Novel Monoclonal Antibodies in B-Cell Non-Hodgkin Lymphoma Treatment

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NMABs represent a heterogeneous group of agents, including naked antibodies, immunotoxins, and T-cell-engaging molecules. Several NMABs have either gained regulatory approval or are on the verge of introduction into clinical practice, addressing multiple therapeutic indications and treatment regimens. Their anticipated impact is expected to be broad, initially in the context of relapsed/refractory (R/R) disease and subsequently extending to early treatment lines.

B-cell non-Hodgkin lymphoma | novel monoclonal antibodies | novel immunotherapies

1. Introduction

The anti-CD20 monoclonal antibody (MAB) rituximab initiated the era of cancer immunochemotherapy more than two decades ago, changing the therapeutic approach for B-cell non-Hodgkin lymphomas (B-NHLs). Since then, response rates and long-term disease-free survival have improved significantly across all B-cell lymphoma subtypes. However, a subset of patients (pts) with recurrent or relapsed (R/R) disease have proven more challenging to treat, showing lower responses to salvage therapies [1].

Novel monoclonal antibodies (NMABs) are a heterogeneous group of anticancer agents, as they include naked antibodies, immunotoxins, and T-cell-engaging molecules [2][3][4][5][6][7][8][9][10]. These innovative therapies are expected to have a broad impact on the treatment of various malignancies, particularly B-NHL. These agents have already found or will soon find applications spanning from treating relapsed disease to becoming first-line treatments, whether used as single agents or in combination with other anticancer drugs or biological agents.

Several NMABs have recently been approved or are about to be introduced into clinical practice for different therapeutic indications and in different treatment schedules. These include the antibody–drug conjugates polatuzumab vedotin (PV) [2][4], loncastuximab tesirine (lonca) [6][7], the anti-CD19 naked antibody tafasitamab [5], and the bispecific antibodis (bsAbs) mosunetuzumab, glofitamab and epcoritamab [2][8][9][10]. Other bsAb, such as odronextamab has achieved promising milestones, showing durable responses in R/R settings, including some pts who had previously experienced disease progression after CAR-T cell therapy [10].

2. The Phylogenic Tree: From Murine Models to Novel Immunotherapies

Therapeutic MABs are a group of molecules targeting one or more specific antigens. These molecules display high heterogeneity in terms of protein sequence, structure, and antigen binding affinity.

Murine antibodies were the first generation of therapeutic MABs ever developed. However, due to their lack of human structural components, they were soon found to trigger a human anti-mouse response (HAMA), resulting in a marked reduction in their efficacy. To overcome these problems, genetic engineering approaches were developed with the production of antibodies structurally closer to humans, known as chimeric MABs [11][12][13].

Rituximab, a chimeric anti-CD20 antibody, was the first member of this class to be introduced into clinical practice, improving B-NHL prognosis. The success of rituximab spurred the development of novel antibodies driven by the dual objective of reducing immunogenicity and enhancing therapeutic effectiveness. As a result, new generations of anti-CD20 antibodies emerged, further increasing the number of treatment options available. The second generation of anti-CD20 MABs comprised fully humanized IgG1 antibodies, while the third generation consisted of both humanized and engineered MABs [13][14][15].

To improve MAB efficacy, immunotoxins were developed, giving rise to a new class of compounds known as antibody–drug conjugates (ADCs), which include MABs connected through a covalent linker to a small cytotoxic payload consisting of chemotherapeutic drugs, bacterial agents, plant protein toxins (defined as immunotoxins), or radiopharmaceutical agents. Once attached to the corresponding cancer-cell-surface antigen, the ADC is internalized, releasing the cytotoxic payload, ultimately leading to cell cycle arrest and apoptosis.

Among ADCs, radiopharmaceutical drugs that combine radioisotopes with anti-CD20 antibodies to enhance tumor cell killing, an approach referred to as radioimmunotherapy (RIT), have seen relatively limited use despite their robust clinical effectiveness, mostly due to the inherent complexity associated with their delivery and management. The most widely employed radioimmunoconjugate was 90Y-ibritumomab tiuxetan, which was employed in both the US and Europe for the treatment of R/R follicular lymphoma (FL) with promising results.

