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Safety and Efficacy of Daratumumab in Immune Thrombocytopenia

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Abstract:
Resistance to B-cell targeted therapies in immune thrombocytopenia (ITP) has been linked to persistence of autoantibody-producing CD38-positive long-lived plasma cells. CD38 antibody daratumumab has been proposed as a potential therapy for ITP. This multicenter, open-label, phase II study evaluated safety and efficacy of daratumumab in 21 previously treated ITP patients. Following a safety run-in, two dosing cohorts were included, receiving eight and ten subcutaneous injections of 1800 mg daratumumab weekly, respectively. Primary endpoints were safety and response (two consecutive platelet counts ≥50x109/L at week 12 for the safety run-in/Cohort 1, and at week 16 for Cohort 2). At baseline, median platelet count was 17x109/L, median number of prior therapies was four. Most treatment-emergent adverse events were transient grade 1-2, most commonly infections (38%).Two patients (4.7%) experienced grade 3 adverse events, one infusion-related reaction, and one SARS-CoV-2 infection with acute renal failure. Ten patients (48%) met the primary efficacy endpoint. Sustained response (two consecutive platelet counts ≥50x109/L at week 24) was achieved in eight patients (38%). Two patients relapsed after week 24. There was no difference in response or relapse rates between cohorts. Patient-reported quality of life measured by SF-36 improved in responding patients. Daratumumab decreased immunoglobulin levels in all patients, and substantially reduced CD38+ cells in peripheral blood and bone marrow. There was no significant difference in anti-platelet antibodies between responders and non-responders. This study confirms CD38 as an important target in ITP. NCT04703621; EudraCT 2019-004683-22.

Conflict of interest: COI declared - see note

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Agreement to Share Publication-Related Data and Data Sharing Statement: Data request will be reviewed on a case-by-case basis by the corresponding and last authors. Such request should be sent along with the research proposal for consideration. Data are not publicly available due to restrictions such as their containing information that could compromise the privacy of research participants. The trial protocol and statistical analysis plan are provided in the appendix.

Clinical trial registration information (if any): NCT04703621 EudraCT 2019-004683-22.

Safety and efficacy of daratumumab in immune thrombocytopenia

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Short running title: Daratumumab for immune thrombocytopenia

Key points

- Treatment resistance in ITP has been linked to autoantibody- producing long-lived plasma cells, emphasizing the role of CD38 depletion.
- CD38 antibody daratumumab demonstrated short- and long-term efficacy with an acceptable safety profile in ITP patients.

Table count: 3

Figure Count: 4

Abstract

Resistance to B-cell-targeted therapies in immune thrombocytopenia (ITP) has been linked to persistence of autoantibody-producing CD38-positive long-lived plasma cells. CD38 antibody daratumumab has been proposed as a potential therapy for ITP. This multicenter, open-label phase 2 study evaluated safety and efficacy of daratumumab in 21 patients with previously treated ITP. Following a safety run-in, 2 dosing cohorts were included, one receiving 8 and the other 10 subcutaneous injections of 1800 mg daratumumab weekly. Primary endpoints were safety and response (two consecutive platelet counts $\geq 50x10^9$/L at week 12 for the safety run-in/cohort 1, and at week 16 for cohort 2). At baseline, median platelet count was $17x10^9$/L, median number of prior therapies was four. Most treatment-emergent adverse events were transient grade 1-2, most commonly infections (38%).Two patients (4.7%) experienced grade 3 adverse events, one infusion-related reaction, and one SARS-CoV-2 infection with acute renal failure. Ten patients (48%) met the primary efficacy endpoint. Sustained response (two consecutive platelet counts $\geq 50x10^9$/L at week 24) was achieved in eight patients (38%). Two patients relapsed after week 24. There was no difference in response or relapse rates between cohorts. Patient-reported quality of life measured by SF-36

improved in responding patients. Daratumumab decreased immunoglobulin levels in all patients, and substantially reduced $CD38^+$ cells in peripheral blood and bone marrow. There was no significant difference in anti-platelet antibodies between responders and non-responders. This study confirms CD38 as an important target in ITP. This study is registered with ClinicalTrials.gov (#NCT04703621) and the European Clinical Trial Register (EudraCT #2019-004683-22).

Introduction

Immune thrombocytopenia (ITP) is an acquired autoimmune bleeding disorder characterized by isolated thrombocytopenia in the absence of other thrombocytopenia-associated disorders.[1] ITP is believed to result from a loss of immune tolerance towards platelet antigens. Immune-mediated attack by antibodies and T cells causes accelerated peripheral platelet destruction and impaired production resulting in thrombocytopenia.[2]

Corticosteroids are the first-line treatment choice, but few patients achieve long-term remissions.[3] Consequently, the majority of patients with ITP require second-line therapies, including thrombopoietin receptor agonist (TPO-RA) or immunomodulatory agents. Nevertheless, patients respond variably to available second-line therapies and many relapse after an initial response. One such example is the CD20 antibody rituximab. Despite initial response of 60%, half of the responders lose response within 2 to 5 years.[4,5] Mechanisms associated with failure/relapse include inadequate B-cell clearance, persistence of autoreactive CD20-$CD19^+$ memory B cells, and emergence of long-lived splenic and bone marrow plasma cells.[6–9] Importantly, long-lived plasma cells in the bone marrow show overexpression of anti-

apoptotic genes and do not express CD20, and thus may contribute to relapse from and resistance to treatments like rituximab and splenectomy.[8]

Based on these observations, plasma cell-depleting therapy is a promising potential treatment for ITP patients with inadequate response to second-line therapies. The CD38 monoclonal antibody, daratumumab, has previously shown therapeutic effects in refractory autoimmune conditions,[10,11] and small case series have shown efficacy in ITP.[12–14] Beyond plasma cells and plasmablasts, daratumumab targets other CD38-expressing cells, including subsets of B and T cells, dendritic cells, and NK cells.[15]

More data on the safety, efficacy, and total cumulative dose of daratumumab were needed to assess its potential as a treatment for adult ITP before the conduct of randomized trial. This led to the conduct of the hypothesis-generating DART trial.

Materials and Methods

Study design

Daratumumab as a treatment for adult immune thrombocytopenia (The DART Study) was an investigator-initiated, multicenter, open-label phase 2 study of subcutaneous daratumumab in patients with ITP conducted in 6 hematology centers in Norway, Denmark and France, with a primary aim to evaluate the safety and efficacy of subcutaneous daratumumab in ITP.

The trial consisted of an initial safety run-in phase involving the first 3 participants, and 2 total dose–increasing cohorts of 9 patients each to assess the impact of total dose on response rates (Fig 1).

The primary efficacy endpoint was evaluated at week 12 for the safety run-in and cohort 1, and week 16 for cohort 2, to avoid a possible effect of corticosteroid premedication on platelet

counts. All patients were followed until week 24 to assess sustained response rate and other secondary endpoints. Patients with sustained responses and nonresponders not requiring initiation of additional platelet-elevating therapy were followed until the end of study (last visit for the last patient).

The trial was conducted according to the International Council on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. The ethics committee of each participating institution approved the trial protocol. Independent Data and Safety monitoring board provided oversight. All patients provided written informed consent before trial entry.

