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# *NTRK* GENE FUSION IN THYROID TUMOURS: DIAGNOSIS AND TREATMENT UPDATE

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# ENTRECTINIB & LAROTRECTINIB: TRK INHIBITORS

- The discovery of *NTRK* gene fusions led to the recent development of therapeutic agents that inhibit TRK fusion proteins[1]
- Two TRK inhibitors are approved by the US FDA (larotrectinib is approved globally in 48 countries) for use in patients with unresectable or metastatic *NTRK* gene fusion-positive cancers, agnostic of tumour type[1]

## ENTRECTINIB[2]

**INDICATION FOR USE:**

Adult and paediatric patients 12 years of age and older with solid tumours that:

- have an *NTRK* gene fusion as detected by an FDA-approved test without a known acquired resistance mutation,
- are metastatic or where surgical resection is likely to result in severe morbidity, and
- have either progressed following treatment or have no satisfactory alternative therapy.

## LAROTRECTINIB[3]

**INDICATION FOR USE:**

Adult and paediatric patients with solid tumours that:

- have an *NTRK* gene fusion without a known acquired resistance mutation,
- are metastatic or where surgical resection is likely to result in severe morbidity, and
- have no satisfactory alternative treatments or that have progressed following treatment.

FDA, Food and Drug Administration; NTRK, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase; US, United States

1. Hechtman JF, et al. Mod Pathol. 2022 Mar;35(3):298-305
2. Rozlytrek (entrectinib) [US prescribing information, July 2022]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/212725s006lbl.pdf. Last accessed: November 23, 2022
3. Vitratki (larotrectinib) [US prescribing information, March 2022]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/210861s006lbl.pdf. Last accessed: November 23, 2022

# ESMO-MCBS NEW THERAPIES/INDICATIONS IN THYROID CANCER

| Therapy | Disease setting | Trial | Control | Absolute survival gain | ESMO-MCBS score[1] |
|---|---|---|---|---|---|
| Entrectinib | Adult and paediatric patients 12 years of age and older with solid tumours expressing an *NTRK* gene fusion, who have disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have not received a prior TRK inhibitor, and who have no satisfactory treatment options | Phase ½:<br>• STARTRK-1 (NCT02097810)<br>• STARTRK-2 (NCT02568267)<br>• ALKA-372-001 (EudraCT 2012-000148-88) | Single arm | ORR: 57%<br>Median DoR: 10.4 months<br>Median PFS: 11.2 months | 3<br>(Form 3) |
| Larotrectinib | Adult and paediatric patients with solid tumours that display an *NTRK* gene fusion, who have disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options | Phase 1/2:<br>• Phase 1 study of the oral<br>• TRK inhibitor larotrectinib<br>• in adult patients with solid<br>• Tumours (NCT02122913)<br>• SCOUT (NCT02637687)<br>• NAVIGATE (NCT02576431) | Single arm | ORR: 79%<br>Median DoR: 35.2 months<br>Median PFS: 28.3 months | 3<br>(Form 3) |

[1] ESMO-MCBS v1.116 was used to calculate scores (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluationforms)

DoR, duration of response; ESMO, European Society for Medical Oncology; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; NTRK, neurotrophic tyrosine receptor kinase; ORR, objective response rate; PFS, progression-free survival; TRK, tropomyosin receptor kinase

Filetti S, et al. Ann Oncol. 2022;33(7):674-684

# SOURCE OF INFORMATION

## American Thyroid Association 2022 Annual Meeting:

- Cabanillas ME, Lin JJ, Brose MS, McDermott R, Almubarak M, Bauman J, Casanova M, Krishnamurthy A, Kummar S, Lee S-H, Leyvraz S, Oh D-Y, Shen L, Norenberg R, Dima L, Mussi CE, Hong DS, Drilon A, Waguespack SG. Updated Efficacy and Safety of Larotrectinib in Patients With Advanced Tropomyosin Receptor Kinase (TRK) Fusion-Positive Thyroid Carcinoma. Thyroid. 2022; 32, Supplement 1:P-1-A-135 (highlighted poster 108; presented at ATA 2022)

## Recent Publications review:

- Vuong HG, Le HT, Le TTB, Le T, Hassell L, Kakudo K. Clinicopathological significance of major fusion oncogenes in papillary thyroid carcinoma: An individual patient data meta-analysis. Pathol Res Pract. 2022;240:154180

