Final Results of Phase 1 MMRC Trial of Selinexor, Carfilzomib, and Dexamethasone in Relapsed/Refractory Multiple Myeloma

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Background

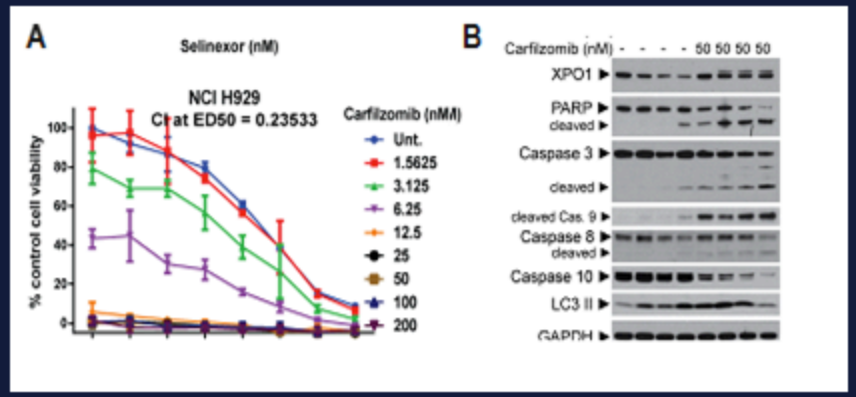
- Increasing number of patients with multiple myeloma (MM) are refractory to currently available drugs, including proteasome inhibitors (PIs)
- For these patients, there is a need to develop agents with novel mechanism of action to overcome treatment resistance
- Selinexor (SEL) is an oral SINE compound which targets XPO1, the only known nuclear export protein for TSPs and eIF4E-bound oncoprotein mRNAs (c-myc, cyclins)[1-4]
- Clinical evaluations show activity of SEL in heavily pretreated patients with relapsed and refractory myeloma
  - **SEL in combination with dexamethasone** (dex) generates **20/21% ≥PR** rate in quad/penta-refractory multiple myeloma[5]

SINE, selective inhibitor of nuclear export; TSPs, tumor suppressor proteins; XPO1, Exportin 1.

1. Rosebeck et al. *Mol Cancer Ther*. 2016;15:60-71. 2. Turner et al. AACR. 2014:abstr 1772. 3. Turner et al. *Oncotarget*. 2016: Epub. 4. Conforti et al. *Clin Cancer Res*. 2015;21:4508-4513. Vogl et al, *ASH* 2016:Abstract 491

Study Rationale

- Rationale for combining SEL with PIs, including carfilzomib (CFZ) was generated in preclinical studies[1-3]
  - Synergistic cell death of myeloma cell lines and primary plasma cells
  - Impaired growth of myeloma cell line-derived tumors in mice
  - Inhibition of NFkB and novel association of caspase-10 and autophagy-associated proteins cascade
  - Overcoming PI resistance, including CFZ resistance



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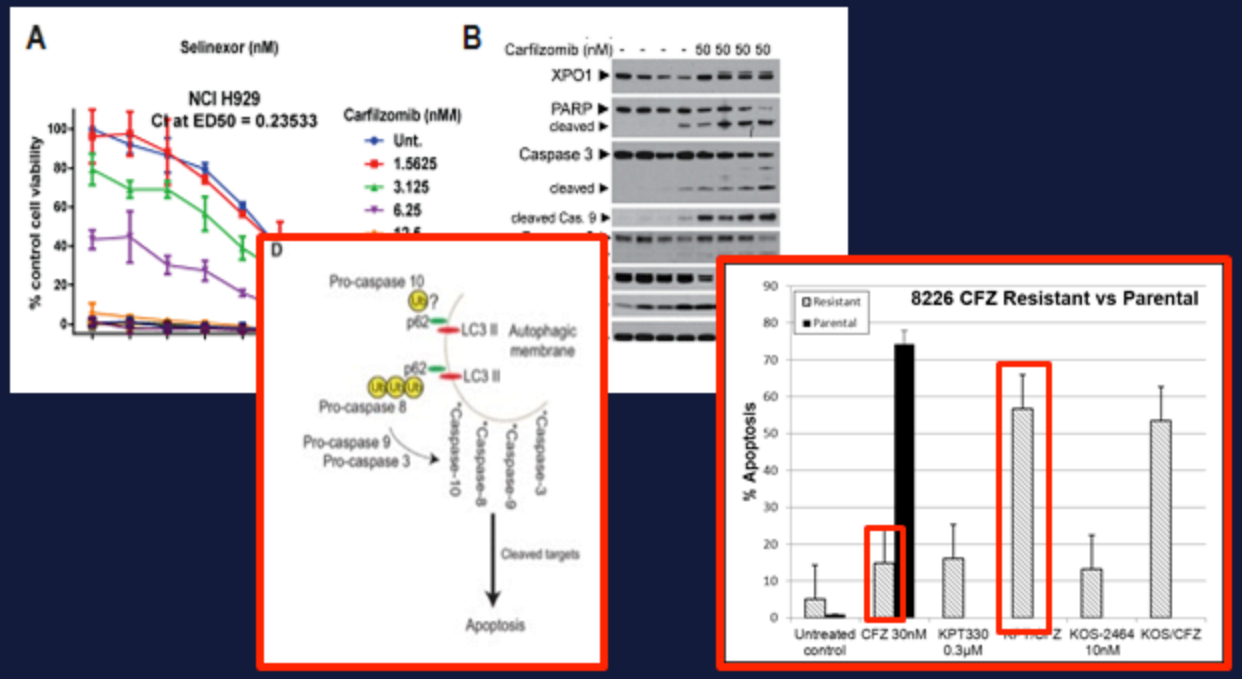

Phase 1 trial to assess novel combination of SEL+CFZ+dex in RRMM patients

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Study Objectives

Primary objectives

- MTD and RP2D of CFZ with SEL and dex

Secondary and exploratory objectives

- Safety and tolerability
- Best response – sCR, CR, nCR, VGPR, PR, MR, SD
- Activity in CFZ-refractory pts
- Time-to-event endpoints

