COMMENTARY

Treatment for triple-negative breast cancer with sacituzumab govitecan

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ABSTRACT

Sacituzumab Govitecan (SG) is an anti-cancer drug that combines a humanized monoclonal antibody that binds to cancer cells that express the Trophoblast cell surface antigen-2 (Trop-2) with the cytotoxic SN-38 (govitecan) moiety. A marketing authorization for SG as a monotherapy for the treatment of adult patients with Metastatic or unresectable Triple-Negative Breast Cancer (mTNBC)

via the buccal route. Although some studies have an in vivo performance, the use of mucoadhesive polymers in buccal medication administration reveals measuring buccal drug penetration and absorption. This review discusses the use of polymers in the production of drug delivery systems (hydrogels, films, and tablets) and presents the outcomes of studies done on how well those systems operate in vivo.

INTRODUCTION

About 15% of invasive breast cancers are Triple-Negative Breast Tumors (TNBC). Ages 40, non-Hispanic Black women, and those with a Breast Cancer susceptibility gene (BRCA) mutation are more likely to develop TNBC. Premenopausal status, obesity, and maternal variables including parity and age at first pregnancy are additional risk factors for the illness. TNBC is characterized by a lack of estrogen receptor, Progesterone Receptor (PR), and Human Epidermal Growth Factor Receptor 2 expression in tumor cells (HER2). Visceral metastases, aggressive tumor biology, and a poor prognosis are all characteristics of TNBC. TNBC with Metastases (mTNBC) is regarded as terminal. Targeted therapies have helped patients with other breast cancer subtypes, and several targeted therapies for Hormone Receptor Positive (HR+) and HER2-positive breast cancer are available; however, sequential single-agent chemotherapy continues to be the standard of care for patients with mTNBC.8 There is no preferred or standard regimen used, and typically, patients first receive standard chemotherapy regimens that either include a taxane or anthracycline. However, a targeted therapy, such as a hormonal therapy or a targeted (e.g. capecitabine, gemcitabine, vinorelbine or albumin-bound paclitaxel, and combination regimens for patients who present with visceral crisis). In patients with previously treated mTNBC, standard chemotherapy is linked to modest response rates (10% to 15%) and brief Progression-Free Survival (PFS) (2 to 3 months). Over the past 20 years, there has been no change in the Overall Survival (OS) of patients with this type of breast cancer, and patients with mTNBC continue to have a significantly worse OS when compared to those with metastatic breast cancer. Both atezolizumab in combination with nab-paclitaxel and pembrolizumab in combination with chemotherapy have been approved for the treatment of adult patients with mTNBC whose tumors are positive for the Programmed Death-Ligand 1 (PD and L1) and who have not previously received chemotherapy for metastatic disease. Olaparib and talazoparib, two Poly-adenosine Diphosphate-Ribose Polymerase Inhibitors (PARPi), have been authorized for use in TNBC patients who have undergone prior chemotherapy and have a hereditary BRCA1 or BRCA2 mutation. Patients who have had two or more regimens in the metastatic context have few treatment alternatives, underscoring the importance of therapeutic advancements for these patients. Sacituzumab Govitecan (SG), a monotherapy for the treatment of adult patients with Metastatic or unresectable Triple-Negative Breast

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Cancer (mTNBC), who have received two or more prior systemic therapies, at least one of which was for advanced disease, was approved by the European Union on November 22, 2021. The applicant requested an accelerated review, and the Committee for Medicinal Products for Human Use (CHMP) granted it because the medicine was deemed to be of significant public health interest. The CHMP undertook the review, and on October 14, 2021, a favorable opinion was released. SG is an Antibody-Drug Conjugate (ADC) made of a humanized antibody (hRS7 IgG1) that is directed against the Trophoblast cell surface antigen-2 (Trop-2) and a topoisomerase I inhibitor molecule (SN38), a metabolite of the drug irinotecan that is covalently linked to the antibody by the hydrolysable linker CL2A. It has been demonstrated that binding of the parental RS7 antibody to Trop-2 causes the targeted cells to internalize and digest the antibody. Because of its hydrolysable linker, SG will release its SN-38 payload in the tumor microenvironment both intracellularly and extracellularly. SG is intended to deliver SN-38 to a tumor that expresses Trop-2 in a considerably greater proportion than traditional irinotecan treatment. The extracellular release of SN-38 from SG also enables the collateral death of tumor cells that lack Trop-2. SG is designed to deliver cytotoxic chemotherapy to tumors, including nearby cancer cells, at concentrations higher than those of traditional chemotherapy and may lessen adverse effects in healthy tissues that do not express the target. In an in vitro mammalian cell micronucleus test using Chinese hamster ovary cells, SN-38 was found to be clastogenic, although it was not mutagenic when tested using an in vitro bacterial reverse mutation (Ames) assay. Intravenous SG administration caused endometrial atrophy, uterine hemorrhage, increased follicular atresia of the ovary, and atrophy of vaginal epithelial cells in a study on the toxicity of repeated doses in cynomolgus monkeys (1.9 times the human recommended dose of 10 mg/kg based on body weight allometric scaling). The clinical pharmacology package for SG includes population Pharmacokinetic (PK) analysis to look at the effects of intrinsic variables on PK variability, noncompartmental PK analyses for studies IMMU-132-01 and IMMU-132-05, and analysesof exposure-efficacy and exposure-safety connections. Until the disease progresses or there is intolerable toxicity, SG should be administered once weekly on days 1 and 8 of 21-day therapy cycles at a dose of 10 mg/kg intravenously. Based on population PK analyses, 2.96 l of SG's core volume distribution. SG and free SN-38 had average half-lives of 15.3 and 19.7 hours, respectively. According to assessments of population PK, the clearance of SG is 0.14 l/h. There has been no research done using SG to study metabolism. Through UGT1A1, SN-38, the small molecule component of SG, is broken down. Age, race, or moderate renal impairment did not appear to have any impact on the PK of SG in patients receiving SG (n = 527). The small molecule component of SG, SN-38, is known to be excreted with just a minor contribution via renal elimination. There are no data available about the PK of SG in individuals with end-stage renal illness, moderate renal impairment, or severe renal impairment. Individuals with mild hepatic impairment [bilirubin > ULN and aspartate aminotransferase (AST) > ULN, or bilirubin > 1.0 to 1.5 ULN with AST of any level; n = 59] have similar exposure to SG to patients with normal hepatic function (bilirubin or AST ULN; n = 191). Patients with moderate or severe hepatic impairment have no known SG exposure. As a result of diminished hepatic UGT1A1 activity, SN-38 exposure may be increased in these patients.