# A systematic literature review of the clinical evidence for treatment of differentiated thyroid cancer after prior systemic therapy

CO69

Aude Houchard,[1,*] Michael C Kreissl,[2] Marius Tham,[1] Hannah van Schoubroeck,[3] Dominika Rekowska,[3] Lisette Nientker,[3] Sophie Leboulleux[4]

*Presenting author

*[1]Ipsen, Paris, Île-de-France, France; [2]University Hospital Magdeburg, Magdeburg, Saxony-Anhalt, Germany; [3]OPEN Health, Rotterdam, Zuid-Holland, The Netherlands; [4]Hôpitaux Universitaires de Genève, Geneva, Switzerland*

## Background

- Differentiated thyroid cancer (DTC) accounts for 90–95% of all newly diagnosed thyroid cancers[1,2] and has a 5-year prevalence of approximately 2 million patients globally.[3]
- Radioactive iodine (RAI) is a treatment option for patients with DTC who have a high risk of recurrence, incompletely resected cancer or distant metastases.[4,5]
  - Overall, 25–30% of patients with DTC have advanced or metastatic disease at diagnosis;[6] only a small proportion of all patients (3%) have distant metastases at diagnosis.[7]
  - Approximately 33% of patients with metastatic DTC become refractory to RAI.[4]
- In the absence of NTRK and RET fusion, European (ESMO) and US (National Comprehensive Cancer Network® [NCCN®]) guidelines recommend lenvatinib and sorafenib as first line systemic therapy options for RAI-refractory DTC.[4,5]
  - Systemic therapy eventually fails and patients need additional options.
- The multi-targeted tyrosine kinase inhibitor cabozantinib was approved in Europe in April 2022 for the treatment of adults with locally advanced or metastatic DTC who are ineligible for RAI or have RAI-refractory disease that has progressed during or after systemic therapy.[8] Cabozantinib was also approved in the USA in September 2021 (for patients aged ≥12 years).[9]
  - European (ESMO) and US (NCCN) guidelines recommend cabozantinib as a second line treatment option for RAI-refractory, advanced/metastatic DTC following disease progression on lenvatinib and/or sorafenib.[4,5]

## Objective

- To perform a systematic literature review (SLR) to identify relevant published clinical evidence (i.e. randomized and non-randomized clinical trials and observational studies) on existing treatment options for patients with RAI-refractory DTC that has progressed on or after prior systemic therapy.

## Methods

- Relevant publications (**Table 1**) were identified by systematic searches of the online bibliographic databases Embase, MEDLINE®, CENTRAL, CSDR and DARE on 27 September 2021; no language or time restrictions were applied.
- Complementary hand searches of conference proceedings from 2015 to 2021 and clinical trial registries were performed.
- Publications were reviewed for eligibility (**Table 1**) by two independent reviewers and data were extracted by one reviewer and checked by a second reviewer; any discrepancies were resolved by a third reviewer.
- Data were analysed descriptively, grouped by study design (randomized controlled trials [RCTs], non-randomized prospective interventional studies and observational studies).

**Table 1.** Search strategy

| Eligibility criteria | Description |
|---|---|
| **Population** | Patients aged ≥12 years with RAI-refractory, locally advanced/metastatic DTC, who had received ≥1 prior targeted therapy, and |
| **Intervention** | Systemic therapy, and |
| **Comparator** | Systemic therapy, placebo or best supportive care, and |
| **Outcomes**[a] | Efficacy/effectiveness, safety, HRQoL/PROs, and |
| **Study design**[b] | RCTs, non-randomized prospective interventional studies, observational studies, SLRs and meta-analyses, and |
| **Time restriction** | Peer-reviewed publications: none<br>Conference proceedings: 2015 to 2021, and |
| **Language restrictions** | None |

[a]Outcomes of interest had to be reported for the relevant population as a total group or as a separate subgroup. Studies reporting on mixed populations (i.e. patients with DTC and medullary thyroid cancer and/or patients receiving first line as well as second or later lines of treatment) were flagged but not included for data extraction.
[b]SLRs and meta-analyses were not included for data extraction but reference lists from the five most recent articles were screened to check for any missing references.
DTC, differentiated thyroid cancer; HRQoL, health-related quality of life; PRO, patient reported outcome; RAI, radioactive iodine; RCT, randomized controlled trial; SLR, systematic literature review.

