Personalized treatment of RET-altered thyroid cancers: What is the value of biomarker testing and targeted therapies?

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Thyroid cancer epidemiology and treatment options: Where are we today?

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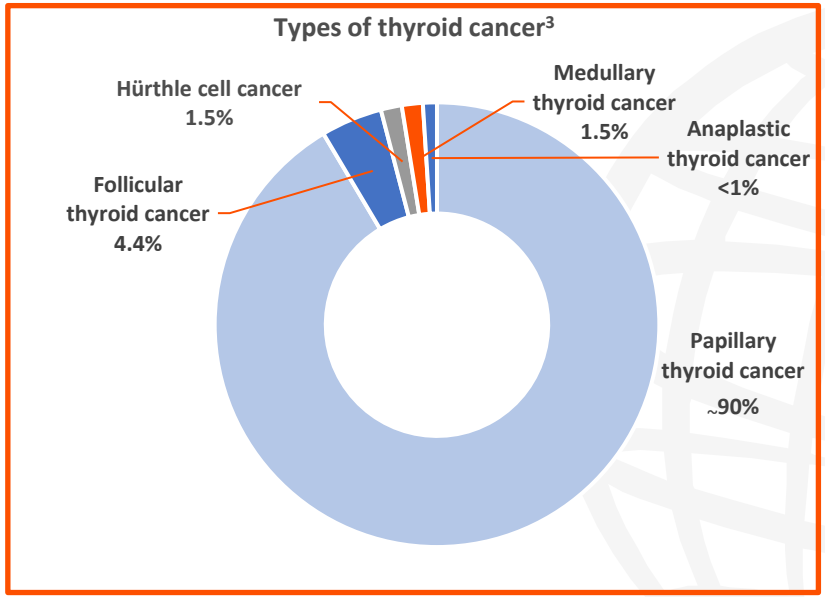
Epidemiology of thyroid cancer

Types, incidence and distribution in the USA

- It is estimated there will be 43,800 new cases of thyroid cancer in 2022[1]
- Incidence is rising – 6% annual increase from 1997 to 2006[2]
- Two to three times more common in women than men[1]
- Peak incidence: 40–49 years in women, 60–69 years in men[2]
- Differentiated thyroid cancer (97%)[3,4]
  - Includes papillary, follicular, Hürthle cell and poorly differentiated thyroid cancer
- Hereditary thyroid cancer:
  - 10% of papillary and 25% of medullary thyroid cancers[5,6]



1. American Cancer Society; Cancer Statistics Center. Thyroid. Available at: https://cancerstatisticscenter.cancer.org/?_ga=2.138871091.1682881696.1638803504-353821412.1637787931#!/cancer-site/Thyroid (accessed 19 January 2022); 2. Rahbari R, et al. *Future Oncol*. 2010;6:1771–9; 3. Rossi ED, et al. *Lancet Diabetes Endocrinol*. 2021;9:193–4; 4. Cabanillas ME, et al. *Endocr Rev*. 2019;40:1573–604; 5. Accardo G, et al. *Int J Surg*. 2017;1(Suppl.):S2–6; 6. Capezzone M, et al. *Eur Thyroid J*. 2020;9:213–20.

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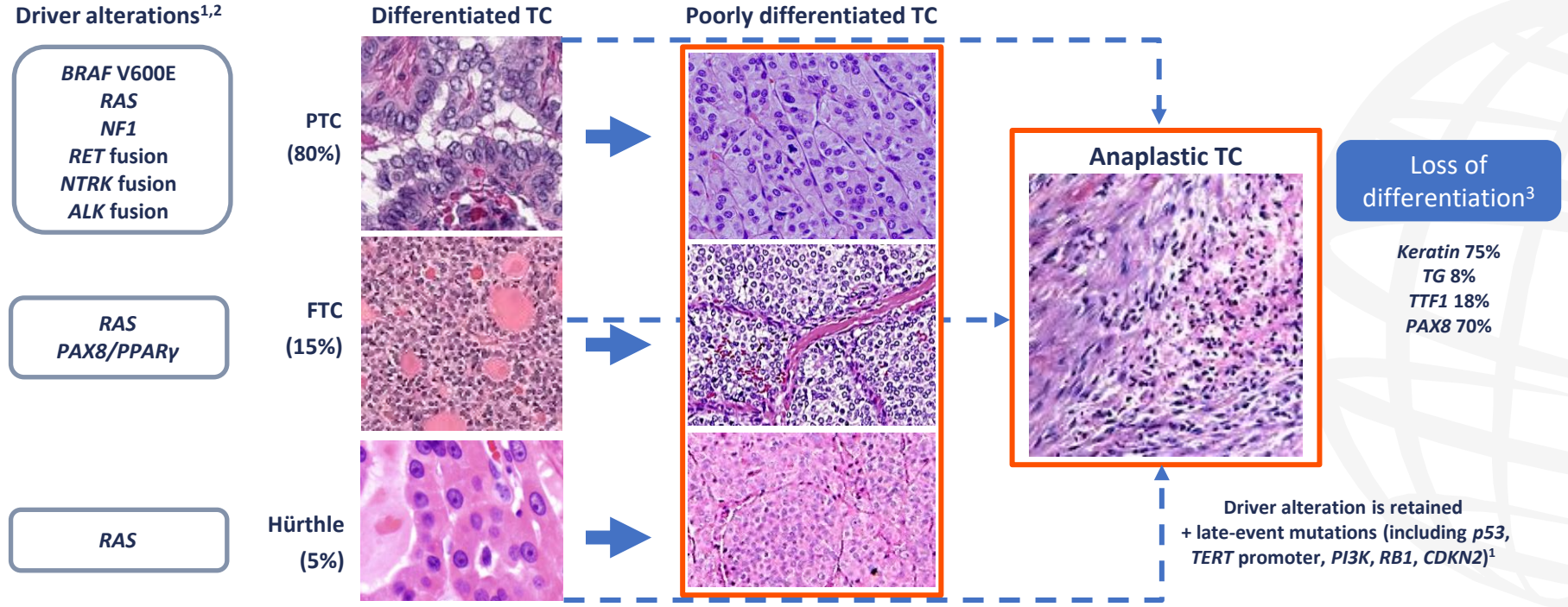
Mutations drive disease progression



- MEN2 syndrome (germline mutations) is associated with hereditary MTC; ~99% are RET mutated[4]
- 40–65% of patients with MTC have somatic RET mutations[5]

Images courtesy of M. Cabanillas. FTC, follicular thyroid cancer; PTC, papillary thyroid cancer.

