Pattern of Use and Efficacy of Daratumumab-based Therapy in Patients With Multiple Myeloma in a Real-world Setting: a Single Institution Experience

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Research Article

Abstract

Purpose: Multiple myeloma (MM) is an incurable hematologic malignancy, caused by the accelerated growth of clonal plasma cells leading to severe multiorgan failure. Several novel agents have been recently approved for the treatment of this diseases, including daratumumab, a human IgG kappa monoclonal antibody that targets CD38 on the surface of plasma cells. The objective of this retrospective study is to explore the pattern of use, safety and efficacy of daratumumab-based therapy among patients with both newly diagnosed multiple myeloma (NDMM) and relapsed/refractory multiple myeloma (RRMM) in a real-world setting at a single institution.

Methods: 57 patients with MM treated with daratumumab based therapy, from 11/16/2015 to 3/16/2020, were included in the study. Kaplan-Meier method was used to estimate time to hematologic response, as well as progression free survival (PFS) after daratumumab initiation. Log-rank tests were applied to compare PFS among subgroups.

Results: The overall hematologic response (ORR) to daratumumab based-therapy was 82.5% and the median progression-free survival (PFS) was 23.5 months. The ORR and PFS among NDMM patients vs RRMM patients were 80% and not reached vs 84.8% and 22 months respectively. Importantly, subgroup analysis based on cytogenetic risks, demonstrated that patients with standard risk cytogenetics sustained a marginally significantly prolonged PFS (24.0 vs 10.0 months, p=0.065) compared to those with high/intermediate risk cytogenetics. When stratified by the treatment line (1st vs 2nd-3rd vs >3rd) and treatment pattern (dara monotherapy vs. combination with PI vs. IMiD vs. PI + IMiD), there were no significant differences in PFS. Daratumumab was generally well tolerated, with no discontinuations due to adverse events.

Conclusion: Daratumumab-based therapy has significant efficacy and very good tolerability among MM patients, in a real-world setting.

Introduction

Multiple myeloma (MM) is an incurable hematologic malignancy that belongs to a spectrum of disorders referred to as plasma cell dyscrasias. MM is caused by the accelerated growth of clonal plasma cells, that can lead to complications including renal failure, anemia, hypercalcemia and lytic bone lesions. [1]. According to Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute database, MM accounts for 1.8% of all new cancer cases with the estimated incidence in 2020 being approximately 32,000. Despite the tremendous pharmacologic advances and continuous evolving therapeutic strategies, the 5-year survival rate remains low at only ~ 54% [2].

Over the past few decades, rigorous research has led to the discovery of new innovative anti-plasma cell therapies that have been established as standard-of-care regimens in patients with MM regardless of transplant eligibility. These novel agents include proteasome inhibitors (PI) and immunomodulators

(IMiD), [3–6] However, despite all these advances, most patients with MM eventually relapse and develop resistance to therapy, emphasizing the need for new effective treatment modalities.

Monoclonal antibodies against plasma cell surface antigens have been recently established as new breakthrough therapeutic modalities for individuals with plasma cell dyscrasias [7]. The most well studied monoclonal antibody is daratumumab, a human IgG kappa antibody that targets CD38, a transmembrane glycoprotein predominately located at the surface of plasma cells. Daratumumab works by inducing cell death through various Fc-dependent immune effector mechanisms. These mechanisms include complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, antibody dependent cellular phagocytosis, apoptosis via crosslinking and modulation of CD38 ectoenzymatic function leading to direct apoptosis of neoplastic cells [8, 9]. Daratumumab additionally has an immunomodulatory activity; it binds to CD38 on the surface of immune suppressor cells (regulatory T, regulatory B and myeloid-derived suppressor cells) which subsequently results in marked increase of T cells in the bone marrow enhancing the activity of the immune system against the neoplastic MM cells [10, 11].