The first and last authors conceived and designed the trial with the input from all the coauthors. Data was collected by investigators and analyzed by the first author with the input from the coauthors. The first author wrote the first draft of the paper with subsequent input from the coauthors. All authors had access to trial data. All authors and Janssen Pharmaceutica NV (Beerse, Belgium) reviewed, revised, and approved the manuscript before it was submitted to publication.

Patients

Patients with primary ITP were eligible if they were ≥18 years of age, had a platelet count of ≤30x10^9/L, had failed to respond or relapsed after corticosteroid treatment and at least one second-line therapy including thrombopoietin receptor agonist (TPO-RA) or rituximab (last infusion ≥ 24 weeks before study inclusion). For the safety run-in phase, a platelet count of 15-30x10^9/L was required. The dose of corticosteroids and TPO-RAs had to remain stable over the two weeks prior to inclusion without increase during the study period. Rescue therapy (IVIG, corticosteroids, anti-D and platelet transfusions) was allowed until the day of the administration of the last injection of study treatment; its use after that qualified the

patient as non-responder. Details on eligibility criteria are presented in the supplemental Appendix.

Treatment

Subcutaneous daratumumab, 1800 mg/dose, was administered weekly for four weeks for the safety run-in, weekly for eight weeks for cohort 1, and weekly for eight weeks followed by every two weeks at weeks ten and twelve for cohort 2.

The 3 safety run-in participants were treated and observed individually for 4 weeks posttreatment. To investigate whether a higher cumulative daratumumab dose could lead to a higher and/or longer response, 2 successive dosing cohorts with 9 patients each were defined, with cohort 2 receiving a 25% higher total dose.

Progress to the next participant in the safety run-in phase and the decision to initiate each cohort was based on safety evaluation conducted by the data safety monitoring board.

Premedication included antihistamines (diphenhydramine 50 mg or equivalent) and paracetamol (acetaminophen) 1000 mg. Methylprednisolone 100 mg, or equivalent preceded the first injection and was reduced to 60 mg for the second and subsequent injections. In addition, methylprednisolone 20 mg (or equivalent) was administered for two consecutive days following the first three daratumumab injections only. Montelukast (10 mg) was given only before the first daratumumab injection.

Methods

Bleeding was assessed using the Khellaf and WHO bleeding scales.[16,17]

Health-related quality of life (HRQoL) was assessed using 36-Item Short Form Health Survey Version 1 (SF-36v1)[18,19] and the Multidimensional Fatigue Inventory (MFI- 20) questionnaire to evaluate fatigue.[20] Participants answered the questionnaires before initiation of therapy, 4 weeks after the last treatment and at study week 24. Minimal important differences (MIDs) values estimated for the EXTEND study population were used to evaluate the clinical significance of changes in SF-36 domains.[21]

Blood for study specific analyses was taken only at Norwegian and French study centers. Mononuclear cells for evaluation of CD38 depletion were cryopreserved from blood and bone marrow at screening and 4 weeks after the last daratumumab infusion, i.e. week 12 for the safety run-in and cohort 1, and week 16 for cohort 2, and blood at study week 24. Flow cytometric analysis of mononuclear cells for evaluation of CD38 depletion was performed with cryopreserved peripheral blood (PBMCs) and bone marrow mononuclear cells (BMMCs) enriched for live cells by magnetic depletion of dead cells (Dead cells removal microbeards, Miltenyi) in the presence of citrate buffer. At least one million cells per patient sample, healthy donor PBMCs, and VeriCells were seeded in a 96-well plate. Cells were washed, and each well was stained with Live/Dead Zombie Near-IR (BioLegend) diluted in PBS. Cells were washed and stained with pre-titrated CD38 antibody (clone HIT-2, BD Biosciences) and B-cell antibody panel for 30 minutes at 4°C.[22] Cells were washed twice before fixation and immediate acquisition on a SONY ID7000 flow cytometer. The staining was analyzed using FlowJo v10 software (BD Life Sciences).

Antiplatelet antibody test was performed for the Norwegian patients only. Platelet IgG autoantibodies to glycoproteins (GP) IIb/IIIa, Ib/IX, Ia/IIa, and V on patients' platelets, were evaluated using in-house indirect and direct monoclonal antibody immobilization of platelet antigens assay (MAIPA).[23,24] Briefly, platelets isolated from EDTA blood tubes were tested in duplicates using 20×10^6 platelets per well. Donor platelets (blood group O) were incubated

with 50 ul patient plasma (for indirect MAIPA), or patient platelets incubated with autologous plasma (for direct MAIPA). Monoclonal antibodies specific for GPIIIa/CD61 (Y2/51), GPIb/CD42b (SZ2), GPIa/CD49b (Gi9) and GPV/CD42d (SW16) were used at 5 µg/mL. For detection, goat anti-human IgG (HRP) and tetramethylbenzidine substrate were used, and the reaction stopped with 0.5 M H_2SO_4. Optical Density (OD) was read at 450 nm. For indirect MAIPA, positive cut-off value were mean OD (negative control) +2SD of control plasma in the setup. For direct MAIPA, OD values OD ≥0.15-0.2 were evaluated as weakly reactive (WR), while a restrictive positive cut-off was set to OD ≥0.2.

For some samples, the number of platelets were not sufficient for direct MAIPA, and the available platelets were used (>5 × 10^6 platelets per well) - if negative in the test, results were considered inconclusive.

Anti-daratumumab antibodies were analyzed using the KRIBIOLISA™ Anti-Daratumumab ELISA kit (Eagle Biosciences, Amherst, NH). CD38 expression (anti-CD38, clone HIT2, BD Biosciences) was measured on an Attune NxT (ThermoFisher) or a SONY ID7000 flow cytometer and analyzed using FlowJo v10 software (BD Life Sciences).

More details on blood- and bone marrow sampling are presented in the supplemental Appendix.

Endpoints

The main primary endpoints were safety and efficacy of subcutaneous daratumumab. Safety was assessed as the number and severity of adverse events grade ≥2 during the study. Adverse events were recorded at least until week 24 and as long as the patient remained in the study.

The primary efficacy endpoint, response, was defined as two consecutive platelet counts ≥50x10^9/L (measured ≥24 hours apart), assessed at least four weeks after the last daratumumab injection (week 12 for safety run-in and cohort 1, and week 16 for cohort 2)

given the high corticosteroid doses in standard daratumumab premedication to allow for corticosteroid washout.

Secondary efficacy endpoints were rates of sustained response defined as two consecutive platelet counts $\geq 50x10^9$/L (measured ≥24 hours apart) at study week 24; duration of response; time to treatment failure; number of bleeding episodes per patient.

Exploratory outcomes were time from first treatment to the first platelet count $\geq 50x10^9$/L; rates of complete response (platelet count $\geq 100x10^9$/L) and partial response (platelet count $>30x10^9$/L but $<50x10^9$/L, or at least doubling of platelet count from baseline); evaluation of patient-reported outcomes; pre- and post-treatment levels of anti-platelet antibodies, and depletion efficacy of CD38+ immune cells in blood and bone marrow. Detailed description of the endpoints is provided in the supplemental Appendix.

