Phase 2 MMRC Trial of Extended Treatment with Carfilzomib (CFZ), Lenalidomide (LEN), and Dexamethasone (DEX) Plus Autologous Stem Cell Transplantation (ASCT) in Newly Diagnosed Multiple Myeloma (NDMM)

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Background

- Clinical benefit of KRd has been demonstrated in both the relapsed[1] and NDMM settings[2,3]
- Phase 1/2 MMRC study evaluated extended treatment with KRd in transplant-eligible/-ineligible NDMM with a design to defer transplant[2,3]
  - KRd was highly active: sCR rate of 55%
  - KRd provided durable disease control: 3-year PFS of 79%
- Strategies to further improve upon the MMRC KRd study results are justified as
  - 45% of patients did not achieve sCR
  - 3-year progression rate of 21% including relapses despite sCR
- ASCT remains an important modality in NDMM
- This phase 2 study was designed to incorporate ASCT into an extended KRd regimen with the objective of further advancing the sCR rate and disease control

KRd, carfilzomib in combination with lenalidomide and dexamethasone; MMRC, Multiple Myeloma Research Consortium; PFS, progression-free survival; sCR, stringent complete response

1. Stewart K, et al. *N Engl J Med*. 2015;372:142-52. 2. Jakubowiak AJ, et al. *Blood*. 2012;120:1801-9. 3. Jasielec J, et al. ASH 2013: Abstract 3220.

Phase 2 Trial of KRd with ASCT in NDMM

Open-label, single-arm, phase 2 study at 5 MMRC centers

- **Primary endpoint:** Rate of sCR (IMWG criteria) after 8 cycles of KRd
- **Secondary endpoints:** ORR, ≥nCR, DOR, TTP, PFS, OS, safety

Key inclusion criteria:

- MM requiring treatment per IMWG criteria
- ≥18 years of age
- Transplant eligible
- ECOG performance status 0–2
- Adequate bone marrow, cardiac, and renal function

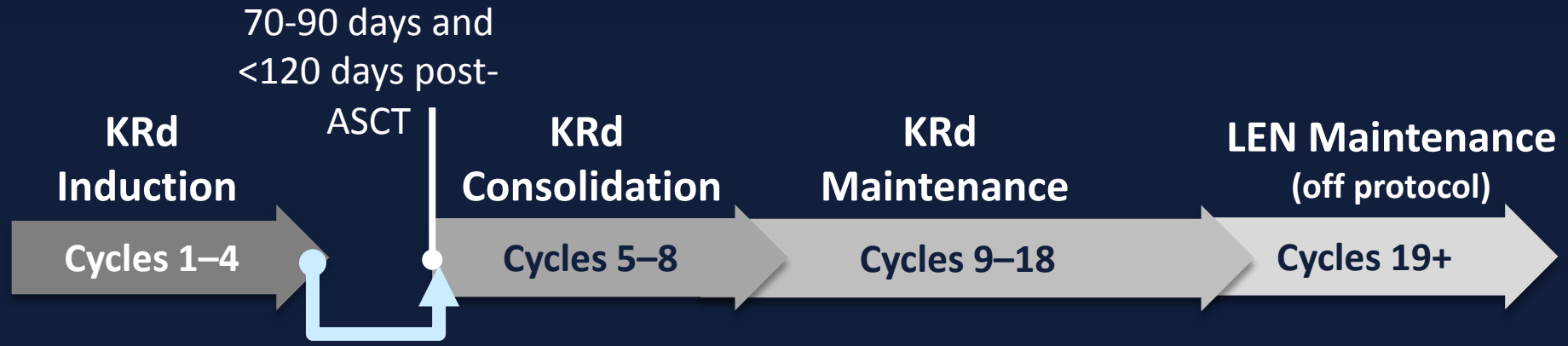
Key exclusion criteria:

- Significant CVD (eg, MI within 6 months, NYHA Class III/IV HF)
- Uncontrolled hypertension or diabetes
- Grade 3/4 neuropathy or Grade 2 with pain
- Known/suspected amyloidosis of any organ

ClinicalTrials.gov NCT01816971

CVD, cardiovascular disease; ECOG; Eastern Cooperative Oncology Group; HF, heart failure; IMWG, International Myeloma Working Group; MI, myocardial infarction; nCR, near CR; NYHA, New York Heart Association; ORR, overall response rate; OS, overall survival; TTP, time to progression

