Am J Cancer Res 2026;16(2):371-387
www.ajcr.us /ISSN:2156-6976/ajcr0168341

Review Article

BRAF mutation and tumor immune microenvironment in new era

Jianing Zhou, Chengyuan Li, Lijun Zhang, Yan Si, Xiang Zhang, Meiping Shen

Department of General Surgery, The First Affiliated Hospital with Nanjing Medical University, Nanjing 210029, Jiangsu, China

Received August 25, 2025; Accepted January 25, 2026; Epub February 15, 2026; Published February 28, 2026

Abstract: Activation of the BRAF kinase is implicated in the oncogenesis of multiple human tumors, particularly thyroid cancer, colorectal cancer and melanoma. BRAF mutations serve as pivotal modulators of the immunomodulatory landscape within tumors, critically shaping host immune responses and modulating efficacy to cancer immunotherapy. Here, we reviewed the impact of BRAF mutations on the composition and function of tumor immune microenvironment and summarized current therapeutic strategies targeting BRAF. Overall, BRAF mutations significantly modulates cancer treatment outcomes through its effects on immune regulation. Targeting BRAF mutations at different stages of tumor initiation and progression may provide valuable insights for the development of innovative clinical interventions.

Keywords: BRAF mutation, tumor microenvironment, immunotherapy

Introduction

Cancer emergence and development occur through the gradual accumulation of diverse genetic and epigenetic alterations, including activating and inactivating somatic mutations, alterations in gene expression profiles, non-coding RNA disruption, and abnormal gene methylation. Among these alterations, somatic mutations manifest early in the transformation sequence and maintain essential significance for cancer advancement. Neoplasia represented by colorectal cancer (CRC), thyroid cancer (TC), and melanoma frequently harbors mutations in critical genes through point mutations or chromosomal rearrangements. Notably, increasing evidence indicates that these two separate mutational processes are linked to particular etiologic factors participating in carcinogenesis.

B-type Raf kinase (BRAF), a serine-threonine kinase, translocates to the cellular membrane following binding and activation by its upstream RAS kinase. This activation triggers phosphorylation and stimulation of mitogen-activated protein kinase (MAPK) along with additional downstream targets, thereby participating in cellular proliferation, differentiation, and programmed cell death. BRAF activation occurs through point mutations, small indels, or chromosomal rearrangements. The most prevalent mechanism is a point mutation at nucleotide position 1799 (T1799A), producing valine-to-glutamate substitution at residue 600 (V600E).

Over the years, there has been increasing acknowledgment that cancer represents an evolutionary and ecological process, defined by ongoing, dynamic, and bidirectional interactions between malignant cells and the tumor microenvironment (TME). The TME consists of host-derived non-malignant components, encompassing fibroblasts, endothelial cells, neurons, adipocytes, adaptive and innate immune cells, along with non-cellular elements. These include the extracellular matrix (ECM) and soluble factors such as chemokines, cytokines, growth factors, and extracellular vesicles (EVs), which are interconnected and engage with the heterogeneous malignant cells. Considering this complexity, numerous therapeutic approaches targeting the TME have been established, including the elimination of cancer-pro-

https://doi.org/10.62347/IRQS3605

moting microenvironmental cells or their reprogramming into phenotypes that exhibit immunostimulatory and tumor-suppressive properties.

However, cancer cells have developed various mechanisms, including deficiencies in antigen presentation, enhanced expression of inhibitory regulatory pathways, and mobilization of immunosuppressive cellular populations, to escape immune surveillance. This results in compromised effector functions of immune cells and reduced anti-tumor immune responses. These downstream immunological consequences are frequently governed by specific driver mutations, among which oncogenic BRAF alterations constitute key regulators.

Therefore, this review aims to reframe the current understanding by deciphering the dynamic reciprocity between oncogenic BRAF signaling and the tumor immune microenvironment. It consolidates evidence on BRAF-driven tumorigenesis and therapy resistance, while constructing an integrated "signaling-microenvironment-therapy" framework that delineates how mutant BRAF actively sculpts an immunosuppressive niche and how immune rewiring subsequently modulates treatment efficacy. Through this deliberately forward-looking synthesis, we establish a conceptual nexus that can inform novel combination strategies and help overcome resistance in BRAF-driven malignancies.

BRAF function and regulation

The Rapidly accelerated fibrosarcoma (RAF) protein kinase family, comprising serine/threonine-specific protein kinases (ARAF, BRAF and CRAF), relays signals through the downstream MAPK pathway to control transcription of genes that govern diverse cellular mechanisms [1]. Activation of this physiological pathway occurs through various growth factors, hormones, and cytokines acting via their corresponding cell membrane receptors. Upon activation, RAF kinases phosphorylate and stimulate the directly downstream mitogen-activated extracellular signal-regulated kinase (MEK), which subsequently phosphorylates and stimulates extracellular regulated protein kinase (ERK), thereby influencing gene expression, leading to alterations in cellular bioactivity and functional outcomes [2].

RAF family proteins possess three conserved regions (CR): CR1, CR2 and CR3. CR1 encompasses the RAS-binding domain and the cysteine-rich domain, which physically interact to bind RAS [3]. CR2 harbors a Ser/Thr-rich sequence, while CR3 consists of a putative kinase domain featuring an N-terminal acidic motif and a C-terminal regulatory tail [4]. RAF isoforms demonstrate diverse kinase activities in the sequence BRAF>CRAF>ARAF, presumably due to distinctive N-terminal acidic motifs that facilitate the dimerization-mediated transactivation of RAFs [5, 6].

The BRAF gene resides on chromosome 7q34 in humans and encodes a cytosolic serine-threonine protein kinase found throughout multiple human tissues, such as cerebral cortex, hippocampus, thyroid gland, colon and lung. BRAF controls the MAPK/ERK signaling cascade, thus influencing cell division, differentiation, and secretion. Disease-causing BRAF mutations result in RAF protein activation, which persistently transmits signals to downstream pathways independent of external signal reception, consequently leading to uncontrolled cell proliferation.

Oncogenic BRAF mutations are categorized into three distinct classes that dictate their responsiveness to inhibitors (**Figure 1**). Class I BRAF mutations (V600E/K/R/D/M) function independently of RAS and demonstrate sensitivity to RAF inhibitors. These genetic changes appear in roughly 50% of melanoma cases, 40% of papillary thyroid carcinoma (PTC) cases, and 10% of CRC cases [7]. Class II BRAF mutations typically emerge in the kinase domain's active portion (including K601 E/N/T, L597V/Q/R) or the P loop (including G464 V/E and G469 A/V/R) and function autonomously from RAS activity, acting as constitutive dimers while showing vemurafenib resistance. These variants may respond to emerging RAF dimer inhibitors or MEK inhibitors. Class III BRAF alterations primarily locate in the kinase domain's P loop (including G466 A/E/R/V), the catalytic loop (including N581I/S/T), and the Asp-Phe-Gly motif (including D594 A/E/G/H/N and D596C/D/R), typically occurring in tumors with enhanced receptor tyrosine kinase (RTK) activity alongside RAS activation or neurofibromatosis type 1 (NF1) function loss [8]. Although CRC patients harboring Class III mutations exhibit

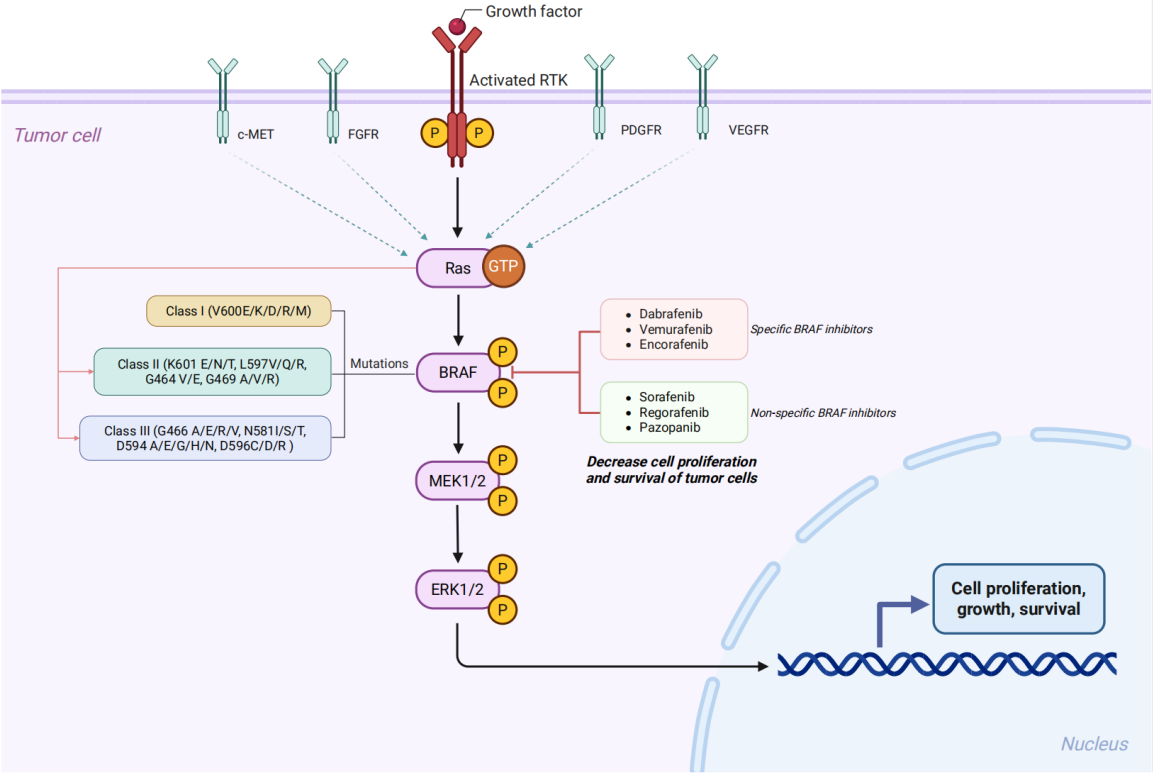

Figure 1. BRAF activation and mutations through MAPK signaling. After activation through binding with GTP, Ras protein interacts with BRAF and activates it. Subsequently, activated MEK1/2 phosphorylate and activate the downstream ERK1 and ERK2, which further phosphorylate downstream proteins, ultimately leading to changes in the expression of various genes involved in cell proliferation, growth, survival, and tumorigenesis within the nucleus. Multiple angiogenesis kinases target RAS and regulate downstream signals. BRAF mutations are classified into three categories based on signaling pathway mechanisms and kinase activity. Class I BRAF mutations (V600E/K/R/D/M) are RAS-independent. Class II BRAF mutations also typically do not rely on RAS activity and signal as constitutive dimers. Class III BRAF mutations often occur in tumors with high receptor tyrosine kinase (RTK) activity and are frequently accompanied by RAS activation or loss of NF1 function. BRAF inhibitors are categorized as specific or non-specific, and they inhibit downstream signaling by binding to the ATP site of the BRAF mutant monomer, decreasing cell proliferation and survival of cancer cells.

heightened epidermal growth factor receptor (EGFR) inhibitor sensitivity and enhanced survival, those carrying Class I mutations display poor EGFR inhibitor response and suboptimal treatment outcomes [9].

