Schjesvold Fredrik (Orcid ID: 0000-0003-1096-0569)
Richardson Paul (Orcid ID: 0000-0002-7426-8865)
Moreau Philippe (Orcid ID: 0000-0003-1780-8746)
Dimopoulos Meletios (Orcid ID: 0000-0001-8990-3254)
Hulin Cyrille (Orcid ID: 0000-0002-3749-5161)

Correspondence

Isatuximab plus pomalidomide and dexamethasone in frail patients with relapsed/refractory multiple myeloma: ICARIA-MM subgroup analysis

Fredrik Schjesvold, MD, PhD,[1] | Sara Bringhen, MD,[2] | Paul Richardson, MD,[3] | Aurore Perrot, MD, PhD,[4] | Xavier Leleu, MD, PhD,[5] | Philippe Moreau, MD,[6] | Meletios Dimopoulos, MD,[7] | Cyrille Hulin, MD,[8] | Christina Tekle, MSc, PhD,[9] | Meredith C. Foster, MPH, ScD,[10] | Elizabeth M. Poole, MSPH, PhD,[10*] | Helgi van de Velde, MD, PhD,[9] | Thierry Facon, MD[11]

[1] Oslo Myeloma Center, Department of Haematology, Oslo University Hospital and KG Jebsen Center for B Cell Malignancies, University of Oslo, Oslo, Norway;

[2] Myeloma Unit, Division of Hematology, University of Torino, Azienda-Ospedaliero Universitaria Città della Salute e della Scienza di Torino, Torino, Italy;

[3] Dana-Farber Cancer Institute, Boston, MA, USA;

[4] CHU de Toulouse, IUCT-O, Université de Toulouse, UPS, Service d'Hématologie, Toulouse, France;

[5] Service d'Hématologie et Thérapie Cellulaire, CHU and CIC Inserm 1402, Poitiers Cedex, France;

[6] University of Nantes, Nantes, France;

[7] Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens School of Medicine, Athens, Greece;

[8] Hôpital Haut-Lévêque CHU, Bordeaux, France;

[9] Sanofi Oncology, Cambridge, MA, USA;

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ajh.26319

[10] Sanofi Genzyme, Global Medical Affairs, Cambridge, MA, USA; *affiliation at time of study, currently bluebird bio, Cambridge, MA, USA;

[11] Hôpital Claude Huriez, Lille, France.

Correspondence: Fredrik Schjesvold, PhD, MD, Oslo Myeloma Center, Oslo University Hospital and KG Jebsen Center for B Cell Malignancies, Sognsvannsveien 20, N-0372 Oslo, Oslo, Norway; Phone: +47 996 97 796; E-mail: fredrikschjesvold@gmail.com.

Keywords: CD38, monoclonal antibody, Phase 3, frail, multiple myeloma, relapsed/refractory

Data availability statement: Qualified researchers can request access to patient-level data and related study documents including the clinical study report, study protocol with any amendments, blank case report forms, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data-sharing criteria, eligible studies, and process for requesting access are at: https://www.clinicalstudydatarequest.com.

Funding statement: The ICARIA-MM study was sponsored by Sanofi.

Conflict of interest statement: F.S.: Honoraria – Amgen, Celgene, Janssen, MSD, Novartis, Oncopeptides, Sanofi, SkyliteDX and Takeda; participation on an entity's Board of Directors or advisory committees – Amgen, Celgene, Janssen, MSD, Novartis, Oncopeptides, Sanofi and Takeda; S.B.: Honoraria – Amgen, Bristol-Myers Squibb, Celgene and Janssen; participation on an entity's Board of Directors or advisory committees – Amgen, Celgene, Janssen and Karyopharm; consultancy – Janssen and Takeda; P.G.R.: Research funding – Bristol-Myers Squibb, Celgene, Oncopeptides and Takeda; honoraria – Celgene, Janssen, Karyopharm, Oncopeptides, Sanofi and Takeda; A.P.: Honoraria – Amgen, Bristol-Myers Squibb/Celgene, Janssen, Sanofi and Takeda; X.L.: Honoraria – AbbVie, Amgen, Bristol-Myers Squibb, Carsgen

