Review

Molecular Mechanisms of Targeted Therapy Resistance in Genitourinary Tumors: A Path to New Therapeutic Horizons

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Review

Molecular Mechanisms of Targeted Therapy Resistance in Genitourinary Tumors: A Path to New Therapeutic Horizons

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Abstract: Targeted therapies have transformed the treatment of genitourinary (GU) malignancies, particularly renal cell carcinoma (RCC), offering significant clinical benefits. However, therapy resistance, driven by intrinsic tumor characteristics and acquired mechanisms, frequently limits their effectiveness. This review comprehensively examines targeted therapies in GU tumors, focusing on their clinical impact and the molecular basis of resistance. While RCC has shown substantial improvements in overall survival, other GU tumors like prostate and bladder cancer have experienced more modest gains due to molecular heterogeneity and complex resistance pathways. These resistance mechanisms are diverse, including genomic alterations, epigenetic modifications, tumor microenvironment influences (immunosuppressive cells, angiogenesis), activation of alternative signaling pathways (PI3K/AKT, MAPK), and metabolic reprogramming. Intratumoral and metastatic site heterogeneity further contribute to resistant subclones. Current strategies to combat resistance involve developing next-generation agents, combination therapies (immunotherapy with TKIs), and personalized medicine guided by genomic profiling and biomarkers like PD-L1, TMB, and ctDNA. Liquid biopsies are increasingly used for real-time monitoring of resistance. Translational research focuses on innovative clinical trial designs (adaptive, basket, umbrella) and real-world evidence. Multidisciplinary collaborations, addressing undertreated populations, and navigating regulatory and cost challenges are crucial. Future directions include breakthroughs in NGS and single-cell analysis, big data and machine learning for predictive modeling, organoids and PDXs for preclinical studies, and novel TME-directed therapies. Ultimately, a more profound understanding of resistance mechanisms and innovative approaches will lead to more effective, personalized, and durable treatments for GU tumors, redefining clinical paradigms and improving patient outcomes.

Keywords: genitourinary neoplasms; molecular targeted therapy; drug resistance; neoplasm; tumor microenvironment; biomarkers; precision medicine

Introduction

Genitourinary (GU) malignancies represent a substantial global health challenge, with prostate, bladder, and kidney cancers accounting for the highest incidence and mortality rates within this category [1–4]. Prostate cancer, for instance, is the second most frequently diagnosed cancer in men worldwide, with over 1.4 million new cases in 2020 and significant mortality, particularly in populations with limited access to early detection [1,2]. Bladder cancer, ranking as the second most common GU malignancy, is responsible for nearly 500,000 new cases annually, whereas kidney cancer (primarily renal cell carcinoma) contributes roughly 400,000 new diagnoses per year, both placing substantial burdens on healthcare systems [3,4]. Disparities in healthcare infrastructure, alongside behavioral and environmental risk factors such as smoking and obesity, exacerbate these statistics, reflecting observed geographical variations in GU cancer outcomes [1,5,6].

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Against this epidemiological backdrop, the treatment landscape for GU tumors has undergone a paradigm shift with the rise of targeted therapies. These modalities include agents directed at specific molecular pathways—most notably immune checkpoint inhibitors (ICIs) and targeted small-molecule inhibitors—that have demonstrated durable remission and improved survival in select patient subgroups [7,8]. Immune-based therapies, such as those targeting PD-1 and PD-L1, have significantly impacted the management of advanced renal cell carcinoma and urothelial carcinoma, often being used in combination with anti-angiogenic agents [8,9]. Meanwhile, the introduction of next-generation androgen receptor (AR) inhibitors (e.g., enzalutamide, abiraterone) has redefined the standard of care in metastatic castration-resistant prostate cancer by extending survival and delaying disease progression [9]. In bladder cancer with identifiable fibroblast growth factor receptor (FGFR) alterations, oral FGFR inhibitors such as erdafitinib have offered new avenues for personalized therapy [10,11].

A key force driving these therapeutic successes is the growing knowledge of GU tumor biology. Molecular studies reveal that genetic abnormalities, dysregulated signaling pathways, and complex interactions in the tumor microenvironment collectively shape tumor progression [12,13]. For example, the frequent presence of AR gene mutations in prostate cancer underscores the value of hormonal pathway inhibition, while alterations in FGFR3 in bladder tumors validate the use of FGFR-targeting agents [14,15]. Epigenetic changes—such as DNA methylation, histone modifications, and regulatory noncoding RNAs—further compound the heterogeneity of GU cancers, influencing their susceptibility to various treatments [16,17]. Consequently, research initiatives increasingly focus on biomarker discovery to elucidate which molecular perturbations drive resistance to specific targeted agents [7].

In the past five years, these molecular insights have fueled personalized medicine approaches that tailor therapies based on individual tumor profiles [18]. Advanced genomic tests, circulating tumor DNA (ctDNA) assays, and dedicated molecular tumor boards (MTBs) help guide the selection of targeted treatments for GU malignancies [19]. This patient-centered framework has enhanced response rates and allowed clinicians to adjust therapies in real time as new resistance mechanisms emerge [14,17]. Additionally, immune checkpoint blockade, guided by PD-L1 expression and other biomarkers, underscores the potential of combining molecular profiling with immunotherapeutic strategies for disease subtypes once considered refractory [7].

Despite these encouraging developments, major challenges persist. Tumor heterogeneity remains a formidable barrier, as varying clonal populations and complex microenvironments within the same tumor can foster both intrinsic and acquired resistance [20,21]. In many instances, robust predictive biomarkers are lacking; without validated markers, it is difficult to discern which patients will derive substantial benefit from targeted agents [22]. Further complicating the landscape are adverse effects related to these treatments, including immune-related toxicities that necessitate therapy adjustments and may limit long-term adherence [23]. Access disparities, driven by socioeconomic variables and healthcare infrastructure, also restrict the real-world impact of these innovations, particularly in low- and middle-income regions [24,25]. These limitations highlight the importance of ongoing research to improve biomarker-based interventions, optimize combination regimens, and locate new anticancer targets to overcome resistance.

