Mind the Gap: Potential for Rebounds during Antiangiogenic Treatment Breaks

John M.L. Ebos and Roberto Pili

VEGF pathway inhibitors have shown benefits in many cancers, yet many (often controversial) questions remain about whether vascular and tumor regrowth can occur when therapy is stopped. Marked increases in endothelial cell proliferation could play a role in putative rebounds, potentially influencing overall efficacy, dosing schedules, and presurgical intervention strategies. Clin Cancer Res; 18(14); 3719–21. ©2012 AACR.
antiangiogenic therapy), which could fuel epithelial-tomesenchymal transition changes and play a role in eventual drug-resistance phenotypes (8). However, evidence of tumor vascular rebounds or increased growth following treatment discontinuation has not been confirmed in all cases (9), and many questions remain, including whether this phenomenon occurs with all types of VEGF pathway inhibitors, whether it depends on disease and disease stage, and whether a clinical impact (if real) can be determined for patients.

Several indicators show that disease stage could play a critical role not only in how tumors respond to VEGF pathway inhibition but also in how they respond when treatment stops. Because preclinical studies have mostly focused on models of localized tumor growth and clinical studies have mainly looked at established metastatic disease, it is possible that drug effects in one may not predict for effects in the other, either on or off treatment (7). For this reason, it is unclear whether, in the study by Griffioen and colleagues, the proliferative endothelial cells after sunitinib treatment reflect a change expected to be seen in metastatic disease. A recent retrospective examination of sunitinib in patients with metastatic RCC yielded evidence that tumors did indeed regrow when therapy was discontinued at a rate similar to that before intervention, but growth rates were not increased in an accelerated manner (10). Also important, differences in inhibition strategies could be significant to whether rebounds are related to one drug or another. Although regrowth has been noted during break periods with sunitinib-treated patients, preclinical (11) and clinical (12) studies with VEGF-neutralizing antibodies have not shown increases in regrowth after treatment discontinuation, a difference that Griffioen and colleagues confirm in the presurgical setting with bevacizumab. Although several reasons could explain this observation, including longer drug half-life for antibodies (which can last several weeks) and target specificity [receptor TKIs, such as sunitinib, have multiple targets in addition to VEGFRs, including c-kit, platelet-derived growth factor receptor (PDGFR), and others; ref. 7], it may account for some differences seen in the clinical success with both types of agents, either alone or with chemotherapy.

Of the many questions that remain about the clinical relevance of changes in presurgical RCC tumors following surgery...

---

**Figure 1.** Tumor vascular rebound following cessation of VEGFR TKI therapy in RCC patients and possible implications: 1. presurgical tumor response (purple line); 2. delayed disease recurrence and increased progression free survival (red line); and 3. potential for increased growth of occult disease or selection of a resistant and/or more aggressive tumor phenotype (green line).aBevacizumab only; bSunitinib only. MVD, microvessel density; VE-cadherin, vascular endothelial cadherin.
sunitinib treatment scheduling, perhaps it is the potential clinical impact that is the most significant. Subsequent studies with larger patient samples will be required to determine whether sunitinib-induced increases in tumoral ECs correlate with rapid vascularization and tumor regrowth and should address whether postsurgical outcomes could be affected. Furthermore, prospective studies, rather than retrospective analyses, will need to be done that coincide with relevant perioperative preclinical studies to monitor the impact of long versus short treatment breaks and their effect prior to or immediately following nephrectomy. Finally, tumor heterogeneity remains a challenge not only for tumor genetic profiling and biomarker discovery but also for the histologic assessment of vasculature changes upon antiangiogenic therapies. In the near future, perhaps technically improved and less expensive noninvasive imaging modalities will contribute to achieving a personalized approach to antiangiogenics, in which optimal dose, schedule, duration, and disease setting will be tailored to each patient.

 Disclosure of Potential Conflicts of Interest
R. Pili: research funding, Regeneron; consultant, Pfizer, Regeneron, Genentech. No potential conflicts of interest were disclosed by the other author.

 Authors' Contributions
Conception and design: J.M.L. Ebos, R. Pili
Writing, review, and/or revision of the manuscript: J.M.L. Ebos, R. Pili

Received May 16, 2012; accepted May 30, 2012; published OnlineFirst June 7, 2012.

References
**Clinical Cancer Research**

**Mind the Gap: Potential for Rebounds during Antiangiogenic Treatment Breaks**

John M.L. Ebos and Roberto Pili


<table>
<thead>
<tr>
<th>Updated version</th>
<th>Access the most recent version of this article at: do:10.1158/1078-0432.CCR-12-1459</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplementary Material</td>
<td>Access the most recent supplemental material at: <a href="http://clincancerres.aacrjournals.org/content/suppl/2012/07/10/1078-0432.CCR-12-1459.DC1">http://clincancerres.aacrjournals.org/content/suppl/2012/07/10/1078-0432.CCR-12-1459.DC1</a></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cited articles</th>
<th>This article cites 12 articles, 7 of which you can access for free at: <a href="http://clincancerres.aacrjournals.org/content/18/14/3719.full.html#ref-list-1">http://clincancerres.aacrjournals.org/content/18/14/3719.full.html#ref-list-1</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>Citing articles</td>
<td>This article has been cited by 5 HighWire-hosted articles. Access the articles at: /content/18/14/3719.full.html#related-urls</td>
</tr>
</tbody>
</table>

**E-mail alerts**  
Sign up to receive free email-alerts related to this article or journal.

**Reprints and Subscriptions**  
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

**Permissions**  
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.