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MONOGRAPH

POMALIDOMIDE

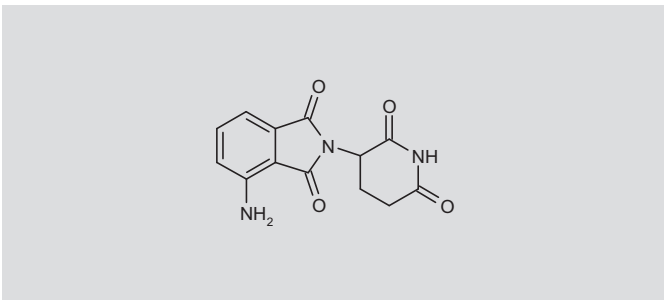
Rec INN; USAN

TNF-α Production Inhibitor
Treatment of Multiple Myeloma
Treatment of Myelofibrosis

CC-4047
CDC-394
IMID-4047
IMiD1

4-Amino-2-(2,6-dioxopiperidin-3-yl)-1,2-dihydroisoindole-1,3-dione

InChI: 1S/C13H11N3O4/c14-7-3-1-2-6-10(7)13(20)16(12(6)19)8-4-5-9(17)15-11(8)18/h1-3,8H,4-5,14H2,(H,15,17,18)



$C_{13}H_{11}N_3O_4$

Mol wt: 273.2441

CAS: 19171-19-8

EN: 269739

SUMMARY

Pomalidomide (CC-4047) is an immunomodulatory drug (termed IMiD®) that is structurally related to thalidomide and exhibits multimodal anticancer activity and is in late-stage clinical development for the oral treatment of refractory multiple myeloma (MM) and myeloproliferative neoplasm-associated myelofibrosis. Early data suggest efficacy for this drug in MM, with up to 49% overall response rates with pomalidomide combined with dexamethasone in patients refractory to both lenalidomide, an IMiD® structurally related to pomalidomide and thalidomide, and bortezomib, a reversible proteasome inhibitor. Response rates in myeloma are measured as the sum of the clinical responses divided by the number of patients studied and include maintenance, decrease or complete removal of serum abnormal myeloma antibodies (M-component) and maintenance, partial or complete eradication of malignant plasma cells in the bone marrow. In myelofibrosis, a 36% overall response rate (measured by maintenance, partial or complete reduction in bone marrow fibrosis and cancer cells, reduction of spleen enlargement and improvement or normalization of anemia) was observed for a cohort of patients on low-dose pomalidomide with prednisone. In 2009, pomalidomide received orphan drug status in the E.U. for the treatment of multiple myeloma, and it has also received orphan drug designation for myelofibrosis. The following article describes the history of pomalidomide, its preclinical pharmacology and mechanisms of action, clinical studies undertaken so far and its potential overall as a multimodal anticancer agent.

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SYNTHESIS*

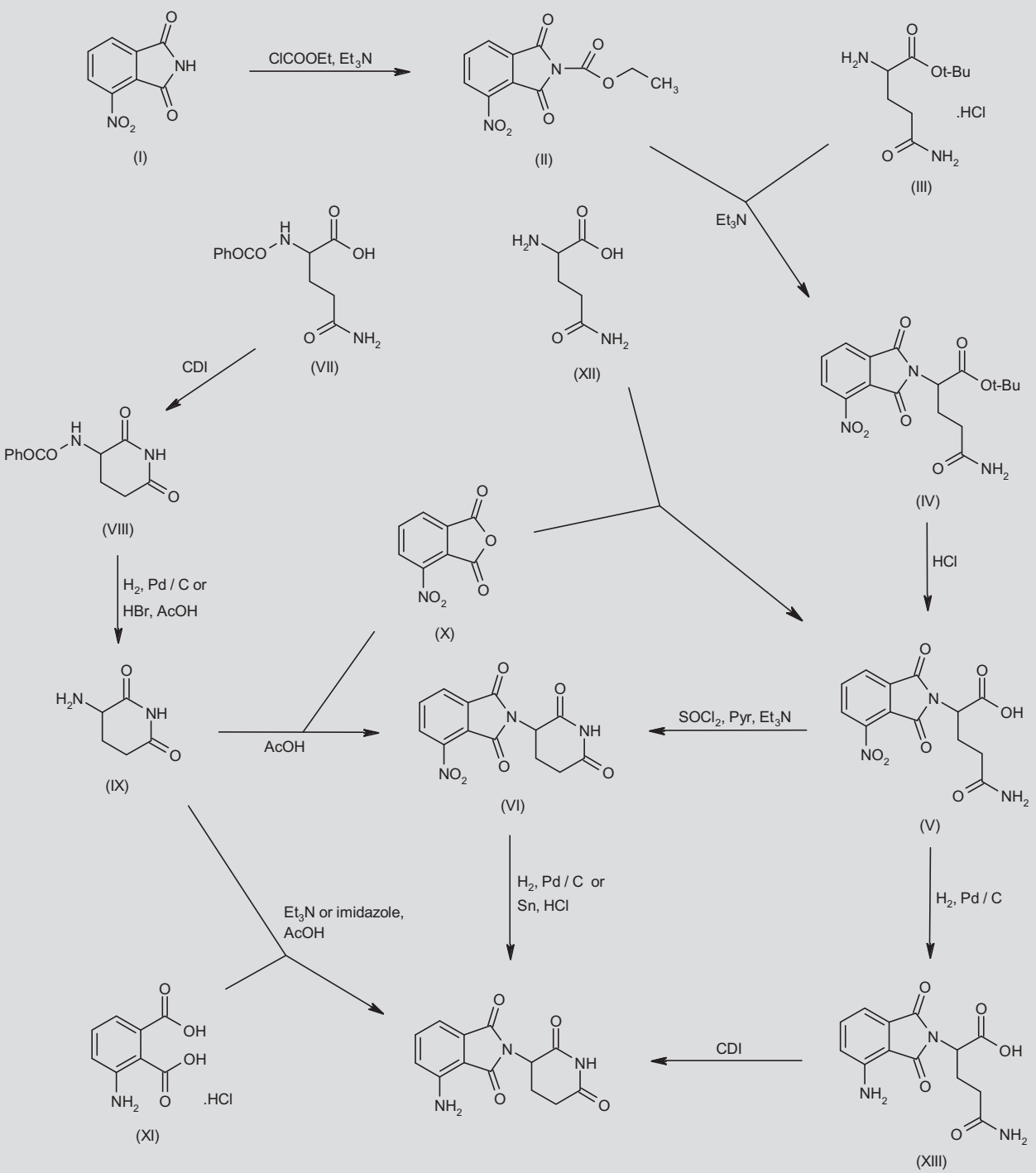
Pomalidomide can be prepared by the following strategies:

1) Treatment of 3-nitrophthalimide (I) with ethyl chloroformate in the presence of Et_3N in DMF produces the *N*-(ethoxycarbonyl)phthalimide derivative (II), which is condensed with glutamine *tert*-butyl ester (III) by means of Et_3N in refluxing THF to afford the phthaloyl-glutamine derivative (IV). Hydrolysis of the *tert*-butyl ester group of compound (IV) with HCl in CH_2Cl_2 yields the corresponding carboxylic acid (V), which is cyclized by means of $SOCl_2$ in the presence of pyridine and Et_3N in CH_2Cl_2, resulting in the corresponding glutarimide (VI) (1-3). Finally, the nitro group of glutarimide (VI) is reduced by catalytic hydrogenation over Pd/C in acetone (1-3) or with Sn/HCl (1, 4). Scheme 1.

Pure enantiomers of pomalidomide can been prepared using the corresponding enantiomers of glutamine *tert*-butyl ester (III), as the cyclization of phthaloyl-glutamine (V) takes place without racemization, resulting in the corresponding enantiomeric glutarimides.

The nitrophthalimide precursor (VI) can be alternatively obtained by cyclization of *N*-(benzyloxycarbonyl)glutamine (VII) by means of CDI

Scheme 1. Synthesis of Pomalidomide



in refluxing THF to afford the glutarimide derivative (VIII), which is then *N*-deprotected to 2-aminoglutarimide (IX) by either hydrogenolysis over Pd/C or by treatment with HBr in AcOH. Finally, aminoglutarimide (IX) is condensed with 3-nitrophthalic anhydride (X) using AcOH at reflux (1, 4). Scheme 1.

2) Cyclization of 3-aminophthalic acid hydrochloride (XI) with 2-aminoglutarimide (IX) using Et_3N or imidazole, optionally in the presence of AcOH in acetonitrile (3). Scheme 1.

3) Condensation of 3-nitrophthalic anhydride (X) with glutamine (XII) in DMF yields *N*-(3-nitrophthaloyl)glutamine (V), which is reduced with H_2 over Pd/C to give the corresponding amine (XIII). Finally, this compound undergoes cyclization by means of CDI (3). Scheme 1.

BACKGROUND

Pomalidomide (CC-4047) and lenalidomide (CC-5013, Revlimid®) are immunomodulatory drugs (IMiD®) that are structural analogues of thalidomide developed by Celgene. Thalidomide has weak antiinflammatory activity, mediated via inhibition of lipopolysaccharide (LPS)-induced signaling in monocytes, leading to decreased TNF-α and other inflammatory cytokines (5), but appears to be most potent as an antiangiogenic agent. The properties of thalidomide as an antiangiogenic agent that inhibits TNF-α from monocytes have led to its use to treat multiple myeloma (MM), where increased TNF-α is associated with angiogenesis and disease progression, and also to its use in leprosy, where increases in TNF-α in the lesions are associated with inflammatory pathogenesis. Pomalidomide and lenalidomide were initially synthesized in the early 1990s and selected based on an improved inhibitory effect on TNF-α production, being far more potent than thalidomide in this regard (6). Following on from the successful use of lenalidomide in MM and myelodysplatic syndrome (MDS; in combination with dexamethasone), pomalidomide is now emerging as an exciting prospect for the treatment of MM patients who have failed other therapies, including lenalidomide and bortezomib. Pomalidomide is also being investigated in a phase III study in patients with myeloproliferative neoplasm-associated myelofibrosis. This review describes preclinical and clinical studies that have so far been undertaken.

