Radio Active Iodine Refractory Thyroid Cancer

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Conficts of interest

- Speaker: Astra Zeneca, Abbott Nutrición, Novartis Oncology, Novo Nordisk, Merck Sharp & Dohme, Roche, Glaxo SmithKline, Sanofi Aventis, Bayer, Pfizer, Novartis, Siegfried
- Advisory Board: Novartis Oncology, Sanofi Aventis, Astra Zeneca, Novo Nordisk, Stendhal, Pfizer, Siegfried
- Research: Astra Zeneca, Novartis Pharma Logistics Inc., Merck Sharp & Dohme, Glaxo SmithKline, Organon, Boehringer Ingelheim, Roche, Novo Nordisk

Agenda

- RAI-refractory epidemiology
- Clinical trials
- Adverse events and its management
- When to start MKI?

Thyroid Cancer

- Approximately 10% of patients will have distant metastases
- 1/3 of patients with advanced disease have low affinity RAI metastases from the start
  - Some will develop during disease
- 2/3 will still be RAI avid and in 1/3 cases may lead to disease remission (negative images)
- 70% of patients with bone metastases will develop a skeletal related event

Tumino D. Front Endocrinol. 2017;8:312

Metastatic disease management

- Any disease that can be removed, remove it!
- Local therapies
- Radiotherapy
- Biphosphonates
- Denosumab

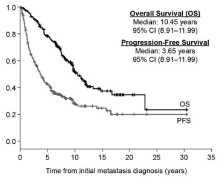
Martinica Criteria

Table 1. Common clinical scenarios that suggest a patient may have I-131 refractory thyroid cancer.

1. No radioiodine uptake is present on a diagnostic radioiodine scan.
2. No radioiodine uptake is present on a radioiodine scan performed several days after I-131 therapy.
3. Radioiodine uptake is only present in some but not other tumor foci.
4. DTC metastasis(es) progress despite radioiodine uptake.
5. DTC metastasis(es) progress despite a cumulative I-131 activity of > 22.2 GBq (600 mCi).

Tuttle RM. Thyroid. 2018.

Cohort of 199 patients with lung metastases



Cumulative percentage of patients demonstrating disease progression over time.

Year	Entire cohort, %	RAI avid disease, %	RAI refractory disease, %
1	17	12	29
2	35	26	53
5	55	41	83
10	65	53	91

RAI, radioactive iodine.

Tuttle RM. Best Pract Res Clin Endocrinol Metab. 2017;3:295

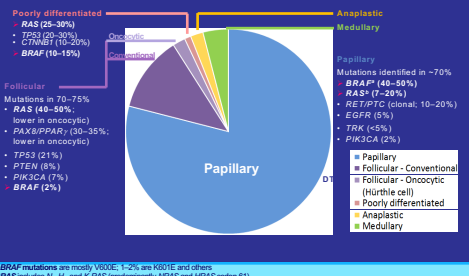
Survival in patients with metastasis

	RAI Uptake	No RAI uptake
10 years	56%	10%
15 years	45%	6%
20 years	40%	

- 10 year survival of 92% in those who are cured of metastatic disease vs 29% for those with residual disease
- Don't forget TSH suppression

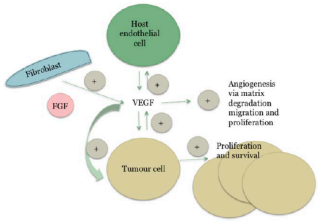
Kreissl M. J Nucl Med. Online Sep 6 2018.

