NHS England Evidence Review:

Pembrolizumab in combination with dabrafenib and trametinib for patients with BRAF-mutated anaplastic thyroid cancer (all ages)

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

Contents

1. Introduction 3
2. Executive summary of the review 4
3. Methodology 8
4. Summary of included studies 9
5. Results 12
6. Discussion 18
7. Conclusion 20
Appendix A PICO document 21
Appendix B Search strategy 21
Appendix C Evidence selection 25
Appendix D Excluded studies table 27
Appendix E Evidence table 28
Appendix F Quality appraisal checklists 34
Appendix G GRADE profiles 35
Glossary 40
References 42

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of pembrolizumab in combination with dabrafenib and trametinib compared to current standard care in patients with inoperable BRAF-mutated anaplastic thyroid cancer (ATC) of all ages with or without metastases.

Pembrolizumab is a monoclonal antibody (a type of biological medicine). It is an immune checkpoint inhibitor and works by deactivating ATC's ability to evade its host's immune system. This slows uncontrolled cell division and tumour growth. Pembrolizumab is typically administered as an infusion once every three weeks.

In healthy patients, programmed cell death protein 1 (PD-1) receptors on T-cells (a type of white blood cell) bind to PD-L1 or PD-L2 ligands on normal cells in the body. This regulates the immune system and prevents the immune-mediated tissue destruction. In ATC, cancer cells produce high levels of PD-L1. ATC PDL-1 binds to PD-1 receptors on the host's T cells. This deactivates T cells and allows ATC to attack the host's tissues and grow uncontrollably without the immune system stopping this. Pembrolizumab binds and blocks PD-1 on T-cells. This prevents ATC from binding to these same receptors and causing uncontrolled cell division.

As ATC is usually diagnosed at a late stage and tumours are close to vital structures, ATC is rarely operable. A small number of patients may be suitable for palliative chemotherapy or radiotherapy. However, the benefit for patients undergoing these treatments is marginal.

For ATCs that carry a BRAF mutation, therapies targeted to this genetic mutation can be used. The introduction of dual therapy with dabrafenib (a BRAF inhibitor) and trametinib (a MEK inhibitor) have significantly improved prognosis and this is the current standard treatment in England. However, patients may eventually develop resistance to this treatment combination leading to disease progression.

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from treatment with pembrolizumab in combination with dabrafenib and trametinib more than others, as well as the age ranges of participants in the included studies.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of pembrolizumab in combination with dabrafenib and trametinib (DTP) compared with dabrafenib and trametinib combined (DT) in patients (all ages) with inoperable BRAF-mutated anaplastic thyroid cancer (ATC). The searches for evidence published since January 2014 were conducted on 3 October 2024 and identified 322 references. The titles and abstracts were screened, and seven full text papers were obtained and assessed for relevance.

Two papers were identified for inclusion, one retrospective cohort study and one subgroup of patients from a retrospective case series. The retrospective cohort study included 71 adults with BRAF-mutated ATC and compared DTP to DT with a follow-up of 28 months (range 3 to 63 months) for the DTP group and 102 months (range 0.6 to 102 months) for the DT group (Hamidi et al 2024). The retrospective case series of 13 adults with locally advanced or metastatic unresectable ATC receiving immune checkpoint inhibitors included a subgroup of seven in scope patients with BRAF-mutated ATC receiving DTP with a follow-up of up to 20 months (Hatashima et al 2022). The studies were each carried out in single centres in the US.

In terms of clinical effectiveness:

Critical outcomes

- **Progression free survival**
  - One retrospective cohort study of patients with inoperable BRAF-mutated ATC provided very low certainty evidence of a *statistically significant* increase in median progression free survival in 30 patients receiving upfront DTP (11.0 months (95% CI 7.0 to 15.0)) compared to 31 patients receiving upfront DT (4.0 months (95% CI 0.7 to 7.3)) at a median follow-up of 28 months for the DTP group and 102 months for the DT alone group.
- **Response to treatment**
  - One retrospective cohort study and one subgroup of a retrospective case series provided very low certainty evidence relating to response to treatment in patients with inoperable BRAF mutated ATC. The retrospective cohort study reported *no statistically significant* difference in the response rate for 30 patients receiving upfront DTP (ORR: 73.3%) compared to 31 patients receiving upfront DT (ORR: 64.5%) at a median follow-up of 28 months for the DTP group and 102 months for the DT group. The subgroup of a retrospective case series reported that six out of seven patients receiving DTP had progressive disease or death at up to 20 months follow-up.
- **Overall survival**
  - One retrospective cohort study (n=71) and one subgroup (n=7) of a retrospective case series (n=13) provided very low certainty evidence on overall survival in patients with inoperable BRAF-mutated ATC. The retrospective cohort study reported a *statistically significant* increase in median overall survival in patients with inoperable BRAF-mutated ATC receiving DTP with pembrolizumab either upfront or on progression (17.0 months) compared to patients receiving DT alone (9.0 months) at a median follow-up of 28 months for DTP group and 102 months for DT group. An increase in 12-months and 24-months overall survival was also reported with DTP; data were not statistically compared. The retrospective case series of adults with locally advanced or metastatic unresectable ATC receiving immune checkpoint inhibitors reported that the median overall survival from diagnosis was 15.6 months for all patients in the case series and

this remained unchanged regardless of BRAF status at up to 20 months follow-up. Four out of the seven patients with BRAF-mutated ATC receiving DTP died at up to 20 months follow-up.

Important outcomes

- **Quality of life**
  - No evidence was identified for this outcome.
- **Performance status/Activities of daily living**
  - No evidence was identified for this outcome.
- **Time to treatment failure**
  - One subgroup (n=7) of a retrospective case series (n=13) provided very low certainty evidence on time to treatment failure in patients with locally advanced or metastatic unresectable BRAF-mutated ATC up to 20 months follow-up. The study reported that one patient had progressive disease and pembrolizumab was discontinued at nine weeks after initiation of pembrolizumab.
- **Symptom control**
  - No evidence was identified for this outcome.

In terms of safety:

- One retrospective cohort study and one subgroup of a retrospective case series provided very low certainty evidence on adverse events in patients with inoperable BRAF-mutated ATC. The retrospective cohort study reported that 13 (27%) patients with inoperable BRAF-mutated ATC receiving DTP with pembrolizumab either upfront or on progression experienced immune related adverse events and no patients experienced Grade 5 adverse events at a median follow-up of 28 months. One subgroup of seven patients with BRAF-mutated ATC from a retrospective case series of locally advanced or metastatic unresectable ATC patients receiving DTP with pembrolizumab either upfront or on progression reported that one patient experienced Grade 2 joint pain, myalgias, and neuropathy and another patient developed diplopia and Bell's palsy at up to 20 months follow-up. No comparative evidence was identified.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness

In terms of subgroups:

- No evidence was identified for subgroups

In terms of age ranges of study participants:

- The age range of participants across the two included studies was 46 to 92 years. The retrospective cohort study included participants with a median age of 67 years (range 46 to 81 years) in the DTP group and 68 years (range 51 to 92 years) in the DT group. The in scope participants in the retrospective case series had an age range of 56 to 82 years.

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

Limitations

Both studies were considered to be at high risk of bias and certainty about the evidence for the critical and important outcomes was very low when assessed using modified GRADE. The main limitations for the retrospective cohort study were that baseline characteristics were not reported for the upfront DT group and upfront DTP group so it was not possible to determine whether the groups were balanced at baseline for the overall response rate and progression free survival outcomes. Furthermore, for these outcomes, effect sizes will be diluted due to both the upfront DT and upfront DTP groups including patients receiving pembrolizumab (the intervention of interest). For all outcomes, confounders were not identified or adjusted for across the groups which may have introduced bias. Median duration of follow-up was longer for the DT group compared to the DTP group (102 months vs 28 months) which may have introduced bias by disproportionately capturing more events and longer survival times in the DT group while potentially underestimating outcomes in the DTP group. Furthermore, for progression free survival and response outcomes, only 30 out of 34 patients in the upfront DTP group and 31 out of 37 patients in the upfront DT group were evaluable for response which may have introduced attrition bias. Finally, adverse events were only reported for the DTP group so the extent to which these are attributable to pembrolizumab is not known. The main limitations relating to the retrospective case series are the lack of a comparator group and the very limited results reported with no summary statistics for the in scope patients. Other limitations include the small sample size and the retrospective nature of both the included studies, and the small number of included studies.

Both studies were conducted in single centres in the US and it is not clear if the patients and aspects of care in the studies reflect that seen in clinical practice in England and care is needed in generalising results to the NHS.

Conclusion

This evidence review includes one retrospective cohort study (n=71) comparing DTP to DT with a median follow-up of 28 months (DTP group) to 102 months (DT group) and one subgroup (n=7) of a retrospective case series of DTP with a follow-up of up to 20 months in patients with inoperable BRAF-mutated ATC.

The studies provide very low certainty evidence for the critical outcomes of progression free survival, response to treatment and overall survival, and the important outcomes of time to treatment failure and safety. No studies were identified that reported the important outcomes of quality of life, performance status/activities of daily living and symptom control.

Evidence from one retrospective cohort study suggests that DTP compared to DT for BRAF-mutated ATC increases median progression free survival (11 months vs 4 months; p=0.049) and median overall survival (17 months vs 9 months; p=0.037). Results for response to treatment and time to treatment failure were inconclusive.

With respect to safety, one retrospective cohort study reported that 27% of patients with BRAF-mutated ATC receiving DTP experienced immune related adverse events and one subgroup of patients with BRAF-mutated ATC receiving DTP from a retrospective case series reported that one patient experienced Grade 2 joint pain, myalgias and neuropathy and another patient developed diplopia and Bell’s palsy. No comparative evidence was found for safety.

No evidence on cost effectiveness was found.

No evidence was identified regarding any subgroups of patients that would benefit more from DTP.

The studies included in this review provide very low certainty evidence of an increase in progression free survival and overall survival with DTP compared to DT in patients with inoperable BRAF-mutated ATC.

