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Systematic review and meta-analysis of the efficacy of dabrafenib and trametinib in the multi-modal treatment of anaplastic thyroid cancer

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Abstract

Objective

This study analyses the current literature to evaluate the effectiveness of dabrafenib and trametinib in the multi-modal treatment of anaplastic thyroid cancer (ATC).

Methods

A systematic review and meta-analysis of the literature were undertaken. The primary endpoint measured was overall response rate defined by the RECIST v1.1 guidelines. Secondary endpoints were 12-month overall survival (OS), median OS and progression-free survival (PFS).

Results

Of 656 identified reports, 8 studies were included which featured 95 patients (median age 68.5 years, 46% male). Median follow-up period of 11.8 months with a 12-month OS of 51%. Median OS was 10.4 months. Progression-free survival (PFS) was 6.5 months. Overall response rate was 71%. 65 patients exhibited a partial or complete response in radiological tumour size. Side effects compared favourably compared to other kinase inhibitors.

Conclusion

Dabrafenib and trametinib exhibit a promising tumour response with a tolerable side profile. BRAF/MEK inhibitors continue to provide robust responses in BRAF-mutated ATC. The heterogeneity and lack of controls in included studies limits the confidence in the conclusions drawn.

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MeSH keywords:

Systematic Review

Meta-Analysis

Thyroid Carcinoma, Anaplastic

Treatment Outcome

Mitogen-Activated Protein Kinase Kinases

Proto-Oncogene Proteins B-raf

Therapeutics

Introduction

Anaplastic thyroid cancer (ATC) is an aggressive form of thyroid cancer with poor prognostic outcomes. Despite its rarity, accounting for only 2% of all thyroid cancers, it is responsible for around 50% of thyroid cancer-associated deaths[1,2,3]. This is due to rapid progression of the disease with metastatic status at the onset of diagnosis [1,4]. Historically, ATC was associated with a mere 4-month median overall survival[5].

Treatment options for ATC encompass surgical intervention, radiotherapy, chemotherapy, and novel adjuvant therapies such as the serine/threonine-protein kinase B-Raf (BRAF) and mitogen-activated protein kinase kinase (MEK) inhibitors [6]. While surgical intervention can be effective for localised disease [3], the majority of patients present with metastatic disease at diagnosis, limiting the impact of surgery alone[1,4]. Combined modalities, often integrating surgery with other treatments, prove to be significantly more effective than surgery in isolation[6,7]. This is demonstrated by a median OS figure of 6.6 months with surgery alone compared to 9.6 months with additional adjuvant therapy [6]. Radiotherapy has an important role in treating ATC, but treatment strategies involving this are usually

combined with surgery or further chemotherapy [7,8]. Radiotherapy alone is commonly unable to control disease progression [7]. This is reflected in overall survival figures, where patients receiving surgical intervention and radiotherapy demonstrate a median overall survival of 10.7 months, compared to 3.9 months with radiotherapy alone[9]. Notably, BRAF/MEK inhibitors have revolutionised the prognostic landscape of ATC, attaining the status of standard care in current US guidelines.

The role of traditional chemotherapy in treating ATC has been limited owing to primary chemoresistance and rapid disease progression [4]. This had led to the subsequent utilisation of BRAF/MEK inhibitors[4]. These inhibitors target protein kinase pathways specific to cancerous cells[10]. The combination of the kinase inhibitors dabrafenib and trametinib has been explored further in patients with ATC. Dabrafenib acts as a BRAF inhibitor whereas trametinib is a mitogen-activated protein kinase (MEK) inhibitor [4,11,12]. Dabrafenib and trametinib, proven effective in increasing overall survival in metastatic melanoma and non-small cell lung cancer [12], were subsequently applied to patients with BRAF-mutated ATC. Following successful phase II clinical trials, this combination has gained recognition and approval from the FDA as a recommended treatment regimen [13].

