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Trial Watch
Lenalidomide-based immunochemotherapy

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Abbreviations: AML, acute myeloid leukemia; CCL, chemokine (C-C motif) ligand; CDKN, cyclin-dependent kinase inhibitor; CLL, chronic lymphocytic leukemia; CRBN, cereblon; EMA, European Medicine Agency; ENL, erythema nodosum leprosum; FDA, Food and Drug Administration; FOXP3, Forkhead box P3; ICAM, intercellular adhesion molecule; IL, interleukin; IMiD, immunomodulatory drug; ITG, integrin; MCL, mantle cell lymphoma; MDS, myelodysplastic syndrome; MM, multiple myeloma; NK, natural killer; PBMC, peripheral blood mononuclear cell; SLL, small lymphocytic lymphoma; TCR, T-cell receptor; TLR, Toll-like receptor; Treg, regulatory T cell; TNFα, tumor necrosis factor α

Lenalidomide is a synthetic derivative of thalidomide currently approved by the US Food and Drug Administration for use in patients affected by multiple myeloma (in combination with dexamethasone) and low or intermediate-1 risk myelodysplastic syndromes that harbor 5q cytogenetic abnormalities. For illustrative purposes, the mechanism of action of lenalidomide can be subdivided into a cancer cell-intrinsic, a stromal, and an immunological component. Indeed, lenalidomide not only exerts direct cell cycle-arresting and pro-apoptotic effects on malignant cells, but also inhi their physical and functional interaction with the tumor microenvironment and mediates a robust, pleiotropic immunostimulatory activity. In particular, lenalidomide has been shown to stimulate the cytotoxic functions of T lymphocytes and natural killer cells, to limit the immunosuppressive impact of regulatory T cells, and to modulate the secretion of a wide range of cytokines, including tumor necrosis factor α, interferon γ as well as interleukin (IL)-6, IL-10, and IL-12. Throughout the last decade, the antineoplastic and immunostimulatory potential of lenalidomide has been investigated in patients affected by a wide variety of hematological and solid malignancies. Here, we discuss the results of these studies and review the status of clinical trials currently assessing the safety and efficacy of this potent immunomodulatory drug in oncological indications.

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Introduction

Together with pomalidomide (Pomalyst®, initially known as CC-4047), lenalidomide (Revlimid®, initially known as CC-5013) is a synthetic derivative of thalidomide (Thalomid®) originally developed in the 1990s to achieve improved potency in the absence of significant side effects.[1] As a matter of fact, in 1957, the release of thalidomide as an over-the-counter sedative, tranquilizer, and antiemetic for morning sickness in Germany was followed by a peak of infants born with malformations of the limbs (phocomelia), resulting in the rapid withdrawal of the drug from the market.[2] Similar measures were rapidly undertaken worldwide, with Canada being the last country to discontinue the use of the drug (in 1962).[3] Current estimates indicate that 10,000–20,000 cases of phocomelia recorded in 46 countries in the late 1950s and early 1960s can be attributed to thalidomide.[2] Irrespective of its high teratogenic potential, the interest around thalidomide increased again in the 1990s, following the demonstration that this agent significantly inhibits the production of tumor necrosis factor α (TNFα), a pro-inflammatory cytokine involved in the etiology of erythema nodosum leprosum (ENL, a complication of leprosy).[4] In 1998, the US Food and Drug Administration (FDA) authorized Celgene Corp. to market thalidomide for the treatment of ENL patients, provided that the drug would be distributed under a strict control. Approximately in the same period, the combination of thalidomide with dexamethasone (a glucocorticoid) turned out to mediate robust antineoplastic effects in subjects affected by some hematological malignancies,[5] eventually leading to the accelerated approval of this regimen by the US FDA for use in newly diagnosed multiple myeloma (MM) patients (in 2006). Alongside, the development and (pre)clinical characterization

of lenalidomide demonstrated that this agent resembles thalidomide in its capacity to robustly inhibit TNFα production, but is associated with significantly reduced neurotoxic effects, although it mediates some degree of teratogenicity.[6–8] Conversely, pomalidomide appears to retain the pharmacological properties of thalidomide and lenalidomide while exerting limited, if any, teratogenic activity.[9] As it stands, lenalidomide is approved by the US FDA for the treatment of individuals affected by MM (in combination with dexamethasone)[10,11] and low or intermediate-1 risk myelodysplastic syndromes that harbor 5q cytogenetic abnormalities (as a standalone intervention).[12,13] Of note, no earlier than a few months ago (February 2013), the US FDA has also authorized the use of pomalidomide in patients with MM who have received at least 2 prior therapies, including lenalidomide and bortezomib, and have demonstrated disease progression on or within 60 d of completion of the last therapy.[14–17] Also the European Medicine Agency (EMA) has approved the clinical use of thalidomide, lenalidomide, and pomalidomide, the latter no earlier than a few days ago (August 2013) (source http://www.ema.europa.eu/).

