Bispecific Antibodies for the Treatment of Lung Cancer

Subjects: Oncology

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Bispecific antibodies are a promising type of therapy for the treatment of cancer due to their ability to simultaneously inhibit different proteins playing a role in cancer progression. The development in lung cancer has been singularly intense because of the increasingly vast knowledge of the underlying molecular routes, in particular, in oncogene-driven tumors.

lung cancer bispecific nanobodies NSCLC SCLC targeted therapies

1. Introduction

Nowadays, numerous antibody-based proteins are being preclinically and clinically developed and have proven to be useful research, diagnosis, and therapy tools due to their particular properties, such as high specificity and affinity [1]. However, their large molecular weight (~150 kDa) and their challenging high-cost production limit their capacities. Thus, other novel strategies, such as nanobodies and bispecific antibodies, are being developed to overcome those limitations and improve their pharmacological properties and efficacy [2][3].

Classical antibodies or immunoglobulins are formed by two identical heavy and two identical light chains connected with disulfide bonds representing a Y-shaped molecule [4]. The heavy chain comprises four domains, and the light chain folds into two domains [5]. At the end of each chain is the antigen-binding fragment, which corresponds to the variable region of the antibody [1][4].

During the early 1990s, Hamers-Casterman and her team discovered a new type of antibody circulating in Camelidae (including camels and llamas) devoid of light chains that are called “heavy chain-only antibodies” [6]. Their heavy chain structure consists of two constant regions, a hinge region and the antigen-binding domain (VHH) [1]. The VHH is the structural and functional equivalent of the antigen-binding fragment of conventional antibodies [5]. It is also referred to as a nanobody or single-domain antibody and is considered to be the smallest antigen-binding unit of an antibody. Its small molecular size (~15 kDa) allows it to penetrate easily into tissues, cross the blood–brain barrier, and invade solid tumors [7][8]. In addition to their small size, other unique advantages, such as their remarkable stability against extreme temperatures, high pressure, chemical denaturants, low pH, or the presence of proteases, make nanobodies an attractive option over conventional antibodies [1][3][7][9]. Hence, nanobodies share characteristics of small molecule drugs and monoclonal antibodies, and they may be a promising alternative to classical antibodies in some applications [1]. Currently, many nanobody-based strategies

are being developed for cancer, molecular imaging, infectious diseases, or inflammatory conditions, among other medical fields [3].

On the other hand, bispecific antibodies are molecules composed of one core unit and two binding units that are specific to two different epitopes, thus being able to attach to two targets simultaneously. The clinical applications of these antibodies are numerous, and they might be particularly useful in cancer because of the great complexity of this disease, with intertwined oncogenic signaling routes able to bypass single target inhibition upstream. Moreover, several clinical trials have demonstrated greater efficacy when patients receive combined targeted therapies, including CTLA4 plus PD-1-blocking antibodies or BRAF- and MEK-targeted antibodies, strongly supporting the potential benefit of this strategy [10][11][12][13][14][15].

Bispecific antibody development strategies can be bifurcated into two categories, the antigen x antigen type and the antigen x cell-engager type. Additionally, from the perspective of molecular format, bispecific antibodies can be classified into the “full antibody type” and the “BiTE type” (**Figure 1**). Depending on the molecular format, different development strategies should be required. For instance, the antigen x antigen bispecific type simultaneously targets two tumor-expressed antigens (TAAs), generally inhibiting two cancer signaling pathways to inhibit tumor growth. Of note, a particular subtype of bispecific antibodies has been named after the acronym BiTE (Bispecific T-cell engager). They are small molecules consisting of two fused scFvs without Fc region; one of them targets a (TAA), and the other one is specific to a T cell-surface receptor, generally CD3, one of the components of the T cell receptor (TCR). When a BiTE engages CD3 and the tumor-associated antigen, it induces T cell activation and proliferation while, at the same time, ensuring the immunological synapse [16] and enhancing T cell cytotoxicity for the recognition and elimination of tumor cells. Currently, several BiTEs are being developed for the treatment of cancer, the one targeting DLL3 and CD3 being the most promising one for the treatment of lung cancer, demonstrating enhanced T-cell cytotoxicity against DDL3+ tumor cells (NCT05882058).

