MCL 1L: eleggibilità a terapia intensificata

Carlo Visco

Verona

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie	X				X	X	
Kite-Gilead					X	X	
Janssen	X		X		X	X	
Gentili					X	X	
Novartis						X	
Pfizer			X		X	X	
Roche					X	X	
Incyte					X	X	
Servier					X		
Astra Zeneca					X		
BMS						X	
Kyowa Kirin					X		
Beigene					X		
Lilly			X		X	X	

NCCN Guidelines Version 2.2025
Mantle Cell Lymphoma

Less Aggressive Induction Therapy

Preferred regimens

- Acalabrutinib[f,g] (continuous) + bendamustine + rituximab
- Bendamustine + rituximab[d]
- VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone)
- RCHOP[e]
- Lenalidomide (continuous) + rituximab

Other recommended regimen

- Acalabrutinib[f,g] (continuous) + rituximab

Aggressive Induction Therapy

Preferred regimens (in alphabetical order)

- LyMA regimen: RDHA (rituximab, dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) x 4 cycles followed by RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) for non-PET CR
- NORDIC regimen: Dose-intensified induction immunochemotherapy with rituximab + cyclophosphamide, vincristine, doxorubicin, prednisone (maxi-CHOP) alternating with rituximab + high-dose cytarabine
- Rituximab, bendamustine[h] followed by rituximab, high-dose cytarabine
- TRIANGLE regimen (fixed duration): Alternating RCHOP + covalent BTKi[f]/RDHA (rituximab, dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) (category 2A for ibrutinib; category 2B for acalabrutinib or zanubrutinib)

Other recommended regimen

- HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab[i] (NOTE: There are conflicting data regarding the need for consolidation with HDT/ASCR)
- RBAC500 (rituximab, bendamustine,[h] cytarabine)

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Aggressive Induction Therapy

Preferred regimens

- LyMA regimen: RD
  + platinum (carbop
  followed by RCHO
  vincristine, prednis
- NORDIC regimen:
  immunochemother
  vincristine, doxorul
  rituximab + high-dc
- Rituximab, bendan
  cytarabine
- TRIANGLE regime
  covalent BTKi[i]/RD
  + platinum (carboplatin, cisplatin, or oxaliplatin) (category 2A for ibrutinib; category 2B for acalabrutinib or zanubrutinib)

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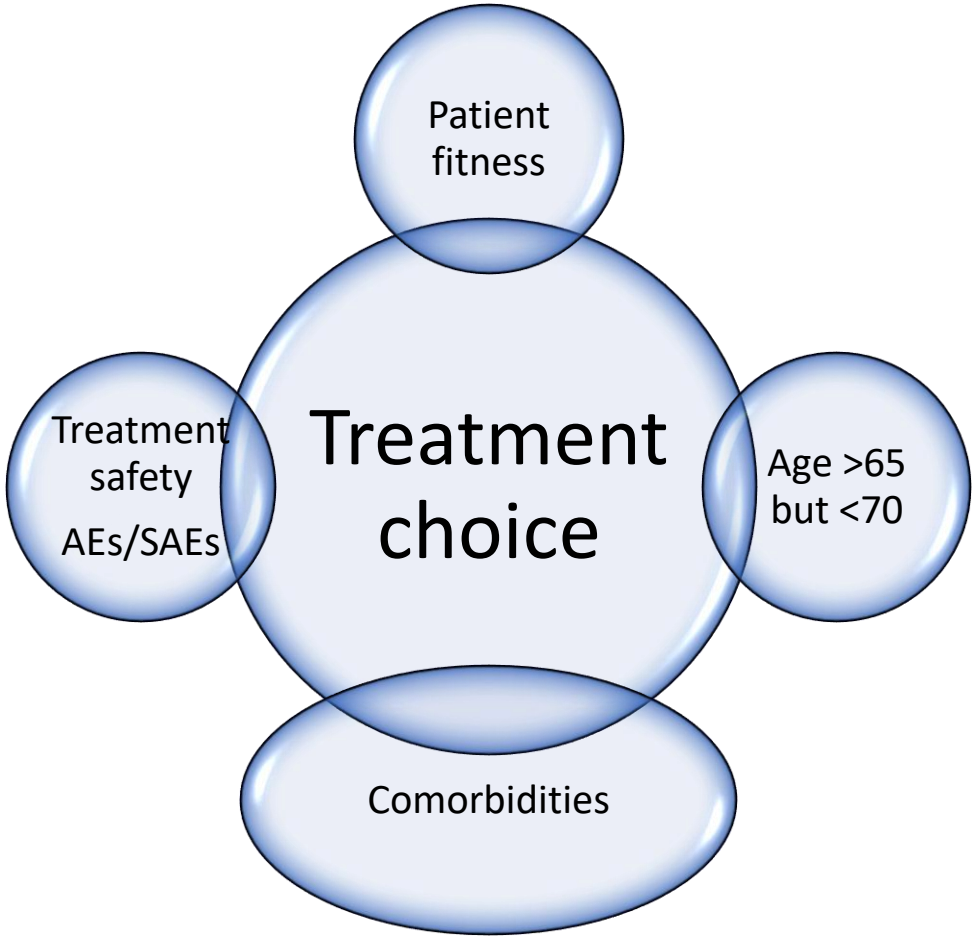
648 for Triangle ongoing

