Review

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Targeted Therapy Resistance in Genitourinary Cancers: From Molecular Mechanisms to Clinical Strategies

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Targeted therapies have revolutionized the treatment landscape of genitourinary (GU) malignancies, offering significant clinical benefits, particularly in renal cell carcinoma (RCC). However, the efficacy of these agents is frequently undermined by the inevitable development of therapy resistance. This review provides a critical analysis of the molecular mechanisms driving resistance in prostate, bladder, and kidney cancers and evaluates emerging clinical strategies to overcome them. We dissect the complex interplay between on-target genomic alterations (e.g., androgen receptor (AR) splice variants, fibroblast growth factor receptor (FGFR) gatekeeper mutations), the activation of compensatory bypass signaling pathways (e.g., phosphoinositide 3-kinase [PI3K]/protein kinase B [AKT] and mitogen-activated protein kinase [MAPK]), and the phenomenon of epigenetic lineage plasticity, such as the neuroendocrine transdifferentiation observed in prostate cancer. Furthermore, we examine the active role of the tumor microenvironment—mediated by cancer-associated fibroblasts and hypoxia—in sheltering tumor cells from therapeutic insults. Beyond defining these mechanisms, this review evaluates the rationale for next-generation therapeutic approaches, including proteolysis targeting chimeras (PROTACs), covalent inhibitors, and epigenetic modifiers. We also address the translational challenges of rational combination therapies, specifically the limitations imposed by cumulative toxicities. Finally, we discuss the pivotal but complex role of biomarkers, such as circulating tumor DNA (ctDNA), in guiding dynamic treatment sequencing and realizing the promise of precision oncology.

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 (Rawla, 2019; Sung *et al.*, 2021) [1,2]. Prostate cancer, for instance, remains the second most frequently diagnosed cancer in men worldwide, with over 1.4 million new cases reported in 2020 [2]. Similarly, bladder and kidney cancers place significant burdens on healthcare systems, driven by aging populations and varying risk factors across different geographies [3,4]. Against this epidemiological backdrop, the treatment landscape has undergone a paradigm shift with the rise of targeted therapies (Table 1). These modalities, including immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs), have demonstrated durable remission and improved survival in select patient subgroups [5,6].

Specifically, agents targeting the vascular endothelial growth factor (VEGF) pathway and immune checkpoints have revolutionized the management of advanced renal cell carcinoma (RCC) [7]. Meanwhile, next-generation androgen receptor (AR) inhibitors have redefined the standard of care in metastatic castration-resistant prostate cancer (mCRPC) [8,9]. However, despite these advances, the initial efficacy of these treatments is often transient. Tumors inevitably develop resistance through complex adaptive mechanisms, leading to disease progression and limiting long-term survival [10]. This acquired resistance is now the primary obstacle in the clinical management of GU cancers.

While several reviews have cataloged isolated molecular mechanisms, a critical synthesis of how these pathways interact and their direct translational implications is lacking. This review aims to fill that gap by moving beyond a simple description of resistance mechanisms to provide a critical analysis of the preclinical and clinical evidence supporting their roles. We dissect the complex interplay between genomic alterations, epigenetic reprogramming, and the tumor microenvironment (TME) [11,12]. Furthermore, we evaluate emerging therapeutic strategies designed to preempt or reverse resistance, with a strong focus on their clinical applicability and the pivotal role of biomarkers in personalized medicine.

Table 1. Major targeted therapies and their mechanisms in genitourinary cancers.

Cancer type	Therapeutic target	Drug class	Example drug(s)
Prostate cancer	Androgen receptor (AR) signaling	Second-generation AR antagonist	Enzalutamide, apalutamide
	Androgen synthesis (CYP17A1)	Androgen synthesis inhibitor	Abiraterone acetate
	DNA repair (PARP)	PARP inhibitor	Olaparib, rucaparib
Urothelial carcinoma	Fibroblast growth factor receptor (FGFR)	Pan-FGFR tyrosine kinase inhibitor	Erdafitinib
	Immune checkpoints (PD-1/PD-L1)	Monoclonal antibodies (ICIs)	Pembrolizumab
			Avelumab
Renal cell carcinoma	Vascular endothelial growth factor receptors (VEGFRs) & Other kinases	Multi-targeted tyrosine kinase inhibitor (TKI)	Sunitinib, cabozantinib
	Immune checkpoints (PD-1/CTLA-4)	Monoclonal antibodies (ICIs)	Nivolumab, ipilimumab

CYP17A1, cytochrome P450 17A1; PARP, poly (ADP-ribose) polymerase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ICIs, immune checkpoint inhibitors.

Molecular Mechanisms of Resistance in GU Tumors

The development of resistance to targeted therapy is a complex and multifactorial process, reflecting the remarkable adaptability of cancer cells under selective pressure. Tumors employ a diverse arsenal of molecular strategies to evade therapeutic blockade, which can be broadly categorized into alterations of the drug target itself, the activation of compensatory signaling pathways, epigenetic reprogramming, and contributions from the tumor microenvironment. Understanding these distinct but often interconnected mechanisms is critical for developing strategies to overcome resistance. This section will dissect the primary molecular escape pathways observed in genitourinary cancers.

