Cancer Chemotherapy Update

Drug Monographs: Olaratumab and Rucaparib

Dominic A. Solimando, Jr, MA, FAPhA, FASHP, BCOP, and J. Aubrey Waddell,
PharmD, FAPhA, BCOP

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. The information presented in this review is based on published data and clinical expertise and includes information not included in the product labeling. Incorporation of such published data provides a more robust assessment of the drugs and assists pharmacists in evaluation of orders for off-label use of these agents.

Drug Name: Olaratumab

Synonyms: Lartravo, IMC-3G3

MECHANISM OF ACTION

Olaratumab is an IgG₁ monoclonal antibody that binds to platelet-derived growth factor (PDGF), blocking the binding and receptor activation of PDGF-AA, PDGF-BB, and PDGF-CC.^{1,2}

PHARMACOKINETICS

Following single doses from 4 mg/kg to 20 mg/kg, the minimum serum concentration ($C_{\min}$) was 20.9 to 149 mcg/mL, the maximum serum concentration ($C_{\max}$) ranged from 74.4 mcg/mL to 760 mcg/mL, the time to maximum serum concentration ($T_{\max}$) was 1.53 to 2.53 hours.³ The area under the 168 hour time versus concentration curve (AUC) was 7220 to 44,500 mcg•h/mL, and the half-life ($T_{1/2}$) was 3.08 to 7.67 days.³ The volume of distribution (V_d) was 3.99 to 4.77 L.³

Following multiple doses from 4 mg/kg to 20 mg/kg, the $C_{\min}$ was 8.167 to 208 mcg/mL, the $C_{\max}$ ranged from 107.348 mcg/mL to 1,610 mcg/mL, and the $T_{\max}$ was 1.08 to 3.17 hours.³ The AUC was 9,290 to 93,600 mcg•h/mL, and the $T_{1/2}$ was 3.69 to 8.96 days.³ The V_d was 3.01 to 4.68 L.³ The elimination $T_{1/2}$ for single and multiple doses is 3.08 to 7.79 days and 3.69 to 11.3 days, respectively.³

In a study of Japanese patients, following single doses of 10 mg/kg, 15 mg/kg, and 20 mg/kg, the $C_{\max}$ ranged from 362.322 to 735 mcg/mL, and $T_{\max}$ was 1.20 to 2.22 hours.⁴ AUC was not calculated for the 10 mg/kg dose; for the 15 mg/kg and 20 mg/kg doses, the AUC was 48,000 and 63,400 mcg•h/mL, respectively.⁴ The $T_{1/2}$ ranged from 5.33 to 7.29 days.⁴

Following single doses of 10 mg/kg, 15 mg/kg, and 20 mg/kg, the $C_{\max}$ ranged from 658.391 to 1160 mcg/mL, and $T_{\max}$ was 1.74 to 2.21 hours.⁴ AUC was not calculated for the 10 mg/kg or 15 mg/kg dose; for the 20 mg/kg dose, the AUC was 123,000 mcg•h/mL.⁴ The $T_{1/2}$ ranged from 4.06 to 8.25 days.⁴

The manufacturer reports the steady-state V_d is 7.7 L, and the elimination $T_{1/2}$ is 6 to 24 days.⁵

Selected therapeutic regimens of olaratumab appear in Table 1.

PREPARATION

1. Use olaratumab injection, 10 mg/mL.
2. Dilute with 250 mL 0.9% sodium chloride (NS).
3. Do not use dextrose-containing solutions.⁵
4. The manufacturer recommends diluting to a final volume of 250 mL.⁵

STABILITY

1. Unopened vials should be stored under refrigeration (2°C to 8°C [36°F to 46°F]).

Table 1. Selected therapeutic regimens of olaratumab

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/cycle	References
4 mg/kg	IV	1,8,15,22	4 weeks	16 mg/kg	3
8 mg/kg	IV	1,8,15,22	4 weeks	32 mg/kg	3
10 mg/kg	IV	1 & 8	3 weeks	20 mg/kg	4
15 mg/kg	IV	1	3 weeks	15 mg/kg	4
15 mg/kg	IV	1 & 15	4 weeks	30 mg/kg	3
15 mg/kg ^a	IV	1 & 8	21 days	30 mg/kg	5-7
16 mg/kg	IV	1,8,15,22	4 weeks	64 mg/kg	3
20 mg/kg	IV	1 & 15	4 weeks	40 mg/kg	3
20 mg/kg	IV	1	2 weeks	20 mg/kg	4,8

Note: IV = intravenous.

