Association of Physician Assistants in Oncology

25th Annual Oncology Symposium for the Healthcare Provider

Recent Advances in Oncology Drugs for Hematologic Malignancies

Grace Baek, PharmD, BCOP

Clinical Hematology/Oncology Pharmacist

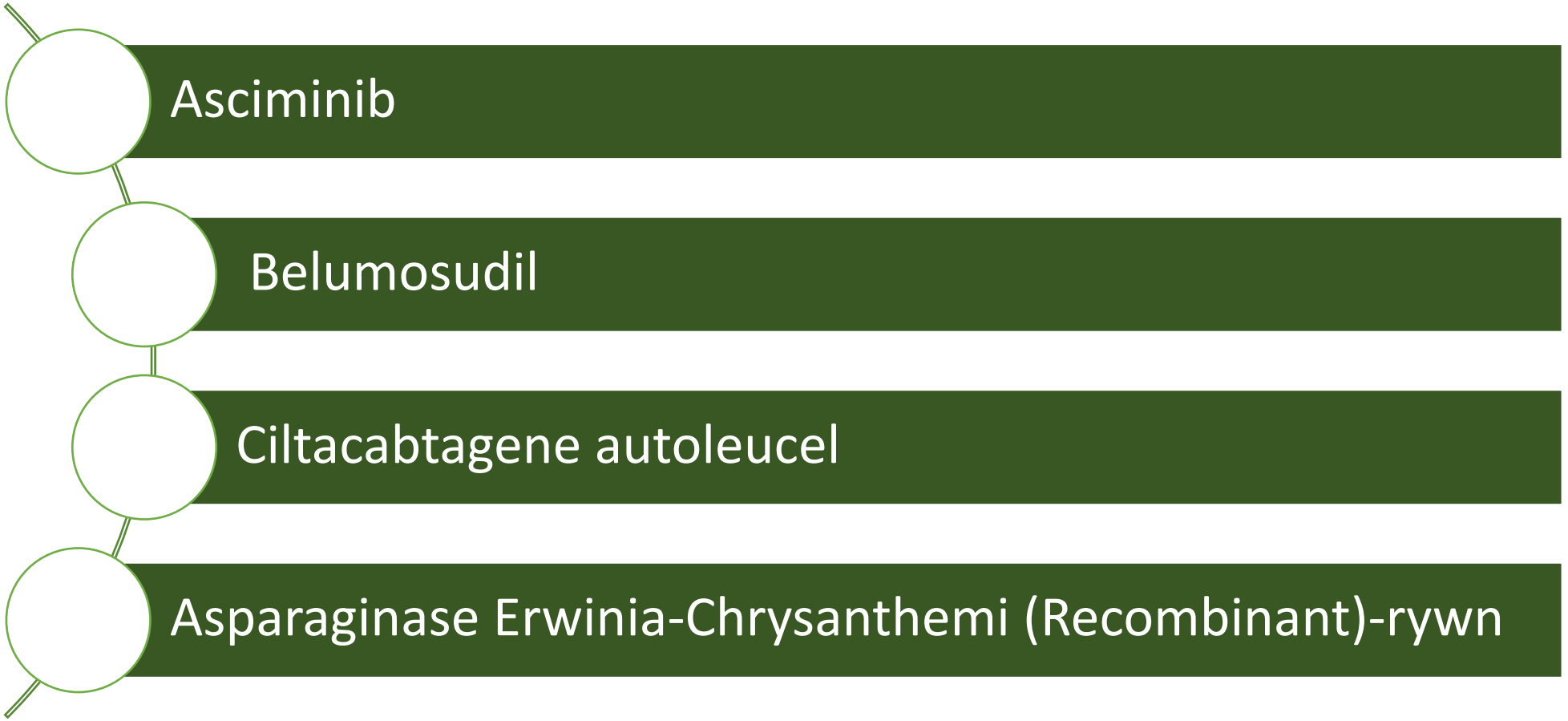
Fred Hutchinson Cancer Center

Seattle, WA

Learning Objectives

1. Identify new medications approved by the FDA for the management of hematologic malignancies
2. Discuss relevant mechanisms of action and dosing of newly approved medications
3. Identify toxicities of new drugs and appropriate interventions to improve adherence

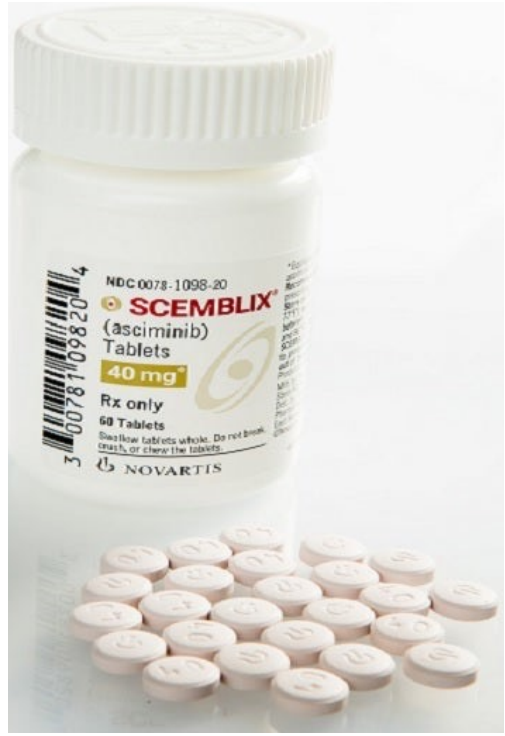
New Drug Approvals from the FDA



FDA=Food and Drug Administration.

Asciminib

- **FDA-approved indication #1**:
  - Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), previously treated with ≥2 tyrosine kinase inhibitors (TKIs) for adult patients
- Other FDA-approved drugs for a similar indication:
  - **Bosutinib** – Ph+ CML-CP with resistance or intolerance to prior therapy for adult patients
  - **Dasatinib** – Ph+ CML-CP with resistance or intolerance to prior therapy including imatinib for adult patients; Ph+ CML-CP for pediatric patients ≥1 yo
  - **Nilotinib** – Ph+ CML-CP resistant to or intolerant to prior therapy that included imatinib for adult patients; Ph+ CML-CP resistant or intolerant to prior TKI therapy for pediatric patients ≥1 year old
  - **Omacetaxine** – CML-CP with resistance and/or intolerance to ≥2 TKIs for adult patients
  - **Ponatinib** – CML-CP with resistance or intolerance to ≥2 prior kinase inhibitors for adult patients

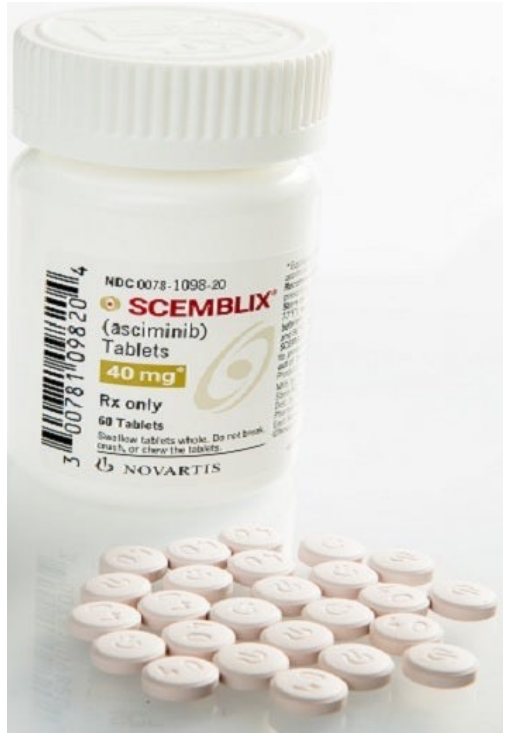


Ph+ CML-CP=Philadelphia chromosome-positive chronic myeloid leukemia-chronic phase. TKI=tyrosine kinase inhibitor. yo=year old.

Asciminib tablets: Package Insert. Revised 10/2021. Novartis Pharmaceuticals: East Hanover, NJ.
Bosutinib tablets: Package Insert. Revised 10/2021. Pfizer Inc: New York, NY.
Dasatinib tablets: Package Insert. Revised 6/2021. Bristol-Myers Squibb: Princeton, NJ.
Image adapted from https://www.clinicaltrialsarena.com/projects/scemblix-asciminib-chronic-myeloid-leukaemia/.
Nilotinib capsules: Package Insert. Revised 9/2021. Novartis Pharmaceuticals: East Hanover, NJ.
Omacetaxine for injection, for subcutaneous use: Package Insert. Revised 5/2021. Teva Pharmaceuticals: Parsippany, NJ.
Ponatinib tablets: Package Insert. Revised 2/2022. Takeda Pharmaceuticals: Lexington, MA.

Asciminib

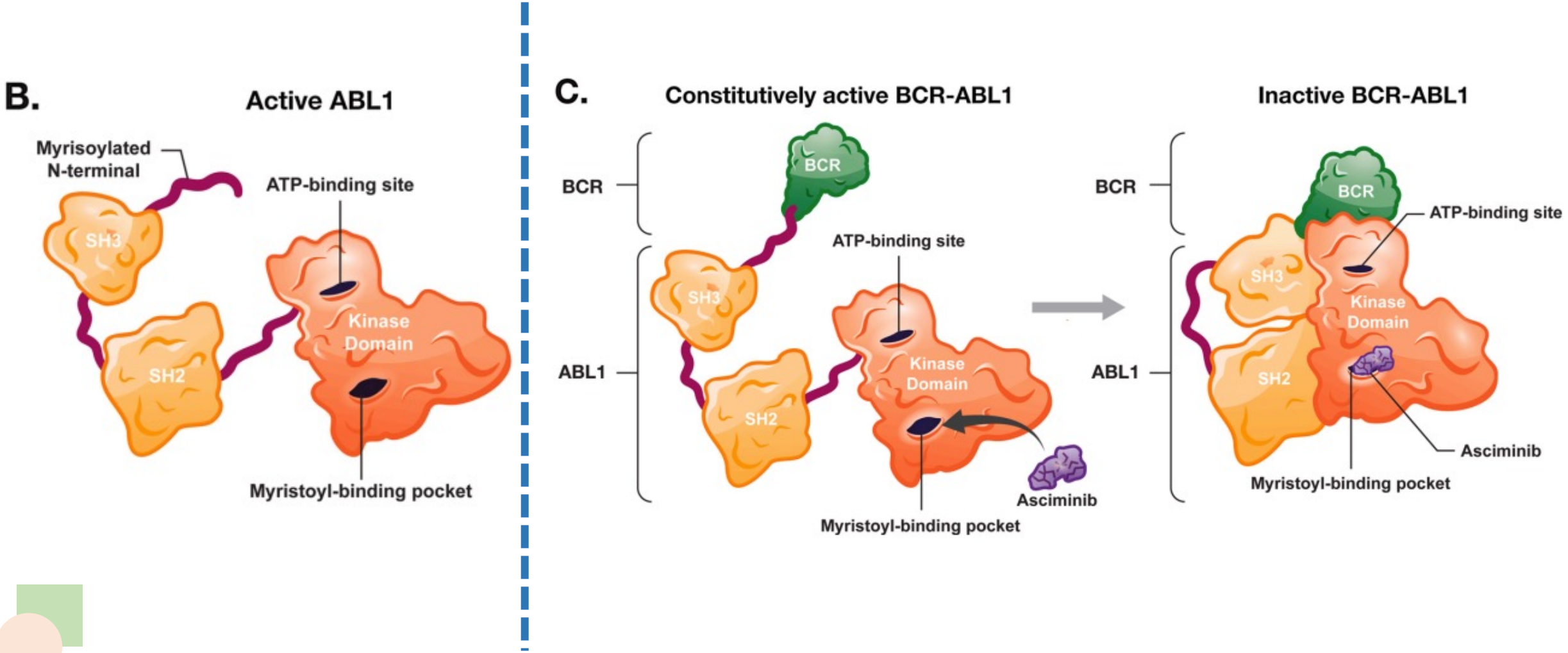
- **FDA-approved indication #2**:
  - Ph+ CML in CP with the T315I mutation for adult patients
- Other FDA-approved drugs for a similar indication:
  - **Ponatinib** – T315I-positive CML-CP for adult patients



Asciminib tablets: Package Insert. Revised 10/2021. Novartis Pharmaceuticals: East Hanover, NJ.
Ponatinib tablets: Package Insert. Revised 2/2022. Takeda Pharmaceuticals: Lexington, MA.
Image adapted from https://www.clinicaltrialsarena.com/projects/scemblix-asciminib-chronic-myeloid-leukaemia/.

Ph+ CML-CP=Philadelphia chromosome-positive chronic myeloid leukemia-chronic phase.
TKI=tyrosine kinase inhibitor.

