2021 ASH Key Studies

Lymphomas	Multiple Myeloma and Nonmalignant Hematologic Disorders	Leukemias
• POLARIX • RE-MIND2 • ZUMA-7 • SEQUOIA	• GMMG-HD7 • GRIFFIN • BELLINI • Fostamatinib (ITP)	• Dasatinib low-dose vs SOC • ASCEMBL • CPX-351 vs HMA-venetoclax • IPSS-M

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CLINICAL QUESTION

POLARIX Clinical Trial

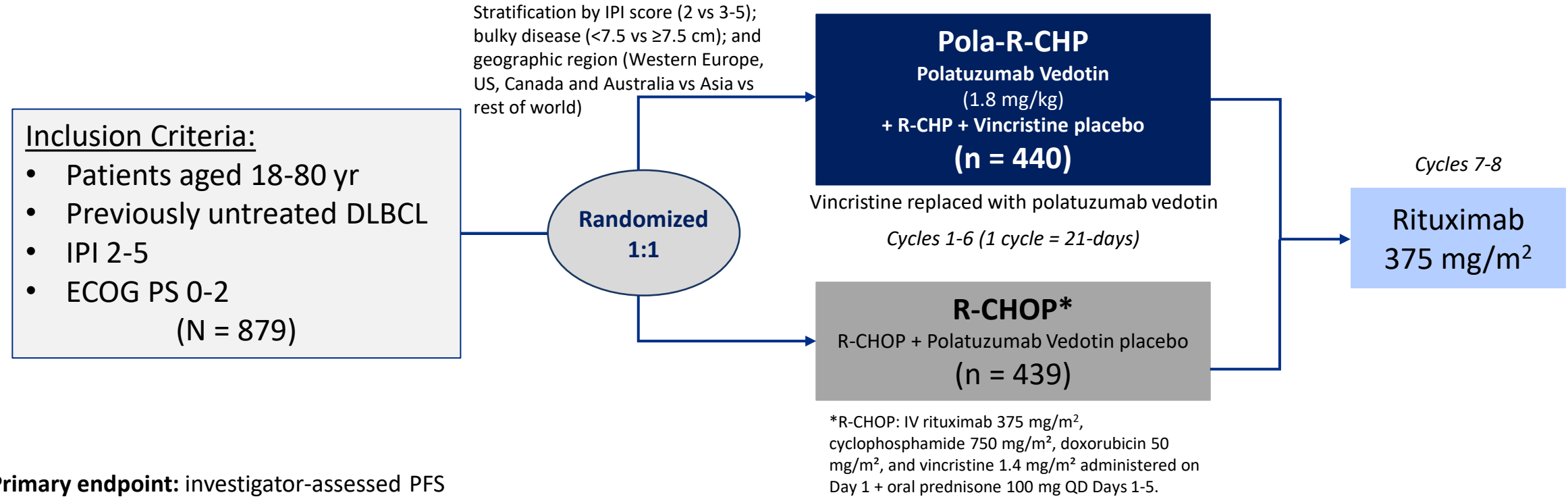
Does polatuzumab vedotin with rituximab, cyclophosphamide, doxorubicin, and prednisone (Pola-R-CHP) provide benefit over SOC (R-CHOP) to patients with diffuse large B-cell lymphoma without prior treatment?

KEY DATA

POLARIX Clinical Trial

Study Design: Multicenter, randomized, double-blind, placebo-controlled phase III trial

Polatuzumab vedotin is an ADC targeting CD79b that is ubiquitously expressed on DLBCL cells



Primary endpoint: investigator-assessed PFS

Secondary Endpoints: EFS, CRR at end of treatment, DFS, OS, Safety

Median follow up at the primary analysis was 28.2 months; June 28, 2021 (clinical cut-off date)

CRR, complete response rate (at end of treatment, PET/CT, IRC-assessed); DFS, disease-free survival; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; IPI, International Prognostic Index; OS, overall survival; PFS, progression-free survival; PS, performance status; R-CHP, rituximab plus cyclophosphamide/doxorubicin/prednisone; R-CHOP, rituximab plus cyclophosphamide/doxorubicin/vincristine/prednisone.

Tilly. ASH 2021. Abstr LBA1.

KEY DATA

POLARIX Clinical Trial

Baseline Characteristics

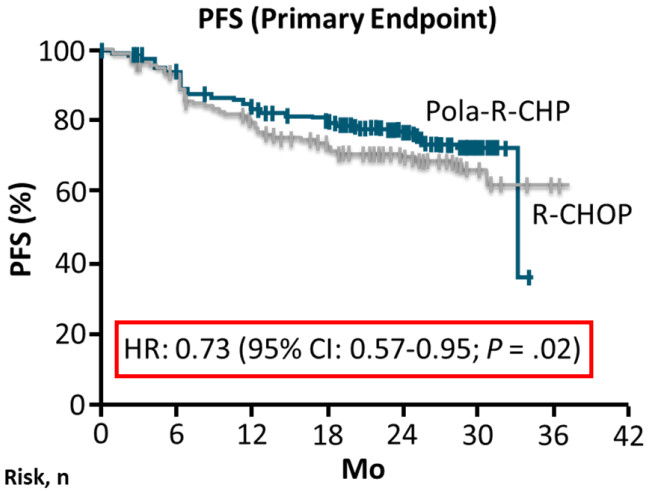
Characteristic	Polatuzumab Vedotin + R-CHP (n = 440)	R-CHOP (n = 439)
Median age, yr (range)	65 (19-80)	66 (19-80)
Male, n (%)	239 (54)	234 (53)
ECOG PS 0/1, n (%)	374 (85)	363 (83)
Bulky disease (≥7.5 cm), n (%)	193 (44)	192 (44)
Elevated LDH, n (%)	291 (66)	284 (65)
Median time from diagnosis to treatment initiation, days	26	27
Ann Arbor stage III/IV, n (%)	393 (89)	387 (88)
Extranodal sites (≥2), n (%)	213 (48)	213 (49)
IPI score		
▪ 2	167 (38)	167 (38)
▪ 3-5	273 (62)	272 (62)
Cell of origin		
▪ ABC (Activated B-Cell)	102 (31)	119 (35)
▪ GCB (Germinal center B-cell)	184 (56)	168 (50)
▪ Unclassified	44 (13)	51 (15)
***MYC/BCL2* expression**	139 (38)	151 (41)
***MYC/BCL2/BCL6* rearrangement**	26 (8)	19 (6)

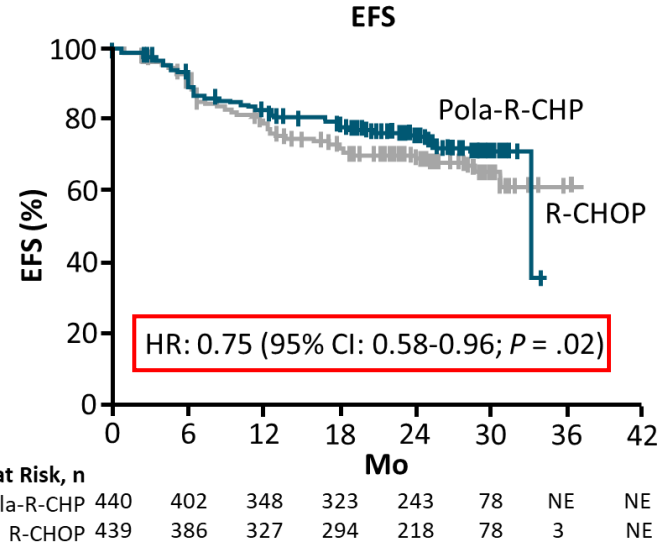
Tilly. ASH 2021. Abstr LBA1.

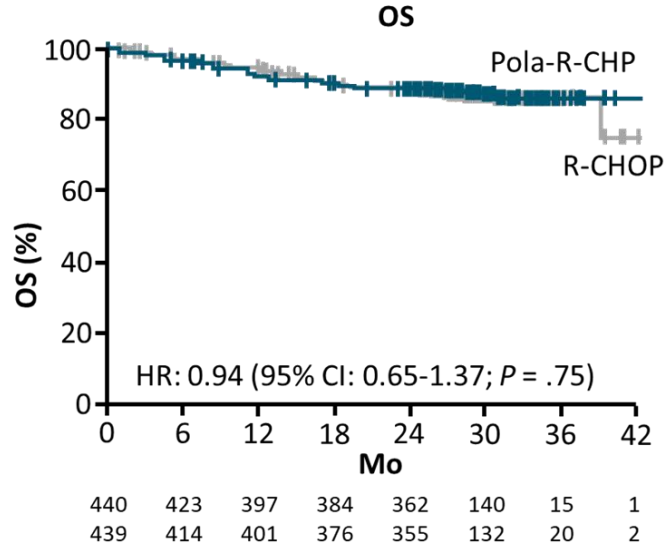
KEY DATA

POLARIX Clinical Trial

Efficacy







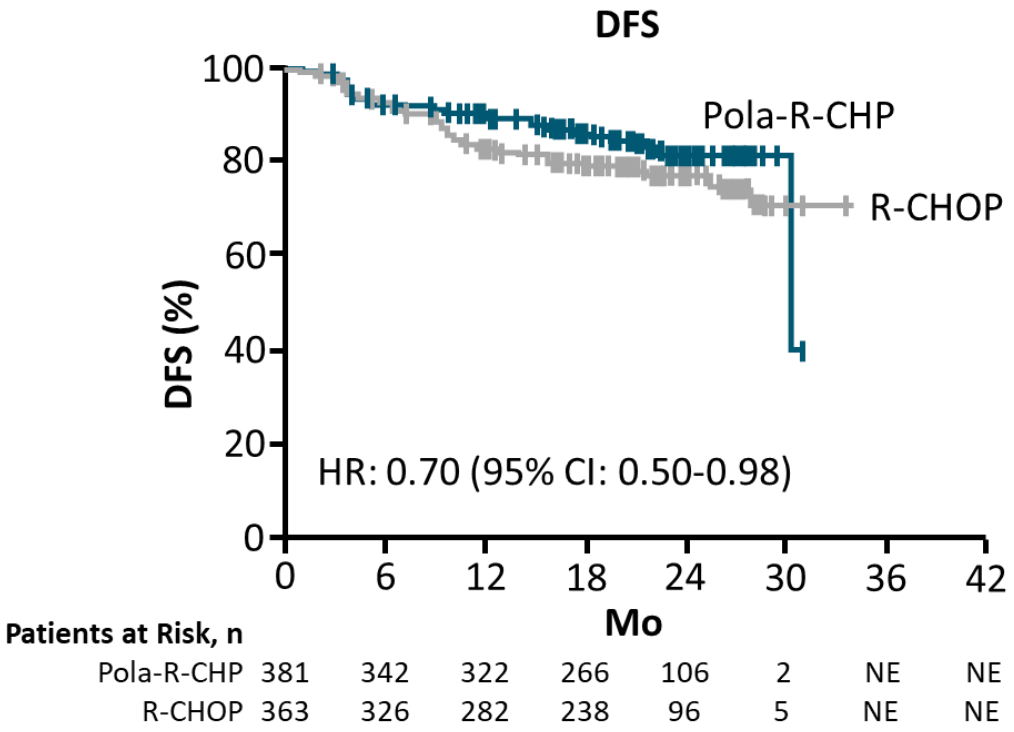
	Polatuzumab Vedotin + R-CHP	R-CHOP
Progression-Free Survival (PFS) at 24 months	**76.7%**	**70.2%**
	Δ 6.5%	

Tilly. ASH 2021. Abstr LBA1.

KEY DATA

POLARIX Clinical Trial

Efficacy



	Polatuzumab Vedotin + R-CHP (n = 440)	R-CHOP (n = 439)
Complete Response (CR)	86.6%	82.7%
Partial Response (PR)	9.3%	11.4%
Overall Survival (OS) at 24 months	88.7%	88.6%
Hazard Ratio (95% CI)	0.94 (0.65, 1.37), *P* = 0.75	

- DFS indicated that patients that achieved a CR with Pola R-CHP were more likely to maintain remission than those that achieved a CR with R-CHOP

Median follow up of 28.2 months

Tilly. ASH 2021. Abstr LBA1.

POLARIX Clinical Trial

Subsequent Therapy (after probation or relapse)

Subsequent Therapy at Data Cutoff, % (n)	Polatuzumab Vedotin + R-CHP	R-CHOP
Any treatment*	22.5 (99)	30.3 (133)
Radiotherapy	9.3 (41)	13.0 (57)
Systemic therapy†	17.0 (75)	23.5 (103)
Stem Cell Transplant	3.9 (17)	7.1 (31)
CAR T-cell	2.0 (9)	3.6 (16)

- At data cutoff, 99 of 440 patients (22.5%) in the polatuzumab vedotin arm and 133 of 439 patients (30.3%) in the R-CHOP arm had received ≥1 subsequent course of therapy not specified in the trial protocol
- Unblinding was permitted for individual patients after disease progression, with 8 patients in the R-CHOP arm receiving polatuzumab vedotin as part of subsequent therapy

*Subsequent lymphoma treatment was defined as non-protocol anti-lymphoma therapy
†Includes any monotherapy, multi-drug, or cell-based regimen

Tilly. ASH 2021. Abstr LBA1.

POLARIX Clinical Trial

Adverse Events

N (%)	Pola-R-CHP (n=435)	R-CHOP (n=438)
Any grade AEs	426 (97.9)	431 (98.4)
Grade 3-4	251 (57.7)	252 (57.5)
Grade 5	13 (3.0)	10 (2.3)
Serious AEs	148 (34.0)	134 (30.6)
AE leading to discontinuation of any study drug	27 (6.2)	29 (6.6)
AE leading to discontinuation of polatuzumab vedotin / vincristine	19 (4.4)	22 (5.0)
Dose reduction of any study drug	40 (9.2)	57 (13.0)

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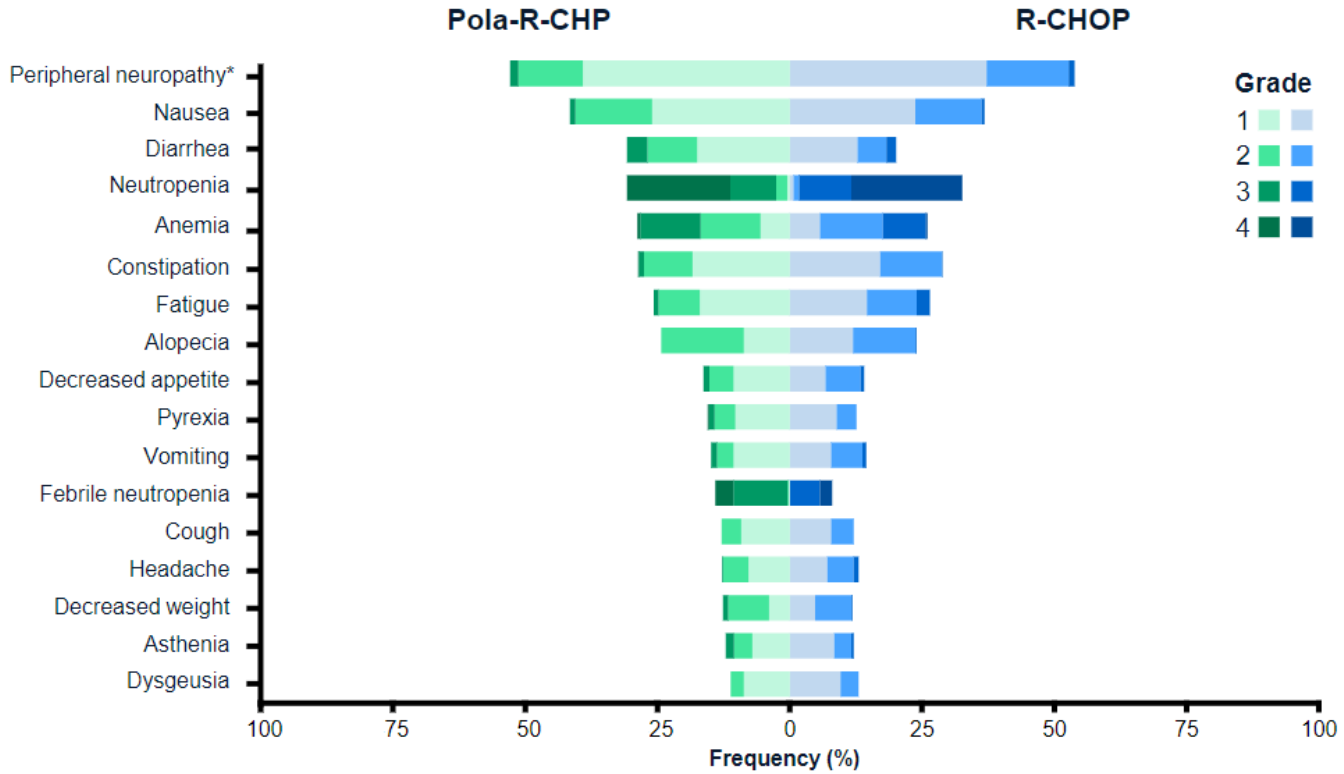
POLARIX Clinical Trial

Common Adverse Events



*The frequency and severity of peripheral neuropathy were similar for Pola-R-CHP vs R-CHOP

- Any grade, 52.9% vs 53.9%
- Grade 3–4, 1.6% vs 1.1%

Tilly. ASH 2021. Abstr LBA1.

SUMMARY

POLARIX Clinical Trial

- POLARIX: First positive study in frontline setting for DLBCL in two decades
- Pola-R-CHP increased PFS and EFS in patients with intermediate- and high-risk previously untreated DLBCL vs standard of care R-CHOP
  - At 2 years, 27% reduction in relative risk of disease progression, relapse of death vs R-CHOP
    - PFS: HR 0.73, 95% CI: 0.57-0.95; *P* <0.02
    - EFS: HR 0.75, 95% CI: 0.58-0.96; *P*=0.02
- Comparable safety profile

In **June 2019**, the FDA granted accelerated approval to polatuzumab vedotin (administered via intravenous infusion at a dosage of 1.8 mg/kg every 21 days for 6 cycles), in combination with bendamustine plus rituximab, for the treatment of adults with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who have received at least two prior therapies.

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POLARIX Clinical Trial

Use of polatuzumab vedotin with R-CHP provided benefit to patients with diffuse large B-cell lymphoma in the frontline setting compared to standard of care (R-CHOP)

Potential to become a standard of care option in the frontline setting
More to come…

2021 ASH Key Studies

Lymphomas	Multiple Myeloma and Nonmalignant Hematologic Disorders	Leukemias
• POLARIX • RE-MIND2 • ZUMA-7 • SEQUOIA	• GMMG-HD7 • GRIFFIN • BELLINI • Fostamatinib (ITP)	• Dasatinib low-dose vs SOC • ASCEMBL • CPX-351 vs HMA-venetoclax • IPSS-M

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RE-MIND2 Study

Does the use of tafasitamab in combination with lenalidomide improve outcomes for patients with relapsed or refractory diffuse large B-cell lymphoma?

An observational, retrospective cohort study
Real-world evidence

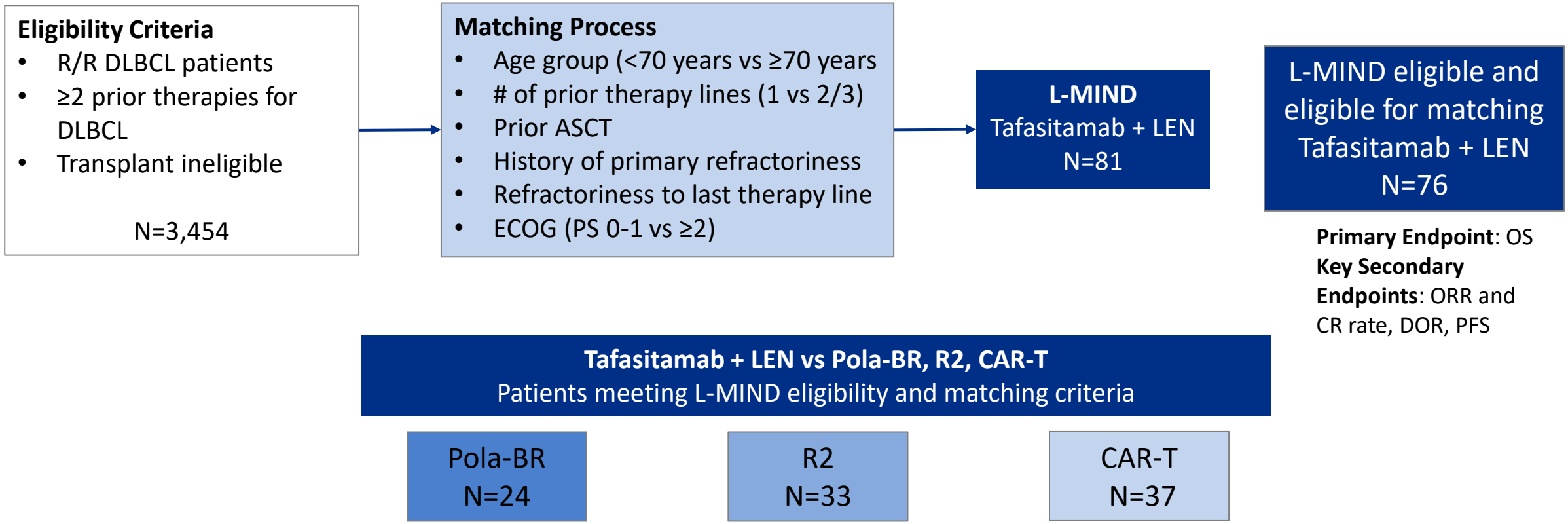
RE-MIND2 primary analysis compared patient outcomes from L-MIND with matched patient populations treated with R-GemOx, BR and pooled systemic NCCN/ESMO recommended therapies for ASCT ineligible patients with R/R DLBCL

cornerstone specialty network™

KEY DATA

RE-MIND2 Study

Study Design: Expanded analysis comparing tafasitamab plus LEN versus Pola-BR, R2 and CAR-T therapies



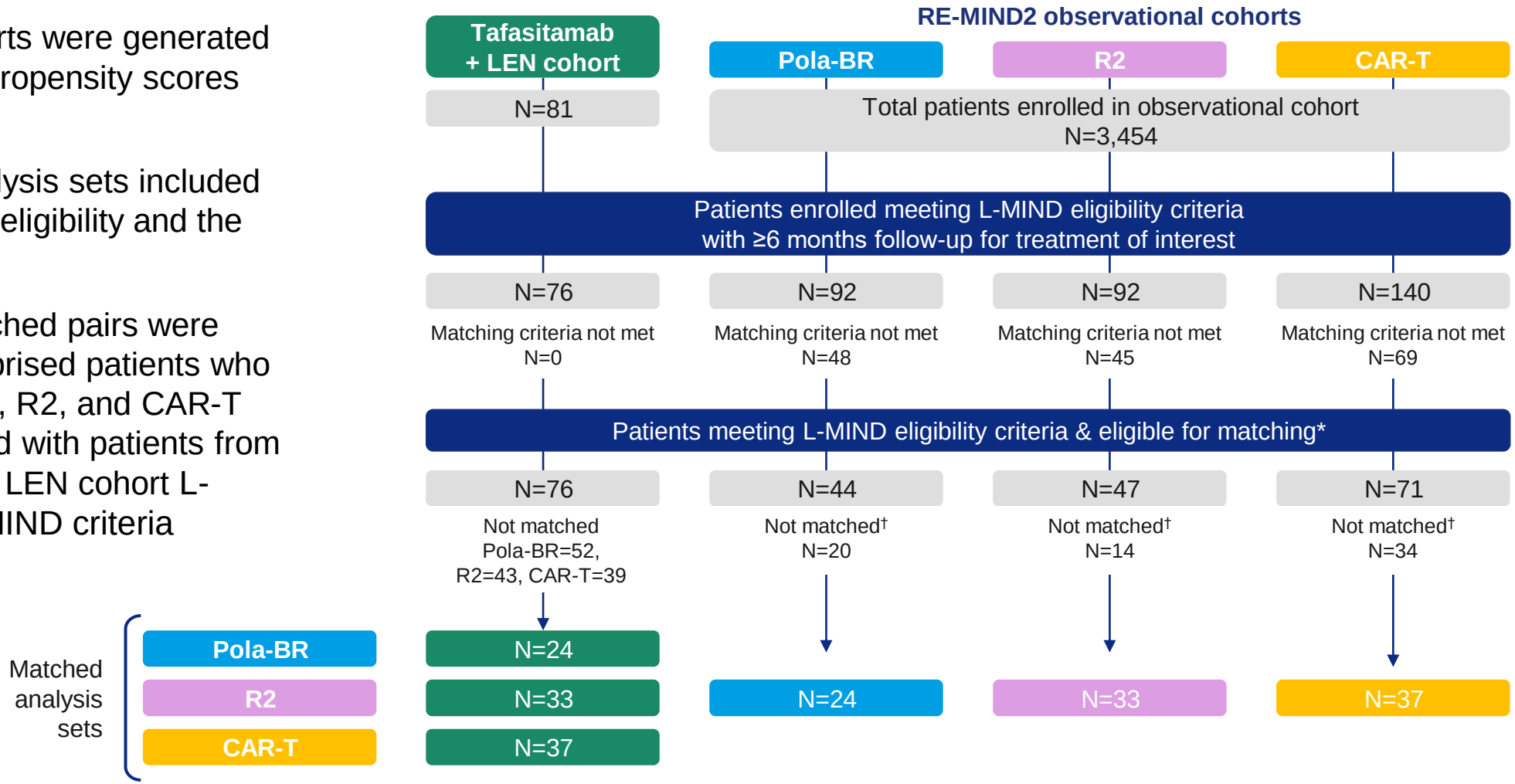
ASCT, autologous stem cell transplant; CAR-T, CD-19 chimeric antigen receptor T-cell therapies; CR, complete response, DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; ECOG, Eastern cooperative Oncology Group performance status; LEN, lenalidimide; ORR, Overall response rate; OS, overall survival; PFS, progression-free survival; Pola-BR, polatuzumab vedotin plus bendamustine and rituximab; R2, rituximab plus lenalidomide

Nowakowski. ASH 2021. Abstr 183.