Statistical analysis

Data were analyzed for all enrolled patients. Baseline characteristics are presented using descriptive statistics. The 95% confidence intervals (CI) for evaluation of primary and secondary endpoints were calculated using the Clopper-Pearson method. Time-to-event estimates were evaluated using the Kaplan-Meier method. No replacement of missing data was performed.

No formal hypothesis was planned in this study, as the statistical power was insufficient to detect differences between dose groups.

Statistical analyses were conducted using GraphPad Prism (version 9.0.0), R Statistical Software (version 4.4.2) , and STATA/SE v.18.0,

Results

Patient characteristics

Between January 2021 and September 2023, 21 patients were enrolled. The data cut-off for analysis was March 12, 2024, six months after last enrollment. All patients completed study treatment and were available for analysis of the primary and secondary endpoints.

Demographics are described in Table 1. Median age was 51 years (range 19-77); 66.7% were males. Median number of previous ITP-directed therapies was four (range, 2-11). Nineteen patients (90%) had previously responded to corticosteroids at least once. Five patients (23.8%) were splenectomized, and 16 had previously received rituximab.Thirteen (62%) patients received concurrent medication at baseline: corticosteroids (14%), TPO-RA (24%) or combination (24%).

Safety endpoints

During the study, nine patients (43%) experienced at least one treatment-related adverse event, all were transient (Table 2). The most common treatment-related adverse events were infusion-related reactions (IRR), occurring in three patients (14%), injection site reactions (9.5%), and diarrhea (9.5%). All IRR were related to the first injection and resolved within 24 hours. Infections were the most common treatment-emergent adverse events (38%) (Table S1). One patient had several upper respiratory tract infections managed with oral antibiotics and without hospitalization.

Two patients experienced grade 3 adverse events. One had an infusion-related reaction. The second patient experienced SARS-CoV-2 infection complicated by acute renal failure, unrelated to the study treatment as considered by investigator. There were no grade 4 adverse events or deaths among participants and no treatment-related thrombotic events. None of the patients discontinued study treatment.

Efficacy endpoints

All 21 included patients were evaluated for efficacy. The primary endpoint, response, was met in ten patients (48%; 95% CI: 25.7-70.2). This included two of three patients in the safety run-in, four of nine patients (44%; 95% CI: 13.7-78.8) in cohort 1, and four of nine patients (44%; 95% CI: 13.7-78.8) in cohort 2 (Table 3). One additional patient in cohort 1 responded shortly after the primary endpoint evaluation, at week 14. Five of eleven responding patients (45%) used concomitant medications at the time of the first daratumumab injection (two were treated with TPO-agonist, two with prednisolone, and one with a combination of TPO-agonist and prednisolone). All responding patients discontinued concomitant ITP medication; median time to discontinuation was six weeks (range 2-12). Eighteen (86%) patients achieved a platelet count of $\geq 50x10^9$/L at least once between the date of the first study treatment and the primary endpoint evaluation with median time to first platelet count $\geq 50x10^9$/L of seven days (range, 6-10).

Of 16 patients who had previously been treated with rituximab, eight (50%) met the primary endpoint, and six out of eight were still responding at week 24. Of those who previously esponded to rituximab (n=4), three showed a response to daratumumab at weeks 12/16, while one did not. By week 24, two prior rituximab responders maintained a response to daratumumab. Although the exact interval since rituximab was not consistently recorded, study eligibility required at least 24 weeks since the last dose; where available, the documented intervals were substantially longer.

None of the five splenectomized patients responded to daratumumab, whereas 11/16 non-splenectomized patients did.

A sustained response defined as two consecutive platelet counts $\geq 50x10^9$/L (measured $\geq$24 hours apart) at study week 24, was achieved in eight patients (38%, 95% CI: 18.1-61.6), one

from the safety run-in, 4 (44%, 95% CI: 13.7-78.8) from cohort 1, and three (33%, 95%: CI 7.4-70.0) from cohort 2 (Figures 2, 3, and S1).

Median duration of follow-up was 10.4 months (range, 5.3-34.8) for the entire study population, 15.4 months (range, 5.5-29.2) in cohort 1, and 8.0 months (range, 5.3- 15.2) in cohort 2.

Median duration of response was 21.5 months (range, 1.2-33.2), and time to treatment failure was 22.3 months (range, 1.2-33.2) (Figure 4). At end of study, six patients (29%) maintained response without additional ITP-directed therapies; one from the safety run-in, two from cohort 1, and three in cohort 2.

Seven patients experienced WHO grade 2 bleeding episodes; none were related to treatment. One patient experienced macroscopic hematuria and another experienced menorrhagia (Table S2).

Rescue medications were used in two patients (9.5%) during the study period, one during the first 24 weeks and another during the later follow-up.

Patient-reported outcomes

Data regarding patient-reported outcomes at baseline and four weeks after the last daratumumab treatment are shown in Figures S2, S3, and Tables S3, S4. Compared to baseline, numerical improvement was observed for responders in all eight dimensions of the SF-36 four weeks after the completion of treatment. In four domains (role limitations due to physical health and emotional problems, energy/fatigue, and general health), the observed improvements were higher than minimal important difference (MID). In the fatigue specific tool, MFI-20, a trend to improvement in the general fatigue domain was observed in responders compared to non-responders, whereas in the four other domains, a very minor improvement in the domains of physical and mental fatigue were obsereved.

Changes in immunologic indicators.

Efficacy of daratumumab-mediated immune cell depletion was evaluated longitudinally in 13 patients with cryopreserved cells derived from bone marrow and peripheral blood at screening and at primary endpoint evaluation and in blood only at study week 24. Median reduction of $CD38^{+}$cells at primary endpoint evaluation was 91% (IQR: 73-93%) in the peripheral blood, 90% (IQR: 69-98%) in bone marrow, and 91% (IQR: 73-93%) in the peripheral blood at week 24. No difference between cohorts in responders versus non-responders was observed.

Serum immunoglobulin levels decreased after the administration of daratumumab in all patients (Table S5), with no association between magnitude of immunoglobulin decline and platelet response.

At baseline, only 3/7 (43%) of the responders, and 4/9 (44%) of the non-responders had anti-platelet antibodies with direct MAIPA (OD cut-off 0.15). Platelet autoantibodies were notably detectable in only six of 16 patients tested at baseline, with the more conservative cut-off OD 0.2. Four weeks after the last treatment, anti-platelet antibodies were still detectable in two (29%) responders and two (22%) non-responders (Table S6). All of the direct MAIPA negative/inconclusive patient samples were also negative in indirect MAIPA.

Anti-drug (daratumumab) antibody samples were analyzed in 12 patients with no antibodies detected.

Discussion

In this phase 2 study, the anti-CD38 antibody daratumumab was administered subcutaneously to an ITP population previously treated with a median of four prior lines of therapy; two-thirds had been previously treated with both rituximab and thrombopoietin receptor agonists, and ~25% had failed splenectomy. The primary endpoint was achieved in 48% of the patients,

with 1 additional patient achieving a response 2 weeks after the primary endpoint evaluation time point.

