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Review Article

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Targeting BRAF pathway in low-grade serous ovarian cancer

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ABSTRACT

Mutations in genes encoding for proteins along the RAS-RAF-MEK-ERK pathway have been detected in a variety of tumor entities including ovarian carcinomas. In the recent years, several inhibitors of this pathway have been developed, whose antitumor potential is currently being assessed in different clinical trials. Low grade serous ovarian carcinoma, is a rare gynecological tumor which shows favorable overall survival, compared to the general ovarian cancer population, but worrying resistance to conventional chemotherapies. The clinical behavior of low grade serous ovarian carcinoma reflects the different gene profile compared to high-grade serous carcinoma: *KRAS*/*BRAF* mutations. BRAF inhibitors as single agents were approved for the treatment of *BRAF* mutated tumors. Nevertheless, many patients face progressive disease. The understanding of the mechanisms of resistance to BRAF inhibitors therapy and preclinical studies showing that BRAF and mitogen-activated protein kinase kinase (MEK) inhibitors combined therapy delays the onset of resistance compared to BRAF inhibitor single agent, led to the clinical investigation of combined therapy. The aim of this paper is to review the efficacy and safety of the combination of BRAF plus MEK inhibitors on ovarian carcinomas, in particularly focusing on low grade serous ovarian carcinoma.

Keywords: BRAF Protein, Human; Ovarian Neoplasms; MEK Inhibitor

Synopsis
RAS-MAPK pathway represents an intriguing target for low-grade ovarian cancer who poorly respond to conventional chemotherapy. In particular, MEK inhibitors showed encouraging activity. Further trials are warrented to identify the optimal (chemotherapy-free) treatment for advanced low-grade ovarian cancer.

INTRODUCTION

In the rapidly evolving landscape of precision medicine, there is an escalating demand to pinpoint target mutations for both research and clinical applications. The identification of numerous oncogenic driver mutations and the subsequent enhancement in patient

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survival through targeted therapy have been extensively cataloged across a spectrum of solid tumors. Non-small cell lung cancer (NSCLC) serves as a prominent illustration of precision cancer medicine, where the identification of a driver mutation significantly reshapes the disease's natural trajectory [1-6]. Molecular/genomic profiling, facilitated by next-generation sequencing (NGS), proves to be a highly effective tool in identifying these pivotal driver mutations. A prime example is the RAS-RAF-MAPK signaling pathway, which frequently undergoes alterations in various malignancies, becoming activated and promoting malignant traits such as autonomous cellular proliferation. BRAF proteins, serving as serine-threonine kinases and encoded on chromosome 7q34, play a pivotal role in mediating signals between RAS and mitogen-activated protein kinase (MAPK) kinase (MEK). A growing body of evidence supports the adoption of BRAF and MEK inhibitors in the treatment of metastatic melanoma, colonic cancer, and NSCLC [1-6]. The combination, particularly involving BRAF and MEK inhibitors, has exhibited promising results and emerged as a transformative therapeutic approach for diverse tumor types. Noteworthy is the observation that in patients with the *BRAF* V600E mutation, the adoption of BRAF and MEK inhibitors correlates with a significantly higher response rate compared to the standard of care, both in adjuvant and metastatic settings among melanoma patients. It is imperative to underscore that while the integration of NGS and targeted therapy is firmly established in various oncologic disciplines, its application is still in its nascent stages in the field of gynecologic oncology. Despite the relatively low prevalence of BRAF alterations compared to other solid tumors, it is essential to recognize their considerable significance in a substantial proportion of gynecological patients. Data extracted from cBioPortal for cancer genomics reveal that BRAF alterations occur in 9%, 6%, 5%, and 5% of patients with high-grade serous ovarian, uterine, vulva/vaginal, and cervical cancer, respectively [2-5]. Moreover, BRAF alteration may be more prevalent in specific subsets of gynecological cancer patients, including those with low-grade ovarian carcinoma (with *BRAF* mutation rates ranging from 2% to 33%), serous borderline ovarian tumors (up to 46%), and mucinous ovarian cancer (up to 80%). Given the notable prevalence of BRAF alterations in gynecological tumors and the ongoing development of more effective targeted therapies, the objective of this paper is to conduct a comprehensive review of current evidence and explore prospective avenues for the adoption of BRAF and MEK inhibitors in gynecological cancers. This exploration commences with a concise overview of the *BRAF* gene and BRAF inhibitors, followed by an in-depth discussion of the potential applications of BRAF (and MEK) inhibitors in the context of ovarian cancer.

OVERVIEW ON *BRAF* GENE

The *BRAF* gene, situated on chromosome 7q34, stands as a pivotal proto-oncogene that encodes a member of the RAF family, specifically a serine/threonine protein kinase. This multifaceted protein assumes a central role in orchestrating the intricacies of the MAP kinase/ERK signaling pathway, exerting influence over fundamental cellular processes like cell division, differentiation, secretion, and survival [2].