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

- Solutions diluted for injection may be stored under refrigeration (2°C to 8°C [36°F to 46°F]) up to 24 hours and for an additional 4 hours at room temperature (<25°C [77°F]).

ADMINISTRATION

Olaratumab is administered as a short (60 to 90 minute) intravenous infusion.

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://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). 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%.

- Cardiovascular:** Hypertension 6%.⁴
- Central Nervous System:** Headache (grade 1) 5% to 20%.³
- Constitutional:** Chills (grade 1) 5% to 20%,³ fatigue (grade 1) 11% to 33%,³ pyrexia (grade 1) 5% to 20%.³

- Dermatologic:** Dermatitis 6%,⁴ rash 6%.⁴
- Endocrine/Metabolic:** Hyperglycemia 6%.⁴
- Gastrointestinal:** Constipation (grade 1) 5% to 33%³; diarrhea 6%,⁴ (grade 1) 5% to 33%³; nausea (grade 1) 5% to 20%³; vomiting (grade 1) 5% to 20%.³
- Hematologic:** Anemia 6%⁴; leukopenia 6%⁴; thrombocytopenia (grade 1) 5% to 33%³; tumor hemorrhage 6%,⁴ (grade 2) 5% to 33%.³
- Hepatic:** Increased alkaline phosphatase (grade 3) 5% to 33%,³ increased aspartate aminotransferase (AST) 13%.⁴
- Hypersensitivity:** Infusion reactions (grade 1) 5% to 20%³; unspecified reactions (grade 1) 5% to 20%,³ (grade 2) 5%.³
- Pulmonary:** Cough 6%.⁴
- Renal:** Proteinuria 25%.⁴

DOSE ADJUSTMENT

- Hepatic**
 - Mild to moderate impairment (bilirubin ≤ 3 times the upper limit of normal [ULN]), no adjustment required.⁵
 - Severe impairment (bilirubin > 3 times the ULN), no information available.⁵
- Renal**
 - Mild to moderate impairment (creatinine clearance ≤ 30 mL/min), no adjustment required.⁵
 - Severe impairment (creatinine clearance < 30 mL/min), no information available.⁵

Drug Name: Rucaparib

Synonyms: Rubraca, AG014699, CO338, PF-01367338

MECHANISM OF ACTION

Rucaparib is a poly (ADP-ribose) polymerase (PARP) inhibitor that inhibits the PARP1, PARP2, and PARP3 enzymes. PARP1 and PARP2 are involved in repairing single-strand breaks in DNA. Inhibition of PARP1 and PARP2 results in an increase in single-strand breaks and “trapping” the PARP at the site of the damaged chromatin, resulting in secondary double-strand breaks.⁹⁻¹⁴ PARP3 is involved with regulating DNA damage response, partially through control of PARP1 activity.^{15,16}

PHARMACOKINETICS

Following oral doses ranging from 92 to 600 mg, the T_{max} is 1.5 to 5.5 hours, the C_{max} is 208 to 839 ng/mL, and the $T_{1/2}$ is 2.9 to 9.6 hours. The AUC is 2,312 to 6,852 ng•h/mL, and the Vd was 544 to 831 L.¹⁷

At doses from 1 mg/m² to 18 mg/m² given as a 30-minute IV infusion, the mean C_{max} ranges from 25 to 863 ng/mL, the mean AUC is 21 to 2882 ng•h/mL, and the mean Vd is 111 to 584 L. The mean $T_{1/2}$ is 1.2 to 23.2 hours.¹⁸

Following 240 to 840 mg given orally twice a day, the mean C_{max} is 1,940 ng/mL, and the mean T_{max} is 1.9 hours. The mean bioavailability of oral rucaparib is 36% (range, 30%-40%); the mean AUC is 16,900 ng•h/mL. Following a high-fat meal, the C_{max} increases 20%, the AUC increases 38%, and the $T_{1/2}$ is delayed by 2.5 hours. Rucaparib is metabolized in the liver by CYP2D6 (primary), CYP1A2, and CYP3A4.¹⁹

The mean terminal $T_{1/2}$ is 17 hours following IV doses of 12 to 40 mg; the Vd is 113 to 262 L. Following a single oral dose of 600 mg, the terminal $T_{1/2}$ is 17 to 19 hours.¹⁹

Selected therapeutic regimens of rucaparib appear in Table 2.

