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Daratumumab Post Maintenance After Relapse in Multiple Myeloma. Report of 4 Cases

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ABSTRACT

Multiple myeloma is considered incurable and requires combined and continuous treatments. We present 4 cases of patients with multiple myeloma who received daratumumab after the administration of combined therapy to achieve the best response possible, 3 patients debuted with high-risk disease. In this case series, 100% of patients achieved a strict complete response with undetectable Minimal Residual Disease (MRD) by flow cytometry, after the administration of daratumumab regardless of the scheme used in induction and consolidation, with or without autologous transplantation. After daratumumab, all patients received lenalidomide for at least 6 months with subsequent discontinuation. Follow-up included MRD.

Keywords

Daratumumab, Maintenance, Response, Minimal residual diseases, Case report.

Introduction

CD38 is expressed at relatively low levels on normal lymphoid and myeloid cells, and in some tissues of non-hematopoietic Origen. The specificity of this target has increased interest in new drugs and triggered the development of the CD38 monoclonal antibodies daratumumab, CD38 antibodies have pleiotropic mechanisms of action including Fc-dependent immune effector mechanisms, direct apoptotic activity, and immunomodulatory effects by the elimination of CD38+ immune suppressor cells.

Monoclonal antibody-based therapy has revolutionized MM therapy in the latest years increasing depth of response as we are observing this rate of cases [1]. Based on their distinct mechanisms of action, favorable toxicity profile, and single agent activity, CD38 antibodies are attractive partners in combination regimens. Indeed, deep responses and prolonged progression- free survival can be achieved in relapsed refractory MM patients when CD38 antibodies are combined with immunomodulatory agents or proteosome inhibitors. In this report we have observed with surprise the benefit of daratumumab with durable and sustained responses in patients with various lines of treatment [2,3]. One study assessed the length of daratumumab use across lines of therapy and the probabilities of treatment discontinuation in patients with MM in the real-world. The duration of use was defined as the time between the first dose and discontinuation of daratumumab as a time-to-event outcome using the Kaplan-Meier method. A gap of more than 60 days between two consequent daratumumab claim dates was defined as daratumumab discontinuation. The median duration of continuous daratumumab use was 16.6 months, by 24 months, 33.1% of patients remained on daratumumab treatment. In a subgroup analysis of patients with 12 months or more continuous insurance coverage (n=1246), the median length of daratumumab use was 24.7 months; by 24 months, 51.8% remained on daratumumab treatment [4]. We are interested in reporting the excellent results obtained in a finite treatment with daratumumab with a deep response.

Post-Maintenance Daratumumab Administration Schedule

All patients received daratumumab according to the following schedule Daratumumab 16 mg/kg weekly for weeks 1-8, every two weeks for weeks 9-16, monthly weeks 17 and 18 (Total: 14 applications).

Patients

Patient one is a 53-year-old Jewish man, with no family history of relevance, without previous pathology, with a weight of 80 kg and a height of 176 cm, who exercised 4 times a week for 40 to 60 minutes, who begins with lower back pain, asthenia, adynamia, weight loss without apparent cause. He goes for a check-up with an internal medicine specialist who finds anemia with an hemoglobin of 10.7 gr/ dl, he was sent to a hematologist who established the diagnosis of myeloma multiple IgA lambda chain, staged with ISSR- 1 with a normal karyotype, bone marrow aspiration with 56% plasma cells, lambda chain 1978 and IgA 5.1 gr/dL. Table 1

Table 1: Diagnostic characteristics.

Gender	Age at diagnosis	MM type	ISS-R	Genetic profile
Male	53 yr	IgA Lambda	I	46, XY
Male	50 yr	IgG Kappa	III	Monosomy Cr. 13, del(3), **t(4;14)** FGFR3-IGH
Fem	65 yr	IgA Kappa	III	46, XX
Fem	67 yr	Kappa	III	**t(14;16),** Monosomy Cr. 13, hypodiploidy (gain Crs.9, 11, and 15)

He received first-line bortezomib, lenalidomide and dexamethasone for 4 cycles and subsequently autologous transplant with melphalan 200, he consolidated with the initial triplet for 2 cycles. Figure 1.