Genetics of Differentiated Thyroid Cancer: aberrant intracellular signaling



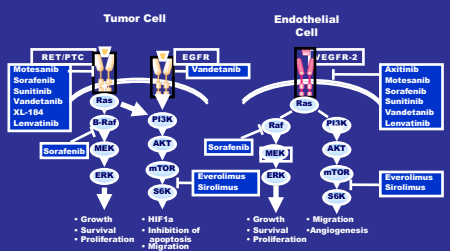
aBRAF mutations are mostly V600E; 1–2% are K601E and others.
bRAS includes N-, H-, and K-RAS (predominantly NRAS and HRAS codon 61)
Nikiforov YE et al. Arch Pathol Lab Med 2011;135:569–77; COSMIC database – Catalog of Somatic Mutations in Cancer

VEGF



Guild ML. Clin Endocrinol. 2018;88:529

Targeting Cell Signaling in Thyroid Cancer



EGFR, epidermal growth factor receptor; VEGFR, vascular endothelial growth factor receptor.
Graphic adapted from Keefe SM, et al. *Clin Cancer Res*. 2010;16:778-783.

Multikinase inhibitor (MKI)

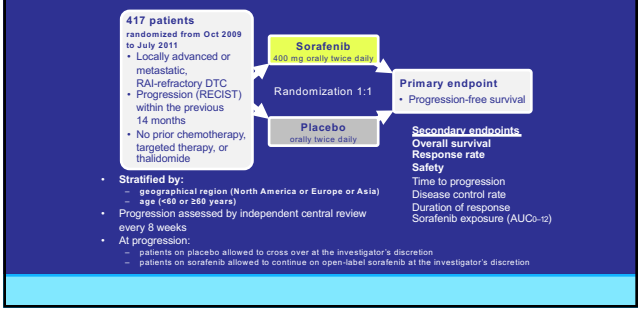
Multikinase inhibitors

- Sorafenib
  - Inhibits VEGFR 1, 2, 3
  - Inhibits PDGFR beta
  - Inhibits Raf-1, RET, BRAF
  - DECISION study
- Lenvatinib
  - Inhibits VEGFR 1, 2, 3
  - Inhibits PDGFR alfa
  - Inhibits FGFR 1-4
  - Inhibits RET, KIT
  - SELECT study

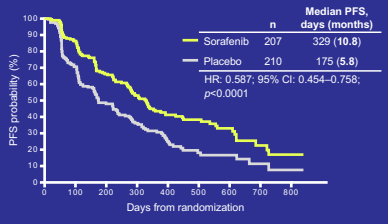
Tumino D. Front Endocrinol. 2017;8:312

Sorafenib: DECISION

DECISION study design (ASCO 2013)



DECISION: Progression-free survival
(by independent central review)



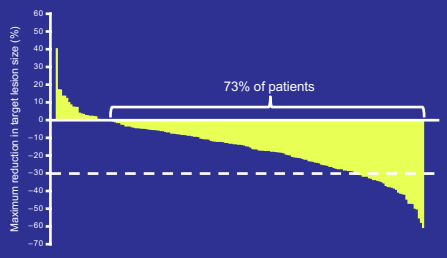
	n	Median PFS, days (months)
Sorafenib	207	329 (**10.8**)
Placebo	210	175 (**5.8**)

HR: 0.587; 95% CI: 0.454–0.758; *p*<0.0001

Overall Survival median PFS has not been reached

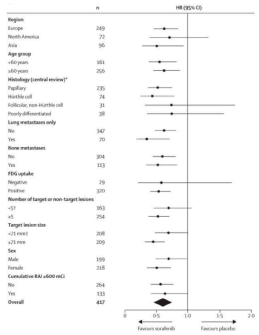
Full analysis set.
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival

Maximum reduction in target lesion size: sorafenib arm
(by independent central review)



Maximum reduction is defined as the difference in the sum of the longest diameter of target lesions from baseline. Negative values refer to maximal reduction and positive values to the minimal increase.

