Comprehensive Cancer Center
Tübingen-Stuttgart

Post ASH 2023 San Diego

Maligne Lymphome / CLL

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Klassisches Hodgkin-Lymphom

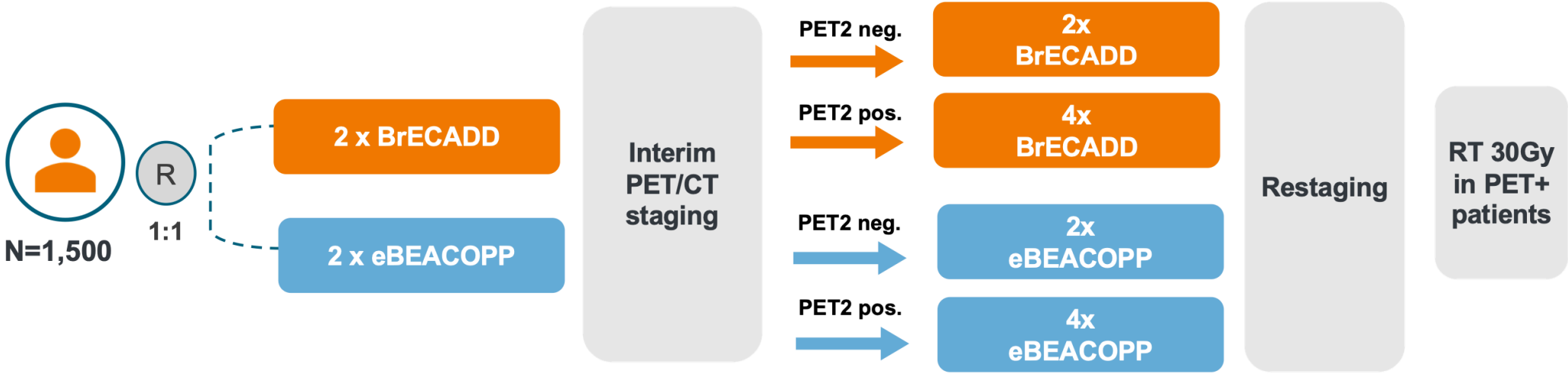
#3057
Comprehensive Analysis of TRM and PFS in the GHSG Phase III HD21 trial

BrECADD

Brentuximab

Etoposid
Cyclophosphamid
Doxorubicin
Dacarbacin
Dexamethason

~~**Bleomycin**~~
~~**Vincristin**~~
~~**Procarbacin**~~
~~**Prednisolon**~~



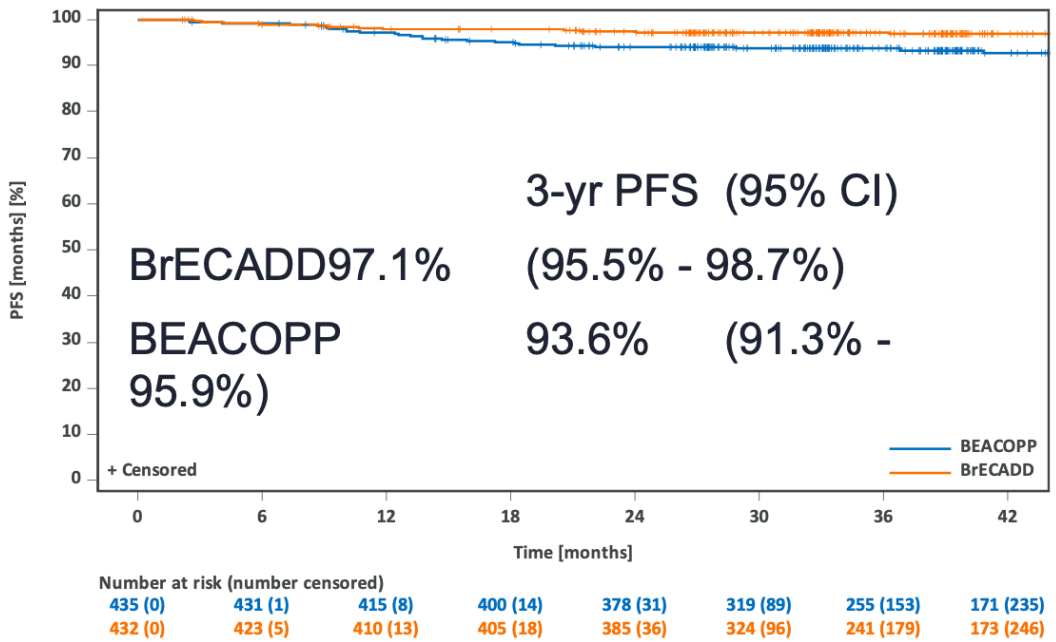
Co-primary objectives achieved:

1. Reduced treatment-related morbidity (TRMB) with BrECADD highly significant.
2. Non-inferiority of 4-6 x BrECADD in terms of PFS already at interim analysis shown

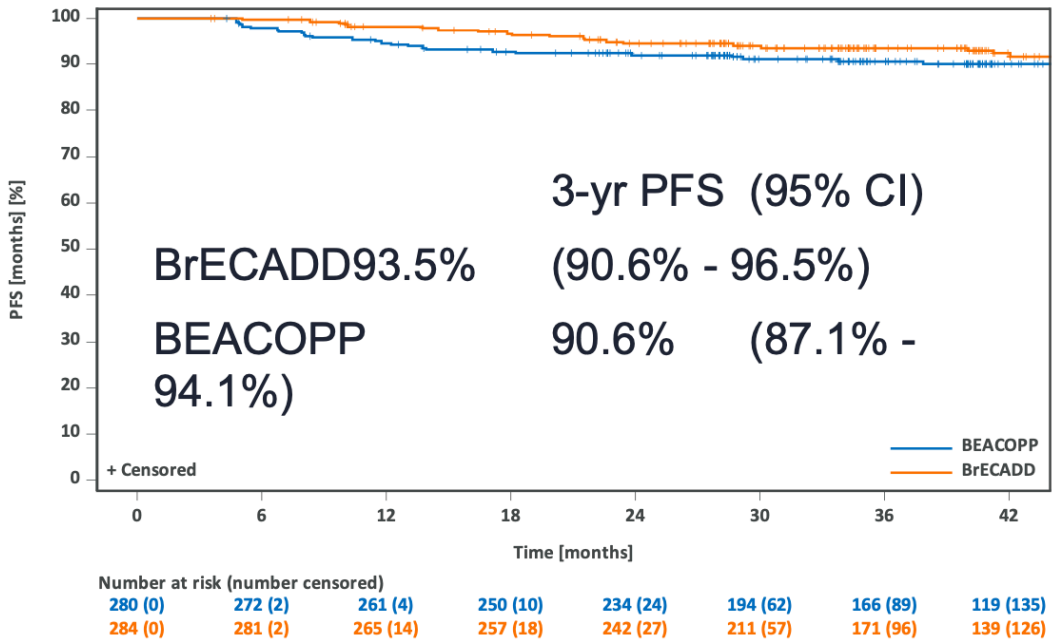
#3057

HD21: 3y progression-free survival and PET2-status by treatment arm

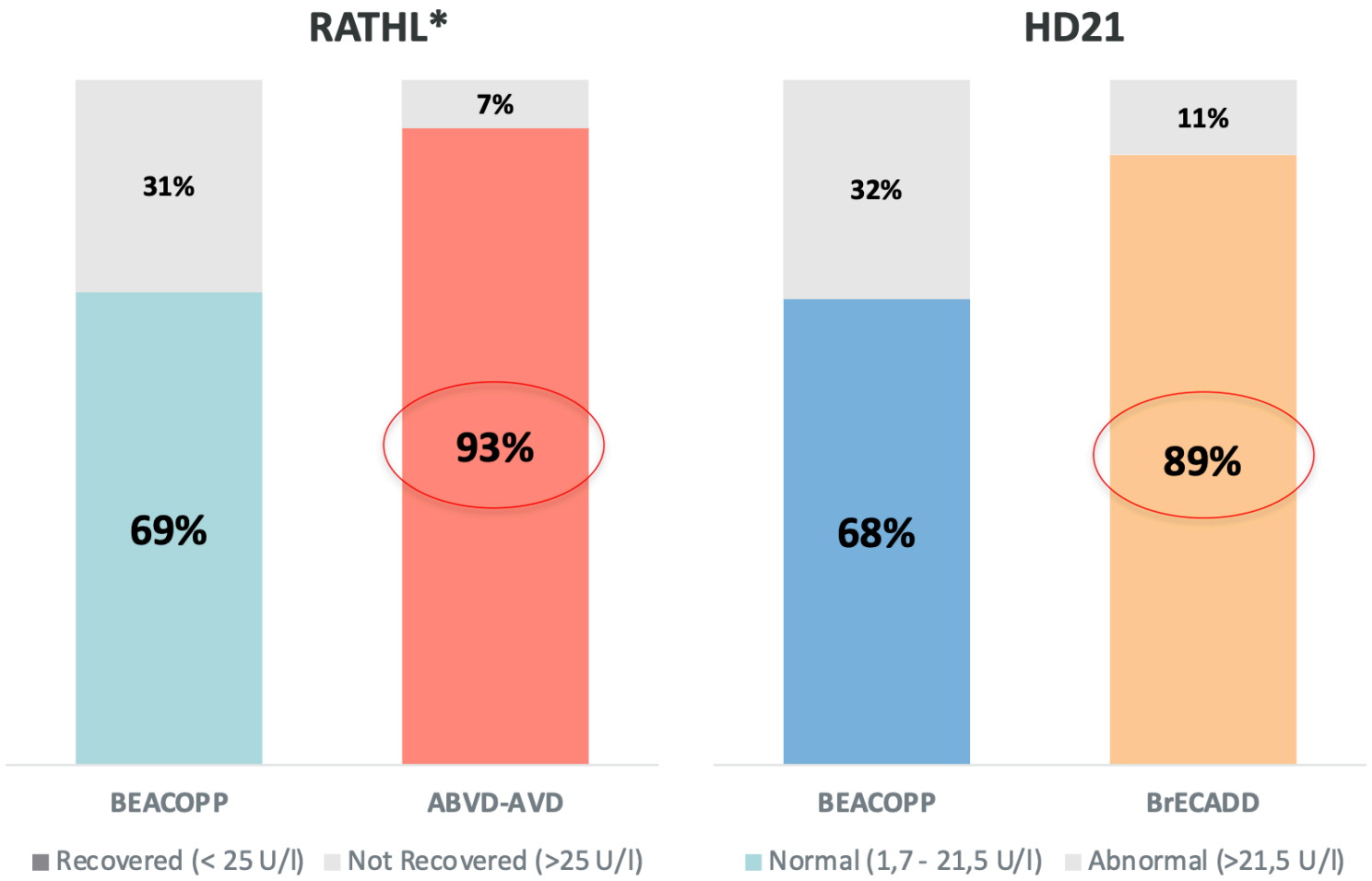
PET2-negative (4 cycles)

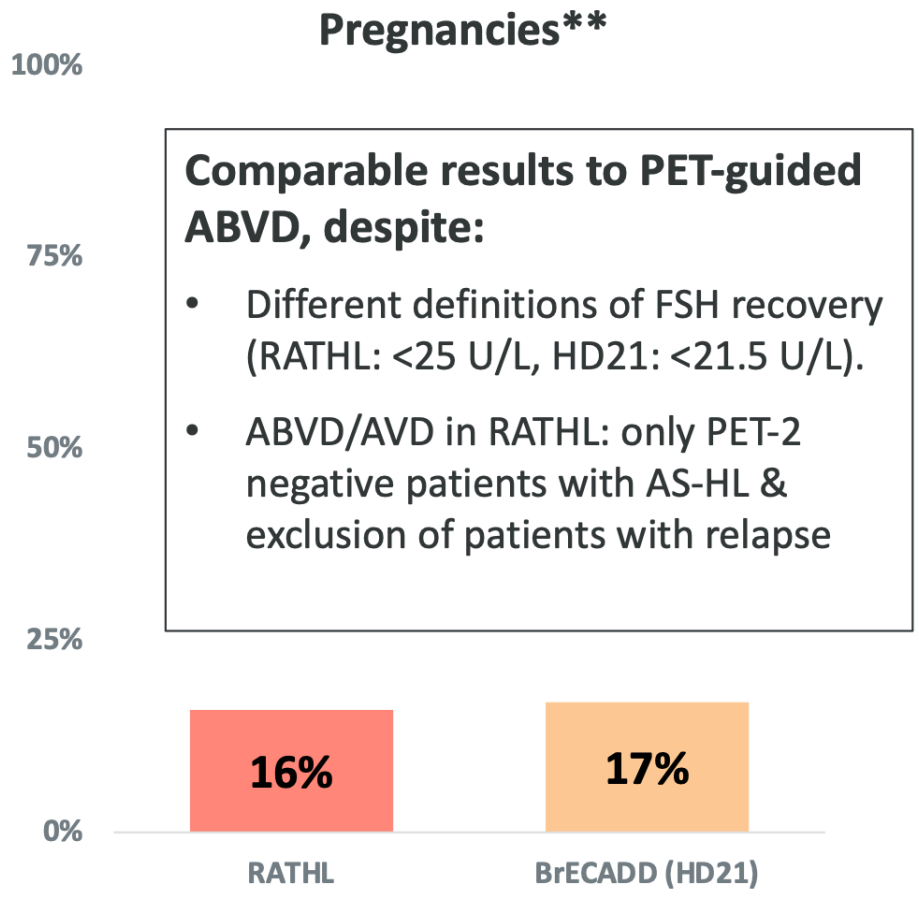


PET2-positive (6 cycles)



#4437: Pregnancies and Childbirth Following Advanced-Stage HL Treatment with BrECADD or BEACOPP in the Randomized Phase III GHSG HD21 Trial

