

Compassionate Approval Process for Experimental Gene-Based Products

TO THE EDITOR: Patients with time-constrained terminal diseases such as cancer may not have ready access to new treatments undergoing clinical development. Many patients and physicians are unaware of the compassionate exemption process for single-patient treatment or believe that the approval process is too lengthy, cumbersome, or complicated. Our experience does not support evidence of difficulty with the compassionate approval process. We will illustrate the processes used to approve and permit single-use treatment of gene-based products and present two case examples.

A patient may qualify for a special exception to be filed with the US Food and Drug Administration (FDA) under an investigational new drug (IND) application entitled single-use (or compassionate-use) IND if either: they do not meet the protocol eligibility criteria for an ongoing clinical trial, or if no other standard or research therapies are available.¹ A product supply letter of authorization is required.² This request letter should state the rationale for requesting the exception and the intent to supply the agent/drug. It is sent as a general correspondence to the appropriate master IND and a copy is sent to the single-use IND. The drug supplier should be able to provide the name of the appropriate review division. The investigator then uses the information from the manufacturer to cross reference in the single-use IND Submission (Master IND number and Division contact). Next, FDA communication is required. The FDA is highly responsive to requests. Conversations with the FDA clinical reviewer provide guidance in properly preparing an acceptable submission. This is followed by the submission of necessary documents:² (1) request for a single-patient IND; (2) brief clinical history; (3) proposed treatment plan; (4) drug supply reference statement; (5) informed consent statement; (6) investigator qualification statement; (7) US Food and Drug Administration form 1571³; and (8) contact telephone number and facsimile number.

The "US Food and Drug Administration only denies access when there is evidence that the risk of using the experimental drug clearly outweighs any potential benefit to the patient."⁴ The investigator must ensure that institutional review board review is conducted and approved before commencing with the trial. Studies using gene-based products have two additional review boards overseeing the conduct of a trial: the Recombinant Advisory Committee (RAC) and the Institutional Biosafety Committee (IBC).⁵ In addition to the protocol, the RAC requires that Appendix M⁶ must be completed along with a scientific abstract and a nontechnical abstract. Appendix M comprises a series of questions that must be answered regarding the design and submission of the protocol. Appendix M outlines the items necessary for RAC review (Appendix M I-A), including the potential safety risks imposed on individuals handling the product and product management. The IBC is a local body responsible for reviewing and approving recombinant DNA research and potentially biohazardous projects. The IBC sets containment levels in accordance with the National Institutes of Health Guidelines and those of the Centers for Disease Control and Prevention.

Two compassionate-use INDs were recently approved in our program: one involving an adenoviral *p53* gene product in a patient with Li Fraumeni syndrome, and another involving a *TGFB2* antisense gene transfected autologous tumor cell vaccine in a pancreatic cancer patient. Below is a summary of the two cases describing the process, timeframe, and results.

Case 1

Patient A was a 25-year-old female with Li Fraumeni syndrome, a hereditary syndrome involving severe DNA repair defect related to the *p53* gene mutation. She had previously been treated with extensive prior chemotherapy for management of advanced embryonal cell tumor. She subsequently developed abdominal pain and lower extremity edema from an expanding, infiltrative pelvic lesion, at which time we elected to design and implement a compassionate-use IND for experimental management with ING 201 (Advexin; Introgen, Houston, TX).⁶ We established a novel compassionate-use IND customized for patient A. The compassionate-use IND approval process time sequence is shown in Table 1.

Within 6 weeks, the compassionate-use use trial was activated. The patient received her first injection on November 9, 2005. Intratumoral injections of Advexin were administered on days 2 and 4 of week 1 every 28 days. She achieved a complete response of the lesion injected and temporary clinical benefit.⁷

Case 2

Patient B was a 68-year-old male with stage IV pancreatic cancer. He previously received gemcitabine and achieved a partial response. We then elected to design and carry out a compassionate-use IND involving resection of a liver lesion to construct an autologous tumor cell vaccine transfected with the *TGFB2* antisense gene.⁸ A compassionate-use protocol was developed. Monthly subcutaneous injections of autologous pancreatic *TGFB2* gene vaccine were to be administered. The *TGFB2* antisense gene was plasmid (NovaRx, San Diego, CA) and the product was good manufacturing practice (Gradalis Inc, Dallas, TX).

Approvals from the regulatory bodies were obtained within 6 weeks (Table 1). The patient unfortunately experienced clinical deterioration due to disease progression before treatment and no longer fulfilled compassionate-inclusion criteria and, therefore, was unable to be treated.

Compassionate-use of investigational gene-based products is attainable under single-use INDs. Approval of both compassionate-use INDs was rapidly secured, although the opportunity to treat the patient was realized only in the first IND. The compassionate-use IND process we outlined above is reproducible and efficient even when considering gene-transfer products.