Throughout the last decade, the molecular and cellular cascades underlying the robust antineoplastic activity of lenalidomide (see below) have been intensively investigated. Thus, lenalidomide has been shown to mediate anticancer effects via (at least) 3 general mechanisms: (1) it inhibits the proliferation of malignant cells and stimulate their apoptotic demise; (2) it interferes with the physical and trophic interaction between neoplastic cells and their stroma; and (3) it exerts a profound and pleiotropic immunomodulatory activity.[18–22]

The antiproliferative effects of lenalidomide mostly originate from its ability to upregulate several cyclin-dependent kinase inhibitors (CDKNs), including CDKN1A (best known as $p21^{CIP1}$), CDKN1B (best known as $p27^{KIP1}$), CDKN2A (best known as $p16^{INK4A}$), and CDKN2B (best known as $p15^{INK4B}$), hence promoting a robust cell cycle arrest.[23–25] In addition, lenalidomide has been shown to trigger both the extrinsic (caspase-8-dependent) and intrinsic (mitochondrial) pathways of apoptosis.[26–31] At least in part, this reflects the capacity of lenalidomide to antagonize pro-survival signals transduced by NFκB, resulting in the downregulation of anti-apoptotic factors such as CASP8 and FADD-like apoptosis regulator (CFLAR) and baculoviral IAP repeat containing 3 (BIRC3).[32] Also the TNFα-suppressing functions of lenalidomide and thalidomide (underpinning the clinical use of the latter against ENL) mainly (though perhaps not entirely) rely on their ability to inhibit NFκB.[33,34]

Besides directly impacting on the proliferative potential and viability of neoplastic cells, lenalidomide inhibits their physical and functional interactions with the tumor stroma. Thus, owing to its capacity to abrogate the self-amplificatory signaling cascade linking the NFκB-mediated secretion of TNFα to further NFκB activation,[35,36] lenalidomide blocks the release of interleukin (IL)-6,[37,38] a crucial trophic and cytoprotective factor for MM cells as well as for other cancer cells, be them of hematological or epithelial origin.[39–43] Upon exposure to lenalidomide, both cancer cells and bone marrow stromal cells have been shown to express reduced levels of multiple adhesion molecules, including (though presumably not limited to) intercellular adhesion molecule 1 (ICAM1), ICAM2, vascular cell adhesion molecule 1 (VCAM1), integrin α8 (ITGA8), as well as integrins β1 and β2 (ITGB1 and ITGB2, also known as VFA-4 and LFA-1, respectively).[44–46] This significantly inhibits the physical interaction between stromal and malignant cells, hence limiting the delivery of contact-dependent survival signals to the latter as well as the secretion of trophic cytokines (including IL-6, IL-8, and insulin-like growth factor 1, IGF1) from the former.[47,48] Among other effects on the tumor microenvironment, lenalidomide inhibits the production of vascular endothelial growth factor (VEGF) and fibroblast growth factor 2 (FGF2),[37,38] thus mediating robust antiangiogenic effects.[30,31] The capacity of lenalidomide to limit TNFα release contributes to this activity.[49,50] Finally, lenalidomide appears to interfere with osteoclastogenesis in vivo, hence inhibiting the generation of a metastatic niche for malignant cells.[51]

