NHS England Evidence Review:

Dabrafenib and trametinib for anaplastic thyroid cancer with BRAF mutation

NHS England URN: 2110

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Dabrafenib and trametinib for anaplastic thyroid cancer with BRAF mutation

Completed: September 2021

Prepared by Solutions for Public Health (SPH) on behalf of NHS England Specialised Commissioning

Contents

1. Introduction

This rapid evidence review examines the clinical effectiveness, safety and cost-effectiveness of dabrafenib and trametinib compared with best supportive care or palliative treatment for patients of all ages with inoperable BRAF-mutated anaplastic thyroid cancer (ATC).

Dabrafenib is a BRAF-kinase inhibitor and is used as a targeted therapy against BRAF-mutated cancers. Trametinib is a protein kinase inhibitor against the enzymes MEK-1 and MEK-2 and is used in combination with dabrafenib in the treatment of BRAF-mutated cancers. As these are targeted therapies, genetic testing of biopsy specimens for BRAF mutation status is a prerequisite for treatment. BRAF mutation testing for this indication is not currently available on the NHS England Genomics Test Directory, although an application for consideration of testing for this indication has been submitted for inclusion in the 2021-2022 Central Test Directory review. Local arrangements for testing will be determined by the respective Genomics Laboratory Hubs (GLHs).

Dabrafenib and trametinib currently have FDA approval in the USA for the treatment of BRAF-mutated melanoma and anaplastic thyroid cancer. In Europe, dabrafenib currently has EMA approval for use in the treatment of BRAF-mutated melanoma as monotherapy and in combination with trametinib.

In patients with advanced inoperable disease, the prognosis is extremely poor with a median survival of about three months. The majority of patients are managed within cancer centres with a specialist interest in thyroid cancer. There is no specific treatment for this condition at present and most patients are managed with best supportive care and palliative radiotherapy. A small proportion of patients that are medically fitter may be candidates for palliative chemotherapy, typically with a platinum/taxane combination.

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from treatment with dabrafenib and trametinib more than others.

2. Executive summary of the review

This rapid evidence review examines the clinical effectiveness, safety and cost-effectiveness of dabrafenib and trametinib compared with best supportive care or palliative treatment for patients of all ages with inoperable BRAF-mutated anaplastic thyroid cancer (ATC). The searches for evidence published since July 2011 were conducted on 27th July 2021 and identified 365 references. The titles and abstracts were screened, and 15 full text papers were obtained and assessed for relevance.

Four papers were identified for inclusion, three case series and a single arm phase II clinical trial, together reporting on a total of 33 patients with BRAF-mutated ATC. Two of the case series included a population broader than the scope of this review (patients with ATC) but reported results separately for in-scope patients with BRAF mutation. The phase II trial was part of a larger worldwide trial of BRAF mutated cancers with the paper reporting the results for the ATC patients only (Subbiah et al 2018). Two case series were from the same institution in the USA, the other from South Korea and the phase II trial was part of a larger worldwide trial of rare cancers. No studies were found comparing dabrafenib and trametinib to best supportive care or palliative treatment.

In terms of clinical effectiveness:

- **Overall survival (critical outcome).** Three studies reported overall survival where there was very low certainty non-comparative evidence of increased overall survival with dabrafenib and trametinib. Median overall survival in the two studies reporting this exceeded the minimal important difference of 3 months (one case series reported median overall survival of 9.3 months, one phase II clinical trial reported that median overall survival was not reached because of ongoing responses that resulted in insufficient death events at the time of data cut off).
- **Progression free survival (critical outcome).** There was very low certainty non-comparative evidence for an increase in progression free survival in three studies reporting this (one case series reported median progression free survival of 5.2 months, one case series and one phase II clinical trial reported that progression free survival was not reached because of ongoing responses that resulted in insufficient progression events at the time of data cut off).
- **Proportion of down staged patients (critical outcome).** This was reported in one case series reporting neoadjuvant use of dabrafenib and trametinib prior to surgery, where complete surgical resection was achieved in all patients who were previously inoperable with a locoregional control rate of 100%. Certainty of evidence was very low.
- **Symptom control (important outcome).** This was reported in one case series reporting neoadjuvant use of dabrafenib and trametinib prior to surgery where in four of six patients who were previously inoperable there was markedly improved dyspnoea and dysphagia. Certainty of evidence was very low.

In terms of safety:

- All four studies reported on adverse events where results were mixed, reporting that these were either absent or serious. Certainty of evidence was very low.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness.

In terms of subgroups:

- Due to the small sample sizes of the included studies, no subgroups of patients who may benefit more from treatment with dabrafenib and trametinib compared to the wider population of interest were identified.

Please see the results table (section 5) in the review for further details of outcomes.

Limitations

No comparative studies were found that met the inclusion criteria so no conclusions could be drawn comparing dabrafenib and trametinib to best supportive care or palliative treatment. Limited evidence was available from three small case series with 17 patients in scope and a single arm phase II clinical trial reporting on 16 patients. Two case studies were retrospective in nature and the phase II trial reported an interim analysis. Certainty about the evidence for all critical and important outcomes was very low when assessed using modified GRADE. There was no evidence found reporting on the effects of dabrafenib and trametinib on time to treatment failure, performance status or quality of life, and no studies found reporting cost-effectiveness. No subgroups were identified that may benefit more from treatment with dabrafenib and trametinib compared with the wider population.

Conclusion

The studies identified for this review provide very low certainty evidence that dabrafenib and trametinib compared with best supportive care or palliative treatment may improve overall survival, progression free survival, proportion of downgraded patients and symptom control in patients with BRAF-mutated ATC. There were mixed findings across the studies for adverse events, with serious treatment related adverse effects reported in the single arm phase II clinical trial. The lack of comparative evidence means that it is not possible to draw reliable conclusions about the clinical effectiveness, safety or cost effectiveness of dabrafenib and trametinib compared with best supportive care or palliative treatment.

3. Methodology

Review questions

The review question(s) for this evidence review are:

1. In people of all ages with BRAF-mutated anaplastic thyroid cancer, what is the clinical effectiveness of dabrafenib and trametinib compared with best supportive care or palliative treatment?
2. In people of all ages with BRAF-mutated anaplastic thyroid cancer, what is the safety of dabrafenib and trametinib compared with best supportive care or palliative treatment?
3. In people of all ages with BRAF-mutated anaplastic thyroid cancer, what is the cost-effectiveness of dabrafenib and trametinib compared with best supportive care or palliative treatment?
4. From the evidence selected, are there any subgroups of patients that may benefit from treatment with dabrafenib and trametinib compared with the wider population of interest?

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 27th July 2021.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text of potentially relevant studies were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE profiles.

4. Summary of included studies

Four papers were identified for inclusion, three case series (Iyer et al 2018, Park et al 2021, Wang et al 2019) and a single arm phase II trial (Subbiah et al 2018). Table 1 provides a summary of the included studies and full details are given in Appendix E. Two of the case series (Iyer et al 2018, Park et al 2021) included a population broader than the scope of this review (patients with ATC) but have been identified for inclusion as they reported results separately for in-scope patients with BRAF mutation. The phase II trial was part of a larger worldwide trial of all BRAF mutated cancers with the paper reporting the results for the ATC patients only (Subbiah et al 2018).