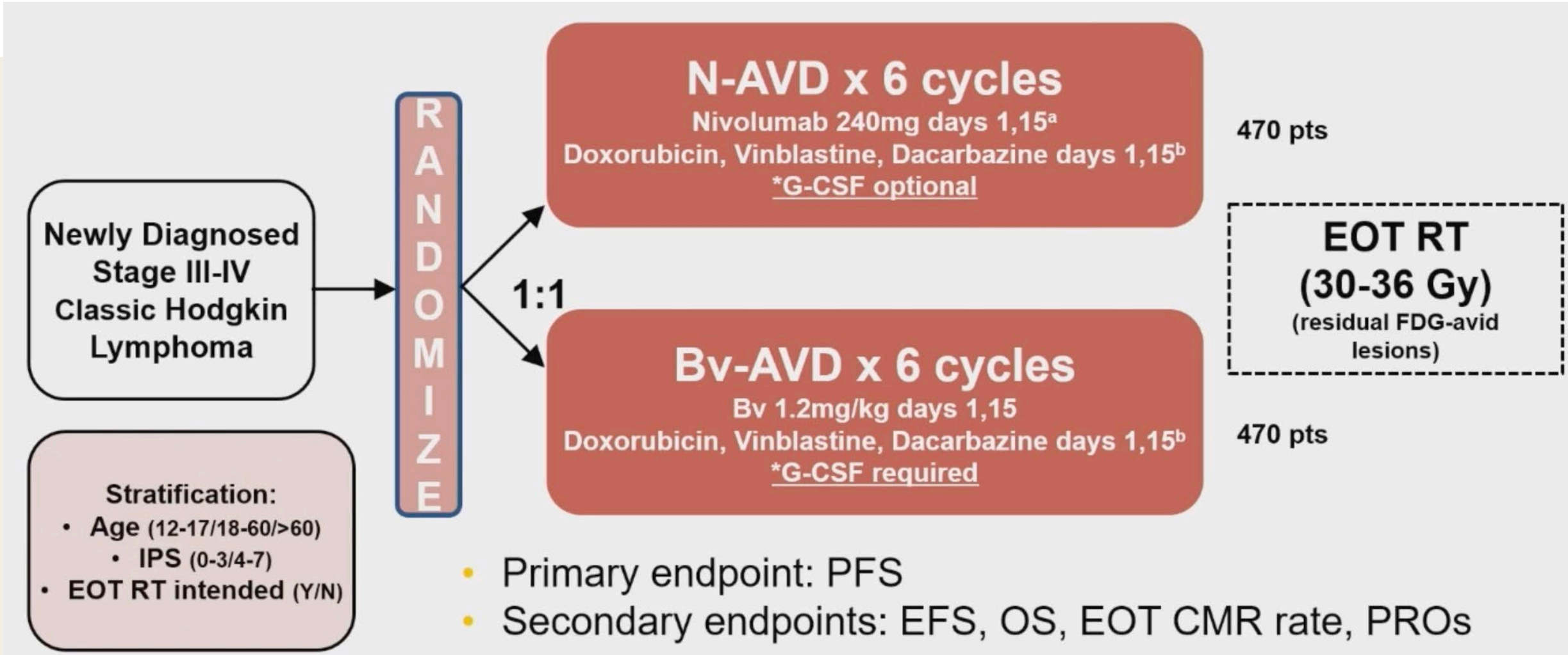




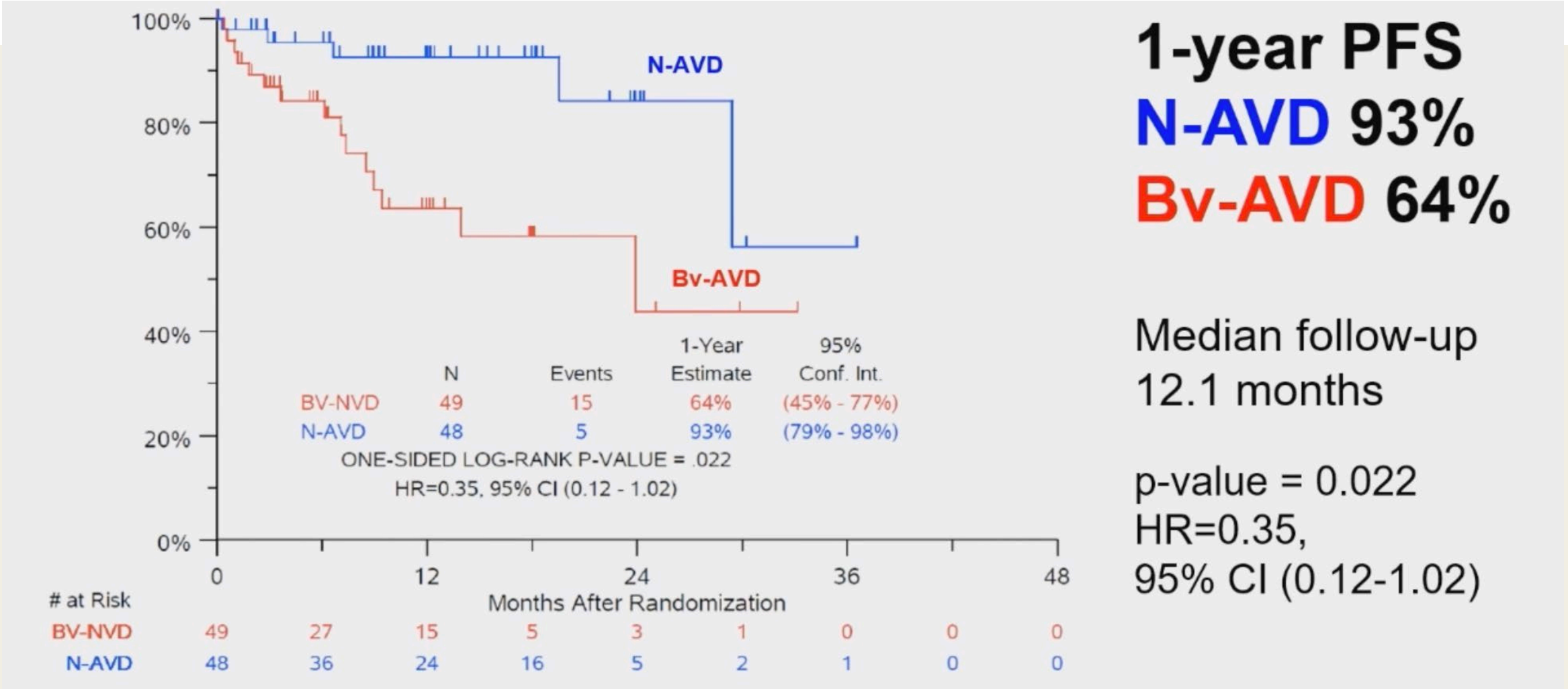
Comparable results to PET-guided ABVD, despite:

- Different definitions of FSH recovery (RATHL: <25 U/L, HD21: <21.5 U/L).
- ABVD/AVD in RATHL: only PET-2 negative patients with AS-HL & exclusion of patients with relapse

#181: Nivolumab-AVD versus Bv-AVD in Older Patients (Aged > 60 Years) with Advanced Stage Hodgkin Lymphoma - SWOG S1826.



#181: Nivolumab-AVD versus Bv-AVD in Older Patients (Aged > 60 Years) with Advanced Stage Hodgkin Lymphoma - SWOG S1826.



1-year PFS

N-AVD 93%

Bv-AVD 64%

Median follow-up
12.1 months

p-value = 0.022
HR=0.35,
95% CI (0.12-1.02)

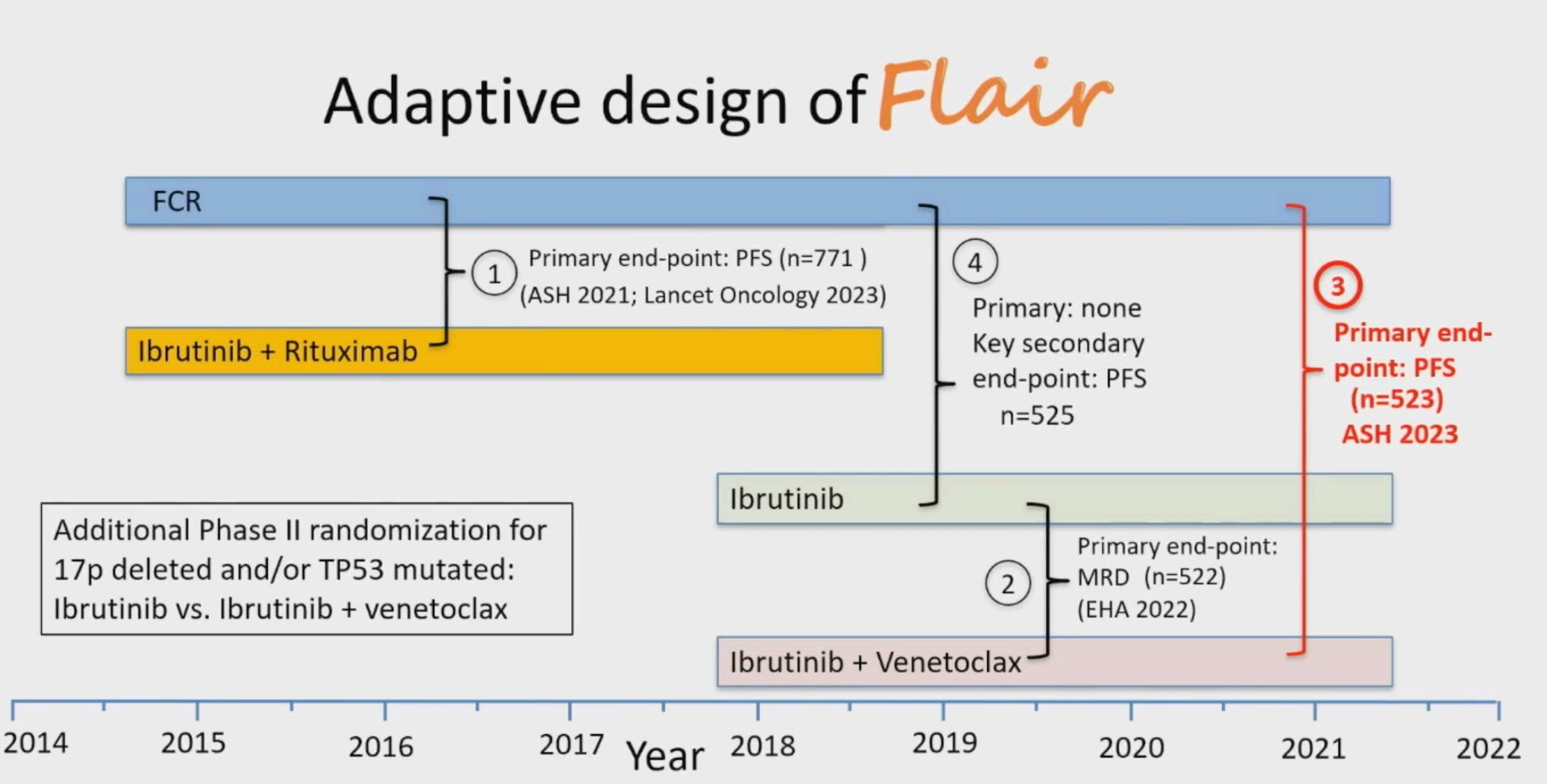
#181: Nivolumab-AVD versus Bv-AVD in Older Patients (Aged > 60 Years) with Advanced Stage Hodgkin Lymphoma - SWOG S1826.

Cause of death	N-AVD	Bv-AVD
Infection	1	3
Sepsis	1	2*
Pneumonitis	0	1
Unknown	0	1
Total OS events	**2**	**7**

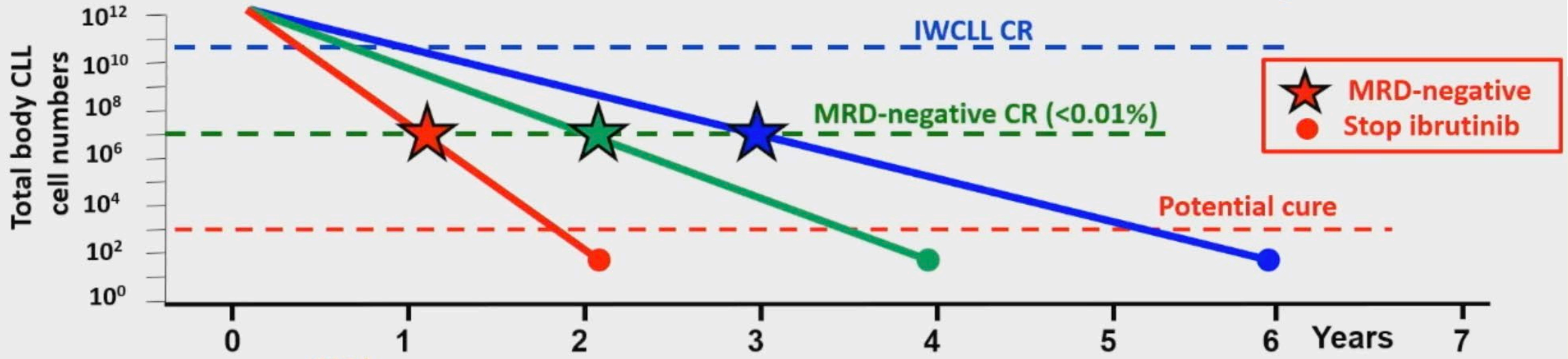
Non-relapse mortality
N-AVD 4% vs Bv-AVD 14%

