Phase I Randomized, Double-Blind Pilot Study of Micronized Resveratrol (SRT501) in Patients with Hepatic Metastases—Safety, Pharmacokinetics, and Pharmacodynamics

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Abstract

The phytochemical resveratrol has undergone extensive preclinical investigation for its putative cancer chemopreventive properties. Low systemic availability of the parent compound due to rapid and extensive metabolism may confound its usefulness as a potential agent to prevent malignancies in organs remote from the site of absorption. Micronization allows increased drug absorption, thus increasing availability. Here we describe a pilot study of SRT501, micronized resveratrol, given as 5.0 g daily for 14 days, to patients with colorectal cancer and hepatic metastases scheduled to undergo hepatectomy. The purpose of the study was to assess the safety, pharmacokinetics, and pharmacodynamics of the formulation. SRT501 was found to be well tolerated. Mean plasma resveratrol levels following a single dose of SRT501 administration were 1,942 ± 1,422 ng/mL, exceeding those published for equivalent doses of nonmicronized resveratrol by 3.6-fold. Resveratrol was detectable in hepatic tissue following SRT501 administration (up to 2,287 ng/g). Cleaved caspase-3, a marker of apoptosis, significantly increased by 39% in malignant hepatic tissue following SRT501 treatment compared with tissue from the placebo-treated patients. SRT501 warrants further clinical exploration to assess its potential clinical utility. Cancer Prev Res; 4(9); 1419–25. ©2011 AACR.

Introduction

Resveratrol (3,5,4’-trihydroxy-trans-stilbene) is a phytoalexin produced by certain plants when damaged by pathogens such as bacteria or fungi. It occurs in the skin of red grapes and in peanuts and has been investigated extensively with respect to its putative cancer chemopreventive properties. Resveratrol is thought to mediate, at least in part, the purported disease-preventing actions of red wine and is also considered to prevent cardiovascular disease and morbidity associated with obesity and old age (1–3). The numerous pharmacologic properties of resveratrol and the suggestion that it may be a calorie-restriction mimetic that can prolong life, has engendered considerable interest by the lay press. An abundance of data obtained in cells in vitro and in preclinical models has highlighted a plethora of potential mechanisms by which resveratrol may prevent malignancies, predominantly those germane to cell survival and proliferation (4) including p53-dependent apoptosis (5) and cell-cycle arrest (6). However, robust clinical data remain scarce. Recent clinical pilot studies of resveratrol, in which it was administered at single or repeat doses of up to 5.0 g daily, focused on its safety, pharmacokinetic properties, and the analysis of potential efficacy biomarkers (4, 7–13). Pharmacokinetic profiles of resveratrol in healthy volunteers revealed rapid and extensive metabolism to resveratrol-4’-O-glucuronide, resveratrol-3’-O-glucuronide, and resveratrol-3-O-sulfate following oral administration of either a single (8) or repeated daily doses (9) of 0.5 to 5.0 g. Despite detection of relatively high resveratrol concentrations in the colorectal tissue of patients, its systemic availability is severely reduced by its avid metabolism. Consequently, although resveratrol has shown activity against a wide variety of malignancies in vitro (including bowel, breast, bladder, prostate, liver, and thyroid) and in vivo (reviewed in refs. 3, 14–16), it is likely that poor bioavailability may limit efficacy at sites distant to the gastrointestinal (GI) tract. Despite this, there is evidence to suggest that resveratrol elicits chemopreventive and therapeutic effects in preclinical models of liver cancer [(reviewed in ref. 17), alluding to potential for efficacy against hepatocarcinogenesis and malignancies that preferentially metastasize to the liver.]
Because of the poor aqueous solubility exhibited by resveratrol, digestive absorption is greatly influenced by drug dissolution rate. In an effort to increase absorption across the GI tract, and thus systemically available parent compound, there has been considerable interest in the pharmaceutical manipulation of resveratrol. Decreasing the particle size of such chemicals can improve their rate of dissolution and thus their absorption (18). Therefore, the aim of this clinical study was to investigate whether consumption of SRT501, a micronized resveratrol formulation designed by Sirtris, a GSK Company, is safe and generates measurable and pharmacologically active levels of parent agent both in the circulation and in the liver. There are currently no clinical data available that determine resveratrol concentrations in human tissues other than the colon. To this end, patients with colorectal cancer earmarked to undergo resection of liver metastases were recruited into a pilot study. They ingested either placebo or SRT501 on 14 consecutive days prior to surgery, and levels of resveratrol were quantified in blood and hepatic resection tissue. Potential pharmacodynamic effects of SRT501 were investigated by comparing the expression/activation of candidate protein biomarkers intrinsically associated with cell survival and apoptosis in the circulation and tissue of patients who received the agent and those who were on placebo.

