Il suono DELL' INNOVAZIONE
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Scenari di Sequencing Terapeutico nel Linfoma Mantellare

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Disclosures of Enrico Derenzini

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Takeda	X					X	
Roche					X	X	
Incyte	X				X	X	
ADC-Therapeutics	X						
Beigene							X
AbbVie					X	X	
Astra Zeneca						X	
Lilly						X	
Sobi					X	X	
Gilead						X	
Regeneron			X				

MCL: 1L past, current & future treatment scenario

FIRST LINE

PAST

≤65 Y
Or T-EL

→ R-CHT/ASCT + R maint

>65 Y
Or T-INEL

→ R-Benda-BASED + R maint

R-BAC

PRESENT

≤65 Y
Or T-EL

→ R-CHT +cBTKi + R maint

Triangle

→ N.B. ASCT in High Risk?

>65 Y
Or T-INEL

≤65 Y UNFIT

→ R-Benda +cBTKi + R maint

Echo

→ De-escalate Benda?

FUTURE

CHEMOFREE
RISK-BASED

→ -RISK-ADAPTED DOUBLETS/TRIPLETS
-BTKi+BCL-2i+BsABs
-SEQUENTIAL
Anti CD20-BTKi-CAR-T
-MRD DRIVEN
CAR-T or BsABs

R/R MCL: 1L past treatment scenario

>1 LINE
BTK naive

FIRST-LINE
R-CHT-ASCT ≤65y
R-BENDA > 65 Y

→ R/R MCL

cBTKi NAIVE

2 L

3 L

IBRUTINIB in r/r MCL

ACALABRUTINIB in r/r MCL

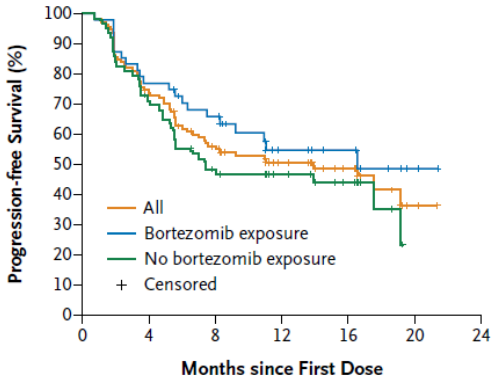
>1 LINE
BTK naive

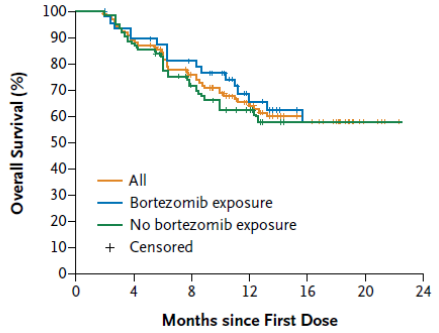
Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma

N=111 pts, ORR 68%, CR 21%**

Table 3. Best Response to Therapy.*

Variable	No Prior Treatment with Bortezomib (N=63)	Prior Treatment with Bortezomib (N=48)	All Patients (N=111)
Response — no. (%)			
Overall	43 (68)	32 (67)	75 (68)
Complete	12 (19)	11 (23)	23 (21)
Partial	31 (49)	21 (44)	52 (47)
None†	20 (32)	15 (31)	35 (32)
Response duration — mo			
Median	15.8	NR	17.5
95% CI	5.6–NR	NR–NR	15.8–NR
Progression-free survival — mo			
Median	7.4	16.6	13.9
95% CI	5.3–19.2	8.3–NR	7.0–NR
Overall survival — mo			
Median	NR	NR	NR
95% CI	10.0–NR	11.9–NR	13.2–NR