Therapeutics Ltd, Celgene, Gilead Sciences, Janssen-Cilag, Karyopharm Therapeutics, Merck, Mundipharma, Novartis, Oncopeptides, Pierre Fabre, Roche, Sanofi and Takeda; Non-financial support – Takeda; P.M.: Honoraria – Amgen, Celgene, Janssen and Sanofi; M.D.: Participation on an entity's Board of Directors or advisory committees – Amgen, Bristol-Myers Squibb, Celgene, Janssen, and Takeda; C.H.: Honoraria – Amgen, Bristol-Myers Squibb/Celgene, and Sanofi; C.T., M.C.F., E.M.P., and H.v.d.V. are employed by Sanofi and may hold shares and/or stock options in the company; T.F.: Participation on an entity's Board of Directors or advisory committees – Amgen, Celgene, Janssen, Karyopharm, Oncopeptides, Roche and Takeda

Ethics approval statement: The protocol was approved by institutional review boards and independent ethics committees of all participating institutions, and was conducted according to the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guideline.

Patient consent statement: All patients provided written informed consent.

Clinical trial registration: ClinicalTrials.gov Identifier: NCT02990338

To the Editor:

Multiple myeloma (MM) typically affects elderly patients, with a median age at diagnosis of 69 years. Treatment is often challenging due to frailty, defined as a state of cumulative decline in physiological function, leading to high risk of adverse health-related outcomes, resulting in increased morbidity and mortality.[1]

The International Myeloma Working Group (IMWG) has developed a frailty score to guide therapy selection in patients with newly diagnosed MM.[2] The IMWG frailty score combines age, comorbidities, and functional status based on the capacity to perform Activities of Daily Living (ADL). Facon et al. developed a simplified frailty score, measuring functional status using the Eastern Cooperative Oncology Group performance status (ECOG PS), a more commonly collected feature in clinical trials than ADL.[3]

On the basis of the pivotal phase 3 ICARIA-MM study (NCT02990338), isatuximab (Isa), a CD38 monoclonal antibody, is approved in a number of countries in combination with pomalidomide and dexamethasone (Pd) for the treatment of adult patients with relapsed/refractory MM (RRMM) who have received ≥ 2 prior therapies, including lenalidomide and a proteasome inhibitor.

ICARIA-MM demonstrated the efficacy and safety of Isa-Pd in patients with RRMM across subgroups.[4] Progression-free survival (PFS) was significantly improved with Isa-Pd versus Pd in patients ≥ 75 years, and health-related quality of life parameters were better maintained in the triplet Isa-Pd arm, including in patients ≥ 75 years.[4,5] This *post-hoc* analysis used a simplified frailty score derived from patient baseline characteristics to investigate the impact of frailty on clinical outcomes and safety.

A total of 307 RRMM patients were randomized to receive Isa-Pd (n = 154) or Pd (n = 153) and stratified by age (< 75 vs ≥ 75 years) and number of prior lines of therapy (2–3 vs > 3). Frailty

scores at baseline were calculated based on age, modified Charlson Comorbidity Index (CCI), and ECOG PS (Supplementary Materials). The modified CCI was calculated using detailed medical history recorded during screening visit and coded with MedDRA version 21.0 for analysis.

The overall ICARIA-MM population comprised 28.0% frail (score sum ≥ 2) and 69.4% fit/intermediate patients; 8 (2.6%) patients were excluded from the analysis because no medical history was available (Table S1). There were more frail patients in the Isa-Pd arm (31.2%) versus Pd arm (24.8%), although this difference is non-significant (p = 0.2167). As expected, frail patients were older and had a higher ECOG PS than fit/intermediate patients in both arms. Additionally, a greater proportion of frail patients had International Staging System (ISS) stage III disease (p = 0.0015). This can be partially explained by the fact that frail patients were on average 10 years older than fit/intermediate patients and the parameters used for ISS staging changes worsen with age, without necessary reflecting increasing tumor load. Other patient baseline characteristics were generally balanced (Table S1).

