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DABRAFENIB IN BRAF V600E-POSITIVE SOLID TUMORS: RESISTANCE, CLINICAL APPLICATIONS, AND DRUG-DELIVERY STRATEGIES

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Abstract

Dabrafenib, particularly in combination with trametinib, is an established targeted therapy for several BRAF V600E-positive solid tumors, although the magnitude and durability of response vary considerably across tumor types. This review summarizes the molecular rationale, clinical applications, resistance mechanisms, pharmacokinetic limitations, and emerging delivery strategies of dabrafenib-based therapy. Treatment outcome is influenced not only by BRAF V600E status but also by tumor lineage, co-occurring genomic alterations, receptor tyrosine kinase feedback, microenvironmental signaling, and lesion-level drug exposure. Resistance develops through MAPK reactivation, PI3K/AKT bypass signaling, cellular plasticity, tumor heterogeneity, stromal protection, and pharmacological underexposure. Dabrafenib efficacy is further constrained by pH-dependent solubility, food-sensitive absorption, CYP-mediated metabolism, autoinduction, drug interactions, limited brain distribution, and heterogeneous intratumoral penetration. Solid-state modification, nanostructured formulations, targeted nanocarriers, locoregional administration, and coordinated dabrafenib–trametinib delivery have shown preclinical promise, but evidence of superiority over standard oral therapy remains limited. Clinical findings across melanoma, lung, thyroid, biliary tract, colorectal, and central nervous system tumors indicate that BRAF V600E is highly actionable but insufficient as a standalone predictor of benefit. Treatment optimization therefore requires a tumor-specific approach integrating molecular selection, resistance profiling, and lesion-level drug exposure.

Keywords: *Dabrafenib, BRAF V600E, Solid tumor, Drug resistance, Nano drug-delivery*

1. Introduction

BRAF V600E is one of the most clinically actionable oncogenic alterations in solid tumors [1]. This mutation constitutively activates the RAS-RAF-MEK-ERK signaling pathway, leading to sustained proliferative and survival signaling [2]. Although BRAF V600E was initially established as a major therapeutic target in

melanoma, its clinical relevance has expanded to several non-melanoma solid tumors, including non-small-cell lung cancer, anaplastic thyroid cancer, pediatric low-grade glioma, biliary tract cancer, and other rare BRAF V600E-positive malignancies [3-6]. Dabrafenib is a selective small-molecule inhibitor of mutant BRAF, with particular activity against BRAF



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V600-driven signaling [4]. In combination with the MEK inhibitor trametinib, dabrafenib provides vertical inhibition of the MAPK pathway and has become an important targeted therapeutic strategy for BRAF V600E-positive tumors [7]. The clinical value of this combination is reflected by its expansion from melanoma to tissue-agnostic treatment of selected BRAF V600E-positive advanced solid tumors [4, 5]. However, the presence of BRAF V600E alone does not guarantee uniform therapeutic benefit across tumor types. Increasing evidence indicates that response to dabrafenib-based therapy is shaped by tumor lineage, BRAF mutation class, co-occurring genomic alterations, receptor tyrosine kinase feedback, tumor microenvironment, and tissue-specific pharmacological barriers [3, 8]. Therefore, BRAF V600E should be considered a powerful but incomplete predictor of response. A major limitation of dabrafenib-based therapy is the emergence of intrinsic or acquired resistance [9]. Tumors may escape treatment through MAPK pathway reactivation [10], PI3K/AKT-mediated bypass signaling [11], EGFR feedback activation [12], cell-cycle deregulation [13], tumor heterogeneity [14],

immune-microenvironmental remodeling [15], and insufficient drug exposure at specific tumor sites.

In addition, pharmacokinetic and formulation-related challenges, including pH-dependent solubility, variable oral absorption, drug-drug interactions, limited tumor penetration, and blood-brain barrier restrictions, may further limit the durability of response in solid tumors [16, 17].

This review aims to integrate the molecular pharmacology, clinical relevance, resistance mechanisms, pharmacokinetic limitations, and emerging drug-delivery strategies of dabrafenib-based therapy in BRAF V600E-positive solid tumors. Unlike reviews focused mainly on melanoma or BRAF/MEK inhibition alone, this article emphasizes the concept that effective dabrafenib therapy requires a context-guided approach in which tumor biology, resistance evolution, tissue-delivery barriers, and formulation design are considered together. This perspective may help define future strategies for improving the therapeutic performance of dabrafenib beyond conventional targeted therapy.

2. Molecular Basis of BRAF Signaling and Dabrafenib-Based Therapy

2.1. The RAS-RAF-MEK-ERK Signaling Pathway

The RAS–RAF–MEK–ERK cascade, commonly referred to as the canonical MAPK/ERK pathway, is a central signaling network that regulates cell proliferation, differentiation, survival, and migration [18]. Under physiological conditions, extracellular growth factors activate receptor tyrosine kinases, leading to the recruitment of adaptor proteins and conversion of RAS to its active GTP-bound state [19]. RAS-GTP subsequently recruits RAF kinases, including ARAF, BRAF, and CRAF, to the plasma membrane, where

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conformational rearrangement and RAF dimerization promote kinase activation [20]. Activated RAF phosphorylates MEK1/2, which in turn activates ERK1/2. ERK then translocates to the nucleus and regulates gene-expression programs involved in cell-cycle progression, differentiation, and survival. Persistent dysregulation of this cascade can promote malignant transformation [21, 22]. Among RAF-family members, BRAF exhibits the highest intrinsic kinase activity and is the RAF isoform most frequently affected by oncogenic mutations [23]. Oncogenic BRAF activation can uncouple MAPK signaling from normal upstream control, producing sustained pathway output that supports uncontrolled tumor-cell proliferation and survival. BRAF V600E is the most prevalent activating BRAF alteration and can function as a dominant oncogenic driver across multiple solid-tumor lineages [3, 8, 24].

RAF proteins contain three conserved regions: CR1, which includes the RAS-binding and cysteine-rich domains; CR2, which contains regulatory phosphorylation sites; and CR3, which comprises the catalytic kinase domain, including the glycine-rich P-loop and activation segment [21]. RAF signaling is strongly influenced by kinase-domain conformation and homo- or heterodimerization, including formation of BRAF–CRAF dimers [21, 23, 25]. In the autoinhibited state, a 14-3-3 dimer interacts with phosphorylated regulatory sites in BRAF and stabilizes a closed conformation [26]. Structural studies further indicate that coordinated interactions among the BRAF cysteine-rich domain, kinase domain, MEK1, and 14-3-3 contribute to maintenance of this inactive state [21, 27]. These structural features help explain why RAF dimerization, conformational state,

and cellular context strongly influence sensitivity to RAF inhibitors.

2.2. BRAF Mutation Classes: Class I, Class II, and Class III

BRAF mutations are commonly classified into three functional classes according to their intrinsic kinase activity, dependence on upstream RAS signaling, and requirement for RAF dimerization. This classification has important therapeutic implications because the three classes differ substantially in their signaling mechanisms and sensitivity to RAF-targeted therapies [3, 8, 25, 28]. Class I mutations comprise substitutions at codon V600, particularly V600E and V600K. These alterations generate highly active BRAF monomers that signal independently of upstream RAS activation and do not require RAF dimerization. Sustained ERK activation imposes negative feedback on RAS, resulting in relatively low RAS-GTP activity in class I BRAF-mutant tumors [29]. Their monomeric and RAS-independent signaling explains why class I mutants are the most sensitive to approved BRAF inhibitors such as dabrafenib, particularly when BRAF inhibition is combined with downstream MEK inhibition [3, 8, 25].