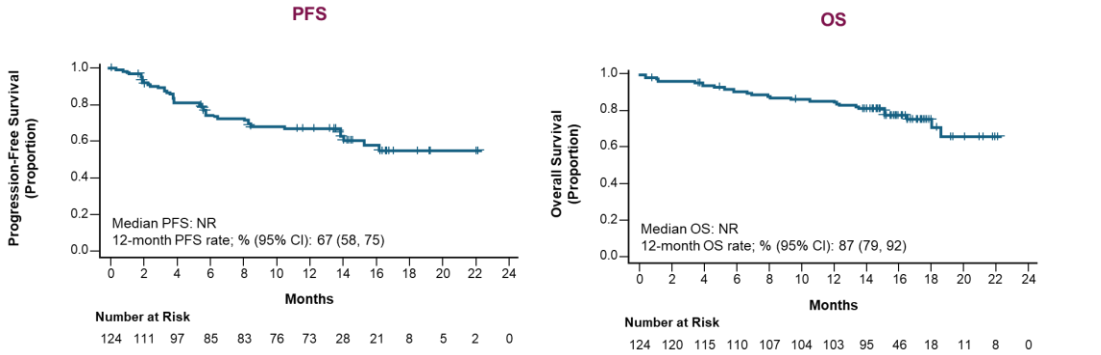


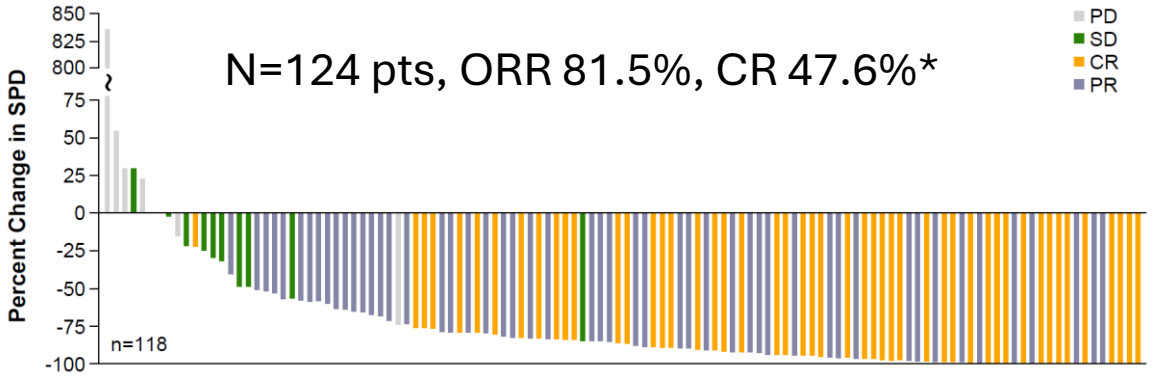
Median N Prior regimens = 3 (1-5)

** Revised response criteria for malignant lymphoma 2007

Wang M et al, NEJM 2013

ACE-LY-004 (Acalabrutinib): Change in Tumor Burden and Best Response Status per Lugano Classification





N=124 pts, ORR 81.5%, CR 47.6%*

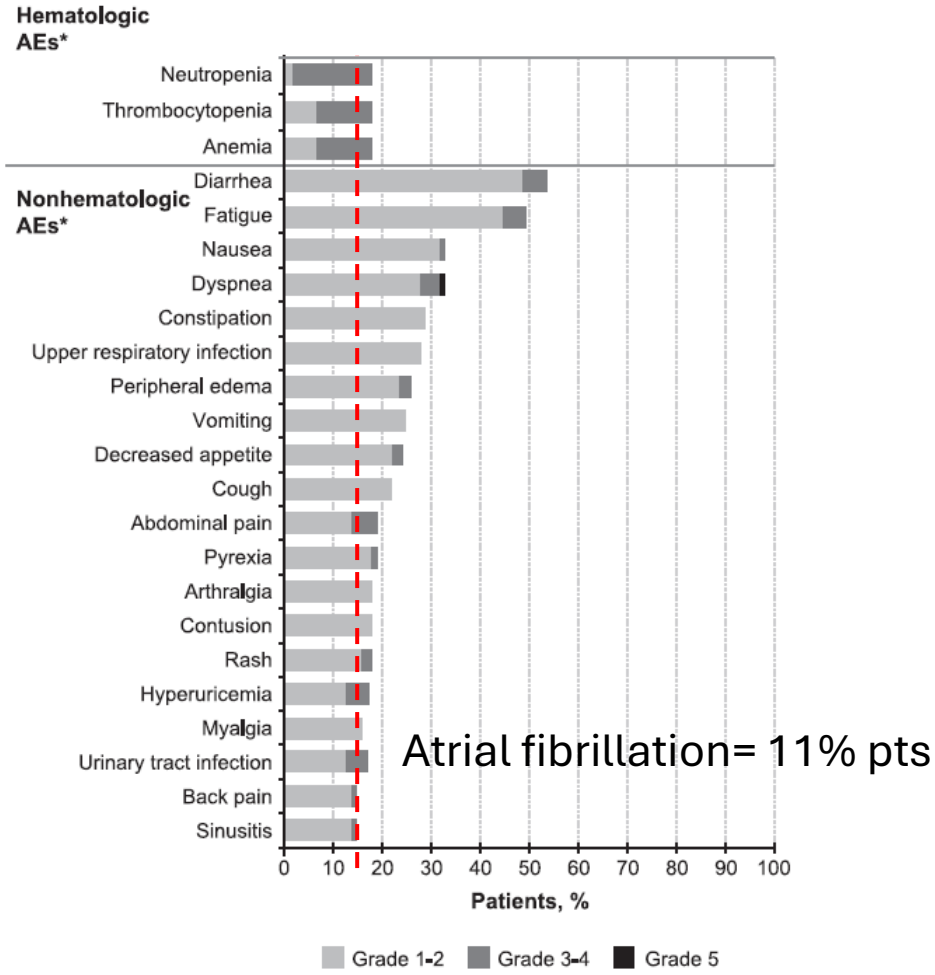
Median N Prior regimens = 2 (1-5)

