# Eltanexor (KPT-8602), a Second Generation Selective Inhibitor of Nuclear Export (SINE) Compound, in Patients with Refractory Multiple Myeloma

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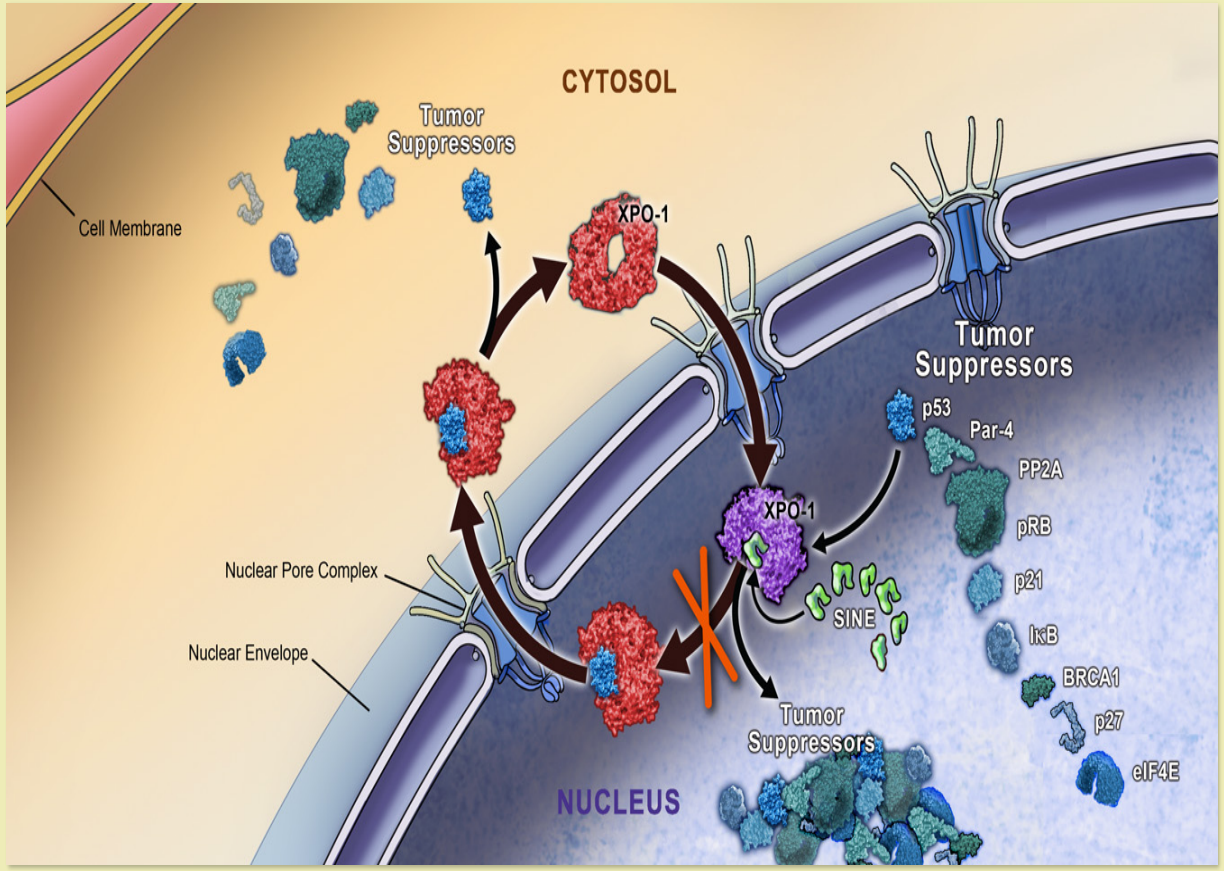
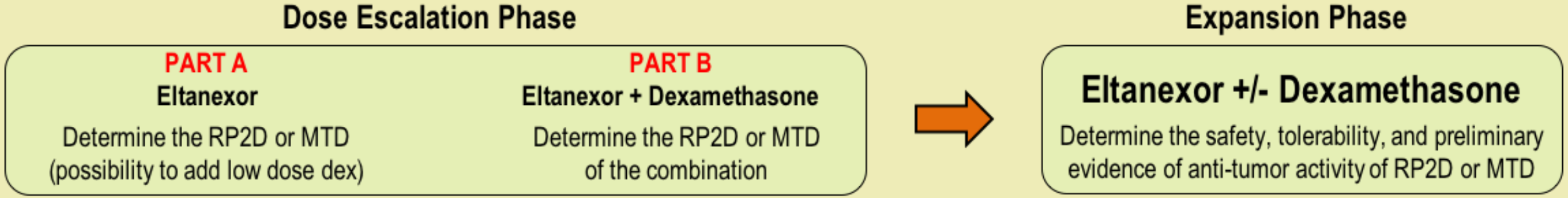
# Eltanexor Mechanism of Action




