Review Article

Targeting RET–MAPK Signaling in Pediatric Solid Tumors: Molecular Biology, Therapeutic Advances, Resistance Mechanisms, and Emerging Combination Strategies

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ABSTRACT

Pediatric solid tumors are biologically heterogeneous, and a subset is driven by actionable alterations in receptor tyrosine kinases. RET (rearranged during transfection) is a clinically validated oncogenic driver in hereditary and sporadic medullary thyroid carcinoma and in RET fusion-positive thyroid cancers, while less common RET alterations have been reported across other pediatric malignancies. The development of selective RET inhibitors, particularly selpercatinib, has changed the therapeutic landscape by providing potent RET blockade with less off-target kinase inhibition than earlier multikinase inhibitors. However, durable control remains limited in some tumors by on-target resistance and, importantly, reactivation of downstream signaling through RAS–RAF–MEK–ERK or alternative receptor tyrosine kinases. This review examines RET biology, the spectrum and detection of RET alterations in pediatric solid tumors, clinical development of RET-directed therapy, pediatric pharmacologic and safety considerations, and mechanisms of therapeutic resistance. Particular emphasis is placed on the emerging rationale for combining RET inhibition with MEK or ERK inhibition as a strategy to suppress residual MAPK signaling and delay acquired resistance. Because pediatric combination evidence remains substantially less mature than adult RET-inhibitor experience, the review distinguishes established clinical evidence from preclinical hypotheses. Future progress will depend on molecularly selected trials, age-appropriate pharmacokinetic studies, longitudinal monitoring of resistance, and careful assessment of growth, skeletal, cardiovascular, hepatic, neurologic, and quality-of-life outcomes.

Key words: RET, pediatric solid tumors, medullary thyroid carcinoma, papillary thyroid carcinoma, selpercatinib, pralsetinib, MAPK, MEK, ERK, drug resistance, precision oncology

Pediatric solid tumors comprise a diverse group of malignancies with distinct developmental, genomic, and tissue-of-origin characteristics [1]. Although multimodal treatment has improved survival for many children, metastatic, relapsed, and biologically high-risk disease remains difficult to treat [2]. Precision oncology has therefore become increasingly important, particularly when a tumor contains a targetable kinase alteration. Rearranged during Transfection (RET) is one of the most clinically relevant examples because both activating mutations and gene fusions can produce constitutive kinase signaling and dependence on downstream pathways [3]. RET encodes a transmembrane receptor tyrosine kinase involved in neural crest development, enteric nervous system development, and other developmental processes [4]. Oncogenic RET activation is best established in medullary thyroid carcinoma (MTC), including germline RET mutations associated with multiple endocrine neoplasia type 2, and in RET rearrangements in papillary thyroid carcinoma (PTC) [5]. Broader genomic profiling is also identifying RET alterations in uncommon pediatric tumors. However, the clinical relevance of an alteration depends on tumor lineage, alteration type, clonality, and degree of RET dependence [6]. Selective RET inhibitors have provided a major therapeutic advance over earlier multikinase inhibitors. Selpercatinib and pralsetinib were designed to inhibit RET more selectively and thereby reduce some toxicities associated with simultaneous vascular endothelial growth factor receptor (VEGFR) and other kinase inhibition [7]. Pediatric development has subsequently generated clinically relevant evidence, particularly for selpercatinib. The FDA has approved selpercatinib for specified RET-altered cancers in pediatric patients aged 2 years and older, making pediatric RET inhibition a current therapeutic reality rather than solely an investigational concept [8].

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Despite high activity, acquired resistance can emerge. Resistance may be RET-dependent, caused by secondary alterations that impair inhibitor binding, or RET-independent, caused by restoration of downstream signaling through rat sarcoma (RAS), rapidly accelerated fibrosarcoma (RAF), mitogen-activated protein kinase kinase (MEK), extracellular signal-regulated kinase (ERK), or alternative receptor tyrosine kinases [9]. This observation provides the central rationale for this review: understanding how RET inhibition interacts with mitogen-activated protein kinase (MAPK) signaling may identify strategies that prolong response while recognizing that RET–MEK/ERK combination therapy remains an emerging approach in children.

