Practical considerations for personalized medicine in thyroid cancer: Which therapies are suited to particular patient profiles?

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Principles of personalized medicine in thyroid cancer: What key genomic alterations can be targeted?

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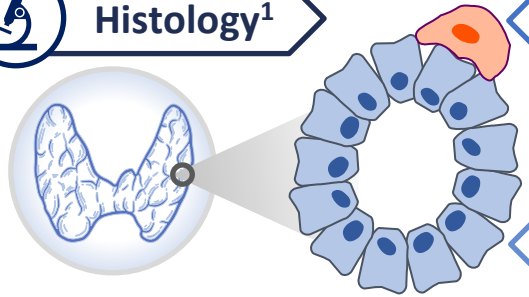
What do we currently know about the molecular pathology of thyroid cancer?

Pathology of thyroid cancers

Histology[1]



Parafollicular 'C' cell

Neuroendocrine origin

- **Medullary TC** — 5–10% cases

Activating *RET* mutations underly hereditary disease and occur in 40–50% sporadic cases[2]

Follicular cell

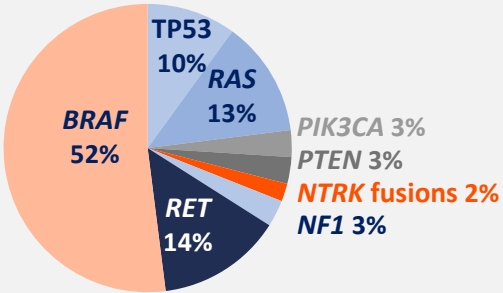
Epithelial origin

- **Undifferentiated** → **Anaplastic TC** — <2% cases
- **Differentiated TC**
  - **Papillary TC** — 70–80% cases
  - **Follicular TC** — 10–15% cases
  - **Other thyroid cancers** — 3% cases

Molecular pathology[2,3]

Genetic lesions*

- Point mutations
- Translocations
- Amplifications
- Deletions



*Top eight most frequent mutations in thyroid cancer (COSMIC database).[2]

TC, thyroid cancer.

1. Pstrąg N, et al. *Mol Cancer*. 2018;17:116; 2. Okafor C, et al. *Front Endocrinol (Lausanne).* 2021;12:708949; 3. Hofmann MC, et al. *Endocr Relat Cancer*. 2022;29:R173–90.

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How are we using our knowledge of the molecular pathology of thyroid cancer to improve treatment and management options?

Evolving role of molecular pathology in solid tumours

Established role adjunctive to histopathological classification[1]

- Resolving diagnostic uncertainty
- Prognostic/predictive biomarkers
- Actionable therapeutic targets

Emerging primacy of molecular pathology

Tumour-agnostic classification[2,3]

Genomically informed treatment strategy regardless of histology for tumours harbouring requisite biomarker(s) e.g.