MTD, maximum tolerated dose; R2PD, recommended phase 2 dose

CR, complete response; MR, minimum response; nCR, near CR; PR, partial response; sCR, stringent CR; SD, stable disease; VGPR, very good PR

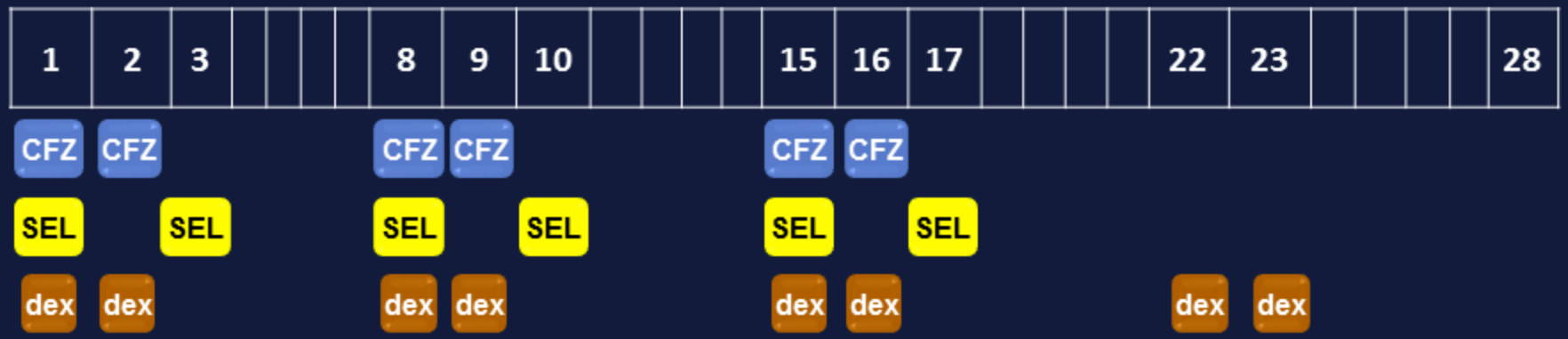
Patients and Methods

- **Eligibility**
  - RRMM with ≥2 prior therapy
  - Measurable disease per IMWG
  - ECOG performance status of 0 to 2
  - Absolute neutrophil count ≥1.0 × 10^9/L, hemoglobin ≥8.0 g/dL, platelets ≥75,000/μL
  - Calculated or measured creatinine clearance ≥30 mL/min
- **Eligibility for expansion cohort**
  - Carfilzomib-refractory required

ECOG, Eastern Cooperative Oncology Group; RR, relapsed/refractory

Schedule and Dosing

28-day cycles



Cycles 1–4

Cycles 5–8: dex reduced from initial 40 mg/wk to 20 mg/wk

Schedule and Dosing

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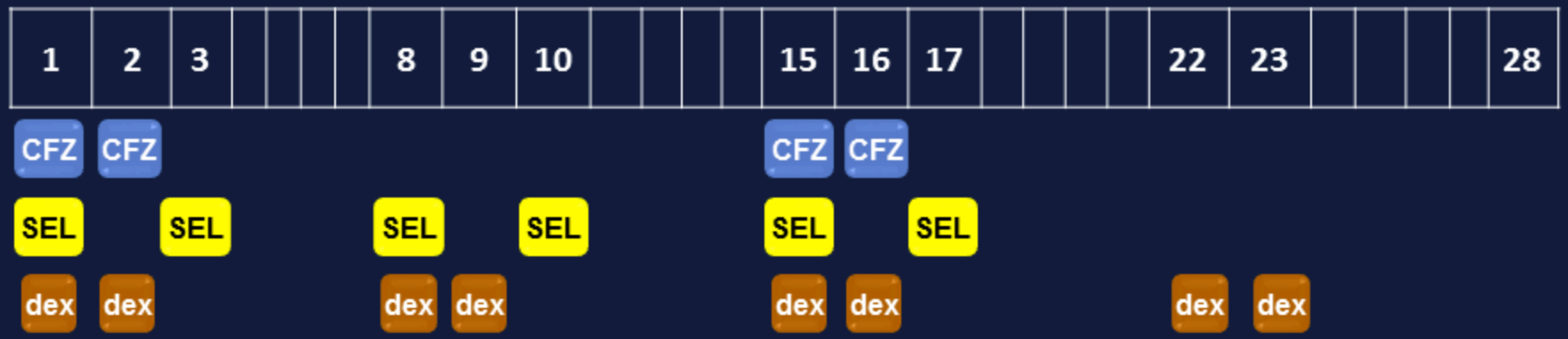

Cycles 1–4

Cycles 5–8: dex reduced from initial 40 mg/wk to 20 mg/wk

Cycles 9+ : CFZ administered on days 1, 2 and 15, 16

Study Design

3+3 dose escalation design

Dose level	SEL	CFZ	dex Cycles 1-4 / 5-8
1	30 mg/m^2/dose	27 mg/m^2*	20/10 mg/dose
2a	30 mg/m^2/dose	36 mg/m^2*	20/10 mg/dose
2b	60 mg/dose	27 mg/m^2*	20/10 mg/dose
3	60 mg/dose	36 mg/m^2*	20/10 mg/dose
4	60 mg/dose	45 mg/m^2*	20/10 mg/dose
5	60 mg/dose	56 mg/m^2*	20/10 mg/dose

*CFZ initiated at 20 mg/m^2 on Days 1-2 of Cycles 1 at all dose levels

Expansion phase

Additional CFZ-refractory pts enrolled at RP2D to a total of 12 CFZ-refractory pts treated at RP2D

