Multiple myeloma is a debilitating disease with an incurable nature, yet the past few years have seen the emergence of many novel agents with proven efficacy and improved tolerability.

For the scope of this paper, the report will detail the chemotherapy treatment of multiple myeloma in the below settings:

- Newly diagnosed Multiple myeloma(NDMM) in transplant eligible patients
    - Young fit transplant eligible patients
    - High risk transplant eligible patients
- Newly diagnosed multiple myeloma in the non-transplant eligible patient (NDMM NTE)
- Relapse Refractory Multiple Myeloma (RRMM)

In addition, the report includes a review of the management of side effects of chemotherapy drugs used in MM, and their implications for treatment.

1-*Treatment Strategies in Newly Diagnosed Multiple Myeloma (NDMM) in Transplant Eligible patients*

The traditional approach has been induction, prior to autologous stem cell transplantation (ASCT), then, consolidation followed by maintenance therapy. While induction aims at inducing complete remission (CR) prior to transplant, consolidation and maintenance therapy aim to extend progression free survival (PFS) and overall survival (OS); while reducing adverse drug events (ADEs).

Combinations of Bortezomib and IMiD based induction therapies (triplet based regimens); such as VTD and VRD, are used in induction treatment. Triplet regimens; such as VRD followed by Lenalidomide maintenance therapy, lead to with very favorable complete response (CR) and very good partial response (VGPR) results, demonstrated post induction and post ASCT.

The GIMEMA study compared the triplet regimen of Velcade® Bortezomib-Thalidomide-Dexamethasone (VTD), to Thalidomide- Dexamethasone (TD), as induction and consolidation therapy post ASCT. The VTD regimen showed a significantly higher complete and near complete response rates to induction therapy (the primary endpoint), than the TD induction regimen (31% vs. 11%).[7]

The CALGB trial compared continuous lenalidomide-based maintenance therapy to placebo, in post ASCT patients. Lenalidomide maintenance resulted in a significant longer time to progression, and improved OS.[8]

In NDDM transplant eligible patients, the treatment strategy is as such:

- In transplant-eligible patients, a regimen of VRD (or other Velcade based triplet VTD or VCD, VAD) induction, consolidation, followed by Lenalidomide maintenance is the established treatment.

- In case of Relapse while on Rd maintenance therapy, switch to Velcade ® Bortezomib (q. 2 weeks). If relapse occurs post therapy, initiate Rd again.

- Consider a 2nd transplant if relapse occurs after 18 months

2-Treatment of Non-Transplant Eligible Newly Diagnosed Multiple Myeloma (TNE NDDM) patients

The mainstay of therapy is melphalan-prednisone-thalidomide (MPT), or bortezomib-melphalan-prednisone (MPV) for patients who are ineligible for high dose therapy and transplant.

The VISTA trial added bortezomib to the standard melphalan-prednisone MP in initial induction therapy. Results showed an improved time to progression TTP (24.4mo vs. 16mo) in the MPV treated group, as opposed to the MP alone group, as well as partial and complete response rates, respectively (71% PR in the bortezomib treated group vs. 35%, and CR of 30% vs. 4%), in patients with multiple myeloma, ineligible for high dose therapy.[5]

In the MM015 trial, a comparison of melphalan prednisone lenalidomide induction, and lenalidomide maintenance (MPR-R) until disease progression; to melphalan-prednisone-lenalidomide (MPR) and melphalan Prednisone (MP), in newly diagnosed MM patients, showed a significant improvement in PFS in the MPR-R group (31 months vs. 14 mo. vs. 13 mo.)[9]
The ongoing FIRST trial compares the efficacy of Rd versus MPT in transplant ineligible patients with multiple myeloma. Patients receiving Rd continuously,

and patients receiving Rd for 18 cycles, had significantly better median PFS, than the MPT group.[10]
In the Interim Analysis, continuous Rd treated groups showed superior results across all secondary end points (OS, overall response rate ORR, time to response, duration of response DOR, safety, and QOL). Results were consistent across all age groups.[10]

- The FIRST trial establishes Rd initiation and lenalidomide maintenance as a standard of care in the TNE NDDM patient; independent of age.

In the Newly Diagnosed Multiple Myeloma, Non-Transplant Eligible patient (TNE NDMM), the below treatment strategies apply:

Patient Characteristics	Options for Treatment
Young Fit patient	Velcade® based triple regimen VTD, VRd x 6 cycles, followed by Rd maintenance
Acute Renal Failure	Velcade® based triple regimen VMP to reverse renal impairment, reassess organ function, then continue with maintenance Rd
High Risk Cytogenetics	Velcade® based triple regimen VMP, VRd x 6 cycles is first line therapy
None of the above conditions are met	*Initiate with Rd and maintain treatment*
Any of the conditions are met	*Velcade® based triple regimen for longer than 9 cycles, at least, to show efficacy*

- In cases of peripheral neuropathy, due to the Velcade® bortezomib based regimens, switch to treatment with Rd