1. Prete A, et al. *Front Endocrinol.* 2020;11:102; 2. Fang Y, et al. *Cell Physiol Biochem* 2018;50:169–78; 3. Cabanillas ME, et al. *Hematol Oncol Clin North Am.* 2015;29:1123–43; 4. Gertner ME, et al. *Curr Treat Options Oncol*. 2004;5:315–25; 5. Mulligan LM. *Front Physiol.* 2019;9:1873.

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Multikinase inhibitor therapies approved in the USA

Drug name	Targets[6]	FDA-approved indication	ORR	Median PFS (drug vs PBO)
Vandetanib[1]	Anti-angiogenic; *VEGFR2/3, EGFR, RET*	Locally advanced or metastatic **MTC**	44%*	NR vs 16.4 mo
Cabozantinib[2,3]	Anti-angiogenic; *VEGFR2, MET, FLT3, RET, c-kit*	1. Progressive, metastatic **MTC** 2. Locally advanced or metastatic **DTC** that has progressed following prior VEGFR-targeted therapy and RAI refractory or ineligible	**MTC:** 27%* **DTC:** 15%*	**MTC:** 11.2 vs 4 mo **DTC:** NR vs 1.9 mo
Sorafenib[4]	Anti-angiogenic; *VEGFR1–3, PDGFR, RET, c-kit, BRAF*	Locally recurrent or metastatic, progressive **DTC** refractory to RAI	12%*	10.8 vs 5.8 mo
Lenvatinib[5]	Anti-angiogenic; *VEGFR1–3, FGFR1–4, PDGFR, RET, c-kit*		65%	18.3 vs 3.6 mo

*Partial responses.

DTC, differentiated thyroid cancer; FDA, US Food and Drug Administration; mo, months; MTC, medullary thyroid cancer; NR, not reached; ORR, overall response rate; PBO, placebo; PFS, progression-free survival; RAI, radioactive iodine therapy; VEGFR, vascular endothelial growth factor.

1. Caprelsa (vandetanib) prescribing information. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022405s017lbl.pdf (accessed 09 February 2022);
2. Cabometyx (cabozantinib) prescribing information. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208692s012lbl.pdf (accessed 09 February 2022);
3. Cometriq (cabozantinib) prescribing information. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/203756s009lbl.pdf (accessed 09 February 2022);
4. Nexavar (sorafenib) prescribing information. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021923s024lblrpl.pdf (accessed 09 February 2022);
5. Lenvima (lenvatinib) prescribing information. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/206947s011lbl.pdf (accessed 09 February 2022);
6. Cabanillas ME, et al. *Endocr Rev.* 2019;40:1573–604.

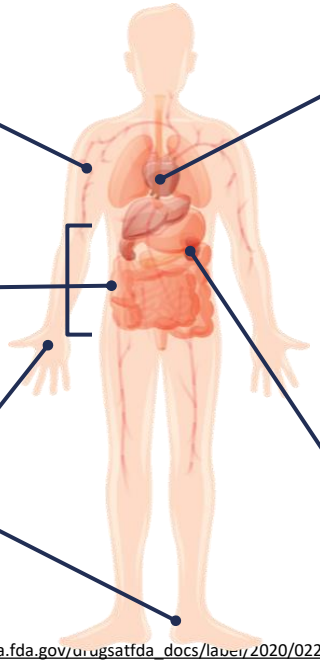
Selected common AEs* associated with MKIs

Studies of MKIs show a significant quantity and grade of AEs[1–6]

Musculoskeletal and connective tissue disorders
- Arthralgia/myalgia (0–5% Gr 3+)

Gastrointestinal disorders
- Diarrhea (6–16% Gr 3+)
- Nausea (0–3% Gr 3+)
- Stomatitis (0–5% Gr 3+)

Skin and cutaneous disorders
- Rash (0–5% Gr 3+)
- Palmar–plantar erythrodysesthesia (0–19% Gr 3+)



Vascular disorders
- Hypertension (8–44% Gr 3+)

General disorders
- Fatigue (5–11% Gr 3+)
- Decreased appetite (2–7% Gr 3+)
- Weight loss (0–13% Gr 3+)

Renal disorders
- Proteinuria (0–11% Gr 3+)

*≥20% of patients. Laboratory abnormalities not included.
AE, adverse events; Gr, grade; MKI, multikinase inhibitor.

1. Caprelsa (vandetanib) prescribing information. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022405s017lbl.pdf (accessed 09 February 2022);
2. Cabometyx (cabozantinib) prescribing information. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208692s012lbl.pdf (accessed 09 February 2022);
3. Cometriq (cabozantinib) prescribing information. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/203756s009lbl.pdf (accessed 09 February 2022); 4. Nexavar (sorafenib) prescribing information. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021923s024lblrpl.pdf (accessed 09 February 2022); 5. Lenvima (lenvatinib) prescribing information. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/206947s011lbl.pdf (accessed 09 February 2022); 6. Ancker OV, et al. *Int J Mol Sci.* 2020;21:10.

