Selinexor (KPT-330) Demonstrates Marked Synergy with Dexamethasone (Sel-Dex) in Preclinical Models and in Patients with Heavily Pretreated Refractory Multiple Myeloma

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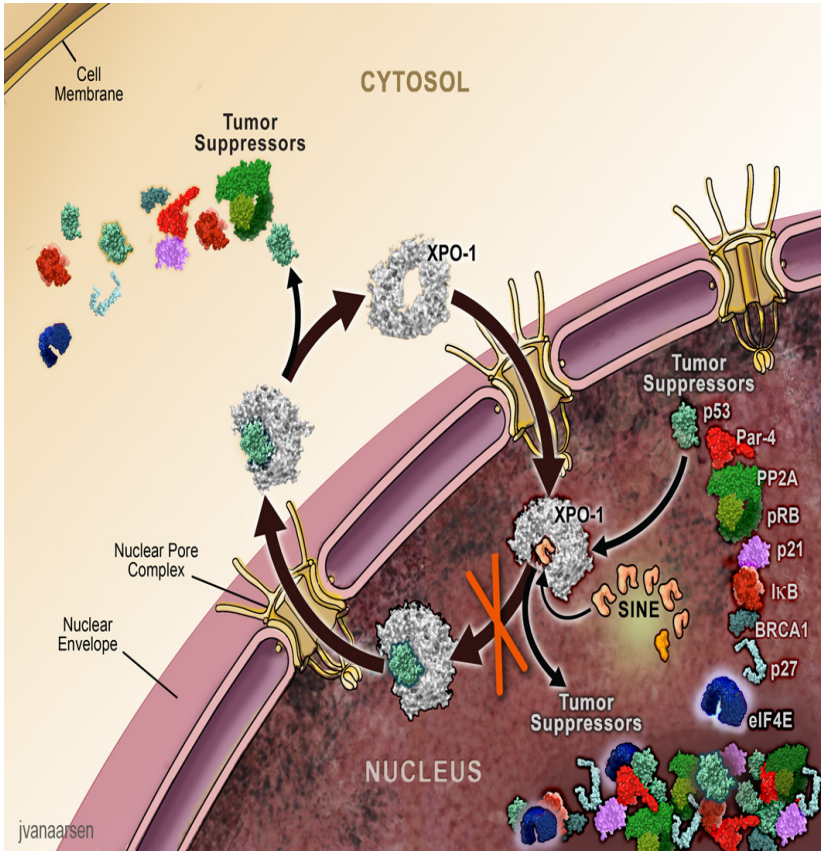
Selinexor Mechanism of Action



- Exportin 1 (XPO1) is the major nuclear export protein for tumor suppressor proteins (TSPs) and eIF4E-bound oncoprotein mRNAs (c-myc, cyclins)
- SINE compounds inhibit XPO1, leading to nuclear retention of oncoprotein mRNAs and reactivation of TSPs, reducing c-myc and cyclin levels and inducing selective tumor cell apoptosis
- Selinexor is a novel oral SINE compound currently being evaluated in solid and hematological cancers

- Multiple myeloma (MM) is a rationale indication for selinexor
  - XPO1 is overexpressed in MM cells and other hematological malignancies and its levels often correlate with poor prognosis
  - Selinexor reactivates p53, which is found as hemizygous deletions in up to 34% of MM pts, and overcomes HDM2/ MDM2 mediated p53 degradation
  - Selinexor increases IκB leading to NF-κB activation, commonly found in MM
  - By trapping mRNAs bound to eIF4E, selinexor reduces expression of c-myc, Cyclin D and Survivin, which are frequently overexpressed in MM

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Study Design

- **Selinexor Phase 1/2 Study Design (NCT01607892)**
  - Open label, dose escalation study in patients with advanced hematological malignancies
  - Doses 3 mg/m^2 – 80 mg/m^2
  - 10 doses/cycle (QoD 2x-3x/wk) or 8 doses/cycle (QoD 2x/wk) or 4 doses/cycle (1x/wk)
  - Modified "3+3" design
- **Primary Endpoint**
  - Safety, tolerability, efficacy, and Recommended Phase 2 Dose (RP2D)
- **Patient Safety Criteria**
  - Patients who have received at least one dose of selinexor
- **Patient Efficacy Criteria**
  - Patients who have completed at least one cycle of dosing with selinexor

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Patient Characteristics - Monotherapy

Characteristic	N
Patients Enrolled	35
Median Age (Range)	62 (47 – 78)
ECOG PS 0 : 1 : 2	5 : 29 : 1
Male : Female	19 Males : 16 Females
Median Prior Treatment Regiments	5 (2 – 13)

