



International Myeloma Foundation 800-452-CURE (2873) http://myeloma.org

Heavily Pretreated Multiple Myeloma and Drugs in Development

CASE #5: Carl\*

\*HIPAA-compliant; not actual patient name:

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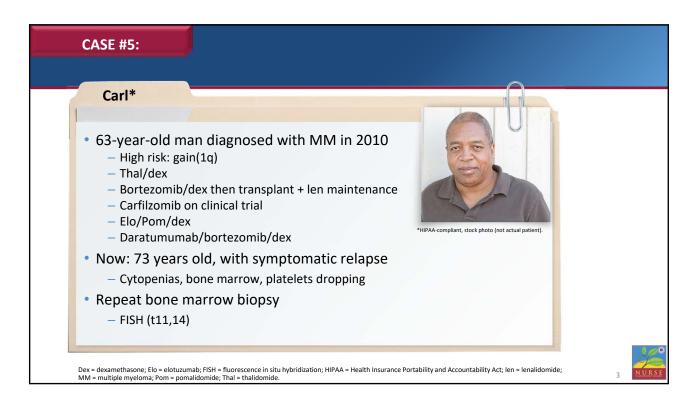


HIPAA = Health Insurance Portability and Accountability Act.

## **Objectives**

- Identify common treatment regimens in heavily pretreated multiple myeloma
- Apply knowledge of nursing management of patients with multiple myeloma, including effective symptom management

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FDA-approved myeloma therapies >2 therapies	Combinations			
Selinexor	Sd			
Panobinostat	PVd			
Cyclophosphamide	KCd, DCEP, VTd-PACE			
Drugs and combinations not previously used, or possibly re-treatment, if patient had good prior response and does not have signs of resistance				
New agents or regimens in clinical trials are always an option				

#### **Selinexor** Oral nuclear export inhibitor: blocks tumor cells from exporting **NEW Drug Class** tumor suppressor proteins → selective apoptosis of tumor cells Selinexor-dex Indication: in combination with dex for the treatment of adult patients FDA approved July 2019 with R/R MM relapsed or refractory multiple myeloma R/R MM who have received at least 4 prior therapies and whose disease is refractory to at least 2 PIs, at least 2 IMiDs, and an anti-CD38 monoclonal antibody (accelerated approval with full approval NEW MOA contingent upon confirmatory trials) CYTOSOL Clinical pearls: patient education, setting expectations are crucial AEs most challenging in first month—significant supportive care up front but decrease for most with time Thrombocytopenia and neutropenia (weekly blood counts in cycle 1) Dose reductions/delays are common in managing AEs Consider/discuss with prescriber starting patients at 80 mg weekly (used at Cleveland Clinic → lower rates of cytopenias) Prophylactic management of nausea and anorexia (start ondansetron day 1; consider adding olanzapine and/or aprepitant) Hyponatremia (salty snacks, oral hydration) Diarrhea (oral hydration) AE = adverse event; dex = dexamethasone; FDA = US Food and Drug Administration; IMiD, immunomodulatory drug; MM = multiple myeloma

MOA = mechanism of action; PI = proteasome inhibitor; R/R = relapsed/refractory.

XPOVIO™ (selinexor) Prescribing Information. Mikhael I, et al. Clin Lymphoma Myeloma Leuk. 2020,20(6):351-357. Beth Faiman. Personal communication



# Selinexor: STORM Part 2 Clinical Trial: 26.2% ORR in Heavily Pretreated Patients With MM

- Patients with MM, with a median of 7 prior treatment regimens
  - ORR of 26.2%
    - 2 patients with sCR
    - 2 patients with previous PD after CAR T-cell therapy achieved PR
  - Median time to response was 1 month (range 1-14 weeks)
- OS: 15.6 months in patients with ≥MR vs
   1.7 months in patients with PD/NE
  - Median OS: 8.6 months for all patients

"The 26.2% ORR ... in the STORM study is highly compelling and reinforces the potential of selinexor in this difficult-to-treat patient population."