PREPARATION

Rucaparib is available as 200 mg and 300 mg tablets.

STABILITY

1. Tablets should be stored at room temperature (20°C to 25°C [68°F to 77°F]).
2. Brief (less than 24 hours) exposure to temperatures from 15°C to 30°C (59°F to 86°F) is acceptable.

ADMINISTRATION

1. Rucaparib is given orally, twice a day.
2. The drug may be taken with or without food.
3. The manufacturer recommends not replacing missed doses or doses that are vomited by the patient.¹⁹

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://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). 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:** Dehydration (grade 1 or 2) 5%,²¹ (grade 3) 3%²¹; edema (peripheral) (grade 1 or 2) 11%²¹; hypotension (grade 1 or 2) 2%,²¹ (grade 3) 1%²¹; hypercholesterolemia (grade 1 or 2) 2% to 5%,²¹ (grade 3) <1% to 1%²¹; lymphedema (grade 1 or 2) <1%,²¹ (grade 3) <1%²¹; pulmonary embolism (grade 1 or 2) <1%,²¹ (grade 3) 1%²¹; prolonged QT interval (grade 4) <1%²¹; tachycardia (grade 1 or 2) <1%,²¹ (grade 3) <1%.²¹
- B. Central Nervous System:** Agitation (grade 3) <1%²¹; dizziness (grade 1) 10%,¹⁷ (grade 1 or 2) 21%,²¹ (grade 2) 1%,¹⁷ (grade 3) <1%²¹; headache (grade 1) 15%,¹⁷ (grade 1 or 2) 17%,²¹ (grade 2) 6%¹⁷; insomnia (grade 1 or 2) 12%²¹; “low mood” (grade 1) 4%,¹⁷ (grade 3) 1%¹⁷; mental status changed (grade 3) <1%²¹; presyncope (grade 1 or 2) 1%,²¹ (grade 3) <1%²¹; syncope (grade 3) 1%.²¹
- C. Constitutional:** Abdominal distension (grade 1 or 2) 21%²¹; asthenia 35%²⁴; arthralgia (grade 1)

Table 2. Selected therapeutic regimens of rucaparib

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/month (cycle)	References
92 mg	PO	1 through 7	3 weeks	644 mg	17
92 mg	PO	1 through 14	3 weeks	1288 mg	17
92 mg	PO	1 through 21	3 weeks	1932 mg	17
120 mg	PO	1 through 21	3 weeks	2520 mg	17
240 mg	PO	1 through 21	3 weeks	5040 mg	17
480 mg	PO	1 through 21	3 weeks	10,080 mg	17
240 mg bid	PO	1 through 21	3 weeks	10,080 mg	17
480 mg bid	PO	1 through 21	3 weeks	20,160 mg	17
600 mg bid	PO	1 through 21	3 weeks	25,200 mg	17
40 mg	PO	Daily	–	1,200 mg	22
80 mg	PO	Daily	–	2,400 mg	22
160 mg	PO	Daily	–	4,800 mg	22
300 mg	PO	Daily	–	9,000 mg	22
500 mg	PO	Daily	–	15,000 mg	22
240 mg bid	PO	Daily	–	14,400 mg	22
360 mg bid	PO	Daily	–	21,600 mg	22
600 mg bid ^a	PO	Daily	–	36,000 mg	19, 21, 23-25
4 mg/m ²	IV ^b	1,2,3,4,5	2 weeks	20 mg/m ²	17
12 mg/m ²	IV	1,2,3,4,5	3 weeks	60 mg/m ²	17
21 mg/m ²	IV	1,2,3,4,5	3 weeks	90 mg/m ²	17
1 mg/m ²	IV	1,2,3,4,5	4 weeks	5 mg/m ²	21
2 mg/m ²	IV	1,2,3,4,5	4 weeks	10 mg/m ²	21
4 mg/m ²	IV	1,2,3,4,5	4 weeks	20 mg/m ²	21
8 mg/m ²	IV	1,2,3,4,5	4 weeks	40 mg/m ²	21
12 mg/m ²	IV	1,2,3,4,5	4 weeks	60 mg/m ²	21, 20
21 mg/m ²	IV	1,2,3,4,5	4 weeks	90 mg/m ²	21