* Lugano criteria 2014

Wang M et al. *Lancet* 2018; Le Gouil er al, Haematologica 2024

>1 LINE
BTK naive

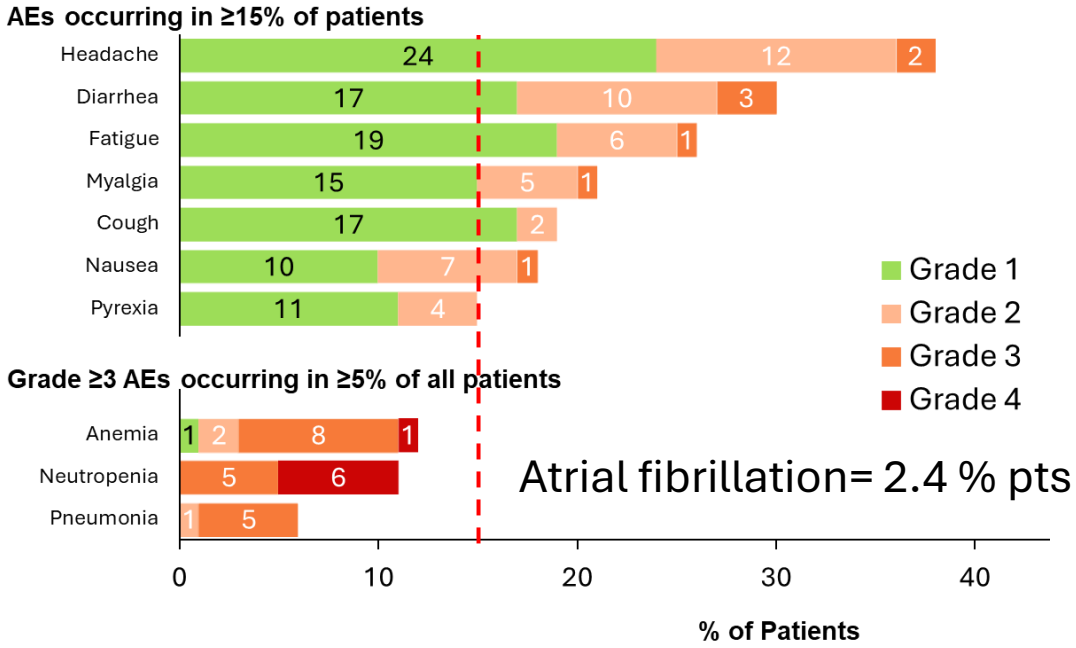
IBRUTINIB in r/r MCL: Most Common Adverse Events



Atrial fibrillation= 11% pts

Wang M et al, NEJM 2013

ACALABRUTINIB in r/r MCL: Most Common Adverse Events



Atrial fibrillation= 2.4 % pts

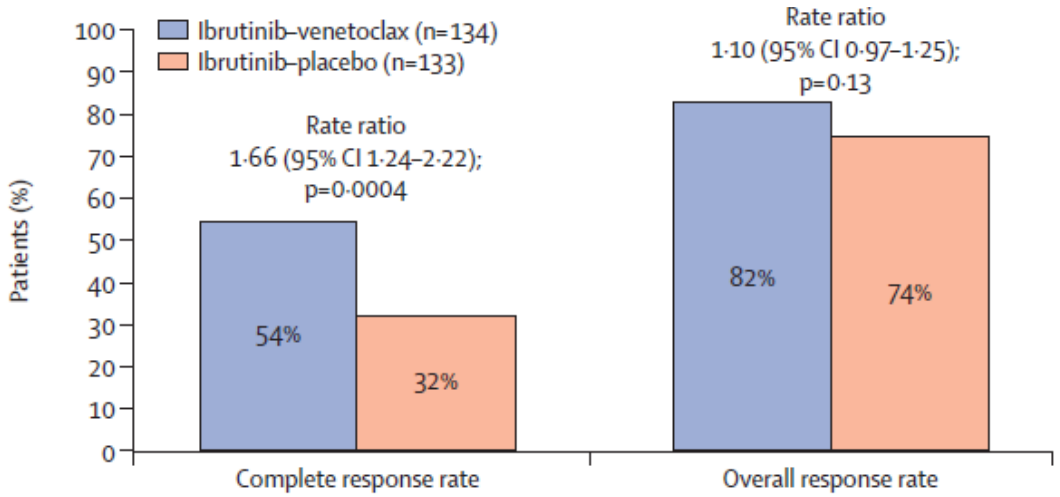
Wang M et al. *Lancet* 2018; Le Gouil er al, Haematologica 2024

>1 LINE
BTK naive

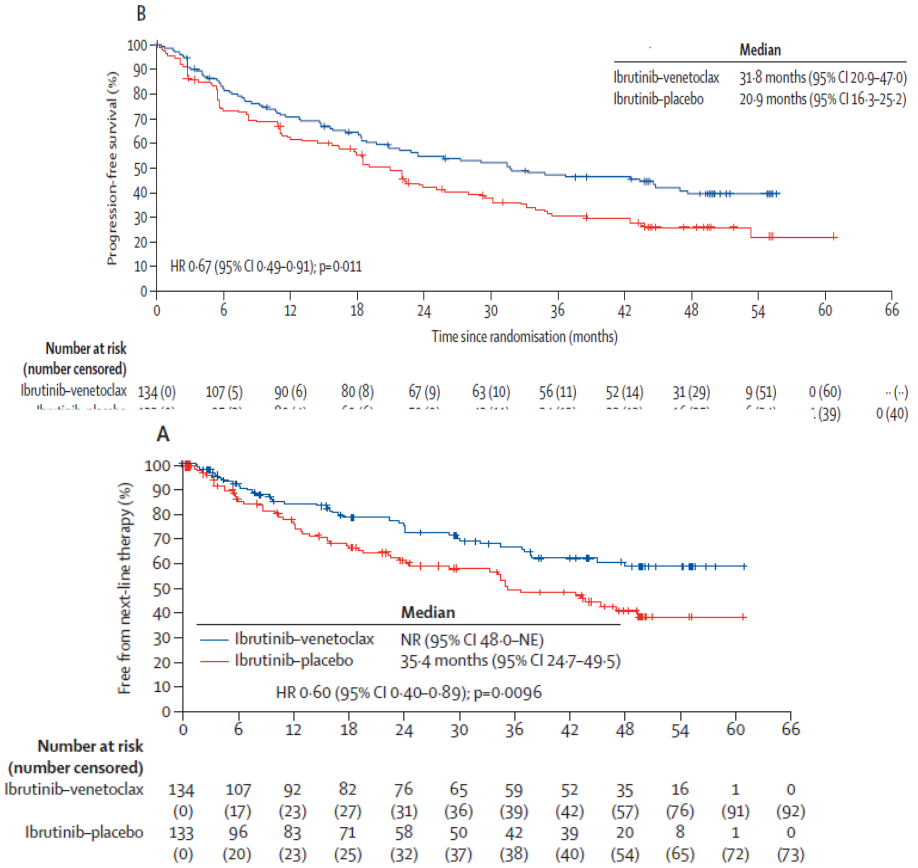
Ibrutinib plus venetoclax in relapsed or refractory mantle cell lymphoma (SYMPATICO): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study