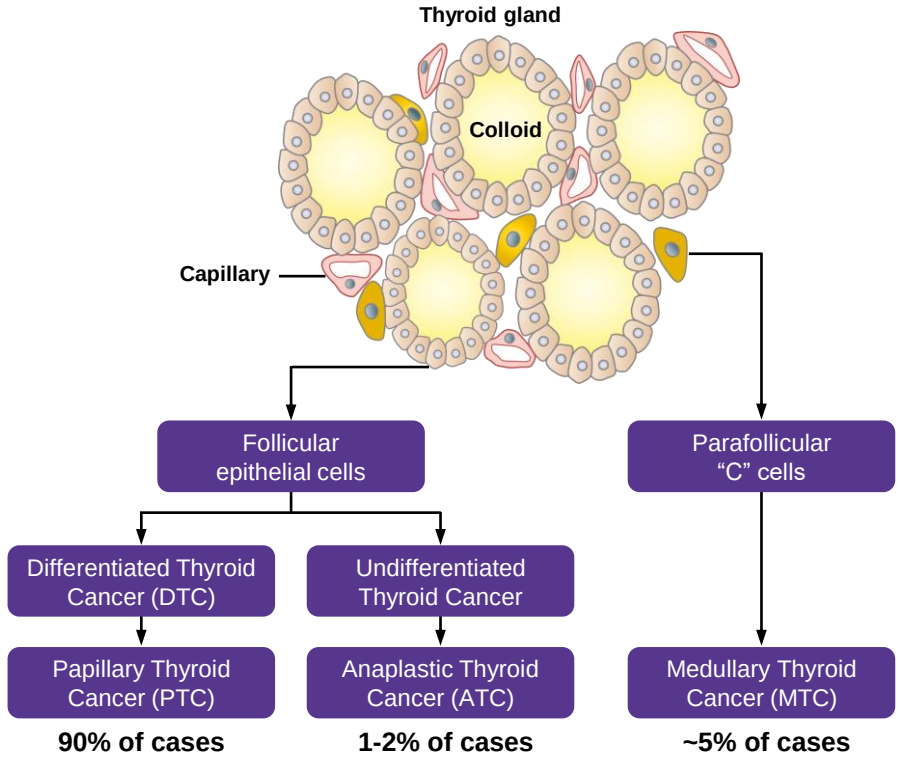
## Latest US, UK and EU guidelines:

- NCCN Clinical Practice Guidelines in Oncology: Thyroid Carcinoma / Version 3.2022 — November 1, 2022
- Wadsley J, Beasley M, Garcez K, Hoy S, Newbold K, Boelaert K. Guidelines on the Use of Systemic Therapy in Patients with Advanced Thyroid Cancer. Clin Oncol (R Coll Radiol). 2022 Nov 3:S0936-6555(22)00493-9
- Filetti S, Durante C, Hartl DM, Leboulleux S, Locati LD, Newbold K, Papotti MG, Berruti A; ESMO Guidelines Committee. ESMO Clinical Practice Guideline update on the use of systemic therapy in advanced thyroid cancer. Ann Oncol. 2022;33(7):674-684
- OncologyPRO: https://oncologypro.esmo.org/oncology-in-practice/anti-cancer-agents-and-biological-therapy/targeting-ntrk-gene-fusions/overview-of-ntrk-gene-fusion-in-specific-tumours

EU, European Union; UK, United Kingdom; US, United States

# THYROID CANCER OVERVIEW

- In 2020, the International Agency for Research on Cancer estimated the worldwide incidence of thyroid cancer to be 586,202 cases with 43,646 deaths and a 5-year prevalence of 1,984,927
- Thyroid cancers account for approximately 4% of malignancies in children
- The most common type of adult thyroid cancer, PTC, accounts for 90% of all thyroid cancer cases, whereas ATC accounts for only 1-2% of cases
- The majority (~93%) of thyroid carcinomas in children are Differentiated Thyroid Cancers - DTC (papillary and follicular), ~5% of cases are medullary (MTC), and ~2% are a mix or rare forms




ATC, anaplastic thyroid cancer; DTC, differentiated thyroid cancer; MTC, medullary thyroid cancer; PTC; papillary thyroid cancer

Available from: https://oncologypro.esmo.org/oncology-in-practice/anti-cancer-agents-and-biological-therapy/targeting-ntrk-gene-fusions/overview-of-ntrk-gene-fusion-in-specific-tumours/thyroid-cancer. Last accessed: November 23, 2022

