

CADTH Health Technology Review

Radioiodine Resensitization for Radioiodine-Refractory Metastatic Differentiated Thyroid Cancer

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Abbreviations

DTC	differentiated thyroid cancer
MAPK	mitogen-activated protein kinase
MEK	mitogen-activated kinase
NTRK	neurotrophic tyrosine receptor kinase
PET	positron emission tomography
PI3K	phosphoinositide 3-kinase
RAIRMDTC	radioiodine-refractory/resistant metastatic differentiated thyroid cancer
RECIST	Response Evaluation Criteria in Solid Tumours
RET	rearranged during transfection

Key Messages

- Evidence of radioiodine resensitization was reported in 4 single-arm clinical trials and 3 uncontrolled retrospective cohort studies, which included between 3 and 20 patients. Over half of patients in these 7 studies demonstrated increased radioiodine avidity after resensitization treatment.
- Where reported, at least half of radioiodine retreated patients remained progression free and/or had not initiated a new treatment by the end of study follow-up.
- Adverse events associated with radioiodine resensitization therapies were typically mild, with skin-related adverse events being most common.
- No studies comparing outcomes of radioiodine resensitization therapies against lenvatinib or to no treatment were identified.
- No evidence on the cost-effectiveness of radioiodine resensitization therapy was found.

Context and Policy Issues

Thyroid cancer was among the 10 most commonly occurring cancers worldwide in 2020.¹ In Canada, there were approximately 6,700 new cases in 2021, ranking eighth among all cancers for age-standardized incidence rate, and fifth among women.²

Over 90% of thyroid cancers involve the follicular cells,³ including papillary carcinoma, follicular carcinoma, and more rarely, Hürthle cell carcinoma; together these are classified as differentiated thyroid cancers (DTC). A specialized function of differentiated thyroid cells is to take up iodine from the blood. Consequently, an effective treatment for DTC is radioiodine (iodine-131, a radioactive iodine isotope), which is absorbed by the cells and causes cell death via beta radiation.⁴ Radioiodine is typically given post-surgery to destroy residual cancer cells, and is offered primarily to high-risk patients, such as those with distant metastases, which represents less than 10% of all DTCs.^{4,5}

In approximately 50% of metastatic DTCs, cells lose the ability to perform specialized functions such as iodine uptake, causing them to be radioiodine-resistant or refractory.⁶ Prognosis is poor for patients with radioiodine-refractory/resistant metastatic DTC (RAIRMDTC), with approximately 90% of patients dying within 10 years of diagnosis.⁵ Treatment options for patients with RAIRMDTC are limited. Recent approvals of multikinase inhibitors have begun to address the unmet need for treatment of RAIRMDTC, demonstrating improvements in progression-free survival over placebo.^{7,8} In 2016, lenvatinib (a multikinase inhibitor) was approved by Health Canada and is currently reimbursed in several Canadian provinces⁹; however, treatment with lenvatinib is associated with substantial toxicity, and must be taken continuously until death or disease progression.⁸

An alternative approach to therapy has been explored in the past decade, using therapies that inhibit specific mediators of the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathways as a means to resensitize DTCs to radioiodine.¹⁰ Mutations within the MAPK pathway, (e.g., the *BRAF* V600E activating mutation) and PI3K pathway (e.g., RAS mutations), have been shown to reduce cells' ability to import iodine (or radioiodine); approximately 70% of papillary thyroid cancers harbour such mutations.¹¹ Targeting specific mutations within these pathways, using therapies such as *BRAF* inhibitors, mitogen-activated kinase (MEK) inhibitors, neurotrophic tyrosine receptor kinase (NTRK)

inhibitors, and rearranged during transfection (RET) inhibitors can to restore cells' ability to uptake iodine, and thereby resensitize previously radioiodine-refractory tumours to radioiodine therapy.

The purpose of the current report is to summarize evidence regarding the clinical effectiveness, safety, and cost-effectiveness of radioiodine resensitization therapies followed by treatment with radioiodine among patients with RAIRMDTC, relative to lenvatinib or no treatment, or as non-comparative estimates.

Research Questions

1. What is the clinical effectiveness of radioiodine resensitization followed by radioiodine in patients with radioiodine-refractory/resistant metastatic differentiated thyroid cancer?
2. What is the cost-effectiveness of radioiodine resensitization followed by radioiodine in patients with radioiodine-refractory/resistant metastatic differentiated thyroid cancer?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the international HTA database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were thyroid cancer and resensitization, or thyroid cancer and radioiodine resensitizing drugs. Conference abstracts were omitted from the search results. The search was limited to English language documents published between January 1, 2013 and March 3, 2022.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published before 2013. Systematic reviews in which all relevant studies were captured in other more recent or more comprehensive systematic reviews were excluded.

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the following tools as a guide: A Measurement Tool to Assess systematic Reviews 2 (AMSTAR 2)¹² for systematic reviews, and the Downs and Black checklist¹³ for randomized and non-randomized studies. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 725 citations were identified in the literature search. Following screening of titles and abstracts, 683 citations were excluded and 42 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 36 publications were excluded for various reasons, and 8 publications met the inclusion criteria and were included in this report. These comprised 1¹⁴ systematic review, and 7¹⁵⁻²¹ non-randomized studies. Appendix 1 presents the PRISMA²² flow chart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Table 1: Selection Criteria

Criteria	Description
Population	Adults with radioiodine-refractory/resistant metastatic thyroid cancer ^a
Intervention	Radioiodine resensitization (also known as redifferentiation) with: dabrafenib, vemurafenib (<i>BRAF</i> inhibitors); trametinib, selumetinib (MEK inhibitors); NTRK inhibitors (e.g., larotrectinib, entrectinib); or RET inhibitors (e.g., selpercatinib, pralsetinib), followed by radioiodine
Comparator	Q1 and 2: Lenvatinib Q1: No treatment (e.g., waitlist, placebo); no comparator
Outcomes	Q1: Clinical effectiveness (e.g., overall survival, progression-free survival [as defined by RECIST guidelines], radioiodine uptake, response rate [e.g., as determined by radiographic imaging], remission rate, health-related quality of life, need for subsequent treatments or change in therapy, emergency department visits, hospitalizations) and safety/harms (e.g., any grade treatment-related adverse events [e.g., hypertension, diarrhea, fatigue], withdrawal due to adverse events, mortality) Q2: Cost-effectiveness (e.g., cost per quality-adjusted life-year gained, cost per unit of health benefit)
Study designs	Health technology assessments, systematic reviews, randomized-controlled trials, non-randomized studies, economic evaluations

NTRK = neurotrophic tyrosine receptor kinase; MEK = mitogen-activated kinase; RET = rearranged during transfection.

^aStudies with mixed populations regarding the stage of cancer (i.e., included metastatic, and locally advanced or early stages of differentiated thyroid cancer) were also eligible for inclusion.

Summary of Study Characteristics

One systematic review was identified, published in 2021, and including studies published up to December 2019.¹⁴ This systematic review was designed to identify studies involving treatment for advanced or refractory DTC, but captured a broader set of interventions than in the current report. Specifically, the systematic review eligibility criteria permitted inclusion of studies involving immunotherapies or tyrosine kinase inhibitor (any type), with or without re-treatment with radioiodine. Studies involving tyrosine kinase inhibitors were restricted to clinical trials of humans, whereas immunotherapy studies also included in vitro studies. Of the 23 studies identified in the systematic review, 3¹⁵⁻¹⁷ were relevant to the current report. In the systematic review, brief summaries of each study were provided; there was no synthesis or additional interpretation provided. As these 3¹⁵⁻¹⁷ studies were also identified as primary studies in the current review, the more comprehensive evidence from the primary studies was selected for inclusion, in lieu of the more limited evidence presented within this secondary source (i.e., the systematic review). As such, the characteristics and results from this systematic review will not be described hereafter, aside from a brief summary of its critical appraisal.

A total of 7¹⁵⁻²¹ primary clinical studies were identified, including the 3¹⁵⁻¹⁷ captured in the aforementioned systematic review, and 4¹⁸⁻²¹ other studies. These 7¹⁵⁻²¹ studies are described in the following subsections.

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Of the 7¹⁵⁻²¹ primary clinical studies identified in this report, none included a control group involving lenvatinib, placebo, or no treatment, nor were any designed to compare outcomes between radioiodine resensitization interventions. Four studies were single-arm clinical trials (i.e., had 1 intervention arm and no control arm) and 3¹⁹⁻²¹ were uncontrolled retrospective cohort studies. In the 4¹⁵⁻¹⁸ single-arm clinical trials and 1²¹ of the retrospective cohort studies, all patients within each study received the same radioiodine resensitization regimen. In the other 2^{19,20} uncontrolled retrospective cohort studies, several different radioiodine resensitization regimens were used; however, the studies were not designed to compare outcomes between these interventions.

Country of Origin

All 4¹⁵⁻¹⁸ clinical trials were conducted in the US, of which 3^{15,16,18} were conducted at the Memorial Sloan Kettering Cancer Centre in New York; the fourth¹⁷ was conducted at Massachusetts General Hospital. Among the 3¹⁹⁻²¹ retrospective cohort studies, 1²⁰ was US-based, conducted at MD Anderson Cancer Centre in Texas, 1²¹ was conducted in Croatia, and 1¹⁹ in Australia.

Patient Population

All 7¹⁵⁻²¹ studies included patients with RAIRMDTC. In 3^{15,17,18} studies, patients with locally advanced or unresectable radioiodine-refractory DTC without distant metastasis were also eligible. In 1¹⁵ of these 3^{15,17,18} studies, 1 patient had locally advanced disease and all other patients had distant metastasis. In the other 2^{17,18} studies, over 86% of patients (which represented all but 1 patient in each study) had distant metastasis to the lungs; it was unclear whether the remaining patient in each of these studies had distant or local metastasis. One²¹

retrospective study captured a broader patient population, but provided data on a relevant subset of patients with RAIRMDTC. The sample size was 3 patients in the relevant subset of the latter study²¹; in the remaining 6¹⁵⁻²⁰ studies, sample size ranged from 6 to 20 patients.

