Development of Investigational Radiation Modifiers

A. Dimitrios Colevas, J. Martin Brown, Stephen Hahn, James Mitchell, Kevin Camphausen, C. Norman Coleman

For the Radiation Modifier Working Group of the National Cancer Institute

Historically, clinically useful modifiers of radiation therapy have been conventional chemotherapeutic agents (e.g., 5-fluorouracil and thymidylate synthase inhibitors, cisplatin and related compounds, and taxanes) (1–4) administered on a schedule designed to optimize the interaction between the agent and radiation. The Cancer Therapy Evaluation Program (CTEP) and the Radiation Research Program (RRP) of the Division of Cancer Treatment and Diagnosis, National Cancer Institute, sponsored a meeting of the Radiation Modifier Working Group June 24–26, 2002, in Rosslyn, VA. The charge of the working group was to review and evaluate past and current preclinical and clinical approaches to the development of combination drug and radiation anticancer therapies and to provide practical guidelines for selecting evaluation criteria for radiation modifiers.

Additional potentially useful molecular targets for agents that modify the effects of radiation are emerging as our knowledge of the human genome and proteome continues to expand. Obstacles to development of such agents include the lack of interdisciplinary coordination, publicly available guidelines concerning what constitutes an interesting candidate for development, and up-to-date guidelines concerning appropriate and efficient pathways to define their clinical utilities. This workshop was convened as a cooperative effort between CTEP and RRP to both encourage and facilitate the development of molecular targets for radiation modification. Although the working group focused primarily on the development process as it relates to the mission of CTEP (5), this consensus statement is intended to provide a platform for the relevant governmental, academic, and pharmaceutical medical constituencies worldwide to discuss the development of radiation modifiers rather than define a rigid standard model of drug development in this arena.

Preclinical Studies of Radiation Modifiers

The response of solid tumors to radiation depends primarily on three factors: 1) the intrinsic radiosensitivity of the tumor cells, 2) the oxygenation of the tumor cells, and 3) the number of tumor cells undergoing division between radiation treatments. Modification or changes in any of these factors would be expected to modify the radiation response of tumors. However, only modifiers of intrinsic radiosensitivity can be assessed with the use of standard in vitro studies. Therefore many candidate radiation modifiers, such as those that change tumor oxygenation, tumor immunogenicity, tumor stroma, or tumor vascularity must be assayed in vivo or in carefully defined in vitro conditions (e.g., hypoxic conditions).

Clinical testing of potential radiation modifiers should be initiated only after convincing preclinical data indicate their potential efficacy in the clinic. Such preclinical studies should simulate, as much as possible, the conditions under which the agent will be used in the clinic to minimize the number of agents that show activity in preclinical studies but not in the clinic.

To be an effective radiation modifier in the clinic, the agent must show specificity for either the tumor or the normal tissue. Such specificity can only be achieved by exploiting some difference that exists between normal tissue and tumor tissue. For example, the radiation modifier amifostine achieves a higher concentration in salivary gland tissue than in tumor tissue (6). Pyrimidine analogs can be used to exploit the higher proliferation rate of tumors compared with that of some surrounding normal tissues (7). Differences in oxygenation between tumors and normal tissues may be exploited with hypoxic cell radiosensitizers such as etanidazole or the hypoxic cytotoxin, tirapazamine (8).

Types of Preclinical Data Needed

Although in vitro data provide useful information, an in vivo demonstration of radiation modification is the gold standard of preclinical evaluation of putative radiation modifiers. However, there are no preclinical studies, to our knowledge, that can accurately predict how effective a given candidate radiation modifier will be in the clinic. Therefore, although preclinical studies will help identify candidate radiation modifiers, such studies may not be definitive with respect to prioritization of such agents.

A candidate radiation modifier should demonstrate in vivo tumor radiosensitization with fractionated radiation (2–4 Gy/fraction) with no (or less) radiosensitization of a normal tissue in two different tumor models. Ideally, the mechanism of action of the agents should be known, and the in vivo response of the tumor to a particular agent should be correlated with that mechanism of action. For example, if an agent is intended to modify a particular molecular target, radiosensitization should be correlated with modification of the target.

Appropriate Assays

In general, short-term assays of cellular response in vitro or of tumor response in vivo are inappropriate for evaluation of antitumor effect because they usually do not mea-
sure the overall level of cell killing but rather the rate at which cells die (9). Following irradiation, most cells in solid tumors die only when they attempt to undergo mitosis. By contrast, normal and malignant cells derived from hematopoietic tissues, particularly lymphoid tissues, often die by apoptosis very soon after irradiation.