Michael Wang, Wojciech Jurczak, Marek Trneny, David Belada, Tomasz Wrobel, Nilanjan Ghosh, Mary-Margaret Keating, Tom van Meerten, Ruben Fernandez Alvarez, Gottfried von Keudell, Catherine Thieblemont, Frederic Peyrade, Marc Andre, Marc Hoffmann, Edith Szafer-Glusman, Jennifer Lin, James P Dean, Jutta K Neuenburg, Constantine S Tam

N=267
60% pts >1L



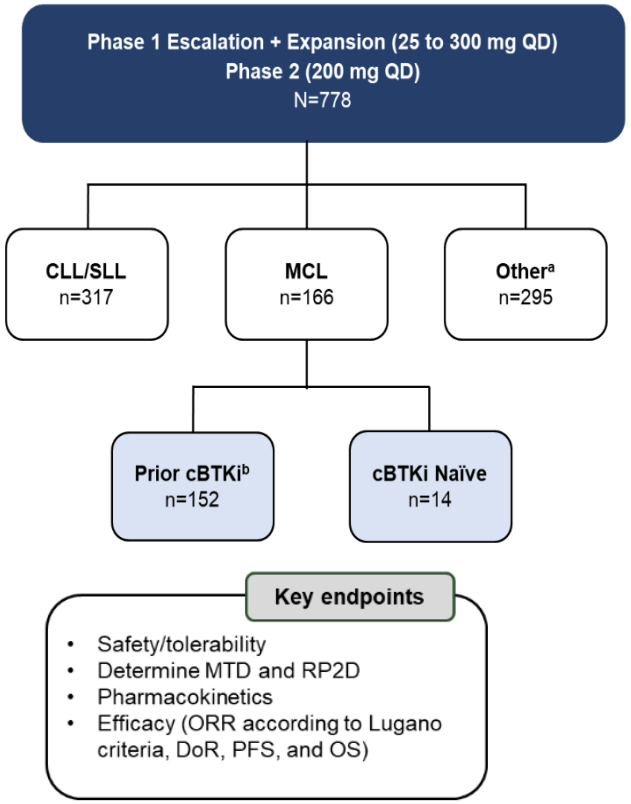
Atrial fibrillation 10%



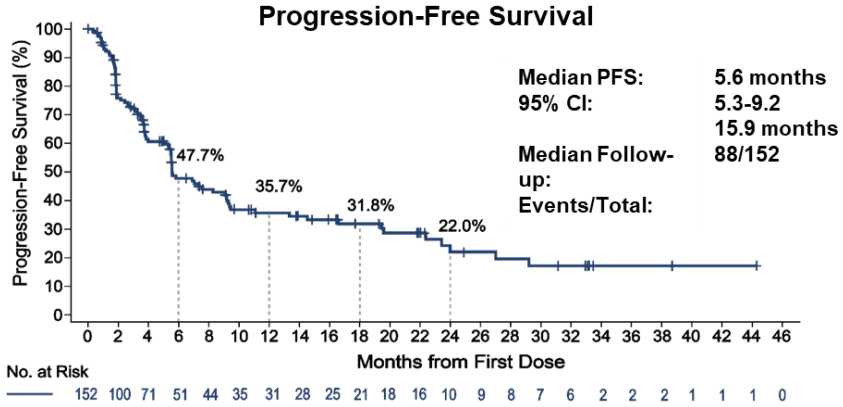
Wang et al, Lancet Oncol 2025

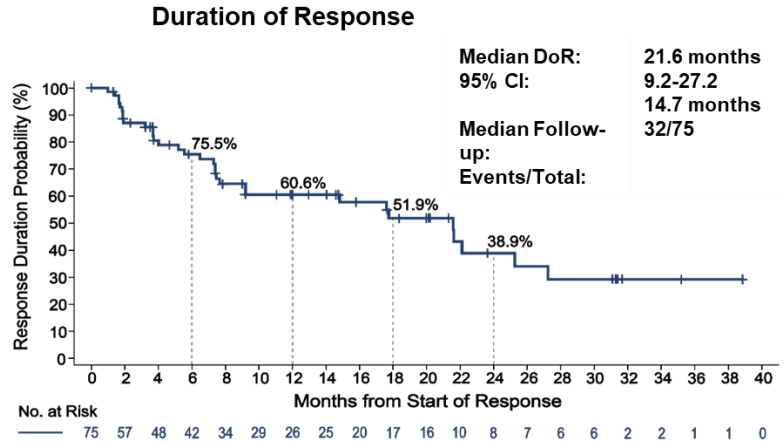
Pirtobrutinib in Relapsed/Refractory (R/R) Mantle Cell Lymphoma (MCL) Patients with Prior cBTKi: Updated Safety and Efficacy including High-Risk Subgroup Analyses from the Phase 1/2 BRUIN Study

