UCCH Pathway

UCCH Guideline
Non-Hodgkin‘s Lymphoma

2.03.01 Anlage 32

Version Apr/2020

Hubertus Wald Tumorzentrum
Universitäres Cancer Center Hamburg
Ein Kompetenznetzwerk des UKE

Guideline Non-Hodgkin‘s Lymphoma

Version 05, Apr/2020

According to WHO classification of lymphoid neoplasms, 4th edition and Ann-Arbor staging system

Non-Hodgkin‘s Lymphoma board members

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Legend of Colours

= Therapeutic procedure

= Clinical or diagnostical condition

= Diagnostic procedure

= Clinical trial

= Supportive measure

= Referral

TB

= Tumorboard (including post tumorboard interaction with patient that follows the principles of shared decision-making)

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Pathway: Non-Hodgkin‘s Lymphoma

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Work up

Baseline:

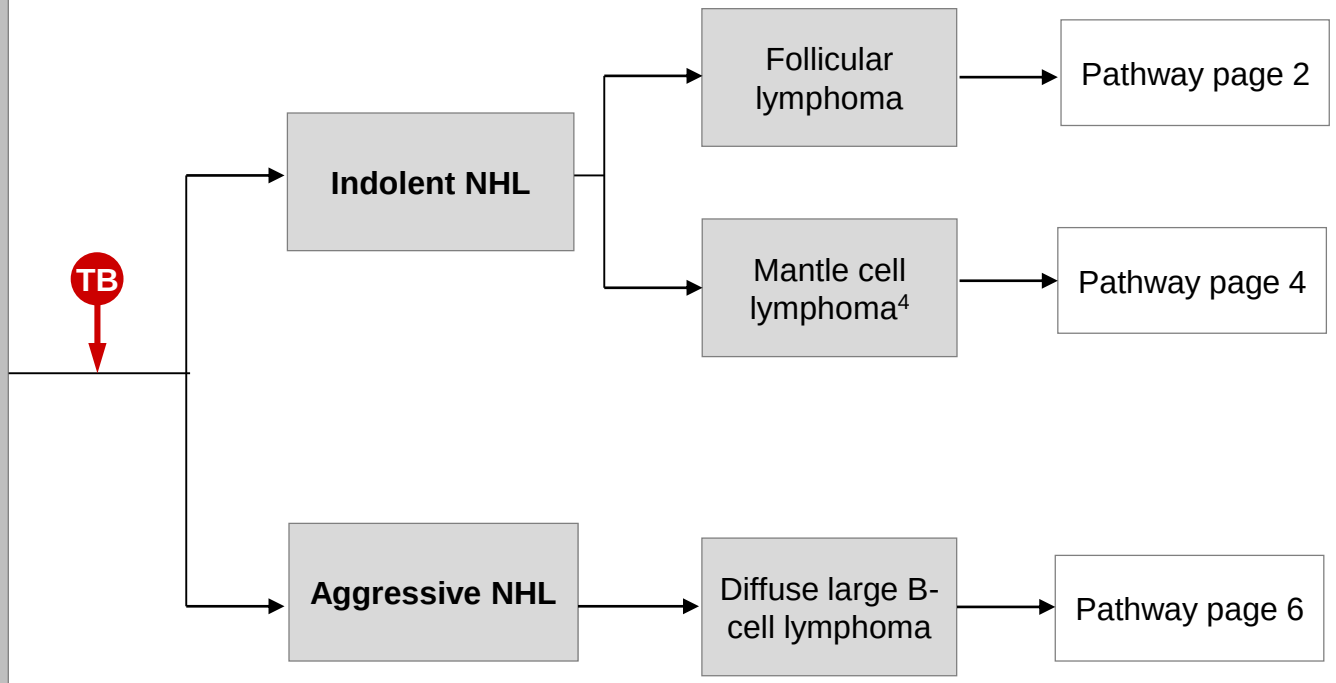
- History (incl. B-symptoms)
- Physical examination (incl. palpation of all lymph node areas, spleen and liver)
- Lab exam (including CBC with differential, LDH, uric acid, β-2 microglobulin, electrophoresis and serum immunoglobulins)
- Hepatitis B[1]/C; HIV serology
- Neck, chest, abdominal and pelvic CT **or** PET-CT[3]
- Bone marrow aspirate & biopsy (including cytogenetics and flow cytometry)
- Biopsy[2]