- **TMB-H**
  pembrolizumab
- ***NTRK* fusions**
  entrectinib; larotrectinib

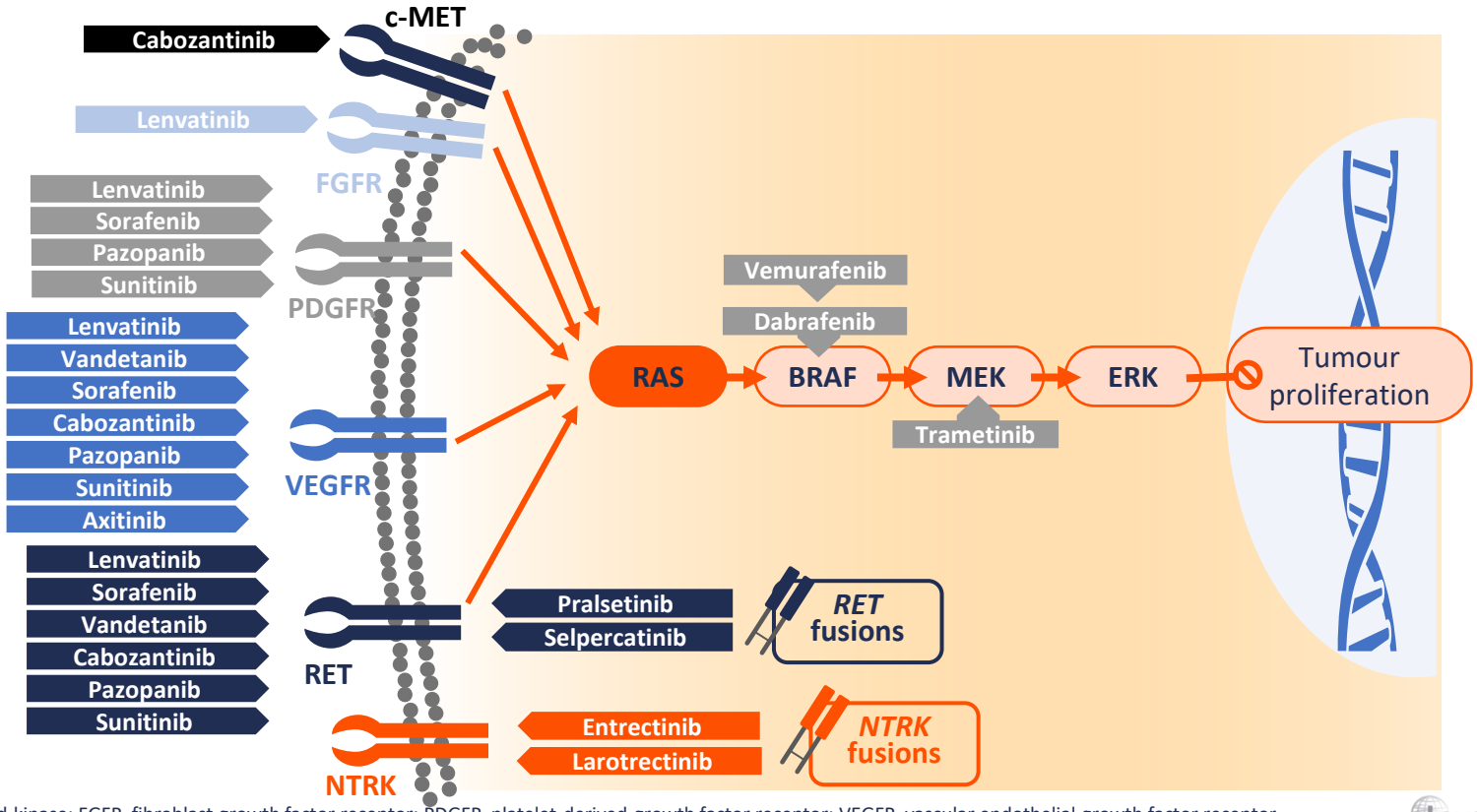
An emerging era of genomically informed precision oncology and personalized medicine in solid tumours (including thyroid cancer), regardless of histological origin

TMB-H, tumour mutational burden high.

1. Sipos JA, Ringel MD. *Best Pract Res Clin Endocrinol Metab.* 2023;37:101680; 2. ESMO OncologyPRO. Available at: https://oncologypro.esmo.org/oncology-in-practice/anti-cancer-agents-and-biological-therapy/targeting-ntrk-gene-fusions/overview-of-cancers-with-ntrk-gene-fusion/precision-medicine/genomic-profiling (accessed 1 September 2023);
3. Alzumaili B, Sadow PM. *Genes (Basel).* 2023;14:1314.

What therapies targeting the molecular pathology of thyroid cancer are currently available?

