A SPECIAL MEETING REVIEW EDITION

Advances in Lymphoma and Leukemia From the 2016 American Society of Hematology Annual Meeting and Exposition

A Review of Selected Presentations From the 2016 American Society of Hematology Annual Meeting and Exposition • December 3-6, 2016 • San Diego, California

Special Reporting on:

• First Analysis of an International Double-Blind Randomized Phase III Study of Lenalidomide Maintenance in Elderly Patients With DLBCL Treated With R-CHOP in First Line, the REMARC Study From LYSA
• Obinutuzumab-Based Induction and Maintenance Prolongs Progression-Free Survival (PFS) in Patients With Previously Untreated Follicular Lymphoma: Primary Results of the Randomized Phase 3 GALLIUM Study
• Rituximab Plus Lenalidomide Versus Rituximab Monotherapy in Untreated Follicular Lymphoma Patients in Need of Therapy. First Analysis of Survival Endpoints of the Randomized Phase-2 Trial SAKK 35/10
• Brentuximab Vedotin Demonstrates Significantly Superior Clinical Outcomes in Patients With CD30-Expressing Cutaneous T Cell Lymphoma Versus Physician’s Choice (Methotrexate or Bexarotene): The Phase 3 ALCANZA Study
• MAGNIFY: Phase IIb Randomized Study of Lenalidomide Plus Rituximab (R2) Followed By Lenalidomide Vs. Rituximab Maintenance in Subjects With Relapsed/Refractory Follicular, Marginal Zone, or Mantle Cell Lymphoma
• Lenalidomide Maintenance After Front Line Therapy Substantially Prolongs Progression Free Survival in High Risk CLL: Interim Results of a Phase 3 Study (CLLM1 Study of the German CLL Study Group)
• Results of the Phase 3 Study of Lenalidomide Versus Placebo As Maintenance Therapy Following Second-Line Treatment for Patients With Chronic Lymphocytic Leukemia (the CONTINUUM Trial)
• Nivolumab Combined With Ibrutinib for CLL and Richter Transformation: A Phase II Trial

PLUS Meeting Abstract Summaries

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Important Safety Information

WARNINGS AND PRECAUTIONS

• **Myelosuppression:** ISTODAX® (romidepsin) for injection can cause thrombocytopenia, leukopenia (neutropenia and lymphopenia), and anemia; monitor blood counts regularly during treatment with ISTODAX; interrupt and/or modify the dose as necessary.

• **Infections:** Fatal and serious infections, including pneumonia, sepsis, and viral reactivation, including Epstein Barr and hepatitis B viruses, have been reported during and within 30 days after treatment with ISTODAX in clinical trials. The risk of life-threatening infections may be greater in patients with a history of prior treatment with monoclonal antibodies directed against lymphocyte antigens and in patients with disease involvement of the bone marrow. Reactivation of Epstein Barr viral infection led to liver failure. Consider monitoring for reactivation and antiviral prophylaxis in patients with evidence of prior hepatitis B infection. Ganciclovir prophylaxis failed to prevent Epstein Barr viral reactivation in one case.

• **Electrocardiographic (ECG) changes:** ECG changes have been observed with ISTODAX. In patients with congenital long QT syndrome, patients with a history of significant cardiovascular disease, and patients taking anti-arrhythmic medicines or medicinal products that lead to significant QT prolongation, consider cardiovascular monitoring of ECGs at baseline and periodically during treatment. Confirm that potassium and magnesium levels are within the normal range before administration of ISTODAX.

• **Tumor lysis syndrome (TLS):** TLS has been reported during treatment with ISTODAX. Patients with advanced stage disease and/or high tumor burden are at greater risk and should be closely monitored and managed as appropriate.

Please see Brief Summary of Full Prescribing Information on the following pages.

*Not an actual patient.*
ISTODAX® (romidepsin) for injection is indicated for treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy. This indication is based on response rate. Clinical benefit such as improvement in overall survival has not been demonstrated.

**ADVERSE REACTIONS**

### Cutaneous T-Cell Lymphoma

The most common Grade 3/4 adverse reactions (>5%) regardless of causality in Study 1 (N=102) were infections (11%) and asthenia/fatigue (8%), and in Study 2 (N=83) were lymphopenia (37%), infections (33%), neutropenia (27%), leukopenia (22%), anemia (16%), asthenia/fatigue (14%), thrombocytopenia (14%), hypophosphatemia (10%), vomiting (10%), dermatitis/exfoliative dermatitis (8%), hypermagnesemia (8%), hyperuricemia (8%), hypocalcemia (6%), nausea (6%), and pruritus (6%).

Infections were the most common type of serious adverse event reported in both Study 1 (N=102) and Study 2 (N=83) with 8 patients (8%) in Study 1 and 26 patients (31%) in Study 2 experiencing a serious infection. The most common Grade 3/4 adverse reactions regardless of causality in Study 1 (N=102) were nausea (56%), asthenia/fatigue (53%), infections (46%), vomiting (34%), and anorexia (23%), and in Study 2 (N=83) were nausea (86%), asthenia/fatigue (77%), anemia (72%), thrombocytopenia (65%), ECG ST-T wave changes (63%), neutropenia (57%), lymphopenia (57%), infections (54%), anorexia (54%), vomiting (52%), hypocalcemia (52%), hyperglycemia (51%), hypoalbuminemia (48%), leukopenia (46%), dysgeusia (40%), and constipation (39%).

**Embryo-fetal toxicity:** ISTODAX may cause fetal harm when administered to a pregnant woman. Advise women of potential hazard to the fetus and to avoid pregnancy while receiving ISTODAX.

**DRUG INTERACTIONS**

- Monitor more frequently prothrombin time and International Normalized Ratio in patients concurrently administered ISTODAX and warfarin or coumarin derivatives
- Romidepsin is metabolized by CYP3A4
  - Monitor patients for toxicity related to increased romidepsin exposure and follow dose modifications for toxicity when ISTODAX is initially co-administered with strong CYP3A4 inhibitors
  - Avoid co-administration of ISTODAX (romidepsin) with rifampin and other potent inducers of CYP3A4
- Exercise caution with concomitant use of ISTODAX and P-glycoprotein (P-gp, ABCB1) inhibitors

**USE IN SPECIFIC POPULATIONS**

- Pregnancy Category D: If this drug is used during pregnancy, or if the patient becomes pregnant while taking ISTODAX, the patient should be apprised of the potential hazard to the fetus
- Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ISTODAX, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother
- Patients with moderate and severe hepatic impairment and/or patients with end-stage renal disease should be treated with caution

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**For more information about CTCL, visit www.ISTODAX.com**
1 INDICATIONS AND USAGE

ISTODAX® (romidepsin) is indicated for:

- Treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy.

This indication is based on response rate. Clinical benefit such as improvement in overall survival has not been demonstrated.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

**Romidepsin** is administered intravenously over 4 hours on days 1, 8, and 15 of a 28-day cycle. Repeated every 28 days provided that the patient continues to benefit from and tolerates the drug.

2.2 Dose Modification

**Nonhematologic toxicities except alopecia**

- **Grade 2 or 3 toxicity**: Treatment with romidepsin should be delayed until toxicity returns to ≤ Grade 1 or baseline, therapy may be restarted at 14 mg/m². If Grade 3 toxicity recurs, treatment with romidepsin should be delayed until toxicity returns to ≤ Grade 1 or baseline and the dose should be permanently reduced to 10 mg/m².
- **Grade 4 toxicity**: Treatment with romidepsin should be delayed until toxicity returns to ≤ Grade 1 or baseline, then the dose should be permanently reduced to 10 mg/m².
- **Romidepsin** should be discontinued if Grade 3 or 4 toxicities recur after dose reduction.

**Hematologic toxicities**

- **Grade 3 or 4 neutropenia or thrombocytopenia**: Treatment with romidepsin should be delayed until the specific cytopenia returns to ANC ≥ 1.5×10⁹/L and platelet count ≥ 75×10⁹/L or baseline, then therapy may be restarted at 14 mg/m².
- **Grade 4 febrile (≥ 38.5°C) neutropenia or thrombocytopenia**: Treatment with romidepsin should be delayed until the specific cytopenia returns to ≤ Grade 1 or baseline, then the dose should be permanently reduced to 10 mg/m².

2.3 Instructions for Preparation and Intravenous Administration

**ISTODAX** is a cytotoxic drug. Use appropriate handling procedures. ISTODAX must be reconstituted with the supplied diluent and further diluted with 0.9% Sodium Chloride Injection, USP before intravenous infusion.

ISTODAX and diltuat vials contain an overfill to ensure the recommended volume can be withdrawn at a concentration of 5 mg/mL.

- Each 10 mg single-dose vial of ISTODAX must be reconstituted with 2.2 mL of the supplied diluent.
- With a suitable syringe, aseptically withdraw 2.2 mL from the supplied diluent vial, and slowly inject it into the ISTODAX (romidepsin) for injection vial. Swirl the contents of the vial until there are no visible particles in the resulting solution. The reconstituted solution will contain ISTODAX 5 mg/mL. The reconstituted ISTODAX vial will contain 2 mL of diluent with the same drug product. The reconstituted ISTODAX solution is chemically stable for up to 8 hours at room temperature.
- Extract the appropriate amount of ISTODAX from the vials to deliver the desired dose, using aseptic technique. Before intravenous infusion, further dilute ISTODAX in 500 mL 0.9% Sodium Chloride Injection, USP.
- Infuse over 4 hours.

