Cancer Chemotherapy Update

Nivolumab and Olaparib

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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.

Name: Nivolumab

Synonyms: *Opdivo*; Anti-PD-1; Anti-PD-1 antibody; BMS-936558; ONO-4538

MECHANISM OF ACTION

Programmed death 1 protein (PD-1) is a T-cell inhibitory receptor similar to the cytotoxic T-lymphocyte-associated antigen (CTLA-4). PD-1 is involved in modulating the initial stages of T-cell activation. Nivolumab is a monoclonal antibody that blocks the PD-1 receptor on T-cells. Inhibiting the interaction between PD-1 and the PD-1 ligand and CD80 enhances T-cell response, potentiating immune response.¹⁻⁵

PHARMACOKINETICS

The time to peak concentration (T_{max}) is 1 to 4 hours after the beginning of the infusion. The maximum concentration (C_{max}) is dose-related.⁶ Following doses of 0.1 to 20 mg/kg, the volume of distribution (V_d) is 8 L, with total clearance of 9.5 mL/h.⁷ The elimination half-life ($T_{1/2}$) is 26.7 days; clearance is increased with increased body weight.⁷

Selected therapeutic regimens of nivolumab appear in Table 1.

PREPARATION

A. Follow institutional policies for preparation of hazardous medications when preparing nivolumab.

- B. Use nivolumab injection, 10 mg/mL.
C. Dilute with 100 to 250 mL 0.9% sodium chloride (NS) or 5% dextrose in water (D5W).

STABILITY

Solutions for infusion are stable to 4 hours at room temperature, or 24 hours under refrigeration (2°C to 8°C [36°F-46°F]).

ADMINISTRATION

Nivolumab is administered as a 1-hour intravenous (IV) infusion.

TOXICITIES (3 MG/KG EVERY 2 WEEKS)

- A. **Constitutional:** Asthenia 10%,³² fatigue 2% to 20%.^{10,32}
B. **Dermatologic:** Pruritus 16% to 17%,^{6,32} (grade 3 or 4) 0.5%³²; rash 15% to 20%,^{6,32} (grade 3 or 4) 0.5% to 5%^{32,37}; rash, macular 2%⁶; rash, pruritic 2%⁶; urticaria 6%⁶; vitiligo 4% to 11%.^{6,32}
C. **Endocrine/Metabolic:** Hyperglycemia (grade 3 or 4) 5%,³⁷ hyperthyroidism 2%,⁶ hypothyroidism 2%,⁶ increased thyroid-stimulating hormone (TSH) 4%,⁶ unspecified endocrine disorders (grade 3 or 4) 2%.¹⁰
D. **Gastrointestinal:** Constipation 11%³²; diarrhea 16% to 19%,^{6,32} (grade 3 or 4) 1% to 5%^{10,32,36}; increased lipase 2%¹⁰; nausea 17%³²; vomiting 6%,³² (grade 3 or 4) 0.5%³²; weight loss (grade 3 or 4) 5%.³⁶

Table 1. Selected therapeutic regimens of nivolumab

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/ cycle	References
0.1-10 mg/kg	IV	1	2 weeks	0.1-10 mg/kg	8,9
0.1 mg/kg	IV	1	2 weeks	0.1 mg/kg	10-12
0.3 mg/kg	IV	1	2 weeks	0.3 mg/kg	10-13
0.3 mg/kg	IV	1	3 weeks	0.3 mg/kg	14-17
0.3 mg/kg	IV	1	Every 3 weeks for 4 cycles, then every 12 weeks for 8 cycles	0.3 mg/kg	18
0.3 mg/kg	IV	1, 5, 29	6 weeks	0.9 mg/kg	19
1 mg/kg	IV	1	2 weeks	1 mg/kg	6,10-13,20-25
1 mg/kg	IV	1	2 weeks for 12 cycles, then every 2 weeks	1 mg/kg	26
1 mg/kg	IV	1	3 weeks	1 mg/kg	14,15
1 mg/kg	IV	1	Every 3 weeks for 4 cycles, then every 2 weeks	1 mg/kg	27,28
1 mg/kg	IV	1	Every 3 weeks for 4 cycles, then every 12 weeks for 8 cycles	1 mg/kg	18
1 mg/kg	IV	1	Every 3 weeks for 4 cycles, then every 2 weeks	1 mg/kg	18,29,30
3 mg/kg				3 mg/kg	
1 mg/kg	IV	1, 5, 29	6 weeks	3 mg/kg	19
2 mg/kg	IV	1	3 weeks	2 mg/kg	16,17,31
3 mg/kg ^a	IV	1	2 weeks	3 mg/kg	6,7,10-13,20-24,32-43
3 mg/kg	IV	1, 29, then every 2 weeks	2 weeks	3 mg/kg	44
3 mg/kg	IV	1	3 weeks	3 mg/kg	14,15
3 mg/kg	IV	1	2 weeks for 12 cycles, then every 2 weeks	1 mg/kg	26
3 mg/kg	IV	1	Every 3 weeks for 4 cycles, then every 2 weeks	3 mg/kg	29,30
3 mg/kg	IV	1	Every 3 weeks for 4 cycles, then every 2 weeks	3 mg/kg	27,28
3 mg/kg	IV	1	Every 3 weeks for 4 cycles, then every 12 weeks for 8 cycles	3 mg/kg	18
3 mg/kg	IV	1, 5, 29	6 weeks	9 mg/kg	19
5 mg/kg	IV	1	3 weeks	5 mg/kg	31
10 mg/kg	IV	1	2 weeks	10 mg/kg	6,10,11, 18,20-25
10 mg/kg	IV	1	2 weeks for 12 cycles, then every 2 weeks	10 mg/kg	26