A major component of the antineoplastic activity of lenalidomide reflects its capacity to modulate humoral as well as cellular aspects of innate and adaptive immune responses. For instance, lenalidomide has been shown to significantly alter the immunological profile of the tumor microenvironment by inhibiting the release of TNFα, IL-1β, and IL-6, while favoring that of IL-2, IL-10, IL-12, and interferon γ (IFNγ) at least under some circumstances.[37,38,52–54] Indeed, lenalidomide appears to promote the secretion of IL-12 by peripheral blood mononuclear cells (PBMCs) exposed to CD3-crosslinking antibodies (mimicking the activation of the T-cell receptor, TCR), but not by PBMCs treated with relatively unspecific immunostimulatory agents such as the Toll-like receptor (TLR) agonist lipopolysaccharide (LPS).[54] Along similar lines, lenalidomide might promote (rather than inhibit) the release of TNFα by T cells upon TCR stimulation.[55,56] Thus, although lenalidomide does not directly stimulate the proliferation of T cells,[57] it significantly amplifies the ability of several stimuli, including CD3 ligation as well as the exposure to mature and immature dendritic cells (DCs), to do so.[54,57–59] Several mechanisms may be involved in such an effect, including (1) an elevated local availability of IL-2, presumably reflecting an increase in the activity of the transcriptional factors AP-1 and/or T-box 21 (TBX21, best known as T-bet);[55,56,60] (2) the downregulation of suppressor of cytokine signaling 1 (SOCS1), a prominent (cytokine-inducible) negative regulator of T-cell activity;[61] (3); the upregulation and/or functional activation of the co-stimulatory receptor CD28 on T cells;[57] and (4) increased levels of co-stimulatory molecules (e.g., CD80, CD86) and MHC Class I or II molecules on the surface of antigen-presenting cells (APCs).[57,62,63] In addition, lenalidomide has been shown to exacerbate the antineoplastic functions of natural killer (NK) and NKT cells, in particular their ability to mediate antibody-dependent cell-mediated cytotoxicity (ADCC), in vitro and in vivo[28,64–68] Such an effect has mainly been attributed to the ability of lenalidomide to upregulate the expression of FAS and granzyme B (2 major mediators of NK-cell cytotoxicity) in NK cells.[28,65] However, both the expansion and antineoplastic potential NK cells may also benefit from an increased local availability of IL-2.[69] Furthermore, lenalidomide (as well as thalidomide and

Table 1. Completed clinical studies assessing the safety and therapeutic profile of lenalidomide in cancer patients*

Cancer type	N° of studies	Phase**	Dose**	Notes	Ref.
Acute myeloid leukemia	8	I-II	5–75 mg/day	As a standalone therapeutic intervention or combined with azacytidine	167,168, 174–179
Chronic lymphocytic leukemia	14	I-III	5–25 mg/day	As a standalone therapeutic intervention or combined with rituximab-based chemotherapy	62,149, 154–165
Lymphoma	17	I-II	10–25 mg/day	As a standalone therapeutic intervention or combined with rituximab or alemtuzumab	66,138–153
Melanoma	4	I-III	5–50 mg/day	As a standalone therapeutic intervention or combined with dacarbazine	180–183
Myelodysplastic syndrome	10	I-III	10–70 mg/day	As a standalone therapeutic intervention or combined with azacytidine	12,13,166–173
Multiple myeloma	42	I-III	5–50 mg/day	Near to invariably combined with dexamethasone and a bortezomib-based chemotherapeutic regimen	10,11,16,38, 77,101–137
Prostate carcinoma	4	I-II	5–25 mg/day	As a standalone therapeutic intervention or combined with GM-CSF or paclitaxel	184–187
Renal cell carcinoma	3	II	25 mg/day	As a standalone therapeutic intervention	188–190
Others	15	I-II	5–70 mg/day	Most often employed as a standalone therapeutic intervention	8,166,180, 247–258

Abbreviations: GM-CSF, granulocyte macrophage colony-stimulating factor. *Published in peer-reviewed scientific journals as of August, 1st 2013 (source http://www.ncbi.nlm.nih.gov/pubmed). **Range.

pomalidomide) has been reported to inhibit the accumulation and immunosuppressive activity of myeloid-derived suppressor cells (MDSCs)[70–72] and regulatory T cells (Tregs),[73–76] in the latter case perhaps as it limits the expression of the transcription factor Forkhead box P3 (FOXP3). However, such an activity may not be a general prerequisite for the therapeutic efficacy of lenalidomide. Indeed, this immunomodulatory drug (IMiD) exhibited robust antineoplastic effects in a cohort of relapsed MM patients previously subjected to allogeneic stem cell transplantation while stimulating a transient increase in $CD4^+FOXP3^+$ Tregs.[77] Interestingly, lenalidomide also reorganizes cytoskeletal fibers, hence restoring the ability of some malignant cells to engage with T lymphocytes in productive immunological synapses.[78,79] Although such an effect is de facto cancer cell-intrinsic, it has a major impact on the interaction between neoplastic cells and the immune system.

