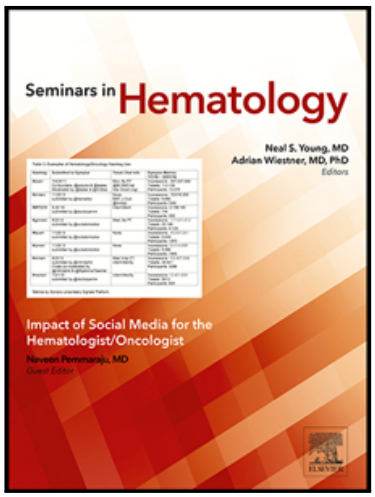

Report of Consensus Panel 7 from the 11th International Workshop on Waldenström Macroglobulinemia on Priorities for Novel Clinical Trials.

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Report of Consensus Panel 7 from the 11th International Workshop on Waldenström Macroglobulinemia on Priorities for Novel Clinical Trials.

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Abstract

Recent advances in the understanding of Waldenström macroglobulinemia (WM) biology have impacted the development of effective novel agents and improved our knowledge of how the genomic background of WM may influence selection of therapy. Consensus Panel 7 (CP7) of the 11th International Workshop on WM was convened to examine the current generation of completed and ongoing clinical trials involving novel agents, consider updated data on WM genomics, and make recommendations on the design and prioritization of future clinical trials. CP7 considers limited duration and novel-novel agent combinations to be the priority for the next generation of clinical trials. Evaluation of *MYD88*, *CXCR4* and *TP53* at baseline in the context of clinical trials is crucial. The common chemoimmunotherapy backbones, bendamustine-rituximab (BR) and dexamethasone, rituximab and cyclophosphamide (DRC), may be considered standard-of-care for the frontline comparative studies. Key unanswered questions include the definition of frailty in WM; the importance of attaining a very good partial response or better (≥VGPR), within stipulated time frame, in determining survival outcomes; and the optimal treatment of WM populations with special needs

Introduction

Consensus Panel 7 (CP7) of the 11th International Workshop on Waldenström Macroglobulinemia (WM; IWWM-11), held in October 2022, was tasked with defining priorities for novel clinical trials in WM. Recent advances in the treatment of WM and related disorders have fostered a vibrant research environment, including phase 2 and 3 studies of chemoimmunotherapy regimens[1-4] and novel agents including Bruton Tyrosine Kinase inhibitors (BTKi)[5-7], B-cell lymphoma 2 (BCL2) antagonists[8] and other targeted agents[9]. Concurrently, rapid advances in the study of the WM genome[10-12] and new understanding of the impact of *MYD88*, *CXCR4* and *TP53* mutation status on therapeutic responses to BTKi[5,12,13] have raised questions about whether genetic stratification should be applied to future clinical trials in WM. In addition, what patients value in terms of treatment characteristics should also be taken into account.[14] In this document, CP7, representing a group of WM experts with diverse interest in clinical trials discusses how novel agents, chemoimmunotherapy and recently-understood biological underpinnings may be incorporated into the future clinical trial designs in WM (**Table 1**).

To describe the current clinical trial landscape, an overview of recently completed (not yet published), currently enrolling and planned investigator-initiated clinical trials and industry-sponsored clinical trials is outlined in Table 2 and Table 3. Clinical trials were identified on the website, clinicaltrials.gov (updated on March 1st, 2023) and all phase II and phase III trials conducted specifically in patients with WM were included. Phase I/II

trials enrolling different B-cell non-Hodgkin lymphoma (B-NHL) entities were also included if an expansion cohort in patients with WM was planned.

Panel Discussion Points

(1) Should limited duration therapy be prioritized?

