Investigational PD-L1–targeted Immunotherapy Safe for Patients With Triple-negative Breast Cancer, Effective in Some

PHILADELPHIA — The investigational immunotherapy MPDL3280A was safe, tolerable, and showed early signs of durable clinical activity in patients with metastatic triple-negative breast cancer, according to data from a first-in-human phase I clinical trial presented here at the AACR Annual Meeting 2015, April 18-22.

“The emergence of approaches for harnessing the immune system to fight cancer is creating a lot of excitement for oncologists and immunologists because many of the responses that are being achieved are prolonged,” said Leisha A. Emens, MD, PhD, Johns Hopkins associate professor of oncology and member of the Cancer Immunology and the Breast and Ovarian Cancer Programs at the Johns Hopkins Kimmel Cancer Center in Baltimore.

“The latest analysis of our data revealed a 24-week progression-free survival rate of 27 percent, with an objective response rate of 19 percent, and three of four responses are ongoing,” continued Emens. “This is very exciting because longer responses are not typical of what occurs when patients with metastatic triple-negative breast cancer are treated with chemotherapy, which is the standard of care for this population. However, we need to validate these findings in larger cohorts of patients.”

Emens explained that the immunotherapy MPDL3280A is a type of drug called a biologic, specifically a monoclonal antibody, and that it blocks the interaction between a protein called PD-L1 and one called PD-1, which is found on T cells (a type of immune cell). She said that normally this interaction shuts off the ability of T cells to attack cancers and that blocking the interaction with MPDL3280A allows the T cells to once again eliminate tumor cells.

The phase I clinical trial is evaluating MPDL3280A as a potential treatment for a variety of advanced solid tumors. Emens and colleagues enrolled 54 patients with metastatic triple-negative breast cancer in the study, 69 percent of whom had PD-L1 on 5 percent or more of immune cells infiltrating samples of their tumors and were considered to have PD-L1–positive disease. Twenty-one of these PD-L1-positive patients could be assessed for signs of clinical activity.
Investigational PD-L1–targeted Immunotherapy Safe for Patients With Triple-negative Breast Cancer, Effective in Some
Page 2 of 3

Of the 54 patients (both PD-L1–negative and PD-L1–positive) who could be assessed for side effects, 63 percent experienced at least one drug-related adverse event, with 11 percent experiencing at least one grade 3 event. One patient experienced a grade 4 event. The most common drug-related adverse events were fatigue, fever, nausea, and loss of appetite.

This study was funded by Genentech. Emens has received research funding from Genentech for another clinical trial and a research grant from Roche. She has also received research funding from Merck, EMD Serono, Amplimmune, and Maxcyte, and consulted for Vaccinex, Celgene, Aveo, and Bristol-Myers Squibb. Under a licensing agreement between Aduro Inc. and Johns Hopkins University, the university and Emens are entitled to milestone payments and royalty on sales of the GM-CSF-secreting breast cancer vaccine. The terms of these arrangements are being managed by Johns Hopkins University in accordance with its conflict-of-interest policies. Emens is a member of the CTGTAC Advisory Committee of the Food and Drug Administration.


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**Title:** Inhibition of PD-L1 by MPDL3280A leads to clinical activity in patients with metastatic triple-negative breast cancer (TNBC)

**Author Block:** Leisha A. Emens¹, Fadi S. Braiteh², Philippe Cassier³, Jean-Pierre Delord⁴, Joseph Paul Eder⁵, Marcella Fasso⁶, Yuanyuan Xiao⁶, Yan Wang⁶, Luciana Molinero⁶, Daniel S. Chen⁶, Ian Krop⁷. ¹Johns Hopkins Univ. School of Medicine, Baltimore, MD; ²Comprehensive Cancer Centers of Nevada, Las Vegas, NV; ³Centre Leon Berard, Lyon, France; ⁴Institut Claudius Regaud, Toulouse, France; ⁵Yale School of Medicine, New Haven, CT; ⁶Genentech, Inc., South San Francisco, CA; ⁷Dana-Farber Cancer Institute, Boston, MA

**Abstract Body:**

Introduction: TNBC is a mutationally complex breast cancer subtype with poor prognosis and no current targeted therapy options. Compared with other intrinsic breast cancer subtypes, TNBC has higher programmed death-ligand 1 (PD-L1) expression levels, which may hinder antitumor T-cell responses. MPDL3280A is a monoclonal anti-PD-L1 antibody, engineered for optimized efficacy and safety, that blocks signaling through the PD-L1/PD-1 and PD-L1/B7.1 pathways.

Methods: MPDL3280A was tested in a metastatic TNBC expansion cohort as part of a multicenter Phase Ia study. Pts received MPDL3280A at 15 mg/kg, 20 mg/kg or 1200 mg flat dose IV q3w. AEs were summarized for the safety follow-up duration from the first dose to 30 days after the last dose before the clinical cutoff on Sept 2, 2014. Responses were assessed by RECIST v1.1 criteria in pts who received MPDL3280A by Jul 21, 2014, evaluable for efficacy (≥ 6-wk follow-up). PD-L1 expression on tumor-infiltrating immune cells (ICs) at baseline was centrally evaluated by IHC in archival or fresh biopsies, and pts were scored as PD-L1 IHC (IC) 0, 1, 2 or 3. Peripheral biomarkers were assayed using FACS and multiplex immunoassays.

Results: In the TNBC cohort, 27 pts were selectively enrolled. These pts had a median age of 48 y (29-82 y) and were evaluable for safety; 52% had ECOG PS 0 and 44% had ECOG PS 1. Visceral and bone metastases were present at baseline in 59% and 11% of pts, respectively. In addition, 85% received ≥ 4 prior systemic regimens (neoadjuvant, adjuvant or metastatic), including anthracyclines (78%), taxanes (82%) and platinum agents (15% cisplatin, 41% carboplatin). All-grade treatment-related AEs occurred in 67% of pts, most frequently fatigue (22%), pyrexia (15%), neutropenia (15%) and nausea (15%). 11% of pts experienced a Grade 3-5 related AE (5 Grade 3 events: adrenal insufficiency, neutropenia, nausea, vomiting, decreased WBC count; 1 Grade 5 pulmonary hypertension event in a pt with an atrial septal defect). Among 21 efficacy-evaluable PD-L1 IHC 2 or 3 pts (13 IHC 2 and 8 IHC 3), the unconfirmed RECIST ORR was 24% (95% CI, 8% to 47%); 3 PRs and 2 CRs were observed. Response duration ranged from 0.1+ to 41.6+ wks, with the median not yet reached. Pts with evidence of durable nonclassical responses suggestive of pseudoprogression were also observed. Overall, the 24-wk PFS rate was 33% (95% CI, 12% to 53%). Biomarker analysis revealed transient elevation of plasma cytokines and proliferating CD8 cells following MPDL3280A treatment. Updated clinical data, including PD-L1-negative pts, will be presented.

Conclusions: MPDL3280A was generally well tolerated and demonstrated promising efficacy in pretreated metastatic PD-L1 IHC 2 or 3 TNBC pts. Furthermore, circulating biomarker analyses revealed pharmacodynamic responses to MPDL3280A. Clinical evaluation of MPDL3280A in metastatic PD-L1 IHC 0 or 1 TNBC is ongoing (NCT01375842).