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R&D INSIGHT REPORT

Pomalidomide: First Global Approval

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Abstract Pomalidomide (Pomalyst®) is a small molecule analogue of thalidomide under development with Celgene Corporation for the oral treatment of haematological and connective tissue diseases. Pomalidomide has been approved in the USA and is awaiting approval in the EU for use with low-dose dexamethasone for the treatment of relapsed and refractory multiple myeloma that has progressed following at least two prior therapies, including lenalidomide and bortezomib. The efficacy and safety of pomalidomide as monotherapy in patients with relapsed and refractory multiple myeloma has also been evaluated in a phase III trial. The agent is in phase III clinical development for the treatment of myelofibrosis and in phase II development for systemic sclerosis. Pomalidomide is also being investigated in patients with amyloidosis, prostate cancer, small cell lung cancer, pancreatic cancer, graft-versus-host disease, and Waldenstrom's macroglobulinaemia. This article summarizes the milestones in the development of pomalidomide leading to this first global approval for relapsed and refractory multiple myeloma.

This report has been extracted and modified from the *Adis R&D Insight* drug pipeline database. *Adis R&D Insight* tracks drug development worldwide through the entire development process, from discovery, through pre-clinical and clinical studies to market launch.

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1 Introduction

Multiple myeloma is a relatively rare haematological malignancy that predominately affects the elderly. Although the disease is treatable, clinical responses are transient and the disease is not currently considered curable. Since the late 1990s, the emergence of novel therapeutic options (e.g. thalidomide, bortezomib, lenalidomide and liposomal doxorubicin) for the treatment of multiple myeloma has markedly improved clinical outcomes for patients with the disease [1–4].

Thalidomide was originally developed as a sedative, but was withdrawn from the market because of teratogenicity. However, in further studies, thalidomide was shown to have beneficial activity as an anti-myeloma agent [5]. Consequently, Celgene initiated the research programme into immunomodulatory derivatives of thalidomide (IMiD®) to replicate the anti-myeloma activity of thalidomide while also reducing side effects associated with the drug. IMiD® compounds potently inhibit tumour necrosis factor (TNF)-α and interleukin (IL)-1β, and stimulate IL-10 [6]. In addition, IMiDs enhance T-cell proliferation, natural killer (NK) cell activity, cytotoxic T-cell activity and IL-2 production [7]. The IMiD® lenalidomide is approved for the treatment of multiple myeloma patients who have received at least one prior anti-myeloma therapy in several countries, including the USA and in Europe [3]. Pomalidomide was identified as a lead candidate from Celgene's IMiD® programme (Fig. 1).

In February 2013, the US FDA approved oral pomalidomide (Pomalyst®) for the treatment of multiple myeloma in patients who have received at least two prior therapies, including lenalidomide and bortezomib, and progressed within 60 days after completion of the last therapy [8, 9]. The recommended initial dosage is 4 mg orally once daily without food for days 1–21 of each 28-day cycle until disease progression. It may be given in

Features and properties of pomalidomide

Alternative names	Pomalyst®; Actimid™; CC 4047; CDC 394
Class	Phthalimides, piperidones, small-molecules
Mechanism of action	Angiogenesis inhibitors, apoptosis stimulants, cytokine modulators, IL-6 inhibitors, TNFα inhibitors
Route of administration	Oral
Pharmacodynamics	Induces foetal haemoglobin production and reduces liver damage in sickle cell mice; reduced multiple myeloma induced osteoclast formation through inhibition of RANKL in vitro
Pharmacokinetics	Good oral absorption; maximum plasma concentration attained at 3 h; widely distributed; elimination half-life of 8.9 h; excreted 73 % in urine and 15 % in faeces; extensively metabolized (CYP1A2 and CYP3A4); metabolites do not contribute to activity
Adverse events	
Most frequent	Neutropenia, thrombocytopenia, anaemia, fatigue
Occasional	Diarrhoea, dyspnoea, exanthema, hyperglycaemia, oedema, pneumonia, pneumonitis, thrombosis
ACT codes	
WHO ATC code	B03 (antianemic preparations), D11 (other dermatological preparations), L04A-X (other immunosuppressants)
EphMRA ATC code	B3 (anti-anaemic preparations), D11 (other dermatological preparations), L4 (immunosuppressants), L4B (anti-TNF products)
Chemical Name	1H-Isoindole-1,3-(2H)dione, 4-amino-2-(2,6-dioxopiperidin-3-yl)-
Molecular formula	$C_{13}H_{11}N_3O_4$
CAS registry number	19171-19-8

CYP cytochrome P450, *IL* interleukin, *TNF* tumour necrosis factor

combination with low-dose dexamethasone [9]. Approval was based on response rate; clinical benefit (e.g. improved survival or symptoms) had not been verified. Pomalidomide will be available in the USA through a restricted distribution programme, called Pomalyst® REMS™. The US label for pomalidomide includes a boxed warning of embryo-foetal toxicity and venous thromboembolism [8, 9].