Facultative:

- PET-CT[3]
- ECG, Echocardiography and lung function test (pretreatment evaluation)
- Pregnancy testing, discussion of fertility issues and sperm banking
- Lumbar puncture
- Gastroscopy, colonoscopy

Supportive:

- Offer contact to self help group
- Offer psychooncological support



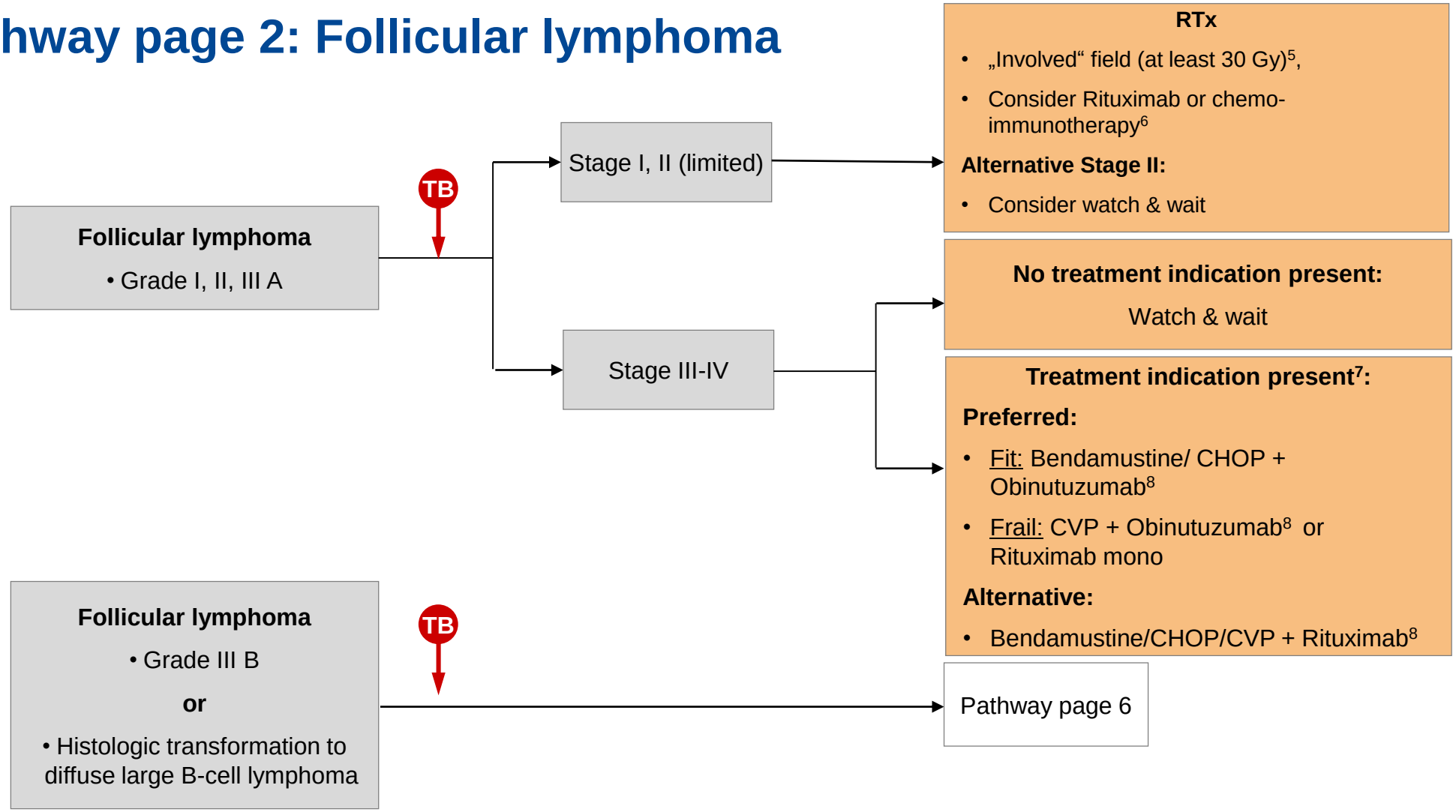
1 Hepatitis B testing is recommended because of the risk of reactivation with immunotherapy and chemotherapy. Antiviral prophylaxis is indicated in patients with positive Hepatitis B serology (HBs Ag positive) including occult carriers (HBs Ag negative and anti-core positive) in dependence of viral load.