PRECLINICAL PHARMACOLOGY

Pomalidomide has been shown to have multiple effects on immune effector cells. Pomalidomide has distinct and opposing effects on TNF-α and tumor necrosis factor receptor superfamily member 1B (tumor necrosis factor receptor 2, TNF-R2) during co-stimulation of both $CD4^+$ and $CD8^+$ T cells. This somewhat paradoxical result suggests that it can enhance antigen-specific co-stimulation while dampening down background activity, and as such, would be an ideal agent to enhance the effect of vaccines (7). This was tested in a whole colon carcinoma CT26 tumor cell-based vaccine model, where pomalidomide, which had no effect on tumor cell growth alone, was shown to enhance the tumor-inhibitory effects of the vaccine and overall survival, and increase the secretion of interferon gamma (IFN-γ) and IL-2 from T cells in a concentration-dependent manner. This suggests that it acts as a vaccine adjuvant and thus would be unique, as it acts orally and would not be premixed with the vaccine before administration, as is usual for vaccine adjuvants (8).

Other studies have also shown that pomalidomide increases IL-2 production after CD3 stimulation of T cells and that this correlates with increased IL-2 promoter activity in Jurkat T cells. This would appear to be dependent on the proximal AP-1 binding site, as well as increasing PKC-Φ activation, and the DNA binding activity of AP-1, but not nuclear factors NF-κB or NF-AT, in the case of stimulated T cells (9, 10). Xu et al. have shown that the increased production of Th1-type cytokines, including IFN-γ and TNF-α, as well as IL-2, is also thought to occur through increased expression of the T-cell-specific T-box transcription factor T-bet in both naive and prepolarized Th2 cells, which leads to upregulation of Th1 markers and cytokine production, and therefore Th2 cells are reverted into Th1 effector cells in vitro (11). This is of interest, as there is a shift towards Th2 cytokines in the peripheral blood, which occurs in the progression of a number of cancers, including MM, gastric and colorectal cancers, and a role for upregulated Th2 cytokines in promoting angiogenesis and inhibiting cell-mediated immunity and subsequent tumor killing has been reported (12).

Using bone marrow cells derived from aspirates of MM patients and healthy controls, Gorgun et al. showed that pomalidomide induces expression of the co-stimulatory molecule CD28, as well as the inducible co-stimulator ICOS and its inducible co-stimulatory ligand ICOSL (13). In order to mimic the MM/bone marrow environment, direct cell-to-cell contact co-culture experiments using healthy peripheral blood mononuclear cells (PBMCs), MM cell lines and MM bone marrow stem cells (MMBMSCs) were used to show that suppressor of cytokine signaling 1 (SOCS-1) protein expression was markedly induced in all effector cell populations in the presence of both MM cell lines and MMBMSCs. SOCS-1 is a protein that inhibits the tyrosine-protein kinase JAK/signal transducer and activator of transcription 3 (STAT3, *STAT3*) pathway which controls PBMC effector cell production of cytokines, such as IFN-γ, which are important in antitumor immunity; therefore, it is deleterious to effector cell activity against tumor cells under these conditions. The effector cells include CD4, CD8, natural killer T (NKT) cells and NK cells. In MM cells, however, SOCS-1 expression is reduced or absent, leading to increased IL-2, IFN-γ and IL-6 in the MM microenvironment, which then leads to upregulation of SOCS-1 in effector cells. Pomalidomide, however, significantly reduced the expression of SOCS-1 in all these effector cells cultured with either MM cell lines alone or with MM cell lines and MMBMSCs. It was also noted that the IFN-γ-dependent JAK/STAT pathway was activated in all the effector cells by pomalidomide. Additionally, the study showed that there were different effects of the drug on MM cells and the effector cells due to differences in the epigenetic effects of the drug on the two cell types. Epigenetic changes are modifications in genes that result in an alteration of gene expression without a change in the underlying gene sequence, and include demethylation of DNA or histone deacetylation. The *SOCS1* gene in MM cells is hypermethylated and therefore SOCS-1 is not transcribed in these cells; pomalidomide can act to demethylate the gene in these cells, thereby specifically increasing SOCS-1. This acts to reduce IL-6 levels, resulting in lower expression of SOCS-1 in the effector cells. Additionally, in effector cells such as CD4 or CD8 T cells, the *SOCS1* gene is not methylated and therefore pomalidomide does not affect transcription of the gene through methylation, but can increase ubiquitinization of the

protein, resulting in an increase in the breakdown and removal of this protein from the cell. Thus, it would appear that pomalidomide has not only a beneficial effect on the immune system, but also a detrimental effect on the tumor cells (12).