Treatment Schema – 28-day Cycle



CFZ	Days 1-2, 8-9, 15-16 20 mg/m²*➔36 mg/m²	Days 1-2, 8-9, 15-16 LTD	Days 1-2, 15-16 LTD	
LEN	Days 1-21 25 mg	Days 1-21 15 mg Cycle 5➔LTD	Days 1-21 LTD	Days 1-21 LTD
dex	Weekly 40 mg	Weekly 20 mg or LTD	Weekly LTD	

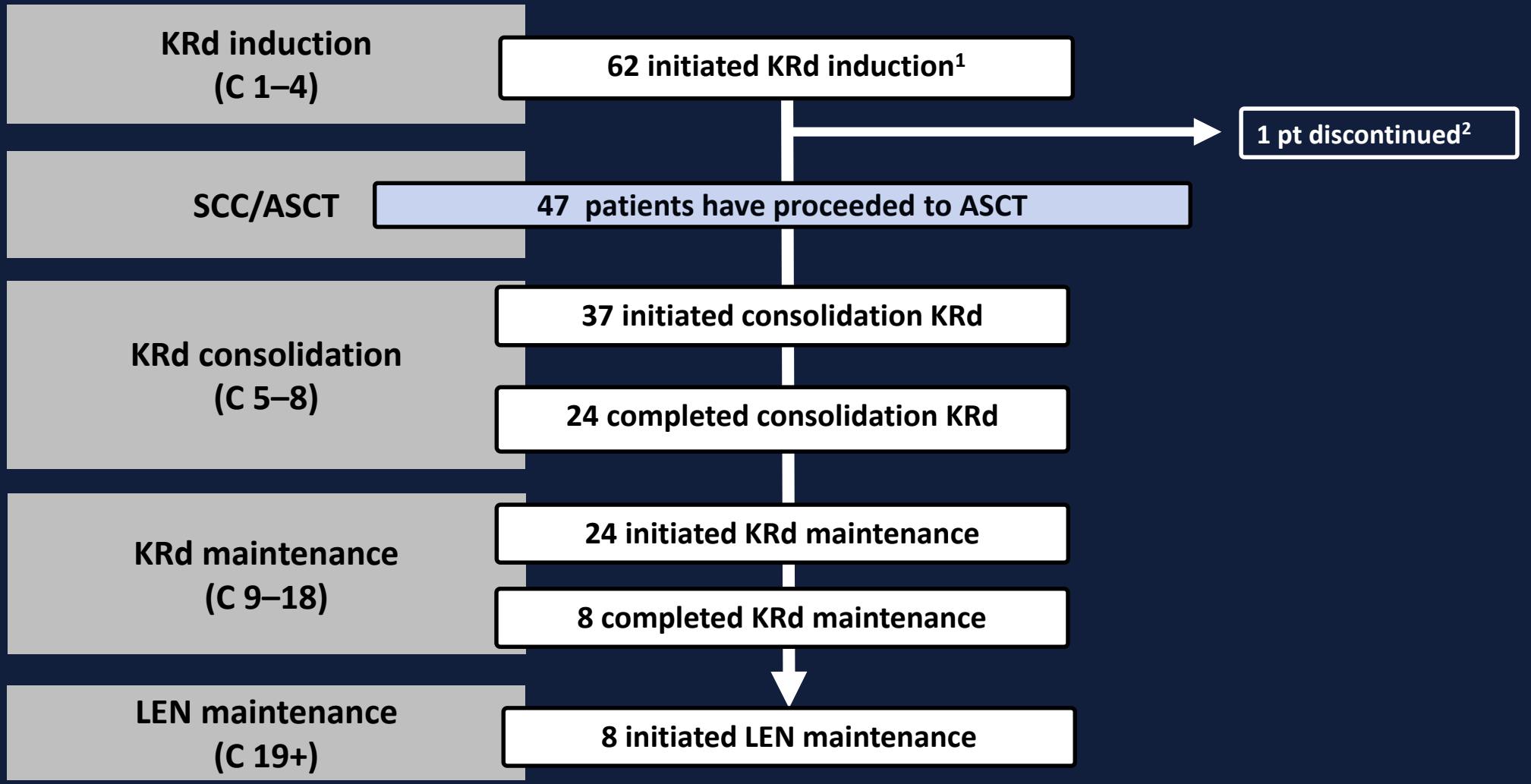
KRd+ASCT considered promising: improvement of ***sCR at the end of 8 cycles*** from historical rate of ***30% for KRd without transplant*** to ***50% for KRd+ASCT***