2 The histological report should give the diagnosis according to the World Health Organization classification. Fine needle aspirations are inappropiate for a reliable diagnosis. For differentiation between the NHL lymphoma subtypes cytogenetics for t14/18 and FISH t11/14 might be useful.

3 CT is not required after PET-CT! PET-CT is obligatory in stage I and regional stage II follicular lymphoma for confirmation of localised disease or optional in follicular lymphoma in initial staging for estimating prognosis and recommendation for initial diagnostic in high grade –NHL.
CAVE: Tests are not generally covered by public health insurance and funding might require special application

4 Classified as indolent lymphoma although most patients follow an aggressive clinical course

Pathway page 2: Follicular lymphoma



RTx Radiotherapy

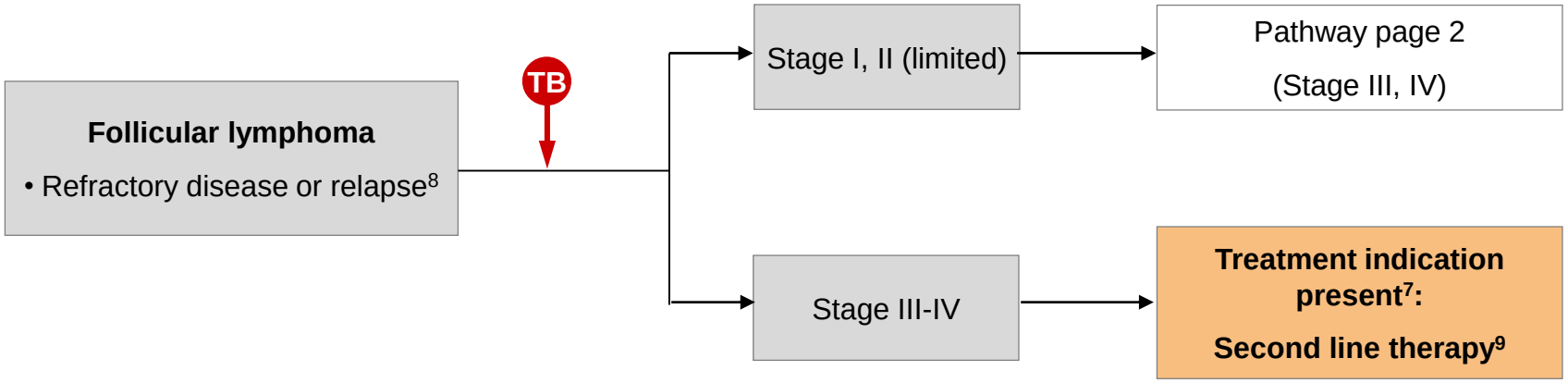
5 Patients with contraindication against RT are treated analogous stage III-IV

6 Consider combination of radiation therapy with Rituximab according to MIR-trial of the German Lymphoma Study Group

7 B-symptoms, hematopoetic impairment, bulky disease, vital organ compression, massive splenomegalia, ascites, pleural effusion, rapid lymphoma progression, susceptibility to infections

