Drug Monographs: Avelumab and Ribociclib

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J. Aubrey Waddell¹ and Dominic A. Solimando, Jr²

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, email: 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.

Avelumab

Synonyms: MSB0010718C, *Bavencio*

Mechanism of Action

Avelumab is a fully human anti-programmed death-ligand 1 (PD-L1) IgG1 antibody.¹⁻¹⁰ The programmed death-1 (PD-1) receptor and its ligand PD-L1 are important targets in reactivating the anticancer immune response.^{1,5} PD-L1 is frequently expressed by tumor cells in the tumor microenvironment and binds to the PD-1 receptor on activated T cells, which results in T-cell inactivation.⁵ Avelumab binds PD-L1 and inhibits PD-L1's binding to PD-1, and therefore, it prevents T-cell inactivation and suppression.⁷ Because avelumab has a native F_c region, it is also capable of inducing antibody-dependent cell-mediated cytotoxicity.⁷⁻¹⁰ Avelumab does not inhibit binding of PD-L2 to PD-1.^{5,8,9}

Pharmacokinetics

Following a 10 mg/kg avelumab dose infused over 60 minutes, peak concentration ($C_{\max}$) was 310 mcg/mL, trough concentration (C_{trough}) was 24 mcg/mL, area under the curve ($\text{AUC}_{0-336\text{h}}$) was 25 900 h·mcg/mL, and half-life ($t_{1/2}$) was 96.6 hours.⁷ In doses from 1 to 20 mg/kg every 2 weeks, the AUC increased dose-proportionally in the range of 10 to 20 mg/kg; steady state concentrations were reached after 4 to 6 weeks.¹⁰ The geometric volume of distribution (V_d) at steady state with 10 mg/kg dosing was 4.72 L, total systemic clearance (CL) was 0.59 L/d, and the terminal $t_{1/2}$ was 146 hours.¹⁰ Proteolytic degradation is the major mechanism of elimination of avelumab.¹⁰ Selected therapeutic regimens of avelumab appear in Table 1.

Preparation

1. Follow institutional policies for handling hazardous medications when dispensing avelumab.
2. Use avelumab injection, 20 mg/mL.
3. The prescribed dose should be diluted in 250 mL of 0.45% or 0.9% Sodium Chloride Injection.¹⁰
4. The diluted solution should be mixed by gently inverting the solution. Do not shake.

Stability

1. Solutions diluted for administration are stable at room temperature (20°C–25°C [68°F–77°F]) for 4 hours or 24 hours refrigerated (2°C–8°C [36°F–46°F]).
2. Protect from light.
3. Do not freeze.

Administration

1. Infuse over 60 minutes through an intravenous line that contains a sterile, nonpyrogenic, low protein binding in-line 0.2-micron filter.
2. Premedication with 25 to 50 mg of diphenhydramine and 500 to 650 mg of acetaminophen is recommended due to high incidence of infusion reactions.^{5,7,8,10}

¹University of Tennessee College of Pharmacy, Knoxville, TN, USA

²Oncology Pharmacy Services, Inc, Arlington, VA, USA

Corresponding Author:

J. Aubrey Waddell, Pharmacy Department, Blount Memorial Hospital, 907 E. Lamar Alexander Parkway, Maryville, TN 37804, USA.
Email: waddfour@charter.net

Table 1. Selected Therapeutic Regimens of Avelumab.

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/cycle	References
10 mg/kg ^a	IV	I	14 days	10 mg/kg	1-10
20 mg/kg	IV	I	14 days	20 mg/kg	7

Note. IV = intravenous.

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

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: Creatine phosphokinase elevations (grade 1 or 2) 1% to 7%,^{5,7} (grade 3 or 4) 1% to 2%;^{2,5,9} embolic stroke (grade 3 or 4) 1%;⁸ hypertension (grade 3 or 4) 1%;⁸ hypovolemia (grade 3 or 4) 1%.⁸

B. Central Nervous System: Syncope (grade 3 or 4) 1%.⁸

C. Constitutional: Asthenia (grade 1 or 2) 8% to 9%,^{5,9} (grade 3 or 4) 2%;⁹ chills (grade 1 or 2) 7% to 15%;^{2,7,8} fall (grade 3 or 4) 1%;⁸ fatigue (all grades) 15% to 20%,^{1,6} (grade 1 or 2) 14% to 67%,^{2,3,7-9} (grade 3 or 4) 2% to 3%;^{1,4,6} fever (all grades) 11%,² (grade 1 or 2) 27%;⁷ influenza-like illness (grade 1 or 2) 20%.⁷