# PREVALENCE OF *NTRK* GENE FUSIONS IN THYROID TUMOURS

| Tumour type | Frequency of *NTRK* gene fusions (*NTRK*$^+$/total) | *NTRK* gene affected | Partner gene | Related reference |
|---|---|---|---|---|
| Thyroid | 2.2% (10/451) | *NTRK1/3* | Information not available per tumour type. Overall, in 26,312 tumours, *NTRK1/2* had no preferred upstream fusion partner, and the most common partner for *NTRK3* was *ETV6* | Rosen et al. 2020 |
| Thyroid | 2.28% (13/571) | *NTRK1/3* | *NTRK1: IRF2BP2, TPM3, TPR, DIAPH1* (each n=1)<br>*NTRK3*: *ETV6* (n=6)<br>*RBPMS, SQSTM1, EML4* (each n=1) | Solomon et al. 2020 |
| Thyroid | 2.3% (12/513) | *NTRK1/3* | Not described | Okamura et al. 2018 |
| Thyroid | 5.7% (4/70) | *NTRK3* | *NTRK3: ETV6* (n=3), *VIM* (n=1) | Gatalica et al. 2019 |
| PTC | 5.3% (2/38) | Not reported | Not reported | Wajjwalku et al. 1992 |
| Thyroid | 2.9% (2/68) | *NTRK1* | *TPM3* | Said et al. 1994 |
| Paediatric PTC | 26% (7/27) | *NTRK1/3* | *NTRK1: TPR* (n=1)<br>*NTRK3*: *ETV6* (n=5)<br>Unknown (n=1) | Prasad et al. 2016 |
| Paediatric thyroid cancer | 7.7% (2/26) | *NTRK3* | *NTRK3: ETV6* (n=6)<br>*NTRK3*: *TPR* (n=1) | Ricarte-Filho et al. 2013 |
| PTC<br>• Sporadic<br>• Post-Chernobyl | <br>2.9% (7/243)<br>14.5 (9/62) | *NTRK3* | *NTRK3: ETV6* | Leeman-Neill et al. 2014 |
| Primary thyroid tumours<br><br>PTC | 3.1% (11/351[a])<br><br>5.9% (11/186) | *NTRK1/3* | *NTRK1: TPR* (n=2), *SQSTM* (n=1)<br><br>*NTRK3: ETV6* (n=4), *RBPMS* (n=2), *SQSTM1* (n=1), and *EML4* (n=1) | Chu et al. 2020 |

[a] One 14-year-old adolescent and 10 adults. All cases were radiation-naïve. One patient with brain metastases.

- Among PTCs with *NTRK* gene fusion, fusions involving *NTRK3* were the most frequent (64.5%) with *ETV6-NTRK3* being the most common fusion type, followed by *SQSTM1-NTRK3, EML4-NTRK3,* and *RBMPS-NTRK3*
- *NTRK1*-fused PTCs accounted for 35.5% of PTCs, with *NTRK* gene fusions with *TPM3-NTRK1* being the most common genotype
- No *NTRK2* fusions have been reported to date
- *ETV6-NTRK3* is the most common rearrangement in PTC. While the prevalence of this rearrangement in adults with PTC is very low (<1%), it is the second most common rearrangement seen in radiation-associated PTC

DIAPH1, diaphanous related formin 1; NTRK, neurotrophic tyrosine receptor kinase; PTC, papillary thyroid cancer; SQSTM1, sequestosome 1; TPM3, tropomyosin 3; TPR, translocated promoter region

1. Available from: https://oncologypro.esmo.org/oncology-in-practice/anti-cancer-agents-and-biological-therapy/targeting-ntrk-gene-fusions/overview-of-ntrk-gene-fusion-in-specific-tumours/thyroid-cancer. Last accessed: November 23, 2022. 2. Vuong HG, et al. Pathol Res Pract. 2022;240:154180

# HISTOPATHOLOGY AND CHARACTERISTICS OF *NTRK* GENE FUSION THYROID TUMOURS

- Multiple infiltrative tumour nodules and extensive lymphovascular spread within intrathyroidal and extrathyroidal vessels of variable calibre (n=11). Direct extrathyroidal extension, at least microscopic (n=9)
- Similar cellular architectural properties in cases with the same gene fusion:

| | ***ETV6-NTRK3* (n=4)<br>*RBPMS-NTRK3* (n=2)** | ***SQSTM1-NTRK3* (n=1)** | ***TPR-NTRK1* (n=2)<br>*SQSTM1-NTRK*** |
|---|---|---|---|
| **Cell architectural features** | Predominantly follicular pattern | Predominantly insular patterns | Predominantly papillary pattern, with scattered glomeruloid structures[a] |
| | Multiple irregularly shaped tumour nodules infiltrating the thyroid | Scattered microfollicles and increased mitotic activity | Immunoreactivity, in 10 out of 11 cases, for TTF1, PAX8, thyroglobulin, and HBME1[b] |
| | | Multifocal features of PTC | |

