REVISTA PORTUGUESA DE Oncologia

PERMANYER

Check for updates

Molecularly targeted agents and tumor biology

Ana Rodrigues

Department of Medical Oncology, IPO-Porto, Porto, Portugal

Regarding the area of "Developmental Therapeutics Molecularly Targeted Agents and Tumor Biology," the presentations selected were:

- Abstract 3002 – Phase I study of iza-bren (BL-B01D1), an epidermal growth factor receptor × human epidermal growth factor receptor 3 (EGFR × HER3) bispecific antibody-drug conjugate (ADC), in patients (pts) with locally advanced or metastatic small cell lung cancer (SCLC).
- Abstract 3004 – Efficacy and safety of the Delta-like ligand 3 (DLL3)/CD3 T-cell engager obrixtamig in pts with extrapulmonary neuroendocrine carcinomas (epNEC) with high or low DLL3 expression – Results from an ongoing phase I trial.
- Abstract 2501 – First-in-human phase I/II trial evaluating BNT142, a first-in-class mRNA-encoded, bispecific antibody targeting Claudin 6 (CLDN6) and CD3, in pts with CLDN6-positive advanced solid tumors.

Iza-bren (BL-B01D1) is a first-in-class ADC composed of an EGFR × HER3 bispecific antibody conjugated to a topo-I inhibitor payload (Ed-04). Unlike existing ADCs, which typically target general tumor antigens, iza-bren specifically targets EGFR and HER3 pathways, both of which are implicated in the aggressive biology of SCLC. This phase 1 study (3002) included 58 pts with locally advanced or metastatic SCLC who had progressed on prior systemic therapies, with a median follow-up of 16.4 months. In the overall population, the confirmed overall response rate (ORR) was 44.8%, median progression-free survival (PFS) was 4.0 months, and median overall survival (OS) was 12.0 months. A promising efficacy was seen in 20 of the 52 patients treated at 2.5 mg/kg, who had progressed after only one prior line of PD(L)-1 and platinum-based chemotherapy. In this subgroup, the confirmed ORR was 75.0%, the median duration of response (DOR) was 5.6 months, the median PFS was 6.9 months, and the median OS was 15.1 months. Regarding the safely profile, the most frequent treatment related adverse events (TRAE) (all grades) were anemia (84.5%), leukopenia (74.1%), thrombocytopenia (72.4%), and neutropenia (70.7%); the most frequent non-hematologic TRAEs were asthenia (41.4%), hypoalbuminemia (39.7%), stomatitis (34.5%), nausea (31.0%), and vomiting (31.0%); the discontinuation rate was 12.1% and no interstitial lung disease was observed. These results position iza-bren as a promising novel therapeutic option for SCLC, a disease that has seen limited advancements in treatment over the decades. A phase III study comparing iza-bren to topotecan as a second-line treatment in SCLC patients who received one prior line of PD(L)-1 and platinum-based chemotherapy is currently underway (NCT06500026) in China. However, considering the results presented at the American Society of Clinical Oncology regarding tarlatamab as a second-line treatment (DeLLphi304), questions may arise about the selected control arm for that trial[1].

Correspondence

Ana Rodrigues

E-mail: ana.fernandes.rodrigues@ipoporto.min-saude.pt

Date of reception: 07-07-2025

Date of acceptance: 09-07-2025

DOI: 10.24875/RPO.25000007

Available online: 13-10-2025

Rev. Port. Oncol. 2025;8(3):92-93

www.rponcologia.com

Moving on to obrixtamig (BI 764532), a DLL3/CD3 immunoglobulin G-like T-cell engager. The phase I dose-escalation trial NCT04429087 evaluated the efficacy of obrixtamig in patients with pulmonary and epNEC DLL3-positive (DLL3+), who did not respond to standard treatments. Abstract 3004 specifically highlights the results for epNEC DLL3+ (60 patients), further divided based on DLL3 expression levels into high (30 patients) versus low (30 patients), using a threshold of and ≥ 50% tumor cells stained with an investigational antibody for DLL3 (SP347, Roche Diagnostics). Gastroenteropancreatic NETs were the most common NECs included (45%), followed by genitourinary NECs (30%) and NECs from other or unknown primary sites (25%). The average age was 69 years in the DLL3-high group compared to 61 years in the DLL3-low group. A higher proportion of patients in the DLL3-low group had undergone more than two previous lines of treatment (50% versus 30%). Patients with epNEC DLL3-high demonstrated better outcomes in ORR, disease control rate (DCR), and DOR compared to those with DLL3-low expression, regardless of the primary tumor site's origin. For the DLL3-high group, the ORR was 40%, DCR was 67%, and the average DOR was 7.9 months. In contrast, the DLL3-low group showed an ORR of 3%, a DCR of 27%, and an average DOR of 2.8 months. Most TRAEs were mild-to-moderate across both groups, with cytokine release syndrome (CRS), pyrexia, dysgeusia, and asthenia being the most frequently observed side effects[2].

