How to initiate a clinical trial

Francine Foss
The steps

– Develop an idea for a clinical trial
– Decide who is going to sponsor it
  • Industrial sponsor
  • NIH grant
  • Institutional grant
  • GCRC
– Letter of intent if sponsor is industry or NIH
Letter of Intent

- Components of a competitive Letter of Intent (LOI)
- As with any application for support, a great idea can be poorly communicated or well communicated. The review criteria for LOI are:
  - 1) Strong scientific hypothesis
  - 2) Supporting preliminary data and/or a strong rationale
  - 3) Adequate patient accrual
  - 4) Innovative and well-justified correlative studies
  - 5) Ability to meet regulatory requirements
  - 6) Not duplicative
  - 7) Agent availability
- Industry sponsor concurrence
Constructing the LOI

- Rationale/Hypothesis section:
  - The rationale for performing the specific clinical trial should be explicitly stated.
  - Reasons might include compelling *in vitro* or *in vivo* experiments, molecular biological rationales (drug “hits” target protein, and this protein is selectively over-expressed in the tumor type to be studied in the LOI.), or prior clinical data such as a significant number of tumor responses in prior studies using the agent or similar agents.
Hypothesis

The hypothesis should be succinctly stated as a question to be asked as the primary endpoint of the study, and the design of the study should permit an unequivocal answer to the question.

- A poorly stated rationale and hypothesis: “Cancer X has a poor prognosis and there is no approved effective therapy. It is possible that agent Y will demonstrate activity against cancer X in humans.”

- A well-stated rationale and hypothesis: “Cancer X is known to over express the Q receptor in 75% of cancer X specimens sampled from patients who have a recurrence after definitive regional therapy. Drug Y binds to and inactivates the growth stimulating effects of receptor Q, and in multiple animal tumor models of cancer X, drug Y has been shown to have twice the tumor shrinkage rate as commercially available drugs, and cures 30% of all mice treated. We hypothesize that drug Y will demonstrate an overall response rate of at least 30% by RECIST criteria when administered to chemotherapy naïve patients with cancer X, whose cancers have recurred following regional therapy, compared to 15% who historically respond when treated with commercially available drugs.”
Supporting the hypothesis

• Supportive data: If you have used this agent in your laboratory or in a clinical trial at your site, and have unpublished data that is relevant, include a summary of that data, with figures, pre-prints or a summary from a grant progress report or grant application, if available, for the reviewers.

• It is helpful to receive data such as: “of 8 patients with prostate cancer in the phase I trial, who had disease progression after prior therapy with docetaxel, 4 receiving docetaxel with agent Y had PR sustained from 3-9 months”, compared to: “we saw some activity in our (unpublished) phase I trial that we want to pursue in this phase II trial”
Endpoints of the trial

- Endpoints/Statistical Considerations: The primary endpoint must be explicitly stated, and the statistics supporting the endpoint and trial design must be provided.
- A poorly-stated endpoint: We will assess progression free survival (PFS), toxicity, serum protein X levels and QOL. We will declare a PFS of 35% to be interesting.
Endpoints of the trial

- A well-stated endpoint: The primary end point will be 6 month progression free survival (PFS). Secondary exploratory evaluations of toxicity and QOL, and serum protein X will be made. Based on our institutions prior 5 trials including 200 patients, the proportion of patients alive without progression following standard therapy is 15% (95% c.i. 10-19%). Therefore, the null hypothesis is that 15% will remain alive without progression at 6 months, and our hypothesis is that use of drug Y will increase the PFS to 35%. A two-stage design will be used. If at least 4/20 patients achieve a PFS of 6 months, a total of 44 patients will be accrued, assuming a 10% ineligibility rate. If 11/40 evaluable patients achieve a PFS of 6 months, we will conclude agent Y should be further explored in this setting.
Typical endpoints for cancer trials

- Drug efficacy - at least 20% response rate is necessary for a drug to be of interest
- Time to treatment failure
- Event free survival
- Overall survival
- Quality of life impact
- Biological endpoints
Patients

• Patient population: demographics, age, diagnoses
• Anticipated accrual rate
• Barriers to accrual and how to overcome them
Laboratory correlative studies

• Laboratory correlates: A discussion concerning the rationale, hypothesis, and methods for laboratory correlates should be succinct, yet specific enough to evaluate the relative merits of the correlates.
Competing trials

• Competing studies: how many are open and when is their projected accrual
• Having 3 open competing studies in the same patient population doesn’t give reviewers great confidence that this trial will receive priority and have adequate accrual.
Sponsors

- Pharmaceutical company
  - One or several
  - Requires CDA prior to disclosure of idea
  - Often budget must be submitted
  - In most instances will require investigator to file IND
  - Beware of conflict of interest
Sponsors

• NCI (CTEP)
  – Investigational agents
  – Industry CREDAAs to make certain agents available for clinical development
  – Requires LOI to CTEP
  – Must follow federal guidelines for protocol development
  – Usually no funding for trial thru this mechanism
CTEP request for proposal

