PRIMARY CNS LYMPHOMA (PCNSL)

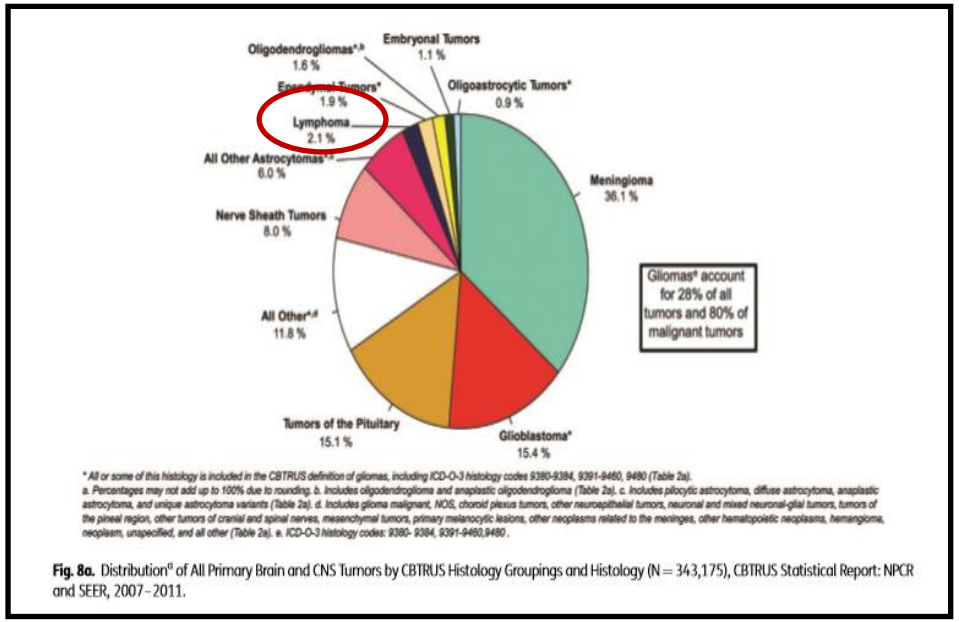
BHS EDUCATIONAL COURSE

March 2023

Virginie De Wilde, MD, PhD
Hematology Unit

1. Epidemiology

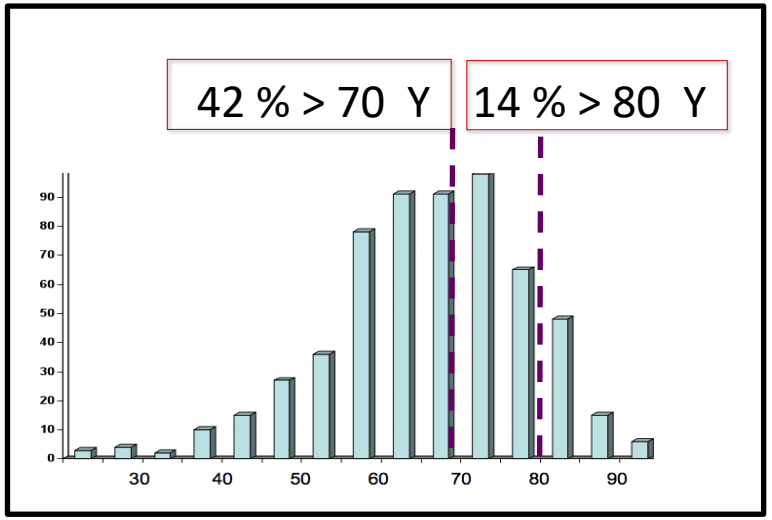
B-cell lymphoma of the brain, the spinal cord, the eyes or the meninges in the absence of systemic lymphoma



* All or some of this histology is included in the CBTRUS definition of gliomas, including ICD-O-3 histology codes 9380-9384, 9391-9460, 9480 (Table 2a).
a. Percentages may not add up to 100% due to rounding. b. Includes oligodendroglioma and anaplastic oligodendroglioma (Table 2a). c. Includes pilocytic astrocytoma, diffuse astrocytoma, anaplastic astrocytoma, and unique astrocytoma variants (Table 2a). d. Includes glioma malignant, NOS, choroid plexus tumors, other neuroepithelial tumors, neuronal and mixed neuronal-glial tumors, tumors of the pineal region, other tumors of cranial and spinal nerves, mesenchymal tumors, primary melanocytic lesions, other neoplasms related to the meninges, other hematopoietic neoplasms, hemangioma, neoplasm, unspecified, and all other (Table 2a). e. ICD-O-3 histology codes: 9380- 9384, 9391-9460,9480 .

Fig. 8a. Distribution[a] of All Primary Brain and CNS Tumors by CBTRUS Histology Groupings and Histology (N = 343,175), CBTRUS Statistical Report: NPCR and SEER, 2007–2011.

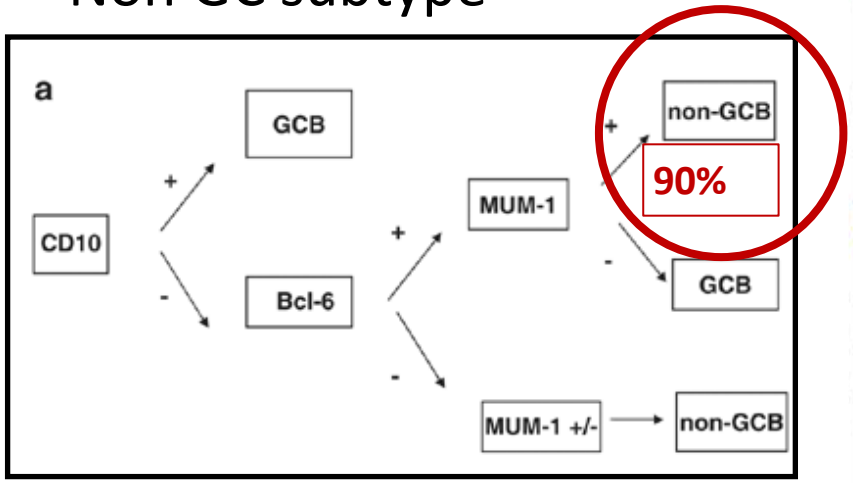
- DLBCL (>95%) >>> other aggressive B cell lymphoma >low grade NHL (MZL) > T cells lymphoma
  - 50% patients > 60 years

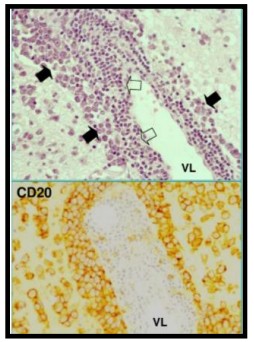


French Loc network 2011-2016 Courtesy to C. Soussain

2. Physiopathology

-Large B cells lymphoma
-Perivascular diffuse proliferation of centroblastic tumor cells
-Frequent large area of necrosis
-CD19+, 20+, 22+, 79a $^{+}$
- Non GC subtype



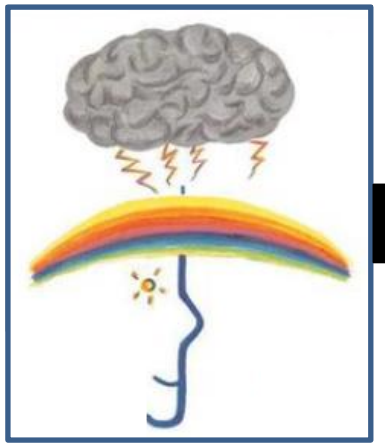


	DLBCL		EBV⁻ PCNSL
Genomic instability	**All**	**ABC-type**	
CDKN2A^{loss}	24% (43/180)[a]	35% (19/55)[a]	71% (15/21)[k]
bi-alleic	19% (8/43)[a]	26% (5/19)[a]	73% (11/15)
CNAs of additional p53/cell cycle components	multiple[a,b]	multiple[a,b]	rare[d]
Total CNAs	high	high	high
Oncogenic TLR and BCR Signaling			
MYD88^{L265P}	12% (6/49)[e]	29% (45/155)[f]	60% (33/55)[l]
NFKBIZ^{gain}	9% (16/180)[a]	20% (11/55)[a]	45% (28/62)[m]
NFKBIZ^{gain} and/or *MYD88*^{L265P}	NA	NA	83% (44/53)[n]
CD79B^{Y196mut}			
Total	16% (8/49)[e]	23% (35/155)[f]	38% (19/50)[o]
Concurrent with *MYD88*^{L265P}	38% (3/8)[e]	43% (15/35)[f]	89% (17/19)
PD-1 Ligand Deregulation			
9p24.1/*PD-L1*^{gain} and/or *PD-L2*^{gain}	6% (11/180)[a]	7% (4/55)[a]	52% (33/63)[p]
PD-L1 or *PDL-2* translocation	NA	NA	6% (4/66)[q]

- Frequent MYD88 mutation
- PDL1/PDL2 expression

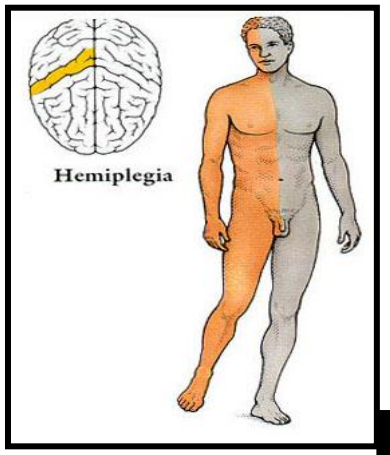
Chapuy Blood 2016

3. Clinical manifestations



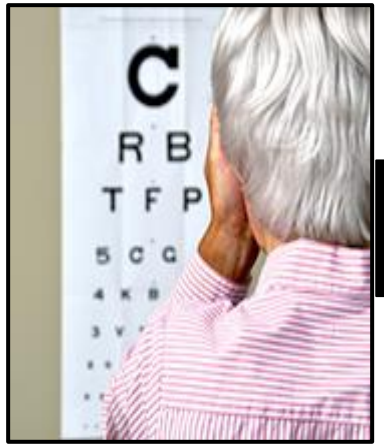
Epilepsy

Personality changes



Focal deficits

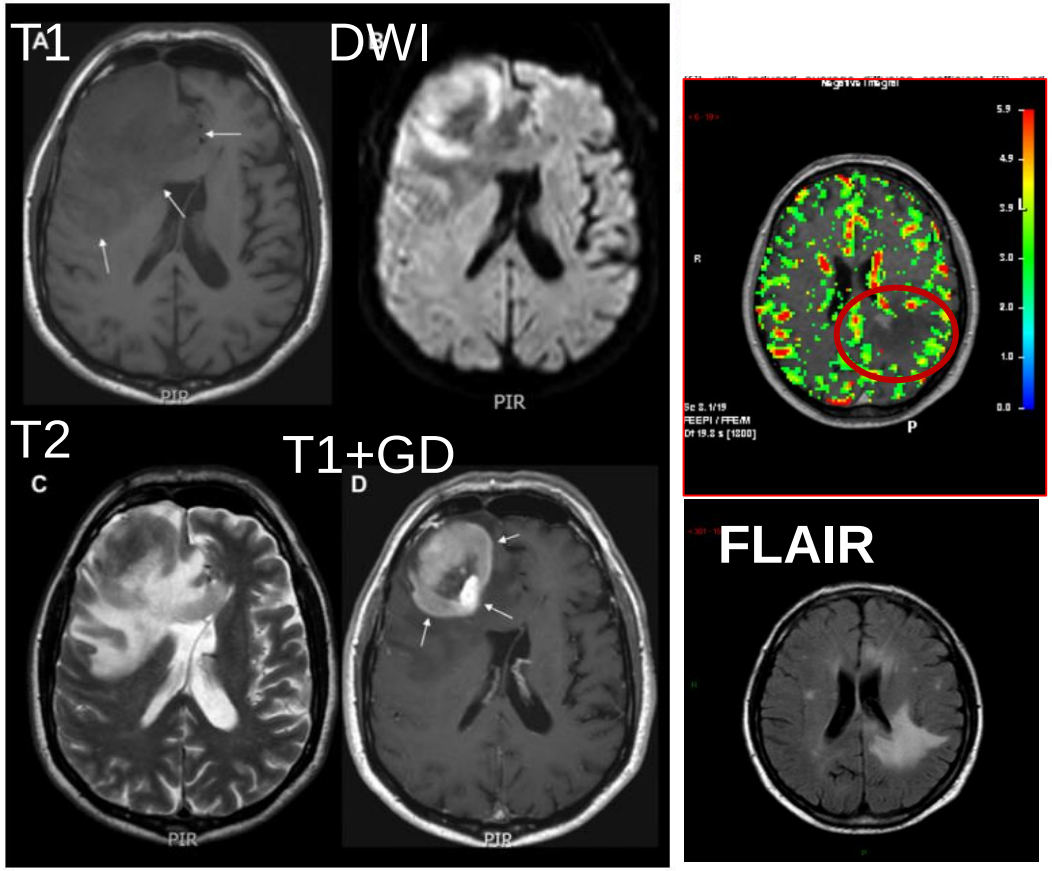
Headache



Ocular symptoms

4. Diagnosis

- Suspected on MRI…



Gadolinium
+
Perfusion

- …**Confirmed by biopsy (stereotaxic needle biopsy)**

Stop corticoid (false negative)

5. Baseline evaluation + staging

-to define the extension of the disease

-to exclude systemic localization (present in 8%)

Baseline evaluation

Usual + neurocognitive testing (MMSE,IADL,..)