Patient and Disease Characteristics at Baseline
Intent-to-treat (ITT) Population (N=62)

Median age, years (range)	**61 (40–76)**
≥65 years, %	**29**
ECOG performance status, %	
0–1	**95.2**
2	**4.8**
Stage II/III*, %	
ISS	**60.3**
D-S	**86.7**
Cytogenetic risk category by FISH†, %	
High‡	**37.7**
Standard	**60.7**
Unknown	**1.6**
Serum β_2-microglobulin§	
≥3.5 mg/L, %	**36.6**

*Based on 58 (ISS) and 60 (D-S) of 62 pts with available data; †based on 60 of 62 pts with available data; ‡defined per IMWG; §based on 60 of 62 pts with available data
D-S, Durie-Salmon; ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; ISS, International Staging System.

Patient Disposition



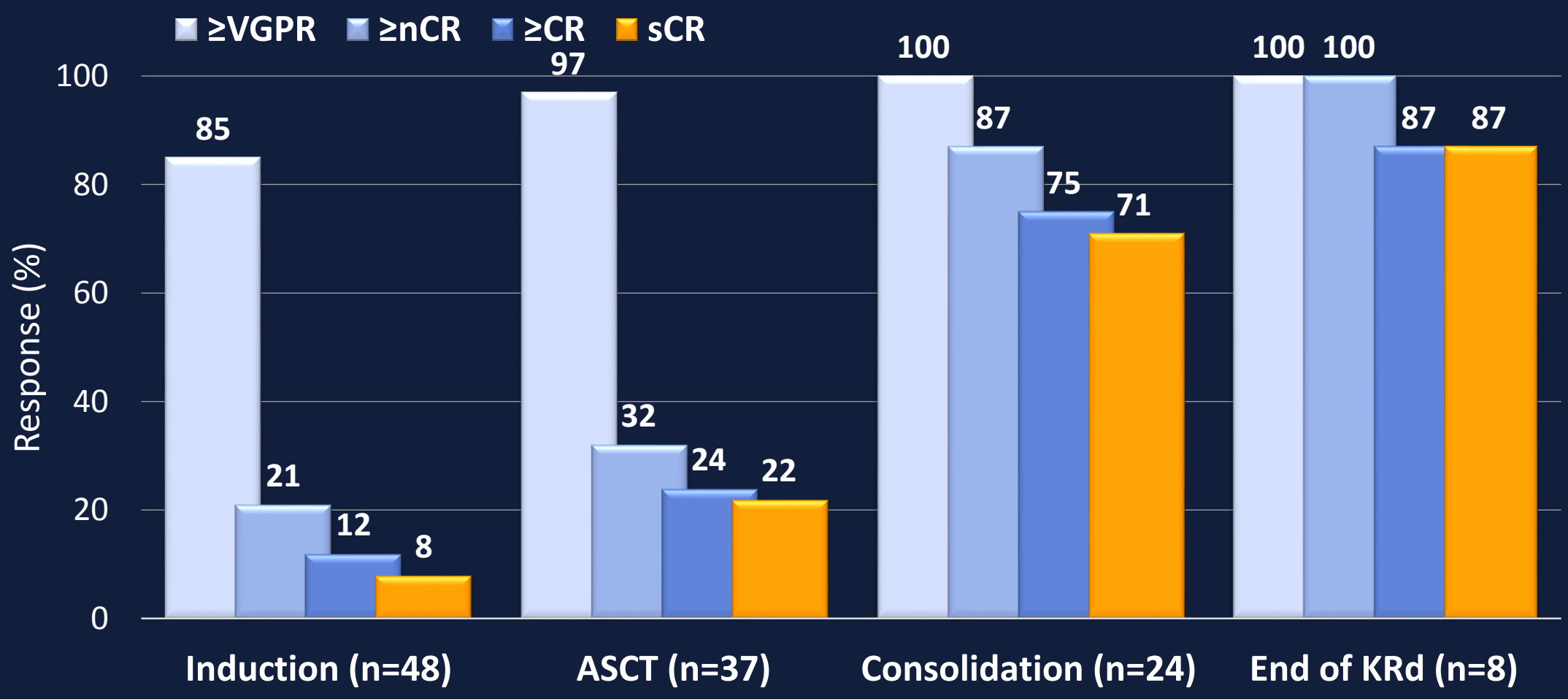
[1]At cut-off date 3/31/15 of 70 planned to enroll (initial enrollment planned for 53, increased for MRD end-point)
[2]Pt was in borderline PR after 4 cycles, transplant was deferred for additional cytoreduction but pt progressed after additional 2 cycles of KRd
MRD, minimal residual disease