The PFS benefit of Isa-Pd versus Pd in frail and fit/intermediate patients was consistent with that in overall study population although not statistically significant (Figure 1A). For frail patients, median PFS was 9.0 months with Isa-Pd versus 4.5 months with Pd (HR 0.81; 95% CI 0.45–1.48; log-rank p = 0.4928). For fit/intermediate patients, median PFS was 12.7 months for Isa-Pd versus 7.4 months for Pd (HR 0.49; 95% CI 0.33–0.73; log-rank p = 0.0004; Figure 1A). At the time of analysis, overall survival (OS) data were not yet mature, and the log-rank p value for the median OS in Isa-Pd versus Pd was 0.3053 for frail and 0.0689 for fit/intermediate patients, respectively (Figure 1B). One-year OS probability in frail patients was 66.9% (95% CI 0.51–0.79) with Isa-Pd versus 58.8% (95% CI 0.41–0.73) with Pd, and in fit/intermediate patients was 75.0% (95% CI 0.65–0.83) with Isa-Pd versus 64.5% (95% CI 0.54–0.73) with Pd.

The overall response rate (ORR) and very good partial response or better (≥VGPR) rate were higher with Isa-Pd versus Pd regardless of frailty status (Figure 1C). In frail patients, ORR was 52.1% with Isa-Pd versus 34.2% with Pd (p = 0.0476). In fit/intermediate patients, ORR was 66.3% with Isa-Pd versus 35.7% with Pd (p < 0.0001). In frail patients, ≥VGPR rate was 29.2% with Isa-Pd versus 2.6% with Pd (p = 0.0013), and in fit/intermediate patients, this rate was 34.7% with Isa-Pd versus 10.7% with Pd (p < 0.0001, Figure 1C). Of note, the difference in the ORR rate between with frail and fit/intermediate patients receiving Isa-Pd was not statistically significant (p = 0.3971).

Whereas no patients in the Pd arm achieved minimal residual disease (MRD) negativity (evaluated with investigator-assessed complete response at 10^{-5} sensitivity by next-generation sequencing), 8/149 (5.4%) patients in the Isa-Pd arm had MRD negativity, with 4 patients each in the frail and fit/intermediate subgroups.

Treatment duration was longer with Isa-Pd for both frail and fit/intermediate patients (Table S2). The median (range) duration of exposure with Isa-Pd versus Pd was 40.8 (1.3–75.1) versus 22.1 (1.6–69.0) weeks for frail patients and 41.6 (4.0–76.7) versus 24.0 (1.0–73.7) weeks for fit/intermediate patients. Additionally, the median (range) number of cycles started with Isa-Pd versus Pd was 9.5 (1–18) versus 5.5 (1–17) in frail patients and 10.0 (1–19) versus 6.0 (1–18) in fit/intermediate patients. The relative dose intensity for the three drugs was slightly lower in frail patients than in fit/intermediate patients, because they had higher reduction rates due to treatment-emergent adverse events (TEAEs; Table S2).

All frail patients in both treatment arms experienced TEAEs (Table S3). All fit/intermediate patients in the Isa-Pd arm experienced TEAEs, versus 98.2% in the Pd arm. The most common any-grade non-hematologic TEAE in Isa-Pd versus Pd was diarrhea for frail patients (33.3% vs 27.8%) and infusion reactions (40.0% vs 0%) for fit/intermediate patients. Fewer infusion reactions were observed in frail patients (31.3%) compared with fit/intermediate patients

(40.0%) treated with Isa-Pd *(p* = 0.3025). In the Isa-Pd arm, TEAEs with the greatest difference in incidence in frail and fit/intermediate patients were dyspnea (25.0% and 10.0%) and pyrexia (20.8% and 12.0%), respectively. There were more upper respiratory tract infections in patients receiving Isa-Pd versus Pd independently of their frail status (Table S3).