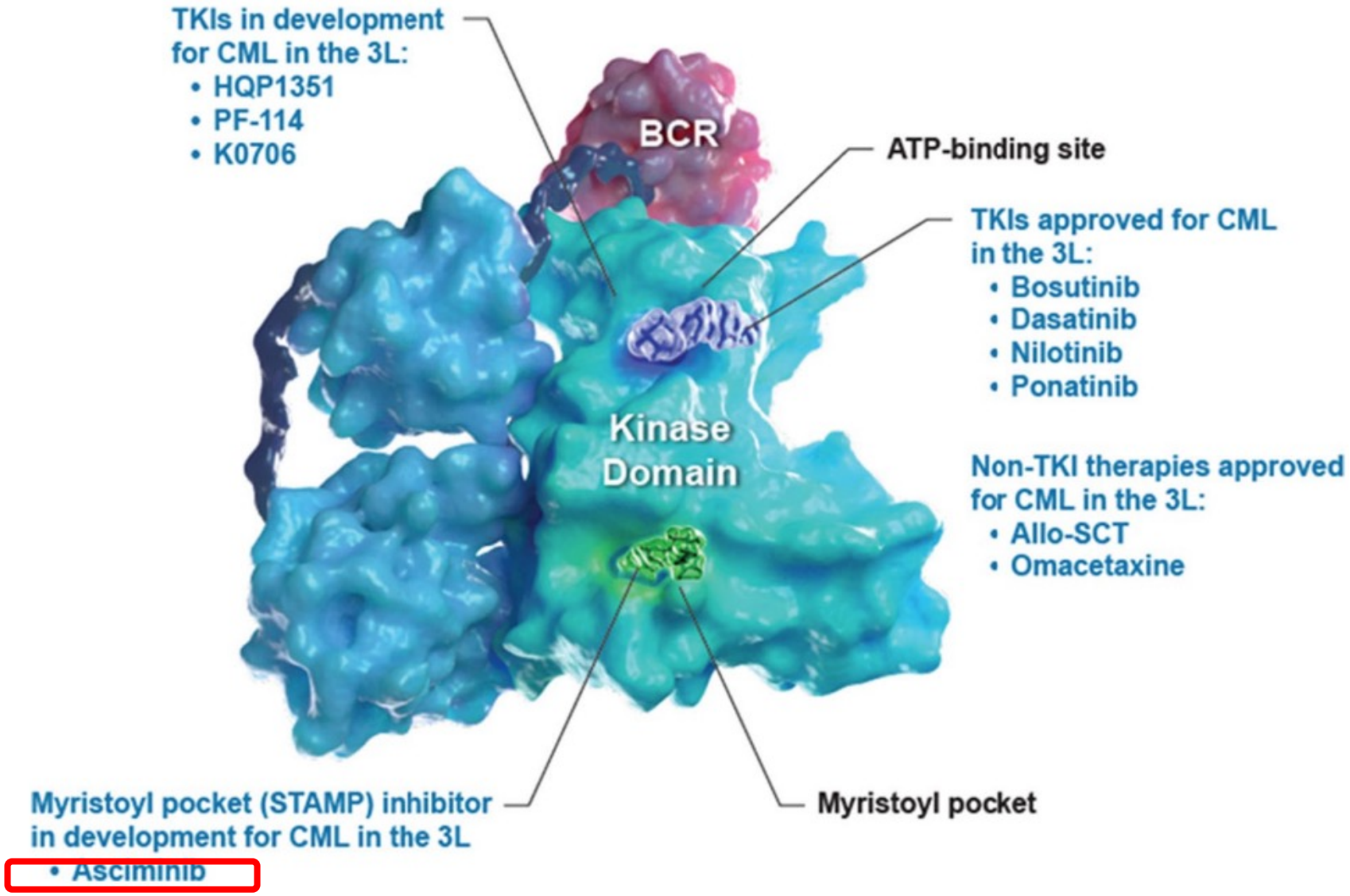
Asciminib : Mechanism of Action



Adapted from Rea D and Hughes TP. Crit Reviews in Oncol/Hematol. 2022; 171: 103580.
Hughes TP, et al. N Engl J Med. 2019; 381: 2315-2326.

ATP=adenosine triphosphate.

Asciminib : Mechanism of Action, *continued*



Adapted from Cortes J and Lang F. J Hematol Oncol. 2021; 14: 44.

CML=chronic myeloid leukemia. TKI=tyrosine kinase inhibitor.

Asciminib: Dosing

- Tablet strengths: 20 mg, 40 mg
- Starting dose: *On an empty stomach, 2 hours after or 1 hour before a meal*
  - Ph+ CML-CP = 80 mg orally once daily or 40 mg twice daily
  - Ph+ CML-CP with T315I mutation = 200 mg orally twice daily

Asciminib tablets: Package Insert. Revised 10/2021. Novartis Pharmaceuticals: East Hanover, NJ.

Ph+ CML-CP=Philadelphia chromosome-positive chronic myeloid leukemia-chronic phase.

Asciminib: Dosing

- Notable drug-drug interactions
  - CYP3A4 substrate/inhibitor, CYP2C9 inhibitor, P-gp inhibitor
  - Strong CYP3A Inhibitors: Closely monitor for ADEs during concomitant use of asciminib at 200 mg twice daily
  - Itraconazole Oral Solution Containing Hydroxypropyl-β-cyclodextrin: **Avoid** asciminib use at all approved doses
  - Certain substrates of CYP3A4: Closely monitor for ADEs during concomitant use of asciminib at 80 mg total daily dose. **Avoid** use of asciminib at 200 mg twice daily.
  - Substrates of CYP2C9: **Avoid** concomitant use of asciminib at all recommended doses. If not possible to avoid use, for asciminib 80 mg total daily dose – reduce the CYP2C9 substrate dosage as necessary; for asciminib 200 mg total daily dose – consider alternative therapy with non-CYP2C9 substrate
  - Certain P-gp substrates: Closely monitor for adverse reactions at all approved doses of asciminib
- Empiric renal dose adjustment: None, even for eGFR as low as 15 mL/min/1.73 m^2 and not requiring dialysis
- Empiric hepatic dose adjustment: None, even for severe hepatic impairment

Asciminib tablets: Package Insert. Revised 10/2021. Novartis Pharmaceuticals: East Hanover, NJ.

eGFR=estimated glomerular filtration rate. ADE=adverse drug event. CYP=cytochrome P450. P-gp=P-glycoprotein.

ASCEMBL trial (Nov 2021)

Phase 3, randomized, open-label multicenter study

Asciminib 40 mg PO BID (n=157) vs. Bosutinib 500 mg PO daily (n=76)

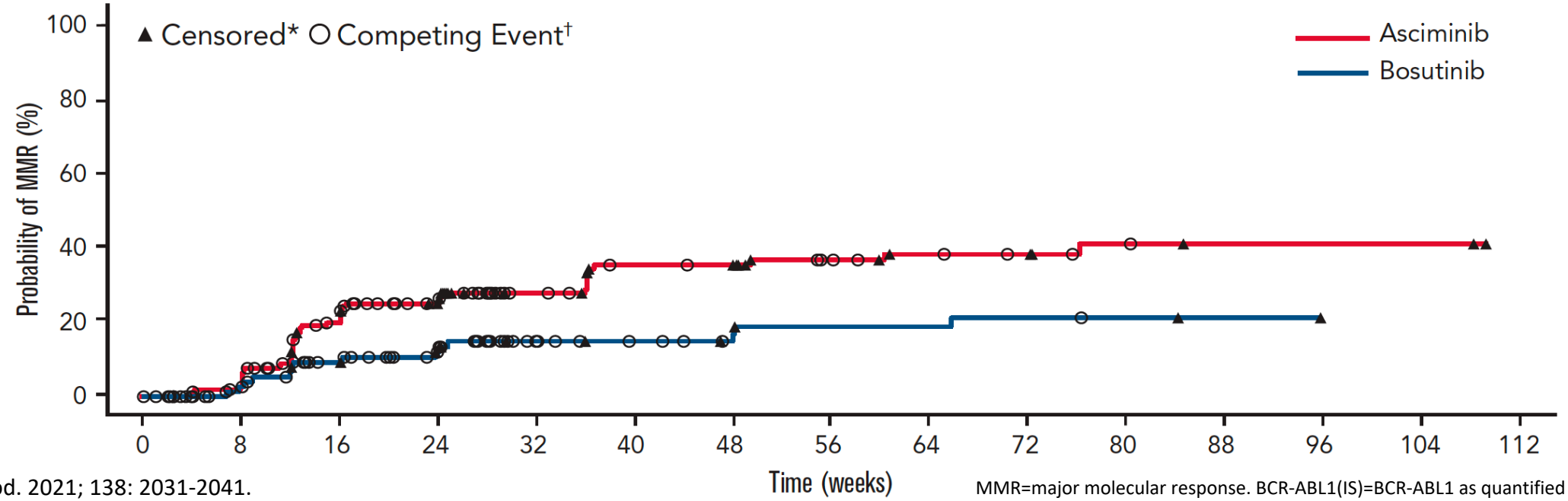
- ≥18yo patients [median age 52yo]
- CML-CP previously treated with ≥2 TKIs [2 prior TKIs 48.1%; ≥5 prior TKIs 6%]
- BCR-ABL1 transcript levels >1% (>0.1% for patients with intolerance to most recent TKI therapy)
- Without known BCR-ABL1 mutations of T315I or V299L

Rea D, et al. Blood. 2021; 138: 2031-2041.

TKI=tyrosine kinase inhibitor. PO=by mouth. BID=twice daily.

ASCEMBL trial

- *Primary Outcome:* rate of MMR (BCR-ABL1^{IS} ≤0.1%) at week 24 → MMR rate at week 24: asciminib 25.5% vs. bosutinib 13.2% at week 24
- CCyR rate at week 24 (in patients without baseline CCyR): asciminib 40.8% vs. bosutinib 24.2%
- Median duration of exposure: asciminib 43.4 weeks vs. bosutinib 29.2 weeks [median f/u 14.9 months]
- Achievement of BCR-ABL1^{IS} ≤1% at week 24: asciminib 49% vs. bosutinib 23.7%



Rea D, et al. Blood. 2021; 138: 2031-2041.

MMR=major molecular response. BCR-ABL1(IS)=BCR-ABL1 as quantified by International Scale.

ASCEMBL trial: Toxicities

40 mg twice daily

All Grades (for ≥9% of all subjects)	
Thrombocytopenia	28.8%
Neutropenia	21.8%
Headache	16%
Diarrhea	11.5%
Hypertension	11.5%
Nausea	11.5%
Fatigue	10.3%
Anemia	9.6%
Nasopharyngitis	9.6%
Arthralgia	9%

Grade ≥3 (for ≥3% of all subjects)	
Thrombocytopenia	9%
Neutropenia	6%
Hypertension	5%
Increased Lipase	3.8%

Deaths *(Asciminib arm)*

- n = 1 : related to asciminib
- n = 1 : during 30d follow-up after treatment discontinuation

Rea D, et al. Blood. 2021; 138: 2031-2041.

Asciminib: Myelosuppression

Monitor complete blood counts regularly during therapy and manage by treatment interruption or dose reduction

Toxicities from ASCEMBL		
	All Grades	**Grades ≥3**
Thrombocytopenia	28.8%	9%
Neutropenia	21.8%	6%
Anemia	9.6%	

Reason for Dose Adjustment	Manufacturer Guidance
ANC <1.0 x 10^9/L	• Hold until resolved to ANC ≥1 x 10^9/L and/or PLT ≥50 x 10^9/L. If resolves within 2 weeks: resume at starting dose. If resolves >2 weeks later: resume at reduced dose. • For **recurrent** severe thrombocytopenia and/or neutropenia, hold until resolved to ANC ≥1 x 10^9/L and PLT ≥50 x 10^9/L, then resume at reduced dose.
PLT <50 x 10^9/L	

Asciminib tablets: Package Insert. Revised 10/2021. Novartis Pharmaceuticals: East Hanover, NJ.
Rea D, et al. Blood. 2021; 138: 2031-2041.

PLT=platelet count. ANC=absolute neutrophil count.

Asciminib: Hypertension & Other CV Toxicity

- Monitor blood pressure as clinically indicated
- Monitor patients with history of cardiovascular risk factors for cardiovascular s/s

Toxicities from ASCEMBL		
	All Grades	**Grades ≥3**
Hypertension	11.5%	5%
Decreased cardiac EF	0.6%	0.6%
Ischemic stroke	0.6%	0.6%

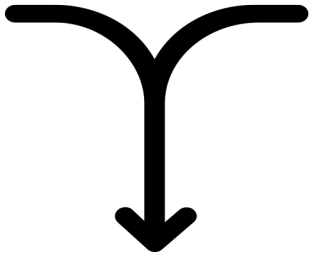
Reason for Dose Adjustment	Manufacturer Guidance
Non-hematologic ADE, Grade ≥3	• Hold until recovery to Grade ≤1. If resolved, resume at reduced dose. If not resolved, permanently discontinue.

Asciminib tablets: Package Insert. Revised 10/2021. Novartis Pharmaceuticals: East Hanover, NJ.
Rea D, et al. Blood. 2021; 138: 2031-2041.

ADE=adverse drug event. CV=cardiovascular. EF=ejection fraction. s/s=signs/symptoms.

Asciminib: Pancreatic Toxicity

Monitor serum lipase and amylase; evaluate for pancreatitis when lipase elevation is accompanied by abdominal symptoms



Toxicities from ASCEMBL *(Phase 1)*		
	All Grades	**Grades ≥3**
Increased amylase	5.8% *(12.7%)*	0.6% *(2.7%)*
Increased lipase	5.1% *(26.7%)*	3.8% *(10%)*
Clinical pancreatitis	*(3%, at >40mg BID)*	*(0.7%)*

Reason for Dose Adjustment	Manufacturer Guidance
Asymptomatic amylase and/or lipase elevation (>2x ULN)	• Hold until resolved to <1.5 x ULN. If resolved, resume at reduced dose. If events reoccur at reduced dose, permanently discontinue. If not resolved, permanently discontinue. Perform diagnostic tests to exclude pancreatitis.

Asciminib tablets: Package Insert. Revised 10/2021. Novartis Pharmaceuticals: East Hanover, NJ.
Rea D, et al. Blood. 2021; 138: 2031-2041.
Hughes TP, et al. N Engl J Med. 2019; 381: 2315-2326.

BID=twice daily.

Additional Counseling Points

- Embryo-Fetal Toxicity: Can cause fetal harm
  - Verify pregnancy status of females of reproductive potential prior to initiating treatment
  - Advise females of reproductive potential to use effective contraceptive during treatment with asciminib and for ≥1 week after the last dose
- Lactation: Advise not to breastfeed during treatment and for ≥1 week after the last dose (lack of data)
- Fertility: Advise females of reproductive potential that asciminib may impair fertility (unclear if reversible)
- Minimal/low emetic risk
- Monitor patients for signs and symptoms of hypersensitivity

Asciminib tablets: Package Insert. Revised 10/2021. Novartis Pharmaceuticals: East Hanover, NJ.
NCCN (Antiemesis). Ettinger DS, et al. V2.2022.

Asciminib: Access

- Medication not currently on shortage
- Select authorized pharmacies and distributors

Copay assistance?*	Free trial?*	Patient Assistance Program?*
Yes 18+yo U.S. resident; private insurance; copay support up to $15,000 per calendar year after possible patient responsibility for first $25; valid through one calendar year	**Yes** U.S. resident; new to asciminib with valid prescription; 30d supply	**Yes** Novartis

**Program availability and eligibility may frequently vary.*

ASHP Drug Shortages List. Accessed at https://www.ashp.org/drug-shortages/current-shortages .
Pharmaceutical assistance program information. Accessed at https://www.hcp.novartis.com/products/scemblix/ph-cml/access/.