Treatment with subcutaneous daratumumab was associated with mainly mild to moderate and transient adverse events, with infections being the most common treatment-emergent adverse event. Infusion reactions were infrequent, manageable, and did not recur with subsequent daratumumab injections. While treatment with subcutaneous daratumumab led to a consistent, substantial decline in immunoglobulin levels in all study participants, only one patient developed recurrent infections requiring antimicrobial therapy. No grade 4 adverse events or deaths occurred, and none discontinued study treatment.

Recently, Chen et al. reported the safety and efficacy of eight weekly intravenous injections of anti-CD38 antibody CM313 in 22 previously treated ITP patients.[25] Similar to our study, the median number of previous therapies was four. Compared to our patient cohort, patients in the CM313 study were younger (median age 36 vs 51 years), mostly female (76 vs 33%), had lower BMI (median of 25.9 vs 29.3), shorter median ITP duration (27.0 vs 60.1 months), and only 36% had previously been treated with rituximab compared to 76% in our study. In CM313 study, overall response at week 12 (platelet counts $\geq 30 \times 10^9$/L) was 86%, and durable sustained response was 64% at week 24 which was higher than in our study. Notably, response was defined as two or more consecutive platelet counts $\geq 50 \times 10^9$/L ($\geq$1 day apart) within 8 weeks of the first CM313 dose. Sustained response was defined as maintenance of a continuous platelet count $\geq 30 \times 10^9$/L, with at least a twofold increase from baseline, maintained over the 24-week period. Differences in study populations and endpoint definitions may have contributed to the varying response rates between this study and ours. Structural differences between the medicaments may also play a role, although knowledge of CM313's structure remains limited beyond its distinct complementarity-determining region sequence, which differs from that of daratumumab.[25]

A previous non-inferiority study comparing intravenous daratumumab at dose 16 mg/kg and subcutaneous daratumumab at fixed dose of 1800 mg in patients with multiple myeloma, showed slower increase in plasma concentrations with a lower peak level in subcutaneous group.[26] However, a maximum trough concentration ($C_{through}$) of the drug was overall higher or similar for subcutaneous daratumumab in an overall study population. Of interest, patients ≤65 kg had a 60% higher, whereas patients >85 kg had a 12% lower values of maximum $C_{through}$ with subcutaneous daratumumab than intravenous daratumumab. As such, these could potentially contribute to observed differences between the two study populations.[26]

The IRR rate was numerically higher among the patients treated with CM313 compared to our study (32% vs 14%) which may be dependent of route of administration as previously shown for daratumumab.[26]

Mezagitimab is another subcutaneous CD38 antibody that has been recently evaluated in a phase 2 trial with promising preliminary results with a 91% platelet response defined as two platelet counts >50×10⁹/L and ≥20 ×10⁹/L above baseline on ≥2 visits.[27]

Although most patients in our study exhibited a rapid initial platelet rise, the primary endpoint response rate was evaluated at least four weeks after the daratumumab injection, and was 48%. suggesting that early increases may reflect corticosteroid premedication effects, or a synergistic effect with daratumumab.

Response and relapse rates did not appear to correlate with the number of subcutaneous daratumumab injections with even distribution between the groups. Furthermore, in the safety run-in, two of three patients responded after only four injections of daratumumab. The small number of patients in each cohort precludes any definite conclusion regarding the optimal dosing, however our results suggest that four doses may be as effective as 8/10 doses with regard to rate and duration of response.

All responding patients in our study were able to discontinue concomitant medications. This indicates that response to daratumumab is largely if not solely related to the drug and is independent of other medications. This effect, if confirmed, may translate into a big advantage to the patient and health care system.

Daratumumab treatment consistently resulted in substantial decreases in $CD38^+$cells in peripheral blood and bone marrow with a reduction of 90% in all assessments, and a decline in IgG levels albeit unrelated to platelet responses. There was no apparent difference in anti-platelet autoantibody positivity between responders and non-responders. The findings may suggest that part of the response mechanisms involves modulation of $CD38^+$ immune cells other than plasma cells, such as NK cells or T cells, and that the heterogeneity of pathophysiology means that not all patients will respond to any single therapeutic approach.[28–30]

Fatigue and impaired health-related quality of life are well-known manifestations of ITP. In the current study, HRQoL measured by SF-36 improved across all dimensions in responding patients. In 4 dimensions the improvement was higher than the MID. There were also trend to improvement in general fatigue (domain one in MFI-20 score) in responders compared to non-responders.

Daratumumab has been in clinical use for multiple myeloma for years, and is commercially available. Importantly, this means that the the safety profile is well-established, and the drug is usually well-tolerated even in elderly frail patients. Of note, we did not observe any additional side effects specific to the ITP population.

We followed all patients not requiring other types of ITP treatment until the end of the study, with the longest follow-up being nearly 35 months. This provides valuable insight into the

durability of response to daratumumab and demonstrates the potential to induce treatment-free remissions.

Our study has several limitations, including a limited number of patients and the non-randomized design. However, at the time our study was initiated, limited data existed on the use of CD38 antibodies in ITP, and therefore the study was intended as a hypothesis-generating study that aimed to assess the safety of daratumumab and explore potential efficacy signals. We also chose to use a dosage and schedule based on multiple myeloma regimens, while the optimal schedule for ITP may be different and should be explored in future studies. The investigated difference in cumulative dose between our cohorts was probably too small to have a major impact on outcomes and response durability. Finally we cannot exclude that the administration of corticosteroids as a premedication may have augmented the response rates during the study drug administration period. To mimimize this potential effect, we measured the primary endpoint four weeks after the last injection and thus last (single) steroid dose.

This phase 2 study demonstrates the safety and efficacy of CD38 antibody daratumumab in heavily-pretreated ITP patients. Together with other recent anti-CD38 trials, these findings highlight the therapeutic potential of CD38-targeted approach in ITP. The consistent, durable responses and favorable safety profile suggest that daratumumab would have utility beyond the refractory setting. Its use earlier in the disease course—either as monotherapy or in combination with corticosteroids or other agents—warrants exploration, particularly given the potential for synergistic effects and reduced reliance on prolonged immunosuppression. Early intervention may also modify disease trajectory in select patients, leading to more sustained remissions. However, prospective, controlled trial is essential to confirm the findings in our study, optimize treatment strategies, and assess the role of re-treatment in relapsed responders.

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The funders of the study had no role in study design, data collection, data interpretation, or writing of the report.

The study schedule and preliminary results of the safety run-in phase were presented as a poster presentation at the 63rd annual meeting of the American Society of Hematology, Atlanta, GA, 11 to 14 December 2021.

Author Contribution Statement

GT and WG conceived, designed and coordinated the study, recruited patients, participated in data analysis. GT wrote statistical analysis plan, was responsible for statistical analysis and wrote the first draft of the manuscript. PAH, HTTT, HF, ET, MM, MarcM screened, recruited

and followed patients. LAM, ED, HK performed and interpreted flow analyses of CD38-positive cells. IHS, MTA supervised and interpreted MAIPA analysis. JB, DJK,THT participated in a designing the study and drafting study protocol. All authors were involved in drafting the manuscript and revising it. All authors approved the final text and were responsible for the decision to submit for publication.

Data requests will be reviewed on a case-by-case basis by the corresponding and last authors. Such request should be sent along with the research proposal for consideration. Data are not publicly available due to restrictions such as their containing information that could compromise the privacy of research participants. The trial protocol and statistical analysis plan are provided in the supplemental appendix.

