Cancer Chemotherapy Update

Drug Monographs: Daratumumab and Osimertinib

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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.

Regimen name: Daratumumab

Synonyms: Darzalex, HuMax-CD38, AB005

MECHANISM OF ACTION

CD38 is a glycoprotein found on the surface of various blood cells. It is weakly expressed on lymphoid and myeloid cells, but highly expressed on myeloma cells.¹ Daratumumab is a human monoclonal antibody that targets CD38. Daratumumab is a human monoclonal antibody that targets CD38 and induces antibody-dependent cellular toxicity and complement-dependent cytotoxicity in myeloma cells.^{1,2} Antibody-dependent cellular phagocytosis of tumor cells³ and induction of apoptosis² have also been described as possible mechanisms of daratumumab's action.

PHARMACOKINETICS

Following an infusion of 16 mg/kg, the mean maximum serum concentration (C_{max}) is 915 mcg/mL. With a dosing regimen weekly for 8 weeks, then every 2 weeks for 16 weeks, the steady state serum concentration is reached at about 5 months. The mean clearance and volume of distribution (V_d) were 171.4 mL/day and 4.7 L, respectively.⁴ Disposition of daratumumab is both concentration- and dose-dependent, with lower clearance at higher concentrations.⁵

Selected therapeutic regimens of daratumumab appear in Table 1.

PREPARATION

1. Follow institutional policies for preparation of hazardous medications when preparing daratumumab.
2. Use daratumumab injection, 20 mg/mL.
3. Dilute in 500 to 1,000 mL 0.9% sodium chloride injection (NS).
4. The manufacturer recommends removing from the NS bag a volume of fluid equal to the volume of drug to be used before adding the drug.⁴
5. Daratumumab should be mixed in a polyvinylchloride, polypropylene, polyethylene, polyolefin blend container.⁴
6. The first infusion should be diluted in 1,000 mL NS; subsequent infusions may be diluted in 500 mL.

STABILITY

Solutions diluted for administration may be stored under refrigeration [2°-8°C (36°-46°F)] for up to 24 hours.

ADMINISTRATION

1. Patients should receive an antihistamine, antipyretic, and steroid prior to daratumumab.
2. Infusion reactions consisting of allergic rhinitis, nausea, vomiting, dyspnea, nasal congestion, hypertension, laryngeal edema, or hypotension occur in more than 50% of patients, usually during the first or second infusion.

Table 1. Selected therapeutic regimens of daratumumab

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/cycle	Reference(s)
2-16 mg/kg	IV	1	Weekly for 8 weeks, then every other week for 16 weeks, then every 4 weeks	16-128 mg/kg 16-128 mg/kg 2-16 mg/kg	6, 7
8 mg/kg	IV	1	Weekly for 8 weeks, then every other week for 16 weeks, then every 4 weeks	64 mg/kg 64 mg/kg 8 mg/kg	8
8 mg/kg	IV	1	Day 1, then weekly for 5 weeks beginning on day 28, then every other week for 16 weeks, then every 4 weeks	8 mg/kg 40 mg/kg 64 mg/kg 8 mg/kg	8
8 mg/kg	IV	1	4 weeks	8 mg/kg	9
16 mg/kg ^a	IV	1	Weekly for 8 weeks, then every other week for 16 weeks, then every 4 weeks	128 mg/kg 128 mg/kg 16 mg/kg	4, 9-11
16 mg/kg	IV	1	Weekly for 6 weeks, then every 3 weeks	96 mg/kg 16 mg/kg	12
16 mg/kg	IV	1	Weekly for 6 weeks, then every 2 weeks	96 mg/kg 16 mg/kg	12
16 mg/kg	IV	1	Day 1, then weekly for 7 weeks beginning on day 28, then every other week for 14 weeks, then every 4 weeks	16 mg/kg 112 mg/kg 112 mg/kg 16 mg/kg	11
16 mg/kg	IV	1	Weekly for 6 weeks, then every 3 weeks for 21 weeks, then every 4 weeks	96 mg/kg 128 mg/kg 16 mg/kg	13

Note: IV = intravenous.

