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Article

Safety and Efficacy of Mosunetuzumab: Experience in the A.O. Card G. Panico

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Abstract

Follicular lymphoma (FL) is the second most common form of non-Hodgkin's lymphoma (NHL) and accounts for about 5% of all hematological malignancies. Despite therapeutic advances, FL follicular lymphoma remains an incurable disease, with frequent relapses and increasingly shorter disease control intervals. Bispecific antibodies (*bsAbs*) are molecules that target two different epitopes or antigens. The mechanism of action is determined by the molecular targets and structure of the *bsAbs*. Several *bsAbs* have already changed the therapeutic landscape of hematological malignancies and some solid tumors. In particular, in this article we review the general principles on follicular lymphoma and established and innovative therapies including *bsAbs*, in particular the *bsAb* mosunetuzumab, a new bispecific antibody that acts on CD3 epitopes of T lymphocytes and CD20 epitopes of B lymphocytes with the aim of inducing T lymphocyte-mediated elimination of malignant B lymphocytes, its safety and efficacy with the analysis of no. 3 patients who completed treatment with the drug mosunetuzumab in the A.O. Pia Fondazione di Culto e Religione 'Card. G. Panico', Tricase (Lecce).

Keywords: bispecific antibodies; mosunetuzumab; follicular lymphoma; refractory relapsed follicular lymphoma; Chemo-Immunotherapy

1. Introduction

Follicular lymphoma (FL) is an indolent lymphoid neoplasm, derived from germinal center B-cells, for which recent therapeutic advances have substantially improved patient survival [1].

However, FL remains an incurable and heterogeneous disease, with groups of patients presenting with early disease, histological transformation or a high risk of treatment-related toxicity [1], in particular first- and second-line chemo-immunotherapies, such as bendamustine plus rituximab (BR), bendamustine plus obinutuzumab (BO), the combination of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) or cyclophosphamide, vincristine and prednisone with obinutuzumab or rituximab.

Although not as widely used as chemo-immunotherapy, autologous stem cell transplantation (SCT) or allogeneic transplantation are also a viable treatment option with potential benefit in patients with early failure of chemo-immunotherapy treatment [2].

Furthermore, FL is a continuously relapsing disease and response rates, and disease control intervals decrease with each subsequent line of therapy [1].

The current therapeutic landscape for relapsed or refractory FL and promising therapies in development offer physicians a wide range of options for the treatment of relapsed or refractory FL [1].

Efficacy is an important parameter for treatment success; however, in the real world, several patient-specific factors, including treatment burden, are taken into account when deciding on the most appropriate treatment strategy [1].

Adequate access to new treatments can be a problem for patients with FL.

Advances in the development of CAR-T cell therapy provide new therapeutic options for patients with FL R/R; however, several barriers limit access to this therapy. Patients may not be eligible for CAR-T cell therapy, and the cost of CAR-T cell therapy often makes it an unlikely option outside of clinical trials [1].

Considering logistical barriers, eligibility and methods of administration, more available, affordable and well-tolerated treatment options can be chosen.

BsAbs, in particular mosunetuzumab, are readily available off-the shelf (ready-to-use) agents with a growing track record in administering and mitigating reactions to infusion [1].

2. Follicular Lymphoma

Follicular lymphoma (FL) is the second most common subtype of non-Hodgkin's lymphoma.

FL is a heterogeneous clinic-pathological entity that has as a common feature the origin from germinal center B-cells [3].

The molecular pathogenesis of FL is a complex, multi-step process during which a single follicular B-cell acquires all the genetic and epigenetic alterations necessary for malignant transformation.

The tumor consists of a variable number of small, cleaved cells (centrocytes) and larger, blastoid cells (Centro blasts) that morphologically resemble the cells found in the light and dark areas of normal germinal centers, respectively [4].

Some common steps in this pathway have been elucidated, in particular chromosomal rearrangements involving BCL-2 and some somatic mutations, some of which are also found in other non-Hodgkin lymphomas. In the uncommon case where FL evolves into a more aggressive lymphoma, usually diffuse large B-cell lymphoma, the molecular lesions found early in the disease course persist and are found together with newly acquired mutations that contribute to histological transformation [5].

Most FL tumors in adults depend on overexpression of BCL-2, an oncogene located on chromosome band 18q21 and responsible for B-cell leukemia/lymphoma. BCL-2 is an oncogene that inhibits apoptosis, the process of programmed cell death. Its overexpression results in increased cell survival. However, overexpression of BCL-2 by itself is not sufficient for FL development and other genetic alterations or host factors are required (**Figure 1**) [5].

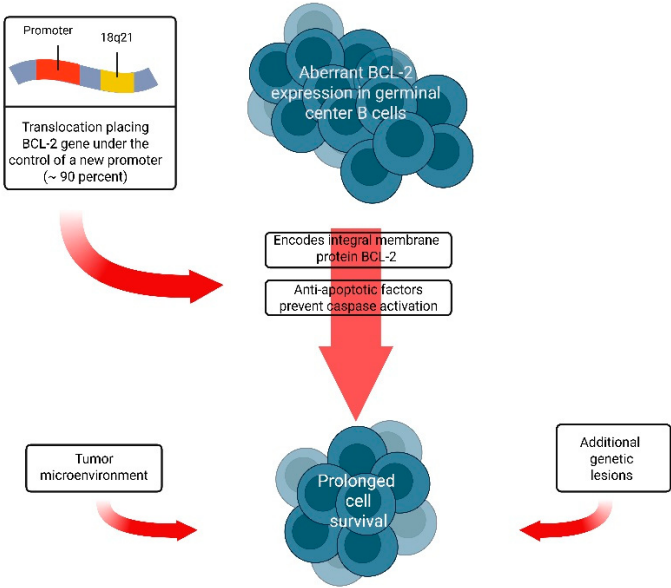


Figure 1. The molecular pathogenesis of follicular lymphoma (FL) is a complex process that leads to the replication of a malignant B-cell clone of germinal origin. While some steps in this process have been elucidated, many remain unknown. Most FL tumors have translocations or mutations that result in increased expression of the *BCL-2* gene, known to be involved in the tumor transformation process. Approximately 85% of cases have a translocation between the long arm of chromosome 18 and the immunoglobulin heavy chain gene on chromosome 14, resulting in *t*(14;18) (*q*32; *q*21). *BCL-2* is an anti-apoptotic factor that prevents the activation of caspases, resulting in prolonged cell survival. Overexpression of *BCL-2* is not sufficient to cause FL and other factors, such as the tumor microenvironment and other genetic lesions, probably contribute to the pathogenesis [5].

Since overexpression of *BCL-2* is not sufficient for FL development, other genetic lesions or host factors must be required [6,7].

Deep sequencing of FL lymphoma genomes and studies of the FL lymphoma microenvironment have led to the identification of mechanisms beyond *BCL-2* overexpression that are involved in the development of lymphomas [5].

The tumor microenvironment, in particular the immunological microenvironment consisting of T-cells and dendritic cells, can influence the development and progression of FL [8,9].

The role of the microenvironment is supported by gene expression profiling and immunophenotypic studies that have correlated patient survival with the types of immune cells that mingle with the lymphoma, rather than with the gene expression program of the lymphoma itself [10,11].

Communication between tumor cells and the microenvironment appears to be bidirectional and probably involves chemokines, chemokine receptors and adhesion molecules, the balance of which determines the stimulation or inhibition of tumor cell growth [12,13].

2.1. Clinical Manifestations and Pathological Features of Follicular Lymphoma

FL is one of the most common forms of non-Hodgkin’s lymphoma (NHL). FL occurs in all races and in all geographical areas. The worldwide incidence of FL is not known exactly, as epidemiological data in some countries are limited by a lack of resources to ascertain cases and for accurate diagnosis. Consequently, most epidemiological data come from retrospective analyses of patients treated at major centers in the United States and Europe [14].

Adults–Most patients with FL present with painless peripheral adenopathy in the cervical, axillary, inguinal and/or femoral regions [15,16].

Despite the presence of diffuse disease at diagnosis, most patients are asymptomatic and lymph node enlargement is the only noticeable abnormality. Only about 20% are present with B symptoms (i.e., fever, night sweats or involuntary weight loss) [17].

Involvement of organs other than lymphatics or bone marrow is uncommon [18,19].

