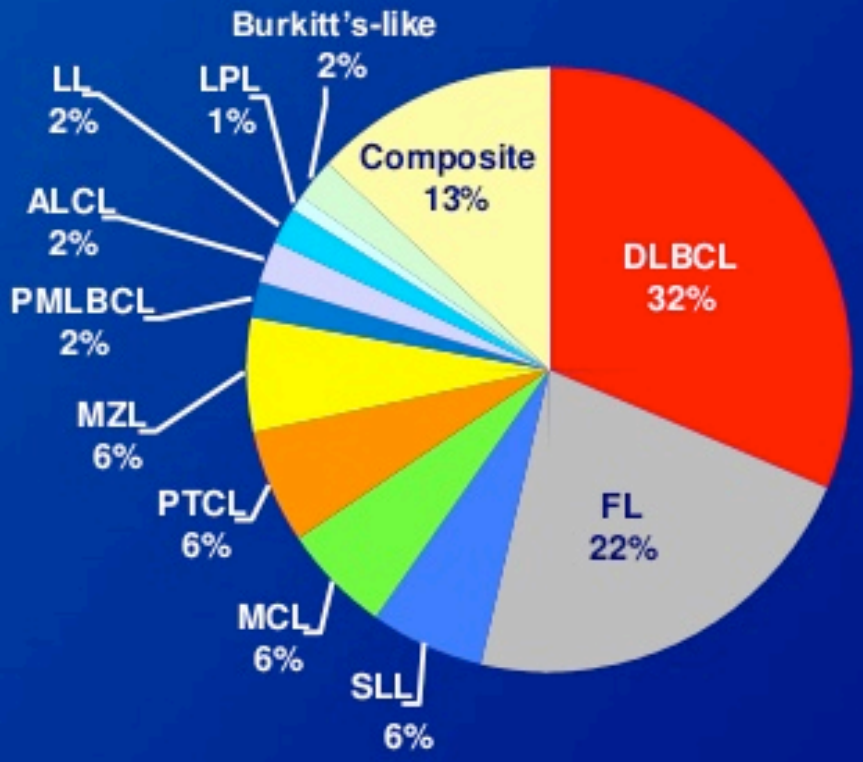
Management of Follicular Lymphoma

Lymphoma Tumor Board

September 22, 2017

Relative Incidence of NHL Subtypes

>71,000 new cases in US in 2015



NHL = non-Hodgkin lymphoma; FL = follicular lymphoma; DLBCL = diffuse large B-cell lymphoma.
Armitage & Weissenburger, 1998; ACS, 2015.

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B-cell Lymphomas

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Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

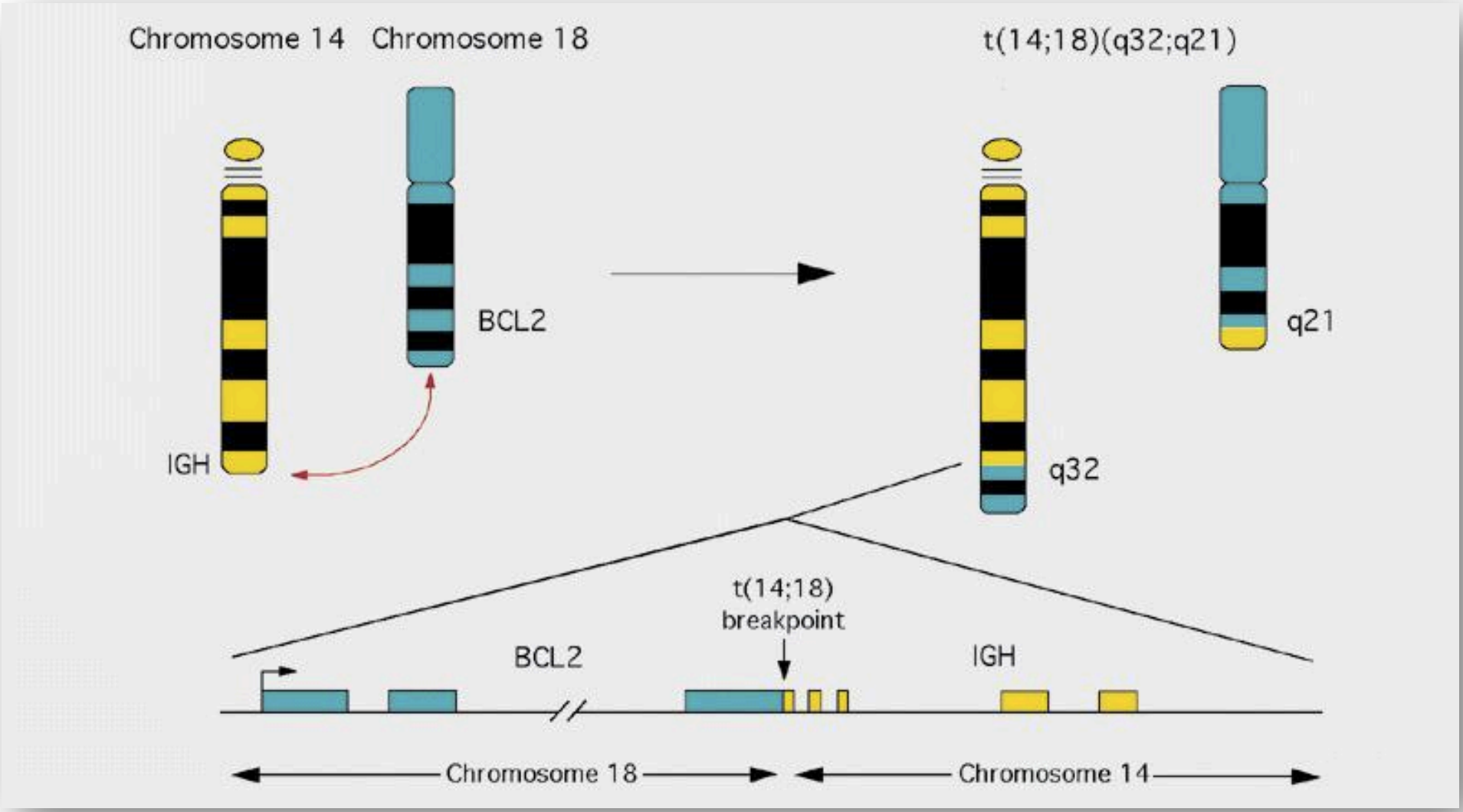
NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus.