Class II mutations are activating non-V600 alterations that signal as constitutively active, RAS-independent RAF dimers. They include selected substitutions involving G469, L597, and K601, as well as many BRAF fusions [29]. Because conventional BRAF V600-selective inhibitors more effectively inhibit monomeric BRAF than RAF dimers, class II alterations generally show limited sensitivity to these agents and may require strategies targeting RAF dimers or downstream MEK–ERK signaling [3, 8, 25, 30]. In contrast, class III mutations have impaired or absent intrinsic kinase activity and depend on

upstream RAS activation [31]. These mutants enhance signaling through interactions with RAS-GTP and CRAF-containing dimers, with RAS activation arising from receptor tyrosine kinase signaling, activating RAS alterations, NF1 loss, or other upstream events [32]. Consequently, class III tumors are generally unsuitable for conventional BRAF V600-selective inhibitor monotherapy, and their treatment must be guided by the upstream driver, tumor lineage, and broader genomic context [3, 8, 28].

2.3. Mechanistic Basis of Dabrafenib and Trametinib Combination Therapy

Dabrafenib is primarily active against class I BRAF V600 alterations, particularly V600E and V600K, which generate constitutively active, RAS-independent BRAF monomers [3, 8, 24, 33]. In vitro, dabrafenib inhibits BRAF V600E, BRAF V600K, and BRAF V600D with IC_{50} values of 0.65, 0.50, and 1.84 nM, respectively, while inhibiting wild-type BRAF and CRAF at higher concentrations, with corresponding IC_{50} values of 3.2 and 5.0 nM [34]. In BRAF V600-mutant cells, inhibition of mutant BRAF reduces downstream MEK–ERK signaling and suppresses MAPK-dependent tumor-cell proliferation. Consistently, dabrafenib inhibits the growth of BRAF V600 mutation-positive tumors in both in vitro and in vivo models [3, 8, 24, 34].

The pharmacological effects of RAF inhibitors depend strongly on mutation status and RAF dimerization. Whereas dabrafenib suppresses MAPK signaling in BRAF V600-mutant cells, RAF inhibition in BRAF wild-type cells with elevated RAS activity may promote RAF dimerization and transactivation, resulting in paradoxical MEK–ERK pathway activation [8, 21]. This context-dependent activity reinforces the

requirement for accurate identification of the BRAF variant and explains why dabrafenib should not be used in molecularly unselected BRAF wild-type or RAS-activated tumors.

Trametinib is a reversible allosteric inhibitor of MEK1 and MEK2 activation and kinase activity, thereby limiting downstream ERK signaling [35–38]. Combining trametinib with dabrafenib therefore provides vertical inhibition of two sequential nodes of the RAS–RAF–MEK–ERK cascade. This dual blockade suppresses residual or recovering MEK–ERK signaling more effectively than BRAF inhibition alone and delays MAPK-pathway reactivation. Preclinical studies demonstrated greater growth inhibition in BRAF V600 mutation-positive tumor-cell lines and more prolonged tumor-growth suppression in xenograft models with the combination than with either drug alone [34, 38]. Clinical studies in BRAF V600-mutant melanoma subsequently showed that dabrafenib plus trametinib improved disease control and delayed resistance compared with BRAF inhibitor monotherapy, while reducing cutaneous hyperproliferative toxicities associated with paradoxical MAPK activation [36, 37].

The mechanistic rationale for this combination is strongest in class I BRAF V600-driven tumors and should not be generalized to all BRAF alterations [39]. Class II mutations signal through RAF dimers, whereas class III mutations depend on upstream RAS or receptor tyrosine kinase activity and CRAF-containing dimers [40]. Accordingly, the therapeutic relevance of dabrafenib–trametinib therapy must be interpreted according to the exact BRAF variant, functional mutation class, and tumor context [3, 8, 25, 28]. The molecular organization of BRAF signaling, the functional classification of BRAF

alterations, and the mechanistic rationale for combined dabrafenib–trametinib therapy are summarized in Figure 1.

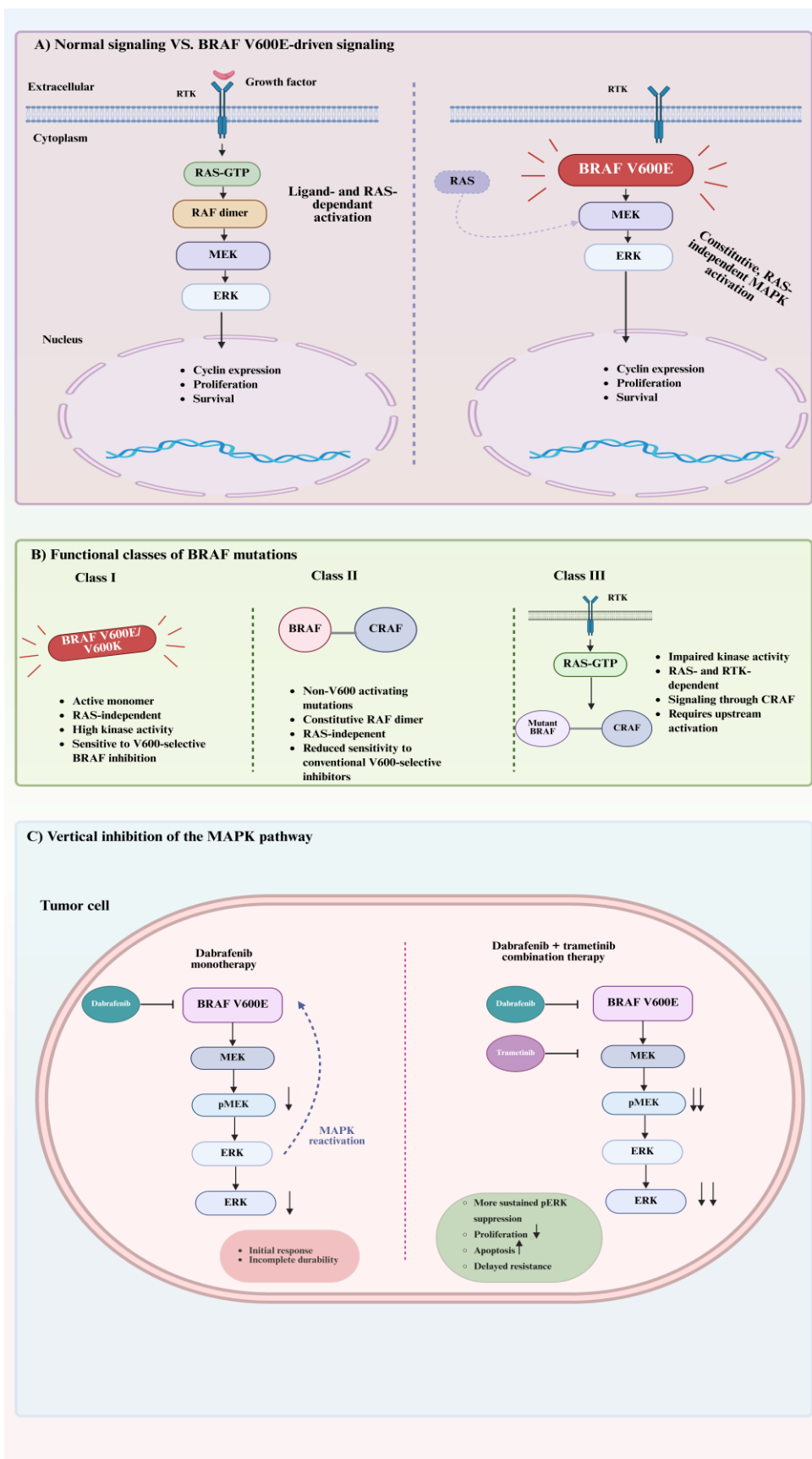


Figure 1. Molecular basis of BRAF signaling and the rationale for combined dabrafenib–trametinib therapy. (A) Comparison of physiological RTK–RAS–RAF–MEK–ERK signaling with constitutive, RAS-independent MAPK activation driven by BRAF V600E. (B) Functional classification of BRAF alterations into class I monomers, class II RAF dimers, and class III RAS-dependent mutants. (C) Dabrafenib inhibits mutant BRAF, whereas combined dabrafenib–trametinib therapy provides vertical BRAF/MEK blockade, more sustained MAPK suppression, and delayed pathway reactivation. Abbreviations: ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; MEK, MAPK/ERK kinase; RTK, receptor tyrosine kinase. This figure was created using BioRender. (BioRender.com, accessed on 17 July, 2026).