Methods

Resveratrol formulation

Microparticulate resveratrol of particle size less than 5 μm (SRT501) was manufactured by Sirtris Pharmaceuticals, a GSK Company. Particle size reduction is believed to enhance the bioavailability of resveratrol primarily due to the increase in surface area and improved suspension properties. A sachet containing SRT501 (5.0 g) was mixed with an aliquot (4 mL) of docusate sodium solution (docusate sodium, citric acid, colorant, glycerin, flavoring, sodium citrate, sodium saccharin, and sorbitol), made up to 20 mL in distilled water forming a uniform suspension, to the increase in surface area and improved suspension properties. A sachet containing SRT501 (5.0 g) was mixed with an aliquot (4 mL) of docusate sodium solution (docusate sodium, citric acid, colorant, glycerin, flavoring, sodium citrate, sodium saccharin, and sorbitol), made up to 20 mL in distilled water forming a uniform suspension, and ingested by patients.

Patients

The pilot study, designed and sponsored by Sirtris, was conducted at the University Hospitals of Leicester (UHL) NHS-Trust (UHL 10507; trial registry: NCT00920803). It was reviewed and approved by the Leicestershire, Northamptonshire, and Rutland Research Ethics Committee (United Kingdom) and conducted in accordance with applicable guidelines on Good Clinical Practices. Nine subjects (18 years or older) presenting with confirmed stage IV colorectal cancer and hepatic metastases, who had not received therapeutic intervention for their cancer within 6 weeks of study commencement and had a life expectancy of less than 3 months, were recruited into the study. All patients were scheduled to undergo resection of liver metastases. Participants had to be physically capable of complying with the protocol and had a normal electrocardiogram and no history of HIV infection or hepatitis B/C. Patients were asked to refrain from large quantities of resveratrol-containing foods and drinks such as peanuts, grapes, mulberries, and alcohol within 48 hours of scheduled pharmacokinetic collection days, and the day of surgical resection.

Study design

The study was a phase I, randomized (2:1), double-blind clinical trial. Six subjects were randomized to receive SRT501 and 3 placebo (titanium dioxide). Interventions were provided in clinical kits as a powder and reconstituted as described earlier. Patients ingested the formulation preoperatively daily for a minimum of 10 days and a maximum of 21 days, depending upon surgical scheduling. Plasma samples for pharmacokinetic assessment were obtained on days 1 and 2, and on the day of surgical resection. Plasma for pharmacodynamic assessment was obtained predose, immediately prior to, and during surgery. Diseased and normal adjacent hepatic tissues were resected 6 to 7 hours after the last dose. Participants completed a daily adverse event (AE) diary, which was assessed using the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) v3.0. Of the 9 patients recruited, 7 completed the study, 1 died because of postoperative complications, and 1 ceased administration early due to AEs (diarrhea). Pharmacokinetic samples were obtained from all 9 subjects. The primary objectives of the study were to determine safety and tolerability of SRT501 and resveratrol pharmacokinetics. The secondary objectives were to explore potential pharmacodynamic changes elicited by SRT501 in blood and tissues.

