TYROSINE KINASE INHIBITORS IN DIFFERENTIATED THYROID CANCER

I. Definition:

- Tyrosine kinases are involved in the MAPK signalling pathway through the phosphorylation/ dephosphorylation of intracellular proteins.
- Tyrosine Kinase inhibitors are Multikinase/ Selective inhibitors that target Tyrosine kinases and their receptor leading to inhibition of signalling pathways leading to thyroid cancer
- It is a type of Targeted therapy for thyroid cancer

II. Indications:

a. ***Advanced or Metastatic, rapidly progressive, Symptomatic, and/or imminently threatening disease not otherwise amenable to local control using other approaches*** **(Standard indication as per guidelines)**

b. ***Neoadjuvant therapy in inoperable locally advanced thyroid cancers*** **(not standard indication yet)**

III. Mechanism of Action:

- Novel, small-molecule protein-kinase inhibitors which are effective against many components of MAPK, PI3K-AKT and other Kinase pathways
- Some are *Multikinase inhibitors*- act on multiple kinases (Eg. Sorafenib, Lenvatinib
- Some are *Selective Kinase inhibitors*- act only on a specific kinase (Eg. Selpercatinib: acts only on RET kinase)

Diagram below

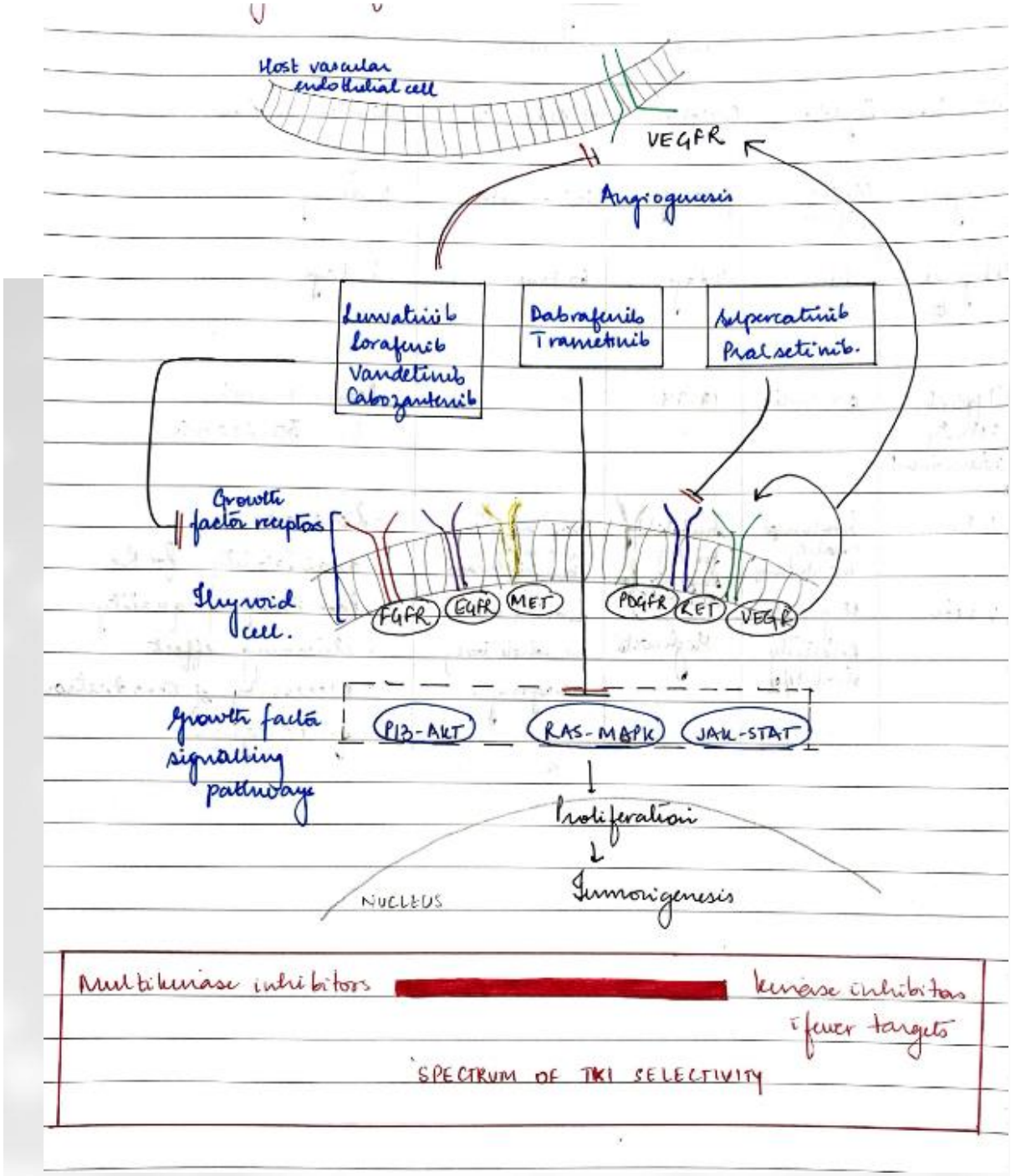


Fig. Mechanism of Action and various targets of Tyrosine Kinase inhibitors

IV. TKIs approved for Thyroid Cancer:

(Immunotherapy, Cancer Vaccines and PRRT mentioned in the diagram are other targeted therapies available for thyroid cancer)

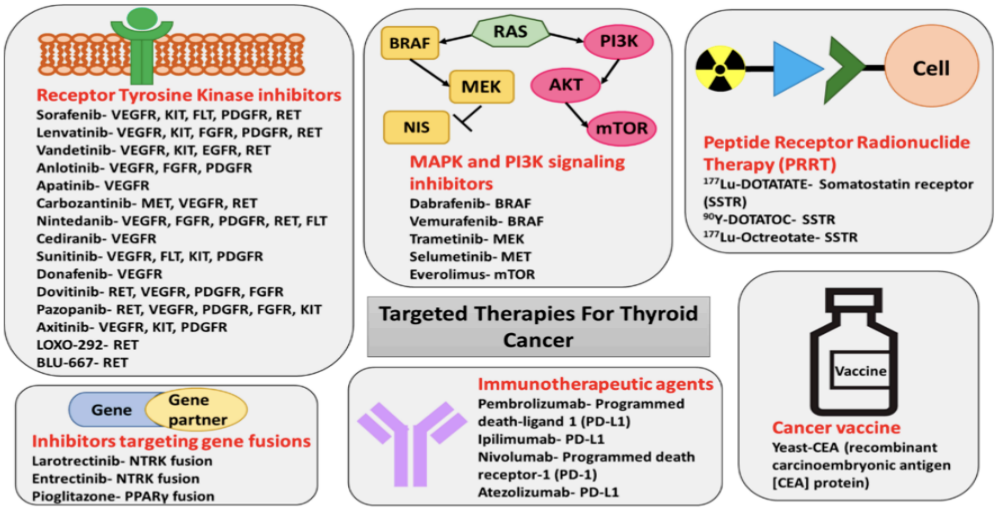


Figure 4. Targeted therapies for the treatment of thyroid cancer. The figure shows inhibitor drug molecules targeting various *RTKs*, components of MAPK and PI3K signaling pathways, and gene fusions in thyroid cancer. The immunotherapeutic agents, PRRT molecules, and a vaccine with the potential for the treatment of thyroid cancer are also included in the figure.