Celgene's New Drug Application (NDA) was based on data from a randomized, open-label, multicentre, phase II trial evaluating oral pomalidomide 4 mg once daily plus low-dose dexamethasone versus pomalidomide alone in patients with relapsed multiple myeloma who were refractory to their last therapy and had received lenalidomide and bortezomib (ClinicalTrials.gov identifier NCT00833833; MM-002) [9, 10]. A marketing application was made for the same indication with the European Medicines Agency (EMA) in May 2012, and the European decision is expected in the second half of 2013 [11].

Under an expanded access programme (EAP), pomalidomide in combination with low-dose dexamethasone is available to patients with relapsed and refractory multiple myeloma in the USA (NCT01632826; PEXIUS; MM-009). The US FDA has granted pomalidomide orphan drug status for the treatment of multiple myeloma and for the treatment of patients with myeloproliferative neoplasm-associated myelofibrosis and anaemia who are red blood cell transfusion-dependent [8]. The EMA has granted pomalidomide orphan drug designation for the treatment of multiple myeloma, systemic sclerosis and primary myelofibrosis, as well as post-essential thrombocythaemia myelofibrosis and post-polycythaemia vera myelofibrosis [12]. Pomalidomide is undergoing phase I trials in Japan for relapsed or refractory multiple myeloma.

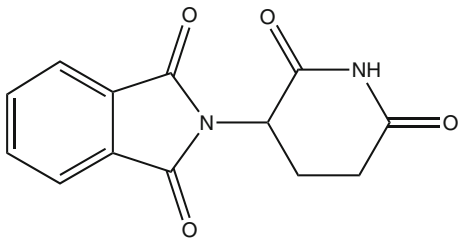
1.1 Patent Information

In November 2001, Celgene was issued US Patent No. 6 316 471, covering the use of pomalidomide to treat cancer and inflammation both as monotherapy and in combination with other therapies. The patent also covers the pharmaceutical compositions of pomalidomide.

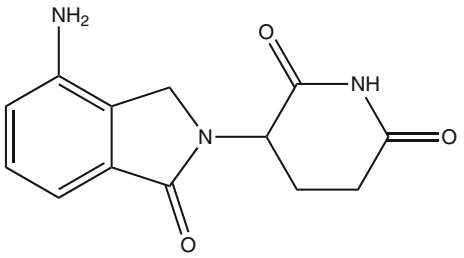
2 Scientific Summary

2.1 Pharmacodynamics

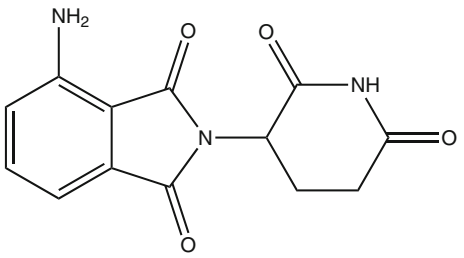
The mechanism of action of pomalidomide is not fully understood. It has immunomodulatory and antineoplastic activity, and has been shown to inhibit the proliferation of multiple myeloma cell lines in vitro and to induce apoptosis [9]. Moreover, pomalidomide inhibits the proliferation of lenalidomide-resistant multiple myeloma cells and shows synergy with dexamethasone to induce tumour cell apoptosis [13]. It inhibits B-cell malignancies in vitro and in vivo, and also displays anti-angiogenic activity in vitro and in vivo in mouse tumour models [9], presumably by reducing the expression of vascular endothelial growth factor (VEGF) and IL-6 [13]. In addition to its immunomodulatory and antineoplastic effects, pomalidomide inhibits cyclooxygenase 2 and prostaglandin production in



Thalidomide



Lenalidomide



Pomalidomide

Fig. 1 Chemical structure of pomalidomide compared with thalidomide and lenalidomide

lipopolysaccharide-stimulated peripheral blood mononuclear cells (PBMCs), suggesting it would exert important anti-inflammatory activity [6, 14].

As noted, pomalidomide inhibits TNFα production from stimulated PBMCs much more potently than thalidomide and also inhibits the production of IL-1β and IL-6. It enhances the production of IL-2 from stimulated PBMCs, which increases the activity of NK cells [7]. The induction of IL-2 and interferon-γ by pomalidomide in peripheral blood or bone marrow cells from patients with multiple myeloma may result from down-regulation of suppressor of cytokine signalling (SOCS)1 [15]. Pomalidomide was also significantly more potent than thalidomide in inhibiting tumour growth and angiogenesis in vivo in a mouse model [16]. The anti-myeloma activity of pomalidomide appears to depend upon the presence of cereblon (*CRBN*), the primary target of thalidomide teratogenicity, as a target for binding on myeloma cells [17].

