Case: The Role of FDA in Clinical Trials of Cancer Treatments

Background:

How is the decision made to conduct a clinical trial of a drug, treatment, or device?

* You cannot just propose something without evidence that it will work. It is impossible to get a clinical trial approved without supporting data.
* Supporting data comes from many sources: chemical modeling in a test tube, cell culture results, and animal studies.
* For some trials, “field observations” have been a critical part of the supporting data. Field observations can include:
  + - Data collected as part of a different (and usually unrelated) clinical trial.
    - Anecdotal observations of patients by their doctors.
    - Historical practices. For example, the National Cancer Institute spent several years looking at various “holistic mind” practices used in Asia as part of cancer therapy. Subsequent controlled clinical trials showed a strong connection between mental state, serum cortisol levels, and tolerance of chemotherapy.
    - Epidemiological data. A good example of this is a clinical trial testing whether regular aspirin use reduces colon cancer risk, which was based on the fact men taking low-dose aspirin for heart disease are less likely to develop colon cancer.

Clinical trials are expensive. In the US, most clinical trials are funded by the NIH, Department of Defense, and private medical device and pharmaceutical companies. NIH is the main public agency funding clinical trials. Any scientist wanting to use NIH money to conduct a clinical trial must submit a proposal to the NIH ‘s Internal Review Panel. This first review panel examines proposals then ranks them in order of priority for funding. A poor priority score means that, even if NIH likes your idea for a clinical trial, they do not like it enough to provide the money needed for it. The Dept. of Defense works similarly. If a clinical trial is funded by a private company, they decide for themselves whether or not to fund the trial. Every company makes that decision in its own way.

Regardless of who is funding the trial, in the United States **only the FDA can give final permission to conduct a clinical trial on human subjects**. Before a trial can begin, a project proposal must be independently reviewed and approved by a second panel of experienced scientists. The procedure for reviewing clinical trial proposals is similar to how research grant proposals are reviewed.

* Individuals working in the field of cancer biology, oncology, and trials management are invited to join a Review Panel.
* A chair for the panel is elected or appointed who ensures:
* All reviewers understand and agree to follow established general procedures.
* That all reviewers know what criteria they will be using to evaluate trials.
* That the same criteria are used to evaluate all trial proposals.
* All administrative requirements and federal regulations are met.
* Often a large Review Panel gets divided into smaller subpanels.
* Each subpanel reviews a few of the applications, then presents the applications they reviewed to the rest of the group for discussion.
* Usually, two subpanels read each application. However, only one subpanel presents the application to the full Review Panel.
* After discussing the proposals, the full Review Panel must make a ***single consensus recommendation*** (yes, revise, or no) regarding each proposal.

For this case you will take on the role of a scientist sitting on the FDA’s Oncology Clinical Trials Pre-Review Panel (OCTP). This panel is responsible for screening clinical trial proposals of new therapies for prevention or treatment of cancer. OCTP reads the Executive Summaries (short abstracts that summarize much longer reports or proposals) of proposals, then makes a recommendation whether the proposal should continue to full review. OCTP makes its decisions based on 3 factors:

1. Does the proposal meet the minimum requirements for a federally funded clinical trial?
2. Do the potential benefits to patients outweigh the potential risks?
3. Does the project design meet minimum requirements of the National Cancer Institute?

Before Class:

Read these two web pages that summarize the clinical trials process, and the background information on the rest of this handout. They will provide you with general background on the purpose, general rules, and basic mechanics of clinical trials before you start reviewing specific examples.

* <https://www.cancer.gov/research/infrastructure/clinical-trials>
* <https://clinicaltrials.gov/ct2/about-studies/learn#ClinicalTrials>

The following questions will help guide your reading.

1. What are the major types of clinical trials? What are the various phases of clinical trials, and what is the goal in each phase? For each of the phases, what types of patients are recruited, and how many?
2. What are the major risks versus benefits to patients in each of the phases of clinical trials? How is safety of patients involved in the trials assured?
3. Every clinical trial is in fact an experiment conducted on humans, although we rarely call them that. Do you think the rules governing clinical trials have any effect on the quality (rigor) of the experimental design? For example, what are the positive and negative controls in a typical clinical trial? Are these the best possible controls? How else might the rules and standards of clinical trials impact experimental design or quality?

What You Will Do In Class:

On Day 1, your sub-panel (small group) will read and discuss two proposals. Your sub-panel will have to decide what additional information you need to make a decision, and until Day 2 to do any outside research or find any background information you think relevant. I have provided some questions at the end of this handout to help guide your discussion.

On Day 2 your sub-panel will present one of the two proposals you examined to the full OTCP (rest of the class). You will have 15 minutes to present your assigned proposal, recommend either approval or denial, and explain your rationale. The full Panel (i.e., the whole class) will discuss it then make a final decision.

A second small group will have read the same Executive Summary as your group, but they will not present the proposed trial. They may have questions about what you recommend and I expect you to back up any recommendations with a rational explanation.

Shared Guide Questions for the Sub-Panels:

These are the criteria on which the decision to permit or refuse a clinical trial should be made.

Scientific Validity:

* Is the proposed therapy based on scientifically valid evidence?
* Is there any opposing evidence (in the proposal or published literature) to suggest this is not a good strategy?

Clinical Relevance and Value:

* What are the potential risks and benefits to clinical trial participants?
* Do the potential benefits outweigh the risks?

