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Daratumumab [Medicare]

Clinical Policy Bulletins | Medical Clinical Policy Bulletins

Number: 0904m

Commercial CPB (0904.html) | Medicare CPB

Medicare Part B Step Therapy Criteria

Darzalex, **Darzalex Faspro**, and **Kyprolis**, for the indications listed below:

- Treatment of adult patients with multiple myeloma

  Are not covered for new starts, unless the member meets ANY of the following:

  1. Inadequate response to a trial of bortezomib or Velcade
  2. Intolerable adverse event to bortezomib or Velcade
  3. Bortezomib or Velcade is contraindicated for the member.

Policy

Note: Requires Precertification:

Policy History

Effective: 01/01/2022

Next Review: 12/08/2022

Definitions

Additional Information

Clinical Policy Bulletin Notes

Precertification of daratumumab (Darzalex) and daratumumab/hyaluronidase-fihj (Darzalex Faspro) are required of all Aetna participating providers and members in applicable plan designs. For precertification of daratumumab or daratumumab/hyaluronidase-fihj, call (866) 752-7021 or fax (866) 267-3277.

I. Criteria for Initial Approval

Aetna considers daratumumab for intravenous use (Darzalex) or daratumumab and hyaluronidase-fihj for subcutaneous use (Darzalex Faspro) medically necessary for the following indications:

A. *Multiple Myeloma (MM) - daratumumab (Darzalex) or daratumumab/hyaluronidase-fihj (Darzalex Faspro)*

When *any* of the following criteria are met:

1. The requested medication will be used in combination with lenalidomide and dexamethasone and *either* of the following criteria is met:

    a. The member is not a candidate for transplant and the regimen will be used as primary therapy; *or*
    b. The member has received one or more prior therapies; *or*

2. The requested medication will be used in combination with bortezomib, melphalan, and prednisone as primary therapy in members who are not a candidate for transplant; *or*
3. The requested medication (for a maximum of 16 doses) will be used in combination with bortezomib, thalidomide, and dexamethasone as primary therapy in members who are eligible for transplant; *or*
4. The requested medication will be used in combination with bortezomib and dexamethasone in members who have received at least one prior therapy; *or*
5. The requested medication will be used in combination with carfilzomib and dexamethasone when the member has

relapsed or progressive disease; *or*

6. The requested medication will be used in combination with pomalidomide and dexamethasone in members who have received at least one prior therapy including a proteasome inhibitor (PI) and an immunomodulatory agent; *or*
7. The requested medication will be used as a single agent in members who have received at least three prior therapies, including a PI and an immunomodulatory agent, or who are double refractory to a PI and an immunomodulatory agent; *or*
8. The requested medication will be used in combination with cyclophosphamide, bortezomib, and dexamethasone; *or*
9. The requested medication will be used in combination with bortezomib, lenalidomide and dexamethasone as primary therapy in members who are eligible for transplant;

B. *Light Chain Amyloidosis*

1. Aetna considers daratumumab (Darzalex) medically necessary for the treatment of systemic light chain amyloidosis when the member has relapsed or refractory disease;
2. Aetna considers daratumumab and hyaluronidase-fihj (Darzalex Faspro) medically necessary for the treatment of light chain amyloidosis in *either* of the following settings:

    a. For newly diagnosed members when used in combination with bortezomib, cyclophosphamide and dexamethasone; *or*
    b. For relapsed or refractory disease.

Aetna considers all other indications as experimental and investigational (for additional information, see Experimental and Investigational and Background sections).

II. **Continuation of Therapy**

Aetna considers continuation of daratumumab (Darzalex) or daratumumab / hyaluronidase-fihj (Darzalex Faspro) therapy medically necessary for members requesting reauthorization for an indication listed in Section I when the following regimen or indication-specific criteria is met:

A. *Multiple Myeloma*

1. All members (including new members) requesting the requested medication in combination with bortezomib, thalidomide, and dexamethasone for multiple myeloma must meet all initial criteria; *or*
2. For all other regimens listed in Section I, there is no evidence of unacceptable toxicity or disease progression while on the current regimen;

B. *Light Chain Amyloidosis*

1. Aetna considers continuation of daratumumab (Darzalex) therapy medically necessary when there is no evidence of unacceptable toxicity or disease progression while on the current regimen;
2. Aetna considers continuation of daratumumab and hyaluronidase-fihj (Darzalex Faspro) therapy medically necessary for members requesting reauthorization for newly diagnosed light chain amyloidosis when the maximum treatment duration is 24 months and there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

See also:

- CPB 0675 - Bortezomib (Velcade) (../600_699/0675.html)
- CPB 0779 - Plerixafor (Mozobil) Injection (../700_799/0779.html)
- CPB 0845 - Carfilzomib (Kyprolis) (../800_899/0845.html) or CPB 0845m - Carfilzomib (Kyprolis) [Medicare] (../800_899/0845m.html)
- CPB 0899 - Elotuzumab (Empliciti) (../800_899/0899.html).

Dosage and Administration

Darzalex (daratumumab)

Darzalex (daratumumab) injection for intravenous use is available as 100 mg/5ml and 400 mg/20 ml single-dose vials.

The Darzalex dosing schedule in Table 1 is for combination therapy (4-week cycle regimens) and monotherapy as follows:

- combination therapy with lenalidomide and low-dose dexamethasone for newly diagnosed persons ineligible for autologous stem cell transplant (ASCT) and in persons with relapsed/refractory multiple myeloma
- combination therapy with pomalidomide and low-dose dexamethasone for persons with relapsed/refractory multiple myeloma
- monotherapy for persons with relapsed/refractory multiple myeloma.

The recommended dosage of Darzalex is 16 mg/kg actual body weight administered as an intravenous infusion according to the following dosing schedules:

Table 1: Darzalex Dosing Schedule in Combination With Lenalidomide or Pomalidomide (4-Week Cycle Dosing Regimens) and Low-Dose Dexamethasone and for Monotherapy

Weeks	**Schedule**
Weeks 1 to 8	weekly (total of 8 doses)
Weeks 9 to 24 (first dose of the every-2-week dosing schedule is given at week 9)	every two weeks (total of 8 doses)
Week 25 onwards until disease progression (first dose of the every-4-week dosing schedule is given at week 25)	every four weeks

Table 2: Combination therapy with bortezomib,melphalan and prednisone (6-week cycle regimen) for persons with newly diagnosed

multiplemyeloma ineligible for ASCT.

Weeks	Schedule
Weeks 1 to 6	weekly (total of 6 doses)
Weeks 7 to 54 (first dose of the every-3-week dosing schedule is given at week 7)	every three weeks (total of 16 doses)
Week 55 onwards until disease progression (first dose of the every-4-week dosing schedule is given at week 55)	every four weeks

Table 3: Combination therapy with bortezomib,thalidomide, and dexamethasone (4-week cycle regimen) for persons with newly diagnosed multiple myeloma eligible for ASCT.

Treatment phase	Weeks	Schedule
Induction	Weeks 1 to 8	weekly (total of 8 doses)
	Weeks 9 to 16 (first dose of the every-2-week dosing schedule is given at week 9)	every two weeks (total of 4 doses)
Stop for high dose chemotherapy and ASCT		
Consolidation	Weeks 1 to 8 (first dose of the every-2-week dosing schedule is given at week 1 upon re-initiation of treatment following ASCT	every two weeks (total of 4 doses)

Table 4: Combination therapy with bortezomib and dexamethasone (3-week cycle regimen) for persons with relapsed/refractory multiple myeloma.

Weeks	Schedule
Weeks 1 to 9	weekly (total of 9 doses)
Weeks 10 to 24 (first dose of the every-3-week dosing schedule is given at week 10)	every three weeks (total of 5 doses)

Week 25 onwards until disease progression (first dose of the every-4-week dosing schedule is given at week 25)	every four weeks

Table 5: Combination therapy with carfilzomib and dexamethasone (4-week cycle regimen) for persons with relapsed/refractory multiple myeloma

Weeks	**Darzalex Dose (based on actual body weight)**	**Schedule**
Week 1	8 mg/kg	days 1 and 2 (total 2 doses)
Weeks 2 to 8	16 mg/kg	weekly (total of 7 doses)
Weeks 9 to 24 (first dose of the every-2-week dosing schedule is given at Week 9)	16 mg/kg	every two weeks (total of 8 doses)
Week 25 onwards until disease progression (first dose of the every-4-week dosing schedule is given at Week 25)	16 mg/kg	every four weeks

Source: Janssen Biotech, 2020c

Darzalex Faspro (daratumumab and hyaluronidase-fihj)

Darzalex Faspro (daratumumab and hyaluronidase-fihj) for subcutaneous injection is available as 1,800 mg daratumumab and 30,000 units hyaluronidase per 15 mL (120 mg and 2,000 units/mL) solution in a single-dose vial. Darzalex Faspro should be administered by a healthcare provider.

Multiple Myeloma

- The recommended dose of Darzakex Faspro is 1,800 mg/30,000 units (1,800 mg daratumumab and 30,000 units hyaluronidase)

administered subcutaneously into the abdomen over approximately 3-5 minutes.
- Tables 6 through 9 provide the recommended dosing schedule when Darzalex Faspro is administered as monotherapy or as part of a combination therapy.