Genomic Alterations in Target Pathways

One of the most direct mechanisms of acquired resistance involves genetic alterations within the gene that encodes the therapeutic target. These alterations, which include point mutations, gene amplifications, or structural rearrangements, can prevent drug binding or restore the target's function despite the presence of the inhibitor.

AR Modifications in Prostate Cancer

In prostate cancer, resistance to second-generation AR inhibitors like enzalutamide and abiraterone is frequently driven by modifications to the AR gene itself. Point mutations in the AR ligand-binding domain (LBD), such as the F877L mutation, can alter the receptor's conformation, reducing drug affinity and paradoxically allowing activation by other steroid hormones [13,14]. Furthermore, AR gene amplification, leading to overexpression of the receptor protein, can overwhelm the inhibitory capacity of standard drug concentrations.

A critical and clinically distinct mechanism is the expression of constitutively active AR splice variants, most notably androgen receptor splice variant 7 (AR-V7), which lacks the LBD. Because AR-V7 is not dependent on ligand binding for its activity, it confers intrinsic resistance to all LBD-targeting agents [15]. While the detection of AR-V7 in circulating tumor cells (CTCs) or circulating tumor DNA (ctDNA) has been validated as a negative predictor for response to AR signaling inhibitors, its clinical utility is nuanced by detection challenges. Recent studies indicate that discordant results between liquid biopsy platforms can occur, and the absence of AR-V7 in ctDNA does not necessarily guarantee a response to hormonal therapy, highlighting the need for highly sensitive, standardized assays before widespread adoption in all clinical settings [16,17].

FGFR Alterations in Urothelial Carcinoma

In urothelial carcinoma, particularly in tumors harboring activating fusions or mutations in the fibroblast growth factor receptor (FGFR), targeted inhibitors like erdafitinib have shown promise. However, acquired resistance commonly arises through secondary point mutations in the FGFR kinase domain [18]. These mutations, such as the "gatekeeper" mutation V561M in FGFR2 or N550K in FGFR3, function similarly to the T790M mutation in EGFR-mutant lung cancer, sterically hindering the drug's ability to bind to the ATP-binding pocket while preserving the kinase's activity [18]. The molecular heterogeneity of these secondary mutations poses a significant challenge, as distinct alterations may confer cross-resistance to some TKIs but sensitivity to others, necessitating dynamic genomic profiling upon disease progression.

VHL and *MET* Alterations in Renal Cell Carcinoma

The therapeutic strategy for clear cell renal cell carcinoma (ccRCC) is built upon targeting the consequences of *von Hippel-Lindau* (*VHL*) inactivation, primarily the upregulation of VEGF. Unlike prostate or bladder cancers, where secondary mutations in the target gene are common, resistance in RCC rarely involves secondary mutations in *VHL* or vascular endothelial growth factor receptor (VEGFR). Instead, resistance is frequently driven by the amplification

or activating mutations of the *mesenchymal-epithelial transition factor (MET)* proto-oncogene [19]. This alteration drives resistance to VEGF inhibitors by providing an alternative, potent pathway for tumor angiogenesis and proliferation, underscoring the redundancy of angiogenic signaling in this tumor type [19].

Activation of Bypass Signaling Tracts

Tumor cells can develop resistance not only by altering the drug's direct target but also by activating alternative signaling pathways that provide parallel survival and proliferation signals, thereby "bypassing" the inhibited node. This mechanism underscores the highly networked nature of intracellular signaling, in which the inhibition of one dominant driver often releases negative feedback on another, leading to its compensatory activation. In GU cancers, the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) and the rat sarcoma (RAS)/Rapidly Accelerated Fibrosarcoma (RAF)/mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK) pathways are two of the most critical bypass routes.

The PI3K/AKT/mTOR Pathway

The PI3K/AKT/mTOR pathway is a central regulator of cell growth, metabolism, and survival, and its aberrant activation is a frequent event in therapy resistance across all GU malignancies [20]. In prostate cancer, a reciprocal feedback loop exists between the AR and the PI3K/AKT pathway. Inhibition of AR signaling relieves the negative feedback on AKT, leading to its phosphorylation and activation, which in turn sustains cell survival [20,21]. Conversely, inhibition of the PI3K pathway can lead to increased AR signaling, creating a "whack-a-mole" therapeutic challenge. This is frequently exacerbated by the loss of the tumor suppressor phosphatase and tensin homolog (PTEN), an event found in approximately 40% of metastatic castration-resistant prostate cancer (mCRPC) cases, which leads to constitutive AKT activation and intrinsic resistance to hormonal therapies [22].

In urothelial tumors treated with FGFR inhibitors, the activation of the PI3K/AKT pathway is a well-documented resistance mechanism. Upregulation of signaling through this pathway, often via activating mutations in phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) or inactivation of PTEN, can sustain cell proliferation even when FGFR is effectively blocked [23]. Although therapies targeting the VEGF pathway are standard in ccRCC, resistance often emerges through the activation of the PI3K/AKT/mTOR axis. This pathway lies downstream of multiple receptor tyrosine kinases, and its activation can promote angiogenesis and tumor growth independently of VEGF signaling, providing a robust escape mechanism.