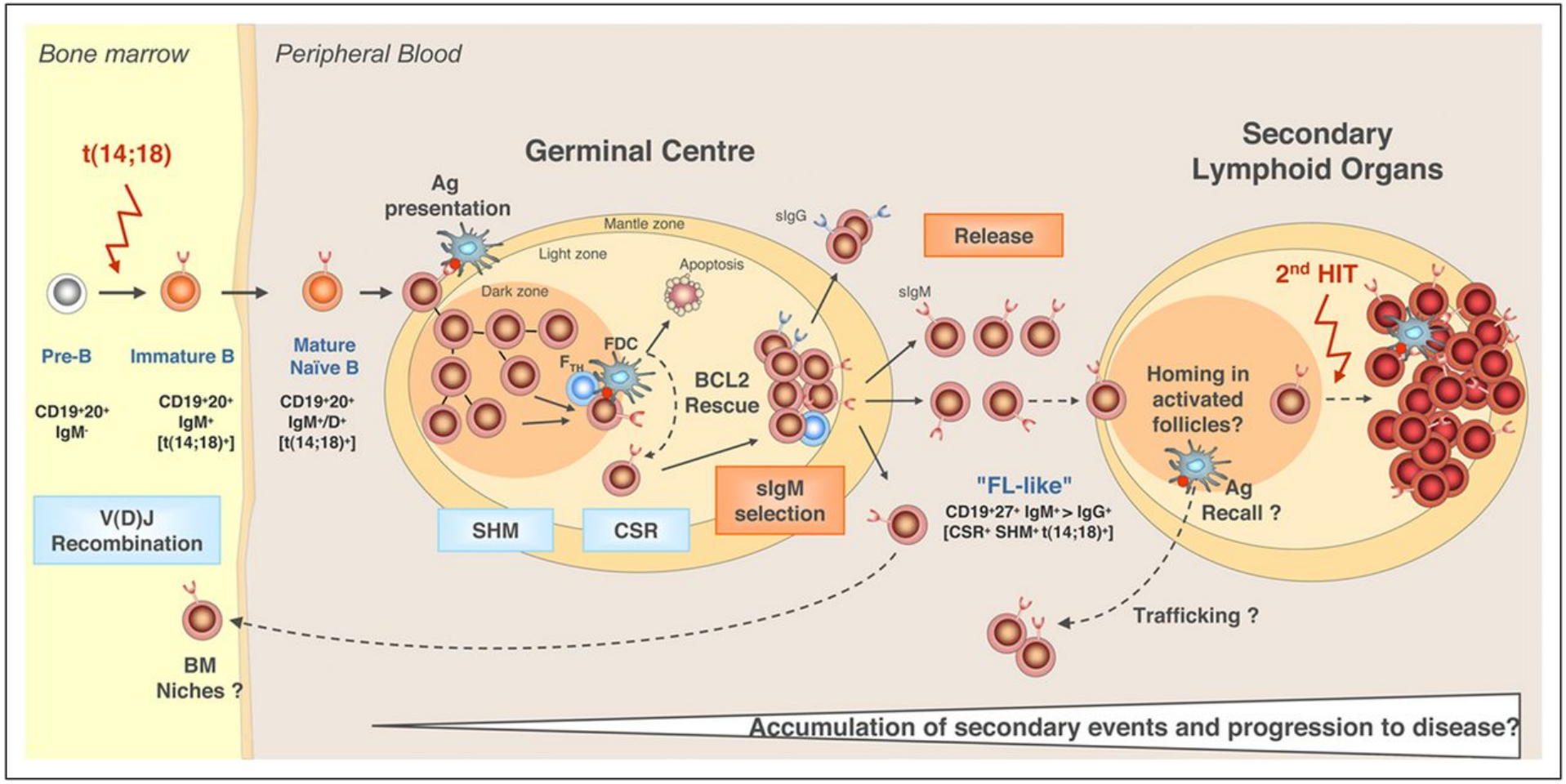
Indolent Non-Hodgkin Lymphomas

- Slow-growing [typically] B-cell malignancies
- Responsive to initial therapy, yet inevitably recur; incurable with conventional therapy
- Most common subtypes:
  - Follicular lymphoma (FL)
  - Marginal zone lymphoma (MZL)
  - Small lymphocytic lymphoma (SLL) – CLL counterpart
- FL is the 2nd most common subtype of NHL
- FL comprises ~25% of NHL and ~70% of indolent NHL
- FL is a malignancy of follicle center B-cells – CD10^{+}
- Also known as CB/CC lymphoma (Centroblastic/Centrocytic lymphoma), nodular lymphoma, and Brill-Symmers Disease
- Hallmark translocation between chromosomes 14 and 18 [t(14;18)] that results in overexpression of *BCL2*

t(14;18) – Cytogenetic hallmark of FL



Model of FL pathogenesis

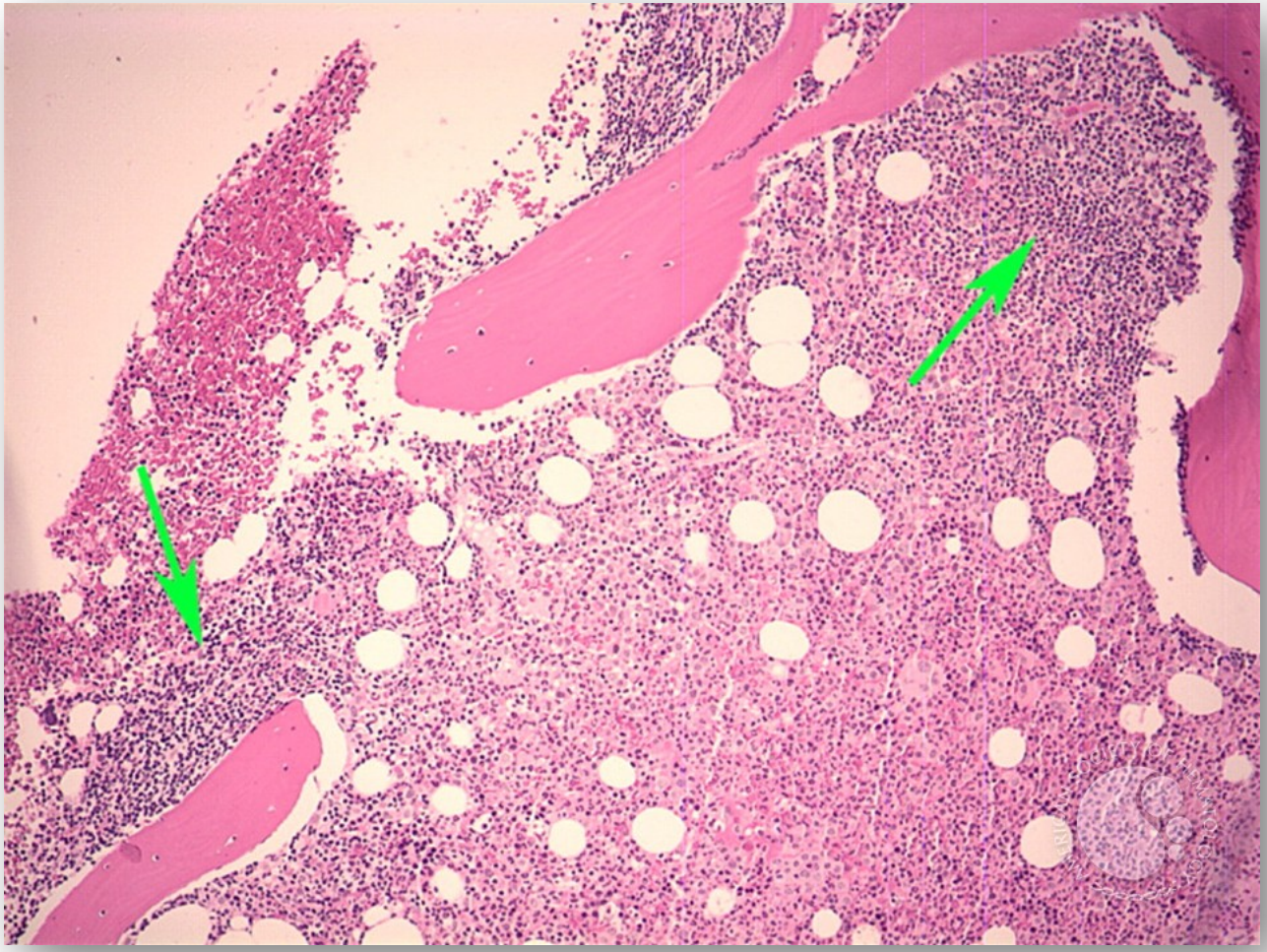


Brad S. Kahl, and David T. Yang Blood 2016;127:2055-2063

Pathology of FL (1)

Follicular lymphoma-bone marrow biopsy - 1.

