Evaluation of HER-2 Specific Humoral Immune Responses in Breast Cancer Patients Treated with MVA-BN®-HER2

Fatema Legrand1, Rachel Owen1, Amanda Enstrom1, Olivia Hwang1, Gayatri Paranjpe1, Joy Su1, Bernadette Callejo1, Alex Chung1, Jess Nolin1, Angela Yu1, Belma Halilovic1, Olga Bandman1, Carsten Goessl1, Ulf Reimer2, Holger Wenschuh2, Reiner Laus1, Wayne Godfrey1, Alain Delcayre1

1BN ImmunoTherapeutics, Inc., 2425 Garcia Ave, Mountain View, CA 94043, USA
2JPT Peptide Technologies GmbH, Volmerstrasse 5 (UTZ), 12489 Berlin, Germany
fatema.legrand@bn-it.com, alain.delcayre@bn-it.com

Abstract

MVA-BN®-HER2 is a poxviral vector that encodes the extracellular domain of human HER-2 as well as two universal tetanus toxin T cell epitopes. Preclinical data have demonstrated MVA-BN®-HER2 to be immunogenic, inducing strong anti-tumor activity (Mandl et al., ISBTC 2010). MVA-BN®-HER2 has also been evaluated in various phase I safety and immunogenicity trials, with 30 HER-2-positive breast cancer patients being tested in the metastatic setting and 15 patients following adjuvant therapy. Preclinical immunological monitoring of MVA-BN®-HER2 treated patient samples revealed that treatment was able to break tolerance against HER-2 in the adjuvant and metastatic settings, inducing humoral and/or T-cell responses in the majority of the patients (Legrand et al., ISBTC 2010 and Owen et al., SITC 2011).

Extended analysis of humoral responses was performed in patients receiving MVA-BN®-HER2 to determine the relevant immune parameters that correlated with clinical benefit. The generation of HER-2 transgene and MVA vector specific antibody responses was assessed with the ELISA IgG titers assay. The breadth of the anti-tumor response was determined using a peptide array comprised of 7590 peptides derived from 46 breast cancer tumor associated antigens (TAA) including HER-2. In addition, the role of vaccine induced HER-2 specific antibodies in eliciting functional anti-tumor activity is being evaluated.

Overall, it was observed that qualitatively different anti-HER-2 antibody responses were induced in patients treated with MVA-BN®-HER2. The peptide array assay revealed that repeated treatment was accompanied by a broadening of the anti-HER-2 humoral response as well as epitope spreading to other TAAs. Strong responses to 15 TAA proteins were detected in at least 12 out of the 30 tested patients. In addition, 42 out of the 7590 total evaluated peptides were identified as being immunodominant. Importantly, the presence of a pre-existing immune response to the MVA vector did not impair the induction of transgene specific immune responses. The broadening of immune responses to non-HER-2 TAAs suggests that the MVA-BN®-HER2-mediated immune activation results in anti-tumor activity. Taken together, these data support MVA-BN®-HER2 treatment to be a potent activator of humoral immune responses in both the metastatic and adjuvant settings.

Summary

Anti-HER-2 IgG ELISA titers were induced both in the adjuvant (BR-003 clinical trial) and metastatic setting (BR-001/BR-002 clinical trial).

• 13 out of 15 adjuvant patients induced a HER-2 specific IgG titer. Of these patients, only one showed evidence of pre-existing HER-2 responses.
• 15 out of 29 metastatic patients induced a HER-2 specific IgG titer. Of these patients, seven had pre-existing responses (data not shown).

Anti-MVA IgG ELISA titers were also induced or boosted both in the adjuvant (BR-003 clinical trial) and metastatic setting (BR-001/BR-002 clinical trial).

• All 15 adjuvant patients induced a specific IgG response to the MVA vector. Of these patients, eight had pre-existing responses.
• 27 out of 30 metastatic patients induced a MVA specific IgG titer (data not shown), nine of whom had pre-existing responses (data not shown).

The higher frequency of HER-2 and MVA specific humoral responses in the adjuvant setting (87% and 100% response rate, respectively) as compared to the metastatic setting (52% and 90% response rate, respectively) may be attributed to the patients’ disease-free status as well as earlier and higher HER2 expression under the synthetic ATI promoter in the second generation MVA-BN®-HER2 vector.

• The JPT RepliTope™ peptide microarrays, comprised of 7590 peptides derived from 46 breast cancer tumor associated antigens (TAAs) including HER-2, revealed a broadening of the anti-HER-2 humoral response as well as epitope spreading to other TAAs.

Anti-HER-2 IgG ELISA titers were induced both in the adjuvant (BR-003 clinical trial) and metastatic setting (BR-001/BR-002 clinical trial).

• In general, variability in detectable responses was evident across the patients.
• Strong responses to 15 TAA proteins were detected in at least 12 out of the 30 tested patients. In addition, 42 out of the 7590 total evaluated peptides were identified as being immunodominant.
• As expected, the highest frequency responses were to breast cancer associated antigens.