Note: bid = twice daily; IV = intravenous; PO = oral.

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

^bAlthough IV rucaparib has been studied, as parenteral formulation is not commercially available.

4%,¹⁷ (grade 2) 3%¹⁷; fatigue 17% to 41%,²²⁻²⁴ (grade 1) 26%,¹⁷ (grade 1 or 2) 69%,²¹ (grade 2) 19%,¹⁷ (grade 3) 6% to 9%,^{17,21} (grade 3 or 4) 11%²⁵; malaise (grade 1 or 2) 1%,²¹ (grade 3) <1%²¹; myalgia (grade 1) 3%,¹⁷ (grade 1 or 2) 7%,²¹ (grade 2) 1%,¹⁷ (grade 3) <1%²¹; pruritus (grade 1) 5%,¹⁷ (grade 2) 1%¹⁷; pyrexia (grade 1 or 2) 12%,²¹ (grade 3) <1%²¹; decreased weight (grade 1 or 2) 8%,²¹ (grade 3) <1%²¹.

D. Dermatologic: Alopecia (grade 1) 8%,¹⁷ (grade 1 or 2) 10%²¹; photosensitivity (grade 1 or 2) 13%.²¹

E. Endocrine/Metabolic: Hyperglycemia (grade 1 or 2) 2%,²¹ (grade 3) 1%²¹; hypomagnesemia (grade 3) <1%²¹; hypokalemia (grade 1 or 2) 3%,²¹ (grade 3) 2%²¹; hyponatremia (grade 1 or 2) <1%,²¹ (grade 3) 2%²¹; hypophosphatemia (grade 1 or 2) <1%,²¹ (grade 3) 2%²¹.

F. Gastrointestinal: Anorexia 10% to 11%,^{22,23} (grade 1) 9%,¹⁷ (grade 1 or 2) 39%,²¹ (grade 2) 1%,¹⁷ (grade 3) 2%²¹; constipation (grade 1) 8%,¹⁷ (grade 1 or 2) 45%,²¹ (grade 2) 1%,¹⁷ (grade 3) 1%²¹; diarrhea 7% to 13%,^{22,23} (grade 1) 14%,¹⁷ (grade 1 or 2) 30%,²¹ (grade 2) 1%,¹⁷

(grade 3) 3%²¹; dysgeusia (grade 1) 5% to 43%,^{17,21} (grade 2) 1%¹⁷; dyspepsia (grade 1 or 2) 9%,²¹ (grade 3) <1%²¹; hemorrhage (rectal) (grade 1 or 2) 2%,²¹ (grade 3) <1%²¹; mucosal inflammation (grade 1 or 2) 3%, (grade 3) <1%²¹; nausea 10% to 55%,²²⁻²⁵ (grade 1) 28%,¹⁷ (grade 1 or 2) 75%,²¹ (grade 2) 5%,¹⁷ (grade 3) 2% to 4%^{17,21,23}; stomatitis (grade 1 or 2) 10%,²¹ (grade 3) <1%²¹; vomiting 10% to 23%,^{22,23} (grade 1) 9%,¹⁷ (grade 1 or 2) 45%,²¹ (grade 2) 4%,¹⁷ (grade 3) 2%²¹; xerostomia (grade 1) 4%.¹⁷