Monotherapy and In Combination with Lenalidomide and Dexamethasone (D-Rd)

Table 6: Darzalex Faspro dosing schedule in combination with lenalidomide and dexamethasone (4-week cycle) and for monotherapy

Weeks	**Schedule**
Weeks 1 to 8	Weekly (total of 8 doses)
Weeks 9 to 24 (first dose of the every-2-week dosing schedule is given at Week 9)	Every two weeks (total of 8 doses)
Week 25 onwards until disease progression (first dose of the every-4-week dosing schedule is given at week 25)	Every four weeks

In Combination with Bortezomib, Melphalan and Prednisone (D-VMP)

Table 7: Darzalex Faspro dosing schedule in combination with bortezomib, melphalan and prednisone (6-week cycle)

Weeks	**Schedule**
Weeks 1 to 6	Weekly (total of 6 doses)
Weeks 7 to 54 (first dose of the every-3-week dosing schedule is given at week 7)	Every three weeks (total of 16 doses)
Week 55 onwards until disease progression (first dose of the every-4-week dosing schedule is given at week 55)	Every four weeks

In Combination with Bortezomib, Thalidomide, and Dexamethasone (D-VTd)

Table 8: Darzalex Faspro dosing schedule in combination with

bortezomib, thalidomide and dexamethasone (4-week cycle)

Treatment phase	Weeks	Schedule
Induction	Weeks 1 to 8	weekly (total of 8 doses)
	Weeks 9 to 16 (first dose of the every-2-week dosing schedule is given at Week 9)	every two weeks (total of 4 doses)
Stop for high dose chemotherapy and ASCT		
Consolidation	Weeks 1 to 8 (first dose of the every-2-week dosing schedule is given at Week 1 upon re-initiation of treatment following ASCT)	every two weeks (total of 4 doses)

In Combination with Bortezomib and Dexamethasone (D-Vd)

Table 9: Darzalex Faspro dosing schedule in combination with bortezomib and dexamethasone (3-week cycle)

Weeks	Schedule
Weeks 1 to 9	Weekly (total of 9 doses)
Weeks 10 to 24 (first dose of the every-3-week dosing schedule is given at week 10)	Every three weeks (total of 5 doses)
Week 25 onwards until disease progression (first dose of the every-4-week dosing schedule is given at week 25)	Every four weeks

Light Chain Amyloidosis

In Combination with Bortezomib, Cyclophosphamide and Dexamethasone (D-VCd)

Table 10: Darzalex Faspro dosing schedule in combination with bortezomib, cyclophosphamide and dexamethasone (4-week cycle)

Weeks	Schedule

Weeks 1 to 8	weekly (total of 8 doses)
Weeks 9 to 24 (first dose of the every-2-week dosing schedule is given at Week 9)	every two weeks (total of 8 doses)
Week 25 onwards until disease progression or a maximum of 2 years (first dose of the every-4-week dosing schedule is given at Week 25)	every four weeks

Source: Janssen Biotech, 2021

Experimental and Investigational

Aetna considers daratumumab or daratumumab and hyaluronidase-fihj experimental and investigational for the treatment of other conditions/diseases including the following (not an all-inclusive list):

- Acute lymphoblastic leukemia
- Acute myelogenous leukemia
- Allergy
- Anal cancer
- Antibody-mediated rejection in lung transplantation
- Breast cancer
- Cervical cancer
- Chronic lymphocytic leukemia
- CNS plasmacytoma
- Colorectal cancer, gastric cancer
- Complex regional pain syndrome
- Head and neck cancer
- Hemolytic anemia
- Lymphomas (e.g., Burkitt's lymphoma, diffuse large B-Cell lymphoma, extra-nodal natural killer/T cell lymphoma, follicular lymphoma, Hodgkin's lymphoma, mantle cell lymphoma, and primary effusion lymphoma)
- Membrano-proliferative glomerulonephritis
- Merkel cell cancer

- Myelodysplastic syndrome
- Nasopharyngeal cancer
- Non-small-cell lung cancer
- Pancreatic cancer
- Penile cancer
- Prostate cancer
- Pure red cell aplasia (PRCA)
- Rheumatoid arthritis
- Smoldering multiple myeloma
- Systemic lupus erythematosus
- Thalassemia
- Vaginal and vulvar cancer
- Waldenstrom macroglobulinemia.

Background

U.S. Food and Drug Administration (FDA)-Approved Indications for Darzalex (daratumumab)

Darzalex is indicated for the treatment of adult patients with multiple myeloma:

- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy;
- in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant;
- in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant;
- in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy;
- in combination with carfilzomib and dexamethasone in patients who have received one to three prior lines of therapy;

- in combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor;
- as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

Compendial Uses for Darzalex (daratumumab)

- Treatment of multiple myeloma in combination with cyclophosphamide, bortezomib, and dexamethasone
- Treatment of multiple myeloma for transplant candidates in combination with bortezomib, lenalidomide and dexamethasone
- Treatment for relapsed/refractory systemic light chain amyloidosis

U.S. Food and Drug Administration (FDA)-Approved Indications for Darzalex Faspro (daratumumab/hyaluronidase-fihj)

Darzalex Faspro is indicated for the treatment of adult patients with multiple myeloma:

- in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant;
- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy;
- in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant;
- in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy;
- in combination with pomalidomide and dexamethasone in patients who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor;
- as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an

immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

Darzalex Faspro is indicated for the treatment of adult patients with newly diagnosed light chain amyloidosis in combination with bortezomib, cyclophosphamide and dexamethasone.

Compendial Uses for Darzalex Faspro (daratumumab/hyaluronidase-fihj)

- For multiple myeloma, may be used as a single agent or in combination with other systemic therapies where intravenous daratumumab is recommended;
- For light chain amyloidosis, may be used as a single agent or in combination with other systemic therapies where intravenous daratumumab is recommended.

Daratumumab (Darzalex)

Multiple Myeloma

Schmidt-Wolf et al (2014) reviewed the development in the treatment of relapsed/refractory multiple myeloma (MM) during the past 10 years. The present standard-of-care in progressive or refractory MM was elaborated by the Working Group "Refractory Multiple Myeloma" using an extensive literature search for studies published between 2003 and 2013. Outside of clinical trials, high-dose chemo-therapy (HDCT) with stem cell transplantation (SCT) is recommended in physically fit patients (up to 75 years of age) without significant co-morbidities. Ongoing studies address the question regarding the least toxic and the most effective treatment; thus, inclusion of patients in therapeutic trials and use of novel agent combinations is highly recommended (e.g., with 3rd generation immunomudulatory drugs [pomalidomide], new proteasome inhibitors [PIs] such as carfilzomib, ixazomib or oprozomib, antibodies, such as elotuzumab, daratumumab or SAR650984, siltuximab, tabalumab, denosumab, romosozumab, Bruton's tyrosine kinase [BTK]-, heat shock protein [HSP]-inhibitors and other innovative agents).

El-Amm and Tabbara (2015) stated that the treatment of MM has evolved significantly over the past 2 decades as a consequence of the use of HDCT and autologous SCT, and the subsequent introduction of the immunomodulatory agents (thalidomide and lenalidomide) and the PI (bortezomib). The median overall survival (OS) of MM patients has increased significantly with patients younger than 50 years of age experiencing a 10-year survival rate of approximately 40 %. However, despite the increased effectiveness of the 1st-line agents, the majority of patients will eventually relapse and become drug-resistant. Promising novel therapies have recently emerged and are being used to treat relapsed and refractory patients. These researchers examined the clinical data regarding these emerging therapies that include new generation of PIs (e.g., carfilzomib, ixazomib, oprozomib, and marizomib), immunomodulatory drugs (pomalidomide), monoclonal antibodies (mAbs) (elotuzumab and daratumumab), signal transduction modulator (perifosine), and histone deacetylase inhibitors (vorinostat and panobinostat).

Daratumumab is an IgG1κ human mAb that binds to cluster of differentiation 38 (CD38; also known as cyclic ADP ribose hydrolase) and inhibits the growth of CD38-expressing tumor cells by inducing apoptosis directly through Fc-mediated cross-linking as well as by immune-mediated tumor cell lysis through complement dependent cytotoxicity, antibody dependent cell mediated cytotoxicity, and antibody dependent cellular phagocytosis. Myeloid derived suppressor cells and a subset of regulatory T cells (CD38+Tregs) express CD38 and are susceptible to daratumumab-mediated cell lysis.