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Targeted kinase inhibitor therapies approved in the USA

Drug name	Target	FDA-approved indication	ORR (CR)
Dabrafenib plus trametinib[1]	*BRAF* V600E	Locally advanced or metastatic ATC with *BRAF V600E* mutation in combination with trametinib	61% (4%)
Entrectinib[2]	*NTRK* fusion	Solid tumors with *NTRK* fusion that are metastatic with no alternative treatments or have progressed following treatment	**Solid tumors:** 59% (13%) **Thyroid cancer:** 60%*
Larotrectinib[3]	*NTRK* fusion		**Solid tumors:** 75% (25%) **Thyroid cancer:** 100%*
Pralsetinib[4]	*RET* alteration	1. Advanced or metastatic *RET*-mutant MTC requiring systemic treatment 2. Advanced or metastatic *RET* fusion-positive thyroid cancer requiring systemic treatment and RAI refractory	**MTC:** 60–66% (2–10%)† ***RET*-fusion +ve:** 89%‡
Selpercatinib[5]	*RET* alteration		**MTC:** 69–73% (9–11%)† ***RET*-fusion +ve:** 79–100% (5–13%)†

*CR/PR not provided; †Ranges incorporate the ORR for patients previously systemically treated and untreated; ‡Partial responses.
ATC, anaplastic thyroid cancer; CR, complete response; FDA, US Food and Drug Administration; MTC, medullary thyroid cancer; ORR, overall response rate; PR, partial response; RAI, radioactive iodine therapy.

1. Mekinist (trametinib) prescribing information. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/204114s020lbl.pdf (accessed 09 February 2022);
2. Rozlytrek (entrectinib) prescribing information. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212725s005lbl.pdf (accessed 09 February 2022);
3. Vitrakvi (larotrectinib) prescribing information. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/210861s006lbl.pdf (accessed 09 February 2022);
4. Gavreto (pralsetinib) prescribing information. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213721s004lbl.pdf (accessed 09 February 2022);
5. Retevmo (selpercatinib) prescribing information. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213246s002lbl.pdf (accessed 09 February 2022).

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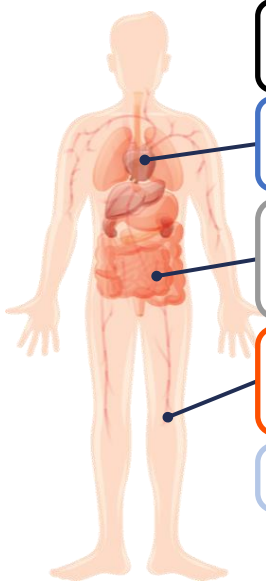
Selected common AEs* associated with targeted kinase inhibitors

BRAF V600E[1]



General disorders
- Pyrexia (5% Gr 3+)
- Chills (<1% Gr 3+)

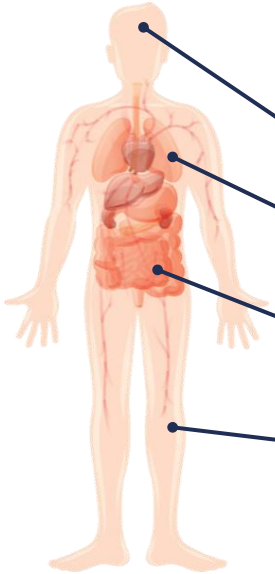
Vascular disorders
- Hypertension (11% Gr 3+)

Gastrointestinal disorders
- Diarrhea (1% Gr 3+)
- Nausea (<1% Gr 3+)

Skin and cutaneous disorders
- Rash (1% Gr 3+)

Laboratory abnormalities
- Lymphopenia (8% Gr 3+)

NTRK fusion[2,3]



General disorders
- Fatigue (3–5% Gr 3+)
- Pyrexia (1–2% Gr 3+)

Nervous system disorders
- Dizziness (<1% Gr 3+)

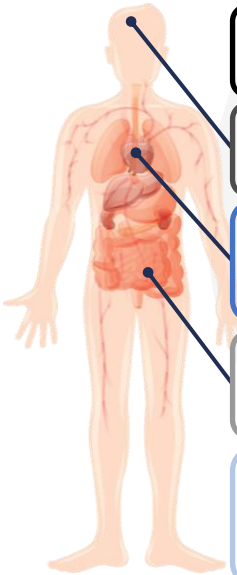
Respiratory, thoracic and mediastinal disorders
- Cough (<1% Gr 3+)

Gastrointestinal disorders
- Diarrhea (1–2% Gr 3+)
- Constipation (<1% Gr 3+)

Musculoskeletal and connective tissue disorders
- Musculoskeletal pain (1–4% Gr 3+)

Laboratory abnormalities
- Lymphopenia (6–12% Gr 3+)

RET alteration[4,5]



General disorders
- Fatigue (2–6% Gr 3+)
- Edema (<1% Gr 3+)

Nervous system disorders
- Headache (0–1% Gr 3+)

Vascular disorders
- Hypertension (18–21% Gr 3+)

Gastrointestinal disorders
- Diarrhea (3–5% Gr 3+)
- Constipation (<1% Gr 3+)

Laboratory abnormalities
- Inc AST (4–8% Gr 3+)
- Inc ALT (4–9% Gr 3+)
- Lymphopenia (Up to 27% Gr 3+)

*≥20% of patients. Not all laboratory abnormalities in the ≥20% category are included. AE, adverse event; ALT, alanine transaminase; AST, aspartate aminotransferase; Gr, grade; Inc, increased.

1. Mekinist (trametinib) prescribing information. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/204114s020lbl.pdf (accessed 09 February 2022); 2. Rozlytrek (entrectinib) prescribing information. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212725s005lbl.pdf (accessed 09 February 2022); 3. Vitrakvi (larotrectinib) prescribing information. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/210861s006lbl.pdf (accessed 09 February 2022); 4. Gavreto (pralsetinib) prescribing information. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213721s004lbl.pdf (accessed 09 February 2022); 5. Retevmo (selpercatinib) prescribing information. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213246s002lbl.pdf (accessed 09 February 2022).

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A personalized approach to treating RET-altered thyroid cancers: How is biomarker testing key to improving outcomes?