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

3. Daratumumab should be infused through a polyvinylchloride, polypropylene, polyethylene, polyolefin blend infusion set.
4. A 0.22-micron low protein-binding polyethersulfone filter should be used.
5. The first and second infusions should begin at a rate of 50 mL/h; subsequent infusions may begin at 100 mL/h.
6. The infusion rate should be increased by 50 mL/h every hour to a maximum rate of 300 mL/h.

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: Atrial fibrillation (grade 3 or 4) 3%⁸; flushing (grade 1 or 2) 6%⁸; hypertension 10%,¹⁰ (grade 1 or 2) 6%,⁸ (grade 3 or 4) 5%¹⁰; hypotension (grade 1 or 2) 6%⁸; palpitations (grade 1 or 2) 3%⁸; peripheral edema 10%,¹⁰ (grade 3 or 4) 1%¹⁰; tachycardia (grade 1 or 2) 6%⁸.

- B. Central Nervous System:** Anxiety 10%¹⁰; confusion (grade 3 or 4) 3%⁸; dizziness 20%,¹⁰ (grade 1 or 2) 6%⁸; headache 10%,¹⁰ (grade 1 or 2) 3%⁸; insomnia 16%,¹⁰ (grade 3 or 4) 1%¹⁰.
- C. Constitutional:** Chills 18%¹⁰; fatigue 36% to 42%,⁸⁻¹⁰ (grade 3 or 4) 1% to 5%^{8,10}; pyrexia 21% to 28%,^{8,10} (grade 3 or 4) 1% to 9%^{8,10}.
- D. Dermatologic:** Pruritus 12%,¹⁰ (grade 1 or 2) 6%⁸; rash (grade 1 or 2) 6%⁸.
- E. Gastrointestinal:** Constipation 3%¹⁰; diarrhea 21% to 34%,^{6,8,10} (grade 3 or 4) 1%¹⁰; lipedema (grade 1 or 2) 3%⁸; nausea 27% to 29%,^{9,10} (grade 1 or 2) 9%⁸; vomiting 14%,¹⁰ (grade 1 or 2) 3%⁸; xerostomia (grade 1 or 2) 3%⁸.
- F. Hematologic:** Anemia 33% to 36%,⁹ (grade 3 or 4) 3% to 21%^{8,10}; febrile neutropenia (grade 1) 3%⁶; leukopenia 25%,¹⁰ (grade 3 or 4) 16%¹⁰; lymphopenia 14%,¹⁰ (grade 3 or 4) 9%¹⁰; neutropenia 23% to 81%,^{6,9,10} (grade 3 or 4) 51% to 75%^{6,10}; thrombocytopenia 22% to 26%,^{9,10} (grade 3 or 4) 3% to 10%^{8,10}.
- G. Hepatic:** Abnormal hepatic function (severe) 3%⁸.
- H. Hypersensitivity:** Infusion reactions 56%,⁶ (grade 1) 24%,¹² (grade 3) 6%⁶; unspecified reactions 43%,⁹ (grade 1 or 2) 6%⁸ (grade 3) 5%,⁹ (grade 3 or 4) 3%⁸.
- I. Infection:** Metapneumovirus 3%⁸; pneumonia 3%⁸; upper respiratory tract 18% to 21%,^{8,10} (grade 3 or 4) 1%¹⁰; urinary tract 3%⁸.
- J. Musculoskeletal:** Arthralgia 12%,¹⁰ (grade 3 or 4) 1%¹⁰; muscle spasms 14% to 44%^{6,10}; spinal compression fracture 3%⁸; tremor 17%,¹⁰ (grade 3 or 4) 3%¹⁰.
- K. Pain:** Abdominal (grade 3 or 4) 3%⁸; back 17% to 23%,^{9,10} (grade 3 or 4) 3%¹⁰; musculoskeletal chest 10%,¹⁰ (grade 3 or 4) 3%¹⁰.
- L. Pulmonary:** Bronchospasm 6%,⁸ (grade 3 or 4) 6%⁸; cough 3% to 38%^{6,8-10}; dyspnea 19% to 26%,^{8,10} (grade 3 or 4) 7%¹⁰.
- M. Respiratory:** Allergic rhinitis 31%⁸; nasal congestion 18%,¹⁰ (grade 1 or 2) 3%⁸; throat irritation 12%¹⁰.

DOSE ADJUSTMENT

A. Hepatic⁴:

1. Mild impairment (bilirubin less than or equal to the upper limit of normal [ULN], aspartate aminotransferase [AST] greater than the ULN), no adjustment required.

