k inhibitors
- BTK inhibitor
- others



Activity of different PI3K inhibitors in patients with follicular lymphoma

Compound	Patient characteristics	No. of pts (FL/total)	ORR	CR	PFS in months (median)	DOR in months (median)	Time on drug in months (median)	Most frequent grade 3-4 AE (5% or more of the pts)*
Idelalisib ¹ (oral; δ specific)	Double			14%	11	11	7	Neutropenia (27%); transaminitis (13%); diarrhea (13%); pneumonia (7%); thrombocytopenia (6%)
Duvelisib ² (oral; γ δ specific)			42%	1%	10*	10*	7*	Neutropenia (25%); diarrhea (15%); anemia (15%); thrombocytopenia (12%); febrile neutropenia (9%); lipase increased (7%); transaminitis (5%); pneumonia (5%); colitis (5%)
Copanlisib ³ (IV; α δ specific)	Relapsed or refractory (80%)	104/142	59%	20%	13*	14*	6*	Hyperglycemia (40%); hypertension (24%); neutropenia (24%); pneumonia (11%); diarrhea (9%); anemia (5%); thrombocytopenia (5%)
Umbralisib ⁴ (oral, δ and CK1 ϵ specific)	Relapsed		5%	5%	11	11	8	Neutropenia (12%); diarrhea (10%); transaminitis (20%); opportunistic infections (3%); rash (2%)

