



Name: Fiona An, MD
Company/Organization: Pfizer Inc.
Address: 235 E 42nd street, New York, NY 10017
Phone: 212.733.2067
Email: Fiona.An@pfizer.com
Date of Request: August 17th, 2017
NCCN Guidelines Panel: Acute Lymphoblastic Leukemia

Dear NCCN ALL panel members:

On behalf of Pfizer Oncology, I respectfully request the NCCN Guideline Panel for Acute Lymphoblastic Leukemia (ALL) to review the enclosed information for inclusion of BESPONSA (inotuzumab ozogamicin) in the treatment recommendation for adults patients with relapse or refractory B-cell precursor ALL.

Specific Changes Requested: Recommend the addition of BESPONSA (inotuzumab ozogamicin) as treatment for adults patients with relapsed or refractory B-cell precursor ALL (ph+ and ph-).

FDA Clearance: On August 17th, 2017, FDA approved BESPONSA (inotuzumab ozogamicin), a CD22-directed antibody-drug conjugate (ADC), for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

Rationale: Based on the FDA-approved indication and data from INO-VATE ALL trial (NCT01564784), BESPONSA (inotuzumab ozogamicin) demonstrated significantly higher rate of complete remission, longer duration of complete remission and higher rate of MRD-negativity ($<1 \times 10^{-4}$ of bone marrow nucleated cells by flow cytometry) compared to standard chemotherapy in adult patients with relapsed or refractory B-cell ALL.

The following resources are submitted in support of this requested change:

1. BESPONSA (inotuzumab ozogamicin), prescribing information. Pfizer Inc.



USPI_BESPONSA_ino
tuzumab ozogamicin_

2. Kantarjian et al., Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia. *N Engl J Med* 2016; 375: 740-753.



Kantarjian 2016
NEJM.pdf

The basis for the approval was a randomized (1:1), open-label, international, multicenter phase 3 study (INO-VATE ALL trial), which evaluated efficacy and safety of inotuzumab ozogamicin in patients with



relapse or refractory B-cell ALL compared with standard chemotherapy. This study enrolled 326 patients with relapse or refractory ALL who are ≥ 18 years of age.

The initial 218 randomized patients were evaluated for rate of Complete Remission and Complete Remission with incomplete recovery of peripheral blood counts (CR/CRi), which demonstrated significant improvement in rate of CR/CRi with inotuzumab ozogamicin compared to standard chemotherapy (80.7% vs. 29.4%; $p < 0.0001$). Among patients who achieved CR/CRi, more patients have achieved MRD-negativity with inotuzumab ozogamicin treatment (78.4% vs. 28.1%; $p < 0.0001$).

Among all 326 patients who were randomized in the study, 79/164 (48%) patients in the inotuzumab ozogamicin arm and 35/162 (22%) patients in the Investigator's choice of chemotherapy arm had a follow-up Hematopoietic Stem Cell Transplantation (HSCT).

There are two black-box warnings in the USPI. Hepatotoxicity, including fatal and life-threatening Venous Occlusive Disease (VOD) occurred in patients who received BESPONSA (inotuzumab ozogamicin). A higher post-HSCT non-relapse mortality rate occurred in patients receiving BESPONSA (inotuzumab ozogamicin). The most common ($\geq 20\%$) adverse reactions are thrombocytopenia, neutropenia, infection, anemia, leukopenia, fatigue, hemorrhage, pyrexia, nausea, headache, febrile neutropenia, transaminases increased, abdominal pain, gamma-glutamyltransferase increased, and hyperbilirubinemia. The most common ($\geq 2\%$) serious adverse reactions were infection, febrile neutropenia, hemorrhage, abdominal pain, pyrexia, VOD, and fatigue.

We appreciate the Panel's thorough consideration of Pfizer's submission for BESPONSA (inotuzumab ozogamicin) for the treatment of adult patients with relapsed or refractory B-cell precursor ALL. We welcome any questions that you may have.

Sincerely,
Fiona

Fiona An MD
Senior Director, US Medical Affairs
Pfizer Inc.