Conflict-of-Interest Disclosure

- GT: lecture honoraria and advisory board for Janssen, Sanofi, SOBI and Grifols.
- PAH: research funding from Bayer, Biogen, CSL, SOBI; speaker honorarium from Bayer, BioMarin, CSL, Novo Nordisk, Octapharma, Pfizer, Roche, Takeda, SOBI.
- HTTT: consultancy fees and participation in ad board for Abbvie, Grifols, Novartis and AstraZeneca.
- HF: research funding from Sanofi, Novartis and Alexion.
- ET: advisory board for Janssen, SOBI, Grifols, Novartis, Alexion, GSK, Beigene and AOP.
- LAM: grants from South East Regional Authority, Research Council of Norway (RCN) and Stiftelsen KG Jebsen.

- MM: speaker's and/or advisory fees received from Novartis, Grifols, Incyte and Amgen; grant from GSK.
- MarcM: speaker's and/or advisory fees received from Amgen, Grifols, Novartis, Sanofi and Sobi. JB declares participation in consulting/ad boards for Novartis, Jannsen, UCB, Argenx, Alpine, RallyBio and Pfizer.
- DJK: research grants from Alnylam, Fulcrum, Hutchmed, Novartis, Principia, Sanofi, Takeda; consulting fees from Alexion, Alpine, Amgen, argenx, BioCryst, Blackstone, Bristol Myers Squibb, Cardurion, Caremark, Chugai, Hengrui, Hutchmed, Iconic Bio, Immunovant, Kaigen, Lilly, Medscape, Merck Sharp Dohme, New York Blood Center, Nexcella, Novartis, Nurix, Nuvig, Ouro, Peerview, PER, Pfizer, Platelet Disorder Support Association, Principia, Regeneron, Rigel, Sanofi, Seismic, Sobi, Takeda, Timberlyne, UCB, Up-To-Date, Verve.
- THAT: lecture honoraria and fees for participation in ad boards from Sanofi, Takeda, Janssen.
- WG: fees for participation in ad boards from Amgen, Novartis, Pfizer, Principia Biopharma Inc- a Sanofi Company, Sanofi, SOBI, Grifols, UCB, Argenx, Cellphire, Alpine, Kedrion, HiBio, Hutchmed, Takeda; lecture honoraria from Amgen, Novartis, Pfizer, Bristol Myers Squibb, SOBI, Grifols, Sanofi and Bayer; research grants from Bayer, BMS/Pfizer, UCB, Sanofi, SOBI, Sanofi.
- ED, HK, HIS and MTA: no conflict of interests.

References

1. Cooper N, Ghanima W. Immune Thrombocytopenia. *N Engl J Med*. 2019;381(10):945-955. doi:10.1056/NEJMcp1810479
2. Provan D, Semple JW. Recent advances in the mechanisms and treatment of immune thrombocytopenia. *EBioMedicine*. 2022;76:103820. doi:10.1016/j.ebiom.2022.103820

3. Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. *Blood Adv*. 2019;3(23):3829-3866. doi:10.1182/bloodadvances.2019000966
4. Ghanima W, Khelif A, Waage A, et al. Rituximab as second-line treatment for adult immune thrombocytopenia (the RITP trial): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet*. 2015;385(9978):1653-1661. doi:10.1016/S0140-6736(14)61495-1
5. Deshayes S, Khellaf M, Zarour A, et al. Long-term safety and efficacy of rituximab in 248 adults with immune thrombocytopenia: Results at 5 years from the French prospective registry ITP-ritux. *Am J Hematol*. 2019;94(12):1314-1324. doi:10.1002/ajh.25632
6. Mahévas M, Patin P, Huetz F, et al. B cell depletion in immune thrombocytopenia reveals splenic long-lived plasma cells. *J Clin Invest*. 2013;123(1):432-442. doi:10.1172/JCI65689
7. Kuwana M, Iki S, Urabe A. The role of autoantibody-producing plasma cells in immune thrombocytopenic purpura refractory to rituximab. *American J Hematol*. 2007;82(9):846-848. doi:10.1002/ajh.20951
8. Crickx E, Chappert P, Sokal A, et al. Rituximab-resistant splenic memory B cells and newly engaged naive B cells fuel relapses in patients with immune thrombocytopenia. *Sci Transl Med*. 2021;13(589):eabc3961. doi:10.1126/scitranslmed.abc3961
9. Patel VL, Mahévas M, Lee SY, et al. Outcomes 5 years after response to rituximab therapy in children and adults with immune thrombocytopenia. *Blood*. 2012;119(25):5989-5995. doi:10.1182/blood-2011-11-393975
10. Holzer MT, Ruffer N, Huber TB, Kötter I, Ostendorf L, Krusche M. Daratumumab for autoimmune diseases: a systematic review. *RMD Open*. 2023;9(4):e003604. doi:10.1136/rmdopen-2023-003604
11. Hofmann K, Clauder AK, Manz RA. Targeting B Cells and Plasma Cells in Autoimmune Diseases. *Front Immunol*. 2018;9:835. doi:10.3389/fimmu.2018.00835
12. Vernava I, Schmitt CA. Daratumumab as a novel treatment option in refractory ITP. *Blood Cells Mol Dis*. 2023;99:102724. doi:10.1016/j.bcmd.2023.102724
13. Crickx E, Audia S, Robbins A, et al. Daratumumab, an original approach for treating multi-refractory autoimmune cytopenia. *Haematologica*. 2021;106(12):3198-3201. doi:10.3324/haematol.2021.279232
14. Strüßmann T, Jung J, Heinz J, et al. Long-term complete remission of refractory severe idiopathic immune thrombocytopenia (ITP) treated with daratumumab. *Ann Hematol*. 2023;102(1):245-247. doi:10.1007/s00277-022-05035-y
15. Piedra-Quintero ZL, Wilson Z, Nava P, Guerau-de-Arellano M. CD38: An Immunomodulatory Molecule in Inflammation and Autoimmunity. *Front Immunol*. 2020;11:597959. doi:10.3389/fimmu.2020.597959
16. Khellaf M, Michel M, Schaeffer A, Bierling P, Godeau B. Assessment of a therapeutic strategy for adults with severe autoimmune thrombocytopenic purpura based on a bleeding score rather than platelet count. *Haematologica*. 2005;90(6):829-832.
17. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer*. 1981;47(1):207-214. doi:10.1002/1097-0142(19810101)47:1<207::AID-CNCR2820470134>3.0.CO;2-6
18. Ware J, MA K, Keller SD. SF-36 Physical and Mental Health Summary Scales: a User's Manual. 1993;8:23-28.
19. Monica 1776 Main Street Santa, California 90401-3208. 36-Item Short Form Survey (SF-36) Scoring Instructions. Accessed October 25, 2024. https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form/scoring.html