Methods

Search and screening

This systematic review adhered to PRISMA guidance, according to a prospectively registered protocol on PROSPERO. On 2 July 2023, MEDLINE, PubMed, Scopus, Embase (via OVID), Web of Science and Google Scholar were searched for the following: (“anaplastic thyroid cancer”) AND (“dabrafenib”) AND (“trametinib”). Abstract and full text screening were undertaken by three

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researchers independently and duplicates were removed. The following inclusion and exclusion criteria were employed:

(1) Publication of full text in English language; (2) primary research study; (3) primary pathology of anaplastic thyroid cancer; (4) dabrafenib and trametinib treatment; (5) reported outcomes; (6) more than 3 participants. There were no restrictions on participant characteristics, cancer grade or other neo-adjuvant and adjuvant treatments. The exclusion criteria consisted of non-evidence-based studies, reviews, evaluations, or case reports with $n \leq 3$.

Data extraction and analysis

Data was extracted into Microsoft Excel TM for processing and analysis. All three researchers undertook blinded data extraction for the included studies. A second round of blinded extraction was conducted, reviewing any discrepancies between the first and second round. The primary endpoint was overall response rate (ORR), defined as a complete or partial response in radiological tumour size in accordance with the Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 guidelines [14]. Secondary endpoints were 12-month overall survival (OS), median OS and median progression-free survival (PFS). Additional data gathered included country of origin, patient recruitment period, total number of patients in the trial, treatment details, median follow-up duration, patient demographics and adverse side effects.

Risk of bias were appraised with the QUADAS-2 framework by one researcher, with a second researcher validating each appraisal [15]. For studies exhibiting Kaplan-Meier plots without reporting figures for median OS or 12-month OS, interpolation was conducted with WebPlotDigitizer (version 4.6.0; Ankit Rohatgi, Pacifica, California, USA). Quantitate data between comparable studies were selected for inclusion in meta-analysis.

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Meta-analysis was carried out using R (version 4.3.0; R Foundation for Statistical Computing, Vienna, Austria) via the "metfor" package and "metaprop" function. Due to the heterogeneity in included studies, a random effects model was employed, with the inverse variance weighting method used to pool effect sizes. The effect size measure used was proportions, with the percentages for both outcomes expressed as a proportion. Knapp-Hartung adjustments were made to calculate the confidence interval of pooled effect sizes, reducing the chance of false positives. Higgins and Thompson's I^2 statistic was used to measure heterogeneity. Prediction intervals were also included.

Results

The undertaken literature search and screening process are summarised in Figure 1. Out of the 656 initially identified reports, 8 studies were included, featuring 95 patients (median age 68.5 years, 46% male). Patient characteristics and data outcomes are shown in Table 1 and 2, respectively. Median follow-up duration was 11.8 months with a 12-month OS of 51%. Median OS was 10.4 months. Progression-free survival (PFS) was 6.5 months. The ORR was 71%, calculated using the random effects model. 65 patients exhibited a partial or complete response in radiological tumour size with an NNT of 1.52. Side effects, reported in 5 studies with 73 total patients, compared favourably to other kinase inhibitors. Frequency of side effects are shown in Table 3 and 4. Side effects that were very common included: pyrexia, fatigue, nausea, decreased appetite, anaemia, diarrhoea, constipation, rash, dyspnoea, pneumonia, chills, dizziness and hyponatremia. Common side effects included: headache, hypertension, hypoalbuminemia, hypotension, anorexia, dysphagia, vomiting and weight loss. Pyrexia was the most common side effect reported (38%), followed by fatigue (34%) and nausea (32%). Side effects tabulated with an incidence of 0 indicates the side effect was not reported.

Forest plots for 12-month OS and ORR are shown in Figure 2 and 3, respectively. Heterogeneity I^2 was calculated to be 0% for both ORR and 12-month OS. Despite strong heterogeneity in the data, the likely explanation is the small number of included studies causing an underestimate of I^2. In a meta-

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analysis with 7 studies and 80% true heterogeneity, I^2 is underestimated by around 28%. With a median I^2 estimate in most meta-analyses of 21%, this can easily generate a 0 value for I^2 [16].