Social, Ethical Concerns:

* Does the proposed trial violate any of the general ethical principles of the clinical trials process?

**Executive Summary of Application A21788**

**European mistletoe extract for treatment of patients with advanced solid tumors**

The NIH National Center for Complementary and Alternative Medicine proposes a Phase II Clinical Trial of mistletoe extract, to be administered in combination with gemcitibine for the treatment of a variety of aggressively growing adenocarcinomas.

**Patient Recruitment Profile**

A. Fifty patients aged 18 or older will be recruited having these characteristics:

* Stage III or IV pancreatic or lung cancer. May be newly diagnosed, or treated unsuccessfully in the past with single or combination chemotherapy regimen that does not include gemcitabine.
* Stage III or IV colorectal or breast cancer that has been treated but has not responded to first line chemotherapy drugs.

B. Exclusion criteria:

* Known adverse reactions to gemcitabine, mistletoe plant or extract
* Metastasis to brain or spinal cord.

**Rationale, Preclinical Studies, and Prior Clinical Trials**

Mistletoe was used by Druids and ancient Greeks as a folk “[cure](http://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=318813&version=Patient&language=English) –all”. Current interest in it as a treatment for cancer originated in the 1920s, when European doctors prescribed extract injections for [cancer](http://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=45333&version=Patient&language=English) patients. Water- or water/ethanol-based solutions continue to be marketed under the brand names Iscador, Helixor, Isorel, and Lektinol.

Mistletoe extract has been shown to kill selected mouse, rat, and human cancer cells in the laboratory; to protect normal leukocyte [DNA](http://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=45671&version=Patient&language=English) from genotoxic [chemotherapy](http://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=45214&version=Patient&language=English) [drugs](http://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=348921&version=Patient&language=English); and counteract generalized immunosuppression. In vitro testing has found mistletoe extracts have potent growth inhibitory effects on a subset of human cancer cells lines while having no effect on other lines. The active components include several identified bioactive alkaloids and lectins, along with molecules that remain uncharacterized. None of the known components show particularly potent cell killing or growth inhibitory activity when used alone, suggesting that the constituents must be supplied together in combination to produce clinical effects.

European trials of mistletoe's ability to stop cancer cell growth in animals have yielded mixed and inconsistent results, depending on the [dose](http://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=44664&version=Patient&language=English) tested, route of administration, and type of cancer. Results of animal studies have suggested that mistletoe may be useful in decreasing the negative [side effects](http://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=46580&version=Patient&language=English) of [standard](http://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=44930&version=Patient&language=English) chemotherapy and [radiation therapy](http://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=44971&version=Patient&language=English), and that it counteracts the effects of general immunosuppressant drugs such as [cortisone](http://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=45186&version=Patient&language=English).

Most human [clinical trials](http://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=45961&version=Patient&language=English) to date have been done in Europe. Although several trials have found mistletoe to be effective, the study designs have one or more weaknesses that raise doubts about their findings: small numbers of patients, incomplete patient data, or inconsistent dosing.

Minimal side effects have been reported from the use of mistletoe extract products. Common side effects include soreness and [inflammation](http://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=44042&version=Patient&language=English) at injection sites, headache, [fever](http://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=450108&version=Patient&language=English), and chills. Rarely, severe [allergic reactions](http://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=443292&version=Patient&language=English) have been reported, including [anaphylactic shock](http://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=285952&version=Patient&language=English).

**Proposed Study Design**

This study has 4 subgroups:

* **Subgroup A**: patients with Stage III or IV pancreatic adenocarcinoma that have been either newly diagnosed, or previously treated unsuccessfully with a single or combination chemotherapy regimen that does not include gemcitabine
* **Subgroup B**: patients with resected Stage III or IV non-small cell lung cancer that have developed metastases despite treatment with a single or combination chemotherapy regimen that does not include gemcitabine
* **Subgroup C**: patients with Stge III or IV colorectal cancer that has been treated but has not responded to first line chemotherapy drugs.
* **Subgroup D**: Patients in Stage III or IV breast adenocarcinoma that has been treated but has not responded to first line chemotherapy drugs.

Patients in each subgroup will be subdivided into 2 arms. Clinical team members will be blinded as to which agent study members receive.

* **Arm I:**  Gemcitabine only.
* **Arm II**: Gemcitabine plus mistletoe extract.

All patients will complete three cycles over a 9-week period of therapy with gemcitabine alone. Patients in Arm II of Subgroups A-D will additionally receive mistletoe extract. Patients will receive gemcitabine IV over 30 minutes on days 1 and 8 and mistletoe subcutaneously daily starting on day 8 of course 1. Treatment repeats every 21 days for at least 3 courses in the absence of disease progression or unacceptable toxicity. Patients then receive escalating doses of gemcitabine and mistletoe in 2 stages.

* Stage I: Cohorts of 3-6 patients receive escalating doses of mistletoe plus a constant dose of gemcitabine until the maximum tolerated dose (MTD) of mistletoe is determined.
* Stage II: Cohorts of 3-6 patients receive escalating doses of gemcitabine in combination with the MTD of mistletoe as determined in stage I until the MTD of gemcitabine is determined.

MTD is defined as the dose preceding that at which 2 patients experience dose-limiting toxicity.

