18TH ULTMANN
CHICAGO LYMPHOMA SYMPOSIUM

THE UNIVERSITY OF CHICAGO
MEDICINE & BIOLOGICAL SCIENCES

18TH INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM

April 30 - May 1, 2021

www.chicagolymphoma.com

Targeted Agents in B-cell Malignancies

Jennifer Santamala, PharmD, BCOP

Clinical Pharmacy Manager, Hematology/Oncology

New York Presbyterian Hospital – Weill Cornell Medical Center

Faculty Disclosures

- No conflicts to disclose

Abbreviations

- R/R: relapsed & refractory
- MM: multiple myeloma
- DLBCL: diffuse large b-cell lymphoma
- NOS: not otherwise specified
- MOA: mechanism of action
- ORR: overall response rate
- DOR: duration of response
- OS: overall survival
- TTP: time to progression
- CR: complete response
- PR: partial response
- PFS: progression free survival

Objectives

- Identify newly approved therapies for B-cell malignancies along with their FDA approved indications
- Explain the mechanism of action of each agent along with the most frequently reported adverse events
- Review dosing recommendations and adjustments required for adverse effects
- Assess recent and ongoing clinical trial data to determine place in therapy

Approvals/Expanded Indications

Generic Name	FDA Approval Date	FDA Approved Indication
Belantamab mafodotin-blmf	August 2020	Adult patients with R/R MM who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent
Tafasitamab-cxix	July 2020	Adult patients with R/R DLBCL NOS, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant (in combination with lenalidomide)
Selinexor	June 2020	R/R DLBCL, NOS, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy
Polatuzumab vedotin	June 2019	R/R DLBCL, not otherwise specified, after at least two prior therapies

https://www.fda.gov/drugs/resources-information-approved-drugs/hematologyoncology-cancer-approvals-safety-notifications. Accessed 03-2021.

LYMPHOMA

Tafasitamab-cxix

Selinexor

Polatuzumab vedotin

Tafasitamab-cxix

Tafasitamab

- **Pharmacologic Category**
  - Anti-CD19 monoclonal antibody

- **FDA approval – July 2020**
  - Treatment of adult patients with R/R DLBCL NOS, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant

Tafasitamab-cxix [package insert]. Morphosys US Inc., July 2020.

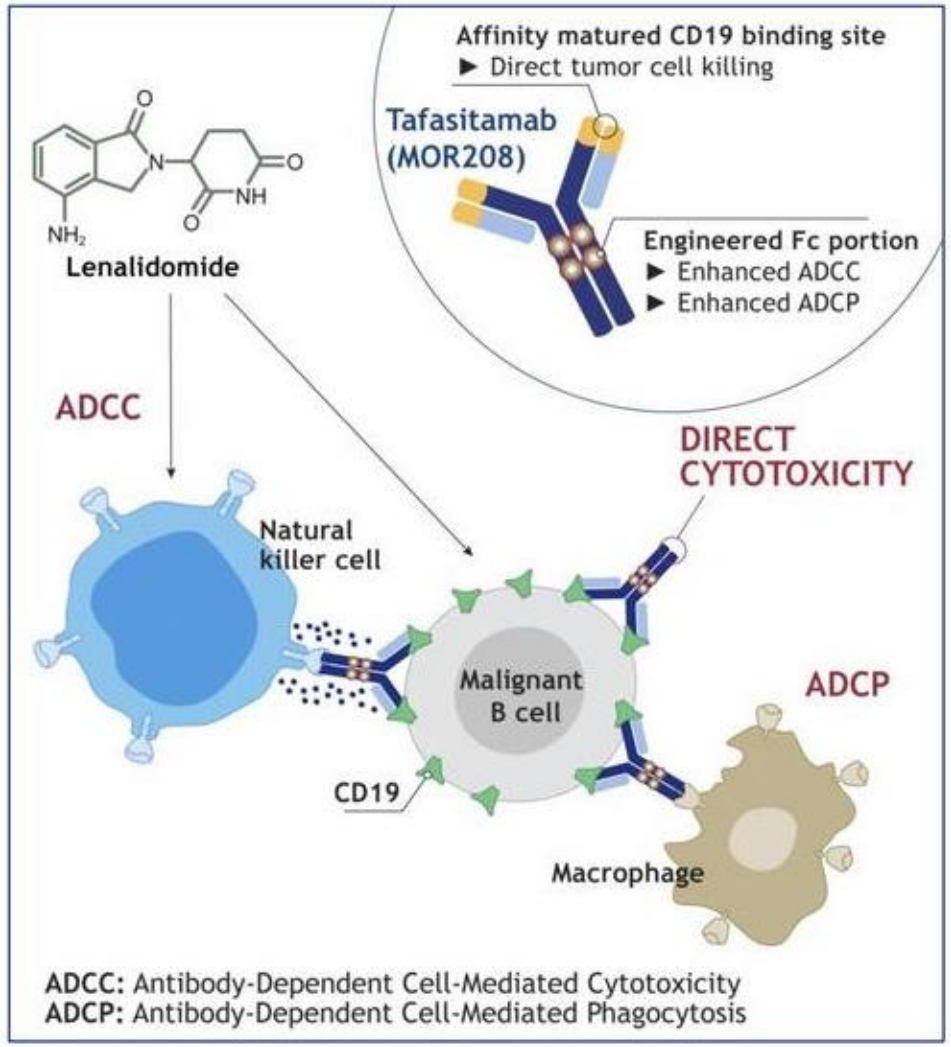
Mechanism of Action

Tafasitamab

- Fc-modified monoclonal antibody that binds to CD19
- Upon binding, mediates lysis through apoptosis and immune effector mechanisms, including ADCC & ADCP

Lenalidomide

- T and NK cell activation/expansion
- Direct cell death



MorphoSys AG, June 2019; Tafasitamab-cxix [package insert]. Morphosys US Inc., July 2020.

Tafasitamab: Dosing and Administration

Each cycle = 28 days

Cycle 1

DAYS	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Tafasitamab 12 mg/kg	■			■				■							■							■						
Lenalidomide 25 mg daily	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●							

Cycles 2 and 3

DAYS	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Tafasitamab 12 mg/kg	■							■							■							■						
Lenalidomide 25 mg daily	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●							

Tafasitamab-cxix [package insert]. Morphosys US Inc., July 2020.