3. Methodology

Review questions

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

1. In people with inoperable BRAF-mutated ATC, what is the clinical effectiveness of pembrolizumab in combination with dabrafenib and trametinib compared to dabrafenib and trametinib combined?
2. In people with inoperable BRAF-mutated ATC, what is the safety of pembrolizumab in combination with dabrafenib and trametinib compared to dabrafenib and trametinib combined?
3. In people with inoperable BRAF-mutated ATC, what is the cost-effectiveness of pembrolizumab in combination with dabrafenib and trametinib compared to dabrafenib and trametinib combined?
4. From the evidence selected, are there any subgroups of patients that may benefit more from pembrolizumab in combination with dabrafenib and trametinib more than the wider population of interest?
5. From the evidence selected, what were the age ranges of study participants?

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 3 October 2024.

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

Two papers were identified for inclusion (Hamidi et al 2024 & Hatashima et al 2022). Hamidi et al (2024) reported results for a retrospective cohort study which compared patients with BRAF-mutated ATC receiving dabrafenib, trametinib and pembrolizumab (DTP) to dabrafenib and trametinib (DT) alone. For the primary outcome, overall survival, DTP with pembrolizumab given upfront or at progression (DTP group) was compared to DT (DT alone group). However, for the secondary outcomes of progression free survival (PFS) and overall response, DTP with pembrolizumab given upfront only (DTP upfront group) was compared to DT given upfront (DT upfront group) which included patients given pembrolizumab at progression. Hamidi et al (2024) also included an exploratory group of patients on neoadjuvant DTP, which is out of scope for this review and, therefore, has not been included. Hatashima et al (2022) reported on a retrospective case series of patients with locally advanced or metastatic unresectable ATC receiving immune checkpoint inhibitor therapy (pembrolizumab or nivolumab) and included a subgroup of in scope patients with BRAF-mutated ATC receiving DTP. Results for these in scope patients only were included in this review. No studies reporting on cost effectiveness were found.

Table 1 provides a summary of the included studies and full details are given in Appendix E.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported

Hamidi et al (2024)
 	
Retrospective cohort study
 	
US (single centre)
	71 patients with inoperable[a] BRAF-mutated[b] ATC
	
	DTP: n=48[c]
	• Upfront DTP: n=34
	• Pembrolizumab added at progression[d]: n=14
	DT alone: n=23
	
	Median (range) age (years):
	• DTP: 67 (46 to 81)
	• DT: 68 (51 to 92)
	
	Female, n (%):
	• DTP: 22 (46)
	• DT: 11 (48)
	
	Distant metastases at initiation of systemic therapy, n (%):
	• DTP: 38 (79)
	• DT: 20 (87)
	
	Prior therapy for ATC, n (%): EBRT to the neck:
	• DTP: 17 (35)
	• DT: 7 (30)
	
	Surgery:
	• DTP: 24 (50)
	• DT: 11 (48)
	
	Bridging cytotoxic chemotherapy:
	• DTP: 4 (8)
		Intervention
		
		DTP
		
		Pembrolizumab added upfront or at progression
		
		A single infusion of pembrolizumab was sufficient to consider the patient as having received pembrolizumab
		
		Median (range) duration of DT (months): 10 (2 to 63)
		
		Median (range) duration of pembrolizumab (months): 5 (1 to 55)
		
		Median (range) time between DT and pembrolizumab (days): 75 (-8 to 1,308)
		
		Dose: not reported
		
		Concomitant treatments: not reported
		
		Comparison
		
		DT alone
		
		Median (range) duration of DT (months): 6 (0.6 to 88)
			Median (range) follow-up (months):
			• DTP: 28 (3 to 63)
			• DT: 102 (0.6 to 102)
			Critical outcomes
			• Progression free survival[e]
			  • Median PFS
			• Response to treatment[f]
			  • Overall response rate
			• Overall survival[g]
			  • Median OS
			  • OS at 12 & 24 months
			Important outcomes
			• Safety
			  • Immune related AEs
			  • Grade 5 AEs

Study	Population	Intervention and comparison	Outcomes reported
	• DT: 1 (4) No subgroups reported		

Hatashima et al (2022)
 	
Retrospective case series
 	
US
	13 patients with locally advanced or metastatic unresectable ATC
	
	Subgroup of 7 patients in scope who had BRAF-mutated ATC
	
	n=7
	Age range (years): 56 to 82
	
	Female, n (%): 5 (71)
	
	Ethnicity White: 6 (86)
	
	Stage:
	• IVA: 2 (29)
	• IVB: 1 (14)
	• IVC: 4 (57)
	
	Prior treatment for ATC:
	• Naïve: 1
	• Surgery: 3
	• Chemotherapy: 4
	• Radiation: 4
	
	No subgroups reported
		Intervention
		
		DTP[h]
		
		Pembrolizumab added upfront or at progression
		
		Pembrolizumab (200 or 400 mg IV every three or six weeks, respectively)
		
		Concomitant treatments: 1 patient received radiation to growing lesion while on pembrolizumab
		
		Median duration of immunotherapy: 1.9 months (range 1 week to 29 months (ongoing)[i]
		
		Comparison
		
		None
			Up to 20 months follow-up for in scope patients[j]
			
			Critical outcomes
			
			• Response to treatment
			  • Objective response[k]
			• Overall survival[l]
			  • Median OS
			  • Deaths[m]
			
			Important outcomes
			
			• Time to treatment failure
			• Safety
			  • AEs

Abbreviations

AE: adverse event; ATC: anaplastic thyroid carcinoma; BRAF: B-type Raf kinase; DNA: deoxyribonucleic acid; DT: dabrafenib and trametinib; DTP: dabrafenib and trametinib plus pembrolizumab; IV: intravenous; n: number; mg: milligram; OS: overall survival; PFS: progression-free survival; US: United States

Footnotes

a. Although not explicitly stated, it was assumed that patients included in the main analysis (n=71) of the paper had inoperable ATC. Operable patients were included in an exploratory neoadjuvant DTP group and these patients were not included in the main analysis of the paper or in this review. Any patients who received surgery in the DT and DTP groups in the main analysis, received surgery prior to pembrolizumab and, therefore, could be deemed inoperable at time of pembrolizumab. Any patients who were treated with neoadjuvant-intent DT or DTP who did not ultimately undergo surgery due to either an inadequate response or patient declining surgery were included in the main analysis DT and DTP groups.

b. Identified by immunohistochemistry and/or next-generation sequencing testing of tumour tissue or cell-free DNA (liquid biopsy).

c. One patient received nivolumab instead of pembrolizumab.

d. For the primary outcome, overall survival, patients receiving DT plus pembrolizumab upfront or at progression (DTP group) were compared to patients receiving DT (DT alone group). For the secondary outcomes, progression free survival and response to treatment, patients receiving DT plus pembrolizumab upfront (DTP upfront) were compared to patients receiving DT upfront which included patients who received pembrolizumab at progression (DT upfront group).

e. Defined as the time between the first dose of pembrolizumab and documented disease progression or death.

f. Response was assessed by percentage change in target lesion size between initial and serial post-treatment computed tomography (CT) scans and/or 18F-fluorodeoxyglucose positron emission tomography combined with CTs, using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Study	Population	Intervention and comparison	Outcomes reported
g. Defined as time between the first dose of pembrolizumab and death from any cause. h. Patients received either pembrolizumab (n=12) or nivolumab (n=1). The seven in scope patients with $BRAF^{V600E}$ mutations all received pembrolizumab. i. Median duration for total sample (n=13). Not reported separately for in scope patients (n=7). j. Taken from Swimmer plot of responses (Figure 3 in paper). Median length of follow-up was not reported for in-scope patients or total sample. k. Response was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Results for in scope patients at an individual level were extracted from the text and a Swimmer plot of responses (Figure 3 in paper). l. Overall survival from diagnosis was defined as the time from collection of the first sample that reported pathology/cytology consistent with ATC to death from any cause or censoring. m. Taken from Swimmer plot of responses (Figure 3 in paper). Median length of follow-up was not reported for in-scope patients or total sample.			

5. Results

In people with inoperable BRAF-mutated ATC, what is the clinical effectiveness and safety of pembrolizumab in combination with dabrafenib and trametinib compared with dabrafenib and trametinib combined?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Progression free survival **Certainty of evidence:** Very low	This outcome is important to patients because it represents the time for which their disease is not progressing. Stable disease may represent longer survival and disease stability may result in patients experiencing fewer symptoms from the disease itself. It can be determined sooner than overall survival outcome measures. One retrospective cohort study provided evidence on progression free survival in patients with inoperable[1] BRAF-mutated ATC receiving DTP compared to DT. **At a median follow-up of 28 months (range 3 to 63 months) for DTP group and 102 months (range 0.6 to 102 months) for DT alone group[2]:** *Upfront DTP vs upfront DT*[3] • One retrospective cohort study (Hamidi et al 2024) reported a *statistically significant* increase (p=0.049) in median progression free survival in adults with inoperable BRAF-mutated ATC receiving upfront DTP (n=30, 11.0 months (95% CI 7.0 to 15.0)) compared to patients receiving upfront DT (n=31, 4.0 months (95% CI 0.7 to 7.3)). **(VERY LOW)** **One retrospective cohort study of patients with inoperable BRAF-mutated ATC provided very low certainty evidence of a *statistically significant* increase in median progression free survival in 30 patients receiving upfront DTP (11.0 months (95% CI 7.0 to 15.0)) compared to 31 patients receiving upfront DT (4.0 months (95% CI 0.7 to 7.3)) at a median follow-up of 28 months for the DTP group and 102 months for the DT alone group.**
Response to treatment **Certainty of evidence:** Very low	Response rate is important to patients as it represents whether the treatment can improve disease burden and improve symptoms. Improving disease burden is important as patients may have sufficient response that their tumour is rendered operable. Operable cancers are amenable to potentially curative resection which significantly improves prognosis. One retrospective cohort study and one subgroup of a retrospective case series provided evidence relating to response to treatment in patients with inoperable BRAF-mutated ATC. One study compared DTP to DT and one study reported non-comparative results for patients receiving DTP for a subgroup of BRAF-mutated ATC patients. **At a median follow-up of 28 months (range 3 to 63 months) for DTP group and 102 months (range 0.6 to 102 months) for DT group:**

[1] Although not explicitly stated, it was assumed that patients included in the main analysis (n=71) of the paper had inoperable ATC. Operable patients were included in an exploratory neoadjuvant DTP group and these patients were not included in the main analysis of the paper or in this review. Any patients who received surgery in the DT and DTP groups in the main analysis, received surgery prior to pembrolizumab and therefore could be deemed inoperable at time of pembrolizumab. Any patients who were treated with neoadjuvant-intent DT or DTP who did not ultimately undergo surgery due to either an inadequate response or patient declining surgery were included in the main analysis DT and DTP groups.
[2] Median follow-up only reported for DTP group (pembrolizumab given upfront and at progression) and DT alone group. Median follow-up not reported for upfront DTP and upfront DT groups.
[3] DT upfront group includes patients given pembrolizumab at progression. Fourteen patients who had DT upfront were given pembrolizumab at progression but the number of these patients who were evaluable for response, and hence included in the PFS results, was not reported.