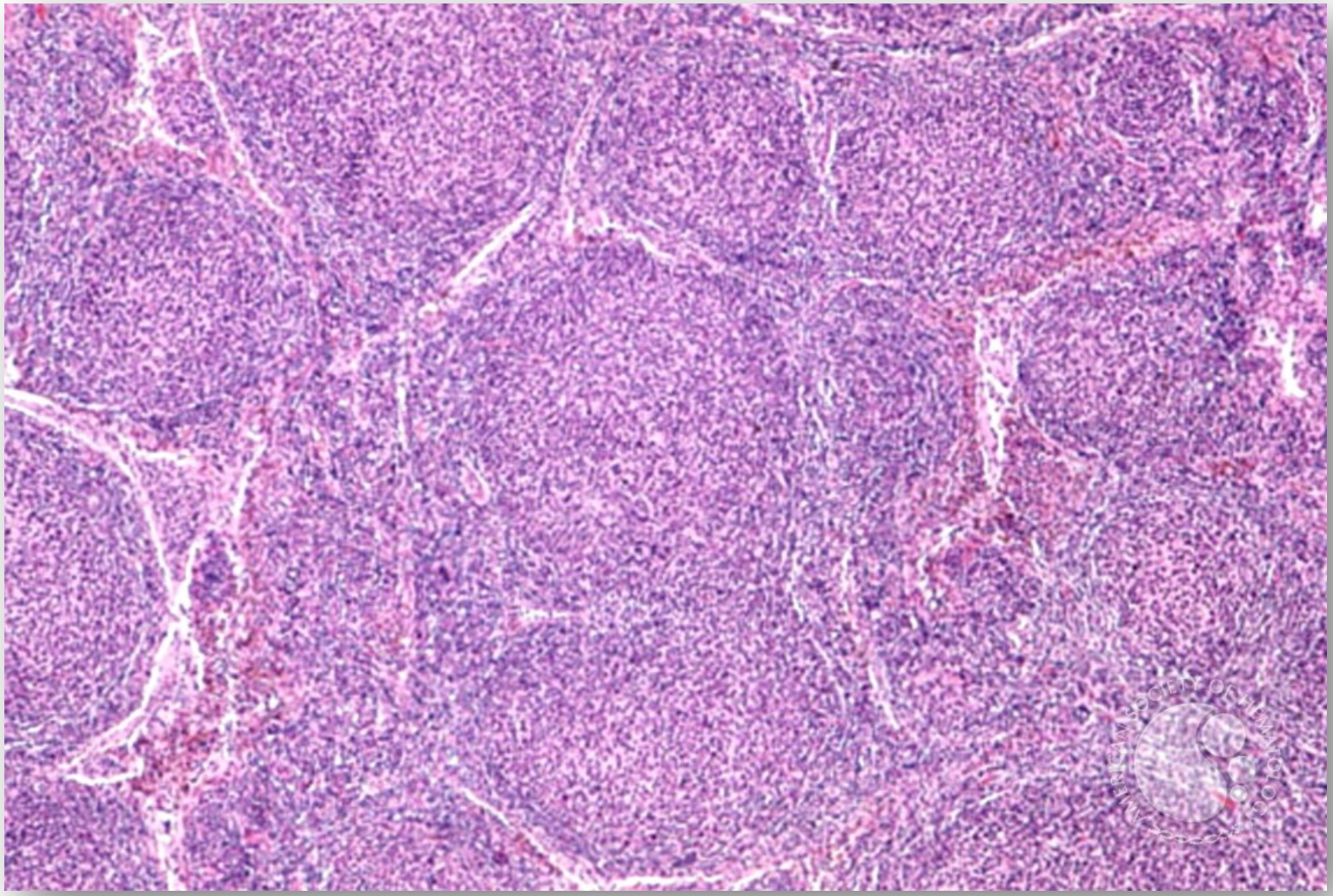
The arrow marks clusters of small lymphocytes (H&E). The paratrabecular distribution of involvement is a classic finding for follicular lymphoma.



Pathology of FL (2)

Follicular Lymphoma - 2.

Medium power showing back to back neoplastic follicles which have "lost" normal mantle zones.



Grading of FL

- According to WHO criteria, FL is morphologically graded into:
  - grade 1 (<5 centroblasts per high-power field (hpf))
  - grade 2 (6–15 centroblasts/hpf)
  - grade 3 (>15 centroblasts/hpf)
- Grade 3 is further subdivided into:
  - grade 3A (centrocytes still present)
  - grade 3B (the follicles consist almost entirely of centroblasts)
- The WHO 2008 update now classifies grades 1 and 2 as low grade follicular lymphoma, grade 3A as high grade follicular lymphoma, and grade 3B as Diffuse Large B Cell Lymphoma (DLBCL).
- Other factors to consider: Extranodal involvement:
  - Bone marrow
  - Peripheral Blood
  - Spleen
  - Liver

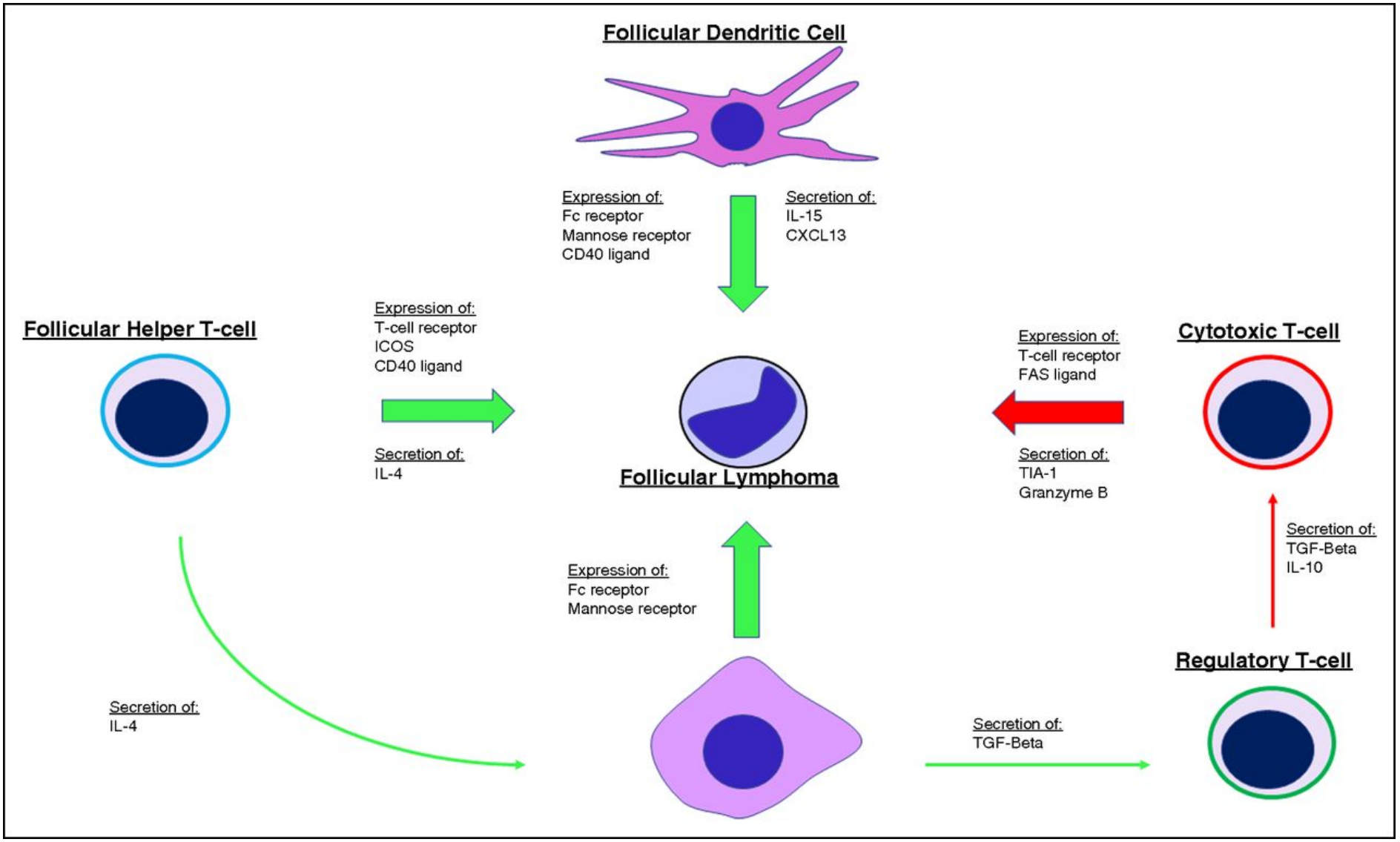
Low Power (Architectural)

Benign	Malignant
1. Loosely packed follicles 2. Polymorphic follicles 3. Prominent mantle zones 4. Polarized follicles 5. Preserved open sinuses 6. No capsular invasion or transgression 7. Polyclonal light chain expression 8. Non-reactive for BCL-2	1. Tightly packed follicles 2. Monomorphic follicles 3. Absent or obscured mantle zones 4. Unpolarized follicles 5. Destroyed and constricted sinuses 6. Extension into perinodal soft tissue 7. Monoclonal light chain expression 8. Reactive for BCL-2

High Power (Cytological)

Benign	Malignant
1. A very high mitotic rate 2. Tingible-body macrophages 3. Between follicles are the usual paracortical lymphoid cells	1. A lower mitotic rate 2. No tingible-body macrophages 3. Between follicles atypical cleaved cells may be found