In a phase I/II clinical trial, Lokhorst et al (2015) examined the safety and effectiveness of daratumumab in patients with relapsed MM or relapsed MM that was refractory to 2 or more prior lines of therapy. In part 1, the dose-escalation phase, these researchers administered daratumumab at doses of 0.005 to 24 mg/kg body weight. In part 2, the dose-expansion phase, 30 patients received 8 mg/kg of daratumumab and 42 received 16 mg/kg, administered once-weekly (8 doses), twice-monthly (8 doses), and monthly for up to 24 months. End-points included safety, effectiveness, and pharmacokinetics. No maximum tolerated dose (MTD) was identified in part 1; in part 2, the median time since diagnosis was 5.7 years. Patients had received a median of 4 prior treatments; 79 % of the patients

had disease that was refractory to the last therapy received (64 % had disease refractory to PIs and immunomodulatory drugs and 64 % had disease refractory to bortezomib and lenalidomide), and 76 % had received autologous SCT. Infusion-related reactions in part 2 were mild (71 % of patients had an event of any grade, and 1 % had an event of grade 3), with no dose-dependent adverse events. The most common adverse events of grade 3 or 4 (in greater than or equal to 5 % of patients) were pneumonia and thrombocytopenia. The overall response rate (ORR) was 36 % (95 % confidence interval [CI]: 21.6 % to 52.0 %) in the cohort that received 16 mg/kg (15 patients had a partial response [PR] or better, including 2 with a complete response [CR] and 2 with a very good PR [VGPR]) and 10 % in the cohort that received 8 mg/kg (3 had a PR). In the cohort that received 16 mg/kg, the median progression-free survival (PFS) was 5.6 months (95 % CI: 4.2 to 8.1), and 65 % (95 % CI: 28 to 86) of the patients who had a response did not have progression at 12 months. The authors concluded that daratumumab monotherapy had a favorable safety profile and encouraging efficacy in patients with heavily pre-treated and refractory MM.

Lonial et al (2015) reported the findings of an open-label trial evaluating daratumumab monotherapy in patients with relapsed or refractory MM who had received at least 3 prior lines of therapy including a PI and an immunomodulatory agent or who were double-refractory to a PI and an immunomodulatory agent. In 106 patients, daratumumab 16 mg/kg was administered with pre- and post-infusion medication. Treatment continued until unacceptable toxicity or disease progression. The median patient age was 63.5 years (range of 31 to 84 years), 49 % were male, and 79 % were Caucasian. Patients had received a median of 5 prior lines of therapy; 80 % of patients had received prior autologous SCT. Prior therapies included bortezomib (99 %), lenalidomide (99 %), pomalidomide (63 %), and carfilzomib (50 %). At baseline, 97 % of patients were refractory to the last line of treatment, 95 % were refractory to both, a PI and an immunomodulatory agent, and 77 % were refractory to alkylating agents. Efficacy results were based on ORR as determined by the Independent Review Committee assessment using the International Myeloma Working Group (IMWG) criteria. Overall response rate was 29.2 % (2.8 % stringent CR [sCR], 0 % CR, 9.4 % VGPR, and

10 % PR) (95 % CI: 20.8 % to 38.9 %). The median time to response was 1 month (range of 0.9 to 5.6 months). The median duration of response was 7.4 months (range of 1.2 to 13.1+ months).

On November 16, 2015, the Food and Drug Administration (FDA) approved daratumumab (Darzalex) for intravenous use for the treatment of patients with MM who have received at least 3 prior treatments. The safety and effectiveness of Darzalex were reported in 2 open-label studies (Lokhorst et al, 2015 and Lonial et al, 2015). This indication was approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.The most common side effects of Darzalex were back pain, cough, fatugue, fever, nausea and infusion-related reactions. Darzalex may also result in anemia, leukopenia, lymphopenia, neutropenia, as well as thrombocytopenia.

The warnings and precautions for Darzalex include infusion reactions, interference with serological testing and interference with determination of complete response. The most frequently reported adverse reactions (incidence greater than or equal to 20 %) were: fatigue, nausea, back pain, pyrexia, cough and upper respiratory tract infection.

In data from 3 pooled clinical studies including a total of 156 patients, 4 % of patients discontinued treatment due to adverse reactions. Infusion reactions were reported in approximately 50 % of all patients treated with Darzalex. Common (greaterthan or equal to 5 %) symptoms of infusion reactions included nasal congestion, chills, cough, allergic rhinitis, throat irritation, dyspnea (shortness of breath) and nausea. Severe infusion reactions, including bronchospasm, dyspnea, hypoxia and hypertension (less than 2 % each).

Darzalex (daratumumab) has not been evaluated in patients with moderate to severe hepatic impairment. Mild hepatic impairment and renal impairment do not require dosage adjustments.

Darzalex (daratumumab) can cause severe infusion reactions. Most reactions occur during the first administration. Darzalex (daratumumab) should be administered with pre-infusion medications including

intravenous corticosteroids, oral antipyretics, and an oral or intravenous anthistamine. An oral corticosteroid should be administered post-infusion.

Prophylaxis for herpes zoster reaction should be initiated.

Safety and efficacy in pediatric patients has not been established.

Safety and efficacy in pregnancy has not been established.

There is no information regarding the presence of daratumumab in human milk, the effects on the breastfed infant, or the effects on milk production.

Combination Therapies

In a phase I/II clinical trial, Plesner and colleagues (2016) examined the effectiveness of combining daratumumab, lenalidomide, and dexamethasone for the treatment of refractory and relapsed/refractory MM. Part 1 (dose-escalation) evaluated 4 daratumumab doses plus lenalidomide (25 mg/day p.o. on days 1 and 21 of each cycle) and dexamethasone (40 mg/week). Part 2 (dose-expansion) evaluated daratumumab at the recommended phase 2 dose (RP2D) plus lenalidomide/dexamethasone. Safety, effectiveness, pharmacokinetics, immunogenicity and accelerated daratumumab infusions were studied. In Part 1 (13 patients), no dose-limiting toxicities (DLT) were observed; 16 mg/kg was selected as the R2PD. In Part 2 (32 patients), median time since diagnosis was 3.2 years, with a median (range) of 2 (1 to 3) prior therapies, including proteasome inhibitors (91 %), alkylating agents (91 %), autologous stem cell transplant (78 %), thalidomide (44 %), and lenalidomide (34 %); 22 % were refractory to last-line of therapy. Grade 3/4 adverse events (AEs greater than or equal to 5 %) included neutropenia, thrombocytopenia, and anemia. In Part 2, infusion-related reactions (IRRs) occurred in 18 patients (56 %); most were less than or equal to grade 2 (grade 3, 6.3 %). Infusion-related reactions predominantly occurred during 1st infusions and were more common during accelerated infusions. In Part 2 (median follow-up of 15.6 months), ORR was 81 % with 8 (25 %) stringent CRs, 3 (9 %) CRs, and 9 (28 %) very good PRs; 18-month PFS and OS rates were 72 % (95 % CI:

51.7 to 85.0) and 90 % (95 % CI: 73.1 to 96.8), respectively. The authors concluded that daratumumab plus lenalidomide/dexamethasone resulted in rapid, deep, durable responses. They stated that the combination was well-tolerated and consistent with the safety profiles observed with lenalidomide/dexamethasone or daratumumab monotherapy.

In a phase III clinical trial, Palumbo and associates (2016) randomly assigned 498 patients with relapsed or relapsed and refractory MM to receive bortezomib (1.3 mg/square meter of body-surface area) and dexamethasone (20 mg) alone (control group) or in combination with daratumumab (16 mg/kg of body weight) (daratumumab group). The primary end-point was PFS. A pre-specified interim analysis showed that the rate of PFS was significantly higher in the daratumumab group than in the control group; the 12-month rate of PFS was 60.7 % in the daratumumab group versus 26.9 % in the control group. After a median follow-up period of 7.4 months, the median PFS was not reached in the daratumumab group and was 7.2 months in the control group (hazard ratio [HR] for progression or death with daratumumab versus control, 0.39; 95 % CI: 0.28 to 0.53; $p < 0.001$). The rate of OS was higher in the daratumumab group than in the control group (82.9 % versus 63.2 %, $p < 0.001$), as were the rates of very good PR or better (59.2 % versus 29.1 %, $p < 0.001$) and CR or better (19.2 % versus 9.0 %, $p = 0.001$). Three of the most common grade 3 or 4 AEs reported in the daratumumab group and the control group were thrombocytopenia (45.3 % and 32.9 %, respectively), anemia (14.4 % and 16.0 %, respectively), and neutropenia (12.8 % and 4.2 %, respectively); IRRs that were associated with daratumumab treatment were reported in 45.3 % of the patients in the daratumumab group; these reactions were mostly grade 1 or 2 (grade 3 in 8.6 % of the patients), and in 98.2 % of these patients, they occurred during the first infusion. The authors concluded that among patients with relapsed or relapsed and refractory MM, daratumumab in combination with bortezomib and dexamethasone resulted in significantly longer PFS than bortezomib and dexamethasone alone and was associated with IRRs and higher rates of thrombocytopenia and neutropenia than bortezomib and dexamethasone alone.

In June 2017, the FDA approved the daratumumab in combination with pomalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least two prior therapies including

lenalidomide and a proteasome inhibitor (PI) (Janssen, 2017).