Tafasitamab: Dosing and Administration

Each cycle = 28 days

Cycles 4 to 12

DAYS	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Tafasitamab 12 mg/kg	■														■													
Lenalidomide 25 mg daily	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●							

Cycles 13 and after

DAYS	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Tafasitamab 12 mg/kg	■														■													

Tafasitamab-cxix [package insert]. Morphosys US Inc., July 2020.

Tafasitamab: Infusion Related Reactions

- Administer pre-medications 30 minutes to 2 hours prior to starting therapy
  - May include: acetaminophen, an H1 receptor antagonist, an H2 receptor antagonist, and/or glucocorticoids

- For patients not experiencing infusion-related reactions during the first 3 infusions, premedication is optional for subsequent infusions.

Severity	Dosage Modification
Grade 2 (moderate)	• Interrupt infusion immediately and manage signs and symptoms • Once signs and symptoms resolve or reduce to Grade 1, resume infusion at no more than 50% of the rate at which the reaction occurred. If the patient does not experience further reaction within 1 hour and vital signs are stable, the infusion rate may be increased every 30 minutes as tolerated to rate at which the reaction occurred.
Grade 3 (severe)	• Interrupt infusion immediately and manage signs and symptoms • Once signs and symptoms resolve or reduce to Grade 1, resume infusion at no more than 25% of the rate at which the reaction occurred. If the patient does not experience further reaction within 1 hour and vital signs are stable, the infusion rate may be increased every 30 minutes as tolerated to a maximum of 50% of the rate at which the reaction occurred • If after re-challenge the reaction returns, stop the infusion immediately.
Grade 4 (life-threatening)	• Stop the infusion immediately and permanently discontinue tafasitamab

Tafasitamab-cxix [package insert]. Morphosys US Inc., July 2020.

Tafasitamab: Myelosuppression

Severity	Dosage Modification
Platelet count of ≤50,000	• Withhold tafasitamab and lenalidomide and monitor complete blood count (CBC) weekly until platelet count is ≥50,000/mcL • Resume tafasitamab at the same dose and lenalidomide at a reduced dose (refer to lenalidomide package insert)
ANC ≤1,000 for at least 7 days **ANC ≤1,000 with an increase of body temperature to ≥100.4°F** **ANC <500**	• Interrupt infusion immediately and manage signs and symptoms • Once signs and symptoms resolve or reduce to Grade 1, resume infusion at no more than 25% of the rate at which the reaction occurred. If the patient does not experience further reaction within 1 hour and vital signs are stable, the infusion rate may be increased every 30 minutes as tolerated to a maximum of 50% of the rate at which the reaction occurred • If after re-challenge the reaction returns, stop the infusion immediately.
Grade 4 (life-threatening)	• Stop the infusion immediately and permanently discontinue tafasitamab

Tafasitamab-cxix [package insert]. Morphosys US Inc., July 2020.

Tafasitamab

- **Warnings and precautions**
  - Infusion Related Reactions
  - Myelosuppression
  - Infections
  - Embryo-Fetal Toxicity

- **Common side effects (>20%)**
  - Neutropenia/anemia/thrombocytopenia
  - Fatigue
  - Diarrhea
  - Cough
  - Peripheral edema
  - Respiratory tract infection
  - Decreased appetite

Tafasitamab-cxix [package insert]. Morphosys US Inc., July 2020.

Tafasitamab: L-Mind Study

Multicenter, open-label, single-arm, phase 2 study

Inclusion Criteria:
- Age ≥ 18 years of age
- DLBCL R/R to at least one, but no more than 3 systemic regimens and were not candidates for high-dose chemotherapy and stem cell transplant
- ECOG 0-2
- ANC ≥1.5, plts ≤90
- Tbili <2.5 x ULN
- LFTs ≤5 x ULN in patients with known liver involvement
- CrCl ≥60 ml/min

Exclusion Criteria:
- Double-hit or triple-hit
- Previous treatment with anti-CD19 therapy or immunomodulatory drugs
- Primary refractory DLBCL, defined as no response to, or progression during or within 6 months of frontline therapy; history of malignancies other than diffuse large B-cell lymphoma, unless disease-free for at least 5* years; seropositivity for hepatitis B or C virus, and seropositivity for or history of HIV
- CNS lymphoma involvement

n=71
(each cycle = 28 days)

Tafasitamab 12 mg/kg
Infusion per protocol*

Lenalidomide 25 mg PO daily
Days 1-21 of each cycle

Cycle 1: Days 1, 4, 8, 15 and 22
Cycle 2/3: Days 1, 8, 15 and 22
Cycles 4 +: Days 1 and 15

Primary Endpoints
- Proportion of patients with objective response
- ORR

Secondary Endpoints
- Proportion of patients with disease control
- Time to next treatment
- DOR
- OS
- TTP

Duell, J, et al. Tafasitamab plus lenalidomide in relapsed or refractory DLBCL (L-MIND). *The Lancet* 2020;21(7):978-988.

Tafasitamab: Efficacy in Clinical Trials

Tafasitamab in combination with lenalidomide was well tolerated and resulted in a high proportion of patients with relapsed or refractory diffuse large B-cell lymphoma ineligible for autologous stem-cell transplantation and might represent a new therapeutic option in this setting.

Median time to response = 1.7 months

Endpoint	N=71
CR, n (%) PR, n (%) Stable disease Progressive disease Objective response	34 (43%) 14 (18%) 11 (14%) 13 (16%) 8 (10%)
Median DOR, months (95% CI)	21.7 (21.7 to NR)

Duell, J, et al. Tafasitamab plus lenalidomide in relapsed or refractory DLBCL (L-MIND). *The Lancet* 2020;21(7):978-988.

