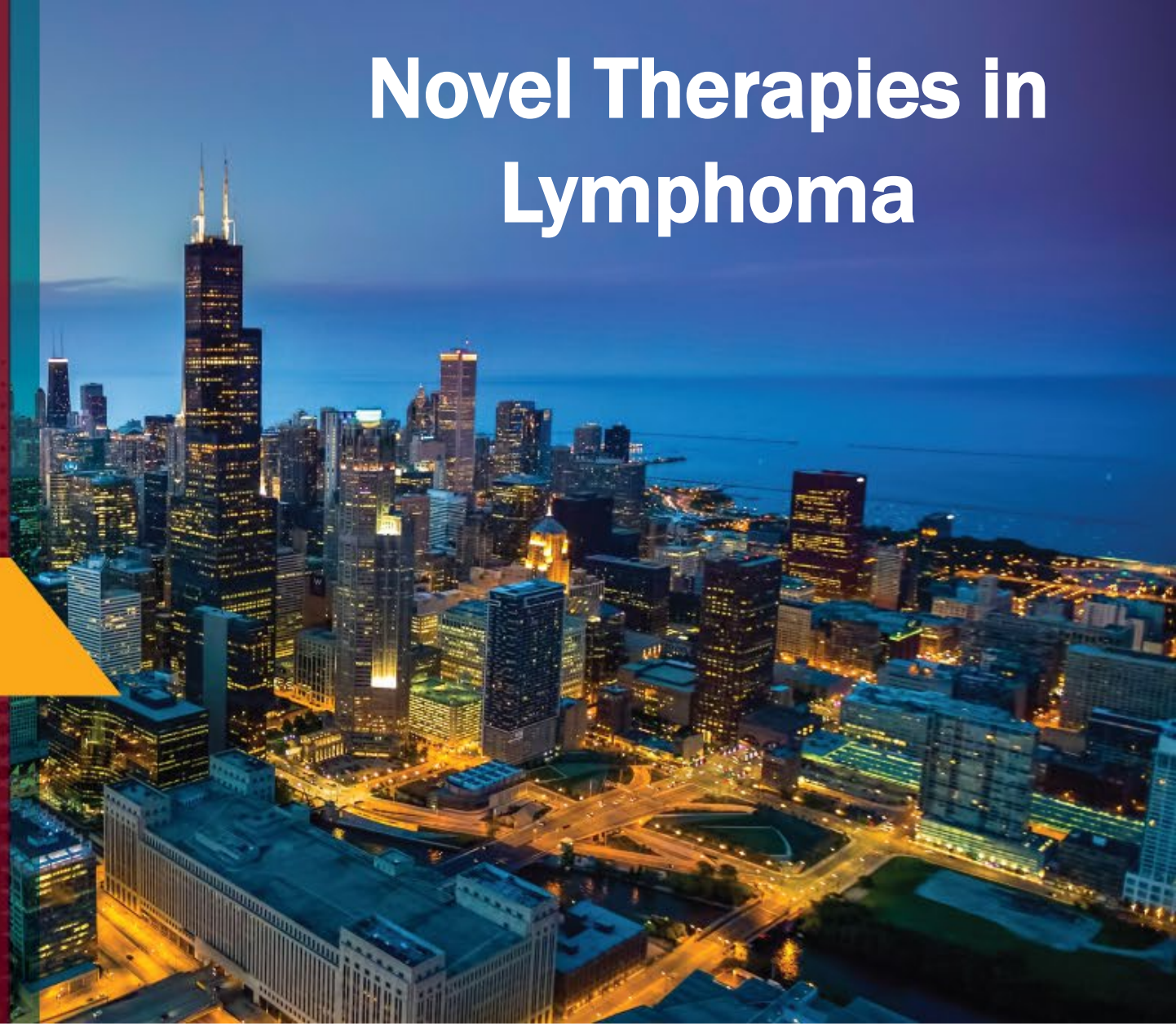
22nd INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM

APRIL 4 - 5, 2025

WESTIN CHICAGO RIVER NORTH

#IUCLS2025



Novel Therapies in Lymphoma

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April 4, 2025

This activity is jointly provided by:

THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

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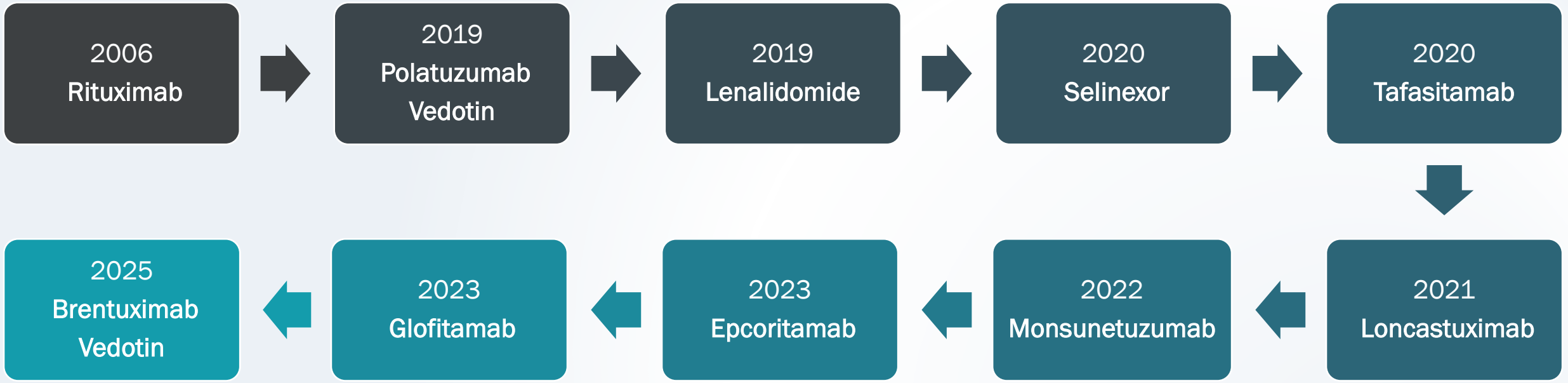
Disclosure

- No relevant conflicts of interest to disclose
- Novel therapies without off-label or FDA approval will be discussed throughout the presentation

Objectives

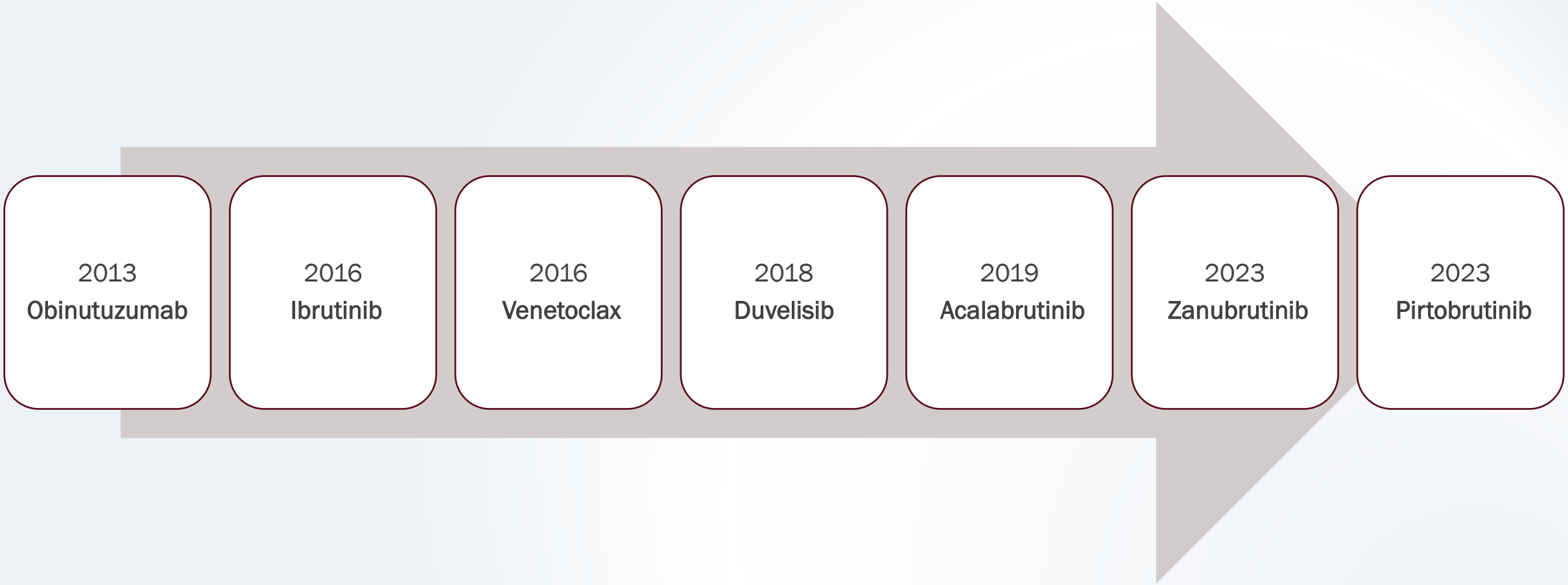
1. Review the history of recent drug therapy approvals in lymphoma
2. Evaluate the mechanism and safety profiles of novel therapies in the pipeline
   - Cereblon E3 Ligase Modulator (CELMoDs)
   - Bruton Tyrosine Kinase (BTK) Degraders

