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Title: MINIMAL RESIDUAL DISEASE (MRD) DETECTION TRENDING AS A PRIMARY ENDPOINT IN CERBA RESEARCH MULTIPLE MYELOMA (MM) TRIALS

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Background:

Cerba Research (CR) is aware of >700 MM trials since 2016 which is the year the Lancet Oncol publication garnered consensus for and refined response categories for MRD negativity with either flow cytometry (FCM) or next generation sequencing (NGS) (Kumar et al. Lancet Oncol 2016). We also previously examined our CAR T MM trials where MRD detection was incorporated into trial design by means of either NGS or FCM (EuroFlow) (EHA 2022). Herein, CR examined 60 of it's MM trials where we participated as a central laboratory with a focus on MRD detection as a surrogate to drug efficacy.

Aims:

The aim of this retrospective analysis is to explore the importance of MRD detection in MM clinical trial designs. For instance, we investigated which MRD detection technique was the most commonly deployed, when MRD detection started to be implemented as an endpoint (primary, secondary or exploratory) and how many times MRD detection was performed during the course of a study. We also evaluated if there is a trend towards using MRD as a primary endpoint overtime within MM trial designs.

Methods:

We analyzed 60 MM trials from our CR oncology portfolio since 2011 which is 5 years prior to the International Myeloma Working Group (IMWG) 2016 publication. We examined the CR trial matrix database and other documents such as laboratory specification documents, trial designs, protocols, endpoints and schedule of assessments. We used descriptive statistics to illustrate MRD detection trends overtime.

Results:

CR participated as a central laboratory in 60 MM trials in the past 11 years (FPFV Jul 2011), in which 32% (19/60) were phase I/first-in-human, 47% (28/60) were phase II and 22% (13/60) phase III. CR performed in house specialty and routine testing in 23% (14/60) of trials. We also performed specialty testing alone in 72% (43/60) of trials, such as, but not limited to exploratory FCM, and 5% (3/60) had laboratory logistics only. Sponsors included biotech (47%, 28/60), large pharma (47%, 28/60) and mid-small pharma (7%, 4/60). MRD detection was incorporated into trial design as follows:

MRD technique by	% of trials where MRD detection was incorporated (total 60)
FCM alone	5% (3/60)
NGS alone	22% (13/60)
NGS and/or FCM	45% (27/60)
Not performed	28% (17/60)

MRD detection was quickly incorporated into trial designs even pre-IMWG publication (first trial started in 2015), with now the possibility to use both gold standards in many cases (45%, 27/60) depending on assay availability. We also observed that NGS was the most commonly deployed technique (67%, 40/60). Additionally, MRD detection was first implemented as an exploratory endpoint (2015-2018), which increasingly became a primary endpoint and a surrogate to progression-free survival (PFS), overall survival (OS) and/or objective response rate

(ORR) for MM treatments (2018-2022). We also observed a trend towards MRD detection as a primary endpoint overtime as indicated in the figure below (Y axis: 4=primary, 3=secondary, 2=exploratory, 1=not performed; X axis: 0=Year 2016). The number of visits for MRD assessment per protocol was variable, ranging from 2-10 per study (median=5 visits/study).

> [CHART]

Summary/Conclusion:

MRD detection has become a reliable indicator of clinical outcomes and response to MM therapies, with NGS being the most commonly deployed technique. Additionally, MRD assessment has increasingly been incorporated as primary endpoint and surrogate to drug efficacy in CR MM trials with an observed trend. As a result, CR is in the process of implementing NGS MRD detection and likely expand its usage of MM MRD FCM (EuroFlow / MSKCC) testing for global MM trials.

Keywords: Clinical outcome, Clinical data, Minimal residual disease (MRD), Multiple myeloma