Anemia and thrombocytopenia rates were similar in the Isa-Pd and Pd arms for both frail and fit/intermediate patients (Table S4). Grade 4 neutropenia was more common in patients in the Isa-Pd versus Pd arm, independent of their frailty status: 68.8% versus 31.4% in frail patients and 58.0% versus 31.8% in fit/intermediate patients (Table S4). The incidence of febrile neutropenia (all Grade ≥ 3) was 12.5% in the Isa-Pd versus none in the Pd arm for frail patients and 12.0% in the Isa-Pd versus 2.7% in the Pd arm for fit/intermediate patients.

Death during treatment with Isa-Pd versus Pd occurred in 10.4% versus 11.1% of frail patients and 6.0% versus 9.0% of fit/intermediate patients. Regardless of frailty status, fewer patients in the Isa-Pd arm discontinued treatment due to TEAEs, and they had greater time to treatment discontinuation compared with the Pd arm. Treatment discontinuation due to TEAEs in Isa-Pd versus Pd occurred in 8.3% versus 16.7% of frail patients and 7.0% versus 11.7% of fit/intermediate patients. Median time to premature or definitive treatment discontinuation for Isa-Pd versus Pd in frail patients was 8.7 versus 4.9 months (HR 0.68; 95% CI 0.40–1.16; *p* = 0.1546) and in fit/intermediate patients was 9.4 versus 5.3 months (HR 0.61; 95% CI 0.43−0.86; *p* = 0.0041) (Figure S1). The reasons for definitive treatment discontinuation are shown on Table S5.

There are limitations to this analysis, as this was not a prespecified subgroup analysis and the ICARIA-MM study did not enroll daratumumab-refractory patients. CCI score modifications were applied to the simplified frailty score to use the available data to classify patients. Although the IMWG frailty score uses the patient-completed ADL questionnaires for functional status,[2] recent frailty analyses have used ECOG PS as a proxy.[3,6,7] ADL questionnaires are time-consuming

and prone to subjectivity,[1] and usually not collected in clinical trials, including ICARIA-MM. Meanwhile, the ECOG PS is assessed by physicians and is commonly used in studies such as ICARIA-MM, and in clinical practice. Additionally, the simplified frailty score was recently externally validated in a large, non-trial, real-world population cohort of transplant ineligible newly diagnosed MM patients.[8]

Two recent analyses showed that the simplified frailty score predicted clinical outcomes in patients with RRMM treated with lenalidomide and dexamethasone (for whom bortezomib treatment had failed),[7] and with carfilzomib-containing regimens (*post-hoc* analysis of the ASPIRE, ENDEAVOR, and ARROW phase 3 trials).[6] To our knowledge, this is the first *post-hoc* analysis to show the benefit of a triplet regimen compared with a doublet therapy in frail patients with RRMM in the later-line setting. Frail patients in either arm had worse outcomes than fit/intermediate patients, suggesting that the simplified frailty score could properly identify the frail cohort.

In ICARIA-MM, clinical outcomes (PFS, 1-year OS, ORR, and ≥VGPR) in frail patients tended to improve for Isa-Pd versus Pd. The prolongation of the median PFS with Isa-Pd in frail patients (4.5 months improvement; HR 0.81; 95% CI 0.45–1.48) was consistent with the increase in median PFS observed in patients ≥ 75 years (6.9 months improvement; HR 0.48; 95% CI 0.24–0.95) and in the overall population (5 months improvement; HR 0.60; 95% CI 0.44–0.81).[4,5] The toxicities observed in frail patients treated with Isa-Pd were manageable and similar to those observed in fit/intermediate patients, with comparable treatment discontinuation rate, treatment duration, and incidence of hematologic TEAEs.