New RIT options are currently undergoing evaluation. Among them, 177Lu-lilotomab satetraxetan, an RIT designed to target a less commonly targeted antigen, CD37, has been investigated in preclinical models, showing remarkable efficacy in clinical trials (LYMRIT-37-01; NCT01796171), making it a potentially attractive agent [16].

Bispecific antibodies (bsAbs) are antibodies, or parts of them, that can bind two different antigens (Ags), simultaneously engaging both tumor and immune effector T cells.

In the past, initial attempts were made to demonstrate that Abs capable of binding to two different domains could be combined, leading to enhanced activities. However, it was only through the improvement in their chemical structures that researchers succeeded in making them suitable for clinical investigation.

Currently, there are two distinct antibody formats available: single-chain fragment variable (scFv)-based Abs, which lack a fragment crystallizable (Fc) region and are often referred to as “non-IgG-like” bsAbs, and full-length IgG molecules, known as “IgG-like” bsAbs. Several non-IgG-like bsAbs are being tested in human trials with different formats, such as bispecific T- or killer-cell engagers (BiTEs or BiKEs), dual-affinity re-targeting antibodies (DARTs), and tandem diabodies (TandAbs). In contrast, most IgG-like bsAbs are in use or about to be utilized for the treatment of B-NHL (e.g., mosunetuzumab, odronextamab, and epcoritamab) [17].

The field of bsAbs is highly dynamic and rapidly expanding, with over one hundred bsAbs currently being tested, extending their applications even beyond cancer treatment. Nevertheless, the most significant advances have taken place in a B-NHL setting, where they have emerged as viable treatment options, both as standalone therapies and in combination with other agents.

Relevant NMABs in clinical development are represented in **Figure 1**.

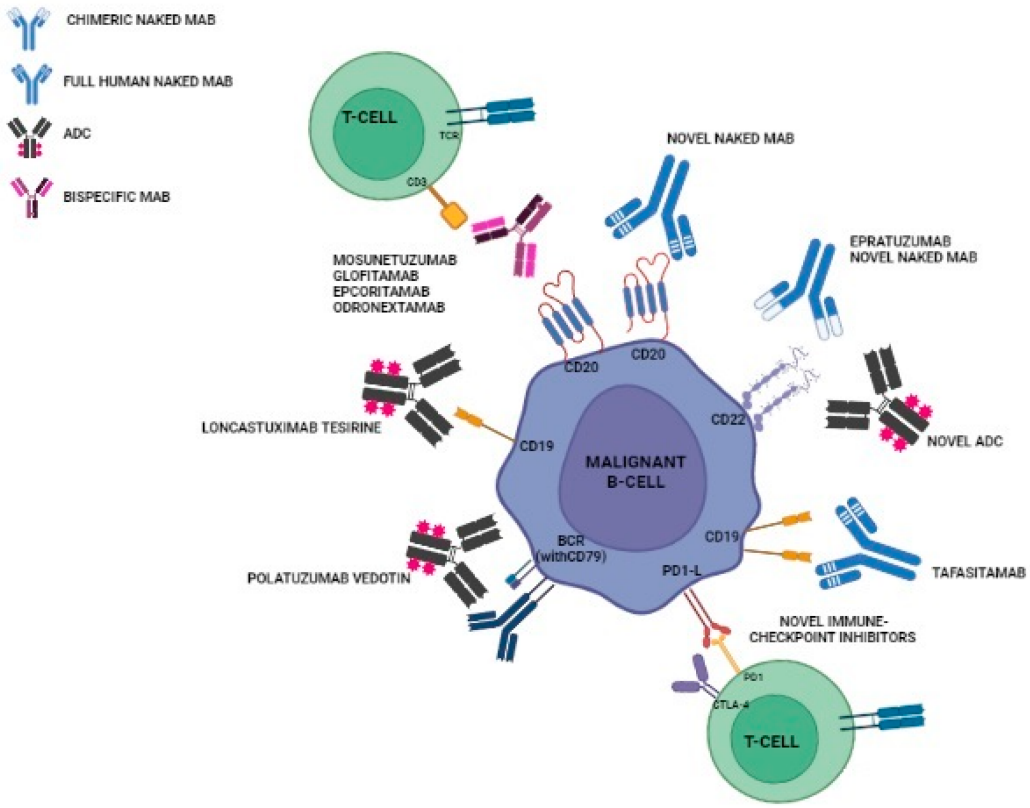

Figure 1. Relevant NMABs in clinical development.