[a] *TPR-NTRK1* fusion-positive tumours also showing multiple nodules of packeted papillae divided by fibrotic septa; for *SQSTM1-NTRK1*, numerous psammomatous calcifications

[b] The other case only expressed low levels of TTF1; final diagnosis was primary thyroid secretory carcinoma of the salivary type

NTRK, neurotrophic tyrosine receptor kinase; PAX8, paired box gene 8; PTC, papillary thyroid cancer; SQSTM1, sequestosome 1; TPR, translocated promoter region; TTF1, transcription termination factor 1

Available from: https://oncologypro.esmo.org/oncology-in-practice/anti-cancer-agents-and-biological-therapy/targeting-ntrk-gene-fusions/overview-of-ntrk-gene-fusion-in-specific-tumours/thyroid-cancer/diagnosis. Last accessed: November 23, 2022

# HISTOPATHOLOGICAL/CLINICAL PROFILES OF PTCs WITH DIFFERENT ONCOGENE FUSION TYPES

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| Variables | *ALK* (N=47) | *BRAF* (N=25) | *NTRK* (N=225) | *RET* (N=143) | p value |
|---|---|---|---|---|---|
| **Age** | | | | | **<0.001** |
| Mean (SD) | 35.9 (18.1) | 22.8 (23.1) | 32.5 (17.3) | 25.7 (15.3) | |
| Median (min, max) | 33.0 (4.50, 69.0) | 13.0 (5.00, 76.0) | 31.0 (4.30, 74.0) | 19.5 (5.10, 69.0) | |
| **Age group** | | | | | **<0.001** |
| Adult | 37 (78.7) | 6 (24.0) | 149 (69.6) | 74 (52.9) | |
| Paediatric | 19 (21.3) | 19 (76.0) | 65 (30.4) | 66 (47.1) | |
| **Gender** | | | | | **0.028** |
| Female | 38 (80.9) | 12 (48.0) | 156 (72.6) | 104 (73.0) | |
| Male | 9 (19.1) | 13 (52.0) | 59 (27.4) | 39 (27.0) | |
| **FNA diagnosis** | | | | | **0.004** |
| Benign | 0 (0) | NA | 1 (3.6) | 0 (0) | |
| Indeterminate | 4 (44.4) | NA | 4 (14.3) | 1 (20.0) | |
| Suspicious for malignant | 5 (55.6) | NA | 6 (21.4) | 0 (0) | |
| Malignant | 0 (0) | NA | 17 (60.7) | 4 (80.0) | |
| **Growth pattern** | | | | | **<0.001** |
| Classic | 20 (44.4) | 15 (62.5) | 59 (33.9) | 62 (54.1) | |
| Follicular variant | 12 (26.7) | 5 (20.8) | 69 (39.7) | 10 (9.0) | |
| Diffuse sclerosing variant | 1 (2.2) | 1 (4.2) | 4 (2.3) | 35 (31.5) | |
| Solid variant | 2 (4.4) | 2 (8.3) | 11 (6.3) | 6 (5.4) | |
| Other variants | 10 (22.2) | 1 (4.2) | 31 (17.8) | 0 (0) | |
| **Psammoma** | | | | | **0.006** |
| No | NA | NA | 65 (75.6) | 1 (16.7) | |
| Yes | NA | NA | 21 (24.4) | 5 (83.3) | |
| **Lymph node metastasis** | | | | | **<0.001** |
| No | 7 (41.2) | 5 (20.8) | 42 (36.5) | 20 (17.1) | |
| Yes | 10 (58.8) | 19 (79.2) | 73 (63.5) | 97 (82.9) | |
| **Extrathyroidal extension** | | | | | **0.001** |
| No | 5 (33.3) | 2 (25.0) | 56 (56.0) | 15 (25.9) | |
| Yes | 10 (66.7) | 6 (75.0) | 44 (44.0) | 43 (74.1) | |
| **Radioactive iodine** | | | | | **<0.001** |
| No | 9 (52.9) | 0 (0) | 17 (32.1) | 4 (7.7) | |
| Yes | 8 (47.1) | 7 (100) | 36 (67.9) | 48(92.3) | |

