VIA MEDICA

NOWOTWORY Journal of Oncology
2024, volume 74, number 6, 357–365
DOI: 10.5603/njo.103026

ISSN: 0029–540X, e-ISSN: 2300–2115
www.nowotwory.edu.pl

Review article

Tumor biology

The phenomenon of the *BRAF* and *TERTp* mutational duet in melanoma and other cancers

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The unique oncogenic duo of *BRAF* and *TERT* promoter (*TERT*p) variants was demonstrated to be associated with aggressiveness and poor prognosis in several different cancer types, including melanoma and thyroid cancer. It has been shown that the coexistence of *BRAF* and *TERT*p variants has a significantly more substantial impact on clinical outcomes than the presence of mutated *BRAF* or *TERT*p alone. At the same time, the co-occurrence of *BRAF* and *TERT*p variants may also be the Achilles Heel of cancer cells in the context of targeted therapies' effectiveness. This paper aims to summarize data from tumors in which clinically significant variants in *BRAF* and *TERT*p were documented as prognostic or predictive markers.

Keywords: *BRAF*, *TERT*p, melanoma, thyroid cancer, glioma

Introduction

Cutaneous melanoma (cuMM) represents only 4% of all skin cancers. However, it is responsible for 80% of all skin cancer deaths, which makes it the most lethal of all primary cutaneous neoplasm types. In the last few decades the cuMM incidence rate has risen steadily worldwide among light-skinned populations. The National Cancer Institute Surveillance, Epidemiology, and End Results Program (SEER) database ranked melanoma of the skin in 5th place of frequency for 2024, estimating it will account for 5% of all new cancer cases in the United States [1]. In Poland, in turn, according to the World Health Organization (WHO) statistics, cuMM was the 16th most common cancer type in men and women in 2022 [2]. While increase of cuMM incidence is still substantial in most European countries, in several high-risk countries, like Australia, a decrease/stabilization in melanoma incidence has been reported, thanks to effective public health campaigns and increased sunscreen accessibility [3].

Early cuMM detection is critical since it gives a better prognosis. According to the SEER database, the 5-year relative survival rate for melanoma skin cancer is 100% when it is localized. However, the 5-year relative survival drops to 74% and 35% in regional and distant cuMM, respectively [1]. Until recently, cuMM was considered a cancer that is highly resistant to traditional treatment involving surgical resection of the lesion and adjuvant treatment (chemo- and radiotherapy). Nevertheless, a better understanding of the biology of melanoma and the introduction of targeted therapies and immunotherapy have significantly improved the effectiveness of therapeutic approaches in recent years. That said, there is a strong need for biomarker identification that would enable the usage of personalized medicine that can be individually tailored to the patient and/or tumor. An ideal solution would be to identify unique molecular markers that would improve patients' diagnostics and/or risk stratification and treatment. However, published data show that many oncogenic drivers

How to cite:
Rusinek D, Pfeifer A, Zajkowicz A, Tęcza K, Pamuła-Piłat J, Czarnecka AM, Oczko-Wojciechowska M. ***The phenomenon of the BRAF and TERTp mutational duet in melanoma and other cancers. NOWOTWORY J Oncol*** 2024; 74: 357–365.

are common for different tumor types and do not segregate by organ of tumor origin. These observations provide new opportunities in therapies by classifying cancers based on genomic aberrations and using similar molecular therapeutic approaches regardless of tumor histology. This has allowed the development of so-called tumor-agnostic targeted therapies that use the same drug to treat different cancer types with the same genetic variant detected [4]. To date, six molecular markers have achieved tissue-agnostic indications in patients with advanced solid tumors. Among them, there is a *BRAF* variant, NM_004333.6(*BRAF*):c.1799T>A (p.Val600Glu) (from now on referred to as the *BRAF* V600E variant), the presence of which is related to the possibility of applying a combination of BRAF and MEK inhibitors. This therapy is used primarily in melanoma and anaplastic thyroid cancer. The presence of *NTRK* fusions in solid tumors, in turn, allows the use of larotrectinib or entrectinib that targets TRK (tyrosine kinase domain). The other biomarkers mentioned above include *RET* fusions, mismatch repair deficiency (dMMR), HER2 overexpression, and TMB-high (tumor mutation burden) [4, 5].