The treatment of WM has seen significant advances since the advent of the first-generation BTKi Ibrutinib[5,6], followed by the availability of other irreversible covalent BTKi, including acalabrutinib and zanubrutinib.[15,16] Advantages in tolerability and somewhat improved activity with zanubrutinib were observed in key subsets of patients carrying high genomic risk features such as wildtype MYD88, mutated CXCR4 and/or mutated TP53[12]. While BTKi's are highly efficacious, treatment is given indefinitely as complete remission is seldom achieved. Moreover, abrupt cessation of ongoing BTKi monotherapy for any reason may lead to IgM paraprotein rebound. The panel believes that the next step in advancing WM management is the development of potent, novel-novel combination regimens capable of achieving deep remission, and thus opening the door to the possibility of limited-duration treatments. The panel recognizes the setbacks encountered when one such trial with limited-duration ibrutinib-venetoclax combination, reported at the IWWM-11[17] was prematurely terminated due to cardiotoxicity and in turn led to the suspension of accrual of a cooperative group study, awaiting an amendment, of ibrutinib, venetoclax plus rituximab (NCT04840602). However, other combinations under investigation (**Table 2**) include ibrutinib plus the second-generation BCL2 antagonist, APG-2575 (NCT04260217), and venetoclax plus rituximab (NCT05099471).

(2) What would be the ideal limited-duration combination therapy (novel-novel, or novel-chemo)?

While the addition of novel agents to established chemoimmunotherapy regimens may further improve response rates[18], they do not negate the disadvantages of chemoimmunotherapy including the risk of myelodysplastic syndrome[19] and may lead to severe toxicities due to overlapping toxicity profiles. The panel views novel-novel regimens as the priority for the next generation of trials, noting that studies of chemoimmunotherapy plus BTKi are already ongoing (e.g., bendamustine, rituximab and acalabrutinib, NCT04624906). Sequential use of novel agent-chemoimmunotherapy has not been explored and may improve the depth of response, potentially overcome IgM rebound associated with abrupt withdrawal of BTKi, and open door to finite duration of therapy with novel agents.

(3) Should a standardized chemoimmunotherapy regimen be adopted as the international backbone going forward for phase 3 studies?

While it is desirable for a single chemoimmunotherapy regimen to be standardized for the next generation of international phase 3 studies, the panel recognizes that differences in geography, drug-access and historical experience imply that the choice of a single regimen would not be feasible at this time. Currently, the two most commonly used chemoimmunotherapy regimens are bendamustine-rituximab (Benda-R)[3,20,21] and dexamethasone-rituximab-cyclophosphamide (DRC).[1,22] Both Benda-R and DRC are highly efficacious therapies that can be regarded as standard-of-care and serve as

optimal control regimens for future phase 3 studies. DRC should be given at the published doses for a total of 6 cycles at 3- or 4-week interval. [1,22] For Benda-R, acknowledging existence of retrospective data regarding equivalence of 4 versus 6 courses of therapy, the panel recommends that 6 cycles, for which prospective data are available, should be considered for use in clinical trials, with an allowance for dose reduction to 70mg/m2 in situations of reduced tolerance (advanced age, cytopenias, reduced renal function).[23] Clinical trials should uniformly report the toxicities of special interest that are known to be potentially associated with the investigational and control regimens (e.g., cardiovascular toxicities with BTKi and prolonged cytopenias and risk of myelodysplastic syndrome/ acute myelogenous leukemia with chemoimmunotherapies).

(4) Can genomic (*CXCR4, TP53*) guided studies be standardized across global studies?

It is desirable to stratify patients by *MYD88* and *CXCR4* status as a minimum, for global studies[15,24-26]. The panel recognizes the lack of uniform means to identify *MYD88* and *CXCR4* mutations, leading to unreliable categorization of patients with the use of less sensitive techniques. The panel recommends that highly sensitive standardized testing methods be consistently employed in future clinical trials for accurate genotyping of the subjects and cross-trial comparisons. There is mounting evidence that *TP53* aberrations[27] lead to low response to chemoimmunotherapy in CLL[28] and to novel therapies in WM, albeit to a lesser degree, as reported at the IWWM-11[12]. Therefore,

the panel considers *TP53* assessment and reporting to be a vital part of clinical trials going forward, although there is insufficient knowledge surrounding *TP53* aberrations to permit patient stratification at this time (see also Consensus Panel 3 in this edition of Seminars in Hematology).