Several clinical trials have already validated the efficacy and safety of daratumumab in treating relapsed/refractory MM (RRMM) as well as newly diagnosed MM (NDMM) in various combinations with traditional backbone therapies [12]. The U.S. Food and Drug Administration (FDA) first approved daratumumab for the treatment of RRMM in 2015, followed by its approval as frontline therapy for ASCT ineligible NDMM patients in 2018 and ASCT eligible NDMM patients in 2019. [13–15]. At present, daratumumab continues to be tested in various combinations with novel agents, in the context of clinical trials with promising results (*NCT02343042, NCT03710603, NCT03180736, NCT03896737, NCT01998971, NCT04280328).*

Although clinical trials provide us with critical information about outcomes, the participants are not representative of the heterogeneous population of patients who will receive this drug and thus, real world observations are equally valuable in shedding light on patterns of use, efficacy and toxicities of new therapies. In order to providing real-world data helping physicians make optimal therapeutic choices, we present a study examining the pattern of use, safety and efficacy of daratumumab-based therapy among patients with NDMM and RRMM in a real-world setting at a single institution.

Methods

2.1. Study population

Patients with MM were included in this retrospective observational study if they were treated with daratumumab-based therapy at Tufts Medical Center between November 16, 2015 and March 16, 2020

2.2. Daratumumab Dosing and Administration

Daratumumab was administered intravenously in the majority of cases as subcutaneous injection was only FDA-approved in 2020. Daratumumab was administered at a dose of 16 mg/kg once weekly for the first 8 weeks (cycles 1 & 2), followed by once every 2 weeks for the following 16 weeks (cycles 3–6), and once every 4 weeks thereafter (≥cycle 7) until disease progression or unacceptable toxicity or death. One patient received daratumumab subcutaneously at dose of 1800 mg. Daratumumab administration, as well as prophylaxis and management of infusion-related reactions (IRR), were carried out in accordance with the package insert.

2.3. Data collection

This is an observational retrospective study with the objective to explore the pattern of use, safety and efficacy of daratumumab based therapy among MM patients in a real-world setting at Tufts Medical Center (MC). With data from the Tufts MC tumor registry, a cohort of 57 myeloma patients who received daratumumab, between November 16, 2015 and March 16, 2020 were identified. Patient baseline demographics, clinical characteristics, laboratory and therapy-related information were obtained via retrospective chart review of the electronic medical record (EMR). For each patient, the Medical Record Number (MRN) recorded by the Tufts MC tumor registry was linked to a unique study ID. Dual data abstraction was performed for all data collected and discrepancies reconciled by study hematologist. The study was approved by the Institutional Review Board (IRB) at Tufts MC. IRB at Tufts MC granted a waiver of consent and a HIPAA waiver of research authorization for this study, in accordance with 45 CFR 46.116(d) and HIPAA.

2.4 Outcome measures

Efficacy of daratumumab was analyzed for patients who received at least one cycle of daratumumab. To define daratumumab efficacy, we evaluated the overall response rate (ORR), the separate response categories (complete response [CR], very good partial response [VGPR], partial response [PR], stable disease [SD] and progressive disease [PD]), as well as the progression-free survival (PFS). The ORR was defined as the proportion of patients achieving at least a partial response (PR). The daratumumab initiation date was defined as the recorded date on which a patient received a first dose of daratumumab. The presence of an IgG-Kappa M protein by immunofixation electrophoresis (IFE), after daratumumab initiation, with an otherwise normal SPEP, UPEP and involved free light chains, was counted as an IgG-Kappa therapeutic monoclonal antibody (t-mAB) and subsequently labeled as a CR, when interpreted as such by the Pathologist who reviewed the IFE. PFS was defined as the duration from daratumumab start date to disease progression, or death. Patients were followed from daratumumab initiation date and up to (1) disease progression, or (2) death or (3) inadequate response requiring addition of extra agent or (4) daratumumab therapy discontinuation due to a) sustained response over time with clinician determining no further daratumumab therapy is required, b) increased frequency of infections or other unacceptable toxicity c) loss to follow up d) plan for stem cell transplant or e) inadequate response requiring different treatment regimen. The medication safety was assessed at each drug administration by adverse events (AEs) assessment, physical examination, and laboratory tests. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 was applied to assess AEs.