The wild-type (wt) BRAF is activated at the plasma membrane through a complex mechanism involving RAS activity, phosphorylation processes, and protein-lipid interactions. BRAF kinase displays a characteristic bilobed architecture similar to all protein kinases [10]. Extracellular signals (mitogens, hormones, and neurotransmitters) induce a tyrosine kinase receptor, and trigger wt BRAF activation. Oncogenic RAS mediates phosphorylation at two conserved sites (T598 and S601), which both sustains BRAF activity and initiates ERK1/2-mediated cell transformation.

As a pivotal regulator within the MAPK signaling pathway, BRAF mutations result in sustained pathway activation and are identifiable across diverse tumor types (**Table 1**), demonstrating extensive carcinogenic potential. Such mutations frequently occur in solid malignancies and correlate with cardiofaciocutaneous, Noonan, and Costello syndromes, which display overlapping clinical phenotypes [11].

Clinical characteristics and prevalence of BRAF mutations in diverse cancer types

Thyroid cancer

Transformation of thyroid follicular cells and thyroid C cells leads to three broad histological categories: Differentiated thyroid cancer (DTC), medullary thyroid cancer and anaplastic thyroid

Table 1. BRAF mutation frequencies, mutation classes and co-mutations in different cancer types

Cancer type	BRAF mutation frequencies	BRAF mutation site	Co-mutations	Ref.
Thyroid cancer	60% in PTC, 45% in ATC	BRAF V600E (70%)	TERT, TP53, PIK3CA	[14, 15]
Melanoma	36.40%	BRAF V600E (80%); BRAF V600K (8%); BRAF V600R (1%); other codons (10%)	CDKN2A, TERT, PTEN	[19, 30]
Colorectal cancer	6.5%-10.2%	BRAF V600E (90%)	APC	[24, 31]
Astrocytoma	56%	*BRAF V600E; BRAF-KIAA1549 fusion	CDKN2A/B, TP53, ATRX	[32, 33]
NSCLC	3%	BRAF V600E (70%)	TP53, STK11	[34, 35]

*BRAF V600E (66% in pleomorphic xanthoastrocytoma), BRAF-KIAA1549 fusion (80% in pilocytic astrocytoma).

cancer. Kimura et al. [12] initially documented BRAF mutations in 35.8% (28/78) of differentiated DTCs during 2003. Subsequent work by Nikiforova et al. [13] demonstrated that BRAF mutations were exclusively present in individuals with PTC or in cases of poorly differentiated or ATC evolving from existing PTC. Current data indicate that most common gene variant is BRAF V600E, occurring in approximately 60% of PTC patients [14] and 45% of ATC patients [15], resulting in high frequency of cervical lymph node metastases, locoregional recurrences, and are less responsive to radioactive iodine [16]. PTCs driven by BRAF V600E disrupt the negative feedback from ERK to RAF, thus resulting in enhanced MAPK signaling and reduction of iodine uptake and metabolism. Based on the American Thyroid Association Risk Stratification System and Initial Treatment Recommendations, multifocal micropapillary thyroid cancer with BRAF gene variant is categorized into the Intermediate-risk group [17].

Melanoma

Melanoma cases are classified into four subtypes per the pattern of the most prevalent markedly mutated genes: mutant BRAF, mutant RAS, mutant NF1, and Triple-wt. Early sun exposure and susceptibility to nevi typically trigger melanoma development through BRAF alterations [18]. In Western populations, BRAF mutations account for 50%-60% of melanoma patients, with Class I BRAF V600E mutations representing over 90% of these alterations. While East Asian populations exhibit lower BRAF mutation frequencies (15%-25%), of which BRAF V600E constitutes over 80% [19, 20]. Histopathological analysis revealed that BRAF V600E mutant melanocytic proliferations are characterized by enlarged cell sizes [21]. Additionally, 3-hydroxy-3-methylglutaryl-CoA lyase (HMGCL) expression demonstrates upregulation in BRAF V600E mutant melanoma. Kang et al. demonstrated that altered BRAF can increase HMGCL transcription via Oct-1 and create a metabolic restructuring mechanism involving cellular signaling pathways through the Oct-1-HMGCL-acetoacetate pathway, wherein acetoacetate ultimately facilitates BRAF V600E and MEK1 binding, leading to enhanced MAPK stimulation [22].

Colorectal cancer

Oncogenic BRAF mutations are present in roughly 10% of CRCs [23], with BRAF V600E accounting for 90% of these cases [24]. BRAF mutations in CRCs correlate with poorer differentiation, mucinous histology, microsatellite instability and larger primary tumors [25, 26], leading to almost doubled mortality rates compared to wt BRAF CRCs in metastatic settings [27]. Previous studies have shown the resistance of BRAF-mutant CRCs to BRAF targeting monotherapy [23], despite the high efficacy of similar strategies in melanoma. A recent study demonstrated that BRAF V600E mutant CRC organoids exhibit significant resistance to radiotherapy, and the combination of radiotherapy and chemotherapy achieved superior tumor suppression on CRC [28]. Following clinical trial evidence [29], the U.S. Food and Drug Administration (FDA) sanctioned the encorafenib-cetuximab combination therapy for BRAF V600E mutant metastatic CRC after progression through first-line therapy, marking a significant therapeutic advance for these patients.

Landscape of tumor immune microenvironment and its interaction with BRAF mutation

The TME represents a sophisticated and ever-changing multicellular system where cancer initiation and progression take place. This environment consists of diverse immune compo-

nents, including T and B lymphocytes, tumor-associated macrophages (TAMs), dendritic cells (DCs), natural killer (NK) cells, neutrophils, myeloid-derived suppressor cells (MDSCs), alongside structural elements such as cancer-associated fibroblasts (CAFs), pericytes, and mesenchymal stromal cells. The ECM plus various secreted substances, specifically growth factors, cytokines, chemokines, and extracellular vesicles (EVs), contribute to this setting. Furthermore, the TME includes a network of blood and lymphatic vessels that interconnect and interact with the heterogeneous cancer cells themselves [36]. Depending on cancer progression phases and the specific organ of tumor formation, these cellular components and molecules within the TME exhibit context-specific functions, either suppressing or promoting tumor expansion.

Compared to wild-type PTC, BRAF-mutant PTC exhibits globally elevated infiltration of stromal cells and diverse immune cell populations, including B cells, $CD4^+$ T cells, neutrophils, macrophages, and dendritic cells. Concomitant with these cellular compositional alterations is the upregulated expression of multiple immune-related genes. BRAF-mutant CRCs also display heightened overall immune cell infiltration, with a notable enrichment of cytotoxic $CD8^+$ T cells and helper Th1 cells. However, despite the prominent immune infiltration, these patients generally have far poorer prognosis than those with BRAF wild-type or KRAS mutant CRCs. Studies indicate that in BRAF-mutant CRC, in addition to effector T cells, immunosuppressive neutrophils and M1-type macrophages are concurrently increased; moreover, tumor cells highly express multiple immune checkpoint molecules such as PD-L1, CTLA-4, LAG-3, and TIM-3, collectively shaping a functionally suppressed TME [37]. In BRAF-mutant melanoma, the infiltration of cytotoxic $CD8^+$ T cells and macrophages is relatively reduced, whereas the proportions of B cells, natural killer (NK) cells, and certain $CD4^+$ T cell subsets are elevated. In the early stages of tumorigenesis, upregulation of the BRAF-MAPK oncogenic signaling pathway leads to a relatively active tumor microenvironment characterized by a neoantigen-driven inflammatory response. During disease progression, persistent BRAF signaling drives the secretion of specific chemokines and cytokines, promoting angiogenesis and the recruitment of immunosuppressive cell populations, while effector T-cell functions become progressively exhausted. In advanced or metastatic disease, immune checkpoint molecules are highly expressed on both tumor and immune cells, resulting in a tumor microenvironment that is highly immunosuppressive and dysfunctional. This evolved state represents a significant therapeutic challenge, underpinning primary resistance to subsequent targeted therapies and necessitating rational combination strategies. In this review, we further explored how BRAF mutations influence the tumor microenvironment, particularly their interactions with classical immune cell subsets (**Figure 2**).

T cells

$CD4^+$ cells encompass distinct categories, including T-helper cells (Th1, Th2, Th9, Th17) and regulatory T cells (Tregs), which influence cytotoxic T-cell functionality and facilitate immunosuppression through cytokine production, such as transforming growth factor β, IL-10, and IL-35 [38]. $CD8^+$ T cells serve as essential effector components in tumor-specific immune responses, although intra tumoral $CD8^+$ T cells commonly exhibit exhausted or impaired phenotypic characteristics [39, 40].