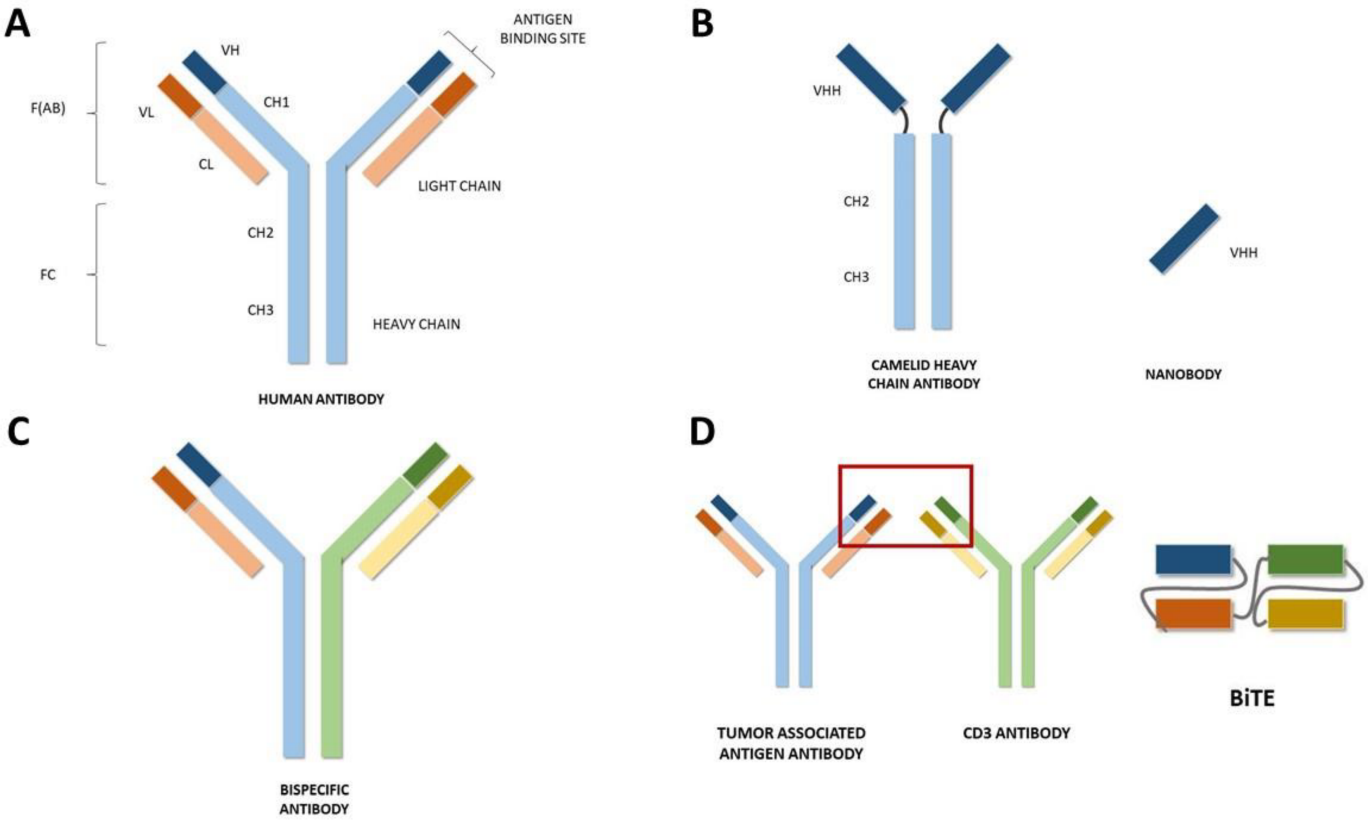

Figure 1. (**A**) Schematic representation of a conventional human antibody. Heavy chain is represented in blue, light chain is represented in orange. CH: Constant domain of heavy chain. CL: Constant domain of light chain. VH: Variable domain of heavy chain. VL: Variable domain of light chain. (**B**) Schematic representation of a nanobody. VHH: Single variable domain on a heavy chain. (**C**) Schematic representation of one modality of a bispecific antibody. The heavy and light chain specific for antigen 1 are represented in blue and orange, respectively. The heavy and light chain specific for antigen 2 are represented in green and yellow. (**D**) Schematic representation of a Bispecific T-cell Engager (BiTE).

2. Approvals in Oncology

In 2009, the first bispecific antibody, catumaxomab, was approved in the European Union as an intraperitoneal therapy for malignant ascites. Unfortunately, it was found to be toxic because of Fc-mediated off-target T-cell activation in the liver and was voluntarily withdrawn from the market.