Non-Hodgkin Lymphoma Treatment Approval Timeline



Novel Drug Approvals at FDA.gov

CLL Treatment Approval Timeline



Novel Drug Approvals at FDA.gov

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Novel Therapies in the Pipeline

IMiDs vs.CELMoDs

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Immunomodulatory Agents (IMiDs)

Mechanism of Action

Direct Antitumor Effects

G0/G1 cell cycle arrest

Decrease Proliferation

- Upregulation of cyclin-dependent kinase inhibitor p21
- Downregulation of interferon regulatory factor 4 (IRF4)

Indirect Antitumor Effects

Co-stimulation and proliferation of T cells, NK cells, and cytokine production

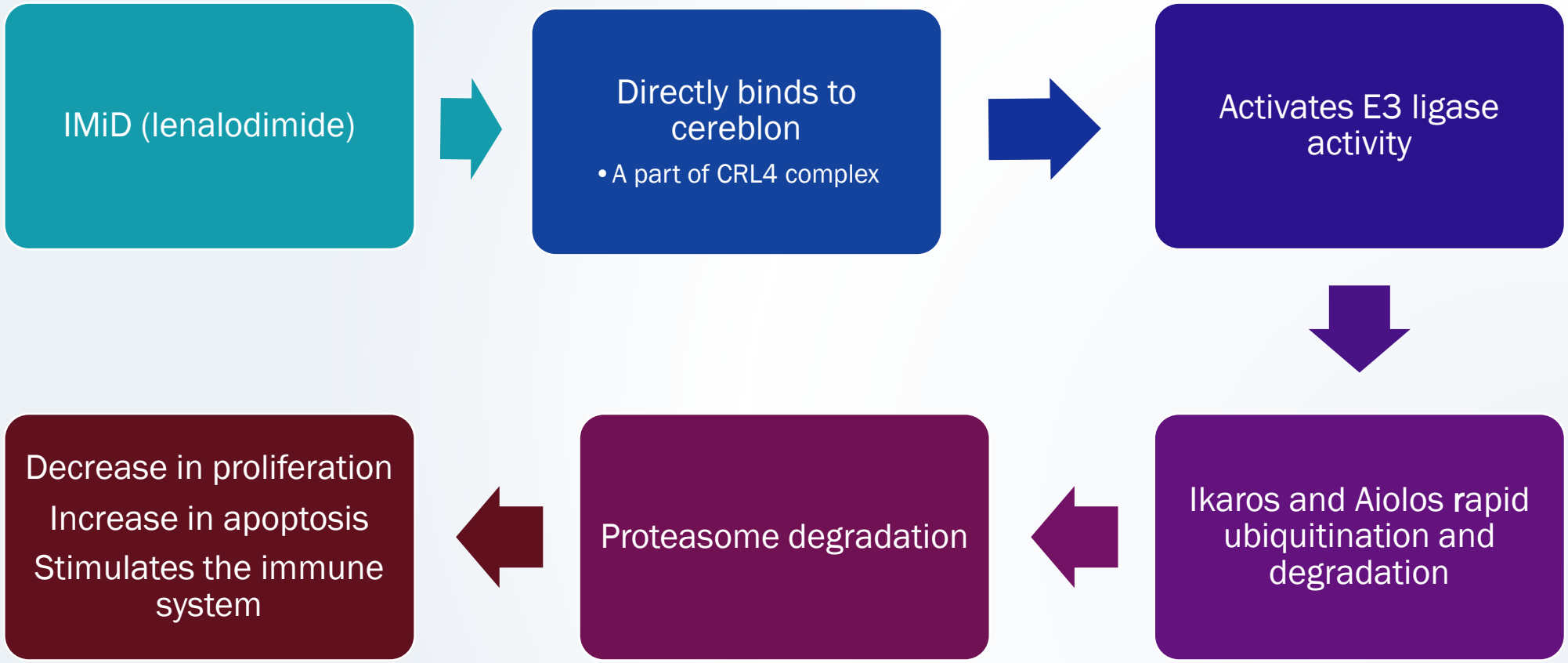
Inhibits angiogenesis

Inhibits bone marrow stromal cell growth factor production

Ioannou N, Jain K, Ramsay AG.. *Int J Mol Sci*. 2021;22(16):8572. Published 2021 Aug 9.

Cereblon as a Direct Target

- **Cereblon:** ubiquitously expressed E3 ligase protein
- **E3 ligase:** final enzyme in the ubiquitination cascade
- **Ikaros and Aiolos:** Transcriptions regulators of B and T-cell development
  - Selectively bound to cereblon



Ioannou N, Jain K, Ramsay AG.. *Int J Mol Sci*. 2021;22(16):8572. Published 2021 Aug 9.
Gribben J et al. JCO. Vol 33 (25) 2015

Cereblon E3 Ligase Modulator (CELMoDs)

Golcadomide

- Potential 10-100 fold potency vs. lenalidomide
  - Driving cereblon to closed formation (bound to Aiolos/Ikaros)
  - Demonstrates ability to cross blood brain barrier