The aim of this review is to synthesize recent insights into the molecular mechanisms underlying targeted therapy resistance in GU tumors and to highlight emerging strategies designed to overcome these challenges. By integrating key findings from clinical trials, meta-analyses, and novel translational research, we will examine the biological drivers of resistance, identify promising therapeutic approaches (including next-generation targeted agents and combination regimens), and discuss the evolving role of precision medicine. Ultimately, this review seeks to provide a structured framework for clinicians, researchers, and healthcare policymakers to better understand resistance mechanisms, leverage current targeted therapies more effectively. It also aims to guide future investigative directions toward more personalized and durable treatment strategies in GU oncology.

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Overview of Targeted Therapies in Gu Tumors

Genitourinary cancers, notably prostate, bladder, and kidney malignancies, are driven by complex webs of signaling cascades and oncogenic processes that promote tumor growth, survival, and spread [26–28]. Research characterizing these pathways has shed light on key molecular targets, and this evolving knowledge underpins the development of therapeutic strategies that aim to inhibit crucial elements of tumor cell biology. A key route commonly dysregulated in GU malignancies is the PI3K/AKT/mTOR pathway [26], which, when activated—often due to inactivating mutations in PTEN—drives uncontrolled cell proliferation. In prostate cancer, this dysregulation contributes to disease progression and therapy resistance [28,29]. Clear cell renal cell carcinoma (ccRCC) tends to display similar upregulation of this pathway through loss of the VHL gene, with stabilized hypoxia-inducible factors (HIFs) stimulating mTOR to support angiogenesis [26]. Drugs such as everolimus, which block the mTOR component, have consequently been introduced, particularly in advanced disease settings [28].

In prostate tumors, Wnt/β-catenin signaling also plays a significant role, promoting enhanced cancer stemness and inducing epithelial-mesenchymal transition [30,31]. This process can escalate when androgen signaling is suppressed [32], indicating extensive crosstalk between Wnt activity and the androgen receptor (AR) pathway and underscoring the complexity of the regulatory network in prostate cancer [33]. Notch signaling, in turn, has been tied to the regulation of cancer stem cells that influence tumor recurrence in prostate cancer [34], and Notch inhibition has shown the potential to enhance the effects of chemotherapy such as docetaxel [35].

The TGF-β/Smad signaling cascade, present in both prostate and bladder tumors, features a dual nature by exerting tumor-suppressive effects in early disease but fostering epithelial-mesenchymal transition and metastatic capacity in later stages [36,37]. Beyond these signaling pathways, oncogenic drivers such as EGFR, VEGF/VEGFR, PD-1/PD-L1, and FGFR have received considerable attention in bladder and kidney cancers [38–40]. EGFR overexpression correlates with high-grade and advanced bladder tumors [41], whereas VEGF production driven by VHL dysfunction is integral to angiogenesis in ccRCC [40]. Clinical trials validating VEGF and EGFR inhibition illustrate how therapeutics can effectively disrupt these pathways to impede tumor growth [41]. Similarly, PD-1/PD-L1 blockade, shown to be effective in advanced bladder cancer and RCC, underlines the importance of immunoregulatory pathways, while FGFR inhibition addresses FGFR3 alterations common in certain bladder tumor subsets [39].

By mapping these intersecting molecular routes, researchers have moved beyond traditional hormone or chemotherapy toward targeted treatments that more precisely inhibit the main biological drivers of GU cancers. Although these targeted agents demonstrate measurable efficacy, many tumors activate multiple or overlapping pathways that contribute to resistance, prompting ongoing investigations into combination regimens that integrate two or more therapeutic approaches, including immunotherapy [7,14]. The continual refinement of biomarker identification and genomic profiling of GU cancers also improves patient selection, ensuring that those with specific pathway dysregulations or relevant molecular signatures receive the most appropriate targeted therapies. The emerging consensus is that an increasingly nuanced view of GU tumors—and the interactions of their central signaling routes—will guide next-generation trials and clinical practice, ultimately advancing patient outcomes.

The introduction of targeted therapies has significantly altered the management of GU malignancies, yet their clinical impact and associated limitations vary considerably across different tumor types [42,43]. Renal cell carcinoma (RCC) stands out as the GU tumor type that has demonstrated the most significant improvement in overall survival (OS) with targeted agents, largely due to its well-defined molecular pathogenesis involving the VHL gene and angiogenic pathways [44–46]. Tyrosine kinase inhibitors (TKIs) and mTOR inhibitors targeting these pathways have translated into marked OS gains, particularly with antiangiogenic agents like sunitinib and pazopanib [44–46]. This success is partly attributed to the identification of robust biomarkers in RCC, such as those related to the VHL pathway, which facilitate patient selection [44,47]. Furthermore,

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the integration of immunotherapy with antiangiogenic agents in RCC has yielded even greater survival benefits, leveraging both direct molecular inhibition and immune modulation [48,49].

In contrast, prostate and bladder cancers have generally lagged behind RCC in terms of OS improvement with targeted therapies [42,43,50]. While agents targeting androgen receptor (AR) signaling in prostate cancer and various pathways in bladder cancer have shown activity, the OS gains have been more modest, often limited to progression-free survival (PFS) endpoints in clinical trials [43,50,51]. This disparity is linked to the greater molecular complexity and heterogeneity of prostate and bladder tumors, which present a broader array of genetic alterations and adaptive resistance mechanisms compared to the more predictable angiogenic dependence of RCC [21,42,50]. Testicular cancer, while a GU malignancy, has historically been highly responsive to conventional chemotherapy, with targeted therapies playing a less significant role in further OS improvement [45,47].

Comparing outcomes from randomized controlled trials (RCTs) and real-world data (RWD) in GU oncology reveals important nuances [52,53]. RCTs, with their stringent selection criteria and controlled environments, frequently demonstrate robust efficacy and safety profiles in relatively homogeneous populations [54]. However, RWD, derived from routine clinical practice, captures a broader spectrum of patients, including those with comorbidities, advanced age, or complex disease presentations typically excluded from trials [53]. Consequently, RWD analyses in mRCC, for example, have sometimes reported more tempered OS outcomes compared to RCTs, reflecting factors such as treatment adherence, comorbidities, and variations in management [54]. While RCTs provide high internal validity, RWD offers essential external validity, highlighting how targeted therapies perform in diverse real-life settings and informing clinical guidelines to better reflect everyday practice [52,53]. Advanced statistical methods are increasingly used to bridge the gap, but differences in data quality and study design persist [52].