IVa. TKIs for DTC: Approved by FDA, used commonly

- **Sorafenib and Lenvatinib (DECISION trial and SELECT trial)**

	Sorafenib (DECISION) * [69]	Lenvatinib (SELECT) * [70]
N	417	392
Target	*RAF, VEGFR 1–3, PDGFR, c-KIT* and *RET*	*FGFR 1–4, VEGFR 1–3, RET, c-KIT* and *PDGFR α*
Treatment line	1st line	1st line or progressed to previous TKI (maximum one; 25%)
Population	RECIST Disease progression within the previous 14 months	IRR evidence of progression within the previous 13 months
Histology	Papillary (56.8%) Poorly differentiated (9.6%) Follicular (25.4%)	Papillary (50%) Poorly differentiated (10.7%) Follicular (20.3%) Hürthle cell (18.4%)
Metastatic location	Bone (27%) Only Lung (16.7%)	Bone (39.8%) Lung (86.6%)
Comparator arm	Placebo	Placebo
Crossover placebo-intervention	Allowed	Allowed
Randomization	1:1	2:1
Primary Endpoint	PFS	PFS
Results	10.8 vs. 5.8 months ($p < 0.0001$)	18.3 vs. 3.6 months ($p < 0.001$)
Secondary Endpoints	OS, TTP, DCR, ORR	ORR, OS
Results	OS: 39.4 vs. 42.8 months (52.8% vs. 54.8% deaths in 8 years) # • Crossover correction: significance not reached	OS: 41.6 vs. 34.5 months + • Subgroup analysis: improved OS in older population (>65 yo) • Crossover correction: significance reached [71]
	TTP: 337 vs. 175 days (p <0.0001)	
	DCR: 86.2% vs. 74.6% ($p = 0.015$) ORR (No CR): 12.2% vs. 0.5% ($p < 0.0001$)	DCR: 87.7% vs. 55.7% ($p < 0.001$) ORR (4 CR): 64.8% vs. 1.5% ($p < 0.001$)
Adverse Effects G3/G4	37.2% (Hand-Foot syndrome)	75.9% (hypertension)
Dose Reduction	64.3%	67%
Discontinuation	19%	14%