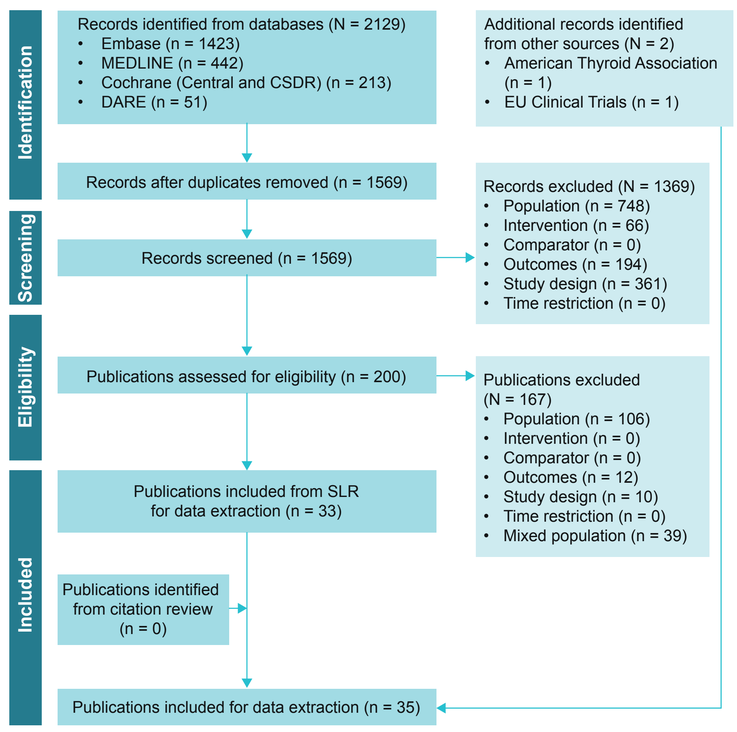
## Results

- Of 2129 publications identified from the database searches, 1569 unique publications underwent title and abstract screening and 200 underwent full-text screening for eligibility (**Figure 1**).
- In total, 35 publications reporting 26 unique studies were eligible for inclusion:
  - three RCTs (nine publications)
  - 10 non-randomized prospective interventional studies (12 publications)
  - 13 observational studies (14 publications).

### Randomized controlled trials

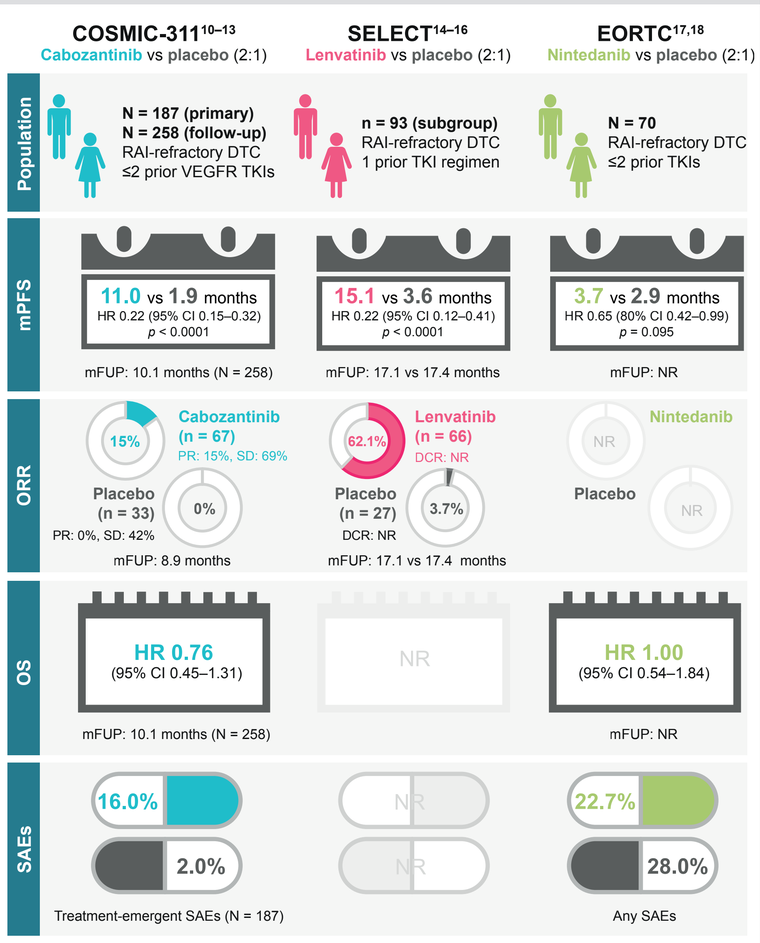
- The three eligible RCTs were the COSMIC-311, SELECT and EORTC trials (**Table 2**).
- Key efficacy and safety data are shown in **Figure 2**.
  - COSMIC-311 (N = 258) demonstrated significantly longer median progression-free survival (mPFS) with cabozantinib in patients progressing on previous tyrosine kinase inhibitor therapy (n = 170) versus placebo (n = 88) (11.0 vs 1.9 months; hazard ratio [HR] 0.22, 95% confidence interval [CI] 0.15–0.32; $p < 0.0001$).
  - SELECT (N = 392) showed significantly longer mPFS in the subgroup (n = 93) receiving second line lenvatinib (n = 66) versus placebo (n = 27) (15.1 vs 3.6 months; HR 0.22, 95% CI 0.12–0.41; $p < 0.0001$).
  - EORTC (N = 70) showed no improvement in mPFS for second or third line nintedanib (n = 45) versus placebo (n = 25) (3.7 vs 2.9 months; HR 0.65, 80% CI 0.42–0.99; $p = 0.095$).