The diluted solution is compatible with polyvinyl chloride (PVC), ethylene vinyl acetate (EVA), polyethylene PE infusion bags as well as glass bottles, and is chemically stable for up to 24 hours when stored at room temperature. However, it should be administered as soon as dilution as possible.

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Treatment with ISTODAX can cause thrombocytopenia, leukopenia (neutropenia and lymphopenia), and anemia. Monitor blood counts regularly during treatment with ISTODAX, and modify the dose as necessary [see Doseage and Administration (2.2) and Adverse Reactions (6)].

5.2 Infections

Fatal and serious infections, including pneumonia, sepsis, and viral reactivation, including Epstein Barr and hepatitis B viruses, have been reported in clinical trials with ISTODAX. These can occur during treatment and within 30 days after treatment. The risk of life-threatening infections may be greater in patients with a history of prior treatment with monoclonal antibodies directed against lymphocyte antigens and in patients with disease involvement of the bone marrow [see Adverse Reactions (6)].

Reactivation of Epstein Barr viral infection has occurred in 1% of PTCL patients in clinical trials in Western populations [see Adverse Reactions (6)]. In patients with evidence of prior hepatitis B infection, consider monitoring for reactivation, and consider antiviral prophylaxis.

Reactivation of Epstein Barr viral infection leading to liver failure has occurred in a small population of patients with relapsed or refractory extranodal NK/T-cell lymphoma. In one case, ganciclovir prophylaxis failed to prevent Epstein Barr viral reactivation.

5.3 Electrocardiographic Changes

Several treatment-emergent morphological changes in ECGs (including T-wave and ST-segment changes) have been reported in clinical studies. The clinical significance of these changes is unknown [see Adverse Reactions (6)].

In patients with congenital long QT syndrome, patients with a history of significant cardiovascular disease, and patients taking anti-arrhythmic medicines or medicinal products that lead to significant QT prolongation, consider cardiovascular monitoring of ECGs at baseline and periodically during treatment.

Confirm that potassium and magnesium levels are within normal range before administration of ISTODAX [see Adverse Reactions (6)].

5.4 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) has been reported to occur in 1% of patients with tumor stage CTCL and 2% of patients with Stage III/IV PTCL. Patients with advanced stage disease and/or high tumor burden are at greater risk, should be closely monitored, and managed as appropriate.

5.5 Use in Pregnancy

There are no adequate and well-controlled studies of ISTODAX in pregnant women. However, based on its mechanism of action and findings in animals, ISTODAX may cause fetal harm when administered to a pregnant woman. In an animal reproductive study, romidepsin was embryocidal and resulted in adverse effects on the developing fetus at exposures below those in patients at the recommended dose of 14 mg/m²/week. If this drug is used during pregnancy, or if the patient becomes pregnant while taking ISTODAX, the patient should be apprised of the potential hazard to the fetus [see Use in Specific Populations (8.1)].

6 ADVERSE REACTIONS

The following adverse reactions are described in more detail in other sections of the prescribing information.

- **Myelosuppression** [see Warnings and Precautions (5.1)]
- **Infections** [see Warnings and Precautions (5.2)]
- **Electrocardiographic Changes** [see Warnings and Precautions (5.3)]
- **Tumor Lysis Syndrome** [see Warnings and Precautions (5.4)]

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.

Cutaneous T-Cell Lymphoma

The safety of ISTODAX was evaluated in 185 patients with CTCL in 2 single-arm clinical studies in which patients received a starting dose of 14 mg/m². The mean duration of treatment in these studies was 5.8 months (range: <1 to 83.4 months).

**Common Adverse Reactions**

Table 1 summarizes the most frequent adverse reactions (>20%) regardless of causality using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 3.0). Due to methodological differences between the studies, the AE data are presented separately for Study 1 and Study 2. Adverse reactions are ranked by their incidence in Study 1. Laboratory abnormalities commonly reported (>20%) as adverse reactions are included in Table 1.

### Table 1. Adverse Reactions

<table>
<thead>
<tr>
<th>Study 1 (n=102)</th>
<th>Study 2 (n=83)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any adverse reactions (%)</strong></td>
<td><strong>Any adverse reactions (%)</strong></td>
</tr>
<tr>
<td>All grades</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>Any adverse reactions</td>
<td>99 (97)</td>
</tr>
<tr>
<td>Nausea</td>
<td>57 (56)</td>
</tr>
<tr>
<td>Anemia/Fatigue</td>
<td>54 (53)</td>
</tr>
<tr>
<td>Infections</td>
<td>47 (46)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>35 (34)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>23 (23)</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>22 (22)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20 (20)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>20 (20)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>19 (19)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>17 (17)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>15 (15)</td>
</tr>
<tr>
<td>Constipation</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Dermatitis/Exfoliative</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>4 (4)</td>
</tr>
</tbody>
</table>

(continued)
**Table 1. Adverse Reactions Occurring in >20% of Patients in Either ETCL Study (N=185)**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Study 1 (n=102)</th>
<th>Study 2 (n=83)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>4 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>4 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>3 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>3 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Hypoaubminemia</td>
<td>3 (3)</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>ST-T wave changes</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Lactic acidemia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Serious Adverse Reactions**

Infections were the most common type of SAE reported in both studies with 8 patients (8%) in Study 1 and 16 patients (31%) in Study 2 experiencing a serious infection. Serious adverse reactions reported in >2% of patients in Study 1 were sepsis and pyrexia (3%). In Study 2, serious adverse reactions in >2% of patients were fatigue (7%), supraventricular arrhythmia, central line infection, neutropenia (6%), hypotension, hypothermia (5%), hypoglycemia (2%), ventricular arrhythmia, thrombocytopenia, anemia, renal failure, dehydration, pyrexia, aspartate aminotransferase increased, sepsis, catheter related infection, hypophosphatemia and dyspepsia (4%).

Most deaths were due to disease progression. In Study 1, there were two deaths due to cardiopulmonary failure and acute renal failure. In Study 2, there were six deaths due to infection (4%), myocardial ischemia, and acute respiratory distress syndrome.

**Discontinuations**

Discontinuations due to an adverse event occurred in 21% of patients in Study 1 and 11% in Study 2. Discontinuations occurring in at least 2% of patients in either study included infection, fatigue, dyspepsia, QT prolongation, and hypoglycemia.

**6.2 Postmarketing Experience**

No additional safety signals have been observed from postmarketing experience.

**7. DRUG INTERACTIONS**

**7.1 Warfarin or Coumarin Derivatives**

Prolongation of PT and elevation of INR were observed in a patient receiving ISTODAX concomitantly with warfarin. Although the interaction potential between ISTODAX and warfarin has not been formally studied, monitor PT and INR more frequently in patients concurrently receiving ISTODAX and warfarin.

**7.2 Drugs That Inhibit Cytochrome P450 3A4 Enzymes**

Romidepsin is metabolized by CYP3A4. Strong CYP3A4 inhibitors increase concentrations of romidepsin. In a pharmacokinetic drug interaction trial the strong CYP3A4 inhibitor ketoconazole increased romidepsin (AUC∞) by approximately 25%. Monitor for toxicity related to increased romidepsin exposure and follow the dose modifications for toxicity [see Dosage and Administration (2.2)] when romidepsin is initially co-administered with strong CYP3A4 inhibitors (e.g., tacrolimus, iraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole).

**7.3 Drugs That Induce Cytochrome P450 3A4 Enzymes**

Avoid co-administration of ISTODAX with rifampin. In a pharmacokinetic drug interaction trial with co-administered rifampin (a strong CYP3A4 inducer), romidepsin exposure was increased by approximately 80% and 60% for AUC∞ and Cmax, respectively. Typically, co-administration of CYP3A4 inducers decrease concentrations of drugs metabolized by CYP3A4. The increase in exposure seen after co-administration with rifampin is likely due to rifampin’s inhibition of an unidentified hepatic uptake process that is predominantly responsible for the disposition of ISTODAX. It is unknown if other potent CYP3A4 inducers (e.g., dexamethasone, carbamazepine, phenytoin, rifabutin, rifampentine, phenobarbital, St. John’s Wort) would alter the exposure of ISTODAX. Therefore, the use of other potent CYP3A4 inducers should be avoided when possible.

**7.4 Drugs That Inhibit Drug Transport Systems**

Romidepsin is a substrate of the efflux transporter P-glycoprotein (P-gp, ABCB1). If ISTODAX is administered with drugs that inhibit P-gp, increased concentrations of romidepsin are likely, and caution should be exercised.

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

*Pregnancy Category D [see Warnings and Precautions (5.5)].*

There are no adequate and well-controlled studies of ISTODAX in pregnant women. However, based on its mechanism of action and findings in animals, ISTODAX may cause fetal harm when administered to a pregnant woman. In an animal reproductive study, romidepsin was embryocidal and resulted in adverse effects on the developing fetus at exposures below those in patients at the recommended dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking ISTODAX, the patient should be apprised of the potential hazard to the fetus.