D. Dermatologic: Maculopapular rash (grade 1 or 2) 6%;⁵ pruritus (grade 1 or 2) 7%;⁹ psoriasis (grade 1 or 2) 1%;⁸ rash (grade 1 or 2) 7% to 9%.^{5,7,9}

E. Endocrine/metabolic: Adrenal insufficiency (grade 1 or 2) 1%;⁸ amylase elevations (grade 1 or 2) 1%;⁸ (grade 3 or 4) 1%;⁸ autoimmune reaction (any type, grade 3 or 4) 14%;⁷ cholesterol elevations (grade 3 or 4) 1%;⁵ hyperthyroidism (grade 1 or 2) 2%;⁵ hypoglycemia (grade 1 or 2) 13%;⁷ hyponatremia (grade 3 or 4) 1%;⁸ hypothyroidism (grade 1 or 2) 1% to 7%;^{5,6,8,9} lipase elevations (grade 1 or 2) 1%;⁸ (grade 3 or 4) 2%;^{3,8} type I diabetes mellitus (grade 1 or 2) 1%.⁵

F. Gastrointestinal: Colitis (grade 3 or 4) 8%;² constipation (grade 1 or 2) 2%;⁸ (grade 3 or 4) 1%;⁸ decreased appetite (grade 1 or 2) 2% to 7%,^{5,8,9} (grade 3 or 4) 2%;⁹ diarrhea (grade 1 or 2) 7% to 13%;^{3,5,7-9} nausea (all grades) 14%,¹ (grade 1 or 2) 9% to 13%;^{5,7-9} vomiting (grade 1 or 2) 5%.⁸

G. Hematologic: Anemia (grade 1 or 2) 3%,⁸ (grade 3 or 4) 1% to 3%;^{1,4,8} lymphopenia (grade 1 or 2) 20%,⁷ (grade 3 or 4) 2% to 7%;^{2,5,7} neutropenia (grade 3 or 4) 1%;⁸ systemic inflammatory response syndrome (grade 3 or 4) 1%;⁸ thrombocytopenia (grade 3 or 4) 3%.⁴

H. Hepatic: Aminotransferase elevations (grade 3 or 4) 1%;^{5,8} alanine aminotransferase (ALT) elevations (grade 1 or 2) 2%,⁹ (grade 3 or 4) 7%;⁷ aspartate aminotransferase (AST) elevations (grade 1 or 2) 2%,⁹ (grade 3 or 4) 2% to 7%;^{7,9} autoimmune hepatitis (grade 3 or 4) 2%;¹ gamma-glutamyl transferase elevations (grade 1 or 2) 1%,⁸ (grade 3 or 4) 1% to 2%.^{1,2,8}

I. Hypersensitivity: Allergic rhinitis (grade 1 or 2) 7%;⁷ anaphylactic reaction (grade 3 or 4) 1%;⁸ infusion reactions (all grades) 12% to 17%,^{1,6} (grade 1 or 2) 7% to 38%,^{2-5,7-9} (grade 3 or 4) 2%.^{6,8}

J. Musculoskeletal: Arthralgia (grade 1 or 2) 5%,⁸ (grade 3 or 4) 1%;¹ arthritis (grade 1 or 2) 1%;⁸ musculoskeletal pain (grade 3 or 4) 1%;⁸ rheumatoid arthritis (grade 1 or 2) 2%;⁹ rheumatoid factor elevations (grade 1 or 2) 1%.⁸

K. Neurologic: Lower abdominal pain (grade 3 or 4) 7%;⁷ monoplegia (grade 3 or 4) 1%.⁸

L. Ocular: Dry eyes (grade 1 or 2) 1%;⁸ iritis (grade 1 or 2) 1%;⁸ uveitis (grade 1 or 2) 2%.⁹

M. Pulmonary: Chronic obstructive pulmonary disease (grade 3 or 4) 1%;⁸ dyspnea (grade 1 or 2) 2%,⁸ (grade 3 or 4) 2%;⁸ hypoxia (grade 3 or 4) 1%;⁸ lung abscess (grade 3 or 4) 1%;⁸ pneumonitis (grade 1 or 2) 1% to 2%,^{5,6,9} (grade 3 or 4) 1%.⁸

N. Renal: Urosepsis (grade 3 or 4) 1%.⁸

O. Treatment-Related Mortality: Acute liver failure/autoimmune hepatitis 1% to 2%;^{1,4} respiratory distress 1%.¹

Dosage Modifications

A. Hepatic

For mild hepatic impairment (bilirubin $\leq$ upper limit of normal [ULN] and AST $>$ ULN; or bilirubin 1-1.5 times ULN and any AST) or moderate hepatic impairment (bilirubin 1.5-3 times ULN), no dose adjustments are necessary.¹⁰ Avelumab data in patients with severe hepatic impairment (bilirubin $>$ 3 times ULN) are limited.¹⁰

Table 2. Selected Therapeutic Regimens of Ribociclib.

