Cancer Chemotherapy Update

Alectinib, Ceritinib, Elotuzumab, and Venetoclax

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The complexity of cancer chemotherapy requires pharmacists be familiar with the complicated regimens and highly toxic agents used. This column reviews various issues related to preparation, dispensing, and administration of antineoplastic therapy, and the agents, both commercially available and investigational, used to treat malignant diseases. Questions or suggestions for topics should be addressed to Dominic A. Solimando, Jr, President, Oncology Pharmacy Services, Inc., 4201 Wilson Blvd #110-545, Arlington, VA 22203, e-mail: OncRxSvc@comcast.net; or J. Aubrey Waddell, Professor, University of Tennessee College of Pharmacy; Oncology Pharmacist, Pharmacy Department, Blount Memorial Hospital, 907 E. Lamar Alexander Parkway, Maryville, TN 37804, e-mail: waddfour@charter.net.

Drug name: Alectinib

Synonyms: *Alecensa*, CH5424802, R05424802

MECHANISM OF ACTION

The anaplastic lymphoma kinase (ALK) rearranged gene is a fusion tyrosine kinase gene made up of the ALK gene and the echinoderm microtubule-associated protein-like 4 (EML4) gene. This ALK rearrangement is a cause of increased transforming activity and tumorigenicity in non-small-cell lung cancer (NSCLC).^{1,2} Alectinib is a highly selective oral ALK inhibitor with high antitumor activity in vitro and in vivo against ALK-rearranged NSCLC. Alectinib overcomes the 2 most common ALK resistance mutations (Leu1196Met and Gly1269Ala) in preclinical models, but it is inactive against the less common Gly1202Arg and Ile1171 mutations.^{3,4}

PHARMACOKINETICS

After 21 days of 300 mg twice-daily oral dosing in the fasting and fed states, mean pharmacokinetic parameters were time to peak serum concentration (T_{max}) 3.99 and 5.32 hours, peak serum concentration (C_{max}) 259 to 575 and 528 ng/mL, trough serum concentration (C_{min}) 145 to 463 and 425 ng/mL, and area under the curve 0 to 10 hours (AUC_{0-10}) 1,800 to 4,970 and 4,220 ng•h/mL, respectively.^{2,5} After 21 days of 600 mg twice-daily oral dosing in the fed state, mean pharmacokinetic parameters were C_{max} 676 ng/mL,

C_{min} 502 ng/mL, and AUC_{0-10} 5400 ng•h/mL, while median T_{max} was 4.17 hours.⁵ After administration of 600 mg orally (PO) twice daily, the extrapolated C_{min} of alectinib in cerebrospinal fluid (CSF) and unbound alectinib in plasma were 2.69 nmol/L and 3.12 nmol/L, respectively.⁵ The major active metabolite of alectinib, M4, demonstrated steady-state values of C_{max} 246 ng/mL and AUC_{0-12} 2,810 ng•h/mL.⁶ The absolute bioavailability of alectinib under fed conditions is 37%.⁶ The apparent volume of distribution (V_d) is 4,016 L for alectinib and 10,093 L for M4.⁶ The plasma protein binding of both alectinib and M4 is greater than 99%, the apparent clearance is 81.9 L/h for alectinib and 217 L/h for M4, and the mean elimination half-life ($t_{1/2}$) is 33 hours for alectinib and 31 hours for M4.⁶ Alectinib is metabolized by CYP3A4 to its major active metabolite M4, which is also metabolized by CYP3A4.⁶ Ninety-eight percent of alectinib and metabolites is excreted through the feces, with alectinib accounting for 84% and M4 6%; urinary excretion accounts for less than 0.5% of alectinib.⁶ Selected therapeutic regimens of alectinib appear in Table 1.

PREPARATION

1. Follow institutional policies for handling hazardous medications when dispensing alectinib.
2. Alectinib is available as 150 mg capsules.⁶
3. The manufacturer recommends that the capsules not be opened or the contents dissolved.⁶

Table 1. Selected therapeutic regimens of alectinib

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/cycle	References
300 mg twice daily	PO	1-28	28 days	16,800 mg	5
600 mg twice daily ^a	PO	1-28	28 days	33,600 mg	5, 7, 8

Note: PO = oral.

^aConforms to dosing information listed in the manufacturer's labeling.

STABILITY

1. Store below 30°C (86°F).⁶
2. The manufacturer recommends that the capsules be kept in the original container until time of administration.⁶

ADMINISTRATION

1. Alectinib should be taken orally twice daily with food. Neither the manufacturer nor the studies reviewed specified the exact time interval of twice daily.^{2,5-8}
2. If a dose of alectinib is missed or vomiting occurs shortly after a dose, take the next dose at its scheduled time.⁶

TOXICITIES

Most of the toxicities listed below are presented according to their degree of severity. Higher grades represent more severe toxicities. Although there are several grading systems for cancer chemotherapy toxicities, all are similar. One of the frequently used systems is the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (<http://ctep.cancer.gov>). Oncologists generally do not adjust doses or change therapy for grade 1 or 2 toxicities but make, or consider, dosage reductions or therapy changes for grade 3 or 4 toxicities. Incidence values are rounded to the nearest whole percent unless incidence was less than or equal to 0.5%.