Patient Characteristics

	N=21
Median age, years (range)	64 (55-74)
≥65 years, %	45
Years since diagnosis, median (range)	4.5 (1.6 – 11.7)
Prior lines of therapy, median (range)	4 (2 – 10)
ECOG PS, n (%)	
0	13 (62)
1–2	8 (38)
Cytogenetics or FISH,* n (%)	
Standard risk	9 (43)
High risk†	12 (57)
Del 17p	5 (29)

*FISH, fluorescence in situ hybridization

†Defined per IMWG; at least one of the following: t(4;14), del(17p), t(14;16), t(14;20), non-hyperdiploidy and gain(1q)

Prior Therapy

	N=21
Prior proteasome inhibitors, n (%)	21 (100)
Carfilzomib	20 (95)
Bortezomib	20 (95)
Prior cereblon-binding agent, n (%)	21 (100)
Lenalidomide	20 (95)
Pomalidomide	17 (81)
Thalidomide/other	4 (19)
Other prior therapies, n (%)	
ASCT	20 (95)
Panobinostat	2 (10)
Daratumumab	1 (5)
Refractory to prior therapy, n (%)	21 (100)
Carfilzomib	20 (95)
Bortezomib	11 (52)
Pomalidomide	17 (81)
Quadruple refractory (BTZ, LEN, CFZ, POM)	17 (81)
Refractory in last line of therapy, n (%)	21 (100)
Carfilzomib	13 (62)
Pomalidomide	11 (52)
Carfilzomib/pomalidomide	9 (43)

BTZ, bortezomib; LEN, lenalidomide; POM, pomalidomide

Enrollment and DLTs

Dose Escalation Phase (3+3 Design)

DL	SEL-CFZ-dex	n	DLT†
1	30 mg/m^2-27 mg/m^2-20 mg	5*	0
2a	30 mg/m^2-36 mg/m^2-20 mg	3	0
2b	60 mg-27 mg/m^2-20 mg	7†	1‡
3-5	60 mg-36/45/56 mg/m^2-20 mg	0	

Expansion Phase

2b Expansion	60 mg-27mg/m^2-20 mg	6	0

Data cutoff 10/1/2016

*2 pt replaced for DLT evaluation for not receiving all scheduled doses (unrelated to toxicity)

†1 pt was replaced for not receiving scheduled doses (unrelated to toxicity)

‡1 DLT: cardiac amyloidosis in pt with a history of CHF and cardiac amyloidosis

**Based on toxicity and tolerability across cycles

Enrollment and DLTs

Dose Escalation Phase (3+3 Design)

DL	SEL-CFZ-dex	n	DLT†
1	30 mg/m²-27 mg/m²-20 mg	5*	0
2a	30 mg/m²-36 mg/m²-20 mg	3	0
2b	60 mg-27 mg/m²-20 mg	7†	1‡

Dose level 2b was selected for expansion**

Expansion Phase

2b Expansion	60 mg-27mg/m²-20 mg	6	0

Total 12 CFZ-Ref pts treated at level 2b

Data cutoff 10/1/2016

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**Based on toxicity and tolerability across cycles

Treatment Duration and Patient Disposition

	Overall (N=21)
Median treatment duration, cycles (range)	3.0 (0.9-14)
Completed 1 cycle, n (%)	19 (90)
Completed 4 cycles, n (%)	8 (38)
Discontinued, n (%)	16 (76)
Pt/physician choice (prior to completion)	3 (14)
Progressive disease, n (%)	12 (57)
Toxicities, n (%)	1 (5)
Dose modifications, n (%)	14 (67)
Selinexor	12 (57)
Carfilzomib	9 (43)
Dexamethasone	7 (33)
New cycle delays, n (%)	7 (33)

