Clinical Development of ADC Drugs Targeting TROP-2

Antibody-drug conjugates (ADCs) combine the powerful cytotoxicity of chemotherapy with antigen-specific targeting of antibodies to protect healthy cells while delivering effective cytotoxicity to tumor cells, thereby reducing toxicity and improving therapeutic index. Trophoblast cell-surface antigen 2 (TROP-2), a transmembrane glycoprotein involved in calcium signaling, is expressed in a variety of tumor types, making it an emerging and hot target for ADC development.

Sacituzumab govitecan (Trodelvy) is the first approved TROP-2-targeted ADC in which anti-Trop-2 antibodies are conjugated to SN-38, a topoisomerase inhibitor, via a hydrolyzable linker. This hydrolyzable linker allows the release of membrane permeable payloads both intracellular and extracellular, thereby achieving the "bystander effect" and increasing the potency of the drug. In pretreated metastatic triple-negative breast cancer (TNBC), Trodelvy significantly improved progression-free survival (PFS) and overall survival (OS) compared with chemotherapy.

Common adverse events (AEs) reported were neutropenia and diarrhea. Datopotamab deruxtecan (Dato DXd) is another TROP-2 ADC that differs from Trodelvy in having a cleavable tetrapeptide linker and a more potent topoisomerase inhibitor payload. Dato DXd has shown initial efficacy in unselected metastatic TNBC, and these novel TROP-2 ADCs have the potential to provide enhanced efficacy and reduced toxicity in metastatic breast cancer (MBC) and early breast cancer (EBC).

TROP-2 Protein

TROP-2 is a transmembrane glycoprotein with extracellular and intracellular components involved in calcium signal transduction. TROP-2 is associated with a variety of cellular

signaling pathways, including intracellular calcium transduction, MAPK signaling pathway, RAF, NF-κB and Cyclin D/E.

TROP-2 is upregulated in cancer cells, and this increased expression has been seen in many different tumor types, including breast cancer, colon cancer, non-small cell lung cancer (NSCLC), esophageal squamous cell cancer, thyroid cancer, and hepatobiliary cancer. The reason for the upregulation of TROP-2 in cancer cells is not clear, but it is hypothesized that TROP-2 plays a key regulatory role in cell proliferation and invasion, implying that overexpression will lead to selective tumor progression. In fact, preclinical data suggest that TROP-2 overexpression stimulates tumor growth, while TROP-2 knockdown suppresses tumor growth.

Especially in breast cancer, elevated TROP-2 expression is associated with reduced survival. TROP-2 gene expression was detected in all breast cancer subtypes, with higher expression levels in HR+/HER2 and triple negative breast cancer (TNBC) compared to HER2+ breast cancer. Therefore, TROP-2 should not be considered as an attractive candidate for targeted therapy of TNBC.

Sacituzumab govitecan (Trodelvy)

Sacituzumab govitecan (Trodelvy) is a novel ADC drug that uses a hydrolyzable linker to conjugate a humanized RS7 anti-TROP-2 antibody to SN-38, the active metabolite of irinotecan. Trodelvy is particularly suitable as an ADC drug for several reasons.

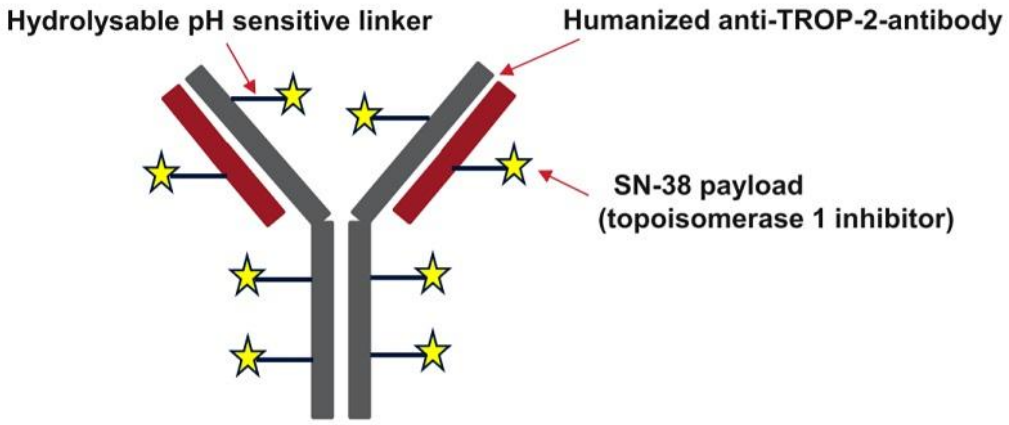
First, its active metabolite, SN-38, is estimated to be 2-3 times more potent than irinotecan and has membrane permeability, allowing it to exert a "bystander effect".