**Figure 1.** PRISMA diagram of included and excluded publications




CSDR, clinical study data request; DARE, Database of Abstracts and Reviews or Effects; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

**Figure 2.** Key efficacy and safety data from RCTs in patients with RAI-refractory DTC who had progressed on prior TKI therapy




CI, confidence interval; DCR, disease control rate; DTC, differentiated thyroid cancer; HR, hazard ratio; mFUP, median follow-up; mPFS, median progression-free survival; NR, not reported; ORR, objective response rate; OS, overall survival; PR, partial response; RAI, radioactive iodine; RCT, randomized controlled trial; SAE, serious adverse event; SD, stable disease; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

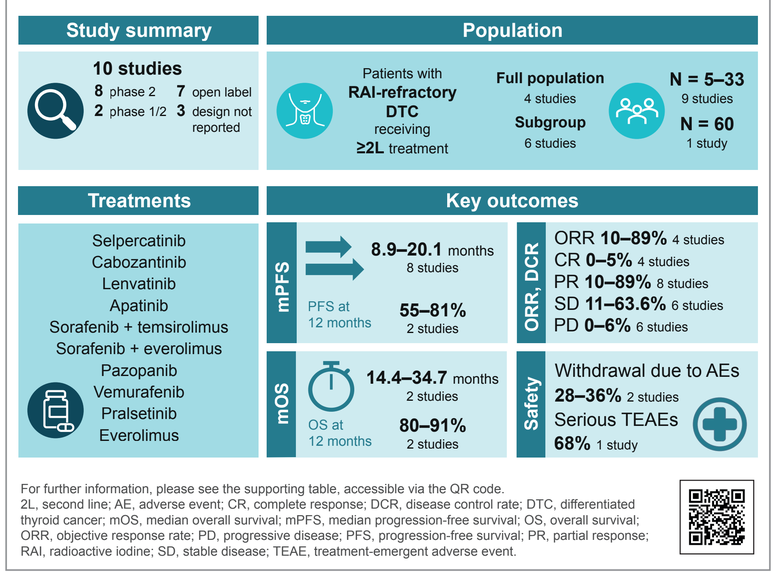
### Non-randomized prospective interventional studies

- Overall, 10 non-randomized prospective interventional phase 1–2 studies (sample size range, 5–60 patients) of 10 different therapies were eligible for inclusion (**Figure 3**).
  - mPFS was the most commonly reported outcome (8 studies) and ranged from 8.9 to 20.1 months.
  - Safety data were limited.

