Early or Delayed Use of TKI

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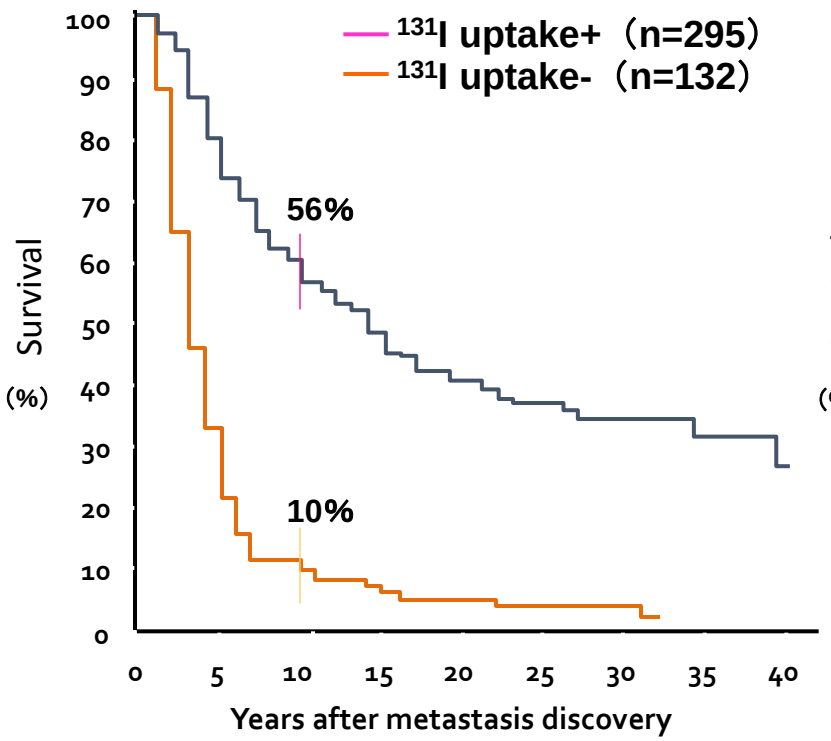
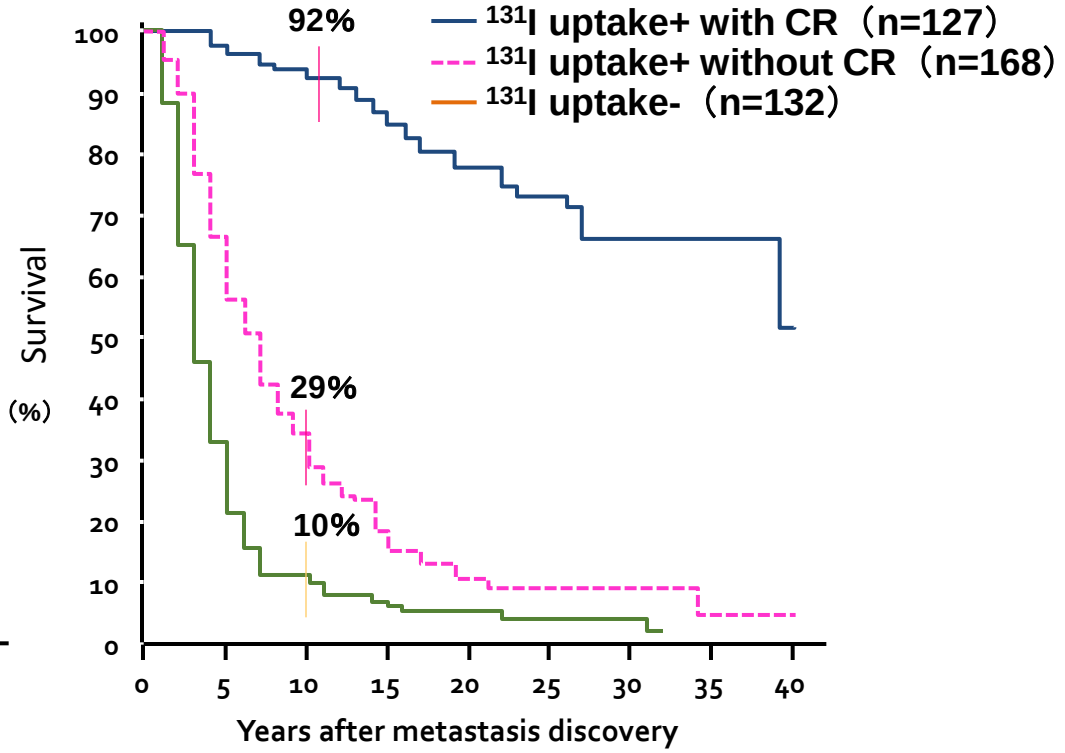
Disclosures

- Grants and contracts: Eisai, Merck Sharp & Dome
- Honoraria and consultation fees: Merck Serono, Bristol-Myers Squibb, Eisai, Otsuka and Bayer

Patients with ^{131}I uptake+ Should Take RAI Initially





RAI: radioactive iodine therapy, CR: complete remission

Durante C, et al. J Clin Endocrinol Metab. 2006 Aug;91(8):2892-9.

DECISION study design

417 patients

- Locally advanced or metastatic, RAI-refractory DTC
- Progression (RECIST) within the previous 14 months
- No prior chemotherapy, targeted therapy, or thalidomide

Sorafenib
400 mg orally twice daily

Randomization 1:1

Placebo
orally twice daily

Primary endpoint
- Progression-free survival

Secondary endpoints
Overall survival
Response rate
Safety
Time to progression
Disease control rate
Duration of response
Sorafenib exposure ($AUC_{0–12}$)

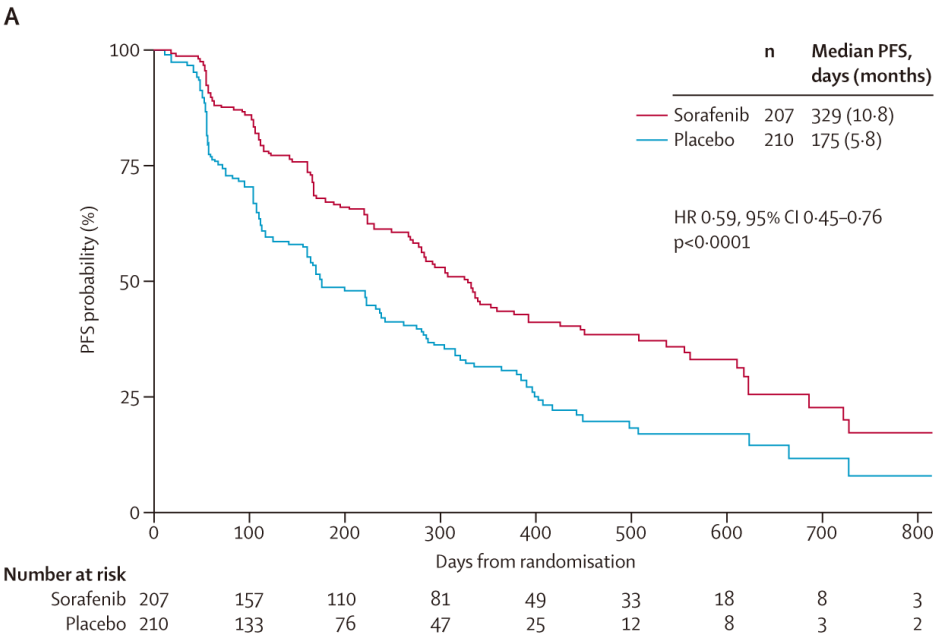
- **Stratified by:**
  - **geographical region (North America or Europe or Asia)**
  - **age (<60 or ≥60 years)**
- Progression assessed by independent central review every 8 weeks
- At progression:
  - patients on placebo allowed to cross over at the investigator's discretion
  - patients on sorafenib allowed to continue on open-label sorafenib at the investigator's discretion

