Penn Medicine

New Therapies for Relapsed Myeloma

Abramson Cancer Center Update in Hematologic Cancers

Dan Vogl, MD MSCE

Assistant Professor of Medicine
Hematology/Oncology Division
Abramson Cancer Center

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the cure is within
ABRAMSON CANCER CENTER

Disclosures

- **Consulting:**
  - Celgene Corporation
  - Millennium/Takeda Pharmaceuticals
  - Karyopharm
  - Teva
  - Janssen
- **Research support:**
  - Millennium/Takeda Pharmaceuticals
  - Acetylon
  - GSK
  - Constellation
  - Calithera

Some of the studies reported in this presentation were presented as an abstract and/or presented at a conference. These data and conclusions should be considered to be preliminary until published in a peer-reviewed journal.

Topics

- **Triplet combinations**
- **Subcutaneous daratumumab**
- **New treatments currently available to you**
  - Venetoclax
  - Nelfinavir
- **New treatments in clinical trials only**
  - Selinexor
  - Eltanexor (KPT-8602)
  - TAK-573

Triplet combinations

Pom/Cyclo/Dex

Dara combinations

RCD vs VCD

Choosing triplets

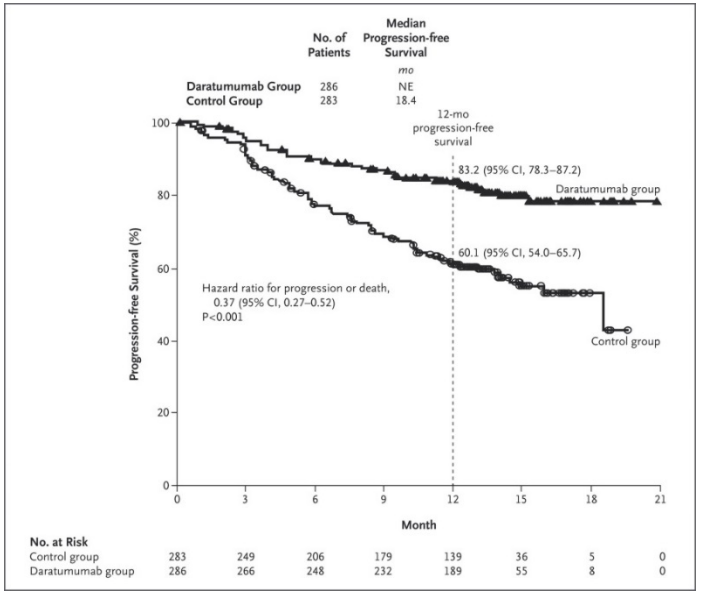
Pom/Cyclo/Dex (IFM 2013-01)

- **Phase II trial in 100 patients relapsing after IFM 2009 (RVD ± ASCT + Len maintenance x1y)**
- **Pomalidomide 4 mg d1-21, Cyclophosphamide 300 mg d1/8/15/22, dexamethasone 40 mg d1-4/15-18**
  - Prior ASCT (50 pts): 9 cycles
  - No Prior ASCT (50 pts): 4 cycles -> ASCT -> 2 cycles
- **ORR 85%, ≥VGPR 34%**
- **Gr 3/4 neutropenia (51%), thrombocytopenia (5%), fatigue (2%)**
- **45/48 evaluable patients w/o prior ASCT proceeded to ASCT**

Gardaret L, et al. ASH 2017. Abstract 837.

Daratumumab combinations

Dara/Len/dex vs Len/dex



	DRd (n = 286)	Rd (n = 283)	HR (95% CI)	*P* Value
Median PFS, mos	NR	17.5	0.44 (0.34-0.55)	< .0001
KM estimated 30-mo PFS, %	58	35	--	--

Dimopoulos MA et al. N Engl J Med 2016;375:1319-1331.

Dimopoulos MA, et al. ASH 2017. Abstract 739.

POLLUX Extended Follow-up: Safety

TEAEs, %	All Grades (In ≥ 25% Pts)		Grade 3/4 (In ≥ 5% Pts)	
	DRd (n = 283)	Rd (n = 281)	DRd (n = 283)	Rd (n = 281)
Hematologic				
▪ Neutropenia	62	47	54	41
▪ Febrile neutropenia	6	3	6	3
▪ Anemia	38	41	16	22
▪ Thrombocytopenia	29	31	14	16
▪ Lymphopenia	7	6	6	4
Nonhematologic				
▪ Diarrhea	56	34	7	4
▪ Upper RTI	41	27	1	1
▪ Viral upper RTI	31	19	0	0
▪ Fatigue	38	31	6	4
▪ Cough	34	15	0.4	0
▪ Constipation	31	27	1	0.7
▪ Muscle spasms	29	21	1	1
▪ Nausea	27	18	2	0.7
▪ Pneumonia	24	16	14	10
▪ Hypokalemia	17	11	5	3

- **Discontinued for TEAEs: 13% per arm**
- **Grade 3/4 infections**
  - DRd: 39%
  - Rd: 26%
- **SPMs: 7% per arm**

Dimopoulos MA, et al. ASH 2017. Abstract 739.