(continued)

Table 1. Selected therapeutic regimens of nivolumab (CONT.)

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/cycle	References
10 mg/kg	IV	1	3 weeks	10 mg/kg	16,17,45,46
10 mg/kg	IV	1	Every 3 weeks for 4 cycles, then every 2 weeks	10 mg/kg	27,28
10 mg/kg	IV	1	Every 3 weeks for 4 cycles, then every 12 weeks for 8 cycles	10 mg/kg	18
10 mg/kg	IV	1, 5, 29	6 weeks	30 mg/kg	19

Note: IV = intravenous.

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

E. Hepatic: Hepatitis (grade 3 or 4) 1%¹⁰; increased alanine aminotransferase (ALT) 4%,⁶ (grade 3 or 4) 5% to 10%^{36,37}; increased aspartate aminotransferase (AST) 4%,⁶ (grade 3 or 4) 2% to 5%.^{6,36,37}

F. Hematologic: Lymphopenia 3%.¹⁰

G. Hypersensitivity: Hypersensitivity/infusion reactions 6%.⁶

H. Pulmonary: Pneumonitis 2%.⁶

I. Renal: Nephritis (grade 2) 5%.³⁶

- a. Delay therapy up to 12 weeks.
- b. If no resolution at 12 weeks, discontinue drug.
3. Life threatening renal impairment (serum creatinine greater than 6 times the ULN), discontinue the drug.⁷

Name: *Olaparib*

Synonyms: *Lynparza*; AZD2281; CBT-1

DOSE ADJUSTMENT

A. Hepatic

1. Mild hepatic impairment, no adjustment required.⁷
2. Moderate hepatic impairment (ALT or AST greater than 3 times the upper limit of normal [ULN] and less than or equal to 5 times the ULN)⁷:
 - a. Delay therapy up to 12 weeks.
 - b. If no resolution at 12 weeks, discontinue drug.
3. Severe hepatic impairment (ALT or AST greater than 5 times the ULN or bilirubin greater than 3 times the ULN), discontinue the drug.⁷

B. Renal

1. Mild renal impairment, no adjustment required.⁷
2. Moderate renal impairment (serum creatinine greater than 1.5 times the ULN and less than or equal to 6 times the ULN)⁷:

MECHANISM OF ACTION

Olaparib is an inhibitor of poly(ADP-ribose) polymerase (PARP) enzymes (PARP-1, PARP-2, PARP-3). PARPs are enzymes needed for repair of single-strand DNA breaks. Inhibition of this pathway leads to accumulation of single-strand breaks, resulting in double-strand breaks in the DNA molecule.⁴⁷⁻⁴⁹

PHARMACOKINETICS

Following oral administration, absorption is rapid, with the peak concentration (C_{max}) between 1 and 3 hours.⁵⁰⁻⁵² The drug is approximately 82% protein bound.⁵² The C_{max} was reported to range from 4.7 mcg/mL to 9.1 mcg/mL; the time to maximum concentration (T_{max}) was 1 to 2 hours and 2 to 3 hours.⁵³⁻⁵⁵ One study found a C_{max} of $2,399.8 \pm 1,371.5$ mcg/L.⁵⁶ For oral doses ranging from 100 mg daily to 600 mg twice a day, the mean V_d is 40.3 L.⁵⁰ Following a 400 mg oral dose, the V_d is reported to be 167 ± 196 L.⁵²

