ASCO Direct Highlights: Lymphoma/Leukemia

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Disclosure of Conflict(s) of Interest

Brian Hess, MD reported the following relevant financial relationships or relationships with ineligible companies of any amount during the past 24 months.

- *Consultant:* ADC Therapeutics.
- *Speaker's Bureau*: AstraZeneca, Bristol Myers Squibb, and Gilead

CLL/SLL Highlights

First Results of a Head-to-Head Trial of Acalabrutinib versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia

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Introduction

- BTK is critical for CLL tumor cell proliferation and survival[1-3]
- Ibrutinib was the first irreversible BTK inhibitor[4] approved for adults with CLL/SLL[5]
    - Ibrutinib treatment is associated with AEs, particularly cardiovascular toxicities, that can lead to treatment discontinuation[6-8]
    - Ibrutinib also binds to non-BTK kinases,[4,9,10] likely contributing to ibrutinib-associated AEs[4,10-12]
- Acalabrutinib is a next-generation, more selective, irreversible BTK inhibitor approved for CLL/SLL[13]
- We report the results from the first head-to-head trial (ELEVATE-RR) comparing the safety and efficacy of acalabrutinib and ibrutinib in patients with previously treated CLL and del(17p) or del(11q)

AE, adverse event; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.

1. Vitale C, Burger JA. *Expert Opin Pharmacother*. 2016;17:1077-89; 2. Lougaris V, et al. *J Allergy Clin Immunol*. 2014;133:1644-50.e4; 3. de Gorter DJ, et al. *Immunity*. 2007;26:93-104; 4. Barf T, et al. *J Pharmacol Exp Ther*. 2017;363:240-52; 5. Imbruvica [package insert]. Pharmacyclics, Janssen Biotech, Inc.; 2020; 6. Byrd JC, et al. *Blood*. 2019;133:2031-42; 7. Mato AR, et al. *Haematologica*. 2018;103:874-879; 8. Dickerson T, et al. *Blood*. 2019;134:1919-1928; 9. Byrd JC, et al. *N Engl J Med*. 2016;374:323-32; 10. Bond DA, Woyach JA. *Curr Hematol Malig Rep*. 2019;14:197-205; 11. Caldeira D, et al. *PLoS One*. 2019;14:e0211228; 12. Caron F, et al. *Blood Adv*. 2017;1:772-8; 13. Calquence [package insert]. AstraZeneca Pharmaceuticals, 2019.

ELEVATE-RR:

Phase 3 Randomized Non-inferiority Open-Label Trial

Patients (N=533)

Key Inclusion Criteria

- Adults with previously treated CLL requiring therapy (iwCLL 2008 criteria[1])
- Presence of del(17p) or del(11q)[a]
- ECOG PS of ≤2

Stratification

- del(17p) status (yes or no)
- ECOG PS (2 vs ≤1)
- No. prior therapies (1–3 vs ≥4)

RANDOMIZE 1:1

- **Acalabrutinib[b] 100 mg PO BID**
- **Ibrutinib[b] 420 mg PO QD**

Primary endpoint

- Non-inferiority on IRC-assessed PFS[c]

Secondary endpoints (hierarchical order):

- Incidence of any grade atrial fibrillation/flutter
- Incidence of grade ≥3 infection
- Incidence of Richter transformation
- Overall survival

Key exclusion criteria: Significant CV disease; concomitant treatment with warfarin or equivalent vitamin K antagonist; prior treatment with ibrutinib, a BCR inhibitor (eg, BTK , PI3K, or Syk inhibitors), or a BCL-2 inhibitor (eg, venetoclax)

NCT02477696 (ACE-CL-006).
[a]By central laboratory testing; [b]continued until disease progression or unacceptable toxicity; [c]conducted after enrollment completion and accrual of ~250 IRC-assessed PFS events.
Afib/flutter, atrial fibrillation/flutter; BCL-2, B-cell leukemia/lymphoma-2; BCR, B-cell receptor; BID, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CV, cardiovascular; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; iwCLL, International Workshop on CLL; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; PO, orally; QD, once daily.
1. Hallek M, et al. *Blood*. 2008;111:5446-56.

Demographics and Baseline Characteristics

Characteristic	Acalabrutinib (n=268)	Ibrutinib (n=265)
Age, median (range), years	66 (41–89)	65 (28–88)
≥75 years	44 (16.4)	43 (16.2)
Male sex	185 (69.0)	194 (73.2)
ECOG PS score		
0–1	247 (92.2)	243 (91.7)
2	20 (7.5)	22 (8.3)
Bulky disease ≥5 cm	128 (47.8)	136 (51.3)
Rai stage 3 or 4	131 (48.9)	134 (50.6)
Cytogenetic abnormalities		
del(17p)	121 (45.1)	120 (45.3)
del(11q)	167 (62.3)	175 (66.0)
Complex karyotype[a]	124 (46.3)	125 (47.2)
TP53 mutated	100 (37.3)	112 (42.3)
IGHV unmutated	220 (82.1)	237 (89.4)
No. prior therapies, median (range)	2 (1–9)	2 (1–12)
1–3	234 (87.3)	237 (89.4)
≥4	33 (12.3)	28 (10.6)

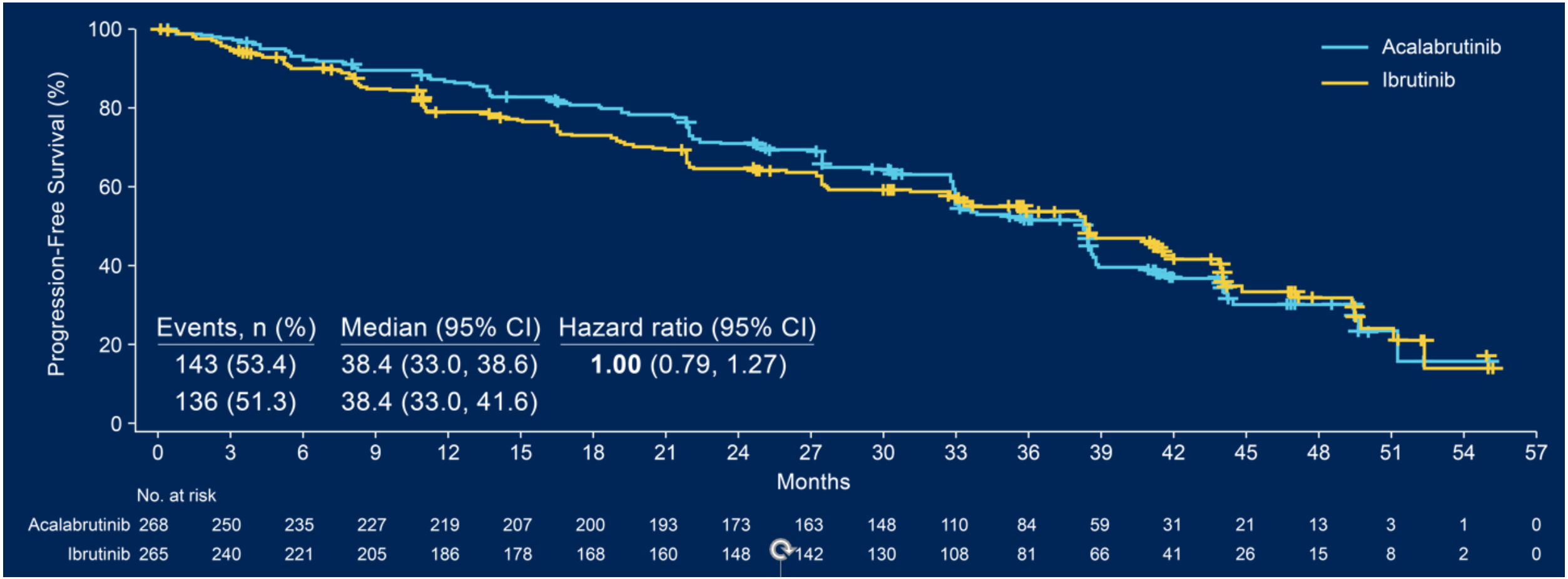
Data are n (%) unless otherwise specified.
[a]Patients with ≥3 chromosomal abnormalities.
ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy chain variable region; *TP53*, tumor protein 53.

Patient Disposition

	Acalabrutinib (n=268)	Ibrutinib (n=265)
Duration of follow-up, median (range), months	41.1 (0.0–58.2)	40.7 (0.2–59.1)
Patients who received treatment	265 (98.9)	264 (99.6)[a]
Patients continuing to receive treatment at data cutoff	124 (46.3)	109 (41.1)
Patients who discontinued treatment	141 (52.6)	155 (58.5)
Reasons for treatment discontinuation		
Disease progression[b]	82 (30.6)	68 (25.7)
Adverse event	40 (14.9)	59 (22.3)
Consent withdrawn	7 (2.6)	7 (2.6)
Death	5 (1.9)	6 (2.3)
Investigator decision	5 (1.9)	5 (1.9)
Other	2 (0.7)[c]	10 (3.8)[d]

Data cutoff date: September 15, 2020.
[a]Includes 1 patient who was randomized to ibrutinib but treated with acalabrutinib and was therefore included in the acalabrutinib arm for safety analyses.
[b]Disease progression includes Richter's transformation.
[c]Includes patients who discontinued treatment due to relocation (n=1) and starting therapy with ibrutinib (n=1) but agreed to remain on study for follow-up.
[d]includes patients who discontinued treatment due to trial noncompliance (n=2), withdrawal of consent for treatment/follow-up but not considered withdrawal from study per electronic case report guidelines (n=1), refusal of medication (n=1), relocation (n=2), medical monitor decision (n=2), early termination due to second primary malignancy (n=1), and IRC- and medical monitor/sponsor-confirmed progressive disease but investigator disagreed and patient continued ibrutinib off-trial (n=1) but agreed to remain on study for follow-up.