Initiating its action upstream of BRAF, the binding of growth factors to receptor tyrosine kinases (RTKs) on the cell surface triggers a cascade of events, including the phosphorylation of RAS proteins, ultimately culminating in the activation of BRAF. This, in turn, sets in motion a series of signal transduction events downstream from BRAF to MEK1 and MEK2, ultimately resulting in ERK activation. The activated ERK subsequently phosphorylates a myriad of cellular targets, thereby propagating the signal [3].

Within the realm of genetic aberrations, mutations in the *BRAF* gene, particularly the frequently identified V600E mutation, stand out as the predominant culprits behind cancer initiation, notably in melanoma. These mutations induce the constitutive activation of BRAF, consequently setting off downstream activation of MEK and ERK. As a corollary, these mutations have been identified in an array of hematological and solid tumors, spanning non-Hodgkin lymphoma, colorectal cancer, thyroid carcinoma, non-small cell lung carcinoma, hairy cell leukemia, and lung adenocarcinoma [4-6]. The pervasive occurrence of these mutations' positions BRAF as an enticing target for inhibition in therapeutic interventions [4,5].

OVERVIEW OF BRAF INHIBITORS

In light of the widespread prevalence and clinical significance of the *BRAF* mutation, numerous studies have meticulously investigated the role of BRAF inhibitors in patients afflicted with both hematological and solid tumors. One of the pioneering explorations in this field focused on scrutinizing the safety and efficacy of sorafenib [6]. Functioning as a multi-kinase inhibitor, sorafenib impedes tumor progression by targeting FLT3, c-Kit, and BRAF. Despite its examination in melanoma patients, a demographic known for the frequent occurrence of *BRAF* mutations, sorafenib exhibited constrained clinical anti-tumor efficacy, whether employed as a sole agent or in combination with chemotherapy. This limitation is attributed to its diminished affinity for mutant BRAF [6,7]. In response to this constraint, a cohort of selective BRAF inhibitors, including dabrafenib, vemurafenib, and encorafenib, were developed with the precise aim of overcoming this drawback. Unlike sorafenib, these groundbreaking kinase inhibitors were intricately engineered to specifically bind to the ATP-binding pocket of the active conformation of BRAF, displaying a pronounced preference for *BRAF* V600E, thereby resulting in heightened potency and specificity [8,9]. **Fig. 1** shows the molecular pathways and mechanisms of BRAF in cancer therapy.

Clinical trials investigating the efficacy of BRAF inhibitors as monotherapy for metastatic melanoma uncovered a notable rate of objective response. Nevertheless, a relatively substantial proportion of patients developed resistance, rendering this therapeutic approach ineffective in the majority of cases [10-12]. A substantial body of evidence substantiates the notion that resistance is typically mediated through the paradoxical reactivation of the MAPK pathway signaling in BRAF wild-type cells. Whereas RAF inhibitors effectively inhibit ERK signaling in cells harboring mutant BRAF, they unexpectedly enhance signaling in cells with wild-type BRAF [13,14]. In an effort to address or preempt resistance, combination therapy targeting both BRAF and MEK, a downstream signaling target of BRAF in the MAPK pathway, was thoroughly investigated and demonstrated synergistic benefits [15]. These compelling findings have culminated in the approval by the U.S. Food and Drug Administration of 3 distinct BRAF and MEK inhibitor combinations, namely dabrafenib plus trametinib (endorsed for metastatic and resected stage III melanoma, NSCLC, and anaplastic thyroid cancer), vemurafenib plus cobimetinib (sanctioned for metastatic melanoma), and encorafenib plus binimetinib (acknowledged for metastatic melanoma) [3].

OVARIAN CANCER

Ovarian cancer looms as a formidable gynecologic malignancy, leaving an indelible impact with an estimated 19,710 new cases and 13,270 deaths in the USA in 2023 [16]. A substantial

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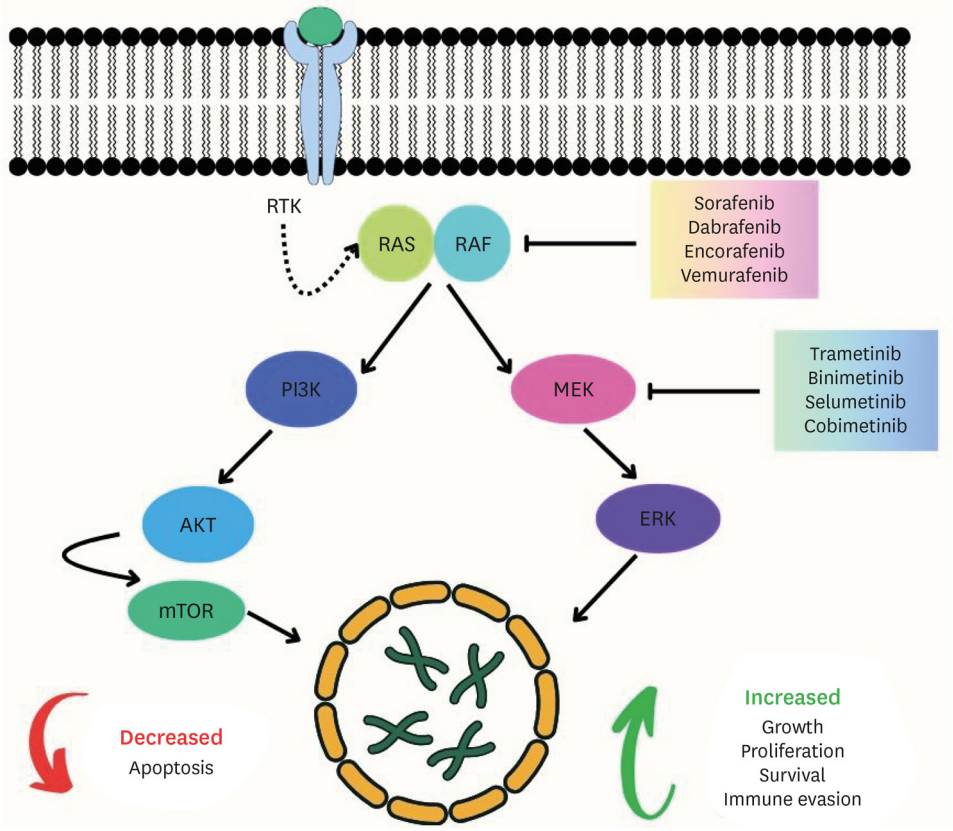