Outcome	Evidence statement

	Upfront DTP vs upfront DT[4]
	• One retrospective cohort study (Hamidi et al 2024) reported *no statistically significant* difference (p=0.205) in the overall response rate[5] in adults with inoperable BRAF-mutated ATC receiving upfront DTP (n=30, ORR: 73.3%; stable disease: 6 (20%), partial response: 14 (47%), complete response: 8 (27%), progressive disease: 0 (0%), non-evaluable: 2 (7%)) compared to patients receiving upfront DT (n=31, ORR: 64.5%; stable disease: 5 (16%), partial response: 16 (52%), complete response: 4 (13%), progressive disease: 3 (10%), non-evaluable: 3 (10%)). **(VERY LOW)**
	
	Up to 20 months follow-up[6]:
	
	DTP
	• One subgroup of patients with BRAF-mutated ATC receiving DTP (with pembrolizumab either upfront or on disease progression, n=7) from a retrospective case series of adults with locally advanced or metastatic unresectable ATC receiving immune checkpoint inhibitors (n=13),[7] reported on response to DTP for individual patients. These were as follows:
	  • Patient #2: progressive disease at nine weeks after initiation of therapy, pembrolizumab discontinued and chemo-radiation followed by chemotherapy initiated, alive with stable disease at 20 months after initiation of pembrolizumab
	  • Patient #4: stable disease at 0.5 to 8.5 months after initiation of therapy, progressive disease at 8.5 months, death at 15.5 months
	  • Patient #5: stable disease at start of therapy, oligoprogression at six months which was also treated with local radiotherapy
	  • Patient #7: stable disease at one to four months after initiation of therapy (ongoing)
	  • Patient #8: progressive disease at one month after initiation of therapy, death at 1.5 months
	  • Patient #10: progressive disease and death at one month after initiation of therapy
	  • Patient #12: death at 0.5 months after initiation of therapy **(VERY LOW)**
	
	One retrospective cohort study and one subgroup of a retrospective case series provided very low certainty evidence relating to response to treatment in patients with inoperable BRAF-mutated ATC. The retrospective cohort study reported *no statistically significant* difference in the overall response rate for 30 patients receiving upfront DTP (ORR: 73.3%) compared to 31 patients receiving upfront DT (ORR: 64.5%) at a median follow-up of 28 months for the DTP group and 102 months for the DT group. The subgroup of a retrospective case series reported that six out of seven patients receiving DTP had progressive disease or death at up to 20 months follow-up.

Overall survival **Certainty of evidence:**	Overall survival is important to patients as ATC has a high mortality rate due to advanced disease and limited treatment options. Improved survival is an important

[4] DT upfront group includes patients given pembrolizumab at progression. Fourteen patients who had DT upfront were given pembrolizumab at progression but the number of these patients who were evaluable for response and hence included in the response results was not reported.
[5] Response was assessed by percentage change in target lesion size between initial and serial post-treatment computed tomography (CT) scans and/or 18F-fluorodeoxyglucose positron emission tomography combined with CTs, using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.
[6] Taken from Swimmer plot of responses (Figure 3 in paper). Median length of follow-up was not reported for in-scope patients or total sample.
[7] Patients received either pembrolizumab (n=12) or nivolumab (n=1). The seven patients with $BRAF^{V600E}$ mutations, in scope for this review, all received pembrolizumab.

Outcome	Evidence statement
Very low	marker of effective treatment. Overall survival does not however give indication to a patient's quality of life during this time. One retrospective cohort study and one subgroup of a retrospective case series provided evidence on overall survival in patients with inoperable BRAF-mutated ATC. One study compared DTP to DT and one study reported non-comparative results for patients receiving DTP for a subgroup of BRAF-mutated ATC patients. Median overall survival **At a median follow-up of 28 months (range 3 to 63 months) for DTP group and 102 months (range 0.6 to 102 months) for DT group:** *DTP vs DT alone*[8] • One retrospective cohort study (Hamidi et al 2024) reported a *statistically significant* increase (p=0.037) in median overall survival[9] in 48 adults with inoperable BRAF-mutated ATC receiving DTP (with pembrolizumab either upfront or on disease progression) (17.0 months (95% CI 11.9 to 22.1)) compared to 23 patients receiving DT alone (9.0 months (95% CI 4.5 to 13.5)). **(VERY LOW)** **Up to 20 months follow-up:** • One subgroup of patients with BRAF-mutated ATC receiving DTP (with pembrolizumab either upfront or on disease progression, n=7) from a retrospective case series of adults with locally advanced or metastatic unresectable ATC receiving immune checkpoint inhibitors (n=13), reported that the median overall survival[10] from diagnosis was 15.6 months for all patients in the case series and this remained unchanged regardless of BRAF status. **(VERY LOW)** 12-months overall survival **At a median follow-up of 28 months (range 3 to 63 months) for DTP group and 102 months (range 0.6 to 102 months) for DT group:** *DTP vs DT alone* • One retrospective cohort study (Hamidi et al 2024) reported a higher 12-month overall survival in 48 adults with inoperable BRAF-mutated ATC receiving DTP (with pembrolizumab either upfront or on progression) (60.2%) compared to 23 patients receiving DT alone (36.7%). No statistical tests were reported. **(VERY LOW)** 24-months overall survival **At a median follow-up of 28 months (range 3 to 63 months) for DTP group and 102 months (range 0.6 to 102 months) for DT group:** *DTP vs DT alone* • One retrospective cohort study (Hamidi et al 2024) reported a higher 24-month overall survival in 48 adults with inoperable BRAF-mutated ATC receiving DTP (with pembrolizumab either upfront or on progression) (36.5%) compared to 23 patients receiving DT alone (31.5%). No statistical tests were reported. **(VERY LOW)** Number of deaths[11]

[8] DTP group included patients receiving DT plus pembrolizumab upfront or at progression. DT alone group included patients receiving DT.
[9] Defined as time between the first dose of pembrolizumab and death from any cause.
[10] Overall survival from diagnosis was defined as the time from collection of the first sample that reported pathology/cytology consistent with ATC to death from any cause or censoring.
[11] Taken from Swimmer plot of responses (Figure 3 in paper). Median length of follow-up was not reported for in-scope patients or total sample.

Outcome	Evidence statement
	Up to 20 months follow-up: • One subgroup of patients with BRAF-mutated ATC receiving DTP (with pembrolizumab either upfront or on disease progression, n=7) from a retrospective case series of adults with locally advanced or metastatic unresectable ATC receiving immune checkpoint inhibitors (n=13), reported that four (57%) patients died. No further details given. **(VERY LOW)** **One retrospective cohort study (n=71) and one subgroup (n=7) of a retrospective case series (n=13) provided very low certainty evidence on overall survival in patients with inoperable BRAF-mutated ATC. The retrospective cohort study reported a *statistically significant increase* in median overall survival in patients with inoperable BRAF-mutated ATC receiving DTP with pembrolizumab either upfront or on progression (17.0 months) compared to patients receiving DT alone (9.0 months) at a median follow-up of 28 months for the DTP group and 102 months for the DT group. An increase in 12-months and 24-months overall survival was also reported with DTP; data were not statistically compared. The retrospective case series of adults with locally advanced or metastatic unresectable ATC receiving immune checkpoint inhibitors reported that the median overall survival from diagnosis was 15.6 months for all patients in the case series and this remained unchanged regardless of BRAF status at up to 20 months follow-up. Four out of the seven patients with BRAF-mutated ATC receiving DTP died at up to 20 months follow-up.**
Important outcomes	
Quality of life **Certainty of evidence:** Not applicable	Quality of life is important to patients as it provides an indication of an individual's general health, their self-perceived well-being and their ability to participate in activities of daily living. Measurement of quality of life can help inform patient-centred decision making and inform health policy. **No evidence was identified for this outcome.**
Performance status/Activities of daily living (ADLs) **Certainty of evidence:** Not applicable	ADLs are important outcomes to patients as they facilitate enablement and independence, allowing individuals to function in education, work, home, and recreational settings. They encompass patients' individual needs and facilitate inclusion and participation. **No evidence was identified for this outcome.**
Time to treatment failure **Certainty of evidence:** Very low	This is important because it reflects overall treatment failure due to disease progression, adverse events or death. One subgroup of a retrospective case series provided evidence relating to time to treatment failure in patients with inoperable BRAF-mutated ATC receiving DTP. **Up to 20 months follow-up:** *DTP* • One subgroup of patients with BRAF-mutated ATC receiving DTP (with pembrolizumab either upfront or on disease progression, n=7) from a retrospective case series of adults with locally advanced or metastatic unresectable ATC receiving immune checkpoint inhibitors (n=13), reported that one patient had progressive disease and pembrolizumab was discontinued at nine weeks after initiation of pembrolizumab. Chemo-radiation followed by chemotherapy was initiated and the patient was reported to be alive with stable disease at 20 months after initiation of pembrolizumab. **One subgroup (n=7) of a retrospective case series (n=13) provided very low certainty evidence on time to treatment failure in patients with locally advanced or metastatic unresectable BRAF-mutated ATC up to 20 months**