Daratumumab combinations

Dara/Btz/dex vs Btz/dex

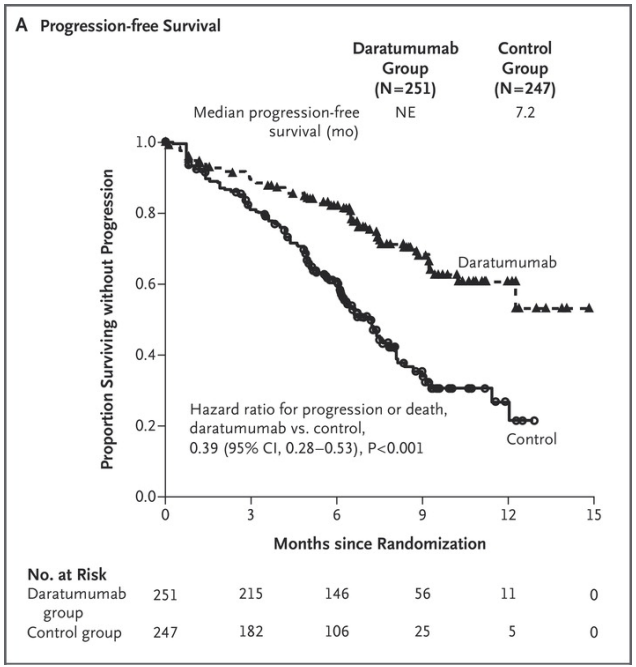


Table 3. Most Common Adverse Events in the Safety Population.*

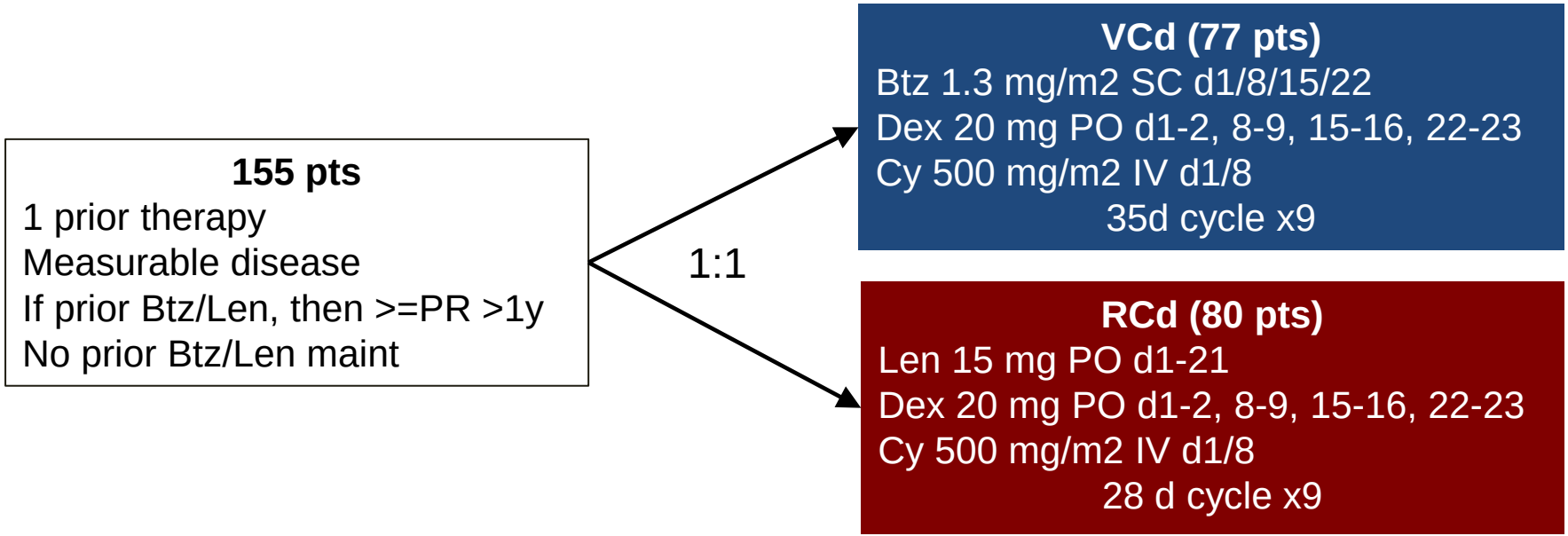
Event	Daratumumab Group (N=243)		Control Group (N=237)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Common hematologic adverse event				
Thrombocytopenia	143 (58.8)	110 (45.3)	104 (43.9)	78 (32.9)
Anemia	64 (26.3)	35 (14.4)	74 (31.2)	38 (16.0)
Neutropenia	43 (17.7)	31 (12.8)	22 (9.3)	10 (4.2)
Lymphopenia	32 (13.2)	23 (9.5)	9 (3.8)	6 (2.5)
Common nonhematologic adverse events				
Peripheral sensory neuropathy	115 (47.3)	11 (4.5)	89 (37.6)	16 (6.8)
Diarrhea	77 (31.7)	9 (3.7)	53 (22.4)	3 (1.3)
Upper respiratory tract infection	60 (24.7)	4 (1.6)	43 (18.1)	2 (0.8)
Fatigue	52 (21.4)	11 (4.5)	58 (24.5)	8 (3.4)
Cough	58 (23.9)	0	30 (12.7)	0
Constipation	48 (19.8)	0	37 (15.6)	2 (0.8)
Dyspnea	45 (18.5)	9 (3.7)	21 (8.9)	2 (0.8)
Insomnia	41 (16.9)	0	35 (14.8)	3 (1.3)
Peripheral edema	40 (16.5)	1 (0.4)	19 (8.0)	0
Asthenia	21 (8.6)	2 (0.8)	37 (15.6)	5 (2.1)
Pyrexia	38 (15.6)	3 (1.2)	27 (11.4)	3 (1.3)
Pneumonia	29 (11.9)	20 (8.2)	28 (11.8)	23 (9.7)
Hypertension	21 (8.6)	16 (6.6)	8 (3.4)	2 (0.8)
Secondary primary cancer†	6 (2.5)	NA	1 (0.4)	NA