ALK, anaplastic lymphoma kinase; BRAF, B-Raf; FNA, fine-needle aspiration; NA, not available; NTRK, neurotrophic tyrosine receptor kinase; PTC; papillary thyroid cancer; RET, ret proto-oncogene; SD, standard deviation



Vuong HG, et al. Pathol Res Pract. 2022;240:154180

# CLINICOPATHOLOGICAL FEATURES OF *NTRK1* VS *NTRK3*-REARRANGED PTC

| Variables | *NTRK1* (N=80) | *NTRK3* (N=145) | p value |
|---|---|---|---|
| **Age** | | | 0.139 |
| Mean (SD) | 35.3 (19.1) | 31.0 (16.1) | |
| Median (min, max) | 36.0 (4.30, 74.0) | 29.0 (5.20, 74.0) | |
| **Gender** | | | <0.001 |
| Female | 43 (56.6) | 113 (81.3) | |
| Male | 33 (43.4) | 26 (18.7) | |
| **Histologic variants** | | | <0.001 |
| Classic | 30 (56.6) | 29 (24.0) | |
| Follicular variant | 10 (18.9) | 59 (48.8) | |
| Diffuse sclerosing variant | 4 (7.5) | 0 (0) | |
| Solid variant | 1 (1.9) | 10 (8.3) | |
| Other variants | 8 (15.1) | 23 (19.0) | |
| **Psammoma** | | | 0.508 |
| No | 55 (77.5) | 65 (75.6) | |
| Yes | 16 (22.5) | 21 (24.4) | |
| **Focality** | | | 0.011 |
| Multifocal | 26 (78.8) | 50 (53.8) | |
| Unifocal | 7 (21.2) | 43 (46.2) | |
| **Vascular invasion** | | | 0.048 |
| No | 4 (44.4) | 46 (78.0) | |
| Yes | 5 (55.6) | 13 (22.0) | |
| **Lymph node metastasis** | | | 0.065 |
| No | 8 (22.2) | 34 (43.0) | |
| Yes | 28 (77.8) | 45 (57.0) | |
| **Extrathyroidal extension** | | | 0.036 |
| No | 8 (36.4) | 48 (61.5) | |
| Yes | 14 (63.6) | 30 (38.5) | |
| **Distant metastasis** | | | 0.061 |
| No | 13 (48.1) | 27 (71.1) | |
| Yes | 14 (51.9) | 11 (28.9) | |

NTRK, neurotrophic tyrosine receptor kinase; PTC, papillary thyroid cancer; SD, standard deviation

Vuong HG, et al. Pathol Res Pract. 2022;240:154180

# TREATMENT RECOMMENDATIONS FOR LAROTRECTINIB AND ENTRECTINIB

- EU guidelines:
  - **Larotrectinib** is an option for the treatment of **adults and paediatric patients** with metastatic *NTRK* gene fusion-positive solid tumours, **not amenable to surgery**, that have **no satisfactory treatment options** [V, B; ESMO-MCBS v1.1 score: 3; ESCAT score: I-C][1]
  - **Entrectinib** is an option for treating **adults and adolescents aged ≥12 years** with metastatic or unresectable *NTRK* gene fusion-positive solid tumours that **have progressed in spite of standard-of-care treatment** [V, B; ESMO-MCBS v1.1 score: 3; ESCAT score: I-C][1]
- US guidelines (NCCN guidelines):
  - **Larotrectinib** or **entrectinib** for patients with *NTRK* gene fusion-positive advanced solid tumours[2]
- UK guidelines:
  - **Larotrectinib** and **entrectinib** are *NTRK* gene fusion inhibitors approved by NICE for the treatment of patients with solid tumours that display a *NTRK* gene fusion who have locally advanced or metastatic disease and who have no satisfactory alternative treatment options[3]

ESCAT score, ESMO Scale for Clinical Actionability of molecular Targets score; ESMO, European Society for Medical Oncology; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; EU, European Union; NICE, National Institute for Health and Care Excellence; NTRK, neurotrophic tyrosine receptor kinase; UK, United Kingdom; US, United States

1. Filetti S, et al. Ann Oncol. 2022;33(7):674-684. 2. NCCN guidelines Thyroid Carcinoma / Version 3.2022 — November 1, 2022. 3. Wadsley J, et al. Clin Oncol (R Coll Radiol). 2022 Nov 3:S0936-6555(22)00493-9