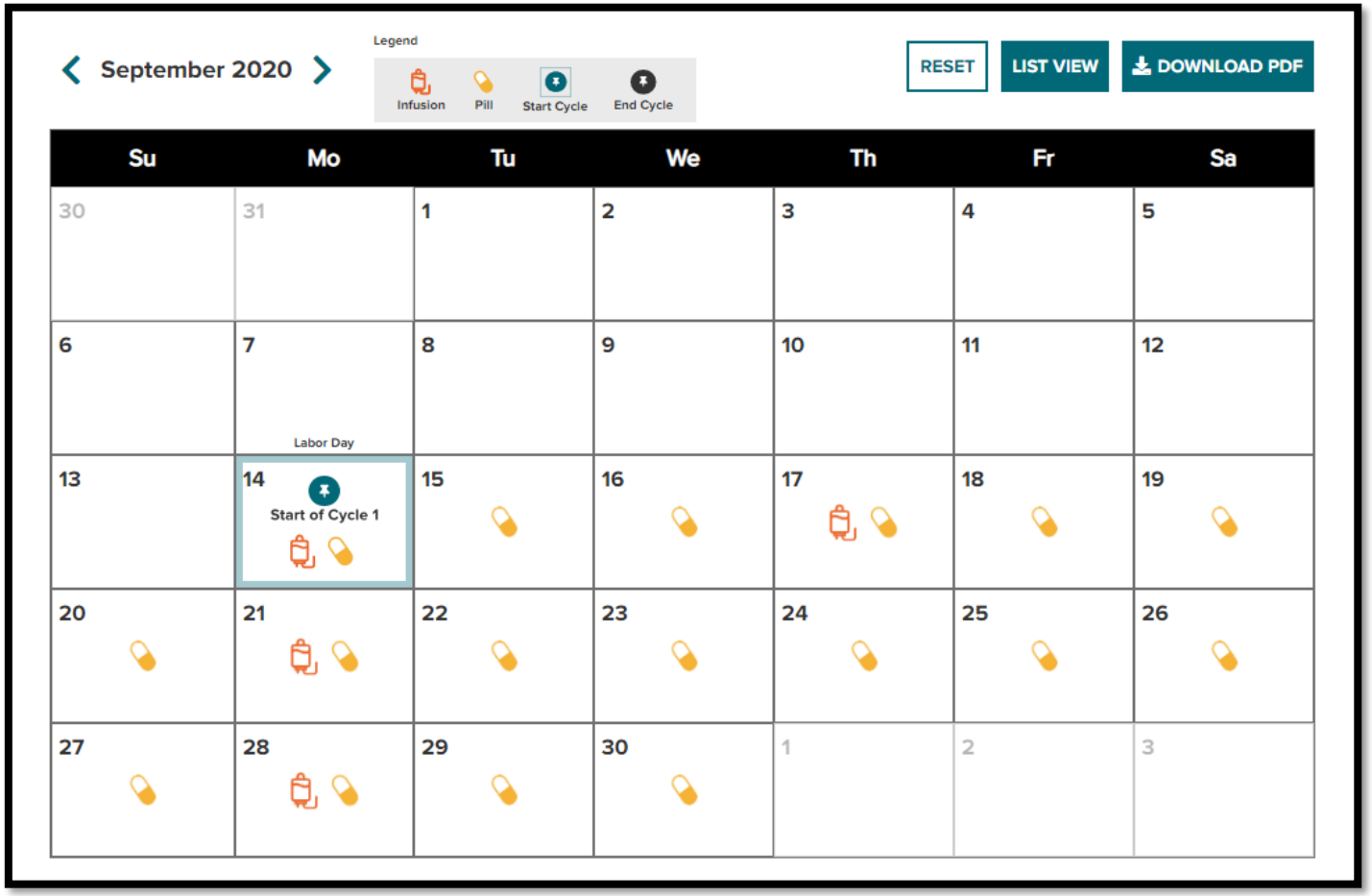
Tafasitamab: Safety in Clinical Trials

Adverse Reaction	Tafasitamab (N=81)	
	All Grades (%)	Grade 3 or 4 (%)
Blood and lymphatic system disorders		
Neutropenia	51	49
Anemia	36	7
Thrombocytopenia	31	17
Febrile neutropenia	12	12
General disorders and administration site conditions		
Fatigue*	38	3.7
Pyrexia	24	1.2
Peripheral edema	24	0
Gastrointestinal disorders		
Diarrhea	36	1.2
Constipation	17	0
Nausea	15	0
Vomiting	15	0
Respiratory, thoracic and mediastinal disorders		
Cough	26	1.2
Dyspnea	12	1.2
Infections		
Respiratory tract infection[+]	24	4.9
Urinary tract infection[†]	17	4.9
Bronchitis	16	1.2
Metabolism and nutrition disorders		
Decreased appetite	22	0
Hypokalemia	19	6
Musculoskeletal and connective tissue disorders		
Back pain	19	2.5
Muscle spasms	15	0

Duell, J, et al. Tafasitamab plus lenalidomide in relapsed or refractory DLBCL (L-MIND). *The Lancet* 2020;21(7):978-988.