20. Shahid A, Wilkinson K, Marcu S, Shapiro CM. Multidimensional Fatigue Inventory (MFI). In: Shahid A, Wilkinson K, Marcu S, Shapiro CM, eds. *STOP, THAT and One Hundred Other Sleep Scales*. Springer New York; 2011:241-243. doi:10.1007/978-1-4419-9893-4_57
21. Khelif A, Saleh MN, Salama A, et al. Changes in health-related quality of life with long-term eltrombopag treatment in adults with persistent/chronic immune thrombocytopenia: Findings from the EXTEND study. *American J Hematol*. 2019;94(2):200-208. doi:10.1002/ajh.25348
22. Kared H, Jyssum I, Alirezaylavasani A, et al. Dynamics of SARS-CoV-2 immunity after vaccination and breakthrough infection in rituximab-treated rheumatoid arthritis patients: a prospective cohort study. *Front Immunol*. 2024;15:1296273. doi:10.3389/fimmu.2024.1296273
23. Kiefel V, Santoso S, Weisheit M, Müeller-Eckhardt C. Monoclonal antibody--specific immobilization of platelet antigens (MAIPA): a new tool for the identification of platelet-reactive antibodies. *Blood*. 1987;70(6):1722-1726.
24. Killie MK, Salma W, Bertelsen E, Skogen B, Husebekk A. Quantitative MAIPA: Comparison of different MAIPA protocols. *Transfusion and Apheresis Science*. 2010;43(2):149-154. doi:10.1016/j.transci.2010.07.001
25. Chen Y, Xu Y, Li H, et al. A Novel Anti-CD38 Monoclonal Antibody for Treating Immune Thrombocytopenia. *N Engl J Med*. 2024;390(23):2178-2190. doi:10.1056/NEJMoa2400409
26. Mateos MV, Nahi H, Legiec W, et al. Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial. *The Lancet Haematology*. 2020;7(5):e370-e380. doi:10.1016/S2352-3026(20)30070-3
27. Kuter DJ, Pulanić D, Patriarca A, Yang R, Sapuranova K, Miura K. LB 01.1 - Safety, tolerability, and efficacy of mezagitamab (TAK-079) in chronic or persistent primary immune thrombocytopenia: Interim results from a phase 2, randomized, double-blind, placebo-controlled study. ISTH 2024. 23 June 2024. Accessed January 16, 2025. https://isth2024.eventscribe.net/fsPopup.asp?PresentationID=1458552&returl=YWpheGNhbGxzL3Nlc3Npb25pbmZvLmFzcD9QcmVzZW50YXRpb25JRD0xMzk5NDM2&mode=presInfo
28. Krejcik J, Casneuf T, Nijhof IS, et al. Daratumumab depletes CD38+ immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. *Blood*. 2016;128(3):384-394. doi:10.1182/blood-2015-12-687749
29. Viola D, Dona A, Caserta E, et al. Daratumumab induces mechanisms of immune activation through CD38+ NK cell targeting. *Leukemia*. 2021;35(1):189-200. doi:10.1038/s41375-020-0810-4
30. Zufferey A, Kapur R, Semple JW. Pathogenesis and Therapeutic Mechanisms in Immune Thrombocytopenia (ITP). *J Clin Med*. 2017;6(2):16. doi:10.3390/jcm6020016

Table 1. Patient and disease characteristics at baseline

Characteristics	All patients (N = 21)	Safety run-in (N = 3)	Cohort 1 (N = 9)	Cohort 2 (N = 9)
Median age (IQR)-yr	51 (34-65)	55 (33-75)	51 (36-67)	49 (33-59)
Sex, no.(%)				
Male	14 (66.7)	2 (66.7)	5 (55.6)	7 (77.8)
Female	7 (33.3)	1 (33.3)	4 (44.4)	2 (22.2)
Median BMI (IQR), kg/m^2	29.3 (26.0-33.3)	35.0 (28.0-42.2)	29.4 (26.0-32.2)	28.7 (25.3-33.3)
Median platelet count at screening (IQR), $10^9/L$	17.0 (10.0-20.0)	17.0 (16.0-26.0)	19.0 (15.0-22.0)	16.0 (10.0-19.0)
Median duration of ITP* (IQR)-months	60.5 (13.5- 231.7)	108.8 (13.5-136.8)	18.3 (7.3-60.5)	231.4 (42.0- 272.9)
Median number of different prior ITP treatments (range)	4 (2-11)	5 (3-6)	4 (2-9)	4 (3-11)
Prior ITP therapy, no.(%)				
Corticosteroids	21 (100)	3 (100)	9 (100)	9 (100)
IVIG	14 (67)	2 (67)	5 (56)	7 (78)
Rituximab	16 (76)	3 (100)	6 (67)	7 (78)
Thrombopoietin receptor agonists†	18 (86)	3 (100)	8 (67)	7 (78)
Fostamatinib	1 (4.8)	0	0	1 (11)
Rilzabrutinib	1 (5)	1 (33)	0	0
Azathioprine	2 (10)	0	1 (11)	1 (11)
Mycophenolate mofetil	2 (10)	0	0	2 (22)
Dapsone	1 (5)	0	0	1 (11)
Danazol	1 (5)	0	1 (11)	0
Cyclosporine	2 (10)	0	0	2 (22)
Hydroxychloroquine	1 (4.8)	0	0	1 (11)
Splenectomy	5 (24)	0	2 (22)	3 (33)
Response to previous steroid therapy	19 (90)	2 (67)	9 (100)	8 (89)
Concomitant ITP-directed therapy (at the date of the first daratumumab injection), no.(%)				
Corticosteroid monotherapy	3 (14)	0	0	3 (33)
Thrombopoietin receptor agonist monotherapy	5 (24)	1 (33)	2 (22)	2 (22)
Thrombopoietin receptor agonists and corticosteroids combined	5 (24)	2 (67)	1 (11)	2 (22)
WHO bleeding score at baseline, no.(%)				
0	11 (52)	1 (33)	8 (89)	2 (22)
1	9 (43)	2 (67)	1 (11)	6 (67)
2	1 (5)	0	0	1 (11)
3/4/5	0	0	0	0
Median IgG level, g/L, at baseline (IQR)	10.1 (8.6-12.7)	10.1 (9.6-12.0)	12.4 (11.7-14.3)	8.6 (6.3-10.1)

* The duration of ITP was defined as a time from date of ITP diagnosis to the date of baseline evaluation
† Thrombopoietin receptor agonists include eltrombopag, avatrombopag and romiplostim
BMI, body mass index
IQR, interquartile range
WHO, World Health Organisation

Table 2. Treatment-related adverse events

Adverse event	No. of patients (%) with treatment-related adverse events*			
	Any grade	**Grade 1**	**Grade 2**	**Grade 3†**
Any adverse event	9 (42.9)	4 (19.0)	5 (23.8)	1 (4.7)
Infusion-related reactions	3 (14.3)	0	2 (9.5)	1 (4.7)
Urticaria	1 (4.7)	0	1 (4.7)	0
Fever	1 (4.7)	0	1 (4.7)	0
Infusion-related reaction	1 (4.7)	0	0	1 (4.7)
Injection site reaction	2 (9.5)	2 (9.5)	0	0
Erythematous rush	2 (9.5)	2 (9.5)	0	0
Injection site discoloration	1(4.7)	1(4.7)	0	0
Infections	1 (4.7)	1 (4.7)	1 (4.7)	0
Upper respiratory tract infections	1 (4.7)	0	1 (4.7)	0
Sinusitis	1 (4.7)	1 (4.7)	0	0
Diarrhea	2 (9.5)	0	2 (9.5)	0
Headache	1 (4.7)	1 (4.7)	0	0
Nausea	1 (4.7)	0	1 (4.7)	0
Vomiting	1 (4.7)	0	1 (4.7)	0
Weight gain	1 (4.7)	1 (4.7)	0	0

* Relatedness to treatment was determined by the study investigators. Four patients had >1 treatment-related adverse event.