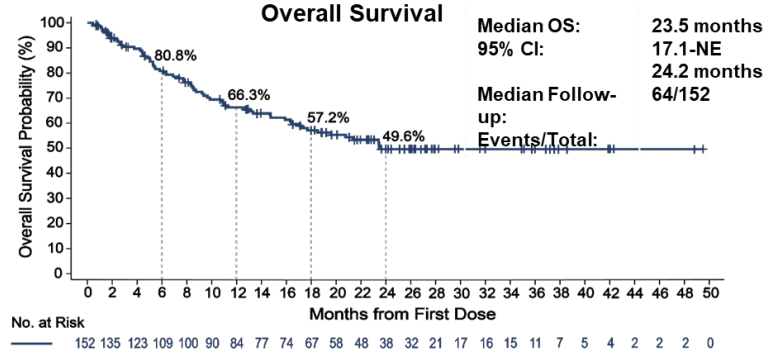
>1 LINE and BTK exposed



Characteristics	Prior cBTKi n=152	cBTKi Naïve n=14
Prior therapy, n (%)		
BTK inhibitor	152 (100)	0 (0)
Anti-CD20 antibody	147 (97)	14 (100)
Chemotherapy	137 (90)	14 (100)
Reason discontinued any prior BTKi[a], n (%)		
Progressive disease	128 (84)	-
Toxicity / Other	21 (14)	-
Unknown	3 (2)	-
Ki-67 index, n (%)		
<30%	18 (12)	2 (14)
≥30%	45 (30)	6 (43)
Missing	89 (59)	6 (43)
Histology, n (%)		
Classic/leukemic	120 (79)	11 (79)
Pleomorphic/Blastoid	32 (21)	3 (21)
sMIPI score, n (%)		
Low risk (0-3)	30 (20)	3 (21)
Intermediate risk (4-5)	79 (52)	5 (36)
High risk (6-11)	43 (28)	6 (43)







Cohen et al, ASH 2023

Pirtobrutinib Safety Profile in MCL Patients

>1 LINE and BTK exposed

	Treatment-Emergent AEs in Patients with MCL (n=166)			
	All Cause AEs, (≥15%), %		Treatment-Related AEs, %	
Adverse Event	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Fatigue	31.9	3.0	21.1	2.4
Diarrhea	22.3	0.0	12.7	0.0
Dyspnea	17.5	1.2	9.0	0.6
Anemia	16.9	7.8	7.2	2.4
Platelet Count Decreased	15.1	7.8	7.8	3.0
AEs of Interest[a]	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Infections[b]	42.8	19.9	15.7	3.6
Bruising[c]	16.3	0.0	11.4	0.0
Rash[d]	14.5	0.6	9.0	0.0
Arthralgia	9.0	1.2	2.4	0.0
Hemorrhage[e]	10.2	2.4	4.2	0.6
Hypertension	4.2	0.6	1.8	0.0
Atrial Fibrillation/Flutter[f,g]	3.6	1.8	0.6	0.0

Median time on treatment was 5.5 months for the MCL cohort

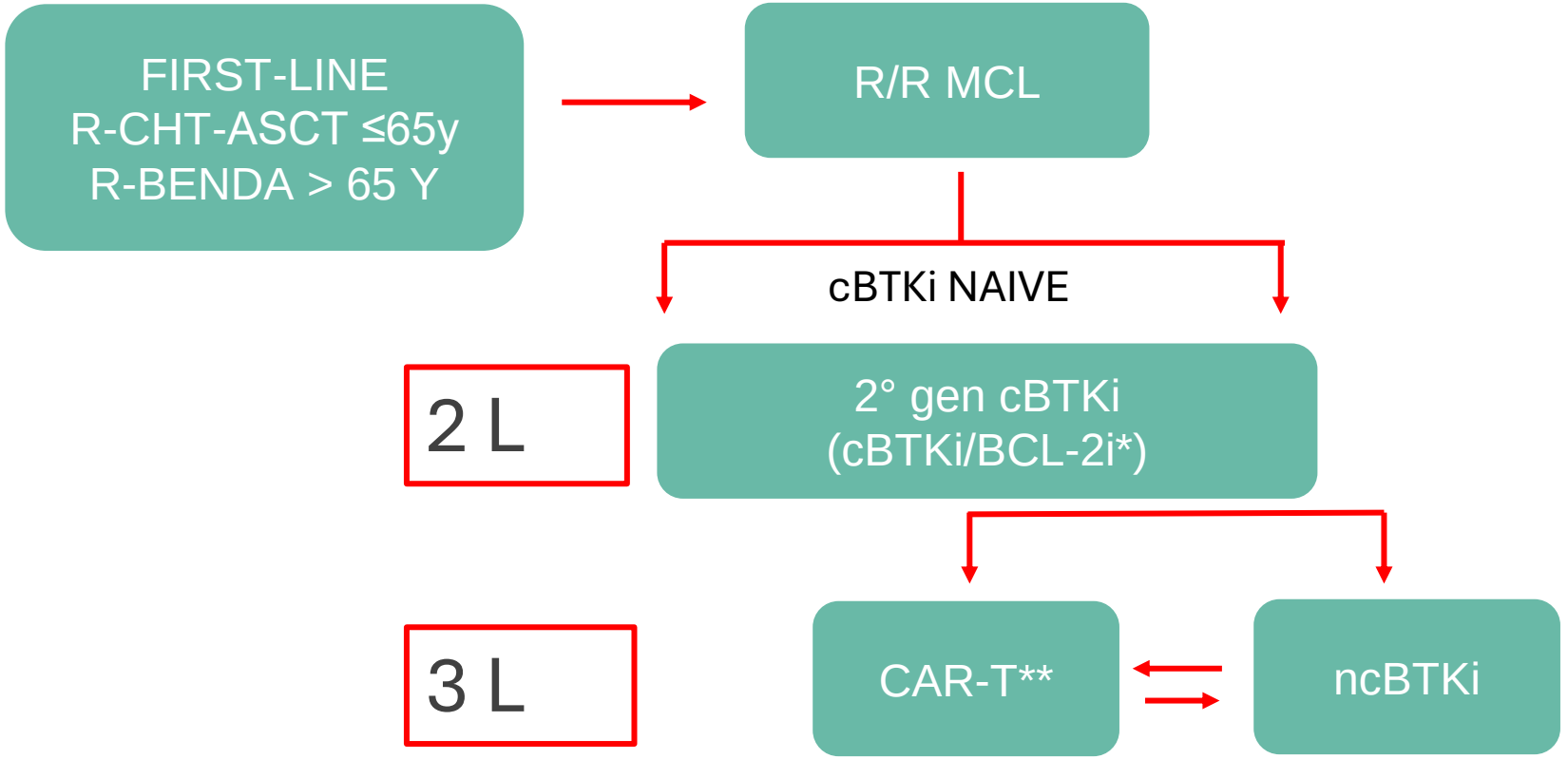
Discontinuations due to TRAEs occurred in 3% (n=5) of patients with MCL