The median age across the 6¹⁵⁻²⁰ studies for which baseline patient characteristics were reported ranged from 56 to 68 years. In 5^{15-18,20} of the 6¹⁵⁻²⁰ studies, there were more males than females (54% female to 86% male); in the remaining 1¹⁹ study, which involved 6 patients, 2 patients (33%) were male.

Five^{15,17-19,21} of the studies were restricted to patients with RAIRMDTC harbouring *BRAF* V600E mutations, 1¹⁹ of which also permitted *NRAS* mutations. In the other 2^{16,20} studies, there were no mutation-related eligibility restrictions. In these studies, tumour genotype was reported among the baseline patient characteristics, and was most commonly *BRAF* V600E.

Where defined, the criteria for establishing radioiodine refractoriness differed slightly across studies. While all studies required 1 or more non-radioiodine-avid lesion(s) (including but not limited to metastatic sites), and/or progression despite previous radioiodine resensitization therapy, specific details within these criteria varied. Additionally, the 3^{15,16,18} clinical trials conducted at the Memorial Sloan Kettering Cancer Center included a criterion that involved assessing ¹⁸F-fluorodeoxyglucose-avidity, whereas this criterion was not used in other studies.

The type of DTC varied within and across studies. The majority of patients had papillary cell thyroid cancer, including classical, tall, columnar, and clear cell papillary cell thyroid cancer. Five^{15,16,18-20} of the 7¹⁵⁻²¹ studies also reported patients with poorly differentiated thyroid cancer, with proportions ranging from 15% to 43%; follicular cell and mixed types were also reported.

Interventions and Comparators

The 4¹⁵⁻¹⁸ included single-arm clinical trials investigated the use of 4 different radioiodine resensitization regimens as interventions; none involved a comparator group. Three^{15,17,18} trials involved *BRAF* inhibitors: dabrafenib 150 mg twice daily,¹⁷ vemurafenib 960 mg twice daily,¹⁵ or vemurafenib 960 mg twice daily in combination with the anti-ErbB3 monoclonal antibody CDX-3379 1,000 mg on alternating weeks (beginning on week 3).¹⁸ The fourth¹⁶ trial investigated the use of the MEK inhibitor selumetinib 75 mg twice daily. Across all 4¹⁵⁻¹⁸ trials, treatment involved up to 8 weeks of treatment. Initially, patients received 4¹⁵⁻¹⁷ to 6¹⁸ weeks of radioiodine resensitization treatment, followed by a scan to re-assess radioiodine uptake (relative to baseline). In 3^{15,16,18} studies, this assessment was done using an iodine-124 PET/CT (PET/CT) scan, and in 1¹⁷ study, this was done using a whole body scan after low-dose (148 MBq) iodine-131. Patients whose tumours showed restored radioiodine avidity received approximately 2 additional weeks of radioiodine resensitization treatment (exact duration not reported in 2^{15,16} studies), followed by a therapeutic dose of iodine-131. In the 3^{15,16,18} studies using iodine-124 PET/CT, a dosimetry threshold had to be met, such that some patients showed radioiodine avidity that was insufficient to warrant a therapeutic dose of iodine-131. Radioiodine resensitization treatment was discontinued 2^{15,16,18} to 5¹⁷ days after receiving iodine-131.

Across the 3¹⁹⁻²¹ uncontrolled retrospective cohort studies, clinical experience with several different radioiodine resensitization regimens were described. In 2²¹ study, treatment was limited to vemurafenib 960 mg twice daily, with no comparison group. In the other 2^{19,20} uncontrolled retrospective cohort studies, interventions included: dabrafenib, vemurafenib, trametinib, dabrafenib in combination with trametinib, dabrafenib in combination with vemurafenib, vemurafenib in combination with cobimetinib, and an investigational MEK

inhibitor (doses provided in Appendix 2, reported by study authors); none of the studies compared outcomes between these interventions, nor did any include a comparison group involving lenvatinib or no treatment. In 2^{20,21} studies, details were sparse regarding the planned duration of radioiodine resensitization regimens, assessment of radioiodine uptake, and subsequent therapeutic treatment with iodine-131, although in both^{20,21} studies it was stated that assessment of radioiodine uptake was evaluated using iodine-131 followed by a whole body scan. In the third¹⁹ study, treatment details were provided: patients received a 4-week course of radioiodine resensitization treatment, followed by an iodine-124 PET/CT scan to assess avidity, and patients with sufficient radioiodine avidity received a therapeutic dose of iodine-131. The duration of radioiodine resensitization treatment described in this study¹⁹ (four weeks) was broadly consistent with the duration reported in the clinical trials; whereas, the duration of radioiodine resensitization treatment described by Jaber et al. (2018),²⁰ varied across patients, from less than 1 month to more than 6 years (median of 3.5 months; range of 0.9 to 76.4 months).

Outcomes

All 7¹⁵⁻²¹ studies reported the proportion of patients with radioiodine resensitization as a key study outcome. Additionally, response, measured radiographically using Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, was reported in all 7¹⁵⁻²¹ studies, with variability around the time point at which response was reported. Three^{15,18,19} studies reported progression-free survival. Mortality was reported in 1²¹ study. All 7¹⁵⁻²¹ studies reported on adverse events, either as radioiodine resensitization treatment-related,^{15,16,18} radioiodine-related,²⁰ or all-cause adverse events.^{17,19,21}

Summary of Critical Appraisal

Systematic Review

The 1¹⁴ systematic review captured studies already included in the current report, and thus did not contribute additional evidence to the review. This systematic review was assessed with a focus on the comprehensiveness and quality of search strategies to understand whether it may have missed key studies; however, was not evaluated for the quality of reporting (Appendix 3).

In this 1¹⁴ systematic review, the search covered multiple bibliographic databases, grey literature, and included a review of the reference lists from included studies; however, the lack of duplicate review during study selection may have led to the omission of relevant studies. Similarly, the search terms may have been overly broad: “TKI” and “tyrosine kinase inhibitor” were the only drug-related search terms (i.e., terms for specific drugs or more specific drug classes such as *BRAF* or MEK inhibitors were not used) and it is unclear whether these terms were applied to subject headings or to titles and abstracts alone. Hence there is a risk that some studies were missed due to the search sensitivity and study selection process.

Primary Clinical Studies

In 5¹⁵⁻¹⁹ of the 7¹⁵⁻²¹ studies, the objectives, outcomes, patient characteristics, interventions and main findings were clearly reported. In the other 2^{20,21} studies, details regarding the intervention were lacking. The duration of treatment with vemurafenib was not described in the methods or results section of the study by Pešorda et al. (2020),²¹ and in the study by Jaber et al. (2018),²⁰ the radioiodine resensitization treatment doses were not reported. Furthermore, in the latter study, the median duration of radioiodine resensitization treatment was reported as being 3.5 months (range 0.9 to 76.4 months), which, for some patients,

vastly exceeded the duration of treatment in the other 5 studies (up to approximately 8 weeks), making it unclear the treatments were initially planned to be used for radioiodine resensitization, or whether this decision was made later in the treatment course. All 7¹⁵⁻²¹ studies reported efficacy or effectiveness outcomes that were considered valid and reliable: radioiodine uptake was evaluated using either iodine-124 PET/CT or iodine-131 whole body scan, and tumour response was measured using RECIST v1.1 criteria. However, in 1¹⁷ study, the timing of response assessment was unclear, with inconsistency between the methods (stating 3 months) and results (stating 6 months). Adverse events were well captured in 6^{15-19,21} of the 7 studies, using the Common Terminology Criteria for Adverse Events version 4.0 classification system, or not stated. In the seventh study, Jaber et al. (2018)²⁰ reported on radioiodine-related adverse events but did not report on adverse events related to the preceding radioiodine resensitization treatment, and hence was assessed as being not well captured.

A main limitation of all 7¹⁵⁻²¹ studies was the non-comparative nature of the study designs. The 4¹⁵⁻¹⁸ clinical trials were designed as single-arm trials; 1²¹ of the retrospective cohort studies captured a single radioiodine resensitization treatment regimen; and the other 2^{19,20} retrospective cohort studies were non-comparative despite capturing multiple treatments, due to the sample size relative to the number of treatments (6 patients and 3 regimens in the study by Iravani et al. [2019]¹⁹; 13 patients and 5 regimens in the study by Jaber et al. [2018]²⁰). Given the non-comparative nature of the 7¹⁵⁻²¹ studies, none involved blinding of patients, investigators, or outcome assessors. The implication of having non-comparative (i.e., uncontrolled) studies of investigational therapies is that direct comparisons of outcomes between groups of patients cannot be made, either between interventions, or against standard of care. As such, the findings from these studies do not enable robust evaluation of the relative benefits and harms of radioiodine resensitization treatment across interventions, or relative to the relevant comparators, lenvatinib or no treatment.

Another limitation related to the external validity of all studies, relative to the Canadian setting. This was assessed as being somewhat low, given that all 7¹⁵⁻²¹ studies were single-centre studies conducted in non-Canadian settings, and therefore may not generalize to expected outcomes in all Canadian centres.

Sample size calculations were performed in 3^{15,16,18} of the 4¹⁵⁻¹⁸ clinical trials, and none of the 3¹⁹⁻²¹ retrospective cohort studies. These 3^{15,16,18} clinical trials were designed to reject a null hypothesis that up to 5% of patients would have radioiodine uptake. In 1¹⁸ of these 3^{15,16,18} studies, accrual was halted early and thus the study was underpowered; however, the primary end point was still met. In the other 2^{15,16} trials, the target sample sizes were achieved and were sufficient for addressing the study objective of determining whether 5% or more of patients have radioiodine uptake.

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Summary of Findings

Appendix 4 presents the main study findings, by outcome.