		STORM Part 2 (N=123)				
	Dayforn d Town	All	Grade	Grade	AE Leading to Dose	AE leading to
	Preferred Term	Grades	3	220/	Modification	Discontinuation
	Thrombocytopenia	73%	27%	32%	47%	3%
ပ	Concurrent bleeding AE	18%	4%	0	NA	NA
HEMATOLOGIC	Neutropenia	38%	19%	3%	16%	0%
Ē	Febrile neutropenia	2%	2%	0	NA	NA
MA	Anemia	66%	42%	1%	23%	2%
Ξ,	Leukopenia	31%	12%	0	NA	NA
	Lymphopenia	16%	8%	3%	NA	NA
	Fatigue	63%	20%	NA	29%	4%
96	Nausea	70%	10%	NA	19%	6%
10.	Weight decrease	49%	0%	NA	12%	4%
NON-HEMATOLOGIC	Hyponatremia	35%	20%	1%	6%	0
	Decreased appetite	54%	4%	0	8%	2%
o N	Vomiting	37%	3%	0	5%	2%
_	Diarrhea	42%	7%	0	NA	NA

\*25.3 ORR and 1 CR in STORM trial in Prescribing Information.

AE = adverse event; CAR = chimeric antigen receptor; CR = complete response; MM = multiple myeloma; MR = minimal response; NA = not applicable; NE = not evaluable;
ORR = overall response rate; OS = overall survival; PD = progressive disease; sCR = stringent complete response.

XPOVIOT (telinexor) Prescribing Information. Chair A, et al. ASH 2018. Abstr #598. Karyopharm Press Release December 3, 2018. https://investors.karyopharm.com/node/11626/pdf. Accessed June 30, 2020. Mikhael J, et al. Clin lymphoma Myeloma Leuk. 2020. 20(6):531-357.

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#### NEW DATA

### **BOSTON Phase 3 Trial: Selinexor Vd Combination**

#### Design

- 402 patients with MM 1-3 prior therapies
- Patients treated with SVd or Vd

#### Results

	SVd	Vd			
PFS	13.93 mo	9.46 mo	HR=0.70 P =0.0066		
ORR	76.4%	62.3%	P =0.0012		
Most-common treatment-related Grade ≥3 AEs					
Thrombocytopenia	35.9%	15.2%			
Fatigue	11.3%	0.5%			
Nausea	7.7%	0%			

#### **Conclusions**

- Once-weekly SVd significantly improved PFS and ORR compared to twice-weekly Vd
- Rates of PN were significantly reduced, with numerically fewer deaths on SVd vs Vd

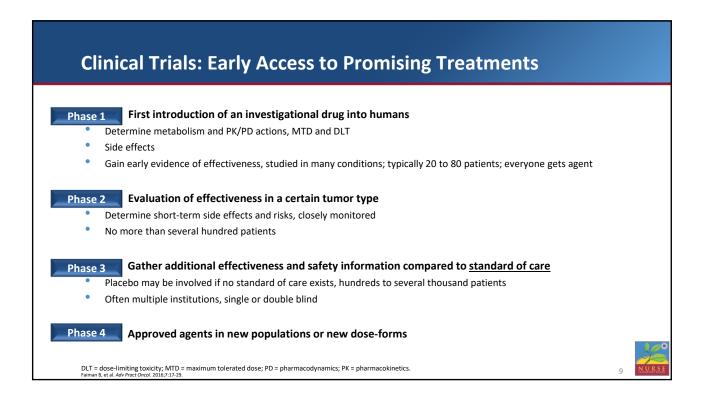
WATCH FOR

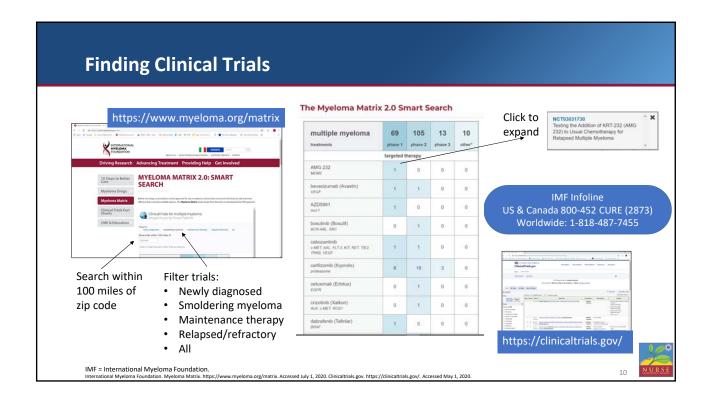
New dosing regimens for selinexor combinations

AE = adverse event; HR = hazard ratio; MM = multiple myeloma; ORR = overall response rate; PN = peripheral neuropathy; PFS = progression-free survival; SVd = selinexor bortezomib dexamethasone; Vd = bortezomib dexamethasone.