No studies were identified reporting on cost-effectiveness.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Iyer et al 2018 Retrospective case series University of Texas, USA	16 patients with new or actively followed ATC treated with targeted therapy at an academic centre between April 2015 and May 2016. Excluded those treated in a clinical trial. Data for 6 patients with BRAF mutation treated with dabrafenib and trametinib were extracted for inclusion in this review. Baseline characteristics not reported separately for the 6 in-scope patients. No subgroups results reported for patients in scope.	**Intervention** 5 of 6 patients were started on a full dose of dabrafenib (150 mg twice daily) and trametinib (2 mg once daily). One patient with CHF was started on half dosing for dabrafenib and same dose for trametinib. **Comparison** No comparator	Median follow-up 11.8 months **Critical outcomes** • Median overall survival • Median progression free survival • Progression free survival at 6 months **Important outcomes** • Adverse events
Park et al 2021 Retrospective case series Samsung Medical Centre, Seoul, South Korea	120 patients with ATC diagnosed at a medical centre between November 1995 and May 2020. Data for 5 patients with BRAF mutation treated with dabrafenib and trametinib were extracted for inclusion in this review. Baseline characteristics not reported separately for the 5 in-scope patients except that 3 had undergone prior surgery. No subgroups results reported for patients in scope.	**Intervention** Dabrafenib and trametinib. Dose not reported. **Comparison** No comparator	Median follow-up not reported **Critical outcomes** • Median progression free survival **Important outcomes** • Adverse events
Subbiah et al 2018 Single arm phase II trial	100 patients with BRAF ^{V600E} mutated rare cancers[1]. Paper reported on the 16 patients with BRAF ^{V600E} mutated ATC only and	**Intervention** Patients received continuous dabrafenib (150 mg twice daily) and trametinib (2 mg once daily).	Median follow-up 47 weeks (range 4 to 120) **Critical outcomes** • Median overall survival and overall survival at 12 months

[1] V600E: a specific mutation in the BRAF gene

47 centres worldwide	therefore all results reported in this paper are applicable to this population. Median age 72 (range 56 to 85), 38% men, 63% of Asian heritage. All patients had received prior radiation treatment and/or surgery, and 6 had received prior systemic therapy. No subgroups results reported.	**Comparison** No comparator	• Median progression free survival and progression free survival at 12 months **Important outcomes** • Adverse events
Wang et al 2019 Case series University of Texas, USA	6 consecutive BRAF ^{V600E} mutated ATC patients with unresectable disease treated at an academic centre between January 2017 and February 2018. Excluded those treated in a clinical trial. Median age 59 years, 2 (33%) were men. At the time of diagnosis, T stage was T4b in 6 (100%), N stage N1a in 1 (17%), N1b in 5 (83%), and M stage M0 in 4 67%), M1 in 2 (33%). No subgroups results reported.	**Intervention** Neoadjuvant dabrafenib 150 mg twice daily and trametinib 2 mg daily followed by surgical resection and adjuvant chemoradiation. **Comparison** No comparator	Median follow-up 15 months (range 6.4 to 25.2) **Critical outcomes** • Overall survival at 6 and 12 months • Proportion of down staged patients **Important outcomes** • Symptom control • Adverse events
Abbreviations ATC: Anaplastic Thyroid Cancer, CHF: Congestive Heart Failure, mg: milligrams			

5. Results

In people of all ages with BRAF-mutated anaplastic thyroid cancer, what is the clinical effectiveness and safety of dabrafenib and trametinib compared with best supportive care or palliative treatment?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Overall survival **Certainty of evidence:** Very low	Overall survival is important because it reflects how long people live after treatment. It is a measure of a treatment's ability to increase survival, although it does not provide information about their health and wellbeing at that time. In ATC, a minimal clinically important difference in overall survival would be 3 months. In total, 3 studies (a multi-centre single arm phase II trial and 2 single centre case series) provided non-comparative evidence relating to overall survival for patients with BRAF-mutated ATC treated with dabrafenib and trametinib. The phase II trial (Subbiah et al 2018) included 16 patients with BRAF-mutated ATC treated with dabrafenib and trametinib. One retrospective case series (Iyer et al 2018) included 16 patients with ATC treated with targeted therapy and reported results for a subgroup of 6 in-scope patients with BRAF-mutated ATC treated with dabrafenib and trametinib. One consecutive case series (Wang et al 2019) included 6 BRAF-mutated ATC patients treated with dabrafenib and trametinib. Median overall survival • One case series (Iyer et al 2018) reported a median overall survival of 9.3 months (95% CI 5.7 to not reached[2]) for a subgroup of 6 patients with BRAF-mutated ATC treated with dabrafenib and trametinib. **(VERY LOW)** • One single arm phase II trial of 16 patients (Subbiah et al 2018) reported that median overall survival was not reached. **(VERY LOW)** Overall survival (proportion of patients still alive) at 6 months • One case series of 6 patients (Wang et al 2019) reported 100% overall survival at 6 months. **(VERY LOW)** Overall survival (proportion of patients still alive) at 12 months • One case series of 6 patients (Wang et al 2019) reported 83% overall survival at 12 months. **(VERY LOW)** • One single arm phase II trial of 16 patients (Subbiah et al 2018) reported 80% overall survival at 12 months. (**VERY LOW**) **These studies provided very low certainty non-comparative evidence that dabrafenib and trametinib increase overall survival in patients with BRAF-mutated ATC. Median overall survival results reported exceed the minimal important clinical difference of 3 months.**
Progression free survival **Certainty of evidence:** Very low	Progression-free survival is important because it measures the length of time during and after treatment during which the disease does not worsen. A longer progression-free survival is an indicator of a treatment's ability to control disease. In total, 3 studies (a multi-centre single arm phase II trial and 2 single centre case series) provided non-comparative evidence relating to progression free survival for patients with BRAF-mutated ATC treated with dabrafenib and trametinib. The phase II trial (Subbiah et al 2018) included 16 patients with BRAF-mutated ATC treated with dabrafenib and trametinib. One retrospective case series (Iyer et al 2018)

[2] Overall survival not reached: means that there are ongoing responses that resulted in insufficient death events at the time of data cut off.

	included 16 patients with ATC treated with targeted therapy and reported results for a subgroup of 6 in-scope patients with BRAF-mutated ATC treated with dabrafenib and trametinib. One retrospective case series (Park et al 2021) included 120 patients with ATC and reported results for a subgroup of 5 in scope patients with BRAF-mutated ATC treated with dabrafenib and trametinib. Median progression free survival • One case series (Iyer et al 2018) reported median progression free survival of 5.2 months (CI 3.7 to not reached[3]) for a subgroup of 6 patients with BRAF-mutated ATC treated with dabrafenib and trametinib. **(VERY LOW)** • One case series (Park et al 2021) reported that median progression free survival was not reached for a subgroup of 5 patients with BRAF-mutated ATC treated with dabrafenib and trametinib. **(VERY LOW)** • One single arm phase II trial of 16 patients (Subbiah et al 2018) reported that median progression free survival was not reached. (**VERY LOW)** Progression free survival at 6 months • One case series (Iyer et al 2018) reported 50% (22% to 100%) progression free survival at 6 months for a subgroup of 6 patients with BRAF-mutated ATC treated with dabrafenib and trametinib. **(VERY LOW)** Progression free survival at 12 months • One single arm phase II trial of 16 patients (Subbiah et al 2018) reported 79% progression free survival at 12 months. **(VERY LOW)** **These studies provided very low certainty non-comparative evidence that dabrafenib and trametinib increase progression free survival in patients with BRAF-mutated ATC.**
Proportion of down staged patients **Certainty of evidence:** Very low	This outcome is important because it measures the response to treatment such that it is rendered operable. Operable cancers are amenable to potentially curative resection which improves prognosis. One consecutive case series (Wang et al 2019) included 6 BRAF-mutated ATC patients treated with dabrafenib and trametinib and reported the number of down staged patients during the study period (median follow-up 15 months). • One case series of 6 patients (Wang et al 2019) reported that surgical resection was complete in all 6 patients who were previously inoperable demonstrating a locoregional control rate of 100%. **(VERY LOW)** **This study provides very low certainty non-comparative evidence that dabrafenib and trametinib increase the proportion of down staged patients with BRAF-mutated ATC.**
Important outcomes	
Time to treatment failure **Certainty of evidence:** Not applicable	This is important because it is a reflection of overall treatment failure due to disease progression, adverse events or death. **No evidence was identified for this outcome.**
Symptom control **Certainty of evidence:** Very low	Symptom control is an important outcome as it is surrogate marker for the ability of the treatment to improve functional capacity and quality of life. One consecutive case series (Wang et al 2019) included 6 BRAF-mutated ATC patients treated with dabrafenib and trametinib and reported symptom control.