Staging

WB-MRI +/-Medullar MRI

CSF Examination

Ophtalmologic evaluation

(Testicular Ultrasonography)

18FDG-PET (**No** Bone marrow biopsy)*

LP: ↑ WBC count (Cytometry +/- PCR)
↑ protein concentration
Normal glucose concentration
IL10

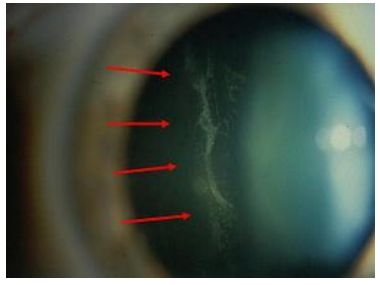
Ocular involvement in 5% of PCNSL

Fundus exam/Fluo /slit lamp +/- OCT

Vitrectomy/ intravitreal Pct:

-Cytometry, IL10 & IL6 dosage:
IL10 > 50 pg/mL
IL10/IL6 > 1

-MYD88 mutations/ PCR B cells clonalitty



*J.Jelicic Ash 2022

6. Prognostic score

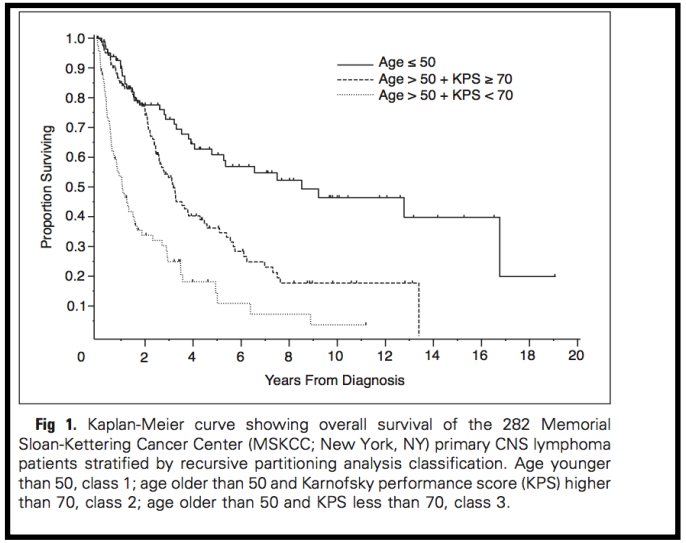
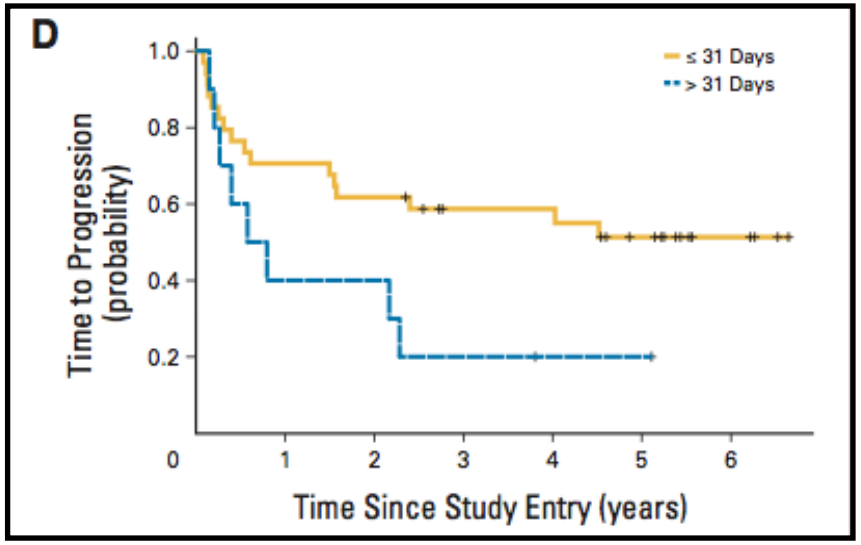


Fig 1. Kaplan-Meier curve showing overall survival of the 282 Memorial Sloan-Kettering Cancer Center (MSKCC; New York, NY) primary CNS lymphoma patients stratified by recursive partitioning analysis classification. Age younger than 50, class 1; age older than 50 and Karnofsky performance score (KPS) higher than 70, class 2; age older than 50 and KPS less than 70, class 3.



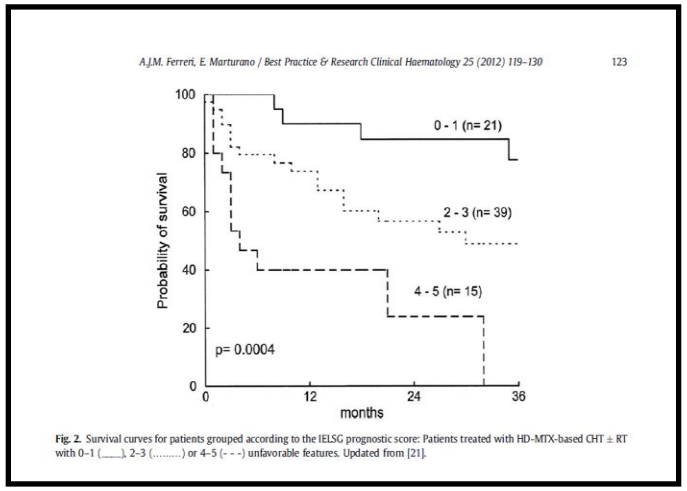


Fig. 2. Survival curves for patients grouped according to the IELSG prognostic score: Patients treated with HD-MTX-based CHT ± RT with 0–1 (____), 2–3 (.....) or 4–5 (- - -) unfavorable features. Updated from [21].

IESLG score**

Age > 61

PS ≥ 2

LDH ↚

CSF Protein level ↚

Deep brain involvement

Abrey JCO 2006,Ferreri JCO 2003*
Rubinstein JCO 2013

8. Treatment: generalities

INDUCTION → **CONSOLIDATION**

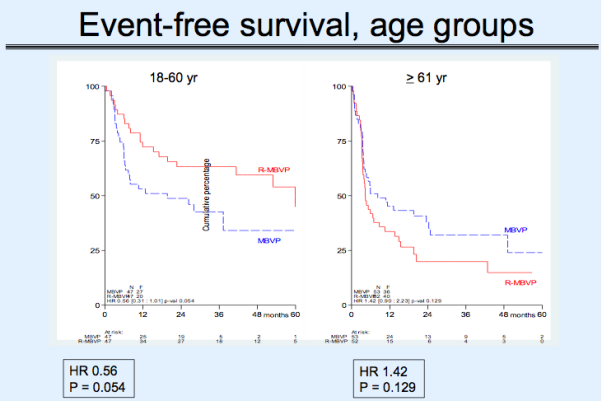
- **Chemotherapy (BBB agents):**
  - HD MTX (3.5gr/m²) *
  - Ara C (4x2gr/m²)**
  - + Other drugs : Thiotepa… etc.

- **Rituximab : 2 Randomized studies**

IESLG
N=219

	Methotrexate–cytarabine (group A; n=75)	Methotrexate–cytarabine plus rituximab (group B; n=69)	Methotrexate–cytarabine plus rituximab and thiotepa (group C; n=75)	HR (95% CI) for group A vs group B	p value	HR (95% CI) for group A vs group C	p value	HR (95% CI) for group B vs group C	p value
Complete remission	17 (23%; 95% CI 14–31)	21 (30%; 95% CI 21–42)	37 (49%; 95% CI 38–60)	0·74 (0·43–1·29)	0·29	0·46 (0·28–0·74)	0·0007	0·61 (0·40–0·94)	0·020
Partial response	23 (31%)	30 (43%)	28 (37%)	..	..	..	..	..	..
Overall response*	40 (53%; 95% CI 42–64)	51 (74%; 95% CI 64–84)	65 (87%; 95% CI 80–94)	0·69 (0·54–0·88)	0·010	0·61 (0·49–0·77)	0·00001	0·89 (0·76–1·03)	0·053

HOVON
N=199



*Ferreri Neurology , 2001
** Ferreri Lancet, 2009
Ferreri, IESLG, Lancet Haematology 2016
Bromberg, HOVON105/ALLG NHL 24, Lancet oncol 2019

8.1 First line treatment : Induction

Studies	N	Age	Chimiotherapy	CR post Induction
Morris et al.	52	60 30-79	R-MPV-(A)	60 %
Ferreri et al. IESLG32 Randomized Phase 2	75	57 53–62	R-MTX-AraC-thiotepa	49%
Rubenstein et al, CALCG	44	61 12-76	R-MTX-Temo	66 %
Omuro et al.MSKCC	32	57 23-67	R-MPV	44% (5 cycles) 66% (7 cycles)
Soussain et al. PRECIS	140	54 27-60	R-MBVP X2 + R-AraC X2	43 %

Majority of no randomized trials / different response criteria

HD MTX:

in 3 hours infusion,

Q 2-3 weeks

Minimum 6 HD-MTX injections, up to 10 if no CR

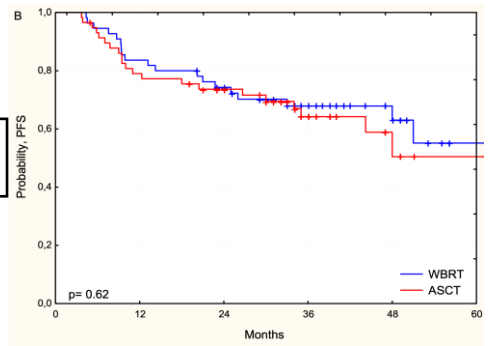
8.2 First line treatment : Consolidation - ASCT

- **2 phase II trials WBRT *vs* ASCT**

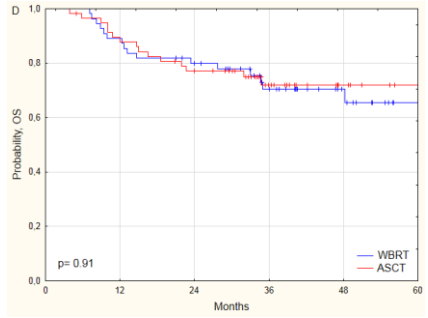
	IELSG32*	PRECIS **
Upper age limit	70	60
Induction regimen	MTX-araC ± rituximab ± thiotepa	R-MBVP - R-AraC
WBRT dose	36 +/- 9 Gy	40 Gy
Conditioning regimen	Thiotepa - BCNU	Thiotepa-busulfan-CTX

IESLG

PFS

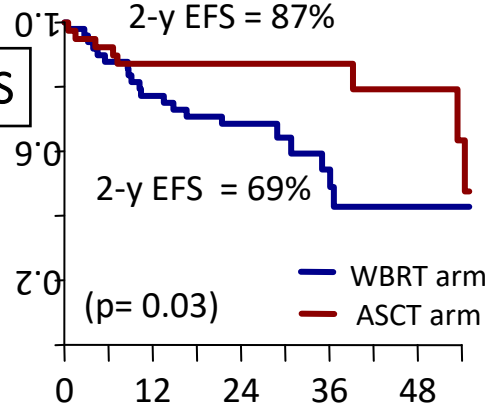


OS



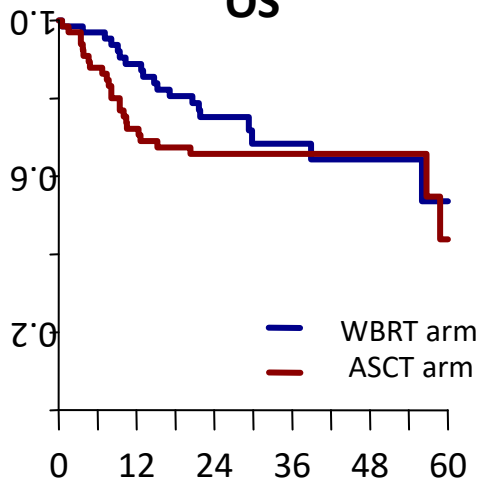
PRECIS

EFS



Time from consolidation (months)

OS



Time from inclusion (months)

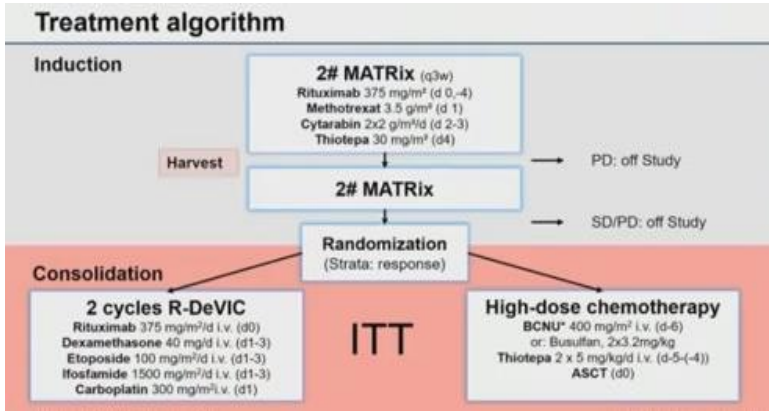
- No OS ≠
- RT: worsening of executive function over time
- **ASCT: improvement of neurocognitive function and QoL**
- **In both trials only 50% of patient will go to consolidation**

**Ferreri, IESLG 32; Lancet Haemato 2017*
**Ferreri, IESLG 32; Leukemia 2022*
*** Houillier C, PRECIS, JCO 2019*

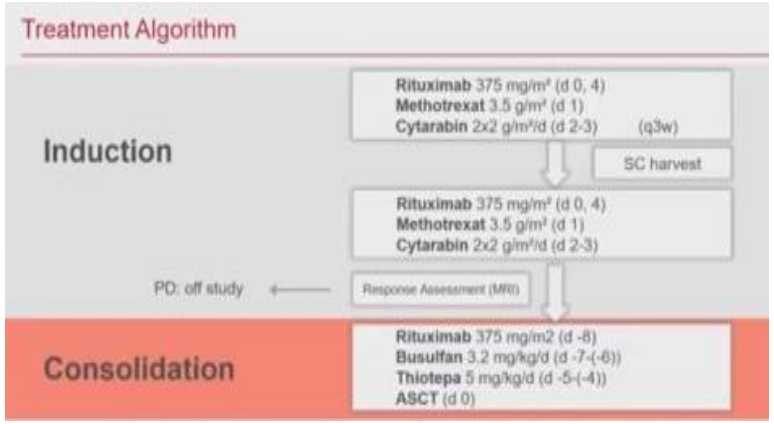
First line treatment : Consolidation - ASCT

