



# EHA-GBMTA-AHA Hematology Tutorial: New aspects in diagnostic choices and treatment options of hematological malignancies

## Session 2

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# Disclosures

- Consultacy: Gilead, Novartis, Kyowa Kirin
- Honoraria: Gilead, Novartis, Kyowa Kirin, Roche, Swixx
- Travel Grants: Gilead, Novartis, Kyowa Kirin, Roche, Takeda

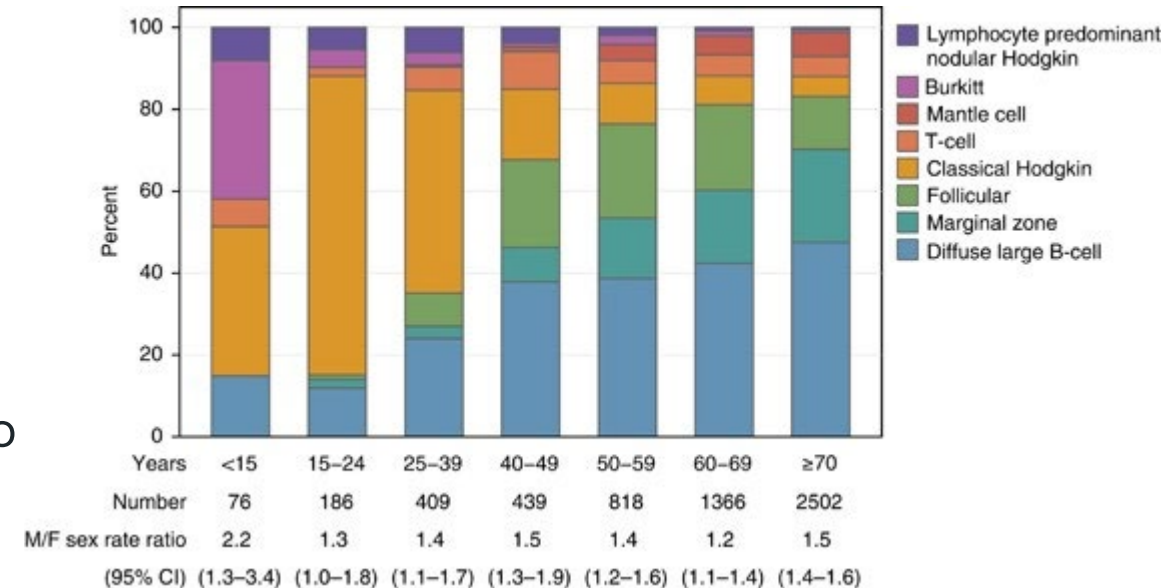
# Aggressive non-Hodgkin lymphomas

- NHL

- the most common hematological malignancy worldwide
- 3-5% of all cancers in west-world countries
- Heterogeneous group of diseases with age dependent distribution
- Increasing incidence (15-20/100 000), but also improved survival

- Aggressive NHLs

- 60% of all NHLs
- **DLBCL** incl. its subtypes
- **MCL**
- Burkitt lymphoma
- AIDS-associated lymphoma
- **PTCL** (incl. different subtypes)



Numbers of cases and sex-rate ratios by sub-type and age: Haematological Malignancy Research Network (HMRN) 2004-2012

# Diffuse large B-cell lymphoma

- Most common aggressive B-NHL (25-30% of all NHL)
- Incidence 5-9/100 00
- Heterogenous disease
  - different subtypes (DLBCL NOS, PMBL, DLBCL leg type, PCNSL, T/HRLBCL, EBV+LBCL, ...)
  - cell of origin (ABC/GCB)
  - molecular classification (C1-C5)<sup>1</sup> x LymphGen classification<sup>2</sup>

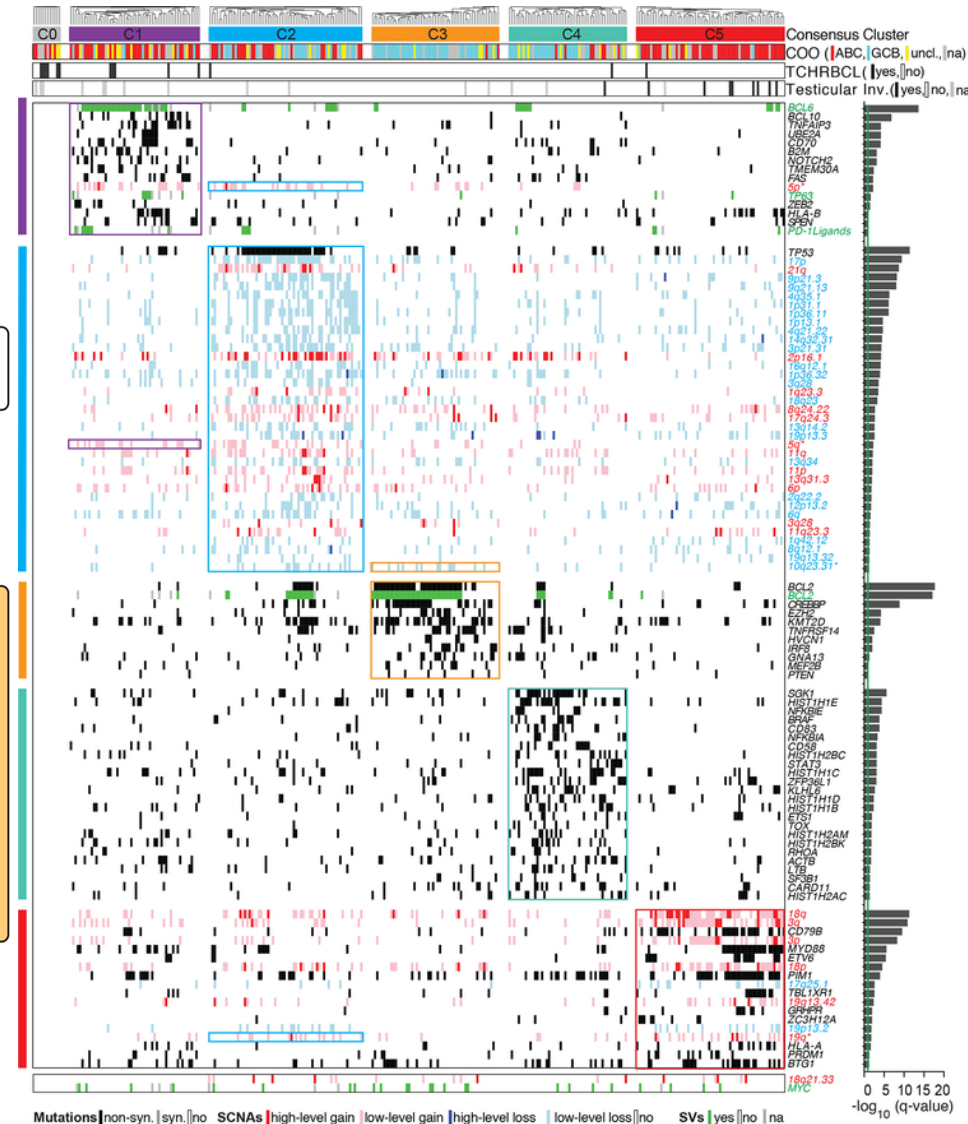
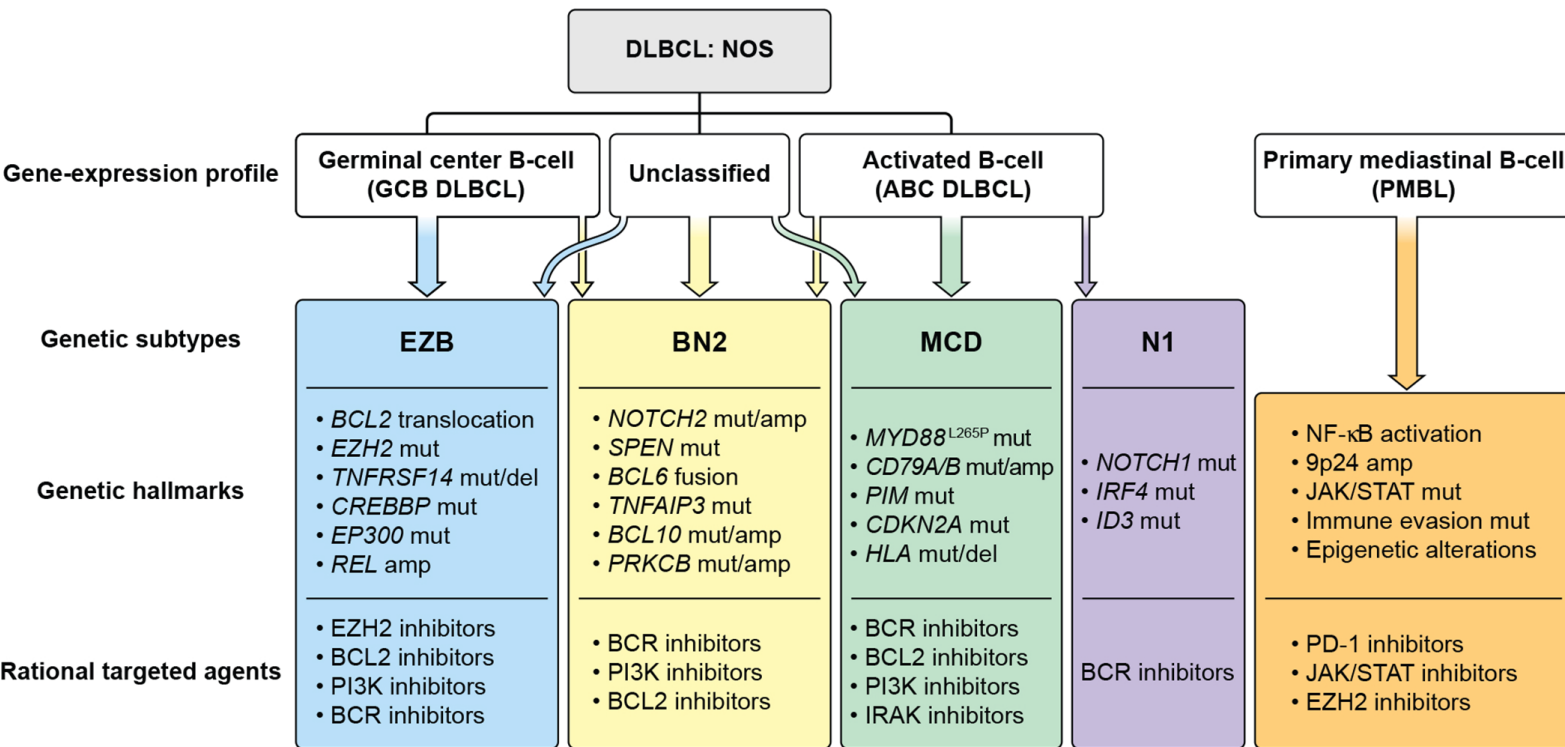
## Prognostic factors

- COO
- molecular changes
- metabolic volume (FDG PET/CT)
- **I**nternational **P**rognostic **I**ndex– age, ECOG, LD, clin. stage, extranodal involvement

# Diffuse large B-cell lymphoma Subtypes

Genetic subtypes

## Oncogenic mechanisms and therapeutic targets within genetic subtypes of DLBCL



# Diffuse large B-cell lymphoma

## Treatment options

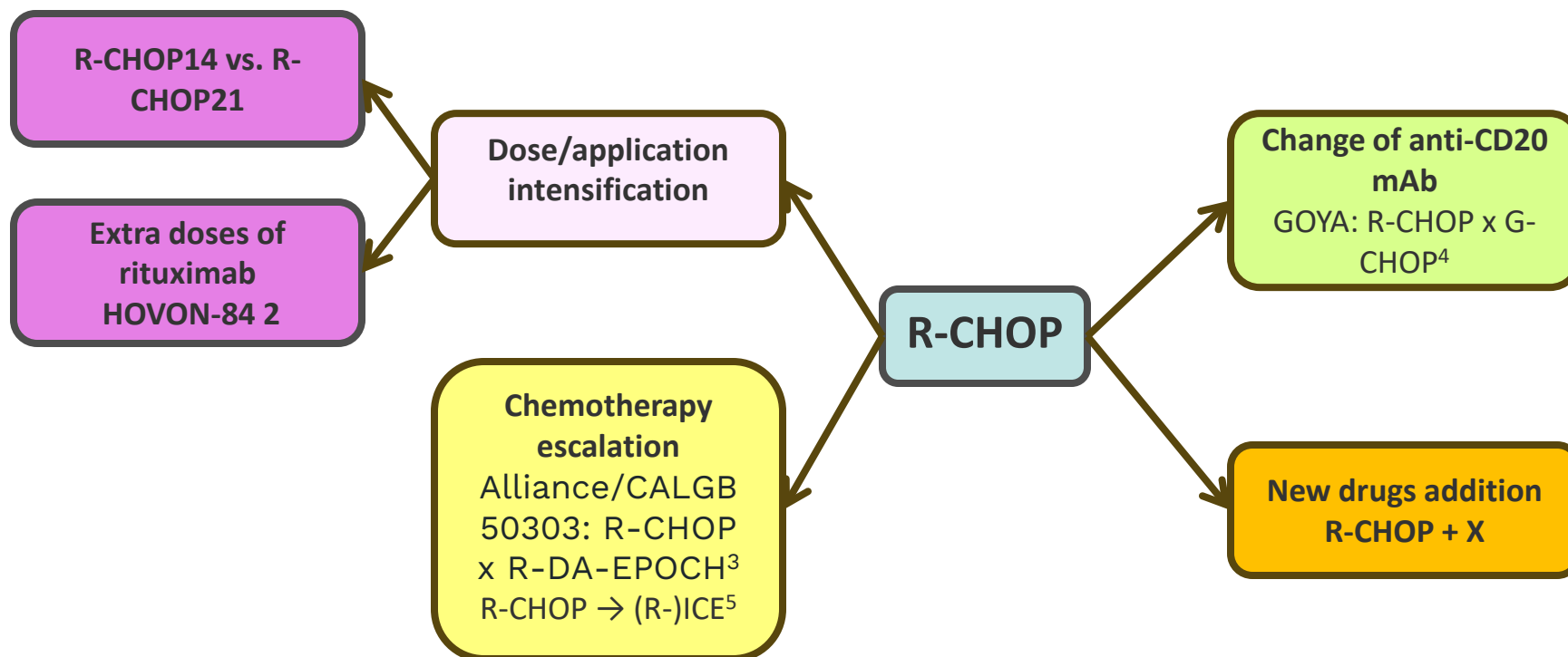
R-CHOP

Therapy is agnostic

Based on rituximab +  
anthracyclin containing  
regimen

# Diffuse large B-cell lymphoma

## Treatment options



<sup>1</sup>Cunningham D et al. Lancet 2013

<sup>2</sup>Lugtenbrug PJ et al. JCO 2020

<sup>3</sup>Barlet NL et al. JCO 2019

<sup>4</sup>Sehn LR et al. Blood 2020

<sup>5</sup>Bantilan KS et al Blood Adv. 2024

# Diffuse large B-cell lymphoma

## R-CHOP+X

- **Bortezomib:** Bor-R-CHOP(PYRAMID<sup>1</sup>, REMoDL<sup>2</sup>):
  - Negative
- **Venetoclax:** VXT (D1-10) + R-CHOP (CAVALLI<sup>3</sup>):
  - Trend for improved 2yrs PFS for BCL2+ pts (78% vs 62%), x higher % of adverse events (gr. 3-4 AE)
- **Ibrutinib:** I-R-CHOP (PHOENIX<sup>4, 5</sup>)
  - No benefit for the whole ABC cohort
  - Possible benefit in young patients with specific genetic subtype
- **Lenalidomide:** R2-CHOP (ROBUST<sup>7</sup>)
  - Negative

