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Breakthroughs in treatment for hematological malignancies: latest updates on molecular glue, PROTACs and RNA degraders from ASH 2024

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Abstract
Degrader therapies have garnered significant attention for their innovative approach to targeting and eliminating malignancy-associated proteins, holding promise for improving outcomes for patients with relapsed or refractory (R/R) hematological malignancies, especially in cases of leukemia, non-Hodgkin lymphoma, and multiple myeloma. Currently, the main categories developed based on degraders include molecular glue (such as Cemsidomide, NX-5948), PROTACs (such as BGB-16673, AC-676, KT-333), and RNA degraders (such as SKY-1214). This correspondence summarizes the preclinical and clinical updates on degrader therapies presented at the ASH 2024 annual meeting.

Keywords Targeted protein degraders, Hematological malignancies, AML, NHL, MM, Therapeutic strategies

To the editor

Degraders are novel therapeutic agents designed to target specific proteins for degradation within cells, utilizing the cell's own protein disposal system (not only the ubiquitin-proteasome system but also the autophagy-lysosome system). The development of degraders is an active area of research, with numerous candidates currently undergoing preclinical studies and clinical trials. This report summarizes the latest updates at the ASH 2024 annual meeting on the research of degraders.

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Preclinical studies

The preclinical studies of degraders are summarized in Table 1. The landscape is predominantly shaped by molecular glue (MG) and Proteolysis Targeting Chimeras (PROTAC) modalities, with a notable emergence of new modalities such as the DAC (Degrader-Antibody Conjugate) represented by HDZ-C123A [1] and the mRNA degrader exemplified by SKY-1214 [2]. The majority of these compounds utilize E3 Ligase Dependent mechanisms for degradation. Notably, SKY-1214 stands out as an mRNA degrader that targets FANCL and FANCI [2]. Current preclinical research is evaluating innovative targets, with IRF4, CBP/p300, MALT1, BCR::ABL1, KAT2A/B, IRAK1/4 and others being identified as promising in broadening treatment options for various hematological disorders (Table 1). In particular, degradation may hold promise for a myriad of lymphocytic malignancies, including Multiple Myeloma (MM), Chronic Lymphocytic Leukemia (CLL), Acute Lymphoblastic Leukemia (ALL), and Non-Hodgkin Lymphoma (NHL).

Table 1 Preclinical studies of degraders presented at ASH 2024

Compound(s)	Administration Route(s)	Modality	Target(s)	Degradation Mechanism	Disease(s)	Abstract number
INNO-220	oral	MG	CK1α	CRBN Dependent	B-cell lymphomas	956
dIRF4	oral	PROTAC	IRF4	CRBN Dependent	MM	155
HDZ-C123A	-	DAC	CD123-GSPT1	CRBN Dependent	AML	156
SH6	-	MG	ZBTB7A	CRBN Dependent	Beta-globinopathies	172
Advanced Analogs of dCBP-1	oral	PROTAC	CBP/p300	CRBN Dependent	MM	2795
ZE66-0205	oral	MG	MALT1	CRBN Dependent	B-cell malignancies	2783
TGRX-3247	oral	PROTAC	BCR::ABL1	CRBN Dependent	CML	1387
LPA81S	-	PROTAC	BCR::ABL1	CRBN Dependent	CML	4157
WH25244	-	PROTAC	mutant BCL2, hyperphosphorylated BCL2, BCL-XL	VHL Dependent	CLL	2786
MLLT1/3 degrader	oral	-	MLLT1/3	-	Advanced AML and ALL	2772
AUTX-703	oral	-	KAT2A and KAT2B	-	AML	3585
SKY-1214	oral	mRNA degrader	FANCL and FANCI	mRNA degradation	R/R MM and R/R NHL	2784
Jh-XIII-05-1	subcutaneous injection	PROTAC	IRAK1/4	-	MYD88-mutated B-NHL	4359

MG: Molecular Glue; CK1α: Casein Kinase 1 Alpha; CRBN: Cereblon; PROTAC: Proteolysis Targeting Chimera; IRF4: Interferon regulatory factor 4; GSPT1: G1 to S Phase Transition 1; AML: Acute Myeloid Leukemia; ZBTB7A: Zinc Finger and BTB Domain-Containing Protein 7 A; CBP/p300: CREB-binding protein/p300; MALT1: Mucosa-associated Lymphoid Tissue Translocation 1; CML: Chronic Myeloid Leukemia; BCL2: B-cell lymphoma 2; BCX-XL: BCL-2-related gene long isoform; VHL: Von Hippel-Lindau; MLLT1/3: Myeloid Leukemia Lineage-specific Transcription Factor 1/3; KAT2A: Lysine Acetyltransferase 2 A; KAT2B: Lysine Acetyltransferase 2B; FANCL: FA Complementation Group L; FANCI: FA Complementation Group I; IRAK1/4: Interleukin-1 Receptor-associated Kinase 1/4

In addition to the first-in-class degrader compounds presented at ASH 2024, recent research advancements on previously reported degrader compounds were also highlighted, as detailed in the supplementary materials Table S1.