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/cycle	References
400-600 mg	PO	1-14 prior to breast surgery	14 days	5600 to 8400 mg	12
600 mg ^a	PO	1-21	28 days	12,600 mg	11, 13, 14, 15

Note. PO = oral.

^aConforms to dosing information listed in the manufacturer's labeling when taken in combination with an aromatase inhibitor.

B. Renal

For mild to severe renal impairment (estimated glomerular filtration rate: 15-89 mL/min/1.73 m²), no dose adjustments are necessary.¹⁰

Ribociclib

Synonyms: LEE011, *Kisqali*

Mechanism of Action

Ribociclib is an orally bioavailable and selective inhibitor of cyclin D-cyclin-dependent kinase (CDK) 4/6-inhibitor, which prevents CDK4/6-retinoblastoma (Rb) phosphorylation. Inhibition of Rb results in G1 cell cycle arrest.¹¹⁻¹³ Ribociclib acts synergistically with aromatase inhibitors in preclinical models of estrogen receptor-positive breast cancer, a malignancy in which CDK-4/6 is frequently overexpressed.¹²⁻¹⁵

Pharmacokinetics

Following oral dosing, ribociclib is rapidly absorbed with a median time to maximum serum concentration (T_{max}) of 1 to 6 hours.^{11,12,15} With daily oral dosing, steady state is reached by about day 8.^{11,12,15} At 600 mg/d oral dosing, ribociclib's mean effective half-life based on accumulation ratio ($T_{1/2}$ acc) is 32 to 32.6 hours^{11,15} and geometric mean apparent oral CL is 25.5 L/h.¹⁵ On day 14 of 600 mg/d oral dosing, the mean C_{max} , AUC_{0-6h} , and AUC_{0-24h} were 3083 ng/mL, 13 348 ng·h/mL, and 38 896 ng·h/mL, respectively.¹² Oral administration of 600-mg ribociclib in the approved dosage form combined with a high-fat meal has no effect on the rate and extent of ribociclib absorption.¹⁵ Plasma protein binding is about 70%, and the apparent V_d is 1090 L.¹⁵ Ribociclib undergoes extensive hepatic metabolism mainly via CYP3A4, with the main metabolic pathway being oxidation.¹⁵ Clinical activity of ribociclib is mainly due to parent drug, with very small contribution from multiple circulating metabolites.¹⁵ Elimination is mainly via feces at 69%, with 23% of dose recovered from urine.¹⁵ The extensive metabolism of ribociclib is reflected by the unchanged drug fractions of 17% and 12% found in feces and urine, respectively.¹⁵ Selected therapeutic regimens of ribociclib appear in Table 2.

Preparation

1. Follow institutional policies for preparation of hazardous medications when dispensing ribociclib.
2. Ribociclib is available in blister packs of film-coated tablets with each tablet containing 200 mg of ribociclib free base.

Stability

Store at 20°C to 25°C (68°F-77°F).

Administration

1. Ribociclib is given orally, once a day.
2. Ribociclib may be given with or without food.
3. When taken with an aromatase inhibitor, ribociclib and the aromatase inhibitor should be taken at the same time each day.

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://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%. The toxicities are reported for ribociclib alone and for the approved ribociclib plus letrozole.

Ribociclib

- A. Cardiovascular:** QT prolonged (all grades) 9%.¹¹
B. Constitutional: Fatigue (grade 3 or 4) 3%, (all grades) 33%.¹¹
C. Gastrointestinal: Decreased appetite (all grades) 7%¹¹; diarrhea (grade 3 or 4) 3%, (all grades) 27%¹¹; nausea (grade 3 or 4) 1%, (all grades) 45%¹¹; vomiting (all grades) 25%.¹¹

