Bristol Myers Squibb™

Targeting Protein Degradation Through Cereblon Modulation

Preclinical Studies

Cereblon mediates protein degradation through the ubiquitin-proteasome pathway.[1] Modulation of cereblon specificity alters target protein degradation and may have therapeutic effects[2]

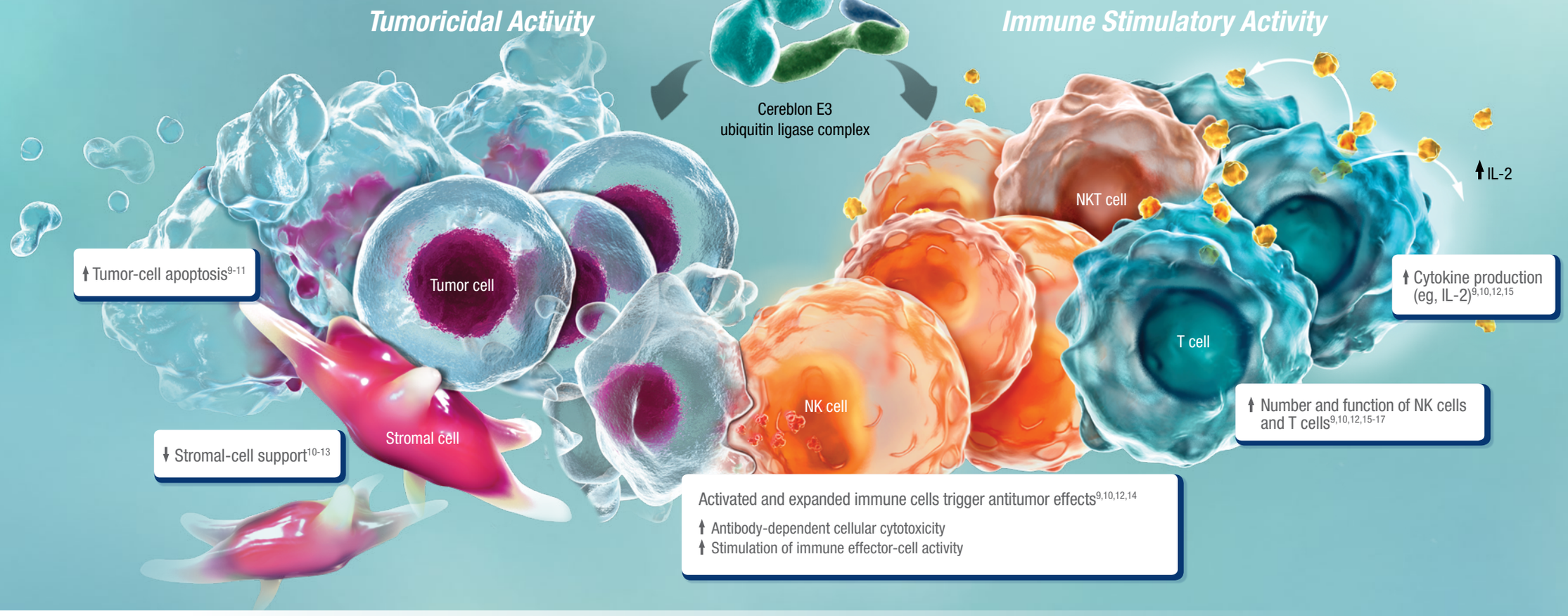
IMiD® Agents

IMiD agents are a subgroup of CELMoD agents and co-opt cereblon E3 ligase to target transcription factors Ikaros and Aiolos for degradation, resulting in downregulation of oncogenes *c-Myc* and *IRF4* in tumor cells and upregulation of *IL-2* in immune effector cells[2-7]

CELMoD® Agents

Investigational CELMoD agents, including iberdomide (CC-220) and CC-92480, are novel, oral compounds. They are the result of a discovery program designed to identify molecules based upon their preclinical activity, demonstrating[8-10]:

- Increased activity due to rapid and efficient substrate degradation compared with IMiD agents
- Enhanced immune stimulatory and tumoricidal activity, notably in the presence of IMiD agent resistance



- Cereblon modulation resulted in the degradation of target proteins in preclinical studies and is a recognized treatment approach in select hematologic malignancies[2]
- In vitro studies showed that the IMiD agents directly induce tumor-cell killing and stimulate immune function and are the foundation of our research in multiple myeloma[10-12,18]
- Preclinical studies showed that the CELMoD agents, including iberdomide (CC-220) and CC-92480, have increased potency for co-opting of cereblon and enhanced immune stimulatory and tumoricidal activity compared with IMiD agents[8-10,19]
- Additional CELMoD agents targeting degradation of novel substrates (eg, CC-90009 targeting GSPT1) are in development[20]

IMiDs belong to the class of cereblon E3 ligase modulators. While they have a shared target with novel agents such as iberdomide and CC-92480, their downstream effects differ.