BRAF mutations modulate T cell functionality in immune-related pathologies and malignancies. PTC specimens harboring BRAF mutations demonstrated elevated expression levels of immune checkpoint molecules CD274 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), accompanied by increased expression of tumor-infiltrating lymphocytes, specifically $CD4^+$ T cells within the peri-tumoral region rather than the intratumoral region [41]. Melanoma cases had demonstrated reduced $CD8^+$ T cell infiltration, patients treated with BRAF inhibitors showed that there was a predominance of $CD8^+$ T cells in comparison with $CD4^+$ T cells [42]. BRAF-wt specimens revealed a tendency toward increased $CD8^+$ effector memory T cells [43]. BRAF mutations increased IL-17-inducing genes expression, which is positively linked to higher infiltration of TH17 cells, leading to downstream effect via MAPK pathway activation [44]. Oncogenic BRAF V600E mutation is a key driver of early Treg recruitment. Upon activation of the signaling pathway, tumor cells express C-C motif chemokine receptor 4 (CCR4) ligand chemokines

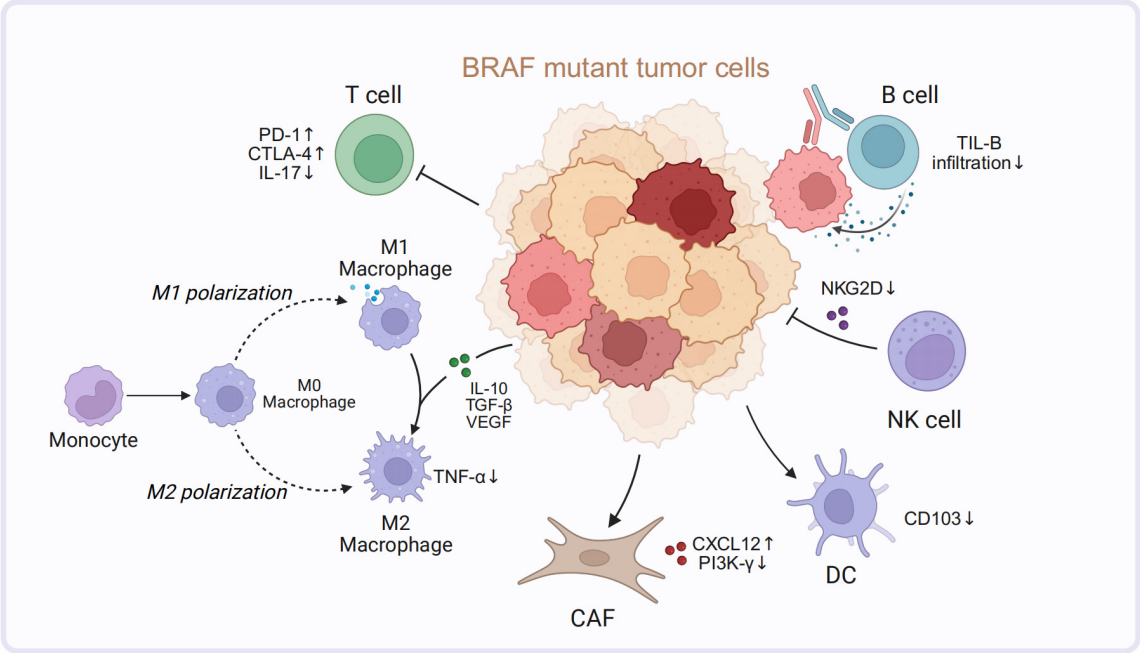

Figure 2. BRAF-mutant tumor immune microenvironment. The tumor microenvironment (TME) consists of various cell types and secretory factors, including cancer cells, immune cells such as T lymphocytes, B lymphocytes, tumor-associated macrophages, dendritic cells, NK cells, myeloid-derived suppressor cells, neutrophils, and stromal cells like cancer-associated fibroblasts. Each cell type can regulate tumor progression and treatment response in a unique manner. In BRAF mutant TME, $CD8^+$ T cells often exhibit functional exhaustion, characterized by increased expression of PD-1 and CTLA-4, and reduced infiltration. Tumor-infiltrating B lymphocytes (TIL-Bs) also show decreased enrichment. BRAF mutations suppress CD103 expression, leading to reduced antigen-presenting capacity of dendritic cells. Downregulation of NKG2D ligands by BRAF mutations allows NK cells to escape recognition, resulting in decreased cytotoxicity and infiltration. Additionally, BRAF mutations promote the release of anti-inflammatory cytokines such as IL-10 and TGF-β through continuous activation of the MAPK pathway, inducing macrophage polarization towards the M2 phenotype characterized by low TNF-α secretion. CAFs are significantly activated and transformed into an immunosuppressive and profibrotic phenotype, facilitating tumor progression and treatment resistance through secreted factors, ECM remodeling, and paracrine signaling.

(CCL17, CCL2, CCL22). These factors bind to the CCR4 receptor on the surface of Tregs, guiding their migration toward the tumor site. Tregs are extensively infiltrated during early tumorigenesis and inhibit the activation and proliferation of $CD8^+$ T cells, thereby hindering their anti-tumor immune response and establishing immunosuppressive microenvironments that evade cancer immunosurveillance [45]. Moreover, BRAF signaling can activate NF-κB, which is the core transcriptional regulator for chemokines such as CCL2 and CXCL8, as well as pro-inflammatory cytokines like IL-6 and TNF-α. Cytokines released by tumor cells and infiltrating immune cells can activate STAT3 via MAPK pathway, further recruiting Tregs [46]. Based on the mechanisms discussed above, BRAF inhibition triggers tumor cell death and tumor antigen release, thus providing a distinctive opportunity to augment T cell immune responses against existing tumor-associated antigens.

B cells

B lymphocytes function as essential components in humoral immune responses. Throughout tumor development, B cells exhibit dual roles: they display anti-tumor activities via antibody-mediated cell destruction and complement system stimulation, while also facilitating tumor growth by enhancing inflammatory processes and immune suppression through the release of anti-inflammatory and pro-angiogenic molecules. Regulatory B cells (Bregs), a specialized immunosuppressive subset, contribute to immunological tolerance [47]. BRAF V600E mutation together with loss of Trp53 or pTEN have been proved to drive the initiation of hairy cell leukemia from B lymphocytes [48], while in solid tumors, minimal established associations

have been identified between B cells and BRAF mutations. PTC may reveal progressive or indolent feature. In BRAF-mutant PTC cases, memory B cells and naive B cells demonstrated positive links to immune checkpoints [49], and a single-cell sequencing analysis indicated a potential link among PTC development, higher incidence of BRAF mutation and less tumor-infiltrating B cells [50]. These indolent PTC cells engaged with tumor-infiltrating cells via PTPRC-CD22 trans-binding interactions, potentially contributing to the distinctive immune microenvironment. Conversely, elevated B cell presence was linked to a tendency toward enhanced survival in BRAF-mutant melanoma patients; however, the fundamental mechanism through which BRAF mutations result in increased B cell infiltration remains undefined [35].

DCs

Dendritic cells (DCs) constitute a diverse group of antigen-presenting cells that serve a crucial function in triggering and regulating adaptive immune responses. Through processing signals from the TME and transmitting them to various immune cells, particularly T cells, DCs exhibit the capacity to influence anti-tumor immune reactions [51, 52]. The accumulation and activation of intratumoral $CD8^+$ T effector cells relies on intratumoral CD103+ DCs [53]. Although both CD103+ and CD11b+ DCs represent minor cellular populations within tumors, their role is crucial. Studies have shown that BRAF-mutant cells infiltrate both murine and human melanoma lesions [54], which indicates that BRAF mutation inhibits the infiltration of CD103+ DCs and thereby weakens $CD8^+$ T cell-mediated immune surveillance. Furthermore, BRAF-inhibition therapy in melanoma transiently mobilizes inflammatory monocytes and plasmacytoid dendritic cells (pDC) into the TME and enhances activated migratory conventional dendritic cell 1 (cDC) and cDC2 infiltration. This process promotes the migration of activated DCs toward tumor-draining lymph nodes [55].

NK cells

Natural killer (NK) cells are cytotoxic innate lymphoid cells marked by the surface markers CD3- CD56+. These lymphocytes recognize and eliminate stressed cells that lack MHC class I expression. NK cell populations, both in circulation and within tumors, function as prognostic markers for improved survival rates among cancer patients. Malignant cells possess the capability to alter NK cell metabolic conditions, evidenced by increased CD25 expression on NK cells post-tumor cell contact, subsequently sustaining anti-tumor metabolic activities through enhanced glycolysis and NK cell persistence, mediated by mTORC1/cMYC pathway activation. Contemporary studies indicate that BRAF-mutant melanoma exhibits elevated numbers of B cells, NK cells and NKT cells [35]. Vemurafenib and PLX4720 function as ATP-competitive inhibitors targeting BRAF V600E, demonstrating inhibition of the MAPK pathway and cellular proliferation in BRAF V600E mutant melanoma [56]. Evidence shows that melanoma cell resistance to BRAF and MEK inhibitors correlates with enhanced immunogenicity toward donor and metastatic patient NK cells, as Vemurafenib resistance in BRAF V600E SK28 and M14 cell lines associates with altered NKG2D/NKG2DL interactions [57]. The BRAF-ERK pathway modulates NKG2DLs expression on stressed cells, resulting in NKG2D downregulation and impaired signaling, thereby promoting NKG2D-mediated lysis by NK cells [58]. Additionally, BRAF inhibitors enhance ERK1/2 phosphorylation, CD69 expression, and multiplication of mouse NK cells in vitro under anti-NKp30 and IL-2 stimulation conditions [59].

TAMs

Tumor-associated macrophages (TAMs) constitute a remarkably adaptable immune cell population exhibiting both pro- and anti-tumorigenic properties, wherein M1-polarized macrophages participate in antitumor activities while M2-polarized macrophages correlate with tumor advancement, metastasis, chemoresistance and unfavorable prognosis [60]. At both primary and metastatic locations, TAMs demonstrate suppressive effects on cytotoxic T cell and natural killer cell activities [61, 62]. Enhanced TAM expression was observed in PTC tumors, particularly in BRAF-mutant cases, when compared to thyroid goiter and follicular adenoma [63]. Furthermore, M1-polarized macrophages demonstrated elevated IL-12 expression, whereas M2-polarized macrophages are distinguished by increased IL-10 production levels [64]. Nevertheless, no significant corre-

lation was observed between BRAF mutations and clinicopathological characteristics such as lymph node metastasis. In BRAF-mutant melanomas treated with BRAF-inhibition therapy, TAMs stimulate the MAPK pathway and enhance vascular endothelial growth factor production, thereby substituting for this growth promoter generated by melanoma cells to facilitate melanoma cell proliferation and survival [65]. Macrophage-generated TNFα emerges as a crucial melanoma growth mediator providing resistance to MAPK pathway inhibitors through the lineage factor microphthalmia transcription factor (MITF). Notably, in BRAF-mutant melanomas from patients and BRAF V600E melanoma allografts, MAPK pathway inhibitors increased TAM numbers, alongside TNF-α and MITF expression. Blocking TNFα signaling via IκB kinase inhibitors directly affects melanoma cells while altering the tumor microenvironment through TAMs, markedly enhancing MAPK pathway inhibitor efficacy [66]. These released cytokines promote macrophage differentiation toward the M2 phenotype, and sustained MEK/ERK pathway activation may enhance chemokine expression, further facilitating this transformation, thereby elucidating the pivotal role of M2 phenotype TAMs in the PTC microenvironment [54].