Tafasitamab: Clinical Pearls

Complicated dosing schedule – manufacturer website has interactive calendar



https://www.monjuvi.com/patient-support-and-resources

Selinexor

Selinexor

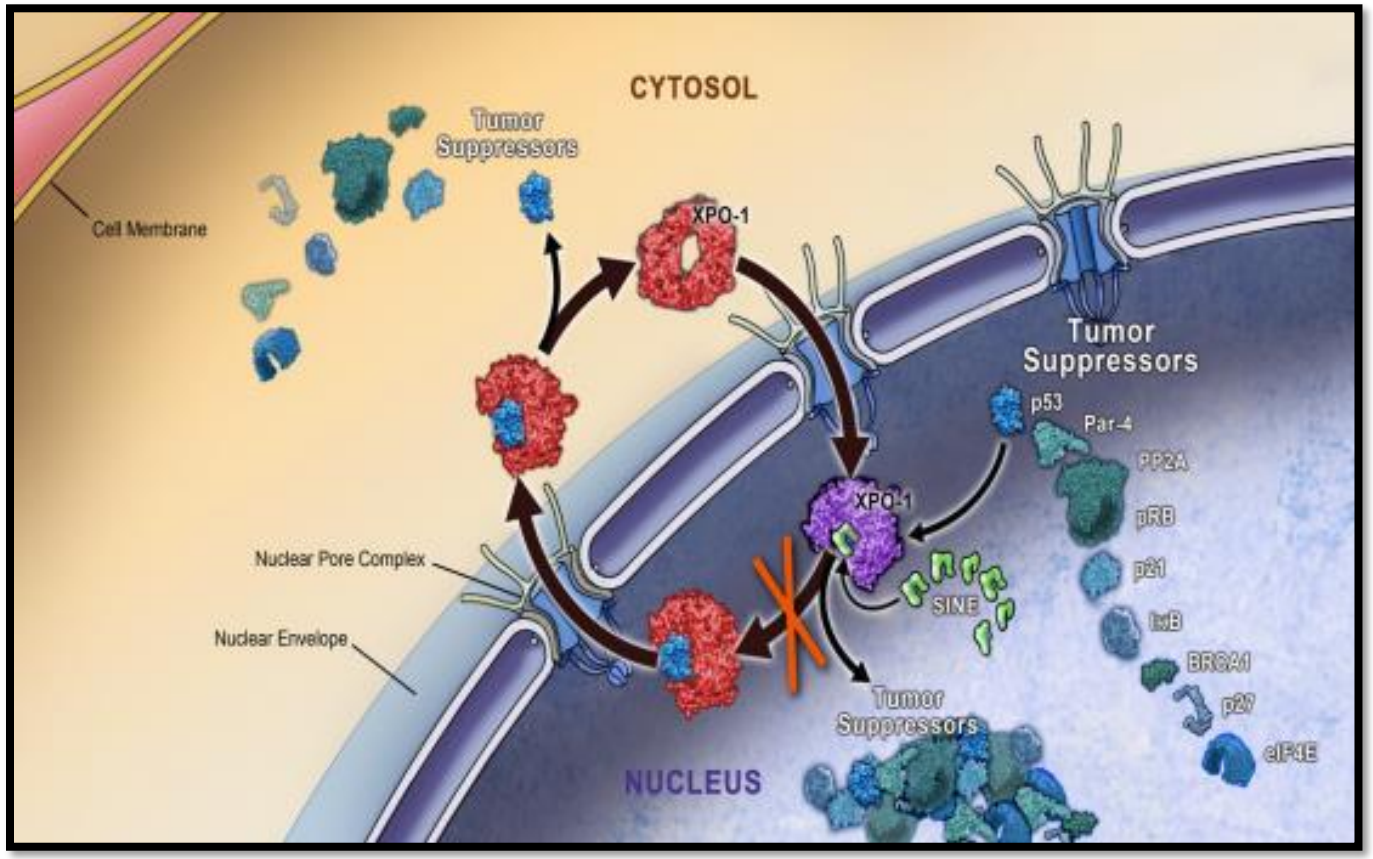
- **Pharmacologic Category**
  - Selective Inhibitor of Nuclear Export (SINE)

- **FDA approval – June 2020**
  - Adult patients with R/R DLBCL NOS after at least 2 lines of therapy

Selinexor [package insert]. Karyopharm Therapeutics Inc., June 2020.

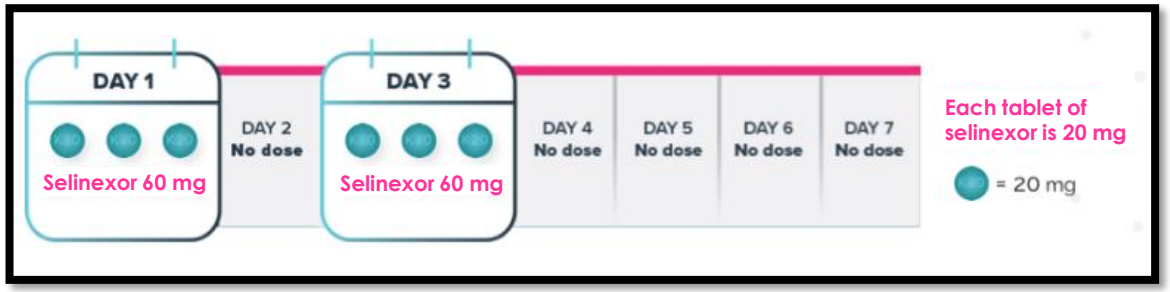
Selinexor: Mechanism of Action

- Selective inhibitor of the transporter XPO1
- XPO1 is responsible for shuttling cargo proteins and messenger RNA between the nucleus and the cytoplasm
- Induces tumor cell apoptosis



Selinexor [package insert]. Karyopharm Therapeutics Inc., June 2020; https://www.karyopharm.com/wp-content/uploads/2019/03/SDD-1.pdf

Selinexor: Dosing and Administration



- **Schedule**
  - Until disease progression or unacceptable toxicity
- **Premedication**
  - 5-HT3 receptor antagonist and/or other anti-nausea agents prior to and during treatment
- **Prophylactic medication**
  - Maintain adequate fluid and caloric intake throughout treatment
  - Consider IV hydration for patients at risk of dehydration
- **Storage considerations**
  - None

Selinexor [package insert]. Karyopharm Therapeutics Inc., June 2020.

Selinexor

- **Dose reduction steps for adverse reactions**
  - Hematologic
    - Thrombocytopenia
    - Neutropenia
    - Anemia
  - Non-hematologic
    - Hyponatremia
    - Fatigue
    - Nausea & vomiting
    - Diarrhea
    - Weight loss & anorexia

Recommended Starting Dose	1st Reduction	2nd Reduction	4th Reduction	Discontinue
60 mg days 1,3 of each week	40 mg days 1,3	60 mg weekly	40 mg weekly	

Selinexor [package insert]. Karyopharm Therapeutics Inc., June 2020.

Selinexor

- **Warnings and precautions**
  - Thrombocytopenia
  - Neutropenia
  - Gastrointestinal Toxicity
  - Hyponatremia
  - Infections
  - Neurological Toxicity

- **Common side effects (>20%)**
  - Thrombocytopenia
  - Fatigue
  - Nausea/vomiting/diarrhea/constipation
  - Decreased appetite
  - Weight loss
  - Dyspnea
  - Upper respiratory tract infections

Selinexor [package insert]. Karyopharm Therapeutics Inc., June 2020.

Selinexor: SADAL Study

Phase 2b, multi-center, single arm, open-label trial

Inclusion criteria
- Age ≥ 18 years of age
- De novo DLBCL or DLBCL transformed lymphoma
- Received 2-5 previous lines of therapy
- ECOG 0-2

Exclusion
- CNS lymphoma
- Meningeal involvement
- CrCl <30 ml/min

Selinexor 60 mg PO Days 1,3 of each week
(n=127)

*all patient received 5-HT3 antagonists before the first dose and continued 2-3 times daily, as needed

Primary endpoint
- ORR

Key secondary endpoints
- DOR
- Disease control rate

Exploratory endpoints
- PFS
- OS
- TTP

Kalakonda N, et al. Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicenter, open label, phase 2 trial. *The* Lancet 2020; 7(7): E511-E522.