Clinical Effectiveness of Radioiodine Resensitization Followed by Radioiodine Resensitization

Across the 7¹⁵⁻²¹ studies, between 50% and 71% of patients showed evidence of restored radioiodine avidity following resensitization therapy with vemurafenib-, dabrafenib-, trametinib- or selumetinib-based therapy, or other investigational MEK inhibitor. In 3^{15,16,18} studies, some patients had evidence of restored radioiodine avidity but did not meet the dosimetry threshold to warrant therapeutic dose of radioiodine. With these patients removed, the proportion of patients who were retreated with radioiodine across the 7¹⁵⁻²¹ studies ranged from 33% and 69%.

Resensitization according to tumour genotype was available in the 3^{16,19,20} studies with mixed genotypes; the other 4^{15,17,18,21} studies were restricted to patients whose tumours harboured *BRAF* V600E mutations. Across all 7¹⁵⁻²¹ studies, the proportion of patients with *BRAF* V600E mutant tumours who were resensitized and retreated with radioiodine was 11% to 100%. Among patients with *NRAS*+ mutations, reported in 3^{16,19,20} studies, the range was 33% to 100%. Two of the multi-genotype studies^{16,20} captured and reported on patients with wild-type tumours: in 1²⁰ study there was 1 patient who was resensitized and retreated with radioiodine (100%) and in the other study,¹⁶ 1 out of 3 patients (33%) was resensitized and retreated with radioiodine. The latter study¹⁶ also reported on 3 patients whose tumours had RET/PTC translocations, of whom 1 was resensitized and retreated with radioiodine (33%).

Response

Tumour response following radioiodine treatment, based on RECIST v1.1 criteria, was reported in 6¹⁵⁻²⁰ of the 7 studies. This was measured as best response at 6 months in 4^{15-18,20} studies, and as best response to the end of follow-up in 2^{19,20} studies. All studies reported the response rates among patients treated with radioiodine, and 2^{17,20} studies also reported response rates among all non-radioiodine-treated patients. The response rates among all included patients in the study was also calculated.

Across the 6¹⁵⁻²⁰ studies, none reported complete responses, either radioiodine-treated patients or those who were not resensitized. Among radioiodine-treated patients, at least 1 partial response was reported in each of the 6 studies, ranging from 33% to 75% of patients (in the 4 studies that reported best overall response at 6 months, this ranged from 33% to 63% of patients). The rest of the radioiodine-treated patients had stable disease at the pre-defined assessment time point (i.e., 6 months or the end of follow-up), with the exception of 1¹⁸ study, in which 2 out of 4 radioiodine retreated patients (50%) had progressive disease by month 6. Details regarding tumour progression were provided by the study authors of that study,¹⁸ explaining that 1 of the 2 patients had initiated a new anti-cancer treatment despite having stable disease at 3 months (and so was categorized as having progressed), and that response had been mixed in second patient, with tumour regression in areas that had shown restored radioiodine avidity, but tumour growth in metastatic lesions that had not shown restored avidity.

Subsequent Therapy

Use of subsequent therapy was specified in 5^{15,18-21} studies, among the subgroup of radioiodine-treated patients.

In 2^{19,20} of these 5 studies, none of the radioiodine-treated patients had received subsequent treatment by the end of follow-up, with median follow-up times of 14.3²⁰ and 16.6¹⁹ months.

In another 2^{15,18} of these 5 studies, 50% of patients had received subsequent treatment by the end of the follow-up period. In 1¹⁸ of these 2^{15,18} studies, patients received unspecified systemic therapy (these patients were classified as having progressive disease). In the other study,¹⁵ patients received either radiation or vemurafenib re-treatment.

In the fifth²¹ of these 5 studies, it was reported that 1 out of 3 vemurafenib-treated patients received second-line sorafenib 2 years after successful redifferentiation with vemurafenib, but that the patient died shortly thereafter.

Progression-Free Survival or Time to Progression

In 1¹⁵ clinical trial involving vemurafenib, individual patient-level data were provided regarding the timing of progression among 4 radioiodine-treated patients: progression events occurred at 9 months and 18 months post-progression, and censoring (i.e., event-free at last follow-up) occurred at 18 and 22 months.

Progression-free survival at 6 months was available from another clinical trial,¹⁸ among 4 radioiodine-treated patients, and findings were consistent with best overall response at 6 months from that trial: 50% patients had progressed by 6 months, and the other 50% of patients remained progression-free and alive at 6 months.

In 1¹⁹ uncontrolled retrospective cohort study involving mixed treatments, all 6 patients (irrespective of treatment with radioiodine) were alive and progression-free at the end of follow-up (median = 16 months; range = 5 months to 40 months).

Mortality

Across the 7¹⁵⁻²¹ studies, 1 death was reported in 1²¹ uncontrolled retrospective cohort study, 2 years after successful resensitization to radioiodine. Mortality was not reported in any of the other 6¹⁵⁻²⁰ studies.

Adverse Events

Among the 6^{15-19,21} studies reporting all-cause or targeted therapy-related adverse events, skin-related adverse events were the most common type of event. Maculopapular rash was common in vemurafenib-based studies, affecting approximately 3/4 of patients, and with grade 3 maculopapular rash affecting approximately 1/4 of patients in 2^{15,18} studies. Rash was the most common selumetinib-related adverse event, affecting 90% of patients in 1¹⁶ study, although all events were mild or moderate (grade 1 or 2). Skin-related lesions or changes were also the most common dabrafenib-related adverse event in the clinical trial by Rothenberg et al. (2015),¹⁷ affecting 80% of patients (all grade 1); these included skin darkening, actinic keratosis, verrucous keratosis, and other skin-related adverse events. Acneiform rash affected 2 out of the 3 trametinib-treated patients (67%) in the study by Iravani et al. (2019),¹⁹ both of which were grade 3 adverse events; grade 1 rash (unspecified) affected 2 out of the 2 (100%) vemurafenib plus cobimetinib-treated patients in that same study.

Other adverse events that affected more than 1 patient in any given study are provided in Table 11. Adverse events with frequencies of 50% or higher in at least 1 study included: nausea, diarrhea, fatigue, hand-foot syndrome (also known as palmar-plantar erythrodysesthesia syndrome), and pooled categories of events, such as increased levels of hepatic enzymes and gastrointestinal symptoms.

Cost-Effectiveness of Radioiodine Resensitization Followed by Radioiodine

No relevant evidence regarding the cost-effectiveness of radioiodine resensitization treatment for RAIMDTC was identified; therefore, no summary can be provided.

Limitations

While the present review captures a comprehensive synthesis of the available evidence on radioiodine resensitization among patients with RAIMDTC, there are several noteworthy limitations.

First, no evidence on cost-effectiveness of radioiodine resensitization therapy was identified in this review and no studies identified that directly compared the efficacy and safety of radioiodine resensitization therapy against lenvatinib or no treatment. While it may be reasonable to assume that de-differentiated cancer cells are unlikely to spontaneously resensitize to radioiodine without treatment, and hence a resensitization rate of 0% might provide a reasonable benchmark against which to compare findings, the current evidence base does not enable robust comparisons of other relevant clinical outcomes (such as tumour response, progression-free survival, overall survival, health-related quality of life, and adverse event rates) against existing standards of care. Additionally, there was no evidence identified for NTRK or RET inhibitors; all identified evidence was related to *BRAF* and/or MEK inhibitor-based therapy.

Another key limitation of the identified evidence was the sample size (with all studies having fewer than 20 patients) and single-centred study design of the included studies. The clinical trials were designed to be adequately powered to reject a null hypothesis of a up to 5% resensitization rate. While the primary end points were met, and provided sufficient evidence for establishing proof-of-principle regarding resensitization, the sample sizes contributed to uncertainty around the true proportion of patients that resensitize to treatment. Precision was further reduced within genotype-specific subgroups, in which sample sizes were smaller (e.g., the sample sizes of patients harbouring a *BRAF* V600E mutation ranged from 3 to 12 patients), as well as for estimating radiographic response rates, as response was typically reported among the subset of patients treated with radioiodine. There are 2 newer single-arm phase II trials not captured in the current review that enrolled larger sample sizes: the SEL-I-METRY trial²³ of selumetinib (n = 60 patients) is ongoing but results have not yet been reported, and the MERAIODE²⁴ trial of trametinib plus dabrafenib (n = 24 patients) has been presented as a conference abstract, but the full-text manuscript is not yet available in the peer-reviewed literature. With their larger sample sizes, these trials should provide slightly more precise estimates of clinical effectiveness and safety. To help achieve these larger sample sizes, both trials were multi-centred, with 8 centres in each trial.^{23,24} In describing the SEL-I-METRY trial, Wadsley et al.²⁵ reflected on the challenges of conducting multi-centred trials of radioiodine resensitization treatments, identifying several barriers such as: access to iodine-124 and to PET scanning facilities using iodine-124 as a tracer; and the calibration and validation of imaging measurements across sites to ensure consistent dosimetry and its associated costs. These barriers may explain the preponderance of single-centred trial designs identified in the current evidence base.

Another limitation of the current evidence base was the heterogeneity across the studies regarding tumour characteristics, including the baseline levels of radioiodine uptake across

lesions. Tchekmedyan et al. (2022)¹⁸ pointed out that over half of patients in their study sample had at least 1 lesion with evidence of radioiodine uptake at baseline, despite meeting the criteria for being defined as radioiodine refractory. The authors posited that there may be differences in outcomes between patients with a lack of radioiodine avidity across all lesions at baseline, compared with those having mixed avidity, and recommended the need to revisit the definition of radioiodine refractoriness. Differences across trials in the definition of radioiodine refractoriness may have led to heterogeneity in the proportion of patients with resensitization as well as tumour response and progression-free survival rates among those who were resensitized to radioiodine. Other relationships between tumour characteristics, disease biomarkers, and clinical outcomes require further exploration.¹⁵

None of the studies were conducted in an entirely Canadian setting, which is a limitation, as the imaging techniques and medications used in the non-Canadian studies may not be available in all Canadian centres. Furthermore, it is unclear whether the patient and tumour characteristics in the US, Australian, and Croatian-based study samples would be similar to those of Canadian patients.

