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TASIGNA for adult patients with newly diagnosed Ph+ CML in chronic phase

TASIGNA DOUBLED THE MAJOR MOLECULAR RESPONSE (MMR) RATE OF IMATINIB AT 12 MONTHS¹

**MMR rates at 12 months¹**

- **TASIGNA 300 mg bid (n=282)**: 44% (95% CI, 38.4%-50.3%)
- **Imatinib 400 mg qd (n=283)**: 22% (95% CI, 17.6%-27.6%)

**P<0.0001**

**Progression to AP/BC¹**

- **TASIGNA 300 mg bid (n=282)**: n=2 (0.7%)
- **Imatinib 400 mg qd (n=283)**: n=17 (6%)

**ENESTnd study design:** A randomized, controlled, open-label, multicenter Phase III trial of 846 patients with newly diagnosed Ph+ CML in chronic phase. Patients were randomized to receive either TASIGNA 400 mg bid (n=281), TASIGNA 300 mg bid (n=282), or imatinib 400 mg qd (n=283). The daily dose of imatinib could be escalated to 800 mg (400 mg bid), but no dose escalation was permitted with TASIGNA. A centralized laboratory was used for PCR testing. The primary end point was MMR at 12 months. MMR was defined as ≤0.1% BCR-ABL/ABL by international scale measured by RQ-PCR, which corresponds to a ≥3-log reduction of BCR-ABL transcripts from standardized baseline.¹ ²

The distinct safety profile of TASIGNA supports its use in adult patients with newly diagnosed Ph+ CML in chronic phase¹

- Discontinuation for adverse events regardless of causality was observed in 7% of patients
- In ENESTnd, most side effects associated with TASIGNA did not lead to discontinuation in the first year

*Definition includes patients with clonal evolution and CML-related death. Time was censored at last assessment on treatment for patients without events.¹ ²
Greater efficacy vs imatinib on every end point at 12 months

TASIGNA (nilotinib) is indicated for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase. The effectiveness of TASIGNA is based on major molecular response and cytogenetic response rates. The study is ongoing and further data will be required to determine long-term outcome.

**Boxed WARNING and Additional Important Safety Information**

TASIGNA prolongs the QT interval. ECGs should be obtained to monitor the QTc at baseline, 7 days after initiation, and periodically thereafter, as well as following any dose adjustments. Sudden deaths have been reported in patients receiving TASIGNA. TASIGNA should not be used in patients with hypokalemia, hypomagnesemia, or long QT syndrome. Hypokalemia or hypomagnesemia must be corrected prior to TASIGNA administration and should be periodically monitored. The concomitant use of strong CYP3A4 inhibitors or anti-arrhythmic drugs (including, but not limited to, amiodarone, disopyramide, procainamide, quinidine, and sotalol) and other drugs that may prolong the QT interval (including, but not limited to, chloroquine, clarithromycin, haloperidol, methadone, moxifloxacin, and pimozide) should be avoided. The concomitant use of strong CYP3A4 inducers should be avoided (including, but not limited to, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, and phenobarbital). Patients should avoid food 2 hours before and 1 hour after taking dose. A dose reduction is recommended in patients with hepatic impairment as nilotinib exposure is increased in patients with impaired hepatic function.

- Treatment with TASIGNA can cause Grade 3/4 thrombocytopenia, neutropenia, and anemia
- Caution is recommended in patients with a history of pancreatitis
- The use of TASIGNA may result in elevations in bilirubin, AST/ALT, and alkaline phosphatase
- TASIGNA can cause hypophosphatemia, hypokalemia, hyperkalemia, hypocalcemia, and hyponatremia (see Boxed WARNING)
- The exposure of nilotinib is reduced in patients with total gastrectomy
- Since the capsules contain lactose, TASIGNA is not recommended for patients with rare hereditary problems of galactose intolerance, severe lactase deficiency with a severe degree of intolerance to lactose-containing products, or of glucose-galactose malabsorption
- Women of childbearing potential should avoid becoming pregnant while taking TASIGNA and should be advised of the potential hazard to the fetus if they do
- In chronic phase patients, the most commonly reported nonhematologic adverse drug reactions (>10%) were rash, pruritus, nausea, fatigue, myalgia, headache, constipation, diarrhea, and vomiting
- In accelerated phase patients, the most commonly reported nonhematologic adverse drug reactions (>10%) were rash, pruritus, and fatigue

**References:**

Please see brief summary of Prescribing Information on the following pages.
**Tasigna® (nilotinib) Capsules**

**Initial U.S. Approval: 2007**

**BRIEF SUMMARY: Please see package insert for full prescribing information.**

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**WARNING: QT PROLONGATION AND SUDDEN DEATHS**

Tasigna prolongs the QT interval (5.2). Sudden deaths have been reported in patients receiving nilotinib (5.3). Tasigna should not be used in patients with hypokalemia, hypomagnesemia, or long QT syndrome (4). Hypokalemia or hypomagnesemia must be corrected prior to Tasigna administration and should be periodically monitored (5.2). Drugs known to prolong the QT interval and strong CYP3A4 inhibitors should be avoided (5.7). Patients should avoid food 2 hours before and 1 hour after taking dose (5.8). A dose reduction is recommended in patients with hepatic impairment (5.9). ECGs should be obtained to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, as well as following any dose adjustments. (5.2, 5.3, 5.6, 5.12)

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**1 INDICATIONS AND USAGE**

**1.1 Newly Diagnosed Ph+ CML-CP**

Tasigna (nilotinib) is indicated for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase. The effectiveness of Tasigna is based on major molecular response and cytogenetic response rates [see Clinical Studies (14.1) in the full prescribing information]. The study is ongoing and further data will be determined to support long-term outcome.

**1.2 Resistant or Intolerant Ph+ CML-CP and CML-AP**

Tasigna is indicated for the treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML) in adult patients resistant or intolerant to prior therapy that included imatinib. The effectiveness of Tasigna is based on hematologic and cytogenetic response rates [see Clinical Studies (14.2) in the full prescribing information].

---

**2 DOSAGE AND ADMINISTRATION**

**2.1 Recommended Dosing**

Tasigna should be taken twice daily at approximately 12 hour intervals and must not be taken with food. The capsules should be swallowed whole with water. No food should be consumed for at least 2 hours before the dose is taken and no food should be consumed for at least one hour after the dose is taken [see Boxed Warning, Warnings and Precautions (5.8), Clinical Pharmacology (12.3) in the full prescribing information]. For patients who are unable to swallow capsules, the contents of each capsule may be dispersed in one teaspoon of applesauce (puréed apple). The mixture should be taken immediately (within 15 minutes) and should not be stored for future use [see Clinical Pharmacology (12.3) in the full prescribing information].

Tasigna may be given in combination with hematopoietic growth factors such as erythropoietin or G-CSF if clinically indicated. Tasigna may be given with hydroxyurea or anagrelide if clinically indicated.

**Newly Diagnosed Ph+ CML-CP**

The recommended dose of Tasigna is 300 mg orally twice daily [see Clinical Pharmacology (12.3) in the full prescribing information].

**Resistant or Intolerant Ph+ CML-CP and CML-AP**

The recommended dose of Tasigna (nilotinib) is 400 mg orally twice daily [see Clinical Pharmacology (12.3) in the full prescribing information].

**2.2 Dose Adjustments or Modifications**

**QT interval prolongation:**

**Table 1: Dose Adjustments for QT Prolongation**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Action</th>
</tr>
</thead>
</table>
| ECGs with a QTc >480 msec | 1. Withhold Tasigna, and perform an analysis of serum potassium and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. Concomitant medication usage must be reviewed.  
2. Resume within 2 weeks at prior dose if QTcF returns to <450 msec and to within 20 msec of baseline.  
3. If QTcF is between 450 msec and 480 msec after 2 weeks, reduce the dose to 400 mg once daily.  
4. If, following dose-reduction to 400 mg once daily, QTc returns to >480 msec, Tasigna should be discontinued.  
5. An ECG should be repeated approximately 7 days after any dose adjustment. |

---

**Myelosuppression**

Tasigna may need to be withheld and/or dose reduced for hematological toxicities (neutropenia, thrombocytopenia) that are not related to underlying leukemia (Table 2).

