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Review Article

# Gamma Secretase Inhibitors in Cancer

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**Abstract:** Gamma secretase inhibitors (GSIs), for Alzheimer's disease treatment, have been repurposed as anticancer agents because they inhibit receptor cleavage. Preclinical studies suggested that GSIs effectively promote the differentiation and apoptosis of cancer stem-like cells while obstructing epithelial-to-mesenchymal transition and increasing sensitivity to conventional chemotherapy and radiotherapies. However, their clinical application remains limited, as GSIs have shown minimal efficacy in the majority of solid tumors, with significant exceptions including central nervous system malignancies and desmoid tumors. It highlights several unresolved questions, including their overall impact on anticancer immune responses and whether targeting tumor-intrinsic compensatory pathways would be necessary for achieving optimal results. Advancing our understanding of GSI mechanisms is critical for effectively integrating these inhibitors into combination therapies and addressing Notch-dependent cancers. This review aims to provide a comprehensive overview of GSI mechanisms, analyze their clinical effects thus far, and propose future research directions. It emphasizes the importance of evaluating GSIs' effects on immune responses in cancer patients and overcoming tumor-intrinsic resistance to unlock their full therapeutic potential, paving the way for more effective combinatorial strategies in oncology.

**Keywords:** GSIs, Notch signaling, Cancer stem-like cells, EMT, Immune responses in cancer, Combinatorial cancer therapy

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## 1. INTRODUCTION

Initiatives to reduce the formation of amyloid beta in Alzheimer's disease have prompted the creation of GSIs, several of which have advanced to phase III clinical trials. However, these drugs have faced challenges, including side effects and insufficient efficacy, despite the widespread activity of the protease involved. The shared processing mechanisms of amyloid beta and the Notch family have contributed to off-target effects. Consequently, several compounds have been repurposed extensively to suppress the Notch signaling pathway. This article analyzes the capacity of GSIs to rectify dysregulated Notch signaling in cancer. Reutilizing these inhibitors to focus on the Notch pathway has demonstrated promise in addressing such dysregulation. By influencing Notch signaling and amyloid beta processing, GSIs may offer a therapeutic approach to improve outcomes for cancer patients. This review focuses on the therapeutic potential of gamma-secretase inhibition for correcting Notch pathway dysregulation in oncology.

### *1.1. Gamma Secretase Inhibitors (GSI) in Targeting the Notch Pathway*

The Notch signaling pathway is a well-preserved system among species that facilitates intercellular communication to govern cell fate decisions. Its components include four Notch receptors and several ligands, comprising three delta-like (Dll) ligands and two jagged ligands. GSI activation occurs through interactions within the same cell cis-activation or trans-activation between adjacent cells [1]. Ligand binding triggers proteolytic cleavages facilitated by ADAM and the γ-secretase complex, leading to the liberation of the NICD. This domain migrates to the nucleus, interacting with the RBP-J/CSL transcription factor and recruiting mastermind-like (MAML) coactivators, altering gene expression[2]. The pathway's versatility in regulating embryonic development and cellular homeostasis stems from ligand glycosylation and dynamic binding behaviors, activating specific target genes. Notch signaling also preserves progenitor cell populations by inhibiting differentiation and facilitating their division. It plays essential roles in developing various tissues, including muscle, vascular, cardiac, hematopoietic, neural, and pancreatic systems. Nonetheless, the function of Notch signaling in cancer is intricate and sometimes necessitates other oncogenic modifications for transformation. Adding oncogene, such as E1A, is essential for the in vivo transformation of rat renal cells [3]. The activation of NICD1 alone is insufficient to produce cancer; however, it can synergistically interact with other oncogenic pathways to promote prostate adenocarcinoma in murine models and augment aggressive characteristics in human prostate cancer cells [4]. In solid tumors, aberrant Notch signaling often results from changes in regulatory proteins, signaling partners, or expression levels rather than direct mutations in Notch itself. Its oncogenic effects are influenced by the cellular context and microenvironment, making it particularly impactful in transformation-prone cells. Beyond tumor initiation, Notch signaling facilitates cancer progression by sustaining populations of cancer stem cells, promoting EMT, and facilitating invasion and metastasis [5]. Dysregulated Notch signaling facilitates disease progression in malignancies such as glioblastoma and breast and colorectal cancers through interactions with the TME [6]. Furthermore, Notch acts as a co-regulator of multiple tumorigenic pathways. It can directly regulate intracellular processes in its nontraditional capacity, further complicating its role in cancer.