    - Preclinical studies

Iberdomide

- Potential over 20 fold potency vs. lenalidomide
  - Driving cereblon to closed formation (bound to Aiolos/Ikaros)

Ioannou N, Jain K, Ramsay AG. *Int J Mol Sci*. 2021;22(16):8572. Published 2021 Aug 9.

CELMoD Safety Profile
Golcadomide Phase 1/2 in R/R NHL

- Part 1: Golcadomide monotherapy
- Part 2: Expansion to rituximab combination therapy (safety results)

Adverse Events	Golcadomide 0.2 mg + Rituximab (n=24)		Golcadomide 0.4 mg + Rituximab (n=20)	
	All Grade (%)	Grade 3(+)	All Grade (%)	Grade 3(+)
Neutropenia	**67%**	**46%**	**70%**	**60%**
Diarrhea	17%	0%	0%	0%
Constipation	8%	0%	10%	0%
Anemia	4%	0%	15%	15%
Asthenia	8%	4%	5%	0%
Fatigue	4%	0%	10%	5%
Pyrexia	4%	0%	10%	5%
Lymphopenia	0%	0%	15%	0%
Thrombocytopenia	0%	0%	15%	15%

Chavez J et al. Efficacy and Safety of Golcadomide Combined with Rituximab in a Phase 1/2 Open label Study, Blood (2023) 142 (Supplement 1): 4496.
Chavez J. Poster Presentation. American Society of Hematology (ASH) Annual Meeting; December 9 – 12, 2023; San Diego, CA

CELMoD Safety Profile
Iberdomide +/- CD20 Therapy in Phase 1/2 Trial in R/R Lymphoma

Cohorts

- All lymphomas: Iberdomide
- BCL: with Rituximab
- MZL or FL: with obinutuzumab

Adverse Events N=45 patients	All Grade (%)	Grade 3(+)
Neutropenia	57%	49%
Anemia	24%	15%
Thrombocytopenia	22%	13%
Constipation	22%	n/a
Diarrhea	13%	2%
Pyrexia	17%	2%
Asthenia	13%	
Back pain	13%	
Muscle spasms	11%	
Cough	11%	
Blood creatinine increase	11%	

