CHILDREN'S ONCOLOGY GROUP

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To Participants/Families with B-ALL on Children's Oncology Group Study AALL1732

Dear study participant:

The Children's Oncology Group (COG) is committed to keeping all families who participate in research aware of new developments. As your child is / you are enrolled on COG trial **AALL1732,** *A Phase 3 Randomized Trial of Inotuzumab Ozogamicin (IND#:133494, NSC#: 772518) for Newly Diagnosed High-Risk B-ALL; Risk-Adapted Post-Induction Therapy for High-Risk B-ALL, Mixed Phenotype Acute Leukemia, and Disseminated B-LLy,* we are writing to let you know of new information for patients who have B-ALL.

When we say "you" in this letter, we mean you or your child; "we" means the doctors and other staff.

All patients participating in COG research studies are followed to see how they do. This includes looking to see if new treatments help. This also includes looking to see if new treatments have side effects.

This information is not based on new results from AALL1732. This new information is based on new results from other studies. Recently, two studies tested to see if adding a drug called blinatumomab to chemotherapy is better than treatment with chemotherapy alone. One study included adults 30-70 years old with newly diagnosed B-ALL. The other included children 1-10 years old with newly diagnosed B-ALL. Both studies found that adding the new drug blinatumomab to chemotherapy is better than chemotherapy alone for many patients. This means more patients treated with chemotherapy alone relapsed, than patients treated with blinatumomab plus chemotherapy. Relapsed means the leukemia came back. It is important to note that for the study in children, most children 1-10 years, most did not relapse, regardless of whether they received the blinatumomab or not. In response to these and other results, the US Food and Drug Administration (FDA) recently approved the use of blinatumomab as part of the chemotherapy regimen in patients with newly diagnosed B-ALL who are older than 1 month of age.

As a result, we are stopping the AALL1732 trial for some patients. This is to make sure that patients with high-risk (HR) B-ALL have access to the treatment that is most well supported by the information available. This does not mean that the study drug given on AALL1732, inotuzumab ozogamicin, is not safe or effective.

This study has two parts, Induction/Consolidation therapy and Post-Consolidation therapy. By the end of Consolidation therapy, patients with B-ALL on AALL1732 are divided into two groups. These groups are called risk groups. The two groups are called high risk-favorable (HR-Fav) and high risk (HR). If you are still in the Induction/Consolidation part of treatment, you are still in the first part of the study. Your doctor may not yet know which risk group you are in, but they will know by the time you finish Consolidation. If you are in the Post-Consolidation part of the study and do not know if you are in the HR-Fav or HR group, your doctor can provide you with this information.

A National Cancer Institute-funded group member of the National Clinical Trials Network

If you are still in the Induction/Consolidation part of the study:
If you are in one of the first two phases of treatment, you are still in the first part of the study. Your doctor may not yet know which risk group you are in, but they will know either by the time you finish Induction, or by the time you finish Consolidation.

1. Your doctor will know if you are in the HR-Fav risk group by the end of Induction. If you are in the HR-Fav group, you belong to a group of patients with ALL who already have such excellent outcomes that they will not receive inotuzumab ozogamicin on this trial. We also do not recommend blinatumomab for this group of patients. Your doctor will talk with you about continuing on the study after Consolidation to receive standard chemotherapy.
2. Your doctor will know if you are in the HR risk group by the end of Induction or by the end of Consolidation. If you are in the HR group, we recommend that you come off protocol therapy following Consolidation and have blinatumomab added to your chemotherapy regimen. It is important for you to talk to your doctor about this recommendation.

If you are in the Post-Consolidation part of the study:
If you are in the Post-Consolidation part of the study, you are in either the HR-Fav or the HR group. If you do not know if you are in the HR-Fav or HR group, your doctor can provide you with this information.

1. **HR-Fav:** If you are in the HR-Fav group, you belong to a group of patients with ALL who already have such excellent outcomes that they will not receive inotuzumab ozogamicin on this trial. We also do not recommend blinatumomab for this group of patients. These patients are recommended to continue to receive standard chemotherapy and may remain on the AALL1732 study. It is important for you to talk with your doctor about this recommendation.
2. **HR:** Patients with HR B-ALL have a higher risk of relapse than HR-Fav patients and so are likely to benefit from the addition of blinatumomab to their treatment. B-ALL therapy includes many phases, and the last phase is called Maintenance. Blinatumomab has only been studied in patients when given before Maintenance.
    a. If you have HR B-ALL and were randomized to standard treatment (Arm A), we recommend that you come off protocol therapy and have blinatumomab added to your chemotherapy regimen.
    b. If you have HR B-ALL and were randomized to the experimental treatment (Arm C), but you have not started the first block of treatment with inotuzumab ozogamicin, we recommend that you come off protocol therapy and have blinatumomab added to your chemotherapy regimen. Once you come off protocol therapy, you will not receive any doses of inotuzumab ozogamicin.
    c. If you have HR B-ALL and were randomized to the experimental treatment (Arm C) and have started inotuzumab ozogamicin block 1, we recommend that you come off protocol therapy after Delayed Intensification Part 1 and have blinatumomab added to your chemotherapy regimen. Once you come off protocol therapy, you will not receive any further doses of inotuzumab ozogamicin.

Not everyone will be able to get blinatumomab as it is not available in all countries. You or your doctor may feel blinatumomab is not the best treatment for you. If you do not have access to blinatumomab or you or your doctor do not want treatment with blinatumomab, your doctor will discuss with the study team if you can continue on protocol therapy. This could mean that you receive two blocks of inotuzumab ozogamicin if you are being treated on the experimental Arm C.

We recommend that you discuss this information with your doctor, who will be in the best position to provide guidance for your child's/your treatment. The specific timing of blinatumomab, if appropriate, will be determined by your treating doctor who will discuss with you the details of blinatumomab treatment and side effects.

Sincerely,
Jennifer McNeer, MD, AALL1732 study co-chair,
Maureen O'Brien MD, AALL1732 study co-chair,
Susan Rheingold MD, AALL1732 study vice chair
David Teachey, MD, COG ALL Disease Committee Chair