**In Vitro Assays**

The clonogenic assay is the only assay that measures total cell killing whether it occurs by mitotic catastrophe, apoptosis, terminal differentiation, or other modes of cell death (10–15). This assay measures colony formation from single cells derived from an established tumor cell line that has a high plating efficiency. We recommend using only cell lines that have a plating efficiency of at least 20% in the clonogenic assay. This clonogenic assay is not to be confused with the Hamburger–Salmon human tumor colony-forming assay, which uses suspensions of fresh surgical samples of a tumor (16). This assay suffers from the fact that the suspension often contains clumps of cells, and those tumor cells often have a low plating efficiency.

The MTT/XTT/trypan blue exclusion assays are often not appropriate for measuring overall killing of cells in vitro associated with radiation modifiers because they measure only the short-term effects of radiation on cells. One exception would be the use of such assays with lymphoid cells, which undergo rapid apoptosis within 4–6 hours of exposure to radiation. Additionally, the MTT assay, if properly optimized for a given cell line, can be used to measure changes in the sensitivity of nonlymphoid cells to radiation or chemotherapy drugs and is therefore more suitable than the clonogenic assay for screening large numbers of potential radiation modification agents (17,18). However, all potential radiation modification candidates identified by such screens should be confirmed by using a definitive clonogenic assay prior to further development.

**In Vivo Assays**

There are three principal assays that are suitable for measuring the changes in the response of a tumor to radiation: *in vivo* /in vitro* tumor excision assays, the tumor re-growth delay assay, and the tumor control/cure dose assay (19,20).

*In vivo* /in vitro* tumor excision assays, experimental animals bearing established tumors are treated with an anticancer therapy and, at some later time (usually within 24 hours), the tumors are removed from the animal, disaggregated into single cells, and assayed for clonogenic survival as described in the previous section. Because complete disaggregation of the excised tumors into single-cell suspensions prior to assay for colony formation is vital, this assay can be used only with tumors for which a single-cell suspension can be made. The clonogenic evaluation is usually performed *in vitro* by platting the disaggregated tumor cells on plastic or in agar or by injecting the disaggregated cells intravenously into animals and then scoring the number of resulting lung colonies (21). Cells destined to die following irradiation must be present in the tumor population at the time of assay for the results to be meaningful.

The tumor re-growth delay assay measures the time required for a tumor to reach a given size after treatment. This predetermined tumor size should be sufficient to allow the tumors to begin re-growing at the same rate as the untreated tumors and is often two to four times the volume of the tumor before treatment. The re-growth delay assay is ideal for both single and fractionated doses of radiation. However, artifacts can be introduced by immunogenicity (which can occur when a human tumor xenograft is used in nude or SCID mice) and when the re-growth rate of the treated tumor is slower than the growth rate of the untreated tumors (22). Finally, it is important that the re-growth time to a specific size be used, not some shorter term endpoint, such as the nadir of the cell growth curves, and that the assay includes a minimum of five mice per group.

The tumor control/cure dose assay measures the x-ray dose at which 50% of the tumors are locally controlled (TCD50) (23). Of the three assays, it is the most relevant for radiotherapy but the most intensive in terms of time and resources, requiring a minimum of 4 months and 30 tumor-bearing mice to obtain one TCD50 value. This assay can suffer from artifacts due to immunogenicity of the system (23).

**Appropriate Solid Tumor Models**

The appropriateness of the tumor model depends on the mechanism of action of the agent being tested. For example, a drug that is known to target an overexpressed mutant protein should be tested in a tumor that expresses the mutant protein. It is usually satisfactory to use a subcutaneously transplanted tumor. However, the tumor must be established and measurable at the time of treatment and, except for the *in vivo* /in vitro* excision assay, the implantation site should allow the tumor to be irradiated without irradiating a substantial amount of normal tissue. In some cases, it may be more appropriate to assay human tumor xenografts than rodent tumors, especially for agents that have been developed against the human versions of specific target proteins. When an evaluation of spontaneous metastasis is needed, orthotopic or spontaneous tumors may be preferable to subcutaneously transplanted tumors (24).