The patient complete response (CR) was achieved after induction. Post-maintenance consolidation with daratumumab began due to loss of CR after 10 months of maintenance with lenalidomide monotherapy. The patient did not present any secondary events

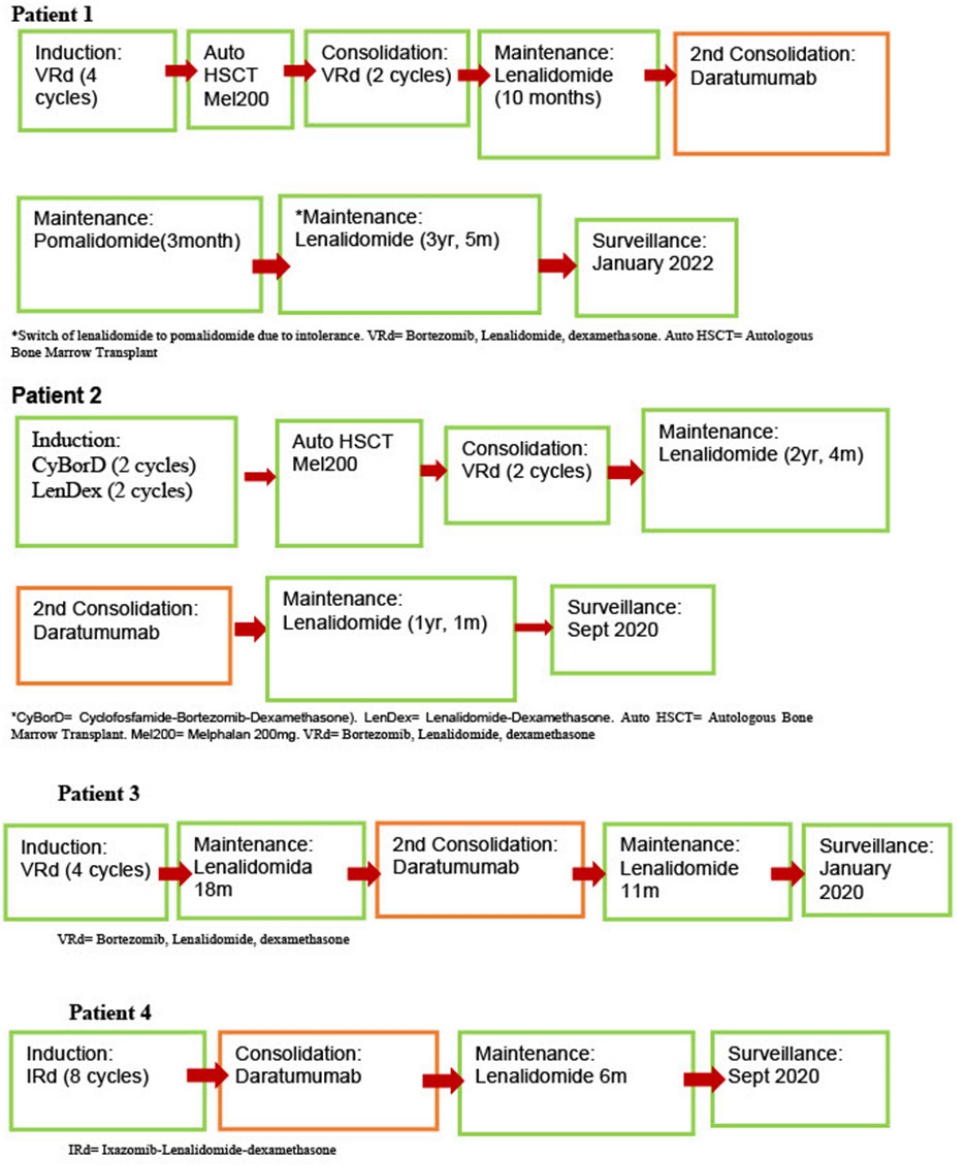

Figure 1: Treatment Protocol.

to daratumumab. Stringent CR (sCR) with negative MRD, for flow cytometry has been documented since October 2020 while he was undergoing his second maintenance with lenalidomide. Surveillance begins in January 2022. Table 2.

Table 2: Follow-up.