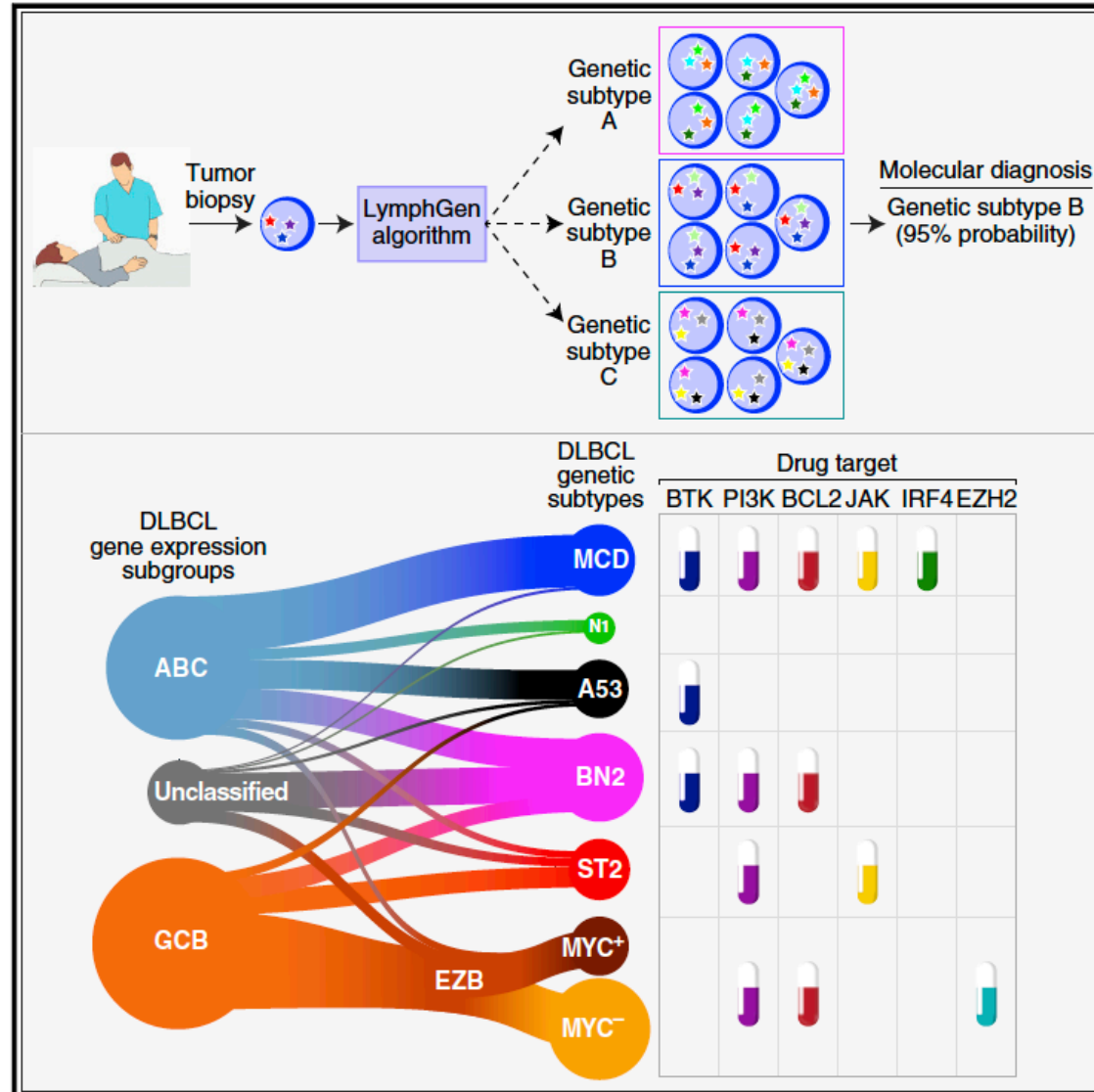
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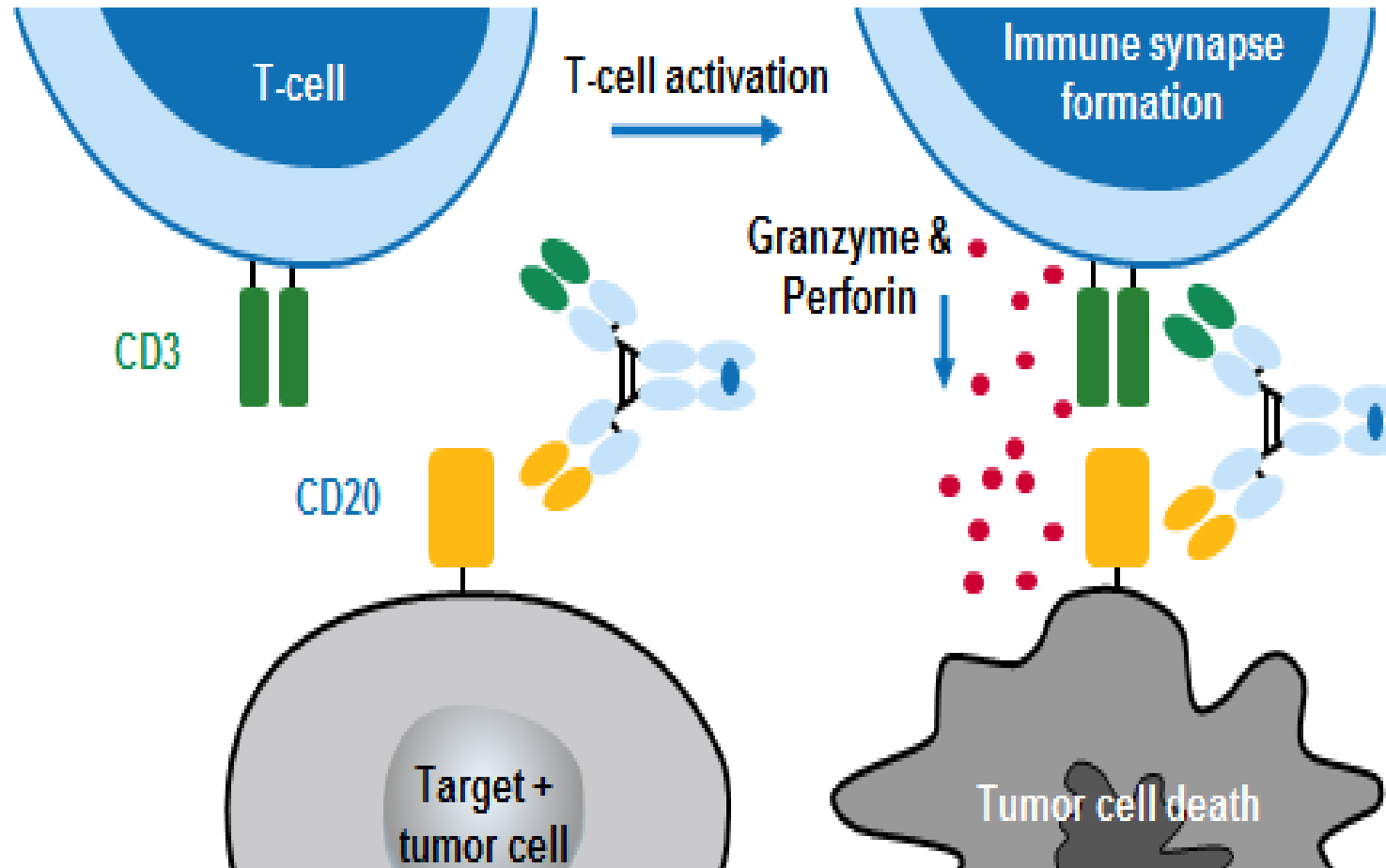
1. Salles G, et al. *Haematologica*. 2017;102(4):e156-e159; 2. Flinn I, et al. *J Clin Oncol*. 2019;37(11):912-922; 3. Dreyling, M, et al. *Am J Hematol*. 2020;95:362-371; 4. Fowler NH, et al. *J Clin Oncol*. 2021. Epub ahead of print.