Subgroup analysis



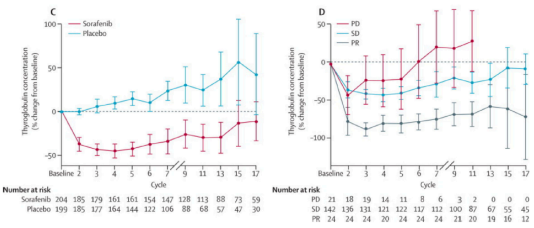
Brose MS. Lancet. 2014;384:319

DECISION: subgroup analysis

- Response was similar in all subgroups
- Lesions with a diameter of <1.5 cm the clinical response was less significant
  - Active surveillance until a higher tumor volume?
  - Patients that were on placebo and received open label sorafenib had similar response
  - Even in those patients who initially had progression, PFS was 6.7 months

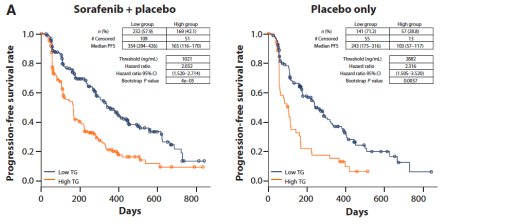
Matrone A. Best Pract Res Clin Endocrinol Metab. 2017;3:319

Thyroglobulin



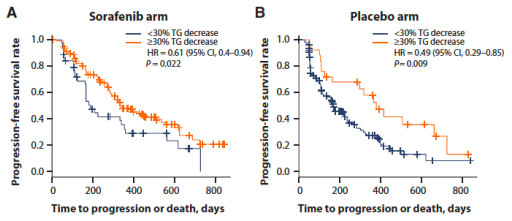
Brose MS. Lancet. 2014;384:319

Tg as predictive marker in the DECISION trial



Brose M. Clin Cancer Res. 2019;25:7370

Tg decrease as predictive of response in DECISION



Brose M. Clin Cancer Res. 2019;25:7370

Some caveats

- No mortality difference between treatment arms because 71.4% of patients in the placebo group received open label sorafenib
- At the end of study, median survival had not been achieved yet
- Partial response 10.2 months
- Stable disease of >4 weeks was present in 74% and >6 months in 41.8%
- Time to progression 11.1 months vs 5.7 months

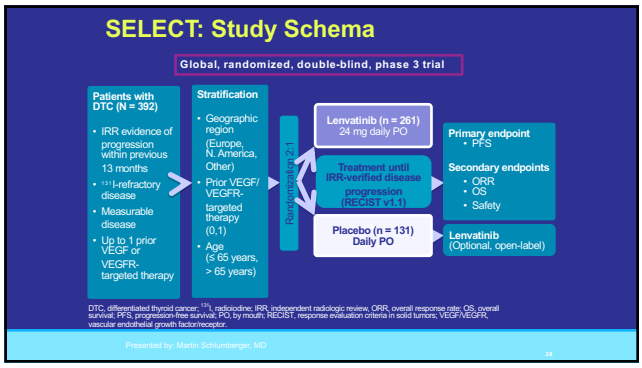
Brose MS. Lancet. 2014;384:319

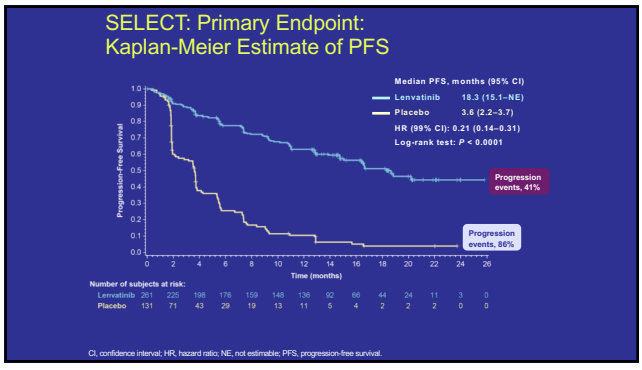
DECISION

- Baseline characteristics that predicted a better outcome:
  - Papillary histology
  - Low tumor burden
  - Abscense of bone metastases
  - Presence of lung-only metastases
- Symptoms did not influence the PFS

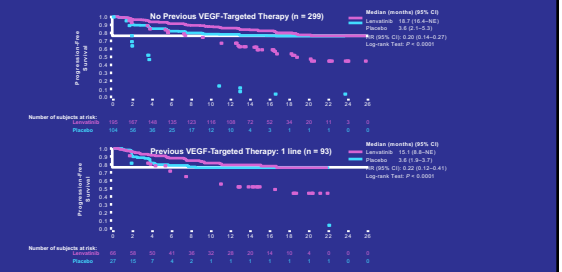
Fouchardiere C. Bull Cancer. 2019;106:812