Risk of bias judged with QUADAS-2 was moderate, as illustrated by Figure 4. Although concerns were highlighted regarding the applicability of study 17, it is a pivotal paper in the literature, so it was ultimately included.

Median OS was calculated from the median of reported median OS from available studies. PFS was calculated from the weighted mean of median PFS from available studies. NNTs, defined as the number of patients that were treated to obtain one partial or complete response, was calculated through weighted means.

Discussion

According to the SEER national cancer database, there has been no significant improvement in overall survival for anaplastic thyroid cancer patients from 1986 to 2015 [25]. The introduction of molecular classification for ATC as the standard in 2014 has played a pivotal role, leading to an increased utilisation of targeted therapies over time [26,27]. The subsequent adoption of BRAF/MEK inhibitors has notably improved survival outcomes, establishing it as the current standard of care in the USA.

Although several studies have published their results concerning the efficacy of BRAF/MEK inhibitors on patients with ATC, to our knowledge this is the first systematic review and meta-analysis of dabrafenib and trametinib in the treatment of anaplastic thyroid cancer. By collating the highest power studies from the literature at present, this data provides a snapshot of where we presently stand with this selective targeted therapy. Both clinicians and policy makers may refer to this data when

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making decisions that necessitate statistical comparison of current or emerging therapies to the current 'standard' of care.

By conducting this review, we aim to inform policymakers on the efficacy of this treatment. This effort holds the potential to expand approval of dabrafenib and trametinib in regions where they are not currently licensed for ATC. With the amalgamated data we present, policymakers can conduct reliable and comprehensive cost-benefit analysis for this expensive therapy, weighing its potential advantages against alternative treatment modalities. Policymakers must carefully deliberate whether reallocating funds to this therapy represents the most efficient use of resources, or if these funds could yield greater benefits when directed towards other stages or aspects of care for this condition. These decisions may pave the way for expanding the approval of dabrafenib and trametinib to include anaplastic thyroid cancer in the United Kingdom, as current licensure restricts their usage to BRAF V600 mutated melanoma and non-small cell lung cancer.

Tumour response

Utilising the random-effects model, the pooled overall response rate (ORR) in the primary tumour was 71%, indicating dabrafenib and trametinib is effective at halting or reducing the primary tumour burden. In certain cases, this was enough to enable surgical intervention on previously inoperable cancer, contributing to improved outcomes. Studies investigating various targeted therapies, including tyrosine kinase inhibitors and other BRAF inhibitors, reported an ORR of approximately 30%, with some novel therapies showing no significant response at all [28].

Survival rates

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The pooled 12-month OS was 51%, and the median OS was 10.4 months. In a single-institution cohort study of 152 patients, the 12-month OS on multi-modal therapy for ATC was reported as 59% [26]. Although multi-modal treatment with dabrafenib and trametinib shows promise in its efficacy on tumour response, it does not offer a significantly greater survival outcome compared to the use of other BRAF/MEK inhibitors in its place. The heterogeneity in the data obfuscates our outcomes, mainly due to the absence randomised controlled trials and a low number of eligible studies.

Side effects

Medication safety is a focal point in novel drug development and integration into clinical practice. Effective side effect management is crucial for therapy continuation. This meta-analysis revealed that almost all patients with reported side effects (n=73) experienced adverse events, experiencing mostly grade 1 or 2. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE). The most common side effects were pyrexia (38%) followed by fatigue (34%), nausea (32%), decreased appetite (23%), anaemia (22%), dyspnoea (22%), diarrhoea (18%), constipation (14%) and rash (14%). Grade 1 and 2 adverse events are generally manageable, with medical treatment available for common adverse effects such as pyrexia, fatigue, nausea, diarrhoea, and constipation. Grade 3 and 4 adverse events often require monitoring measures. In the included studies, patients sustaining grade 3 or 4 adverse events often needed a dose reduction or cessation of BRAF/MEK treatment.