In the following review, we will focus on two molecular markers that co-occur in different cancer types, including melanoma, and are used as diagnostic, prognostic, and predictive markers: *BRAF* V600 pathogenic variants with emphasis on the *BRAF* V600E one and *TERT* promoter (*TERT*p) pathogenic variants. These two genes are mutated in a variety of different cancer types and have been associated with aggressiveness and poor prognosis. However, even though their prognostic role in some cancers is beyond doubt, in others, it is still a matter of debate.

BRAF as an oncogene

BRAF is one of the most commonly mutated and best-known oncogenes in human tumorigenesis. BRAF kinase belongs to the RAF family of serine/threonine kinases, and is a part of the mitogen-activated kinase pathway (MAPK), altered in most cancers. Its activation results from a ligand binding to receptor tyrosine kinases (RTKs), followed by RTKs phosphorylation that leads to RAS GTPases activation and dimerization of RAF family members. Activated RAF kinases, including BRAF, trigger activation of MEK1/2 and ERK1/2 kinases, leading to direct and indirect regulation of transcription of genes involved in cell proliferation and survival [6].

Germline pathogenic variants in the *BRAF* gene are rarely observed and are associated with developmental syndromes termed RASopathies, like Noonan and LEOPARD syndromes, but mainly the cardiovascular-cutaneous (CFC) syndrome. *BRAF* germline activating variants are present in 50–75% of patients with CFC syndrome [7, 8]. It is a rare autosomal dominantly inherited disorder characterized by several birth defects, including a distinctive facial appearance, short stature, ectodermal tissue abnormalities, congenital heart defects, gastrointestinal motility disorders, and intellectual disability. There are isolated reports in the literature indicating a germline mutation of the V600 variant in CFC syndrome. Most observed germline variants of the *BRAF* gene typically involve codons other than V600, and are characterized by milder ERK/MAPK pathway activation. Analyses performed on cell lines show that germline *BRAF* variants present reduced transforming capability compared to the most frequent somatic *BRAF* V600E mutation, and have less potency in deregulating BRAF function [7]. In turn, somatic variants of the *BRAF* gene are strong oncogenic events reported in aggressive and indolent tumors — solid and liquid — in both children and adults. The frequency of *BRAF* oncogenic variants in human malignancies is reported at 6% [9]. These are the most prevalent molecular alterations in melanoma (40–60% of cases), hairy cell leukemia (circa 100% of patients), and papillary thyroid carcinoma (PTC; 29–83% of cases) [10–12]. *BRAF* V600 variants are reported to be present also in many other cancers, including cholangiocarcinoma, colorectal cancer, chronic lymphocytic leukemia, glioblastoma, GIST (gastrointestinal stromal tumors), lung cancer adenocarcinoma, ovarian cancer, kidney cancer, pancreatic cancers and others [13]. More than 200 *BRAF*-mutant alleles have been discovered, with 30 variants functionally characterized [14]. *BRAF* V600E is the most common one (accounts for 70–90% of all *BRAF* variants) and has the highest oncogenic potential. This alteration and other variants within the 600 codon belong to class 1 *BRAF* variants, which are RAS-independent and enable BRAF kinase to function as an active monomer [15]. Although *BRAF* V600E presence is usually related to a more aggressive course of cancer, it is not only present in malignant tumors. It has been reported in some benign lesions and neoplasms of low malignant potential, like endosalpingiosis [16], metanephric adenoma [17], Erdheim-Chester disease, and Langerhans cell histiocytosis [18] or papillary craniopharyngioma [19]. *BRAF* V600E is also present in about 80% of melanocytic nevi, suggesting that it is insufficient alone to drive oncogenesis [20]. It is well known that despite the mutated BRAF kinase activity, most melanocytic nevi remain harmless over the course of an individual's lifetime. It has been indicated that oncogenic *BRAF* plays a dual role: induce hyperproliferation and subsequent cell cycle arrest. This intriguing duality in the role of oncogenic *BRAF* adds a layer of complexity to our understanding of cancer biology. The prevalent theory explaining this phenomenon is oncogene-induced senescence (OIS), with elevated expression of p16INK4a and other cyclin-dependent-kinase inhibitors. However, the term "senescence", conventionally defined as permanent cell-cycle arrest, has been questioned for the proliferation arrest of melanocytic nevi because nevus recurrence and transformation to primary melanoma is associated with cell cycle re-entry. McNeal et al. [21] identified that *BRAF* V600E induces a reversible arrest in human melanocytes directed by MIR211-5p/MIR328-3p regulation of *AURKB* (aurora