2.5 Statistical analysis

The distributions of baseline characteristic distribution were summarized. Kaplan-Meier method was used to estimate median time to hematologic response, and PFS after daratumumab initiation. Log-rank tests were applied to compare PFS among subgroups. Results were considered to be statistically significant if two-sided P-value was less than or equal to 0.05. R software (version 3.6.2; www.r-project.org) was used for statistics.

Table 1
Baseline characteristics and therapy patterns of MM patients receiving daratumumab.

Clinical Characteristics		Total n = 57
Age at initiation of Dara, years	Median (range)	67 (34, 85)
	Distribution (N%)	
	<65	23 (40.4%)
	65−74	24 (42.1%)
	≥75	10 (17.5%)
Gender	Female	25 (43.9%)
n (%)	Male	32 (56.1%)
Race	White	42 (73.7%)
n (%)	Black	8 (14.0%)
	Hispanic	1 (1.8%)
	Asian	6 (10.5%)
ISS stage at diagnosis	I	7 (12.3%)
n (%)	II	15 (26.3%)
	III	19 (33.3%)
	Not Available	14 (24.6%)
Treatment line of Dara	1st	11 (19.3%)
n (%)	2nd or 3rd	19 (33.3%)
	> 3rd	27 (47.4%)
Therapy combination	Dara only	5 (8.8%)
n (%)	Dara + PI + d	19 (33.3%)
	Dara + IMiD + d	22 (38.6%)
	Dara + PI + IMiD + d	9 (15.8%)
	Dara + others (e.g. Alkylator)	2 (3.5%)
Prior Treatments	IMiD	3 (5.3%)
n (%)	PI	6 (10.5%)

*High risk: del(17/17p), t(14;16), t(14;20), nonhyperdiploidy, Intermediate risk: t(4;14), gain(1q), Standard risk: *all other*, d = *dexamethasone*

Clinical Characteristics		Total n = 57
	IMiD + PI	37 (64.9%)
	None	11 (19.3%)
Transplant status	Yes	23 (40.4%)
	No	34 (59.6%)
Cytogenetic profile n (%)	Standard risk	34 (59.6%)
	High + Intermediate risk*	15 (26.3%)
	Not Available	8 (14.0%)
M-spike, median (range), g/dL		0.34 (0, 6.7)
Plasma cell % in bone marrow, median (range)		40 (0, 90)
Isotype n (%)	IgG	33 (57.9%)
	IgA	10 (17.5%)
	IgD	3 (5.3%)
	No heavy chain	11 (19.3%)
	κ (kappa)	31 (54.4%)
	λ (lambda)	26 (45.6%)
Renal function n (%)	Normal or slightly impaired (GFR > 30 1.73m^2)	43 (75.5%)
	Markedly impaired (GFR < 30 ml/min/1.73m^2)	14 (24.5%)

*High risk: del(17/17p), t(14;16), t(14;20), nonhyperdiploidy, Intermediate risk: t(4;14), gain(1q), Standard risk: *all other*, d = *dexamethasone*

Results

3.1. Patient characteristics

Fifty-seven patients were included in the study. Baseline demographics and disease characteristics are described in Table 1. Median age was 67 years (range, 34–85 years). Among these patients, 32 (56.1%) were female and 42 (73.7%) were non-Hispanic White. One third had an International Staging System of III at diagnosis. High/intermediate risk cytogenetics (defined as the presence of del17p, t(4;14), t(14;16),

t(14;20), and gain(1q) by Fluorescence in situ hybridization [FISH]), was present in 15 (26.3%) of the participants, whereas 34 (59.6%) patients harbored standard risk cytogenetics.

The vast majority of patients received daratumumab at relapse (80.7%): 33.3% as 2/3rd line of therapy and 47.4% as 4th line of therapy or higher. Only 11 patients received daratumumab as frontline therapy for newly diagnosed MM during the study period. Amongst patients who received daratumumab at relapse, 80.4% (37) had already been treated with both IMiD and PI in the past, whereas only 13% and 6.5% had already received prior treatment with only PI and IMiD respectively. More than half (59.6%) of the MM subjects were stem cell transplant-naïve prior to the initiation of daratumumab. Only 5 patients (8.8%) received daratumumab monotherapy while 19 (33.3%) received daratumumab + proteasome inhibitor (PI), 22 (38.6%) received daratumumab + immunomodulator (IMiD), and 9 (15.8%) received daratumumab + PI + IMiD.