Table 5 summarises adverse events from comparable studies in the literature. Temporary dose interruptions of dabrafenib and trametinib were reported as effective management strategies for medication-induced pyrexia, and similar control measures were observed for medication-induced hypertension and proteinuria [29,30]. In a phase III trial of dabrafenib and trametinib for unresectable

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metastatic melanoma, 98% of the cohort experienced adverse events but few were reported as grade ≥3 or more. Despite this, 18% adverse events led to treatment discontinuation [34].

The side effect profile for dabrafenib and trametinib seems promising when compared to other kinase inhibitors trialed for ATC. However, it is important to consider other therapies' contributions to adverse effects, as patients receiving chemotherapy and radiotherapy may experience overlapping side effects. Since it was at the investigators discretion to decide if an adverse event was due to dabrafenib and trametinib, there may have been unidentified reporting bias. Notably, in the phase II ROAR basket trial, 36 patients experienced adverse events but only 27 were said to be attributed to dabrafenib and trametinib. The adverse events were reported for all 36 patients without isolating those that were due to dabrafenib and trametinib [17].

Costs

The treatment regime of dabrafenib 150mg twice daily and trametinib 2mg once daily costs £2520 per week at list price [35]. Considering these costs at The National Institute for Health and Care Excellence (NICE) reported market value, the range of dabrafenib and trametinib treatment for the phase II ROAR basket trial would be £10'950-£689'850. Whilst specific discounts are commercial in confidence, the high costs of dabrafenib and trametinib should be considered when comparing healthcare economics with other therapies on the market.

Limitations

This review and analysis faced several limitations:

(1) Limited number of published studies.

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(2) Small sample sizes in included studies, making data outcomes prone to variability [26].

(3) Predominance of case series over randomised control trials in included studies [3].

(4) Many patients experienced treatment interruptions and dose reductions within each study, affecting the reliability of drawn conclusions.

(5) High variability in treatment duration, ranging from weeks to many months. Undertreatment could obfuscate any true effect dabrafenib and trametinib may have had. It could also under report potential side effects.

(6) There was high variability in the multi-modal therapies each patient received. Many permutations of treatment were seen which likely skewed outcomes. For example, Chang and colleagues found that in ATC patients, surgery before dabrafenib and trametinib had a significantly better overall survival when compared to no prior surgery[23].

(7) Reporting bias in several studies due to missing outcome data (Table 2).

(8) Exclusion of the largest BRAF-mutated ATC paper in the literature (Zhao et al., 2023) because BRAFi/MEKi treatment was grouped, and isolated combination therapy of dabrafenib and trametinib was not reported.

While we recognised the limitations inherent in our study from the outset, the rationale for conducting this review remained strong. To date, there has been a lack of consolidation of the diverse data surrounding this emerging therapy. While future meta-analyses will undoubtedly be necessary as additional trials are conducted, synthesising the existing data provides a less biased yet valuable foundation for understanding the treatment landscape. Despite its limitations, this approach offers more informed insights than having no data aggregation at all.

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Conclusion

The conducted meta-analysis reports that dabrafenib and trametinib exhibit a promising tumour response with a well-tolerated side-effect profile. Given the poor prognosis and rarity of ATC, improvements in overall survival, overall response rate and progression-free survival are significant in the context of this disease. Given the often palliative nature of ATC diagnoses, monitoring side effects from targeted therapies is crucial, as it directly impacts patient comfort and medication compliance. In this meta-analysis, multiple factors limit the confidence in conclusions. These include the inherent heterogeneity amongst studies, selection bias and reliance on data derived from case studies rather than controlled clinical trials. The rarity of BRAF-mutated ATC poses a challenge in designing robust clinical trials, as clinicians would ethically hesitate to randomise these patients to anything other than BRAF/MEK inhibitors. To determine the true effect of dabrafenib and trametinib on morbidity and mortality, a global effort is necessary to include and report studies with substantial statistical power. Continued reporting of outcomes from clinical trials and cohort studies remains paramount to further build upon the already promising results. In the interim, it would be beneficial to delve into additional research and experimentation concerning the side effects of these selective inhibitors. Are there strategies available to mitigate these side effects, consequently enhancing long-term adherence to treatment and maximising efficacy? Despite the historically dire prognosis associated with anaplastic thyroid cancer, the advent of BRAF/MEK inhibitors marks a significant stride in the development of therapeutics for this relentless disease, offering an optimistic outlook for the treatment landscape to come.