**Table 2: Dose Adjustments for Neutropenia and Thrombocytopenia**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Action</th>
</tr>
</thead>
</table>
| Newly diagnosed Ph+ CML in chronic phase at 300 mg twice daily | 1. Stop Tasigna, and monitor blood counts  
2. Resume within 2 weeks at prior dose if ANC >1.0 x 10^9/L and platelets >50 x 10^9/L  
3. If blood counts remain low for >2 weeks, reduce the dose to 400 mg once daily |
| Resistant or intolerant Ph+ CML in chronic phase or accelerated phase at 400 mg twice daily | ANC* <1.0 x 10^9/L and/or platelet counts <50 x 10^9/L |

*ANC = absolute neutrophil count

---

**3 Other Non-hematologic Toxicities**

If other clinically significant moderate or severe non-hematologic toxicity develops, withhold dosing, and resume at 400 mg once daily when the toxicity has resolved. If clinically appropriate, escalation of the dose back to 300 mg (newly diagnosed Ph+ CML-CP) or 400 mg (resistant or intolerant Ph+ CML-CP and CML-AP) twice daily should be considered. For Grade 3 to 4 lipase elevations, dosing should be withheld, and may be resumed at 400 mg once daily. Test bilirubin and hepatic transaminase levels monthly or as clinically indicated. For Grade 3 to 4 bilirubin or hepatic transaminase elevations, dosing should be withheld, and may be resumed at 400 mg once daily. Test bilirubin and hepatic transaminases levels monthly or as clinically indicated [see Warnings and Precautions (5.4, 5.5), Use in Specific Populations (8.7) in the full prescribing information].

---

**Hepatic Impairment**

If possible, consider alternative therapies. If Tasigna must be administered to patients with hepatic impairment, consider the following dose reduction:

**Table 4: Dose Adjustments for Hepatic Impairment (At Baseline)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Action</th>
</tr>
</thead>
</table>
| Newly diagnosed Ph+ CML in chronic phase at 300 mg twice daily | 1. Mild, Moderate or Severe*  
Mild or Moderate*  
Severe* |
| Resistant or intolerant Ph+ CML in chronic phase or accelerated phase at 400 mg twice daily | 1. An initial dosing regimen of 200 mg twice daily followed by dose escalation to 300 mg twice daily based on tolerability  
2. An initial dosing regimen of 300 mg twice daily followed by dose escalation to 400 mg twice daily based on tolerability |

*Mild = mild hepatic impairment (Child-Pugh Class A); Moderate = moderate hepatic impairment (Child-Pugh Class B); Severe = severe hepatic impairment (Child-Pugh Class C) [see Boxed Warning, Warnings and Precautions (5.9), Use in Specific Populations (8.7) in the full prescribing information].

**Concomitant Strong CYP3A4 Inhibitors**

Avoid the concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, azithromycin, indinavir, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole). Grapefruit products may also increase serum concentrations of nilotinib and should be avoided. Should treatment with any of these agents be required, it is recommended that therapy with Tasigna be interrupted. If patients must be co-administered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, consider a
dose reduction to 300 mg once daily in patients with resistant or intolerant Ph+ CML or to 200 mg once daily in patients with newly diagnosed Ph+ CML-CP. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inhibitors. If the strong inhibitor is discontinued, a washout period should be allowed before the Tasigna dose is adjusted upward to the indicated dose. Close monitoring for prolongation of the QT interval is indicated for patients who cannot avoid strong CYP3A4 inhibitors [see Boxed Warning, Warnings and Precautions (5.2, 5.7, Drug Interactions (7.2) in the full prescribing information]).

Concomitant Strong CYP3A4 Inducers
Avoid the concomitant use of strong CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital). Patients should also refrain from taking St. John’s Wort. Based on the non-linear pharmacokinetic profile of nilotinib, increasing the dose of Tasigna when co-administered with such agents is unlikely to compensate for the loss of exposure [see Drug Interactions (7.2) in the full prescribing information].

3 DOSAGE FORMS AND STRENGTHS
150 mg red opaque hard gelatin capsules with white axial imprint “NVR/8CR”.
200 mg light yellow opaque hard gelatin capsules with a red axial imprint “NVR/TKI”.

4 CONTRAINDICATIONS
Do not use in patients with hypokalemia, hypomagnesemia, or long QT syndrome [see Boxed Warning].

5 WARNINGS AND PRECAUTIONS
5.1 Myelosuppression
Treatment with Tasigna can cause Grade 3/4 thrombocytopenia, neutropenia and anemia. Perform complete blood counts every two weeks for the first 2 months and then monthly thereafter, or as clinically indicated.

Myelosuppression was generally reversible and usually managed by withholding Tasigna temporarily or dose reduction [see Dosage and Administration (2.2)].

5.2 QT Prolongation
Tasigna has been shown to prolong cardiac ventricular repolarization as measured by the QT interval on the surface ECG in a concentration-dependent manner [see Adverse Reactions (6.1), Clinical Pharmacology (12.4) in the full prescribing information]. Prolongation of the QT interval can result in a type of ventricular tachycardia called torsade de pointes, which may result in syncope, seizure, and/or death. ECGs should be performed at baseline, seven days after initiation, periodically as clinically indicated and following dose adjustments [see Warnings and Precautions (5.12)].

Tasigna should not be used in patients who have hypokalemia, hypomagnesemia or long QT syndrome. Hypokalemia or hypomagnesemia must be corrected prior to initiating Tasigna and these electrolytes should be monitored periodically during therapy [see Warnings and Precautions (5.12)].

Significant prolongation of the QT interval may occur when Tasigna is inappropriately taken with food and/or strong CYP3A4 inhibitors and/or medicinal products with a known potential to prolong QT. Therefore, co-administration with food must be avoided and concomitant use with strong CYP3A4 inhibitors and/or medicinal products with a known potential to prolong QT should be avoided [see Warnings and Precautions (5.7, 5.8)]. The presence of hypokalemia and hypomagnesemia may further enhance this effect [see Warnings and Precautions (5.6, 5.12)].

5.3 Sudden Deaths
Sudden deaths have been reported in patients with CML treated with nilotinib in clinical studies (n= 5,561; 0.3%). The relative early occurrence of some of these deaths relates to the initiation of nilotinib suggests the possibility that ventricular repolarization abnormalities may have contributed to their occurrence.

5.4 Elevated Serum Lipase
The use of Tasigna can cause increases in serum lipase. Caution is recommended in patients with a previous history of pancreatitis. If lipase elevations are accompanied by abdominal symptoms, interrupt dosing and consider appropriate diagnostics to exclude pancreatitis. Test serum lipase levels monthly or as clinically indicated.

5.5 Hepatotoxicity
The use of Tasigna may result in elevations in bilirubin, AST/ALT, and alkaline phosphatase. Hepatic function tests should be checked monthly or as clinically indicated [see Warnings and Precautions (5.12)].

5.6 Electrolyte Abnormalities
The use of Tasigna can cause hypophosphatemia, hypokalemia, hyperkalemia, hypocalcemia, and hyponatremia. Electrolyte abnormalities must be corrected prior to initiating Tasigna and these electrolytes should be monitored periodically during therapy [see Warnings and Precautions (5.12)].

5.7 Drug Interactions
The administration of Tasigna with agents that are strong CYP3A4 inhibitors or anti-arrhythmic drugs (including, but not limited to amiodarone, disopyramide, procainamide, quinidine and sotalol) and other drugs that may prolong QT interval (including, but not limited to chloroquine, clarithromycin, haloperidol, methadone, moxifloxacin and pimozide) should be avoided. Should treatment with any of these agents be required, it is recommended that therapy with Tasigna be interrupted. If interruption of treatment with Tasigna is not possible, patients who require treatment with a drug that prolongs QT or strongly inhibits CYP3A4 should be closely monitored for prolongation of the QT interval [see Boxed Warning, Dosage and Administration (2.2), Drug Interactions (7.2) in the full prescribing information].

5.8 Food Effects
The bioavailability of nilotinib is increased with food. Tasigna must not be taken with food. No food should be taken at least 2 hours before and at least one hour after the dose is taken. Grapefruit products and other foods that are known to inhibit CYP3A4 should be avoided [see Boxed Warning, Drug Interactions (7.2) and Clinical Pharmacology (12.3) in the full prescribing information].

5.9 Hepatic Impairment
Nilotinib exposure is increased in patients with impaired hepatic function. A lower starting dose is recommended for patients with mild to severe hepatic impairment (at baseline) and QT interval should be monitored closely [see Boxed Warning, Dosage and Administration (2.2) and Use in Specific Populations (8.7) in the full prescribing information].

5.10 Total Gastrectomy
The exposure of nilotinib is reduced in patients with total gastrectomy. More frequent follow-up of these patients should be considered. Dose increase or alternative therapy may be considered in patients with total gastrectomy [see Clinical Pharmacology 12.3) in the full prescribing information].

5.11 Lactose
Since the capsules contain lactose, Tasigna is not recommended for patients with rare hereditary problems of galactose intolerance, severe lactase deficiency with a severe degree of intolerance to lactose-containing products or of glucose-galactose malabsorption.

5.12 Monitoring Laboratory Tests
Complete blood counts should be performed every two weeks for the first two months and then monthly thereafter. Chemistry panels, including the lipid profile, should be checked periodically. ECGs should be obtained at baseline, seven days after initiation and periodically thereafter, as well as following dose adjustments [see Warnings and Precautions (5.2)]. Laboratory monitoring for patients receiving Tasigna may need to be performed more or less frequently at the physician’s discretion.