BCL: B-cell lymphoma; MZL: marginal zone lymphoma; FL: follicular lymphoma

Thieblemont C et al. Blood (2022) 140 (Supplement 1): 569–572

CELMoD Safety Profile
Avadomide + Rituximab in Phase 1b Trial in R/R DLBCL and FL

Adverse Events N=68 patients	All Grade (%)	Grade 3(+)
Neutropenia	92.6%	66.2%
Febrile Neutropenia	7.4%	7.4%
Infections	23.5%	8.8%
Fatigue	22.1%	2.9%
Diarrhea	19.1%	2.9%
Rash	13.2%	1.5%
Nausea	16.2%	0%

*GCSF permitted Cycle 2 and on

Nastoupil LJ, Kuruvilla J, Chavez JC, et al. *EJHaem.* 2022;3(2):394-405.

CELMoD Summary

In the Pipeline

- Golcadomide
- Iberdomide
- Avadomide

Safety Takeaways

- Neutropenia
- Anemia
- Thrombocytopenia
- GI toxicity

Future Questions

- Dosing and Frequency
- Place in Therapy
  - After lenalidomide?
  - To be compared to lenalidomide?

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Novel Therapies in the Pipeline

BTK Degraders

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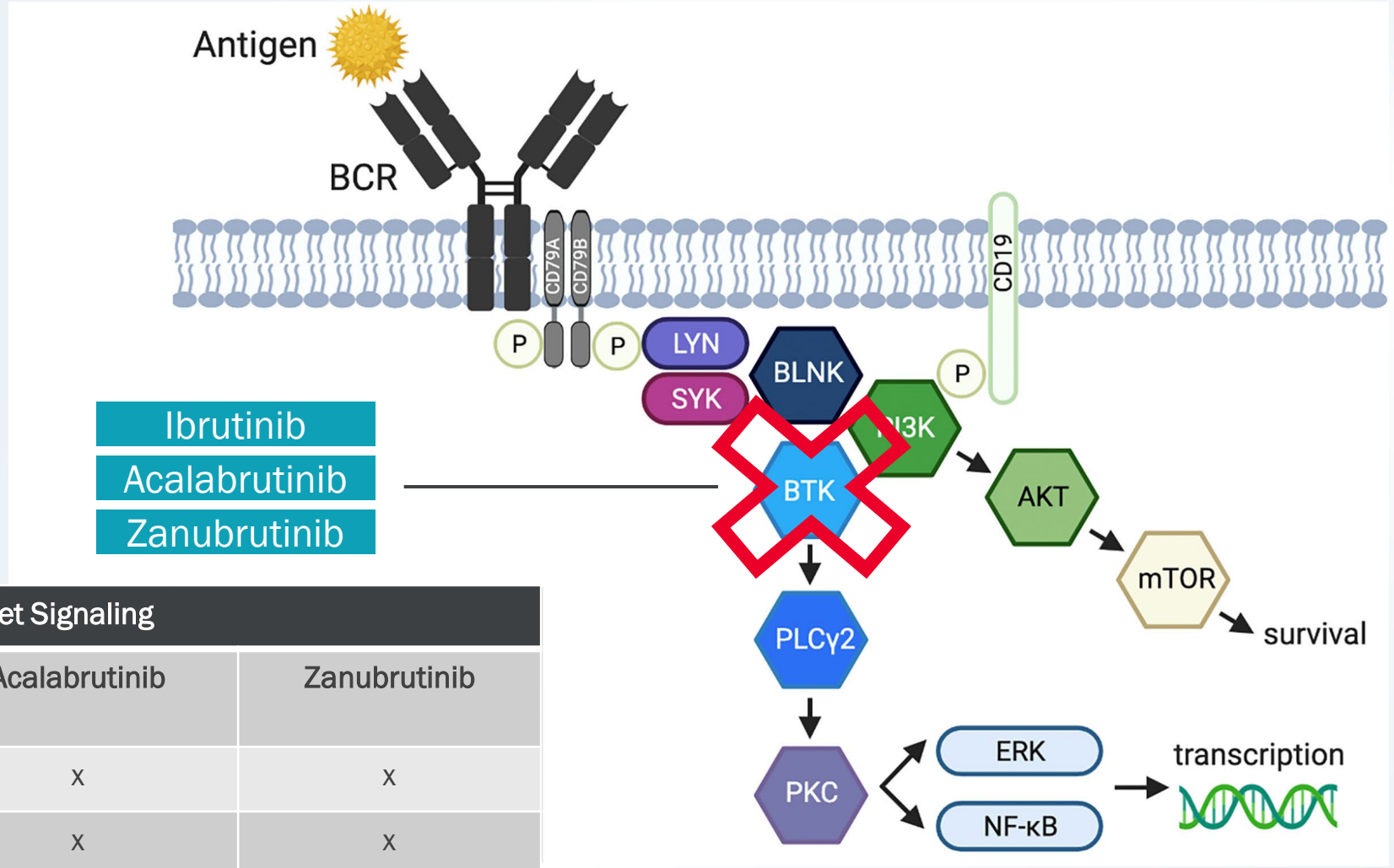
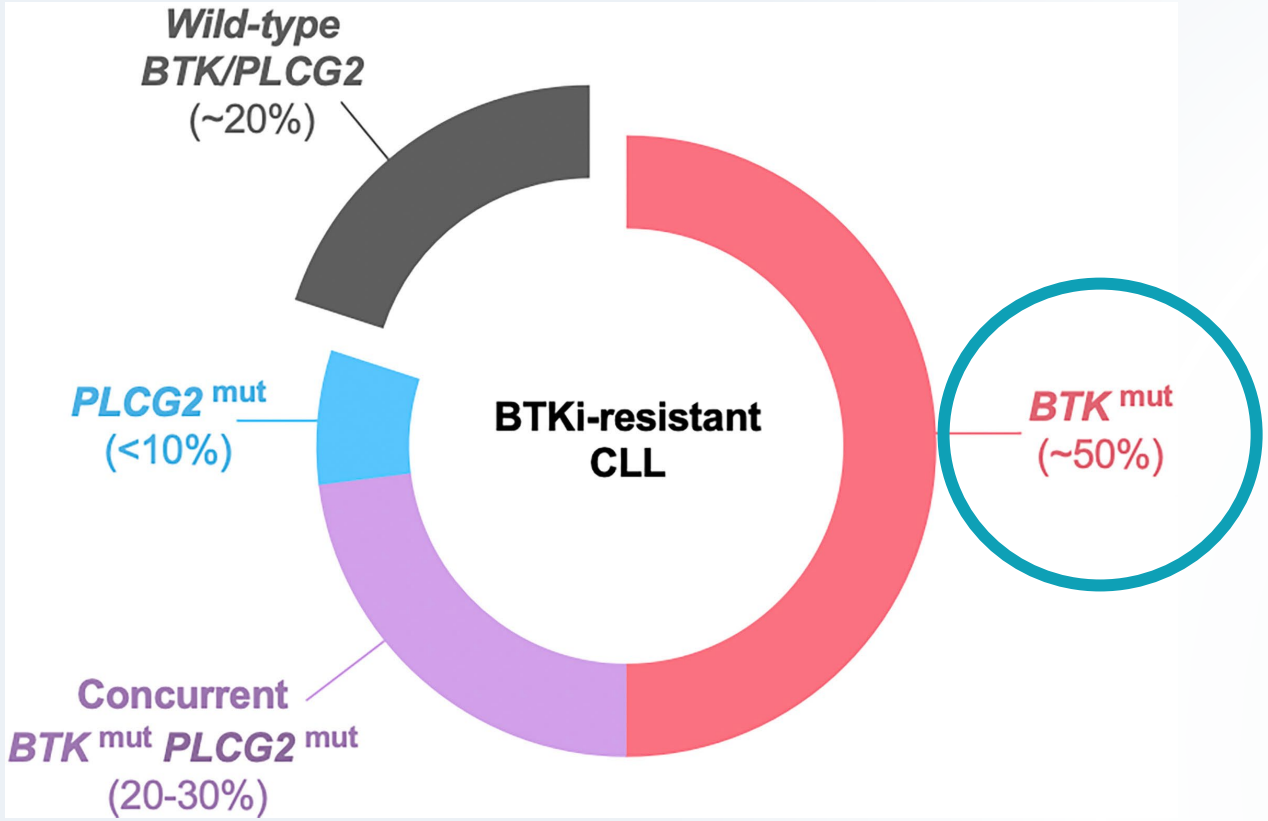
Bruton Tyrosine Kinase Inhibitors (BTKi)



