Updates in Systemic Therapies for Refractory Thyroid Cancer

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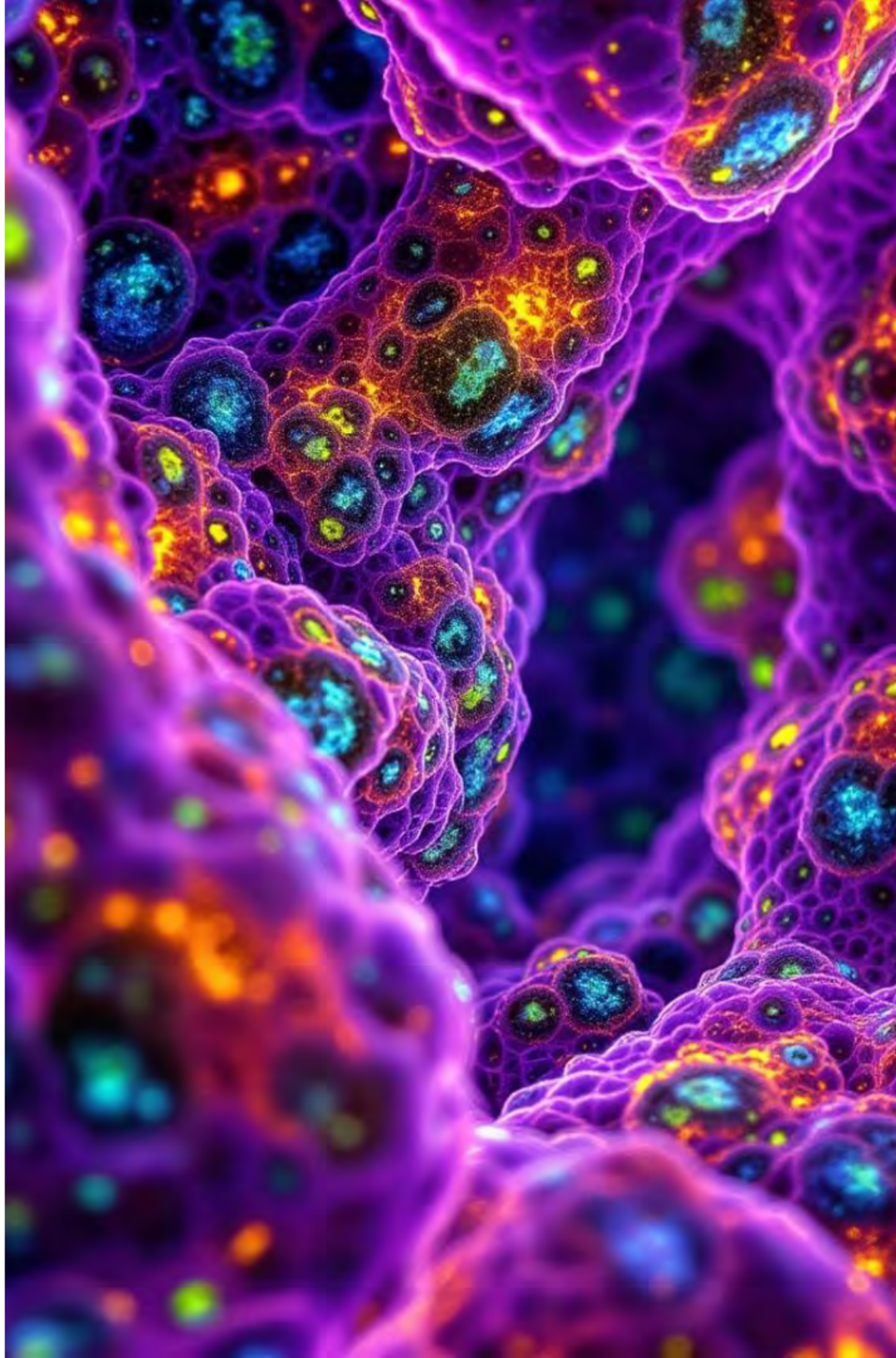
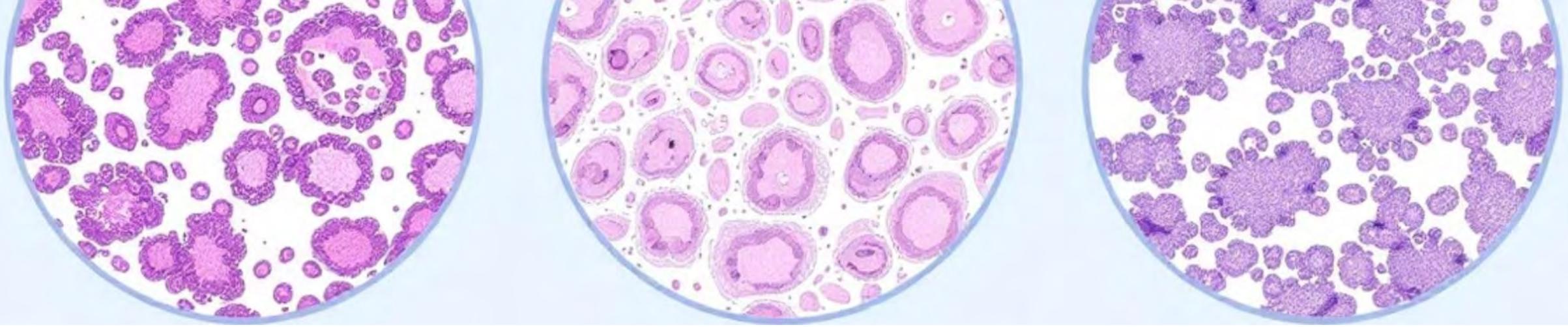