G. Hematologic: Anemia 37% to 41%,^{24,25} (grade 1 or 2) 14%,²¹ (grade 2) 5% to 29%,^{17,23} (grade 3) 21% to 29%,^{21,23} (grade 3 or 4) 26%,²⁵ (grade 4) 1%²¹; febrile neutropenia (grade 4) <1%²¹; granulocytopenia (grade 3) <1%²¹; intestinal obstruction (large) (grade 4) <1%,²¹ (small) (grade 1 or 2) <1%,²¹ (grade 3) 5%²¹; intestinal perforation febrile neutropenia (grade 4) <1%²¹; leukopenia (grade 1 or 2) 1% to 5%,²¹ (grade 3) <1%²¹; lymphopenia (grade 1) 1%,¹⁷ (grade 1 or 2) <1%,²¹ (grade 2) 3%,¹⁷ (grade 4) <1%²¹; neutropenia (grade 1) 4%,¹⁷ (grade 1 or 2) 5%,²¹ (grade 2) 1% to 29%,^{17,23} (grade 3) 4%,²¹ (grade 4) 3%²¹; thrombocytopenia (grade 1 or 2) 12%,²¹ (grade 3) 2% to 14%,^{21,23} (grade 3 or 4) 16%.²⁵

H. Hepatic: Ascites (grade 1 or 2) 3%,²¹ (grade 3) 3%²¹; bile duct obstruction (grade 3) <1%²¹; increased bilirubin (grade 1 or 2) <1% to 3%,²¹ (grade 3) <1%,²¹ (grade 4) <1%²¹; elevated alkaline phosphatase (grade 1 or 2) 8%,²¹ (grade 3) 1%²¹; elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) 41%,²⁴ (grade 1 or 2) 30%,²¹ (grade 3) 12%,²¹ (grade 4) <1%²¹; elevated AST (grade 1) 4%¹⁷; increased gamma glutamyltransferase (grade 1 or 2) <1%,²¹ (grade 3) 2%,²¹ (grade 4) <1%²¹; increased transaminases (grade 1 or 2) 1%,²¹ (grade 3) 1%.²¹

I. Hypersensitivity: Infusion site reactions (grade 1) 11%,¹⁷ (grade 2) 2%.¹⁷

J. Infection: Empyema (grade 3) <1%²¹; peritonitis (grade 3) <1%²¹; pneumonia (grade 3) 1%²¹; sepsis (grade 3) <1%,¹⁹ (grade 4) 1%,²¹ upper respiratory tract (grade 1 or 2) 10%²¹; urinary tract (grade 1 or 2) 16%,²¹ (grade 3) 2%.²¹

K. Neurologic: Sensory neuropathy (grade 1) 4%.¹⁷

L. Ophthalmic: Cataracts (grade 3) <1%.²¹

M. Pain: Abdominal (grade 1) 3%,¹⁷ (grade 1 or 2) 11% to 27%,²¹ (grade 2) 3%,¹⁷ (grade 3) 1% to

2%^{17,21}; back (grade 1 or 2) 15%,²¹ (grade 3) 1%²¹; pain in extremities (grade 1 or 2) 8%,²¹ (grade 3) <1%.²¹

N. Pulmonary: Bronchitis (grade 1 or 2) 2%,²¹ (grade 3) <1%²¹; cough (grade 1 or 2) 16%²¹; dyspnea (grade 1 or 2) 23%,²¹ (grade 3) <1%.²¹

O. Renal: Acute kidney injury (grade 1 or 2) <1%,²¹ (grade 3) 1%²¹; hydronephrosis (grade 1 or 2) 4%,²¹ (grade 3) 1%²¹; increased serum creatinine (grade 1 or 2) 17%.²¹

P. Treatment-Related Mortality: Sepsis <1%.²¹

DOSE ADJUSTMENT

A. Hepatic¹⁹

1. Mild impairment (bilirubin less than or equal to the ULN and AST greater than the ULN, or bilirubin greater than the ULN and ≤ 1.5 times the ULN and any AST), no adjustment required.
2. Moderate to severe impairment (bilirubin >1.5 times the ULN), no information available.

B. Renal¹⁹

1. Mild to moderate impairment (creatinine clearance ≥ 30 mL/min), no adjustment required.
2. Severe impairment (creatinine clearance <30 mL/min), no information available.

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