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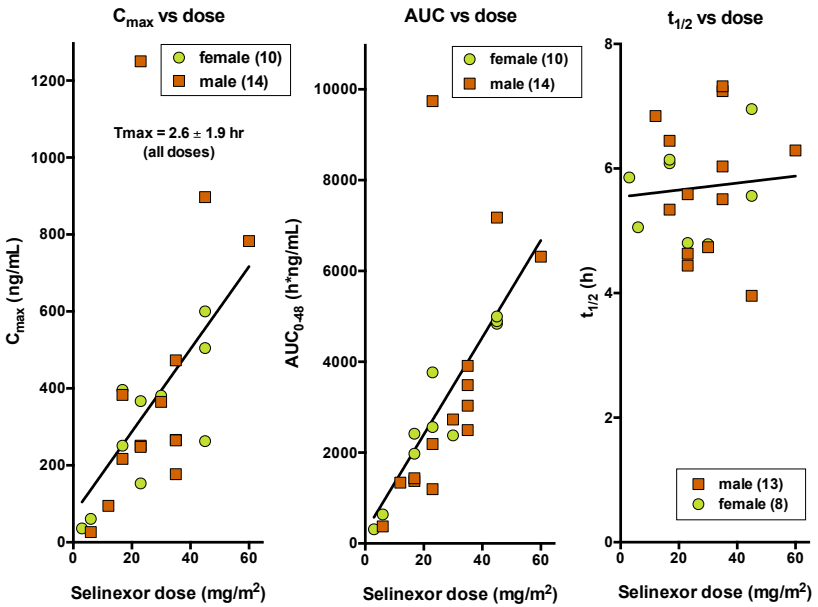
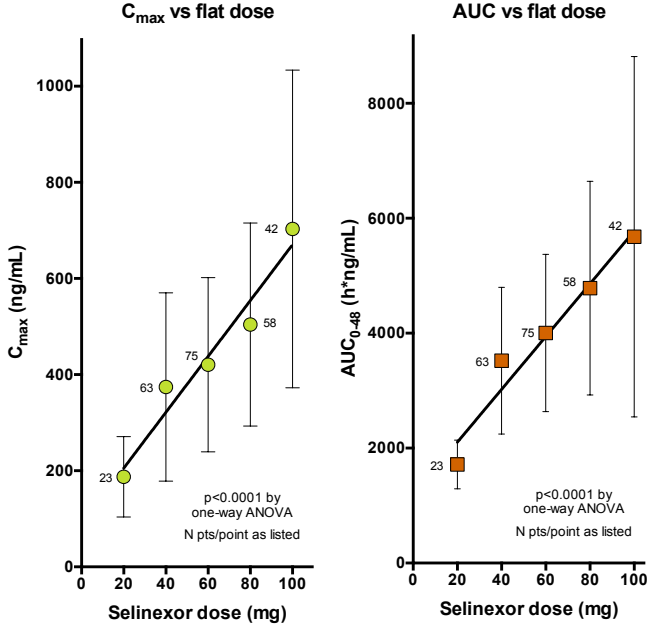
Selinexor Pharmacokinetics in MM Patients

A BSA-Adjusted Doses



B Flat Doses



(**A**) In MM pts, C_{max} and AUC are linear with BSA-adjusted dose (mg/m^2) up to MTD and $t_{1/2}$ is independent of dose

(**B**) In all hematological cancer pts from Phase 1, C_{max} and AUC are linear with flat dose (mg), based upon typical BSA range (1.5-2.3 m^2), which justifies transition to flat dosing in future trials

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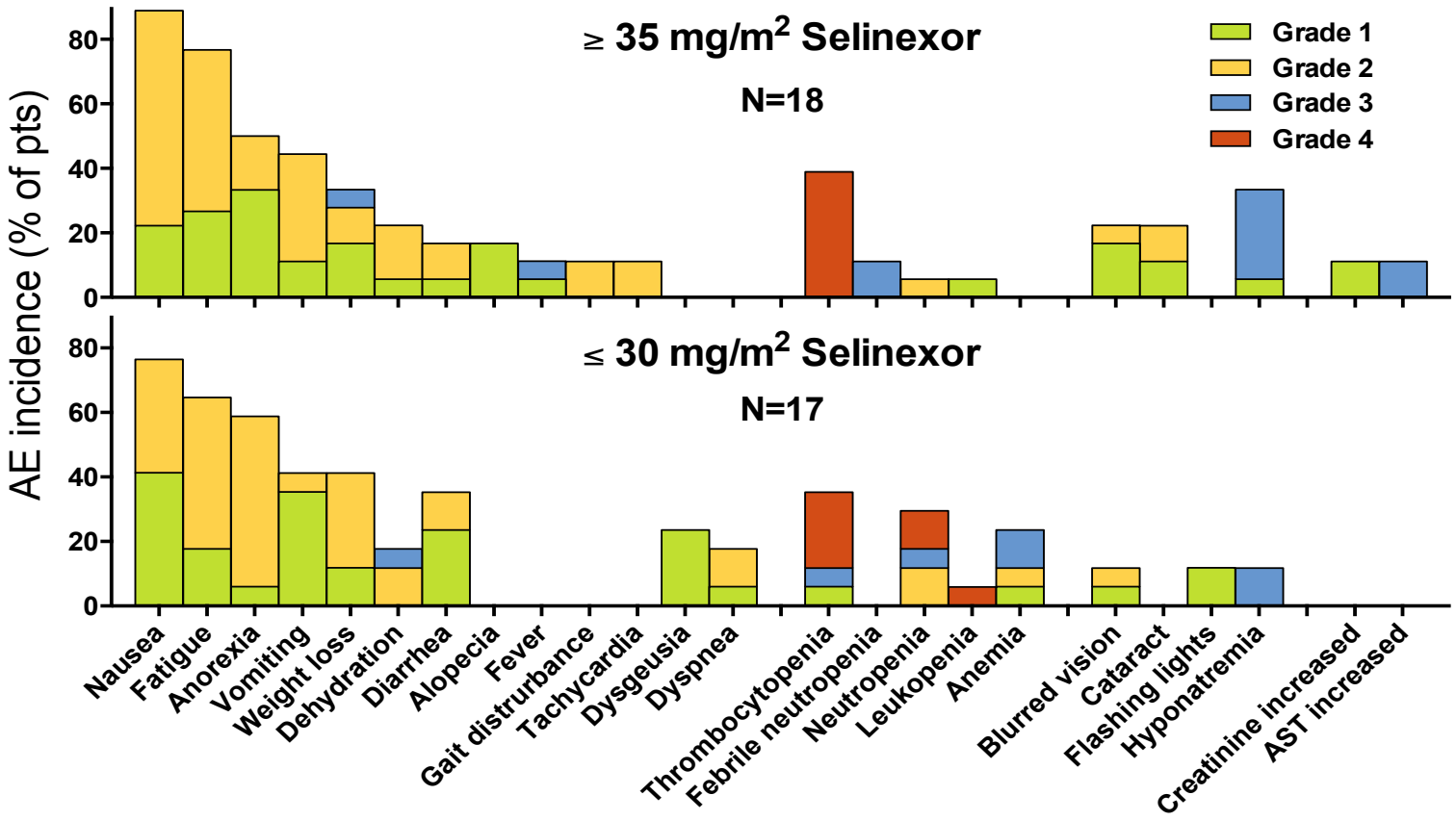
Selinexor-Related Adverse Events Occurring in ≥ 2 pts
All Cycles (28 – 744 Days)