- A. Cardiovascular:** Cerebrovascular accident (grade 3) 1%⁷; embolic stroke (grade 4) 1%⁷; generalized edema (grade 3) 1%⁷; peripheral edema (grade 1 or 2) 8% to 23%, (grade 3) 1%^{7,8}; QT interval prolongation (grade 3) 1%.⁷
- B. Constitutional:** Asthenia (grade 1 or 2) 10%, (grade 3) 1%⁸; fatigue (grade 1 or 2) 13% to 33%, (grade 3) 1%.^{7,8}
- C. Central Nervous System:** Brain edema (grade 4) 1%⁷; cerebral ventricle dilatation (grade 3) 1%⁷; confusional state (grade 3) 1%⁷; dizziness (grade 1

or 2) 10%⁷; headache (grade 1 or 2) 21%⁷; hemiparesis (grade 1 or 2) 1%, (grade 3) 1%⁷; insomnia (grade 1 or 2) 11%⁷; seizure (grade 1 or 2) 2%, (grade 3) 1%.⁷

- D. Dermatologic:** Dry skin (grade 1 or 2) 5%,⁸ photosensitivity (grade 1 or 2) 9% to 10%,^{7,8} rash (grade 1 or 2) 9%.⁸
- E. Endocrine/Metabolic:** Creatine phosphokinase (CPK) elevations (grade 1 or 2) 14%, (grade 3) 8%⁷; decreased albumin (grade 1 or 2) 5%, (grade 3) 1%⁷; decreased calcium (grade 1 or 2) 2%, (grade 3) 1%⁷; decreased phosphorous (grade 1 or 2) 2%, (grade 3) 2%⁷; decreased potassium (grade 1 or 2) 7%, (grade 3) 2%⁷; decreased sodium (grade 1 or 2) 2%, (grade 4) 1%⁷; impaired glucose tolerance (grade 3) 1%⁷; triglyceride elevations (grade 1 or 2) 6%, (grade 3) 2%.⁷
- F. Gastrointestinal:** Constipation (grade 1 or 2) 14% to 36%^{7,8}; diarrhea (grade 1 or 2) 4% to 21%, (grade 3) 1%^{7,8}; intestinal obstruction (grade 3) 1%⁷; malnutrition (grade 3) 1%⁷; nausea (grade 1 or 2) 6% to 22%^{7,8}; vomiting (grade 1 or 2) 11%⁷; weight increase (grade 1 or 2) 16%.⁷
- G. Hematologic:** Anemia (grade 1 or 2) 17%, (grade 4) 1%⁷; lymphopenia (grade 1 or 2) 1%, (grade 3) 1%⁷; neutropenia (grade 1 or 2) 3%, (grade 3) 1%⁷; prolonged activated partial thromboplastin time (grade 1 or 2) 5%, (grade 3) 1%.⁷
- H. Hepatic:** Alkaline phosphatase elevations (grade 1 or 2) 13%⁷; ammonia elevations (grade 3) 1%⁷; alanine aminotransferase (ALT) elevations (grade 1 or 2) 8% to 13%, (grade 3) 1% to 6%, (grade 4) 1%^{7,8}; aspartate aminotransferase (AST) elevations (grade 1 or 2) 9% to 16%, (grade 3) 1% to 5%, (grade 4) 1%^{7,8}; drug-induced liver injury (grade 3) 1%⁷; total bilirubin elevations (grade 1 or 2) 6% to 7%, (grade 3) 1%.^{7,8}
- I. Infection:** Influenza (grade 3) 1%⁷; lung (grade 1 or 2) 1%, (grade 3) 1%⁷; staphylococcal sepsis (grade 3) 1%⁷; upper respiratory tract (grade 1 or 2) 10%.⁷

- J. Musculoskeletal:** Back pain (grade 1 or 2) 10%⁷; myalgia (grade 1 or 2) 16% to 24%, (grade 3) 1%.^{7,8}
- K. Pulmonary:** Cough (grade 1 or 2) 17%⁷; dyspnea (grade 1 or 2) 15%, (grade 3) 3%⁷; obstructive airway disorder (grade 3) 1%.⁷
- L. Treatment-Related Mortality:** Hemorrhage while also on anticoagulants (1%),⁷ intestinal perforation (1%).⁸

DOSAGE MODIFICATIONS (ASSUMING A DOSAGE OF 600 MG ORALLY TWICE DAILY)

