Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2025**; 30(11): 39310
https://doi.org/10.31083/FBL39310

Review

Interrogating the Involvement of Autophagy, Senescence, and the Immune System in the Actions of Sacituzumab Govitecan as an Anticancer Agent

Melanie M. Sinanian[1,2], Eesha Chakraborty[1,2], Ahmed M. Elshazly[1,2,3], Shady Azzam[1,2], Nada Nassif[1,2], David A. Gewirtz[1,2,*]

[1]Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, VA 23298, USA
[2]Massey Comprehensive Cancer Center, Virginia Commonwealth University, Richmond, VA 23298, USA
[3]Department of Pharmacology and Toxicology, Faculty of Pharmacy, Kafrelsheikh University, 33516 Kafrelsheikh, Egypt
*Correspondence: david.gewirtz@vcuhealth.org (David A. Gewirtz)

Academic Editor: Pedro Fonte
Submitted: 27 March 2025 Revised: 7 August 2025 Accepted: 14 August 2025 Published: 27 November 2025

Abstract

Antibody-drug conjugates (ADCs) are an emerging class of cancer therapeutics comprised of a tumor-targeting antibody linked to a cytotoxic payload. Sacituzumab govitecan (SG or IMMU-132) is comprised of a trophoblast cell-surface antigen 2 (TROP-2)-directed antibody linked to the topoisomerase 1 inhibitor, SN-38. SG was designed to exploit the overexpression of TROP-2, observed in a variety of different epithelial cancers, to enhance tumor-selective cytotoxicity while minimizing damage to normal tissues. SG is approved for pretreated metastatic triple-negative breast cancer (mTNBC) and hormone receptor-positive human epidermal growth factor receptor 2 (HER2) negative breast cancer patients. While SG has shown significant clinical benefit, the objective response rate (ORR) observed with SG in pretreated mTNBC patients in the Phase I/II basket study was 33.3%, indicating a heterogeneous response profile to SG. This article explores the potential influence of autophagy, senescence, and the patient's immune system on the treatment response.

Keywords: antibody-drug conjugates; sacituzumab govitecan; TROP-2; autophagy; senescence; immune system; drug combinations

1. Introduction

Antibody-drug conjugates (ADCs) are a promising class of biopharmaceuticals that consist of monoclonal antibodies linked to a cytotoxic payload. As a targeted therapeutic, ADCs are designed to selectively deliver a cytotoxic drug to cancer cells based on their overexpression of specific antigenic proteins, thereby minimizing the impact on healthy cells [1]. These drugs have recently emerged at the forefront of targeted cancer therapy. Currently, there are 15 Food and Drug administration (FDA)-approved ADCs and more than 78 ADC drugs at different stages in clinical trials. While this commentary focuses specifically on sacituzumab govitecan (SG) [2,3], the concepts discussed herein are likely to be generally relevant to all or most classes of ADCs.

SG is an FDA-approved ADC that targets Trophoblast cell-surface antigen 2 (TROP-2), a 40-kDa transmembrane glycoprotein that is overexpressed in a variety of cancers, including breast, lung, prostate, bladder and colorectal carcinomas [3–10]. High levels of TROP-2 expression are often associated with higher metastatic potential and increased tumor aggressiveness [5–7]. As a targeted approach, SG offers an alternative treatment option for patients with TROP-2-expressing cancers, particularly those with limited response to conventional therapies [2–4,6,11,12]. The main constituents of SG include the anti-TROP-2 monoclonal antibody, the SN-38 payload, which is a topoisomerase I inhibitor that is the active metabolite of the chemotherapeutic drug, irinotecan, and a pH-sensitive, hydrolysable linker, which binds the antibody to the drug [3,4,11–13].

All ADCs have three main components: an antibody targeted against a tumor-associated antigen, a linker, and a cytotoxic payload. The mechanism of action of SG (as well as majority of ADCs) involves tumor-targeted monoclonal antibody binding, endocytic internalization, lysosomal degradation and payload release, allowing for the cytotoxic action of SN-38 to be expressed largely at the tumor site. This process has been described quite extensively in previous literature [2,10,11]. While the dissociation of SN-38 from the antibody is a critical step, the overall efficacy of SG is a result of the combined effects of targeted delivery, effective internalization, and the potent cytotoxic action of SN-38 once it is released inside the cancer cell. Importantly, ADCs such as SG are not only capable of killing antigen-expressing cells following internalization, but also eliminate adjacent tumor cells that do not express the target antigen by releasing the drug in the tumor microenvironment due to its cleavable linker (often termed a bystander effect) [12–15].

To our knowledge, while both autophagy and senescence are well-established responses to both chemother-

apy and radiation that may influence therapeutic outcomes, there have been no published studies of either autophagy or senescence in response to SG in any preclinical models or cancer in the clinic. Studies of autophagy induced by other ADCs are indicated below.

2. Autophagy

Autophagy is a cellular process that is activated in response to various stressors, including nutrient deprivation, starvation, infection and hypoxia [16,17]. The autophagic machinery degrades unfolded proteins and damaged organelles to maintain cellular homeostasis and generate energy. Tumor cells also exploit autophagy for energy production, which facilitates their survival under stress. This form of autophagy, known as cytoprotective autophagy, plays a critical role in protecting tumors from the cytotoxic effects of various antineoplastic modalities [18–20]. Inhibiting cytoprotective autophagy through pharmacological or genetic methods typically increases the sensitivity of tumor cells to radiation or chemotherapy in preclinical models [19–24]. In addition to cytoprotective autophagy, other forms of autophagy that have been identified include cytotoxic, non-protective, and cytostatic autophagy, where the latter form is generally accompanied by senescence induction [25–28]. Targeting the cytoprotective form of autophagy utilizing autophagy inhibitors such as chloroquine (CQ) or hydroxychloroquine (HCQ) [16,18,29] or exploiting the autophagic machinery to degrade cellular proteins [30,31] also represents a promising strategy to enhance the efficacy of current antineoplastic therapies.

Although the relationship between autophagy and SG remains largely unexplored, the induction of autophagy in response to other ADCs have been documented in several studies [32–35]. For instance, trastuzumab conjugated with emtansine (T-DM1) induced autophagy in human epidermal growth factor receptor 2 (HER2)-positive human breast cancer cell lines, such as BT-474 and SK-BR-3 [32]. The induction of autophagic flux was confirmed through increased LC3I/II levels, autophagosome formation observed by transmission electron microscopy (TEM), and Cyto-ID autophagy green dye labeling. This study showed that autophagy inhibition using CQ suppressed the apoptosis induced by T-DM1 treatment, indicative of a cytotoxic role for the autophagic machinery in this tumor model [32]. Similar results were obtained with the autophagy inhibitor, LY294002, which partially suppressed the cytotoxicity of T-DM1 in both cell lines. Mechanistically, this study showed that autophagy induction was primarily mediated by suppression of the mTOR pathway.