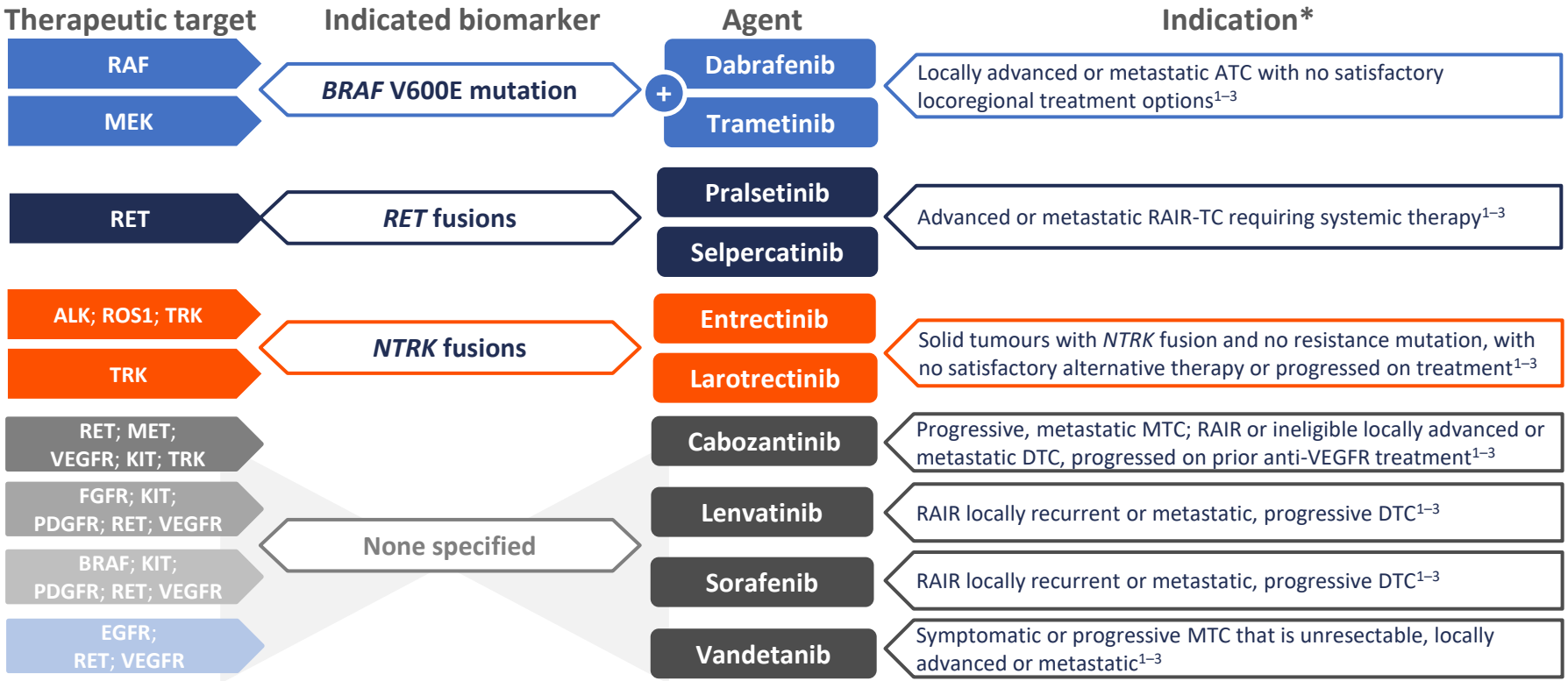
Targeting the molecular pathology of thyroid cancer



ERK, extracellular-regulated kinase; FGFR, fibroblast growth factor receptor; PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor.

Agosto Salgado S, et al. *Am Soc Clin Oncol Educ Book.* 2023;43:e389708.

Approved molecularly targeted therapies and biomarkers



*Correct as of August 2023. ATC, anaplastic TC; DTC, differentiated TC; MTC, medullary TC; PDGFR, platelet-derived growth factor receptor; RAIR, radioactive iodine refractory; TC, thyroid cancer; VEGFR, vascular endothelial growth factor receptor.

1. Sipos JA, Ringel MD. *Best Pract Res Clin Endocrinol Metab.* 2023;37:101680; 2. Agosto Salgado S, et al. *Am Soc Clin Oncol Educ Book.* 2023;43:e389708;
3. FDA. Available at: www.accessdata.fda.gov/scripts/cder/daf/ prescribing information searchable by drug name (accessed 25 August 2023).