The RAS/RAF/MEK/ERK (MAPK) Pathway

The MAPK pathway is another fundamental signaling cascade that, when hyperactivated, can drive resistance to various targeted agents [24]. While less universally implicated as a primary resistance driver to AR inhibition in prostate cancer compared to the PI3K pathway, RAS/RAF/MEK/ERK signaling is a key bypass mechanism in urothelial and kidney cancers. For instance, in urothelial cells resistant to FGFR inhibitors, amplification or mutation of *RAS* genes can reactivate the MAPK pathway downstream of the blocked receptor, rendering the FGFR inhibitor ineffective [25]. This reactivation highlights the necessity of considering vertical or horizontal combination blockades to achieve durable disease control.

Epigenetic Reprogramming and Lineage Plasticity

Beyond fixed genomic alterations, tumors can evade targeted therapies through dynamic, non-mutational mechanisms involving epigenetic modifications. This process allows cancer cells to alter their gene expression programs and switch their cellular identity, a phenomenon known as lineage plasticity. By adopting a different cellular state, tumors can become independent of the signaling pathway being targeted, rendering the therapy ineffective.

Neuroendocrine Transdifferentiation in Prostate Cancer

The most striking example of lineage plasticity in GU cancers is the emergence of neuroendocrine prostate cancer (NEPC) as a mechanism of resistance to intense AR signaling inhibition. Under the selective pressure of potent AR-targeted therapies, a subset of prostate adenocarcinoma cells undergoes lineage transdifferentiation. This shift is often facilitated by the concurrent loss of the tumor suppressors *retinoblastoma 1 (RB1)* and *tumor protein p53 (TP53)*, which creates a permissive genomic environment for plasticity [26]. Subsequent epigenetic reprogramming, driven by the overexpression of enhancer of zeste homolog 2 (EZH2) and the upregulation of pluripotency factors like SRY-box transcription factor 2 (SOX2), silences the AR signaling axis while upregulating neuroendocrine lineage markers such as synaptophysin and chromogranin A [26,27]. The resulting NEPC phenotype is aggressive, AR-independent, and inherently resistant to hormonal therapies, necessitating alternative therapeutic strategies such as platinum-based chemotherapy or EZH2 inhibitors.

Subtype Switching in Urothelial Carcinoma

In urothelial carcinoma, molecular subtyping has revealed distinct biological behaviors that influence drug response. Resistance to FGFR-targeted therapies can arise through a "subtype switch" from a luminal phenotype—which is dependent on FGFR3 signaling—to a more basal or squamous-like phenotype. This transition is governed by epigenetic regulators and transcription factors, such as the downregulation of peroxisome proliferator-activated recep-

tor gamma (PPARG) and GATA binding protein 3 (GATA3) [28]. The basal subtype is less reliant on FGFR signaling and more driven by EGFR or Signal Transducer and Activator of Transcription 3 (STAT3) pathways, effectively bypassing the therapeutic blockade [29]. Understanding these plastic states is crucial, as the basal phenotype may exhibit different vulnerabilities, such as increased sensitivity to immunotherapy or EGFR inhibitors.

Epigenetic Silencing in Renal Cell Carcinoma

While lineage plasticity is less defined in RCC compared to prostate or bladder cancer, epigenetic silencing of tumor suppressor genes plays a pivotal role in resistance. For instance, global hypomethylation or specific promoter hypermethylation can lead to the silencing of genes that regulate sensitivity to TKIs [30]. Furthermore, alterations in chromatin remodeling complexes, such as the loss of *polybromo 1 (PBRM1)* or *BRCA1-associated protein 1 (BAP1)*, are frequent in clear cell RCC and distinctively modulate the tumor's response to both anti-angiogenic agents and immune checkpoint inhibitors, highlighting the intersection between the epigenome and therapeutic efficacy [31].

The Role of the Tumor Microenvironment

Resistance to targeted therapy is not solely a tumor cell-autonomous process. The surrounding tumor microenvironment (TME)—a complex ecosystem of stromal cells, immune cells, blood vessels, and the extracellular matrix (ECM)—plays a critical, active role in protecting cancer cells from therapeutic insults and fostering their survival.

CAFs and Paracrine Protection

Cancer-associated fibroblasts (CAFs) are a dominant component of the stroma in GU malignancies, particularly in prostate and bladder cancers. CAFs mediate resistance through the secretion of a diverse array of soluble factors that activate survival pathways in adjacent tumor cells. For instance, CAFs can secrete hepatocyte growth factor (HGF), which binds to the MET protein receptor (c-MET) receptor on tumor cells, potently activating the PI3K/AKT and MAPK bypass pathways [32]. This paracrine loop provides a robust survival signal that can sustain proliferation even when the primary therapeutic target (e.g., AR or EGFR) is inhibited. Furthermore, CAFs are a major source of Interleukin-6 (IL-6), a cytokine that activates STAT3 signaling, promoting an apoptosis-resistant phenotype in castration-resistant prostate cancer [33].