Gender	Age at diagnosis	MM type	ISS-R	Surveillance time (Free treatment period)
Male	53 yr	IgA Lambda	I	9 months (january 2022)
Male	50 yr	IgG Kappa	III	25 months (september 2020)
Fem	65 yr	IgA Kappa	III	33 months (january 2020)
Fem	67 yr	Kappa	III	25 months (september 2020)

In the last evaluation in May 2024, he had a complete blood count with hemoglobin of 13.4 gr/dL, leukocytes 6300/mcl, platelets 340,000/mcl, Immunoglobulin A 127 mg/dL, normal protein electrophoresis, free light chains with a kappa/lambda ratio 2:1. and flow cytometry with MRD at 0.000. Figure 2

Patient number two is a 50-year-old man, previously healthy, with a history of parents with diabetes mellitus and hypertension, maternal grandmother who died of neoplasia unknown site and type, economically active, engineer with no history of exposure to hydrocarbons, only occasional smoking and occasional alcoholism, which begins with generalized bone pain, worsening in the lumbar region, a PET scan was performed and bone lesions were observed in the lumbar region, sacrum, right femur and skull, immunoglobulin G of 7.9 gr/dL was found with hypogammaglobulinemia with restriction of kappa chain with initial value of 3521, with kappa/lambda ratio 10/1, the karyotype showed monosomy of chromosome 13, del (3), t (4; 14) FGFR3-IGH, the bone marrow aspirate with 87% plasmatic cells, it was concluded that multiple myeloma IgG Kappa ISSR-III high risk.

CR was achieved after induction with two cycles of cyclophosphamide, bortezomib, and dexamethasone and two