<sup>5</sup>Wilson WH et al. Cancer Cell 2021

<sup>6</sup>Hervé T et al. NEJM 2022

<sup>7</sup>Nowakowski GS et al. JCO 2021

<sup>8</sup>Topp MS et al. Blood 2023

<sup>9</sup>Olszewski AJ et al. Blood 2023

<sup>10</sup>Sehn LH et al. ASCO 2023

<sup>1</sup>Leonard JP et al. JCO 2017

<sup>2</sup>Davies A et al. Lancet 2019

<sup>3</sup>Morschauer F et al. Blood 2021

<sup>4</sup>Jounes A et al. JCO 2019



# Diffuse large B-cell lymphoma

## R-CHOP+X

- **Polatuzumab-vedotin: Pola-R-CHP** (POLARIX<sup>6</sup>)
  - Improved 2yrs PFS in Pola-R-CHP group (77% vs. 70%)
  - Higher benefit for pts > 60 yrs, IPI 3-5, ABC, no bulk
- **BsAb:**
  - Glofitamab<sup>8</sup> and Mosunetuzumab<sup>9</sup> + (R)-CHOP – non-randomized – high response rate; immature data
  - Epcoritamab<sup>10</sup> + R-CHOP – results are pending
- **Tafasitamab+Lenalidomid:** Tafa-R2-CHOP (FRONT-MIND)
  - Result are pending

<sup>5</sup>Wilson WH et al. Cancer Cell 2021

<sup>6</sup>Hervé T et al. NEJM 2022

<sup>7</sup>Nowakowski GS et al. JCO 2021

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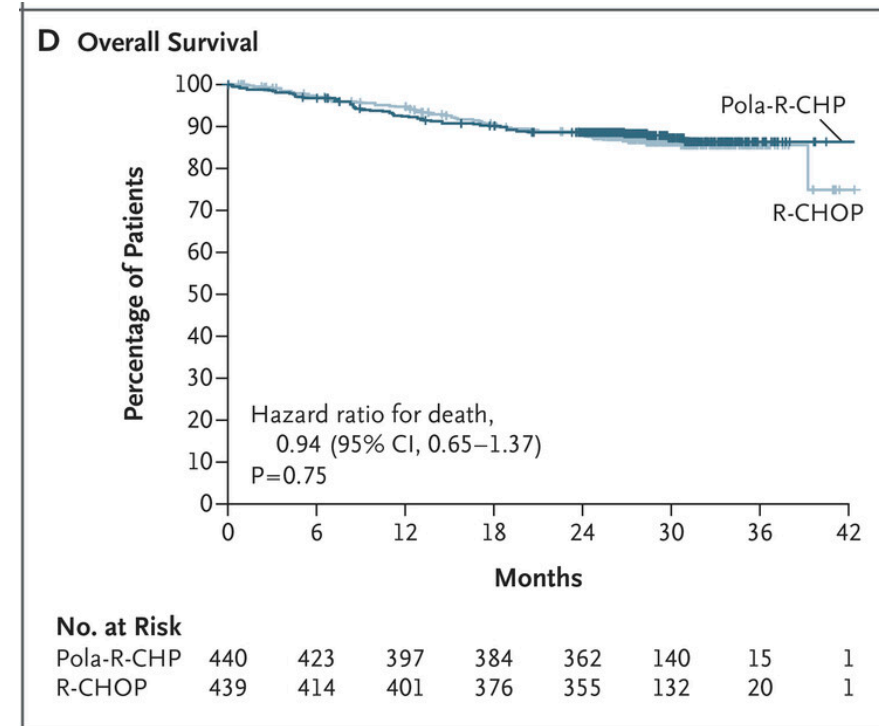
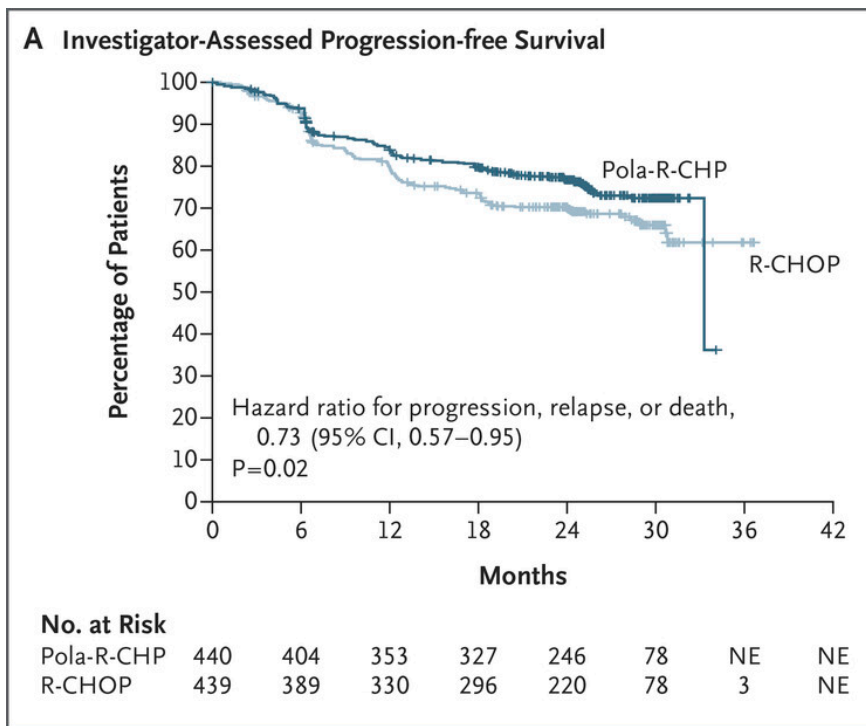
<sup>3</sup>Morschauer F et al. Blood 2021

<sup>4</sup>Jounes A et al. JCO 2019

# Diffuse large B-cell lymphoma

## - R-CHP + polatuzumab vedotin

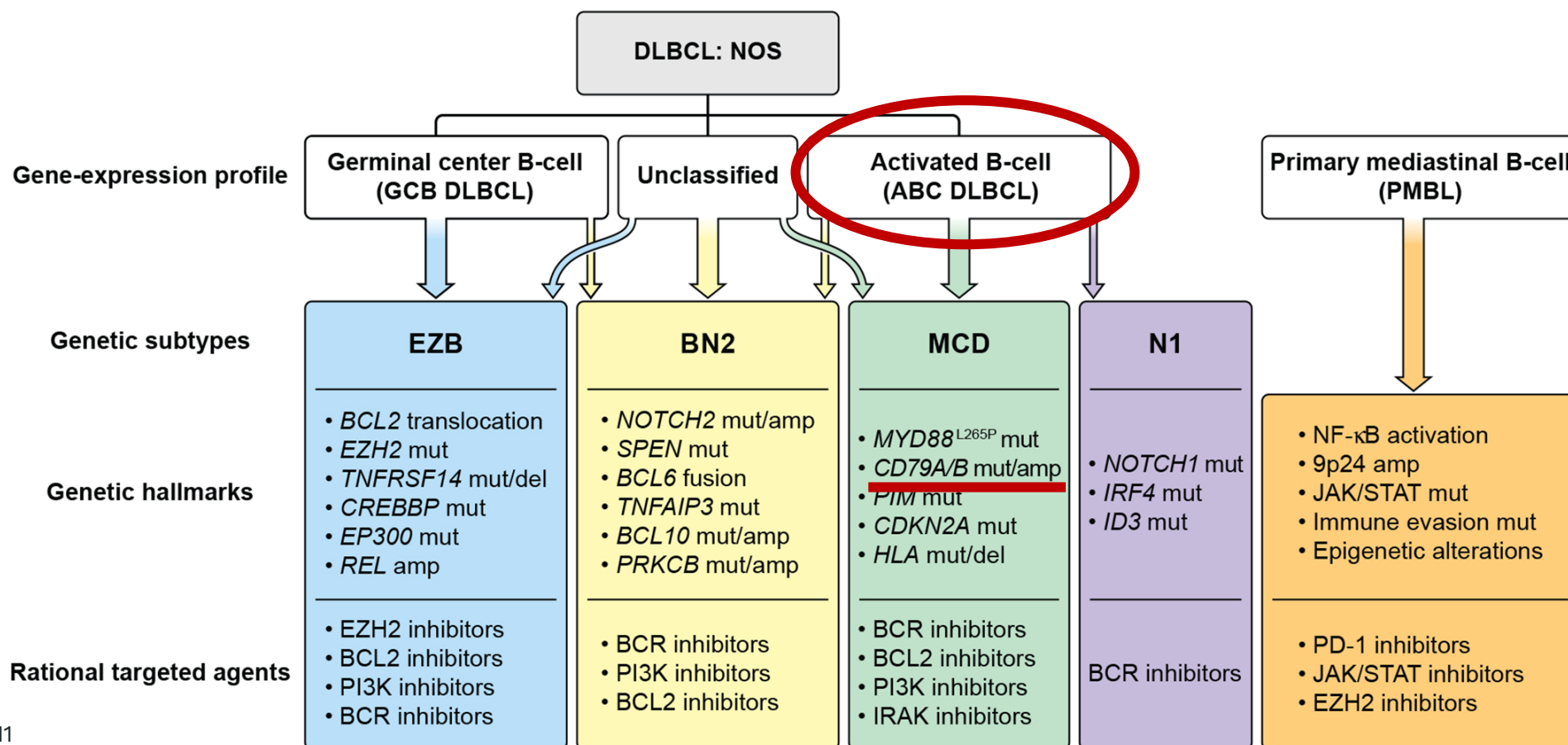
- 879 pts w DLBCL randomized 1:1 R-CHOP x pola-R-CHP as 1st line Th
- IPI 2-5
- Age 65 yrs (19-80)
- Median follow-up 28m
- CR 74% vs 78%
- 2yrs PFS 70% vs 77%