- All patients treated ≥ 35 mg/m^2 selinexor received 8 doses/cycle
- 14 of 17 patients treated ≤ 30 mg/m^2 selinexor received 10 doses/cycle

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Clinical Activity of Selinexor Monotherapy

Best Responses in Evaluable* MM Patients – Oral Selinexor Only (as of 1-December-2014)						
Treatment	**N**	**CBR**	**PR**	**MR**	**SD**	**PD**
Selinexor Low Dose ≤ 30 mg/m^2	15	4 (27%)	--	4 (27%)	8 (53%)	3 (20%)
Selinexor High Dose ≥ 35 mg/m^2	14	3 (21%)	1 (7%)	2 (14%)	8 (57%)	3 (21%)
Total	**29**	**7 (24%)**	**1 (3%)**	**6 (21%)**	**16 (55%)**	**6 (21%)**

Responses were adjudicated according to the *International Myeloma Working Group* criteria
CBR=Clinical Benefit Response (PR+MR), PR=Partial Response, MR=Minor Response,
SD=Stable Disease, PD=Progressive Disease (*Six patients were not evaluable for response)

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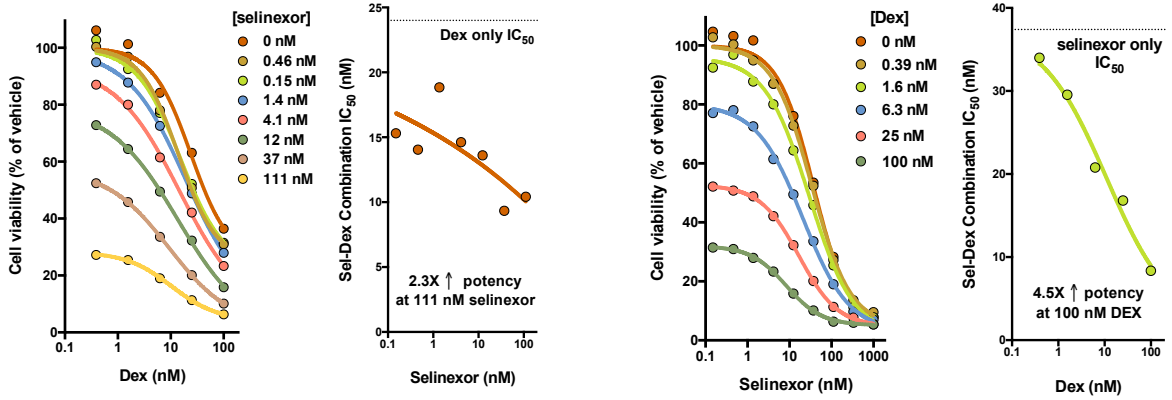
Dexamethasone Synergistically Enhances Selinexor Anti-MM Effects

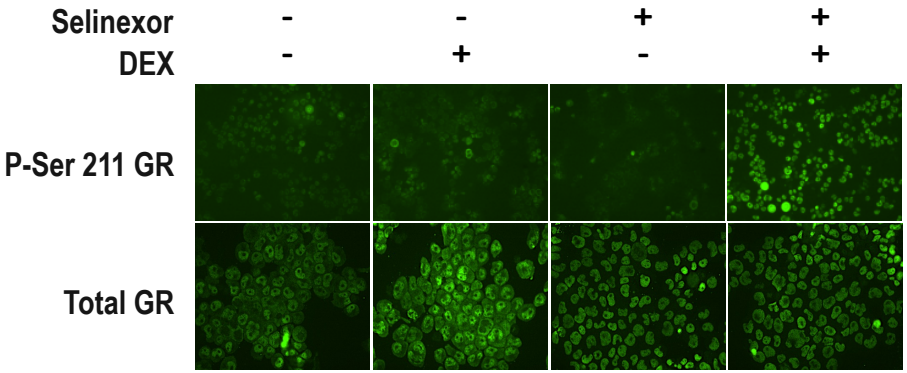
A



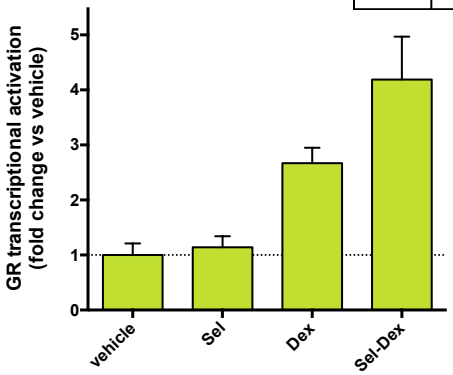
B

Cell line		MM1.S	MM1.R
Sel IC_{50} (nM)	alone	37.4	30.0
	+ 100 nM Dex	8.4	40.2
Dex IC_{50} (nM)	alone	24.0	>>100
	+ 111-120 nM Sel	10.4	>>100