**Fig 1: Core Components of Notch Signaling**

### *1.2. Structure and Function of Gamma Secretase*

Gamma secretase (GS) is an essential heterotetrameric protein complex within the cell membrane. It consists of four equimolar ratios. GS consists of a 19-pass transmembrane architecture with a central cleft. Surrounded by its components, while Nct's large ectodomain sits above the cleft [7]. Nct plays a key role in recognizing and positioning substrates into this intermembrane cleft, adjacent to the catalytic site of PS, following an initial "ectodomain shedding" process. One well-known substrate of GS is the Notch receptor. Its cleavage liberates to drive transcriptional activity. Beyond Notch signaling, GS processes over 90 substrates, including a substantial portion of human receptor tyrosine kinases, integral to cell growth, differentiation, and survival. The precise mechanism by which GS and Nct identify and cleave substrates implies their significance in controlling signaling pathways. This understanding reveals the broader functional scope of GS, emphasizing its pivotal role in regulating cellular processes and determining cell fate.

### *1.3. Gamma Secretase Inhibitors in Cancer Therapy*

Gamma-secretase (GS) cleaves Notch receptors 1 to 4; nevertheless, pharmacological suppression with GSIs does not occur consistently to block the activation of all Notch receptors. Each clinical GSI has distinct pharmacological properties, resulting in unique inhibition profiles [8]. Interestingly, GSIs can enhance the cleavage of specific Notch receptors at low doses. These differences likely contribute to their varying therapeutic effectiveness. However, the molecular understanding of GSIs remains incomplete, partly due to observational bias, as many studies have focused primarily on Notch or APP cleavage. Further investigation is needed to explore the distinctive features of GSIs, including their half-maximal inhibitory concentration values for several Notch receptors and APP across various developmental stages. Broadening the scope of research to include a wider range of molecular interactions while addressing observational bias is essential in understanding the therapeutic potential of GSIs fully.

### *1.4. Investigating the Mechanisms of Gamma Secretase Inhibition in Oncology*

The inhibition of the Notch signaling system using gamma-secretase inhibitors (GSIs) has been associated with dysfunction, as this pathway is significantly elevated in several cancer models, contributing to tumor growth and cell proliferation. However, this impact can be attenuated by the enforced expression of NICD via transfection. Enhanced apoptosis after GSI therapy is believed to stem from proteasome suppression. The integration of GSI-XII with the proteasome inhibitor bortezomib has demonstrated the ability to cause apoptosis in several multiple myeloma cell lines and primary patient samples in vitro, irrespective of other factors of NICD overexpression [9]. Edaravone has been found to restore proteasome activity and reduce apoptosis in human breast carcinoma cell lines [10]. In Glioblastoma, tumor-initiating cells demonstrated efficient apoptotic induction following GSI-I therapy. These data indicate that proteasome inhibition may assume a more critical function than Notch pathway inhibition in these contexts, highlighting a need for more clarity regarding the specificity of Notch-targeted inhibitors.

### *1.5. Using Gamma Secretase Inhibitors to Combat Treatment Resistance*

GSIs can obstruct tumor advancement through various pathways and may augment the effectiveness of standard therapies by diminishing resistance linked to Notch upregulation. The sequential administration of cisplatin demonstrated significant growth suppression in vitro, in contrast to concurrent therapy or reverse sequencing, and showed potential efficacy in vivo [11]. In human NSCLC cells, radiation applied before GSI therapy more successfully inhibited Notch-1 or Notch-3 overexpression, contingent upon the specific cell line, thus postponing tumor progression [12]. These mixed outcomes may reflect differences in baseline Notch signaling, with resistant cell lines potentially exhibiting increased Notch signaling in the development of platinum resistance. Additional research is needed to unravel the intricate role of Notch signaling in cancer therapy. The variable responses across cell lines highlight the potential need for tailored therapeutic approaches targeting the Notch pathway to achieve optimal outcomes. Furthermore, modulating Notch signaling could offer a strategy to overcome resistance to standard chemotherapeutic agents in certain cancer types.

## 2. GAMMA SECRETASE INHIBITOR CLINICAL TRIALS

Stem cells have shown the potential to promote tumor cell differentiation and reduce malignancy, enhancing tumor sensitivity to standard chemoradiotherapy. This capability has led to clinical trials investigating gamma-secretase inhibitors (GSIs) use across various cancer types. Preliminary findings from these trials suggest that GSIs can improve the effectiveness of conventional cancer therapies and patient results. By focusing on cancer stem cells and encouraging their differentiation, GSIs may represent a promising strategy for addressing cancer and overcoming resistance to treatment. However, additional research and clinical validation are required to ascertain their therapeutic potential comprehensively.