Despite the clinical benefits, targeted therapies in GU tumors are associated with a spectrum of adverse events (AEs) and toxicities that can lead to treatment discontinuation or dose reduction [55–59]. Frequently reported AEs include hematologic toxicities (anemia, thrombocytopenia, leukopenia) with VEGFR inhibitors like pazopanib, gastrointestinal disturbances (nausea, diarrhea), and fatigue, which is a common nonhematologic toxicity across many targeted agents [57]. Cutaneous toxicities, ranging from rash to severe reactions like Stevens–Johnson syndrome, are notable with antibody-drug conjugates (ADCs) such as enfortumab vedotin, particularly in combination with immune checkpoint inhibitors [56]. Immune checkpoint inhibitors themselves are associated with immune-related adverse events (irAEs) affecting various organs, including colitis, hepatitis, endocrinopathies, and renal toxicities like acute tubulointerstitial nephritis [57,58]. FGFR inhibitors can cause hyperphosphatemia and stomatitis [59].

Factors predicting treatment discontinuation or dose reduction due to toxicity are multifaceted. Patient-specific characteristics such as advanced age, higher baseline comorbidity burden, and poor performance status are consistently identified predictors [60,61]. Pharmacokinetic variability, prior treatment history, baseline laboratory abnormalities, and concurrent medications also influence tolerance [60,62]. Early onset of severe AEs, high-grade hematologic or cardiovascular toxicities, and inadequate supportive care infrastructure are further predictors [60,61,63]. Patient-reported outcomes and psychological factors like anxiety can also influence decisions to modify or discontinue therapy [64]. Multidisciplinary collaboration and institutional experience in toxicity management can mitigate these risks [63].

Despite the identification of promising predictive factors for targeted therapy benefit, large-scale meta-analyses have not yet conclusively identified specific patient subgroups most likely to benefit across all GU tumors [65–69]. While early tumor shrinkage or certain molecular markers show promise in individual studies or smaller cohorts, heterogeneity in study designs, patient populations, and biomarker assays limits the ability to draw definitive conclusions from pooled analyses. The

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complexity and molecular diversity of GU tumors, along with the evolving landscape of targeted agents, contribute to this challenge.

Primary reasons for therapy failure or limited duration of response in targeted treatments for GU tumors include intrinsic tumor heterogeneity, acquired resistance mechanisms (such as de novo mutations or epigenetic changes), and the influence of the tumor microenvironment [70–72]. Other factors include the induction of EMT, the presence of cancer stem cells, metabolic reprogramming, alterations in drug metabolism and pharmacokinetics, immune evasion, and the activation of alternative signaling pathways [72–76]. Inefficient drug penetration into the tumor and dynamic interactions between tumor and stromal cells also contribute to resistance [70].

Pharmacokinetic (PK) and pharmacodynamic (PD) factors significantly impact targeted therapy efficacy across different GU cancer subtypes [77]. PK variability, influenced by age, organ function, and genetics, affects drug exposure at the tumor site [78,79]. PD factors, such as the degree of target pathway inhibition, are measured through biomarkers and reflect the drug's effect on tumor biology [77]. The interplay of PK and PD, including drug absorption, distribution, metabolism, and excretion, shapes the therapeutic window and influences efficacy and toxicity [77,78]. PK/PD modeling is particularly important for complex agents like ADCs [80].

While complete cures remain rare, long-term follow-up studies have demonstrated durable responses with targeted agents in subsets of patients with advanced GU cancers, particularly with immune checkpoint inhibitors [7,81–84]. These durable responses, sometimes lasting for years, have translated into significant improvements in OS and quality of life, fundamentally altering the disease trajectory for some patients [7,81,83]. Combination regimens have also shown promise in producing durable responses in rare GU tumor subtypes [85].

The high costs of targeted therapies and variable insurance coverage significantly affect clinical decision-making in GU tumor treatment [64,86,87]. Financial toxicity can lead to delayed treatment initiation, dose reductions, or selection of less expensive, potentially less effective, alternatives [86,88]. Insurance policies and reimbursement frameworks dictate access, with disparities observed across regions and socioeconomic groups [64,86]. Cost-effectiveness evaluations, genomic testing costs, and administrative hurdles like prior authorizations further influence decisions [87,89]. Multidisciplinary tumor boards and financial navigators are increasingly involved to address these challenges [87,90].

Combination regimens with targeted therapies have demonstrated the best outcomes in advanced or metastatic GU cancers, particularly in mRCC and urothelial carcinoma [91,92]. Dual checkpoint inhibition (nivolumab plus ipilimumab) has shown superior OS and response rates compared to monotherapy in intermediate- and poor-risk mRCC [91]. Combinations of VEGF inhibitors with immune checkpoint inhibitors (e.g., axitinib plus pembrolizumab) also improve outcomes by modulating the tumor microenvironment [93]. In urothelial carcinoma, combinations of checkpoint inhibitors with other targeted agents or chemotherapy are being explored to overcome resistance [94]. Rational design, patient selection based on biomarkers, and careful toxicity management are crucial for optimizing these combinations [91–94].

Definitions and Classifications of Therapy Resistance

Therapy resistance in GU tumors presents a significant challenge in achieving durable clinical responses to targeted agents. This resistance can be broadly categorized into two fundamental types: intrinsic and acquired, each driven by distinct molecular mechanisms and influencing therapeutic outcomes differently. Intrinsic resistance refers to the inherent lack of response to a therapy from the outset, often linked to pre-existing molecular characteristics of the tumor [11,95]. Conversely, acquired resistance develops over time in tumors that initially responded to treatment but subsequently evolve mechanisms to evade its effects [96,97].

The molecular distinctions between intrinsic and acquired resistance are rooted in their underlying genomic and epigenetic alterations. Intrinsic resistance can arise from inherent genomic features such as specific mutations or genomic instability present before therapy initiation [98,99]. For example, mutations in the FGFR3-TACC3 axis in bladder cancer have been associated with

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primary resistance to FGFR-targeted therapies [98]. Similarly, loss-of-function mutations in JAK1/2 can confer intrinsic resistance to PD-1 blockade by disrupting antigen presentation [100,101]. Epigenetic modifications, including DNA methylation and histone alterations, also contribute to intrinsic resistance by silencing genes involved in drug response or activating survival pathways [102,103]. In contrast, acquired resistance often involves the selection and expansion of subclones with new genomic alterations or adaptive epigenetic changes that emerge under therapeutic pressure [104,105]. These changes can lead to the activation of alternative signaling pathways or the upregulation of immunosuppressive features in the tumor microenvironment (TME) [106,107].

