

Analysis of Daratumumab Benefit in High- and Standard-Risk Patients in the PERSEUS/EMN017 Study Using IMS/IMWG Risk Criteria by NGS

Introduction^{1,2}

- Prognostic factors based on the use of older therapies for multiple myeloma (MM) are insufficient in an era of novel triplet and quadruplet therapies¹
- Updates in risk stratification systems are needed to ensure relevance for current MM treatment options¹
- The IMS/IMWG recently proposed novel Consensus Genomic Staging (CGS) high-risk criteria for newly diagnosed MM (NDMM), including genetic alterations not identifiable by classic fluorescence in situ hybridization (FISH) but by next-generation sequencing (NGS) (e.g., *TP53* mutations)¹
- PERSEUS is a phase 3 clinical trial of patients with transplant eligible (TE)-NDMM randomized 1:1 to receive DVRd or VRd²
- The use of DVRd plus DR maintenance led to a greater depth of response and longer PFS than with VRd plus R maintenance²

DARZALEX FASPRO® is indicated for the treatment of adult patients with multiple myeloma in combination with bortezomib, lenalidomide, and dexamethasone for induction and consolidation in newly diagnosed patients who are eligible for ASCT³

Please read full [Prescribing Information](#), including complete list of indications for DARZALEX FASPRO®

DARZALEX FASPRO®
Safety Information
Summary



PERSEUS study⁴

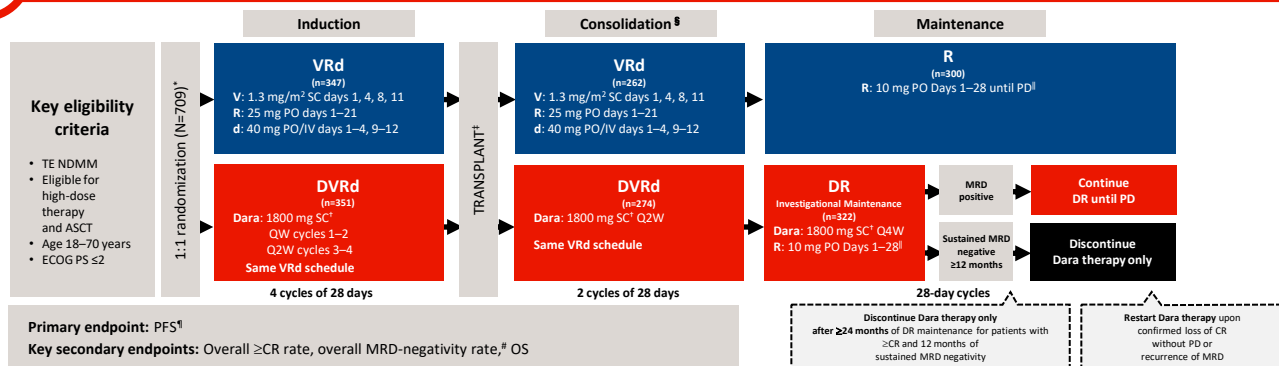


Figure adapted with permission from Sonneveld P, et al. Presented at ASH 2023. Oral presentation LBA-1. "Stratified by ISS stage and cytogenetic risk." Dara 1800 mg co-formulated with rHuPH20 (2000 U/mL; ENHANZE® drug delivery technology, Halozyme, Inc., San Diego, CA, USA). [†]Stem cell mobilization was performed within 6 weeks after completion of induction cycle 4 using local standard of care, for example, cyclophosphamide, granulocyte colony-stimulating factor, and plerixafor. [‡]Consolidation began 30–60 days post-ASCT. [§]R maintenance increased to 15 mg after 3 cycles, if tolerated. [¶]PFS was defined as the time from randomization to disease progression or death (whichever occurred first). ^{¶¶}Overall MRD-negativity was defined as occurring in patients who achieved both MRD negativity (at or below a threshold of 10⁻⁵) and a ≥CR at any time during the study after randomization.

These results are based on the full treatment regimen and include investigational maintenance of DARZALEX FASPRO® + R following post-transplant consolidation. The trial was not designed to isolate the effect of DARZALEX FASPRO® in the maintenance phase of treatment. The efficacy of DARZALEX FASPRO® + R for maintenance has not been established.