SCC and ASCT

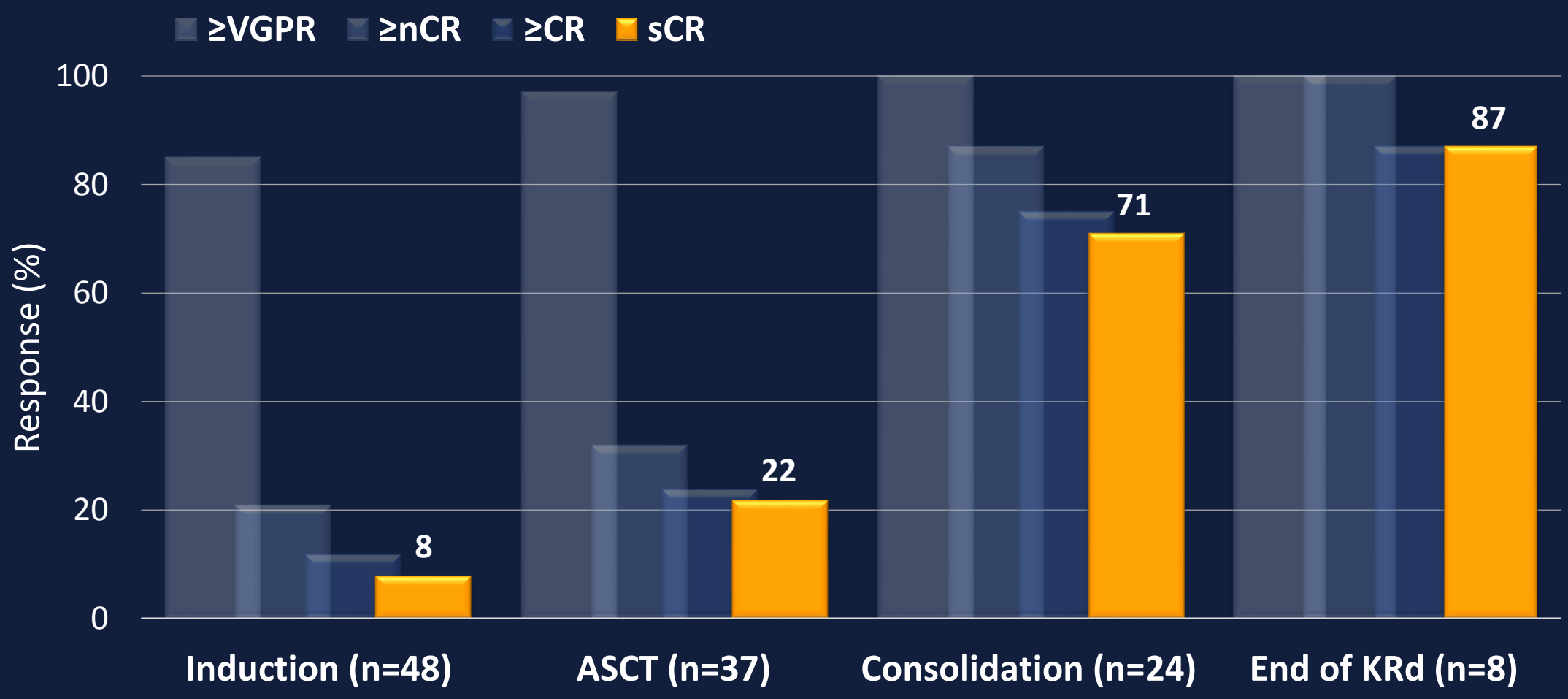
- Stem cells were collected from patients following G-CSF ± plerixafor treatment
  - Median 9.0 x 10^6 CD34+ cells/kg (range 2.9–16.8 x 10^6) after a median of 2 days of collection (range 1–8)[1]
  - 6 patients collected less than 4 x 10^6 $CD34^+$ cells/kg, of which 2 were re-collected[2] for a total of 4.2 and 9.8 x 10^6 total $CD34^+$ cells/kg, respectively
- There were no unusual events during ASCT

[1]Based on SCC from 47/53 evaluable patients
[2]Second collection of 1 patient following cyclophosphamide + G-CSF + plerixafor

