Letter to The Editor

Clinical Cancer Research

FCGR, Cetuximab, and Colorectal Cancer Survival—Letter

Francesca V. Negri, Daniela Boggiani, Anita Rimanti, and Antonino Musolino

Some common single-nucleotide polymorphisms (SNP) in the coding regions of the *FcγRIIIa* and *FcγRIIa* genes have been associated with differential mAb-binding affinities and clinical outcomes. In their study (1), Liu and colleagues performed a validation of these polymorphisms in a randomized trial of cetuximab (anti-EGFR mAb) monotherapy in metastatic colorectal cancer (mCRC). Study results confirmed previous reported data showing that cetuximab worked best for patients with *KRAS* wild-type colorectal cancers carrying the "high binding affinity" *FcγRIIa* H/H genotype (1). Interestingly, and somewhat paradoxically, the authors also observed that among patients in the best supportive care arm, who were not treated with cetuximab, the "low binding affinity" *FcγRIIa* R/R and H/R genotypes were associated with improved overall survival (OS). According to these data, in our retrospective analysis of 86 mCRC patients treated with cetuximab therapy (2), a statistically significant difference in OS was observed in favor of *FcγRIIa* R/R carriers (17.5 months) in comparison with both *FcγRIIa* H/R and H/H genotypes (9.4 and 9.9 months, respectively). We also observed that peripheral mononuclear blood cells (PBMC) of individuals bearing the favorable prognostic genotype (*FcγRIIa* R/R) showed a significantly worse cetuximab-mediated antibody-dependent cell-mediated cytotoxicity (ADCC) than other *FcγRIIa* variants.

A possible explanation for the apparently paradoxical effect of the *FcγRIIa* R/R genotype on cetuximab activity and OS can be hypothesized. Affinity of Fc portion of immunoglobulins to FcγRs does not influence only ADCC (3). Monocytes/macrophages express both FcγRIIIa and FcγRIIa, while neutrophils express FcγRIIa but not FcγRIIIa (3). Therefore, *FcγRIIa* variants might affect not only monocyte/macrophage function, which is responsible for ADCC activity of mAbs, but also the function of other immune cells such as tumor-associated neutrophils, which have been *associated* with unfavorable overall *survival* (4). The differences of identified *FcγRIIa* genotypes according to either cetuximab activity or prognosis may, thus, reflect the different functions of FcγRIIa expressed on various immune effector cells.

We agree with the authors that the prognostic role of *FcγR* polymorphisms, unrelated to mAb administration, remains, to date, exploratory. Further investigation is warranted in a prospectively accrued population.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Received June 10, 2016; accepted June 10, 2016; published online October 3, 2016.

Medical Oncology Unit, University Hospital of Parma, Parma, Italy.

Corresponding Author: Antonino Musolino, Medical Oncology Unit, University Hospital of Parma, via Gramsci 14, Parma 43126, Italy. Phone: 3905-2170-2316; Fax: 3905-2199-5448; E-mail: antoninomusolino@hotmail.com

doi: 10.1158/1078-0432.CCR-16-1470

References

1. Liu G, Tu D, Lewis M, Cheng D, Sullivan LA, Chen Z, et al. Fc-γ receptor polymorphisms, cetuximab therapy, and survival in the NCIC CTG CO.17 trial of colorectal cancer. Clin Cancer Res 2016;22:2435–44.
2. Negri FV, Musolino A, Naldi N, Bortesi B, Missale G, Laccabue D, et al. Role of immunoglobulin G fragment C receptor polymorphism-mediated antibody-dependant cellular cytotoxicity in colorectal cancer treated with cetuximab therapy. Pharmacogenomics J 2014;14:14–19.
3. van der Heijden J, Nagelkerke S, Zhao X, Geissler J, Rispens T, van den Berg TK, et al. Haplotypes of FcγRIIa and FcγRIIIb polymorphic variants influence IgG-mediated responses in neutrophils. J Immunol 2014;192:2715–21.
4. Benarafa C. Tumor-induced inflammation alters neutrophil phenotype and disease progression. Breast Cancer Res 2015;17:135.