Romidepsin was administered intravenously to rats during the period of organogenesis at doses of 0.1, 0.2, or 0.5 mg/kg/day. Substantial resorption or post-implantation loss was observed at the high-dose of 0.5 mg/kg/day, resulting in a maternally toxic dose. Adverse embryo-fetal effects were noted at romidepsin doses of ≥0.1 mg/kg/day, with systemic exposures (AUC) ≥0.2% of the human exposure at the recommended dose of 14 mg/m²/week. Drug-related fetal effects consisted of folded retina, rotated limbs, and incomplete skeletal ossification.

**8.3 Nursing Mothers**

It is not known whether romidepsin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ISTODAX, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

**8.4 Pediatric Use**

The safety and effectiveness of ISTODAX in pediatric patients has not been established.

**8.5 Geriatric Use**

Of the approximately 300 patients with CTCL or PTCL in trials, about 25% were >65 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects; however, greater sensitivity of some older individuals cannot be ruled out.

**8.6 Hepatic Impairment**

No dedicated hepatic impairment study for ISTODAX has been conducted. Mild hepatic impairment does not alter pharmacokinetics of romidepsin based on a population pharmacokinetic analysis. Patients with moderate and severe hepatic impairment should be treated with caution.

**8.7 Renal Impairment**

No dedicated renal impairment study for ISTODAX has been conducted. Based upon the population pharmacokinetic analysis, renal impairment is not expected to significantly influence drug exposure. The effect of end-stage renal disease on romidepsin pharmacokinetics has not been studied. Thus, patients with end-stage renal disease should be treated with caution.

**10 OVERDOSAGE**

No specific information is available on the treatment of overdosage of ISTODAX. Toxicities in a single-dose study in rats or dogs, at intravenous romidepsin doses up to 22fold the recommended human dose based on the body surface area, included irregular respiration, irregular heartbeat, staggering, gait, tremor, and tonic convulsions. In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., clinical monitoring and supportive therapy, if required. There is no known antidote for ISTODAX and it is not known if ISTODAX is dialyzable.

**17 PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (Patient Information).

- **Instructions**
  - Nausea and Vomiting
    - Advise patients that nausea and vomiting are common following treatment with ISTODAX. Prophylactic antiemetics are recommended for all patients.
    - Advise patients to report symptoms so that appropriate treatment can be instituted [see Adverse Reactions (6)].
  - Low Blood Counts
    - Advise patients that treatment with ISTODAX can cause low blood counts and that frequent monitoring of hematologic parameters is required. Patients should be instructed to report fever or other signs of infection, significant fatigue, shortness of breath, or bleeding [see Warnings and Precautions (5.1)].
  - Infections
    - Advise patients that infections may occur during treatment with ISTODAX. Advise patients to report fever, cough, shortness of breath with or without chest pain, burning on urination, flu-like symptoms, muscle aches, or worsening skin problems. Advise patients to report any previous history of hepatitis B before starting romidepsin [see Warnings and Precautions (5.2)].
  - Tumor Lysis Syndrome
    - Advise patients of the risk of tumor lysis syndrome (especially those with advanced stage disease and/or high tumor burden) to maintain high fluid intake for at least 72 hours after each dose [see Warnings and Precautions (5.4)].
  - Use in Pregnancy
    - If pregnancy occurs during treatment with ISTODAX, female patients should be advised to seek immediate medical advice and counseling [see Warnings and Precautions (5.5)].
    - Patients should be instructed to read the patient insert carefully.

Manufactured for: Celgene Corporation, Summit, NJ 07901
Manufactured by: Ben Venue Laboratories, Inc., Bedford, OH 44146 or Baxter Oncology GmbH, Halle/Westfalen, Germany

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Pat. www.celgene.com/therapies IST_CTCCL_HCP_B5v007 7/2016
First Analysis of an International Double-Blind Randomized Phase III Study of Lenalidomide Maintenance in Elderly Patients With DLBCL Treated With R-CHOP in First Line, the REMARC Study From LYSA

For elderly patients with diffuse large B-cell lymphoma (DLBCL), standard first-line therapy consists of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). However, approximately 30% of patients will require treatment for relapsed disease. Dr Catherine Thieblemont presented results from the international, multicenter, double-blind, phase 3 REMARC trial (Study of Lenalidomide Maintenance Versus Placebo in Responding Elderly Patients With DLBCL and Treated With R-CHOP), which evaluated lenalidomide maintenance in elderly DLBCL patients who had achieved a response to R-CHOP. The study enrolled patients ages 60 to 80 years with previously untreated DLBCL, stage IIIIB follicular lymphoma, or transformed lymphoma. Patients received standard R-CHOP therapy, administered as either six 21-day cycles or eight 14-day cycles. Patients who showed a partial response (PR) or complete response (CR) were randomly assigned to receive 24 months of maintenance lenalidomide (25 mg daily for 21 of every 28 days) or placebo. The study’s primary endpoint was progression-free survival (PFS), based on independent, centralized review. Secondary endpoints were safety, PR-to-CR conversion rate, and overall survival (OS).

The study included 784 patients; 437 were enrolled before receiving R-CHOP and 347 had completed 6 or 8 cycles. At the time of diagnosis, the patients had a median age of 68 years (range, 58-80 years), 44% were older than 70 years, and 56% of patients were male. The age-adjusted international prognostic index was high in 57.5% of patients and low in 38.5% of patients. (Data were lacking for 4% of patients.)

After treatment with R-CHOP, CRs were reported in 495 patients and PRs in 152. These patients were then randomly assigned to receive maintenance treatment with lenalidomide (n=323) or placebo (n=327). (Three patients with stable or progressive disease were erroneously randomly assigned into the lenalidomide arm.)

After a median follow-up of 40 months, median PFS was not reached with lenalidomide vs 58.8 months with placebo (hazard ratio [HR], 0.708; 95% CI, 0.537-0.933; P=.0135; Figure 1). The rate of conversion from PR to CR was 21% (18 patients) in the lenalidomide arm vs 14% (13 patients) in the placebo arm.

After a median follow-up of 52 months, OS was similar in both arms (HR, 1.22; 95% CI, 0.86-1.72; P=.2640). The lack of a difference in OS was not explainable by lymphoma relapse, the development of secondary cancers, or safety issues in the lenalidomide arm.
The median time from the last dose of study drug to death was 277 days (range, 20–1291 days) in the lenalidomide arm vs 334 days (range, 41–1594 days) in the placebo arm. During maintenance treatment, the most common grade 3/4 adverse events (AEs) were neutropenia (56% with lenalidomide vs 22% with placebo), rash (5% vs 1%), infection (8% vs 6%), and thrombocytopenia (3% vs 1%). Toxicity led to study drug discontinuation in 59% of patients receiving lenalidomide vs 40% of patients receiving placebo ($P < .001$). Patients received a median of 15 lenalidomide cycles vs 25 placebo cycles ($P < .001$).

References

Obinutuzumab-Based Induction and Maintenance Prolongs Progression-Free Survival (PFS) in Patients With Previously Untreated Follicular Lymphoma: Primary Results of the Randomized Phase 3 GALLIUM Study

Follicular lymphoma makes up approximately 70% of indolent non-Hodgkin lymphoma (NHL) cases and is considered incurable. High response rates can be achieved with standard first-line therapy, but ever-shorter remission intervals are achieved with each successive treatment. Rituximab is an anti-CD20 antibody that dramatically improves outcomes in patients with follicular lymphoma when added to first-line induction chemotherapy and as maintenance therapy. Randomized clinical trials that investigated the addition of rituximab to various types of chemotherapy demonstrated improvements in objective response rate (ORR), PFS, and OS. In patients with advanced, symptomatic follicular lymphoma, median PFS is now longer than 6 years, and median OS has reached at least 12 years. To achieve further survival improvements for patients with this incurable disease, rituximab was reengineered by modifying glycosylation of the Fc fragment and by amino acid substitution, yielding a 100-fold increase in antibody-directed cellular toxicity and a concomitant decrease in complement-directed cytotoxicity.

Two phase 2 clinical trials showed...
that obinutuzumab plus lenalidomide or chemotherapy was active in patients with relapsed or refractory indolent NHL, and the addition of obinutuzumab to bendamustine prolonged PFS compared with bendamustine alone in patients with rituximab-refractory indolent NHL.6-8

GALLIUM (A Study of Obinutuzumab [RO5072759] Plus Chemotherapy in Comparison With MabThera/Rituxan [Rituximab] Plus Chemotherapy Followed by GA101 or MabThera/Rituxan Maintenance in Patients With Untreated Advanced Indolent Non-Hodgkin’s Lymphoma) compared the efficacy and safety of obinutuzumab vs rituximab when added to chemotherapy in patients with previously untreated indolent NHL.9 The open-label, international, phase 3 trial enrolled adults with treatment-naive, CD20-positive follicular lymphoma of grade 1 to 3a or splenic, nodal or extranodal marginal zone lymphoma of stage III/IV or bulky stage II disease. Dr Robert Marcus presented results for patients with follicular lymphoma at the plenary session of the 2016 American Society of Hematology (ASH) meeting.9

There is no international consensus regarding optimal first-line chemotherapy for patients with follicular lymphoma. Therefore, each institution was permitted to select an induction chemotherapy backbone for its patients from among the following regimens: CHOP; cyclophosphamide, vincristine, and prednisone (CVP); or bendamustine. Patients received eight 21-day cycles of CHOP or CVP or six 28-day cycles of bendamustine. Rituximab (375 mg/m²) was administered on day 1 of each treatment cycle. Obinutuzumab (1000 mg) was administered on days 1, 8, and 15 of treatment cycle 1, and thereafter on day 1 only. Following induction, patients with a PR or CR continued maintenance treatment with the same antibody administered every 8 weeks for 2 years. The study was designed to have an 80% power to detect an HR of 0.74 in patients with follicular lymphoma, reflecting a projected improvement in median PFS from 6.0 years to at least 8.1 years, with a projected requirement of 370 PFS events. The primary endpoint was investigator-assessed PFS. Secondary endpoints included PFS by independent review, OS, time to next treatment, and safety.