In addition to the strong co-stimulatory effect of pomalidomide on T cells, it also inhibits the proliferation and function of both natural and induced regulatory T cells, with a corresponding downregulation of forkhead box protein P3 (*FOXP3*) expression (14; Meyer et al., in preparation). The mechanism by which forkhead box protein P3 is inhibited in TGF-β-induced regulatory T cells (Tregs) appears to be due to the inhibition of translocation to the nucleus of the TGF-β signaling proteins mothers against decapentaplegic homolog 2 (SMAD 2) and 3 (SMAD 3). SMAD 2/3 facilitate nuclear expression of forkhead box protein P3 when translocated to the nucleus. Treg production is also inhibited by pomalidomide in response to tumor challenge in mice, in marked contrast to thalidomide, which has no effect on natural Treg activity whatsoever, either in vitro or in vivo.

Pomalidomide increases NK-mediated cytotoxicity towards both solid tumor and hematological tumor targets, such as human prostate adenocarcinoma PC-3 cells and Raji lymphoma cells, through at least two mechanisms: firstly, through increased activation of NK cells, and secondly, through an increase in antibody-mediated cellular cytotoxicity when target B-cell leukemia cells are preincubated with the antibody rituximab, which targets the CD20 antigen (15). The work by Payvandi et al. (10) shows that the effect on NK cells is indirect and via increased IL-2 production from T cells, while activating PKC-Φ and AP-1 DNA binding activity, resulting in augmented IL-2 synthesis. In murine models without active immune systems, such as the SCID and nude mouse models, there is a significant increase in the recruitment of NK cells to tumor sites in the presence of pomalidomide. This appears to be mediated via stimulation of dendritic cells and modification of the cytokine microenvironment, associated with an increase in C-C motif chemokine 2 (monocyte chemotactic protein 1), TNF and IFN-γ. In addition, there is a significant antiangiogenic effect seen in these models (16). The effect of pomalidomide on these systems is in stark contrast to other chemotherapies, such as melphalan and bortezomib, which can exert marked immune suppression in MM (17-20).

Pomalidomide has been shown to have direct effects on the in vitro and in vivo growth of a number of hematopoietic cancer cell lines and primary cancer cells. Pomalidomide induces cell cycle arrest in a variety of hematological tumor cell lines, including Namalwa and HS-Sultan Burkitt's lymphoma cells, and human myeloma LP-1 and U266 cells (21, 22). In lenalidomide-refractory MM patients there is evidence that MM cells chronically exposed to lenalidomide may retain sensitivity to pomalidomide and, in particular, pomalidomide plus dexamethasone (23); however, the mechanisms of lenalidomide resistance and how pomalidomide can overcome this are not clear. Pomalidomide has been shown to enhance the epigenetic induction of tumor suppressor genes such as *CDKN1A* (*WAF1*), and this could explain the direct inhibition of myeloma cell growth and increased apoptosis (24, 25). Pomalidomide is associated with a switch from methylated to acetylated histone H3 on the cyclin-dependent kinase inhibitor 1 (p21) promoter, which is a cellular tumor antigen p53 transcriptional target that mediates growth arrest.

Pomalidomide also inhibits interferon regulatory factor 4 (IRF-4), which is a key protein controlling the aberrant proliferation of MM cells via a paracrine loop with proto-oncogene c-Myc. Marked overexpression of this protein can also lead to pomalidomide resistance in MM cells (26).

In contrast to the effect on malignant cells, pomalidomide has no apparent proapoptotic growth arrest properties in normal B cells and can expand $CD34^+$ progenitor cell populations, which may partially explain the restorative effect on bone marrow, while malignant cells are reduced, a phenomenon readily recognized in myeloma patients treated with pomalidomide (27).

Another mechanism of clinical benefit may well be the ability to inhibit the formation of osteoclasts, which control bone resorption, a major cause of myeloma morbidity, and this would appear to be through the chemokine tumor necrosis factor ligand superfamily member 11 (receptor activator of nuclear factor kappa-B ligand, RANKL) and transcription factor PU.1 (28). Pomalidomide can also induce apoptosis through tumor necrosis factor receptor superfamily member 6 (apoptosis-mediating surface antigen FAS)- and tumor necrosis factor ligand superfamily member 10 (TNF-related apoptosis-inducing ligand, TRAIL)-induced mediation of MM cells. The drug can also increase activation of the apoptotic mediator caspase-8 by downregulating the expression of baculoviral IAP repeat-containing protein 3 (apoptosis inhibitor 2, C-IAP2) and CASP8 and FADD-like apoptosis regulator (cellular FLICE-like inhibitory protein, c-FLIP), which are both inhibitors of caspase-8 activation. As with the other IMiDs, there also appears to be synergy with dexamethasone, as both agents can inhibit NF-κB and dexamethasone can also activate caspase-9, which complements caspase-8 activation, leading to increased cleavage of caspase-3 (29).

Direct effects on cell growth in vitro have not been observed using pomalidomide as a single agent. However, pomalidomide can inhibit anchorage-independent growth of solid tumor cells, as demonstrated by the reduction in colony formation of colorectal tumor cells in soft agar (30). Moreover, pomalidomide may combine with other chemotherapeutic agents to increase their tumor growth-inhibitory activity or to restore the sensitivity of cells resistant to certain chemotherapeutic agents, in addition to its ability to restore chemosensitivity in myeloma cells. For example, hyperadditive inhibitory effects of pomalidomide have been shown with gemcitabine in pancreatic cells (R. Fryer, PhD Thesis, University of London, 2010).

