Editorial

Folate Receptor, Trop 2, Ovarian Cancer, and Antibody-Drug Conjugate (ADC)

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The identification of targetable proteins/glycoproteins for ovarian cancer was initiated in the 1980s, primarily for tumor marker research. Many tumor-associated antigens were discovered using monoclonal antibodies (MAbs). Hence, such antibody-drug conjugates (ADCs) could bring hope. The recent success of studies on folate receptor and Trop2 antibody prompted a search into its development. Pfizer had world's first ADC for acute myeloid leukemia, gemtuzumab ozogamicin (Mylotarg), which was approved in 2000 but it failed later.[1] In 2017, many other ADCs started entering the market. The first full approval for the use of the ADC in solid tumors was for ado-trastuzumab emtansine (T-DM1) in 2019. The MAb Trop was first detected in human malignant trophoblastic cells of the choriocarcinoma cell line BeWo.[2] With the advent of hybridoma technology, many MAbs have been identified, one of them having tremendous success in screening (CA 125),[3] which, however, did not fully succeed due to the rarity and occult nature of this cancer.

In 1987, an Italian group worked on the OvCa 4343/83 cell line since it was completely negative with all of the MAbs produced thus far.[4] These authors identified three new MAbs (MOv16, MOv18, and MOv19). The MAb, MOv16 reacted mainly to ovarian and other carcinomas and to some normal tissues. It matched with MAbs of Trop-2, as shown by genomic deoxyribonucleic acid (DNA) transfection.[5] MOv18 and MOv19 were specific for ovarian carcinomas and cystadenomas but not for nonepithelial tumors or normal tissues. Dr. Coney and team cloned MOv18 and MOv19 to show them to be highly homologous to that of the human folate-binding protein.[4]

EC145 (vintafolide), a conjugate of folic acid and a vinca alkaloid, came first. It was developed by Endocyte, Inc but it failed to improve progression-free survival (PFS). Morphotek, Inc. developed MORAb-003 or farletuzumab, a MAb against folate receptor α (FRα) but it failed to meet the primary endpoint of PFS.[6]

Dr. Baruj Benacerraf, a Venezuelan-American Nobel laureate immunologist, founded ImmunoGen, later acquired by AbbVie. He selected another FRα antibody M9346A and combined it with maytansinoid payload to create IMGN853 or mirvetuximab soravtansine (Elahere)[7] for targeted delivery in FRα positive ovarian cancer cells. In December 2019, the U.S. Food and Drug Administration gave it accelerated approval for FRα -high platinum-resistant ovarian cancer (PROC). It received full approval in 2024.

Professor Goldenberg of New Jersey established Immunomedics in 1982 and was developing radioimmunotherapeutic agents from Trop2 MAbs. Later, he developed an ADC, IMMU-132 (sacituzumab govitecan) from RS73G11 (RS7). In April 2020, Trodelvy (sacituzumab govitecan-hziy) got approval for the treatment of adult patients with metastatic triple-negative breast cancer who have received at least two prior therapies for metastatic disease. A phase 2 study (NCT06028932) of sacituzumab govitecan (IMMU-132) in PROC patients has started in Yale University.

MK-2870 or SKB264 is another sacituzumab with new payload tirumotecan from Merck Sharpe & Dohme (MSD) and Kelun-Biotech. Datopotamab deruxtecan (Dato-DXd) is another investigational TROP2-directed ADC designed using Daiichi Sankyo's proprietary DXd ADC technology and developed by AstraZeneca. It is in early phase study with advanced/metastatic solid tumors, including ovarian cancer (NCT05417594, NCT05489211, and NCT04644068). In January 2025, it is approved in previously treated metastatic breast cancer.

The use of the ADC for the treatment of ovarian cancer has been successful because of the use of folate receptors, and the use of the Trop 2-related ADC has also been attempted. There

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are several new ADCs and new combinations with existing ADCs in the pipeline. Mirvetuximab soravtansine with pembrolizumab in PROC was tested in FORWARD II, a phase Ib study (NCT02606305). ADCs with antiangiogenic compounds, HER2-targeting drugs, DNA damage response agents, and immunotherapy are being developed. The identification of new targets and their antibody, linkers, and payloads will help to achieve greater success in ovarian cancer treatment.

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Conflict of Interest
None declared.

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