Central nervous system involvement is rare, but peripheral nerve compression and epidural tumor masses causing cord compression may occur. Other patients present with disease localized to the small intestine, most commonly to the second portion of the duodenum, often identified as an incidental finding during an endoscopy performed for other reasons [20].

Children—Rarely, FL occurs in children or adolescents aged 8 to 11 years [21,22].

Unlike normal reactive follicles, FL nodules are typically tightly packed and vary in size and shape.

Neoplastic follicles may be present throughout the tumor tissue or only in a part of it, with a diffuse component occupying the rest of the tumor [15].

Bone marrow involvement is common and manifests itself mainly in the form of para-trabecular lymphoid aggregates [23].

Low-level peripheral blood involvement is often detected by flow cytometry, but overt blood involvement is unusual [24].

Morphologically, these circulating cells usually present indentations or slits and correspond to centrocytes.

Cytoplasmic BCL2 protein staining is strongly positive in almost all grade 1/2 tumors, in contrast to normal hyperplastic germinal center B cells, which are BCL2 negative. However, a high fraction of cutaneous FL, infantile FL and grade 3B FL is BCL2 negative [25,26].

2.2. Diagnosis

The diagnosis of FL is preferably made by excisional biopsy of tissue, most commonly a lymph node. Histological examination is essential, while immunophenotypic and molecular genetic studies can confirm the diagnosis.

Most patients present with systemic FL. The World Health Organization's 2016 Classification of Tumors of Hematopoietic and Lymphoid Tissues recognize four additional clinical variants of FL: Follicular Lymphoma, Intrafollicular Neoplasm/Follicular Neoplasm 'in situ', Follicular Lymphoma of the Duodenal Type, Predominantly Disseminated Follicular Lymphoma with IRF4 rearrangement [14].

Follicular lymphoma—The diagnosis of systemic FL is made on the basis of the histological examination of a lymph node biopsy, usually in a patient with a history of increasing and decreasing lymphadenopathy [15].

Typically, the tumor shows a distinctly nodular growth pattern and consists of a mixture of centrocytes and Centro blasts.

Mitosis and apoptotic cells, which are common in reactive follicles, are hardly visible.

The diagnosis can also be made by fine-needle aspiration of the involved lymph nodes, but this procedure does not allow the growth pattern to be assessed and classification is problematic. In this case, immunophenotypic analysis (generally performed by flow cytometry) plays a central role in establishing the diagnosis [14].

Follicular neoplasm in situ—Follicular neoplasm in situ (FCI) [27], also known as B-cell neoplasm in situ, is a pathological diagnosis used to describe the identification of follicles, usually numerous, that have a high B-cell content expressing high levels of BCL2 within a lymph node that otherwise lacks the diagnostic features of FL [15,27].

In some patients with this diagnosis, disseminated FL is found upon further assessment; in these cases, the intra-follicular component presumably represents early seeding of FL in a partially involved lymph node. Most patients, however, show no signs of FL at further evaluation [28,29].

Duodenal type FL—Duodenal type FL is recognized as a tumor confined to the intestine (usually the duodenum) and typically presents as multiple small polyps [30].

This is a rare entity [31,32]. Duodenal type FL is typically confined to the mucosa, shows at least a partial follicular growth pattern and has cytological features of grade 1 or 2 [31].

2.3. Prognosis

The course of FL is variable. In some patients, the disease may persist intermittently for five years or more without treatment [33]. Other patients, with more disseminated disease and more rapid tumor growth, require treatment because massive lymph node or organ enlargement causes pain, lymphatic obstruction or organ dysfunction [34].

At the time of diagnosis, initial work suggests that the presence of particular pathogenic mutations acquired in FL has prognostic value, but further studies are needed to support the incorporation of FL genome sequencing into routine care [14].

Tumor grade–The International Consensus Classification (ICC) classifies FL on a scale of 1 to 3 [27], while the World Health Organization Classification, compresses FL into two grades, classical follicular lymphoma (comprising grades 1 to 3a in the ICC) and follicular large B-cell lymphoma (grade 3b in the ICC) [27]. Grade appears to have some prognostic value, particularly grade 3b, which is believed to have a more aggressive course than the other FL grades [35,36].

2.4. Treatment of FL in Stage I-IV

Pre-treatment assessment–The pre-treatment assessment allows the extent and aggressiveness of the disease to be determined and provides information on the individual's health status and comorbidities that may affect treatment options.

In addition to the history and physical examination, the preliminary assessment of FL patients includes the following elements: review of the pathological evaluation to confirm the appropriateness of the histological specimen, laboratory tests [37,38], basic imaging which can be performed by computed tomography (CT) with diagnostic quality contrast medium or positron emission tomography combined with computed tomography (FDG PET/CT) and fluorodeoxyglucose [39,40]. The speed at which treatment should be initiated varies depending on the individual patient's condition and available treatment options.

Initial treatment–The approach to patients with FL depends on the histological grade and location of the disease.

Stage I FL: grades 1, 2 or 3a: treatment with radiotherapy (RT) with curative intent is preferred, provided that all involved sites can be contained in a radiation field with minimal toxicity. If RT is not feasible, initial observation is preferred [37,38].

Stage I FL: grade 3b: Treatment with regimens used for other clinically aggressive lymphomas, such as diffuse large B-cell lymphoma, is preferred [37,38].

Stage II: grade 1, 2 or 3a: treatment similar to that used for stage III or IV FL is preferred. Other physicians offer radiotherapy to a subgroup of these patients [37,38].

Only about 15-30% of FL patients have stage I or II disease [41,42].

Initial management–At the time of diagnosis, the vast majority of patients with FL present with stage II (11 to 16%), stage III (22 to 33%) or stage IV (26 to 40%) [43,44].

The approach to patients with stage III or stage IV FL depends on the histological grade, the presence of symptoms or organ dysfunction, and the rhythm of the disease [37,38].

Single-agent rituximab–Single-agent rituximab is an alternative to the 'watch and wait' strategy for patients with asymptomatic, stable, stage II, III or IV FL who want immediate treatment.

One of the administration schedules used in randomized trials in this context is as follows [45,46]: Weekly Rituximab for a total of four doses (days 1, 8 and 22) or weekly Rituximab for four weeks, followed by dosing every two months for two years [46].

Immunotherapy-based treatment–immunotherapy with an anti-CD20 monoclonal antibody (e.g., rituximab, obinutuzumab) is a key component of the treatment of patients with symptomatic FL [47,48].

Experts differ in their preferred strategy and may choose different approaches depending on the patient's preferences. The three main options, listed in order of increasing intensity, are: rituximab administered as a single agent for a defined cycle, rituximab plus chemotherapy administered for six to eight cycles, Immunotherapy (rituximab or obinutuzumab) plus chemotherapy, administered for six to eight cycles, followed by two years of single agent immunotherapy as maintenance.

Typically, rituximab plus chemotherapy is administered rather than single-agent rituximab because indirect comparisons suggest that this approach produces a more rapid and profound response. The single-agent rituximab is an acceptable alternative for patients with comorbid conditions that make them poor candidates for chemotherapy and for those with a low tumor burden and/or disease that progresses slowly over years [37,38].

Chemo-immunotherapy—In prospective studies, many chemotherapy regimens have been combined with rituximab or obinutuzumab.

In general, the BR regimen (bendamustine plus rituximab) is preferred as it has fewer side effects and recent studies suggest similar efficacy compared to R-CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone plus rituximab) [37,38].

R-CVP (cyclophosphamide, vincristine and prednisone plus rituximab) is an alternative but is expected to result in a lower response rate.

Obinutuzumab is used in combination with bendamustine, CHOP and CVP, followed by maintenance obinutuzumab. In one study, this strategy improved PFS, but was associated with increased toxicity and costs [49].

Fludarabine-based regimens are no longer recommended and are not used due to high toxicity in this population [50,51].

Although combinations of lenalidomide plus rituximab and lenalidomide plus obinutuzumab are emerging as treatment options for patients with FL, they are generally reserved for patients with relapsed or refractory FL [37,38].