CAFs

Cancer-associated fibroblasts (CAFs) produce ECM and control metabolic and immune modifications within the TME, leading to therapeutic resistance in cancer. CAFs also shape immune cell populations and their activities in TME by producing chemokines, such as C-X-C motif chemokines CXCL12 and CXCL13, while modifying the stromal environment through C-C motif chemokine secretion of CCL2, CCL3 and CCL4, which draws myeloid cells, including macrophages and MDSCs [67]. CAF-produced CXCL13 facilitates epithelial-mesenchymal transition (EMT) in tumor cells, while plasmid DNA codes for a CXCL13 trap that reduces Bregs differentiation and stabilizes EMT, ultimately decreasing PI3K-γ production, thereby suppressing tumor growth and improving patient survival in BRAF-mutant melanoma [68]. Earlier research by Zhang's group revealed that the β-catenin/YAP signaling axis functions as an essential controller of melanoma-associated fibroblasts in enhancing ECM remodeling and cancer cell characteristics [69]. Their follow-up study identified matricellular protein periostin as a crucial downstream mediator of b-catenin in CAFs, which restores ERK signaling in BRAF-mutant melanoma cells to bypass BRAFi and MEKi inhibition, contributing to melanoma resistance [70]. In PTCs, the BRAF V600E mutation correlated with increased CAFs but reduced ECs, which associated with advancement of pathological N stage and pathological stage [40]. Additionally, the BRAF-like subtype exhibited a notably higher proportion of CAFs compared to the RAS-like subtype, especially in BRAF-like-B tumors, which were anticipated to possess the highest CAF levels regardless of myoCAF or iCAF phenotypes [71].

Impact of co-mutations on the immune system

Patients harboring BRAF alterations represent a markedly heterogeneous group, attributable to intricate signaling networks, tumor-immune interactions within the TME, and diverse co-occurring genetic alterations. For BRAF-mutant CRCs, the occurrence of inactivating APC mutations, a β-catenin degradation complex element, shows substantial age-related decline, falling from roughly 60% in 40-year-old diagnosed cases to under 10% in those identified after age 90. The simultaneous presence of BRAF and APC alterations in CRCs yields a particularly aggressive disease pattern, exhibiting diminished survival rates (12% at 5 years) [31]. Compared with BRAF V600E, class II/III BRAF variants and their coexistence with KRAS/NRAS alterations exhibited higher frequency in metastatic CRC, particularly in cases suggesting previous anti-EGFR treatment [72]. Additionally, concurrent mutations in the TERT promoter, TP53, PTEN, and PIK3CA are also common in BRAF-mutant (approximately 10%) advanced adult thyroid tumors [14]. TERT enhances BRAF mutation-mediated TC dedifferentiation and advancement through ribosomal synthesis regulation [73]. Like BRAF, NRAS also activates the MAPK pathway. The co-mutation of BRAF and NRAS inhibits $CD8^+$ T cell activity by up-regulating immune checkpoint molecules like PD-L1 and recruits Tregs and MDSCs to further suppress anti-tumor immune responses, which indicates a poorer prognosis [74]. Moreover, CDKN2A (encoding p16 and p14ARF proteins) mutations were identified in 7% of pri-

mary melanomas and 14% of metastases [75]. The combination of BRAF V600E mutation and loss of p16 expression disrupts cell-cycle control and alters cytokine profiles in the TME, accelerating the growth rate of melanomas *in vivo* [20].

Treatments for patients with BRAF mutations

BRAF mutations constitute crucial therapeutic targets across multiple solid malignancies, where targeted combination therapies, particularly BRAF inhibitors, have emerged as a fundamental treatment strategy for various BRAF-mutant solid tumors. The initial BRAF-targeted monoclonal antibody approval in 2011 revolutionized melanoma treatment approaches by markedly improving overall survival (OS). Currently, BRAF inhibitors are categorized mainly into selective BRAF inhibitors and non-selective BRAF inhibitors based on their targeting mechanisms. Selective BRAF inhibitors include dabrafenib, vemurafenib, and encorafenib. Non-selective BRAF inhibitors consist of sorafenib, regorafenib, pazopanib, and donafenib. Regarding advanced thyroid cancer, 9 drugs or medication combinations have gained FDA approval, and dabrafenib/trametinib received FDA approval in 2018 for BRAF V600E mutant anaplastic thyroid carcinoma. A retrospective 2010-2016 observational study in the USA analyzing real-world prescription patterns among advanced thyroid cancer patients demonstrated that sorafenib tosilate remained the primary therapy in first-line and second-line treatment until 2015 - when lenvatinib obtained FDA approval for treating advanced differentiated TC and subsequently became the dominant first-line option [76]. Nevertheless, these agents are not curative, and their side effects restrict their usage in certain patients [77]. The FDA granted accelerated approval for dabrafenib/trametinib in 2022 for treating adult and pediatric patients 6 years and older with unresectable or metastatic solid tumors containing a BRAF V600E mutation who experienced disease progression after prior treatment and lack adequate alternative treatment options. BRAF inhibitors enhance T-cell infiltration, and their combination with immune checkpoint inhibitors (ICIs), such as anti-PD-1/PD-L1 antibodies, may increase therapeutic efficacy. The combination of BRAFi/MEKi with immune checkpoint inhibitors is grounded in a synergistic remodeling of the tumor immune microenvironment. Targeted therapy induces tumor cell apoptosis, releasing neoantigens and alleviating MAPK-mediated suppression of MHC class I expression, thereby enhancing antigen presentation [78, 79]. Concurrently, BRAFi reduces intratumoral immunosuppressive cells such as Tregs and reverses T-cell exhaustion, leading to functional reinvigoration of effector T cells. This creates an immunogenic milieu characterized by increased antigen availability and diminished suppression. ICIs further potentiate this response by blocking inhibitory pathways such as PD-1/PD-L1, thereby unleashing pre-activated T cells and driving a robust, coordinated antitumor immune response with improved clinical outcomes. The combination of ICIs with BRAFi and MEKi appears logical but risky and might induce severe adverse reactions [80], a combination of a PD-L1-antibody with Dabrafenib and Trametinib in metastatic melanoma patients carrying mutated BRAF V600E shows that such combination remains viable [81], offering novel approaches for BRAFi resistance. Furthermore, a recent case report revealed that BRAF mutation positive PD-L1 overexpressed lung adenocarcinoma with metastatic musculoskeletal lesions can respond positively to combined vemurafenib and pembrolizumab [82]. Patients carrying BRAF V600E often respond to targeted therapy using small molecule inhibitors of monomeric BRAF V600E combined with MEK inhibition. This approach, however, may prove ineffective due to feedback activation of the pathway through induction of BRAF dimer formation [83]. A phase III, open-label trial (STARBOARD, NCT04657991) enrolled 37 treatment-naïve adult patients with BRAF V600-mutant unresectable or metastatic cutaneous melanoma in its safety run-in cohort [84]. The triplet combination of encorafenib, binimetinib and pembrolizumab demonstrated promising preliminary antitumor activity, with an objective response rate (ORR) of 65.0% (24/37 patients; 95% CI: 47.1-80.0).

The core mechanisms encompass reactivation of the MAPK pathway through BRAF splice variants, RAS mutations, and upregulation of receptor tyrosine kinases, leading to restor-

ed ERK signaling. Compensatory activation of alternative pathways, notably the PI3K-AKT-mTOR axis, also supports cell survival and proliferation [85].

The tumor microenvironment also significantly impacts on the response to targeted therapies. Hepatocyte growth factor (HGF) secreted by CAFs can activate the HGF receptor MET, thereby activating the MAPK and PI3K-AKT-mTOR signaling cascades in BRAF inhibitor-resistant melanoma cells [86]. CAF-derived Secreted Phosphoprotein 1 enhances sorafenib and lenvatinib combination resistance in hepatocellular carcinoma via bypass activation of oncogenic pathways and EMT promotion [87].

Emerging strategies to overcome these resistance pathways include ERK inhibitors to directly block terminal MAPK signaling, SHP2 inhibitors to disrupt RTK-RAS transduction [88, 89], combination with PI3K-AKT-mTOR pathway inhibitors to suppress bypass activation, and the integration of immune checkpoint inhibitors to remodel the immunosuppressive tumor microenvironment, thereby systematically overcoming resistance and improving therapeutic outcomes.

Building upon the paradigm of targeted therapy, the field has increasingly shifted towards leveraging and enhancing the intrinsic power of the immune system. This shift is exemplified by the development of chimeric antigen receptor (CAR) T-cell therapy, which represents a convergence of cellular therapy and genetic engineering. The CAR-T therapy has emerged as a promising immunotherapeutic approach against cancers, especially malignant hematologic diseases including leukemias, myeloma, and non-Hodgkin B-cell lymphomas. Studies indicate that radiation increases melanoma cell vulnerability to CAR-T cell-mediated lysis through enhancement of the targeted tumor antigen and disruption between pro- and anti-apoptotic molecules. At lower effector to target cell ratios, CAR-T cells demonstrate improved in vitro anti-tumor efficacy against irradiated BRAF inhibitor resistant melanoma cells [90]. Vemurafenib alone significantly inhibited these CAR-T cells' cytolytic function, while Dabrafenib plus Trametinib also decreased the cytolytic capacity, though less extensively [91]. Furthermore, a Phase I clinical trial (NCT-04420754) presented at the 2025 annual meeting of the American Association for Cancer Research confirmed that AIC100, a third-generation CAR-T cell therapy targeting ICAM-1, has an ORR of up to 50% in treating patients with relapsed and refractory BRAF mutant ATC [92]. Moreover, it was observed that some patients achieved complete remission, which brings new hope for the treatment of ATC patients.

