2015 Strategic Priorities

Myeloma Steering Committee (MYSC)

The NCTN Group Myeloma Committee Chairs from Alliance, ECOG, and SWOG and NCIC as well as designated representatives from the BMT CTN, presented their respective strategic plans to the MYSC over several teleconferences. The MYSC then discussed them at a face-to-face meeting. The MYSC has approved the following strategic plan for the NCTN Myeloma portfolio (please note the numerical position does not represent any order of relative hierarchy).

1) An important NCTN priority is to design and conduct studies to answer whether early therapy can improve survival or cure myeloma. The thesis here is that by waiting to treat multiple myeloma until after CRAB events occur, the curative potential and other clinical benefit is diminished because the disease burden has become too great, and the tumor biology may have already become more refractory to therapy. In the era of modern myeloma therapeutics, treatment at an early disease stage such as for ultra-high risk smoldering multiple myeloma may provide the opportunity to change the treatment paradigm in plasma cell dyscrasias.

2) Another high priority of the NCTN is to generate definitive data addressing whether continuous or intermittent treatment is required for MM. This question is important because the data currently available suggest that continuous maintenance therapy until progression is superior to limited duration of maintenance therapy (data from transplant maintenance trials primarily); however, as additional therapeutic agents become available, it will be increasingly important to understand whether maintenance drugs should be combined, used sequentially, continuously, or stopped and started according to clinical findings such as M protein, or sensitive MRD measurements (see priority 3 below).

3) It is not known whether there is clinical benefit in driving myeloma that is already in clinical complete response into MRD negative status. Therefore, an essential priority of the NCTN

myeloma portfolio will be to definitively answer whether changing therapy in order to achieve MRD negative status confers meaningful clinical benefit. Given the increasing potency and expanding classes of myeloma therapeutics available (proteasome inhibitors, IMIDS, antibodies/immunotherapy, cellular therapy and transplant), there are many ways to induce MRD negativity. However, the financial cost and the toxicity burden is substantial, and it is not known whether OS or HRQoL is improved by efforts to achieve MRD negativity.

4) Validation of MRD assessment and defining its clinical utility are essential strategic priorities for MM, and the other strategic priorities depend on it. Therefore, studies that inform the role of MRD in guiding therapy are an immediate priority. A longer-term priority, and a much more difficult undertaking, is to understand whether MRD might be developed as a valid surrogate marker of clinical benefit (e.g. OS). The strategy will include validation of selected cross-platform MRD assessments. MRD assessment in myeloma is complex and may require more than one platform (e.g. imaging combined with flow cytometry may be required for clinical utility). It is not a priority to confirm, for example, that NGS and flow measure the same thing. One strategic goal of MRD platform combinations is to replace bone marrow biopsy, or at least to reduce the frequency needed in obtaining them. Such an advance would serve both patients and the clinical trials effort well.

5) HRQoL studies should be leveraged strategically in the NCTN myeloma portfolio as an integral component when more traditional study endpoints such as EFS, PFS, and OS are not feasible or may not be definitive. In such cases, HRQoL would be of high scientific rigor and would be essential to inform the primary study outcome objective.

6) The MYSC invited the Grant PI of the BMT CTN and her designees (beyond those who are MYSC members representing BMT CTN) to present their plans, which were in large part a product of a meeting they held in early 2015 on the state of the science in transplant. Several themes emerged regarding myeloma, including the need to understand the optimal timing of autologous transplantation (i.e. are outcomes better if the transplant is delayed and novel therapeutics are used early in the disease course?), revisiting the role of

allogeneic transplant in myeloma, incorporating novel therapies as maintenance in an effort to allow GVMM to develop as the effector of alloimmunity. The MYSC regarded these as areas of potential cooperation, provided that the design and long-term endpoints were informative and definitive. Short-term PFS, for example, would rarely be useful for an allogeneic transplant question with an objective therapeutic question rather than transplant question per se.