Cancer Chemotherapy Update
Drug Monographs: Ibrutinib and Ramucirumab

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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.

**PREPARATION**

A. Ibrutinib is available as a 140 mg capsule.
B. The manufacturer recommends that the capsules not be opened, broken, or chewed.10
C. The manufacturer recommends the drug be dispensed in the original container.10

**STABILITY**

A. Ibrutinib should be 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**

Ibrutinib is usually taken once a day, with water.

**TOXICITIES**

A. Cardiovascular: Edema 29%,19 (grade 1) 26%,19 (grade 2) 1%,19 hypertensive increase 29%,19 (grade 1) 6%,19 (grade 2) 16%,19 (grade 1 or 2) 13%,8 (grade 3) 6%,19 (grade 3 or 4) 5%.8
B. Central Nervous System: Anxiety (grade 1) 16%,19 (grade 2) 8%,19 (grade 3) 3%,19 (grade 3 or 4) 1%; headache 19% to 27%,12,19 (grade 1) 10%,19 (grade 2) 6%,19 (grade 1 or 2) 16% to 25%,19 (grade 3) 3%,19 (grade 3 or 4) 1%; insomnia 16%,19 (grade 1) 13%,19 (grade 2) 3%,19 (grade 1 or 2) 11%.5
C. Constitutional: Fatigue 30% to 32%,12,19 (grade 1) 16%,19 (grade 2) 16%,19 (grade 1 or 2) 14%.

**MECHANISM OF ACTION**

Ibrutinib is an irreversible inhibitor of the Bruton tyrosine kinase (BTK).1 BTK is a critical factor in B-cell receptor activation,2,3 Inhibition of BTK results in apoptosis, decreased cell proliferation, and B-cell receptor signaling.1,4 Ibrutinib also binds to IL-2-inducible kinase (ITK), inhibiting a signal pathway responsible for cellular activation and proliferation and cytokine release.7

**PHARMACOKINETICS**

The time to peak concentration (T_max) occurs at 1 to 2 hours following oral administration; the terminal half-life (T½) is 6 to 9 hours.5,8 The mean area under the time versus concentration curve (AUC) is 953 ng•h/mL and 680 ng•h/mL following a 560 mg and 420 mg oral dose, respectively. Administration with food increases the AUC about 2-fold.10 Ibrutinib is highly (97.3%) bound to plasma proteins and has a volume of distribution (V_d) of about 10,000 L.10 The drug is metabolized in the liver, primarily by CYP3A and CYP2D6, to an active metabolite PCI-45227.10 Ibrutinib is eliminated primarily (about 80%) in the feces, with about 1% as unchanged drug. About 10% is excreted in the urine.10

Selected therapeutic regimens of ibrutinib appear in Table 1.
Table 1. Selected therapeutic regimens of ibrutinib

<table>
<thead>
<tr>
<th>Daily dose</th>
<th>Route of administration</th>
<th>Administered on day(s)</th>
<th>Cycle length</th>
<th>Total dose/month</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.25-12.5 mg/kg</td>
<td>PO</td>
<td>Daily –</td>
<td>–</td>
<td>37.5-375 mg</td>
<td>5</td>
</tr>
<tr>
<td>1.25-12.5 mg/kg</td>
<td>PO</td>
<td>1 through 28</td>
<td>35 days</td>
<td>35-350 mg/cycle</td>
<td>5</td>
</tr>
<tr>
<td>280 mg</td>
<td>PO</td>
<td>Daily –</td>
<td>–</td>
<td>8,400 mg</td>
<td>11, 12</td>
</tr>
<tr>
<td>420 mg&lt;sup&gt;a&lt;/sup&gt;</td>
<td>PO</td>
<td>Daily –</td>
<td>–</td>
<td>12,600 mg</td>
<td>8-10, 12-20</td>
</tr>
<tr>
<td>560 mg&lt;sup&gt;a&lt;/sup&gt;</td>
<td>PO</td>
<td>Daily –</td>
<td>–</td>
<td>16,800 mg</td>
<td>10-12, 21-25</td>
</tr>
<tr>
<td>840 mg</td>
<td>PO</td>
<td>Daily –</td>
<td>–</td>
<td>25,200 mg</td>
<td>8, 9, 19, 20</td>
</tr>
</tbody>
</table>

Note: PO = oral.
<sup>a</sup>Conforms to dosing information listed in the manufacturer’s labeling.