In contrast to the results reported by Liu *et al*. [32], Zhang *et al*. [33] investigated trastuzumab-emtansine in HER2-positive gastric cancer and found that this antibody-drug conjugate induced cytoprotective autophagy. These investigators observed autophagy induction in NCI-N87 cells through multiple methods, including upregulation of LC3II, degradation of p62/SQSMT1, and Cyto-ID and Lysotracker double staining. Notably, the autophagy inhibitors 3-MA and LY294002 significantly enhanced the toxicity of T-DM1, suggesting a cytoprotective role for autophagy in this experimental model system. These findings were further confirmed *in vivo*, where combining T-DM1 with LY294002 resulted in greater antitumor activity compared to either treatment alone, with evidence for autophagy inhibition such as reduced LC3II levels and increased p62/SQSTM1 accumulation. The results of these studies by Liu *et al*. [32] and Zhang *et al*. [33] underscore the cell-context-dependent nature of autophagy [34,35], in addition to highlighting the autophagic switch phenomenon where one form of autophagy can transition into another, in part depending on the genetic makeup of the experimental model [36,37].

Another ADC linked to autophagic flux is Rituximab-Monomethyl Auristatin E (Rituximab-MMAE), in which rituximab binds to the anti-tubulin drug, MMAE [38–40]. Wang *et al*. [40] investigated the effects of Rituximab-MMAE in non-Hodgkin lymphoma (NHL) using Ramos and Daudi cells. Their *in vitro* studies demonstrated that Rituximab-MMAE induced significant dose-dependent cell death. These results were further confirmed *in vivo* using BABL/c nude mice, which were subcutaneously injected with Ramos or Daudi cells. In these models, MMAE showed notable anti-tumor activity. The study then explored autophagy induction, which was evidenced by autophagosome formation observed through transmission electron microscopy, increased LC3I/II levels, and degradation of p62/SQSTM1. Mechanistically, the authors found that Rituximab-MMAE induced autophagy through inhibition of the AKT/mTOR pathway. Interestingly, autophagy inhibition using CQ partially suppressed Rituximab-MMAE-induced toxicity. In contrast, treatment with rapamycin, a mammalian target of rapamycin (mTOR) inhibitor that promotes autophagy [27], further augmented the toxicity of Rituximab-MMAE, both *in vitro* and *in vivo*. These findings demonstrated the cytotoxic role of the autophagic machinery induced by Rituximab-MMAE in the NHL tumor model.

Similarly, Xu *et al*. [41] investigated the effects of MMAE conjugated to a TROP-2-targeted antibody, αTROP2, in pancreatic cancer. This study confirmed the cytotoxicity of αTROP2-MMAE *in vitro* using TROP-2-positive BxPC3 and PK59 cell lines, as measured by the cell counting kit 8 (CCK-8) assay. These findings were further validated *in vivo* in immunodeficient NCG mice injected subcutaneously with BxPC3 cells, where αTROP2-MMAE demonstrated significant antitumor activity. The induction of autophagic flux in this system was confirmed through autophagosome formation visualized by TEM, Cyto-ID staining, and increased LC3I/II levels alongside p62/SQSTM1 degradation. Autophagy induction was shown to be primarily mediated by inhibition of the mTOR pathway, as ev-

idenced by the reduced phosphorylation levels of key proteins such as Ak strain transforming (AKT), mTOR, Ribosomal protein S6 kinase beta-1 (P70S6K), and Eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1). Notably, autophagy inhibition using LY294002 enhanced the cytotoxicity of αTROP2-MMAE, as reflected by increased levels of apoptosis. Conversely, treatment with rapamycin, an mTOR activator, attenuated the antitumor efficacy of αTROP2-MMAE, suggesting a cytoprotective role of autophagic flux induced by this ADC in pancreatic cancer cells. These results were further confirmed *in vivo*, where the combination of αTROP2-MMAE and LY294002 showed significantly greater antitumor activity compared to either treatment alone.

In addition to the aforementioned conjugates, several other ADCs that utilize MMAEas a payload have also been investigated. For instance, αCLDN18.2-MMAE demonstrated cytoprotective autophagy in gastric cancer [42], while Nectin-4-MMAE induced cytoprotective autophagy in pancreatic cancer cells [43]. The latter conjugate mediated this autophagy response through inhibition of the mTOR pathway. Collectively, these findings provide strong evidence that autophagy is likely to also be induced in response to SG. It is important to note that different forms of autophagy have been induced by SN-38, the active metabolite of irinotecan, in several tumor models. These include cytoprotective autophagy in colorectal cancer [44], cytotoxic autophagy in gastric cancer [45], and cytoprotective autophagy in breast cancer [46], and in the HCT116-TP53 KO colon cancer cell line [47]. This raises the question of whether SG compounds will induce similar forms of autophagy to SN-38, or if the nature of autophagy will differ, as well as whether the autophagy induction would be through mTOR inhibition. Additionally, it prompts the inquiry of whether targeting autophagy could be a valid strategy to overcome or at least limit the development of resistance to the SG compound in those cases where the SG compound induces the cytoprotective form of autophagy.

3. Senescence

Another essentially ubiquitous response to cancer therapy that could influence tumor cell sensitivity to SG is cellular senescence. Senescence refers to a stable form of growth arrest, where tumor cells adapt to overcome the detrimental effects of radiation and chemotherapeutic agents, in part by suppressing apoptosis [48,49]. In addition to therapy-induced senescence (TIS), oncogene-induced senescence (OIS) and replicative senescence are well-established forms of prolonged growth arrest that reflect, respectively, efforts by the cell to prevent transformation and the shortening of telomeres after multiple cycles of replication in normal cells [50,51]. Extensive findings in recent literature have reported the recovery/escape of tumor populations from therapy-induced senescence [52,53]. Notably, these recovered populations often exhibit a more aggressive nature, suggesting that senescence may act as a reservoir for tumor cells that evade the cytotoxicity of chemotherapy and radiation, contributing to tumor dormancy and ultimately, disease recurrence [54,55].

