NDA 212306: Selinexor

Oncologic Drugs Advisory Committee Meeting

Introductory Comments

February 26, 2019

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Approved Drugs for the Treatment of MM

- Nine drugs are approved for the treatment of relapsed or refractory multiple myeloma (MM).

- Four new drugs or biologics have been approved since 2015, including a histone deacetylase (HDAC) inhibitor, an oral proteasome inhibitor, and two monoclonal antibodies (targeting CD38 and SLAMF7).

Approved Drugs for the Treatment of MM

Drug	Approval	Indication
Velcade (bortezomib)	Accelerated (2003)	MM, 2 or more prior lines
Velcade (bortezomib)	Regular (2005)	MM, 1 or more prior lines
Doxil (doxorubicin HCL liposome)	Regular (2007)	MM, 1 or more prior lines
Revlimid (lenalidomide) (with dex)	Regular (2005)	MM, 1 or more prior lines, in combo with dex
Kyprolis (carfilzomib)	Accelerated (2012)	MM, 2 or more prior lines
Kyprolis (with Rd)	Regular (2015)	MM, 1-3 prior lines
Kyprolis (with dex)	Regular (2016)	MM, 1-3 prior lines
Pomalyst (pomalidomide) (with dex)	Accelerated (2013)	MM, 2 or more lines, prior tx with Len and PI, in combo with dex
Pomalyst (pomalidomide) (with dex)	Regular (2015)	MM, 2 or more lines, in combo with dex
Farydak (panobinostat) (with Vd)	Accelerated (2015)	MM, 2 or more prior lines, prior tx with bort and an IMiD, in combo with Vd
Ninlaro (ixazomib) (with Rd)	Regular (2015)	MM, 1 or more prior lines, in combo with Rd
Darzalex (daratumumab)	Accelerated (2015)	MM, 3 or more prior lines, prior tx with PI, IMiD or double refractory to both (median 5 prior lines)
Darzalex (with Rd)	Regular (2016)	MM, 1 or more prior lines , in combo with Rd (median 1 prior line)
Darzalex (with Vd)	Regular (2016)	MM, 1 or more prior lines, in combo with Vd (median 2 prior lines)
Darzalex (with Pd)	Regular (2017)	MM, 2 or more prior lines, prior tx with Len and PI, in combo with Pd (median 4 prior lines)
Empliciti (elotuzumab) (with Rd)	Regular (2015)	MM, 1-3 prior lines, in combo with Rd
Empliciti (elotuzumab) (with Pd)	Regular (2018)	MM, 2 or more prior lines, prior tx with len and PI, in combo with Pd

Dex= dexamethasone;
Rd= lenalidomide/ dexamethasone;
Vd= bortezomib/ dexamethasone;
Pd= pomalidomide/ dexamethasone;
Len= lenalidomide;
PI= Proteasome inhibitor;
tx= treatment;
bort= bortezomib,
IMiD= immunomodulatory agent

Selinexor: Proposed Indication

- An oral XPO1 inhibitor, is indicated in combination with dexamethasone, for the treatment of patients with relapsed refractory multiple myeloma who have received at least three prior therapies and whose disease is refractory to at least one proteasome inhibitor (PI), at least one immunomodulatory agent (IMiD), and an anti-CD38 monoclonal antibody

Study KCP-330-012, Part 2 (STORM)

- Design: Single-arm trial of the combination of Selinexor and dexamethasone
- Key Eligibility Criteria:
  - Patients with multiple myeloma who had received ≥ 3 prior therapies including an alkylating agent, lenalidomide, pomalidomide, bortezomib, carfilzomib, daratumumab, and a glucocorticoid
  - Refractory to glucocorticoid, PI (i.e., bortezomib and/or carfilzomib), IMiD (i.e., lenalidomide and/or pomalidomide), and daratumumab
  - Refractory to their most recent anti-myeloma therapy

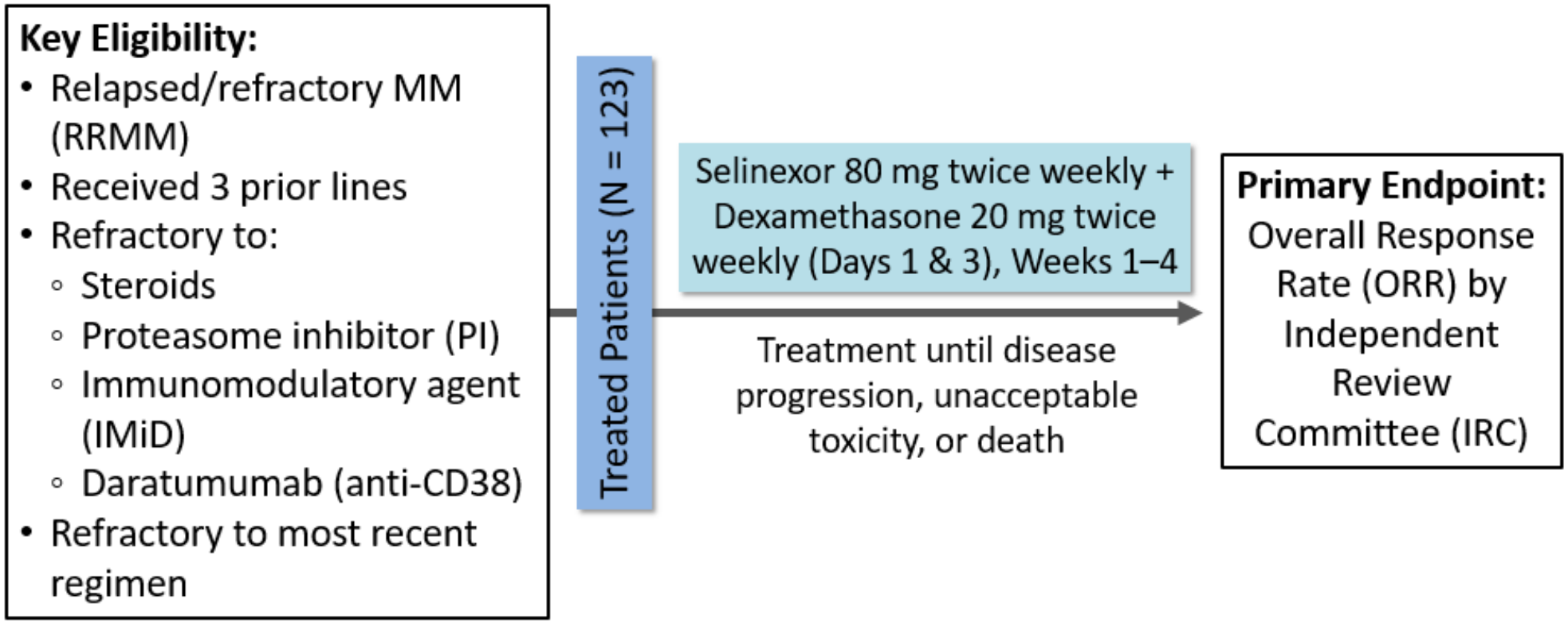
Study KCP-330-012, Part 2 (STORM)

- Design Elements: Single arm trial of a combination regimen
  - Considerations for development of combination therapy
    - Strong biological rationale for the use of the combination (e.g., inhibit different targets in the same pathway)
    - Demonstration of the contribution of each individual drug in the combination
      - Factorial Designs (e.g., studies of AB vs. A. vs. B vs. Standard of care (SOC))

FDA Guidance for Industry: Co-development of Two or More New Investigational Drugs for Use in Combination

Study KCP-330-012, Part 2 (STORM)

- Design Elements: Single arm trial of a combination regimen



Study KCP-330-012, Part 2 (STORM)