28% to 38%,<sup>5,8</sup> (grade 3) 3%,<sup>19</sup> (grade 3 or 4) 4%<sup>5,8</sup>; pain 13%,<sup>19</sup> (grade 1) 3% to 19%,<sup>19</sup> (grade 2) 6%,<sup>19</sup> (grade 1 or 2) 15% to 63%,<sup>5,8</sup> (grade 3) 1%,<sup>19</sup> (grade 3 or 4) 2%; pyrexia (grade 1 or 2) 21% to 22%,<sup>5,8</sup> (grade 3 or 4) 2% to 5%.<sup>5,8</sup>

D. Dermatologic: Alopecia 27%<sup>12</sup>; rash (grade 1 or 2) 16% to 27%,<sup>5,8</sup> (grade 3 or 4) 9%<sup>11</sup>; contusion (grade 1) 16%,<sup>19</sup> (grade 1 or 2) 16%; erythema (grade 1) 13%,<sup>19</sup>; pruritus (grade 1) 13%; pruritic rash (grade 1) 13%.<sup>19</sup>

E. Gastrointestinal: Anorexia/dyspepsia (grade 1 or 2) 30%,<sup>5</sup> (grade 3 or 4) 4%; constipation 27%,<sup>12</sup> (grade 1) 23%,<sup>19</sup> (grade 1 or 2) 14% to 16%,<sup>5,8</sup> (grade 3 or 4) 1%; diarrhea 30% to 68%,<sup>12,19</sup> (grade 1) 45%,<sup>19</sup> (grade 1 or 2) 43% to 47%,<sup>5,8</sup> (grade 2) 10%,<sup>19</sup> (grade 3) 13%,<sup>19</sup> (grade 3 or 4) 4%; dyspepsia 26%,<sup>19</sup> (grade 1) 23%,<sup>19</sup> (grade 2) 3%; epistaxis (grade 1) 16%; gastrointestinal reflux 19%,<sup>19</sup> (grade 1) 13%,<sup>19</sup>,<sup>12</sup> (grade 2) 6%; nausea 48% to 67%,<sup>12,19</sup> (grade 1) 39%,<sup>19</sup> (grade 1 or 2) 16%,<sup>8</sup> (grade 2) 10%,<sup>19</sup> (grade 3 or 4) 1%; nausea or vomiting (grade 1 or 2) 41%,<sup>5</sup> (grade 3 or 4) 2%; pancreatitis (grade 1 or 2) 9%,<sup>11</sup>; stomatitis 16%,<sup>19</sup> (grade 1) 13%,<sup>19</sup> (grade 2) 3%; vomiting 23% to 48%,<sup>12,19</sup> (grade 1) 13%,<sup>19</sup> (grade 2) 10%,<sup>19</sup> (grade 1 or 2) 15%,<sup>8</sup> (grade 3 or 4) 1% to 9%.<sup>8,11</sup>

F. Hematologic: Anemia 16% to 36%,<sup>12,19</sup> (grade 1) 6%,<sup>19</sup> (grade 2) 10%,<sup>19</sup> (grade 3 or 4) 7% to 13%,<sup>5,12</sup>; lymphopenia (grade 3 or 4) 64%; neutropenia 67%,<sup>12</sup> (grade 2) 2%,<sup>5</sup> (grade 3 or 4) 13% to 44%,<sup>5,8,11,12</sup>; petechiae (grade 1) 16%; thrombocytopenia 13% to 61%,<sup>12,19</sup> (grade 1) 3%,<sup>19</sup> (grade 2) 6%,<sup>19</sup> (grade 3 or 4) 7% to 18%,<sup>5,11,12</sup> (grade 4) 3%.<sup>19</sup>

G. Hypersensitivity: (grade 3) 2%.<sup>5</sup>

H. Infection: Cellulitis 13%,<sup>19</sup> (grade 1) 6%,<sup>19</sup> (grade 2) 6%; shingles (grade 3 or 4) 9%; sinusitis 13%,<sup>19</sup> (grade 1) 6%,<sup>19</sup> (grade 2) 6%,<sup>19</sup> (grade 1 or 2) 13%;<sup>8</sup> (grade 3 or 4) 5%; upper respiratory tract 26%,<sup>19</sup> (grade 1) 6%,<sup>19</sup> (grade 2) 19%,<sup>19</sup> (grade 1 or 2) 33%; urinary tract 23%,<sup>19</sup> (grade 2) 19%,<sup>19</sup> (grade 3) 3%.<sup>19</sup>