D. Hematologic: Anemia (grade 3 or 4) 3%, (all grades) 28%¹¹; leukopenia (grade 3 or 4) 19%, (all grades) 46%¹¹; lymphopenia (grade 3 or 4) 22%, (all grades) 22%¹¹; neutropenia (grade 3 or 4) 28%, (all grades) 46%¹¹; thrombocytopenia (grade 3 or 4) 9%, (all grades) 34%.¹¹

E. Renal: Serum creatinine increased (all grades) 6%.¹¹

Ribociclib plus letrozole

A. Cardiovascular: Hypertension (grade 3 or 4) 10%¹³; increase >60 ms from baseline QTcF interval (all grades) 3%¹³; QTcF interval >480 ms (all grades) 3%¹³; QTcF prolongation (all grades) 50%.¹²

B. Central Nervous System: Headache (grade 3 or 4) 0.3%, (all grades) 22%.¹³

C. Constitutional: Asthenia (all grades) 25%¹²; decreased appetite (grade 3 or 4) 2%,¹³ (all grades) 19% to 50%^{12,13}; fatigue (grade 3 or 4) 2%,¹³ (all grades) 25% to 37%^{12,13}; hot flush (grade 3 or 4) 0.3%,¹³ (all grades) 21% to 25%.^{12,13}

D. Dermatologic: Alopecia (all grades) 33%¹³; rash (grade 3 or 4) 1%, (all grades) 17%.¹³

E. Gastrointestinal: Constipation (grade 3 or 4) 1%, (all grades) 25%¹³; diarrhea (grade 3 or 4) 1%,¹³ (all grades) 25% to 35%^{12,13}; nausea (grade 3 or 4) 2%,¹³ (all grades) 50% to 52%^{12,13}; vomiting (grade 3 or 4) 4%,¹³ (all grades) 25% to 29%.^{12,13}

F. Hematologic: Anemia (grade 3 or 4) 1%, (all grades) 19%¹³; febrile neutropenia (all grades) 2%¹³; leukopenia (grade 3 or 4) 2% to 21%,^{13,14} (all grades) 33%¹³; lymphopenia (grade 3 or 4) 4% to 7%^{13,14}; neutropenia (grade 3 or 4) 43% to 59%,^{13,14} (all grades) 74%.¹³

G. Hepatic: Increased ALT (grade 3 or 4) 9%, (all grades) 16%¹³; increased AST (grade 3 or 4) 6%, (all grades) 15%.¹³

H. Infection: Any (grade 3 or 4) 4%, (all grades) 50%¹³; upper respiratory tract infections (all grades) 11%¹³; urinary tract infections (grade 3) 1%, (all grades) 11%.¹³

I. Musculoskeletal: Arthralgia (grade 3 or 4) 1%, (all grades) 27%.¹³

J. Pain: Abdominal pain (all grades) 25%¹²; back pain (grade 3 or 4) 2%, (all grades) 20%.¹³

K. Pulmonary: Cough (all grades) 20%.¹³

L. Treatment-Related Mortality: Sudden death in association with grade 3 hypokalemia and grade 2 prolongation of QTcF interval, 0.3%.¹³

Dosage Modifications

Dose levels are 600, 400, and 200 mg daily on 21 of 28 day cycle.

A. Hepatic¹⁵

1. Grade 1 AST and/or ALT without increase in total bilirubin > 2 × ULN—No dosage adjustment needed.

2. Grade 2 AST and/or ALT without increase in total bilirubin > 2 × ULN—No dosage adjustment needed if grade 2 is baseline. If baseline < grade 2, interrupt dosing until AST and/or ALT ≤ baseline, then resume at same dose level. If grade 2 recurs, resume at next lower dose level.
3. Grade 3 AST and/or ALT without increase in total bilirubin > 2 × ULN—Interrupt dosing until AST and/or ALT ≤ baseline, then resume at next lower dose level. If grade 3 recurs, discontinue ribociclib.
4. Grade 4 AST and/or ALT without increase in total bilirubin > 2 × ULN—Discontinue ribociclib.
5. AST and/or ALT > 3 × ULN with total bilirubin > 2 × ULN, discontinue ribociclib.

B. Renal¹⁵

1. Creatinine clearance 30 mL/min to ULN—No dosage adjustment.
2. Creatinine clearance < 30 mL/min—No dosage information available.

C. Neutrophils¹⁵

1. Grade 1 or 2—No dosage adjustment needed.
2. Grade 3—Interrupt dosing until recovery to grade ≤ 2, then resume at same dose level. If grade 3 recurs, interrupt dosing until recovery to grade ≤ 2, then resume dosing at next lower level.
3. Grade 4—Discontinue ribociclib.

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