- **MATRIX/IESLG43 phase III Trials**
  ASCT vs Chemo *

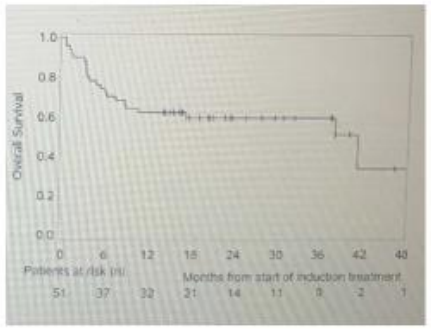
<70y
ASCT ↑PFS and OS



- **MARTA multicenter prospective Study:**
  ASCT for elderly

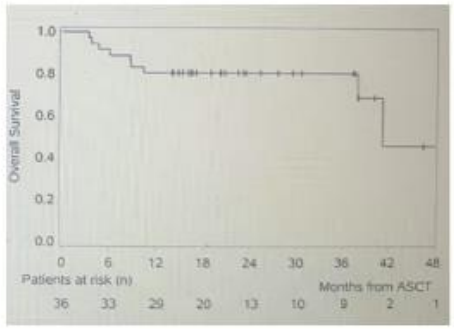


OS ITT



1-year OS: 62.7%

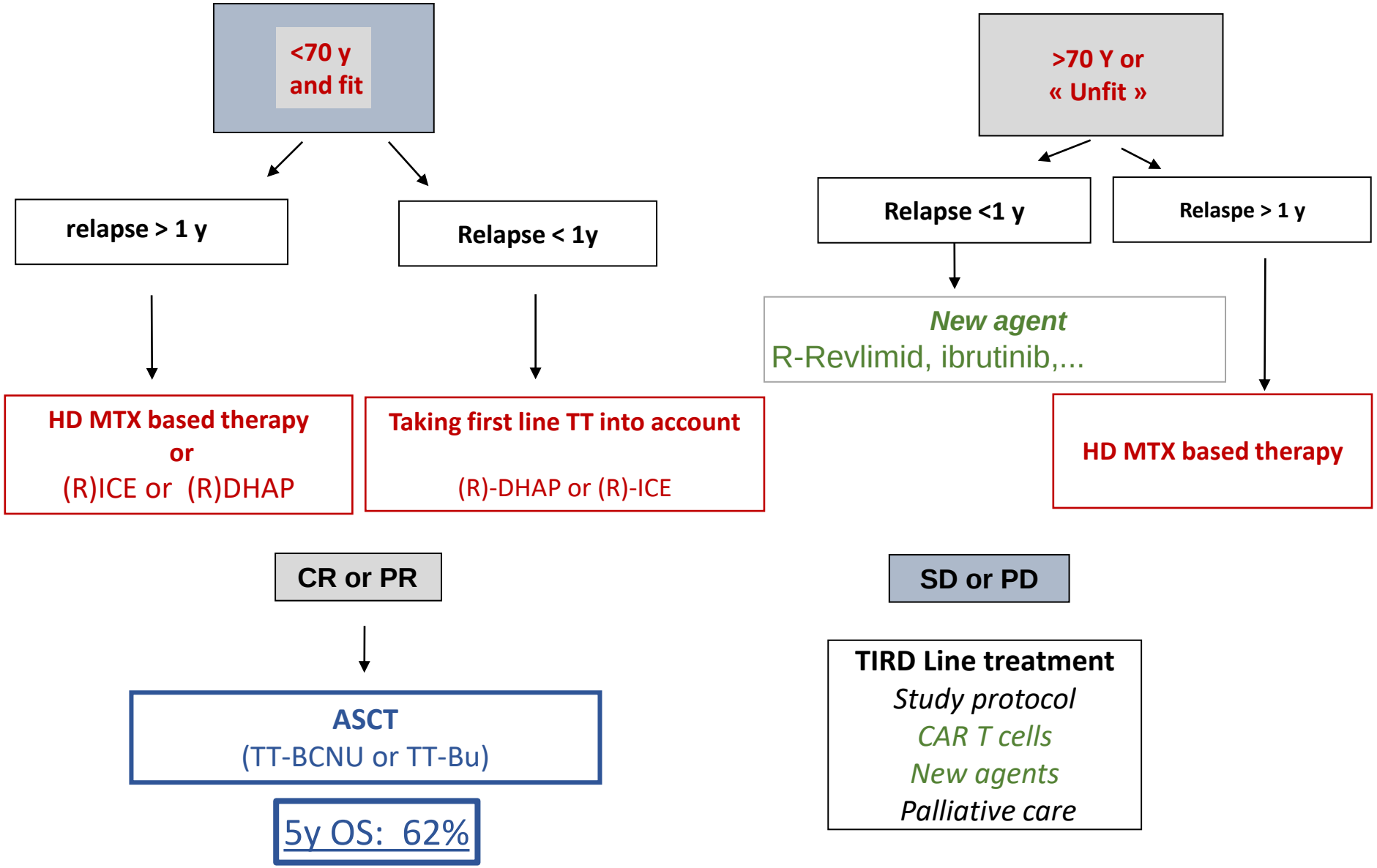
OS PP



1-year OS: 80.6%

**Ferreri ASH 2022*
*** Schorb, ASH 2022*

9. Relapse treatment



Adapted from LOC recommendations 2023

Take-home messages for PCNSL

- Biopsy before steroids
- Always address to an **experienced center** (high dose treatment)

- Induction chemotherapy:
  - Based on **high-dose methotrexate** (3.5 g/m2, over 2-3 hours)
  - Dose intensity = every 2-3weeks, minimum 6 HD-MTX injections more cycles if not in CR
- Consolidation: for **fit patients**
  - ASCT (Thiotepa BCNU/Thiotepa Busulfan , NOT BEAM !)

- Salvage treatment:
  - depends on age, performance status, and type(s) of previous treatment(s).

Contacts and references for PCNSL

- *L R Schaff. Primary central nervous system lymphoma: Review Series. Blood . 2022.*
- *L R Schaff. Primary central nervous system lymphoma: a narrative review of ongoing clinical trials and goals for future studies. Ann Lymphoma. 2021.*
- *T. Calimeri. How we treat primary central nervous system lymphoma. ESMO Guidelines 2021*
- *LOC Recommendations. France. 2023.*
- *UK Guidelines : C.P. Fox. Guidelines for the diagnosis and management of primary CNS diffuse large B-cell. BJH.2019.*

LOC

RCP nationale – web conf

Coordinatrice : Caroline HOUILLIER
caroline.houillier@psl.aphp.fr

Responsable Neuro : Pr. Khé HOANG - XUAN

Responsable Hémato : Dr Carole SOUSSAIN

Denis Parson BURKITT
(1911-1993)
surgeon

BURKITT'S LYMPHOMA

BHS EDUCATIONAL COURSE

March 2023

Virginie De Wilde, MD, PhD
Hematology Unit

H.U.B
HÔPITAL UNIVERSITAIRE DE BRUXELLES
ACADEMISCH ZIEKENHUIS BRUSSEL

INSTITUT JULES BORDET INSTITUUT
Hôpital Erasme | ULB
Hôpital Universitaire des Enfants Reine Fabiola
Universitair Kinderziekenhuis Koningin Fabiola

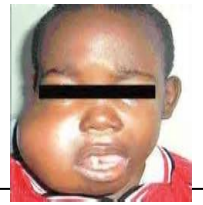
European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Epidemiology

3 different clinical sub-types

Endemic BL

- Equatorial Africa
- Median age: 6-9 y
- EBV+ 100% and association with malaria
- ♂/♀= 2:1
- Involvement facial bone, jaw



Sporadic BL

- Worldwilde
- Median age: 30 y

(3 peaks 10,40 and 75 y)

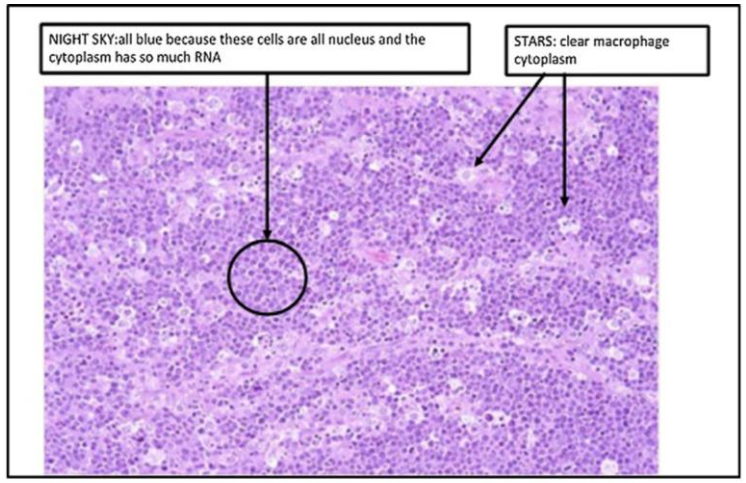
- 1-2% of all NHL
- 20-30% EBV^+
- ♂/♀=3:1
- Frequent abdominal involvement, other extranodal sites

Associated-ID BL

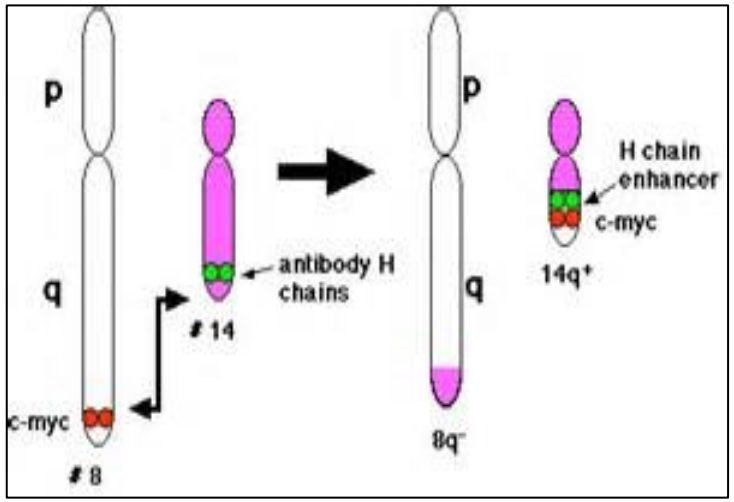
- Worldwide
- In HIV patients (and all other ID patients)
- 25-40% EBV+
- Nodal presentation most common

M.Roschewski. Burkitt's Lymphoma. NEJM. 2022

Pathology



- Diffuse, Monomorphic medium size cells. Starry sky appearance



- **Immunophenotype:**

  CD19, 20, 22,79 + **Ki67 >97%**

  GC profile:CD10 +, BCL6 but no BCL2

- **Cytogenetics: single translocation**
  - **t(8;14)(q24;q32) <=> cMYC (80%)**
  - t(8;22)(q24;q11)
  - t(2;8)(q24;q12)
  - (11q alteration) new WHO sub-entity

Clinical manifestations

Extra nodal localizations

- Abdominal masses (ileocecal), bowel obstruction
- Kidney, testis, ovarian & breast involvement
- Nodal involvement (adult patient)

- CNS: 15%
- BM: 30% Bad prognosis factors

Work-up

Must be completed rapidly
Treatment must start within 48 hours !!

- Personal history & clinical examination;
- Laboratory analyzes: CBC, liver & renal function, uric acid, LDH, HIV, EBV, HBV & HCV
- **BM biopsy**
- **Lumbar puncture with CSF examination (cerebral MRI C+)**
- Cardiac evaluation
- Pet scan for staging
- Discussion about fertility issues

Prognostic markers

Performance status >1 – ↑LDH

CNS and BM involvement (any of those = high risk)

Table 4. Risk Stratification in Adults According to the Burkitt Lymphoma International Prognostic Index.*

Risk factor
CNS involvement
LDH >3 × ULN
ECOG performance-status score ≥2
Age ≥40 yr
Risk category
Low risk: no risk factors
Intermediate risk: 1 risk factor
High risk: ≥2 risk factors

M.Roschewski. Burkitt's Lymphoma. NEJM. 2022

Treatment: generalities

- Rare entity, few randomized studies
- **Corticoid Pre-phase:** finish staging; ↓ Tumor lysis syndrome
- **Rituximab: after debulking > start at Cycle 2 (Tumor lysis syndrome !!!)**
- **CNS active agents: IT or high dose sytemic MTX or cytarabine**

2 types of chemo:

Intensive short-cycle chemotherapies (ISCC):

- BBB crossing (AraC, Metho)
- high hematological toxicities

LYSA-GRAAL – GMALL – DANA FARBER

Children and adolescents
Fit adults with high risk disease or CNS involvement

Low intensity Chemotherapies (LIC):

- Prolonged exposure to low-concentration drug
-Less toxic
- Not in case of CNS involvement

DA-EPOCH-R

Low risk disease and unfit patients

Intensive short cycle chemotherapy

Cooperative group	Chemotherapy regimen	Event-Free Survival	Overall Survival

HOVON 127 BL/ SAKK 37/16 version 07, 31 JAN 2018

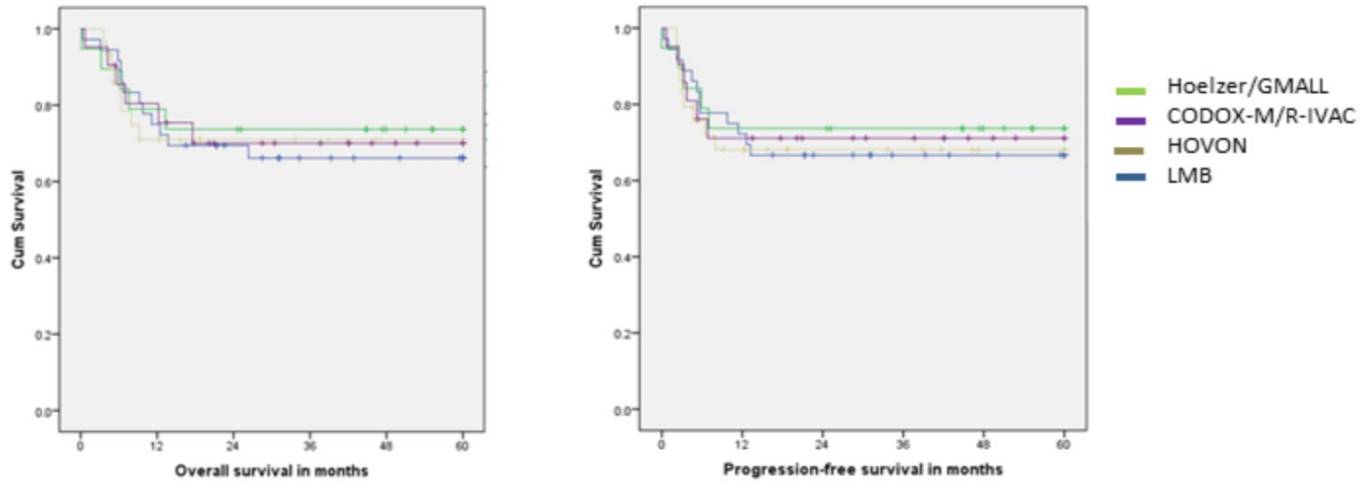


Figure 1. OS and PFS of patients treated with different protocols in the Netherlands (1995 -2010)[13]