- Design
  - Single arm trial of a combination regimen
    - Overall Response Rate in STORM: 25%
      - Duration of response of 4.4 months
    - Historical Data with High-dose Dexamethasone
      - Overall response rates between 18-27%
      - MM-003 trial- Pom-dex vs. Dex alone
        - » ORR of dexamethasone alone 4% (IRC), 10% (Investigator)

Alexanian Ann Intern Med 1986,
Friedenberg Am J Hematol 1991,
Dimopoulos Blood 2005
San Miguel Lancet Oncol 2013

Single Arm Trial of a Combination

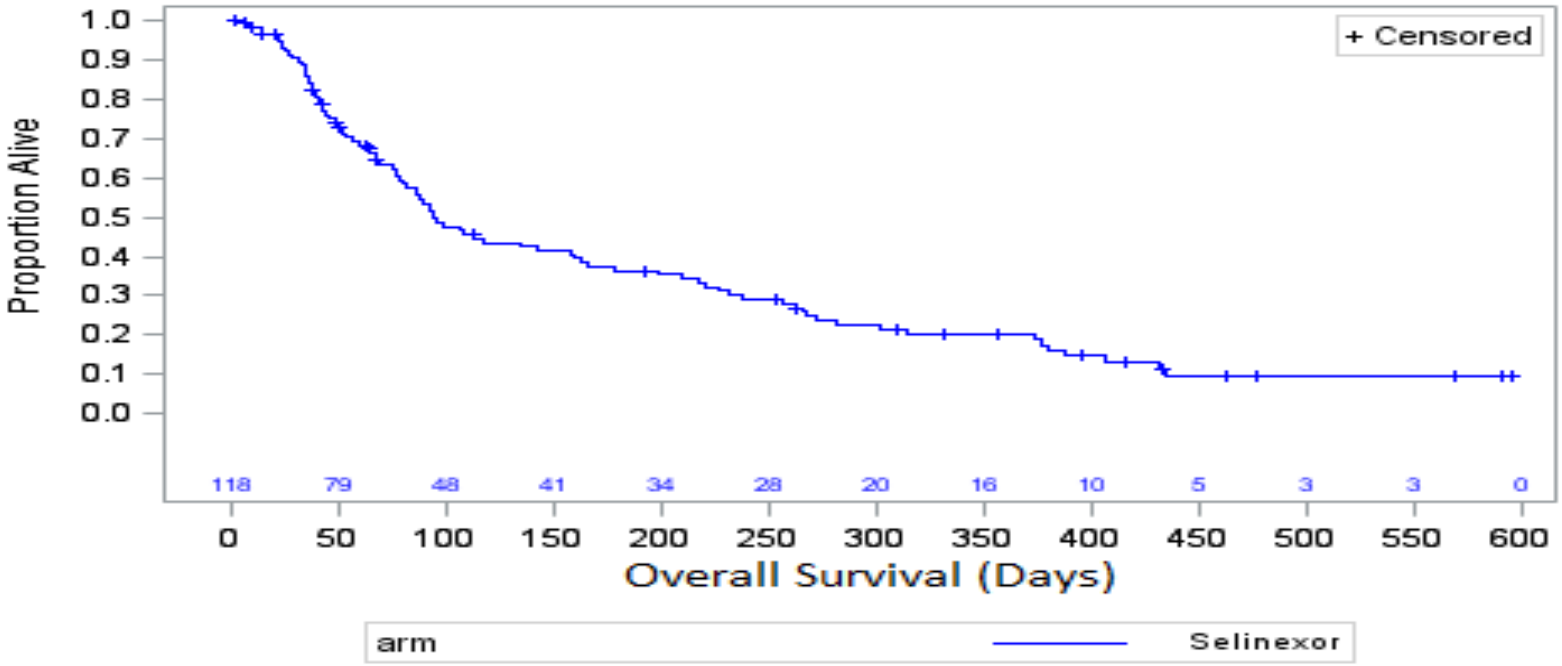
- Study KCP-330-001
  - In total, 81 patients with MM treated
  - There was 1 response (ORR- 1.8%) among 56 patients who received Selinexor alone
  - There were 6 responses (ORR-24%) among 25 patients who received Selinexor in combination with dexamethasone

Study KCP-330-012, Part 2 (STORM)

- Design Elements
  - Single arm trial of a combination
  - Single arm trials can be challenging to interpret

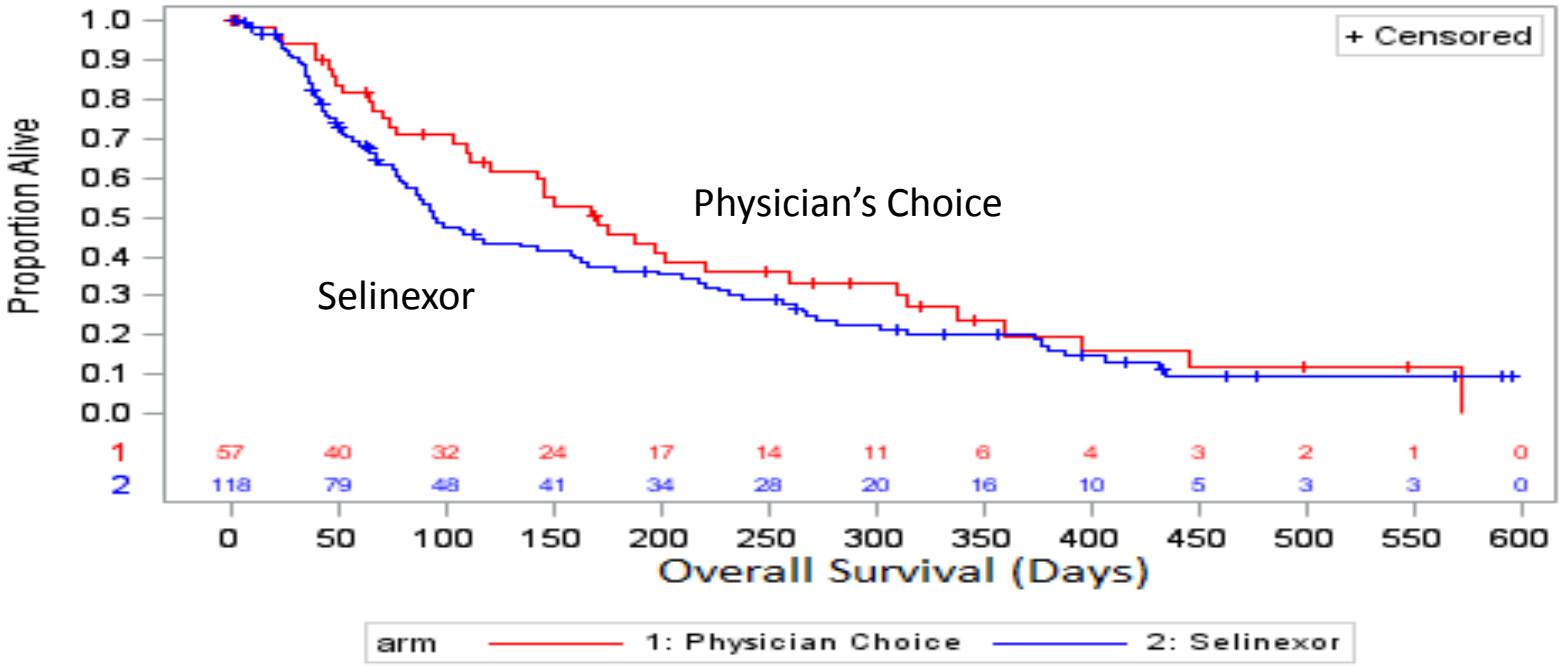
Single Arm Trial Interpretation

- AML Trial, KCP-330-008



Single Arm Trial Interpretation

- AML Trial, KCP-330-008



Study KCP-330-012, Part 2 (STORM)- Efficacy

- Primary Endpoint: Overall Response based on International Myeloma Working Group (IMWG) criteria
- Evaluable patient population: 122
- Results:
  - Overall Response Rate: 25%
  - Median Duration of Response: 4.4 months