This indication for daratumumab was supported by data from the Phase 1b EQUULEUS study, which included 103 patients with multiple myeloma who had received a prior PI and an immunomodulatory agent (Janssen, 2017). Patients received 16 mg/kg of daratumumab in combination with pomalidomide and low-dose dexamethasone until disease progression. The median patient age was 64 years, with 8 percent of patients aged 75 or older. Patients in the study had received a median of four prior lines of therapy, and 74 percent of patients had received prior autologous stem cell transplant (ASCT). Ninety-eight percent of patients received prior bortezomib treatment and 33 percent of patients received prior carfilzomib treatment. All patients received prior lenalidomide treatment, with 98 percent of patients previously treated with the combination of bortezomib and lenalidomide. Eighty nine percent of patients were refractory to lenalidomide, 71 percent were refractory to bortezomib, and 64 percent of patients were refractory to bortezomib and lenalidomide. The study showed that the combination of daratumumab with pomalidomide and dexamethasone resulted in an ORR of 59.2 percent (95 percent CI: 49.1, 68.8), with very good partial response (VGPR) achieved in 28.2 percent of patients. Complete response (CR) was achieved in 5.8 percent of patients, stringent CR (sCR) was achieved in 7.8 percent of patients, and partial response (PR) was achieved in 17.5 percent of patients. The median time to response was one month (range: 0.9 to 2.8 months), and the median duration of response was 13.6 months (range: 0.9+ to 14.6+ months).

The investigators reported that, overall, the safety of the daratumumab combination therapy was consistent with the known safety profiles of daratumumab monotherapy and pomalidomide plus dexamethasone, respectively (Janssen, 2017). In the EQUULEUS trial, the most frequent (>20 percent) adverse reactions (ARs) were infusion reactions (50 percent), diarrhea (38 percent), constipation (33 percent), nausea (30 percent), vomiting (21 percent), fatigue (50 percent), pyrexia (25 percent), upper respiratory tract infection (50 percent), muscle spasms (26 percent), back pain (25 percent), arthralgia (22 percent), dizziness (21 percent), insomnia (23 percent), cough (43 percent) and dyspnea (33 percent). The overall incidence of serious ARs was 49 percent. Serious ARs (Grade 3/4) reported in ≥5 percent of patients included pneumonia (7

percent). Thirteen percent of patients discontinued therapy due to an AR. The most common treatment-emergent hematology laboratory abnormalities were neutropenia (95 percent), lymphopenia (94 percent), thrombocytopenia (75 percent) and anemia (57 percent). The most common Grade 3 treatment-emergent hematology laboratory abnormalities were lymphopenia (45 percent), neutropenia (36 percent), anemia (30 percent) and thrombocytopenia (10 percent). The most common Grade 4 treatment-emergent hematology laboratory abnormalities were neutropenia (46 percent), lymphopenia (26 percent) and thrombocytopenia (10 percent).

The dosing schedule for daratumumab in combination with pomalidomide and dexamethasone begins with weekly administration (weeks 1-8) and reduces in frequency over time to every two weeks (weeks 9-24) and ultimately every four weeks (week 25 onwards until disease progression) (Janssen, 2017). The recommended dose of daratumumab is 16 mg/kg body weight administered as an intravenous infusion.

The approval of daratumumab in newly diagnosed multiple myeloma patients who are ineligible for autologous stem cell transplant was based on findings from phase 3 of the ALCYONE study, a randomized, open-label, multicenter study with results. In this trial, Mateos et al (2018) stated the combination of bortezomib, melphalan, and prednisone is a standard treatment for patients with newly diagnosed multiple myeloma who are ineligible for autologous stem-cell transplantation. Daratumumab has shown efficacy in combination with standard-of-care regimens in patients with relapsed or refractory multiple myeloma. In this phase 3 trial, the authors randomly assigned 706 patients with newly diagnosed multiple myeloma who were ineligible for stem-cell transplantation to receive nine cycles of bortezomib, melphalan, and prednisone either alone (control group) or with daratumumab (daratumumab group) until disease progression. The primary end point was progression-free survival. At a median follow-up of 16.5 months in a prespecified interim analysis, the 18-month progression-free survival rate was 71.6% (95% confidence interval [CI], 65.5 to 76.8) in the daratumumab group and 50.2% (95% CI, 43.2 to 56.7) in the control group (hazard ratio for disease progression or death, 0.50; 95% CI, 0.38 to 0.65; P<0.001). The overall response rate was 90.9% in the daratumumab group, as compared with 73.9% in the control group (P<0.001), and the rate of

complete response or better (including stringent complete response) was 42.6%, versus 24.4% (P<0.001). In the daratumumab group, 22.3% of the patients were negative for minimal residual disease (at a threshold of 1 tumor cell per 105 white cells), as compared with 6.2% of those in the control group (P<0.001). The most common adverse events of grade 3 or 4 were hematologic: neutropenia (in 39.9% of the patients in the daratumumab group and in 38.7% of those in the control group), thrombocytopenia (in 34.4% and 37.6%, respectively), and anemia (in 15.9% and 19.8%, respectively). The rate of grade 3 or 4 infections was 23.1% in the daratumumab group and 14.7% in the control group; the rate of treatment discontinuation due to infections was 0.9% and 1.4%, respectively. Daratumumab-associated infusion-related reactions occurred in 27.7% of the patients. The authors concluded that among patients with newly diagnosed multiple myeloma who were ineligible for stem cell transplantation, daratumumab combined with bortezomib, melphalan, and prednisone resulted in a lower risk of disease progression or death than the same regimen without daratumumab. The daratumumab-containing regimen was associated with more grade 3 or 4 infections.

On June 27, 2019, the U.S. FDA approved the use of daratumumab (Darzalex, Janssen Biotech, Inc) in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

FDA approval was based on an open-label, randomized (1:1), active-controlled phase 3 study (MAIA, NCT02252172), comparing daratumumab (16 mg/kg) in combination with lenalidomide and low-dose dexamethasone (DRd) to lenalidomide and low-dose dexamethasone (Rd), in 737 patients with newly diagnosed multiple myeloma who were ineligible for autologous stem cell transplant (FDA, 2019; Janssen Biotech, 2019).

Facon and colleagues (2019) state that the randomized, phase 3 MAIA trial found that among patients with newly diagnosed multiple myeloma who were ineligible for autologous stem-cell transplantation, the risk of disease progression or death was significantly lower among those who received daratumumab plus lenalidomide and dexamethasone (DRd) than among those who received lenalidomide and dexamethasone (Rd)

alone. Patients (n=737) were randomized (1:1) to receive either daratumumab in combination with lenalidomide and low-dose dexamethasone (DRd) or lenalidomide and low-dose dexamethasone (Rd) alone in 28-day cycles. In the DRd treatment arm, patients received daratumumab 16 mg/kg IV weekly for cycles 1 – 2, every two weeks for cycles 3 – 6 and every 4 weeks for cycle 7 and thereafter. Patients in the DRd and Rd treatment arms received 25 mg of lenalidomide on days 1 – 21 of each 28-day cycle, and dexamethasone at 40 mg once a week for each cycle. Treatment was continued in both arms until disease progression or unacceptable toxicity. The primary end point was progression-free survival (PFS) based on International Myeloma Working Group (IMWG) criteria. At the median follow-up of 28 months, the authors found that disease progression or death had occurred in 26.4% in the DRd group and 38.8% in the Rd group. The estimated percentage of patients who were alive without disease progression at 30 months was 70.6% in the DRd group and 55.6% in the Rd group ($p < 0.001$). The percentage of patients with a complete response or better was 47.6% in the DRd group and 24.9% in the Rd group ($p < 0.001$). A total of 24.2% of the patients in the DRd group, as compared with 7.3% of the patients in the Rd group, had results below the threshold for minimal residual disease (1 tumor cell per 105 white cells) ($p<0.001$). The most common adverse events of grade 3 or 4 were neutropenia (50.0% in the DRd group vs. 35.3% in the Rd group), anemia (11.8% vs. 19.7%), lymphopenia (15.1% vs. 10.7%), and pneumonia (13.7% vs. 7.9%). The authors concluded the MAIA trial demonstrated an improvement in PFS in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm compared to 31.9 months in the Rd arm, representing 44% reduction in the risk of disease progression or death in patients treated with daratumumab in combination with lenalidomide and low-dose dexamethasone (DRd).

Inclusion criteria for the study required that participants have documented MM satisfying the CRAB criteria (calcium elevation, renal insufficiency, anemai and bone abnormalities), monoclonal plasma cells in the bone marrow greater than or equal to (>=) 10 percent (%) or presence of a biopsy proven plasmacytoma and measurable disease as defined by any of the following: (a) immunoglobulin (Ig) G myeloma (serum monoclonal paraprotein [M-protein] level >=1.0 gram/deciliter [g/dL] or urine M-protein level >=200 milligram[mg]/24 hours[hrs]; or (b) IgA, IgM, IgD, or IgE

multiple myeloma (serum M-protein level >=0.5 g/dL or urine M-protein level >=200 mg/24 hrs); or (c) light chain multiple myeloma without measurable disease in serum or urine (serum immunoglobulin free light chain >=10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio). Participants must have had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2 (Janssen Research & Development, 2019).

Participants with a diagnosis of primary amyloidosis, monoclonal gammopathy of undetermined significance, smoldering MM (asymptomatic MM with absence of related organ or tissue impairment end organ damage), Waldenstrom's disease, or history of malignancy (other than MM) within 5 years before date of randomization were excluded from the clinical trial (Janssen Research & Development, 2019).