KEY DATA

RE-MIND2 Study

- Comparator cohorts were generated using estimated propensity scores and 1:1 matching
- The resulting analysis sets included patients who met eligibility and the matching criteria
- Patient-level matched pairs were created and comprised patients who received Pola-BR, R2, and CAR-T therapies matched with patients from the tafasitamab + LEN cohort L-MIND criteria L-MIND criteria



*With complete data for six matching covariates, Based on 1:1 nearest neighbor propensity score.
CAR-T, CD19 chimeric antigen receptor T-cell therapies; LEN, lenalidomide; Pola-BR, polatuzumab vedotin plus bendamustine and rituximab; R2, rituximab plus lenalidomide; R/R, relapsed/refractory.

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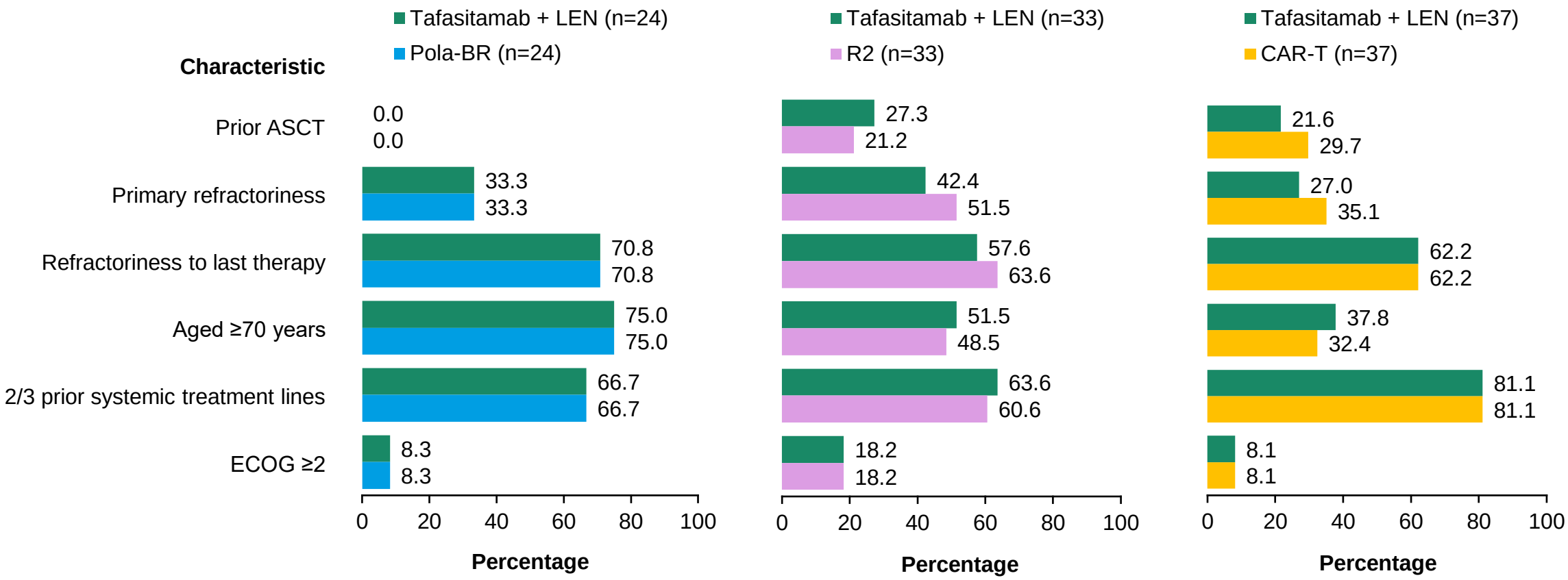
KEY DATA

RE-MIND2 Study

A high degree of covariate balance was achieved



ASCT, autologous stem-cell transplant; CAR-T, CD19 chimeric antigen receptor T-cell therapies; ECOG, Eastern Cooperative Oncology Group; LEN, lenalidomide; Pola-BR, polatuzumab vedotin plus bendamustine plus rituximab; R2, rituximab plus lenalidomide.

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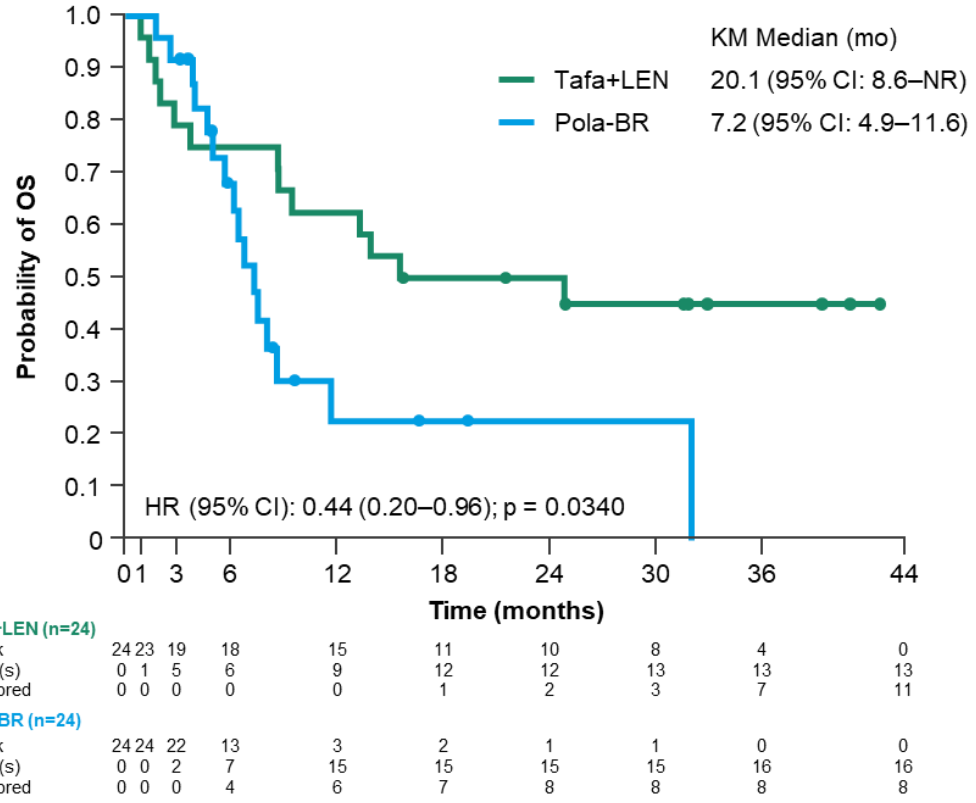
KEY DATA

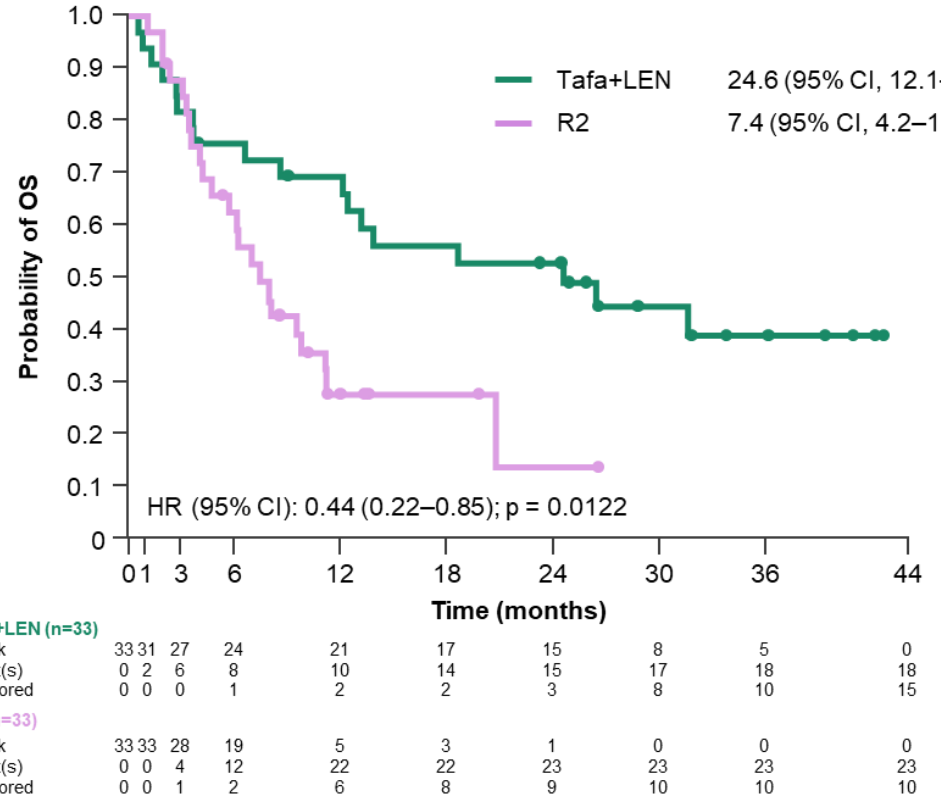
RE-MIND2 Study

Primary Endpoint: OS

Tafasitamab + LEN was associated with statistically significant improvements in OS versus Pola-BR and versus R2



Median duration of follow-up: tafasitamab plus + LEN: 32 mo; Pola-BR: 16.6 mo



Median duration of follow-up: tafasitamab plus + LEN: 32; mo; R2: 13.4 mo

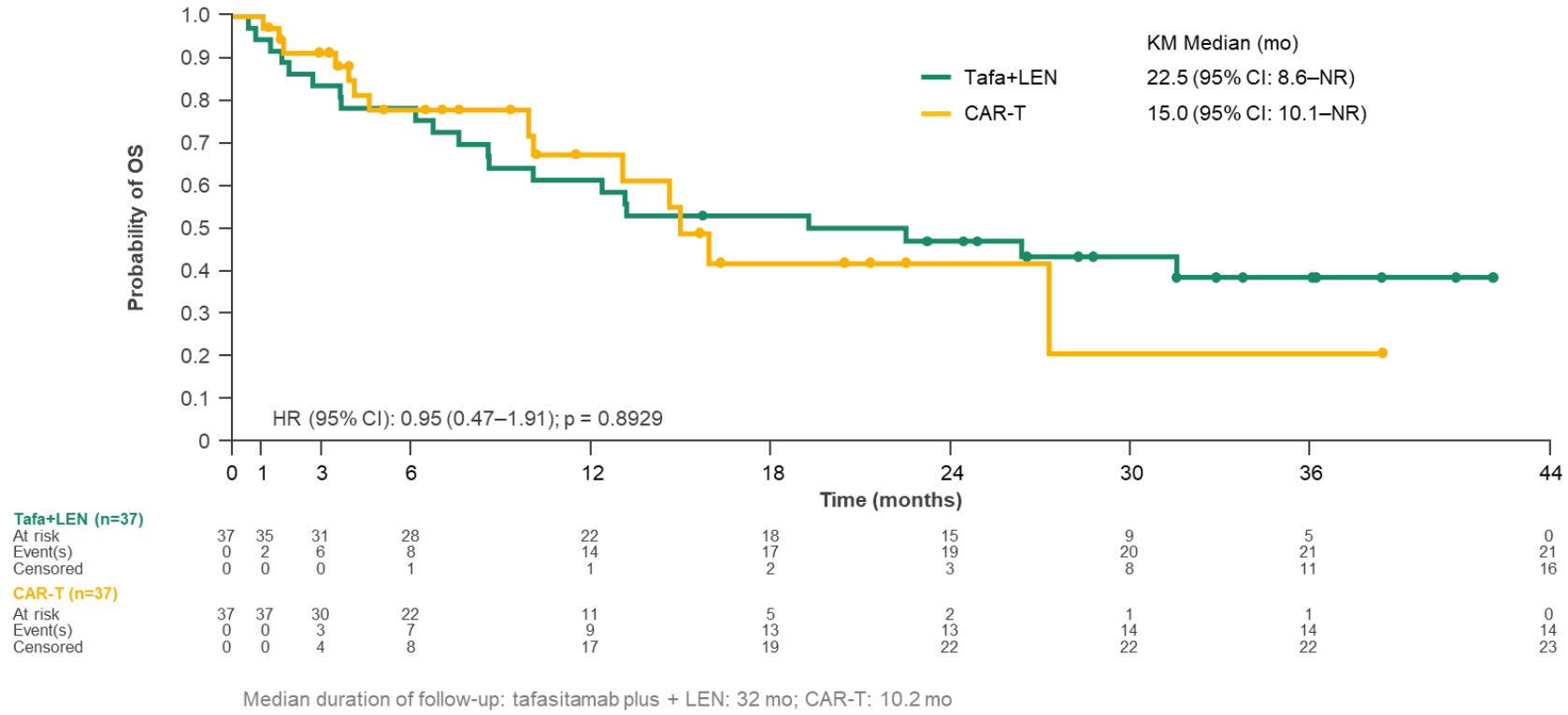
CI, confidence interval; KM, Kaplan-Meier; LEN, lenalidomide; mo, month; NR, not reached; Pola-BR, polatuzumab vedotin plus bendamustine plus rituximab; OS, overall survival; R2, rituximab plus lenalidomide; Tafa, tafasitamab. P values were calculated using Log-rank test.

Nowakowski. ASH 2021. Abstr 183.

KEY DATA

RE-MIND2 Study

Primary Endpoint: OS



Median duration of follow-up: tafasitamab plus + LEN: 32 mo; CAR-T: 10.2 mo

CAR-T, CD19 chimeric antigen receptor T-cell; CI, confidence interval; KM, Kaplan-Meier; LEN, lenalidomide; mo, month; NR, not reached; OS, overall survival; Tafa, tafasitamab.

- A comparable OS benefit with tafasitamab + LEN versus CAR-T (22 versus 15 months), without statistical significance, was observed

Nowakowski. ASH 2021. Abstr 183.

KEY DATA

RE-MIND2 Study

Secondary Endpoint: ORR and CR

	Tafasitamab + LEN (n=24) Median duration of follow-up 32 months	Pola-BR (n=24) Median duration of follow-up 16.6 months	P Value
ORR (95% CI)	62.5% (40.6 – 81.2)	58.3% (36.6 – 77.8)	Not significantly different
CR (95% CI)	29.2% (12.6 – 51.1)	20.8% (7.1 – 42.2)	

	Tafasitamab + LEN (n=33) Median duration of follow-up 32 months	R2 (n=33) Median duration of follow-up 13.4 months	P Value
ORR (95% CI)	**63.6%** (45.1 – 79.6)	**30.3%** (15.6 – 48.7)	**0.0130**
CR (95% CI)	**39.4%** (22.9 – 57.9)	**15.2%** (5.1 – 31.9)	0.0514

	Tafasitamab + LEN (n=37) Median duration of follow-up 32 months	CAR-T (n=37) Median duration of follow-up 10.2 months	P Value
ORR (95% CI)	59.5% (42.1 – 75.2)	75.7% (58.8 – 88.2)	Not significantly different
CR (95% CI)	37.8% (22.5 – 55.2)	43.2% (27.1 – 60.5)	

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KEY DATA

RE-MIND2 Study

Secondary Endpoint: PFS and DOR

	Tafasitamab + LEN (n=24) Median duration of follow-up 32 months	Pola-BR (n=24) Median duration of follow-up 16.6 months	HR (95% CI) P Value
Median PFS, months (95% CI)	8.0 (1.9 – 19.9)	5.0 (2.5 – 5.6)	0.482 (0.217 – 1.073) 0.0689
Median DOR (95% CI)	17.7 (3.6 – 34.8)	2.3 (0.3 – 6.1)	

	Tafasitamab + LEN (n=33) Median duration of follow-up 32 months	R2 (n=33) Median duration of follow-up 13.4 months	HR (95% CI) P Value
Median PFS, months (95% CI)	5.9 (3.6 – 36.7)	2.8 (2.0 – 5.8)	0.511 (0.281 – 0.927) **0.0252**
Median DOR (95% CI)	34.8 (3.6 – 34.8)	12.4 (2.8 – 19.3)	

	Tafasitamab + LEN (n=37) Median duration of follow-up 32 months	CAR-T (n=37) Median duration of follow-up 10.2 months	HR (95% CI) P Value
Median PFS, months (95% CI)	6.3 (3.6 – 22.5)	4.0 (3.1 – 12.8)	0.612 (0.302 – 1.240) 0.1696
Median DOR (95% CI)	26.1 (4.4 – NR)	5.9 (2.0 – 10.0)	

Nowakowski. ASH 2021. Abstr 183.

SUMMARY

RE-MIND2 Study

- In this retrospective cohort analysis, OS was statistically different with tafasitamab plus lenalidomide versus pola-BR and R2 in patients with relapsed or refractory DLBCL who are ineligible for transplant
  - Tafasitamab + LEN 20.1 months compared to Pola-BR 7.2 months (p=0.034)
  - Tafasitamab + LEN 24.6 months compared to R2 7.4 months (p=0.012)
- A comparable but not significant OS was observed with tafasitamab + LEN vs CAR-T
- ORR and CR were improved with treatment with tafasitamab + LEN vs R2
  - ORR: tafasitamab plus lenalidomide at 63.6% versus R2 at 30.3% (p=0.013)
  - CR: tafasitamab plus lenalidomide 39.4% versus 15.2% for R2 (p=0.0514)

July 31, 2020: The FDA granted accelerated approval for MONJUVI® (tafasitamab-cxix), a CD19-directed cytolytic antibody, indicated combination with lenalidomide for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant (ASCT).

Nowakowski. ASH 2021. Abstr 183.

RE-MIND2 Study

Use of tafasitamab + LEN provides benefit to patients with DLBCL in the 2L setting and offers another valuable treatment option for patients

2021 ASH Key Studies

Lymphomas	Multiple Myeloma and Nonmalignant Hematologic Disorders	Leukemias
• POLARIX • RE-MIND2 • ZUMA-7 • SEQUOIA	• GMMG-HD7 • GRIFFIN • BELLINI • Fostamatinib (ITP)	• Dasatinib low-dose vs SOC • ASCEMBL • CPX-351 vs HMA-venetoclax • IPSS-M

CLINICAL QUESTION

ZUMA-7 Clinical Trial

Does the use of CAR-T (axicabtagene ciloleucel) in the 2L setting provide benefit over SOC for patients with relapsed/refractory large B-cell lymphoma (LBCL)?

KEY DATA

ZUMA-7 Clinical Trial

Study Design: Global, multicenter, randomized phase III trial

Stratified by 1L treatment response, 2L age-adjusted IPI

Inclusion Criteria:
Patients ≥18 yr with LBCL, ECOG PS 0-1, R/R disease with ≤12 mo of adequate 1L CIT (including anti-CD20 mAb and an anthracycline), and intent to proceed to HDT-ASCT
(N = 359)

R 1:1

Axicabtagene ciloleucel
(Axi-Cel; 2 x 10^6 CAR T-cells/kg) after conditioning chemotherapy**
(n = 180)

SOC*
(2-3 cycles of investigator-selected, protocol defined, platinum-based CIT)
(n = 179)

**Conditioning regimen: cyclophosphamide 500 mg/m^2/day + fludarabine 30 mg/m^2/day on Days 5, 4, and 3 prior to CAR t-cell infusion. Optional bridging therapy limited to corticosteroids (no CIT).

Responders (CR/PR)
HDT-ASCT (n = 64)

Non-responders
Off-protocol Tx‡

*SOC included R-GDP, R-DHAP, R-ICE, or R-ESHAP.

‡56% received subsequent cellular immunotherapy.

- Refractory disease was defined as no CR to 1L therapy; relapsed disease was defined as CR followed by biopsy-proven disease relapse ≤12 months from completion of 1L therapy.
- Axi-cel patients underwent leukapheresis followed by conditioning chemotherapy with cyclophosphamide (500 mg/m2/day) and fludarabine (30 mg/m2/day) 5, 4, and 3 days before receiving a single axi-cel infusion (target intravenous dose, 2×10^6 CAR-T cells/kg).
- EFS was defined as time from randomization to the earliest date of disease progression per Lugano Classification, commencement of new lymphoma therapy, or death from any cause.

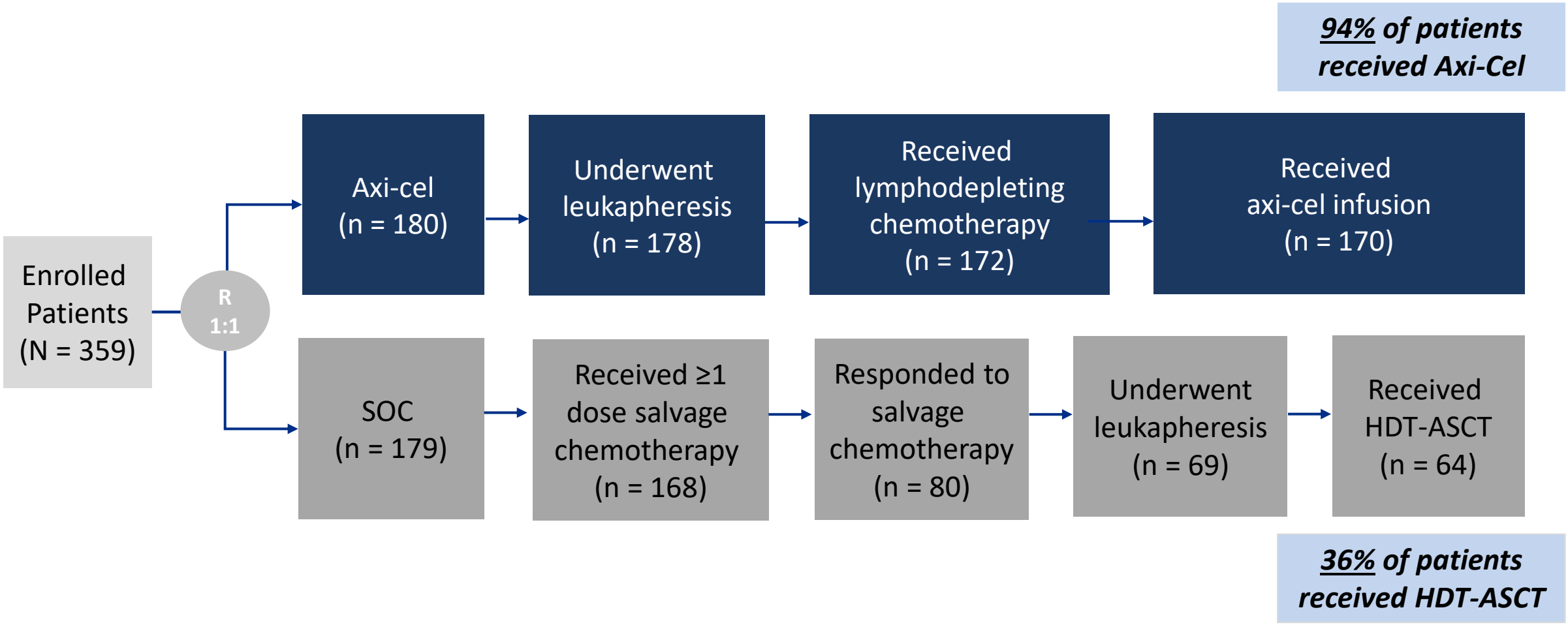
Primary endpoints: EFS (BICR)
Key secondary endpoints: ORR and OS (tested hierarchically)
Secondary endpoints: PFS, safety, PROs

No protocol-specified crossover; median follow-up: 24.9 months
Data cutoff: March 18, 2021

Locke. ASH 2021. Abstr 2.