Outcome	Evidence statement
	follow-up. The study reported that one patient had progressive disease and pembrolizumab was discontinued at nine weeks after initiation of pembrolizumab.
Symptom control **Certainty of evidence:** Not applicable	Symptom control is an important outcome as it is a marker for the ability of the treatment to improve functional capacity and quality of life. **No evidence was identified for this outcome.**
Safety	
Adverse events **Certainty of evidence:** Very low	These outcomes are important to patients because they will an impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects (AEs) of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment. One retrospective cohort study and one subgroup of a retrospective case series provided evidence on AEs in patients with inoperable BRAF-mutated ATC. Both studies reported non-comparative results for patients receiving DTP. **At a median follow-up of 28 months (range 3 to 63 months):** *DTP* • One retrospective cohort study (Hamidi et al 2024) reported that 13 (27%) out of 48 adults with inoperable BRAF-mutated ATC receiving DTP (with pembrolizumab either upfront or on progression) experienced immune related AEs. These were, n (%): colitis: 4 (8), nephritis: 3 (6), hepatitis: 2 (4), encephalopathy: 1 (2), DRESS: 1 (2), elevation in creatine kinase: 1 (2), pneumonitis: 1 (2), polyneuropathy: 1 (2), Sjogren: 1 (2), STEMI: 1 (2%), and thrombocytopenia: 1 (2). None of the patients experienced Grade 5 adverse events. **Up to 20 months follow-up:** *DTP* • One subgroup of patients with BRAF-mutated ATC receiving DTP (with pembrolizumab either upfront or on disease progression, n=7) from a retrospective case series of adults with locally advanced or metastatic unresectable ATC receiving immune checkpoint inhibitors (n=13), reported that one patient experienced Grade 2 joint pain, myalgias, and neuropathy, which were responsive to steroids and another patient developed diplopia and Bell's palsy which the authors reported was not likely to be treatment related, but causation could not be completely ruled out. **One retrospective cohort study and one subgroup of a retrospective case series provided very low certainty evidence on adverse events in patients with inoperable BRAF-mutated ATC. The retrospective cohort study reported that 13 (27%) patients with inoperable BRAF-mutated ATC receiving DTP with pembrolizumab (either upfront or on progression) experienced immune related adverse events and no patients experienced Grade 5 adverse events at a median follow-up of 28 months. One subgroup of seven patients with BRAF-mutated ATC from a retrospective case series of locally advanced or metastatic unresectable ATC patients receiving DTP (with pembrolizumab either upfront or on progression) reported that one patient experienced Grade 2 joint pain, myalgias, and neuropathy and another patient developed diplopia and Bell's palsy at up to 20 months follow-up. No comparative evidence was identified.**

Abbreviations
ADL: activities of daily living; AE: adverse event; ATC: anaplastic thyroid carcinoma; BRAF: B-type Raf kinase; CI: confidence interval; CT: computed tomography; DRESS: drug reaction with eosinophilia and systemic symptoms; DT: dabrafenib and trametinib; DTP: dabrafenib and trametinib plus pembrolizumab; n: number;

Outcome	Evidence statement
ORR: overall response rate; PFS: progression free survival; RECIST: Response Evaluation Criteria in Solid Tumors; STEMI: ST elevation myocardial infarction	

In people with inoperable BRAF-mutated ATC, what is the cost effectiveness of pembrolizumab in combination with dabrafenib and trametinib compared with dabrafenib and trametinib combined?

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 pembrolizumab in combination with dabrafenib and trametinib more than the wider population of interest?

Subgroup	Evidence statement
Subgroups	**No evidence was identified for subgroups**

From the evidence selected, what were the age ranges of study participants?

Subgroup	Evidence statement
Age ranges	The participants included in the retrospective cohort study (Hamidi et al 2024) had a median age of 67 years (range 46 to 81 years) in the DTP group and 68 years (range 51 to 92 years) in the DT group. The subgroup of in scope participants in the retrospective case series (Hatashima et al 2022) had an age range of 56 to 82 years. **The age range of participants across the two included studies was 46 to 92 years. The retrospective cohort study included participants with a median age of 67 years (range 46 to 81 years) in the DTP group and 68 years (range 51 to 92 years) in the DT group. The in scope participants in the retrospective case series had an age range of 56 to 82 years.**

6. Discussion

This evidence review considered the clinical effectiveness, safety and cost effectiveness of pembrolizumab in combination with dabrafenib and trametinib (DTP) compared with dabrafenib and trametinib combined (DT) in patients (all ages) with inoperable BRAF-mutated anaplastic thyroid cancer (ATC). The critical outcomes of interest were progression free survival, response to treatment and overall survival. Important outcomes were quality of life, performance status/activities of daily living, time to treatment failure, symptom control and safety.

Evidence for the clinical effectiveness and safety was available from two studies, one retrospective cohort study and one subgroup of in scope patients from a retrospective case series. The retrospective cohort study included 71 patients with inoperable BRAF-mutated ATC and compared DTP to DT with a follow-up of 28 months (range 3 to 63 months) for the DTP group and 102 months (range 0.6 to 102 months) for the DT group (Hamidi et al 2024). The retrospective case series of 13 patients with locally advanced or metastatic unresectable ATC receiving immune checkpoint inhibitors included a subgroup of seven in scope patients with BRAF-mutated ATC receiving DTP with a follow-up of up to 20 months (Hatashima et al 2022). Between the two studies, the study outcomes reported included the critical outcomes of progression free survival (one study), response to treatment (two studies) and overall survival (two studies), and the important outcomes of time to treatment failure (one study) and safety (two studies). No studies were identified that reported on the important outcomes of quality of life, performance status/activities of daily living and symptom control. No cost effectiveness studies were identified.

The retrospective cohort study (Hamidi et al 2024) compared patients with BRAF-mutated ATC receiving DTP (with pembrolizumab added upfront or at progression) to patients receiving DT alone, for the primary outcome of overall survival. For the secondary outcomes of progression free survival and overall response, the study compared DTP upfront (excluding patients given pembrolizumab at progression) to DT upfront (including patients given pembrolizumab at progression). Concomitant treatments were not reported. The study also included an additional exploratory group of patients on neoadjuvant DTP, which is out of scope for this review; these patients were not included in this review. The subgroup of in scope patients from the retrospective case series (Hatashima et al 2022) included patients receiving DTP (with pembrolizumab either added upfront, one patient, or at progression, six patients). One patient was reported to have received radiation to a growing lesion while on pembrolizumab.

Both studies only included adults with BRAF-mutated ATC. Patients in the retrospective cohort study (Hamidi et al 2024) had a median age of 68 years (range 51 to 92 years) for the DT group and 67 years (range 46 to 81 years) for the DTP group and patients in the subgroup of the retrospective case series (Hatashima et al 2022) had an age range of 56 to 82 years. Although not explicitly stated, it was assumed that patients in both studies had inoperable ATC. Hatashima et al (2022) stated in the abstract that the study included patients with locally advanced or metastatic unresectable ATC and any patients who received surgery received this prior to initiation of pembrolizumab (three patients). Hamidi et al (2024) included operable patients in an exploratory neoadjuvant DTP group; these patients were not included in the main analysis of the study. Any patients who received surgery in the DT and DTP groups in the main analysis, received surgery prior to initiation of pembrolizumab (48% of DT group and 50% of DTP group) and therefore could be deemed inoperable at time of first dose of pembrolizumab. Six patients who were treated with neoadjuvant-intent DT or DTP did not ultimately undergo surgery due to either an inadequate response (five patients) or patient declining surgery (one patient); these patients were included in the main analysis DT and DTP groups.

The treatment response outcomes for both studies were evaluated in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Survival outcomes for both studies were calculated using the Kaplan-Meier method.

None of the studies commented on what minimal clinically important thresholds would be for any of the outcomes considered.

No evidence was identified regarding any subgroups of patients that would benefit more from DTP.

Both studies were considered to be at high risk of bias and certainty about the evidence for the critical and important outcomes was very low when assessed using modified GRADE. The main limitations for the retrospective cohort study were that baseline characteristics were not reported for the upfront DT group and upfront DTP group, so it was not possible to determine whether the groups were balanced at baseline for the overall response rate and progression free survival outcomes. Furthermore, for these outcomes, effect sizes will be diluted due to both the upfront DT and upfront DTP groups including patients receiving pembrolizumab (the intervention of interest). For all outcomes, confounders were not identified or adjusted for across the groups which may have introduced bias. Median duration of follow-up was longer for the DT group compared to the DTP group (102 months vs 28 months) which may have introduced bias by disproportionately capturing more events and longer survival times in the DT group while potentially underestimating outcomes in the DTP group. Furthermore, for progression free survival and response outcomes, only 30 out of 34 patients in the upfront DTP group and 31 out of 37 patients in the upfront DT group were evaluable for response which may have introduced attrition bias. Finally, adverse events were only reported for the DTP group so the extent to which these are attributable to pembrolizumab is not known. The main limitations relating to the retrospective case series are the lack of a comparator group and the very limited results reported with no summary statistics for the in scope patients. Other limitations include the small sample size and the retrospective nature of both included studies, and the small number of included studies.

Both studies were conducted in single centres in the US, and it is not clear if the patients and aspects of care in the studies reflect that seen in clinical practice in England and care is needed in generalising results to the NHS.

7. Conclusion

This evidence review includes one retrospective cohort study (n=71) comparing DTP to DT with a median follow-up of 28 months (DTP group) to 102 months (DT group) and one subgroup (n=7) of a retrospective case series of DTP with a follow-up of up to 20 months in patients with inoperable BRAF-mutated ATC.