### Observational studies

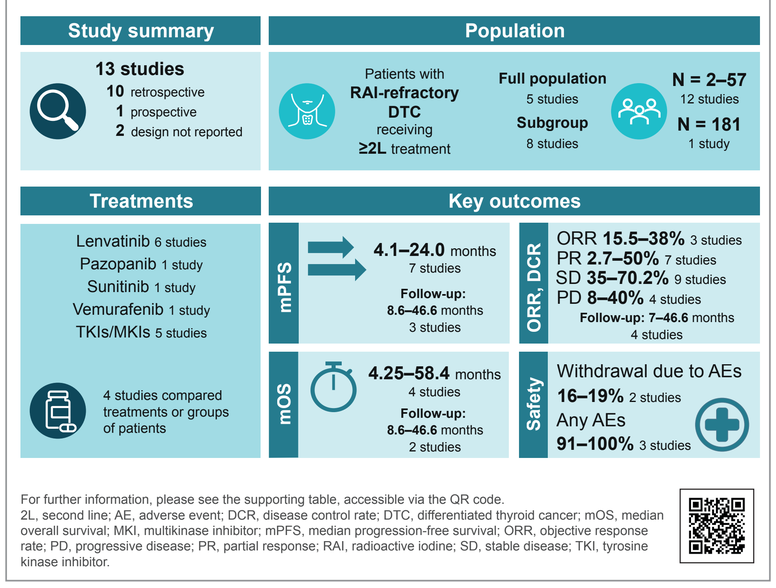
- Overall, 13 studies (sample size range, 2–181 patients), which were mostly retrospective and typically included patients receiving second line or later therapy as a subgroup of a larger population, were eligible for inclusion (**Figure 4**).
  - mPFS was the most commonly reported outcome (7 studies) and ranged from 4.1 to 24.0 months.
  - Safety data were limited.

**Figure 3.** Non-randomized prospective interventional studies




For further information, please see the supporting table, accessible via the QR code.
2L, second line; AE, adverse event; CR, complete response; DCR, disease control rate; DTC, differentiated thyroid cancer; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; RAI, radioactive iodine; SD, stable disease; TEAE, treatment-emergent adverse event.

**Figure 4.** Observational studies




For further information, please see the supporting table, accessible via the QR code.
2L, second line; AE, adverse event; DCR, disease control rate; DTC, differentiated thyroid cancer; mOS, median overall survival; MKI, multikinase inhibitor; mPFS, median progression-free survival; ORR, objective response rate; PD, progressive disease; PR, partial response; RAI, radioactive iodine; SD, stable disease; TKI, tyrosine kinase inhibitor.

## CONCLUSIONS

- Limited comparative evidence is available for cabozantinib as a second line or later treatment for patients with RAI-refractory DTC.
- The studies included in this SLR were predominantly non-randomized or observational setting trials; few RCTs were included. A variety of interventions were assessed and efficacy/effectiveness and safety outcomes were heterogeneous.
  - COSMIC-311 is the only phase 3 study identified that exclusively evaluated patients who had progressed on prior systemic therapy.
- These findings highlight evidence gaps in the treatment landscape, which must be addressed to improve outcomes for patients with RAI-refractory DTC that has progressed during or after systemic therapy.

**Table 2.** Randomized controlled trials

| Study | Phase | Treatment | Patients | N | Line of therapy | Stratification factors | Prior treatment | Median follow-up, months | Primary outcome | Other outcomes |
|---|---|---|---|---|---|---|---|---|---|---|
| COSMIC-311[10–13] (NCT03690388) | 3 | Cabozantinib vs placebo (2:1) | • RAI-refractory DTC<br>• Received prior lenvatinib and/or sorafenib<br>• Progressed during or after treatment with ≤2 VEGFR TKIs | 187 (258)[a] | ≥2L (100%) | Age, prior lenvatinib treatment | • Sorafenib (37%)<br>• Lenvatinib (40%)<br>• Sorafenib + lenvatinib (23%) | ITT, 6.2<br>OITT, 8.9<br>(ITT, 10.1)[a] | ORR (OITT)<br>PFS (ITT)[b] | OS, DoR, safety |
| SELECT[14–16] (NCT01321554) | 3 | Lenvatinib vs placebo (2:1) | • RAI-refractory DTC<br>• No prior TKI therapy or 1 prior TKI regimen | 392 (93)[c] | 2L (23.7%) | Age, geographic region, receipt or non-receipt of a prior TKI | • Sorafenib (18.4%)<br>• Sunitinib (2.0%)<br>• Pazopanib (1.3%)<br>• Other (2.0%) | 17.1 vs 17.4 | PFS | RR, OS, ORR, DoR, safety |
| EORTC[17,18] (NCT01788982) | 2 | Nintedanib vs placebo (2:1) | • Locally advanced or metastatic DTC<br>• 1 or 2 lines of prior TKI | 70 | ≥2L (100%) | NR | NR | NR | PFS | OS, safety |