Pomalidomide reduced multiple myeloma-induced osteoclast formation from CD14+ progenitor cells in the presence of RANKL and macrophage-colony stimulating factor [18], presumably due to down-regulation of PU.1 [19]. In primary bone marrow stromal cells and osteoprogenitor cells, obtained from patients with multiple myeloma, pomalidomide inhibited RANKL expression and secretion. This was not observed in activated T lymphocytes at concentrations of 2–100 μmol/L. Further studies showed pomalidomide reduced expression of CD49d, which is involved in the upregulation of RANKL. No changes in levels of the pro-osteoclastogenic factors CCL/MIP-1a, IL-3 and IL-7 were observed [18].

An 8-week preclinical trial in a knockout-transgenic mouse model of sickle cell anaemia demonstrated that pomalidomide enhanced erythropoiesis and augmented foetal haemoglobin, while the total white blood cell count was largely unaffected [20]. Pomalidomide-treated animals showed a trend towards increased marrow hyperplasia, while liver histology revealed decreased tissue inflammation and focal necrosis in approximately 50 % of animals. Pomalidomide was also shown to improve erythropoiesis and enhance foetal haemoglobin in human CD34+ cells [21]. These results suggest that pomalidomide may prove useful in the treatment of sickle-cell disease and β-thalassaemia.

2.2 Pharmacokinetics

Following single-dose oral administration of radiolabeled pomalidomide 2 mg suspension in healthy male volunteers, the mean maximum plasma concentration (C_{max}) of 13 ng/mL was attained after a time (t_{max}) of 3.0 h [22]. The area under the plasma concentration–time curve from time zero to infinity (AUC_{∞}) was 189 ng · h/mL. The mean total recovery of radioactivity was 88 %, indicating good bioavailability [22]. In patients with multiple myeloma receiving pomalidomide 4 mg once daily, the steady-state C_{max} was 75 ng/mL and the AUC at steady-state (AUC_{τ}) was 400 ng · h/mL [9]. The mean apparent volume of distribution in patients was 62–138 L [9].

Pomalidomide was extensively metabolized, but unchanged pomalidomide accounted for 70 % of the circulating radioactivity, and the exposure (AUC) to metabolites ranged from only 1.7 % to 6.3 % of total radioactivity [22]. However, unchanged pomalidomide in the urine accounted for <3 % of the dose, whereas three of the metabolites in urine together accounted for 52 % of the dose. The elimination half-life ($t_{½}$) of pomalidomide was 8.9 h, and the mean recovery of radioactivity was 73 % in urine and 15 % in faeces. More than 80 % of the radioactivity was recovered in the first 48 h after administration. The t_{max} and $t_{½}$ values for the metabolites were similar to those for the parent drug [22].

Pomalidomide was primarily metabolized (43 % of the dose) by cytochrome P450 (CYP) enzymes in the liver, predominantly CYP1A2 and CYP3A4, with minor contributions from CYP2C19 and CYP2D6 [22]. The metabolites were ≥26-fold less pharmacologically active than the parent drug [22].

2.3 Therapeutic Trials

2.3.1 Multiple Myeloma

Pomalidomide in combination with low-dose dexamethasone significantly improved progression-free survival (PFS) (primary endpoint) compared with high-dose dexamethasone (median 15.7 weeks vs. 8.0 weeks; hazard ratio [HR] 0.45; $p < 0.001$) in the phase III MM-003 trial, in patients with relapsed or refractory multiple myeloma [23]. This trial investigated the efficacy and tolerability of pomalidomide in combination with low-dose dexamethasone versus high-dose dexamethasone alone in patients with relapsed or refractory multiple myeloma who had received at least two prior therapies including both lenalidomide and bortezomib. A total of 455 patients were randomized (2:1) to receive oral pomalidomide 4 mg on days 1–21 of each 28-day cycle plus low-dose (40 mg weekly) oral dexamethasone ($n = 302$) or high-dose dexamethasone (40 mg on days 1–4, 9–12 and 17–20 of each 28-day cycle) alone ($n = 153$) until disease progression. Patients age >75 years received 20-mg doses of dexamethasone instead of 40-mg doses within each arm according to the relevant schedules. OS was also significantly better in the pomalidomide group at interim analysis (median overall survival [OS] not reached vs. 34 weeks; HR 0.53; $p < 0.001$). This analysis included 45 patients who received pomalidomide after progressing on high-dose dexamethasone [23].