Primary Endpoint: Non-inferiority Met on IRC-Assessed PFS

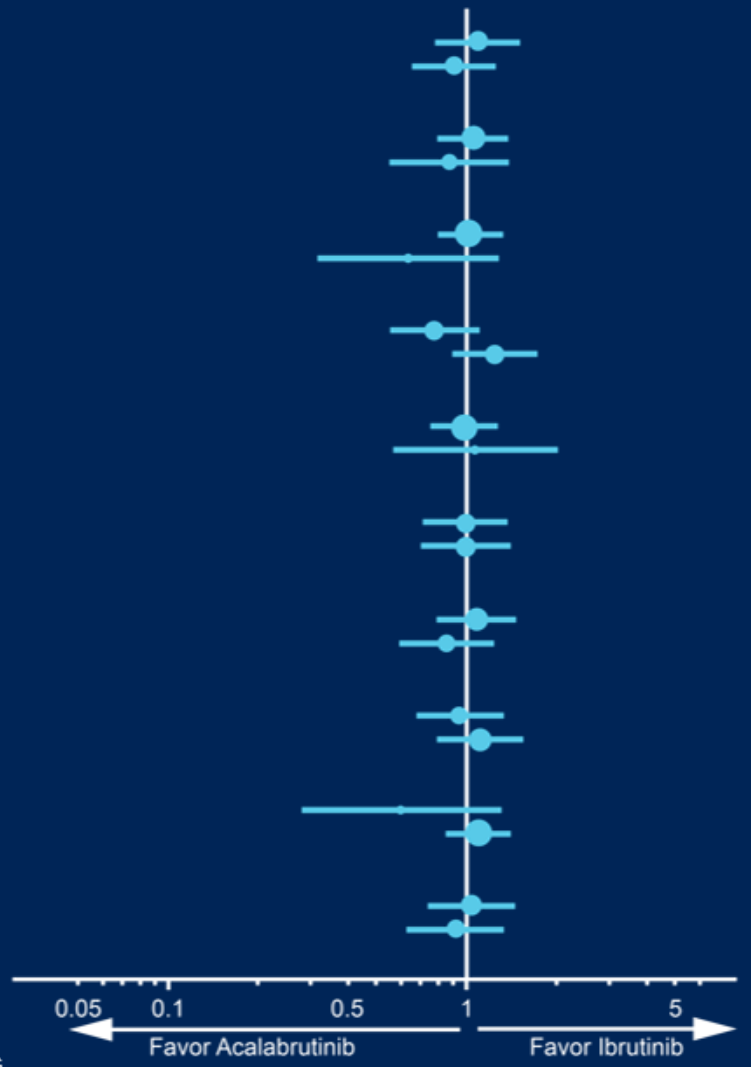


Median follow-up: 40.9 months (range, 0.0–59.1).

CI, confidence interval; IRC, independent review committee; PFS, progression-free survival.

IRC-Assessed PFS Comparable Across Prespecified Subgroups [8]

Subgroup Analysis	No. of Events/Patients: Acalabrutinib	No. of Events/Patients: Ibrutinib	Hazard Ratio (95% CI)
Age group			
<65 years	77/124	66/122	1.09 (0.79, 1.52)
≥65 years	66/144	70/143	0.91 (0.65, 1.27)
Sex			
Male	105/185	101/194	1.06 (0.81, 1.40)
Female	38/83	35/71	0.88 (0.56, 1.40)
ECOG at randomization[a]			
0,1	128/248	119/244	1.03 (0.80, 1.33)
2	15/20	17/21	0.64 (0.32, 1.29)
Bulky disease			
<5 cm	66/138	66/127	0.79 (0.56, 1.11)
≥5 cm	77/128	70/136	1.25 (0.90, 1.74)
Number of prior therapies[a]			
1–3	122/239	117/238	0.99 (0.77, 1.27)
≥4	21/29	19/27	1.07 (0.57, 2.02)
Presence of del(17)(p13.1)[a]			
Yes	76/124	72/121	1.00 (0.73, 1.38)
No	67/144	64/144	1.00 (0.71, 1.41)
Presence of del(11)(q22.3)			
Yes	85/167	79/175	1.08 (0.80, 1.47)
No	58/100	57/90	0.86 (0.59, 1.24)
TP53 mutation			
Yes	64/100	73/112	0.95 (0.68, 1.33)
No	79/167	63/153	1.11 (0.80, 1.55)
IGHV			
Mutated	13/44	13/28	0.60 (0.28, 1.31)
Unmutated	130/220	123/237	1.09 (0.85, 1.40)
Complex karyotype[b]			
Yes	74/124	66/125	1.04 (0.74, 1.44)
No	52/116	56/116	0.92 (0.63, 1.35)



[a]Randomization stratification factors.
[b]Patients with 3 or more chromosomal abnormalities and one or more structural abnormalities.

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; IRC, independent review committee; PFS, progression-free survival.

Secondary Endpoint:

Incidence of Any-Grade Atrial Fibrillation/Flutter Significantly Lower With Acalabrutinib

	Any grade	
	Acalabrutinib (n=266)	**Ibrutinib (n=263)**
Afib/flutter	**25 (9.4)*,[a]**	**42 (16.0)[a]**
Events/100 person-months	0.366	0.721
Time to onset, median (range), months	28.8 (0.4–52.0)	16.0 (0.5–48.3)
Leading to treatment discontinuation[b]	0	7 (16.7)
Afib/flutter incidence among patients without prior history of afib/flutter	15/243 (6.2)	37/249 (14.9)

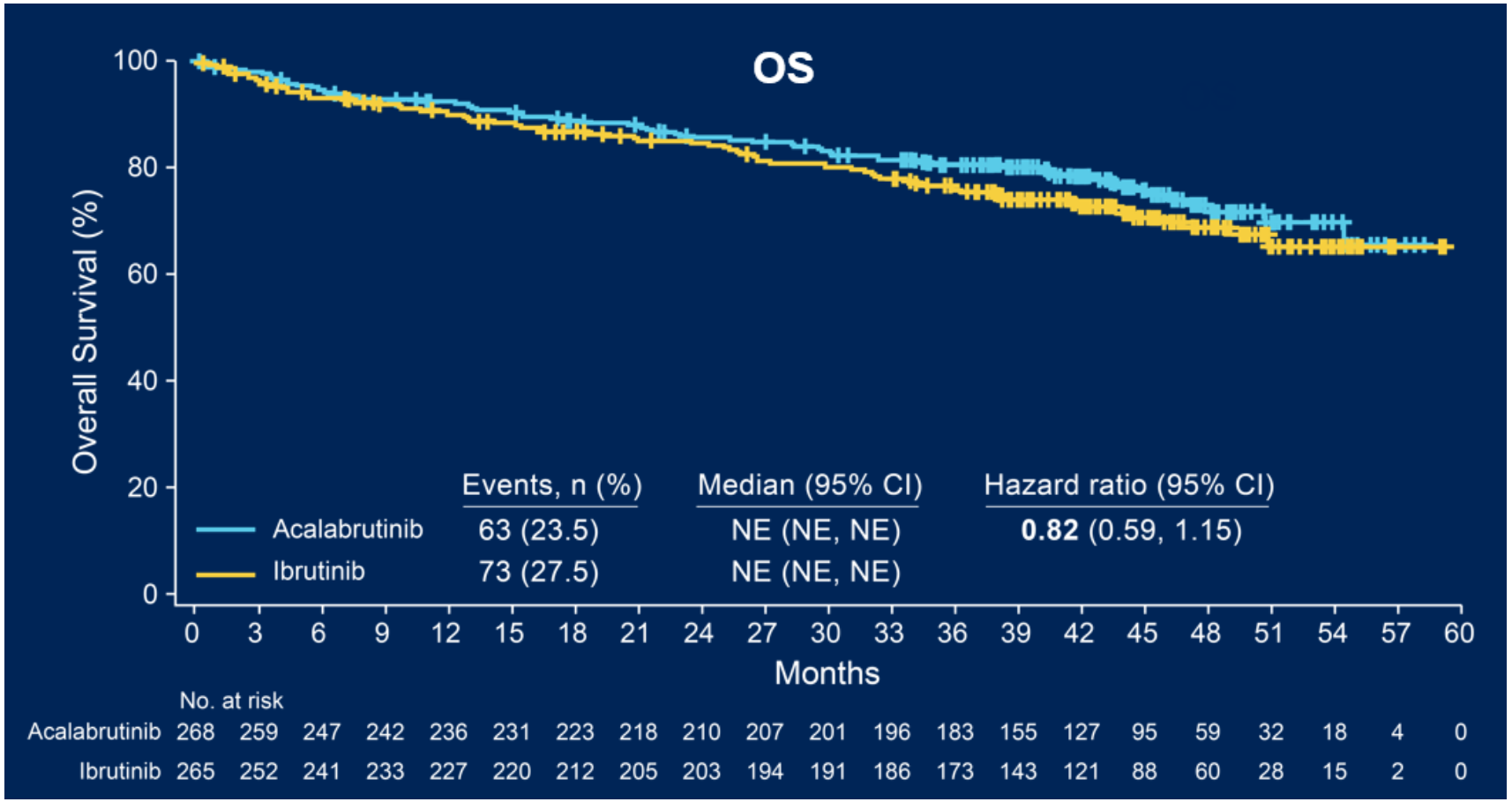
***Difference in any-grade incidence rates: −6.6% (95% CI −12.2 to −0.9), *P*=0.02.**

[a]Grade ≥3 afib/flutter was reported in 13 (4.9%) in the acalabrutinib arm vs 10 (3.8%) in the ibrutinib arm; [b]Among patients with events of afib/flutter.
Afib/flutter, atrial fibrillation/flutter.

Additional Secondary Endpoints:

Gr≥3 Infection, Richter's Transformation, Overall Survival

- Comparable incidence of Gr≥3 infection (*P*=0.8777):
  - Acalabrutinib: n=82 (30.8%)
  - Ibrutinib: n=79 (30.0%)
- Comparable incidence of RT:
  - Acalabrutinib: n=10 (3.8%)
  - Ibrutinib: n=13 (4.9%)



CI, confidence interval; Gr, grade; HR, hazard ratio; OS, overall survival; RT, Richter transformation.

Safety Summary

Event	Acalabrutinib (n=266)	Ibrutinib (n=263)
Duration of treatment exposure, median (range), months	38.3 (0.3–55.9)	35.5 (0.2–57.7)
Any grade AEs	260 (97.7)	256 (97.3)
Grade ≥3 AEs	183 (68.8)	197 (74.9)
AEs leading to treatment discontinuation	39 (14.7)	56 (21.3)
Serious AEs	143 (53.8)	154 (58.6)
Deaths due to AEs[a]	17 (6.4)	25 (9.5)

Values are reported as n (%) unless stated otherwise.
[a]Includes deaths occurring within 30 days of last dose; deaths occurring after the start of subsequent anticancer therapy were not included in the assessment of deaths within 30 days of last dose, regardless of time after last dose.
AE, adverse event.