3. Clinical Applications of Dabrafenib-Based Therapy Across Solid Tumors

Dabrafenib-based therapy has expanded from melanoma to several BRAF V600E-positive solid tumors, particularly when combined with trametinib [3, 8, 41]. However, clinical benefit varies across tumor types because response is influenced by tumor lineage, co-occurring alterations, feedback signaling, the tumor

microenvironment, and tissue-specific drug accessibility [3, 5]. As illustrated in Figure 2, the clinical performance of dabrafenib-based therapy is determined by the interaction between BRAF dependency and tumor-specific factors, including lineage, mutation class, co-occurring alterations, feedback signaling, and drug accessibility.

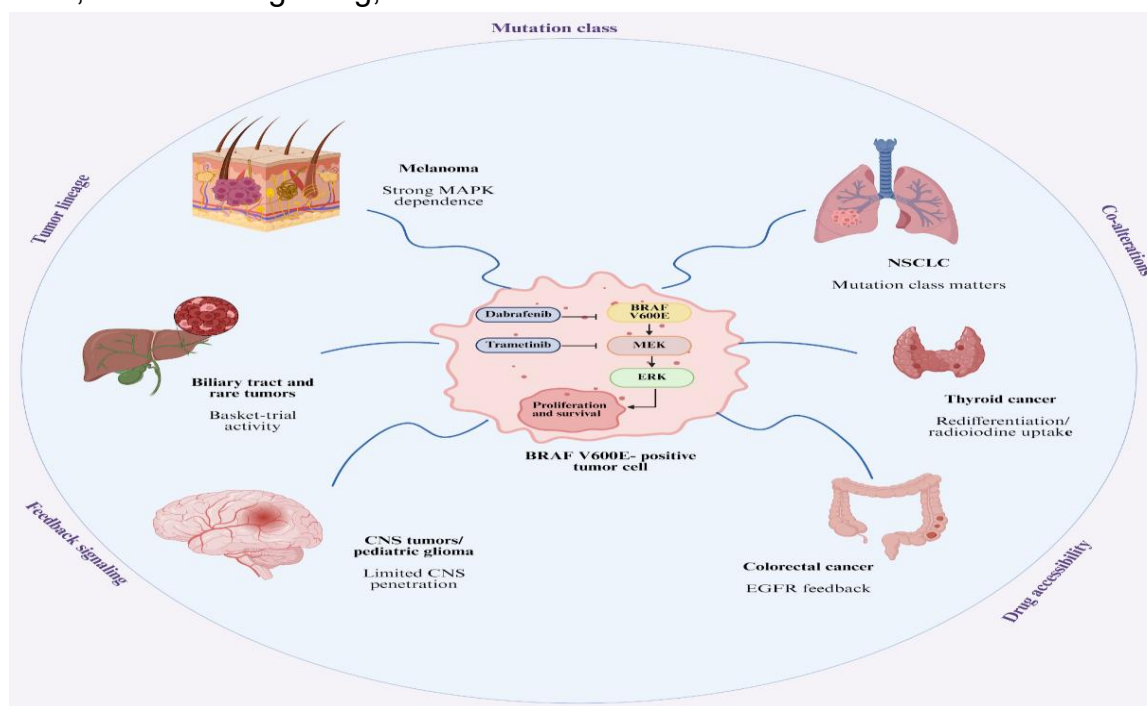


Figure 2. Tumor-context-dependent determinants of dabrafenib-based therapy across BRAF V600E-positive solid tumors. The therapeutic performance of BRAF/MEK inhibition is shaped by tumor lineage, BRAF mutation class, co-occurring molecular alterations, feedback signaling, and tissue-specific drug accessibility. The illustrated clinical contexts include strong MAPK dependence in melanoma, mutation-class-dependent sensitivity in NSCLC, redifferentiation potential in selected differentiated thyroid cancers, EGFR-mediated feedback in colorectal cancer, restricted CNS penetration in brain tumors, and clinical activity observed in basket trials of biliary tract and other rare tumors. Abbreviations: CNS, central nervous system; EGFR, epidermal growth factor receptor; MAPK, mitogen-activated protein kinase; NSCLC, non-small-cell lung cancer. This figure was created using BioRender. (BioRender.com, accessed on 17 July, 2026).

3.1. Established Clinical Applications: Melanoma and Non-Small-Cell Lung Cancer

Melanoma provided the initial clinical evidence supporting BRAF-targeted therapy [42]. Dabrafenib monotherapy improved outcomes compared with dacarbazine in patients with previously untreated BRAF V600E-mutant metastatic melanoma [43]. However, the rapid emergence of MAPK-pathway reactivation limited the durability of monotherapy. Subsequent phase III studies demonstrated that combining dabrafenib with trametinib improved disease control and clinical outcomes compared with single-agent BRAF inhibition, establishing dual BRAF/MEK inhibition as a standard treatment for BRAF V600-mutant melanoma [44, 45].

In non-small-cell lung cancer, BRAF V600E represents a clinically actionable but uncommon molecular subgroup [46]. Phase II studies showed that dabrafenib plus trametinib produced objective response rates of approximately 63–64% in both previously treated and treatment-naïve patients with metastatic BRAF V600E-positive NSCLC [3, 47]. These findings established dabrafenib plus trametinib as an important targeted option for BRAF V600E-mutant NSCLC. However, clinical evidence in NSCLC is best established for class I BRAF V600E disease, because non-V600 BRAF alterations exhibit distinct signaling mechanisms and variable sensitivity to conventional BRAF inhibitor [3, 6, 48, 49].

3.2. Thyroid, Biliary Tract, and Other Rare Solid Tumors

BRAF V600E has important therapeutic implications in thyroid cancer. In differentiated thyroid cancer, sustained MAPK activation suppresses thyroid-

specific genes involved in iodine uptake and contributes to radioactive iodine resistance [1, 50]. BRAF/MEK inhibition may partially restore iodine avidity and enable redifferentiation in selected patients with BRAF-mutant radioactive iodine-refractory disease [51].

Dabrafenib plus trametinib has also demonstrated clinically meaningful activity in BRAF V600E-mutant anaplastic thyroid carcinoma, an aggressive malignancy with historically limited treatment options [5, 52]. These findings support routine molecular testing in advanced thyroid tumors and illustrate how the clinical role of BRAF inhibition may differ according to histological subtype [53].

Among other rare solid tumors, biliary tract cancer represents an important application of dabrafenib-based therapy [54]. In the ROAR basket trial, dabrafenib plus trametinib produced meaningful responses in patients with BRAF V600E-mutant biliary tract cancer [5]. Its activity has also been reported across selected rare BRAF V600E-positive tumors, although interpretation remains limited by small and heterogeneous patient cohorts [55]. These data support broad molecular profiling in rare cancers for which standard therapeutic options are limited [5].

3.3. Colorectal Cancer as a Model of Tumor-Context Dependence

BRAF V600E-mutant colorectal cancer illustrates why the presence of an actionable mutation does not necessarily predict uniform sensitivity to BRAF inhibition across tumor types [55]. Unlike melanoma, BRAF inhibitor monotherapy has limited activity in colorectal cancer because suppression of mutant BRAF rapidly relieves MAPK-dependent negative feedback and promotes EGFR-mediated reactivation of RAS–RAF–MEK–ERK

signaling [3, 56]. Consequently, effective treatment requires simultaneous blockade of BRAF and EGFR. The BEACON CRC trial demonstrated that encorafenib plus cetuximab improved clinical outcomes in previously treated BRAF V600E-mutant metastatic colorectal cancer, establishing combined BRAF/EGFR inhibition as a standard therapeutic strategy [56-58].