The studies provide very low certainty evidence for the critical outcomes of progression free survival, response to treatment and overall survival, and the important outcomes of time to treatment failure and safety. No studies were identified that reported the important outcomes of quality of life, performance status/activities of daily living and symptom control.

Evidence from one retrospective cohort study suggests that DTP compared to DT for BRAF-mutated ATC increases median progression free survival (11 months vs 4 months; p=0.049) and median overall survival (17 months vs 9 months; p=0.037). Results for response to treatment and time to treatment failure were inconclusive.

With respect to safety, one retrospective cohort study reported that 27% of patients with BRAF-mutated ATC receiving DTP experienced immune related adverse events and one subgroup of patients with BRAF-mutated ATC receiving DTP from a retrospective case series reported that one patient experienced Grade 2 joint pain, myalgias and neuropathy and another patient developed diplopia and Bell's palsy. No comparative evidence was found for safety.

No evidence on cost effectiveness was found.

No evidence was identified regarding any subgroups of patients that would benefit more from DTP.

The studies included in this review provide very low certainty evidence of an increase in progression free survival and overall survival with DTP compared to DT in patients with inoperable BRAF-mutated ATC.

Appendix A PICO document

The review questions for this evidence review are:

1. In people with inoperable BRAF-mutated ATC, what is the clinical effectiveness of pembrolizumab in combination with dabrafenib and trametinib compared to dabrafenib and trametinib combined?

2. In people with inoperable BRAF-mutated ATC, what is the safety of pembrolizumab in combination with dabrafenib and trametinib compared to dabrafenib and trametinib combined?

3. In people with inoperable BRAF-mutated ATC, what is the cost-effectiveness of pembrolizumab in combination with dabrafenib and trametinib compared to dabrafenib and trametinib combined?

4. From the evidence selected, are there any subgroups of patients that may benefit more from pembrolizumab in combination with dabrafenib and trametinib more than the wider population of interest?

5. From the evidence selected, what were the age ranges of study participants?

P –Population and Indication	People with inoperable BRAF-mutated anaplastic thyroid cancer of all ages with or without metastases [Inoperable in this setting implies that it is either not technically possible to remove the cancer due to involvement or invasion of adjacent structures, and/or the patient is not fit enough for surgery (e.g. due to pre-existing comorbidities or the effects of cancer). Patients may have undergone surgery previously but need to be inoperable at the point of receiving pembrolizumab. Patients may also be down staged following initial treatment with dabrafenib and trametinib and pembrolizumab and undergo surgical resection with curative intent] [Other mutations, such as RAS, are excluded]
I – Intervention	Pembrolizumab + dabrafenib + trametinib [Pembrolizumab is an infusion typically given once every 3 weeks (200mg) or once every 6 weeks (400mg). Dabrafenib and trametinib are capsules that are taken twice daily and once daily respectively. The proposed regime is 150mg dabrafenib twice a day and 2mg trametinib once a day. Patients may be started on pembrolizumab, dabrafenib and trametinib all at once, or dabrafenib and trametinib may be started initially with pembrolizumab being added on disease progression. Patients may be receiving other supportive treatments such as steroids, radiotherapy, chemotherapy, antibiotics, analgesia, bisphosphonates, or denosumab. Patients may have previously undergone surgery; however, the cancer is inoperable at the point pembrolizumab, dabrafenib and trametinib is started]
C – Comparator(s)	Standard care for patients with BRAF-mutated ATC would be treatment with combined dabrafenib and trametinib [All patients may be receiving other supportive treatments such as steroids, radiotherapy, chemotherapy, antibiotics, analgesia, bisphosphonates, or denosumab. Patients may have previously undergone surgery; however, the cancer is inoperable at the point dabrafenib and trametinib is started]

O – Outcomes	Unless stated, the MCIDs for these outcomes are not known **<u>Clinical Effectiveness</u>** *<u>Critical to decision-making:</u>* • **Progression free survival** *This outcome is important to patients because it represents the time for which their disease is not progressing. Stable disease may represent longer survival and disease stability may result in patients experiencing fewer symptoms from the disease itself. It can be determined sooner than overall survival outcome measures.* [Progression free survival would be measured in months. Progression free survival assessed at 6, 12 and 24 months is of particular interest] • **Response to treatment** *Response rate is important to patients as it represents whether the treatment can improve disease burden and improve symptoms. Improving disease burden is important as patients may have sufficient response that their tumour is rendered operable. Operable cancers are amenable to potentially curative resection which significantly improves prognosis* [Other terms used to describe or indicate 'response to treatment' include, but are not limited to: best overall response, partial response, stable disease, progressive disease, disease control/remission, proportion of down staged patients] • **Overall survival** *Overall survival is important to patients as ATC has a high mortality rate due to advanced disease and limited treatment options. Improved survival is an important marker of effective treatment. Overall survival does not however give indication to a patient's quality of life during this time.* [Overall survival would be measured in months. In ATC, a minimal clinically important difference in OS would be 2 months (irrespective of immediate or later pembrolizumab treatment addition). Overall survival measured at 6 months is of particular interest although longer time frames are also relevant.] *<u>Important to decision-making:</u>* Outcomes (apart from time to treatment failure) measured at 3-6 months after pembrolizumab treatment are of particular interest although longer time frames are also of interest. • **Quality of life** *Quality of life is important to patients as it provides an indication of an individual's general health, their self-perceived well-being and their ability to participate in activities of daily living. Measurement of quality of life can help inform patient-centred decision making and inform health policy*. [Examples of generic quality of life tools include Short Form (SF-36), Quality of Life Questionnaire – ovarian cancer (QLQ-OV28), Quality of Life Questionnaire – core (QLQ-C30) and EuroQuality of Life Five Dimensions (EQ-5D). Examples of specific quality of life tools for patients with cancer, including thyroid cancer, include Functional assessment of Cancer Therapy General (FACT-General) and Quality of Life – Thyroid Version (QOL-TV).] • **Performance status/Activities of daily living (ADLs)** *ADLs are important outcomes to patients as they facilitate enablement and independence, allowing individuals to function in education, work, home,*

	and recreational settings. They encompass patients' individual needs and facilitate inclusion and participation. [ADLs can be measured using assessments such as: • Timed task completion (e.g., timed repeatable test such as dressing, meal preparation or patient specific ADL goal) • ADLs assessment using a tool (e.g., Barthel Index (BI) or Independence in Activities of Daily Living (ADL)) • Subjective/self-reported assessment (e.g., by the individual, carer, or multidisciplinary team (MDT). This could include self-reported questionnaires such as participation in work and other activities). • Performance status scales such as ECOG/Karnofsky status] • **Time to treatment failure** *This is important because it reflects overall treatment failure due to disease progression, adverse events or death.* [This may be defined as the interval time between initiation of targeted therapy to premature discontinuation] • **Symptom control** *Symptom control is an important outcome as it is a marker for the ability of the treatment to improve functional capacity and quality of life.* [Local symptoms for anaplastic thyroid cancer result from compression of local structures. Symptoms include breathlessness, pain, dysphonia (hoarseness) dysphagia (difficulty swallowing), fatigue and weight loss] **Safety** *These outcomes are important to patients because they will an impact on their treatment choices, recovery and could have long term sequelae if they are irreversible. They reflect the tolerability and adverse effects (AEs) of the treatment. From a service delivery perspective, they reflect the additional demands placed on the health system to manage the adverse consequences of the treatment.* **[**Examples of measures include, but are not limited to: • Frequency of adverse events • Frequency of grade 3 or 4 adverse events • Adverse events leading to discontinuation • Treatment related adverse events – e.g. fatigue, anorexia, hepatitis, colitis, etc] **Cost effectiveness**
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	2014-2024

Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-prints 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, commentaries, letters, editorials and case reports were excluded.

Search dates: 1 January 2014 to 3 October 2024

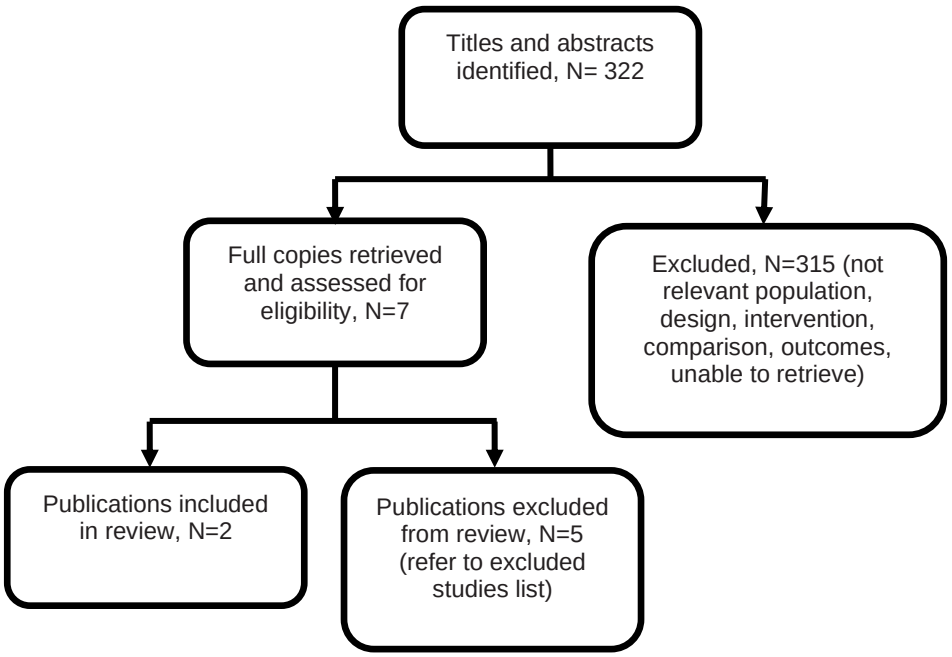
Medline search strategy

1	exp Thyroid Neoplasms/
2	(thyroid adj3 (cancer* or carcinoma* or neoplas* or tumo* or malignan*)).ti,ab,kf. or atc.mp.
3	1 or 2
4	(pembrolizumab or keytruda or pembro or lambrolizumab or xtrud? or ((pdl1 or pdl-1 or pd1 or pd-1 or checkpoint or checkpoint) adj3 inhibit*)).mp.
5	(dabrafenib or tafinlar or dab or (braf adj3 inhibit*)).mp.
6	(trametinib or mekinist or tram or ((kinase or mek?) adj3 inhibit*)).mp.
7	3 and 4 and 5 and 6