Alternative signaling pathways and compensatory mechanisms are commonly activated in GU tumors to bypass targeted therapy, contributing significantly to both intrinsic and acquired resistance. The PI3K/AKT pathway is a frequent bypass route, activated when upstream targets like FGFR or AR are inhibited, promoting cell survival and proliferation [108–110]. The RAS/RAF/MEK/ERK pathway also serves as a compensatory mechanism; for instance, ERBB2/3 upregulation can bypass FGFR inhibition in bladder cancer [111]. Tumors can also engage alternative receptor tyrosine kinases (RTKs) or activate feedback loops to sustain growth signaling despite targeted blockade [112–115]. The TME further facilitates these bypass mechanisms through paracrine signaling, such as the transfer of resistance signals via extracellular vesicles [116].

The patterns and mechanisms of resistance differ among prostate, bladder, and kidney cancers, reflecting their unique molecular landscapes. Prostate cancer resistance often involves modifications in AR signaling, including mutations and amplifications, alongside epigenetic dysregulation like hypermethylation of tumor suppressor genes [117,118]. Bladder cancer resistance is influenced by genomic instability, mutations in oncogenes like FGFR3 and TP53, and immune evasion mechanisms mediated by PD-L1 expression and the TME [7,119–121]. Kidney cancer resistance, particularly in ccRCC, is strongly linked to VHL loss and subsequent dysregulation of hypoxia-mediated pathways, promoting angiogenesis and metabolic changes that confer resistance to VEGF-targeted therapies [119].

Intratumoral and metastatic site heterogeneity significantly contributes to targeted therapy resistance in GU tumors. Intratumoral heterogeneity involves diverse clonal populations with varying genetic alterations and biomarker expression levels within a single tumor [122–124]. Metastatic sites can exhibit distinct molecular characteristics and microenvironments compared to the primary tumor, influencing drug response and resistance patterns [125–128]. This spatial and temporal heterogeneity allows resistant subclones to survive and proliferate under selective pressure [129].

Clonal evolution under targeted therapy pressure leads to the emergence of resistant subclones. Various models describe this process, where pre-existing resistant clones expand or new resistance-conferring mutations arise and are selected for, eventually dominating the tumor population [130–132]. Subclonal alterations in driver genes and the dynamic interplay with the TME influence this evolutionary trajectory [133–135].

The tumor microenvironment plays a crucial role in mediating resistance and shaping clonal dynamics in GU tumors. Immunosuppressive cells like TAMs, the physical properties of the ECM, and factors like hypoxia, create a protective niche for tumor cells and promote resistance [136–139]. The TME also exerts selective pressures, favoring the survival and proliferation of resistant clones and influencing the tumor's overall clonal composition [131,140].

Validated and emerging biomarkers (tissue or liquid) are crucial for predicting intrinsic resistance or the likelihood of developing acquired resistance. Established biomarkers include PD-L1 expression and TMB for predicting immunotherapy response, although their predictive value for targeted agents varies [141–143]. FGFR alterations are validated predictors for FGFR inhibitor response in urothelial carcinoma [144]. Emerging liquid biopsy biomarkers like ctDNA and CTCs offer non-invasive monitoring of resistance mechanisms and clonal evolution [145–147]. Other emerging biomarkers include TIL characteristics, MSI status, and microRNA signatures [148,149].

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Liquid biopsies, specifically ctDNA and CTCs, are increasingly used to monitor the emergence of acquired resistance and clonal evolution in real-time. Analyzing ctDNA allows for the detection of resistance-conferring mutations as they arise under therapeutic pressure [150,151]. CTC analysis provides insights into the phenotypic and genetic evolution of tumor cells circulating in the bloodstream [147,152]. Serial liquid biopsies enable dynamic tracking of the tumor's molecular landscape, helping to identify shifts in clonal composition and predict treatment failure before radiographic progression [153–155].

Cross-resistance, where resistance to one agent confers resistance to others, is documented through preclinical models and clinical observations [156–158]. This phenomenon is often mediated by shared resistance mechanisms, such as the activation of common bypass pathways or the influence of the TME [159,160]. Novel strategies to overcome established resistance mechanisms include targeting the TME (e.g., inhibiting FAP or reprogramming TAMs), enhancing immunotherapy (e.g., dendritic cell activation), inhibiting alternative oncogenic pathways (e.g., targeting HGF/c-MET), and utilizing innovative drug delivery systems like bioresponsive hydrogels [161–168].

Molecular Mechanisms of Resistance

Resistance to targeted therapies in GU tumors is a complex phenomenon driven by a multitude of molecular mechanisms, encompassing genomic alterations, epigenetic modifications, interactions within the TME, activation of alternative signaling pathways, and metabolic adaptations. Understanding these mechanisms is crucial for developing strategies to overcome resistance and improve patient outcomes.

Genomic alterations represent a fundamental driver of targeted therapy resistance in GU tumors. These include frequent mutations, copy number variations (CNVs), and gene fusions [169–171]. Alterations in the androgen receptor (AR) and PI3K pathway components are particularly common in prostate cancer, contributing significantly to resistance [169]. Resistance can emerge through mechanisms such as receptor amplification or aberrant activation of downstream signaling pathways driven by mutations [169,172]. Copy number alterations, including gains in loci like MYC, PIK3CA, and CCNE1 have been associated with increased aggressiveness and resistance in various cancers, including GU tumors [173,174]. Furthermore, gene fusions can render targeted therapies ineffective by altering downstream effects or eliminating targetable proteins [171,172].

Alterations in tumor suppressor genes, such as PTEN and TP53, also play a critical role in resistance. Loss of function in TP53 leads to impaired cell cycle control and apoptosis, promoting uncontrolled proliferation and therapeutic escape [175–177]. Inactivation of PTEN, a negative regulator of the PI3K/AKT pathway, results in constitutive AKT activation, enhancing cell survival and resistance to therapies targeting this pathway [176,178]. The emergence of AR splice variants, particularly AR-V7, is a significant mechanism of resistance to AR-targeted therapies in prostate cancer, driving androgen-independent growth and bypassing conventional hormonal treatments [179,180]. These variants lack the ligand-binding domain, allowing them to remain active despite low androgen levels, and their presence is associated with poor prognosis and diminished response to agents like enzalutamide and abiraterone [179,181].

