ASH Rehash 2019

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- No conflicts of interest

In case you needed some ways to properly express your feelings to your Valentine today

- Valentine, your HgbA1c must be > 7 because you are so sweet!
- Dauno is red, vyxeos is purple, being around you prolongs my survival
- Valentine, I'm attracted to you like idecabtagene vicleucel is attracted to BCMA
- Valentine, were are a great combo like an ADC
- If I were to measure my love for you, the level would be supratherapeutic
- Being with you is like being on continuous infusion oxytocin

Summary

- Over 5000 abstracts submitted and 3000 abstracts accepted
- Many great studies are not summarized in this presentation
- I focused on MM, AML, and NHL at this meeting

- If I did not include your favorite study, I am sorry

Top Abstracts that I will not discuss

- **ABSTRACT 13:** Time from diagnosis to treatment does not affect outcome in intensively treated (7+3) patients with newly diagnosed AML (ClinicalTrials.gov identifier NCT03188874)

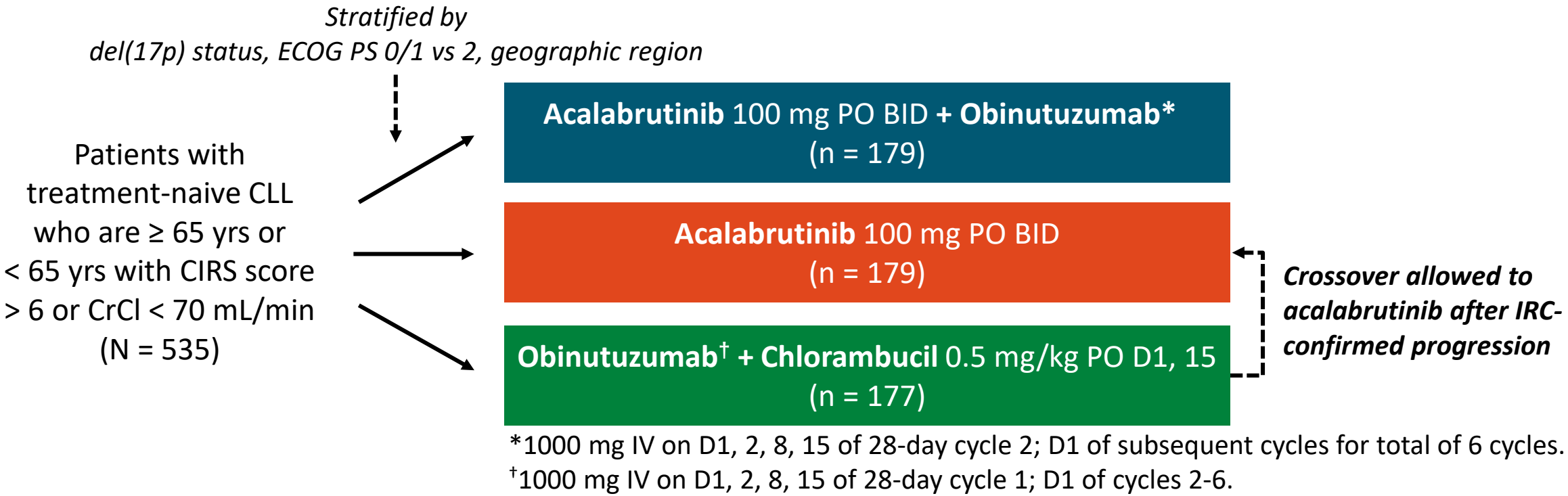
- **ABSTRACT 115:** Maintenance decitabine (20 mg/m^2 for 3 days/month x 12 months) improves disease-free and overall survival after intensive therapy for AML in older adults (median age of 69 years), particularly in *FLT3-ITD*–negative patients: ECOG-ACRIN (E-A) E2906 randomized study (NCT02085408)

Top Abstracts that I will not discuss

- **ABSTRACT 175:** Precision medicine treatment in older adults (≥ 60 years) with newly diagnosed AML: Results of multicenter BEAT AML Master trial (NCT03013998)
  - ***Methods:*** The BEAT AML trial was designed to assess the feasibility of using genetic profiling (local cytogenetics and Foundation Medicine) to assign older adults to molecularly defined, subtype-specific therapies within 7 days of the initial diagnosi
  - ***Results:*** The median age of eligible patients was 72 years, with 38% 75 years of age or older, and 16% had treatment-related AML. Of the 395 eligible patients, 374 (94.7%) were assigned to the different cytogenetic/genomic groups within 7 days. The most common groups were *TP53*-mutated (19%) and marker-negative (18%) molecular groups.

Previously Untreated CLL

Phase III ELEVATE TN (ACE-CL-007): Study Design



*1000 mg IV on D1, 2, 8, 15 of 28-day cycle 2; D1 of subsequent cycles for total of 6 cycles.
†1000 mg IV on D1, 2, 8, 15 of 28-day cycle 1; D1 of cycles 2-6.

- Primary endpoint: PFS by IRC with acalabrutinib + obinutuzumab vs obinutuzumab + chlorambucil
- Key secondary endpoints: PFS of acalabrutinib vs obinutuzumab + chlorambucil, ORR by IRC and investigators, time to next treatment, OS, safety

Sharman. ASH 2019. Abstr 31.

ELEVATE TN: Progression-Free Survival

Outcome*	Acalabrutinib + Obinutuzumab (n = 179)	Acalabrutinib (n = 179)	Obinutuzumab + Chlorambucil (n = 177)
Median PFS, mos (95% CI)	Not reached	Not reached	22.6 (20.2-27.6)
24-mo PFS (by IRC), %	93	87	47
PFS HR			
▪ HR vs Acala (95% CI)	0.49 (0.26-0.95)	--	--
▪ HR vs Obin + Chlor (95% CI)	0.10 (0.06-0.17)†	0.20 (0.13-0.30)†	--

*Median follow-up: 28.3 mos. †*P* < .0001 vs obinutuzumab/chlorambucil

- PFS benefit of acalabrutinib consistent across subgroups, including bulky disease (< 10 cm or ≥ 10 cm), presence or absence of del(17p) or *TP53* mutations, presence or absence of del(11q)(q22.3), *IGHV* mutated or unmutated, and presence or absence of complex karyotype

Sharman. ASH 2019. Abstr 31.

ELEVATE TN: ORR and OS

Outcome	Acalabrutinib + Obinutuzumab (n = 179)	Acalabrutinib (n = 179)	Obinutuzumab + Chlorambucil (n = 177)
ORR (by IRC), % (95% CI)	93.9 (89.3-96.5)*	85.5 (79.6-89.9)†	78.5 (71.9-83.9)
▪ CR, n (%)	23 (13)	1 (1)	8 (5)
▪ CR/incomplete marrow, n (%)	1 (1)	0	0
▪ PR, n (%)	144 (81)	152 (85)	131 (74)
SD, n (%)	4 (2)	8 (5)	15 (9)
OS events (death), n (%)	9 (5.0)	11 (6.1)	17 (9.6)
▪ HR vs Obin + Chlor (95% CI)	0.47 (0.21-1.06)§	0.60 (0.28-1.27)¶	--

*$P < .0001$; †$P = .0763$; §$P < .0577$; ¶$P < .1556$

- In obinutuzumab + chlorambucil arm, 82 patients (46%) has disease progression and 45 of those (55%) crossed over to receive acalabrutinib

Sharman. ASH 2019. Abstr 31.

