

this kind may well limit the ability of patients to tolerate this regimen, because they may collectively reduce quality of life and may affect patient willingness to continue treatment. Despite this, the combination was considered tolerable and was associated with inhibition of several pharmacodynamic end points at the identified maximum-tolerated dose (including inhibition of 4E binding protein 1 phosphorylation, a surrogate of mTOR pathway activity).

A PK drug-drug interaction was also partly assessed in this trial. Although clinically relevant PK interactions were not noted, there appeared to be acceptable interpatient variability of capecitabine levels, whereas a greater degree of variability was observed for ridaforolimus. Importantly, ridaforolimus (just like rapamycin) inhibited dihydropyrimidine dehydrogenase, suggesting a class effect for mTOR inhibitors on the enzyme. It is interesting to note that at its nadir, dihydropyrimidine dehydrogenase activity was always above the threshold level associated with risk of severe fluoropyrimidine-associated toxicity, which is reassuring, given that the toxicity profile of this combination is further refined in future studies.

Although Perotti et al<sup>2</sup> suggest that this combination is clinically active, it is impossible to know whether this was related to either of the single agents alone, or whether a prolonged period of stable disease was related to the tumor's natural history in the absence of therapy. In this respect, phase I combination studies,<sup>5</sup> as well as nonrandomized phase II studies,<sup>4,7</sup> are limited in their ability to accurately assess clinical activity. This is partly because such studies are commonly performed in populations of patients that are either extensively pretreated or highly selected because of toxicity-related concerns.<sup>8</sup> In addition, homogeneous groups of patients are typically not treated at the maximum-tolerated dose of the regimen. Although we list clinical activity as a criterion in Table 1, it is considered a minor element because response data in phase I trials are unreliable surrogates for the ultimate value of the combination. Thus, clinical activity in a phase I trial will not be considered a sufficient reason for acceptance in the absence of the major criteria listed in Table 1.

It is likely that the success of targeted therapies will depend on their rational use in combination with other agents that affect intersecting pathways of tumor growth, survival, angiogenesis, and drug resistance. As such, the editors recognize the importance of performing combination phase I studies using targeted agents, but at the same time realize that not all combination studies will be informative. The criteria outlined in Table 1 should serve as a guide to readers as they assess the relative merits of combination phase I trials, and will be

helpful to prospective authors considering such articles for publication in *JCO*.

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#### AUTHOR CONTRIBUTIONS

**Conception and design:** Jaap Verweij, Mary L. Disis, Stephen A. Cannistra

**Collection and assembly of data:** Jaap Verweij

**Data analysis and interpretation:** Jaap Verweij, Mary L. Disis, Stephen A. Cannistra

**Manuscript writing:** Jaap Verweij, Mary L. Disis, Stephen A. Cannistra

**Final approval of manuscript:** Jaap Verweij, Mary L. Disis, Stephen A. Cannistra

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## VICTOR Spoiled?

Richard M. Goldberg, *Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC*  
Monica M. Bertagnolli, *Brigham and Women's Hospital, Boston, MA*

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The notion that nonsteroidal anti-inflammatory drugs (NSAIDs) can alter the natural course of colonic neoplasia debuted 30 years ago when Pollard and Luckert<sup>1</sup> reported that chemically induced polyps in Sprague-Dawley rats regressed after indomethacin treatment. Wad-

dell and Loughry<sup>2</sup> brought this observation into the clinic, documenting regression of rectal polyps after administration of the NSAID sulindac to four members of a family with familial adenomatous polyposis. These observations led to key insights into the aberrant

biology that leads to colonic neoplasia and, when those aberrant pathways are uninterrupted, culminates in the development of colon cancer in some patients.

C colorectal cancer develops as a result of successive losses of tumor suppressor genes and the gain of oncogenes, events that are facilitated by a permissive tissue microenvironment.<sup>3</sup> Prostaglandins are highly reactive molecules that are produced as a tissue-specific response to conditions that require cellular activation, such as infection, wounding, and other stressors. These agents are metabolized from lipid cell membrane components by enzymes that are specific to particular tissues. Inflammatory or mitogenic activity in the mucosa of the large intestine produces prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) through a reaction catalyzed by the cyclooxygenase-2 (COX-2) enzyme. PGE<sub>2</sub>, in turn, exerts powerful local effects that promote wound healing, including promotion of epidermal growth factor signaling, epithelial cell invasion, and angiogenesis.<sup>4</sup> COX-2 is also induced in response to tumor promoters, and its overexpression is observed in approximately two thirds of human adenomas and colon cancers, compared with background activity in healthy colonic epithelium.<sup>5</sup> During colorectal cancer development, production of PGE<sub>2</sub> by COX-2 seems to be an early, critical, stuck accelerator that drives multiple tumorigenic responses. Animal studies confirmed that the antitumor effects of NSAIDs in the intestine depend on the ability of these drugs to inhibit COX-2 activity.<sup>6</sup>