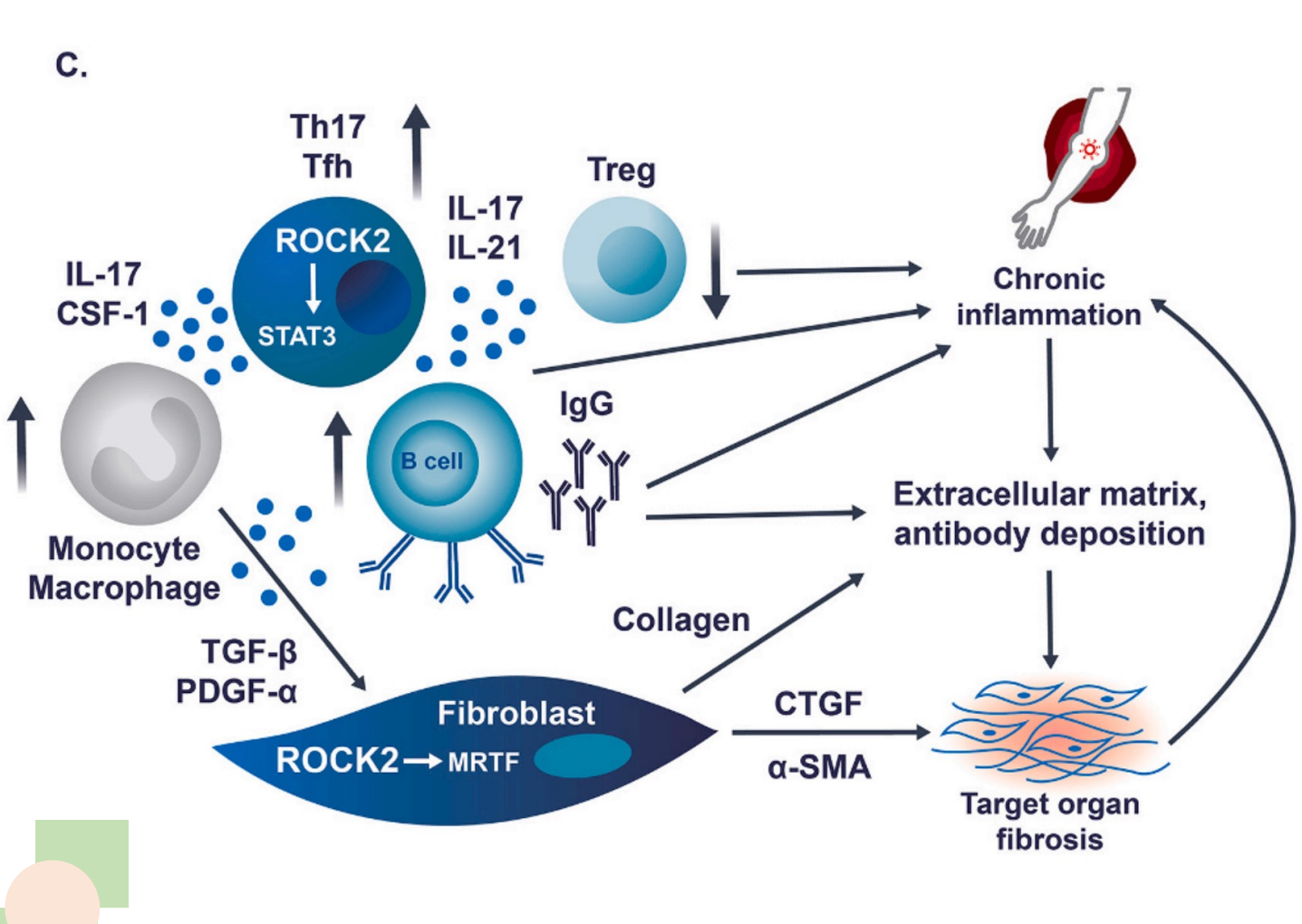
Belumosudil

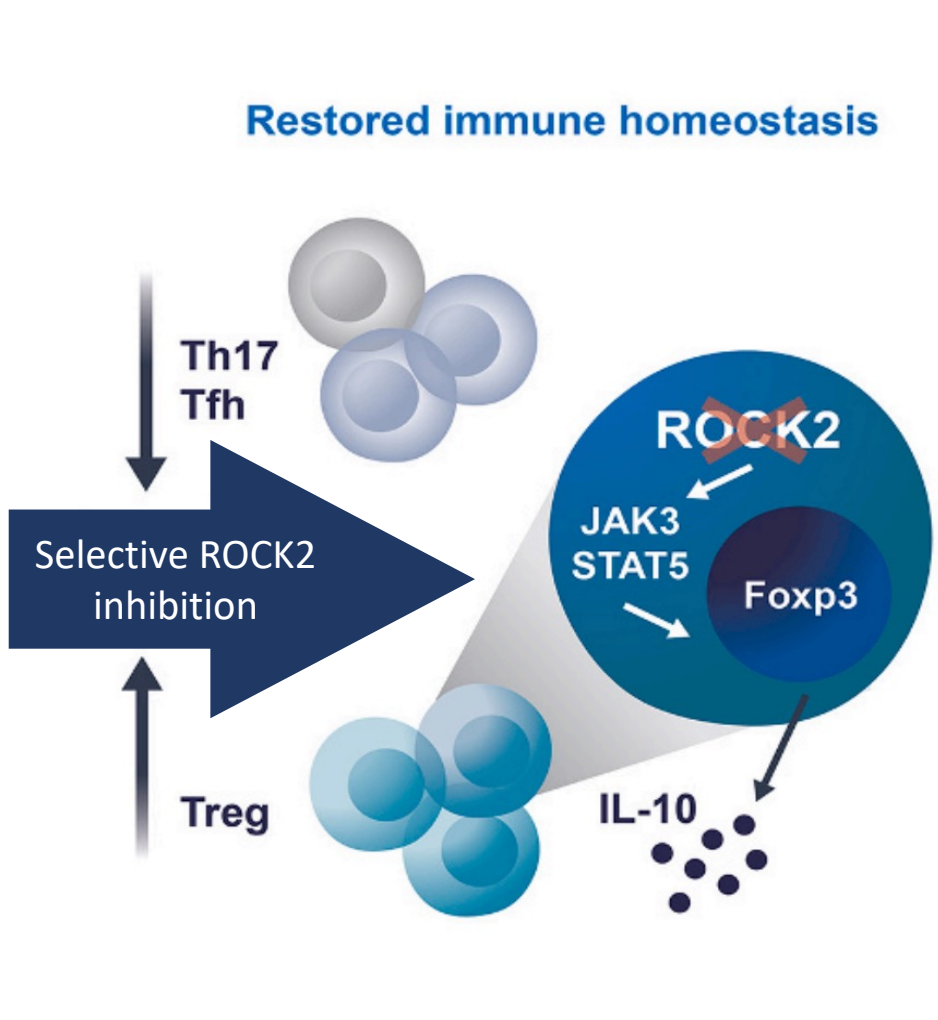
- **FDA-approved indication**:
  - Chronic graft-versus-host disease (cGVHD) after failure of ≥2 prior lines of systemic therapy for patients ≥12 years old
- Other FDA-approved drugs for a similar indication:
  - **Ruxolitinib** – cGVHD after failure of 1-2 lines of systemic therapy for patients ≥12 years old
  - **Ibrutinib** – cGVHD after failure of ≥1 lines of systemic therapy for adult patients only

Belumosudil tablets: Package Insert. Revised 7/2021. Kadmon Pharmaceuticals: Warrendale, PA.
Ruxolitinib tablets: Package Insert. Revised 9/2021. Incyte Corporation: Wilmington, DE.
Ibrutinib capsules/tablets: Package Insert. Revised 5/2022. Janssen Biotech: Horsham, PA.
Image adapted from https://www.clinicaltrialsarena.com/projects/rezurock-belumosudil-cgvhd/.

cGVHD=chronic graft-versus-host disease.

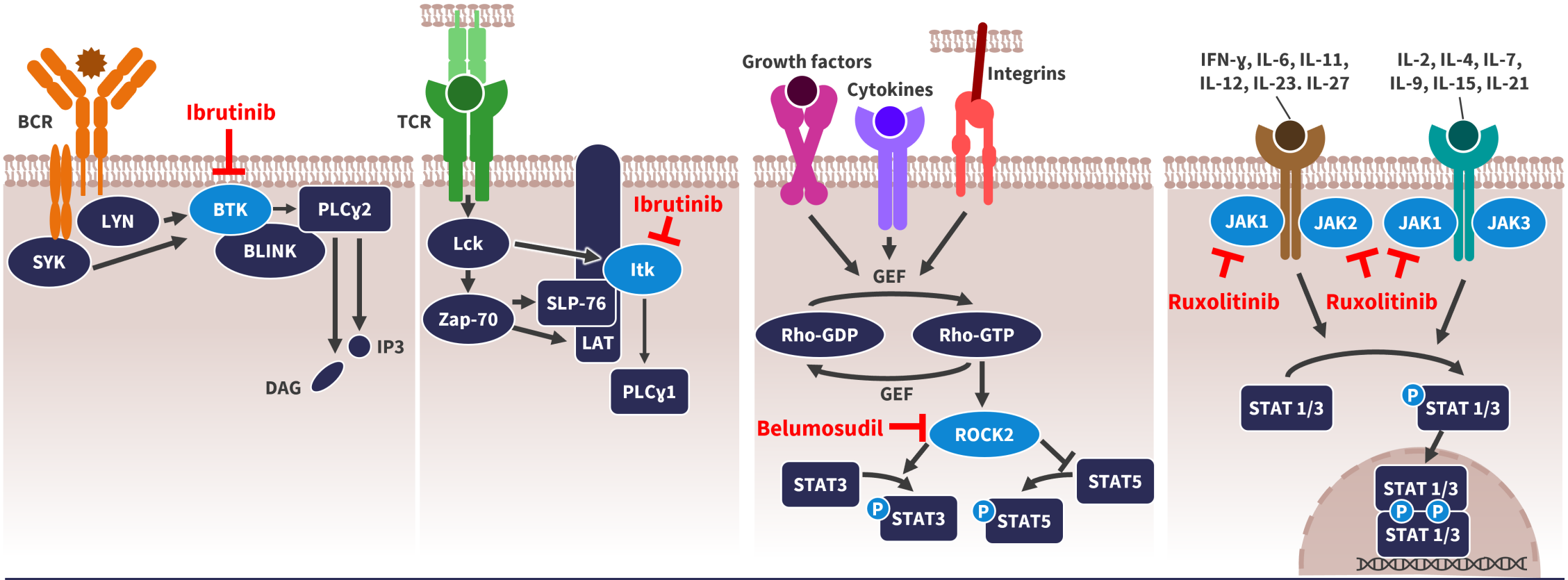
Belumosudil: Mechanism of Action





Adapted from Zanin-Zhorov A and Blazar BR. Clin Immunol. 2021; 230: 108823.

Belumosudil: Mechanism of Action, *continued*



Treatment effects in cGvHD

Ibrutinib		Belumosudil	Ruxolitinib
↓ cell survival	↓ cytokine production IL-9, IL-17A, IL-2	↓ cytokine production	↓ cytokine production
↓ cell proliferation		↓ proliferation	↓ proliferation
↓ autoantibody production		↓ Th17 cells	↓ Th17 cells
		↓ follicular helper T cells	↑ Treg cells
		↑ Treg cells	↓ collagen/ECM production
		↓ collagen/ECM production	

Adapted from Zeiser R and Lee SJ. Blood. 2022; 139: 1642-45.

Belumosudil: Dosing

- Tablet strengths: 200 mg
- Starting dose: *With food,* 200 mg taken orally once daily
- Notable drug-drug interactions
  - Substrate of CYP2C8, CYP2D6, P-gp/ABCB1, and UGT1A9
  - Strong CYP3A Inducers: **Increase** dosage to 200 mg twice daily
  - Proton Pump Inhibitors: **Increase** dosage to 200 mg twice daily
- Empiric renal dose adjustment: None for mild to moderate impairment
  - Severe renal impairment (eGFR <30 mL/min/1.72m^2) not studied; consider risks vs. benefits before initiating treatment
- Empiric hepatic dose adjustment: No specific recommendations are available

Belumosudil tablets: Package Insert. Revised 7/2021. Kadmon Pharmaceuticals: Warrendale, PA.

CYP=cytochrome P450. eGFR=estimated glomerular filtration rate. P-gp=P-glycoprotein. UGT=UDP glucuronosyltransfase.