Dose reductions due to TRAEs occurred in 5% (n=8) of patients with MCL

[a]AEs of interest are those that were previously associated with covalent BTK inhibitors. [b]Aggregate of all preferred terms including infection and COVID-19. [c]Aggregate of contusion, bone contusion, ecchymosis, and increased tendency to bruise. [d]Aggregate of all preferred terms including rash. [e]Aggregate of all preferred terms including hemorrhage or hematoma. [f]Aggregate of atrial fibrillation and atrial flutter. [g]Of 6 total atrial fibrillation and atrial flutter TEAEs, 3 occurred in patients with a prior medical history of atrial fibrillation. In the MCL cohort, treatment-related AEs leading to discontinuation included weight decrease/alopecia/fatigue (1), neutropenia (1), platelet count decreased (1), pneumonitis (1), and cholecystitis (1).

R/R MCL: 1L past treatment scenario

SECOND & THIRD LINE



*Not approved by EU regulatory authorities

** consider allo-SCT consolidation if young, high risk

R/R MCL: 1L current treatment scenario

FIRST LINE

1 L

FIRST-LINE
R-CHT+IBRUTINIB*
≤65y

→ Time-limited BTKi

R/R MCL

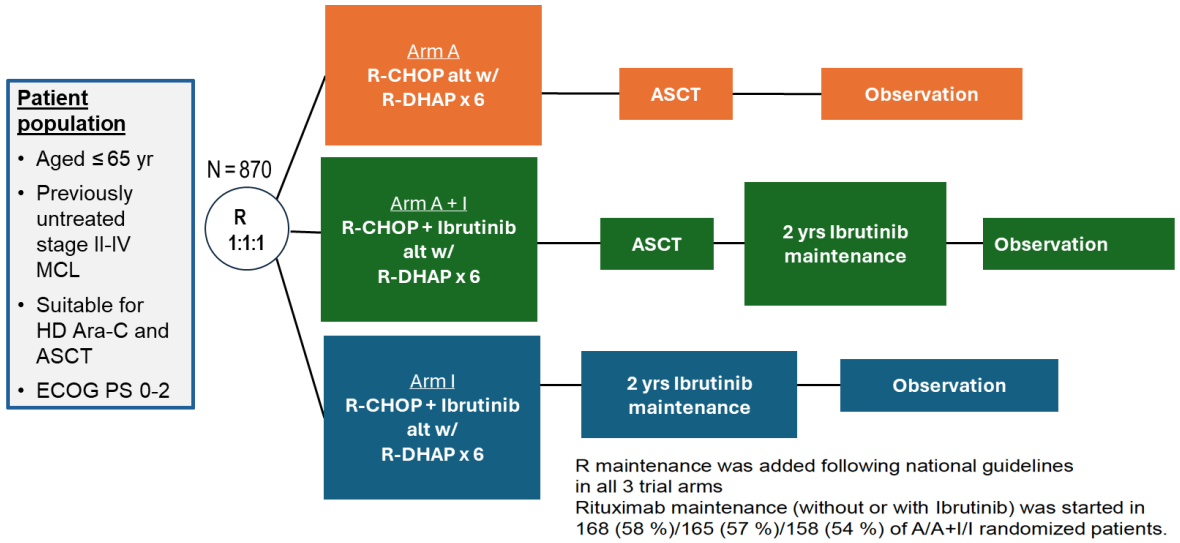
R-BENDA-
ACALABRUTINIB > 65 Y

→ Continous BTKi

* Second generation BTKi in Ibrutinib intolerant?