The hallmarks of a senescent cell population are diverse, and include enlarged and flattened cell morphology, distorted nuclear morphology, genomic instability, upregulation of the lysosomal enzyme, β-galactosidase, apoptosis resistance due to the accumulation of anti-apoptotic proteins, cell cycle arrest associated with the upregulation of cell cycle regulatory proteins such as p16 and p21, generation of reactive oxygen species (ROS), altered metabolism, surface protein alteration, and mitochondrial disfunction [56]. Another critical element is the secretion of various chemokines, cytokines, growth factors and metalloproteinases [55–57] collectively termed the senescence-associated secretory phenotype (SASP) [57]. SASP factors can significantly alter the local tissue microenvironment and modulate both innate and adaptive immune responses, ultimately preventing the elimination of senescent cells. This can contribute to chronic inflammation, cancer progression and metastasis [49,57,58].

To our knowledge, there is essentially no information regarding the relationship between senescence and SG, or any other ADC, but some studies suggest that senescence may contribute to the development of resistance in SG or ADCs in general. For instance, one hallmark of senescence is the upregulation of anti-apoptotic proteins, which has been reported in resistance to the ADC, gemtuzumab-ozogamicin, in acute myeloid leukemia and to anti-CD79b-vc-MMAE in NHL cell lines [59,60]. Additionally, p21 accumulation, which almost universally accompanies senescence, was reported in the studies by Cardillo *et al.* [61] upon treatment with SG in HCC1806 (triple-negative breast cancer (TNBC)), S637 (human head and neck squamous cell carcinoma) and RT4 (bladder carcinoma) cell lines. ADC-induced senescence is likely to be related to the capacity of the ADC payloads to induce DNA damage (e.g., alkylating agents or topoisomerase inhibitors such as SN-38), whereas microtubule-targeting agents (auristatins and maytansinoids) may preferentially trigger apoptotic cell death [62]. Therefore, it appears highly likely that senescence will also prove to be a component of the tumor cell response to SG, given the evidence for senescence induction by both irinotecan and SN-38 [63–66].

4. Immunogenic Properties

Virtually all preclinical literature relating to SG (as well as other ADCs) involves studies in human tumor cells and cell lines either in culture or in immune-deficient tumor-bearing mice. This is chiefly due to ADCs being comprised of humanized antibodies, which are specific for the human antigen and not necessarily the mouse antigen [67] as well as that TROP-2 is largely considered to be a human tumor antigen. Consequently, there is little infor-

mation on the potential involvement of the immune system in sensitivity (or resistance) to ADCs.

Whereas SG is presumed to act primarily by delivering the potent cytotoxic agent, SN-38 to TROP-2 expressing cancer cells, the antibody itself may have intrinsic antitumor properties. TROP-2, the target antigen, is involved in regulating cell proliferation, survival, and migration, and TROP-2 overexpression is associated with aggressive tumor behavior in various cancers [5,7,8]. The anti-TROP-2 antibody component of SG may inhibit these tumor-promoting functions by blocking the ligand-receptor interactions necessary for TROP-2 signaling [3,68].

The antibody itself could mediate additional immune-related effects that contribute to the overall anti-tumor activity of SG by flagging the tumor cells for destruction by immune cells via antibody-dependent cellular cytotoxicity (ADCC) [69,70]. However, the native antibody's ADCC activity has been reported to be substantially reduced (by up to 60%), when it is conjugated to SN-38 to create SG [9]. In ADCC, antibodies enhance anti-cancer immunity when the Fc portion of the antibody binds to Fc receptors on immune effector cells, such as natural killer (NK) cells, macrophages and neutrophils. This binding triggers the immune cells to release cytotoxic molecules that induce the death of the target cancer cells [71,72], which could serve as an additional mechanism to target and eliminate TROP-2 positive tumor cells, enhancing the overall therapeutic effect of SG [73]. In addition to ADCC, complement-dependent cytotoxicity (CDC) is another possible immune-related mechanism that could enhance the action of SG. When the antibody binds to its target, TROP-2 , on the surface of tumor cells, it may activate the complement cascade, leading to the formation of the membrane attack complex (MAC), which can cause lysis of the tumor cells [74,75]. Although CDC is typically less potent than ADCC in the context of most ADCs, it could still play a role in enhancing SG's anti-tumor effects, particularly in tumors that are susceptible to complement activation [76]. However, there is currently no evidence for CDC activity associated with hRS7 (a humanized monoclonal antibody that targets the TROP-2 protein), or SG in the existing literature.

Finally, the tumor microenvironment (TME) can impact the effectiveness of SG and its immune-mediated mechanisms [77–79]. Tumors with an immunosuppressive microenvironment, characterized by the presence of regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs) or immune checkpoint molecules, may inhibit the ability of immune effector cells to fully engage in ADCC or CDC [80]. Conversely, treatment with SG might indirectly modulate the immune microenvironment by inducing tumor cell death, which could release neoantigens and promote the activation of adaptive immune responses [81]. This process, often referred to as immunogenic cell death, could contribute to the development of long-term immune memory and prevention of tumor recurrence [82]. Understanding these immune-related effects is crucial for optimizing ADC design and for identifying strategies to combine SG with other immunotherapies, ultimately paving the way for more effective and personalized cancer treatment regimens.

5. Combination and Sequential Treatments

Although monotherapies remain a highly relevant treatment approach, especially within the context of targeted treatments such as ADCs, combination and sequential treatments represent critically important therapeutic modalities [83]. Concurrent exposure to multiple agents allows for more effective elimination of the tumor cell population, with the therapies working additively, synergistically, or more likely through independent drug action [84]. While more pronounced and extensive tumor cell eradication observed in combination therapies translates to a more durable response and reduces the chance for acquired drug resistance, it is often associated with worse side effects for the patient [85]. Sequential treatments involving multiple therapies administered in a consecutive and scheduled manner may yield similar benefits without the disadvantage of additional toxicities.

While targeted therapies such as ADCs are designed to improve specificity towards cancer cells, enhancing the overall tumor response as well as limiting exposure to healthy cells, their utilization also faces the hurdles of tumor heterogeneity and drug resistance [86]. Thus, targeted therapies such as ADCs used in combination or in sequence with other treatments, including chemotherapies, immunotherapies, and hormone therapies, represent an appealing therapeutic approach. A number of combinational preclinical studies have been reported, with the aims of confirming and understanding mechanisms, evaluating for efficacy, assessing treatment design, and testing for safety profiles.

A study performed by Chang *et al.* [87] demonstrated an improved response to SG in combination with the ATP-binding cassette sub-family G member 2 (ABCG2) inhibitors Ko143 and YHO-13351 in SN-38-resistant breast and stomach cancer cell lines. The results from their *in vivo* studies, which evaluated the combination treatment of YHO-13351 and SG in NCr female athymic nude (*nu*/*nu*) mice bearing SN-38-resistant stomach cell line xenografts, indicated a 64% increased survival versus untreated animals [87].