Results from the pivotal phase II trial that supported the NDA in the USA (trial MM-002) showed that pomalidomide (4 mg once daily for days 1–21 of each 28-day cycle) plus low-dose dexamethasone (20–40 mg once daily on days 1, 8, 15 and 22 of each 28-day cycle) ($n = 113$) resulted in a partial response (PR) rate (or better) of 34 %, compared with 13 % for pomalidomide alone ($n = 108$) in heavily pretreated (including two or more cycles of lenalidomide and bortezomib separately or in combination) patients with relapsed or refractory multiple myeloma [10]. The primary endpoint was PFS, and after a median treatment duration of 5.0 months, median PFS was 4.6 months and 2.6 months in the two study groups, respectively. The comparison indicated that pomalidomide in combination with low-dose dexamethasone was associated with greater clinical benefit and no increased toxicity compared with pomalidomide alone [10], and at progression, patients receiving pomalidomide alone could receive the addition of dexamethasone at the investigator's discretion [24]. In updated results from the end of March 2012 in patients receiving pomalidomide plus low-dose dexamethasone ($n = 113$), PFS and OS were 4.6 and 16.5 months, respectively [24], and treatment was associated with improvement in clinically important end-organ functional parameters with potential prognostic significance [25]. The phase I part of this trial had earlier identified 4 mg/day as the maximum tolerated dose (MTD) and the recommended dose for the phase II trial [26].

A five-cohort, sequential phase II trial (NCT00558896) conducted by the Mayo Clinic investigated pomalidomide combined with low-dose dexamethasone in 225 patients with relapsed or refractory multiple myeloma. Patients were grouped according to disease status: relapsed/refractory myeloma; lenalidomide refractory myeloma (2-mg dose); lenalidomide- and bortezomib-refractory myeloma (2-mg dose); lenalidomide- and bortezomib-refractory myeloma (4-mg dose); and lenalidomide-refractory myeloma, 1–3 prior regimens, (4-mg dose) [27]. Pomalidomide was administered on days 1–28 of a 28-day cycle and oral dexamethasone 40 mg daily on days 1, 8, 15 and 22 of each cycle [27–30]. Responses were assessed using the criteria published by the International Myeloma Working Group [31].

Pomalidomide plus low-dose dexamethasone was highly active in the population with relapsed myeloma ($n = 60$) with 38 patients (63 %) achieving an objective response to therapy, including three (5 %) patients with a complete response (CR), 17 patients (28 %) with very good partial response (VGPR), and 18 (30 %) with a PR [28]. Lack of cross resistance with lenalidomide was established in the cohort of 34 patients with lenalidomide-refractory disease receiving pomalidomide 2 mg daily, with an overall response rate (ORR) of 47 % [29]. This included three patients (9 %) with VGPR, eight (23 %) with PR and five (15 %) with minor response (MR). The median duration of response was 9.1 months, median PFS was 4.8 months and the median OS 13.9 months [29]. Pomalidomide was shown to overcome resistance in myeloma refractory to both lenalidomide and bortezomib [30]. Pomalidomide 2 mg daily or 4 mg daily (both on days 1–28 of a 28-day cycle) were evaluated in two sequentially treated cohorts in patients who had failed both these agents. The ORR (MR or better) was 49 % in the pomalidomide 2-mg cohort ($n = 35$) and 43 % in the pomalidomide 4-mg cohort ($n = 35$). Event-free survival at 6 months was 78 % and 67 % in the 2-mg and 4-mg cohorts, respectively, suggesting no advantage for the 4-mg dose with the continuous regimen used in this study [30]. The confirmed response rate (≥PR) was 37 % for the cohort with lenalidomide-resistant myeloma (1–3 prior regimens) receiving the higher pomalidomide dose of 4 mg ($n = 60$), with the PFS 63 % and OS 93 % at 6 months [27]. A confirmed response rate (≥PR) of 21 % was reported with pomalidomide 4 mg daily in an

additional 6th cohort of 120 patients with lenalidomide-resistant myeloma [32]. The 6-month PFS and OS were 34 % and 74 %, respectively.

A 31 % response was seen in 13 patients with extramedullary disease (EMD) in a substudy of 174 patients in the Mayo Clinic phase II trial [33]. This included one CR and two PRs (≥50 % reduction in EMD.

The intermittent regimen of pomalidomide 4 mg/day on days 1–21 per 28-day cycle and the continuous regimen of pomalidomide 4 mg daily were similarly effective in 84 patients with multiple myeloma refractory to lenalidomide and bortezomib. The ORR was 34.5 %, and 47 % of patients had stable disease (SD). Also similar across groups were duration of response, time to progression (TTP) and PFS of 7.3 (95 % CI 5–15), 5.4 (4–8) and 4.6 (4–7) months, respectively. OS at 18 months was 14.9 (95 % CI 11–20) months, with 44 % of patients alive at 18 months. All patients received oral dexamethasone 40 mg/day in this phase II trial conducted by the Intergroupe Francophone du Myélome [IFM 2009-02; NCT01053949] [34].