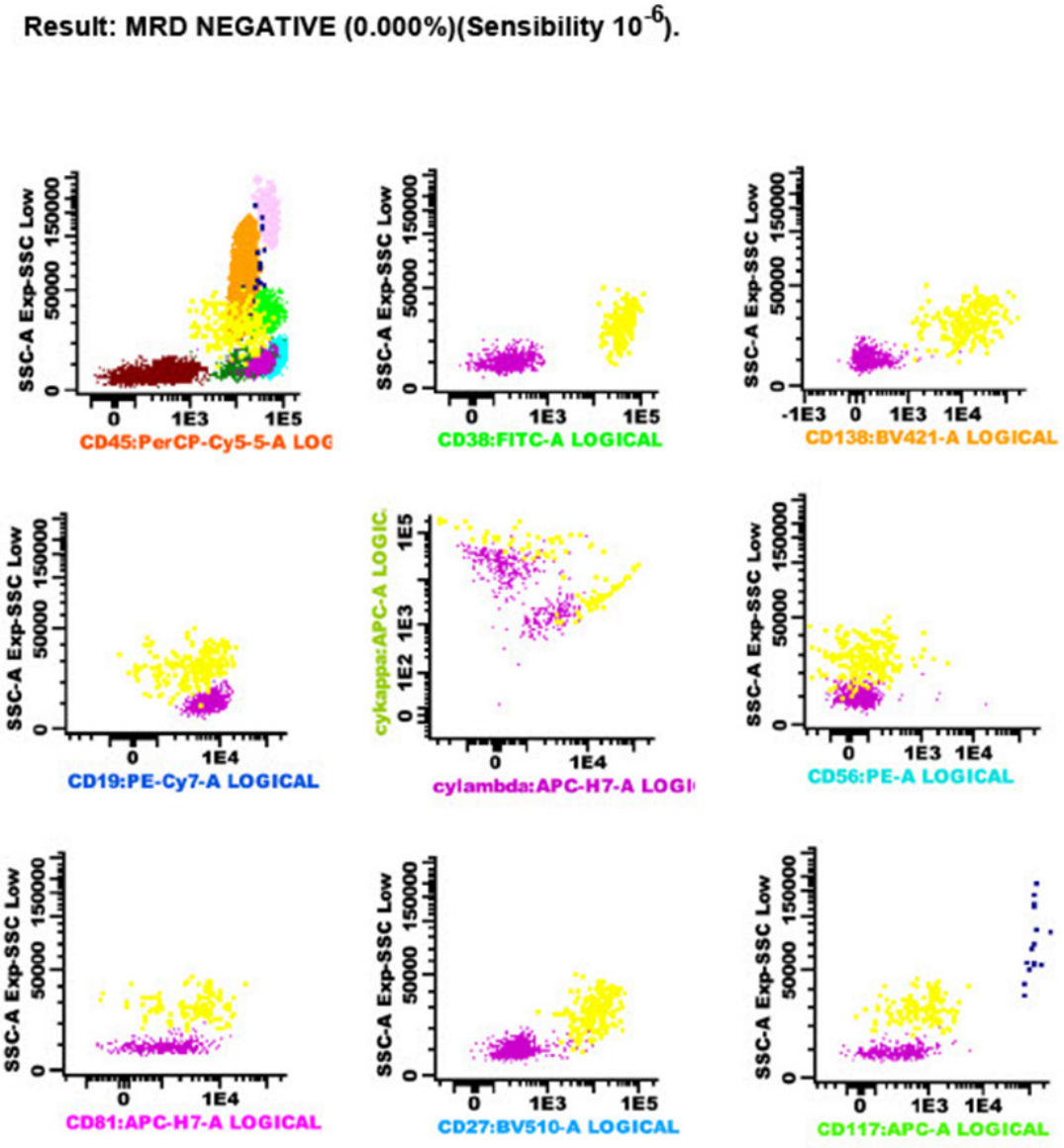

Figure 2: Minimal Residual Disease Patient 1.

cycles of lenalidomide with dexamethasone; the change was due to bortezomib-induced neuropathy. Figure 1. An autotransplant was performed with intravenous melphalan 200 and was consolidated with two triplet cycles that included lenalidomide. Subsequently, maintenance with immunomodulatory therapy was started. After two years and four months, loss of response due to an increase in monoclonal protein was documented. IgG was documented at 2.9 gr/dL at his scheduled consultation visit, so daratumumab was started as shown in Figure 1 followed by of 1 year and 1 month of lenalidomide, which was discontinued with strict complete response measured by flow cytometry with MRD at 0.000.

The patient did not present any secondary events to daratumumab. So far, there is still no evidence of progression. At his last visit in April 2024, he had hemoglobin 12.9 gr/dL, leukocytes 7,550/mcl, platelets 210,000/mcl, IgG 1.2 gr/dL, normal protein electrophoresis, normal immunofixation and no changes in MRD in relation to that previously reported.

The third patient is a 65-year-old woman, an active independent professional, with no family history of importance for her condition, without previous pathology, in whom hypercalcemia was detected with corrected calcium of 13.4 and alteration of renal function with creatinine of 2.9 mg without need for replacement. The studies showed monoclonality of IgA kappa, with an initial immunoglobulin A of 6.9 gr/dL, kappa light chain of 2821, with a kappa/lambda ratio of 17/1, bone marrow infiltrated by 60% plasmatic cells and a normal karyotype. High-risk ISSR-III multiple myeloma was concluded Table 1. Treatment was started with bortezomib, lenalidomide and dexamethasone. Figure 1. CR was documented, so maintenance with lenalidomide was started. She did not accept an autologous transplant. Due to the loss of complete response after 18 months, documented in the appearance of a monoclonal band on immunofixation, and a slight increase in the kappa light chain after it had normalized, daratumumab was started and a strict complete response with negative MRD was documented. 0.000. The patient did not present any secondary