Demographic and baseline characteristics*²

DVRd (n=355)	Characteristics	VRd (n=354)
1.2 (0–46.5)	Median time since MM dx (range), mo	1.1 (0.1–184.6)
61 (32–70)	Median age (range), years	59 (31–70)
211 (59.4)	Male sex, n (%)	205 (57.9)
4 (1.1)	Race, n (%)	6 (1.7)
5 (1.4)	Asian	4 (1.1)
330 (93.0)	Black	323 (91.2)
4 (1.1)	White	3 (0.8)
12 (3.4)	Other	18 (5.1)
221 (62.3)	Missing data	230 (65.0)
14 (4.1)	ECOG PS, n (%) [†]	108 (30.5)
19 (5.4)	0	16 (4.5)
1 (0.3)	1	0
204 (57.5)	2	0
65 (18.3)	3	0
13 (3.7)	Type of measurable disease, n (%)	185 (52.3)
43 (12.1)	IgG	85 (24.0)
29 (8.2)	IgA	11 (3.1)
1 (0.3)	Other [§]	46 (13.0)
186/355 (52.4)	Detected in urine only	27 (7.6)
114/355 (32.1)	Detected in s free light chains only	0
55/355 (15.5)	Type could not be evaluated	0
264/354 (74.4)	ISS disease stage, n/total n (%)	178/353 (50.4)
76 (21.4)	I	125/353 (35.4)
15 (4.2)	II	50/353 (14.2)
	III	266 (75.1)
	Cytogenetic risk, n (%) [¶]	78 (22.0)
	Standard	10 (2.8)
	High	0
	Indeterminate	0

*DVRd group received DVRd induction/consolidation and DR maintenance; VRd group received VRd induction/consolidation and R maintenance alone. ITT included all randomized patients. [†]Race was patient-reported. [‡]ECOG PS ranges 0–5; higher scores indicate greater disability (1 patient scored 0 at randomization, 3 at baseline). [§]Other measurable disease: IgD, IgM, IgE, biconal. ^{||}ISS stages (higher = more severe): I, serum β₂-microglobulin <3.5 mg/L (300 nmol/L) and albumin ≥3.5 g/dL; II, neither I nor III; III, serum β₂-microglobulin ≥5.5 mg/L (470 nmol/L). [¶]Cytogenetic risk assessed by FISH; high risk = del(17p), t(4;14), or t(14;16).

ASCT, autologous stem cell transplant; CI, confidence interval; CGS, Consensus Genomic Staging; CR, complete response; d, dexamethasone; Dara, daratumumab; DR, daratumumab and lenalidomide; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; dx, diagnosis; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; HR, hazard ratio; Ig, immunoglobulin; IMWG, International Myeloma Working Group; IMS, International Myeloma Society; ISS, international staging system; ITT, intention to treat; IV, intravenous; MM, multiple myeloma; mo, month; MRD, minimal residual disease; NDMM, newly diagnosed MM; NGS, next-generation sequencing; OS, overall survival; PD, progressive disease; PFS, progression free survival; PO, oral; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; R, lenalidomide; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous; s, serum; TE, transplant eligible; V, bortezomib; VRd, bortezomib, lenalidomide, and dexamethasone.

1. Avet-Loiseau H, et al. *J Clin Oncol* 2025;43:2739–2751. 2. Sonneveld P, et al. *N Engl J Med*. 2024;390(4):301–313. 3. DARZALEX FASPRO® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.; 4. Sonneveld P, et al. Presented by at the American Hematology Society (ASH) Annual Meeting; Dec 9–12, 2023; San Diego, CA, US. 5. Data on file. Janssen Biotech, Inc.