**Demonstration of Radiosensitization of Tumors or Tumor Cells**

Changes in intrinsic radiation sensitivity are usually seen as changes in the slope of the survival curve under conditions when the agent itself produces little or no toxicity. However, changes in the low-dose (i.e., “shoulder”) region of the survival curve can also reflect alterations in cellular radiosensitivity, although care must be taken when interpreting results obtained using an agent that by itself kills cells. In this case, demonstration of radiosensitization or synergistic action requires isobologram analysis, which consists of a separate, full dose–response curve for each agent (25,26). When isobologram evaluation provides no evidence for intrinsic radiosensitization by an agent, appropriate models of antitumor effect additivity, such as *in vivo* assays demonstrating improved local tumor control and survival, are necessary to justify further development of that agent.

The drug dosing and timing must fit the mechanism of the drug. For example, if the drug is a hypoxic cell radiosensitizer, it can work only if it is present at the time of irradiation. In fact, giving the drug after irradiation can be a useful negative control for such an agent. For other agents, extended exposure prior to radiation is necessary, for example, with DNA base analogs that need to be metabolized or incorporated into the cells.

**Demonstration of Lack of Sensitization in Normal Cells or Tissues**

Ideally, assays demonstrating a difference in radiation modulation between tumor and normal tissue should be obtained to
support the rationale for improved therapeutic ratio for the agent combined with radiation. One of the easiest assays to perform is skin reaction evaluation in rodents, but other endpoints, particularly late normal tissue endpoints, can be more relevant to demonstrate the differential effect. In many cases, suitable models for evaluation of normal tissue are lacking. If no appropriate in vivo normal tissue toxicity models are available, lack of radiosensitization of non-immortalized human cells in vitro should be obtained.

**Need for Clinically Relevant Exposures**

Both radiation and drug doses need to be appropriate to the clinical situation. For radiation, data with fractionated radiation at clinically appropriate doses (2–4 Gy/fraction) are essential. In terms of drug doses, clinically relevant doses should be used in the preclinical test system if the pharmacokinetics and pharmacodynamics of the drug in humans are known. If this is not possible, a range of doses of the agent should be used in combination with fractionated irradiation to obtain evidence that the efficacy of the agent can be correlated with changes in the target or physiologic process that is being targeted.

We strongly recommend that sponsors of clinical trials identify a panel of scientists who have relevant preclinical and clinical experience with radiation modifiers to give advice on the preclinical data supporting proposals to conduct phase I trials of radiation modifiers plus radiation.

**Phase I Studies of Radiation Modifiers**

The goals of a phase I trial are to identify the toxicities of combined radiation modifiers and radiotherapy and to define a recommended phase II dose. In the context of a phase I trial investigating the combination of a radiation modifier and radiation, the recommended phase II dose is defined as the doses and schedules of both the radiation modifier and radiation therapy when they are used in combination with each other. This recommended phase II dose is not necessarily equivalent to the maximally tolerated dose of the radiation modifier alone plus a standard dose and schedule of radiation. The schedule used when the modifier is combined with radiation may be substantially different from that of the modifier by itself or when used with chemotherapy.

**Prerequisites of Phase I Trials**

All phase I trials of radiation modifiers must be based on some reasonable rationale, e.g., conclusions derived from specific preclinical experiments. Alternatively, the rationale for studying an agent in combination with radiation may be based on extrapolation from other clinical scenarios where radiation modification activity has been demonstrated. In general, prior to proceeding with a combination drug and radiation trial, the following data should be available.

**Single-agent radiation modifier pharmacokinetic data.** Often these data are already available from studies of single agents in humans. When a drug is being developed exclusively as a radiation modifier, relevant animal model pharmacokinetic studies should support the schedule of administration proposed for the human trial. In many cases, the proposed schedule of drug administration in combination with radiation will be different than the schedule explored in drug-only studies, necessitating a pharmacokinetic evaluation of sufficient detail to confirm that the relevant exposures are attained using the proposed schedule.

**Single-agent pharmacodynamic data.** Such data will ideally describe the modifier’s effect on a relevant molecular target. Preclinical experiments should, whenever possible, include assays to confirm that a purported target is altered. Phase I trials should be designed to assay the alteration of relevant targets in humans once relevant drug levels are achieved. Therefore, measurement of the target should generally include baseline and post-therapy evaluations. Phase I radiation modifier trials do not necessarily have to be limited to patients with a particular molecular target if the presence of that target will not be used to determine the recommended phase II dose. For example, if the modifier being studied acts as a sensitizer exclusively in hypoxic tumors without altering the level of hypoxia, trial eligibility should not necessarily be limited to patients whose tumors are hypoxic. Such an eligibility restriction is relevant only when the question being asked relates to efficacy. On the other hand, if an agent’s purported mechanism of action and toxicity depend on metabolism of that agent in the hypoxic region, determination of the recommended phase II dose may require that eligibility for the phase I trial be restricted to patients with appropriately hypoxic tumors to define the relevant toxicity.