Conclusions and future directions

The critical role of BRAF mutations, particularly the V600E variant, in carcinogenesis and its impact on the TME have been identified. BRAF mutations are prevalent in cancers such as melanoma, thyroid cancer, and colorectal cancer, driving tumor progression through the MAPK signaling pathway. These mutations not only promote oncogenesis but also modulate the TME, influencing immune cell infiltration and function, encompassing T cells, B cells, dendritic cells, and tumor-associated macrophages. Activation of BRAF mutations is associated with immune evasion mechanisms, such as increased Treg recruitment and reduced $CD8^+$ T cell activity, which contribute to resistance against immune checkpoint therapies.

Present therapeutic approaches, particularly BRAF and MEK inhibition strategies, demonstrate effectiveness but face limitations due to resistance pathways and MAPK cascade reactivation. The integration of BRAF inhibition with checkpoint immunotherapy represents an encouraging strategy for strengthening anticancer immune responses. However, challenges remain, including managing toxicity and overcoming resistance. Consequently, additional investigation into BRAF inhibitor combinations with checkpoint immunotherapies or alternative targeted agents merits consideration to address resistance issues and enhance clinical outcomes. Developing strategies to reprogram the TME, such as targeting tumor-associated macrophages or cancer-associated fibroblasts to enhance immune responses, constitutes a critical area of focus. Investigating the potential of CAR-T cell therapy and other immunotherapeutic approaches in BRAF-mutant cancers, especially in resistant cases represents another meaningful direction.

In conclusion, understanding the interplay between BRAF mutations and the TME is crucial

for developing more effective, personalized cancer therapies. Subsequent research efforts should address resistance mechanisms and optimize immune-based tumor suppression, while comprehensive clinical studies are needed to determine optimal treatment sequences and appropriate intervention durations.

Acknowledgements

This work was supported by grants from Jiangsu Province Capability Improvement Project through Science, Technology and Education (Jiangsu Provincial Medical Key Discipline, ZDXK202222), the Young Scholars Fostering Fund of the First Affiliated Hospital of Nanjing Medical University (PY2022051) and the Natural Science Foundation of Jiangsu Province (BK20241140).

Disclosure of conflict of interest

None.

Abbreviations

Bregs, Regulatory B cells; CAFs, Cancer-associated fibroblasts; CAR-T, Chimeric Antigen Receptor T-Cell Therapy; cDC, Conventional dendritic cell; CR, Conserved region; CRC, Colorectal cancer; DCs, Dendritic cells; DTC, Differentiated thyroid cancer; ECM, Extracellular matrix; EGFR, Epidermal Growth Factor Receptor; EMT, Epithelial-mesenchymal transition; ERK, Extracellular regulated protein kinase; EVs, Extracellular vesicles; FDA, Food and Drug Administration; HGF, Hepatocyte growth factor; HMGCL, 3-hydroxy-3-methylglutaryl-CoA lyase; ICI, Immune checkpoint inhibitor; IL, Interleukin; MAPK, Mitogen-activated protein kinase; MDSCs, Myeloid-derived suppressor cells; MEK, Mitogen-activated extracellular signal-regulated kinase; MITF, Microphthalmia transcription factor; NF1, Neurofibromatosis type 1; NK cells, Natural killer cells; NKT cells, Natural killer T cells; pDC, plasmacytoid dendritic cell; PTC, Papillary thyroid carcinoma; RAF, Rapidly accelerated fibrosarcoma; TAMs, Tumor-associated macrophages; TME, Tumor microenvironment; Tregs, Regulatory T cells; wt, wild type.

Address correspondence to: Drs. Xiang Zhang and Meiping Shen, Department of General Surgery, The First Affiliated Hospital with Nanjing Medical University, 300 Guangzhou Road, Nanjing 210029, Jiangsu, China. E-mail: zhangxiang@njmu.edu.cn (XZ); Tel: +86-13813955969; E-mail: shenmeiping@jsph.org.cn (MPS)

References

[1] Santarpia L, Lippman SM and El-Naggar AK. Targeting the MAPK-RAS-RAF signaling pathway in cancer therapy. Expert Opin Ther Targets 2012; 16: 103-119.

[2] Xing M. BRAF mutation in papillary thyroid cancer: pathogenic role, molecular bases, and clinical implications. Endocr Rev 2007; 28: 742-762.

[3] Fischer A, Hekman M, Kuhlmann J, Rubio I, Wiese S and Rapp UR. B- and C-RAF display essential differences in their binding to Ras: the isotype-specific N terminus of B-RAF facilitates Ras binding. J Biol Chem 2007; 282: 26503-26516.

[4] Kondo Y, Ognjenović J, Banerjee S, Karandur D, Merk A, Kulhanek K, Wong K, Roose JP, Subramaniam S and Kuriyan J. Cryo-EM structure of a dimeric B-Raf:14-3-3 complex reveals asymmetry in the active sites of B-Raf kinases. Science 2019; 366: 109-115.

[5] Hu J, Stites EC, Yu H, Germino EA, Meharena HS, Stork PJS, Kornev AP, Taylor SS and Shaw AS. Allosteric activation of functionally asymmetric RAF kinase dimers. Cell 2013; 154: 1036-1046.

[6] Yuan J, Ng WH, Lam PYP, Wang Y, Xia H, Yap J, Guan SP, Lee ASG, Wang M, Baccarini M and Hu J. The dimer-dependent catalytic activity of RAF family kinases is revealed through characterizing their oncogenic mutants. Oncogene 2018; 37: 5719-5734.

[7] Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, Teague J, Woffendin H, Garnett MJ, Bottomley W, Davis N, Dicks E, Ewing R, Floyd Y, Gray K, Hall S, Hawes R, Hughes J, Kosmidou V, Menzies A, Mould C, Parker A, Stevens C, Watt S, Hooper S, Wilson R, Jayatilake H, Gusterson BA, Cooper C, Shipley J, Hargrave D, Pritchard-Jones K, Maitland N, Chenevix-Trench G, Riggins GJ, Bigner DD, Palmieri G, Cossu A, Flanagan A, Nicholson A, Ho JW, Leung SY, Yuen ST, Weber BL, Seigler HF, Darrow TL, Paterson H, Marais R, Marshall CJ, Wooster R, Stratton MR and Futreal PA. Mutations of the BRAF gene in human cancer. Nature 2002; 417: 949-954.

[8] Yao Z, Yaeger R, Rodrik-Outmezguine VS, Tao A, Torres NM, Chang MT, Drosten M, Zhao H, Cecchi F, Hembrough T, Michels J, Baumert H, Miles L, Campbell NM, De Stanchina E, Solit DB, Barbacid M, Taylor BS and Rosen N. Tumours with class 3 BRAF mutants are sensitive

to the inhibition of activated RAS. Nature 2017; 548: 234-238.
[9] Summers MG, Smith CG, Maughan TS, Kaplan R, Escott-Price V and Cheadle JP. BRAF and NRAS locus-specific variants have different outcomes on survival to colorectal cancer. Clin Cancer Res 2017; 23: 2742-2749.
[10] Nucera C, Lawler J and Parangi S. BRAF(V600E) and microenvironment in thyroid cancer: a functional link to drive cancer progression. Cancer Res 2011; 71: 2417-2422.
[11] Wang W, Lian B, Xu C, Wang Q, Li Z, Zheng N, Liu A, Yu J, Zhong W, Wang Z, Zhang Y, Liu J, Zhang S, Cai X, Liu A, Li W, Mao L, Zhan P, Liu H, Lv T, Miao L, Min L, Chen Y, Yuan J, Wang F, Jiang Z, Lin G, Huang L, Pu X, Lin R, Liu W, Rao C, Lv D, Yu Z, Li X, Tang C, Zhou C, Zhang J, Xue J, Guo H, Chu Q, Meng R, Liu X, Wu J, Zhang R, Zhou J, Zhu Z, Li Y, Qiu H, Xia F, Lu Y, Chen X, Feng J, Ge R, Dai E, Han Y, Pan W, Pang F, Huang X, Hu M, Hao Q, Wang K, Wu F, Song B, Xu B, Wang L, Zhu Y, Lin L, Xie Y, Lin X, Cai J, Xu L, Li J, Jiao X, Li K, Wei J, Feng H, Wang L, Du Y, Yao W, Shi X, Niu X, Yuan D, Yao Y, Huang J, Feng Y, Zhang Y, Sun P, Wang H, Ye M, Wang D, Wang Z, Hao Y, Wang Z, Wan B, Lv D, Yang S, Kang J, Zhang J, Zhang C, Li W, Fu J, Wu L, Lan S, Ou J, Shi L, Zhai Z, Wang Y, Li B, Zhang Z, Wang K, Ma X, Li Z, Liu Z, Yang N, Wu L, Wang H, Jin G, Wang G, Wang J, Shi H, Fang M, Fang Y, Li Y, Wang X, Chen J, Zhang Y, Zhu X, Shen Y, Ma S, Wang B, Song Y, Song Z, Fang W, Lu Y and Si L. Expert consensus on the diagnosis and treatment of solid tumors with BRAF mutations. Innovation (Camb) 2024; 5: 100661.
[12] Kimura ET, Nikiforova MN, Zhu Z, Knauf JA, Nikiforov YE and Fagin JA. High prevalence of BRAF mutations in thyroid cancer: genetic evidence for constitutive activation of the RET/PTC-RAS-BRAF signaling pathway in papillary thyroid carcinoma. Cancer Res 2003; 63: 1454-1457.
[13] Nikiforova MN, Kimura ET, Gandhi M, Biddinger PW, Knauf JA, Basolo F, Zhu Z, Giannini R, Salvatore G, Fusco A, Santoro M, Fagin JA and Nikiforov YE. BRAF mutations in thyroid tumors are restricted to papillary carcinomas and anaplastic or poorly differentiated carcinomas arising from papillary carcinomas. J Clin Endocrinol Metab 2003; 88: 5399-5404.
[14] Agrawal N, Akbani R, Aksoy BA, Ally A, Arachchi H, Asa Sylvia L, Auman JT, Balasundaram M, Balu S, Baylin Stephen B, Behera M, Bernard B, Beroukhim R, Bishop Justin A, Black Aaron D, Bodenheimer T, Boice L, Bootwalla Moiz S, Bowen J, Bowlby R, Bristow Christopher A, Brookens R, Brooks D, Bryant R, Buda E, Butterfield Yaron SN, Carling T, Carlsen R, Carter Scott L, Carty Sally E, Chan Timothy A, Chen Amy Y, Cherniack Andrew D, Cheung D, Chin L, Cho J, Chu A, Chuah E, Cibulskis K, Ciriello G, Clarke A, Clayman Gary L, Cope L, Copland John A, Covington K, Danilova L, Davidsen T, Demchok John A, DiCara D, Dhalla N, Dhir R, Dookran Sheliann S, Dresdner G, Eldridge J, Eley G, El-Naggar Adel K, Eng S, Fagin James A, Fennell T, Ferris Robert L, Fisher S, Frazer S, Frick J, Gabriel Stacey B, Ganly I, Gao J, Garraway Levi A, Gastier-Foster Julie M, Getz G, Gehlenborg N, Ghossein R, Gibbs Richard A, Giordano Thomas J, Gomez-Hernandez K, Grimsby J, Gross B, Guin R, Hadjipanayis A, Harper Hollie A, Hayes DN, Heiman David I, Herman James G, Hoadley Katherine A, Hofree M, Holt Robert A, Hoyle Alan P, Huang Franklin W, Huang M, Hutter Carolyn M, Ideker T, Iype L, Jacobsen A, Jefferys Stuart R, Jones Corbin D, Jones Steven JM, Kasaian K, Kebebew E, Khuri Fadlo R, Kim J, Kramer R, Kreisberg R, Kucherlapati R, Kwiatkowski David J, Ladanyi M, Lai Phillip H, Laird Peter W, Lander E, Lawrence Michael S, Lee D, Lee E, Lee S, Lee W, Leraas Kristen M, Lichtenberg Tara M, Lichtenstein L, Lin P, Ling S, Liu J, Liu W, Liu Y, LiVolsi Virginia A, Lu Y, Ma Y, Mahadeshwar Harshad S, Marra Marco A, Mayo M, McFadden David G, Meng S, Meyerson M, Mieczkowski Piotr A, Miller M, Mills G, Moore Richard A, Mose Lisle E, Mungall Andrew J, Murray Bradley A, Nikiforov Yuri E, Noble Michael S, Ojesina Akinyemi I, Owonikoko Taofeek K, Ozenberger Bradley A, Pantazi A, Parfenov M, Park Peter J, Parker Joel S, Paull Evan O, Pedamallu Chandra S, Perou Charles M, Prins Jan F, Protopopov A, Ramalingam Suresh S, Ramirez Nilsa C, Ramirez R, Raphael Benjamin J, Rathmell WK, Ren X, Reynolds Sheila M, Rheinbay E, Ringel Matthew D, Rivera M, Roach J, Robertson AG, Rosenberg Mara W, Rosenthal M, Sadeghi S, Saksena G, Sander C, Santoso N, Schein Jacqueline E, Schultz N, Schumacher Steven E, Seethala Raja R, Seidman J, Senbabaoglu Y, Seth S, Sharpe S, Shaw Kenna RM, Shen John P, Shen R, Sherman S, Sheth M, Shi Y, Shmulevich I, Sica Gabriel L, Simons Janae V, Sinha R, Sipahimalani P, Smallridge Robert C, Sofia Heidi J, Soloway Matthew G, Song X, Sougnez C, Stewart C, Stojanov P, Stuart Joshua M, Sumer SO, Sun Y, Tabak B, Tam A, Tan D, Tang J, Tarnuzzer R, Taylor Barry S, Thiessen N, Thorne L, Thorsson V, Tuttle RM, Umbricht Christopher B, Van Den Berg David J, Vandin F, Veluvolu U, Verhaak Roel GW, Vinco M, Voet D, Walter V, Wang Z, Waring S, Weinberger Paul M, Weinhold N, Weinstein John N, Weisenberger Daniel J, Wheeler D, Wilkerson Matthew D, Wilson J, Williams M, Winer Daniel A, Wise L, Wu J, Xi L, Xu Andrew W, Yang L, Yang L, Zack