Most Common AEs

Events, n (%)	Any grade		Grade ≥3	
	Acalabrutinib (n=266)	Ibrutinib (n=263)	Acalabrutinib (n=266)	Ibrutinib (n=263)
Diarrhea[a,b]	92 (34.6)	**121 (46.0)**	3 (1.1)	**13 (4.9)**
Headache[a,b]	**92 (34.6)**	53 (20.2)	**4 (1.5)**	0
Cough[a]	**77 (28.9)**	56 (21.3)	2 (0.8)	1 (0.4)
URTI	71 (26.7)	65 (24.7)	5 (1.9)	1 (0.4)
Neutropenia	56 (21.1)	65 (24.7)	52 (19.5)	60 (22.8)
Pyrexia	62 (23.3)	50 (19.0)	8 (3.0)	2 (0.8)
Arthralgia[a]	42 (15.8)	**60 (22.8)**	0	2 (0.8)
Hypertension[a,b]	23 (8.6)	**60 (22.8)**	11 (4.1)	**23 (8.7)**
Anemia	58 (21.8)	49 (18.6)	31 (11.7)	34 (12.9)
Fatigue[b]	54 (20.3)	44 (16.7)	**9 (3.4)**	0
Nausea	47 (17.7)	49 (18.6)	0	1 (0.4)
Contusion[a]	31 (11.7)	**48 (18.3)**	0	1 (0.4)
Pneumonia	47 (17.7)	43 (16.3)	28 (10.5)	23 (8.7)
Atrial fibrillation[a]	24 (9.0)	**41 (15.6)**	12 (4.5)	9 (3.4)
Thrombocytopenia	40 (15.0)	35 (13.3)	26 (9.8)	18 (6.8)

Higher incidence in **bold yellow** for terms with statistical differences.
Among most common AEs above, grade 5 were reported in 5 (1.9%) acalabrutinib patients (pyrexia, n=1; pneumonia, n=4) and 4 (1.5%) ibrutinib patients (URTI, n=1; pneumonia, n=3).
[a]Based on Barnard's exact test, two-sided *P*-value <0.05 without multiplicity adjustment for any grade events.
[b]Based on Barnard's exact test, two-sided *P*-value <0.05 without multiplicity adjustment for grade ≥3 events.
Includes AEs reported at ≥15% incidence (any grade) in either arm.
AE, adverse event; URTI, upper respiratory tract infection.

Events of Clinical Interest

Events, n (%)	Any grade		Grade ≥3	
	Acalabrutinib (n=266)	Ibrutinib (n=263)	Acalabrutinib (n=266)	Ibrutinib (n=263)
Cardiac events	64 (24.1)	79 (30.0)	23 (8.6)	25 (9.5)
Atrial fibrillation[a]*	25 (9.4)	**42 (16.0)**	13 (4.9)	10 (3.8)
Ventricular arrhythmias[b]	0	3 (1.1)	0	1 (0.4)
Bleeding events*	101 (38.0)	**135 (51.3)**	10 (3.8)	12 (4.6)
Major bleeding events[c]	12 (4.5)	14 (5.3)	10 (3.8)	12 (4.6)
Hypertension[d]*	25 (9.4)	**61 (23.2)**	11 (4.1)	**24 (9.1)**
Infections[e]	208 (78.2)	214 (81.4)	82 (30.8)	79 (30.0)
ILD/pneumonitis*	7 (2.6)	**17 (6.5)**	1 (0.4)	2 (0.8)
SPMs excluding NMSC	24 (9.0)	20 (7.6)	16 (6.0)	14 (5.3)

Higher incidence indicated in **bold yellow** for terms with statistical differences.
*Two-sided P-value for event comparisons <0.05 without multiplicity adjustment.
[a]Includes events with preferred terms atrial fibrillation and atrial flutter.
[b]Includes events with preferred terms torsade de pointes, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation, ventricular flutter, ventricular tachyarrhythmia, and ventricular tachycardia.
[c]Defined as any hemorrhagic event that was serious, grade ≥3 in severity, or a central nervous system hemorrhage (any severity grade).
[d]Included events with the preferred terms of hypertension, blood pressure increased, and blood pressure systolic increased.
[e]Most common grade ≥3 infections were pneumonia (acalabrutinib, 10.5%; ibrutinib, 8.7%), sepsis (1.5% vs 2.7%, respectively), and UTI (1.1% vs 2.3%).
ILD, interstitial lung disease; NMSC, nonmelanoma skin cancer; SPMs, second primary malignancies; UTI, urinary tract infection.

Key Conclusions

- Acalabrutinib was non-inferior to ibrutinib on the primary endpoint of IRC-assessed PFS (HR: 1.00 [95% CI: 0.79, 1.27])
- Acalabrutinib demonstrated lower frequencies of common AEs, grade ≥3 AEs, SAEs, and treatment discontinuations due to AEs overall
- Cardiovascular events were less common with acalabrutinib vs ibrutinib
    - Afib/flutter events (any grade) were significantly less frequent with acalabrutinib vs ibrutinib (9.4% vs 16%; *P*=0.02)
    - Hypertension also was less frequent with acalabrutinib
- Other commonly reported AEs, including diarrhea, arthralgia, and bruising (any grade bleeding) events, were also less frequent with acalabrutinib vs ibrutinib
- These results demonstrate that acalabrutinib is better tolerated and has similar efficacy to ibrutinib in patients with previously treated CLL

AE, adverse event; Afib/flutter, atrial fibrillation/flutter; CLL, chronic lymphocytic leukemia; IRC, independent review committee; PFS, progression-free survival; SAE, serious adverse event.

CLL: Fixed Duration of therapy

Fixed-duration (FD) first-line treatment (tx) with ibrutinib (I) plus venetoclax (V) for chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): Primary analysis of the FD cohort of the phase 2 captivate study.

Ghia et al.

Methods

- ≤ 70 y/o previously untreated; included 17p deleted (17%), 11q deleted (18%), complex karyotype (19%)
- Ibrutinib 420 mg (3 cycles) → Ibrutinib + Venetoclax ramp up to 400 mg (12 cycles)
- Primary endpoint: CR + Cri

Results

- AE's led to discontinuation of Ibr (4%) and Ven (2%)

Efficacy	Pts without del(17p) n=136	All pts N=159
CR/CRi, n (%)	76 (56)	88 (55)
Durable CR/CRi, n/N (%)*	66/76 (87)	78/88 (89)
ORR, n (%)	130 (96)	153 (96)
uMRD in PB, n (%)	104 (76)	122 (77)
uMRD in BM, n (%)	84 (62)	95 (60)
24-mo PFS rate, % (95% CI)	96 (91-98)	95 (90-97)
24-mo OS rate, % (95% CI)	98 (93-99)	98 (94-99)

*Progression-free ≥12 cycles from first CR.

CAR T-cell Therapy Highlights

Phase 2 Results of the ZUMA-3 Study Evaluating KTE-X19, an Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy, in Adult Patients With Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia

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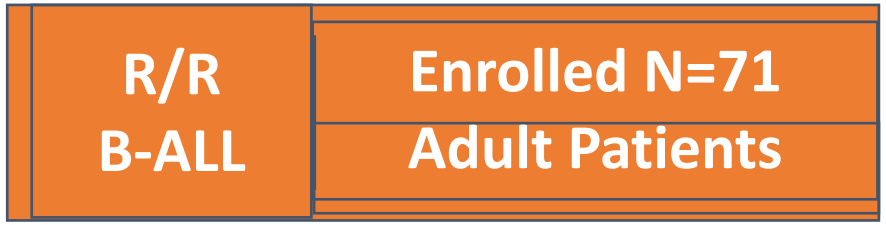
Background

- Approximately 40%–50% of adults with B-ALL experience relapse after initial treatment, with an overall poor prognosis[1,2]
  - The 1-year OS rate for patients with R/R B-ALL is 26% after first salvage and decreases with subsequent lines of therapy[2]
  - Although the novel agents blinatumomab and inotuzumab ozogamicin lead to CR/CRi rates of 35.1% and 80.7%, respectively, OS remains <8 months and is largely contingent on alloSCT[2-7]
- KTE-X19 is an autologous anti-CD19 CAR T-cell therapy approved for the treatment of R/R MCL[8,9]
- ZUMA-3 is a Phase 1/2, international, multicenter study evaluating KTE-X19 in adults with R/R B-ALL
  - In Phase 1, KTE-X19 demonstrated a manageable safety profile with an overall CR/CRi rate of 83%, and the recommended Phase 2 dose was established as 1×10^6 CAR T cells/kg[10]
- Here, we report the Phase 2 results from ZUMA-3, the pivotal study of KTE-X19 in the largest adult-only R/R B-ALL population to date

ZUMA-3: Phase 2 Study Design

Phase 2



Key Eligibility Criteria

- ≥18 years of age with R/R B-ALL[a] and BM blasts >5%
- Patients could have received prior blinatumomab

Conditioning Chemotherapy

- Fludarabine 25 mg/m^2 IV on Days −4, −3, −2 and cyclophosphamide 900 mg/m^2 IV on Day −2