Conclusions and Implications for Decision- or Policy-Making

This report identified 4¹⁵⁻¹⁸ single-arm clinical trials, 3¹⁹⁻²¹ uncontrolled retrospective cohort studies, and 1¹⁴ systematic review informing the clinical effectiveness and safety of radioiodine resensitization treatments for patients with RAIRMDTC. No relevant cost-effectiveness analyses were identified.

All 4¹⁵⁻¹⁸ clinical trials met their primary objective of demonstrating radioiodine resensitization following treatment with a *BRAF* or MEK inhibitor (with or without the anti-ErbB3 monoclonal antibody CDX-3379), establishing the proof-of-concept that *BRAF* and MEK inhibitors can resensitize tumour to radioiodine. The clinical experience reported in the 3¹⁹⁻²¹ uncontrolled retrospective cohort studies similarly showed increased radioiodine uptake following treatment, and study authors considered this to be a feasible strategy. Across all 7¹⁵⁻²¹ studies, all patients who were resensitized and retreated with radioiodine had partial responses or stable disease at the pre-defined response assessment time point (typically 6 months^{15-18,21}), with the exception of 2 patients in 1¹⁸ study, who had had stable disease or mixed response at 3 months, but subsequently initiated a new anti-cancer therapy and were categorized as having progressive disease. Adverse events in the included studies were primarily mild or moderate, although there was evidence of grade 3 acneiform rash associated with trametinib (in 2 out of 3 patients in 1¹⁹ study), and grade 3 maculopapular rash associated with vemurafenib (in approximately 1-quarter of patients in 2^{15,18} studies).

The demonstrated ability to resensitize tumours to radioiodine using *BRAF* and/or MEK inhibitors is consistent with emerging evidence from the MERAIODE²⁴ trial, in which radioiodine resensitization rate was achieved in 95% of trametinib plus dabrafenib-treated patients with *BRAF* V600E mutated RAIRMDTC (95% confidence interval, 76% to 100%). The MERAIODE²⁴ trial was not included in the current review as it was reported as a conference abstract and estimates may change when the full report is published reported in the peer-reviewed literature. However, this consistent evidence of resensitization, along

with the evidence of tumour response among those re-sensitized, suggests there may be clinical benefit with radioiodine re-sensitization strategies using a shorter course of treatment (typically no more than 2 months) than the current standard of care with lenvatinib for which long-term maintenance treatment is required until death or progression. Furthermore, whereas the toxicity associated with lenvatinib has been cited as a concern (severe or life-threatening adverse events were experienced by approximately 3-quarters of patients in the lenvatinib arm of the SELECT trial),⁸ the re-sensitization therapies in the current review were primarily mild.

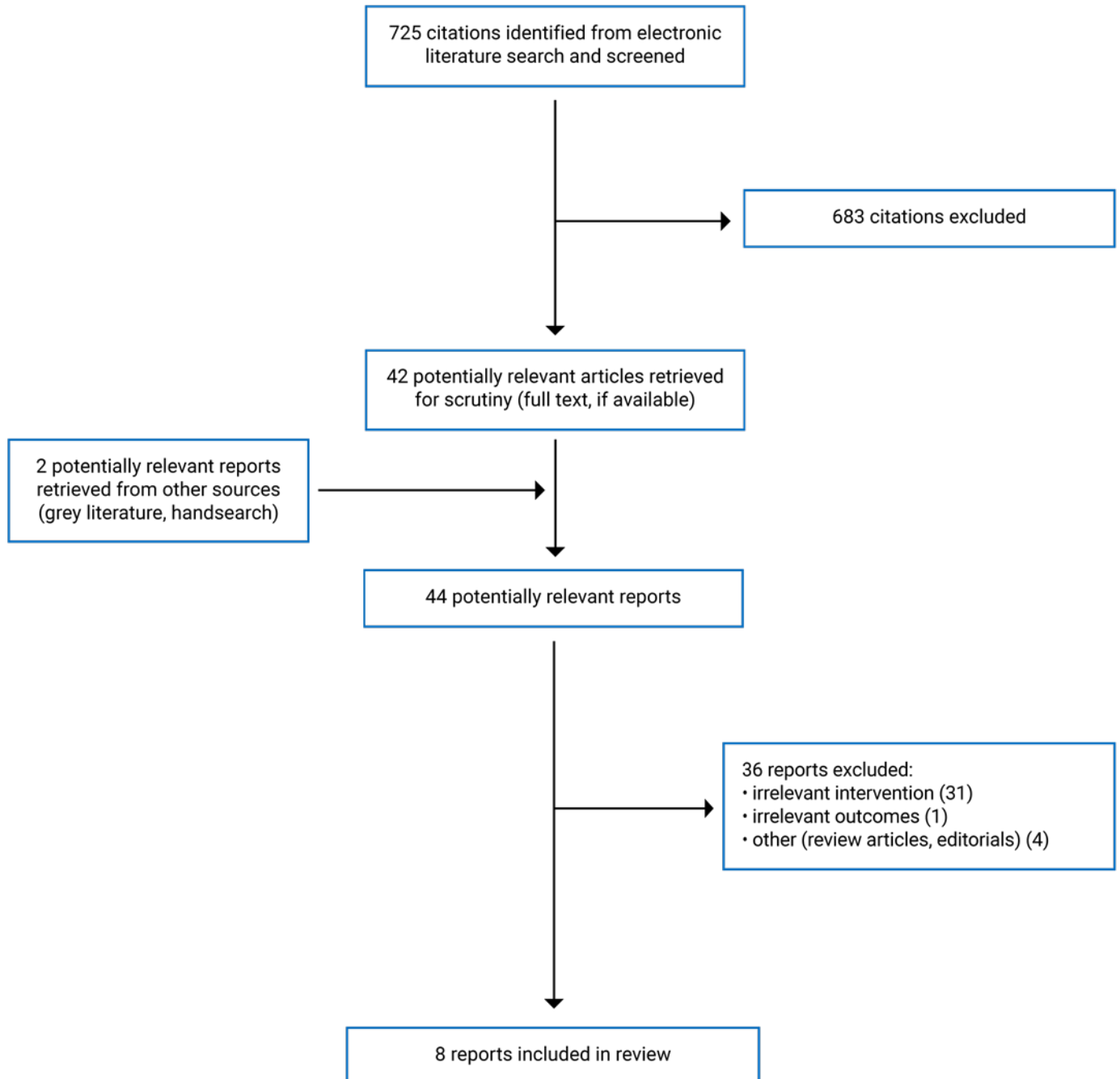
The limitations of the included literature, such as the small sample size of the included studies and the non-comparative evidence base does not lend itself to robust conclusions, and these limitations should be considered when interpreting the findings from this report. Given the potential challenges of setting up large, randomized trials of radioiodine re-sensitization treatment among patients with RAIRMDTC, even single-arm trials and observational studies involving multiple centres and larger sample sizes would improve the accuracy and precision of the proportion of patients whose tumours can be re-sensitized to radioiodine and other patient-relevant clinical outcomes, as well as enable exploration of predictive factors for successful re-sensitization. Findings from the SEL-I-METRY trial²³ of selumetinib and the MERAIODE²⁴ trial of trametinib plus dabrafenib, as well as additional data from new clinical trials and other evidence syntheses, may help better inform the role of radioiodine re-sensitization followed by radioiodine for the treatment of patients with RAIRMDTC.

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Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Note that this appendix has not been copy-edited.

Table 2: Characteristics of Included Systematic Review

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Jones et al. (2021) ¹⁴ UK Funding source: None	<p>Study designs included: This systematic review captured clinical trials involving tyrosine kinase inhibitors, and any study design involving immunotherapies.</p> <p>Number primary studies included: 23 primary studies were included; 3 were relevant to the current report.</p>	<p>Eligible populations: For tyrosine kinase inhibitors: Patients with advanced/treatment refractory</p> <p>DTC. For immunotherapies: patients/tissues/cells of advanced/treatment refractory</p> <p>DTC</p> <p>Relevant population: patients with RAIRMDTC</p>	<p>Eligible interventions and comparators: Tyrosine kinase inhibitors or immunotherapies.</p> <p>Relevant interventions and comparators: Dabrafenib, vemurafenib, selumetinib.</p>	<p>Outcomes: Not restricted</p> <p>Follow-up: Not specified.</p>

DTC = differentiated thyroid cancer; RAIRMDTC = radioiodine-refractory/resistant metastatic differentiated thyroid cancer.

Table 3: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design	Population characteristics	Intervention	Clinical outcomes, length of follow-up
<p>Tchekmedyian et al. (2022)¹⁸</p> <p>US (Memorial Sloan Kettering Cancer Center)</p> <p>Funding: Kolltan Pharmaceuticals, NIH/NCI, and others^a</p>	<p>Study design: Single-arm single-centre pilot clinical trial</p> <p>Study period: 2015 to 2016</p> <p>Relevant study objective: to evaluate the safety, tolerability, and redifferentiation potential of vemurafenib plus CDX-3379 in <i>BRAF</i> V600E+ RAIR patients.</p>	<p>Number patients: 7</p> <p>Key eligibility criteria</p> <ul style="list-style-type: none"> • <i>BRAF</i> V600E + • RAIR^b • No requirement for metastatic, although at least 6 / 7 of patients had metastatic disease. <p>Key baseline characteristics</p> <ul style="list-style-type: none"> • Median age: 67 years • Sex: 86% male • Histology: <ul style="list-style-type: none"> ◦ 29% classical PTC ◦ 29% tall cell PTC ◦ 42% PDTC • Metastatic sites: <ul style="list-style-type: none"> ◦ 86% lung ◦ 29% distant nodes ◦ 14% soft tissue nodules ◦ 14% bone 	<p>Intervention</p> <ul style="list-style-type: none"> • Oral vemurafenib 960 mg b.i.d. for up to 8 weeks • IV CDX-3379 1000 mg administered during weeks 3, 5, and possibly 7 • ¹³¹I on week 8. 	<p>Outcomes</p> <ul style="list-style-type: none"> • Tumoural iodine incorporation • Overall response • 6-month PFS • Subsequent treatments and change in therapy • Adverse events. <p>Follow-up: Up to 47 months</p>
<p>Pešorda et al. (2020)²¹</p> <p>Croatia</p> <p>Funding source not reported</p>	<p>Study design: Uncontrolled retrospective cohort study</p> <p>Study period: 2014 to 2020</p> <p>Relevant study objective: to present experience with vemurafenib and its influence on tumour redifferentiation</p>	<p>Number patients: 3 (subgroup, among 17)</p> <p>Key eligibility criteria (for subgroup)</p> <ul style="list-style-type: none"> • <i>BRAF</i> V600E + • RAIR, defined as progressive metastatic disease despite RAI. • Progressive metastatic disease <p>Key baseline characteristics: Not reported for subgroup</p>	<p>Intervention</p> <ul style="list-style-type: none"> • Oral vemurafenib 960 mg • ¹³¹I 	<p>Outcomes</p> <ul style="list-style-type: none"> • Restoration of RAI uptake • Disease progression • Death • Adverse events. <p>Follow-up: Unclear^c</p>

