1. BACKGROUND:

The DF/HCC Data Safety Monitoring Board (DSMB) reviews safety, efficacy and study progress for randomized DF/HCC investigator-sponsored protocols that otherwise do not have an independent DSMB assigned. The DF/HCC DSMB is an advisory committee to the DF/HCC Senior Vice President for Research and study principal investigators.

2. ASSOCIATED DF/HCC POLICIES:

2.1. COM-100
2.2. DATA-100

3. PROCEDURE:

3.1. Protocols Requiring Monitoring:

3.1.1. The Scientific Review Committees (SRC and PSRC), Institutional Review Board (IRB) and/or the Clinical Investigations Leadership Committee (CLC) establish the criteria for DF/HCC investigator-sponsored protocols that require monitoring by the DSMB. These protocols include but are not limited to Phase II and Phase III randomized protocols that otherwise do not have an independent DSMB assigned.

3.1.2. Trials monitored by the DF/HCC DSMB will remain under the DF/HCC DSMB review until either the last enrollment occurs, or until the DSMB feels there are no patient safety concerns that require further monitoring. The DSMB will determine the length of continued review on a study-by-study basis.

3.2. Committee Membership and Meeting Structure

3.2.1. Membership Composition:

3.2.1.1. The Senior Vice President for Research appoints all members of the DSMB. The DSMB membership includes both voting and non-voting members. There will be five permanent voting members of the DSMB, at least three of who must come from institutions outside the DF/HCC. The DSMB chair is selected from the voting members by the voting members.

3.2.1.2. Voting members will include physicians, statisticians, other scientists, based on their experience, reputation for objectivity, absence of conflicts of interest, and knowledge of clinical trial methodology. For studies requiring special expertise, the Senior Vice President for Research may appoint ad hoc non-voting members to provide advice on protocols. The voting members of the DSMB typically include, but are not limited to, the following:

- [2] Medical Oncologists (External, outside DF/HCC)
- [1] Medical Oncologist (DF/HCC)
- [1] Other Scientist (Radiation Oncologist or Surgeon – with DF/HCC)
- [1] Statistician (External, outside DF/HCC)
- Ad-hoc membership (if special expertise is needed)

3.2.1.3. The Chair of the Department of Biostatistics and Computational Biology or his designee will serve ex officio as a non-voting member of the DSMB.

3.2.1.4. A quorum consists of the DSMB Chair, at least one other medical oncologist and the external statistician.

3.2.1.5. Each member of the DSMB must sign a confidentiality agreement. DSMB members will be expected to follow the Harvard Medical School guidelines for disclosing conflicts of interest and will sign a statement agreeing to that policy at every meeting.

3.2.1.6. The DSMB members, both internal and external, are indemnified by DFCI against possible liabilities. DFCI's general and professional liability policies, under the insurer CRICO, cover DFCI and non-DFCI DSMB members serving in a volunteer capacity.

3.2.1.7. With the prospective permission of the DSMB Chair, guests may attend a DSMB meeting to observe for educational purposes. The invited guest will be required to sign a confidentiality agreement prior to the meeting. If the invited guest is affiliated with any of the trials under review, he/she will be asked to leave for the closed session review of that trial.

3.2.1.8. The ODQ provides administrative report to the committee; therefore, representatives of ODQ will attend each DSMB meeting as necessary to facilitate DSMB procedures.

3.3. Protocol Review Procedures

3.3.1. Prior to the meeting:

3.3.2. The study biostatistician and sponsor-investigator, or designee, will prepare a DF/HCC Data and Safety Monitoring Report for each protocol being monitored by the DSMB. The reports will be sent to the DSMB by the Office of Data Quality (ODQ) at least two weeks in advance of the meeting.

3.3.2.1. The report will follow a standard template maintained by ODQ and include a summary of the study status, enrollment and toxicity information, and any recommendations for consideration by the DSMB.

3.3.2.2. The submission may also include the full protocol document (new protocols), and, at the discretion of the DSMB, continuing renewal applications and SAE reports to the DFCI IRB.