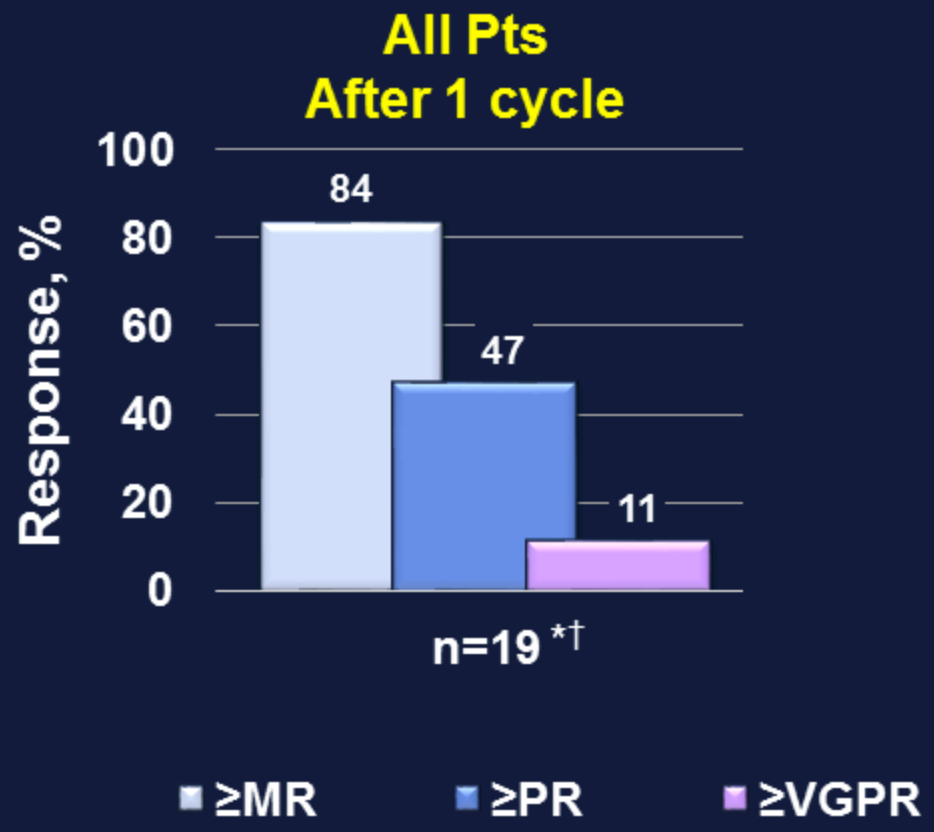
Adverse Events

	N=21	
	All Grade	Grade 3/4
Hematologic, n (%)		
Thrombocytopenia	16 (77)	13 (64)
Anemia	12 (59)	3 (14)
Lymphopenia	9 (45)	6 (27)
Neutropenia	7 (32)	6 (27)
Non-hematologic, %		
GI disorders	16 (77)	4 (18)
Fatigue	16 (77)	3 (14)
Dyspnea	8 (36)	1 (5)
Elevated liver and pancreatic enzymes	7 (32)	1 (5)
Edema	3 (14)	1 (5)
Musculoskeletal disorders	7 (32)	1 (5)
Eye disorders	7 (32)	0 (0)
Infection	2 (9)	1 (5)
Hyponatremia	1 (5)	1 (5)
Psychosis	1 (5)	1 (5)
Confusion	1 (5)	1 (5)
Syncope	1 (5)	1 (5)

- **2 SAEs:** 1 upper respiratory infection, 1 upper GI bleeding (unrelated and with platelets $167x10^3/\mu l$ at the time of AE)

GI, gastrointestinal; SAE, serious adverse event

Response Rates



*1 pt not evaluable (DLT prior to response evaluation);
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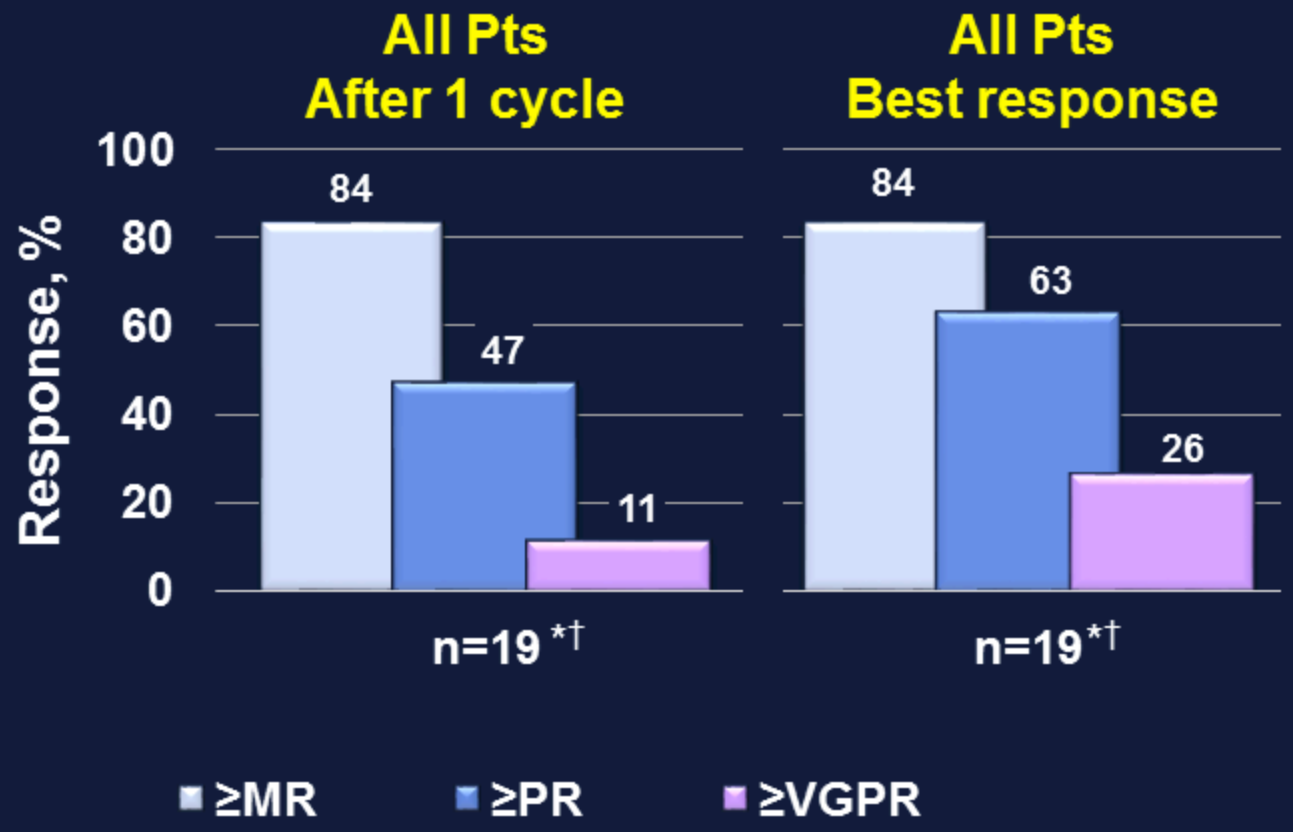