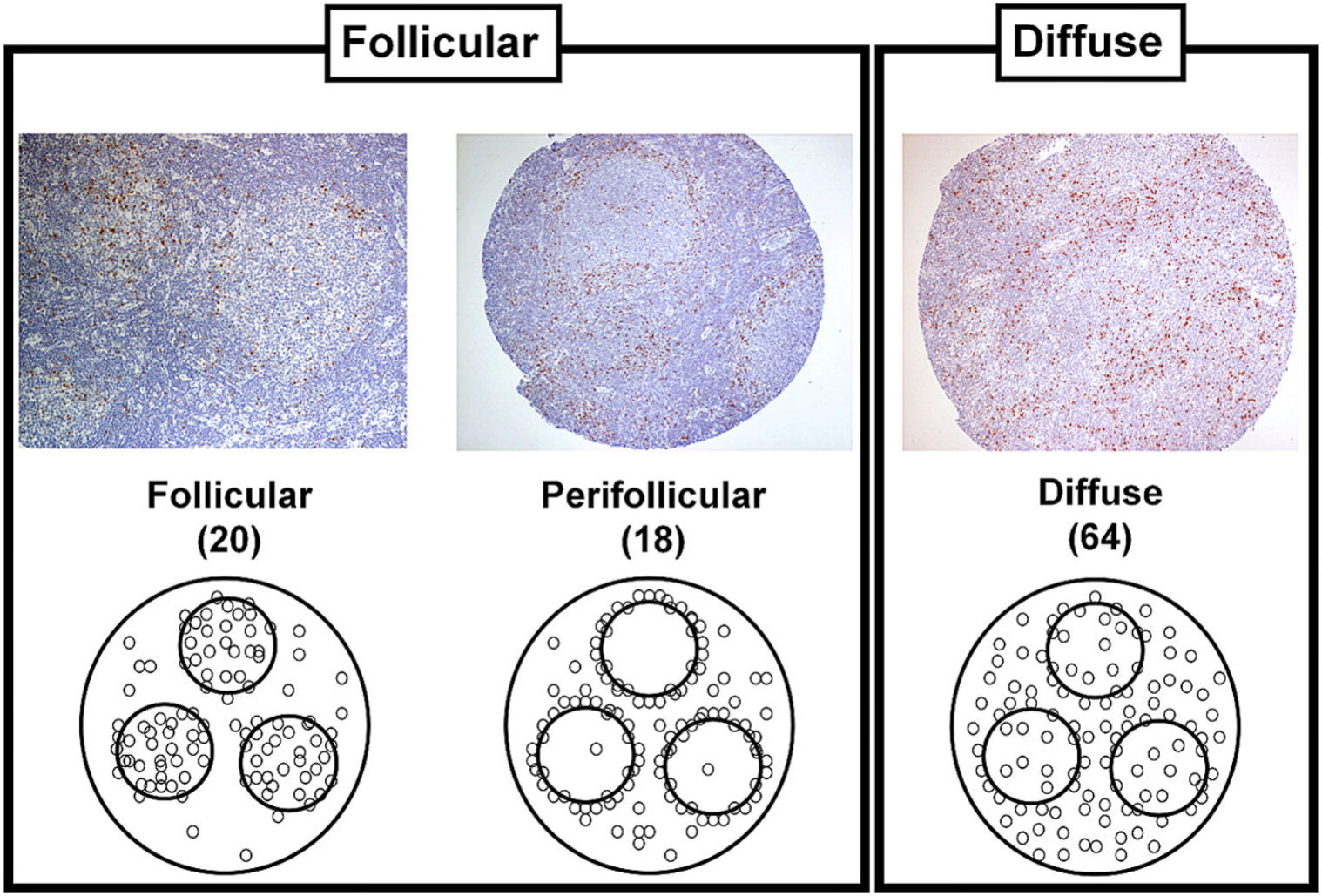
Influence of the tumor microenvironment on FL



Brad S. Kahl, and David T. Yang Blood 2016;127:2055-2063

blood

Representative tissue microarray cores of follicular lymphoma stained for FOXP3



Pedro Farinha *et al*. Blood 2010;115:289-295

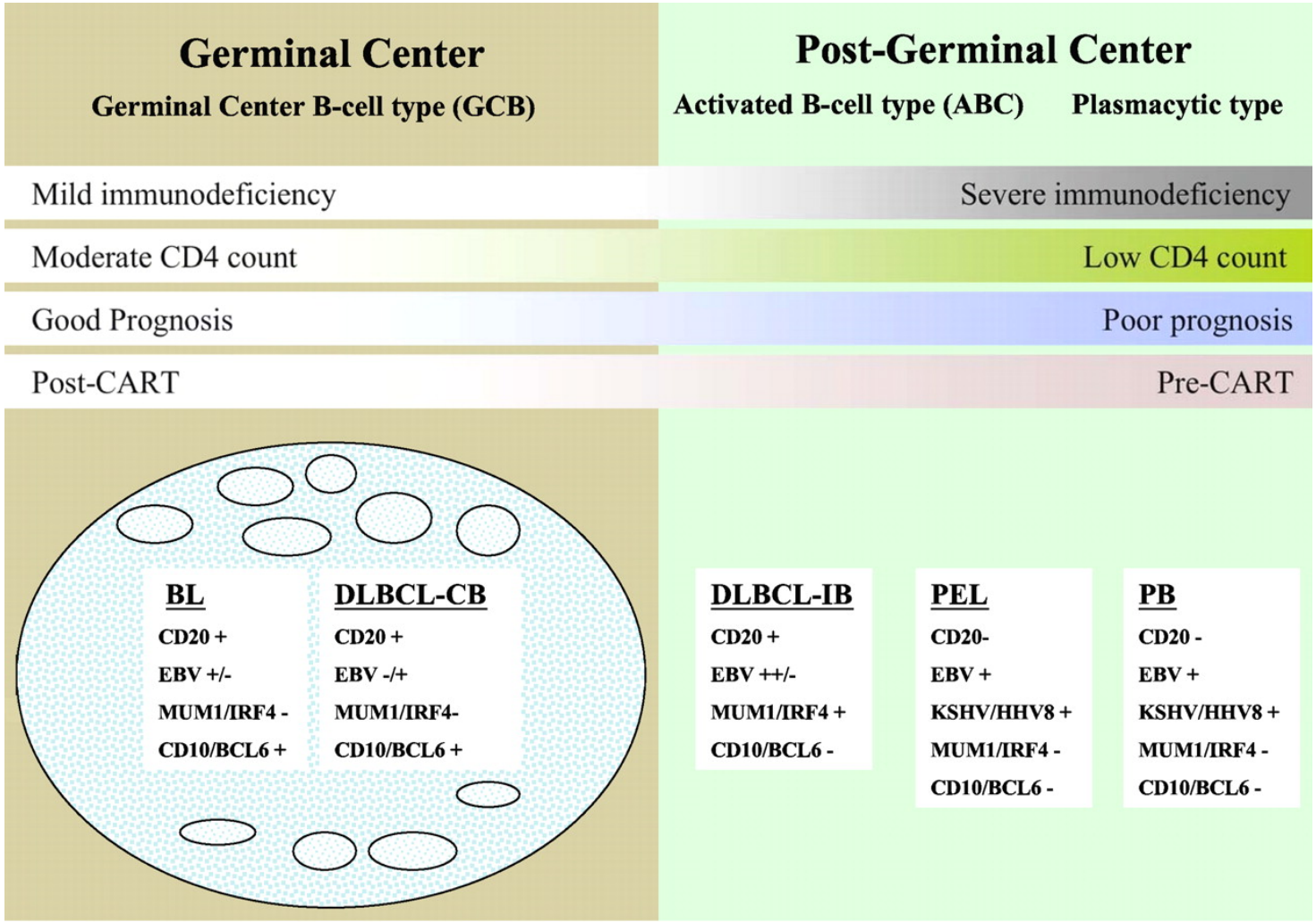
Prevalence of HIV infection in US lymphoma patients in the HAART era

179,520 patients with lymphoma from the US National Cancer Database, 2004-2009:

- Follicular lymphoma: 1.0%
- Peripheral T-cell lymphoma: 3.3%
- Hodgkin lymphoma: 4.7%
- Diffuse large B cell lymphoma: 5.4%
- Burkitt lymphoma: 29.0%

Han *et al*., Cancer Epidemiol Biomarkers Prev March 1 2017 (26) (3) 303-311; DOI: 10.1158/1055-9965.EPI-16-0595

A model for the histogenesis of HIV-associated lymphomas showing molecular and viral pathogenesis and DLBCL taxonomy



Kieron Dunleavy, and Wyndham H. Wilson Blood 2012;119:3245-3255

NCCN Guidelines Version 3.2017
Follicular Lymphoma (grade 1-2)

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GELF CRITERIA[a,b]

- Involvement of ≥3 nodal sites, each with a diameter of ≥3 cm
- Any nodal or extranodal tumor mass with a diameter of ≥7 cm
- B symptoms
- Splenomegaly
- Pleural effusions or peritoneal ascites
- Cytopenias (leukocytes <1.0 x 10^9/L and/or platelets <100 x 10^9/L)
- Leukemia (>5.0 x 10^9/L malignant cells)