8 Followed by antibody maintenance with Obinutuzumab (in case of Rituximab containing first line therapy with Rituximab) for two years

Pathway page 3: Follicular lymphoma refractory disease or relapse



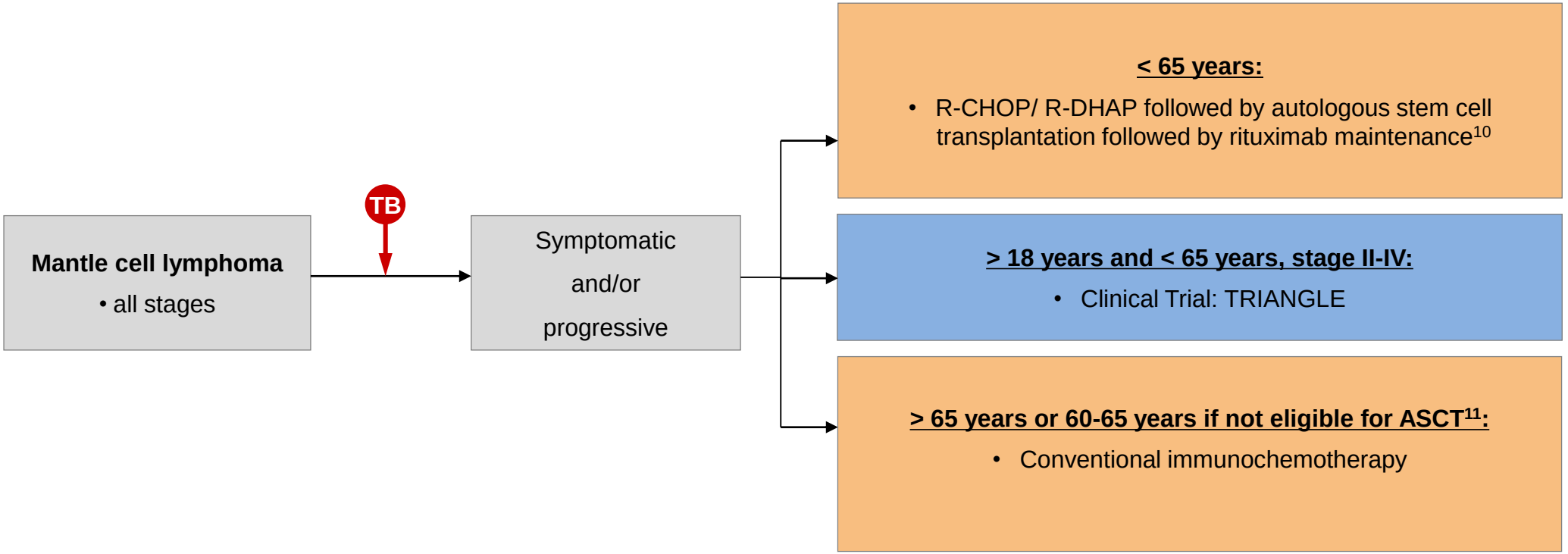
[7] B-symptoms, hematopoetic impairment, bulky disease, vital organ compression, massive splenomegalia, ascites, pleural effusion, rapid lymphoma progression, susceptibility to infections

[8] Repeated biopsy is strongly recommended to rule out a secondary transformation into aggressive lymphoma. Consider PET-CT for performing targeted biopsy.