SELECT


SELECT: Study Schema
Global, randomized, double-blind, phase 3 trial
Patients with DTC (N = 392)
• IRR evidence of progression within previous 13 months
• 131I-refractory disease
• Measurable disease
• Up to 1 prior VEGF or VEGFR-targeted therapy
Stratification
• Geographic region (Europe, N. America, Other)
• Prior VEGF/VEGFR-targeted therapy (0,1)
• Age (≤ 65 years, > 65 years)
Randomized 2:1
Lenvatinib (n = 261) 24 mg daily PO
Treatment until IRR-verified disease progression (RECIST v1.1)
Placebo (n = 131) Daily PO
Primary endpoint
• PFS
Secondary endpoints
• ORR
• OS
• Safety
Lenvatinib (Optional, open-label)
DTC, differentiated thyroid cancer; 131I, radioiodine; IRR, independent radiologic review; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, by mouth; RECIST, response evaluation criteria in solid tumors; VEGF/VEGFR, vascular endothelial growth factor/receptor.
Presented by: Martin Schlumberger, MD

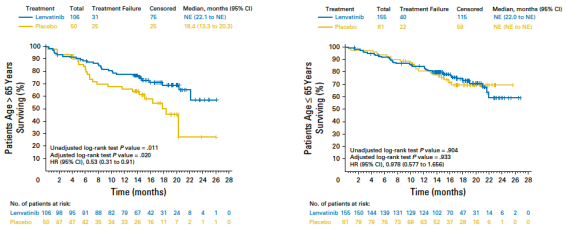

SELECT: Primary Endpoint: Kaplan-Meier Estimate of PFS
Median PFS, months (95% CI)
Lenvatinib 18.3 (15.1–NE)
Placebo 3.6 (2.2–3.7)
HR (99% CI): 0.21 (0.14–0.31)
Log-rank test: P < 0.0001
Progression events, 41%
Progression events, 86%
Progression-Free Survival
Time (months)
Number of subjects at risk:
Lenvatinib 261 225 198 176 159 148 136 92 66 44 24 11 3 0
Placebo 131 71 43 29 19 13 11 5 4 2 2 2 0 0
CI, confidence interval; HR, hazard ratio; NE, not estimable; PFS, progression-free survival.

SELECT: PFS by Previous VEGF-Targeted Therapy



CI, confidence interval; HR, hazard ratio; NE, not estimable; PFS, progression-free survival; VEGF, vascular endothelial growth factor.

Survival and age



Brose MS. J Clin Oncol. 2017;36:2692

SELECT

- Tumor response:
  - 25% regression in the first 8 weeks and then 1.3% per month
  - First line of therapy in patients with large tumor mass and/or rapidly progressive disease?
- Higher toxicity in >65 years of age

Fouchardiere C. Bull Cancer. 2019;106:812

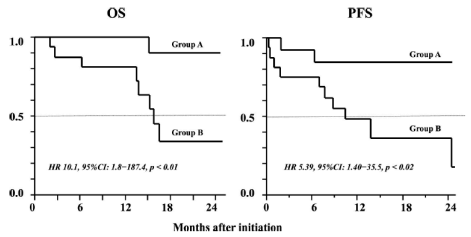
Lenvatinib in real life

Factors	PFS			OS		
	HR	95% CI	*p*	HR	95% CI	*p*
Age (>65 years)	1.77	0.55–6.64	*ns*	3.06	0.74–20.56	*ns*
Gender (male)	1.50	0.40–5.00	*ns*	2.33	0.27–8.90	*ns*
Histology (follicular)	0.94	0.21–3.26	*ns*	1.17	0.25–4.47	*ns*
Tg doubling time	0.85	0.48–1.20	*ns*	1.02	0.61–1.41	*ns*
TL (other than lung)	1.37	0.39–4.66	*ns*	1.93	0.47–7.48	*ns*
Symptom present (yes)	5.39	1.40–35.5	<0.02	10.06	1.57–187.4	<0.01
Tumor size (>median)	1.20	0.37–3.86	*ns*	1.17	0.29–4.50	*ns*