KEY DATA

ZUMA-7 Clinical Trial



Locke. ASH 2021. Abstr 2.

KEY DATA

ZUMA-7 Clinical Trial

Baseline Characteristics

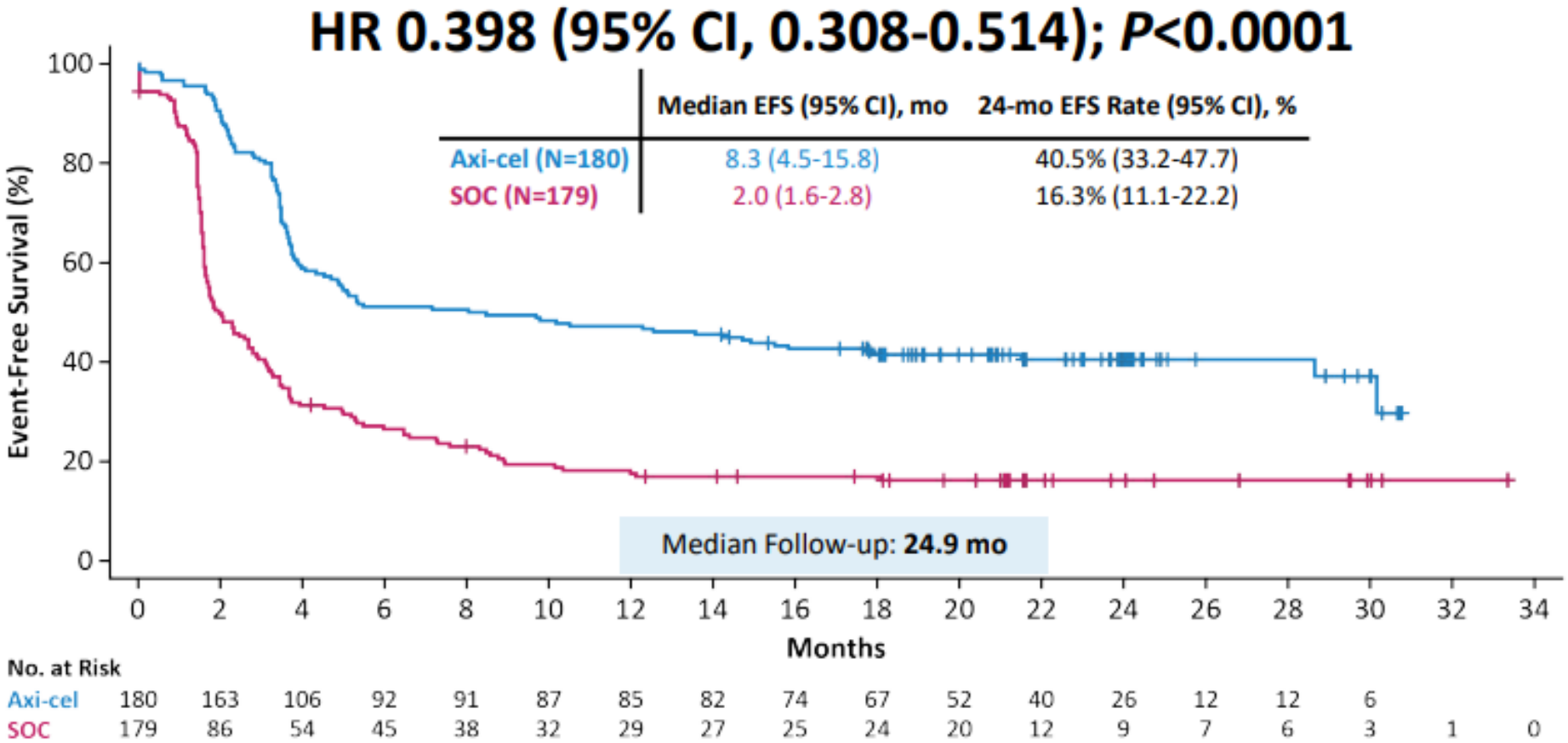
Characteristic	Axi-cel (n = 180)	SOC (n = 179)	Overall (N = 359)
Median age, yr (range)	58 (21-80)	60 (26-81)	59 (21-81)
▪ ≥65 yr, n (%)	51 (28)	58 (32)	109 (30)
Disease stage III-IV, n (%)	139 (77)	146 (82)	285 (79)
2L age-adjusted IPI 2-3, n (%)	82 (46)	79 (44)	161 (45)
Response to 1L therapy, n (%)			
▪ Primary refractory	133 (74)	131 (73)	264 (74)
▪ Relapse within 12 mo	47 (26)	48 (27)	95 (26)
Prognostic marker per central lab, n (%)			
▪ HGBL (including double/triple hit)	31 (17)	25 (14)	56 (16)
▪ Double expressor lymphoma	57 (32)	62 (35)	119 (33)
▪ MYC rearrangement	15 (8)	7 (4)	22 (6)
Elevated LDH, n (%)	101 (56)	94 (53)	195 (54)

Locke. ASH 2021. Abstr 2.

KEY DATA

ZUMA-7 Clinical Trial

Efficacy



Locke. ASH 2021. Abstr 2.

KEY DATA

ZUMA-7 Clinical Trial

Efficacy by Subgroups

	Axi-Cel EFS Event/N	SOC EFS Event/N	HR (95% CI)
Overall	108/180	144/179	**0.398** (0.308-0.514)
Age <65 yr	81/129	96/121	**0.490** (0.361-0.666)
Age ≥65 yr	27/51	48/58	**0.276** (0.164-0.465)
Response to 1L therapy			
▪ Primary refractory	85/133	106/131	**0.426** (0.319-0.570)
▪ Relapse within 12 mo	23/47	48/58	**0.342** (0.202-0.579)
2L age-adjusted IPI			
▪ 0-1	54/98	73/100	**0.407** (0.285-0.582)
▪ 2-3	54/82	71/79	**0.388** (0.269-0.561)
Prognostic marker per central lab			
▪ HGBL (including double/triple hit)	15/31	21/25	**0.285** (0.137-0.593)
▪ Double expressor lymphoma	35/57	50/62	**0.424** (0.268-0.671)

Median Follow-up: 24.9 months

Locke. ASH 2021. Abstr 2.

KEY DATA

ZUMA-7 Clinical Trial

Efficacy

Response, %	Axi-cel (n = 180)	SOC (n = 179)	Odds Ratio (95% CI)	P Value
ORR ▪ CR ▪ PR	**83** 65 18	**50** 32 18	5.31 (3.1-8.9)	<0.0001
SD	3	18		
PD	12	21		
NE	2	10		

Outcome	Axi-cel (n = 180)	SOC (n = 179)	HR (95% CI)	P Value
Median OS, mo (95% CI)	NR (28.3-NR)	35.1 (18.5-NE)	0.730 (0.530-1.007)	0.0270 (NS)

Note: 56% of patients in SOC arm received subsequent cellular immunotherapy off protocol; OS benefit likely confounded by SOC treatment switching

CR, complete response; NE, not evaluable; NR, not reached; NS, not significant; ORR, objective response rate; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease; SOC, standard of care.

Locke. ASH 2021. Abstr 2.

KEY DATA

ZUMA-7 Clinical Trial

Safety

AE (Incidence ≥30%), n (%)[a]	Axi-cel (n = 170)		SOC (n = 168)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any AE	**170 (100)**	**155 (91)**	**168 (100)**	**140 (83)**
Pyrexia	158 (93)	15 (9)	43 (26)	1 (1)
Neutropenia[b]	121 (71)	118 (69)	70 (42)	69 (41)
Hypotension	75 (44)	19 (11)	25 (15)	5 (3)
Fatigue	71 (42)	11 (6)	87 (52)	4 (2)
Anemia	71 (42)	51 (30)	91 (54)	65 (39)
Diarrhea	71 (42)	4 (2)	66 (39)	7 (4)
Headache	70 (41)	5 (3)	43 (26)	2 (1)
Nausea	69 (41)	3 (2)	116 (69)	9 (5)
Sinus tachycardia	58 (34)	3 (2)	17 (10)	1 (1)
Leukopenia[c]	55 (32)	50 (29)	43 (26)	37 (22)
Any serious AE	**85 (50)**	**72 (42)**	**77 (46)**	**67 (40)**

Reason for Death	Axi-cel (n = 170)	SOC (n = 168)
Progressive disease, n (%)	**47 (28)**	**64 (38)**
Grade 5 AE during protocol-specified reporting period, n (%)	7 (4)[d]	2 (1)[e]
Definitive therapy-related mortality, n/N (%)	1/170 (1)[f]	2/64 (3)[e]

[a] Included are any adverse events of any grade occurring in ≥20% of patients in either the axi-cel or SOC arm. [b] Combined preferred terms of neutropenia and neutrophil count decreased. [c] Combined preferred terms of leukopenia and white blood cell count decreased. [d] COVID-19 (n=2) and lung adenocarcinoma, myocardial infarction, progressive multifocal leukoencephalopathy, sepsis, and hepatitis B reactivation (n=1 each). [e] Cardiac arrest and acute respiratory distress syndrome (n=1 each). [f] Hepatitis B reactivation

Locke. ASH 2021. Abstr 2.

KEY DATA

ZUMA-7 Clinical Trial

Safety

CRS Parameter	Axi-Cel (n = 170)
Cytokine Release Syndrome, n (%)	
▪ Any grade	157 (92)
▪ Grade ≥3	11 (6)
▪ Grade 5	0
Most common symptoms (all grades), n (%)	(n = 157)
▪ Pyrexia	155 (99)
▪ Hypotension	68 (43)
▪ Sinus tachycardia	49 (31)
Management	
▪ Tocilizumab	111 (65)
▪ Corticosteroids	40 (24)
▪ Vasopressors	11 (6)
Median time to onset, days	3
Mediation duration, days	7

Neurologic Event Parameter	Axi-Cel (n = 170)	SOC (n = 168)
Neurologic events, n (%)		
▪ Any grade	102 (60)	33 (20)
▪ Grade ≥3	36 (21)	1 (1)
▪ Grade 5	0	0
Most common symptoms (all grades), n (%)		
▪ Tremor	44 (26)	1 (1)
▪ Confusional state	40 (24)	4 (2)
▪ Aphasia	36 (21)	0
Management		
▪ Corticosteroids	54 (32)	--
Median time to onset, days	7	23
Mediation duration, days	9	23

Locke. ASH 2021. Abstr 2.

SUMMARY

ZUMA-7 Clinical Trial

- Treatment with Axi-Cel vs SoC in the 2L setting in R/R LBCL resulted in improvement in EFS and in response rates
  - EFS benefit was maintained across all subgroups
- Manageable safety profile with no new safety concerns
  - No grade 5 CRS or NE events

October 18, 2017: The FDA approved YESCARTA (axicabtagene ciloleucel), a CD19-directed genetically modified autologous T cell immunotherapy, for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Locke. ASH 2021. Abstr 2.

ZUMA-7 Clinical Trial

Use of Axi-Cel provides benefit over SOC for patients with R/R LBCL in the 2L setting and should be considered for eligible patients

Where does CAR-T fit within community oncology…?

Patient identification and management

2021 ASH Key Studies

Lymphomas

- POLARIX
- RE-MIND2
- ZUMA-7
- SEQUOIA

Multiple Myeloma and Nonmalignant Hematologic Disorders

- GMMG-HD7
- GRIFFIN
- BELLINI
- Fostamatinib (ITP)

Leukemias

- Dasatinib low-dose vs SOC
- ASCEMBL
- CPX-351 vs HMA-venetoclax
- IPSS-M

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CLINICAL QUESTION

SEQUOIA Clinical Trial

Does the BTK inhibitor zanubrutinib provide benefit to patients with untreated chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)?

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CLINICAL QUESTION

SEQUOIA Clinical Trial

Study Design: Multicohort, open-label, phase III trial

Eligibility Criteria
- Patients with untreated CLL/SLL
- Met iwCLL criteria for treatment
- Aged ≥65 yr or unsuitable for FCR treatment
- Anticoagulation and CYP3A inhibitors allowed

Stratification by age, Binet stage, IGHV status, and geographic region

Cohort 1 without del(17p) by central FISH (N=479)

Cohort 2* with del(17p) (n ~100)

Cohort 3* with del(17p) (n ~80)

R 1:1

Zanubrutinib (160 mg BID until PD, intolerable toxicity, or study end) (n = 241)
Median follow-up: 26.4 months

Bendamustine (90 mg/m^2 on Days 1 and 2) **+ Rituximab** (375 mg/m^2 in cycle 1, then 500 mg/m^2 in cycles 2-6) (n = 238)
Median follow-up: 25.9 months

*Cohort 2 patients received zanubrutinib monotherapy; cohort 3 patients received zanubrutinib + venetoclax; treatment allocation without randomization in cohorts 2 and 3.

Prespecified interim analysis planned at ~86 events.

Cohort 1 Endpoints

Primary endpoint: PFS per IRC assessment

Secondary endpoints: Investigator-assessed PFS, ORR, OS, Safety

CLL, chronic lymphocytic leukemia; CYP3A, cytochrome P450, family 3, subfamily A; del(17p), chromosome 17p deletion; FCR, fludarabine, cyclophosphamide, and rituximab; FISH, fluorescence in situ hybridization; IRC, independent review committee; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; OS overall survival; SLL, small lymphocytic lymphoma.

Tam. ASH 2021. Abstr 396.

KEY DATA

SEQUOIA Clinical Trial

Baseline Characteristics (cohort 1)

Characteristic	Zanubrutinib (n = 241)	Bendamustine + Rituximab (n = 238)
Median age, yr (IQR)	70 (66-75)	70 (66-74)
Aged ≥65 yr, n (%)	196 (81.3)	192 (80.7)
Male, n (%)	154 (63.9)	144 (60.5)
ECOG PS 2, n (%)	15 (6.2)	20 (8.4)
Region, n (%)		
▪ North America	34 (14.1)	28 (11.8)
▪ Europe	174 (72.2)	172 (72.3)
▪ Asia/Pacific	33 (13.7)	38 (16.0)
Binet stage C*, n (%)	70 (29.0)	70 (29.4)
Bulky disease ≥5 cm, n (%)	69 (28.6)	73 (30.7)
Cytopenia†, n (%)	102 (42.3)	109 (45.8)
del(11q), n (%)	43 (17.8)	46 (19.3)
***TP53* mutation, n/N (%)**	15/232 (6.5)	13/223 (5.8)
Unmutated *IGHV* gene, n/N (%)	125/234 (53.4)	121/231 (52.4)

*Patients with SLL had Binet stage calculated as if they had CLL.

†Defined as anemia (hemoglobin ≤110 g/L), thrombocytopenia (platelets ≤100 x 10^9/L), or neutropenia (absolute neutrophil count ≤1.5 x 10^9/L).

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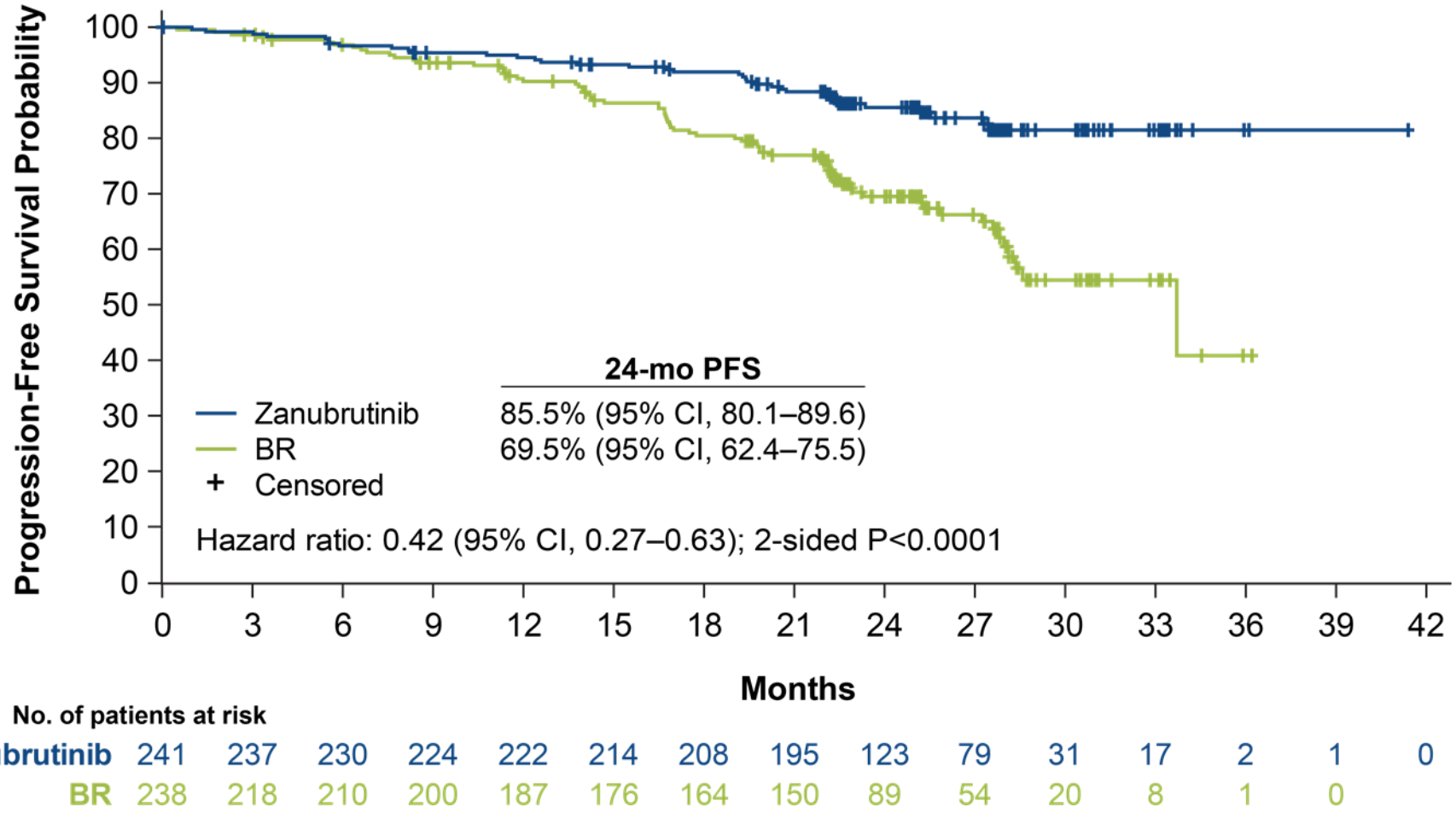
KEY DATA

SEQUOIA Clinical Trial

PFS by IRC (cohort 1)



BR, bendamustine + rituximab; IRC, independent review committee; PFS, progression-free survival.

IGHV, immunoglobulin heavy chain

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KEY DATA

SEQUOIA Clinical Trial

PFS by IRC (cohort 1) by Subgroups

Events n/N	Zanubrutinib	Bendamustine + Rituximab	HR (95% CI)
All patients	**85.5% (80.1 – 89.6), 36/241**	**69.5% (62.4 – 75.5), 71/238**	**0.42 (0.27-0.63), *P* <0.0001**
Age (years)			
<65	6/45	19/46	**0.25** (0.10-0.62)
≥65	30/196	52/192	0.47 (0.30-0.74)
Sex			
Male	24/154	47/144	0.39 (0.24-0.64)
Female	12/87	24/94	0.45 (0.23-0.91)
Binet stage			
A or B	24/171	52/168	0.39 (0.24-0.64)
C	12/70	19/70	0.48 (0.23-1.00)
ECOG			
0	12/110	24/101	0.39 (0.19-0.78)
≥1	24/131	47/137	0.43 (0.26-0.71)
Bulky disease (LDi <5 cm vs ≥5 cm)			
<5 cm	21/172	44/165	0.37 (0.22-0.63)
≥5 cm	15/69	27/73	0.52 (0.27-0.97)
IGHV mutational status			
Mutated	18/109	25/110	0.67 (0.36-1.22), *P*=0.186
Unmutated	15/125	45/121	**0.24 (0.13-0.43), *P<0.001***
Cytopenias at baseline			
Yes	21/102	34/109	0.55 (0.32-0.95)
No	15/139	37/129	0.31 (0.17-0.57)
Chromosome 11q deletion			
Yes	7/43	22/46	**0.21** (0.09-0.50)
No	29/198	49/192	0.50 (0.32-0.80)

IGHV, immunoglobulin heavy chain

Tam. ASH 2021. Abstr 396.

KEY DATA

SEQUOIA Clinical Trial

Adverse Events (cohort 1)

AEs, n (%)	Zanubrutinib (n = 240)*	Bendamustine + Rituximab (n = 227)*
Any AE	224 (93.3)	218 (96.0)
Grade ≥3 AE	126 (52.5)	181 (79.7)
Serious AE	88 (36.7)	113 (49.8)
Fatal AE	11 (4.6)	11 (4.8)
AE leading to dose reduction	18 (7.5)	84 (37.4)
AE leading to dose interruption or delay	111 (46.3)	154 (67.8)
AE leading to discontinuation	20 (8.3)	31 (13.7)

*Safety was assessed in patients who received ≥1 treatment dose; 1 patient in the zanubrutinib arm and 11 patients in the combination arm did not receive treatment.