Gladice Wallraven and John J. Nemunaitis

Department of Regulatory Affairs, Mary Crowley Cancer Research Centers, Dallas, TX

Phillip B. Maples

Gradalis Inc, Dallas, TX

Table 1. Compassionate IND Approval Process Time Sequence for Case 1

Week	Patient A	Patient B
1	Patient identified, protocol drafted (08/02/05); cross-reference letter received (08/03/05); submission to FDA (08/05/05)	Patient identified, protocol drafted (07/07/06)
2		Cross-reference letter received from NovaRx Corporation, San Diego, CA (07/13/06); submission to FDA (07/17/06) & RAC (07/18/06)
3	IND approval granted by FDA (08/30/05)	IND approval granted by FDA (07/21/06)
4		IBC Submission (07/25/06)
5	RAC (09/14/05) & IBC Submission (09/15/05)	
6	IRB Approval Granted (09/14/05); RAC exemption letter (09/23/05); IBC Approval Granted (09/23/05); Clinical team educated; protocol/activated (10/20/05)	IRB Approval Granted (08/11/06); RAC exemption letter (08/15/06)

Abbreviations: IND, investigational new drug; FDA, US Food and Drug Administration; RAC, recombinant advisory committee; IBC, institutional biosafety committee; IRB, institutional review board.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: John J. Nemunaitis, Gradalis Inc (C) **Consultant or Advisory Role:** None **Stock Ownership:** Phillip B. Maples, Gradalis Inc; John J. Nemunaitis, Gradalis Inc **Honoraria:** None **Research Funding:** None **Expert Testimony:** None **Other Remuneration:** None

REFERENCES

1. US Food and Drug Administration: Oncology tools: Access to unapproved drugs. www.fda.gov/cder/cancer/access.htm

2. US Food and Drug Administration: Oncology Tools. <http://www.fda.gov/cder/cancer/SingleIND.htm>

3. US Food and Drug Administration: FDA Forms Distribution Page for Center for Drug Evaluation and Research (CDER). <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>

4. Thompson L: Experimental treatments: Unapproved but not always unavailable. *FDA Consumer Magazine* 34:8-13, 2000

5. National Institutes of Health notice pertinent to the April 2002 revisions of the NIH guidelines for research involving recombinant DNA molecules. http://www4.od.nih.gov/oba/rac/guidelines_02/Appendix_M.htm

6. Nemunaitis J, Swisher SG, Timmons T, et al: Adenovirus-mediated p53 gene transfer in sequence with cisplatin to tumors of patients with non-small-cell lung cancer. *J Clin Oncol* 18:609-622, 2000

7. Senzer N, Nemunaitis J, Nemunaitis M, et al: p53 therapy in a patient with Li-Fraumeni syndrome. *Mol Cancer Ther* 6:1478-1482, 2007

8. Nemunaitis J, Dillman RO, Schwarzenberger PO, et al: Phase II study of belagenpumatuce-L, a transforming growth factor beta-2 antisense gene-modified allogeneic tumor cell vaccine in non-small-cell lung cancer. *J Clin Oncol* 24:4721-4730, 2006

DOI: 10.1200/JCO.2008.16.2156

Could the Efficacy of Docetaxel in Prostate Cancer Patients Be Potentiated by Concomitant High-Dose Calcitriol Administration?

TO THE EDITOR: Docetaxel is widely recognized as the most efficacious chemotherapeutic agent in hormone-refractory prostate cancer patients. One important question is how can we improve the efficacy of this drug. Preclinical data have shown that calcitriol [(1,25-dihydroxycholecalciferol, 1,25(OH)₂-D₃] has a significant antitumor activity and could potentiate chemotherapy efficacy.

Beer et al¹ recently published a phase III trial, the AIPC Study of Calcitriol Enhancing Taxotere (ASCENT), aiming to show whether the addition of high-dose calcitriol to docetaxel in patients with hormone-refractory metastatic disease could result in a greater activity than docetaxel alone. The results showed that the combination of docetaxel and calcitriol failed to show a greater reduction of prostate-specific antigen (PSA) as opposed to docetaxel alone (primary aim of the study) but significantly prolonged the overall survival. How

should we interpret this discrepancy? One possible explanation is that 50% PSA reduction from baseline is not a reliable surrogate parameter of docetaxel efficacy, as recently reported²; alternatively, the absence of correlation between PSA reduction and survival improvement in this trial suggests that calcitriol administration can affect survival independently from docetaxel efficacy.

Most patients (85% to 90%) in this trial¹ had bone metastases and were at risk of skeletal-related events (SREs). Zoledronic acid was not mandatory but was administered in 85 patients (40 placebo treated; 45 calcitriol treated). Overall, calcitriol administration resulted in a prolongation of skeletal morbidity-free survival that just failed to attain statistical significance. Interestingly, if patients are categorized according to whether or not they received zoledronic acid, the SRE incidence rate in the calcitriol group was lower than in the placebo group in zoledronic acid-treated patients (29% v 40%, respectively), but not in patients not receiving zoledronic acid (31% v 34%).

Prostate cancer patients tend to be elderly, so a high incidence of hypovitaminosis D is expected in this setting. Zoledronic acid administration could lead to hypocalcemia and secondary hyperparathyroidism, and the occurrence of this metabolic disturbance is influenced by hypovitaminosis D status.³ Parathyroid hormone