Sample collection

Blood samples were collected prior to administration on day 1, for pharmacokinetic analyses at 0.25, 0.5, 1, 2, 4, 8, and 24 hours after the first dose, and prior to and during surgery. Plasma (sodium heparin tubes) and serum were obtained and stored at −80°C until analysis. Tissues were harvested from resected material, part of which was formalin-fixed and paraffin-embedded and part immediately frozen and stored at −80°C until analysis.

Sample preparation and analysis

Quantitation of resveratrol in plasma and tissues was conducted by Charles River Laboratories. The methodology complied with the U.S. Food and Drug Administration (21CFR part 58) Good Laboratory Practice regulations, using an in-house validated liquid chromatography/tandem mass spectrometry (LC/MS-MS) method. In brief, 50 μL of plasma samples were extracted using acidified methanol (ascorbic acid/methanol/formic acid, 50:50:0.025; 5 μL) containing resveratrol-[13C] as an internal standard. Samples were then centrifuged (14,000 rpm/0°C/10 min), and the supernatant aliquoted into a 96-well collection plate for analysis. Separation,
quantitation, and characterization of resveratrol was achieved using a Symbiosis Pharma system (XLC method) in conjunction with an MDS Sciex API 3000 mass spectrometer. A Waters YMC ODS-AQ column (3 μm, 4.6 × 50 mm²) was linked to a PEEK precolumn 0.5 μm filter. The eluant consisted of a binary mobile phase [A: water/formic acid, 100:0.025 (v/v), B: methanol/acetonitrile/formic acid, 20:80:0.025 (v/v/v)]. The elution gradient was A 85%/B 15% to A 5%/B 95% for 4 minutes. Resveratrol was characterized by electrospray mass spectrometry (negative ionization mode) with ion spray voltage −4,500 V, declustering potential −25 V, focusing potential −30 V, entrance potential −12 V, collision energy −27 V, collision exit potential 40 V, and temperature 550°C. Lower limit of quantitation (LLOQ) was 5 ng/mL and upper limit of quantitation (ULOQ) was 1,000 ng/mL. Tissue samples were minced on ice and approximately 100 mg was used for analysis. Acidified methanol (ascorbic acid/methanol/formic acid, 50:50:0.025; 5 μL) containing resveratrol was linked as an internal standard, 100 μL matrix green beads, and 500 μL ethanol were added to each sample, the mixture vortexed, and left on ice (10 minutes). Samples were homogenized (Fastprep, 2.4–5.5 m/s, 20 s), left on ice (10 minutes), and the homogenization repeated prior to centrifugation (14,000 rpm/0°C/10 min). An aliquot (100 μL) of the supernatant was added to 100 μL water/formic acid (100:0.25). Separation, quantitation, and characterization of resveratrol were achieved using an Agilent 1100 chromatograph with an MDX Sciex API 5000 mass spectrometer. A Waters YMC ODS-AQ column (3 μm, 4.6 × 50 mm²) was linked to a PEEK precolumn 0.5 μm filter. The eluant was as that for the plasma analysis; gradient elution was over 6.5 minutes from A 70%/B 30% to A 0%/B 100%, then back to A 70% B 30%. Mass spectrometric conditions were as described earlier except: ion spray voltage −4,500 V, declustering potential −120 V, entrance potential −10 V, collision energy −27 V, collision exit potential −10 V, and temperature 700°C. For tissue samples, LLOQ was set at 2.5 ng/g and ULOQ at 500 ng/g. Data collection was done using Analyst version 1.4.2. (MDX Sciex).

Analysis of cell proliferation and apoptosis

Formalin-fixed tissues were analyzed for markers of proliferation and apoptosis by using the NovoLink Polymer Detection System (Novocea Laboratories) in conjunction with anti-Ki-67 (Dako) and cleaved anti-caspase-3 (Cell Signaling Technology) antibodies. In brief, paraffin-embedded sections were dewaxed at 65°C and rehydrated through a series of alcohol washes. Antigen retrieval was via microwaving in either Tris-EDTA (pH 9.0) for Ki-67 or citrate buffer (pH 6.0) for cleaved caspase-3. Sections were visualized at 40× magnification, using a Leica DC300 inverted light microscope and camera system. Images were processed using Adobe Photoshop v7.0.1. Positive staining cells were scored on 10 random fields of view on each slide and expressed as percent positively stained cells. All analyses were carried out blinded.