A. Hepatic:

1. For ALT or AST elevations greater than 5 times the upper limit of normal (ULN) with total bilirubin less than or equal to 2 times ULN, hold alectinib until recovery of ALT/AST to less than or equal to 3 times ULN, then resume at 450 mg twice daily.⁶
2. For ALT or AST elevations greater than 3 times ULN with total bilirubin greater than 2 times ULN in absence of cholestasis or hemolysis, permanently discontinue alectinib.⁶
3. For total bilirubin elevation greater than 3 times ULN, hold alectinib until total bilirubin is less than or equal to 1.5 times ULN, then resume at 450 mg twice daily.⁶

B. CPK:

1. For CPK elevation greater than 5 times ULN, hold alectinib until recovery to less than or equal to 2.5 times ULN, then resume at 450 mg twice daily.⁶
2. For CPK elevation greater than 10 times ULN or second occurrence of CPK elevation greater than 5 times ULN, hold until recovery to less than or equal to 2.5 times ULN, then resume at 300 mg twice daily.⁶

downstream signaling pathways and causing inhibition of ALK-positive cells. Ceritinib also inhibits insulin-like growth factor 1 receptor (IGF-1R), insulin receptor (InsR), and ROS1; it does not inhibit MET.⁹⁻¹²

PHARMACOKINETICS

Ceritinib is highly (97%) protein bound; the V_d is 4,230 L.¹⁰ The C_{max} is 800 ± 205 ng/mL at approximately 4 to 6 hours following a single dose of 750 mg. At day 8, the mean AUC was $16,500 \pm 4,750$ ng•mL/h; steady-state concentration is reached at about day 15. The mean terminal half-life ($T_{1/2}$) is approximately 40 to 41 hours.¹²

Ceritinib is metabolized in the liver primarily by the CYP3A isoenzyme.¹¹ Approximately 92% of the drug is excreted in the feces (68% as unchanged drug); 1.3% is excreted in the urine.¹⁰ Selected therapeutic regimens of ceritinib appear in **Table 2**.

PREPARATION

1. Follow institutional policies for preparation of hazardous medications when dispensing ceritinib.
2. Ceritinib is available as 150 mg capsules.

STABILITY

1. Ceritinib should be stored at room temperature (25°C [77°F]).
2. Brief (less than 24 hours) exposure to temperatures between 15°C and 30°C (59°F and 86°F) is acceptable.

ADMINISTRATION

1. Ceritinib is given orally, preferentially on an empty stomach (not within 2 hours of a meal).
2. Missed doses should not be taken within 12 hours of the next scheduled dose.

TOXICITIES

Most of the toxicities listed below are presented according to their degree of severity. Higher grades represent more severe toxicities. Although there are several grading systems for cancer chemotherapy toxicities, all are similar. One of the frequently used systems is the NCI Common Terminology Criteria for Adverse Events (<http://ctep.cancer.gov>). Oncologists generally do not adjust doses or change therapy for grade 1 or 2 toxicities but make, or consider, dosage reductions or therapy changes for grade 3 or 4 toxicities. Incidence

Drug name: Ceritinib

Synonyms: LDK 378, LDK-378, LDK378, NVP-LDK378, Zykadia

MECHANISM OF ACTION

Ceritinib is a small-molecule tyrosine kinase inhibitor that inhibits several targets. Ceritinib's primary mechanism of action is phosphorylation of the anaplastic lymphoma kinase (ALK) and ALK-mediated phosphorylation of STAT3, suppressing

Table 2. Selected therapeutic regimens of ceritinib

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/ month	References
50 mg	PO	Daily	–	1,500 mg	12
100 mg	PO	Daily	–	3,000 mg	12
200 mg	PO	Daily	–	6,000 mg	12
300 mg	PO	Daily	–	9,000 mg	12
300-560 mg	PO	Daily	–	9,000-16,800 mg	18
400 mg	PO	Daily	–	12,000 mg	12
500 mg	PO	Daily	–	15,000 mg	12
600 mg	PO	Daily	–	18,000 mg	12
650 mg	PO	Daily	–	19,500 mg	12
700 mg	PO	Daily	–	21,000 mg	12
750 mg ^a	PO	Daily	–	22,500 mg	10, 12-17, 19, 20
900 mg	PO	Daily	–	27,000 mg	12
1,050 mg	PO	Daily	–	31,500 mg	12

Note: PO = oral.

^aConforms to dosing information listed in the manufacturer's labeling.

values are rounded to the nearest whole percent unless incidence was less than or equal to 0.5%.