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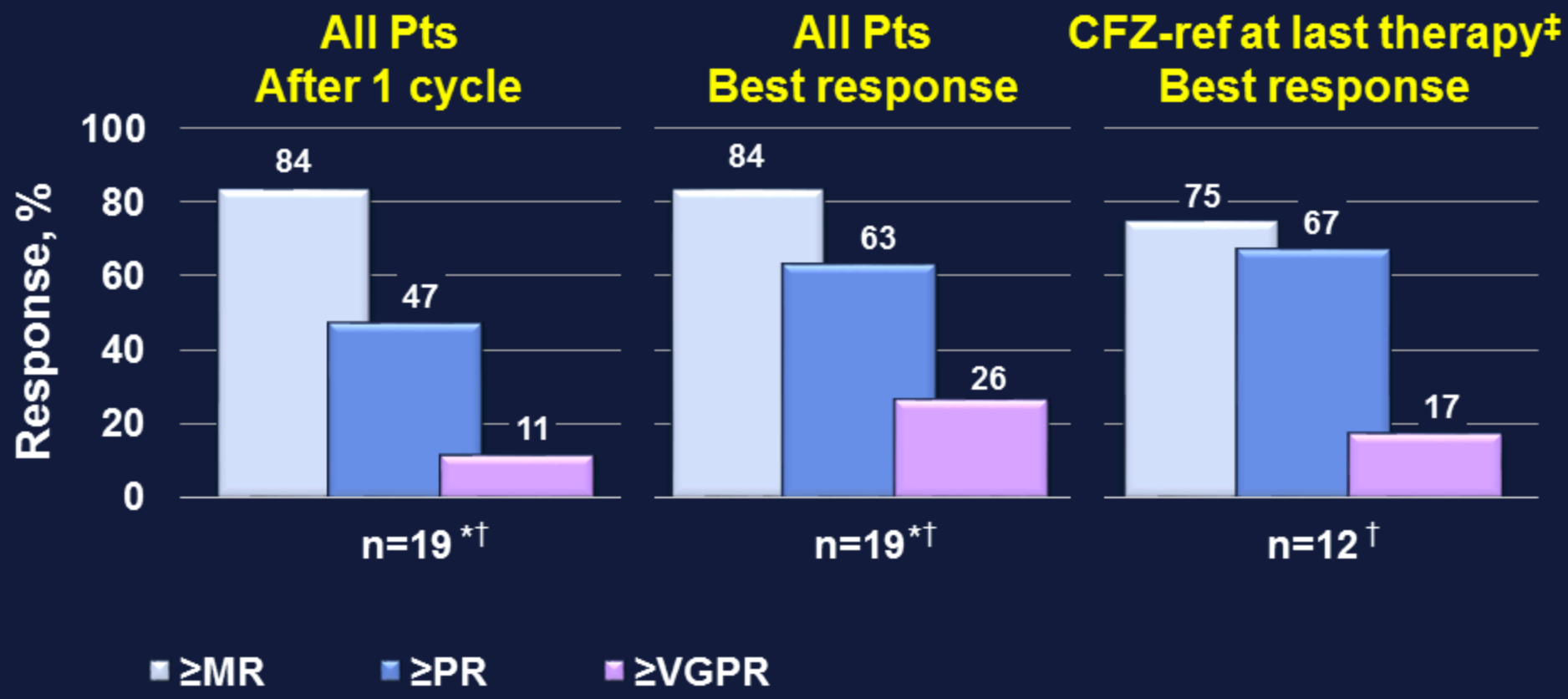
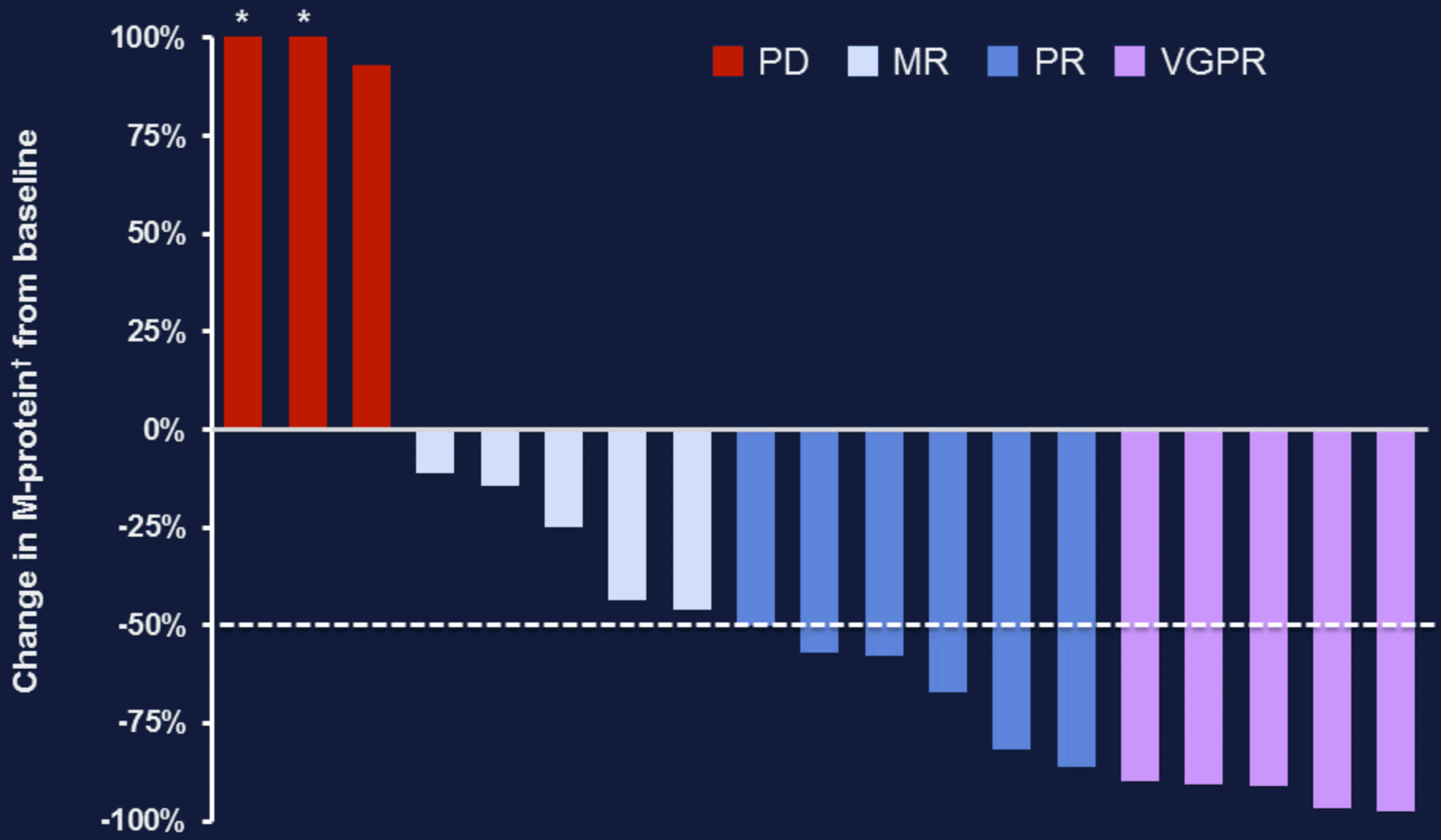