How do we test for genetic biomarkers in thyroid cancer?

Considerations for genetic testing lesions

Different detection methods identify different genetic lesions[2,3]

NGS	Somatic mutations
Sanger sequencing	Single nucleotide variants
PCR	Mutations at known gene loci
MLPA	Single nucleotide (point) mutations
FISH	Genetic aberrations, e.g. fusion genes
IHC	Protein-level confirmation

FISH, fluorescence in situ hybridization; FNA, fine needle aspiration; IHC, immunohistochemistry; MLPA, multiplex ligation-dependent probe amplification; NGS, next-generation sequencing; PCR, polymerase chain reaction.

1. Marotta V, et al. *Cancers (Basel).* 2022;14:5370; 2. Agosto Salgado S, et al. *Am Soc Clin Oncol Educ Book.* 2023;43:e389708;
3. THANC Guide. Available at https://thancguide.org/cancer-basics/diagnosis/genetic-molecular-testing/thyroid/ (accessed 30 August 2023).

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What are the key considerations when testing for specific genetic alterations to guide treatment decisions in thyroid cancer?

Guidelines on biomarker testing for molecular therapy

NGS is the preferred method for genetic evaluation given the potential for actionable therapeutic targets in TC[1–3]

Biomarker[2]	Preferred detection method[2]	Targeted therapy[2]	Additional considerations
***BRAF* mutations**	**NGS or SS**	**BRAF inhibitors** e.g. dabrafenib	**ATC:** Initial rapid *BRAF V600E* IHC evaluation is recommended while awaiting NGS results to support early treatment where appropriate[1]
***RET* mutations or fusions**	**NGS, SS or allelic-specific RT-PCR**	**RET inhibitors** e.g. pralsetinib; selpercatinib	**MTC:** *RET* mutation testing should be strongly considered[2]
***NTRK* fusions**	**NGS or SS**	**NTRK inhibitors** e.g. entrectinib; larotrectinib	*NTRK* fusion testing should be considered before or during the standard treatment of advanced solid tumours (including TC)[3]

RAIR-TC

Perform comprehensive molecular testing (on historical specimens or newly biopsied lesions) prior to initiation of a systemic targeted therapy[4]

ATC, anaplastic TC; IHC, immunohistochemistry; MTC, medullary TC; NGS, next-generation sequencing; RAIR, radioactive iodine refractory; SS, Sanger sequencing; TC, thyroid cancer.

1. Agosto Salgado S, et al. *Am Soc Clin Oncol Educ Book.* 2023;43:e389708; 2. Filetti S, et al. *Ann Oncol.* 2022;33:674; 3. Yoshino T, et al. *Ann Oncol.* 2020;31:861–72;
4. Sipos JA, Ringel MD. *Best Pract Res Clin Endocrinol Metab.* 2023;37:101680.

What is the latest clinical evidence for personalized, targeted treatments for thyroid cancer?

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What are the limitations of standard systemic treatment of thyroid cancer?

Standard systemic therapies: Remaining unmet needs

Challenges with established MKIs[1–5]

Timing
- Therapies are not curative
- Continuous therapy required to maintain response
- Limited duration of treatment effect/benefit

Selection
- Lack of companion diagnostics/indicated biomarkers to guide treatment selection and sequencing (for some agents)
- Lack of target oncogenic driver selectivity and specificity

Toxicities
- Poor pharmacokinetics (drug accumulation; long half-life)
- Off-target effects and toxicities can lead to dose interruptions, reductions or treatment discontinuation

Resistance
- Challenge of tumour heterogeneity
- Inherent resistance mutations may limit treatment options
- Acquired resistance emerging on treatment

Newer TKIs with greater specificity for oncogenic lesion and with companion biomarkers have been developed to optimize systemic treatments in thyroid cancer[6]

MKI, multikinase inhibitor; TKI, tyrosine kinase inhibitor.