C



D



(**A**) **Sel-Dex synergistic cytotoxicity:** MM1.S cells were incubated with selinexor or Dex alone or in combination for 72 hr. Resulting cell viability was determined using an MTT-based assay (CellTiter 96®/Promega). (**B**) **Dex sensitivity is not essential for selinexor sensitivity:** Cytotoxic potency of selinexor or Dex alone or in combination in Dex-sensitive (MM1.S) vs Dex-resistant (MM1.R) MM cells. (**C**) **Sel-Dex synergistic nuclear retention of activated nuclear GR:** MM1.S cells were treated with selinexor, Dex or Sel-Dex, fixed and stained for P-Ser211-GR* or total GR** (*4 nM selinexor ± 25 nM DEX for 24 hr; **1 µM selinexor ± 100 nM Dex for 4 hr). (**D**) **Sel-Dex synergistic GR transcriptional activation:** MM1.S cells were treated with 1 µM selinexor ± 100 nM DEX for 4 hr and GR binding to GR promoters was quantified in nuclear extracts using GR ELISA Kit /Affymetrix ($p<0.001$ for all pairs except Sel vs vehicle)

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Selinexor + Dexamethasone Combination (Sel-Dex) Study Design

- **Selinexor + Dexamethasone (Dex) Study Design**
  - Planned approximately 20 patients to be enrolled at two target dose levels:
    - **Group A:** 45 mg/m^2 selinexor + 20 mg Dex (10 patients)
    - **Group B:** 60 mg/m^2 selinexor + 20 mg Dex (11 patients)
- **Dose Evaluation**
  - Determine the safety & most tolerable dose of selinexor in combination with Dex
    - During the dose evaluation part of the study, 60 mg/m^2 was deemed intolerable (see next column AEs) Analysis below is based upon **Group A** patients treated with selinexor 45 mg/m^2 plus 20 mg Dex

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Patient Characteristics: Selinexor + Dexamethasone Combination

Characteristic	N
Patients Enrolled (**Group A**, **Group B**)	10 pts 45 mg/m^2, 11 pts 60 mg/m^2
Median Age (Range)	63 (43 – 75)
ECOG PS 0 : 1 : 2	5 : 15 : 1
Male : Female	12 Males : 9 Females
Median Prior Treatment Regiments (Range)	8 (2 – 16)

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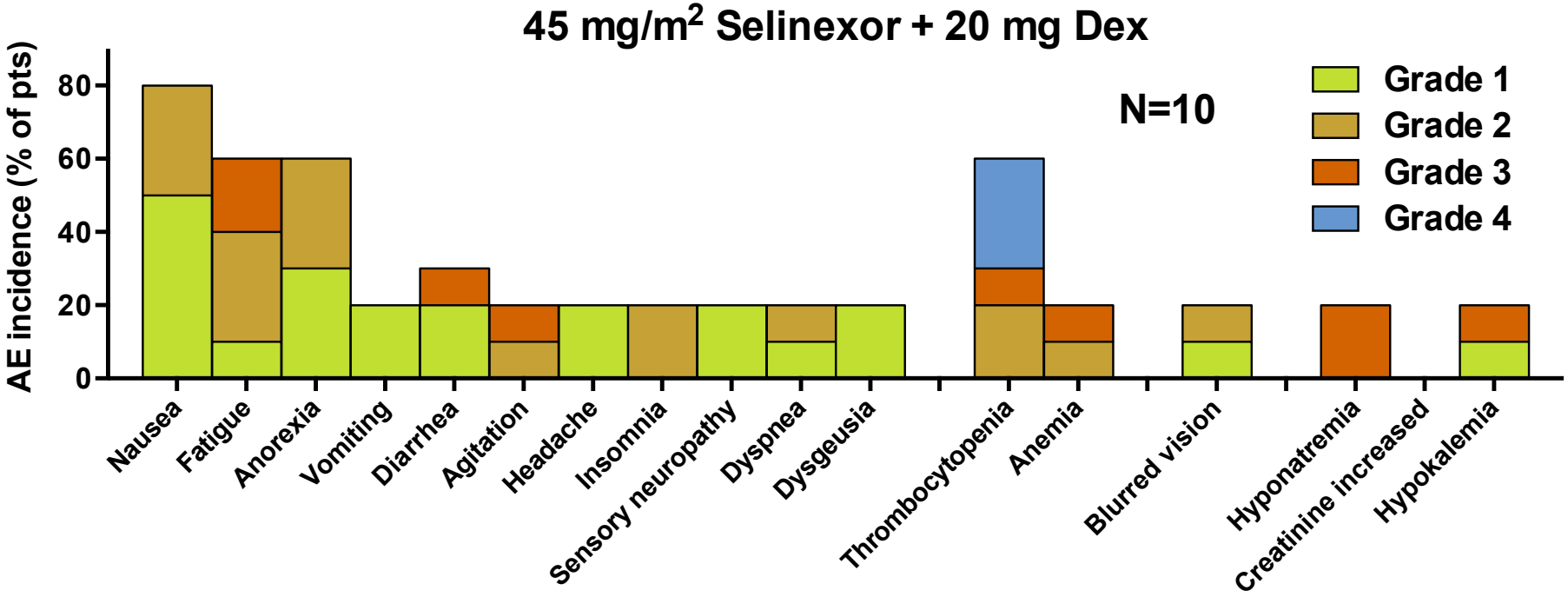
Sel (45 mg/m^2)-Dex Related Adverse Events in ≥ 2 pts Group A