* The safety population included all patients who received at least one dose of trial treatment. Adverse events of any grade that were reported in at least 15% of patients in either treatment group and grade 3 or 4 adverse events that were reported in at least 5% of patients in either treatment group are listed. NA denotes not applicable.
† The presence of a secondary primary cancer was prespecified in the statistical analysis plan as an adverse event of clinical interest. The other adverse events of clinical interest included infusion-related reactions, infections or infestations, peripheral neuropathies, and cardiac disorders.

Palumbo A et al. N Engl J Med 2016;375:754-766.

RCD vs VCD

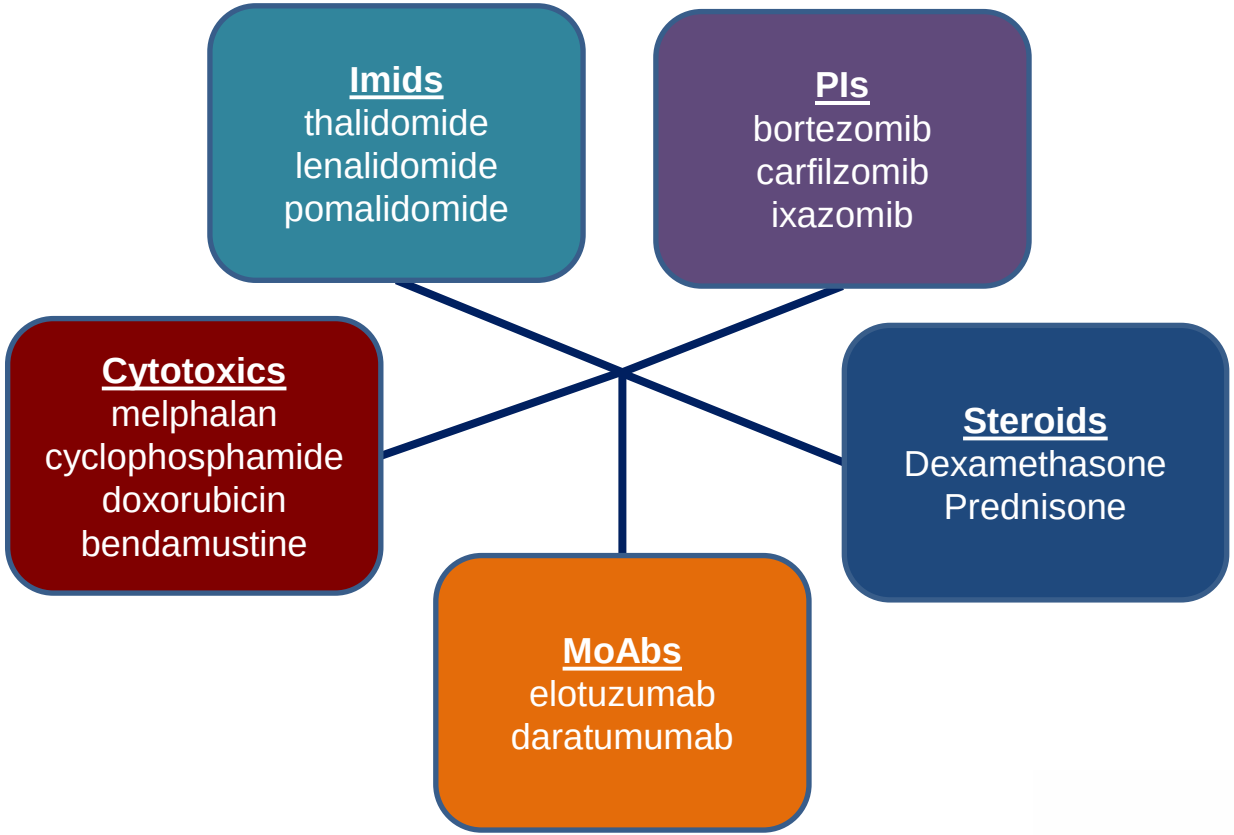
- **Multicenter, open label, phase III study**



RCd vs VCd

- **Primary endpoint: ≥VGPR at 6 weeks after 9 courses**
  - 12 (16%) and 16 (20%) pts in VCD and RCD, respectively (p=0.70).
- **Median PFS: 16.3 (VCD) and 20.2 (RCD) months (p=0.70)**
- **Median OS: 31.1 (VCD) and 36.2 (RCD) months (p=0.83)**
- **Grade III and IV toxicities not significantly different**

Choosing triplets for relapsed myeloma



Choosing triplets for relapsed myeloma

- **Limited data comparing triplets or sequencing**
- **General principles**
  - Most patients should receive triplets
  - Carefully assess treatment history
    - What worked?
    - What caused side effects?
  - Consider pace of progression and symptom burden
  - Include cost and convenience in the decision
- **My favorite triplets**
  - Any proteasome inhibitor / Imid combination
  - Daratumumab combinations
  - Cyclophosphamide / proteasome inhibitor combinations