At the time of daratumumab initiation, markedly impaired renal function (GFR < 30 ml/min) was present in 14 cases (24.5%), including one patient who had already been on hemodialysis (HD). None of the subjects with renal impairment required renal replacement therapy after daratumumab initiation except the aforementioned patient who was already on HD. Three subjects were diagnosed with cast nephropathy prior to daratumumab initiation, as they were found to have severe acute renal injury, and Bence Jones protein in UPEP/IFE in the context of significantly elevated involved free light chains (> 10,000 mg/dL). Of note, no renal biopsy was obtained in these individuals to confirm this diagnosis.

3.2. Daratumumab efficacy

The overall hematologic response rate for the entire cohort was 82.5%, including 22 CR, 14 VGPR, and 11 PR. (see Table 2 and Fig. 1). In detail, among the NDMM patients (n = 11), the ORR was 80%, whereas for those who received daratumumab-based therapy at relapse, the ORR was 84.8%. The estimated median time to best hematologic response was 2.0 months (95% CI, [1.0, 2.5 months]). During the follow up period, 23 (40.4%) of all subjects demonstrated disease progression. The estimated median PFS for the entire cohort was 23.5 months (95% CI, [12.2 months, NE]) (see Fig. 2). The estimated median PFS for NDMM and RRMM groups were not reached vs 22 months respectively. When stratified by the treatment line (1st vs 2nd-3rd vs > 3rd, p = 0.145), treatment pattern (monotherapy vs. combination with PI vs. IMiD vs. PI + IMiD, p = 0.767), and renal function (GFR > = 30 vs < 30 ml/min/1.73m^2, p = 0.800) there were no significant differences in PFS between the aforementioned subgroups. However, subgroup analysis based on cytogenetic risks demonstrated that patients with standard risk cytogenetics sustained a marginally significantly prolonged PFS (24.0 vs 10.0 months, p = 0.065) compared to those with high/intermediate risk cytogenetics (see Fig. 3).

Table 2
Best overall response to daratumumab based therapy in the entire cohort – no. (%)

Complete response or better	22 (38.6%)
Very good partial response or better	36 (63.2%)
Very good partial response	14 (25.6%)
Partial response	11 (19.3%)
Stable disease	5 (8.8%)
Progressive disease	4 (7%)
Unknown*	1 (1.8%)
Overall response rate	47 (82.5%)
* due to loss of follow up before assessing for response.	

3.3. Daratumumab safety

Daratumumab was generally well tolerated. There were no instances of interruption or discontinuation from medication related AEs. The most frequent side effect was infusion-related reactions (IRR), which were observed in only 10 (17.5%) patients. IRR were mild to moderate (grade 1–2) in the vast majority of subjects and occurred during the first dose of daratumumab infusion only. The most common and serious (grade 3–4) infection was pneumonia. There was no death related to daratumumab. The major daratumumab-related AEs are highlighted in Tables 5

Table 3
Side Effects of daratumumab therapy in MM patients

Adverse Events:	Any grade N (%)	Grade 3 or 4 N (%)
Infusion-related reaction	10 (17.5%)	1 (1.75%)
Viral upper respiratory tract infection	10 (17.5%)	2 (3.5%)
Pneumonia (viral, bacterial, fungal)	14 (24.6%)	10 (17.5%)
CNS infection	1 (1.75%)	1 (1.75%)
Urinary tract infection	1 (1.75%)	1 (1.75%)
Disseminated VZV infection	1 (1.75%)	1 (1.75%)

Discussion

The significant improvement in survival of patents with multiple myeloma over recent years can largely be explained by the introduction and broad incorporation of several new novel agents into clinical practice. In clinical trials, daratumumab has demonstrated unquestionable benefit compared to prior traditional treatments. The use of daratumumab in a real-world setting may have its own challenges and limitations, leading to different degrees of clinical benefit from the ones observed in clinical trials. These discrepancies mainly derive from patient-related (age, comorbidities, demographics), disease-related (stage, subtype, cytogenetics) and treatment-related (toxicity burden, prior exposures, available healthcare resources, cost) factors. As a result, we often observe decreased efficacy in the real-world when compared to strictly controlled clinical trials. The current retrospective study resulted from real-world setting and showed substantial efficacy and safety of daratumumab in a heterogenous group of MM patients.