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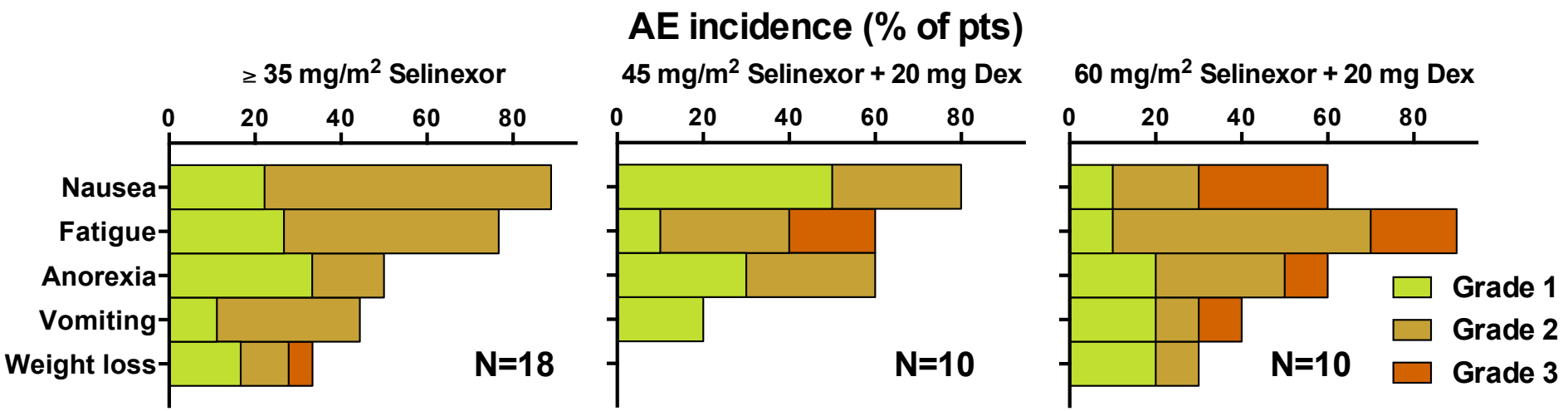
Common Related Adverse Events in ≥ 2 pts



A comparison of common AE's for patients treated on selinexor alone ≥ 35 mg/m^2, Sel(45)-Dex, Sel(60)-Dex is shown above. Sel(45)-Dex shows reduction in nausea grades and very little weight loss compared with selinexor alone. AE analysis of **Group B** patients at 60 mg/m^2 was not feasible as only 3 out of the 11 patients received **≥ 7** doses of selinexor at 60 mg/m^2 in Cycle 1 (1 MR, 2 SD). Although no formal DLT was observed, higher grade toxicities were shown as compared to selinexor alone and Sel(45)-Dex. The Sel(60)-Dex high dose combination was very poorly tolerated and none of the patients continued on twice weekly selinexor 60 mg/m^2 in Cycle 2. Therefore, Sel(60)-Dex represents an intolerable dose. The MTD/RP2D of Sel-Dex is 45 mg/m^2 + 20 mg Dex, twice weekly.

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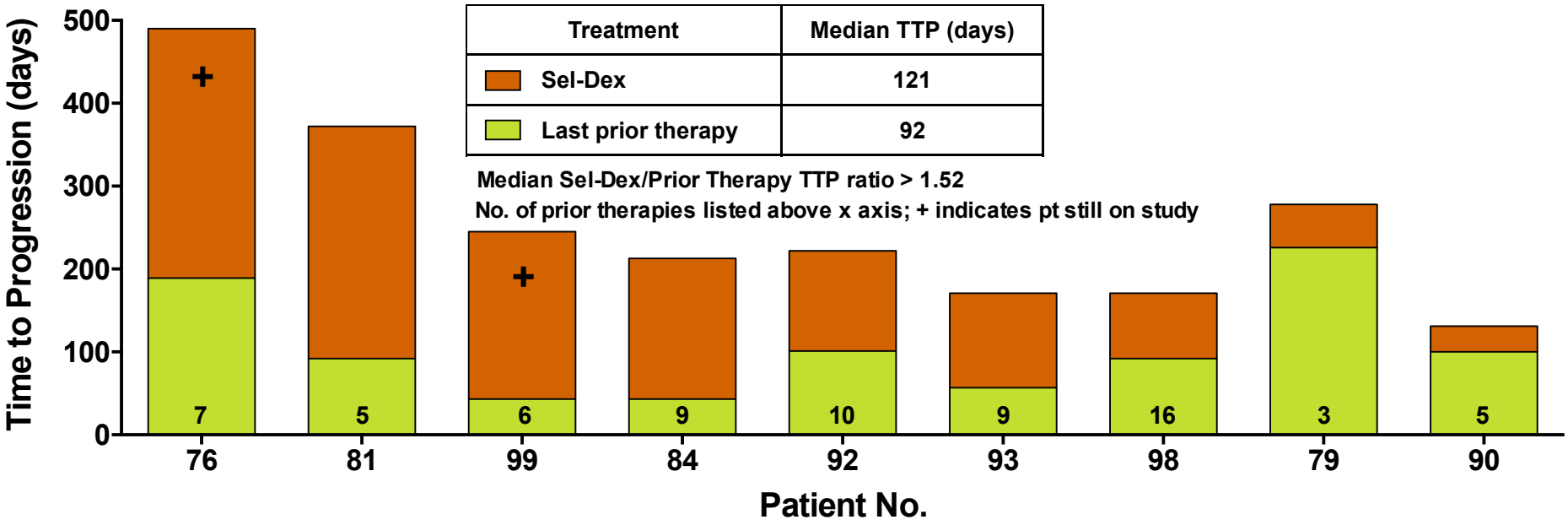
Time to Progression (TTP) on Sel-Dex is Longer than Last Prior Therapy