[9] Second or third line therapy options depending on previous therapy, age, comorbidities and response duration:

- Immunochemotherapy: In early relapses (<12 months) a non-cross-resistant scheme should be preferred (e.g. CHOP or CVP after Bendamustine and vice versa). Re-exposition of rituximab is recommended if the previous antibody containing scheme achieved > 6-12 months duration of remission. Obinutuzumab is approved in combination with bendamustine in Bendamustine sensitive Rituximab refractory cases. Consider rituximab maintenance for two years in patients who have not received antibody as first line therapy.
- Combination of Lenalidomide with rituximab in pretreated patients with follicular lymphoma (grade I-IIIa)
- Monotherapy with Idelalisib in patients whose disease has relapsed or did not respond to two previous treatments.
- Especially in patients with short term remissions (< 2-3 years) autologous stem cell transplantation (ASCT) after high-dose chemotherapy should be considered.
- In selected younger patients with high risk profile or relapse after ASCT, early relapses or refractory disease a potentially curative allogeneic stem cell transplantation might be discussed.

Pathway page 4: Mantle cell lymphoma

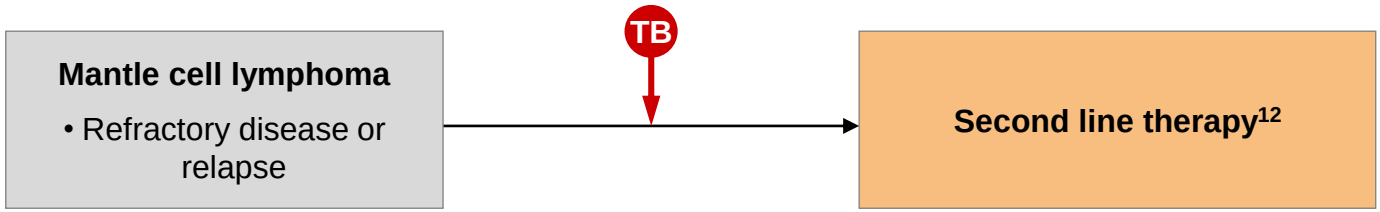


10 In case of NR or PD after R-CHOP/R-DHAP: Allogeneic stem cell transplantation

11 Alternative therapy options for patients > 65 years or 60-65 years not eligible for ASCT depending on performance status and comorbidities:

- Immunochemotherapy: R-CHBoP, R-CHOP, R-Bendamustine, R-Chlorambucil or rituximab monotherapy, consider subsequent rituximab maintenance for three years
- Radiotherapy: In case of symptomatic localised disease