- Exportin 1 (XPO1) is the major nuclear export protein for tumor suppressor proteins (TSPs), the glucocorticoid receptor (GR), and eIF4E-bound oncoprotein mRNAs (e.g., c-Myc, BCL-xL, MDM2, cyclins)
- Eltanexor, an oral second generation selective inhibitor of XPO1-mediated nuclear export (SINE) compound, reactivates multiple TSPs relevant to MM including p53, IkB and FOXO, reactivates the GR when given with steroids, reduces c-myc levels, and overcomes MDM2-mediated p53 degradation
- Eltanexor has demonstrated single agent activity in patients with heavily pretreated refractory myeloma

# Study Design in MM

KCP-8602-801 is a phase 1/2 open-label study of the safety, tolerability and efficacy of eltanexor ± dexamethasone (dex) in patients with relapsed/refractory cancer indications (NCT02649790). The study design (MM arm) consists of 2 phases:




- **Objectives**
  - Determine MTD, RP2D, dosing schedule, and evaluate the safety and tolerability, including dose-limiting toxicity for eltanexor +/- dex
  - Assess the preliminary evidence of anti-tumor activity
- **Dose Limiting Toxicity (DLT) Definition**
  - Grade ≥3 nausea/vomiting or any other Grade ≥3 non-hematological toxicity
  - Grade 4 neutropenia > 5 days; febrile neutropenia; Grade 4 thrombocytopenia; Grade 3 thrombocytopenia with bleeding, or any requirement for platelet transfusion
  - >4 missed doses of eltanexor within cycle 1 is considered a DLT

# Key Inclusion Criteria, Patient Characteristics, Demographics

- Patients with confirmed symptomatic relapsed or refractory MM, measurable and progressive disease (IMWG guidelines)
- Previously treated with ≥3 prior therapies including: an alkylator, an immunomodulator, a proteasome inhibitor, and a steroid
- Refractory to (progression on or within 60 days of) the most recent anti-MM regimen
- **Quad**: Refractory to bortezomib, carfilzomib, lenalidomide, and pomalidomide; **Penta**: Also refractory to daratumumab or isatuximab

| Characteristic | N=39 |
|---|---|
| Median Age (Range) | 64 (48 – 83) |
| Male : Female | 24 : 15 |
| Median Prior Treatment Regimens (Range) | 7 (3 – 16) |
| ISS at Diagnosis (I : II : III) | 9 : 14 : 16 |
| Median Time Since Diagnosis (Range) | 6.2 years (1.3 – 29.9) |
| Prior PI and IMID % | 100% |
| Prior Anti-CD38 Ab % | 62% |
| Refractory Status (quad : penta : other) | 2 : 9 : 28 |

| Cohort | Dose | Schedule | N |
|---|---|---|---|
| 1 | 5 mg | qdx5 | 3 |
| 2 | 10 mg | qdx5 | 3 |
| 3 | 20 mg | qdx5 | 5 |
| 4 | 30 mg | qdx5 | 3 |
| 5 | 40 mg | qdx5 | 6 |
| 6 | 60 mg | qodx3 | 4 |
| 3B | 20 mg + dex | qdx5 | 5 |
| 4B | 30 mg + dex | qdx5 | 10 |