ELEVATE TN: AEs of Clinical Interest for Acalabrutinib

AE, n (%)	Acalabrutinib + Obinutuzumab (n = 178)		Acalabrutinib (n = 179)		Obinutuzumab + Chlorambucil (n = 169)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Atrial fibrillation	6 (3.4)	1 (0.6)	7 (3.9)	0	1 (0.6)	0
Hypertension	13 (7.3)	5 (2.8)	8 (4.5)	4 (2.2)	6 (3.6)	5 (3.0)
Bleeding	76 (42.7)	3 (1.7)	70 (39.1)	3 (1.7)	20 (11.8)	0
▪ Major bleeding	5 (2.8)	3 (1.7)	3 (1.7)	3 (1.7)	2 (1.2)	0
Infection	123 (69.1)	37 (20.8)	117 (65.4)	25 (14.0)	74 (43.8)	14 (8.3)
Second primary malignancy*	10 (5.6)	6 (3.4)	5 (2.8)	2 (1.1)	3 (1.8)	2 (1.2)

*Excluding nonmelanoma skin cancer.

Sharman. ASH 2019. Abstr 31.

ELEVATE TN: Investigator Conclusions

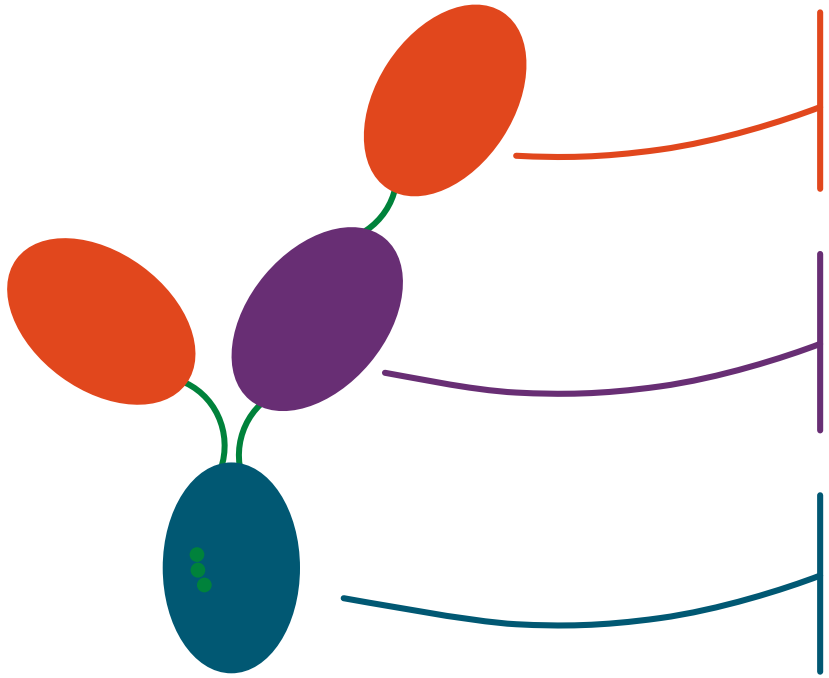
- In the phase III ELEVATE TN trial, acalabrutinib ± obinutuzumab significantly improved PFS compared with obinutuzumab + chlorambucil in treatment-naive CLL
  - In addition, acalabrutinib monotherapy significantly improved PFS vs obinutuzumab + chlorambucil in this patient population
- Acalabrutinib ± obinutuzumab associated with tolerable safety profile
- Fewer deaths in either acalabrutinib treatment arm vs obinutuzumab + chlorambucil, but longer follow-up needed to assess OS
- Acalabrutinib now FDA approved for patients with treatment-naive and relapsed/refractory CLL

Sharman. ASH 2019. Abstr 31.

Relapsed/Refractory Myeloma

CC-93269: BCMA- and CD3ε-Targeted BiTE Antibody

- CC93269: humanized, IgG1 T-cell engager that binds BCMA on myeloma cells with CD3ε on T-cells, enabling tight, specific BCMA binding[1,2]



Anti-BCMA (bivalent)[1-5]
Bivalent binding to BCMA in a 2+1 format for better potency, tumor targeting, and retention

Anti-CD3ε (monovalent)[1-5]
BCMA- and CD3ε-binding Fab domains with a flexible linker

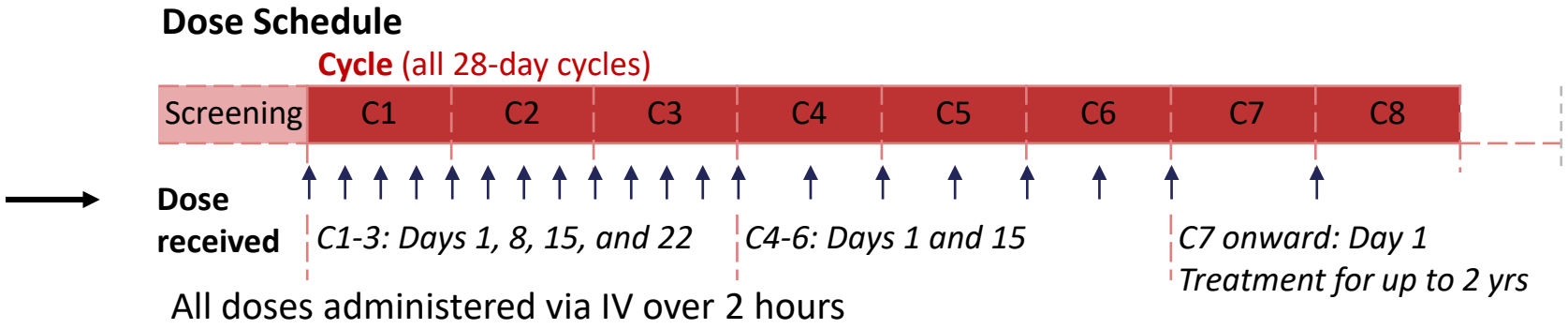
Heterodimeric FcγR-silent Fc[1-6]
No binding to FcγR and C1q to minimize IRRs; binding to FcRn retained for IgG-like PK

- CC-93269 induces tumor regression in animal models of myeloma and promotes myeloma cell apoptosis in primary patient bone marrow aspirates[1,2]

1. Seckinger. Cancer Cell. 2017;31:396. 2. Vu. ASH 2015. Abstr 2998. 3. Klein. AACR 2017. Abstr 3629. 4. Bacac. Clin Cancer Res. 2016;22:3286.
5. Lehmann. Clin Cancer Res. 2016;22:4417. 6. Schlothauer. Prot Eng Des Sel. 2016;29:457.