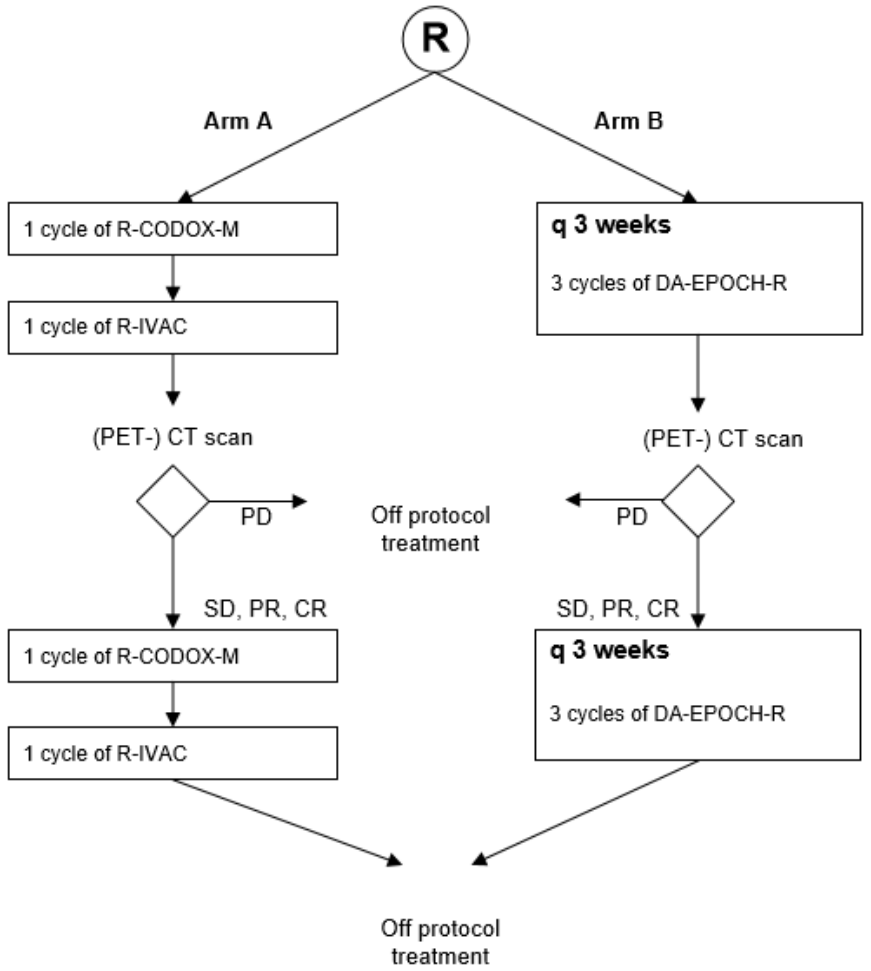
†: Ribrag V. & al, The Lancet Oncology, April 11, 2016 (Phase III randomized)

‡: rituximab 375mg/m² on d1 & d6 of each COPADEM

A*: dexamethasone, vincristine, ifosfamide, HD-methotrexate, etoposide, cytarabine
B**: dexamethasone, vincristine, cyclophosphamide, HD-methotrexate, adriamycine
C***: dexamethasone, vindesine, HD-methotrexate, etoposide, HD-cytarabine

ISCC or LIC: *which one is better?*

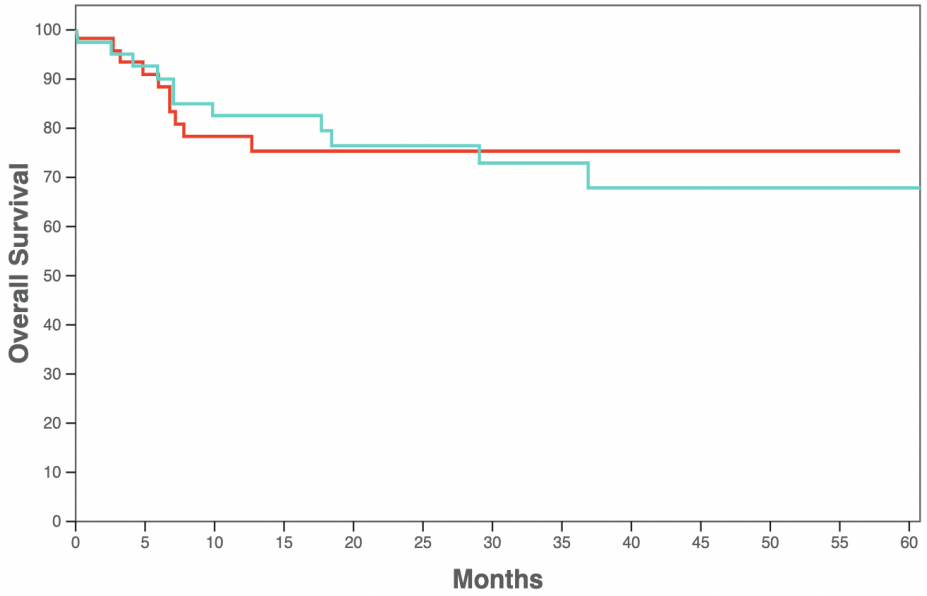
Randomized phase II study comparing R-CODOX-M/R-IVAC versus dose-adjusted EPOCH-R (DA-EPOCH-R) for patients with newly diagnosed high risk Burkitt lymphoma



HOVON

DA-EPOCH-R

Overall survival: Preliminary analysis



Curves	N
A: R-CODOX-M/R-IVAC	43
B: DA-EPOCH-R	41

	P-value
A: R-CODOX-M/R-IVAC vs B: DA-EPOCH-R	0.85

CONCLUSIONS

R-CODOX-M/R-IVAC vs DA-EPOCH-R:

Premature closure, 89 patients, mFU 19.1 months

1. **Comparable** PFS, OS and ORR
2. **DA-EPOCH-R** associated with **significantly less**
   - infectious complications
   - transfusions
   - hospitalization nights

Treatement summary

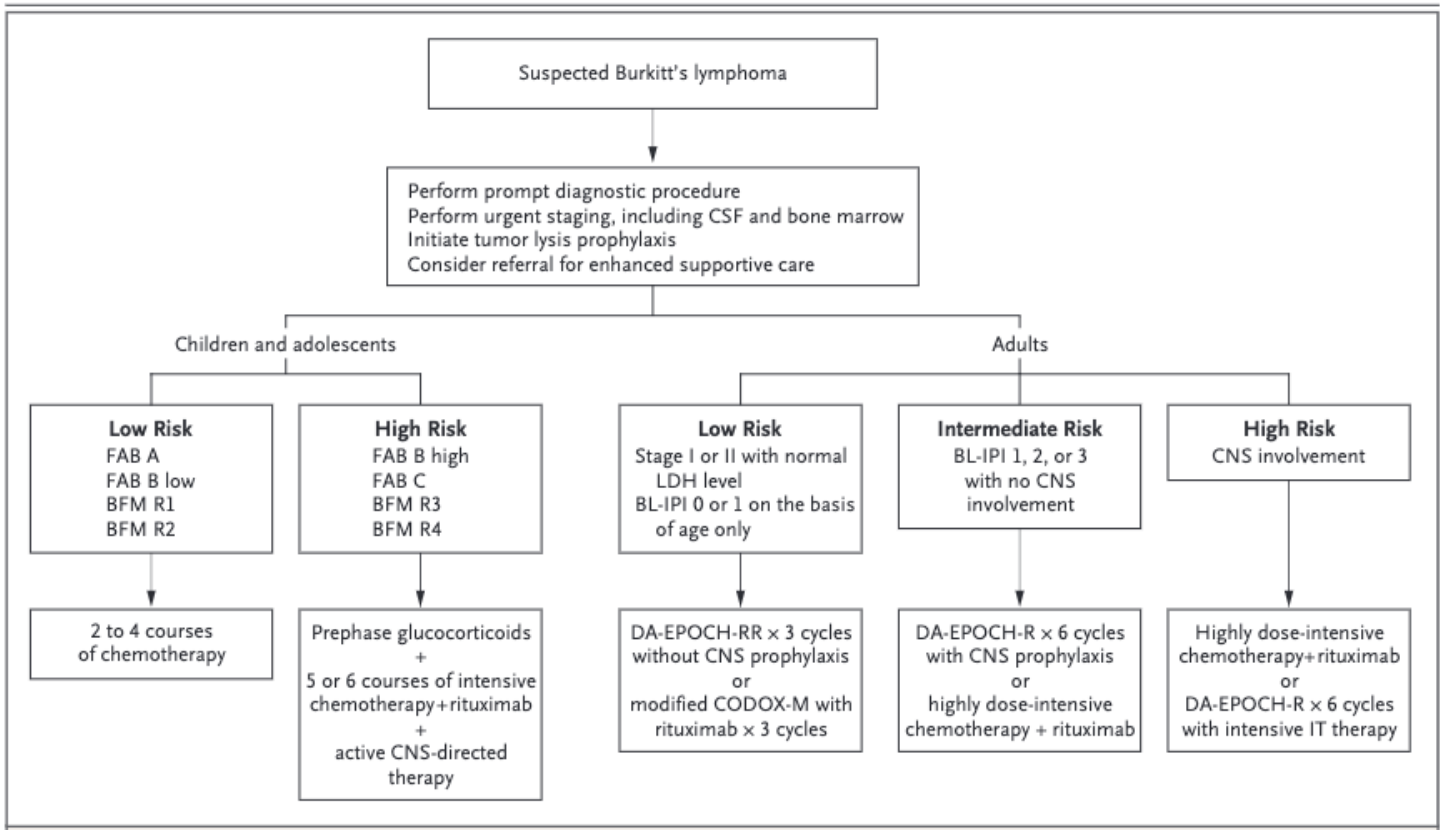


Figure 4. Clinical Approach to Suspected Burkitt's Lymphoma.

Clinicians should recognize the distinctive clinical signs and symptoms that are suggestive of Burkitt's lymphoma, including rapidly enlarging masses and markedly elevated LDH levels. The diagnostic and staging approach should be performed urgently, and intensive supportive care should be initiated before therapy. Risk stratification in adults must carefully balance acute toxic effects with efficacy. All intermediate-risk patients should receive CNS prophylaxis, and high-risk patients may require more intensive CNS-directed therapy. BFM denotes Berlin–Frankfurt–Münster, BL-IPI Burkitt Lymphoma International Prognostic Index, CODOX-M cyclophosphamide, vincristine, doxorubicin, and methotrexate, FAB French–American–British, and IT intrathecal.

M.Roschewski. Burkitt's Lymphoma. NEJM. 2022

Relapse

very bad prognosis

- Studies : new drugs and CAR T cells

- ASCT: for PR or chemo sensitive relapse

  EBMT retrospective study 3years OS*:

  37% for chemo-sensitive

  7% for chemo-refractory

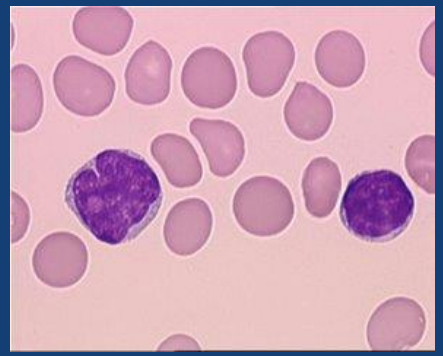
**Sweetenham J JCO 1996*

TAKE-HOME MESSAGES

- **Isolated translocation t(8;14)(q24;q32)**
- Treatment must be started within **48 hours**
- **Debulking risk of Tumor lysis**
- **CNS prophylaxis !**
- After achievement of CR, 80% of patients have a sustained remission after 1 year and are considered **cured**

References for Burkitt lymphoma:

- M.Roschewski. Burkitt’s Lymphoma. *NEJM*. 2022.
- V. Ribrag. Rituximab and dose-dense chemotherapy for adults withBrukkt’s lymphoma: a randomised, controlled, open-label, phase 3 trial.*Lancet.* 2016.
- JM. Dermot. HIV-associtaed Burkitt lymphoma. *The Lancet Hematology*. 2020
- M.Roschewski. Multicenter Study of Risk-Adapted Therapy With Dose-Adjusted EPOCH-R in Adults With Untreated Burkitt Lymphoma. *JCO*. 2020.



MANTEL CELL LYMPHOMA

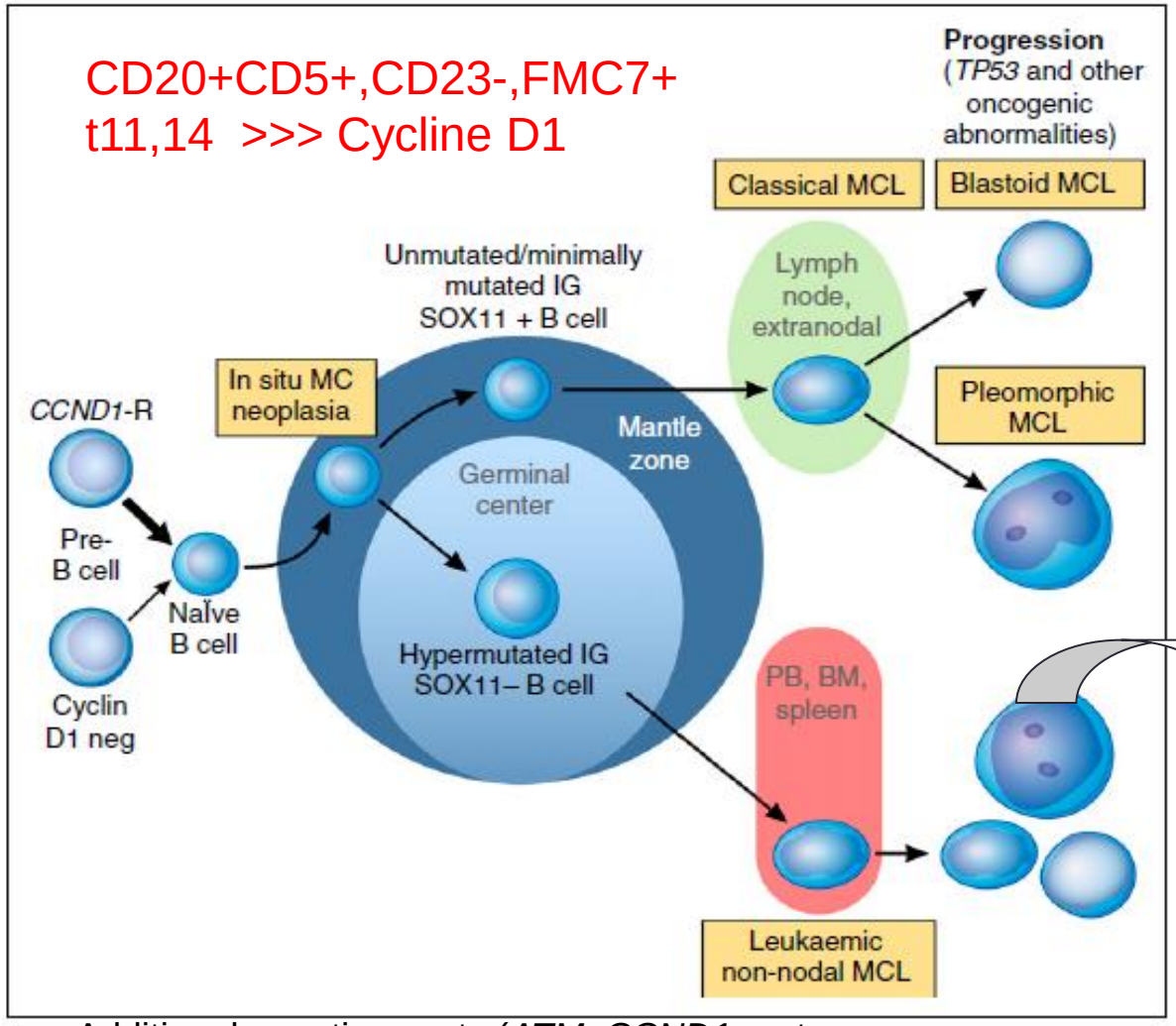
BHS EDUCATIONAL COURSE

March 2023

Virginie De Wilde, MD, PhD
Hematology Unit

Table of content

1. CLASSIFICATION:
WHO 2016: MCL subtypes



Classical MCL:
- **IGHV unmutated**
- expression of SOX11
- genetically unstable
- nodal disease
- poor outcome