2. RET BIOLOGY AND ONCOGENIC SIGNALING

RET activation normally depends on glial cell line-derived neurotrophic factor (GDNF) family ligands and GFRα coreceptors [10]. Ligand-induced receptor dimerization promotes autophosphorylation of intracellular tyrosine residues, creating docking sites for adaptor proteins and signaling complexes. Among these sites, Y1062 is a major signaling hub that connects RET to SHC–GRB2–SOS and RAS activation [11]. Downstream signaling includes the RAS–RAF–MEK–ERK cascade, PI3K–AKT–mTOR signaling, PLCγ, JAK–STAT, and SRC-family pathways [12].

Oncogenic RET activation occurs principally through activating point mutations and chromosomal rearrangements. Mutations may affect extracellular cysteine residues or the kinase domain and can produce ligand-independent signaling [13,14]. RET fusions generally retain the RET kinase domain while replacing the normal extracellular and transmembrane regions with a partner that promotes constitutive dimerization or activation [15] These molecular configurations can differ in cellular localization and downstream signaling, an issue that may influence treatment response. The MAPK pathway is a central proliferative output of RET signaling. Activated RAS recruits RAF kinases, which activate MEK1/2 and subsequently ERK1/2 [16]. ERK regulates transcriptional and cytoplasmic substrates involved in proliferation, differentiation, protein synthesis, and cell survival [17]. Thus, RET inhibition can suppress MAPK output, while reactivation of the pathway can provide a mechanism of therapeutic escape. PI3K–AKT–mTOR signaling may provide an additional survival route, emphasizing that RET-driven cancers are not necessarily dependent on a single downstream pathway at all times [18].