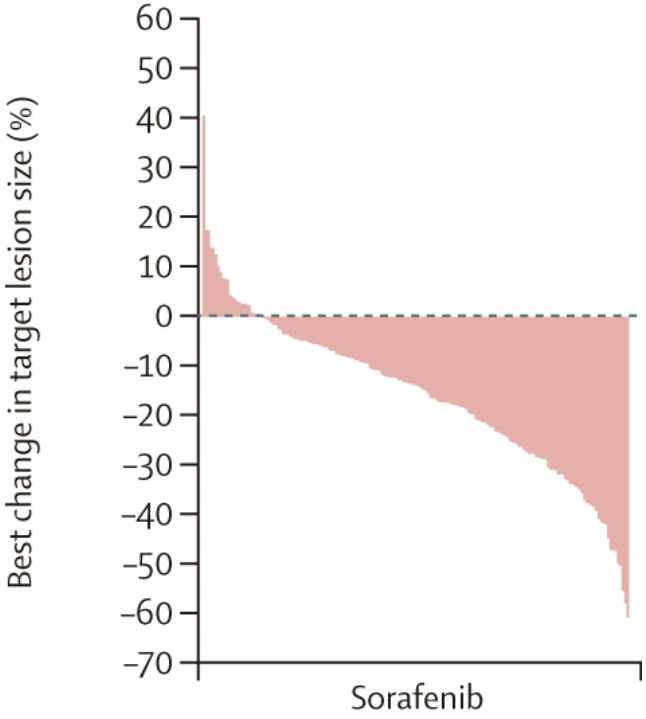
Brose M, et.al, Lancet 2014

Efficacy in the DECISION study

	n	Median PFS (months)	Overall response
Sorafenib	**207**	**10.8**	**12.2% (24/196)**
Placebo	**210**	**5.8**	**0.5% (1/201)**

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

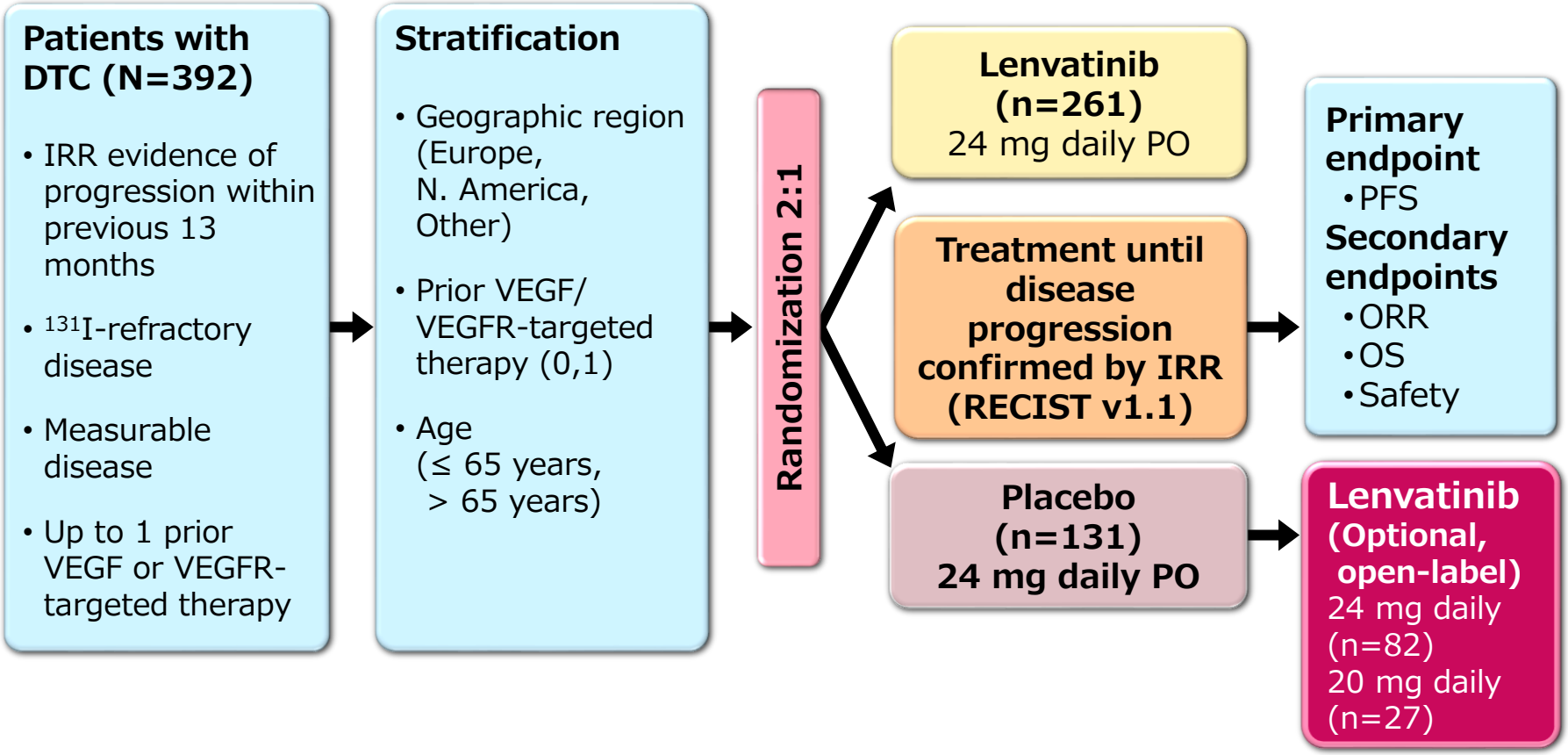




Brose M, et.al, Lancet 2014

SELECT Study: Study Schema

Global, randomized, double-blind, phase 3 trial



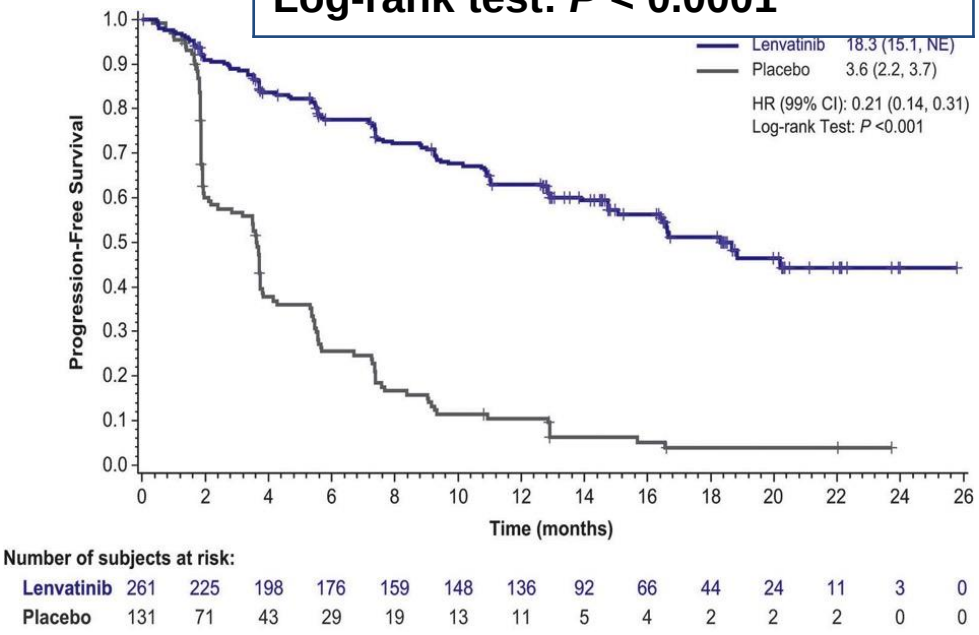
As of cut-off date for primary analysis (November 15, 2013)

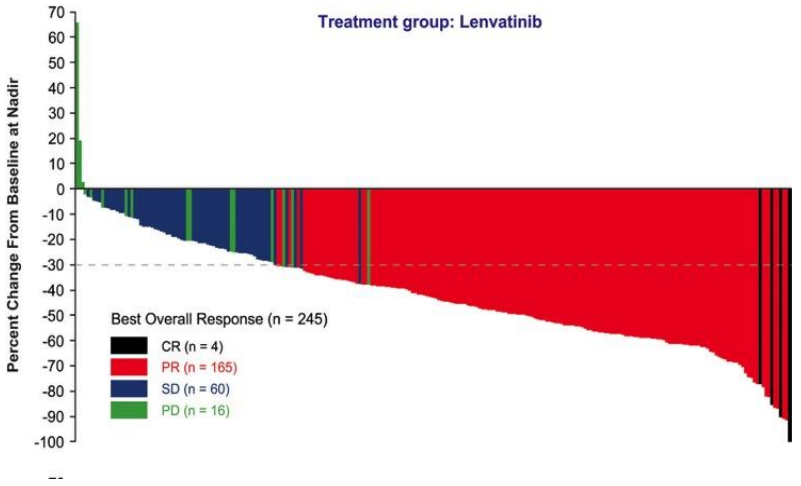
Schlumberger, M et.al, N Engl J Med 2015;372:621-30.