2.5. Treatment of Relapsed or Refractory Follicular Lymphoma

Evaluation of suspected relapses or resistance—A biopsy is performed prior to treatment with a low threshold in order to confirm relapse and assess histological transformation. Imaging with a combined positron emission tomography/computed tomography (PET/CT) scan provides a new baseline of disease activity, allowing information to be obtained on anatomical areas of involvement and their metabolic activity. The biopsy must be performed on a lymph node with the highest PET activity. Biopsy is crucial to identify patients with histological transformation, as treatment and prognosis differ from those with relapsed FL [52].

Indications for treatment—Patients with asymptomatic recurrent FL do not necessarily need immediate treatment but should be closely monitored for signs of symptomatic disease. In general, the same indications for treatment used for first-line therapy also apply in case of disease recurrence or progression [52].

Treatment goals and therapy selection—Most patients who relapse more than 24 months after initial chemo-immunotherapy or more than 12 months after administration of rituximab as a single agent require intermittent treatment for decades and survival rates similar to those of the general population [53,54]. Although not curative, modern therapies lead to complete or partial remissions in series. Treatment focuses on alleviating symptoms, reversing cytopenia and improving quality of life.

For most patients with late relapses, treatment with an anti-CD20 monoclonal antibody (rituximab or obinutuzumab), alone or in combination with lenalidomide, rather than immunological chemotherapy is suggested.

Chemotherapy combined with immunotherapy is an acceptable alternative involving more intensive therapy administered for a limited duration followed by a period without treatment [52].

Since patients with FL present relapses in series, many of them will be treated with several of these options and other therapies during the course of the disease. No preferential order for their use

has been established. At each relapse, the choice between these options must consider the response to previous therapies, comorbidities that may affect suitability for current and future therapies, the impact of current treatment decisions on future therapies, and patient preferences. For example, treatments that alter T-cell function may have an impact on therapies that rely on the patient's own T-cells (such as chimeric antigen receptor T-cell therapy and bispecific antibodies) [52].

Lenalidomide plus anti-CD20 antibody—For most patients, the preferred regimens for the treatment of late relapse are lenalidomide plus anti-CD20 antibody, rituximab (R2) and obinutuzumab (O-R). These regimens appear to have similar efficacy to chemotherapy combined with immunotherapy but have different toxicity [55].

Single-acting anti-CD20 antibody—Single-acting rituximab and obinutuzumab are acceptable alternatives for patients with relapsed FL who have comorbid conditions that make them poor candidates for combination therapy and for those with a low tumor burden and/or disease that progresses slowly over years. These drugs have a low toxicity profile, good response rates and have been shown to delay disease progression in these populations. However, long-term follow-up is limited, and it is not known whether OS has improved [52].

Chemo-immunotherapy—Some experts may offer chemo-immunotherapy at first relapse, especially in settings where access to lenalidomide is limited.

For the majority of patients with relapsed or refractory FL treated with chemotherapy, the use of obinutuzumab rather than rituximab is suggested. This preference demonstrated an OS benefit for bendamustine plus obinutuzumab over single-agent bendamustine in the relapsed setting [56,57].

When using chemoimmunotherapy for relapsed FL, the selection of the regimen is mainly based on the patient's exposure to previous chemotherapy, expected toxicities and the physician's experience with the specific regimen [52].

The combination of BO or BR may be preferred for the patient who has previously received therapy that included CVP or CHOP. According to some experts, retreatment with a bendamustine-based regimen is reasonable for those who have had a long duration of initial remission with BR (e.g., five years) [58].

CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) plus obinutuzumab (O-CHOP) or rituximab (R-CHOP) may be preferred for a patient with late recurrence who has previously received bendamustine [59,60].

Early treatment failure—With conventional chemotherapy regimens, about 20% of patients with early treatment failure experience frequent relapses and substantially reduced survival [53,54].

For most patients with FL and early treatment failure, lenalidomide plus obinutuzumab is suggested rather than chemo-immunotherapy; compared to the latter, lenalidomide plus rituximab has similar efficacy and a different toxicity profile [52].

For patients who can benefit from cell therapy, there is the option of consolidating treatment with CAR-T cell therapy, if available, with the aim of achieving long-term remission. Autologous HCT is an alternative but more toxic option for patients who achieve complete remission (CR) [52].

Cell therapy and bispecific antibodies—Mosunetuzumab and epcoritamab are bispecific monoclonal antibodies directed against both CD20 of FL and CD3 of cytotoxic T cells. If available, these agents are considered an option for patients with multiple relapsed FL with a short duration of previous remission (e.g., <24 months). Both can be used instead of or after CAR-T therapy. Although initial studies have shown high response rates, they have not been directly compared with other therapies or with each other, and longer follow-up is needed to better understand efficacy and toxicity. The choice between these drugs is largely driven by the toxicity profile, availability and administrative considerations.

Mosunetuzumab is approved by the FDA and the European Medicines Agency for adults with relapsed or refractory FL who have received at least two prior systemic therapies [61,62]. The drug is administered intravenously. After an initial stepwise dosing schedule, the drug is administered once every 21 days. Patients who achieve a complete response (CR) receive 8 cycles in total, while those with a partial response (PR) or stable disease receive up to 17 cycles. The prescribing information

contains warnings regarding CRS (cytokine release syndrome), severe infection, tumor flare, tumor lysis syndrome and the need to avoid live and/or live-attenuated vaccines [61,62].

Epcoritamab is an FDA-approved for adults with relapsed or refractory FL who have received at least two prior systemic therapies [63]. Epcoritamab is administered subcutaneously. After an initial stepwise dosing schedule, the drug is administered once every 28 days until disease progression or unacceptable toxicity. The prescribing information contains warnings about CRS and immune effector cell-associated neurotoxicity syndrome (ICANS). There are also warnings and precautions for severe infections and cytopenias [63].

Data on the efficacy and safety of these agents in FL come from phase 2, multicenter and single-arm studies.

CAR-T cell therapy is an option for patients with multiple relapsed FL. The use of CAR-T therapy is individualized according to the disease course, availability of other therapies and expected toxicity. Since most patients with relapsed FL have favorable outcomes with other less toxic treatment options, CAR-T therapy is usually reserved for patients with multiple relapsed FL with a short duration of remission (e.g., less than 24 months). Although initial studies suggest that CAR-T therapy is effective against relapsed or refractory FL, the quality of evidence is low, the treatment is associated with significant toxicity, and the manufacturing process is complex and expensive [52].

Transplantation—High-dose chemotherapy with autologous HCT (hematological salvage) has been offered to eligible patients who achieve CR after treatment of multiple relapsed disease and to patients who achieve CR after treatment of early treatment failure. Both high-dose chemotherapy with autologous HCT (hematological salvage) and non-myeloablative or reduced-intensity allogeneic HCT are used for the treatment of FL [52].

Both autologous HCT and allogeneic HCT appear to have a positive impact on the survival of patients with relapsed FL [64].

3. Bispecific Antibodies: Focus on Mosunetuzumab

The Bispecific antibodies (*bsAbs*) are engineered molecules designed to target two different epitopes or antigens. The mechanism of action is determined by the molecular targets and the structure (or format) of the *bsAbs*, which can be manipulated to create variable and novel functionalities, including binding between immune cells and cancer cells or blocking the dual signaling pathway. Several *bsAbs* have already changed the therapeutic landscape of hematological malignancies and some solid tumors.

However, the mechanisms of resistance to these agents are poorly studied and the management of toxicities remains challenging.

Unlike other forms of immunotherapy and targeted therapies, *bsAbs* can target multiple antigens [65].

However, the clinical application of this class of agents presents challenges and toxicities, such as cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), infusion-related reactions (IRRs) and opportunistic infections [66,67].

The structure and biological function of bivalent antibodies inspired the design of *bsAbs* [68,69] (Figure 2).

Engineered antibody production methods have made it possible to generate *bsAbs* formats with different structures, composition and pharmacological properties. With *bsAbs*, there is no single format that can be considered universally optimal, given the need and opportunity to customize individual *bsAbs* for various clinical contexts and specific therapeutic goals [70].