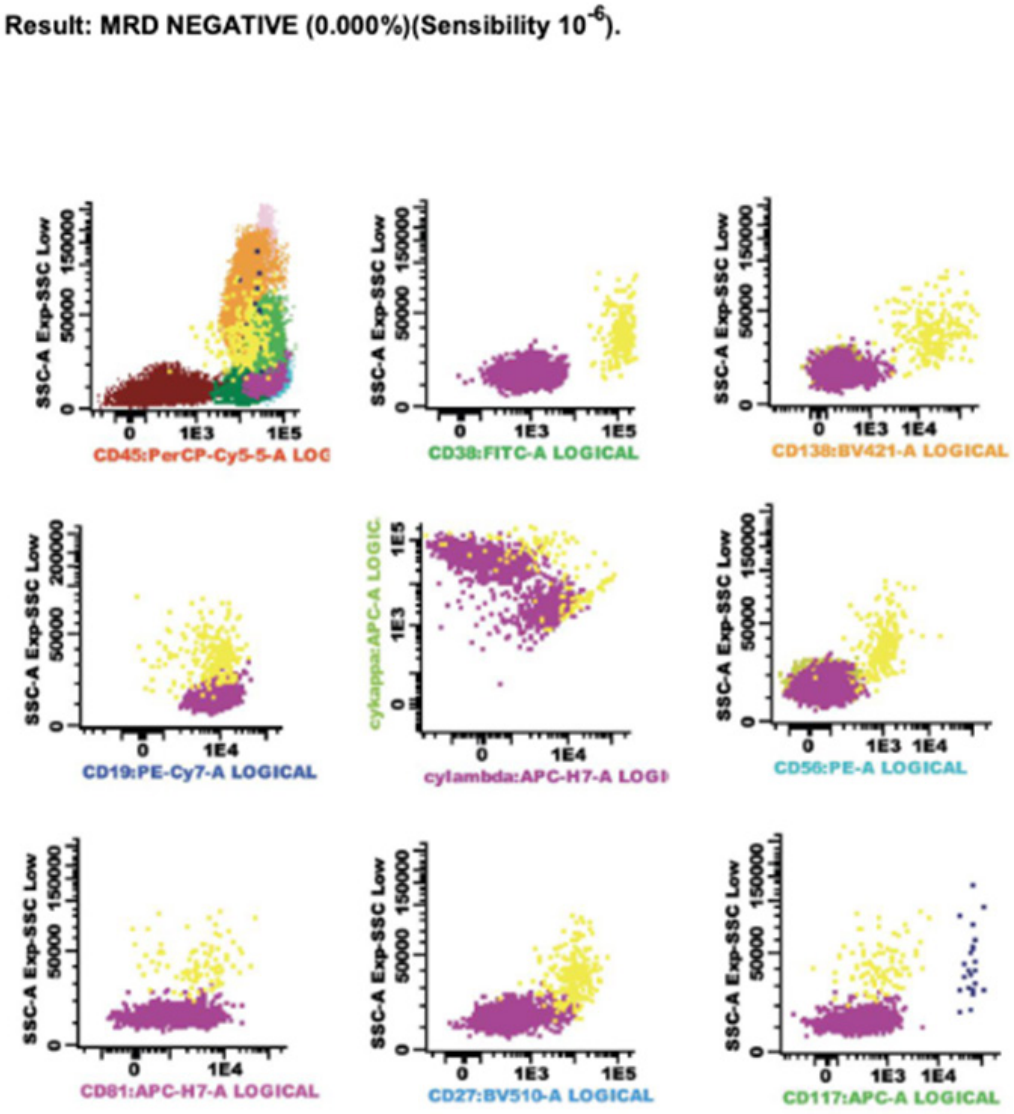

Figure 3: Minimal Residual Disease Patient 2.

events to daratumumab. Maintenance lenalidomide was restarted and 11 months later it was discontinued and monitoring was initiated. The suspension was at the initiative of the patient who no longer wished to continue with oral treatment. In his last control in March 2024, he remains in strict complete response, the blood count shows hemoglobin of 12.7 gr/dL, leukocytes 5,800/mcl, platelets 250,000/mcl, normal immunoglobulins, protein electrophoresis without monoclonal peak and the MRD negative Figure 4.

The fourth patient is a 67-year-old woman, retired, belonging to a group that exercises and travels, who comes to a hematology consultation due to bone pain that is progressive in intensity, decreased appetite, and dyspnea with medium effort, especially when climbing stairs. Extension studies showed hemoglobin of 10.7 g, restriction of kappa light chains with 4221 and kappa/lambda ratio 18/1, bone marrow aspirate with infiltration of plasmatic cells in 90%, PET showed more pronounced disseminated bone lesions in the skull, long bones and spine; the karyotype with t (14; 16), monosomy 13, hyperdiploidy due to gain of chromosomes 9, 11 and 15. High risk was concluded. The induction consisted of 8 cycles of ixazomib, lenalidomide and dexamethasone without achieving a strict complete response. Daratumumab was started and then maintenance lenalidomide. The patient did not present any secondary events to daratumumab, which was only tolerated for 6 months and the patient decided to suspend lenalidomide because she reported cramps in the lower limbs and tingling in hands, toxicity attributed to lenalidomide. Electromyography showed mixed polyneuropathy. She achieved a strict complete response and now in his last check-up she has hemoglobin of 13.4 g, leukocytes 11,100/mcl, platelets 195,000/mcl, normal immunoglobulins without monoclonality, light chains with a kappa/lambda ratio of 2.5/1, normal protein electrophoresis and MRD negative.