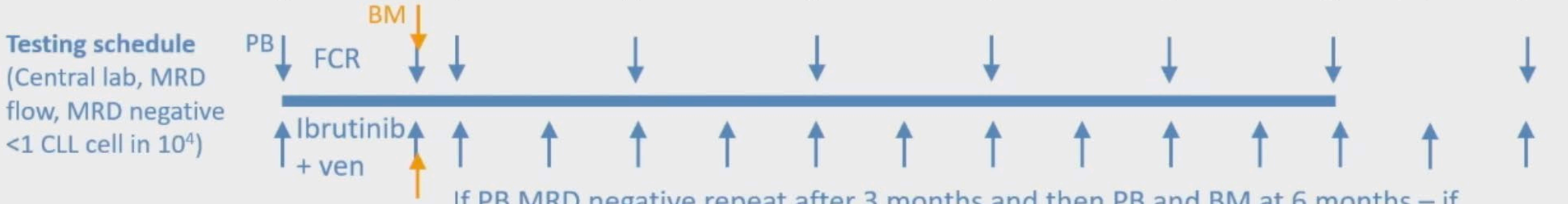
Chronische lymphatische Leukämie

#631: Ibrutinib Plus Venetoclax with MRD-Directed Duration of Treatment Is Superior to FCR and Is a New Standard of Care for Previously Untreated CLL: Report of the Phase III UK NCRI FLAIR Study



Stopping rules for ibrutinib + venetoclax in Flair





If PB MRD negative repeat after 3 months and then PB and BM at 6 months – if all MRD negative then first PB MRD negative result is time to MRD negativity

Defining treatment duration
2 to 6 years Ibrutinib or both ibr+venetoclax
Double time after MRD negative

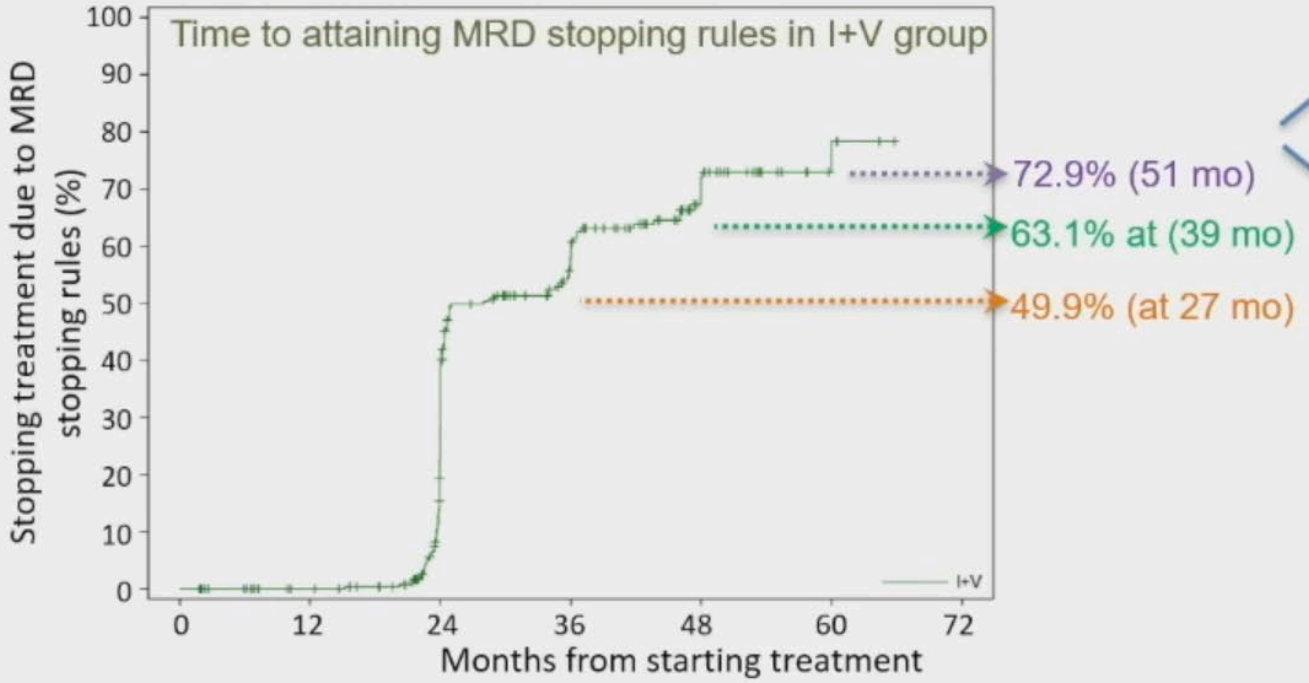
Restart ibrutinib + venetoclax if becomes MRD positive prior to Year 6

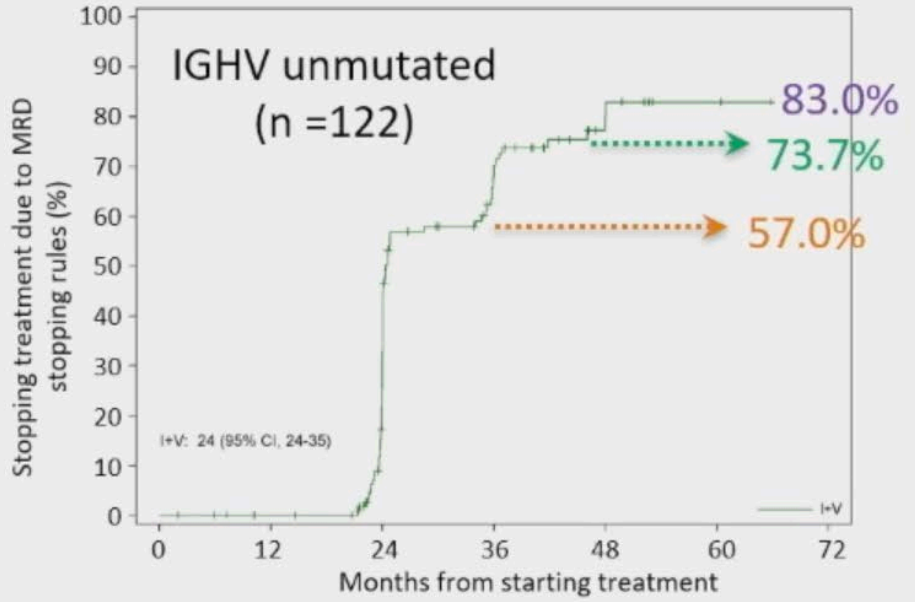
Flair

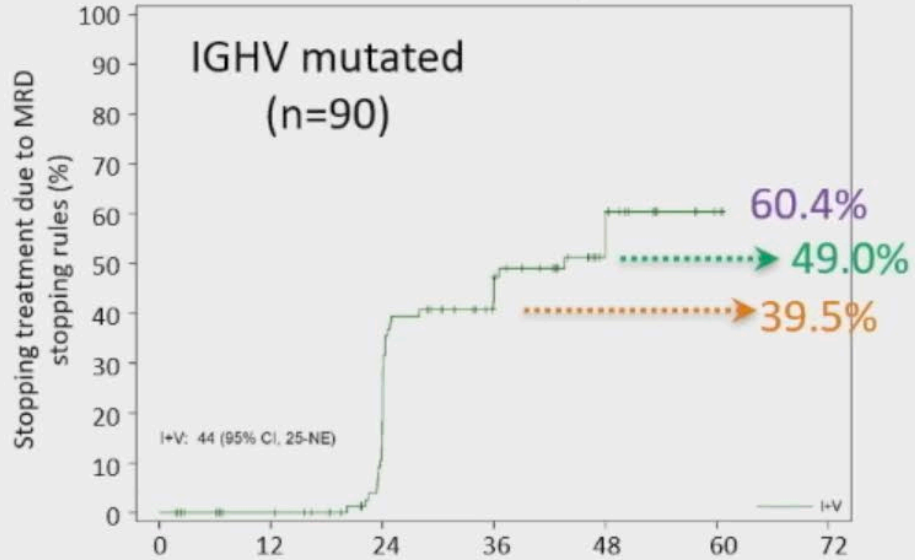
iwCLL response and MRD stopping rules

iwCLL Responses

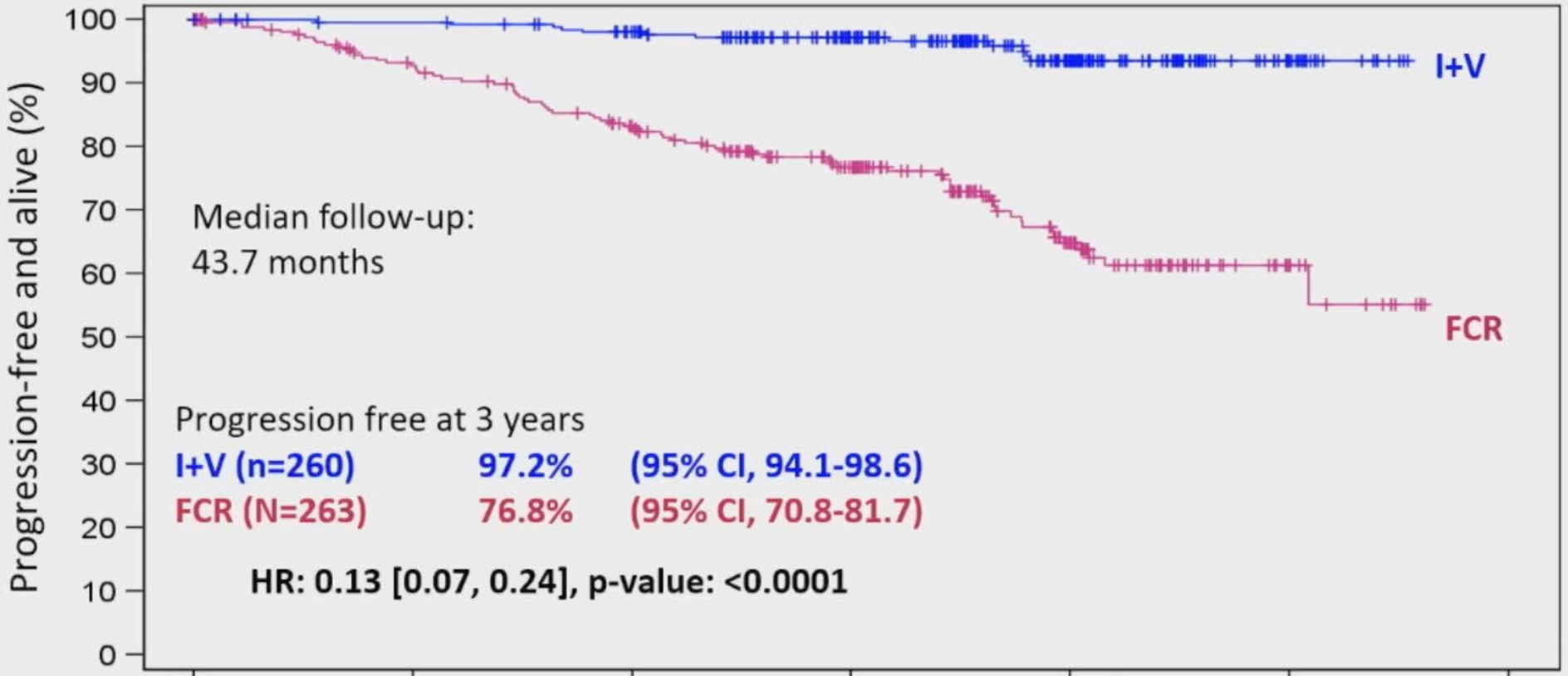
	Complete Response/CRi		Overall Response		BM uMRD
	9 months	Anytime	9 months	Anytime	Anytime
FCR	49%	71.5%	76.4%	83.7%	40.3%
I+V	59.2%	92.3%	86.5%	95.4%	61.9%
	Odds ratio: 1.51 P<0.05		Odds ratio: 2.0 P<0.005		







Flair Primary end-point: PFS for FCR versus I+V



No. at risk						
I+V	260	253	239	183	99	21	0
FCR	263	227	194	145	68	12	0

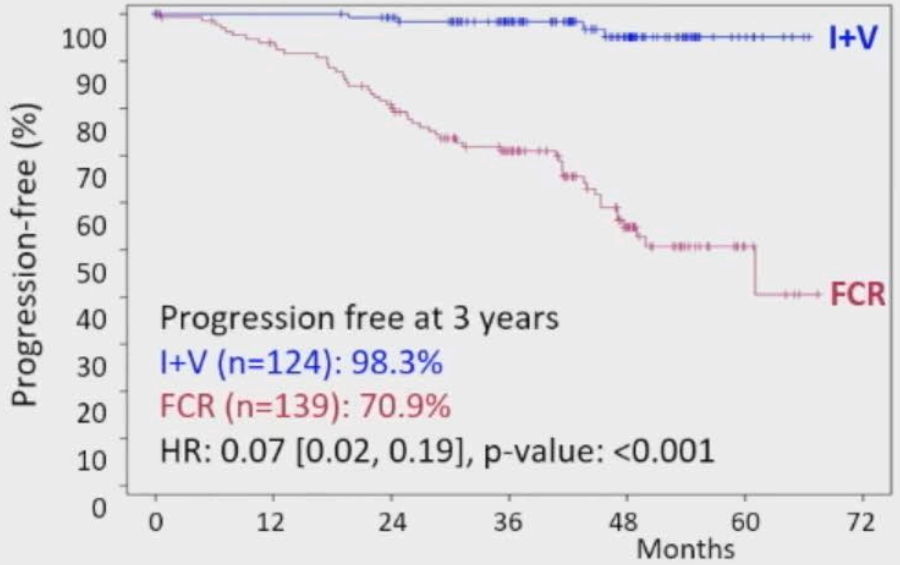
Outcome by IGHV mutation status

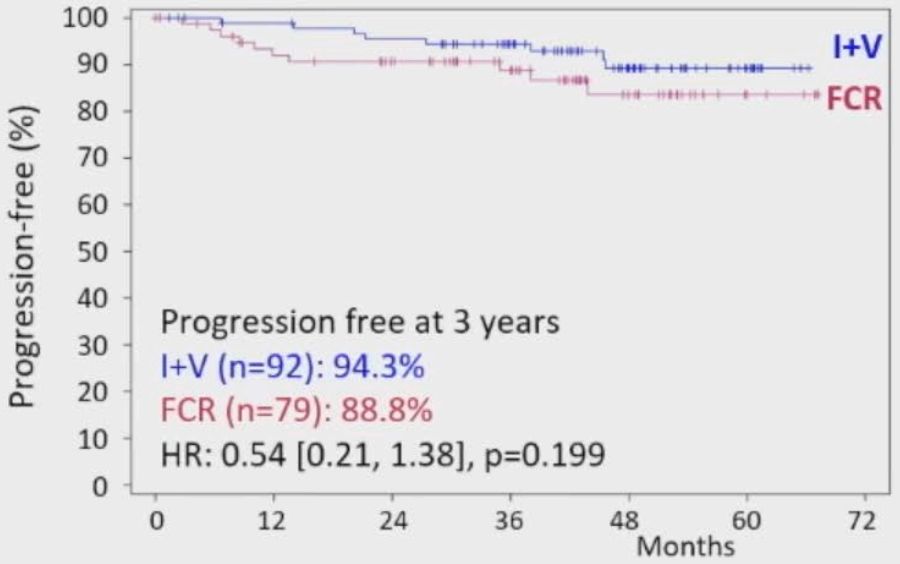
Flair

IGHV unmutated (excl. Subset 2)