(5) Discuss financial and access issues if recommended drugs and tests are not approved or available, and alternatives.

Sponsors performing clinical trials in low health resource settings must provide all investigational agents (including standard of care, where not locally available), and make available central testing of key prognostic and predictive markers. Additionally, sponsor reimbursement of the trial-associated travel costs for subjects living at distance from the cancer center is encouraged. Accurate and validated testing of genomic aberrations are vital for the interpretation of clinical trial outcomes. Acquisition and storage of biosamples from the subjects enrolled in prospective trials, after obtaining appropriate voluntary consent, is also desirable. Trials incorporating cross-over to the experimental arm in case of progression on the control arm are especially important in countries where access to the experimental drug is otherwise unavailable. Additionally, the panel encourages adequate representation of minority populations in future clinical trials in WM that would allow stratification for race or ethnicity in large planned international studies, in accordance with the country-specific regulations.

(6) What should be the comparator arms in frontline and relapsed/refractory clinical trials for WM?

For frontline clinical trials, acceptable chemoimmunotherapy comparator arms include BR[3,19,21] and DRC[1,22]. For BTKi-naïve patients known to carry *MYD88* mutation, acceptable novel agent comparator (control or reference) arms in the frontline and relapsed settings include ibrutinib[5], ibrutinib-rituximab[6] and zanubrutinib[14]. Additionally, repetition of the previously administered fixed-duration chemoimmunotherapy may be considered an acceptable comparator, provided the heterogeneity of the control arm is limited and the duration of the first response exceeds 3 years or the median PFS for the previously used regimen, whichever interval is longer.

(7) Discuss the importance of PFS2 as well as TTNT in evaluating clinical trial outcomes.

In studies where combination vs sequential use of two classes of agents is compared (e.g. chemoimmunotherapy plus BTKi, vs chemoimmunotherapy followed by BTKi), the panel regards PFS2, defined as the time from randomization (or registration in non-randomized trials) to the second disease progression, i.e. progression after first subsequent therapy, or death from any cause, whichever occurs first, as a relevant endpoint reflecting the "total duration of benefit" from both classes of agents. Time-to-next therapy (TTNT) is another important clinical endpoint in WM, both from the physician and patient perspective, that measures the interval from the date of initiation of a treatment to the date of commencement of the next line of therapy, or death from any cause, whichever comes first. Allowing for easy appraisal of the duration of therapeutic benefit, TTNT can potentially overcome some limitations of endpoints such

PFS and duration of response (DOR), and must be routinely included in the secondary trial endpoints as a standalone assessment of the duration of treatment efficacy.

(8) Discuss the appropriateness of VGPR or better as an endpoint in clinical trials

Deep clinical response, i.e. VGPR or better, has been used as a surrogate marker of treatment efficacy in comparative studies[7], but the optimal timing of its assessment and its predictive value for PFS and OS endpoints is incompletely delineated, particularly in the case of continuous BTKi use. Also, a deep response is not always necessary for clinical benefit, which is an important treatment goal especially in the elderly population. The panel proposes an international collaborative study assessing the importance of attaining VGPR and its association with PFS, OS and QoL, both in limited-duration chemoimmunotherapy-based regimens and in continuous BTKi-based regimens. The panel also encourages consistency in the trial clinical endpoints (outlined in CP4 recommendations), trial conduct and its reporting. Trial protocols must address the nuances related to the management of patients with WM, including IgM rebound or IgM flare that could be miscategorized as disease progression.

(9) Define criteria for dose reduction in clinical trials for WM.

The panel feels that dose reduction criteria depend on the agent under study, and as such need to be study specific.

(10) Address the need for trials enrolling unfit patients – how should patient fitness be evaluated?

As WM is predominantly a disease of the elderly, with nearly 25% of patients over the age of 75 at the time of initiation of treatment, there is a clear need for studies examining chemoimmunotherapy-unfit population, as previously evaluated in other B-cell malignancies (e.g., CLL, MCL, multiple myeloma)[29,30]. The panel suggests that frailty scores established in other diseases (e.g. CIRS[31], FIL score[32]) should be studied through international efforts to identify the best instrument (and cut-off) for defining frailty in WM. Special effort should be paid to neuropathy which can accompany older age and WM, and can compound frailty.