### *2.1. Lung Cancer*

Critical elements of the Notch signaling system, including DLL3 and HES1, were associated with unfavorable prognoses in individuals with NSCLC [13]. Notch inhibition in NSCLC through GSIs has shown the potential to enhance the sensitivity of NSCLC cells to standard chemotherapy while delaying the development of resistance [14]. In phase I trials, a small group of lung cancer patients were administered as monotherapies for advanced solid tumors resistant to standard treatments; nevertheless, these medications have shown little therapeutic benefit in patients with NSCLC [15]. Phase I/II research Investigated the combination of erlotinib in patients with NSCLC to assess potential resistance to erlotinib. Among them, one patient exhibited a partial response, four achieved stable illness, and the median progression-free survival (PFS) for those who had previously experienced disease progression on erlotinib [16]. The limited efficacy observed in these trials may be attributed to the inclusion of heavily pretreated patients with advanced disease.

### *2.2. Pancreatic Cancer*

The protein APH1A, a constituent of the GSIs complex, is significantly overexpressed in malignant pancreatic tissue compared to normal tissue and may be linked to poorer patient outcomes. Notch receptors 1–4 and their downstream effector Hes1 are also notably upregulated in pancreatic ductal adenocarcinoma (PDAC) [17]. This pronounced expression and the established role of these pathways in tumor progression have prompted the exploration of therapeutic interventions targeting GS. In the phase II clinical trial, eighteen individuals with metastatic, treatment-resistant pancreatic ductal adenocarcinoma (PDAC) were administered the gamma-secretase inhibitor of the evaluable patients; three exhibited stable illness [18]. Tumor biopsies demonstrated a marked decrease in HeyL expression throughout treatment. Nonetheless, several phase I trials examining GSIs restricted clinical efficacy in individuals with advanced solid tumors, including PDAC. Preclinical studies indicate that combining GSIs and gemcitabine may augment antimetastatic effects, necessitating more exploration [19]. In a phase I experiment, one out of three individuals with PDAC attained stable disease by a combination of gemcitabine. A separate phase I trial concentrating solely on stage III or IV PDAC determined that the clinical efficacy in conjunction with gemcitabine was

comparable to gemcitabine alone, leading researchers to recommend against further evaluation of this combination. These findings highlight the need for additional research to understand better the potential benefits of combining GSIs with gemcitabine in treating PDAC. Continued investigation into innovative therapeutic strategies is essential to improve survival rates and results for those afflicted by this complex ailment.

### *2.3. Melanoma*

A Phase I trial with GSIs in melanoma patients evaluated for advanced stages, treatment-resistant solid tumors. Significant improvement was observed in melanoma patients, including one case of nearly complete remission [20]. While RECIST criteria revealed only one weak response, another was detected using fluorodeoxyglucose–positron emission tomography [21]. Four out of 24 melanoma patients experienced clinical benefit. Encouraged by these results, a Phase II trial was launched to evaluate monotherapy in chemotherapy-naïve individuals with metastatic melanoma. Of the patients assessed, one exhibited a partial response. In contrast, eight cases demonstrated stable illness compared to those in the Phase I trial, which scientists believe may account for the reduced number of responses.

### *2.4. Gliomas*

Notch signaling is often active in human gliomas and is crucial for maintaining the self-renewal properties of glioma stem cells. Notch-1 expression correlates with worse survival rates in patients with proneural and conventional glioblastomas [22]. Elevated articulation of the elements of Notch signaling is intricately linked with the response of glioma tumor-initiating cells to gamma-secretase inhibitors (GSIs) [23]. These findings have paved the way for the clinical advancement of GSIs for Gliomas and other central nervous system cancers. A Phase I trial of GSIs, including pediatric patients with solid tumor-resistant central nervous system malignancies, showed an adequate safety profile [24]. However, none of the nine glioma patients experienced significant responses, with only one showing extended stable disease. Hes1 and Hes5 staining was consistently observed in all the tumors, indicating considerable Notch signaling activation in pediatric brain cancers [25]. The study sponsor retracted support before the conclusion. However, better outcomes were reported in adult glioma patients treated with alone. In a cohort study of GSIs in glioma patients, complete remission was noted in cases of anaplastic astrocytoma beyond one year. In contrast, stable disease lasting over a year was observed in glioblastoma multiforme [26]. Ten patients, or 24% of the study group, demonstrated stable disease.