In conclusion, the response, long-term treatment benefit, and safety profile of frail patients treated with Isa-Pd are consistent with the elderly and the overall study populations, showing the feasibility of this triplet regimen in the frail population. Fewer frail patients discontinued Isa-Pd than Pd treatment due to TEAEs, further supporting the benefit of Isa-Pd in both frail and

fit/intermediate patients with RRMM, and the translation of this triplet regimen to real-world practice.

Author contributions

F.S., S.B., A.P., X.L., P.M., M.D., C.H., P.G.R., and T.F. were investigators in the study and contributed to data acquisition. P.G.R. was a coprimary investigator of the ICARIA-MM study. C.T., M.C.F., E.M.P., and H.v.d.V. contributed to the analysis and interpretation of data for the work. All authors revised the work for important intellectual content and assume responsibility for data integrity and the decision to submit this manuscript for publication; had full access to the study data; and edited, and reviewed manuscript drafts, and approved the final version for submission.

Acknowledgements

The ICARIA-MM study was sponsored by Sanofi. We thank the participating patients and their families, and the study centers and investigators, for their contributions to the study. We thank Professor Michel Attal from the Institut Universitaire du Cancer de Toulouse-Oncopole, Toulouse, France, who was a coprimary investigator of the ICARIA-MM study. Medical writing support was provided by Camile Semighini Grubor, PhD, of Elevate Medical Affairs, contracted by Sanofi Genzyme for publication support services.

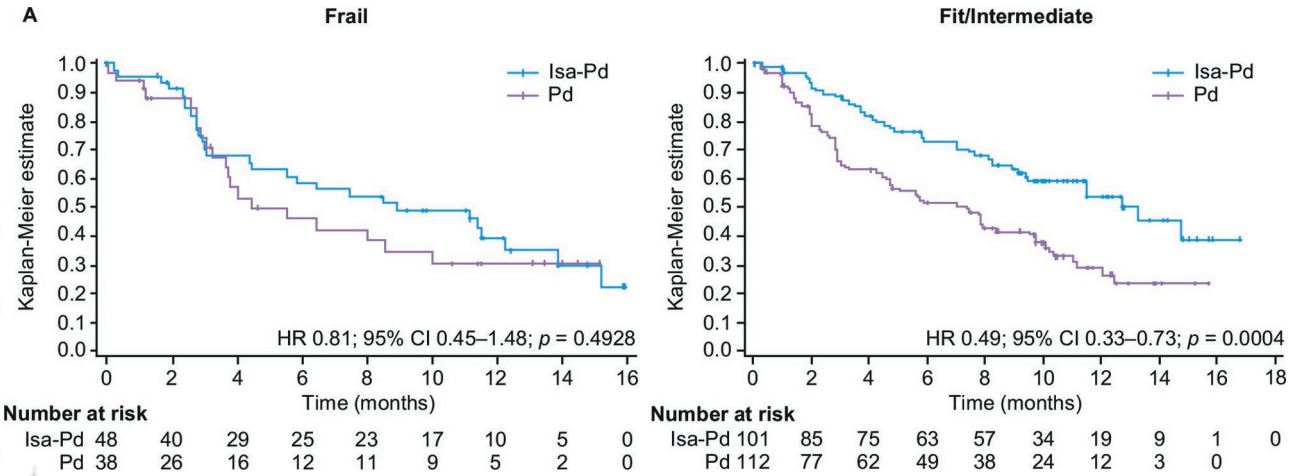
References

1. Cook G, Larocca A, Facon T, Zweegman S, Engelhardt M. Defining the vulnerable patient with myeloma-a frailty position paper of the European Myeloma Network. *Leukemia*. 2020;34(9):2285-2294.
2. Palumbo A, Bringhen S, Mateos M-V, et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report. *Blood*. 2015;125(13):2068-2074.
3. Facon T, Dimopoulos MA, Meuleman N, et al. A simplified frailty scale predicts outcomes in transplant-ineligible patients with newly diagnosed multiple myeloma treated in the FIRST (MM-020) trial. *Leukemia*. 2020;34(1):224-233.
4. Attal M, Richardson PG, Rajkumar SV, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and