- AZD0530 (NSC 735464)
- REQUEST FOR PHASE 2 TRIALS
- Letters of Intent due **August 24, 2005**
- CONTACT: John J. Wright, M.D., Ph.D.  wrightj@ctep.nci.nih.gov
- AZD0530 is a 5-, 7-substituted anilinoquinazoline molecule that is a highly selective, orally available inhibitor of non-receptor tyrosine kinases, which includes c-Src, c-Yes, Lck, and Bcr-Abl. AZD0530 is being developed by CTEP as an anticancer agent in collaboration with AstraZeneca Pharmaceuticals. CTEP is soliciting for single-agent phase 2 trials of AZD0530 for the treatment of solid tumors including breast, non-small cell lung cancer, small cell lung cancer, colorectal, pancreas, gastric/GEJ, prostate, ovary, melanoma, sarcoma, and head and neck cancer. Phase 1 dose escalation studies are ongoing, and an MTD for AZD0530 has yet to be established. All studies have been orally administering AZD0530 on a once daily schedule.
CTEP REVIEW TYPES DIAGRAM

CTEP IND

CTEP FUNDING

NO CTEP IND

NO CTEP FUNDING

CTEP Funded Consortium or International Collaboration

Cooperative Group

No Submission Required

(Examples: Industry sponsored Cancer Center Trials, investigator Initiated, charitable-funded trials, Trials with investigator IND's, etc.)

NIH Type Peer Review of Protocol

Expected Accrual

R21 type detailed Peer Review of Protocol

YES

Safety Review

NO

≥ 100

Treatment / Ancillary Studies

YES

Full Review

Phase 2

Phase 1

< 100

Developmental Strategy

Safety Review

File Only

No Treatment

Phase 1

Treatment / Ancillary Studies

YES

Phase 2
When concept is approved

- Agree on budget
- Write protocol
- IND submission or waiver letter
- Begin contract negotiations
Applying for the IND

IND submission should contain the following elements:
• Cover letter
• Form FDA 1571
• Table of contents
• Introductory statement and general investigational plan
• The letter to cross-reference sponsor’s IND
• Protocol(s)
• Form FDA 1572
• Investigator curricula vitae
• IRB approval documentation
• Informed Consent Form approved by IRB
Sample IND letter

• I am submitting, in triplicate, a sponsor-investigator investigational New Drug Application (IND) for ONTAK (denileukin diftitox, DAB389IL-2). The purpose of this IND is to evaluate the safety and tolerability of the combination of ONTAK and CHOP in patients who failed ONTAK alone or in newly diagnosed patients who have poor prognostic factors and are deemed candidates for chemotherapy. We will also collect the response rate and time to treatment failure with the combination of ONTAK administered in combination with CHOP.

• The study described briefly in this application is a pilot phase II study where 35 eligible patients will enter with the intent to participate for the full treatment period, estimated to be approximately 18 weeks at approximately 5 sites nationally. Patients will receive ONTAK at 18 mcg/kg/day for 2 days (Days 1, 2) every 21 days for a total of 18 weeks plus CHOP therapy (Day 3) every 21 days for 6 cycles (Cyclophosphamide 750 mg/m2 IV, doxorubicin 50 mg/m2 IV, vincristine 1.4 mg/m2 IV, and Prednisone 100 mg PO every day #3-7). All patients will be evaluated for response every 2 cycles of treatment and will receive up to a maximum of 6 cycles of treatment. Patients who have progressive disease while receiving the study treatment will be discontinued from the study at any time. A dose escalation to 24 mcg/kg/day for 2 days will be allowed for patient who have no Grade 3 or greater toxicity and have partial response or stable disease at 6 weeks.

• I am requesting a waiver of the 30-day waiting period as I would like to begin this study as soon as possible.
1. NAME OF SPONSOR: Francine Foss, MD  
3. ADDRESS: New England Medical Center  
750 Washington Street, NEMC 542  
Boston, MA  02111  
5. NAME(S) OF DRUG: ONTAK (denileukin diftitox, DAB389IL-2)  
7. INDICATION(S): Peripheral T-Cell Lymphoma  
9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), DRUG MASTER FILES (21 CFR Part 314.420), AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION: N/A  
11. THIS SUBMISSION CONTAINS THE FOLLOWING: (Check all that apply)  
   - CLINICAL HOLD  
   - INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)  
   - RESPONSE TO PROTOCOL AMENDMENT(S):  
   - INFORMATION AMENDMENT(S):  
   - IND SAFETY REPORT(S):  
   - NEW PROTOCOL  
   - CHANGE IN PROTOCOL  
   - NEW INVESTIGATOR  
   - RESPONSE TO FDA REQUEST FOR INFORMATION  
   - ANNUAL REPORT  
   - GENERAL CORRESPONDENCE  
   - REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED  
   - OTHER (Specify)  
   - TREATMENT IND 21 CFR 312.35(b)  
   - TREATMENT PROTOCOL 21 CFR 312.35(a)  
   - CHARGE REQUEST NOTIFICATION 21 CFR 312.7(d)  
   - justification statement must be submitted with application for any checked below. refer to the cited CFR section for further information.
Writing the protocol

• Develop from the concept sheet
• Use template from company if they have a boilerplate using their drug
• Use CTEP templates on website
Phase I studies

• Endpoint is usually toxicity (MTD)
• Now studies are being developed to look at biologic endpoints
• Cohort dose escalation design
• Random block design
Phase I trial

This is a Phase I, open-label, safety and efficacy, oral, dose-escalating, multi-center study in patients with CTCL.