Off Target Signaling			
	Ibrutinib	Acalabrutinib	Zanubrutinib
TEC	X	x	x
ITK	X	x	x
EGFR	X	x	x

Ahn IE, Brown JR. *Front Immunol*. 2021;12:687458. Published 2021 Jun 23.

BTKi Resistance



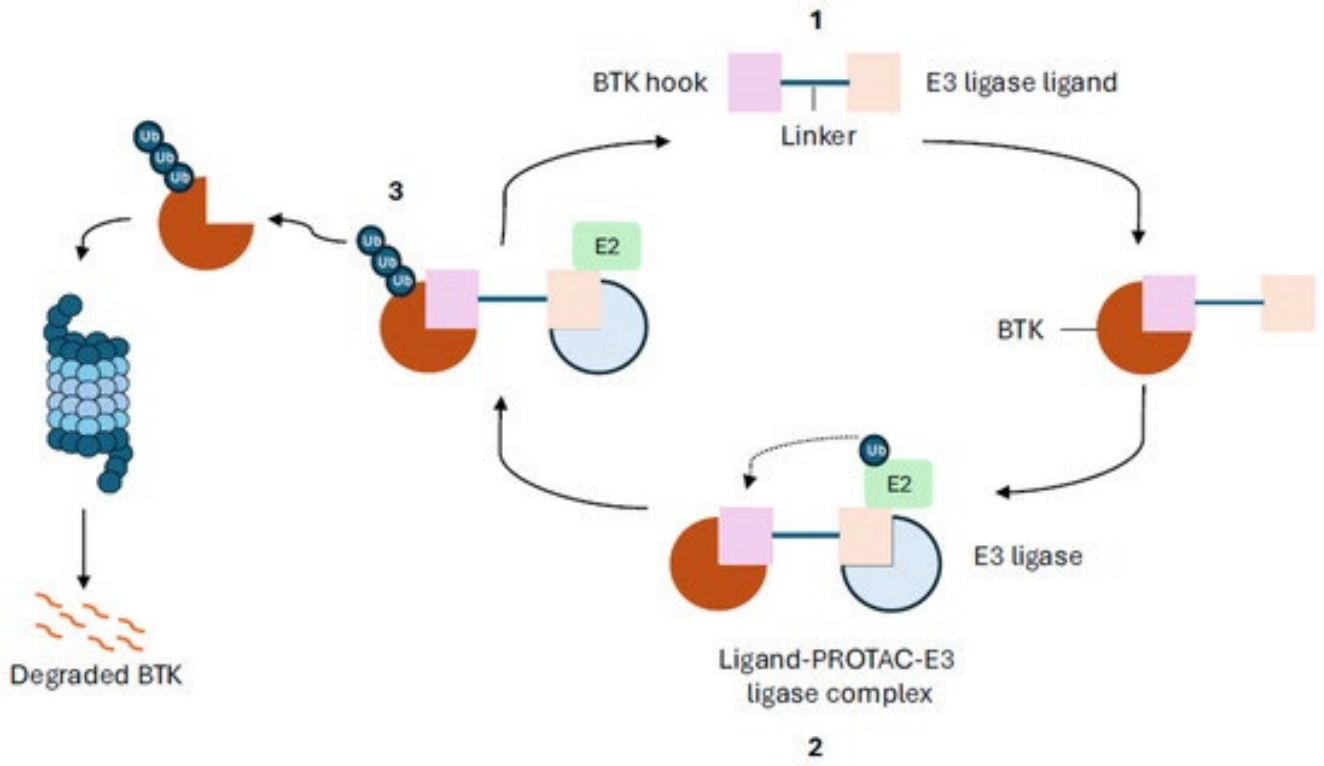
Pirtobrutinib
Noncovalent reversible inhibition
BTK C481 mutation

Other Clinical Resistance
(covalent and noncovalent BTK's)
L528W, T474I, V416L, A428D, M327R

Ahn IE, Brown JR. *Front Immunol*. 2021;12:687458. Published 2021 Jun 23.