Studies by Cardillo *et al.* [88] explored combination treatments of SG with the Poly(ADP-ribose) polymerase (PARP) inhibitors, olaparib, rucaparib, or talazoparib in BRCA1/2–wild-type TNBCs. The combination synergistically inhibited the growth of multiple breast cancers, causing increased DNA damage (double-strand-DNA breaks evaluated through Phospho-Histone H2AX, a histone variant protein crucial for DNA repair) and appeared to work independently of *BRCA1/2* status. Fur-

thermore, results from tumor-bearing NCr female athymic nude (*nu*/*nu*) mice demonstrated significant antitumor effects and survival benefits versus any monotherapy administration alone. These results, along with the favorable toxicity profiles generated from additional studies in BALB/c mice demonstrated a promising therapeutic strategy and influenced the design of clinical trials (NCT04039230) and (NCT03992131). In the former, sequential treatment of SG followed by talazoparib, but not simultaneous combination therapy, was shown to be effective for patients with TNBC (NCT04039230) [89]. In the latter trial (NCT03992131), the PARP inhibitor rucaparib, FGFR and VEGFR inhibitor Lucitanib, and SG were evaluated in combination, and although the initial studies showed favorable antitumor effects, this study was terminated due to dose-limiting toxicities.

A recent finding by Cardillo *et al*. [61] demonstrated additive-like interactions of carboplatin or cisplatin with SG in TNBC, urothelial, and NSLC cell lines, which trended toward synergism at higher concentrations. Their *in vitro* work also demonstrated that the combination treatment, shifted cell fates towards apoptosis, indicated by relative ratios of pro- and anti-apoptotic proteins including B-cell lymphoma 2 (BCL-2) associated X, apoptosis regulator (Bax) ratio to BCl-2 (Bax:Bcl-2), and induced myeloid leukemia cell differentiation protein (MCL-1) and survivin expression. *In vivo* investigations showed significant antitumor effects versus controls of SG with carboplatin as well as SG with cisplatin in models of triple negative breast cancer, and small cell lung cancer (SCLC) tumor-bearing mice. Importantly, the combinations were well tolerated by the animals [61].

Bardia *et al*. [89] performed *in vitro* studies in TNBC cell lines which influenced the design of sequential treatment of SG followed by PARP inhibition in a clinical trial (NCT04039230). Sequential treatment with SG followed by talazoparib stabilized the (topoisomerase 1) TOP1 cleavage complex, leading to increased DNA damage, as indicated by Phospho-Histone H2AX levels, and ultimately promoting apoptosis. This design of sequential treatment with SG followed by PARPi not only proved to be efficacious but also exhibited a much more tolerable toxicity profile than the concurrent combination treatment [89].

Similarly, preclinical analyses evaluating the combination of the investigational compound and WEE1 G2 checkpoint kinase (WEE1) tyrosine kinase inhibitor, Debio123, with SG [90] informed a currently recruiting clinical trial (NCT06612203), WIN-B, which is evaluating the safety and activity of the combination in patients with TNBC as well as HR+/HER2- BC. Preclinical *in vitro* studies showed that the combination exhibited synergy in breast, colorectal cancer (CRC), and glioblastoma cell lines. *In vivo* studies of TNBC xenografts in the highly immunodeficient (NSG) laboratory mice lacking T cells, B cells, and natural killer (NK) cells showed sustained complete regression in TROP-high expressing tumors as well as reduced metastasis and improved response in TROP-low expressing tumors [90].

Parameters that could be investigated in preclinical settings to better guide clinical studies include the determination of novel efficacious combinational treatments with SG, elimination and/or inclusion of cancer types for a proposed treatment combination, determination of necessity and prevalence of specific biomarkers or characteristics of a malignancy, discovery of the best treatment scheduling and regimens, and assessments for toxicity profiles.

6. Conclusions

SN-38, the payload for SG, is approximately 1000 times more potent than irinotecan, and its conjugation with an antibody targeting TROP-2 was hypothesized to enhance its efficacy by concentrating its action specifically within tumor cells, thus minimizing off-target toxicity. However, tumor cell overexpression of TROP-2, while often associated with SG efficacy, is unlikely to be the sole predictor of its effectiveness. Tumor-specific factors that influence ADC efficacy can include the promotion of autophagy and senescence and the potential involvement of the immune system. The latter has received little attention since virtually all tumor-bearing animal studies have been performed with immune-deficient mice implanted with human tumors. Finally, integrating SG with other chemotherapeutic agents, targeted therapies, or immune checkpoint inhibitors could potentially improve patient outcomes. However, there are only a limited number of preclinical studies in which such combinations or sequential treatments have been evaluated.

Author Contributions

AME, SA, NN, and DAG prepared the initial draft and contributed to early conceptual development. MMS and EC substantially revised and rewrote the manuscript, conducted the literature search, expanding and refining the overall content. All authors contributed to critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

Given his role as the Guest Editor, David A. Gewirtz had no involvement in the peer-review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Pedro Fonte. The other authors declare no conflict of interest.

References

[1] Tarantino P, Carmagnani Pestana R, Corti C, Modi S, Bardia A, Tolaney SM, *et al*. Antibody-drug conjugates: Smart chemotherapy delivery across tumor histologies. CA: a Cancer Journal for Clinicians. 2022; 72: 165–182. https://doi.org/10.3322/caac.21705.

[2] Desai A, Abdayem P, Adjei AA, Planchard D. Antibody-drug conjugates: A promising novel therapeutic approach in lung cancer. Lung Cancer (Amsterdam, Netherlands). 2022; 163: 96–106. https://doi.org/10.1016/j.lungcan.2021.12.002.

[3] Rossi V, Turati A, Rosato A, Carpanese D. Sacituzumab govitecan in triple-negative breast cancer: from bench to bedside, and back. Frontiers in Immunology. 2024; 15: 1447280. https://doi.org/10.3389/fimmu.2024.1447280.

[4] Bardia A, Messersmith WA, Kio EA, Berlin JD, Vahdat L, Masters GA, *et al*. Sacituzumab govitecan, a Trop-2-directed antibody-drug conjugate, for patients with epithelial cancer: final safety and efficacy results from the phase I/II IMMU-132-01 basket trial. Annals of Oncology. 2021; 32: 746–756. https://doi.org/10.1016/j.annonc.2021.03.005.