Epigenetic modifications, including DNA methylation, histone alterations, and noncoding RNAs, are crucial drivers of resistance phenotypes. Aberrant DNA methylation, particularly hypermethylation of tumor suppressor gene promoters, can silence gene expression and contribute to resistance [182,183]. Histone modifications, such as acetylation and methylation, alter chromatin structure and gene accessibility, influencing the expression of genes involved in drug response [184,185]. Histone deacetylase (HDAC) inhibitors are being explored to reverse these changes and restore sensitivity [186,187]. Noncoding RNAs, including microRNAs and long noncoding RNAs, regulate resistance-related pathways by modulating gene expression, affecting drug metabolism, apoptosis, and proliferation [188–190]. Chromatin remodeling and accessibility, influenced by these epigenetic mechanisms, mediate gene expression changes that enable cancer cells to adapt and resist therapy [191,192].

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The tumor microenvironment (TME) significantly contributes to therapy resistance and shapes clonal dynamics. Cellular components like tumor-associated macrophages (TAMs) and regulatory T cells (Tregs) create an immunosuppressive environment that hinders antitumor immunity and promotes resistance, including to immunotherapy [136,193,194]. Cancer-associated fibroblasts (CAFs) secrete growth factors and cytokines, remodel the extracellular matrix, and can induce drug efflux pumps, creating a protective niche for tumor cells and enhancing resistance [195–197]. TME factors such as cytokines (e.g., IL-6, TGF-β), angiogenesis, and hypoxia promote resistance and metabolic adaptations [194,198–200]. Hypoxia induces metabolic reprogramming, shifting cells towards glycolysis (Warburg effect) and activating survival pathways like those driven by HIF-1α, enabling survival under therapeutic stress [201–203].

Activation of alternative signaling pathways and compensatory feedback loops is a common mechanism for bypassing targeted therapy. The PI3K/AKT/mTOR pathway is frequently activated upon inhibition of upstream targets, promoting survival and proliferation [204–206]. The MAPK pathway (RAS/RAF/MEK/ERK) also serves as an alternative route, with feedback activation allowing tumor cells to escape targeted inhibition [26,207,208]. Crosstalk between key signaling pathways, such as AR signaling and the PI3K/AKT/mTOR or MAPK pathways, facilitates resistance in GU tumors, particularly prostate cancer [26,209–212]. The interaction between HIF-1α and AR signaling also contributes to resistance under hypoxic conditions [212,213].

Drug efflux pumps, primarily ABC transporters, and broader metabolic reprogramming significantly reduce drug efficacy. Overexpression of ABC transporters like P-glycoprotein actively extrudes drugs from cells, contributing to multidrug resistance [214,215]. Metabolic adaptations, including enhanced glycolysis, altered glutamine and lipid metabolism, and activation of the pentose phosphate pathway, provide alternative energy sources and support cell survival under therapeutic pressure [216–221]. The interplay between efflux pumps and metabolic shifts creates a complex resistance landscape [222,223].

Genomic alterations and the TME can differ significantly between primary and metastatic sites, influencing resistance patterns. Metastatic lesions often acquire distinct mutations and CNVs that promote survival in new microenvironments [224,225]. The TME at metastatic sites can vary in fibroblast composition, immune cell populations (e.g., predominance of M2 macrophages), and metabolic characteristics, creating site-specific resistance profiles [196,226–229]. These differences contribute to increased drug efflux and altered vulnerability to therapies, complicating treatment strategies for advanced disease [230,231].

Strategies to Overcome Therapy Resistance

Overcoming therapy resistance is a critical objective in the management of advanced GU tumors. As tumors develop complex mechanisms to evade treatment, novel strategies focusing on next-generation targeted agents, rational combination therapies, personalized medicine approaches, and emerging experimental modalities are being actively investigated to restore sensitivity and improve patient outcomes.

Novel classes of targeted agents and next-generation inhibitors are being developed to specifically target resistant GU tumors by exploiting their unique molecular vulnerabilities. Research into bromodomain and extraterminal (BET) inhibitors, particularly for tumors with NUTM1 rearrangements, has shown promise in preclinical models, targeting chromatin interactions crucial in these resistant subtypes [232–234]. Next-generation sequencing (NGS) plays a pivotal role by identifying actionable genetic alterations, such as microsatellite instability (MSI) or DNA mismatch repair (dMMR) deficiencies, which predict response to immune checkpoint inhibitors like pembrolizumab [235–237]. Emerging RNA-based therapies, including those involving long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs), are also being explored as potential biomarkers and therapeutic targets to influence tumor behavior and resistance [238,239]. Additionally, innovative modalities like photothermal and photodynamic therapy (PDT) using

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nanoparticles are being investigated for their ability to induce localized damage in resistant tumors [240,241].

Combination therapy approaches have shown significant promise in overcoming resistance in advanced GU cancers by targeting multiple pathways simultaneously. Combinations of targeted agents with immunotherapy, such as enfortumab vedotin (an ADC targeting Nectin-4) with pembrolizumab (a PD-1 inhibitor) in metastatic urothelial carcinoma, leverage synergistic effects to counteract immune evasion [7,242]. In castration-resistant prostate cancer, combining androgen receptor inhibitors like enzalutamide with immunotherapeutic approaches has demonstrated efficacy by targeting both androgen signaling and immune responses [243–245]. Similarly, combining multi-tyrosine kinase inhibitors like cabozantinib with nivolumab has shown favorable outcomes in advanced renal cell carcinoma [246,247]. Combinations of targeted agents with chemotherapy, such as docetaxel with abiraterone or enzalutamide, are also explored, sometimes employing strategic cycling to exploit treatment-induced vulnerabilities [243,248].

Personalized medicine strategies, including genomic profiling and biomarker identification, are essential for selecting patients for resistance-overcoming therapies. Comprehensive genomic profiling via NGS identifies actionable mutations and alterations, enabling tailored treatment plans based on individual tumor characteristics [249–251]. Liquid biopsies, analyzing circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs), provide real-time monitoring of tumor dynamics and emerging resistance mutations, guiding adaptive treatment decisions [18,252,253]. Biomarkers like high tumor mutational burden (TMB) or specific mutations (e.g., TP53, FGFR3) predict response to checkpoint inhibitors and targeted therapies [253]. Patient-derived xenograft (PDX) models also aid in testing therapies against a patient's unique tumor profile [254].