DISCLOSURES

- **EMD Serano: Consulting or Advisory Role**
- **BeiGene: Consulting or Advisory Role**
- **Pfizer: Consulting or Advisory Role**

- **i3 Health and FLASCO have mitigated all relevant financial relationships**



Overview of Thyroid Cancer Subtypes

Differentiated Thyroid Cancer (DTC)

Includes papillary and follicular subtypes. Maintains some normal thyroid tissue functions. Most common form, generally has favorable prognosis.

Medullary Thyroid Cancer (MTC)

Arises from calcitonin-producing C cells. Often associated with RET mutations. Can be sporadic or hereditary.

Anaplastic Thyroid Cancer (ATC)

Highly aggressive undifferentiated form. Poor prognosis with rapid progression. Requires urgent multidisciplinary management.

Common Genomic Abnormalities in Thyroid Cancer

Mutation	DTC (%)	MTC (%)	ATC (%)
BRAF	60%	<1%	20-45%
RET	10%	65-80%	5%
NTRK	5%	<1%	3%
TP53	10%	<1%	70%
RAS	15%	10%	30%

Yamasaki et al. Endocrine 2024 Aug;85(2):766-776.

Systemic Therapies for Refractory DTC

First-Line Approved Agents

- Sorafenib: VEGFR, PDGFR, RET inhibitor
- Lenvatinib: VEGFR, FGFR inhibitor with improved PFS

Second-Line Option

- Cabozantinib: Targets MET, VEGFR2, RET

Mutation-Specific Therapy

- Dabrafenib: For BRAF V600E mutations
- Larotrectinib/Entrectinib: For NTRK gene fusions

Systemic Therapies for Differentiated Thyroid Cancer

Agent	Trial Name	Median PFS	ORR
Sorafenib	DECISION	10.8 months	12.2%
Lenvatinib	SELECT	18.3 months	64.8%
Cabozantinib	COSMIC-311	11.0 months	15%