Study KCP-330-012, Part 2 (STORM)- Safety

- Treatment-emergent Adverse Events (TEAEs): 100%
  - Most frequent TEAEs (≥ 20%): thrombocytopenia, anemia, neutropenia, leukopenia, nausea, diarrhea, vomiting, constipation, fatigue, weight decreased, decreased appetite, hyponatremia, dyspnea
- Severe TEAEs (≥ Grade 3): 95%
- Serious Adverse Events (SAEs): 60%
- TEAE leading to dose modification or discontinuation: 89%
  - The median duration on treatment at the proposed dose was 3.5 weeks
- Deaths: 23 deaths- 13 disease progression, 10 due to TEAEs

Safety of Recently Approved MM Therapies

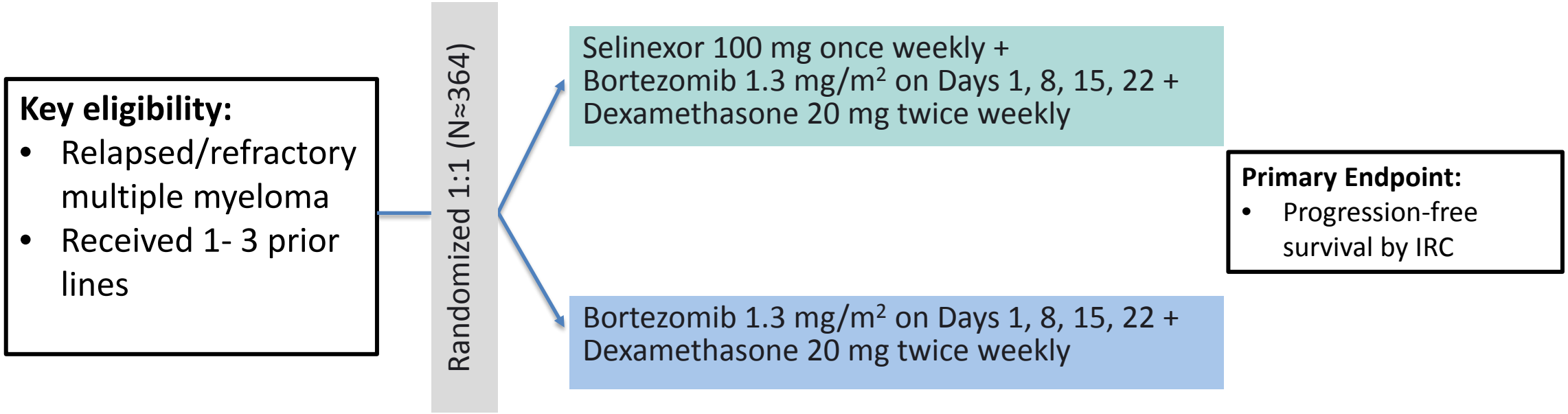
	Selinexor (%)	Carfilzomib (%)	Pomalidomide (%)	Daratumumab (%)
SAEs	60	50	62	33
TEAE resulting in dose interruption	73	21	64	15
TEAE resulting in dose reduction	49	17	39	N/A
TEAE resulting in Tx Discontinuation	27	12	7	4
TEAE resulting in death	10	4	5	2

Daratumumab U.S. Prescribing Information
Pomalidomide U.S. Prescribing Information
FDA Clinical Review of Initial Pomalidomide NDA
Lonial Lancet 2016
Siegel Blood 2012
Carfilzomib U.S. Prescribing Information

Issues

1. Single arm trial of a combination regimen
   - No single agent activity of selinexor alone in RRMM
   - Cannot isolate the treatment effect of selinexor vs. dexamethasone
   - Challenging to interpret single arm trial data
2. Selinexor associated with significant toxicity
3. High rate of dose modifications and discontinuations suggests that the optimal dose has not been identified

BOSTON Trial
Study KCP-330-023



- Accrual complete
- Top line data expected end of 2019

Expanded Access Options

- 21 CFR 312, Subpart I
  - Individual Patient INDs, including for emergency use
  - Intermediate-size patient population IND or Protocol
  - Treatment IND or Protocol

Evidentiary Criteria for Approval

- Drugs granted accelerated approval or traditional approval must meet the same statutory standards for safety and effectiveness
- Effectiveness
  - Substantial evidence of effectiveness based on adequate and well-controlled clinical investigations
- Safety
  - Sufficient information to determine whether the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling.

Guidance for Industry: Expedited Programs for Serious Conditions-Drugs and Biologics.

Issues for Discussion

- Discuss whether the KCP-330-012 (STORM) data are conclusive to allow for an adequate assessment of the safety and efficacy in the proposed patient population, and whether selinexor provides a benefit that outweighs the risks.

Voting Question

- Should the approval of selinexor be delayed until results of the randomized phase 3 trial, BOSTON, are available?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NDA 212306

Selinexor

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February 26, 2019

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Discussion Topic

Discuss whether the KCP-330-012 (STORM) data are conclusive to allow for an adequate assessment of the safety and efficacy in the proposed patient population, and whether selinexor provides a benefit that outweighs the risks.

Voting Question

Should the approval of selinexor be delayed until results of the randomized phase 3 trial, KCP-330-023 (BOSTON), are available?

Overview of Clinical Studies

Trial	Design	Regimen	Population	Primary Endpoint
Pivotal				
KCP-330-012 (STORM) Part 2	Phase 2b, open-label, single-arm	Selinexor-dex	Triple-class refractory MM (N = 123)	ORR
Supportive				
KCP-330-012 (STORM) Part 1	Phase 2b, open-label, single-arm	Selinexor-dex	Triple- or double-class refractory MM (N = 79)	ORR
KCP-330-001 (STOMP)	Phase 1, dose escalation/expansion	Selinexor or Selinexor-dex	Advanced hematologic malignancies (N = 286)	Safety and tolerability
KCP-330-008 (SOPRA)	Phase 2, open-label, randomized	Selinexor vs. Physician Choice	Relapsed/refractory AML (N = 317)	OS
KS-50039	Retrospective, observational	N/A	Flatiron Health Analytic Database (N = 64)	OS

Abbreviations: Dex = dexamethasone; MM = multiple myeloma; AML = acute myeloid leukemia; ORR = overall response rate; OS = overall survival

STORM Part 2: Trial Design

Key Eligibility:

- Relapsed/refractory MM (RRMM)
- Received 3 prior lines
- Refractory to:
  - Steroids
  - Proteasome inhibitor (PI)
  - Immunomodulatory agent (IMiD)
  - Daratumumab (anti-CD38)
- Refractory to most recent regimen

Treated Patients (N = 123)

Selinexor 80 mg twice weekly + Dexamethasone 20 mg twice weekly (Days 1 & 3), Weeks 1–4

Treatment until disease progression, unacceptable toxicity, or death

Primary Endpoint: Overall Response Rate (ORR) by Independent Review Committee (IRC)

Issues

1. Single arm trial of a combination regimen
   - No single agent activity of selinexor alone in RRMM
   - Cannot isolate treatment effect of selinexor vs. dexamethasone
   - Challenging to interpret single arm trial data
2. Selinexor is associated with significant toxicity
3. High rate of dose modifications and discontinuations suggests the optimal dose has not been identified