GALLIUM randomly assigned 1202 follicular lymphoma patients to treatment with obinutuzumab or rituximab. The median age of the follicular lymphoma population was 59 years (range, 23-88 years), and 53% of patients were female. At diagnosis, 91% of patients had Ann Arbor stage III/IV disease, one-third had B symptoms, and 42% had high-risk disease. There was involvement of the bone marrow in 52% and extranodal involvement in 66%. Bulky disease was reported in 44% of patients. In approximately 60% of patients, the induction therapy was bendamustine.

A preplanned interim efficacy analysis was performed with a data cutoff of January 31, 2016, at which point 245 PFS events had occurred. The analysis demonstrated superior PFS with obinutuzumab, leading to unblinding of the study based on the recommendation of the data monitoring committee.

Based on investigator assessment, the ORR at the end of induction treatment was 86.9% with rituximab vs 88.5% with obinutuzumab, including CR rates of 23.8% vs 19.5%, respectively. After a median follow-up of 34.5 months, the estimated 3-year PFS by investigator assessment was 73.3% with rituximab vs 80.0% with obinutuzumab (HR, 0.66; 95% CI, 0.51-0.85; P=.0012; Figure 2). Three-year PFS was also superior with
obinutuzumab based on assessment by independent review (HR, 0.71; 95% CI, 0.54-0.93; \( P = .014 \)). OS was similar for treatment with either antibody (\( P = .21 \)).

AEs of grade 3 or higher were reported in 74.6% of patients treated with obinutuzumab vs 67.8% of those treated with rituximab. Grade 3/4 febrile neutropenia was observed in 6.9% vs 4.9% of patients, respectively. Obinutuzumab was associated with increased rates of grade 3/4 infection (20.0% vs 15.6%), grade 3/4 infusion-related reactions (12.4% vs 6.7%), and serious AEs (46.1% vs 39.9%). The rate of fatal AEs was higher than expected in both treatment arms (4.0% vs 3.4%, respectively).

References


Rituximab Plus Lenalidomide Versus Rituximab Monotherapy in Untreated Follicular Lymphoma Patients in Need of Therapy. First Analysis of Survival Endpoints of the Randomized Phase-2 Trial SAKK 35/10

Lenalidomide in combination with rituximab has demonstrated promising activity in indolent B-cell NHL and mantle cell lymphoma (MCL), improving efficacy over rituximab monotherapy and demonstrating responses in patients who have rituximab-resistant disease. The phase 2 Swiss Group for Clinical Cancer Research (SAKK) 35/10 trial compared rituximab monotherapy vs rituximab plus lenalidomide in previously untreated patients with symptomatic follicular lymphoma. The trial enrolled patients with histologically confirmed follicular lymphoma of grade 1, 2, or 3a who required systemic therapy. The primary endpoint was the rate of CR, including unconfirmed CR (CRu). The study was designed to detect an increase of at least 20% for rituximab plus lenalidomide over rituximab alone with 90% power and a type I error of 0.10. All patients received rituximab (375 mg/m²) on day 1 of weeks 1, 2, 3, 4, 12, 13, 14, and 15, with or without lenalidomide (15 mg daily). Lenalidomide was administered from 14 days before initiation of rituximab until 14 days after the last administration of rituximab. Treatment was discontinued in patients who did not achieve a reduction of at least 25% in the sum of the products of tumor diameters at week 10.

The study randomly assigned 154 patients to the 2 arms. In the rituximab monotherapy arm, patients had a median age of 63 years, and 52% had stage IV disease. In the combination arm, patients had a median age of 61 years, and 48% had stage IV disease. In each arm, 47% of patients had poor-risk disease based on the Follicular Lymphoma International Prognostic Index.

The inclusion of lenalidomide...
increased the CR/CRu rate based on independent review of computed tomography scans (61% vs 36%) and by investigator assessment (36% vs 25%). The CR/CRu rate at 30 months was also superior with the combination regimen (42% vs 19%; \(P = .001\)). The median time to next treatment was also improved in patients treated with lenalidomide plus rituximab (not reached vs 2.1 years; \(P = .02\); Figure 3).

After a median follow-up of 3.5 years, median PFS was not reached for combination treatment vs 2.3 years for monotherapy. This difference was not statistically significant. At 3 years, median OS was 93% for patients treated with lenalidomide plus rituximab vs 92% for those treated with rituximab monotherapy. However, the trial was not powered to detect differences in survival.

Patients in the combination arm experienced more AEs of grade 3 or higher than those who received monotherapy (56% vs 22%). These events included neutropenia (23% vs 7%), maculopapular rash (5% vs 0), and thrombocytopenia (3.9% vs 0).

**References**


Brentuximab Vedotin Demonstrates Significantly Superior Clinical Outcomes in Patients With CD30-Expressing Cutaneous T Cell Lymphoma Versus Physician’s Choice (Methotrexate or Bexarotene): The Phase 3 ALCANZA Study

Brentuximab vedotin is approved for the treatment of relapsed Hodgkin lymphoma and systemic anaplastic large-cell lymphoma (ALCL) and as maintenance therapy in patients with Hodgkin lymphoma who have undergone autologous stem cell transplant. Two single-arm, phase 2 studies of brentuximab vedotin in patients with cutaneous T-cell lymphoma showed acceptable safety and marked clinical activity, yielding ORRs of approximately 70%. ALCANZA (A Phase 3 Trial of Brentuximab Vedotin [SGN-35] Versus Physician’s Choice [Methotrexate or Bexarotene] in Patients With CD30-Positive Cutaneous T-Cell Lymphoma) is a randomized, open-label, phase 3 trial that investigated brentuximab vedotin vs standard of care in patients with previously treated CD30-positive mycosis fungoides or primary cutaneous ALCL. Patients were enrolled from 52 centers in 13 countries. Enrolled patients had at least 10% CD30-positive cells on either neoplastic cells or lymphoid infiltrate by central review. Mycosis fungoides patients were required to have 2 biopsies and to have received at least 1 prior systemic therapy. Patients with primary cutaneous ALCL were required to have received prior radiotherapy or at least 1 prior systemic therapy. The study excluded patients who had previously progressed on methotrexate or bexarotene.

Study participants were stratified by diagnosis and then randomly assigned to receive brentuximab vedotin (1.8 mg/kg every 3 weeks) or physician’s choice of methotrexate (5-50 mg weekly) or bexarotene (300 mg/m² daily) for up to 48 weeks in 21-day cycles. Methotrexate and bexarotene were managed as the standard of care, with dose adjustments to achieve the maximum tolerated effective dose. The primary endpoint was the proportion of patients achieving an objective response lasting at least 4 months (ORR4), based on independent review following consensus guidelines. This endpoint encompassed skin evaluation, radiographic assessment, and Sézary cell enumeration, and was selected to incorporate both response rate and duration. Key secondary endpoints included the CR rate, PFS, and symptom burden as measured by the symptom domain of the Skindex-29 quality-of-life instrument.

The intent-to-treat population included 64 patients in each arm. Patients had a median age of 60.5 years (range, 22-83 years), and 56% were male. At baseline, the average CD30 expression was a median of 32% (range, 3-100%), and the median number of prior systemic therapies was 2 (range, 0-11). Approximately one-fourth of patients in each arm had primary cutaneous ALCL. Among these patients, there were more cases of extracutaneous disease in the brentuximab vedotin arm (44% vs 27%). Patients received a median of 12 cycles of treatment.

ABSTRACT SUMMARY CheckMate 205 Update With Minimum 12-Month Follow Up: A Phase 2 Study of Nivolumab in Patients With Relapsed/Refractory Classical Hodgkin Lymphoma

The phase 2 CheckMate study evaluated nivolumab treatment in patients with classical Hodgkin lymphoma who progressed after autologous stem cell transplant (Abstract 1110). Cohort A included patients who had not been treated with subsequent brentuximab vedotin, and cohort B included patients who had been treated with brentuximab vedotin. Patients had a median age of 35 years, an ECOG performance status of 0 or 1, and a median of 3 lines of prior therapy (range, 2-15). In cohorts A (n=63) and B (n=80), grade 3/4 AEs were observed in 11% vs 30% of patients, respectively. In cohort B, after a median follow-up of 15.4 months, 54% of patients were still receiving treatment, and the independently assessed ORR was 68% (95% CI, 56%-78%), including 8% CRs. Median PFS was 14.8 months (95% CI, 11 months to not reached), and median OS was not reached. In cohort A, patients had a minimum follow-up of 9 months. The independently assessed ORR was 68%, including 22% CRs. Median PFS was not reached (95% CI, 11 months to not reached), and 9-month OS was 97%.
of brentuximab vedotin, 6 of bexarotene, and 3 of methotrexate.