EC decision has been released by EMA for ECHO («transplant ineligible») and *second line Acala approval*

EAP active in Italy for Acala-BR upfront

Fitness and biology balance: How to deal with patients between Triangle and ECHO?



TRIANGLE: Inclusion criteria

- MCL patients
- previously untreated
- stage II-IV
- younger than 66 years
- suitable for HA and ASCT
- ECOG 0-2

Dreyling et al, 2024

TRIANGLE: Demographics and baseline characteristics

	Group A (N=288)	Group A+I (N=292)	Group I (N=290)
Age (years)*	57 (52–61)	57 (52–61)	57·5 (52– 61)
Sex			
Male	218 (76%)	216 (74%)	228 (79%)
Female	70 (24%)	76 (26%)	62 (21%)
Race			
White	283 (98%)	283 (97%)	290 (100%)
Other	5 (2%)	9 (3%)	0 (0%)
Histology*			
Mantle cell lymphoma	286 (99%)	288 (99%)	288 (99%)
Ann Arbor stage			
I	0	0	0
II	11/285 (4%)	12/290 (4%)	18/289 (6%)
III	24/285 (8%)	21/290 (7%)	29/289 (10%)
IV	250/285 (88%)	257/290 (89%)	242/289 (84%)
B-symptoms	72/285 (25%)	78/290 (27%)	87/285 (31%)
Eastern Cooperative Oncology Group performance status			
0	213 (74%)	213 (73%)	208 (72%)
1	70 (24%)	77 (26%)	77 (27%)
2	5 (2%)	2 (1%)	5 (2%)
LDH/ULN	0·94 (0·78–1·20)	0·94 (0·77–1·18)	0·87 (0·74–1·12)
LDH>ULN	123 (43%)	120 (41%)	105 (36%)
Leukocytes (white blood cells, G/L)	7·34 (5·50–10·91)	7·09 (5·28–11·11)	7·4 (5·77–11·92)
MIPI score	5·62 (5·40–5·91)	5·64 (5·35–5·95)	5·61 (5·39–5·92)
Low	168 (58%)	168 (58%)	168 (58%)
Intermediate	79 (27%)	80 (27%)	77 (27%)
High	41 (14%)	44 (15%)	45 (16%)
Ki-67 index (%)	18 (n=249) (10–38)	18 (n=262) (12–40)	18·5 (n=259) (10–35)
Ki-67 index ≥30%	81/249 (33%)	81/262 (31%)	82/259 (32%)
Cytology blastoid	28/253 (11%)	34/261 (13%)	31/265 (12%)
P53 expression >50%	21/183 (11%)	25/175 (14%)	31/189 (16%)
High-risk biology	31/185 (17%)	37/179 (21%)	44/192 (23%)

Mainly driven by younger age, the trial population was generally of lower risk as reflected by **only 15% of patients** being **clinically high-risk according to MIPI**

