Cancer Chemotherapy Update

Drug Monographs: Ixazomib and Necitumumab

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ABSTRACT

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.

Regimen name: Ixazomib

Synonyms: MLN-2238, Ninlaro

MECHANISM OF ACTION

Ixazomib is a 20S proteasome inhibitor that specifically binds to and inhibits the chymotrypsin-like site of the β_5 subunit of the 20S proteasome.¹ At higher concentrations, ixazomib also inhibits the β_1 and β_2 subunits of the 20S proteasome.² In vitro, ixazomib has demonstrated induction of apoptosis of multiple myeloma cells, including activity against cells from patients with relapsed and refractory multiple myeloma.

PHARMACOKINETICS

Ixazomib pharmacokinetics follows a 3-compartment model with first-order elimination. Oral absorption is rapid, with a time to maximum concentration (T_{max}) of approximately 0.5 to 2 hours. Absolute oral bioavailability is estimated to be between 58% and 62%.^{3,4} After a weekly 4 mg oral dose of ixazomib, day 15 plasma maximum mean concentration (C_{max}) ranged from 43.9 to 73.6 ng/mL.^{5,6} The area under the time-concentration curve ($AUC_{0-168\text{ h}}$) ranged from 1,250 to 1,610 h•ng/mL, and increased proportionally with increasing doses.⁵⁻⁷ The

volume of distribution (V_d) of ixazomib is 543 L.³ Ixazomib is 99% bound to plasma proteins. Terminal elimination half-life ranges from 4 to 8 days, with mean clearance estimated at 1.9 L/h.^{4,7} Following weekly oral administration, the accumulation ratio of ixazomib is 2.4.⁵ Drug-drug interactions with strong CYP3A4 inhibitors and inducers suggest ixazomib is metabolized by multiple CYP enzymes and non-CYP proteins.^{3,8,9} Twenty-two percent of ixazomib is excreted in feces and 62% in urine.³ Selected therapeutic regimens of ixazomib appear in Table 1.

PREPARATION

1. Follow institutional policies for handling hazardous medications when dispensing ixazomib.
2. Ixazomib is available as 2.3 mg, 3 mg, and 4 mg capsules.
3. The manufacturer recommends that the capsule should be swallowed whole with water.
4. The manufacturer recommends the capsules not be crushed, chewed, or opened.³

STABILITY

1. Store at room temperature below 30°C (86°F). Do not freeze.
2. The manufacturer recommends that capsules be kept in the original blister pack until time of administration.³

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Table 1. Selected therapeutic regimens of ixazomib

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/cycle	References
4 mg ^a	PO	1, 8, 15	28 days	12 mg	3, 11, 5, 6, 10
5.5 mg	PO	1, 8, 15	28 days	16.5 mg	17
2.97 mg/m ²	PO	1, 8, 15	28 days	8.91 mg/m ²	12

Note: PO = oral.

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

ADMINISTRATION

1. Ixazomib should be taken orally, once a week for 3 weeks of a 4-week cycle.
2. Doses should be taken on the same day of each week at approximately the same time.
3. Ixazomib should be taken on an empty stomach, at least 1 hour before or at least 2 hours after food.
4. If a dose of ixazomib is missed, the dose may be taken as long as the next scheduled dose is greater than or equal to 72 hours away.

TOXICITIES

The data below are presented as toxicity rates for ixazomib plus lenalidomide and dexamethasone/lenalidomide and dexamethasone/ixazomib alone (NR = not reported). The combination of ixazomib plus lenalidomide and dexamethasone is the only US Food and Drug Administration (FDA)-approved use for ixazomib.