In both solid and hematological tumors, pomalidomide can inhibit tumor progression in vivo via inhibitory effects on angiogenesis, metastasis, migration and tumorigenicity. Pomalidomide, like lenalidomide and thalidomide, can inhibit the formation of sprouting from human arterial rings in the human arterial explant assay (31). Pomalidomide is also able to inhibit vascular endothelial growth factor (VEGF)-induced hypoxia-induced endothelial cell core formation, and both pomalidomide and lenalidomide have a more potent effect than thalidomide. Pomalidomide, as well as lenalidomide, can inhibit the expression of hypoxia-inducible factor 1-α (HIF-1-α) but not endothelial PAS domain-containing protein 1 (EPAS-1, hypoxia-inducible factor 2-α, HIF-2-α) (32). These proteins are upregulated under hypoxic conditions and induce angiogenesis via upregulation of VEGF. Additionally, HIF-2-α induces erythropoietin synthesis and therefore the lack of effect on HIF-2-α is beneficial, as

erythropoiesis is not inhibited by pomalidomide. In the tumor milieu, the reduction of VEGF and IL-6 secretion from tumor and stromal cells also contributes to the inhibition of angiogenesis in endothelial cells (33). Pomalidomide also inhibits the migration and invasiveness of colon carcinoma CT26 cells, and the metastasis of these cells has been shown to be abolished or reduced in a BALB/c mouse model (30). This is in contrast to the migration of monocytes and T cells, which is increased. This may be due to the differential effects of pomalidomide on cytoskeletal arrangements in monocytic and tumor cells. For instance, it has been shown that whereas transforming protein RhoA and Ras-related C3 botulinum toxin substrate 1 (p21-Rac1) are induced in monocytes, leading to a migratory cytoskeletal rearrangement, only RhoA is activated in 3T3 fibroblasts, and this may also apply to tumor cells (34). It is interesting to note that the effects of pomalidomide in the lung metastasis assay (30) are via a direct effect on the tumor cells and not activation of the immune system; the metastasis of CT26 cells pretreated with pomalidomide is inhibited to a similar extent as for pomalidomide treatment in vivo in tumor-challenged animals.

With regard to the antitumor properties of pomalidomide, it is important to remember that, like its analogue lenalidomide, both were selected for their potent antiinflammatory effects by decreasing TNF-α production by LPS-induced monocyte activation in vitro. Pomalidomide can also inhibit prostaglandin G/H synthase 2 (cyclooxygenase-2, COX-2) production, reducing COX-2 levels in human LPS-stimulated monocytes. This results in reduced production of prostaglandin in these cells. This would appear to be at the level of gene transcription, as pomalidomide reduces LPS-stimulated transcription of the *PTGS2* gene (35). This property may allow it to be used for other inflammatory disorders, such as tuberculous meningitis (36) and sickle cell disease (37), as well as autoimmune disorders, without the side effects associated with common nonsteroidal antiinflammatory drugs (NSAIDs) that concomitantly inhibit COX-2 expression.

PHARMACOKINETICS AND METABOLISM

Pomalidomide is a thalidomide analogue with an additional amino group in the fourth carbon of the phthaloyl ring. It differs from lenalidomide by having an additional carbonyl group in the phthaloyl ring. It exists as a racemic mixture of active (*S*)-(–)- and (*R*)-(+)-forms, which spontaneously interconvert in the blood (38). The antiinflammatory and immunomodulatory properties are more prominent with the (*S*)-isomer of pomalidomide. Metabolic and clearance studies show the elimination of hydrolysis produced via the renal route, but < 5% of the unchanged product secreted through this route, unlike lenalidomide, where 66% of the drug is renally excreted as the parent product. No definitive liver metabolism studies have been published. The half-life of pomalidomide is 7 hours compared to 3.5 hours for lenalidomide (39). The maximum tolerated dose (MTD) was established at 2 mg/day, or 5 mg on alternate days, in relapsed/refractory MM patients (40), when the doses investigated were 1, 2, 5 and 10 mg, although results from an ongoing phase II study (MM-002) in relapsed refractory myeloma patients have shown that doses of 4 mg/day are tolerated in combination with low-dose dexamethasone (41). Up to 10 mg/day has been tolerated in pancreatic cancer patients (42).

Results from a phase II study in myeloma patients suggest that the main toxicities are neutropenia, occurring in 26-66% of patients at grade 3-4. Other toxicities are similar to those observed with lenalidomide, with anemia occurring in 5-28% of patients and thrombocytopenia in 3-30% of patients (see Table I). Some uncommon toxicities have also been observed, such as deep vein thrombosis (DVT), which is also seen with thalidomide and lenalidomide. There appears to be a lower incidence of neurosedative toxicity than that observed with thalidomide, where somnolence and peripheral neuropathy are commonly seen (43).