On September 26, 2019, Janssen Pharmaceuticals announced the U.S. FDA approval of Darzalex (daratumumab) in combination with bortezomib, thalidomide and dexamethasone (VTd) for newly diagnosed patients with multiple myeloma who are eligible for autologous stem cell transplant (ASCT). The approval was based on results from the Phase 3 CASSIOPEIA (MMY3006) transplant study that showed the adding Darzalex to VTd before and after ASCT resulted in deeper responses, as indicated by the higher stringent complete response (sCR) rate and improved progression-free survival (PFS) compared to VTd alone (29 percent vs. 20 percent) (p=0.0010). The addition of Darzalex to VTd at a median follow-up of 18.8 months resulted in a 53 percent reduction in the risk of disease progression or death compared to VTd alone (p<0.0001) (Janssen, 2019).

Light Chain Amyloidosis

Kaufman et al (2017) noted that the majority of patients with immunoglobulin light chain amyloidosis (AL) fail to achieve a complete response (CR) to standard light chain suppressive chemotherapy, and almost all patients eventually experience hematologic relapse and progression of organ involvement. Additional well-tolerated therapeutic options are needed. These researchers presented their retrospective experience of 25 consecutive previously treated AL patients who received daratumumab, a CD38-directed monoclonal antibody approved for the

treatment of multiple myeloma. Daratumumab was administered at 16 mg/kg weekly for 8 weeks, then every 2 weeks for 8 doses, and then every 4 weeks. Patients had received a median of 3 prior lines of therapy, with a previous hematologic CR in only 5 patients. The overall hematologic response rate to daratumumab was 76 %, including CR in 36 % and very good partial response (PR) in 24 %. Median time to response was 1 month. Therapy was well-tolerated, even among the 72 % of patients with cardiac AL involvement. Grade 1-2 infusion reactions occurred in 15 patients, but no grade 3 or 4 reactions were observed. The authors concluded that daratumumab is a highly effective agent that produced rapid and deep hematologic responses without unexpected toxicity in this cohort of heavily pre-treated AL patients. Moreover, they stated that prospective studies of daratumumab alone or in combination with chemotherapy in patients with AL amyloidosis are needed. This was a small (n = 25), retrospective study.

In a multi-center, prospective trial, Roussel et al (2017) examined if daratumumab could be an option for patients with previously treated AL amyloidosis. A total of 40 people were included in this study (median age = 69 years; range of 45 to 81 years). All had previously treated measurable AL amyloidosis that had not responded to therapy, as well as at least 1 major vital organ involvement, an Eastern Cooperative Oncology Group (ECOG) performance status score of less than or equal to 2, and measurable plasma cell dyscrasia with difference between involved and uninvolved free AL levels (dFLC) greater than 50 mg/L. Patients had received a median of 2.5 prior therapies (range of 1 to 5 therapies), including melphalan and dexamethasone (n = 13), bortezomib (n = 28), and lenalidomide (n = 14). Intravenous daratumumab 16 mg/kg was administered once-weekly during the first two 28-day cycles, then every other week during cycles 3 to 6, for a total of six 28-day cycles; 4 patients discontinued the study treatment before 6 cycles because of disease progression (n = 2), death (n = 1), or lung cancer (n = 1). Hematologic responses were measured after each injection and at the end of each cycle. As of July 31, 2017 (data cut-off), patients had been followed for a median of 23 months (range of 3.5 to 116 months). A total of 32 patients completed at least 1 cycle of daratumumab treatment (at least 4 injections) and were evaluable for response. At 6 months after treatment initiation, or at last evaluation, 19 patients responded to daratumumab, for an overall response rate (ORR) of 59.4 %. This

included 14 very good partial responses or better (≥ VGPR; 43.8 %) and 5 partial responses (PR; 15.6 %); the remaining 13 patients (40.6 %) did not respond. After a single daratumumab injection, all 19 responding patients had a greater than 30 % reduction in dFLC from baseline, with a median dFLC decrease after 1 injection of 57 % (range of 31 to 96 %). "The administration of daratumumab was associated with a good safety profile and non-severe adverse events (AEs), mostly after the first infusion," the authors reported; 6 patients experienced at least 1 grade greater than or equal to 3 AE, and only 1 event (lymphopenia) was considered related to daratumumab. The most common drug-related AEs were infusion-related reaction in 10 patients, all of which were grade 1 or 2. "Daratumumab demonstrates encouraging efficacy in previously treated patients with AL amyloidosis with deep and rapid responses," the authors concluded. They noted that these results warrant larger and longer-term studies of daratumumab in this setting. The study's findings were limited by the small number of patients enrolled and the lack of a comparator arm.

Gran et al (2018) noted that immunoglobulin light-chain amyloidosis (AL) affects multiple organs, most prominently the kidney and the heart. Renal and cardiac impairment are both associated with poor prognosis and most patients die as a consequence of renal or cardiac failure. Monoclonal antibodies such as daratumumab (human IgG1 anti-CD38) and elotuzumab (anti-SLAMF7) have shown promising efficacy for the treatment of relapsed and refractory multiple myeloma. In this case report, these researchers showed 2 patients with severe AL, 1 with severe heart failure and 1 with heart and renal failure, undergoing treatment with daratumumab. Both patients showed a rapid decrease in FLC in response to daratumumab infusions, with few associated adverse events (AEs). The authors concluded that using therapeutic CD38 antibodies as a front-line treatment for AL could induce rapid responses while maintaining a tolerable safety profile in these ultra-fragile patients. This was a case-report with 2 patients; its findings need to be validated by well-designed studies.

Sidiqi and Gertz (2018) noted that autologous stem cell transplantation (ASCT) has been used as treatment for AL amyloidosis for over 20 years with improving outcomes; however, the majority of patients are not candidates for this therapy at diagnosis. Novel agents such as

immunomodulatory drugs, proteasome inhibitors, and immunotherapy with monoclonal antibodies targeting CD38 have been adopted from the MM spheres with encouraging results. These investigators discussed the role of daratumumab in the treatment of AL amyloidosis. They focused on its mechanism of action, tolerability, and the current published data on its use in AL amyloidosis. The authors stated that early data from phase-I and phase-II clinical trials showed that daratumumab was well-tolerated in this population and induced rapid and deep responses; phase-III trials are currently accruing and they envision daratumumab becoming a key component in the treatment of AL amyloidosis in the future.

An UpToDate review on “Treatment and prognosis of immunoglobulin light chain (AL) amyloidosis and light and heavy chain deposition diseases” (Rajkumar and Dispenzieri, 2018) states that “Monoclonal antibodies -- There is limited experience with monoclonal antibodies for the treatment of amyloidosis. We reserve their use primarily for patients enrolled on clinical trials. As examples: Daratumumab is an anti-CD38 monoclonal antibody used in multiple myeloma. Case reports and a retrospective study described the safety and efficacy of daratumumab in patients with relapsed or refractory AL amyloidosis. In the retrospective study, 19 of 25 patients achieved a hematologic response (9 complete response, 6 very good partial response, 4 partial response) with a median time to deepest hematologic response of 1 month (range 7 to 188 days). Toxicity was similar to that seen in patients with multiple myeloma”.

In March 2020, an UpToDate review on "What's new" stated that "Data are limited for the management of relapsed or refractory AL amyloidosis, but two prospective studies have recently evaluated the anti-CD38 monoclonal antibody daratumumab in this setting:

- In a single-center phase 2 trial that enrolled 22 patients with a median of two prior therapies, hematologic very good partial response (VGPR) or better was seen in >85 percent of patients with a median progression-free survival (PFS) of 28 months
- In a multicenter phase 2 trial that enrolled 40 patients with a median of three prior therapies, hematologic VGPR or better was seen in approximately half of patients with a median PFS of 25 months

Both studies reported renal and cardiac responses. Adverse events were mostly low grade and similar to those reported in other populations. Based on these and other data, we now consider daratumumab and daratumumab-based combination regimens as off-label treatment options in relapsed or refractory AL amyloidosis. These regimens may be particularly attractive for patients with severe cardiac involvement."

An UpToDate review on "Treamtent and prognosis of immunoglobuin light chain (AL) amyloidosis and light and heavy chain deposition disease" (Dispenzieri, 2020) state that "for patients who relapse after or are refractory to initial therapy (bortezomib-based regimen, melphalan plus dexamethasone, or hematopoietic cell transplantation [HCT]), treatment options include daratumumab, proteasome inhibitor-based regimens, and immunomodulatory-based regimens".

The National Comprehensive Cancer Network Compendium (NCCN, 2021) provides a category 2A recommendation for use of daratumumab (Darzalex), as a single agent, for the treatment of relapsed/refractory systemic light chain amyloidosis.

Daratumumab and Hyaluronidase-fihj (Darzalex Faspro)

Multiple Myeloma

On May 1, 2020, the U.S. Food and Drug Administration (FDA) announced the approval of Darzalex Faspro (Janssen Biotech, Inc) for the treatment of adult patients with newly diagnosed or relapsed/refractory multiple myeloma. Darzalex Faspro is a combination of daratumumab, a CD38-directed cytolytic antibody, and hyaluronidase, and endoglycosidase. Darzalex Faspro is available as a subcutaneous injection to be administered by a healthcare provider (FDA, 2020; Janssen, 2020b).