The AUC following 200 mg and 400 mg doses was 25.8 mcg•h/L and 58.1 mcg•h/L, respectively.⁵³ Following daily administration of 10 mg to 80 mg per day for 14 days, the AUC increased by approximately 26%. After twice-daily dosing with 60 mg to 600 mg per day for 14 days, the mean AUC increase was 49%.⁵⁰ Administration with a high-fat meal slows the T_{max} , but does not significantly increase the AUC.^{52,56} Plasma clearance is 4.6 L/h; the elimination $T_{1/2}$ is 5 to 11 hours.^{50,51}

Olaparib is metabolized by oxidation followed by glucuronide or sulfate conjugation in the liver by CYP3A4.⁵² Renal excretion accounts for about 44% of the drug, primarily as unchanged drug; about 15% is excreted as metabolites.⁵² Forty-two percent of the drug is excreted in the feces, primarily as metabolites.⁵²

Selected therapeutic regimens of olaparib appear in Table 2.

PREPARATION

- A. Follow institutional policies for preparation of hazardous medications when dispensing olaparib.
- B. Olaparib is available as 50 mg capsules.
- C. Olaparib should be stored at 25°C (77°F).

STABILITY

- A. Olaparib is stored at controlled room temperature (20°C to 25°C [68°F to 77°F]).
- B. Brief (less than 24 hours) exposure to temperatures up to 30°C (86°F) is acceptable.

ADMINISTRATION

- A. Olaparib is administered orally, usually twice a day.
- B. Patients should be advised to avoid grapefruit and Seville oranges while taking olaparib.

TOXICITIES (400 MG TWICE DAILY)

- A. **Central Nervous System:** Dizziness 13%,⁸⁹ (grade 1) 10%,⁸⁸ (grade 2) 2%,⁸⁸ (grade 1 or 2) 6% to 16%,^{61,87} (grade 3 or 4) 12%⁵⁰; headache 21% to 25%,^{53,89} (grade 1) 9% to 12%,^{77,88} (grade 2) 7%,⁸⁸ (grade 1 or 2) 6% to 7%.^{61,64}
- B. **Constitutional:** Asthenia 14% to 50%,^{54,89} (grade 1) 7%,⁸⁸ (grade 2) 4%,⁸⁸ (grade 1 or 2) 6% to 34%,^{61,82} (grade 3 or 4) <1%⁸⁹; fatigue 7% to 75%,^{51,53,81,89} (grade 1) 24% to 30%,^{77,88} (grade 2) 15% to 18%,^{77,88} (grade 1 or 2) 30% to 62%,^{50,61,64-66,82,87,90} (grade 3) 11%,⁷⁷ (grade 3 or 4) 3% to 15%^{61,64,66,67,78,82,87-89}; hot flushes (grade 1) 3%,⁸⁸ (grade 2) 1%.⁸⁸

Table 2. Selected therapeutic regimens of olaparib

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/month (cycle)	References
10 mg qd	PO	1 through 14	21 days	140 mg	50
10 mg bid	PO	1,2,3,4,5,6,7	21	140 mg	57
10 mg bid	PO	1,2,3,4,(5)	Before surgery	80 mg (100 mg)	58
20 mg qd	PO	1 through 14	21 days	280 mg	50
20 mg bid	PO	1,2,3,4,5,6,7	21	280 mg	57
30 mg bid	PO	1,2,3,4,(5)	Before surgery	240 mg (300 mg)	58
40 mg bid	PO	1,2,3,4,5,6,7	21	560 mg	57
40 mg qd	PO	1 through 14	21 days	560 mg	50
50 mg qd	PO	1	28 days	350 mg	54
50 mg bid		2,3,4,5,6,7			
50 mg bid	PO	Daily	–	3,000 mg	59
50 mg bid	PO	Daily	21 days for 6 cycles then daily	2,100 mg	60
400 mg bid				24,000 mg	
60 mg bid	PO	1 through 14	21 days	1,680 mg	50
80 mg qd	PO	1 through 14	21 days	1,120 mg	50

(continued)

Table 2. Selected therapeutic regimens of olaparib (CONT.)