CLINICAL STUDIES

The first single-center, dose-escalation, open-label (nonblinded) phase Ib study of pomalidomide was performed in patients with relapsed or refractory MM and was used to define the MTD for further studies (44). It is important to note that at this time the drug was known by its generic code CC-4047 and had been preliminarily labeled as Actimid™. The conclusion of this study was that there was

Table I. *Summary of clinical studies of pomalidomide in multiple myeloma patients.*

Study	Overall response rates	Median survival times	Dosage regimen	Evaluable patient size	Major side effects	Ref.
2004 Pomalidomide monotherapy; phase I relapsed refractory MM	71%	90 weeks	Dose escalation: 1, 2, 5 and 10 mg given orally; maximum responses seen at 2 mg daily	24	33% of patients with grade 3 neutropenia, 25% of patients with grade 4 neutropenia, 16% with DVT	44
2008 Pomalidomide monotherapy; phase I relapsed refractory MM	55%	33 months	Dose escalation: 1, 2, 5 and 10 mg on alternate days	20	30% of patients with grade 3 neutropenia, 15% with grade 4 neutropenia (only at 10 mg)	40

Continued

Table I. *Cont. Summary of clinical studies of pomalidomide in multiple myeloma patients.*

Study	Overall response rates	Median survival times	Dosage regimen	Evaluable patient size	Major side effects	Ref.
2009 Pomalidomide + dexamethasone; phase II relapsed and refractory MM	63%	11.6 months	Pomalidomide 2 mg/day on days 1-28 of a 28-day cycle; dexamethasone 40 mg/day on days 1, 8, 15 and 22 of each cycle	60	Anemia (5%), thrombocytopenia (3%) and neutropenia (32%)	46
2009 Pomalidomide + dexamethasone; phase II relapsed and refractory MM –lenalidomide-refractory patients	47%	13.9 months (95% CI: NA)	Pomalidomide 2 mg/day on days 1-28 of a 28-day cycle; dexamethasone 40 mg/day on days 1, 8, 15 and 22 of each cycle	34	Anemia (12%), thrombocytopenia (9%) and neutropenia (29%)	47
2009 Pomalidomide + dexamethasone; phase II relapsed and refractory MM –lenalidomide- and bortezomib-refractory patients; comparison of dosing schedules	38% for 4 mg/day given on days 1-28 of a 28-day cycle; 42% for 4 mg/day given on days 1-21 of a 28-day cycle	Arm 1 88% and Arm 2 88% of patients alive at 6 months	Arm 1: pomalidomide 4 mg/day on days 1-28 of a 28-day cycle; Arm 2: 4 mg/day on days 1-21 of a 28-day cycle; dexamethasone 40 mg/day on days 1, 8, 15 and 22 of each cycle	83	Arm 1 : 23.5% anemia, neutropenia and thrombocytopenia; Arm 2: 26.5% anemia, neutropenia and thrombocytopenia	53
2010 Pomalidomide + dexamethasone; phase II relapsed and refractory MM –lenalidomide- and bortezomib-refractory patients: comparison of 2 mg/day and 4 mg/day pomalidomide	Arm 1: ORR 49%, (95% CI: 31-66); Arm 2: ORR 40% (95% CI: 23-58)	At 6 months Arm 1 = 78% (95% CI: 65-94) and Arm 2 = 69% (95% CI: 53-89)	Arm 1: pomalidomide 2 mg/day on days 1-28 of a 28-day cycle; Arm 2: 4 mg/day on days 1-28 of a 28-day cycle; dexamethasone 40 mg/day on days 1, 8, 15 and 22 of each cycle	70 patients (35 in each arm)	Arm 1: 28% grade 3 anemia, 50% grade 3-4 neutropenia and 25% grade 3-4 thrombocytopenia; Arm 2: 28% grade 3-4 anemia, 55% grade 3-4 neutropenia and 30% grade 3-4 thrombocytopenia; 50% more grade 4 hematological toxicity in Arm 2 than Arm 1	54

MM, multiple myeloma, DVT, deep vein thrombosis; CI, confidence interval; NA, not applicable; ORR, overall response rate.

evidence of efficacy in over two-thirds of the patients and that the MTD of the drug (defined as the highest dose of a biologically active agent given during a chronic study that will not reduce longevity from effects other than carcinogenicity) was established at 2 mg/day. There was also documented evidence of in vivo cell co-stimulation by pomalidomide in these patients. The side effect profile included two patients with DVT, secondary to inguinal lymphadenopathy, and 58% having grade IV neutropenia. Thrombocytopenia and lethargy were also noted. Marked activity was shown, with a > 25% reduction of *para* proteins in 67% of patients, 17% entering complete remission. All treated patients showed increased CD45 RO (memory lymphocyte) expression on CD4 and CD8 cells, with a concomitant decrease in CD45 RA^+ cells (naive T cells); this indicates that a greater level of T cells had become exposed to antigen and had gained antitumor activity. Significantly increased serum IL-2 receptor and IL-12 levels were also observed in these patients, consistent with activation of T cells and monocyte macrophages.