[3] Progression free survival not reached: means that there are ongoing responses that resulted in insufficient progression of disease events at the time of data cut off.

	• One case series of 6 patients (Wang et al 2019) reported symptom control in 4/6 patients where dyspnoea and dysphagia were markedly reduced. **(VERY LOW)** **This study provides very low certainty non-comparative evidence that dabrafenib and trametinib improve symptom control in patients with BRAF-mutated ATC.**
Performance status **Certainty of evidence:** Not applicable	This is an important outcome as it is a measure of how well a person is able to carry on ordinary daily activities while living with cancer and provides an estimate of what treatments a person may tolerate. **No evidence was identified for this outcome.**
Quality of life **Certainty of evidence:** Not applicable	Quality of life is important to patients because of the impact on the patient's function, activities of daily living and self-perceived well-being. Improvement in quality of life is a marker of successful treatment. **No evidence was identified for this outcome.**
Safety	
Adverse events **Certainty of evidence:** Very low	Adverse events are an important outcome as they reflect the safety profile of an intervention. Adverse events are graded according to severity (grades 1-4). All 4 included studies reported on adverse events (three case series and a phase II trial). • One case series (Iyer et al 2018) reported grade 3 fatigue (1 patient), anaemia (1 patient), hypercalcaemia (1 patient) and hyponatremia (2 patients), and no grade 4 or higher adverse events for a subgroup of 6 patients with BRAF-mutated ATC treated with dabrafenib and trametinib. (**VERY LOW)** • One case series (Park et al 2021) reported no treatment discontinuations due to adverse events, and 4 patients were still being treated without adverse events at the time of data collection for a subgroup of 5 patients with BRAF-mutated ATC treated with dabrafenib and trametinib. **(VERY LOW)** • One phase II trial of 16 patients (Subbiah et al 2018) reported grade 3 and 4 adverse events in 50% of the patients, including anaemia, fatigue, diarrhoea and hyperglycaemia. Three patients with ATC experienced treatment-related serious adverse events (acute kidney injury and rhabdomyolysis, pyrexia, and hyponatremia). **(VERY LOW)** • One case series of 6 patients (Wang et al 2019) reported post-op complications that led to treatment interruption in three patients including wound infection, temporary unilateral vocal cord paresis and pulmonary embolism. **(VERY LOW)** **These studies provided very low certainty non-comparative evidence on the safety of dabrafenib and trametinib. One study reported serious adverse effects in 3 of 16 patients and two report grade 3 or 4 adverse effects, the remainder reporting on either no treatment discontinuations or treatment discontinuations due to surgery rather than the drugs themselves.**
Abbreviations ATC: Anaplastic Thyroid Cancer, CI: Confidence Interval	

In people of all ages with BRAF-mutated anaplastic thyroid cancer, what is the cost-effectiveness of dabrafenib and trametinib compared with best supportive care or palliative treatment?

Outcome	Evidence statement
Cost-effectiveness	**No evidence was identified for cost effectiveness.**

From the evidence selected, are there any subgroups of patients that may benefit from treatment with dabrafenib and trametinib compared with the wider population of interest?

Outcome	Evidence statement
Subgroups	**No evidence was identified regarding any subgroups of patients that would benefit from treatment with dabrafenib and trametinib more than the wider population of interest.**

6. Discussion

This rapid evidence review considered the evidence for the clinical effectiveness, safety and cost-effectiveness of dabrafenib and trametinib compared to best supportive care or palliative treatment in people of all ages with inoperable BRAF-mutated ATC. The critical outcomes of interest were overall survival, progression free survival and the proportion of down staged patients. The important outcomes of interest were time to treatment failure, symptom control, performance status, quality of life and adverse events. Evidence on cost effectiveness was also sought.

No comparative studies were found that met the inclusion criteria so no conclusions could be drawn comparing dabrafenib and trametinib to best supportive care or palliative treatment. Limited evidence was available from three small case series with a total of 17 patients in scope (Iyer et al 2018, Park et al 2021, Wang et al 2019) and a single arm phase II clinical trial reporting on 16 patients (Subbiah et al 2018). Two of the case series (Iyer et al 2018, Park et al 2021) included a population broader than the scope of this review (patients with ATC) but have been identified for inclusion as they reported results separately for in-scope patients with BRAF mutation. The phase II trial was part of a larger worldwide trial of BRAF mutated cancers with the paper reporting the results for the ATC patients only (Subbiah et al 2018). Two case series were retrospective in nature (Iyer at al 2018, Park et al 2021) and the phase II trial reported an interim analysis (Subbiah et al 2018). Two case series from the same institution specifically excluded participants recruited to clinical trials to report on the “real world” experience with dabrafenib and trametinib (Iyer et al 2018, Wang et al 2019). One of these focused on the use of dabrafenib and trametinib as neoadjuvant targeted therapy in patients with previously inoperable BRAF-mutated ATC (Wang et al 2019). Dosing for dabrafenib was 150 mg twice daily and trametinib 2 mg once daily for all studies except for one patient in a case series (Iyer et al 2018) with chronic heart failure who was started on a lower dose. All four studies reported findings from outside of the UK context.

Three studies reported overall survival (Iyer et al 2018, Subbiah et al 2018, Wang et al 2019) where there was very low certainty non-comparative evidence of increased overall survival with dabrafenib and trametinib. Median overall survival in the two studies reporting this (Iyer et al 2018, Subbiah et al 2018) exceeded the minimal important difference of 3 months. There was very low certainty non-comparative evidence for an increase in progression free survival in three studies reporting this (Iyer et al 2018, Park et al 2021, Subbiah et al 2018). The one case series reporting neoadjuvant use of dabrafenib and trametinib prior to surgery, reported on the proportion of down staged patients where complete surgical resection was achieved in all patients who were previously inoperable with a locoregional control rate of 100% (Wang et al 2019). Symptom control was reported in the same case series where in four of six patients there was markedly improved dyspnoea and dysphagia (Wang et al 2019). All four studies reported on adverse events where results were mixed. None of the included studies reported on time to treatment failure, performance status, quality of life. No studies were identified reporting on cost-effectiveness. No studies were identified that reported on subgroups of patients who may benefit more from treatment with dabrafenib and trametinib compared to the wider population of interest. This is not surprising given the small sample sizes of the studies identified.

Iyer et al 2018 reported a retrospective case series of patients from one institution in the USA who had not been treated in the context of a clinical trial. Of 16 evaluable patients, eight had the BRAF ^{V600E} mutation and six were treated with dabrafenib and trametinib. Baseline and clinical characteristics were reported in the cohort of 16 patients where 81% had previous treatment for ATC, but not separately for the six in-scope patients. The number of inoperable patients was not explicitly reported for this cohort, but all had distant metastases or radiation-resistant primary disease at the time of treatment. Median follow-up was 11.8 months with overall survival at 9.3

months and progression free survival at 5.2 months. No grade 4 or higher adverse events were reported but dose reduction was needed in two patients with lower extremity oedema. Risk of bias was rated as low overall.

Park et al 2021 reported a retrospective case series from a single institution in South Korea. The study reported 120 patients with ATC, 35 of which were tested for the BRAF ^{V600E} mutation of which 20 were positive and five of these were treated with dabrafenib and trametinib. Baseline and clinical characteristics were reported for the cohort of 120 overall and not reported separately in the subgroup of interest. The number with inoperable disease was not explicitly reported, but all patients treated with tyrosine kinase inhibitors (TKI) had either surgery or radiotherapy, or radiotherapy and chemotherapy prior to targeted treatment, and three of five treated with dabrafenib and trametinib had undergone prior surgery. Follow-up time was not reported. Progression free survival was not reached so within the follow-up period disease did not progress, and no adverse events leading to treatment discontinuation were reported. Overall risk of bias was rated as unclear due to poor reporting, and this study was downgraded for serious limitations due to unclear reporting of study participants as well as serious indirectness.