3.4. CNS Tumors and Pediatric Low-Grade Glioma

BRAF alterations occur in several pediatric and adult central nervous system tumors, including pediatric low-grade glioma, ganglioglioma, pleomorphic xanthoastrocytoma, and selected high-grade gliomas [55]. However, therapeutic sensitivity depends on the exact alteration because BRAF V600 mutations, BRAF fusions, and other non-V600 variants differ substantially in their signaling biology and response to RAF-targeted therapy [3, 59]. Dabrafenib plus trametinib has demonstrated clinically meaningful activity in BRAF V600E-positive low- and high-grade gliomas, supporting its use in molecularly selected CNS tumors [5]. The CNS setting nevertheless presents an important pharmacological challenge. Blood–brain barrier integrity, transporter-

mediated drug efflux, tumor location, and heterogeneous vascular permeability may restrict intracranial and intratumoral exposure despite adequate systemic concentrations [60, 61]. These limitations help explain the growing development of brain-penetrant RAF inhibitors and highlight the need for delivery strategies capable of improving drug distribution within CNS tumors [3, 59]. Thus, CNS tumors provide a direct link between molecular sensitivity to dabrafenib and the tissue-specific barriers that may limit durable therapeutic response [4]. The clinical relevance of dabrafenib-based therapy and the major tumor-context-specific factors that shape or limit its use across selected BRAF V600E-positive solid tumors are summarized in Table 1. Collectively, these clinical experiences demonstrate that BRAF V600E is a broadly actionable molecular target, but the therapeutic performance of dabrafenib-based therapy remains strongly influenced by tumor lineage, feedback signaling, co-occurring alterations, and tissue-specific drug accessibility. Accordingly, treatment selection should integrate BRAF mutation status with the biological and pharmacological context of each tumor.

Table 1. Clinical applications and tumor-context-specific limitations of dabrafenib-based therapy in selected BRAF V600E-positive solid tumors.

Tumor context	Clinical role of BRAF targeting	Main context-specific issue	Reference
Melanoma	Dabrafenib plus trametinib is an established treatment for BRAF V600-mutant advanced melanoma	Acquired resistance and CNS progression may limit durability.	[62, 63]
NSCLC	The combination produces meaningful responses in metastatic BRAF V600E-positive NSCLC	Benefit is mainly established for class I V600E tumors	[47, 64]
Thyroid cancer	It is active in anaplastic thyroid cancer and may restore iodine	Treatment goals differ by histological subtype.	[65, 66]

	avidity in selected differentiated tumor		
Colorectal cancer	BRAF V600E is actionable, but dabrafenib-based therapy is not a standard regimen	EGFR-mediated reactivation requires combined BRAF/EGFR inhibition.	[67, 68]
Biliary tract cancer and rare tumors	Dabrafenib plus trametinib has shown activity in BRAF V600E-positive biliary and rare tumors	Evidence is limited by small, heterogeneous cohorts.	[4, 5]
CNS tumors/pediatric glioma	The combination is active in selected BRAF V600E-positive gliomas	BBB restriction, efflux transporters, and variant heterogeneity may reduce response.	[4, 69]
Abbreviations: BBB: blood–brain barrier, CNS: central nervous system, EGFR: epidermal growth factor receptor, MAPK: mitogen-activated protein kinase, NSCLC: non-small-cell lung cancer.			

4. Pharmacokinetic and Formulation Challenges

Although dabrafenib has high molecular potency and substantial oral bioavailability after a single dose, its clinical exposure is influenced by pH-dependent solubility, formulation and food effects, time-dependent pharmacokinetics, drug–drug interactions, and restricted distribution into selected tumor compartments. These factors may produce variable systemic exposure or inadequate drug concentrations at pharmacologically protected sites, particularly within the central nervous system and poorly penetrated tumor regions [70–75]. Accordingly, the principal formulation challenge is not simply to increase total exposure, but to achieve reproducible and site-appropriate drug availability.

4.1. Oral Biopharmaceutical Limitations: Solubility, Formulation, and Food Effects

Dabrafenib mesylate is a weakly basic compound with strongly pH-dependent aqueous solubility. According to the prescribing information, it is very slightly soluble at pH 1 and practically insoluble above pH 4. Passage from the acidic

stomach to the higher-pH intestinal environment may therefore reduce drug solubility and promote precipitation from a transiently supersaturated state, limiting the fraction that remains available for absorption [34, 76, 77]. Dabrafenib also exhibits a complex solid-state landscape comprising polymorphs, hydrates, perhydrates, and multiple solvates. Consequently, crystal form and solid-state stability may substantially influence dissolution behavior and formulation performance [70, 71].

Clinical formulation studies confirm that oral exposure is sensitive to apparently conventional formulation variables. In patients with BRAF mutation-positive tumors, particle size, capsule-shell composition, and prandial state altered the relative bioavailability of dabrafenib. Hypromellose capsules produced higher exposure than gelatin capsules, whereas the nonmicronized drug substance unexpectedly showed greater bioavailability than the micronized form [72]. These findings indicate that particle-size reduction does not necessarily improve in vivo exposure when dissolution, supersaturation, capsule disintegration,

and precipitation interact dynamically. They also demonstrate that conventional in vitro dissolution results may not always predict clinical performance. Food significantly reduces and delays dabrafenib absorption. Administration with a high-fat meal decreases C_{max} by approximately 51% and AUC by 31% and delays T_{max} relative to fasting conditions; consequently, dabrafenib should be administered at least 1 h before or 2 h after food [34, 78, 79]. These findings support oral formulations that maintain dabrafenib in a dissolved or supersaturated state and reduce precipitation. Solid-form engineering, polymers, amorphous systems, and nanocarriers may improve exposure, but their clinical value requires in vivo validation [70, 71, 80].

4.2. Metabolism, Autoinduction, and Drug–Drug Interactions

Dabrafenib undergoes extensive oxidative metabolism, primarily through CYP2C8 and CYP3A4. Hydroxy-dabrafenib is subsequently converted to carboxy-dabrafenib, which can undergo decarboxylation to form desmethyl-dabrafenib [73, 74]. Fecal excretion is the major elimination route, accounting for approximately 71% of the administered radioactive dose, whereas urinary recovery accounts for approximately 23% and consists of metabolites rather than unchanged dabrafenib. Hydroxy-dabrafenib and desmethyl-dabrafenib retain pharmacological activity and may contribute to the overall clinical effects of treatment [34, 73, 74].

A distinctive pharmacokinetic property of dabrafenib is time-dependent autoinduction. Repeated administration increases apparent clearance, resulting in lower-than-expected accumulation and less-than-dose-proportional exposure at

steady state. Population pharmacokinetic analyses estimate an induction half-life of approximately 67 h, with steady state reached within about 14 days [73, 81]. Consequently, exposure measured after an initial dose may not represent the concentrations achieved during chronic twice-daily therapy.

Dabrafenib acts as both a substrate and an inducer of drug-metabolizing enzymes. Ketoconazole, a strong CYP3A4 inhibitor, increased dabrafenib AUC by 71%, whereas the strong CYP2C8 inhibitor gemfibrozil increased AUC by 47% [82]. Conversely, repeated dabrafenib administration reduced midazolam AUC by 65% and decreased the AUCs of S-warfarin and R-warfarin by 37% and 33%, respectively, reflecting induction of CYP3A4, CYP2C9, and related pathways [82, 83]. These interactions may increase dabrafenib toxicity when its metabolism is inhibited or reduce the effectiveness of concomitant medications when enzyme induction accelerates their clearance.