Common AEs in ≥12% of Patients, n (%)	Zanubrutinib (n = 240)*		Bendamustine + Rituximab (n = 227)*	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Contusion	46 (19.2)	0 (0.0)	8 (3.5)	0 (0.0)
Upper respiratory tract infection	41 (17.1)	2 (0.8)	27 (11.9)	2 (0.9)
Neutropenia	37 (15.4)	27 (11.3)	129 (56.8)	116 (51.1)
Diarrhea	33 (13.8)	0 (0.0)	30 (13.2)	4 (1.8)
Arthralgia	32 (13.3)	2 (0.8)	20 (8.8)	1 (0.4)
Fatigue	28 (11.7)	3 (1.3)	36 (15.9)	2 (0.9)
Rash	26 (10.8)	0 (0.0)	44 (19.4)	6 (2.6)
Constipation	24 (10.0)	1 (0.4)	43 (18.9)	0 (0.0)
Nausea	24 (10.0)	0 (0.0)	74 (32.6)	3 (1.3)
Pyrexia	17 (7.1)	0 (0.0)	60 (26.4)	8 (3.5)
Vomiting	17 (7.1)	0 (0.0)	33 (14.5)	3 (1.3)
Anemia	11 (4.6)	1 (0.4)	43 (18.9)	4 (1.8)
Thrombocytopenia	9 (3.8)	4 (1.7)	31 (13.7)	16 (7.0)
Infusion-related rx due to amphotericin B infusion	1 (0.4)	0 (0.0)	43 (18.9)	6 (2.6)

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SEQUOIA Clinical Trial

Adverse Events of Interest (cohort 1)

AEs, n (%)	Zanubrutinib (n = 240)[a]		Bendamustine + Rituximab (n = 227)[a]	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Anemia	11 (4.6)	1 (0.4)	44 (19.4)	4 (1.8)
Neutropenia[b]	38 (15.8)	28 (11.7)	129 (56.8)	116 (51.1)
Thrombocytopenia[c]	11 (4.6)	5 (2.1)	40 (17.6)	18 (7.9)
Arthralgia	32 (13.3)	2 (0.8)	20 (8.8)	1 (0.4)
Atrial fibrillation	8 (3.3)	1 (0.4)	6 (2.6)	3 (1.3)
Bleeding[d]	108 (45.0)	9 (3.8)	25 (11.0)	4 (1.8)
Major bleeding[e]	12 (5.0)	9 (3.8)	4 (1.8)	4 (1.8)
Diarrhea	33 (13.8)	2 (0.8)	31 (13.7)	5 (2.2)
Hypertension[f]	34 (14.2)	15 (6.3)	24 (10.6)	11 (4.8)
Infections[g]	149 (62.1)	39 (16.3)	127 (55.9)	43 (18.9)
Myalgia	9 (3.8)	0 (0.0)	3 (1.3)	0 (0.0)
Other cancers	31 (12.9)	17 (7.1)	20 (8.8)	7 (3.1)
Dermatologic	16 (6.7)	2 (0.8)	10 (4.4)	2 (0.9)

[a]Safety was assessed in patients who received ≥1 dose of treatment; 1 patient in Arm A and 11 patients in Arm B did not receive treatment. [b]Neutropenia, neutrophil count decreased, or febrile neutropenia. [c]Thrombocytopenia or platelet count decreased. [d]Pooled term of all-cause bleeding including bruising, petechiae, purpura, and contusion. [e]Major bleeding included all grade ≥3, serious, and any-grade central nervous system hemorrhage. [f]Hypertension, blood pressure increased, or hypertensive crisis. [g]All infection terms pooled.

AE, adverse event.

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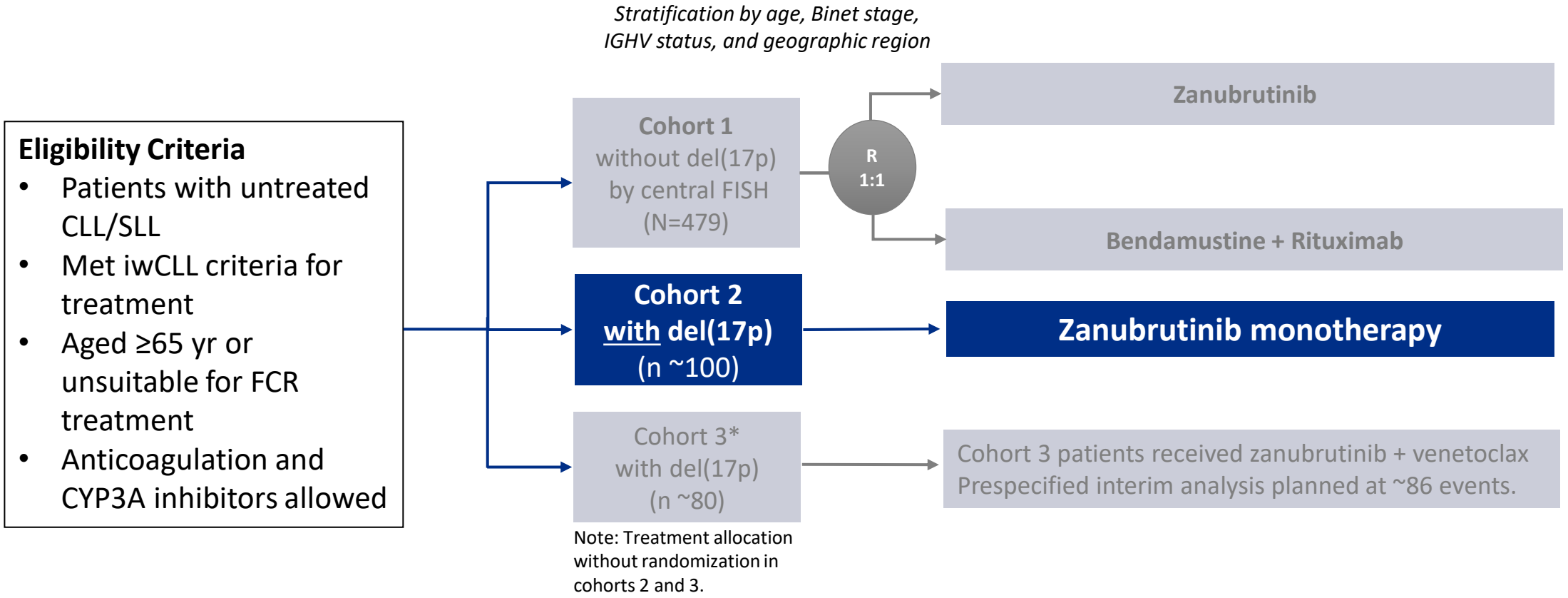
CLINICAL QUESTION

SEQUOIA Clinical Trial

Study Design: Multicohort, open-label, phase III trial



CLL, chronic lymphocytic leukemia; CYP3A, cytochrome P450, family 3, subfamily A; del(17p), chromosome 17p deletion; FCR, fludarabine, cyclophosphamide, and rituximab; FISH, fluorescence in situ hybridization; IRC, independent review committee; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; OS overall survival; SLL, small lymphocytic lymphoma.

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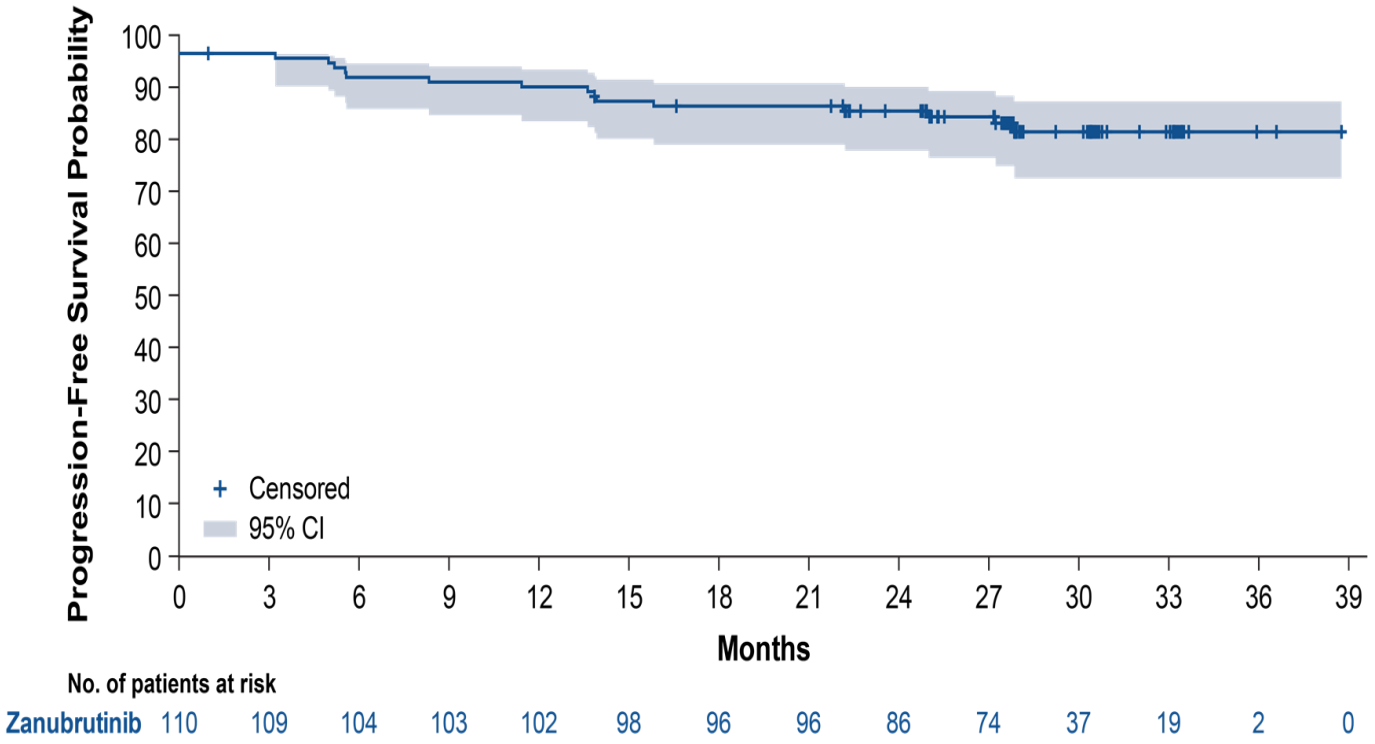
CLINICAL QUESTION

SEQUOIA Clinical Trial

Cohort 2: PFS Per IRC Assessment in Patients With Del(17p)



Updated result of non-randomized arm (cohort 2)

- Median follow-up of 30.5 months
- 24-month PFS: **88.9%**
  (95% CI 81.3 – 93.6)
- Remains effective in patients with del(17p)

Tam. ASH 2021. Abstr 396.

CLINICAL QUESTION

SEQUOIA Clinical Trial

Study Design: Multicohort, open-label, phase III trial

Eligibility Criteria

- Patients with untreated CLL/SLL
- Met iwCLL criteria for treatment
- Aged ≥65 yr or unsuitable for FCR treatment
- Anticoagulation and CYP3A inhibitors allowed

Stratification by age, Binet stage, IGHV status, and geographic region

Cohort 1 without del(17p) by central FISH (N=479)

R 1:1

- **Zanubrutinib**
- **Bendamustine + Rituximab**

Cohort 2* with del(17p) (n~100)

*Cohort 2 patients received zanubrutinib monotherapy

Cohort 3 with del(17p) /TP53 mut (n~80)

Zanubrutinib (160 mg twice daily for ≥27 cycles; 3 cycle lead in prior to addition of venetoclax; Starting at C28, discontinue zanubrutinib upon confirmed uMRD)
+ Venetoclax (ramp-up cycle, then 400 mg once daily for 12-24 cycles)

Prespecified interim analysis planned at ~86 events.

Note: Treatment allocation without randomization in cohorts 2 and 3.

Cohort 3 Endpoints
Key endpoint: Safety, ORR, PFS, DOR, uMRD
Exploratory endpoints: OS, PROs, time to MRD after EOT

Data Cutoff Date: September 7, 2021; 49 patients enrolled

CLL, chronic lymphocytic leukemia; CYP3A, cytochrome P450, family 3, subfamily A; del(17p), chromosome 17p deletion; FCR, fludarabine, cyclophosphamide, and rituximab; FISH, fluorescence in situ hybridization; IRC, independent review committee; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; OS overall survival; SLL, small lymphocytic lymphoma.

Tedeschi. ASH 2021. Abstr 396.

KEY DATA

SEQUOIA Clinical Trial

Baseline Demographics and Characteristics (cohort 3)

	n=49
Age, median (range), y	65.0 (25–86)
Male, n (%)	27 (55.1)
ECOG PS ≥1, n (%)	26 (53.1)
Months since diagnosis, median (Q1-Q3)	19.8 (5.7–38.1)
SLL, n (%)	3 (6.1)
Binet stage C for patients with CLL, n/N (%)	22/46 (47.8)
Absolute lymphocyte count (×10^9/L), median	76.3
Hemoglobin (g/L), median	112.0
Platelet count (×10^9/L), median	159.0
Bulky disease, n (%)	
Any target lesion LDi ≥5 cm	20 (40.8)
Any target lesion LDi ≥10 cm	3 (6.1)

	n=49
del(17p) by central lab FISH, n (%)	
Positive	**46 (93.9)**
Negative (eligible by local lab TP53 mutation)	**3 (6.1)**
del(17p) percent of abnormal nuclei, median	**77.5**
del(13q), n (%)	25 (51.0)
del(11q), n (%)	1 (2.0)
Trisomy 12, n (%)	11 (22.4)
Retrospective TP53 mutation,[a] n/N (%)	**34/37 (91.9)**
IGHV mutational status, n (%)	
Unmutated	**43 (87.8)**
Mutated	6 (12.2)
Complex karyotype,[b] n/N (%)	
Non-complex (0–2 abnormalities)	4/24 (16.7)
Complex (3 or more abnormalities)	20/24 (83.3)
Complex (5 or more abnormalities)	**17/24 (70.8)**

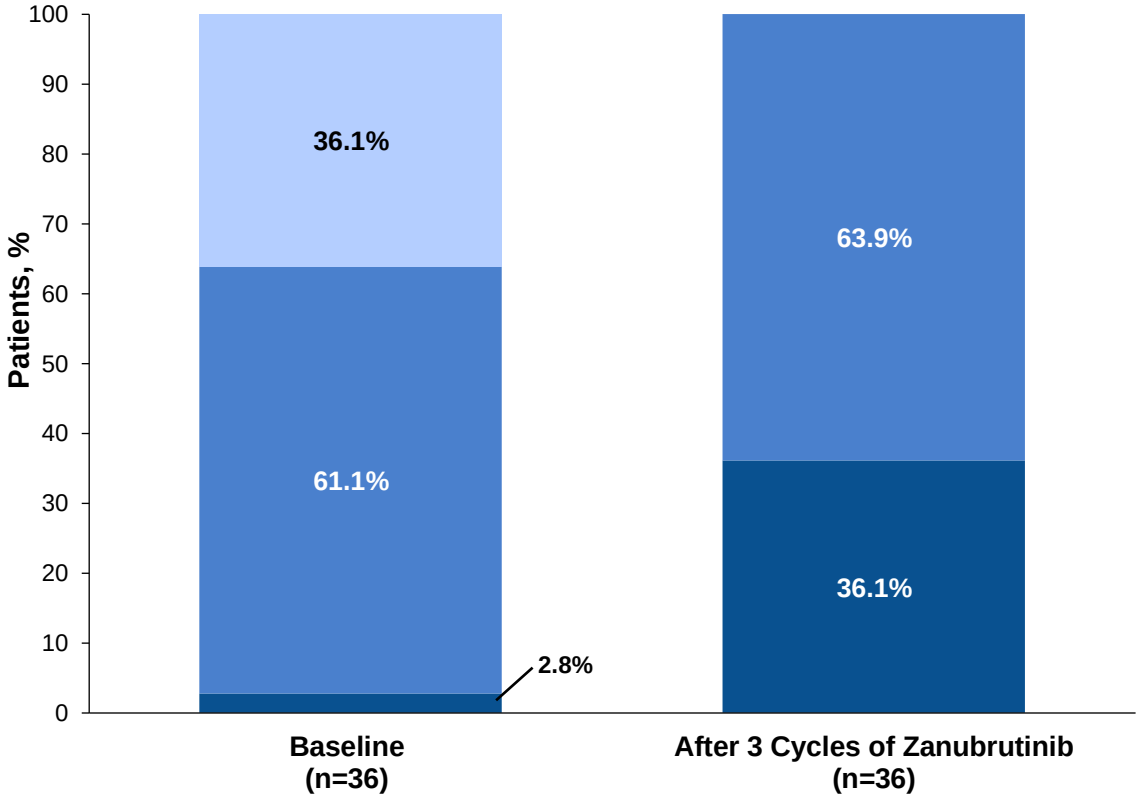
CLL, chronic lymphocytic leukemia; del(11q), chromosome 11q deletion; del(13q), chromosome 13q deletion; del(17p), chromosome 17p deletion; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence *in situ* hybridization; IGHV, gene encoding the immunoglobulin heavy chain variable region; lab, laboratory; LDi, longest diameter; Q, quartile; SLL, small lymphocytic lymphoma; TP53, gene encoding tumor protein p53.
[a]Ongoing analysis by next-generation sequencing. [b]Ongoing analysis.

Tedeschi. ASH 2021. Abstr 396.

KEY DATA

SEQUOIA Clinical Trial

3 cycles of Zanubrutinib prior to venetoclax decreases tumor lysis syndrome risk (cohort 3)



TLS high risk: Presence of any LN ≥10 cm with the largest diameter by radiographic assessment OR presence of both ALC ≥25×10^9/L and one LN ≥5 cm

TLS medium risk: Presence of all measurable LNs with the largest diameter ≥5 cm and <10 cm by radiographic assessment OR ALC ≥25×10^9/L

TLS low risk: Presence of all measurable LNs with the largest diameter <5 cm by radiographic assessment AND ALC <25×10^9/L

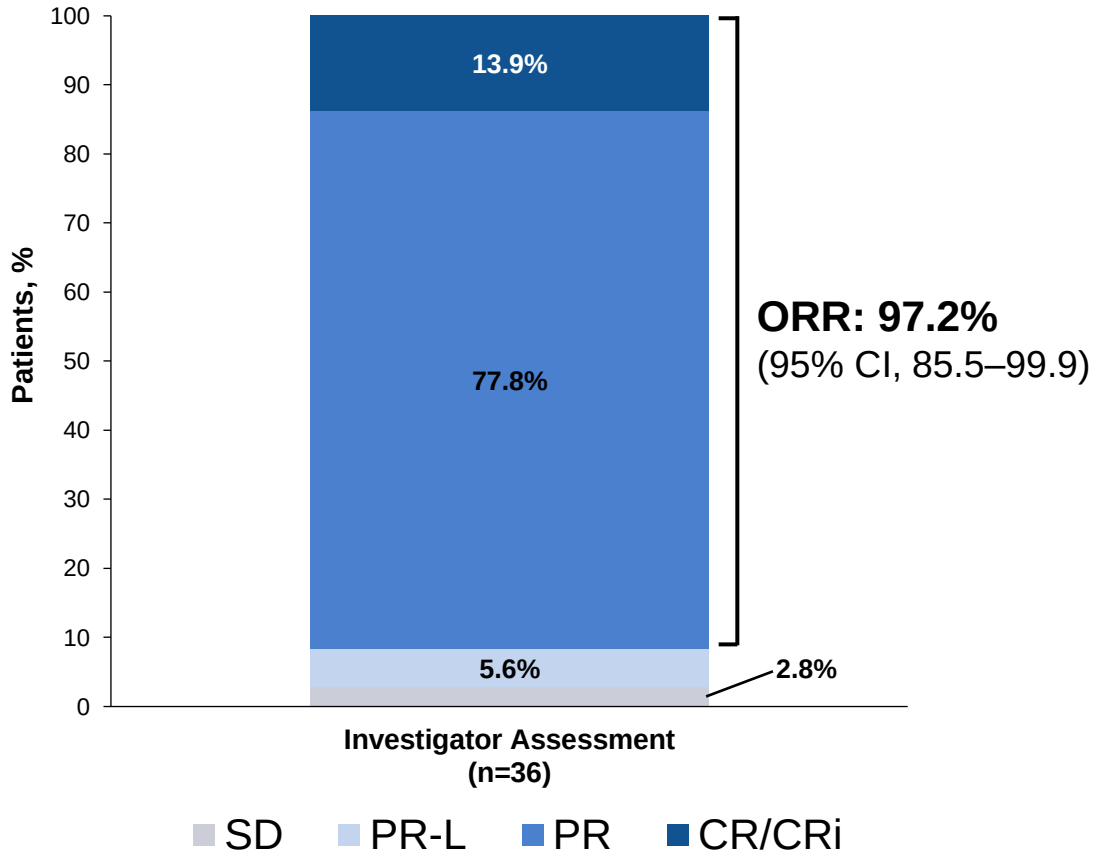
ALC, absolute lymphocyte count; LN, lymph node; TLS, tumor lysis syndrome.

Tedeschi. ASH 2021. Abstr 396.

KEY DATA

SEQUOIA Clinical Trial

ORR (cohort 3), median follow-up of 12.0 months (3.0 – 21.7)



- Thirty-six patients had post-baseline response evaluations by the data cutoff date
- Of the 36 patients, 14 were treated with the combination therapy for at least 12 months
  - Five (5) of 14 (36%) patients achieved confirmed CR/Cri by bone marrow assessment
  - Four (4) additional patients in this subgroup met criteria for CR/CRi but not confirmed by bone marrow assessment (due to COVID-19 restrictions)

Data cutoff date: September 7, 2021.
CR, complete response; CRi, complete response with incomplete bone marrow recovery; ORR, overall response rate; PR, partial response; PR-L, PR with lymphocytosis; SD, stable disease.

Tedeschi. ASH 2021. Abstr 396.

KEY DATA

SEQUOIA Clinical Trial

Adverse Events (cohort 3)

n (%)	All Patients (n=49)	Patients on combination treatment (n=34)
Any AE	40 (81.6)	29 (85.3)
Grade ≥3 AE	16 (32.7)	13 (38.2)
Serious AE	4[a] (8.2)	3[c] (8.8)
Fatal AE	1[b] (2.0)	0 (0.0)
AE leading to dose interruption	10 (20.4)	10 (29.4)
AE leading to dose reduction	0 (0.0)	0 (0.0)
AE leading to treatment discontinuation	1[b] (2.0)	0 (0.0)

AE, adverse event.
[a]Serious AEs included anemia, drug hypersensitivity, COVID-19 pneumonia, thoracic vertebral fracture, and lung carcinoma. [b]Lung carcinoma (unrelated) leading to discontinuation of zanubrutinib and death prior to initiating venetoclax treatment. [c]Serious AEs included anemia, COVID-19 pneumonia, and drug hypersensitivity.

Tedeschi. ASH 2021. Abstr 396.

SUMMARY

SEQUOIA Clinical Trial

Cohort 1:

- With median follow-up of 26.2 months, patients with untreated CLL/SLL, IRC-assessed PFS was significantly improved with zanubrutinib compared with bendamustine + rituximab
  - 24-mo PFS: **85.5%** (95% CI: 80.1-89.6) vs **69.5%** (95% CI: 62.4-75.5);
  - HR: **0.42** (95% CI: 0.27-0.63; *P* <.0001)
- PFS was also improved with zanubrutinib in high-risk subgroups [unmutated *IGHV* and with del(11q)]
- OS was not different between the two arms; patients on bendamustine + rituximab were eligible for cross-over to zanubrutinib (n=15)

Cohort 2:

- With median follow-up of 30.5 months, zanubrutinib remains effective in patients with del(17p)

Cohort 3:

- With short median follow-up, zanubrutinib + venetoclax resulted in a high response rate in high risk del(17p)/TP53 mutant CLL/SLL patients (more mature follow-up to come)

Overall, no new safety signals were observed; atrial fibrillation was infrequent

SEQUOIA Clinical Trial

Use of zanubrutinib, either in combination or as a monotherapy, in the frontline setting provides benefit for patients with CLL/SLL

More to come…

2021 ASH Key Studies

Lymphomas

- POLARIX
- RE-MIND2
- ZUMA-7
- SEQUOIA

Multiple Myeloma and Nonmalignant Hematologic Disorders

- GMMG-HD7
- GRIFFIN
- BELLINI
- Fostamatinib (ITP)

Leukemias

- Dasatinib low-dose vs SOC
- ASCEMBL
- CPX-351 vs HMA-venetoclax
- IPSS-M

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CLINICAL QUESTION

GMMG-HD7 Clinical Trial

Does the addition of the CD38 monoclonal antibody isatuximab to RVd (lenalidomide, bortezomib, and dexamethasone) improve outcomes over standard of care for patients with newly diagnosed, ASCT-eligible multiple myeloma?

FDA APPROVAL

GMMG-HD7 Clinical Trial

On **March 2, 2020**, the Food and Drug Administration approved isatuximab-irfc (SARCLISA®, sanofi-aventis U.S. LLC) in combination with pomalidomide and dexamethasone for adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

On **March 31, 2021**, the Food and Drug Administration approved isatuximab-irfc (SARCLISA®, sanofi-aventis U.S. LLC) in combination with carfilzomib and dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy.