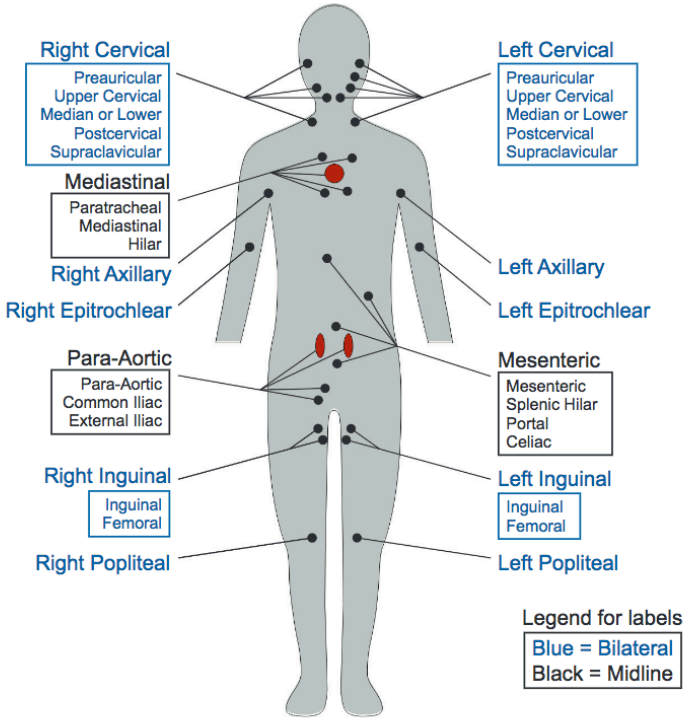
FLIPI - 1 CRITERIA[a,c,d]

Age	**≥60 y**
Ann Arbor stage	**III–IV**
Hemoglobin level	**<12 g/dL**
Serum LDH level	**>ULN (upper limit of normal)**
Number of nodal sites[d]	**≥5**

Risk group according to FLIPI chart

	Number of factors
Low	**0–1**
Intermediate	**2**
High	**≥3**

Nodal Areas



Mannequin used for counting the number of involved areas.[e]

[a]This provides useful prognostic information that may be used to guide therapeutic decisions.

[b]Solal-Celigny P, Lepage E, Brousse N, et al. Doxorubicin-containing regimen with or without interferon alfa 2b for advanced follicular lymphomas: final analysis of survival and toxicity in the Groupe d'Etude des Lymphomes Folliculaire 86 trial. J Clin Oncol 1998;16:2332-2338.

[c]This research was originally published in Blood. Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood 2004;104:1258-1265. (c) the American Society of Hematology.

[d]FLIPI-2 (Federico M, Bellei M, Marcheselli L, et al. J Clin Oncol 2009;27:4555-4562) predicts for outcomes after active therapy; see Discussion.

[e]The map is used to determine the number of nodal sites in FLIPI-1 criteria and is different than the conventional Ann Arbor site map.

Note: All recommendations are category 2A unless otherwise indicated.
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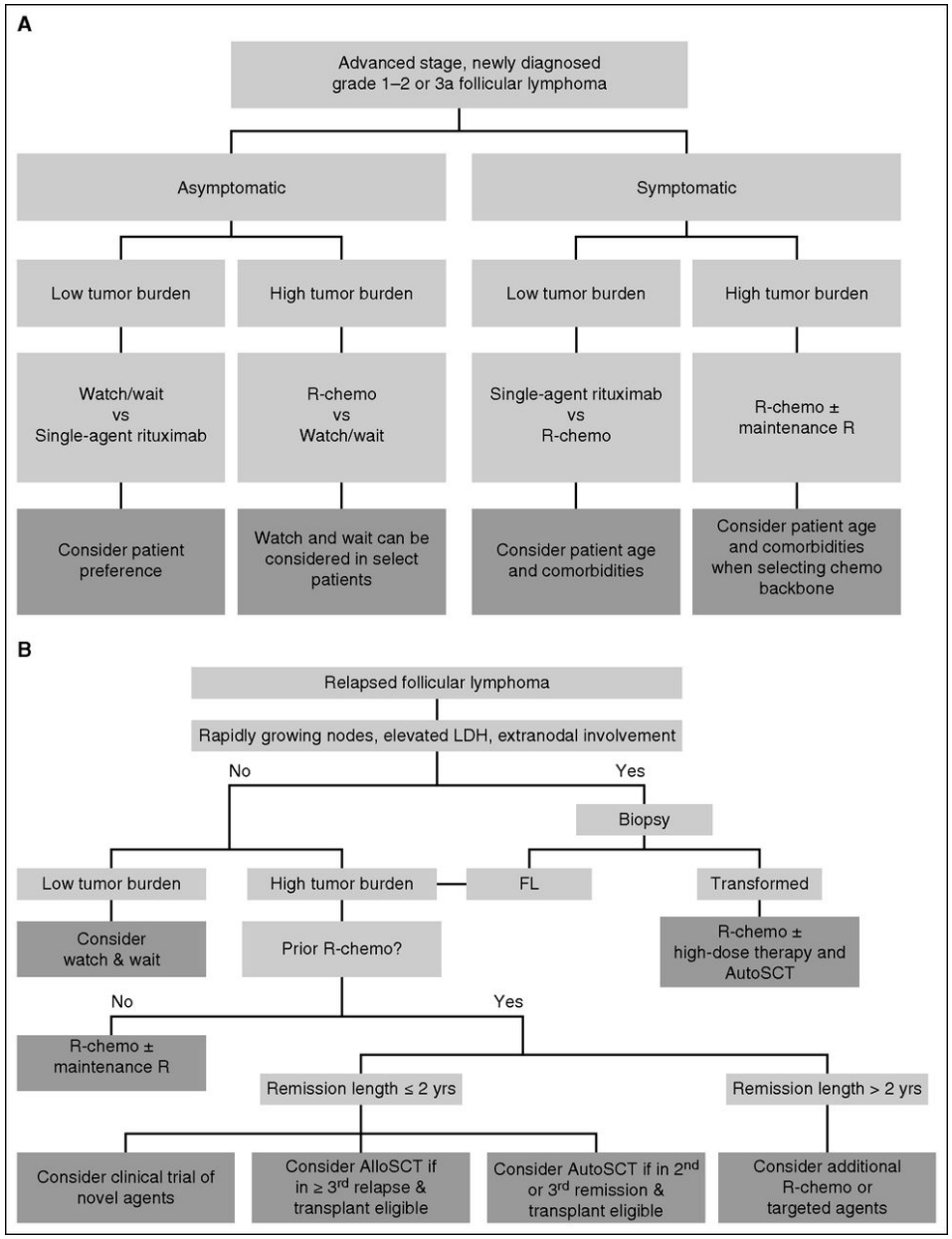
An algorithmic approach to management of FL



Brad S. Kahl, and David T. Yang Blood 2016;127:2055-2063

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Follicular Lymphoma (grade 1-2)

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SUGGESTED TREATMENT REGIMENS[a,b]
(in preference order)

First-line Therapy

- **Bendamustine + rituximab (category 1)**
- **Bendamustine + obinutuzumab[c]**
- **RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)**
- **CHOP + obinutuzumab[c]**
- **RCVP (rituximab, cyclophosphamide, vincristine, prednisone) (category 1)**
- **CVP + obinutuzumab[c]**
- **Rituximab (375 mg/m² weekly for 4 doses) (consider for low tumor burden)[d]**
- **Lenalidomide + rituximab (category 2B)**

First-line Therapy for Elderly or Infirm (if none of the above are expected to be tolerable in the opinion of treating physician)

- **Rituximab (preferred) (375 mg/m² weekly for 4 doses)**
- **Single-agent alkylators (eg, chlorambucil or cyclophosphamide) ± rituximab**
- **Radioimmunotherapy[e,f] (category 2B)**

First-line Consolidation or Extended Dosing (optional)

- **Rituximab maintenance 375 mg/m² one dose every 8 wks for 12 doses for patients initially presenting with high tumor burden (category 1)[g]**
- **Obinutuzumab maintenance (1000 mg every 8 weeks for 12 doses)**
- **If initially treated with single-agent rituximab, consolidation with rituximab 375 mg/m² one dose every 8 weeks for 4 doses**
- **Radioimmunotherapy (after induction with chemotherapy or chemoimmunotherapy)[e,f,h] (category 2B)**

See Second-line and Subsequent Therapy on FOLL-B 2 of 4

[a] See references for regimens FOLL-B 3 of 4 and FOLL-B 4 of 4.