3. Relevant Novel MABs in Clinical Practice

3.1. Naked Antibodies

Rituximab has revolutionized the treatment course of CD20-positive B-NHL. Even though it remains the most administered MAB in the management of CD20-positive lymphomas, several NMABs have been developed to

improve its effectiveness or overcome rituximab-refractory conditions [18][19][20][21]. These approaches involve the use of chemically modified anti-CD20 MABs or the investigation of alternative target antigens.

New generations of anti-CD20, either humanized or fully human, have been developed. Ofatumumab, a second-generation anti-CD20 MAB, has been approved for the treatment of R/R CLL, but the efficacy of ofatumumab in B-NHL pts has been far from convincing [14]. Third-generation anti-CD20 MABs are a group of fully humanized and engineered antibodies, which include obinutuzumab, ocaratuzumab, and PRO1319216. Among them, only obinutuzumab (GA101) has so far been approved by the FDA and European Medicine Agency (EMA) for the treatment of CLL and FL.

Although anti-CD20 still remains one of the most important targets in B-NHL therapy, the search for novel targets has led to the development of several attractive NMABs. Among them, the most established one is the anti-CD19 antibody tafasitamab, which obtained accelerated approval from the FDA and EMA in 2020.

Tafasitamab

The receptor for CD19 is an important functional regulator of normal and malignant B-cell proliferation and is expressed on all B-cell precursors. Notably, CD19 expression persists upon the downregulation of CD20 after rituximab exposure. Tafasitamab is the first-in-class, humanized monoclonal antibody engineered with an Fc region targeting CD19. Indeed, the engineering of FcγRIIa has led to not only enhanced binding to the stimulatory FcγRIIIa region but also reduced binding to inhibitory receptors, resulting in more potent ADCC [3].

Given its immunomodulatory properties, lenalidomide (LEN) emerged as the ideal companion for tafasitamab. This combination was evaluated in 80 R/R DLBCL pts ineligible for autologous stem cell transplantation (ASCT) [5]. The treatment regimen consisted of intravenous (IV) tafasitamab (12 mg/kg) and oral LEN (25 mg/day) administered for up to 12 cycles, each lasting 28 days. Subsequently, pts with stable disease or better continued with tafasitamab monotherapy until progressive disease (PD). With a median follow-up (mFU) of 13 months, all 80 pts achieved an objective response, resulting in an objective response rate (ORR) of 61%, including a complete response rate (CRR) of 43% and a 12-month progression-free survival (PFS) of 50% (95% CI: 38–61). Encouragingly, responses were seen across various risk categories, including cell of origin subtype and refractory status. The toxicity profile remained acceptable, with the most common adverse event being neutropenia (all grades), G1–2 diarrhea, and rash (32% and 27%, respectively) [5].

However, various real-world experiences were conducted with discordant results. The RE-MIND trial (NCT04150328) evaluated pts treated with tafasitamab + LEN monotherapy, confirming significantly better outcomes of this combination in ASCT-ineligible R/R DLBCL pts [22]. In contrast, a retrospective analysis of 82 R/R DLBCL cases treated with tafasitamab reported lower ORR, CRR, PFS, and OS compared to what was observed in the L-MIND trial. The authors attributed these differences to a greater incidence of high-risk conditions, increased rates of comorbidities, treatment delays, and dose reductions among real-world pts. Notably, pts with relapsed disease, low–moderate IPI scores (0–3), and fewer prior lines of therapy (LOT) (0–2) showed better

outcomes, suggesting that individuals with lower-risk characteristics are the most suitable candidates for tafasitamab treatment [23].