[5] Ohmachi T, Tanaka F, Mimori K, Inoue H, Yanaga K, Mori M. Clinical significance of TROP2 expression in colorectal cancer. Clinical Cancer Research. 2006; 12: 3057–3063. https://doi.org/10.1158/1078-0432.CCR-05-1961.

[6] Tagawa ST, Balar AV, Petrylak DP, Kalebasty AR, Loriot Y, Fléchon A, *et al*. TROPHY-U-01: A Phase II Open-Label Study of Sacituzumab Govitecan in Patients With Metastatic Urothelial Carcinoma Progressing After Platinum-Based Chemotherapy and Checkpoint Inhibitors. Journal of Clinical Oncology. 2021; 39: 2474–2485. https://doi.org/10.1200/JCO.20.03489.

[7] Trerotola M, Jernigan DL, Liu Q, Siddiqui J, Fatatis A, Languino LR. Trop-2 promotes prostate cancer metastasis by modulating β(1) integrin functions. Cancer Research. 2013; 73: 3155–3167. https://doi.org/10.1158/0008-5472.CAN-12-3266.

[8] Pak MG, Shin DH, Lee CH, Lee MK. Significance of EpCAM and TROP2 expression in non-small cell lung cancer. World Journal of Surgical Oncology. 2012; 10: 53. https://doi.org/10.1186/1477-7819-10-53.

[9] Cardillo TM, Govindan SV, Sharkey RM, Trisal P, Arrojo R, Liu D, *et al*. Sacituzumab Govitecan (IMMU-132), an Anti-Trop-2/SN-38 Antibody-Drug Conjugate: Characterization and Efficacy in Pancreatic, Gastric, and Other Cancers. Bioconjugate Chemistry. 2015; 26: 919–931. https://doi.org/10.1021/acs.bioconjchem.5b00223.

[10] Sakach E, Sacks R, Kalinsky K. Trop-2 as a Therapeutic Target in Breast Cancer. Cancers. 2022; 14: 5936. https://doi.org/10.3390/cancers14235936.

[11] Pavone G, Motta L, Martorana F, Motta G, Vigneri P. A New Kid on the Block: Sacituzumab Govitecan for the Treatment of Breast Cancer and Other Solid Tumors. Molecules (Basel, Switzerland). 2021; 26: 7294. https://doi.org/10.3390/molecules26237294.

[12] Bardia A, Mayer IA, Vahdat LT, Tolaney SM, Isakoff SJ, Diamond JR, *et al*. Sacituzumab Govitecan-hziy in Refractory Metastatic Triple-Negative Breast Cancer. The New England Journal of Medicine. 2019; 380: 741–751. https://doi.org/10.1056/NEJMoa1814213.

[13] Goldenberg DM, Sharkey RM. Antibody-drug conjugates targeting TROP-2 and incorporating SN-38: A case study of anti-TROP-2 sacituzumab govitecan. MAbs. 2019; 11: 987–995. https://doi.org/10.1080/19420862.2019.1632115.

[14] Staudacher AH, Brown MP. Antibody drug conjugates and bystander killing: is antigen-dependent internalisation required? British Journal of Cancer. 2017; 117: 1736–1742. https://doi.org/10.1038/bjc.2017.367.

[15] Khera E, Dong S, Huang H, de Bever L, van Delft FL, Thurber GM. Cellular-Resolution Imaging of Bystander Payload Tissue Penetration from Antibody-Drug Conjugates. Molecular Cancer Therapeutics. 2022; 21: 310–321. https://doi.org/10.1158/1535-7163.MCT-21-0580.

[16] Elshazly AM, Gewirtz DA. Is Autophagy Inhibition in Combination with Temozolomide a Therapeutically Viable Strategy? Cells. 2023; 12: 535. https://doi.org/10.3390/cells12040535.

[17] Kroemer G, Mariño G, Levine B. Autophagy and the integrated stress response. Molecular Cell. 2010; 40: 280–293. https://doi.org/10.1016/j.molcel.2010.09.023.

[18] Moreau K, Luo S, Rubinsztein DC. Cytoprotective roles for autophagy. Current Opinion in Cell Biology. 2010; 22: 206–211. https://doi.org/10.1016/j.ceb.2009.12.002.

[19] Zhang L, Zhu Y, Zhang J, Zhang L, Chen L. Inhibiting Cytoprotective Autophagy in Cancer Therapy: An Update on Pharmacological Small-Molecule Compounds. Frontiers in Pharmacology. 2022; 13: 966012. https://doi.org/10.3389/fphar.2022.966012.

[20] Xiao M, Benoit A, Hasmim M, Duhem C, Vogin G, Berchem G, *et al*. Targeting Cytoprotective Autophagy to Enhance Anticancer Therapies. Frontiers in Oncology. 2021; 11: 626309. https://doi.org/10.3389/fonc.2021.626309.

[21] Chaachouay H, Ohneseit P, Toulany M, Kehlbach R, Multhoff G, Rodemann HP. Autophagy contributes to resistance of tumor cells to ionizing radiation. Radiotherapy and Oncology. 2011; 99: 287–292. https://doi.org/10.1016/j.radonc.2011.06.002.

[22] Elshazly AM, Gewirtz DA. Making the Case for Autophagy Inhibition as a Therapeutic Strategy in Combination with Androgen-Targeted Therapies in Prostate Cancer. Cancers. 2023; 15: 5029. https://doi.org/10.3390/cancers15205029.

[23] Yang ZJ, Chee CE, Huang S, Sinicrope FA. The role of autophagy in cancer: therapeutic implications. Molecular Cancer Therapeutics. 2011; 10: 1533–1541. https://doi.org/10.1158/1535-7163.MCT-11-0047.

[24] Hassan AMIA, Zhao Y, Chen X, He C. Blockage of Autophagy for Cancer Therapy: A Comprehensive Review. International Journal of Molecular Sciences. 2024; 25: 7459. https://doi.org/10.3390/ijms25137459.

[25] Gewirtz DA. The four faces of autophagy: implications for cancer therapy. Cancer Research. 2014; 74: 647–651. https://doi.org/10.1158/0008-5472.CAN-13-2966.

[26] Elshazly AM, Gewirtz DA. Cytoprotective, Cytotoxic and Cytostatic Roles of Autophagy in Response to BET Inhibitors. International Journal of Molecular Sciences. 2023; 24: 12669. https://doi.org/10.3390/ijms241612669.

[27] Elshazly AM, Elzahed AA, Gewirtz DA. The Cytoprotective and Cytotoxic Functions of Autophagy in Response to mTOR Inhibitors. Frontiers in Bioscience (Landmark Edition). 2024; 29: 231. https://doi.org/10.31083/j.fbl2906231.