PFS, progression free survival; OS, overall survival; HR, hazard ratio; CI, confidence intervall; Tg, thyroglobulin; TL, target lesion

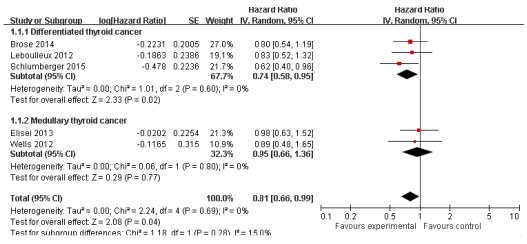
Sugino K. Endocrine J. 2018;65:299

Lenvatinib: impact of symptoms



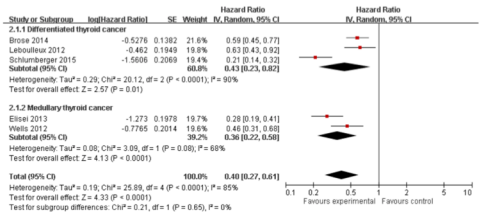
Sugino K. Endocrine J. 2018;65:299

Meta-analysis: overall survival



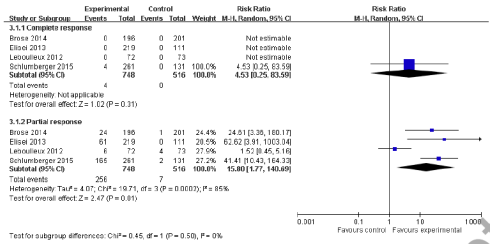
Liu JW. Curr Med Res Opin. 2017; online aug 16

Meta-analysis: Progression free survival



Liu JW. Curr Med Res Opin. 2017; online aug 16

Meta-analysis: Objective response



Liu JW. Curr Med Res Opin. 2017; online aug 16

How to choose between lenvatinib and sorafenib?

- Due to its antiangiogenic effect, lenvatinib have a faster reduction in tumor volume
  - Favorable in those circumstances where a fast tumor reduction is needed, for example, a lesion with vertebral compression
  - Unfavorable when it may lead to fistulas, such as esophagus or trachea infiltration
- Comorbidities such as hypertension
- availability

Matrone A. Best Pract Res Clin Endocrinol Metab. 2017;3:319

Adverse events and management

Sorafenib (*N* = 207)			Lenvatinib (*N* = 261)		
	All grades (%)	Grade ≥3 (%)		All grades (%)	Grade ≥ 3 (%)
Hand–foot skin reaction	76.3	20.3	Hypertension	67.8	41.8
Diarrhea	68.6	5.3	Serum thyroid-stimulating hormone (TSH) increase[a]	61.5	–
Alopecia	67.1	-	Diarrhea	59.4	8
Rash/desquamation	50.2	4.8	Fatigue	59.0	9.2
Fatigue	49.8	5.8	Anorexia	50.2	5.4
Weight loss	46.9	5.8	Weight loss	46.4	9.6
Hypertension	40.6	9.7	Nausea	41.0	2.3
Serum TSH increase[a]	33.3	-	Stomatitis	35.6	4.2
Anorexia	31.9	2.4	Hand–foot skin reaction	31.8	3.4
Oral mucositis	23.2	1	Proteinuria	31	10
Pruritus	21.3	1	Vomiting	28.4	1.9
Nausea	20.8	0	Headache	27.6	2.7
Headache	17.9	0	Dysphonia	24.1	1.1
Cough	15.5	0	Arthralgia	18	0
Constipation	15	0	Dysgeusia	16.9	0
Dyspnea	14.5	4.8	Rash	16.1	0.4
Neuropathy (sensory)	14.5	1	Constipation	14.6	0.4
Abdominal pain	14	1.4	Myalgia	14.6	1.5
Pain (extremity)	13.5	0.5	Dry mouth	13.8	0.4
Dermatology (other)	13	1	Upper abdominal pain	13	0
Voice changes	12.1	0.5	Abdominal pain	11.5	0.4
Fever	11.1	1.5	Peripheral edema	11.1	0.4
Vomiting	11.1	0.5	Alopecia	11.1	0
Back pain	10.6	1	Dyspepsia	10	0
Pain (other)	10.6	0.5	Oropharyngeal pain	10	0.4
Pain (throat, pharynx, larynx)	10.1	0	QTc prolongation	8	1.5
Hypocalcemia	18.8	9.2	Hypocalcemia	6.9	2.7
Increased ALT	12.6	2.9	Arterial thromboembolic effects	5.4	2.7
Increased AST	11.1	1			