All patients had MM refractory to most recent therapy including Dexamethasone. Time To Progression on last therapy versus Sel(45)-Dex. As of 1-December-2014

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Prior Treatment Regimens – Group A Patients

(As of 1-December-2014)					Group A Patients with Rel/Ref MM Treated with Twice Weekly Oral Combination – Selinexor 45 mg/m^2 + Dexamethasone 20 mg	
Patient ID	MM Type	Maximal Δ	Response	# Prior Tx	Prior Therapies	Study Days
76	IgG-κ	–71%	PR	7	Dox-Vinc-Dex, TD-Dex, Carfil-Dex, VRD, Cyclo-Pred-BCNU, Doxil-Carfil-Dex	301+
77	FLC-λ	--	NE	8	Len-Dex, Cyclo-Etop-Cis-Mel-Dex-ASCT, VRD, Carfil-Cyclo-Dex, Carfil-Cyclo-Dex-Len, Carm-TD-Cis-Etop-Cyta-Vel-Mel, Cyclo-Carfil-Pom-Dex, Vor-Len-Dex	15
79	FLC-κ	–53%	PR	3	TD-Pred-Dex-ASCT, Cyclo-Vel-Dex, Len-Dex	52
81	FLC-κ	–99%	sCR	5	Vinc-Adria-Dex-ASCT, ASCT, Len-Dex, Cyclo-Pred, Pom-Carfil-Dex	280
84	IgG-κ	–84%	PR	9	Vel-Dex, ASCT, Len-Dex, Vel-Dex, Vel, Carfil, Pom-Dex, Carfil, DT-PACE-TD	170
90	IgG-κ	41%	PD	5	Cyclo-Vel-Len-Dex (x2), Carfil-Mel-ASCT, Cyclo-Vel-Dex, Pom-Carfil-Dex	31
92	IgA-κ	–55%	PR	10	Vel-Dex, VRD-ASCT, Len, Reolysin, TG02, Carfil-Dex, Carfil-Cyclo-Dex, Carfil-Pom-Dex	121
93	IgG-κ	–41%	MR	9	VAD, VTD+ASCT, Vel-Len-Dex, Experim, Carfil-Panob, Len-Elotu-Dex, Experim, Pom-Dex, Benda-Pom-Dex	114
98	IgG-λ	–48%	MR	16	Len-Dex, ASCT (x2), Vel-Len-Dex, Vid-Len, Benda-Vel-Dex, VAD, Ritux, Vel-TD, Carfil-Dex, Carfil-Dex-Cis-Adria, Len-Ritux-Inter, Carfil-Pom, Vel-TD-Dex-Adria-Cis-ATRA-Arsenic Trioxide, Len-Dex, TG02-Carfil	79
99	IgA-κ	–82%	PR	6	Sal, TD-Dex, Len, ASCT, Ibrut, Vel-Dex	201+

(+) indicates patient still on study

Prior treatment regimens for patients treated with 45 mg/m^2 selinexor + 20 mg Dexamethasone. Note all patients received combinations including steroids prior to study entry

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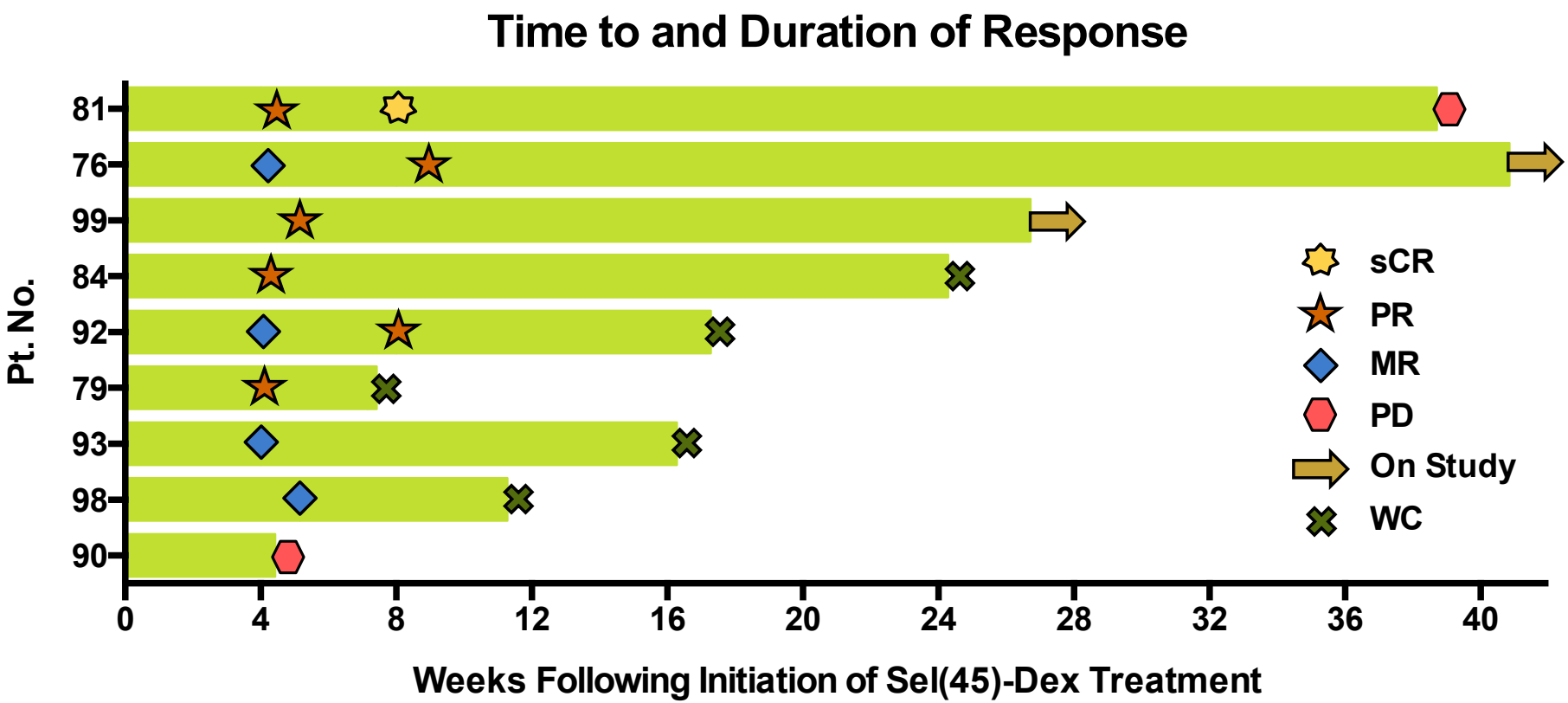
Time to and Duration of Response – Group A Patients