5.13 Use in Pregnancy
There are no adequate and well controlled studies of Tasigna in pregnant women. However, Tasigna may cause fetal harm when administered to a pregnant woman. Nilotinib caused embryo-fetal toxicities in animals at maternal exposures that were lower than the expected human exposure at the recommended doses of nilotinib. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of child-bearing potential should avoid becoming pregnant while taking Tasigna [see Use in Specific Populations (8.1) in the full prescribing information].

6 ADVERSE REACTIONS
The following serious adverse reactions can occur with Tasigna and are discussed in greater detail in other sections of the package insert [see Boxed Warning, Warnings and Precautions (5)].

Myelosuppression [see Warnings and Precautions (5.1)]
QT prolongation [see Boxed Warning, Warnings and Precautions (5.2)]
Sudden deaths [see Boxed Warning, Warnings and Precautions (5.3)]
Elevated serum lipase [see Warnings and Precautions (5.4)]
Hepatotoxicity [see Warnings and Precautions (5.5)]
Electrolyte abnormalities [see Boxed Warning, Warnings and Precautions (5.6)]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Newly diagnosed Ph+ CML-CP
The data below reflect exposure to Tasigna from a randomized trial in newly diagnosed patients with Ph+ CML in chronic phase treated at the recommended dose of 300 mg twice daily (n=279). The median time on treatment in the nilotinib 300 mg twice daily group was 18.6 months. The median actual duration of exposure [see Boxed Warning, Warnings and Precautions (5.12)] may result in syncope, seizure, and/or death. ECGs should be performed at baseline, seven days after initiation, periodically as clinically indicated and following dose adjustments [see Warnings and Precautions (5.12)].

The following serious adverse reactions can occur with Tasigna and are discussed in greater detail in other sections of the package insert [see Boxed Warning, Warnings and Precautions (5)].

Myelosuppression [see Warnings and Precautions (5.1)]
QT prolongation [see Boxed Warning, Warnings and Precautions (5.2)]
Sudden deaths [see Boxed Warning, Warnings and Precautions (5.3)]
Elevated serum lipase [see Warnings and Precautions (5.4)]
Hepatotoxicity [see Warnings and Precautions (5.5)]
Electrolyte abnormalities [see Boxed Warning, Warnings and Precautions (5.6)]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data below reflect exposure to Tasigna from a randomized trial in newly diagnosed patients with Ph+ CML in chronic phase treated at the recommended dose of 300 mg twice daily (n=279). The median time on treatment in the nilotinib 300 mg twice daily group was 18.6 months. The median actual dose intensity was 593 mg/day in the nilotinib 300 mg twice daily group. The most common (>10%) non-hematologic adverse drug reactions were rash, pruritus, headache, nausea, fatigue and myalgia. Upper abdominal pain, alopecia, constipation, diarrhea, dry skin, muscle spasms, arthralgia, abdominal pain, peripheral edema and ascites were observed less commonly
(≤10% and >5%) and have been mild to moderate severity, manageable and generally did not require dose reduction. Pleural and pericardial effusions occurred in 1% of patients. Gastrointestinal toxicity was reported in 0.4% of patients.

Increase in QTcF >500 msec from baseline was observed in 1 patient (0.4%) in the 300 mg twice daily treatment group. No patient had an absolute QTcF of >500 msec.

The most common hematologic adverse drug reactions (all grades) were myelosuppression including: thrombocytopenia (17%), neutropenia (15%) and anemia (7%). See Table 7 for Grade 3/4 laboratory abnormalities.

Discontinuation due to adverse events regardless of causality was observed in 7% of patients.

**Resistant or intolerant Ph+ CML-CP and CML-AP**

In the single open-label multicenter clinical trial, a total of 458 patients with Ph+ CML-CP and CML-AP resistant to or intolerant to at least one prior therapy including imatinib were treated (CML-CP=321; CML-AP=137) at the recommended dose of 400 mg twice daily.

The median duration of exposure in days for CML-CP and CML-AP patients is 561 (range 1-1096) and 264 (range 2-1160), respectively. The median dose intensity for patients with CML-CP and CML-AP was 789 mg/day (range 151-1110) and 780 mg/day (range 150-1149), respectively, and corresponded to the planned 400 mg twice daily dosing.

The median cumulative duration in days of dose interruptions for the CML-CP patients was 20 (range 1-345), and the median duration in days of dose interruptions for the CML-AP patients was 23 (range 1–234).

In patients with CML-CP, the most commonly reported non-hematologic adverse drug reactions (>10%) were rash, pruritus, nausea, fatigue, headache, constipation, diarrhea, vomiting and myalgia. The common serious drug-related adverse reactions (>1%) were thrombocytopenia, neutropenia and anemia.

In patients with CML-AP, the most commonly reported non-hematologic adverse drug reactions (>10%) were rash, pruritus and fatigue. The common serious adverse drug reactions (>1%) were thrombocytopenia, neutropenia, febrile neutropenia, pneumonia, leukopenia, intracranial hemorrhage, elevated lipase and pyrexia.

Sudden deaths and QT prolongation were reported. The maximum mean QTcF change from baseline at steady-state was 10 msec. Increase in QTcF >60 msec from baseline was observed in 4.1% of the patients and QTcF change from baseline at steady-state was 10 msec. Increase in QTcF >60 msec from baseline was observed in 4 patients (<1%) [see Boxed Warning, Warnings and Precautions (5.2, 5.3), Clinical Pharmacology (12.4) in the full prescribing information].

Discontinuation due to drug-related adverse reactions was observed in 16% of CML-CP and 10% of CML-AP patients.

### Most Frequently Reported Adverse Reactions

Tables 5 and 6 show the percentage of patients experiencing treatment-emergent adverse reactions (excluding laboratory abnormalities) regardless of relationship to study drug. Adverse reactions reported in greater than 10% of patients who received at least one dose of Tasigna are listed.

#### Table 5: Most Frequently Reported Non-hematologic Adverse Reactions (Regardless of Relationship to Study Drug) in Patients with Newly Diagnosed Ph+ CML-CP (≥10% in Tasigna 300 mg twice daily or Gleevec 400 mg once daily groups)a

<table>
<thead>
<tr>
<th>Body System and Preferred Term</th>
<th>Patients with Newly Diagnosed Ph+ CML-CP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=279 (TASIGNA 300 mg twice daily)</td>
</tr>
<tr>
<td><strong>All Grades</strong></td>
<td>All CTC Grades b 3 / 4 (%)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>36 (16)</td>
</tr>
<tr>
<td>Rash</td>
<td>36 (16)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>19 (10)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>19 (10)</td>
</tr>
<tr>
<td>Constipation</td>
<td>15 (8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14 (8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>15 (8)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12 (6)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Headache</td>
<td>28 (16)</td>
</tr>
<tr>
<td>Nerve system disorders</td>
<td>28 (16)</td>
</tr>
</tbody>
</table>

#### Table 6: Most Frequently Reported Non-hematologic Adverse Reactions in Patients with Resistant or Intolerant Ph+ CML Receiving Tasigna 400 mg Twice Daily (Regardless of Relationship to Study Drug) (≥10% in any Group)a

<table>
<thead>
<tr>
<th>Body System and Preferred Term</th>
<th>CML-CP</th>
<th>CML-AP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=321</td>
<td>N=137</td>
</tr>
<tr>
<td><strong>All Grades</strong></td>
<td>All CTC Grades b 3 / 4 (%)</td>
<td>All CTC Grades b 3 / 4 (%)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>36 (2)</td>
<td>19 (2)</td>
</tr>
<tr>
<td>Rash</td>
<td>36 (2)</td>
<td>19 (2)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>32 (2)</td>
<td>20 (2)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>11 (1)</td>
<td>12 (1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>37 (3)</td>
<td>26 (3)</td>
</tr>
<tr>
<td>Constipation</td>
<td>28 (2)</td>
<td>29 (2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25 (2)</td>
<td>15 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>25 (2)</td>
<td>15 (2)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>11 (1)</td>
<td>12 (1)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10 (1)</td>
<td>14 (1)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>10 (1)</td>
<td>14 (1)</td>
</tr>
<tr>
<td>Headache</td>
<td>35 (2)</td>
<td>20 (1)</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Body System and Preferred Term</th>
<th>CML-CP</th>
<th>CML-AP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Musculo-skeletal and connective tissue disorders</strong></td>
<td>All Grades (%)</td>
<td>CTC Grades (3/4)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>13</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Bone pain</td>
<td>14</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Back pain</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>11</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>27</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Orpharyngeal pain</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Nasopharyngitis</td>
<td>24</td>
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<tr>
<td>Upper respiratory tract infection</td>
<td>12</td>
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</tr>
<tr>
<td>Metabolism and nutritional disorders</td>
<td>Anorexia</td>
<td>12</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
<td>12</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
<td>10</td>
</tr>
</tbody>
</table>

*Excluding laboratory abnormalities

†NCI Common Terminology Criteria for Adverse Events, Version 3.0

**Laboratory Abnormalities**

Table 7 shows the percentage of patients experiencing treatment-emergent Grade 3/4 laboratory abnormalities in patients who received at least one dose of Tasigna.