IVb. TKI in Medullary Thyroid Cancer

- **Cabozantinib and Vandetinib** (MKIs) became the first-line systemic therapy for progressive metastatic MTC after being approved by the regulatory agencies based on their ability to improve survival in phase III randomized clinical trials (EXAM and ZETA).

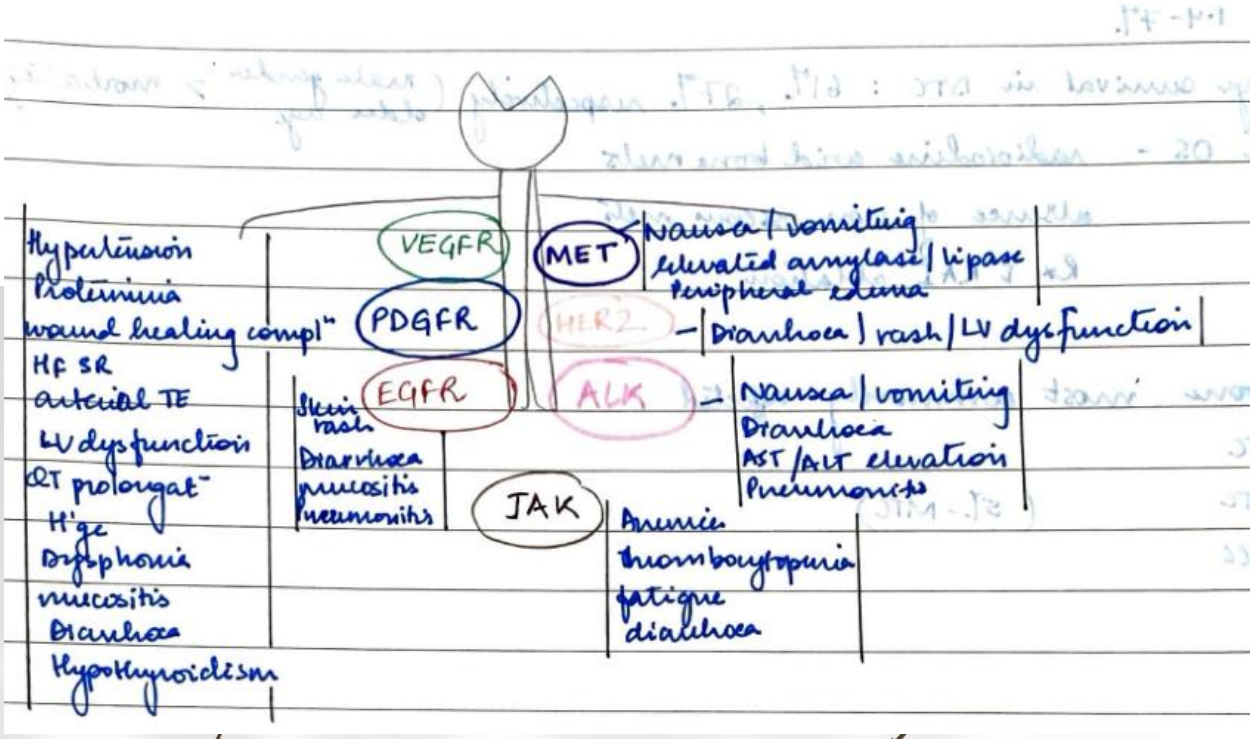
	ZETA [83]	EXAM [84]
Study design	Randomized (2:1), double blind, placebo-controlled, phase III	Randomized (2:1), double blind, placebo-controlled, phase III
Experimental arm	Vandetanib 300mg/24h	Cabozantinib 140 mg/24 h
Target	*VEGFR, EGFR, RET*	*MET, VEGFR2, FLT3, cKIT and RET*
Number of patients	331	330
Tumor stage	Unresectable/Metastatic	Unresectable/Metastatic Documented RECIST progression
Previous treatment lines	132 (40%) previously treated	128 (40%) previously treated
RET mutational status: RET+/RET-/RET unknown	56% (187)/2.4% (8)/41% (136)	48% (159)/12% (41)/39% (130)
Primary endpoint	PFS	PFS
Progressive disease	Not mandatory	Yes
Overall Response Rate	45% vs. 13%	28% vs. 0%
Disease Control Rate	87% vs. 71%	55.3% vs. 13.5%
Progression Free Survival (PFS)	30.5 m vs. 19.3 m (HR 0.27)	11.2 m vs. 4 m (HR 0.28)