kinase B) and conditional on the melanocyte differentiation state (differentiated melanocytes *vs.* melanocyte progenitor or stem cells). The Aurora B kinase, as an enzymatic component of the Chromosomal Passenger Complex, plays a critical role in cell division, but also cell cycle checkpoint, DNA damage response by interaction with p53, and normal physiological processes. Overexpression and amplification of Aurora B have been observed in several human cancers, including melanoma, and predict tumor recurrence and poor prognosis [22]. McNeal et al. [21] suggested that acquiring the *BRAF* V600E variant permits melanocytes to switch between hyperproliferation and mitotic arrest. Moreover, many studies have shown that in most tumors with *BRAF* variants, inactivation of tumor suppressor genes is essential for malignant transformation [23–25].

TERT as an oncogene

The *TERT* gene encodes the telomerase's catalytic subunit, which regulates telomeres' length. The telomerase activity is silenced in most normal cells, which is related to the shortening of telomeres in each round of cell division until a critical length is reached and the cell enters replicative senescence. The number of cell divisions before the senescence is known as the Hayflick limit [26–28]. Telomerase expression is maintained in selected cells, like stem-like cells and germ cells. In cancer cells, telomerase reactivation is a known hallmark of tumorigenesis, as more than 90% of all human cancers express this enzyme [29]. *TERT* induction leads to telomerase activation, which, by stabilizing the length of telomeres, gives cancer cells unlimited proliferative potential. Recent studies indicated additional telomere-independent, oncogenic TERT functions. These include the impact on non-telomeric DNA damage responses, promotion of cell growth and proliferation, control of mitochondrial integrity following oxidative stress, and participation in the transcriptional regulation of gene expression [30]. TERT was found to interact with β-catenin, which stimulates epithelial-mesenchymal transformation (EMT), stemness of cancer cells, and thereby cancer metastasis and recurrence [31]. Moreover, via interaction with NF-kappaB p65, TERT is involved in the up-regulation of metalloproteinases (MMPs) expression, contributing to cancer progression [32]. Those mentioned above and many more TERT molecular linkages and mechanisms of action indicate its strong involvement in multiple cancer hallmarks.

The reactivation of TERT in most tumors is mainly a consequence of *TERT*p variants and focal amplification/rearrangements [33]. The most common *TERT*p variants are C>T transitions, located at hot spots -124 bp and -146 bp from the transcription start site, referred to as NM_198253.3(*TERT*):c.-124C>T (from now on referred to as C228T variant) and NM_198253.3(*TERT*):c.-146C>T (from now on referred to as C250T variant), respectively. These variants were initially found in 2013 and reported in 71% of melanoma cases [34, 35]. It has been indicated that C228T and C250T affect *TERT* expression, telomerase activity, and telomere length. Both these alterations generate an 11 bp nucleotide fragment, "CCCGGAAGGGG", that provides a new binding site for E-twenty-six (ETS) family transcription factors [34, 36]. Not long after the discovery, *TERT*p variants were reported as frequent in several different tumor types, including 83% of glioblastoma [37], 66% of bladder cancer [38], and 47% of hepatocellular carcinoma (HCC) [39]. There is a clear separation in the frequency of *TERT*p alterations between tumors with high and low proliferative potential [36]. *TERT*p variants are more prevalent in tumors with low proliferative potential, like the melanoma mentioned above, glioblastoma, bladder cancers, and HCC, and less frequent in tumors that have high proliferative potential like breast cancer (0.9%) [40], testicular germ cell tumors (~3%) [41], and myeloid malignancies [42]. So far, *TERT*p variants have been reported in more than 50 distinct cancer types. These two hot spot alterations are believed to be a secondary genetic event following the deregulation of MAPK or Wnt signaling pathways [43]. Moreover, a recent study by Zarif et al. [44] demonstrated that the prevalence of *TERT*p variants varies among patients with different cancer types based on race and sex [44]. The authors observed a higher frequency of *TERT*p variants in melanomas of patients self-reported as White compared to melanomas of patients self-reported as Asian and Black. However, Asian patients had more often *TERT*p-mutated head and neck cancer than White patients. Regarding the association with sex, in males, *TERT*p variants were more frequent in melanoma, hepatobiliary, and thyroid cancers compared to females. In contrast, females were more enriched for *TERT*p variants than males for head and neck cancer.