Mechanism of BTK Degrader

- Degrader: Linker with a ligand for BTK and another for E3 ligase
- The degrader binds to BTK protein and E3 ligase, forming a complex
- Ubiquitination begins, leading to proteasome degradation



Salvaris RT et al.. *Cancers (Basel)*. 2025;17(3):557.

BTK Degrader Safety Profile
BGB-16673 Phase 1 in R/R CLL or SLL

- Degradation of both wild type and mutant forms of BTK
- Preliminary Pharmacokinetic data:
  - Metabolized by CYP3A4
  - Interaction with pH lowering medications

Adverse Events N=49 patients	All Grade (%)	Grade 3+ (%)
Fatigue	33%	Not reported
Contusion	29%	Not reported
Anemia	22%	Not reported
Diarrhea	22%	Not reported
Neutropenia	22%	20%

*No hypertension, atrial fibrillation/flutter reported to date

Thompson M et al. *Blood* (2024) 144 (Supplement 1): 885.

BTK Degrader Safety Profile
NX-5948: Phase 1 in R/R B-cell malignancies

- Degradation of wild type and mutant forms of BTK
- Preliminary Pharmacokinetic data:
  - Ability to cross the blood-brain barrier

Adverse Events N=87 patients	All Grade (%)	Grade 3+ (%)
Purpura/contusion	44.1%	0%
Thrombocytopenia	23.5%	2.9%
Petechiae	29.4%	0%
Fatigue	20.6%	0%
Neutropenia	17.6%	14.7%
Rash	23.5%	2.9%
Headache	23.5%	0%

*No new onset of atrial fibrillation/flutter or hypertension

Shah N. et al. *Blood* (2024) 144 (Supplement 1): 884.

BTK Degrader + Immunomodulatory Activity Safety Profile
NX-2127: Phase 1 in R/R B-cell malignancies

- BTK Degrader + ubiquitination of targets (Ikaros and Aiolos) to increase T-cell activation
- Degrades wild type and C481-mutated BTK protein

Adverse Events N=47 patients	All Grade (%)	Grade 3(+)
Fatigue	48.9%	n/a
Neutropenia	38.3%	n/a
Hypertension	14.9%	n/a
Anemia	12.8%	n/a
Contusion	27.7%	n/a
Atrial Fibrillation	12.8%	6.4%

Danilov A et al. *Blood* (2023) 142 (Supplement 1): 4463.

BTK Degrader Summary

In the Pipeline

- BGB-16673
- NX-5948
- NX-2127

Safety Takeaways

- Fatigue
- Neutropenia
- Bruising/thrombocytopenia
- Atrial fibrillation and hypertension
  - Only NX-2127 (so far)

Future Questions

- Dosing and frequency
- Place in Therapy

Summary

- Positive preliminary data so far utilizing CELMoDs and BTK Degraders to overcome resistance in the relapsed/refractory setting
- Future areas of interest
  - Safety and efficacy in combination therapy
  - Safety and efficacy in refractory patients with known resistance
  - Comparison to standard of care therapy

Clinical Trials at University of Chicago Medicine

- A Phase IB, Open-Label, Multicenter Study Evaluating the Safety, Pharmacokinetics, and Efficacy of Mosunetuzumab or Glofitamab in Combination with CC-220 and CC-99282 in Patients with B-Cell Non-Hodgkin Lymphoma
- A Phase 1, Dose Escalation, Safety and Tolerability Study of NX-2127, a Bruton's Tyrosine Kinase (BTK) Degrader, in Adults with Relapsed/Refractory B-cell Malignancies.

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Questions?

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