Selinexor: Efficacy in Clinical Trials

Overall response rate of 28%

Endpoint	N=127
DOR, median	9.3 months • 23 months for patient with CR • 4.4 months for patients with PR
Disease control rate	37%
PFS, median	2.6 months
OS, median	9.1 months

Kalakonda N, et al. Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicenter, open label, phase 2 trial. *The* Lancet 2020; 7(7): E511-E522.

Selinexor: Safety in Clinical Trials

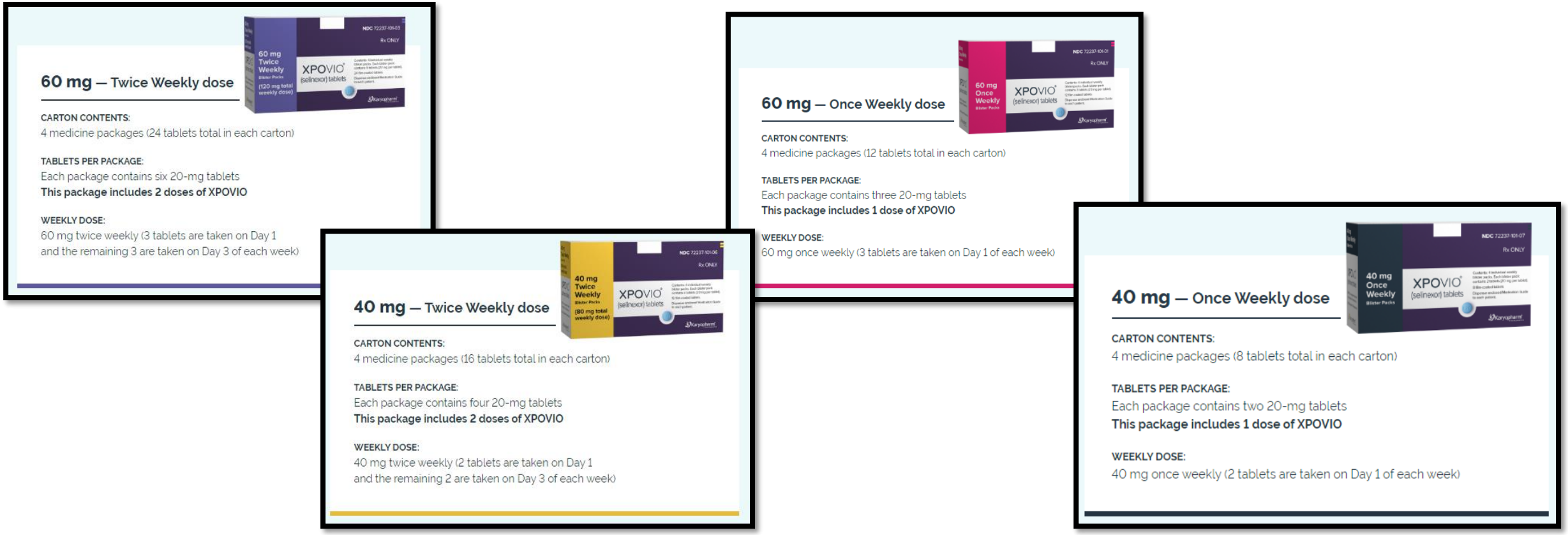
	Grade 1–2	Grade 3	Grade 4
Thrombocytopenia	20 (16%)	39 (31%)	19 (15%)
Nausea	66 (52%)	8 (6%)	0
Fatigue	46 (36%)	14 (11%)	0
Anaemia	26 (21%)	27 (21%)	1 (1%)
Decreased appetite	42 (33%)	5 (4%)	0
Diarrhoea	41 (32%)	4 (3%)	0
Constipation	39 (31%)	0	0
Neutropenia	7 (6%)	20 (16%)	11 (9%)
Weight loss	38 (30%)	0	0
Vomiting	35 (28%)	2 (2%)	0
Pyrexia	23 (18%)	5 (4%)	0
Asthenia	21 (17%)	6 (5%)	0
Cough	23 (18%)	0	0
Upper respiratory tract infection	18 (14%)	1 (1%)	0
Dizziness	18 (14%)	0	0
Hypotension	13 (10%)	4 (3%)	0
Oedema peripheral	14 (11%)	1 (1%)	0
Dyspnoea	12 (10%)	1 (1%)	1 (1%)
Hyponatraemia	4 (3%)	10 (8%)	0

- 17% patients discontinued treatment due to adverse events
- 70% patients had dose modification (interruption or dose reduction)

Kalakonda N, et al. Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicenter, open label, phase 2 trial. *The* Lancet 2020; 7(7): E511-E522.

Selinexor: Clinical Pearls

- GI symptoms are significant
- Product available in many various blister packs



Kalakonda N, et al. Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicenter, open label, phase 2 trial. *The* Lancet 2020; 7(7): E511-E522.

Polatuzumab Vedotin

Polatuzumab

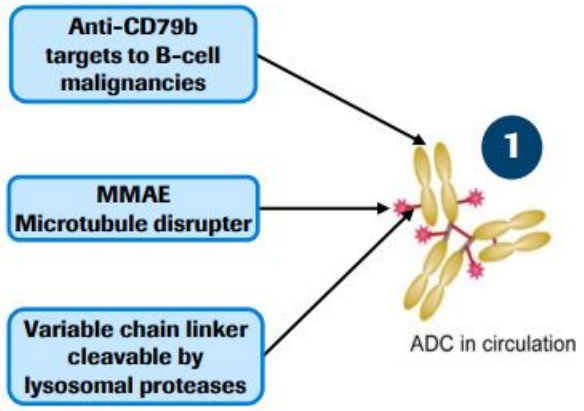
- **Pharmacologic Category**
  - CD79b-directed antibody drug conjugate

