Summary of CLL Working Group Meeting
Rockville, MD
November 17, 2010

The CLL Working Group held an in-person meeting on November 17, 2010 in Rockville, MD. The group included members from each of the US and Canadian Cooperative Groups, CLL Research Consortium, P01 and SPORE grants focused on CLL. Experts in 1) clinical investigation of phase I/II/III agents; 2) transplantation; 3) statistical design and 4) correlative studies were in attendance. The major goal of the meeting was to discuss current and prospective clinical trials and correlative sciences that will improve the treatment of CLL. There was a great deal of openness, not to mention expertise, among the participants which resulted in novel ideas being presented.

The first third of the meeting was comprised of presentations from Working Group Members on topics such as current and planned U.S., Canadian, and European phase II/III trials, prospective trial designs, transplant initiatives, small molecules and new immune therapies in CLL. At the present time there are no Cooperative Group early intervention studies as CALGB 10501 closed prematurely due to poor accrual.

For previously untreated, symptomatic CLL patients, CALGB has an open intergroup randomized phase II study examining different types of chemoimmunotherapy with risk stratification based upon high risk genomic features (C 10404). This study has met more than 50% of accrual. While this study includes older patients, fludarabine based therapies were felt to be less optimal for this group. In response, ECOG is about to open a new phase II clinical trial examining alemtuzumab with low or standard dose rituximab for patients age 70 and older (E1908). One study of Pentostatin, cyclophosphamide, and rituximab [PCR] with alemtuzumab (recently modified to lenalidomide after PCR) in relapsed patients is active in ECOG (E2903). One non-myeloablative transplant study focusing on high risk CLL in first or subsequent remission is open in CALGB and the BMT CTN (C-100701). Collectively, these form a basis for growth and collaborative research among the different groups.

In this open session there was significant interest expressed in the data from kinase inhibitors that target the B-cell receptor pathway (i.e. CAL-101 and PCI-32765) in the future. Biologic therapies with lenalidomide, new antibodies such as GA-101, Ofatumumab and Tru-016 were also enthusiastically discussed as being beyond early phase testing with single agent activity. Other targeted agents which are very effective against refractory disease including del(17p) patients include the CDK inhibitors which were discussed. Of the different therapies, the oral kinase inhibitor agents (CAL-101 and PCI32765) emerging from phase I/II trials are quite positive and likely will be easy to translate to large phase III trials. There is interest in attaining these agents through the CTEP CRADA as they are high priority and have the potential to form the basis of future phase III CLL trials. Not having this available through a CRADA agreement makes it very difficult to design and implement phase III Cooperative Group trials.

The second-third of the meeting took the form of breakout subgroups, with approximately one-third of the members attending each subgroup session.

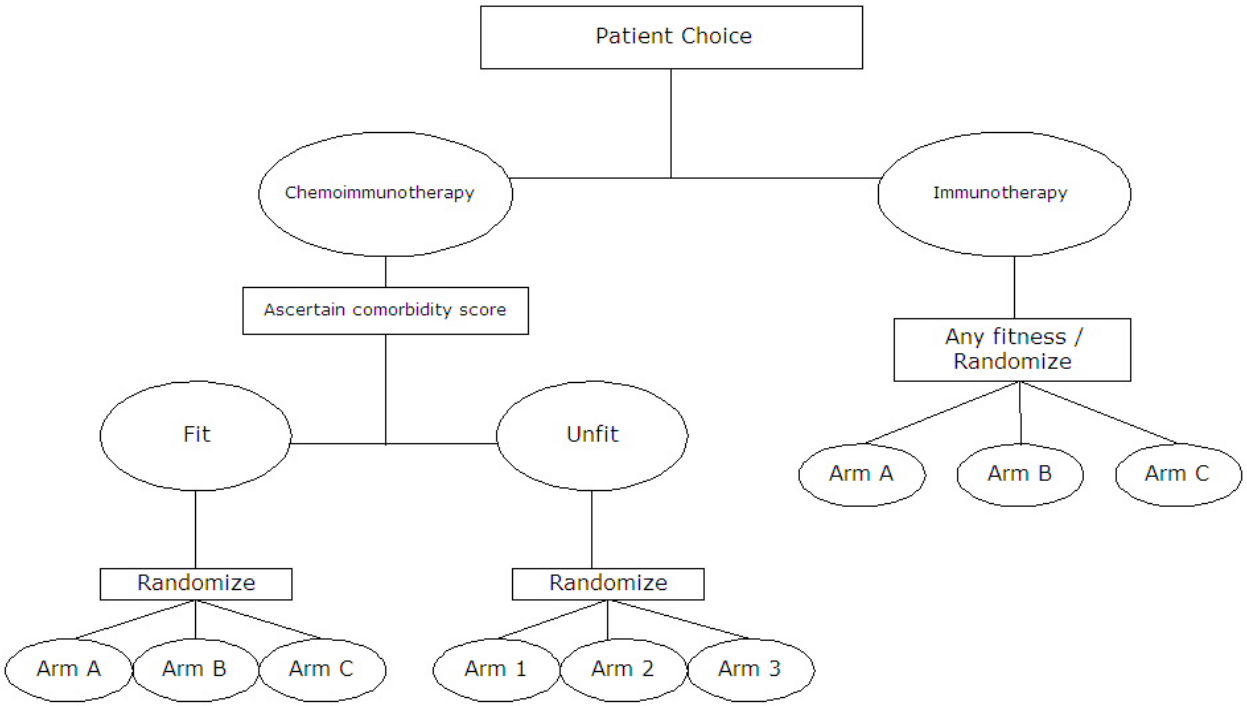
- **Group 1 – Symptomatic, Previously Untreated CLL**