These promising findings highlight obrixtamig's potential for further exploration in this context. A Phase II trial (DAREON-5) is currently underway to evaluate obrixtamig in patients with relapsed or refractory DLL3-high epNEC[2].

Finally, BNT142 is a prodrug in the form of an mRNA encapsulated in a lipidic nanoparticle. The final drug, RiboMab02.1, is an anti-CLDN6/CD3 bispecific antibody. Claudin 6 is an oncofetal tight junction protein silenced in normal adult tissues, but aberrantly activated in some tumors such as testicular, ovarian, and non-SCLC (NSCLC), making it an excellent target. Abstract 2501 presents the results of 65 patients with CLDN6+ metastatic or unresectable solid tumors, including ovarian cancer, germ cell tumors, non-squamous NSCLC, and other rare cancers, who had undergone all available standard therapies and were enrolled in the trial. The median age was 57 years, with the majority being female (75%) and presenting an Eastern Cooperative Oncology Group performance status of 1 (60%). Most patients were heavily pre-treated, with 66.2% having received at least four lines of prior therapy (median of five lines, range of 1-14). Ovarian cancer was the most common cancer (67.7%), predominantly platinum-resistant ovarian cancer (77.3%), followed by germ cell tumors (18.5%) and NSCLC (7.7%). BNT142-01 presented encouraging preliminary anti-tumor activity in heavily pre-treated cancer patients, with most of the responses in ovarian cancer, particularly in platinum-resistant cancer. In ovarian cancer, seven partial responses and a DCR of 76.2% were observed. Regarding the exploratory analysis of CLDN6 expression levels and RECIST 1.1 response, no correlation was found. Most TRAEs were mild-to-moderate (63%), and the most common were CRS (22%) and aspartate or alanine aminotransferase increased[3].

BNT142 stands as the first clinical proof-of-concept for an mRNA-encoded bispecific T-cell engager antibody produced *in vivo*, demonstrating some activity, particularly in platinum-resistant ovarian cancer.

In summary, Iza-bren and obrixtamig emerge as promising therapies for diseases with poor prognoses and unmet treatment needs. Meanwhile, BNT142 paves the way for mRNA-encoded drugs in cancer therapy, extending beyond anti-cancer vaccines.

References

1. Yunpeng Yang, Li Zhang, Yuxiang Ma, Yuanyuan Zhao, Wenfeng Fang, Hongyun Zhao, et al. Phase I study of iza-bren (BL-B01D1), an EGFR x HER3 bispecific antibody-drug conjugate (ADC), in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with driver genomic alterations (GA) outside of classic EGFR mutations. Journal of Clinical Oncology 2025, Volume 43, Number 16_suppl. https://doi.org/10.1200/JCO.2025.43.16_suppl.3001
2. Capdevila J, Gambardella V, Kuboki Y, Alese O.B., Morgensztern D, Sayehli C, et al. Efficacy and Safety of the Dll3/Cd3 T-Cell Engager Obrixtamig in PTS with Extrapulmonary Neuroendocrine Carcinomas (Epnec) with High or Low Dll3 Expression - Results from an Ongoing Phase I Trial. Journal of Clinical Oncology 2025 Volume 43, Number 16_suppl https://doi.org/10.1200/JCO.2025.43.16_suppl.3004
3. Yap TA, Hernando-Calvo A, Calvo E, Moreno V, Marquez R, Papadopoulos KP, et al. First-in-human phase I/II trial evaluating BNT142, a first-in-class mRNA encoded, bispecific antibody targeting Claudin 6 (CLDN6) and CD3, in patients (pts) with CLDN6-positive advanced solid tumors. J Clin Oncol. 2025;43(16_suppl). https://doi.org/10.1200/JCO.2025.43.16_suppl.2501