American Association for Cancer Research

FINDING CURES TOGETHER℠

Embargoed for Release: 8 a.m. ET, April 3, 2017

To interview Amy K. Erbe, contact Julia Gunther at julia.gunther@aacr.org or 215-446-6896 (office) or 267-250-5441 (cell). For a photo of Erbe, click here. Visit our newsroom.

Biomarker May Identify Neuroblastoma Patients Most Likely to Benefit from Immunotherapy

WASHINGTON — Among patients with high-risk neuroblastoma, those who had a certain combination of genotypes gained substantial benefit from adding immunotherapy to isotretinoin treatment, while it is uncertain whether those who lacked the combination gained benefit from immunotherapy, according to results from a randomized phase III clinical trial presented here at the AACR Annual Meeting 2017, April 1-5.

Previously reported data from the phase III clinical trial, which involved 226 patients, showed that adding immunotherapy, in the form of dinutuximab (Unituxin), aldesleukin, and sargramostim, to isotretinoin significantly improved event-free and overall survival for patients with high-risk neuroblastoma. These data led to a U.S. Food and Drug Administration approval for this dinutuximab regimen in this indication.

However, not all patients who received immunotherapy had a response and many had significant adverse events.

"We wanted to determine if certain genotypes that are related to immune cells called NK cells—KIR/KIR-ligand genotypes—could be predictive of how patients with high-risk neuroblastoma respond to immunotherapy," said Amy K. Erbe, PhD, an associate scientist in the Department of Human Oncology at the University of Wisconsin School of Medicine and Public Health in Madison. "Identifying biomarkers of response to immunotherapy may allow us to personalize therapy for patients in the future, helping to spare those unlikely to respond from the potential of adverse events."

"Our data show that a certain combination of KIR/KIR-ligand genotypes may be predictive of benefit from immunotherapy" continued Erbe. "However, these findings need to be validated before we can consider making clinical decisions for patients with high-risk neuroblastoma based on KIR/KIR-ligand genotype."

Erbe and colleagues determined the KIR/KIR-ligand genotypes of the 174 patients from the phase III trial for whom sufficient DNA was available for analysis. They then assessed whether certain genotypes were associated with event-free and overall survival.

Among the 49 patients who were positive for both the KIR2DL2/HLA-C1 genotype and the KIR3DL1/HLA-Bw4 genotype, 23 had received isotretinoin plus immunotherapy and 26 had received isotretinoin only. The researchers found that those who received immunotherapy and isotretinoin had significantly improved event-free and overall survival; at five years, the addition of immunotherapy improved event-free survival from 27 percent to 61 percent and overall survival from 34 percent to 91 percent for this group.

Among the 125 patients who were not positive for both the KIR2DL2/HLA-C1 genotype and the KIR3DL1/HLA-Bw4 genotype, 65 had received isotretinoin plus immunotherapy and 60 had received isotretinoin only. There was no significant difference in either event-free or overall survival between the two treatment groups; at five years, event-free survival was 57 percent for those receiving immunotherapy and isotretinoin versus 53 percent for those receiving only isotretinoin and overall survival was 68 percent for both treatments.

"Our data not only identify KIR/KIR-ligand genotypes associated with differences in outcome following treatment with immunotherapy but also indicate that the immune cells that are regulated by KIR/KIR-ligand interactions, namely NK cells, play a major role in mediating the anticancer effects of this immunotherapy treatment," said Erbe. "It is important to show that NK cells are involved because this helps us to understand the therapy and provides clues as to how we might improve it."

According to Erbe, the main limitation of this study is that the number of patients in the two treatment groups was relatively small, and the subgroups with the different KIR/KIR-ligand genotypes were even smaller. Thus, the conclusions from this single study cannot be viewed as definitive and need to be validated, she explained.

This study was funded in part by Hyundai Hope on Wheels Grant, Midwest Athletes Against Childhood Cancer, Stand Up To Cancer, The St. Baldrick's Foundation, the American Association of Cancer Research (AACR), the University of Wisconsin Carbone Cancer Center, and Public Health Service Grants from the National Cancer Institute. Erbe declares no conflicts of interest.

Follow the AACR Annual Meeting 2017 on Twitter: #AACR17

# # #

Follow us: *Cancer Research Catalyst* http://blog.aacr.org; Twitter @AACR; and Facebook http://www.facebook.com/aacr.org

For AACR information, visit Fast Facts.