Issue #1: Single Arm Trial of a Combination

- Phase 1 trial KCP-330-001: No single agent activity of selinexor in RRMM
- Historical Data: Single agent activity of dexamethasone
- Real-World Data Study KS-50039
- Phase 2 trial KCP-330-008 (AML): Worse overall survival trend with selinexor vs. Physician's Choice

KCP-330-001: Trial Design

Arm/Population	Regimen	Study Phase	Schedule(s)
1: DLBCL, **MM**	Selinexor	Dose Escalation/Expansion	1, 2, 3, 4, 5, 7, 8
2: AML			1, 2, 3, 5, 7, 8, 10
3: PTCL, CTCL		Dose Expansion	3
4: CML			
5: ALL			
6: **MM**, WM	Selinexor + Dexamethasone		6
7: NHL, DLBCL	Selinexor + Rituximab	Dose Escalation/Expansion	9
8: **MM**	Selinexor	Dose Evaluation	11

Abbreviations: DLBCL = diffuse large B-cell lymphoma; PTCL = peripheral T-cell lymphoma; CTCL = cutaneous T-cell lymphoma; CML = chronic myelogenous leukemia; ALL = acute lymphoblastic leukemia; WM = Waldenström's macroglobulinemia; NHL = non-Hodgkin's lymphoma

KCP-330-001: RRMM Cohorts

Key Eligibility:
- RRMM
- ≥3 prior lines
- Prior treatment:
  - Alkylating agent
  - PI
  - IMiD
  - Steroids

Arm 1
(Selinexor)
N = 45

Arm 6
(Selinexor + Dex)
N = 25

Arm 8
(Selinexor)
N = 11

Schedule 3: Selinexor ≥35 mg/m^2 twice weekly, Weeks 1-4 (dexamethasone permitted as concomitant medication)

Schedule 6: Selinexor 45 mg/m^2 or 60 mg/m^2 twice weekly + dexamethasone 20 mg twice weekly, Weeks 1-4

Schedule 11: Selinexor 40 mg, 60 mg, or 80 mg (~45 mg/m^2) twice weekly, Weeks 1-3 (dexamethasone permitted after Cycle 2)

KCP-330-001: No Single-Agent Activity in RRMM

Response Category	All RRMM (N = 81) n (%)	Selinexor + Dexamethasone (N = 25) n (%)	Selinexor Monotherapy (N = 56) n (%)
Overall Response Rate (ORR)	**7 (8.6)**	**6 (24)**	**1 (1.8)***
Stringent Complete Response (sCR)	1 (1.2)	1 (4)	0
Complete Response (CR)	0	0	0
Very Good Partial Response (VGPR)	0	0	0
Partial Response (PR)	6 (7.4)	5 (20)	1 (1.8)*

* Patient received dexamethasone as a concomitant medication

KCP-330-001: Activity in Other Hematologic Malignancies

Disease Type	ORR, % (95% CI)	Response Categories
Selinexor monotherapy		
DLBCL (N = 43)	25.6 (14, 41)	4 CR, 7 PR
NHL (N = 27)	33.3 (17, 54)	1 CR, 8 PR
AML (N = 95)	11.6 (6, 20)	4 CR, 3 CRi, 4 PR
CLL (N = 16)	6.3 (0, 30)	1 PR
MM (N = 56)	1.8*	1 PR*
Selinexor combination therapy		
DLBCL (N = 15)•	6.7 (0, 32)	1 CR
MM (N = 25)†	24 (9, 45)	1 sCR, 5 PR

* Dexamethasone 12 mg twice weekly received as a concomitant medication

• Selinexor in combination with rituximab

† Selinexor in combination with dexamethasone

Single-Agent Activity of Dexamethasone in MM

Population	Trial/Regimen	Response Rate	Response Definition	Reference
Relapsed/Refractory MM (RRMM)				
RRMM	HD-dex* (N = 49)	27% (refractory), 21% (relapsed)	75% ↓ tumor mass, Bence-Jones protein disappearance	Alexanian *et al*. Ann Int Med (1986)
RRMM, 1-3 prior lines	HD-dex (N = 312) vs. bortezomib	18%	European Group for Bone Marrow Transplantation (EBMT) Criteria	Richardson *et al*. NEJM (2005)
RRMM, failed bortez and len	HD-dex (N = 153) vs. pomalidomide/dex	10% (4% by IRC)	EBMT or International Myeloma Working Group (IMWG) 2006 Criteria	San Miguel *et al*. Lancet Oncol (2013)
Newly Diagnosed MM (NDMM)				
NDMM	HD-dex	43%	75% ↓ serum M-protein, Bence-Jones protein disappearance, marrow plasmacytosis ↓ to <5%	Alexanian *et al*. Blood (1992)
NDMM	HD-dex vs. thalidomide/HD-dex	46%	EBMT criteria	Rajkumar *et al*. J Clin Oncol (2008)
NDMM	HD-dex	50%	IMWG 2006 Criteria	Sinha *et al*. Brit J Hematol (2009)

*HD-dex = high-dose dexamethasone (40 mg or 20 mg/m^2 x 4 days beginning on Days 1, 9, and 17 of a 28-day cycle)

STORM Part 2: Efficacy Results

IRC Assessment	**n (%); (95% CI)**
mITT Population (N = 122)	
ORR sCR CR VGPR PR	**31 (25.4); (18.0, 34.1)** 2 (1.6); (0.2, 5.8) 0 6 (4.9); (1.8, 10.4) 23 (18.9); (12.3, 26.9)
Responders (N = 31)	
DOR, median; [range]	**4.4 months; [0.8, 9.0 months]**

Abbreviations: mITT = modified Intent-to-Treat; CI = confidence interval; DOR = duration of response

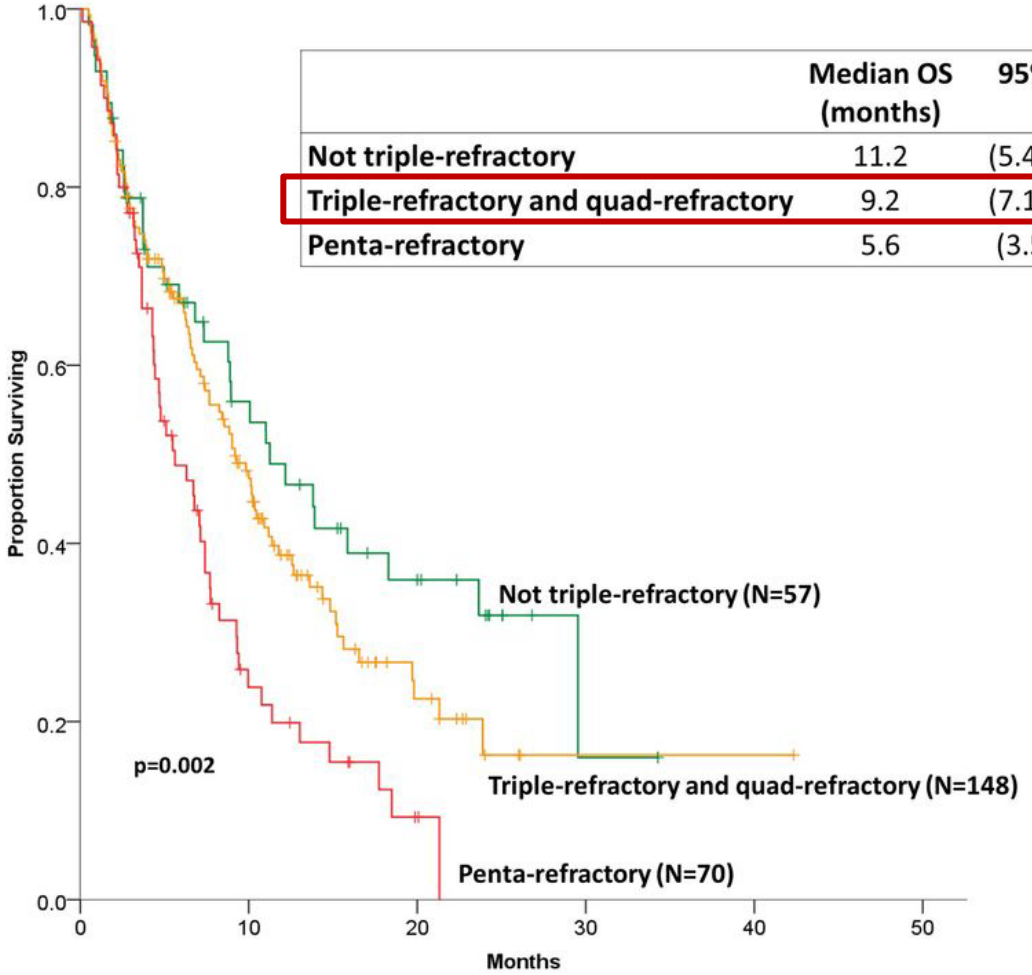
Efficacy of Recently Approved MM Therapies