Table 1. Demographics for patients randomized to 5.0 g/day SRT501 and placebo

<table>
<thead>
<tr>
<th>SRT501 (N = 6)</th>
<th>Placebo (N = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
</tr>
<tr>
<td>68.5 ± 10.8</td>
<td>64.3 ± 6.35</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
</tr>
<tr>
<td><strong>Body mass index</strong></td>
<td>28.10 ± 4.35</td>
</tr>
<tr>
<td><strong>Race, Caucasian</strong></td>
<td>100%</td>
</tr>
<tr>
<td><strong>Days on study</strong></td>
<td>13.3 ± 1.03</td>
</tr>
<tr>
<td><strong>Cumulative dose per subject, g</strong></td>
<td>66.7 ± 5.16</td>
</tr>
</tbody>
</table>

Prostaglandin E2, VEGF, and insulin-like growth factor-I analysis

ELISAs were undertaken to assess VEGF (Invitrogen) levels in serum, prostaglandin E2 (PGE2; Cayman Chemicals) levels in plasma, and insulin-like growth factor (IGF-I; R&D Systems) levels in liver tissue extracts. Assays were carried out according to the manufacturers’ instructions, and ELISA plates were analyzed using a Fluostar Optima plate reader (BMG Labtech).

Statistical analysis

Statistical analyses for pharmacokinetic data included linear regression with 1/concentration weighting and descriptive statistics; arithmetic means, and SD, accuracy and precision were calculated using the Watson Laboratory Information Management System (LIMS; version 7.2.0.02) and Microsoft Excel (version 2000/2003).

Statistical analyses for pharmacodynamic data were undertaken using SPSS 16.0 for Windows. Means were compared via one-way, one-sided ANOVA followed by Tukey’s post hoc test. A P value of less than 0.05 was deemed significant.

Results

Safety of SRT501

Nine patients were recruited into the study (for demographics, see Table 1). Six individuals ingested 5.0 g of SRT501, and 3 received placebo, daily for approximately 14 days prior to surgery. One patient on SRT501 ceased dosing on day 13. AEs possibly or probably attributable to agent intake are shown in Table 2. They were primarily of a GI nature, including nausea and diarrhea, and mild in grade (grade 1 NCI CTC v3.0). Other AEs included chills, lethargy, rash, skin irritation, and vascular flushing, which resolved without sequelae, with the exception of 1 case of lethargy in the placebo group, which was ongoing at follow-up. One patient developed postoperative peritonitis and liver failure and died during follow-up. The principle investigator deemed this serious AE unrelated to study drug.
Resveratrol pharmacokinetics and concentration in liver tissue

Patients’ plasma was analyzed by high-performance liquid chromatography (HPLC)/MS-MS for resveratrol. Resveratrol concentrations were below the LLOQ for all samples from subjects receiving placebo and measurable in patients who received SRT501. Pharmacokinetic parameters for resveratrol are shown in Table 3, and plasma concentration versus time curves for individual subjects in Figure 1. Maximal plasma concentration ($C_{\text{max}}$) levels were reached 2.8 hours postdose, and the mean $C_{\text{max}}$ was 1,942 ng/mL (8.51 nmol/mL). The mean plasma elimination half-life was just over 1 hour.

Resveratrol was quantified in tumor and normal adjacent hepatic tissues. Levels of resveratrol were below the LLOQ in all subjects on placebo and 1 of the 6 patients on SRT501. Mean resveratrol levels in the remaining 5 patients receiving SRT501 were 1,098 /–1,393 ng/g (4.81 nmol/g; range = 52–2,834 ng/g) and 420 /–341 ng/g (1.84 nmol/g; range = 46–914 ng/g) in tumor and normal tissue, respectively.