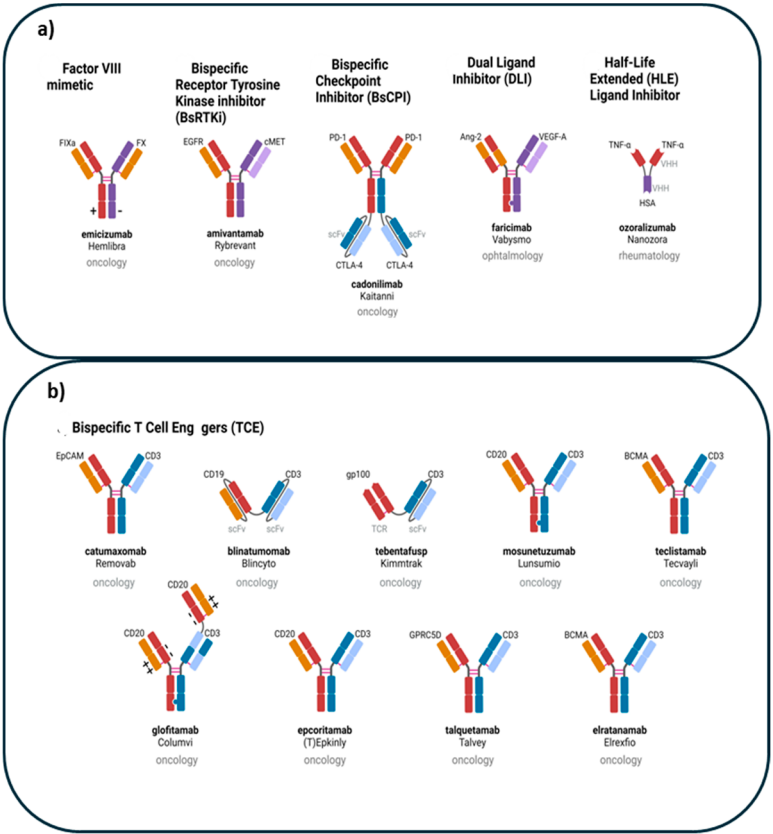


Figure 2. Molecular structure of novel engineered antibodies:.

(a) mimetic of factor VIII, inhibition of dual signaling, bispecific receptor tyrosine kinase (*RTK*) inhibitor (*BsRTI*), bispecific checkpoint inhibitor (*BsCPI*), double ligand inhibitor (*DLI*), extended half-life ligand inhibitor (*HLE*)

(b) T cell engager (*TCE*). Imagine modified from [65].

The *bsAbs* are classified into two categories: IgG-like (with Fc regions) and non-IgG-like (without Fc regions). IgG-like *bsAbs* offer greater solubility, stability, purification and half-life, avoiding antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity through genetic modification [71].

Non-IgG-like *bsAbs* have better tissue penetration and faster renal clearance, but a shorter plasma half-life. Non-IgG-like *bsAbs*, produced using Fab fragments or linking variable domains, include *bsAbs* based on scFv (single-chain variable fragments), nanobodies and dock-and-lock (DNL) antibodies [72].

Single-chain variable fragments (scFv) retain specificity and antigen-binding capacity. ScFv-based *bsAbs* offer excellent tissue permeability and reduced immunogenicity but have a short half-life [65].

Mechanisms of action of bispecific antibodies–The biological targets of *bsAbs* dictate their mechanisms of action and therapeutic effect, and *bsAbs* can be classified accordingly (**Figure 3A, B, C**): Immune cell engagers: bispecific T cell engagers (TCEs) are designed to link endogenous CD4+ and CD8+ T cells with tumor cells by simultaneously binding to the CD3 epsilon subunit of T cell receptor (TCR) complexes and selected tumor-associated antigen (TAA) [73,74]. This interaction activates T cells, some of which are cytotoxic or demonstrate pro-inflammatory activity that facilitates tumor cell killing [75], Modulation of the immune checkpoint: dual ICP-blocking *bsAbs* bind an inhibitory ICP receptor (e.g., PD-1, CTLA-4, LAG-3 or TIGIT) on the T-cell surface with one arm, while the other arm binds another ICP receptor on the T-cell, tumor cell or antigen-presenting cell. [76], Blocking signaling pathways: *BsAbs* can block two distinct antigens or several regions of a single

antigen in signaling pathways. The dual targeting of driver signaling pathways may increase the efficacy of *bsAbs* treatment [77] and reduce the occurrence of resistance [78].

There are several ways in which *bsAbs* can affect two pathways.

The main mechanism of action is to block receptor-ligand interactions, thereby inhibiting downstream signaling cascades.

Secondly, *bsAbs* can induce receptor internalization, thus preventing receptor cross-linking (homodimerization and/or heterodimerization), resulting in downstream effects such as suppression of angiogenesis and inhibition of cell proliferation [79].

Third, IgG-based *bsAbs* carrying the Fc structure can promote ADCP (antibody-dependent cellular phagocytosis) and ADCC (antibody-dependent cellular cytotoxicity) by further inducing apoptosis [80].

BsAbs can address emerging resistance to tyrosine kinase inhibitors (TKIs). This may occur through TKI-induced up-regulation of alternative pathways, such as the activation of the mesenchymal-epithelial transition (MET) pathway observed in EGFR-mutated NSCLC [81].

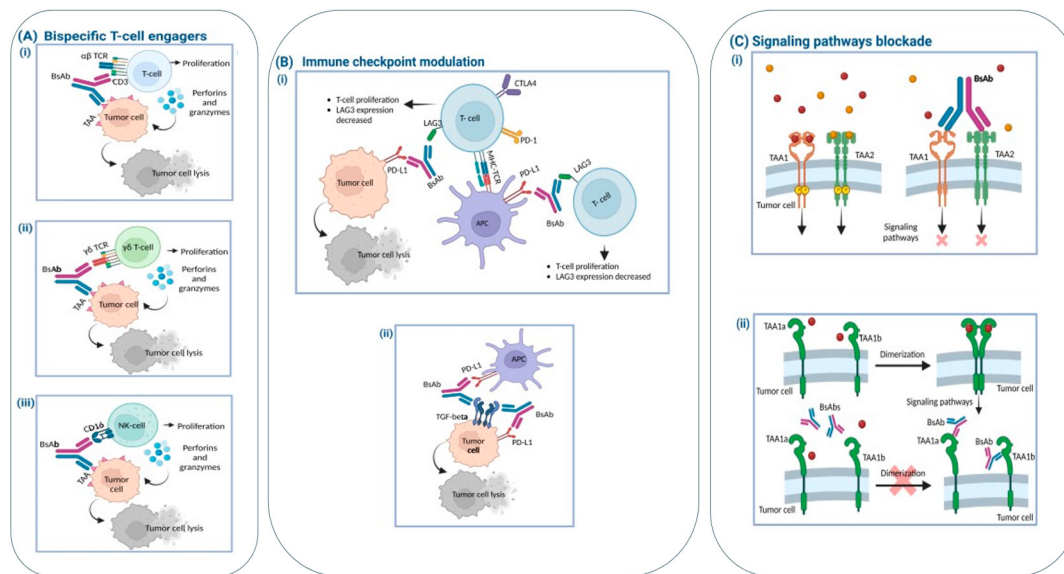


Figure 3. Mechanisms of action of bispecific antibodies (*bsAbs*):.

(A) Bispecific T-cell engagers.

(i) *bsAb* binds the CD3 subunit of the T-cell receptor (TCR) and the selected tumor-associated antigen (TAA) to facilitate the formation of a synapse between the two cell types; the synapse activates the T-cells, which can release perforins and granzymes to lyse the tumor cells.

(ii) Bispecific $\gamma\delta$ T cell engagers simultaneously bind $V\gamma 9V\delta 2$ receptors and a specific TAA to activate T cells, release perforins and granzymes and lyse tumor cells.

(iii) Bispecific natural killer (NK) cell engagers simultaneously bind CD16 receptors and a specific TAA to activate NK cells, release perforins and granzymes and lyse tumor cells.

(B) Modulation of the immune checkpoint (ICP).

(i) Immune checkpoint-blocking *bsAb* simultaneously bind lymphocyte activation gene 3 (LAG3) on the T-cell surface and programmed death ligand 1 (PD-L1) on tumor or antigen-presenting cells, amplifying T-cell activation, which release perforins and granzymes and lyse tumor cells, reducing LAG3 expression.

(ii) *BsAb* affects the ICP simultaneously with a molecule involved in other signaling pathways.

(C) Blocking the signal pathway.

(i) *BsAb* simultaneously bind the epidermal growth factor receptor (*EGFR*) and *cMET*, blocking ligand-induced phosphorylation, promoting inhibition of downstream signaling cascades and stimulating receptor degradation.

