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OPINION ARTICLE

Tomić and Vranić: B7-H3-directed therapies

Hannibal ante portas: B7-H3-directed therapies at the gates of precision oncology

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ABSTRACT

Precision oncology has revolutionized cancer treatment, improving outcomes and extending survival even in aggressive cancers like small-cell lung cancer. Molecularly targeted therapies and immune checkpoint inhibitors (e.g., PD-1/PD-L1) are now standard. Recently, the immune checkpoint regulator B7-H3 (CD276) has emerged as a promising therapeutic target, especially for novel antibody-drug conjugates (ADCs). This article highlights recent advances in B7-H3-targeted ADCs, emphasizing the urgent need for reliable predictive biomarkers to guide patient selection and optimize treatment.

Keywords: B7-H3, CD276, antibody–drug conjugates, ADCs, predictive biomarkers, precision oncology, small-cell lung cancer, SCLC

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INTRODUCTION

For decades, small-cell lung cancer (SCLC) has been the ugly duckling of thoracic oncology. Despite its initial sensitivity to chemotherapy, patients with extensive-stage disease historically experienced poor overall survival (OS), while therapeutic progress remained frustratingly limited [1]. While precision oncology approaches have markedly transformed the treatment landscape and outcomes of non-small-cell lung cancer patients, SCLC remained largely without validated molecular predictive biomarkers to guide treatment and very limited targeted therapeutic options. In our previous editorial, we argued that SCLC was approaching the threshold of targeted therapy [2]. Yet an important question remains: does the ability to target a tumor-associated antigen necessarily bring us closer to precision oncology in SCLC?

The addition of immune checkpoint inhibitors atezolizumab and durvalumab to first-line chemotherapy marked the first breakthrough after decades of limited therapeutic progress in extensive-stage SCLC (ES-SCLC) [3, 4]. Nevertheless, despite high initial response rates, most patients ultimately experience disease relapse and die. After decades of therapeutic stagnation also in relapsed SCLC, a breakthrough came with tarlatamab, a bispecific T-cell engager targeting delta-like ligand 3 (DLL3) on tumor cells and CD3 on T cells. In the phase III DeLLphi-304 trial, tarlatamab significantly improved median OS compared with chemotherapy (13.6 vs. 8.3 months) in patients with SCLC progressing after platinum-based chemotherapy, demonstrating that a tumor-associated antigen could be therapeutically exploited [5].

Despite this major advance, treatment options for relapsed SCLC remain limited, highlighting the need for new therapeutic strategies and a deeper understanding of tumor biology. Antibody–drug conjugates (ADCs), which have transformed the treatment of several malignancies, offer a distinct approach to antigen-directed therapy. Whereas tarlatamab redirects T cells toward DLL3-expressing tumor cells, ADCs exploit tumor-associated antigens as molecular addresses for cytotoxic drug delivery. Among these targets, B7-H3 (CD276), a member of the B7 immunoregulatory family first described in 2001, is frequently overexpressed in SCLC and other malignancies, with relatively limited expression in normal tissues [6, 7]. Its involvement in immune evasion and tumor progression further supports its potential as a therapeutic target.

More than two decades after its discovery, B7-H3 has emerged as a promising therapeutic target. The phase II IDeate-Lung01 trial provided compelling evidence of clinical activity, with ifinatamab deruxtecan achieving an objective response rate (ORR) of 48.2% in

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previously treated patients with ES-SCLC [8]. However, whether the antitumor activity of B7-H3-directed ADCs would translate into a survival benefit remained uncertain.

The answer came from two randomized phase III trials, both demonstrating a significant survival benefit with different B7-H3-directed ADCs. ARTEMIS-008 evaluated risvutatug rezetecan, while TAISHAN-302 evaluated tambotatug pelitecan; both compared with topotecan in relapsed SCLC [9, 10]. Median OS was 18.5 versus 10.3 months in ARTEMIS-008 and 13.3 versus 9.4 months in TAISHAN-302, respectively. Remarkably, both trials reported a hazard ratio for death of approximately 0.46. Yet identical hazard ratios should not be mistaken for identical clinical outcomes. Differences in baseline characteristics, including a higher proportion of patients with platinum-resistant disease and brain metastases in TAISHAN-302, may partly explain the differences in absolute survival. However, cross-trial comparisons cannot establish the superiority of one ADC over another.

Beyond demonstrating the therapeutic potential of B7-H3, these findings raise another important question: what will ultimately distinguish one B7-H3-directed ADC from another? Both agents achieved remarkably similar ORR (59.1% versus 58.3%) and median progression-free survival (PFS) of approximately seven months [9, 10]. Both carry topoisomerase I inhibitor payloads and were associated with expected hematologic toxicities, although severe adverse events were generally less frequent than with topotecan. However, their pulmonary safety profiles appear to differ, with interstitial lung disease (ILD) reported in 4.9% of patients receiving tambotatug pelitecan compared with 11.7% receiving risvutatug rezetecan. Although cross-trial comparisons preclude definitive conclusions, these differences may become particularly relevant when considering future combination strategies. Ultimately, the best ADC may not simply be the most effective as monotherapy, but the one that offers the most favorable balance between efficacy, toxicity, and compatibility with future combination strategies.