# Eltanexor Human Pharmacokinetic (PK) Profile

| Dose (mg) | N | $C_{max}$ (ng/mL) | $T_{max}$ (h) | $AUC_{0\text{-}inf}$ (ng*h/mL) | $t_{½}$ (h) |
|---|---|---|---|---|---|
| 5 | 3 | 30.6 | 1.0 | 164 | 4.0 |
| 10 | 3 | 60.5 | 3.0 | 347 | 5.1 |
| 20 | 5 | 123 | 2.0 | 754 | 5.0 |
| 20 + dex | 4 | 147 | 2.0 | 916 | 6.2 |
| 30 | 3 | 269 | 1.0 | 1,635 | 7.1 |
| 30 + dex | 10 | 268 | 2.0 | 1,859 | 5.5 |
| 40 | 5 | 147 | 3.0 | 1,204 | 5.8 |
| 60 | 4 | 284 | 2.0 | 2,581 | 6.4 |

## Cycle 1 Day 1 PK Profile of Eltanexor

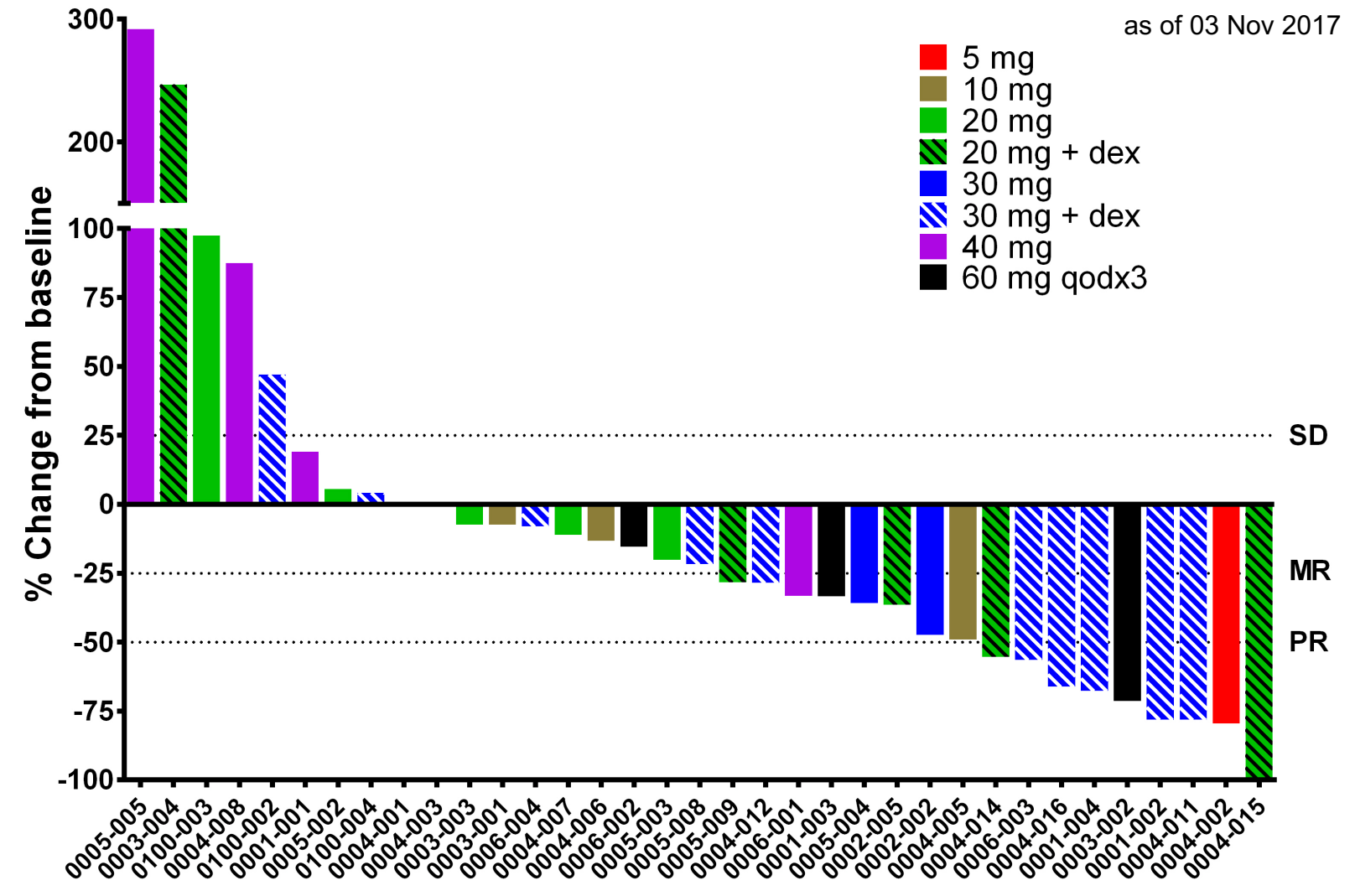
- Eltanexor was absorbed with a $T_{max}$ of ~2 hours
- Plasma concentration ($C_{max}$) generally increased with increasing dose from 5 to 60 mg
- Exposure ($AUC_{0\text{-}inf}$) generally increased in a dose-proportional fashion
- The terminal elimination phase ($t_{½}$) was relatively short, independent of dose
- There is no clear evidence of accumulation across the dose range over the 28-day cycle