Dreyling et al, Lancet 2024

Dreyling et al, 2024

ECHO: Demographics and Baseline Characteristics

	Acalabrutinib + BR (n=299)	Placebo + BR (n=299)
Age, median (range), y	71 (65–85)	71 (65–86)
≥75 y, n (%)	84 (28.1)	77 (25.8)
Male, n (%)	214 (71.6)	209 (69.9)
ECOG PS, n (%)		
1	129 (43.1)	132 (44.1)
2	12 (4.0)	23 (7.7)
Tumor bulk ≥5 cm, n (%)	112 (37.5)	113 (37.8)
Blastoid/pleomorphic histology, n (%)	41 (13.7)	38 (12.7)
Simplified MIPI score, n (%)		
Low risk	99 (33.1)	101 (33.8)
Intermediate risk	128 (42.8)	125 (41.8)
High risk	72 (24.1)	73 (24.4)
Extranodal disease, n (%)	264 (88.3)	277 (92.6)
TP53 status, n (%)[a]		
Mutated	22 (7.4)	29 (9.7)
Unmutated	97 (32.4)	83 (27.8)
Ki-67, n (%)		
<30%	133 (44.5)	126 (42.1)
≥30%	139 (46.5)	147 (49.2)

Wang et al. 2025

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Wang et al. 2025

ECHO: demographics characteristics

- One third of patients ≥ 75 years
- 41.1% of patients between 65 and 70 years
- Maximum age: 85 years

TABLE 1. Demographics and Baseline Characteristics

Characteristic	Acalabrutinib + Bendamustine-Rituximab (n = 299)	Placebo + Bendamustine-Rituximab (n = 299)
Age, years, median (range)	71 (65-85)	71 (65-86)
≥70, No. (%)	176 (58.9)	182 (60.9)
≥75, No. (%)	84 (28.1)	77 (25.8)

Age range	Number of patients	Percentage of total patients
65–69 years	123	41.1%
≥70 years	176	58.9%
Total	299	100%