Phase I Study of CC-93269 in Relapsed/Refractory Myeloma (CC-93269-MM-001): Study Design

Patients with relapsed/refractory myeloma after ≥ 3 regimens; progressive disease within 60 days of last regimen; no prior BCMA-targeted treatment
(N = 30)

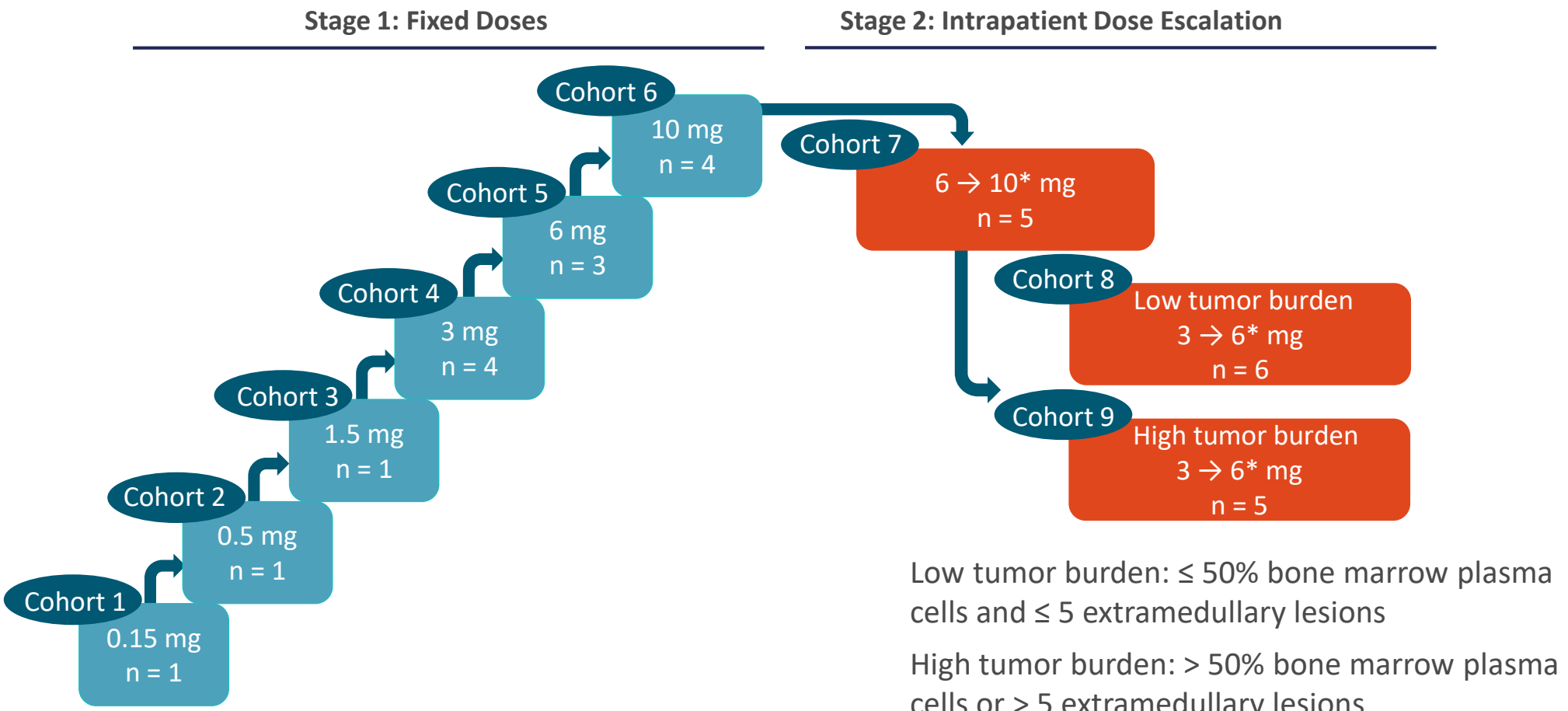


- Part A: dose escalation
  - Stage 1: fixed doses
  - Stage 2: step-up in dose on cycle 1, Day 18
- Part B: cohort expansion

- Primary endpoints: safety (DLTs, AEs, NTD, MTD)
- Secondary endpoints: efficacy (MRD, PK, ADA, PD)

Costa. ASH 2019. Abstr 143.

CC-93269-MM-001: Dose Escalation



Low tumor burden: ≤ 50% bone marrow plasma cells and ≤ 5 extramedullary lesions

High tumor burden: > 50% bone marrow plasma cells or > 5 extramedullary lesions

Costa. ASH 2019. Abstr 143.