Time to response and duration of response as of 1-December-2014. Median DOR of ~7 months Patients with responses (PR or MR) who withdrew consent (WC) were continuing to respond at WC.

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Clinical Activity

Best Responses in Evaluable (N=9) Group A MM Patients Oral Sel (45 mg/m^2)-Dex (as of 1-Dec-2014)							
Treatment	**N**	**CBR**	**ORR**	**sCR**	**PR**	**MR**	**PD**
Selinexor (45 mg/m^2) + Low Dex (20 mg)	**9**	**8 (89%)**	**6 (67%)**	**1 (11%)**	**5 (55%)**	**2 (22%)**	**1 (11%)**

CBR=Clinical Benefit Response (sCR+PR+MR), ORR=Overall Response Rate (sCR+PR), sCR=Stringent Complete Response, PR=Partial Response, MR=Minor Response, PD=Progressive Disease (*One patient was not evaluable)
Responses were adjudicated according to the *International Myeloma Working Group* criteria

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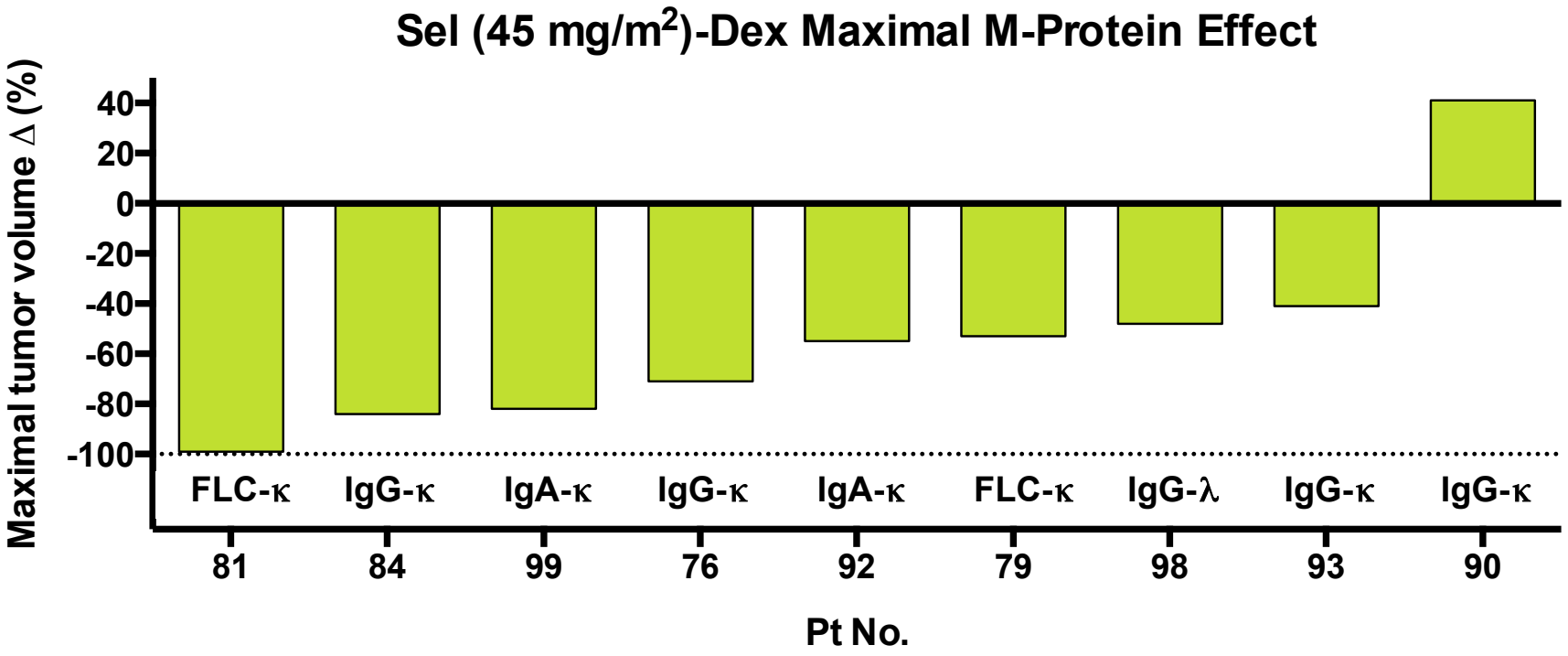
Clinical Activity