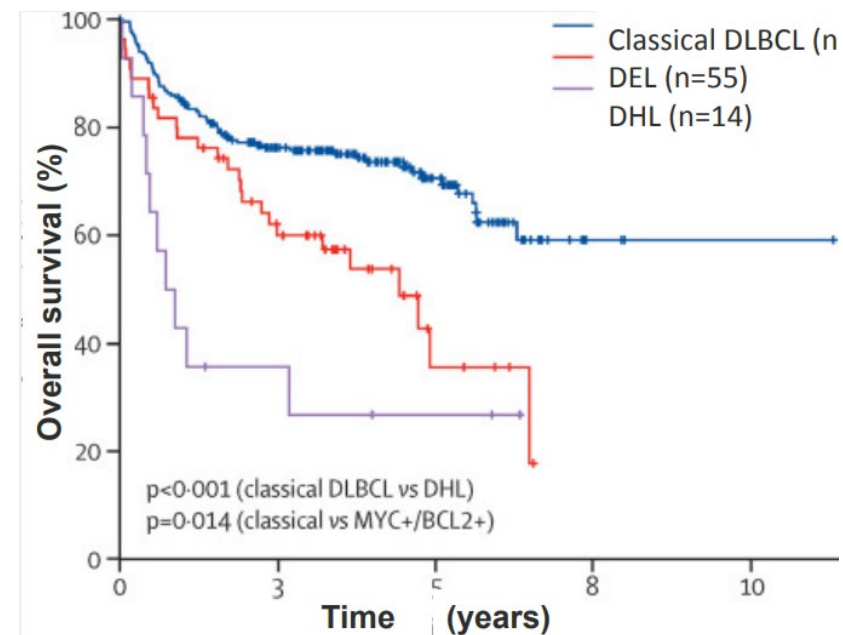
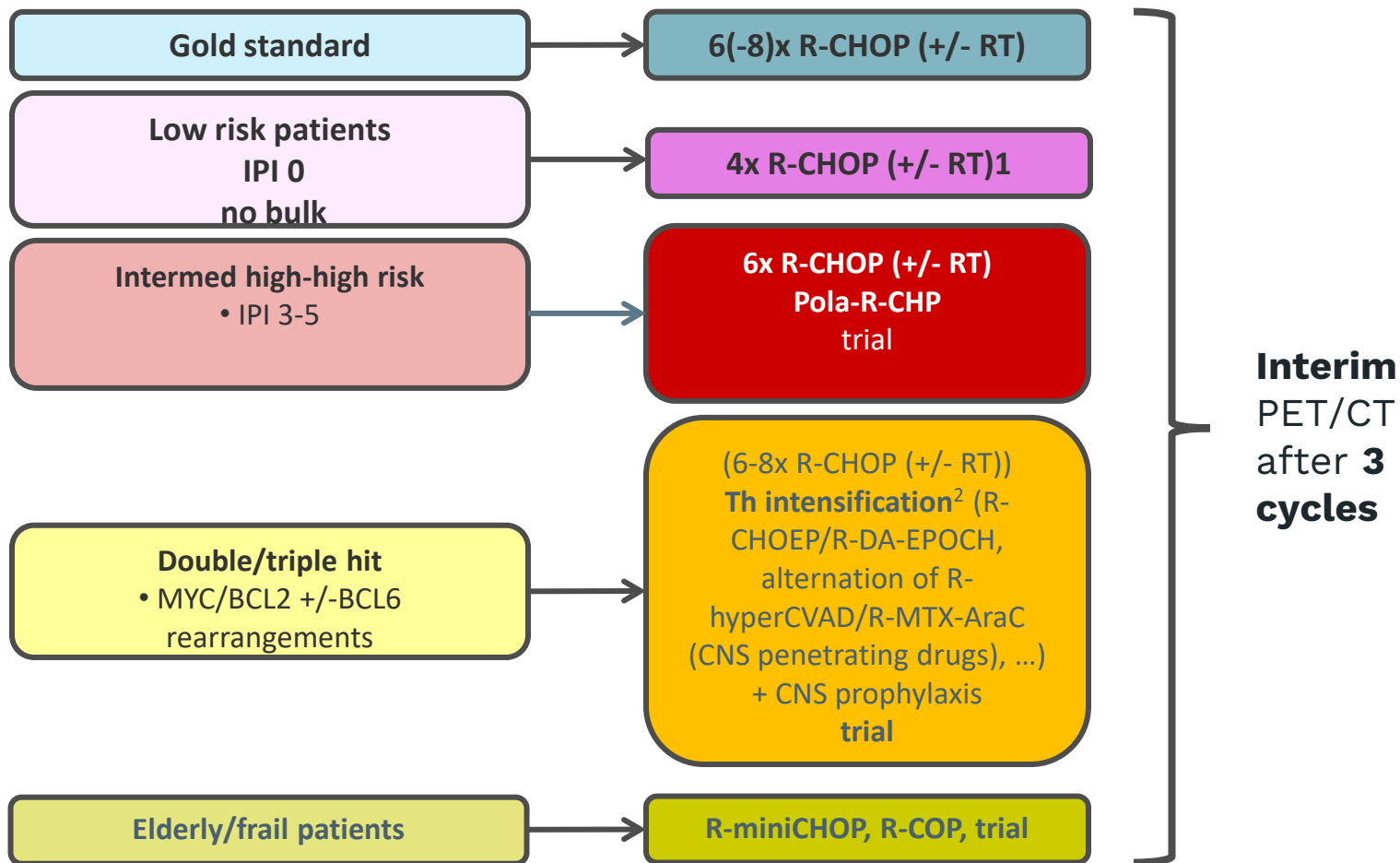
# Diffuse large B-cell lymphoma

## - R-CHP + polatuzumab vedotin

### Oncogenic mechanisms and therapeutic targets within genetic subtypes of DLBCL



# Diffuse large B-cell lymphoma treatment options



Survival of patients with DLBCL +/- MYC+/BCL2 expression or rearrangements

<sup>1</sup>Poeschel V. et al. Lancet 2019

<sup>2</sup>Dunleavy K ASH 2021

NCCN guidelines 2024

# Diffuse large B-cell lymphoma CNS prophylaxis

## Population

- Lumbar puncture (incl. flow cytometry) for all pts with CNS IPI  $\geq 2$
- LP and CNS prophylaxis for all pts with DH/TH lymphoma
- LP and CNS prophylaxis for all pts with DLBCL of immune-privileged sites / gonades
- To be **discussed**:
- pts with CNS IPI  $\geq 4$
- pts with “high-risk features” – renal/adrenal involvement, paranasal/Waldayer site involvement, vertebral involvement

## Administration

- **Systemic** prophylaxis:
  - HD MTX 2-3.5g/m<sup>2</sup> 2hrs infusion
  - Intercalated D15 of cycle 1, 3, 5 chemotherapy (risk of complications with postponing CHT)
  - after 3rd a 6th cycle
  - 2x after 6th cycle
- **Intrathecal** prophylaxis:
  - MTX
  - Triple CHT (MTX, AraC, hydrocortison)

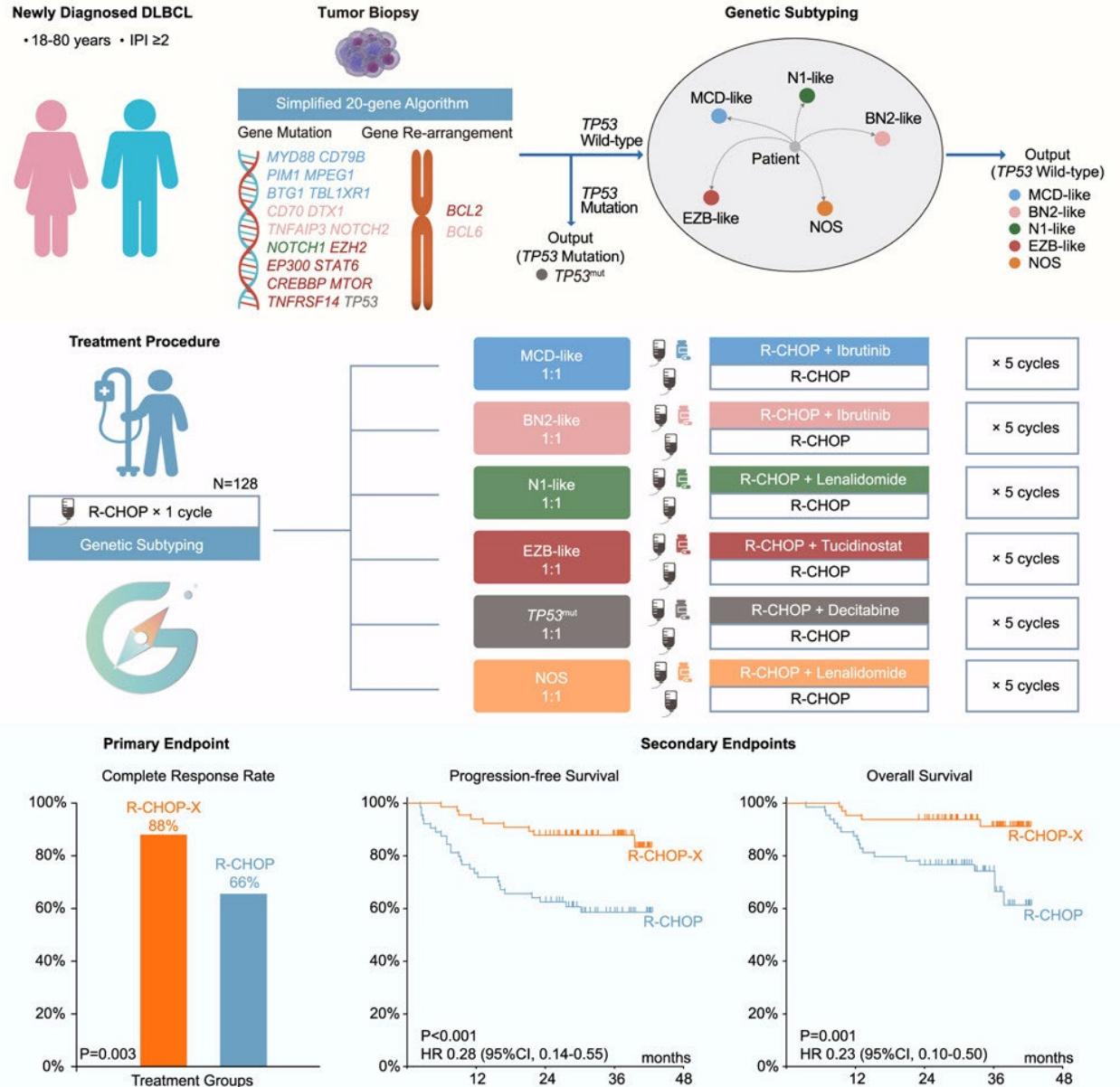
## Risk-benefit

- Use CNS prophylaxis remains controversial
- Lewis et al 2021<sup>5</sup>:
  - Syst. HD MTX does not reduce risk of CNS relapse
- Bobillo S et al 2021<sup>1</sup>:
  - CNS relapse is inevitable, but can be postponed by prophylaxis
  - No difference between i.t. MTX a syst. HD-MTX
- Wilson et al<sup>4</sup>:
  - No difference between interim x EoT MTX
- Benefit for HR pts <sup>3, 4</sup>
- Change in conventional therapy approach? <sup>2</sup>
  - R-ACVPB + HD-MTX +/- consolidation according to aaIPI (0-1 vs 2-3) → CNS relapse risk decreased in comparison to R-CHO(E)P + HD-MTX

# Diffuse large B-cell lymphoma Perspectives

## Further options

- “personalized” regimen
  - **GUIDANCE-01**
    - 128 pts, 1:1 randomization
- Chemo-free regimen
- BsAb+/- (R)-CHT
  - Mosunetuzumab
  - Glofitamab
  - Epcoritamab
- CAR T-ly (cost-effectiveness)
  - ZUMA12

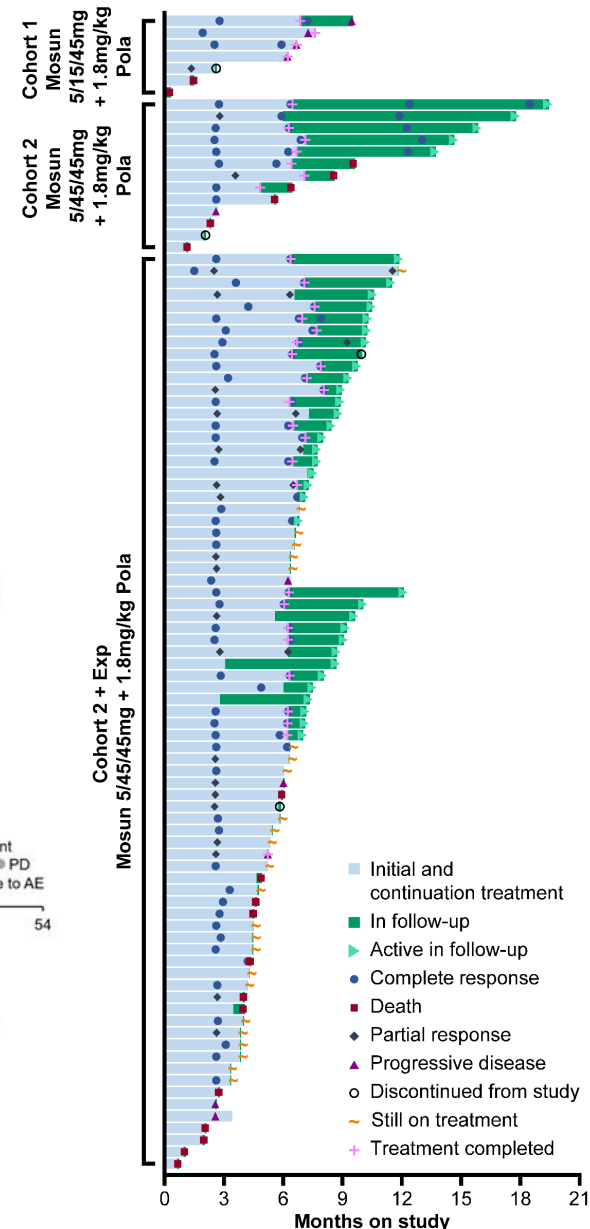


# Diffuse large B-cell lymphoma Perspectives – frail patient

## Chemo-free / low dose chemo regimens

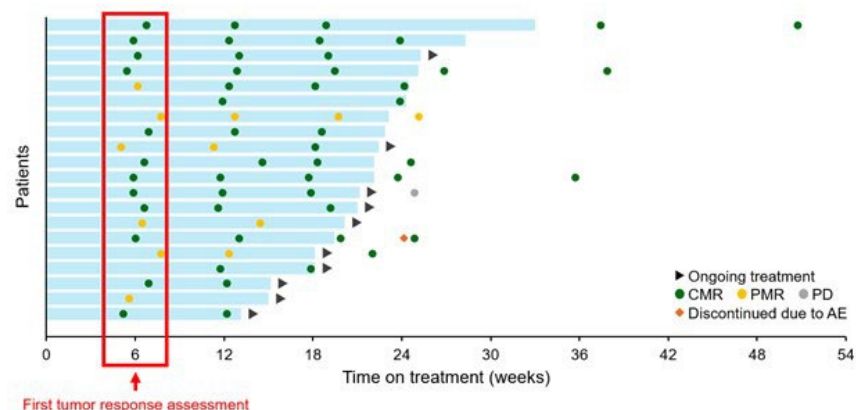
- BsAb
- BsAb+pola
- BsAb+miniCHOP
- Targeted agents
- Ibrutinib+R-miniCHOP