(11) What patient-related QOL instruments and quality of toxicity data should be included in clinical trials?

As no WM-specific QOL instrument exists, all standard instruments such as EORTC-QLC30, FACT-LYM and EQ-5D should be evaluated in clinical trials. In studies of patients with IgM-associated polyneuropathy and/or the use of potentially neurotoxic drugs such as proteasome inhibitors, the EORTC QLQ-CIPN20) should be included.

The panel encourages the development of more patient-centric trials that go beyond the conventional methods such as the Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) and its patient-reported outcomes version (PRO-CTCAE) to improve the quality of the toxicity data captured. The use of longitudinal approaches to analyzing toxicities, e.g. the Tox T approach, may provide a more comprehensive

depiction of adverse events that evolve with continuous BTK inhibitor-based therapies. The panel also suggests incorporating data on the supportive care measures used, including their type and timing. Additionally, the panel recognizes the value of improving efficiency of trial logistics and promoting hybrid or decentralized trials aimed at enhancing patient accrual and reducing patient burden through modern technology to remotely monitor, capture data for a rare malignancy such as WM. In addition, the incorporation of patient priorities regarding treatment characteristics should also help guide research priorities.

(11) What risk-adapted trial designs should be considered in WM?

Risk-adapted trial designs seek to target the intensity of treatment to the individual risk of the subject, so that those at low risk can minimize treatment-associated toxicity, and those at high risk can minimize the risk of under-treatment. The panel proposes two main types of risk-adapted trial designs for consideration:

1) Trials driven by the baseline risk (e.g., mutations of *CXCR4, TP53*)

2) Trials driven by the dynamic risk (e.g., failure to achieve VGPR at a specific timepoint triggers the addition of another drug)

Such innovative trial designs are particularly suitable at the level of individual expert institutions and national collaborative groups where nimble trial designs can rapidly yield

promising results to be subsequently confirmed in large, international collaborative trials.

(12) Are there other groups of WM patients with "special needs" that should be studied?

The panel recommends that trials be conducted addressing the following groups of WM with special needs, e.g. NCT05131022 trial evaluating a BTK degrader, NX-5948, permits patients with WM and secondary CNS involvement, NCT05065554 and MAGNAZ studies are evaluating BTK inhibitors in WM associated peripheral neuropathy. As many of these understudied subpopulations with special needs are typically excluded from WM trials, several vital questions regarding their optimal management remain unanswered. These include:

a) Coexisting AL(H) IgM paraprotein related amyloidosis: What is the optimal approach for managing patients with end-organ (especially cardiac) dysfunction?

b) WM-associated neuropathy: What is the relationship between IgM reduction and clinical improvement in neuropathy? Does the rapidity and/or the depth of IgM response matter? Are there specific classes of agents that may be particularly effective in WM-associated neuropathy?

c) Bing-Neel syndrome: What agents combinations of agents) have the best central nervous system penetration?

d) Smouldering WM: What are the risk factors for progression to symptomatic WM? Are there interventions in high-risk patients with smoldering WM that may delay this progression?

e) Transformed WM: Does the addition of novel agents to chemoimmunotherapy improve outcomes? What is the role of novel agents, high-dose consolidation and/or maintenance therapy in these patients?

f) WM related Cold Agglutinin Disease: Do patients benefit more from attacking hemolysis only with the novel complement inhibitors such as sutimlimab or is a clone-direct approach (such as CIT or BTK-i) more beneficial?