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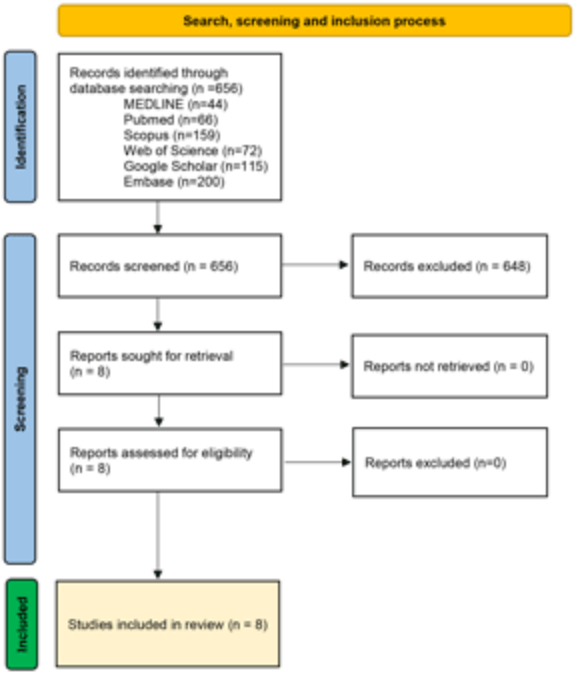

Figure 1. PRISMA flowchart

Illustrating the literature search, screening process, and articles included in this review. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta Analyses.

MEDLINE = Medical Literature Analysis and Retrieval System Online

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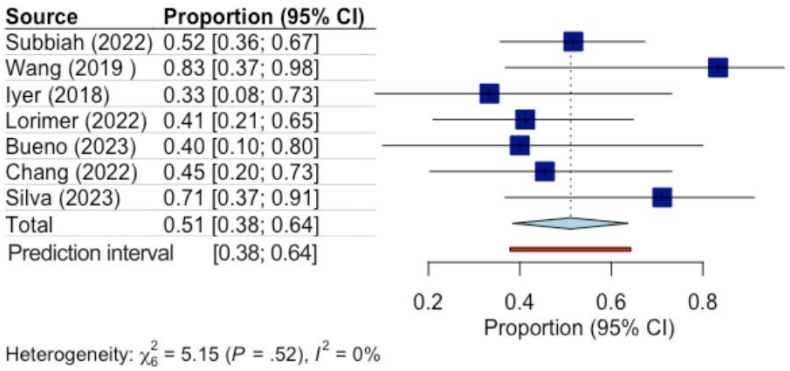