Gemcitabine is a validated treatment for metastatic carcinomas. Its inclusion ensures all patients are receiving an accepted standard treatment. Given that the effects of gemcitabine on tumor progression have been well defined in prior trials for each of the four subgroups being evaluated, any differences in tumor growth or progression caused by addition of mistletoe extract should be readily observable

***Primary Clinical Endpoint Indicators***

* Overall survival time
* Time to relapse
* Progression-free survival
* Liver function

***Secondary Clinical Endpoint and Metrics***

* Overall response rates (complete and partial)
* Overall tumor mass
* Numbers of tumors
* Progression of existing masses
* Formation of new metastases
* ECOG quality of life score

**Supplemental Background Information on This Trial**

1. This will be one of the first clinical trial applications for a cancer treatment ever submitted by NCCAM. Other alternative therapies have undergone clinical trials, but this will be a test case for an entirely new type of clinical trial. So it is likely to be scrutinized much more closely than other more traditional trials might be.
2. Mistletoe extract is different from nearly every clinical trial agent approved to date for testing by FDA. It is not composed of a single well-defined molecule, a combination of chemically related isomers, nor a combination of specific drugs. Instead, the extract is a complex mixture of hundreds of molecules from multiple molecular families. Not all of the components in the mixture are known.

**Executive Summary of Application B41935:**

**Retroviral Gene Therapy for T-Lymphocytic Adult Acute Lymphocytic Leukemia (T-ALL)**

The Adult Leukemia Study Group of the University of Texas School of Medicine proposes a phase II clinical trial to investigate whether retroviral over-expression of a dominant negative version of a T-cell oncogene can accelerate remission of T-cell acute lymphocytic leukemia (T-ALL) in adults.

**Patient Recruitment Profile**

A. Forty patients will be recruited having these characteristics:

* Age between 25 and 64 years
* Initial diagnosis of T-ALL within last 5 years
* Relapse beginning within 2 years after start of clinical remission
* Adequately functioning liver (serum bilirubin level < 2.0 mg/dL), kidneys (serum creatinine level < 2.0 mg/dL), & heart (ejection fraction >50%, no severe abnormalities).
* Written informed consent to participate in the trial.

B. Exclusion criteria include:

* Uncontrolled active infection.
* Positive for HIV antibody and/or hepatitis B virus antigen tests.
* Another primary malignancy that is clinically active or requires medical intervention.
* Pregnant and/or lactating women.

**Background, Preclinical Studies, and Prior Clinical Trials**

T-cell acute lymphoblastic leukemia (T-ALL) is an aggressive hematopoietic cancer in which excessive immature T-lymphoblasts are found in the bone marrow and blood. It is alternatively called precursor T-lymphoblastic leukemia or T-cell acute lymphocytic leukemia.

Two subtypes are recognized: pediatric, and adult-onset. Multi-agent chemotherapy coupled with high-dose methotrexate yields consistently positive outcomes with long-term remission/cure for pediatric patients. Conversely, prognosis for adult T-ALL is poor; 60-80% of adult patients treated with aggressive chemotherapy for 18-36 months will achieve remission (defined as having lymphoblasts comprising <5% of bone marrow white blood cells). On average, 60% patients relapse, with the average time from start of remission to relapse of 15 months.

Relapsed T-ALL often is resistant to a second round of intensive chemotherapy. Most patients require chemotherapy followed by bone marrow transplantation. Unfortunately, 51-53% of patients with relapsing adult T-ALL lack a suitable sibling donor, limiting their treatment options. This clinical trial will evaluate whether retroviral gene therapy can disrupt proliferation of T-lymphoblasts associated with relapsed T-ALL sufficiently to eliminate the need for bone marrow transplantation.

***Rationale for the Proposed Therapy***

Patients with inherited X-linked severe combined immunodeficiency (X-SCID, or “boy in the bubble” disease) have a mutation that inactivates IL-2 gamma common receptor. As a result they lack both functional T and B lymphocytes. In 2000, Fischer, et al. began a clinical trial of retroviral gene therapy to correct the X-SCID mutation. In evaluating possible risks it was assumed that the retrovirus carrying wild type IL2-gamma receptor DNA would integrate in patients’ genomes randomly, and the trial was approved. Initially all 10 participants given retrovirus produced normal B and T lymphocytes, but in 2003, 2 of 10 patients developed pediatric T-ALL. Subsequent testing determined that the Moloney murine leukemia (MML) retrovirus vector used in the trial had not integrated randomly; in both boys with T-ALL, retroviral and IL2-gamma receptor DNA had integrated near the promoter for *LMO2* (a T-cell proto-oncogene). Viral sequences constitutively activated the adjacent oncogene and triggered subsequent uncontrolled T-cell proliferation (McCormack, 2004).

The clinical trial proposed here will turn the negative outcome from Fischer’s 2000 X-SCID trial to advantage. The original MML retrovirus vector has been modified by deleting the coding region for the IL2-gamma receptor. It has been replaced with a dominant negative version of the *LMO2* T-cell oncogene (dn-LMO2), under control of a strongly inducible retinoic acid response element. Synthesis of the dominant negative oncoprotein by the construct is induced simply by giving patients all-*trans* retinoic acid (Tretinoin). This strategy also eliminates safety concerns about activation of the LMO-2 locus by integrated virus.