**Single-agent safety data.** If there is no prior information concerning the safety of administering a radiation modifier to humans, appropriate animal safety studies must be conducted to anticipate the spectrum of toxicities that might occur in humans and to determine a safe starting dose for the human phase I study. If single-agent human safety data are known, preclinical toxicity studies of the combination of radiation and modifier may still be useful to determine the appropriate starting dose for human trials of a radiation modifier and radiation.

**Evaluation of therapeutic index.** Although there should be some preclinical basis for combining an agent with radiation in terms of tumor tissue selective effect, specific guidelines concerning such assays are not possible because there are no accepted standard preclinical assays for evaluating effects of radiation in combination with modifiers on normal or cancer tissue. Preclinical therapeutic index evaluation is an area in need of further research.

**Phase I Design and Implementation**

Enrollment in radiation modifier clinical trials should be limited to patients for whom radiation therapy, either curative or palliative, is indicated. Therefore, phase I trials should be designed to determine the dose of the modifier that is to be administered concurrently with an appropriate (curative or palliative) dose and schedule of radiation, rather than administering fixed doses of the modifier and titrating the dose of radiation up from a subtherapeutic dose. Phase I radiation modifier trials will include a variety of acceptable radiation doses and schedules, depending on the tumor type and clinical situation. Because the spectrum of acceptable radiation treatments and locoregional toxicity associated with these treatments differ by cancer site and type, the recommended phase II dose determination must be based on data derived from cancer-specific and site-specific phase I trials. Translation of dose and schedule from animals to humans is imprecise. Therefore, whereas clinical trialists should look to the preclinical radiation modifier plus radiation dose–toxicity and dose–activity relationship data when choosing a phase I starting dose, the initial dose of the radiation modifier to
be used in combination with radiation with humans is well below the maximal dose tolerated in animals. When there are no human pharmacokinetic or toxicology data for a radiation modifier, toxicology data from single-agent and combined therapy animal studies are used to choose the initial human dose, which is typically one-tenth of the dose lethal to 10% of treated animals (LD10) of either the single-agent or combined therapy (agent plus radiation) dose, whichever is lower (27,28).

All phase I trials should have predefined dose escalation schemes, toxicity criteria, and dose-limiting toxicity definitions. Radiation toxicity is incrementally cumulative over the duration of treatment. Therefore, toxicity assessment for each dose level should include evaluation during the entire radiation period rather than only during the first course or cycle of combined therapy. The window of evaluation should be specifically defined, e.g., up to 30 days after completion of radiation. Subsequent cohorts generally should not be treated until that evaluation window is closed. An exception to this situation would be in the case of cyclically administered chemotherapy plus radiation in settings where the typical adverse event profile is not incrementally cumulative (29). Collection of late toxicity data should be prospectively included in the trial design, despite the fact that it is impractical to use late toxicities to define the maximum tolerated dose. Under certain circumstances, these data may provide a rationale for choosing a recommended phase II dose other than that defined by the acute maximum tolerated dose.

The definition of dose-limiting toxicities (i.e., type, grade, and duration of adverse event) for radiation modifier trials will necessarily be different than those for chemotherapy trials. Patients are not typically exposed to recurring risks in chemotherapy plus radiation trials because therapy is not cyclical; the dose-limiting toxicity is often organ- and site-confined, as determined by the port of radiation, and phase I radiation modifier trials are often performed in a potentially curative, rather than palliative, setting.

When choosing dose levels for radiation modifier phase I trials, several things must be considered. Dose escalation is normally based on acute adverse events seen in cohorts of three to six patients treated per dose level. However, because substantial variability in locoregional and interpatient toxicities is seen with definitive radiation alone, accelerated accrual designs permitting the simultaneous treatment of up to six patients are often used. In general, documentation of lack of anticipated biologic effect of a targeted modifier at the maximum tolerated dose should discourage further development of that combination schedule, although mechanistic data may emerge in a phase I study that would allow for a revised plan of development of the radiation modifier. In cases where the maximum tolerated dose of the single-agent modifier for humans is known, or the maximum tolerated dose for the combination of the modifier and radiation is known for another anatomic site, as few as two or three dose levels can be used to perform an efficient and safe phase I trial.