Response and time on Mosu-Pola



Response and time on Epc+R-miniCHOP

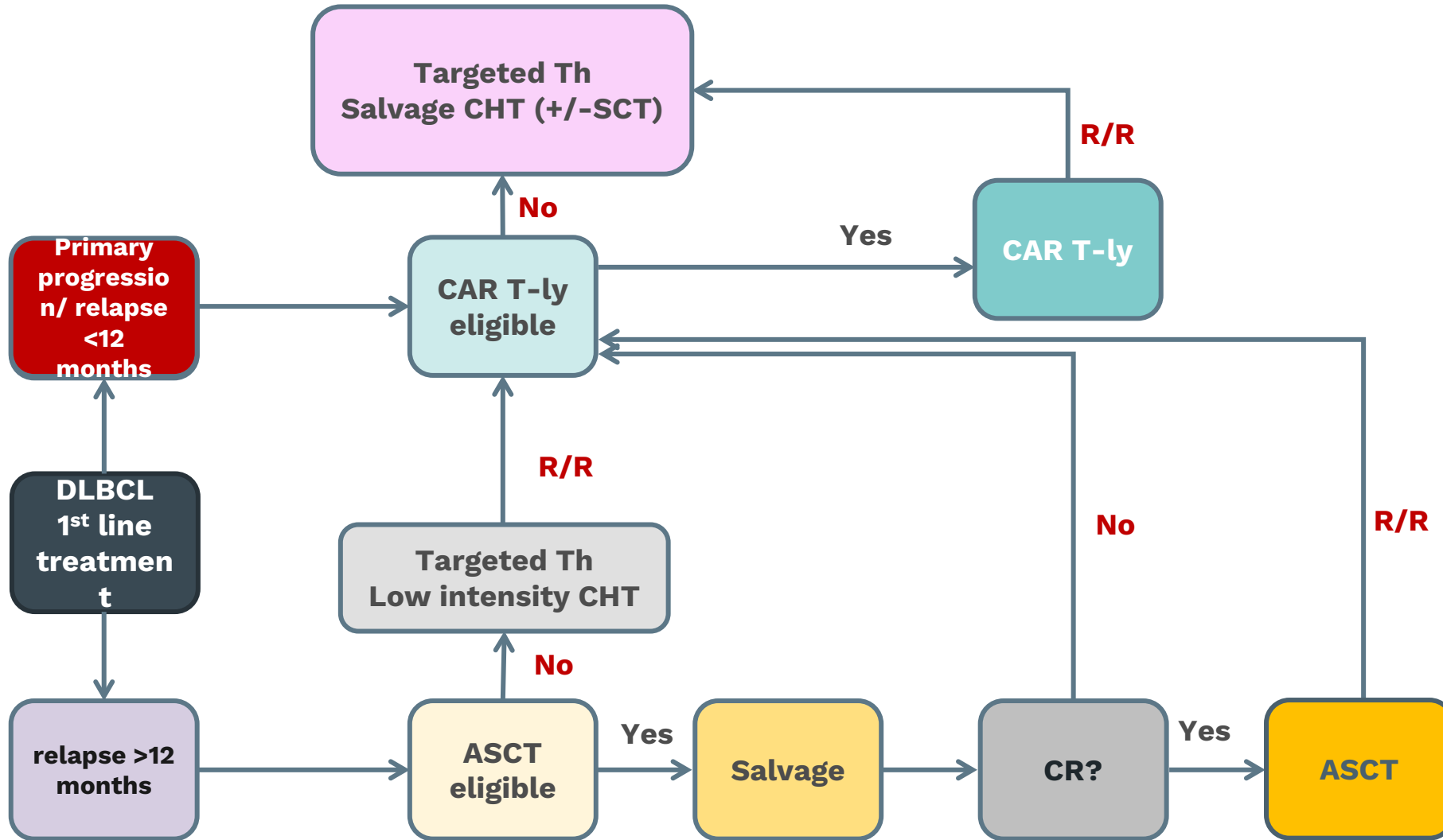
Figure. Onset and durability of responses



Per protocol, patients continued to receive scans if they discontinued treatment for reasons other than PD.  
AE, adverse event; CMR, complete metabolic response; PD, progressive disease; PMR, partial metabolic response.

# Diffuse large B-cell lymphoma

## Further treatment

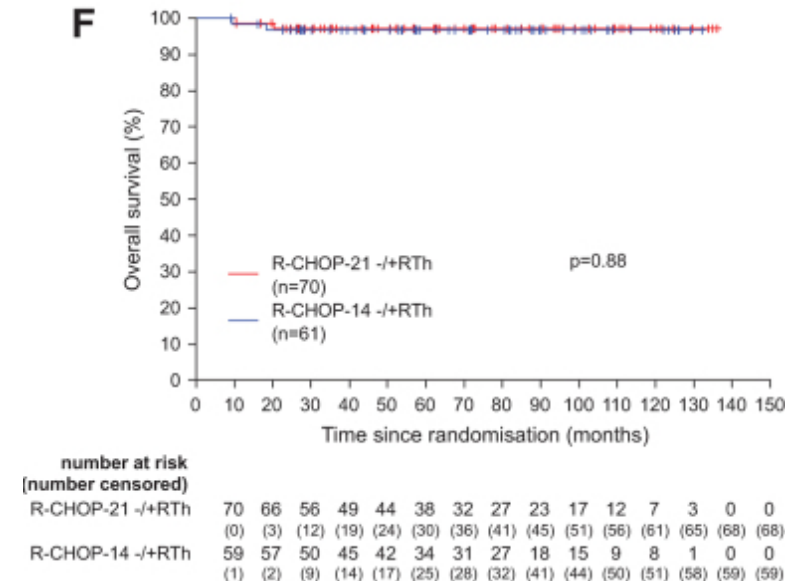
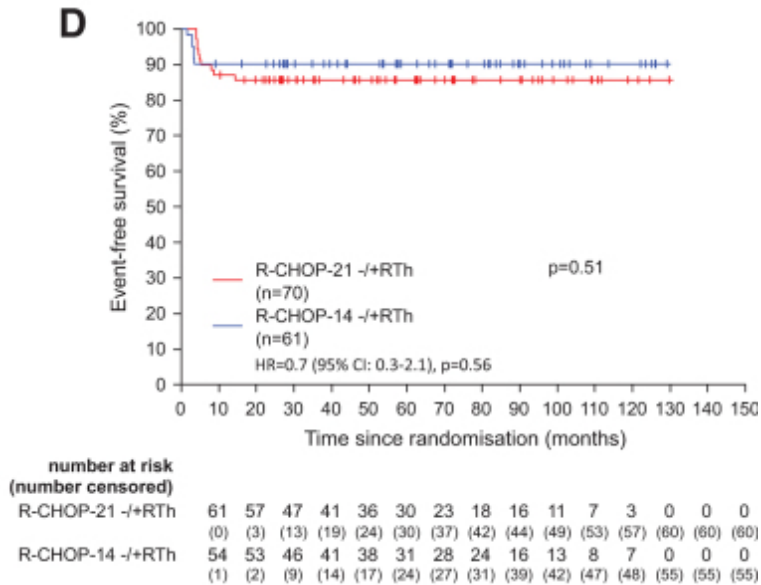




# Primary mediastinal B-cell lymphoma

- Trend to better PFS w R-CHOP14 vs R-CHOP21 (5yrs PFS 83 vs 79%)
- Not confirmed in all published data<sup>2</sup>
- Better survival with intensified regimens
  - R-DA-EPOCH
  - R-CHOEP
- CHT +/- RT

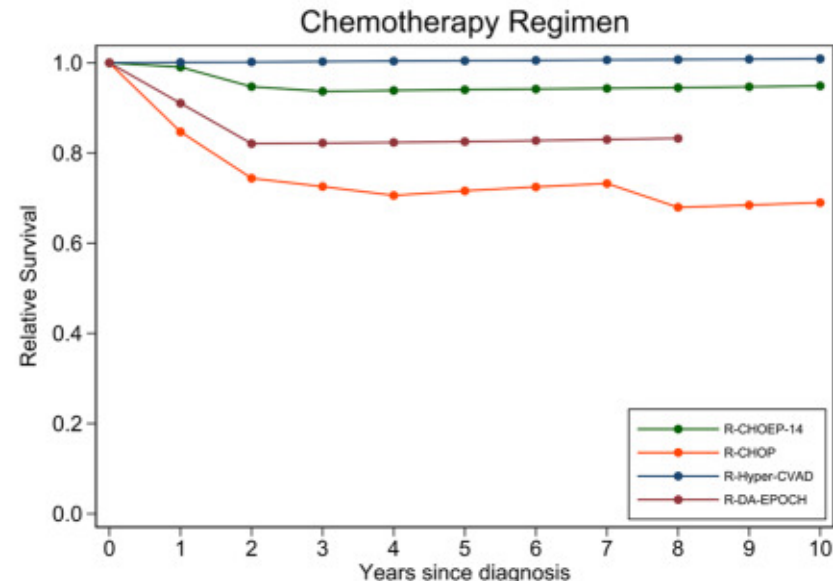
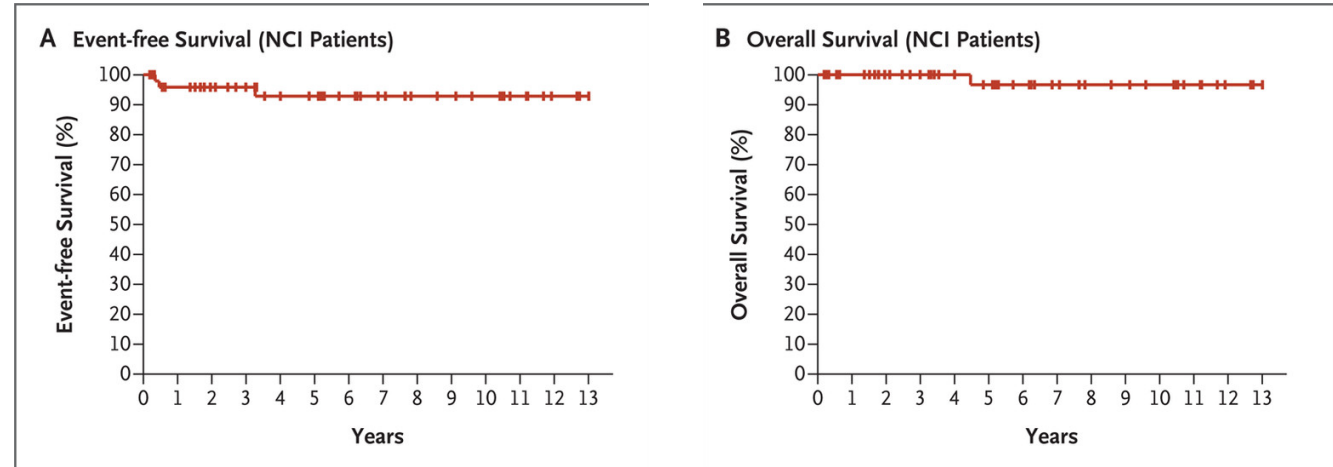
EFS and OS after R-CHOP21 vs R-CHOP14 +/- RT



# Primary mediastinal B-cell lymphoma

- Trend to better PFS w R-CHOP14 vs R-CHOP21 (5yrs PFS 83 vs 79%)
- Not confirmed in all published data
- Better survival with intensified regimens
  - R-DA-EPOCH
  - R-CHOEP
- R-CHOP21/14 x R-DA-EPOCH (R-CHOEP)
- CHT +/- RT

R-DA-EPOCH w/o RT (n=51)



# Primary mediastinal B-cell lymphoma

## Role of EoT PET/CT

### Final PET/CT

- DS 1-3 – CR
- D4-5?
- IELSG37 survival according to final PET/CT

- **530 pts**
- **230 CR (DS1-3) -**
- **174 DS4**

12 obs

149 RT

13 salvage CHT +/-

ASCT +/- RT

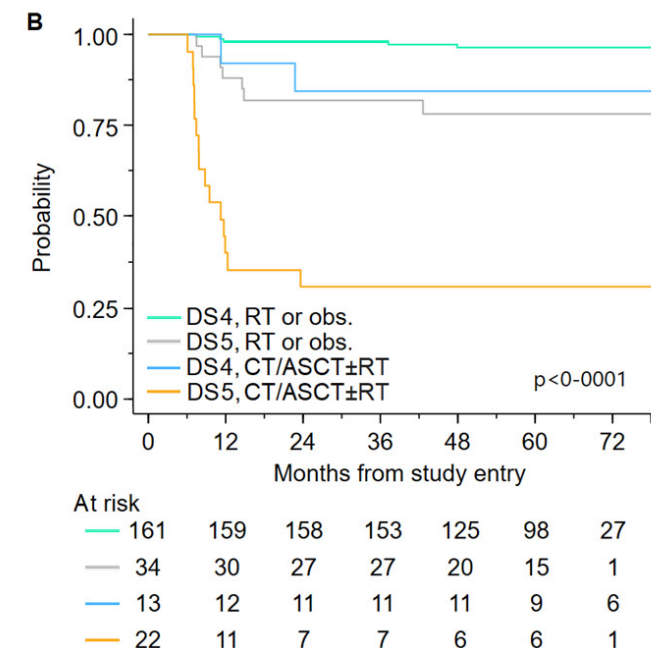
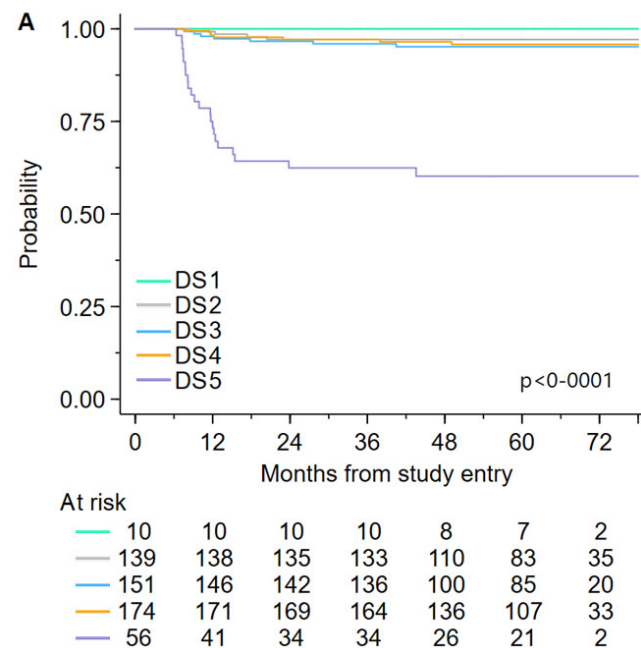
- **56 DS5**