3.2. ADCs

ADCs are sophisticated molecules composed of an antibody linked to a cytotoxic drug. ADCs combine the targeting precision of MABs with the potent cancer-killing capabilities of drugs, allowing them to discern between healthy and diseased tissues [24].

In recent years, three ADCs, namely, brentuximab vedotin (BV) [25][26], PV [4], and lonca [6][7], have received approval from both the FDA and EMA, consolidating their role in the lymphoma treatment landscape. It is worth pointing out that BV, despite being the most established ADC, is primarily indicated for HL and T-cell NHL, limiting its use to these specific diseases. In addition, ongoing development efforts in this field are yielding several novel ADC molecules [27][28].

3.2.1. Polatuzumab Vedotin

CD79b is an essential component of the B-cell receptor (BCR) signaling pathway expressed on normal B cells and lymphomas [29]. PV is the first-in-class, humanized anti-CD79b monoclonal antibody linked to the cytotoxic drug monomethyl auristatin E (MMAE). In addition to MMAE-mediated cell death, PV can induce target cell death via antibody-mediated opsonization and antibody-dependent cell cytotoxicity [30].

PV was initially approved in combination with BR (bendamustine/rituximab) for R/R DLBCL pts after two or more lines of treatment who were ineligible for ASCT [4]. Approval was based on the results of a small, randomized phase Ib/II trial comparing PV in combination with BR vs. BR alone. This study enrolled 80 R/R DLBCL pts—40 in each arm (PV-BR vs. BR)—and showed improved rates of complete metabolic response (CMR), PFS, and OS in the experimental arm compared to the standard BR regimen. ORR and CR were 45% vs. 17.5% and 40% vs. 17.5%, respectively. The median OS was 12.4 vs. 4.7 months (p = 0.002). No substantial difference was reported across risk groups, albeit higher-grade (G > 3) toxicity, particularly neutropenia, was more prevalent in the PV-BR arm. Nevertheless, there was no excessive occurrence of infection-related adverse events (AEs) [4].

While PV is approved for use in combination with bendamustine, some major considerations need to be raised. Bendamustine has a long wash-out time of at least 12 weeks, which may be problematic for patients who are scheduled for CAR-T therapy. However, PV may serve as a bridge to CAR-T treatment. To address this issue, researchers have explored the potential benefits of PV in combination with other immunotherapies in various studies. Specifically, in the phase II, randomized ROMULUS trial, pts were randomly assigned (1:1) to receive either R-PV or R-pinatuzumab (375 mg/m^2 rituximab plus 2.4 mg/kg ADCs) every 21 days until PD or unacceptable toxicity for up to 1 year. The trial enrolled 81 pts with DLBCL and 42 with FL. The results showed an ORR of 26% in R-pinatuzumab-treated pts vs. 54% in the R-PV arm. Among the 21 FL pts who received R-pinatuzumab, 62% achieved ORR, while R-PV-treated pts obtained a 70% ORR. An overall benefit–risk favoring R-PV was also reported. Considering these results, PV was selected by the study funder for further development in B-NHL [28].

3.2.2. Loncastuximab Tesirine

Lonca (ADCT-402) is an ADC combining a humanized anti-CD19 MAB CD19 with a pyrrolobenzodiazepine (PBD) dimer cytotoxin [31]. PBD molecules are sequence-selective, non-distorting, and potent cytotoxic DNA crosslinking agents that lock DNA strands, disrupting all DNA metabolic processes [6]. Preclinically, lonca has shown highly targeted antitumor effects, with DNA-PBD crosslinks persisting for up to 36 h [31].

More recently, the FDA and EMA have granted accelerated approval to lonca for the treatment of pts with R/R DLBCL after two or more prior LOT. Indications include DLBCL not otherwise specified (NOS), DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma. This approval was based on data from studies that included pts with adverse prognostic factors.