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RET alterations in thyroid cancer

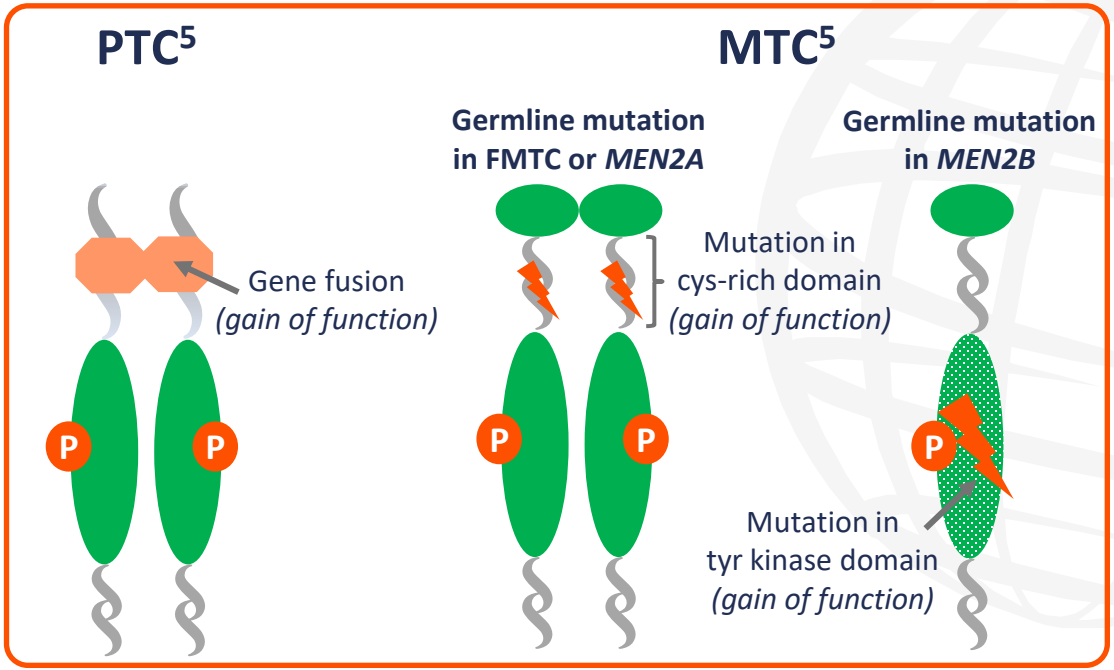
The presence of a RET fusion protein or RET mutation is a biomarker of malignancy[1]

RET fusions

- Present in **10–20%** of PTCs and **~1%** of ATCs[1,2]
- RET rearrangement is an **early event** in tumorigenesis[1]
- Most common in young patients (<39 years)[3]

RET mutations

- Present in **40–65%** of sporadic MTCs[1]
- Gain-of-function point mutation is associated with **aggressive disease**[1]
- Early thyroidectomy is required in children who have inherited MEN2[4]



ATC, anaplastic thyroid cancer; cys, cysteine; FMTC, familial medullary thyroid cancer; MEN2, multiple endocrine neoplasia type 2 syndromes; MTC, medullary thyroid cancer; P, phosphorylation; PTC, papillary thyroid cancer; RET, rearranged during transfection.

1. Mulligan LM. *Front Physiol*. 2019;9:1873; 2. Santoro M, et al. *Genes*. 2020;11:424; 3. Vanden Borre P, et al. *Oncologist*. 2017;22:255–63; 4. Prete FP, et al. *Br J Surg*. 2018;105:1319–27; 5. Kohno T, et al. *Cancer Sci*. 2013;104:1396–400.

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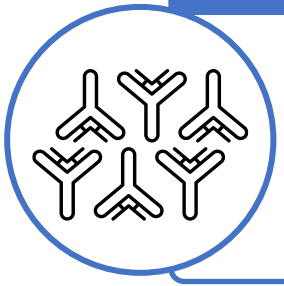
Detection of RET alterations (1/2)



Immunohistochemistry[1]

- Diagnostic aid that detects overexpression of RET protein
- Not suitable for screening due to issues related to reliability and accuracy

FISH[1,2]

- Well-established method for detecting RET fusions
- Difficult to interpret and has low specificity
- Not suitable for multiplex screening

PCR-based techniques[1]

DNA based

- Suitable for known mutations in familial MTC
- Can screen for hotspot mutations; limited by number of primers used
- Not suitable for detecting fusions

RNA based

- Suitable for detecting fusions provided the primer is present
- Detection of unknown fusion partners depends on expression level and is therefore unreliable

FISH, fluorescence *in situ* hybridization; MTC, medullary thyroid cancer; PCR, polymerase chain reaction; RET, rearranged during transfection.

1. Belli C, et al. *Ann Oncol.* 2021;32:337–50; 2. Penault-Llorca F, et al. *J Clin Pathol*. 2019;72:460–7.

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Detection of RET alterations (2/2)

NGS assays[1]

DNA based

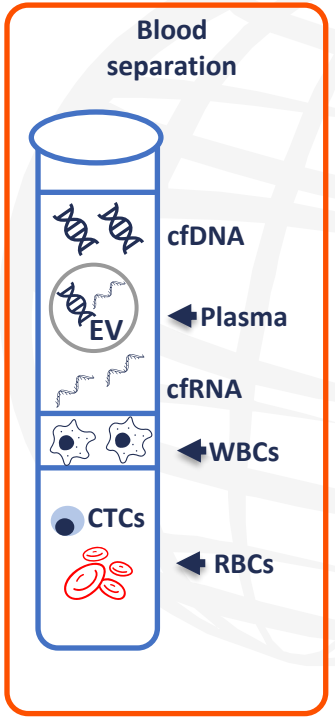
- High sensitivity, allowing detection of low-variant allele frequencies
- Multiplex possible – reduces the amount of tissue required

RNA based

- Removes the challenge of intron coverage
- Determines whether a RET fusion is in frame
- Quality assessment of RNA is necessary to ensure accuracy

Liquid biopsies[1,2]

- Testing of nucleic acids isolated from biological fluids (e.g. blood)
- Suitable for patients with limited or no tumor tissue available
- Minimally invasive
- Highly sensitive with NGS
- Compatible with monitoring during follow-up
- Limited quantity of cfDNA and cfRNA in plasma may mean additional testing is required



cfDNA, cell-free DNA; cfRNA, cell-free RNA; CTC, circulating tumor cell; EV, extracellular vesicles; NGS, next-generation sequencing; RBC, red blood cells; WBC, white blood cells.