Dimpopuls Mk, et al. ASCO 2020. Abstr #801.







## NEW DATA at ASCO 2020

### **BELLINI Phase 3 Clinical Trial: Vd ± Venetoclax**

#### Design

- 291 patients with MM 1-3 prior therapies
- Patients treated with Vd ± venetoclax

#### Results

	Vd + Ven	Vd	
Median PFS	23.22 mo	11.41 mo	HR=0.60; P =0.0013
Median OS	33.5 mo	NR	HR=1.46; P =0.112
ORR	84%	70%	P =0.013
MRD <10 <sup>-5</sup>	15%	4%	P < 0.002
Median DoR	NR	12.8	HR=0.46; P <0.001

• PFS benefit for patients with t(11;14) or high BCL2 expression

#### **Conclusions:**

- Venetoclax + Vd significantly improved PFS, ORR, and MRD vs Vd, but was associated with worse OS
  - Increased deaths attributed to infection
- Favorable risk-benefit of venetoclax for patients with t(11;14) or high BCL2 expression

ASCO = American Society of Clinical Oncologists; BCL2 = B-cell lymphoma 2; DoR = duration of response; HR = hazard ratio; MM = multiple myeloma; MRD = minimal residual disease; NR = not reached; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; Vd = bortezomib dexamethasone; Ven = venetoclax. Kumars, et al. ASCO 2020. Abstr #88509.

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### **Venetoclax Clinical Pearls**

- Venetoclax currently FDA-approved for CLL and AML (off label for MM)
- Deep responses in patients with MM, but increased infections
- Particular efficacy in patients with MM with t(11,14) or high expression of BCL2
- AEs associated with venetoclax in other indications (eg, TLS) may not be similar in patients with MM
- Expanded access program provides free drug if insurance denies coverage for patients with MM
- · Clinical trials are available

New clinical data on venetoclax in patients with MM
 FDA approval

AE = adverse event; AML = acute myeloid leukemia; *BCL2* = B-cell lymphoma 2; CLL = chronic lymphocytic leukemia; FDA = US Food and Drug Administration; MM = multiple myeloma; TLS = tumor lysis syndrome.

Venetata\* (venetoday Prescribing Information. Kumar, § et al. ASCO 2020. Abstr 48509. Falman B. Cleveland Clinic Experience.

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### **CAR T-Cell Treatment: Engineered Patient's Own T Cells**

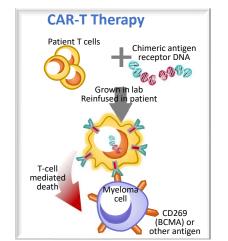
CAR-T example	Target
Orva-cel (JCARH 125)	BCMA
JNJ-4528	BCMA
Idecabtagene vicleucel (Ide-cel; bb2121)	BCMA
LCAR-B38M	CD38
CT053	BCMA
MCARH171	BCMA

#### **Clinical Pearls**

- CAR-T engineers patients own T cells, which takes
   ≈4-6 weeks
  - Must have sufficient blood counts to be eligible
  - Must be able to wait/have bridging therapy for CAR-T to be produced
- Different CAR-T products have different methods and targets; different safety profiles for different products
  - CRS experienced by nearly all patients; mild to severe

BCMA = B-cell maturation antigen; CAR-T = chimeric antigen receptor T cell; CRS = cytokine release syndrome.