[a]Non-bracketed data represent values at the preplanned interim analysis. Bracketed data represent values at final analysis.
[b]Objective response per RECIST v1.1 was evaluated in the first 100 randomly assigned patients (OITT population) and PFS (time to the earlier event of disease progression per RECIST v1.1 or death) was evaluated in all patients (ITT population).
[c]Subgroup receiving 2L therapy.
2L, second line; DoR, duration of response; DTC, differentiated thyroid cancer; ITT, intention to treat; mPFS, median progression-free survival; NR, not reported; OITT; objective response intention to treat; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RAI, radioactive iodine; RR, response rate; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

### Abbreviations

CSDR, clinical study data request; DARE, Database of Abstracts and Reviews or Effects; DTC, differentiated thyroid cancer; CI, confidence interval; ESMO, European Society for Medical Oncology; HR, hazard ratio; mPFS, median progression-free survival; NCNN, National Comprehensive Cancer Network®; RAI, radioactive iodine; RCT, randomized controlled trial; SLR, systematic literature review.

### References

1. Lirov R *et al. Drugs* 2017;77:733–45.
2. Kent WD *et al. CMAJ* 2007;177:1357–61.
3. World Health Organization. GLOBOCAN 2020. Available from: https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf (accessed September 2022).
4. Filetti S *et al. Ann Oncol* 2022;33:674–84.
5. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Thyroid Cancer V.2.2022. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed October 18, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org.
6. Cerner Enviza. Thyroid cancer, EU5. Kansas City, MO, USA: Cerner Enviza, 2021.
7. National Cancer Institute – Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Thyroid Cancer. Available from: https://seer.cancer.gov/statfacts/html/thyro.html (accessed October 2022).
8. European Medicines Agency. Cabometyx SmPC. Available from: https://www.ema.europa.eu/en/documents/product-information/cabometyx-epar-product-information_en.pdf (accessed September 2022).
9. Food and Drug Administration. Cabometyx Prescribing Information. Available from: https://www.cabometyxhcp.com/sites/default/files/2021-03/prescribing-information.pdf (accessed October 2022).
10. Brose MS *et al. Lancet Oncology* 2021;22:1126–38.
11. Brose MS *et al. J Clin Oncol* 2021;39:doi 10.1200/JCO.2021.39.15_suppl.6001.
12. Capdevila JR *et al. Ann Oncol* 2021;32:S1343.
13. Robinson B *et al.* Presented at the 90th Annual Meeting of the American Thyroid Association. Late breaking highlighted poster 9. Available from: https://www.liebertpub.com/doi/10.1089/thy.2021.29118.lb.abstracts (accessed September 2022).
14. Schlumberger MT *et al. N Engl J Med* 2015;372:621–30.
15. Gianoukakis AG *et al. Endocr Relat Cancer* 2018;25:699–704.
16. Newbold KE *et al. Asia Pac J Clin Oncol* 2015;11:173.
17. Schlumberger MN *et al. J Clin Oncol* 2018;36: doi 10.1200/JCO.2018.36.15_suppl.6021.
18. EU Clinical Trials Register. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-004295-19/results (accessed September 2022).

**Author contributions** All authors contributed to the design and implementation of the research, to the interpretation of the results and to the writing of the poster.

**Disclosures** AH and MT are employees of Ipsen, which funded this study. HvS, DR and LN are employees of OPEN Health, which received funding from Ipsen to carry out the SLR. MCK received research funding from Exelixis, General Electric, ITM, Sanofi Genzyme and Sirtex; honoraria from Bayer HealthCare, Eisai, Exelixis, Factfiled/Focus, General Electric, Ipsen Pharma, Liam GmbH, Lilly, Novartis/AAA, Onkowissen GmbH, Pfizer, Roche, Sanofi Genzyme, Sirtex, Takeda and Thieme Publishing; sponsoring from Bayer HealthCare, Curium, Eisai, General Electric, Ipsen Pharma, ITM, Novartis/AAA, Sanofi Genzyme, Siemens, Sirtex and Takeda. SL has been an advisory board member for Bayer, Eisai, Lilly and Ipsen.

NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

**Medical writing support** The authors thank Emma Bolton, DPhil, of Oxford PharmaGenesis, Oxford, UK, for providing medical writing and editorial support, which was sponsored by Ipsen, in accordance with Good Publication Practice (GPP 2022) guidelines.

For further information, please send your question(s) to Aude Houchard (aude.houchard@ipsen.com).





This study was sponsored by Ipsen