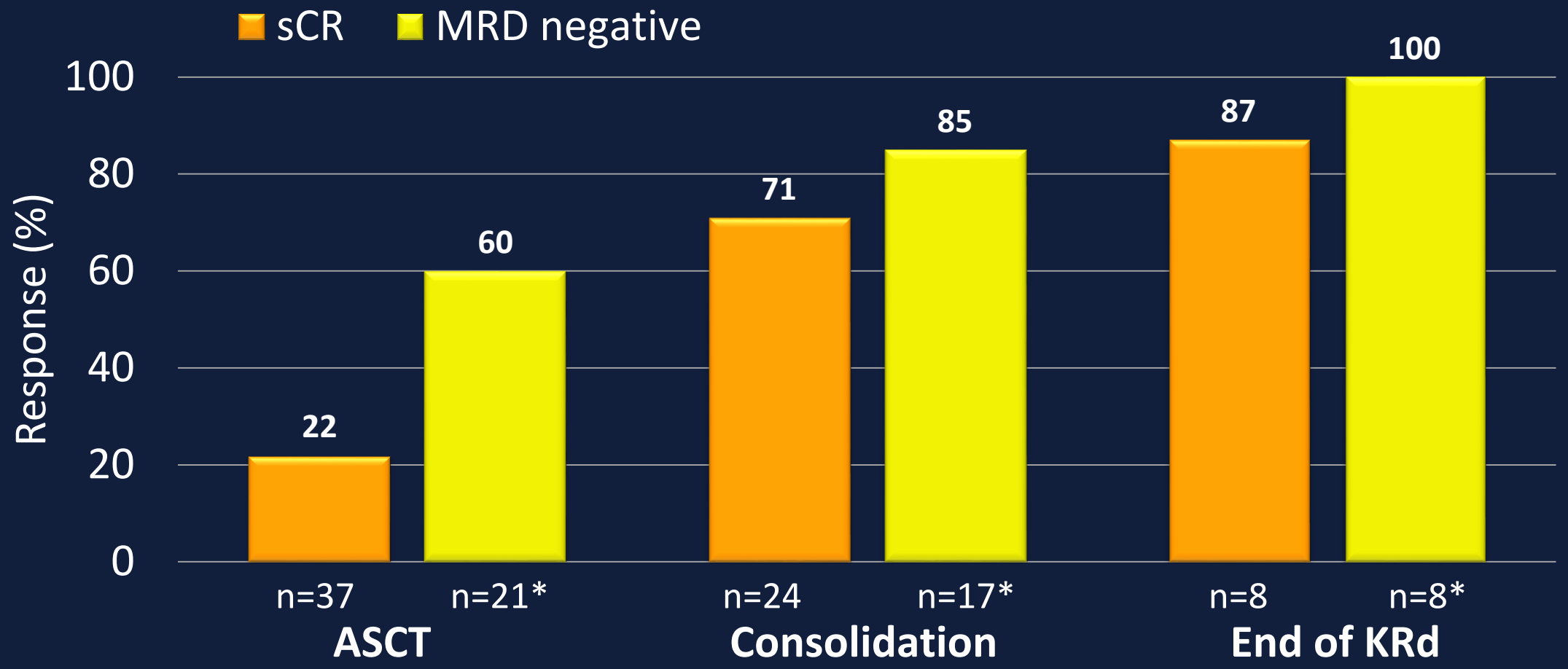
Response Rates Over the Course of Treatment