(ii) Biparatopic *bsAb* binds two separate epitopes on the same target.

Abbreviations: *APC*, antigen-presenting cell; *CD*, differentiation cluster; *CTLA4*, cytotoxic T lymphocyte antigen 4; *MHC*, major histocompatibility complex; *PD-1*, programmed death 1 [65].
Imagine modified from [65].

Limitations and toxicities of bispecific antibodies—Cytokine release syndrome: CRS results from excessive and rapid activation of immune cells leading to hypersecretion of circulating pro-inflammatory cytokines such as interleukin (IL)-6, interferon-gamma (IFN- γ) and TNF- α [82,83]. The severity of CRS can vary from mild and transient to life-threatening with refractory hypotension, capillary leak syndrome and multi-organ dysfunction. While CRS of any grade is common and expected with *bsAb* treatment (particularly those targeting CD3, given its mechanism of action), severe CRS (G $\geq$ 3) is uncommon [65]. The onset of *bsAb*-associated CRS generally occurs within 48 hours of the first dose [84] and subsides with subsequent treatments. The fact that cytokine induction and IL-6 release were commonly associated with the first administration suggests that strategies such as gradual dosing or fractionation of the first dose would contribute to optimal immune system ‘priming’ with gradual activation rather than the early and uncontrolled inflammatory response expected with a fixed-dose regimen [85].

Immune effector cell-associated neurotoxicity syndrome: ICANS (Immune effector cell-associated neurotoxicity syndrome) is a severe neurological toxicity of immunotherapies, including *bsAb*. Although it often co-occurs with CRS, it is considered a separate syndrome with distinct onset time and pathophysiology [86].

ICANS results from the hyperactivation of immune effector cells, including T cells redirected by *bsAb*. This leads to the release of cyto/chemokines that result in endothelial cell activation, disruption of the blood-brain barrier (BBB-brain barrier) and damage to neuronal cells by neurotoxins [87].

Infusion-related reactions: IRRs (infusion-related reactions) typically occur between 10 minutes and 4 hours after the start of administration but may appear up to 24 hours later [88].

The severity of symptoms may vary from mild to moderate to fatal [89,90].

IRRs are referred to as ‘type B, bizarre’ adverse drug reactions. These reactions are unpredictable, dose-independent and unrelated to the pharmacology of the molecule. IRRs can be divided into allergic and non-allergic reactions, although the exact mechanism remains incompletely defined [89,91].

Opportunistic infections: The use of *bsAbs* may be associated with opportunistic infections [66], particularly in the context of hematological malignancies. Infections associated with *bsAbs* may present variably, e.g., as respiratory or lineage-related infections. Gram-negative bacterial infections are common, but fungal (e.g., *Aspergillus* spp.) and viral (e.g., cytomegalovirus) infections also occur [92].

Mosunetuzumab—Mosunetuzumab, a pioneering *BsAb* CD20 $\times$ CD3, targets CD20 on B cells and CD3 on T cells, with a full-length humanized IgG1 structure [93], **Figure 4**.

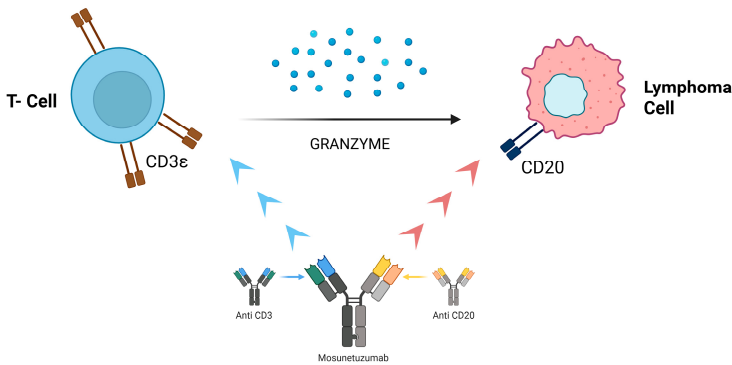


Figure 4. Mosunetuzumab binds simultaneously to CD3ε, a component of the *T-lymphocyte receptor (TCR)* complex, and CD20, a *B-cell* surface protein expressed in most B-cell malignancies. Image modified from [94].

Mosunetuzumab utilizes a native antibody structure that allows concomitant monovalent binding to the target epitopes CD3ε (on T cells) and CD20 (on B cells) [93–95].

Mosunetuzumab is administered intravenously (EV) in 21-day cycles, with cycle 1 consisting of a stepwise dosage: 1 mg on day 1 of cycle 1, 2 mg on day 8 of cycle 1, 60 mg on day 15 of cycle 1, 60 mg on day 1 of cycle 2, 30 mg on day 1 of cycle 3 and thereafter.

Treatment is stopped after cycle 8 for patients with complete response (CR), while patients with partial response (PR) or stable disease (SD) continue treatment for up to 17 cycles (**Figure 5**) [96]. The approval of mosunetuzumab was based on the results of an international, multicenter, phase 2 study of 90 patients with FL RR (relapsed refractory follicular lymphoma) after at least two previous lines of systemic therapy [97].

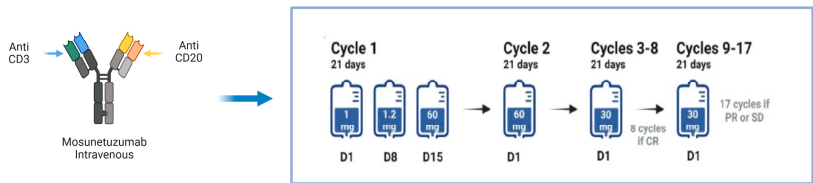


Figure 5. Mosunetuzumab doses and schedule of administration. Image modified from [97].

4. Experience in the “A.O. Card G. Panico”: Patient Cases

Follicular lymphoma (FL) is the second most common form of non-Hodgkin’s lymphoma (NHL) and accounts for about 5% of all hematological malignancies [98].

In Western countries, the age-standardized incidence rate is 2-4 cases of FL per 100,000 people per year, with an estimated 13,960 new cases diagnosed in the United States in 2016 and approximately 2,220 and 2,500 new cases diagnosed per year in the United Kingdom and France, respectively [98].

Developments in the treatment of FL in the new millennium, primarily the introduction of anti-CD20 therapies, have led to substantial improvements in survival [99,100].

Despite therapeutic advances, FL lymphoma remains an incurable disease, with continuing patterns of relapse and increasingly shorter disease control intervals with each line of treatment. Although most patients have an indolent disease and remain asymptomatic for decades, and many

die with lymphoma rather than from it, some patients have an aggressive clinical course, and lymphoma remains the most common cause of death [100].

The clinical heterogeneity of *FL* represents a challenge for physicians, who must consider age, comorbidities, likelihood of relapse and accessibility to treatment in order to decide on the most appropriate therapeutic strategy at any given time.

First-line therapy for *FL* is well defined, and most patients achieve a sustained response to chemo-immunotherapy for many years [101,102].

Patients with localized *FL* can also be treated with radiotherapy alone or in combination with chemo-immunotherapy [103,104].

Radiotherapy alone may be an appropriate treatment for localized and relapsed *FL*. However, in general, the prognosis in patients with *R/R FL*, particularly those who have received 2 prior therapies, remains poor [105].

Patients with multiple relapses require new treatment to address the poor response to previous lines of treatment [106].

When deciding between treatment options for advanced *FL R/R*, physicians must weigh the risks and benefits of the available options for each specific patient, considering age, comorbidities, previous lines of therapy and disease burden, as well as the availability of treatments according to the region and patient preferences. With increasing evidence of new treatment options, the treatment landscape for *FL R/R* is constantly evolving.

Therapies approved in recent years as second- and third-line treatment strategies involve various drugs, including rituximab, which may also be useful after standard first-line treatments such as bendamustine plus rituximab, particularly in those who achieve a partial response [107].

Autologous stem cell transplantation (SCT) is a viable treatment option with potential benefit in patients with early failure of chemo-immunotherapy treatment [108].

For patients with relapsed or refractory *FL* who have received at least two previous systemic therapies, so-called bispecific *BsAbs* antibodies are commercially available.

BsAbs involving *T* cells are designed to simultaneously bind antigens on the surface of tumor cells and *CD3* on *T* cells, thus directing *T* cells to engage and eliminate tumor cells [109].