[28] Bai Z, Peng Y, Ye X, Liu Z, Li Y, Ma L. Autophagy and cancer treatment: four functional forms of autophagy and their therapeutic applications. Journal of Zhejiang University. Science. B. 2022; 23: 89–101. https://doi.org/10.1631/jzus.B2100804.

[29] Mulcahy Levy JM, Zahedi S, Griesinger AM, Morin A, Davies KD, Aisner DL, *et al*. Autophagy inhibition overcomes multiple mechanisms of resistance to BRAF inhibition in brain tumors.

eLife. 2017; 6: e19671. https://doi.org/10.7554/eLife.19671.
[30] Ji CH, Kim HY, Lee MJ, Heo AJ, Park DY, Lim S, *et al*. The AUTOTAC chemical biology platform for targeted protein degradation via the autophagy-lysosome system. Nature Communications. 2022; 13: 904. https://doi.org/10.1038/s41467-022-28520-4.
[31] Elshazly AM, Hosseini N, Shen S, Neely V, Harada H, Grant S, *et al*. Proteasome Inhibition Enhances Lysosome-mediated Targeted Protein Degradation. bioRxiv. 2025. https://doi.org/10.1101/2025.01.31.634950. (preprint)
[32] Liu P, Fan J, Wang Z, Zai W, Song P, Li Y, *et al*. The role of autophagy in the cytotoxicity induced by trastuzumab emtansine (T-DM1) in HER2-positive breast cancer cells. AMB Express. 2020; 10: 107. https://doi.org/10.1186/s13568-020-01044-0.
[33] Zhang J, Fan J, Zeng X, Nie M, Chen W, Wang Y, *et al*. Correction: Targeting the autophagy promoted antitumor effect of T-DM1 on HER2-positive gastric cancer. Cell Death & Disease. 2023; 14: 633. https://doi.org/10.1038/s41419-023-06061-y.
[34] Finnegan RM, Elshazly AM, Schoenlein PV, Gewirtz DA. Therapeutic Potential for Targeting Autophagy in ER+ Breast Cancer. Cancers. 2022; 14: 4289. https://doi.org/10.3390/cancers14174289.
[35] Elshazly AM, Elzahed AA, Gewirtz DA. Evidence for cytoprotective autophagy in response to HER2-targeted monoclonal antibodies. The Journal of Pharmacology and Experimental Therapeutics. 2025; 392: 100007. https://doi.org/10.1124/jpet.123.002048.
[36] Gewirtz DA. The Switch between Protective and Nonprotective Autophagy; Implications for Autophagy Inhibition as a Therapeutic Strategy in Cancer. Biology. 2020; 9: 12. https://doi.org/10.3390/biology9010012.
[37] Gewirtz DA. An autophagic switch in the response of tumor cells to radiation and chemotherapy. Biochemical Pharmacology. 2014; 90: 208–211. https://doi.org/10.1016/j.bcp.2014.05.016.
[38] Best RL, LaPointe NE, Azarenko O, Miller H, Genualdi C, Chih S, *et al*. Microtubule and tubulin binding and regulation of microtubule dynamics by the antibody drug conjugate (ADC) payload, monomethyl auristatin E (MMAE): Mechanistic insights into MMAE ADC peripheral neuropathy. Toxicology and Applied Pharmacology. 2021; 421: 115534. https://doi.org/10.1016/j.taap.2021.115534.
[39] Hingorani DV, Allevato MM, Camargo MF, Lesperance J, Quraishi MA, Aguilera J, *et al*. Monomethyl auristatin antibody and peptide drug conjugates for trimodal cancer chemo-radioimmunotherapy. Nature Communications. 2022; 13: 3869. https://doi.org/10.1038/s41467-022-31601-z.
[40] Wang Y, Zhang X, Fan J, Chen W, Luan J, Nan Y, *et al*. Activating Autophagy Enhanced the Antitumor Effect of Antibody Drug Conjugates Rituximab-Monomethyl Auristatin E. Frontiers in Immunology. 2018; 9: 1799. https://doi.org/10.3389/fimmu.2018.01799.
[41] Xu C, Huang X, Hu Q, Xue W, Zhou K, Li X, *et al*. Modulating autophagy to boost the antitumor efficacy of TROP2-directed antibody-drug conjugate in pancreatic cancer. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie. 2024; 180: 117550. https://doi.org/10.1016/j.biopha.2024.117550.
[42] Xue W, Xu C, Zhang K, Cui L, Huang X, Nan Y, *et al*. Enhancing antitumor efficacy of CLDN18.2-directed antibody-drug conjugates through autophagy inhibition in gastric cancer. Cell Death Discovery. 2024; 10: 393. https://doi.org/10.1038/s41420-024-02167-0.
[43] Fu R, Wang C, Yin T, Zhang X, Xu Y, Shi Y, *et al*. A novel and promising therapeutic approach for treating pancreatic cancer: Nectin 4 targeted antibody drug conjugates alone or combined with autophagy inhibitors. International Journal of Molecular Medicine. 2025; 55: 66. https://doi.org/10.3892/ijmm.2025.5507.
[44] Chen P, Luo X, Nie P, Wu B, Xu W, Shi X, *et al*. CQ synergistically sensitizes human colorectal cancer cells to SN-38/CPT-11 through lysosomal and mitochondrial apoptotic pathway via p53-ROS cross-talk. Free Radical Biology & Medicine. 2017; 104: 280–297. https://doi.org/10.1016/j.freeradbiomed.2017.01.033.
[45] Zhu Q, Guo Y, Chen S, Fu D, Li Y, Li Z, *et al*. Irinotecan Induces Autophagy-Dependent Apoptosis and Positively Regulates ROS-Related JNK- and P38-MAPK Pathways in Gastric Cancer Cells. OncoTargets and Therapy. 2020; 13: 2807–2817. https://doi.org/10.2147/OTT.S240803.
[46] Zhang S, Dong Y, Chen X, Tan CSH, Li M, Miao K, *et al*. Toosendanin, a late-stage autophagy inhibitor, sensitizes triple-negative breast cancer to irinotecan chemotherapy. Chinese Medicine. 2022; 17: 55. https://doi.org/10.1186/s13020-022-00605-8.
[47] Paillas S, Causse A, Marzi L, de Medina P, Poirot M, Denis V, *et al*. MAPK14/p38α confers irinotecan resistance to TP53-defective cells by inducing survival autophagy. Autophagy. 2012; 8: 1098–1112. https://doi.org/10.4161/auto.20268.
[48] McGrath MK, Abolhassani A, Guy L, Elshazly AM, Barrett JT, Mivechi NF, *et al*. Autophagy and senescence facilitate the development of antiestrogen resistance in ER positive breast cancer. Frontiers in Endocrinology. 2024; 15: 1298423. https://doi.org/10.3389/fendo.2024.1298423.
[49] Zeng S, Shen WH, Liu L. Senescence and Cancer. Cancer Translational Medicine. 2018; 4: 70–74. https://doi.org/10.4103/ctm.ctm_22_18.
[50] HAYFLICK L, MOORHEAD PS. The serial cultivation of human diploid cell strains. Experimental Cell Research. 1961; 25: 585–621. https://doi.org/10.1016/0014-4827(61)90192-6.
[51] Serrano M, Lin AW, McCurrach ME, Beach D, Lowe SW. Oncogenic ras provokes premature cell senescence associated with accumulation of p53 and p16INK4a. Cell. 1997; 88: 593–602. https://doi.org/10.1016/s0092-8674(00)81902-9.
[52] Saleh T, Tyutyunyk-Massey L, Gewirtz DA. Tumor Cell Escape from Therapy-Induced Senescence as a Model of Disease Recurrence after Dormancy. Cancer Research. 2019; 79: 1044–1046. https://doi.org/10.1158/0008-5472.CAN-18-3437.
[53] Saleh T, Khasawneh AI, Himsawi N, Abu-Raideh J, Ejeilat V, Elshazly AM, *et al*. Senolytic Therapy: A Potential Approach for the Elimination of Oncogene-Induced Senescent HPV-Positive Cells. International Journal of Molecular Sciences. 2022; 23: 15512. https://doi.org/10.3390/ijms232415512.
[54] Saleh T, Gewirtz DA. Considering therapy-induced senescence as a mechanism of tumour dormancy contributing to disease recurrence. British Journal of Cancer. 2022; 126: 1363–1365. https://doi.org/10.1038/s41416-022-01787-6.
[55] DeLuca VJ, Saleh T. Insights into the role of senescence in tumor dormancy: mechanisms and applications. Cancer Metastasis Reviews. 2023; 42: 19–35. https://doi.org/10.1007/s10555-023-10082-6.
[56] Liu Y, Lomeli I, Kron SJ. Therapy-Induced Cellular Senescence: Potentiating Tumor Elimination or Driving Cancer Resistance and Recurrence? Cells. 2024; 13: 1281. https://doi.org/10.3390/cells13151281.
[57] Cuollo L, Antonangeli F, Santoni A, Soriani A. The Senescence-Associated Secretory Phenotype (SASP) in the Challenging Future of Cancer Therapy and Age-Related Diseases. Biology. 2020; 9: 485. https://doi.org/10.3390/biology9120485.
[58] Elshazly AM, Shahin U, Al Shboul S, Gewirtz DA, Saleh T. A Conversation with ChatGPT on Contentious Issues in Senescence and Cancer Research. Molecular Pharmacology. 2024; 105: 313–327. https://doi.org/10.1124/molpharm.124.000871.