Efficacy in the SELECT study

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	

	Lenvatinib (n=261)
Response rate	169 (64.8%)
CR	4 (1.5%)
PR	165(63.2)
SD	60 (23.0)

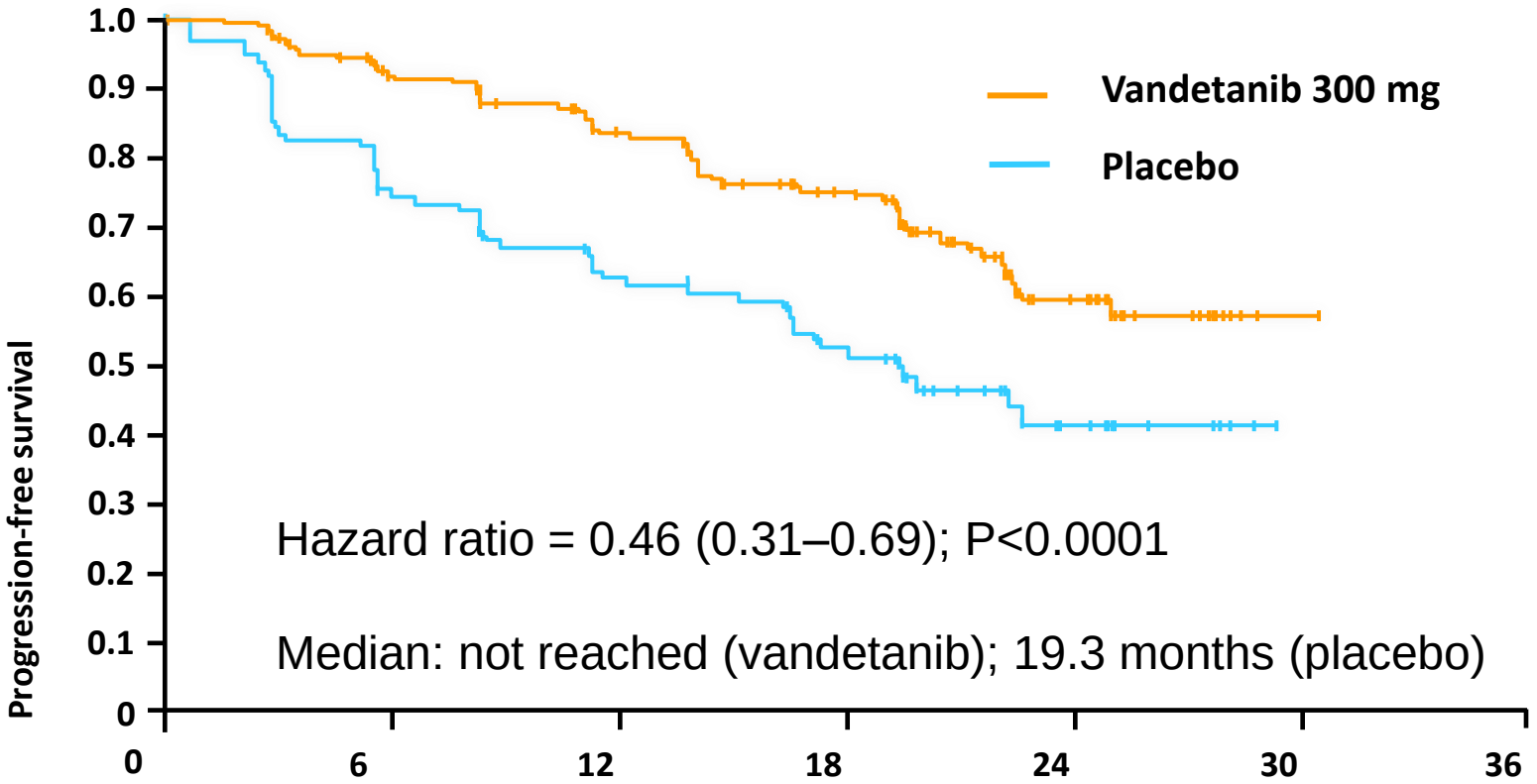




CI, confidence interval; HR, hazard ratio; NE, not estimable; PFS, progression-free survival.

Schlumberger, M et.al, N Engl J Med 2015;372:621-30.

Vandetanib in Locally Advanced or Metastatic Medullary Thyroid Cancer: Phase 3 study