Immunosuppressive Barriers and Metabolic Competition

The immune landscape of the TME directly dictates the efficacy of immune checkpoint inhibitors (ICIs). In many resistant GU tumors, the TME is characterized by an influx of immunosuppressive cells, such as myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs) polarized towards a pro-tumorigenic M2 phenotype [34]. These cells create a hostile environment for cytotoxic T cells by depleting essential nutrients (e.g., via arginase expression) and expressing high levels of programmed death-ligand 1 (PD-L1), effectively erecting a barrier against immune attack [35].

Hypoxia and Metabolic Reprogramming

Hypoxia is a hallmark of the GU tumor microenvironment, particularly in renal cell carcinoma (RCC). The stabilization of Hypoxia-Inducible Factors (HIFs) drives a profound metabolic reprogramming in tumor cells, shifting them towards aerobic glycolysis (the Warburg effect) [36]. This metabolic shift supports rapid proliferation and contributes to drug resistance by acidifying the microenvironment, which can impair the uptake and efficacy of weak-base chemotherapeutics and targeted agents. Moreover, hypoxia-induced stress responses can activate the Unfolded Protein Response (UPR), further enhancing cell survival mechanisms under therapeutic pressure [37]. Finally, the dense extracellular matrix (ECM) acts as a physical barrier limiting drug penetration and initiates integrin-mediated signaling that confers adhesion-dependent drug resistance [38].

Strategies to Overcome Therapy Resistance

A detailed understanding of the molecular mechanisms driving therapeutic failure is not merely an academic exercise; it is the foundation for developing rational strategies to preempt, overcome, or reverse resistance. As our knowledge of the escape pathways detailed in the previous section has grown, so too has our armamentarium of strategies to counter them. These approaches range from designing more potent, next-generation inhibitors that can neutralize on-target resistance mutations to implementing intelligent combination therapies that block parallel survival pathways.

Developing Next-Generation Inhibitors to Counter On-Target Resistance

As established above, a primary driver of acquired resistance involves genomic alterations in the therapeutic target, which can render existing drugs ineffective. Therefore, a key research priority is not merely the discovery of new targets, but the continuous development of next-generation inhibitors specifically engineered to overcome these known resistance mutations. This drives a clinical paradigm of sequential therapy, where the molecular profile of the resistant tumor dictates the next line of defense.

In prostate cancer, the clinical challenge posed by resistance to second-generation AR inhibitors (e.g., enzalutamide, abiraterone) frequently involves point mutations (e.g., F877L) and the emergence of splice variants (e.g., AR-V7). Since AR-V7 lacks the ligand-binding domain targeted by current drugs, the logical therapeutic evolution

involves agents that do not rely on this domain. Novel strategies currently under investigation include N-terminal domain inhibitors and, more radically, Proteolysis Targeting Chimeras (PROTACs). Unlike traditional inhibitors, PROTACs exploit the cell's ubiquitin-proteasome system to degrade the AR protein entirely [39]. This shift from inhibition to degradation represents a potential route to overcome the structural intransigence of splice variants and high-copy-number amplifications.

A similar principle of structure-guided drug design applies to urothelial carcinoma and RCC. In bladder cancer, resistance to the FGFR inhibitor erdafitinib often emerges through secondary "gatekeeper" mutations in the FGFR kinase domain that sterically hinder drug binding. This has spurred the development of next-generation covalent inhibitors designed to bind irreversibly to the mutant kinase, maintaining potency even in the presence of structural alterations [40]. In RCC, the standard of care has evolved into a paradigm of sequential TKI administration. For example, third-generation inhibitors like cabozantinib are strategically deployed to overcome resistance mechanisms—such as *MET* upregulation—that are induced by first-line agents like sunitinib [7,19].

Rational Combination Therapies to Block Escape Pathways

Given that tumors often circumvent targeted therapies by activating parallel or downstream survival pathways, a powerful strategy to overcome resistance is the use of rational combination therapies. The core principle is a "horizontal blockade", simultaneously inhibiting the primary therapeutic target and the identified escape route (e.g., PI3K/AKT or MAPK pathways).

However, while biologically compelling, the clinical translation of these combinations is frequently limited by overlapping toxicities. For instance, in prostate cancer, combining AR inhibitors with PI3K/AKT pathway inhibitors has shown efficacy in PTEN-deficient tumors, but these regimens are associated with significant adverse events, including severe hyperglycemia, rash, and gastrointestinal toxicity [20]. These cumulative toxicities often necessitate dose reductions or treatment discontinuation, potentially compromising antitumor efficacy. Therefore, future success in this arena relies not just on identifying the right targets but on optimizing dosing schedules (e.g., pulsatile dosing) to maintain pressure on the tumor while allowing normal tissue recovery [41].

Similarly, in advanced RCC, the combination of immune checkpoint inhibitors with VEGFR-TKIs has become a standard of care, leveraging the immunomodulatory effects of anti-angiogenic therapy to normalize the tumor vasculature and enhance immune cell infiltration [42]. Yet, this approach requires vigilant management of immune-related adverse events (irAEs) superimposed on TKI-associated toxicities (e.g., hypertension, hepatotoxicity), highlighting the need for multidisciplinary management in the era of combination therapy [43].