Study citation, country, funding source	Study design	Population characteristics	Intervention	Clinical outcomes, length of follow-up
<p>Dunn et al. (2019)¹⁵ US (Memorial Sloan Kettering Cancer Center) Funding: Genentech, NIH/NCI, and others^a</p>	<p>Study design: Single-arm single-centre pilot clinical trial</p> <p>Study period: 2014 to 2015</p> <p>Relevant study objective: to investigate enhancement of lesional iodide uptake with vemurafenib in patients with RAIR.</p>	<p>Number patients: 12</p> <p>Key eligibility criteria</p> <ul style="list-style-type: none"> • <i>BRAF</i> V600E + • RAIR^b • No requirement for metastatic, although at least 11 / 12 patients had metastasis <p>Key baseline characteristics</p> <ul style="list-style-type: none"> • Median age: 68 years • Sex: 58% male • Histology: <ul style="list-style-type: none"> ◦ 17% classical PTC ◦ 42% tall cell PTC ◦ 17% columnar cell PTC ◦ 25% PDTC • Metastatic sites: <ul style="list-style-type: none"> ◦ 92% lung • 17% bone 	<p>Intervention</p> <ul style="list-style-type: none"> • Vemurafenib 960 mg orally b.i.d. for ~4 weeks. • ¹³¹I after 4 weeks (exact timing not specified) at or under the maximum tolerable activity. 	<p>Outcomes</p> <ul style="list-style-type: none"> • Iodine incorporation • Best overall response • 6 month PFS • Adverse events. <p>Follow-up</p> <ul style="list-style-type: none"> • Protocol-defined follow-up of 6 months • Patients were followed up off-protocol for up to 31 months.
<p>Iravani et al. (2019)¹⁹ Australia No external funding</p>	<p>Study design: Uncontrolled retrospective cohort study</p> <p>Study period: 2015 to 2017</p> <p>Relevant study objective: to assess the feasibility of MAPK-pathway blockade combined with thyroid hormone withdrawal for redifferentiation.</p>	<p>Number patients: 6</p> <p>Key eligibility criteria:</p> <ul style="list-style-type: none"> • <i>BRAF</i> V600E+ or <i>NRAS</i>+ • RAIR^d • Metastatic <p>Key baseline characteristics</p> <ul style="list-style-type: none"> • Median age: 61 years • Sex: 33% male • Histology: <ul style="list-style-type: none"> ◦ 50% PTC ◦ 33% FTC and PDTC ◦ 17% PDTC • Metastatic sites: <ul style="list-style-type: none"> ◦ 100% lung • 33% bone 	<p>Intervention</p> <ul style="list-style-type: none"> • <i>NRAS</i>+: Trametinib 2 mg daily for 4 weeks • <i>BRAF</i> V600E+: dabrafenib 150 mg b.i.d. + trametinib 2 mg daily; or vemurafenib 960 mg b.i.d. + cobimetinib 60 mg daily • ¹³¹I after 4 weeks of resensitization treatment 	<p>Outcomes</p> <ul style="list-style-type: none"> • RAI avidity • Response over duration of follow-up • Adverse events. <p>Follow-up: Median follow-up: 16 months; range: 5 to 40 months.</p>

Study citation, country, funding source	Study design	Population characteristics	Intervention	Clinical outcomes, length of follow-up
<p>Jaber et al. (2018)²⁰ US (MD Anderson) Funding: NCI grant</p>	<p>Study design: Uncontrolled retrospective cohort study</p> <p>Study period: Not reported</p> <p>Relevant study objective: to describe patients receiving targeted therapy with demonstrated RAI uptake allowing for ¹³¹I administration.</p>	<p>Number patients: 13</p> <p>Key eligibility criteria</p> <ul style="list-style-type: none"> • No genotype-based restrictions • RAIR^e • Metastatic <p>Key baseline characteristics</p> <ul style="list-style-type: none"> • Median age: 56 years • Sex: 54% male • Histology: <ul style="list-style-type: none"> ◦ 77% PTC ◦ 8% FTC ◦ 15% PDTC • Metastatic sites not reported. 	<p>Intervention</p> <ul style="list-style-type: none"> • <i>BRAF</i> V600E+: dabrafenib (n=7) vemurafenib (n=1) or dabrafenib + vemurafenib (n=1). • RAS+: trametinib (n=2), or investigational MEK inhibitor (n=1). • No mutations: trametinib (n=1). • Median duration prior to diagnostic WBS: 14.3 (range: 0.9 to 76.4 months). • ¹³¹I if WBS showing meaningful RAI uptake 	<p>Outcomes</p> <ul style="list-style-type: none"> • Additional radiologic response ¹³¹I therapy achieved over that seen with targeted treatment alone • Response (best response, duration of response including time off systemic therapy) <p>Follow-up: Median follow-up among post-RAI therapy: 14.3 months</p>
<p>Rothenberg et al. (2015)¹⁷ US (Massachusetts General Hospital) Funding: GlaxoSmithKline; Ellison Foundation grant</p>	<p>Study design: Single-arm single-centre clinical trial</p> <p>Enrolment period: 2012 to 2013</p> <p>Relevant study objective: to determine if dabrafenib can stimulate RAI among <i>BRAF</i> V600E+ RAIR patients.</p>	<p>Number patients: 10</p> <p>Key eligibility criteria</p> <ul style="list-style-type: none"> • <i>BRAF</i> V600E + • RAIR^e • Metastatic or unresectable <p>Key baseline characteristics</p> <ul style="list-style-type: none"> • Median age: 66 years • Sex: 60% male • Histology: <ul style="list-style-type: none"> ◦ 50% classical PTC ◦ 40% tall cell PTC ◦ 10% clear cell PTC • Metastatic sites: 90% lung 	<p>Intervention</p> <ul style="list-style-type: none"> • Oral dabrafenib 150 mg b.i.d. for up to 37 days (5.5 weeks) • ¹³¹I, 5.5 GBq, on day 37. 	<p>Outcomes</p> <ul style="list-style-type: none"> • RAI uptake • Best response at 6 months^f <p>Follow-up: Unclear^f</p>

Study citation, country, funding source	Study design	Population characteristics	Intervention	Clinical outcomes, length of follow-up
Ho et al. (2013) ¹⁶ US (Memorial Sloan Kettering Cancer Center) Funding: AstraZeneca, Genzyme, NIH, and others ^a	Study design: Single-arm single-centre clinical trial Enrolment period: 2010 to 2011 Relevant study objective: to determine whether selumetinib could reverse refractoriness to RAI among patients with metastatic TC.	Number patients: 20 Key eligibility criteria <ul style="list-style-type: none"> • No genotype-based restrictions • RAIR^b • Metastatic Key baseline characteristics <ul style="list-style-type: none"> • Median age: 61 years • Sex: 55% male • Histology: <ul style="list-style-type: none"> ◦ 25% classical PTC ◦ 40% tall cell PTC ◦ 35% PDTC • Metastatic sites: not reported 	Intervention <ul style="list-style-type: none"> • Oral selumetinib 75 mg b.i.d. for up to 5 weeks • ¹³¹I at 5 weeks at or under the maximum tolerable activity. 	Outcomes <ul style="list-style-type: none"> • RAI uptake in index tumour(s) • Response at 2 and 6 months • RAI uptake by <i>BRAF</i> mutational status • Best response at 6 months • Adverse events Follow-up: 6 months

¹³¹I = iodine-131; b.i.d. = twice a day; FTC = follicular thyroid carcinoma; GBq = gigabecquerel; IV = intravenous; NIH/NCI = National Institutes of Health/National Cancer Institute; PDTC = poorly differentiated thyroid cancer; PFS = progression-free survival; PTC = papillary thyroid cancer; RAI = radioiodine; RAIR = radioiodine-refractory/resistant; WBS = whole body scan.

^aAdditional funding source information: Dunn et al. (2019)¹⁵ and Tchekmedyan et al. (2022)¹⁸: Various NIH/NCI grants, the Geoffrey Beene Cancer Research Center and Cycle for Survival at Memorial Sloan Kettering Cancer Center; Ho et al. (2013)¹⁶: Grants from the American Thyroid Association, the Society of Memorial Sloan Kettering Cancer Centre, the NIH, the Lefkowsky Family, Margot Rosenberg Pulitzer, Byrne, and J Randolph Hearst foundations.

^bRAIR definition: **A**) non-RAI-avid metastatic lesion on a diagnostic scan ≤ 2 years before enrolment; **B**) an RAI-avid lesion that is of stable size or that progressed despite RAI ≥ 6 months prior to study entry; or **C**) ≥ 1 ¹⁸F-fluorodeoxyglucose-avid lesion(s). Note: for criterion C, Dunn et al. (2019)¹⁵ and Tchekmedyan et al. (2022)¹⁸ further specify a maximum standardized uptake value (SUV_{max}) ≥ 5 .

^cOf the 3 patients, 1 was followed for 2 years post-radioiodine treatment; duration of follow-up for the other 2 patients was not reported.