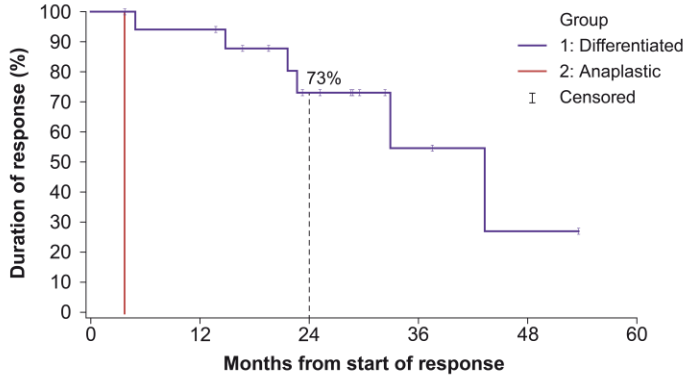
# UPDATED EFFICACY: LAROTRECTINIB IN ADVANCED TRK FUSION-POSITIVE THYROID CARCINOMA

## Cut off date: July 2021

- 30 patients with TRK fusion-positive TC were enrolled, including 29 with an additional year of follow-up. There were 23 patients with differentiated TC (DTC) and seven patients with anaplastic TC (ATC).
- In this small sample, patients with TRK fusion-positive ATC had worse outcomes compared to TRK fusion-positive DTC

**DoR**

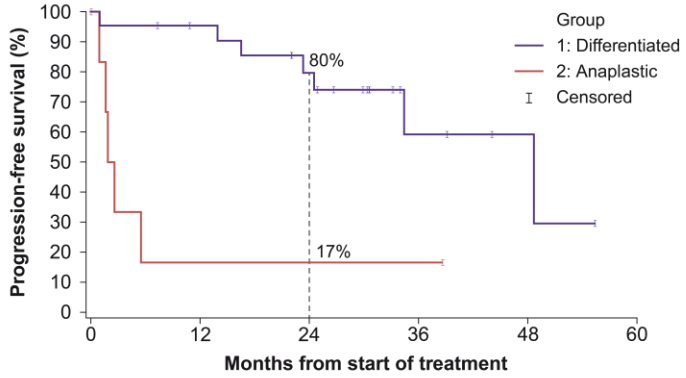
| | Differentiated | Anaplastic |
|---|---|---|
| Median DoR, months (95% CI) | 43.3 (22.7–NE) | 3.7 (NE–NE) |
| Median follow-up, months | 28.8 | NE |
| 24-month DoR, % (95% CI) | 73 (50–96) | 0 |




| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| 1 | 18 | 16 | 9 | 3 | 1 | 0 |
| 2 | 1 | 0 | 0 | 0 | 0 | 0 |

**PFS**

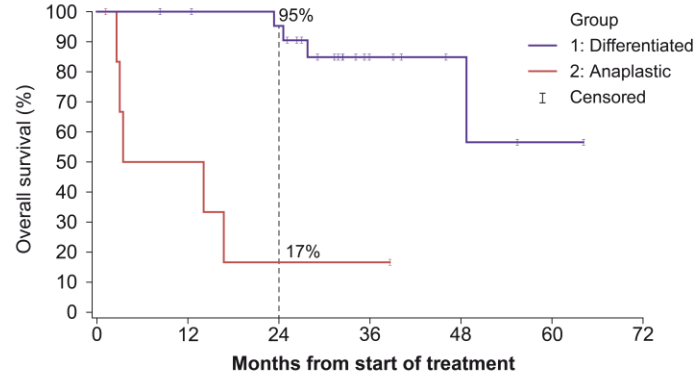
| | Differentiated | Anaplastic |
|---|---|---|
| Median PFS, months (95% CI) | 48.7 (24.6–NE) | 2.2 (0.9–NE) |
| Median follow-up, months | 30.6 | 38.7 |
| 24-month PFS, % (95% CI) | 80 (62–98) | 17 (0–46) |




| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| 1 | 23 | 19 | 14 | 4 | 2 | 0 |
| 2 | 7 | 1 | 1 | 1 | 0 | 0 |

**OS**

| | Differentiated | Anaplastic |
|---|---|---|
| Median OS, months (95% CI) | Not reached | 8.8 (2.6–NE) |
| Median follow-up, months | 34.1 | 38.7 |
| 24-month OS, % (95% CI) | 95 (86–100) | 17 (0–46) |