Promising emerging and experimental therapies are being investigated to address resistance mechanisms. Cell therapies, such as CAR T cells targeting PSMA in prostate cancer, aim to overcome resistance associated with AR signaling [14,235]. Gene editing technologies like CRISPR/Cas9 are used to identify and potentially modify genes linked to resistance or target metabolic vulnerabilities in cancer stem cells [255]. Radioligand therapies, such as ^177Lu-PSMA-617, deliver targeted radiation to resistant cells, particularly in castration-resistant prostate cancer [256]. Strategies targeting the TME, including inhibiting STAT3 signaling or modulating hypoxia, aim to reduce tumor resilience and sensitize tumors to existing treatments [257–260]. Experimental combinations, like PARP inhibitors with immunotherapy or autophagy inhibitors, are also explored [261,262].

Next-generation targeted agents and combination regimens are designed to counteract specific resistance mechanisms, such as bypass pathways or AR splice variants. To address bypass pathways, strategies include dual kinase inhibitors targeting primary drivers and compensatory routes [263,264], multi-kinase inhibitors, and approaches manipulating ROS levels [26,265]. For AR splice variants like AR-V7, next-generation antiandrogens and combinations targeting alternative pathways like the glucocorticoid receptor (GR) are being developed to restore sensitivity [266–268]. Combinations targeting AR interactions with co-factors or upstream pathways like FGF and MAPK are also explored [269,270].

Strategies targeting the tumor microenvironment (TME) enhance targeted therapy efficacy and overcome resistance. Targeting tumor-associated fibroblasts (TAFs) can disrupt their pro-tumorigenic and immunosuppressive roles [271,272]. Modulating hypoxia, for example, through improved oxygenation or hypoxia-activated prodrugs, can enhance drug activity [259,273,274]. Immune modulation within the TME, using checkpoint inhibitors or targeting immunosuppressive cells like Tregs and TAMs, promotes antitumor immunity [275,276]. ECM remodeling strategies can improve drug penetration [277,278]. Combination approaches addressing TME factors alongside tumor cells aim to prevent clonal expansion and enhance responses [279–283].

Liquid biopsies and dynamic biomarker monitoring play a crucial role in guiding adaptive treatment strategies to manage evolving resistance. Analyzing ctDNA and CTCs provides real-time insights into tumor evolution and the emergence of resistance mutations [284–290]. This allows for timely treatment adjustments based on the dynamic molecular landscape [285,286,289–291].

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Sequential monitoring of biomarkers like ctDNA levels or circulating miRNAs can indicate therapeutic effectiveness or failure and inform adaptive strategies [289,292–294].

Epigenetic therapies and other novel modalities are being explored, alone or in combination, to reverse resistance phenotypes. DNA methylation inhibitors (e.g., azacitidine, decitabine) reverse aberrant methylation, reactivating silenced tumor suppressor genes [295–297]. HDAC inhibitors alter histone acetylation to promote gene expression [298,299]. Combining epigenetic therapies with immunotherapy can enhance tumor immunogenicity [189,300]. These approaches also target specific resistance mechanisms, such as reactivating silenced tumor suppressor genes or reprogramming cancer stem cells [297,301–303].

Key considerations and challenges in designing clinical trials for resistant GU tumors include selecting appropriate, often heterogeneous, patient populations based on biomarkers and prior treatments [304–307]. Trial design must accommodate adaptive methodologies and carefully evaluate combination therapies, considering sequencing, timing, and potential interactions [308–310]. Integrating biomarkers and liquid biopsies for dynamic monitoring requires standardization and validation [311,312]. Understanding TME-mediated resistance and temporal changes in resistance mechanisms is also crucial for trial design [313–316].

Translational challenges and future directions for integrating these strategies into routine clinical practice involve standardizing liquid biopsy technologies and interpreting complex biomarker changes [145,317,318]. Addressing clinical heterogeneity and navigating regulatory and economic considerations for novel agents and biomarkers are also critical [319]. Education for healthcare providers on interpreting emerging data and managing complex regimens is essential [318,320,321]. Future directions include integrating multi-modal biomarkers, utilizing AI and big data for decision support, and employing innovative trial designs to accelerate clinical translation [145,322,323].

Clinical Implications and Translational Perspectives

Translating the growing understanding of therapy resistance mechanisms in GU tumors into clinical practice is paramount for improving patient outcomes. This process involves integrating the latest research findings into clinical trial designs, leveraging validated and emerging biomarkers for personalized therapy, utilizing real-world evidence, fostering multidisciplinary collaboration, navigating regulatory landscapes, and addressing cost-effectiveness considerations.

Latest research findings on resistance mechanisms are profoundly influencing clinical trial designs for GU tumors. Insights into intrinsic and extrinsic factors contributing to resistance, such as mutations affecting antigen presentation or immunosuppressive cells in the TME, are guiding the development of innovative methodologies [324]. Biomarker-driven approaches, utilizing exploratory biomarkers and non-invasive tools like circulating tumor DNA (ctDNA), are essential for stratifying patients and tailoring therapies based on individual tumor profiles [7,18]. This understanding also promotes the design of rational combination therapies to anticipate and mitigate resistance pathways, as seen in studies exploring combinations based on transcriptomic analyses of resistant pathways like FGFR [325,326]. Innovative trial designs, such as basket trials, are gaining traction to test drugs across multiple tumor types based on specific genetic alterations [327,328].

Validated biomarkers guide personalized therapies in routine clinical practice for GU oncology patients. Tumor mutational burden (TMB) and microsatellite instability (MSI)/mismatch repair deficiency (dMMR) status are established predictors of response to immune checkpoint inhibitors (ICIs) in GU cancers [7,141,329,330]. Circulating tumor DNA (ctDNA) is an emerging non-invasive biomarker for monitoring treatment responses, detecting relapses, and identifying actionable mutations that guide targeted therapies [18,331]. While PD-L1 expression remains crucial for patient stratification, its predictive power is enhanced when combined with other biomarkers [141,330]. Gene expression profiles, including lncRNAs and genes involved in DNA repair or EMT, are also being explored as potential biomarkers to inform treatment choices and combination strategies [332,333].