Details of construction and validation of dn-LMO2 oncoprotein and MML retroviral carrier are provided in *Appendix A* of the full proposal. Data from cell culture studies confirming that dn-LMO2 oncoprotein blocks T-cell proliferation, and is strongly induced by retinoic acid, are provided in *Appendix B*. Whole animal studies (summarized in *Appendix C*) confirm retinoic acid induces production of dn-LMO2, and blocks leukemia progression in three established transgenic mouse models (TAL-JAK2, SCA-1+, and RHOM/LMO-2) for this disease.

**Proposed Study Design**

In Stage 1 of this trial, patients will be treated with the retroviral study agent. With the patients under general anesthesia, 30 to 150 ml of bone marrow will be obtained, and CD34+ cells in the marrow selected for, as described in *Appendix D* (Clinical Protocols). Cells will be stimulated to grow in DMEM containing 4% fetal-calf serum, 300 ng/ml stem-cell factor, 300 ng/ml Flt-3 ligand, 60 ng/ml IL-3, and 100 ng/ml polyethylene glycol–conjugated megakaryocyte growth and differentiation factor. This procedure increases number of CD34+ cells ~5-8-fold.

After 3 days, marrow cells will be treated for 24 hours with a suspension containing 5 x 109 dn-LMO2-bearing modified MML retroviral particles/ml. After washing, 2 x 107 CD34+ cells per kilogram of body weight will be infused via a central line back into the patient from which the cells originated.

Six weeks after infusion, peripheral blood will be screened by PCR for lymphocytes bearing the unique splice sequence found in the coding region of dn-LMO2, but not in the wild type homologue. Participants positive for retroviral integration will progress to Stage 2 of the trial.

During Stage 2 clinical personnel will evaluate study participants quarterly for up to 5 years. All patients will receive a standard course of re-induction chemotherapy including prednisone, vincristine, anthracycline, and asparaginase. Concurrently, study participants will take 45 mg/m2 body surface area per day of tretinoin (all-*trans* retinoic acid) to stimulate production of the T-lymphocyte growth inhibitor dn-LMO2.

The control cohort for this study consists of patients who complete Stage 1 but not Stage 2 of the trial (i.e., receive retrovirus but fail to produce genetically modified T-cells). Additional historic population data will be obtained from records of T-ALL patients treated by UT School of Medicine from 1998 to 2008.

***Primary Clinical Endpoint Indicators***

|  |  |
| --- | --- |
| **Indicator** | **Predicted Outcome For Patients Producing dn-LMO2** |
| 5-year overall survival | Significantly greater 5-year overall survival rate after initial diagnosis. |
| CNS involvement | Reduced secondary infiltration of T-lymphoblasts into brain, meninges. |
| Bone marrow lymphoblast density | Significant reduction in bone marrow lymphoblasts in response to retinoic acid. |

**Supplemental Background Information on This Trial**

This case proposal is based on actual events. The failure of the X-SCID gene therapy trial, identification of the LMO-2 oncogene, and subsequent investigation are matters of public record (to find more information, look up:

McCormack MP, Rabbitts TH. 2003. Activation of the T-cell oncogene LMO2 after gene therapy for X-linked severe combined immunodeficiency. *N Engl J Med.* 350:913-922.

**Executive Summary of Application C02876:**

**Implantation of encapsulated hepatic adenoma to inhibit growth of hepatocellular carcinoma**

The Cell and Cancer Biology Branch of the Center for Cancer Research, National Cancer Institute proposes a Phase II Clinical Trial of a new procedure to reduce the rate of metastasis of hepatocellular carcinoma.

**Patient Recruitment Profile**

A. One hundred patients will be recruited (50 per study group) having these characteristics:

* Group A: subjects who have undergone surgical resection of HCC no more than 4 weeks before admission to the trial.
* Group B: subjects identified with localized and locally advanced unresectable tumors.

B. Other inclusion criteria:

* Male or female subjects > 18 years of age
* CT scan indicating patient has no metastases in remaining liver
* Intermediate or High Risk of recurrence, based on tumor marker typing at time of resection
* ECOG Performance Status of 0.
* Adequate bone marrow, liver and renal function

C. Exclusion criteria:

* Low risk of recurrence based on tumor marker typing
* History of GI bleeding within 30 days of randomization
* Prior anti cancer therapy for HCC (including sorafenib or any other molecular therapy)
* Investigational drug therapy outside of this trial during or within 4 weeks of study entry.

**Background, Preclinical Studies, and Prior Clinical Trials**

Hepatocellular carcinoma is less uncommon in the United States, but its incidence is rising, mainly due to the spread of hepatitis C infection. In contrast, it is the most common cancer in certain parts of the world, with more than 1 million new cases diagnosed each year. Hepatocellular carcinoma is associated with cirrhosis in 50% to 80% of patients. Hepatitis B and C infection appear to be the most significant causes of hepatocellular carcinoma worldwide. Male patients older than 50 years who have both hepatitis B and hepatitis C infection are at particularly high risk. Aflatoxin is often a causal factor in areas where this mycotoxin is found in high levels in food.

Surgical resection is the primary means of treatment, but this is feasible in a small fraction of patients with localized disease. Prognosis depends on the size of local tumors and the extent of liver function impairment.

