Reviewer's report

Title: Venetoclax in combination with carfilzomib and dexamethasone in relapsed/refractory multiple myeloma harboring t(11,14)(q13;q32); a report of two cases and review of literature

Version: 0 Date: 09 Feb 2020

Reviewer: Tugrul Elverdi

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an interesting and enlightning report to read real life experience of outcomes of bcl-2 inhibititon in MM.

one or two suggestions:

1) in the second case "Venetoclax was dosed at mg per day, page 8, line 49-50", you forgot to write the dose of venetoclax

2) karyotyping and FISH and molecular analysis is challenging in MM as it should be done preferably with plasma cell sorting and if possible in new acquired plasmocytomas as well. (which is of course mostly not possible). So in case 1 , it may be that during the 2014 investigations t(11,14) may have been overlooked due the technical difficulties. Thus it may not be an acquired anomaly, but maybe rather you got more luck to catch it in 2018.

3) It is known that additional mutations must accompany everytime a malignant disease progresses or develops resistance to a therapy; thus Non-response to bcl-2 inhibititon tells us that RR-MM is not a disease with one target mutation , but rather a composition with multiple mutations and maybe different mutations in different subclones. FISH analysis can only show us really the top of an iceberg. So the lack response or rapid loss of response could be further discussed in the anarchical mutational status of RR-MM. More brave suggestion would be to test the drug in newly diagnosed 11,144 MM, which would be expected to harbour less additional mutations then RR-MM.

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