[59] Walter RB, Raden BW, Cronk MR, Bernstein ID, Appelbaum FR, Banker DE. The peripheral benzodiazepine receptor ligand PK11195 overcomes different resistance mechanisms to sensitize AML cells to gemtuzumab ozogamicin. Blood. 2004; 103: 4276–4284. https://doi.org/10.1182/blood-2003-11-3825.

[60] Dornan D, Bennett F, Chen Y, Dennis M, Eaton D, Elkins K, *et al*. Therapeutic potential of an anti-CD79b antibody-drug conjugate, anti-CD79b-vc-MMAE, for the treatment of non-Hodgkin lymphoma. Blood. 2009; 114: 2721–2729. https://doi.org/10.1182/blood-2009-02-205500.

[61] Cardillo TM, Zalath MB, Arrojo R, Sharkey RM, Govindan SV, Chang CH, *et al*. Sacituzumab govitecan plus platinum-based chemotherapy mediates significant antitumor effects in triple-negative breast, urinary bladder, and small-cell lung carcinomas. Oncotarget. 2024; 15: 144–158. https://doi.org/10.18632/oncotarget.28559.

[62] Čermák V, Dostál V, Jelínek M, Libusová L, Kovář J, Rösel D, *et al*. Microtubule-targeting agents and their impact on cancer treatment. European Journal of Cell Biology. 2020; 99: 151075. https://doi.org/10.1016/j.ejcb.2020.151075.

[63] Milczarek M. The Premature Senescence in Breast Cancer Treatment Strategy. Cancers. 2020; 12: 1815. https://doi.org/10.3390/cancers12071815.

[64] te Poele RH, Okorokov AL, Jardine L, Cummings J, Joel SP. DNA damage is able to induce senescence in tumor cells in vitro and in vivo. Cancer Research. 2002; 62: 1876–1883.

[65] Pioger A, Loison I, Metatla I, Spruyt N, Abbadie C, Dehennaut V. Comparative analysis of senescence induction by different chemotherapeutic agents in HCT116 colon cancer cells. Biochemical and Biophysical Research Communications. 2025; 752: 151482. https://doi.org/10.1016/j.bbrc.2025.151482.

[66] Sallbach J, Woods M, Rasenberger B, Christmann M, Tomicic MT. The cell cycle inhibitor p21^{CIP1} is essential for irinotecan-induced senescence and plays a decisive role in resensitization of temozolomide-resistant glioblastoma cells to irinotecan. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie. 2024; 181: 117634. https://doi.org/10.1016/j.biopha.2024.117634.

[67] Cardillo TM, Govindan SV, Sharkey RM, Trisal P, Goldenberg DM. Humanized anti-Trop-2 IgG-SN-38 conjugate for effective treatment of diverse epithelial cancers: preclinical studies in human cancer xenograft models and monkeys. Clinical Cancer Research. 2011; 17: 3157–3169. https://doi.org/10.1158/1078-0432.CCR-10-2939.

[68] Tong Y, Fan X, Liu H, Liang T. Advances in Trop-2 targeted antibody-drug conjugates for breast cancer: mechanisms, clinical applications, and future directions. Frontiers in Immunology. 2024; 15: 1495675. https://doi.org/10.3389/fimmu.2024.1495675.

[69] Bignotti E, Ravaggi A, Romani C, Falchetti M, Lonardi S, Facchetti F, *et al*. Trop-2 overexpression in poorly differentiated endometrial endometrioid carcinoma: implications for immunotherapy with hRS7, a humanized anti-trop-2 monoclonal antibody. International Journal of Gynecological Cancer. 2011; 21: 1613–1621. https://doi.org/10.1097/IGC.0b013e318228f6da.