- A. Cardiovascular:** Embolism (all grades) 2%/NR,¹⁰ (grade 3 or 4) 2%/NR/NR¹⁰; heart failure (all grades) 4%/3%/NR,¹¹ (grade 3 or 4) 2%/2%/NR¹¹; orthostatic hypotension (all grades) 2%/NR/NR¹⁰; peripheral edema (all grades) 18%/NR/NR,¹⁰ (grade 3 or 4) 2%/NR/NR.¹⁰
- B. Constitutional:** Dehydration (grade 3 or 4) 2%/NR/3% to 14%,^{6,10,12} (all grades) 2%/NR/16%,^{10,12} (grade 3 or 4) 2%/NR/3% to 14%,^{6,10,12}; fatigue (all grades) 16% to 52%/NR/42%,^{5,10,12} (grade 3 or 4) 9% to 12%/NR/13%,^{5,10,12}; pyrexia (all grades) NR/NR/16%.¹²
- C. Dermatologic:** Maculo-papular rash (grade 3 or 4) NR/NR/3% to 14%,^{6,12}; skin and subcutaneous tissue reactions (all grades) 35% to 54%/21%/35%,^{5,10-12} (grade 3 or 4) 4% to 14%/1%/3%.¹⁰⁻¹²
- D. Endocrine/metabolic:** Hyperglycemia (all grades) 6%/NR/NR,¹⁰ (grade 3 or 4) 2%/NR/NR¹⁰; hypokalemia (all grades) 7% to 14%/NR/NR,^{5,10}

- E. Gastrointestinal:** Abdominal distention (all grades) 10%/NR/NR,¹⁰ (grade 3 or 4) 2%/NR/NR¹⁰; abdominal pain (grade 3 or 4) NR/NR/14%⁶; constipation (all grades) 26%/NR/NR¹⁰; decreased appetite (all grades) 10% to 19%/NR/35%,^{5,10,12} (grade 3 or 4) 2%/NR/13%^{10,12}; diarrhea (all grades) 40% to 46%/36%/45%,^{5,10-12} (grade 3 or 4) 6% to 14%/2%/23%^{5,10-12}; dysgeusia (all grades) 22%/NR/NR¹⁰; gastroesophageal reflux disease (all grades) 14%/NR/NR,¹⁰ (grade 3 or 4) 2%/NR/NR¹⁰; intestinal perforation (all grades) 2%/NR/NR,¹⁰ (grade 3 or 4) 2%/NR/NR¹⁰; nausea (all grades) 16% to 48%/21%/42%,^{5,10-12} (grades 3 or 4) 2%/0%/3%¹⁰⁻¹²; vomiting (all grades) 21% to 30%/11%/42%,^{5,10-12} (grade 3 or 4) 1% to 2%/1%/3%.¹⁰⁻¹²
- F. Hematologic:** Anemia (all grades) 14%/NR/23%,^{10,12} (grade 3 or 4) 4% to 9%/13%/6%^{5,10-12}; decreased neutrophil count (all grades) 2%/NR/NR,¹⁰ (grade 3 or 4) 2%/NR/NR¹⁰; decreased platelet count (all grades) 4% to 12%/NR/NR,^{5,10} (grade 3 or 4) 2%/NR/NR¹⁰; decreased white blood cell count (all grades) 2%/NR/NR,¹⁰ (grade 3 or 4) 2%/NR/NR¹⁰; leukopenia (all grades) 12%/NR/16%,^{10,12} (grade 3 or 4) 6%/NR/10%^{10,12}; lymphopenia (all grades) 6%/NR/16%,^{10,12} (grade 3 or 4) 4%/NR/10%^{10,12}; neutropenia (all grades) 19% to 24%/NR/32%,^{5,10,12} (grade 3 or 4) 14% to 19%/16%/26%^{5,10-12}; thrombocytopenia (all grades) 19% to 28%/NR/45%,^{5,10,12} (grade 3 or 4) 8% to 13%/5%/28% to 39%.^{5,6,10-12}
- G. Hepatic:** Increased alanine aminotransferase (ALT) (all grades) 12%/NR/NR,¹⁰ (grade 3 or 4) 2%/NR/NR¹⁰; increased aspartate aminotransferase (AST) (all grades) 8%/NR/NR,¹⁰ (grade 3 or 4) 2%/NR/NR.¹⁰
- H. Infection:** Bone abscess (grade 3 or 4) 2%/NR/NR¹⁰; pneumonia (all grades) 2% to 6%/8%/NR,^{10,11} (grade 3 or 4) 2% to 6%/8%/NR.^{10,11}