Conclusions

CP7 of IWWM-11 considers limited duration of therapy and novel-novel combinations to be the priority for the next generation of clinical trials. Central, validated testing of *MYD88*, *CXCR4* and *TP53* is crucial for trial reporting, and *MYD88* and *CXCR4* should be considered as stratification factors. In the frontline, BR and DRC may be regarded as standard-of-care chemoimmunotherapy for comparative studies. BTKi-based regimens are the standard-of-care comparators for studies in relapsed and/or refractory populations. However, repeat application of limited-duration frontline chemoimmunotherapy in subjects with durable responses are also considered acceptable. Quality of life should be in included as an endpoint for trials. Key unanswered questions include the definition of frailty in WM; the importance of attaining VGPR or deeper in determining survival outcomes; timing and depth of response as a

predictive tool for PFS determination; and the optimal treatment of WM populations with challenging disease related morbidities.

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Author Contributions

CST, MJK, PK, RGS, JSM, and SPT prepared, reviewed and submitted key questions for Consensus Panel 7 (CP7). Questions were reviewed in an open general assembly by attendants of IWWM-11, and additional questions for CP7 deliberations were formulated and submitted. CST wrote the first draft of CPT responses, and draft was reviewed and modified by MJK, PK, RGS, JSM, MA and SPT. Final draft was submitted to CP7 general panel for review and commentary. CP7 general panel was composed of individuals with experience in the care of WM patients who attended IWWM-11 and volunteered to be on CP7 panel.

Disclosures

CST reports research funding from Janssen, AbbVie and Beigene; Honoraria from Janssen, Pharmacyclics, Beigene and AbbVie.

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MJK reports honoraria from Kite, Novartis, and Miltenyi Biotech, Roche, and Bristol Myers Squibb/Celgene; consultancy or advisory role for Kite, Roche, Bristol Myers Squibb/Celgene, Novartis, Adicet Bio and Miltenyi Biotech; research funding from Kite; and travel support from Kite, Roche, Novartis, and Miltenyi Biotech.

SPT received research funding, and/or consulting fees from Abbvie/Pharmacyclics Inc., Janssen Oncology Inc., Beigene Inc., Eli Lilly Pharmaceuticals, and Bristol Myers Squibb.

JSM declares participation on advisory boards and consulting services, on behalf of my Institution, for Abbvie, Amgen, BMS, Celgene, GSK, Haemalogix, Janssen-Cilag, Karyopharm, MSD, Novartis, Pfizer, Takeda, Regeneron, Roche, Sanofi, and SecuraBio.

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QL declares participation on advisory boards and consulting services for Beigene, Xi'an Janssen, Pfizer, Sanofi, AstraZeneca.

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JMIV received institutional honoraria for research support (Beigene, Abbvie/Genmab); Advisory Board/consultancy (Sanofi); Speakers buro (BMS, Sanofi)

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	Table 1: Summary of IWWM-11 Consensus Panel 7 Recommendations for Novel Clinical Trials in WM
1	Limited duration novel-novel combinations and sequential use of novel agent-CIT combinations should be the priority for the next generation of trials.
2	Genetic stratification should be considered for future clinical trials and highly sensitive standardized testing methods should be employed to accurately genotype all trial subjects for baseline *MYD88*, *CXCR4* and *TP53* mutations.
3	Six courses of one of the two commonly used CIT, BR or DRC should be considered standard of care for frontline comparative studies.
4	Continuous ibrutinib, ibrutinib-rituximab and zanubrutinib are acceptable novel agent comparator arms for patients in the frontline setting, and for patients in the relapsed setting who are BTKi-naïve.
5	Trials should uniformly report toxicities of special interest known to be potentially associated with the investigational and control regimens.
6	Minority populations should be adequately represented in future clinical trials.
7	PFS2 is a relevant endpoint in studies where combination vs sequential use of two classes of agents is compared e.g., CIT + BTKi, vs CIT followed by BTKi upon progression.
8	TTNT is an important endpoint of clinical relevance that must be included as a secondary endpoint of trials

9	The value of ≥ VGPR as a surrogate marker for PFS and OS is unclear and requires international collaborative studies for its assessment prior using ≥ VGPR as a primary endpoint.
10	Frailty scores established in other diseases should be validated through international efforts to identify the best instrument for assessment of frailty in WM.
11	Until a WM specific QOL instrument is established, the standard instruments such as EORTC-QLC30, FACT-LYM and EQ-5D should be evaluated in trials.
12	Trials should focus on improving the quality of toxicity data gathered through incorporation of newer methods to comprehensively capture toxicities, including their longitudinal cumulative burden, to enhance understanding.
13	Risk-adapted innovative trial designs driven by the baseline risk, e.g., *CXCR4/TP53* mutations or dynamic risk, e.g., failure to attain ≥ VGPR should be considered.
14	Trials focusing on WM populations with "special needs", e.g., coexisting ALH amyloidosis, WM associated neuropathy, Bing-Neel syndrome, Smouldering WM, transformed WM should be conducted.