1. Belli C, et al. *Ann Oncol*. 2021;32:337–50; 2. Romano C, et al. *Int J Mol Sci*. 2021;22:7707.

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Treatment of genetically altered thyroid cancer

Advanced or metastatic thyroid cancer requiring systemic therapy[1–6]

Tumor molecular testing

RET mutation/RET fusion +ve

Pralsetinib[1,7]

RET receptor TKI

- FDA approval: 2020
- **ORR:** *RET*-mutant MTC, 60–~70%; RET fusion +ve TC, ~90%
- **12-mo PFS rate**: 75–~80%

Selpercatinib[2,8]

RET receptor TKI

- FDA approval: 2020
- **ORR:** *RET*-mutant MTC, ~70%; RET fusion +ve TC, ~80%
- **12-mo PFS rate:** RET-mutant MTC, ~80–90%; RET fusion +ve TC, ~70%

Safety: Both well tolerated with low rates of discontinuation[1,3]

Other common alterations[9]

***NTRK* fusion +ve**[3–5]

- Entrectinib
- Larotrectinib
- Selitrectinib – enroll in an ongoing clinical trial

***BRAF V600E* mutation**[6]

- Dabrafenib + trametinib

FDA, US Food and Drug Administration; MTC, medullary thyroid cancer; mo, month; NTRK, neurotrophic tyrosine receptor kinase; ORR, overall response rate; PFS, progression-free survival; RET, rearranged during transfection; TC, thyroid cancer; TKI, tyrosine kinase inhibitor.

1. FDA. 2020. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pralsetinib-lung-cancer-ret-gene-fusions (accessed 11 January 2022); 2. FDA. 2020. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-selpercatinib-lung-and-thyroid-cancers-ret-gene-mutations-or-fusions (accessed 11 January 2022); 3. Rozlytrek (entrectinib) prescribing information. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212725s005lbl.pdf (accessed 09 February 2022); 4. Vitrakvi (larotrectinib) prescribing information. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/210861s006lbl.pdf (accessed 09 February 2022); 5. ClinicalTrials.gov. NCT03215511. Available at: https://www.clinicaltrials.gov/ct2/show/NCT03215511 (accessed 10 January 2022); 6. Mekinist (trametinib) prescribing information. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/204114s020lbl.pdf (accessed 09 February 2022); 7. Subbiah V, et al. *Lancet Diabetes Endocrinol*. 2021;9:491–501; 8. Sherman EJ, et al. *J Clin Oncol*. 2021;39(Suppl. 15):6073; 9. Prete A, et al. *Front Endocrinol*. 2020;11:102.

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The promise of targeted therapies for RET-altered thyroid cancers: What do the latest clinical data show?

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Trials of the RET inhibitor pralsetinib in patients with advanced or metastatic thyroid cancer

Ongoing — **ARROW**[1,2]

Phase I/II trial of pralsetinib in RET-altered solid tumors

RET-mutant MTC and RET fusion +ve TC
≥18 years; unresectable, locally advanced or metastatic tumors; PS 0–2

- RET-mutant MTC (prior tx cabo/vande) **n=61**
- RET-mutant MTC (no prior systemic tx) **n=23**
- RET fusion +ve TC (all prior systemic tx) **n=11**

Efficacy phase – pralsetinib 400 mg PO QD (28-day cycles) until disease progression, intolerance, withdrawal of consent, or investigator decision

Outcomes
Primary: ORR
Secondary: DoR, CBR, DCR, PFS, OS

Not yet recruiting — **AcceleRET-MTC**[3]

Phase III trial of pralsetinib vs SOC for RET-mutant MTC

RET-mutant MTC (no prior systemic tx)
≥12 years; unresectable, locally advanced or metastatic tumors; PS 0–2

- **Arm A:** Pralsetinib 400 mg PO QD (28-d cycles)
- **Arm B: Investigator's choice** Cabo 140 mg PO QD or Vande 300 mg PO QD (both 28-d cycles)

Outcomes
Primary: PFS
Secondary: TTF, ORR, OS, safety, DoR, DCR, CBR, time to deterioration, QoL, capsule acceptability

Cabo, cabozantinib; CBR, clinical benefit rate; DCR, disease control rate; DoR, duration of response; MTC, medullary thyroid cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, orally; PS, performance status; QD, once daily; QoL, quality of life; RET, rearranged during transfection; SOC, standard of care; TC, thyroid cancer; TTF, time to treatment failure; tx, treatment; vande, vandetanib.

1. Subbiah V, et al. *Lancet Diabetes Endocrinol*. 2021;9:491–501; 2. ClinicalTrials.gov. NCT03037385. Available at: https://clinicaltrials.gov/ct2/show/NCT03037385 (accessed 08 December 2021); 3. ClinicalTrials.gov. NCT04760288. Available at: https://clinicaltrials.gov/ct2/show/NCT04760288 (accessed 08 December 2021).

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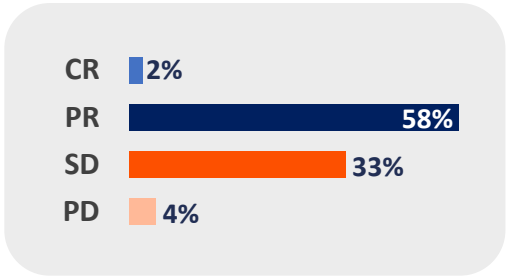
ARROW trial: Overall response rate[1,2]