A second phase Ib/II study was carried out to examine combination with or without low-dose dexamethasone in subjects who had received two prior treatments and who did not achieve at least a partial response to lenalidomide or bortezomib. In this study, the MTD

was 4 mg/day, and of 26 evaluable subjects, a response was seen in approximately two-thirds of the patients (45). In this study, patients who ceased responding to pomalidomide alone were given dexamethasone and the overall response rate was 47%. Dexamethasone is used in myeloma to prevent leukocyte recruitment to cancer lesions, which causes inflammation and associated swelling and pain. However, a direct comparison of response rates for patients on pomalidomide versus pomalidomide and dexamethasone could not be established (41). Previous trials using pomalidomide alone have shown very good overall response rates compared with trials where pomalidomide has been used with dexamethasone (71% and 55% for pomalidomide alone in two trials vs. 63% for pomalidomide and dexamethasone in one trial) using refractory myeloma patients, but the trials using pomalidomide alone were with patients who had fewer treatments and had not received bortezomib or lenalidomide.

Lacy et al. performed an open-label phase II study of continuous pomalidomide 2 mg/day plus low-dose dexamethasone in subjects with relapsed refractory myeloma who had received one to three prior regimens (46). In this study, 60 patients were enrolled and, again, 63% of the subjects responded to pomalidomide, with 40% of lenalidomide-refractory subjects and 37% of thalidomide-refractory subjects responding and > 60% of those previously failing bortezomib responding. Neutropenia was the most common grade 3-4 hematological toxicity, with 35% of the patients being affected.

Lacy et al. conducted another study in patients who were previously refractory to lenalidomide (being defined as relapsing on or within 60 days of stopping lenalidomide) (47). The study included 34 patients who had also received thalidomide and bortezomib in addition to lenalidomide. An overall clinical response rate of 47% was seen, with 35% having stable disease. The median duration of response in 11 patients achieving a partial response or greater was 9.1 months, with a median progression-free survival of 4-8 months.

Since this article was commenced, a review providing more detailed information regarding myeloma clinical trial data has been published (48).

Myelofibrosis is a myeloproliferative disease of stem cells in the bone marrow, which leads to the formation of collagenous connective tissue fibers. The main symptoms are anemia and thrombocytopenia. Pomalidomide has been assessed in this disorder to determine its effects on anemia, with transfusion independence as the primary endpoint. In the first phase II trial with pomalidomide in myelofibrosis, two doses were used (0.5 and 2 mg/day, with and without prednisone). The highest response rate was 36% (anemia response; 95% confidence interval [CI]: 16-56%), and a response rate of 27% was achieved in patients with transfusion independence treated with 0.5 mg/day of pomalidomide and 30 mg/day of prednisone (49). Toxicities in this group were neutropenia and thrombocytopenia (≤ grade 3) in only 5% and 9% of patients, respectively. Another study comparing several doses of pomalidomide (0.5-3 mg/day) also showed that the lowest dose used (0.5 mg) was most effective in the 19 patients studied, with a 63% anemia response and a reduction in palpable spleen mass (for a period of 2 months or greater) in 29% of patients (50). This dose also produced the least toxic reactions in the patients with no neutropenia or thrombocytopenia above grade 3.

The latest trial in patients with primary or post-polycythemia vera/essential thrombocythemia myelofibrosis treated with 0.5 mg pomalidomide alone has also shown some benefit, with 17% of patients having an anemia response and 15% becoming transfusion-independent (51).

Although pomalidomide is not being developed for solid tumors, a few phase I studies have been performed. For example, preliminary data from eight patients with metastatic pancreatic cancer treated with pomalidomide and gemcitabine showed that stable disease was achieved in six of eight patients, with a 45% decrease in plasma CA19-9. Updated results from this study in 20 evaluable patients showed that 3 of the 20 patients (15%) had partial responses and 10 patients (50%) had a > 50% decrease in CA19-9 levels (43).

In another study using pomalidomide alone in 24 patients with 15 different solid cancer types, including colon, pancreas, NSCLC, adrenal, thyroid, hepatic and seminal vesicle, stable disease occurred in 17% of patients with hepatic, NSCLC and seminal vesicle cancer (52).

CONCLUSIONS

Pomalidomide has significant anti-MM activity, both directly and via indirect effects on the stroma and immune system affecting angiogenesis, migration and metastases formation (see Fig. 1). This activity occurs even against myeloma cells that have been rendered resistant to lenalidomide, the structural analogue of pomalidomide, by continued dosing with the drug, as well as in myeloma patients who have become resistant to lenalidomide. This may suggest that mechanisms are non-immune-regulatory. Pomalidomide, in combination with dexamethasone, appears to have potential for use in the treatment of lenalidomide-refractory MM. Future and ongoing trials in patients with myeloma will determine a number of unanswered questions about the efficacy of pomalidomide. Firstly, does dexamethasone enhance the efficacy of the drug in the disease and what dose of dexamethasone will work best with pomalidomide? There are indications that higher doses of dexamethasone may inhibit NK and T-cell effector functions, thereby negating the activating effects of pomalidomide on these cells. Secondly, the benefits of single versus continuous dosing with pomalidomide are being explored.