Munshi NC, et al. ASCO 2020. Abstr #8503. Mailankody; S, et al. ASCO 2020. Abstr #8504. Berdja JG, et al. ASCO 2020. Abstr #8505. Mailankody S, et al. ASCO 2020. Abstr #8504. Berdja JG, et al. ASCO 2020. Abstr #8505. Mailankody S, et al. ASD 2021. Abstr #8504. Berdja JG, et al. ASD 2021. Abstr #8505. Mailankody S, et al. ASD 2021. Abstr #8504. Berdja JG, et al. ASD 2021. Abstr #8505. Mailankody S, et al. ASD 2021. Abstr #8504. Berdja JG, et al. ASD 2021. Abstr #8505. Mailankody S, et al. ASD 2021. Abstr #8504. Berdja JG, et al. ASD 2021. Abstr #8505. Mailankody S, et al. ASD 2021. Abstr #8504. Berdja JG, et al. ASD 2021. Abstr #8505. Mailankody S, et al. ASD 2021. Abstr #8505. Abstr #8505. Abstr #8505. Abstr #8505. Abstr #8505. Abstr #850





### KarMMa Phase 2 Clinical Trial: Ide-Cel in R/R MM

#### Design

- Idecabtagene vicleucel (ide-cel; bb2121): CAR-T therapy targeting BCMA
- 128 patients with R/R MM treated with
  - ≥3 prior therapies, including PI, IMiD, and anti-CD38 <u>OR</u> refractory to last regimen
  - Median of 6 prior therapies

### Results

- Dose-escalation study
- 73% ORR (31% CR/sCR)
- Median DoR: 10.6 months
- 84% CRS with 5% grade ≥3
- ORR, DoR, and AEs higher at higher doses

ORR=73%
(N=128)

80 - (N=128)

31% CR/sCR

20 - 42% PR

Ide-cel

AE = adverse event; BCMA = B-cell maturation antigen; CAR-T = chimeric antigen receptor T cell; CR = complete response; CRS = cytokine release syndrome; DoR = duration of response; IMID = immunomodulary agent; MM = multiple myeloma; ORR = overall response rate; PI = proteasome inhibitor; PR = partial response; R/R = relapsed/refractory; SCR = stringent complete response.

Multiple (March 2670 2010 Abstruct 2870 301)

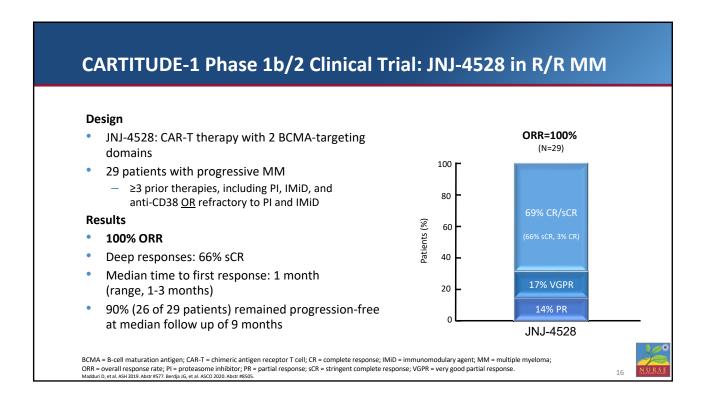
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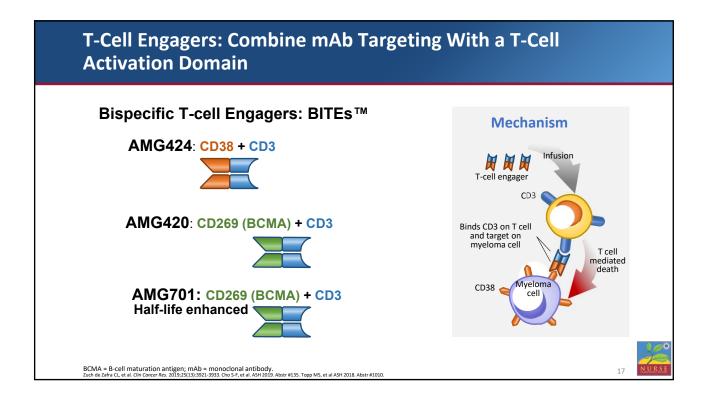
#### **EVOLVE Phase 1/2 Clinical Trial: Orva-Cel in R/R MM** Design Orvacabtagene autoleucel (orva-cel): CAR-T therapy targeting BCMA ORR=91% 100 (N=44) 44 patients with R/R MM ≥3 prior therapies, including PI, IMiD, and anti-CD38 80 Median 6 prior therapies Results Patients (%) 60 91% ORR 40 CRS managed with tocilizumab and/or steroids (78%), **25% VGPR** anakinra (14%), and/or vasopressors (6%) 20 27% PR Median PFS not reached at a median follow-up of 5.9 months Orva-Cel BCMA = B-cell maturation antigen; CAR-T = chimeric antigen receptor T cell; CR = complete response; CRS = cytokine release syndrome; IMiD = immunomodulary agent;