BRAF and *TERT*p variants separately and as a molecular duet in cutaneous melanoma

Most *BRAF* variants in melanoma are missense ones determining amino acid substitution at valine 600. *BRAF* V600E accounts for 70–88% of all *BRAF* variants in melanoma, followed by variants: NM_004333.6(*BRAF*):c.1798_1799delinsAA (p.Val600Lys) (referred to V600K; 5-12%), and NM_004333.6(*BRAF*):c.1799_1800delinsAT (p.Val600Asp) (referred to V600D), which, together with the NM_004333.6(*BRAF*):c.1798_1799delinsAG (p.Val600Arg) variant (referred to V600R) account for ≤ 5% [45]. Detection of *BRAF* mutational status — post-chemotherapy — plays a crucial role in determining prognosis, together with other factors like age, gender, metastases, Eastern Cooperative Oncology Group (ECOG) scale, and lactate dehydrogenase (LDH) levels [46]. Shinozaki et al. [47] showed decreased overall survival (OS) in patients treated with bio-chemotherapy for melanoma when the *BRAF* variant was detected in ctDNA compared to patients in whom the *BRAF* variant was not found in serum (13 *vs.* 30.6 months). In a study by Ardekani et al. [48], higher *BRAF* expression was also associated with poor OS in primary melanoma patients, and a correlation between *BRAF* expression and both thickness and ulceration

of the tumor was demonstrated [48]. Nevertheless, the presence of the *BRAF* V600 variant is a predictive marker determining the targeted therapy choice. The first inhibitor of mutated BRAF approved by the U.S. Food & Drug Administration (FDA) was vemurafenib, and it showed objective response rates of ~50% in patients with metastatic melanoma and tumors positive for *BRAF* V600E [49, 50]. Melanomas treated with BRAF inhibitors only, develop mechanisms to reactivate MAPK/PI3K/Akt/alternative pathways in a short time, and resistance occurs. These pathways may be activated through mutations, copy-number alterations, and other mechanisms. The most frequent are *NRAS* variants and *MEK1/2* variants. Less frequently, PI3K/Akt pathway alterations are observed [51]. In order to overcome this resistance, a combination of BRAF and MEK inhibitors has been proposed. Compared to vemurafenib monotherapy, it provides improved OS and a more than 64% response rate [52]. At present, analysis of *BRAF* mutational status is recommended in tumors of cutaneous melanoma stage III or IV, and when a *BRAF* V600 variant is detected, a combined BRAF/MEK inhibitors therapy is advised (dabrafenib/trametinib; vemurafenib/ /cobimetinib; encorafenib/binimetinib). This targeted therapy may be applied as the first-line or after progression on immunotherapy with PD-1 inhibitors [53]. Nevertheless, the efficacy and effects of this combined therapy may be highly different. In some cases, it may result in tumor shrinkage or even complete tumor resolution; in others, drug resistance/tumor recurrence may be the effect [54, 55]. For this reason, new therapeutic strategies are being sought to combat resistance mechanisms, and attention has turned to other processes whose inhibition could aid in inhibiting cancer cell growth. Inhibition of mitotic cell division may be a goal. Targeting Aurora B, the kinase we mentioned earlier, with inhibitors is a promising therapeutic strategy for cancer treatment [56]. Nevertheless, at present, there are no markers that would support clinicians in predicting therapeutic responses of *BRAF*-altered cancers to BRAF/ /MEK inhibitors.