*1 pt not evaluable (DLT prior to response evaluation);
†1 pt not evaluable (had not completed 1 cycle)

‡Defined as progressing on CFZ at ≥20 mg/m^2 on twice-weekly schedule (i.e. on days 1, 2, 8, 9, 15, 16)

Depth of Response



*Increase >100%

†Serum protein electrophoresis (13), urine protein electrophoresis (2), or serum free light chain (4)

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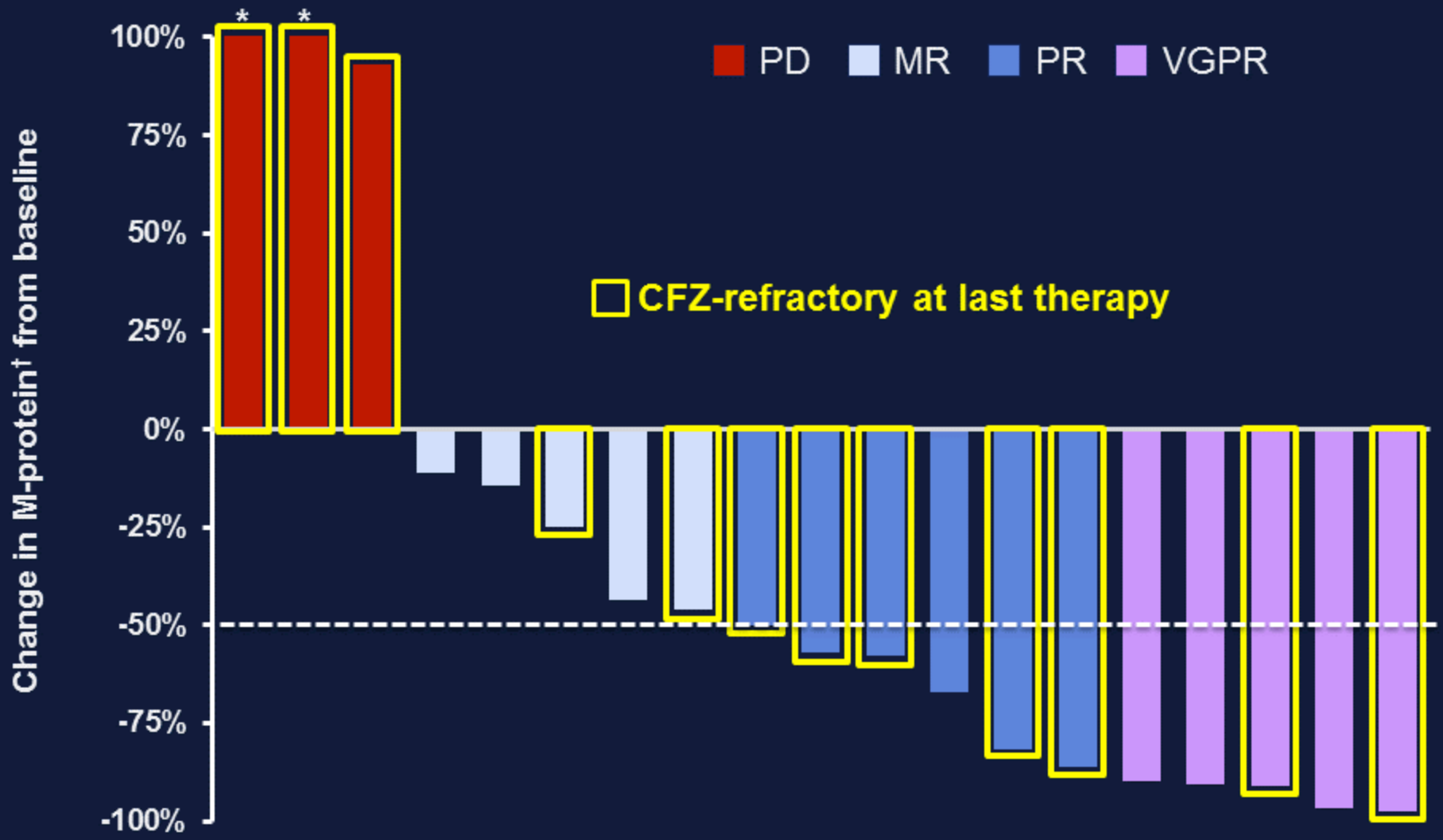