Daratumumab has been officially approved by the FDA for the treatment of RRMM and NDMM as monotherapy or in various combinations with conventional backbone therapies. The initial pivotal SIRUS phase 2 trial successfully tested the efficacy and safety of daratumumab monotherapy in patients with RRMM [16], followed by the landmark phase 3 CASTOR and POLLUX trials that studied the synergism of daratumumab when combined with bortezomib and lenalidomide respectively in RRMM patients [17, 18]. Both trials showed that the addition of daratumumab resulted in significantly improved ORR (> 80%) and PFS. Daratumumab has also been studied in combination with Carfilzomib and Pomalidomide in EQUULEUS and CANDOR clinical trials, respectively, for patients with RRMM, which confirmed its efficacy as well as safety when combined with these above in this particular patient population [19, 20].

There is limited literature reporting real-world data regarding the use of daratumumab treatment in patients with MM. This mainly comes from European countries including Czech, France, Hungary and Poland, describing real-life data in heavily pretreated patients with RRMM. In detail, a Czech group reported that amongst 14 heavily pretreated RRMM patients (median 4.5 previous lines), daratumumab monotherapy resulted in an ORR of 38.5% with a median PFS of 4.5 months with overall survival not reached [21]. In France, *Jullien et al*, retrospectively studied 41 individuals from a single institution, with RRMM (median 3 prior lines), all were previously exposed to PI and IMID, who received daratumumab as monotherapy. Their results showed an ORR of 24.4% with a median PFS and OS of 1.5 and 6.5 months respectively, whereas the median PFS for the subgroup of patients achieving at least a PR was 10.1 months [22]. In Hungary, *Lovas et al*, reported results of 99 patients with RRMM who received either daratumumab monotherapy or combination with IMiD (mainly lenalidomide) or PI (bortezomib). ORR was assessable in 88 patients, of whom 56 had ≥PR. PFS was 17 months for the entire cohort, with superior PFS achieved in the subgroup of patients who 1) had early-stage disease (ISS1), 2) receiving combination of daratumumab and lenalidomide, and 3) were less heavily pretreated and 4) had standard risk cytogenetics [23]. In Poland, a retrospective study of 30 patients with RRMM, treated with daratumumab single agent, revealed ORR of 42.8% with PFS and OS 9.5 and 13.8 months respectively. Double refractory individuals had a significantly shorter PFS than other patients [24].

Our study included at total of 57 MM patients, of whom 46 had RRMM. Amongst the RRMM patients, 22 received daratumumab in combination with an IMiD + dexamethasone (19 received pomalidomide, and 3

lenalidomide), 14 received PI + dexamethasone (5 received Ixazomib, 7 bortezomib and 2 carfilzomib), 5 received daratumumab monotherapy and a small minority received therapy with PI + IMiD or Alkylator. The ORR was 91% and 85.7% in patients who received daratumumab with IMiD and PI respectively. Median PFS was 14.5 (7.5, NE) months and 24 (9.5, NE) months in the above groups respectively. Out of these 46 patients, 27 received daratumumab-based therapy as 4th line of therapy or higher, and 19 as 2nd – 3rd line, as are result most of our RRMM patients were heavily pretreated and resistant to their prior therapies. However, their treatment responses and survival results were still comparable to the data of the above-mentioned clinical trials and real-world studies.