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/month (cycle)	References
100 mg bid	PO	Daily	–	6,000 mg	50,51,53,54,59,61-72
100 mg bid	PO	1,2,3,4,5,6,7	21	1,400 mg	57
100 mg bid	PO	1,2,3,4,5,6,7	28 days	1,400 mg	54
100 mg bid	PO	1,2,3,4,(5)	Before surgery	800 mg (1,000 mg)	58
100 mg bid	PO	1,2,3,4	21 days for 6 cycles	800 mg	56
100 mg bid	PO	-2,-1,0,1,2	21 days for 6 cycles	1,000 mg	73
100 mg qd	PO	-2,-1,0,1,2	21 days for 6 cycles	500 mg	73
100 mg qd	PO	1,2,3,4	21 days for 6 cycles	400 mg	56
100 mg bid	PO	1 through 14	21 days	2,800 mg	50
100 mg bid 100 mg then 100 mg bid	PO	1,2,3 4 1 through 42	8 weeks	700 mg 8,400 mg	74
100 mg bid	PO	1,2,3,4,5,6,7 then daily	–	1,400 mg 24,000 mg	75
100 mg bid	PO	Daily	21 days for 6 cycles then daily	4,200 mg 24,000 mg	60
100 mg bid	PO	1,2,3,4,5,6,7 then daily	–	1,400 mg 24,000 mg	75
100 mg bid	PO	Daily to progression then daily	–	6,000 mg 12,000 mg	76
150 mg bid	PO	Daily	–	9,000 mg	71
200 mg bid	PO	Daily	–	12,000 mg	50,51,53,54,59,62,63, 67,72,77-81
200 mg bid	PO	1,2,3,4,5,6,7	21 days	2,800 mg	54,82
200 mg bid	PO	1,2,3,4,5,6,7	28 days	2,800 mg	54,82
200 mg bid 200 mg then 200 mg bid	PO	1,2,3 4 1 through 42	8 weeks	1400 mg 16,800 mg	74
200 mg bid	PO	1,2,3,4,(5)	Before surgery	1,600 mg (2,000 mg)	58
200 mg bid	PO	Daily	21 days for 6 cycles then daily	8,400 mg 24,000 mg	60,83
200 mg bid	PO	Daily	28 days for 6-10 cycles then daily	8,400 mg 24,000 mg	84
200 mg tid	PO	Daily	–	18,000 mg	72,85
250 mg bid	PO	Daily	–	22,500 mg	72
300 mg bid	PO	Daily	–	18,000 mg	78,86

(continued)

Table 2. Selected therapeutic regimens of olaparib (CONT.)

Daily dose	Route of administration	Administered on day(s)	Cycle length	Total dose/month (cycle)	References
400 mg bid ^a	PO	Daily	–	24,000 mg	50-55,61,63-69, 77-82,87-90
400 mg bid	PO	1,2,3,4,(5)	Before surgery	3,200 mg (4,000 mg)	58
400 mg bid	PO	1,2,3,4,5,6,7	21 days	5,600 mg	62
400 mg bid	PO	1,2,3,4,5,6,7	28 days	5,600 mg	54
500 mg qd	PO	1,2,3,4,5,6,7	One time	3,500	91
600 mg bid	PO	Daily	–	36,000 mg	50

Note: bid = twice a day; PO = oral; qd = once a day; tid = three times a day.

