Insight from Randomized Controlled Trials on the Efficacy and Safety of Pharmacological Therapies for Differentiated Thyroid Cancer: A Systematic Review

Bisen R, Thakur L, Shivsingwale G, Gunde D, Mukta Y

SRS HEOR, A division of SRS Pharmaceuticals Pvt. Ltd., Mumbai, India

CO106

OBJECTIVES

- Differentiated thyroid cancer (DTC) is a common endocrine malignancy with increasing incidence. While surgical resection and radioiodine therapy are standard treatments, the role of targeted pharmacological therapies remains evolving.
- This systematic review aimed to evaluate the efficacy and safety of various pharmacological treatments for DTC, including the radioactive iodine-resistant (RAIR) subpopulation.

METHODS

- A comprehensive searches of MEDLINE®, Embase®, Evidence-based Medicine Reviews (EBMR), and grey literature were conducted.
- All records were screened against predefined inclusion criteria (**Table 1**).
- Bibliographic lists of relevant systematic literature review (SLRs) were also conducted.
- All included studies were extracted and evaluated using National Institute for Health and Care Excellence (NICE) critical appraisal checklist.

Table 1: Eligibility criteria

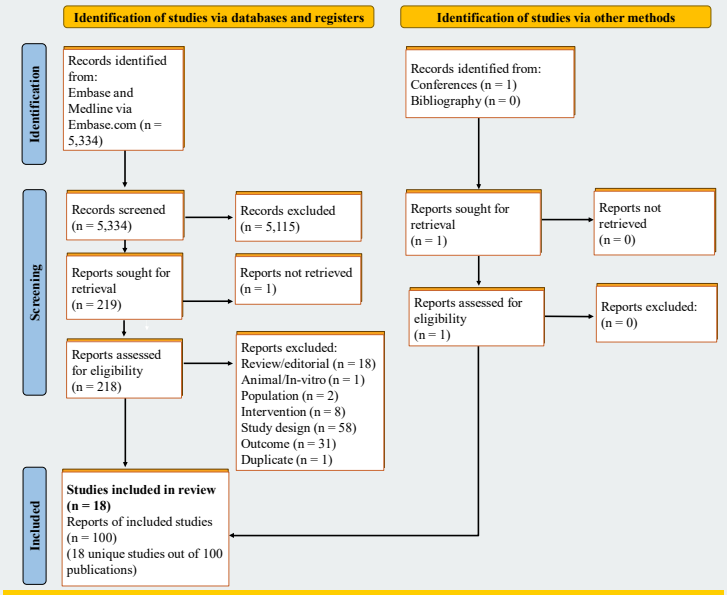
PICOS	Eligibility criteria
Population	Patients (≥18-year-old) with DTC
Intervention	Any pharmacological intervention
Comparator	Any pharmacological interventions
Outcome	Clinical efficacy, safety, tolerability, and HRQoL data
Study design	▪ RCTs ▪ SLR*
Language	English language

Key: DTC, differentiated thyroid cancer; HRQoL, health related quality of life, RCT, randomized controlled trial; SLR, systematic literature review
* Bibliographies of existing systematic reviews were reviewed to ensure that all relevant studies were identified for inclusion in the SLR

RESULTS

- Of 5,334 publications screened, 18 studies met inclusion criteria.
- Two studies evaluated treatments in the DTC population, while 16 focused on the RAIR subpopulation, including one open-label extension study.

Figure 1: PRISMA flow diagram



Broader DTC population

Broader DTC population

Study summary	Population
2 studies **EORTC1209**[2] **Phase 2** **ASTRA**[15] **Phase 3** Both studies were multicenter, double-blind	**EORTC 1209/ASTRA studies** • Median Age: 42- 65.8 years • Male: 41% to 49%, Female: 51% to 59% • 94% patient: Caucasian ethnicity • 6% patient: Ethnic background

Treatment	Key outcome	
Nintedanib: EORTC 1209 **Selumetinib: ASTRA**	**EORTC 1209** • **mPFS:** 3.7 vs 2.86 months • **HR [80% CI]:** 0.65 [0.42, 0.99] • **PFS:** 46% vs 36.8% • **OS:** 89% vs 84.2%	**ASTRA study** **CR**: Investigating selumetinib in combination with RAI did not show a significant improvement in CR rates at 18 months when compared with placebo + RAI (40% vs. 38%).