These data led investigators to mount several phase III studies in humans. Because of the potential for bleeding and GI toxicity associated with the ingestion of nonselective NSAIDs such as sulindac, studies focused on the use of selective COX-2 inhibitors for adenoma prevention as well as for the adjuvant treatment of patients with resected colon cancer. The Adenoma Prevention Study (APC) enrolled 2,035 patients with adenomas that had been removed via colonoscopy and randomly assigned them to receive 3 years of treatment with the COX-2 inhibitor celecoxib or a placebo.<sup>7</sup> The patients treated with the placebo had a cumulative incidence of adenomas at 3 years of 60.7%, which was reduced to 43.2% for those receiving 200 mg of celecoxib twice daily, and 37.5% for those assigned to receive 400 mg of celecoxib twice daily.<sup>8</sup> Results were similar in adenoma prevention trials that studied celecoxib at a dose of 400 mg administered once daily (Prevention of Spontaneous Adenomatous Polyps [PreSAP] study), and rofecoxib at 25 mg per day (Adenomatous Polyp Prevention with VIOXX [APPROVE] study).<sup>9,10</sup> After the APC and APPROVE trials had completed enrollment, indications arose that treatment with the selective COX-2 inhibitors rofecoxib and celecoxib led to an increased risk of cardiovascular and thrombotic events. The data from both trials were heavily scrutinized to examine the experiences of enrolled patients relevant to those events. In the APC trial, the risk of any cardiovascular event was 4.9% for patients assigned to the placebo group, 6% (relative risk, 1.2) for patients who received the lower dose of celecoxib, and 7.9% (relative risk, 1.6) for patients who received the higher dose of celecoxib. A baseline history of atherosclerotic cardiovascular disease was a significant predictor of this increased risk ( $P = .004$ ).

The final report on efficacy from the Vioxx in Colorectal Cancer Therapy: Definition of Optimal Regime (VICTOR) study is reported in this issue of *Journal of Clinical Oncology* by Midgley et al.<sup>11</sup> Although the VICTOR study was designed to include 7,000 patients with stage II or III resected colorectal cancer in an effort to detect a reduction in the hazard risk of death of 0.80, the emergence of the cardiovascular risk

data noted above led to premature closure of the study after 2,327 patients had been enrolled. A report of the cardiovascular safety data related to this trial has been published previously.<sup>12</sup> Those data recapitulate the observations of the APC trial. One could argue that the frequency and severity of adverse events in a trial onto which people with cancer are enrolled, who have a high risk for recurrence and subsequent death as a result of their illness, should differ from that which is reasonable in a prevention trial. Nonetheless, rofecoxib was withdrawn from the market and the VICTOR trial was aborted. This report addressing the efficacy end points of the aborted trial contains mature data with a median follow-up period of nearly 5 years. However, rather than the intended 3 to 5 years of exposure to rofecoxib or a placebo, the median exposure time was 7.4 months, with just one third of patients receiving the drug for at least 1 year.

Mounting and running this trial was a massive endeavor. The study was well conducted by an experienced investigative team. In accordance with the principles of the senior investigator, Kerr, the study had liberal entry criteria permitting patients with stage II and III cancer, colon and rectal cancers, no or some adjuvant chemotherapy or radiation, and aspirin intake of less than 100 mg per day or no aspirin use. The philosophy of the trial design was to achieve larger sample sizes to over-ride any heterogeneity in a study population characterized by liberal enrollment criteria. No investigator plans for early trial termination, but that is exactly what occurred in this case. Because of the broad entry criteria and the reduced sample size actually accrued, the interpretation of these data is difficult. The investigators must be applauded for requiring tumor block submission for assessment of COX-2 expression via immunohistochemistry to correlate those expression levels with outcomes.

The study was a negative one, showing no significant differences in outcomes with respect to overall, disease-free, or recurrence-free survival. The finding that 110 of 297 recurrences in the rofecoxib group occurred in the first year compared with 141 of 329 recurrences in the placebo group ( $P = .04$ ) suggests that COX-2 inhibition may have had some discernable biologic effect. However, there was a lack of association between COX-2 expression and outcomes in this study. The authors note that this lack of activity may be a consequence of too few patients, too little drug exposure, not targeting the drug to the optimal population, or a lack of drug efficacy. It may also have been a result of the broad eligibility criteria that permitted enrollment of a relatively heterogeneous patient population. Additional trials might help us ferret out which of the explanations are relevant.