Taken together, these observations suggest that the antineoplastic potential of lenalidomide originate from both cancer cell-intrinsic and -extrinsic mechanisms. The ability of lenalidomide to influence several aspects of innate and adaptive immune responses is actually shared by pomalidomide, and these agents are cumulatively referred to as second-generation IMiDs.[80] The molecular target of thalidomide and IMiDs has been identified relatively recently.[81] In particular, the E3 ubiquitin ligase cereblon (CRBN) has been shown to underlie both the therapeutic and the teratogenic activity of these agents.[81–83] The CRBN-elicited signaling cascades that may account for the immunomodulatory effects of lenalidomide have just begun to emerge.[82,84,85] In this setting, a prominent role may be played by interferon-regulatory factor 4 (IRF4), a CRBN-regulated transcription factor implicated in several facets of innate and adaptive immunity.[82,84,85] In addition, CRBN has been shown to influence the activity of the proteasome[86] and AMP-activated protein kinase (AMPK).[87,88] Of note, high expression levels of CRBN[89,90] and IRF4[91] have been associated with improved disease outcome among MM patients receiving lenalidomide or thalidomide, but not with the sensitivity of human myeloma cell lines to these agents in vitro.[92] Taken together, these observations suggest that the cell-extrinsic component of the antineoplastic activity of lenalidomide generally prevails over its cell-intrinsic counterpart. In line with this notion, the therapeutic efficacy of lenalidomide is decreased upon the depletion of $CD4^+$ T cells as well as in the presence of immunosuppressive agents (including dexamethasone), raising the possibility that the combination of lenalidomide with glucocorticoids might yield suboptimal therapeutic effects.[93]

Along the lines of our monthly Trial Watch series,[58,59,94–100] here we discuss recently completed and currently ongoing clinical trials investigating the safety and therapeutic potential of lenalidomide in cancer patients.

Clinical Profile of Lenalidomide

During the last decade, the safety profile and efficacy of lenalidomide have been investigated in clinical trials involving patients affected by a wide variety of neoplasms (**Table 1**). As of 2013, July 27th, we retrieved no less than 112 scientific publications reporting the results of such an intensive effort (source http://www.ncbi.nlm.nih.gov/pubmed). The vast majority of these clinical trials (88 studies) were conducted on patients bearing hematological malignancies, most often MM (42 studies),[10,11,16,38,77,101–137] various forms of lymphoma (17 studies),[66,138–153] chronic lymphocytic leukemia (CLL) (14 studies),[62,149,154–165] myelodysplastic syndrome (MDS) (10 studies),[12,13,166–173] and acute myeloid leukemia

Table 2. Clinical trials recently started to assess the safety and therapeutic profile of lenalidomide in cancer patients*

Indications	Phase	Status	Notes	Ref.
Advanced cancers	I	Recruiting	Combined with ipilimumab	NCT01750983
AITL	II	Recruiting	Combined with CHOP	NCT01553786
AML CMML MDS	I	Recruiting	As single agent	NCT01615042
	I	Recruiting	As single agent	NCT01578954
	I	Recruiting	Combined with clofarabine	NCT01629082
	I	Recruiting	Combined with conventional chemotherapy	NCT01681537
	II	Recruiting	Combined with azacytidine	NCT01522976
	II	Recruiting	Combined with azacytidine	NCT01556477
	II	Recruiting	Combined with azacytidine	NCT01743859
Astrocytoma Glioma	II	Recruiting	As single agent	NCT01553149
B-cell lymphoma	I	Recruiting	Combined with BTK inhibitors	NCT01766583
	I/II	Recruiting	Combined with ublituximab	NCT01744912
	I/II	Recruiting	Combined with rituximab-based chemotherapy	NCT01788189
	II	Not yet recruiting	Combined with rituximab-based chemotherapy	NCT01856192
CLL	n.a.	Active not recruiting	As single agent	NCT01649791
	I	Recruiting	As a conditioning regimen before the infusion of allogeneic cord blood-derived NK cells	NCT01619761
	I/II	Recruiting	Combined with autologous tumor cells expressing IL-2 and CD40L	NCT01604031
	I/II	Recruiting	Combined with rituximab-based chemotherapy	NCT01703364
	II	Recruiting	As single agent	NCT01600053
	II	Recruiting	Combined with rituximab-based chemotherapy	NCT01723839
	III	Recruiting	As single agent	NCT01556776
CLL SLL	I	Recruiting	Combined with BTK inhibitors	NCT01732861
	I	Recruiting	Combined with ibrutinib	NCT01886859
	II	Not yet recruiting	Combined with rituximab-based chemotherapy	NCT01754857
	II	Not yet recruiting	Combined with rituximab-based chemotherapy	NCT01754870
Follicular lymphoma	I	Recruiting	Combined with rituximab-based chemotherapy	NCT01644799
	I	Recruiting	Combined with rituximab-based chemotherapy	NCT01829568
	III	Recruiting	Combined with rituximab-based chemotherapy	NCT01650701
HCC	II	Recruiting	As single agent	NCT01545804
Lymphoma	I	Recruiting	Combined with rituximab-based chemotherapy	NCT01542918
	I	Recruiting	As single agent	NCT01750762
	I/II	Recruiting	Combined with obinutuzumab	NCT01582776
	I/II	Recruiting	Combined with romidepsin	NCT01742793
	I/II	Recruiting	As single agent	NCT01575860
	II	Recruiting	As single agent	NCT01556035