Safety

Both nintedanib and selumetinib demonstrated manageable safety profiles, but selumetinib was linked to a higher incidence of grade 3 AEs compared to placebo (18% vs. 1%) and more frequent treatment discontinuations.

Quality assessment

The EORTC 1209 study did not specify its randomization method, leading to an unclear risk of bias in this area. On the other hand, the ASTRA study used central randomization, which resulted in a low risk of bias. Both studies had an unclear risk of bias regarding allocation concealment owing to insufficient information. The baseline comparability between the treatment groups was deemed low in both studies. Blinding was considered adequate in both cases because of their double-blind design. For incomplete outcome data, the ASTRA study had a low risk, as dropout rates were similar across treatment groups, while EORTC 1209 had an unclear risk due to inadequate information. Both studies had a low risk for outcome selection and reporting, as well as for statistical analysis, attributed to their use of intention-to-treat analyses.

Key: CR, complete remission; HR, hazard ratio; mPFS, median progression free survival; OS, overall survival; PFS, progression free survival; RAI, radioactive iodine-refractory

RAIR subpopulation

Study summary	Population
16 studies[1,3-14,16-18] **6** open-label[8-10,12,14,17] **10** double blind[1,3-7,11,13,16,18] Among **16** studies **15** trials were multicentred[1,3-13,16-18], **one** lacking clarity[14] **8** Phase II trails[3,5,8-10,12,17,18] **7** Phase III trails[1,4,6,7,11,13,16] **1** Unspecified[14]	Mean Age: 54.28-65.6 years **8 studies**[3,8,10,11,13,16-18] Median Age: 56-67 years **9 studies**[3,4,6,7,9,12,13,16,18] Male: 33.33% to 88.2% **13 studies**[3,4,6,7,9-13,16-18] Female: 11.8% to 66.67% **13 studies**[3,4,6,7,9-13,16-18] White patient: 51.9%[3] to 96%[9] Black: 0%[17] to 12.8%[8] Asian: 0%[17] to 100%[1,4-6,10] Other races: 0%[9,13] to 31.2%[3]

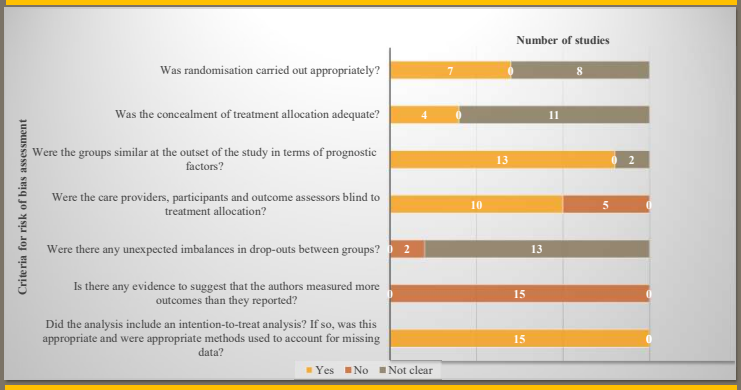
Treatment	Key outcome	
Lenvatinib **4 studies**[3,4,13,14] Donafenib **2 studies**[1,10] Vandetanib **2 studies**[11,18] Sorafenib **2 studies**[16,17] Apatinib **1 study**[6] Anlotinib **1 study**[5] Carbozantinib **1 study**[7] Cediranib meleate **1 study**[8] Cediranib meleate + lenalidomide **1 study**[8] Dabrafenib **1 study**[9] Dabrafenib + trametinib **1 study**[9] Pazopanib **1 study**[12]	ORR	2% for intermittent pazopanib[12] to 69.9% for lenvatinib[4] **15 studies**[1,3-10,12-14,16-18]
	mOS	• The median OS was reported in **10** studies, with **6** studies not reaching the median OS, suggesting the potential for longer survival.[1,3,4,6,7,9,12,13,16,17] • 19.4 months with Cabozantinib[7] • 47.5 months with Dabrafenib + Trametinib[9]
	mPFS	• 5.7 months with intermittent Pazopanib[12] • 40.54 months with Anlotinib[5]
	HRQoL	In **2** studies assessing HRQoL suggest that while there were some HRQoL differences between the treatment groups in these studies, the overall impact of lenvatinib or sorafenib on patients' QoL was minimal.[3,16]

