Trodelvy® (sacituzumab govitecan-hziy) Resistance

This document is in response to your request for information regarding resistance to Trodelvy® (sacituzumab govitecan-hziy [SG]).

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The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/oncology/trodelvy/trodelvy_pi.

Summary

Relevant Product Labeling[1]

There is no information regarding resistance to SG available in the SG US FDA-approved Prescribing Information.

SG is a Trop-2–directed ADC. SG is a humanized antibody that recognizes Trop-2. The small molecule SN-38, is a TOP1 inhibitor, which is covalently attached to the antibody by a linker. Pharmacology data suggest that SG binds to Trop-2-expressing cancer cells and is internalized with the subsequent release of SN-38 via hydrolysis of the linker. SN-38 interacts with TOP1 and prevents re-ligation of TOP1-induced single strand breaks. The resulting DNA damage leads to apoptosis and cell death. SG decreased tumor growth in mouse xenograft models of TNBC.

Clinical Data on Resistance to SG

In a retrospective pre-treatment biopsy analysis (SG, n=204) that assessed the association of drug efflux gene expression with DOT and OS, there was no association between efflux pump expression and DOT; however, higher pre-treatment *ABCC1* and *ABCC4* gene expression was associated with significantly worse OS (*P*=0.034 and *P*=0.042, respectively).[2]

A genomic and transcriptomic analysis of tumor tissue from 3 patients with mTNBC who received SG demonstrated that resistance to SG was associated with parallel genomic alterations in both antibody and payload targets. An association was found between lowered Trop-2 expression and decreased cellular sensitivity to SG.[3]

Pre-Clinical Data on Resistance to SG

A study in mice evaluated the use of an ABCG2 inhibitor (YHO-13351) to overcome resistance to SN-38 and to improve the efficacy of SG.[4]

- Administration of SG with YHO-13351 in mice with SN-38–resistant NCI-N87-S120 tumors resulted in a 64% improvement in survival compared with no treatment (*P*=0.0278).

Background

SG is an ADC made from a humanized anti-Trop-2 monoclonal antibody (hRS7) conjugated with SN-38, a TOP1 inhibitor, the active metabolite of irinotecan via a hydrolysable linker, CL2A.[3] Although SG has been studied in multiple tumor types, there are limited data available on resistance to SG, and the specific underlying mechanisms associated with this resistance have yet to be formally established.

Clinical Data on Resistance to SG

Retrospective Study of Transcriptomic Biomarkers of Therapeutic Response and Resistance[2]

Study design

A retrospective study was conducted to assess the transcriptomic profile of drug efflux genes in metastatic breast cancer before ADC treatment to evaluate biomarkers of response and resistance to ADCs, including SG (n=204). Biopsies were collected before SG treatment was administered and included tumors with the following breast cancer subtypes: TNBC (62%), HR+/HER2- (20%), not otherwise specified (17%), HR+/HER2+ (0.5%), and HR-/HER2+ (0.5%). Six drug efflux genes from transcriptomic data were considered genes of interest (*ABCB1, ABCC1-4, and ABCG2*), and the relationship between efflux gene expression and DOT and OS were assessed. The analysis was exploratory, and *P*-values were uncorrected.

Results

Patients received SG as first line (25%), second line (36%), third line (19%), and fourth line or later (20%) therapy, with a median (IQR) DOT of 116 (62–198) days. There was no significant association between efflux pump expression and DOT with SG. With SG, higher pre-treatment *ABCC1* (HR, 1.34; 95% CI: 1.02–1.75; *P*=0.034) and *ABCC4* gene expression (HR, 1.19; 95% CI: 1–1.41; *P*=0.042) was associated with a significantly worse OS.

Parallel Genomic Alterations of Antigen and Payload Targets Mediate Polyclonal Acquired Clinical Resistance to SG in mTNBC[3]

Study design

A genomic and transcriptomic analysis of tumor tissue from patients with mTNBC who were treated with SG was conducted to determine mechanisms of SG resistance. Three patients (MGH-18, MGH-19, and MGH-20) with available pre-treatment and multisite post-progression specimens were included in this analysis. All patients had previously received SG after they experienced disease progression with ≥2 prior therapies for mTNBC. Trop-2 gene expression and genomic copy number were analyzed in pre- and post-treatment specimens. Whole-exome sequencing for MGH-18 was performed on the pre-SG treatment and 9 post-progression rapid autopsy tumor lesions.