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; AML, acute myeloid leukemia; BTK, Bruton agammaglobulinemia tyrosine kinase; CD40L, CD40 ligand; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CLL, chronic lymphocytic leukemia; CMML, chronic myelomonocytic leukemia; HCC, hepatocellular carcinoma; IL-2, interleukin-2; MDS, myelodysplastic syndrome; n.a., not available; NK, natural killer; SLL, small lymphocytic lymphoma. *Started after 2012 January, 1st and not withdrawn, terminated or suspended at the day of submission (source www.clinicaltrials.gov).

(AML) (8 studies).[167,168,174–179] In addition, 24 clinical trials were performed to assess the therapeutic profile of lenalidomide in subjects affected by solid tumors, including melanoma (4 studies),[180–183] prostate carcinoma (4 studies),[184–187] and renal cell carcinoma (3 studies).[188–190] In this setting, lenalidomide was most often employed at doses ranging from 10 to 25 mg/day, either as a standalone therapeutic intervention or in combination with standard regimens, such as dexamethasone, prednisone,

Table 2 (Continued). Clinical trials recently started to assess the safety and therapeutic profile of lenalidomide in cancer patients*

Indications	Phase	Status	Notes	Ref.
MALT lymphoma	II	Recruiting	Combined with rituximab-based chemotherapy	NCT01611259
MCL	I/II	Recruiting	Combined with rituximab-based chemotherapy	NCT01729104
	I/II	Recruiting	Combined with rituximab-based chemotherapy	NCT01838434
	II	Recruiting	Combined with rituximab-based chemotherapy	NCT01737177
	III	Not yet recruiting	Combined with rituximab, as maintenance therapy	NCT01865110
MDS	II	Recruiting	As single agent	NCT01673308
	II	Recruiting	As single agent or combined with recombinant erythropoietin	NCT01718379
	II	Recruiting	Combined with eltrombopag	NCT01772420
MM	I	Recruiting	Combined with MLN9708 and dexamethasone	NCT01645930
	I/II	Recruiting	Combined with daratumumab and dexamethasone	NCT01615029
	II	Recruiting	Combined with bortezomib and dexamethasone, as maintenance therapy	NCT01548573
	II	Terminated	As maintenance therapy	NCT01617213
	II	Recruiting	Combined with bortezomib, as maintenance therapy	NCT01706666
	II	Recruiting	Combined with bortezomib, as maintenance therapy	NCT01729338
	II	Recruiting	As conditioning and maintenance therapy, in the latter case in combination with bortezomib	NCT01790737
	II	Recruiting	Combined with minocycline	NCT01793051
	II	Recruiting	Combined with bortezomib, as maintenance therapy	NCT01849783
	II	Not yet recruiting	Combined with taladafil ± MILs, as maintenance therapy	NCT01858558
NB	I	Recruiting	Combined with Ch14.18 ± isotretinoin	NCT01711554
NHL	I/II	Recruiting	Combined with romidepsin	NCT01755975
	II	Active not recruiting	Combined with rituximab-based chemotherapy	NCT01830478
Pancreatic cancer	I/II	Recruiting	Combined with gemcitabine	NCT01547260
PPCL	II	Completed	Combined with dexamethasone	NCT01553357
T-cell leukemia T-cell lymphoma	II	Recruiting	As single agent	NCT01724177
Waldenstrom macroglobulinemia	II	Recruiting	Combined with rituximab and thalidomide	NCT01779167