2 obs

32 RT

22 salvage CHT +/-

ASCT



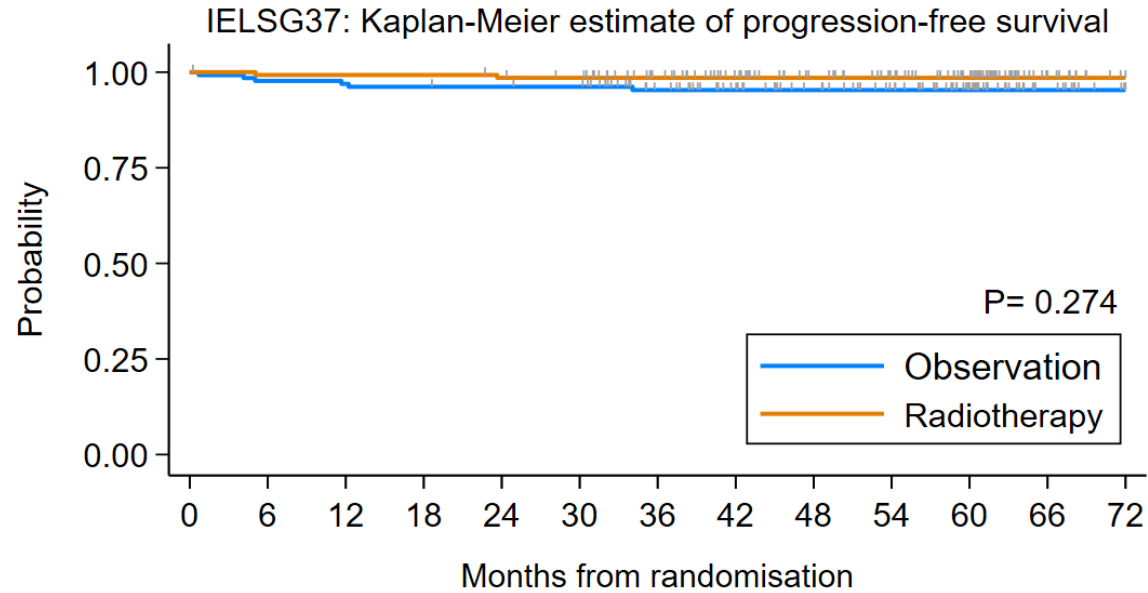
*Figure 1.* Kaplan-Meier estimates of progression-free survival of PMBCL patients enrolled in the IELSG37 trial, according to the Deauville score at the end of frontline immunochemotherapy (A), and according to the subsequent treatment in the subset of patients not achieving a complete metabolic response (B). Treatment of patients with DS4 and DS5 was based on investigator choice, but those receiving aggressive treatment (second-line chemotherapy with or without autologous transplantation and/or radiotherapy) exhibited significantly higher residual metabolic tumor volume and uptake.

# Primary mediastinal B-cell lymphoma

## Role of radiotherapy

### Radiotherapy consolidation

- Role of RT after reaching metabolic CR (FDG PET/CT DS 1-3)
- Risk x benefit ratio - long term toxicity
- IELSG37 trial – no PFS nor OS benefit RT x observation



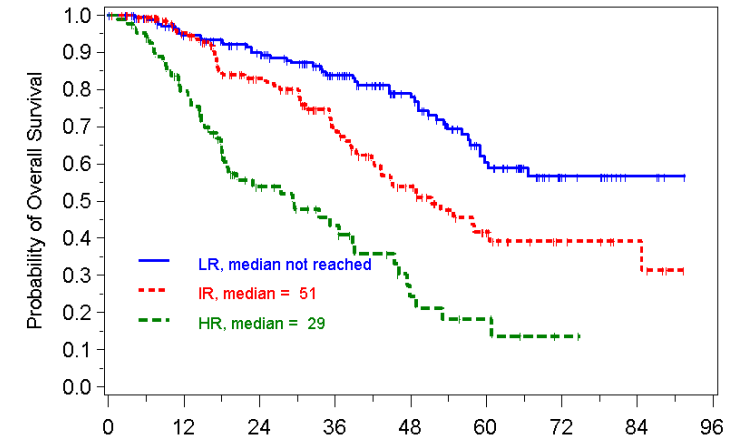
Number at risk

—	132	128	127	126	125	124	109	94	84	74	49	23	13
—	136	135	135	135	133	131	116	102	87	77	61	27	16

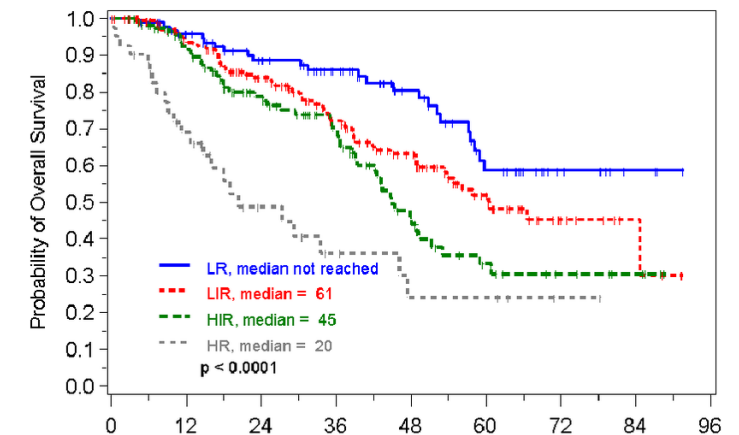
# Mantle cell lymphoma

- 2-10% of NHL, more common in men (3:1 ratio)
- Variable course – aggressive x indolent “CLL like” phenotype
- t(11;14) (q13;q32) translocation leading to constitutive expression of cell cycle regulator cyclin D1
- Higher risk of CNS involvement (esp. in blastoid variant, high Ki67% index)
  - CSF evaluation
- **Risk factors:**
  - cytogenetic changes (complex karyotype)
  - mutation of TP53, CDKN2A, RB1, KMT2D
  - MIPI(b): age, WBC, LDH, ECOG, Ki67 index

**Overall survival according to MIPI and MIPIb**

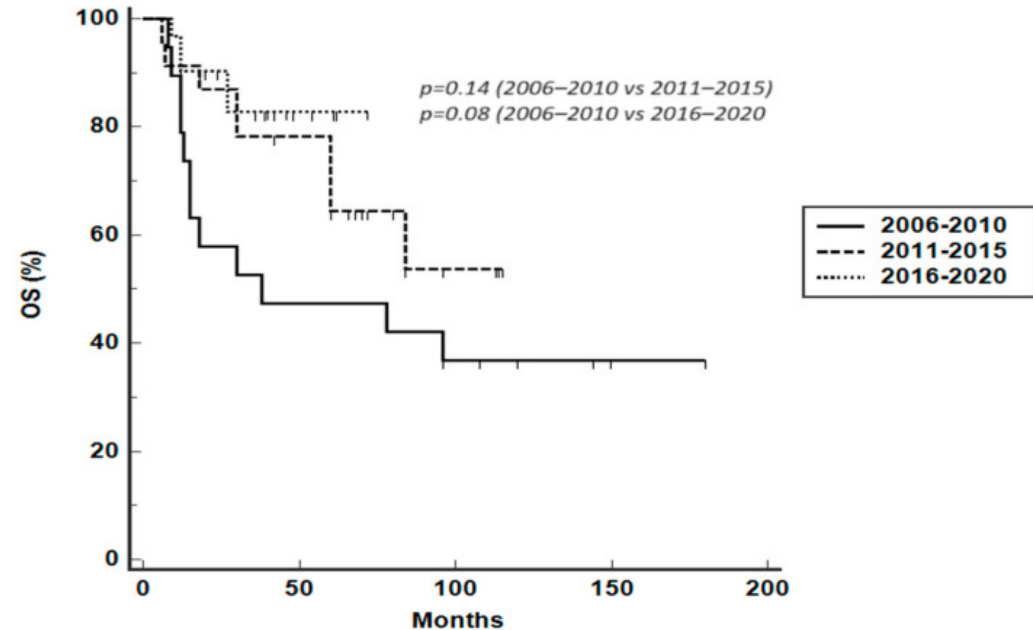
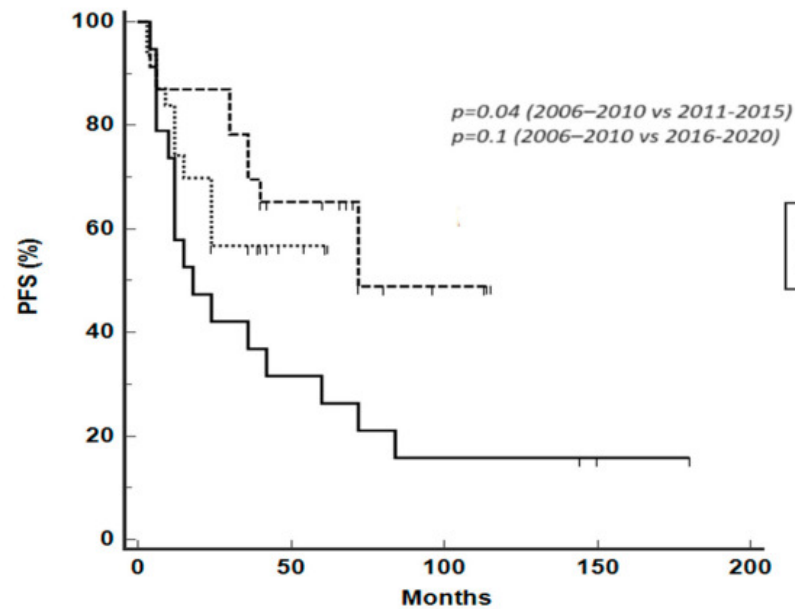


	numbers of patients at risk								
	0	12	24	36	48	60	72	84	96
LR	180	153	131	99	69	39	15	4	
IR	145	116	83	57	37	19	9	5	
HR	84	58	29	19	8	5	1	0	

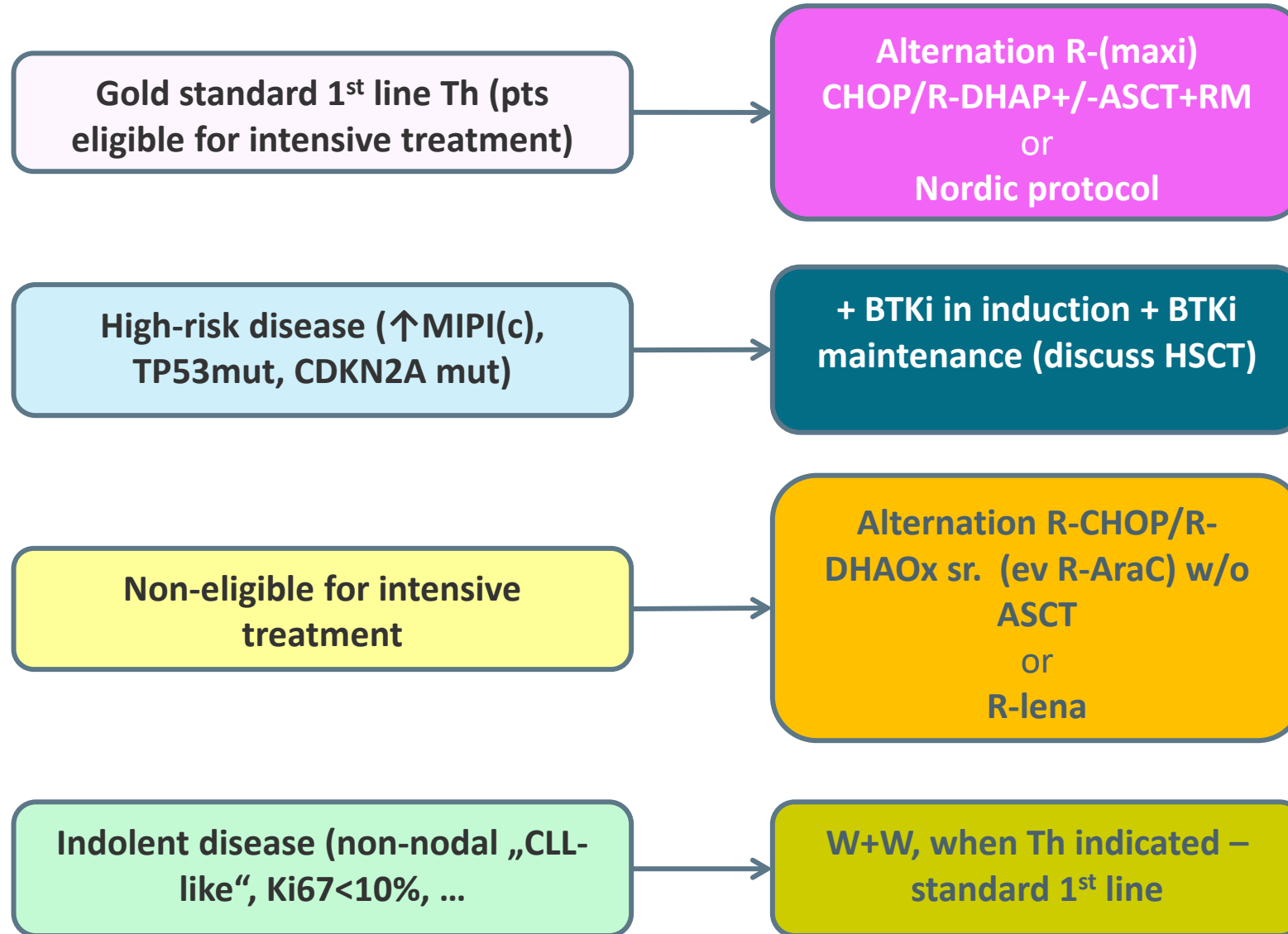


	numbers of patients at risk								
	0	12	24	36	48	60	72	84	96
LR	99	86	70	55	38	21	9	3	
LIR	173	142	111	78	53	30	9	3	
HIR	119	94	65	47	25	13	7	4	
HR	41	24	12	7	4	1	0		