Travis I, Zeiger Martha A, Zeng D, Zenklusen Jean C, Zhao N, Zhang H, Zhang J, Zhang J, Zhang W, Zmuda E and Zou L; Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. Cell 2014; 159: 676-690.

[15] Landa I, Ibrahimpasic T, Boucai L, Sinha R, Knauf JA, Shah RH, Dogan S, Ricarte-Filho JC, Krishnamoorthy GP, Xu B, Schultz N, Berger MF, Sander C, Taylor BS, Ghossein R, Ganly I and Fagin JA. Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers. J Clin Invest 2016; 126: 1052-1066.

[16] Xing M, Westra WH, Tufano RP, Cohen Y, Rosenbaum E, Rhoden KJ, Carson KA, Vasko V, Larin A, Tallini G, Tolaney S, Holt EH, Hui P, Umbricht CB, Basaria S, Ewertz M, Tufaro AP, Califano JA, Ringel MD, Zeiger MA, Sidransky D and Ladenson PW. BRAF mutation predicts a poorer clinical prognosis for papillary thyroid cancer. J Clin Endocrinol Metab 2005; 90: 6373-6379.

[17] Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM and Wartofsky L. 2015 American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid 2016; 26: 1-133.

[18] Guo W, Wang H and Li C. Signal pathways of melanoma and targeted therapy. Signal Transduct Target Ther 2021; 6: 424.

[19] Bai X, Kong Y, Chi Z, Sheng X, Cui C, Wang X, Mao L, Tang B, Li S, Lian B, Yan X, Zhou L, Dai J, Guo J and Si L. MAPK pathway and TERT promoter gene mutation pattern and its prognostic value in melanoma patients: a retrospective study of 2,793 cases. Clin Cancer Res 2017; 23: 6120-6127.

[20] Lian B, Cui CL, Zhou L, Song X, Zhang XS, Wu D, Si L, Chi ZH, Sheng XN, Mao LL, Wang X, Tang BX, Yan XQ, Kong Y, Dai J, Li SM, Bai X, Zheng N, Balch CM and Guo J. The natural history and patterns of metastases from mucosal melanoma: an analysis of 706 prospectively-followed patients. Ann Oncol 2017; 28: 868-873.

[21] Tschandl P, Berghoff AS, Preusser M, Pammer J, Pehamberger H and Kittler H. Impact of oncogenic BRAF mutations and p16 expression on the growth rate of early melanomas and naevi in vivo. Br J Dermatol 2016; 174: 364-370.

[22] Kang HB, Fan J, Lin R, Elf S, Ji Q, Zhao L, Jin L, Seo JH, Shan C, Arbiser JL, Cohen C, Brat D, Miziorko HM, Kim E, Abdel-Wahab O, Merghoub T, Fröhling S, Scholl C, Tamayo P, Barbie DA, Zhou L, Pollack BP, Fisher K, Kudchadkar RR, Lawson DH, Sica G, Rossi M, Lonial S, Khoury HJ, Khuri FR, Lee BH, Boggon TJ, He C, Kang S and Chen J. Metabolic rewiring by oncogenic BRAF V600E links ketogenesis pathway to BRAF-MEK1 signaling. Mol Cell 2015; 59: 345-358.

[23] Barras D. BRAF mutation in colorectal cancer: an update. Biomark Cancer 2015; 7 Suppl 1: 9-12.

[24] Sanz-Garcia E, Argiles G, Elez E and Tabernero J. BRAF mutant colorectal cancer: prognosis, treatment, and new perspectives. Ann Oncol 2017; 28: 2648-2657.

[25] Clancy C, Burke JP, Kalady MF and Coffey JC. BRAF mutation is associated with distinct clinicopathological characteristics in colorectal cancer: a systematic review and meta-analysis. Colorectal Dis 2013; 15: e711-8.

[26] Ogino S, Brahmandam M, Cantor M, Namgyal C, Kawasaki T, Kirkner G, Meyerhardt JA, Loda M and Fuchs CS. Distinct molecular features of colorectal carcinoma with signet ring cell component and colorectal carcinoma with mucinous component. Mod Pathol 2006; 19: 59-68.

[27] Morris V, Overman MJ, Jiang ZQ, Garrett C, Agarwal S, Eng C, Kee B, Fogelman D, Dasari A, Wolff R, Maru D and Kopetz S. Progression-free survival remains poor over sequential lines of systemic therapy in patients with BRAF-mutated colorectal cancer. Clin Colorectal Cancer 2014; 13: 164-171.

[28] Mu P, Mo S, He X, Zhang H, Lv T, Xu R, He L, Xia F, Zhou S, Chen Y, Wang Y, Shen L, Wan J, Huang L, Lu W, Liang X, Li X, Lu P, Peng J, Hua G, Hu K, Zhang Z and Wang Y. Unveiling radiobiological traits and therapeutic responses of BRAFV600E-mutant colorectal cancer via patient-derived organoids. J Exp Clin Cancer Res 2025; 44: 92.

[29] Tabernero J, Grothey A, Van Cutsem E, Yaeger R, Wasan H, Yoshino T, Desai J, Ciardiello F, Loupakis F, Hong YS, Steeghs N, Guren TK, Arkenau HT, Garcia-Alfonso P, Elez E, Gollerkeri A, Maharry K, Christy-Bittel J and Kopetz S. Encorafenib plus cetuximab as a new standard of care for previously treated BRAF V600E-mutant metastatic colorectal cancer: updated survival results and subgroup analyses from the BEACON study. J Clin Oncol 2021; 39: 273-284.