Subcutaneous daratumumab

Subcutaneous Daratumumab (PAVO Phase Ib)

- **Co-formulation with recombinant human hyaluronidase (rHuPH20) allows SC administration with higher daratumumab concentration, lower injection volume, shorter injection time**

Group 1: DARA-MD
Daratumumab 1200 mg SC +
rHuPH20 30,000 U SC
via syringe pump x 20 min
(n = 8)

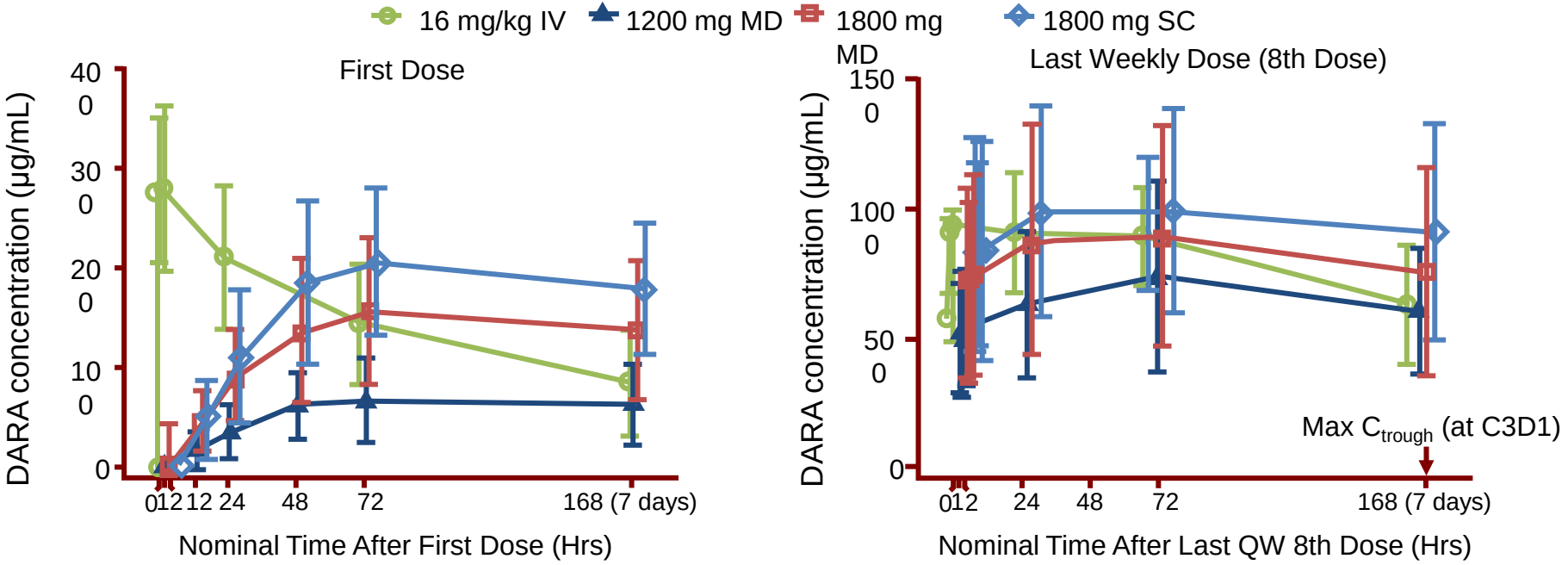
Group 2: DARA-MD
Daratumumab 1800 mg SC +
rHuPH20 45,000 U SC
via syringe pump x 30 min
(n = 45)

Group 3 DARA-SC:
Daratumumab 1800 mg SC +
rHuPH20 30,000 U SC manually x 3-5 min
(n = 25)

- Pre/postadministration medication includes acetaminophen, diphenhydramine, montelukast, and methylprednisolone

Chari A, et al. ASH 2017. Abstract 838.

PAVO: Daratumumab Serum Concentration



- **SC administration results in slower systemic absorption compared with IV**
- **Maximum C_{trough} is similar or higher following 1800 mg SC compared with 16 mg/kg IV**

Chari A, et al. ASH 2017. Abstract 838.