All of these patients come for consultation every three months with studies that include monitoring of immunoglobulins, free light chains and immunofixation and every 6 months minimal residual

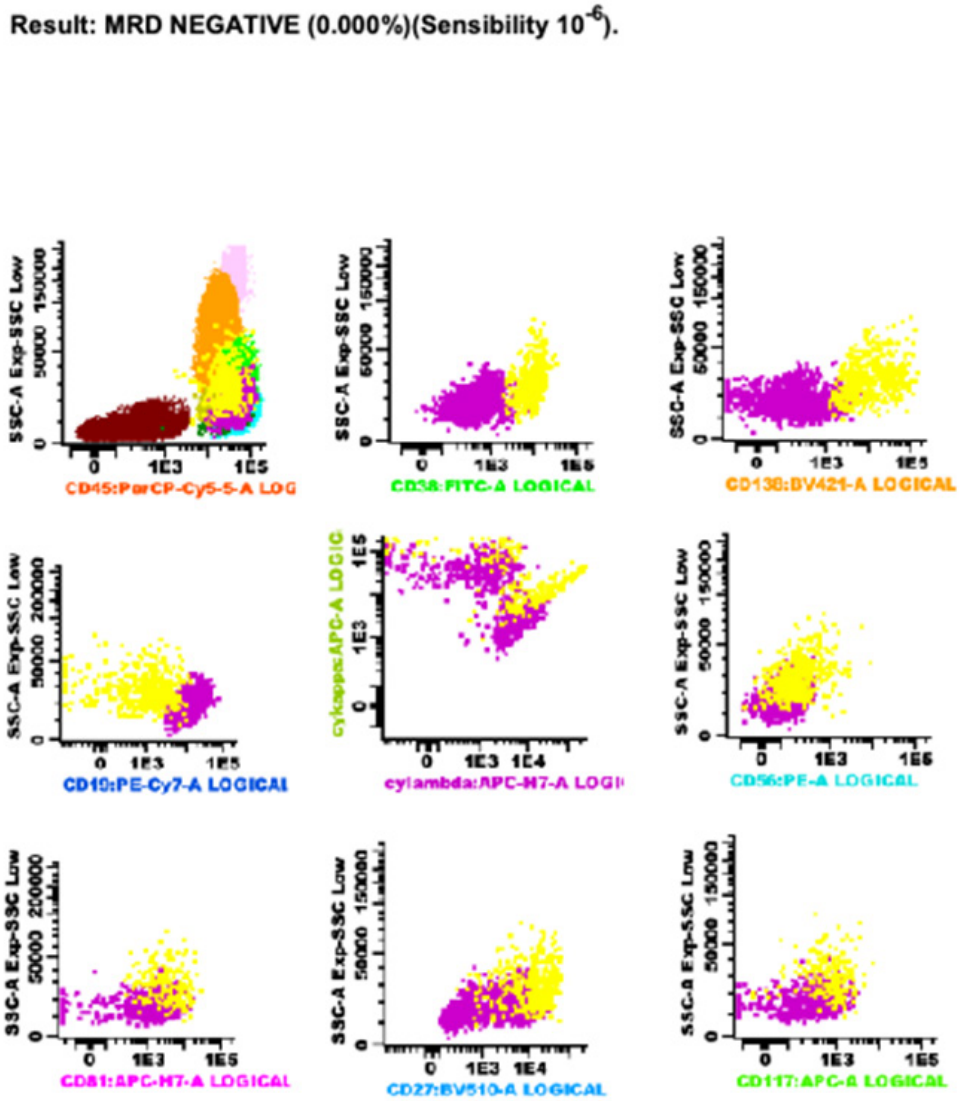

Figure 4: Minimal Residual Disease Patient 3.

disease by flow cytometry and PET. In this series of 4 cases 100% of the patients achieved a strict complete response with undetectable MRD after post-maintenance consolidation with daratumumab regardless of the scheme used as induction/consolidation, as well as whether they had received HSCT. Until the last follow-up the patients are under surveillance with no evidence of progression. It should be noted that 3 out of 4 of these patients debuted with high-risk disease (ISS-R III) as presented in table 2.

Discussion

The present work shows the benefit derived from adding monoclonal antibodies as consolidation post-maintenance with lenalidomide. Although this strategy is not performed in a standard way the results are promising, achieving deep responses in 100% of patients. As already well described these responses translated into excellent post-treatment prognoses keeping patients without evidence of disease progression even after discontinuation of treatment. The surveillance period was observed in a range of 9-33 months with no relapse events, follow-up was performed monthly with serum and urinary electrophoresis and immunofixation measurements, as well as minimal residual disease, Positron Emission Tomography (PET), serum free light chains, and bone marrow biopsy. Anti CD38 monoclonal antibodies such as daratumumab and isatuximab have been protagonists in improving the depth of the response [5,6]. Its use in induction and consolidation has been widely documented in studies, that evaluated the results of bortezomib, thalidomide and dexamethasone (VTD) with or without daratumumab showed an increase in Minimal Residual Disease negativity of 64% vs 44% in patients who received the quadruplet, this increase translated into a 53% decrease in the risk of progression or death as well as in PFS, with a follow-up of 44.5 months the median PFS had not been reached in the Daratumumab -VTD arm while in the VTD arm was