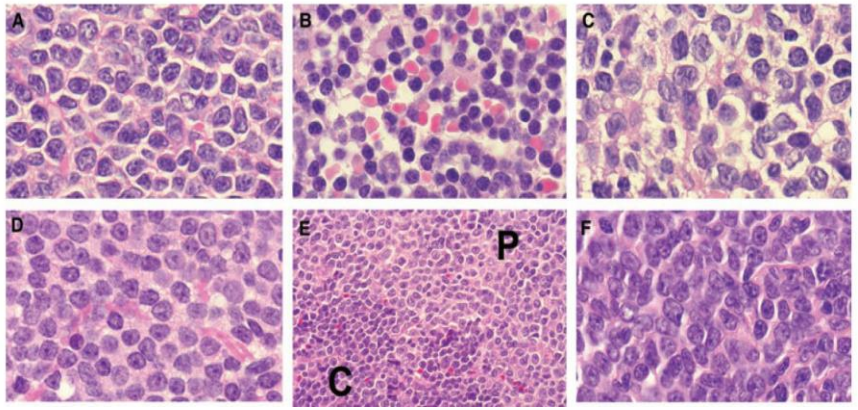
Indolent non nodal MCL:
- **IGHV mutated (underwent germinal center transit)**
-Lacks expression of SOX11
-Distinct gene expression profile
-Often presents as splenic or non-nodal diseases

- Additional genetic events (*ATM, CCND1 mut, TP53, NOTCH1, NOTCH2, ..*)

Swerdlow et al. Blood 2016
adapted from Jares P et al. J Clin Invest 2012

Histology and biological aspects

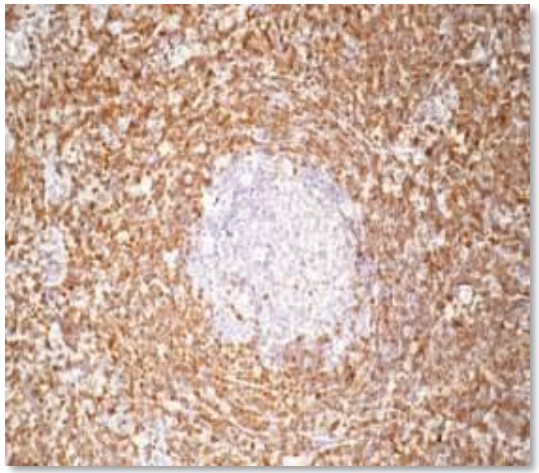
- Mantle zone, Nodular, Diffuse
  - A. Classical
  - B. Small cell
  - C. Pleiomorphic
  - D. Blastoide
  - E. Classical and pleomprphic



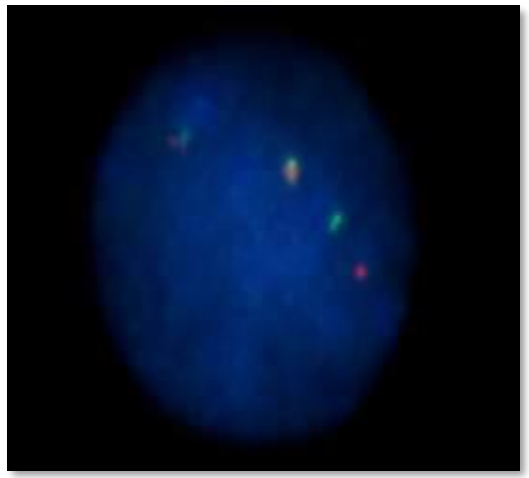
- Immunophenotype

sIg++, λ > κ, CD19/20/22+, CD5+, CD10–, CD23–, CD11c– HLA-DR++, CD43+

- t(11;14)



Cyclin D1 staining



FISH t(11;14)(q13;q32)

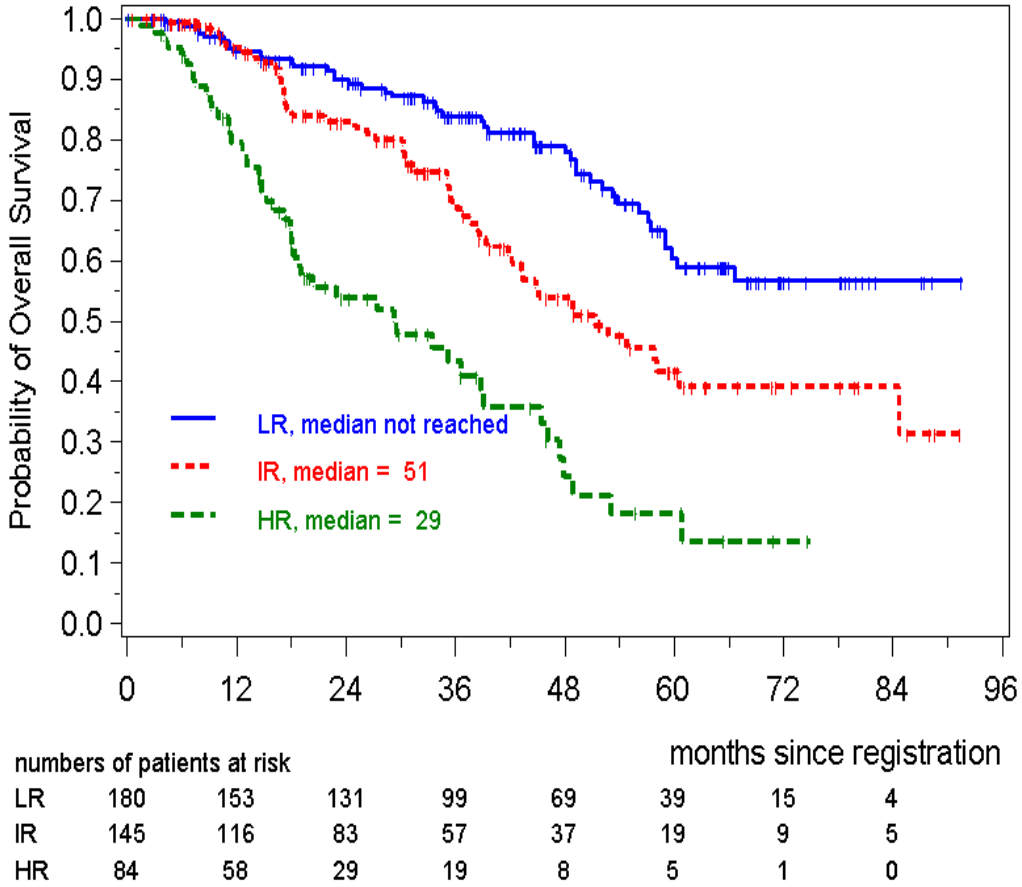
2. RISK STRATIFICATION

- 2.1 Clinical risk stratification = MIPI
- 2.2 Combined MIPI = MIPI + Ki67
- 2.3 Molecular and genetic alterations : P53 and others

2.1 Clinical risk factors: MIPI

Univariate risk factors

- age
- ECOG performance status
- B-symptoms
- spleen involvement
- tumor size
- leukocyte or lymphocyte count
- LDH
- hemoglobin
- albumin
- beta2-microglobulin



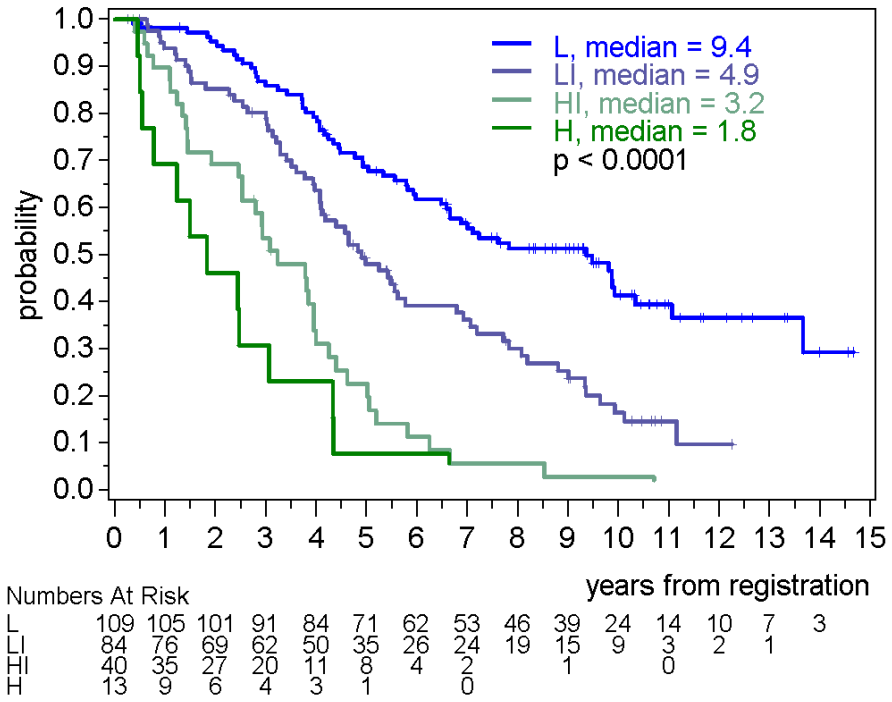
(PALL: PS, age, LDH, leucocyte count, Ki67)