Daratumumab and hyaluronidase-fihj (Darzalex Faspro) is approved in four regimens across five indications in multiple myeloma patients, including newly diagnosed, transplant-ineligible patients as well as relapsed or refractory patients. The following indications for Darzalex Faspro include indications that intravenous daratumumab had previously received (FDA, 2020; Janssen, 2020b):

- in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant,
- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy,
- in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy, and
- as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

FDA approval for Darzalex Faspro was based on the phase 3 COLUMBA and Phase 2 PLEIADES studies.

Mateos and colleagues (2020) conducted a multicenter, open-label, non-inferiority, randomized, phase 3 trial (COLUMBA) to evaluate the efficacy of subcutaneous daratumumab and hyaluronidase-fihj (monotherapy) to intravenous daratumumab in patients with relapsed or refractory multiple myeloma. Patients were included if they were 18 years and older with confirmed relapsed or refractory multiple myeloma; received at least three previous lines of therapy, including a proteasome inhibitor and immunomodulatory drug, or were double refractory to both a proteasome inhibitor and immunomodulatory drug; and had an Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or lower. The trial included 522 patients randomly assigned patients (subcutaneous group n=263; intravenous group n=259). Patients received 1800 mg of subcutaneous daratumumab co-formulated with 2000 U/mL recombinant human hyaluronidase PH20 or 16 mg/kg of intravenous daratumumab once weekly (cycles 1-2), every 2 weeks (cycles 3-6), and every 4 weeks thereafter (28-day cycles) until progressive disease or toxicity. In the arm that received subcutaneous daratumumab, patients were given a fixed volume of 15 mL over three to five minutes; the median injection time was five minutes. In the arm that received the intravenous administration, the median durations of the first, second and subsequent intravenous daratumumab infusions were 7.0, 4.3 and 3.4 hours, respectively. The co-primary endpoints were overall response and maximum trough

concentration (Ctrough; cycle 3, day 1 pre-dose). The non-inferiority margin for overall response was defined using a 60% retention of the lower bound (20·8%) of the 95% CI of the SIRIUS trial. Efficacy analyses were done by intention-to-treat population. The pharmacokinetic-evaluable population included all patients who received all eight weekly daratumumab doses in cycles 1 and 2 and provided a pre-dose pharmacokinetics blood sample on day 1 of cycle 3. The safety population included all patients who received at least one daratumumab dose. The authors found that at a median follow-up of 7.5 months, overall response and Ctrough met the predefined non-inferiority criteria. An overall response was seen in 108 (41%) of 263 patients in the subcutaneous group and 96 (37%) of 259 in the intravenous group. The geometric mean ratio comparing daratumumab and hyaluronidase-fihj to daratumumab IV for maximum Ctrough was 108% (90% CI: 96,122). The most common grade 3 and 4 adverse events were anemia (34 [13%] of 260 patients evaluable for safety in the subcutaneous group and 36 [14%] of 258 patients in the intravenous group), neutropenia (34 [13%] and 20 [8%]), and thrombocytopenia (36 [14%] and 35 [14%]). Pneumonia was the only serious adverse event in more than 2% of patients (seven [3%] in the subcutaneous group and 11 [4%] in the intravenous group). There was one death resulting from a treatment-related adverse event in the subcutaneous daratumumab group (febrile neutropenia) and four in the intravenous group (sepsis [n=2], hepatitis B reactivation [n=1], and Pneumocystis jirovecii pneumonia [n=1]). The authors concluded that subcutaneous daratumumab was non-inferior to intravenous daratumumab in terms of efficacy and pharmacokinetics and had an improved safety profile in patients with relapsed or refractory multiple myeloma.

The non-randomized, open-label, parallel assignment Phase 2 PLEIADES study included more than 240 adults with multiple myeloma, including 67 patients with newly diagnosed multiple myeloma who were treated with 1,800 mg of Darzalex Faspro in combination with bortezomib, melphalan, and prednisone (D-VMP) and 65 patients with relapsed or refractory disease who were treated with 1,800 mg of Darzalex Faspro plus lenalidomide and dexamethasone (D-Rd). The primary endpoint for the D-VMP and D-Rd cohorts was overall response rate (FDA, 2020; Janssen, 2020).

Efficacy of D-VMP was evaluated in a single-arm cohort of PLEIADES (NCT03412565), a multi-cohort, open-label trial. Eligible patients were required to have newly diagnosed multiple myeloma and were ineligible for transplant. The major efficacy outcome measure, ORR, was 88.1% (95% CI: 77.8, 94.7). Efficacy of D-Rd in relapsed or refractory patients was also evaluated in a single-arm cohort of this trial. Eligible patients had received at least one prior line of therapy. ORR was 90.8% (95% CI: 81.0, 96.5) (FDA, 2020; Janssen, 2020).

The most common adverse reaction (≥20%) with Darzalex Faspro monotherapy is upper respiratory tracts infection. The most common adverse reactions (≥20%) with D-VMP are upper respiratory tract infection, constipation, nausea, fatigue, pyrexia, peripheral sensory neuropathy, diarrhea, cough, insomnia, vomiting, and back pain. The most common adverse reactions (≥20%) with D-Rd are fatigue, diarrhea, upper respiratory tract infection, muscle spasms, constipation, pyrexia, pneumonia and dyspnea. The most common hematology laboratory abnormalities (≥40%) with Darzalex Faspro are decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin.

Warnings and precautions include the following:

- Hypersensitivity and other administration reactions
- Neutropenia
- Thrombocytopenia
- Embryo-fetal toxicity
- Interference with cross-matching and red blood cell antibody screening: Type and screen patients prior to starting treatment. Inform blood banks that a patient has received Darzalex Faspro.

Light Chain Amyloidosis

In January 2021, the FDA granted accelerated approval to daratumumab plus hyaluronidase (Darzalex Faspro, Janssen Biotech Inc.) in combination with bortezomib, cyclophosphamide and dexamethasone for newly diagnosed light chain (AL) amyloidosis.

FDA approval was based on the efficacy outcomes that was evaluated in an open-label, randomized, active-controlled trial (ANDROMEDA; NCT03201965). The trial included 388 patients (median age 64 years) with newly diagnosed AL amyloidosis with measurable disease and at least one affected organ according to consensus criteria. Patients were randomized to receive bortezomib (1.3 mg/m2 administered subcutaneously), cyclophosphamide (300 mg/m2 (max dose 500 mg) administered orally or intravenously), and dexamethasone (40mg) administered orally or intravenously (n= 193; VCd arm) on Days 1, 8, 15, and 22 of each 28-day cycle or with Darzalex Faspro (n=195; D-VCd arm) 1,800 mg/30,000 units subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or a maximum of two years. The hematologic complete response (HemCR) rate based on established consensus response criteria as evaluated by an independent review committee was 42.1% for the D-VCd arm and 13.5% for the VCd arm ($p<0.0001$) (FDA, 2021; Janssen Biotech, 2021).

The prescribing information includes a Warnings and Precautions that serious or fatal cardiac adverse reactions occurred in patients with light chain (AL) amyloidosis who received Darzalex Faspro in combination with bortezomib, cyclophosphamide and dexamethasone. Darzalex Faspro is not indicated and is not recommended for the treatment of patients with light chain (AL) amyloidosis who have NYHA Class IIIB or Class IV cardiac disease or Mayo Stage IIIB outside of controlled clinical trials. The most common adverse reactions (≥20%) in patients with light chain (AL) amyloidosis who received the D-VCd regimen include upper respiratory tract infection, diarrhea, peripheral edema, constipation peripheral sensory neuropathy, fatigue, nausea, insomnia, dyspnea and cough (FDA, 2021; Janssen Biotech, 2021).

The National Comprehensive Cancer Network Compendium (NCCN, 2021) provides a category 2A recommendation for systemic light chain amyloidosis that Darzalex Faspro may be used as a single agent or in combination with other systemic therapies where intravenous daratumumab is recommended, and a category 1 recommendation as preferred treatment for newly diagnosed disease or consider for

relapse/refractory disease as a repeat of initial therapy if relapse-free for several years in combination with bortezomib, cyclophosphamide, and dexamethasone.

Experimental Indications

According to ClinialTrials.gov, there are quite a few clinical trials on the use of daratumumab for the treatment of various malignancies including acute lymphoblastic leukemia, AML, anal cancer, breast cancer, cervical cancer, colorectal cancer, gastric cancer, head and neck cancer, Hodgkin's lymphoma, membrano-proliferative glomerulonephritis, Merkel cell cancer, myelodysplastic syndrome, nasopharyngeal cancer, non-small-cell lung cancer, pancreatic cancer, penile cancer, prostate cancer, vaginal and vulvar cancer, and Waldenstrom macroglobulinemia.