BRAF V600E was found to be associated with the presence of *TERT*p variants in human cancers, particularly in melanoma and thyroid cancers [57–59]. Moreover, this duet has also been reported in gliomas [60] and low-grade serous ovarian carcinoma [61]. Most *TERT*p variants in melanoma include two aforementioned hot spots — C228T and C250T — that have a UV signature with C>T nucleotide substitution [62]. *TERT*p variants were indicated as an independent marker of poor survival in patients with cutaneous melanoma [59]. Several studies have also demonstrated an association between *TERT*p variants and increased Breslow thickness, as well as tumor ulceration [59, 63, 64].

The frequency of *BRAF* V600 and *TERT*p variant co-occurrence in melanoma was reported at 20–25% [63, 65]. In a study concerning a selected *BRAF*-mutated melanoma cohort, 72% of cases were positive for *TERT*p alterations [66]. However, there are population-dependent differences in the *TERT*p variant's frequency. In the Asian population, for instance, the prevalence of *TERT*p C228T and C250T in melanoma was significantly lower compared to the Caucasian population, reported as 5.9% and 5.5%, respectively [67]. These differences may be due to the dominance of acral and mucosal melanomas in the Asian population. Similar to the Caucasian population, *TERT*p mutations were more commonly observed in *BRAF*-mutated tumors. The unique coexistence of these two genes' hot spot alterations is an important discovery due to its biological and clinical consequences since *BRAF* V600 and *TERT*p variants as a duet are a robust driver for the aggressiveness of human cancer. In cutaneous melanoma, this mutational duet was reported to be strongly correlated with adverse clinicopathological parameters, like thickness, high mitotic rate, sentinel node metastases, presence of ulceration, and absence of regression [63], and these correlations were not significant when each of these variants was analyzed alone (*BRAF* V600 and *TERT*p variants). This synergistic oncogenicity of *BRAF* V600E and *TERT*p alterations is associated with strong cooperation between these two oncogenes. The mechanism of *BRAF* V600E/ /MAPK pathway-dependent up-regulation of *TERT* expression is the following: the *BRAF* V600E/MAPK pathway promotes the expression of GABPB protein via FOS transcription factor phosphorylation and its binding to the GABPB promoter; increased GABPB expression leads to formation of the GABPA-GABPB complex, which selectively binds to the mutated *TERT* promoter and in consequence, strongly up-regulates its expression (Fig. 1) [65, 68]. Despite the strong negative impact of this molecular duo on the clinical course of melanoma, recent studies emphasize its simultaneous potential as a therapeutic target. Tan et al. [69] showed that the genetic duet of *BRAF* V600E and *TERT*p variants is the Achilles Heel of cancer cells, the most vulnerable therapeutic target. Using thyroid cancer, melanoma, and colon cancer cell models, the authors showed that dabrafenib and trametinib induced apoptosis of cancer cells harboring both variants. Yet, they displayed little proapoptotic effect in cells with only the *BRAF* variant. The same results were observed *in vivo*. What is more, after drug withdrawal, tumors harboring only the *BRAF* variant regrew rapidly in contrast to tumors with both alterations that remained hardly measurable. It has been hypothesized that cancer cells with these alterations evolve to rely on *BRAF* V600E-dependent high *TERT* expression, which results in apoptosis suppression. Therefore, using BRAF/MEK inhibitors may lead to apoptosis of cancer cells and tumor elimination. In a clinical setting, Thielmann et al. [66] also demonstrated better therapeutic responses in patients with melanoma harboring *BRAF*/*TERT*p variants with more prolonged progression-free survival (PFS) and OS compared to patients with only *BRAF*-positive melanoma. However, the authors did not observe a plateau of durable responses, as reported by Tan et al. [69] in an *in vitro* study.