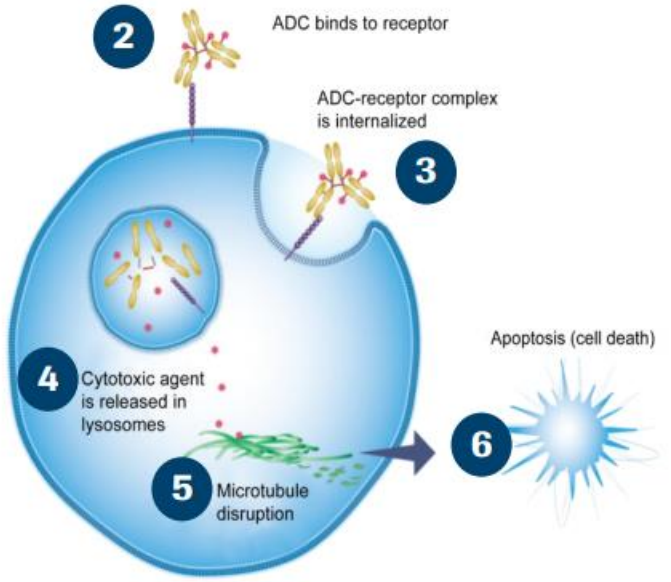
- **FDA approval – November 2019**
  - Granted accelerated approval based on complete response rate (CRR)
  - In combination with bendamustine and rituximab for the treatment of patients with relapsed or refractory DLBCL who have received ≥ 2 prior therapies

Polatuzumab [package insert]. Genentech. June 2019

Polatuzumab: Mechanism of Action

- Selectively binds to CD79b, a protein expressed on the surface of B-cells
- Binding triggers internalization. The stable VC linker is cleaved, releasing MMAE which binds to binds to microtubules
- MMAE inhibits microtubule polymerization, disrupts cell division and triggers apoptosis





Palanca-Wessels MC, et al. *Lancet Oncol*. 2015; 16:704-715; Polson A, et al. *Blood*. 2007;110:616-623; Dornan D, et al. *Blood*. 2009;114:2721–2729; Schrama D, et al. *Nat Rev Drug Discov*. 2006; 5:147-159; Francisco JA, et al. *Blood*. 2003;102:1458-1465; Beck A, et al. *mAbs*. 2012;4:637-647

Polatuzumab: Dosing and Administration

- **Dose**
  - First infusion: 1.8 mg/kg IV over 90 minutes
  - Subsequent infusions: 1.8 mg/kg IV over 30 minutes

- **Schedule**
  - Every 21 days x 6 cycles in combination with bendamustine and rituximab (any order)
    - Bendamustine 90 mg/m2/day on Day 1 and 2
    - Rituximab 375 mg/m2 on Day 1

- **Premedication**
  - Antihistamine and antipyretic

- **Prophylaxis**
  - *Pneumocystis jiroveci* pneumonia and HSV throughout treatment
  - TLS prophylaxis if high risk – high tumor burden and rapidly proliferating tumors

- **Storage considerations**
  - None

Polatuzumab [package insert]. Genentech. June 2019

Polatuzumab

- **Warnings and precautions**
  - Peripheral neuropathy
  - Infusion-related reactions
  - Myelosuppression
  - Opportunistic infections
  - Progressive multifocal leukoencephalopathy
  - Tumor lysis syndrome
  - Hepatotoxicity

- **Common side effects (>20%)**
  - Neutropenia/thrombocytopenia/anemia
  - Fatigue
  - Diarrhea
  - Decrease appetite

Polatuzumab [package insert]. Genentech. June 2019

Polatuzumab: Management of Adverse Reactions

Event	Dose Modification
Grade 2-3 Peripheral Neuropathy	• Hold polatuzumab until improvement to Grade 1 or lower • If recovered to Grade 1 or lower on or before Day 14, restart polatuzumab with the next cycle at a permanently reduced dose of 1.4mg/kg • If a prior dose reduction to 1.4 mg/kg has occurred, discontinue polatuzumab • If not recovered to Grade 1 or lower on or before Day 14, discontinue polatuzumab
Grade 4 Peripheral Neuropathy	Discontinue polatuzumab

Polatuzumab [package insert]. Genentech. June 2019

Polatuzumab: Management of Adverse Reactions

Event	Dose Modification
Grade 1-3 Infusion-Related Reaction	• Interrupt polatuzumab infusion and give supportive treatment. • For the first instance of Grade 3 wheezing, bronchospasm, or generalized urticaria, permanently discontinue polatuzumab. • For recurrent Grade 2 wheezing or urticaria, or for recurrence of any Grade 3 symptoms, permanently discontinue polatuzumab. • Otherwise, upon complete resolution of symptoms, infusion may be resumed at 50% of the rate achieved prior to interruption. In the absence of infusion-related symptoms, the rate of infusion may be escalated in increments of 50 mg/hr every 30 minutes. • For the next cycle, infuse polatuzumab over 90 minutes. If no infusion-related reaction occurs, subsequent infusions may be administered over 30 minutes. Administer pre-medication for all cycles
Grade 4 Infusion-Related Reaction	• Stop polatuzumab infusion immediately. • Give supportive treatment. • Permanently discontinue polatuzumab.

Polatuzumab [package insert]. Genentech. June 2019

Polatuzumab: Management of Adverse Reactions

Event	Dose Modification
Grade 3-4 Neutropenia	• Hold all treatment until ANC recovers to greater than 1000/microliter • IF ANC recovers to greater than 1000/microliter on or before Day 7, resume all treatment without any additional dose reductions. Consider granulocyte colony stimulating factor prophylaxis for subsequent cycles, if not previously given. • If ANC recovers to greater than 1000/microliter after Day 7: – Restart all treatment. Consider granulocyte colony stimulating factor prophylaxis for subsequent cycles, if not previously given. If prophylaxis was given, consider dose reduction of bendamustine. – If dose reduction of bendamustine has already occurred, consider dose reduction of polatuzumab to 1.4 mg/kg
Grade 3-4 Thrombocytopenia	• Hold all treatment until platelets recover to greater than 75,000/microliter • If platelets recover to greater than 75,000/microliter on or before Day 7, resume all treatment without any additional dose reductions • If platelets recover to greater than 75,000/microliter after Day 7: – Restart all treatment, with dose reduction of bendamustine – If dose reduction of bendamustine has already occurred, consider dose reduction of polatuzumab to 1.4 mg/kg

Polatuzumab [package insert]. Genentech. June 2019

Polatuzumab: G029365 Study

Inclusion Criteria

- Patients with DLBCL who have received at least 1 prior regimen and were not candidates for autologous HSCT

Exclusion Criteria

- Patients with Grade 2 or higher peripheral neuropathy, prior allogeneic HSCT, active central nervous system lymphoma, or transformed lymphoma