# Mantle cell lymphoma changes in survival in targeted therapy era



# Mantle cell lymphoma



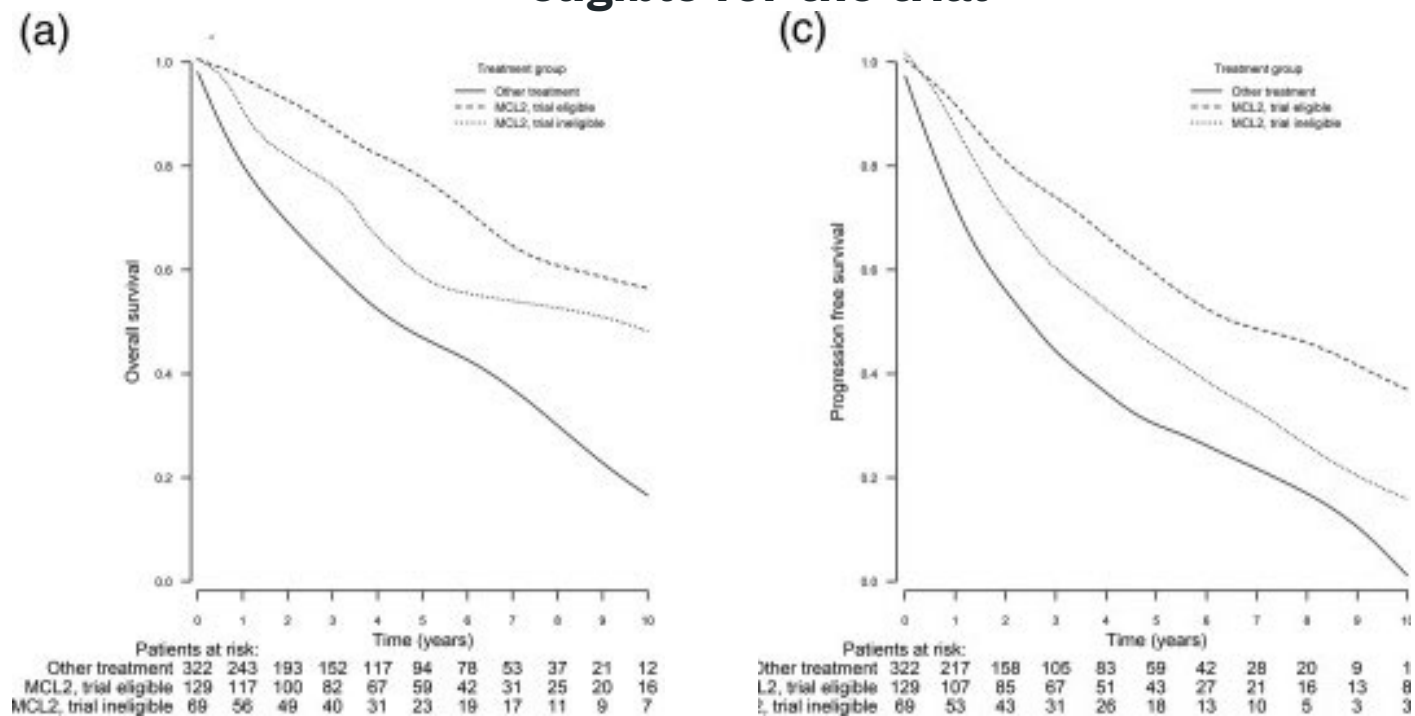
# Mantle cell lymphoma

## Intensive induction therapy

### MCL2 results in trial ineligible pts

- Retrospective trial
- 520 pts
  - 322 other treatment (R-CHOP(like), RB, R-AraC) +/-RM
  - 198 MCL2 (R-maxi-CHOP alt. R-HDAC followed by ASCT (cond. BEAM) +/- RM)
    - 129 trial eligible
    - 69 trial ineligible (mostly due to age)
- OS 14yrs x 9.8 yrs (trial ineligible)
- PFS 6.4yrs x 4.4 yrs (trial ineligible)
- Not signif. difference in net survival

### Overall and progression free survival of pts treated by Nordic MCL2 protocol not eligible for the trial





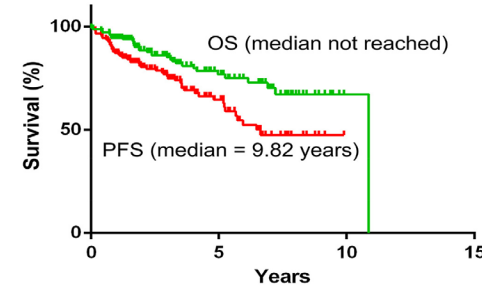
# Mantle cell lymphoma

## Rituximab maintenance

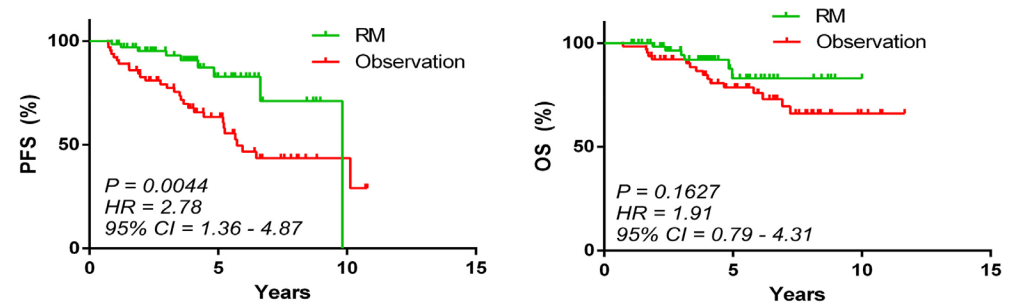
### RM prolongs PFS

- Retrospective trial
- 143 pts w MCL
- Induction
  - Nordic MCL2 protocol followed by ASCT
- 138 pts completed induction
  - 119 incl. ASCT
  - Rituximab maintenance (RM) (n=64)
  - x observation (n=66)

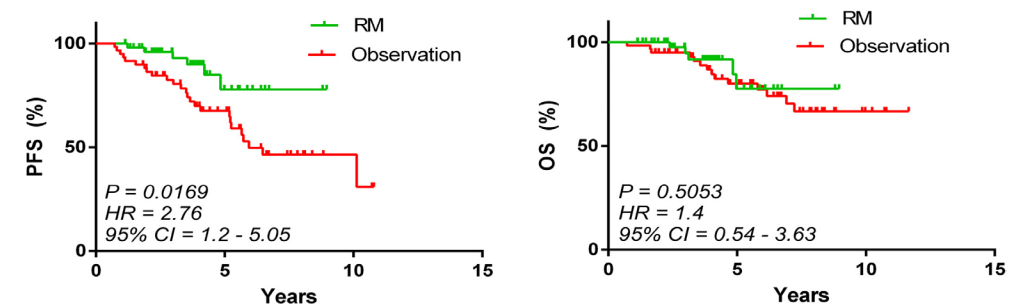
(A) All analyzed patients (n = 143)



(B) All patients assessable to RM or observation

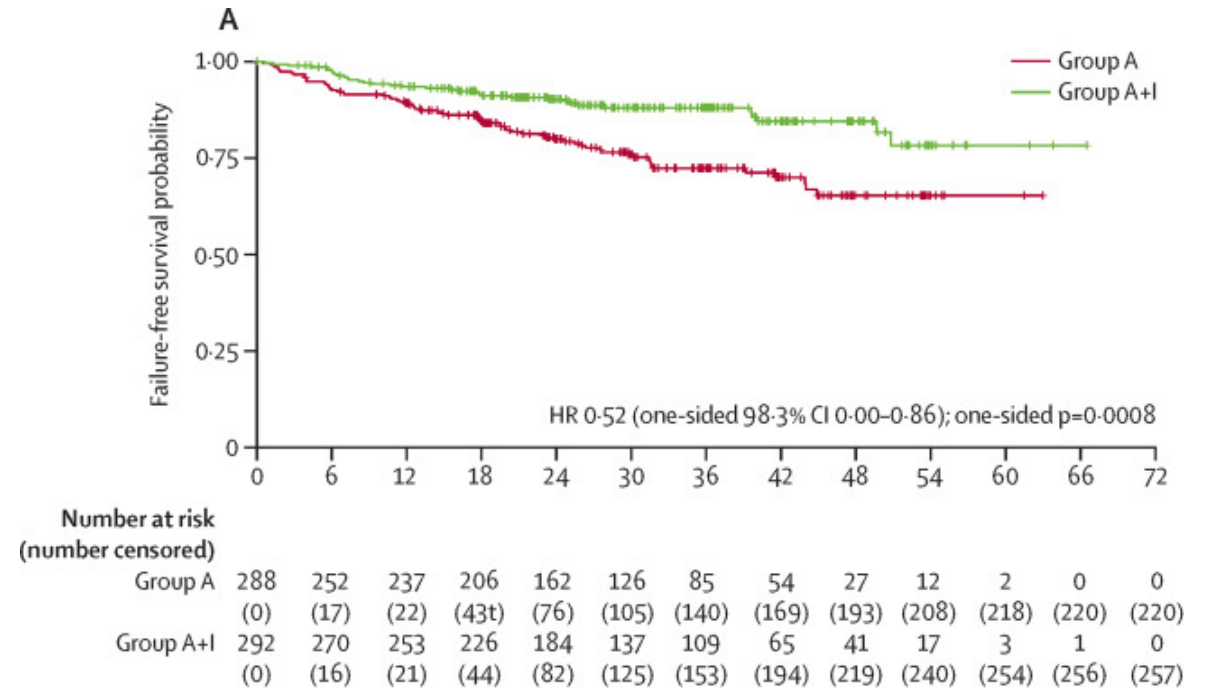
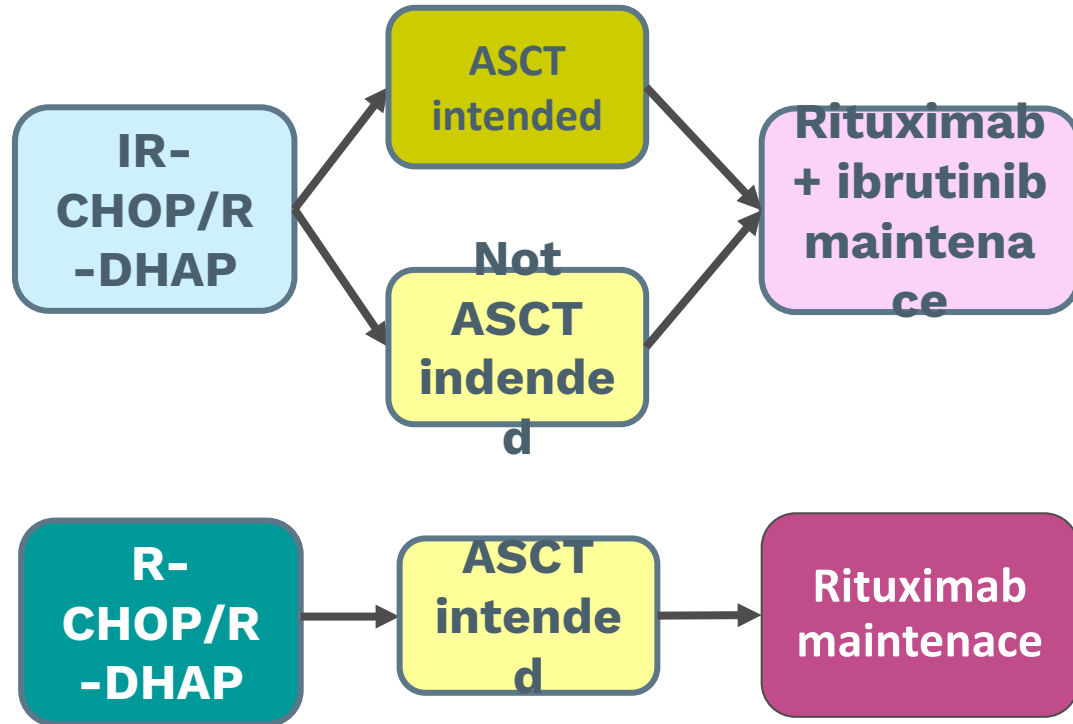