- **Selpercatinib and Praseltinib**: Selective RET inhibitors for MTC

IVc. TKIs in Anaplastic Thyroid Cancer

- Combination of BRAF and MEK inhibitors -**Dabrafenib and Trametinib** - recently approved by the FDA for this subset of patients based on a recent phase II, open-label basket trial.
- ORR of 69%
- Several mutations and genomic aberrations, although rare, seem to be potentially targetable, such as ALK rearrangements, NTRK fusions, TSC2 mutations or RET rearrangements
- VEGFR inhibitors, such as vandetanib or sunitinib have shown antineoplastic activity in ATC cells

V. Adverse effects of TKIs:



VI. Contraindications to TKIs:

- Major surgery within 28 days
- Active bleeding
- Untreated hemorrhagic brain metastasis
- Encasement by tumour of major arteries
- Arterial thrombo-embolic event within last 6-12 months

VII. Challenges with TKIs:

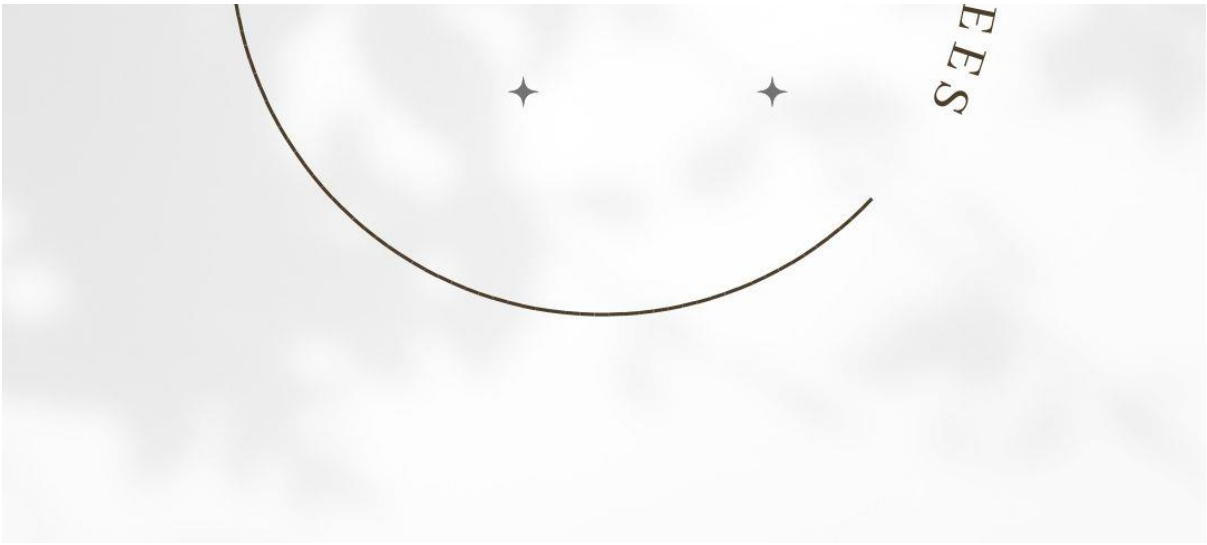
- Resistance to TKIs
- Induction of alternate signalling pathways
- Upregulating the expression of tyrosine kinase receptors on cell surface
- Various other theories – less understood
- Challenge – identification of alternate pathways can help in combining standard therapies to overcome the development of resistance against targeted therapies

VIII. Monitoring in TKI therapy:

Table 17. Potential Toxicities and Recommended Screening or Monitoring Approaches in Patients Started on Kinase Inhibitor Therapy