Randomized 1:1

Polatuzumab 1.8 mg/kg + BR
Every 21 days x 6 cycles
(n=40)

BR
Every 21 days x 6 cycles
(n=40)

Primary endpoint

- Complete response (CR)

Additional endpoints

- Objective response rate (ORR)
- Best overall response of CR or partial remission (PR)
- Duration of response (DoR)

Randomized phase 2 trial of polatuzumab vedotin with bendamustine and rituximab in relapsed/refractory FL and DLBCL. DOI: 10.1200/JCO.2018.36.15_suppl.7507 *Journal of Clinical Oncology* 36, no. 15_suppl (May 20, 2018) 7507-7507

Polatuzumab: Efficacy in Clinical Trials

Higher CR rates vs BR at end of treatment (EOT)*
63% of patients in the polatuzumab + BR arm achieved a best overall response

Response per IRC, n(%)	Polatuzumab + BR n=40	BR n=40
Objective response at EOT	18 (45%)	7 (18%)
CR rate	16 (40%)	7 (18%)
Difference in CR rates	22%	
Best overall response of CR or PR	25 (63%)	10 (25%)
Best response of CR	20 (50%)	9 (23%)

*EOT defined as 6 to 8 weeks after Day 1 of cycle 6 of last study treatment

Randomized phase 2 trial of polatuzumab vedotin with bendamustine and rituximab in relapsed/refractory FL and DLBCL. DOI: 10.1200/JCO.2018.36.15_suppl.7507 *Journal of Clinical Oncology* 36, no. 15_suppl (May 20, 2018) 7507-7507

Polatuzumab: Safety in Clinical Trials

Select Grade 3 or higher adverse reactions in both study arms
Events were graded using the NCI STCAE version 4

Adverse Reaction by Body System		Polatuzumab + BR (n=45) Grade ≥3 (%)	BR (n=39) Grade ≥3 (%)
Blood and lymphatic system disorders	Neutropenia Thrombocytopenia Anemia Lymphopenia	42 40 24 13	36 26 18 8
Nervous system disorders	Peripheral neuropathy	0	0
Gastrointestinal disorders	Diarrhea Vomiting	4.4 2.2	5 0
General disorders	Infusion-related reaction Pyrexia Decreased appetite	2.2 2.2 2.2	0 0 0
Infections	Pneumonia	16*	2.6^

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events
*Includes 2 events with fatal outcome ; ^ Includes 1 event with fatal outcome

Randomized phase 2 trial of polatuzumab vedotin with bendamustine and rituximab in relapsed/refractory FL and DLBCL. DOI: 10.1200/JCO.2018.36.15_suppl.7507 *Journal of Clinical Oncology* 36, no. 15_suppl (May 20, 2018) 7507-7507

MULTIPLE MYELOMA

Belantamab mafodotin-blmf

Belantamab mafodotin-blmf

Belantamab

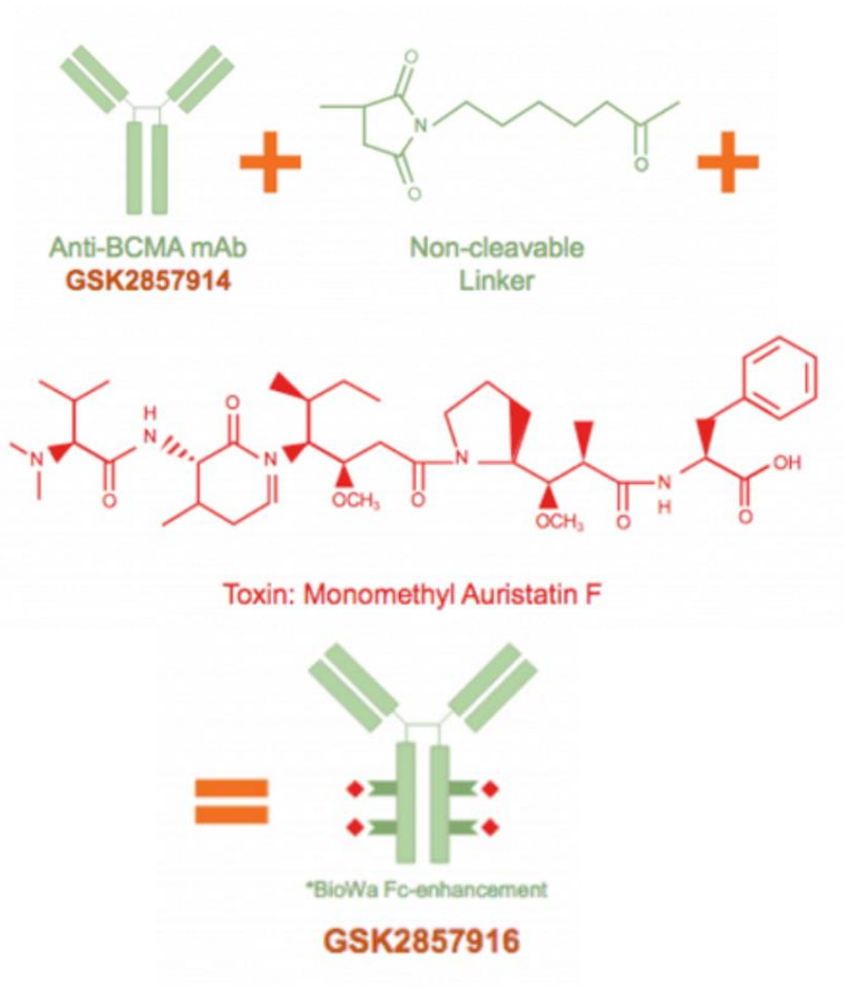
- **Pharmacologic Category**
  - B-cell maturation antigen (BCMA)-directed antibody and microtubule inhibitor conjugate

- **FDA approval – August 2020**
  - Adult patients with R/R MM who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent

Belantamab mafodotin [package insert]. GlaxoSmithKline, August 2020.

Belantamab: Mechanism of Action

- Antibody-drug conjugate
  - The antibody component is an afucosylated IgG1 directed against BCMA, a protein expressed on normal B lymphocytes and multiple myeloma cells
  - The small molecule component is MMAF, a microtubule inhibitor
- MMAF-induced apoptosis
- Tumor cell lysis through ADCC and ADCP



Belantamab mafodotin [package insert]. GlaxoSmithKline, August 2020.