* ***Localized resectable cancer*** is confined to a solitary mass or limited number of tumors within one lobe, that allow complete surgical removal of the tumor plus a margin of normal tissue. Only a small percentage of liver cancer patients will have such localized tumors.
* ***Localized and locally advanced unresectable cancer*** appears to be confined to the liver, but removal is not appropriate because of location within the liver.
* ***Advanced cancer*** is present in both lobes of the liver or has metastasized to distant sites. The most common metastatic sites for hepatocellular cancer are lungs and bone.

Median survival is 2-4 months without resection. Average disease-free survival after resection is 13.6-36.2 months, with a 5-year survival rate of 30%. In clinical trials, the kinase inhibitors Nexavar and Sutent each extended disease-free survival by 12-16 months compared to resection alone, but generally chemotherapeutic agents do little to inhibit reappearance or growth. Injection of 131I-radiolabeled lipiodol into the hepatic artery increased mean disease-free survival from 13.6 months to 57 months.

Even patients with resected tumors have high rates of recurrence. The frequency and number of metastases arising after resection suggests the primary tumor releases large numbers of cells that form dormant micrometastases in multiple body tissues; this occurs well before the primary tumor grows large enough to produce symptoms. In animal models, the primary hepatic mass has been shown to release several factors that repress growth. When the primary tumor is removed, multiple micrometastases exit the dormant state and begin growing concurrently. (See *Appendix A* for supporting studies.)

Hepatic adenomas (HAs) are non-malignant well-encapsulated tumors of the liver. Most HAs produce no symptoms, and usually discovered accidentally during abdominal CT/MRI scans to diagnose other conditions. Unlike hepatocellular carcinomas (HCC), HAs are restricted to a single site. While there are rare reports of HAs progressing to malignancy, HCC is almost never seen if an HA mass is present.

We isolated a clonal human HA cell line, HA-133, that represses growth of primary HCC-derived tumor lines, as well as established clonal tumor cell lines. In pre-clinical animal studies, SCID mice failed to develop primary masses or metastases when injected with SH-J1, SMMC-7721, or HHCC hepatocellular carcinoma cell lines if there was already a primary tumor present that was composed of HA-133 cells. Similar results were obtained using HCC cells isolated from patients undergoing HCC resection. Explants of larger tissue fragments also failed to survive or engraft in SCID mice carrying HA-133 primary tumors.

The nature of the signal is unknown. HA-133 conditioned medium is not sufficient to inhibit HCC growth, suggesting ongoing bi-directional communication between HA and HCC cells is required. To that end, we propose testing whether the tumor inhibitory activity of HA-133 cells can: 1) retard growth of primary non-resectable HCC, and/or 2) delay metastatic relapse in patients with resected HCC.

***Cell Encapsulation and Modification:***

HA-133 cells for implantation will be grown on thin three-dimensional Type IV collagen matrices, as described in *Appendix B*. Cells plus supporting matrix will be encapsulated in a porous non-biodegradable polytetrafluoroethylene (GoreTex) membrane (US Patent # 4,194,041; see *Appendix C*). Restricted pore size of the membrane permits diffusion of soluble molecules but prevent escape of HA-133. As an added safety measure the HA-133 cell line has been modified to express viral thymidine kinase. This provides a positively selective “suicide switch” by sensitizing cells to gancyclovir. If for any reason HA-113 cells escape the capsule, they can be ablated with a standard course of gancyclovir.

**Proposed Study Design**

This study has 2 subgroups: Subgroup A consists of patients with localized, resectable tumors. Subgroup B consists of patients with localized or locally advanced, non-resectable tumors. Patients in both subgroups will be randomly assigned to one of four treatment arms:

1. ***Placebo***. Surgical implantation of uncolonized collagen/Goretex capsules
2. ***Placebo plus Nexavar/Sutent.*** Arm #1, plus a cocktail of two kinase inhibitors.
3. ***Encapsulated HA-133 only***. Implanted capsule contains modified hepatic adenocarcinoma cells.
4. ***Encapsulated HA-133 plus Nexavar/Sutent.*** Arm #3, plus a cocktail of two kinase inhibitors.

A sheet of encapsulated cells or placebo will be anchored to the upper right abdominal wall of each participant. See *Appendix D* for surgical protocols.

It should be noted that injection of 131I-radiolabeled lipiodol at the time of resection is the current standard of care for Subgroup A. Given that HA-133 cells also are sensitive to lipiodol, patients who receive lipiodol radiotherapy will be dropped from the study.

***Primary Clinical Endpoint Indicators***

Overall survival time, time to relapse, progression-free survival, liver function

***Secondary Clinical Endpoint and Metrics***

Overall response rates (complete and partial), EORTC quality of life, immune reaction to the capsule.

**Supplemental Background Information on This Trial**

There are some additional facts that you are unlikely to be aware of, but that are relevant to this proposal, and that should be considered.

1. **Sorafenib tosylate** (Nexavar) is given post-surgery to reduce the rate of recurrence. Sorafenib targets growth signaling and angiogenesis by blocking the enzyme RAF kinase, a critical component of the RAF/MEK/ERK signaling pathway that controls cell division and proliferation. In addition, sorafenib inhibits the VEGFR-2/PDGFR-beta signaling cascade, thereby blocking tumor angiogenesis.
2. **Sunitinib malate** (Sutent) is a tyrosine kinase inhibitor with potential antineoplastic activity. Sunitinib blocks tyrosine kinase activities of vascular endothelial growth factor receptor 2 (VEGFR2), platelet-derived growth factor receptor b (PDGFRb), and c-kit, thereby inhibiting angiogenesis and cell proliferation. This agent also inhibits the phosphorylation of Fms-related tyrosine kinase 3 (FLT3), another receptor tyrosine kinase expressed by some leukemic cells.