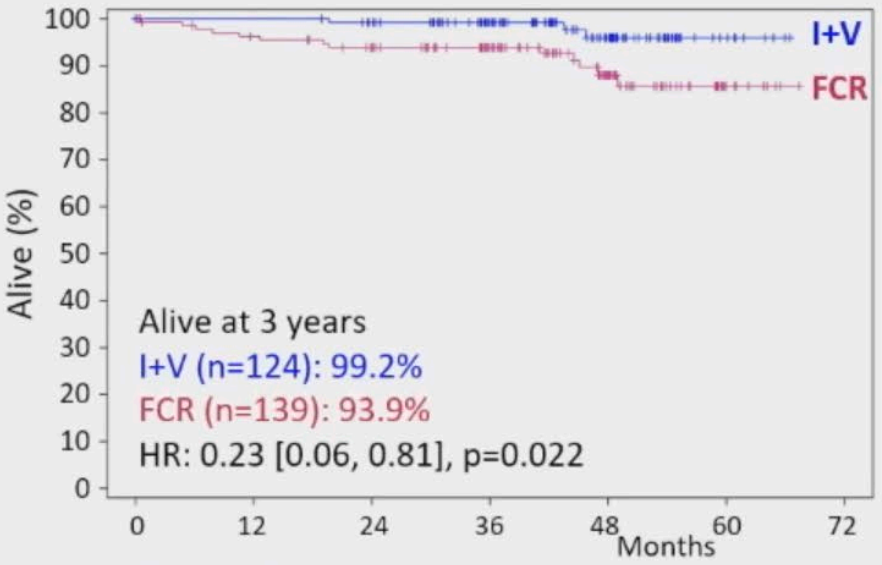
IGHV mutated (excl. Subset 2)

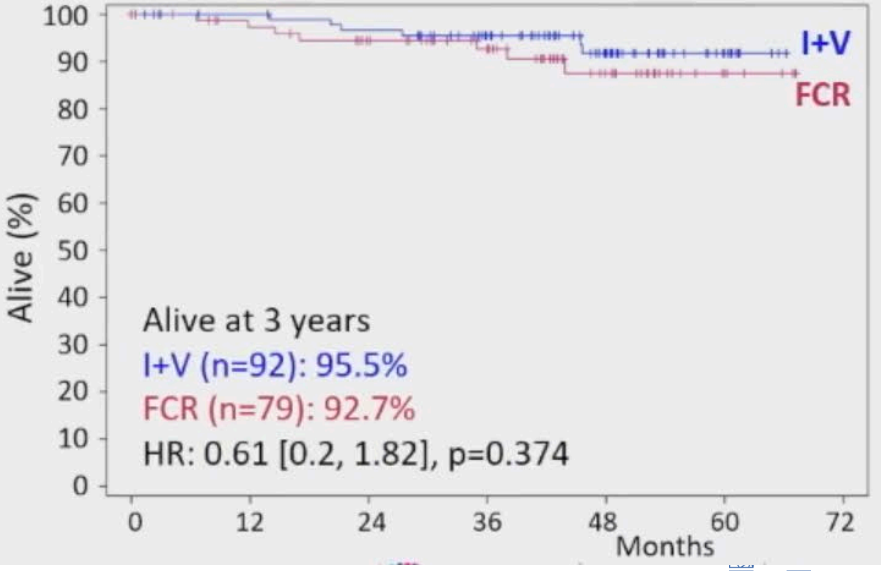
Progression Free Survival





Overall Survival





Flair

Serious Adve

SAEs, by MedDRA System organ clas

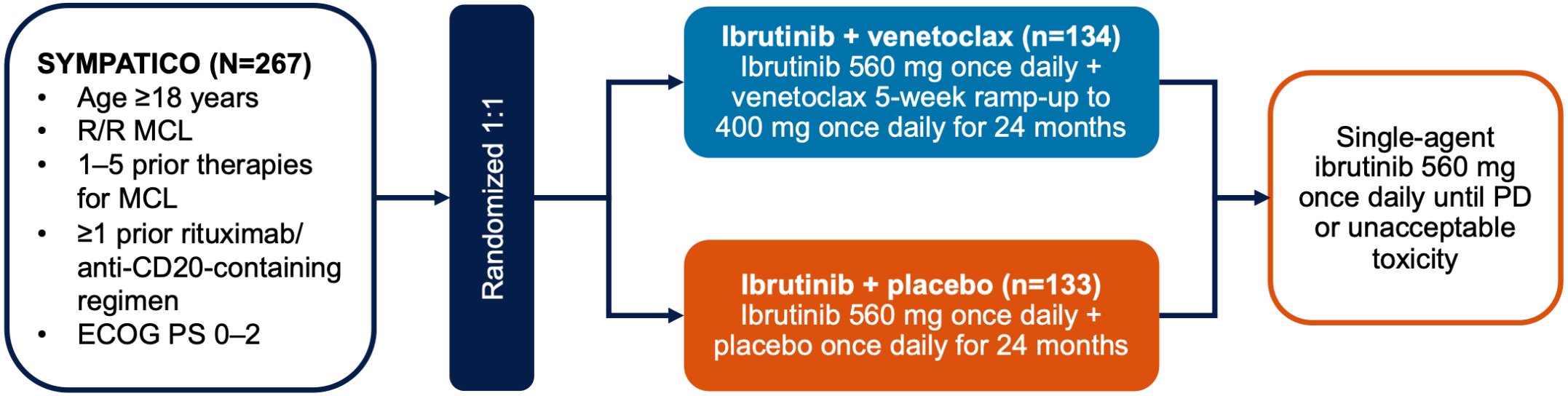
	Number of participants
	FCR (n=239)
Infections and infestations	45 (18.8%)
Blood and lymphatic system disorders	**74 (31%)**
Cardiac disorders	**1 (0.4%)**
Gastrointestinal disorders	19 (7.9%)
General disorders and administration site conditions	**12 (5%)**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	5 (2.1%)
Metabolism and nutrition disorders	**0 (0%)**
Respiratory, thoracic and mediastinal disorders	6 (2.5%)
Musculoskeletal and connective tissue disorders	3 (1.3%)
Skin and subcutaneous tissue disorders	5 (2.1%)
Nervous system disorders	2 (0.8%)
Eye disorders	**0 (0%)**

Todesfälle	FCR	I+V
Infection	7	1
Sudden/Cardiac	2	3
COVID-19	2	2
Richter's transformation	2	1
Non-haem malignancy	2	1
Allogeneic SCT – infection	1	0
Allogeneic SCT – GvHD	1	0
Disease progression	1	0
Hemorrhage	1	0
Lymphoma	1	0
Treatment related MDS/BMF	3	0
Total:	**23**	**8**

Mantelzell-Lymphom

LBA-2 Ibrutinib Combined with Venetoclax in Patients with Relapsed/Refractory Mantle Cell Lymphoma: Primary Analysis Results from the Randomized Phase 3 Sympatico Study

- SYMPATICO (NCT03112174) is multinational, randomized, double-blind, placebo-controlled, phase 3 study



Stratification: ECOG PS, prior lines of therapy, TLS risk[a]

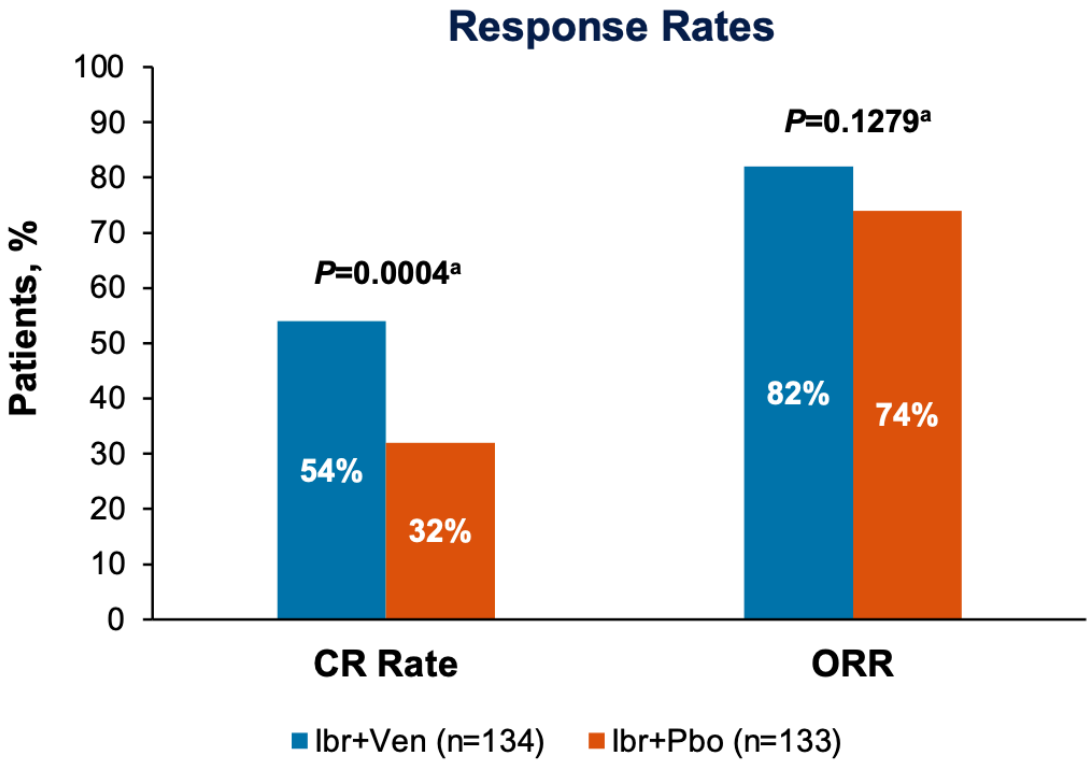
- **Primary endpoint:**
  - PFS by investigator assessment using Lugano criteria
- **Secondary endpoints (tested hierarchically in the following order):**
  - CR rate by investigator assessment
  - TTNT[b]
  - OS (interim analysis)
  - ORR by investigator assessment

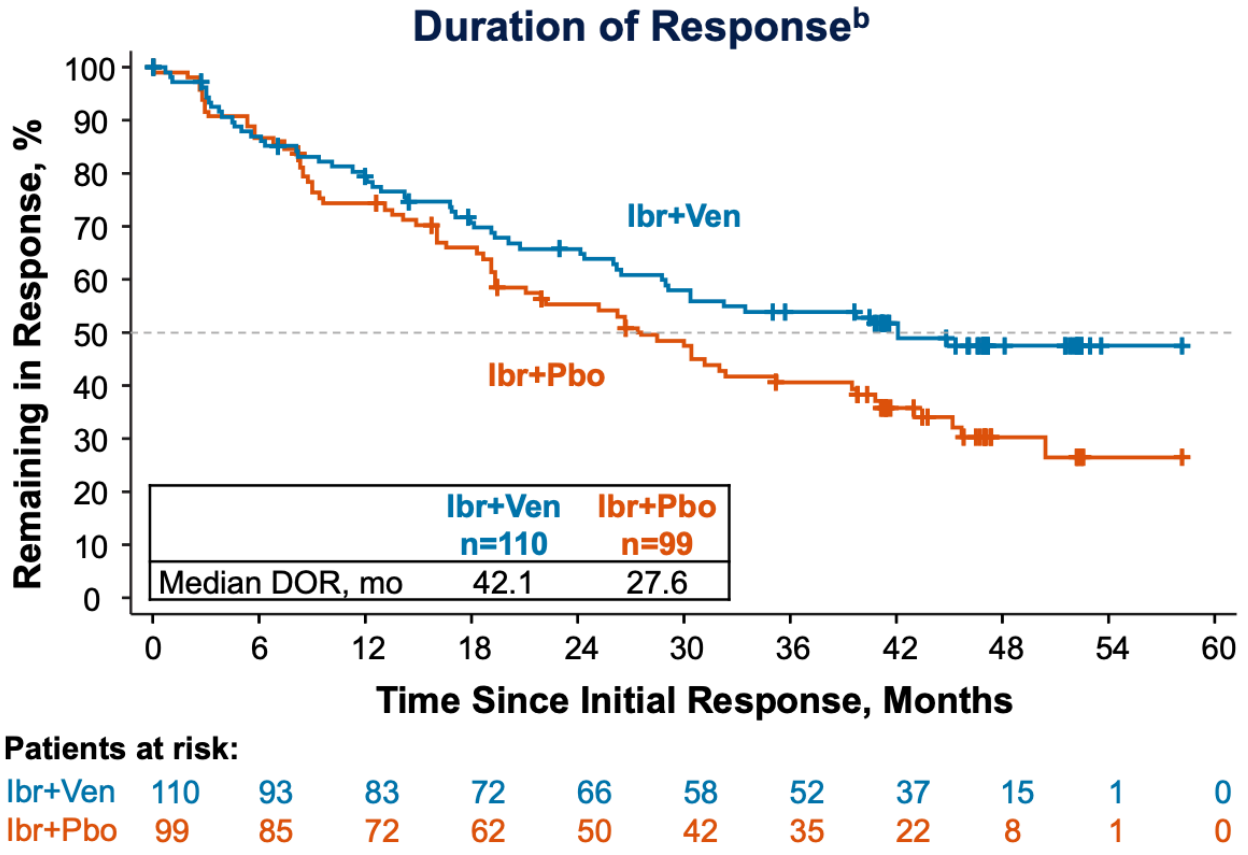
LBA-2 Ibrutinib & Venetoclax in R/R Mantle Cell Lymphoma: Patientencharakteristika