	Selinexor (N = 123)	Carfilzomib (N = 266)	Pomalidomide + Dex (N = 113)	Daratumumab (N = 106)
Population	Triple-class refractory MM, at least 3 prior lines	RRMM, at least 2 prior lines, including bortezomib and IMiD	RRMM, at least 2 prior lines, including bortezomib and lenalidomide	RRMM, at least 3 prior lines, including PI and IMiD or double-class refractory
Median prior lines of therapy	7	5	5	5
ORR (%)	25.4	23	29.2	29.2
Median DOR (months)	4.4	7.8	7.4	7.4

Single Arm Trials

- FDA routinely considers single arm trials with a disease response rate as the primary endpoint, supported by duration of response
- Single arm trials cannot adequately characterize time-to-event endpoints such as progression-free survival (PFS) and overall survival (OS)
- Survival estimates are complicated and depend on factors that cannot be addressed without a control arm
- Assessment of risk-benefit can be challenging in a single arm trial
- Median OS of 8 months derived from Part 2 of STORM is not interpretable

MAMMOTH Study: OS in CD38-Refractory MM



	Median OS (months)	95% C.I.
Not triple-refractory	11.2	(5.4-17.1)
Triple-refractory and quad-refractory	9.2	(7.1-11.2)
Penta-refractory	5.6	(3.5-7.8)

STORM inclusion criteria more closely align with the triple-refractory cohort

(Source: Gandhi HU *et al*, Blood 2018; 132:3233 (Abstract))

KS-50039: Real-World Data Study

- KS-50039: “Real-World Overall Survival in Patients with Penta-Exposed, Triple-Class Refractory Multiple Myeloma”
- Agency is committed to the use of Real-World Data (RWD) to support regulatory decision-making and recently published a Framework outlining considerations for RWD studies
- RWD analyses should be pre-specified and discussed with the Agency to ensure they are carefully designed to minimize bias
- KS-50039 was not pre-specified or discussed with the Agency and has design issues that lead to bias and confounding

KS-50039: Flatiron (FHAD) Population

ICD code for MM, ≥2 visits on or after 01 January 2011: **(N = 38679)**

↓

Medication orders for bortezomib, carfilzomib, and daratumumab: (N = 364)

↓

Pathology consistent with MM on or after 01 January 2011: (N = 258)

↓

Oral episodes for lenalidomide and pomalidomide: (N = 174)

↓

Treatment initiation no more than 30 days before the start of structured activity: (N = 144)

↓

Confirmed treatment with bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab; treatment not received in clinical trial setting: (N = 126)

↓

MM documented as triple-class refractory: (N = 69)

↓

Baseline ECOG performance status ≤2: **(N = 64)**

Abbreviations: FHAD = Flatiron Health Analytic Database; ECOG = Eastern Cooperative Oncology Group

KS-50039: Baseline Characteristics

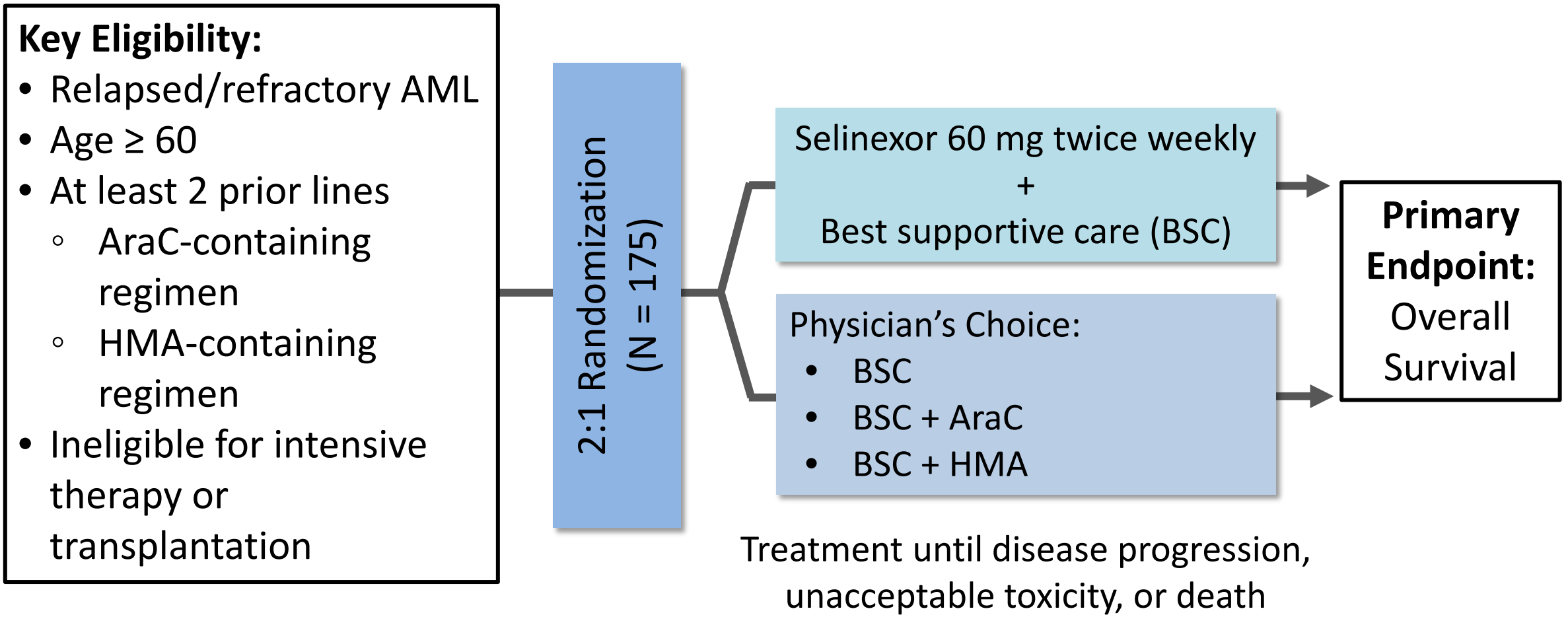
Parameter	FHAD (N = 64)	STORM (N = 122)
ECOG Status, n (%)		
Missing	20 (31.3)	3 (2.5)
0	4 (6.3)	37 (30.3)
1	33 (51.6)	71 (58.2)
2	7 (10.9)	11 (9.0)
Carfilzomib, pomalidomide, and daratumumab refractory prior to index date, n (%)	34 (53.1)	117 (95.9)
# prior regimens before index date, median	5	7
Daratumumab as last line prior to index date, n (%)	43 (67.2)	58 (47.5)
Stem cell transplant prior to index date, n (%)	38 (59.4)	102 (83.6)

