DLBCL Working Group Meeting
October 31, 2010
Meeting Summary

Meeting Participants

Oliver Press, MD, PhD (Leader)
Bruce D. Cheson, MD, FACP
Richard I. Fisher, MD
Deborah Jaffe, PhD
LeeAnn Jensen, PhD
Brad S. Kahl, MD
Richard Little, MD
Ariela Noy, MD
Louis M. Staudt, MD, PhD
Julie M. Vose, MD
Thomas Witzig, MD

I. Summary of Discussion from September 20th Teleconference

Oliver Press initiated the DLBCL WG meeting by summarizing the conclusions of the DLBCL WG teleconference held on September 20, 2010, as below:

- Identified categories of DLBCL for clinical trials
    a. Early stage DLBCL, newly diagnosed
        i) Bulky vs Nonbulky
        ii) With or Without IPI Risk Factors
    b. Advanced stage DLBCL, newly diagnosed (e.g. CALGB 50303)
        i) Entire population
        ii) ABC vs GCB Targeted Trials
    c. Relapsed/refractory DLBCL
        i) transplant-eligible
        ii) non-transplant candidates
        iii) transplant failures

- Debated conducting trials in the entire population of DLBCL versus targeting subgroups. Also, it was discussed how to define ABC versus GCB subgroups:
    a. by IHC (new IHC algorithms [Choi et al.]).
    b. by GEP on paraffin-embedded tissue

  Most discussants favored enrolling the entire population of DLBCL, with stratification to GCB or non-GCB using IHC. It was mentioned that IHC may not perform well in a multi-center or distributed fashion, however, it performs extremely well in the single center setting and centralized testing might be required. It was also noted that the paraffin-embedded tissue method for GEP may not be ready to be performed prospectively for trials opening in the near future.

- Enumerated the most exciting new drugs for DLBCL
- Reviewed and updated the list of ongoing and planned clinical trials in DLBCL in the Co-op Groups
- Enumerated biomarkers/correlative studies that should be considered in future DLBCL trials

II. Ongoing DLBCL Trials

The WG briefly reviewed these ongoing trials:

- R-CHOP versus DA-R-EPOCH (CALGB 50303)
  - This study is approximately two-thirds completed.
- R-CHOP +/- Lenalidomide Maintenance (GELA)
  - This study is for patients aged 60 years and older.
- R-CHOP14 versus R-CHOP21 +/- RT (GHGSG)
  - It was noted that this may be incorrect. R-CHOP21 has been alleged by the Germans to be an inferior treatment option and German researchers reportedly refuse to participate.
- R-CHOP +/- RAD001 (Novartis – *PILLAR-2*)
  - This is a very large international phase III trial that is set to accrue ~915 patients.
- SWOG 9704
  - This trial is evaluating upfront versus delayed auto transplant in intermediate and high-risk patients. The general consensus is that the results of this trial will change the attitude toward this treatment approach.
- Eli Lilly – Enzastaurin
  - This is a large, randomized phase III trial investigating the prevention of relapse in non-hodgkin's lymphoma using daily enzastaurin.
- Roche
  - Roche, with Genentech, launched a randomized phase III trial comparing the efficacy of Avastin (bevacizumab) in combination with R-CHOP versus R-CHOP in previously untreated patients with CD20-positive DLBCL. However, an independent DSMB recommended halting enrollment in the trial. "The DSMB's recommendation [was] based on data from a recent safety and efficacy analysis of the first 720 patients enrolled into the study, which showed an unfavorable risk-benefit assessment of the addition of Avastin to the standard of care treatment R-CHOP."*

III. Potential Study Designs

Oliver Press suggested that several possible outcomes could be envisioned from the DLBCL WG deliberations. Among the possible scenarios, might be a large Phase III randomized trial, a randomized Phase II trial, or several different single-armed Phase II trials. A recent presentation by John Crowley, lead statistician for SWOG was highlighted. In this presentation, Dr. Crowley identified 3 possible trial designs for Targeted/Biologic Agents, namely:
a. "Randomize All" Designs. Enroll, treat, and test for the relevant biomarker in all patients with DLBCL. Then analyze outcomes in those with and without the marker.
b. "Targeted Designs" (Test all patients for maker but treat only those positive for marker with agent)

* excerpt from http://www.roche.com/investors/ir_update/inv-update-2010-06-03.htm

c. "Strategy Designs": Randomized to a marker based design or not.

Finally, Dr. Press reviewed the design of "Octopus Trials" such as the ISPY2 trial for breast cancer in which there is a control arm and multiple phase II arms that are added as attractive new agents are identified and dropped as negative interim results are obtained.

IV. Defining the Criteria for Intergroup Testing of Novel Agents

Richard Fisher next led a discussion to define the criteria that should be used to determine when a novel agent is ready to be tested in a large US intergroup randomized Phase II or III Study. The discussants concluded that these criteria might vary from agent to agent depending on the mechanisms of action and toxicity profiles. However, in general it was felt that the following criteria were appropriate:

1. Good Phase II data with an overall response rate of at least 30% and a CR rate of at least 10% for conventional agents. Lower ORR and CR rates might be acceptable for biologic agents with very favorable toxicity profiles (e.g. antibodies).
2. Encouraging multi-center Phase II data should be available.
3. For front line studies with additive agents to R-CHOP, the endpoint should be two year progression-free survival and the goal should be to demonstrate an 8-10% improvement in the 2 year PFS compared to R-CHOP.
4. In view of the relatively high PFS and OS with R-CHOP in DLBCL (particularly GCB) it was suggested that future studies target patients with either adverse IPI scores or in the ABC subset.
5. Agents showing preclinical synergy might also be acceptable with lower individual activity in Phase II.