KTE-X19

- 1×10^6 anti-CD19 CAR T cells/kg on Day 0

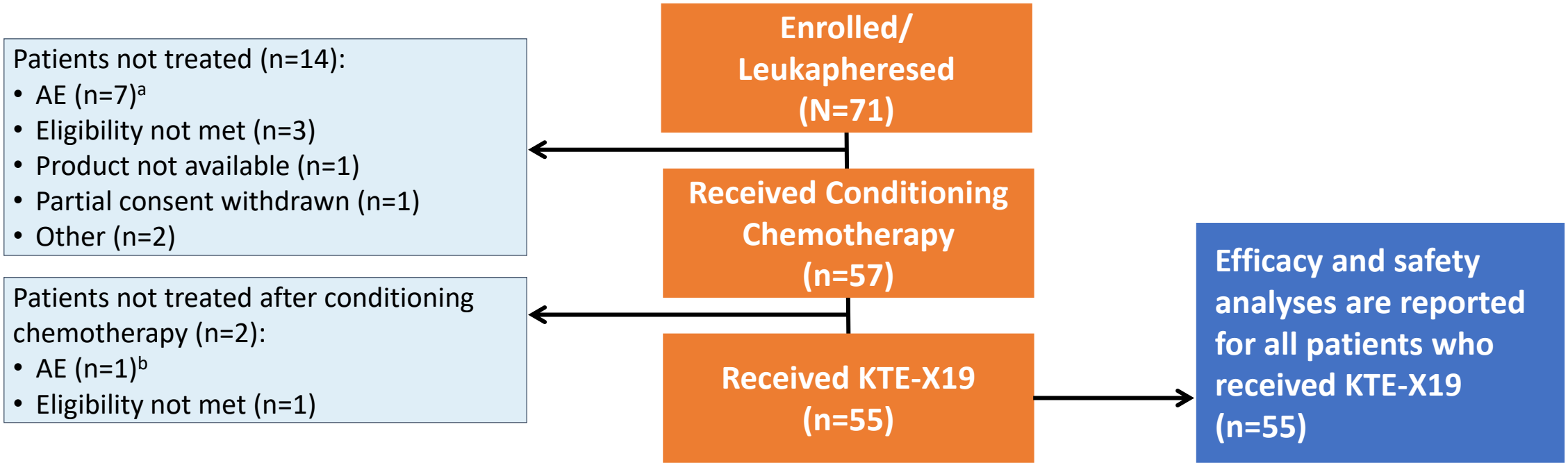
Primary Endpoint

- CR/CRi rate by central assessment

Key Secondary Endpoints

- MRD-negativity rate (10^{-4} sensitivity)
- DOR
- RFS
- OS
- Safety
- CAR T-cell levels in blood and cytokine levels in serum

ZUMA-3: Phase 2 Disposition

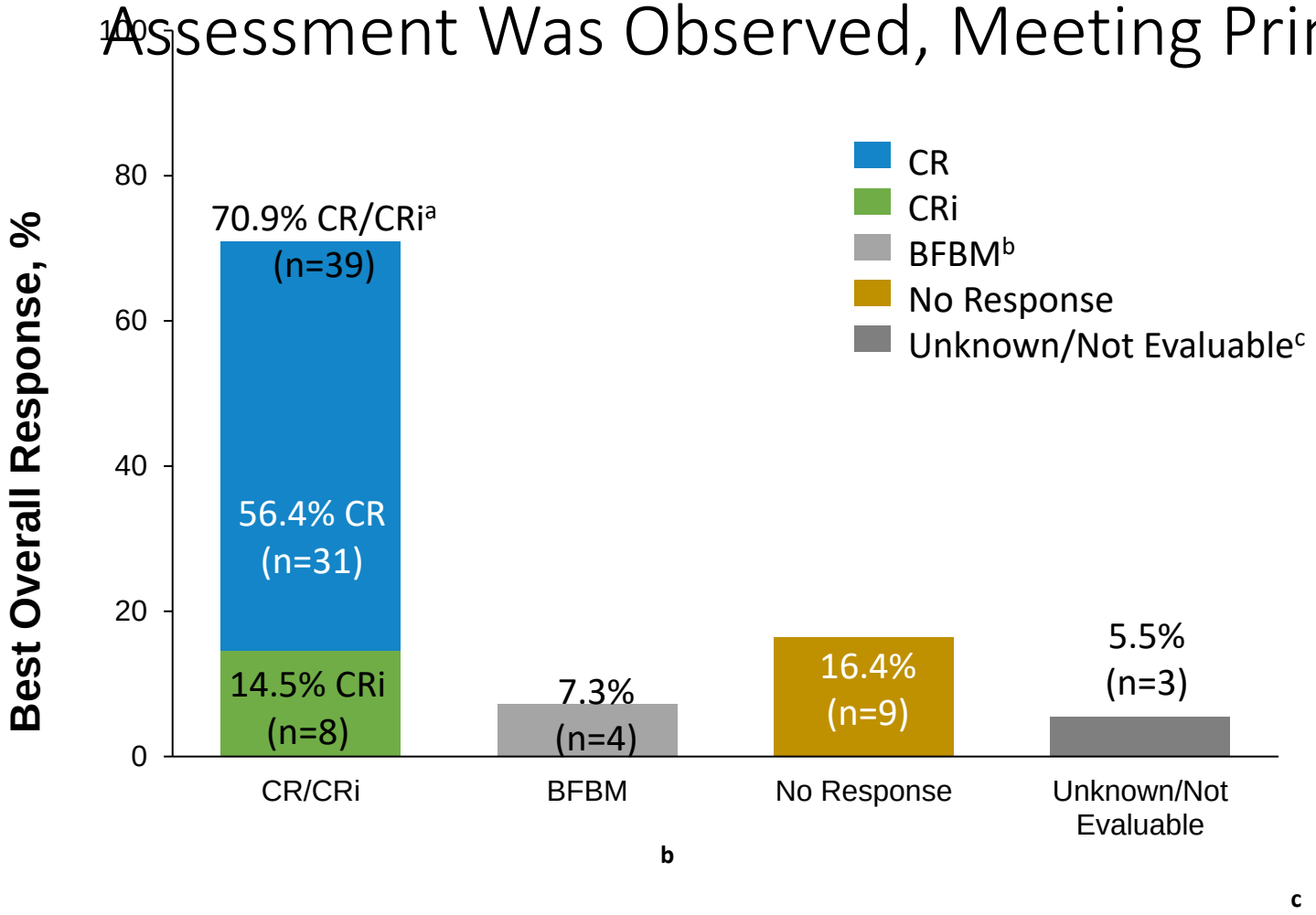


- As of September 9, 2020, the median follow-up for all treated patients was 16.4 months (range, 10.3–22.1)
- KTE-X19 was successfully manufactured for 65 of 71 enrolled patients (92%)[c]
- The median time from leukapheresis to KTE-X19 manufacturing release was 13 days for US patients and 14.5 days for European patients

ZUMA-3: Baseline Characteristics

Characteristics	N=55
Age, median (range), years	40 (19–84)
Male, n (%)	33 (60)
ECOG PS of 1, n (%)	39 (71)
Philadelphia chromosome-positive, n (%)	15 (27)
CNS-1 disease at baseline, n (%)[a]	55 (100)
Number of prior therapies, median (range)	2 (1–8)
≥3 prior lines of therapy, n (%)	26 (47)
Prior blinatumomab, n (%)	25 (45)
Prior inotuzumab ozogamicin, n (%)	12 (22)
Prior alloSCT, n (%)	23 (42)
Relapsed/refractory subgroup, n (%)	
Primary refractory	18 (33)
Relapsed/refractory to ≥2 prior systemic therapy lines	43 (78)
First relapse with remission ≤12 months	16 (29)
Relapsed/refractory post-SCT[b]	24 (44)
BM blasts at screening, median (range), %	65.0 (5–100)
BM blasts at preconditioning after bridging chemotherapy, median (range), %[c]	59.0 (0–98)

ZUMA-3: A CR/CRi Rate of 70.9% and CR Rate of 56.4% by Central Assessment Was Observed, Meeting Primary Endpoint

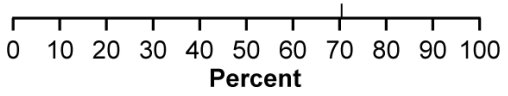


All Treated Patients (N = 55)

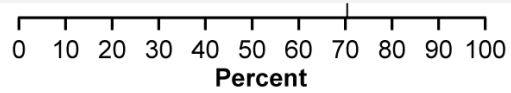
- The median time to initial CR/CRi was 1.1 months (range, 0.85–2.99)
- The MRD-negativity rate was 97% in responders, with samples unavailable for 1 patient
- Ten patients (18%), including 9 with CR/CRi and 1 with BFBM, received alloSCT at a median 98 days (range, 60–207) post–KTE-X19 infusion

ZUMA-3: CR/CRi Rate by Central Assessment Was Generally Consistent Across Subgroups

Covariates		Responding Patients/ Evaluable Patients	Percent of Patients With Response (95% CI)
Overall		39/55	71 (57–82)
Sex	Male	25/33	76 (58–89)
	Female	14/22	64 (41–83)
Age (years)	18-39	16/26	62 (41–80)
	40-64	15/21	71 (48–89)
	≥65	8/8	100 (63–100)
Baseline extramedullary disease	Yes	3/6	50 (12–88)
	No	36/49	73 (59–85)
CNS status at screening	CNS-1	34/47	72 (57–84)
	CNS-2	4/5	80 (28–99)
CD19 % lymphoblast baseline category based on central lab	≥95	29/41	71 (54–84)
	<95	9/12	75 (43–95)
% blasts in bone marrow at baseline	0–5	4/5	80 (28–99)
	>5–25	9/10	90 (55–100)
	>25–50	10/11	91 (59–100)
	>50–75	8/10	80 (44–97)
	>75–100	8/19	42 (20–67)
Philadelphia chromosome	Yes	12/15	80 (52–96)
	No	27/40	68 (51–81)