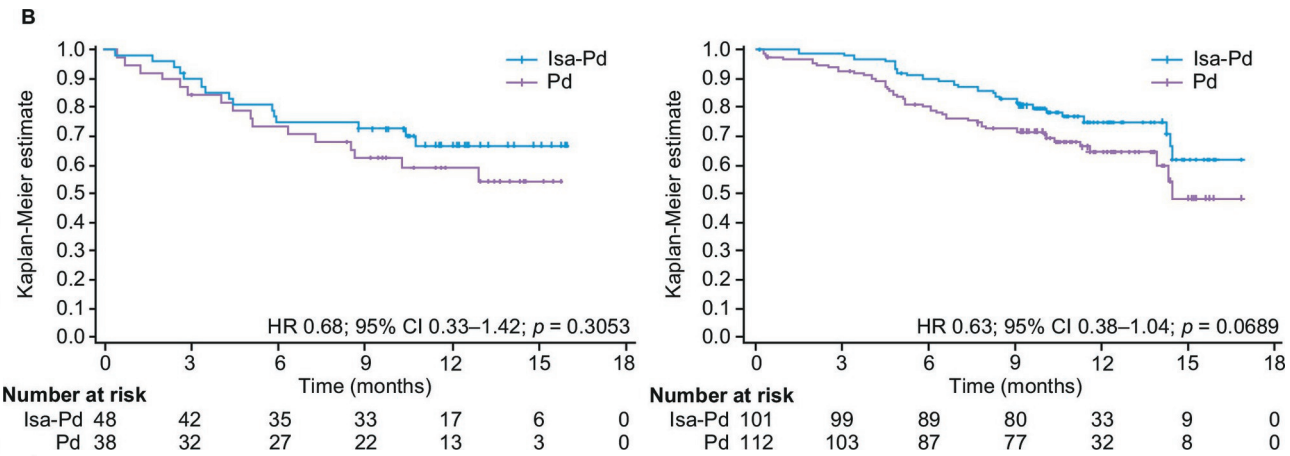
refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. *Lancet*. 2019;394(10214):2096-2107.
5. Schjesvold F, Richardson P, Facon T, et al. Efficacy of Isatuximab with Pomalidomide and Dexamethasone in Elderly Patients with Relapsed/Refractory Multiple Myeloma: Icaria-MM Subgroup Analysis. *Haematologica*. 2020;105.
6. Facon T, Niesvizky R, Mateos MV, et al. Efficacy and safety of carfilzomib-based regimens in frail patients with relapsed and/or refractory multiple myeloma. *Blood Adv*. 2020;4(21):5449-5459.
7. Lee HS, Kim K, Lee JJ, et al. Clinical impact of frailty on treatment outcomes of elderly patients with relapsed and/or refractory multiple myeloma treated with lenalidomide plus dexamethasone. *Int J Hematol*. 2020.
8. Mian HS, Giri S, Wildes TM, et al. External validation of the FIRST trial's simplified frailty score in a population-based cohort. *Leukemia*. 2021;35(6):1823-1827.

Figure Legend

FIGURE 1 (A) Progression-free survival, (B) overall survival and (C) overall response rate in frail vs fit/intermediate patients in the ICARIA-MM study. (A) Kaplan-Meier analysis of progression-free survival in the intention-to-treat population as assessed by an Independent Response Committee. HR and corresponding 95% CI are from a Cox proportional hazard model stratified by age and number of previous lines of therapy. P values were derived from a log-rank test. (B) Kaplan-Meier analysis of overall survival in the intention-to-treat population, at the time of the primary analysis on progression-free survival. HR and corresponding 95% CI are presented. P values were derived from a log-rank test. Patients remaining alive at their last contact were censored at the last date known to be alive or the cut-off date, whichever was earlier. (C) Overall response rate based on Independent Response Committee assessment in the Isa-Pd vs Pd arms of the ICARIA-MM study in frail and fit/intermediate patients. CI, confidence interval; CR, complete response; d, dexamethasone; HR, hazard ratio; Isa, isatuximab; ORR, overall response rate; P, pomalidomide; PR, partial response; sCR: stringent complete response; VGPR, very good partial response