- I. Musculoskeletal:** Muscle spasms (all grades) 16%/NR/NR¹⁰; non-cardiac chest pain (all grades) 2%/NR/NR,¹⁰ (grade 3 or 4) 2%/NR/NR.¹⁰
- J. Neurologic:** Agitation (all grades) 2%/NR/NR¹⁰; dizziness (all grades) 16%/NR/NR,¹⁰ (grade 3 or 4) 2%/NR/NR¹⁰; insomnia (all grades) 12% to 32%/NR/NR,^{5,10} (grade 3 or 4) 2%/NR/NR¹⁰; peripheral neuropathy (all grades) 26% to 38%/21%/32%,^{5,10-12} (grade 3 or 4) 2% to 4%/2%/3%.¹⁰⁻¹²
- K. Pulmonary:** Dyspnea (all grades) 14%/NR/21%,^{6,10} (grade 3 or 4) 0%/NR/21%.^{6,10}
- L. Renal:** Increased serum creatinine (all grades) 6%/NR/NR,¹⁰ (grade 3 or 4) 2%/NR/NR¹⁰; renal failure (all grades) 4%/6%/NR,¹¹ (grade 3 or 4) 2%/3%/NR.^{5,11}
- M. Treatment-Related Mortality:** Respiratory syncytial viral pneumonia 2%/NR/NR.¹⁰

DOSAGE MODIFICATIONS

- A. Hepatic:** For moderate hepatic impairment (total bilirubin greater than 1.5 to 3 times ULN) or severe hepatic impairment (total bilirubin greater than 3 times ULN), reduce ixazomib starting dose to 3 mg.³
- B. Renal:**
1. For severe renal impairment (creatinine clearance less than 30 mL/min or patients on dialysis), reduce ixazomib starting dose to 3 mg.³
 2. May administer ixazomib without regard to timing of dialysis.³

Regimen name: Necitumumab

Synonyms: IMC-11F8, LY3012211, Portrazza

MECHANISM OF ACTION

Necitumumab is a fully humanized immunoglobulin G₁ (IgG₁) monoclonal antibody that targets epidermal growth factor receptor (EGFR) and competes with natural ligands, preventing signaling and proliferation of EGFR-dependent tumor cells.¹³ This

fully human monoclonal antibody (mab) has shown antibody-dependent cellular cytotoxicity in EGFR-expressing cancer cells in vitro.¹⁴

PHARMACOKINETICS

Necitumumab demonstrates nonlinear pharmacokinetics; clearance is not affected by body weight. The half-life ($t_{1/2}$) of necitumumab is 5 days. Peak concentration (C_{max}) after an 800 mg dose is 509 ± 100 mcg/mL and AUC_{0-inf} $59,071 \pm 16,571$ mcg•h/mL. Estimated mean clearance at steady state is 14.1 mL/h. The elimination half-life of necitumumab is estimated at 14 days.^{13,14} Monoclonal antibodies are degraded via proteolytic enzymes into amino acids. The manufacturer believes that necitumumab is metabolized in a similar manner. Currently there are no trials that examine the metabolism or excretion of necitumumab.¹⁵

Selected therapeutic regimens of necitumumab appear in Table 2.

PREPARATION

1. Follow institutional policies for preparation of hazardous medications when dispensing necitumumab.
2. Use necitumumab injection, 16 mg/mL.
3. Dilute the drug in 250 mL 0.9% sodium chloride (NS) injection for intravenous infusion.
4. Do not freeze or shake the solution and do not dilute with other solutions.