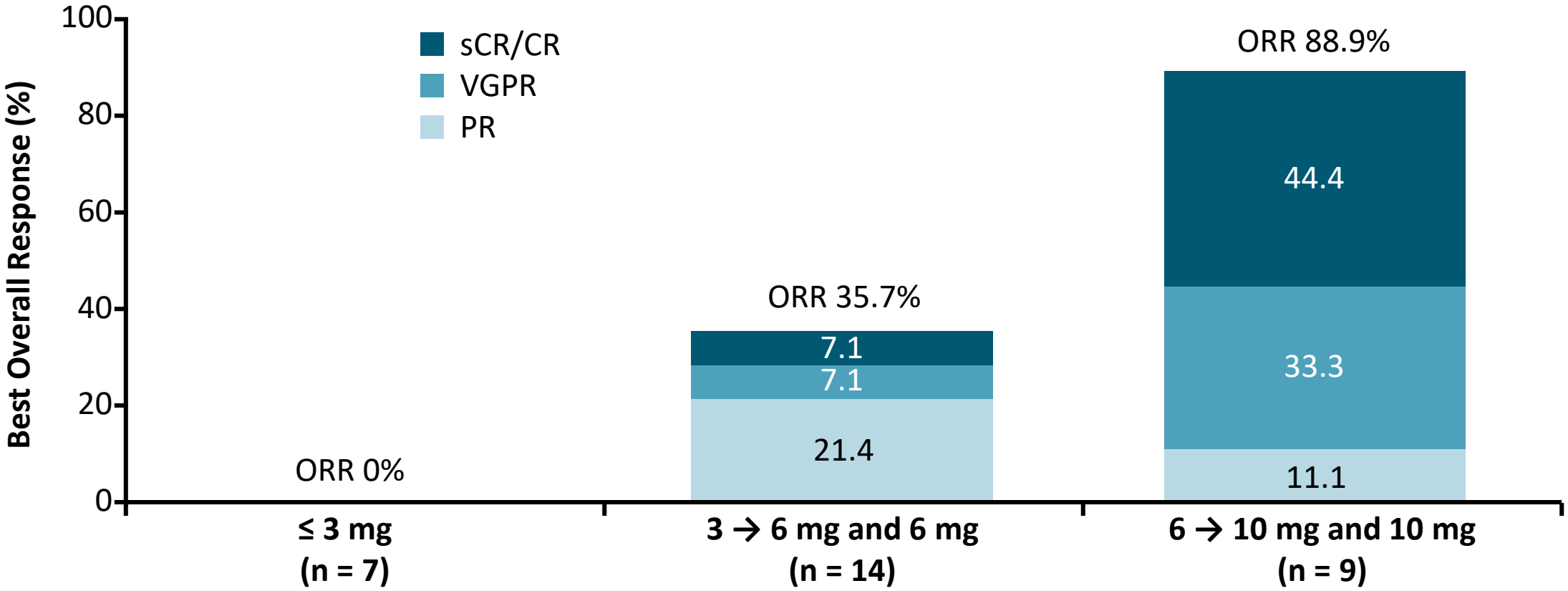
CC-93269-MM-001: Safety

TEAE in ≥ 20%, n (%)	All Grade	Grade ≥ 3
≥ 1 TEAE	29 (96.7)	22 (73.3)
Hematologic TEAEs		
▪ Neutropenia	14 (46.7)	13 (43.3)
▪ Anemia	13 (43.3)	11 (36.7)
▪ Thrombocytopenia	9 (30.0)	5 (16.7)
Nonhematologic TEAEs		
▪ Cytokine-release syndrome	23 (76.7)	1 (3.3)
▪ Infections and infestations	17 (56.7)	9 (30.0)
▪ Diarrhea	8 (26.7)	1 (3.3)
▪ Vomiting	8 (26.7)	0
▪ Back pain	7 (23.3)	0
▪ Fatigue	6 (20.0)	0
▪ Infusion-related reaction	6 (20.0)	0
▪ Nausea	6 (20.0)	0

4 deaths during treatment period: 1 cytokine-release syndrome possibly related to CC-93269, plus unrelated sepsis in a patient with advanced prostate cancer, sudden cardiac death, and progressive myeloma (n = 1 each)

Costa. ASH 2019. Abstr 143.

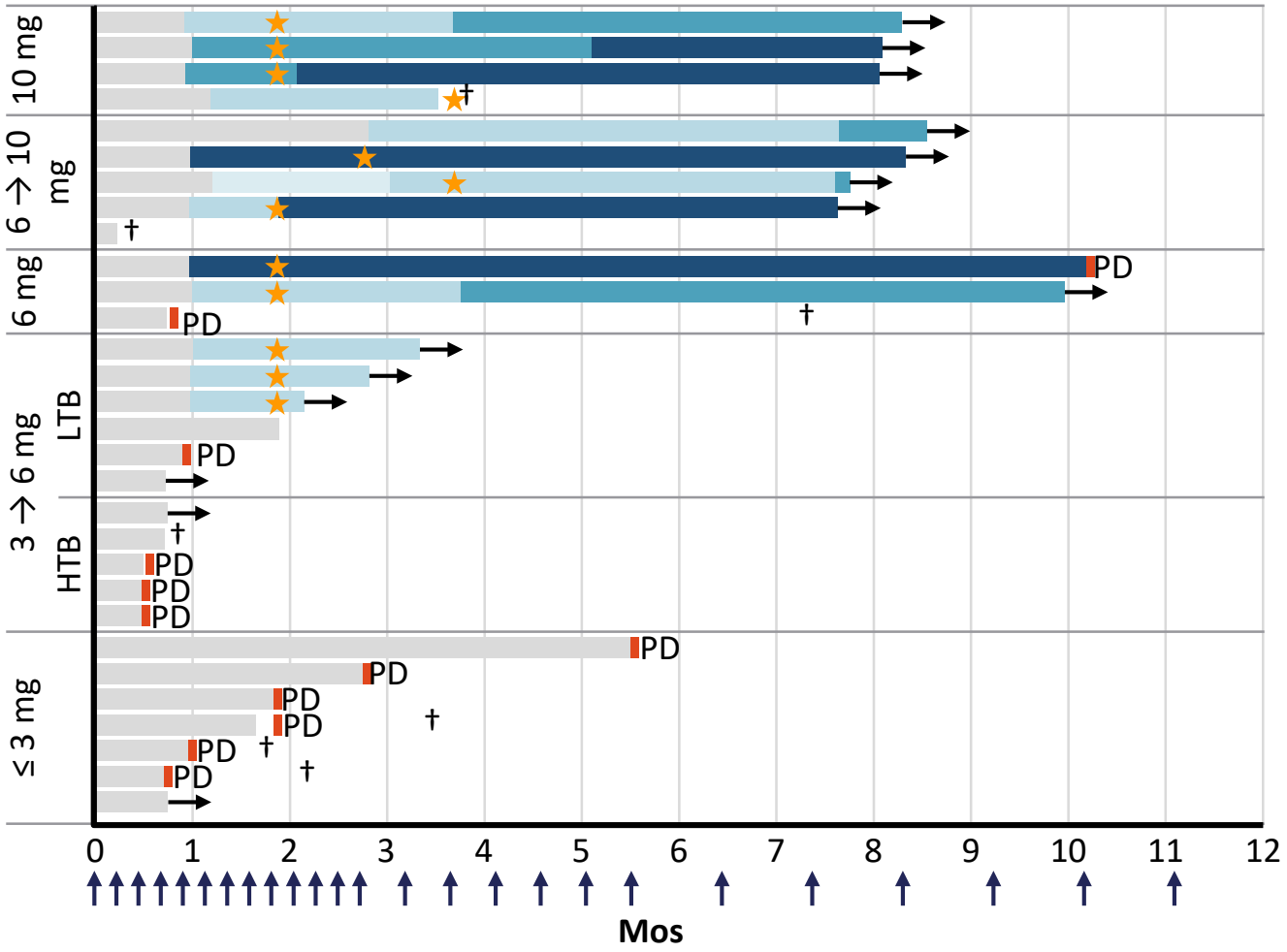
CC-93269-MM-001: Preliminary Efficacy



- ORR, all patients (N = 30): 43.3%
  - sCR/CR: 16.7%
- ORR, patients receiving 10 mg (n = 9): 88.9%
  - sCR/CR: 44.4%

Costa. ASH 2019. Abstr 143.

CC-93269-MM-001: Responses Over Time



- Median time to first response: 4.1 wks (range: 4.0-13.1)
- MRD-negative sCR/CR: 5/30 (16.7%)
  - Of 13 responding patients, 92.3% achieved MRD negativity (≤ $1/10^5$) in BM by C4D1 (Euroflow analysis)

Costa. ASH 2019. Abstr 143.