### Table 7: Percent Incidence of Clinically Relevant Grade 3/4 Laboratory Abnormalities

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Newly Diagnosed Ph+ CML-CP</th>
<th>Resistant or Intolerant Ph+</th>
</tr>
</thead>
<tbody>
<tr>
<td>TASIGNA 300 mg twice daily N=279 (%)</td>
<td>TASIGNA 400 mg twice daily N=321 (%)</td>
<td>TASIGNA 400 mg twice daily N=137 (%)</td>
</tr>
<tr>
<td>TASIGNA 400 mg once daily N=280 (%)</td>
<td>GLEEVEC 400 mg once daily N=321 (%)</td>
<td>GLEEVEC 400 mg once daily N=137 (%)</td>
</tr>
</tbody>
</table>

### Hematologic Parameters

- **Thrombocytopenia**: 10 / 9 / 30 / 42
- **Neutropenia**: 12 / 20 / 31 / 42
- **Anemia**: 4 / 5 / 11 / 27

### Biochemistry Parameters

- **Elevated lipase**: 7 / 3 / 18 / 18
- **Hyperglycemia**: 6 / 0 / 12 / 6
- **Hypophosphatemia**: 5 / 8 / 17 / 15
- **Elevated bilirubin (total)**: 4 / <1 / 7 / 9
- **Elevated SGPT (ALT)**: 4 / 3 / 4 / 4
- **Hyperkalemia**: 2 / 1 / 6 / 4
- **Hypokalemia**: <1 / <1 / 7 / 7
- **Elevated SGOT (AST)**: 1 / 1 / 3 / 2
- **Decreased albumin**: 0 / 0 / 4 / 3

(continued)


**Gastrointestinal Disorders:** Common: pancreatitis, abdominal discomfort, abdominal distension, dyspepsia, flatulence. Uncommon: gastrointestinal hemorrhage, melena, mouth ulceration, gastroesophageal reflux, stomatitis, esophageal pain, dysgeusia, dry mouth. Unknown frequency: gastrointestinal ulcer perforation, retroperitoneal hemorrhage, hematemesis, gastric ulcer, esophagitis ulcerative, subleues, gastritis, hemorrhoids, hiatus hernia, rectal hemorrhage, sensitivity of teeth, gingivitis.


**Skin and Subcutaneous Tissue Disorders:** Common: night sweats, eczema, urticaria, erythema, hyperhidrosis, contusion, acne, dermatitis, dry skin. Uncommon: exfoliative rash, drug eruption, pain of skin, ecchymosis, swelling of face. Unknown frequency: erythema nodosum, skin ulcer, palmar-plantar erythrodysesthesia syndrome, petechiae, photosensitivity, blister, dermal cyst, sebaceous hyperplasia, skin atrophy, skin discoloration, skin exfoliation, skin hyperpigmentation, skin hypertrophy.


**Reproductive System and Breast Disorders:** Uncommon: breast pain, gynecomastia, erectile dysfunction. Unknown frequency: breast induration, menorrhagia, nipple swelling.

**General Disorders and Administration Site Conditions:** Common: pyrexia, chest pain, pain (including neck pain and back pain), chest discomfort, malaise. Uncommon: face edema, gravitational edema, influenza-like illness, chills. Unknown frequency: feeling hot, localized edema.

**Investigations:** Common: blood amylase increased, gamma-glutamyltransferase increased, blood creatinine phosphokokinase increased, weight decreased, weight increased. Uncommon: hemoglobin decreased, blood lactate dehydrogenase increased, blood urea increased. Unknown frequency: blood insulin increased, very low density lipoprotein increased, blood parathyroid hormone increased, blood pressure increased.

---

**6.3 Postmarketing Experience**

The following additional adverse reactions have been reported during post approval use of Tasigna. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Cases of tumor lysis syndrome have been reported in Tasigna treated patients with resistant or intolerant CML. Malignant disease progression, high WBC counts and/or dehydration were present in the majority of these cases.

**10 OVERDOSAGE**

Overdose with nilotinib has been reported, where an unspecified number of Tasigna capsules were ingested in combination with alcohol and other drugs. Events included neutropenia, vomiting, and drowsiness. In the event of overdose, the patient should be observed and appropriate supportive treatment given.

**16 HOW SUPPLIED/STORAGE AND HANDLING**

Tasigna (nilotinib) 150 mg capsules are red opaque hard gelatin capsules, size 1 with black axial imprint “NVR/BCR”. Tasigna (nilotinib) 200 mg capsules are light yellow opaque hard gelatin capsules, size 0 with the red axial imprint “NVR/TKI.” Tasigna capsules are supplied in blister packs.

- **150 mg**
  - Carton of 4 blister packs of (4x28) ..................................NDC 0078-0592-87
  - Blisters of 28 capsules ....................................................NDC 0078-0592-51
- **200 mg**
  - Carton of 4 blister packs of (4x28) ..................................NDC 0078-0526-87
  - Blisters of 28 capsules ....................................................NDC 0078-0526-51

Each blister pack contains one folded blister card of 28 capsules each, for dosing two in the morning and two in the evening at 12 hour intervals over a 7 day period.

Tasigna (nilotinib) capsules should be stored at 25°C (77°F); excursions permitted between 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].

T2010-104

Manufactured by: Novartis Pharma Stein AG
Stein, Switzerland

Distributed by: Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

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The ASH-SAP website contains the full contents of the book, presented in a searchable format with interactive multiple-choice questions. Access to the electronic version is included with the purchase price of the print version.

![Price Details Table]

<table>
<thead>
<tr>
<th></th>
<th>Print Copy with Online Access</th>
<th>Online Access Only</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Members</strong></td>
<td>$335</td>
<td>$260</td>
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<tr>
<td><strong>Non-Members</strong></td>
<td>$435</td>
<td>$360</td>
</tr>
<tr>
<td><strong>Associates/Trainees</strong></td>
<td>$240</td>
<td>$165</td>
</tr>
</tbody>
</table>

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The overall 5-year survival for patients with multiple myeloma has improved over the past 10 years.\(^1\) However, myeloma remains a largely incurable disease, and almost all patients will relapse.\(^2\)

**PROGRESS HAS BEEN MADE, BUT NEW THERAPIES ARE URGENTLY NEEDED.**


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A randomized, double-blind, placebo-controlled, multicenter phase III trial to evaluate the efficacy and safety of the CD30-targeted antibody-drug conjugate brentuximab vedotin (SGN-35) and best supportive care (BSC) compared with placebo and BSC in treating residual Hodgkin lymphoma following autologous stem cell transplant (ASCT).

The primary end point is progression-free survival; secondary end points include overall survival, safety and tolerability.

**Key Inclusion Criteria:**
- Histologically confirmed HL
- ASCT after relapsed/refractory HL
- ECOG performance status of 0 or 1
- Adequate organ function

For full inclusion and exclusion criteria, please visit www.clinicaltrials.gov (NCT01100502), contact Seattle Genetics at 866-333-7436 (US only) or e-mail clinicaltrials@seagen.com.

*Antibody-drug conjugate.

SGN-35 is an investigational drug; its efficacy and safety have not been established. There is no guarantee that SGN-35 will become commercially available.
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RESPONSE is a global, randomized, open-label, multicenter, phase III study of INC424 in polycythemia vera (PV) subjects who are resistant to or intolerant of hydroxyurea.

**Primary Endpoint**
- Composite endpoint of spleen reduction and phlebotomy independence

**Secondary Endpoints**
- Proportion of patients who maintain the primary response endpoint for ≥48 weeks
- Proportion of patients who achieve complete hematologic remission at 32 weeks

**Eligibility Criteria**
- Age ≥18 years
- Resistant to or intolerant of HU
- Phlebotomy requirement due to inadequate hematocrit control at least once every 3 months
- Palpable splenomegaly ≥5 cm below the costal margin
- Elevated white blood cell and/or platelet counts

For more information or to enroll a patient outside the United States in RESPONSE, please contact your local Novartis Medical Science Liaison or visit [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

RESPONSE is sponsored by Novartis Oncology and Incyte Corporation.

Abbreviations: HU, hydroxyurea; IFN, interferon; IMiD, immunomodulator.