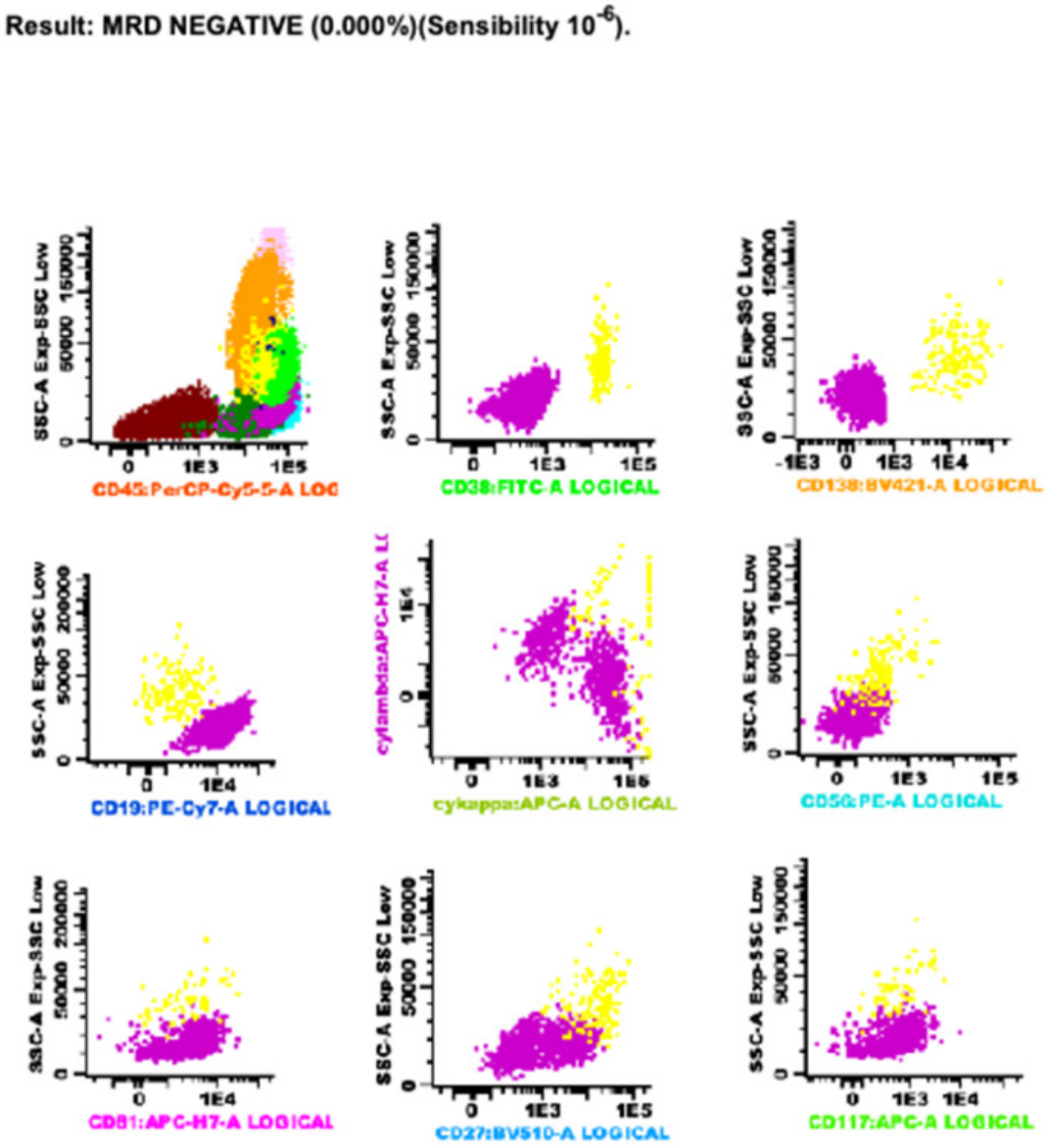

Figure 5: Minimal Residual Disease Patient 4.