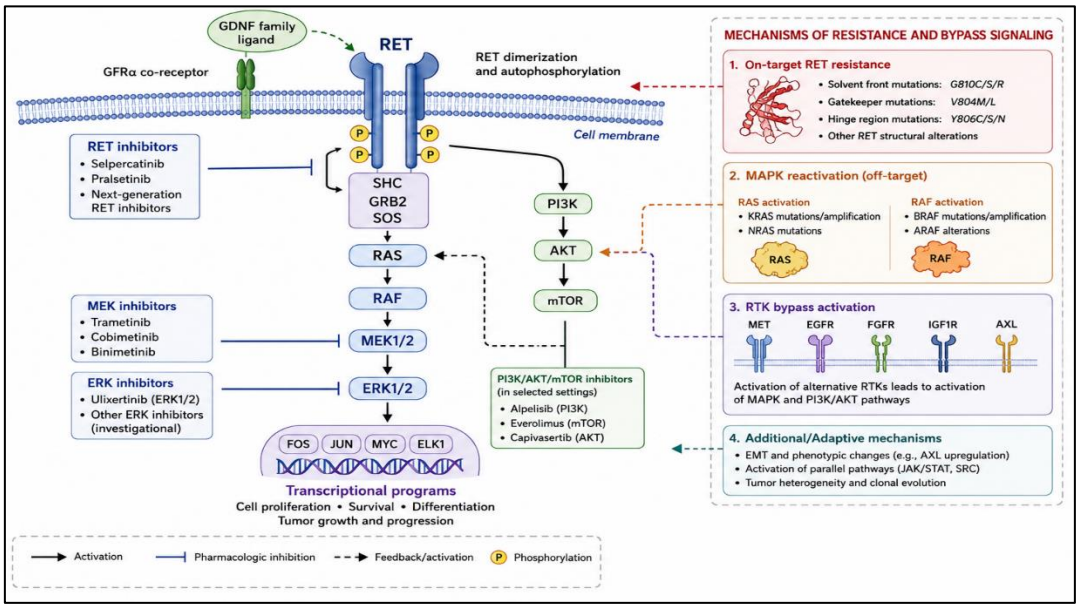


Figure 1. RET–MAPK signaling pathway and therapeutic intervention points in pediatric solid tumors. Abbreviations: RET, rearranged during transfection; GDNF, glial cell line-derived neurotrophic factor; GFRα, GDNF family receptor alpha; SHC, Src homology 2 domain-containing transforming protein; GRB2, growth factor receptor-bound protein 2; SOS, Son of Sevenless; RAS, rat sarcoma virus protein; RAF, rapidly accelerated fibrosarcoma; MEK, mitogen-activated protein kinase kinase; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; mTOR, mechanistic target of rapamycin; RTK, receptor tyrosine kinase; MET, mesenchymal–epithelial transition factor; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; IGF1R, insulin-like growth factor 1 receptor; AXL, AXL receptor tyrosine kinase; EMT, epithelial–mesenchymal transition; JAK, Janus kinase; STAT, signal transducer and activator of transcription; FOS, Fos proto-oncogene; JUN, Jun proto-oncogene; MYC, MYC proto-oncogene; ELK1, ETS transcription factor ELK1; ctDNA, circulating tumor DNA.)

3. RET ALTERATIONS ACROSS PEDIATRIC SOLID TUMORS

Medullary thyroid carcinoma

MTC is the clearest pediatric example of a RET-driven malignancy. Germline activating RET variants underlie MEN2 syndromes, with genotype influencing disease aggressiveness and timing of prophylactic intervention [19]. The M918T variant associated with MEN2B is particularly aggressive and can present very early in life. Somatic RET alterations are also frequent in sporadic MTC [20]. Because RET is a defining molecular driver in many cases, molecular testing has direct implications for diagnosis, surveillance, family counseling, and targeted treatment.

Papillary thyroid carcinoma

RET rearrangements are an important molecular class in pediatric PTC, particularly in radiation-associated disease [21]. RET/PTC rearrangements, including CCDC6–RET and NCOA4–RET, produce constitutive RET signaling and activate MAPK signaling [22]. The enrichment of RET rearrangements in radiation-associated pediatric thyroid cancer illustrates how environmental or treatment-related DNA damage can generate targetable kinase fusions.

Neuroblastoma

RET biology in neuroblastoma is more complex than in RET-driven thyroid cancer. RET expression and signaling have been implicated in neural crest biology and neurotrophic signaling, and RET alterations have been reported in subsets of neuroblastoma [23]. However, the frequency and functional importance of RET alterations vary among datasets. RET expression alone should therefore not be equated with a RET oncogenic driver, and the therapeutic significance of RET inhibition in neuroblastoma remains less clinically established than in RET-altered thyroid cancer.

Other pediatric tumors

Broad next-generation sequencing has identified rare RET alterations across pediatric solid tumors. These findings are important because a highly selective inhibitor can potentially create a therapeutic opportunity independent of conventional histology. Nevertheless, rare RET fusions should be interpreted cautiously, with attention to fusion structure, kinase retention, tumor clonality, and supporting functional evidence. RET should also be distinguished from other kinase-fusion entities, particularly NTRK-driven tumors, which have characteristic pediatric associations such as infantile fibrosarcoma [24].

4. DETECTION OF RET ALTERATIONS

Accurate identification of RET alterations is essential for precision treatment. DNA-based targeted sequencing can detect point mutations and selected rearrangements, while RNA-based sequencing is particularly useful for identifying expressed gene fusions and novel fusion partners [25]. Fluorescence in situ hybridization and targeted RT-PCR may be useful when a specific rearrangement is suspected, but they can be less comprehensive than sequencing-based approaches [26].

For fusion-positive disease, integrated DNA and RNA testing can improve diagnostic sensitivity and provide information on the actual expressed fusion transcript. Liquid biopsy and circulating tumor DNA are promising tools for longitudinal monitoring, particularly when tissue re-biopsy is difficult [27]. However, their sensitivity in small-volume pediatric disease and their role in routine RET resistance monitoring require further validation.