^dRAIR definition: **A**) minimal or no RAI avidity in some or all measurable sites of disease on appropriately performed RAI scans; **B**) imaging or biochemical progression despite RAI treatment within the past 12 months.

^eRAIR definition: **A**) no RAI uptake at known sites of metastases; **B**) progressive disease despite previous RAI treatment with confirmed uptake; **C**) progressive disease within 1 year of RAI therapy.

^fMethods state the end point of best response at 3 months; however, the results describe best response at 6 months.

Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has not been copy-edited.

Table 4: Strengths and Limitations of the Systematic Review Using AMSTAR 2¹²

Strengths	Limitations
Jones et al. (2021)^{14, a}	
<ul style="list-style-type: none"> • A rationale for including different study designs for different interventions was provided. • 3 different bibliographic databases were searched, along with a search for grey literature and review of the references from included studies. 	<ul style="list-style-type: none"> • Study selection was not done in duplicate. • It was unclear whether extraction was done in duplicate. • The population was not explicitly defined in a PICO statement, although could be inferred from the body of the manuscript. • No evidence that the review methods were established prior to the start of the study. • The search terms were very broad ('thyroid AND TKI OR tyrosine kinase inhibitor' for the component relevant to the current report) although did not include keywords.

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; PICO = population, intervention, comparator group, outcome; TKI = tyrosine kinase inhibitor.

^aThe relevant studies captured within this systematic review are included as primary studies in the current report; therefore, the assessment focused on the comprehensiveness of the literature search, to assess whether any other relevant studies were potentially missed.

Table 5: Strengths and Limitations of Clinical Studies Using the Downs and Black Checklist¹³

Strengths	Limitations
Tchekmedyan et al. (2022)¹⁸	
<ul style="list-style-type: none"> • Clearly described objectives, outcomes, patient characteristics, interventions, and main findings. • Important adverse events were captured and classified using CTCAE v4.0. • Follow-up time and timing of outcomes clearly captured. • Clear reporting of non-compliance with study drugs. • Outcome measures considered valid and reliable. • Provided a power calculation to determine the number of patients to enrol to detect ≥ 5% of patients having increased radioiodine uptake. 	<ul style="list-style-type: none"> • Patients were recruited from a single centre (Memorial Sloan Kettering Cancer Centre) in the US; outcomes may not be representative of cancer centres across Canada. • This was a single-arm trial with no control arm; study findings were non-comparative. • Neither patients nor investigators were blinded to study treatment. • Study was terminated before target accrual was met.

Strengths	Limitations
Pešorda et al. (2020)²¹	
<ul style="list-style-type: none"> • Clearly described objectives. • Adverse events were captured. 	<ul style="list-style-type: none"> • There was a lack of clear reporting for patient characteristics for the subgroup relevant to the current review. • The intervention was unclear with respect to the duration of treatment with vemurafenib, and the re-treatment with iodine-131 once radioiodine uptake was established. • Unclear validity and reliability of the main outcome measure (i.e., restoration of radioiodine uptake). • Patients were recruited from a single centre in Croatia; outcomes may not be representative of cancer centres across Canada. • The retrospective cohort study was non-comparative. • Neither patients nor investigators were blinded to study treatment.
Dunn et al. (2019)¹⁵	
<ul style="list-style-type: none"> • Clearly described objectives, outcomes, patient characteristics, interventions, and main findings. • Important adverse events were captured and classified using CTCAE v4.0. • Timing of outcomes clearly captured with respect to follow-up. Clear description of patients who discontinued the study. • Outcome measures considered valid and reliable. • Provided a power calculation to determine the number of patients to enrol to detect $\geq 5\%$ of patients having increased radioiodine uptake. 	<ul style="list-style-type: none"> • Patients were recruited from a single centre (Memorial Sloan Kettering Cancer Centre) in the US; outcomes may not be representative of cancer centres across Canada. • This was a single-arm trial with no control arm; study findings were non-comparative. • Neither patients nor investigators were blinded to study treatment.
Iravani et al. (2019)¹⁹	
<ul style="list-style-type: none"> • Clearly described objectives, outcomes, patient characteristics, interventions, and main findings. • Important adverse events were captured and classified using CTCAE v4.0. • Timing of outcomes clearly captured with respect to follow-up. 	<ul style="list-style-type: none"> • Patients were recruited from a single centre in Australia; outcomes may not be representative of cancer centres across Canada. • Although multiple treatment regimens were captured, the sample size ($n = 6$) relative to the number of resensitization treatment regimens ($n = 3$) was insufficient for making valid comparisons between treatments; hence no estimates of relative treatment effect were presented in this retrospective cohort study. • Outcome of best overall response not explicitly stated however could be inferred from figure. • Neither patients nor investigators were blinded to study treatment.

Strengths	Limitations
Jaber et al. (2018)²⁰	
<ul style="list-style-type: none"> • Clearly described objectives, outcomes, patient characteristics, and main findings. • Timing of outcomes clearly captured with respect to follow-up. 	<ul style="list-style-type: none"> • The intervention was unclear with respect to the initially planned duration of treatment. • Only radioiodine-related adverse events were reported. Adverse events associated with resensitization treatment with targeted therapies were not reported. • Patients were recruited from a single centre (MD Anderson) in the US; outcomes may not be representative of cancer centres across Canada. • Although multiple treatment regimens were captured, the sample size (n = 13) relative to the number of resensitization treatment regimens (n = 5) was insufficient for making valid comparisons between treatments; hence no estimates of relative treatment effect were presented. • Neither patients nor investigators were blinded to study treatment.
Rothenberg et al. (2015)¹⁷	
<ul style="list-style-type: none"> • Clearly described objectives, outcomes, patient characteristics, interventions, and main findings. • Important adverse events were captured and classified using CTCAE v4.0. • Outcome measures considered valid and reliable. 	<ul style="list-style-type: none"> • The follow-up time was unclear, and the timing of response post-radioiodine treatment was inconsistent between the methods (secondary end point defined as best response at 3 months) and the results (only reported at 6 months). The intervention was unclear with respect to the initially planned duration of treatment. • Patients were recruited from a single centre (Massachusetts General Hospital) in the US; outcomes may not be representative of cancer centres across Canada. • This was a single-arm trial with no control arm; study findings were non-comparative. • Neither patients nor investigators were blinded to study treatment.
Ho et al. (2013)¹⁶	
<ul style="list-style-type: none"> • Clearly described objectives, outcomes, patient characteristics, interventions, and main findings. • Important adverse events were captured. • Timing of outcomes clearly captured with respect to follow-up. • Outcome measures considered valid and reliable. • Provided a power calculation to determine the number of patients to enrol to detect $\geq 5\%$ of patients having increased radioiodine uptake. 	<ul style="list-style-type: none"> • Patients were recruited from a single centre (Memorial Sloan Kettering Cancer Centre) in the US; outcomes may not be representative of cancer centres across Canada. • This was a single-arm trial with no control arm; study findings were non-comparative. • Neither patients nor investigators were blinded to study treatment.

CTCAE = Common Terminology Criteria for Adverse Events.

Appendix 4: Main Study Findings

Note that this appendix has not been copy-edited.

Table 6: Summary of Findings by Outcome – Resensitization

Intervention	Study citation and study design	Resensitization definition (as described by study authors)	Estimate, n/N (%)
Vemurafenib + CDX-3379	Tchekmedyan et al. (2022) ¹⁸ Single-arm trial <i>BRAF</i> V600E+ Sample size: n = 7	Evaluable for ¹²⁴ I avidity	6 / 7 (86)
		Increased ¹²⁴ I avidity after treatment	5 / 7 (71)
		Sufficient change in avidity to warrant therapeutic dose of ¹³¹ I	4 / 7 (57) ^a
Vemurafenib	Pešorda et al. (2020) ²¹ Uncontrolled retrospective cohort <i>BRAF</i> V600E+ Sample size n = 3	Showed restoration of RAI uptake evaluated with ¹³¹ I imaging	2 / 3 (67) ^b
Vemurafenib	Dunn et al. (2019) ¹⁵ Single-arm trial <i>BRAF</i> V600E+ Sample size n = 12	New or increased RAI avidity in at least one tumour	6 / 12 (50) ^c
		Met the lesional dosimetry threshold to warrant therapeutic dose of ¹³¹ I (i.e., ¹²⁴ I responders)	4 / 12 (33) ^c
Mixed ^d	Iravani et al. (2019) ¹⁹ Uncontrolled retrospective cohort <i>BRAF</i> V600E+ or <i>NRAS</i> + Sample size n = 6	Restoration of iodine avidity (based on ¹²⁴ I dosimetry)	4 / 6 (67)
		Restoration of iodine avidity (based on ¹²⁴ I dosimetry) and received ¹³¹ I RAI	4 / 6 (67)
		Restoration of iodine avidity and received ¹³¹ I RAI, among <i>BRAF</i> V600E+ patients receiving combination therapy ^d	3 / 3 (100)
		Restoration of iodine avidity and received ¹³¹ I RAI among <i>NRAS</i> + patients receiving trametinib ^d	1 / 3 (33)
Mixed ^e	Jaber et al. (2018) ²⁰ Uncontrolled retrospective cohort No genotype-based restrictions Sample size = 13	Clinically meaningful uptake on pre-treatment WBS to warrant therapeutic dose of ¹³¹ I	8 / 13 (62)
		Received ¹³¹ I ^f	9 / 13 (69)
		Received ¹³¹ I ^f , among <i>BRAF</i> V600E+ patients	5 / 9 (56)
		Received ¹³¹ I ^f , among <i>NRAS</i> / <i>KRAS</i> + patients	3 / 3 (100)
		Received ¹³¹ I ^f , among wild-type patients	1 / 1 (100)
Dabrafenib	Rothenberg et al. (2015) ¹⁷ Single-arm trial <i>BRAF</i> V600E + Sample size = 10	Developed new RAI uptake after treatment	6 / 10 (60)
		Developed new RAI uptake after treatment and received ¹³¹ I RAI	6 / 10 (60)

Intervention	Study citation and study design	Resensitization definition (as described by study authors)	Estimate, n/N (%)
Selumetinib	Ho et al. (2013) ¹⁶ Single-arm trial No genotype-based restrictions Sample size n = 20	¹²⁴ I uptake that was new and/or increased after treatment	12 / 20 (60)
		Received ¹³¹ I ^g	8 / 20 (40)
		Received ¹³¹ I ^g , among <i>NRAS</i> + patients	5 / 5 (100)
		Received ¹³¹ I ^g , among <i>BRAF</i> V600E + patients ^h	1 / 9 (11)
		Received ¹³¹ I ^g , among RET/PTC+ patients ^h	1 / 3 (33)
		Received ¹³¹ I ^g , among wild-type patients ^h	1 / 3 (33)

¹²⁴I = iodine-124; ¹³¹I = iodine-131; RAI = radioiodine

^a1 patient was not treated with ¹³¹I despite showing increased ¹²⁴I avidity, including a new/increased iodine uptake in lung metastasis, because “a structural correlate for the former could not be identified on CT imaging.”