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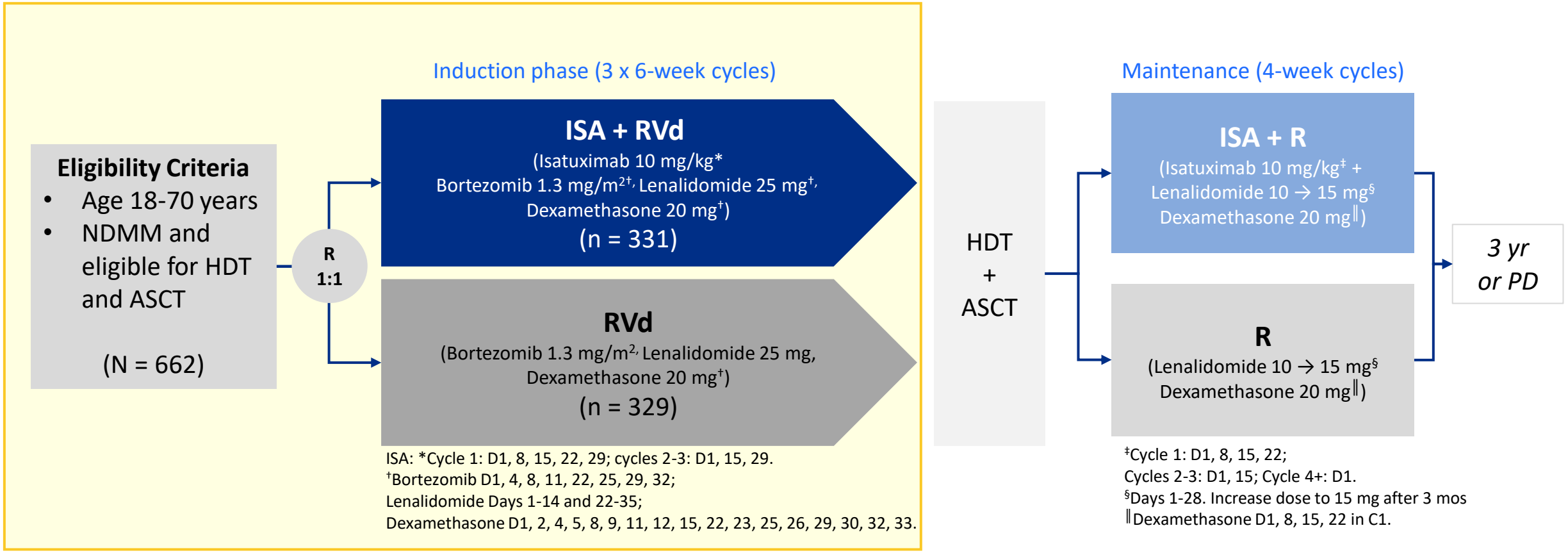
KEY DATA

GMMG-HD7 Clinical Trial

Study Design: Multicenter, open-label, randomized, phase III trial



Primary endpoint: MRD negativity at end of induction (week 18; NGF, sensitivity 10^{-5}) stratified according to R-ISS

Secondary endpoints: CR after induction, safety

MRD negativity assessed after cycle 3 (week 18), HDT, 12 mos, and 24 mos as well as at end of study

Data cutoff: April 2021

Goldschmidt. ASH 2021. Abstr 463.

KEY DATA

GMMG-HD7 Clinical Trial

Baseline Characteristics

Characteristic	Isa-RVd (n = 331)	RVd (n = 329)
Median age, yr (range)	59 (37-70)	60 (26-70)
Male, n (%)	204 (61.6)	206 (62.6)
WHO PS, n (%)		
0	158 (47.7)	168 (51.1)
1	137 (41.4)	130 (39.5)
>1	35 (10.6)	30 (9.1)
Heavy chain type, n (%)		
IgG	194 (58.6)	192 (58.4)
IgA	68 (20.5)	69 (21.0)
Light-chain only	59 (17.8)	61 (18.5)
Renal impairment,* n (%)		
No	312 (94.3)	307 (93.3)
Yes	19 (5.7)	22 (6.7)

*Estimated creatinine clearance <40 mL/min or serum creatinine >177 µmol/L.

Characteristic	Isa-RVd (n = 331)	RVd (n = 329)
ISS stage, n (%)		
I	124 (37.5)	149 (45.3)
II	127 (38.4)	114 (34.7)
III	80 (24.2)	66 (20.1)
High-risk cytogenetics,† n (%)		
No	254 (76.7)	235 (71.4)
Yes	58 (17.5)	66 (20.1)
Unknown	19 (5.7)	28 (8.5)
Elevated LDH, n (%)		
No	268 (81.0)	286 (86.9)
Yes	63 (19.0)	43 (13.1)
R-ISS stage, n (%)		
I	77 (23.3)	99 (30.1)
II	218 (65.9)	185 (56.2)
III	28 (8.5)	26 (7.9)
Not classified	8 (2.4)	19 (5.8)

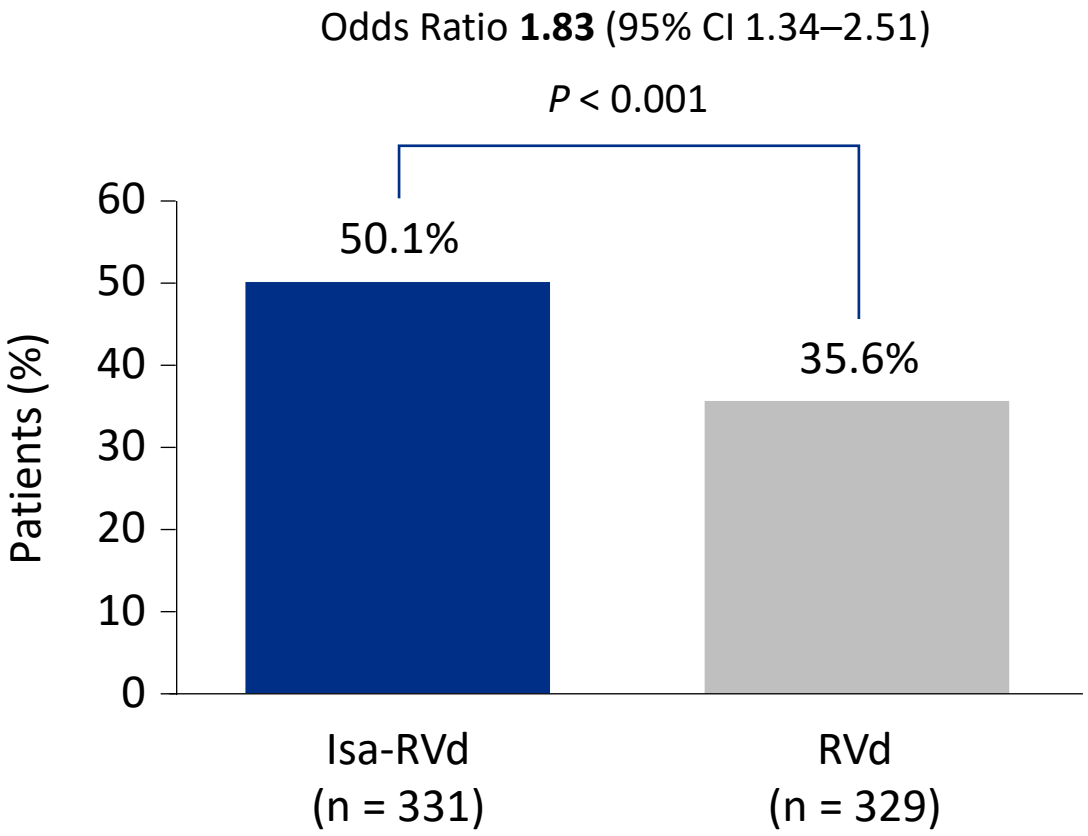
†presence of at least one of the following abnormalities: translocation t(4,14), translocation t(14,16), or deletion 17p.

Goldschmidt. ASH 2021. Abstr 463.

KEY DATA

GMMG-HD7 Clinical Trial

Primary Endpoint: End of induction MRD negativity by NGF (10^{-5}) (ITT)



Low number of not assessable/missing* MRD status: Isa-RVd, 10.6%; RVd, 15.2%

(*Due to loss to follow-up, missing bone-marrow samples, or technical failures)

Goldschmidt. ASH 2021. Abstr 463.

KEY DATA

GMMG-HD7 Clinical Trial

Subgroup Analysis

MRD Negative at End of Induction Subgroup		Pts, n	Odds Ratio (95% CI)
Overall		660	
Age, yr	26-60 60-70	373 287	2.12 (1.39-3.24) 1.57 (0.98-2.54)
Sex	Female Male	250 410	1.88 (1.13-3.13) 1.84 (1.24-2.75)
WHO PS	0/1 >1	593 65	1.86 (1.34-2.59) 1.84 (0.68-5.15)
Renal impairment	No Yes	619 41	1.88 (1.36-2.61) 1.45 (0.40-5.40)
ISS	I II III	273 241 146	1.74 (1.07-2.83) 2.08 (1.23-3.55) 1.90 (0.96-3.82)
High-risk cytogenetics	No Yes	489 124	1.93 (1.34-2.80) 1.71 (0.84-3.53)
Elevated LDH	No Yes	554 106	1.78 (1.26-2.51) 2.58 (1.14-6.09)
R-ISS stage	I II III	176 403 54	1.70 (0.93-3.15) 2.11 (1.41-3.19) 1.25 (0.41-3.81)

Goldschmidt. ASH 2021. Abstr 463.

KEY DATA

GMMG-HD7 Clinical Trial

Response Rates after Induction Therapy

Response	ISA-RVd	RVd	P value
Complete Response (CR)	24.2%	21.6%	0.46
Near Complete Response (≥nCR)	41.7%	36.2%	0.15
Very Good Partial Response (≥VGPR)	**77.3%**	**60.5%**	**<0.001**
Partial Response (≥PR)	**90.0%**	**83.6%**	**0.02**

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KEY DATA

GMMG-HD7 Clinical Trial

Safety

CTCAE Grade ≥3 AE, n (%)	Isa-RVd (n = 330)	RVd (n = 328)
Any AE	210 (63.6)	201 (61.3)
Any serious AE (any grade)	115 (34.8)	119 (36.3)
Deaths	4 (1.2)	8 (2.4)
Investigations (SOC)	79 (23.9)	77 (23.5)
Blood and lymphatic system disorders (SOC)	**85** (25.8)	**55** (16.8)
Infections and investigations (SOC)	43 (13.0)	34 (10.4)
Nervous system disorders (SOC)	28 (8.5)	33 (10.1)
Gastrointestinal disorders (SOC)	27 (8.2)	31 (9.5)
Metabolism and nutrition disorders (SOC)	12 (3.6)	26 (7.9)
Specific hematologic AE (PT)		
▪ Leukocytopenia/neutropenia	**87** (26.4)	**30** (9.1)
▪ Lymphopenia	48 (14.5)	65 (19.8)
▪ Anemia	13 (3.9)	20 (6.1)
▪ Thrombocytopenia	21 (6.4)	15 (4.6)
Specific nonhematologic AE (PT)		
▪ Peripheral neuropathy	25 (7.6)	22 (6.7)
▪ Thrombotic events	5 (1.5)	9 (2.7)
▪ Infusion-related reactions	4 (1.2)	NA

Note: A similar percentage of patients discontinued induction therapy due to AEs in the Isa-RVd (n=7, 2.1%) vs RVd arm (n=8, 2.4%)
Overall fewer patients discontinued treatment in the Isa-RVd arm (n=18, 5.4%) vs RVd arm (n=35, 10.6%) on induction therapy

Goldschmidt. ASH 2021. Abstr 463.

KEY DATA

GMMG-HD7 Clinical Trial

The addition of Isa did not impact RVd dose intensity

Outcome	Isa-VRd (n = 331)	VRd (n = 328)
Relative dose intensity,* median % (range)		
▪ Isatuximab	100 (32.4-110)	NA
▪ Lenalidomide	100 (22.6-102)	98.8 (7.1-104)
▪ Bortezomib	98.1 (24.9-106)	97.6 (35.1-104)
▪ Dexamethasone	100 (11.1-133)	100 (31.8-120)
Dose reductions, n (%)		
▪ Isatuximab	6 (1.8)	NA
▪ Lenalidomide	102 (30.9)	98 (29.9)
▪ Bortezomib	89 (27.0)	97 (29.6)
▪ Dexamethasone	51 (15.5)	47 (14.3)

*Calculated based on planned dose per half-cycle (either Isa-VRd or VRd). Number of patients with ≥5 half cycles: Isa-VRd, 214 (95.1%); VRd, 291 (92.7%).

Goldschmidt. ASH 2021. Abstr 463.

SUMMARY

GMMG-HD7 Clinical Trial

- In patients with ASCT-eligible, newly diagnosed MM, the addition of isatuximab to RVd resulted in better rates of MRD negativity vs treatment with RVd alone
  - MRD-negative rate at end of 18-week induction: 50.1% vs 35.6%, respectively
  - Benefit observed across subgroups
- The addition of Isa to RVd did not impact the safety profile or dose density of RVd
  - No increase in early discontinuation was noted for patients receiving Isa-RVd vs RVd alone
- Trial is ongoing: more results to come following the second randomization for maintenance

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GMMG-HD7 Clinical Trial

The addition of Isa to RVd resulted in improved rates of MRD negativity and has the potential to be considered as a new standard of care in patients with ASCT-eligible, newly diagnosed Multiple Myeloma

More to come…

2021 ASH Key Studies

Lymphomas	Multiple Myeloma and Nonmalignant Hematologic Disorders	Leukemias
• POLARIX • RE-MIND2 • ZUMA-7 • SEQUOIA	• GMMG-HD7 • GRIFFIN • BELLINI • Fostamatinib (ITP)	• Dasatinib low-dose vs SOC • ASCEMBL • CPX-351 vs HMA-venetoclax • IPSS-M

cornerstone specialty network™

GRIFFIN Clinical Trial

Does the addition of daratumumab (Dara) to RVd (lenalidomide, bortezomib, and dexamethasone) followed by Dara-R maintenance improve outcomes for patients with newly diagnosed, ASCT-eligible multiple myeloma?

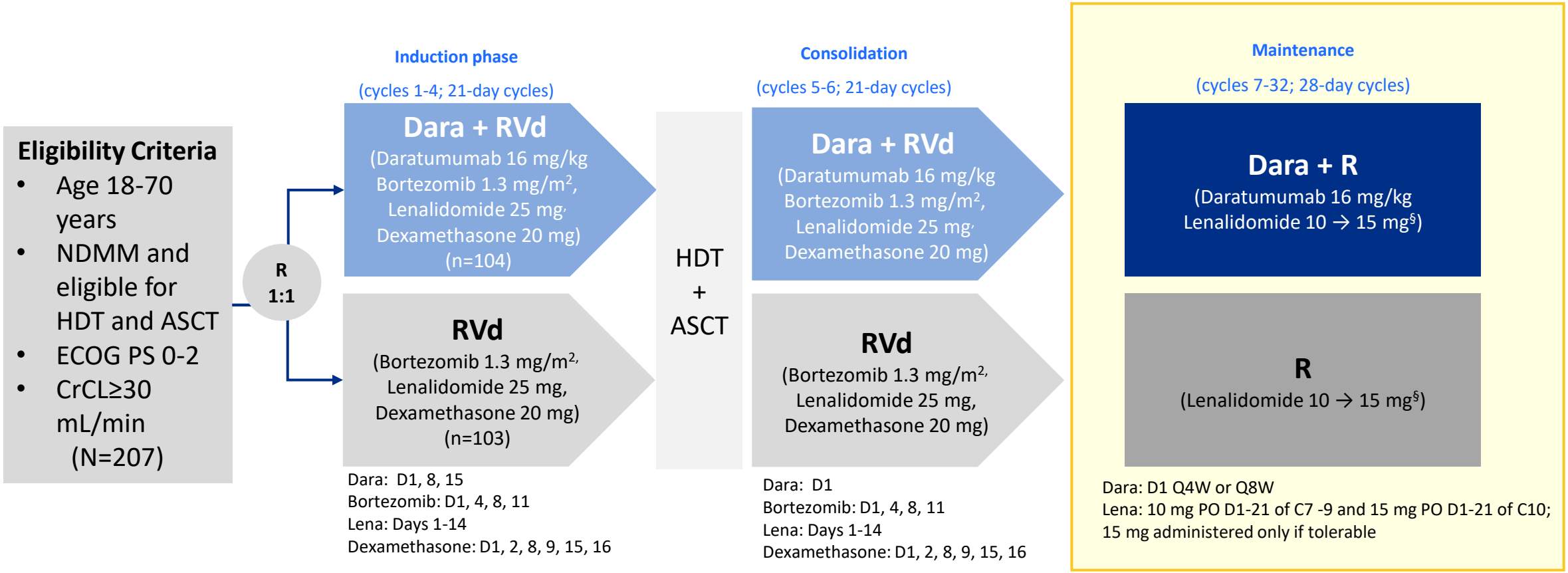
Updated analysis post 24 months of maintenance therapy

cornerstone specialty network™

KEY DATA

GRIFFIN Clinical Trial

Study Design: Multicenter, open-label, randomized, phase II trial



Primary endpoint: sCR rate (by end of consolidation); 1-sided α of 0.1

Secondary endpoints: rates of MRD negativity, ORR, ≥VGPR, CR, PFS, OS

Note: Lenalidomide dose was adjusted in patients with CrCl ≤50 mL/min. Consolidation began 60-100 days after transplant. Patients completing maintenance phase were permitted to continue single-agent lenalidomide.

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GRIFFIN Clinical Trial

Baseline Characteristics

Characteristic	D-RVd (n = 104)	RVd (n = 103)
Median age, yr (range)	59 (29-70)	61 (40-70)
≥65 yr, n (%)	28 (27)	28 (27)
Male, %	58 (56)	60 (58)
ECOG PS, n (%)	(n = 101)	(n = 102)
0	39 (39)	40 (39)
1	51 (50)	52 (51)
2	11 (11)	10 (10)
Baseline CrCl, n (%)		
30-50 mL/min	9 (9)	9 (9)
>50 mL/min	95 (91)	94 (91)
Median time since MM diagnosis, mo	(n = 103) 0.7	(n = 102) 0.9
ISS stage, n (%)		
I	49 (47)	50 (49)
II	40 (38)	37 (36)
III	14 (13)	14 (14)
Missing	1 (1)	2 (2)

Characteristic	D-RVd (n = 104)	RVd (n = 103)
Cytogenetic profile, n (%)	(n=98)	(n=97)
Standard risk	82 (84)	83 (86)
High risk[a]	16 (16)	14 (14)
del17p	8 (8)	6 (6)
t(4;14)	8 (8)	6 (6)
t(4:16)	1 (1)	3 (3)
Revised cytogenetic profile, n (%)	(n=98)	(m=97)
Standard risk	56 (57)	60 (62)
High risk[b]	42 (43)	37 (38)
del17p	8 (8)	6 (6)
t(4;14)	8 (8)	6 (6)
t(4:16)	1 (1)	3 (3)
gain 1q	34 (35)	28 (29)
t(14:20)	1 (1)	1 (1)

[a] High risk was defined as presence of del(17p), t(4;14), or t(14;16).

[b]High risk was defined as presence of del17p, t(4;14), t(14;16), t(14;20), or gain 1q (≥3 copies of chromosome 1q21).

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KEY DATA

GRIFFIN Clinical Trial

Maintenance Phase Update: Response

Response, %	D-RVd (n = 100)					RVd (n = 97)				
	Induction	ASCT	Consol	1-Yr Maint	2-Yr Maint	Induction	ASCT	Consol	1-Yr Maint	2-Yr Maint
sCR	12	21	42	63	**66***	7	14	32	46	**47***
CR	7	6	9	17	**16****	6	5	10	13	**13****
≥CR	**19**	**27**	**52**	**80**	**82**	13	19	42	60	61
VGPR	53	60	39	14	14	43	46	31	19	18
PR	26	12	8	4	3	35	26	19	14	14
SD/PD/NE	2	1	1	2	1	8	8	8	7	7

*P = 0.0096 for comparison of sCR for D-VRd vs VRd. **P = 0.0013 for comparison of CR for D-VRd vs VRd.

Median follow-up: 38.6 months

sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response; NE, not estimable; PD, progressive disease; SD, stable disease.

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KEY DATA

GRIFFIN Clinical Trial

Maintenance Phase Update: MRD Status

MRD Negativity After 24-Mo Maintenance, %	D-RVd (n = 104)	RVd (n = 103)	P Value
MRD at 10^{-5} threshold, %			
ITT population	**64**	**30**	<0.0001
≥CR	78	47	0.0003
MRD at 10^{-6} threshold, %			
ITT population	**36**	**15**	0.0007
≥CR	43	22	0.0121
Sustained MRD negativity lasting ≥6 mo, %	48	15	<0.0001
Sustained MRD negativity lasting ≥12 mo, %	**44**	**13**	<0.0001

MRD negativity: improved outcomes in all subgroups analyzed with Dara-RVd including high-risk subgroups

MRD Neg (10^{-5}) After 24-Mo Maintenance, n/N (%)		D-RVd (n = 104)	RVd (n = 103)	OR (95% CI)
Cytogenetic risk	High risk	4/14 (28.6)	7/16 (43.8)	1.94 (0.42-8.92)
	Standard risk	27/83 (32.5)	58/82 (70.7)	5.01 (2.59-9.71)
Revised cytogenetic risk	High risk	12/37 (32.4)	23/42 (54.8)	2.52 (1.01-6.32)
	Standard risk	19/60 (31.7)	42/56 (75.0)	6.47 (2.87-14.60)

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KEY DATA

GRIFFIN Clinical Trial

Maintenance Phase Update: PFS and OS in ITT Population

PFS*	D-VRd (n = 104)	VRd (n = 103)	HR (95% CI)
24-mo PFS, %	91.6	88.9	0.46 (0.21-1.01)
36-mo PFS, %	89.7	81.2	

*Study not powered for PFS analysis.

OS	D-VRd (n = 104)	VRd (n = 103)	HR (95% CI)
24-mo OS, %	94.8	93.3	0.90 (0.32-2.57)
36-mo OS, %	92.6	92.2	

- Median PFS and OS were not reached in either treatment arm; OS data immature
- Data suggest PFS benefit to prolonged D-R therapy due to separation of curves beyond 1 year of maintenance

Median follow-up: 38.6 months

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KEY DATA

GRIFFIN Clinical Trial

Maintenance Phase Update: AEs of Interest with first onset during maintenance therapy

TEAE, %		D-RVd, D-R Maintenance (n = 89)		RVd, R Maintenance (n = 71)	
		Any	Grade 3/4	Any	Grade 3/4
Infection during maintenance		26	18	32	21
Most common infections	Upper respiratory tract infection	53	2	41	3
	Pneumonia	16	7	15	13
	Urinary tract infection	11	0	3	0
	Sinusitis	10	0	10	0
	Influenza	10	0	7	0
	Nasopharyngitis	10	0	3	0
	Bronchitis	8	1	7	1
	Cellulitis	8	1	3	1
Secondary primary malignancy		4	--	3	--
Type of secondary primary malignancy	SCC of the skin	3		0	
	Basal cell carcinoma	2		0	
	Nasal cavity cancer	1		0	
	SCC	1		0	
	Breast cancer	1		0	
	Malignant melanoma in situ	0		1	
	Nodular melanoma	0		1	
	Uterine cancer	0		1	

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SUMMARY

GRIFFIN Clinical Trial

- Treatment with Dara + RVd followed by Dara + R maintenance improved sCR and rates of sustained MRD negativity vs treatment with RVd followed by R maintenance
  - sCR after 24-mo maintenance: 66.0% vs 47.4% (*P* = 0.0096)
  - MRD negativity after 24-mo maintenance at 10^{-5} threshold: 64.4% vs 30.1% (*P* < 0.0001)
    at 10^{-6} threshold: 35.6% vs 14.6% (*P* = 0.0007)
- The addition of Dara to 2 years of R maintenance did not impact the safety profile

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GRIFFIN Clinical Trial

The addition of Dara to RVd followed by Dara plus R maintenance resulted in improved rates of MRD negativity and support the use of Dara-RVd as induction, consolidation, and maintenance for patients with transplant eligible, newly diagnosed Multiple Myeloma

More to come…PERSEUS trial

2021 ASH Key Studies

Lymphomas

- POLARIX
- RE-MIND2
- ZUMA-7
- SEQUOIA

Multiple Myeloma and Nonmalignant Hematologic Disorders

- GMMG-HD7
- GRIFFIN
- BELLINI
- Fostamatinib (ITP)

Leukemias

- Dasatinib low-dose vs SOC
- ASCEMBL
- CPX-351 vs HMA-venetoclax
- IPSS-M

cornerstone specialty network™

BELLINI Clinical Trial

Does the addition of venetoclax to bortezomib and dexamethasone improve outcomes for patients with relapsed or refractory multiple myeloma?