This is an investigational study; efficacy and safety have not been established for this use. There is no guarantee that INC424 will become commercially available for this indication.
Important Safety Information

Warnings and Precautions

FOLOTYN may suppress bone marrow function, manifested by thrombocytopenia, neutropenia, and anemia. Monitor blood counts and omit or modify dose for hematologic toxicities.

Mucositis may occur. If ≥Grade 2 mucositis is observed, omit or modify dose. Patients should be instructed to take folic acid and receive vitamin B12 to potentially reduce treatment-related hematological toxicity and mucositis.

Fatal dermatologic reactions may occur. Dermatologic reactions may be progressive and increase in severity with further treatment. Patients with dermatologic reactions should be monitored closely, and if severe, FOLOTYN should be withheld or discontinued.

Tumor lysis syndrome may occur. Monitor patients and treat if needed.

FOLOTYN can cause fetal harm. Women should avoid becoming pregnant while being treated with FOLOTYN and pregnant women should be informed of the potential harm to the fetus.

Use caution and monitor patients when administering FOLOTYN to patients with moderate to severe renal function impairment.

Elevated liver function test abnormalities may occur and require monitoring. If liver function test abnormalities are ≥Grade 3, omit or modify dose.
The indication for FOLOTYN is based on overall response rate. Clinical benefit such as improvement in progression-free survival or overall survival has not been demonstrated.

**Adverse Reactions**
The most common adverse reactions were mucositis (70%), thrombocytopenia (41%), nausea (40%), and fatigue (36%). The most common serious adverse events are pyrexia, mucositis, sepsis, febrile neutropenia, dehydration, dyspnea, and thrombocytopenia.

**Use in Specific Patient Populations**
Nursing mothers should be advised to discontinue nursing or the drug, taking into consideration the importance of the drug to the mother.

**Drug Interactions**
Co-administration of drugs subject to renal clearance (e.g., probenecid, NSAIDs, and trimethoprim/sulfamethoxazole) may result in delayed renal clearance.

Please see FOLOTYN Full Prescribing Information.

*Per independent central review

---

**Demonstrated response in relapsed or refractory PTCL**

27% overall response rate (CR+CRu+PR) by central review (95% CI, 19-36)*

Of the responders

66% responded within Cycle 1*  
— Median time to first response was 45 days (range=37-349 days)

9.4-month median duration of response by central review (range=1-503 days)*  
— 12% (95% CI, 7-20) of patients had responses lasting ≥14 weeks (range=98-503 days)

Demonstrated response in PROPEL—  
the largest prospective single-arm, open-label clinical trial in PTCL

INDICATIONS AND USAGE
FOLOTYN is indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). This indication is based on overall response rate. Clinical benefit such as improvement in progression-free survival or overall survival has not been demonstrated.

WARNINGS AND PRECAUTIONS
Bone Marrow Suppression
FOLOTYN can suppress bone marrow function, manifested by thrombocytopenia, neutropenia, and anemia. Dose modifications are based on ANC and platelet count prior to each dose.

Mucositis
Treatment with FOLOTYN may cause mucositis. If ≥ Grade 2 mucositis is observed, omit dose and follow guidelines in Table 1.

Dermatologic Reactions
FOLOTYN has been associated with severe dermatologic reactions, which may result in death. These dermatologic reactions have been reported in clinical studies (14/663 patients (2.1%) and post-marketing experience, and have included skin exfoliation, ulceration, and toxic epidermal necrolysis (TEN). These reactions may be progressive and increase in severity with further treatment, and may involve skin and subcutaneous sites of known lymphoma. Patients with dermatologic reactions should be monitored closely, and if severe, FOLOTYN should be withheld or discontinued.

Tumor Lysis Syndrome
Tumor lysis syndrome has been reported in patients with lymphoma receiving FOLOTYN. Patients receiving FOLOTYN should be monitored closely and treated for complications.

Folic Acid and Vitamin B12 Supplementation
Patients should be instructed to take folic acid and receive vitamin B12 to potentially decrease treatment-related hematological toxicity and mucositis.

Pregnancy Category D
FOLOTYN can cause fetal harm when administered to a pregnant woman. FOLOTYN was embryotoxic and fetotoxic in rats and rabbits. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Decreased Renal Function
Although FOLOTYN has not been formally tested in patients with renal impairment, caution is advised when administering FOLOTYN to patients with moderate to severe impairment. Monitor patients for renal function and systemic toxicity due to increased drug exposure.

Lever Liver Functions
Liver function test abnormalities have been observed in clinical trials. Liver function test abnormalities may be indicators of liver toxicity and require dose modification. Monitor patients for liver function.

ADVERSE REACTIONS
The most common adverse reactions observed in patients with peripheral T-cell lymphoma (PTCL) treated with FOLOTYN were mucositis, thrombocytopenia, nausea, and vomiting.

Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The safety of FOLOTYN was evaluated in 111 PTCL patients in a single-arm clinical study in which patients received a starting dose of 30 mg/m2 once weekly for 6 weeks in 7-week cycles. The median duration of treatment was 70 days (range 1-540 days).

Most Frequent Adverse Reactions
Table 4 summarizes the most frequent adverse reactions, regardless of causality, using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE, version 3.0).

Table 4 Adverse Reactions Occurring in PTCL Patients (Incidence ≥10% of patients)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
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<tbody>
<tr>
<td><em>ANY ADVERSE REACTION</em></td>
<td>111</td>
<td>100</td>
<td>48</td>
<td>43</td>
<td>34</td>
<td>31</td>
</tr>
<tr>
<td>Mucositis*</td>
<td>78</td>
<td>70</td>
<td>19</td>
<td>17</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>75</td>
<td>68</td>
<td>15</td>
<td>14</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>Nausea</td>
<td>44</td>
<td>40</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Fatigue</td>
<td>40</td>
<td>36</td>
<td>5</td>
<td>5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Anemia</td>
<td>38</td>
<td>34</td>
<td>17</td>
<td>15</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>37</td>
<td>33</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>36</td>
<td>32</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
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<td>30</td>
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<td>1</td>
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<td>0</td>
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<tr>
<td>Cough</td>
<td>31</td>
<td>28</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>29</td>
<td>26</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26</td>
<td>25</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Neutropenia</td>
<td>27</td>
<td>24</td>
<td>14</td>
<td>13</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22</td>
<td>21</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>21</td>
<td>19</td>
<td>8</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>17</td>
<td>15</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3 FOLOTYN Dose Modifications for Mucositis

<table>
<thead>
<tr>
<th>Mucositis Grade* on Day of Treatment</th>
<th>Action</th>
<th>Dose upon Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1-2</td>
<td>Omit dose</td>
<td>Continue prior dose</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Stop therapy</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>Stop therapy</td>
<td></td>
</tr>
</tbody>
</table>

* Per National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE, version 3.0)

Table 2 FOLOTYN Dose Modifications for Hematologic Toxicities

<table>
<thead>
<tr>
<th>Blood Count on Day of Treatment</th>
<th>Duration of Toxicity</th>
<th>Action</th>
<th>Dose upon Restart</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet</td>
<td>≤50,000/µL</td>
<td>≤3 weeks</td>
<td>Omit dose</td>
</tr>
<tr>
<td>ANC 500-1,000/µL</td>
<td>≤3 weeks</td>
<td>Omit dose</td>
<td>20 mg/m²</td>
</tr>
<tr>
<td>ANC ≤500/µL</td>
<td>≤3 weeks</td>
<td>Omit dose</td>
<td>G-CSF or GM-CSF support</td>
</tr>
</tbody>
</table>

* Per National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE, version 3.0)
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BD Biosciences
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bdbiosciences.com
TREANDA® is his chemo.

This is his therapy.
TREANDA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL). Efficacy relative to first-line therapies other than chlorambucil has not been established.

Selected Safety Information

- Serious adverse reactions, including myelosuppression, infections, infusion reactions and anaphylaxis, tumor lysis syndrome, skin reactions including SJS/TEN, other malignancies, and extravasation, have been associated with TREANDA. Some reactions, such as myelosuppression, infections, and SJS/TEN (when TREANDA was administered concomitantly with allopurinol and other medications known to cause SJS/TEN), have been fatal. Patients should be monitored closely for these reactions and treated promptly if any occur.
- Adverse reactions may require interventions such as decreasing the dose of TREANDA, or withholding or delaying treatment. Myelosuppression is frequently severe and should be expected when treating patients with TREANDA.
- TREANDA is contraindicated in patients with a known hypersensitivity to bendamustine or mannitol. Women should be advised to avoid becoming pregnant while using TREANDA.
INDICATIONS AND USAGE: TREANDA is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) in two settings: as monotherapy (bendamustine hydrochloride) for Injection, 100 mg in 20 mL amber single-use vial. (Label Code: 00016287.03) All rights reserved.