Mosunetuzumab targeting *CD3* and *CD20*, is approved for patients with *FL R/R* who have received ≥ 2 previous lines of treatment [110].

In the A.O. *Pia Fondazione di Culto e Religione 'Card. G. Panico' in Tricase*, in the province of Lecce, bispecific antibody therapies have been in use for three years.

In particular, *bsAb* mosunetuzumab, first launched as compassionate use programmed in May 2022 approved at Local Ethical Committee of I.R.C.C.S., Oncology Hospital, Giovanni Paolo II Bari (CEL), and still in use today as a *reimbursable* drug authorized by AIFA, was approved for the treatment of eight patients in the A.O. *Pia Fondazione di Culto e Religione 'Card. G. Panico' in Tricase*, in the province of Lecce.

4.1. Patient Cases

Patients with relapsed or refractory *FL* treated with the drug mosunetuzumab, from 2022 to date in the A.O. *Pia Fondazione di Culto e Religione "Card. G. Panico"*, Tricase (Lecce), are number of patients= 8.

6 patients have completed treatment with mosunetuzumab, 1 patient is being treated with mosunetuzumab, and 1 patient has changed treatment.

Below is the clinical history of 3 patients who completed treatment with mosunetuzumab.

4.1.1. Patient 1

Patient 75 years old, ex-smoker, normo-phagic, denies allergic diathesis.

Medical history: hypertension being treated with anti-hypertensive medication, benign prostatic hypertrophy, COPD (chronic obstructive pulmonary disease), in 2004 diagnosis of B-cell non-Hodgkin's lymphoma (subdiaphragmatic lymph adenomegaly) stage IIa for which he had R CHOP

(rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) for 6 cycles in another site, PORT type CVC wearer since 28/10/2023 (catheter with central venous access), in 2023 diagnosis of peripheral B-cell lymphoma Centro follicular type, stage IIA, bulky abdomen, FLIPI 2 2, GELF score 2 (follicular lymphoma international prognostic index).

On 21/09/23 PET CT (Positron Emission Tomography) performs with hyperaccumulation of the radiotracer at the known tissue with development in the sn obturator iliac region. In addition, another area of hyperaccumulation is observed projecting close to the sigma wall.

The patient also performs histological examination of abdominal lymph node with histopathological findings compatible with peripheral B-cell lymphoma of the Centro follicular type.

Patient informed about the diagnosis and prognosis of the pathology, also informed about the need for chemo-immunotherapy treatment according to the R-BENDA scheme (bendamustine, rituximab); this therapy involves the infusion of the drugs for 2 consecutive days every 28 days, for a maximum of 6 cycles.

After an appropriate interview in which the possible benefits and both short- and long-term side effects of the proposed treatment were explained, on 13/10/2023 the patient signed informed consent to the treatment and received a copy of it.

The patient is undergoing therapy R-BENDA (rituximab and bendamustine) from 30/10/23 to 26/03/2024, for 2 consecutive days every 28 days, for a maximum of 6 cycles, without any particular complications, good general condition, no symptoms, no neurological disorders, regular feeding, no respiratory symptoms, treatable abdomen not painful on palpation, no declivous oedemas, cleansed oral cavity.

On 30/04/24 PET scan (Positron Emission Tomography) performs with persistence of hyperaccumulation of the radiotracer at the known tissue located in the left iliac-obturator region, diffuse hyperactivity in the parietal thickenings of the colon.

On 31/05/2024, after further clinical examinations, the patient was nominated for treatment with bispecific *BsAb* antibody mosunetuzumab, as he was refractory to two previous lines: R CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) and R-BENDA (rituximab and bendamustine).

The patient is informed of the diagnosis and prognosis of the disease, and is also informed of the need for immunotherapeutic treatment with mosunetuzumab; this treatment involves the infusion of the following drugs: 1 mg on day 1 of cycle 1, 2 mg on day 8 of cycle 1, 60 mg on day 15 of cycle 1, 60 mg on day 1 of cycle 2, 30 mg on day 1 of cycle 3 and thereafter.

After an appropriate interview in which the possible benefits and both short- and long-term side effects of the proposed treatment were explained, on 24/06/2024 the patient signed informed consent to the treatment and received a copy of it.

Administration of the first cycle of mosunetuzumab as step-up dosing, performed in an in-patient setting, under observation for possible adverse events.

The patient is on mosunetuzumab therapy from 25-6-24 to 29-11-24, for a total of 8 cycles (as per protocol with complete response), for up to 17 cycles if partial response or stable disease, with good general condition, normal objectivity, regular appetite.

He reports myalgias, especially in the upper limbs, and in particular a few days after the first administration of mosunetuzumab (1 mg on day 1 of cycle 1) the patient manifests an itchy skin rash at the level of the axillary cords, in the sub-mental region, lumbar region and at the level of the groin. He also reported a body temperature of 38.8°.

All these symptoms can be traced back to side effects of the drug mosunetuzumab, such as CRS (cytokine release syndrome), which subsequently resolved.

On 12/12/2024 he performed PET CT (Positron Emission Tomography).

Encephalon: no occurrence of encephalic changes before and after MDC (contrast medium). Ventricular system in axis, regular for morpho volumetry.

Neck: no obvious lymph adenomegaly in bilateral latero-cervical site.

Thorax: no newly appeared nodular lesions; unchanged were the 8 mm nodulation with polygonal morphology on the small scissure on the right, the 4 mm solid nodule in the lateral segment of the LID and the 2 mm micro-nodule in the upper segment of the lingula. No ilo mediastinal or axillary lymph adenomegaly. No plural or pericardial effusion.

Abdomen: slight reduction of solid tissue along the left iliac vessels, slight reduction of grade I hydronephrosis on the left. Ectasis left common iliac vein. Reduced edematous suffusion of mesentery adipose tissue and confluent millimetric lymph nodes at the root of the mesentery. No suspicious focal lesions of liver, spleen, pancreas, kidneys and adrenals. No free fluid in abdomen.

Bone: No osteo-structural changes of a repetitive nature in the bone segments examined.

Conclusions: Complete metabolic response to established treatment.

STABLE FINAL PICTURE OF COMPLETE REMISSION.

On 21/05/2025, a PET CT (Positron Emission Tomography) scan was performed for monitoring purposes.

The patient was in good general condition: afebrile, with no cough, pharyngodynia or peripheral edema.

Chest: No new nodular lesions. No plural or pericardial effusion.

Abdomen: The solid tissue along the left iliac vessels is unchanged.

FINAL STABLE PICTURE OF COMPLETE REMISSION CONFIRMED (imagine available but not for publication).

4.1.2. Patient 2

Patients 48 years old, ex-smoker, congenital monoreme, denies allergy.

In history: April 2017, Diagnosis of Follicular Lymphoma Grade 3A, Stage IV, FLIPI2=2 (Above and below diaphragmatic PET capturing adenopathy's at left inguinal level, mass at left flank level) diagnosed on biopsy right inguinal adenopathy package, during hospitalization, PORT type CVC wearer since 02/02/2021 (catheter with central venous access), patient enrolled in Experimental Protocol since 05/2017, I dose SARS COV 2 vaccine on 10/4/2021. II dose on 03/5/2021. III dose on 9/12/22.

The patient is started on chemo-immunotherapy according to the R-CHOP schedule (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) for 6 cycles from 03/05/2017 to 23/10/2017 showing a reduction of about 70% of localized adenopathy's in the neck and abdomen, also confirmed by PET CT (Positron Emission Tomography).

In the final re-evaluation in November 2017, complete remission with MRD (minimal residual disease) is confirmed, which is why the patient resumes therapy with only Rituximab from 14/12/2018 to 13/05/2020.

The patient is re-evaluated in December 2020 and January 2021 by performing PET CT (Positron Emission Tomography) and lymph node biopsy left inguinal with result of: Recurrence of Grade 2 Follicular Lymphoma (induction ended in October 2017) STAGE IVa.

Second-line therapy is started from 02/02/2021 to 06/03/2021 according to scheme R-DHAOX (rituximab, dexamethasone, cytarabine, oxaliplatin), at 30% reduced doses of oxaliplatin because the patient is mono-renal, followed by collection of peripheral stem cells for subsequent autologous transplantation, performed on 09/06/2021 after conditioning chemotherapy with FEAM (fotemustine, cytarabine, etoposide, melphalan) scheme, reduced by 30%, from 01/06/2021 to 07/06/2021.