3.3.3. The members of the DSMB will:

3.3.3.1. Familiarize themselves with the research protocol(s) and plans for the data and safety monitoring

3.3.3.2. Evaluate study summary data to determine protocol progress and whether the trial should continue as originally designed, should be changed, or should be terminated based on these data

3.3.3.3. Review reports of related studies to determine whether new information means the monitored study needs to be changed or terminated

3.3.3.4. Review major proposed modifications to the study prior to their implementation (e.g. termination, dropping an arm based on toxicity results or other reported trial outcomes, increasing target sample size)

3.3.4. **Meeting Structure and Logistics**

3.3.4.1. Meetings will be held at least twice each year and are administratively coordinated by the ODQ. Depending on the nature and volume of the trials being monitored, one of these meetings may take place by conference call. Each protocol will be discussed in both an open and a closed session.

3.3.4.1.1. In the open session, members of the study team, including the study statistician, may be present to review the conduct of the trial and to answer questions from members of the DSMB. The focus of this open session will be on accrual, protocol compliance, and general toxicity issues. Outcome results will normally not be discussed during the open session.

3.3.4.1.2. The closed session of the DSMB will include only the voting, non-voting and ad hoc members, along with ODQ staff, and will include discussion of the general conduct of the trial and outcome results, including toxicities, and adverse events. The study statistician may be asked to present outcome data during the closed session.

3.3.5. The DSMB meeting will close with an executive session to summarize and evaluate the overall meeting, finalize recommendations, and plan the next meeting.

3.3.6. **Following the Meeting:**

3.3.6.1. The ODQ will prepare the DSMB meeting minutes. These minutes will be sent to the DSMB members for review and approval, and copies will be sent to the DFCI IRB and DF/HCC Clinical Investigations Leadership Committee (CLC).

3.3.6.2.The DSMB chair will send memoranda to each sponsor-investigator summarizing the DSMB recommendations regarding their study. The sponsor-investigator must acknowledge receipt of the DSMB report.

3.3.6.2.1. For studies that remain blinded, outcome data will not be made available to individuals outside of the DSMB. Outcome data for protocols still enrolling patients are considered confidential and are not to be discussed outside the DSMB meetings. The release of data for any study actively monitored by the DSMB must be approved by the DSMB. The protocol assigned statistician and the ODQ will address any requests for toxicity or other data necessary for reporting to the FDA or other regulatory authority.

3.3.6.2.2. No communications of the deliberations (either written or oral) or recommendations of the DSMB will be made outside the DSMB except as provided for in this DF/HCC Operation.

3.3.7. **Review Outcomes and Follow-Up:**

3.3.7.1.In instances where the DSMB recommends changes to the design of a study (including early stopping of enrollment or changes in one or more of the treatments), the DSMB will provide said recommendations in writing to the sponsor-investigator.

3.3.7.2.The study team must respond to the recommendations from the DSMB expeditiously. When requested by the DSMB, the sponsor-investigator will respond in writing to the DSMB and DFCI IRB to confirm actions taken in response to the recommendations. The DFCI IRB will adjudicate any disagreements between the DSMB and the sponsor-investigator.

3.3.7.2.1. In cases where an immediate judgment is necessary based upon the severity of patient safety issues, the Chair of the IRB is empowered to suspend or close the study. When the DSMB recommends accrual suspension as a result of patient safety concerns, the Chair of the IRB is responsible for ensuring that the study is closed as soon as possible, but no longer than 24 hours after receiving the recommendation.

3.3.7.3.In cases where the DSMB recommendation does not involve trial closure for patient safety, the Chair of the IRB may decide to place the DSMB recommendation on the IRB agenda for a more complete discussion (if it is not time dependent). The Chair of the IRB may also confer with the Chair of Scientific Review Committee (SRC) as well as with the DF/HCC Medical Director, Clinical Trials Operations.

3.3.7.3.1. Alternatively, the DSMB recommendation may be referred to SRC if it involves accrual or scientific design issues that warrant a more in-depth evaluation.

3.3.7.4. In any case where the Chair of the IRB is not available, the DF/HCC Medical Director, Clinical Trials Operations is responsible for receiving and acting upon the DSMB recommendations. For administrative management, all communications to the Chairs of the IRB and/or SRC will be copied to the Director of the Office for Human Research Studies.