

Practical Considerations for CELMoDs in NHL



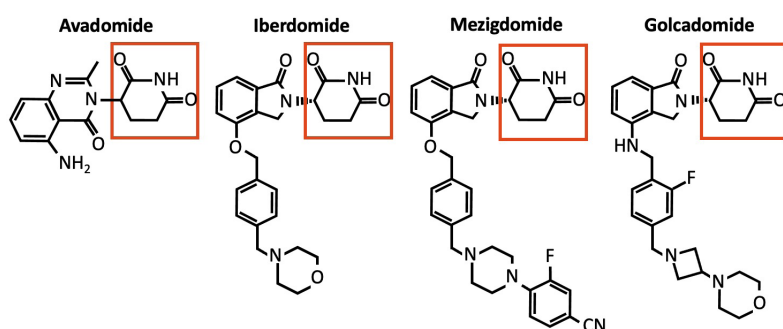
What is cereblon?¹⁻⁵

- A protein involved in the degradation of other proteins in the cell
- Regulates the expression, assembly, and activities of other crucial proteins involved in cell proliferation and metabolism
- Molecular target for IMiDs and CELMoDs

What are cereblon E3 ligase modulating drugs (CELMoDs)?¹⁻⁵

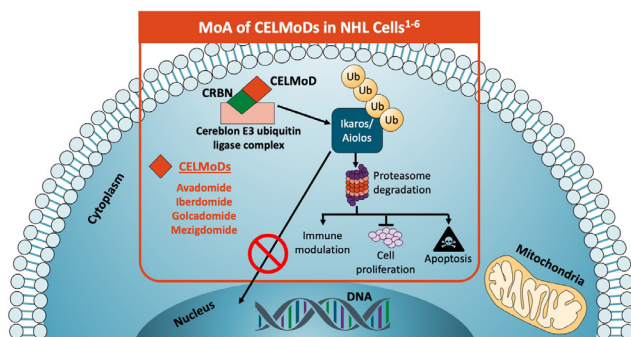
- Modeled after thalidomide analogues (IMiDs) and share many similarities with IMiDs
- Have chemical structures that are specifically designed to promote binding to cereblon and inducing targeted protein degradation of transcription factors
- Novel investigational CELMoDs include: avadomide, golcadomide iberdomide, and mezigdomide

CELMoDs Currently in Development³⁻⁵



CELMoDs bind with high affinity to CRBN, leading to¹⁻⁶:

Modulation of activity of CRBN E3 ubiquitin ligase complex → increased polyubiquitination of TFs, ikaros and aiolos → immune modulation, decreased cell proliferation and increased apoptosis



CC-99282-NHL-001⁶⁻⁷

Nonrandomized multicenter, 2-part, first-in-human, open-label, phase I/II trial (study start date: May 20, 2019)

Patients aged ≥18 yr with R/R NHL; received ≥2 previous lines of therapy (or received ≥1 previous line of therapy and ineligible for any other tx); ECOG PS 0-2 (Target N = 438)

Dose-escalation Phase (Part A)	Multi-cohort Expansion Phase (Part B)
Golcadomide monotherapy	Golcadomide ± antilymphoma agent
Endpoints: MTD/RP2D, safety, tolerability	Endpoints: Pharmacokinetics, efficacy, safety

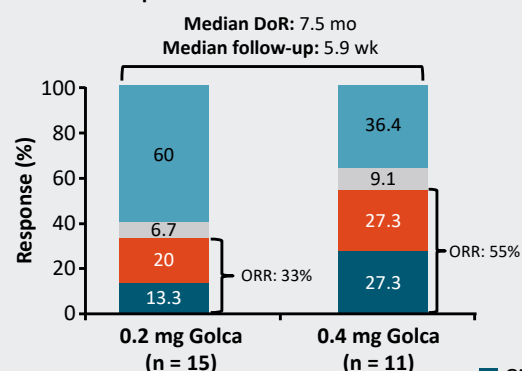
Important detail: trial is still accruing →



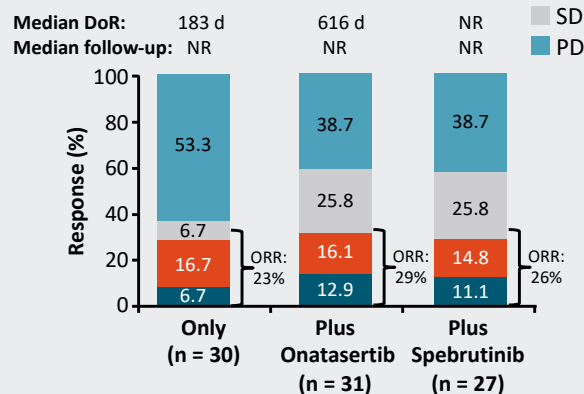
Total DoT: 2 yr

Phase I/II Trials: Efficacy of CELMoDs in R/R DLBCL⁶⁻⁹

Response With Golcadomide + R^{6,7}



Response With Avadomide + R^{8,9}



CC-223 (onatasertib) inhibits mTOR, CC-292 (spebrutinib) inhibits BTK



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Common Side Effects of CELMoDs⁶⁻⁹

Common side effects associated with CELMoDs include:

- Neutropenia, anemia, thrombocytopenia
- Constipation, diarrhea
- Fatigue, asthenia
- Infections, pyrexia
- Hypokalemia, hyperglycemia



Please talk to your healthcare team for medical advice about side effects.