Effect of SRT501 on pharmacodynamics

Potential effects of SRT501 on processes relevant to cell survival and apoptosis were measured in plasma and tissue. There was no difference between patients who received placebo or SRT501 in terms of plasma/serum levels of PGE2 and VEGF (not shown). Tissue samples were analyzed by immunohistochemistry, ELISA, or Western blotting for SRT501-induced changes to levels of IGF-I, Ki-67, phospho-Akt (ser473), Akt1, phospho-GSK3, GSK3, phospho-ERK, ERK, phospho-JNK, JNK, β-catenin, survivin, Bcl-2, Bax, or PARP. In all cases, there were no significant differences between placebo and SRT501 (data not shown).

Apoptosis, as reflected by immunohistochemistry for cleaved caspase-3 in tumor tissue, was significantly increased by 39% (to 1.44% total apoptotic cells, $P = 0.038$) in patients on SRT501 compared with those taking placebo (Fig. 2).

Discussion

This trial represents the first description of pharmacokinetic parameters for resveratrol after ingestion of SRT501, micronized resveratrol, in subjects with colorectal cancer. The dose of resveratrol employed (5.0 g) is equivalent to one of the dose levels at which nonmicronized resveratrol

Table 2. AE listings deemed to be possibly or probably related to SRT501/placebo intervention

<table>
<thead>
<tr>
<th>AE</th>
<th>SRT501 (N = 6)</th>
<th>Placebo (N = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of events</td>
<td>No. of patients</td>
</tr>
<tr>
<td>GI disorders</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Anal pruritus</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Nausea</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>General disorders</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Chills</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lethargy</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Skin/tissue disorders</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Flushing</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 3. Descriptive statistics for resveratrol pharmacokinetics from plasma of patients receiving SRT501

<table>
<thead>
<tr>
<th></th>
<th>$C_{\text{max}}$, ng/mL</th>
<th>$t_{\text{max}}$, h</th>
<th>$t_{1/2}$, h</th>
<th>AUC (0–24 h), ng/h/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>6</td>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Geometric mean</td>
<td>1,942.00</td>
<td>2.80</td>
<td>1.06</td>
<td>6,327.40</td>
</tr>
<tr>
<td>SD</td>
<td>1,422.62</td>
<td>1.10</td>
<td>0.39</td>
<td>2,247.20</td>
</tr>
<tr>
<td>Range</td>
<td>896–4,890</td>
<td>2.0–4.0</td>
<td>0.81–1.54</td>
<td>5,030–9,140</td>
</tr>
</tbody>
</table>

NOTE: All samples from patients randomized to placebo group were below limit of quantitation at all time points (data not shown).
Abbreviations: $t_{\text{max}}$, time of $C_{\text{max}}$; $t_{1/2}$, apparent first-order elimination half-life; AUC, area under the plasma concentration versus time curve from time 0 to 24 hours.

Figure 1. Plasma concentration of resveratrol in individual patients who received 1 dose (5.0 g) of SRT501. Analysis was by HPLC/MS-MS (for details, see Methods).
was recently administered to healthy volunteers (9). In the healthy volunteer study, 10 subjects on 5.0 g of nonmicronized resveratrol reported 20 AEs, possibly or probably related to ingestion of resveratrol capsules, which compares with 17 AEs reported for 6 patients who received SRT501. The 2 formulations therefore seem to cause a similar incidence of AEs, although in the previous study, nonmicronized resveratrol was administered for a longer duration (29 days) than SRT501. All AEs reported following SRT501 administration were mild, whereas 2 of the 10 healthy volunteers on nonmicronized resveratrol presented with moderate and 1 with severe GI AEs (9). This comparison provides the possibility that SRT501 formulated as a suspension may be better tolerated than nonmicronized resveratrol given as ten 0.5 g capsules per day. Because micronized resveratrol was expected to afford higher systemic concentrations (19), this finding also suggests that ingestion of a large number of capsules or the presence of nonabsorbed resveratrol in the GI tract may be responsible for the adverse effects, rather than the actual plasma concentrations achieved.