Characteristic	Ibrutinib + venetoclax n=134	Ibrutinib + placebo n=133
Age		
Median (range), years	69 (42–84)	67 (44–88)
≥65 years, n (%)	93 (69)	86 (65)
ECOG PS, n (%)		
0	74 (55)	74 (56)
1–2	60 (45)	59 (44)
Prior lines of treatment, n (%)		
1	80 (60)	79 (59)
2	32 (24)	31 (23)
≥3	22 (16)	23 (17)
MCL histology, n (%)		
Typical	88 (66)	95 (71)
Blastoid	19 (14)	17 (13)
Pleomorphic	8 (6)	6 (5)
Round cell (CLL-like)	1 (1)	0
Other	18 (13)	15 (11)

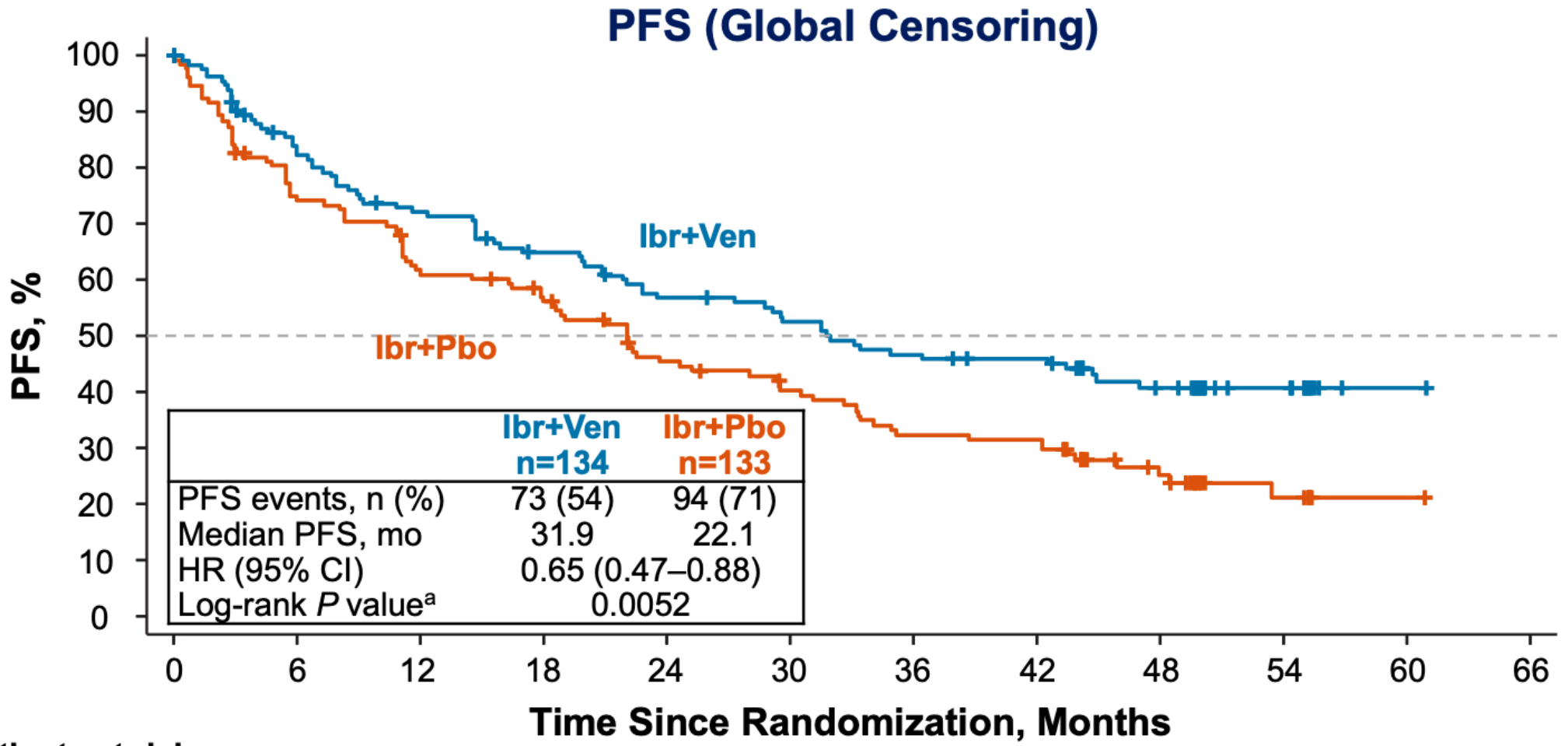
Characteristic	Ibrutinib + venetoclax n=134	Ibrutinib + placebo n=133
Simplified MIPI score, n (%)		
Low risk	18 (13)	23 (17)
Intermediate risk	63 (47)	68 (51)
High risk	51 (38)	41 (31)
***TP53* status, n (%)**		
Mutated	40 (30)	37 (28)
Not mutated	66 (49)	57 (43)
Missing	28 (21)	39 (29)
Bulky disease, n (%)		
≥5 cm	62 (46)	53 (40)
≥10 cm	13 (10)	10 (8)
Extranodal disease, n (%)	64 (48)	61 (46)
BM involvement, n (%)	62 (46)	54 (41)
Splenomegaly, n (%)	42 (31)	33 (25)

LBA-2 Ibrutinib & Venetoclax in R/R Mantle Cell Lymphoma: Ansprechrate und -dauer

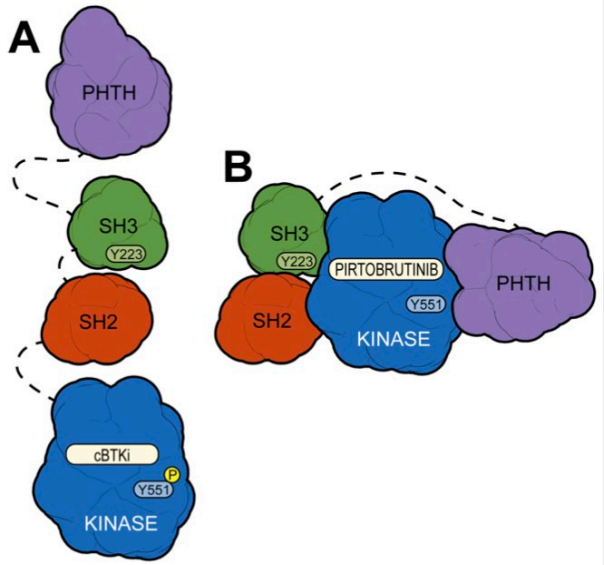




LBA-2 Ibrutinib & Venetoclax in R/R Mantle Cell Lymphoma: Progressionsfreies Überleben



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



Gomez et al, Blood 2023

Baseline Characteristics of Patients with MCL

Characteristics	Prior cBTKi n=152	cBTKi Naïve n=14
Median age, years (range)	70 (46-88)	67 (60-86)
Male, n (%)	120 (79)	10 (71)
Histology, n (%)		
Classic/leukemic	120 (79)	11 (79)
Pleomorphic/Blastoid	32 (21)	3 (21)
ECOG PS, n (%)		
0	93 (61)	5 (36)
1	56 (37)	8 (57)
2	3 (2)	1 (7)
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)
Bulky Lymphadenopathy (cm), n (%)		
<5	94 (62)	8 (57)
≥5	36 (24)	5 (36)
No Measurable Lymph Node	22 (15)	1 (7)
Bone marrow involvement, n (%)		
Yes	81 (53)	4 (29)
No	71 (47)	10 (71)
Median number of prior lines of systemic therapy, n (range)	3 (1-9)	2 (1-3)

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)
Immunomodulator	26 (17)	1 (7)
Stem cell transplant	33 (22)	7 (50)
Autologous	30 (20)	7 (50)
Allogeneic	7 (5)	0 (0)
BCL2 inhibitor	24 (16)	0 (0)
CAR-T	13 (9)	0 (0)
PI3K inhibitor	6 (4)	1 (7)
Reason discontinued any prior BTKi[a], n (%)		
Progressive disease	128 (84)	-
Toxicity / Other	21 (14)	-
Unknown	3 (2)	-
TP53 Mutation status, n (%)		
Yes	30 (20)	3 (21)
No	30 (20)	4 (29)
Missing	92 (61)	7 (50)
Ki-67 index, n (%)		
<30%	18 (12)	2 (14)
≥30%	45 (30)	6 (43)
Missing	89 (59)	6 (43)

Pirtobrutinib Safety Profile in MCL Patients

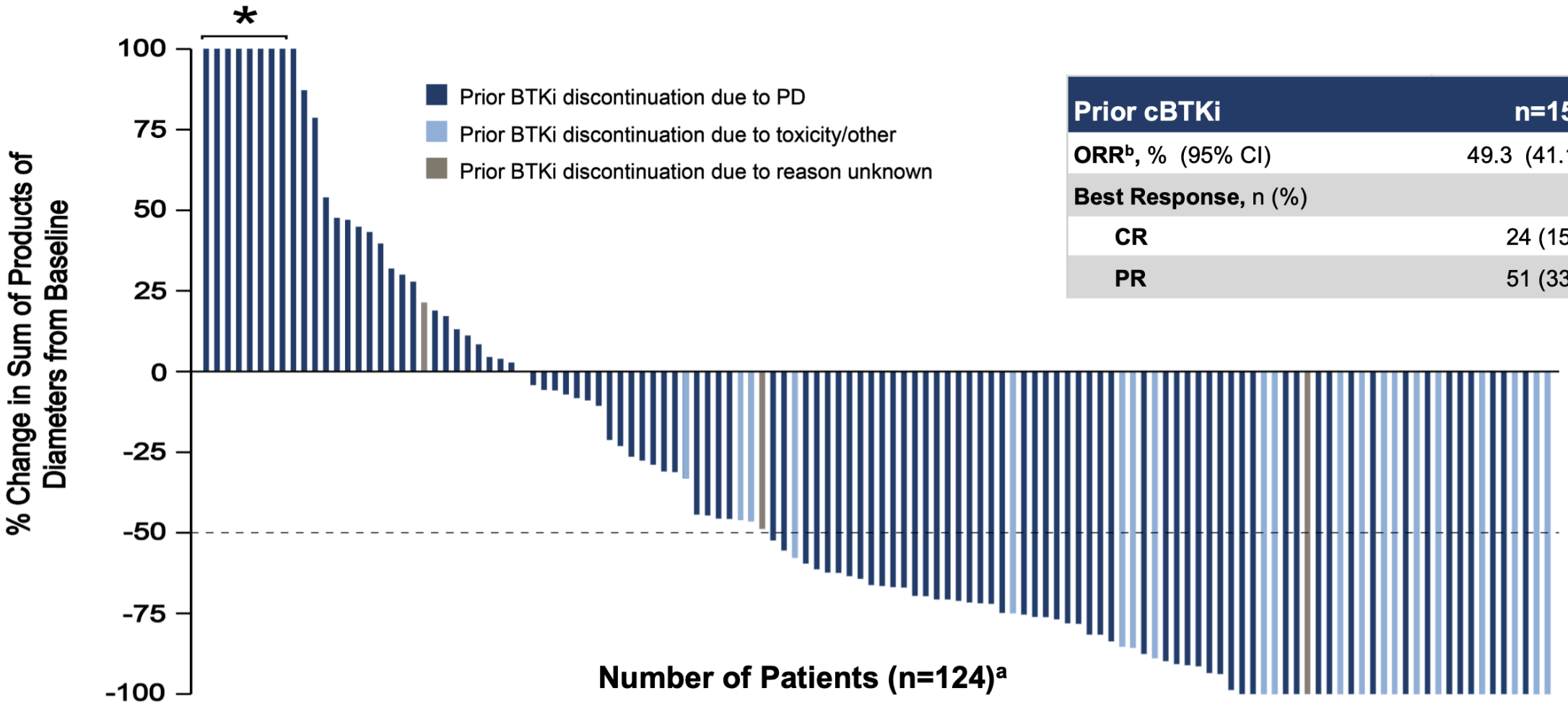
	Treatment-Emergent AEs in Patients with MCL (n=166)			
	All Cause AEs, (≥15%), %		Treatment-Related AEs, %	
Adverse Event	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Fatigue	31.9	3.0	21.1	2.4
Diarrhea	22.3	0.0	12.7	0.0
Dyspnea	17.5	1.2	9.0	0.6
Anemia	16.9	7.8	7.2	2.4
Platelet Count Decreased	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