In a large phase I study involving 183 highly pretreated R/R B-NHL pts, lonca monotherapy was administered in 21-day cycles until either PD or unacceptable toxicity occurred. These pts achieved an ORR and CR rate of 45.6% and 27%, respectively. When categorized through histology, the ORR was 42% for pts with DLBCL (137 evaluable), 47% for pts with MCL (15 evaluable), and a remarkable 79% among pts with FL (14 evaluable). The median DOR for all pts was 5.4 months (95% CI: 4.0 months to not reached). In particular, it was 4.5 months (95% CI: 4–10 months) in DLBCL pts and “not reached” in MCL or FL pts. The most frequently reported AEs were hematologic alongside fatigue [6].

3.3. Bispecific Antibodies

Bispecific antibodies (bsAbs) are specifically designed to target molecules present on both tumor and T cells, triggering T-cell activation and immune-mediated cytotoxicity [32]. Importantly, all bsAb effects occur in an MHC-independent fashion, thus bypassing the restrictions imposed via MHC-T-cell receptor interaction. This feature is critically important as many B-NHLs, particularly DLBCL, frequently harbor genetic aberrations that result in the loss of MHC class I molecule expression [33].

BsAbs target a variety of cell-surface antigens, and they come in different formats. The FDA and EMA paved the way for bsAb R&D in 2014 with the approval of the first-in-class bsAb, blinatumomab, indicated for B-cell acute lymphoblastic leukemia (ALL), mainly due to its high efficacy in R/R ALL pts. However, when applied as a salvage strategy in B-cell lymphomas, blinatumomab only showed modest efficacy and limited feasibility, precluding further investigation in B-NHL trials. However, full-length bsAbs exhibited pharmacokinetic properties akin to those of MABs and endogenous IgG. This similarity allowed extending the dosing intervals, a key factor driving their development in the R/R B-NHL setting.

Within this group, anti-CD20xCD3 bsAbs have shown remarkable single-agent activity in heavily pretreated B-NHL pts while maintaining a manageable toxicity profile. CD20xCD3 bsAbs possess one or more CD20-binding sites, each targeting tumors with distinct avidity and antigen-binding capacity [33].

3.3.1. Mosunetuzumab

Mosunetuzumab (M) is a fully humanized bispecific IgG1 antibody recognizing CD20 on tumor cells and CD3 on T cells. What sets M apart is its modified Fc fragment, lacking both FcγR and the complement binding site while retaining a single CD20 binding site. M has recently received approval from both the FDA and EMA for its use in B-NHL as a result of its impressive effectiveness.

The clinical potential of M monotherapy in pts with B-NHL R/R—both aggressive and indolent forms, aNHL and iNHL, respectively—was initially assessed in a phase I/Ib study. The dosing regimen of M involved a stepwise escalation on days 1, 8, and 15 of cycle 1, followed by a fixed dose on day 1 of each subsequent cycle, with a maximum of 17 cycles, depending on tumor response. A total of 230 heavily pretreated pts were enrolled. Of them, 129 (77%) had aggressive NHL, including DLBCL, tfFL, and MCL, whereas 68 (23%) had indolent NHL, consisting of marginal zone lymphoma, FL, and SLL. Of note, 18% of these pts had received previous CAR T-cell therapy.

An updated analysis with a median follow-up of 28.3 months showed durable responses in pts achieving CR at the end of treatment (EOT). A high proportion of pts remained event-free at the two-year mark. In exploratory analyses, a similar DOR benefit was observed, regardless of whether pts achieved an early or late CR [34].

Its well-known immunomodulatory characteristics make LEN an attractive candidate for combination with bsAbs. In an ongoing phase Ib study, a preliminary analysis is underway to assess the safety and efficacy of M plus LEN in R/R FL pts who had previously received at least one LOT. At the DOC date, 27 heavily treated pts were enrolled, showing a remarkable OOR of 92% and an acceptable safety profile [35]. These promising preliminary findings have provided the basis for the initiation of a randomized phase III study comparing the efficacy of the M plus LEN combination with the standard of care, rituximab plus LEN (R2) (NCT04712097). The primary endpoint for this study is PFS.