Fig. 1. Molecular pathways and mechanisms of BRAF in cancer therapy.
PI3K, phosphoinositide 3-kinase; MEK, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin.

90% of ovarian cancers trace their origins to epithelial cells [17], rendering them a pivotal focus in both clinical and research domains.

Epithelial ovarian tumors exhibit a spectrum of histologic types, encompassing serous, endometrioid, mucinous, and clear cell variants. Despite their histologic diversity, these tumors are classified into benign, borderline malignant (tumors of low malignant potential), and malignant forms. Serous ovarian carcinomas, constituting around 50% of all invasive carcinomas among epithelial ovarian cancers, carry particular significance [18].

The historical categorization of serous ovarian carcinomas into high-grade (International Federation of Gynecology and Obstetrics [FIGO] grade 3), intermediate grade (FIGO grade 2), or low-grade (FIGO grade 1) by Malpica et al. [19] in 2004 instigated subsequent refinements. The introduction of a 2-tier grading system, primarily based on nuclear atypia and the mitotic rate, showcased its superiority in predicting clinical outcomes compared to the traditional 3-tier FIGO grading system [19,20]. This refinement garnered further validation from Bodurka et al. [21] in 2012.

Validation of the 2-tier grading system for serous carcinoma, substantiated by distinct molecular, clinical, and epidemiological features, identified approximately 5% to 8% of ovarian carcinomas as low-grade serous ovarian cancers (LGSOCs) [22]. This classification ignited discussions on the continuum between borderline serous tumors and low-grade serous carcinomas, distinguishing them from high-grade serous cancers [23,24].

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Crucially, the clinical trajectory sets apart LGSOC from high-grade serous ovarian cancer (HGSOC). LGSOC progresses slowly, presenting a distinct clinical course compared to the rapid evolution characteristic of HGSOC. Demographic disparities, such as age at diagnosis (55.5 years for LGSOC and 62.6 years for HGSOC), and familial predispositions underscore the unique nature of low-grade serous cancers [25,26].

Molecular disparities contribute to the uniqueness of LGSOC, with the majority (91%) of women with a *BRCA1* mutation and ovarian cancer presenting high-grade serous cancer. Notably, mutations in *KRAS* and *BRAF*, key regulators of the MAPK pathway, emerge as distinctive features of LGSOC and its potential precursors, serous borderline tumors [27]. While supporting the close association between low-grade serous cancers and serous borderline tumors, the latter exhibits a higher frequency of *BRAF* mutations [28,29].

Further investigations suggest that advanced-stage low-grade serous cancers often originate from serous borderline tumors lacking *BRAF* mutations. Intriguingly, the presence of a *BRAF* mutation in a serous borderline tumor may act protectively against the development of subsequent low-grade serous carcinoma [30-32].

Despite their low-grade classification, a majority of LGSOC cases present at an advanced stage, and approximately 70% of women with low-grade serous cancer succumb to the disease. Remarkably, the presence of a *KRAS*/*BRAF* mutation in low-grade serous cancers appears to be a favorable prognostic factor, paving the way for tailored therapies targeting these specific RAS-RAF-MEK pathway components [33].

Ongoing trials actively explore the efficacy of BRAF/MEK inhibitors, either as standalone treatments or in combination with other investigational drugs, for the treatment of recurrent or persistent low-grade serous cancer. Presently, the standard treatment for women with low-grade serous cancers mirrors that for high-grade serous cancers, involving surgical debulking followed by a combination of platinum/taxane-based chemotherapy for 6 to 8 cycles. Despite the relative chemo-resistance of low-grade cancers, this approach remains the established norm [32,34].

While surgery plays a pivotal role in the treatment of LGSOC, targeted systemic treatments are deemed essential. Encouragingly, several studies highlight the potential of BRAF/MEK inhibitors in ovarian cancer, especially in LGSOC, showing promising results compared to standard therapy (**Table 1**).