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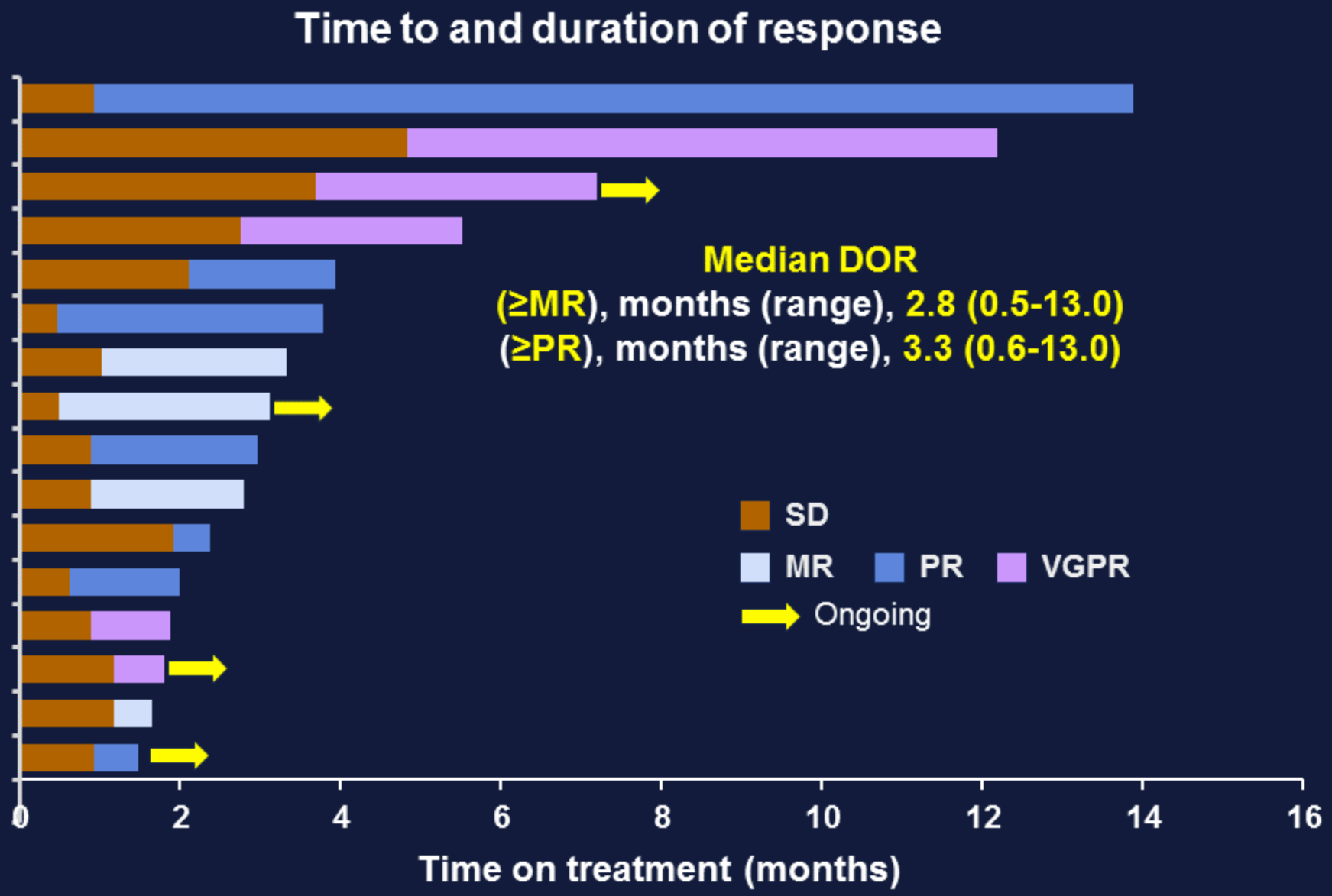
Durability of Response