Subbiah et al 2018 reported an open label phase II single arm clinical trial which formed part of a larger study in 100 patients with BRAF ^{V600E} mutated rare cancers recruited from 47 centres worldwide. This study reported on an interim analysis of 16 patients with BRAF-mutated ATC where there was no standard locally or regionally available treatment options. Early efficacy was shown for the ATC cohort, so this was closed, and an expansion cohort opened where enrolment continues. All patients had received prior radiation and or surgery, and six patients had received prior systemic therapy. Median follow-up was 47 weeks, and median overall survival and progression free survival were not reached which means that there were ongoing responses that resulted in insufficient death events or progression of disease at the time of data cut off. Half of the patients reported grade 3 or 4 adverse effects and three patients experienced treatment-related serious adverse events (acute kidney injury and rhabdomyolysis, pyrexia, and hyponatremia). Risk of bias was rated as low overall.

Wang et al 2019 report a case series from a single institution in the USA, the same group as Iyer et al 2018, but with different recruitment dates and criteria. Six patients with BRAF V600E mutated ATC and unresectable disease were studied. Patients who had been treated in the context of a clinical trial were excluded. Baseline and clinical characteristics were reported. Neoadjuvant dabrafenib and trametinib were administered for a median of 3.6 months, stopped prior to surgery, and restarted following wound healing. Complete surgical resection was achieved in all patients who were previously inoperable. Follow-up was a median of 15 months with overall survival of 100% at 6 months and 83% at 12 months. There were marked improvements in symptom control (dyspnoea, dysphagia) and adverse events reported were associated with post-operative complications that led to treatment interruption. Overall risk of bias was rated as low.

Whilst limited to three small case series and a single arm phase II clinical trial, preliminary findings suggest positive effects of dabrafenib and trametinib on overall survival, progression free survival, proportion of downgraded patients and symptom control in patients with BRAF-mutated ATC, but there were mixed findings across the studies for adverse events, with serious treatment related adverse effects reported in the phase II clinical trial. Further larger controlled studies reporting these outcomes will add clarity to these initial findings.

7. Conclusion

There is very little evidence reporting on the clinical effectiveness and safety of dabrafenib and trametinib for patients of all ages with BRAF-mutated ATC. No comparative studies were found that assessed the effects against best supportive care or palliative treatment, and current evidence is limited to three small case series and a single arm phase II clinical trial together reporting on 33 in-scope patients.

Despite the limitations in terms of study design and sample size, positive effects were reported in terms of overall survival, progression free survival, down grading of patients and symptom control in those patients evaluated, where overall survival exceeded the minimal important difference of 3 months. Included studies varied in their findings for adverse events where these were either absent or serious. Certainty about the evidence for all critical and important outcomes was very low when assessed using modified GRADE.

There was no evidence found reporting on the effects of dabrafenib and trametinib on time to treatment failure, performance status or quality of life, and no studies found reporting cost-effectiveness. No subgroups were identified that may benefit more from treatment with dabrafenib and trametinib compared with the wider population.

The studies identified for this review provide very low certainty evidence that dabrafenib and trametinib compared with best supportive care or palliative treatment may improve overall survival, progression free survival, proportion of downgraded patients and symptom control in patients with BRAF-mutated ATC. Initial positive findings need to be corroborated in larger comparative studies and safety needs to be established to determine the balance between benefits and harms. The lack of comparative evidence means that it is not possible to draw reliable conclusions about the clinical effectiveness, safety or cost effectiveness of dabrafenib and trametinib compared with best supportive care or palliative treatment.

Appendix A PICO document

The review questions for this evidence review are:

1. In people of all ages with BRAF-mutated anaplastic thyroid cancer, what is the clinical effectiveness of dabrafenib and trametinib compared with best supportive care or palliative treatment?
2. In people of all ages with BRAF-mutated anaplastic thyroid cancer, what is the safety of dabrafenib and trametinib compared with best supportive care or palliative treatment?
3. In people of all ages with BRAF-mutated anaplastic thyroid cancer, what is the cost-effectiveness of dabrafenib and trametinib compared with best supportive care or palliative treatment?
4. From the evidence selected, are there any subgroups of patients that may benefit from treatment with dabrafenib and trametinib compared with the wider population of interest?

P–Population and Indication	People of all ages with inoperable BRAF-mutated anaplastic thyroid cancer with or without metastases [Patients may have previously had surgery for ATC]
I – Intervention	Dabrafenib and trametinib [The proposed regimen would be 150mg Dabrafenib twice daily and 2mg trametinib once daily until progressive disease or intolerable toxicity]
C – Comparator(s)	Best supportive care, which may include palliative radiotherapy and palliative chemotherapy. [There is no current treatment for anaplastic thyroid cancer. Patients are typically managed with best supportive care and palliative radiotherapy. Rarely, fitter patients may be considered for palliative chemotherapy.]
O – Outcomes	**Clinical effectiveness** *Critical to decision-making* • **Overall survival (OS)** *Overall survival is important because it reflects how long people live after treatment. It is a measure of a treatment's ability to increase survival, although it does not provide information about their health and wellbeing at that time.* OS would be measured in months. In ATC, a minimal clinically important difference in OS would be 3 months. • **Progression-free survival (PFS)** *Progression-free survival is important because it measures the length of time during and after treatment during which the disease does not worsen. A longer progression-free survival is an indicator of a treatment's ability to control disease.* PFS would be measured in months. • **Proportion of down staged patients** *This outcome is important because it measures the response to treatment such that it is rendered operable. Operable cancers are amenable to potentially curative resection which improves prognosis.* This outcome would be measured as a percentage of total patients treated with dabrafenib and trametinib. *Important to decision-making (specify up to 4)* • **Time to treatment failure** This is important because it is a reflection of overall treatment failure due to disease progression, adverse events or death. Defined as the interval between initiation of chemotherapy/treatment to premature discontinuation. • **Symptom control**

	Symptom control is an important outcome as it is surrogate marker for the ability of the treatment to improve functional capacity and quality of life. Local symptoms from anaplastic thyroid cancer result from compression of surrounding structures and include breathlessness, pain, dysphonia (hoarseness) and dysphagia (difficulty swallowing). • **Performance status** This is an important outcome as it is a measure of how well a person is able to carry on ordinary daily activities while living with cancer and provides an estimate of what treatments a person may tolerate. Performance status is usually reported using (but may not be limited to) the ECOG/WHO Performance Status or Karnofsky Performance Status scores. • **Quality of life** Quality of life is important to patients because of the impact on the patient's function, activities of daily living and self-perceived well-being. Improvement in quality of life is a marker of successful treatment. Measured using a validated general questionnaire such as (but not limited to) HRQOL or a disease specific questionnaire such as (but not limited to) Quality of Life – Thyroid Version (QOL-TV). • **Safety** Adverse events are an important outcome as they reflect the safety profile of an intervention. Adverse events are graded according to severity (grades 1-4). All grades of adverse events should be considered, however serious adverse events (grade 3 or 4) are of particular importance to decision-making.
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher-level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date Limits	2011-2021
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase and the Cochrane Library were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, guidelines, case reports and resource utilisation studies were excluded.