Wang et al. 2025

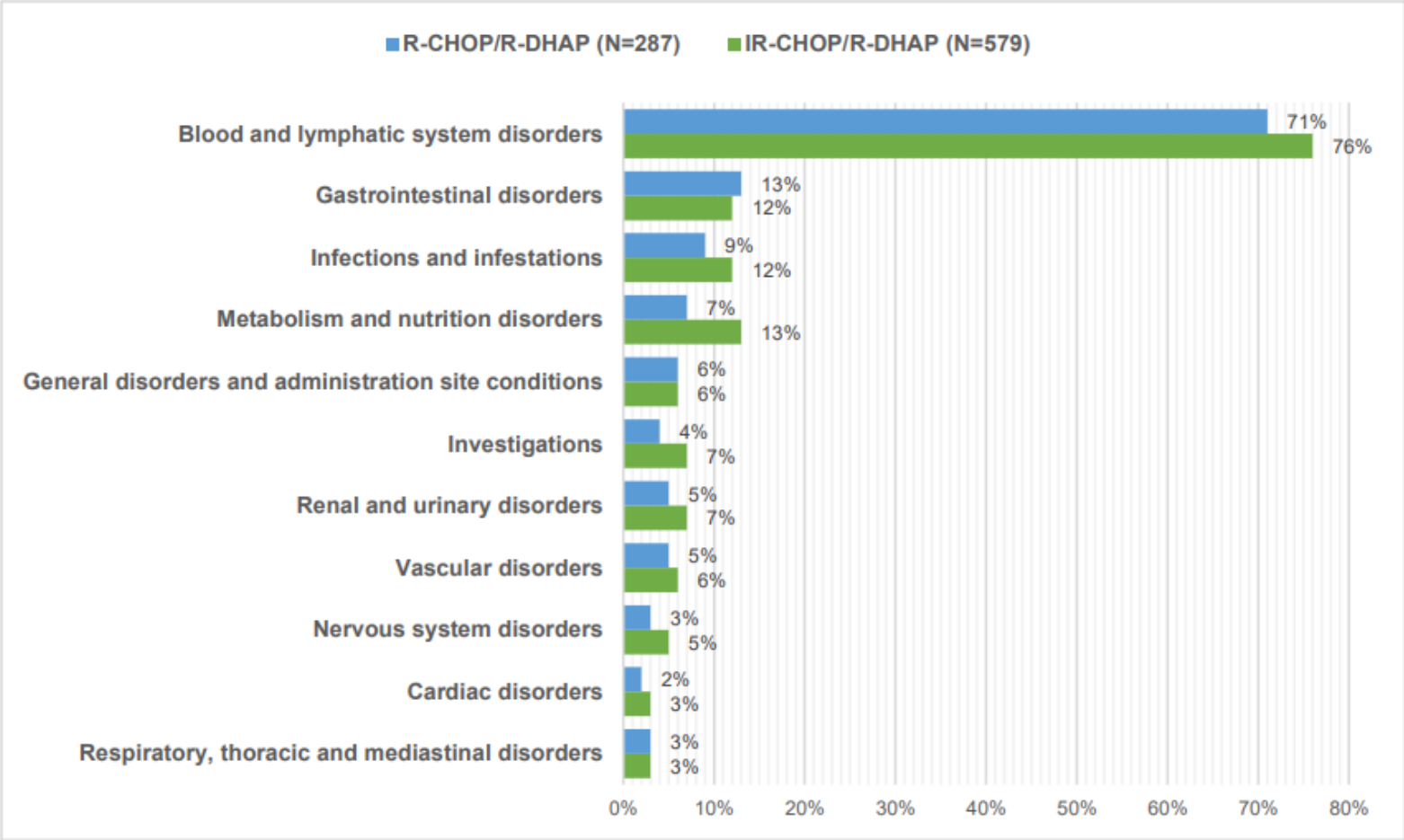
High risk patients in ECHO

Characteristic, % [n]	Acalabrutinib + BR (n = 299)	Placebo + BR (n = 299)	Total (N = 598)
High-risk MIPI (6–11)	24.1 [72]	24.4 [73]	24.2 [145]
Ki-67 ≥30%	46.5 [139]	49.2 [147]	47.8 [286]
Ki-67 ≥50%	20.7 [62]	24.7 [74]	22.7 [136]
Blastoid/pleomorphic histology	13.7 [41]	12.7 [38]	13.2 [79]
TP53 mutation	7.4 [22]	9.7 [29]	8.5 [51]
TP53 status missing	60.2 [180]	62.5 [187]	61.4 [367]
Total high-risk	**62.5 [187]**	**61.2 [183]**	**61.9 [370]**

Wang et al. 2025

TRIANGLE safety data:

During induction treatment



Dreyling, ASH 2024

ECHO safety data: AEs of interest

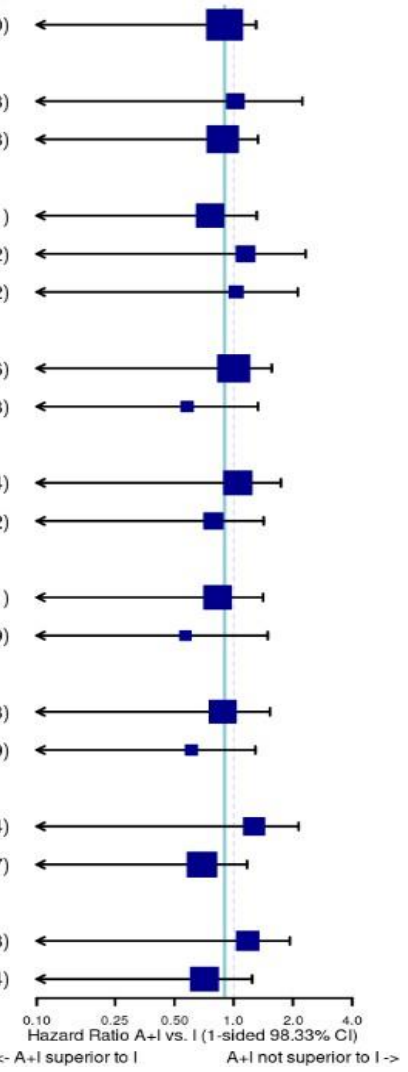
	Acalabrutinib + BR (n=297)		Placebo + BR (n=297)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Event, n (%)				
Atrial fibrillation	18 (6.1)	11 (3.7)	13 (4.4)	5 (1.7)
Hypertension	36 (12.1)	16 (5.4)	47 (15.8)	25 (8.4)
Major bleeding[a]	7 (2.4)	6 (2.0)	16 (5.4)	10 (3.4)
Infections[b]	232 (78.1)	122 (41.1)	211 (71.0)	101 (34.0)
Second primary malignancies (excluding non-melanoma skin)[b]	29 (9.8)	16 (5.4)	32 (10.8)	20 (6.7)
Median treatment exposure (range), months	29 (0.1, 80.1)		25 (0.03, 76.4)	