FIRST LINE

TRIANGLE



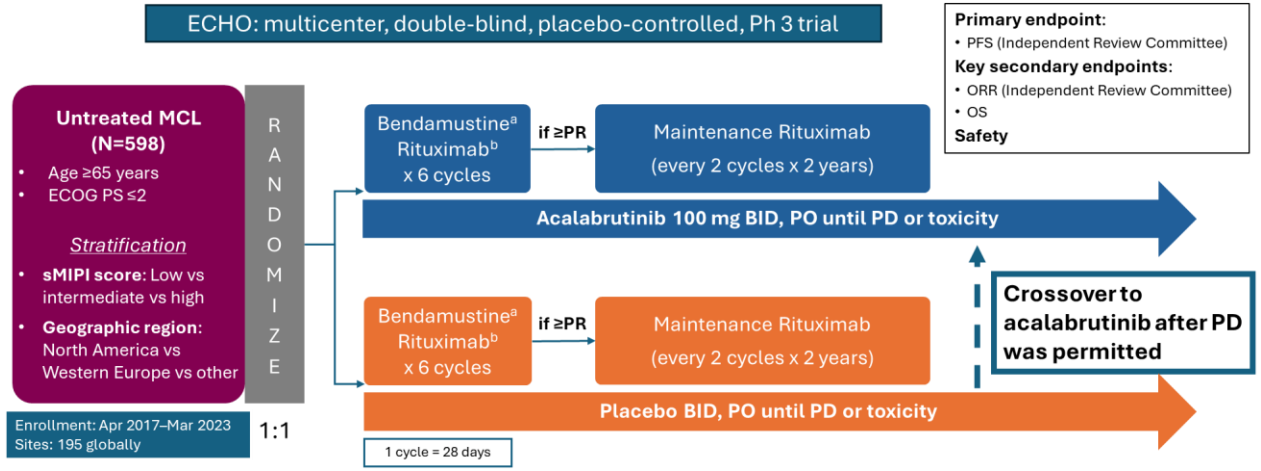
Primary Endpoint
• FFS
Key Secondary Endpoints
• Response rates • PFS • RD • OS • Safety

MIPI int-high 41-43%

Ki67 ≥30% 31-33%

Blastoid 11-13%

ECHO



Primary Endpoint
• PFS by independent review committee (IRC)
Key Secondary Endpoints
• PFS by investigator (INV) • ORR by INV and IRC • DoR by IRC • OS

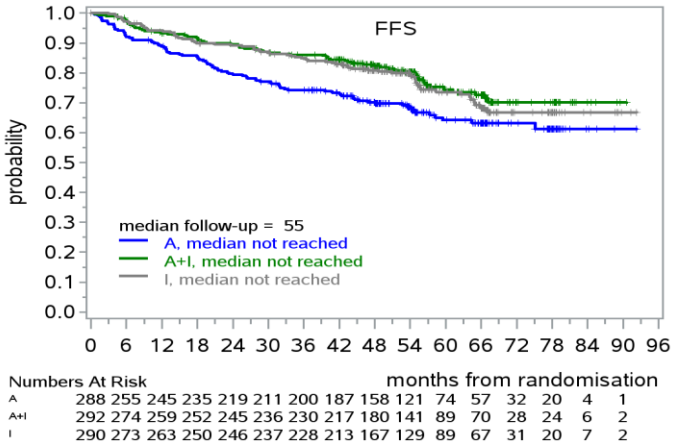
sMIPI int-high 66-67%

Ki67 ≥30% 46-49%

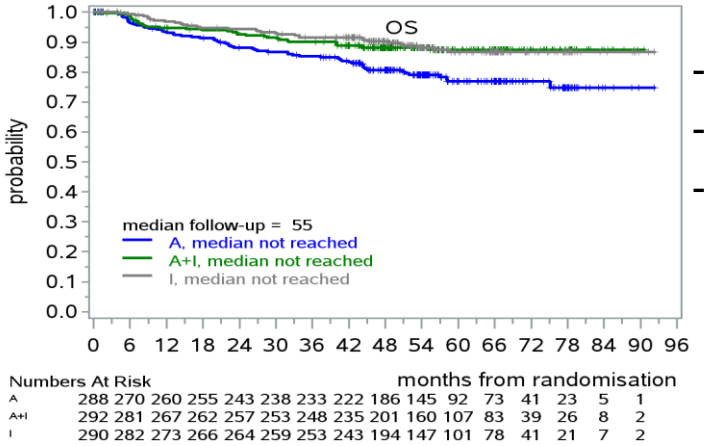
Blastoid/pleomorphic 13-14%

FIRST LINE

TRIANGLE



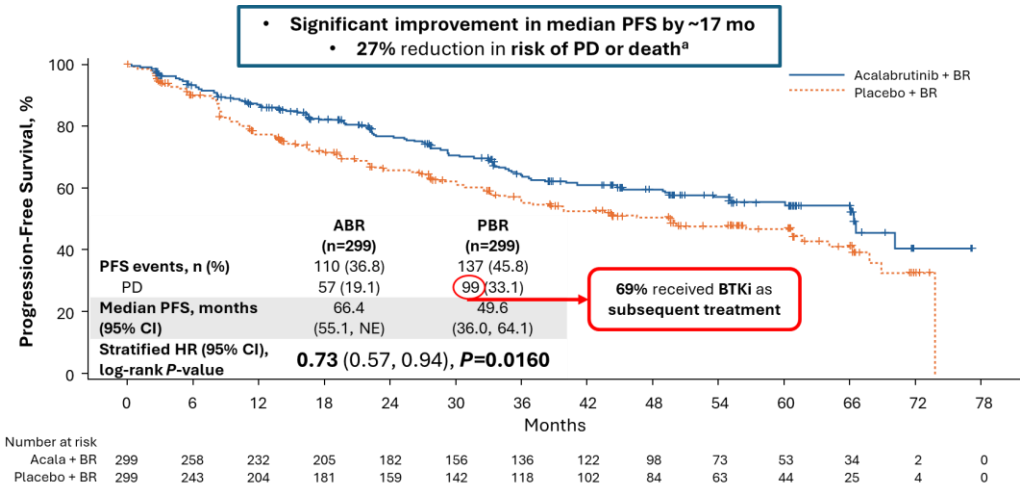
- 4-year FFS A: 70%
- 4-year FFS A+I: 82%
- 4-year FFS I: 81%