Response Rates Over the Course of Treatment

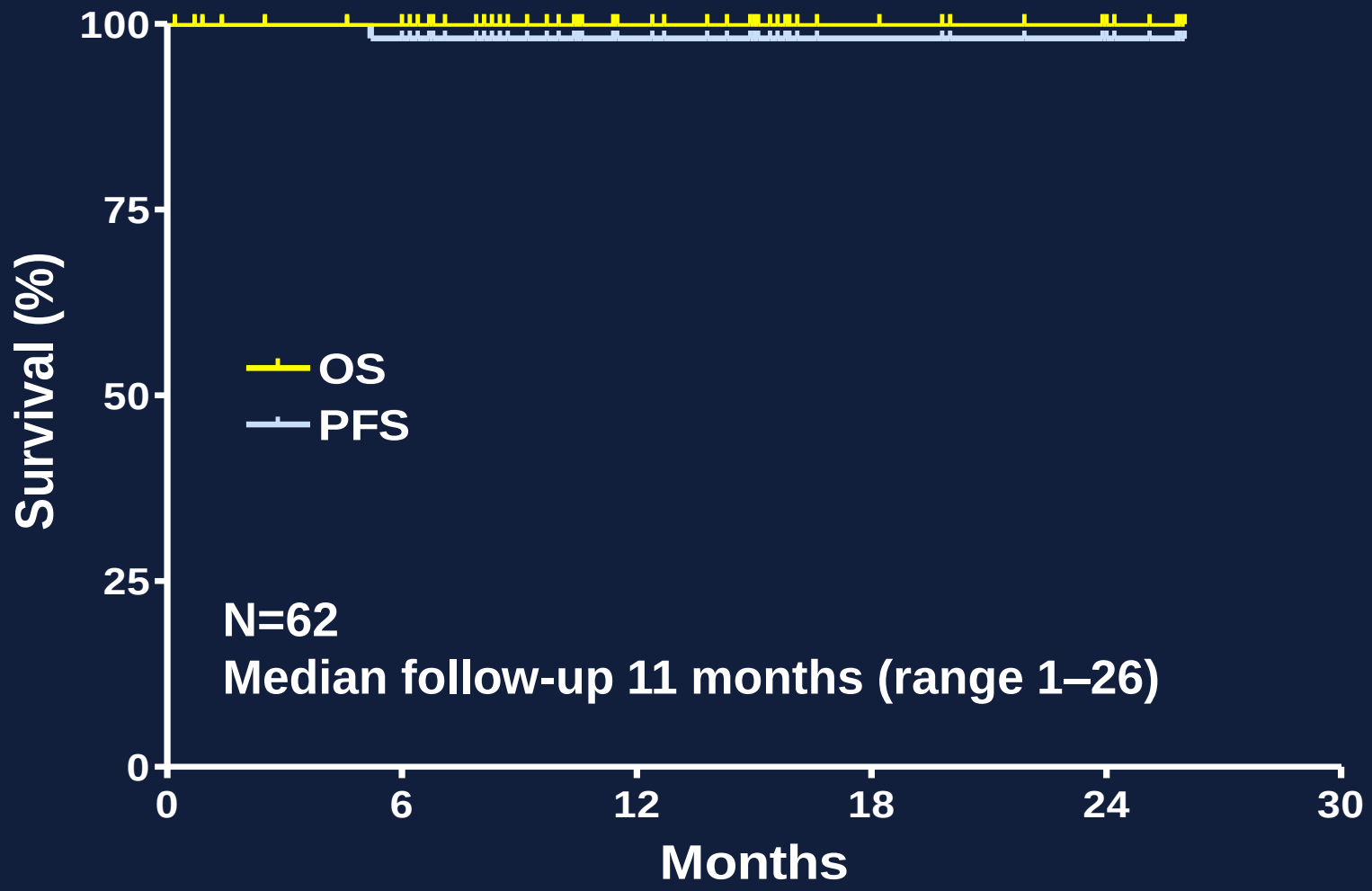


MRD Evaluation



*MRD by 10-color flow cytometry from indicated number of patients available for MRD evaluation

Treatment Outcomes



All patients were alive and 61/62 were progression free

AEs Occurring in ≥25% of Patients

N=62

AE, %	All Grade	Grade ≥3
Hematologic AEs		
Thrombocytopenia	58.1	11.3
Leukopenia	37.1	9.7
Lymphopenia	35.5	25.8
Anemia	32.3	6.5

AEs Occurring in ≥25% of Patients

N=62

AE, %	All Grade	Grade ≥3
Non-hematologic AEs		
Fatigue	48.4	1.6
Hyperglycemia	38.7	6.5
Rash	38.7	3.2
Pyrexia	29.0	1.6
Dyspnea	27.4	3.2
Peripheral neuropathy*	25.8	0

*Grouped term

Other AEs of Interest

	N=62	
AE, %	All Grade	Grade ≥3
Upper Respiratory Infection	19.4	1.6
Thromboembolic event*	17.7	8.1
Hypertension	9.7	1.6
Cardiac event*	3.2	1.6
Acute renal failure*	3.2	0

*Grouped term

Conclusions

- KRd + ASCT produced a **higher rate of sCR at end of 8 cycles** than historical KRd without transplant (**71% *vs* 30%**)
- Depth of response improved with duration of treatment
  - sCR rate improved further to **87%** after KRd maintenance
  - High MRD rates at the end of consolidation and KRd maintenance in subset analysis (**85% and 100%**, respectively)
- AE rates and types were within range of historical data with KRd
- Results to date indicate further improvement of outcome when combining KRd and transplant compared to KRd without transplant
- These results warrant further evaluation in randomized studies

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