Is it safe and worthwhile to perform additional studies to elucidate the potential role of COX-2 inhibition on recurrence of localized colon cancer, given the issue of cardiovascular risk that, after all, led to the withdrawal of rofecoxib from the market? The answer to that is a resounding yes on the basis of a 3-year development process that culminated in the opening of the Cancer and Leukemia Group B/Southwest Oncology Group (CALGB/SWOG) C80702 trial by the US Gastrointestinal Cancer Intergroup in July 2010. Patients with surgically resected stage III colon cancer are being enrolled onto this trial and randomly assigned to receive 3 versus 6 months of infusional fluorouracil, leucovorin, and oxaliplatin chemotherapy with a secondary random assignment to receive celecoxib 200 mg twice daily or a placebo. The study will include 2,500 patients, which is the sample size necessary to address the COX-2 question.

The results will be pooled with those of trials underway in Europe to address the duration of therapy issue, which requires a sample size

exceeding 15,000 to prove or disprove equivalence. This study has been heavily discussed and finally vetted by the National Cancer Institute's Gastrointestinal Cancer Steering Committee. The COX-2 pathway is highly relevant to colon cancer oncogenesis, and its inhibition may be a useful therapeutic tool. The trial addresses the need to examine patients exposed to COX-2 inhibitors for extended periods, given that data from the Nurses' Health Study suggest that a longer duration of COX-2 inhibition is advantageous in the prevention of colorectal cancer.<sup>13</sup>

Is the use of celecoxib safe in this setting? It seems that by excluding potential enrollees with a history of atherosclerotic cardiovascular disease, the risk of cardiovascular and thrombotic events can be minimized. In addition, the lower dose of 200 mg and the twice daily administration schedule are associated with a low risk of cardiovascular and thrombotic events.<sup>14</sup> Finally, the toxicity profile of celecoxib is far less troubling than that of standard cytotoxic chemotherapy agents commonly used in the treatment of patients with stage III colon cancer. In the setting of adjuvant therapy, rather than a prevention trial, the prospect of receiving this potentially active and relatively well-tolerated agent should not be daunting to patients, nor should the task of supervising its administration be daunting to their physicians. When the CALGB/SWOG C80702 trial completes accrual and data are analyzed, the benefit of evaluating COX-2 inhibition pioneered by VICTOR trialists should be realized. That will be a fitting tribute to the patients who participated in the VICTOR trial and the investigators who conceived the study and cared for those patients.

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#### AUTHOR CONTRIBUTIONS

**Conception and design:** Richard M. Goldberg, Monica M. Bertagnolli  
**Administrative support:** Richard M. Goldberg, Monica M. Bertagnolli  
**Collection and assembly of data:** Richard M. Goldberg  
**Data analysis and interpretation:** Richard M. Goldberg  
**Manuscript writing:** Richard M. Goldberg, Monica M. Bertagnolli

**Final approval of manuscript:** Richard M. Goldberg, Monica M. Bertagnolli

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# Insights Into the Place of Fulvestrant for the Treatment of Advanced Endocrine Responsive Breast Cancer

Anthony Howell, *Christie Hospital National Health Services Trust, Manchester, United Kingdom*  
 Jonas Bergh, *Karolinska Institutet, Stockholm, Sweden*

See accompanying article on page 4594

Endocrine therapy remains a highly important approach for the treatment of endocrine-responsive locally advanced and metastatic breast cancer, and responses may be seen to several agents given in sequence. However, questions remain concerning the optimal endocrine agent and the optimal sequence. Summarizing all randomized trials comparing therapies published up to 2004, Mauri et al<sup>1</sup> demonstrated that the modern aromatase inhibitors (AIs) produced a significant survival advantage compared with tamoxifen, progestogens, and the older AIs.<sup>1</sup> These data were

largely from the prefulvestrant era, and a question arises concerning the place of fulvestrant in the endocrine sequence. Recent studies, including the one reported by Di Leo et al,<sup>2</sup> are beginning to clarify this issue.

Fulvestrant is an analog of 17 $\beta$ -estradiol that binds the estrogen receptor (ER) with a similar affinity to the parent molecule.<sup>3</sup> However, because of the alkynylsulphonyl side chain in the 7- $\alpha$  position of the molecule, the ER is disrupted when fulvestrant binds, which leads to increased receptor degradation and decreased receptor half-life.<sup>3,4</sup>