4.3. Tissue Distribution and Penetration Barriers

Adequate plasma exposure does not necessarily ensure sufficient drug concentrations within every tumor compartment. This distinction is particularly important in the central nervous system, where the blood–brain barrier and active efflux transporters restrict drug entry. Preclinical studies demonstrated that dabrafenib is a substrate of both P-glycoprotein and breast cancer resistance protein and that simultaneous activity of these transporters markedly limits its brain distribution when the blood–brain barrier is intact [75]. Trametinib is also subject to transporter-mediated restriction at the blood–brain barrier, which may further limit

coordinated intracranial exposure during combination therapy [75, 84].

Distribution heterogeneity is not limited to the CNS. Experimental imaging and computational analyses have shown that BRAF inhibitors differ in their penetration across tumors and metastatic sites. High albumin binding, lipophilicity, systemic clearance, and target-dissociation kinetics were identified as factors that may restrict the depth and duration of dabrafenib exposure within visceral lesions [85]. Consequently, some tumor regions may receive subtherapeutic concentrations despite apparently adequate plasma levels, creating pharmacological niches in which residual or drug-tolerant cells can persist. The development of brain-penetrant and efflux-evasive RAF inhibitors demonstrates that molecular and physicochemical optimization can improve intracranial

distribution[86-89]. However, these agents are distinct from dabrafenib and should not be presented as evidence that current dabrafenib formulations overcome the blood–brain barrier. For dabrafenib itself, the available evidence instead supports investigation of brain-targeted carriers, efflux-evasive delivery systems, and platforms capable of producing more uniform intratumoral distribution. Hence, Dabrafenib delivery strategies should be tailored to the specific pharmacokinetic barrier, including poor oral absorption, metabolic interactions, or limited tissue penetration. The sequential pharmacokinetic and anatomical barriers that shape dabrafenib exposure from oral administration to tumor and central nervous system delivery are summarized in Figure 3.

Table 2. Key pharmacokinetic and formulation barriers limiting dabrafenib delivery.

Barrier	Main mechanism	Clinical relevance	Potential delivery response
Poor/pH-dependent solubility	Dissolution-limited absorption; supersaturation followed by precipitation	Variable oral exposure and formulation sensitivity	Solid-form engineering, precipitation inhibitors, nanocarriers
Food/formulation effects	Meal-dependent changes in dissolution, gastric emptying, and precipitation	Need for fasted administration and reduced exposure consistency	Food-effect-resistant oral formulations and controlled-release systems
CYP metabolism and autoinduction	CYP2C8/CYP3A4 metabolism; time-dependent increase in clearance	Changing exposure during chronic therapy and potential DDIs	Exposure-stabilizing formulations; careful co-medication management
BBB and efflux transporters	P-gp/BCRP-mediated restriction of CNS entry	Reduced intracranial exposure, especially in intact BBB regions	Brain-targeted or efflux-evading delivery strategies
Heterogeneous tumor penetration	Spatial differences in drug distribution across lesions and tumor regions	Site-specific response variability	Tumor-penetrating, stimuli-responsive, or locally triggered delivery platforms

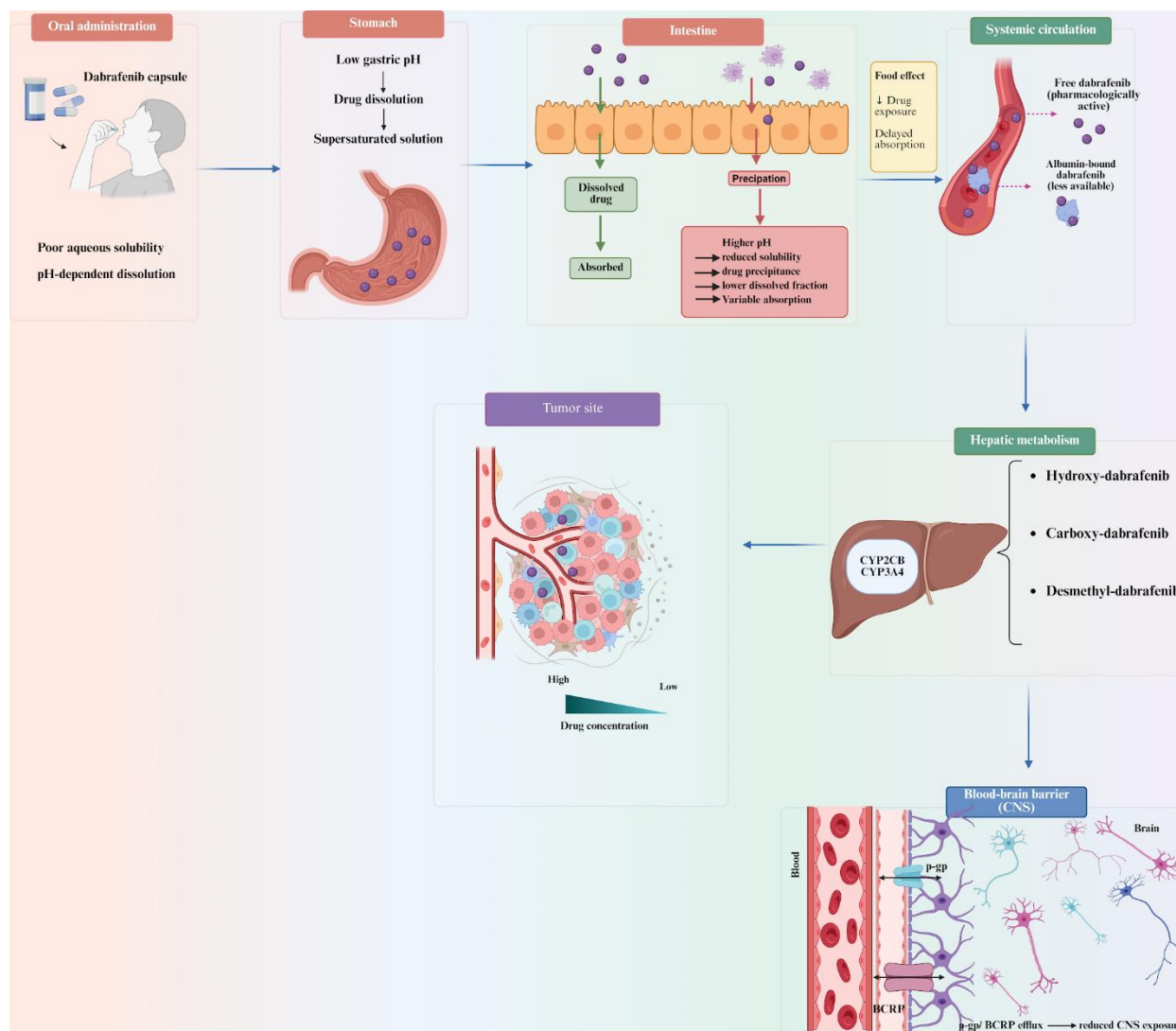


Figure 3. Pharmacokinetic and anatomical barriers affecting dabrafenib exposure. This figure was created using BioRender (BioRender.com, accessed on 17 July, 2026).

5. Resistance to Dabrafenib-Based Therapy

Resistance remains the principal limitation to durable dabrafenib-based therapy in BRAF V600E-positive solid tumors. It may arise from pre-existing insensitivity, acquired molecular alterations, adaptive signaling, tumor-cell plasticity, microenvironmental protection, or insufficient drug exposure within specific tumor compartments [3, 8, 21, 90]. Although many mechanisms were initially characterized in melanoma, their relevance extends across BRAF V600E-positive tumors, with their relative importance

determined by tumor lineage and biological context [3-6, 91].

5.1. Intrinsic and Acquired Resistance, Tumor Heterogeneity, and Adaptive Plasticity

Intrinsic resistance occurs when a BRAF V600E-positive tumor shows limited initial sensitivity despite the presence of the therapeutic target. Pre-existing receptor tyrosine kinase activity, compensatory survival pathways, co-occurring genomic alterations, stromal support, and inadequate drug accessibility may reduce dependence on BRAF signaling and weaken the response to dabrafenib-based

therapy [3, 8]. These factors vary among tumor lineages, explaining why BRAF V600E does not predict equivalent therapeutic sensitivity across all solid tumors.