(C) Transplanted patients assessable to RM or observation



# Mantle cell lymphoma

## 1<sup>st</sup> line ibrutinib - TRIANGLE

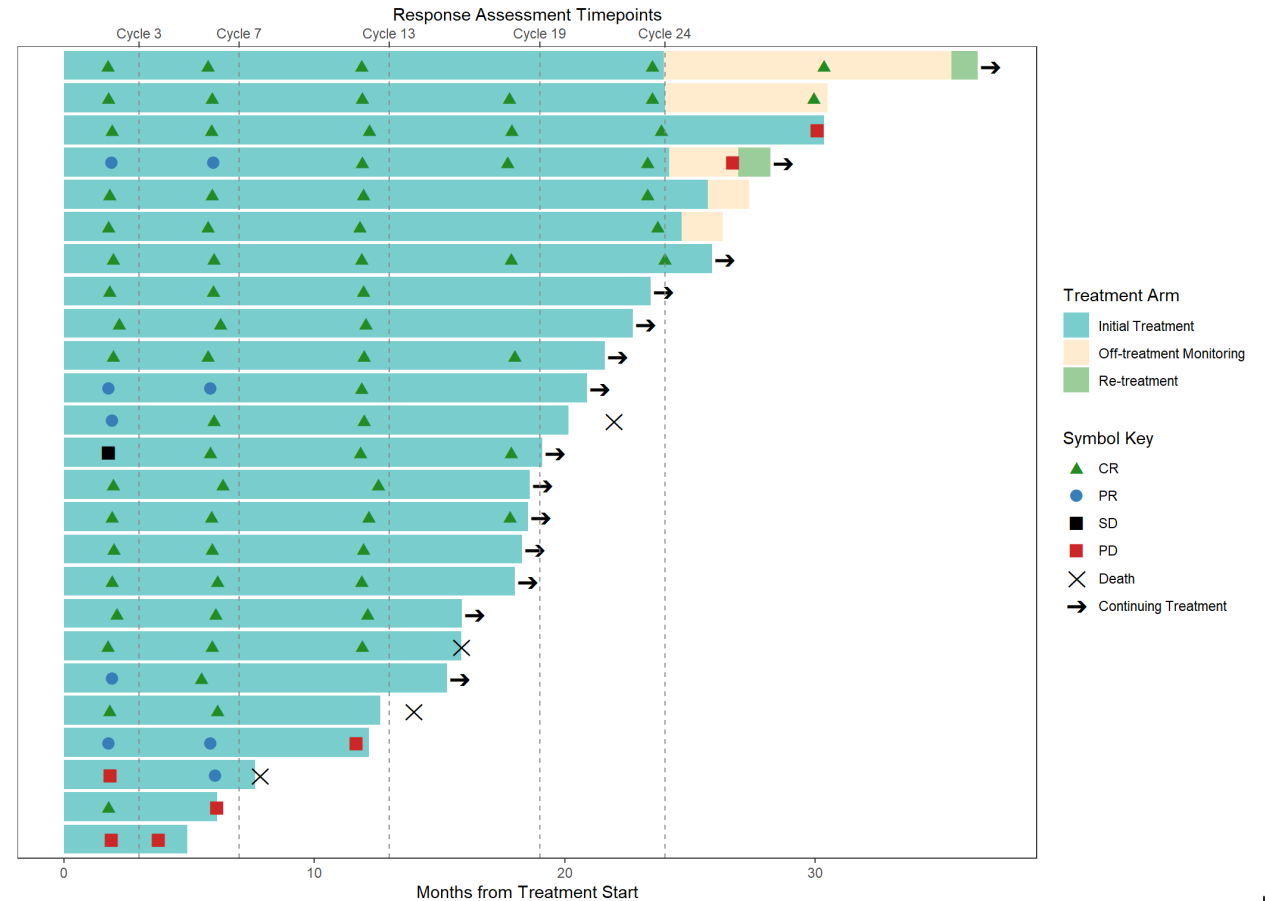


# Mantle cell lymphoma TP53 mutated pts - BOVen

## BOVen trial

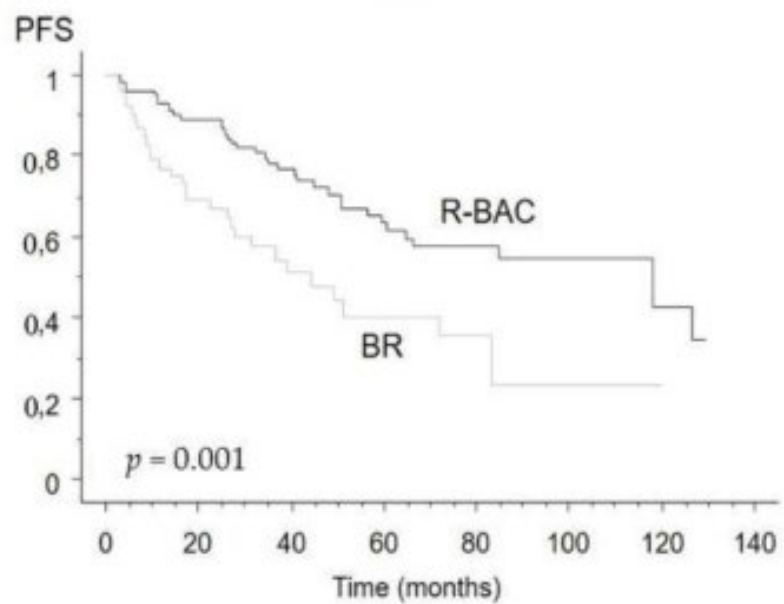
- 28-day cycles:
  - Zanu 160 mg PO BID starting D1;
  - Obin 1000 mg IV D1 or split D1-2, 8, 15 of C1, D1 of C2-8;
  - Ven ramp up initiated C3D1 (target 400 mg QD).
  - Treatment duration is 2 years
- 25 pts
- ORR 95%, CR 88%
- 16months PFS: 75%

## Responses of pts with TP53mut MCL after BOVen

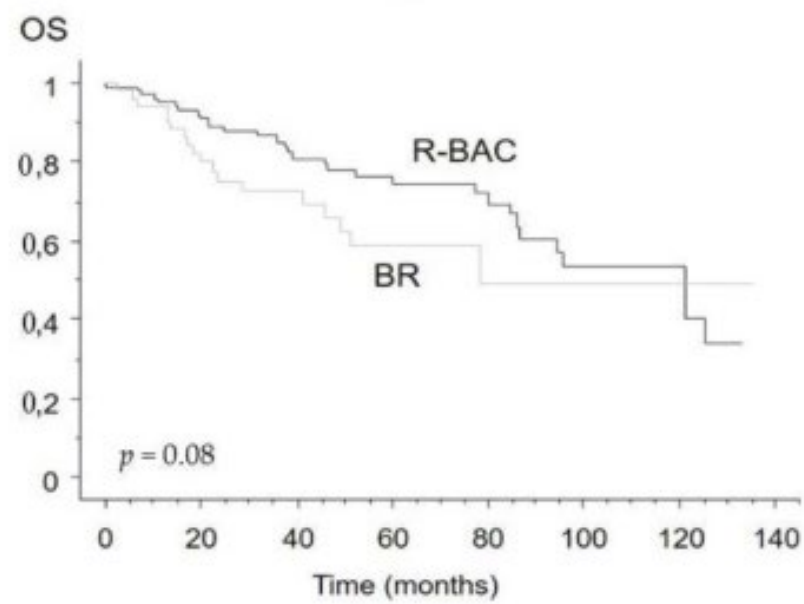


# Mantle cell lymphoma

## Frail population



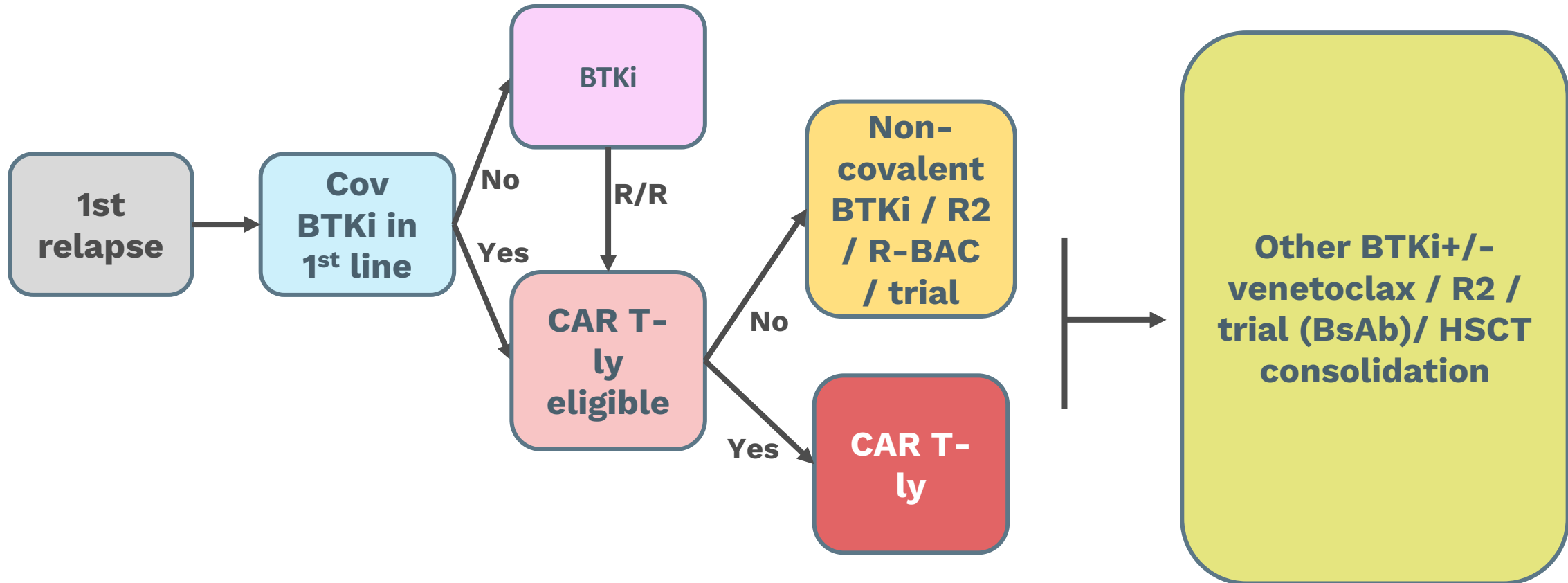
(c)



(d)

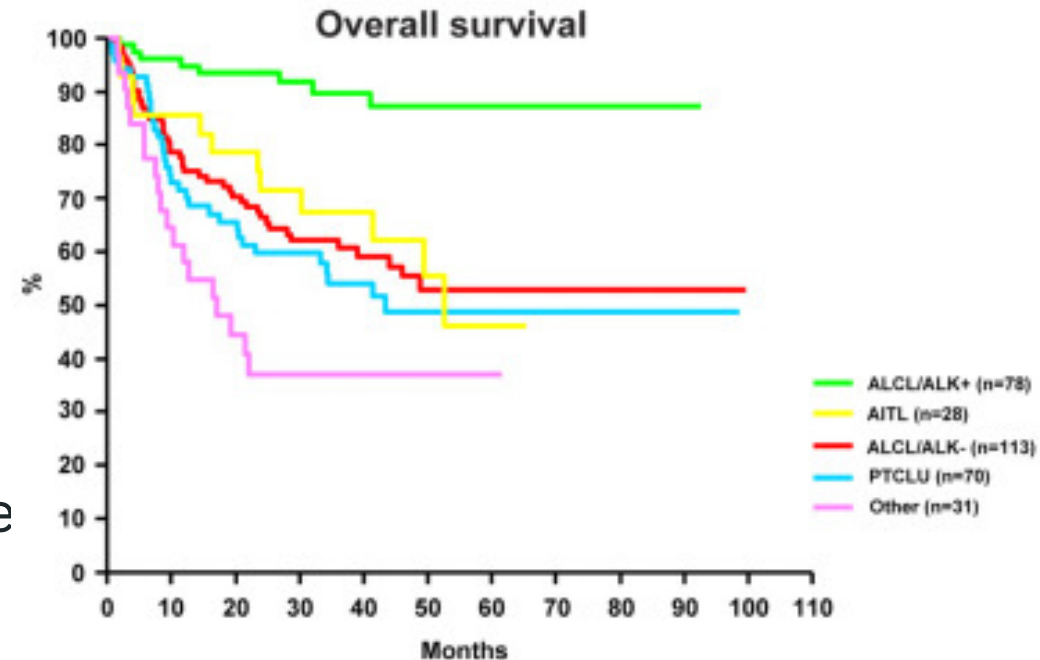
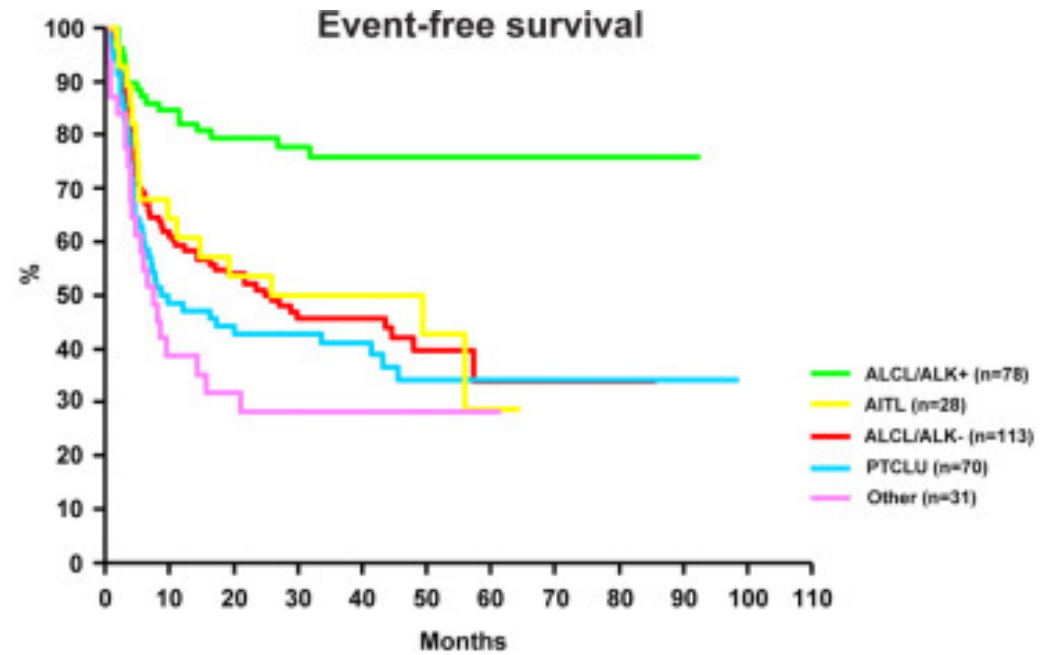
# Mantle cell lymphoma