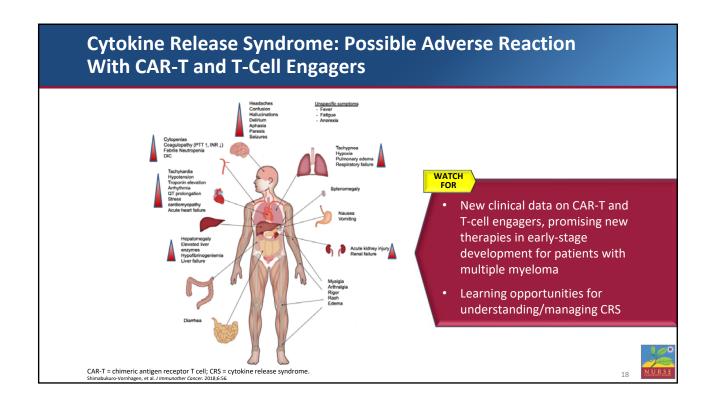
 $MM = multiple\ myeloma; ORR = overall\ response\ rate; PFS = progression-free\ survival; PI = proteasome\ inhibitor; PR = partial\ response; R/R = relapsed/refractory; PR = partial\ response; R/R = relapsed/r$ 

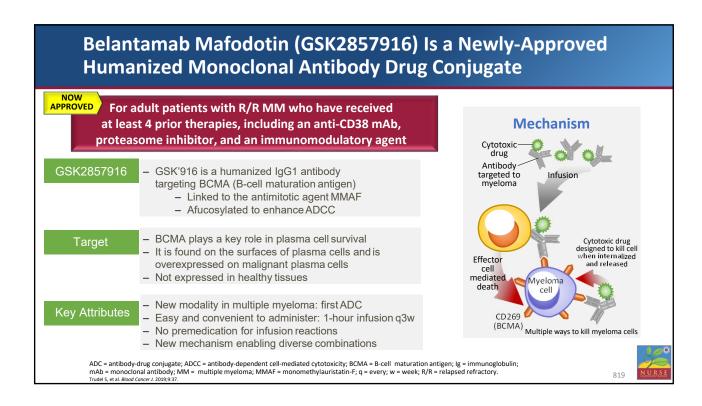
sCR = stringent complete response; VGPR = very good partial response.

Mailankody SM, et al. ASCO 2020. Abstr #8504









# DREAMM-2 Phase 2 Clinical Trial: Belantamab Mafodotin (GSK2857916)

#### Design

196 patients with R/R MM

- Progressive disease
- Refractory to IMiDs and PIs and refractory/intolerant to anti-CD38

	2.5 mg/kg (n=97) (safety population n=95)	3.4 mg/kg (n=99) (safety population n=99)				
ORR	31%	34%				
Most-common Grade 3/4 AEs						
Keratopathy	27%	29%				
Thrombocytopenia	20%	33%				
Anemia	20%	25%				
Any SAE	40%	47%				

**Conclusion:** Single-agent belantamab mafodotin shows antimyeloma activity with a manageable safety profile in patients with R/R MM

#### **Clinical Pearls**

- Convenient dosing: 1-hour infusion q3w
- New mechanism, new AE profile (keratopathy)

## NEW DATA at ASCO 2020

### DREAMM-6 clinical trial

 Combination belantamab + Vd in patients with MM and ≥1 prior therapy line was safe

### WATCH

- FDA approval
- Learning opportunities about this novel antibody-drug conjugate

AE = adverse event; ASCO = American Society of Clinical Oncologists; FDA = US Food and Drug Administration; IMiD = immunomodulary agent; mAb = monoclonal antibody; MM = multiple myeloma; ORR = overall response rate; PI = proteasome inhibitor; q = every; R/R = relapsed/refractory; SAE = serious adverse event; Vd = bortezomib dexamethasone; w = week.

Lonial S, et al. Loncet Oncol. 2020;21(2):207-221. Noola AK, et al. ASCO 2020. Abstr #8502.

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