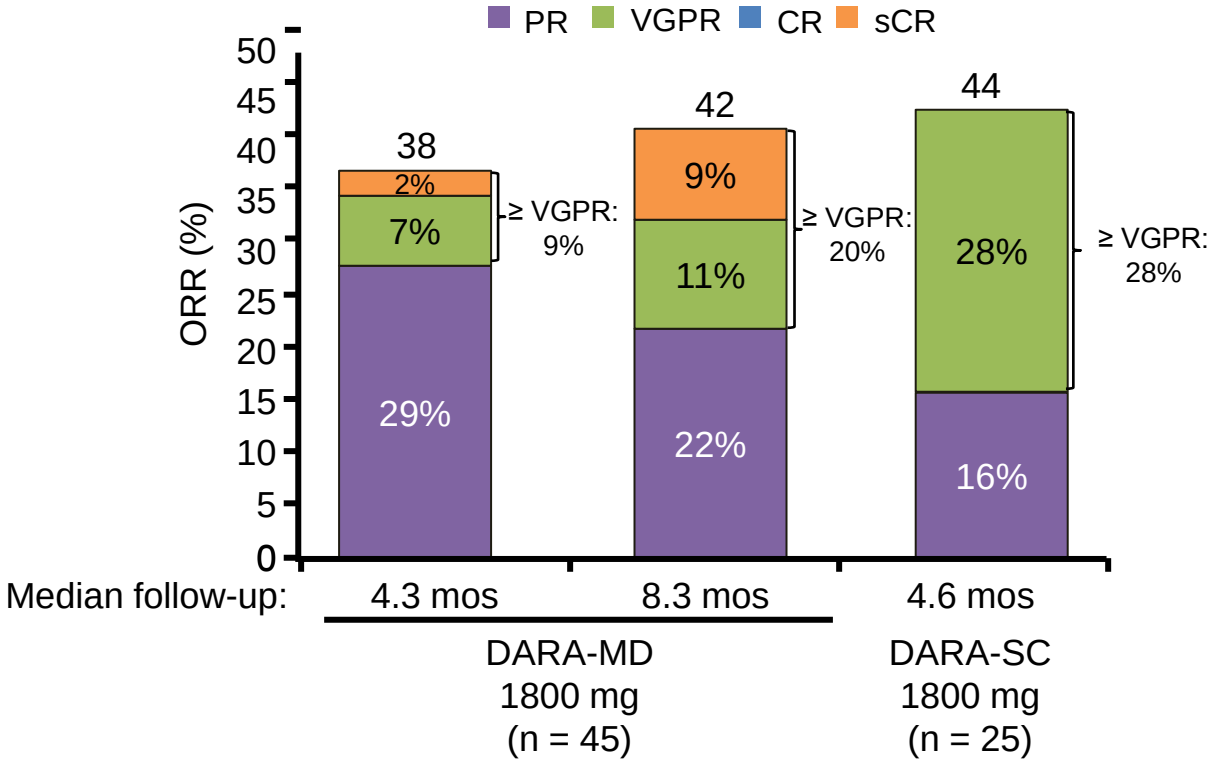
SC Daratumumab: Injection-Related Reactions

Reaction, n (%)	DARA-SC 1800 mg in 15 mL/3-5 min (n = 25)
Pt-reported IRR	All at first injection (within 6 h)
▪ Pt 1	Grade 3 hypertension, grade 2 chills, grade 2 dyspnea
▪ Pt 2	Grade 1 allergic rhinitis
▪ Pt 3	Grade 1 sneezing
Investigator-reported injection-site TEAEs	
▪ Induration	1 (4)
▪ Erythema	1 (4)
▪ Injection-site discoloration	1 (4)
▪ Hematoma	1(4)
▪ Injection-site measurement of erythema	5 (20)

- **Safety profile similar between SC and historical IV data**
- **Low IRR incidence and severity with DARA-SC**
  - No grade 4 IRRs, discontinuations due to IRRs, or delayed IRRs
- **Few injection-site TEAEs with DARA-SC**
  - Measurable erythema reversible within 1 hr

Chari A, et al. ASH 2017. Abstract 838.b

PAVO: Responses in Dara 1800-mg Groups



- **Deepening responses seen in DARA-MD 1800-mg group**
- **Similar ORR with DARA-MD and DARA-SC**

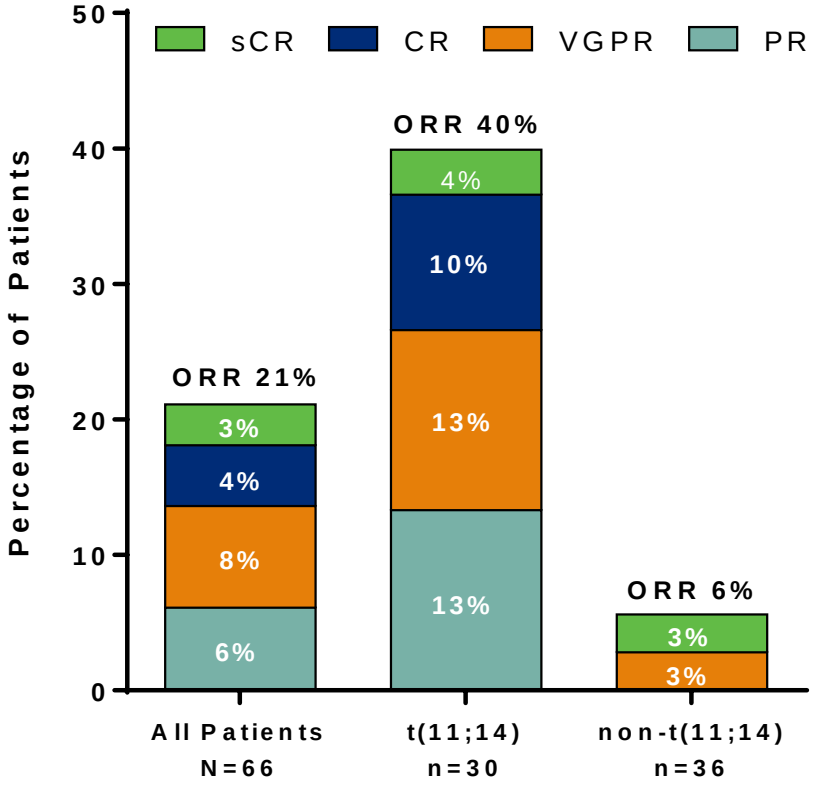
Chari A, et al. ASH 2017. Abstract 838.