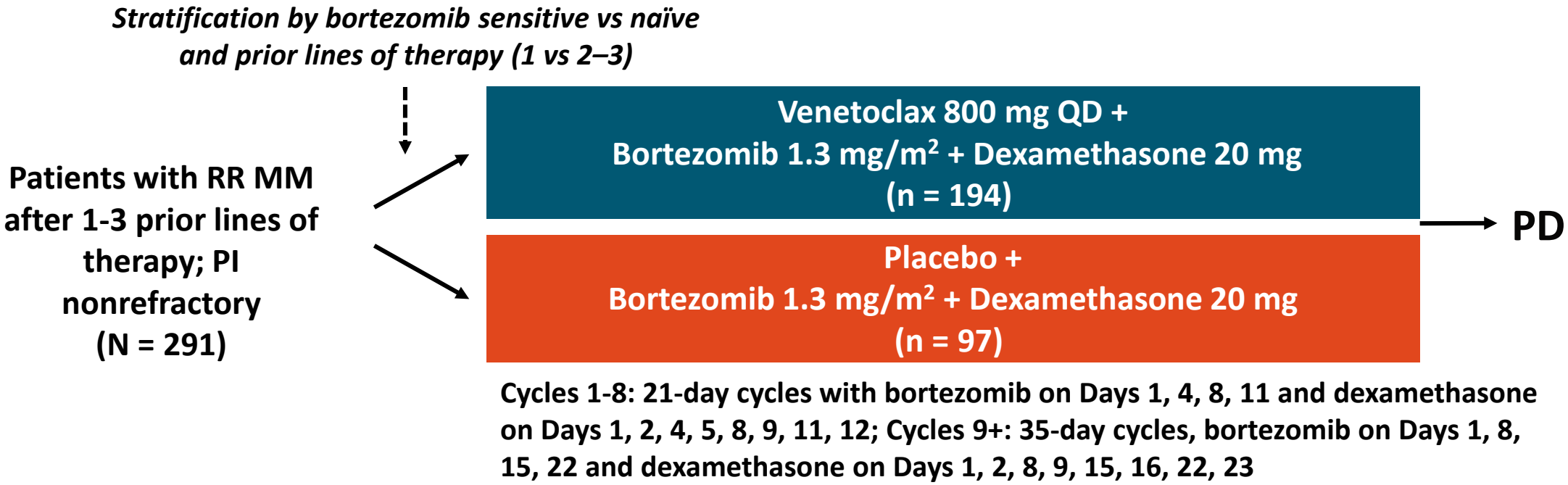
CC-93269-MM-001: Investigator Conclusions

- Initial results from ongoing phase I study suggest CC-93269 is safe with promising dose-dependent activity in relapsed/refractory myeloma
  - Enrollment ongoing to define RP2D
  - Most common grade ≥ 3 TEAEs: neutropenia (43.3%), anemia (36.7%), infections (30.0%)
  - CRS: 76.7%, majority grade 1/2
  - No encephalopathy observed
- ORR in 10-mg group: 88.9% (sCR/CR: 44.4%)
- All patients who achieved sCR/CR were MRD negative
  - MRD in BM in responding patients: 92.3%

Costa. ASH 2019. Abstr 143.

BELLINI Biomarker Subgroup Analysis: Study Design

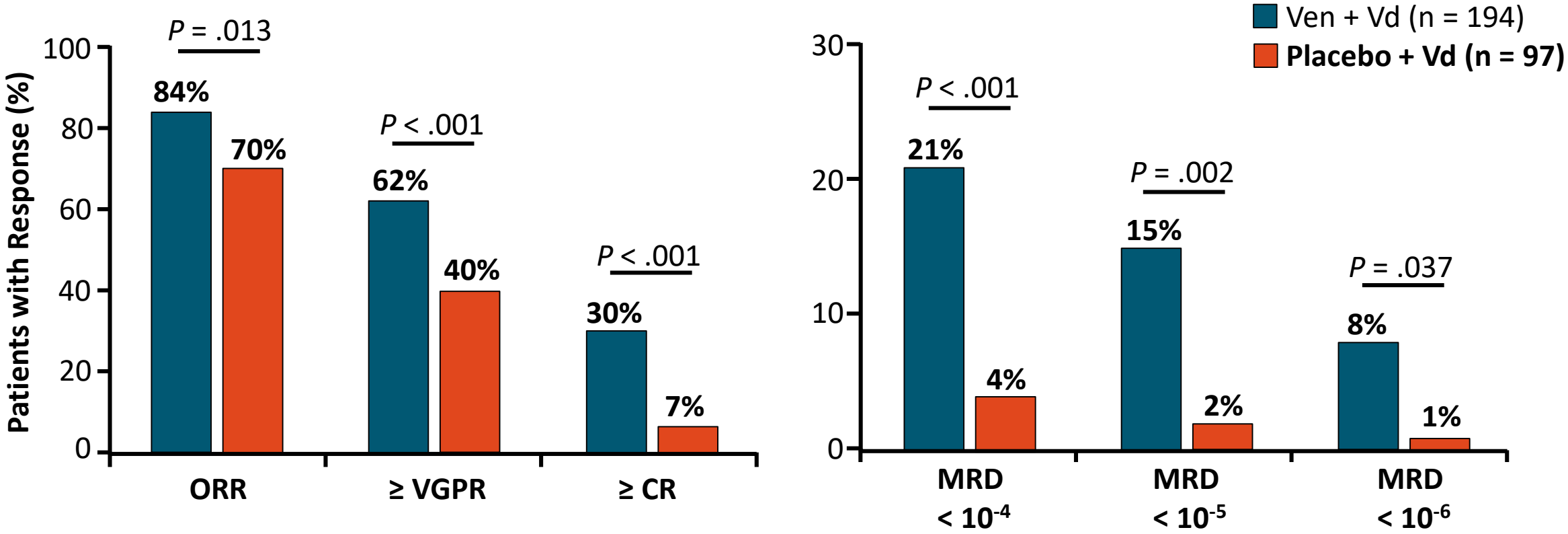
- Double blind, randomized 2:1, placebo-controlled phase III trial



- Primary Endpoint: PFS (per IRC)
- Key Secondary Endpoints: ORR, ≥ VGPR, OS, QoL/PRO parameters

Harrison. ASH 2019. Abstr 142.