[a]*More than 0.5 μU/L.*

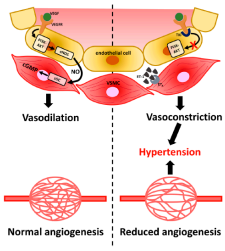
Tumino D. Front Endocrinol. 2017;8:312

Adverse events management

- Most are mild to moderate
- A closer follow up during the first 2 months
- Report adverse events right from the start
- Dose reduction
- Stop MKI for a few days

Guild ML. Clin Endocrinol. 2018;88:529

Hypertension as adverse event



- VEGF:
  - Arterioles and venules vasodilation
- Usually in the first 6 weeks
  - Measure blood pressure at least once a week
- Mechanisms:
  - A lower NO production
  - Increase in ET-1
  - Decrease in capillarity and an increase in peripheral vascular resistance

Ancker OV. Int J Mol Sci. 2017;18:625

Hypertension treatment

- Verapamil and diltiazem should not be used
  - Metabolized via CYP3A4 and they interact with MKI
- Nitric oxide donors? (nebivolol?)
- No specific recommendations and should be treated with current guidelines
- Some patients will develop proteinuria
  - Favors ACEi or ARB

Ancker OV. Int J Mol Sci. 2017;18:625

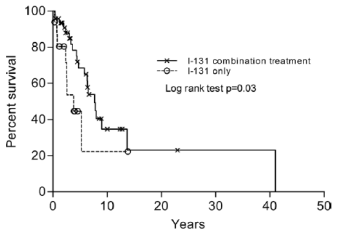
Hypothyroidism mechanisms

- In patients with thyroid tissue
  - "vascular" thyroiditis
  - No autoimmune mechanism
  - It's a therapeutic response predictor
- Patients with thyroidectomy
  - Lower MCT8 expression leads to a decrease in brain T3 and T4 transport
  - Increase in type 2 deionidase
  - Hypothalamus-pituitary-thyroid axis dysfunction
  - Lower TSH clearance (glycoprotein endocytosis in liver is mediated by tyrosin kinase)
  - MKI may interfere with heterodimerization process between retinoic acid receptors and thyroid hormone receptors

Drui D. Ann Endocrinol. 2018; online.

What to do if the patient have progressive disease despite MKI?

Don’t forget other therapies!



Wu D. Thyroid. 2018

Switching to another MKI?

Switch to lenvatinib

- PFS 18.7 months in those patients who had not received a MKI and 15.1 months in those who did

Schlumberger M. N Engl J Med. 2015;372:621

Sunitinib

Table 1 Baseline features and clinical outcome of patients subjected to sequential treatment sorafenib-sunitinib