Select Ongoing Studies of CELMoDs in B-Cell Lymphomas⁹⁻¹⁴

Trial ID	Phase	Status*	Target N	Patient Population	Treatment Arm(s)	1° Endpoint
GOLSEEK-1 (NCT06356129)	III	Not yet recruiting	850	Previously untreated high-risk LBCL	▪ Golcadomide + R-CHOP ▪ Placebo + R-CHOP	▪ PFS
CARMOD (NCT06271057)	II	Not yet recruiting	65	Post CAR T-cell tx in R/R aggressive LBCL at high risk of relapse	▪ Golcadomide	▪ CMR rate
NCT04884035	I	Recruiting	174	Previously untreated aggressive B-cell lymphoma	▪ Ibrdomide + R-CHOP-21 or Pola-R-CHP ▪ Golcadomide + R-CHOP-21 or Pola-R-CHP	▪ MTD ▪ RP2D ▪ Safety and tolerability
OSU-23214 (NCT06209619)	I	Recruiting	18	Post CAR T-cell tx for B-cell NHL	▪ Golcadomide + R	▪ MTD ▪ AEs
CA092-1000 (NCT05688475)	I	Active not recruiting	12	Currently receiving avadomide	▪ Avadomide + dexamethasone	▪ SAEs ▪ Deaths

*As of May 23, 2024.

GOLSEEK-1¹⁰

Multicenter, randomized, double-blind, placebo-controlled phase III trial (study start date: June 24, 2024)

Patients aged 18-80 yr with previously untreated high-risk LBCL,* including DLBCL-NOS, HGBCL with MYC/BCL2 rearrangements, HGBCL-NOS, T-cell/histiocyte-rich LBCL, EBV + DLBCL, no CNS involvement

(Target N = 850)

Golcadomide + R-CHOP

Placebo + R-CHOP

***Excluded patients:** any other subtype of lymphoma not specified; primary mediastinal (thymic) LBCL, primary cutaneous DLBCL-leg type, grade 3b FL, FL transformed to a-BCL, ALK+ LBCL, primary effusion lymphoma, and Burkitt lymphoma

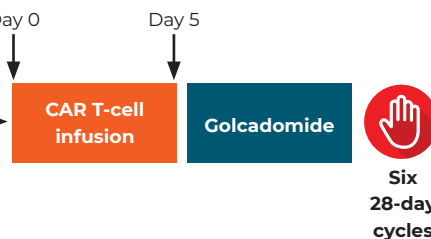
- **Primary endpoint:** PFS per investigator
- **Secondary endpoints include:** OS, EFS, CMR rate/ PFS by IRAC, MRD negativity, ORR, DoR, PFS2, safety, and quality of life

CARMOD¹¹

Multicenter, open-label, proof-of-concept, phase II trial in France (study start date: April 22, 2024)

Patients aged ≥18 yr with aggressive LBCL, including DLBCL, PMBCL, any transformed FL or MZL, HGBCL, with indication for CAR T-cell therapy as 2L-4L, ECOG PS 0-1, CNS involvement allowed, no PCNSL

(Target N = 65)



- **Primary endpoint:** CMR rate
- **Secondary endpoints include:** OS, PFS, EFS, ORR, CR rate, DoR, time to next antilymphoma treatment, and safety

Why Should Patients With NHL Enroll on the Ongoing Trials of CELMoDs?

- All patients with NHL should have access to novel treatment options to improve outcomes
- In the frontline NHL setting, the field is advancing with novel agents and new combinations, with the goal of improving efficacy and safety of available treatments
- CELMoDs are novel agents with a high potential to change treatment approach for patients with previously untreated or R/R NHL
 - Especially post CAR T-cell therapy, CELMoDs can significantly improve standard of care
- Access to promising investigational agents such as CELMoDs in the community practice setting is still very challenging
 - Enrollment on ongoing clinical trials increases patient access to more cutting-edge treatment options

2L, second line; 4L, fourth line; AE, adverse event; CAR, chimeric antigen receptor; CELMoDs, cereblon E3 ligase modulating drugs; CMR, complete metabolic rate; CNS, central nervous system; CR, complete response; CRBN, cereblon; DLBCL, diffuse large B-cell lymphoma; DoR, duration of response; DoT, duration of treatment; EBV, Epstein-Barr virus; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; FL, follicular lymphoma; Golca, golcadomide; HGBCL, high-grade B-cell lymphoma; IMiD, immunomodulatory agent; IRAC, independent response adjudication committee; LBCL, large B-cell lymphoma; MRD, minimal residual disease; MTD, maximal tolerated dose; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified; NR, not reached; ORR, objective/overall response rate; OS, overall survival; PCNSL, primary CNS lymphoma; PMBCL, primary mediastinal B-cell lymphoma; PD, progressive disease; PFS, progression-free survival; PR, partial response; PS, performance status; R, rituximab; R/R, relapsed/refractory; Pola-R-CHP, polatuzumab vedotin + rituximab, cyclophosphamide/doxorubicin/prednisone; RP2D, recommended phase II dose; SAE, serious adverse event; TF, transcription factor; Ub, ubiquitination.

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