† In total, three adverse events of grade 3 were reported in two patients. Only one (infusion-related reaction) was related to treatment. Second patient contracted SARS-CoV-2 infection complicated with acute renal failure. None grade 4 or grade 5 adverse events appeared during the study.

Table 3. Efficacy endpoints.

End point	All patients (n = 21)	Cohort 1 (n = 9)	Cohort 2 (n = 9)
Primary endpoint*			
Response rate, n % (95% CI)	10 48 (25.7-70.2)	4 44 (13.7-78.8)	4 44 (13.7-78.8)
Secondary endpoints			
Sustained response rate, n % (95% CI)	8 38 (18.1-61.6)	4 44 (13.7-78.8)	3 33 (7.4-70.0)
Median duration of response, months (range)	21.5 (1.2-33.2)	18.7 (3.2-26.2)	8.1 (1.2-11.5)
Time to treatment failure, months (range)	22.3 (1.2-33.2)	18.7 (12.0-26.2)	8.1 (1.2-11.5)
Median time from first daratumumab injection to first platelet count $\geq 50x10^9$/L, days (range)	7 (6-10)	6.5 (6-8)	7 (6-10)
Number of patients with platelet count $\geq 100x10^9$/L (complete response) n % (95%CI)†	9 43 (21.8-66.0)	3 33 (7.4-70.0)	4 44 (13.7-78.8)
Number of patients with platelet count $<50x10^9$/L but $>30x10^9$/L(partial response) n % (95%CI)†	1 5 (0.1-23.0)	0 0	1 11 (0.3-48.2)

* The primary endpoint response was defined as proportion of patients who achieve platelet count $\geq 50x10^9$/L in 2 measurements (taken at least 24 hours apart) during week 12 after first study drug injection for safety run-in and cohort 1, and week 16 for cohort 2, without having received rescue therapy for the last four weeks, nor having had dose increment of TPO-RA or corticosteroids during the study period. The 95% confidence intervals were based on the Clopper-Pearson method. The width of the confidence intervals has not been adjusted for multiplicity and should not be used to definitively infer efficacy.

† Evaluation of complete and partial response displayed at this table was done at 12 weeks for patients in safety run-in and cohort 1, and at week 16 for patients in cohort 2. Complete response was defined as platelet count $\geq 100x10^9$/L. Partial response was defined as platelet count $>30x10^9$/ but $<50x10^9$/L (or at least doubling of the platelet count from baseline).

CI, confidence interval

Figure 1 CONSORT Flow Diagram of the Study. The first three patients participated in safety run-in cohort and received four weekly subcutaneous daratumumab injections of 1800 mg. Each patient in safety run-in cohort was treated and observed individually for four weeks post-treatment. In the subsequent phases of the study, nine patients were included in cohort 1, and received eight weekly subcutaneous daratumumab injections. Last nine patients were included in cohort 2, and received eight weekly subcutaneous daratumumab injections, followed by two bi-weekly injections (total of 10 injections). Primary endpoint, response, was evaluated at week 12 in safety run-in and cohort 1, and week 16 in cohort 2. All patients were followed until study week 24. Patients with sustained response and non- responders without a need for other ITP-directed therapy were followed until the end of study.

Figure 2. Platelet Counts Over Time in Patients Included in (A) Safety run-in, (B) Study Cohort 1, (C) Cohort 2 and (D) Response Rates. The median platelet count from screening through the 24-week treatment period is shown for the three patients in Safety run-in (A), nine patients in cohort 1 (B), the nine patients in cohort 2 (C). Bars represent interquartile range. Horizontal lines at platelet counts of $50x10^9$/L represent the threshold for response. (D) The bar diagram shows the percentage of patients who met criteria for the primary (response) and secondary (sustained response) endpoints.

Figure 3. Swimmers Plot of the Duration of Response in Patients Receiving Subcutaneous Daratumumab Injection. Responses shown from baseline to study week 24, week 1 is a week of the first daratumumab treatment. The color indicates platelet count: $<30x10^9$/L (red), 30-$50x10^9$/L (yellow), $>50x10^9$/L (light-blue). Black line indicates exposure to corticosteroids including those used as a concomitant therapy and as a part of daratumumab premedication. At the point of evaluation of response, concomitant therapy was administered to 8 of 21 patients, including thrombopoietin receptor agonist only (n=1), corticosteroids (n=2), both (n=4), and thrombopoietin receptor agonist with sirolimus (n=1). At the point of evaluation for sustained response, concomitant therapy was administered to 8 of 21 patients, including thrombopoietin receptor agonist (n=3), corticosteroids (n=1), both (n=2), mycophenolate mofetil (n=1), and thrombopoietin receptor agonist with sirolimus (n=1); none were responders.

Figure 4. Duration of Response (A) and Time to Treatment Failure (B). Duration of response was defined as the duration of platelet count $\geq 50x10^9$/L in two consecutive blood samples taken at least 24 hours apart, without having received any platelet elevating therapy or having had dose increment of TPO-RA and/or corticosteroids, and starting from minimum 4 weeks following the last daratumumab injection. Loss of response was defined as platelet count $<50x10^9$/L after achieving response, in 2 consecutive blood samples taken at least 24 hours apart. Time to treatment failure was defined as a time with platelet count $\geq 50x10^9$/L from 4 weeks after the last daratumumab injection to the first platelet count $<30x10^9$/L of 2 counts taken in 2 consecutive measurements at least 24 hours apart, or administration of any platelet-elevating therapy after achieving response.

Figure 1. CONSORT Flow Diagram.