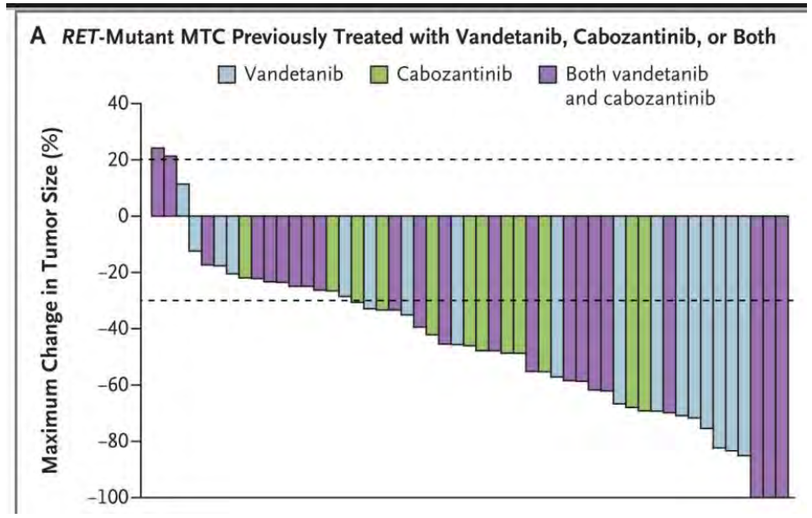
SELECT Trial - N Engl J Med. Schlumberger et al. 2015 Feb 12;372(7):621-30
COSMIC 311 – Cancer. 2022 Dec 15;128(24):4203-4212

Systemic Therapies for Refractory MTC

RET-Specific Inhibitors

These agents directly target RET mutations with higher selectivity and fewer off-target effects.

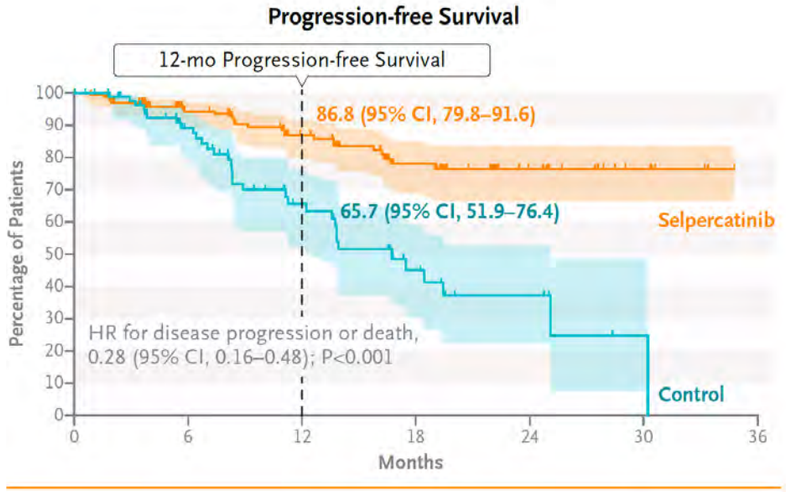
- Selpercatinib (LOXO-292): 69% ORR in RET+ patients
- Pralsetinib (BLU-667): 60% ORR with durable responses