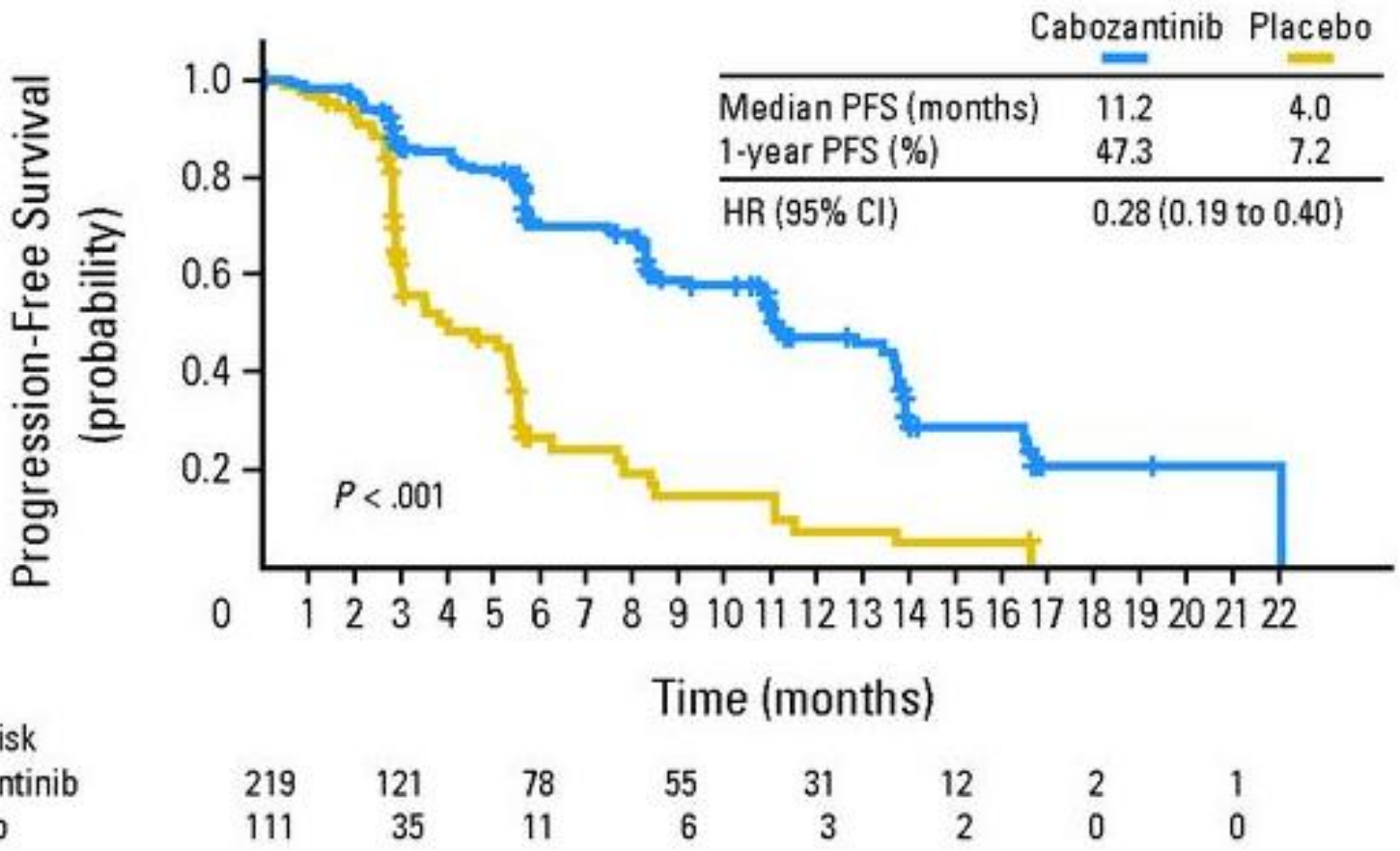


At risk (n)							
Vandetanib	231	198	171	141	42	1	0
Placebo	100	72	57	45	13	0	0

Hazard ratio <1 favors vandetanib

Wells AS, et.al, JCO 2012, 30(2): 134-141

Cabozantinib in Progressive MTC



Elisei R et al. JCO 2013;31:3639-3646

Adverse Events of VEGFR-targeted TKI

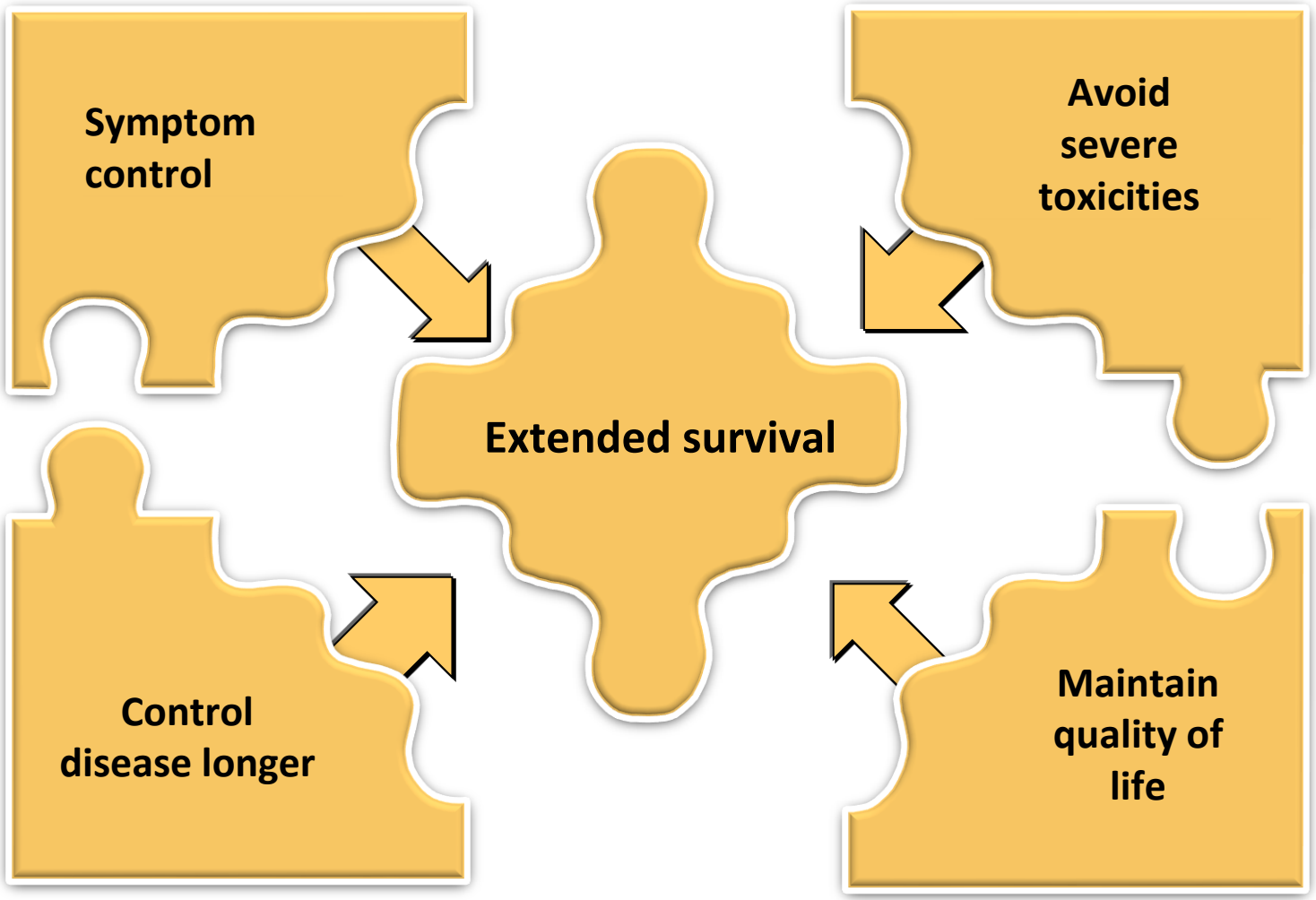
- Hand-foot skin reaction
- Diarrhea
- Rash
- Fatigue
- Anorexia
- Hypertension
- Proteinuria