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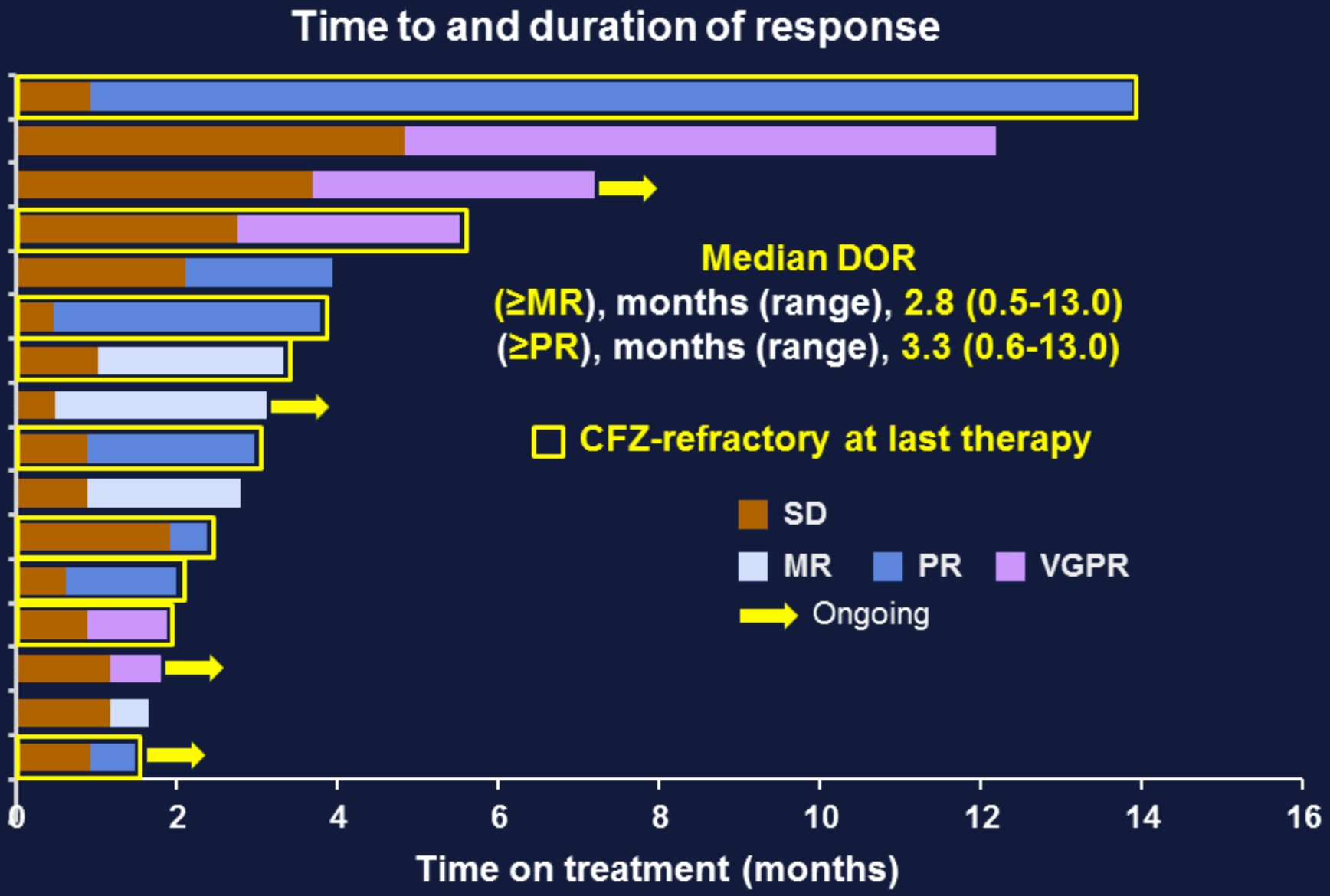
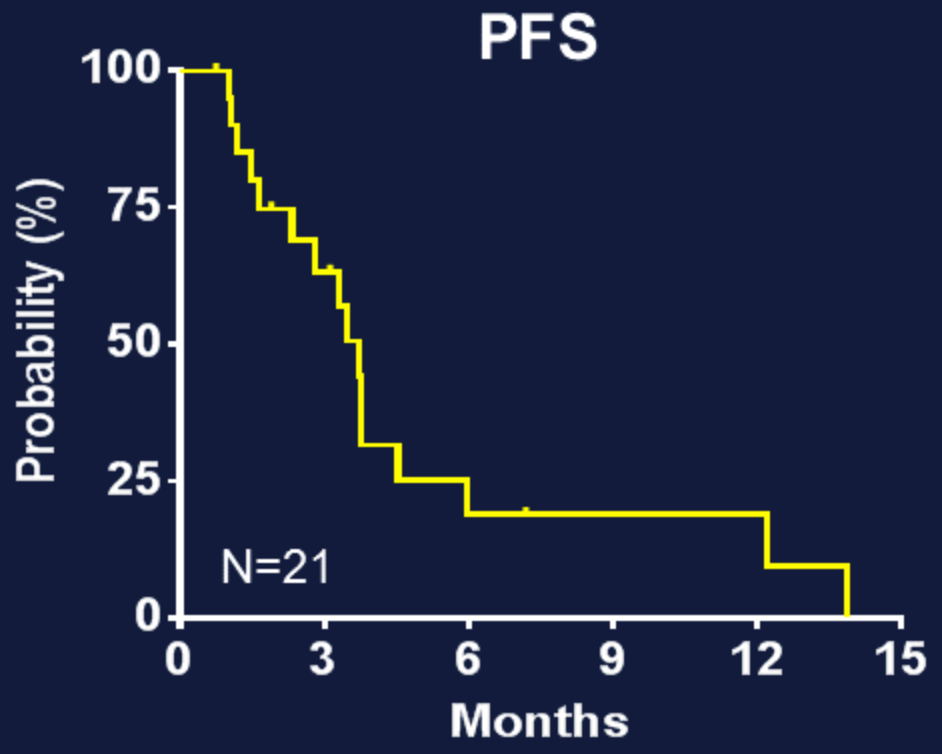
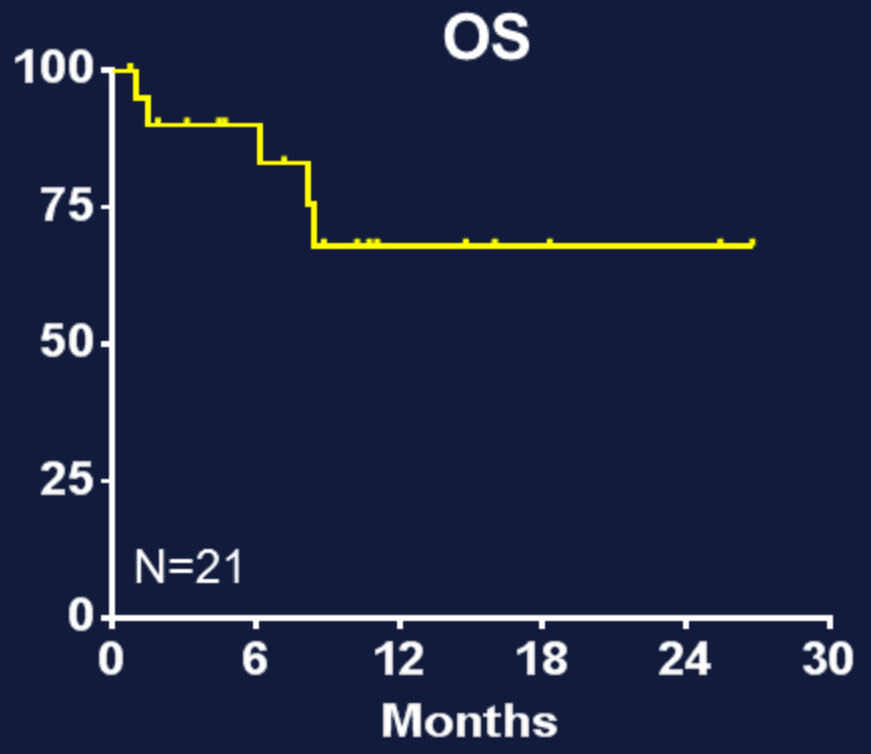


PFS and OS





Median (range) follow-up
8.2 mo (0.8–26.8)

	Median
PFS	3.7 mo
OS	NR

Conclusions

- SEL+CFZ+dex combination appears safe and has acceptable tolerability in patients with RRMM
  - Main toxicities are thrombocytopenia and neutropenia, which are manageable with dose modifications
- SEL+CFZ+dex shows encouraging activity in heavily pretreated RRMM pts
  - ≥PR 63% overall
  - ≥PR 67% for pts refractory to CFZ in their last prior therapy
  - Responses are rapid, most within 1 cycle, and show encouraging durability for up 13 months for this RR patient population
- These results provide early clinical evidence that the addition of selinexor has the ability to overcome CFZ resistance
- Further investigations of the regimen include evaluation of weekly schedule and evaluation of activity of the combination also in less pre-treated patients

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