Results

MGH-20 demonstrated evidence of PD at the first radiologic assessment, which led to drug discontinuation. MGH-19 exhibited SD for 5 months as per the RECIST v1.1, and MGH-18 had a PR, followed by multisite PD. MGH-20 had no Trop-2 protein expression observed with immunohistochemistry, and RNA sequencing of tumor specimens showed nearly undetectable Trop-2 RNA expression. Both MGH-18 and MGH-19 had detectable Trop-2 RNA expression in all analyzed specimens.

Table 1. Trop-2 Expression and Response to SG[3]

Parameter	MGH-18	MGH-19	MGH-20
Age at diagnosis, years	41	59	62
Time on SG, days	253	150	34
Time from last SG dose to death, days	138	305	56
Treatments before SG, n	2	5	4
Treatments after SG, n	2	4	1
Lesions sequenced at autopsy, n	9	8	6
Best response per RECIST	PR	SD	PD
Extent of best response, %	-45	-21.9	+78

The focus of this analysis was MGH-18, a 42-year-old female patient who was diagnosed with metastatic disease that spread to other organs within weeks of completion of standard preoperative chemotherapy for TNBC. The patient then underwent a mastectomy and received two investigational combinations in sequence but did not experience an objective response. Treatment with SG was initiated, and a PR (45% tumor regression) as per RECIST v1.1 was observed for >8 months. After 8 months, restaging scans exposed PD at multiple sites, and the patient died.

Whole-exome sequencing discovered a truncal *TP53* (K132R) mutation, which is commonly observed in TNBC, in the pre-SG primary tumor and all 9 post-progression lesions. Two major phylogenetic branches (*TOP1* and *TACSTD2*) exhibited distinct mutations that were found at high frequencies in multiple, mutually exclusive metastatic lesions. E418K, a *TOP1* missense mutation, was frequently present within abdominal lesions in the liver and periaortic lymph nodes. This mutation is established to induce resistance to clinical TOP1 inhibitors. This mutation was accompanied by a frameshift *TOP1* mutation. T256R, a missense mutation of *TACSTD2/Trop-2*, was frequently present in thoracic metastatic lesions, including those in the chest wall and hilar lymph node.

Complementary DNA that encoded either WT or mutant Trop-2 were synthesized and reconstituted into multiple Trop-2-negative–based models to determine the significance of the *TACSTD2/Trop-2* mutation. It was found that *TACSTD2/Trop-2*^{T256R} encoded a stable protein that could be expressed in both TNBC (BT549) cells and non-transformed (NIH 3T3) cells, with both types of cells lacking endogenous Trop-2 expression. In TNBC cells that were reconstituted with the Trop-2 mutant, binding of hRS7 (the antibody component of SG), was reduced by >80% compared with WT Trop-2; similar results were observed in 3T3 cells.

Reconstitution of WT Trop-2 into Trop-2-negative TNBC and 3T3 cells resulted in significant increases in sensitivity to SG. There was no effect on SN-38 sensitivity in either TNBC or 3T3 cells when WT or mutant Trop-2 was reconstituted. Trop-2T^{256R} had resistance to SG via altered plasma membrane localization and reduced cell-surface binding to the anti-Trop-2 antibody, hRS7. Mutant Trop-2 as compared with WT Trop-2 was associated with decreased cellular sensitivity to SG, which indicated the role of Trop-2 as a response determinant in SG resistance.

This analysis highlighted the parallel genetic mechanisms of acquired resistance under selective pressure from SG.

