Clinical Cancer Research

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Letter to the Editor

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Clinical Cancer Research recently published an important study by Coward and colleagues (1) examining interleukin-6 as a target in ovarian cancer and last year published an investigation of the same target in prostate cancer by Dorff and colleagues (2). Examining these two studies together may yield additional insights.

In the 4 of 18 patients with ovarian cancer who had stable disease for 6 months or more, the plasma concentration of VEGF declined significantly during treatment. This raises the possibility that the mechanism of action of siltuximab may involve the reduction of VEGF levels.

Dorff and colleagues examined a cohort of 53 patients with castration-resistant prostate cancer, finding that overall survival following siltuximab treatment was significantly better in patients with higher baseline levels of soluble epidermal growth factor receptor (sEGFR) than those with lower levels.

What is the relationship between these two findings? It is well established that IL-6 signaling can upregulate hypoxia-inducible factor-1 (HIF-1) via STAT3 (3) and that HIF-1 in turn promotes VEGF expression. EGFR signaling can also promote VEGF expression through both HIF-1–dependent and HIF-1–independent mechanisms (4).

We hypothesize that the effect of siltuximab on VEGF may depend on the level of EGFR signaling present. In patients with low levels of EGFR signaling (as may be indicated by high levels of sEGFR), siltuximab alone should be sufficient to reduce VEGF production. However, in patients with high levels of EGFR signaling, a combination of siltuximab and an agent targeting the EGFR pathway may be necessary.

This hypothesis is supported by the recent findings of Song and colleagues that the combination of siltuximab with an EGFR inhibitor was significantly more effective than either therapy alone in reducing tumor volume in mice bearing non–small cell lung cancer (NSCLC) xenografts (5).

Coward and colleagues articulate the need to identify subgroups of patients most likely to respond to siltuximab. Examining baseline levels of sEGFR, and other markers of EGFR signaling, is one possible approach. If subsequent studies confirm that siltuximab is more efficacious in patients with lower EGFR signaling, it would suggest that patients with higher EGFR signaling could derive increased benefit from the combination of siltuximab and agents targeting EGFR.

Disclosure of Potential Conflicts of Interest

J.W. Locasale and B. Zeskind are employees of Immuneering Corporation and B. Zeskind has ownership interest in Immuneering Corporation.

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