The safety profile of acalabrutinib + BR is consistent with that of the individual drugs; the updated safety findings at ASH 2025 further support the favorable benefit–risk profile of acalabrutinib in TN MCL

Wang et al. 2025

TRIANGLE: forest plot of failure-free survival data

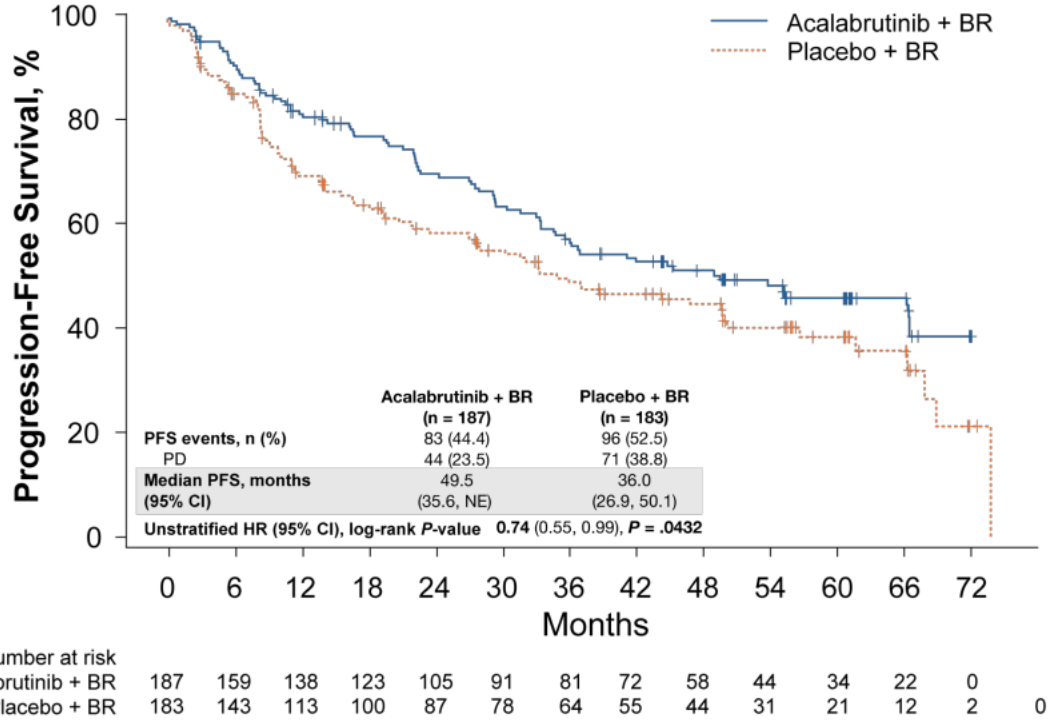
Subgroup (interaction p-value)	No. of patients	No. of events	Hazard ratio (1-sided 98.33% CI)
All	582	134	0.90 (0 - 1.30)
Sex (p=0.71)			
Female	138	30	1.02 (0 - 2.23)
Male	444	104	0.88 (0 - 1.33)
MIPI			
Low	336	62	0.76 (0 - 1.31)
Intermediate (p=0.33)	157	37	1.15 (0 - 2.32)
High (p=0.56)	89	35	1.03 (0 - 2.12)
Cytology (p=0.15)			
Non-blastoid	461	92	1.00 (0 - 1.56)
Blastoid	65	27	0.58 (0 - 1.33)
Ki-67 (p=0.41)			
Low	357	71	1.05 (0 - 1.74)
High	164	54	0.79 (0 - 1.42)
P53 expression (p=0.43)			
Low	342	67	0.83 (0 - 1.41)
High	59	21	0.57 (0 - 1.49)
High risk biology (p=0.33)			
Low	323	60	0.88 (0 - 1.53)
High	64	34	0.61 (0 - 1.29)
R maintenance ITT (p=0.081)			
No	196	66	1.27 (0 - 2.14)
Yes	386	68	0.69 (0 - 1.17)
R maintenance mAT (p=0.14)			
No	228	76	1.18 (0 - 1.93)
Yes	354	58	0.71 (0 - 1.24)