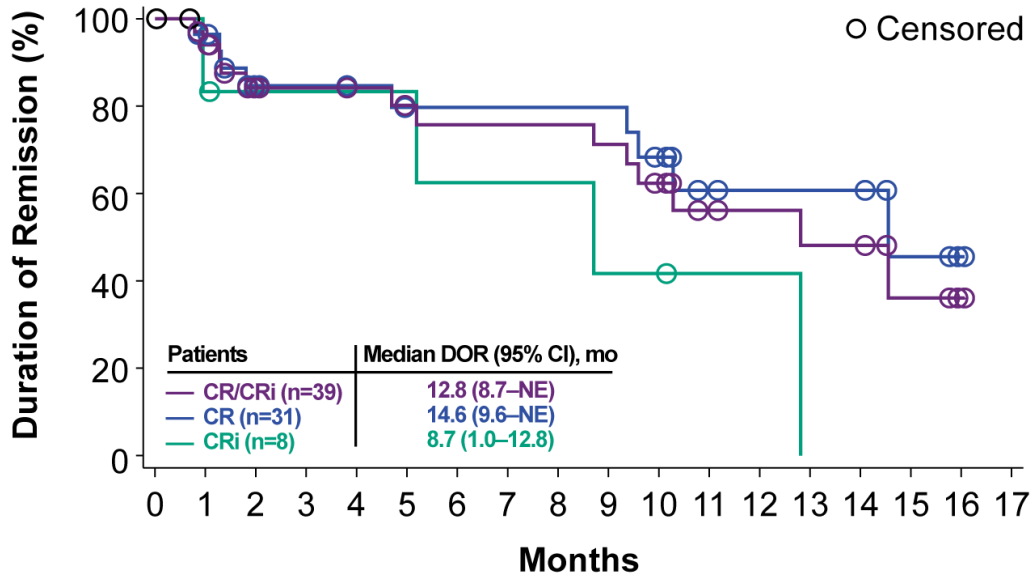


Covariates		Responding Patients/ Evaluable Patients	Percent of Patients With Response (95% CI)
Overall		39/55	71 (57–82)
Prior lines of therapy	1	9/10	90 (55–100)
	2	12/19	63 (38–84)
	3	9/14	64 (35–87)
	≥4	9/12	75 (43–95)
Prior alloSCT	Yes	16/23	70 (47–87)
	No	23/32	72 (53–86)
Prior blinatumomab	Yes	15/25	60 (39–79)
	No	24/30	80 (61–92)
Prior inotuzumab ozogamicin	Yes	8/12	67 (35–90)
	No	31/43	72 (56–85)
First relapse ≤12 months	Yes	11/16	69 (41–89)
	No	28/39	72 (55–85)
Primary refractory	Yes	14/18	78 (52–94)
	No	25/37	68 (50–82)
Relapsed/refractory post-SCT[a]	Yes	17/24	71 (49–87)
	No	22/31	71 (52–86)
Relapsed/refractory after ≥2 lines of prior therapy	Yes	28/43	65 (49–79)
	No	11/12	92 (62–100)



ZUMA-3: Median DOR Was 12.8 Months With and Without Censoring Patients at Subsequent AlloSCT

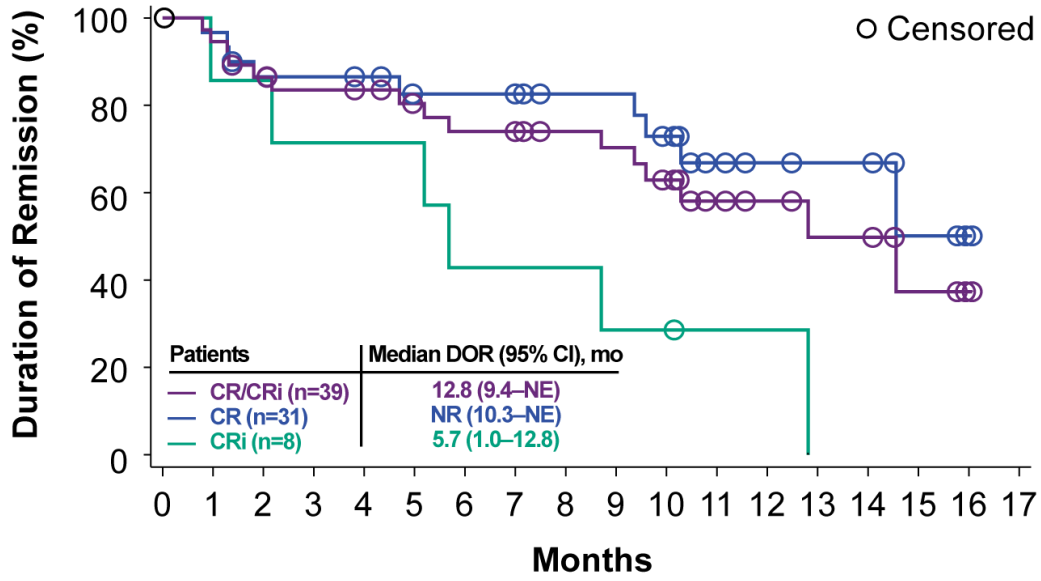
DOR With Censoring at Subsequent AlloSCT



No. at Risk

CR	31	26	19	18	17	14	14	14	14	14	11	7	6	6	6	3	1	0
CRi	8	5	4	4	4	4	3	3	3	2	2	1	1	0	0	0	0	0
CR/CRi	39	31	23	22	21	18	17	17	17	16	13	8	7	6	6	3	1	0

DOR Without Censoring at Subsequent AlloSCT

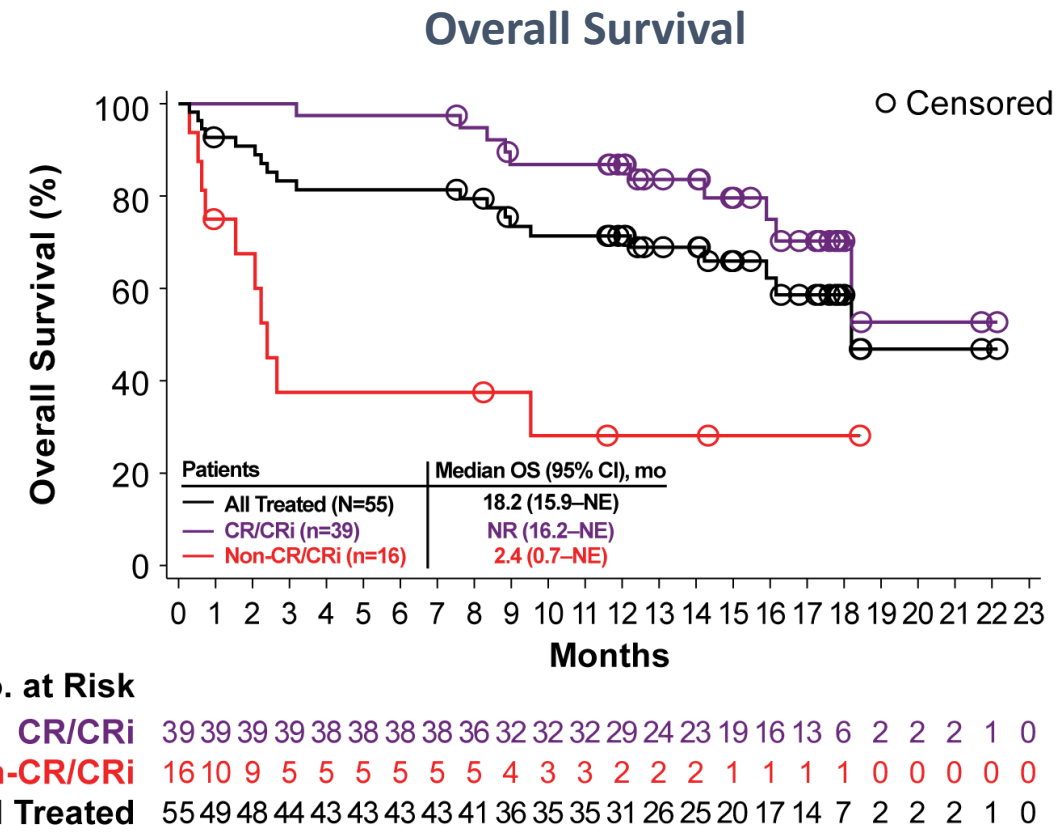


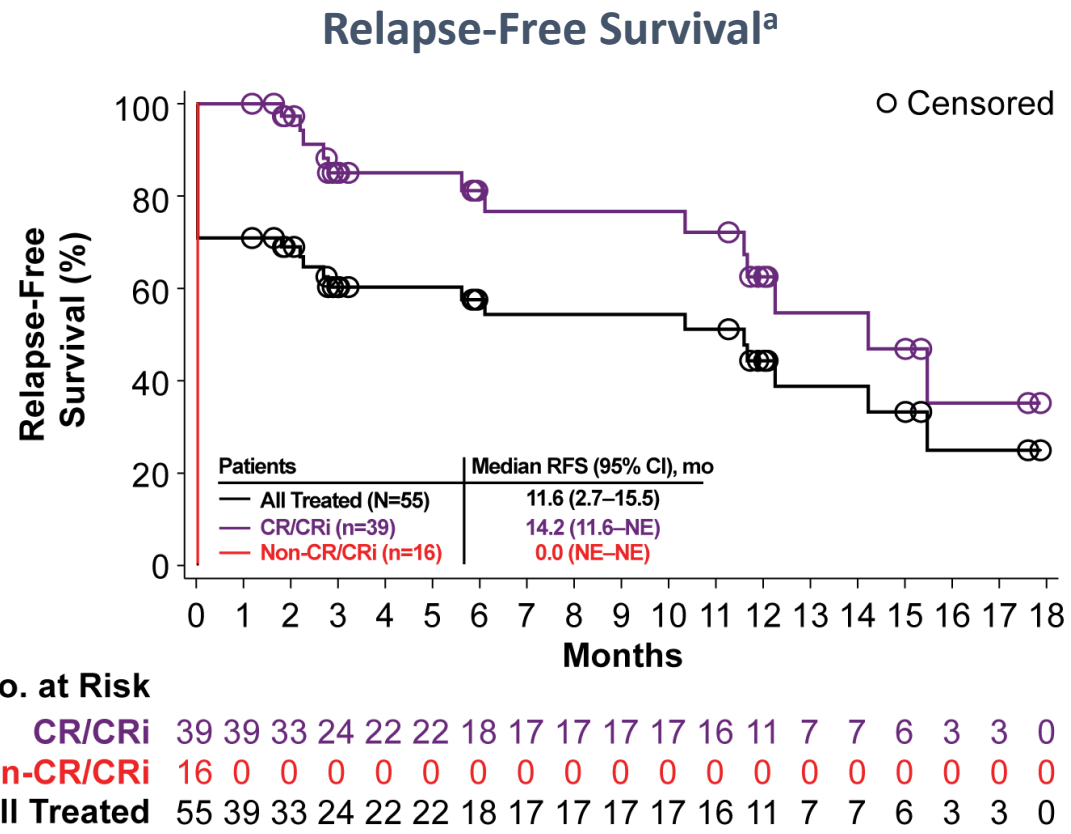
No. at Risk

CR	31	29	25	24	23	20	20	19	17	17	14	9	7	6	6	3	1	0
CRi	8	6	6	5	5	5	3	3	3	2	2	1	1	0	0	0	0	0
CR/CRi	39	35	31	29	28	25	23	22	20	19	16	10	8	6	6	3	1	0