The safety and efficacy of the agents and/or uses under investigation have not been established.
There is no guarantee that the agents will receive health authority approval or become commercially available in any country for the uses being investigated.

GSPT1, G1 to S phase transition 1; **IL-2**, interleukin-2; **IRF4**, interferon regulatory factor 4; **NK**, natural killer; **NKT**, natural killer T.

1. Ito T, et al. Identification of a primary target of thalidomide teratogenicity. *Science*. 2010;327:1345-1350. **2.** Collins I, et al. Chemical approaches to targeted protein degradation through modulation of the ubiquitin-proteasome pathway. *Biochem J*. 2017;474:1127-1147. **3.** Krönke J, et al. Lenalidomide causes selective degradation of IKZF1 and IKZF3 in multiple myeloma cells. *Science*. 2014;343:301-305. **4.** Gandhi AK, et al. Immunomodulatory agents lenalidomide and pomalidomide co-stimulate T cells by inducing degradation of T cell repressors Ikaros and Aiolos via modulation of the E3 ubiquitin ligase complex CRL4 (CRBN). *Br J Haematol*. 2014;164:811-821. **5.** Lu G, et al. The myeloma drug lenalidomide promotes the cereblon-dependent destruction of Ikaros proteins. *Science*. 2014;343:305-309. **6.** Bjorklund CC, et al. Rate of CRL4 (CRBN) substrate Ikaros and Aiolos degradation underlies differential activity of lenalidomide and pomalidomide in multiple myeloma cells by regulation of c-Myc and IRF4. *Blood Cancer J*. 2015;5:e354. **7.** Lopez-Girona A, et al. Cereblon is a direct protein target for immunomodulatory and antiproliferative activities of lenalidomide and pomalidomide. *Leukemia*. 2012;26:2326-2335. **8.** Matyskiela ME, et al. A cereblon modulator (CC-220) with improved degradation of Ikaros and Aiolos. *J Med Chem*. 2018;61:535-542. **9.** Niels WCJ, et al. First results of iberdomide (IBER; CC-220) in combination with dexamethasone (DEX) and daratumumab (DARA) or bortezomib (BORT) in patients with relapsed/refractory multiple myeloma (RRMM). Poster presentation at ASH 2020. Abstract 724. **10.** Kotla V, et al. Mechanism of action of lenalidomide in hematological malignancies. *J Hematol Oncol*. 2009;2:36. **11.** Borrello I. Can we change the disease biology of multiple myeloma? *Leuk Res*. 2012;36:S3-S12. **12.** Quach H. Mechanism of action of immunomodulatory drugs (IMiDS) in multiple myeloma. *Leukemia*. 2010;24:22-32. **13.** Schafer PH, et al. Cereblon modulator iberdomide induces degradation of the transcription factors Ikaros and Aiolos: immunomodulation in healthy volunteers and relevance to systemic lupus erythematosus. *Ann Rheum Dis*. 2018;77:1516-1523. **14.** Galustian C, et al. Thalidomide-derived immunomodulatory drugs as therapeutic agents. *Expert Opin Biol Ther*. 2004;4:1963-1970. **15.** Sehgal K, et al. Clinical and pharmacodynamic analysis of pomalidomide dosing strategies in myeloma: impact of immune activation and cereblon targets. *Blood*. 2015;125:4042-4051. **16.** Amatangelo M, et al. Preclinical and translational support for clinical development of iberdomide in combination with proteasome inhibitors: mechanism of synergy in clinical trial CC-220-MM-001. Poster presentation at ASH 2020. Abstract 1358. **17.** Amatangelo M, et al. Preclinical and translational data support development of iberdomide in combination with CD38- and SLAMF7-directed monoclonal antibodies: evidence for rational combinations. Poster presentation at ASH 2020. Abstract 1359. **18.** Larocca A, et al. Emerging drugs and combinations to treat multiple myeloma. *Oncotarget*. 2017;8:60656-60672. **19.** Lopez-Girona A, et al. CC-92480 is a novel cereblon E3 ligase modulator with enhanced tumoricidal and immunomodulatory activity against sensitive and resistant multiple myeloma cells. Poster presentation at ASH 2019. Abstract 1812. **20.** Lopez-Girona A, et al. CC-90009, a novel cereblon E3 ligase modulator, targets GSPT1 for degradation to induce potent tumoricidal activity against acute myeloid leukemia (AML). Poster presentation at ASH 2019. Abstract 2703.