Our study also included a small number of individuals (11/57) who received daratumumab-based regimen as frontline therapy for newly diagnosed MM (NDMM). This group was very heterogenous regarding their treatment pattern; 5 patients received the doublet of daratumumab and bortezomib, and 6 patients received triple therapy with daratumumab and PI/IMiD (3 received lenalidomide/bortezomib, 2 pomalidomide/bortezomib, 1 pomalidomide/ ixazomib). The ORR in this subgroup was 80% (assessable in 10/11). So far, FDA has approved three combinations of daratumumab with traditional therapies as frontline treatment options: 1) bortezomib/melphalan/dexamethasone, and 2) lenalidomide/dexamethasone for individuals with NDMM ineligible for ASCT, whereas for individuals eligible for ASCT FDA has approved daratumumab with bortezomib/thalidomide/dexamethasone as an initial therapeutic option [12]. Interestingly, our patients with NDMM received different patterns of daratumumab-based therapy from the aforementioned, mainly due to individualized factors including insurance and cost barriers, as well as physician's preference.

In our study, Kaplan Meier analysis for our entire MM cohort did not show a statistically significant difference in the PFS when patients were stratified based on their lines of treatment and pattern of use, which was not consistent with for the real-life findings of the Hungarian group. However, the small number of patients in our study make it difficult to make any true. In general, based on our results, daratumumab-based therapy seems to be very efficient regardless of its pattern or line of use, resulting in good hematologic responses as well as PFS. On the other hand, our study found cytogenetic risk may play a prognostic role in patients treated with daratumumab, as the patient subgroup harboring high risk cytogenetics, had a less pronounced PFS benefit.

As mentioned above, three individuals were diagnosed with cast nephropathy in the context of markedly elevated involved free light chains and severe acute renal failure, prior to daratumumab initiation. In all three patients, daratumumab promoted rapid decline in the involved serum light chain levels down within days after a single dose. Of note, one of these subjects had previously undergone one session of plasmapheresis. Renal function normalized in 2/3 patients, and notably improved in the third. None of these three individuals required plasmapheresis after treatment with daratumumab nor required hemodialysis, raising the question whether daratumumab can actually reduce light chains at the same speed as plasmapheresis, a labor intensive and expensive procedure, in this particular patient population.

In terms of safety, our results confirmed the benign side effect profile of daratumumab. Serious adverse events occurred in 5 individuals, and were mostly related to infections, one of which was lethal. Fortunately, most of our patients developed no or only minor side effects. According to our observations, daratumumab can also be safely used in patients with marked renal impairment (GFR < 30 ml/min) without any safety concerns or additional toxicity occurrence.

We acknowledge several limitations of this study. Firstly, it was a study with small number of patients thus large conclusions cannot be made. Secondly, we included both NDMM and RRMM patients in current study and the effects of daratumumab on each subgroup in real world setting were hard to interpret. Lastly, the retrospective nature from a single institute did not allow for exploring longitudinal effects of daratumumab. The primary strengths are the heterogenous patient population and mostly complete data via close follow-up in present study.

Conclusion

Daratumumab-based therapy led to high and rapid overall response rates among the entire cohort. Our data suggest that patients with standard risk cytogenetics have improved outcomes from dara-based therapy in terms of progression free survival compared to those who have high risk cytogenetics. Patients with severely impaired renal function had similar PFS results compared to those who had normal and/or slightly impaired renal function. Daratumumab was also equally effective despite pattern of use and line of therapy, though our numbers were small. Our study also confirms the acceptable safety profile of daratumumab, including individuals with severely impaired renal function in real world setting. Overall, this data justifies the widespread adoption of daratumumab as part of a backbone therapy in MM.

Declarations

Funding: Not applicable.

Conflicts of interest/Competing interests: All authors declare that they have no conflict of interest.