After a median follow-up of 17.5 months, the trial met its primary endpoint, demonstrating a superior ORR with brentuximab vedotin (56.3% vs 12.5%; \( P < 0.001 \)). Brentuximab vedotin was also superior in terms of CR rate (15.6% vs 1.6%; \( P = 0.0046 \)) and median PFS (16.7 months vs 3.5 months; HR, 0.270; 95% CI, 0.169-0.430; \( P < 0.001 \); Figure 4). Brentuximab vedotin yielded a superior ORR in patients with mycosis fungoides (50% vs 10%) and those with primary cutaneous ALCL (75% vs 20%), as well as in subgroups based on mycosis fungoides disease stage, extracutaneous involvement (for primary cutaneous ALCL patients), performance status, and sex. Brentuximab vedotin was also associated with a superior PFS across key subgroups. As revealed by Skinindex-29 symptom domain scores, brentuximab vedotin yielded a greater improvement in skin symptoms in the overall study population (-27.96 points vs -8.62 points; \( P < 0.001 \)), reflecting a meaningful improvement in quality of life.

Toxicity data were consistent with the established safety profile. Rates of grade 3 or higher AEs were 41% with brentuximab vedotin vs 47% with physician’s choice. In both arms, 29% of patients experienced serious AEs. The brentuximab vedotin arm had a higher proportion of patients who discontinued study treatment owing to an AE (24% vs 8%), reflected largely by the increase in peripheral neuropathy (14% vs 0%). Four patients (6%) in the brentuximab vedotin arm died within 30 days of receiving the last dose of study treatment. One patient, with primary cutaneous ALCL, died from multiple organ dysfunction syndrome caused by tumor necrosis induced by brentuximab vedotin. Peripheral neuropathy was the most common treatment-emergent AE of any grade and occurred in 67% of patients treated with brentuximab vedotin vs 6% of patients in the comparator arm. Other common treatment-emergent AEs of any grade included nausea (36% with brentuximab vedotin vs 13% with the control), diarrhea (29% vs 6%), and fatigue (29% vs 27%). Rates of peripheral neuropathy in the brentuximab vedotin arm varied according to grade, at 26% for grade 1, 32% for grade 2, 9% for grade 3, and 0% for grade 4 (vs 2%, 5%, 0%, and 0%, respectively, for the control). After a median follow-up of 22.9 months, peripheral neuropathy had improved or resolved in 82% of affected patients in the brentuximab vedotin arm.

References

2. Duvic M, Tetzlaff MT, Gangar P, Clos AL, Sui D, Talpur R. Results of a phase II trial of brentuximab

![Figure 4](image-url)

**Figure 4.** In the phase 3 ALCANZA trial, brentuximab vedotin was associated with superior PFS. ALCANZA, A Phase 3 Trial of Brentuximab Vedotin (SGN-35) Versus Physician’s Choice (Methotrexate or Bexarotene) in Patients With CD30-Positive Cutaneous T-Cell Lymphoma; PFS, progression-free survival. Adapted from Kim YH et al. ASH abstract 182. Blood. 2016;128(suppl 22).4

**MAGNIFY: Phase IIIb Randomized Study of Lenalidomide Plus Rituximab (R²) Followed By Lenalidomide Vs. Rituximab Maintenance in Subjects With Relapsed/Refractory Follicular, Marginal Zone, or Mantle Cell Lymphoma**

Although rituximab has yielded immense gains as frontline therapy, a large proportion of NHL patients have refractory disease, and devising effective treatment for relapsed and refractory NHL continues to present a difficult challenge. In recent studies, the combination of rituximab plus lenalidomide has demonstrated high activity and acceptable tolerability in patients with indolent NHL or MCL, in both the treatment-naive and relapsed/refractory settings.¹,²

Dr David Andorsky presented interim data from the phase 3 MAGNIFY trial (Lenalidomide Plus Rituximab Followed by Lenalidomide Versus Rituximab Maintenance for Relapsed/Refractory Follicular, Marginal Zone or Mantle Cell Lymphoma). The open-label, multicenter study evaluated induction with rituximab plus lenalidomide followed by maintenance monotherapy in patients with relapsed or refractory grade 1 to 3b follicular lymphoma, MCL, or marginal zone lymphoma.³ Eligible patients had measurable disease and had received at least 1 prior therapy. Patients received 12 cycles of oral lenalidomide (20 mg daily) on days 1 to 21 of each 28-day cycle plus intravenous rituximab (375 mg/m²) on days 1, 8, 15, and 22 of cycle 1 and the same dose of rituximab on day 1 of cycles 3, 5, 7, 9, and 11.

After induction therapy, patients with stable disease or better were randomly assigned to receive maintenance therapy consisting of lenalidomide plus rituximab followed by optional lenalidomide monotherapy (arm A) or rituximab monotherapy (arm B). For

**ABSTRACT SUMMARY DYNAMO: A Phase 2 Study Demonstrating the Clinical Activity of Duvelisib in Patients With Relapsed Refractory Indolent Non-Hodgkin Lymphoma**

The phase 2 DYNAMO trial (A Phase 2 Study of Duvelisib in Subjects With Refractory Indolent Non-Hodgkin Lymphoma) evaluated the efficacy and safety of duvelisib, an oral inhibitor of the phosphoinositide 3–kinases δ and γ, in patients with refractory, indolent NHL (Abstract 1218). Patients were treated with duvelisib at 25 mg twice daily. The study population for the final analysis included 83 patients with follicular lymphoma, 28 with small lymphocytic lymphoma, and 18 with marginal zone lymphoma. Patients had a median age of 65 years, and had received a median of 3 prior regimens (range, 1-18). The median ORR was 46%, with no CRs. After a median follow-up of 11.5 months, the median PFS was 8.4 months (95% CI, 5.8-11.3 months), and the median OS was 18.4 months (95% CI, 15.7 months to not reached). The most common AEs of grade 3 or higher were transient cytopenias and diarrhea. Among the 6 reported deaths, 4 were considered related to treatment.

Clinical Advances in Hematology & Oncology  Volume 15, Issue 3, Supplement 3  March 2017  13
maintenance therapy, patients in arm A received 18 cycles of lenalidomide (10 mg daily) on days 1 to 21 of each 28-day cycle plus rituximab (375 mg/m²) on day 1 of each odd-numbered cycle, followed by optional lenalidomide monotherapy (10 mg daily) on days 1 to 21 of each 28-day cycle until disease progressed. Patients in arm B received 18 cycles of rituximab (375 mg/m²) on day 1 of odd-numbered cycles as maintenance treatment. The primary endpoint was PFS, with secondary endpoints of safety, OS, and response rates.

The enrolled population included 104 patients with follicular lymphoma, 27 with marginal zone lymphoma, 22 with MCL, and 2 with transformed lymphoma. Most patients (55%) had stage IV disease, and 35% were refractory to rituximab. The median number of prior therapies was 2 (range, 1-10).

At the ASH meeting, data were presented for the induction period. In 121 patients evaluable for response, the ORR was 60%. The CR rate was 15%, the CRu rate was 24%, and the PR rate was 21% (Table 1). Stable disease was reported in 28% of patients. Responses were observed in all histologies.

Among the safety population of 152 patients, treatment-emergent AEs led to dose reduction or interruption in 59% of the lenalidomide arm and 22% of the rituximab arm. The most common grade 3/4 AEs during induction were neutropenia (30%), leukopenia (9%), thrombocytopenia (8%), and fatigue (6%). Most of the deaths that occurred during the study were attributable to progressive disease.

**References**


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**Table 1. Best Response During Induction With Rituximab and Lenalidomide in the MAGNIFY Trial**

<table>
<thead>
<tr>
<th>Best Response, n (%)</th>
<th>Follicular Lymphoma, a n (%)</th>
<th>Marginal Zone Lymphoma, n (%)</th>
<th>Mantle Cell Lymphoma, n (%)</th>
<th>Evaluable, b n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>83</td>
<td>22</td>
<td>16</td>
<td>121</td>
</tr>
<tr>
<td>Complete response</td>
<td>11 (13)</td>
<td>4 (18)</td>
<td>3 (19)</td>
<td>18 (15)</td>
</tr>
<tr>
<td>Complete response, unconfirmed</td>
<td>20 (24)</td>
<td>6 (27)</td>
<td>3 (19)</td>
<td>29 (24)</td>
</tr>
<tr>
<td>Partial response</td>
<td>23 (28)</td>
<td>2 (9)</td>
<td>1 (6)</td>
<td>26 (21)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>22 (27)</td>
<td>9 (41)</td>
<td>3 (19)</td>
<td>34 (28)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>7 (8)</td>
<td>1 (5)</td>
<td>6 (38)</td>
<td>14 (12)</td>
</tr>
<tr>
<td>Overall response rate</td>
<td>54 (65)</td>
<td>12 (55)</td>
<td>7 (44)</td>
<td>73 (60)</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>31 (37)</td>
<td>10 (45)</td>
<td>6 (38)</td>
<td>47 (39)</td>
</tr>
</tbody>
</table>

aIncludes 1 patient with transformed lymphoma.

bFor 34 patients in the trial, it was too early to assess efficacy at the time of this analysis.

MAGNIFY, Lenalidomide Plus Rituximab Followed by Lenalidomide Versus Rituximab Maintenance for Relapsed/Refractory Follicular, Marginal Zone or Mantle Cell Lymphoma.