Worsen QOL

- Myocardial infarction
- Pulmonary embolism
- Hemorrhagic stroke

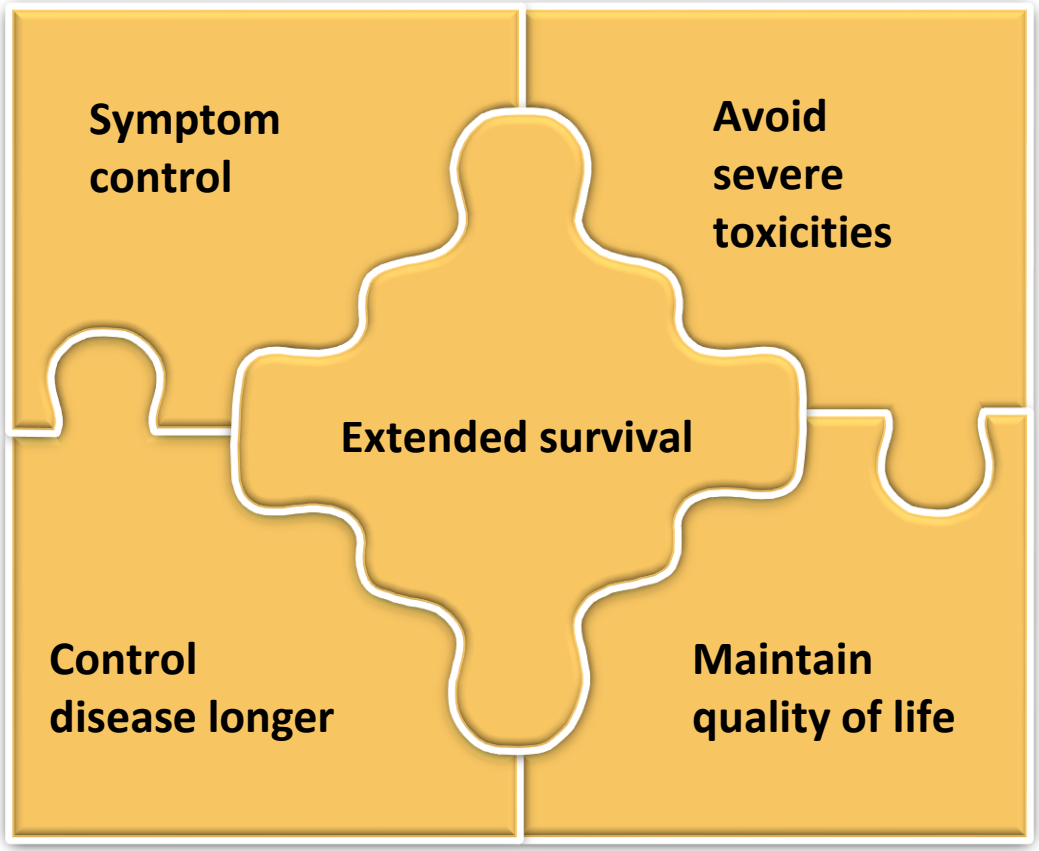
Fatal

Goal of Treatment for Patients with R/M Cancer



Quality of Survival: R/M cancer

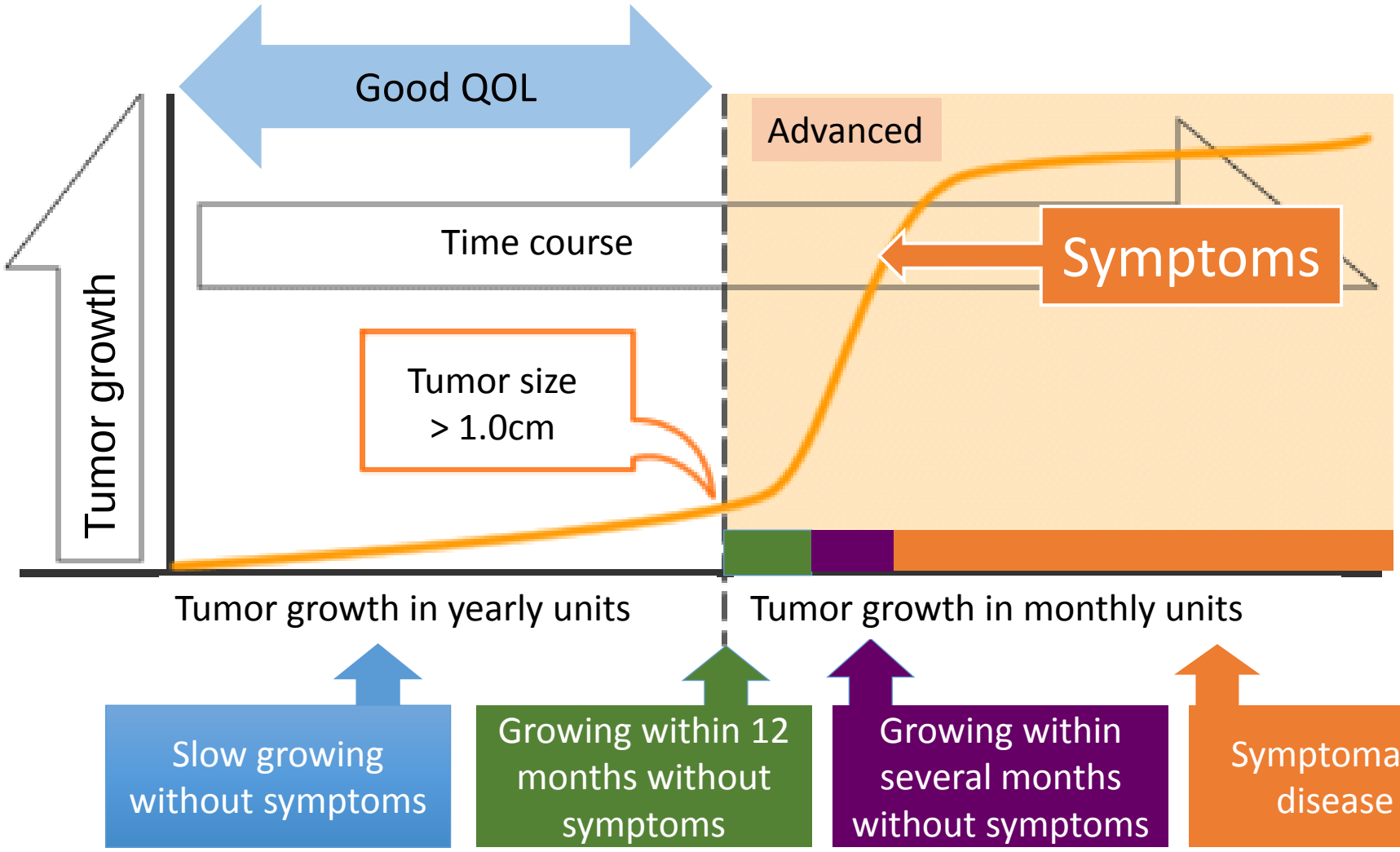
Ideally, treatment extends survival while ensuring the good quality of this survival



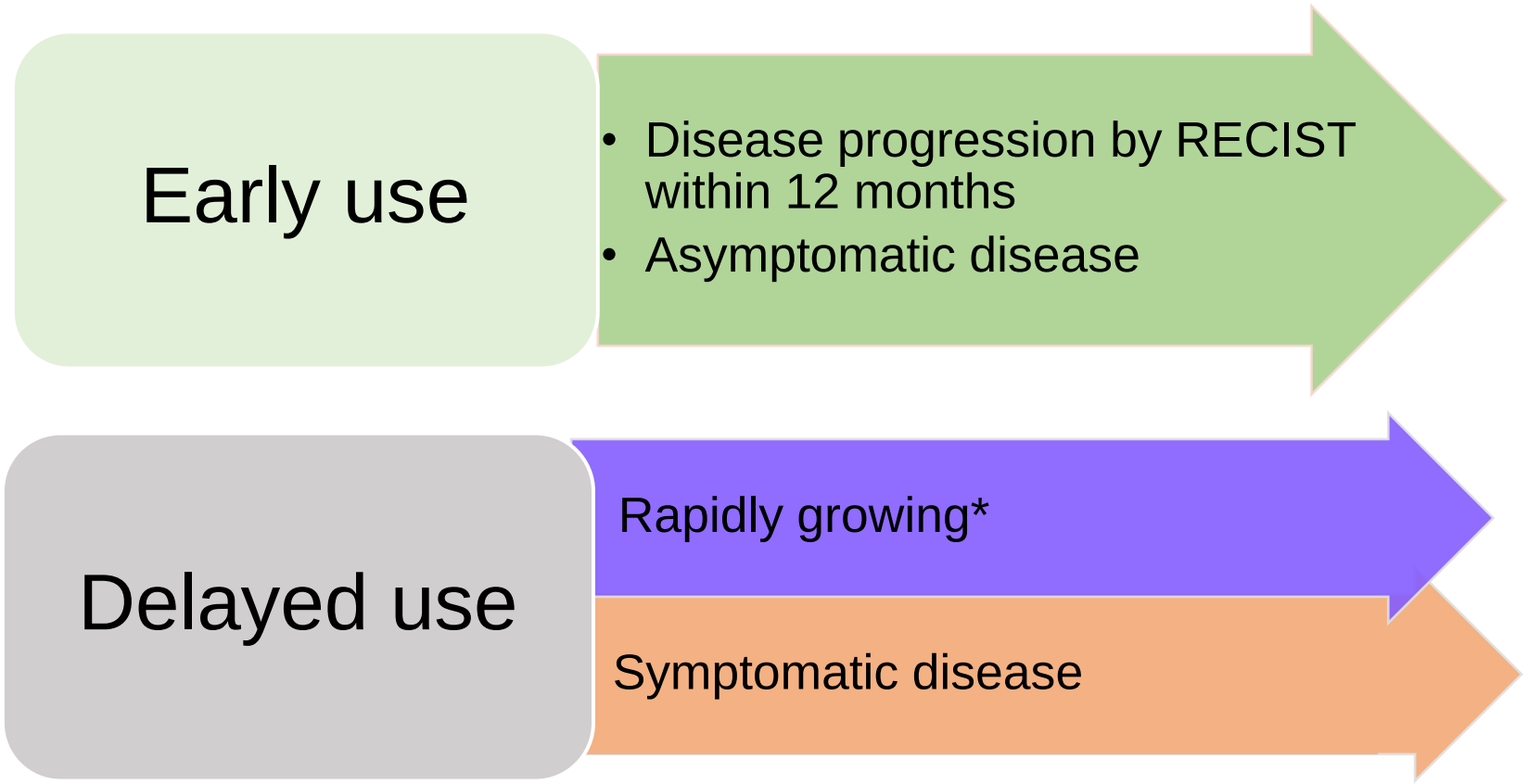
Comments to the SELECT study by ASCO discussant

- My Conclusions
  - Lenvatinib is clinically superior to placebo and sorafenib and should be considered a new standard
  - There is no need for an RCT of lenvatinib versus sorafenib
  - These trials may have initiated treatment too early. Don’t start treatment just because tumors are growing.

Appropriate Timing to Start TKI



Early or Delayed Use of TKI for RAI-refractory DTC



*Disease progression by RECIST within several months

RAI: radioactive iodine

Early Use of TKI

- Merits
  - Reduced complications due to disease progression
  - Reduced other distant metastasis, included brain metastasis
  - Reduced anaplastic transformation
- Demerits
  - Adverse events：worsened QOL
  - Cost
  - Survival benefits?

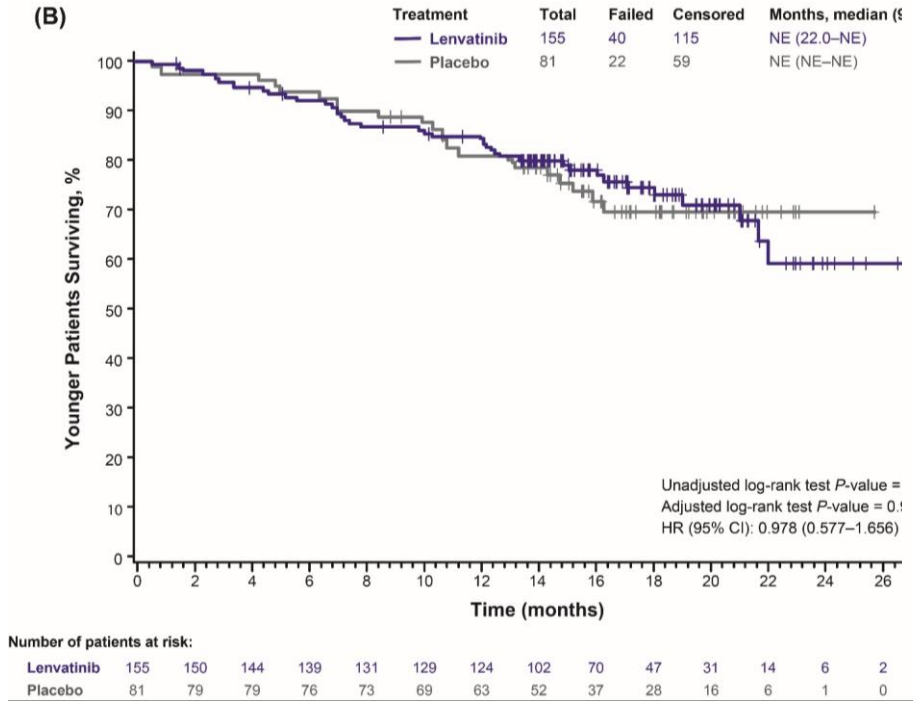
Delayed Use of TKI

- Merits
  - Reduced cost
  - Awareness of symptom improvement
- Demerits
  - Risk of worsening patient QOL
    - ✓Spinal cord paralysis and compression
  - Risk of brain metastasis, which VEGFR-targeted TKIs have no beneficial effect on
  - Worsened outcomes in patients with older age or FTC
  - Increased risk of bleeding by watch & wait
    - ✓ Invasion to the carotid artery in area that was previously irradiated
    - ✓ Skin invasion and disintegration