Targeting Epigenetic Plasticity

As detailed previously, tumors can develop resistance by fundamentally altering their cellular identity through epigenetic reprogramming, a process known as lineage plasticity. This is particularly evident in the transition of prostate adenocarcinoma to an aggressive, androgen-receptor-independent neuroendocrine phenotype (NEPC) under therapeutic pressure. Since this transformation is driven by changes in the epigenetic landscape rather than new genomic mutations, it requires a unique therapeutic approach focused on reprogramming the cell state.

The most direct strategy to combat this form of resistance is to target the epigenetic "writers" and "readers" responsible for cellular reprogramming. In prostate cancer, the overexpression of EZH2 works in concert with lineage transcription factors to silence AR signaling and activate stem-like programs. Consequently, EZH2 inhibitors (e.g., tazemetostat) are being investigated not merely as cytotoxic agents, but as "differentiation therapies" designed to restore sensitivity to hormonal agents or prevent the phenotypic switch entirely [26]. Similarly, Bromodomain and Extra-Terminal motif (BET) inhibitos (targeting bromodomain-containing protein 4 [BRD4]) have shown preclinical efficacy in disrupting the transcriptional machinery that sustains oncogene expression in castration-resistant models, providing a rationale for clinical trials targeting chromatin readers [44].

Beyond reversing lineage plasticity, epigenetic therapies offer a mechanism to overcome immune evasion. DNA methyltransferase inhibitors (DNMTi) and histone deacetylase (HDAC) inhibitors can induce a state of "viral mimicry" by de-repressing endogenous retroviral elements within the tumor genome. This process triggers an interferon response that turns "cold", resistant tumors into "hot" targets susceptible to immune checkpoint blockade [45]. However, the clinical implementation of these strategies faces significant hurdles, primarily due to the lack of predictive biomarkers to identify patients whose resistance is driven primarily by epigenetic rather than genomic mechanisms. The challenge is delivering effective doses without unacceptable systemic toxicity.

The Role of Biomarkers in Guiding Therapeutic Strategy

The successful implementation of the strategies discussed above—from next-generation inhibitors to rational combination therapies—is critically dependent on the ability to select the right treatment for the right patient at the right time. A one-size-fits-all approach is insufficient in the face of such diverse resistance mechanisms. This underscores the essential role of predictive biomarkers in guiding therapeutic decisions and realizing the vision of personalized medicine.

Table 2. Clinical summary of resistance pathways, biomarkers, and overcoming strategies.

Cancer type	Common resistance mechanism	Potential biomarker	Corresponding overcoming strategy
Prostate cancer	Expression of AR splice variant (e.g., AR-V7)	ctDNA or tissue analysis for AR-V7 RNA	Switch to therapy not targeting the AR ligand-binding domain (e.g., taxanes, PARP inhibitors)
	Activation of PI3K/AKT pathway (e.g., via PTEN loss)	Immunohistochemistry for PTEN; sequencing for PIK3CA mutations	Combine AR inhibitor with PI3K/AKT pathway inhibitor (clinical trials)
	Epigenetic shift to neuroendocrine phenotype (NEPC)	Tissue biopsy with neuroendocrine markers (e.g., synaptophysin, chromogranin A)	Combine with epigenetic modifiers (e.g., EZH2 inhibitors) or platinum-based chemotherapy
Urothelial carcinoma	Secondary "gatekeeper" mutations in the FGFR kinase domain	ctDNA or tissue sequencing upon progression	Switch to a next-generation FGFR inhibitor designed to overcome the specific mutation.
	Activation of PI3K/AKT pathway as a bypass pathway	Sequencing for PIK3CA mutations or other pathway alterations	Combine FGFR inhibitor with PI3K/AKT pathway inhibitor
Renal cell carcinoma	Upregulation/amplification of alternative pro-angiogenic pathways (e.g., *MET*)	FISH or sequencing for *MET* amplification	Combine primary TKI with a *MET* inhibitor (e.g., cabozantinib)
General (Pan-GU)	TME-mediated immunosuppression (e.g., M2 TAMs, Hypoxia)	PD-L1 status; Hypoxia signatures	Combination of VEGF-TKIs with Immune checkpoint inhibitors

AR-V7, androgen receptor splice variant 7; PI3K/AKT, phosphoinositide 3-kinase/protein kinase B; *MET*, *mesenchymal-epithelial transition factor*; M2 TAMs, M2-polarized tumor-associated macrophages; FISH, fluorescence *in situ* hybridization; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin homolog; EZH2, enhancer of zeste homolog 2; FGFR, fibroblast growth factor receptor; ctDNA, circulating tumor DNA; VEGF, vascular endothelial growth factor.

By prospectively identifying the specific mechanism of resistance active in a patient's tumor, clinicians can tailor therapy accordingly. For example, assessing the tumor's status for the PTEN tumor suppressor via immunohistochemistry or sequencing can provide a clear rationale for adding a PI3K/AKT pathway inhibitor to a patient's regimen [21,46]. Similarly, identifying specific *FGFR* alterations is standard practice for guiding the use of erdafitinib in urothelial carcinoma, and detecting secondary resistance mutations in ctDNA could eventually guide the use of next-generation covalent inhibitors [16].