2. Moderate or severe impairment (bilirubin greater than 1.5 times the ULN, any AST), no information available.

B. Renal⁴: No adjustment is required.

Regimen name: Osimertinib

Synonyms: Tagrisso, AZD9291

MECHANISM OF ACTION

Osimertinib is an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor that irreversibly binds to both the activating EGFR and the EGFR T790M resistance mutation.¹⁴

PHARMACOKINETICS

AZD9291 has a median time to time to maximum serum concentration (T_{max}) of 6 hours^{15,16} and a mean half-life of 55 hours.¹⁵ Steady state concentration is reached in 22 days. Following 80 mg/day, the mean AUC_{tau} is 12,120 nM•h on day 22; and the mean maximum serum concentration (C_{max}) is 635.4 nM. The AUC of the metabolites AZ5104 and AZ7550 is approximately 10% of the AUC of the parent drug.¹⁵

With daily dosing, the time to steady state concentration is 15 days. Osimertinib is highly bound to serum protein, and has a mean volume of distribution (V_d) of 986 L. The drug is metabolized by oxidation by the CYP3A and dealkylation in the liver to 2 active metabolites: AZ5104 and AZ7550. Osimertinib has a mean half-life ($T_{1/2}$) of 48 hours and an oral clearance of 14.2 L/h. Osimertinib is excreted primarily in the feces (68%), with about 14% excreted in the urine. About 2% of the drug is excreted unchanged.¹⁶

Selected therapeutic regimens of osimertinib appear in Table 2.

PREPARATION

1. Follow institutional policies for preparation of hazardous medications when dispensing osimertinib.
2. Osimertinib is available as 40 mg and 80 mg tablets.

STABILITY

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

Table 2. Selected therapeutic regimens of osimertinib

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/month	References
20 mg	PO	Daily	—	600 mg	15, 17
40 mg	PO	Daily	—	1,200 mg	15, 17
80 mg ^a	PO	Daily	—	2,400 mg	15-20
160 mg	PO	Daily	—	4,800 mg	15, 17
240 mg	PO	Daily	—	7,200 mg	15, 17

Note: PO = oral.

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

ADMINISTRATION

- Osimertinib should be taken once daily.
- The drug may be taken with, or without, food.
- For patients unable to swallow tablets:
 - Mix the tablet in approximately 50 mL of non-carbonated water and stir until it is completely dispersed.
 - Drink the mixture or administer through a feeding tube; rinse the container with 4 to 8 ounces of water and drink or administer through a feeding tube.

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%.

80 mg daily

- Central Nervous System:** Headache 10%.¹⁵
- Constitutional:** Fatigue 10%.¹⁵
- Dermatologic:** Acne or rash 32%,¹⁵ (grade 1 or 2) 46%¹⁷; dry skin 11%¹⁵; paronychia 12%¹⁵; pruritus 17%.¹⁵

- Gastrointestinal:** Anorexia 16%,¹⁵ (grade 3 to 5) 1%¹⁵; constipation 17%¹⁵; diarrhea 33%,¹⁵ (grade 1 or 2) 50%,¹⁷ (grade 3 or 4) 1%¹⁵; nausea 30%¹⁵; stomatitis 10%¹⁵; vomiting 10%.¹⁵
- Hematologic:** Anemia 12%,¹⁵ (grade 3 to 5) 3%.¹⁵
- Infection:** Upper respiratory tract 10%.¹⁵
- Pulmonary:** Cough 13%¹⁵; dyspnea 10%,¹⁵ (grade 3 to 5) 1%.¹⁵

DOSE ADJUSTMENT

- Hepatic**¹⁶:
 - Mild impairment:
 - Bilirubin less than the ULN and AST less than or equal to 1.5 times the ULN, no adjustment required.
 - Bilirubin greater than 1.5 times the ULN and any AST, no adjustment required.
 - Moderate or severe impairment, no information available.
- Renal**¹⁶:
 - Creatinine clearance (Cl_{cr}) greater than or equal to 60 mL/min and less than or equal to 89 mL/min, no adjustment required.
 - Cl_{cr} greater than or equal to 30 mL/min and less than or equal to 9 mL/min, no adjustment required.
 - Cl_{cr} less than 30 mL/min, no information available.

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