# Treatment Related Adverse Events Observed in ≥3 Patients

| TRAEs | 5 mg (N=3) | | | 10 mg (N=3) | | | 20 mg (N=5) | | | 30 mg (N=3) | | | 40 mg (N=6) | | | 60 mg (N=4) | | | 20 mg + dex (N=5) | | | 30 mg + dex (N=10) | | | Total (N=39) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | G1/2 | G3 | G4 | G1/2 | G3 | G4 | G1/2 | G3 | G4 | G1/2 | G3 | G4 | G1/2 | G3 | G4 | G1/2 | G3 | G4 | G1/2 | G3 | G4 | G1/2 | G3 | G4 | |
| Thrombocytopenia | 2 | 1 | | 1 | 1 | | 2 | 2 | 1 | | | 1 | 3 | 1 | 1 | | 3 | | 1 | 3 | | 2 | 3 | 5 | 33 (85%) |
| Neutropenia | 3 | | | | 1 | 1 | 1 | 3 | | | 1 | | 1 | | | 1 | 1 | | 4 | | | 2 | 3 | | 22 (56%) |
| Anemia | | | | | 1 | | 1 | 1 | | 3 | | | 2 | 1 | | 3 | | | 2 | | | 4 | 3 | | 21 (54%) |
| Nausea | 2 | | | | | | 1 | | | 2 | | | 5 | | | 3 | | | 2 | | | 6 | | | 21 (54%) |
| Fatigue | 1 | | | 1 | | | 2 | | | | | | 5 | | | 2 | 1 | | 2 | | | 5 | | | 19 (49%) |
| Leukopenia | 1 | | | | 2 | | 2 | | | 1 | | | 3 | | | | 2 | | 2 | 1 | | 2 | 1 | | 17 (44%) |
| Diarrhea | 2 | | | 1 | | | 2 | | | 1 | | | 5 | | | 1 | | | 1 | | | 2 | 1 | | 16 (41%) |
| Dysgeusia | 2 | | | 1 | | | 2 | | | | | | 2 | | | 1 | | | 3 | | | 2 | | | 13 (33%) |
| Weight decreased | | | | | | | | | | 2 | | | 4 | | | 1 | | | 2 | | | 4 | | | 13 (33%) |
| Appetite decreased | | | | | | | | | | | | | 5 | | | 1 | | | 1 | | | 5 | | | 12 (31%) |
| Hyponatremia | 1 | | | 1 | | | 1 | 1 | | 1 | | | 2 | | | | 1 | | | | | 2 | 2 | | 12 (31%) |
| Vomiting | 1 | | | | | | | | | 2 | | | 3 | | | 1 | | | 2 | | | 3 | | | 12 (31%) |
| Creatinine increased | | | | | | | 1 | | | | | | | | | | | | | | | 1 | 1 | | 3 (8%) |
| Dehydration | | | | | | | 1 | | | | | | | | | | | | | | | 1 | 1 | | 3 (8%) |
| Hypomagnesemia | | | | 1 | | | | | | 1 | | | | | | 1 | | | | | | | | | 3 (8%) |
| Hypophosphatemia | | | | | 1 | | | | | 1 | | | | | | | 1 | | | | | | | | 3 (8%) |
| Vision blurred | | | | | | | | | | | | | | | | | | | 2 | | | 1 | | | 3 (8%) |