- As of the data cutoff, 12 of 39 patients who achieved CR/CRi (31%) were in ongoing remission without subsequent alloSCT[a]

ZUMA-3: Median OS Was 18.2 Months and Median RFS Was 11.6 Months





- Among patients with CR/CRi, median OS was not reached and median RFS[a] was 14.2 months

ZUMA-3: CRS and Neurologic Events

Parameter	N=55
CRS	
Any grade CRS, n (%)[a,b]	49 (89)
Grade ≥3	13 (24)
Most common any grade symptoms, n (%)[c]	
Pyrexia	46 (94)
Hypotension	33 (67)
Median time to onset (range), days	5
Median duration of events, days	7.5
Neurologic Events	
Any grade neurologic event, n (%)[b]	33 (60)
Grade ≥3	14 (25)
Most common any grade symptoms, n (%)	
Tremor	15 (27)
Confusional state	14 (25)
Median time to onset (range), days	9
Median duration of events, days	7

- No Grade 5 CRS occurred
- One patient had Grade 5 brain herniation related to KTE-X19
- Tocilizumab, steroids, and vasopressors were given to 80%, 75%, and 40% of patients, respectively

ZUMA-3: Conclusions

- At a median follow-up of 16.4 months, a single infusion of KTE-X19 showed a high and durable response rate in heavily pretreated adults with R/R B-ALL, most of whom had high disease burden
  - The CR/CRi rate was 70.9%, with a CR rate of 56.4%; 31% of responding patients were in ongoing remission at the data cutoff
  - The CR/CRi rate was consistent across subgroups
  - The median OS was 18.2 months in all treated patients and was not yet reached in patients with CR/CRi
- The safety profile was manageable, and AEs were largely reversible
- The efficacy, rapid manufacturing, and manageable safety support the promising potential of KTE-X19 to provide long-term clinical benefit in adults with R/R B-ALL

CD19 CAR-T for Follicular Lymphoma

Efficacy and safety of tisagenlecleucel (Tisa-cel) in adult patients (Pts) with relapsed/refractory follicular lymphoma (r/r FL): Primary analysis of the phase 2 Elara trial.

Schuster et al.

Background

- CD19 CAR-T currently approved for NHL:
  - DLBCL: Axi-cel, Tisa-cel, Liso-cel
  - MCL: Axi-cel
  - FL: Axi-cel

Methods

- Patients ≥ 18 years, FL grade 1-3A, ≥ 2 lines of therapy
- Primary endpoint CR

Results

- 98 patients enrolled → 97 received Tisa-cel/Kymriah → 94 evaluable for efficacy

Efficacy	N=94
ORR CR	86% (95% CI, 78-92) 66% (95% CI, 56-75)
6 month PFS	76% (95% CI, 65-84)
6 month DOR(CR)	94% (95% CI, 82-98)

Toxicity	N=97
CRS any grade ≥ 3	49% 0%
Neuro AE any grade ≥ 3	9% 1%

DLBCL Highlights

DLBCL: Tafasitamab + Lenalidomide

Long-term analyses from L-MIND, a phase II study of tafasitamab (MOR208) combined with lenalidomide (LEN) in patients with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL).

Düll et al.

Background

- Tafasitamab (Taf) is a CD19 monoclonal antibody
- Taf + len previously approved for DLBCL R/R ≥ 1 line of therapy based on phase 2 study in ASCT ineligible patients
- Abstract provided analysis ≥ 35 month cut off

Methods

- Pts received 28-day cycles
- Taf (12 mg/kg IV), once weekly during C1–3, with a loading dose on Day 4 of C1, then every 2 weeks during C4–12
- LEN (25 mg PO) was administered on Days 1–21 of C1–12.
- After C12, progression-free pts received tafasitamab Q2W until disease progression

Tafasitamab + LEN	1 prior Tx (N=40)	2+ prior Tx (N=40)	Overall (N=80)
Best Objective Response, n (%)			
CR	19 (47.5)	13 (32.5)	32 (40.0)
PR	8 (20.0)	6 (15.0)	14 (17.5)
SD	7 (17.5)	6 (15.0)	13 (16.3)
PD	5 (12.5)	8 (20.0)	13 (16.3)
NE*	1 (2.5)	7 (17.5)	8 (10.0)
ORR (CR + PR), n (%) [95% CI]†	27 (67.5) [50.9–81.4]	19 (47.5) [31.5–63.9]	46 (57.5) [45.9–68.5]
Median DoR, months (95% CI)‡	43.9 (9.1–NR)	NR (15.0–NR)	43.9 (26.1–NR)
Median PFS, months (95% CI)‡	23.5 (7.4–NR)	7.6 (2.7–NR)	11.6 (6.3–45.7)
Median OS, months (95% CI)‡	45.7 (24.6–NR)	15.5 (8.6–NR)	33.5 (18.3–NR)

DLBCL: Loncastuximab Tesirine

Duration of response to loncastuximab tesirine in relapsed/refractory diffuse large B-cell lymphoma by demographic and clinical characteristics: Subgroup analyses from LOTIS 2.

Caimi et al.

Background

- Loncastuximab Tesirine (Lonca) is a CD19 antibody drug conjugate
- Lonca was previously approved for DLBCL R/R ≥ 2 lines of therapy based on phase 2 LOTIS-2 study
- Abstract provided subgroup analysis of duration of response (DOR)

Methods

- Lonca given 150 µg/kg every 3 weeks for 2 doses, followed by 75 µg/kg thereafter for up to 1 year

Efficacy	N=144
ORR	48.3%
CR	24.8%
PR	23.4%
Median DOR:	
All responders	12.5 months
Double HIT/Triple Hit	13.3 months
Transformed DLBCL	12.6 months
≥ 75 years old	13.4 months
Refractory to most recent line of treatment	9.3 months

DLBCL: Bispecific T-cell Engager (BITE) updates

Phase 3 trial (GCT3013-05) of epcoritamab versus standard of care in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL).

Promising tolerability and efficacy results from dose-escalation in an ongoing phase Ib/II study of mosunetuzumab (M) with polatuzumab vedotin (Pola) in patients (pts) with relapsed/refractory (R/R) B-cell non-Hodgkin's lymphoma (B-NHL).

Classical Hodgkin Lymphoma Highlights

2021 ASCO ANNUAL MEETING

CALGB 50801 (ALLIANCE): PET ADAPTED THERAPY IN BULKY STAGE I/II CLASSIC HODGKIN LYMPHOMA (CHL)

Ann S. LaCasce, Travis Dockter, Amy S. Ruppert, Stephanie Peterson, Lale Kostakoglu, Heiko Schöder, Eric D. Hsi, Jeffrey A Bogart, Bruce D. Cheson, Nina D. Wagner-Johnston, Jeremy S. Abramson, Kami J. Maddocks, John P. Leonard, Nancy L. Bartlett

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Classic HL with Bulky Disease: PET2 negative

Study	Eligibility	bulky	PET2-	Therapy	PFS/EFS
ECOG 2496[1]	Stage I-IIX n=264	n=264	N/A	ABVD x 6 + RT Stanford 5 + RT	5 yr EFS: 85% 5 yr EFS: 79%
					BULKY ONLY
RATHL[2]	Unfavorable II, III/IV n=1203	N/A	n=119	PET2 negative subset ABVD x 6 vs ABVD x 2 + AVD x 4	3 yr PFS: 91.5%
					ALL UNFAVORABLE
EORTC H10 [3]	Unfavorable I/II n=1196	n=515	n=375	ABVD x 6 vs ABVD x 4 + RT	5 yr PFS: 90% vs 92%
HD17[4]	Unfavorable I/II n=1096	n=199	N/A	Esc BEACOPP x 2/ABVD x 2 + RT vs PET directed RT	5 yr PFS: 97% vs 96%

[1] Advani JCO 2015; [2] Johnson NEJM 2016; [3] Andre JCO 2017; [4] Borchmann Lancet Onc 2021

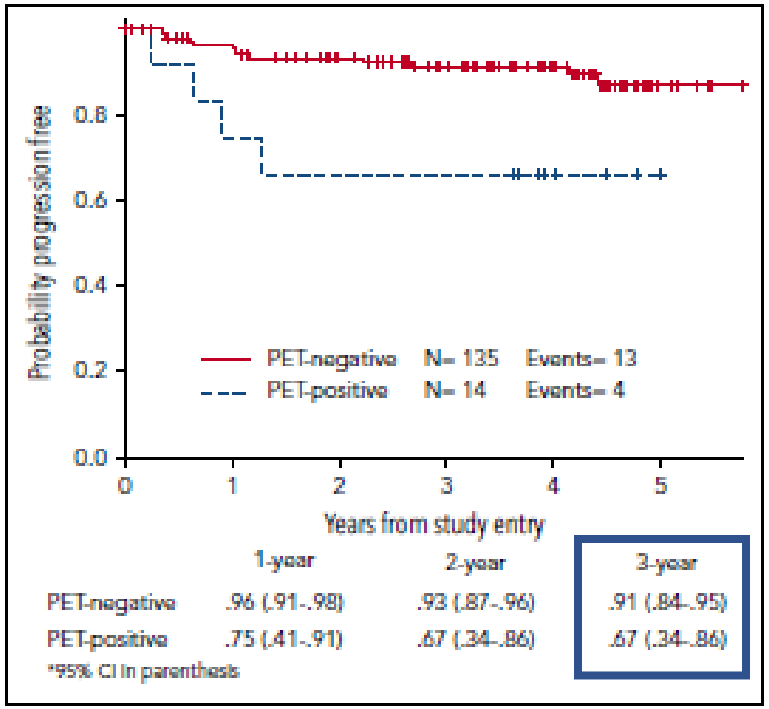
Classic HL with Bulky Disease: PET2 positive