**Executive Summary of Application D73396:**

**Personalizing Treatment for Early Stage Breast Cancer**

The **T**rial of **R**elative **R**isk for **A**dvancing **D**is**E**ase (TRRADE) is a multi-center project to determine if genes frequently associated with risk of recurrence for women with early-stage breast cancer can be used to assign patients to the most appropriate and effective treatment subgroups. TRRADE is co-sponsored by the Department of Defense and National Cancer Institute (NCI), and is being conducted jointly by the Eastern Cooperative Oncology Group (ECOG) and Veterans’ Administration Hospitals.

**Patient Recruitment Profile**

A. 11,248 female patients will be recruited at 900 participating sites with these characteristics:

* Age between 18 and 70 years
* Histologically confirmed adenocarcinoma
* Hormone receptor status: estrogen and/or progesterone receptor positive tumor
* Her2/neu negative by immunohistochemistry
* Surgery to remove primary tumor (mastectomy or local excision plus sentinel lymph node biopsy) within the past 84 days
* Axillary nodes are negative
* Tissue specimen from primary tumor available for testing to determine Recurrence Score
* Written informed consent to participate in the trial.

B. Exclusion criteria include:

* Over-expression of Her2/neu gene
* Pregnant and/or lactating
* Breast cancer developed while taking a selective estrogen-receptor modulator (tamoxifen, toremifene, or raloxifene) or aromatase inhibitor (anastrazole, letrozole, or exemestane)
* Prior breast cancer
* Prior chemotherapy or radiotherapy for this cancer

**Background**

Breast cancer is the most frequently diagnosed cancer in women, with an estimated 192,370 new cases of invasive breast cancer expected in the United States in 2009. Of these, over half (>56%) of primary tumors are estrogen receptor positive, lymph node negative adenocarcinoma. For 80-85% of women, the current standard treatment practice is surgical resection (either lumpectomy or mastectomy), followed by radiation and hormonal therapy. Chemotherapy is also recommended for most women, but the relative numbers of women who actually benefit substantially, versus receive it unnecessarily, are unknown. TRRADE aims to more accurately identify women who are likely to benefit from chemotherapy, and those who are not.

The primary goal of TRRADE is to determine the most effective approach to cancer treatment, with the fewest side effects, for women with early-stage breast cancer, by integrating a panel of pre-defined molecular profiling tests into the clinical decision making process. Oncome-22 is a validated diagnostic test panel developed by Oncogenomics, Inc. (Reston, VA) in collaboration with the National Surgical Adjuvant Breast and Bowel Project.

Oncome-22 measures levels of expression of 22 genes in breast tumors, including 5 proliferation markers, 3 invasion markers, 2 markers of Her2 status, 4 markers of PR/ER status, 3 predictor markers identified by gene array profiling, and 5 reference markers of sample integrity. Based on the Oncome-22 gene expression analysis, an algorithm generates a **relative recurrence score** from 0 to 100 that is proportional to likelihood of a recurrence if treated with hormonal therapy alone. This panel-based assessment can more precisely estimate risk of recurrence than standard characteristics, such as tumor size and grade. Published studies (see *Appendix A* for a review) support the predictive value of Oncome-22 profiling, and provide the basis for the TRRADE trial.

**Study Design**

Patients will be assigned to 1 of 3 treatment groups based on their risk of distant recurrence determined by Oncome-22 Assay.

***Group 1 (Oncome-22 relative recurrence score [ORRS] < 11):***

Patients will receive standard hormonal therapy (e.g., oral tamoxifen alone, oral aromatase inhibitor [e.g., anastrozole, letrozole, or exemestane] alone, or oral tamoxifen followed by oral aromatase inhibitor) at the discretion of the treating physician for 5 or 10 years.

***Group 2 (Primary study group; ORRS 11-25):***

Because the degree of benefit of chemotherapy for women with recurrence scores between 11 and 25 is uncertain, TRRADE seeks to determine if the Oncome-22 test will be helpful in future treatment planning for this group.Patients will be stratified according to tumor size (≤ 2.0 cm vs ≥ 2.1 cm), menopausal status (post, peri, or pre-menopausal), planned chemotherapy, planned radiotherapy, and Oncome-22 relative recurrence score (11-15 vs 16-20 vs 21-25). Patients then will be randomized to receive either hormonal therapy alone or combination chemotherapy and hormonal therapy.

* ***Arm I (experimental):*** Patients receive hormonal therapy as in Group 1 at the discretion of the treating physician.
* ***Arm II (standard):*** Patients receive standard combination chemotherapy at the discretion of the treating physician. Within 4 weeks after the last dose of chemotherapy, patients receive hormonal therapy as in group 1 at the discretion of the treating physician.

***Group 3 (Secondary study group 2; ORRS > 25):***

Patients will receive combination chemotherapy as in group 2, Arm II followed by hormonal therapy as in Group 1. Hormonal therapies will be assigned based on menopausal status.