I. Musculoskeletal: Arthralgia 23%,<sup>19</sup> (grade 1) 16%,<sup>19</sup> (grade 2) 6%,<sup>19</sup> (grade 1 or 2) 16% to 27%,<sup>5,8</sup>; muscle spasms/myalgia 13%,<sup>19</sup> (grade 1) 10%,<sup>19</sup> (grade 2) 3%,<sup>19</sup> (grade 1 or 2) 38%; muscle spasms (grade 1 or 2) 19%,<sup>8</sup> (grade 3 or 4) 1%.<sup>8</sup>

J. Neurologic: Peripheral sensory neuropathy (grade 1) 13%.<sup>19</sup>

K. Ophthalmic: Dry eye (grade 1) 13%.<sup>19</sup>

L. Pulmonary: Cough (grade 1 or 2) 31% to 32%,<sup>5,8</sup>; unspecified respiratory effects (grade 1 or 2) 50%,<sup>3</sup> (grade 3 or 4) 7%.<sup>5</sup>

M. Treatment-Related Mortality: Infections 4%,<sup>8</sup> systemic inflammatory response syndrome 1%.<sup>8</sup>

N. 420 mg daily

1. Cardiovascular: Atrial fibrillation 2%,<sup>16</sup> edema 11%,<sup>15</sup> hypertension (grade 2 or higher) 2%.<sup>16</sup>

2. Central nervous system: Dizziness 11%;<sup>15</sup> headache 14%,<sup>15</sup> (grade 3 or 4) 1%;<sup>15</sup> subdural hematoma (grade 1) 3%.<sup>18</sup>

3. Constitutional: Fatigue 5% to 47%,<sup>15,17,18</sup> (grade 3 or 4) 2% to 10%,<sup>15,17</sup>; night sweats 5%,<sup>15</sup> (grade 3 or 4) 1%;<sup>15</sup> pain 10% to
13%,15,18  (grade 3 or 4) 1%15; pyrexia 24%,15  
(grade 3 or 4) 2%.15

4. Dermatologic: Bruising (grade 1 or 2) 18%,18 
contusion 11%,15  maculopapular rash  
(grade 3 or 4) 10%.17

5. Gastrointestinal: Constipation 15%,15  
diarrhea 3% to 70%,15,17,18 (grade 2 or 
higher) 2%,16  mucositis (grade 3) 3%18; 
nausea 26% to 67%,15,17  (grade 3 or 4) 2%15; 
stoamitis (grade 3) 3%18; nausea 26% to 67%,15,17  
(grade 3 or 4) 2%15; vomiting 14%15.

6. Hematologic: Anemia 23%,15  (grade 3 
or 4) 5%15; epistaxis (grade 2 or higher) 2%16; 
nutropenia (grade 3 or 4) 16% to 40%,15,17; 
petechiae 14%15; thrombocytopenia 17%,15  
(grade 2 or higher) 2%16; neutropenia 22%,15  
(grade 2 or higher) 19%,16  (grade 3 or 4) 6%,15  
(grade 2 or higher) 14%,16  (grade 3 or 4) 7%16.

7. Infection: Cellulitis (grade 3 or 4) 7%17; 
herpes zoster (grade 2 or higher) 2%16; 
epididymitis 15%18  (grade 3 or 4) 7%17; 
sinusitis 11%,15  (grade 3 or 4) 1%15; 
upper respiratory tract 8% to 37%,15,17,18  
(grade 3 or 4) 1%15; urinary tract 10%,15  
(grade 3 or 4) 4%14.

8. Musculoskeletal: Arthralgia 13% to 17%,15,18  
(grade 3 or 4) 1%15; muscle spasms 13%15; 
myalgia 10% to 13%,15,18  (grade 3 or 4)  
1%15.

9. Neurologic: Peripheral neuropathy 3% to  
4%,15,18

10. Ophthalmic: Blurred vision 10%.15

11. Pulmonary: Cough 19%,15; dyspnea 12%,15  
(grade 3 or 4) 2%.15

12. Treatment-related mortality: Infection 8%,18  
respiratory and cardiovascular failure 3%.18

O. 560 mg daily

1. Cardiovascular: Edema 28%,21  (grade 1)  
19%,21  (grade 2) 7%,21  (grade 3) 1%,21  
(grade 4) 1%,21

2. Constitutional: Fever 18%,21  (grade 1)  
13%,21  (grade 2) 5%,21  (grade 3) 1%21; 
pain 17%,21  (grade 1) 9%,21  (grade 2) 3%,21  
(grade 3) 6%.21