STABILITY

1. Store necitumumab vials in a refrigerator at 2°C to 8°C (36°F to 46°F). Do not freeze.
2. Diluted solutions are stable for no more than 24 hours refrigerated at 2°C to 8°C (36°F to 46°F) and no more than 4 hours at room temperature of up to 25°C (77°F).

ADMINISTRATION

Necitumumab is infused intravenously over 60 minutes.

Table 2. Selected therapeutic regimens of necitumumab

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/cycle	References
800 mg ^a	IV	1 and 8	21 days	1,600 mg	16,14,18
800 mg	IV	1, 8, 15, 22, 29, and 36	42 days	4,800 mg	13

Note: IV = intravenous.

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

TOXICITIES

The data below is presented as toxicity rates for necitumumab plus gemcitabine and cisplatin/gemcitabine and cisplatin/necitumumab alone (NR = not reported). The combination of necitumumab plus gemcitabine and cisplatin is the only FDA-approved use for necitumumab.

- A. Constitutional:** Fatigue (all grades) 44%/43%/35%,^{13,16} (grade 3 or 4) 7%/7%/0%^{13,16}; hypersensitivity/infusion-related reaction (all grades) 1%/2%/NR,¹⁶ (grade 3 or 4) 0.3%/0%/NR¹⁶; pyrexia (all grades) NR/NR/35%.¹³
- B. Dermatologic:** Acne (all grades) NR/NR/55%,¹³ (grade 3 or 4) NR/NR/3%¹³; acneform dermatitis (all grades) NR/NR/10%¹³; dry skin (all grades) NR/NR/24%,¹³ (grade 3 or 4) NR/NR/7%¹³; pruritus (all grades) NR/NR/21%¹³; rash (all grades) 76%/10%/NR,¹⁶ (grade 3 or 4) 7%/0.4%/NR¹⁶; skin fissures (all grades) NR/NR/21%¹³; skin reactions (all grades) 3%/2%/NR,¹⁶ (grade 3 or 4) 1%/0.2%/NR.¹⁶
- C. Endocrine/metabolic:** Hypokalemia (all grades) NR/NR/31%¹³; hypomagnesemia (all grades) 31%/16%/3%,^{13,16} (grade 3 or 4) 9%/1%/0%.^{13,16}
- D. Gastrointestinal:** Diarrhea (all grades) 16%/11%/41%,^{13,16} (grade 3 or 4) 2%/1%/0%^{13,16}; nausea (all grades) NR/NR/10%.¹³
- E. Hematologic:** Anemia (all grades) 42%/46%/3%,^{13,16} (grade 3 or 4) 11%/11%/0%^{13,16}; arterial thromboembolic events (all grades) 5%/4%/NR,¹⁶ (grade 3 or 4) 3%/2%/NR¹⁶; febrile neutropenia (all grades) 1%/1%/NR,¹⁶ (grade 3 or 4) 1%/1%/NR¹⁶; neutropenia (all grades) 43%/46%/NR,¹⁶ (grade 3 or 4) 24%/28%/NR¹⁶; thrombocytopenia (all grades) 22%/26%/NR,¹⁶ (grade 3 or 4) 10%/10%/NR¹⁶; venous thromboembolic events (all grades) 9%/5%/NR,¹⁶ (grade 3 or 4) 5%/2%/NR.¹⁶
- F. Ocular:** Conjunctivitis (all grades) 7%/2%/NR,¹⁶ (grade 3 or 4) 0.3%/0%/NR.¹⁶
- G. Pulmonary:** Interstitial lung disease (all grades) 1%/1%/NR,¹⁶ (grade 3 or 4) 0.2%/1%/NR.¹⁶
- H. Treatment-Related Mortality:** Arterial thromboembolic events 0.6%/0.2%/NR¹⁶; interstitial lung disease 0.2%/0%/NR¹⁶; venous thromboembolic events 0.2%/0.2%/NR.¹⁶

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