PFS was 10.5 months and median OS was 33 months in 17 patients who continued pomalidomide 1 mg, 2 mg or 5 mg on alternate days after an expanded access extension of a 4-week phase I dose-escalation study to determine the MTD. The MTD of pomalidomide 1 mg, 2 mg, 5 mg and 10 mg on alternate days was defined as 5 mg in this dose-escalating phase I trial in 20 patients with relapsed myeloma [35]. An earlier phase I dose-escalating study of daily pomalidomide 1 mg, 2 mg, 5 mg and 10 mg for 4 weeks by these researchers had defined the MTD as 2 mg/day, with neutropenia the dose-limiting toxicity (DLT) in 24 patients with relapsed or refractory myeloma [36].

2.3.1.1 In Combination with Other Anticancer Agents
The ORR (≥PR) was 53.6 %, and median PFS was 8.2 months in a phase II trial of clarithromycin 500 mg twice daily with pomalidomide (4 mg on days 1–21 of a 28-day cycle) and low-dose dexamethasone in 100 patients with relapsed/refractory multiple myeloma. Eligible patients had at least three prior lines of therapy, including lenalidomide. Median OS had not been reached after a mean follow-up of 10.1 months [37].

The 1-year PFS and OS rates were 52 % and 78 %, respectively, after a median follow-up of 11 months in an early trial investigating alternate day cyclophosphamide in combination with pomalidomide and prednisone. Patients with multiple myeloma relapsed/refractory to lenalidomide ($n = 52$) received pomalidomide 2.5 mg/day, cyclophosphamide 50 mg every other day and prednisone 50 mg every other day on days 1–28 for six cycles, followed by pomalidomide plus prednisone [38].

Phase I studies to determine the MTD for pomalidomide in combination with low-dose dexamethasone plus bortezomib [39], low-dose dexamethasone plus carfilzomib [40], and prednisone plus oral weekly cyclophosphamide [41] have been completed, with further trials of these combinations now underway or planned.

2.3.2 *Myelofibrosis*

Pomalidomide, with or without concomitant prednisone therapy, was efficacious in the treatment of patients ($n = 84$) with myelofibrosis and associated anaemia in a phase II trial conducted by the Mayo Clinic (NCT00463385) [42]. Patients were equally randomized to receive pomalidomide 2 mg/day + placebo, pomalidomide 2 mg/day + prednisone 30 mg/day, pomalidomide 0.5 mg/day + prednisone 30 mg/day or prednisone 30 mg/day + placebo. Therapy was given for up to 12 treatment cycles of 28 days. After a median treatment period of 4.6 months, the anaemia response rates in the four arms were 23 %, 16 %, 36 % and 19 %, respectively. Pomalidomide had no effect on other features of myelofibrosis, such as splenomegaly or fibrosis. The median duration of anaemia response for the 16 patients responding to pomalidomide (with or without prednisone) was 7.8 months, and two relapsed during this period (compared with three of four prednisone-alone responders who relapsed) [42].

In an earlier phase II study also by the Mayo Clinic (NCT00669578) in which patients with myelofibrosis ($n = 58$) received low-dose pomalidomide 0.5 mg once daily for 21 days per 28-day cycle, the anaemia response rate was 17 %, and nine of the ten responders became transfusion independent [43]. Seventy-two percent of the patients were positive for the *JAK2*V617F allele, and a response was only seen in those patients with the allele (24 vs. 0 %; $p = 0.03$) [43].

The MTD of pomalidomide in myelofibrosis was confirmed as 3.0 mg/day in 19 patients treated with pomalidomide 2.5, 3.0 or 3.5 mg/day in a phase I dose-escalation study [44]. The DLT (bone marrow suppression) was observed in two of three subjects in the 3.5 mg/day cohort. Patients did not respond at a dose of 3.0 mg/day, but seven of eight had durable responses (i.e. anaemia response [plus a decrease in splenomegaly in two patients]) when the dose was reduced to 0.5 mg/day [44].

A recent report of long-term follow-up (median 27 months) of 94 patients from these Mayo Clinic studies concluded that pomalidomide has palliative value in patients with myelofibrosis and anaemia. Overall anaemia response was 27 % and was more likely to occur in patients without marked splenomegaly (46 vs. 12 %; $p = 0.0005$), the presence of <5 % circulating blasts (32 vs. 0 %; $p = 0.03$), and the presence of *JAK2*V617F (32 vs. 17 %; $p = 0.17$) [45].