KS-50039: Conclusions

FHAD:	STORM:
• Excluded patients who received therapy on a clinical trial • Included patients who did not receive subsequent anti-myeloma therapy • High % of ECOG status missing • No requirements for minimum platelet count, hemoglobin or organ function	• Excluded patients with life expectancy < 4 months • Excluded patients with severe disease presentation (i.e., amyloidosis, plasma cell leukemia) • Minimum thresholds for platelet count, hemoglobin and organ function

- Selection criteria were not aligned resulting in critical differences between the FHAD population and the population evaluated in STORM
- Comparison of survival between FHAD and STORM is not appropriate

KCP-330-008: Trial Design



Abbreviations: AraC = cytarabine; HMA = hypomethylating agent

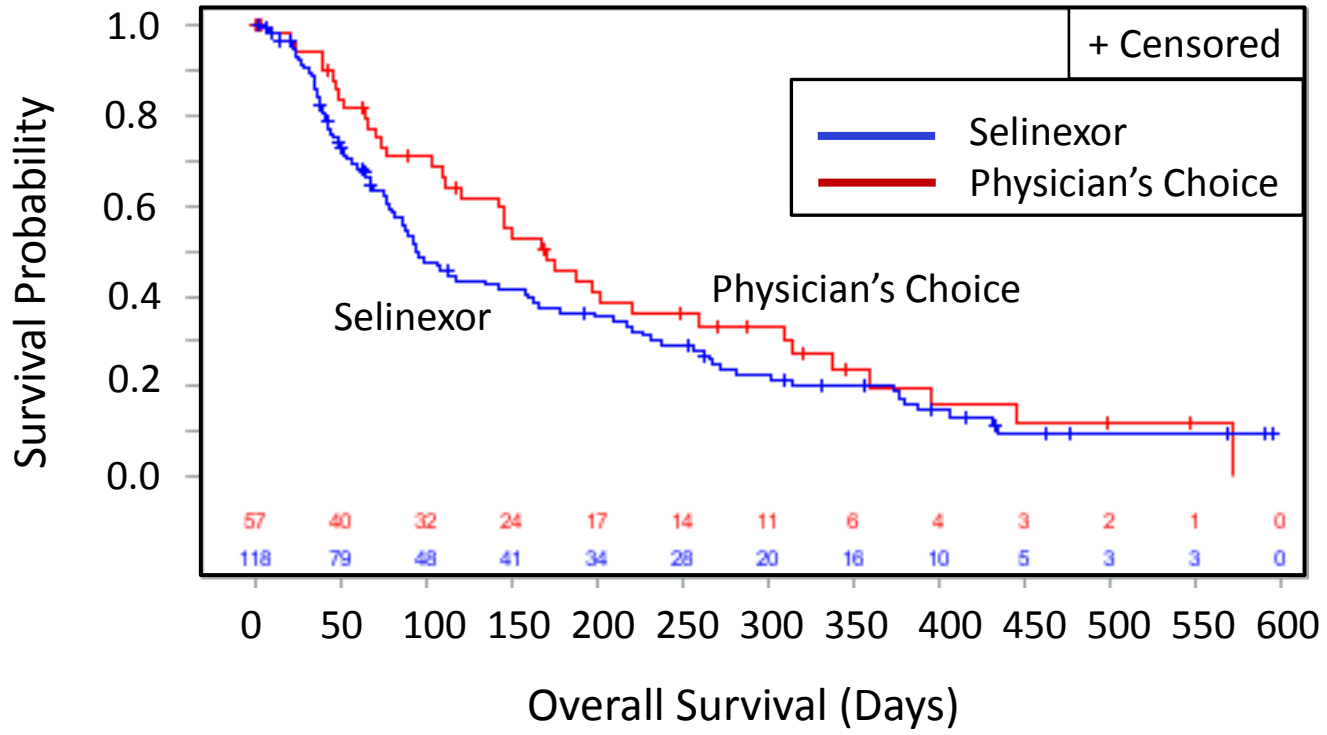
KCP-330-008: Baseline Characteristics

	Selinexor 60 mg (N = 118) n (%)	Physician's Choice (N = 57) n (%)	Total (N = 175) n (%)
Age			
Median (range)	73 (60 – 94)	75 (60 – 87)	74 (60 – 94)
ECOG Score			
0	29 (25)	8 (14)	37 (21)
1	67 (56)	24 (42)	91 (52)
2	16 (14)	11 (19)	27 (15)
Missing	6 (5)	14 (25)	20 (11)
Disease Characteristics			
Prior MDS	13 (11)	3 (5)	16 (9)
TP53 Mutations	14 (12)	3 (5)	17 (14)
ANC < 0.5 x 10^9/L	50 (42)	12 (21)	62 (35)

Randomized but not treated: 1.7% in selinexor arm vs. 21% in Physician's Choice arm

Abbreviations: MDS = myelodysplastic syndrome; TP53 = tumor protein 53; ANC = absolute neutrophil count

KCP-330-008: Overall Survival



	Selinexor 60 mg (N=118)	Physician's Choice (N= 57)
OS (days), median (95% CI)	94 (78, 158)	170 (111, 220)
HR (95% CI)	1.18 (0.79, 1.75)	

Abbreviations: HR = hazard ratio

KCP-330-008: Overall Response Rate

	Selinexor 60 mg (N = 118) n (%)	Physician's Choice (N = 57) n (%)
Complete Remission (CR)	6 (5)	0
Complete Remission with Incomplete Recovery (CRi)	8 (7)	2 (4)
Complete Remission with Platelet Recovery (CRp)	0	0
Partial Response (PR)	2 (2)	3 (5)
Stable Disease	44 (37)	18 (32)
Progressive Disease	12 (10)	6 (11)
Not evaluable	4 (3)	2 (4)
Unknown/Missing*	42 (36)	26 (46)

*Patients did not have at least one efficacy assessment

KCP-330-008: Safety Overview

	Selinexor 60 mg (N = 115) n (%)	**Physician's Choice (N = 45) n (%)**
Treatment-emergent adverse event (TEAE)	115 (100)	42 (93)
Serious TEAE	92 (80)	30 (67)
TEAE leading to permanent discontinuation	54 (47)	9 (20)
Fatal TEAE	23 (20)	9 (20)

KCP-330-008: Conclusions

- Remission rate higher for selinexor vs. Physician's Choice
- Overall survival trend worse for selinexor
- Disparate response and survival trends can be observed with therapies that have significant toxicity
- Results underscore the importance of randomized controlled trials to fully characterize risk-benefit

Issue #2: Toxicity of Selinexor

- Patients treated with selinexor experienced high rates of treatment-emergent adverse events (TEAEs), including severe TEAEs, serious TEAEs and fatal TEAEs
- Treatment with selinexor is associated with a unique toxicity profile: hyponatremia, GI toxicity and mental status changes

STORM: Safety Overview

AE Category	Part 1 (N = 79) n (%)	Part 2 (N = 123) n (%)	Total (N = 202) n (%)
Treatment-emergent adverse event (TEAE)	79 (100)	123 (100)	202 (100)
Grade 3-4 TEAE	75 (95)	115 (94)	190 (94)
Serious TEAE	44 (56)	74 (60)	118 (58)
TEAE leading to permanent discontinuation	21 (27)	33 (27)	54 (27)
Fatal TEAE	8 (10)	10 (8)	18 (9)

STORM Part 2: Treatment-Emergent AEs

- All patients (100%) experienced at least one treatment-emergent AE (TEAE)