RET-mutant MTC
Prior systemic tx

Median follow-up 11 months

ORR 60%

n/N=33/55

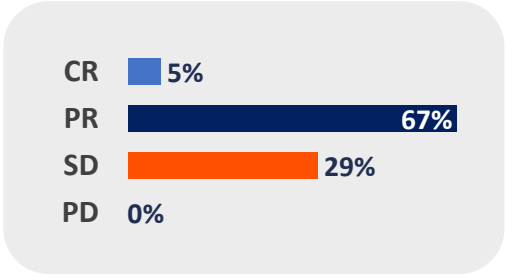


RET-mutant MTC
No prior systemic tx

Median follow-up 11 months

ORR 71%

n/N=15/21

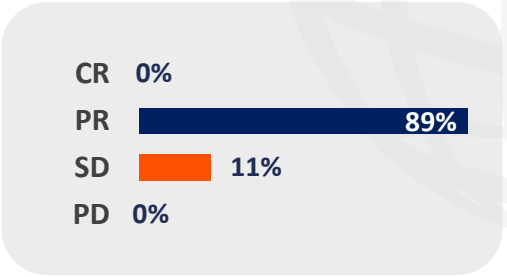


RET fusion +ve TC

Median follow-up 10 months

ORR 89%

n/N=8/9



CR, complete response; MTC, medullary thyroid cancer; ORR, overall response rate; PD, progressive disease; PR, partial response; RET, rearranged during transfection; SD, stable disease; TC, thyroid cancer; tx, treatment.

1. Subbiah V, et al. *Lancet Diabetes Endocrinol*. 2021;9:491–501; 2. ClinicalTrials.gov. NCT03037385. Available at: https://clinicaltrials.gov/ct2/show/NCT03037385 (accessed 08 December 2021).

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ARROW trial: Duration of response[1,2]

	RET-mutant MTC Prior systemic tx	RET-mutant MTC No prior systemic tx	RET fusion +ve TC
	Median follow-up 11 months	**Median follow-up** 11 months	**Median follow-up** 10 months
Median time to first response (months)	3.7	5.6	1.9
Median duration of response (95% CI)	NR (15.1–NE)	NR (NE–NE)	NR (NE–NE)
Probability of ongoing response, 12 mo.	92%	84%	86%



CI, confidence interval; MTC, medullary thyroid cancer; NE, not estimable; NR, not reached; RET, rearranged during transfection; TC, thyroid cancer; tx, treatment.

1. Subbiah V, et al. *Lancet Diabetes Endocrinol*. 2021;9: 491–501; 2. ClinicalTrials.gov. NCT03037385. Available at: https://clinicaltrials.gov/ct2/show/NCT03037385 (accessed 08 December 2021).

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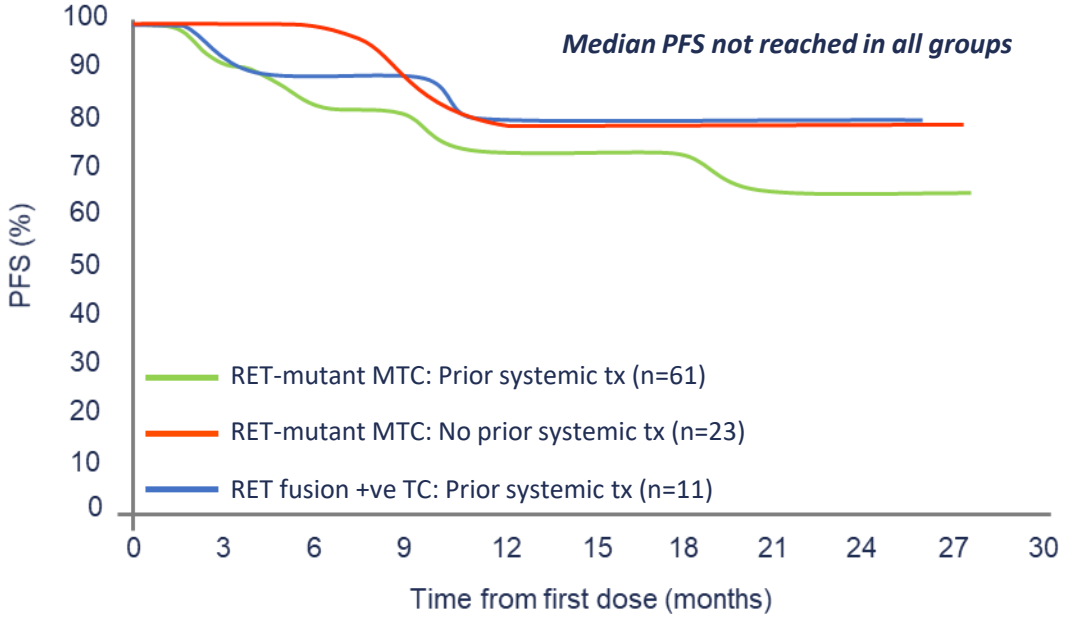
ARROW trial: Progression-free survival[1,2]

PFS in patients with RET-mutant MTC and RET fusion +ve TC



12-month PFS rate

Median follow-up 15 months

75%

Median follow-up 15 months

81%

Median follow-up 13 months

81%

MTC, medullary thyroid cancer; PFS, progression-free survival; RET, rearranged during transfection; TC, thyroid cancer; tx, treatment.

1. Subbiah V, et al. *Lancet Diabetes Endocrinol*. 2021;9:491–501; 2. ClinicalTrials.gov. NCT03037385. Available at: https://clinicaltrials.gov/ct2/show/NCT03037385 (accessed 08 December 2021).

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Trials of the RET inhibitor selpercatinib in patients with advanced or metastatic thyroid cancer

Ongoing **LIBRETTO-001**

Phase I/II study of selpercatinib in RET fusion +ve solid tumors[1–4]

RET-mutant MTC and RET fusion +ve TC

≥12 years; unresectable, locally advanced or metastatic tumors; PS 0–2

- RET-mutant MTC (prior tx cabo/vande) **n=143**
- RET-mutant MTC (no prior systemic tx) **n=112**
- RET fusion +ve TC (prior systemic tx) **n=22**
- RET fusion +ve TC (no prior systemic tx) **n=12**

Efficacy phase – selpercatinib 160 mg twice daily (28-day cycles) until disease progression, death, unacceptable toxic effects, or withdrawal of consent

Outcomes

Primary: ORR

Secondary: DoR, PFS, CBR, safety

Recruiting **LIBRETTO-531**

Phase III trial of selpercatinib vs SOC for RET-mutant MTC[5]

RET-mutant MTC (no prior systemic tx)

≥12 years; unresectable, locally advanced or metastatic tumors; PS 0–2

- **Arm A:** Selpercatinib PO
- **Arm B: Investigator's choice** Cabo PO or Vande PO

Outcomes

Primary: PFS

Secondary: TFFS, ORR, OS, DoR, PFS2 by investigator, safety

AE, adverse event; cabo, cabozantinib; CBR, clinical benefit rate; DoR, duration of response; MTC, medullary thyroid cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival, PFS2, time to second objective disease progression; PO, orally; PS, performance status; RET, rearranged during transfection; SOC, standard of care; TC, thyroid cancer; TFFS, treatment failure-free survival; tx, treatment; vande, vandetanib.