Pirtobrutinib Efficacy in Patients with MCL who Received Prior cBTKi



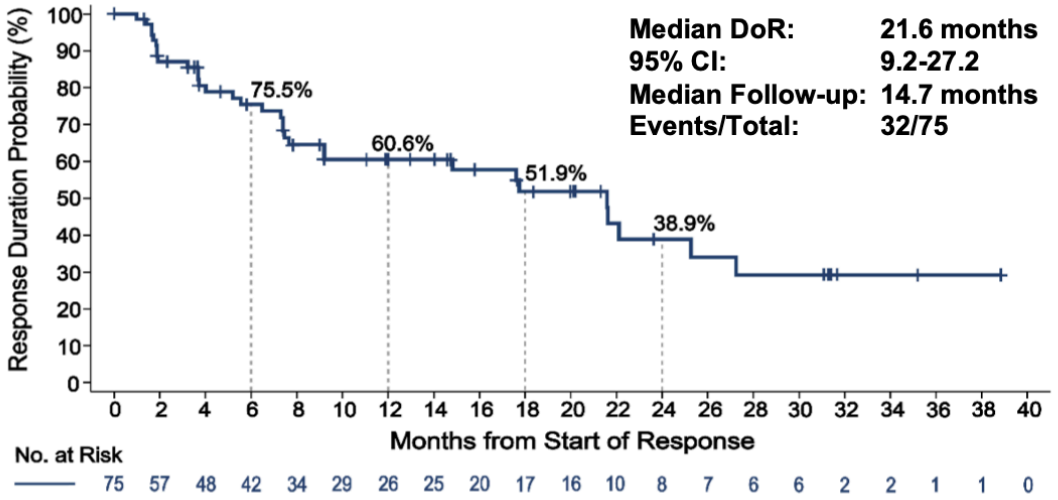
Prior cBTKi	n=152
ORR[b], % (95% CI)	49.3 (41.1-57.6)
Best Response, n (%)	
CR	24 (15.8)
PR	51 (33.6)

Median Time to First Response was 1.8 months (range: 0.8-13.8)

Pirtobrutinib Outcomes in Prior cBTKi Patients with MCL

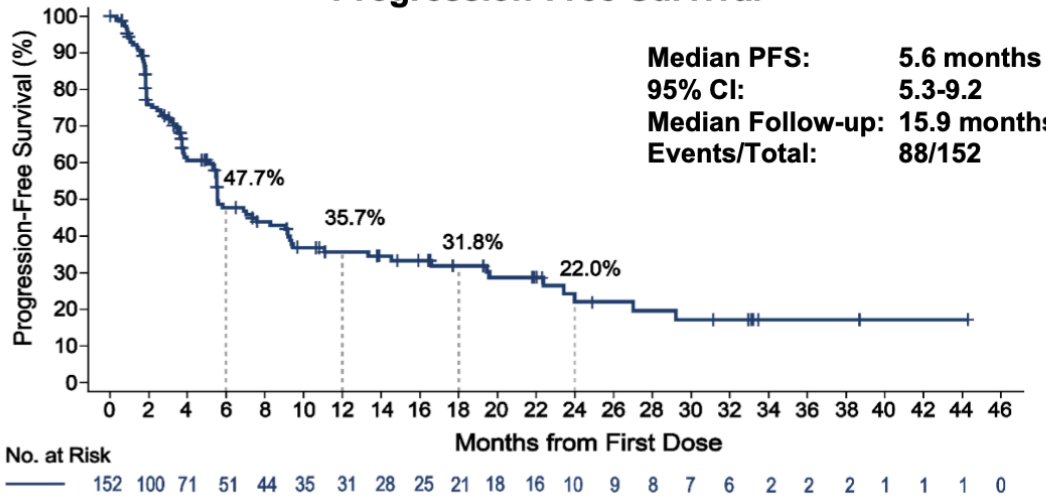
#981

Duration of Response



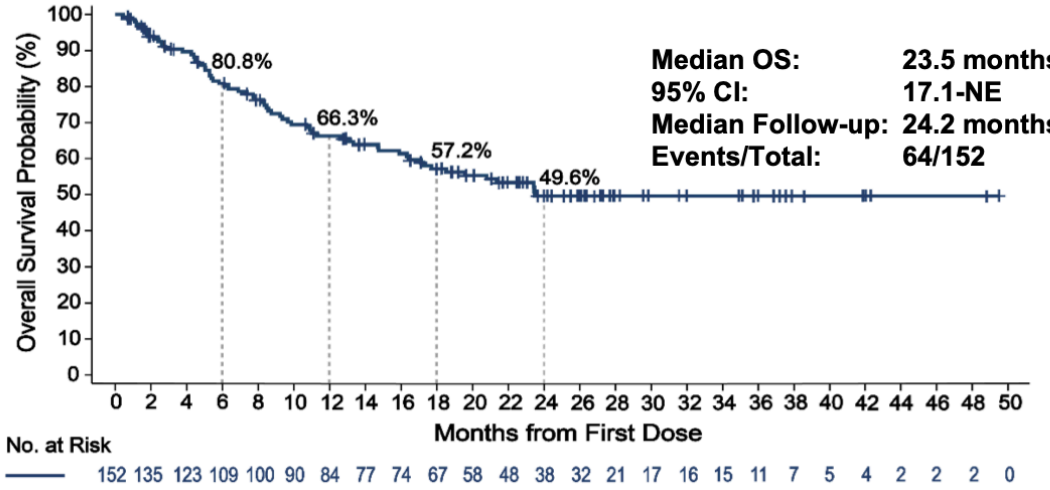
Median DoR:	21.6 months
95% CI:	9.2-27.2
Median Follow-up:	14.7 months
Events/Total:	32/75

Progression-Free Survival



Median PFS:	5.6 months
95% CI:	5.3-9.2
Median Follow-up:	15.9 months
Events/Total:	88/152

Overall Survival

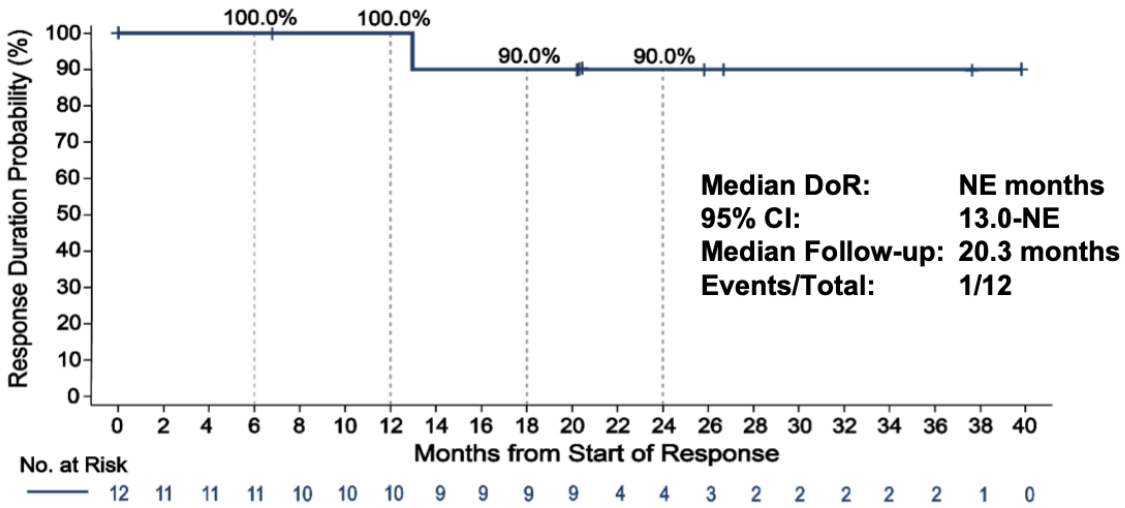


Median OS:	23.5 months
95% CI:	17.1-NE
Median Follow-up:	24.2 months
Events/Total:	64/152

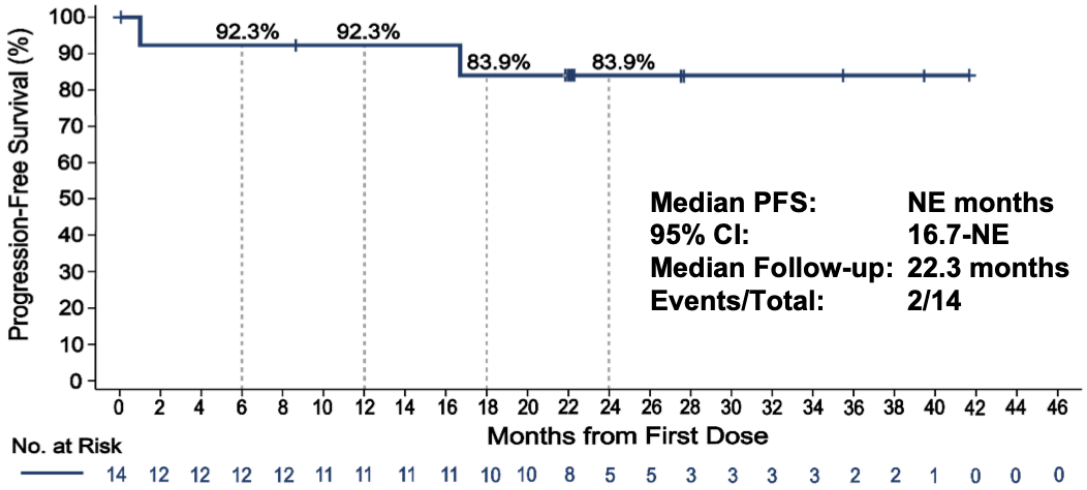
Pirtobrutinib Outcomes in cBTKi Naïve Patients with MCL

#981:

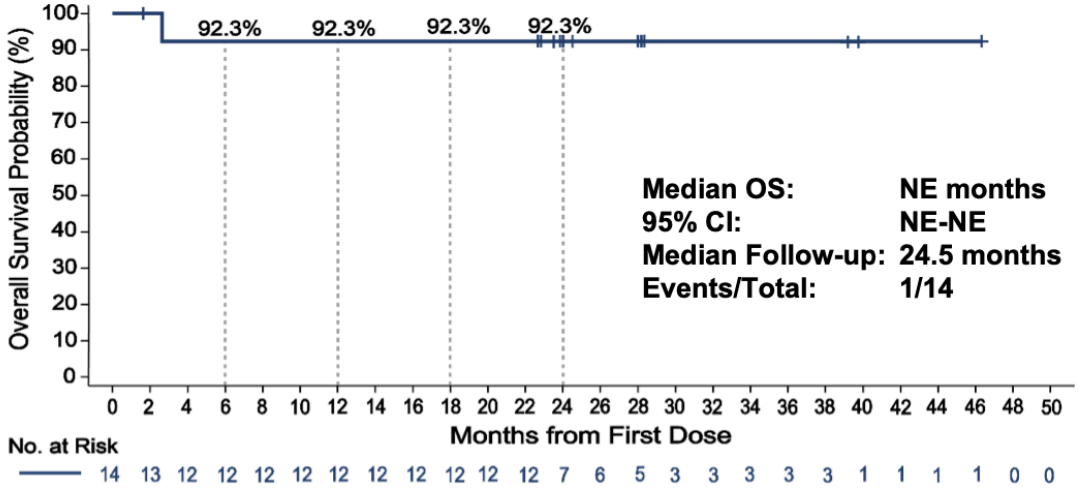
Duration of Response



Progression-Free Survival



Overall Survival



cBTKi Naive Cohort:

- The ORR[a] was 85.7% (95% CI: 57.2-98.2)
  - 6 CR (42.9%) and 6 PR (42.9%)

Large B cell lymphoma – LBCL - DLBCL

#438 Subcutaneous Epcoritamab Plus Lenalidomide in Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma From EPCORE NHL-5

Key inclusion criteria: arm 1

- Adults ≥18 y
- Histologically confirmed CD20+ DLBCL[a]
  - DLBCL, NOS
  - High-grade B-cell lymphoma with *MYC* and *BCL-2* and/or *BCL-6* translocations
  - FL grade 3B
- R/R disease[b] with ≥1 prior anti-CD20 mAb–containing systemic therapy
- ASCT ineligible or failed prior ASCT
- Prior CAR T allowed, but prior CD3/CD20 bispecific antibodies not allowed
- ECOG PS 0–2
- Measurable disease

Data cutoff: Oct 6, 2023
Median follow-up: 8.2 mo

Dose escalation and dose expansion

Arm 1	Arm 2	Arm 3	Arms 4–5	Arms 6–7
Epcoritamab + lenalidomide (12 x 28-day cycles) R/R DLBCL	Epcoritamab + ibrutinib + lenalidomide R/R DLBCL	Epcoritamab + polatuzumab + R-CHP 1L DLBCL	Epcoritamab + CC-99282 (CELMoD) R/R DLBCL, R/R FL	Epcoritamab + ibrutinib ± venetoclax R/R MCL, 1L MCL

Epcoritamab dosing schedule

Step-up dosing (SUD)

- Cycle 1, day 1: SUD1 (0.16 mg)
- Cycle 1, day 8: SUD2 (0.8 mg)
- Cycle 1, days 15, 22: full dose (48 mg)
- Cycles 2–3, days 1, 8, 15, 22: full dose (48 mg)
- Cycles 4–12, day 1: full dose (48 mg)

Lenalidomide dosing schedule

Cycles 1–12: 25 mg once daily on days 1–21

Premedication and CRS prophylaxis

Diphenhydramine, acetaminophen, and corticosteroids were mandatory for CRS prophylaxis with the first 4 epcoritamab doses