Pre-Clinical Data on Resistance to SG

Combining ABCG2 Inhibitors With SG to Investigate Resistance to SN-38 in Pre-Clinical Models of Breast and Gastric Cancers[4]

Study design

A study was performed in mice to evaluate the use of a known ABCG2 inhibitor (YHO-13351) to overcome SN-38 resistance and to improve the efficacy of SG. NCI-N87, a human gastric cancer cell line, was utilized to establish NCI-N87-S120, a cell line resistant to SN-38. Mice with NCI-N87-S120 were divided into six study groups: SG + YHO-13351, irinotecan + YHO-13351, SG monotherapy, irinotecan monotherapy, YHO-13351 monotherapy, or no treatment. Mice with NCI-N87 served as a control to evaluate the efficacy of SG and irinotecan in NCI-N87-S120 tumors. These mice were divided into three study groups: SG monotherapy, irinotecan monotherapy, or no treatment. Irinotecan 40 mg/kg was administered IV every other day for 5 doses. SG 0.5 mg was administered IV twice weekly for 4 weeks. YHO-13351 was coadministered at the start of irinotecan or SG therapy and 4 hours after therapy. Mice in the SG group received a third dose of YHO-13351 24 hours after therapy. YHO-13351 control mice received YHO-13351 on the same schedule as when combined with irinotecan. Mice were euthanized and were classified as treatment failures when tumor size was >1 cm^3.

Additional in vitro testing was performed with additional ABCG2 agents and additional lines of SN-38-resistant tumor cell lines. The detailed description of the in vitro tests performed, and their results can be located in the cited literature.

Results

In mice with NCI-N87 tumors, both SG and irinotecan treatment resulted in a >2-fold increase in survival compared with no treatment (P<0.0001). No significant increase in survival was observed in mice with NCI-N87-S120 tumors. Compared with no treatment, administration of SG with YHO-13351 in mice with SN-38–resistant NCI-N87-S120 tumors resulted in a 64% improvement in survival (P=0.0278).

References

1. TRODELVY®, Gilead Sciences Inc. Trodelvy (sacituzumab govitecan-hziy) for injection, for intravenous use. U.S. Prescibing Information. Foster City, CA.
2. Alkassis S, Lipsyc-Sharf M, Traverso C, et al. Transcriptomic biomarkers of therapeutic response and resistance to antibody-drug conjugates in metastatic breast cancer: a comprehensive multi-center stutdy (#1041). Presented at: American Society of Clinical Oncology (ASCO); May 30 - June 3, 2025; Chicago, IL.
3. Coates JT, Sun S, Leshchiner I, et al. Parallel Genomic Alterations of Antigen and Payload Targets Mediate Polyclonal Acquired Clinical Resistance to Sacituzumab Govitecan in Triple-Negative Breast Cancer. *Cancer Discov.* 2021;11(10):2436-2445.

4. Chang CH, Wang Y, Zalath M, Liu D, Cardillo TM, Goldenberg DM. Combining ABCG2 Inhibitors with IMMU-132, an Anti-Trop-2 Antibody Conjugate of SN-38, Overcomes Resistance to SN-38 in Breast and Gastric Cancers. *Mol Cancer Ther.* 2016;15(8):1910-1919.

Abbreviations

ABC=ATP-binding cassette
ADC=antibody-drug conjugate
CL2A=hydrolysable linker
DOT=duration of treatment
HER2=human epidermal growth factor receptor 2
HR+/-=hormone receptor positive/negative
HR=hazard ratio
hRS7=humanized anti-Trop-2 monoclonal antibody
MGH=Massachusetts General Hospital
mTNBC=metastatic triple-negative breast cancer
OS=overall survival
PD=progressive disease
PFS=progression-free survival
PR=partial response
RECIST=Response Evaluation Criteria in Solid Tumors
SD=stable disease
SG=sacituzumab govitecan-hziy
SN-38=active metabolite of irinotecan
TACSTD2=tumor-associated calcium signal transducer 2
TNBC=triple-negative breast cancer
TOP1=topoisomerase 1
TP53=tumor protein p53
Trop-2=trophoblast cell surface antigen-2
WT=wild-type
YHO-13351=chemical inhibitor that targets the ABCG2 gene

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Trodelvy US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/oncology/trodelvy/trodelvy_pi.

Follow-Up

For any additional questions, please contact Gilead Medical Information at:

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