*Patients with follicular and other iNHL.

What can we expect from targeted therapies?

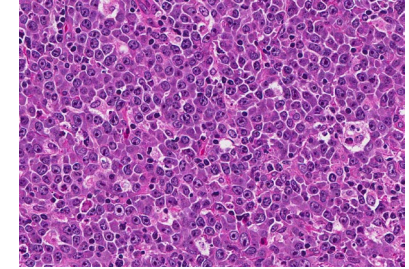


Bispecific CD3xCD20 MoAb :



No ex-vivo T cell manipulation required ('off-the-shelf' and no delay in treatment)

CD3xCD20 bispecifics antibodies in DLBCL



	Mosunetuzumab^{a)} (RG7828)	Odronextumab^{b)} (REGN1979)	Glofitamab^{c)} (RG6026)	Epcoritamab^{d)} (GEN3013)
Patients	82	45	155	157
ORR	33%	40%	52%	63%
CR	20%	36%	39%	39%

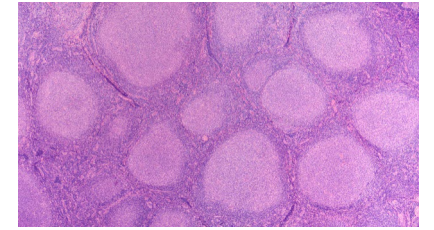
a) Budde LE et al. *J Clin Oncol*. 2022;40(5):4810491.

b) Bannerji R et al. *Lancet Haematol*. 2022;9(5):e339.

c) Dickinson M et al. *N Engl J Med*. 2022 Dec 15;387(24):2220-2231

d) Thieblemont C et al. *J Clin Oncol*. 2022 Dec 22;JCO2201725. doi: 10.1200/JCO.22.01725. Online ahead of print.PMID: 36548927

Bi-Specifics CD3 x CD20 in patients with R/R FL (updated January 2023)



	Mosunetuzumab (RG7828) ¹	Odronextumab (REGN1979) ²	Glofitamab (RG6026) ³	Epcoritamab (GEN3013) ⁴
Patients	90	131	53	10
ORR	78%	82%	81 %	90%
CR	60%	75%	70 %	50%
Median PFS	24 months	20 months	NA	NA

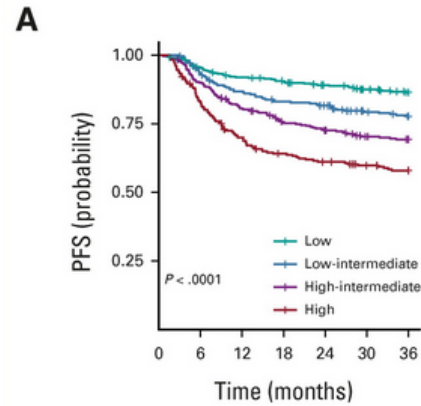
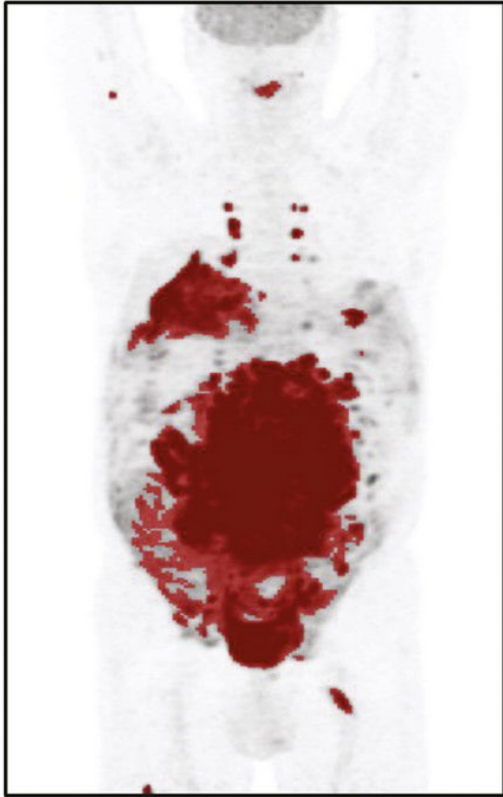
1. Budde L et al, Lancet Oncology 2022; updated Bartlett N et al, ASH 2022; abstract 610
2. Kim TM et al. ASH 2022, abstract 949
3. Morschhauser F et al. ASH 2021 ;
4. Hutchings M, et al. Lancet Onc 2021