However, the transition from research validation to routine clinical use faces significant practical hurdles. While liquid biopsies (ctDNA/CTCs) offer a non-invasive method to monitor molecular evolution (e.g., detecting *AR-V7* in prostate cancer), their sensitivity can be limited in non-metastatic or low-shedding tumors, leading to discordant results with tissue biopsies [17,47]. Furthermore, the high cost of comprehensive genomic profiling (CGP) and variable insurance coverage create substantial disparities in patient access to these precision tools [48]. Therefore, the future of precision oncology depends not only on discovering new markers but also on standardizing assays and demonstrating their cost-effectiveness in guiding treatment modification.

Ultimately, the systematic integration of molecular biomarkers into clinical practice is necessary to translate our growing understanding of resistance into improved patient outcomes. This involves routine molecular profiling of tumors at baseline and upon disease progression to dynamically adjust treatment strategies as the tumor evolves (Table 2).

Conclusion

The advent of targeted therapies has marked a significant step forward in the management of genitourinary malignancies, yet the development of resistance remains the primary obstacle to long-term patient survival. As this review has detailed, resistance is a complex and multifaceted challenge, driven not by a single cause but by an interconnected network of molecular mechanisms. These include direct genomic alterations in the drug's target, the activation of compensatory bypass signaling pathways, profound epigenetic reprogramming that alters cellular identity, and supportive signaling from the surrounding tumor microenvironment. Effectively combating such a dynamic process requires a similarly sophisticated and rational approach. The future of cancer care in this domain will rely on the strategic development of next-generation inhibitors, the intelligent use of combination therapies designed to block these escape routes, and the clinical integration of predictive biomarkers to guide treatment decisions. By continuing to unravel the complexities of resistance, we can move closer to a paradigm of truly personalized medicine and of-

fer more durable and effective treatments for patients with genitourinary cancers.

Availability of Data and Materials

Not applicable.

Author Contributions

AC is the sole contributor to this manuscript. The author confirms sole responsibility for the conception and design of the study; the acquisition, analysis, and interpretation of data; the preparation of the manuscript; and for being accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

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References

[1] Rawla P. Epidemiology of Prostate Cancer. World Journal of Oncology. 2019; 10: 63–89. https://doi.org/10.14740/wjon1191.

[2] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: a Cancer Journal for Clinicians. 2021; 71: 209–249. https://doi.org/10.3322/caac.21660.

[3] Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, *et al*. Cancer statistics for the year 2020: An overview. International Journal of Cancer. 2021; 149: 778–789. https://doi.org/10.1002/ijc.33588.

[4] Ridyard DG, Buller DM, Ristau BT. The Current State of Adjuvant Therapy Following Surgery for High-risk Renal Cell Carcinoma. European Urology Focus. 2019; 5: 935–938. https://doi.org/10.1016/j.euf.2019.03.020.

[5] Labadie BW, Balar AV, Luke JJ. Immune Checkpoint Inhibitors for Genitourinary Cancers: Treatment Indications, Investigational Approaches and Biomarkers. Cancers. 2021; 13: 5415. https://doi.org/10.3390/cancers13215415.

[6] Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, *et al*. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. The New England Journal of Medicine. 2015; 373: 1803–1813. https://doi.org/10.1056/NEJMoa1510665.

[7] Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, *et al*. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. The New England Journal of Medicine. 2018; 378: 1277–1290. https://doi.org/10.1056/NEJMoa1712126.

[8] Jacob A, Raj R, Allison DB, Myint ZW. Androgen Receptor Signaling in Prostate Cancer and Therapeutic Strategies. Cancers. 2021; 13: 5417. https://doi.org/10.3390/cancers13215417.

[9] Maughan BL, Antonarakis ES. Androgen pathway resistance in prostate cancer and therapeutic implications. Expert Opinion on Pharmacotherapy. 2015; 16: 1521–1537. https://doi.org/10.1517/14656566.2015.1055249.

[10] Aldea M, Andre F, Marabelle A, Dogan S, Barlesi F, Soria JC. Overcoming Resistance to Tumor-Targeted and Immune-Targeted Therapies. Cancer Discovery. 2021; 11: 874–899. https://doi.org/10.1158/2159-8290.CD-20-1638.

[11] Barth DA, Juracek J, Slaby O, Pichler M, Calin GA. lncRNA and Mechanisms of Drug Resistance in Cancers of the Genitourinary System. Cancers. 2020; 12: 2148. https://doi.org/10.3390/cancers12082148.

[12] Datta D, Aftabuddin M, Gupta DK, Raha S, Sen P. Human Prostate Cancer Hallmarks Map. Scientific Reports. 2016; 6: 30691. https://doi.org/10.1038/srep30691.

[13] Joseph JD, Lu N, Qian J, Sensintaffar J, Shao G, Brigham D, *et al*. A clinically relevant androgen receptor mutation confers resistance to second-generation antiandrogens enzalutamide and ARN-509. Cancer Discovery. 2013; 3: 1020–1029. https://doi.org/10.1158/2159-8290.CD-13-0226.

[14] Watson PA, Arora VK, Sawyers CL. Emerging mechanisms of resistance to androgen receptor inhibitors in prostate cancer. Nature Reviews. Cancer. 2015; 15: 701–711. https://doi.org/10.1038/nrc4016.