This group was originally two separate groups with one focusing on young, fit patients and the other focusing on the elderly cohort. However, the members felt that the approach to these patient cohorts should not differ and combined the groups. They began by identifying problems

in prior cooperative group trials: failing patient interest in trials, groups not heeding community oncologists' feedback and continuing with therapy that was perceived as too aggressive, and lack of trials with novel agents. Some doctors and patients believe that survival has improved with chemoimmunotherapy; conversely, there are those who are not convinced and would like to further explore immuno-based therapy. Group 1 suggested that offering patients a choice between chemotherapy trials and immunotherapy or targeted agent trials not involving chemotherapy agents might provide a solution.

According to their plan, patients categorized as symptomatic would be offered a choice between two study sub-types. One sub-study would be based on best standard chemoimmunotherapy and the second sub-study based on immunotherapy or targeted non-chemotherapy only. Each sub-study would randomize patients to a standard or novel therapy. This design would allow the patient and their doctor to have input, albeit within a guided setting, regarding the type of therapy.

Disease progression in this patient population is usually slow; therefore, minimal residual disease is currently an ideal endpoint at least for some genetic sub-types. These studies should be incorporated into future studies. At least one CCOP member should be on the planning committee for this trial. The idea for this trial design was well-received by the senior investigators including the statisticians present at the meeting.



- **Group 2 – Relapsed CLL**

This group focused on approaches to make CLL a chronic disease. Outside of transplant, the disease will likely not be cured. In addition to response, trial endpoints should focus on infections, prolonged stable disease, and improved symptoms. The role of new agents and their ability to control the disease were discussed. New agents, such as CAL-101, PCI-32765, ABT-

263, flavopiridol, and SCH727965 need to be further explored to learn how to administer them safely and induce/maintain remission for as long as possible.
Group 2 expressed concern about the regulatory requirements for registration studies of new agents in CLL, in particular because several of these agents can result in discordant responses, with marked improvement in lymphadenopathy, resulting in major clinical benefit, but stable or increased lymphocytosis. They asked NCI to approach FDA about the concerns of the community regarding response criteria for registration trials and for help in developing study designs that will move the field forward.

Regarding specific studies, Dr. Jennifer Brown from CALGB presented a randomized phase II trial of two different schedules of CAL101 consolidation for relapsed patients completing a chemoimmunotherapy regimen. This study has been approved by the CALGB executive committee. Other studies discussed focused on PCI-32765 as consolidation after chemotherapy.

- **Group 3 – Special Groups: del(17p13.1) and transplant**

This group focused on the special needs of CLL high-risk and transplant patients. The CALGB/BMT CTN phase II reduced-intensity allo transplant trial is a model of collaboration and if successful, will proceed to a phase III trial. Sites choose between two conditioning regimens and two GVH prophylaxis regimens. The trial needs endorsement from all of the cooperative groups. It was agreed that this trial should be endorsed and emphasized by all CLL doctors in their grand round and education talks.

It was noted that 17p deletion patients comprise a very small population of CLL patients in the upfront setting (3-5%) but a significantly greater proportion of relapsed patients. Because of their poor prognosis with standard therapy, 17p patients who do not have a donor should be enrolled in a national phase II clinical trial of novel agents. (These patients should be treated in centers capable of opening this trial.) Also, patients who have relapsed after allo-transplant should be eligible for this trial so that important information can be obtained from this small patient cohort.

In conclusion, there is a need for studies evaluating novel agents as part of the preparative regimens for patients with MRD or residual disease pre-allo (such as CAL101, lenalidomide, PCI-32765). In addition, other studies in need include evaluating novel agents in patients post-transplant particularly for patients with MRD as well as allowing patients with residual disease or relapse post-allo to be enrolled on non-transplant protocols.

Follow up Plan: Following review of the minute meetings by all the CLL Working Group members, a conference call will be scheduled with the Group Leukemia Chairs for direction on whether a concept should move forward through a traditional single group development followed by involvement of other groups or using a study team approach from each of the groups, with the goal of rapid completion of the study. Following this discussion, plans to move forward with prioritized trials in each area will occur. In the interim time period, each cooperative group will continue moving forward with concepts that they have in development.

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