Acute Myeloid Leukemia

Fatehchand and colleagues (2016) stated that acute myeloid leukemia (AML) is characterized by the proliferation of immature myeloid lineage blasts. Due to its heterogeneity and to the high rate of acquired drug resistance and relapse, new treatment strategies are needed. These researchers demonstrated that interferon-gamma (IFNγ) promotes AML blasts to act as effector cells within the context of antibody therapy. Treatment with IFNγ drove AML blasts toward a more differentiated state, wherein they showed increased expression of the M1-related markers HLA-DR and CD86, as well as of FcγRI, which mediates effector responses to therapeutic antibodies. More importantly, IFNγ was able to up-regulate CD38, the target of the therapeutic antibody daratumumab. Because the antigen (CD38) and effector receptor (FcγRI) were both simultaneously up-regulated on the AML blasts, these investigators tested whether IFNγ treatment of the AML cell lines THP-1 and MV4-11 could stimulate them to target one another after the addition of daratumumab. Results showed that IFNγ significantly increased daratumumab-mediated cytotoxicity, as measured both by 51Cr release and lactate dehydrogenase release assays. These researchers also found that the combination of IFNγ and activation of FcγR led to the release of granzyme B by AML cells. Finally, using a murine NSG model of subcutaneous AML, the authors found that treatment with IFNγ plus

daratumumab significantly attenuated tumor growth. They stated that the findings of these studies showed a novel mechanism of daratumumab-mediated killing and a possible new therapeutic strategy for AML.

Allergy

Blankestijn and colleagues (2017) tested the hypothesis that treatment with daratumumab reduces the levels of total and specific IgE via depletion of IgE-producing plasma cells. These investigators collected residual blood samples from patients with relapsed or refractory MM treated with daratumumab monotherapy or daratumumab plus lenalidomide-dexamethasone. A total of 8 patients with MM were included in this study, 5 treated with daratumumab monotherapy (16 mg/kg) and 3 with daratumumab (16 mg/kg) plus lenalidomide-dexamethasone (25 and 40 mg, respectively); 4 patients had a detectable IgE level (greater than 2 kU/L) at baseline. All 4 subjects demonstrated a decrease in both benign and malignant plasma cells at 8 or 12 weeks of treatment. Only for patient 1, total IgE levels were elevated above reference levels and a positive Phadiatop as well as sIgE against inhalant allergens were detected. Additional samples from patient 1 at week 4, 8, 12, 16, and 20 were analyzed, demonstrating a decrease of more than 80 % in both total and specific IgE levels for timothy grass pollen and house dust mite after 20 weeks. Patient 1 achieved a CR as determined by evaluation of plasma cell percentages in bone marrow aspirate and M-protein levels. The other 3 patients with detectable IgE levels also demonstrated a decrease in total IgE level after 8 weeks of treatment. For patient 2, total IgE levels decreased 88 % (41 to 5 kU/L). For the other 2 patients, baseline IgE levels were very low and dropped below detection limit after 8 weeks. This proof of concept demonstrated that levels of total and specific IgE gradually decreased during daratumumab treatment in a single patient sensitized to 2 common inhalant allergens. The authors concluded that although this proof of concept study demonstrate the potential value of daratumumab in the management of severe IgE-mediated diseases, its effect on clinical parameters of allergy has yet to be investigated.

Antibody-Mediated Rejection in Lung Transplantation

Hulbert and colleagues (2018) noted that there is increasing recognition of the importance of antibody-mediated rejection (AMR) after lung transplantation. The development of donor-specific antibodies, a key feature of AMR, occurs in approximately 30 % of lung transplant recipients and is associated with poor post-transplant outcomes. These investigators highlighted recently developed AMR diagnostic criteria in lung transplantation, potential mechanisms that mediate the development of AMR, and discussed current and emerging treatment strategies for this significant, graft-limiting complication. A major advance is the development of consensus guidelines to precisely define AMR among lung transplant. Regimens for the treatment of AMR continue to evolve with varying success reported with regards to antibody clearance and improving clinical outcomes. A multi-modality treatment approach is common, typically involving a combination of intravenous immunoglobulin (IVIG), plasmapheresis, rituximab, and bortezomib or carfilzomib. Recent studies suggested several new agents including tocilizumab, belimumab, daratumumab, plerixafor, and C1 esterase inhibitor as potentially novel and effective therapies to employ in AMR treatment. The authors concluded that despite advancements in the diagnosis of AMR through well-defined consensus guidelines, there is limited evidence to guide treatment; available data suggested that conventional approaches are of sub-optimal efficacy, but emerging therapeutic agents with diverse biological mechanisms offer promise for improved AMR treatment.

Chronic Lymphocytic Leukemia

Matas-Cespedes and associates (2017) established a proof-of-concept for the effectiveness of daratumumab in the poor prognosis CD38+ chronic lymphocytic leukemia (CLL) subtype. The mechanism of action of daratumumab was assessed in CLL primary cells and cell lines using peripheral blood mononuclear cells to analyze antibody-dependent cell cytotoxicity (ADCC), murine and human macrophages to study antibody-dependent cell phagocytosis (ADCP), or human serum to analyze complement-dependent cytotoxicity (CDC). The effect of daratumumab on CLL cell migration and adhesion to extracellular matrix was characterized. Daratumumab activity was validated in 2 in-vivo models. Daratumumab demonstrated efficient lysis of patient-derived CLL cells and cell lines by ADCC in-vitro and ADCP both in-vitro and in-vivo whereas exhibited negligible CDC in these cells. To demonstrate the

therapeutic effect of daratumumab in CLL, these researchers generated a disseminated CLL mouse model with the CD38+ MEC2 cell line and CLL patient-derived xenografts (CLL-PDX). Daratumumab significantly prolonged OS of MEC2 mice, completely eliminated cells from the infiltrated organs, and significantly reduced disease burden in the spleen of CLL-PDX. The effect of daratumumab on patient-derived CLL cell dissemination was demonstrated in-vitro by its effect on CXCL12-induced migration and in-vivo by interfering with CLL cell homing to spleen in NSG mice. Daratumumab also reduced adhesion of CLL cells to VCAM-1, accompanied by down-regulation of the matrix metalloproteinase MMP9. The authors concluded that these unique and substantial effects of daratumumab on CLL viability and dissemination supported the investigation of its use in a clinical setting of CLL.

CNS Plasmacytoma

Elhassadi and co-workers (2018) stated that CNS myelomatous involvement is a rare complication of MM with dismal outcome. This disease's optimal treatment is unclear. Combined approach of systemic therapy, radiotherapy, and intra-thecal (IT) injections chemotherapy should be considered and ASCT consolidation is offered to eligible patients. These investigators presented a challenging case of relapsed MM with CNS plasmacytoma treated with radiotherapy, IT chemotherapy, and daratumumab, which achieved a durable CR. The authors stated that this was the first report evaluating the efficacy of daratumumab therapy in CNS plasmacytoma in combination with craniospinal radiotherapy and IT chemotherapy; they noted that the role of daratumumab in this disease deserves further evaluation.

Combination of Daratumumab and Doxorubicin Liposomal for the Treatment of Multiple Myeloma

An UpToDate review on “Selection of initial chemotherapy for symptomatic multiple myeloma” (Rajkumar, 2018) states that “The US Food and Drug Administration approved daratumumab in combination with bortezomib, melphalan, and prednisone for the treatment of patients with newly diagnosed MM who are ineligible for autologous stem cell transplant based on these results. While these results suggest that the addition of daratumumab during induction and maintenance can deepen

responses and delay progression, it is not known whether PFS was improved due to the addition of daratumumab, the use of maintenance, or both. It is also not known whether this improved PFS will translate into a survival benefit. Studies combining daratumumab with novel agents are ongoing". This review does no mention the combination of daratumumab and doxorubicin liposomal as a therapeutic option for MM.

Lymphoma

Overdijk and colleagues (2015) examined the contribution of antibody-dependent, macrophage-mediated phagocytosis to daratumumab's mechanism of action. Live cell imaging revealed that daratumumab efficiently induced macrophage-mediated phagocytosis, in which individual macrophages rapidly and sequentially engulfed multiple tumor cells. Using a range of MM and Burkitt's lymphoma cell lines, daratumumab-dependent phagocytosis by mouse and human macrophages was also observed in an in-vitro flow cytometry assay. Phagocytosis contributed to daratumumab's anti-tumor activity in-vivo, in both a subcutaneous and an intravenous leukemic xenograft mouse model. Furthermore, daratumumab was shown to induce macrophage-mediated phagocytosis of MM cells isolated from 11 of 12 MM patients that showed variable levels of CD38 expression. The authors concluded that they showed that phagocytosis is a fast, potent and clinically relevant mechanism of action that may contribute to the therapeutic activity of daratumumab in MM and potentially other hematological tumors.