[15] Antonarakis ES, Lu C, Wang H, Luber B, Nakazawa M, Roeser JC, *et al*. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. The New England Journal of Medicine. 2014; 371: 1028–1038. https://doi.org/10.1056/NEJMoa1315815.

[16] Gerke MB, Jansen CS, Bilen MA. Circulating Tumor DNA in Genitourinary Cancers: Detection, Prognostics, and Therapeutic Implications. Cancers. 2024; 16: 2280. https://doi.org/10.3390/cancers16122280.

[17] Di Meo A, Bartlett J, Cheng Y, Pasic MD, Yousef GM. Liquid biopsy: a step forward towards precision medicine in urologic malignancies. Molecular Cancer. 2017; 16: 80. https://doi.org/10.1186/s12943-017-0644-5.

[18] Lau DK, Jenkins L, Weickhardt A. Mechanisms of acquired resistance to fibroblast growth factor receptor targeted therapy. Cancer Drug Resistance (Alhambra, Calif.). 2019; 2: 568–579. https://doi.org/10.20517/cdr.2019.42.

[19] Shuch B, Falbo R, Parisi F, Adeniran A, Kluger Y, Kluger HM, *et al*. MET Expression in Primary and Metastatic Clear Cell Renal Cell Carcinoma: Implications of Correlative Biomarker Assessment to MET Pathway Inhibitors. BioMed Research International. 2015; 2015: 192406. https://doi.org/10.1155/2015/192406.

[20] Shorning BY, Dass MS, Smalley MJ, Pearson HB. The PI3K-AKT-mTOR Pathway and Prostate Cancer: At the Crossroads of AR, MAPK, and WNT Signaling. International Journal of Molecular Sciences. 2020; 21: 4507. https://doi.org/10.3390/ijms21124507.

[21] Crumbaker M, Khoja L, Joshua AM. AR Signaling and the PI3K Pathway in Prostate Cancer. Cancers. 2017; 9: 34. https://doi.org/10.3390/cancers9040034.

[22] Gasmi A, Roubaud G, Dariane C, Barret E, Beauval JB, Brureau L, *et al*. Overview of the Development and Use of Akt Inhibitors in Prostate Cancer. Journal of Clinical Medicine. 2021; 11: 160. https://doi.org/10.3390/jcm11010160.

[23] Adelaiye-Ogala R, Gryder BE, Nguyen YTM, Alilin AN, Grayson AR, Bajwa W, *et al*. Targeting the PI3K/AKT Pathway Overcomes Enzalutamide Resistance by Inhibiting Induction of the Glucocorticoid Receptor. Molecular Cancer Therapeutics.

2020; 19: 1436–1447. https://doi.org/10.1158/1535-7163.MCT-19-0936.

[24] Braicu C, Buse M, Busuioc C, Drula R, Gulei D, Raduly L, *et al*. A Comprehensive Review on MAPK: A Promising Therapeutic Target in Cancer. Cancers. 2019; 11: 1618. https://doi.org/10.3390/cancers11101618.

[25] Bockorny B, Rusan M, Chen W, Liao RG, Li Y, Piccioni F, *et al*. RAS-MAPK Reactivation Facilitates Acquired Resistance in *FGFR1*-Amplified Lung Cancer and Underlies a Rationale for Upfront FGFR-MEK Blockade. Molecular Cancer Therapeutics. 2018; 17: 1526–1539. https://doi.org/10.1158/1535-7163.MCT-17-0464.

[26] Beltran H, Prandi D, Mosquera JM, Benelli M, Puca L, Cyrta J, *et al*. Divergent clonal evolution of castration-resistant neuroendocrine prostate cancer. Nature Medicine. 2016; 22: 298–305. https://doi.org/10.1038/nm.4045.

[27] Bao Y, Oguz G, Lee WC, Lee PL, Ghosh K, Li J, *et al*. EZH2-mediated PP2A inactivation confers resistance to HER2-targeted breast cancer therapy. Nature Communications. 2020; 11: 5878. https://doi.org/10.1038/s41467-020-19704-x.

[28] Weyerer V, Eckstein M, Compérat E, Juette H, Gaisa NT, Allory Y, *et al*. Pure Large Nested Variant of Urothelial Carcinoma (LNUC) Is the Prototype of an *FGFR3* Mutated Aggressive Urothelial Carcinoma with Luminal-Papillary Phenotype. Cancers. 2020; 12: 763. https://doi.org/10.3390/cancers12030763.

[29] Bernardo C, Eriksson P, Marzouka NAD, Liedberg F, Sjödahl G, Höglund M. Molecular pathology of the luminal class of urothelial tumors. The Journal of Pathology. 2019; 249: 308–318. https://doi.org/10.1002/path.5318.

[30] Matthews BG, Bowden NA, Wong-Brown MW. Epigenetic Mechanisms and Therapeutic Targets in Chemoresistant High-Grade Serous Ovarian Cancer. Cancers. 2021; 13: 5993. https://doi.org/10.3390/cancers13235993.

[31] Bennett RL, Licht JD. Targeting Epigenetics in Cancer. Annual Review of Pharmacology and Toxicology. 2018; 58: 187–207. https://doi.org/10.1146/annurev-pharmtox-010716-105106.