3.3.2. Glofitamab

Glofitamab is another fully humanized IgG1-like bsAb with a unique 2:1 structure. Even though, similar to M, its Fc structure lacks FcγR and the complement binding site, glofitamab features two CD20-binding domains—derived from type II CD20 IgG1 glycoengineered obinutuzumab— which improves its affinity for CD20-positive tumor cells. In a preclinical study, glofitamab has recently shown its superior potency compared to that of M [36]. Glofitamab has recently received approval from both the FDA and EMA for its use in B-NHL.

In a phase I/Ib trial, glofitamab was used as a single agent for the treatment of R/R B-NHL. The trial consisted of giving anti-CD20 obinutuzumab before initiating glofitamab treatment to prevent CRS by both binding to surface lymphomatous CD20 and depleting peripheral B cells. Glofitamab was administered IV with an escalated dosing schedule, either every 14 or 21 days, for up to 12 cycles. This study evaluated 171 pts, including both aggressive and indolent NHL (grades 1–3A FL), with a median age of 64 (22–85) years. These pts had undergone a median of 3 (1–13) prior LOT, with 91% of them displaying refractory disease. A promising clinical activity was observed across all doses. Among pts with aggressive B-NHL, ORR and CR were 48.0% and 33%, respectively—41% and 29% in pts with DLBCL and 55% and 35% in pts with transformed FL. In the FL cohort, 71% of pts achieved an ORR with a CR rate of 48% [9]. The median DOR reached 10.8 months (95% CI: 3.8 months—NE) accompanied

by a median PFS of 11.8 months (95% CI: 6.3–24.2 months). AEs were reported in 98% of pts. The most common AE was CRS, occurring in 86 of 171 (50.3%) pts (G3 or 4: 3.5%). The incidence of CRS increased with dose but significantly declined after the first administration. Symptoms of ICANS were uncommon and resolved in all cases. G ≥ 3 neutropenia occurred in 25% of pts. Infections and febrile neutropenia manifested in 52% and 3% of pts, respectively [9]. Additional long-term analysis confirmed the induction of high CR rates thanks to the fixed-duration monotherapy offered to heavily pretreated MCL pts, most of whom had prior BTKi therapy. CRS events were manageable and mostly low-grade [37].

3.3.3. Epcoritamab

Epcoritamab (GEN3013), a full-length human IgG1 bsAb recognizing CD3 and CD20, was generated through controlled Fab-arm exchange and further developed for SC administration [38]. To optimize its use, several mutations were introduced to silence the Fc domain.

Phase 1 of the EPCORE NHL-1 study, which enrolled R/R B-NHL pts, adopted a dose-escalation approach. Specifically, patients received SC epcoritamab according to a step-up protocol, which included predefined priming doses given over a 2-week period, followed by full doses ranging from 0.0128 mg to 60 mg, depending on the specific cohort. This strategy aimed to mitigate the severity of CRS. Epcoritamab was administered in 28-day cycles until PD or unacceptable toxicity. The primary endpoint of phase 1 (dose-escalation part) was to determine the maximum tolerated dose (MTD) to be used in the following phase 2 of the study.

As of the DOC date, the primary reason for discontinuing the study was PD, accounting for 46 (68%) out of 68 pts. Among the most frequently reported TAETs, pyrexia was prevalent in 47 (69%) pts, which was primarily associated with CRS in 40 (59%) of these subjects, while injection site reactions were documented in 32 (47%) pts. No cases of febrile neutropenia nor dose-limiting toxicities were reported [39].