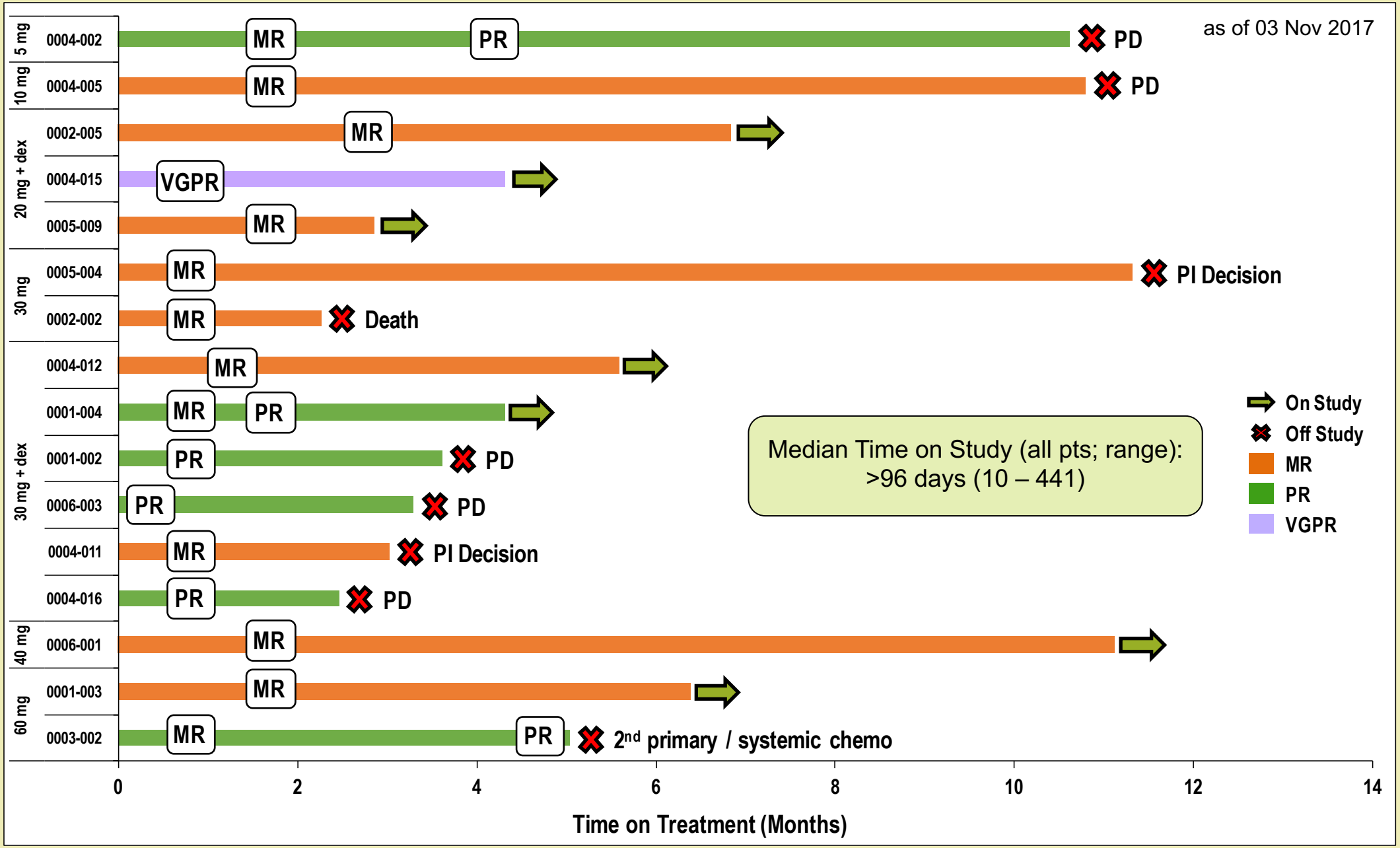
- 39 patients were evaluable for safety; there was one DLT (>4 missed doses) observed at 40 mg
- The most common Grade 3/4 AEs are thrombocytopenia, neutropenia, and anemia as expected for this patient population
- Nausea, fatigue, diarrhea, and vomiting are nearly all Grade 1, manageable, and transient
- Decreased appetite and weight loss more frequently observed at ≥ 30 mg
- Protocol defined MTD was not reached, however, dose escalation was halted based on efficacy reached
- AEs of interest in 2 patients were hypokalemia G4 (60 mg), G2 (30 mg + dex); lymphopenia G4 (40 mg), G2 (60 mg); acute kidney injury G4 (30 mg + dex), G2 (40 mg)