Abbreviations: WM: Waldenström Macroglobulinemia; IWWM: International Workshop on Waldenström Macroglobulinemia; CIT: chemoimmunotherapy, *MYD88:* myeloid differentiation primary response 88, *CXCR4:* C-X-C Chemokine receptor 4; *TP53:* tumor protein 53, BR: Bendamustine-rituximab; DRC: dexamethasone, rituximab and cyclophosphamide; BTKi: Bruton's tyrosine kinase inhibitor; PFS2: progression-free survival 2; TTNT: time to next therapy; VGPR very good partial response; PFS: progression-free survival; OS overall survival, QOL: quality of life; EORTC-QLC30: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; FACT-LYM Functional Assessment of Cancer Therapy – Lymphoma; EQ5D EuroQol-5D

Table 2 Overview of recently completed, currently enrolling and planned investigator-initiated trials in WM or IgM MGUS

Name of Study	Study Group	Phase	TN or R/R	Study drug	Type of drug	Enrolment status[1] Planned Accrual[1]
Recently completed studies (not yet published)						
Mavorixafor	DFCI	I/II	TN or R/R	mavorixafor, ibrutinib	CXCR4-antagonist	Enrolled

NCT04274738						N=18
ECWM-2 NCT03620903	ECWM	II	TN	rituximab, bortezomib, ibrutinib	PI, BTK-i	Enrolled N=53
NCT01592981	UCL	II	TN	BCR vs FCR	PI	Enrolled N=60
Currently enrolling studies						
Dara NCT03679624	Weill Cornell, Mayo	II	R/R ibrutinib-naive or ibrutinib plateau	daratumumab, ibrutinib	MoAb, BTK-i	Enrolling N=24
BRAWM NCT04624906	Sunnybrook Canada	II	TN	rituximab, bendamustine, acalabrutinib	BTK-i	Enrolling N=59
R-acalabrutinib NCT05065554	DFCI	II	TN or R/R anti-MAG	rituximab, acalabrutinib	BTK-i	Enrolling N=33
Obinutuzmab-acalabrutinib NCT04883437	Emory	II	TN	obinutuzumab, acalabrutinib	BTK-i	Enrolling n=49
CZAR-1 NCT04263480	ECWM	III	TN and R/R	ibrutinib +/- carfilzomib	BTK-i, PI	Enrolling N=184
ZID NCT04463953	China	II	TN	zanubrutinib, ixazomib, dexamethasone	BTK-i, PI	Enrolling N=55
Rainbow NCT04061512	UK	II/III	R/R	ibrutinib R-ibru vs DRC	BTK-i	Enrolling 60/148
Dasatinib NCT04115059	DFCI	II	R/R, PD on ibrutinib	dasatinib	TKI	N=6
Obinutuzumab	Polish Myeloma	II	R/R	obinutuzumab	MoAb	Enrolling

	Consortium			monotherapy		N=30
PembroWM NCT03630042	UK/UCL	II	R/R	pembrolizumab, rituximab	CPI	Enrolling N=42
Ballondor NCT03697356	South Korea	II	TN	Lenalidomide, Bortezomib, Rituximab, Dexamethasone	MoAb, PI, IMiD,	Enrolling N=54
MAGNAZ	HOVON	II	R/R anti-MAG	zanubrutinib	BTK-i	2023 N=40
CaZa	HOVON	II	R/R CAD	zanubrutinib	BTK-i	2023 N=25
WaZaBi	FILO	II	R/R	zanu + BGB-11417	BTK-I + BCL-2-i	2023 N=102
VIWA-1 NCT05099471	ECWM	II-R	TN	venetoclax, rituximab vs DRC	BCL-2-i	2023 N=80
WM-Epco	HOVON	I/II	R/R WM	Epcoritamab	BsAb	2023 N=26