The outcomes of ongoing trials affirm that tumors characterized by alterations in the MAPK pathway, such as low-grade serous ovarian cancer, may significantly benefit from treatment with BRAF/MEK inhibitors. Comprehensive details of ongoing trials, encompassing adverse events, toxicities, and the efficacy of new molecules inhibiting the aberrant activation of the RAS-RAF-MEK pathway in patients with ovarian carcinoma, are outlined in **Table 2**. These innovative therapeutic agents hold immense potential to optimize tumor efficacy, minimize toxicity, and markedly enhance outcomes for women grappling with epithelial ovarian cancer.

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Table 1. Clinical studies on BRAF/MEK inhibitors in ovarian cancer

Reference	Year	Study design	Patients	Median age	Setting	Agents	Dose	No. of cycles	Previous regimen	ORR %	mOS	mPFS	Note
Falchook et al. [35]	2012	Phase 1 trial	184 (only one with ovarian cancer)	24	Histologically confirmed solid tumor BFRAF mutated for which no curative treatment was available	Dabrafenib	150 mg BID	Until disease progression, in tolerable toxic effects, or withdrawal of consent	2	/	/	/	Stable disease for ovarian cancer (28% decrease)
Infante et al. [36]	2012	Multicentre phase 1 study	206	58.5	Advanced solid tumor or lymphoma	Trametinib	2 mg daily		0 to >3	10%	/	30 weeks	With or without a mutation in BRAF; stable disease for ovarian cancer
Farley et al. [37]	2013	Open-label, single-arm, phase II study	52	51	Recurrent low-grade serous ovarian or peritoneal carcinoma		50 mg PO BID	4.5	1–4 (including CHT, hormonal)	15%	Not reached	11 months	
Bedard et al. [38]	2015	Open-label, dose-finding, phase Ib study comprised dose escalation, followed by expansion part	113	49	RAS- or BRAF-mutant non-small cell lung, ovarian, or pancreatic cancer	Buparlisib (BKM120) with trametinib (GSK1120212)	Buparlisib 60 mg, trametinib 1.5 mg daily	Until disease progression, in tolerable toxic effects, or withdrawal of consent	3 median	29%		7 months	
Hyman et al. [39]	2015	Histology-independent phase II "basket" study	122 (among 27 of them there were patients with ovarian cancer)	55	*BRAF* V600 mutation-positive nonmelanoma cancers	Vemurafenib	960 mg PO BID	Daily until disease progression, death, or withdrawal from the study	0 to >3	Not reached	not reached	12.9 months	Also cervical
Grisham et al. [40]	2018	Open-label, multicenter, phase Ib dose-escalation	34	63	Platinum-resistant or refractory epithelial ovarian cancer	Binimetinib + paclitaxel	Cohort 1: Binimetinib 30 mg PO BID + 80 mg/m^2 IV paclitaxel Cohort 2: Binimetinib 45 mg PO BID + 80 mg/m^2 IV paclitaxel Cohort 3: Binimetinib 45 mg PO BID intermittent dosing + 80 mg/m^2 IV paclitaxel		Median 4	14%	/	/	

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Table 1. (Continued) Clinical studies on BRAF/MEK inhibitors in ovarian cancer

Reference	Year	Study design	Patients	Median age	Setting	Agents	Dose	No. of cycles	Previous regimen	ORR %	mOS	mPFS	Note
Monk et al. [41]	2019	Multinational, randomized, two-arm, open-label, phase III study	201	51.6	LGSOC, fallopian tube or primary peritoneum cancer	Binimetinib	45 mg PO BID		1–3 (including CHT, hormonal)	16%	25.33 months	9.1 months	MILO/ENGOT: early study closure because PFS (primary end point) was > in chemotherapy cohort than binimetinib
Gershenson et al. [42]	2019	Randomized phase II/III trial	260	Not reported	Recurrent low-grade serous carcinoma of the ovary/ peritoneum	Trametinib	2 mg daily	Until disease progression	0 to >3	26.2%	37 months	13 months	NCT02101788
Subbiah Et al. [43]	2020	Multi-histology, single-arm, phase II study	172 (of which only 4 with ovarian cancer)	60	Solid tumors with *BRAF* V600 mutation	Vemurafenib			Median 2 (0–10)	32.60%	17.6 months	5.8 months	Also cervical
Desai Et al. [48]	2020	Dose-escalation/ dose-expansion, phase I study	96 (of which only 1 with ovarian cancer)	63	The primary end point during dose expansion is ORR in *B-RAF*, *N-RAS*, or *K-RAS* mutation-positive solid tumors	Lifirafenib	During dose expansion: 30 mg/d administered in 21-day cycles	>1 year	1 to >3	17% in B-RAF mut; 3% in K-RAS mut/N-RAS mut	Not reached	Not reported	Also endometrial

ORR, overall response rate; mOS, median overall survival; mPFS, median progression-free survival; PO, orally; BID, twice daily; IV, intravenously; CHT, chemotherapy.