Wang et al (2015) stated that no standard chemotherapeutic regimens have been defined yet for extra-nodal natural killer/T cell lymphoma (ENKTL), and the prognosis of patients with advanced or relapsed disease is very poor. Daratumumab has been of great interest in the treatment of CD38-expressing malignancies, especially MM. In this study, these investigators reviewed the clinical data of 94 patients with ENKTL, investigated the expression of CD38, and analyzed the prognostic value of CD38 expression; 47 patients had weak expression of CD38, and the other 47 patients had strong expression. The CR rate was significantly higher in patients who were treated with asparaginase-based therapy (83.8 % versus 59.6 %, p = 0.025). There was a trend towards higher CR rate in CD38 weak expression group (78.7 % versus 59.6 %, p = 0.074). At a median follow-up time of 42 months, the 2-year and 5-year

PFS rates were 53.0 % and 39.0 %, respectively, and the 2-year and 5-year OS rates were 68.0 % and 58.0 %, respectively. In multi-variate survival analysis including CD38 expression status, International Prognostic Index (IPI) score, local tumor invasion, and chemotherapeutic regimens, it was found that strong expression of CD38 and non-asparaginase-based chemo-regimens were independent adverse prognostic factors for PFS (p = 0.009 and 0.027, respectively), while local tumor invasion and higher IPI score were independent adverse prognostic factors for OS (p = 0.002 and 0.035, respectively). In subgroup analysis, strong expression of CD38 significantly correlated with inferior survival outcomes in patients without local tumor invasion (p = 0.011) or with stage I-II disease (p = 0.008). The authors concluded that they found that the majority of ENKTL cases were CD38-positive, with 50 % had strong expression of CD38, which significantly correlated with poor outcomes, indicating the potential role of CD38 as a therapy target for ENKTL.

Furthermore, daratumumab is also being investigated for use in (i) relapsed/refractory mantle cell lymphoma, diffuse large B-cell lymphoma, and follicular lymphoma, and (ii) smoldering MM.

A phase II clinical trial on “An Efficacy and Safety Proof of Concept Study of Daratumumab in Relapsed/Refractory Mantle Cell Lymphoma, Diffuse Large B-Cell Lymphoma, and Follicular Lymphoma” is currently recruiting participants (last verified December 2015).

Primary Effusion Lymphoma

Shah and colleagues (2018) noted that primary effusion lymphoma is a rare type of non-Hodgkin’s lymphoma (NHL) that is associated with human immunodeficiency virus (HIV) and human herpesvirus 8 (HHV-8) infections. It typically manifests with lymphomatous pleural and peritoneal effusions. Neoplastic cells have an immunoblastic to plasmablastic appearance, and the diagnosis requires the presence of HHV-8 infection. Most primary effusion lymphomas have lymphocyte activation markers (CD30 and CD38) without normal B-cell markers (CD19 and CD20). The most appropriate treatment regimens for primary effusion lymphoma have not been established, but patients generally receive combination chemotherapy. Although CR rates range from 43 to 57 %, the prognosis remains poor, with an estimated median survival of

approximately 6 months. In a single-case study, these investigators reported the successful use of daratumumab to treat primary effusion lymphoma. The authors concluded that since most patients with primary effusion lymphoma have CD38 expression, daratumumab has the potential to be an effective treatment for patients with this uncommon and aggressive disease. This patient had a clinical response coincident with treatment; this response was confirmed both by imaging and by a reduction in the viral load. They stated that given the rarity of primary effusion lymphoma, large clinical trials evaluating treatment regimens for this condition are unlikely; case series may be a more practical way to evaluate treatment response.

Pure Red Cell Aplasia (PRCA)

Chapuy et al (2018) noted that daratumumab is used to treat multiple myeloma (MM). These researchers described successful treatment with daratumumab in a case of treatment-refractory pure red-cell aplasia after ABO-mismatched allogeneic stem-cell transplantation. The patient was a 72-year old man with the myelodysplastic syndrome who received a transplant from an HLA-matched, unrelated donor with a major ABO incompatibility (blood group A in the donor and blood group O in the recipient). The patient had persistent circulating anti-A antibodies and no red-cell recovery 200 days after transplantation. Standard treatments had no effect. Within 1 week after the initiation of treatment with daratumumab, he no longer required transfusions. The authors concluded that daratumumab might be a valid therapeutic option for patients with no response to standard treatments. This was a single-case study.

Rheumatoid Arthritis and Systemic Lupus Erythematosus

Cole and associates (2018) stated that plasmablasts and plasma cells play a key role in many autoimmune diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). These researchers examined the potential of targeting CD38 as a plasma cell/plasmablast depletion mechanism by daratumumab in the treatment of patients with RA and SLE. RNA-sequencing analysis of synovial biopsies from various stages of RA disease progression, flow cytometry analysis of peripheral blood mononuclear cells (PBMC) from patients with

RA or SLE and healthy donors, immunohistochemistry assessment (IHC) of synovial biopsies from patients with early RA, and ex-vivo immune cell depletion assays using daratumumab were used to evaluate CD38 as a therapeutic target. These investigators demonstrated that the plasma cell/plasmablast-related genes CD38, XBP1, IRF4, PRDM1, IGJ and TNFSF13B were significantly up-regulated in synovial biopsies from patients with arthralgia, undifferentiated arthritis (UA), early RA and established RA as compared to healthy controls and control patients with osteoarthritis (OA). In addition, the highest CD38 expression was observed on plasma cells and plasmablasts compared to natural killer (NK) cells, classical dendritic cells (DCs), plasmacytoid DCs (pDCs) and T cells, in blood from healthy controls and patients with SLE and RA. Furthermore, IHC showed CD38 staining in the same region as CD3 and CD138 staining in synovial tissue biopsies from patients with early RA. Most importantly, these findings showed for the first time that daratumumab effectively depleted plasma cells/plasmablasts in PBMC from patients with SLE and RA in a dose-dependent manner ex-vivo. The authors concluded that these findings suggested that CD38 may be a potential target for RA disease interception and daratumumab should be evaluated clinically for the treatment of both RA and SLE.

Smoldering Multiple Myeloma

A phase II clinical trial on “A Study to Evaluate 3 Dose Schedules of Daratumumab in Participants With Smoldering Multiple Myeloma” is currently recruiting participants (last verified December 2015).

Thalassemia

An UpToDate review on "Management and prognosis of the thalassemias" (Benz and Angelucci, 2019) does not mention daratumumab as a therapeutic option.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

Code	Code Description
Code	**Code Description**
Other CPT codes related to the CPB:	
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
96413 - 96416	Intravenous chemotherapy administration
HCPCS codes covered if selection criteria are met:	
J9144	Injection, daratumumab 10 mg and hyaluronidase-fihj
J9145	Injection, daratumumab, 10 mg
Other HCPCS codes related to the CPB:	
Pomalidomide, lenalidomide, ixazomib, thalidomide - no specific code:	
J1094	Injection, dexamethasone acetate, 1 mg
J1100	Injection, dexamethasone sodium phosphate, 1 mg
J7512	Prednisone, immediate release or delayed release, oral, 1 mg
J8530	Cyclophosphamide; oral, 25 mg
J8540	Dexamethasone, oral, 0.25 mg
J8600	Melphalan; oral, 2 mg
J9041	Injection, bortezomib, 0.1 mg
J9044	Injection, bortezomib, not otherwise specified, 0.1 mg
J9047	Injection, carfilzomib, 1 mg
J9070	Cyclophosphamide, 100 mg
J9176	Injection, elotuzumab, 1 mg
J9245	Injection, melphalan hydrochloride, 50 mg
ICD-10 codes covered if selection criteria are met:	
C90.00, C90.01, C90.02	Multiple myeloma
E85.81	Light chain (AL) amyloidosis
ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):	
C11.0 - C11.9	Malignant neoplasm of nasopharynx
C16.0 - C16.9	Malignant neoplasm of stomach
C18.0 - C18.9	Malignant neoplasm of colon

Code	Code Description
C21.0 - C21.8	Malignant neoplasm of anus and anal canal
C25.0 - C25.9	Malignant neoplasm of pancreas
C34.00 - C34.92	Malignant neoplasm of bronchus and lung
C4A.0 - C4A.9	Merkel cell carcinoma
C50.911 - C50.929	Malignant neoplasm of breast
C51.0 - C51.9	Malignant neoplasm of vulva
C53.0 - C53.9	Malignant neoplasm of cervix uteri
C60.0 - C60.9	Malignant neoplasm of penis
C61	Malignant neoplasm of prostate
C76.0	Malignant neoplasm of head, face and neck
C81.00 - C88.9	Malignant neoplasms of lymphoid
C90.20 - C90.22	Extramedullary plasmacytoma
C91.00 - C91.02	Acute lymphoblastic leukemia
C91.10 - C91.12	Chronic lymphocytic leukemia of B-cell type
C92.00 - C92.02	Acute myeloblastic leukemia
D46.20 - D46.Z	Myelodysplastic syndromes
D56.0 - D56.9	Thalassemia
D58.0 - D58.9	Other hereditary hemolytic anemias
D59.0 - D59.9	Acquired hemolytic anemia
D60.0 - D60.9	Acquired pure red cell aplasia [erythroblastopenia]
D61.01	Constitutional (pure) red blood cell aplasia
E85.82 - E85.9	Other and unspecified amyloidosis

Code	Code Description
G90.50 - G90.59	Complex regional pain syndrome I (CRPS I)
J30.2	Other seasonal allergic rhinitis
M05.00 - M06.9	Rheumatoid arthritis with rheumatoid factor
M32.0 - M32.9	Systemic lupus erythematosus (SLE)
N05.0 - N05.9	Unspecified nephritic syndrome [membrano-proliferative glomerulonephritis]
T86.810 - T86.819	Complications of lung transplant

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