3.3.4. Odronextamab

In the NHL R/R setting, odronextamab (REGN1979) stands out as a first-in-class, fully human IgG4-based CD20/CD3 bsAb, characterized by a hinge-stabilized structure. Its evaluation took place in a phase I study, conducted across multiple centers, featuring both dose-escalation and dose-expansion approaches, known as the ELM-1 trial. In this study, odronextamab was administered according to a step-up dosing regimen over three weeks, followed by a fixed weekly dose regimen until week 12. Successively, maintenance dosing was implemented. This study enrolled 145 heavily pretreated pts, with 94 participating in the dose-escalation phase and 51 in the dose-expansion phase. The median age of the enrolled pts was 67 years, and 42 (29%) pts had previously undergone CAR T-cell therapy. Furthermore, 119 (82%) pts had developed resistance to their most recent LOT. At the DOC date, in FL pts receiving 5 mg doses, the cumulative ORR was 51% (ORR = 91%; CR = 72%), whereas all DLBCL pts receiving >80 mg doses achieved CR, with an ORR of 53%. In CAR-T-cell-treated DLBCL, the ORR was 33%, with 27% of pts displaying CR [40]. The most common G ≥ 3 AEs were anemia (36 [25%]), lymphopenia (28 [19%]), hypophosphatasemia (27 [19%]), neutropenia (27 [19%]), and thrombocytopenia (20 [14%]). Serious AEs occurred in 89 (61%) out of 145 pts, with the most frequent events being CRS (41 [28%]),

pyrexia (11 [8%]), pneumonia (9 [6%]), and infusion-related reaction (6 [4%]). Four deaths were recorded and considered related to odronextamab, with causes including gastric perforation, lung infection, pneumonia, and tumor lysis syndrome. G 3 neurologic AEs were noted in three (2.3%) pts, but only one of these events required treatment discontinuation. There were no G 4 or higher neurologic AEs [40].

4. Novel Promising Agents in Clinical Development

Recent advances in protein engineering and manufacturing technologies have spurred the development of more effective and practical NMABs. While several novel naked MABs are under investigation, the results of these studies are still in the early stages, and future research will be required to fully understand their potential [41].

In this exciting backdrop, the discovery of novel cellular pathways has ignited renewed interest in the field of cancer therapy. One promising target appears to be ROR1, a receptor tyrosine kinase expressed on the surface of malignant B cells and in some solid tumors, such as carcinoma, sarcoma, and melanoma. NVG-111 is the first humanized bsAb under evaluation that has shown preliminary tumor-cell-killing activity in vitro [42]. Currently, an ongoing phase 1/2 study in R/R CLL and MCL pts is evaluating an escalating dose schedule given via continuous infusion over 21 days followed by a 7-day period during which pts are kept off the drug. As of July 2022, 10 subjects, with a median age of 60 years, had been enrolled in the study. ORR was observed in 66% of subjects and included two CRs. AEs were predominantly limited to week 1 of C1 and were all reversible.

One of the most potent anticancer mechanisms involves the action of immune cells.

Furthermore, there is evidence that bsAb therapy can increase immune checkpoint expression, which is considered a significant escape mechanism in this type of therapy. To overcome these inadequate T-cell responses, bsAbs may be combined with checkpoint inhibitors, chemotherapy, costimulatory molecules, or oncolytic viruses [43].

5. Conclusions

The monoclonal antibody revolution, which started with rituximab in the 1990s but is only now fully realizing its potential, together with the development of cellular therapies employing chimeric antigen receptor constructs, is fundamentally reshaping the therapeutic paradigm for these neoplasms. Several of these non-chemotherapeutic agents can elicit profound and prolonged remissions, potentially leading to cures when used as single agents, even in highly pretreated pts—an opportunity that would have been unthinkable until recently. Moreover, the prospect of developing countless rational combinations among biologics—including small molecules, which may not be curative on their own in most settings but might offer substantial synergistic potential—stands as one of the most attractive fields of investigation across various NHL subtypes. These hold promise for effective and well-tolerated approaches in nearly all clinical settings [44].

However, several questions remain about the optimal sequencing and usage of NMABs throughout the treatment process, particularly in the context of CAR T-cell therapies. In this regard, it is important to highlight that NMABs offer the advantage of swift administration as off-the-shelf treatment, which would not be possible with CAR T cells.

In addition, older patients with R/R B-NHL or comorbidities may not be suitable candidates for CAR T-cell therapy. Nevertheless, many uncertainties persist regarding the application of these agents. Indeed, it is only through extensive integration into routine clinical practice that the oncology community will be able to develop a learning curve, fostering wider adoption of these drugs. Concerns also extend to the adequacy of T-cell collection, which can influence the effectiveness of bsAbs, and the potential for increased infection risk associated with the Abs.

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