VOLUME 28 · NUMBER 15 · MAY 20 2010

JOURNAL OF CLINICAL ONCOLOGY

CORRESPONDENCE

EpCAM As a Target in Cancer Therapy

TO THE EDITOR: In their editorial, Schmoll and Arnold[1] discussed possible reasons for the ultimate failure of anti–epithelial cell-cell adhesion molecule (EpCAM) murine monoclonal antibody edrecolomab in the treatment of patients with colorectal cancer.[2-4] While we appreciate their analysis and conclusions, certain aspects are missing or need correction that may be important for the future development of anti-EpCAM therapies and better understanding of EpCAM as a target.

Like for every targeted therapy, the level of EpCAM target expression will have an impact on the outcome of a trial. This was evident for the human anti-EpCAM antibody adecatumumab in patients with metastatic breast cancer.[5] Although a high level and frequency of EpCAM expression can be assumed for patients with colorectal cancer,[6] none of the previous trials prospectively or retrospectively analyzed patients for levels of EpCAM expression on tumor tissue. Particularly for a low-affinity antibody, such as edrecolomab, it may be of importance that tumor cells express EpCAM at a high and not just at an intermediate level. Even for the high-affinity antibody trastuzumab only patients with a high level of *HER2* target expression are eligible for treatment. Future studies will certainly benefit from stratifying patients for their level of EpCAM target expression.

The initial trial by Riethmueller et al[3] used edrecolomab, which had been produced by hybridoma cells in ascites of mice. All subsequent larger trials used edrecolomab produced by fermentation technology with a selected hybridoma clone. The known modes of action of edrecolomab—antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and induction of an anti-idiotypic response—will all critically rely on the carbohydrate composition in the CH2 domain of the antibody, which can largely differ in production. The comparability of the clinical trial materials used in the Riethmueller et al trial and in the subsequent larger trials has never been established and is highly unlikely to be the case. Hence, more than misty eyes, a potential difference in biologic activity of clinical trial materials may serve to explain the discrepant outcome of clinical trials.

The notion that leukocyte immunoglobulin-like receptor 1 is a ligand of EpCAM is wrong. The initial publication by Meyaard et al[7] has been retracted.[8,9]

In the meantime, a trifunctional bispecific antibody targeting EpCAM on cancer cells and CD3 on T cells called catumaxomab (Removab; TrionPharma, Munich, Germany) has gained approval from the European Medicines Agency for the treatment of malignant ascites. This highlights the utility of EpCAM as target for antibody-based therapies.

At the time this editorial[1] was published, EpCAM has been reported to be an oncogenic signaling molecule that is activated by regulated intramembrane proteolysis.[10-12] According to this study, EpCAM deploys oncogenic effects on members of the *wnt* pathway, which explains well why EpCAM is expressed in many cancers and also on cancer-initiating cells from various tumor entities including colon.[13,14] The involvement of proteases in the activation of EpCAM may provide for novel therapeutic targets preventing EpCAM signaling in cancer.

Determination of EpCAM expression as a biomarker in future clinical trials and novel anti-EpCAM therapies based on human antibodies or bispecific T-cell engaging formats may finally allow leveraging the widely expressed target for cancer therapy.

Olivier Gires
Clinical Cooperation Group Molecular Oncology, Head and Neck Research Department, Ludwig Maximilians University Munich and Helmholtz Center, Munich, Germany

Patrick A. Bauerle
Micromet AG, Munich, Germany

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: Patrick A. Baeuerle, Micromet Inc (C) **Consultant or Advisory Role:** None **Stock Ownership:** Patrick A. Baeuerle, Micromet Inc **Honoraria:** None **Research Funding:** None **Expert Testimony:** None **Other Remuneration:** None

REFERENCES

1. Schmoll HJ, Arnold D: When wishful thinking leads to a misty-eyed appraisal: The story of the adjuvant colon cancer trials with edrecolomab. J Clin Oncol 27:1926-1929, 2009

2. Riethmuller G, Holz E, Schlimok G, et al: Monoclonal antibody therapy for resected Dukes' C colorectal cancer: Seven-year outcome of a multicenter randomized trial. J Clin Oncol 16:1788-1794, 1998

3. Riethmüller G, Schneider Gadicke E, Schlimok G, et al: Randomised trial of monoclonal antibody for adjuvant therapy of resected Dukes' C colorectal carcinoma. Lancet 343:1177-1183, 1994

4. Fields AL, Keller A, Schwartzberg L, et al: Adjuvant therapy with the monoclonal antibody Edrecolomab plus fluorouracil-based therapy does not improve overall survival of patients with stage III colon cancer. J Clin Oncol 27:1941-1947, 2009

5. Schmidt M, Scheulen ME, Dittrich C, et al: An open-label, randomized phase II study of adecatumumab, a fully human anti-EpCAM antibody, as monotherapy in patients with metastatic breast cancer. Ann Oncol 21:275-282, 2010

6. Went P, Vasei M, Bubendorf L, et al: Frequent high-level expression of the immunotherapeutic target Ep-CAM in colon, stomach, prostate and lung cancers. Br J Cancer 94:128-135, 2006

7. Meyaard L, van der Vuurst de Vries AR, de Ruiter T, et al: The epithelial cellular adhesion molecule (Ep-CAM) is a ligand for the leukocyte-associated immunoglobulin-like receptor (LAIR). J Exp Med 194:107-112, 2001

8. Meyaard L, van der Vuurst de Vries AR, de Ruiter T, et al: Retraction. J Exp Med 198:1129, 2003

© 2010 by American Society of Clinical Oncology

Downloaded from jco.ascopubs.org on March 18, 2016. For personal use only. No other uses without permission.
Copyright © 2010 American Society of Clinical Oncology. All rights reserved.

9. Nechansky A, Kircheis R: EpCAM is not a LAIR-1 ligand! Cancer Biol Ther 4:357, 2005; author reply 358, 2005

10. Maetzel D, Denzel S, Mack B, et al: Nuclear signalling by tumour-associated antigen EpCAM. Nat Cell Biol 11:162-171, 2009

11. Munz M, Baeuerle PA, Gires O: The emerging role of EpCAM in cancer and stem cell signaling. Cancer Res 69:5627-5629, 2009

12. Carpenter G, Red Brewer M: EpCAM: Another surface-to-nucleus missile. Cancer Cell 15:165-166, 2009

13. Visvader JE, Lindeman GJ: Cancer stem cells in solid tumours: Accumulating evidence and unresolved questions. Nat Rev Cancer 8:755-768, 2008

14. Gires O, Klein CA, Baeuerle PA: On the abundance of EpCAM on cancer stem cells. Nat Rev Cancer 9:143, 2009; author reply 143, 2009

DOI: 10.1200/JCO.2009.26.8540; published online ahead of print at www.jco.org on April 12, 2010

 © 2010 by American Society of Clinical Oncology

Downloaded from jco.ascopubs.org on March 18, 2016. For personal use only. No other uses without permission.
Copyright © 2010 American Society of Clinical Oncology. All rights reserved.