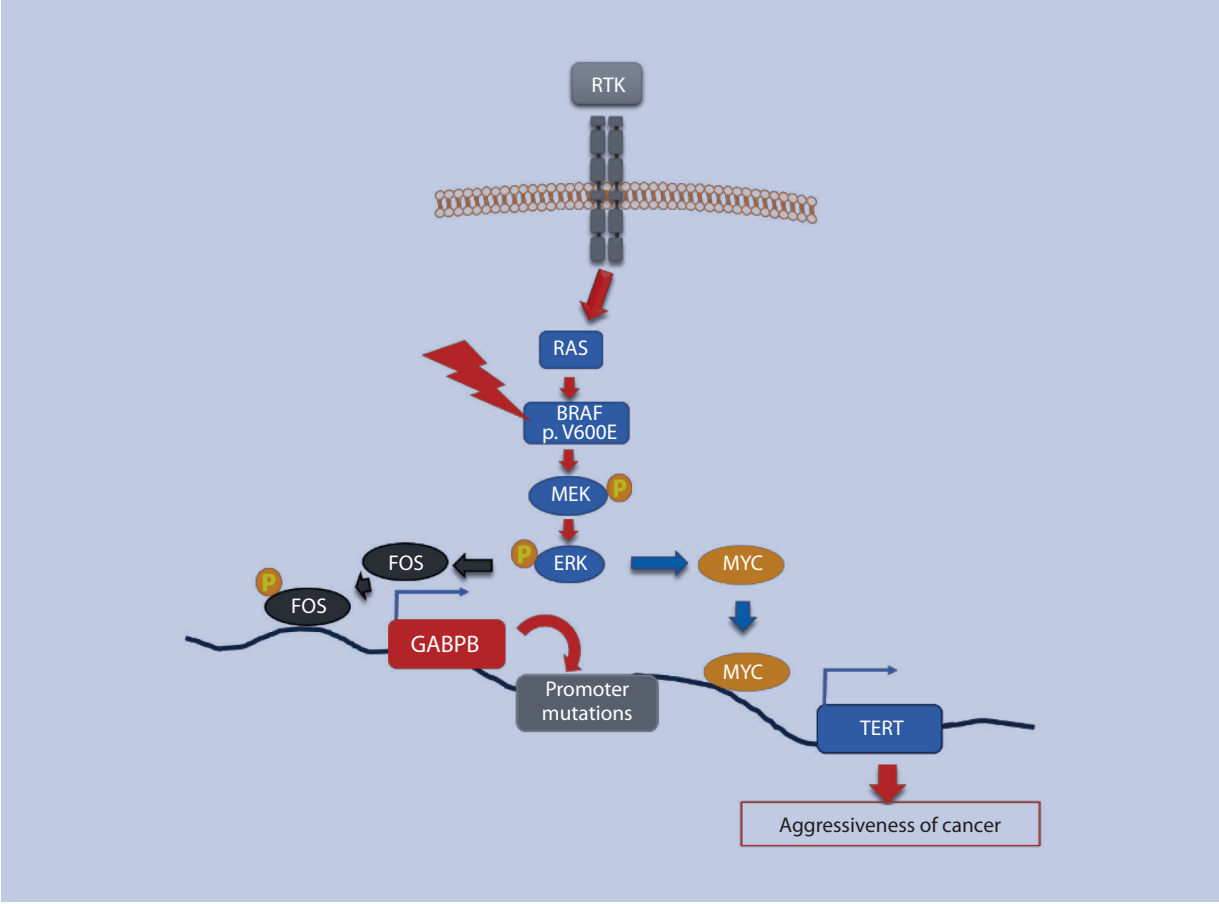

Figure 1. *BRAF* and *TERT* oncogenic cooperation mechanisms. The main model of *BRAF* V600E and *TERT*p variants' oncogenic cooperation is through the *BRAF* V600E-activated MAPK pathway — FOS phosphorylation — acting as a transcription factor of the *GABPB* gene. The GABPB, in turn, is part of the GABP complex that recognizes the ETS binding motif within the *TERT* gene promoter, created de novo due to either C228T or C250T variants. The *BRAF* V600E-activated MAPK pathway may also promote *TERT* expression via MYC. This model is *TERT*p variant independent