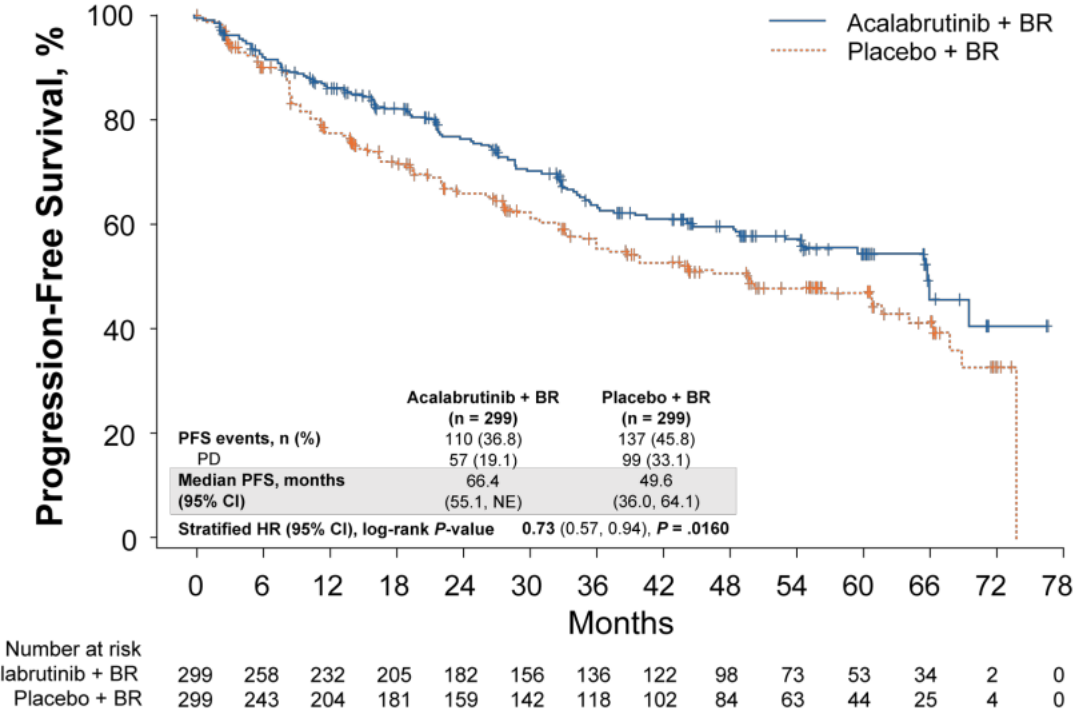
Dreyling, ASH 2024

ECHO: PFS data in the overall and HR population

PFS in High-risk Population



PFS in Full Analysis Population[1]



- **mPFS was 72.5 and 47.8 mo in the ABR and PBR arms**, respectively (HR 0.68; 95% CI 0.53–0.87; P=0.002). In total, 108 (36.1%) and 116 (38.8%) pts in each arm died
- **mOS was NR in both arms** (HR 0.87; 95% CI 0.67–1.13), with a 36-mo OS rate of 73.8% with ABR vs 68.3% with PBR.

Treatment drivers in high risk patients

Treatment drivers in high risk patients

- ASCT seems beneficial in HR patients if we use the **TRIANGLE**
- **ECHO** seems beneficial (and better tolerated that ASCT containing regimen) in HR patients

TRIANGLE preference: younger patients with very high-risk disease (i.e. *TP53* mutation and blastoid), in order to avoid bendamustine

How to deal with borderline patients (i.e. 60-70) between Triangle and ECHO?*

- **ECHO but not TRIANGLE**: - ineligible to anthracyclines
  - recent ablation for multiple AF relapses
  - cardiac comorbidities
  - not willing for alopecia
  - uncontrolled or severe hypertension
  - neuropathies or contraindications to platinum
  - high risk but no ASCT

*but we will see the approval of ECHO….age or fitness?

Thanks for your attention

FONDAZIONE ITALIANA LINFOMI

UNIVERSITÀ di VERONA

Unmet needs: patients who will still be BTKi naive

- **Exclusion criteria of TRIANGLE and ECHO:**
- Warfarin
- eGFR<50
- PLT < 75000/mmc
- vWd or emophilia
- stroke or intracranial hemorrage, gastric ulcer
- strong cytochrome p450 inducers

But also:

Doublet antiaggregation

Very elderly and unfit patients (ECHO maximum age 85y)

In low-risk patients with contraindications to cBTKis: RBAC