After decades of limited progress, the expanding treatment landscape of relapsed SCLC raises another important question: how should B7-H3-directed ADCs be sequenced with DLL3-directed therapy? In the phase III DeLLphi-304 trial, tarlatamab achieved a median OS of 13.6 months, similar to the 13.3 months reported with tambotatug pelitecan in TAISHAN-302 [5, 9]. However, cross-trial comparisons cannot establish comparative efficacy. Intracranial activity has been reported with both therapeutic approaches, although differences in patient populations and response assessments limit direct comparisons. Importantly, tarlatamab has demonstrated a survival benefit in a global phase III trial, whereas the two

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pivotal B7-H3 ADC studies were conducted exclusively in China and still require global confirmation.

However, the treatment sequence may already be changing. The recently reported phase III DeLLphi-305 trial demonstrated a substantial survival benefit with tarlatamab plus durvalumab compared with durvalumab alone as first-line maintenance therapy following platinum-based chemotherapy and durvalumab, extending median OS from 12.7 to 21.1 months (HR 0.42) [11]. Indeed, following regulatory approval, these remarkable results could establish DLL3-directed therapy as a new standard of care for first-line maintenance in ES-SCLC, potentially positioning B7-H3-directed ADCs as a new standard in the second-line setting.

But SCLC may be only the beginning of the success for anti-B7-H3-based therapies (Figure 1). Another glimmer of hope is emerging in sarcomas, a rare and highly heterogeneous group of mesenchymal malignancies with limited treatment options. Although B7-H3 is frequently overexpressed in sarcomas, its expression varies considerably across soft tissue tumor subtypes and according to detection and scoring methods [12]. Despite this heterogeneity, osteosarcoma, the most common malignant bone tumor, has emerged as a particularly promising sarcoma subtype for B7-H3-directed ADCs. In the phase II ARTEMIS-002 trial, risvutatug rezetecan demonstrated promising antitumor activity in relapsed or refractory osteosarcoma [13]. These findings were followed by positive results from the phase III ARTEMIS-011 trial, which demonstrated a significant PFS benefit over gemcitabine and docetaxel chemotherapy [14]. Although OS data remained immature, a favorable trend was observed with risvutatug rezetecan (HR 0.51). Despite a higher incidence of severe adverse events with risvutatug rezetecan (92.5% vs. 83.3%), treatment discontinuation due to treatment-related adverse events remained low in both groups (3.8% vs. 2.4%). These results highlight a promising new treatment option for relapsed or refractory osteosarcoma, a disease in which therapeutic progress and novel treatment modalities have been limited for decades.

But does the presence of B7-H3 across different malignancies imply a comparable sensitivity to B7-H3-directed treatment? Encouraging antitumor activity has been reported with risvutatug rezetecan in metastatic castration-resistant prostate cancer and with SYS6043 in ovarian, endometrial, and cervical cancers, where objective response rates ranged from 33.3% to 45.7% [15, 16]. In colorectal cancer, B7-H3 expression is also frequent but heterogeneous, and risvutatug rezetecan-based combinations are being investigated in the ongoing ARTEMIS-102 trial [17, 18]. The challenge is no longer simply to demonstrate that

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B7-H3 can be targeted across malignancies, but to determine whether its expression can meaningfully guide treatment selection.

The complexity of B7-H3 targeting becomes even more apparent when we consider therapeutic approaches beyond ADCs. In gliomas, higher B7-H3 expression has been associated with higher tumor grade [19]. More than two decades after the landmark Stupp trial established radiotherapy with concomitant and adjuvant temozolomide as a cornerstone of glioblastoma treatment, however, meaningful therapeutic progress remains limited [20]. Given the limited therapeutic progress, T cells genetically engineered to recognize B7-H3 on tumor cells (B7-H3-directed CAR-T cells) offer a promising new therapeutic approach. In a phase I trial involving 15 patients with recurrent glioblastoma, intracranially administered B7-H3-directed CAR-T cells (TX103) were associated with a median OS of 19.1 months [21].