***Tissue Analysis, Other Tests***

* Tissue obtained at surgery (performed prior to study entry) is examined by the Oncome-22 Recurrence Score Assay and other assays to correlate response with various biomarkers.
* Women in the study will have a physical exam performed by their doctor every three to six months for the first five years, then once a year after that for up to 20 years. An annual mammogram will check for signs of recurrence.
* Patients may complete quality-of-life assessments at baseline and at 3, 6, 12, 24, and 36 months.
* After completion of study treatment, patients are followed up periodically for up to 20 years

**Clinical Endpoints**

***Primary Clinical Endpoint Indicators***

Disease-free survival, distant recurrence-free interval, recurrence-free interval, overall survival

***Secondary Clinical Endpoint and Metrics***

ECOG quality of life score, differences between all groups and arms on other patient-reported outcomes measures

**Gene Markers Used in the Oncome-22 Assay** (developed by Oncogenomics, Inc., Reston, VA)

**Proliferation**

* KI-67
* STK15
* Survivin
* Cyclin B1
* MYBL2

**Invasion**

* Stromelysin 3
* Cathepsin L2

**Her2 Status**

* GRB7
* HER2

**Estrogen**

* ER
* PR
* Bcl2
* SCUBE2

**Other**

* GSTM1
* CD68
* BAG1

**Reference**

* Beta actin
* GAPDH
* RPLPO
* GUS
* TFRC

Instructor Notes

*Background*

**How Realistic Is This Case Scenario?**

I modeled this case on how the FDA and NIH actually operate. In practice NIH and FDA reviewers read the full proposal, not just the Executive Summary. However, like this case, only some of the panel members will be assigned to read each proposal. Panelists who were not assigned to read the proposal can ask questions of their colleagues, but rarely do they have time to go back and extract the information for themselves. Often the decision of the full panel to fund or approve a trial (or not) is based entirely on the evidence and arguments which the smaller subpanel group presents.

The summaries are based on actual proposals in the **ClinicalTrials.gov** public database. The shared guide questions for panelists were designed to focus students’ attention on three primary criteria of each study: scientific validity, clinical value, and ethical concerns. This models how reviews are done normally, but also keeps students focused on the key issues that I want them to pull out of the case itself.

The primary focus of the case as written is to teach students:

* How clinical trials are approved;
* To evaluate proposals using standard criteria; and
* Basic ethical reasoning skills.

The overall case framework can be revised to teach students about the federal grant proposal process, how scientific literature is reviewed, or other review processes. Where students will direct most of their attention is determined by the shared evaluation criteria and guide questions.

**Relevance of the Belmont Report**

Students very likely already can judge the general scientific rigor of the studies based on their prior training. Students in the cancer biology course for which this case was developed would have read articles describing similar studies already, so would be equipped to understand the specifics of each study, and the biology of the disease process. What they lack is any experience evaluating the ethical issues, which is why the case introduces the Belmont Report.

Various documents like the Nuremburg Code, Geneva Convention, Helsinki Accord, etc. have been used to establish guiding principles for ethical and humane treatment of others in war, after natural disasters, or whenever one group has power over another. In 1973, the US Dept. of Health, Education, and Welfare issued a report entitled “Ethical Principles and Guidelines for the Protection of Human Subjects of Research,” commonly known as the Belmont Report. It codified three fundamental ethical principles relating to the use of any human subjects for research. These principles are the basis for all current human subject protection regulations. These principles are:

1. **Respect for persons**: protecting the autonomy of all people and treating them with courtesy and respect and allowing for informed consent.
2. **Beneficence**: maximizing benefits for the research project while minimizing risks to the research subjects.
3. **Justice**: ensuring reasonable, non-exploitative, and well-considered procedures are administered fairly, and there is fair distribution of costs and benefits to potential research participants.

The Belmont Report remains an essential reference for both the federal and institutional review boards (IRBs) that review and approve all research on human subjects. It also guides reviewers when they decide whether to permit clinical trials.

Class Management

*How Sub-Panels Are Arranged*

The order listed below means each group reads one proposal as primary reviewers, and a second as the secondary reviewers. The secondary reviewers for every proposal are staggered so that each proposal is seen by the maximum number of independent reviewers.

|  |  |  |  |
| --- | --- | --- | --- |
| **Subpanel** | **Students in Group** | **1st Proposal** | **2nd Proposal** |
| *Day 1* |  |  |  |
| Group 1 |  | A (mistletoe) | D |
| Group 2 |  | B (gene therapy for T-ALL) | C |
| *Day 2* |  |  |  |
| Group 3 |  | C (control 1 tumor with another) | A |
| Group 4 |  | D (breast cancer gene profile) | B |

Sample questions the instructor might ask during panel presentations:

*General Questions*

* Is it possible for a patient to provide truly informed consent in the case of a complex disease?  
   In the case of a radically different treatment protocol?
* Has anyone heard of, or read, the Belmont Report?

*Mistletoe Extract:*

* Is it acceptable to conduct a clinical trial based on ethnobotanical and epidemiological data, but lacking controlled animal trials?
* Is it acceptable to test a product or extract for which we do not know the constituent molecules?
* Given this trial is looking at 4 different types of cancer, is it going to be large enough?

*Retroviral Correction of T-Cells:*

* X-SCID treatment was correcting a defect. In contrast this treatment could lead to a heritable germ line change (at least in theory). Should it be allowed?