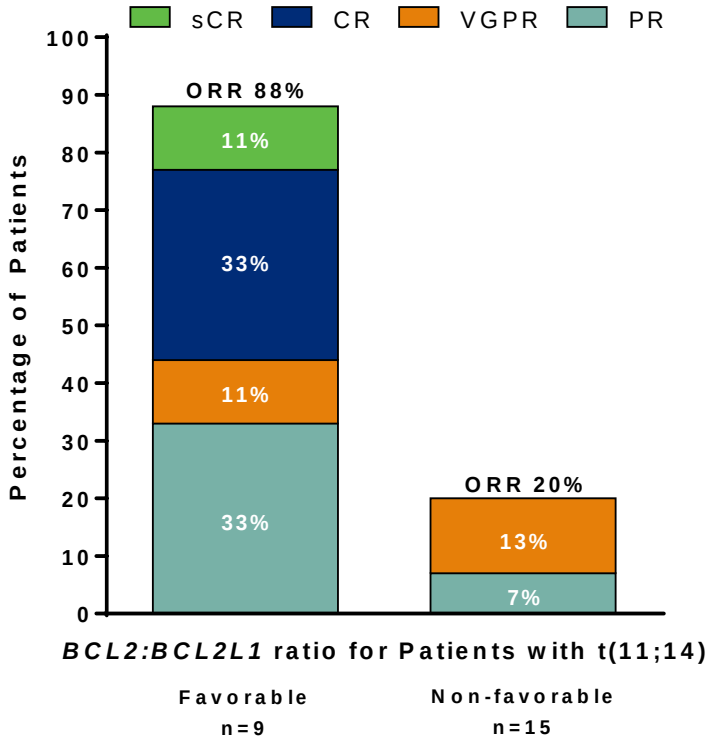
New treatments available now

Venetoclax

Nelfinavir

Venetoclax in t(11;14) myeloma

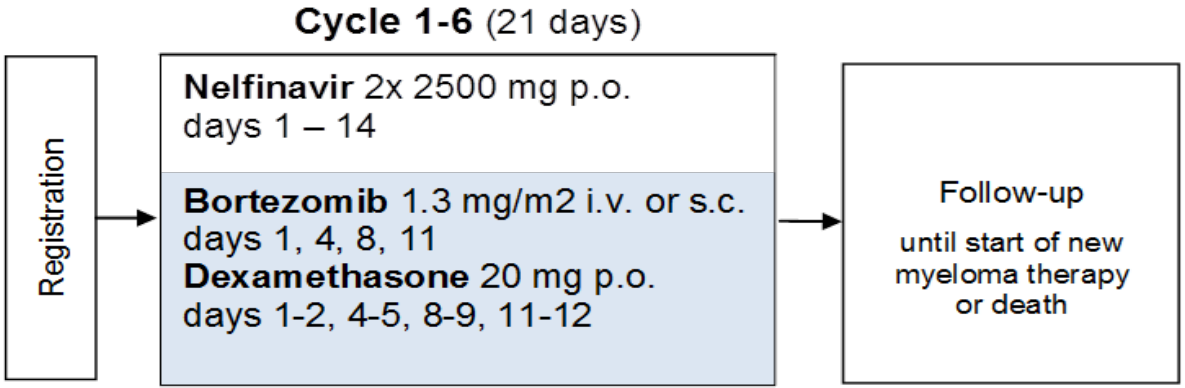




Kumar, ASH 2016, Abstract 488

Nelfinavir with bortezomib/dex

- **Prospective, single-arm, multi-center, open-label phase II**



- IMID-exposed or intolerant
- Refractory to most recent proteasome inhibitor-containing regimen
- **ORR 65%**

Nelfinavir and lenalidomide

- **Pts progressing on or within 60 days after lenalidomide-containing therapy**
- **NFV (1250-2500 mg bid) with lenalidomide 25 mg (d1–21) and dexamethasone 40/20 mg (days 1/8/15/22) for up to 4 cycles**
- **Phase I: 10 pts**
  - 2 DLTs (diarrhea grade 3 and thrombocytopenia grade 4) at 1850 mg bid
  - NFV 1250 mg bid identified as recommended dose for phase II
- **Phase II: 29 pts (including 6 from phase I)**
  - 16 pts (55%) achieved MR or better (10% VGPR, 21% PR, 24% MR)
  - Median duration of response 4 months (95% CI 1.8-5.7)
  - 14/29 pts discontinued trial treatment due to: unacceptable toxicity (4 pts), progressive disease (8 pts), patient refusal (2 pts).
  - Adverse events: grade 1 GI symptoms (9 pts) and metabolic disorders (9 pts), grade >=3 anemia (7 pts), thrombocytopenia (6 pts) and neutropenia (7 pts, including 2 with febrile neutropenia).
- **Pharmacodynamic analysis showed mean overall reduction of proteasome activity of 45% in PBMC at days 8 or 15 compared to baseline.**