ROCKstar trial

Phase 2, randomized, multicenter study

Belusomudil 200 mg PO daily (n=66) vs. Belusomudil 200 mg PO BID (n=66)

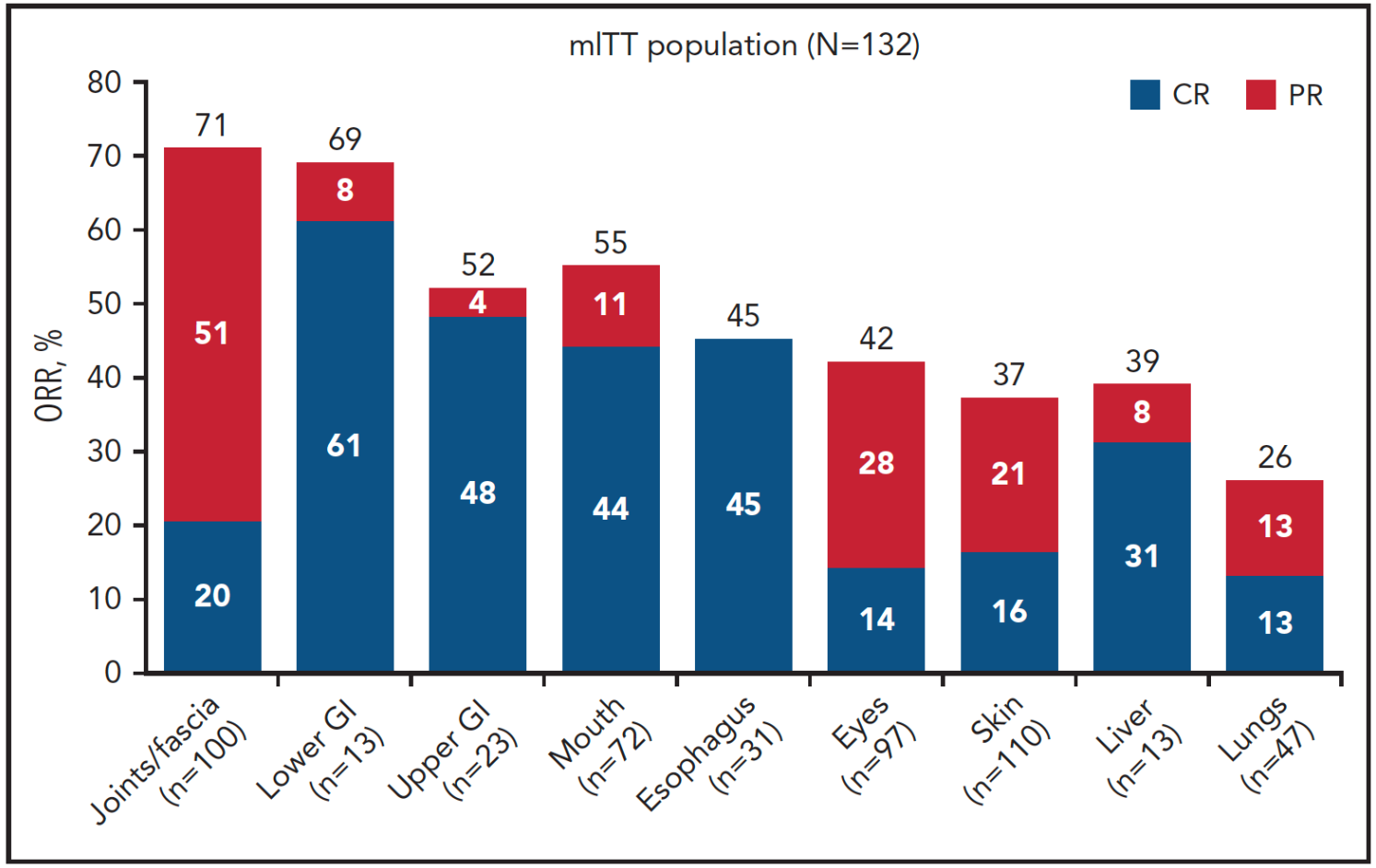
- ≥12yo alloHSCT recipients [median age 56yo]
- persistent cGVHD manifestations after 2-5 prior systemic lines of therapy [median 3 systemic lines of therapy]
- stable corticosteroid therapy for 2 weeks pre-screening (excluding ibrutinib) [baseline median corticosteroid dose 0.2 mg/kg/day]
- KPS/LPS ≥60
- [52% cGVHD involvement of ≥4 organs]

Cutler C, et al. Blood. 2021; 138: 2278-2289.

KPS/LPS=Karnofsky/Lansky Performance Scale. alloHSCT=allogeneic hematopoietic stem cell transplant. PO=by mouth.

ROCKstar trial

- *Primary Outcome:* Best ORR (CR or PR) at any time → ORR 74% vs. 77% at median f/u 14 months
- Median time to response 5 weeks
- Median DOR 54 weeks
- 44% patients on therapy for >1 year
- Mean corticosteroid dose reduction of 54%
- Symptom reduction for 59% vs. 62% patients



Cutler C, et al. Blood. 2021; 138: 2278-2289.

ORR=overall response rate. CR=complete response. PR=partial response. f/u=follow-up. DOR=duration of response.

ROCKstar trial: Toxicities

Arm: 200 mg once daily

All Grades (for ≥20% of all subjects)	
Fatigue	46%
Diarrhea	35%
Nausea	35%
Dyspnea	32%
Cough	30%
Vomiting	27%
Upper respiratory tract infection	26%
Peripheral edema	26%
Headache	20%
Muscle spasms	20%

Grade ≥3 (for ≥5% of all subjects)	
Pneumonia	9%
Hypertension	6%
Hyperglycemia	5%

Deaths

- n=2 : multiorgan failure and infection possibly related to belumosudil
- n = 2 : cardiac arrest
- n = 1 : hemothorax secondary to lung biopsy
- n = 1 : AML recurrence
- n = 6 : during long-term follow-up

Cutler C, et al. Blood. 2021; 138: 2278-2289.

ROCKstar trial: Toxicities, *continued*

Arm: 200 mg once daily

All Grades *(for 18% of all subjects)*	
GGT increased	9%
AST increased	8%
ALT increased	6%
Blood alkaline phosphatase increased	6%
Hypoalbuminemia	3%
Transaminases increased	2%
Bilirubin conjugated increased	2%
LFT increased	2%

Cutler C, et al. Blood. 2021; 138: 2278-2289.

GGT=gamma-glutamyl transferase. AST=aspartate aminotransferase. ALT=alanine aminotransferase. LFT=liver function test.

Belumosudil: Transaminitis

Monitor AST and ALT at least monthly

Toxicities from ROCKstar, All Grades	
AST increased	8%
ALT increased	6%
Transaminases increased	2%
LFT increased	2%

Reason for Dose Adjustment	Manufacturer Guidance
Grade 3 AST or ALT elevation (5x to 20x ULN)	Hold belumosudil until recovery of bilirubin, AST, and ALT to Grade 0-1, then resume at same dose
Grade 4 AST or ALT elevation (>20x ULN)	Discontinue belumosudil permanently

Belumosudil tablets: Package Insert. Revised 7/2021. Kadmon Pharmaceuticals: Warrendale, PA.
Cutler C, et al. Blood. 2021; 138: 2278-2289.

AST=aspartate aminotransferase. ALT=alanine aminotransferase. LFT=liver function test. ULN=upper limit of normal.

Belumosudil: Hyperbilirubinemia

Monitor Tbili at least monthly

Toxicities from ROCKstar, All Grades	
Bilirubin conjugated increased	2%

Reason for Dose Adjustment	Manufacturer Guidance
Grade 2 bilirubin elevation (1.5x to 3x ULN)	Hold belumosudil until recovery of bilirubin, AST, and ALT to Grade 0-1, then resume at same dose
Grade ≥3 bilirubin elevation (>3x ULN)	Discontinue belumosudil permanently

Belumosudil tablets: Package Insert. Revised 7/2021. Kadmon Pharmaceuticals: Warrendale, PA.
Cutler C, et al. Blood. 2021; 138: 2278-2289.

AST=aspartate aminotransferase. ALT=alanine aminotransferase. LFT=liver function test. ULN=upper limit of normal.

Belumosudil: Serious Toxicities

Toxicities from ROCKstar, Grade ≥3 (≥5% incidence)	
Pneumonia	9%
Hypertension	6%
Hyperglycemia	5%

Reason for Dose Adjustment	Manufacturer Guidance
Other ADE, Grade 3	Hold belumosudil until recovery of bilirubin, AST, and ALT to Grade 0-1, then resume at same dose
Other ADE, Grade 4	Discontinue belumosudil permanently

Belumosudil tablets: Package Insert. Revised 7/2021. Kadmon Pharmaceuticals: Warrendale, PA.
Cutler C, et al. Blood. 2021; 138: 2278-2289.

AST=aspartate aminotransferase. ALT=alanine aminotransferase. LFT=liver function test. ADE=adverse drug event.

Belumosudil: Infections & CBC Abnormalities

Select Pooled Toxicities from ROCKstar and KD025-08		
	All Grades	**Grades 3-4**
Infection (pathogen not specified)	53%	16%
Viral infection	19%	4%
Bacterial infection	16%	4%
Lymphocytes decreased	29% (gr2-4)	13%
Neutrophils decreased	8% (gr2-4)	4%
Hgb decreased	11% (gr2-4)	1%
PLT decreased	10% (gr2-4)	5%

→

- Standard/institutional infection prophylaxis and treatment – as well as management of anemia and thrombocytopenia – unless otherwise appropriate

Cutler C, et al. Blood. 2021; 138: 2278-2289.
Jagasia M, et al. Blood. 2018; 132: 602.
Belumosudil tablets: Package Insert. Revised 7/2021. Kadmon Pharmaceuticals: Warrendale, PA.

CBC=complete blood count.

Belumosudil: Other Considerations

Select Pooled Toxicities from ROCKstar and KD025-08		
	All Grades	**Grades 3-4**
Nausea	42%	4%
Diarrhea	35%	1%

- Likely moderate emetic risk
- Standard nausea, diarrhea management unless otherwise appropriate

Cutler C, et al. Blood. 2021; 138: 2278-2289.
Jagasia M, et al. Blood. 2018; 132: 602.
Belumosudil tablets: Package Insert. Revised 7/2021. Kadmon Pharmaceuticals: Warrendale, PA.

Additional Counseling Points

- Embryo-Fetal Toxicity: Can cause fetal harm
  - Verify pregnancy status of females of reproductive potential prior to initiating treatment (e.g., negative urine pregnancy test)
  - Advise females of reproductive potential AND males with female partners of reproductive potential to use effective contraceptive during treatment with belumosudil and for ≥1 week after the last dose
- Lactation: Advise not to breastfeed during treatment and for ≥1 week after the last dose
- Fertility: Advise males and females of reproductive potential that belumosudil may impair fertility (reversible effect)
- Store at room temperature (68-77°F) in original container to protect from moisture; keep desiccant
- Phase I study: QTc prolongation – no effect >10 msec

Belumosudil tablets: Package Insert. Revised 7/2021. Kadmon Pharmaceuticals: Warrendale, PA.
Schueller O, et al. Clin Pharmacol in Drug Devel. 2022; doi: 10.1002/cpdd.1142.

QTc=corrected QT interval. msec=milliseconds.

Belumosudil: Access

- Medication not currently on shortage
- Select authorized pharmacies and distributors

Copay assistance?*	Free trial?*	Patient Assistance Program?*
Yes 18+yo U.S. resident; commercial or private insurance; copay support up to $25,000 per calendar year; limit one 30d supply per 30d; valid through Dec 31 of year of activation	**Yes** 1) 18+yo U.S. resident; new to belumosudil; 30d supply if delay in coverage decision or submitted PA denied 2) 18+yo U.S. resident; commercial insurance but with interruption; 30d supply	**Yes** Kadmon Pharmaceuticals

**Program availability and eligibility may frequently vary.*

ASHP Drug Shortages List. Accessed at https://www.ashp.org/drug-shortages/current-shortages .
Pharmaceutical assistance program information. Accessed at https://rezurockhcp.com/kadmon-assist/ .

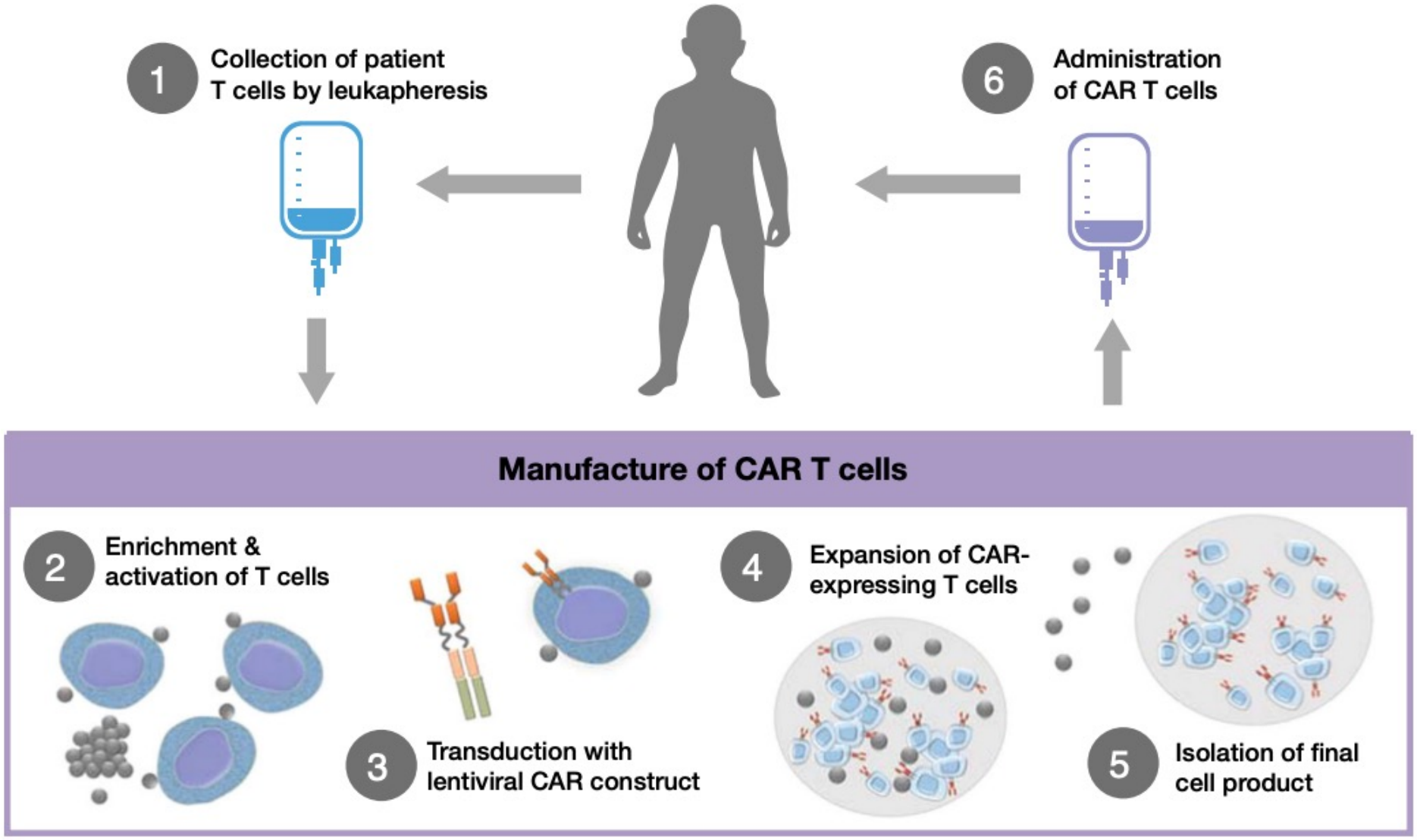
Ciltacabtagene autoleucel (Cilta-cel)

- **FDA-approved indication**:
  - Relapsed or refractory multiple myeloma (RRMM) after ≥4 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody
- Other FDA-approved drugs for a similar indication:
  - **Idecabtagene vicleucel** – RRMM after ≥4 prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody

Ciltacabtagene autoleucel suspension for intravenous infusion: Package Insert. Revised 2/2022. Janssen Biotech: Horsham, PA.
Idecabtagene vicleucel suspension for intravenous infusion: Package Insert. Revised 3/2021. Bristol-Myers Squibb: Summit, NJ.