Figure 2. 12-month OS forest plot

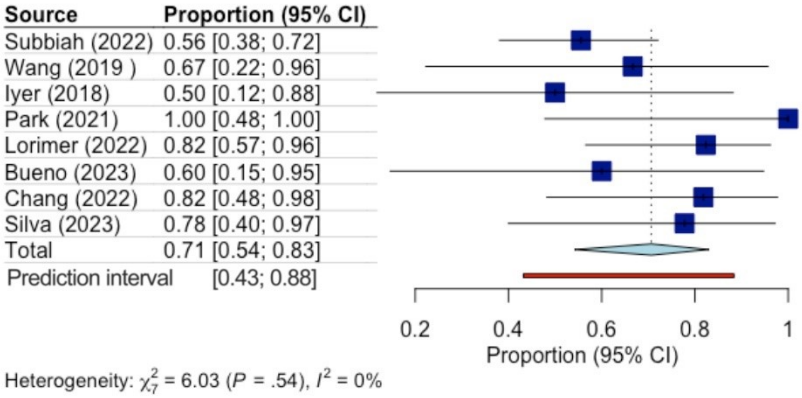

Figure 3. ORR forest plot

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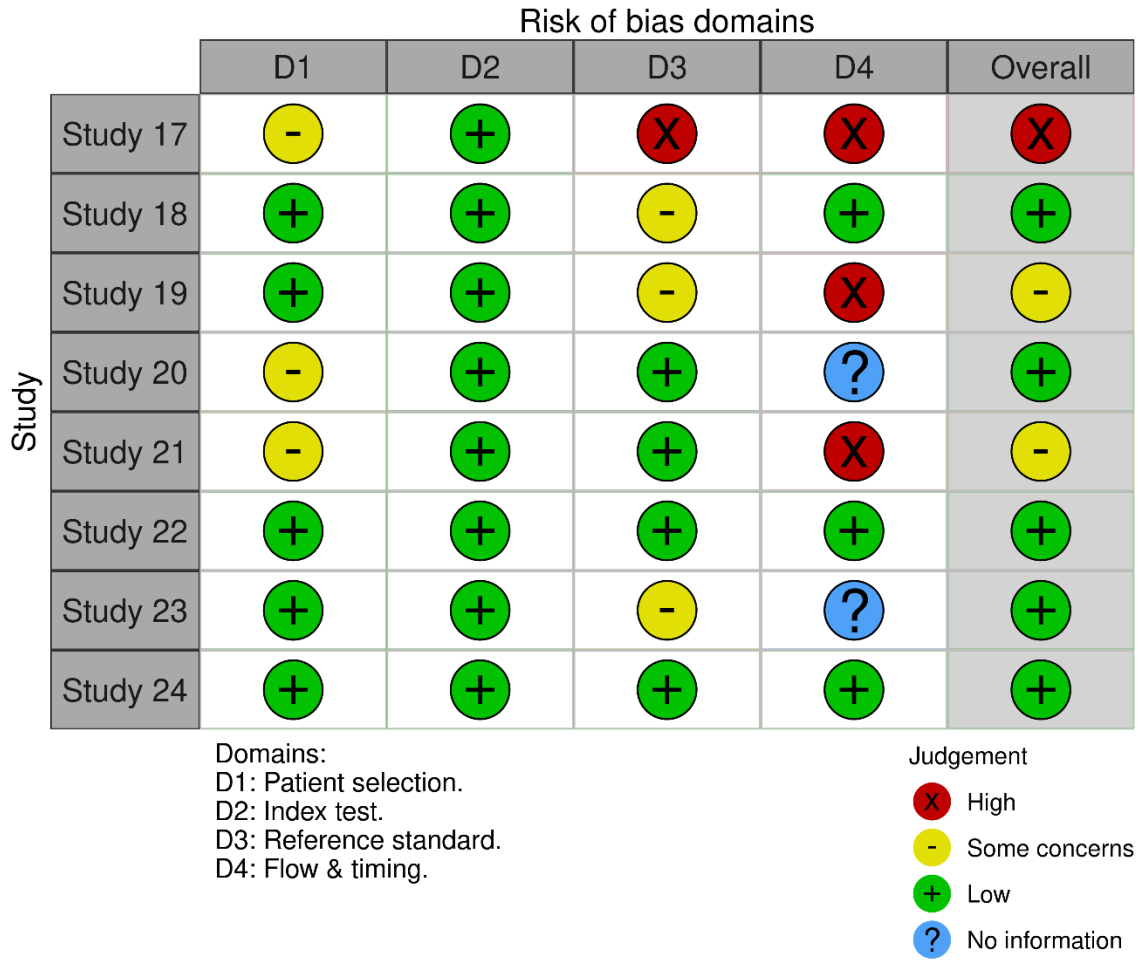

Figure 4. Risk of bias appraisals

Appraised with the QUADAS-2 framework. QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies 2; RoB = risk of bias.