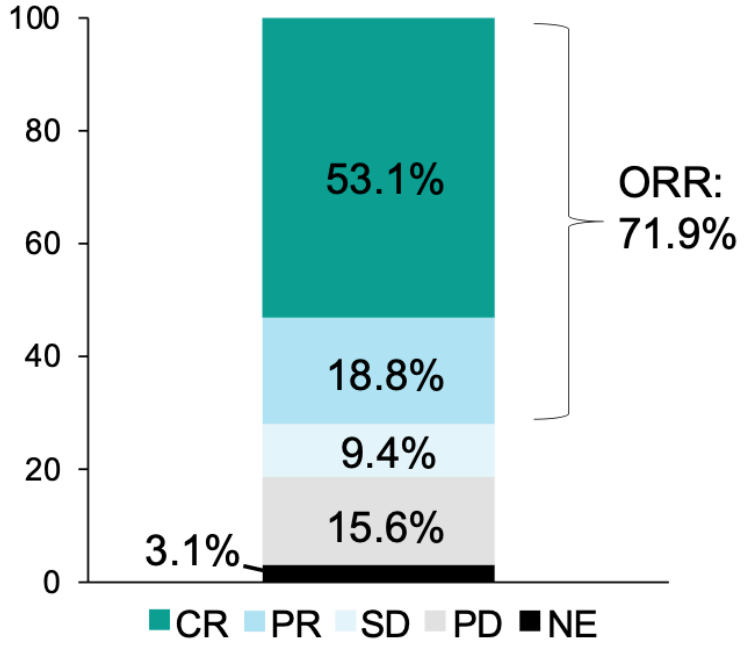
- Prednisone 100 mg for 4 d was initially recommended
- Current recommendation is dexamethasone 15 mg for 4 d[c]

Objectives

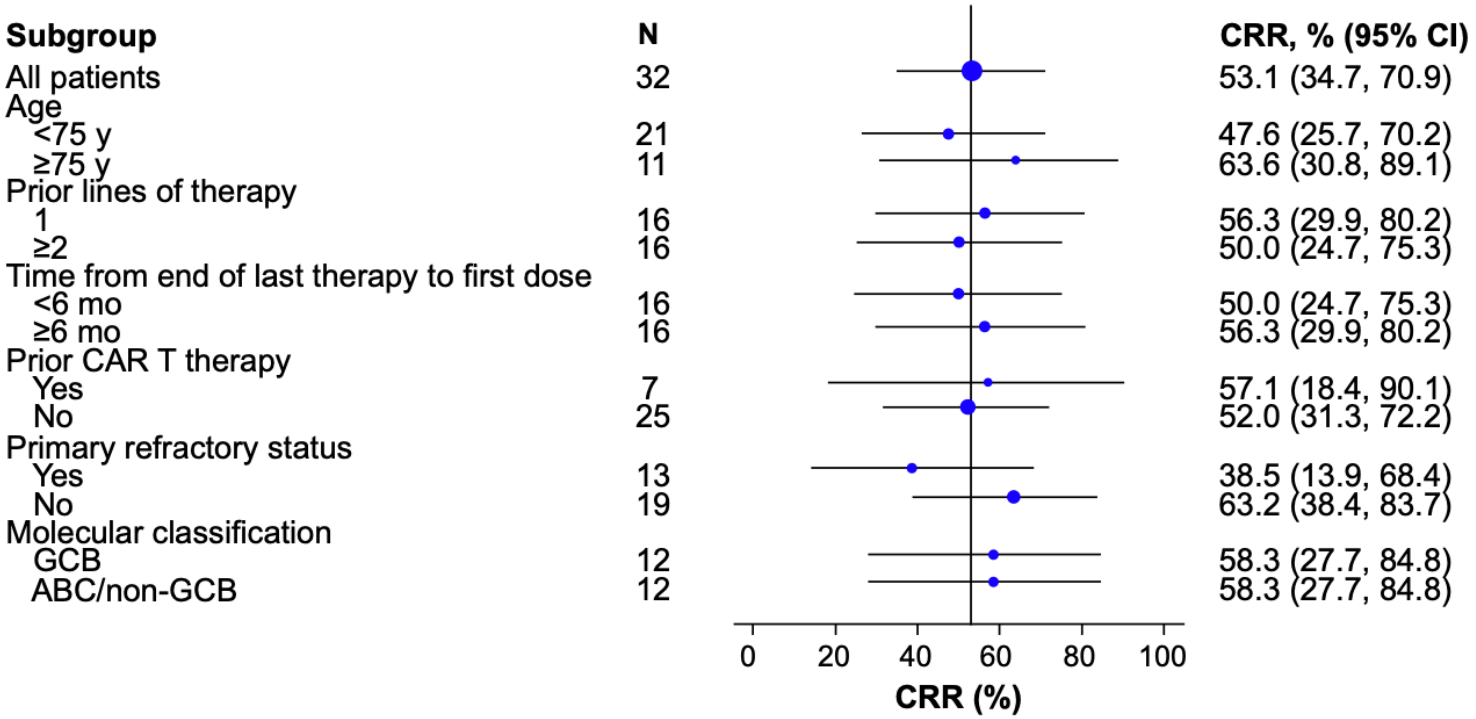
Dose escalation: safety, tolerability, and identify expansion dose (RP2D)
Dose expansion: safety, tolerability, and antitumor activity

#438 Epcoritamab Plus Lenalidomide in R/R DLBCL EPCORE NHL-5
Therapieansprechen und Subgruppen

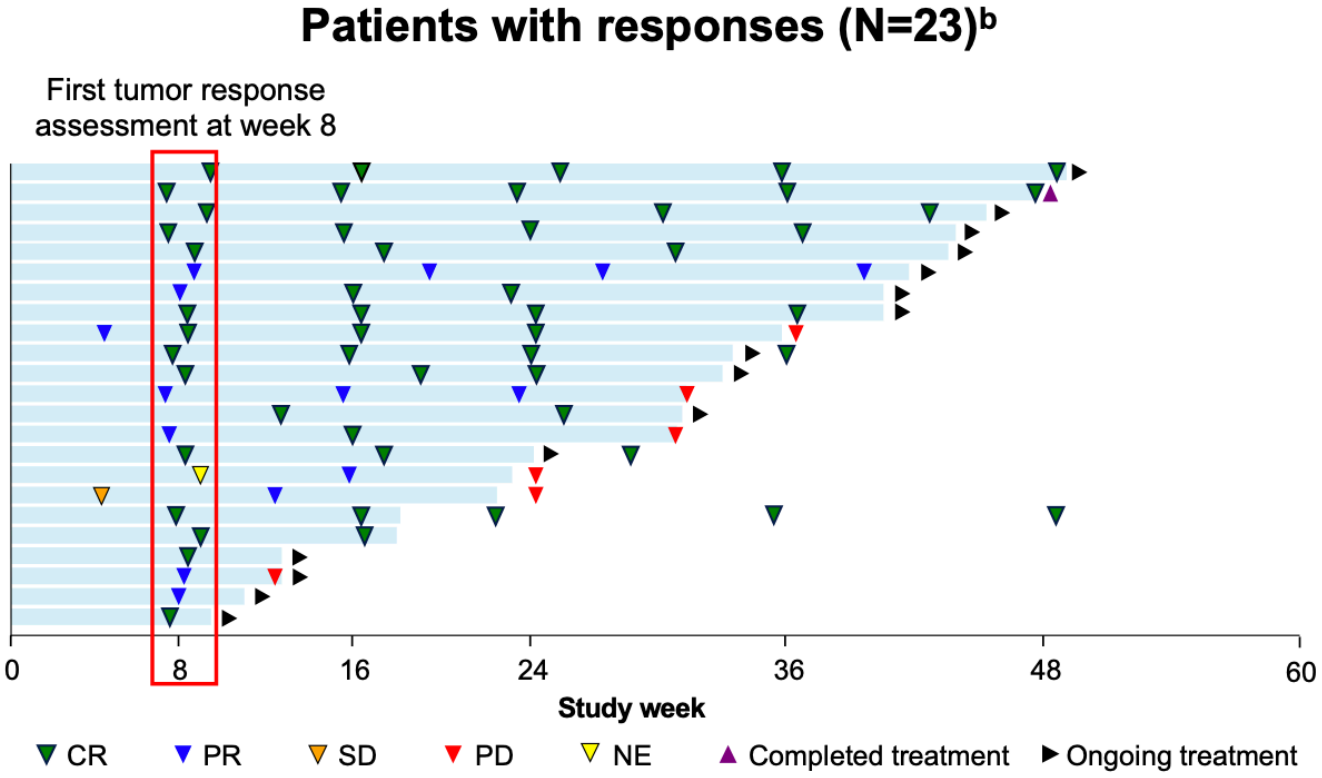
Best overall response[a] (N=32)

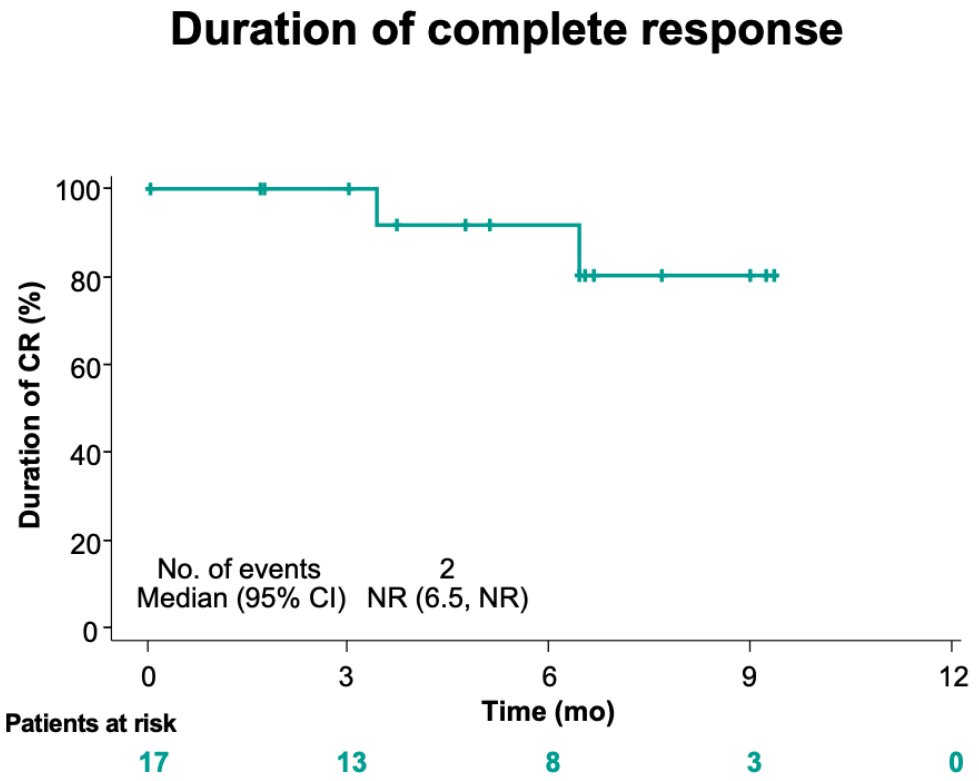


Complete response in subgroups (N=32)



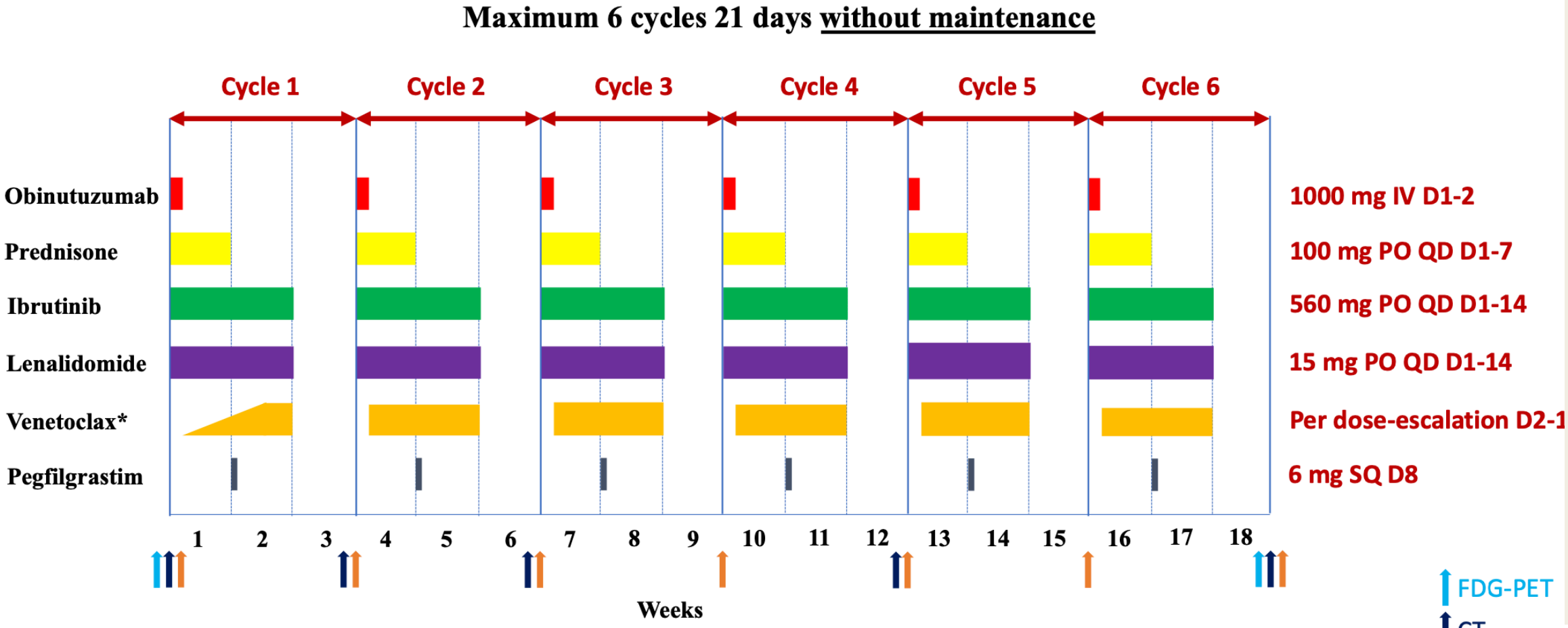
#438 Subcutaneous Epcoritamab Plus Lenalidomide in Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma From EPCORE NHL-5





- Median time to response was 1.8 mo (range: 1.0–3.6)
- Median time to CR was 1.9 mo (range: 1.6–3.6)
- Median duration of CR was not reached