Belantamab: Dosing and Administration

- **Dose**
  - 2.5 mg/kg IV over 30 minutes
- **Schedule**
  - Once every 3 weeks until disease progression or unacceptable toxicity
- **Premedication**
  - Only for subsequent cycles if reaction on 1st infusion
- **Prophylactic medication**
  - Preservative-free lubricant eye drops at least 4 times a day starting with the first infusion and continuing until end of treatment
- **Storage considerations**
  - None

Belantamab mafodotin [package insert]. GlaxoSmithKline, August 2020.

Belantamab: REMS Program

- **REMS Requirements for Risk of Ocular Toxicity**
  - Prescribers must be certified with the program by enrolling and completing training in the BLENREP REMS
  - Prescribers must counsel patients about the risk of ocular toxicity and the need for ophthalmic examinations prior to each dose
  - Patients must be enrolled in the REMS program and comply with monitoring
  - Healthcare facilities must be certified with the program and verify that patients are authorized to receive belantamab mafodotin

- **Monitoring and Patient Instruction**
  - Conduct ophthalmic examinations at baseline, prior to each dose, and promptly for worsening symptoms
  - Perform baseline examinations within 3 weeks prior to the first dose
  - Perform each follow-up examination at least 1 week after the previous dose and within 2 weeks prior to the next dose
  - Avoid use of contact lenses unless directed by an ophthalmologist

Belantamab mafodotin [package insert]. GlaxoSmithKline, August 2020.

Belantamab: Dosage Modifications

Dosage Modifications for Corneal Adverse Reactions per the KVA scale		
	Corneal Adverse Reaction	**Recommended Dosage Modifications**
Grade 1	Mild superficial keratopathy Change in BCVA: Decline from baseline of 1 line on Snellon Visual Acuity	Continue treatment at current dose
Grade 2	Moderate superficial keratopathy Change in BCVA: Decline from baseline of 2 or 3 lines on Snellon Visual Acuity and not worse than 20/200	Withhold dose until improvement in both corneal examination findings and change in BCVA to Grade 1 or better and resume at same dose
Grade 3	Severe superficial keratopathy Change in BCVA: Decline from baseline by more than 3 lines on Snellon Visual Acuity and not worse than 20/200	Withhold dose until improvement in both corneal examination findings and change in BCVA to Grade 1 or better and resume at reduced dose
Grade 4	Corneal epithelial defect Change in BCVA: Snellen Visual Acuity worse than 20/200	Consider permanent discontinuation. If continuing treatment, withhold dose until improvement in both corneal examination findings and change in BCVA to Grade 1 or better and resume at reduced dose

Belantamab mafodotin [package insert]. GlaxoSmithKline, August 2020.

Belantamab: Dosage Modifications

Dosage Modifications for Other Adverse Reactions		
	Severity	**Recommended Dosage Modifications**
Thrombocytopenia	Platelet count 25,000 – 50,000/mcL	Consider withholding and/or reducing dose
	Platelet count <25,000/mcL	Withhold until platelet count improves to Grade 3 or better. Consider resuming at reduced dose.
Infusion-related reactions	Grade 2 (moderate) or Grade 3 (severe)	Interrupt infusion and provide supportive care. Once symptoms resolve, resume at lower infusion rate; reduce the infusion rate by at least 50%
	Grade 4 (life-threatening)	Permanently discontinue and provide emergency care

Belantamab mafodotin [package insert]. GlaxoSmithKline, August 2020.

Belantamab

- **Warnings and precautions**
  - Thrombocytopenia
  - Infusion-related reactions
  - Embry-fetal Toxicity

- **Common side effects (>20%)**
  - Keratopathy (corneal epithelium change on eye exam)
  - Decreased visual acuity
  - Nausea
  - Blurred vision
  - Pyrexia
  - Infusion-related reactions
  - Fatigue

Belantamab mafodotin [package insert]. GlaxoSmithKline, August 2020.

Belantamab: DREAMM-2 Study

Inclusion criteria

- Age ≥ 18 years of age
- R/R MM with disease progression after 3+ lines of therapy and who were refractory/intolerant to CD-38 monoclonal antibody, immunomodulatory agent and proteasome inhibitor
- ECOG 0-2

Belantamab mafodotin 2.5 mg/kg (n=97)

OR

3.4 mg/kg every 3 weeks (n=99)

Primary endpoint

- ORR

Key secondary endpoints

- DOR

Lonial S, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2). *The Lancet*. 2020;21(2):207-221.

Belantamab: Efficacy in Clinical Trials

Median time to first response = 1.4 months
73% of responders had a duration of response of ≥6 months

	Belantamab mafodotin (n=97)
Overall response rate (ORR), n (%) (97% CI)	30 (31%) (21%, 43%)
Median duration of response in months (range)	NR (NR to NR)

Lonial S, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2). *The Lancet*. 2020;21(2):207-221.

Belantamab: Safety in Clinical Trials

Table 3. Adverse Reactions (≥10%) in Patients Who Received belantamab in DREAMM-2

Adverse Reactions	Belantamab N = 95	
	All Grades (%)	Grade 3-4 (%)
Eye disorders		
Keratopathy[a]	71	44
Decreased visual acuity[b]	53	28
Blurred vision[c]	22	4
Dry eyes[d]	14	1
Gastrointestinal disorders		
Nausea	24	0
Constipation	13	0
Diarrhea	13	1
General disorders and administration site conditions		
Pyrexia	22	3
Fatigue[e]	20	2
Procedural complications		
Infusion-related reactions[f]	21	3
Musculoskeletal and connective tissue disorders		
Arthralgia	12	0
Back pain	11	2

- 8% patients discontinued for adverse event (2.1% for keratopathy)
- 54% patients had dosage interruptions due to adverse reaction
  - 47% keratopathy
  - 5% blurry vision
  - 3.2% dry eye
  - 3.2% pneumonia
- 29% patients had dosage modifications due to adverse reaction
  - 23% keratopathy
  - 5% thrombocytopenia

Lonial S, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2). *The Lancet*. 2020;21(2):207-221.

Targeted Agents in B-cell Malignancies

Jennifer Santamala, PharmD, BCOP

Clinical Pharmacy Manager, Hematology/Oncology

NewYork Presbyterian Hospital – Weill Cornell Medical Center