Abbreviations: MALT, mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma; MDS, myelodysplastic syndrome; MIL, marrow-infiltrating lymphocyte; NB, neuroblastoma; NHL, non-Hodgkin's lymphoma; PPCL, primary plasma cell leukemia. *Started after 2012 January, 1st and not withdrawn, terminated or suspended at the day of submission (source www.clinicaltrials.gov).

melphalan, or bortezomib (a proteasomal inhibitor)[191] in MM patients; with rituximab (a CD20-targeting monoclonal antibody) in CLL patients;[192] or with azacytidine (a demethylating agent)[193,194] in subjects affected by AML. Taken together, these trials (14 of which were Phase III) report a low incidence of adverse events related to the use of lenalidomide. Common toxicities included (1) myelosuppression, mainly manifesting with neutropenia, thrombocytopenia, leukopenia, or anemia, as well as with an increased susceptibility to infections; (2) thromboembolic events; (3) tumor flare, and (4) relatively mild effects including fatigue, nausea, diarrhea, headache, and skin rashes.[8,195,196] Myelosuppression is currently considered as the most common dose-limiting (grade III or higher) toxicity of lenalidomide.[197] Of note, the teratogenicity of this agent is being actively prevented in the context of a Risk Evaluation and Mitigation Strategy (REMS) approach, formerly known as RevAssist,[198] a tightly controlled distribution program established by Celgene upon an explicit request formulated by US FDA along with the approval of lenalidomide for use in humans (source http://www.revlimidrems.com/). Similar programs are also in place for what concerns thalidomide (source http://www.thalomidrems.com/) and pomalidomide (source http://www.pomalystrems.com/).[6] Similar to thalidomide, lenalidomide has been suggested to increase the risk of patients to develop a second primary cancer,[102,120,124,199] yet the underlying molecular mechanisms have not yet been elucidated.

The intense wave of clinical investigation that developed around lenalidomide in the late 2000s resulted in the approval of this immunomodulatory drug by the US FDA as well as by

several other international regulatory agencies (e.g., EMA) for use in MM patients and in subjects affected by MDSs that harbor 5q cytogenetic abnormalities.[10-13] In addition, lenalidomide-based chemotherapeutic regimens were shown to exert promising therapeutic effects not only in patients affected by various other hematological neoplasms, including AML,[167,168,174–179] CLL,[62,149,154–165] and various forms of lymphoma,[66,138–153] but also in individuals bearing advanced, metastatic or recurrent solid tumors, such as melanoma,[180–183] prostate cancer,[184–187] and renal cell carcinoma.[188–190] Although in the vast majority of these studies patients were not routinely monitored for immunological parameters, some evidence indicates that the clinical effects of lenalidomide may correlate with early signs of ongoing immunomodulation, such as (1) the upregulation of CD80 on leukemic cells or that of MHC Class II molecules on circulating $CD4^+$ and $CD8^+$ T lymphocytes;[62,113] (2) the downregulation of CD56 on the surface of peripheral NK cells;[113] (3) an increase in circulating macrophages, T lymphocytes, Tregs, and NK cells;[77,113,141,152,200] (4) a surge in the serum levels of TNFα, IL-8, IL-12, and granulocyte macrophage colony-stimulating factor (GM-CSF);[180,201,202] or (5) a reduction in the amounts of circulating chemokine (C-C motif) ligand 3 (CCL3), and CCL4.[155] Of note, several signs of immunomodulation were documented in transplanted MM patients receiving lenalidomide as a maintenance regimen, a setting in which this IMiD turned out to provoke a high rate of severe graft-vs.-host reactions.[113] Thus, the immunomodulatory activity of lenalidomide does not necessarily translate into a clinical benefit, in particular among transplanted patients. Irrespective of this caveat, an intense wave of clinical investigation has demonstrated that lenalidomide is generally well tolerated and exert promising antineoplastic activity, in particular in patients affects by hematological tumors.