About the American Association for Cancer Research
Founded in 1907, the American Association for Cancer Research (AACR) is the world's first and largest professional organization dedicated to advancing cancer research and its mission to prevent and cure cancer. AACR membership includes more than 37,000 laboratory, translational, and clinical researchers; population scientists; other health care professionals; and patient advocates residing in 108 countries. The AACR marshals the full spectrum of expertise of the cancer community to accelerate progress in the

prevention, biology, diagnosis, and treatment of cancer by annually convening more than 30 conferences and educational workshops, the largest of which is the AACR Annual Meeting with nearly 19,500 attendees. In addition, the AACR publishes eight prestigious, peer-reviewed scientific journals and a magazine for cancer survivors, patients, and their caregivers. The AACR funds meritorious research directly as well as in cooperation with numerous cancer organizations. As the Scientific Partner of Stand Up To Cancer, the AACR provides expert peer review, grants administration, and scientific oversight of team science and individual investigator grants in cancer research that have the potential for near-term patient benefit. The AACR actively communicates with legislators and other policymakers about the value of cancer research and related biomedical science in saving lives from cancer. For more information about the AACR, visit www.AACR.org.

Abstract: LB-048

Presentation Session: LBPO.CL01 - Late-Breaking Research: Clinical Research 1, Monday, April 3, 8 a.m. ET, Section 34

Title: Impact of KIR/KIR ligand genotype for neuroblastoma patients in a Phase 3 COG immunotherapy trial

Authors: Amy K. Erbe[1], Wei Wang[1], Lakeesha Carmichael[1], KyungMann Kim[1], Patrick K. Reville[1], Wendy B. London[2], Jacquelyn A. Hank[1], Mitchell B. Diccianni[3], Arlene Naranjo[4], Michael Hogarty[5], Julie R. Park[6], Alice L. Yu[3], Paul M. Sondel[1]. [1]University of Wisconsin, Madison, WI; [2]Dana–Farber Cancer Institute, Boston, MD; [3]University of California, San Diego, CA; [4]University of Florida, Gainesville, FL; [5]Children's Hospital of Philadelphia and University of Pennsylvania School of Medicine, Philadelphia, PA; [6]Seattle Children's Hospital/University, Seattle, WA

Introduction: High-risk neuroblastoma (NBL) patients (pts) enrolled in a COG Phase 3 clinical trial (ANBL0032) were randomized to isotretinoin (RA) alone or Immunotherapy: dinutuximab (anti-GD2 mAb) + IL2 + GMCSF + RA (Yu et al., NEJM, 2010). Dinutuximab acts via antibody-dependent cell-mediated cytotoxicity by innate immune cells, including NK cells. NK cells express Killer Immunoglobulin-like Receptors (KIRs); most of the inhibitory KIRs have KIR-ligands that belong to the HLA class I family. Specifically, KIR2DL1 is a receptor for HLA-C2, KIR2DL2 and KIR2DL3 are receptors for HLA-C1, and KIR3DL1 is a receptor for HLA-Bw4. Some prior studies of anti-GD2 mAb immunotherapies have shown associations with outcome based on the genotypes of these inhibitory KIR/KIR ligand relationships. We investigated whether certain KIR/KIR-ligand genotypes were associated with event-free survival (EFS) and overall survival (OS) in this trial.

Methods: Of the 226 pts randomized, 174 pts had DNA allowing evaluation of genotype correlations with outcome (RA: n=86; Immunotherapy: n=88; >5yr follow-up if no event). We looked for associations of inhibitory KIRs with their respective KIR-ligands and clinical outcome. Log-rank tests and Cox proportional hazards regression models were used to compare EFS/OS by genotype group; adjustment was made for non-proportional hazards as needed using time-dependent covariates.

Results: We found that certain, hypothesis-identified, inhibitory KIR/KIR-ligand combinations were associated with improved clinical outcome. Namely, pts that were **both** KIR2DL2+/HLA-C1+ **and** KIR3DL1+/HLA-Bw4+ had improved EFS and OS if treated with Immunotherapy (n=23) vs. RA (n=26) (5-yr EFS: 61% vs. 27%, p=0.02; 5-yr OS: 91% vs. 34%, p=0.007). Conversely, for pts that were ***not*** **both** KIR2DL2+/HLA-C1+ **and** KIR3DL1+/HLA-Bw4+, we found insufficient evidence to support an

improvement in EFS or OS with Immunotherapy (n=65) vs. RA (n=60) (5-yr EFS: 57% vs. 53%, p=0.76; 5-yr OS: 68% vs. 68%, p=0.66).

Conclusions: Our data suggest that KIR/KIR-ligand genotype may be predictive of benefit from Immunotherapy. The impact of immunotherapy appears different for pts that were **both** KIR2DL2+/HLA-C1+ **and** KIR3DL1+/HLA-Bw4+ vs. those that were ***not*** **both** KIR2DL2+/HLA-C1+ **and** KIR3DL1+/HLA-Bw4+. Validation of these KIR/KIR-ligand associations in similarly treated high-risk NBL patients would be required prior to proposing their prospective use in the aid of clinical treatment decisions. Further investigation of KIR/KIR-ligand genotypes may also clarify their role and the role of NK cells in the activity of this form of cancer immunotherapy