Lenalidomide Maintenance After Front Line Therapy Substantially Prolongs Progression Free Survival in High Risk CLL: Interim Results of a Phase 3 Study (CLLM1 Study of the German CLL Study Group)

In patients with chronic lymphocytic leukemia (CLL), minimal residual disease (MRD) and genetic markers can inform prognosis following first-line chemo-immunotherapy. Achievement of a CR is associated with superior PFS and OS. Highly sensitive techniques are used to accurately quantitate MRD after treatment, and detection of residual malignant cells requires subsequent therapy to obtain durable CRs. Effective maintenance regimens with acceptable tolerability are therefore under evaluation. Dr Anna Maria Fink presented results of the first interim analysis of the phase 3 CLLM1 study, which evaluated lenalidomide vs placebo as maintenance therapy in high-risk CLL patients who achieved a PR or better after at least 4 cycles of first-line treatment.

First-line therapy was the investigator’s choice of fludarabine, cyclophosphamide, and rituximab; fludarabine and rituximab; bendamustine and rituximab; or fludarabine and cyclophosphamide. Patients were defined as being at high risk of progression after first-line therapy if they had MRD levels of at least $10^{-2}$; or MRD levels between $10^{-4}$ and $10^{-2}$ plus either del(17p), unmutated immunoglobulin heavy chain variable (IgHV), or mutated TP53. The primary endpoint was PFS as assessed by independent review. For maintenance treatment, patients were stratified by risk factors and then randomly assigned 2:1 to receive lenalidomide or placebo. Maintenance lenalidomide was administered at 5 mg daily during cycle 1 and, if tolerated, was escalated to 10 mg daily during cycles 2 to 6 and then to 15 mg daily in cycles 7 to 12. Among patients who achieved negative MRD after cycle 12, lenalidomide was continued at 15 mg daily for cycles 13 to 18. For patients with positive MRD after cycle 12, the lenalidomide dose was increased to 20 mg daily for cycles 13 to 18. Another assessment of MRD was made after cycle 18 to determine the dose for all subsequent cycles until disease progression. Patients who were MRD-negative after cycles 12 and 18 continued on lenalidomide at 15 mg daily. Patients who achieved MRD-negativity only after cycle 18 received lenalidomide at 20 mg daily. Patients who were still MRD-positive after cycle 18 received lenalidomide at 25 mg daily. Patients in the placebo arm received matching doses.

The first interim analysis included data from 89 patients, including 60 patients randomly assigned to lenalidomide and 29 randomly assigned to placebo. Patients had a median age of 64 years (range, 32-80 years), and a median cumulative illness rating scale score of 2 (range, 0-8). Most patients (85.2%) were male. At the time of randomization, 90.2% had unmutated IgHV, 20.5% had TP53 mutation, and 11.4% had del(17p). The MRD level was at least $10^{-2}$ in 37% of patients. Frontline treatment consisted of bendamustine plus rituximab in approximately 60% of patients, and of fludarabine, cyclophosphamide, and rituximab in approximately 39% of patients. After first-line treatment, most patients achieved a PR (87.7% of those in the lenalidomide group and 89.6% of those in the placebo group).

ABSTRACT SUMMARY
Phase III Randomized Study of R-CHOP Versus DA-EPOCH-R and Molecular Analysis of Untreated Diffuse Large B-Cell Lymphoma: CALGB/Alliance 50303

A phase 3 trial compared R-CHOP vs dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin plus rituximab (EPOCH-R) in patients with newly diagnosed DLBCL (Abstract 469). Patients had stage 2 or higher disease, and characteristics were similar in both treatment arms. The analysis provided efficacy data for 233 patients in the R-CHOP arm and 232 patients in the dose-adjusted EPOCH-R arm. In the dose-adjusted EPOCH-R arm, event-free survival rates were 79% at 3 years and 66% at 5 years. These rates were 81% and 69% with R-CHOP. Overall survival at 3 years was 85% in both arms. ORRs were approximately 89% in each arm, with CR rates of 62% for R-CHOP and 61% for dose-adjusted EPOCH-R. There was more toxicity among the patients treated with dose-adjusted EPOCH-R. Grade 3 to 5 neutropenia occurred in 96% of the EPOCH-R arm vs 68% of the R-CHOP arm. Patients treated with dose-adjusted EPOCH-R were more likely to discontinue treatment early (6.5% vs 1.5%; P=.004).
months, median PFS was not reached in patients who received lenalidomide maintenance therapy vs 13.3 months in those who received placebo (Figure 5). Lenalidomide maintenance was associated with a risk reduction of 80% (HR, 0.148; 95% CI, 0.063-0.347; \( P < 0.0001 \)). The benefit associated with lenalidomide maintenance was observed in patients with high or intermediate MRD at baseline. In patients with MRD levels of at least 10^{-4} and less than 10^{-2}, median PFS was not reached with lenalidomide vs 19.4 months with placebo (HR, 0.125; 95% CI, 0.033-0.477). In patients with MRD levels of 10^{-2} or greater, median PFS was 32.3 months with lenalidomide vs 3.7 months with placebo (HR, 0.167; 95% CI, 0.054-0.510). OS was similar in the 2 arms (HR, 0.262; 95% CI, 0.024-2.891). During the study, several patients in the lenalidomide arm achieved MRD-negative status vs none in the placebo arm (Figure 6).

**Figure 5.** In the phase 3 CLLM1 study, median PFS as assessed by independent review was not reached in patients who received lenalidomide maintenance therapy vs 13.3 months for those who received placebo after a median follow-up of 17.5 months. PFS, progression-free survival. Adapted from Fink AM et al. ASH abstract 229. *Blood*. 2016;128(suppl 22).

**Figure 6.** During the phase 3 CLLM1 study, several patients in the lenalidomide arm achieved MRD-negative status vs none in the placebo arm. MRD, minimal residual disease. Adapted from Fink AM et al. ASH abstract 229. *Blood*. 2016;128(suppl 22).
During the maintenance phase, patients received a median of 11.1 cycles of lenalidomide and a median of 8.3 cycles of placebo. More patients in the placebo arm discontinued treatment (72.4% vs 42.0%). In the lenalidomide arm, treatment discontinuations were attributed to AEs (32.1%), disease progression (7.1%), and other reasons (3.6%). These rates were 20.7%, 44.8%, and 6.9%, respectively, in the placebo arm. AEs of any grade that were more common with lenalidomide included neutropenia (30% vs 3%), gastrointestinal disorders (55% vs 28%), nervous system disorders (30% vs 14%), respiratory disorders (36% vs 14%), and skin disorders (61% vs 28%). Rates of venous thrombotic events were low owing to the use of low-dose aspirin or other anticoagulant therapy. Based on the results from the first interim analysis, the data monitoring safety board recommended unblinding of the study.

References

Results of the Phase 3 Study of Lenalidomide Versus Placebo As Maintenance Therapy Following Second-Line Treatment for Patients With Chronic Lymphocytic Leukemia (the CONTINUUM Trial)

Because CLL remains incurable with current regimens, most patients require multiple lines of therapy, and a key goal of treatment is to achieve durable remissions.1,2 For patients with refractory disease and those who relapse within a short time after completing therapy, alternate regimens are needed. Lenalidomide is active in CLL and has shown promise as maintenance therapy in various hematologic malignancies.3,4 Dr Robin Foà presented results from the multicenter, double-blind, phase 3 CONTINUUM trial (A Study to Evaluate the Efficacy and Safety of Lenalidomide as Maintenance Therapy for Patients With B-Cell Chronic Lymphocytic Leukemia [CLL] Following Second Line Therapy), which investigated lenalidomide vs placebo as maintenance therapy in patients with previously treated CLL.5 Enrolled patients were required to have received prior treatment with a purine analogue, bendamustine, chlorambucil, an anti-CD20 antibody, or a regimen that contained alemtuzumab in the first and/or second line of treatment. All patients had achieved at least a PR with second-line therapy. They had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. Patients were randomly assigned to receive either lenalidomide at 2.5 mg daily or placebo during the
The primary analysis included data obtained through September 30, 2015 from 314 patients. Patients had a median age of 63 years (range, 37-84 years). Approximately 19% of patients were older than 70 years, and 72% were male. Approximately 10% of patients had an MRD-negative CR after their first 28-day cycle. In patients who tolerated treatment, the dose of lenalidomide was escalated to 5 mg daily from cycle 2 onward and to 10 mg daily from cycle 7 onward. At the end of second-line therapy and before randomization, patients were stratified based on response categories of MRD-negative vs PR, nodular PR, CR, or CR with incomplete bone marrow recovery; age (≤70 years vs >70 years); presence vs absence of del(11q), del(17p), and unmutated IGHV; and β-2 microglobulin level (≤0.4 mg/L vs >0.4 mg/L). Primary endpoints included PFS based on independent review and OS. Secondary endpoints included safety, tumor response, response duration, PFS from time of randomization until second disease progression or death, and health-related quality of life.

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months in the placebo arm (HR, 0.46; 95% CI, 0.29-0.70; \( P < .001 \)).

Thirty-six deaths occurred. Grade 3/4 AEs included neutropenia (59.9% with lenalidomide vs 22.7% with placebo), thrombocytopenia (16.6% vs 6.5%), and diarrhea (8.3% vs 0.6%). Grade 3/4 infections occurred in 16.6% vs 10.4% of patients, respectively. Rates of invasive second primary malignancies were 8.3% in the lenalidomide group vs 9.1% in the placebo group, corresponding to an annual incidence rate per 100 patients of 2.99 and 3.44, respectively. There were no clinically meaningful differences in quality of life between the treatment arms.