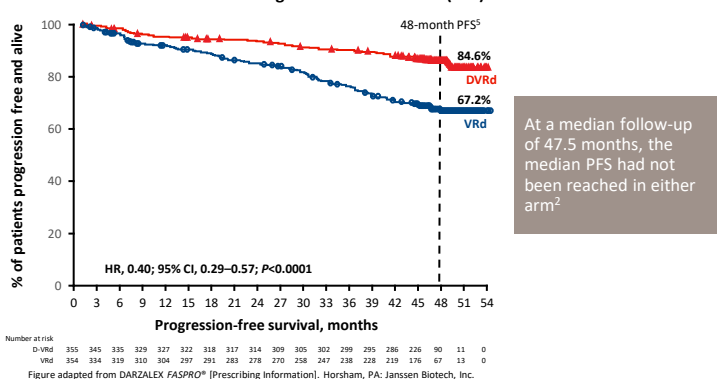
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Progression-free survival (PFS)³



Minimal residual disease (MRD)

	DVRd (n=355)	VRd (n=354)
MRD negativity rate ^{¶, ,¶¶} n (%)	204 (57.5)	115 (32.5)
95% CI (%) ^{¶¶}	52.1–62.7	27.6–37.6
MRD negativity rate in patients with CR or better	n=158	n=123
MRD negativity rate n (%)	121 (76.6)	72 (58.5)
95% CI (%) ^{¶¶}	(69.2–82.9)	(49.3–67.3)

^{||} Based on intent-to-treat population; ^{||} Based on threshold of 10⁻⁵ using a next-generation sequencing assay (clonoSEQ); [¶] Patients achieved both MRD negativity (threshold of 10⁻⁵) and response of CR or better; ^{¶¶} Exact 95% confidence interval

Adverse reactions (≥10%) in patients who received DVRd through the end of consolidation³

	DVRd (N=351)		VRd (N=347)	
Adverse reaction	All grades (%)	Grade 3 or 4 (%)	All grades (%)	Grade 3 or 4 (%)
Nervous system disorders				
Peripheral neuropathy [†]	52	5	54	4
Paresthesia	11	<1 [#]	11	<1 [#]
General disorders and administration site conditions				
Fatigue [‡]	35	3 [#]	37	5 [#]
Edema [‡]	22	1	21	1 [#]
Pyrexia	21	2 [#]	22	3 [#]
Infections				
URTI [§]	32	1 [#]	26	2 [#]
Pneumonia [‡]	14	9	10	6 [¶]
Gastrointestinal disorders				
Constipation	31	2 [#]	30	2 [#]
Diarrhea	23	3 [#]	25	5 [#]
Nausea	16	1 [#]	12	1 [#]
Abdominal pain [‡]	11	0	12	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain [‡]	26	1 [#]	23	1 [#]
Muscle spasm	12	0	9	<1 [#]
Psychiatric disorders				
Insomnia	26	2 [#]	16	2 [#]
Skin and subcutaneous tissue disorders				
Rash [‡]	25	3 [#]	31	5
Hepatobiliary disorders				
Hepatotoxicity [¶]	16	6 [#]	16	5
Respiratory, thoracic and mediastinal disorders				
Cough [‡]	12	<1 [#]	8	0

[†]Denominator is based on number of subjects with a baseline and post-baseline lab value for each lab test. [‡]Peripheral neuropathy includes neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, and peripheral sensory neuropathy. [§]Includes other related terms. [¶]Upper respiratory tract infection includes fungal pharyngitis, h1n1 influenza, influenza, influenza like illness, laryngitis, nasopharyngitis, oral candidiasis, oropharyngeal candidiasis, parainfluenzae virus infection, pharyngitis, respiratory moniliasis, respiratory syncytial virus infection, respiratory tract infection, respiratory tract infection viral, rhinitis, rhinovirus infection, sinusitis, tonsillitis, upper respiratory tract infection, viral tonsillitis, and viral upper respiratory tract infection. [‡]Pneumonia includes bronchopulmonary aspergillosis, lower respiratory tract infection, pneumocystis jirovecii pneumonia, pneumonia, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia influenza, pneumonia klebsiella, pneumonia legionella, and pneumonia streptococcal. [¶]Hepatotoxicity includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic cytolysis, hepatic failure, hepatic function abnormal, hepatotoxicity, hyperbilirubinemia, hypertransaminasemia, and liver disorder. [#]Only Grade 3 adverse reactions occurred. [¶]Fatal adverse reactions included Pneumonia: n=1 (0.3%) in the VRd arm.

The cytogenetic subgroup analyses are not included in the Prescribing Information for DARZALEX Faspro® and have not been evaluated by the FDA. These analyses were conducted post hoc, and there are insufficient numbers of patients per subgroup to make conclusions of efficacy among the subgroups.