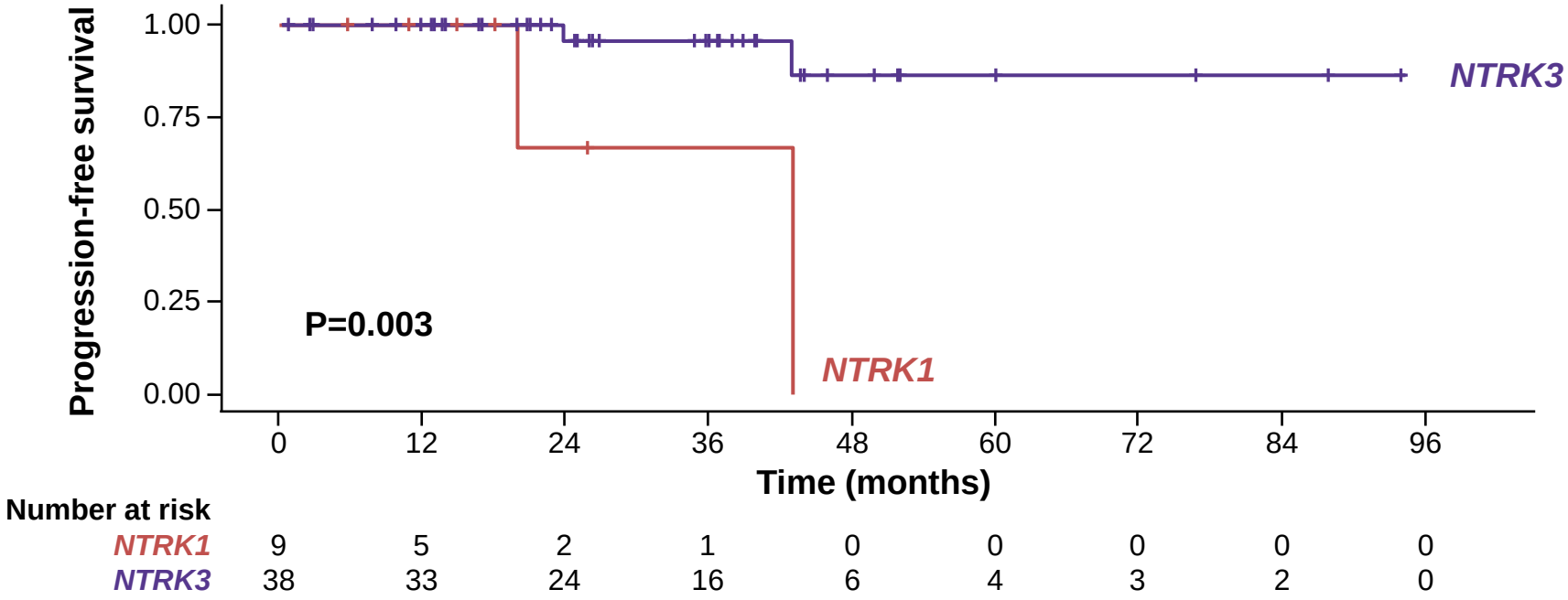

| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| 1 | 23 | 22 | 20 | 7 | 3 | 1 | 0 |
| 2 | 7 | 3 | 1 | 1 | 0 | 0 | 0 |

ATA, American Thyroid Association; ATC, anaplastic thyroid cancer; CI, confidence interval; DoR, duration of response; DTC, differentiated thyroid cancer; NE, not estimable; OS, overall survival; PFS, progression-free survival; TC, thyroid cancer; TRK, tropomyosin receptor kinase

Cabanillas ME, et al. Thyroid. 2022; 32, Supplement 1:P-1-A-135 (highlighted poster 108; presented at ATA 2022)

# PROGRESSION-FREE SURVIVAL OF PTCs WITH *NTRK1* VERSUS *NTRK3* FUSIONS

- *NTRK1*-rearranged PTCs demonstrated increased aggressiveness and shorter PFS compared to *NTRK3*-positive cases




NTRK, neurotrophic tyrosine receptor kinase; PFS, progression-free survival; PTC, papillary thyroid cancer

Vuong HG, et al. Pathol Res Pract. 2022;240:154180

# CONCLUSION

- PTCs with different fusion types have:
  - unique demographic, histological, and clinicopathological features
  - *NTRK3* and *NTRK1* most frequent fusions, no *NTRK2* fusions

- DNA and RNA based NGS: best approach method for testing for *NTRK* gene fusions