[b] The choice of initial therapy requires consideration of many factors, including age, comorbidities, and future treatment possibilities (eg, HDT with SCR). Therefore, treatment selection is highly individualized.

[c] The clinical trial evaluating this regimen included obinutuzumab maintenance. The use without maintenance was an extrapolation of the data.

[d] Rituximab may be appropriate in patients initially observed and with progression of low tumor burden disease not meeting GELF criteria (FOLL-A). Immediate initial therapy with rituximab in patients not meeting GELF criteria has not improved OS (Ardeshna K, et al. Lancet Oncol 2014;15:424-435).

[e] Selection of patients requires adequate marrow cellularity >15% and <25% involvement of lymphoma in bone marrow, and platelets >100,000. In patients with prior autologous stem cell rescue, referral to a tertiary care center is highly recommended for radioimmunotherapy.

[f] If radioimmunotherapy is considered, bilateral cores are recommended and the pathologist should provide the percent of overall cellular elements and the percent of cellular elements involved in the marrow. Cytogenetics ± FISH for known MDS markers. As of 2010, updates suggest a trend towards an increased risk of MDS with RIT.

[g] This is based on the PRIMA study for patients with high tumor burden treatment with RCVP and RCHOP. There are no data following other regimens.

[h] The full impact of an induction regimen containing rituximab on RIT consolidation is unknown.

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

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BR vs R-CHOP Non-Heme Toxicities

	B-R (n=261)	R-CHOP (n=253)	p value
Alopecia	0	245 (100%)*	<0·0001
Paresthesia	18 (7%)	73 (29%)	<0·0001
Stomatitis	16 (6%)	47 (19%)	<0·0001
Skin (erythema)	42 (16%)	23 (9%)	0·024
Skin (allergic reaction)	40 (15%)	15 (6%)	0·0006
Infectious episodes	96 (37%)	127 (50%)	0·0025
Sepsis	1 (<1%)	8 (3%)	0·019

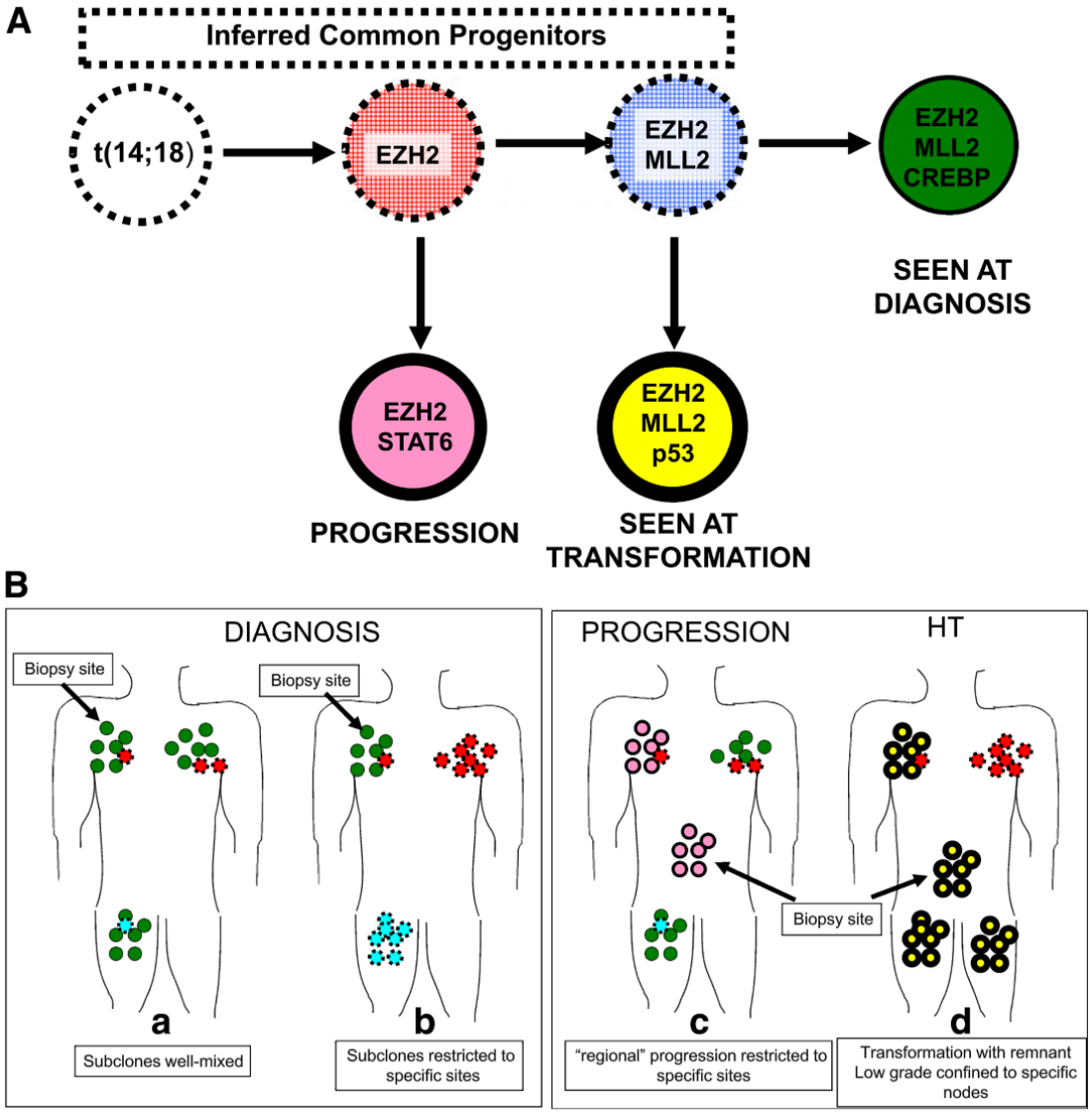
B-R=bendamustine plus rituximab. R-CHOP=CHOP plus rituximab. *Includes only patients who received three or more cycles.

Rummel et al, 2013.