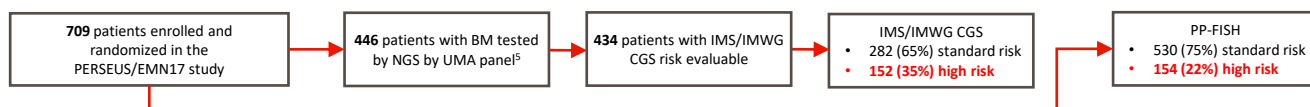
IMS/IMWG CGS high-risk criteria for NDMM^{1,2,4}

Risk subgroup	Definition
PP-FISH high risk ^{2,4}	Defined per protocol as ≥1 del17p, t(4;14), and/or t(14;16)
IMS/IMWG CGS high risk ^{1,4}	Defined as the presence of at least one of the following: • del17p[#] and/or TP53 mutation** • t(4;14) or t(14;16) or t(14;20) with additional amp1q or biallelic del1p • Monoallelic del1p with additional amp1q, or biallelic del1p** • High β2M with normal renal function

[#]Cancer cell fraction (CCF) ≥20%, by analyses conducted on CD138+/purified cells; **Assessed using an NGS-based method.

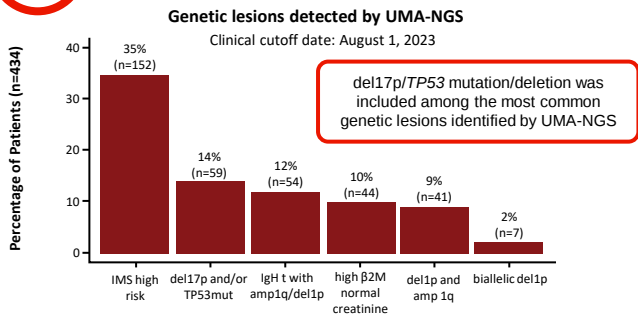
PERSEUS cytogenetic/genomic analysis^{4,5}

AIM: This expanded post hoc analysis investigated clinical outcomes based on the presence of high-risk MM, as defined by the new IMS/IMWG CGS risk criteria utilizing the recently developed NGS-based UMA target panel^{4,5}.

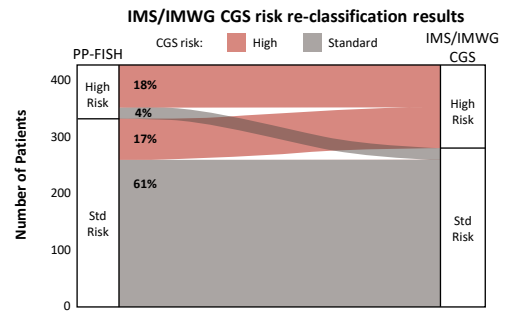


The UMA-NGS panel stratified risk according to CGS, identifying ≥12% more high-risk patients in the PERSEUS study vs those identified using PP-FISH⁴

Risk re-classification⁴

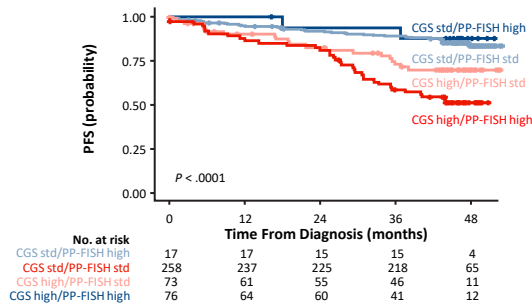


- IMS/IMWG CGS reclassified 17% of patients from standard to high risk,¹ with only 4% being reclassified from high to standard risk with improved risk classification
- The most common genetic lesions were del17p/TP53 (n=59, 14%), IgH translocation with amp1q/del1p (12%), and del1p with amp1q (9%); 2% had biallelic focal del1p