5. EVOLUTION OF RET-DIRECTED THERAPY

Multikinase inhibitors

Vandetanib and cabozantinib provided early proof that RET inhibition could control advanced MTC, but their activity against multiple kinases also produced toxicities related to VEGFR and other targets [28]. In children, these toxicities are particularly important because treatment may occur during periods of growth and development.

Selective RET inhibitors

Selpercatinib and pralsetinib represent a major pharmacologic advance because they inhibit RET with greater selectivity than earlier multikinase inhibitors [7]. Adult trials demonstrated substantial activity in RET-mutant MTC and RET fusion-positive thyroid and lung cancers [29]. Pediatric development has subsequently established selpercatinib as the most clinically mature selective RET inhibitor in children.

The LIBRETTO-121 study evaluated selpercatinib in pediatric patients with RET-altered cancers. Updated results in patients aged 2–20 years demonstrated clinically meaningful responses across RET-mutant MTC, RET fusion-positive PTC, and other RET-altered tumors [30]. These data, together with regulatory evidence, support the current pediatric role of selpercatinib in specified RET-altered malignancies. Pralsetinib remains an important selective RET inhibitor, but its pediatric evidence base is less mature and should not be presented as equivalent to selpercatinib.

Regulatory landscape

The regulatory status of selpercatinib has evolved rapidly. FDA approval now includes specified RET-altered cancers in patients aged 2 years and older. In July 2026, the FDA granted traditional approval for selpercatinib in locally advanced or metastatic RET fusion-positive solid tumors after prior systemic treatment or when no satisfactory alternative therapy exists [31]. These developments should be incorporated into any current review because they materially change the clinical context of pediatric RET targeting (Table 1).

6. PEDIATRIC PHARMACOLOGY, SAFETY, AND PRACTICAL CONSIDERATIONS

Pediatric targeted therapy cannot be approached as simple adult dose scaling. Age-dependent drug metabolism, organ maturation, body composition, concomitant medications, food effects, and formulation can influence exposure. Pharmacokinetic studies therefore need age-stratified analysis and should distinguish infants, young children, older children, and adolescents when sample size permits [32].

Long-term safety is particularly important for MAPK-directed combinations. Potential concerns include growth and skeletal development, cardiovascular effects, hepatic abnormalities, hematologic toxicity, gastrointestinal effects, ocular toxicity depending on the MAPK inhibitor, and neurodevelopmental consequences [33]. The evidence for long-term developmental effects of RET inhibition remains incomplete, making systematic follow-up essential. Practical factors such as formulation, swallowing ability, adherence, school disruption, caregiver burden, and quality of life should also be incorporated into pediatric trials [34]. These outcomes are not secondary considerations; they can determine whether prolonged oral targeted therapy is feasible in real-world pediatric practice.

7. MECHANISMS OF RESISTANCE TO RET INHIBITORS

Resistance can be broadly divided into on-target and off-target mechanisms. On-target resistance occurs when secondary RET alterations reduce inhibitor binding while retaining kinase activity. Important examples include solvent-front alterations such as G810 substitutions and changes around the hinge region, including Y806 alterations [35]. Gatekeeper-region changes involving V804 can also influence inhibitor sensitivity [36]. These structural changes have stimulated development of next-generation RET inhibitors capable of overcoming resistant kinase conformations. Off-target resistance restores downstream signaling without necessarily altering RET itself. RAS or BRAF alterations can reactivate the MAPK cascade downstream of RET [37]. Amplification or activation of alternative receptor tyrosine kinases, including MET, EGFR, FGFR, and IGF1R, may similarly restore RAS–RAF–MEK–ERK signaling [16]. Other adaptive processes, including changes in cell state and survival signaling, can further reduce drug dependence (Table 2).