Challenges in Bispecific developments

Managing first infusions AEs	<ul style="list-style-type: none">• Optimal step-up dosing, drug formulation, prophylaxis• Outpatient administration• Patient and provider education
Duration of response	<ul style="list-style-type: none">• Optimal duration of BsAb therapy• Predictors of durable response
Moving to earlier lines of therapy	<ul style="list-style-type: none">• Ongoing studies, in a competitive field• Randomized studies challenging (high risk patients?)
Optimal combinations	<ul style="list-style-type: none">• Moving beyond cytotoxic agents as partners• Rational (rather than expedient) combinations
Understand mechanisms of resistance	<ul style="list-style-type: none">• Antigen loss ? Intrinsic resistance to immune killing?• T-cell exhaustion ?• Other inhibitory signals (cells, molecules) in the microenvironment

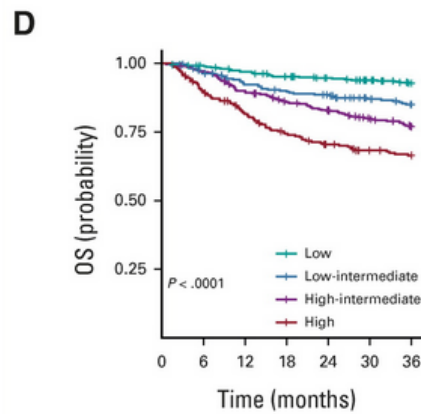
Better monitor the disease during therapy

Imaging of glucose metabolism with FDG



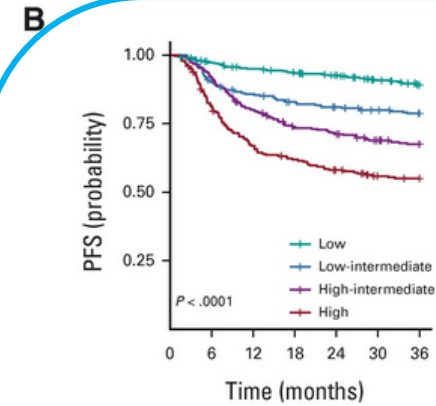
No. at risk:

Low	401	378	362	353	342	328	314
Low-intermediate	276	255	235	224	218	201	194
High-intermediate	321	288	256	234	225	211	205
High	242	199	166	150	142	133	128



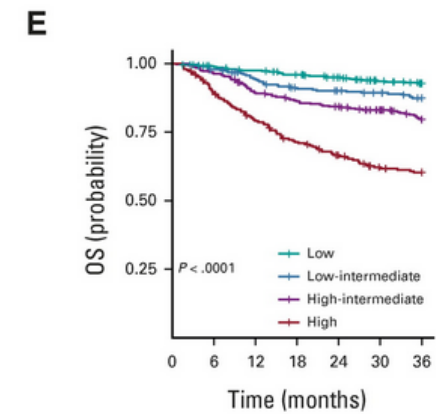
No. at risk:

Low	401	393	382	371	362	350	333
Low-intermediate	276	263	248	241	235	220	212
High-intermediate	321	310	285	267	256	240	226
High	242	215	192	173	161	150	145



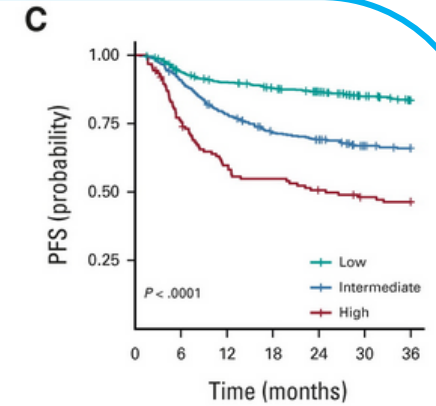
No. at risk:

Low	401	383	371	362	353	334	319
Low-intermediate	276	248	234	223	216	208	202
High-intermediate	321	295	255	230	223	209	201
High	242	194	159	146	135	122	119