1. Cabanillas ME, et al. *Endocr Rev*. 2019;40:1573–1604; 2. Lorusso L, et al. *Int J Mol Sci.* 2021;22:3117; 3. Efstathiadou ZA, et al. *Eur Thyroid J.* 2021;10:125–39;
4. Sipos JA, Ringel MD. *Best Pract Res Clin Endocrinol Metab.* 2023;37:101680; 5. Wirth LJ, et al. *Future Oncol.* 2022;18:3143–50; 6. Masaki C, et al. *Drugs Real World Outcomes.* 2023;10:145–58.

What are we learning from the latest clinical data about new and emerging treatment options for thyroid cancer with *NTRK* gene fusions?

Clinical evidence: *NTRK*-targeting agents

Larotrectinib[1]

100 mg BD

Phase I/II trials*

Basket trial (NCT02576431)
NAVIGATE (NCT02122913)
SCOUT (NCT02637687)

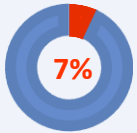
Integrated long-term analysis in *NTRK*-fp TC

	Full efficacy set	DTC	ATC
	N=30	n=23	n=7
ORR	**63%** (95% CI 44–80)	**78%** (95% CI 56–93)	**14%** (95% CI 0–58)

Safety N=30

Most TRAEs were grade 1/2

Grade 3 TRAEs



- Anaemia
- Lymphocytopenia

Discontinuations due to TRAEs

0

Entrectinib[2,3]

≥600 mg QD†

Phase I/II trials

STARTRK-1 (NCT02097810)
STARTRK-2 (NCT02568267)
ALKA-372-001 (EudraCT 2012-000148-88)

Integrated analysis in *NTRK*-fp solid tumours

	All 17 solid tumour types	Thyroid cancer
	N=150	n=16
ORR	**61%** (95% CI 53.1–69.2)	**63%** (95% CI not specified)

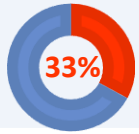
Safety N=235*

Most TRAEs were grade 1/2

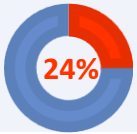
- Dysgeusia 37%
- Diarrhoea 30%
- Weight gain 29%

TRAEs leading to:

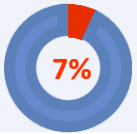
Interruption



Reduction



Discontinuation



*Safety analysis also included TAPISTRY (NCT04589845) participants. Data cut-off: 20 July 2022. †Patients received at least the phase II recommended dose of 600 mg once daily.
AE, adverse event; ATC, anaplastic TC; BD, twice daily; CI, confidence interval; DTC, differentiated TC; NTRK-fp, NTRK-fusion positive; ORR, overall response rate; QD, once daily; TC, thyroid cancer; TRAE, treatment-related AE.

1. Cabanillas ME, et al. *J Clin Oncol*. 2023;41(Suppl. 16):6091; 2. Krzakowski MJ, et al. *J Clin Oncol.* 2022;40(Suppl. 16):3099; 3. Doebele RC, et al. *Lancet Oncol.* 2020;21:271–82.

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What are we learning from the latest clinical data about new and emerging treatment options for *RET*-altered thyroid cancer?

Clinical evidence: *RET*-targeting agents

Selpercatinib[1–3]

160 mg BD

Phase II LIBRETTO-001[1]

(NCT03157128)

		ORR	mPFS
RET-mutant MTC	Prior CAB/VAN n=55	69% (95% CI 55–81)	NE (95% CI 24.4–NE)
	TKI-naive n=88	73% (95% CI 62–82)	23.6 months (95% CI NE–NE)
RET-fp TC	Prev. treated n=19	79% (95% CI 54–94)	20.1 months (95% CI 9.4–NE)

Safety N=531

Dose reduction: 30%

Discontinued treatment: 2%

Phase III LIBRETTO-531[2,3]

(NCT04211337; data anticipated at ESMO 2023)

RET-altered MTC

- Met primary end point (PFS by BICR)
- Interim safety findings consistent with prior LIBRETTO-001 data

Pralsetinib[4]

400 mg QD

Phase I/II ARROW[4]

(NCT03037385)

Data cut-off: 18 Oct 2021

		ORR	mPFS
RET-fp TC	Prev. treated n=25	84% (95% CI 63.9–95.5)	25.4 months (95% CI 17–NE)