- A. **Cardiovascular:** Acute pericarditis 33%.¹³
- B. **Constitutional:** Fatigue (grade 2) 33% to 36%,^{13,20} (grade 3 or 4) 5% to 10%¹²; fever 26%.¹⁸
- C. **Endocrine/Metabolic:** Hyperglycemia 2% to 4%,¹² hypophosphatemia (grade 3 or 4) 3% to 10%,¹² increased alkaline phosphatase (grade 3 or 4) 2% to 20%.¹²
- D. **Gastrointestinal:** Anorexia 41%¹⁸; diarrhea/abdominal discomfort (grade 1 or 2) 33%¹³; diarrhea 80% to 86%,^{16-18,20} (grade 1) 33%,¹³ (grade 3 or 4) 7% to 10%^{12,18}; increased amylase (grade 3 or 4) 2% to 10%¹²; nausea 54% to 81%,^{16,17,20} (grade 3 or 4) 5% to 10%¹²; nausea (grade 3 or 4) 5% to 10%¹²; vomiting 63% to 82%,^{16,18,20} (grade 1) 33%,¹³ (grade 3 or 4) 5% to 10%.¹²
- E. **Hepatic:** Increased ALT 36% to 46%,^{18,20} (grade 3 or 4) 21%²⁰; increased AST 36%,¹⁸ (grade 3 or 4) 8% to 18%^{18,20}; increased ALT/AST (grade 3) 33%,¹³ (grade 3 or 4) 20% to 80%¹²; elevated lipase level (grade 3 or 4) 5% to 10%.¹²
- F. **Pain:** Abdominal 41%,¹⁸ (grade 3 or 4) 9%.¹⁸

DOSE ADJUSTMENT

A. Hepatic¹⁰:

1. Bilirubin less than or equal to the ULN

and AST greater than ULN, no adjustment needed.

2. Bilirubin greater than 1 to 2 times the ULN and any AST, no adjustment needed.
3. Moderate or severe impairment, no information available.

B. Renal: No information available.¹⁰

Drug name: Elotuzumab

Synonyms: *Empliciti*, HuLuc63

MECHANISM OF ACTION

Signaling lymphocyte activation molecule family member 7 (SLAMF7), also known as CS1, CD2 subset-1, CD2-like receptor-activating cytotoxic cell (CRACC), and CD319, is a glycosylated cell surface protein that is highly and uniformly expressed on primary multiple myeloma cells. It is also expressed at lower levels on natural killer (NK) cells. Engagement of SLAMF7 on NK cells and myeloma cells by SLAMF7-specific antibodies results in enhanced antibody-directed cellular cytotoxicity of NK cells against primary multiple myeloma cells. Elotuzumab is a humanized monoclonal immunoglobulin G antibody that targets SLAMF7. In vitro studies show that elotuzumab enhances the antibody-dependent cellular cytotoxicity of NK cells

against myeloma cells and that this effect is further amplified if elotuzumab is given with lenalidomide.^{21,22}

PHARMACOKINETICS

Mean pharmacokinetic parameters after a single intravenous (IV) infusion of elotuzumab 10 mg/kg were $T_{1/2}$ 4.6 days, T_{max} 4.2 hours, C_{max} 337.4 mcg/mL, V_d 2976.9 mL, CL 15.3 mL/h, and AUC_{inf} 28,378.2 mcg•h/mL.²³ When given in combination with lenalidomide 25 mg PO once daily and dexamethasone 40 mg PO once weekly, mean pharmacokinetic parameters after a single dose of IV elotuzumab 10 mg/kg in patients with normal renal function ($CrCl \geq 90$ mL/min) were C_{max} 217 mcg/mL, AUC_{inf} 46,401 mcg•h/mL, and total body CL 0.22 mL/h/kg. In patients with serious renal impairment ($CrCl < 30$ mL/min) given elotuzumab, lenalidomide (with renal dose reductions), and dexamethasone in the same fashion, there were no significant differences in these pharmacokinetic parameters compared with the patients with normal renal function.²⁴ Selected therapeutic regimens of elotuzumab appear in Table 3.

PREPARATION

1. Follow institutional policies for preparation of hazardous medications when preparing elotuzumab.
2. Use elotuzumab lyophilized powder for reconstitution.

3. Reconstitute the 300 mg vial with 13 mL of sterile water for injection (SWFI) and the 400 mg vial with 17 mL of SWFI to produce drug to a concentration of 25 mg/mL.²⁵
4. After addition of SWFI, the vial may be inverted or swirled, but vigorous agitation should be avoided.²⁵
5. Dilute the drug in 230 mL 0.9% sodium chloride (NS) injection or 5% dextrose injection (D5W) for intravenous infusion.²⁵

STABILITY

1. Store elotuzumab vials in a refrigerator at 2°C to 8°C (36°F to 46°F). Do not freeze.²⁵
2. Diluted solutions are stable for no more than 24 hours refrigerated at 2°C to 8°C (36°F to 46°F) and protected from light and no more than 8 hours at room temperature of 20°C to 25°C (68°F to 77°F).²⁵

ADMINISTRATION

1. Patients should be premedicated with a steroid, H1 and H2 antagonist, and acetaminophen prior to administration of elotuzumab. The manufacturer recommends the following regimen²⁵:
 - A. Dexamethasone: 28 mg PO between 3 and 24 hours prior to elotuzumab and 8 mg IV between 45 and 90 minutes before elotuzumab.