2.3.3 Prostate Cancer

In a phase II noncomparative trial, pomalidomide administered daily for 12 weeks resulted in disease stabilization in 42 % of patients with castration-resistant prostate cancer [46]. Patients received oral pomalidomide 1 mg/day ($n = 15$) or 2 mg/day ($n = 16$) continuously for 12 weeks. Three patients in the 2-mg arm and none in the 1-mg arm showed a reduction in prostate-specific antigen (PSA) level of >50 %. With respect to tumour response, one patient in the 1-mg arm had a PR and seven had SD, while seven patients in the 2-mg arm had SD. Median times to progression in the 1-

Key clinical trials

Drugs	Indication	Study phase	Study status	Study location	Trial identifier	Association
Pomalidomide, dexamethasone	Multiple myeloma (combination therapy, second-line or greater, relapsed and/or refractory)	EAP	Recruiting	USA	NCT01632826; PEXIUS; MM-009	Celgene
Pomalidomide, dexamethasone	Multiple myeloma (combination therapy, second-line or greater, relapsed and/or refractory)	III	Recruiting	Multinational	NCT01712789; STRATUS; MM-010	Celgene
Pomalidomide, dexamethasone, bortezomib	Multiple myeloma (combination therapy, second-line or greater, relapsed and/or refractory)	III	Recruiting	USA	NCT01734928; OPTIMISMM; MM-007	Celgene
Pomalidomide, dexamethasone	Multiple myeloma (combination therapy, second-line or greater, relapsed and/or refractory)	III	Active, not recruiting	Multinational	NCT01311687; NIMBUS; MM-003	Celgene
Pomalidomide	Multiple myeloma (monotherapy, second-line or greater, relapsed and/or refractory)	III	Recruiting	Multinational	NCT01324947; MM-003/C	Celgene
Pomalidomide, dexamethasone	Multiple myeloma (combination therapy, second-line or greater, relapsed and/or refractory)	II	Active, not recruiting	North America	NCT00833833; MM-002	Celgene
Pomalidomide, dexamethasone	Multiple myeloma (combination therapy, second-line or greater, relapsed and/or refractory)	II	Active, not recruiting	USA	NCT00558896	Mayo Clinic; National Cancer Institute; Celgene
Pomalidomide, dexamethasone	Multiple myeloma (combination therapy)	II	Recruiting	France	NCT01745640; IFM2010-02	University Hospital, Lille; Celgene
Pomalidomide, dexamethasone	Multiple myeloma (combination therapy, second-line or greater, relapsed and/or refractory)	II	Active, not recruiting	France	NCT01053949; IFM2009-02	University Hospital, Lille; Celgene
Pomalidomide, dexamethasone, melphalan	Multiple myeloma (combination therapy, second-line or greater, relapsed and/or refractory)	II	Recruiting	USA	NCT01745588	Celgene
Pomalidomide, dexamethasone, clarithromycin	Multiple myeloma (combination therapy, second-line or greater, relapsed and/or refractory)	II	Recruiting	USA	NCT01159574	Celgene
Pomalidomide	Multiple myeloma (monotherapy, second-line or greater, relapsed and/or refractory)	II	Recruiting	USA	NCT01319422	Celgene
Pomalidomide	Multiple myeloma (monotherapy, second-line or greater, relapsed and/or refractory)	II	Completed	USA	NCT01177735	Celgene
Pomalidomide	Myelofibrosis	III	Recruiting	Multinational	NCT01178281; RESUME; MF-002	Celgene
Pomalidomide	Myelofibrosis	II	Recruiting	USA	NCT00946270	Celgene
Pomalidomide	Myelofibrosis	II	Active, not recruiting	Multinational	NCT00463385; MMM-001	Celgene
Pomalidomide	Systemic sclerosis	II	Recruiting	Multinational	NCT01559129; SSC-001	Celgene

EAP expanded access programme

and 2-mg arms were 2.9 and 5.9 months, while OS values were 34.17 and 46.97 months, respectively [46].

2.3.4 Immunoglobulin Light-Chain (AL) Amyloidosis

A confirmed haematological response (primary endpoint) was achieved in 48 % of previously treated patients with immunoglobulin light-chain (AL) amyloidosis ($n = 33$) as part of a sequential phase II trial of pomalidomide 2 mg daily plus oral dexamethasone 40 mg/week (NCT00558896) [47]. The breakdown of haematological responses was PR 30 %, VGPR 15 % and CR 3 %. The median PFS was 14.1 months and the median OS was 27.9 months. The 1-year PFS and OS rates were 59 % and 76 %, respectively [47].

2.3.5 Other Indications

Preliminary data from a pilot phase II trial (NCT00770757) have shown that pomalidomide was active in advanced corticosteroid-resistant, chronic graft-versus-host-disease (cGVHD). Eight patients have been enrolled to date and three have completed 6 months of therapy. Two patients have a CR and one has a PR of erythematous skin changes and a CR of gastrointestinal symptoms. It is suggested that pomalidomide 3 mg/day is too high a starting dose in this patient population and pomalidomide 1–2 mg/day is recommended for future trials [48, 49].

Phase I dose-escalation trials have investigated the use of pomalidomide as monotherapy in patients with advanced solid tumours (NCT00540579) [50], in combination with gemcitabine in metastatic pancreatic cancer [51], and in combination with cisplatin and etoposide in small cell lung cancer (NCT00537511).