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Liquid biopsy technology is being harnessed to guide therapy modifications and monitor resistance in real time. By analyzing ctDNA and circulating tumor cells (CTCs), clinicians can assess treatment efficacy and detect emerging resistance mechanisms, such as acquired mutations, allowing for prompt therapy adjustments [334–337]. This continuous monitoring provides insights into tumor evolution and guides adaptive treatment strategies based on the dynamic molecular landscape [324,338]. While challenges remain in standardizing methodologies and interpreting results, liquid biopsy facilitates personalized care by providing real-time information on tumor dynamics and responsiveness.

Real-world evidence (RWE) and patient registries inform clinical decision-making about therapy resistance by providing insights beyond controlled clinical trials. RWE captures data from diverse populations in routine practice, revealing how therapies perform across various demographics and treatment contexts [339,340]. Patient registries track long-term outcomes and treatment patterns, highlighting common resistance patterns in broader populations [341]. RWE helps address knowledge gaps in underrepresented subgroups and enhances the external validity of clinical trial findings, supporting evidence-based decision-making [340,342].

Certain GU tumor subpopulations remain undertreated or understudied in clinical trials, including those of advanced age, with significant comorbidities, racial and ethnic minorities, and individuals facing sociodemographic and geographic barriers [1,343–346]. Adolescents and young adults also face unique challenges and disparities in care [347]. These disparities highlight the need for more inclusive clinical trial designs and tailored approaches to ensure equitable access to advanced therapies and address resistance in these specific populations [307,343].

Multidisciplinary approaches involving pathologists, oncologists, molecular biologists, and bioinformaticians have proven highly effective in tackling resistance. Molecular tumor boards integrate complex genomic data with clinical insights to personalize treatment plans and identify alternative therapies for resistant tumors [348,349]. Pathologists contribute by identifying relevant histopathological features and genetic alterations, while bioinformaticians analyze complex datasets to inform predictive models [349,350]. Collaboration among these experts, along with the use of advanced imaging techniques, facilitates a comprehensive understanding of tumor biology and guides individualized treatment protocols [351–353].

Collaborative models exist between academia, industry, and regulatory agencies to accelerate translational research in GU cancers. Cooperative research networks like EORTC facilitate large-scale clinical trials [354]. Innovative frameworks like Pfizer's Centers for Therapeutic Innovation promote hybrid partnerships [355]. Multi-stakeholder platforms like CAREFOR enhance academic clinical trials and bridge communication gaps [356]. Regulatory agencies establish frameworks and guidelines, streamlining approval processes [357]. These collaborations, often integrating RWE, are pivotal in understanding resistance and accelerating novel therapy development [358,359].

Regulatory hurdles can hinder the rapid integration of novel assays or targeted agents into clinical use. Complex regulatory frameworks, differences across regions, and the evolving nature of therapies pose challenges [360–362]. Demonstrating value and efficacy, especially for combination therapies, requires robust trial designs [362]. Manufacturing and quality control for novel modalities also present unique hurdles [363]. Regulatory pathways need to be adaptable to accommodate emerging therapies, particularly for rare diseases and precision medicine approaches [364,365].

Cost-effectiveness considerations are crucial when deploying novel targeted or combination therapies. High costs and variable insurance coverage significantly affect clinical decision-making, influencing treatment choice and patient access [366–370]. Cost-effectiveness analyses, considering efficacy, safety, and quality of life, are essential for justifying the financial burden [366,368](Castellano et al., 2022; Benjamin et al., 2024). RWE informs these analyses by providing data on real-world costs and outcomes [369].

Consensus statements and international collaborations push forward new standards in GU tumor care. International consensus recommendations establish standardized outcome measures [371]. Global statistics like GLOBOCAN inform strategies [372]. Organizations like ESMO and

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ANZUP develop evidence-based guidelines and promote collaborative research [373,374]. These efforts foster uniformity in treatment protocols and accelerate the integration of novel therapies into clinical practice.

Future Directions

The landscape of GU oncology is continuously evolving, driven by a more profound understanding of tumor biology and the mechanisms underlying therapy resistance. Future directions in this field are poised to revolutionize diagnosis, treatment, and patient management through technological advancements, innovative therapeutic strategies, and enhanced collaborative models.

Significant breakthroughs in next-generation sequencing (NGS) and single-cell analysis are on the horizon for mapping resistance phenomena. Single-cell technologies, such as single-cell RNA sequencing (scRNA-seq) and multidimensional mass cytometry, are crucial for uncovering the heterogeneity within tumors and identifying resistant subpopulations that bulk sequencing might miss [375–380]. These methods allow for granular analysis of tumor progression, drug responses, and the identification of cellular states contributing to resistance [377,381]. Integrated bioinformatics tools are essential for analyzing the complex data generated, deciphering resistance mechanisms, and identifying potential targets [382,383]. Advancements in targeted NGS and digital microfluidics are also providing insights into resistance in microbial pathogens, highlighting the broader applicability of these technologies [384–386]. Emerging single-cell metabolomics will further enhance our understanding of metabolic adaptations in resistant cells, integrating genomic, transcriptomic, and metabolomic data for biomarker discovery [383,387–389].

Big data and machine learning (ML) approaches will refine our predictive models for resistance in GU oncology. Leveraging vast datasets from multiomics sources, ML can identify complex patterns and biomarkers predictive of disease progression and treatment responses [390,391]. Integrating circulating tumor DNA (ctDNA) profiling into these models shows promise for predicting responses to immunotherapy and identifying hypermutated environments [392,393]. ML accelerates the identification and validation of novel biomarkers from high-dimensional data [14,394]. Circulating tumor cell (CTC) analysis also enhances predictive models by providing real-time insights into tumor evolution and resistance [395].

Future clinical trial designs, such as adaptive, basket, and umbrella trials, will accelerate novel therapy testing in GU tumors. Adaptive trials offer flexibility to modify protocols based on interim results, accelerating the identification of effective therapies [396,397]. Umbrella trials test multiple therapies targeting different biomarkers within a single disease type, while basket trials assess a single treatment across various tumor types sharing a common molecular feature [327,398–400]. Biomarker integration enhances the predictive power of these designs, stratifying patients based on molecular profiles [327,397]. Regulatory bodies are increasingly supportive of these innovative designs to expedite drug development [248,401].