Table 3. Selected therapeutic regimens of elotuzumab

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/cycle	References
5 mg/kg	IV	1, 8, 15, 22 Cycles 1-2	28 days	20 mg/kg	22, ^a 23, ^b
5 mg/kg	IV	1, 15 Cycles 3→	28 days	10 mg/kg	
10 mg/kg ^c	IV	1, 8, 15, 22 Cycles 1-2	28 days	40 mg/kg	22, ^a 23, ^b 24, ^a 26, ^a 27 ^a
10 mg/kg ^c	IV	1, 15 Cycles 3→	28 days	20 mg/kg	
20 mg/kg	IV	1, 8, 15, 22 Cycles 1-2	28 days	80 mg/kg	22, ^a 23, ^b 26 ^a
20 mg/kg	IV	1, 15 Cycles 3→	28 days	40 mg/kg	

Note: IV = intravenous.

^aIn combination with lenalidomide and dexamethasone.

^bElotuzumab given on days 1 and 15 in all cycles.

^cConforms to dosing information listed in the manufacturer's labeling.

- B. An H₁ blocker, H₂ blocker, and acetaminophen premedication between 45 and 90 minutes before elotuzumab.
2. Infuse elotuzumab through a 0.2 to 1.2 micron low-protein-binding filter.²⁵
3. The first dose of elotuzumab should be infused at 0.5 mL/min for the first 30 minutes, 1 mL/min for the next 30 to 60 minutes, and 2 mL/min for any infusion time over 60 minutes.²⁵
4. The second dose of elotuzumab should be infused at 1 mL/min for the first 30 minutes and 2 mL/min for any infusion time over 30 minutes. All subsequent doses may be infused at 2 mL/min.²⁵
5. For grade 2 or higher infusion reactions, stop the infusion. Upon resolution of infusion reaction to grade 1 or lower, resume infusion at 0.5 mL/min and gradually increase the infusion rate by 0.5 mL/min every 30 minutes until the rate at which the infusion reaction occurred is reached. If the infusion reaction does not recur, then infusion rate escalation may continue as described in 3 above. If the infusion reaction recurs, do not restart the infusion on that day.²⁵

TOXICITIES

The data below are presented as toxicity rates for elotuzumab alone and for elotuzumab and lenalidomide and dexamethasone. The combination of elotuzumab and lenalidomide and dexamethasone is the only FDA-approved use of elotuzumab.

Most of the toxicities listed below are presented according to their degree of severity. Higher grades represent more severe toxicities. Although there are several grading systems for cancer chemotherapy toxicities, all are similar. One of the frequently used systems is the NCI Common Terminology Criteria for Adverse Events (<http://ctep.cancer.gov>). Oncologists generally do not adjust doses or change therapy for grade 1 or 2 toxicities but make, or consider, dosage reductions or therapy changes for grade 3 or 4 toxicities. Incidence values are rounded to the nearest whole percent unless incidence was less than or equal to 0.5%.

Elotuzumab Alone

- A. **Cardiovascular:** Bradycardia (grade 2) 3%²³; chest discomfort (all grades) 9%, (grade 2) 3%²³; sinus tachycardia (all grades) 9%.²³
- B. **Constitutional:** Anorexia (all grades) 6%²³; chills (all grades) 32%, (grade 2) 3%²³; fatigue (all grades) 9%²³; flushing (all grades) 12%²³; pyrexia (all grades) 18%, (grade 2) 3%.²³

- C. **Gastrointestinal:** Vomiting (all grades) 9%.²³
- D. **Hypersensitivity:** Hypersensitivity reaction (grade 3) 3%,²³ infusion reactions during first infusion (all grades) 59%,²³ infusion reactions during subsequent infusions 29%.²³
- E. **Neurologic:** Headache (all grades) 9%.²³
- F. **Pulmonary:** Dyspnea (all grades) 6%.²³
- G. **Renal:** Acute renal failure (grade 4) 3%²³; serum creatinine increase (all grades) 6%, (grade 3) 1%.²³