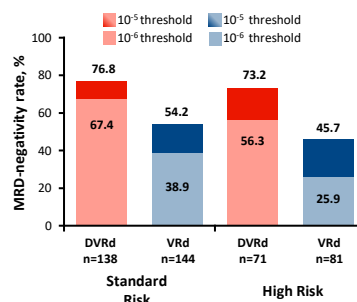


Risk re-classification (cont.)⁴

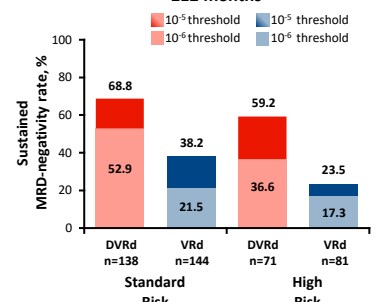
PFS in patients with re-classified risk status based on PP-FISH and IMS/IMWG CGS



Overall MRD-negative ≥CR rates[†]

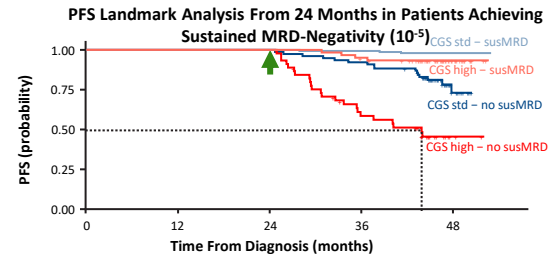
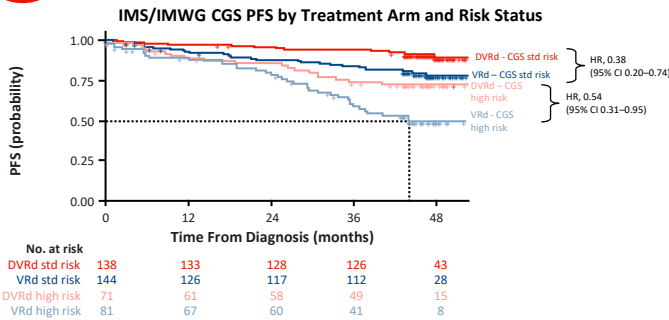


Sustained MRD-negative ≥CR rates for ≥12 months[‡]



[†]Bone marrow MRD was assessed using NGS (clonoSEQ[®]). [‡]Overall MRD-negativity rate was defined as the proportion of patients who achieved both ≥CR and MRD-negative status. [§]Sustained MRD negativity was defined, in patients with ≥CR, as confirmed MRD negativity ≥12 ± 1 months apart without any MRD positivity in between.

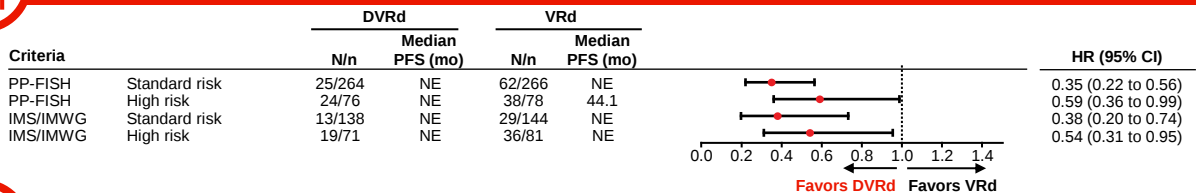
PFS and MRD negativity⁴



No. at risk

Time From Diagnosis (months)	0	12	24	36	48
CGS std - susMRD	150	150	150	149	55
CGS high - susMRD	61	61	61	57	19
CGS std - no susMRD	77	77	77	71	12
CGS high - no susMRD	46	46	46	24	3

PFS based on cytogenetic risk by PP-FISH and IMS/IMWG CGS risk by UMA-NGS⁴



Conclusions⁴

- In these post hoc analyses, outcomes observed with DVRd treatment were generally consistent across cytogenetic risk and risk classification subgroups in TE NDMM
- This study is the first to re-stratify patients with TE NDMM from a Phase 3 trial using IMS/IMWG CGS

SAFETY INFORMATION SUMMARY: DARZALEX FASPRO®

CONTRAINDICATIONS: DARZALEX FASPRO® is contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase, or any of the components of the formulation.

WARNINGS AND PRECAUTIONS

Hypersensitivity and Other Administration Reactions

Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO®. Fatal reactions have been reported with daratumumab-containing products, including DARZALEX FASPRO®.

Systemic Reactions

In a pooled safety population of 1446 patients with multiple myeloma (N=1235) or light chain (AL) amyloidosis (N=193) who received DARZALEX FASPRO® as monotherapy or as part of a combination therapy, 7% of patients experienced a systemic administration-related reaction (Grade 2: 3%, Grade 3: 0.8%, Grade 4: 0.1%).