References


Nivolumab Combined With Ibrutinib for CLL and Richter Transformation: A Phase II Trial

A pproximately 5% of CLL patients will develop Richter transformation, in which CLL transforms into an aggressive lymphoma, most commonly DLBCL. In the majority of DLBCL cases, the disease is clonally related to the original CLL disease, and these patients have a median survival of approximately 1 year. In contrast, patients with clonally unrelated DLBCL have a prognosis that is similar to that of patients with untreated DLBCL. Sequencing has revealed many of the genetic underpinnings of Richter transformation, prompting a search for more effective therapies. T cells from CLL patients show increased expression of programmed death receptor 1 (PD-1), while the ligand, PD-L1, is overexpressed on CLL cells, leading to failure of the antitumor response. In a mouse model, blockade of the immune checkpoint by means of antibodies to PD-L1 prevented the development of CLL while reactivating CD8 T-cell cytotoxicity, normalizing T-cell cytokines, and promoting immune synapse formation. Ibrutinib is an established inhibitor of Bruton tyrosine kinase, but it also binds irreversibly to interleukin-2–inducible kinase and promotes expansion of the population of Th1 cells. In a mouse model of lymphoma, the combination of an anti–PD-L1 antibody and ibrutinib synergistically suppressed tumor growth.

Dr Nitin Jain presented results of an investigator-initiated phase 2 trial of nivolumab, an anti–PD-1 antibody, plus ibrutinib in patients with relapsed/ refractory CLL or Richter transformation. The study’s primary objective was the rate of CRs, including CRs with incomplete bone marrow recovery. Secondary objectives were safety, PFS, and OS. Cohort 1 included patients with relapsed or refractory CLL or Richter transformation. Cohort 2 included CLL patients who achieved a PR after at least 9 months of treatment with ibrutinib. Patients had an ECOG performance status of 0 to 2 and adequate renal and hepatic function. Patients with autoimmune diseases were excluded. Patients in cohort 1 received nivolumab (3 mg/kg every 2 weeks) during cycle 1, with ibrutinib (420 mg daily) added in cycle 2 and both agents administered during subsequent cycles. Patients in cohort 2 were already receiving ibrutinib upon study entry; these patients continued with ibrutinib, and nivolumab (3 mg/kg every 2 weeks) was added from cycle 1 onward.

Cohort 1 included 5 patients with CLL and 5 with Richter transformation. Cohort 2 included 3 patients with CLL. Patients had a median age of 64 years (range, 42-78 years) and had received a median of 1 prior therapy (range, 1-4). Across the entire study population, genetic aberrations included del(17p) or TP53 mutation in 46%, del(13q) in 23%, trisomy 12 in 15%, and del(11q) in 8%. There were no aberrations in 8%.

In cohort 1, a male patient with del(13q) achieved a CR that lasted...
Single-Agent Ibrutinib Demonstrates Efficacy and Safety in Patients With Relapsed/Refractory Marginal Zone Lymphoma: A Multicenter, Open-Label, Phase 2 Study

An open-label, phase 2 trial evaluated single-agent ibrutinib in patients with relapsed/refractory marginal zone lymphoma (Abstract 1213). Ibrutinib was administered at a dosage of 560 mg orally once daily until disease progression or unacceptable toxicity. The trial enrolled 63 patients: 32 with extranodal disease, 17 with nodal disease, and 14 with splenic disease. Patients had an ECOG performance status of 2 or less. Their life expectancy was at least 3 months. Bone marrow involvement was reported in 33%. Prior treatments included radiotherapy in 14% and splenectomy in 6%. The ORR was 46%, which included a CR rate of 3.2%. After a median follow-up of 19.4 months, the median duration of response was not reached (range, 16.7 months to not reached). The median time to initial response was 4.5 months (range, 2.3-16.4 months). The median PFS was 14.2 months (95% CI, 8.3 months to not reached). The median time to initial response was 4.5 months (range, 2.3-16.4 months). The median PFS was 14.2 months (95% CI, 8.3 months to not reached). At a median follow-up of 19.4 months, the OS was not yet reached. The most common AEs of any grade were thrombocytopenia (49%), fatigue (44%), anemia (43%), diarrhea (43%), bruising (41%), and musculoskeletal pain (40%). The most common AEs of grade 3 or 4 included decreases in hemoglobin (13%), decreases in neutrophils (13%), and pneumonia (10%).

Table 2. Responses in a Phase 2 Trial of Nivolumab in CLL

<table>
<thead>
<tr>
<th>Age</th>
<th>FISH</th>
<th>IgHV Status</th>
<th>Prior Therapies</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>55</td>
<td>del(13q)</td>
<td>Mutated</td>
<td>Ofatumumab</td>
<td>CR (10+ months)</td>
</tr>
<tr>
<td>57</td>
<td>Negative</td>
<td>Mutated</td>
<td>Ofatumumab</td>
<td>PR (9+ months)</td>
</tr>
<tr>
<td>42</td>
<td>del(13q)</td>
<td>Unmutated</td>
<td>Rituximab, FCR</td>
<td>PR (8+ months)</td>
</tr>
<tr>
<td>57</td>
<td>del(13q)</td>
<td>Mutated</td>
<td>Ofatumumab</td>
<td>PR (7+ months)</td>
</tr>
<tr>
<td>70</td>
<td>del(17p)</td>
<td>Mutated</td>
<td>Chlorambucil, CVP, FBR</td>
<td>No response</td>
</tr>
</tbody>
</table>

Cohort 1: Patients with relapsed or refractory CLL or Richter transformation

65 del(17p) Unmutated Ibrutinib (13 months) Stable disease
55 del(17p) Unmutated Ibrutinib (26 months) Stable disease
64 del(13q) – Ibrutinib (32 months) Stable disease

Cohort 2: Patients who achieved a PR after at least 9 months of treatment with ibrutinib

CLL, chronic lymphocytic leukemia; CR, complete response; CVP, cyclophosphamide, vincristine, and prednisone; FBR, fludarabine, bendamustine, and rituximab; FCR, fludarabine, cyclophosphamide, rituximab; FISH, fluorescence in situ hybridization; IgHV, immunoglobulin heavy chain variable; PR, partial response.

Adapted from Jain N et al. ASH abstract 59. Blood. 2016;112(suppl 22).7

more than 10 months (Table 2). Three patients in cohort 1 achieved a PR that lasted more than 7 months, including 2 patients with del(13q) and 1 patient with no genetic risk factors. One patient with del(17p) had no response. In cohort 2, all 3 patients had stable disease, 2 patients with del(17p) and 1 patient with del(13q). Among the 5 patients with Richter transformation, 2 patients had a CR for Richter transformation with a concomitant PR for CLL; 1 patient had a PR for CLL; and 2 patients had no response and left the study. A CR for Richter transformation and a PR for CLL was reported in a 66-year-old woman with TP53 mutation and unmutated IgHV. At baseline, this patient had PD-1 overexpressed on the CLL cells, the Richter cells, and T cells. PD-L1 and PD-L2 expression were at least 10% on the patient’s CLL and Richter cells. The second patient with relapsed or refractory CLL and Richter transformation who achieved a response was a 62-year-old woman with del(17p), unmutated IgHV, and a complex karyotype. Her diagnostic lymph node specimen showed B-cell infiltration and high levels of PD-1 expression.

Immune-related AEs included 1 case each of grade 2 pneumonitis and grade 2 thyroiditis. There were no immune-related AEs of grade 3 or higher. No patients discontinued treatment owing to an AE.

References
Advances in Lymphoma and Leukemia From the 2016 American Society of Hematology Annual Meeting and Exposition: Commentary

Nathan H. Fowler, MD

At the 2016 American Society of Hematology (ASH) conference, many exciting studies were presented that highlighted the potential and limitations of several of the most promising new drugs in chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma. Key abstracts provided the results of several long-awaited and potentially practice-changing randomized trials, as well as early clinical data from promising early-phase studies exploring novel drugs in new indications.

Chronic Lymphocytic Leukemia

In CLL, several abstracts evaluated the long-term effects of novel agents, as well as exciting new combinations, in both the frontline and relapsed settings.

Ibrutinib

Dr Julia von Tresckow presented initial results of the CLL2-BIG study.1 This innovative frontline trial evaluated ibrutinib plus GA101 followed by ibrutinib and GA101 maintenance in 61 patients with CLL. Patients with bulky disease also received 2 cycles of bendamustine prior to treatment with ibrutinib and GA101.

The results were impressive, with an overall response rate of 100%. A secondary endpoint of the trial was achievement of negative minimal residual disease (MRD). In this initial report, 29 patients (47.5%) achieved MRD negativity in the peripheral blood at the end of induction. The study also attempts to tackle one of the hottest questions in current CLL therapy: what is the optimal duration of therapy? The study is designed to explore the possibility of discontinuing treatment with a kinase inhibitor—which are otherwise given indefinitely—in patients who achieve MRD negativity. Mature follow-up from this study is eagerly awaited.