Elotuzumab and Lenalidomide and Dexamethasone

- A. **Cardiovascular:** Peripheral edema (all grades) 26% to 33%, (grade 3 or 4) 1%.^{26,27}
- B. **Constitutional:** Asthenia (all grades) 19%, (grade 3 or 4) 3%²⁶; decreased appetite (all grades) 28%, (grade 3 or 4) 1%²⁶; dizziness (grade 1 or 2) 31%²⁶; fatigue (all grades) 47% to 67%, (grade 3 or 4) 7% to 8%^{26,27}; insomnia (all grades) 23% to 28%, (grade 3 or 4) 2% to 3%^{26,27}; night sweats (grade 1 or 2) 22%¹⁴; pyrexia (all grades) 37% to 39%, (grade 3 or 4) 3%.^{26,27}
- C. **Dermatologic:** Rash (all grades) 22%, (grade 3 or 4) 3%.²⁶
- D. **Endocrine/Metabolic:** Hyperglycemia (all grades) 25%, (grade 3 or 4) 10%.²⁶
- E. **Gastrointestinal:** Constipation (all grades) 36%, (grade 1 or 2) 50%, (grade 3 or 4) 1%^{26,27}; diarrhea (all grades) 47% to 67%, (grade 3 or 4) 5% to 10%^{26,27}; dysgeusia (grade 1 or 2) 25%²⁶; dyspepsia (grade 1 or 2) 22%²⁶; nausea (all grades) 50%, (grade 3 or 4) 1%²⁶; vomiting (all grades) 28%, (grade 3 or 4) 1%.²⁶
- F. **Hematologic:** Anemia (all grades) 47% to 96%, (grade 3 or 4) 15% to 19%^{26,27}; leukopenia (all grades) 22%, (grade 3 or 4) 10%²⁶; lymphocytopenia (all grades) 35% to 99%, (grade 3 or 4) 21 to 77%^{26,27}; neutropenia (all grades) 31% to 82%, (grade 3 or 4) 19% to 34%^{26,27}; thrombocytopenia (all grades) 36% to 84%, (grade 3 or 4) 18% to 19%.^{26,27}
- G. **Hypersensitivity:** Infusion reactions (all grades) 11%, (grade 3) 1%²⁶; neutralizing anti-drug antibodies (all grades) 11%.²⁶
- H. **Infection:** Bronchitis (all grades) 22%, (grade 3 or 4) 3%¹⁴; influenza (all grades) 22%, (grade 3 or 4) 1%²⁶; nasopharyngitis (grade 1 or 2) 25% to 28%^{26,27}; rhinitis (grade 1 or 2) 14%²⁶; upper respiratory tract infections (all grades) 53%, (grade 3 or 4) 3%.²⁶

- I. Musculoskeletal:** Arthralgia (all grades) 28%, (grade 3 or 4) 1%¹⁴; back pain (all grades) 28% to 47%, (grade 3 or 4) 5%^{26,27}; bone pain (all grades) 11%, (grade 3 or 4) 3%²⁶; muscle spasms (all grades) 30% to 61%, (grade 3 or 4) 1% to 3%^{26,27}; pain in extremity (grade 1 or 2) 25%.²⁶
- J. Neurologic:** Headache (all grades) 36%, (grade 3 or 4) 1%¹⁴; peripheral neuropathy (grade 1 or 2) 22%.²⁶
- K. Ocular:** Blurred vision (grade 1 or 2) 25%.²⁶
- L. Pulmonary:** Cough (all grades) 31%, (grade 1 or 2) 33%, (grade 3 or 4) 1%^{26,27}; dyspnea (all grades) 28%, (grade 3 or 4) 5%²⁶; dyspnea, exertional (grade 1 or 2) 25%.²⁶
- M. Second Malignancies:** Second hematologic malignancies (all grades) 2%²⁷; solid tumors (all grades) 3%²⁷; myelodysplastic syndrome (all grades) 1%²⁷; non-melanoma skin cancers (all grades) 3%.²⁷

DOSAGE MODIFICATIONS

- A. Hepatic:** Stop elotuzumab for grade 3 or higher elevations of AST, ALT, or total bilirubin. Elotuzumab may be continued when AST, ALT, and total bilirubin return to baseline values.²⁵
- B. Renal:** No dose adjustment required.²⁴

Drug name: Venetoclax

Synonyms: ABT-199, GDC-0199, *Venclexta*

MECHANISM OF ACTION

Venetoclax inhibits the BCL2 protein by mimicking BH3 protein, one of the BCL2 targets. Inhibition of BCL2 results in increased apoptosis in malignant cells.²⁸

PHARMACOKINETICS

Following a single dose of 20 to 200 mg PO, the mean T_{max} was 6 to 8 hours, the mean maximum concentration (C_{max}) was 0.07 to 1.15 mcg/mL. The mean terminal $T_{1/2}$ was 16.9 to 40.9 hours; the mean AUC was 2.0 to 49.5 mcg•h/mL.²⁹

At steady state, oral doses of 100 to 800 mg daily, the mean T_{max} was 5 to 8 hours, and the mean C_{max} was 1.58 to 2.99 mcg/mL. The mean area under the time versus concentration curve (AUC) was 22 to 46 mcg•h/mL.²⁹

Other investigators report the T_{max} as 6 to 8 hours and the $T_{1/2}$ as 15 to 19 hours, respectively.^{30,31}

The drug is highly bound (>99%) to plasma proteins, with a V_d of 256 to 321 L. The $T_{1/2}$ is approximately 26 hours. Venetoclax is metabolized in the liver, primarily by CYP3A4/5. The major metabolite, M27, is much less active than the parent drug. More than 99.9% of the drug is excreted in the feces; less than 0.1% is found in the urine within 9 days. About 20.8% of the dose is excreted as unchanged drug.³²

Selected therapeutic regimens of venetoclax appear in Table 4.