BRAF and *TERT*p variants as a molecular duet in other cancers

Thyroid cancers

Thyroid cancers (TC) are at the forefront in terms of *BRAF* V600E frequency, which plays a fundamental role in tumorigenesis and progression of TC, and papillary thyroid carcinoma (PTC) in particular. *TERT*p variants — C228T and C250T — are most common in more aggressive TCs with a frequency as follows: 11.3% in PTC, 17.1% in follicular thyroid carcinoma (FTC), 14.6% in Hurthle cell carcinoma (HCC), 43.2% in poorly differentiated carcinoma (PDTC), and 40.1% in anaplastic thyroid carcinoma (ATC) [57]. No *TERT*p variants were found in medullary thyroid carcinoma or benign thyroid tumors. Regarding the clinical impact of *BRAF* V600E and *TERT*p variants in TCs, mutated *BRAF* alone demonstrated associations with poor prognosis factors. However, the coexistence of *BRAF* V600E/*TERT*p variants showed a much more substantial negative impact in terms of clinical outcome. Shen et al. [70], in the analysis of the 388 PTC cohort (TCGA database), reported that *BRAF*/*TERT*p positive mutational status was associated with older patient age, extrathyroidal invasion, advanced disease stages III/IV, larger tumors, distant metastases, disease recurrence and patient mortality. *BRAF* V600E alone, in turn, was only associated with extrathyroidal invasion. In our study, although a smaller PTC cohort was analyzed, similar data were obtained supporting the meaning of the *BRAF* V600E/*TERT*p duet in the progression of PTC [71]. We reported a strong association of *BRAF* and *TERT*p alteration coexistence with gender, advanced age of patients, T3 and T4 stage of disease, lymph node metastases, larger tumor size, and infiltration of the tumor capsule. It was also demonstrated that these two alterations might play a role in the dedifferentiation of thyroid cancer, leading to TC formation with a status known as RAI (radioactive iodine)-refractory DTC (RAIR-DTC) [72]. Currently, multikinase inhibitors — sorafenib and lenvatinib — are recommended for treating patients with RAIR-DTC. Yet, these drugs are associated with significant adverse effects that lead to dose reduction and temporary or permanent discontinuation in many patients. Because of the positive effects of BRAF/MEK inhibitors in *BRAF*-mutated melanoma patients, their use was also studied in RAIR-DTC patients with promising results in some cases [73, 74]. However, the mutational status of *TERT*p was not considered in these studies. Su et al. [75] were

the first to report the effectiveness of anlotinib (a multitarget tyrosine kinase inhibitor) treatment in a patient with *BRAF*- and *TERT*p-mutated RAIR-DTC. The authors speculated that the presence of *BRAF* V600E/*TERT*p mutational duet might be a predictive marker for the beneficial effect of anlotinib therapy. More data is needed to confirm this hypothesis.

The interaction of mutated *BRAF* and *TERT*p on the molecular level in TCs may differ from mechanisms observed in melanoma, as reported by Song et al. [76]. The Authors demonstrated that GABP and ETS1 expression, previously associated with *BRAF* V600E/MAPK-dependent up-regulation of *TERT*, was not significantly affected by mutated *BRAF* in PTCs. Instead, *BRAF* V600E/MAPK activation triggered ETV1, ETV4, and ETV5 up-regulation in TCs. These ETS factors, induced by mutated *BRAF*, bind directly to the *TERT*p and activate it.

Gliomas

Gliomas represent the most common central nervous system (CNS) tumors. The prevalence of *BRAF* V600 variants in gliomas is reported as 15.4% in adults and 17.0% in pediatric patients [77]. *TERT*p variants, in turn, are present in 24.4%, 38.7%, and 44.9% of glioma cases with grades II, III, and IV (according to the WHO classification from 2016), respectively [78]. Discovery of *BRAF* alterations in CNS tumors opened new therapeutic possibilities for these patients [79]. Still, the efficacy of mutated BRAF inhibitors varies qualitatively by glioma histologic subtype. It has been demonstrated that additional molecular events, including loss of *CDKN2A* or telomerase reactivation, may significantly influence the clinical outcome in *BRAF*-mutated tumors [80, 81]. According to the latest WHO classification of CNS tumors, *TERT*p variants should be analyzed in patients with IDH-wild type diffuse glioma, and their presence is sufficient for diagnosing glioblastoma G4 [82]. The role of *TERT*p mutations in glioblastoma oncogenesis is beyond any doubt. Nevertheless, its prognostic impact remains controversial [83]. It has been indicated that the prognostic value of *TERT*p variants may depend on tumor grade and *IDH* mutational status [84]. The co-occurrence of *TERT*p and *IDH* variants in low-grade gliomas (LGG) was shown to be associated with better overall survival, similar to gliomas with *TERT*p, *IDH* variants, and 1p/19q co-deletion. However, patients without *TERT*p and *IDH* variants and those with 1p/19q co-deletion showed poor survival. The presence of *TERT*p variants only, in turn, seems to be associated with aggressive tumors and poor prognosis [85].