In all patients (N=1639), systemic administration-related reactions occurred in 7% of patients with the first injection, 0.5% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 4 minutes to 3.5 days). Of the 283 systemic administration-related reactions that occurred in 135 patients, 240 (85%) occurred on the day of DARZALEX FASPRO® administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

Severe reactions included hypoxia, dyspnea, hypertension, tachycardia, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension, and blurred vision.

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen, and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO®. Consider administering corticosteroids and other medications after the administration of DARZALEX FASPRO® depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions.

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with daratumumab-containing products. If ocular symptoms occur, interrupt DARZALEX FASPRO® and seek immediate ophthalmologic evaluation prior to restarting DARZALEX FASPRO®.

Local Reactions

In this pooled safety population of 1446 patients with multiple myeloma (N=1253) or light chain amyloidosis (N=193), injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 1.1%. The most frequent (>1%) injection-site reaction was injection-site erythema and injection-site rash. In patients with high-risk smoldering multiple myeloma (N=193), injection-site reactions occurred in 28% of patients, including Grade 2 reactions in 3%. These local reactions occurred at a median of 6 minutes (range: 0 minutes to 6.5 days) after starting administration of DARZALEX FASPRO®. Monitor for local reactions and consider symptomatic management.

Infections DARZALEX FASPRO® can cause serious, life-threatening, or fatal infections. In patients who received DARZALEX FASPRO® in a pooled safety population including patients with smoldering multiple myeloma and light chain (AL) amyloidosis (N=1639), serious infections, including opportunistic infections, occurred in 24% of patients, Grade 3 or 4 infections occurred in 22%, and fatal infections occurred in 2.5%. The most common type of serious infection reported was pneumonia (8.5%).

Monitor patients for signs and symptoms of infection prior to and during treatment with DARZALEX FASPRO® and treat appropriately. Administer prophylactic antimicrobials according to guidelines.

Neutropenia Daratumumab may increase neutropenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX FASPRO® until recovery of neutrophils. In lower body weight patients receiving DARZALEX FASPRO®, higher rates of Grade 3-4 neutropenia were observed.

Thrombocytopenia Daratumumab may increase thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer’s prescribing information for background therapies. Consider withholding DARZALEX FASPRO® until recovery of platelets.

Embryo-Fetal Toxicity Based on the mechanism of action, DARZALEX FASPRO® can cause fetal harm when administered to a pregnant woman. DARZALEX FASPRO® may cause depletion of fetal immune cells and decreased bone density.

Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX FASPRO® and for 3 months after the last dose.

The combination of DARZALEX FASPRO® with lenalidomide, thalidomide, or pomalidomide is contraindicated in pregnant women because lenalidomide, thalidomide, and pomalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide, thalidomide, or pomalidomide prescribing information on use during pregnancy.

Interference With Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive indirect antiglobulin test (indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum. The determination of a patient’s ABO and Rh blood type are not impacted.

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX FASPRO®. Type and screen patients prior to starting DARZALEX FASPRO®.

Interference With Determination of Complete Response: Daratumumab is a human immunoglobulin G (IgG) kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some DARZALEX FASPRO®-treated patients with IgG kappa myeloma protein.

ADVERSE REACTIONS In multiple myeloma, the most common adverse reaction (≥20%) with DARZALEX FASPRO® monotherapy is upper respiratory tract infection. The most common adverse reactions with combination therapy (≥20% for any combination) include fatigue, nausea, diarrhea, dyspnea, sleep disorder, headache, rash, renal impairment, motor dysfunction, pyrexia, cough, muscle spasms, back pain, vomiting, hypertension, musculoskeletal pain, decreased appetite, urinary tract infection, abdominal pain, upper respiratory tract infection, peripheral neuropathy, peripheral sensory neuropathy, constipation, pneumonia, edema, dizziness, bruising, and COVID-19.

The most common hematology laboratory abnormalities (≥40%) with DARZALEX FASPRO® are decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin.

DARZALEX FASPRO® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.



Please read full Prescribing Information for DARZALEX FASPRO®.

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