Safety N=175

sTRAEs: 17%

Dose reduction: 53%

Discontinued treatment: 6%

BD, twice daily; BICR, blinded independent central review; CAB, cabozantinib; CI, confidence interval; ESMO, European Society for Medical Oncology; fp, fusion positive; m, median; MTC, medullary TC; NE, not estimable; ORR, objective response rate; PFS, progression-free survival; QD, once daily; Prev., previously; sTRAE, serious treatment-related adverse event; TC, thyroid cancer; TKI, tyrosine kinase inhibitor; VAN, vandetanib.

1. Wirth LJ, et al. *N Engl J Med.* 2020;383:825–35; 2. Wirth LJ, et al. *Future Oncol.* 2022;18:3143–50; 3. Tucker N. Available at: www.targetedonc.com/view/selpercatinib-extends-pfs-in-advanced-metastatic-ret-mutant-mtc (accessed 21 September 2023); 4. Hu MI, et al. *Ann Oncol.* 2022;33(Suppl. 7):S1298–9.

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What are we learning from the latest clinical data about new and emerging treatment options for thyroid cancer with *BRAF-V600E* mutations?

Clinical evidence: *BRAF-V600E*-targeting agents

Vemurafenib[1]

960 mg BD

Phase II trial
(NCT01286753)

***BRAF*-mutated RAIR PTC**

	VEGFRi-naive	Prior VEGFRi
	n/N=10/26	n/N=6/22
BOR (PR)	**38.5%** (95% CI 20.2–59.4)	**27.3%** (95% CI 10.7–50.2)

Single-agent vemurafenib: Most frequent AEs — **Rash, fatigue, weight loss, dysgeusia and alopecia**

Dabrafenib[2,3]

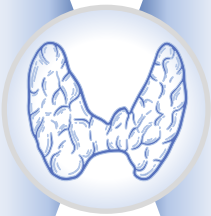
150 mg BD

Phase II trial
(NCT01723202)

***BRAF*-mutated RAIR DTC**

	Dabrafenib	Dabrafenib + trametinib
	n/N=9/26	n/N=8/27
ORR*	**35%** (95% CI 17–56)	**30%** (95% CI 14–51)

Single-agent dabrafenib: Most frequent TRAEs — **Skin disorders, fever and hyperglycaemia**



Dabrafenib + Trametinib[4]

150 mg BD/2 mg QD

Phase II ROAR
(NCT02034110)

***BRAF-V600E*-mutant advanced rare cancers**

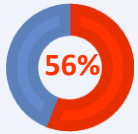
	ATC	BTC	HGG	LGG	ASI	HCL	MM
	n=36	n=43	n=45	n=13	n=3	n=55	n=10
ORR	56%	53%	33%	54%	67%	89%	50%

Safety ATC cohort n=36

Most frequent AEs

- Pyrexia 47%
- Fatigue 36%
- Nausea 33%

SAEs



*ORR by RECIST 1.1 criteria. AE, adverse event; ASI, adenocarcinoma (small intestine); ATC, anaplastic TC; BD, twice daily; BOR, best overall response; BTC, biliary tract cancer; CI, confidence interval; DTC, differentiated TC; HCL, hairy cell leukaemia; HGG, high-grade glioma; LGG, low-grade glioma; MM, multiple myeloma; ORR, objective response rate; PR, partial response; PTC, papillary TC; QD, once daily; RAIR, radioactive iodine-refractory; SAE, serious AE; TC, thyroid cancer; TRAE, treatment-related AE; VEGFRi, vascular endothelial growth factor receptor inhibitor.

1. Brose MS, et al. *Lancet Oncol.* 2016;17:1272–82; 2. Busaidy L, et al. *Thyroid.* 2022;32:1184-92; 3. NCT01723202. Available at: https://clinicaltrials.gov/ct2/show/NCT01723202 (accessed 20 September 2023); 4. Subbiah V, et al. *Nature Med.* 2023;29:1103–12.