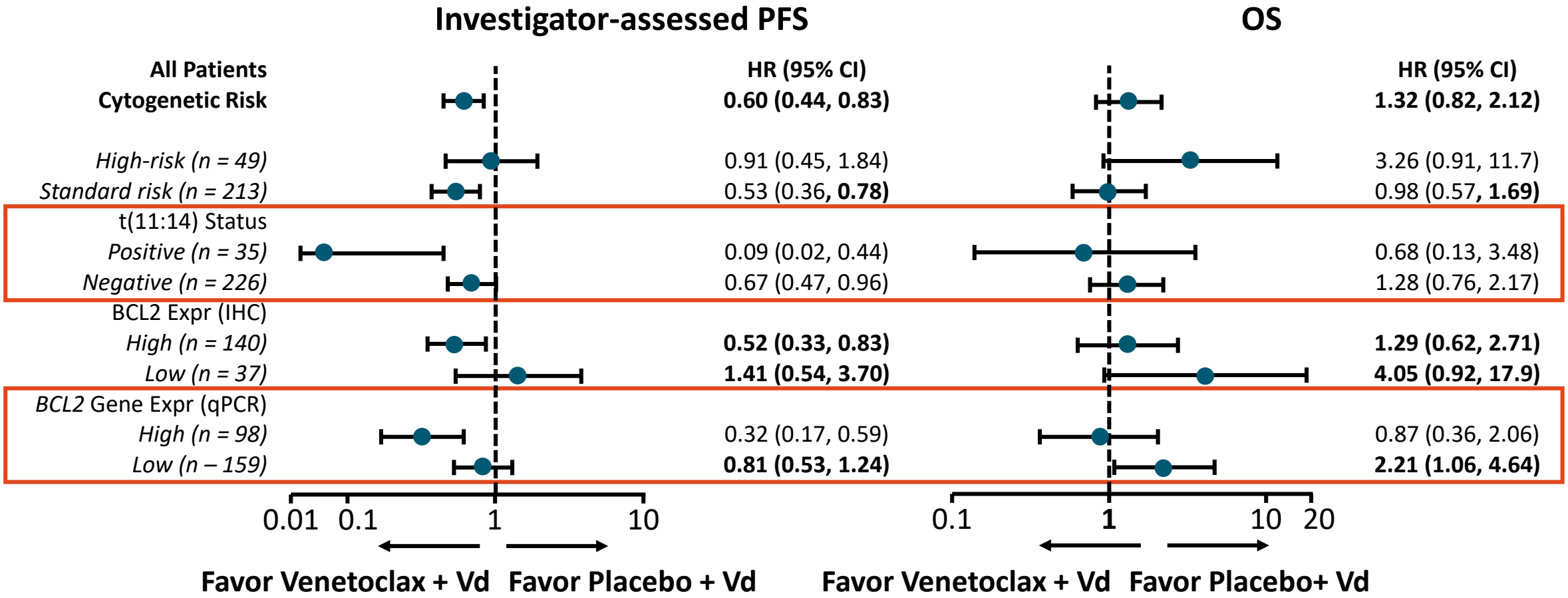
BELLINI Biomarker Subgroup Analysis: Response and MRD Negativity Rates in All Patients



- Overall response, ≥ VGPR, ≥ CR, and MRD negativity rates were significantly higher with Ven+Vd
- MRD assessment by NGS on BM aspirate at time of CR/sCR and 6- and 12-mos post confirmation of CR/sCR

Harrison. ASH 2019. Abstr 142.

BELLINI Biomarker Subgroup Analysis: PFS and OS Analysis in Key Biomarker Subgroups



- PFS significantly extended with venetoclax vs placebo in pts with t(11;14) or $BCL2^{high}$ gene expression

Harrison. ASH 2019. Abstr 142.

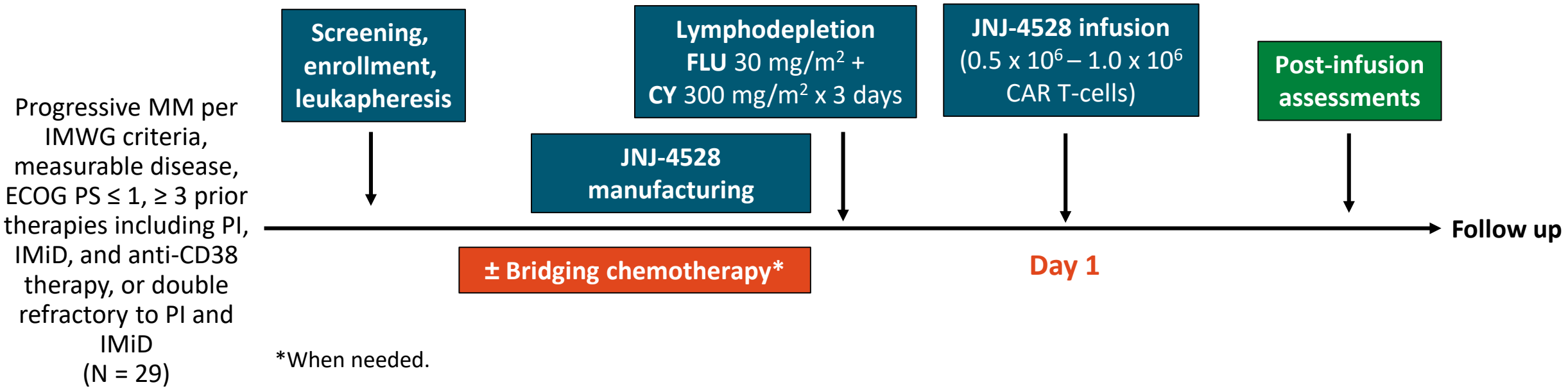
BELLINI Biomarker Subgroup Analysis: Investigator Conclusions

- Addition of venetoclax to bortezomib/dexamethasone was efficacious in patients with R/R multiple myeloma harboring either t(11;14) or tumor cells with $BCL2^{high}$ expression
  - $BCL2^{high}$ gene expression associated with extended PFS and increased response rates in the venetoclax arm independent of t(11;14)
  - OS in pts with t(11;14) or $BCL2^{high}$ gene expression was similar in either arm
- In pts without t(11;14) and expressing low BCL2 levels, PFS not significantly improved with venetoclax, and OS favored placebo
- Additional biomarker-selected trials for patients with MM, including t(11;14) or $BCL2^{high}$ gene expression, are ongoing:
  - CANOVA: VenDex vs PomDex in RRMM,[NCT03539744] M15-538: VenKd vs Kd in RRMM,[NCT02899052] M15-654: VenDd vs VenDVd in RRMM[NCT03314181]

Harrison. ASH 2019. Abstr 142.

CARTITUDE-1: Study Design

- Phase Ib/II trial conducted in the United States



- Primary endpoints: safety and RP2D (phase Ib), efficacy (phase II)

Madduri. ASH 2019. Abstr 577.

CARTITUDE-1: Safety

AEs (≥ 25% All Grade), n (%)	All Patients (N = 29)	
	All Grade	≥ Grade 3
Neutropenia	27 (93)	27 (93)
Anemia	25 (86)	16 (55)
Thrombocytopenia	25 (86)	20 (69)
Leukopenia	15 (52)	15 (52)
Lymphopenia	13 (45)	9 (31)
Elevated AST/ALT	9 (31)/8 (28)	2 (7)/1 (3)
Diarrhea	8 (28)	1 (3)
URTI	8 (28)	0