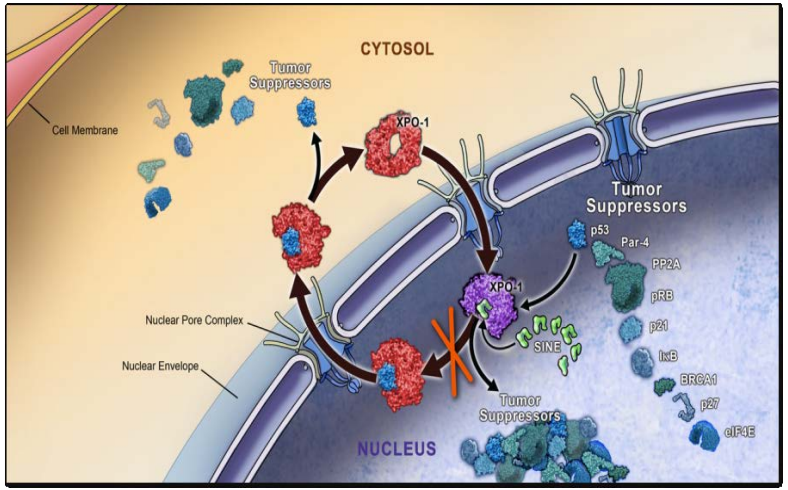
New treatments in trials

Selinexor

Eltanexor (KPT-8602)

TAK-573

Selinexor/dexamethasone



- Exportin 1 (XPO1) is the nuclear exporter for the majority of tumor suppressor proteins (TSPs), the glucocorticoid receptor (GR), and eIF4E-bound oncoprotein mRNAs
- Selinexor is a first-in-class XPO1 inhibitor that induces nuclear retention and activation of TSPs and the GR in the presence of steroids and suppresses oncoprotein expression

- STORM (Selinexor Treatment of Refractory Myeloma):
- Patients with **refractory** MM (*≤ 25% response or PD during or within 60 days)*:
  - To most recent anti-MM regimen
  - To bortezomib, carfilzomib, lenalidomide, and pomalidomide (“***Quad*** refractory”)
    - Subset also refractory to daratumumab or isatuximab (“***Penta*** refractory”)

Vogl, ASH 2016, Abstract 491

Treatment Related Adverse Events ≥10%

AE Term	Grade 1	Grade 2	Grade 3	Grade 4	Total (N=79)
Gastrointestinal					
Nausea	41%	25%	8%	–	**73%**
Anorexia	19%	28%	3%	–	**49%**
Vomiting	30%	10%	4%	–	**44%**
Diarrhea	34%	4%	5%	–	**43%**
Dehydration	1%	8%	3%	–	**11%**
Dysgeusia	6%	5%	--	–	**11%**
Constitutional					
Fatigue	15%	33%	15%	–	**63%**
Weight Loss	19%	13%	1%	–	**33%**
Hematologic					
Thrombocytopenia	6%	8%	25%	34%	**73%**
Anemia	3%	19%	27%	1%	**49%**
Leukopenia	4%	14%	13%	1%	**32%**
Neutropenia	3%	4%	11%	6%	**24%**
Lymphopenia	--	4%	9%	1%	**14%**
Other					
Hyponatremia	20%	–	22%	–	**42%**
CPK Increase	3%	5%	3%	–	**10%**
Dizziness	9%	1%	--	–	**10%**
Fever	6%	3%	1%	–	**10%**

Selinexor Dose Modifications:

- Interruptions:
  41 patients (52%)
- Reductions:
  29 patients (37%)
- Discontinuation:
  14 patients (18%)

Supportive Care:

- Antiemetics
- Appetite stimulants
- Hematopoietic growth factors
- Thrombopoietin receptor agonists
- Salt supplementation

Independent Review Committee (IRC) Assessed Efficacy

Category	N*	ORR (%)	CBR (%)	VGPR (%)	PR (%)	MR (%)	SD (%)	PD (%)	NE (%)
Overall	78	**16 (21%)**	26 (33%)	4 (5%)	12 (15%)	10 (13%)	27 (35%)	9 (12%)	16 (21%)
Quad Refractory	48	**10 (21%)**	14 (29%)	2 (4%)	8 (17%)	4 (8%)	21 (44%)	4 (8%)	9 (19%)
Penta Refractory	30	**6 (20%)**	12 (40%)	2 (7%)	4 (13%)	6 (20%)	6 (20%)	5 (17%)	7 (23%)
6 Doses / Month	51	**10 (20%)**	15 (29%)	3 (6%)	7 (14%)	5 (10%)	21 (41%)	4 (8%)	11 (22%)
8 Doses / Month	27	**6 (22%)**	11 (41%)	1 (4%)	5 (19%)	5 (19%)	6 (22%)	5 (19%)	5 (19%)