Final survival analysis

KEY DATA

BELLINI Clinical Trial

Study Design: multicenter, double-blind, randomized, phase III trial

Stratification by bortezomib sensitive vs naive and prior lines of therapy (1 vs 2 or 3)

Key eligibility:
- Patients with R/R MM
- 1-3 prior lines of therapy
- Not refractory to PI therapy

(N = 291)

R 2:1

Venetoclax 800 mg QD + **Bortezomib** 1.3 mg/m^2 + **Dexamethasone** 20 mg (n = 194)

Placebo + **Bortezomib** 1.3 mg/m^2 + **Dexamethasone** 20 mg (n = 97)

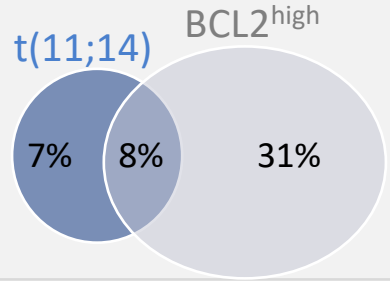
→ *PD*

Cycles 1-8: 21-day cycles, bortezomib on Days 1, 4, 8, 11 and dexamethasone on Days 1, 2, 4, 5, 8, 9, 11, 12
Cycles 9+: 35-day cycles, bortezomib on Days 1, 8, 15, 22 and dexamethasone on Days 1, 2, 8, 9, 15, 16, 22, 23

Primary endpoint: PFS (per IRC)
Key secondary endpoints: ORR, ≥VGPR, OS, QoL/PRO parameters (PFS was investigator-assessed in final OS analysis)

Median follow-up: 45.6 months

Key Subgroup Analysis by Biomarkers
(n=114)



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KEY DATA

BELLINI Clinical Trial

Baseline Characteristics

Characteristic	Ven + Vd (n = 194)	Pbo + Vd (n = 97)
Median age, yr (range)	66 (36-87)	65 (44-83)
≥65 yr, n (%)	108 (56)	52 (54)
Male, n (%)	97 (50)	55 (57)
Multiple myeloma ISS,* n (%)		
Stage I	81 (42)	48 (49)
Stage II	69 (36)	32 (33)
Stage III	39 (20)	13 (13)
ECOG PS,* n (%)		
0	101 (52)	47 (49)
1 or 2	92 (48)	49 (51)
No. of prior lines of therapy, n (%)		
1	91 (47)	44 (45)
2 or 3	103 (53)	53 (55)
Prior stem cell transplant, n (%)	116 (60)	57 (59)

At data cutoff (March 15, 2021), 28 patients remained on Ven and 5 remained on Pbo.
PI, proteasome inhibitor; IMiD, immunomodulatory drug

Characteristic, n (%)	Ven + Vd (n = 194)	Pbo + Vd (n = 97)
Prior exposure to PI	135 (70)	68 (70)
Prior exposure to IMiD	131 (68)	65 (67)
Cytogenetics		
High risk†	31 (16)	18 (19)
Standard risk	141 (73)	72 (74)
Unknown/missing§	22 (11)	7 (7)
t(11;14) status*		
Positive	20 (10)	15 (15)
Negative	152 (78)	74 (76)
Unknown§	22 (11)	8 (8)
BCL-2 expression (qPCR)*		
High	66 (39)	32 (37)
Low	104 (61)	55 (63)

*Percentage calculated without including patients with missing data.
†High Risk: t(4;14) or t(14;16) or del(17p). §Sample tested but results inconclusive.

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KEY DATA

BELLINI Clinical Trial

PFS and OS in All Patients and in Key Biomarker Subgroup

Median PFS, months	N	Ven + Bd	Placebo + Bd	HR (95% CI)	P value
All patients	291	**23.4**	**11.4**	0.58 (0.43 – 0.78)	0.0003
Patients with t(11:14)	35	**36.8**	**9.3**	**0.12** (0.03 – 0.44)	0.0014
Patients with $BCL2^{high}$	98	**30.1**	**9.9**	**0.37** (0.21 – 0.64)	0.0005
All Patients with t(11:14), $BCL2^{high}$	114	**34.3**	**9.9**	**0.32** (0.20 – 0.53)	0.0001

Median OS, months	N	Ven + Bd	Placebo + Bd	HR (95% CI)	P value
All patients	291	NR	NR	1.19 (0.80 – 1.77)	NS
Patients with t(11:14)	35	NR	NR	**0.61** (0.16 – 2.32)	NS
Patients with $BCL2^{high}$	98	NR	NR	**0.70** (0.32 – 1.51)	NS
Patients with t(11:14), $BCL2^{high}$	114	NR	NR	0.82 (0.40 – 1.70)	NS

NR, not reached; NS, not significant

Median follow-up: 45.6 months

Kumar. ASH 2021. Abstr 84.

KEY DATA

BELLINI Clinical Trial

Response in All Patients and in Key Biomarker Subgroups

	Overall Population			Patients With t(11;14)			Patients With High BCL2		
Outcome, %	**Ven + Vd (n = 194)**	**Pbo + Vd (n = 97)**	**P Value**	**Ven + Vd (n = 20)**	**Pbo + Vd (n = 15)**	**P Value**	**Ven + Vd (n = 194)**	**Pbo + Vd (n = 97)**	**P Value**
ORR	84	70	0.0126	95	47	0.0044	88	75	0.1848
≥VGPR	63	40	0.0004	80	27	0.0050	77	31	<0.0001
≥CR	31	7	<0.0001	55	7	0.0088	41	0	0.0001
MRD									
$<10^{-4}$	24	4	0.0001	45	0	0.0087	35	3	0.0015
$<10^{-5}$	15	2	0.0012	30	0	0.0605	23	0	0.0085
$<10^{-6}$	9	1	0.0202	25	0	0.1088	12	0	0.0966

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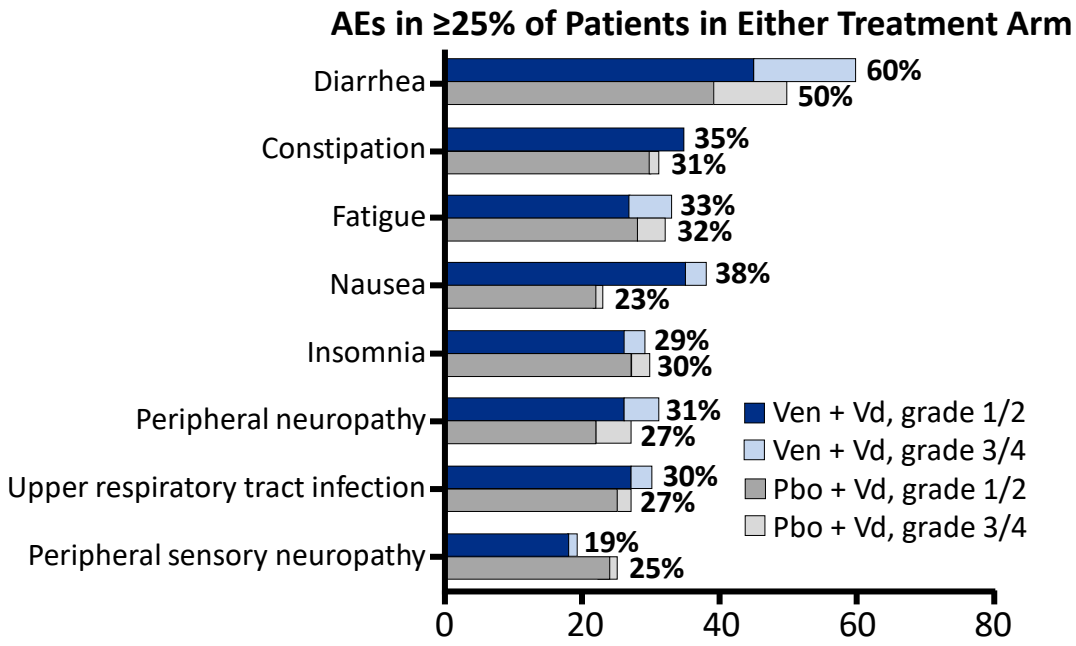
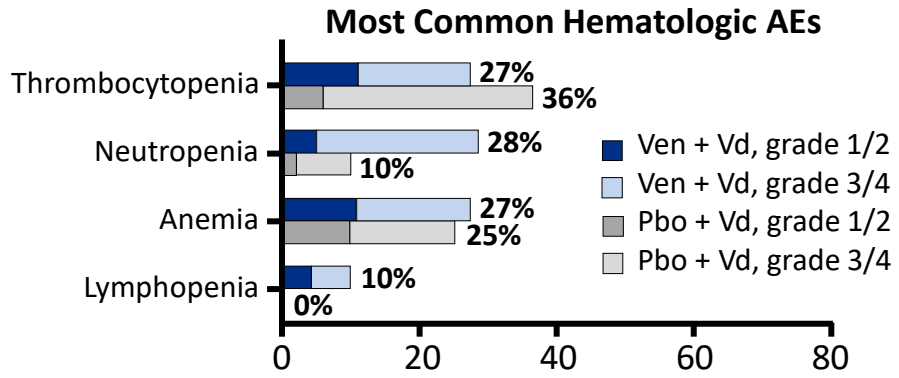
KEY DATA

BELLINI Clinical Trial

Safety





Infection, (%)	Ven + Vd (n = 193)	Pbo + Vd (n = 96)
Any	82	78
Grade 3/4	41	29
Serious	35	29

51 (26%) patients discontinued venetoclax vs 11 (11%) patients who discontinued placebo due to AEs

n (%)	Ven + Vd (n = 193)	Pbo + Vd (n = 96)
All deaths	77 (40)	36 (38)
Treatment-emergent deaths	14 (7)	2 (2)
Any AE*	12 (6)	1 (1)
Infection	9 (5)	0
Progressive disease	2 (1)	1 (1)
Non-treatment-emergent deaths	63 (33)	34 (35)

*AEs leading to 12 deaths in the Ven+Bd arm (9 due to serious infection) and 1 death in the Pbo+Bd arm

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SUMMARY

BELLINI Clinical Trial

- Treatment with venetoclax in combination with Bd significantly improved PFS compared with placebo in patients with relapsed/refractory multiple myeloma (HR: 0.58; 95% CI: 0.43-0.78; *P* = .0003)
  - Largest PFS improvement was seen in patients with t(11;14) or high *BCL2* expression
- Addition of venetoclax to Bd resulted in more frequent and deeper responses compared with placebo, especially in patients with t(11;14) or high *BCL2* expression
- Trend towards improved OS in patients with t(11;14) and or high *BCL2* expression

Kumar. ASH 2021. Abstr 84.

BELLINI Clinical Trial

The addition of venetoclax to bortezomib and dexamethasone resulted in benefit for patients with relapsed/refractory multiple myeloma

Potential for biomarker-driven approach

2021 ASH Key Studies

Lymphomas

- POLARIX
- RE-MIND2
- ZUMA-7
- SEQUOIA

Multiple Myeloma and Nonmalignant Hematologic Disorders

- GMMG-HD7
- GRIFFIN
- BELLINI
- Fostamatinib (ITP)

Leukemias

- Dasatinib low-dose vs SOC
- ASCEMBL
- CPX-351 vs HMA-venetoclax
- IPSS-M

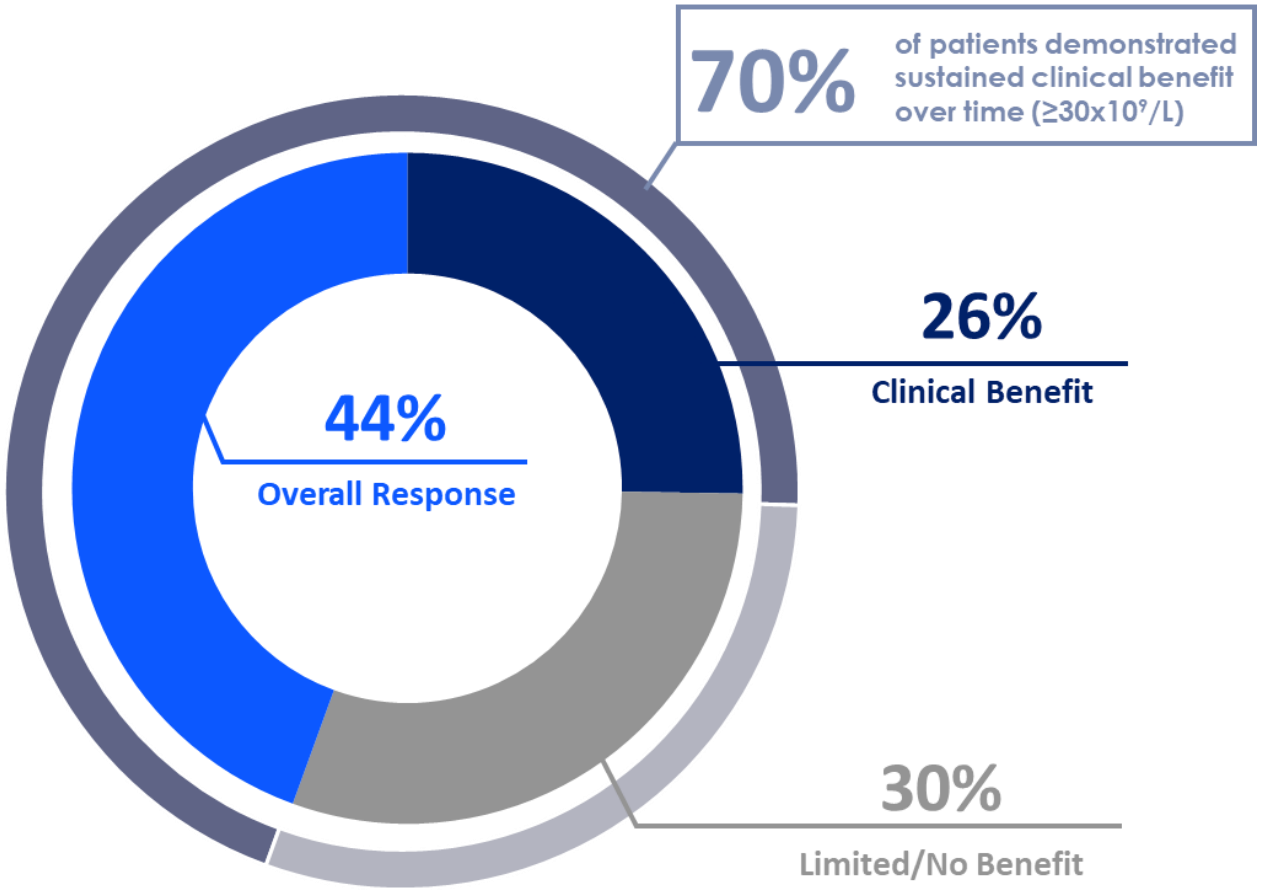
cornerstone specialty network™

FDA APPROVAL

***April 17, 2018**: The FDA approved TAVALISSE (fostamatinib disodium hexahydrate), a kinase inhibitor, indicated for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment*

KEY DATA

Robust Improvements With Long-term Use of Fostamatinib



5-year interim analysis assessed response by the proportion of patients achieving platelet count thresholds over time:

44% Overall Response: Patients who achieved platelet counts **≥50 x 10^9/L** during the first 12 weeks of treatment

26% Clinical Benefit: Patients with platelet counts **≥30 x 10^9/L** who were not classified as overall responders because 50 x 10^9/L was not reached by Week 12

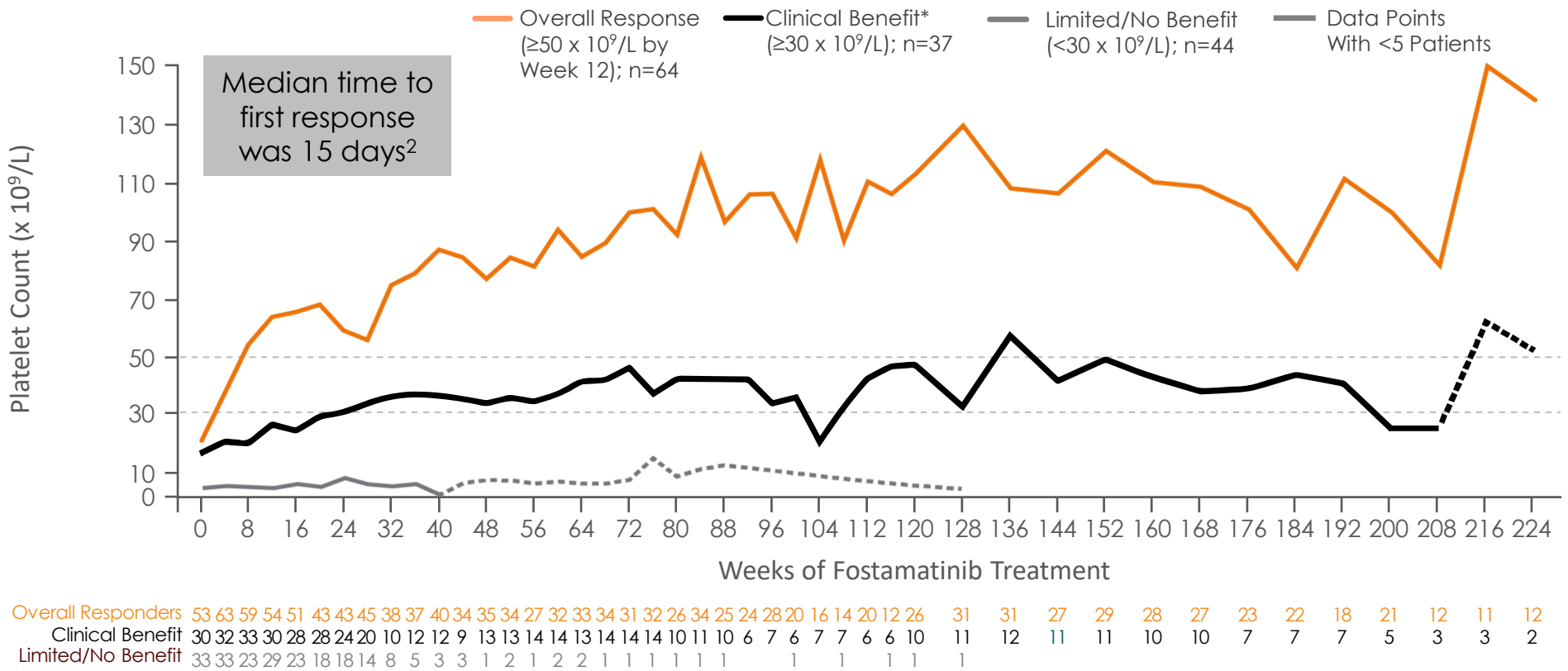
30% Limited/No Benefit: Patients with platelet counts <30 x 10^9/L

Cooper N, et al. *Ther Adv Hematol*. 2021;12:20406207211010875.

KEY DATA

Durable Benefit in a 5-Year Efficacy Post-hoc Analysis

Median Platelet Counts Over Time (combined results from FIT-1, FIT-2, and FIT-3)



While patients achieving a clinical benefit had a more gradual response to treatment, fostamatinib demonstrated a durable response, with median post-baseline platelet counts that on average stabilized between 30 x 10^9/L and 50 x 10^9/L

Data cutoff December 2019.

*Patients achieving clinical benefit achieved platelet counts ≥ 30 x 10^9/L and < 50 x 10^9/L within 12 weeks of treatment.

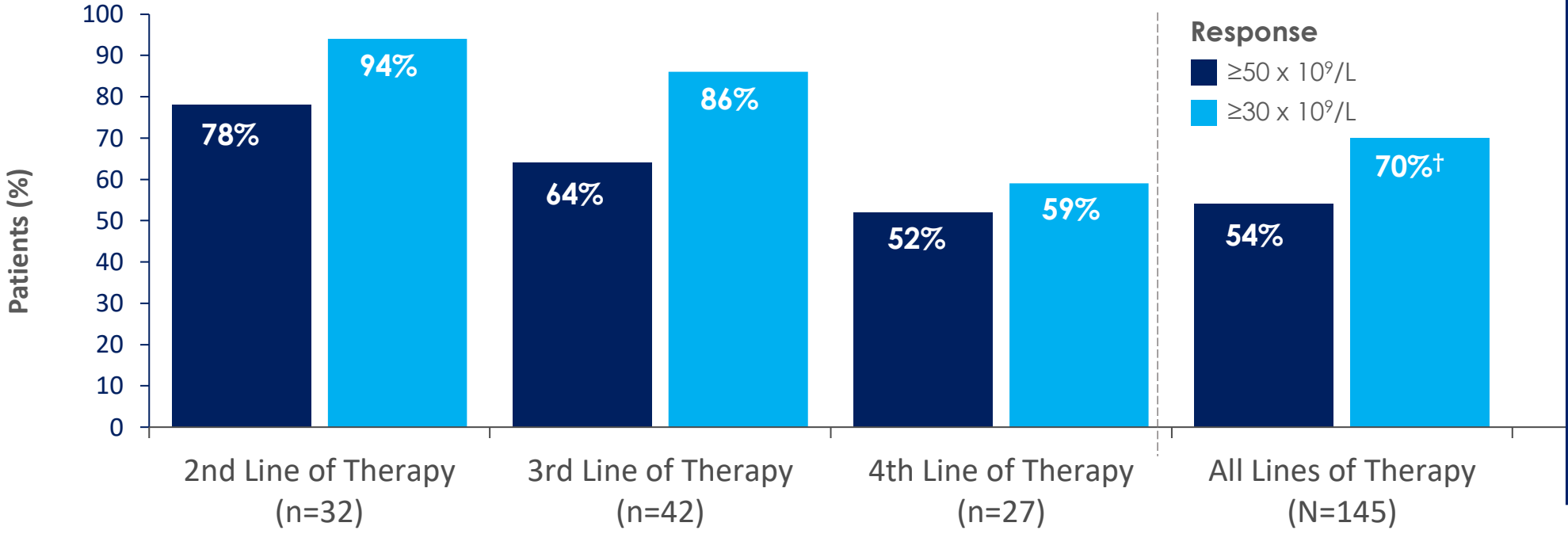
1. Cooper N, et al. *Ther Adv Hematol*. 2021;12:20406207211010875.
2. 2. Bussel J, et al. *Am J Hematol*. 2018;93(7):921-930.

KEY DATA

Response to Fostamatinib Was Seen in Patients Across All Lines of Therapy

Percentage of Patients Achieving Target Platelet Counts at Any Visit*

(Patients who received fostamatinib in FIT-1 + FIT-2 + FIT-3)



Time to response‡ in responders to fostamatinib

- **56%** of 2nd-line patients responded within 4 weeks
- **76%** of 2nd-line patients responded within 12 weeks
- **81%** of patients across all lines of therapy responded within 12 weeks

Use of fostamatinib in earlier lines resulted in higher response rates

Data cutoff December 2019.

*Platelet response was assessed by the proportion of patients achieving platelet counts of ≥50 x 10^9/L and of ≥30 x 10^9/L at any visit (without rescue therapy within 4 weeks).
†Percentage of patients achieving platelet counts of ≥30 x 10^9/L calculated using data on file.[2] ‡Time to response included patients who reached a platelet count ≥50 x 10^9/L.

1. Boccia R, et al. *Br J Haematol*. 2020;190(6):933-938. 2. Data on file, Rigel Pharmaceuticals, Inc. December 2019.

KEY DATA

5-Year Safety Analysis Supports the Long-term Use of Fostamatinib

				RANDOMIZED + EXTENSION	RANDOMIZED TRIALS (FIT-1 AND FIT-2)	
COMMON AEs	MILD (%)	MODERATE (%)	SEVERE (%)	Fostamatinib N=146 229 PT-YEARS (%)	Fostamatinib N=102 29 PT-YEARS (%)	PLACEBO N=48 12 PT-YEARS (%)
Diarrhea	17	17	2	36	29	15
Hypertension	12	10	1	22	20	8
Nausea	17	2	0	19	19	8
Epistaxis	12	7	0	19	16	10
Petechiae	10	4	1	15	4	6
Headache	10	4	1	14	11	19
Upper respiratory tract infection	10	3	0	12	6	4
Dizziness	9	2	1	12	11	8
Contusion	9	1	1	12	6	2
ALT increased	6	4	0	10	11	0

1. Cooper N, et al. *Ther Adv Hematol*. 2021;12:20406207211010875. 2. Bussel JB, et al. *Am J Hematol*. 2019;94(5):546-553.