Acquired resistance develops under continued treatment pressure as residual tumor cells adapt and repopulate the tumor. It may result from selection of pre-existing resistant subclones or from initially reversible, non-genetic states that allow cells to tolerate BRAF/MEK inhibition before stable resistance mechanisms emerge [8, 21, 90]. Genetic and phenotypic heterogeneity facilitates this process: drug-sensitive populations regress, whereas resistant subclones and drug-tolerant persister-like cells survive through transcriptional, epigenetic, metabolic, or differentiation-state plasticity [21, 90]. Resistance should therefore be viewed as an evolutionary process that progresses from baseline insensitivity or transient drug tolerance to stable molecular and phenotypic escape, rather than as the consequence of a single newly acquired mutation.

Cell-cycle deregulation and adaptive transcriptional rewiring may further stabilize resistant states. CDK4 alterations, CCND1 amplification, and CDKN2A loss weaken G1/S checkpoint control and may permit continued proliferation despite incomplete MAPK suppression [3, 92]. Co-occurring alterations in PTEN, TP53, the TERT promoter, and lineage-specific pathways may also modify baseline sensitivity and the route through which resistance develops [3, 8, 92]. In parallel, YAP and androgen receptor signaling can support transcriptional adaptation and reduced dependence on BRAF/MEK signaling, although the available evidence remains

largely preclinical and melanoma-derived [3, 8, 92].

5.2. MAPK Reactivation and Bypass Signaling

Reactivation of MAPK signaling is a major mechanism of resistance to dabrafenib-based therapy. Tumor cells may restore ERK activity through RAS activation, RAF dimerization, BRAF amplification or alternative isoforms, MEK alterations, and compensatory activation of receptor tyrosine kinases [8, 90]. Although trametinib delays pathway recovery by inhibiting MEK1/2, dual BRAF/MEK blockade may still be overcome by downstream alterations or reduced dependence on mutant BRAF. Non-canonical signaling may also contribute; ERK5 activation has been associated with acquired resistance to dabrafenib in BRAF V600E-mutant melanoma cells, and combined ERK5 and MEK inhibition reduced resistant-cell growth [93].

Resistance may also arise through bypass pathways that maintain survival without fully restoring canonical MAPK signaling. Activation of EGFR, PDGFR, IGF-1R, MET, and related receptors can stimulate PI3K–AKT–mTOR signaling and reduce dependence on BRAF–MEK–ERK activity [8, 90]. Tumor- or stromal-derived ligands may further promote this rescue: HGF can activate both MAPK and PI3K signaling, whereas IGF and NRG1 predominantly support PI3K-dependent survival and EGF or FGF can restore MAPK output [3]. The importance of these mechanisms varies according to receptor expression, stromal composition, and tumor lineage. ALDH1A1-associated stem-like states provide another form of bypass survival by maintaining PI3K/AKT signaling without necessarily restoring canonical MAPK activity [94].

BRAF V600E-mutant colorectal cancer provides the clearest clinical example of lineage-specific feedback resistance. BRAF inhibition relieves ERK-dependent negative feedback, leading to rapid EGFR activation and renewed RAS–RAF–MEK–ERK signaling [3, 8, 95]. Consequently, BRAF inhibitor monotherapy has limited activity in this setting, and effective pathway suppression requires concurrent EGFR blockade. This example demonstrates that resistance is shaped not only by the BRAF alteration itself but also by the signaling network of the tissue in which it occurs.

5.3. Tumor-Microenvironmental and Pharmacological Resistance

The tumor microenvironment can protect residual tumor cells during dabrafenib-based therapy. Cancer-associated fibroblasts, immune cells, extracellular matrix components, hypoxia, abnormal vasculature, and soluble mediators may activate RTK-dependent survival pathways, reduce effective drug penetration, and create protective niches for cells exposed to BRAF/MEK inhibition [3, 8, 21, 90]. Immune remodeling, including regulatory T-cell expansion, M2-like macrophage polarization, and CD73-mediated adenosine signaling, may further suppress antitumor immunity and support tumor-cell persistence under therapeutic pressure [21, 96].

Pharmacological resistance may also occur when dabrafenib exposure is insufficient or uneven across the tumor, even when cancer cells remain molecularly sensitive to BRAF inhibition. Heterogeneous perfusion, elevated interstitial fluid pressure, hypoxia, and variable vascular permeability can create underexposed regions in which residual or drug-tolerant cells survive [3, 85]. Experimental and computational analyses have further shown that

lipophilicity, albumin binding, systemic clearance, and target-dissociation kinetics may influence the depth and duration of dabrafenib penetration into visceral lesions [85].

This problem is particularly relevant in CNS tumors and brain metastases, where the blood–brain and blood–tumor barriers, active efflux transporters, and heterogeneous vascular permeability may create pharmacological sanctuary sites [3, 57]. Accordingly, delivery strategies should aim to reduce spatial underexposure, improve tumor- and brain-specific accumulation, and coordinate dabrafenib–trametinib exposure rather than merely increasing plasma drug concentrations [3, 57, 85].

6. Emerging Drug-Delivery Strategies for Dabrafenib in Solid Tumors

The pharmacokinetic, anatomical, and microenvironmental barriers that limit dabrafenib exposure provide a rationale for delivery strategies aimed at improving drug solubilization, tumor-site accumulation, and coordination with trametinib. Current approaches include oral formulation and solid-state engineering, nanocarrier-based delivery, and locoregional or co-delivery platforms; however, most remain preclinical and require comparison with standard oral therapy.

6.1. Oral Formulation and Solid-State Engineering

Oral formulation development for dabrafenib should primarily aim to improve dissolution robustness and maintain supersaturation rather than simply increase overall absorption. Clinical formulation studies have shown that capsule composition, particle properties, and precipitation behavior can substantially influence systemic exposure, despite the

high absolute bioavailability of dabrafenib under fasting conditions [97, 98].

Crystal engineering offers one strategy for modifying dabrafenib dissolution. Rai et al. (2020) developed several salts and cocrystals, among which a dabrafenib–ethylenediamine hydrate salt showed an approximately 11-fold higher dissolution rate than the free drug and dissolved more rapidly than dabrafenib mesylate at pH 1.2. However, these findings were limited to in vitro solid-state and dissolution analyses, and the pharmacokinetic, stability, and therapeutic advantages of this alternative form remain unconfirmed [70].

Nanostructured oral formulations have also been investigated. β -Cyclodextrin nanosponges and PLGA-based particles described as dabrafenib nanobubbles produced several-fold increases in systemic exposure after oral administration in rats [99, 100]. Nevertheless, neither platform demonstrated improved tumor accumulation, MAPK-pathway inhibition, or antitumor efficacy in a genetically confirmed BRAF V600E-positive model. These systems should therefore be regarded as preliminary approaches for modifying oral exposure rather than established improvements over conventional dabrafenib formulations.

6.2. Nanocarrier-Based and Tumor-Targeted Delivery

Nanocarrier-based formulations have been explored to improve dabrafenib solubilization and release while enhancing cellular uptake and, in selected preclinical models, tumor-site accumulation. Russi et al. (2023) encapsulated dabrafenib in approximately 10-nm self-assembled nanomicelles formed from an amphiphilic dendrimer, achieving an encapsulation efficiency of approximately 70% and a drug-loading capacity of 27%. The formulation

showed greater drug release at pH 5.0 than at pH 7.4 and enhanced antiproliferative activity compared with free dabrafenib in four melanoma cell lines [101]. However, the study was limited to in vitro experiments and did not assess pharmacokinetics, biodistribution, safety, or antitumor efficacy in vivo.