Availability of data and material: Available.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
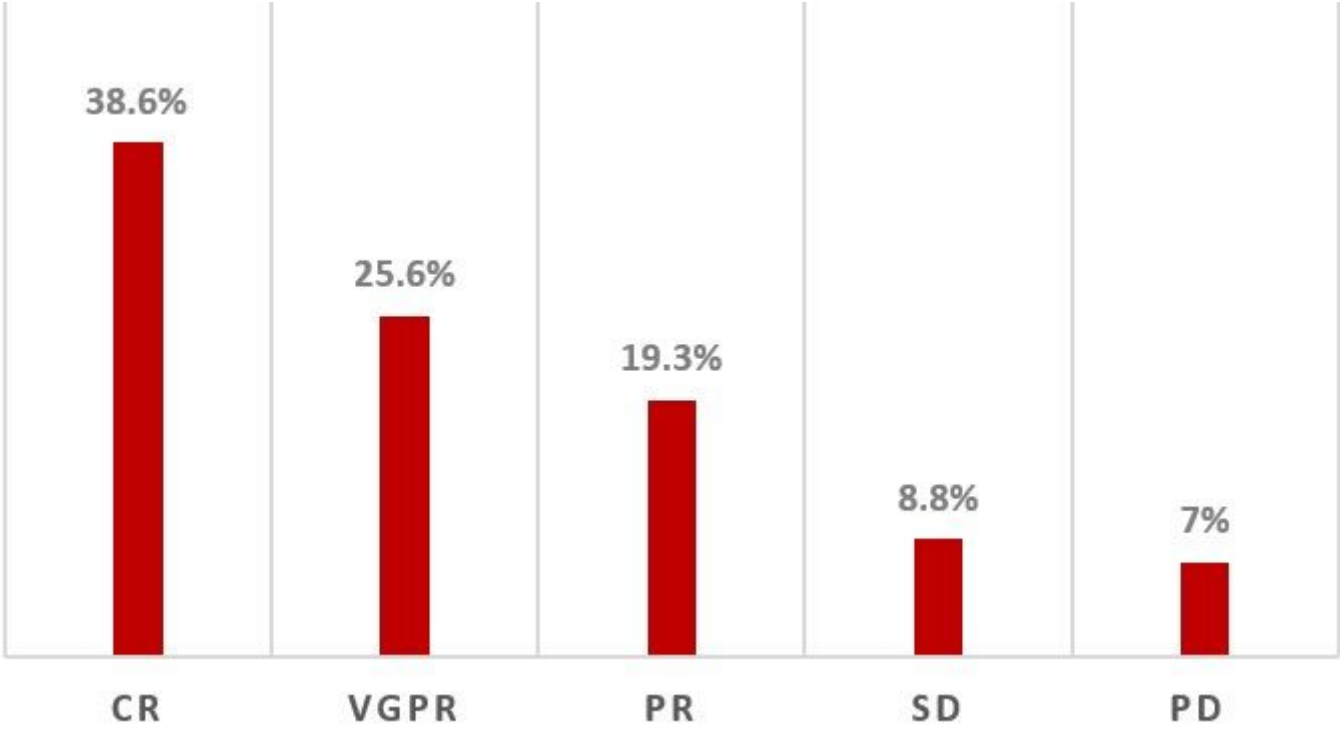
Informed consent: The study was approved by the Institutional Review Board (IRB) at Tufts Medical Center (MC). IRB at Tufts MC granted a waiver of consent and a HIPAA waiver of research authorization for this study, in accordance with 45 CFR 46.116(d) and HIPAA.