Non-Specific Multikinase Inhibitors

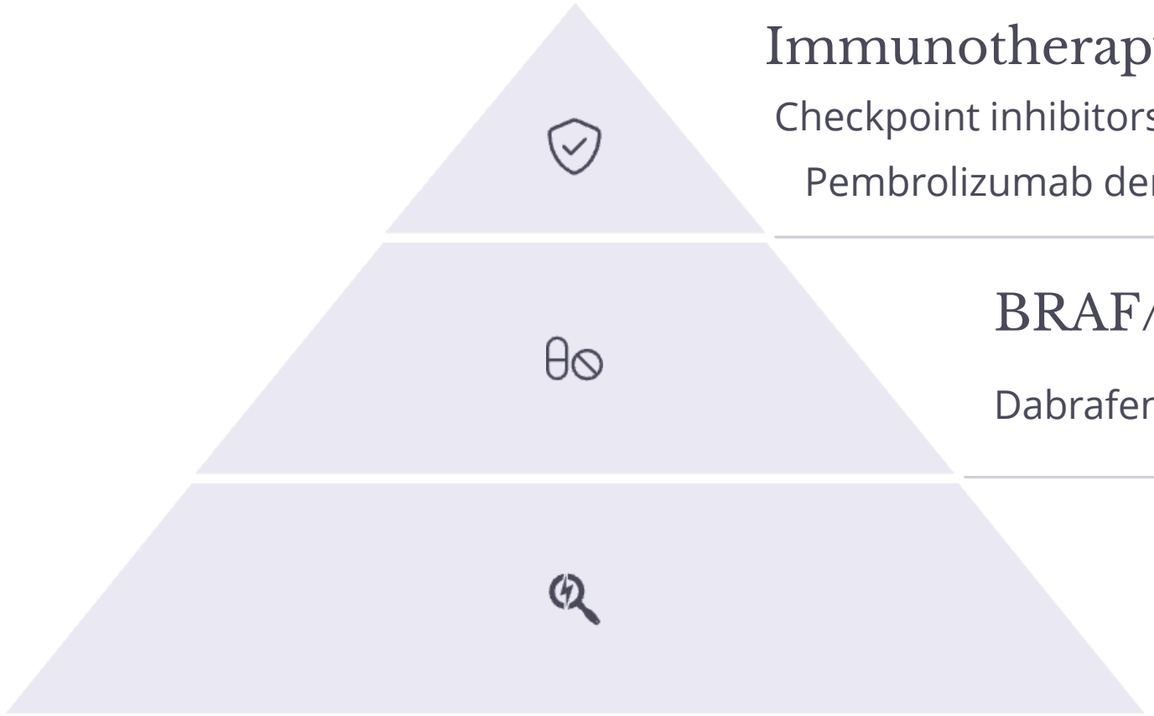
These earlier agents target multiple kinases including RET but with broader toxicity profiles.

- Cabozantinib: Approved for progressive disease
- Vandetanib: Targets RET, VEGFR, EGFR pathways



LIBRETTO-531 – Hadoux et al. Selpercatinib vs Cabo/Vandetanib. N Engl J Med. 2023 Nov 16;389(20):1851-1861

Systemic Therapies for Refractory ATC



Immunotherapy

Checkpoint inhibitors showing promise in ATC:

Pembrolizumab demonstrates 18% ORR, Spartalizumab 19%, mostly in PD-L1+ disease

BRAF/MEK Inhibition

Dabrafenib + trametinib for BRAF+ ATC – FDA approval based on ROAR

Recent Trials

Phase II ATLEP trial Lenvatinib+Pembrolizumab 34.3% (12/35 PR)

Neoadjuvant dabrafenib/trametinib shows 69% response rate.

.Nivolumab ± ipilimumab has shown clinical benefit in selected patients.

ROAR trial – Subbiah. Ann Oncol. 2022 Apr;33(4):406-415.
Phase II ATLEP – ESMO 2022 Volume 33, Supplement 7S1295

Emerging Therapies and Clinical Trials

Novel Targets

ALK, ROS1, and TERT inhibitors in development

Combination Strategies

Immunotherapy + targeted therapy combinations

Drug Delivery

Nanoparticle formulations to enhance efficacy

Innovative Trial Designs

Basket and umbrella trials for rare mutations

Conclusion and Future Directions

Comprehensive Genomic Profiling

Next-generation sequencing is essential for all refractory patients. It enables precision therapy selection based on actionable mutations.

Multimodal Approaches

Combined local and systemic therapies may improve outcomes. Sequencing strategies remain an active area of investigation.

Clinical Trial Enrollment

Patients should be considered for innovative trials. Novel combinations may overcome resistance mechanisms.