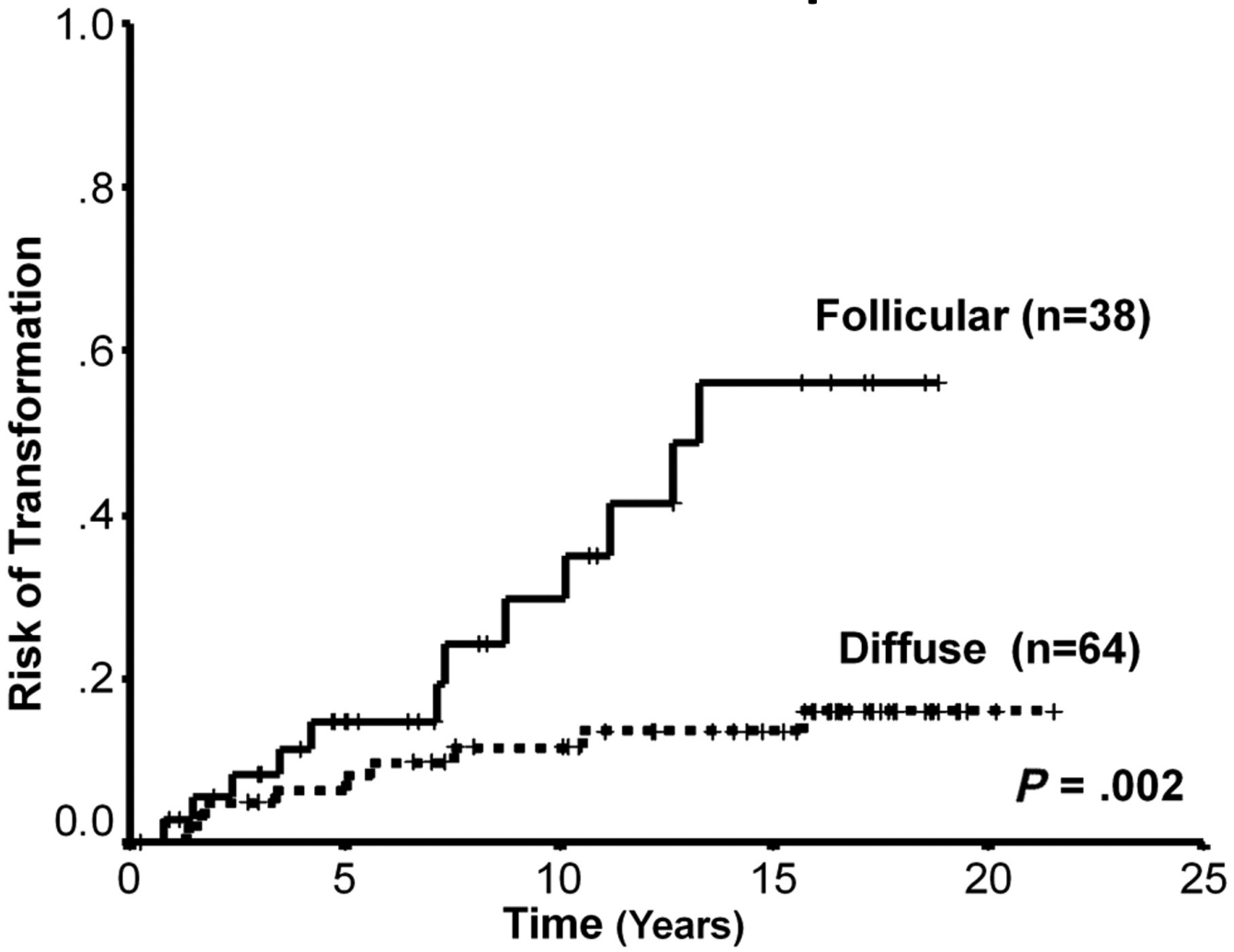
Histologic transformation of FL

- Histologic transformation: a biologic event leading to the development of a high-grade, aggressive non-Hodgkin lymphoma in patients with an underlying follicular lymphoma (FL).
- Transformation to diffuse large B-cell lymphoma (DLBCL) or Burkitt lymphoma is also known to take place in other subtypes of indolent lymphoma such as marginal zone lymphoma, lymphoplasmacytic lymphoma, small lymphocytic lymphoma/chronic lymphocytic leukemia (Richter's syndrome), and lymphocyte predominant Hodgkin lymphoma, but is best described as occurring in FL.
- Survival after transformation has historically been poor, but has improved in the rituximab era.

Mutational analyses of FL clonal architecture yields insights into histologic transformation