## Further options



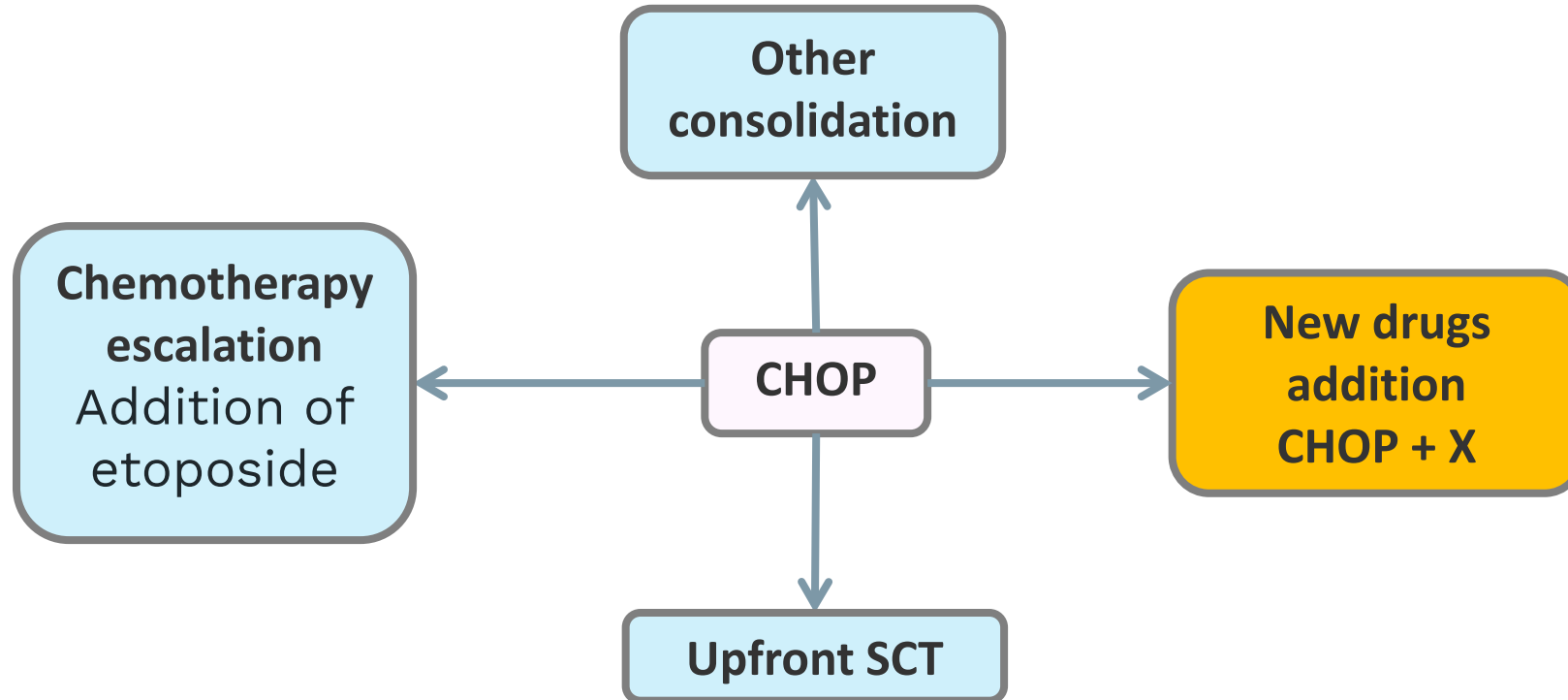
# T-NHL

- Heterogenous group
  - ALCL (ALK+/-)
  - AITL
  - EATL
  - PTCL NOS
- Molecular profiling
  - TFH phenotype
  - AITL
  - PTCL NOS
- Prognostic factors:
  - IPI
  - PIT (age, ECOG, LD, BM involve



# T-NHL

## Treatment options

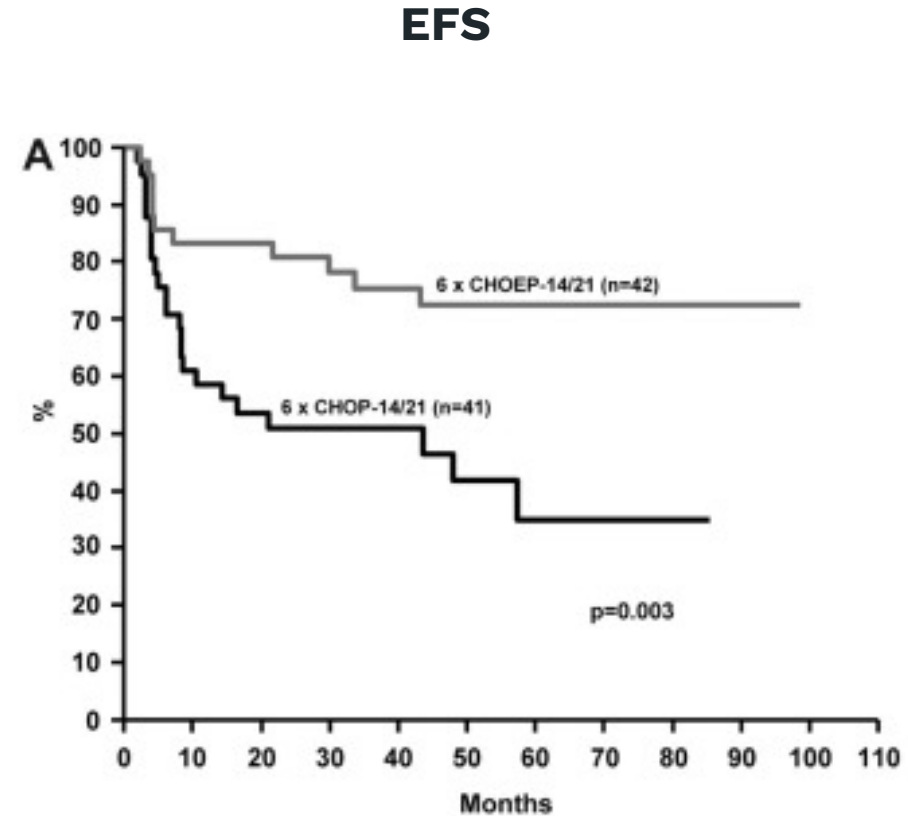


# T-NHL

## CHOEP

### Addition of etoposide

- Higher toxicity
- No benefit for older population
- Recomm. for pts  $\leq 65$  yrs
- No benefit in pts for EATL
- No benefit in further dose escalation (“megaCHOEP”)
- Upfront ASCT in CR1 for high risk population



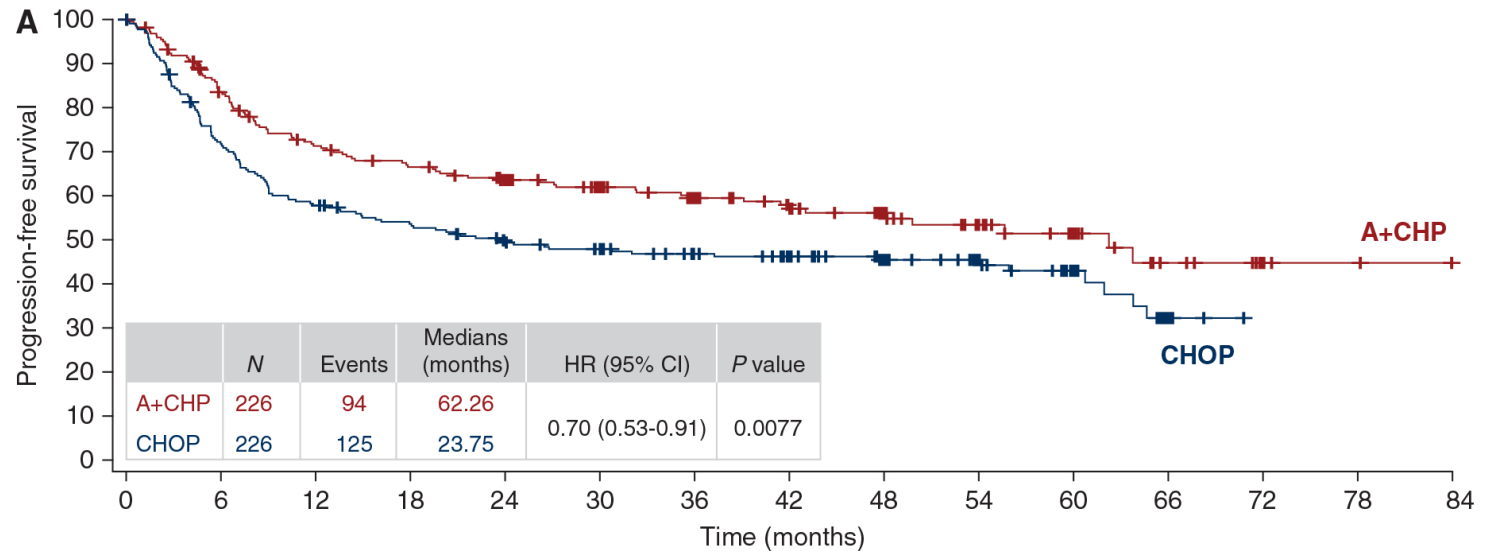


# T-NHL

## Brentuximab vedotin+CHT

### ECHELON-2

- Brentuximab-vedotin+CHP for CD30+ PTCL
- 452 pts 1:1 randomised
- 70% sALCL
- ORR 83% x 72%
- CR 68% x 56%
- Improvement of
  - PFS (48m x 21m)
  - OS (median not met)
- Not powered enough to extrapolate for all PTCL subtypes



at risk (events)

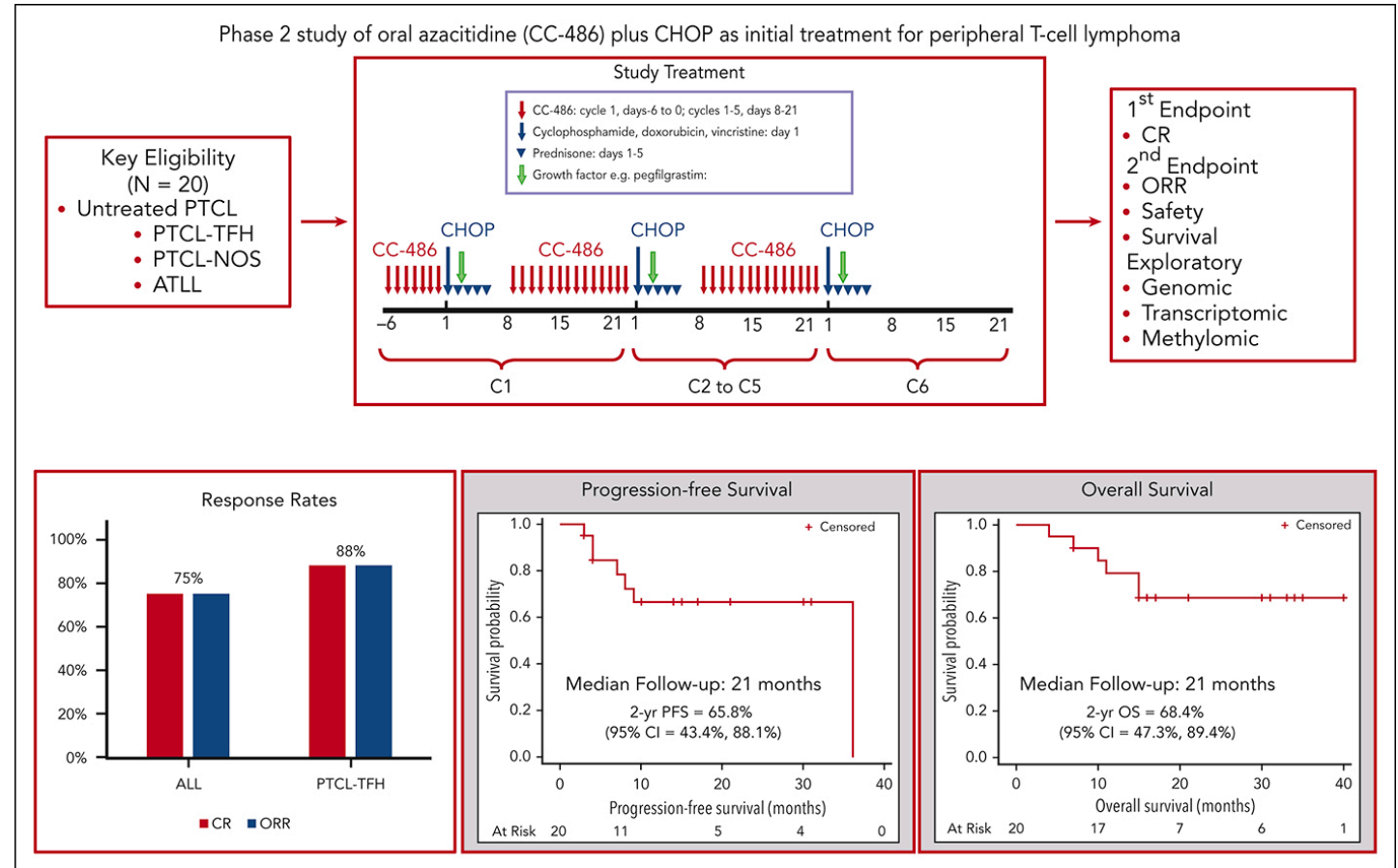
A+CHP	226 (0)	179 (36)	150 (62)	138 (72)	123 (78)	104 (81)	85 (85)	67 (88)	44 (89)	31 (91)	21 (92)	10 (94)	4 (94)	2 (94)	0 (94)
CHOP	226 (0)	159 (63)	128 (94)	116 (103)	101 (112)	94 (115)	79 (117)	70 (118)	55 (119)	39 (119)	24 (121)	6 (125)	0 (125)	0 (125)	0 (125)

# T-NHL

## further perspectives

### Addition of azacitidine

- Pts with PTCL-TFH phenotype
- 20 pts
- CR 75%
- 2 yrs PFS 65%
- Further evaluation in randomized trial



# Thank you for your attention!



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