Preface

The focus of this special issue of *Critical Reviews™ in Oncogenesis* is resistance to anticancer antibody-mediated immunotherapy. Brief synopses are offered in the following sections.

I. ANTI-HERCEPTIN ANTIBODIES

Parakh et al., in “Sensitization of Cancers Resistant to HER2 Antibodies,” examine observed resistance of HER2-positive breast cancer patients to trastuzumab (an anti-HER2 mAb) and its underlying mechanisms. The authors discuss the various strategies for overcoming this resistance, which include a number of novel anti-HER2 treatments such as HER2 ADCs, which have shown activity in HER2 high and low tumors; novel HER2 antibodies; T cell-bispecific antibodies; and HER2 antibodies in combination with PI3K/mTOR inhibitors, immunotherapy, and CDK4/6 inhibitors.

Rajarajan et al., in “Strategies to Combat HER2 Resistance in HER2-Positive Breast Cancer,” look at the complex signaling pathways and messengers involved in HER2-overexpressing tumors which have encouraged development of many promising drugs for the treatment of unresponsive breast cancer patients. These include vaccines and engagement of the immune response, which shows great promise; and improvement in the molecular genetics of tumors and personalized therapies. Both novel approaches offer a way to overcome resistance and, ultimately, to eradicate HER2+ breast cancer.

Nitta and Li, in “Breast HER2 Intratumoral Heterogeneity as a Biomarker for Improving HER2-Targeted Therapy” review *HER2* gene amplification and HER2 protein overexpression, which are the primary predictors for selecting invasive breast cancer patients for treatment. According to the authors, however, HER2-targeted therapy is not completely successful. Among various mechanisms of resistance to this therapy are HER2 intratumoral heterogeneity (ITH) as determined by a concomitant *HER2* gene and protein analyses. Two groups of tumor heterogeneity subtypes are reviewed. The

authors also explore further improvements in cancer therapy via new therapeutic targets for patients with HER2 ITH.

In “HER2 Tyrosine Kinase Inhibitors in Sensitization to Cancers Resistant to HER2 Antibodies,” Singla and Munshi discuss overexpression of HER2 protein or gene amplification that results in HER2 dimerization, tyrosine kinase (TK) phosphorylation, activation of different signaling pathways (including mitogen-activated protein kinase, or MAPK, and phosphoinositide 3-kinase, or PI3K, pathways). HER2 antibodies like trastuzumab and pertuzumab act on the extracellular domain (ECD) of the HER2 receptor and effectively inhibit HER2 dimerization and thereby further signaling. However, antibody resistance leading to disease relapse has emerged as a serious consequence. To overcome the therapeutic resistance associated with trastuzumab, TK inhibitors (TKIs) have been developed and used in combination with HER2 antibodies. The authors take a look at the HER2 TKIs lapatinib, neratinib, afatinib, sapitinib, CP-724,714, dacomitinib, tucatinib, pyrotinib, and poziotinib as promising clinical tools in sensitizing resistant cancers to HER2 antibodies.

II. ANTI-CD20 ANTIBODIES

Arp et al., in “Improving Therapeutic CD20 Antibodies Requires Insight into Their Mechanism of Action,” review the underlying mechanisms of resistance to anti-CD20 antibodies by which patients either do not respond initially and/or become refractory to further treatments. Along with the mechanisms of both responsiveness and unresponsiveness, the authors discuss new antibody-based therapeutics to overcome resistance.

In “Reversal of Resistance to Anti-CD20 Antibody Therapies: Targeting Intracellular Resistant Factors,” Navasardyan and Bonavida discuss the various mechanisms of resistance to rituximab, a chimeric mouse/human monoclonal antibody that targets CD20. Targeting of CD20 by monoclonal antibodies *in vivo* is poorly understood. In addition

to implicated mechanisms that have been reported, the authors discuss postulated mechanisms, speculating that better understanding of the underlying mechanisms of resistance will result in novel approaches to early diagnosis and therapeutic response.

Bonavida discusses anti-CD20 mAbs in “Cross-talk Cell Signaling between Anti-CD20 Antibodies and Nitric Oxide Donors,” revealing that anti-CD20 mAbs and nitric oxide (NO) donors have pleiotropic effects in common. He briefly describes the mechanisms of activities mediated by anti-CD20 antibodies and NO donors and establishes the existence of cell-signaling crosstalk between them. It is postulated that the use of well-designed subtoxic NO donations in combination with anti-CD20 mAbs will result in improved treatment of patients

who are initially unresponsive and/or refractory to treatment.

Overall, this special issue provides selective examples of the mechanisms of resistance to anti-HER2 and anti-CD20 mAbs encountered in breast cancer patients, and suggests how various sensitizing agents reverse resistance and thus open the door to clinical study of their validation and therapeutic applications in refractory patients.

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