Image adapted from https://www.empr.com/home/news/carvykti-approved-for-relapsed-refractory-multiple-myeloma/.

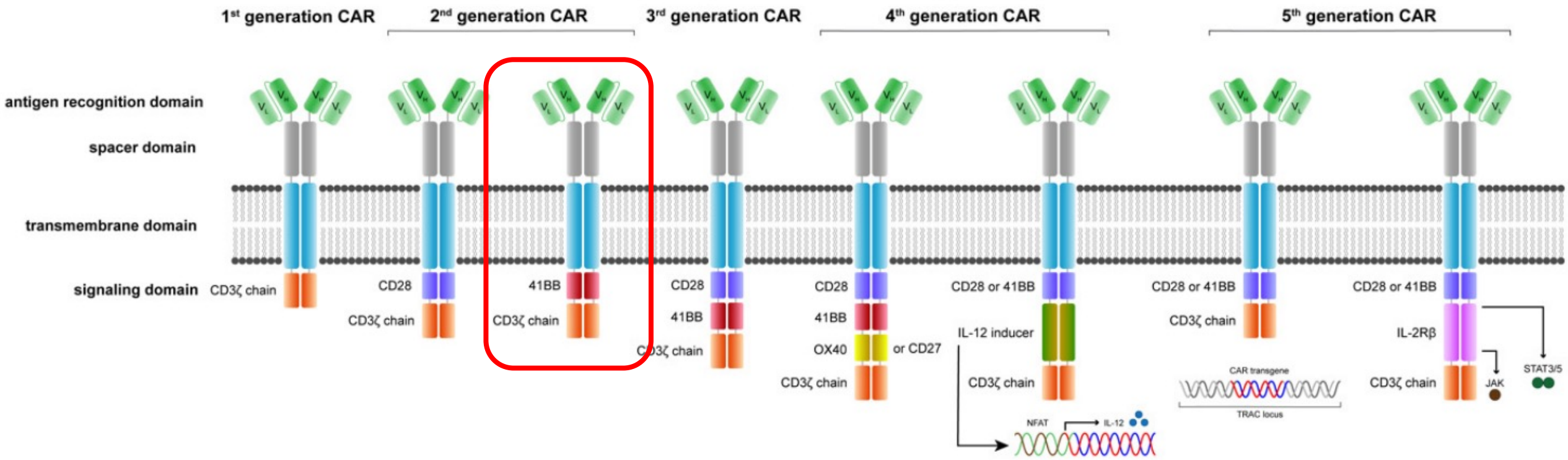
Overview of CAR-T Process



Hucks G and Rheingold SR. Blood Cancer J. 2019; 9: 10.

CAR T=Chimeric antigen receptor T cell (therapy).

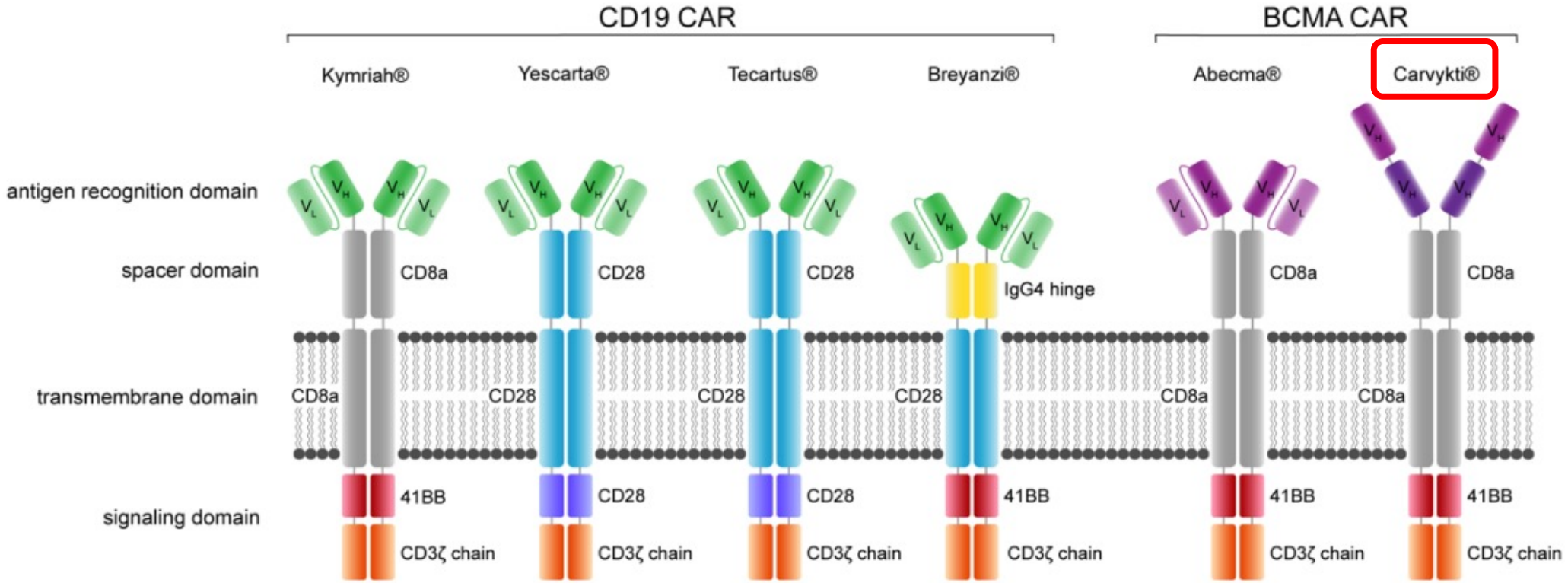
Cilta-cel: Mechanism of Action



Boettcher M, et al. J Clin Med. 2022; 11: 2158.

CAR T=Chimeric antigen receptor T cell (therapy).

Cilta-cel: Mechanism of Action, *continued*



	Kymriah®	Yescarta®	Tecartus®	Breyanzi®	Abecma®	Carvykti®
Gene transfer	SIN Lentivirus	Gammaretrovirus	Gammaretrovirus	SIN Lentivirus	SIN Lentivirus	SIN Lentivirus
Company	Novartis	Kite	Kite	BMS	BMS	Janssen
Promotor	EF1α Promotor	MSCV Promotor	MSCV Promotor	EF1α Promotor	EF1α Promotor	EF1α Promotor
Cell source	T cells	T cells	T cells	CD4/CD8 T cells 1:1	PBMC	PBMC
Activation	CD3/CD28 magnetic beads, cytokine ND	CD3 mAb, IL-2	CD3/CD28 mAb, IL-2	ND	CD3/CD28, IL-2	CD3/CD28, IL-2

Adapted from Boettcher M, et al. J Clin Med. 2022; 11: 2158.

CAR T=Chimeric antigen receptor T cell (therapy).

Cilta-cel: Dosing

- Dose per infusion bag: Cell suspension of 0.5–1×10^6 CAR-positive viable T cells per kg
  - Maximum dose: 1×10^8 CAR-positive viable T cells per single infusion
- Preparation: Once thawed, intravenous infusion must be completed within 2.5 hours at room/ambient temperature (20°C to 25°C)
- Infusion: 30-60 minutes
- No notable drug-drug interactions
  - Some commercial HIV nucleic acid tests (NATs) can yield false-positive results in patients who have received ciltacabtagene autoleucel
- Autologous use only

Ciltacabtagene autoleucel suspension for intravenous infusion: Package Insert. Revised 2/2022. Janssen Biotech: Horsham, PA.

CAR T=Chimeric antigen receptor T cell (therapy).

CARTITUDE-1 trial

Phase 1b/2, randomized, multicenter study

1) Leukapheresis →
2) Lymphodepletion: (300 mg/m² cyclophosphamide + 30 mg/m² fludarabine) IV daily x3 days →
3) Infusion: cilta-cel at target dose 0.75 × 10^6 CAR-positive viable T cells/kg, 5–7 days after start of lymphodepletion

(n=29/phase 1b, n=68/phase 2)

- ≥18yo patients with measurable MM [median age 61yo]
- ≥3 previous lines of therapy or double refractory to PI and IMiD, and have received PI, IMiD, anti-CD38 Ab with documented disease progression at ≤12 months after the last line of therapy [triple-class refractory 88% overall and phase 2]
- ECOG 0-1
- [high risk cytogenetics (del17p, t(14;16), t(4;14) in 24% enrolled patients]

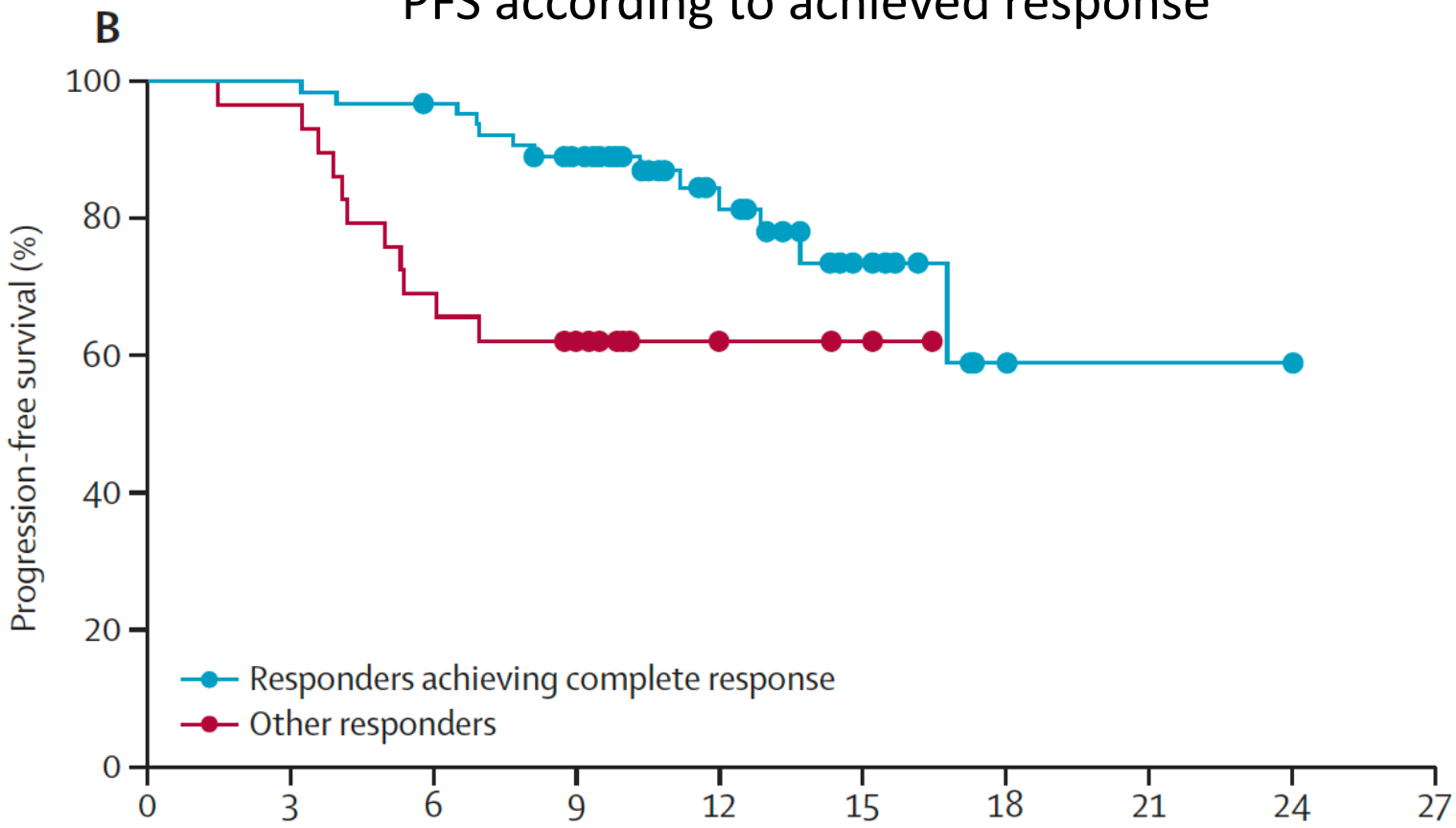
Berdeja JG, et al. Lancet. 2021; 398: 314-324.

CAR T=Chimeric antigen receptor T cell (therapy). IV=intravenous. PI=proteasome inhibitor. IMiD=immunomodulatory drug. Ab=antibody. MM=multiple myeloma. yo=years old.

CARTITUDE-1 trial

- *Primary Outcome (Phase 2):* ORR (proportion of patients who achieved ≥PR) → ORR 97% at median f/u 12.4 months
  - sCR 67%
- Median time to first response: 1 month
  - Median time to best response: 2.6 months
- Median DOR not reached
- 12-month PFS rate 77%
- OS rate 89%

PFS according to achieved response



Berdeja JG, et al. Lancet. 2021; 398: 314-324.

ORR=overall response rate. PR=partial response. DOR=duration of response. f/u=follow-up. PFS=progression-free survival. OS=overall survival.

CARTITUDE-1 trial: Toxicities

All Grades (for ≥29% of all subjects)	
Neutropenia	96%
Cytokine release syndrome	95%
Anemia	81%
Thrombocytopenia	79%
Leukopenia	62%
Lymphopenia	53%
Fatigue	37%
Cough	35%
Hypocalcemia	32%
Hypophosphatemia	31%
Diarrhea	30%
ALT increased	29%
Decreased appetite	29%

Grade ≥3 (for ≥7% of all subjects)	
Neutropenia	95%
Anemia	68%
Thrombocytopenia	60%
Leukopenia	61%
Lymphopenia	50%
Neurotoxicities	9%
Hypophosphatemia	7%

Deaths

- n = 2 : sepsis/septic shock
- n = 1 : CRS and hemophagocytic lymphohistiocytosis
- n = 1 : lung abscess
- n = 1 : respiratory failure
- n = 1 : neurotoxicity
- n = 8 : PD or unrelated to treatment

Berdeja JG, et al. Lancet. 2021; 398: 314-324.