1. Wirth JL, et al. *N Engl J Med.* 2020;383:825–35; 2. Sherman EJ, et al. *J Clin Oncol.* 2021;39(Suppl. 15):6073; 3. ClinicalTrials.gov. NCT03157128; Available at: https://clinicaltrials.gov/ct2/show/NCT03157128 (accessed 14 December 2021); 4. Sherman EJ, et al. Presented at: ASCO, Virtual Online, 04–08 June 2020. Abstr #6073; 5. ClinicalTrials.gov. NCT04211337. Available at: https://clinicaltrials.gov/ct2/show/NCT04211337 (accessed 19 January 2022).

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LIBRETTO-001 trial: ORR and DoR

RET-mutant MTC[1]

Prior systemic tx	No prior systemic tx
Median follow-up 17 & 10 months	**Median follow-up** 9 months
PAS (n=55) & IAS (n=143)	**(n=112)**
ORR 69%	**ORR 71%**
DoR NE	**DoR 22 mo.**

RET fusion +ve TC[1,2]

Prior systemic tx	No prior systemic tx
Median follow-up 20 months	**Median follow-up** 9 months
(n=22)	**(n=12)**
ORR 77%	**ORR 92%**
DoR 18 mo.	**DoR NE**

- **PAS:** First 55 enrolled patients
- **IAS:** MTC patients previously treated with cabo/vande

DoR figures are median.
Cabo, cabozantinib; DoR, duration of response; IAS, integrated analysis set; mo, months; MTC, medullary thyroid cancer; NE, not estimable; ORR, overall response rate; PAS, primary analysis set; RET, rearranged during transfection; TC, thyroid cancer; tx, treatment; vande, vandetanib.

1. Sherman EJ, et al. *J Clin Oncol.* 2021;39(Suppl. 15):6073; 2. Sherman EJ, et al. Presented at: ASCO, Virtual Online, 04–08 June 2020. Abstr #6073.

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LIBRETTO-001 trial: Progression-free survival

RET-mutant MTC[1]

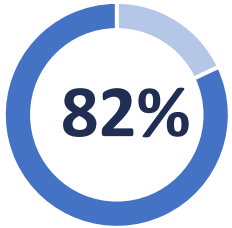
Prior systemic tx

Median follow-up
17 & 10 months

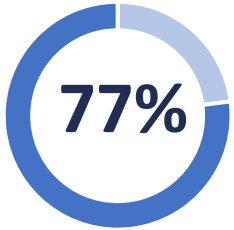
PAS (n=55) & IAS (n=143)

12-month PFS rate

PAS



IAS

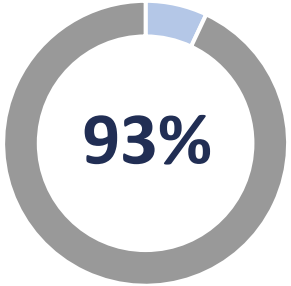


No prior systemic tx

Median follow-up 9 months

(n=112)

12-month PFS rate



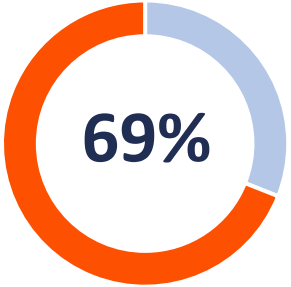
RET fusion +ve TC[1,2]

Prior systemic tx

Median follow-up 20 months

(n=22)

12-month PFS rate



No prior systemic tx

Median follow-up 9 months

(n=12)

12-month PFS rate

IAS, integrated analysis set; MTC, medullary thyroid cancer; PAS, primary analysis set; PFS, progression-free survival; RET, rearranged during transfection; TC, thyroid cancer; tx, treatment.

1. Sherman EJ, et al. *J Clin Oncol.* 2021;39(Suppl. 15):6073; 2. Sherman EJ, et al. Presented at: ASCO, Virtual Online, 04–08 June 2020.

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ARROW and LIBRETTO-001: Safety

ARROW – Pralsetinib[1]

- **Most common TRAEs (≥25%):** increased AST, decreased WBC count, neutropenia, hypertension, anemia, constipation, asthenia
- **Most common (≥10%) Gr 3+ TEAEs**: hypertension (17%), neutropenia (13%), lymphopenia (12%), anemia (10%)
- **Serious TRAEs** occurred in 15% of pts
  - 4% discontinued due to TRAEs
  - One (1%) death* due to a TRAE

LIBRETTO-001 – Selpercatinib[2]

- **Most common TEAEs (≥25%):**
  - Both MTC and TC pts: dry mouth, diarrhea, hypertension, fatigue, constipation
  - MTC pts: increased ALT/AST, peripheral edema, headache
  - TC pts: nausea
- Majority of TEAEs were **low grade**
- **Discontinuations** due to TRAEs
  - 2% of MTC pts
  - No TC pts

Safety population: ARROW, n=142; LIBRETTO-001, MTC n=315, TC n=42. *This patient was diagnosed with interstitial pneumonitis on day 44 and later discontinued pralsetinib after two cycles owing to treatment-related *Pneumocystis jirovecii* pneumonia.

ALT, alanine transaminase; AST, aspartate aminotransferase; Gr, grade; MTC, medullary thyroid cancer; pts, patients; TC, thyroid cancer; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; WBC, white blood cell.