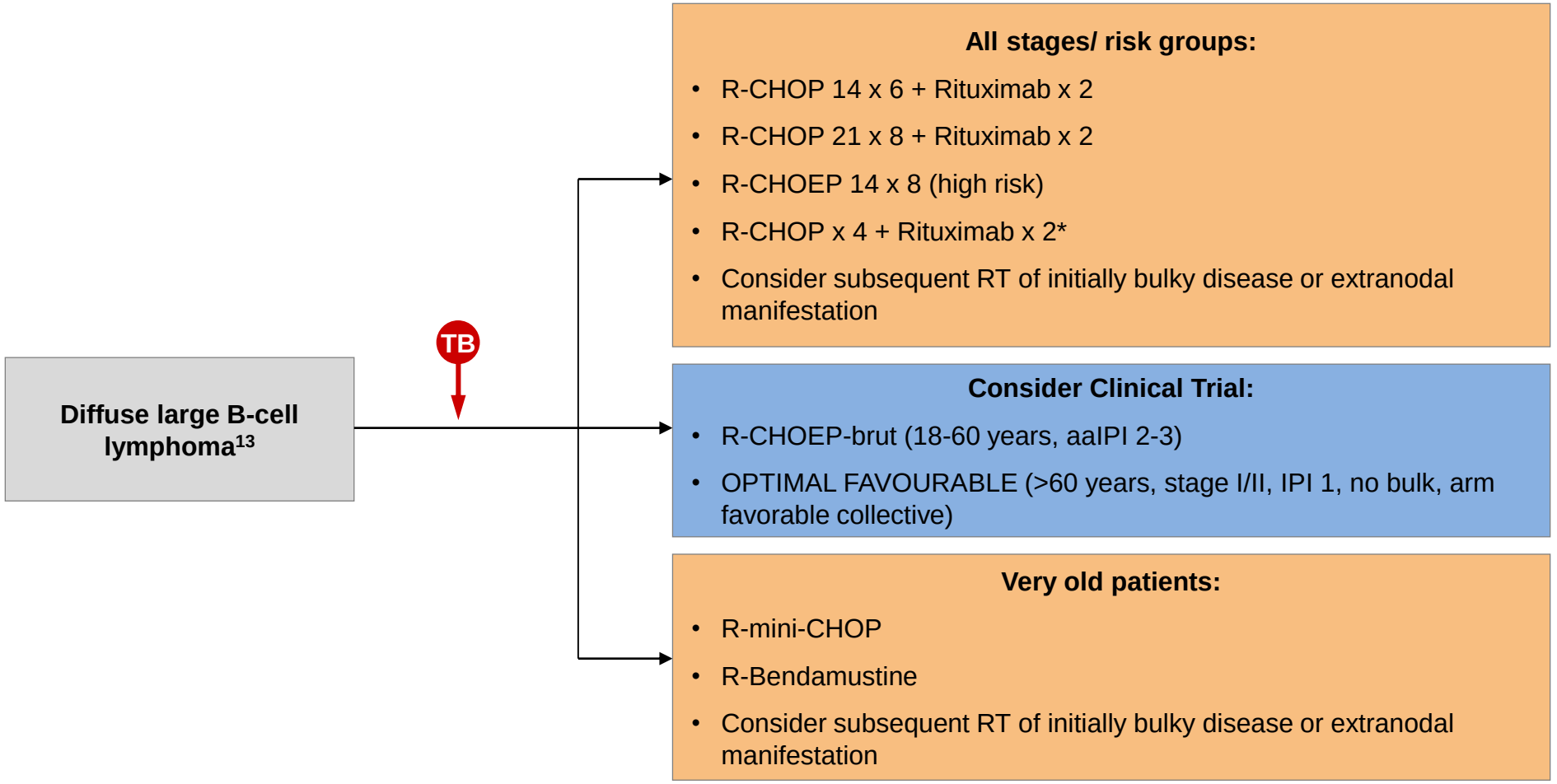
Pathway page 5: Mantle cell lymphoma refractory disease or relapse



[12] Second line therapy options depending on previous therapy, age, comorbidities and response duration:

- Immunotherapy
  - •A non cross resistant scheme should be prefererred in early relapses (< 12-24 months)
  - •Discuss ASCT in patients progressive or relapsed after conventional first-line therapy
  - •Discuss allogeneic stem-cell transplantation in young and fit patients relapsed after ASCT
- Other options: Ibrutinib, Lenalidomid (+/- Rituximab), Temsirolimus, Bortezomib, Venetoclax (off label), RT in case of localised symptomatic disease
- R-BAC