- Most frequent TEAEs: Anemia (66%), leukopenia (31%), neutropenia (38%), thrombocytopenia (72%), diarrhea (42%), nausea (70%), vomiting (37%), fatigue (72%), weight decreased (49%), decreased appetite (54%), and hyponatremia (35%)

STORM Part 2: Grade 3-4 TEAEs

- Grade 3 or 4 TEAEs: severe, debilitating, or life-threatening
- 94% experienced at least one Grade 3-4 TEAE
- Most frequent Grade 3 or 4 TEAEs: Anemia (43%), leukopenia (12%), lymphopenia (11%), neutropenia (22%), thrombocytopenia (57%), fatigue (25%), and hyponatremia (20%)

STORM Part 2: Serious Adverse Events

- Serious adverse events (SAEs): may result in death, be life-threatening, or require hospitalization
- 60% of patients experienced at least one SAE
- Most frequent SAEs: Pneumonia (11%), sepsis (9%) and mental status changes (7%)

STORM Part 2: On-Study Deaths

- 23 (11%) patients died on or within 30 days of study treatment
- 13 deaths due to disease progression
- 10 deaths due to a fatal TEAE
- Causes of death: Pneumonia (2), sepsis (2), fungal sepsis, septic shock, subdural hematoma, cardiac disorder, respiratory arrest, multiple organ dysfunction syndrome

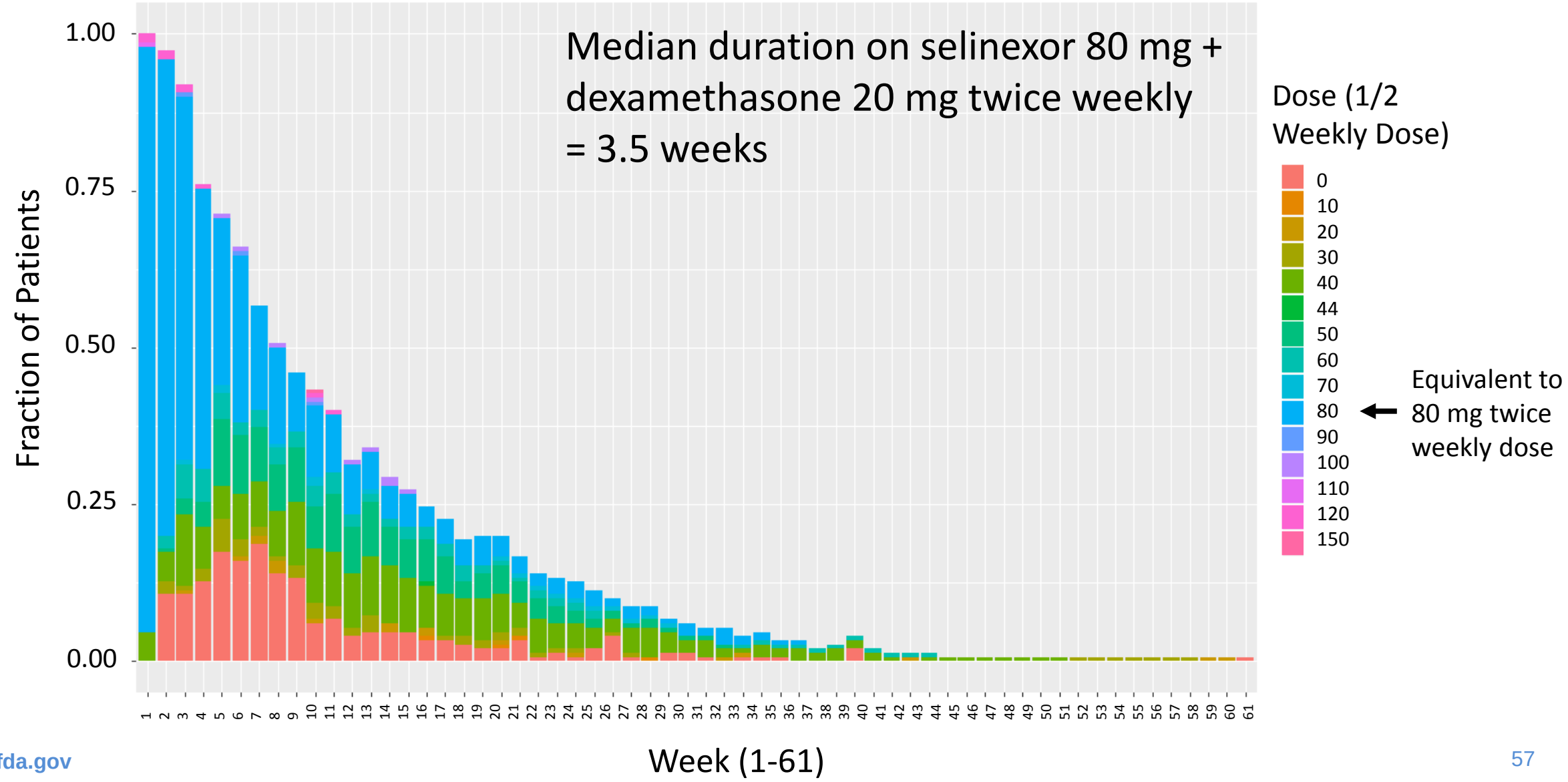
Issue #3: Uncertain Dose of Selinexor

- Limited dose finding in KCP-330-001
  - No doses lower than 45 mg/m^2 tested in combination with dexamethasone 20 mg twice weekly in RRMM
- Proposed dose of selinexor is poorly tolerated
  - High rates of dose modification/discontinuation
  - Limited duration of treatment on proposed dose

STORM Part 2: Dose Modifications

Action Taken with Selinexor	Part 2 (N = 123) n (%)
Dose modification due to TEAE	109 (89)
Dose reduced	71 (58)
Dose interrupted	84 (68)
Drug permanently discontinued	35 (29)