*Implantation of encapsulated hepatic adenoma as a prophylactic inhibitor of hepatocellular carcinoma.*

* Is it possible for a patient to provide truly informed consent in the case of a complex disease?  
   In the case of a radically different treatment protocol?
* Why can’t we conduct Phase I safety trials on healthy volunteers?
* If we cannot conduct Phase I, is it ethical to go straight to Phase II?
* Does it violate the federal standards for Phase II trials?
* FDA stringency rules are lower for cancer drugs; is this sufficient reason to allow a more risky therapy into trials?
* How would you evaluate this for efficacy?
* Would this therapy be a viable alternative? Why or why not?

*Genomic Profiling to Pick Treatment Group for Breast Cancer*

* Is it possible for a patient to provide truly informed consent to this procedure?
* Does anyone have a problem with a single company being sole provider of the preferred diagnostic tool to be used nationwide?
* There is no control on the decision-making process of the treating physician in Group 1, or Group 2, Arms 1 and 2. Any problems there?
* Can a clinical trial operator use the argument that they were given approval to conduct a long-term study as an *a priori* reason to receive funding to continue the study?

*Supplemental Information For Specific Proposals*

**Application** **A21788:** European mistletoe extract for treatment of patients with advanced solid tumors

As the notes to students pointed out, clinical trials for cancer follow very strict guidelines. Any clinical trial that deviates from the current “intention to treat” standard is subject to much greater scrutiny and more likely to be denied. This scenario was designed to give students an opportunity to discuss the limitations and benefits of this practice.

**Application B41935:** Retroviral Gene Therapy for T-Lymphocytic Adult Acute Lymphocytic Leukemia (T-ALL)

This proposal was written to highlight the challenges of developing gene therapies for cancer. It is based on a scenario that was in the news in 2003.

In 2003, two cases of T-cell leukemia were reported as unanticipated complications of a gene therapy trial for a pioneering retrovirus-mediated treatment for X-linked severe combined immunodeficiency (X-SCID). The October 17 Science reported that inappropriate insertion of the retroviral vector near the proto-oncogene LMO2 promoter led to uncontrolled clonal proliferation of mature T cells (Science, 302:415-419, October 17, 2003).

The affected children were the youngest of 10 boys with X-SCID enrolled in the gene therapy trial at Hôpital Necker Enfants Malades. X-SCID is due to a defect in the common γ (γ c) chain of the interleukin 2 receptor on chromosome Xq13. The gene therapy used ex vivo transfer of the γc gene into autologous hematopoietic precursor cells, carried by defective Moloney murine leukemia virus as a vector.

Fourteen children with X-SCID—10 in France and four at Great Ormond Street Hospital in London—were subsequently treated and showed an impressive and sustained clinical response. Then in 2002, the first patient exhibited a “leukemia-like syndrome” 30 months after therapy. A second participant in the French trial had similar problems, which triggered a moratorium on the trial.

Subsequent work found that both patients had retrovirus inserted near the promoter of LMO2, which encodes a transcription factor required for hematopoiesis. Why the vector preferentially targeted the LMO2 promoter remained an open question, but the evidence was clear: retroviral gene therapy could lead to insertional mutagenesis that produced clinically important negative effects.

Supporting Reference Articles

* S. Hacein-Bey-Abina et al., “LMO2-associated clonal T-cell proliferation in two patients after gene therapy for SCID-X1,” Science, 302:415-419, October 17, 2003.
* M. Noguchi et al., “Interleukin-2 receptor g chain mutation results in X-linked severe combined immunodeficiency in humans,” Cell, 73:147-157, April 9, 1993.
* M. Cavazzana-Calvo et al., “Gene therapy of human severe combined immunodeficiency (SCID)-X1 disease,” Science, 288:669-672, April 28, 2000.
* A. Maher, “Gene therapy trials hit obstacle,” The Scientist, 16:26, October 28, 2002. http://www.the-scientist.com/yr2002/oct/maher\_p26\_021028.html
* McCormack MP, Rabbitts TH. 2003. Activation of the T-cell oncogene LMO2 after gene therapy for X-linked severe combined immunodeficiency. *N Engl J Med.* 350:913-922.
* A. Williams, C. Baum, “Gene therapy: New challenges ahead,” Science, 302:400-401, October 17, 2003.
* Z. Li et al., “Murine leukemia induced by retroviral gene marking,” Science, 296:497, April 19, 2002.

**Application C02876:** Implantation of encapsulated hepatic adenoma to inhibit growth of hepatocellular carcinoma

This scenario was designed to challenge students’ fundamental understanding of cancer. One of the emerging ideas in cancer biology is that not all cancers should be treated aggressively. Some tumors are self-limiting and fail to progress to life-threatening metastases. Multiple studies have found that surgical removal of a primary tumor can stimulate growth of dormant micrometastases. The idea of leaving cancer in place does not align with the public’s perception of cancer and is likely to meet strong resistance. The scenario provides students with another opportunity to evaluate a clinical trial from an ethical perspective, not just a scientific one.

**Application D73396:** Personalizing Treatment for Early Stage Breast Cancer

The proposal is based on the TAILORx Trial, which was one of the first to demonstrate the benefits of panel-based genetic profiling in cancer therapies. The Oncome-22 Assay is actually the Oncotype DX Profile Assaymarketed by Genomic Health, Inc.; Redwood City, CA. The original name and vendor were changed to keep students from simply looking up product information online. Instead students must rely on their prior knowledge from class or look up the relevant genes.