The pharmacokinetic analysis revealed that the mean plasma $C_{\text{max}}$ for resveratrol measured after ingestion of SRT501 [mean = 1,942 ng/mL; coefficient of variation (CV) = 73.3%] was 3.6-fold higher than that achieved following a single dose of nonmicronized resveratrol in healthy volunteers (mean = 538.8 ng/mL (CV = 72.5%; ref. (8)), consistent with the superior bioavailability of resveratrol when administered as SRT501 compared with nonmicronized agent. The time taken to reach the $C_{\text{max}}$ for resveratrol was 2.8 hours in the case of SRT501 compared with 1.5 hours for nonmicronized resveratrol (8).

Concentrations of resveratrol achieved in hepatic metastases after administration of SRT501 (0.22–12.4 μmol/L) were of the order of magnitude observed to elicit non-physiological effects, as shown by the increase in caspase-3 activity in hepatic normal and tumor tissue of patients who consumed SRT501 (n = 6, black bars) or placebo (n = 3, white bars) daily for 14 days. Values are the mean ± SD. a, significant difference between normal and tumor tissue for SRT501 group. b, significant difference between normal and tumor tissue for placebo group. c, significant difference between SRT501 and placebo tumor tissue. $P \leq 0.05$, one-way ANOVA followed by Tukey’s post hoc test.
pharmacologic effect in human colorectal cancer cells in vitro and in preclinical models in vivo. This interpretation is corroborated by the finding that SRT501 caused a small but significant increase in cleaved caspase-3 immunoreactivity in tumor tissue when compared with equivalent tissue from subjects on placebo. Although we were not able to confirm these effects via other pharmacodynamic markers, this may be due to low sensitivity of the techniques used. Mechanisms by which low concentrations of resveratrol have been observed to induce apoptotic and antiproliferative effect in vitro include induction of Fas redistribution and its association with the death-inducing signaling complex (DISC; ref. 20) and via inhibition of Wnt signaling and subsequent decrease in nuclear β-catenin localization (21). In a preclinical model of diethylnitrosamine-initiated hepatocarcinogenesis, significant resveratrol-mediated apoptosis likely resulted from increased Bax expression and consequent increase in the Bax to Bcl-2 ratio (22). Although tissue resveratrol levels were not determined in this study, extrapolation of data from rodent pharmacokinetic studies (23, 24) would suggest that hepatic resveratrol concentrations necessary for apoptosis induction to be only moderately higher than the maximum achieved in the SRT501 study described here.

This is the first demonstration that resveratrol can reach potentially active concentrations in human tissues that are distant to the GI tract.

In summary, the results of this pilot study of SRT501 allow 3 conclusions: (i) its daily consumption for 14 days seems to be well tolerated in colorectal cancer patients, (ii) \( C_{\text{max}} \) for SRT501 was higher than reported for equivalent dose of nonmicronized resveratrol, and (iii) its ingestion furnished measurable resveratrol levels in a tissue distant to the GI tract (in particular the liver), and these concentrations were accompanied by a significant pharmacologic effect.

Micronized resveratrol, as exemplified by SRT501, warrants further clinical exploration in larger cohorts of subjects to test the hypothesis that resveratrol may be of use as a cancer chemopreventive or chemotherapeutic agent.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Grant Support

This work was supported by Cancer Research UK on a program grant (C325/A6691), by Cancer Research UK in conjunction with the U.K. Department of Health on an Experimental Cancer Medicine Centre grant (C325/A7241), and by Sirtris, a GSK company.

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Received March 25, 2011; revised May 16, 2011; accepted June 1, 2011. Published OnlineFirst June 16, 2011.

References


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doi:10.1158/1940-6207.CAPR-11-0148

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