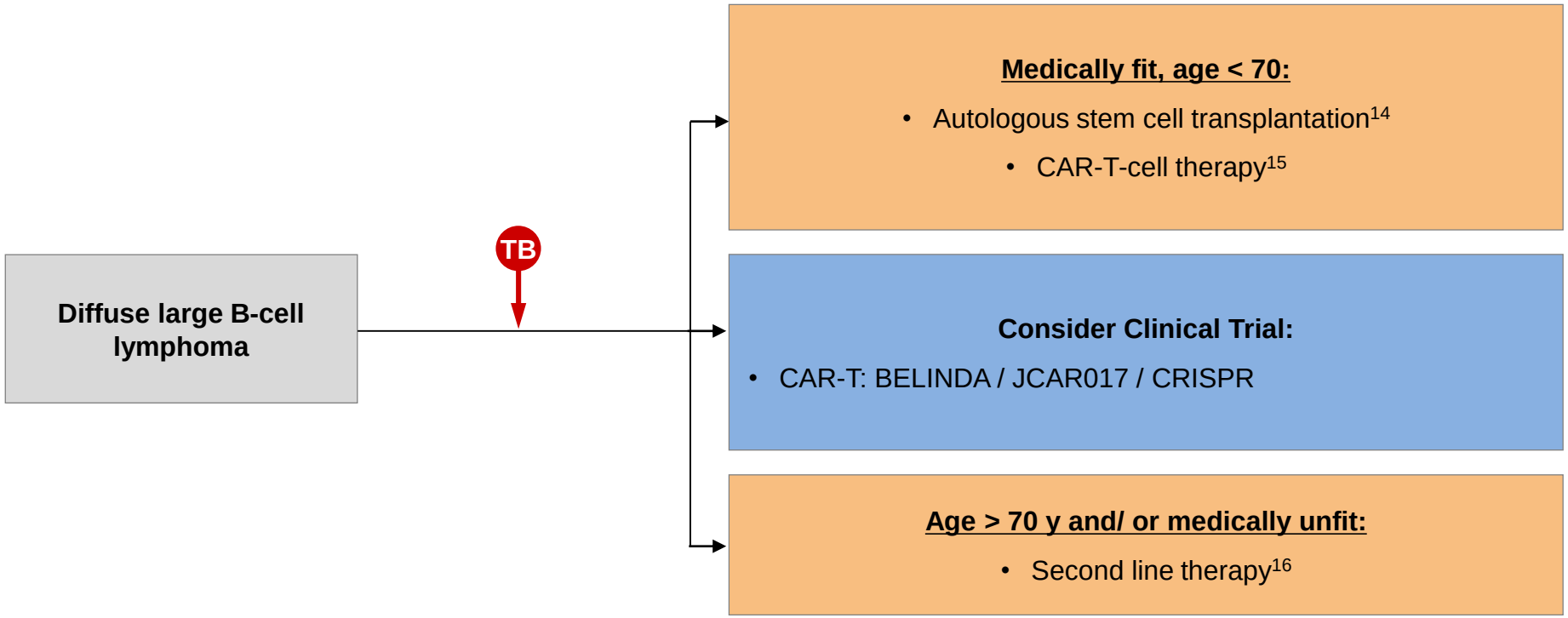
Pathway page 6: Diffuse large B-cell lymphoma



13 Consider iv-MTX for high-risk CNS-IPI (4-6 of IPI-factors and involvement of kidney/adrenal gland or involvement of testis), CNS-IPI see page 12

*According to Poeschel et al.: Excellent outcome of younger patients (18 - 60 years) with favorable-prognosis diffuse large B-cell lymphoma (DLBCL) treated with 4 cycles CHOP plus 6 applications of rituximab: results of the 592 patients of the FLYER trial of the DSHNHL/GLA. Blood 2018; 132(suppl), abstract 781

Pathway page 7: Diffuse large B-cell cell lymphoma refractory disease or relapse



14 Consider allogeneic stem cell transplantation in young and fit patients with refractory disease, early relapse or relapse after ASCT

15 Consider CAR-T-cell therapy as alternative option in patients with relapsed or refractory DLBCL after two or more lines of systemic therapy

16 Second line therapy options depending on age, comorbidities and response duration include: R-DHAP, R-ICE, R-Gem/Ox, CAR-T-cell therapy, Pixantrone, RT of localised disease, Polatuzumab/BR

Page 8: Follow up

<u>After systemic treatment:</u>

Every 3 months for 2 years, then every 6 months until year 5, afterwards yearly

- History and clinical examination, lab exam (including full blood count and differential)
- Minimal adequate radiological or ultrasound examinations every 6 months for two years with focus on initially pathological findings, additional imaging as clinically indicated
- Annual evaluation of thyroid function in patients with irradiation of the neck
- Offer contact to self help group and psychooncological support whenever necessary
- Make recommendationens for screening measures for the early detection of cancer

<u>After local radiotherapy:</u>

Every 6 months for 2 years, subsequently once a year if clinically indicated:

- History and physical examination
- Offer contact to self help group and psychooncological support whenever necessary
- Make recommendationens for screening measures for the early detection of cancer

Page 9: Follicular lymphoma risk stratification: Follicular lymphoma specific International prognostic index (FLIPI)

FLIPI -Criteria	
Age	≥ 60 y
Number of nodal sites	≥ 4
Ann Arbor stage	III or IV
Serum LDH level	> ULN (upper limit of normal)
Serum hemoglobin level	< 12 g/dl

Risk group according to FLIPI chart	
	Number of factors
Low	0-1
Intermediate	2
High	≥ 3

According to Solal-Celigny et al: Follicular lymphoma international prognostic index. Blood, September 2004, Volume 104 (5): 1258-65

Page 10: Mantle cell lymphoma risk stratification: MCL International prognostic index (MIPI)

Simplified MIPI prognostic index				
Points	Age y	ECOG	LDH (ULN)	WBC, 10^9/L
0	< 50	0-1	< 0.67	< 6.700
1	50-59	-	0.67 - 0.99	6.700 – 9.999
2	60-69	2-4	1.000 – 1.49	10.000 – 14.999
3	≥ 70	-	≥ 1.50	≥ 15.000

According to Hoster et al: A new prognostic index (MIPI) for patients with advanced stage mantle cell lymphoma. Blood, January 2008, Volume 111 (2): 558-65

Page 11: Diffuse Large B-Cell Lymphoma risk stratification

International prognostic index (IPI) and age-adjusted international prognostic index (aaIPI) in patients ≤ 60 years

IPI -Criteria	
Age	≥ 60 y
Extranodal sites	> 1
Ann Arbor stage	III or IV
Serum LDH level	> ULN (upper limit of normal)
Performance status	2 - 4

aaIPI –Criteria (patients ≤ 60 years)	
Ann Arbor stage	III or IV
Serum LDH level	> ULN (upper limit of normal)
Performance status	2 - 4

Risk categories according to IPI chart	
	Number of factors
Low	0-1
Low intermediate	2
High intermediate	3
High	4 - 5

Risk categories according to aaIPI chart	
	Number of factors
Low	0
Low intermediate	1
High intermediate	2
High	3

According to: A predictive model for aggressive non-Hodgkin’s lymphoma. The International Non-Hodgkin’s Lymphoma Prognostic Factors Project. N Engl J Med 1993; 329: 987–994

Page 12: Diffuse Large B-Cell Lymphoma risk stratification

International prognostic index (IPI) for assessing risk of CNS relapse (CNS-IPI) in patients treated with R-CHOP

CNS-IPI –Criteria (each one point)[17]	
Age	≥ 60 y
Extranodal involvement	• Involvement of >1 sites
	• Kidney and/or adrenal gland
Ann Arbor stage	III or IV
Serum LDH level	> ULN (upper limit of normal)
ECOG Performance status	> 1

CNS-IPI: Sum of points[18]	
	Sum of points
Low	0-1
Intermediate	2-3
High	4 - 6

Risk of CNS relapse after two years	
Low	0.6%
intermediate	3.4%
High	10.2%

[17] Involvement of testis is an independent risk factor; iv-MTX and radiotherapy of the contralateral testis is indicated.

[18] For high-risk CNS-IPI (4-6 of IPI-factors and involvement of kidney/adrenal gland) consider iv-MTX.

According to:

- The number of extranodal sites assessed by PET/CT scan is a powerful predictor of CNS relapse for patients with diffuse large B-cell lymphoma, Eur J Cancer. 2017;75:195. Epub 2017 Feb 23
- Validation of a prognostic model to assess the risk of CNS disease in patients with aggressive B-cell lymphoma, Blood. 2014;124(21):394
- CNS International Prognostic Index: A Risk Model for CNS Relapse in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP, J Clin Oncol. 2016;34(26):3150.