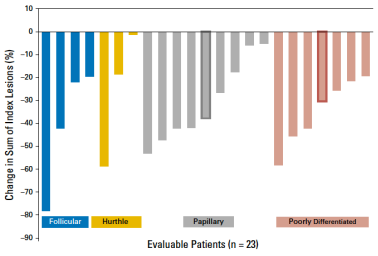
Parameter	Patient 1	Patient 2	Patient 3
Gender	F	F	M
Age at diagnosis (years)	56	63	55
Histology	Follicular	Papillary, classic variant	Papillary, classic variant
Stage	III	IV	III
ECOG status at the beginning of treatment	2 (2)	1 (2)	1 (1)
Sorafenib (Sunitinib)			
Site of metastases before starting TKIs' treatment	Lymph nodes (cervical and mediastinal), lung, liver, bone	Relapse in thyroid bed, cervical lymph nodes, lung	Mediastinal lymph nodes, lung
Follow-up since TKIs treatment (months)	41	38	35
Reasons for sorafenib failure	Disease progression	Disease progression	Untreatable toxicity (hand-foot syndrome)
Radiological response (according to RECIST)	SD (SD)	PR (PR)	SD (SD)
Sorafenib (Sunitinib)			
PFS (months)	9 (16)	11 (18)	14 (17)
Sorafenib (Sunitinib)			

F female, *M* male, *SD* stable disease, *ECOG* eastern cooperative oncology group, *PR* partial response *PFS* progression-free survival

Marotta V. Endocrine. 2015;49:854

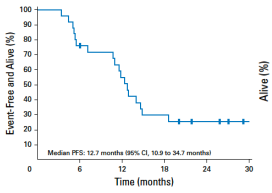
Cabozatinib

- c-MET, RET, VEGFR inhibitor
- Approved for medullary thyroid cancer

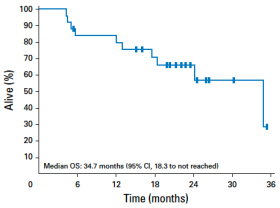


Cabanilla ME. J Clin Oncol. 2017;35:3315

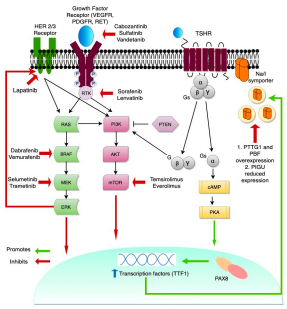
PFS



OS



Cabanilla ME. J Clin Oncol. 2017;35:3315



Sorafenib + temsirolimus

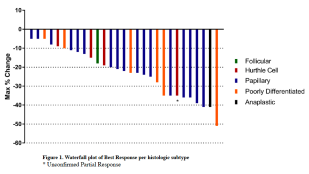


Figure 1. Waterfall plot of Best Response per histologic subtype
* Unconfirmed Partial Response

- 58% stable disease
- 22% partial response
- 38% of those without previous systemic therapy had partial response vs 10%
- 1 year PFS 30.5%
- Average survival 24.6 months
- Toxicity: perforation, fatigue, neumonitis

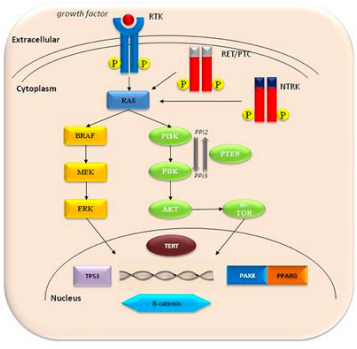
Sherman EJ. Cancer. 2017;123(21):4114

In case of progressive disease..

- Should we stop MKI?
- Tumor may increase rapidly
- >80% of blood vessels are destroyed during MKI therapy but there is a fast revascularization once the MKI is stopped
  - In animal models, after stopping the drug for 1 week the tumor is totally revascularized
  - Therefore, dose reduction is preferred over drug suspension

Matrone A. Best Pract Res Clin Endocrinol Metab. 2017;3:319

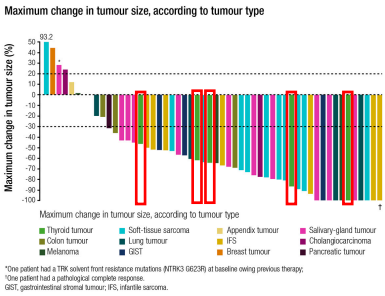
Molecular targeted therapies and immunotherapies