#434 Phase Ib/II Study of Multi-Targeted Therapy with Venetoclax, Ibrutinib, Prednisone, Obinutuzumab, and Lenalidomide (ViPOR) in Relapsed/Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL)



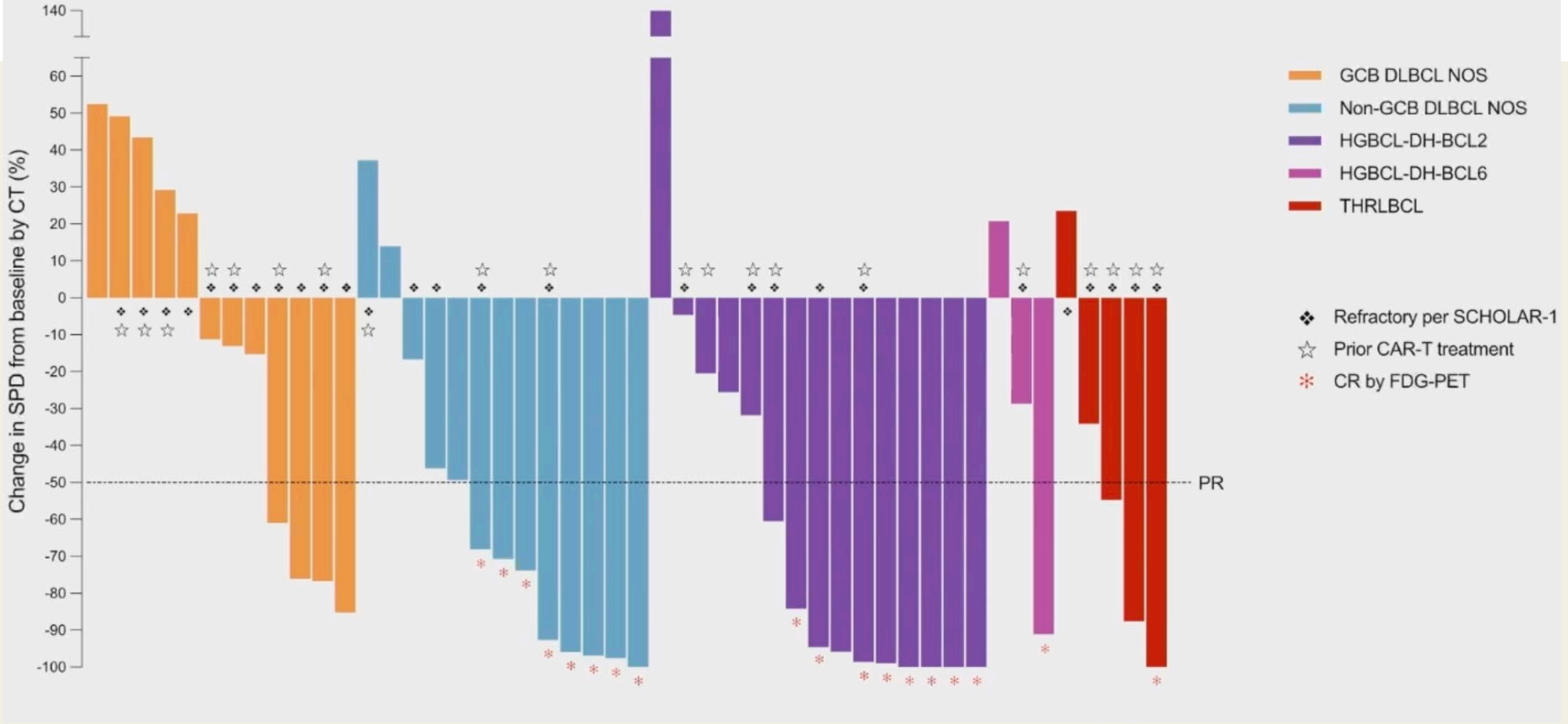
*Venetoclax starts cycle 2 for the first patient cohort

#434

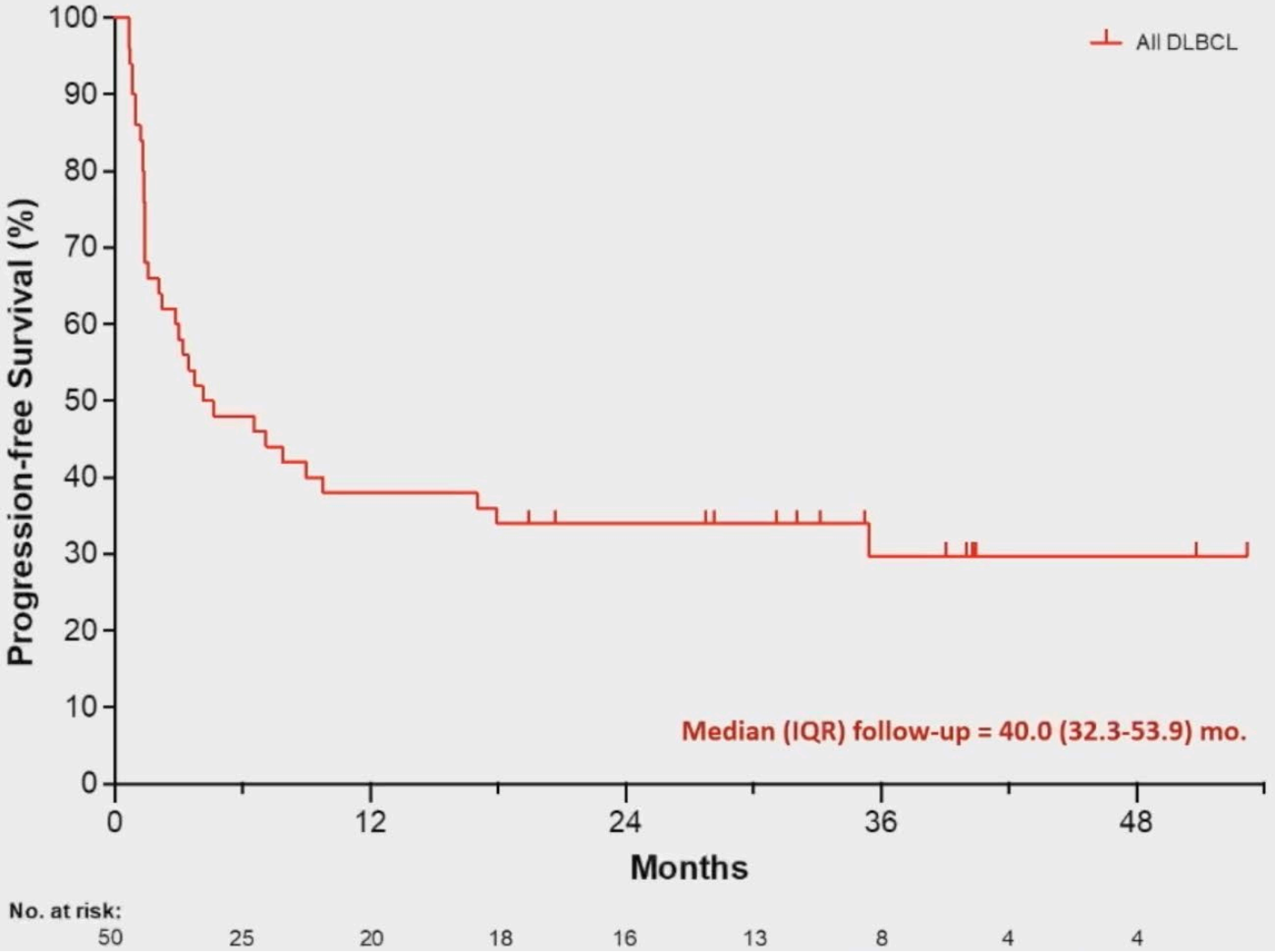
Baseline Characteristics in DLBCL Patients

Characteristic	All DLBCL (N=50)
Median (range) age – yr.	61 (29-77)
Male sex – no. (%)	33 (66%)
Disease histology – no. (%)	
Non-GCB DLBCL NOS	13 (26%)
GCB DLBCL NOS	12 (24%)
HGBCL-DH-BCL2	17 (34%)
HGBCL-DH-BCL6	3 (6%)
THRLBCL	5 (10%)
Transformed lymphoma – no. (%)	17 (34%)
Stage III/IV – no. (%)	46 (92%)
IPI $\geq$ 3 – no. (%)	34 (68%)
Median (range) prior therapies	3 (1-9)
Prior CAR-T therapy - no. (%)	20 (40%)
Refractory per SCHOLAR-1 - no. (%)	29 (58%)

#434 Change in Tumor Burden at End-of-Therapy (EOT)

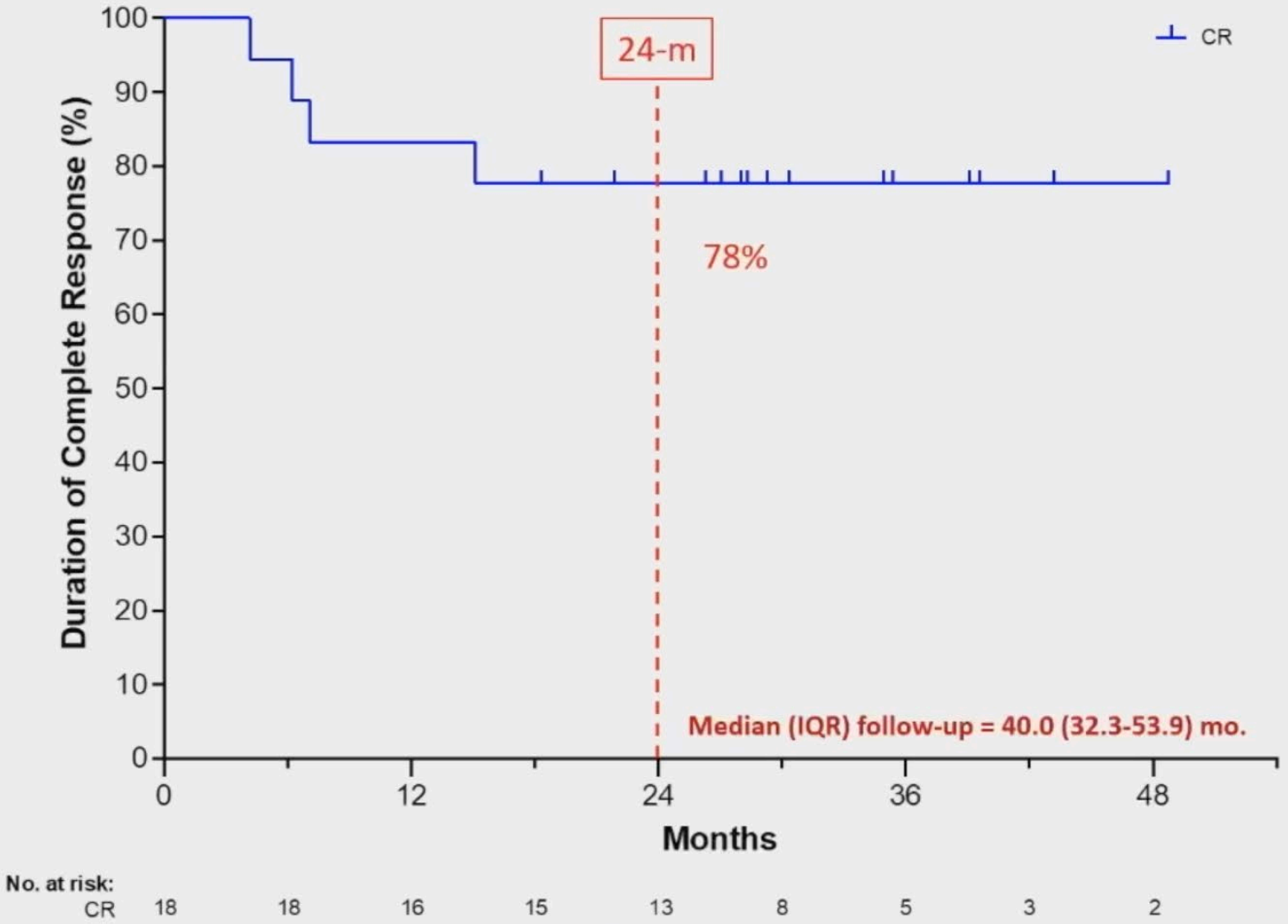


#434 Progression-free Survival in All DLBCL Patients



#434

Duration of Complete Response



Zusammenfassung

Klassisches Hodgkin-Lymphom

Erstlinientherapie für fortgeschrittene Stadien: BrECADD mit geringer gonadaler Toxizität und nicht-unterlegenem Ansprechen

Nivolumab-AVD ist Bretuximab-AVD in fortgeschrittenen Stadien bei älteren Patienten überlegen

Chronische lymphatische Leukämie

Die Kombination von Venetoclax mit Ibrutinib ist FCR bei IgHV-unmutierter CLL fitter Pat in der 1L deutlich überlegen

mehr Sekundärmalignome und Todesfälle mit FCR

MRD-abhängige Therapiedauer

Mantelzell-Lymphom

Im Rezidiv ist Venetoclax-Ibrutinib gegenüber Ibrutinib alleine überlegen

Pirtobrutinib zeigt auch bei BTKi-refraktären (und unverträglichen) Patienten Wirksamkeit

insbesondere aber bei BTKi-naiven MCL

Large B cell lymphoma – LBCL

Im Rezidiv zeigt Epcoritamab in Kombination mit Lenalidomid Wirksamkeit nach allen Vortherapien, inkl. CAR-T

verbesserte Wirksamkeit gegenüber der Monotherapie spekulativ

Die Kombination aus Venetoclax – Ibrutinib – Prednisolon – Obinutuzumab – Lenalidomide **ViPOR** ist bei ungünstigen Subtypen überraschend effektiv - in günstigen (GCB) dagegen nicht

und am Ende….

Vielen Dank für Ihre Aufmerksamkeit

Universitätsklinikum Tübingen