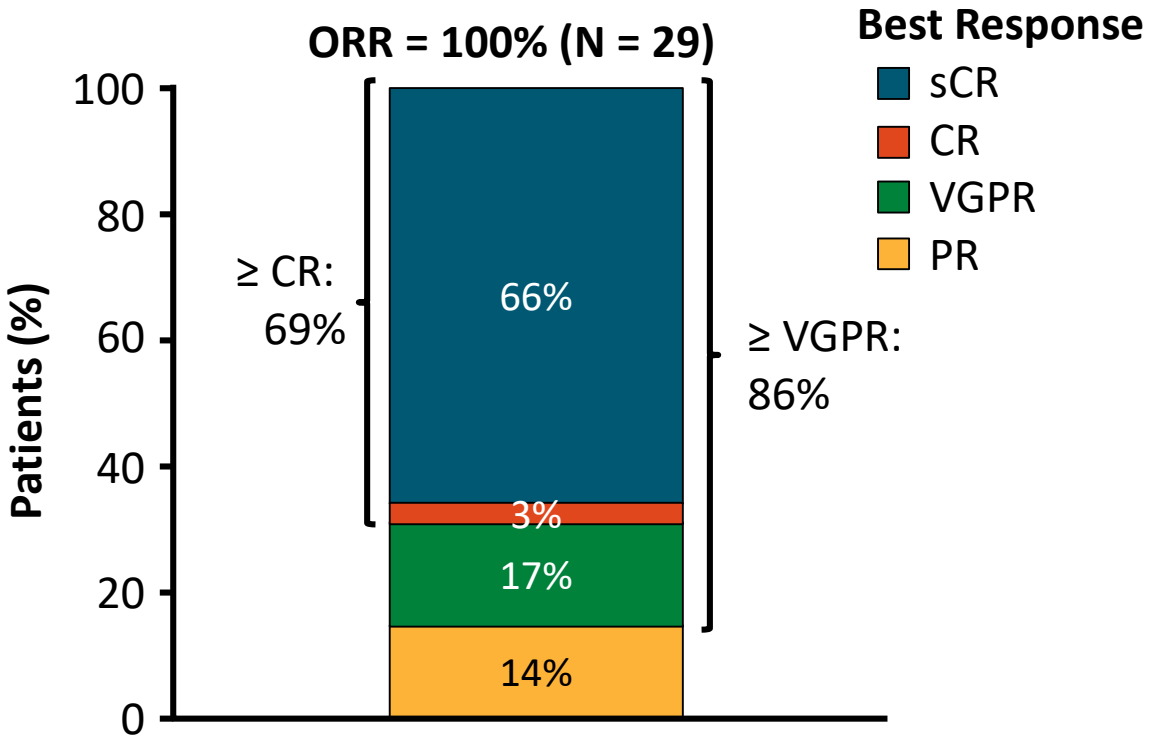
- Neurotoxicity consistent with ICANS occurred in 3 pts; 1 pt had grade ≥ 3 concurrently with grade 3 CRS

Cytokine Release Syndrome	All Patients (N = 29)
Patients with CRS, n (%)	27 (93)
Maximum grade, n (%)	
▪ 0	2 (7)
▪ 1	14 (48)
▪ 2	11 (38)
▪ ≥ 3	2 (7)*
Median time of onset, days (range)	7 (2-12)
Median duration, days (range)	4 (1-60)
Supportive measures, n (%)	
▪ Tocilizumab	22 (76)
▪ Anakinra	6 (21)
▪ Corticosteroids	6 (21)
▪ Vasopressor	2 (7)
▪ Other†	23 (79)

*1 pt w/ grade 3, 1 pt w/ grade 5; †Includes intubation/mechanical ventilation, antibiotics, cyclophosphamide, etanercept, levetiracetam, and supportive care.

Madduri. ASH 2019. Abstr 577.

CARTITUDE-1: ORR and MRD



- Median time to first response: 1 month (range, 1-3 months)
- Median time to ≥ CR: 1 month (range, 1-9 months)

MRD negativity at day 28, n (%)	Evaluable Patients* (N = 17)
Overall	17 (100)
▪ 10^{-6}	9 (53)
▪ 10^{-5}	5 (29)
▪ 10^{-4}	3 (17)

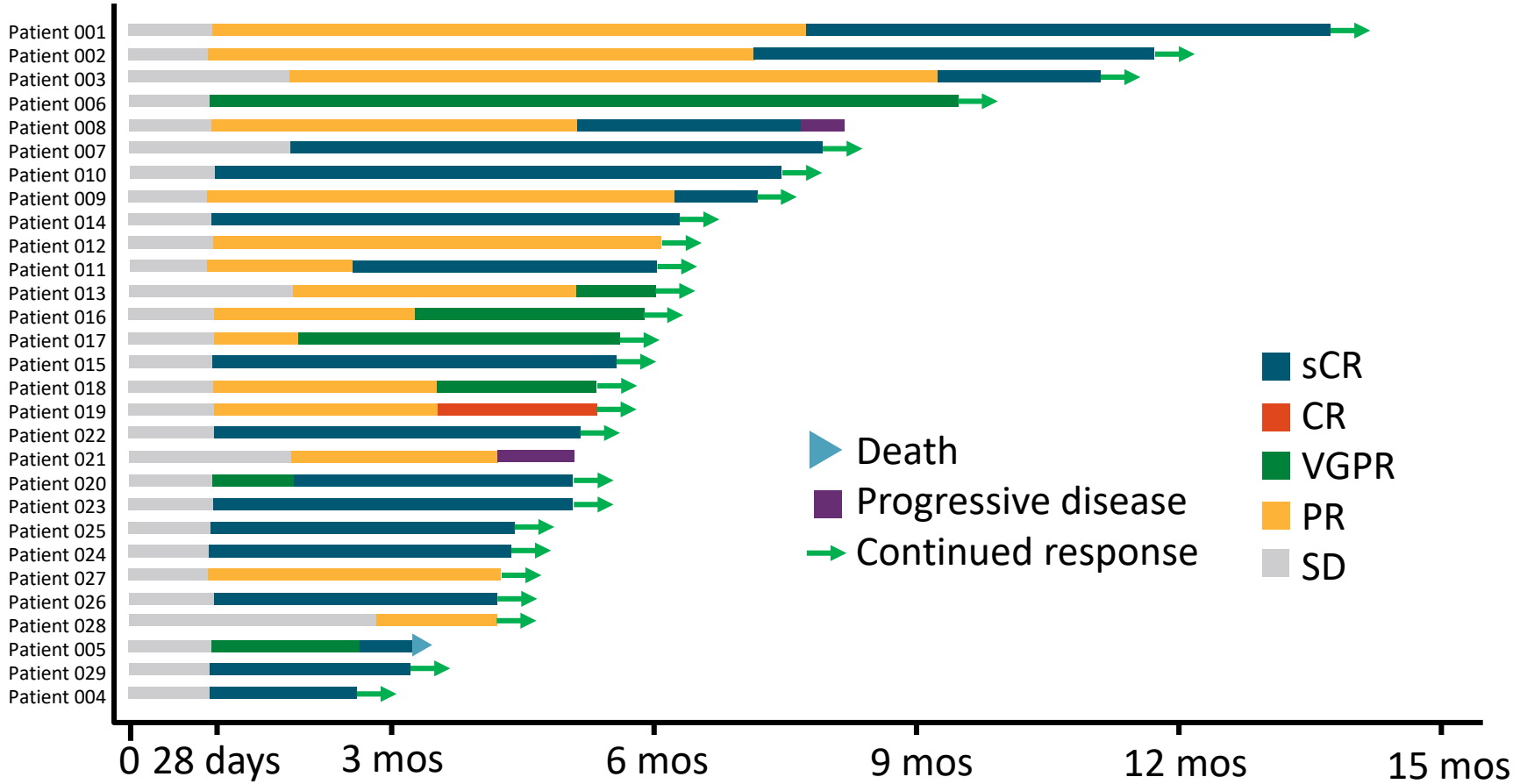
*Pts w/ baseline and ≥ 1 post-baseline BM samples available for NGS assessment, with identifiable clone at baseline

- At day 184, 3 patients were MRD negative at 10^{-6} and 2 patients were MRD negative at 10^{-5}
- At day 365, 1 patient was MRD negative at 10^{-6}

Madduri. ASH 2019. Abstr 577.