Search dates: 27th July 2021

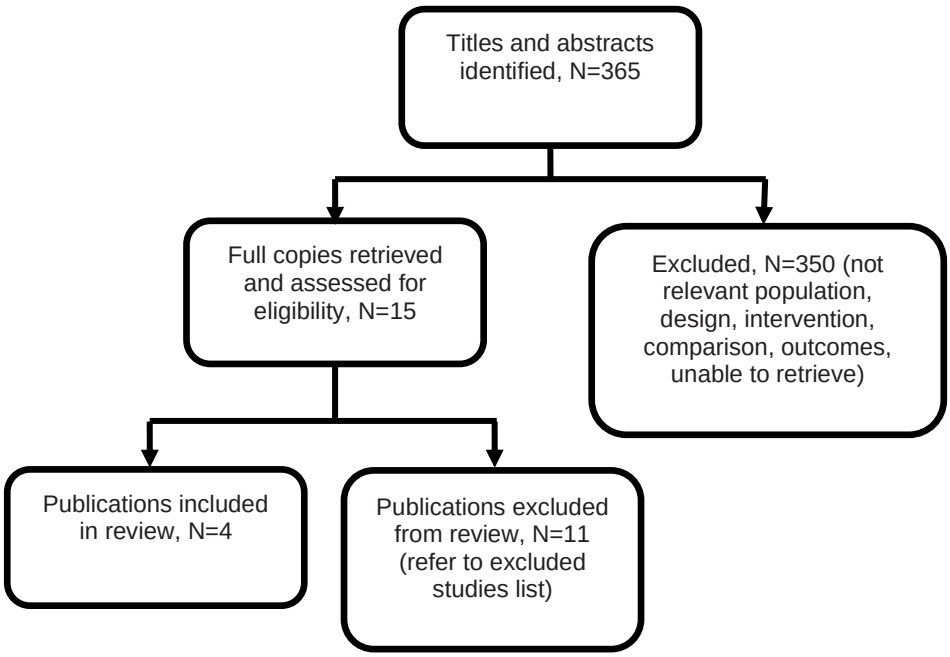
Medline search strategy:

1	Thyroid Carcinoma, Anaplastic/
2	exp Thyroid Neoplasms/
3	(thyroid adj5 (cancer? Or carcinoma? Or tumo?r? or neoplas* or malignan* or metasta*)).ti,ab,kw.
4	1 or 2 or 3
5	(dabrafenib or tafinlar or trametinib or mekinist).ti,ab,kw.
6	((braf* or mek) adj2 inhibitor?).ti,ab,kw.
7	5 or 6
8	4 and 7
9	exp animals/ not humans/
10	8 not 9
11	limit 10 to (english language and yr="2011 -Current")
12	(comment or editorial or letter).pt. or case report.ti,ab.
13	11 not 12

Appendix C Evidence selection

The literature searches identified 365 references. These were screened using their titles and abstracts and 15 references were obtained in full text and assessed for relevance. Of these, 4 references are included in the evidence summary. The remaining 11 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection – decision and rationale if excluded
Subbiah V, Kreitman RJ, Wainberg ZA, Cho JY, Schellens JHM, Soria JC, et al. Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600-Mutant Anaplastic Thyroid Cancer. J Clin Oncol. 2018;36(1):7-13.	Included
Wang JR, Zafereo ME, Dadu R, Ferrarotto R, Busaidy NL, Lu C, et al. Complete Surgical Resection Following Neoadjuvant Dabrafenib Plus Trametinib in BRAF(V600E)-Mutated Anaplastic Thyroid Carcinoma. Thyroid. 2019;29(8):1036-43.	Included
Bible KC, Kebebew E, Brierley J, Brito JP, Cabanillas ME, Clark TJ, et al. 2021 American Thyroid Association Guidelines for Management of Patients with Anaplastic Thyroid Cancer. Thyroid 2021; 31(3):337-86	Excluded – As per PICO, guidelines are to be excluded. Guidelines checked for additional relevant studies. Studies included in guidelines already included in the review. Guideline report additional data from Subbiah 2018 (23 patients rather than 16) but this is unpublished data with limited information on patients and has not been peer reviewed.

Appendix D Excluded studies table

Study reference	Reason for exclusion
Gentile D, Orlandi P, Banchi M, Bocci G. Preclinical and clinical combination therapies in the treatment of anaplastic thyroid cancer. Medical Oncology. 2020;37(3).	Only relevant data reported from one study already included in the review, a phase II clinical trial (Subbiah 2018).
Ljubas J, Ovesen T, Rusan M. A systematic review of Phase II targeted therapy clinical trials in anaplastic thyroid cancer. Cancers. 2019;11(7):04.	Only relevant data reported from two studies already included in the review, a phase II clinical trial (Subbiah 2018) and a case series (Iyer 2018), and SR did not meta-analyse the results of the 2 studies.
Abdel-Rahman O, ElHalawani H, Ahmed H, Ellithy M. Risk of selected gastrointestinal toxicities in cancer patients treated with MEK inhibitors: a comparative systematic review and meta-analysis. Expert Rev Gastroenterol Hepatol. 2015;9(11):1433-45.	Systematic review does not include studies in patients with BRAF mutated ATC.
Abdel-Rahman O, ElHalawani H, Ahmed H. Risk of selected dermatological toxicities in cancer patients treated with MEK inhibitors: a comparative systematic review and meta-analysis. Future Oncol. 2015;11(24):3307-19.	Full paper not obtained but systematic review is very unlikely to include studies in patients with BRAF mutated ATC given the other reports from the same study group.
Abdel-Rahman O, ElHalawani H, Ahmed H. Risk of selected cardiovascular toxicities in patients with cancer treated with MEK inhibitors: A comparative systematic review and meta-analysis. J Glob Oncol. 2015;1(2):73-82.	Systematic review does not include studies in patients with BRAF mutated ATC.
2021 American Thyroid Association Guidelines for management of patients with anaplastic thyroid cancer. Thyroid. 2021;31(3):337-86.	As per PICO guidelines are to be excluded. Guidelines checked for additional relevant studies. Studies included in guidelines already included in the review. Guideline report additional data from Subbiah 2018 (23 patients rather than 16) but this is unpublished data with limited information on patients and has not been peer reviewed.
European Society of Medical Oncology. Clinical Practice Guidelines – Thyroid Cancer 2020 [Available from: https://www.esmo.org/guidelines/endocrine-and-neuroendocrine-cancers/thyroid-cancer].	As per PICO guidelines are to be excluded. These guidelines are not based on a SR, instead based on evidence selected by expert authors. Only relevant data reported from one study already included in the review, a phase II clinical trial (Subbiah 2018).
Kieran MW, Geoerger B, Dunkel IJ, Broniscer A, Hargrave D, Hingorani P, et al. A Phase I and Pharmacokinetic Study of Oral Dabrafenib in Children and Adolescent Patients with Recurrent or Refractory BRAF V600 Mutation-Positive Solid Tumors. Clinical Cancer Research. 2019;25(24):7294-302.	Study did not include patients with BRAF mutated ATC (one patient with papillary thyroid cancer) and dabrafenib not administered with trametinib.
Haraldsdottir S, Janku F, Poi M, Timmers C, Geyer S, Schaaf LJ, et al. Phase I trial of dabrafenib and pazopanib in BRAF mutated advanced malignancies. JCO Precision Oncology. 2018;2:1-19.	Dabrafenib plus pazopanib rather than trametinib, and patients not BRAF mutated ATC.
Falchook GS, Millward M, Hong D, Naing A, Piha-Paul S, Waguespack SG, et al. BRAF inhibitor dabrafenib in patients with metastatic BRAF-mutant thyroid cancer. Thyroid. 2015;25(1):71-7.	Reports effects of dabrafenib rather than dabrafenib plus trametinib, and patients were not BRAF mutated ATC.

Falchook GS, Long GV, Kurzrock R, Kim KB, Arkenau TH, Brown MP, et al. Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose-escalation trial. Lancet. 2012;379(9829):1893-901.	Reports effects of dabrafenib rather than dabrafenib plus trametinib, and patients were not BRAF mutated ATC.