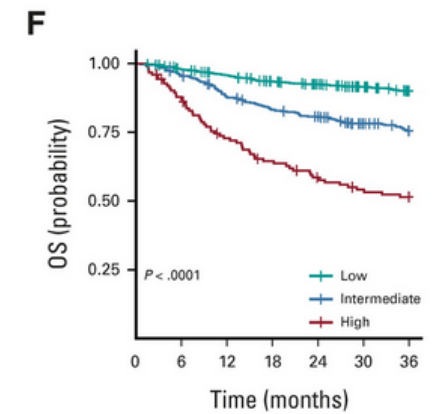
No. at risk:

Low	401	390	382	372	361	342	329
Low-intermediate	276	269	255	243	238	232	224
High-intermediate	321	309	284	271	264	250	232
High	242	213	186	166	151	136	131



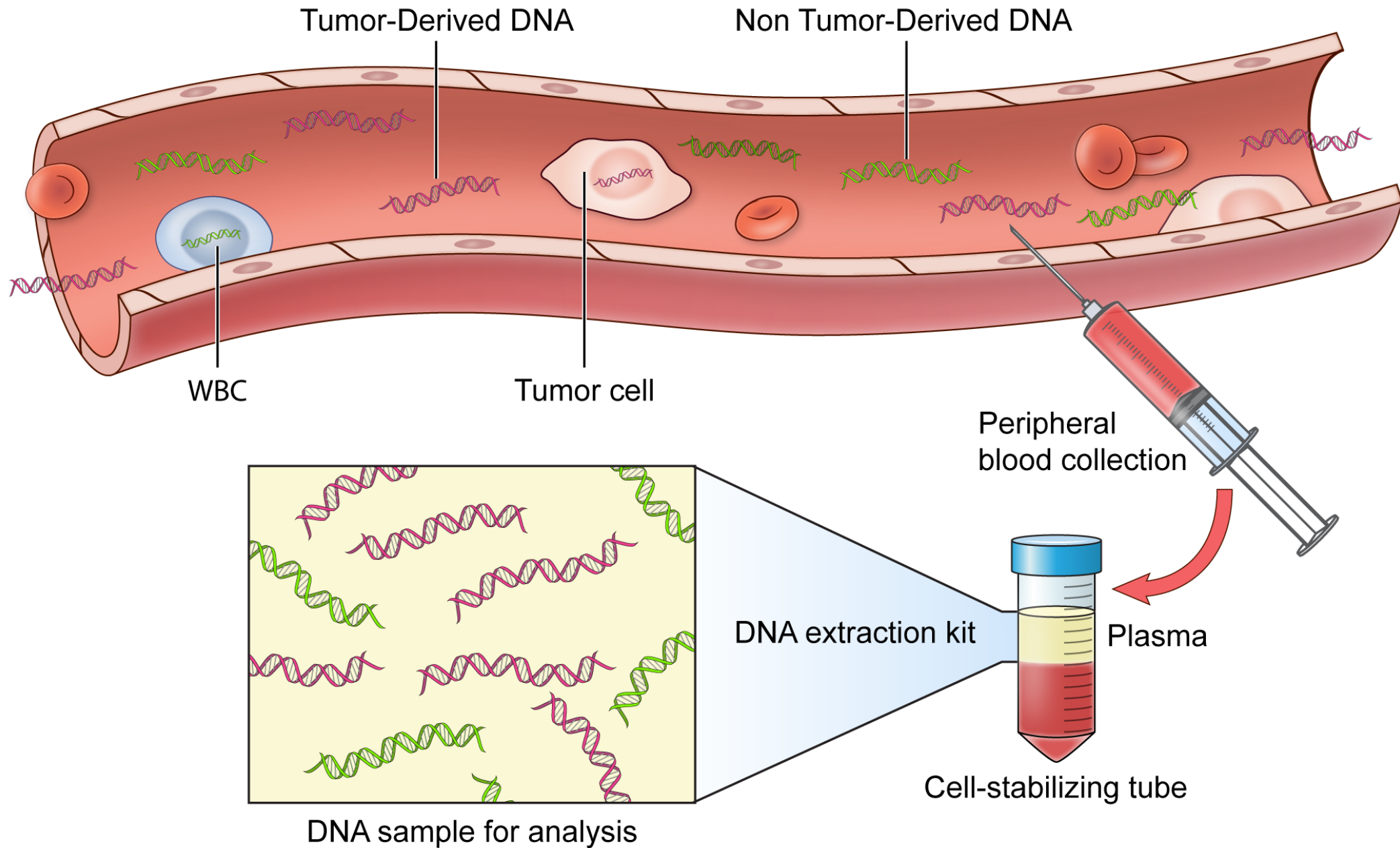
No. at risk:

Low	744	691	658	636	618	588	565
Intermediate	372	337	289	259	249	230	223
High	124	92	72	66	60	55	53



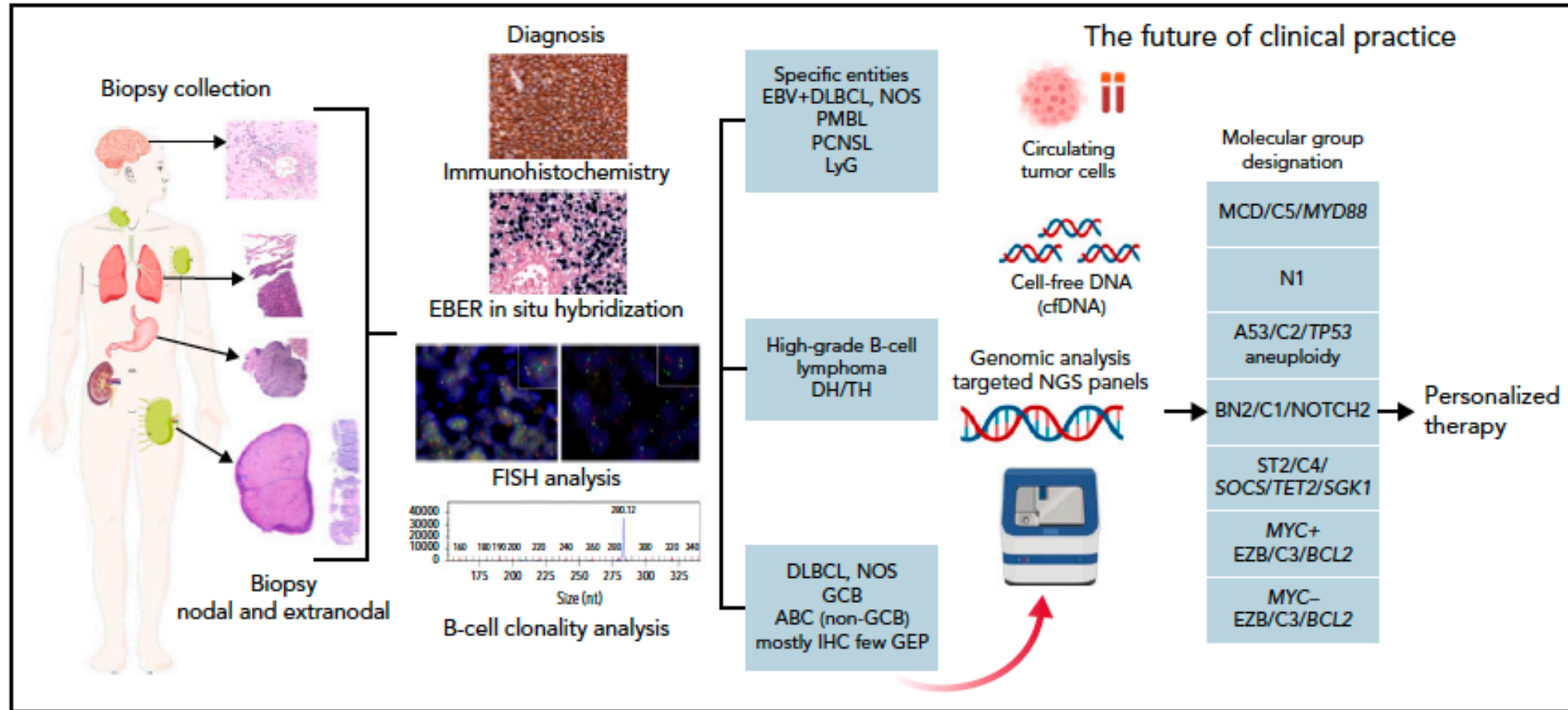
No. at risk:

Low	744	721	697	673	655	630	604
Intermediate	372	354	323	303	292	269	254
High	124	106	87	76	67	61	58



Roschewski et al. *Blood Cancer Discov* 2022 Jan;3(1):5-15

Personalisation of therapy



Acknowledgements – Merci !