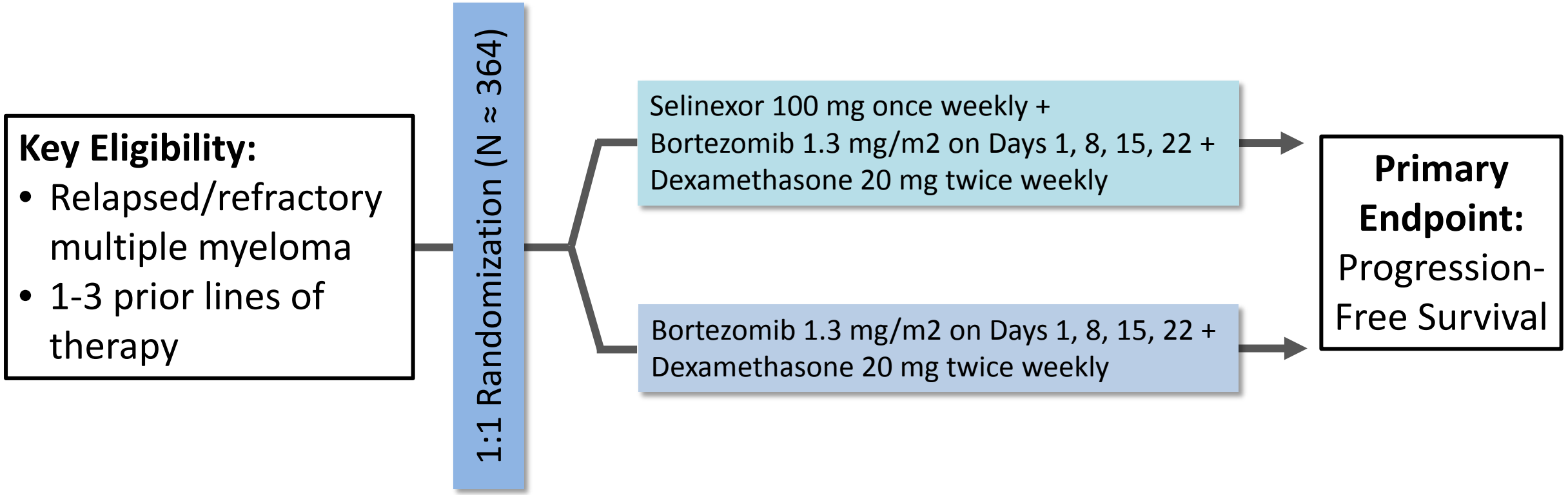
Proposed Dose is Poorly Tolerated



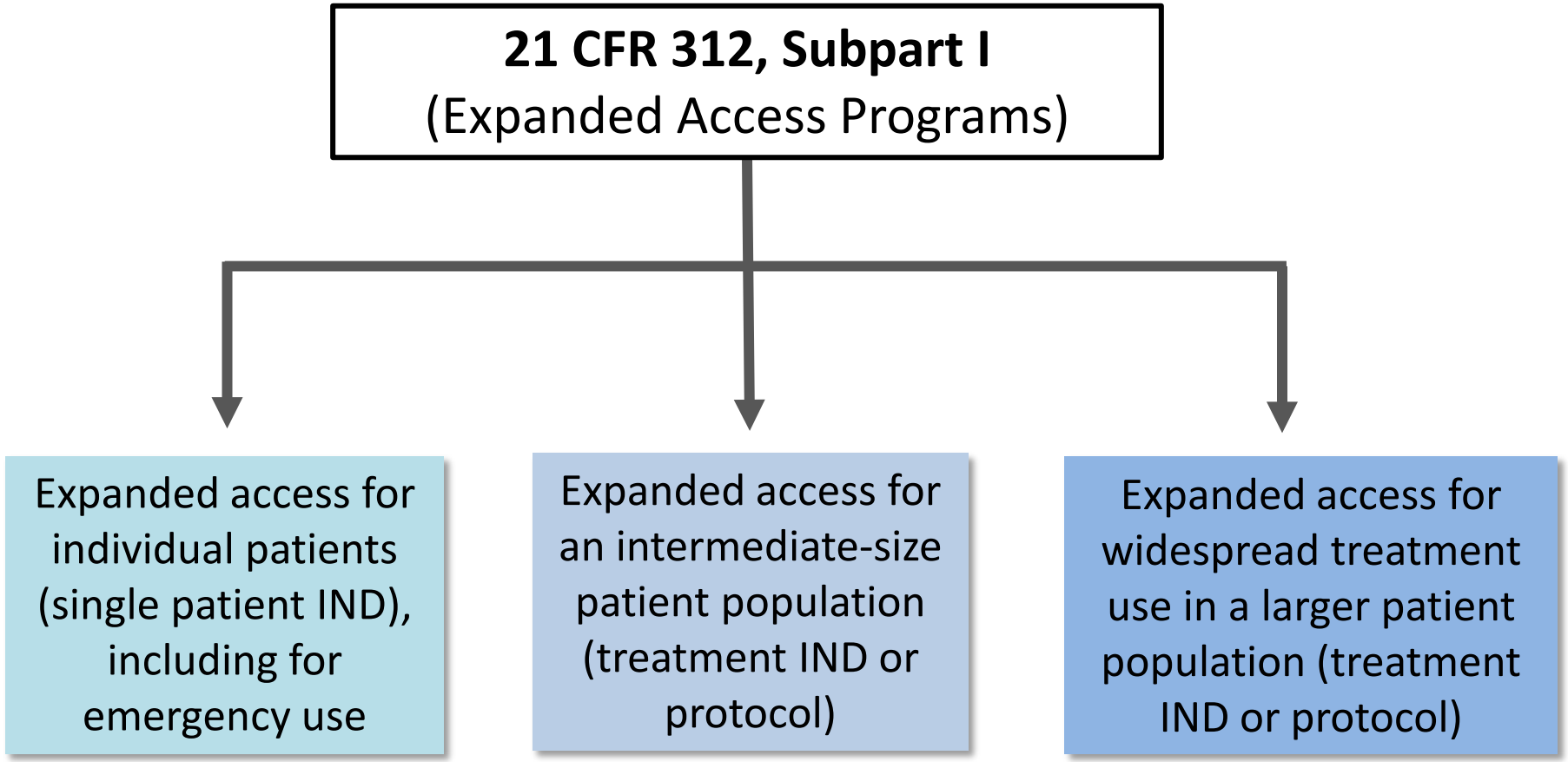
Conclusions

- STORM was a single arm trial of selinexor + dexamethasone
- No single agent activity in RRMM in the phase 1 trial; limited efficacy in the pivotal trial (ORR 25.4%, DOR 4.4 months)
- Selinexor is associated with significant toxicity; worse overall survival trend in randomized trial in AML
- High rates of dose modifications and short duration of treatment (3.5 weeks) with selinexor
- Given these issues, it is unclear whether the benefit of selinexor outweighs the risks

KCP-330-023 (BOSTON)



Options for Access to Selinexor



Discussion Topic

Discuss whether the KCP-330-012 (STORM) data are conclusive to allow for an adequate assessment of the safety and efficacy in the proposed patient population, and whether selinexor provides a benefit that outweighs the risks.

Voting Question

Should the approval of selinexor be delayed until results of the randomized phase 3 trial, KCP-330-023 (BOSTON), are available?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BACK-UP SLIDES SHOWN

Daratumumab Retreatment

Response to Daratumumab, pomalidomide and dexamethasone

	Cohort 1	Cohort 2	Cohort 3		
	DARA and POM naïve (19)	DARA or POM refractory (22)	DARA and POM refractory (12)	DARA refractory (13)	POM refractory (21)
ORR	17 (89%)	9 (40.9%)	4 (33.3%)	5 (38.5%)	8 (38.1%)
SCR	7 (36.8%)				
CR	1 (5.3%)				
VGPR	1 (5.3%)	1 (4.5%)	1 (8.3%)	1 (7.7%)	1 (4.8%)
PR	8 (42.1%)	8 (36.4%)	3 (25%)	4 (30.8%)	7 (33.3%)
SD	1 (5.3%)	9 (40.9%)	6 (50%)	6 (46.2%)	9 (42.9%)
PD	1 (5.3%)	4 (18.2%)	2 (16.7%)	2 (15.4%)	4 (19%)
Median lines of therapy	3 (1-7)	5 (3-13)	6.5 (3-13)	6 (3-13)	5 (3-13)

Retrospective, single-center review of 41 patients with RRMM treated with daratumumab, pomalidomide, and dexamethasone

(Source: Nooka, Blood 2016; 128: 492 (Abstract))

Daratumumab Retreatment

- Lakshman
  - Patients refractory to daratumumab and/or pomalidomide, ORR 43%
  - 9 patients refractory to daratumumab and 22 patients refractory to pomalidomide
- Hussain
  - Patients refractory to daratumumab or pomalidomide, ORR 55% (n=11)
  - Patients refractory to daratumumab and pomalidomide, ORR 13% (n=8)

(Sources: Lakshman Am J Hematol 2017; Hussain, BJH 2018)

DPd Approval

- Daratumumab
  - Approved as monotherapy in 2015
    - Single arm trial, ORR 29%
  - Approved in combination with lenalidomide and dexamethasone and bortezomib and dexamethasone in 2016
- Pomalidomide
  - Approved in combination with dexamethasone in 2013
    - RCT, ORR 29%
- Daratumumab/Pomalidomide/Dex (DPd)
  - Approved in 2017
    - Single arm trial, ORR 59%