Organoids and patient-derived xenografts (PDXs) hold significant potential for preclinical identification of resistance mechanisms. Patient-derived organoids (PDOs) closely mimic patient tumors, allowing for personalized drug sensitivity testing and elucidation of resistance mechanisms related to specific mutations or adaptations [402–405]. PDX/organoid platforms capture genomic and phenotypic heterogeneity, facilitating preclinical therapeutic investigations [406]. These models enable the combination of genomic profiling with phenotypic analyses to identify and validate new resistance biomarkers [403,407]. Ultimately, organoids and PDXs support personalized medicine by allowing functional drug testing that replicates patient-specific tumor biology [408].

TME-directed therapies are expected to evolve to encompass more holistic control of immunosuppression and angiogenesis. Targeting hypoxia, for instance, through HIF inhibitors or hypoxia-activated prodrugs, can reduce immunosuppression and enhance therapy efficacy [409–412]. Modulating tumor-associated macrophages (TAMs) to a pro-inflammatory phenotype is crucial [412,413]. Combination therapies targeting both angiogenic pathways and immune responses, such

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as VEGF inhibitors with immune checkpoint inhibitors, can normalize tumor vasculature and improve immune cell infiltration [414–417]. Innovative drug delivery systems using nanoparticles or extracellular vesicles (EVs) can enhance the precision of TME-directed therapies and modulate TME components [418–423].

Cross-disciplinary partnerships are needed to push GU tumor research into truly personalized or "precision" territory. Interdisciplinary collaboration among basic scientists, oncologists, and clinical researchers is vital for translating laboratory findings into clinical applications [424,425]. Partnerships with bioinformaticians and data scientists are essential for analyzing large datasets and developing predictive models [426]. Patient-engaged research provides valuable insights into patient needs and preferences [427,428]. Global and public health collaborations enhance the generalizability of findings and address disparities [429–431]. Collaboration with regulatory bodies and policymakers streamlines the process of bringing new therapies to market [432]. Translational research consortia facilitate synergistic efforts across institutions [433].

Advanced genomic editing or personalized cell-based therapies face ethical and logistical challenges. Ethical concerns include informed consent, patient autonomy, the potential for eugenics with germline editing, and unintended consequences [434–439]. Logistical challenges involve navigating complex regulatory frameworks, ensuring technical standardization and reproducibility, managing long-term monitoring and follow-up, and integrating these innovative therapies into existing healthcare systems [363–365,440,441]. Addressing these challenges requires collaboration among stakeholders to ensure responsible application and equitable access.

"Drug holiday" protocols or "dynamic dosing" strategies show potential success in delaying the onset of resistance by reducing selective pressure or adjusting dosages based on tumor response [442–445]. These approaches align with precision medicine principles, tailoring treatment based on individual patient and tumor characteristics.

Conclusions

The landscape of targeted therapy in GU oncology is characterized by significant advancements and ongoing challenges, particularly concerning the emergence of therapy resistance. A major consensus in the literature is that resistance mechanisms are multifaceted, deeply rooted in the TME, immune evasion strategies, and metabolic reprogramming of cancer cells [7,446–453]. The TME, with its complex interplay of CAFs, TAMs, and other immune cells, actively facilitates resistance by creating an immunosuppressive niche and promoting immune evasion [7,447,448]. Metabolic reprogramming further enables tumor cells to adapt and survive under therapeutic pressure, often impairing immune cell function and contributing to treatment failure [450,452,453]. Additionally, the inherent plasticity of tumor cells, driven by genetic and epigenetic alterations, allows for adaptive resistance mechanisms to emerge, necessitating continuous monitoring and dynamic treatment strategies [454,455].

Several pressing unanswered questions require further investigation to fully validate new therapeutic strategies. A more profound understanding of TME-mediated resistance, particularly the specific interactions between CAFs and TAMs and how they modulate immune responses, is crucial [456]. Reliable biomarkers for predicting patient responses to combination therapies, especially those involving metabolic inhibitors, are needed to guide patient stratification [70,453]. Addressing on-target, off-tumor toxicity of therapies targeting common tumor antigens remains a significant hurdle, requiring the identification of more tumor-specific targets or structural variants [119,457]. The role of epigenetic modulation in enhancing treatment responses, particularly with agents like PARP inhibitors, and the impact of the gut microbiome on therapy efficacy and toxicity also warrant further exploration [458–461].

Insights into these resistance mechanisms have reshaped the philosophical and clinical approach to treating GU cancers. There is a clear shift from traditional single-agent therapies towards more personalized, combination-based strategies that aim to circumvent the multifaceted nature of resistance [462,463]. Recognizing tumor heterogeneity and the dynamic evolution of resistance has

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led to the development of adaptive treatment strategies, including the use of liquid biopsies for real-time monitoring of tumor genomics [70,464–468]. Combination therapies targeting multiple pathways simultaneously are increasingly explored to reduce the likelihood of resistance development [469–471].

Leading experts offer several recommendations for the future of targeted therapy in GU tumors. Precision medicine, guided by genomic and molecular profiling, is paramount for tailoring individualized treatment plans [14]. Targeting TAMs and other TME components, improving biomarker discovery for patient selection, and considering factors like circadian rhythms in treatment regimens are key areas of focus [141,472,473]. Multi-histology clinical trials and the development of innovative therapeutic agents targeting specific pathways, such as FGFR3, are encouraged [95,474]. Furthermore, strengthening supportive care and fostering interdisciplinary collaborations are vital for advancing GU cancer treatment and addressing complex resistance mechanisms [119].

Finally, healthcare systems must better integrate new evidence on resistance mechanisms into standard treatment guidelines. This involves regularly updating guidelines based on emerging research, implementing multidisciplinary tumor boards, incorporating validated biomarkers into clinical pathways, utilizing clinical decision support tools, encouraging participation in clinical trials focused on resistance, educating and involving patients in shared decision-making, and fostering research collaborations [475–483]. Balancing evidence-based decisions with patient-centered values and preferences, including economic considerations and quality of life, is crucial for optimizing care [484–488]. Strategies such as “drug holidays” or “dynamic dosing” are also being explored to delay the onset of resistance by managing selective pressure [489–497].

In conclusion, the future of targeted therapy in GU oncology lies in a holistic, personalized, and adaptive approach. By addressing the complexities of resistance through innovative research, collaborative efforts, and patient-centered care, the field aims to significantly improve outcomes for patients with genitourinary malignancies.

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