Safety, PK and PD, the MTD for this indication, and preliminary evidence of efficacy of oral forodesine hydrochloride will be assessed.

Three cohorts of patients (at least 3 patients per cohort) will be evaluated sequentially.

- Patients in Cohort 1 will receive 40 mg/m2,
- Cohort 2 will receive 80 mg/m2
- Cohort 3 will receive 160 mg/m2 once a day for 28 days.

Doses will be rounded to the nearest 50 mg.
Phase I trial

• If 1 of the 3 patients within a cohort experiences a DLT, 3 additional patients will be added to that cohort. If a second patient experiences DLT at that dose level, the next cohort will not be initiated. All patients at each dose level will be evaluated for at least 2 weeks from the start of the treatment course before additional patients can be treated at a higher dose level.
• If DLTs are observed in 2 or more patients out of a cohort, the MTD will have been exceeded. No further patients will be treated at that dose level.
Phase II studies

• Usually a dose has been established or there is toxicity data
• Major endpoint is efficacy
• 2-Stage design
  – At least one response in first 14 to satisfy the null hypothesis that the drug is active
  – Expand cohort to 35-40+ based on the eventual statistical plan
  – If no response in first 14 patients, the study is closed
Phase II open label study

- This is an open-label Phase II study. ONTAK will be administered by IV (18 µg/kg/day) once daily on Days 1-5 every 3 week cycle. Patients may continue to receive ONTAK as long as a response has been observed (CR or PR), and that patient may receive 2 additional cycles beyond CR. Patients with evidence of progressive disease (PD) after the first cycle of ONTAK will receive an additional cycle since delayed responses have been reported. Patients with evidence of PD after 2 or more cycles of ONTAK will discontinue study treatment. Patients with stable disease (SD) will remain on study treatment as long as the ONTAK dose is tolerated.
Randomized phase II

- Compares two different doses or schedules of a drug
- Can determine overall response rate as well as difference between two arms
- Open label or blinded assignment
Simon two stage approach

- Given the published experience with gallium nitrate and rituximab in this patient population, the design is to exclude a minimum level of a 20% response rate and to seek a possible response of at least 38%.
- Subjects will be stratified into two cohorts. Cohort I will include subjects with 1-3 prior treatment regimens. Cohort II will include subjects with > 4 prior treatment regimens.
- The intent is for both cohorts to have approximately equal number of subjects (40 subjects) by the end of the study.
- For each cohort a minimum of 22 subjects will be recruited to the initial stage of this trial. A failure to observe 5 or more subjects with responses in the first 22 “evaluable” subjects will exclude a minimum level of 20% clinical response (power of 80%; \( a = 0.05 \)).
- If a cohort in the initial stage of the study observes 5 or more responses, then an additional 18 subjects will be enrolled into that cohort in the second stage. A total of 80 “evaluable” subjects will be accrued to the study.
Phase III study design

Phase III double-blind, randomized (2:1), placebo-controlled, multi-center evaluation of intravenous OvaRexÒ MAb-B43.13 as post chemotherapy consolidation in the treatment of female patients with Stage III/IV epithelial adenocarcinoma of ovarian, tubal or peritoneal origin. Up to 80 investigational sites will participate in the OVA-Gy-17(A/B) program.

Approximately 177 eligible female patients will participate in the each Phase III study (approximately 118 patients randomized to OvaRexÒ MAb-B43.13 treatment and 59 patients randomized to placebo treatment). About 354 eligible female patients will participate in the combined OVA-Gy-17(A/B) program (approximately 177 in study OVA-Gy-17(A) and 177 in OVA-Gy-17(B).

Patients will be randomly assigned to receive treatment with 2.0 mg of OvaRexÒ MAb-B43.13 or placebo in the double-blind phase of the study.
Data endpoint review committee

- Two independent committees, identified as the Endpoint Monitoring Committees (EMC), will verify the clinical endpoint of disease relapse for patients randomized and treated in this study. One endpoint monitoring committee will verify the clinical endpoint for patients randomized into Study OVA-Gy-17(A) and the other endpoint monitoring committee will verify the clinical endpoint for patients randomized into Study OVA-Gy-17(B).
- The EMC assessment date of disease relapse will be used for primary analyses of TTR for study OVA-Gy-17(A) and OVA-Gy-17(B). TTR will be calculated as the duration until the date of first recorded unequivocal evidence of confirmed progression determined by the EMC relative to the date of randomization.