Single-agent pomalidomide is proving beneficial for patients with myeloproliferative neoplasm (MPN)-associated myelofibrosis. A phase III trial with single-agent pomalidomide in MPN-associated myelofibrosis is now in progress, which will assess endpoints of anemia response and transfusion independence. It is expected that pomalidomide will be an important addition to the therapy of these hematological malignancies, and may have significant activity with other agents against solid tumor cancers as well. It may also be an ideal maintenance drug for high-risk relapsed tumors despite complete response to other therapies.

SOURCE

Celgene Corp. (US).

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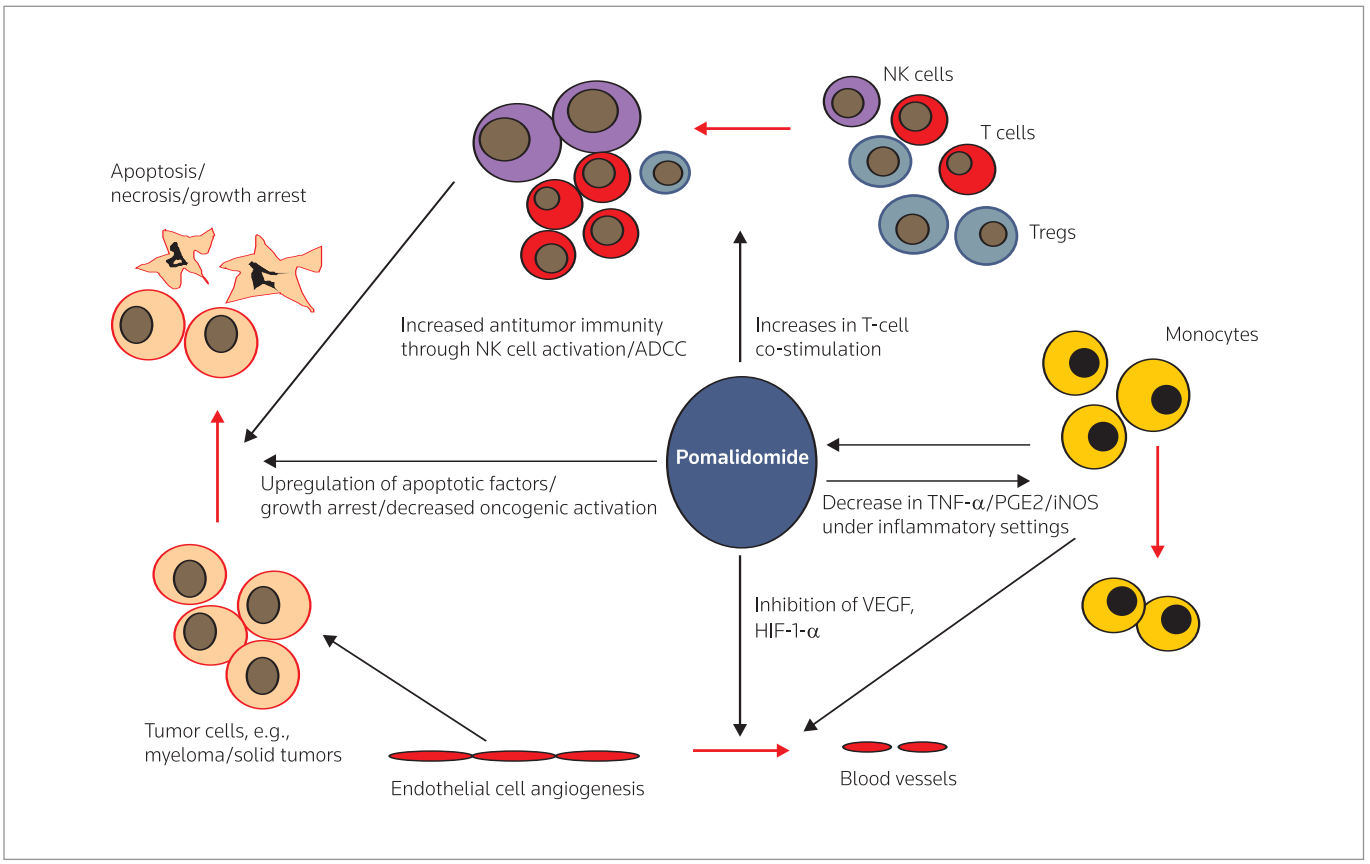

Figure 1. Antitumor mechanisms of pomalidomide. NK, natural killer; Tregs, regulatory T cells; ADCC, antibody-dependent cell-mediated cytotoxicity; PGE2, prostaglandin E2; iNOS, inducible nitric oxide synthase; VEGF, vascular endothelial growth factor; HIF-1-α, hypoxia-inducible factor 1-α. Reproduced with permission from C. Galustian and A. Dalgleish, *Lenalidomide: a novel anticancer drug with multiple modalities*, Expert Opin Pharmacother 2009, 10(1): 125-33.

DISCLOSURES

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