Table 2. Ongoing clinical trials on the adoption of BRAF/MEK inhibitors in ovarian cancer

Identifier	Agents	Phase	Mechanism of Action	Participants	Primary endopoint	Estimated completion date
NCT04190628	ABM-1310 as monotherapy in Part A, or in combination with cobimetinib in Part B	Phase I	ABM-1310 is a BRAF inhibitor, cobimetinib is reversible inhibitor of MEK1 and MEK2	112 participants Patients with documented *BRAF* V600 mutation	· MTD and/or RP2D · Number of participants with treatment-related adverse events as assessed by CTCAE v5.0 · Number of participants with abnormal laboratory values	2025-01 (Recruiting)
NCT03634982	RMC-4630	Phase I	RMC-4630 is a selective inhibitor of SHP2, a central protein in the RAS signaling pathway	133 participants Relapsed/refractory solid tumors harboring certain specific mutations/ rearrangements that result in hyperactivation of the RAS-MAPK pathway	· Number of participants with AEs (time frame: up to 3 years) · Number of participants with DLTs (time frame: 28 days)	2023-05-31 (Unknown status)
NCT04931342	Cobimetinib	Phase II	Reversible inhibitor of MEK1 and MEK2	200 participants	· Confirmed objective response rate according to RECIST v1.1	2026-03-31 (Recruiting)
NCT02407509	VS-6766 (RO512676)	Phase I	Dual RAF/MEK Inhibitor	104 participants	· Recommend a phase II dose and dosing schedule for VS-6766, as a single agent and also in combination with everolimus · Assess the safety and toxicity profile of each schedule of administration of VS-6766 both as a single agent and in combination with everolimus.	2024-05 (Recruiting)

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Table 2. (Continued) Ongoing clinical trials on the adoption of BRAF/MEK inhibitors in ovarian cancer

Identifier	Agents	Phase	Mechanism of Action	Participants	Primary endopoint	Estimated completion date
NCT05238831 (SMMART trial)	25 drugs (among them: vemurafenib cobimetinib)	Phase I	*BRAF* V600E kinase inhibitor and MEK Inhibitor	25 participants Patients with advanced ovarian carcinoma	· Proportion of participants who receive an ACT based an ACT Tumor Board recommendation.	2026-05-31 (Not recruiting yet)
NCT05768178 (DETERMINE trial)	Vemurafenib and cobimetinib	Phase II and III	*BRAF* V600E kinase inhibitor and MEK inhibitor	30 participants Cancer *BRAF* V600 mutation-positive	· OR (time frame: disease assessments to be performed up to 24 weeks from the start of trial treatment) · DCB (time frame: disease assessments to be performed up to 24 weeks from the start of trial treatment)	2029-10 (Recruiting)
NCT03905148	BGB-283 (lifirafenib) and PD-0325901 (mirdametinib) combination	Phase I	RAF dimer inhibitor BGB-283 in combination with MEK inhibitor PD-0325901	105 participants Estimated enrollment of patients with advanced or refractory solid tumors (ovarian and endometrial)	· Adverse events and serious adverse events · Incidence of DLT events and treatment-emergent AEs · Objective response rate	2026-02-28 (Recruiting)
NCT02465060	32 drugs (among them: dabrafenib, trametinib, ulixertinib)	Phase II	Patients with *BRAF* V600E/R/K/D mutation receive dabrafenib and trametinib. Patients with BRAF fusion or *BRAF* non-V600 mutation receive trametinib. Patients with a *BRAF* non-V600 mutation or *BRAF* fusion, or another BRAF aberration receive ulixertinib cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	6,452 participants Estimated participants	· To evaluate the proportion of patients with OR to targeted study agent(s) in patients with advanced refractory cancers/lymphomas/multiple myeloma	2025-12-31 (Unknown status)
NCT03634982	RMC-4630 vociprotafib)	Phase I	Vociprotafib is a SHP2 inhibitor, involved in diverse signalling pathways such as RAS-MAPK.	133 participants Relapsed/refractory solid tumors harboring certain specific mutations/rearrangements that result in hyperactivation of the RAS-MAPK pathway	· Number of participants with AEs · Number of participants with DLTs	2023-05-31 (Unknown status)
NCT04488003	Ulixertinib	II	ERK1/2 kinase inhibitor with potent preclinical activity in BRAF- and RAS-mutant cell lines	101 participants	· Part A: Overall response rate according to RECIST 1.1 (time frame: up to 30 months) · Part B: Progression-free survival according to RECIST 1.1 (time frame: 18 months)	2022-12-21 (Terminated due to enrollment challenges)

These studies are extracted from Clinical Trial (www.ClinicalTrial.gov) on January 31, 2024.
MTD, maximum tolerated dose; RP2D, recommended phase II dose; AE, adverse event; DLT, dose limiting toxicity; ACT, adaptive clinical treatment; OR, objective response; DCB, durable clinical benefit; DLT, dose-limiting toxicity.