TN, treatment-naïve; R/R, relapsed/refractory; NCT; national clinical trial; DFCI, Dana Farber Cancer Institute; ECWM, European Consortium Waldenstrom Macroglobulinemia; PI, proteasome inhibitor; BTK-i, Bruton's tyrosine kinase inhibitor; UCL, University Colleges London; BCR, bortezomib, cyclophosphamide, rituximab; FCR, fludarabine, cyclophosphamide, rituximab; dara, daratumumab; R, rituximab; anti-MAG, anti-myelin associated glycoprotein; NHL, non-Hodgkin lymphoma; ZID, zanubrutinib, ixazomib, dexamethasone;

ibru, ibrutinib; PD, progressive disease; TKI, tyrosine kinase inhibitor; MoAb, monoclonal antibody; CPI, checkpoint inhibitor; zanu, zanubrutinib; HOVON, Hematologie-oncologie Volwassenen Nederland; CAD, cold agglutinin disease; FILO, French Innovative Leukemia Organization; BCL2-i, BCL-2 inhibitor; II-R, phase II

randomized clinical trial; DRC, dexamethasone, rituximab, cyclophosphamide; epco, epcoritamab; BsAb, bispecific antibody.

[1]Enrollment or planned accrual based on last posted updates on clinical trials.gov and may not be current or accurate.

Table 3: Recently completed and currently enrolled industry-sponsored clinical trials in WM

Name of Study	Sponsor	Phase	TN or R/R	Study drug	Type of drug	Status
Recently completed studies (not yet published)						
LOXO-305 NCT03740529	Eli Lilly	I/II	R/R B-NHL	Pirtobrutinib	BTK-i non-covalent	Enrolled N=860
Currently enrolling studies						
MAPLE-1 NCT04260217	Ascentage Pharma	Ib/II	TN or R/R B-NHL	APG-2575 +/- rituximab or acalabrutinib	BCL-2-i	Enrolling N=123
CLOVER-1 NCT02952508	Cellectar Biosciences	II	R/R B-NHL	lopofoscine I^{131}	RIC	Enrolling N=120
Loncastuximab NCT05190705	Sobi Pharmaceuticals	II	R/R	loncastuximab tesirine	ADC	Enrolling N=36
NX-5948 NCT05131022	Nurix	Ia/Ib	R/R B-NHL	NX-5948	BTK-degrader	Enrolling N=130
NX-2127 NCT04830137	Nurix	Ia/Ib	R/R B-NHL	NX-2127	BTK-degrader	Enrolling N=160
XMab-13676 NCT02924402	Xencor	Ia/Ib	R/R B-NHL	plamotomab	BsAb	Enrolling N=270
PSB-202 NCT05003141	Sound Biologics	Ia/Ib	R/R B-NHL	PSB-202 CD20 and CD37 Ab	MoAb	Enrolling N=110
ZUMA-25 NCT05537766	Kite/Gilead	II	R/R B-NHL	brexucabtagene ciloleucel	CD19 CAR T	Enrolling N=170
MB-106 NCT05360238	Mustang Biotech	I/II	R/R B-NHL	MB-106 CD20 CAR T-cells	CD20 CAR T	Enrolling N=287

NCT04775745	Newave Pharmaceuticals	1	RR	LP-168	Small molecule inhibitor	Enrolling N=60

TN, treatment-naïve; R/R, relapsed/refractory; B-NHL, B-cell non-Hodgkin lymphoma; BTK-i, Bruton's tyrosine kinase inhibitor; BCL-2-i, B-cell lymphoma 2 inhibitor; RIC, radio-immunoconjugate; ADC, antibody drug conjugate; BsAb, bispecific antibody; Ab, antibody; MoAb, monoclonal antibody; CAR T, chimeric antigen receptor T-cell

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