[70] Varughese J, Cocco E, Bellone S, Ratner E, Silasi DA, Azodi M, *et al*. Cervical carcinomas overexpress human trophoblast cell-surface marker (Trop-2) and are highly sensitive to immunotherapy with hRS7, a humanized monoclonal anti-Trop-2 antibody. American Journal of Obstetrics and Gynecology. 2011; 205: 567.e1–7. https://doi.org/10.1016/j.ajog.2011.06.093.

[71] Wang W, Erbe AK, Hank JA, Morris ZS, Sondel PM. NK Cell-Mediated Antibody-Dependent Cellular Cytotoxicity in Cancer Immunotherapy. Frontiers in Immunology. 2015; 6: 368. https://doi.org/10.3389/fimmu.2015.00368.

[72] van Erp EA, Luytjes W, Ferwerda G, van Kasteren PB. Fc-Mediated Antibody Effector Functions During Respiratory Syncytial Virus Infection and Disease. Frontiers in Immunology. 2019; 10: 548. https://doi.org/10.3389/fimmu.2019.00548.

[73] Hubert P, Amigorena S. Antibody-dependent cell cytotoxicity in monoclonal antibody-mediated tumor immunotherapy. Oncoimmunology. 2012; 1: 103–105. https://doi.org/10.4161/onci.1.1.17963.

[74] Shastry M, Jacob S, Rugo HS, Hamilton E. Antibody-drug conjugates targeting TROP-2: Clinical development in metastatic breast cancer. Breast (Edinburgh, Scotland). 2022; 66: 169–177. https://doi.org/10.1016/j.breast.2022.10.007.

[75] ADCC and CDC Assay: Validation and Optimization. BioAgilytix. 2022. Available at: https://www.bioagilytix.com/blog/adcc-and-cdc-assay-validation-and-optimization/ (Accessed: 14 March 2025).

[76] Rogers LM, Veeramani S, Weiner GJ. Complement in monoclonal antibody therapy of cancer. Immunologic Research. 2014; 59: 203–210. https://doi.org/10.1007/s12026-014-8542-z.

[77] Bai R, Cui J. Development of Immunotherapy Strategies Targeting Tumor Microenvironment Is Fiercely Ongoing. Frontiers in Immunology. 2022; 13: 890166. https://doi.org/10.3389/fimmu.2022.890166.

[78] Czajka-Francuz P, Prendes MJ, Mankan A, Quintana Á, Pabla S, Ramkissoon S, *et al*. Mechanisms of immune modulation in the tumor microenvironment and implications for targeted therapy. Frontiers in Oncology. 2023; 13: 1200646. https://doi.org/10.3389/fonc.2023.1200646.

[79] Tang T, Huang X, Zhang G, Hong Z, Bai X, Liang T. Advantages of targeting the tumor immune microenvironment over blocking immune checkpoint in cancer immunotherapy. Signal Transduction and Targeted Therapy. 2021; 6: 72. https://doi.org/10.1038/s41392-020-00449-4.

[80] Chaudhary B, Elkord E. Regulatory T Cells in the Tumor Microenvironment and Cancer Progression: Role and Therapeutic Targeting. Vaccines. 2016; 4: 28. https://doi.org/10.3390/vaccines4030028.

[81] Calvillo-Rodríguez KM, Lorenzo-Anota HY, Rodríguez-Padilla C, Martínez-Torres AC, Scott-Algara D. Immunotherapies inducing immunogenic cell death in cancer: insight of the innate immune system. Frontiers in Immunology. 2023; 14: 1294434. https://doi.org/10.3389/fimmu.2023.1294434.

[82] Aghanejad A, Bonab SF, Sepehri M, Haghighi FS, Tarighatnia A, Kreiter C, *et al*. A review on targeting tumor microenvironment: The main paradigm shift in the mAb-based immunotherapy of solid tumors. International Journal of Biological Macromolecules. 2022; 207: 592–610. https://doi.org/10.1016/j.ijbiomac.2022.03.057.

[83] Bayat Mokhtari R, Homayouni TS, Baluch N, Morgatskaya E, Kumar S, Das B, *et al*. Combination therapy in combating cancer. Oncotarget. 2017; 8: 38022–38043. https://doi.org/10.18632/oncotarget.16723.

[84] Plana D, Palmer AC, Sorger PK. Independent Drug Action in Combination Therapy: Implications for Precision Oncology. Cancer Discovery. 2022; 12: 606–624. https://doi.org/10.1158/2159-8290.CD-21-0212.

[85] Palmer AC, Sorger PK. Combination Cancer Therapy Can Confer Benefit via Patient-to-Patient Variability without Drug Additivity or Synergy. Cell. 2017; 171: 1678–1691.e13. https://doi.org/10.1016/j.cell.2017.11.009.

[86] Lopez JS, Banerji U. Combine and conquer: challenges for targeted therapy combinations in early phase trials. Nature Reviews. Clinical Oncology. 2017; 14: 57–66. https://doi.org/10.1038/nrclinonc.2016.96.

[87] 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. Molecular Cancer Therapeutics. 2016; 15: 1910–1919. https://doi.org/10.1158/1535-7163.MCT-16-0219.

[88] Cardillo TM, Sharkey RM, Rossi DL, Arrojo R, Mostafa AA, Goldenberg DM. Synthetic Lethality Exploitation by an Anti-Trop-2-SN-38 Antibody-Drug Conjugate, IMMU-132, Plus PARP Inhibitors in *BRCA1/2*-wild-type Triple-Negative Breast Cancer. Clinical Cancer Research. 2017; 23: 3405–3415. https://doi.org/10.1158/1078-0432.CCR-16-2401.

[89] Bardia A, Sun S, Thimmiah N, Coates JT, Wu B, Abelman RO, *et al*. Antibody–Drug Conjugate Sacituzumab Govitecan Enables a Sequential TOP1/PARP Inhibitor Therapy Strategy in Patients with Breast Cancer. Clinical Cancer Research. 2024; 30: 2917–2924. https://doi.org/10.1158/1078-0432.CCR-24-0428.

[90] Anti-Tumor Activity of Debio 0123 in Combination with Sacituzumab Govitecan in Preclinical Models of Breast Cancer. Debiopharm. 2024. Available at: https://www.debiopharm.com/drug-development/publications/anti-tumor-activity-of-debio-0123-in-combination-with-sacituzumab-govitecan-in-preclinical-models-of-breast-cancer/ (Accessed: 17 July 2025).