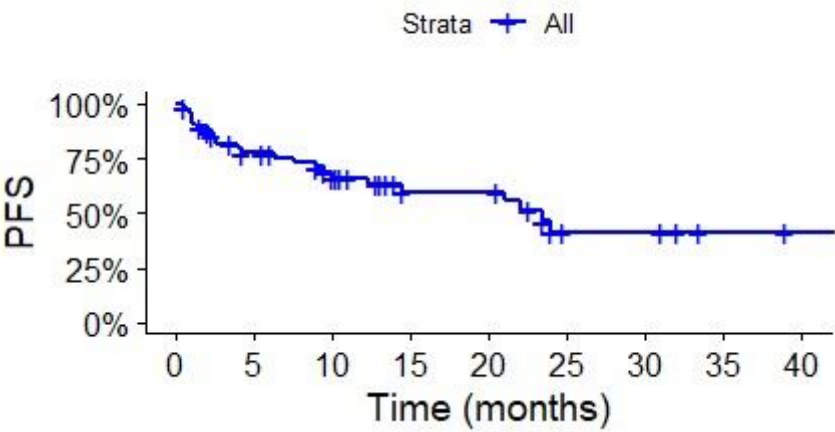
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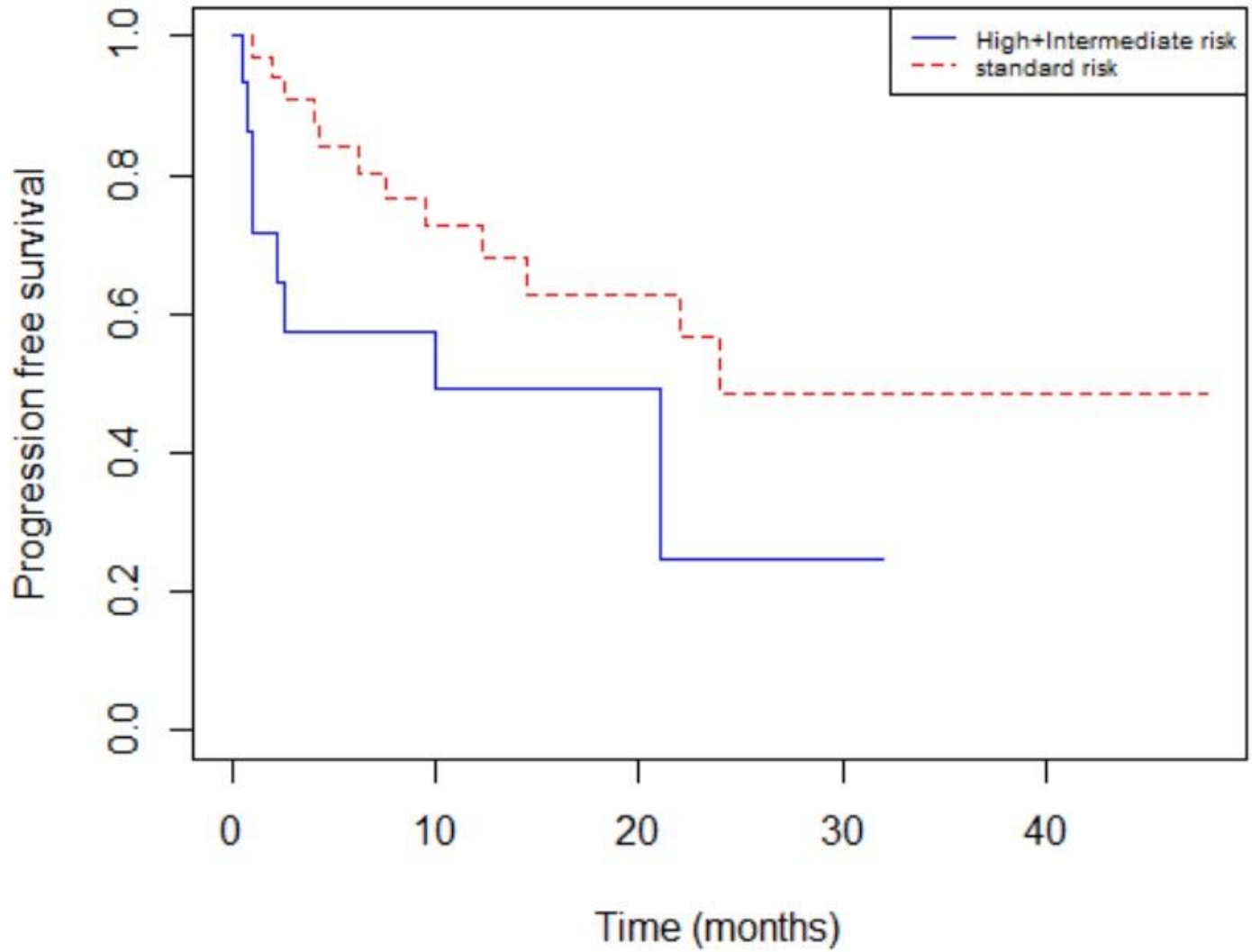
Figures

Figure 1

The overall response rate to daratumumab based therapy

Figure 2

The overall Kaplan-Meier curve of progression free survival (PFS) for the entire cohort

Figure 3

The Kaplan-Meier curves when stratifying by cytogenetic risks (p=0.065)