NTRK fusion gene

- This mutation is present in 5-25% of thyroid cancers
- larotrectinib
  - 5 patients with thyroid cancer, all of them had >30% reduction of their tumor
  - Approved by FDA in November 2018
- Entrectinib
  - Approved by FDA in August 2019

Kirtane K.Curr Treat Options in Oncol. 2020;21:18

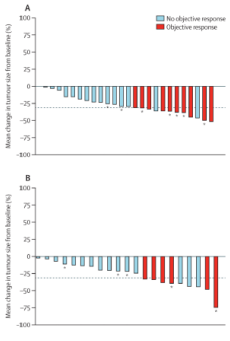


Drilon A. N Engl J Med. 2018;378:731

BRAF V600E

- Non randomized multicenter phase II study
- Vemurafenib
- 39% partial response
- PFS 18 months

- Daprafenib in phase I study
- 33% response rate in 12 patients



Immunotherapy

- Pembrolizumab: 22 patients
  - Objective response rate 9.1%
  - 54.5% stable disease
- Combination with angiogenic drugs?
- Currently being evaluated in clinical trials

Fouchardiere C. Bull Cancer. 2019;106:812

Current guidelines

2019 ETA Guidelines

- In patients with radiologically proven lesiones, RAI-R disease is almost certain in the abscense of RAI uptake on SPECT-CT, performed after high-activity RAI and prepared with high TSH and a diet with low iodine content
- Particular attention should be paid to clinical manifestations of advanced disease and quality of life
- Serial imaging at 6 to 12 month intervals is useful to assess dynamics of tumor growth
- Histopathology together with molecular pathology may be predictive of the course of TC but so far has limited impact on management

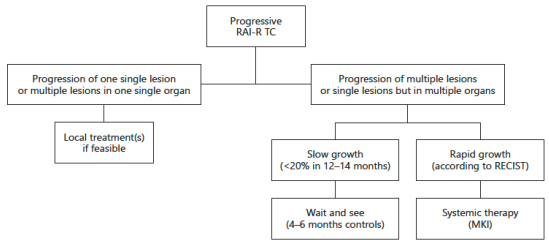
Fugazzola L. Eur Thyr J. 2019;8:227

2019 ETA Guidelines: when to start MKIs?

- Should only be considered in patients with progressive RAI-R disease, with considerable tumor load and when refraining from treatment with MKIs would lead to considerable harm/clinical complications within the near future
- MKIs should be continued as long as there is evidence of clinical benefit
- MKI should be stopped only when another therapeutic option is available or the side effects are intolerable or treatment is no longer providing clinical benefit

Fugazzola L. Eur Thyr J. 2019;8:227

2019 ETA Guidelines



Fugazzola L. Eur Thyr J. 2019;8:227

2019 ETA Guidelines: parameters to be evaluated at baseline and each visit

	Parameters to be evaluated
Clinical data	Weight, appetite, fatigue, diarrhoea, skin manifestations, patient's diary on side effects and/or symptoms
Blood tests	TSH, fT4 (thyroglobulin, Tg antibodies at periodical intervals) Electrolytes (Ca, Na, K, Mg) Full blood count ALT, ALP, GGT Glucose, total HDL, LDL cholesterol, triglycerides
Cardiac parameters	ECG (QTc interval) Blood pressure
Imaging	Whole-body imaging (CT scan with contrast medium and/or MRI and/or 18-FDG-PET/CT scan) (first visit, then periodical evaluation metastatic sites) Bone scintigraphy (optional)

Fugazzola L. Eur Thyr J. 2019;8:227

Take home messages

- Fortunately, advanced thyroid carcinoma or RAI-R are present in the lesser of patients
- MKI are therapeutic options that increased PFS
- MKI should be started in the presence of RAI-R progressive disease
- It is controversial when to start MKI specially if asymptomatic
- Adverse event management and counseling
- Therapeutic choices in case of progression

Questions…

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This presentation can be downloaded in:

www.EndoDrChen.com