Table 1. RET-directed therapies in pediatric RET-altered solid tumors

Drug	Selectivity	Major development context	Pediatric interpretation
Vandetanib	Multikinase	RET/VEGFR/EGFR activity; established MTC drug	Historical/limited; off-target toxicity relevant
Cabozantinib	Multikinase	RET and VEGFR activity	Limited pediatric role; toxicity considerations
Selpercatinib	Highly selective RET	Strong clinical activity; pediatric development and FDA indication	Most mature pediatric evidence
Pralsetinib	Highly selective RET	Clinical activity in RET-altered cancers	Pediatric evidence less mature

Table 2. Mechanisms of resistance to selective RET inhibitors and therapeutic strategies

Mechanism	Representative alteration/process	Biological consequence	Potential strategy
On-target	RET G810 substitutions	Reduced inhibitor binding	Next-generation RET inhibition
Gatekeeper-region	RET V804 alterations	Reduced drug sensitivity	Alternative RET inhibitor design
Hinge-region	RET Y806 alterations	Altered inhibitor interaction	Next-generation inhibitor
RAS pathway	KRAS/NRAS activation	MAPK reactivation	MEK/ERK-directed therapy
BRAF pathway	BRAF alteration/amplification	MAPK reactivation	MAPK pathway inhibition
RTK bypass	MET/EGFR/FGFR/IGF1R activation	RET-independent signaling	Mechanism-guided combination
Cell-state adaptation	EMT/AXL and survival changes	Persistence despite RET blockade	Experimental combination strategies

8. RET–MAPK COMBINATION STRATEGIES

The central translational hypothesis of this review is that downstream MAPK suppression may complement RET inhibition. RET blockade reduces the initiating oncogenic signal, while MEK or ERK inhibition can suppress residual or restored MAPK output. This creates a form of vertical pathway inhibition. The approach is conceptually different from blocking parallel receptor tyrosine kinases, which represents horizontal or bypass-directed inhibition. Preclinical studies in RET-dependent models have provided a rationale for combining selective RET inhibitors with MEK inhibitors such as trametinib, cobimetinib, or binimetinib, and with investigational ERK inhibitors [38]. Combination treatment can produce greater pathway suppression and, in experimental systems, delay the emergence of resistance. However, preclinical synergy should not be interpreted as evidence that routine upfront combination therapy is clinically beneficial in children.

A major challenge is the therapeutic window. MEK inhibition has clinically relevant toxicities, and combining two targeted agents may increase cumulative adverse effects. In children, the potential effects on growth, skeletal maturation, cardiac function, vision, liver function, and quality of life require particular attention. Consequently, pediatric trials should begin with careful dose-finding and pharmacokinetic assessment rather than directly adopting adult combination doses. An alternative strategy is resistance-guided combination therapy. Instead of exposing all patients to two inhibitors, molecular progression can identify tumors with MAPK reactivation and select a downstream inhibitor only when biologically justified. This approach may reduce unnecessary toxicity while preserving the ability to target an emergent resistance pathway (Table 3).

9. CNS Disease and Blood–Brain Barrier Considerations

CNS involvement creates an additional pharmacologic challenge because effective systemic exposure does not necessarily translate into adequate intracranial exposure. Selpercatinib has demonstrated intracranial activity in adult RET-altered cancers, supporting its potential usefulness when RET-driven disease involves the CNS [39]. Nevertheless, pediatric CNS-specific evidence remains limited and should be distinguished from adult data. Future pediatric studies should incorporate standardized assessment of CNS disease, pharmacokinetic characterization where ethically feasible, and systematic recording of neurologic outcomes. CNS activity should be evaluated as a defined endpoint rather than inferred from systemic response.

10. Preclinical and Translational Models

Cell-line models remain useful for defining RET dependence, testing pathway inhibition, and generating resistance [40]. Isogenic models can separate the effect of a specific RET mutation or fusion from the genetic background of the tumor. CRISPR-based approaches can also be used to introduce or remove resistance alterations and determine their causal role. Patient-derived xenografts and organoids provide additional opportunities to evaluate drug combinations in more representative tumor contexts [41]. Pediatric organoids are particularly attractive because they can be integrated with genomic and transcriptomic profiling to identify biomarkers of response. Phosphoproteomic approaches may provide functional evidence of pathway suppression, including changes in phospho-ERK and downstream substrates.