[30] Kim SY, Kim SN, Hahn HJ, Lee YW, Choe YB and Ahn KJ. Metaanalysis of BRAF mutations and clinicopathologic characteristics in prima-

ry melanoma. J Am Acad Dermatol 2015; 72: 1036-1046, e2.
[31] Fennell LJ, Kane A, Liu C, McKeone D, Fernando W, Su C, Bond C, Jamieson S, Dumenil T, Patch AM, Kazakoff SH, Pearson JV, Waddell N, Leggett B and Whitehall VLJ. APC Mutation marks an aggressive subtype of BRAF mutant colorectal cancers. Cancers (Basel) 2020; 12: 1171.
[32] Andrews LJ, Thornton ZA, Saincher SS, Yao IY, Dawson S, McGuinness LA, Jones HE, Jefferies S, Short SC, Cheng HY, McAleenan A, Higgins JPT and Kurian KM. Prevalence of BRAFV600 in glioma and use of BRAF Inhibitors in patients with BRAFV600 mutation-positive glioma: systematic review. Neuro Oncol 2022; 24: 528-540.
[33] Zahedi S, Riemondy K, Liu T, Griesinger AM, Donson AM, Apfelbaum AA, Fu R, Grandvallet Contreras J, Crespo M, DeSisto J, Groat MM, Bratbak E, Green A, Hankinson TC, Handler M, Vibhakar R, Willard N, Foreman NK, Phang T and Mulcahy Levy J. Multi-pronged analysis of pediatric low-grade glioma and ganglioglioma reveals a unique tumor microenvironment associated with BRAF alterations. Brain Pathol 2025; 35: e70023.
[34] Chen D, Zhang LQ, Huang JF, Liu K, Chuai ZR, Yang Z, Wang YX, Shi DC, Liu Q, Huang Q and Fu WL. BRAF mutations in patients with non-small cell lung cancer: a systematic review and meta-analysis. PLoS One 2014; 9: e101354.
[35] Tan AC and Tan DSW. Targeted therapies for lung cancer patients with oncogenic driver molecular alterations. J Clin Oncol 2022; 40: 611-625.
[36] Bejarano L, Jordão MJC and Joyce JA. Therapeutic targeting of the tumor microenvironment. Cancer Discov 2021; 11: 933-959.
[37] Edin S, Gylling B, Li X, Stenberg A, Lofgren-Burstrom A, Zingmark C, van Guelpen B, Ljuslinder I, Ling A and Palmqvist R. Opposing roles by KRAS and BRAF mutation on immune cell infiltration in colorectal cancer - possible implications for immunotherapy. Br J Cancer 2024; 130: 143-150.
[38] Speiser DE, Chijioke O, Schaeuble K and Münz C. CD4+ T cells in cancer. Nat Cancer 2023; 4: 317-329.
[39] Philip M and Schietinger A. CD8+ T cell differentiation and dysfunction in cancer. Nat Rev Immunol 2022; 22: 209-223.
[40] van der Leun AM, Thommen DS and Schumacher TN. CD8+ T cell states in human cancer: insights from single-cell analysis. Nat Rev Cancer 2020; 20: 218-232.
[41] Mohanty A, Afkhami M, Reyes A, Pharaon R, Yin H, Li H, Do D, Bell D, Nam A, Chang S, Gernon T, Kang R, Amini A, Sampath S, Kulkarni P, Pillai R, Villaflor V, Salgia R, Maghami E and Massarelli E. Exploring markers of immunoresponsiveness in papillary thyroid carcinoma and future treatment strategies. J Immunother Cancer 2024; 12: e008505.
[42] Mochel MC, Hammond MR, Frederick DT, Alora-Palli MB, Piris A, Flaherty KT and Hoang MP. Melanocytic nevi excised during B-Raf proto-oncogene (BRAF) inhibitor therapy: a study of 19 lesions from 10 patients. J Am Acad Dermatol 2015; 73: 491-499, e492.
[43] Wang M, Zadeh S, Pizzolla A, Thia K, Gyorki DE, McArthur GA, Scolyer RA, Long G, Wilmott JS, Andrews MC, Au-Yeung G, Weppler A, Sandhu S, Trapani JA, Davis MJ and Neeson PJ. Characterization of the treatment-naive immune microenvironment in melanoma with BRAF mutation. J Immunother Cancer 2022; 10: e004095.
[44] Váraljai R, Zimmer L, Al-Matary Y, Kaptein P, Albrecht LJ, Shannan B, Brase JC, Gusenleitner D, Amaral T, Wyss N, Utikal J, Flatz L, Rambow F, Reinhardt HC, Dick J, Engel DR, Horn S, Ugurel S, Sondermann W, Livingstone E, Sucker A, Paschen A, Zhao F, Placke JM, Klose JM, Fendler WP, Thommen DS, Helfrich I, Schadendorf D and Roesch A. Interleukin 17 signaling supports clinical benefit of dual CTLA-4 and PD-1 checkpoint inhibition in melanoma. Nat Cancer 2023; 4: 1292-1308.
[45] Shabaneh TB, Molodtsov AK, Steinberg SM, Zhang P, Torres GM, Mohamed GA, Boni A, Curiel TJ, Angeles CV and Turk MJ. Oncogenic BRAFV600E governs regulatory T-cell recruitment during melanoma tumorigenesis. Cancer Res 2018; 78: 5038-5049.
[46] Zhao K, Lu Y, Chen Y, Cheng J and Zhang W. Dual inhibition of MAPK and JAK2/STAT3 pathways is critical for the treatment of BRAF mutant melanoma. Mol Ther Oncolytics 2020; 18: 100-108.
[47] Laumont CM, Banville AC, Gilardi M, Hollern DP and Nelson BH. Tumour-infiltrating B cells: immunological mechanisms, clinical impact and therapeutic opportunities. Nat Rev Cancer 2022; 22: 414-430.
[48] Yap J, Yuan J, Ng WH, Chen GB, Sim YRM, Goh KC, Teo J, Lim TYH, Goay SM, Teo JHJ, Lao Z, Lam P, Sabapathy K and Hu J. BRAF(V600E) mutation together with loss of Trp53 or pTEN drives the origination of hairy cell leukemia from B-lymphocytes. Mol Cancer 2023; 22: 125.
[49] Yang Z, Wei X, Pan Y, Xu J, Si Y, Min Z and Yu B. A new risk factor indicator for papillary thyroid cancer based on immune infiltration. Cell Death Dis 2021; 12: 51.
[50] Pu W, Shi X, Yu P, Zhang M, Liu Z, Tan L, Han P, Wang Y, Ji D, Gan H, Wei W, Lu Z, Qu N, Hu J, Hu

X, Luo Z, Li H, Ji Q, Wang J, Zhang X and Wang YL. Single-cell transcriptomic analysis of the tumor ecosystems underlying initiation and progression of papillary thyroid carcinoma. Nat Commun 2021; 12: 6058.
[51] Wculek SK, Cueto FJ, Mujal AM, Melero I, Krummel MF and Sancho D. Dendritic cells in cancer immunology and immunotherapy. Nat Rev Immunol 2020; 20: 7-24.
[52] Gerhard GM, Bill R, Messemaker M, Klein AM and Pittet MJ. Tumor-infiltrating dendritic cell states are conserved across solid human cancers. J Exp Med 2021; 218: e20200264.
[53] Broz ML, Binnewies M, Boldajipour B, Nelson AE, Pollack JL, Erle DJ, Barczak A, Rosenblum MD, Daud A, Barber DL, Amigorena S, Van't Veer LJ, Sperling AI, Wolf DM and Krummel MF. Dissecting the tumor myeloid compartment reveals rare activating antigen-presenting cells critical for T cell immunity. Cancer Cell 2014; 26: 638-652.
[54] Salmon H, Idoyaga J, Rahman A, Leboeuf M, Remark R, Jordan S, Casanova-Acebes M, Khudoynazarova M, Agudo J, Tung N, Chakarov S, Rivera C, Hogstad B, Bosenberg M, Hashimoto D, Gnjatic S, Bhardwaj N, Palucka AK, Brown BD, Brody J, Ginhoux F and Merad M. Expansion and activation of CD103+ dendritic cell progenitors at the tumor site enhances tumor responses to therapeutic PD-L1 and BRAF inhibition. Immunity 2016; 44: 924-938.
[55] Hornsteiner F, Vierthaler J, Strandt H, Resag A, Fu Z, Ausserhofer M, Tripp CH, Dieckmann S, Kanduth M, Farrand K, Bregar S, Nemati N, Hermann-Kleiter N, Seretis A, Morla S, Mullins D, Finotello F, Trajanoski Z, Wollmann G, Ronchese F, Schmitz M, Hermans IF and Stoitzner P. Tumor-targeted therapy with BRAF-inhibitor recruits activated dendritic cells to promote tumor immunity in melanoma. J Immunother Cancer 2024; 12: e008606.
[56] Joseph EW, Pratilas CA, Poulikakos PI, Tadi M, Wang W, Taylor BS, Halilovic E, Persaud Y, Xing F, Viale A, Tsai J, Chapman PB, Bollag G, Solit DB and Rosen N. The RAF inhibitor PLX4032 inhibits ERK signaling and tumor cell proliferation in a V600E BRAF-selective manner. Proc Natl Acad Sci U S A 2010; 107: 14903-14908.
[57] Frazao A, Rethacker L, Jeudy G, Colombo M, Pasmant E, Avril MF, Toubert A, Moins-Teisserenc H, Roelens M, Dalac S, Maubec E and Caignard A. BRAF inhibitor resistance of melanoma cells triggers increased susceptibility to natural killer cell-mediated lysis. J Immunother Cancer 2020; 8: e000275.
[58] Schmiedel D and Mandelboim O. NKG2D ligands-critical targets for cancer immune escape and therapy. Front Immunol 2018; 9: 2040.
[59] Wu SY, Fu T, Jiang YZ and Shao ZM. Natural killer cells in cancer biology and therapy. Mol Cancer 2020; 19: 120.
[60] Cassetta L and Pollard JW. A timeline of tumour-associated macrophage biology. Nat Rev Cancer 2023; 23: 238-257.
[61] DeNardo DG and Ruffell B. Macrophages as regulators of tumour immunity and immunotherapy. Nat Rev Immunol 2019; 19: 369-382.
[62] Güç E and Pollard JW. Redefining macrophage and neutrophil biology in the metastatic cascade. Immunity 2021; 54: 885-902.
[63] Qing W, Fang WY, Ye L, Shen LY, Zhang XF, Fei XC, Chen X, Wang WQ, Li XY, Xiao JC and Ning G. Density of tumor-associated macrophages correlates with lymph node metastasis in papillary thyroid carcinoma. Thyroid 2012; 22: 905-910.
[64] Sica A, Saccani A, Bottazzi B, Polentarutti N, Vecchi A, van Damme J and Mantovani A. Autocrine production of IL-10 mediates defective IL-12 production and NF-κB activation in tumor-associated macrophages. J Immunol 2000; 164: 762-767.
[65] Wang T, Xiao M, Ge Y, Krepler C, Belser E, Lopez-Coral A, Xu X, Zhang G, Azuma R, Liu Q, Liu R, Li L, Amaravadi RK, Xu W, Karakousis G, Gangadhar TC, Schuchter LM, Lieu M, Khare S, Halloran MB, Herlyn M and Kaufman RE. BRAF inhibition stimulates melanoma-associated macrophages to drive tumor growth. Clin Cancer Res 2015; 21: 1652-1664.
[66] Smith MP, Sanchez-Laorden B, O'Brien K, Brunton H, Ferguson J, Young H, Dhomen N, Flaherty KT, Frederick DT, Cooper ZA, Wargo JA, Marais R and Wellbrock C. The immune microenvironment confers resistance to MAPK pathway inhibitors through macrophage-derived TNFα. Cancer Discov 2014; 4: 1214-1229.
[67] Kalluri R. The biology and function of fibroblasts in cancer. Nat Rev Cancer 2016; 16: 582-598.
[68] Shen L, Li J, Liu Q, Das M, Song W, Zhang X, Tiruthani K, Dorosheva O, Hu H, Lai SK, Liu R and Huang L. Nano-trapping CXCL13 reduces regulatory B cells in tumor microenvironment and inhibits tumor growth. J Control Release 2022; 343: 303-313.
[69] Liu T, Zhou L, Yang K, Iwasawa K, Kadekaro AL, Takebe T, Andl T and Zhang Y. The β-catenin/YAP signaling axis is a key regulator of melanoma-associated fibroblasts. Signal Transduct Target Ther 2019; 4: 63.
[70] Liu T, Zhou L, Xiao Y, Andl T and Zhang Y. BRAF inhibitors reprogram cancer-associated fibroblasts to drive matrix remodeling and therapeutic escape in melanoma. Cancer Res 2022; 82: 419-432.