Further on, blinatumomab (Blincyto), a bispecific CD19-directed CD3 T-cell engager, received accelerated approval by the FDA in December 2014 and by the EMA in 2015 for the treatment of adult and pediatric patients with B-cell precursor acute lymphoblastic leukemia (ALL). Regular approval was obtained in July 2017 after the results of the phase III trial TOWER (NCT02013167), finding a benefit in overall survival (7.7 vs. 4.0 months, HR 0.71, $p = 0.01$) and event-free survival (6-months 31% vs. 12%, $p < 0.001$) compared with standard chemotherapy in patients with B-cell precursor ALL that had progressed to at least one line of therapy [17].

During the last few years, other bispecific antibodies have been approved for the treatment of hematological malignancies. BCMA-targeted therapies have proven to be effective in patients with multiple myeloma. Belantamab mafodotin (Blenrep) was the first one to receive authorization for its use in August 2020, shortly followed by teclistamab (Tecvayli), with a breakthrough designation in 2022 by the FDA and also approved by the EMA the same year based on the results of the phase Ib trial MajesTEC-1. Moreover, in patients with multiple myeloma, talquetamab, a bispecific antibody targeting GPRC5D and CD3, was named a breakthrough therapy after the results of phase I MonumenTAL-1.

For the treatment of relapsed follicular lymphoma, the anti-CD20/CD3 antibody mosunetuzumab (Lunsumio) was approved in June 2022 by the EMA as a therapy after progression to two previous lines of treatment. A single-arm phase II trial found a complete response rate of 60%, much higher than the 14% obtained with copanlisib in previous trials [18].

To conclude, bispecific antibodies have also proven effective for the treatment of solid tumors, and two drugs for the treatment of neoplasms other than lung cancer have been approved in 2022. Tebentafusp (Kimmtrak), targeting gp100, was approved by the FDA and EMA for the treatment of uveal melanoma with HLA-A*02:01. Phase III IMCgp100-202 compared tebentafusp with the therapy chosen by the investigator (pembrolizumab/ipilimumab/dacarbazine), and found a benefit in progression-free survival (31% vs. 19% at 6 months, $p = 0.01$) and overall survival (83% vs. 59% at 1 year). Lastly, cadonilimab (anti-PD1/CTLA4) was approved in China in June 2022 for patients with relapsed or metastatic cervical cancer after progression to platinum-based chemotherapy [19]. Even though a phase III trial is still ongoing, the approval was granted based on the promising results of a single-arm phase II with patients that had progressed to one or two lines of treatment, obtaining an overall response rate (ORR) of 33%, median progression free survival (mPFS) of 3.75 months and, more interestingly, median overall survival (mOS) of 17.51 months [20].

3. Non-Small-Cell Lung Cancer

NSCLC is one of the tumor types with the higher incidence worldwide. It is usually classified into two groups, squamous and non-squamous. The greater knowledge of the mutational landscape that drives tumor progression in NSCLC allowed a further division based on gene mutation, particularly in non-squamous tumors. In this context, different targeted therapies have been developed, having demonstrated a higher efficacy with a more favorable toxicity profile compared with conventional treatments.

At this moment, amivantamab-vmjw is the only bispecific antibody available for the treatment of lung cancer. It is a human IgG1-based antibody that targets EGFR and MET, and it also induces Fc-dependent trogocytosis (an active transfer of a fraction of a cell to another, including the membrane and/or surface molecules) by macrophages and antibody-dependent cytotoxicity (ADCC) by natural killer (NK) cells [21]. It was granted accelerated approval by the Federal Drug Agency (FDA) in May 2021 and was approved by the European Medicines Agency (EMA) that same year for patients with NSCLC and *EGFR* ex20ins mutations that have progressed to platinum-based chemotherapy. Approval was granted on the basis of the results of the phase I CHRYSALIS, which included 81

patients, and reported an ORR of 40% and median duration of response (mDOR) of 11.1 months. The most frequent adverse events were rash (86%) and paronychia (45%), but no G3-4 toxicities surpassed 5%, hypokalemia (5%), rash (4%), PE (4%), diarrhea (4%) and neutropenia (4%) being the most common [22].