The coexistence of *BRAF* V600E and *TERT*p variants was observed to be enriched in more aggressive, high-grade tumors [81, 86]; still, it is not as common as in melanoma or PTC. The molecular mechanism of mutated *BRAF* and *TERT*p interaction in glioma is similar to that described in melanoma, and is based on the ETS1 up-regulation via the MAPK pathway and its binding to mutated *TERT*p, which leads to *TERT* activation [60].

Serous ovarian carcinoma

Serous carcinoma is a predominant type of epithelial ovarian cancer (EOC) and is classified into two main subtypes: high-grade serous carcinoma and less common low-grade serous carcinoma (LGSC). The frequency of the *BRAF* V600E variant varies from 2% to 38% in LGSC [87–89]. It is also found in up to 48% of serous borderline tumors [90]. There are studies showing an association between the presence of the *BRAF* V600E and early-stage disease and improved prognosis in LGSC [89]. Moujaber et al. [91], in turn, reported that most women with *BRAF*-mutated LGSC were diagnosed at an advanced stage. Moreover, recurrent *BRAF* V600E-positive LGCS was not responsive to chemotherapy. However, the use of a BRAF inhibitor, dabrafenib, gave a sustained response. The data about *BRAF/TERT*p mutational duet in ovarian cancer are scarce. Tavallaee et al. [61] first reported a case study of LGSC recurring as a carcinosarcoma in a lymph node with *BRAF* V600E and *TERT*p C228T alterations present in both primary and recurrent tumors. This case may support a hypothesis of the synergistic effect of this mutational duet in this patient's LGSC that led to an aggressive clinical course and high-grade transformation.

Soft tissue sarcoma

BRAF alterations are rare in soft tissue sarcoma (STS) cases, with a frequency of 1.2% and *BRAF* V600E presence between 0.3–0.6% [92]. Kobayashi et al. also showed that the most frequent variants accompanying *BRAF* V600E mutation in STS concerned the *CDKN2A* gene and *TERT*p. The percentage of *BRAF/TERT*p mutated STS is small, yet it should not be marginalized considering the clinical importance of these two molecular events' co-occurrence. Several case reports have documented the presence of the *BRAF* variant in various sarcoma subtypes, including malignant peripheral nerve sheath tumors (MPNST), clear cell sarcoma, synovial sarcoma GIST, undifferentiated pleomorphic sarcoma, and Ewing sarcoma. However, these cases exhibit significant differences in treatment approaches, such as the use of specific drugs and whether BRAF/MEK inhibition was combined or used as monotherapy [93–96].

Conclusions

There is no doubt that the *BRAF/TERT*p mutational duet plays an important role in tumorigenesis, progression, and the aggressiveness of cancer cells. It has also been demonstrated that the coexistence of these two alterations makes cancer cells more sensitive to BRAF and MEK inhibitors, as their survival becomes dependent on *BRAF* V600E-induced *TERT* up-regulation. Further studies are needed to elucidate the dual role of this molecular duet and its translation into targeted therapies that could be used in different types of cancer.

Article information and declarations

Authors contributions

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Anna M. Czarnecka — writing — review & editing.
Małgorzata Oczko-Wojciechowska — writing — review & editing.

Funding

None.

Acknowledgments

None.

Conflicts of interest

The author declare no conflict of interest.

Supplementary material

None.

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Received: 10 Oct 2024
Accepted: 5 Nov 2024
Early publication: 16 Dec 2024

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