Clinical trials

Table 2 provides a detailed overview of the results from clinical trials of degraders presented at the ASH 2024 conference. BGB-16,673 targets BTK (Bruton's Tyrosine Kinase) and is undergoing Phase 1/2 clinical trials. It is being tested for R/R waldenström macroglobulinemia (WM) with 22 participants (NCT05006716) and for R/R CLL/small lymphocytic lymphoma (SLL) with 49 participants. BGB-16,673 demonstrated an impressive overall response rate (ORR) of 90% in patients with R/R WM [3] and a 78% ORR in those with R/R CLL/SLL [4]. NX-5948 also targets BTK and is in phase 1a/b trials for R/R B-cell malignancies, showed a 76.7% ORR in patients with R/R CLL (NCT06691828) [5]. AC676, another PROTAC targeting BTK, is in phase 1 clinical trials for R/R B-cell malignancies(NCT05780034) [6]. Cemsidomide, which targets IKZF1/3 (Ikaros Family Zinc Finger Proteins 1 and 3), is in phase 1/2 trials for NHL with 20 patients and for R/R MM with 32 patients, achieved a 25% ORR in NHL patients [7], many of which being T-cell lymphomas, and a 22% ORR in R/R MM (NCT04756726) [8]. KT-333, a PROTAC that targets STAT3 with a VHL Dependent mechanism, is in phase 1a/1b trials for a broad range of conditions including R/R B- and T-cell lymphomas, classical Hodgkin lymphoma (cHL), solid tumors (ST), and large granular lymphocytic-leukemia/T-cell prolymphocytic leukemia (LGL-L/T-PLL), exhibiting a 31.4% ORR with 51 patients enrolled (NCT05225584) [9]. Preliminary data from these phase 1 trials suggest that these degraders exhibit favorable safety and tolerability profiles, along with promising clinical activity.

These updates from ASH 2024 underscore the dynamic progress in the field of targeted protein degradation, with a focus on innovative approaches to combat hematological diseases and other malignancies. The innovative aspects of these degraders, such as dual targeting, immunomodulatory activity, and combination therapies, highlight the potential for more effective and personalized treatment options in the future.

Table 2 Outcomes of clinical trials of degraders presented at ASH 2024

Compound	Administration Route	Modality	Target(s)	Degradation Mechanism	Disease(s)	Patient Number	ORR	Clinical Stage	NCT Number	Abstract Number
BGB-16673	oral	PROTAC	BTK	CRBN Dependent	R/R WM	22	90%	phase 1/2	NCT05006716	860; 885
					R/R CLL/SLL	49	78%			
NX-5948	oral	MG	BTK	CRBN Dependent	R/R B-cell malignancies	87	76.7% (R/R CLL)	Phase 1a/b	NCT06691828	884
AC676	oral	PROTAC	BTK	CRBN Dependent	R/R B-cell malignancies	60	-	Phase 1	NCT05780034	4422.1
Cemsidomide	oral	MG	IKZF1/3	CRBN Dependent	NHL	20	25%	phase 1/2	NCT04756726	467;3366
					R/R MM	32	22%			
KT-333	IV	PROTAC	STAT3	VHL Dependent	R/R B- and T-cell lymphomas, cHL, ST and LGL-L/T-PLL	51	31.4%	Phase 1a/1b	NCT05225584	4433

BTK: Bruton's Tyrosine Kinase; IKZF1/3: Ikaros Family Zinc Finger Proteins 1 and 3; IV: Intravenous/Intravenously; STAT3: Signal Transducer and Activator of Transcription 3

Abbreviations

ASH	American Society of Hematology
R/R	Relapsed or Refractory
MG	Molecular Glue
PROTAC	Proteolysis Targeting Chimeras
CRBN	Cereblon
VHL	Von Hippel-Lindau
DAC	Degrader-Antibody Conjugate
MM	Multiple Myeloma
CLL	Chronic Lymphocytic Leukemia
ALL	Acute Lymphoblastic Leukemia
NHL	Non-Hodgkin Lymphoma
BTK	Bruton's Tyrosine Kinase
cHL	Classical Hodgkin Lymphoma
ORR	Overall Response Rate
SLL	Small Lymphocytic Lymphoma
WM	Waldenström Macroglobulinemia

Supplementary Information

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Supplementary Material 1

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