Appendix E Evidence table

For abbreviations see list after table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Iyer PC, Dadu R, Ferrarotto R, Busaidy NL, Habra MA, Zafereo M, et al. Real-world experience with targeted therapy for the treatment of anaplastic thyroid carcinoma. Thyroid. 2018;28(1):79-87. **Study location** The Anderson Cancer Centre at the University of Texas, USA **Study type** Retrospective case series **Study aim** To investigate the efficacy and tolerability of targeted therapies in ATC patients who were treated outside of the context of a clinical trial. **Study dates** April 2015 to May 2016	**Inclusion criteria** New or actively followed ATC patients receiving targeted therapy identified from the institution's database during the study period. **Exclusion criteria** Patients who were treated in a clinical trial and who received targeted therapy outside the institution were excluded. **Total sample size** n=16 n=6 in-scope patients with BRAF-mutated ATC treated with dabrafenib and trametinib. Relevant outcomes for the 6 in-scope patients were extracted for inclusion in this review.	**Interventions** n=6 5 patients were started on a full dose of dabrafenib (150 mg twice daily) and trametinib (2 mg once daily). 1 patient due to a pre-existing CHF was started on 75 mg of dabrafenib twice daily (half dose) with 2 mg of trametinib daily. **Comparators** None	Median follow-up 11.8 months. **Critical outcomes** **Overall survival** Median overall survival was 9.3 months (CI 5.7 to not reached[4]). **Progression free survival (PFS)** Median PFS was 5.2 months (CI 3.7 to not reached[5]). Six-month PFS was 50% (22% to 100%). **Important outcomes** **Adverse events** **All grades (n):** Fatigue: 4 Hypertension: 1 Nausea: 4 Anorexia: 2 Hyponatremia: 3 Hypothyroidism: 2 Hand–foot skin reaction: 3 Weight loss: 3 Anaemia: 3 Diarrhoea: 2 Transaminitis: 1	This study was appraised using the JBI checklist for case series. 1. Unclear 2. Yes 3. Yes 4. Yes 5. Unclear 6. No 7. No 8. Yes 9. Yes 10. Yes **Other comments:** Retrospective case series of 16 patients with ATC with outcomes reported separately for 6 patients with BRAF mutation treated with dabrafenib and trametinib. Overall risk of bias rated as unclear, reporting of inclusion criteria and the numbers included were rated unclear, and baseline characteristics

4 Overall survival not reached: means that there are ongoing responses that resulted in insufficient death events at the time of data cut off.

[5] Progression free survival not reached means that there are ongoing responses that resulted in insufficient progression of disease events at the time of data cut off.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Baseline characteristics Not reported separately for the 6 in-scope patients. Total population (n=16): Median age 67 years, 10 (63%) were men. At the time of diagnosis, 4 (25%) patients were stage IVB, and 12 (75%) were stage IVC. 13 (81%) had previous treatment for ATC: Surgery 8 (50%), Radiation/chemo sensitizing 7 (44%), Chemotherapy 9 (56%). All had distant metastases or radiation-resistant primary disease at the time of treatment.		Elevated alkaline phosphatase: 1 Vomiting: 2 Lower extremity oedema: 2 Bleeding: 1 Constipation: 1 Fever: 1 Hypercalcemia: 1 **Grade 3 (n):** Fatigue: 1 Hyponatremia: 2 Anaemia: 1 Hypercalcemia: 1 No grade 4 or higher adverse events were noted. One patient had grade 3 anaemia requiring blood transfusion, and one with a history of chronic hyponatremia at baseline demonstrated worsening hyponatremia. Dose reduction was needed in two patients on dabrafenib and trametinib who developed lower extremity oedema. One of them had CHF at baseline, but there was not a significant change in the ejection fraction, so oedema was not attributed to CHF. The other patient had a normal echocardiogram.	were not reported separately for in-scope patients. **Source of funding:** This study was supported in part through The University of Texas MD Anderson Cancer Centre's Cancer Centre Support Grant CA16672.
Park J, Jung HA, Shim JH, Park WY, Kim TH, Lee SH, et al. Multimodal treatments and outcomes for anaplastic thyroid cancer before and after tyrosine kinase inhibitor therapy: a real-world	**Inclusion criteria** Patients with pathologically confirmed ATC, de novo ATC, and anaplastic transformation from differentiated thyroid	**Interventions** n=5 Dabrafenib 150 mg twice daily and trametinib 2 mg once daily. **Comparators**	Median follow-up not reported. **Critical outcomes** **Progression free survival (PFS)** The PFS for the group with dabrafenib plus trametinib was not reached. Four patients were still	This study was appraised using the JBI checklist for case series. 1. Unclear 2. Yes 3. Yes

Study details	Population	Interventions	Study outcomes	Appraisal and funding
experience. European Journal of Endocrinology. 2021;184(6):837-45. **Study location** Samsung Medical Centre, Seoul, South Korea **Study type** Retrospective case series **Study aim** To demonstrate the effectiveness of multimodal treatments where TKI therapy is added to standard treatments, such as surgery, EBRT, and cytotoxic chemotherapy. **Study dates** November 1995 to May 2020	cancer were identified from the institution's database. **Exclusion criteria** Those lost to follow-up or transferred to other centres. **Total sample size** n=120 n=5 in-scope patients with BRAF-mutated ATC treated with dabrafenib and trametinib. Relevant outcomes for the 5 in-scope patients were extracted for inclusion in this review. **Baseline characteristics** 3/5 patients treated with dabrafenib and trametinib had undergone prior surgery. No further characteristics were reported separately for the 5 in-scope patients. All patients treated with TKI had either surgery and radiotherapy or radiotherapy and chemotherapy prior to targeted treatment.	None	being treated at the time of the data collection. **Important outcomes** **Adverse events** Adverse events leading to discontinued treatment were not reported in the 5 patients treated with dabrafenib plus trametinib. Four out of five patients were still being treated without adverse events at the time of data collection.	4. Yes 5. Unclear 6.No 7. Unclear 8. Yes 9. Unclear 10. Unclear **Other comments:** Retrospective case series of 120 patients with ATC with outcomes reported separately for 5 patients with BRAF mutation treated with dabrafenib and trametinib. Overall risk of bias rated as unclear as there was a lack of reporting detail for the relevant subgroup. **Source of funding:** This study was supported by the Samjung Scholarship Foundation.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Subbiah V, Kreitman RJ, Wainberg ZA, Cho JY, Schellens JHM, Soria JC, et al. Dabrafenib and trametinib treatment in patients with locally advanced or metastatic BRAF V600-mutant anaplastic thyroid Cancer. J Clin Oncol. 2018;36(1):7-13. **Study location** 47 centres worldwide **Study type** Multicentre, single arm, phase II trial **Study aim** To report the efficacy and safety of dabrafenib and trametinib combination therapy in $BRAF^{V600E}$–mutated ATC. **Study dates** March 12th 2014 to August 26th 2016	Multicentre study of 100 patients with $BRAF^{V600E}$ mutated rare cancers[6] in 7 prespecified histologies. This paper reports the results for the 16 ATC patients only. **Inclusion criteria for ATC cohort** 18 years or more, no standard locally or regionally available treatment options as determined by the treating physician, measurable disease, confirmed $BRAF^{V600E}$ mutation, ECOG performance status of 0 to 2, ability to swallow orally administered medication, and adequate baseline organ function. **Exclusion criteria for ATC cohort** Prior treatment with BRAF and/or MEK inhibitor(s). Radiotherapy was not permitted within 7 days and any treatment-	**Interventions** Patients received continuous dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) until disease progression, unacceptable toxicity, death, or discontinuation for any other reason. Median durations of exposure to dabrafenib and trametinib were 10 and 9 months, respectively. **Comparators** None	Median follow-up 47 weeks (range 4 to 120 weeks) **Critical outcomes** Confirmed responses in the ATC cohort were durable[7], with 7 of 11 responses ongoing at the time of data cut off. **Overall Survival** Median overall survival was not reached because of ongoing responses that resulted in insufficient death events at the time of data cut off. Kaplan-Meier estimates at 12 months of overall survival was 80%. **Progression Free Survival** Median progression free survival was not reached because of ongoing responses that resulted in insufficient progression events at the time of data cut off. Kaplan-Meier estimates at 12 months of progression free survival was 79% **Important outcomes** **Adverse events** **All grades, n (%):** Any: 15 (94) Fatigue: 7 (44) Pyrexia: 5 (31) Nausea: 5 (31) Chills: 4 (25) Vomiting: 4 (25) Headache: 3 (19)	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes **Other comments:** Overall risk of bias rated as low risk due to clear and detailed reporting in the ATC cohort. The ATC cohort reported here was part of a larger cohort of $BRAF^{V600E}$ mutated rare cancers. Enrolment in each primary analysis cohort was capped at 25 patients and futility and efficacy analyses were conducted quarterly. If a cohort closed early for efficacy, an expansion cohort was opened to accommodate additional patient enrolment. On November 6, 2015, the study independent data monitoring committee recommended