DOSAGE AND ADMINISTRATION:

HOW SUPPLIED/STORAGE AND HANDLING: Safe Handling and Disposal. As with all potentially toxic anticancer agents, care should be exercised in the handling and preparation of solutions prepared from this drug. An impermeable barrier such as gloves and safety glasses should be worn to avoid skin contact. This drug is supplied in individual cartons as follows: NDC 63459-390-08 TREANDA (bendamustine hydrochloride) for Injection, 100 mg in 20 mL amber single-use vial and NDC 63459-391-20 TREANDA (bendamustine hydrochloride) for Injection, 25 mg in 8 mL amber single-use vial and NDC 63459-399-20 TREANDA (bendamustine hydrochloride) for Injection, 5 mg in 2 mL amber single-use vial.

Table 1: Non-Hematologic Adverse Reactions Occurring in Randomized CLL Clinical Study in at Least 5% of Patients

<table>
<thead>
<tr>
<th>Treatment/Preparation</th>
<th>All Grades</th>
<th>Grade 3/4</th>
<th>All Grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorambucil</td>
<td>121 (79)</td>
<td>52 (34)</td>
<td>96 (67)</td>
<td>45 (34)</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>121 (79)</td>
<td>52 (34)</td>
<td>96 (67)</td>
<td>45 (34)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea</td>
<td>31 (20)</td>
<td>1 (1)</td>
<td>21 (15)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>24 (16)</td>
<td>1 (1)</td>
<td>9 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14 (9)</td>
<td>2 (1)</td>
<td>11 (7)</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Pyrexia</td>
<td>36 (24)</td>
<td>6 (4)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14 (9)</td>
<td>2 (1)</td>
<td>6 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td>9 (6)</td>
<td>0</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity</td>
<td>7 (5)</td>
<td>2 (1)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Infections and infections</td>
<td>Infection</td>
<td>10 (7)</td>
<td>0</td>
<td>12 (8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (6)</td>
<td>3 (2)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Hematopoietic</td>
<td>5 (3)</td>
<td>0</td>
<td>4 (3)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Investigations</td>
<td>Weight loss</td>
<td>11 (7)</td>
<td>0</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hyperuricemia</td>
<td>11 (7)</td>
<td>3 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Renal and hepatic and mediastinal disorders</td>
<td>Cardiac disorders</td>
<td>6 (4)</td>
<td>1 (1)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Pruritis</td>
<td>12 (8)</td>
<td>4 (3)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Platelets Decreased</td>
<td>116 (77)</td>
<td>16 (11)</td>
<td>110 (78)</td>
<td>14 (10)</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>60 (40)</td>
<td>7 (5)</td>
<td>53 (36)</td>
<td>6 (4)</td>
</tr>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
<td>All Grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td></td>
<td>Hemoglobin Decreased</td>
<td>134 (89)</td>
<td>20 (13)</td>
<td>115 (82)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>134 (89)</td>
<td>20 (13)</td>
<td>115 (82)</td>
</tr>
</tbody>
</table>

In the randomized CLL clinical study, 34% of patients had blinlum reactions, some without associated significant elevations in AST and ALT. Grade 3 or 4 increased bilirubin occurred in 3% of patients. Increases in AST and ALT of grade 3 or 4 were limited to 2% and 4% of patients, respectively. Patients treated with TREANDA may also have changes in their creatinine levels. If abnormalities are detected, monitoring of these parameters should be continued to ensure that significant deterioration does not occur. Post-Marketing Experience. The following adverse reactions have been identified during post-marketing use of TREANDA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Skin Reactions. Monitor clinically and discontinue drug for severe reactions. Patients should be asked about symptoms suggestive of infusion reactions after their first cycle of therapy. Patients who experienced grade 3 or 4 worse-allergic type reactions were not typically rechallenged. Measures to prevent severe reactions, including antihistamines, antacids and corticosteroids should be considered in subsequent cycles in patients who have previously experienced grade 1 or 2 infusion reactions. Discontinuation should be considered in patients with grade 3 or 4 infusion reactions. Lymphoma Syndrome. Lymphoma syndrome associated with TREANDA treatment has been reported in patients in clinical trials and in post-approval use of TREANDA. The syndrome includes one or more of the following features: fever, rash, fatigue, lymphadenopathy, hepatosplenomegaly, neutropenia, thrombocytopenia, weight loss, weight gain, changes in laboratory parameters [e.g., increased bilirubin, alkaline phosphatase, alanine transaminase (ALT) and aspartate transaminase (AST)], and increased risk of severe skin toxicity when TREANDA and allopurinol are administered concomitantly. The onset tends to be within the first treatment cycle of TREANDA and, without intervention, may lead to acute renal failure and death. Preventive measures include maintaining adequate volume status, and close monitoring of blood chemistry, particularly potassium and uric acid levels. All patients should receive pre-emptive therapy. Hoening et al, there may be an increased risk of severe skin toxicity when TREANDA and allopurinol are administered concomitantly. Skin Reactions. One or more skin reactions have been observed in patients in clinical trials and post-approval use of TREANDA. These events have included rash, toxic skin reactions and bullous exanthema. Some events occurred when TREANDA was given in combination with allopurinol and other medications known to cause these syndromes. These skin reactions, regardless of attribution, that were reported in less than 1 adverse reaction out of 121 (79) and 52 (34) patients receiving TREANDA and chlorambucil, respectively. Where skin reactions occur, they may be progressive and increase in severity with further treatment. Therefore, patients with skin reactions should be monitored closely. If skin reactions are severe or progressive, TREANDA should be withdrawn or discontinued. Other Maligancies. There are reports of pre-malignant and malignant diseases that have developed in patients who have been treated with TREANDA, including myelodysplasia-syndromes, myeloproliferative disorders, acute myeloid leukemia and bronchial carcinoma. The association with TREANDA has not been determined. Extramedullary T-Cell Lymphoma. There are postmarketing reports of bendamustine extrusions resulting in hospitalizations from erythema, marked swelling, and pain. Precautions should be taken to avoid extravasations, including monitoring of the intravenous infusion site for signs of extravasation, and discontinuing the infusion if extravasation is suspected before administration. Pregnancy. TREANDA can cause fetal harm when administered to a pregnant woman. Single intravenous doses of bendamustine in mice and rats administered during organogenesis caused an increase in resorptions, skeletal and visceral malformations, and decreased fetal body weights.

ADVERSE REACTIONS: The data described below reflect exposure to TREANDA in 153 patients. TREANDA was studied in an active-controlled trial for the treatment of CLL. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The following serious adverse reactions have been associated with TREANDA in clinical trials and are discussed in greater detail in other sections [See Warnings and Precautions].

Reinitiation of Treatment: Anaphylaxis; and injection or infusion site reactions including pruritus, irritation, pain, and swelling. Skin reactions including SJS and TEN have occurred when TREANDA was administered concomitantly with allopurinol and other medications known to cause these syndromes. (See Warnings and Precautions). The use of gloves and safety glasses is recommended to avoid exposure in case of breakage of antineoplastic. Beneath the black glass, TREANDA (bendamustine hydrochloride) for Injection, 100 mg in 20 mL amber single-use vial.

Table 2: Incidence of Hematologic Laboratory Abnormalities in CLL Patients Who Received TREANDA or Chlorambucil in the Randomized CLL Clinical Study

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grade 3/4</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>TREANDA</td>
<td>(N=153)</td>
<td>(N=143)</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>121 (79)</td>
<td>52 (34)</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>134 (89)</td>
<td>20 (13)</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>60 (40)</td>
<td>7 (5)</td>
</tr>
</tbody>
</table>

The Grade 3 and 4 hematology laboratory test values by treatment group in the randomized CLL clinical study are described in Table 2. These findings confirm the myelosuppressive effects seen in patients treated with TREANDA. Red blood cell transfusions were administered to 20% of patients receiving TREANDA compared with 6% of patients receiving chlorambucil.

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- Includes midostaurin/placebo continuation therapy for up to 12 months
- Primary endpoint: overall survival

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  - Grupo Cooperativo de Tratamiento de las Leucemias Agudas y Mielodisplasias
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- SAL
  - Study Alliance Leukemia

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Richard M. Stone, M.D.
Dana Farber Cancer Institute
rstone@partners.org

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Primary research articles will be published under the following scientific categories: Clinical Trials and Observations; Gene Therapy; Hematopoiesis and Stem Cells; Immunobiology; Myeloid Neoplasia; Lymphoid Neoplasia; Phagocytes, Granulocytes and Myelopoiesis; Platelets and Thrombopoiesis; Red Cells, Iron and Erythropoiesis; Thrombosis and Hemostasis; Transfusion Medicine; Transplantation; and Vascular Biology. Authors are invited to contact the Editor-in-Chief (bloodeditor@hematology.org) prior to submission if they are uncertain whether their work falls within the general scope. Immunobiology encompasses a wide spectrum of research, but Blood can accommodate only papers that have clear and important implications for hematology. Preference is given to papers focusing on human immunobiology and which have significant implications for understanding of normal or malignant hematologic processes. Papers on tumor immunology and tumor vaccine development may be appropriate if the target cells are hematologic malignancies, but Blood can no longer accommodate tumor immunology papers that focus solely on nonhematologic tumor models. Papers focusing on autoimmunity and utilizing nonhematologic models are not within the scope of Blood. Papers on the immune response to specific microbiologic pathogens are also generally outside the scope of Blood, except those focusing on the direct links of Epstein-Barr virus, hepatitis virus, or HTLV to hematologic malignancies. These and other papers felt to be outside the scope of Blood and more appropriate for an immunology, infectious diseases, or tumor immunology Journal will be returned to the author without full peer review.