The patient is re-evaluated after R-DHAOX and ASCT (autologous stem cell transplantation in candidate patients) with: Complete remission picture.

The patient subsequently underwent various hematological follow-up examinations until 23/04/2024, when he underwent a repeat PET scan (Positron Emission Tomography) on 23/01/2024 and a lymph node biopsy in which several peri centimetric lymph nodes were recognizable, more numerous and voluminous on the right at the level of the neck and in the jugular region homolaterally, voluminous inguinofemoral lymph nodes on the left at the level of the inguinal canal, subcutaneously in the lower left cervical region and at the level of the right shoulder. Two focal and

intense accumulations at the level of nodular lesions on the femur also of pathological significance, tenuous accumulation at the level of the lungs of phlogistic nature.

Conclusion: disease with high metabolic activity in the lymph node and soft tissue context, (Figure 6).

FINAL PICTURE: RECOVERY OF ILLNESS.

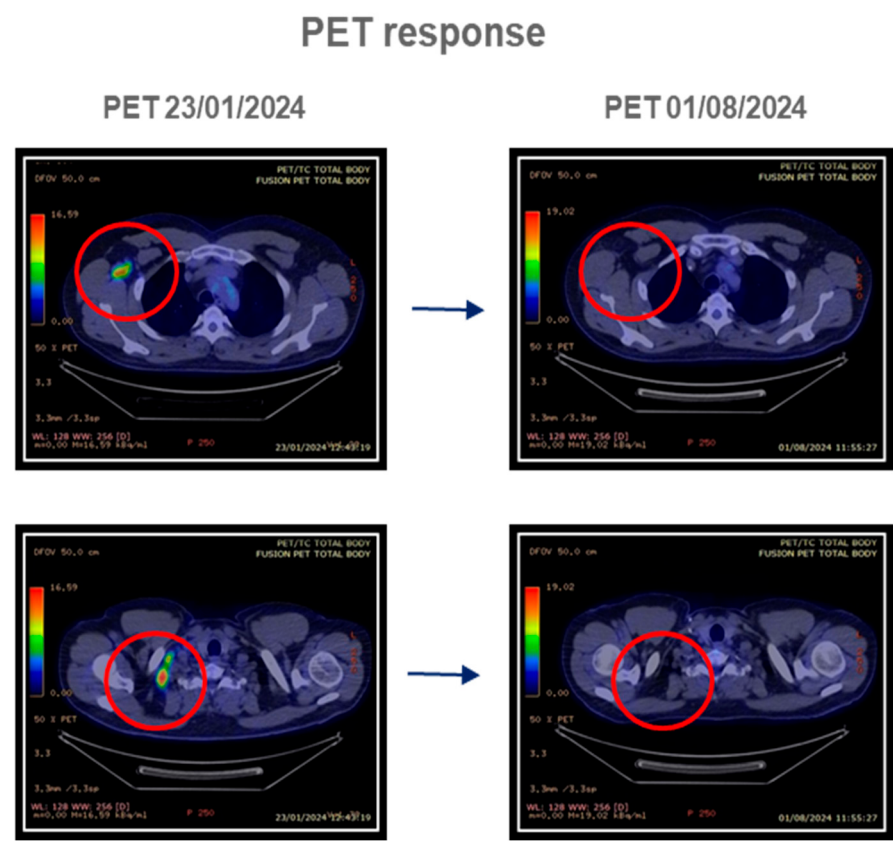


Figure 6. Differences *Pet* patient 2 before treatment with mosunetuzumab (23/01/2024) and after 4 cycles of mosunetuzumab therapy (01/08/2024).

The patient is a candidate for treatment with bispecific *BsAb* antibody mosunetuzumab, as he is refractory to two previous lines: R CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) and R-DHAOX (rituximab, dexamethasone, cytarabine, oxaliplatin) plus ASCT (autologous stem cell transplantation in candidate patients).

The patient is informed of the diagnosis and prognosis of the disease, and is also informed of the need for immunotherapy treatment with mosunetuzumab; this treatment involves the infusion of the following drugs: 1 mg on day 1 of cycle 1, 2 mg on day 8 of cycle 1, 60 mg on day 15 of cycle 1, 60 mg on day 1 of cycle 2, 30 mg on day 1 of cycle 3 and thereafter.

After an appropriate interview in which the possible benefits and both short- and long-term side effects of the proposed treatment are explained, the patient signs an informed consent to the treatment and receives a copy of it.

Administration of the first cycle of mosunetuzumab as step-up dosing, performed in an in-patient setting, under observation for possible adverse events.

The patient is on mosunetuzumab therapy from 08-05-2024 to 01-10-2024, for a total of 8 cycles (as per protocol with complete response), up to a maximum of 17 cycles (if partial response or stable disease), with excellent coenesthesia, normal blood count and liver and kidney function.

The patient, in particular, had mild problems a few days after the first administration of mosunetuzumab (1 mg on day 1 of cycle 1), which were attributable to side effects of the drug mosunetuzumab, such as grade 1 CRS (cytokine release syndrome), which later resolved.

Subsequently, on 01/08/2024 (after 4 cycles of mosunetuzumab) and 11/11/2024 (after 8 cycles of mosunetuzumab), the patient underwent PET-CT (Positron Emission Tomography), both of which were superimposable in terms of outcome:

Neck: Overall reduction of the previously reported lymph adenomegalies, most of them all with a sub centimetric short axis; markedly reduced the major one in the subclavian area.

Abdomen: Complex reduction of previously reported lymph adenomegalies in the groin-femoral area on the left, some of which were not parametrizable and in any case all with a sub centimetric short axis. No appearance of focal densitometric changes in the abdominal organs. Non-dilated bile ducts. No hydroureteronephrosis on the left, no hydroureteronephrosis on the right. No free fluid.

Bone: No focal bone lesions detectable by the method.

Conclusions: Complete metabolic response to established treatment.

STABLE FINAL PICTURE OF COMPLETE REMISSION (**Figure 6**).

On 19/03/2025, 19/06/2025 and 17/09/2025 (respectively 4, 8 and 12 months after the last mosunetuzumab cycle), the patient underwent hematological examinations and PET-CT (Positron Emission Tomography) scans:

The patient is in a stable general condition, is afebrile, and has normal objective findings.

Thyroid and hepatorenal function are normal. The gallbladder is distended. There is no dilatation of the bile ducts. The spleen is normal in terms of morphology and volume. The abdominal aorta is of normal caliber.

FINAL STABLE IMAGE OF COMPLETE REMISSION CONFIRMED.

4.1.3. Patient 3

Patient 61 years old, anxiety syndrome, allergy: severe reaction to pegfilgrastim

September 2022, diagnosed with Follicular Lymphoma Grade 2, Stage IVa, FLIPI-1 score 2 and FLIPI-2 score 1, patient wearing PORT-type CVC (catheter with central venous access) since 24/06/2023, April 2022 SARS-Cov2 infection, (post 3 doses vaccine) and treatment with Evusheld (anti-covid drug).

The patient is started on first-line chemo-immunotherapy according to the schedule O-CHOP (obinutuzumab, cyclophosphamide, doxorubicin, vincristine, prednisone) from 18-10-2022 to 30-3-2023. This therapy involves infusion of the drugs on the first day of each 21-day cycle, for a maximum of 6 cycles. At the end of therapy, 2 further administrations of obinutuzumab are planned. In addition to the first cycle, weekly administration of obinutuzumab for 3 consecutive weeks.

The patient was re-evaluated in May 2023 by performing PET scan (positron emission tomography) with reduction of radiopharmaceutical accumulation in the known adenopathy formation along the mesenteric root, in the lymph nodes in the pre-sacral, bilateral external iliac.

New tracer uptake in a lymph node at the right internal iliac site. Result of:

Persistence of disease Follicular lymphoma grade 2 STAGE IVa.

Second-line therapy (salvage therapy) is started from 15/06/2023 to 20/07/2023, in an in-patient setting, according to the schedule R-DHAP (rituximab, dexamethasone, cytarabine and cisplatin) for the duration of 1 cycle followed by DHAOX (dexamethasone, cytarabine, oxaliplatin) for the duration of 1 cycle.