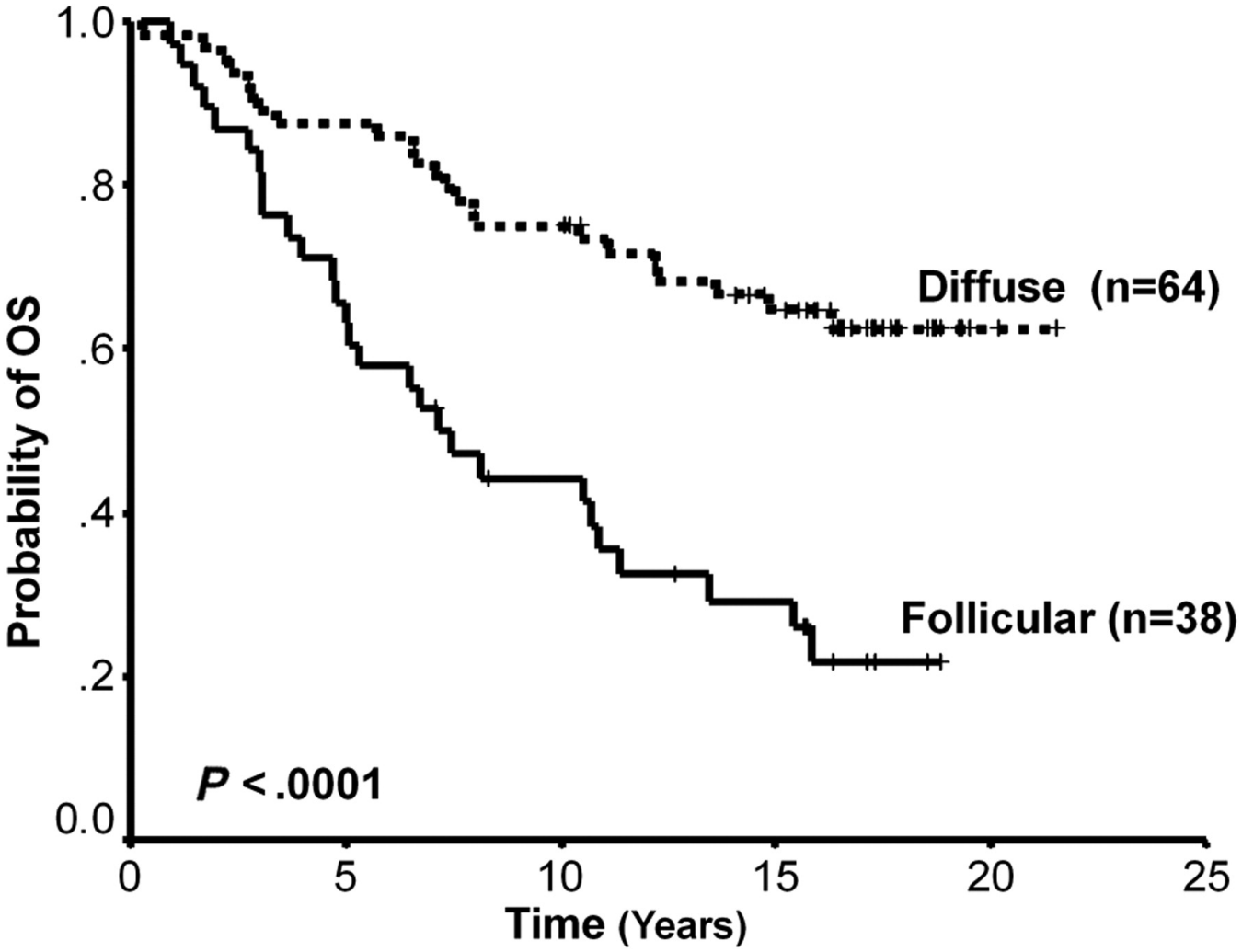


Risk of transformation curve based on FOXP3 immunoarchitectural patterns



Pedro Farinha et al. Blood 2010;115:289-295

Overall survival curve based on FOXP3 immunoarchitectural patterns



Pedro Farinha et al. Blood 2010;115:289-295

Approach to treatment of transformed FL

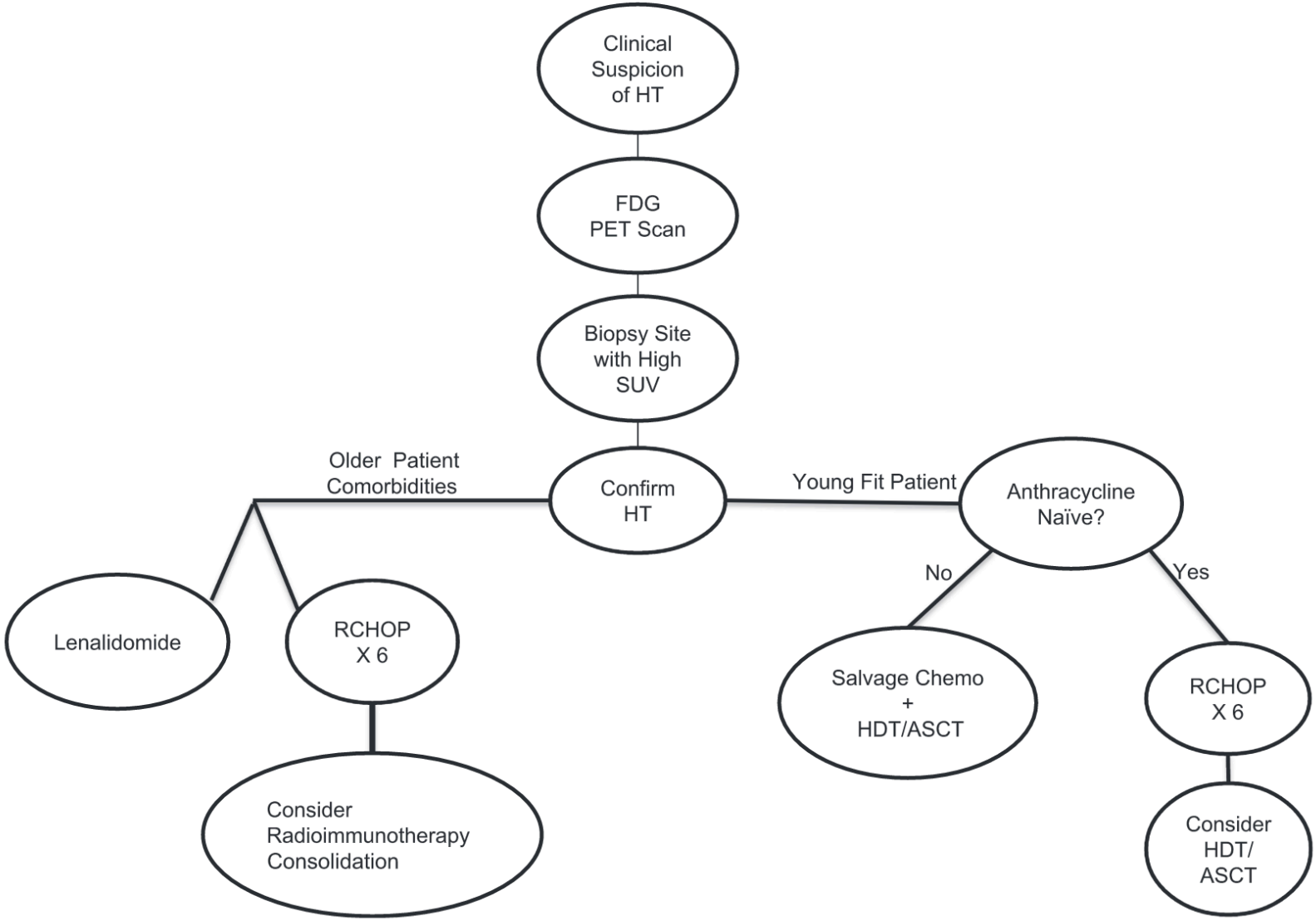
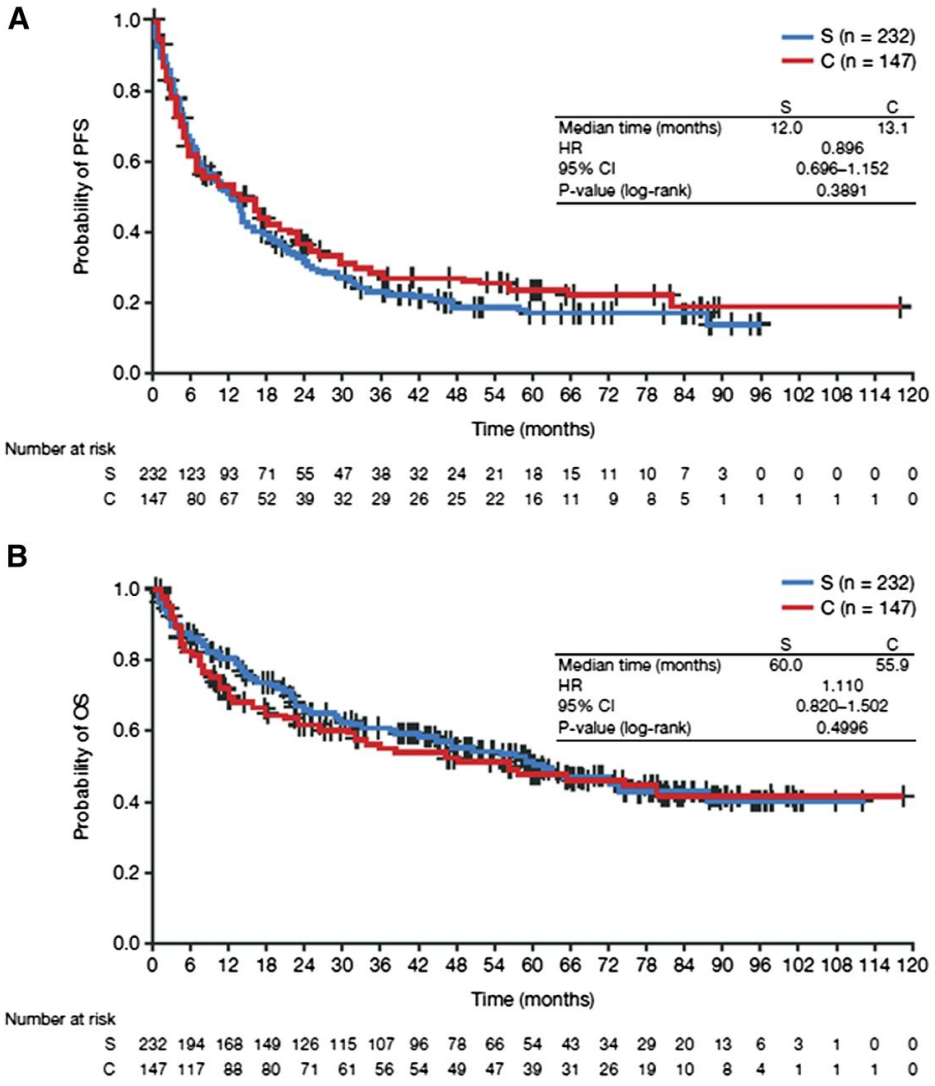


Figure 2. Approach to treatment of transformed FL.

Post transformation survival for confirmed and suspected histologic transformation of FL



Nina D. Wagner-Johnston et al. Blood 2015;126:851-857

blood

Survival curves of HIV+ individuals with lymphoma

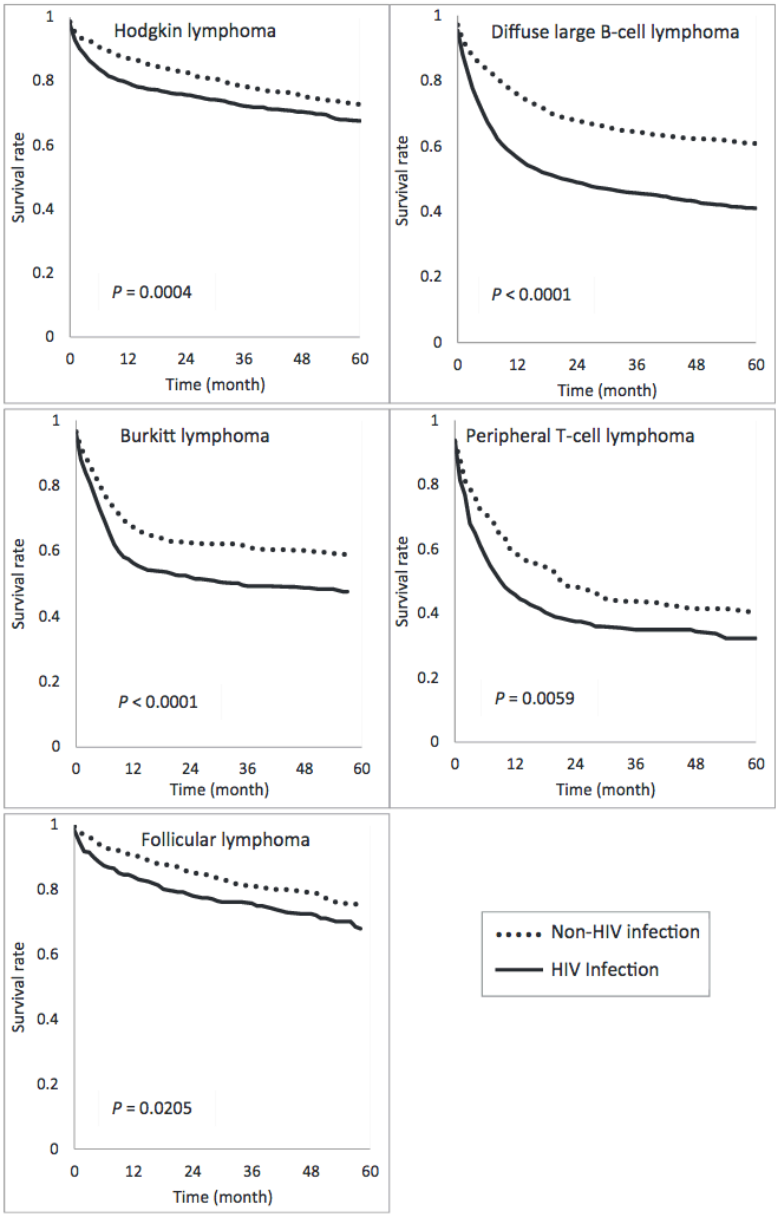


Figure 1.
Survival curves by HIV infection status, patients with lymphoma, NCDB 2004–2009.

Han *et al.*, Cancer Epidemiol Biomarkers Prev March 1 2017 (26) (3) 303-311; DOI: 10.1158/1055-9965.EPI-16-0595

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