SUMMARY

- Tavalisse is an oral spleen tyrosine kinase (SYK) inhibitor that targets the underlying autoimmune cause of chronic ITP by blocking platelet destruction
  - New treatment option with novel mechanism

- 5-year safety analysis supports the long-term use of fostamatinib in patients with ITP

- Real-world study; completion date December 2022
  - *Observational Study of Fostamatinib as Second Line Therapy in Adult Patients With Immune Thrombocytopenia (ITP) and Insufficient Response to a Prior Therapy (FORTE)*
    ClinicalTrials.gov Identifier: NCT04904276

WHAT'S NEXT

- Enrollment Complete for wAIHA Phase 3 Clinical Trial
  - *A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Study of Fostamatinib Disodium in the Treatment of Warm Antibody Autoimmune Hemolytic Anemia*
    - Initial dose is 100 mg PO bid. At week 4 dose will be increased to 150 mg PO bid if subjects have adequately tolerated the study drug in the opinion of the Investigator.
    - 90 participants, 45 participants per arm
    - Primary endpoint: durable hemoglobin response
    - Estimated study completion date: April 2022

- IRAK1/4 inhibitor study has therapeutic potential for multiple inflammatory and autoimmune diseases
    - Currently initiating Phase 1b/2 study in low-risk myelodysplastic syndromes (MDS)

2021 ASH Key Studies

Lymphomas	Multiple Myeloma and Nonmalignant Hematologic Disorders	Leukemias
• POLARIX • RE-MIND2 • ZUMA-7 • SEQUOIA	• GMMG-HD7 • GRIFFIN • BELLINI • Fostamatinib (ITP)	• Dasatinib low-dose vs SOC • ASCEMBL • CPX-351 vs HMA-venetoclax • IPSS-M

Dasatinib low-dose vs SOC Clinical Study

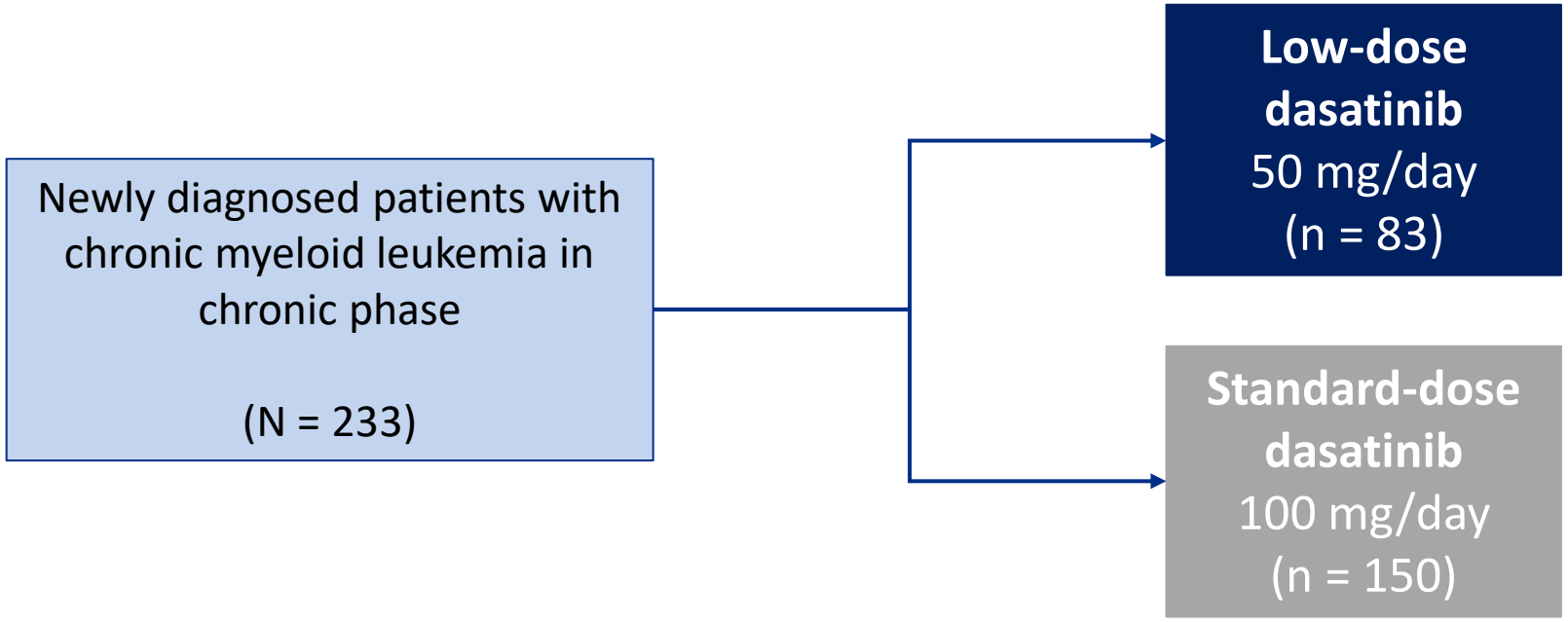
Is low-dose dasatinib as effective as standard-dose dasatinib for patients with chronic myeloid leukemia in chronic phase in the frontline setting?

A propensity score analysis

KEY DATA

Dasatinib low-dose vs SOC Clinical Study

Study Design



Patients receiving 50 mg dasatinib could receive 100 mg dasatinib if suboptimal response by ELN 2013 criteria

Endpoints assessed:

- Failure-free survival (FFS): from the TKI start date to the dates of Rx discontinuation for any reason except of TFR
- Event-free survival (EFS): from the TKI start date to the date of any of the events while on study as defined in the IRIS study
- Transformation-free survival (TFS): from the TKI start date to the date of transformation to accelerated or blast phases during study
- Overall survival (OS): from the TKI start date to the date of death from any cause at any time or date of last follow-up
- Safety

Sasaki. ASH 2021. Abstr 631

KEY DATA

Dasatinib low-dose vs SOC Clinical Study

Baseline Characteristics: Pre- and Post-Matched

Characteristic	Prematched			Postmatched*		
	Low-dose 50 mg (n = 83)	Std-dose 100 mg (n = 150)	P Value	Low-dose 50 mg (n = 77)	Std-dose 100 mg (n = 77)	P Value
Median age, yr (range)	47 (19.9-84.3)	48 (16.2-82.5)	.129	47 (19.9-84.3)	49 (16.2-82.5)	.918
Spleen, cm (range)	0 (0-12)	0 (0-23)	.040	0 (0-12)	0 (0-16)	.719
Median WBC, 10^6/L (range)	35.7 (2.5-290.8)	28.2 (0.8-294.7)	.330	35.7 (2.5-290.8)	23.9 (0.8-172.7)	.125
Median Hgb, 10 g/L (range)	12.1 (8.1-17.1)	11.9 (6.7-16.4)	.538	12.3 (8.2-17.2)	12.0 (8.0-16.2)	.774
Median platelet count, x 10^6/L	344 (103-1956)	316 (28-2171)	.527	344 (103-1956)	309 (86-2171)	.401
Basophils in PB, % (range)	0 (0-15)	3 (0-19)	.135	3 (0-15)	3 (0-19)	.616
Blasts in PB, % (range)	0 (0-5)	0 (0-5)	.289	0 (0-5)	0 (0-3)	.430
Blasts in BM, % (range)	1 (0-9)	2 (0-8)	.766	1 (0-9)	2 (0-8)	.839
Clonal evolution, n (%)	5 (6)	14 (10)	.298	5 (7)	2 (3)	.221
Sokal risk group, n (%) ▪ Low ▪ Intermediate ▪ High	 53 (64) 25 (30) 5 (6)	 104 (69) 35 (23) 11 (7)	.515	 50 (65) 22 (29) 5 (7)	 53 (69) 20 (26) 4 (5)	.863

*Propensity score matching identified 77 patients in each cohort without significant baseline difference

- Calculated with logistic regression from baseline characteristics including age, WBC, hemoglobin, spleen size (by examination), platelets, % blasts (BM and PB), % basophils (PB), clonal evolution, and Sokal risk classification

KEY DATA

Dasatinib low-dose vs SOC Clinical Study

Efficacy: post-matched

Outcome, % (95% CI)	Low-dose 50 mg (n = 77)	Standard-dose 100 mg (n = 77)	P Value
4-yr FFS	89 (80.9-97.2)	77 (67.7-86.7)	0.041
4-yr EFS	95 (88.7-100)	92 (86.4-98.4)	0.556
4-yr TFS	100 (100-100)	100 (100-100)	1.000
4-yr OS	97 (93.4-100)	96 (91.9-100)	0.781

Cumulative Incidence of Response: post-matched

Outcome, %	Low-dose 50 mg (n = 77)	Standard-dose 100 mg (n = 77)	P Value
36-mo CCyR	96	88	0.141
36-mo MMR	92	84	0.234
36-mo MR4	77	66	0.038
36-mo MR4.5	77	62	0.021

CCyR, complete cytogenetic response; MMR, major molecular response; MR4.0 corresponds to a BCR/ABL1 ratio of less than 0.01%; MR4.5 corresponds to a ratio of less than 0.0032%

Note: Median follow-up low-dose 50 mg and standard-dose 100 mg: 48 months vs 131 months, respectively

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KEY DATA

Dasatinib low-dose vs SOC Clinical Study

Adverse Events: post-matched

AE, n (%)	Low-dose 50 mg (n = 77)		Standard dose 100 mg (n = 77)		P Value
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	
Leukopenia	31 (40)	1 (1)	39 (51)	3 (4)	.315
Neutropenia	23 (30)	6 (8)	30 (39)	7 (9)	.481
Hemoglobin	54 (70)	4 (5)	50 (65)	2 (3)	.500
Thrombocytopenia	27 (35)	5 (7)	39 (51)	4 (5)	.095
Hyperbilirubinemia	5 (7)	0	9 (12)	0	.215
Alanine transaminase	53 (69)	2 (3)	46 (60)	2 (3)	.495
Alkaline phosphatase	11 (14)	0	16 (21)	1 (1)	.388
Creatinine	**15** (20)	0	**28** (36)	0	.015
Pleural effusions	**4** (5)	2 (3)	**16** (21)	8 (10)	.016

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KEY DATA

Dasatinib low-dose vs SOC Clinical Study

Dose at or within 12 months of treatment

	Low-dose 50 mg (n = 77)	Standard-dose 100 mg (n = 77)
Discontinued TKI therapy within 12 mo of treatment, n (%)	2 (3)	8 (10)
Dose at 12 mo of treatment, n (%)		
▪ 20 mg	1 (1)	0
▪ 40 mg	1 (1)	7 (9)
▪ **50 mg**	**72 (94)**	2 (3)
▪ 60 mg	0	2 (3)
▪ 70 mg	0	2 (3)
▪ 80 mg	0	13 (17)
▪ **100 mg**	1 (1)	**43 (56)**
Mean dose at 12 mo, mg	49	78
Dose escalation within 12 mo, n (%)	2 (3)	0
Dose interruptions within 12 mo, n (%)	5 (7)	40 (52)
Median time to first interruption within 12 mo, days (range)	29 (16-47)	29 (1-350)
Duration of first interruption, days (range)	10 (7-22)	11 (1-50)

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SUMMARY

Dasatinib low-dose vs SOC Clinical Study

- Low-dose dasatinib (50 mg/day) is as effective as standard dose dasatinib (100 mg/day) in patients with newly diagnosed chronic myeloid leukemia in chronic phase
  - 4-year OS: 97% vs 96%, *P*-value 0.781

- Safety data suggests that low-dose dasatinib results in less intolerance

Sasaki. ASH 2021. Abstr 631

Dasatinib low-dose vs SOC Clinical Study

Use of low-dose dasatinib provides comparable efficacy to standard-dose dasatinib and should be considered for patients with newly diagnosed chronic myeloid leukemia in chronic phase

2021 ASH Key Studies

Lymphomas	Multiple Myeloma and Nonmalignant Hematologic Disorders	Leukemias
• POLARIX • RE-MIND2 • ZUMA-7 • SEQUOIA	• GMMG-HD7 • GRIFFIN • BELLINI • Fostamatinib (ITP)	• Dasatinib low-dose vs SOC • ASCEMBL • CPX-351 vs HMA-venetoclax • IPSS-M

CLINICAL QUESTION

ASCEMBL Clinical Trial

Does the use of STAMP inhibitor, asciminib, vs bosutinib provide benefit for patients with chronic myeloid leukemia in chronic phase after prior TKIs?

Updated analysis after 48 weeks

ASCEMBL Clinical Trial

Asciminib is a first-in-class STAMP inhibitor, which targets a myristoyl site of the BCR-ABL1 protein

On October 29, 2021, the FDA granted accelerated approval to asciminib (Scemblix®) for patients with Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase, previously treated with two or more tyrosine kinase inhibitors, *and* approved asciminib for adult patients with Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase with the T315I mutation.

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KEY DATA

ASCEMBL Clinical Trial

Study Design: Multicenter, open-label, randomized phase 3 trial; 48-week update

Inclusion Criteria

- Adults with CML-CP,
- ≥2 prior TKIs,
- Failure* or intolerance of most recent TKI (if intolerant, must have *BCR-ABL1*^{IS} > 0.1% at screening)
- No *T315I* or *V299L* mutation

(N = 233)

Stratified by *MCyR vs no MCyR at baseline*

Randomized 2:1

Asciminib
40 mg BID
(n = 157)

Bosutinib
500 mg QD†
(n = 76)

Treatment up to 96 wk after last patient's first dose or 48 wk after last patient switches to asciminib, whichever is longer

Median follow-up: 19.2 mo.
*Per 2013 ELN recommendations.
†Switch to asciminib 40 mg BID allowed for treatment failure on bosutinib.

Primary End Point: MMR rate at Wk 24 (meeting no tx failure criteria before Wk 24)
Secondary Endpoints: MMR rate at Wk 96 (meeting no tx failure criteria before Wk 96), safety and tolerability, CCyR/MMR rates, time to and duration of CCyR/MMR, time to treatment failure, PFS, OS, and pharmacology parameters

CCyR, complete cytogenetic response; CML-CP, chronic myeloid leukemia in chronic phase; ELN, European LeukemiaNet; MCyR, major cytogenetic response; MMR, major molecular response; PFS, progression-free survival; OS, overall survival; TKI, tyrosine kinase inhibitor; tx, treatment.

KEY DATA

ASCEMBL Clinical Trial

Patient Disposition

Variable, n (%)	Asciminib (n = 157)	Bosutinib (n = 76)
Treated patients	156 (99.4)*	76 (100)
Treatment ongoing†	89 (**56.7**)	17 (**22.4**)
Discontinued treatment	67 (42.7)	59 (77.6)
▪ <Wk 24	26 (16.6)	25 (32.9)
▪ ≥Wk 24 and <Wk 48	25 (15.9)	29 (38.2)
▪ ≥Wk 48 and <Wk 96	15 (9.6)	3 (3.9)
▪ >Wk 96	1 (0.6)	2 (2.6)
Reason for discontinuation		
▪ Lack of efficacy	37 (**23.6**)	27 (**35.5**)
▪ Adverse event	9 (5.7)	18 (23.7)
▪ Physician decision	13 (8.3)	6 (7.9)
▪ Patient decision	4 (2.5)	3 (3.9)
▪ Progressive disease	1 (0.6)	3 (3.9)
▪ Lost to follow-up	1 (0.6)	2 (2.6)
▪ Death	1 (0.6)	0
▪ Protocol deviation	1 (0.6)	0
Switched to asciminib	--	24 (31.6)

*1 patient not treated in asciminib arm per investigator due to cytopenia. †At data cutoff: January 6, 2021.

KEY DATA

ASCEMBL Clinical Trial

MMR Rates at Week 48

Outcome, %	Asciminib (n = 157)	Bosutinib (n = 76)	Common Treatment Difference, % (95% CI)
MMR at Week 48	**29.3%**	**13.2%**	16.1 (5.7-26.6)
▪ If used third line	30.5% (n/N = 25/82)	26.7% (n/N = 8/30)	
▪ If used fourth line	31.8% (n/N = 14/44)	6.9% (n/N = 2/29)	
▪ If used ≥ fifth line	22.6% (n/N = 7/31)	0% (n/N = 0/17)	
Outcome,† %	**Asciminib (n = 142)**	**Bosutinib (n = 72)**	**Treatment Difference**
BCR:ABL1^{IS} ≤1%	**42.3%**	**19.4%**	22.9

*Adjusted for MCyR status at baseline. †Based on patients without this level of response at baseline.

Outcome	Asciminib (n = 157)	Bosutinib (n = 76)
Cumulative incidence of MMR at Week 48, %	**33.2%**	**18.6%**
Probability of maintaining MMR for ≥48 week, % (95% CI)	96.1% (85.4-99.0)	90.0% (47.3-98.5)
Maintained MMR at time of last assessment, n/N	60/62	17/18
Cumulative incidence of BCR:ABL1^{IS} ≤1% at Week 48, %	50.8%	33.7%

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ASCEMBL Clinical Trial

Additional Efficacy Results

Outcome	Asciminib (n = 157)	Bosutinib (n = 76)
MR^4 at week 48, %	10.8%	3.9%
$MR^{4.5}$ at week 48, %	7.6%	1.3%
Treatment failure*, % (# of events)	**48.4%** (76)	**80.3%** (61)
Hazard Ratio (95% CI), *P* value	0.4 (03-0.6), *P* < 0.0001	
K-M estimated proportion of patients without treatment failure by 12 mo, % (95% CI)	57.7% (49.5-65.0)	25.0% (15.9-35.1)
Median time to treatment failure, mo	NR	6

*Defined as lack of efficacy or discontinuation for any reason.

KEY DATA

ASCEMBL Clinical Trial

Adverse Events

AE, %	Asciminib (n = 156)		Bosutinib (n = 76)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any AE	**91.0**	**54.5**	**97.4**	**67.1**
AEs leading to: Discontinuation*	**7.1**	**6.4**	**25.0**	**18.4**
Fatal AEs	1.3	1.3	1.3	1.3
Dose reduction / Dose interruption	23.1 / 40.4		44.7 / 60.5	

*Included thrombocytopenia (3.2%), neutropenia (2.6%) with asciminib; increased ALT (5.3%) and neutropenia (3.9%) with bosutinib.

AEs Occurring in ≥20% of Patients, %	Asciminib (n = 156)	Bosutinib (n = 76)
Thrombocytopenia	**29.5**	19.7
Neutropenia	**23.1**	**21.1**
Diarrhea	11.5	**71.1**
Nausea	11.5	**46.1**
Rash	7.7	**23.7**
Vomiting	7.1	**26.3**
Increased ALT	3.8	**28.9**
Increased AST	5.1	**21.1**

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KEY DATA

ASCEMBL Clinical Trial

Asciminib Related Hematologic Adverse Events

AE by Time Period, %	Thrombocytopenia*	Neutropenia†	Anemia‡
Incidence of first-ever all-grade AEs			
▪ **0 to <6 mo**	**28.8**	**21.8**	**9.6**
▪ 6 to <12 mo	0	0	0
▪ 12 to <18 mo	1.2	2.3	0
▪ ≥18 mo	0	0	0
Prevalence of first-ever, recurring, and ongoing AEs			
▪ 0 to <6 mo	28.8	21.8	9.6
▪ 6 to <12 mo	18.8	7.0	3.1
▪ 12 to <18 mo	12.5	4.8	1.9
▪ ≥18 mo	6.8	5.1	1.7

*Includes thrombocytopenia and platelet count decreased.
†Includes neutropenia and neutrophil count decreased.
‡Includes anemia, decreased hemoglobin, and normocytic anemia.

A patient with multiple occurrences of an AE is counted only once in that time interval.

Greatest incidence hematological AEs occurs in the first 6 months of treatment

Mauro. ASH 2021. Abstr 310. NCT03106779

KEY DATA

ASCEMBL Clinical Trial

Arterial Occlusion Events

Arterial Occlusive Event (AOE), n (%)	Asciminib (n = 156)	Bosutinib (n = 76)
Patients with AOEs, n (%)	7 (4.5)	1 (1.3)
Patients with events by cutoff for primary analysis		
▪ Myocardial ischemia	2 (1.3)*	0
▪ Acute coronary syndrome	0	1 (1.3)
▪ Coronary artery disease	1 (0.6)†	0
▪ Ischemic stroke	1 (0.6)	0
▪ Mesenteric artery embolism/thrombosis‡	1 (0.6)	0
Additional patients with events by cutoff for current analysis		
▪ Cerebral infarction	1 (0.6)	0
▪ Myocardial infarction	1 (0.6)	0
Exposure-adjusted event rate (per 100 patient-yr)		
▪ Primary analysis	3.3	2.0
▪ Current analysis at week 48	3.4	1.6

*Based on per protocol ECG or †coronary arteriography due to medical history; no clinical manifestations.
‡Occurred 15 days after d/c of asciminib and after ponatinib treatment for 7 days.

- Of the 7 patients with AOEs receiving asciminib, 7 had prior exposure to nilotinib, 5 to dasatinib, and 3 to ponatinib
- The majority of patients receiving bosutinib discontinued early, preventing a meaningful comparison between the arms

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SUMMARY

ASCEMBL Clinical Trial

- Updated analysis at week 48: asciminib continued to deliver greater efficacy over bosutinib among patients with CML-CP previously treated with ≥2 TKIs
  - Higher MMR rate of 29.3% vs 13.2%, respectively; treatment difference after adjustment for MCyR at baseline: 16.1% (95% CI: 5.7-26.6)
  - More patients continued to achieve *BCR:ABL1*^{IS} ≤1%: 50.8% vs 33.7%, respectively
  - More patients achieved deep molecular response
    - MR^{4}: 10.8% vs 3.9%, respectively; MR$^{4.5}$: 7.6% vs 1.3%, respectively
  - More patients remained on treatment at time of data cutoff: 56.7% vs 22.4%, respectively
- Safety results are consistent with the primary analysis; no new safety concerns

Mauro. ASH 2021. Abstr 310. NCT03106779

ASCEMBL Clinical Trial

Use of asciminib continues to provide benefit to patients with chronic myeloid leukemia in chronic phase after prior TKIs and may be considered as a new standard of care treatment option

2021 ASH Key Studies

Lymphomas

- POLARIX
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- ZUMA-7
- SEQUOIA

Multiple Myeloma and Nonmalignant Hematologic Disorders

- GMMG-HD7
- GRIFFIN
- BELLINI
- Fostamatinib (ITP)

Leukemias

- Dasatinib low-dose vs SOC
- ASCEMBL
- CPX-351 vs HMA-venetoclax
- IPSS-M

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CPX-351 vs HMA + Ven Clinical Trial

Does the use of CPX-351 or HMA + Ven provide greater benefit for patients with acute myeloid leukemia in the frontline setting?

