2023 Strategic Priorities

Myeloma Steering Committee (MYSC)

The NCTN Group Myeloma Committee Chairs from Alliance, ECOG, SWOG, and CCTG, as well as designated representatives from the BMT CTN, presented their respective strategic plans to the MYSC over several teleconferences in 2015, shortly after the advent of the NCTN in 2014. The MYSC then discussed them at a face-to-face meeting and approved the plan. This update to the MYSC strategic plan was conducted by email polling of the membership and MYSC leadership discussions. 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 hypothesis is that by waiting to treat multiple myeloma until after evidence of end organ damage emerges, 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. Studies launched since 2015 address this question, though there remain scientific opportunities.

2) The strategic use of smaller randomized phase 2 trials, exploring multiple options, with early endpoints to inform phase 3 priorities, remains an important component of the NCTN myeloma portfolio.

3) Another high priority of the NCTN is to generate definitive data addressing the ideal duration of therapy (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 5 below). Adapting the intensity and duration of therapy to the depth of response, considering the disease risk status, needs to be addressed in prospective clinical trials.

4) It is unknown whether there is a clinical benefit in driving myeloma 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 to achieve MRD negative status confers a meaningful clinical benefit. Given the increasing potency and expanding classes of myeloma therapeutics available (proteasome inhibitors, IMIDS, antibodies/immunotherapy, cellular therapy, and transplant), many ways exist to induce MRD negativity. However, the financial cost and the toxicity burden are substantial, and it is unknown whether OS or HRQoL is improved by efforts to achieve MRD negativity in all patients.

5) Validation of MRD assessment and defining its clinical utility are essential strategic priorities for MM, and the other strategic priorities depend on it. Studies initiated since the 2015 MYSC Strategic Priorities will mature in the next few years and help inform further research strategies. Therefore, studies that report the role of MRD in guiding therapy continue to be a priority. A longer-term priority in multiple myeloma and not specific to NCTN trials evaluated by the MYSC is the much more difficult undertaking to understand whether MRD might be developed as a valid surrogate marker of clinical benefit (e.g., PFS, OS). Although this remains of interest, the use of MRD as a serial prognostic marker is also of interest and is more straightforward to incorporate into clinical trials. MRD clinical utility assessment includes 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 biopsies or reduce the frequency needed to obtain them. Such an advance would serve both patients and the clinical trials effort well.

6) HRQoL studies should be leveraged strategically in the NCTN myeloma portfolio in the phase 3 setting 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 essential to inform the primary study outcome objective. In these selected settings where defining OS as a primary endpoint is not feasible and where PFS alone does not adequately define phase 3 clinical benefit, including HRQoL as a co-primary endpoint with PFS can be considered. In such cases, long-term follow-up of OS as a safety assessment would be necessary.

7) In 2015, 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. A recent State of the Science Symposium was also held in 2022. Several themes emerged from the 2015 SOSS and new ones in 2022. The role of novel therapeutics and the need to understand the optimal timing of autologous transplantation remains an important question. In 2023, the MYSC views the role of allogeneic transplant in myeloma as less important. Still, instead, the priority should be on incorporating novel cellular and immunotherapies earlier in treatment and also as salvage. The MYSC regarded these as potential cooperation between the BMT CTN and the NCTN, provided that the design and long-term endpoints were informative and definitive in the phase 3 setting.

8) Myeloma is a heterogeneous disease with outcomes driven by the cytogenetic and other risk characteristics at the baseline modulated over time by the depth and duration of response. Risk adapted strategies will allow more individualization of treatment approaches and should be an important aspect of future investigations.