### *2.5. Breast Cancer*

Notch signaling has been linked to breast cancer, which accounts for around 30% of all new cancer diagnoses in women in the United States. Elevated levels of Notch-1 and Jagged1 correlate with reduced overall survival [27]. This link prompted an examination of the feasibility of GSIs as a treatment option, specifically for breast cancer, and found no significant therapeutic benefit in breast cancer. Similar phase I trials showed no substantial efficacy for advanced solid tumors. Despite their limited effectiveness as monotherapies, GSIs have demonstrated preclinical potential in reducing cancer stem cell proliferation and overcoming chemotherapy resistance, leading to the exploration of combination therapies. A phase Ib trial of GSIs of combined Exemestane for estrogen receptor-positive metastatic breast cancer has demonstrated modest efficacy, with one partial response, six instances of stable disease, and seven cases of disease progression [28]. A particular phase I experiment of GSIs evaluating the combination of gemcitabine in patients with advanced solid tumors, which had five persons with breast cancer, did not exhibit efficacy for breast cancer alone [29]. A phase Ib trial in combination with docetaxel had moderate clinical efficacy in advanced triple-negative breast cancer, with four partial responses among 25 evaluable patients and a median progression-free survival of 4.1 months [30]. A phase I trial on GSIs combining docetaxel for breast cancer patients resulted in 11 partial responses, 9 cases of stable disease, and 3 instances of disease progression among 24 evaluable patients [31]. This combined therapy decreased breast cancer stem cells and inhibited mammosphere proliferation in a patient cohort. Despite the current moderate response rates, extensive patient screening and customized combinatorial approaches may enhance the future effectiveness of GSIs in breast cancer treatment.

### *2.6. Ovarian Cancer*

Cytoplasmic NICD1 demonstrates significant expression in human ovarian carcinoma correlates with diminished overall survival prognosis [32]. Encouraging results from preclinical studies showing extended responses to cyclical GSI inhibition has led to the implementation of similar strategies in various Phase I clinical studies aimed at patients with advanced ovarian carcinoma exhibiting resistance to conventional treatment [33]. These methodologies encompass the utilization of, either independently or in conjunction with, gemcitabine, temsirolimus, a mTOR inhibitor, or cediranib, a VEGF antagonist. The trials demonstrated that these therapies, both separately and together, displayed an acceptable safety profile. It demonstrated therapeutic benefits from monotherapy, followed by temporary stabilization or disease progression. A phase II trial of GSIs with 45 patients suffering from recurrent or metastatic platinum-resistant ovarian cancer showed no objective responses, resulting in a median progression-free survival of 1.3 months, leading researchers to determine that GSI monotherapy is unsuccessful for ovarian cancer [34]. The delivery of enoticumab, a fully human immunoglobulin G1 that targets Dll4 to inhibit Notch signaling, resulted in one partial response, six instances of stable disease, and two incidences of reduced cancer antigen-125, meeting response criteria in ovarian cancer patients [35]. These data suggest that enhancing the regulation of Notch signaling, either independently or in conjunction with other therapies, could offer a more promising approach to ovarian cancer therapy.

### *2.7. Colorectal Cancer*

The nuclear localization of NICD1 and NICD3 signaling, observed through immunohistochemistry, is linked to recurrence and negative outcomes in patients with stage II and III colon cancer; nevertheless, Notch 2 signaling may provide protective advantages [36]. The increased expression of Notch target genes, such as Hes1, Hey1, and Sox9, which are downstream of the Notch receptors, correlates with chemoresistance to 5-FU, increased activation of the Wnt pathway, metastasis at diagnosis, and reduced overall survival [37]. In patient-derived xenografts treated with increased activation, the Notch and Wnt pathways corroborated data

from clinical studies. A Phase I trial of advanced solid tumors comprising colorectal cancer showed that PF-03084014 monotherapy significantly reduced Hes4 expression, although it resulted in a median progression-free survival of only 1.6 months [38]. Clinical trials with other Notch inhibitors exhibited no antitumor engagement. A phase II trial as a monotherapy for metastatic, resistant colorectal cancer revealed no objective responses, six instances of stable disease, and twenty-one cases of disease progression, yielding a median progression-free survival of 1.8 months, which indicates the treatment's limited efficacy. Due to the inadequate effectiveness of monotherapy, combination therapies have been explored. A Phase I trial of combination therapy with cediranib in patients with advanced solid malignancies, which included six colorectal cancer patients, recorded one partial response and stable disease in eleven patients [39]. The combination of dalotuzumab for blocking the Insulin-like growth factor I receptor was ineffective since all colorectal cancer patients demonstrated disease progression during the initial radiologic evaluation [40]. A phase I trial of GSIs with 30 advanced-stage patients, including 18 with colorectal cancer, revealed that the combination with capecitabine produced two partial responses out of three, suggesting potential benefits for fluoropyrimidine-resistant metastatic colorectal cancer[41].