Some combinations of amivantamab with other drugs are also in the advanced stages of development. Phase II CHRYSALIS-2, evaluating the combination of amivantamab with the third generation EGFR TKI inhibitor lazertinib in patients with EGFR mutant NSCLC after progression to osimertinib and platinum-based chemotherapy, was presented in ASCO Congress 2022, describing an ORR of 33% with mDOR of 9.6 months, irrespective of the original mutation or the sequence of treatment. Toxicity was comparable with the one reported in the CHRYSALIS trial [23]. A confirmatory phase III trial called MARIPOSA-2 (NCT04988295), comparing chemotherapy plus amivantanab and Llzertinib with chemotherapy in patients that have progressed to osimertinib, is enrolling patients at this moment. Moreover, phase III trial MARIPOSA (NCT04487080), which will compare this combination with osimertinib or lazertinib monotherapy as a frontline treatment, is currently ongoing [24]. Finally, phase III trial PAPILLON (NCT04538664) is evaluating the benefit of the addition of amivantamab to platinum-based chemotherapy in patients with NSCLC and *EGFR* exon 20 insertions, and preliminary results are expected to be published within the next few years.

To conclude, zenocutuzumab, an HER2 and HER2 bispecific antibody, is also under evaluation, with a special focus on patients with NRG1 fusion. NRG1 is a membrane glycoprotein involved in cell growth and differentiation, which acts as a ligand for ERBB3 and ERBB4. Under common circumstances, NRG1 is cleaved by proteases and released in its mature form, limiting its activity. However, NRG1 fusions are poorly attached to proteases, favoring the accumulation of the protein in the membrane and its binding to HER3, causing heterodimerization with HER2 and downstream signal transduction. The combined results of the phase II part of the basket trial and the early expanded access program revealed an ORR of 34% among the 41 patients with NSCLC, with an mDOR of 9.1 months for the whole cohort, and less than 5% of G3 adverse events.

4. Small-Cell Lung Cancer

SCLC is a neoplasm of neuroendocrine origin strongly associated with a smoking habit. It is characterized by a poor prognosis, with cancer cells presenting a very high proliferative rate and early metastatization. The high cellular heterogeneity, with a high mutation burden, is a major barrier to the incorporation of new treatments into the therapeutic arsenal, as targets expressed by all the cells are uncommon. From a molecular point of view, the inactivation of tumor suppressor genes defines this disease, with TP53 and RB1 being dysfunctional in most cases.

In recent years, immunotherapy has been positioned in the frontline treatment of small-cell lung cancer, and at this very moment, two immune-checkpoint inhibitors, atezolizumab and durvalumab, are widely used combined with chemotherapy [25][26]. However, the efficacy is modest, probably due to the great cell plasticity and tumor heterogeneity, and new treatment strategies combining different approaches might be advantageous.

Delta-like ligand 3 (DLL3) is an inhibitory ligand of the NOTCH pathway frequently upregulated in SCLC that promotes cell invasion and metastases through epithelial-to-mesenchymal transition (EMT) [27]. Several early trials evaluating the efficacy of tarlatamab, a novel DLL3-targeted BiTE, in patients with SCLC, have reported appealing outcomes. In ASCO Annual Meeting 2021, the results of the phase I trial DeLLphi-300, in which patients with SCLC were treated with tarlatamab after progression to platinum-based chemotherapy, were presented. Even though 40% had previously received immune-checkpoint inhibitors (ICI) and 47% had liver metastases, usually associated with resistance to ICI, ORR was 20% with mDOR of 8.7 months, and disease control was achieved in 47%. The drug's toxicity was manageable; 27% presented G3 treatment-related adverse events (TRAEs), which forced the interruption of the treatment in 7.6% of patients; additionally, 44% of patients experienced cytokine-release syndrome (CRS) [28]. The final results were recently published, reporting an ORR of 23.4% with an mDOR of 12.3 months, an mPFS of 3.7 months, and a mOS of 13.2 months. Tumor DLL3 expression was associated with better outcomes. The main TRAEs were CRS (52.3%), pyrexia (40.2%), constipation (30.8%), and 30.8% experienced toxicity ≥ G3 [29].

5. Toxicity of Bispecific Antibodies

Up to date, TRAEs caused by bispecific antibodies being evaluated for the treatment of lung cancer appear manageable, although the very structure of the BiTE tarlatamab and its immune-stimulating effect confers a less favorable toxicity profile compared with zenocutuzumab and amivantamab.

Patients treated with tarlatamab experience G3-5 TRAEs more frequently than those receiving zenocutuzumab or amivantamab, with CRS and neurological adverse events (AEs) being particularly concerning. Moreover, it should be taken into account that most oncologists treating lung cancer might not have any previous experience in the management of either CRS or immune effector cell-associated neurotoxicity syndrome (ICANS), so an additional effort to ensure proper handling would be of great interest [29].

Regarding zenocutuzumab and amivantamab, besides the aforementioned TRAEs, infusion reactions were frequent, as high as 66% in patients receiving the latter [22]. Tight surveillance and patient education might be useful to adequately manage these episodes.

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