Pham et al. (2021) developed an acid-responsive, CD47-functionalized human serum albumin nanoconstruct for systemic dabrafenib delivery. The approximately 220-nm formulation increased cellular uptake, tumor accumulation, apoptosis, and tumor-growth inhibition compared with free dabrafenib or non-targeted nanoconstructs in a murine melanoma model. Nevertheless, the B16F10 model was not genetically validated as BRAF V600E-positive; therefore, the findings demonstrate the carrier's delivery and immunomodulatory potential but do not directly establish improved dabrafenib efficacy in molecularly appropriate BRAF V600E-driven disease [102].

Overall, these studies support the potential of nanomicellar and albumin-based platforms to modify dabrafenib release and tumor delivery. However, evidence remains limited to in vitro or melanoma-focused preclinical models, and future studies should quantify intratumoral drug exposure and MAPK inhibition in genetically confirmed BRAF V600E-positive tumors.

6.3. Locoregional and Dabrafenib–Trametinib Co-Delivery

Locoregional delivery and drug co-encapsulation offer complementary strategies for improving dabrafenib-based therapy. Locoregional administration may increase drug deposition in accessible cutaneous tumors, whereas co-delivery systems aim to coordinate the distribution of dabrafenib and trametinib within the

same tumor compartments. However, evidence for both approaches remains limited to preclinical melanoma models. Tham et al. (2018) developed photodynamically active mesoporous organosilica nanoparticles loaded with dabrafenib and trametinib. Microneedle pretreatment facilitated nanoparticle transport across the epidermal barrier and increased penetration into deeper porcine skin. The integrated platform also inhibited melanoma spheroids and improved tumor control in an A375 xenograft model. Nevertheless, it was not compared directly with standard oral dabrafenib–trametinib therapy, and its application is largely restricted to accessible cutaneous or subcutaneous lesions [103]. Koshrovski-Michael et al. (2024) developed sulfate-functionalized PLGA–PEG nanoparticles that co-encapsulated dabrafenib and trametinib at a preselected synergistic ratio and targeted P-selectin expressed by melanoma cells and tumor-associated vasculature. In murine melanoma models, the targeted nanoparticles increased tumor

accumulation, preserved the drug ratio within tumor tissue, and improved MAPK-pathway suppression, tumor-growth inhibition, and survival compared with the corresponding free-drug combination at matched low doses. However, their performance may depend on tumor P-selectin expression, and clinical superiority over conventional oral therapy remains unproven [104]. Overall, these studies support locoregional delivery and coordinated BRAF/MEK inhibitor co-delivery as promising strategies, but further evaluation requires pharmacokinetic comparisons, systemic safety assessment, and validation in genetically confirmed BRAF V600E-positive tumors beyond melanoma. As summarized in Table 3, dabrafenib-specific delivery research encompasses oral formulation optimization, nanocarrier-based solubilization, locoregional administration, and coordinated dabrafenib–trametinib delivery; however, the supporting evidence remains predominantly preclinical and heterogeneous.

Table 3. Dabrafenib-specific oral formulation, nanocarrier, locoregional, and combination-delivery strategies

Delivery approach	Formulation/platform	Administration route	Experimental model	Main findings	Key limitations	Reference
Oral formulation optimization	Hypromellose versus gelatin capsules; micronized versus nonmicronized drug substance	Oral	Randomized single-dose study in patients with BRAF mutation-positive tumors	Fasting, capsule-shell composition, and particle size altered systemic exposure. Hypromellose prolonged supersaturation	Single-dose formulation study; no assessment of lesion-level tumor exposure or clinical efficacy.	[97]

				tion and reduced precipitation of dabrafenib free base.		
Crystal engineering	Dabrafenib salts and cocrystals, including an ethylenediamine hydrate salt	Proposed oral use	In vitro solid-state and dissolution studies	The ethylenediamine hydrate salt showed an approximately 11-fold faster dissolution rate than dabrafenib free base and dissolved faster than dabrafenib mesylate at pH 1.2.	No pharmacokinetic, biodistribution, safety, or efficacy evaluation.	[70]
Nanosponge formulation	Diphenyl-carbonate-crosslinked beta-cyclodextrin nanosponges	Oral	Formulation studies and rat pharmacokinetics	The optimized formulation had a mean size of approximately 158 nm and increased Cmax and systemic exposure relative to free dabrafenib.	No BRAF V600E-positive tumor model; no tumor accumulation, pathway-inhibition, or antitumor-efficacy data.	[99]
Nanobubble formulation	PLGA-based dabrafenib nanobubbles	Oral; ultrasound-responsive release evaluated in vitro	Formulation studies and rat pharmacokinetics	The optimized particles were approximately 191 nm and increased Cmax and	No genetically confirmed BRAF V600E-positive tumor model; no demonstrati	[100]

				systemic exposure after oral administration in rats.	on improved tumor delivery or therapeutic efficacy.	
Nanomicellar delivery	Self-assembled amphiphilic dendrimer nanomicelles	In vitro	Four melanoma cell lines	Approximately 10-nm micelles improved dabrafenib solubilization, showed greater release at pH 5.0 than at pH 7.4, and enhanced antiproliferative activity relative to free drug.	No in vivo pharmacokinetic, biodistribution, safety, or efficacy assessment.	[101]
Protein-based nanocarrier	Acid-responsive, CD47-conjugated human-serum-albumin nanoconstruct	Systemic	B16F10 murine melanoma model	The carrier increased cellular uptake, tumor accumulation, and tumor-growth inhibition relative to free dabrafenib.	B16F10 tumors express wild-type rather than V600E-mutant BRAF; therefore, the study does not directly validate dabrafenib delivery in BRAF V600E-positive disease.	[102]
Locoregional multimodal delivery	Microneedle-assisted topical delivery of photodynamically active mesoporous	Topical/locoregional with near-infrared irradiation	Porcine skin, melanoma spheroids, and A375 xenografts	Microneedle pretreatment increased penetration into deeper	No direct comparison with standard oral dabrafenib-	[103]

	organosilica nanoparticles loaded with dabrafenib and trametinib			tissue, while the integrated platform combined BRAF/MEK inhibition with photodynamic cytotoxicity and improved tumor control.	trametinib therapy; applicable mainly to accessible cutaneous or subcutaneous lesions; individual contribution of enhanced dabrafenib delivery was not isolated.	
Targeted combination co-delivery	Sulfated, P-selectin-targeted PLGA-PEG nanoparticles co-encapsulating dabrafenib and trametinib	Intravenous	Murine and human melanoma cell lines and D4M.3A murine melanoma models	The nanoparticles increased tumor accumulation, maintained the initial drug ratio in tumor tissue, and improved MAPK suppression, tumor-growth inhibition, and survival relative to free drugs or nontargeted particles at matched low doses.	Preclinical evidence only; performance may depend on tumor P-selectin expression and vascular distribution; clinical superiority over oral therapy is unproven.	[104]

7. Future Directions and Translational Priorities

Clinical translation of dabrafenib delivery systems requires evidence of improved tumor-site exposure and MAPK-pathway

inhibition compared with standard oral therapy. Future studies should also address formulation reproducibility, scalable manufacturing, biodistribution, clearance, chronic toxicity, immunological effects, and

off-target accumulation, because preclinical antitumor activity alone does not ensure clinical feasibility or safety [105].

Next-generation RAF inhibitors may address resistance mechanisms or molecular contexts that are poorly controlled by conventional BRAF V600-selective inhibition. Tovorafenib, a type II RAF inhibitor, demonstrated clinically meaningful activity in relapsed or refractory BRAF-altered pediatric low-grade glioma in the FIREFLY-1 trial [59]. The investigational brain-penetrant pan-mutant BRAF inhibitor PF-07799933 also produced systemic and intracranial responses in heavily pretreated patients with BRAF-mutant cancers, including tumors with dimerization-associated resistance [39]. However, these agents should not be considered universal replacements for dabrafenib; their relevance depends on the exact BRAF alteration, resistance mechanism, tumor lineage, treatment history, and anatomical site of disease.