Appendix C Evidence selection

The literature searches identified 322 references. These were screened using their titles and abstracts and seven references were obtained in full text and assessed for relevance. Of these, two references are included in the evidence summary. The remaining five 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
Hamidi S, Iyer PC, Dadu R, Gule-Monroe MK, Maniakas A, Zafereo ME, et al. Checkpoint Inhibition in Addition to Dabrafenib/Trametinib for $BRAF^{V600E}$-Mutated Anaplastic Thyroid Carcinoma. Thyroid. 2024;34(3):336-46.	Included
Iyer PC, Dadu R, Gule-Monroe M, Busaidy NL, Ferrarotto R, Habra MA, et al. Salvage pembrolizumab added to kinase inhibitor therapy for the treatment of anaplastic thyroid carcinoma. J Immunother Cancer. 2018;6(1):68.	Excluded. Retrospective case series of 12 ATC patents on salvage therapy with pembrolizumab plus kinase inhibitors including 6 in scope patients with BRAF-mutated ATC treated with pembrolizumab plus dabrafenib and trametinib. These 6 patients are included in Hamidi et al 2024 as they were recruited from the same centre during 2016 to 2017 which is within the recruitment period of Hamidi et al 2024 (2014 to 2023). Hamidi et al 2024 has been included in this review. No additional outcomes reported in this study that are missing from Hamidi et al 2024.

Appendix D Excluded studies table

Study reference	Reason for exclusion
Iyer PC, Dadu R, Gule-Monroe M, Busaidy NL, Ferrarotto R, Habra MA, et al. Salvage pembrolizumab added to kinase inhibitor therapy for the treatment of anaplastic thyroid carcinoma. J Immunother Cancer. 2018;6(1):68.	Retrospective case series of 12 ATC patents on salvage therapy with pembrolizumab plus kinase inhibitors including 6 in scope patients with BRAF-mutated ATC treated with pembrolizumab plus dabrafenib and trametinib. These 6 patients are included in Hamidi et al 2024 as they were recruited from the same centre during 2016 to 2017 which is within the recruitment period of Hamidi et al 2024 (2014 to 2023). Hamidi et al 2024 has been included in this review. No additional outcomes reported in this study that are missing from Hamidi et al 2024.
Kuang BH, Zhang WX, Lin GH, Fu C, Cao RB, Wang BC. Tyrosine kinase inhibitors in patients with advanced anaplastic thyroid cancer: an effective analysis based on real-world retrospective studies. Front Endocrinol (Lausanne). 2024;15:1345203.	Systematic review of tyrosine kinase inhibitors in advanced ATC including one potentially in scope study on pembrolizumab plus dabrafenib and trametinib. This study has been considered separately for eligibility for inclusion in this review.
Maniakas A, Dadu R, Busaidy NL, Wang JR, Ferrarotto R, Lu C, et al. Evaluation of overall survival in patients with anaplastic thyroid carcinoma, 2000-2019. JAMA Oncology. 2020;6(9):1397-404.	Results not reported separately for BRAF-mutated ATC patients on pembrolizumab plus dabrafenib and trametinib.
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.	Case series of 6 patients with BRAF-mutated ATC including 4 in scope patients treated with pembrolizumab plus dabrafenib and trametinib. These 4 patients are included in Hamidi 2024 as they were recruited from the same centre during 2017 to 2018 which is within the recruitment period of Hamidi et al 2024 (2014 to 2023). Hamidi et al 2024 has been included in this review. No additional outcomes reported in this study that are missing from Hamidi et al 2024.
Zhao X, Wang JR, Dadu R, Busaidy NL, Xu L, Learned KO, et al. Surgery after BRAF-directed therapy is associated with improved survival in $BRAF^{V600E}$ mutant anaplastic thyroid cancer: A single-center retrospective cohort study. Thyroid. 2023;33(4):484-91.	Intervention out of scope - BRAF and MEK inhibitor with or without checkpoint inhibitor immunotherapy. Results not reported separately for patients on pembrolizumab plus dabrafenib and trametinib.

Appendix E Evidence table

For abbreviations see list after table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Hamidi S, Iyer PC, Dadu R, Gule-Monroe MK, Maniakas A, Zafereo ME, et al. Checkpoint inhibition in addition to dabrafenib/trametinib for BRAF^{V600E}-mutated anaplastic thyroid carcinoma. Thyroid. 2024;34(3):336-46. **Study location** US (single centre) **Study type** Retrospective cohort study **Study aim** To study the efficacy and safety of DTP compared with current standard of care DT alone as an initial	Patients with inoperable[12] BRAF-mutated ATC[13] **Inclusion criteria** • Patients treated with DT for at least 2 weeks • Patients initially treated with DT but later switched to another BRAF/MEK inhibitor combination due to intolerable adverse effects to DT **Exclusion criteria** • Patients treated within a clinical trial that has not yet been published	**Interventions** DTP Pembrolizumab added upfront or at progression A single infusion of pembrolizumab was sufficient to consider the patient as having received pembrolizumab. Duration of DT (months), median (range): 10 (2 to 63) Duration of pembrolizumab, median (range): 5 (1 to 55) Time between DT and pembrolizumab (days), median (range): 75 (-8 to 1,308) Dose: not reported	Median (range) follow-up (months)[17]: • DTP: 28 (3 to 63) • DT alone: 102 (0.6 to 102) **Critical outcomes** **Progression free survival (PFS)[18]** Median PFS, months *Upfront DTP vs upfront DT[19]* • Upfront DTP (n=30): 11.0 (95% CI 7.0 to 15.0) • Upfront DT (n=31): 4.0 (95% CI 0.7 to 7.3) • p=0.049 **Response to treatment[20]** *Upfront DTP vs upfront DT* Upfront DTP (n=30): Overall response rate: 73.3% n (%) • Stable disease: 6 (20) • Partial response: 14 (47) • Complete response: 8 (27)	This study was appraised using the JBI checklist for cohort studies. 1. UNCLEAR 2. N/A 3. N/A 4. NO 5. NO 6. N/A 7. YES 8. UNCLEAR 9. YES 10. N/A 11. YES **Other comments:** This retrospective cohort study included patients with BRAF-mutated ATC treated with DT for at least two weeks with or without pembrolizumab in a single centre in the US over nine years.

[12] Although not explicitly stated, it was assumed that patients included in the main analysis (n=71) of the paper had inoperable ATC. Operable patients were included in an exploratory neoadjuvant DTP group and these patients were not included in the main analysis of the paper or in this review. Any patients who received surgery in the DT and DTP groups in the main analysis, received surgery prior to pembrolizumab and therefore could be deemed inoperable at time of pembrolizumab. Any patients who were treated with neoadjuvant-intent DT or DTP who did not ultimately undergo surgery due to either an inadequate response or patient declining surgery were included in the main analysis DT and DTP groups.
[13] BRAF^{V600E} mutation was identified by immunohistochemistry and/or next-generation sequencing testing of tumour tissue or cell-free DNA (liquid biopsy)
[17] Median follow-up only reported for DTP group (pembrolizumab given upfront and at progression) and DT alone group. Median follow-up not reported for upfront DTP and upfront DT groups.
[18] Defined as the time between the first dose of pembrolizumab and documented disease progression or death
[19] Patients initially treated with DT who had pembrolizumab added at progression and were evaluable for response were analysed as part of the ‘‘upfront DT’’ group
[20] Response was assessed by percentage change in target lesion size between initial and serial post-treatment computed tomography (CT) scans and/or 18F-fluorodeoxyglucose positron emission tomography combined with CTs, using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

Study details	Population	Interventions	Study outcomes	Appraisal and funding
treatment, as well as in the neoadjuvant setting **Study dates** 1 January 2014 to 1 March 2023	• Patients previously treated with another KI • Patients with anaplastic transformation of a differentiated thyroid carcinoma while on a KI • Patients who received radioiodine while on DT for treatment of suspected well-differentiated distant metastases **Total sample size** n=71[14] **No. of participants in each treatment group** DTP: n=48[15] • Upfront DTP: n=34 • Pembrolizumab added at progression: n=14 DT alone: n=23 **Baseline characteristics** Age (years), median (range): • DT: 68 (51 to 92)	Concomitant treatments: not reported **Comparators** DT alone Duration of DT (months), median (range): 6 (0.6 to 88)	• Progressive disease: 0 (0) • Non-evaluable: 2 (7) Upfront DT (n=31): Overall response rate: 64.5%; p=0.205 (DTP vs DT) n (%) • Stable disease: 5 (16) • Partial response: 16 (52) • Complete response: 4 (13) • Progressive disease: 3 (10) • Non-evaluable: 3 (10) **Overall survival (OS)[21]** Median OS, months *DTP vs DT alone* • DTP (n=48): 17.0 (95% CI 11.9 to 22.1) • DT alone (n=23): 9.0 (95% CI 4.5 to 13.5) • p=0.037 *Upfront DTP vs upfront DT* • Upfront DTP (n=34): 17 (95% CI 0.24 to 33.8) • Upfront DT (n=14): 16 (95% CI 6.4 to 25.6) • p=0.523 12-months OS *DTP vs DT alone* • DTP (n=48): 60.2% • DT alone (n=23): 36.7% • No CIs or p-value reported	For the primary outcome, OS, results were compared between patients treated with DT alone (DT group) and patients treated with upfront DTP or upfront DT plus pembrolizumab at progression (DTP group). For the secondary outcomes, which included overall response rate and PFS, results were compared between patients treated with upfront DT which included patients initially treated with DT who had pembrolizumab at progression (upfront DT group) and patients treated with upfront DTP (upfront DTP group). It should be noted that effect sizes for these outcomes will be diluted due to patients receiving pembrolizumab in both groups. A third exploratory group was also included (neoadjuvant group) which included patients treated with neoadjuvant DT followed by definitive surgery for primary disease and pembrolizumab added either before or after surgery. The results for this group have not been extracted as the patients are out of scope for this review. It should be noted that that the authors reported that six patients who were treated with neoadjuvant-intent DT (n=3) or DTP (n=3) did not ultimately undergo surgery and these patients