Ongoing Clinical Trials

When this Trial Watch was being redacted (August 2013), official sources listed 60 clinical trials initiated after 2012, January 1st to investigate the safety and therapeutic potential of lenalidomide in cancer patients (**Table 2**) (source http://www.clinicaltrials.gov). The vastest majority of these trials (55 studies) involve patients affected by hematological malignancies, including (but not limited to) various forms of MDS or leukemia (23 studies), lymphoma (26 studies), and MM (13 studies). Thus, lenalidomide is being tested: (1) as a standalone conditioning intervention in leukemia patients destined to a not-better specified form of bone marrow transplantation (NCT01615042); (2) in combination with melphalan as a conditioning regimen in CLL patients allocated to receive allogeneic cord blood-derived NK cells (NCT01619761); (3) as a standalone maintenance/consolidation regimen following standard induction chemotherapy in AML patients with more than 60 y of age (NCT01578954) as well as in CLL patients (NCT01556776; NCT01600053); (4) as a single therapeutic agent in patients with high-risk, early-stage B-cell CLL (NCT01649791), MDS patients who failed to respond to hypomethylating agents (NCT01673308), or adult patients with relapsed or recurrent T-cell leukemia or lymphoma (NCT01724177); (5) alone or combined with recombinant erythropoietin or eltrombopag (a synthetic agonist of the thrombopoietin receptor) in low and intermediate-1 risk MDS patients harboring no chromosome 5q abnormalities (NCT01718379; NCT01772420); (6) in combination with azacytidine for the treatment of high-risk MDS or AML patients exhibiting chromosome 5q defects (NCT01556477), relapsed or refractory AML patients (NCT01743859), or subjects affected by high-risk MDS or chronic myelomonocytic leukemia (NCT01522976); (7) together with rituximab-based chemotherapeutic regimens in previously untreated CLL or small lymphocytic lymphoma (SLL) patients (NCT01703364; NCT01723839; NCT01754857; NCT01754870); (8) in combination with a potentially immunogenic chemotherapeutic cocktail[203–206] in AML patients (NCT01681537); (9) combined with clofarabine (a nucleoside analog) for the treatment of high-risk MDS and AML patients (NCT01629082); (10) together with an autologous cell-based anticancer vaccine in B-cell CLL patients (NCT01604031); (11) combined with inhibitors of the enzymatic activity of Bruton agammaglobulinemia tyrosine kinase (BTK)[207] in subjects with CLL or SLL (NCT01732861; NCT01886859); and (12) combined with dexamethasone in previously untreated patients affected by primary plasma cell leukemia (NCT01553357).

Lenalidomide is also being investigated: (1) as a standalone maintenance intervention in lymphoma patients who previously received (rituximab-based) chemotherapy (NCT01556035; NCT01575860) or allogeneic bone marrow/stem cell transplantation (NCT01750762); (2) together with a potentially immunogenic chemotherapeutic cocktail (including the alkylating agent cyclophosphamide and bortezomib)[203–206] as a first-line approach to angioimmunoblastic T-cell lymphoma (NCT01553786); (3) in combination with rituximab-containing chemotherapeutic regimens in individuals affected by recurrent or refractory lymphomas of the central nervous system or the eye (NCT01542918), mucosa-associated lymphoid tissue lymphoma (NCT01611259), recurrent or previously untreated follicular lymphoma (NCT01644799; NCT01650701; NCT01829568), relapsed or refractory mantle cell lymphoma (MCL) (NCT01729104; NCT01737177; NCT01838434); relapsed aggressive B-cell lymphomas (NCT01788189), indolent non-Hodgkin's lymphoma (NCT01830478); or newly-diagnosed Stage II-IV diffuse large B-cell lymphoma (NCT01856192); (4) together with rituximab as a maintenance regimen for old (> 60 y-old) patients with MCL (NCT01865110); (5) combined with romidepsin (an experimental histone deacetylase inhibitor)[208,209] in subjects with relapsed/refractory lymphoma or MM (NCT01742793; NCT01755975); (6) in combination with obinutuzumab (an experimental monoclonal antibody targeting CD20)[210,211] for the treatment of relapsed or refractory follicular and aggressive B-cell lymphoma (NCT01582776); (7) combined with ublituximab (yet another CD20-targeting monoclonal antibody)[212] in patient with B-cell lymphoid neoplasms who have relapsed upon (or are primarily refractory to) CD20-directed therapies (NCT01744912); and (8) together with CC-292 in adult patients with relapsed or refractory B-cell lymphoma (NCT01766583).