1. Subbiah V, et al. *Lancet Diabetes Endocrinol.* 2021;9:491–501; 2. Sherman EJ, et al. *J Clin Oncol.* 2021;39(Suppl. 15):6073.

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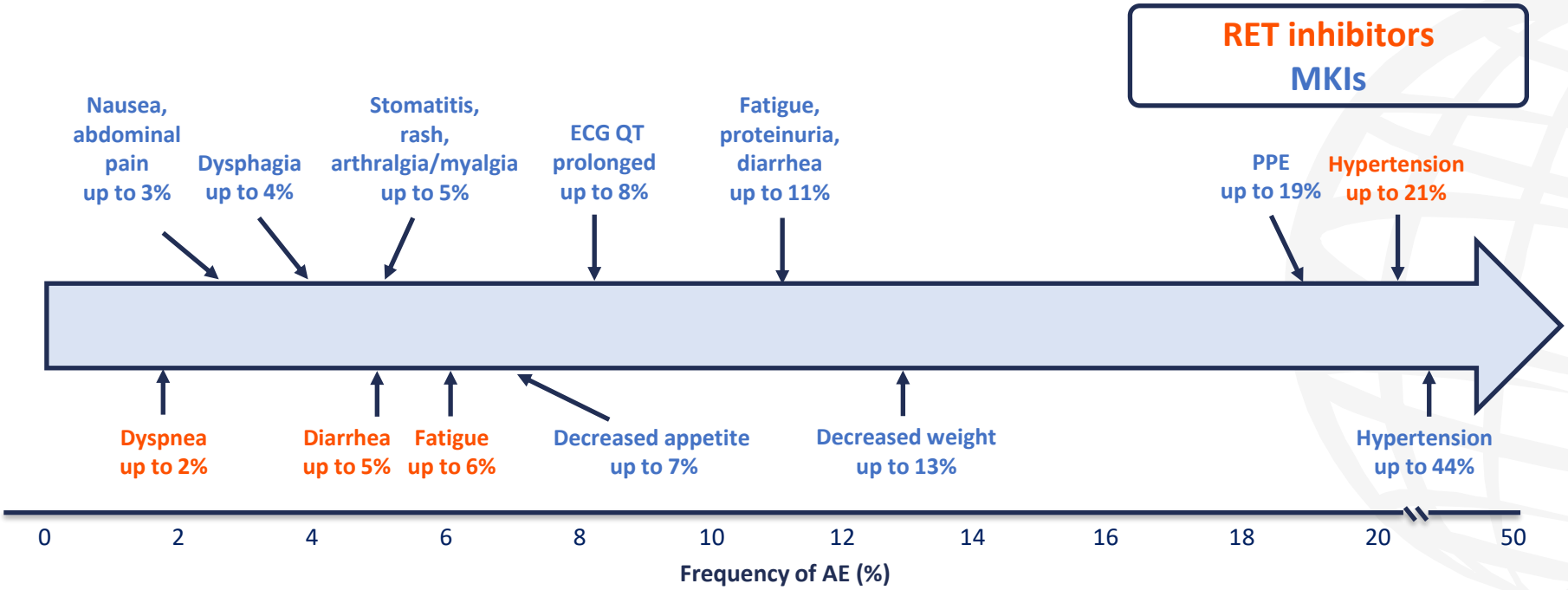
Grade 3+ AEs* with RET inhibitors and MKIs[1–7]



*In ≥2% of patients. Laboratory abnormalities not included.

AE, adverse event; ECG, electrocardiogram; MKI, multikinase inhibitor; PPE, palmar–plantar erythrodysesthesia; RET, rearranged during transfection.

1. Caprelsa (vandetanib) prescribing information. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022405s017lbl.pdf (accessed 09 February 2022); 2. Cabometyx (cabozantinib) prescribing information. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208692s012lbl.pdf (accessed 09 February 2022); 3. Cometriq (cabozantinib) prescribing information. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/203756s009lbl.pdf (accessed 09 February 2022); 4. Nexavar (sorafenib) prescribing information. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021923s024lblrpl.pdf (accessed 09 February 2022); 5. Lenvima (lenvatinib) prescribing information. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/206947s011lbl.pdf (accessed 09 February 2022); 6. Gavreto (pralsetinib) prescribing information. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213721s004lbl.pdf (accessed 09 February 2022); 7. Retevmo (selpercatinib) prescribing information. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213246s002lbl.pdf (accessed 09 February 2022).

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Practical implications: Toxicity management

Both agents[1–3]

- **Hypertension:** Antihypertensives for BP >140/90 mmHg
  - Withhold for persistent Gr 3*; discontinue for Gr 4
- **Hemorrhagic events:** Withhold for Gr 3; discontinue for life-threatening events
- **Hepatotoxicity:** Withhold and monitor AST/ALT weekly for Gr 3+ AE*; discontinue upon recurrence
- **Diarrhea:** Lifestyle/dietary changes; medication
- **Fatigue:** Treat underlying causes
- **Other AEs:** Withhold until improvement for Gr 3+ AEs*; discontinue for recurrent Gr 4 AEs

Pralsetinib[1]

- **ILD/pneumonitis:** Withhold for Gr 1–2*; discontinue for Gr 3+ or if recurrent

Selpercatinib[2]

- **QT interval prolongation:** Withhold for Gr 3*; discontinue for Gr 4
- **Hypersensitivity:** Withhold until resolution for all Gr AEs†; initiate corticosteroids

*Resume at a reduced dose; †Resume at reduced dose by three dose levels.
AE, adverse event; ALT, alanine transaminase; AST, aspartate aminotransferase; BP, blood pressure; Gr, grade, ILD, interstitial lung disease.
1. Gavreto (pralsetinib) prescribing information. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213721s004lbl.pdf (accessed 09 February 2022); 2. Retevmo (selpercatinib) prescribing information. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213246s002lbl.pdf (accessed 09 February 2022); 3. Cabanillas ME, et al. *Endocr Rev*. 2019;40:1573–604.

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