CONCLUSION

Together, these developments highlight the expanding therapeutic potential of B7-H3-directed therapies while raising a fundamental question: is antigen expression alone sufficient to predict clinical benefit? To date, a consistent association between B7-H3 expression levels and treatment response has not been established. A recent analysis found that nearly half of ADC clinical trials did not require biomarker-based patient selection [22]. Here lies the central paradox of ADC therapeutic strategy: identifying a therapeutic target does not necessarily identify the patients most likely to benefit. This paradox reflects the complex mechanisms underlying ADC activity, which depend not only on antigen expression but also on target accessibility, internalization, linker processing, payload sensitivity, and the bystander effect. Without validated predictive biomarkers, the promise of B7-H3-directed therapy remains only partly realized.

We are currently relying on single immunohistochemical measurements (e.g., HER2 in the case of trastuzumab deruxtecan) or no specific biomarker at all, as in the case of B7-H3 status and response to risvutatug rezetecan. Perhaps the future of ADC in precision oncology is related to the development of ADC-specific and mechanism-informed biomarkers rather than having a single predictive biomarker. One of the most intriguing questions is whether payload sensitivity is more informative than a certain antigen abundance, like B7-H3 protein on the surface of cancer cells. Also, if patients with higher antigen expression have better outcomes (e.g., longer OS) after receiving ADC-based therapies, that does not necessarily prove that the biomarker predicts a specific benefit from ADC. It may just reflect differences in cancer

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biology and prognosis. Nevertheless, we are becoming increasingly precise in how we deliver anticancer treatment, but far less precise in deciding who should receive it. Hannibal is at the gates of targeted therapy; crossing into precision oncology will require knowing which patients stand to benefit most.

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TABLES AND FIGURES WITH LEGENDS

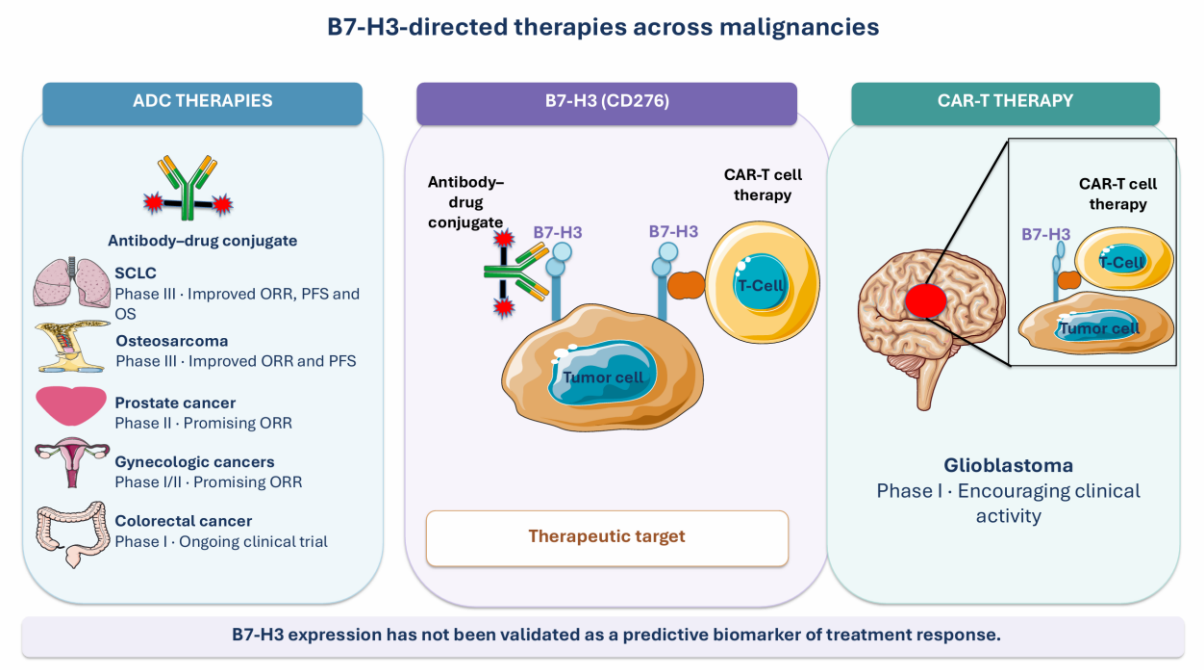


Figure 1. B7-H3-directed therapies across malignancies. The left panel summarizes clinical development of B7-H3-directed antibody–drug conjugates (ADCs) in small-cell lung cancer (SCLC), osteosarcoma, prostate cancer, gynecologic cancers, and colorectal cancer. The central schematic illustrates antigen-directed drug delivery and CAR-T-cell recognition of tumor-associated B7-H3. The right panel depicts investigational B7-H3-directed CAR-T-cell therapy for glioblastoma. The evidence ranges from early-phase clinical activity to randomized phase III results. B7-H3 expression has not been validated as a predictive biomarker of treatment response.

Abbreviations: ADC, antibody–drug conjugate; CAR-T, chimeric antigen receptor T-cell; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SCLC, small-cell lung cancer.

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