Table 3. Emerging RET–MAPK combination strategies in pediatric solid tumors

Combination strategy	Molecular rationale	Example agents	Evidence	Potential benefit	Major concerns
RET + MEK	Vertical suppression of MAPK pathway	Selpercatinib + trametinib	Preclinical/emerging	Greater MAPK suppression; resistance delay	Growth, skeletal, cardiac, hepatic toxicity
RET + ERK	Direct blockade of downstream ERK	Selpercatinib + ERK inhibitor	Preclinical/early clinical concept	Suppress persistent ERK signaling	Limited pediatric evidence
RET + BRAF/MEK	Target acquired RAF activation	RET inhibitor + MAPK-directed therapy	Mechanism-dependent	Resistance-specific control	Toxicity
RET + MET/RTK	Block bypass activation	RET inhibitor + MET/RTK inhibitor	Preclinical	Prevent bypass signaling	Patient selection
Resistance-guided combination	Match treatment to resistance mechanism	Molecularly selected	Future clinical strategy	Avoid unnecessary combination toxicity	Requires serial molecular testing

The translational challenge is to connect these models to clinical decision-making. A promising future framework would integrate tumor sequencing, RNA expression, phosphoproteomics, functional drug testing, and serial ctDNA to identify the dominant resistance mechanism in each patient.

11. CLINICAL TRANSLATION AND FUTURE DIRECTIONS

Several priorities should guide the next generation of pediatric RET research. First, molecular testing should be incorporated early enough to identify RET alterations before treatment options are exhausted. Second, pediatric trials should generate robust pharmacokinetic and pharmacodynamic data across developmental stages. Third, resistance should be studied prospectively using tissue and liquid biopsy when feasible. Fourth, combination strategies should be tested in carefully selected populations rather than assuming that all RET-positive tumors share identical biology.

The most important unanswered question is whether adding MAPK inhibition improves clinically meaningful outcomes enough to justify additional toxicity. Trials should therefore compare not only response rate but also duration of response, event-free survival, quality of life, cumulative toxicity, growth outcomes, and the incidence and timing of resistance. Basket trials may be valuable because RET-altered pediatric cancers are rare, but histology-specific biological differences must be retained in trial interpretation.

International collaboration will be essential. Pediatric oncology networks can provide sufficient numbers for molecularly selected trials, while harmonized definitions of response, resistance, CNS disease, and long-term toxicity will improve cross-study comparison. Regulatory frameworks that encourage pediatric development should be accompanied by post-approval evidence generation and long-term surveillance.

CONCLUSION

RET has evolved from a molecular marker of selected thyroid cancers into a clinically actionable target in pediatric precision oncology. The strongest evidence supports RET-directed therapy in RET-driven MTC and RET fusion-positive thyroid cancer, while the significance of RET alterations in other pediatric solid tumors remains more heterogeneous. Selective RET inhibition, particularly with selpercatinib, has improved the therapeutic precision of RET targeting and has established a pediatric clinical role.

The next challenge is durability. Resistance can arise through secondary RET alterations or restoration of signaling downstream of the inhibited receptor. MAPK reactivation is therefore a compelling therapeutic vulnerability, providing a rationale for RET plus MEK or ERK inhibition. However, this combination remains an emerging strategy in children, and its clinical value must be demonstrated in prospective trials with rigorous developmental safety monitoring.

Future progress will depend on integrating molecular diagnosis, pharmacology, longitudinal resistance profiling, functional models, and pediatric-specific outcome measures. The most informative studies will not simply ask whether RET inhibition works, but will determine which children remain RET-dependent, how resistance evolves, when downstream MAPK inhibition is justified, and how these strategies can be delivered safely during development.

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