[14] These patients were included in the primary analyses. An additional exploratory group was included in the study of patients on neoadjuvant DTP (n=23). This group has not been included in this review as the patients are out of scope.
[15] One patient received nivolumab instead of pembrolizumab.
[21] Defined as time between the first dose of pembrolizumab and death from any cause.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	• DTP: 67 (46 to 81) Female, n (%): • DT: 11 (48) • DTP: 22 (46) ATC transformation[16], n (%): • DT: 9 (39) • DTP: 17 (36) ATC stage at diagnosis, n (%): IVB: • DT: 7 (30) • DTP: 12 (25) IVC: • DT: 16 (70) • DTP: 36 (75) Distant metastases at initiation of systemic therapy, n (%): • DT: 20 (87) • DTP: 38 (79) Prior therapy for ATC, n (%): EBRT to the neck: • DT: 7 (30) • DTP: 17 (35) Surgery: • DT: 11 (48) • DTP: 24 (50) Bridging cytotoxic chemotherapy: • DT: 1 (4)		24-months OS *DTP vs DT alone* • DTP (n=48): 36.5% • DT alone (n=23): 31.5% • No CIs or p-value reported **Important outcomes** **Safety** Immune related adverse events, n (%) *DTP (n=48*) • Any: 13 (27) • Colitis: 4 (8) • Nephritis: 3 (6) • Hepatitis: 2 (4) • Encephalopathy: 1 (2) • DRESS: 1 (2) • Elevation in creatine kinase: 1 (2) • Pneumonitis: 1 (2) • Polyneuropathy: 1 (2) • Sjogren: 1 (2) • STEMI: 1 (2) • Thrombocytopenia: 1 (2) *DT alone* • not reported Grade 5 adverse events • DTP: 0 • DT alone: not reported	were included in the DT and DTP groups, respectively. Five of the patients had an inadequate response with either disease progression or a short duration of response, which precluded surgery, and one patient (in DTP group) declined surgery. Baseline characteristics for the DT and DTP groups were similar with the exception of distant metastases at initiation of systemic therapy which was higher in the DT group (87% vs 79%). Baseline characteristics were not reported for the upfront DT group and upfront DTP group so it is not possible to determine whether the groups were balanced at baseline. Potential confounders were not identified or adjusted for across the groups. Median duration of follow-up was longer for the DT group compared to the DTP group (102 vs 28 months). Only one patient (DT group) was lost to follow-up. For PFS and response outcomes, only 30 out of 34 patients in the upfront DTP group and 31 out of 37 patients in the upfront DT group were evaluable for response which may have introduced attrition bias. Adverse events were only reported for the DTP group so comparisons

[16] No further explanation given in the paper.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	• DTP: 4 (8) PD-L1 status, n (%): <1%: • DT: 1 (4) • DTP: 1 to 49%: • DT: 5 (22) • DTP: 12 (25) ≥50%: • DT: 2 (9) • DTP: 19 (40) Not evaluated/available: • DT: 15 (65) • DTP: 17 (35)			could not be made with the DT group. The Kaplan–Meier method was used to analyse PFS and OS endpoints. **Source of funding:** The paper states that no funding was received for the work
Hatashima A, Archambeau B, Armbruster H, Xu M, Shah M, Konda B, et al. An evaluation of clinical efficacy of immune checkpoint inhibitors for patients with anaplastic thyroid carcinoma. thyroid. 2022;32(8):926-36. **Study location** US (single centre) **Study type** Retrospective case series **Study aim**	**Inclusion criteria** • Patients aged 18 years of age or older • Patients who received at least one infusion of pembrolizumab or nivolumab • Patients who received concomitant BRAF and/or MEK inhibitors **Exclusion criteria** • Patients who received any other	**Interventions** DTP[23] Pembrolizumab (200 or 400 mg IV every 3 or 6 weeks, respectively) All infusions were administered over 30 minutes in an outpatient infusion centre 6 patients were given pembrolizumab following progression with DT 1 patient was on concurrent DTP as first line systemic therapy (patient #7)	Up to 20 months follow-up for in scope patients[25] **Critical outcomes** **Response to treatment[26]** • Patient #2: progressive disease at 9 weeks after initiation of therapy, pembrolizumab discontinued and chemo-radiation followed by chemotherapy initiated, alive with stable disease at 20 months after initiation of pembrolizumab • Patient #4: stable disease at 0.5 to 8.5 months after initiation of therapy, progressive disease at 8.5 months, death at 15.5 months	This study was appraised using the JBI checklist for case series. 1. UNCLEAR 2. YES 3. YES 4. YES 5. YES 6. YES 7. YES 8. NO 9. YES 10. NO **Other comments:** This retrospective case series included patients with locally advanced or metastatic unresectable ATC who received

[23] Patients received either pembrolizumab (n=12) or nivolumab (n=1). The seven patients with $BRAF^{V600E}$-mutations all received pembrolizumab.
[25] Taken from Swimmer plot of responses (Figure 3 in paper). Median length of follow-up was not reported for in-scope patients or total sample.
[26] Response was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Results for in scope patients at an individual level were extracted from the text and a Swimmer plot of responses (Figure 3 in paper).

Study details	Population	Interventions	Study outcomes	Appraisal and funding
To evaluate the real-world benefit of utilising available immune checkpoint inhibitors at a major academic medical centre **Study dates** June 2016 and June 2021[22]	targeted therapeutic agents or concomitant chemotherapy while on immunotherapy • Protected populations such as prisoners and pregnant women • Patients treated with pembrolizumab or nivolumab as a part of a clinical trial **Total sample size** n=13 n=7 patients in scope (patients with $BRAF^{V600E}$ mutation who received pembrolizumab) **Baseline characteristics** n=7 Age (years), range: 56 to 82 Female, n (%): 5 (71) Ethnicity White: 6 (86) Stage: • IVA: 2 (29) • IVB: 1 (14)	Concomitant treatments: 1 patient received radiation to growing lesion while on pembrolizumab (patient #5) Median duration of immunotherapy: 1.9 months (range 1 week to 29 months (ongoing))[24] **Comparators** None	• Patient #5: stable disease at start of therapy, oligoprogression at 6 months which was also treated with local radiotherapy • Patient #7: stable disease at 1 to 4 months after initiation of therapy (ongoing) • Patient #8: progressive disease at 1 month after initiation of therapy, death at 1.5 months • Patient #10: progressive disease and death at 1 month after initiation of therapy • Patient #12: death at 0.5 months after initiation of therapy **Important outcomes** **Overall survival[27]** The authors reported that the "median OS from diagnosis was 15.6 months and remained unchanged regardless of BRAF status" Deaths, n (%): 4 (57%)[28] **Time to treatment failure** • Patient #2: progressive disease at 9 weeks after initiation of therapy, pembrolizumab discontinued and chemo-radiation followed by chemotherapy initiated, alive	immune checkpoint inhibitor therapy (pembrolizumab or nivolumab) at a single centre in the US. Out of the 13 patients included in the study, seven patients had a $BRAF^{V600E}$-mutation and received pembrolizumab and were in scope for this review. Although not explicitly stated, it was assumed that the patients had inoperable ATC as the abstract states that the study included patients with locally advanced or metastatic unresectable ATC and patients only received surgery prior to pembrolizumab. Objective response rate, progression free survival and overall survival from initiation of pembrolizumab, and total number of adverse events were reported for the total sample only and therefore these results have not been included in this review. Median length of follow-up was not reported for in scope patients or total sample. Very limited individual patient level results were reported for in scope patients. No summary statistics reported for in-scope patients. **Source of funding:**

[22] Patients received their first dose of immune checkpoint inhibitor during this time.
[24] Median duration for total sample (n=13). Not reported separately for in scope patients (n=7).
[27] Overall survival from diagnosis was defined as the time from collection of the first sample that reported pathology/cytology consistent with ATC to death from any cause or censoring.
[28] Taken from Swimmer plot of responses (Figure 3 in paper). Median length of follow-up was not reported for in-scope patients or total sample.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	• IVC: 4 (57) Prior treatment for ATC: • Naïve: 1 • Surgery: 3 • Chemotherapy: 4 • Radiation: 4		with stable disease at 20 months after initiation of pembrolizumab **Safety** • Patient #4 experienced Grade 2 AEs joint pain, myalgias, and neuropathy, which were responsive to steroids • Patient #5 developed diplopia and Bell's palsy. The authors reported that Bell's palsy was likely not treatment related, but causation could not be completely ruled out	The papers states that no funding was received for the article

Abbreviations

AE: adverse event; ATC: anaplastic thyroid carcinoma; BRAF: B-type Raf kinase; CI: confidence interval; CT: computed tomography; DRESS: drug reaction with eosinophilia and systemic symptoms; DT: dabrafenib and trametinib; DTP: dabrafenib and trametinib plus pembrolizumab; EBRT: external beam radiotherapy; IV: intravenous; JBI: Joanna Briggs Institute; KI: kinase inhibitor; n: number; OS: overall survival; PD-L1: programmed death-ligand 1; PFS: progression-free survival; RECIST: Response Evaluation Criteria in Solid Tumors; STEMI: ST elevation myocardial infarction; US: United States

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for Cohort Studies

1. Were the two groups similar and recruited from the same population?
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?
3. Was the exposure measured in a valid and reliable way?
4. Were confounding factors identified?
5. Were strategies to deal with confounding factors stated?
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
7. Were the outcomes measured in a valid and reliable way?
8. Was the follow-up time reported and sufficient to be long enough for outcomes to occur?
9. Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored?
10. Were strategies to address incomplete follow-up utilized?
11. Was appropriate statistical analysis used?