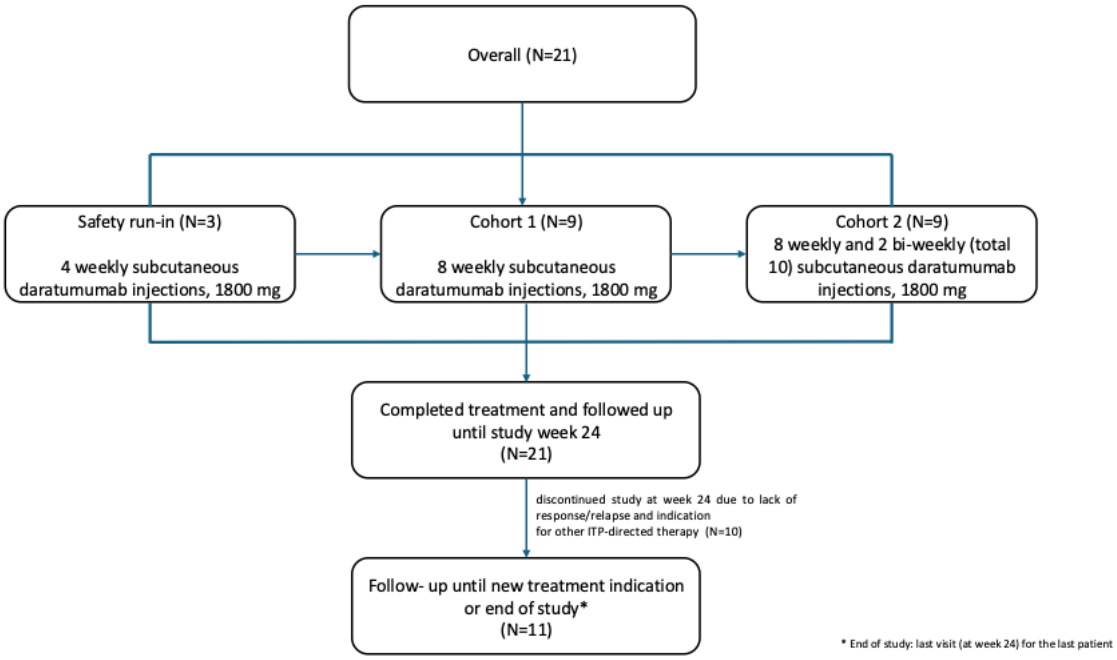

Figure 2. Platelet Counts Over Time in Patients Included in (A) Safety run-in, (B) Study Cohort 1, (C) Cohort 2 and (D) Response Rates.

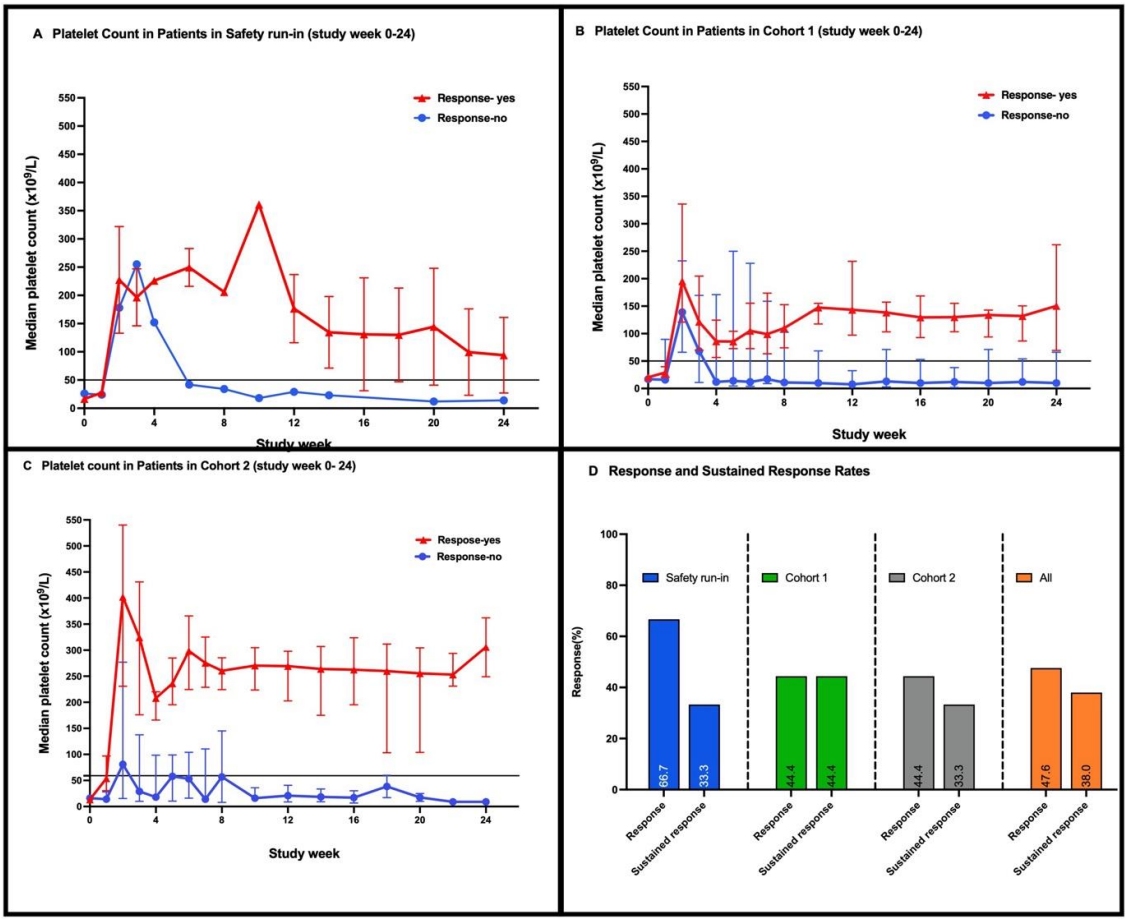

Figure 3. Swimmers Plot of the Duration of Response in Patients Receiving Subcutaneous Daratumumab Injection.

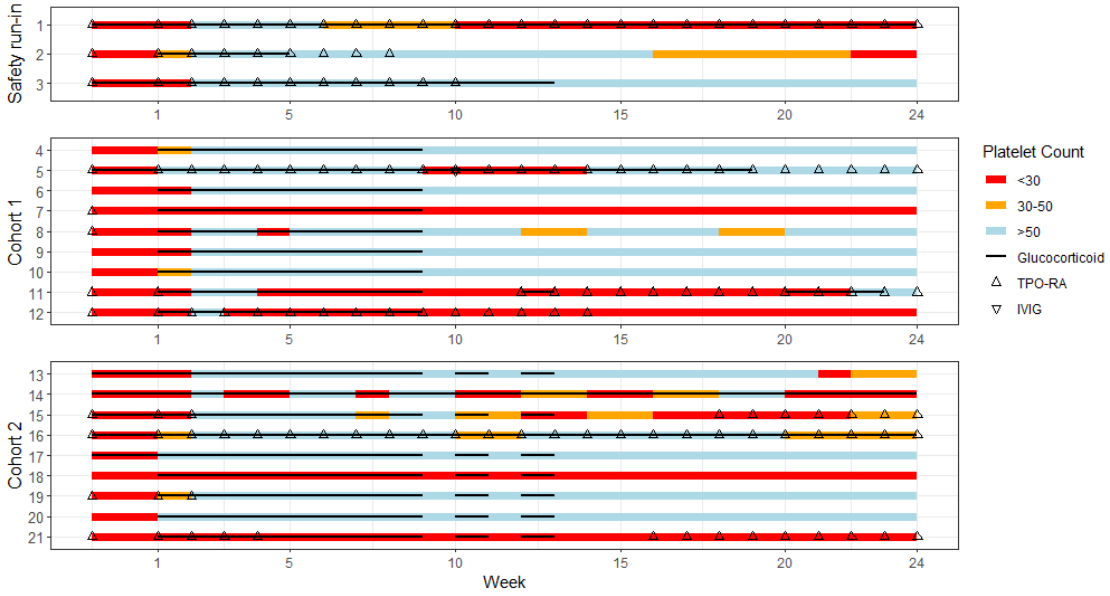

Figure 4. Duration of Response (Panel A) and Time to Treatment Failure (Panel B)