[71] Minna E, Brich S, Todoerti K, Pilotti S, Collini P, Bonaldi E, Romeo P, Cecco L, Dugo M, Perrone F, Busico A, Vingiani A, Bersani I, Anichini A, Mortarini R, Neri A, Pruneri G, Greco A and Borrello MG. Cancer associated fibroblasts and senescent thyroid cells in the invasive front of thyroid carcinoma. Cancers (Basel) 2020; 12: 112.

[72] Saito Y, Kage H, Kobayashi K, Kamogashira T, Fukuoka O, Yamamura K, Yamashita S, Tanabe M, Oda K and Kondo K. Comprehensive genomic profiling from C-CAT database unveiled over 80% presence of oncogenic drivers in anaplastic thyroid carcinoma including BRAF, RAS family, NF1, and FGFR1. Clin Endocrinol (Oxf) 2024; 101: 170-179.

[73] Yu P, Qu N, Zhu R, Hu J, Han P, Wu J, Tan L, Gan H, He C, Fang C, Lei Y, Li J, He C, Lan F, Shi X, Wei W, Wang Y, Ji Q, Yu FX and Wang YL. TERT accelerates BRAF mutant-induced thyroid cancer dedifferentiation and progression by regulating ribosome biogenesis. Sci Adv 2023; 9: eadg7125.

[74] Colombino M, Capone M, Lissia A, Cossu A, Rubino C, De Giorgi V, Massi D, Fonsatti E, Staibano S, Nappi O, Pagani E, Casula M, Manca A, Sini M, Franco R, Botti G, Caracò C, Mozzillo N, Ascierto PA and Palmieri G. BRAF/NRAS mutation frequencies among primary tumors and metastases in patients with melanoma. J Clin Oncol 2012; 30: 2522-2529.

[75] Dacosta Byfield SA, Adejoro O, Copher R, Chatterjee D, Joshi PR and Worden FP. Real-world treatment patterns among patients initiating small molecule kinase inhibitor therapies for thyroid cancer in the United States. Adv Ther 2019; 36: 896-915.

[76] Cabanillas ME and Takahashi S. Managing the adverse events associated with lenvatinib therapy in radioiodine-refractory differentiated thyroid cancer. Semin Oncol 2019; 46: 57-64.

[77] Ascierto PA, Puzanov I, Agarwala SS, Blank C, Carvajal RD, Demaria S, Dummer R, Ernstoff M, Ferrone S, Fox BA, Gajewski TF, Garbe C, Hwu P, Lo RS, Long GV, Luke JJ, Osman I, Postow MA, Sullivan RJ, Taube JM, Trinchieri G, Zarour HM, Caracò C and Thurin M. Perspectives in melanoma: meeting report from the "Melanoma Bridge" (December 5th-7th, 2019, Naples, Italy). J Transl Med 2020; 18: 346.

[78] Bradley SD, Chen Z, Melendez B, Talukder A, Khalili JS, Rodriguez-Cruz T, Liu S, Whittington M, Deng W, Li F, Bernatchez C, Radvanyi LG, Davies MA, Hwu P and Lizee G. BRAFV600E Co-opts a conserved MHC class I internalization pathway to diminish antigen presentation and CD8+ T-cell recognition of melanoma. Cancer Immunol Res 2015; 3: 602-609.

[79] Brea EJ, Oh CY, Manchado E, Budhu S, Gejman RS, Mo G, Mondello P, Han JE, Jarvis CA, Ulmert D, Xiang Q, Chang AY, Garippa RJ, Merghoub T, Wolchok JD, Rosen N, Lowe SW and Scheinberg DA. Kinase regulation of human MHC class I molecule expression on cancer cells. Cancer Immunol Res 2016; 4: 936-947.

[80] Atkins MB, Lee SJ, Chmielowski B, Tarhini AA, Cohen GI, Truong TG, Moon HH, Davar D, O'Rourke M, Stephenson JJ, Curti BD, Urba WJ, Brell JM, Funchain P, Kendra KL, Ikeguchi AP, Jaslowski A, Bane CL, Taylor MA, Bajaj M, Conry RM, Ellis RJ, Logan TF, Laudi N, Sosman JA, Crockett DG, Pecora AL, Okazaki IJ, Reganti S, Chandra S, Guild S, Chen HX, Streicher HZ, Wolchok JD, Ribas A and Kirkwood JM. Combination dabrafenib and trametinib versus combination nivolumab and ipilimumab for patients with advanced BRAF-mutant melanoma: the DREAMseq trial-ECOG-ACRIN EA6134. J Clin Oncol 2023; 41: 186-197.

[81] Lito P, Pratilas CA, Joseph EW, Tadi M, Halilovic E, Zubrowski M, Huang A, Wong WL, Callahan MK, Merghoub T, Wolchok JD, de Stanchina E, Chandarlapaty S, Poulikakos PI, Fagin JA and Rosen N. Relief of profound feedback inhibition of mitogenic signaling by RAF inhibitors attenuates their activity in BRAFV600E melanomas. Cancer Cell 2012; 22: 668-682.

[82] Ngelangel CA and Sy FF. BRAF mutant PD-L1 positive metastatic musculoskeletal lesions from primary lung adenocarcinoma treated with combination vemurafenib and pembrolizumab: a case report. J Med Case Rep 2024; 18: 450.

[83] Corcoran RB, Ebi H, Turke AB, Coffee EM, Nishino M, Cogdill AP, Brown RD, Della Pelle P, Dias-Santagata D, Hung KE, Flaherty KT, Piris A, Wargo JA, Settleman J, Mino-Kenudson M and Engelman JA. EGFR-mediated re-activation of MAPK signaling contributes to insensitivity of BRAF mutant colorectal cancers to RAF inhibition with vemurafenib. Cancer Discov 2012; 2: 227-235.

[84] Dudnichenko O, Penkov K, McKean M, Mandala M, Kukushkina M, Panella T, Csoszi T, Gerletti P, Thakur M, Polli A, di Pietro A and Schadendorf D. First-line encorafenib plus binimetinib and pembrolizumab for advanced BRAF V600-mutant melanoma: safety lead-in results from the randomized phase III STARBOARD study. Eur J Cancer 2024; 213: 115070.

[85] Irvine M, Stewart A, Pedersen B, Boyd S, Kefford R and Rizos H. Oncogenic PI3K/AKT promotes the step-wise evolution of combination BRAF/MEK inhibitor resistance in melanoma. Oncogenesis 2018; 7: 72.

[86] Straussman R, Morikawa T, Shee K, Barzily-Rokni M, Qian ZR, Du J, Davis A, Mongare MM, Gould J, Frederick DT, Cooper ZA, Chapman PB, Solit DB, Ribas A, Lo RS, Flaherty KT, Ogino S, Wargo JA and Golub TR. Tumour micro-environment elicits innate resistance to RAF inhibitors through HGF secretion. Nature 2012; 487: 500-504.

[87] Eun JW, Yoon JH, Ahn HR, Kim S, Kim YB, Lim SB, Park W, Kang TW, Baek GO, Yoon MG, Son JA, Weon JH, Kim SS, Cho HJ and Cheong JY. Cancer-associated fibroblast-derived secreted phosphoprotein 1 contributes to resistance of hepatocellular carcinoma to sorafenib and lenvatinib. Cancer Commun (Lond) 2023; 43: 455-479.

[88] Ma W, Tian M, Hu L, Ruan X, Zhang W, Zheng X and Gao M. Early combined SHP2 targeting reverses the therapeutic resistance of vemurafenib in thyroid cancer. J Cancer 2023; 14: 1592-1604.

[89] Kang D, Wang Y, Lin Y, Ma WW, Morgensztern D, Leventakos K, Bi C, Ding Y, Xiong J, Yan M, Sun X, Wang P, Ma C and Wang Y. JAB-3312, a potent allosteric SHP2 inhibitor that enhances the efficacy of RTK/RAS/MAPK and PD-1 blockade therapies. Clin Cancer Res 2025; 31: 3019-3032.

[90] Dörrie J, Babalija L, Hoyer S, Gerer KF, Schuler G, Heinzerling L and Schaft N. BRAF and MEK inhibitors influence the function of reprogrammed T cells: consequences for adoptive T-cell therapy. Int J Mol Sci 2018; 19: 289.

[91] Elnaggar M, Agte S, Restrepo P, Ram M, Melnekoff D, Adamopoulos C, Stevens MM, Kappes K, Leshchenko V, Verina D, Jagannath S, Poulikakos PI, Parekh S and Laganà A. Triple MAPK inhibition salvaged a relapsed post-BCMA CAR-T cell therapy multiple myeloma patient with a BRAF V600E subclonal mutation. J Hematol Oncol 2022; 15: 109.

[92] Srour SA, Lorch JH and Zafereo ME. Abstract CT206: ICAM-1 directed chimeric antigen receptor (CAR) T cells (AIC100) in patients with advanced thyroid cancers: clinical and translational data from the phase 1 dose escalation study. Cancer Res 2025; 85.