# Depth of the Response Across All Doses




- Many patients received low dose dex starting ≥ C2D1; separate cohorts received 20 or 30 mg eltanexor + dex from C1D1
- Deeper and faster responses observed when dexamethasone was started on C1D1
- Overall, amongst 35 response-evaluable patients, 25 (71%) had a reduction in M protein

# Time on Study for Patients with ≥ MR

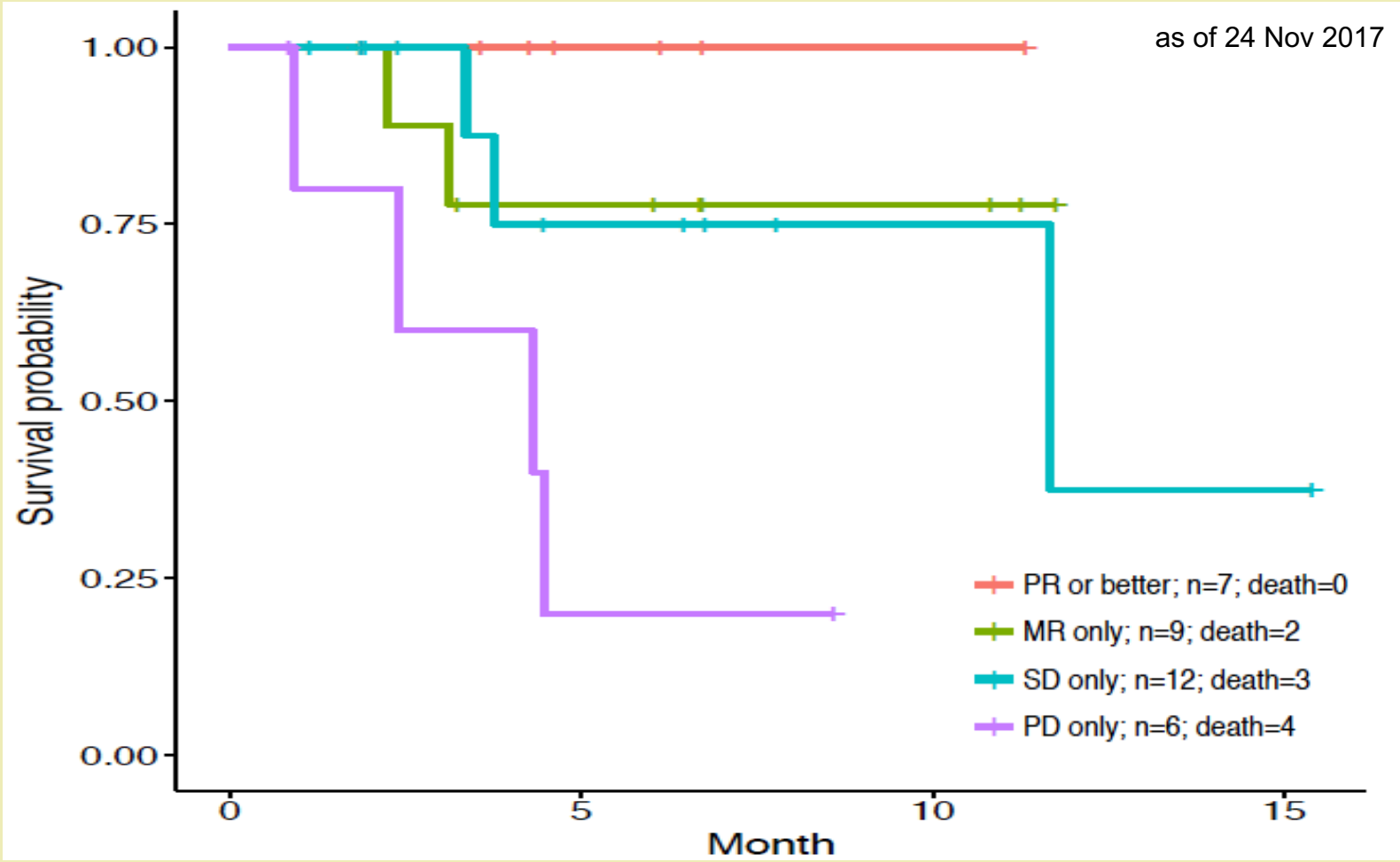


# Summary of Responses

| Best Response – All Patients | | | | | | | |
|---|---|---|---|---|---|---|---|
| N* | ORR (%) | VGPR (%) | PR (%) | MR (%) | SD (%) | PD (%) | CBR (%) |
| 34 | 7 (21%) | 1 (3%) | 6 (18%) | 9 (26%) | 12 (35%) | 6 (18%) | 16 (47%) |
| **Best Response at 20 and 30 mg + dex** | | | | | | | |
| 14 | 5 (35.7%) | 1 (7.1%) | 4 (28.6%) | 4 (28.6%) | 4 (28.6%) | 1 (7.1%) | 9 (64.3%) |

Responses were adjudicated according to the *International Myeloma Working Group* (IMWG) criteria. *5 Non-Evaluable Patients: 1 DLT, 2 Pt decision, 1 lost to follow up, 1 PI decision. **ORR**: Overall Response Rate (VGPR+PR), **PR**: Partial Response, **MR**: Minor Response, **SD**: Stable Disease, **CBR**: Clinical Benefit Rate (VGPR+PR+MR), **PD**: Progressive Disease. Responses as of **03-Nov-2017** based on interim unaudited data.

# Overall Survival by Best Response




- Objective responses correlate with longer survival
- All pts with a PR or VGPR are still alive or censored as of 24 November 2017

# Summary and Conclusions

- In patients with refractory MM whose disease had progressed despite most available therapies, eltanexor alone or in combination with dexamethasone (dex) induces responses or disease control
  - Low dose dex can safely be given with eltanexor and improves eltanexor's anti-MM activity, especially if started on C1D1
  - Responses to eltanexor +/- dex were associated with prolonged survival
- The most common Grade 3/4 AEs have been cytopenias; GI and systemic adverse events were mainly Grade 1 and were lower than those reported with first generation SINE compound selinexor
- Enrollment of the MM cohorts is complete; 7 pts remain on study as of 24 Nov 2017
- Based on preliminary efficacy, safety and tolerability data, the RP2D / schedule of eltanexor is determined to be 20 mg + dex / qd x 5
- Enrollment is ongoing for patients with advanced colorectal cancer, castrate resistant prostate cancer (mCRPC), and High Risk MDS