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CURRENT EVIDENCE ON BRAF INHIBITORS IN OVARIAN CANCER

Explorations into the dysregulation of the MAPK and phosphoinositide 3-kinase (PI3K) pathways initially concentrated on a single facet of the pathway, specifically targeting patients with incurable solid tumors harboring *BRAF* mutations. This marked the initial foray into understanding the intricate mechanisms of these pathways and their potential implications in cancer therapeutics. In a pivotal development in 2012, Falchook et al. [35] undertook a phase 1 trial aimed at determining the recommended phase 2 dose in patients with BRAF-mutant tumors. This trial included diverse cohorts such as metastatic melanoma, melanoma with untreated brain metastases, and non-melanoma solid tumors. The investigative agent in focus was Dabrafenib (GSK2118436), a potent ATP-competitive inhibitor of BRAF kinase with selectivity for mutant BRAF tumors. The trial enrolled 184 patients, with melanoma being the predominant cohort, and only one patient presented with ovarian cancer. Notably, the solitary patient with BRAF-mutant ovarian cancer, who had not received prior BRAF or MEK inhibitor treatment, exhibited a notable achievement of stable disease with a 28% decrease. This highlighted the potential therapeutic impact of targeting the BRAF pathway in ovarian cancer. Adverse events of grade 2 or higher mainly included cutaneous squamous-cell carcinoma or keratoacanthoma, fatigue, and pyrexia. Dabrafenib demonstrated mild toxicity, with only three grade 2 or higher toxic effects recorded in more than 5% of patients. These findings emphasized the manageable safety profile of dabrafenib. While the study primarily focused on patients with melanoma and brain metastases, a population with historically limited survival, the results were intriguing. All 10 patients in this cohort were alive at the specified juncture, and 2 displayed durable antitumor activity with survival extending beyond 12 months. This highlighted the potential efficacy of dabrafenib, particularly as the first drug of its class to demonstrate activity in treating melanoma brain metastases.

Despite these promising outcomes, the emergence of acquired resistance to dabrafenib necessitated further investigation. This led to a subsequent phase 1 study examining the combination of dabrafenib with the MEK inhibitor, trametinib (GSK1120212) [36]. This combination demonstrated significant improvements in progression-free survival (PFS), suggesting a synergistic effect with BRAF and MEK inhibition.

In 2013, Farley et al. [37] initiated another significant study. This open-label, single-arm phase 2 study focused on selumetinib (AZD6244, ARRY-142886), a potent and selective inhibitor of MEK1/2, in women with recurrent LGSOC or peritoneal carcinoma. The rationale behind this study was grounded in the high frequency of mutational alterations in the MAPK pathway observed in low-grade serous ovarian cancers. The study enrolled 52 patients, and its conclusion revealed that 8 patients (15%) exhibited a best response of complete or partial response, while 65% displayed stable disease. The median PFS was reported as 11.0 months, and the 2-year overall survival (OS) was 55%, showcasing substantial activity in recurrent low-grade serous tumors. Crucially, this approach presented favorable tolerability compared to cytotoxic regimens, making selumetinib an appealing candidate for further exploration in low-grade serous ovarian cancers.

The intricate dynamics of the PI3K and MAPK pathways, known for their intricate interplay and convergence at multiple points, underscore the need for a nuanced therapeutic approach. The premise lies in the understanding that inhibiting one pathway might trigger compensatory activation of the other. Recognizing this intricate relationship, researchers have delved into the potential synergies of dual blockade, utilizing both PI3K and MEK

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inhibitors. This novel approach has sparked interest, particularly in patients with tumors characterized by genetic aberrations in these pathways.

In a pivotal phase Ib dose-escalation study conducted in 2015 by Bedard et al. [38], the focus was on combining the oral pan-PI3K inhibitor, buparlisib (BKM120), with the oral MEK1/2 inhibitor, trametinib (GSK1120212). This meticulously designed study, with its open-label, dose-finding approach, involved dose escalation followed by an expansion part. The patient cohort was strategically selected, encompassing those with RAS- or BRAF-mutant non–small cell lung, ovarian, or pancreatic cancer.

Buparlisib (BKM120) emerged as a potent and highly specific oral pan-class I PI3K inhibitor, with a notable characteristic of sparing mTOR and Vps34 kinases. On the other hand, trametinib (GSK1120212; Mekinist) played its role as a reversible, highly selective allosteric inhibitor of MEK1/MEK2 activation and kinase activity.