^b1 patient did not want to perform a radioiodine scan. It is assumed that patients received a therapeutic dose of ¹³¹I however, this is unclear from the text.

^creported by the authors as 6/10 (60%), as 2 patients did not receive a post-baseline ¹²⁴I scan due to adverse events that precluded continuation of drug treatment. In the current report, the proportion has been re-calculated according to the intention-to-treat principle, for consistency across studies.

^d3 patients with *NRAS* mutations received trametinib; 1 patient with *BRAF* V600E mutation received dabrafenib and trametinib; 2 patients with *BRAF* V600E mutation received vemurafenib and cobimetinib.

^e3 patients with *NRAS/KRAS* mutations received trametinib (n=2) or investigational MEK inhibitor; 9 patients with *BRAF* V600E mutation received dabrafenib, vemurafenib, or dabrafenib and vemurafenib; 1 patient with wild-type tumour genotype received trametinib.

^fDecision to administer ¹³¹I based on clinically meaningful uptake on pre-treatment scan to warrant therapeutic dose of ¹³¹I, or physician’s clinical judgment despite no evidence of uptake.

^gDecision based on an “absorbed radiation dose in the lesion that would equal or exceed 2000 cGy with 300 mCi of RAI or less.” – Ho et al. (2013)¹⁶.

^hAuthors also reported the proportion with ¹²⁴I uptake by tumour genotype, irrespective of whether the uptake was sufficient to warrant a therapeutic dose of ¹³¹I: 4 / 9 (44%) patients with *BRAF* V600E+, 2 / 3 (67%) with RET/PTC+, and 1 / 3 (33%) with wild-type tumours.

Table 7: Summary of Findings by Outcome – Response

Response (RECIST v1.1)	Tchekmedyan et al. (2022) ¹⁸ Single-arm trial	Dunn et al. (2019) ¹⁵ Single-arm trial	Iravani et al. (2019) ¹⁹ Uncontrolled retrospective cohort	Jaber et al. (2018) ²⁰ Uncontrolled retrospective cohort	Rothenberg et al. (2015) ¹⁷ Single-arm trial	Ho et al. (2013) ¹⁶ Single-arm trial
	Vemurafenib + CDX-3379	Vemurafenib	Mixed ^a	Mixed ^b	Dabrafenib	Selumetinib
Assessment timing	6 months	6 months	End of follow-up	End of follow-up	6 months	6 months
Among all patients						
Best overall response, n/N (%)						
CR	0 / 7 (0)	0 / 12 (0)	0 / 6 (0)	0 / 13 (0)	0 / 10 (0)	0 / 20 (0)
PR	2 / 7 (29)	2 / 12 (17)	3 / 6 (50)	3 / 13 (23)	2 / 10 (20)	5 / 20 (25)
SD	0 / 7 (0)	2 / 12 (17)	1 / 6 (17)	9 / 13 (46) ^c	7 / 10 (70)	3 / 20 (15)
PD	2 / 7 (29)	3 / 12 (25)	0 / 6 (0)	0 / 13 (0)	1 / 10 (10)	0 / 20 (0)
Mixed response	–	–	–	1 / 13 (8) ^d	–	–
Not assessed	3 / 7 (43)	5 / 12 (42)	2 / 6 (33) ^e	–	–	12 / 20 (60)

Response (RECIST v1.1)	Tchekmedyan et al. (2022) ¹⁸ Single-arm trial	Dunn et al. (2019) ¹⁵ Single-arm trial	Iravani et al. (2019) ¹⁹ Uncontrolled retrospective cohort	Jaber et al. (2018) ²⁰ Uncontrolled retrospective cohort	Rothenberg et al. (2015) ¹⁷ Single-arm trial	Ho et al. (2013) ¹⁶ Single-arm trial
	Vemurafenib + CDX-3379	Vemurafenib	Mixed ^a	Mixed ^b	Dabrafenib	Selumetinib
Among ¹³¹I treated patients						
Best overall response, n/N (%)						
CR	0 / 4 (0)	0 / 4 (0)	0 / 4 (0)	0 / 9 (0)	0 / 6 (0)	0 / 8 (0)
PR	2 / 4 (50)	2 / 4 (50)	3 / 4 (75)	3 / 9 (33)	2 / 6 (33)	5 / 8 (63)
SD	0 / 4 (0)	2 / 4 (50)	1 / 4 (25)	6 / 9 (66) ^c	4 / 6 (67)	3 / 8 (38)
PD	2 / 4 (50)	0 / 4 (0)	0 / 4 (0)	0 / 9 (0)	0 / 6 (0)	0 / 8 (0)
Mixed response	–	–	–	0 / 9 (0)	–	–
Not assessed	–	–	–	–	–	–
Among non-¹³¹I treated patients						
Best overall response, n/N (%)						
CR	–	–	–	0 / 4 (0)	0 / 4 (0)	–
PR	–	–	–	0 / 4 (0)	0 / 4 (0)	–
SD	–	–	–	3 / 4 (75)	3 / 4 (75)	–
PD	–	3 / 8 (38) ^e	–	0 / 4 (0)	1 / 4 (25)	–
Mixed response	–	–	–	1 / 4 (25) ^d	–	–
Not assessed	3 / 3 (100)	5 / 8 (63)	2 / 2 (100) ^f	–	–	12 / 12 (100)

¹³¹I = iodine-131; CR = complete response; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SD = stable disease.

^a3 patients with *NRAS* mutations received trametinib; 1 patient with *BRAF* V600E mutation received dabrafenib and trametinib; 2 patients with *BRAF* V600E mutation received vemurafenib and cobimetinib.

^b3 patients with *NRAS/KRAS* mutations received trametinib (n=2) or investigational MEK inhibitor; 9 patients with *BRAF* V600E mutation received dabrafenib, vemurafenib, or dabrafenib and vemurafenib; 1 patient with wild-type tumour genotype received trametinib.

^cReported in the text as 5 ¹³¹I-treated patients with stable disease; however, Figure 3b shows 6 ¹³¹I-treated patients with stable disease. Extraction is based on the estimate from Figure 3b.

^dSome lesions stable and others enlarged.

^e3 patients were assessed off-protocol.

^fPatients were reported as being “responsive” to subsequent treatment with lenvatinib at end of follow-up.

Table 8: Summary of Findings by Outcome – Subsequent Therapy

Intervention	Study citation and study design	Subsequent therapy definition	Estimate, n/N (%)
Vemurafenib + CDX-3379	Tchekmedyan et al. (2022) ¹⁸ Single-arm trial Sample size: n=7	Initiated systemic treatment after study, among ¹³¹I-treated	2 / 4 (50)
		Did not initiate systemic treatment > 3 years post-study, among ¹³¹I-treated	2 / 4 (50)
		Initiated systemic treatment after study, among non-¹³¹I-treated	3 / 3 (100) ^a
Vemurafenib	Pešorda et al. (2020) ²¹ Uncontrolled retrospective cohort Sample size n = 3	Received second-line sorafenib, among all patients	1 / 3 (33) ^b
Vemurafenib	Dunn et al. (2019) ¹⁵ Single-arm trial Sample size n = 12	Subsequent therapy, among ¹³¹I treated	–
		Radiation, ~9 months post- ¹³¹ I	1 / 4 (25)
		Vemurafenib retreatment, ~18 months post ³¹ I	1 / 4 (25)
		No subsequent treatment ≥ 22 months post ¹³¹ I	2 / 4 (50)
Mixed ^c	Iravani et al. (2019) ¹⁹ Uncontrolled retrospective cohort <i>BRAF</i> V600E+ or <i>NRAS</i> + Sample size n = 6	Did not initiate new treatment by end of follow-up, among ¹³¹I-treated	4 / 4 (100)
		Initiated lenvatinib, among non-¹³¹I-treated^d	2 / 2 (100)
Mixed ^e	Jaber et al. (2018) ²⁰ Uncontrolled retrospective cohort No genotype-based restrictions Sample size = 13	Median (range) time off systemic targeted therapy, post- ¹³¹ I, among ¹³¹I treated^f	14.3 months (4.5 to 20.6)

¹³¹I = iodine-131

^aInitiated immediately for 1 patient, and initiated ~3 years after study treatment in 2 patients.

^bDetails on subsequent treatment were provided for 1 patient. This patient (female) received second-line sorafenib 2 years after successful redifferentiation with vemurafenib. The patient died shortly after starting the second-line treatment.

^c3 patients with *NRAS* mutations received trametinib; 1 patient with *BRAF* V600E mutation received dabrafenib and trametinib; 2 patients with *BRAF* V600E mutation received vemurafenib and cobimetinib.

^dAll non-¹³¹I-treated patients received trametinib and had tumours harbouring *NRAS* mutations.

^e3 patients with *NRAS*/*KRAS* mutations received trametinib (n=2) or investigational MEK inhibitor; 9 patients with *BRAF* V600E mutation received dabrafenib, vemurafenib, or dabrafenib and vemurafenib; 1 patient with wild-type tumour genotype received trametinib.