Both the maximum tolerated dose and the recommended phase II dose are classically defined as the highest dose level at which fewer than two of six patients experience dose-limiting toxicities. However, depending on what is known about the agent, other clinical or biologic endpoints could be used to define the recommended phase II dose. Although investigation of the biologic effects of the agent should be obtained, the optimal biologic dose, in general, cannot be the endpoint for a phase I trial because the definition of optimal is not available at the time of phase I development. In some situations, a peak or plateau biologic effect of an agent can be used to define the recommended phase II dose, but the strength of this conclusion will be inexorably bound to the validity of this endpoint as a surrogate for clinical efficacy, and these efficacy data are typically not available during phase I development. Most investigators agree that, in most circumstances, data derived from six patients treated at the maximum tolerated dose, while not definitive, are adequate to justify proceeding to the next phase of clinical development.

**Phase II Trials and Beyond: Design and Implementation**

Radiation modifier trials are essentially analogous to radiation-alone therapy trials with respect to design and endpoints. Response rates are often not useful for selecting promising radiation modifiers because of delayed time to response, residual unmeasurable masses, difficulty discriminating between locoregional toxicity and residual cancer, progressive disease outside the radiation field, and underlying high response rates to radiation therapy itself. In addition, the absence of an increase in response rate to radiation plus a modifier compared with radiation-alone controls does not necessarily indicate a lack of clinical benefit. Therefore, endpoints such as complete response rates, local control rates, locoregional time to progression, and survival are generally preferable to overall response rates. The actual efficacy endpoint used in a phase II study will be highly dependent upon the primary tumor being studied and the current standard therapy that is used in the clinic. Survival is a strong efficacy endpoint, and a phase II study that demonstrates a survival gain compared with that in historical controls should be prioritized for advancement into the phase III setting.

Collection of additional toxicology data, both acute and late, is an essential component of phase II radiation modifier trials. Although evaluation of acute toxicity within the 90 days surrounding radiation is usually the focus of toxicity evaluation, the collection and analysis of data on late toxicity effects are essential because such data can often assist with interpretation of late events seen in the initial stages of phase III trials. Early stopping rules for low response rates using limited accrual in a multiple stage design are often not applicable to radiation modifier trials because the response rates to radiation alone in most settings are high and the final response evaluation is often not possible for several weeks to months after the completion of the combined therapy. Therefore, unless there is a dramatic deviation in response compared with responses seen in historical controls early in the conduct of a phase II radiation modifier trial, the trial should proceed without interruption to allow for timely accrual.

Eligibility criteria for radiation modifier trials are usually designed to include patients for whom definitive or adjuvant radiation therapy alone is an appropriate standard of care. Exceptions to this eligibility criterion would be those patients being treated palliatively or with re-irradiation for whom the local impact of the radiation modifier could be assessed. Whenever potentially curative therapy is available, the base therapy to which the radiation modifier is added should not be compromised. The issues surrounding the decision to add an investigational radiation modifier to radiation alone versus adding a radiation modifier to definitive chemotherapy and radiation are dependent upon the toxicities and efficacy of the current standard for the underlying disease being treated. If curative therapy
exists, the addition of a radiation modifier to the standard chemoradiation regimen is preferred, unless there are compelling preclinical or clinical data to support substitution of the radiation modifier for the usual concurrent chemotherapy. It is possible that combinations of new agents with radiotherapy may have less toxicity than current chemoradiation regimens with similar or greater efficacy. In clinical circumstances in which the standard chemoradiation approach is not curative and/or is associated with substantial toxicity, it might be reasonable to evaluate the radiation modifiers with radiation alone.

Trials whose primary goal is to test agents as radiation modifiers should be designed so that the agents are administered exclusively concurrently with radiation. If agents are incorporated into the trial both during and before or after radiation, it will be difficult to attribute the outcome to a radiation modifier effect. Development strategies for agents thought to possess both radiation modifier properties and direct anticancer properties should include separate concurrent and sequential therapy trials before a combination of concurrent and sequential therapy is tested.