The patient was subsequently re-evaluated by performing PET CT (Positron Emission Tomography) in which there was progression by extension and metabolic gradient of the voluminous radiopharmaceutical accumulation at the level of the right presacral lymph node root and appearance of further intense accumulation at the level of nodular thickening in the hypogastric region. Disease with high metabolic activity in the pelvic abdominal region.

FINAL PICTURE: DISEASE IN PROGRESSION.

The patient is a candidate for Rituximab and lenalidomide therapy for 6 cycles.

He is advised of the need for oral treatment with lenalidomide; this oral treatment is performed for 28-day cycles with 21 consecutive days of therapy and 7 days off; it is usually continued until tolerance/efficacy.

Third-line therapy with Rituximab and lenalidomide was started from 15/9/2023 to 01/03/2024, with several periods of lenalidomide withdrawal due to the appearance of itching and papillomatous lesions on the legs and forearms, which then resolved.

The patient was subsequently re-evaluated by performing PET CT (Positron Emission Tomography) on 28/03/2024: stable disease with substantially stable adenopathy mass mesenteric and the small iliac femoral lymph nodes (**Figure 7**).

FINAL PICTURE: STABLE DISEASE

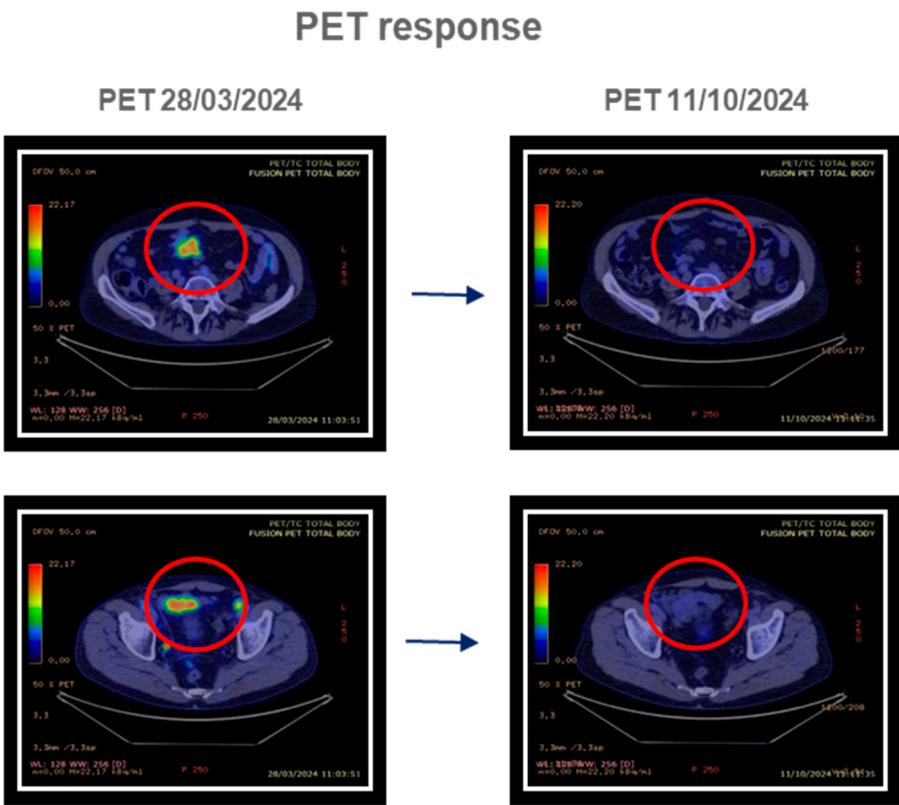


Figure 7. Differences Patient 2 before treatment with *mosunetuzumab* (28/03/2024) and after 8 cycles of *mosunetuzumab* therapy (11/10/2024).

The patient is a candidate for treatment with bispecific *BsAb* antibody *mosunetuzumab*, as he is refractory to three previous lines: O-CHOP (obinutuzumab, cyclophosphamide, doxorubicin, vincristine, prednisone), R-DHAP (rituximab, dexamethasone, cytarabine and cisplatin) and DHAOX (rituximab, dexamethasone, cytarabine, oxaliplatin), rituximab and lenalidomide.

The patient is informed of the diagnosis and prognosis of the disease, and is also informed of the need for immunotherapy treatment with *mosunetuzumab*; this treatment involves the infusion of the following drugs: 1 mg on day 1 of cycle 1, 2 mg on day 8 of cycle 1, 60 mg on day 15 of cycle 1, 60 mg on day 1 of cycle 2, 30 mg on day 1 of cycle 3 and thereafter.

After an appropriate interview in which the possible benefits and both short- and long-term side effects of the proposed treatment are explained, the patient signs an informed consent to the treatment and receives a copy of it.

Administration of the first cycle of *mosunetuzumab* as step-up dosing, performed in an in-patient setting, under observation for possible adverse events.

The patient is on mosunetuzumab therapy from 29/04/2024 to 27/09/2024, for a total of 8 cycles (as per protocol), for a maximum of 17 cycles, with good general condition, normal cardiopulmonary objectivity, treatable abdomen, not painful on palpation, regular appetite.

The patient complained of occasional headaches of a familiar character during the first cycle of therapy and therefore these were not attributable to the mosunetuzumab infusion. No CRS (cytokine release syndrome) was detected and no changes referred to ICANS (immune effector cell associated neurotoxicity syndrome).

The patient underwent PET CT (Positron Emission Tomography) on 16/07/2024 after 4 cycles of mosunetuzumab: reduction in extent and capturing entity of the pathological accumulation of radiopharmaceuticals at the level of the known lesion at the root of the mesentery, of which only a faint capturing remains today. Almost total disappearance of the pathological uptake at the expense of the further localizations of disease in the mesogastric, paravesical and retro vesical areas and in the lymph node area at the previously described presacral, right external iliac and obturator and left external iliac formations. Excellent response to established treatment.

PET scan (Positron Emission Tomography) performed again on 11/10/2024 after 8 cycles of mosunetuzumab: almost complete disappearance of the previously described residual fading at the level of the mesentery root, (**Figure 7**).

Conclusions: Complete metabolic response to established treatment.

STABLE FINAL PICTURE OF COMPLETE REMISSION.

The patient underwent hematological examinations and PET CT (Positron Emission Tomography) scans on 30 May, 12 September and 4 November 2025, (respectively 7, 11 and 13 months after the last cycle of mosunetuzumab).

The patient is in good general condition, afebrile, and there is nothing to report on physical examination.

Chest: No hilar-mediastinal or axillary lymphadenopathy. Dilatation of the ascending thoracic aorta is essentially stable.

Abdomen: Initially, there was intense and focal accumulation of lymph node tracer in multiple areas of the lateral cervical region, likely related to disease localization. However, after biopsy, no cell populations with a pathological tumor marker phenotype were identified. There are no focal lesions in the parenchymal organs of the upper abdomen.

Bone: No suspicious focal bone lesions.

FINAL STABLE IMAGE OF COMPLETE REMISSION CONFIRMED.

5. Conclusions

Follicular lymphoma is the second most common lymphoma in the world. The course of this tumor is often characterized by relapsing diseases, increasing refractoriness to *anti-CD20* antibodies and chemotherapy, and decreasing survival rates with each subsequent therapy.

Patients with refractory disease or early relapses may have a particularly poor prognosis.

New effective drugs are needed to overcome treatment resistance and improve the outcome of patients with relapsed or refractory follicular lymphoma, with innovative mechanisms of action.

BsAbs have revolutionized the therapeutic landscape, including *FL*. The activity of these single-agent drugs is among the most promising in the field and has led to multiple regulatory approvals. *BsAbs*, such as mosunetuzumab (a bispecific, full-length, *IgG1-based* monoclonal antibody that engages *CD20*×*CD3* *T* cells and redirects them to eliminate malignant *B* cells) have produced incremental improvements in response rates and duration without new or excessive toxicities and are challenging existing and new standards of care, including *CAR-Ts*, as reflected in the clinical history and complete remission of the 3 *PATIENT CASES*, reviewed. Future research will aim to define the optimal role of these agents in the *FL* treatment algorithm, analyses and address relevant toxicities, including cytopenias, infections and high costs, identify mechanisms of resistance and ideally suggest strategies to overcome them.

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