Hoster, Blood 2008

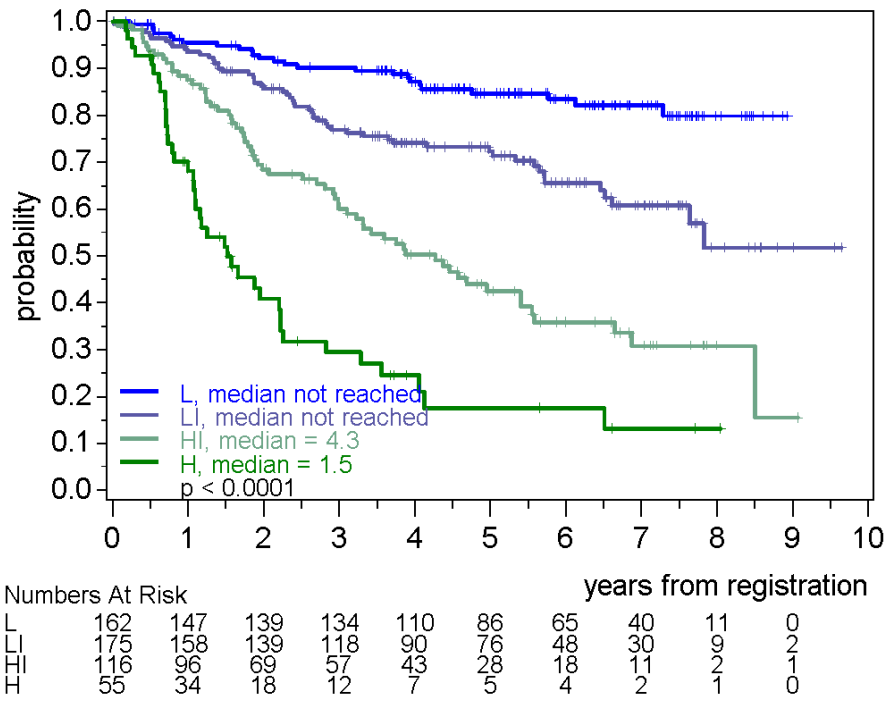
2.2 Combined MIPI: MIPI-c

MIPI + Ki-67 index = independent prognostic factors

GLSG1996/2000

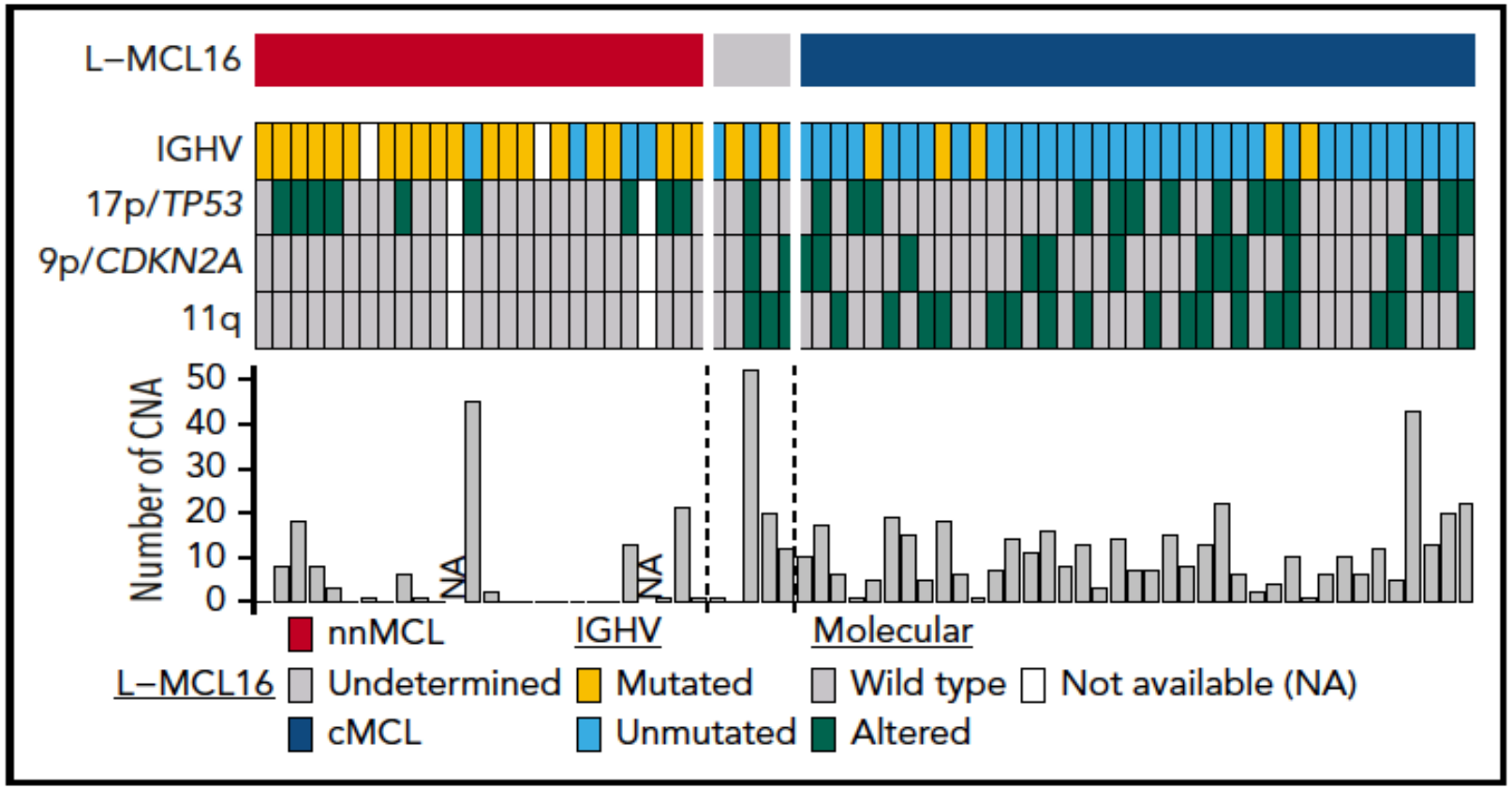


MCL Younger/MCL Elderly



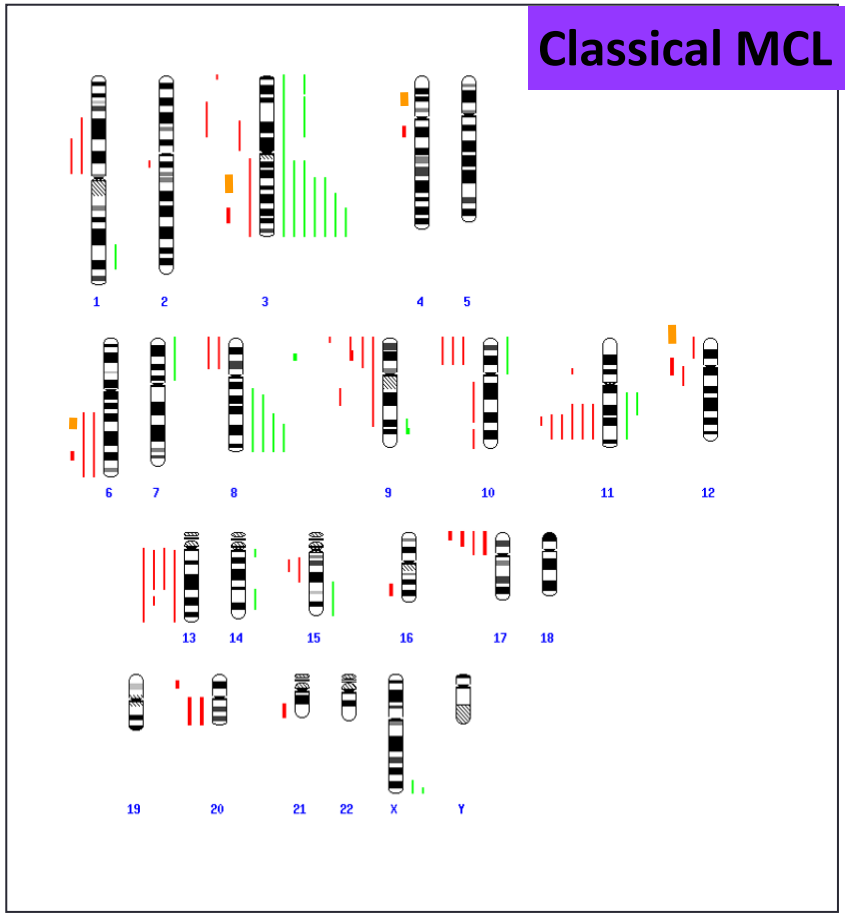
Hoster et al, J Clin Oncol 2016

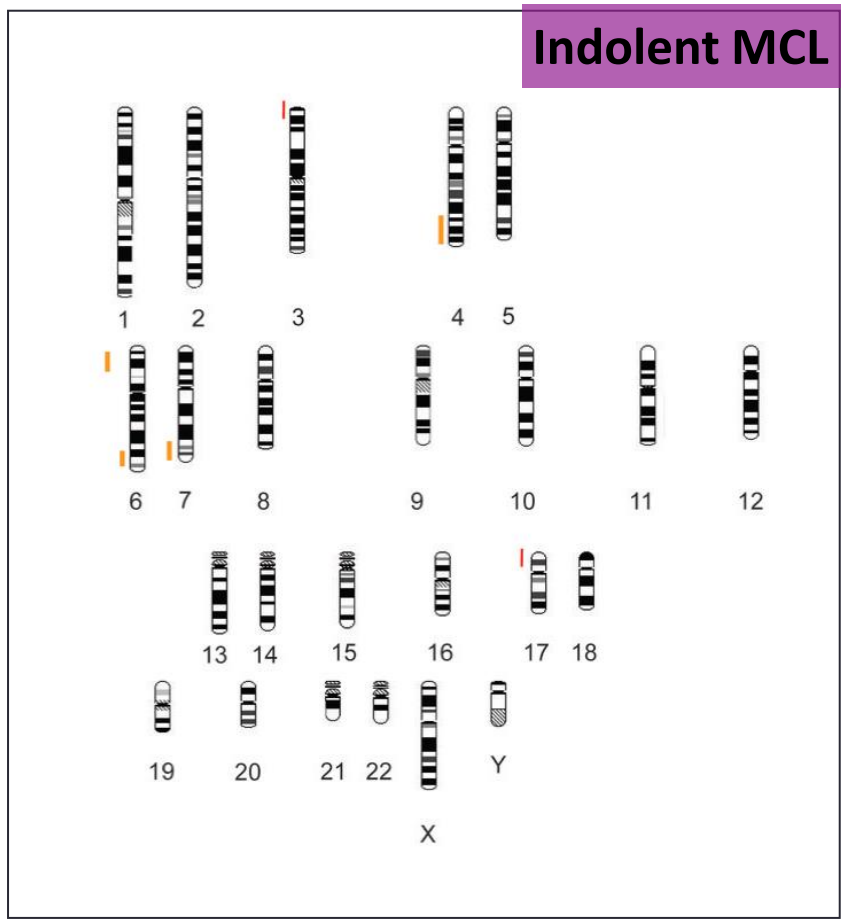
2.3 Molecular alterations



Fernandez V. Cancer Res 2010
Seto M. Blood 2013
Ferrando A. Blood 2013
Vegliante. Blood 2013
O Hermine. Lancet 2016
MH Delfau –Larue. Blood 2016