Second, the hydrolyzable linker of sacituzumab govitecan allows extracellular release of SN-38 as well as intracellular release, thus creating another mechanism of the "bystander

effect". This potential for extracellular release may be particularly beneficial for tumors with heterogeneous TROP-2 expression.

Third, sacituzumab govitecan provides a high DAR of 7.6:1, and its unique antibody and linker design allows sacituzumab govitecan to maintain a higher DAR without compromising antibody binding or pharmacokinetic properties.

Finally, the reduced toxicity of sacituzumab govitecan compared to other topoisomerase inhibitors is thought to be due to the lower rate of glucuronidation of the SN-38 molecule conjugated to the antibody rather than the SN-38 directly metabolized from irinotecan.



1. Phase I/II study of Trodelvy in Epithelial carcinoma (NCT01631552)

The phase I clinical trial tested the safety and tolerability of IMMU-32 against 13 different epithelial tumors in 25 patients. The study included patients with different tumor types, including breast cancer, colorectal cancer, endometrial cancer, small cell lung cancer and non-small cell lung cancer.

At the end of the study, 2 patients had a partial response (PR), 16 patients had stable disease (SD), and 6 of them survived for 15-20 months or more. In this study, there were no treatment-related grade 4 toxicities and grade 3 toxicities were limited to diarrhea (n=1),

fatigue (n=3), and neutropenia (n=2). The results showed that IMMU-132 was generally a well tolerated therapeutic agent.

The results of the second phase in different tumor types are as follows:

2. Phase II study of Trodelvy in breast cancer patients

Results showed that of the 69 patients, 2 had a complete response and 19 had a partial response. The clinical benefit rate (defined in this study as complete response + partial response + stable condition ≥6 months) in this group was 46%. Median response was 8.9 months, median overall survival was 16.6 months, and median progression-free survival was 6.0 months. Grade 3 adverse events included anemia (14%), diarrhea (13%), leukopenia (16%), and neutropenia (39%).

3. Phase I/ II study of Trodelvy in patients with urothelial carcinoma

Three of the six patients had clinically significant responses with progression-free survival of 6.7 to 8.2 months and overall survival of 7.5 + to 11.4 + months. Two of the six patients experienced grade 3 adverse events (lumbago and bacteremia) and no grade 4 adverse events were observed.

4. Phase II study of Trodelvy in NSCLC patients

Among the 54 patients with metastatic NSCLC, the clinical benefit rate (defined in this study as complete response + partial response + stable disease) ≥4 months was 43%. In addition, the median duration of response to treatment was 6 months, median overall survival was 9.5 months, and median progression-free survival was 5.2 months.

For toxicity, grade 3 adverse events included diarrhea (7%), fatigue (6%), neutropenia (4%), nausea (7%), and neutropenia (28%).

5. Phase II study of Trodelvy in SCLC patients

In another study of patients with metastatic small cell lung cancer, 60% of patients showed tumor shrinkage compared to baseline CT, with a clinical benefit rate of 34% (defined in this study as complete response + partial response + stable disease ≥4 months). Median overall survival was 7.5 months and median progression-free survival was 3.7 months.

For toxicity, grade 3 adverse events included anemia (6%), diarrhea (9%), fatigue (13%), and neutropenia (34%).

6. Phase II study of Trodelvy in urothelial carcinoma (NCT03547973)

TROPHY is a single-arm, international multi-center phase II clinical study, which recruited a total of 112 patients with locally advanced or metastatic UC who had previously received platinum-based chemotherapy and PD-1 or PD-L1 inhibitors.

The results of the study showed that the ORR of 112 curative effect-evaluable patients was 27.7%, of which 5.4% achieved CR and 22.3% achieved PR. The median duration of response (mDoR) was 7.2 months (95% CI: 4.7-8.6). The most common adverse reactions (incidence >25%) included neutropenia, nausea, diarrhea, fatigue, alopecia, anemia, vomiting, constipation, decreased appetite, rash, and abdominal pain.