[6] V600E: a specific mutation in the BRAF gene.

[7] Durable response: means a long-lasting positive reaction to therapy.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	related adverse events must have been resolved before enrolment. Patients with ATC who were potentially curable by surgical excision alone, had not received standard-of-care treatment, or had thyroid lymphoma, sarcoma, or metastatic disease from other sites were also excluded. **Total sample size** n=16 **Baseline characteristics** Median age 72 (range 56 to 85), 38% men, 63% of Asian heritage. All patients had received prior radiation treatment and/or surgery, and 6 had received prior systemic therapy.		Cough: 2 (13) Diarrhoea: 4 (25) Anaemia: 4 (25) Rash: 4 (25) Constipation: 4 (25) Hyperglycaemia: 5 (31) **Grades 3 and 4, n (%):** Any: 8 (50) Fatigue: 1 (6) Diarrhoea: 1 (6) Anaemia: 2 (13) Hyperglycaemia: 1 (6) **Treatment-related serious adverse events, n (%):** 3 (19) patients with ATC experienced treatment-related serious adverse events (acute kidney injury and rhabdomyolysis, pyrexia, and hyponatremia).	early closure on the basis of the ATC cohort meeting the protocol-specified rules for early efficacy. An ATC expansion cohort was opened; treatment of the first patient began on May 20, 2016, and enrolment continues. The results presented here are results from an interim analysis of data that were available as of August 26, 2016. **Source of funding:** Funded by Novartis Pharmaceuticals and the National Institutes of Health (Grant No. P30-CA016672).
Wang JR, Zafereo ME, Dadu R, Ferrarotto R, Busaidy NL, Lu C, et al. Complete surgical resection following neoadjuvant dabrafenib plus trametinib in BRAF(V600E)-mutated anaplastic thyroid	**Inclusion criteria** Consecutive $BRAF^{V600E}$- mutated ATC patients presenting at the institution with unresectable disease between January 2017 and February 2018 and treated with	**Interventions** Neoadjuvant dabrafenib 150mg twice daily and trametinib 2mg daily were given orally. In patients unable to swallow pills, dabrafenib capsules were dissolved into a suspension	Duration of follow-up from start of BRAF-directed therapy, median 15 months (range: 6.4 to 25.2) **Critical outcomes** **Overall survival** Overall survival at 6 months and 12 months was 100% and 83%, respectively.	This study was appraised using the JBI checklist for case series. 1. Unclear 2. Yes 3. Yes 4. Yes

Study details	Population	Interventions	Study outcomes	Appraisal and funding
carcinoma. Thyroid. 2019;29(8):1036-43. **Study location** The Anderson Cancer Centre at the University of Texas, USA **Study type** Case series **Study aim** To determine the feasibility and effectiveness of a neoadjuvant regimen by using dabrafenib with trametinib followed by surgical resection in patients with initially unresectable $BRAF^{V600E}$-mutated ATC. **Study dates** January 2017 to February 2018	neoadjuvant dabrafenib with trametinib followed by surgical resection. **Exclusion criteria** Participation in a clinical trial. **Total sample size** n=6 **Baseline characteristics** Median age 59 years, 2 (33%) were men. At the time of diagnosis, T stage was T4b in 6 (100%), N stage N1a in 1 (17%), N1b in 5 (83%), and M stage M0 in 4 (67%), M1 in 2 (33%).	and trametinib tablets were crushed. Duration of neoadjuvant treatment median 3.6 months (range 1.6 to 12). When dabrafenib and trametinib were not immediately accessible, cytotoxic chemotherapy (paclitaxel – carboplatin) was utilised as bridging chemotherapy (n not reported). As MEK inhibitors have antiangiogenic properties, trametinib was stopped 5 to 7 days before surgery and dabrafenib was held on the day before or day of surgery with both drugs restarted following wound healing. Surgical resection R0 (no cancer cells seen microscopically at the primary tumour site) in 4/6 patients and R1 (cancer cells present microscopically at the primary tumour site) in 2/6. Adjuvant chemoradiation in 5/6 patients initiated within two to three weeks of surgery when trametinib and dabrafenib are held due to the risk of exaggerated acute toxicity but are resumed when the patient recovers from radiation.	**Proportion of down staged patients** Complete surgical resection was achieved in all 6 patients who were previously inoperable. Locoregional control rate was 100%. Two patients died of distant metastases without evidence of locoregional disease at 8 and 14 months from diagnosis. The remaining four patients had no evidence of disease at the last follow-up. **Important outcomes** **Symptom control** In 4 of 6 patients there was marked improvement in dyspnoea and dysphagia. **Adverse events** Post-op complications that led to treatment interruption included wound infection in 1/6 patients, temporary unilateral vocal cord paresis in 1/6 patients and pulmonary embolism in 1/6 patients.	5. Unclear 6. Yes 7. Yes 8. Yes 9. Yes 10. Unclear **Other comments:** Reported as a consecutive case series but not clear if this was prospective or retrospective. Overall risk of bias rated as low. Limited reporting of inclusion criteria, the numbers included, and statistical analysis where Kaplan Meier curves were not presented as patients were described individually. Overall survival was estimated at 6 and 12 months. **Source of funding:** Not reported

Study details	Population	Interventions	Study outcomes	Appraisal and funding
		Comparators None		
Abbreviations ATC: Anaplastic Thyroid Cancer, CHF: Chronic Heart Failure, CI: Confidence Interval, EBRT: External Beam Radiation Therapy, ECOG: Eastern Cooperative Oncology Group, MEK: Mitogen-activated Protein Kinase, mg: Milligrams, N: Number, TKI: Tyrosine Kinase Inhibitor.				