2.3 Chromosomal alterations



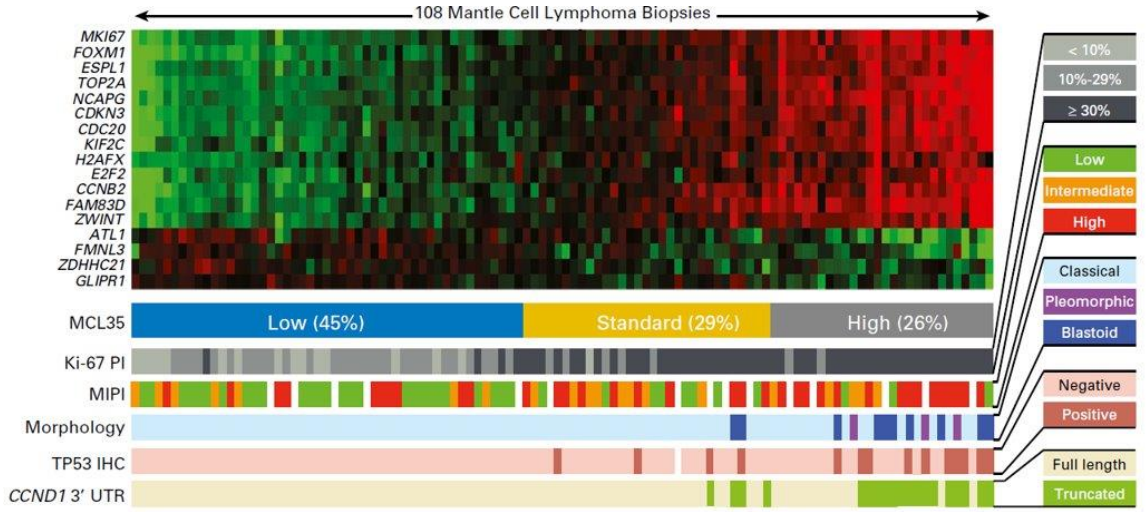


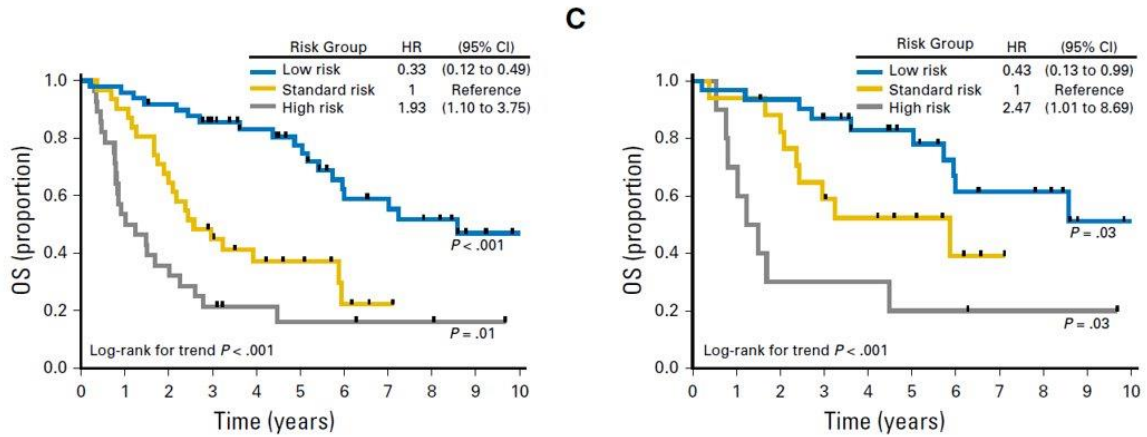
Chromosomal alterations
SNP Arrays

- Gain
- Loss
- pUPD

Fernandez V et al Cancer Res 2010

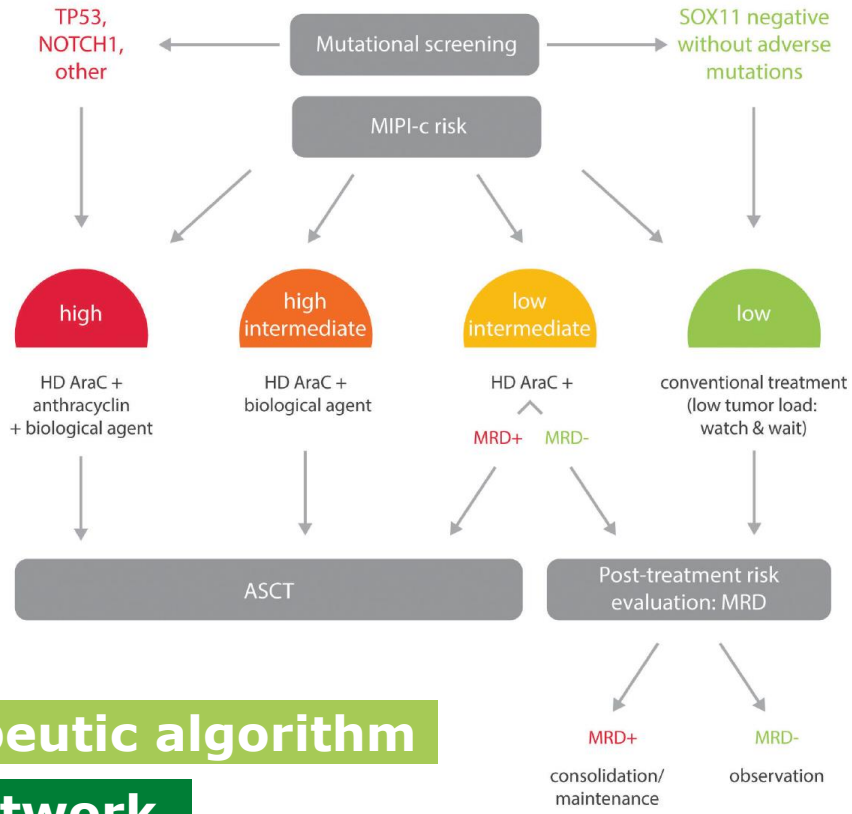
Risk stratification: conclusions





Scott, JCO 2017

Risk stratification: conclusions

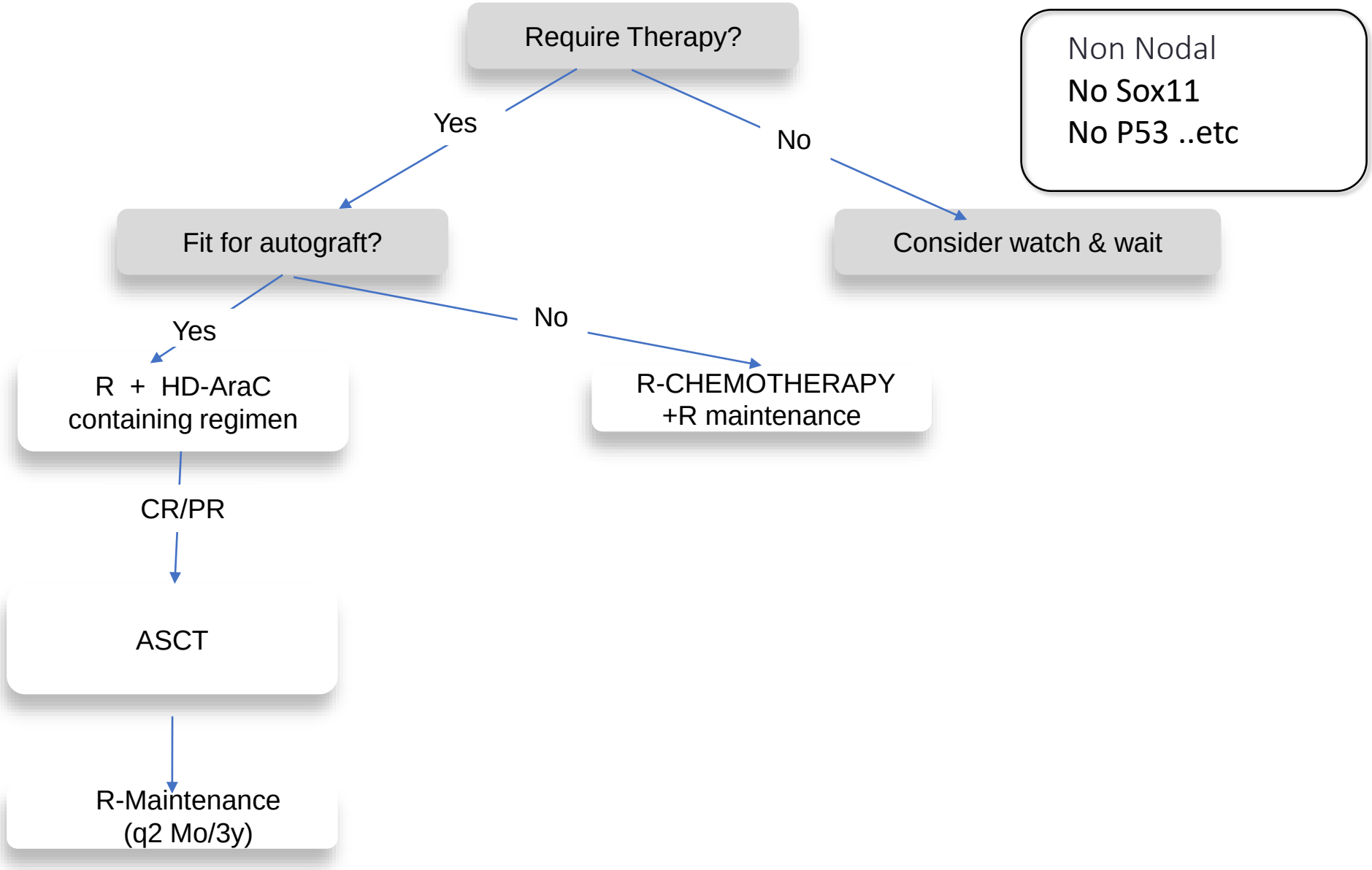


Suggested therapeutic algorithm

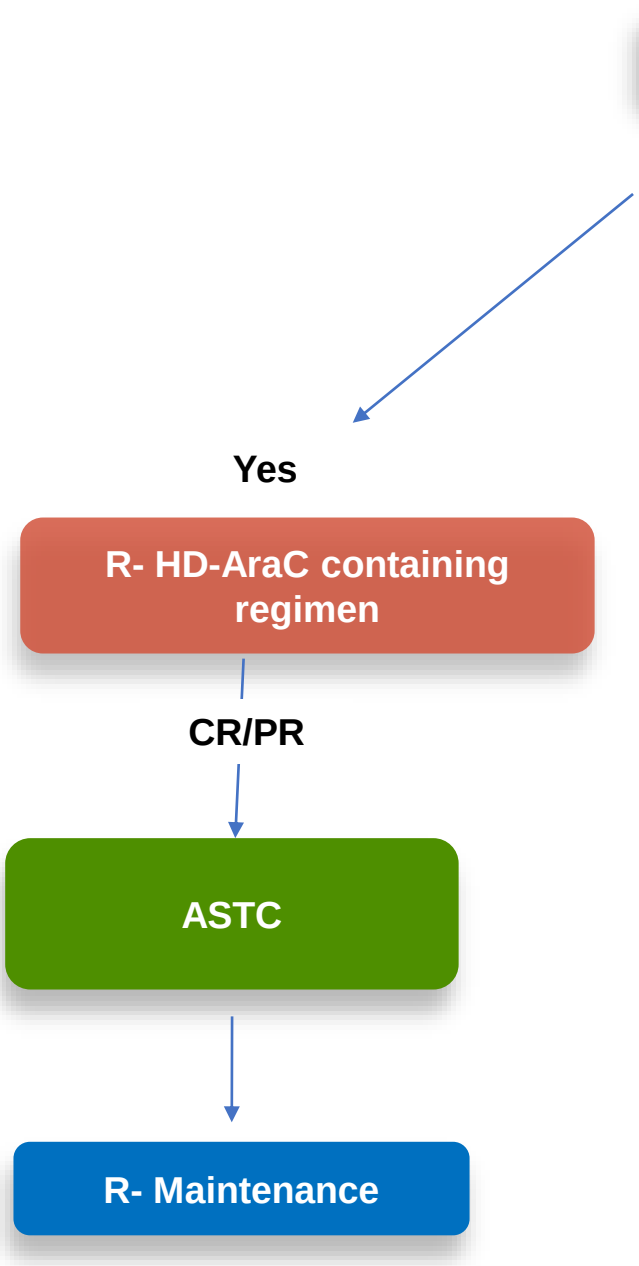
European MCL Network

Dreyling, Haematologica 2016; Jain, JCO 2021

3. FRONT LINE TREATEMENT



3.1 Management of fit patients



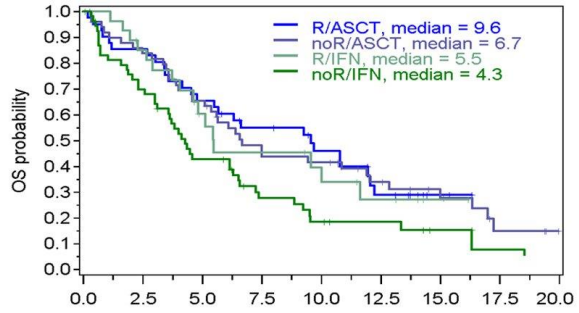
Selected HD AraC trials

Phase	Induction	Consolidation	N	OR (CR) %	Median Response	Median OS	TRM	Reference
II (Single Centre)	R-Hyper-CVAD	-	97	97 (87)	48% 8yr FFS	56% 8yr	8%	Romaguera
II (Multi Centre)	R-Hyper-CVAD	-	60	83 (72)	61% 5yr PFS	73% 5yr	6.50%	Merli
II (Multi Centre)	R-Hyper-CVAD	-	49	(86 (55)	4.8yr PFS	6.8yr	2%	Bernstein
III (Randomised)	R-CHOP v. R-CHOP/R-DHAP	Dexa BEAM ASCT ASCT	455	98 (63) v. 99 (61)	3.8yr PFS v. 7.3yr PFS	6.8yr v. NR	4%	Hermine Lancet 2016
III (Randomised) LyMa	R-DHAP	ASCT v. ASCT + Rituximab Maintenance	299	ORR 89% (CR77%) Before ASCT	64% 4yr PFS v. 83% 4yr PFS	80 4yr OS v. 89 4yr OS	NA	Le Gouill NEJM 2017
II (Multi Centre)	R-Maxi-CHOP + HD AraC	ASCT	160	96 (54)	7.4yr EFS	70% 6yr	5%	Geisler
II (Multi Centre)	R-CHOP / R-DHAP	ASCT	60	100 (96)	7yr EFS	75% 5yr	1.50%	Delarue
II (Multi Centre)	R-Maxi-CHOP + HD AraC	ASCT + RIT if not CR	160	97(82)	71% 4yr PFS	78% 4yr OS	3%	Kolstad
II (2 Centre)	RB / HD AraC	ASCT	23	96(96)	96% 1yr PFS	96% 1yr OS	0%	Armand BJH2016

Autologous Stem Cells Transplantation

Phase III Randomized trial (post –hoc analysis)*

High-dose radiochemotherapy followed by autologous stem cell transplantation (ASCT) and interferon-α (IFN) maintenance in MCL.



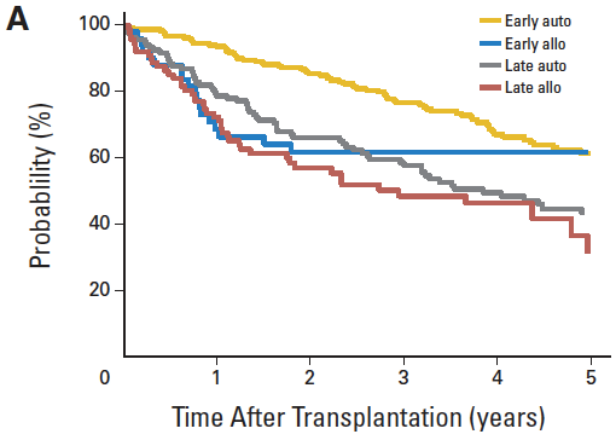
Multi-center retrospective analysis ASCT vs No ASCT ***

n= 1007 Median OS: No ASTC 115 Months *vs* ASCT 147 Months (P=0,02)

Multi-center retrospective study ****

Autologous and RIC Stem Cell transplantation for Young Patients with Mantle Cell Lymphoma