3. Dermatologic: Contusion 17%,21  (grade 1)  
15%,21  (grade 2) 2%21; fatigue 41%,21  
(grade 1) 20%,21  (grade 2) 17%,21  (grade 3)  
5%21; rash 15%,21  (grade 1) 10%,21  (grade 2)  
4%,21  (grade 3) 2%,21

4. Gastrointestinal: Anorexia 21%, (grade 1)  
10%,21  (grade 2) 9%,21  (grade 3) 2%21; 
constipation 25%,21  (grade 1) 18%,21  
(grade 2) 7%21; diarrhea 50%,21  (grade 1)  
32%,21  (grade 2) 12%,21  (grade 3) 6%21; 
nausea 31%,21  (grade 1) 23%,21  (grade 2)  
7%21; vomiting (23%, (grade 1) 17%,21  
(grade 2) 5%21.

5. Hematologic: Neutropenia 18%,21  (grade 1)  
1%,21  (grade 2) 1%,21  (grade 3) 6%,21  
(grade 4) 10%,21; thrombocytopenia 18%,21  
(grade 1) 4%,21  (grade 2) 4%,21  (grade 3)  
7%,21  (grade 4) 4%.21

6. Infection: Upper respiratory tract 23%,  
(grade 1) 5%,21  (grade 2) 18%.21

7. Pulmonary: Cough 18%,21  (grade 1) 12%,21  
(grade 2) 6%,21; dyspnea 27%,21  (grade 1)  
13%,21  (grade 2) 10%,21  (grade 3) 4%.21

8. Treatment-related mortality: Dyspnea 1%.21

DOSAGE MODIFICATIONS

A. Hepatic: Moderate hepatic impairment (Child- 
Pugh B), increased ibrutinib levels are reported. No 
guidelines for dose modification are available.10

B. Renal10

1. Creatinine clearance (Clcr) greater than 
25 mL/min, no adjustment required.

2. Clcr less than 25 mL/min, no information 
available.

Name: Ramucirumab

Synonyms: Cyramza, IMC-1121B, LY3009806

MECHANISM OF ACTION

Ramucirumab is a monoclonal antibody that 
binds to the extracellular domain of vascular endo-
theial growth factor (VEGF) receptor-2 (VEGFR-2). 
By binding to VEGFR-2, ramucirumab blocks VEGF 
signaling, resulting in inhibition of angiogenesis and 
cell metastases.26-29

PHARMACOKINETICS

Following an 8 mg/kg infusion given weekly, 
ramucirumab has a peak concentration (Cmax) of 
325 mcg/mL following the initial infusion and 
497 mcg/mL following multiple infusions. It has an 
AUC of 43,824 ng•h/mL and 132,789 ng•h/mL 
following the initial and multiple infusions, 
respectively, with a clearance of 0.190 mL/h/kg and 0.067 mL/h/kg 
following the initial and multiple infusions.
The elimination T½ is 123 hours and 318 hours following the initial and multiple infusions, respectively. Following a 10 mg/kg infusion weekly, the peak concentration (C max) is 406 mcg/mL following the initial infusion and 616 mcg/mL following multiple infusions. The AUC is 40,333 ng•h/mL and 156,840 ng•h/mL following the initial and multiple infusions, respectively, with a clearance of 0.264 mL/h/kg and 0.069 mL/h/kg following the initial and multiple infusions. The elimination T½ is 110 hours and 205 hours following the initial and multiple infusions, respectively.

Selected therapeutic regimens of ramucirumab appear in Table 2.

**PREPARATION**

A. Use ramucirumab injection 10 mg/mL or 50 mg/mL.

B. Dilute the solution in 250 mL 0.9% sodium chloride injection (NS).

**STABILITY**

Solutions for infusion are stable for 24 hours under refrigeration [2°C to 8°C (36°F to 46°F)] or 4 hours at room temperature [below 25°C (77°F)].

**ADMINISTRATION**

1. Ramucirumab is given as a 1 hour intravenous (IV) infusion.

2. The manufacturer recommends that the drug be infused through a protein-sparing 0.22 micron filter.

**TOXICITIES**

A. 8 mg/kg

1. Cardiovascular: Arterial thromboembolism 2%,33 (grade 3 or 4) 1%33; cardiac failure <1%33; cardiac ischemia/myocardial infarction (grade 4) 3%35; hypertension 16% to 46%,33,34,40 (grade 3) 12%34, (grade 3 or 4) 7% to 15%,33,40,42,43 (grade 4) 2%34; venous thromboembolism 4%,33 (grade 3 or 4) 1%33.