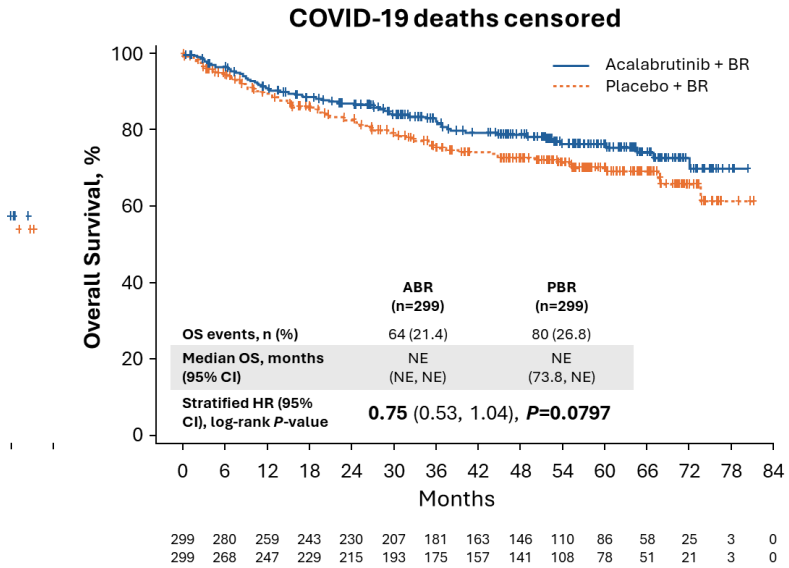


- 4-year OS A: 81%
- 4-year OS A+I: 88%
- 4-year OS I: 90%

Dreyling et al ASH 2022; Dreyling at al *Lancet* 2024

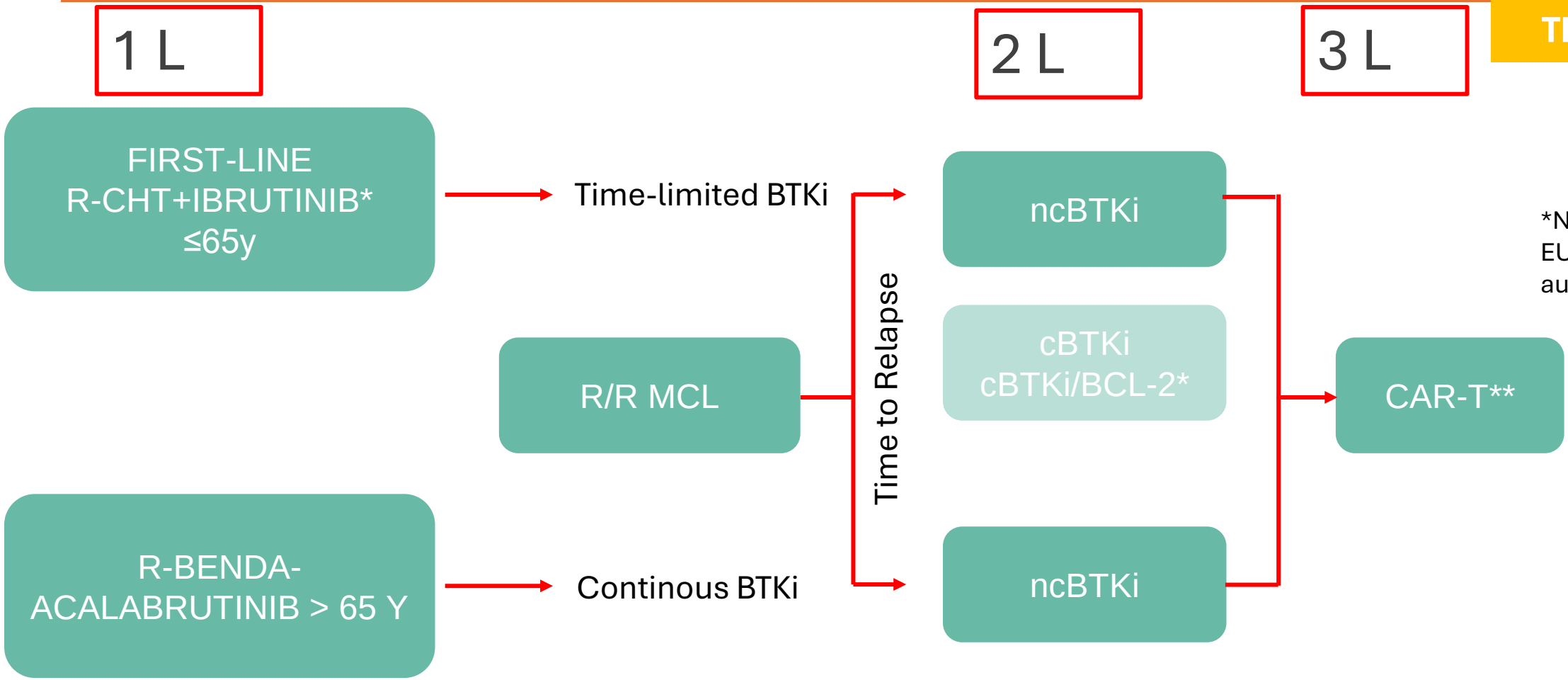
ECHO





R/R MCL: 1L current treatment scenario

SECOND & THIRD LINE



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** consider allo-SCT consolidation if young, high risk

* Second generation BTKi in Ibrutinib intolerant?

CONCLUSIONS