n =519 patients



* *Up date Zöellner, Lancet hemato 2021*

** *Gerson JN, Blood 2017*

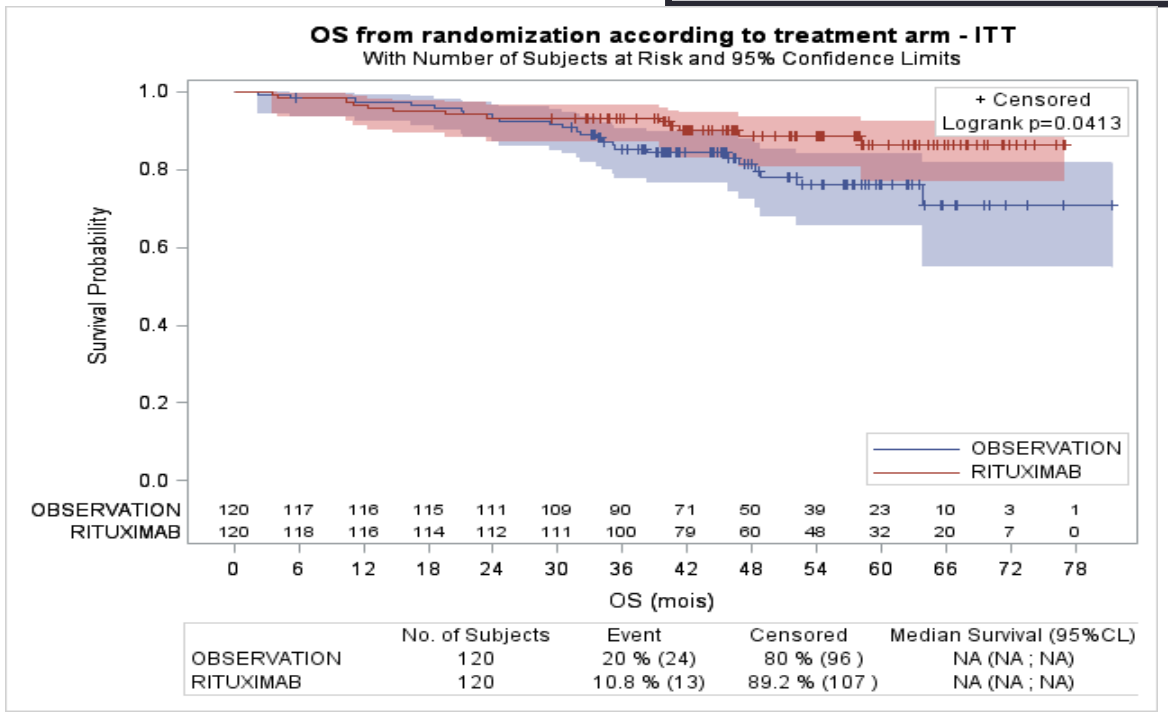
*** *Fenske et al. J Clin Oncol 2014*

Maintenance strategy after ASCT

Phase III randomized trial: LYMA

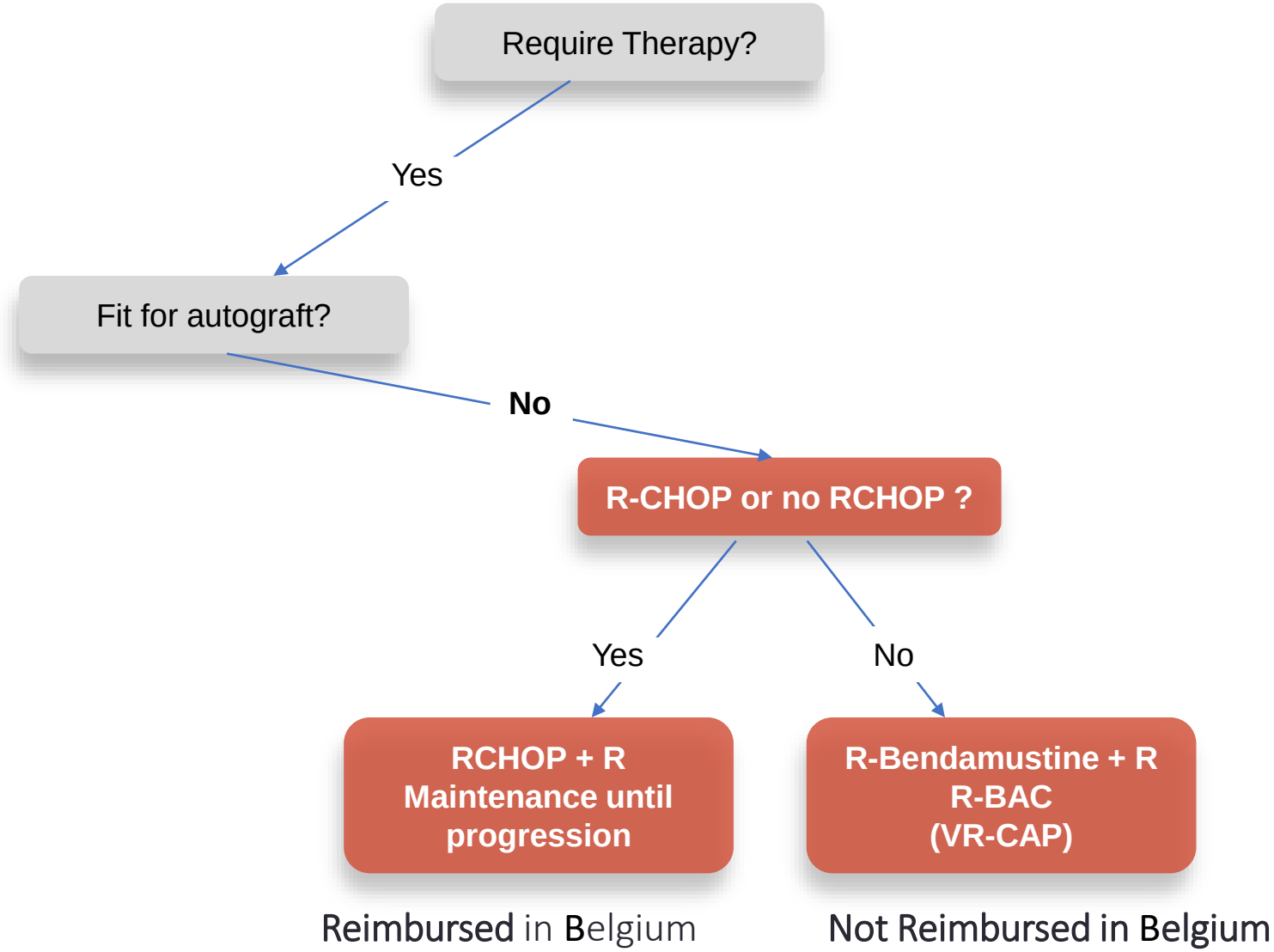
R-DHAP R-DHAP R-DHAP R-DHAP R-BEAM

- OBSERVATION
- RITUXIMAB MAINTENANCE **every 2 months for 3 years**



Le Gouill, NEJM 2017

3.2 Management of patients unfit for ASCT

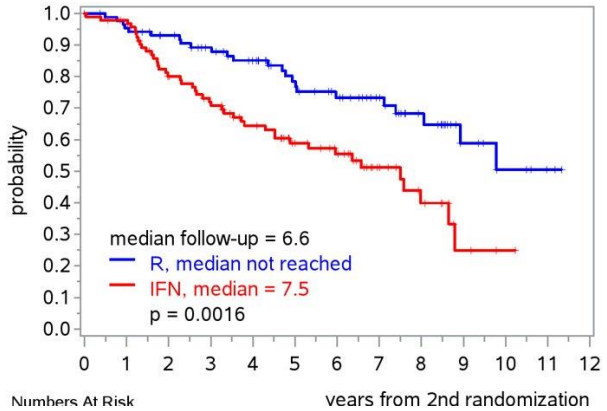


Maintenance strategy after R-Chemo

Phase III Randomized trial *

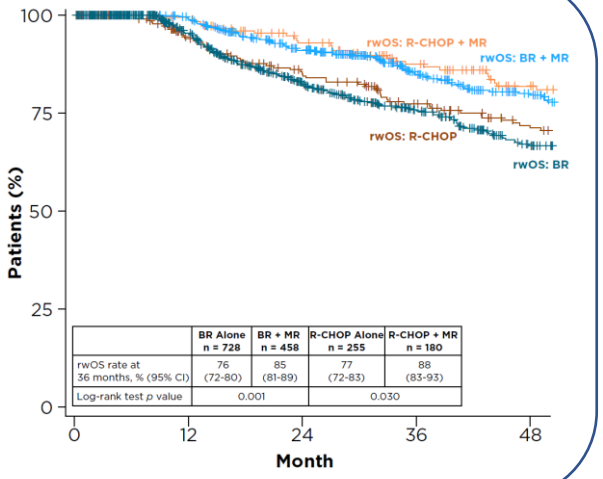
Rituximab maintenance vs interferon-α (IFN) after R-CHOP

5Y OS : Rituximab 79 % vs IFN 59%



Multicentric US real world Cohort **

Role of maintenance rituximab after R-CHOP or R-Benda



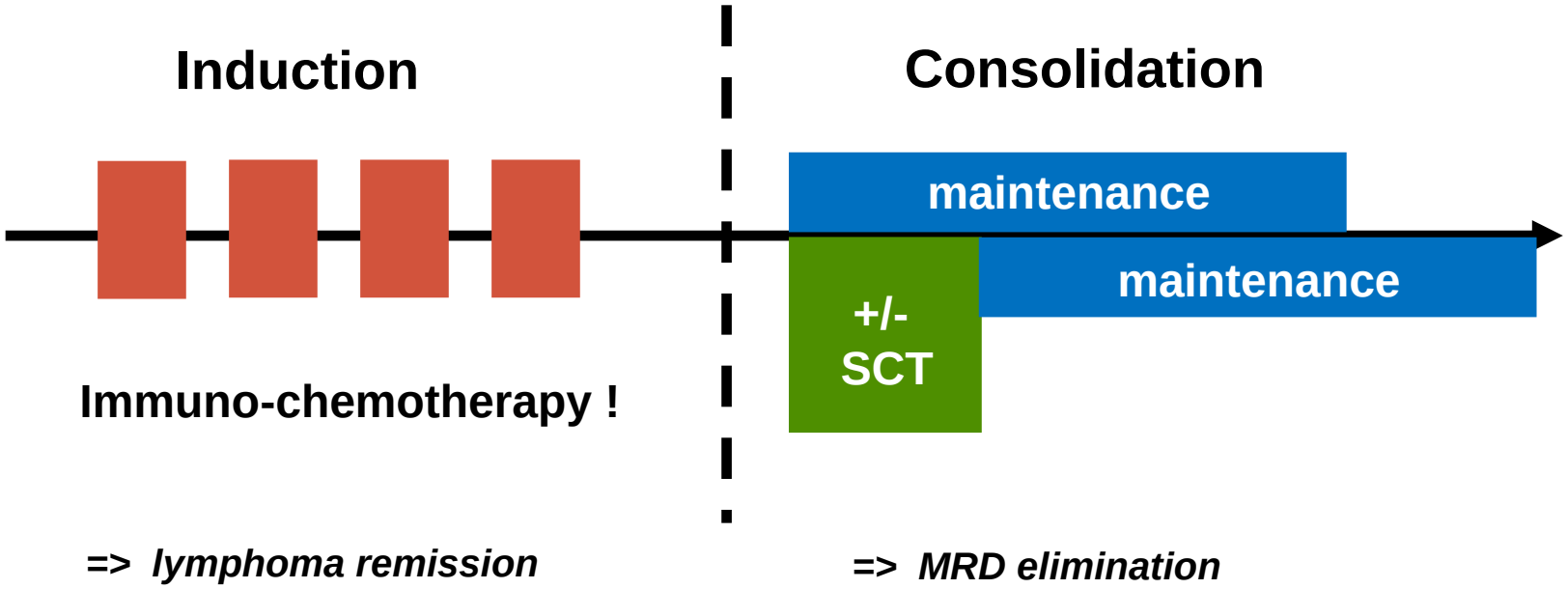
**Kluin-Nelemans HC et al. NEJM 2012*

**Up date Kluin-Nelemans, 2020*

***Wang et al., ICML 2021*

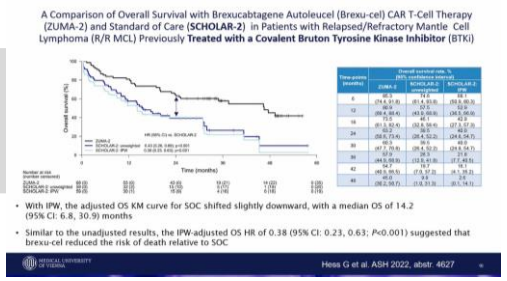
***Salles, EHA 2021*

3.3 Conclusion for first line treatement:



4. MCL R/R TREATEMENT

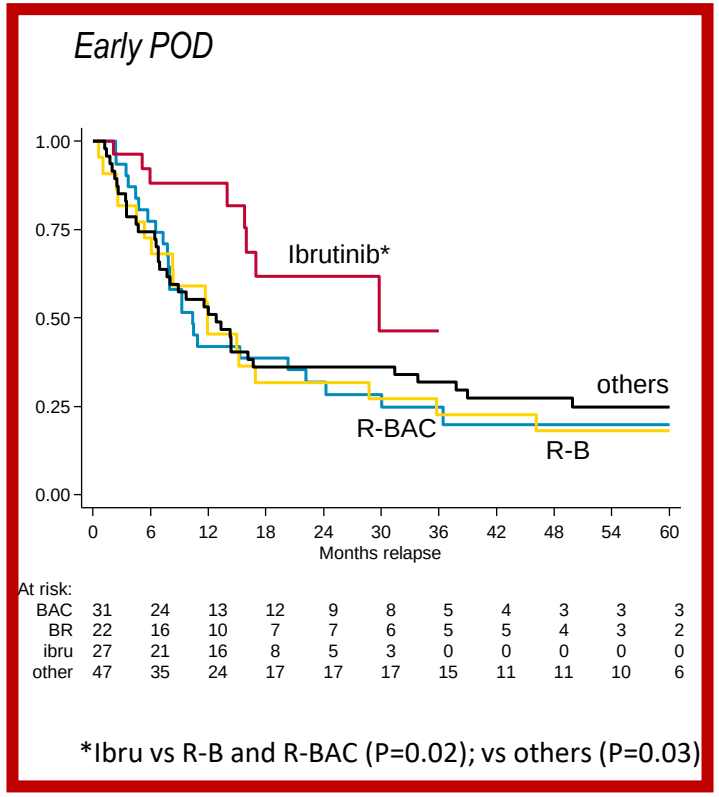
Young patient (≤65)	Elderly patient (>65)	Compromised patient
First line treatment		
dose-intensified immuno-chemotherapy (high dose Ara-C) ⇒ Autologous SCT ⇒ Rituximab maintenance	conventional immuno-chemotherapy (VR-CAP, R-CHOP,BR, R-BAC) ↓ Rituximab maintenance	Best supportive care? R-Chlorambucil BR (dose-reduced) R-CVP
1. relapse		
immuno-chemotherapy (R-BAC, BR) or targeted approaches ↓ discuss: - allogeneic SCT	immuno-chemotherapy (BR, R-BAC) or targeted approaches ↓ discuss: - Rituximab maintenance - radioimmunotherapy	Immuno-chemotherapy (BR) or targeted approaches
higher relapse		
CAR T Cells		



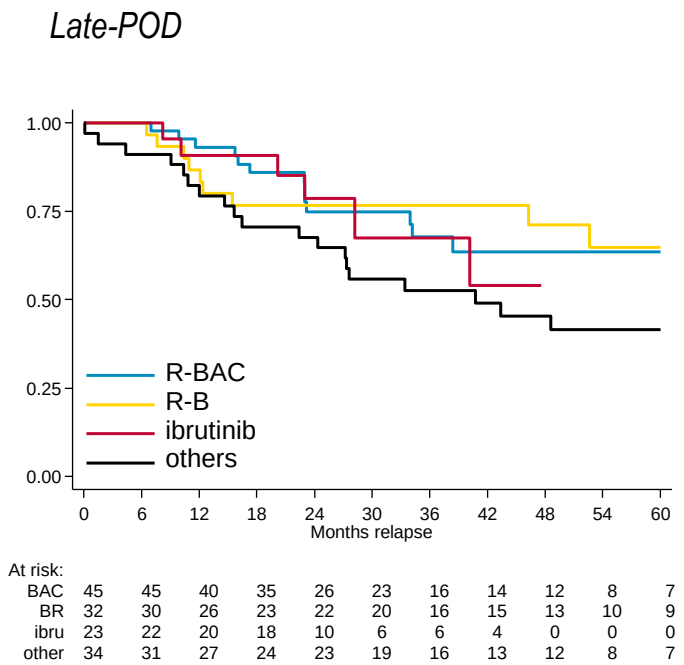
Dreyling, ESMO CR MCL 2017 (updated)

Ibrutinib VS Chemotherapy in relapsed MCL (POD 24)

Overall survival

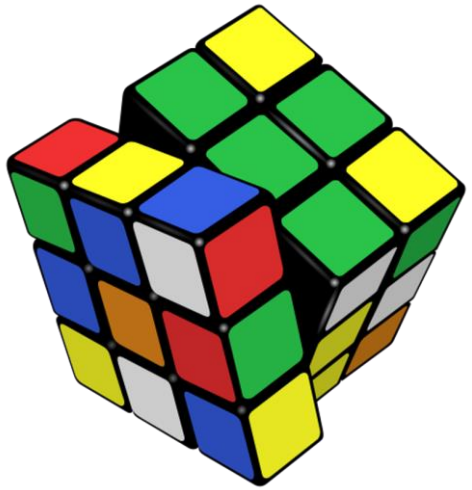


*Ibru vs R-B and R-BAC (P=0.02); vs others (P=0.03)



Visco, Leukemia 2020

6. PERSPECTIVES:



First Line

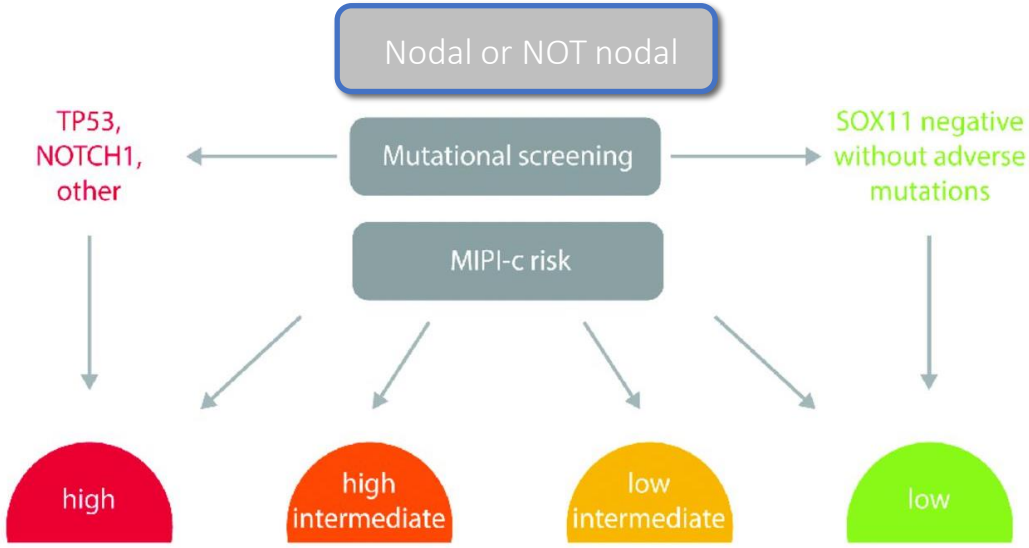
	< 65 years	> 60 years	> 65 years	
New drugs + chemo	*MCL younger:* R-CHOP/DHAP =>ASCT R-CHOP+I/DHAP =>ASCT => I R-CHOP+I/DHAP => I	*MCL elderly R2:* R-CHOP vs R-CHOP/Ara-C => Rituximab M +/- Lenalidomide	BR +/- BTK ⇒ Rituximab M +/- BTK	*VR-BAC:* R-BAC ⇒ Venetoclax ⇒ (only high risk)
News drugs *vs* chemo	*CARMAN (high risk):* R-Ibrutinib => CAR T-cells	*ENRICH:* R-CHOP/Benda vs R-Ibrutinib	BR vs. BTK-R	*OASIS 2:* R-Ibrutinib +/- Venetoclax	*MCL elderly 3:* BR (Ibrutinib) vs R-Venetoclax-Ibrutinib

Relapse

R-HAD +/- Bortezomib	Ibrutinib/ Bortezomib	Ibrutinib/ R-Lenalidomide	Venetoclax/ R-Lenalidomide	Ibrutinib +/- ABT-199

7. TAKE HOME MESSAGE

First Stratified patients



Watch and wait is an option !

Relapse : New Drugs, CAR T cells

REFERENCES

- *Mantle cell lymphoma*
  M. Dreyling et al.
  Crit Rev Oncol Hematol 2020

- *BJH Guidelines 2018 and up date*
  S.Rule et al.

- *Mantle cell lymphoma - advances in molecular biology, prognostication and treatment approaches.Silkenstedt E, Linton K, Dreyling M.Br J Haematol. 2021*