2.4 Adverse Events

2.4.1 Multiple Myeloma

The major toxicity in all trials reported has been neutropenia, followed by anaemia and thrombocytopenia. The rate of grade 3/4 neutropenia varies with the dose of pomalidomide and how heavily pre-treated the patient population is [52]. Venous thromboembolism (VTE) occurred with a frequency similar to those of other IMiDs, and thromboprophylaxis (mostly as low-dose daily aspirin) was administered in all trials [9, 52].

In the MM-003 phase III study ($n = 455$), the most common grade 3/4 haematological toxicities for the pomalidomide plus low-dose dexamethasone group and high-dose dexamethasone group, respectively, were neutropenia (42 vs. 15 %), thrombocytopenia (21 vs. 24 %), and febrile neutropenia (7 vs. 0 %). Other grade 3/4 toxicities were mainly infections (24 vs. 23 %), haemorrhage (3 vs. 5 %), and glucose intolerance (3 vs. 7 %), for the pomalidomide and comparator groups, respectively. VTE developed in 1 vs. 0 % of patients, and peripheral neuropathy occurred in 1 vs. 1 %. Progressive disease was the main reason for discontinuation: 35 % for pomalidomide plus low-dose dexamethasone recipients and 49 % for the high-dose dexamethasone recipients [23].

The most common grade 3 or 4 haematological adverse events occurring in ≥5 % of patients ($n = 113$) receiving pomalidomide plus low-dose dexamethasone in the pivotal MM-002 trial were neutropenia (41 %), anaemia (22 %), thrombocytopenia (19 %) and leukopenia (10 %) [24]. Other grade 3/4 events were pneumonia (22 %), fatigue (14 %), dyspnoea (13 %), back pain (10 %) and urinary tract infection (9 %). Neutropenia led to a dose reduction in 4 % of patients, and overall, 26 % of patients required a dose reduction for an adverse event. There were no reports of grade 3 or 4 neuropathy, and deep vein thrombosis (any grade) occurred in two patients (2 %) [24].

In the Mayo Clinic phase II series (NCT00558896) of pomalidomide combined with low-dose dexamethasone ($n = 345$), the most common toxicity was myelosuppression [32]. Grade 3 or 4 neutropenia occurred in 31 % of patients, anaemia in 16 %, thrombocytopenia in 12 %, and pneumonia and fatigue each in 8 %. Ten patients (3 %) experienced VTE [32]. In the heavily pre-treated patients refractory to both lenalidomide and bortezomib ($n = 70$), grade 3 or 4 neutropenia regardless of attribution was seen in 51 %, and 66 % of patients receiving pomalidomide 2 mg and 4 mg, respectively [30]. Peripheral neuropathy was experienced by 60 of these patients during treatment, with 16 experiencing a worsening grade; however, baseline neuropathy was present in 53 [30].

2.4.2 Myelofibrosis

In the phase II trial (NCT00463385) in patients with myelofibrosis ($n = 84$) who received pomalidomide, with or without prednisone, or prednisone alone, grade ≥3 adverse events included fatigue/asthenia (12 % of patients), thrombocytopenia (11 %), pneumonia/sepsis (11 %), anaemia (10 %), neutropenia (8 %), fatigue (7 %), hyperglycaemia (5 %), thrombosis (4 %), diarrhoea (4 %) and bleeding (4 %) [42]. Six patients discontinued therapy as a result of adverse events. Thrombocytopenia (10 %), anaemia (8 %) and neutropenia (7 %) were the most common drug-related adverse events with pomalidomide 0.5 mg/day in the earlier phase II study (NCT00669578; $n = 58$) [43]. Grade 1 sensory neuropathy developed in 4 (13 %) of 30 patients from these Mayo Clinic trials who were treated for ≥12 months,

suggesting the incidence of treatment-emergent peripheral neuropathy may increase with treatment duration [45].

2.5 Ongoing Clinical Trials

2.5.1 Multiple Myeloma

2.5.1.1 With Dexamethasone Celgene is conducting the phase III STRATUS trial, which will assess the tolerability, efficacy and pharmacokinetics of pomalidomide and dexamethasone in patients with refractory, or relapsed and refractory multiple myeloma (NCT01712789; MM-010). This trial will enrol approximately 507 subjects from Europe.

A phase II trial is investigating the efficacy and tolerability of pomalidomide plus dexamethasone, in multiple myeloma patients with deletion 17p or translocation (4;14) adverse karyotypic abnormalities. Approximately 55 patients are expected to be enrolled into the trial in France. The trial is sponsored by the University Hospital, Lille, in collaboration with Celgene (NCT01745640; IFM2010-02).

A phase I study was initiated in June 2012 to assess the pharmacokinetics of pomalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma and renal impairment (NCT01575925; MM-008; POM Renal). The non-randomised, open-label, dose-escalation study expects to enrol approximately 36 patients in the USA.