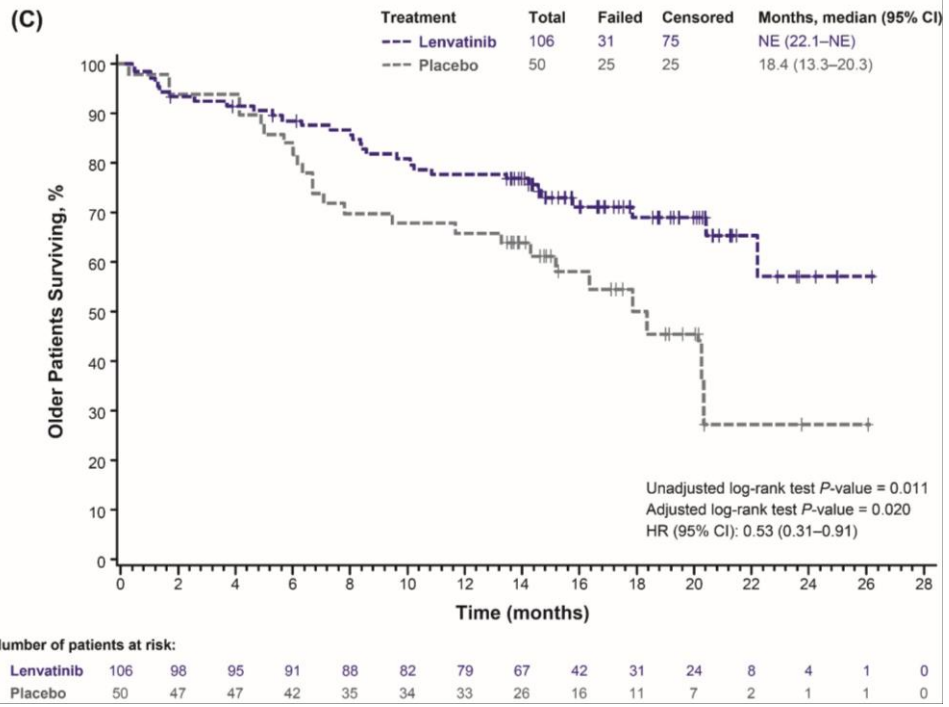
Lenvatinib vs. Placebo: SELECT study

Overall survival

Aged ≤ 65 years



Aged > 65 years



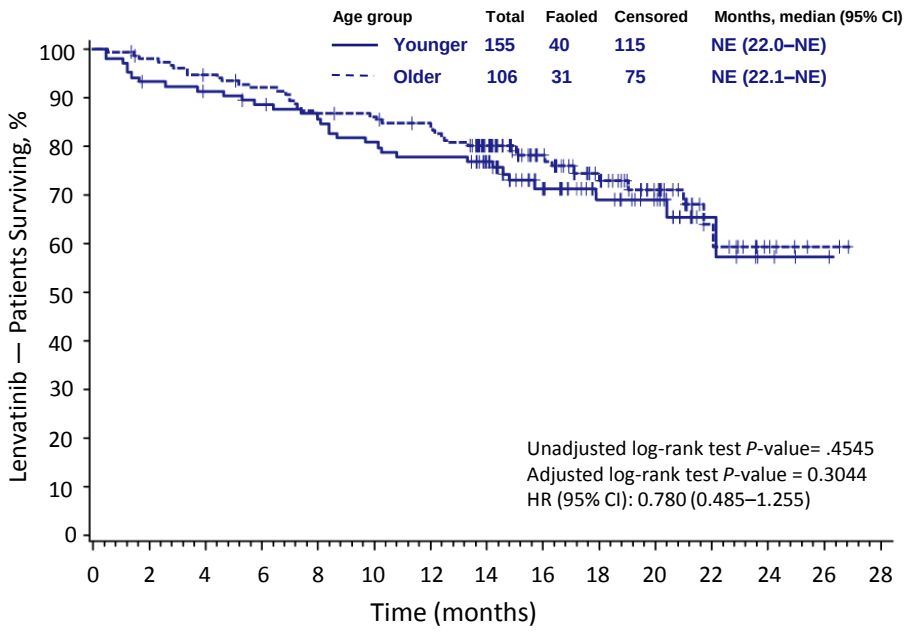
Delayed use of lenvatinib would worsen patient outcomes in elderly patients

CI, confidence interval; HR, hazard ratio; NE, not evaluable.

Brose M, et al, ASCO 2015, abstract 6048

Lenvatinib vs. Placebo: SELECT study
Overall survival

lenvatinib arm by age group

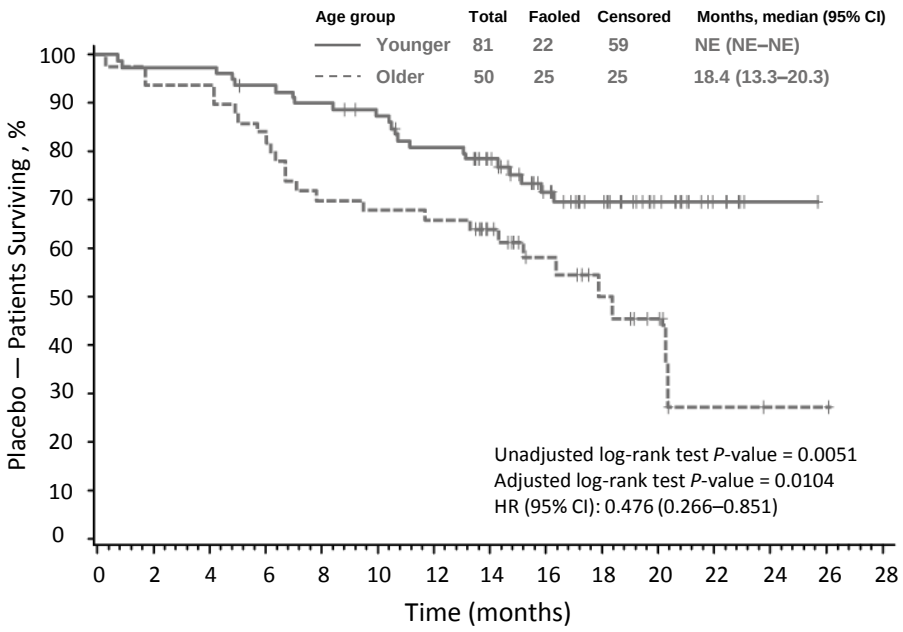


Number of patients at risk:

Lenvatinib by age group:

Younger	155	150	144	139	131	129	124	102	70	47	31	14	6	2	0
Older	106	98	95	91	88	82	79	67	42	31	24	8	4	1	0

placebo arm by age group



Number of patients at risk:

Placebo by age group:

Younger	81	79	144	139	131	129	124	102	70	47	31	14	6	2	0
Older	50	98	95	91	88	82	79	67	42	31	24	8	4	1	0