Study	Eligibility	bulky	PET2+	Therapy	PFS/EFS
					ALL UNFAVORABLE
EORTC H10[3]	Unfavorable I/II n=1196	n=515	n=140	ABVD x 4 + RT vs ABVD x 2/esc BEACOPP x 2 + RT	5 yr PFS: 78% vs 91%
HD17[4]	Unfavorable I/II n=1096	n=199	N/A	Esc BEACOPP x 2/ABVD x 2 + RT	5 yr PFS: 82%

[3] Andre JCO 2017; [4] Borchmann Lancet Onc 2021

Background: Classic HL with Bulky Disease

Alliance 50604
Stage I/II without bulk

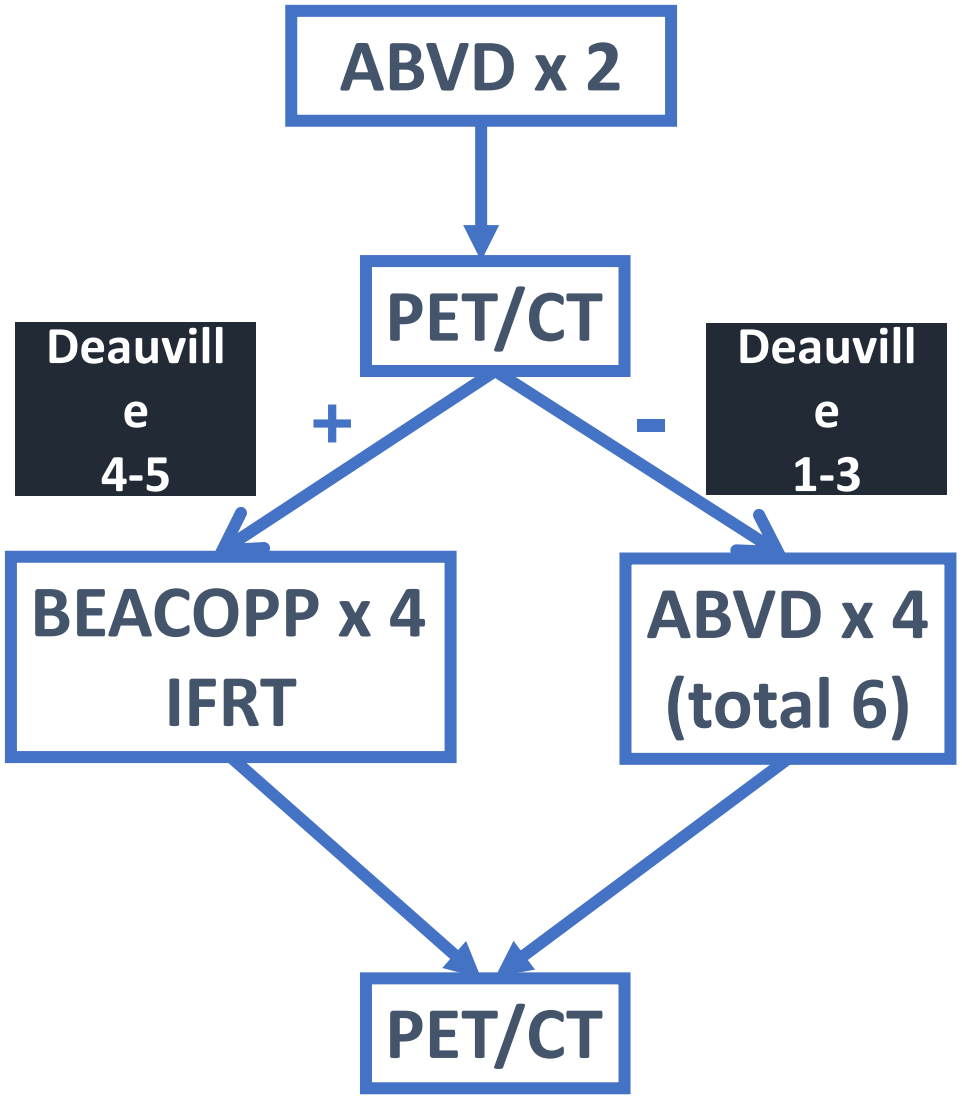


Straus et al. Blood 2018

- **Radiotherapy is associated with late toxicities.**
- **Interim PET following 2 cycles of ABVD is associated with progression free survival.**

Hypotheses:

- **PET2 negative patients do not require RT.**
- **PET2 positive patients will benefit from escalation to BEACOPP + RT.**



Eligibility:

Histologically documented stage I and II classical HL

Mass > 10 cm or mediastinal mass > .33 maximal intrathoracic diameter on CXR

Performance status 0-2

LVEF by ECHO or MUGA within normal limits*

DLCO ≥ 60% with no symptomatic pulmonary disease *

Age ≥ 18

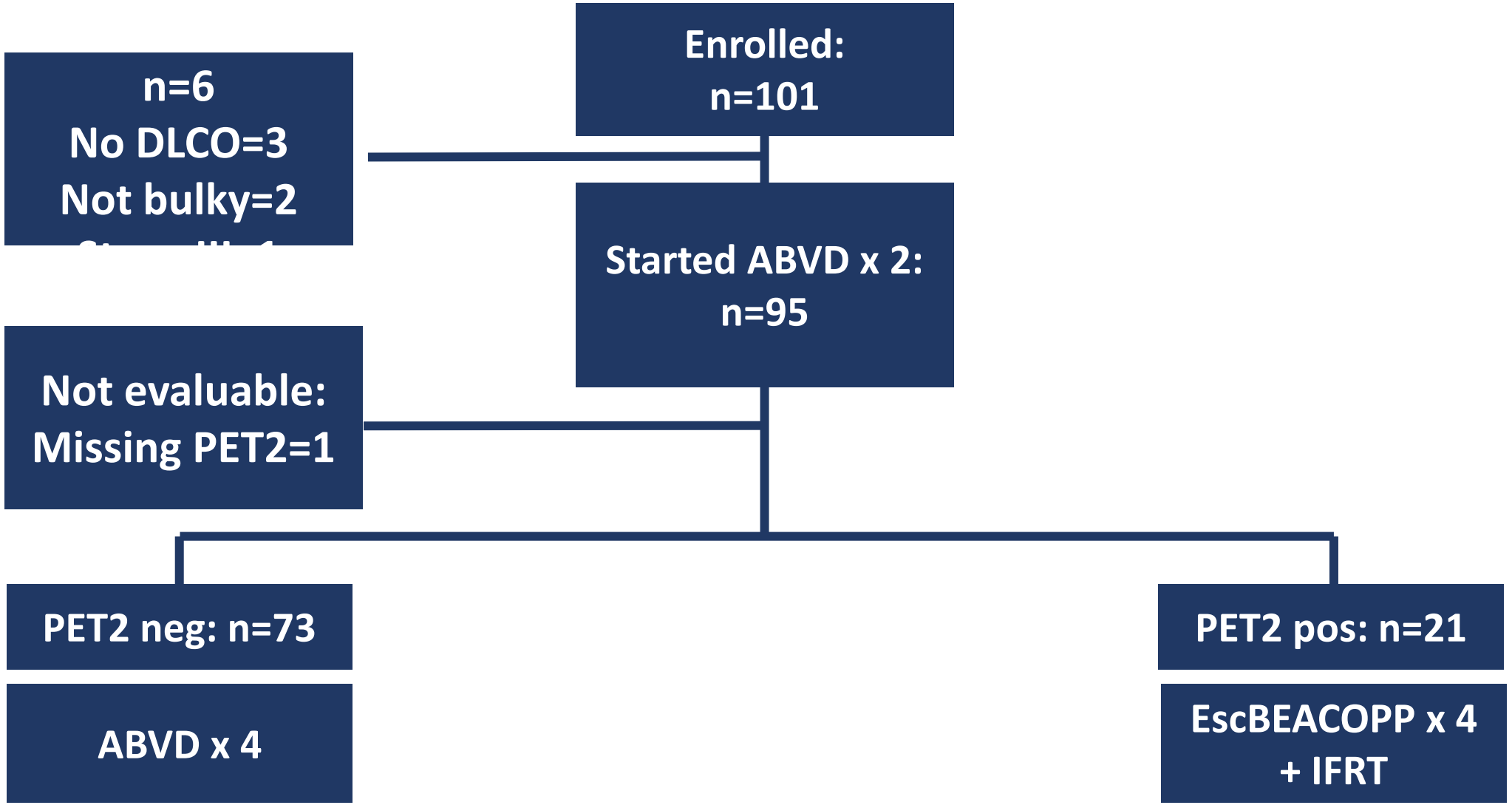
Patients s/p up to 1 cycle of ABVD eligible assuming all baseline eligibility met

* Unless disease related

Study Design

- Primary endpoint: progression-free survival (PFS), defined as the time from study entry to disease progression or death
- Sample size: 93
  - 30% PET2 positive
  - Testing: Hazard ratio = 4.10 (3-yr PFS: 40% PET2+ vs. 80% PET2-)
    vs. Hazard ratio = 2.29 (3-yr PFS: 60% PET2+ vs. 80% PET2-)
  - Power = 80%
  - Type I error rate = 0.15 (1-sided)
- Final analysis after all patients had been followed for at least 3 years post-study entry.