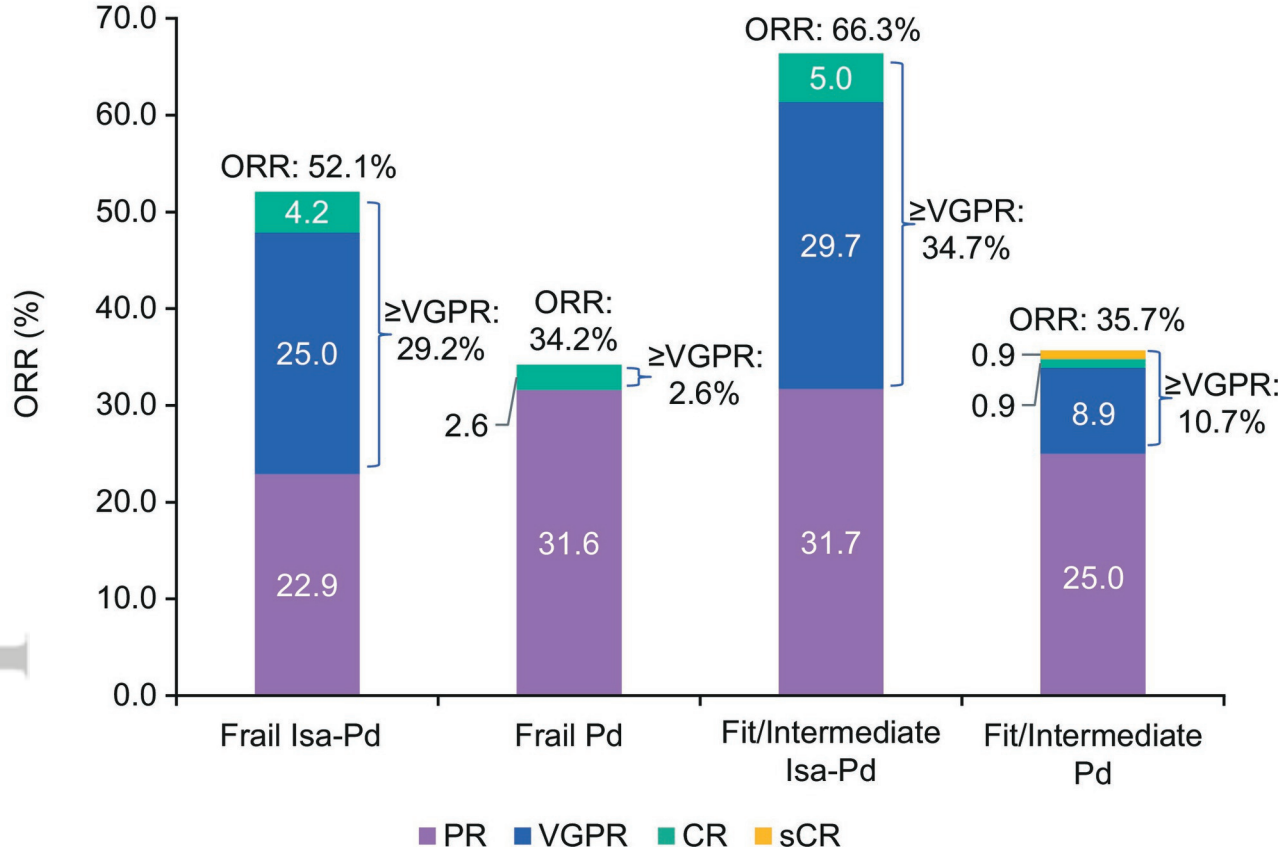


ajh_26319_ajh-21-0850_figure 1a.eps



ajh_26319_ajh-21-0850_figure 1b.eps

c



ajh_26319_ajh-21-0850_figure 1c.eps