[32] Hartmann S, Bhola NE, Grandis JR. HGF/Met Signaling in Head and Neck Cancer: Impact on the Tumor Microenvironment. Clinical Cancer Research: an Official Journal of the American Association for Cancer Research. 2016; 22: 4005–4013. https://doi.org/10.1158/1078-0432.CCR-16-0951.

[33] Wang Z, Liu J, Huang H, Ye M, Li X, Wu R, *et al*. Metastasis-associated fibroblasts: an emerging target for metastatic cancer. Biomarker Research. 2021; 9: 47. https://doi.org/10.1186/s40364-021-00305-9.

[34] Larionova I, Tuguzbaeva G, Ponomaryova A, Stakheyeva M, Cherdyntseva N, Pavlov V, *et al*. Tumor-Associated Macrophages in Human Breast, Colorectal, Lung, Ovarian and Prostate Cancers. Frontiers in Oncology. 2020; 10: 566511. https://doi.org/10.3389/fonc.2020.566511.

[35] Anderson NM, Simon MC. The tumor microenvironment. Current Biology: CB. 2020; 30: R921–R925. https://doi.org/10.1016/j.cub.2020.06.081.

[36] Semenza GL. The hypoxic tumor microenvironment: A driving force for breast cancer progression. Biochimica et Biophysica Acta. 2016; 1863: 382–391. https://doi.org/10.1016/j.bbamcr.2015.05.036.

[37] Chipurupalli S, Kannan E, Tergaonkar V, D'Andrea R, Robinson N. Hypoxia Induced ER Stress Response as an Adaptive Mechanism in Cancer. International Journal of Molecular Sciences. 2019; 20: 749. https://doi.org/10.3390/ijms20030749.

[38] Kalli M, Li R, Mills GB, Stylianopoulos T, Zervantonakis IK. Mechanical Stress Signaling in Pancreatic Cancer Cells Triggers p38 MAPK- and JNK-Dependent Cytoskeleton Remodeling and Promotes Cell Migration via Rac1/cdc42/Myosin II. Molecular Cancer Research: MCR. 2022; 20: 485–497. https://doi.org/10.1158/1541-7786.MCR-21-0266.

[39] Bansal D, Reimers MA, Knoche EM, Pachynski RK. Immunotherapy and Immunotherapy Combinations in Metastatic Castration-Resistant Prostate Cancer. Cancers. 2021; 13: 334. https://doi.org/10.3390/cancers13020334.

[40] Chehade CH, Ozay ZI, Agarwal N. Targeting the FGFR Pathway in Patients with Advanced Solid Tumors. Clinical Cancer Research: an Official Journal of the American Association for Cancer Research. 2024; 30: 4549–4551. https://doi.org/10.1158/1078-0432.CCR-24-1711.

[41] Gumusay O, Vitiello PP, Wabl C, Corcoran RB, Bardelli A, Rugo HS. Strategic Combinations to Prevent and Overcome Resistance to Targeted Therapies in Oncology. American Society of Clinical Oncology Educational Book. American Society of Clinical Oncology. Annual Meeting. 2020; 40: e292–e308. https://doi.org/10.1200/EDBK_280845.

[42] Lee WS, Yang H, Chon HJ, Kim C. Combination of anti-angiogenic therapy and immune checkpoint blockade normalizes vascular-immune crosstalk to potentiate cancer immunity. Experimental & Molecular Medicine. 2020; 52: 1475–1485. https://doi.org/10.1038/s12276-020-00500-y.

[43] Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, *et al*. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2018; 36: 1714–1768. https://doi.org/10.1200/JCO.2017.77.6385.

[44] Sun C, Yin J, Fang Y, Chen J, Jeong KJ, Chen X, *et al*. BRD4 Inhibition Is Synthetic Lethal with PARP Inhibitors through the Induction of Homologous Recombination Deficiency. Cancer Cell. 2018; 33: 401–416.e8. https://doi.org/10.1016/j.ccell.2018.01.019.

[45] Sun F, Li L, Yan P, Zhou J, Shapiro SD, Xiao G, *et al*. Causative role of PDLIM2 epigenetic repression in lung cancer and therapeutic resistance. Nature Communications. 2019; 10: 5324. https://doi.org/10.1038/s41467-019-13331-x.

[46] Zarrabi K, Paroya A, Wu S. Emerging therapeutic agents for genitourinary cancers. Journal of Hematology & Oncology. 2019; 12: 89. https://doi.org/10.1186/s13045-019-0780-z.

[47] Alix-Panabières C, Pantel K. Clinical Applications of Circulating Tumor Cells and Circulating Tumor DNA as Liquid Biopsy. Cancer Discovery. 2016; 6: 479–491. https://doi.org/10.1158/2159-8290.CD-15-1483.

[48] Yabroff KR, Sylvia Shi K, Zhao J, Freedman AN, Zheng Z, Nogueira L, *et al*. Importance of Patient Health Insurance Coverage and Out-of-Pocket Costs for Genomic Testing in Oncologists' Treatment Decisions. JCO Oncology Practice. 2024; 20: 429–437. https://doi.org/10.1200/OP.23.00153.