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Brief Reports. Short manuscripts definitively documenting either experimental results or informative clinical observations will be considered for publication in this category. Single-case reports or case series can almost never be accommodated, unless they elucidate novel and important disease biology or approaches to therapy. Brief Reports are not intended to allow publication of incomplete or preliminary findings. The review process is equally rigorous as for Regular Articles and the acceptance rate is lower. Brief Reports may not exceed 1,200 words of text not counting the abstract, figure legends, and references; abstracts must not exceed 150 words and should be a single paragraph with no subheadings. Only 2 figures/tables and 25 references may be included. The sections of a Brief Report should be ordered Abstract, Introduction, Methods sufficiently informative to allow reproduction of the data, followed by a combined Results and Discussion section, Acknowledgments, Authorship Contributions and Disclosure of Conflicts of Interest, References, Tables, Figure Legends, and Figures.

Blood, e-Blood is a new manuscript category for publication of very well designed systems biology work (e.g., genomics, proteomics etc.) that is largely descriptive. Such work will be published as an online-only paper if utilization of the data by others will significantly advance the field. e-Blood articles will be fully citable, and will represent genuine Blood publication. They will undergo standard rigorous peer review if deemed potentially appropriate for publication by Blood Editors. Accepted e-Blood articles will be published in First Edition and then copyedited and composed identical to other Blood papers, but will not be included in a print edition of the Journal, although they will be listed in a printed Table of Contents when their final typeset version is available online. Papers may be submitted by authors directly for consideration as e-Blood articles, or may be recommended by Editors for publication as an e-Blood article after being considered for publication as a Regular Article, if deemed more appropriate for the e-Blood article type. The maximum length for an
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Review Articles should not exceed 5,000 words in length, must include an abstract of 200 words or fewer, and may not have more than 100 references. The use of tables and color figures to summarize critical points is encouraged; the Journal offers assistance with preparation or improvement of figures by professional illustrators, once the article is accepted.

Any involvement of medical writers/researchers, particularly those employed or supported by the pharmaceutical industry, in the writing of a Review Article must be clearly defined and disclosed in the Authorship section. For Review Articles, this type of involvement must be discussed with the Editor-in-Chief before the submission of the article. Generally, involvement of medical writers/researchers supported by the pharmaceutical industry is not acceptable for Review Articles published in Blood.

**How I Treat.** The Journal welcomes articles written by expert clinicians offering up-to-date information and guidance regarding diagnosis and treatment of hematological diseases and clinical situations. Clear distinctions should be made between evidence-based versus experience-based recommendations. The pieces can be constructed as a standard narrative or be structured around a case or cases illustrating specific clinical situations. These pieces are generally solicited by the Editor-in-Chief, but any interested author is invited to correspond with the Editor-in-Chief prior to submission to discuss the suitability of the proposed subject matter. The length should not exceed 5,000 words; the abstract must not exceed 200 words; and references are limited to 100.

Any involvement of medical writers/researchers, particularly those employed or supported by the pharmaceutical industry, in the writing of an article must be clearly defined and disclosed in the Authorship section. For How I Treat articles, this type of involvement must be discussed with the Editor-in-Chief before the submission of the article. Generally, involvement of medical writers/researchers supported by the pharmaceutical industry is not acceptable for How I Treat articles published in Blood.

**Perspectives.** Perspectives are articles discussing significant topics and controversies relevant to hematology, generally from a more personal or opinion-based standpoint than a Review Article. Interested authors should correspond with the Editor-in-Chief prior to submission to discuss the suitability of the proposed subject matter. The length should not exceed 5,000 words; the abstract must not exceed 200 words; and references are limited to 100. Typically, Perspectives should state the topic and background information concisely, discuss opposing viewpoints, and make recommendations for further investigations or actions.

**Inside Blood.** The Editors invite experts in the field to write brief commentaries introducing and placing into context several selected primary research articles included in each issue of Blood.

**Plenary Papers.** Definitive original research articles of exceptional scientific importance may be considered for designation as Plenary Papers. The decision to highlight an article as a Plenary Paper rests entirely with the Editors.

**Data Supplements.** The Journal encourages the submission of Data Supplements linked to primary research articles, including videos and short movies, that enhance the understanding of the science discussed in the manuscript. Data Supplements must be submitted for peer review during the initial submission of the manuscript. The Editors will review the supplemental material along with the manuscript, but acceptance of the manuscript does not guarantee ultimate acceptance of the supplement.

**Blood Work.** Blood welcomes submissions of photo micrographs and brief case descriptions to serve as a regular teaching feature and comprehensive reference accessible to physicians and hematology students around the world. These images and cases are published by the Journal monthly in the Blood Work section, in the first issue of each month. Each submission must contain a single, or at most two related, high-resolution figure(s) formatted as TIFFs (minimum 300 dpi) and a discussion of no more than 200 words describing the clinical case linked to the image(s). Generally each piece should have a single or very few authors and no references. If your submission is accepted, your figure(s) will also be submitted for consideration to the ASH Image Bank. All other policies governing submissions to the Journal also apply to Blood Work. There will be no submission fee and no color figure charges for publication if accepted.

**Letters to the Editor.** Constructive comments on published articles or on current topics in hematology are welcome and will be published if appropriate and based on priority and interest to readership. Letters should include no more than 500 words of text, 5–10 references, and 1 figure or table. No abstract is required, but please include a brief title. Submission fees and page charges do not apply to Letters. Letters are screened by the Editor-in-Chief and, if deemed appropriate and relevant, may also be peer reviewed and/or accompanied by a Response from the authors of the initial article.

**Public Access.** The American Society of Hematology supports free access to Blood on the broadest possible basis, although ASH and Blood cannot adopt or support a publishing model that is not economically sustainable over a long horizon. Blood maintains a 12-month access embargo to non-subscribers while offering an inexpensive pay-per-view option; however, online content older than 12 months is free to all. Also, significant sections of each new issue are immediately free-to-all online, including abstracts and tables of contents, Inside Blood commentaries, How I Treat articles, and 5 clinically relevant research articles or Review Articles per issue selected by the Editor-in-Chief. In addition, Blood ensures that patients looking for pertinent information can access any article without charge by contacting the Journal.

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Important Safety Information

Treatment with DACOGEN is associated with neutropenia and thrombocytopenia. Complete blood and platelet counts should be performed as needed to monitor response and toxicity but at a minimum prior to each dosing cycle. After administration of the recommended dosage for the first cycle, treatment for subsequent cycles should be adjusted if indicated by dose adjustment guidelines. Clinicians should consider the need for early institution of growth factors and/or antimicrobial agents for the prevention or treatment of infections in patients with MDS.

DACOGEN may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with DACOGEN and for 1 month following completion of treatment. Women of childbearing potential should be counseled to use effective contraception during this time. Men should be advised not to father a child while receiving treatment with DACOGEN and for 2 months following completion of treatment. DACOGEN may cause fetal harm. Men with female partners of childbearing potential should use effective contraception during this time.

In the phase 3 clinical trial, the highest incidence of Grade 3 or Grade 4 adverse events in the DACOGEN arm was neutropenia (87%), thrombocytopenia (85%), febrile neutropenia (23%), and leukopenia (22%). Bone marrow suppression was the most frequent cause of dose reduction, delay, and discontinuation. Six patients had fatal events associated with their underlying disease and myelosuppression (anemia, neutropenia, and thrombocytopenia) that were considered at least possibly related to drug treatment. Of the 83 DACOGEN-treated patients, 8 permanently discontinued therapy for adverse events compared to 1 of 81 patients in the supportive care arm.

In the single-arm study, the highest incidence of Grade 3 or Grade 4 adverse events was neutropenia (37%), thrombocytopenia (24%), and anemia (22%). Seventy-eight percent of patients had dose delays, the median duration of this delay was 7 days. Hematologic toxicities and infections were the most frequent causes of dose delays and discontinuation. Eight patients had fatal events due to infection and/or bleeding that were considered at least possibly related to drug treatment. Nineteen of 99 patients permanently discontinued therapy for adverse events.