PD=progressive disease. ALT=aminotransferase. CRS=cytokine release syndrome.

Cilta-cel: Myelosuppression

- Monitor blood counts prior to and after infusion
- Monitor patients for s/s of infection
- Monitor and consider immunoglobulin replacement therapy

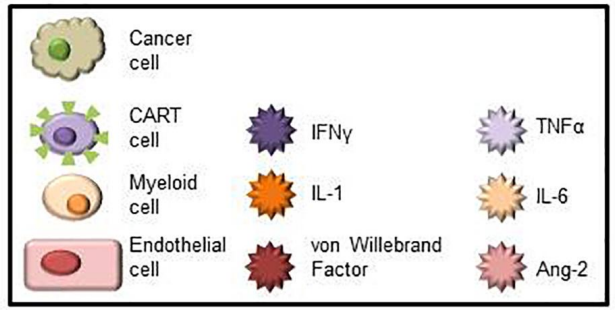
Toxicities from CARTITUDE-1		
	All Grades	**Grades ≥3**
Neutropenia	96%	95%
Anemia	81%	68%
Thrombocytopenia	79%	60%
Leukopenia	62%	61%
Lymphopenia	53%	50%

- Standard/institutional infection prophylaxis and treatment – as well as management of cytopenias – unless otherwise appropriate

Ciltacabtagene autoleucel suspension for intravenous infusion: Package Insert. Revised 2/2022. Janssen Biotech: Horsham, PA.
Berdeja JG, et al. Lancet. 2021; 398: 314-324.

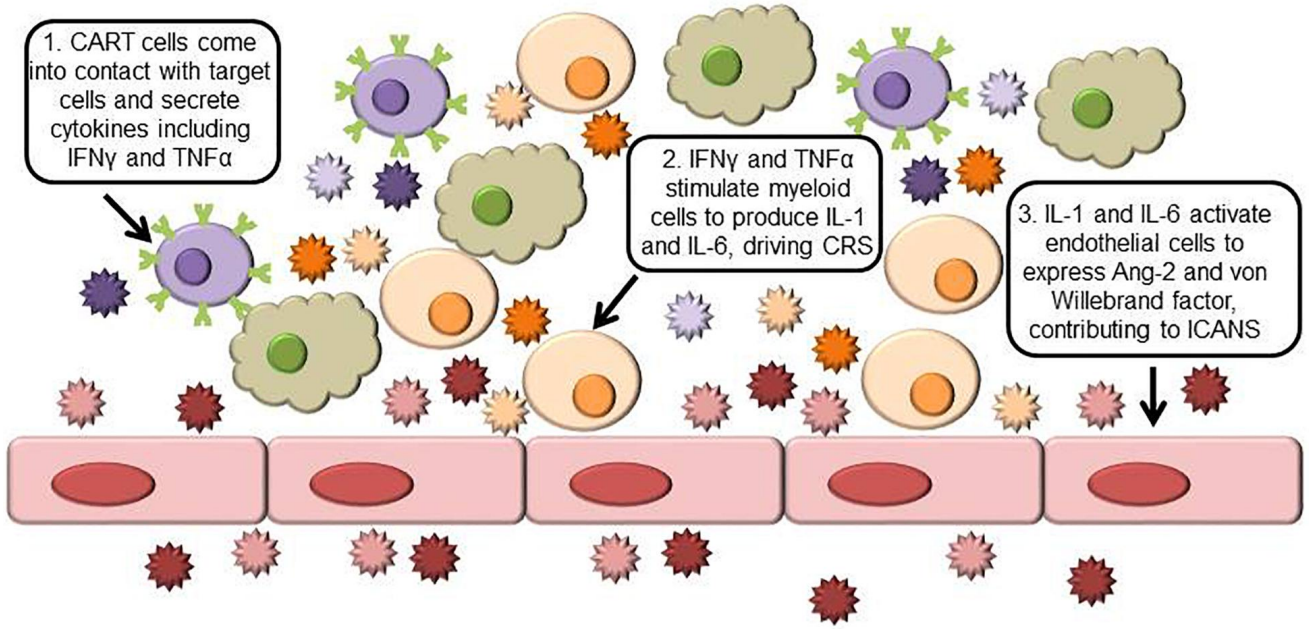
s/s=signs/symptoms.

Cilta-cel: CRS & Neurologic Toxicities



REMS Program

- Monitor patients at least daily for 10 days following infusion at a certified healthcare facility for s/s of CRS and neurologic toxicities
- Monitor periodically for 4 weeks for s/s of delayed neurologic toxicity



Toxicities from CARTITUDE-1		
	All Grades	**Grades ≥3**
Cytokine release syndrome	95%	4%
Neurotoxicities	21%	9%

Ciltacabtagene autoleucel suspension for intravenous infusion: Package Insert. Revised 2/2022. Janssen Biotech: Horsham, PA.
Berdeja JG, et al. Lancet. 2021; 398: 314-324.
Siegler EL and Kenderian SS. Front Immuno. 2020; doi: 10.3389/fimmu.2020.01973.

REMS=Risk Evaluation and Mitigation Strategies. s/s=signs/symptoms.

CRS Management

CRS Grade	Tocilizumab	Corticosteroids
Grade 1 Temperature ≥38°C	*For early (<72 hours post-cilta-cel) onset of fever* **Could consider** tocilizumab 8 mg/kg IV over 1 hour (max 800 mg)	N/A
Grade 2 *Moderate intervention needed* **Gr1 +** HoTN not requiring vasopressors **AND/OR** Hypoxia requiring oxygen via canula or blow-by **OR** Gr2 organ toxicity	**Administer tocilizumab** 8 mg/kg IV over 1 hour (max 800 mg) Repeat tocilizumab q8h PRN if not responsive to IV fluids up to 1L or increasing supplemental oxygen	**Consider** dexamethasone 10 mg IV q12-24h
	If no improvement within 24 hours or rapid progression, **repeat tocilizumab and escalate dexamethasone** to 20 mg IV q6-12h → **If no improvement** within 24 hours or rapid progression, **switch to methylprednisolone** 2 mg/kg IV q12h After 2 doses tocilizumab, consider alternative anti-cytokine; max 3 doses tocilizumab in 24 hours (or 4 doses total)	
Grade 3 *Aggressive intervention needed* **Gr1 +** HoTN requiring 1 vasopressor **AND/OR** Hypoxia requiring more intensive support (e.g., oxygen via HF nasal canula) **OR** Gr3 organ toxicity or Gr4 transaminitis	See Grade 2	**Administer dexamethasone** 10 mg IV q12-24h
	See Grade 2	
Grade 4 *Life-threatening sx; requiring ventilator, CVVHD* **Gr1 +** HoTN requiring >1 vasopressor (this excludes vasopressin) **AND/OR** Hypoxia requiring + pressure **OR** Gr4 organ toxicity (excl. transaminitis)	See Grade 2	Administer **dexamethasone 20** mg IV q12-24h
	After 2 doses tocilizumab, consider alternative anti-cytokine; max 3 doses tocilizumab in 24 hours (or 4 doses total) **If no improvement** within 24 hours, **consider methylprednisolone 1-2 g** IV q24h PRN with taper as clinically indicated OR other immunosuppressants	

Ciltacabtagene autoleucel suspension for intravenous infusion: Package Insert. Revised 2/2022. Janssen Biotech: Horsham, PA.

CRS=cytokine release syndrome.
HoTN=hypotension. IV=intravenous. PRN=as needed. qXh=every X hours.

ICANS Management

CRS Grade	Corticosteroids
Grade 1 ICE score 7-9 **OR** depressed level of consciousness/awakens spontaneously	**Consider** dexamethasone 10mg IV q12-24h for 2-3 days. Consider non-sedating, anti-seizure medications for seizure prophylaxis.
Grade 2 ICE score 3-6 **OR** depressed level of consciousness/awakens to voice	**Administer dexamethasone** 10mg IV q12-24h for 2-3 days or longer for persistent sx. Consider steroid taper if total steroid exposure >3 days. **If no improvement** within 24 hours or rapid progression, **escalate dexamethasone** to **max** 20 mg IV q6h Consider non-sedating, anti-seizure medications for seizure prophylaxis.
Grade 3 ICE score 0-2 (0 only if patient arousable and able to perform assessment) **OR** depressed level of consciousness/awakens to tactile stimulus **OR** seizures (clinical, that resolves rapidly *OR* non-convulsive on EEG that resolves with intervention) **OR** raised ICP (focal/local edema on neuroimaging)	Administer **dexamethasone 10-20mg IV q6h** **If no improvement** within 24 hours or worsening of neuro toxicity, **escalate dexamethasone** to **≥20 mg** IV q6h OR escalate to methylprednisolone 1-2 g/day, repeating q24h PRN. Taper as clinically indicated. Consider non-sedating, anti-seizure medications for seizure prophylaxis. If cerebral edema suspected, consider hyperventilation and hyperosmolar therapy; administer methylprednisolone 1-2 g/day, repeating q24h PRN. Taper steroids as clinically indicated.
Grade 4 ICE score 0 **OR** unarousable, requiring vigorous or repetitive tactile stimuli to arouse *OR* stupor or coma **OR** seizures (life-threatening, >5 min *OR* repetitive clinical or electrical without return to baseline in between) **OR** deep focal motor weakness **OR** raised ICP/cerebral edema with s/s	Administer **dexamethasone 20mg IV q6h** **If no improvement** within 24 hours or worsening of neuro toxicity, **escalate to methylprednisolone** 1-2 g/day, repeating q24h PRN. Taper steroids as clinically indicated. Consider non-sedating, anti-seizure medications for seizure prophylaxis. If cerebral edema suspected, consider hyperventilation and hyperosmolar therapy; administer methylprednisolone 1-2 g/day, repeating q24h PRN. Taper steroids as clinically indicated. Consider neurology and/or neurosurgery consult.

Ciltacabtagene autoleucel suspension for intravenous infusion: Package Insert. Revised 2/2022. Janssen Biotech: Horsham, PA.

ICANS=Immune effector cell-associated neurotoxicity syndrome. ICE=immune effector cell encephalopathy. s/s=signs/symptoms. qXh=every X hours. PRN=as needed.

Additional Counseling Points

- Embryo-Fetal Toxicity: Theoretically could cause fetal harm
  - Verify pregnancy status of females of child-bearing age prior to initiating treatment
  - Not recommended for women who are pregnant, or for women of childbearing potential not using contraception
  - Clinical trials recommended female patients of childbearing potential to practice a highly effective method of contraception AND male patients with partners of childbearing potential or whose partners were pregnant were instructed to use a barrier method of contraception, until 1 year after patient received the infusion
- Lactation: Weigh risks vs. benefits
- If secondary malignancy occurs after treatment, patient to contact manufacturer
- Monitor for hypersensitivity reactions during and 2 hours after infusion for s/s of severe reaction
- Advise patients to refrain from driving and engaging in hazardous activities (e.g., operating heavy or potentially dangerous machinery) for at least 8 weeks after receiving cilta-cel and in the event of any new onset of neurologic toxicities
- Patient to seek immediate medical attention for: CRS, neurologic toxicities, Parkinsonism, Guillain Barré Syndrome, peripheral neuropathy, cranial nerve palsies, infections, prolonged and recurrent cytopenias, hypersensitivity reactions

Ciltacabtagene autoleucel suspension for intravenous infusion: Package Insert. Revised 2/2022. Janssen Biotech: Horsham, PA.

CRS=cytokine release syndrome.

Cilta-cel: Access

- (Fludarabine injection currently on shortage)
- Manufacturer-sourced only
- Administered only at REMS-certified hospitals and associated clinics

Copay assistance?*	Free trial?*	Patient Assistance Program?*
N/A	**N/A**	**Yes** Janssen (assistance with transportation, lodging, and out-of-pocket costs for meals and other travel expenses related to treatment)

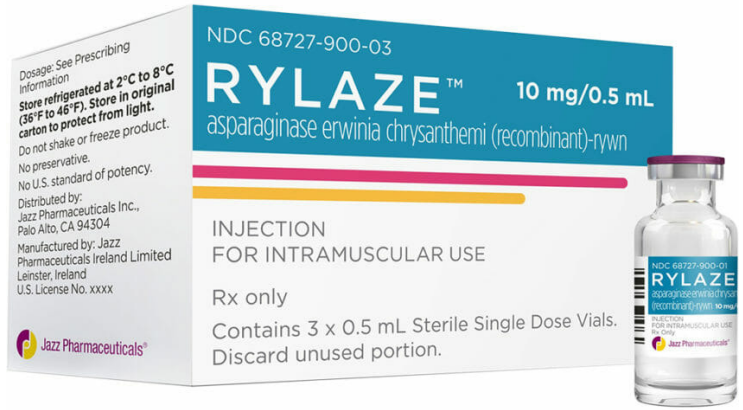
**Program availability and eligibility may frequently vary.*

ASHP Drug Shortages List. Accessed at https://www.ashp.org/drug-shortages/current-shortages .
Pharmaceutical assistance program information. Accessed at https://www.carvyktihcp.com/patient-support.

REMS=Risk Evaluation and Mitigation Strategies.