^fUnclear if subsequent treatments were received if patients remained off systemic targeted therapy at the end of the follow-up period.

Table 9: Summary of Findings by Outcome – Progression-Free Survival or Time to Progression

Intervention	Study citation and study design	Progression-free survival or time to progression
Vemurafenib + CDX-3379	Tchekmedyian et al. (2022) ¹⁸ Single-arm trial Sample size: n=7	Progression-free survival at 6 months, among ¹³¹ I treated (n=4): • 2 / 4 (50%) patients progressed • 2 / 4 (50%) patients remained progression-free and alive
Vemurafenib	Dunn et al. (2019) ¹⁵ Single-arm trial Sample size n = 12	Time to progression, among ¹³¹ I treated (n=4): • 2 / 4 (50%) patients progressed ^a (1 patient at 9 months post- ¹³¹ I treatment, and 1 patient at 18 months post- ¹³¹ I treatment) • 2 / 4 (50%) patients remained progression-free at date of last follow-up (last follow-up was 18 months post- ¹³¹ I treatment for 1 patient, and 22 months post- ¹³¹ I treatment for 1 patient)
Mixed ^b	Iravani et al. (2019) ¹⁹ Uncontrolled retrospective cohort <i>BRAF</i> V600E+ or <i>NRAS</i> + Sample size n = 6	All patients (n=6) were alive and progression-free at the end of follow-up, irrespective of radioiodine treatment.

¹³¹I = iodine-131.

^aProgression assumed based on initiation of new anti-cancer therapy.

^b3 patients with *NRAS/KRAS* mutations received trametinib (n=2) or investigational MEK inhibitor; 9 patients with *BRAF* V600E mutation received dabrafenib, vemurafenib, or dabrafenib and vemurafenib; 1 patient with wild-type tumour genotype received trametinib.

Table 10: Summary of Findings by Outcome – Mortality

Intervention	Study citation and study design	Deaths
Vemurafenib	Pešorda et al. (2020) ²¹ Uncontrolled retrospective cohort Sample size n = 3	One patient died 2 years after successful redifferentiation, shortly after starting a second-line treatment. The other two patients were not reported to have died prior to the end of follow-up.

Table 11: Summary of Findings by Outcome – Adverse Events

Intervention sample size	Adverse events experienced by > 1 patient	Grade 1 to 2 n (%)	Grade 3 to 5 n (%)	Any grade n (%)
Tchekmedyan et al. (2022)¹⁸				
Vemurafenib + CDX-3379 Sample size: n=7	Vemurafenib-related:	Total = 7	Total = 7	Total = 7
	At least 1 adverse event	Not reported	Not reported	Not reported
	Maculopapular rash	3 (43)	2 (29)	5 (71)
	Nausea	4 (57)	0 (0)	4 (57)
	Diarrhea	2 (29)	1 (14)	3 (43)
	Arthralgia	2 (29)	0 (0)	2 (29)
	Alanine aminotransferase elevation	2 (29)	0 (0)	2 (29)
	Alkaline phosphatase elevation	2 (29)	0 (0)	2 (29)
	Fatigue	2 (29)	0 (0)	2 (29)
	Hand-foot syndrome ^a	2 (29)	0 (0)	2 (29)
	Pruritis	2 (29)	0 (0)	2 (29)
Acneiform rash	2 (29)	0 (0)	2 (29)	
Vemurafenib + CDX-3379 Sample size: n=6 ^b	CDX-3379-related:	Total = 6^b	Total = 6^b	Total = 6^b
	At least 1 adverse event	Not reported	0 (0)	Not reported
	Diarrhea	3 (50)	0 (0)	3 (50)
	Nausea	3 (50)	0 (0)	3 (50)
	Arthralgia	2 (33)	0 (0)	2 (33)
	Hand-foot syndrome ^a	2 (33)	0 (0)	2 (33)
	Alkaline phosphatase elevation	2 (33)	0 (0)	2 (33)
Pešorda et al. (2020)²¹				
Vemurafenib Sample size n = 3	Any adverse event:	Total = 3	Total = 3	Total = 3
	At least 1 adverse event	Not reported	Not reported	Not reported
	Squamous cell carcinoma of the skin	Not reported	Not reported	2 (67)
	Keratoacanthoma	Not reported	Not reported	0 (67)

Intervention sample size	Adverse events experienced by > 1 patient	Grade 1 to 2 n (%)	Grade 3 to 5 n (%)	Any grade n (%)
Dunn et al. (2019)¹⁵				
Vemurafenib Sample size n = 12	Vemurafenib-related:	Total = 12	Total = 12	Total = 12
	At least 1 adverse event	Not reported	Not reported	Not reported
	Maculopapular rash	7 (58)	2 (17)	9 (75)
	Fatigue	8 (67)	0 (0)	8 (66)
	Hand-foot syndrome ^a	6 (50)	1 (8)	7 (58)
	Nausea	6 (50)	0 (0)	6 (50)
	Alkaline phosphatase increased	5 (42)	0 (0)	5 (42)
	Arthralgia	5 (42)	0 (0)	5 (42)
	Bilirubin increased	5 (42)	0 (0)	5 (42)
	Alanine aminotransferase increased	3 (25)	0 (0)	3 (25)
	Diarrhea	3 (25)	0 (0)	3 (25)
	Neoplasm, benign (warts)	3 (25)	0 (0)	3 (25)
	Alopecia	3 (25)	0 (0)	3 (25)
	Skin/subcutaneous tissue disorders ^c	2 (17)	0 (0)	2 (17)
	Creatinine increased	2 (17)	0 (0)	2 (17)
	Aspartate aminotransferase increased	2 (17)	0 (0)	2 (17)
	Myalgia	2 (17)	0 (0)	2 (17)
Dysgeusia	2 (17)	0 (0)	2 (17)	
Pruritus	2 (17)	0 (0)	2 (17)	
Iravani et al. (2019)¹⁹				
Trametinib Sample size = 3	Any adverse event:	Total = 3	Total = 3	Total = 3
	At least 1 adverse event	1 (33)	2 (67)	3 (100)
	Acneiform rash	0 (0)	2 (67)	2 (67)
Vemurafenib + cobimetinib Sample size = 3	Any adverse event:	Total = 2	Total = 2	Total = 2
	At least 1 adverse event	2 (100)	0 (0)	2 (100)
	Rash	2 (100)	0 (0)	2 (100)
Jaber et al. (2018)²⁰				
Mixed ^d Sample size = 13	RAI-related adverse events	Not reported by grade	Not reported by grade	Total = 9
	At least 1 adverse event			3 (33)
	Pneumonitis			2 (22)

Intervention sample size	Adverse events experienced by > 1 patient	Grade 1 to 2 n (%)	Grade 3 to 5 n (%)	Any grade n (%)
Rothenberg et al. (2015)¹⁷				
Dabrafenib Sample size = 10	Any adverse event:	Total = 10	Total = 10	Total = 10
	At least 1 adverse event	9 (90)	1 (10) ^e	10 (100)
	Skin lesions or changes	8 (80)	0 (0)	8 (80)
	Fatigue	5 (50)	0 (0)	5 (50)
	Electrolyte abnormalities	4 (40)	1 (10) ^e	5 (50)
	Gastrointestinal symptoms	5 (50)	0 (0)	5 (50)
	Hand-foot syndrome ^a	4 (40)	0 (0)	4 (40)
	Headache	3 (30)	0 (0)	3 (30)
	Epistaxis	2 (20)	0 (0)	2 (20)
	Eye disorders	2 (20)	0 (0)	2 (20)
	Creatinine increase	2 (20)	0 (0)	2 (20)
Ho et al. (2013)¹⁶				
Selumetinib Sample size n = 20	Selumetinib-related:^f	Total = 20	Total = 20	Total = 20
	At least 1 adverse event	Not reported	0 (0)	Not reported
	Rash	18 (90)	0 (0)	18 (90)
	Fatigue	16 (80)	0 (0)	16 (80)
	Hepatic enzymes increased	14 (70)	0 (0)	14 (70)
	Diarrhea	9 (45)	0 (0)	9 (45)
	Nausea	8 (40)	0 (0)	8 (40)
	Mucositis oral	7 (35)	0 (0)	7 (35)
	Edema limbs	6 (30)	0 (0)	6 (30)
	Constipation	4 (20)	0 (0)	4 (20)
	Hypoalbuminemia	3 (15)	0 (0)	3 (15)
	Pain	3 (15)	0 (0)	3 (15)
	White blood cell decreased	3 (15)	0 (0)	3 (15)
	Dry mouth	2 (10)	0 (0)	2 (10)
	Dry skin	2 (10)	0 (0)	2 (10)
	Edema face	2 (10)	0 (0)	2 (10)
Hyperglycemia	2 (10)	0 (0)	2 (10)	
Hypoglycemia	2 (10)	0 (0)	2 (10)	

CTCAE = Common Terminology Criteria for Adverse Events.

^aPlantar-palmar erythrodysesthesia syndrome.

^b1 patient did not receive CDX-3379 due to vemurafenib-related toxicity (maculopapular rash) prior to initiating CDX-3379.

^c1 case of seborrheic keratosis; 1 case of keratosis pilaris-like reaction.

^d3 patients with *NRAS/KRAS* mutations received trametinib (n=2) or investigational MEK inhibitor; 9 patients with *BRAF* V600E mutation received dabrafenib, vemurafenib, or dabrafenib and vemurafenib; 1 patient with wild-type tumour genotype received trametinib.

^eDeemed unrelated to study drug. In text this was listed as grade 2 but in table it was listed as severe according to CTCAE v4.0, which corresponds to grade 3.

^fAdverse events deemed unrelated to selumetinib were reported by the study authors separately.

Appendix 5: References of Potential Interest

Note that this appendix has not been copy-edited.

Previous CADTH Reports

CADTH. Lenvima for differentiated thyroid cancer - details. 2016; <https://www.cadth.ca/lenvima-differentiated-thyroid-cancer-details>. Accessed 2022 Mar 25.

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