Other commonly occurring reactions include fatigue, pyrexia, nausea, cough, petechiae, constipation, diarrhea, and hyperglycemia.

If hematologic recovery from a previous DACOGEN treatment cycle requires more than 6 weeks when administering the 3-day dosing, then the next DACOGEN cycle should be delayed and dosing temporarily reduced. When administering the 5-day dosing, the DACOGEN cycle should be delayed until there is hematologic recovery. If the following nonhematologic toxicities are present, DACOGEN treatment should not be restarted until the toxicity is resolved: (1) serum creatinine ≥2 mg/dl; (2) SGPT, total bilirubin ≥2 × ULN; and (3) active or uncontrolled infection.

Because there are no data on use of DACOGEN in patients with renal or hepatic dysfunction, DACOGEN should be used with caution in these patients.

Please see the accompanying brief summary of full Prescribing Information on the following page.

Reference: 1. Dacogen (decitabine) for Injection full prescribing information.
Neutropenia (23%) and leucopenia (22%). Bone marrow suppression was the most frequent cause of dose reduction, delay and discontinuation. Of the 83 Dacogen-treated patients, 8 permanently
between patients >65 years of age and younger patients in these myelodysplasia trials. No significant gender differences in safety or efficacy
due to infection and/or bleeding (seven of which occurred in the clinical setting of myelosuppression) that were considered at least possibly related
toxicities. Hematologic toxicities and infections were the most frequent causes of dose delays and discontinuation. Eight patients had fatal events

Secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess
[see Dosage and Administration]

The information below presents all adverse events regardless of causality occurring in at least 5% of patients.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly
measured to establish relative incidence or to establish drug equivalence among clinical studies. Because it is impractical, if not impossible, to prespecify all
mechanisms by which a drug may cause an adverse reaction, each adverse event should be considered as being due to the drug unless it is clearly unrelated.

In the single-arm study (N=99) when Dacogen was dosed at 20 mg/m 2 intravenous, infused over one hour daily for 5 consecutive days, the

The 3 mg/m 2 dose elicited characteristic fetal defects for each treatment day, including supernumerary ribs (both dose levels), fused vertebrae
3.6 or 6 mg/m 2 (approximately 5, 8, or 13% the daily recommended clinical dose, respectively) on gestation days 9-12, no maternal
for foetal therapy administration. Dacogen is an injectable stock solution. Each vial contains 50 mg of Dacogen in 1.5 ml of aqueous solution.

The safety and effectiveness of Dacogen in pediatric patients have not been established.

Deoxycytidine is converted to deoxyadenosine and dTMP in normal and neoplastic cells. The mechanism of action of Dacogen is inhibition of DNA synthesis and DNA repair.

Drug interaction studies with decitabine have not been conducted.

Because it is impractical, if not impossible, to prespecify all mechanisms by which a drug may cause an adverse reaction, each adverse event should be considered as being due to the drug unless it is clearly unrelated.

In a 6-week, randomized, double-blind, placebo-controlled study in patients 55 to 85 years old, Dacogen 50 mg/m 2 was administered weekly for 4 weeks (as a 1-hour infusion)

The 3 mg/m 2 dose elicited characteristic fetal defects for each treatment day, including supernumerary ribs (both dose levels), fused vertebrae

In utero fetal loss was 6% and 12% in the 0.3 and 0.60 mg/m2 dose groups, respectively. Based on in utero observations, decitabine causes chromosomal

In a single-arm study, investigators reported adverse events observed based on clinical signs and symptoms rather than predetermined laboratory abnormalities.

This effect caused hematologic findings in both normal and neoplastic cells. The mechanism of action of Dacogen is inhibition of DNA synthesis and DNA repair.

Based on the expected mechanism of action and data from preclinical studies, Dacogen is not expected to be a substrate for HLM, CYP2C19, CYP2D6, CYP3A4, or CYP1A2.

In a single-arm study, investigators reported adverse events observed based on clinical signs and symptoms rather than predetermined laboratory abnormalities.

The safety and effectiveness of Dacogen in pediatric patients have not been established.

In a single-arm study, investigators reported adverse events observed based on clinical signs and symptoms rather than predetermined laboratory abnormalities.

The safety and effectiveness of Dacogen in pediatric patients have not been established.
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NOW ENROLLING PATIENTS WITH POLYCYTHEMIA VERA

RESPONSE
Randomized Study of Efficacy and Safety in Polycythemia Vera with JAK Inhibitor
INCB018424 Versus Best Available Care

A PHASE III STUDY INVESTIGATING INCB018424—
AN ORAL JAK1 AND JAK2 INHIBITOR

The RESPONSE trial is a global, randomized, open-label, multicenter, phase III study of the oral JAK1 and JAK2 inhibitor INCB018424 in patients with polycythemia vera (PV) who are resistant to or intolerant of hydroxyurea. RESPONSE is sponsored by both Incyte and Novartis.

Primary endpoint
Composite endpoint of phlebotomy independence and spleen volume reduction at Week 32

Secondary endpoints
- Proportion of patients who maintain the primary endpoint response for ≥48 weeks
- Proportion of patients achieving complete hematologic remission at 32 weeks

Patients with PV (N=300)
Randomized 1:1

<table>
<thead>
<tr>
<th>INCB018424 (oral) 10 mg bid</th>
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<tbody>
<tr>
<td>Best available therapy as selected by physician*†</td>
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The treatment duration for the study will be 80 weeks.
* Physician’s choice: hydroxyurea, interferon, anagrelide, pipobroman, IMIDs, or observation.
† Patients randomized to best available therapy may be eligible to cross over to INCB018424.

If you have a PV patient who is at least 18 years of age and who meets the following criteria, he/she may be eligible for enrollment in RESPONSE:
- Resistant to or intolerant of hydroxyurea
- Phlebotomy requirement due to inadequate hematocrit control at least once every 3 months
- Palpable splenomegaly ≥5 cm below the costal margin
- Elevated white blood cell and/or platelet counts

To enroll a US patient in RESPONSE or to find out more about this trial, please call 1-877-4-PV-TRIAL or visit www.responsetrial.com.

INCB018424 is an investigational compound. Its efficacy and safety have not been established. There is no guarantee that this compound will become commercially available.
ASH is proud to introduce the new and enhanced categories for the Honorific Awards. The honorific awards acknowledge illustrious achievements to the field of hematology by both basic science researchers and clinical researchers.

The Society’s highest honors, the ASH Honorific Awards are presented annually during the ASH annual meeting. The portfolio of honorific awards includes:

- Wallace H. Coulter Award for Lifetime Achievement in Hematology
- Ernest Beutler Lecture and Prize
- William Dameshek Prize
- Henry M. Stratton Medal
- E. Donnall Thomas Lecture and Prize

**Eligibility Criteria**

- Both nominees and nominators must be members of ASH (Stratton Medal, Dameshek Prize and Thomas Lecture only).
- Nominees of all nationalities and all countries of residence are eligible.

The nomination cycle for the 2012 honorific awards is now open, and the deadline to nominate a colleague is July 1, 2011.

Please visit [www.hematology.org/HonorificAwards](http://www.hematology.org/HonorificAwards) to view the updated award criteria and download the nomination form.

**Questions?**

For more information or questions about the honorific awards, please contact ASH Awards, at awards@hematology.org, or by phone at 202-776-0544.
Blood Tier Definitions

Tier Definition
1 Single-site Two-year colleges, Small hospitals (<500 beds)
2 Single-site Masters and baccalaureate colleges, Charitable organizations (excl. hospitals), Large hospitals (500+ beds)
3 Single-site Doctorate-granting research universities, Medical schools, Teaching or research hospitals, Non-profit research institutes, Government research institutes, For-profit companies or organizations
3.2 Tier 3 organizations with 2 geographic locations
3.3 Tier 3 organizations with 3 geographic locations
4 University systems, State-wide academic institutions, Regional health care systems or networks, Non-profit research organizations or healthcare networks with multiple locations, For-profit companies or organizations with 4 geographic locations
4.5 For-profit companies or organizations with 5 geographic locations
4.6 For-profit companies or organizations with 6 geographic locations
4.7 For-profit companies or organizations with 7 geographic locations
4.8 For-profit companies or organizations with 8 geographic locations
5 Global License for Large/multinational for-profit companies or organizations, National research laboratories and government agencies
6 Consortia, National, or Special Licenses

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ASPIRE: a Phase III trial investigating carfilzomib-based combination therapy

- ASPIRE compares carfilzomib plus lenalidomide and dexamethasone (CRd) and lenalidomide and dexamethasone (Rd)
- The trial includes patients with multiple myeloma who have received 1 to 3 prior treatment regimens

ASPIRE is one of many ongoing trials investigating agents in the Onyx proteasome inhibitor pipeline.

To learn more about the ASPIRE trial, visit www.OnyxTrials.com or www.clinicaltrials.gov.