Asparaginase Erwinia-Chrysanthemi (Recombinant)-rywn (ERW-rywn)

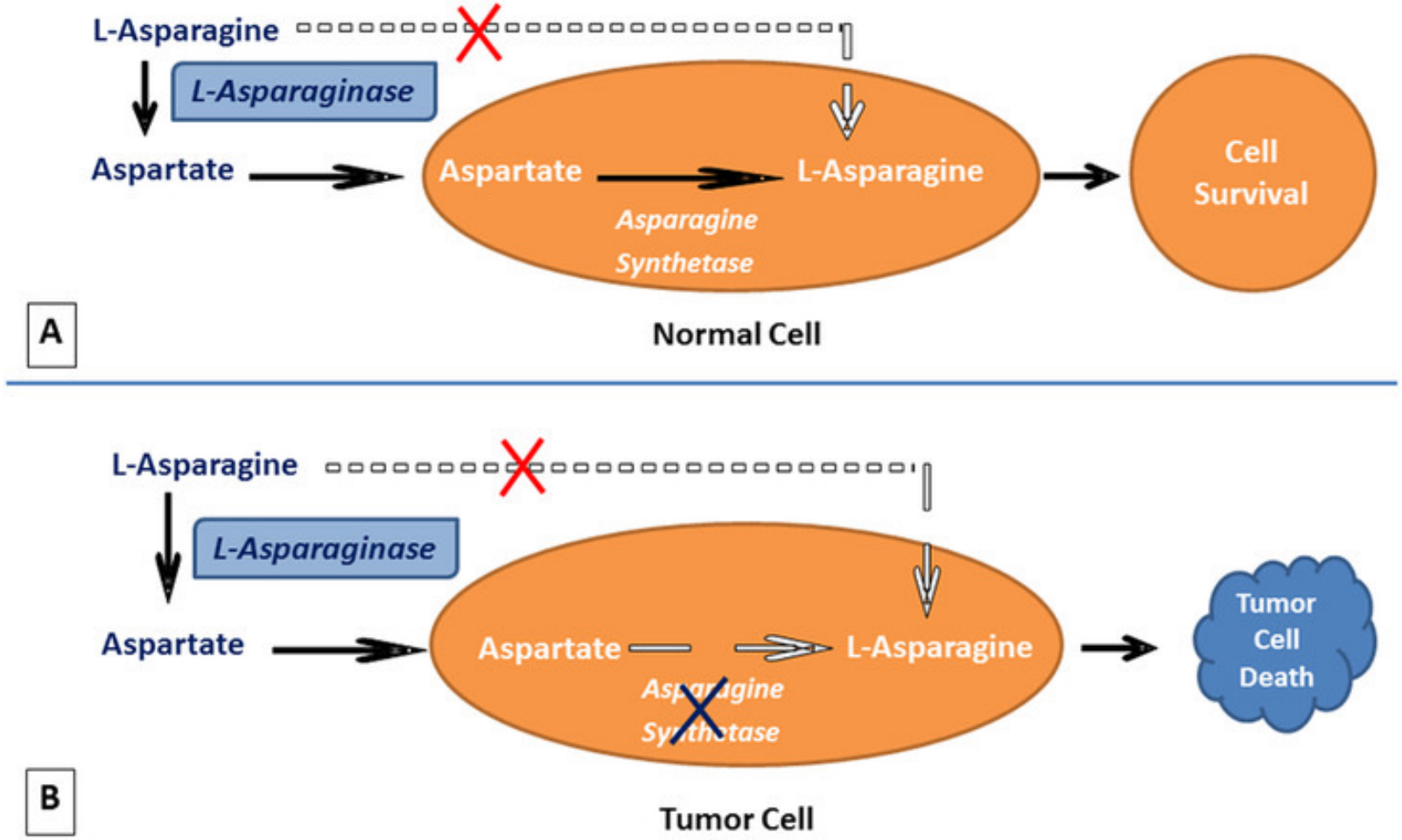
- **FDA-approved indication**:
  - As a component of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) in patients ≥1 month or older who have developed hypersensitivity to E. coli-derived asparaginase
- Other FDA-approved drugs for a similar indication:
  - **Asaparaginase erwinia chrysanthemi** – as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with ALL who have developed hypersensitivity to E. coli-derived asparaginase
  - **Pegaspargase** – indicated as a component of a multi-agent chemotherapeutic regimen for treatment of pediatric and adult patients with ALL and hypersensitivity to asparaginase



Asparaginase erwinia chrysanthemi (recombinant)-rywn injection, for intramuscular use: Package Insert. Revised 6/2021. Jazz Pharmaceuticals: Palo Alto, CA.
Asparaginase erwinia chrysanthemi injection, intramuscular or intravenous use: Package Insert. Revised 3/2016. Jazz Pharmaceuticals: Palo Alto, CA.
Pegaspargase, intramuscular or intravenous use: Package Insert. Revised 11/2021. Servier Pharmaceuticals: Boston, MA.
Image adapted from https://www.clinicaltrialsarena.com/projects/rylaze-asparaginase/.

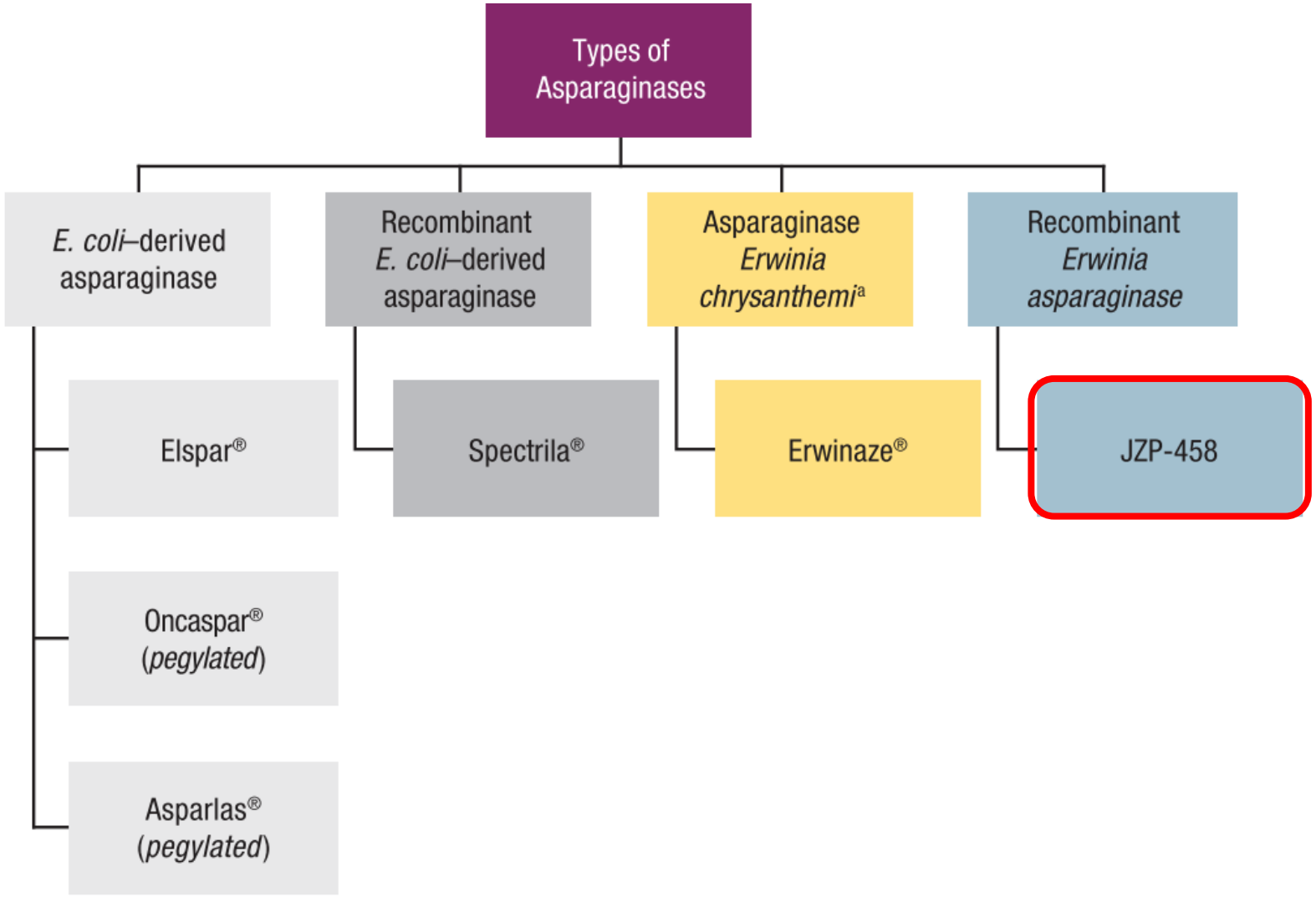
E. coli=Escherichia coli.

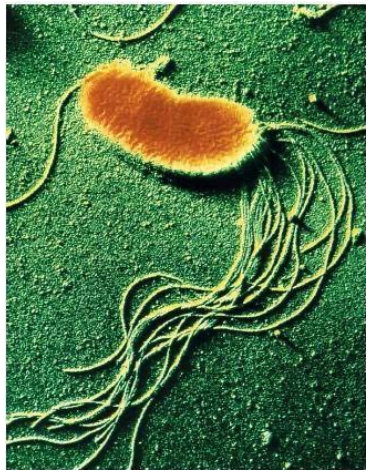
ERW-rywn: Mechanism of Action



Chand S, et al. Biotech and Appl Biochem. 2020; 67: 619-647.

ERW-rywn: Mechanism of Action, *continued*





Adapted from Maese L, et al. Pediat Blood and Cancer. 2021; doi: 10.1002/pbc.29169.
Image from Pseudomonoas fluroescens. Accessed at https://web.mst.edu/~djwesten/MoW/BIO221_2009/P_fluorescens.html.

JZP-458=recombinant Erwinia asparaginase.

ERW-rywn: Dosing

- Injection forms: 10 mg/0.5 mL solution per single-dose vial
- Starting dose: 25 mg/m^2 administered intramuscularly every 48 hours
- No notable drug-drug interactions
- Empiric renal dose adjustment: None recommended (not studied)
- Empiric hepatic dose adjustment: None recommended (not studied)

Asparaginase erwinia chrysanthemi (recombinant)-rywn injection, for intramuscular use: Package Insert. Revised 6/2021. Jazz Pharmaceuticals: Palo Alto, CA.

AALL1931 trial

Phase 2/3, open-label, multicenter, pharmacokinetic study

Cohort 1a, ERW-rywn 25 mg/m^2 M/W/F (n=33)
vs. Cohort 1b, ERW-rywn 37.5 mg/m^2 M/W/F (n=83)
vs. Cohort 1c, ERW-rywn 25 mg/m^2 M/W and 50 mg/m2 F (n=51)

- ALL/LBL patients, regardless of age [median age 10yo]
- History of a grade ≥3 allergic reaction or silent inactivation to a pegylated E. coli–derived asparaginase

Subsequent results: Maese LD, et al. J Clin Oncol. 2022; 40: 7001.
Initial results: Maese L, et al. Blood. 2021; 138: 2307.
Protocol: Maese L, et al. J Clin Oncol. 2020; 38: no. 15_suppl.

M/W/F=Monday/Wednesday/Friday. E. coli=Escherichia coli. ALL/LBL= acute lymphoblastic leukemia/lymphoblastic lymphoma.

AALL1931 trial

- *Primary Outcome:* proportion of patients who achieved last **72-hour** nadir serum asparaginase activity (NSAA) levels ≥0.1 IU/mL in first treatment course → [Maese et al. 2021] 65.5% Cohort 1a, 80.4% Cohort 1b, 93.3% Cohort 1c
  - At **48 hours**: [Maese et al. 2021] 96.9% Cohort 1a, 98.1% Cohort 1b, 93.8% Cohort 1c
- Mean SAA levels (IU/mL) at **72 hours**:
  - 0.16 for Cohort 1a, 0.33 for Cohort 1b, 0.47 for Cohort 1c
- Mean SAA levels at **48 hours**:
  - 0.45 for Cohort 1a, 0.88 for Cohort 1b, 0.66 for Cohort 1c

Maese LD, et al. J Clin Oncol. 2022; 40: 7001.
Maese L, et al. Blood. 2021; 138: 2307.

IU=international units.

AALL1931 trial: Toxicities

Arm 1a: 25 mg/m² (M/W/F)

All Grades (for ≥24% of all subjects)		Grade 3-4 (for ≥9% of all subjects)	
Abnormal LFTs (Hepatotoxicity)	70% (9%)	Febrile neutropenia	24%
Nausea	46%	Infection	12%
Musculoskeletal pain	39%	Abnormal LFTs	12%
Fatigue	36%	Nausea	9%
Infection	30%	Stomatitis	9%
Headache	30%	Dehydration	9%
Pyrexia	27%		
Febrile neutropenia	24%		
Drug hypersensitivity (Allergic reaction)	24% (6%)		

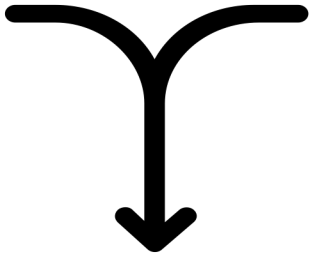
Deaths
(n = 0)

Maese LD, et al. J Clin Oncol. 2022; 40: 7001.
Maese L, et al. Blood. 2021; 138: 2307.
Asparaginase erwinia chrysanthemi (recombinant)-rywn injection, for intramuscular use: Package Insert. Revised 6/2021. Jazz Pharmaceuticals: Palo Alto, CA.

ERW-rywn: Hypersensitivity

Arm 1a: 25 mg/m ^{2} (M/W/F)

Monitor for signs or symptoms of hypersensitivity



Toxicities from AALL1931 *(subsequent results)*		
	All Grades	**Grades ≥3**
Drug hypersensitivity *(Allergic reaction)*	24% *(6%)*	6%

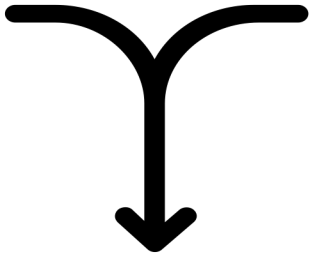
Reason for Dose Adjustment	Manufacturer Guidance
Hypersensitivity	• Grade 2: Treat symptoms • Grade 3-4: Discontinue permanently

Maese LD, et al. J Clin Oncol. 2022; 40: 7001.
Maese L, et al. Blood. 2021; 138: 2307.
Asparaginase erwinia chrysanthemi (recombinant)-rywn injection, for intramuscular use: Package Insert. Revised 6/2021. Jazz Pharmaceuticals: Palo Alto, CA.

ERW-rywn: Hepatotoxicity

Arm 1a: 25 mg/m ^{2} (M/W/F)

- Monitor Tbili, transaminases prior to treatment every 2-3 weeks and as indicated clinically
- Contraindicated: Serious hemorrhagic events during previous L-asparaginase therapy



Toxicities from AALL1931 *(subsequent results)*		
	All Grades	**Grades ≥3**
Abnormal LFTs (Hepatotoxicity)	70% *(9%)*	12%

Reason for Dose Adjustment	**Manufacturer Guidance**
Hepatotoxicity	• Tbili >3x to ≤10x ULN: Hold until Tbili decreases to ≤1.5x ULN • Tbili >10x ULN: Discontinue; do not make up missed doses

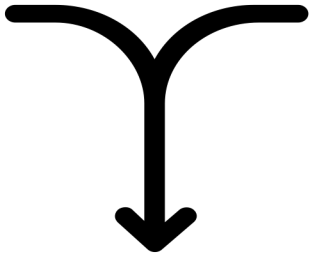
Maese LD, et al. J Clin Oncol. 2022; 40: 7001.
Maese L, et al. Blood. 2021; 138: 2307.
Asparaginase erwinia chrysanthemi (recombinant)-rywn injection, for intramuscular use: Package Insert. Revised 6/2021. Jazz Pharmaceuticals: Palo Alto, CA.