51.5 months [7], the impact was also demonstrated in other study that compared Bortezomib-Lenalidomide-Dexametasone (VRd) versus daratumumab plus VRd, the quadruplet achieve negative MRD in 51% of patients compared to 20.4% in patients in the VRd arm directly impacting PFS al 24 months (95.8 vs 89.8%) [8]. One of the most important achievements in the outcomes of the grou was the negativization on MRD. Minimal residual disease detection represents a great advancement in multiple myeloma. The International Myeloma Working Group recommends using next-generation flow cytometry (NGF) or next-generation sequencing (NGS) to search for MRD in clinical trials. Best sensitivity thresholds must be confirmed, as well as timing to detect it. MRD has proven as the best prognosticator in many trials and promises to enter also in clinical practice to guide future therapy. Each improvement in the depth of MRD testing has led to superior discrimination of outcomes, and sustained MRD negativity seems to be paramount to durable responses. Peripheral blood assays to assess for MRD are still under investigation but hold promise as complementary tools to bone marrow MRD assays such as next-generation sequencing and flow cytometry. In our work we were able to demonstrate that some patients breach and maintain depth in the response [9-11].

In a retrospective study, was presented the outcomes from a multinational and multicenter series of 400 patients with MRD monitoring during front-line therapy with the aim of exploring how clinical decisions made based on those MRD results affected outcomes. As expected, achievement of MRD negativity at any point was associated with improved PFS versus persistent MRD positivity (median PFS 104 vs. 45 months, $p < 0.0001$). In addition, however, 67 out of 400 patients underwent a clinical decision (treatment discontinuation, intensification, or initiation of a new therapy) based on MRD results. Those patients in whom a treatment change was made showed a prolonged PFS in comparison with those 333 patients in which MRD results were not acted upon (respectively, PFS 104 vs. 62 months, $p = 0.005$). In patients who achieved MRD negativity during maintenance ($n = 186$) on at least one occasion, stopping therapy in 24 patients vs. continuing in 162 did not alter PFS (PFS 120 months vs. 82 months, $p = 0.1$) [12].

In our study practically 100% of the patients present with negative MRD in different periods of the use of daratumumab, supporting the idea that the use of the monoclonal antibody helps in get a profound response even when the initial response to the treatment line wasn´t that good. More sophisticated and less invasive studies to measure are already in practice, this is the case of the spectrometry which have enabled reliable and highly sensitive detection of low abundance serum biomarkers making it a viable and significantly less invasive approach. Mass spectrometry can achieve dynamic monitoring of MRD and identify therapeutic monoclonal antibodies as well as oligoclonal proteins. In this review we summarize mass spectrometry methods in M protein detection and their applications of MRD detection in MM. Mass Spectrometry was established as a sensitive assay for disease monitoring. In different studies was evaluate the performance of EasyM-a noninvasive, sensitive, MS-based assay for M-protein monitoring [13-15].

Although recent data have demonstrated very promising results in Daratumumab clinical practice and trials, some patients may do get a complete response or may experience a relapse. Several mechanisms contribute to the development of Daratumumab resistance, including CD38 reduction, the antibody dependent cell-mediated cytotoxicity, the antibody-dependent cellular phagocytosis, the complement-dependent cytotoxicity, and immune-mediated processes [16]. The reduction in CD38 cell surface expression is a transient phenomenon, because CD38 levels are restored to baseline levels on the MM cells 6 months after the last daratumumab infusion [17,18]. Daratumumab-mediated CD38 reduction is also observed on non-tumor cells, such as normal B-cells, T-cells, NK-cells, and monocytes [19]. In addition, recent studies showed that daratumumab treatment results in the clustering of CD38 molecules into distinct polar aggregates, which can subsequently be released as tumor-derived microvesicles [20]. Direct internalization may also contribute to loss of CD38. Finally, active transfer of CD38-daratumumab complexes and accompanying cell membrane from MM cells to monocytes and granulocytes also contributes to CD38 reduction. This process of trogocytosis is in part FcγR-dependent [20,21].

In conclusion, the addition of daratumumab at any time during treatment improves its results and therefore improves the survival of patients, with little impact on their quality of life, giving the opportunity to develop more flexible therapeutic schemes in real life that allow clinicians to do use of medications at times other than those strictly indicated based on clinical trials, which are sometimes not so easy to adhere to due to the peculiar characteristics of each patient. Today there are different study methods to measure MRD and be able to design personalized treatment strategies. At this moment no daratumumab resistance has been demonstrated in our patients.

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