7. Phase III study of Trodelvy in triple-negative breast cancer (NCT02574455)

ASCENT is an international, open-label phase III clinical study that enrolled 529 patients with relapsed and refractory metastatic triple-negative breast cancer who had previously received at least 2 types of chemotherapy (including paclitaxel).

The median PFS in the treatment group was 5.6 months (4.3-6.3), and that in the chemotherapy control group was 1.7 months (1.5-2.6). The Trodelvy treatment group could reduce the risk of disease progression by 59%. In terms of secondary endpoints, Trodelvy significantly improved the patient's OS (12.1 vs 6.7 months), the risk of death was reduced by 52%, and the ORR in the treatment group was 35% (82/235), while the chemotherapy control group was only 5% (11/233).

In terms of safety, compared with the control group, treatment-related adverse events above grade 3 mainly included neutropenia (51% vs 33%), diarrhea (10% vs 1%), and leukopenia (10% vs 5%), anemia (8% vs 5%), and neutropenic fever (6% vs 2%).

Datopotamab deruxtecan (Dato-DXd)

Dato DXd is a TROP-2-directed ADC in which humanized anti-TROP-2 IgG1 monoclonal caonti is conjugated to a topoisomerase I inhibitor payload via a tetrapeptide-based cleavable linker. The DAR in this structure is ~4:1, which is highly stable in circulation because the linker is only designed for cleavage in the presence of lysosomal proteases. While the payload (DXd) has the same mechanism of action (MOA) as the payload in Trodelvy (SN-38), there are some important differences between them. DXd is 10 times more potent than SN-38, and the longer half-life of Dato DXd allows for a 3-week dosing schedule. Furthermore, DXd showed an improved therapeutic index, releasing only 5% of the payload after 21 days, compared to 90% of the net load released by sacituzumab after 3 days.

ROPION-PanTumor01 is a phase 1 clinical trial for TNBC. Among 21 evaluable patients receiving datopotamab deruxtecan, the preliminary objective response rate (ORR) was 43% by blinded independent center evaluation.

At the data cutoff on January 8, 2021, 5 patients had confirmed complete or partial response (CR/PR), and another 4 patients had CR/PR awaiting confirmation. The disease

control rate (DCR) is 95%. In the TNBC cohort, the observed safety profile of datopotamab deruxtecan was consistent with that previously reported in the trial's non-small cell lung cancer (NSCLC) cohort.

PF-06664178

PF-06664178 is an ADC of antibody-conjugated Aur0101 (an auristatin microtubule inhibitor) targeting TROP-2 that has been terminated from clinical development. In the conducted phase 1 clinical study, 31 patients with metastatic solid tumors were treated with escalating doses (0.15-4.8 mg/kg) of PF-0664178. 11 of the 31 cases had stable disease and no complete or partial response.

With regard to toxicity, at 3.6mg/kg, 33% of patients experienced dose-limiting toxicity with grade 4 neutropenia and grade 3 mucosal inflammation. At a dose of 4.2mg/kg, 1 in 1 (100%) patients developed dose-limiting toxicity, grade 3 maculopapular eruption. At a dose of 4.8mg/kg, 4 out of 8 patients (50%) developed dose-limiting toxicity, including grade 4 febrile neutropenia, grade 4 toxic epidermal necrolysis, grade 4 dehydration, and grade 3 rash.

Conclusion

ADC drugs have greatly expanded treatment options for breast cancer patients. Early development of ADCs in MBC focused on HER2 targeting. However, the emerging ADCs have been expanded to target TROP-2 for multiple breast cancer subtypes. The success of targeting TROP-2 via ADC in MBC and uroepithelial carcinoma and the trials conducted in NSCLC have established that TROP-2 targeting is an effective and promising strategy.

In addition, several other targeted ADCs are being explored in clinical trials. These include patritumab deruxtecan, a HER3-targeted ADC with the same payload as T-DXd, and enfortumab vedotin, an ADC targeting Nectin-4 antibodies and MMAE payload.

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References:

[1].Targeting Trop-2 in solid tumors: future prospects. Onco Targets Ther. 2019; 12: 1781–1790.

[2].Antibody-drug conjugates targeting TROP-2: Clinical development in metastatic breast cancer. Breast. 2022 Dec;66:169-177.

Related articles:

[1].The Rise of the TROP2-Directed ADCs for Solid Tumors

[2].ADC Drug Trodelvy Shows Positive Efficacy In three Types of Cancers

[3].Key To The Successful Design of ADC Drugs