### *2.8. Desmoid Tumors*

Desmoid cancers frequently develop due to disturbances in the Wnt signaling pathway, with the growing acknowledgment that augmented Notch signaling contributes toward disease progression [42]. A Phase I clinical trial investigating advanced solid tumors resistant to current therapies has nine participants with desmoid tumors, 43 of which seven were assessable. The findings revealed that five patients demonstrated partial responses per RECIST criteria, while two demonstrated extended illness stabilization. Among those who attained partial responses, all sustained their Response duration, which ranged from 47.9 to 73.6 months, with just one out of seven patients demonstrating illness relapse. The mean duration of clinical improvement was 64 months, in contrast to only 13 months with other therapy. A Phase II trial commenced to further assess 17 patients with unresectable desmoid tumors that have advanced despite various treatment regimens [44]. Among the 16 assessable patients, 5 (29%) had a partial response according to RECIST criteria, whereas 11 exhibited stable diseases, with no progression observed. Owing to the promising efficacy of the Phase III trial, GSI (Nirogacestat) for adults with desmoid tumors was commenced, and the medicine received breakthrough approval from the U.S. Food and Drug Administration, in addition to orphan medication classification from the European Commission [45]. Comprehending the molecular alterations triggered by GSIs, particularly tumors, may facilitate their application in treating other malignancies.

## 3. CURRENT LIMITATIONS

A significant constraint in comprehending the potential and the absence of immune-competent models in their research is a limitation of these drugs. Inhibiting Notch signaling may hinder tumor proliferation, and GSIs might reduce the effectiveness of the anticancer immune response. CD8 T cells, crucial for antitumor immunity, rely on Notch signaling to produce essential effector molecules such as interferon-γ and granzyme B. Reduced Notch-1/2 levels in CD8 T lymphocytes in tumors were associated. At the same time, cytotoxicity was diminished, enhanced Notch-1 signaling increased cytotoxicity, and facilitated tumor control. GSIs can suppress the activation of human T cells and the proliferation of murine CD8 T cells in a dose-dependent manner. Another challenge comes from regulatory T cells (Tregs), key immune suppressors in the TME. Initially, Notch signaling can suppress the Treg program, but GSIs may increase Treg-mediated immune suppression, further impairing antitumor immunity. While boosting Notch-1 signaling could enhance tumor control by improving CD8 T cell cytotoxicity, using GSIs might inhibit T cell activation and expansion. The presence of Tregs in the TME adds to the challenge, as GSIs may increase their suppressive effects, further dampening the immune response. These findings underscore the complexity of the relationship between Notch signaling, Tregs, and immune responses in the TME, highlighting the need for careful consideration when targeting these pathways in cancer therapy.

## 4. CONCLUSION

Addressing significant knowledge gaps is crucial to advancing the development of gamma-secretase inhibitors (GSIs). While these drugs have demonstrated promising preclinical efficacy in reducing tumor growth, their potential still needs to be realized in clinical settings, apart from desmoid tumors. A deeper understanding of GSIs and tumorNotch expression profiles will be critical for selecting optimal patient populations. Designing effective combination therapies can enhance the sensitivity of tumors to conventional chemotherapeutics while reducing their ability to develop treatment resistance. These findings highlight the substantial potential of GSIs to improve patient outcomes and address treatment resistance across various cancer types. By refining our knowledge of GSIs and their interactions with tumor Notch pathways, treatments can be more precisely tailored to individual patients. Developing combinatorial strategies will be vital to maximizing the effectiveness of these therapies and improving overall survival rates for cancer patients.

## 5. AUTHORS CONTRIBUTION STATEMENT

Dr. V. Aruna, Dr. Anand Mohan Jha wrote the initial draft. Dr Riffat A Fatima And Dr. Abikesh Prasada Kumar Mahapatra contributed to critical revision and supervision. All authors reviewed the manuscript.

## 6. CONFLICT OF INTEREST

Conflict of interest declared none.

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