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Table 1. Patient characteristics

Study details			Patient flow		Details of interventions	Follow-up	Demographics				
Citation	Country where study was conducted	Recruitment period	Total number of patients included in trial on D+T	Number of patients who withdrew from study	Details of dabrafenib and trametinib treatment	Median follow-up duration (months)	Average age (years)	Number of males	% of males	Number of females	% of females
Subbiah et al 2022 (17)	International	2014 to 2018	36	6	Dabrafenib 150 mg twice daily plus trametinib 2 mg once daily until disease progression, unacceptable toxicity, or death.	11.1	71	16	44	20	56
Wang et al 2019 (18)	South Korea	2017 to 2018	6	0	Dabrafenib 150 mg twice daily plus trametinib 2 mg once daily (some plus Pembrolizumab (various doses))	15	59	2	33	4	66

Iyer et al 2018 (19)	USA	2015 to 2016	6	0	5 out of 6 patients: Dabrafenib 150 mg twice daily plus trametinib 2 mg once daily. 1 out of 6 patients: Dabrafenib 75 mg twice daily plus trametinib 2 mg once daily	11.8	67	NA	NA	NA	NA
Park et al 2021 (20)	South Korea	1995 to 2020	5	0	Dabrafenib 150mg twice daily plus Trametinib 2mg once daily	NA	66	NA	NA	NA	NA
Lorimer et al 2023 (21)	UK	2018 to 2021	17	1	Dabrafenib 150 mg twice daily plus trametinib 2 mg once daily until disease progression, unacceptable toxicity, or death.	12	68	9	53	8	47
Bueno et al 2023 (22)	Argentina	2018 to 2021	5	0	Dabrafenib 150 mg twice daily plus trametinib 2 mg once daily until disease progression, unacceptable toxicity, or death.	5	70	3	60	2	40
Chang et al 2022 (23)	Taiwan	2000 to 2020	11	0	Dabrafenib 150 mg twice daily plus trametinib 2 mg once daily	3.6	70	5	46	6	54

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Silva et al 2023 (24)	Portugal	2018 to 2022	9		Dabrafenib 150 mg twice daily plus trametinib 2 mg once daily until disease progression, unacceptable toxicity, or death.	17.7	77	4	44	5	56

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Table 2. Data outcomes of the included studies.

Citation	Overall survival			Disease progression	Response to treatment			Adverse Events	Numbers needed to treat
	Deaths	Median OS (months)	12 month OS (%)	Number of patients with outcome	Number of complete or partial responses	stable disease	median PFS (months)	Number of patients	The number of patients you need to treat in order to have one partial or complete response
Subbiah et al 2022 (17)	24	14.5	51.7	22	20	11	6.7	36	1.8
Wang et al 2019 (18)	2	not reached	83	2	4	NI	Not reached	NI	1.5
Iyer et al 2018 (19)	5	9.3	33	1	3	2	5.2	≥4	2
Park et al 2021 (20)	1	NA	NA	0	5	0	Not reached	NI	1
Lorimer et al 2023 (21)	10	6.9	Not reached. Kalpan Meier curve predction was 41%	3	14	0	4.7	≥7	1.21
Bueno et al 2023 (22)	NA	not reached	40	NI	3	1	13.8	5	1.67

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Chang et al 2022 (23)	NA	10.4	45.5	2	9	NI	7.4	NI	1.22
Silva et al 2023 (24)	NA	15.8	71	NI	7	NI	9	≥5	1.29

OS: overall survival

PFS: progression-free survival

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Table 3. Side effect heat map

