

Clinical Trials Planning Meeting (CTPM) Executive Summary

NCI Leukemia Steering Committee (LKSC)

Acute Lymphocytic Leukemia (ALL)

November 2, 2011

Chaired by Wendy Stock

The Acute Lymphoblastic Leukemia (ALL) Working Group of the Leukemia Steering Committee held an in-person meeting on November 2nd, 2011 in Rockville, MD to discuss ALL treatment strategies, consider trials for disease subtypes, and obtain a general consensus on the next clinical trial(s).

Background presentations included a summary of the use of asparaginase in adults and children with ALL, a summary of current trends in immunotherapy for ALL, and a review of ongoing NCI funded Cooperative Group clinical trials.

Participants met in six breakout groups to address different aspects of research needed in ALL. Each group developed several recommendations.

Group I: Minimal Residual Disease: How to Validate MRD as a Marker? MRD (determined by flow cytometry) is a useful marker that correlates with clinical outcome. It is of interest in ALL, as well as AML and CLL. Methods need to be compared across laboratories to ensure that results are comparable and reliable. NCI will hold a workshop in Spring 2012 to assess strategies for validating MRD assays across laboratories. The goal is to incorporate MRD for stratification in the upcoming trial blinatumomab trial discussed by Group V. This is an immediate priority.

Group II: Ph+ ALL: Challenges for Current Trials. Two ongoing Ph+ ALL trials ([SWOG S0805](#) for younger patients and [CALGB 10701](#) for older patients) face accrual issues for this rare disease. Suggestions to enhance accrual included amending the studies to add novel agents and/or to allow some initial treatment prior to enrollment. Future trials should include mutation analysis, gene expression profiling, IKAROS, T/NK cell proliferation, and the use of MRD to predict outcome. B-cell specific antibodies (rituxin, epratuzamab, and blinatumomab) and the role of transplant (allo and auto) need to be investigated in older and younger patients. New studies will not be needed for several years. Attention should be given to enhancing enrollment in the ongoing trials.

Group III: T-ALL. A trial of 2 cycles of nelarabine using this chemotherapy schema was proposed: A → D → B → C → A → D → B → C → maintenance, where

A = induction phase (cytoxan, daunorubicin, vincristine, dexamethasone, PEG-asparaginase)

B = early intensification (cytoxan, cytarabine, vincristine, PEG-asparaginase, methotrexate [IT-MTX])

C = CNS prophylaxis (methotrexate [IV-PO-IT], 6-MP, IT-MTX)

D = Nelarabine x 2 cycles

Maintenance phase = vincristine, dexamethasone, 6-MP, MTX (PO)

Correlative studies include T-cell immunophenotype and MRD assessment. The primary endpoint will be continuous complete remission (CCR) at one year. Support from all the Groups is needed to accrue 150 of these rare patients. This study should be opened no later than the first quarter of 2013.

Group IV: Adolescent/Young Adult ALL. The current trial for these patients, CALGB 10403 will finish accrual in 2012. A follow up trial of high risk patients was proposed in which patients would be selected by

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gene expression signature (perhaps including kinase phenotype) and treated with a novel agent, such as an Hsp90 inhibitor.

Group V: Precursor B – Adults 40+. A randomized phase III trial of the bi-specific antibody blinatumomab in frontline ALL was proposed. After achieving complete remission on standard induction therapy (to be determined), patients would be randomized to consolidation with or without blinatumomab. Patients would be stratified on MRD status and transplant intention. The endpoint would be overall survival. The age of patients to be enrolled, the details of the induction regimen, and use of asparaginase need resolution. This trial should be opened no later than the first quarter of 2013.

Group VI: Novel Therapeutics for Relapsed Disease. Phase I trials of investigational agents are best done at a single institution or small consortium. The possibility of multi-site, multi-arm randomized Phase II trials comparing to standard of care should be investigated with the goal to determine which agent(s) to move into a Phase III trial. Investigators should work with CTEP to identify promising agents and begin phase I studies. Phase I trials could start immediately. Plans for multi-site phase II trials should be developed and implemented as phase I trials end.

Consensus and Recommendations: This Executive Summary contains the consensus arising from the CTPM. These recommendations are not meant to address all clinical settings, but rather represent priorities for publicly funded clinical research.

Anticipated Actions:

- Assess strategies for validating MRD assays across laboratories; incorporate MRD as a stratification factor in upcoming clinical trials (2012)
- Develop and open Blinatumomab trial for newly diagnosed B-ALL patients (2013)
- Develop and open Nelarabine trial for T-ALL patients (2013)

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AGENDA

8:00 – 8:10AM	Welcome, Introduction and Goals of Meeting	Wendy Stock Malcolm Smith
8:10 – 8:30AM	Role of and Novel Strategies for Use of Asparaginase in Adults with ALL	Dan Douer
8:30 – 8:50AM	Incorporation of Immunotherapy into ALL Therapy: What are the Options?	Steve Forman
8:50 – 9:00AM	Biomarker, Imaging, and Quality of Life Studies Funding Program (BIQSFP)	Ray Petryshyn
9:15 – 11:30AM	Breakout Sessions	

Group I: Minimal Residual Disease: How to Validate MRD as a Marker (and satisfy the FDA)

Group Leader: Jerry Radich

Participants: Stan Frankel, John Jessup, Tracy Lively, Gerald Lozanski, Lisa McShane, Elisabeth Paietta, Ray Petryshyn, Alan Wayne, Brent Wood

Group II: Ph+ ALL – Challenges for Current Trials: Can We Accrue? Shall We Change Course? How Can We Incorporate Biology?

Group Leader: Debi Thomas

Participants: Veronica Bachanova, Stephen George, Danilo Perrotti, Ellen Ritchie, Jacob Rowe

Group III: T-ALL: How Can We Get the Planned Study Submitted? And Incorporate Biology?

Group Leader: Steve Coutre

Participants: Dan DeAngelo, Adolfo Ferrando, Boris Freidlin**, Francine Garrett-Bakelman, Steve Nothwehr, Jae Park, Martin Tallman, Alan Wayne**

Group IV: Adolescent/Young Adult: What Should Our Next Trial Be? How Can We Incorporate Pharmacokinetics/Molecular Genetics?

Group Leader: Wendy Stock

Participants: Anjali Advani, Dan DeAngelo, Dan Douer, Francine Garrett-Bakelman, Mignon Loh, Donna Neuberg, Nita Seibel, Cheryl Willman, Jun Yang

Group V: Precursor B – Adults 40+: Blinatumumab: Extend Age or Do Something Different for Adults > 65 Years?

Group Leader: Mark Litzow

Participants: Fred Appelbaum, Deborah Banker, Clara Bloomfield, Stephen Couban, Francine Garrett-Bakelman, Stephen George

Group VI: Novel Therapeutics for Relapsed Disease: Can We Design Biologically Assigned Phase I/II Trials That Can Be Done in the Intergroup?

Group Leader: Susan O'Brien

Participants: Scott Armstrong, Steve Forman, Boris Freidlin, Donna Neuberg, Malcolm Smith, Rich Stone, Roy Wu

12:00 – 3:30PM **Breakout Sessions Presentations and Discussions**

3:30 – 3:45PM **Wrap-Up, Future Directions and Assignments** Wendy Stock

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