Tbili=Total bilirubin. LFTs=liver function tests. ULN=upper limit of normal.

ERW-rywn: Thrombosis

Arm 1a: 25 mg/m ^{2} (M/W/F)

Contraindicated: Serious thrombosis during previous L-asparaginase therapy



Toxicities from AALL1931 *(subsequent results)*		
	All Grades	**Grades ≥3**
(Thrombosis)	-- *(9%)*	--

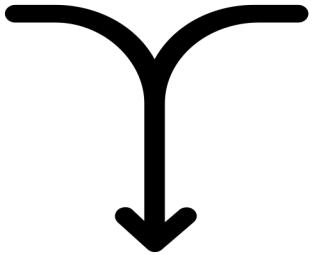
Reason for Dose Adjustment	Manufacturer Guidance
Thrombosis	• Uncomplicated: Hold and treat with appropriate antithrombotic therapy. Upon resolution of symptoms, consider resuming while continuing antithrombotic therapy • Severe/Life-threatening: Discontinue permanently; treat with appropriate antithrombotic therapy

Maese LD, et al. J Clin Oncol. 2022; 40: 7001.
Maese L, et al. Blood. 2021; 138: 2307.
Asparaginase erwinia chrysanthemi (recombinant)-rywn injection, for intramuscular use: Package Insert. Revised 6/2021. Jazz Pharmaceuticals: Palo Alto, CA.

ERW-rywn: Pancreatitis

Arm 1a: 25 mg/m ^{2} (M/W/F)

- Monitor for symptoms
- Contraindicated: serious pancreatitis during previous L-asparaginase therapy



Toxicities from AALL1931 *(subsequent results)*		
	All Grades	**Grades ≥3**
Pancreatitis	-- *(0)*	--
Abdominal pain	18%	0

Reason for Dose Adjustment	Manufacturer Guidance
Pancreatitis	• Grade 2-4: Hold for elevated lipase or amylase >2x ULN or symptomatic pancreatitis. Resume treatment when lipase and amylase are <1.5x ULN and symptoms resolved. Discontinue permanently if clinical necrotizing or hemorrhagic pancreatitis confirmed

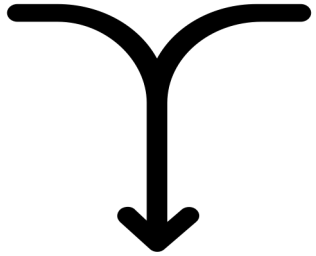
Maese LD, et al. J Clin Oncol. 2022; 40: 7001.
Maese L, et al. Blood. 2021; 138: 2307.
Asparaginase erwinia chrysanthemi (recombinant)-rywn injection, for intramuscular use: Package Insert. Revised 6/2021. Jazz Pharmaceuticals: Palo Alto, CA.

ULN=upper limit of normal.

ERW-rywn: Hyperglycemia

Arm 1a: 25 mg/m ^{2} (M/W/F)

Monitor glucose prior to treatment every 2-3 weeks and as indicated clinically



Toxicities from AALL1931 *(Not reported in subsequent results)*		
	All Grades	**Grades ≥3**
Hyperglycemia	21%	3%

- Standard/institutional hyperglycemia management unless otherwise appropriate

Maese LD, et al. J Clin Oncol. 2022; 40: 7001.
Maese L, et al. Blood. 2021; 138: 2307.
Asparaginase erwinia chrysanthemi (recombinant)-rywn injection, for intramuscular use: Package Insert. Revised 6/2021. Jazz Pharmaceuticals: Palo Alto, CA.

ERW-rywn: Hemorrhage

Arm 1a: 25 mg/m ^{2} (M/W/F)

Contraindicated: Serious hemorrhagic events during previous L-asparaginase therapy

Toxicities from AALL1931 *(Not reported in subsequent results)*		
	All Grades	**Grades ≥3**
Hemorrhage	21%	0

Reason for Dose Adjustment	Manufacturer Guidance
Hemorrhage	• Grade 3-4: Hold therapy; evaluate for coagulopathy and consider clotting factor replacement PRN. Resume with next scheduled dose if bleeding controlled

Maese LD, et al. J Clin Oncol. 2022; 40: 7001.
Maese L, et al. Blood. 2021; 138: 2307.
Asparaginase erwinia chrysanthemi (recombinant)-rywn injection, for intramuscular use: Package Insert. Revised 6/2021. Jazz Pharmaceuticals: Palo Alto, CA.

PRN=as needed.

ERW-rywn: Myelosuppression

Arm 1a: 25 mg/m ^{2} (M/W/F)

Monitor complete blood counts regularly during therapy and manage by treatment interruption or dose reduction

Toxicities from AALL1931
(Not reported in subsequent results)

	All Grades	Grades ≥3
Febrile neutropenia	24%	24%
Infection	30%	12%

- Standard/institutional infection prophylaxis and treatment unless otherwise appropriate

Maese LD, et al. J Clin Oncol. 2022; 40: 7001.
Maese L, et al. Blood. 2021; 138: 2307.
Asparaginase erwinia chrysanthemi (recombinant)-rywn injection, for intramuscular use: Package Insert. Revised 6/2021. Jazz Pharmaceuticals: Palo Alto, CA.

Additional Counseling Points

- Embryo-Fetal Toxicity: Can cause fetal harm
  - Recommended to verify pregnancy status of females of reproductive potential prior to initiating treatment
  - Advise females of reproductive potential to use effective non-hormonal contraception during treatment with asparaginase erwinia-chrysanthemi (recombinant)-rywn and for 3 months after the last dose
- Lactation: Advise not to breastfeed during treatment and for ≥1 week after the last dose (lack of data)
- Minimal emetic risk vs. reported incidence of nausea for Cohort 1a in initial results of AALL1931 (all-grade: 45%, grades 3-4: 9%)
- Hypertriglyceridemia: NCCN guidelines for ALL recommend for Grade 4 hypertriglyceridemia – hold asparaginase and resume when normalized; treat as indicated. Some experts consider gemfibrozil or other fibrates, particularly for high-grade triglyceridemia (>1000 mg/dL).

Asparaginase erwinia chrysanthemi (recombinant)-rywn injection, for intramuscular use: Package Insert. Revised 6/2021. Jazz Pharmaceuticals: Palo Alto, CA.
Maese L, et al. Blood. 2021; 138: 2307.
NCCN (Antiemesis). Ettinger DS, et al. V2.2022.
NCCN (Acute Lymphoblastic Leukemia). Shah B, et al. V1.2022.
Juluri KR, et al. Blood Lymphat Cancer. 2022; 55-79.

ALL= acute lymphoblastic leukemia. NCCN=National Comprehensive Cancer Network.

ERW-rywn: Access

- Medication not currently on shortage
- Select authorized distributors

Copay assistance?*	Free trial?*	Patient Assistance Program?*
Yes U.S. resident; commercial insurance; copay support with annual maximum after copay of $10+; valid through one calendar year *Other conditions may apply.*	**No**	**Yes** Jazz Pharmaceuticals

**Program availability and eligibility may frequently vary.*

ASHP Drug Shortages List. Accessed at https://www.ashp.org/drug-shortages/current-shortages .
Pharmaceutical assistance program information. Accessed at https://jazzcares.com/hcp/rylaze/.

Audience Question

Which of the following would be the most appropriate counseling point or intervention?

A. For Ph+ CML-CP with T315I mutation, the approved dosing regimen for asciminib is 80 mg by mouth daily with a full meal
B. With concomitant omeprazole, the starting dose of belumosudil should be increased to 200 mg twice daily
C. For grade 2 CRS and grade 2 ICANS after cilta-cel infusion, an appropriate starting dose of dexamethasone is 20 mg IV q6h
D. For a total bilirubin increase to 6x ULN (compared to normal baseline), permanently discontinue ERW-rywn

Ph+ CML-CP=Philadelphia chromosome-positive chronic myeloid leukemia-chronic phase. CRS=cytokine release syndrome. ICANS=immune effector cell-associated neurotoxicity syndrome. Cilta-cel=ciltacabtagene autoleucel. ERW-rywn=asparaginase erwinia chrysanthemi (recombinant)-rywn. IV=intravenous. qXh=every X hours. ULN=upper limit of normal.

Reference: New Agents for Non-Malignant Hematologic Indications

Approval Date	Medication	Indication	Mechanism of Action & Starting Dose	Common Adverse Effects
2/28/22	**Pacritinib**	adults with intermediate or high-risk primary or secondary (post-PCV or post-essential TCP) MF with platelet <50 × 10^9/L	• kinase inhibitor against wt JAK2, mut JAK2V617F, and FLT3 → impacts signaling of cytokines and growth factors important for hematopoiesis and immune function (MF associated with dysregulated JAK2 signaling) • 200 mg PO twice daily, with(out) food	(≥20% patients): diarrhea, thrombocytopenia, nausea, anemia, peripheral edema
2/5/22	**Sutimlimab-jome**	decrease the need for RBC transfusion due to hemolysis in adults with CAD	• IgG4 mAb inhibits classical complement pathway by binding to complement protein component 1, s subcomponent that cleaves C4 • 39 kg to <75 kg: 6,500 mg IV • ≥75 kg: 7,500 mg IV	(≥10% patients): respiratory tract infection, viral infection, diarrhea, dyspepsia, cough, arthralgia, arthritis, peripheral edema
11/12/21	**Ropeginterferon alfa-2b-njft**	adults with PCV	• IFNa binds to a transmembrane receptor (IFNa receptor) → initiates signaling cascade via activation of JAK1, TYK2, and STAT proteins → impacts gene-expression programs • 100 mcg SQ every 2 weeks (50 mcg if receiving hydroxyurea)	(>40% patients): influenza-like illness, arthralgia, fatigue, pruritus, nasopharyngitis, musculoskeletal pain

FDA Oncology (Cancer) / Hematologic Malignancies Approval Notifications. Accessed at https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications.

PCV=polycythemia vera. TCP=thrombocytopenia. MF=myelofibrosis. wt JAK2=wild type Janus associated kinase 2. mut=mutated. FLT3= FMS-like tyrosine kinase 3. PO=by mouth. RBC=red blood cell. CAD=cold agglutinin disease. IV=intravenously. IgG(4)=immunoglobulin G (subclass 4). mAb=monoclonal antibody. SQ=subcutaneously. JAK1= Janus kinase 1. TYK2= tyrosine kinase 2. STAT= activator of transcription. IFNa=interferon alfa.

Reference: New Malignant Hematology Indications for Agents with ≥1 Prior Approval

Approval Date	Medication	Indication
6/24/22	**Lisocabtagene maraleucel**	adult patients with LBCL refractory to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy; or refractory to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and not eligible for HSCT due to comorbidities or age
5/27/22	**Tisagenlecleucel**	adult patients with relapsed or refractory FL after ≥2 lines of systemic therapy
5/25/22	**Ivosidenib *plus* Azacitidine**	newly diagnosed AML with susceptible IDH1 mutation in adults 75 years or older or with comorbidities
5/20/22	**Azacitadine**	pediatric patients with newly diagnosed JMML
4/1/22	**Axicabtagene ciloleucel**	adult patients with LBCL refractory to first-line chemoimmunotherapy or relapsed within 12 months of first-line chemoimmunotherapy
12/15/21	**Abatacept (*plus* CNI and MTX)**	prophylaxis of aGVHD in patients ≥2 y.o. undergoing HSCT from a matched or 1 allele-mismatched unrelated donor
12/2/21	**Rituximab *plus* chemotherapy**	pediatric patients (≥6 months to <18 years) with previously untreated, advanced stage, CD20-positive DLBCL, BL, BLL, or mature B-AL

FDA Oncology (Cancer) / Hematologic Malignancies Approval Notifications. Accessed at https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications.

LBCL=large B-cell lymphoma. HSCT=hematopoietic stem cell transplantation. FL=follicular lymphoma. DLBCL=diffuse large B-cell lymphoma. aGVHD=acute graft-versus-host disease. CNI=calcineurin inhibitor. MTX=methotrexate. B(L)L= Burkitt(-like) lymphoma. B-AL=B-cell acute leukemia.

Reference: New Malignant Hematology Indications for Agents with ≥1 Prior Approval, *continued*

Approval Date	Medication	Indication
11/30/21	**Daratumumab/hyaluronidase-fihj *plus* Carfilzomib *plus* Dex**	adult patients with relapsed or refractory MM who have received 1–3 prior lines of therapy
10/1/21	**Brexucabtagene autoleucel**	adult patients with relapsed or refractory B-cell precursor ALL
9/22/21	**Ruxolitinib**	cGVHD s/p failure of 1–2 lines of systemic therapy in patients ≥12 y.o.
9/15/21	**Zanubrutinib**	adult patients with relapsed or refractory MZL who have received ≥1 anti–CD20-based regimen
9/1/21	**Zanubrutinib**	adult patients with Waldenström's macroglobulinemia
7/9/21	**Daratumumab/hyaluronidase-fihj *plus* Pomalidomide *plus* Dex**	adult patients with MM who have received ≥1 prior line of therapy, including lenalidomide and a proteasome inhibitor
6/16/21	**Avapritinib**	adult patients with advanced systemic mastocytosis, systemic mastocytosis with associated hematologic neoplasm, and mast cell leukemia

FDA Oncology (Cancer) / Hematologic Malignancies Approval Notifications. Accessed at https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications.

HSCT=hematopoietic stem cell transplantation. Dex=dexamethasone. MM=multiple myeloma. ALL=acute lymphoblastic leukemia. cGVHD=chronic graft-versus-host disease. y.o.=years old. s/p=status post. MZL= marginal zone lymphoma.

Thank You

Grace Baek, PharmD, BCOP
Clinical Hematology/Oncology Pharmacist
Fred Hutchinson Cancer Center
gbaek@uw.edu