CARTITUDE-1: Duration of Response

- At median follow up of 6 months, 27 of 29 patients remained progression free



Madduri. ASH 2019. Abstr 577.

CARTITUDE-1: Investigator Conclusions

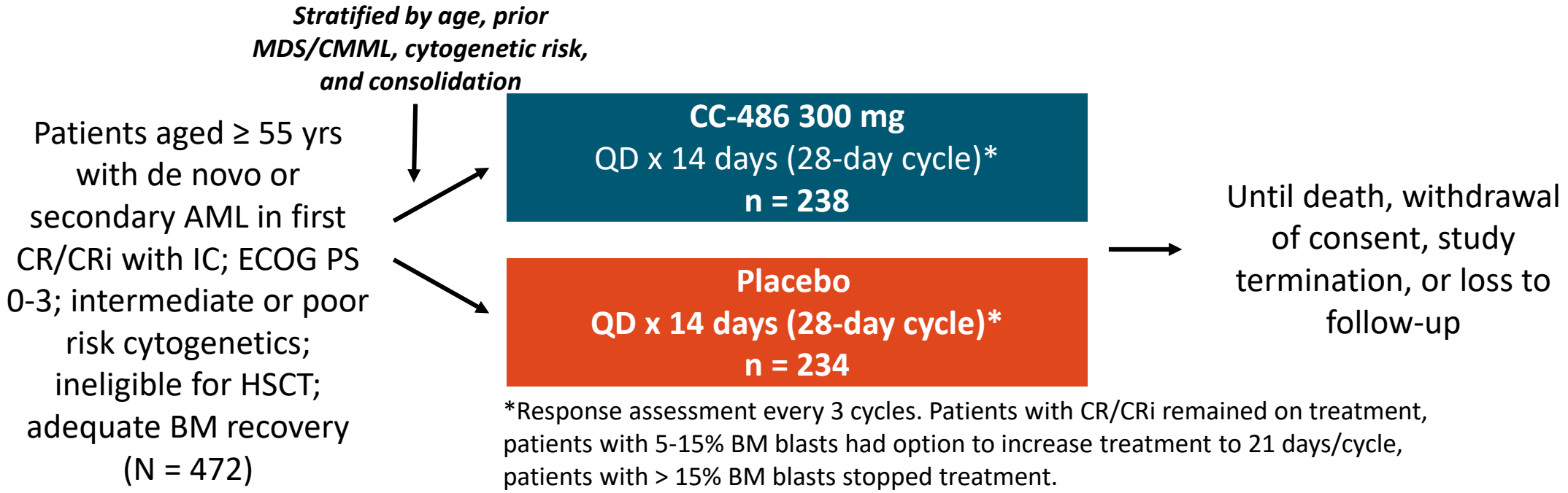
- JNJ-4528 demonstrated a manageable safety profile
  - Most cases of CRS were grade 1/2 with median time to onset of 7 days
  - Neurotoxicity (ICANS) was infrequent and generally low-grade with 1 grade 3 event
- Responses occurred early and deepened
  - ORR: 100% with ≥ 69% CR rate at median 6 months follow up
  - Median time to first response: 1 month
  - At most recent assessment, 100% of evaluable patients were MRD negative
  - 27 of 29 patients were progression-free at median 6 months follow up
- RP2D confirmed at 0.75 x 10^6 viable CAR T-cells/kg and phase II portion fully accrued
- Phase II/III studies are ongoing (NCT03548207; NCT04181827) and JNJ-4528 recently received FDA breakthrough designation for R/R MM

Madduri. ASH 2019. Abstr 577.

Acute Myeloid Leukemia

Phase III QUAZAR AML-001: CC-486 as Maintenance Therapy in First-Remission AML—Study Design

- Multicenter, randomized, placebo-controlled, double-blind, phase III study



*Response assessment every 3 cycles. Patients with CR/CRi remained on treatment, patients with 5-15% BM blasts had option to increase treatment to 21 days/cycle, patients with > 15% BM blasts stopped treatment.

- Primary endpoint: overall survival
- Key secondary endpoints: relapse-free survival, health-related QoL, and safety

Wei. ASH 2019. Abstr LBA_3.

QUAZAR AML-001: Survival

Outcome	CC-486 n = 238	Placebo n = 234
Median OS, mos (95% CI)	24.7 (18.7-30.5)	14.8 (11.7-17.6)
▪ Stratified *P* value	.0009	
▪ Stratified HR (95% CI)	0.69 (0.55-0.86)	
1-yr survival rate, % (95% CI)	73 (67-78)	56 (49-62)
2-yr survival rate, % (95% CI)	51 (44-57)	37 (31-43)
Relapse-free survival, mos (95% CI)	10.2 (7.9-12.9)	4.8 (4.6-6.4)
▪ Stratified *P* value	.0001	
▪ Stratified HR (95% CI)	0.65 (0.52-0.81)	

- Median follow up: 41.2 months
- 1-yr relapse rate was 53% (95% CI: 46-59) in CC-486 arm vs 71% (95% CI: 65-77) in placebo arm

Wei. ASH 2019. Abstr LBA_3.

QUAZAR AML-001: Adverse Events Resulting in Dosing Modification or Treatment Discontinuation

AEs leading to d/c for > 1 patient, n (%)	CC-486 n = 238	Placebo n = 234
Any AE	31 (13)	10 (4)
GI events	11 (4.7)	1 (0.4)
Abdominal pain	2 (1)	0
Fatigue	2 (1)	0
Thrombocytopenia	1 (0.4)	2 (1)

- Dose interruptions: 43% in CC-486 arm vs 17% in placebo arm
- Dose reductions: 16% in CC-486 arm vs 3% in placebo
- Neutropenia most common reason for dose modifications
- Median treatment duration was 12 cycles for CC-486 and 6 cycles for placebo
- Overall HRQoL preserved with CC-486 vs placebo

Wei. ASH 2019. Abstr LBA_3.

QUAZAR AML-001: Investigator Conclusions

- Maintenance therapy with CC-486 demonstrated significant improvement vs placebo in OS and RFS in patients with AML in first remission following IC
  - Median OS extended 9.9 mos and median RFS extended 5.3 mos with CC-486
  - OS and RFS benefit maintained across patient subgroups
- Safety and tolerability were manageable with CC-486
- HRQoL was preserved with CC-486 vs placebo

Wei. ASH 2019. Abstr LBA_3.