PREPARATION

1. Follow institutional policies for preparation of hazardous medications when dispensing venetoclax.
2. Venetoclax is available as 10 mg, 50 mg, and 100 mg tablets.
3. Prepackaged blister packs are available for the 4-week escalation dose regimen that is recommended by the manufacturer.

STABILITY

1. Venetoclax should be stored at temperatures no greater than 30°C (86°F).
2. During the dose escalation phase, the manufacturer recommends the tablets not be removed from the blister packs until the time the dose is taken.

ADMINISTRATION

1. Venetoclax should be taken once a day with a meal.
2. Patients should avoid grapefruit, Seville oranges, or starfruit while taking venetoclax.
3. Missed doses may be taken within 8 hours of the original scheduled time.

TOXICITIES

Most of the toxicities listed below are presented according to their degree of severity. Higher grades represent more severe toxicities. Although there are several grading systems for cancer chemotherapy toxicities, all are similar. One of the frequently used systems is the NCI Common Terminology Criteria for Adverse Events (<http://ctep.cancer.gov>). Oncologists generally do not adjust doses or change therapy for grade 1 or 2 toxicities but make, or consider, dosage reductions or therapy changes for grade 3 or 4 toxicities. Incidence values are rounded to the nearest whole percent unless incidence was less than or equal to 0.5%.

Table 4. Selected therapeutic regimens of venetoclax

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/month	References
50-400 mg	PO	1, 2, 3	28 days	150-11,200 mg	44
50-400 mg	PO	1, 2, 3, 4, 5, 6, 7	28 days	350-12,800 mg	44
50-400 mg	PO	1 through 28	28 days	1,400-12,000 mg	40, 44
50-500 mg	PO	1 through 28	28 days	1,400-15,000 mg	36
50-800 mg	PO	1,2,3	28 days	150-2,400 mg	47
50-800 mg	PO	1, 2, 3, 4, 5, 6, 7	28 days	350-5,600 mg	47
50-800 mg	PO	1 through 28	28 days	1,400-24,000 mg	47
50 mg	PO	Daily	–	1,500 mg	38
100 mg	PO	Daily	–	3,000 mg	38
150 mg	PO	Daily	–	4,500 mg	29, 30
200 mg	PO	Daily	–	6,000 mg	29-31, 35, 38, 42,43
300 mg	PO	Daily	–	9,000 mg	29-31, 35, 38, 45, 49
400 mg	PO	Daily	–	12,000 mg	29-31, 35, 43, 48
400 mg	PO	Days 2-28 (Cycle 1) then Days 1-28	–	10,800 mg 11,200 mg	37
600 mg	PO	Daily	–	18,000 mg	29-31, 35, 38, 45, 49
800 mg	PO	Days 2-28 (Cycle 1) then Days 1-28	–	21,600 mg 22,400 mg	37
800 mg	PO	Daily	–	24,000 mg	29, 30, 35, 38
900 mg	PO	Daily	–	27,000 mg	31, 42, 45, 49
1,200 mg	PO	Daily	–	36,000 mg	29, 30, 35, 45, 49
20 mg ^a	PO	Days 1-7	–	140 mg	32-34, 41, 46, 50
50 mg		Days 8-14		350 mg	
100 mg		Days 15-21		700 mg	
200 mg		Days 22-27		1,400 mg	
400 mg		Daily		12,000 mg	
20 mg	PO	Days 1-7	–	140 mg	51
50 mg		Days 8-14		350 mg	
100 mg		Days 15-21		700 mg	
200 mg		Days 22-27		1,400 mg	
20 mg	PO	Days 1-7	–	140 mg	51
50 mg		Days 8-14		350 mg	
100 mg		Days 15-21		700 mg	
200 mg		Days 22-27		1,400 mg	
400 mg		Days 28-34		2,800 mg	
600 mg		Daily		18,000 mg	

Note: PO = oral.

^aConforms to dosing information listed in the manufacturer's labeling.