The majority of clinical trials recently registered (after January 1st, 2012) at http://www.clinicaltrials.gov that involve MM patients aim at investigating the safety and therapeutic profile of lenalidomide as a conditioning (NCT01790737) or maintenance (NCT01548573; NCT01617213; NCT01706666; NCT01790737; NCT01849783; NCT01858558) regimen in the context of bone marrow or hematopoietic stem cell transplantation. In this setting, lenalidomide is invariably combined with dexamethasone and optionally with melphalan (NCT01617213), bortezomib-based chemotherapy (NCT01548573; NCT01706666; NCT01790737; NCT01849783), or tadalafil (an inhibitor of phosphodiesterase 5A best known for its use in the treatment of erectile dysfunction)[213] plus autologous marrow-infiltrating lymphocytes (NCT01858558). In addition, lenalidomide is being tested: (1) in combination with dexamethasone and daratumumab (a CD38-targeting monoclonal antibody)[214] in patients with relapsed or refractory MM (NCT01615029); (2) together with dexamethasone and MLN9708 (an experimental inhibitor of the proteasome)[215,216] in adults bearing refractory MM (NCT01645930); (3) combined with minocycline, in the context of not-better specified maintenance therapy for MM patients (NCT01793051); (4) as a maintenance regimen in newly diagnosed MM patients receiving first-line bortezomib-based chemotherapy (NCT01729338); and (5) together with rituximab and thalidomide in patients affected by Waldenstrom macroglobulinemia,[217] another neoplasm originating from the hyperproliferation of plasma cells (NCT01779167).

Finally, lenalidomide is being evaluated: (1) as a second-line standalone therapeutic intervention in advanced hepatocellular carcinoma patients (NCT01545804); (2) in combination with gemcitabine (a potentially immunogenic nucleoside analog)[218,219] in individuals with pancreatic carcinoma (NCT01547260); (3) as a single agent in children affected by recurrent, refractory or progressive pilocytic astrocytoma or optic pathway glioma (NCT01553149); (4) together with isotretinoin (a retinoid)[220] and/or Ch14.18 (a monoclonal antibody directed against ganglioside GD2)[221–223] in children with refractory or recurrent neuroblastoma (NCT01711554); and (5) combined with ipilimumab (an FDA-approved monoclonal antibody that inhibits the immunological checkpoint mediated by cytotoxic T lymphocyte-associated protein 4, CTLA4)[224,225] in patients affected by advanced tumors (NCT01750983).

Taken together, these observations suggest that the interest of clinicians into lenalidomide remains high, though it focuses on the use of this IMiD for the treatment of hematological, rather than solid, malignancies.

Concluding Remarks

A significant amount of clinical experience has nowadays accumulated to indicate that lenalidomide not only is well tolerated by a majority of cancer patients, but also exerts robust antineoplastic effects, in particular among individuals affected by hematological tumors. Although the molecular and cellular cascades underlying such a consistent anticancer activity have just begun to emerge, it is clear already that lenalidomide does not only exert direct antiproliferative and cytotoxic effects, but also influences in several ways the interaction between malignant cells and their microenvironment, including stromal and immune components. In particular, lenalidomide exhibits a pronounced and multipronged immunomodulatory activity.[18,19,226]

Lenalidomide is currently approved by international regulatory agencies for use in patients bearing specific hematological neoplasms, including MM and MDSs with chromosome 5q abnormalities.[10–13] Of note, in both these settings, lenalidomide is administered in combination with low-dose glucocorticoids (most often dexamethasone or prednisone), which are well known for their immunosuppressive potential.[227,228] Indeed, glucocorticoids not only exert profound transcriptional effects on immune cells, de facto suppressing their ability to elicit an inflammatory reaction, but also actively trigger their demise.[229–231] At least in part, this explains the clinical success of glucocorticoids in the treatment of hematological malignancies. At the same time, however, it should raise doubts on whether combining an immunostimulatory agent such as lenalidomide with glucocorticoids might yield optimal therapeutic effects. Recent preclinical data actually argue against such a possibility, suggesting that the clinical potential of lenalidomide may be restricted, rather than maximized, by dexamethasone.[93,232] In this scenario, it would be interesting to test whether the antineoplastic activity of lenalidomide can be potentiated by the co-administration of immunomodulatory agents such as TLR agonists,[233–235] immunological checkpoint inhibitors,[224,225,236,237] immunostimulatory cytokines,[201,202,238,239] or immunogenic chemotherapy.[71,240,241] The possibility of using lenalidomide as an adjuvant in support of more specific immunotherapeutic interventions including anticancer vaccines[242,243] and adoptively transferred cells[244–246] also warrants further investigation.

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