2. Central nervous system: Headache 38%,34 (grade 1 or 2) 23%,35 (grade 3) 2% to 10%,34,39

3. Constitutional: Fatigue 36% to 62%,33,34 (grade 1, 2 or 3) 18%,35 (grade 3) 8% to 10%,34,39 (grade 3 or 4) 4% to 7%33,34,42,43; pain 29%,33 (grade 3 or 4) 5% to 6%;33,34,42,43

4. Endocrine/metabolic: Hyponatremia (grade 3 or 4) 3%42

5. Gastrointestinal: Anorexia 24%,33 (grade 3 or 4) 3%33,34; constipation 15%,33 (grade 3 or 4) less than 1%;33 diarrhea 31%,40 (grade 3 or 4) 2%33; dysphagia 11%,33 (grade 3 or 4) 2%33; fistula formation (grade or 4) <1%,33 (grade 4) 2%33; hemorrhage (grade 3) 7%34; nausea 19%,40 (grade 1) 13%34; perforation (grade 3 or 4) <1%,33 (grade 4) 2%39; vomiting 20%,33 (grade 3 or 4) 3%.33

6. Hematologic: Anemia 15%,33 (grade 3) 17%,33 (grade 3 or 4) 6% to 9%,32,34,42,43 hemoptysis (grade 2) 3%35; hemorrhage 13%,33 (grade 3 or 4) 3%33; leucopenia (grade 3 or 4) 17%,41; neutropenia (grade 3) 33%,41 (grade 3 or 4) 41%,41 (grade 4) 50%,41; thrombocytopenia (grade 3) 17%,41

7. Hepatic: Ascites 4%.42

8. Hypersensitivity: Infusion reactions <1% to 19%.33,40

9. Neurologic: Asthenia (grade 3 or 4) 6%33

10. Pulmonary: Dyspnea 9%,33 (grade 3 or 4) 2%33

11. Renal: Proteinuria 3%,33 (grade 2) 3%35 (grade 3) 33%,41 (grade 3 or 4) <1%33

### Table 2. Selected therapeutic regimens of ramucirumab

<table>
<thead>
<tr>
<th>Daily dose</th>
<th>Route of administration</th>
<th>Administered on day(s)</th>
<th>Cycle length</th>
<th>Total dose/cycle</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-16 mg/kg</td>
<td>IV</td>
<td>Weekly</td>
<td></td>
<td>8-64 mg/kg/month</td>
<td>30</td>
</tr>
<tr>
<td>6 mg/kg</td>
<td>IV</td>
<td>Weekly</td>
<td></td>
<td>24 mg/kg/month</td>
<td>32</td>
</tr>
<tr>
<td>8 mg/kg</td>
<td>IV</td>
<td>1</td>
<td>2 weeks</td>
<td>8 mg/kg</td>
<td>31, 33-43</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>IV</td>
<td>1</td>
<td>3 weeks</td>
<td>10 mg/kg</td>
<td>44-50</td>
</tr>
</tbody>
</table>

Note: IV = intravenous.

*aConforms to dosing information listed in the manufacturer’s labeling.
12. Treatment-related mortality: Cardiopulmonary arrest/myocardial infarction 3% to 4%, gastrointestinal hemorrhage 2%, gastrointestinal perforation 2%. 

B. 10 mg/kg

1. Cardiovascular: Hypertension 20%, (grade 1 or 2) 13%, (grade 3 or 4) 10%. 

2. Central nervous system: Headache 20% to 38%, (grade 3 or 4) 2%. 

3. Constitutional: Fatigue 24% to 50%, (grade 3 or 4) 2%. 

4. Gastrointestinal: Nausea (grade 1 or 2) 50%, (grade 3 or 4) 2%. 

5. Hematologic: Anemia 2%, epistaxis (grade 1 or 2) 13%, thrombocytopenia 8%, (grade 3 or 4) 2%, febrile neutropenia (grade 3) 13%, (grade 4) 9%, neutropenia (grade 3) 50%. 

6. Hypersensitivity: Infusion reactions 14%, (grade 3 or 4) 6%. 

7. Neurologic: Sensory neuropathy (grade 1 or 2) 13%. 

8. Pulmonary: Pneumothorax (grade 2) 9%, (grade 3 or 4) 2%. 

9. Renal: Proteinuria 8%, (grade 3 or 4) 2%. 

DOSAGE MODIFICATIONS

A. Hepatic: Moderate to severe hepatic impairment (Child-Pugh B or C), use with caution. No specific guidelines are available. 

B. Renal: No information is available. 

REFERENCES