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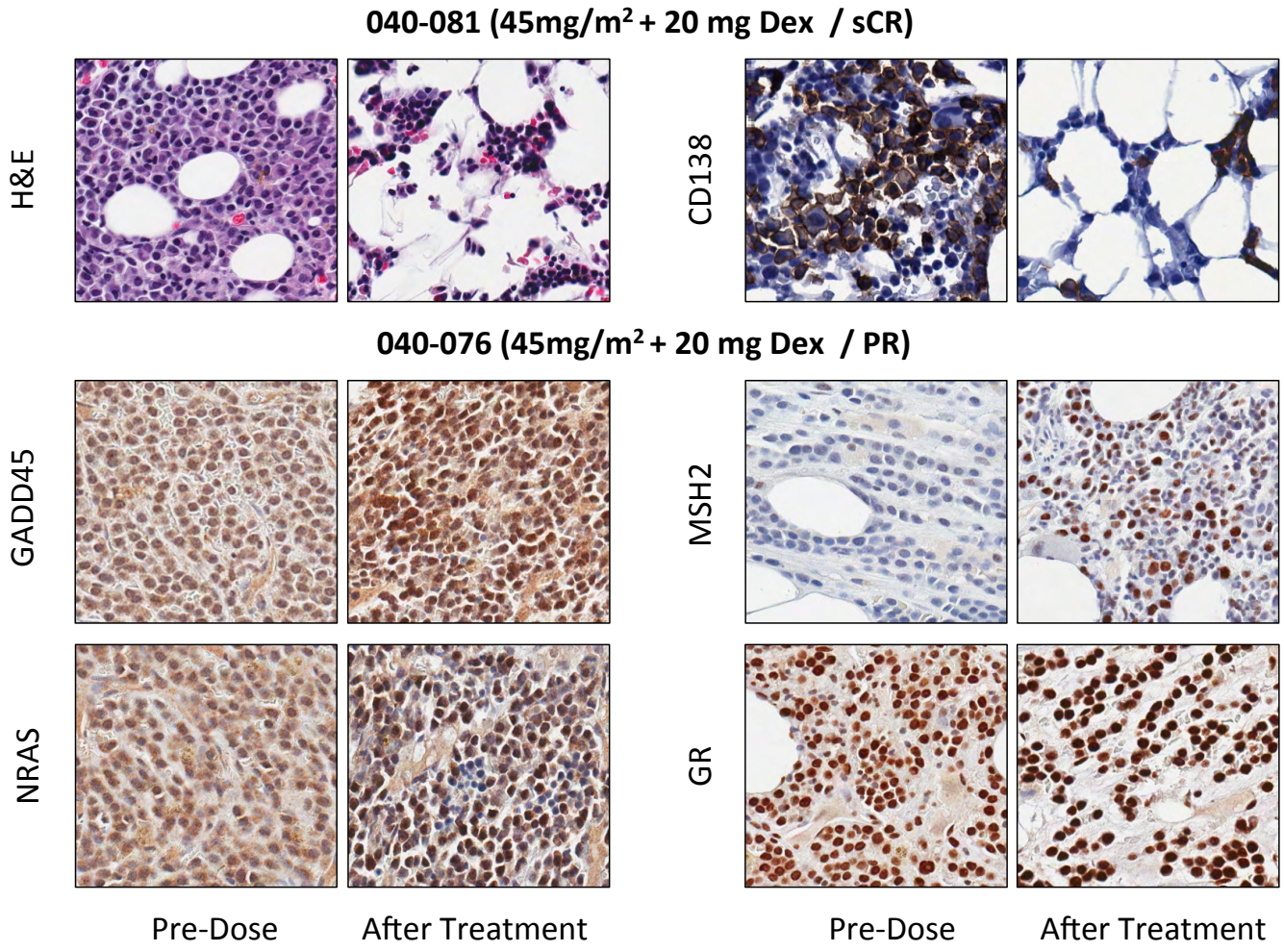
MM Immunohistochemistry



Bone marrow biopsies from two multiple myeloma patients obtained pre-dose and 3-4 weeks post Sel-Dex treatment. Staining included CD138, NRAS (frequently mutated in MM), GR (Dex receptor) and GADD45 and MSH2 (DNA damage induced proteins). Entire sections were imaged using Aperio ScanScope AT Turbo at 20x magnification. Selinexor + Dex reduced CD138^{+} MM, induced GADD45 and MSH2, and increased nuclear GR levels.

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Summary and Conclusions

- XPO1 is overexpressed in MM, resulting in functional inactivation of TSPs and increased levels of oncoproteins such as c-Myc
- XPO1 inhibition by selinexor (KPT-330) leads to nuclear accumulation and activation of TSPs, as well as reduction in c-Myc levels
- Selinexor (oral) shows durable minor responses (MR) and disease stabilization (SD) as a single agent in patients with heavily pretreated MM
- Selinexor causes nuclear retention and activation of the glucocorticoid receptor, with synergistic anti-MM activity in combinations with steroids
- Selinexor 45 mg/m^2 + dexamethasone (Dex) 20 mg, both twice weekly, leads to high rates of durable responses in patients with heavily pretreated refractory MM
- This combination will be taken forward in additional studies, including registration-directed trials, in relapsed and/or refractory MM

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