Toxicity	*Recommended screening/monitoring*
Hypertension	Frequent blood pressure monitoring, most critical during the first 8 weeks of therapy; if hypertension is induced, therapy should be individualized to patient response • Note: effective and expeditious management of hypertension is critical - and may reduce potential for cardiotoxicity. If antihypertensive therapy is needed, calcium channel blockers (e.g., amlodipine) may be most effective.
Cutaneous/mucocutaneous toxicities	Careful patient reporting of rash/mouth sores, patient awareness and education related to increased potential for photosentization/sunburn.
Hepatotoxicity	Serial assessment of alanine serum transferase (AST), alkaline phosphatase and bilirubin - most critical during the first 8 weeks of therapy • Note: dose reduction of kinase inhibitor therapy is commonly required due to hepatic toxicity
Cardiotoxicity	ECG pretherapy and frequently during therapy • Hold (or do not initiate) kinase inhibitor therapy if QTc >480 ms Echocardiogram: elective, but recommended in any patient with cardiac history and especially important in patient with hypertension, symptoms consistent with congestive heart failure or coronary artery disease and in patients receiving sunitinib
Hypothyroidism	TSH should be assessed frequently, with levothyroxine dosage altered in response to rising TSH if observed
Nephrotoxicity	Serial serum creatinine, urine analysis with protein determination,
Hematological toxicities	Serial CBC/diff
Pancreatitis	Serial amylase
Teratogenicity	Pretherapy pregnancy testing and effective contraception in women and men of childbearing potential

CBC, complete blood count; ECG, electrocardiography.



INTRAOPERATIVE ULTRASOUND (USG) FOR PARATHYROID DISEASE

- Ultrasound can be relied upon at multiple phases in a patient with hyperparathyroidism.

1. Principle:

- Sound waves demonstrate differing impedance properties in different mediums.
- The speed with which waves propagate also is based on the intensity and composition of the medium.
- This difference results in the reflection of sound waves thereby allowing high resolution imaging of anatomical structures.

- High frequency of wave → Shorter distance through tissue → Superficial structures
- Lower frequency → Depth more → Deeper structures

2. Indications of USG in hyperparathyroidism:

a. To reconfirm the predicted location of parathyroid lesion,
b. plan appropriate incision and approach.
c. After excision, the ultrasound of the resected specimen to confirm that it resembles the candidate target preoperatively,
d. To detect any thyroid pathology,
e. To take FNA PTH sample intraoperatively if suspicion of intra thyroidal parathyroid is present,
f. To detect four- gland hyperplasia in SHPT and familial HPT.

3. Technique of Intraoperative ultrasound:

- Thorough survey of central compartment
  →From Hyoid to Thoracic inlet
- Identify the innominate as it courses through superior mediastinum and branches into right CCA and right subclavian artery (normal anatomy to rule out non-recurrent laryngeal nerve)

- Then right carotid sheath to larynx and trachea in caudal to cephalad direction with transducer in transverse orientation

- Examine the right lobe of thyroid and look for parathyroid (sagittal probe)

- Same procedure to be done on the left side. ‘

- Watch for esophagus on left with a ryle’s tube inside showing acoustic shadow

- Deep planes like prevertebral, retropharyngeal and retroesophageal should be thoroughly searched after adjusting frequencies accordingly

- Thymus and superior mediastinum may be explored too as well.

4. **Identification of parathyroid lesion**:
- A ***homogeneous, ovoid, hypoechoic lesion with the hyperechoic rim,*** 2 - 3 times of normal parathyroid gland.
- On Doppler, ***a polar vessel seen entering the lesion*** and typically terminates at superior pole of the parathyroid gland
- Best appreciated in the sagittal orientation of the probe

- In ***SHPT, THPT, MEN-1 and 2A, Multiglandular Hyerplasia*** is appreciated on ultrasound as *all glands may be of different sizes*. Ultrasound helps plan the order of exploration from largest to smallest.

- However, in ***Sporadic Multiglandular disease***, enlarged parathyroid gland may ***not*** be available for visualization on ultrasound.

- Superior gland is usually posterior/dorsal to a thyroid lobe in a plane below the ITA or deep border of carotid.

- Inferior gland is anterior and superficial to ITA, deep border of the carotid.

5. **Advantages:**
- Lower cost
- Non-ionizing,
- Speed of procedure,
- Planning of incision and approach
- Can be done repeatedly in real time even through the incision if required
- FNA PTH may be utilized.

6. **Disadvantages:**
- Adenoma in deeper planes like mediastinum can be missed
- Surgeon bias about the location of the lesion if preoperative findings of MIBI and preoperative ultrasound are known

7. **Recent Advances**

- Endobronchial Ultrasound for visualizing Retropharynx, retroesophagus, and mediastinum
- These are not usually visualized with percutaneous transcervical ultrasound.
- Endobronchial ultrasound-assisted FNA PTH levels are also being measured for confirmation.

8. **Conclusion:**

- Surgeons should not be biased while performing intraoperative ultrasound, rather should use the full potential of ultrasound to map out entire at-risk neck spaces.