*1 patient did not have measurable disease at baseline

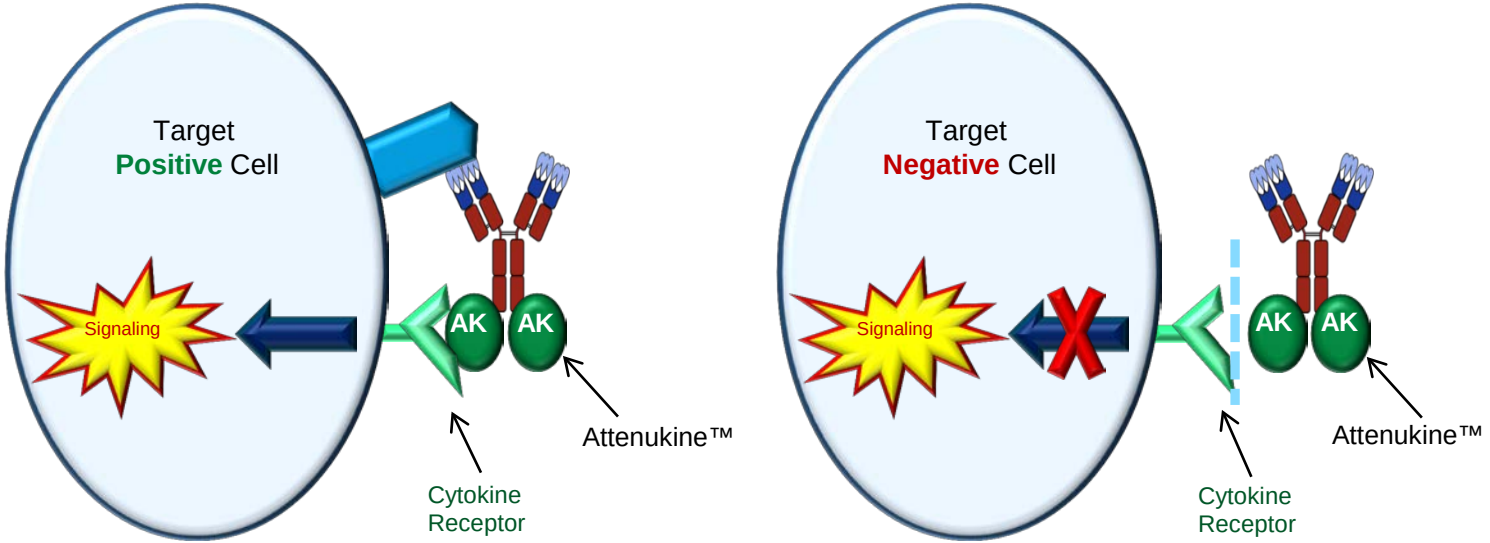
KPT8602 (eltanexor) and dexamethasone

- 39 pts, ≥3 prior therapies, refractory to most recent regimen
- Treatment:
  - Escalating doses as single agent from 5 to 40 mg daily x5/7
  - Combined at 20 or 30 mg with dexamethasone 20 mg twice weekly
- Only 1 protocol-defined DLT at 40 mg, but decreased appetite and weight loss more frequently observed at ≥ 30 mg
- Most common Grade 3/4 AEs: thrombocytopenia, neutropenia, and anemia. Nausea, fatigue, diarrhea, and vomiting mostly Grade 1.

- ORR 21%
  - 36% at 20 or 30 mg in combination with dexamethasone

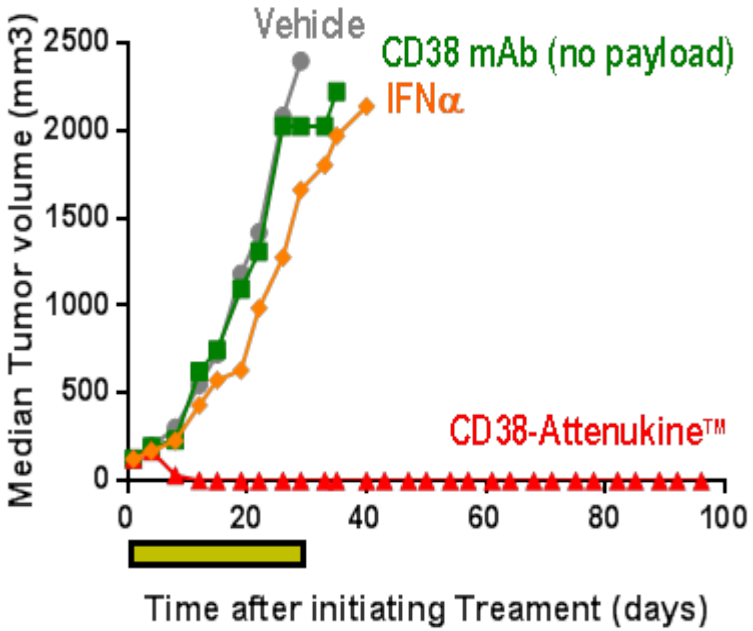
TAK573 in myeloma

- **First-in-human, phase 1 trial**
- **Anti-CD38 / attenuated interferon fusion protein**



TAK573 in myeloma

H929 Human Myeloma in Mouse Xenograft



Summary

- **Most patients should receive triplet combinations**
  - Daratumumab
  - PI/Imid
  - Cyclophosphamide/PI
- **Subcutaneous daratumumab is coming**
- **Off-label approved agents may be reasonable:**
  - Venetoclax alone [in t(11;14)] or with bortezomib [all patients]
  - Nelfinavir with bortezomib or lenalidomide
- **New agents are promising**
  - XPO1 inhibitors (selinexor, eltanexor) with dexamethasone
  - TAK-573 (anti-CD38 / attenuated interferon)
  - Immunotherapy

Trials at Penn

- **Myeloma, relapsed/refractory**
  - Phase 2 venetoclax with carfilzomib and dexamethasone

  - Phase 2 selinexor (SINE / XPO1 inhibitor)
  - Phase 1 TAK-573 (anti-CD38 / attenuated interferon fusion)
  - Phase 1 anti-CD48 antibody drug conjugate

  - Salvage autologous transplant with blinatumomab
  - Phase 1 anti-FcRH5 / CD3 bispecific T cell engager
  - Phase 1 BCMA-directed CAR memory T cells (soon to open)
  - Phase 1 CD38-directed allogeneic CAR T cells
  - Phase 1 NYESO-directed PD1-deleted T cells