The primary objectives of this groundbreaking study were 2-fold. Firstly, the focus was on determining the maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D) for the combination of buparlisib and trametinib when administered orally to adult patients with selected advanced solid tumors. Subsequently, the study aimed to evaluate the safety and preliminary antitumor activity of the established MTD and/or RP2D in patients with advanced non-small cell lung cancer (NSCLC), ovarian cancer, or pancreatic cancer harboring *RAS* or *BRAF* mutations during the expansion phase of the study, as identified by the clinicaltrials.gov registry with identifier NCT01155453. The initial MTD was pegged at 70 mg buparlisib and 1.5 mg trametinib, but this dose underwent revision during RP2D due to a high incidence of adverse events, primarily stomatitis and rash. Ultimately, the dose chosen for the dose expansion phase was established at 60 mg buparlisib and 1.5 mg trametinib. Of the 21 patients with ovarian cancer, 4 participated in the dose-escalation phase, and 17 entered the dose-expansion phase. These patients, with a substantial prior treatment history averaging 3 prior lines of therapy, demonstrated a noteworthy overall response rate (ORR) of 29%, with 1 confirmed complete response and 5 confirmed partial responses. This response rate further improved to 50% at RP2D, with 1 confirmed complete response and 3 confirmed partial responses. Additionally, 2 patients (10%) showcased a best target lesion reduction of at least 30%, although not subsequently confirmed. The median PFS for all patients with ovarian cancer was a commendable 7 months (95% confidence interval=4.2–12.9). As of the data cutoff date, the median OS had not been reached, with the majority (18 patients, 86%) of ovarian cancer patients still alive. This phase 1b study not only established the safety of combining the oral pan-PI3K inhibitor buparlisib and the oral MEK1/2 inhibitor trametinib but also identified a robust RP2D. This promising combination exhibited notable antitumor efficacy, particularly for patients with RAS/BRAF-mutant ovarian cancer.

A fascinating observation surfaced regarding patients with KRAS-mutant ovarian cancer, displaying a higher ORR compared to a single-agent MEK inhibitor in the same population. This observation opens intriguing possibilities, suggesting that PI3K and MEK inhibitor combination therapy might be more active in specific KRAS-mutant genotypes, such as *G12V*. This underscores the importance of recognizing the nuanced biology within the KRAS-mutant subgroup, hinting at potential differential responses to the same treatment.

While these findings are certainly promising, it's essential to approach them with caution, given the non-statistical significance and the study's limited sample size. Numerous questions

arise, prompting the need for further investigation. These include exploring the role of *KRAS* mutation as a predictive biomarker in low-grade serous ovarian cancer and understanding the potential benefits of MEK inhibitor therapy or PI3K and MEK inhibitor combinations in other histologic subtypes of ovarian cancers with *RAS* mutations. The study provides a crucial foundation, but additional data from larger-scale studies are imperative to draw definitive conclusions and unlock the full potential of this innovative therapeutic approach.

In the same year, Hyman et al. [39] conducted a groundbreaking histology-independent phase 2 "basket" study examining the use of vemurafenib in *BRAF* V600 mutation-positive non-melanoma cancers. Their comprehensive findings emphasized the crucial role of histologic context in determining responses to *BRAF* V600-mutated cancers. Despite observing partial responses and tumor regression in ovarian cancer patients, the study's limited sample size, particularly in the ovarian cancer subgroup, with fewer than 27 patients, underscores the need for cautious interpretation. It became evident that *BRAF* V600-mutated tumor types exhibit varied responses to BRAF-targeted therapy, challenging the notion of solely relying on molecular nosology. Pending more definitive data, these findings present a potential therapeutic avenue, especially for clinicians using tumor genomic profiling, though interpretation must be approached with caution.

In 2018, a noteworthy phase Ib dose-escalation study with binimetinib (MEKi) in combination with weekly paclitaxel for platinum-resistant or refractory epithelial ovarian cancer reported an overall response rate of 14% [40]. However, the subsequent multinational, randomized phase III trial on binimetinib (MILO/ENGOT-ov11 ClinicalTrials.gov identifier: NCT01849874) [41], in which Grisham participated, did not demonstrate a significant difference in the primary endpoint of PFS compared to physician's choice chemotherapy in patients with recurrent or persistent LGSOC. Despite the early closure of the study, binimetinib displayed activity in LGSOC across secondary efficacy endpoints. The study did not reach its primary PFS endpoint, showing median PFS of 9.1 months for binimetinib and 10.6 months for physician choice, though secondary efficacy endpoints like overall response rate, duration of response, and OS were comparable between the 2 groups. While the trial did not meet its primary objective, binimetinib remains a viable treatment option for LGSOC.

Subsequently, a randomized phase II/III trial [42] presented at European Society for Medical Oncology 2019 indicated that the MEK inhibitor Trametinib offers significant benefits in OS, overall response rate, and PFS for women with recurrent low-grade serous ovarian cancer compared to physician's choice standard of care. This study showcased trametinib's efficacy, with patients experiencing a median PFS of 13.0 months compared to 7.2 months in the control arm. This underscores trametinib's potential as a robust treatment option for recurrent low-grade serous ovarian cancer, especially considering its efficacy in patients with a history of multiple prior chemotherapies, offering a notable advantage over previous studies like the binimetinib trial (MILO/ENGOT-ov11) [41], which was limited to patients with a maximum of 3 prior lines of chemotherapy. The apparent PFS benefit of trametinib regardless of *KRAS*, *BRAF*, or *NRAS* mutation status suggests that MAPK pathway activity is important, even in the absence of a canonical mutation. This benefit could be due to less common gene mutation events or to activation of the pathway at the epigenetic, transcriptional, or post-transcriptional levels. By comparison, the MILO/ENGOT-ov11 study reported improvements in PFS and ORR in the KRAS-mutant group compared with the wild-type KRAS group of patients given binimetinib; however, the study did not directly address whether this mutation was predictive. Despite differences in inclusion criteria, both studies highlight the promising

efficacy of MEK inhibitors in the treatment landscape, with trametinib demonstrating significant clinical benefits in patients with recurrent low-grade serous ovarian cancer.