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

For abbreviations and footnotes see end of tables

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	DTP	DT	Result		
Progression free survival (PFS) (1 retrospective cohort study)									
Median PFS[a] at a median follow-up of 28 months (range 3 to 63 months) for DTP group and 102 months (range 0.6 to 102 months) for DT alone group[b], months									
Retrospective cohort study Hamidi et al 2024	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	30	31	• Upfront DTP: 11.0 (95% CI 7.0 to 15.0) • Upfront DT[c]: 4.0 (95% CI 0.7 to 7.3) • p=0.049	Critical	Very low
Response to treatment (1 retrospective cohort study & 1 retrospective case series)									
Overall response rate[d] at a median follow-up of 28 months (range 3 to 63 months) for DTP group and 102 months (range 0.6 to 102 months) for DT alone group[b], %									
Retrospective cohort study Hamidi et al 2024	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	30	31	Upfront DTP: 73.3% n (%): • Stable disease: 6 (20) • Partial response: 14 (47) • Complete response: 8 (27) • Progressive disease: 0 (0) • Non-evaluable: 2 (7) Upfront DT: 64.5%; p=0.205 (DTP vs DT) n (%): • Stable disease: 5 (16) • Partial response: 16 (52) • Complete response: 4 (13) • Progressive disease: 3 (10) • Non-evaluable: 3 (10)	Critical	Very low
Objective response[e] at up to 20 months follow-up[f]									
Retrospective case series	Very serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	7	0	• Patient #2: progressive disease at 9 weeks after initiation of therapy, pembrolizumab discontinued and chemo-radiation followed by	Critical	Very low

Hatashima et al 2022							chemotherapy initiated, alive with stable disease at 20 months after initiation of pembrolizumab • Patient #4: stable disease at 0.5 to 8.5 months after initiation of therapy, progressive disease at 8.5 months, death at 15.5 months • Patient #5: stable disease at start of therapy, oligoprogression at 6 months which was also treated with local radiotherapy • Patient #7: stable disease at 1 to 4 months after initiation of therapy (ongoing) • Patient #8: progressive disease at 1 month after initiation of therapy, death at 1.5 months • Patient #10: progressive disease and death at 1 month after initiation of therapy • Patient #12: death at 0.5 months after initiation of therapy		
Overall survival (1 retrospective cohort study & 1 retrospective case series)									
Median overall survival[g] at a median follow-up of 28 months (range 3 to 63) for DTP group and 102 months (range 0.6 to 102 months) for DT alone group, months									
Retrospective cohort study Hamidi et al 2024	Very serious limitations[5]	Serious indirectness[4]	Not applicable	Not calculable	48	23	• DTP (n=48): 17.0 (95% CI 11.9 to 22.1) • DT alone (n=23): 9.0 (95% CI 4.5 to 13.5) • p=0.037	Critical	Very low
Median overall survival[h] at up to 20 months follow-up[f], months									
Retrospective case series Hatashima et al 2022	Very serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	7	0	The authors reported that the "median OS from diagnosis was 15.6 months and remained unchanged regardless of BRAF status"	Critical	Very low
12-month overall survival[g] at a median follow-up of 28 months (range 3 to 63 months) for DTP group and 102 months (range 0.6 to 102 months) for DT alone group, %									

Retrospective cohort study Hamidi et al 2024	Very serious limitations[6]	No serious indirectness	Not applicable	Not calculable	48	23	• DTP (n=48): 60.2% • DT alone (n=23): 36.7% • No CIs or p-value reported	Critical	Very low
24-month overall survival[g] at a median follow-up of 28 months (range 3 to 63 months) for DTP group and 102 months (range 0.6 to 102 months) for DT alone group, %									
Retrospective cohort study Hamidi et al 2024	Very serious limitations[6]	No serious indirectness	Not applicable	Not calculable	48	23	• DTP: 36.5% • DT alone: 31.5% • No CIs or p-value reported	Critical	Very low
Deaths[i] at up to 20 months follow-up[f], n									
Retrospective case series Hatashima et al 2022	Very serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	7	0	4 (57%)	Critical	Very low
Time to treatment failure (1 retrospective case series)									
Time to treatment failure at up to 20 months follow-up[f], months									
Retrospective case series Hatashima et al 2022	Very serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	7	0	One patient had progressive disease at 9 weeks and pembrolizumab was discontinued after initiation of therapy. Chemo-radiation followed by chemotherapy was initiated and patient reported to be alive with stable disease at 20 months after initiation of pembrolizumab	Important	Very low
Safety (1 retrospective cohort study & 1 retrospective case series)									
Immune related adverse events at a median follow-up of 28 months (range 3 to 63 months), n (%)									
Retrospective cohort study Hamidi et al 2024	Serious limitations[7]	Serious indirectness[8]	Not applicable	Not calculable	48	0	• Any: 13 (27) • Colitis: 4 (8) • Nephritis: 3 (6) • Hepatitis: 2 (4) • Encephalopathy: 1 (2) • DRESS: 1 (2) • Elevation in creatine kinase: 1 (2) • Pneumonitis: 1 (2) • Polyneuropathy: 1 (2)	Important	Very low

							• Sjogren: 1 (2) • STEMI: 1 (2) • Thrombocytopenia: 1 (2)		
Grade 5 adverse events at a median follow-up of 28 months (3 to 63), n (%)									
Retrospective cohort study Hamidi et al 2024	Serious limitations[7]	Serious indirectness[8]	Not applicable	Not calculable	48	0	0	Important	Very low
Adverse events at up to 20 months follow-up[f], n									
Retrospective case series Hatashima et al 2022	Very serious limitations[3]	Serious indirectness[4]	Not applicable	Not calculable	7	0	Patient #4 experienced Grade 2 joint pain, myalgias, and neuropathy, which were responsive to steroids Patient #5 developed diplopia and Bell's palsy. The authors reported that Bell's palsy was likely not treatment related, but causation could not be completely ruled out	Important	Very low

Abbreviations

CI: confidence interval; DRESS: drug reaction with eosinophilia and systemic symptoms; DT: dabrafenib and trametinib; DTP: dabrafenib and trametinib plus pembrolizumab; IV: intravenous; OS: overall survival; STEMI: ST elevation myocardial infarction

a. Defined as the time between the first dose of pembrolizumab and documented disease progression or death.
b. Median follow-up only reported for DTP group (pembrolizumab given upfront and at progression) and DT alone group. Median follow-up not reported for upfront DTP and upfront DT groups.
c. DT upfront group includes patients given pembrolizumab at progression. Fourteen patients who had DT upfront were given pembrolizumab at progression but the number of these patients who were evaluable for response and hence included PFS results was not reported.
d. Response was assessed by percentage change in target lesion size between initial and serial post-treatment computed tomography (CT) scans and/or 18F-fluorodeoxyglucose positron emission tomography combined with CTs, using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.
e. Response was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Results for in scope patients at an individual level were extracted from the text and a Swimmer plot of responses (Figure 3 in paper).
f. Taken from Swimmer plot of responses (Figure 3 in paper). Median length of follow-up was not reported for in-scope patients or total sample.
g. Defined as time between the first dose of pembrolizumab and death from any cause.
h. Overall survival from diagnosis was defined as the time from collection of the first sample that reported pathology/cytology consistent with ATC to death from any cause or censoring.
i. Taken from Swimmer plot of responses (Figure 3 in paper). Median length of follow-up was not reported for in-scope patients or total sample.

1 Risk of bias: very serious limitations due to baseline characteristics not reported for upfront DTP and upfront DT groups, potential confounders were not identified or adjusted for across the groups, a difference in length of follow-up between the groups and incomplete follow up.
2 Indirectness: serious limitations due to the inclusion of patients taking pembrolizumab at progression in the upfront DT comparator group.
3. Risk of bias: very serious limitations due to unclear inclusion criteria, follow-up length not reported and very limited individual patient level results only reported for in scope patients.
4. Indirectness: serious indirectness due to lack of comparator group.
5. Risk of bias: very serious limitations due to potential confounders not being identified or adjusted for across the groups and a difference in length of follow-up between the groups.

6. Risk of bias: very serious limitations due to potential confounders not being identified or adjusted for across the groups, a difference in length of follow-up between the groups and no confidence intervals or p-values reported.
7. Risk of bias: serious limitations due to non-reporting of the results from the comparator group.
8. Indirectness: serious indirectness due to no comparison between intervention and comparator groups.

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.
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	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.
Comparative cohort study	An observational study with two or more groups (cohorts) of people with similar characteristics. One group has a treatment, is exposed to a risk factor or has a particular symptom and the other group does not.
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 (CI)	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 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 confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
Control group	A group of people in a study who do not have the intervention or test being studied. Instead, they may have the standard intervention. The results for the control group are compared with those for a group having the intervention being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible to those in the intervention group, to make it as easy as possible to detect any effects due to the intervention.
Cost effectiveness study	An analysis that assesses the cost of achieving a benefit by different means. The benefits are expressed in non-monetary terms related to health, such as life years gained (that is, the number of years by which life is extended as a result of the intervention). Options are often compared on the cost incurred to achieve 1 outcome (for example, cost per life year gained).
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
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.
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that 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).
P-value (p)	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
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.

Term	Definition
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.

References

Included studies

- Hamidi S, Iyer PC, Dadu R, Gule-Monroe MK, Maniakas A, Zafereo ME, et al. Checkpoint inhibition in addition to dabrafenib/trametinib for $BRAF^{V600E}$-mutated anaplastic thyroid carcinoma. Thyroid. 2024;34(3):336-46.
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