- A. Cardiovascular:** Bradycardia (grade 3 or 4) 8%³³; coronary artery disease (grade 3 or 4) 3%³⁴; dehydration (severe) 3%³⁵; edema, peripheral 1% to 50%^{29,36-38}; fluid overload (serious) 2%²⁹; hypertension (grade 3 or 4) 7%³⁴; hypotension 23%³³; myocardial infarction 3%³⁴.
- B. Central Nervous System:** Dizziness 20% to 23%^{33,34}; headache 24%²⁹ (grade 3 or 4) 1%²⁹; insomnia 28% to 33%³⁶⁻³⁸; syncope (grade 3 or 4) 15%³³.
- C. Constitutional:** Asthenia 20% to 29%^{34,38}; fatigue 16% to 44%^{29-31,34,35,37,39,40-49} (grade 3 or 4) 3%

to 9%^{29,35}; hypoxia (grade 3 or 4) 11%⁵⁰; pyrexia 16% to 37%,^{29,33,37,40,43,48} (grade 3 or 4) 1% to 7%,^{29,33} (serious) 2%.²⁹

D. Endocrine/Metabolic: Hyperglycemia 15% to 36%,^{29,33,44,47} (grade 3 or 4) 6% to 10%,^{29,30,33,41} (serious) 2%²⁹; hyperkalemia 39%³³; hypokalemia 7% to 42%,^{34,44,47,51} (grade 3 or 4) 3% to 6%^{34,41}; hyponatremia (severe) 4%³⁵; hypophosphatemia (grade 3 or 4) 11%.⁵⁰

E. Gastrointestinal: Anorexia 40%³⁷; constipation 21% to 41%,^{29,36-38,47} (grade 3 or 4) 1%²⁹; diarrhea 20% to 53%,^{29-31,33-37,39-51} (grade 3 or 4) 2% to 10%,^{29,34} (serious) 2% to 3%^{29,35}; dyspepsia 16%⁴⁰; nausea 20% to 75%,^{29,31,33-35,37-45,47,49-51} (grade 3 or 4) 2% to 3%²⁹; vomiting 16% to 33%.^{29,31,33,35,37,40,44,49}

F. Hematologic: Anemia 22% to 42%,^{29,34,36,38,44-47,50,51} (grade 3 or 4) 7% to 29%^{29-31,34,35,38,40-44,47,48-51}; febrile neutropenia (grade 3 or 4) 3% to 67%,^{30,31,34,35,37,41,44,47,48,50} (serious) 6%²⁹; immune thrombocytopenia (serious) 3%²⁹; leukopenia 13%,³⁴ (grade 3 or 4) 8% to 21%^{33,34,44,47,48,50}; lymphopenia 13% to 28%,^{34,47} (grade 3 or 4) 10% to 21%^{34,44,47}; neutropenia 21% to 57%,^{29,30,37,41,43-48,50,51} (grade 3 or 4) 11% to 57%^{29-31,34,37,39-45,47-50}; thrombocytopenia 21% to 45%,^{29,34,36-38,44,47} (grade 3 or 4) 6% to 25%.^{29-31,33-35,36,38,39,41-51}

G. Hepatic: Increased AST (grade 3 or 4) 3%³⁴; increased lactate dehydrogenase (LDH) 7%,³⁴ (grade 3 or 4) 3%³⁴; increased transaminases (grade 3 or 4) 8%.⁵⁰

H. Infection: Gastroenteritis norovirus (grade 3 or 4) 3%³⁴; herpes virus (grade 3 or 4) 3%,³⁴ pneumonia (grade 3 or 4) 5% to 11%,^{46,50} (serious) 4%²⁹; upper respiratory tract 22% to 48%,^{29-31,39,41,42,48} (grade 3 or 4) 1%,²⁹ (serious) 3%²⁹; urinary tract 23%,³⁴ (grade 3 or 4) 7%³⁴; unspecified 39%,⁵⁰ (grade 3 or 4) 15% to 20%.^{33,46}

I. Musculoskeletal: Arthralgia 18%,²⁹ (grade 3 or 4) 1%.²⁹

J. Neurologic: Peripheral 27% to 28%^{41,50} VIIth nerve paralysis 3%.³⁴

K. Pain: Abdominal 30%,⁴⁵ back (grade 3 or 4) 3%.³⁴

L. Pulmonary: Bronchitis 17%,³⁴ cough 16% to 33%,^{29,30,33,37,39,40,43} dyspnea 24% to 25%.^{36,38}

DOSE ADJUSTMENT

A. Hepatic³²:

1. Mild impairment (bilirubin less than or equal to the upper limit of normal, and AST greater than the ULN; or bilirubin greater than 1 to 1.5 times the ULN), no dose adjustment required.
2. Moderate impairment (bilirubin greater than 1.5 to 3 times the ULN), no dose adjustment required.
3. Severe impairment (bilirubin greater than 3 times the ULN), no information available.

B. Renal³²:

1. CrCl greater than or equal to 30 mL/min, no dose adjustment needed.
2. CrCl less than 30 mL/min, no information available.

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