- Larotrectinib and entrectinib:
  - TRK inhibitors have demonstrated strong and durable responses, with manageable safety profile
  - Both included as treatment options in EU, US and UK guidelines for thyroid tumours treatment

- Recent updated clinical data show:
  - A difference in progression-free survival between *NTRK1* and *NTRK3* fusion-positive thyroid tumours
  - A difference in the treatment outcome between DTC and ATC

ATC, anaplastic thyroid cancer; DTC, differentiated thyroid cancer; NGS, next-generation sequencing; NTRK, neurotrophic tyrosine receptor kinase; PTC, papillary thyroid cancer; TRK, tropomyosin receptor kinase

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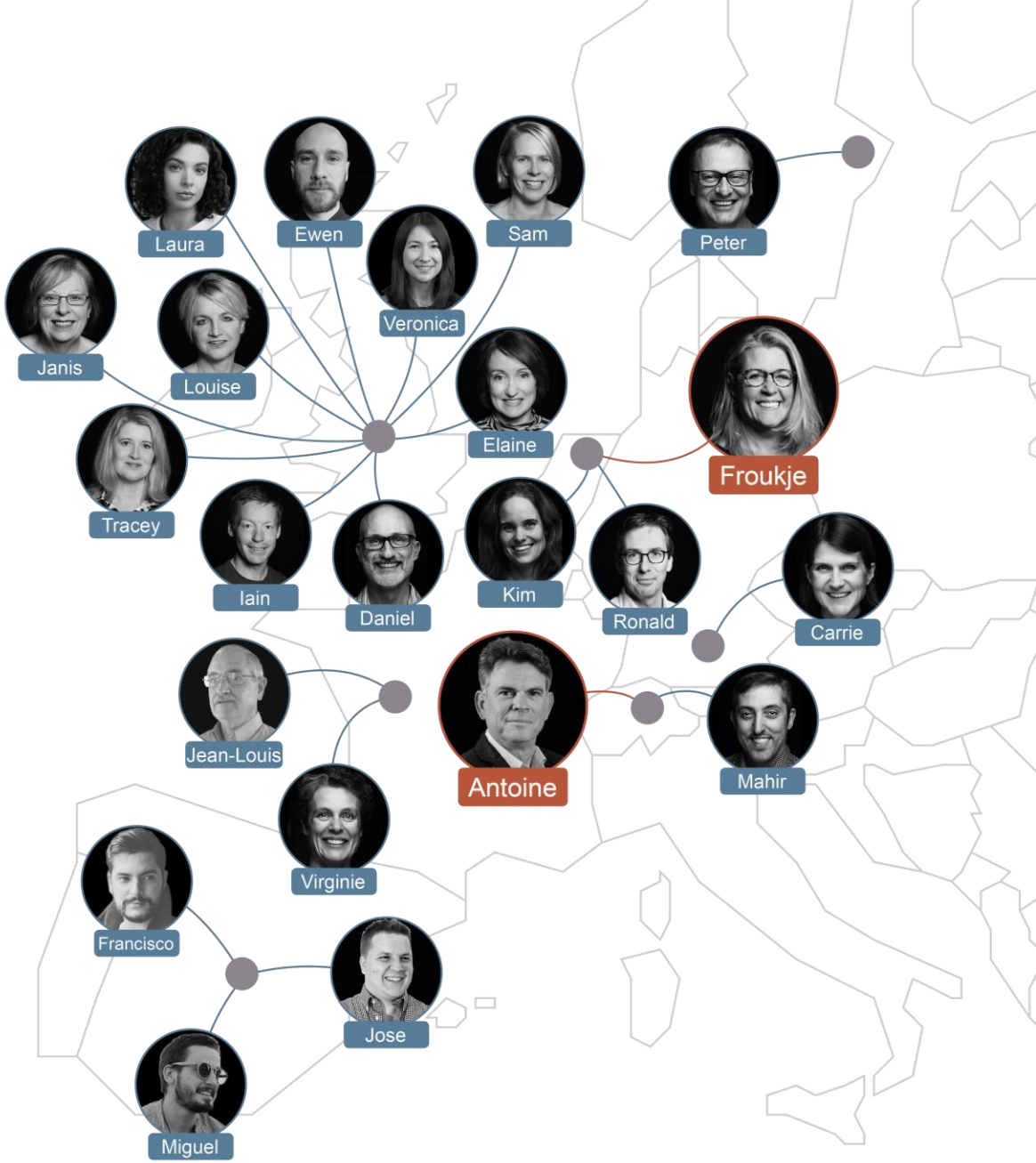


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