Dr Susan O’Brien presented long-term follow-up from the early-phase studies of ibrutinib in patients with untreated and relapsed CLL.2,3 The authors reported impressive 5-year rates of progression-free survival (PFS), at 92% for treatment-naive patients and 43% for relapsed/refractory patients. In addition, most patients appeared to tolerate prolonged exposure to ibrutinib without significant adverse events. Many of the grade 3 adverse events decreased with subsequent years of therapy. At 5 years of follow-up, the most common adverse events associated with ibrutinib use included hypertension in 26% of patients, pneumonia in 22%, and atrial fibrillation in 9%. Overall, the study suggested that prolonged exposure to ibrutinib can control CLL, and adverse events were manageable in most patients.

Lenalidomide

Dr Anna Fink presented results of the CLLM1 Study, which was performed by the German CLL Study Group.5 This study enrolled 89 patients with CLL at high risk for early relapse, such as those who achieved at least a partial response after 4 cycles of frontline chemotherapy, yet had persistent MRD levels or unmutated immunoglobulin heavy chain variable (IgHV), deletion 17, or TP53 mutation at baseline. After frontline therapy, patients were treated with lenalidomide or placebo. They underwent MRD assessments every 6 months. An interim analysis showed improvement in PFS in the lenalidomide arm compared with placebo (not reached vs 13.3 months). Based on this analysis, an independent data monitoring committee recommended unblinding of the study, as well as continued treatment with lenalidomide.

There were, however, increased adverse events with lenalidomide, leading 18 patients in this arm to discontinue treatment vs 6 patients in the placebo arm. Overall, the strategy of using lenalidomide maintenance in these high-risk patients appeared to provide clinical benefit and was fairly tolerable.

Indolent Lymphomas

Several interesting abstracts were presented in low-grade lymphoma, including the results of trials with obinutuzumab, lenalidomide, ibrutinib, and duvelisib.
**Obinutuzumab**
The GALLIUM study randomly assigned newly diagnosed patients with follicular lymphoma or marginal zone lymphoma to receive induction chemoimmunotherapy with either rituximab or obinutuzumab, followed by maintenance treatment with the same therapy. The study enrolled 1202 patients, and all had bulky disease or were in need of treatment per criteria from the Groupe d’Etude des Lymphomes Folliculaires (GELF).

A statistically significant benefit was observed with obinutuzumab. At 3 years, the median PFS in the obinutuzumab-plus-chemotherapy arm was 80% compared with 73% in the rituximab-plus-chemotherapy arm. Although this difference was only 7%, it resulted in a hazard ratio of 0.66, translating into a 1.5-times longer median PFS in the obinutuzumab arm compared with the rituximab arm. Obinutuzumab-containing regimens had a slightly higher frequency of grade 3 or higher adverse events compared with rituximab, although adverse events leading to treatment discontinuation between the 2 arms were similar. Based upon the results of this trial, obinutuzumab-containing chemotherapy combinations will likely become a new standard in the management of untreated follicular and marginal zone lymphoma.

**Lenalidomide**
A randomized trial presented by Dr Eva Kimby described the results of lenalidomide plus rituximab vs rituximab monotherapy in untreated patients with follicular lymphoma in need of therapy. This analysis of survival endpoints provided data for 153 patients who were randomly assigned to receive either the doublet of lenalidomide and rituximab or rituximab alone. At 3.5 years, the rate of complete responses (CR)/unconfirmed complete responses (CRu) was higher with lenalidomide and rituximab compared with rituximab alone (42% vs 19%; *P*=.001). The median PFS was not reached with lenalidomide and rituximab vs 2.3 years with rituximab alone. Overall survival rates between the 2 regimens were similar. Ongoing studies are comparing lenalidomide and rituximab vs rituximab plus chemotherapy (eg, REL-R) and results will hopefully be presented at upcoming meetings.

**Duvelisib**
The phosphoinositide 3 (PI3)-kinase inhibitors have been shown to be active in patients with relapsed follicular lymphoma. The phase 2 DYNAMO study explored the activity of the novel PI3-kinase inhibitor duvelisib in patients with relapsed or refractory indolent lymphoma. This study enrolled 129 patients who were significantly pretreated, with a median of 3 prior regimens. In addition, the study required patients to be refractory to both rituximab and chemotherapy. All patients received single-agent duvelisib in 28-day cycles until disease progression or toxicity. A response was noted in 46% of patients, including 41% of patients with follicular lymphoma and 68% of patients with small lymphocytic leukemia (SLL). PFS was 8.3 months in patients with follicular lymphoma and 11.3 months in patients with SLL. Adverse events included cytomegalovirus, reported in 2.3% of patients, and grade 3/4 diarrhea, which occurred in 15%.

**Ibrutinib**
Ibrutinib, a small molecule that inhibits BTK, has shown significant activity in CLL and mantle cell lymphoma. Marginal zone lymphomas are likely dependent on signaling through the B-cell receptor pathway and may be an ideal target for B-cell receptor inhibitors. Dr Ariela Noy presented results of a multicenter, phase 2 study exploring ibrutinib in marginal zone lymphoma. In this study, the investigators enrolled 63 patients with extranodal, nodal, and splenic marginal zone lymphoma. Treatment with ibrutinib led to an impressive 46% overall response rate. Clinical benefit was reported in 89% of patients, including some with stable disease, and 87% of patients had a reduction in tumor volume. The results of this study led to the recent approval by the US Food and Drug Administration of ibrutinib in marginal zone lymphoma. Combination studies with the agent are ongoing, and results are expected at upcoming meetings.

**Aggressive Lymphomas**
The awaited results of several large, randomized, phase 3 trials in DLBCL, as well as studies exploring interesting new combination concepts, were a highlight of the 2016 ASH meeting.

**R-CHOP vs EPOCH-R**
A phase 3, randomized study from the Cancer and Leukemia Group B>Alliance 50303 compared R-CHOP with dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin plus rituximab (EPOCH-R) in patients with untreated DLBCL. This multicenter study enrolled 524 patients who were randomly assigned to receive 1 of the 2 regimens as frontline therapy. With mature follow-up, there was no reported statistical difference in PFS between R-CHOP and EPOCH-R. In addition, there did not appear to be a benefit in overall survival with either regimen.

Furthermore, rates of toxicity were higher in the EPOCH-R arm, with 6.5% of patients discontinuing therapy early owing to adverse events vs 1.5% in the R-CHOP arm. Grade 3 to 5 febrile neutropenia was reported in 35% of the EPOCH-R arm vs 17% of the R-CHOP arm. Grade 3 to 5 neutropenia occurred in 96% vs 68%, respectively, and grade 3 to 5 thrombocytopenia occurred in 65% vs 11%. EPOCH-R was also associated with higher rates of grade 3 sensory and motor neuropathies. The value of EPOCH-R in a higher-risk population remains unknown. Subset analyses of more aggressive histologies, such as double-hit or high-risk disease, were not presented.
Rituximab vs Obinutuzumab

Rituximab has been shown to improve outcomes when added to combination chemotherapy in untreated aggressive B-cell lymphomas. The GOYA study compared R-CHOP vs obinutuzumab plus CHOP in patients with previously untreated DLBCL. In this open-label, phase 3 study, 1418 patients were randomly assigned to receive 6 or 8 cycles of CHOP (including preplanned radiotherapy in patients with bulky disease), plus rituximab or obinutuzumab. Patient characteristics were well-balanced.

Unfortunately, the primary endpoint of this study was not met. Obinutuzumab plus CHOP did not significantly improve investigator-assessed PFS compared with R-CHOP in DLBCL. The grade 3 adverse events were slightly higher in the obinutuzumab arm, and included neutropenia (57% vs 48%) and infusion-related reactions (45% vs 32%).

Lenalidomide

Lenalidomide has been shown to have activity as a single agent and in combination with rituximab in patients with relapsed large-cell lymphoma. The international REMARC study explored lenalidomide maintenance in elderly patients with large-cell lymphoma who were treated with R-CHOP. This study randomly assigned 580 patients to receive maintenance therapy or observation. Following 2 years of lenalidomide maintenance, PFS was 58.8 months in the placebo arm vs not reached in the lenalidomide arm. In addition, 21% of patients converted from a partial response to a CR in the maintenance lenalidomide arm vs only 14% in the placebo arm.

Grade 3/4 neutropenia occurred in 56% of the lenalidomide arm vs 22% of the placebo arm. Infections, however, did not appear dramatically different between the 2 arms. Further follow-up will be needed to understand how lenalidomide exposure in this group of patients affects overall survival.

Nivolumab

Finally, long-term follow-up was presented for the phase 2 CheckMate 205 study of nivolumab in patients with relapsed and refractory Hodgkin lymphoma. This study was initially designed to evaluate the efficacy and safety of nivolumab in patients with Hodgkin lymphoma who relapsed after autologous stem cell transplant. Dr John Timmerman reported data for the 80 patients who were treated in this study. The median duration of response in patients who achieved a CR was not reached vs 13 months in patients with partial remission. Most patients (54%) remained on therapy. The most common reasons for discontinuation were disease progression, allogeneic transplant, and adverse events.

The report further emphasizes the exciting activity of this class of agents in patients with relapsed Hodgkin lymphoma. Whether a subset of patients who achieve CR following exposure to inhibitors of programmed death receptor 1 (PD1) will remain disease-free long-term is yet to be seen, but remains an exciting possibility.

Disclosure

Dr. Fowler has served on the advisory board for and received research funding from Roche, Celgene, Infinity, AbbVie, and Janssen.

References
