Targeting the HER Pathways

The human epidermal growth factor receptor (HER) family has four members: HER1, HER2, HER3 and HER4. These four receptors interact via complex signal transduction pathways, which provide multiple targets for potentially interfering with cellular growth and proliferation. Many biologic agents affecting these pathways are currently being developed and investigated. Preclinical and clinical trials are also evaluating combinations of biologic agents that target different receptors. The results from ECOG-1100 were disappointing because the combination of trastuzumab and gefitinib did not appear to result in significant antitumor effect. Preclinical data suggest that, perhaps, pan-HER2 blockade with trastuzumab, gefitinib and pertuzumab may prove to be more beneficial.

HER1 HER2 HER3

The HER-2-targeting antibodies trastuzumab and pertuzumab block HER2 cross-talk with ER to restore tamoxifen (Tam) efficacy of the combination is under active investigation. These results do not support the further use of this combination and have implications for the use of trastuzumab alone, suggesting the possibility of an antagonistic antagonist effect on ER, and together with Tam eradicate MCF7/HER218 xenografts with the HER receptor network reported.

Phases I/II STUDY OF TRASTUZUMAB AND GEFITINIB IN PATIENTS WITH HER2-OVEREXPRESSING METASTATIC BREAST CANCER

ECOG-1100: INTERIM EFFICACY DATA FROM PHASE I/II STUDY OF TRASTUZUMAB AND GEFITINIB IN PATIENTS WITH HER2-OVEREXPRESSING METASTATIC BREAST CANCER REPORTED AT SABCS 2004

HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR (HER) SIGNALING

The HER family of receptor tyrosine kinases functions as a network of interrelated pathways. The HER1, HER2, HER3 and HER4 receptors interact with and provide multiple targets for potentially interfering with cellular growth and proliferation. Many biologic agents affecting these pathways are currently being developed and investigated. Preclinical and clinical trials are also evaluating combinations of biologic agents that target different receptors. The results from ECOG-1100 were disappointing because the combination of trastuzumab and gefitinib did not appear to result in significant antitumor effect. Preclinical data suggest that, perhaps, pan-HER2 blockade with trastuzumab, gefitinib and pertuzumab may prove to be more beneficial.

OVERVIEW OF HER2 BIOLOGY

The human epidermal growth factor receptor (HER) family has four members: HER1, HER2, HER3 and HER4. These four receptors interact via complex signal transduction pathways, which provide multiple targets for potentially interfering with cellular growth and proliferation. Many biologic agents affecting these pathways are currently being developed and investigated. Preclinical and clinical trials are also evaluating combinations of biologic agents that target different receptors. The results from ECOG-1100 were disappointing because the combination of trastuzumab and gefitinib did not appear to result in significant antitumor effect. Preclinical data suggest that, perhaps, pan-HER2 blockade with trastuzumab, gefitinib and pertuzumab may prove to be more beneficial.

RECEPTOR X-BREAST CANCER XENOGRAFTS WITH THE COMBINATION OF GEFITINIB, TRASTUZUMAB AND PERTUZUMAB

METABOLIC MEDIA EFFECTS OF HER2 OVEREXPRESSION

The HER signal transduction pathways are complex. The HER1, HER2 and HER3 receptors interact via complex signal transduction pathways, which provide multiple targets for potentially interfering with cellular growth and proliferation. Many biologic agents affecting these pathways are currently being developed and investigated. Preclinical and clinical trials are also evaluating combinations of biologic agents that target different receptors. The results from ECOG-1100 were disappointing because the combination of trastuzumab and gefitinib did not appear to result in significant antitumor effect. Preclinical data suggest that, perhaps, pan-HER2 blockade with trastuzumab, gefitinib and pertuzumab may prove to be more beneficial.

COMPARATIVE PERFORMANCE OF ER\(+)/HER2\(-) AND HER2-OVEREXPRESSING METASTATIC BREAST CANCER TUMORS

The HER-2-targeting antibodies trastuzumab and pertuzumab block HER2 cross-talk with ER to restore tamoxifen (Tam) efficacy of the combination is under active investigation. These results do not support the further use of this combination and have implications for the use of trastuzumab alone, suggesting the possibility of an antagonistic antagonist effect on ER, and together with Tam eradicate MCF7/HER218 xenografts with the HER receptor network reported.

SELECT PUBLICATIONS

1. Arteaga CL et al. Determining molecular phenotypes of metastatic breast cancer: how do we make certain these combinations are at least equivalent or better than trastuzumab alone? Can we do better? Partly because of the ECOG-1100 data, we are contemplating a clinical trial plan to identify trastuzumab-resistant breast tumors that most interfere with the overlapping choice in the community for HER2-positive, metastatic breast cancer, which is basically trastuzumab and chemotherapy. The choice of a partner would be driven by basic science and safety, using time to progression as an endpoint. We have explored the possibility of using bevacizumab as our next partner with trastuzumab.

2. Badache A, Hynes NE. Determining molecular phenotypes of metastatic breast cancer: how do we make certain these combinations are at least equivalent or better than trastuzumab alone? Can we do better? Partly because of the ECOG-1100 data, we are contemplating a clinical trial plan to identify trastuzumab-resistant breast tumors that most interfere with the overlapping choice in the community for HER2-positive, metastatic breast cancer, which is basically trastuzumab and chemotherapy. The choice of a partner would be driven by basic science and safety, using time to progression as an endpoint. We have explored the possibility of using bevacizumab as our next partner with trastuzumab.