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

C. Dermatologic: Pruritus 33%⁵¹; rash 17%,⁵¹ (grade 1 or 2) 9%.^{61,82}

D. Endocrine/Metabolic: Hyperglycemia 17%,⁵¹ hypothyroidism (grade 2) 2%.⁷⁷

E. Gastrointestinal: Abdominal distension 13%,⁸⁹ (grade 1) 10%,⁸⁸ (grade 2) 1%,⁸⁸ (grade 1 or 2) 19%⁸⁷; anorexia 21% to 33%,^{51,54,89} (grade 1) 13%,⁸⁸ (grade 2) 6%,⁸⁸ (grade 1 or 2) 11% to 37%,^{64,87} (grade 3 or 4) 1%⁸⁷; constipation 17% to 21%,^{51,89} (grade 1) 9%,⁸⁸ (grade 2) 4%,⁸⁸ (grade 1 or 2) 7% to 16%^{64,82}; diarrhea 25% to 27%,^{51,89} (grade 1) 2% to 23%,^{77,88} (grade 2) 4%,⁸⁸ (grade 1 or 2) 12% to 38%,^{50,61,64,82,87} (grade 3 or 4) 2% to 3%⁸⁷⁻⁸⁹; dysgeusia 25% to 33%,^{51,53,89} (grade 1) 13%,⁸⁸ (grade 2) 2%,⁸⁸ (grade 1 or 2) 12% to 17%^{50,87}; dyspepsia 18%,⁸⁹ (grade 1) 14%,⁸⁸ (grade 2) 2%,⁸⁸ (grade 1 or 2) 6% to 12%^{50,61,64}; flatulence (grade 1 or 2) 7%⁶⁴; gastritis (grade 1 or 2) 6%⁶¹; gastroesophageal reflux (grade 1 or 2) 7% to 9%^{61,64}; mucosal inflammation 25%⁵³; nausea 67% to 75%,^{51,53,54,89} (grade 1) 48% to 52%,^{77,88} (grade 2) 14% to 26%,^{77,88} (grade 1 or 2) 26% to 72%,^{61,64-66,82,87,90} (grade 3) 7%,⁶⁵ (grade 3 or 4) 2% to 15%^{50,61,64,66,78,82,87-89}; stomatitis 92%,⁵⁴ (grade 3 or 4) 17%⁵⁴; vomiting 17% to 34%,^{51,54,89} (grade 1) 20%,⁸⁸ (grade 2) 10%,⁸⁸ (grade 1 or 2) 9% to 47%,^{61,64,66,82,87,90} (grade 3 or 4) 1% to 12%^{50,61,64,82,87-89}; xerostomia 25%.⁵¹

F. Hematologic: Anemia 21% to 50%,^{51,89} (grade 1) 2% to 13%,^{77,88} (grade 2) 4% to 10%,^{77,88} (grade 1 or 2) 4% to 19%,^{61,64-66,82} (grade 3 or 4) 3% to 25%^{61,64,66,67,78,82,88-90}; decreased hematocrit 33%⁵¹; decreased hemoglobin 33%⁵¹; decreased red blood cell count 33%⁵¹; decreased white blood cells (grade 1) 2%,⁷⁷ (grade 2) 7%⁷⁷;

leukopenia 50%,⁵¹ (grade 3) 5%⁶⁵; lymphopenia 33%,⁵¹ (grade 3 or 4) 12%⁵⁰; neutropenia 5% to 17%,^{54,89} (grade 1) 2%,⁷⁷ (grade 2) 9%,⁷⁷ (grade 3 or 4) <1% to 17%^{54,61,67,89}; thrombocytopenia 33%,⁵¹ (grade 1) 7%,⁷⁷ (grade 3 or 4) 20%.⁶⁷

G. Hepatic: Increased ALT 17%,⁵¹ increased AST 17%,⁵¹ increased gamma-glutamyltransferase (GGT) 17%.⁵¹

H. Hypersensitivity: (grade 3 or 4) 13%.⁶⁷

I. Infections: Urinary tract (grade 1 or 2) 34%.⁸²

J. Musculoskeletal: Arthralgia 17%,⁸⁹ (grade 1) 7%,⁸⁸ (grade 2) 4%,⁸⁸ (grade 3 or 4) <1%.⁸⁹

K. Neurologic: Palmar-plantar erythrodysesthesia 33%,⁵⁴ (grade 3 or 4) 8%.⁵⁴

L. Pain: Abdominal 25%,⁸⁹ (grade 1) 8%,⁸⁸ (grade 2) 8%,⁸⁸ (grade 1 or 2) 7% to 25%,^{61,64,82,87} (grade 3 or 4) 2%⁸⁷⁻⁸⁹; back pain 16%,⁸⁹ (grade 1) 7%,⁸⁸ (grade 2) 3%,⁸⁸ (grade 3 or 4) 2%^{88,89}; upper abdominal pain 18%,⁸⁹ (grade 1) 9%,⁸⁸ (grade 2) 4%.⁸⁸

M. Respiratory: Cough 18%,⁸⁹ (grade 1) 10%,⁸⁸ (grade 2) 3%,⁸⁸; dyspnea (grade 1 or 2) 3%,⁸⁷ (grade 3 or 4) 3%⁸⁷; nasopharyngitis 15%,⁸⁹ (grade 1) 9%,⁸⁸ (grade 2) 4%.⁸⁸

N. Renal: Increased blood urea nitrogen (BUN) 67%.⁵¹

DOSE ADJUSTMENT

A. Hepatic: No information available.⁵²

B. Renal:

1. Creatinine clearance greater than or equal to 50 mL/min and less than or equal to 80 mL/minute, no adjustment needed.⁵²
2. Creatinine clearance less than 50 mL/min, no information available.⁵²

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