Dr. Fisher noted that large multi-institution phase II trials are more predictive of successful phase III trials; single institution phase II trials are prone to false positive results. WG members noted that although there are many attractive new agents in development, few are ready for exploration in the phase III setting. Agents such as bcl inhibitors, BTK inhibitors, and CAL101 need to be tested in small trials in a limited-institution setting and possibly in conjunction with R-CHOP before being tested in a large randomized trial.

V. Proposed ER-CHOP vs R-CHOP Trial

Dr. Witzig presented information on a proposed phase III trial for new, untreated DLBCL and results from NCCTG N0489. N0489 was a multi-center, phase II trial that studied the efficacy of ER-CHOP in previously untreated patients. Additionally, the serum free light chain biomarker was also analyzed. From February 2006 to August 2007, 107 patients were accrued with 80 patients found to be eligible. At 36-month follow-up, the OS was 79%, with PFS and EFS 74% and 69%, respectively. At a median follow-up of 39 months, 31 patients (29%) have had an event and 22 patients (21%) have died. This trial presented a

better FFS and OS than ECOG E4494, although it was noted that a British Columbian study was a better fit for comparison.

Dr. Witzig proposed a randomized, phase III trial, with an embedded phase II, of ER-CHOP versus R-CHOP. Patients on each arm would receive six cycles of treatment, with the only difference being the addition of Epratuzumab to one arm. The study would need to accrue ~875 patients, and with intergroup cooperation, could hopefully accrue 25 patients/month for a total of 35 months of accrual. It would also seek to validate serum free light chain as a marker of prognosis and predictor or relapse and the PET strategy, both of which were originally studied in N0489.

Dr. Witzig noted that the enrollment criteria should be kept as simple as possible. He also noted that because most of the decline in PFS curves for DLBCL occurs by 18-24 months, 2 year PFS was an appropriate endpoint.

Following presentation of the ER-CHOP vs R-CHOP proposal, a discussion ensued concerning whether this study should be pursued as the next Intergroup trial. Several participants were reluctant to invest the resources of all 3 cooperative groups for the 3 + years required to accrue the 875 patients needed for this trial, particularly when many other exciting agents are emerging.

VI. Discussion

Given Dr. Fisher's remarks regarding the need for encouraging multi-site phase II data before launching a Phase III trial, the WG favored a coordinated multi-site Phase II approach. In addition, Dr. Little noted that the NCI is currently reimbursing sites $5000/patient for randomized phase II trials but only $2000/patient for phase III trials. This financial incentive makes randomized Phase II trials attractive.

The WG discussed a "Hydra" design similar to the I-SPY 2 Trial which is being done in breast cancer in the phase II setting. The proposed study would allow multiple treatment arms: unsuccessful arms could be dropped as data are collected and analyzed; arms could be added treatment as promising treatments emerge. Treatment arms that are ready for testing included:

- R-CHOP (control)
- R-CHOP + Bortezomib
- R-CHOP + Epratuzumab
- R-CHOP + Lenalidomide

A biostatistician is needed to help in the design of such a trial. In addition to analyzing the efficacy of new agents, researchers may need to determine the most beneficial dose and schedule for each agent. Factors to be considered in choice of agent also include ease of administration, outpatient administration, low toxicity, a cooperative drug company, a high benefit: low risk ratio to patients, and an easily explained and understood consent process.

It was suggested that a template protocol be drafted which could be used for all arms, with appropriate modifications for each added agent.

VII. Biomarkers and Correlative Studies

Biomarkers identified in the September 20 teleconference call as worthy of consideration for inclusion in cooperative group trials of DBLCL included: β2M, LDH, Ki67 proliferative index, IHC (to differentiate GCB vs non-GCB, c-myc, TP53, and HLA-DR), GEP, Micro-RNA, Cytogenetics/FISH (e.g. t(14;18), c-myc rearrangements) and flow cytometry for immunophenotyping. Dr. Staudt emphasized that the stromal-1 signature identified by GEP is highly associated with lymphoma-associated macrophages (LAM) and is worthy of further study. Dr. Staudt also noted that mutations of CD79B are found in 18-29% of DCLBL patients within the ABC subtype and should be considered for adding to the list. Dr. Randy Gascoyne was unable to attend the meeting and should be consulted for his thoughts prior to the next call.

VIII. Action Items

1. LeeAnn Jensen will contact researchers from the I-SPY 2 trial and invite them to the next DLBCL teleconference to explain the study and answer questions.

2. WG members will discuss possible biostatisticians for the DLBCL WG.

3. A follow-up teleconference is planned to occur after ASH and before the holidays, possibly the 2nd to 3rd week of December.

4. Contact Dr. Gascoyne regarding biomarker studies.