In 2020, Subbiah et al. [43] create a histology-independent, *BRAF* V600E-mutant basket study with vemurafenib that showed differential activities between histologies. In this study, melanoma and papillary thyroid cancer were excluded because previous studies had already shown that they were responsive to BRAF inhibition in those with the mutation [44,45], therefore they focused on different histologies and found similar efficacy results. But this study has some important limitations. Notably, it was launched before numerous studies demonstrated that the combination of BRAF and MEK inhibition is often superior to BRAF inhibition alone [46,47]. Therefore, the efficacy reported here may represent a lower bound estimate of what could have been achieved if the same population had been treated with a RAF/MEK combination, although this remains unproven. Therefore, we can only infer that these data further contribute to our understanding of the therapeutic relevance of BRAF inhibition in *BRAF* V600 mutated cancers.

In the same year, the American Society of Clinical Oncology published the results of a phase I study on lifirafenib [48], an experimental and reversible inhibitor of *BRAF* V600E, wild-type A-RAF, B-RAF, C-RAF and EGFR, conducted on adult patients with advanced/metastatic solid tumors carrying a *B-RAF*, *N-RAS* or *K-RAS* mutation. Lifirafenib demonstrated an acceptable benefit-risk profile given the safety outcomes and responses in patients with *BRAF* V600 mutated solid tumors, including melanoma and LGSOC, as well as K-RAS mutated NSCLC and endometrial cancer. Lifirafenib could potentially benefit patients with MAPK pathway-associated kinase alterations in addition to *BRAF* V600 mutations, including activated K-RAS. Further studies on the safety/efficacy of lifirafenib as monotherapy or in combination are needed, in fact enrollment has recently begun in a phase I/II study of lifirafenib in combination with a MEK inhibitor in patients with tumors with *BRAF* mutations and RAS (ClinicalTrials.gov identifier: NCT03905148).

The MILO/ENGOT-ov11 study was the largest randomized study of patients with LGSOC but it suffered a premature closure because PFS of the binimetinib cohort (which was the primary end point) was superior to that of chemotherapy cohort. Although the primary endpoint of this study was not met, the data generated were further analyzed in 2023 [49] evaluating the association between MAPK pathway alterations and patient outcomes. Indeed, this post hoc tumor tissue analysis showed higher response rates and significantly longer PFS in patients with LGSOC treated with binimetinib and, to a lesser extent, in those treated with physician-chosen chemotherapy, who had alterations of the MAPK pathway. These findings provide compelling evidence of how the altered state of the MAPK pathway has prognostic implications for patients with LGSOC. Somatic tumor testing should be considered for all patients with recurrent LGSOC to aid in clinical decision making regarding the relative benefit of systemic therapy and used as a stratification factor in future prospective studies of LGSOC.

Recently, the preliminary results of the ENGOT-ov60/GOG-3052/RAMP 201 part A (NCT04625270) reporting data combination between avutometinib and defactinib were reported at the 2024 Society of Gynecologic Oncology meeting. The study showed that 45% of patients (n=29) achieved a confirmed responses rate. *KRAS* mutations correlated with response to treatment. The response rate was 60% and 29% in patients with and without *BRAF* mutation, respectively [50]. Another interesting ongoing study is the ENGOT-GYN2/GOG-3051/BOUQUET project [51]. The phase II BOUQUET is a biomarker-directed platform

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study, investigating different approaches in rare ovarian cancer types [51]. Preliminary data on the cobimetinib arm were presented. Data of 20 heavily pretreated patients showed interesting results in patients with low-grade serous ovarian cancer and mesonephric-like adenocarcinoma. In this group the objective response rate and disease control rate was 33% and 89%, respectively [51]. All these results contribute to advancing our understanding of tailored therapeutic approaches for distinct ovarian cancer subtypes, encouraging further research to refine treatment paradigms and improve outcomes. Ongoing studies (including the DETERMINE trial) will clarify the value of different combination in this setting [52].

CONCLUSIONS

A conventional clinical trial design approach may not be feasible to demonstrate the effectiveness of a targeted agent against rare molecular mutations in each cancer type. Therefore, it would be appropriate to set up clinical studies by classifying tumors based on their genomic sequencing, rather than on the basis of the organ of origin. Nowadays most of clinical trials (ClinicalTrials.gov) are targeted to relapsed/refractory solid tumors harboring certain specific mutations/rearrangements that result in hyper-activation of the RAS-MAPK pathway. The partial results (because many studies are still in the recruitment phase) of these trials confirm the activity of MAPK in ovarian cancer and suggest that MEK inhibitors might be appropriate for the treatment of this malignancy.

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