Sequential phase II radiation modifier trials can be particularly efficient in the development of a radiation modifier agent, especially when they incorporate the agent into a multimodality treatment plan. Although there is no need to perform definitive phase III studies at each step of such a development pathway, before any “final product” is incorporated into routine clinical practice, the new regimen is almost invariably tested against a standard of care in a phase III setting. One exception to this rule is the case of a novel regimen that is associated with extraordinary survival in a disease setting where standard therapy is routinely associated with a dismal outcome. Randomized phase II trials that contain contemporaneous control groups may, under rare circumstances, be of value when historical data are extremely heterogeneous or when there is concern that the outcome for the experimental arm is subject to selection bias. However, such phase II trials cannot substitute for a definitive phase III randomized trial.

SUMMARY

Positive, appropriate, preclinical data that are adequately reviewed are a prerequisite for clinical trials of radiation modifiers. The appropriate tumor models, dosing schedules, and assays should be based on the mechanism of action of the proposed radiation modifier. The activity of a radiation modifier should be correlated with its activity against a target. Priority for clinical development should be given to agents that have known, assayable targets or that produce extraordinary preclinical efficacy data.

Phase I trials of radiation modifiers with radiation should efficiently and safely determine a recommended phase II dose. The recommended phase II dose for radiation modifier plus radiation trials is not necessarily the maximum tolerated dose of the combination, nor is it necessarily related to the recommended phase II dose of the agent alone or in combination with other drugs. The schedule of the combination of radiation modifier and radiation should be based on preclinical optimization experiments. Clinically useful endpoints in radiation modifier plus radiation trials usually include time to progression, locoregional control, and survival rather than overall response rates. Clinical development of radiation modifiers plus radiation should consist of building the radiation modifier into acceptable standard of care regimens utilizing full-dose radiation.

APPENDIX

The Radiation Modifier Working Group of the NCI, 2002: Kevin Camphausen, M.D. (Radiation Oncology Branch), C. Norman Coleman, M.D. (Radiation Oncology Sciences Program), A. Dimitrios Colevas, M.D. (Investigational Drug Branch), Barbara Conley, M.D. (Diagnostics Research Branch), Richard Cumberlin, M.D., Helen B. Stone, Ph.D., and Rosemary Wong, Ph.D. (Radiation Research Program), Boris Freidlin, Ph.D. (Biometric Research Branch), Ken Kobayashi, M.D. (Investigational Drug Branch), James Mitchell, Ph.D. (Radiation Biology Branch), Anthony J. Murgo, M.D. (Investigational Drug Branch), Robert Shoemaker, Ph.D. (Developmental Therapeutics Program), and Philip J. Tofilon, Ph.D. (Molecular Radiation Therapeutics), all of the National Cancer Institute; J. Martin Brown, Ph.D., Stanford Medical Center, Stanford University; Hak Choy, M.D., Department of Radiation Oncology, Vanderbilt University Medical Center; Adam Dicker, M.D., Ph.D., Department of Radiation Oncology, Thomas Jefferson University; James H. Doroshow, M.D., Department of Medical Oncology and Therapeutics Branch, City of Hope Comprehensive Cancer Center; Silvia C. Formenti, M.D., Department of Radiation Oncology, New York University School of Medicine; Adam Garden, M.D., University of Texas M. D. Anderson Cancer Center; Stephen Gately, Ph.D., NeoPharm, Inc.; Stephen Hahn, M.D., University of Pennsylvania; Richard Hill, Ph.D., Ontario Cancer Institute, University of Toronto; Timothy J. Kinsella, M.D., Department of Radiation Oncology, Case Western Reserve University; Malcolm Moore, M.D., Department of Medicine, Princess Margaret Hospital; Jann Sarkaria, M.D., Radiation Oncology, Mayo Clinic; Dietmar Siemann, Ph.D., Department of Radiation Oncology, University of Florida; Gerald Sokol, M.D., M.S., F.C.P., Food and Drug Administration Center for Drug Evaluation Research; Beverly A. Teicher, Ph.D., Genzyme Corporation; Andy Trotti, M.D., Radiation Therapy Program, H. Lee Moffitt Cancer Center at the University of South Florida; Andrew T. Turrisi III, M.D., Department of Radiation Oncology, Medical University of South Carolina; Raul Urtasun, M.D., Cross Cancer Institute, University of Alberta; Everett E. Vokes, M.D., Department of Medicine, University of Chicago Medical Center.

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Journal of the National Cancer Institute, Vol. 95, No. 9, May 7, 2003


**NOTE**

Manuscript received July 31, 2002; revised February 27, 2003; accepted March 12, 2003.