Side effects	Incidence (%)							
Anaemia	36	19	0	0	0		0%	
Anorexia	0	13	0	80	0			
Bleeding	0	6	0	0	0			
Chills	22	0	0	0	0			
Constipation	22	6	12	0	0			
Decreased appetitie	33	0	29	0	0			
Depression	0	0	0	20	0			
Diarrhoea	19	13	18	20	0			
Dizziness	22	0	0	0	0			
Dry skin	0	0	24	0	0			
Dysphagia	17	0	0	0	0			
Dyspnoea	25	0	41	0	0			
Elevated ALP	0	6	0	0	0			
Eye symptoms	0	0	18	0	0			
Fatigue	33	25	35	60	0			
Hand-foot skin reaction	0	19	0	0	0			
Headache	19	0	0	0	0			
Hepatotoxicity	0	0	0	40	0			
Hypercalcemia	0	6	0	0	0			
Hyperglycaemia	0	0	0	20	0		40%	
Hypertension	0	6	6	0	56			
Hypoalbuminemia	19	0	0	0	0			

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Hyponatremia	22	19	0	0	0			
Hypotension	17	0	0	20	0			
Hypothyroidism	0	13	0	0	0			
Increased Blood AP	17	0	0	0	0			
Low mood	0	0	18	0	0			
Lower extremity oedema	0	13	0	0	0			
MSK pain	0	0	12	0	0			
Nausea	33	25	24	60	0			
Oral mucositis	0	0	24	0	0			
Pneumonia	25	0	0	0	0			
Pyrexia	47	6	24	20	56			
Rash	28	0	0	0	0			
Subclavian vein thrombosis	0	0	0	20	0			
Transaminitis	0	6	0	0	0			
Upper GI bleeding	0	0	0	20	0			
Vomiting	17	13	0	0	0			
Weight loss	0	19	0	40	0		80%	
	Subbiah 2022	Iyer 2018	Lorimer 2023	Bueno 2023	Silva 2023			

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Table 4. Pooled side effect incidence

Side effect	Incidence (n)	Incidence (%)
Pyrexia	28	38
Fatigue	25	34
Nausea	23	32
Decreased appetitie	17	23
Anaemia	16	22
Dyspnea	16	22
Diarrhea	13	18
Constipation	10	14
Rash	10	14
Pneumonia	9	12
Chills	8	11
Dizziness	8	11
Hyponatremia	8	11
Headache	7	10
Hypertension	7	10
Hypoalbuminemia	7	10
Hypotension	7	10
Anorexia	6	8
Dysphagia	6	8
Increased Blood AP	6	8
Vomiting	6	8
Weight loss	5	7

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Table 5. SIde effect incidence from various studies

NSCLC: Non-small cell lung carcinoma

ATC: Anaplastic thyroid cancer

Study type	Population	Cancer	Therapeutic	Reported side effects	Reference
Multi-trial analysis	1076	NSCLC and melanoma	Dabrefnib and trametinib	Pyrexia (61.3%)	(29)
Meta-analysis	176	ATC	Lenvatinib	Hypertension (56%) Proteinuria (32.6%) Fatigue (32%)	(30)
Phase II trial	20	ATC	Sorafenib	Rash (65%) Fatigue (60%) Weight loss (60%) Diarrhoea (35%) Hypertension (20%)	(31)
Phase II trial	15	ATC	Pazopanib	Fatigue (73%) Anorexia (53%) Hypertension (53%) Diarrhoea (47%) Nausea (40%)	(32)

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Phase II trial	71	ATC and medullary thryoid cancer	Sunitinib	Fatigue (27.8%) Mucosal (9.9%) Cutaneous toxicity (18.3%) Cardiac event (14.1%) Death (7.5%)	(33)
Phase III trial	559	Unresectable or metastatic melanoma	Dabrafenib and Trametinib	Pyrexia (58%) Nausea (37%) Diarrhoea (36%) Fatigue (35%) Headache (35%) Chills (34%)	(34)

Summary

- BRAF/MEK inhibitors are effective in treating BRAF mutated cancers
- Dabrafenib and trametinib is effective at reducing tumour burden
- Side effects are tolerable in comparison to similar therapies
- Almost all patients experienced side effects, mostly manageable
- High costs need to be considered in this drug
- Clinical Relevance: analysing efficacy and side effects of recently FDA approved dabrafenib and trametinib

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