Patient Disposition



Characteristic	Total n=94	PET2 negative n=73	PET2 positive n=21	P value
Female Sex, n (%)	50 (53)	41 (56)	9 (43)	0.33
Age median (range)	30 (18-58)	30 (18-58)	28 (19-56)	0.39
Stage, n (%)				0.78
IA/IAE	7 (7)	6 (8)	1 (5)	
IB	2 (2)	2 (3)	0 (0)	
IIA/IIAE	37 (39)	30 (41)	7 (33)	
IIB/IIBE	48 (51)	35 (48)	13 (62)	
ECOG PS, n (%)				0.14
0	64 (68)	52 (71)	12 (57)	
1	29 (31)	21 (29)	8 (38)	
2	1 (1)	0 (0)	1 (5)	
Prior ABVD, n (%)	15 (16)	13 (18)	2 (10)	0.51

Baseline Characteristics

78% PET2 negative

Pulmonary Toxicity

PET2 negative
ABVD x 6
51 of 73 (70%) received all 6 cycles of bleomycin

Adverse Event	Any grade	Grade 3	Grade 4
Cough	45 (62%)	2 (3%)	0 (0%)
Dyspnea	42 (58%)	2 (3%)	0 (0%)
Hypoxia	1 (1%)	1 (1%)	0 (0%)
Pneumonitis	3 (4%)	1 (1%)	0 (0%)

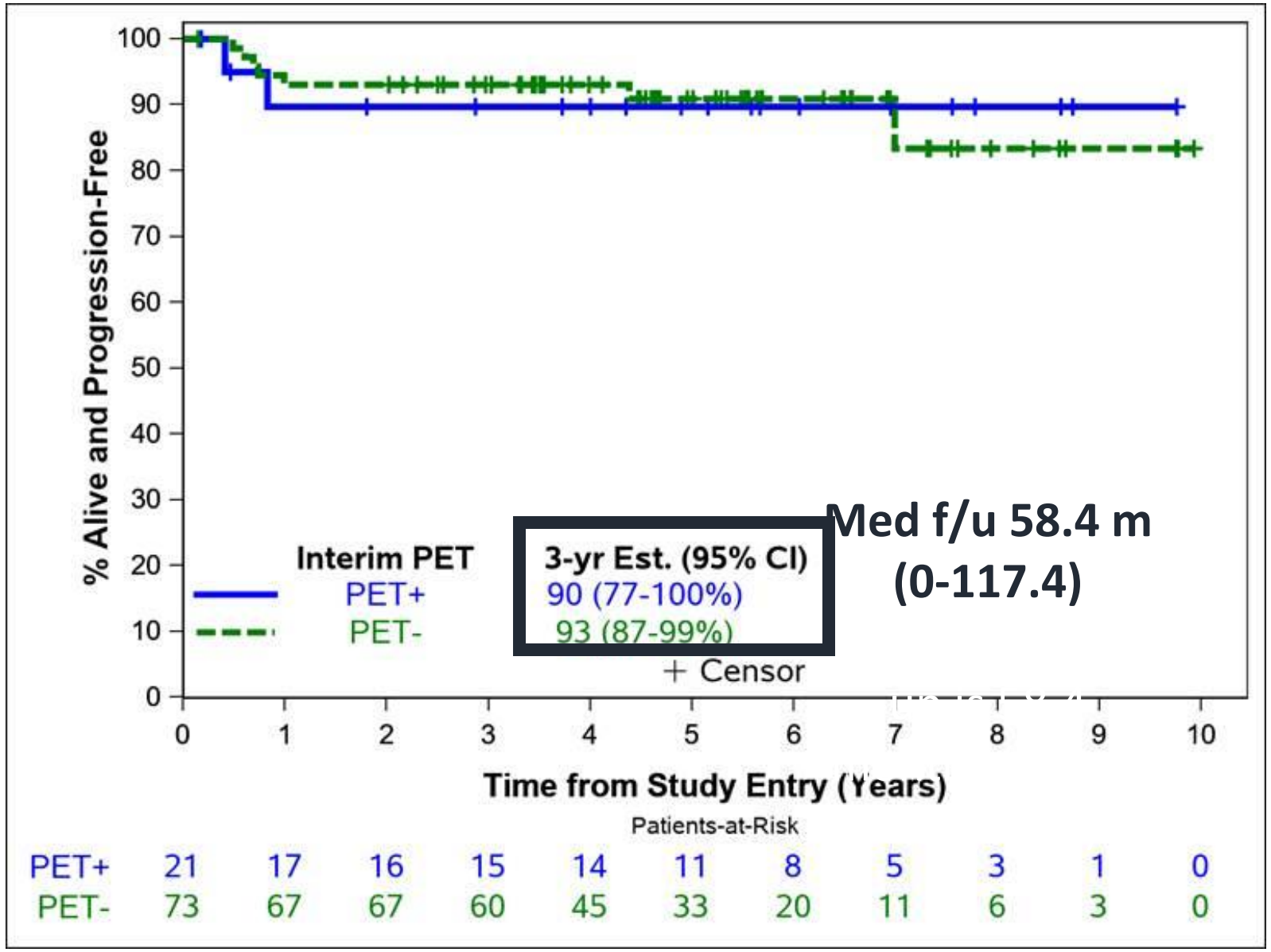
PET2 positive
ABVD x 2/BEACOPP x 4 + RT
16 of 21 (76%) received all 6 cycles of bleomycin

Adverse Event	Any grade	Grade 3	Grade 4
Cough	13 (62%)	0 (0%)	0 (0%)
Dyspnea	7 (33%)	0 (0%)	0 (0%)
Hypoxia	0 (0%)	0 (0%)	0 (0%)
Pneumonitis	0 (0%)	0 (0%)	0 (0%)

Hematologic/Infectious Toxicity

PET2 negative ABVD x 6			
Adverse Event	Any grade	Grade 3	Grade 4
Neutrophils	68 (93%)	9 (12%)	54 (74%)
Platelets	6 (8%)	1 (1%)	1 (1%)
F+N	6 (8%)	6 (8%)	0 (0%)
Sepsis	0 (0%)	0 (0%)	0 (0%)

PET2 positive ABVD x 2/BEACOPP x 4 + RT			
Adverse Event	Any grade	Grade 3	Grade 4
Neutrophils	21 (100%)	6 (29%)	12 (57%)
Platelets	15 (71%)	3 (14%)	3 (14%)
F+N	2 (10%)	2 (10%)	0 (0%)
Sepsis	1 (5%)	0 (0%)	1 (5%)



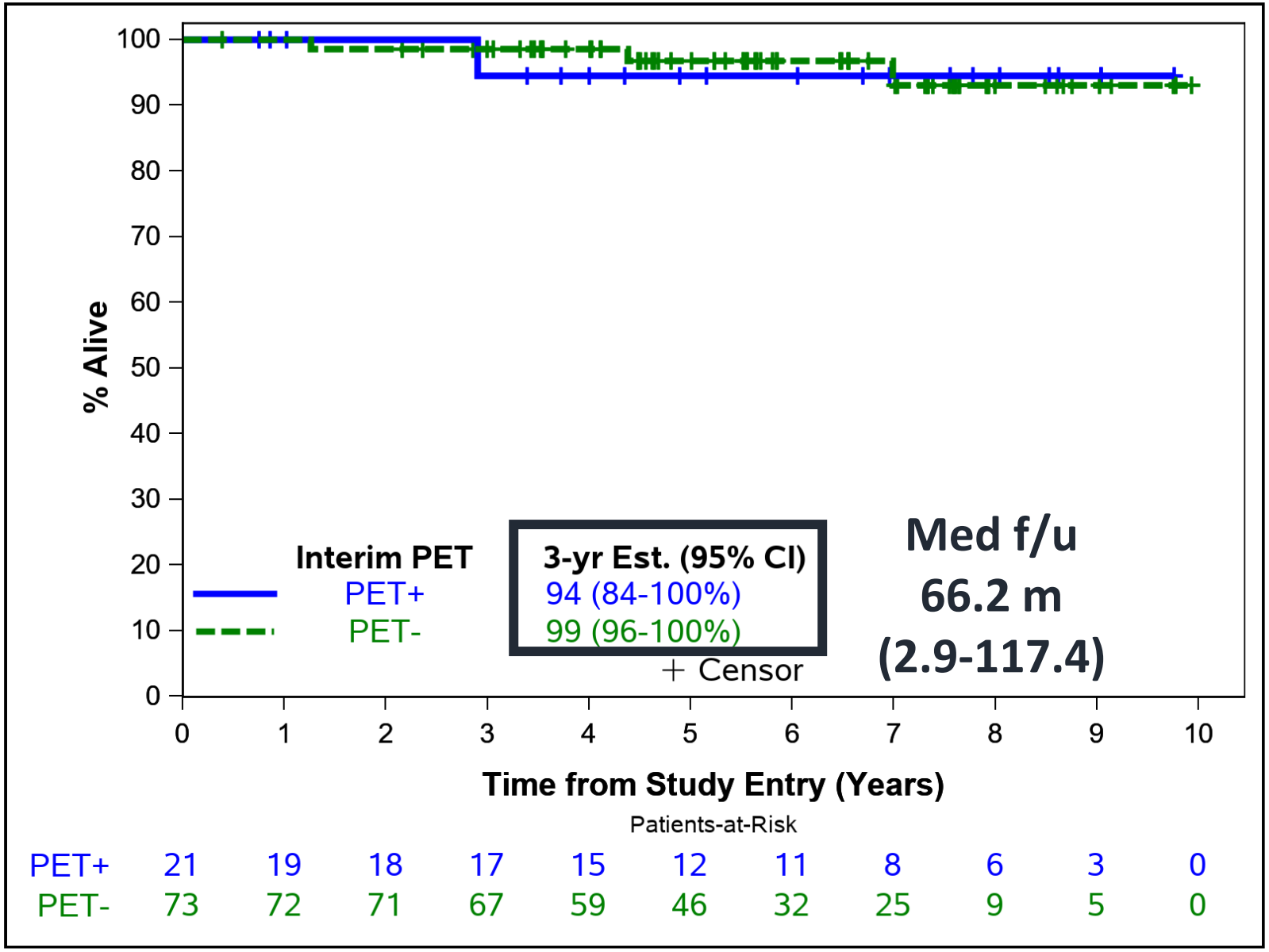
Med f/u 58.4 m (0-117.4)

Progression-free survival

PET2+ vs PET2-

Hazard Ratio = 1.03

85% Upper Confidence Bound = 2.38



- Overall Survival

1 death in PET2 positive:

Pneumonia, lymphoma

3 deaths in PET2 negative:

Lymphoma
Anaplastic astrocytoma
COPD

Conclusions

- First prospective study limited to bulky stage I/II cHL
- PET adapted therapy was associated with excellent PFS in all patients
- 78% of patients did not require radiotherapy or exposure to escBEACOPP
- Unexpectedly, PET2 positive patients with bulky disease appear to have improved outcomes compared to stage I/II patients with non-bulky disease (Alliance 50604)
  - **Small patient numbers : bulky = 21, non-bulky = 14**
  - **4 versus 2 cycles of escBEACOPP**

Conclusions

- Limitations:
  - **Small number of PET2 positive patients**
  - **Non-randomized**
- Recommend: omit RT in PET2 negative patients who receive 6 cycles of A(B)VD
- Future directions: comparison for future studies incorporating novel agents with respect to efficacy, safety and cost