2.5.1.2 In Combination with Other Anticancer Agents Celgene is recruiting approximately 782 patients in the USA into a phase III trial to evaluate the safety and efficacy of pomalidomide, bortezomib and low-dose dexamethasone for the treatment of relapsed or refractory multiple myeloma (NCT01734928; OPTIMISMM). This randomized, open-label trial will evaluate the effect of pomalidomide added to bortezomib and low-dose dexamethasone compared with bortezomib and low-dose dexamethasone. The primary endpoint is PFS assessed for up to 1 year.

In December 2012, a Tristate Consortium in the USA in collaboration with Celgene, initiated a phase II trial to compare the efficacy and tolerability of pomalidomide and dexamethasone, with or without melphalan plus autologous stem cell transplantation, in approximately 44 patients with relapsed multiple myeloma (NCT01745588). A phase I/II clinical trial is evaluating pomalidomide, dexamethasone and pegylated liposomal doxorubicin in approximately 40 patients with relapsed/refractory multiple myeloma in the USA (NCT01541332) [53]. Celgene, in collaboration with Duke University, is planning a phase I/II study to investigate the tolerability and efficacy of the combination of bendamustine and pomalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma in the USA (NCT01754402). However, the recruitment has not commenced as of December 2012.

2.5.1.3 Monotherapy A phase III clinical trial has been initiated to evaluate the efficacy and safety of pomalidomide monotherapy in approximately 85 patients who enrolled into the NIMBUS study and discontinued treatment with high-dose dexamethasone due to disease progression (NCT01324947). As of May 2012, enrolment of patients is still ongoing in Australia, France, Germany, Italy, Spain and the UK.

The University of Arkansas initiated a phase II trial of pomalidomide in gene-expression profiling (GEP)-defined, high-risk relapsing/refractory multiple myeloma, in collaboration with Celgene in October 2011 (NCT01177735). The trial is attempting to determine GEP changes over time following treatment initiation. Enrolment of approximately 30 patients from the USA is planned. However, in August 2012, enrolment was suspended because of regulatory non-compliance. There were no safety risks or concerns.

In June 2011, Yale University initiated a phase II trial in collaboration with Celgene to assess the efficacy and tolerability of continuous versus intermittent pomalidomide in the treatment of patients with relapsed or refractory multiple myelom. The primary endpoint is the clinical response rate after two cycles of treatment (56 days). The open-label, parallel assignment trial aims to enrol 48 patients in the USA (NCT01319422).

Celgene is conducting a phase I trial in Japan to determine the MTD and evaluate the pharmacokinetics of pomalidomide in approximately 12 patients with relapsed or relapsed and refractory multiple myeloma (NCT01568294).

2.5.2 Myelofibrosis

Celgene has initiated a phase III trial to assess the safety and efficacy of pomalidomide in reversing red blood cell transfusion dependence in 210 patients with myeloproliferative neoplasm-associated myelofibrosis (NCT01178281; RESUME; MF-002). Enrolment was completed in the first quarter of 2012 at sites in the USA, Canada, Australia, the EU, Russia and Japan. Data from this trial are expected in 2013.

Celgene is collaborating with the University of Texas M.D. Anderson Cancer Centre, which is conducting a phase II clinical trial to assess the efficacy of pomalidomide in approximately 50 patients with myelofibrosis (NCT00946270).

2.5.3 Other Indications

Celgene is evaluating the safety, pharmacokinetics and pharmacodynamics of pomalidomide in a phase II trial in

patients with diffuse cutaneous systemic sclerosis with interstitial lung disease. Approximately 88 patients are expected to be enrolled in this randomised, double-blind, proof-of-concept, placebo-controlled trial in the USA, Australia, Germany, Italy, Spain, Switzerland, and the United Kingdom. The trial may expand to France, Poland and Russia (NCT01559129; SSC-001; EudraCT2010-023047-15).

Celgene is collaborating with the University of Texas M.D. Anderson Cancer Centre, which is conducting a phase I trial of pomalidomide in patients with relapsed or refractory Waldenstrom's macroglobulinaemia (WM) (NCT01198067). The non-randomised, open-label trial will evaluate the MDT of the agent that can be administered, as well as the overall safety of the drug. Approximately 30 patients will be enrolled in the USA. A phase I clinical trial is evaluating pomalidomide in combination with dexamethasone and rituximab in the treatment of WM (NCT01078974). Recruitment of participants was completed in mid-2012. This open-label trial, which began in May 2010, is being conducted in approximately 24 subjects from the Dana-Farber Cancer Institute in the USA and is expected to be completed in the second half of 2013.

3 Current Status

Pomalidomide received its first global approval on the 8th of February 2013 in the USA for the treatment of patients with multiple myeloma who have received at least two prior therapies, including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy.

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