Future combination strategies should likewise be selected according to tumor biology. In BRAF V600E-mutant colorectal cancer, combined PD-1, BRAF, and MEK inhibition with spartalizumab, dabrafenib, and trametinib demonstrated proof-of-concept activity but remains investigational and should not replace established BRAF–EGFR-based treatment strategies [67]. More broadly, treatment selection should integrate BRAF mutation class, fusions, co-occurring alterations, resistance pathways, and tissue-specific drug accessibility. Next-generation sequencing and, where sufficiently validated, longitudinal circulating tumor DNA analysis may support treatment selection and early resistance monitoring [67]. Thus, future improvement of dabrafenib-based therapy will require coordinated consideration of molecular

context, resistance biology, delivery performance, and tumor-site accessibility.

8. Conclusion

The clinical activity of dabrafenib, particularly in combination with trametinib, confirms BRAF V600E as an important therapeutic target across multiple solid tumors. Nevertheless, mutation status alone does not determine the magnitude or durability of response. Tumor lineage, co-occurring alterations, adaptive signaling, microenvironmental protection, and lesion-level drug exposure collectively shape therapeutic outcome. Pharmacokinetic and tissue-distribution barriers may further generate poorly exposed tumor compartments in which residual or drug-tolerant cells persist. Emerging approaches, including solid-state engineering, nanocarriers, locoregional administration, and coordinated dabrafenib–trametinib co-delivery, offer potential means of improving drug availability, but their clinical advantage over standard oral therapy remains unproven. Future studies should therefore employ molecularly appropriate tumor models, directly quantify intratumoral drug concentrations and MAPK inhibition, and compare new formulations with current treatment standards. Ultimately, durable improvement in dabrafenib-based therapy will require an integrated framework that aligns molecular selection and resistance profiling with tumor-specific pharmacology and drug-delivery performance.

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BRAF V600E-POZITIV SOLİD ŞİŞLƏRDƏ DABRAFENİB: REZİSTENTLİK, KLİNİK TƏTBİQLƏR VƏ DƏRMAN ÇATDIRILMA STRATEGİYALARI

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Xülasə

Dabrafenib, xüsusilə trametinib ilə kombinasiyada, BRAF V600E-pozitiv bir sıra solid şişlərin müalicəsində artıq təsdiqlənmiş hədəflənmiş terapiyadır. Bununla belə, müalicəyə cavabın dərəcəsi və davamlılığı şiş növündən asılı olaraq əhəmiyyətli dərəcədə dəyişir. Bu icmalda dabrafenib əsaslı terapiyanın molekulyar əsasları, klinik tətbiqləri, rezistentlik mexanizmləri, farmakokinetik məhdudiyyətləri və inkişaf etməkdə olan dərman çatdırılma strategiyaları ümumiləşdirilir.

Müalicənin nəticəsinə yalnız BRAF V600E statusu deyil, həmçinin şişin mənşəyi, yanaşı mövcud olan genomik dəyişikliklər, reseptor tirozin kinazalarının əks-əlaqə mexanizmləri, mikroətraf mühit siqnalları və dərmanın ayrı-ayrı lezyonlarda ekspozisiyası təsir göstərir. Rezistentlik MAPK yolunun yenidən aktivləşməsi, PI3K/AKT alternativ siqnal ötürülməsi, hüceyrə plastikliyi, şiş heterogenliyi, stromal qoruyucu təsirlər və farmakoloji cəhətdən kifayət qədər ekspozisiyanın olmaması vasitəsilə inkişaf edir. Dabrafenibin effektivliyi pH-dan asılı həllolma, qida qəbuluna həssas sorulma, CYP vasitəçiliyi ilə metabolizm, autoinduksiya, dərman qarşılıqlı təsirləri, beyinə məhdud paylanma və şişdaxili toxumaya qeyri-bərabər nüfuzetmə ilə daha da məhdudlaşır. Bərk hal modifikasiyası, nanostruktur formulları, hədəflənmiş nanodaşıyıcılar, lokoregional tətbiq və dabrafenib–trametinibin koordinasiya şəkildə çatdırılması prekliniki tədqiqatlarda ümidverici nəticələr göstərmişdir. Lakin onların standart oral terapiyadan üstünlüyünü təsdiqləyən sübutlar hələ də məhduddur.

Melanoma, ağciyər, qalxanabənzer vəz, öd yolları, kolorektal və mərkəzi sinir sistemi şişləri üzrə klinik nəticələr göstərir ki, BRAF V600E mühüm terapevtik hədəf olsa da, müalicədən faydanı müstəqil şəkildə proqnozlaşdırmaq üçün kifayət etmir. Buna görə də müalicənin optimallaşdırılması molekulyar

seçim, rezistentlik profilinin müəyyənləşdirilməsi və dərmanın ayrı-ayrı lezyonlarda ekspozisiyasını birləşdirən şişə spesifik yanaşma tələb edir.

Açar sözlər: Dabrafenib, BRAF V600E, solid şiş, dərmana rezistentlik, nanodərman çatdırılması

ДАБРАФЕНИБ ПРИ СОЛИДНЫХ ОПУХОЛЯХ С BRAF V600E-ПОЛОЖИТЕЛЬНЫМ СТАТУСОМ: РЕЗИСТЕНТНОСТЬ, КЛИНИЧЕСКОЕ ПРИМЕНЕНИЕ И СТРАТЕГИИ ДОСТАВКИ ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ

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Резюме

Дабрафениб, особенно в комбинации с траметинибом, является признанной таргетной терапией для лечения ряда **BRAF V600E**-положительных солидных опухолей, хотя выраженность и продолжительность ответа на лечение значительно различаются в зависимости от типа опухоли. В настоящем обзоре обобщены молекулярное обоснование применения дабрафениба, его клиническое использование, механизмы резистентности, фармакокинетические ограничения и перспективные стратегии доставки препаратов. Результаты лечения определяются не только статусом **BRAF V600E**, но и тканевым происхождением опухоли, сопутствующими геномными изменениями, механизмами обратной регуляции рецепторных тирозинкиназ, сигнальными процессами в микроокружении опухоли и уровнем воздействия препарата непосредственно в очаге поражения. Резистентность развивается вследствие реактивации сигнального пути **MAPK**, обходной активации сигнального пути **PI3K/AKT**, клеточной пластичности, внутриопухолевой гетерогенности, защитного воздействия стромы и недостаточной фармакологической экспозиции. Эффективность дабрафениба дополнительно ограничивается зависимой от pH растворимостью, зависящим от приема пищи всасыванием, метаболизмом, опосредованным системой **CYP**, аутоиндукцией, лекарственными взаимодействиями, ограниченным проникновением в головной мозг и неоднородным распределением препарата в ткани опухоли.

Модификация твердой лекарственной формы, наноструктурированные лекарственные формы, таргетные нанопереносчики, локально-регионарное введение и согласованная доставка дабрафениба и траметиниба продемонстрировали перспективные доклинические результаты, однако доказательства их превосходства над стандартной пероральной терапией остаются ограниченными. Клинические данные, полученные при лечении меланомы, рака лёгкого, рака щитовидной железы, опухолей желчных путей, колоректального рака и опухолей центральной нервной системы, свидетельствуют о том, что **BRAF V600E** представляет собой важную терапевтическую мишень, однако его наличие само по себе недостаточно для прогнозирования эффективности лечения.

Таким образом, оптимизация терапии требует индивидуализированного подхода с учётом типа опухоли, объединяющего молекулярный отбор пациентов, профилирование механизмов резистентности и оценку уровня воздействия препарата непосредственно в опухолевом очаге.

Ключевые слова: *дабрафениб, BRAF V600E, солидная опухоль, лекарственная резистентность, нанодоставка лекарственных препаратов*