Safety

Any-grade AEs	Reported in 63.0%[6] to 100%[5] of the patients, with anlotinib and apatinib having the highest rates.
Grade ≥3 TEAEs	Lenvatinib had the highest rates, up to 87.4%[4], whereas donafenib reported 43.8% of grade ≥3 TRAEs.[1]
SAEs	Ranged from 24.7% with vandetanib[11] to 72.9% with lenvatinib 24 mg.[14]
Hypertension	The most common AE, experienced by 3.4%[13] to 94.1%[17] of patients, with the highest rates observed with sorafenib (88.2%),[17] apatinib (87%), [6] lenvatinib (81.6%),[4] and anlotinib (84.2%).[5]
Diarrhea	Another frequent AE observed and reported in 0.8%[13] to 73.97% of patients, with vandetanib having the highest rate.[18]
Hand-foot skin reactions	It was seen in 0% to 87% of patients, particularly in those treated with apatinib (87%)[6] and sorafenib (76.3%).[16]

Key: AE, adverse event; HRQoL, health-related quality of life ORR, overall response rate; OS, overall survival; SAE, serious adverse events; TEAE, treatment emergent adverse events

Figure 2: Quality assessment of included studies for RAIR-DTC using the NICE critical appraisal checklist[19]



CONCLUSION

In summary, while there has been limited advancement in the treatment of the broader DTC population, lenvatinib has notably improved outcomes for patients with RAIR-DTC. Lenvatinib has demonstrated a significant increase in response rates and survival, albeit with a higher incidence of adverse events compared to other treatments. The systematic review highlights the need for further research, especially within the RAIR-DTC population, to optimize therapeutic strategies and manage the safety profiles of these pharmacological interventions. Continued exploration into novel treatments is essential to improve both efficacy and quality of life for DTC patients.

REFERENCES

1. Lin Y, et al. Ann. Oncol. 2022;33(7):S1294.
2. Schlumberger M, et al. JCO. 2018;36(15).
3. Brose M S, et al. JCEM. 2022;107(3):776-787.
4. Zheng X, et al. Clinical Cancer Research. 2021;27(20):5502-5509.
5. Chi Y, et al. Ann. Oncol. 2020;31(6):S1347.
6. Lin Y, JAMA oncology. 2022;Vol.8(2):242-250p.
7. Brose M S, et al. Cancer. 2022;128(24):4203-4212.
8. Liao, CY. ClinicalTrials.gov identifier: NCT01208051, Accessed March 8, 2024. ClinicalTrials.gov
9. Busaidy N L, et al. Thyroid. 2022;32(10):1184-1192.
10. Lin Y-S, Thyroid. 2021;31(4):607-615.
11. ClinicalTrials.gov identifier: NCT01876784, Accessed March 8, 2024.
12. de la Fouchardière, C, EJC. 2021;157:153-164.
13. Schlumberger M, et al. NEJM. 2015;372(7):621-630.
14. Robinson B, et al. Endocrine Reviews. 2015;36(Supplement).
15. Ho A L, et al. JCO. 2022;40(17):1870-1878.
16. Brose, M S, The Lancet. 2014;384(9940):319-328.
17. Sherman, E ClinicalTrials.gov identifier: NCT02143726, Accessed March 8, 2024.
18. Leboulleux S, et al. The lancet oncology. 2012;13(9):897-905.
19. NICE (https://www.nice.org.uk/article/pmg24/chapter/4-Clinical-effectiveness#quality-assessment-of-the-relevant-randomised-controlled-trials), Accessed March 8, 2024.

Financial Support: This study was funded by SRS Pharmaceuticals Pvt Ltd, Mumbai, India

Poster presented at the ISPOR EU 2024; 17-20 November 2024; Barcelona, Spain