A retrospective Comparative (Subgroup) Analysis

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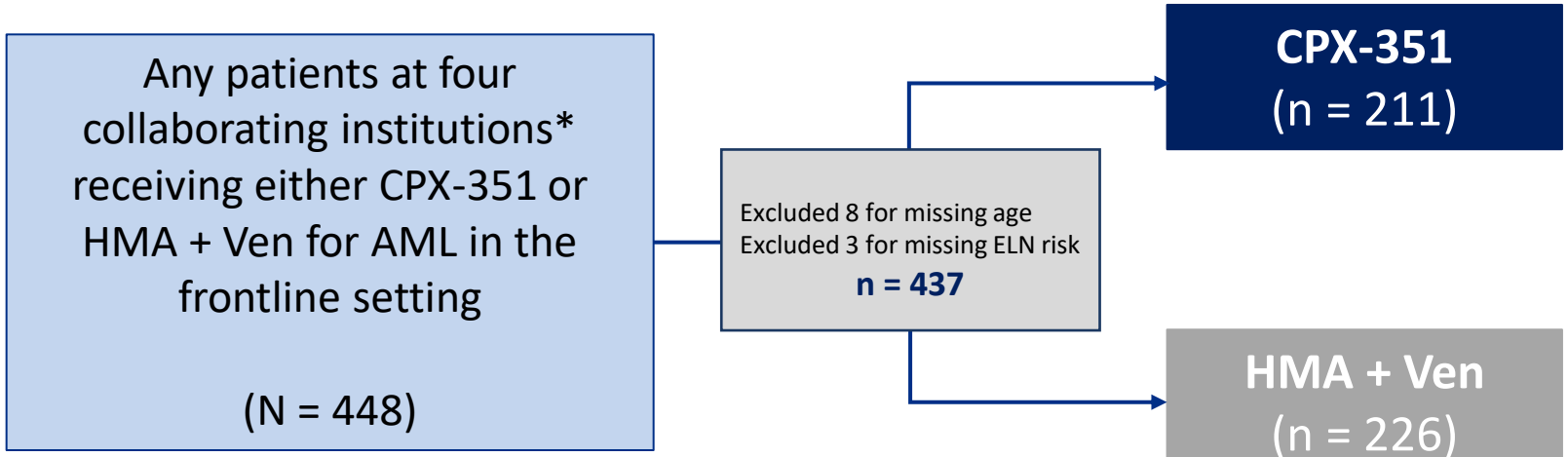
KEY DATA

CPX-351 vs HMA + Ven

Study Design: real world analysis of patient characteristics and outcomes



*MSKCC, Northwestern, Moffitt, Cornell
AML, acute myeloid leukemia
CPX-351, liposomal daunorubicin/cytarabine
HMA + Ven, hypomethylating agent + venetoclax

Primary Outcomes:

- Response rate (CR + CRi)
- Relapse-free survival (RFS)
- Overall survival (OS)

- Analysis was conducted for the overall population (age range 34 – 93 yrs) and subgroup of 60-75 yrs
  - Most overlap occurred in the 60-75 yrs age group between the two treatment arms
  - Subgroup analyses: TP53, Adverse ELN Risk, Prior myeloid malignancy, prior HMA therapy

KEY DATA

CPX-351 vs HMA + Ven

Baseline characteristics

Characteristic	Overall Population			Patients Aged 60-75 Yr		
	CPX-351 (n = 211)	**HMA + Ven (n = 226)**	**P Value**	**CPX-351 (n = 152)**	**HMA + Ven (n = 100)**	**P Value**
Median age, yr (IQR)	**66.8** (60.8-71.6)	**75.2** (69.7-78.8)	**<.001**	**68.5** (64.4-71.7)	**70.3** (67.5-73.0)	**.002**
Male, n (%)	121 (57.4)	138 (61.1)	.430	87 (57.2)	59 (59.0)	.782
AML ELN risk, n (%)						
▪ Favorable/intermediate	82 (38.9)	64 (28.3)		67 (44.1)	23 (23.0)	
▪ Adverse	**129 (61.1)**	**162 (71.7)**		85 (55.9)	77 (77.0)	
Mutations, n (%)*						
▪ TP53	37 (19.1)	58 (26.7)	.066	**22 (14.5)**	**25 (25.0)**	**.036**
▪ FLT3	12 (6.1)	19 (8.8)	.311	10 (7.2)	9 (9.4)	.547
▪ NPM1	13 (6.6)	23 (10.7)	.150	10 (7.2)	7 (7.3)	.977
▪ RUNX1	44 (22.7)	54 (24.9)	.601	**27 (19.7)**	**32 (33.0)**	**.021**
▪ ASXL1	**32 (16.5)**	**59 (27.1)**	**.010**	**24 (17.5)**	**30 (31.3)**	**.015**
▪ IDH1/IDH2	38 (19.7)	40 (18.4)	.729	32 (23.4)	18 (18.8)	.399
Antecedent hematologic malignancy, n (%)						
▪ Prior myeloid disorder	**114 (54.0)**	**92 (40.7)**	**.005**	80 (52.6)	41 (41.0)	.071
▪ Prior HMA therapy: yes/no/other	**43/136/32 (20.4/64.5/15.2)**	**22/180/24 (9.7/79.7/10.6)**	**.001**	32/97/23 (21.1/63.8/15.1)	12/75/13 (12.0/75.0/13.0)	.127

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KEY DATA

CPX-351 vs HMA + Ven

CR/CRi Rates

Efficacy Outcome	CPX-351 (n = 211)	HMA + Ven (n = 226)	P Value
Overall: CR/CRi, n (%)	**122 (57.8)**	**128 (56.6)**	**0.803**
▪ CR	98 (46.4)	62 (27.4)	<0.001
▪ CRi	24 (11.4)	66 (29.2)	<.0.001
TP53+ (n=95): CR/CRi, n (%)	**11 (29.7)**	**28 (48.3)**	**0.073**
▪ CR	9 (24.3)	16 (27.6)	0.725
▪ Cri	2 (5.4)	12 (20.7)	0.072
Prior Myeloid Malignancy (n=206): CR/CRi, n (%)	**57 (50.0)**	**38 (41.3)**	**0.213**
▪ CR	49 (43.0)	16 (17.4)	<0.001
▪ Cri	8 (&.0)	22 (23.9)	0.001
Prior HMA Therapy (n=65): CR/CRi, n (%)	**18 (41.9)**	**9 (40.9)**	**0.941**
▪ CR	16 (37.2)	2 (9.1)	0.020
▪ Cri	2 (4.7)	7 (31.8)	0.005
ELN-Adverse (n=291): CR/CRi, n (%)	**65 (50.4)**	**85 (52.5)**	**0.724**
▪ CR	49 (38.0)	40 (24.7)	0.015
▪ Cri	16 (12.4)	45 (27.8)	0.001

CR, complete response; CRi, incomplete blood count recovery

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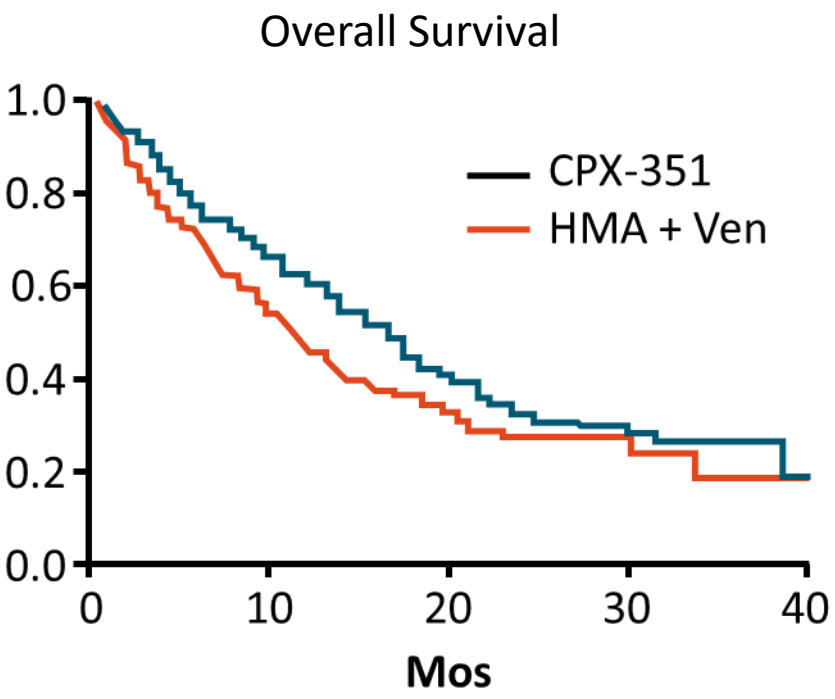
KEY DATA

CPX-351 vs HMA + Ven

Efficacy in Overall Population



Efficacy outcome	CPX-351 (n = 211)	HMA + Ven (n = 226)	P Value
Median RFS, mo (95% CI)	33.7 (27.4-NA)	15.8 (11.8-NA)	0.132
Median OS, mo (95% CI)	**17.3 (13.8-20.5)**	**11.1 (9.3-13.6)**	**0.007**

Overall Survival	Hazard ratio (95% CI)	P value
Overall	0.742 (0.563, 0.995)	0.045
***TP53* status**	0.406 (0.224, 0.735)	0.003
Prior myeloid malignancy	0.640 (0.440, 0.931)	0.02
Prior HMA use	0.489 (0.276, 0.806)	0.014
ELN adverse	0.668 (0.482, 0.925)	0.015

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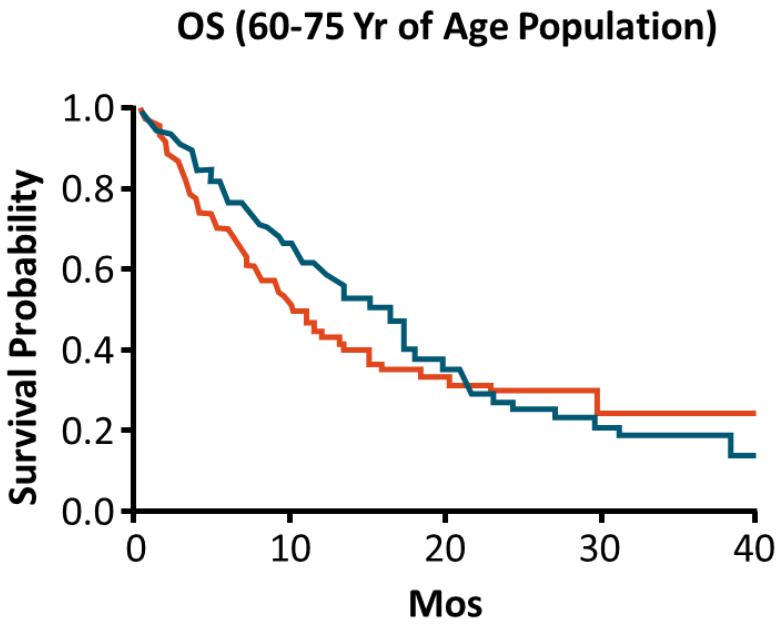
KEY DATA

CPX-351 vs HMA + Ven

Efficacy in 60-75 yrs of Age Population

Efficacy outcome	CPX-351 (n = 152)	HMA + Ven (n = 100)	P Value
Median RFS, mo	32.5	13.3	0.80
Median OS, mo	17.1	10.3	0.12

Outcome, %	CPX-351 (n = 152)	HMA + Ven (n = 100)	*P* Value
CR/CRi, %	59.2	54.0	0.41
Underwent HSCT, %	47.7	19.0	<0.001



Overall Survival	Hazard ratio (95% CI)	P value
Overall	0.802 (0.57, 1.127)	0.204
No HSCT	0.991 (0.684, 1.436)	0.96
***TP53* status**	**0.395 (0.191, 0.820)**	**0.013**
Prior myeloid malignancy	0.656 (0.414, 1.038)	0.072
Prior HMA use	0.682 (0.314, 1.480)	0.333
ELN adverse	0.735 (0.506, 1.067)	0.105

- No significant difference in OS among responders only
- No significant difference in post-transplant OS

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SUMMARY

CPX-351 vs HMA + Ven

- There was no significant difference in response rate (CR/CRi) between CPX-351 and HMA + Ven in the overall population or in patients aged 60-75 yrs
- In the overall population, OS was greater in the CPX-351 arm compared to the HMA + Ven arm
- OS was not significantly different in the 60-75 yrs population
  - Higher rate of HSCT in the CPX-351 group compared to the HMA + Ven group did not result in a significant difference in OS
- Subgroup analyses showed a higher OS with CPX-351 for patients with *TP53* mutations aged 60-75 yrs

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CPX-351 vs HMA + Ven

Use of CPX-351 may result in a more favorable survival benefit over treatment with HMA + Ven in patients with acute myeloid leukemia regardless of age

However, prospective clinical trial is needed to truly compare the results of CPX-351 vs HMA + Ven in patients with AML

2021 ASH Key Studies

Lymphomas	Multiple Myeloma and Nonmalignant Hematologic Disorders	Leukemias
• POLARIX • RE-MIND2 • ZUMA-7 • SEQUOIA	• GMMG-HD7 • GRIFFIN • BELLINI • Fostamatinib (ITP)	• Dasatinib low-dose vs SOC • ASCEMBL • CPX-351 vs HMA-venetoclax • IPSS-M

IPSS-M

Will the Molecular International Prognosis Scoring System (IPSS-M) improve risk stratification and lead to better treatment decisions for patients with myelodysplastic syndromes (MDS)?

KEY DATA

IPSS-M

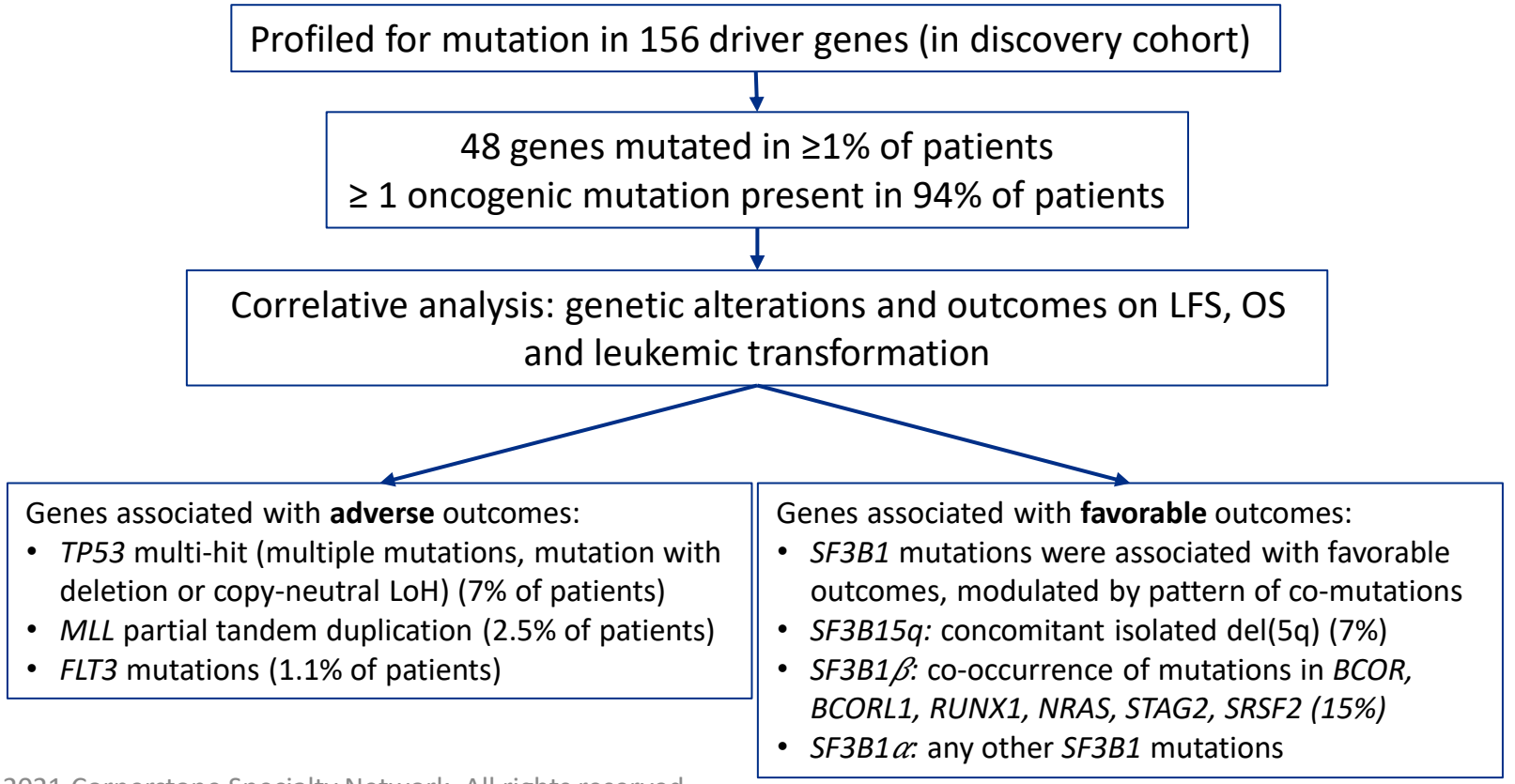
Study Objective: Integrate gene mutations into the IPSS/IPSS-R

Development and validation of a Molecular International Prognostic Scoring System (IPSS-M) in 3,675 representative MDS patients

International Working Group for the Prognosis of MDS cohort (discovery), n =2,957
Japan cohort (validation), n=754

Inclusion Criteria
Diagnostic samples:
- Blast percentages < 20%
- WBC count < $13x10^9$/L

Median age of presentation 72 years (39-88)
8% of pts had therapy-related MDS
30% pts treated with disease-modifying agents
OS available for 95% of pts
Leukemia-free survival available for 88% of pts
Median follow-up of 3.8 years



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IPSS-M

IPSS-M: Model Development Steps

- LFS used as the primary endpoint
- Model development included:
  - Encoding for clinical and molecular variables
  - Determination of independent IPSS-M prognostic variables
    - 17 genetic variables from 16 main effect genes
    - 1 genetic variable from 15 residual genes (*BCOR, BCORL1, CEBPA, ETNK1, GATA2, GNB1, IDH1, NF1, PHF6, PPM1D, PRPF8, PTPN11, SETBP1, STAG2, WT1*)
  - Construction of IPSS-M risk score as a continuous patient-specific score
  - Definition of IPSS-M risk categories for discrete risk grouping
    - 6 risk groups established

- IPSS-M demonstrated improved prognostic discrimination vs IPSS-R with 5-point increase in concordance index across all endpoints
- 46% of patients were re-stratified from IPSS-R to IPSS-M
  - 7% re-stratified by >1 strata
- Validated in the Japanese MDS cohort (n=754), with 42% of patients re-stratified

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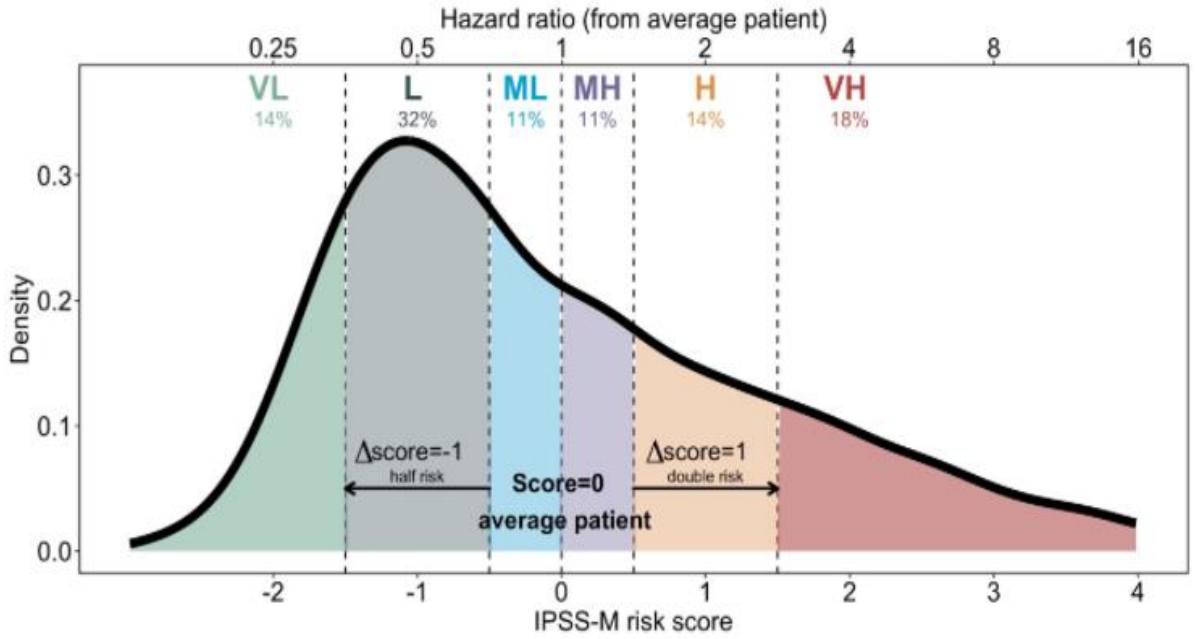
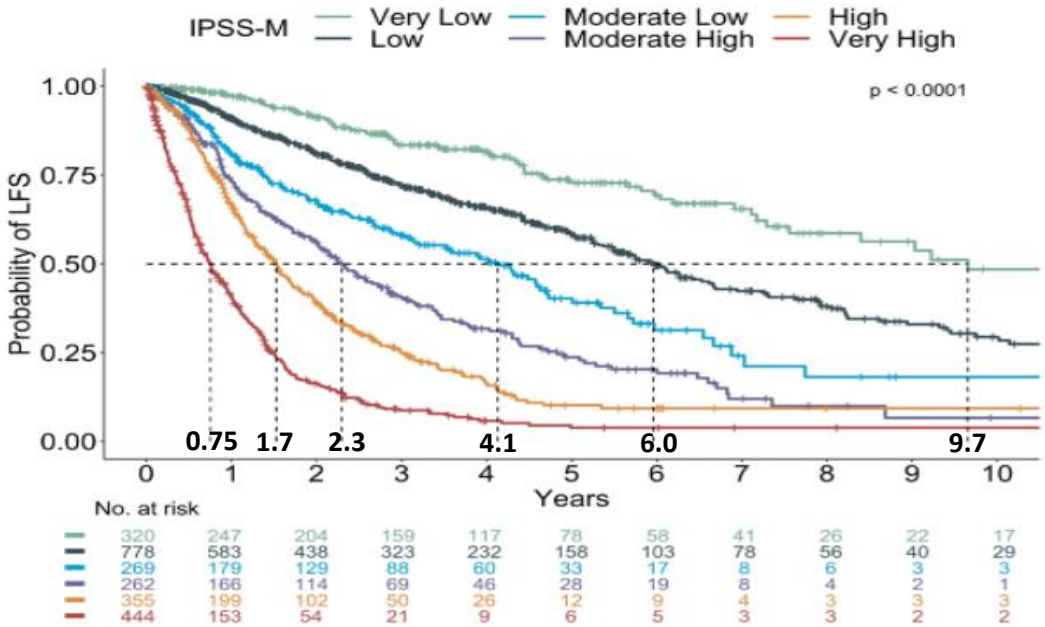
IPSS-M

IPSS-M: Risk Score and Risk Categories

Density distribution of the IPSS-M risk score from the discovery cohort (n=2,701)



K-M curves and associated risk table for LFS for each IPSS-M risk category



VL: very low; L: low; ML: moderate low; MH: moderate high; H: high; VH: very high

The six risk category schema was defined based on score cutoffs: Very Low (14% n=387); Low (32%, n=876), Moderate Low (11%, n=299), Moderate High (11%, n=284), High (14%, n=382) and Very High (18%, n=473)

SUMMARY

IPSS-M

Currently, there are three main prognostic scoring systems:

1. IPSS (International Prognostic Scoring System)
   - Uses three factors to predict the course of the patient's disease:
     i. The percentage of leukemic blast cells in the marrow
     ii. The type of chromosomal changes, if any, in the marrow cells (cytogenetics)
     iii. The presence of one or more low blood cell counts (cytopenias)

2. IPSS-R (Revised International Prognostic Scoring System)
   - Uses five factors to predict the course of the patient's disease:
     i. Blasts
     ii. Cytogenetics
     iii. Hemoglobin
     iv. Platelet count
     v. Absolute neutrophil count

3. WPSS (WHO classification-based Prognostic Scoring System)
   - Includes the MDS subtype as a prognostic factor.
   - Assigns a score based on the presence or absence of severe anemia.

Utilization of the **IPSS-M** could improve risk stratification and lead to better treatment decisions for patients with myelodysplastic syndromes (MDS)

- IPSS-M combines conventional parameters with mutations in **31** key genes to improve MDS risk stratification
- Risk score is personalized as a continuous score, reproducible, and interpretable, as 1-unit increase in score doubles risk
- **6-category** risk schema developed
- Includes a strategy to handle missing data: provides IPSS-M score for best, average, and worst case scenarios
- Web calculator returns individualized risk score and category

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