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for Case Series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series
3. Were valid methods used for the identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

Appendix G GRADE profiles

Outcome measure, units and timepoint in study (for continuous outcomes indicate if benefit is indicated by higher or lower result)									
QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Dabrafenib and trametinib	No comparators	Result		
Overall survival (2 case series, 1 phase II trial)									
Median overall survival (months)									
1 case series Iyer et al 2018	Serious limitations[2]	Serious indirectness[1]	Not applicable	Not calculable	6		Median overall survival was 9.3 months (CI 5.7 to not reached).	Critical	Very low
1 phase II trial Subbiah et al 2018	No serious limitations	Serious indirectness[1]	Not applicable	Not calculable	16		Median overall survival was not reached.	Critical	Very low
Overall survival at 6 months (%)									
1 case series Wang et al 2019	No serious limitations	Serious indirectness[1]	Not applicable	Not calculable	6		Overall survival at 6 months was 100%.	Critical	Very low
Overall survival at 12 months (%)									
1 phase II trial Subbiah et al 2018	No serious limitations	Serious indirectness[1]	Not applicable	Not calculable	16		Overall survival at 12 months was 80%.	Critical	Very low
1 case series Wang et al 2019	No serious limitations	Serious indirectness[1]	Not applicable	Not calculable	6		Overall survival at 12 months was 83%.	Critical	Very low
Progression free survival (3 case series, 1 phase II trial)									
Median progression free survival (months)									
1 case series Iyer et al 2018	Serious limitations[2]	Serious indirectness[1]	Not applicable	Not calculable	6		Median progression free survival was 5.2 months (CI 3.7 to not reached).	Critical	Very low
1 case series	Serious limitations[3]	Serious indirectness[1]	Not applicable	Not calculable	5		Median progression free survival was not reached.	Critical	Very low

Park et al 2021									
1 phase II trial Subbiah et al 2018	No serious limitations	Serious indirectness[1]	Not applicable	Not calculable	16		Median progression free survival was not reached.	Critical	Very low
Progression free survival at 6 months (%)									
1 case series Iyer et al 2018	Serious limitations[2]	Serious indirectness[1]	Not applicable	Not calculable	6		Progression free survival at 6 months was 50% (22% to 100%).	Critical	Very low
Progression free survival at 12 months (%)									
1 phase II trial Subbiah et al 2018	No serious limitations	Serious indirectness[1]	Not applicable	Not calculable	16		Progression free survival at 12 months was 79%.	Critical	Very low
Proportion of down staged patients									
Down staged patients during the study period									
1 case series Wang et al 2019	No serious limitations	Serious indirectness[1]	Not applicable	Not calculable	6		Complete surgical resection was achieved in all 6 patients who were previously inoperable. Locoregional control rate was 100%.	Critical	Very low
Symptom control (1 case series)									
Symptom control during the study period									
1 case series Wang et al 2019	No serious limitations	Serious indirectness[1]	Not applicable	Not calculable	6		In 4 of 6 patients there was marked improvement in dyspnoea and dysphagia.	Important	Very low
Safety/Adverse events (3 case series, I phase II trial)									
Adverse events during study period (N/%)									
1 case series Iyer et al 2018	Serious limitations[2]	Serious indirectness[1]	Not applicable	Not calculable	6		**All grades (N):** Fatigue 4 Hypertension 1 Nausea 4 Anorexia 2 Hyponatremia 3 Hypothyroidism 2 Hand–foot skin reaction 3 Weight loss 3 Anaemia 3	Important	Very low

							Diarrhoea 2 Transaminitis 1 Elevated alkaline phosphatase 1 Vomiting 2 Lower extremity oedema 2 Bleeding 1 Constipation 1 Fever 1 Hypercalcemia 1 **Grade 3 (N):** Fatigue 1 Hyponatremia 2 Anaemia 1 Hypercalcemia 1 No grade 4 or higher adverse events were noted.		
1 case series Park et al 2021	Serious limitations[3]	Serious indirectness[1]	Not applicable	Not calculable	5		Four out of 5 patients were still being treated without adverse events at the time of data collection.	Important	Very low
1 Phase II trial Subbiah 2018	No serious limitations	Serious indirectness[1]	Not applicable	Not calculable	16		**All grades, N (%):** Any 15 (94) Fatigue 7 (44) Pyrexia 5 (31) Nausea 5 (31) Chills 4 (25) Vomiting 4 (25) Headache 3 (19) Cough 2 (13) Diarrhoea 4 (25) Anaemia 4 (25) Rash 4 (25) Constipation 4 (25) Hyperglycaemia 5 (31) **Grades 3 and 4, N (%):** Any 8 (50) Fatigue 1 (6) Diarrhoea 1 (6) Anaemia 2 (13) Hyperglycaemia 1 (6)	Important	Very low

							Three patients with ATC experienced treatment-related serious adverse events (acute kidney injury and rhabdomyolysis, pyrexia, and hyponatremia).		
1 case series Wang 2019	No serious limitations	Serious indirectness[1]	Not applicable	Not calculable	6		Post-op complications that led to treatment interruption included wound infection in 1/6 patients, temporary unilateral vocal cord paresis in 1/6 patients and pulmonary embolism in 1/6 patients.	Important	Very low
Abbreviations CI: Confidence Interval, N: Number of participants									

1 Indirectness: Serious indirectness due to no comparison across treatment arms
2 Risk of bias: Serious limitations due to limited reporting of inclusion criteria, limited information reported to determine whether study included all eligible patients and no demographics and clinical information reported for in-scope patients
3 Risk of bias: Serious limitations due to limited reporting of inclusion criteria, limited information reported to determine whether study included all eligible patients, limited reporting of demographic and clinical data for in-scope patients and limited information reported on statistical analysis in order to determine if methods were appropriate

Glossary

Term	Definition
Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether or not the event is suspected to be related to or caused by the drug, treatment or intervention.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
Case series	Reports of several patients with a given condition, usually covering the course of the condition and the response to treatment. There is no comparison (control) group of patients.
Clinical importance or significance	A benefit from treatment that relates to an important outcome such as length of life and is large enough to be important to patients and health professionals. As an example, it might include a general reduction in symptoms, less pain or improved breathing. Effects identified as statistically significant are not always clinically significant, because the effect is small, or the outcome is not important. For example, if a treatment might lower blood pressure but there may be no evidence that this leads to an important clinical outcome, such as a lower risk of stroke or heart attack.
Comparator	The standard (for example, another intervention or usual care) against which an intervention is compared in a study. The comparator can be no intervention (for example, best supportive care).
Confidence interval	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval (CI) indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow CI indicates a more precise estimate (for example, if a large number of patients have been studied). The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that 'based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110'. In such a case the 95% CI would be 110 to 150.
Data	Data are the information collected through research. They can include written information, numbers, sounds and pictures.
Diagnosis	The process of identifying a disease or condition by carrying out tests or by studying the symptoms.
Evidence statement	A brief summary of the key findings from a review of evidence.
GRADE	GRADE, or grading of recommendations assessment, development and evaluation, is a systematic and explicit approach to grading the quality of evidence and the strength of recommendations.
Health-related quality of life	A combination of a person's physical, mental and social well-being; not merely the absence of disease.
Intervention	In medical terms this could be a drug treatment, surgical procedure, diagnostic test or psychological therapy. Examples of public health interventions could include action to help someone to be physically active

	or to eat a healthier diet. Examples of social care interventions could include safeguarding or support for carers.
Minimal clinically important difference	The smallest change in a treatment outcome that people with the condition would identify as important (either beneficial or harmful), and that would lead a person or their clinician to consider a change in treatment.
NICE guidance	Evidence-based recommendations produced by NICE. There are 6 types of guidance: guidelines covering clinical topics, medicines practice, public health and social care diagnostics guidance highly specialised technology guidance interventional procedures guidance medical technologies guidance technology appraisals guidance. All guidance is developed by independent committees and is consulted on. NICE may also publish a range of supporting documents for each piece of guidance, including advice on how to put the guidance into practice, and on its costs, and the evidence it is based on.
Objective measure	A measurement that follows a standardised procedure which is less open to subjective interpretation by potentially biased observers and people in the study.
Outcomes	The impact that a test, treatment, policy, programme or other intervention has on a person, group or population. Depending on the intervention, outcomes could include changes in knowledge and behaviour related to health or in people's health and wellbeing, the number of patients who fully recover from an illness or the number of hospital admissions, and an improvement or deterioration in someone's health, symptoms or situation.
PICO	A PICO (population, intervention, comparison and outcome) framework is a structured approach for developing review questions. It divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
Population	A group of people with a common link, such as the same medical condition or living in the same area or sharing the same characteristics. The population for a clinical trial is all the people the test or treatment is designed to help (such as adults with diabetes). The group of people taking part in a clinical trial need to be typical of the whole population of interest.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.

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Included studies

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