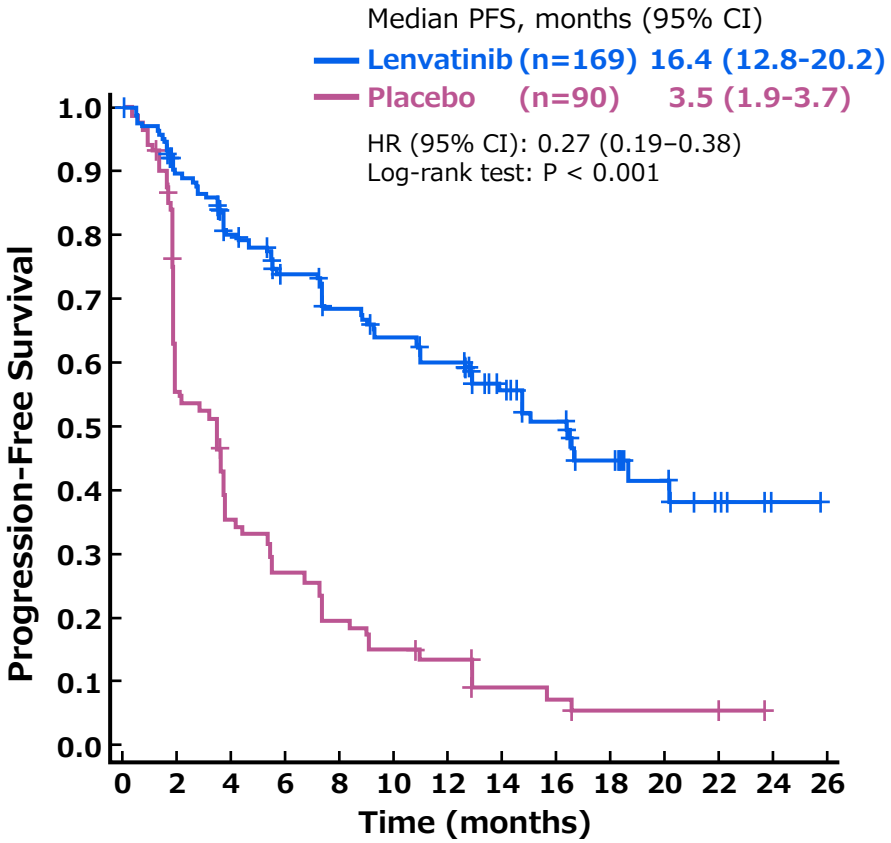
Lenvatinib would recover patient outcomes in elderly patients

CI, confidence interval; HR, hazard ratio; NE, not evaluable.

Brose M, et al, ASCO 2015, abstract 6048

Lenvatinib vs. Placebo: SELECT study
PFS by Histology

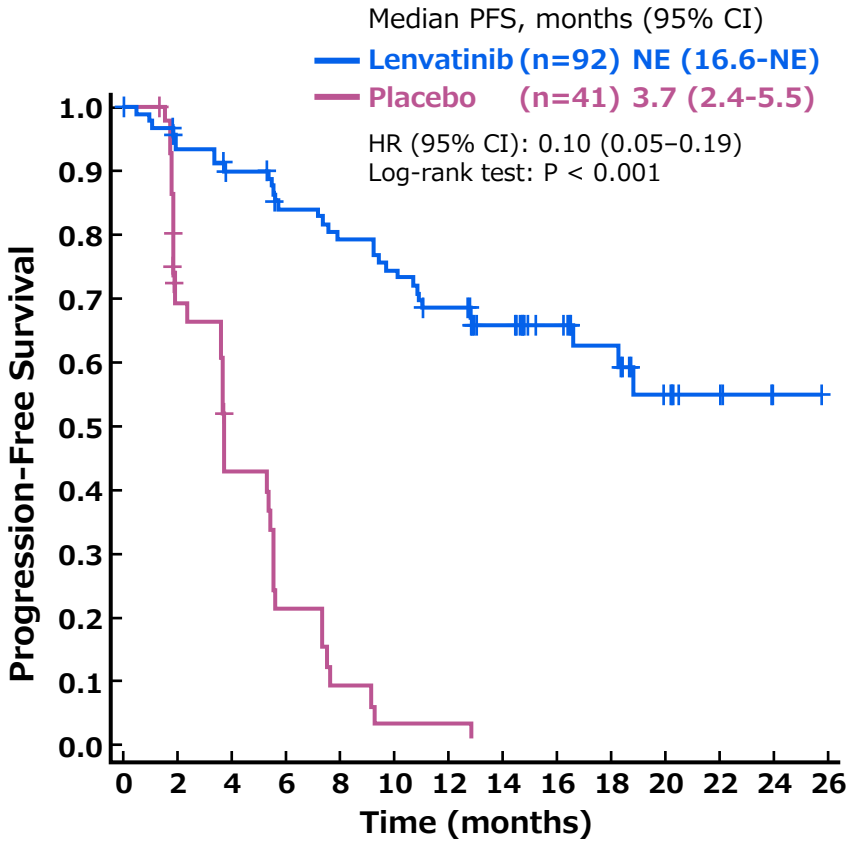
Papillary Thyroid Cancer



Number of subjects at risk:

Lenvatinib	169	142	121	106	93	86	80	53	39	25	13	5	1	0
Placebo	90	47	29	22	16	12	10	5	4	2	2	2	0	0

Follicular Thyroid Cancer



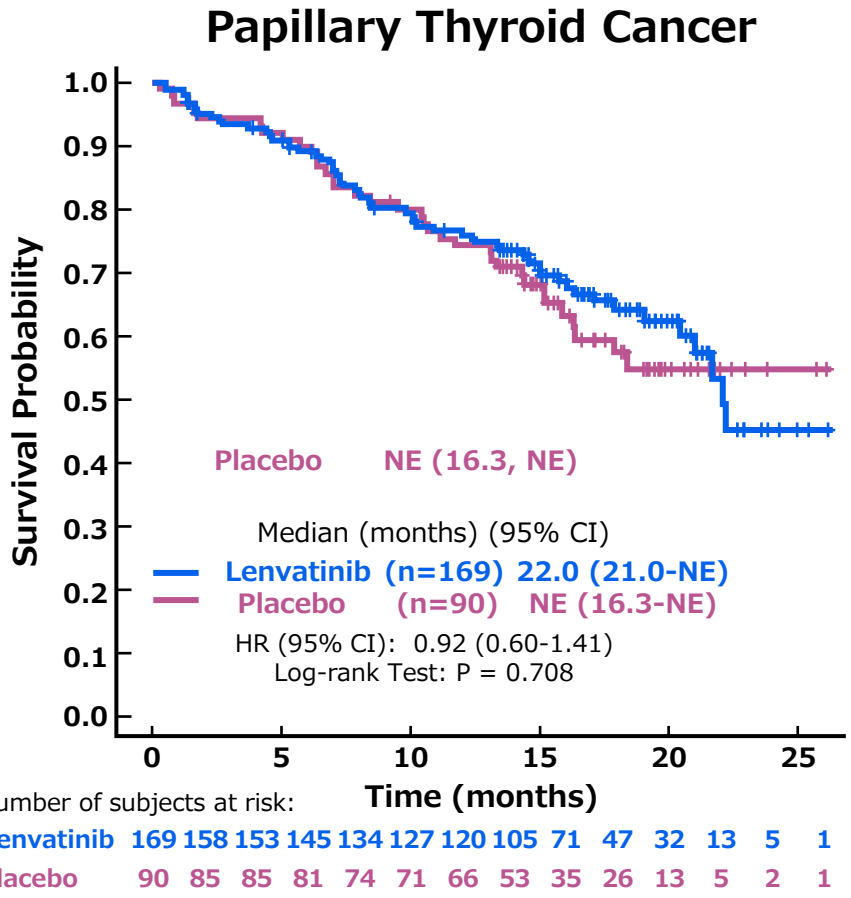
Number of subjects at risk:

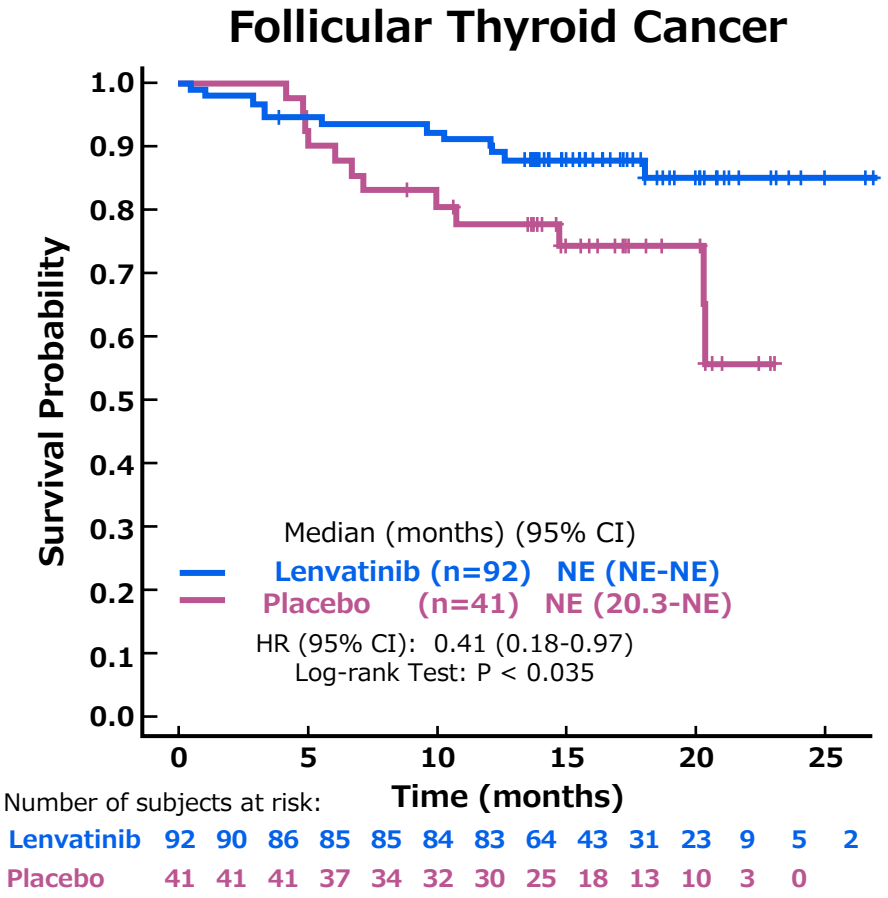
Lenvatinib	92	83	77	70	66	62	56	39	27	19	11	6	2	0
Placebo	41	24	14	7	3	1	1	1	0	0	0	0	0	0

Brose M, et al, ASCO 2015, abstract 6048

CI, confidence interval; HR, hazard ratio; NE, not estimable.

Lenvatinib vs. Placebo: SELECT study
Overall Survival by Histology





Delayed use of lenvatinib would worsen overall survival in follicular thyroid cancer

Brose M, et al, ASCO 2015, abstract 6048

Delayed Use of TKI

- Merits
  - Cost
  - Recognize improved QOL
- Demerits
  - Risk of worsening patient QOL
    - ✓Spinal cord paralysis and compression
  - Risk of brain metastasis, which VEGFR-targeted TKIs have no beneficial effect on
  - Worsened outcomes in patients with older age or FTC
  - Increased risk of bleeding by watch & wait
    - ✓ Invasion to the carotid artery in an area that was previously irradiated
    - ✓ Skin invasion and disintegration

Phase II study of sunitinib in R/M SCCHN: GORTEC 2006-01 (N=38)

- **Head and Neck Bleeding**

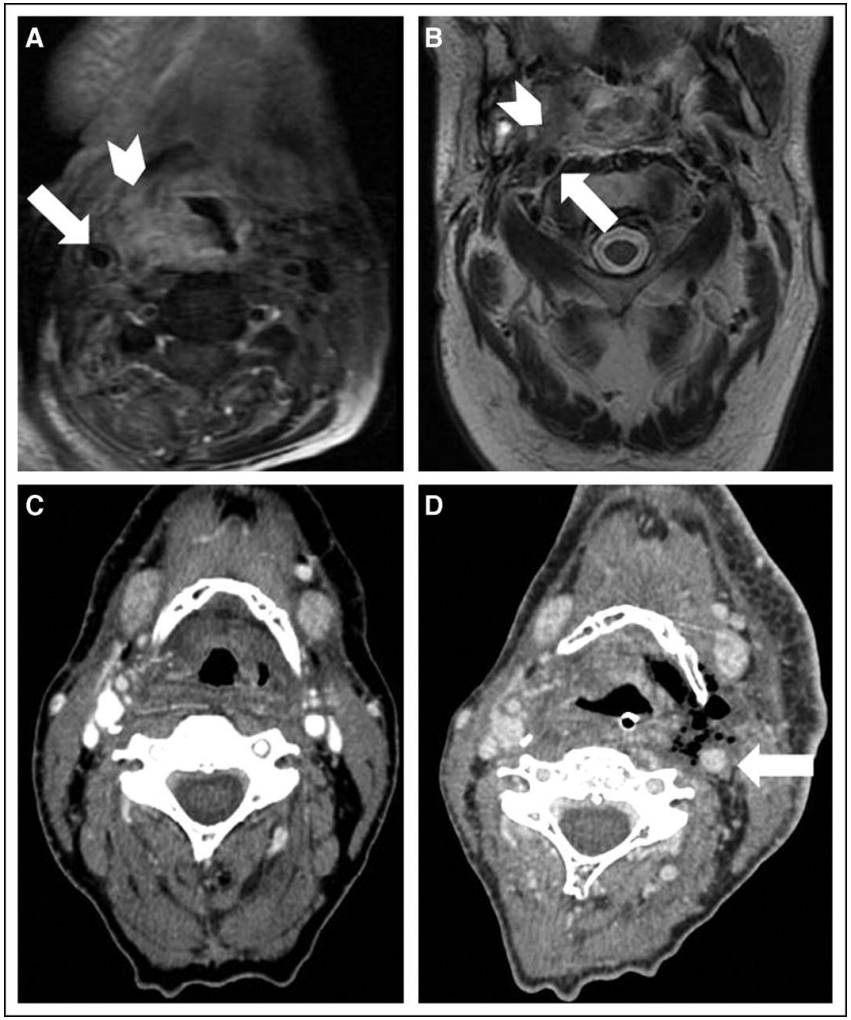
	No. of patients (%)		
	Gr 1-2	Gr 3-4	Gr 5
Head and neck bleeding	7 (18)	2 (5)	4 (11)
with local relapse	7 (18)	2 (5)	3*(8)
with no local relapse	0	0	1#(3)

- *Tumor located less than 5 mm from carotid artery
- #A large ulcer with subsequent carotid rupture in an area that was previously irradiated

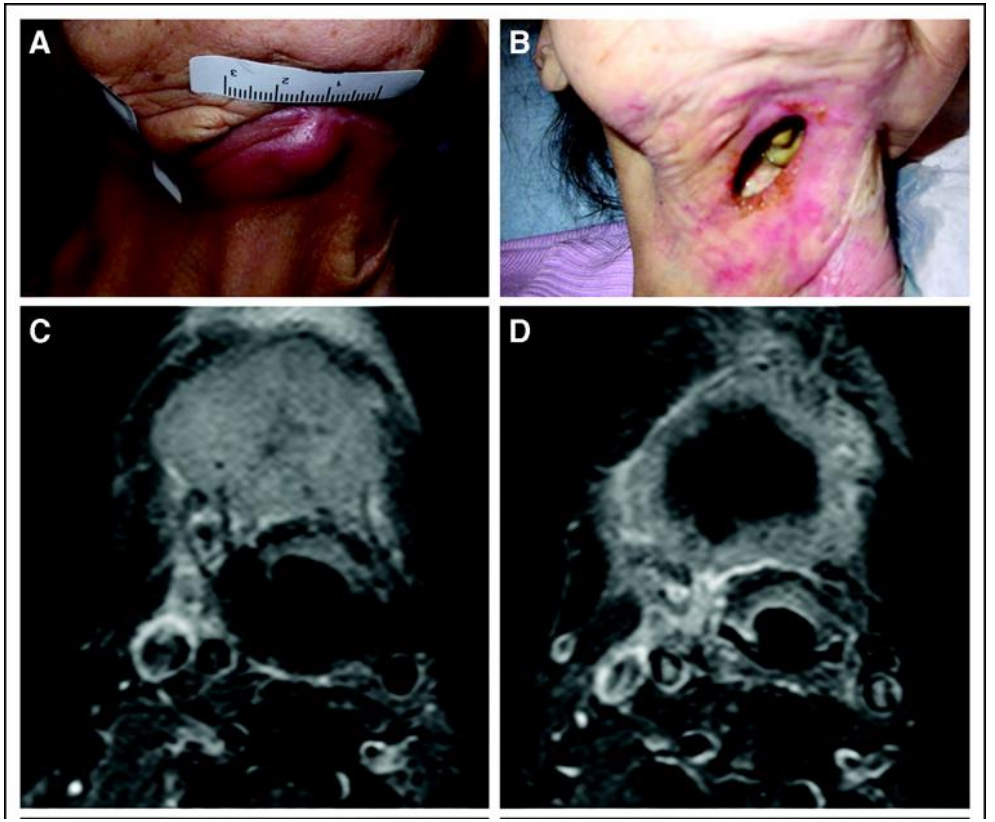
Machiels J H et al. JCO 2010;28:21-28

Grade 5 Bleeding Complications

Tumor located less than 5 mm from carotid artery



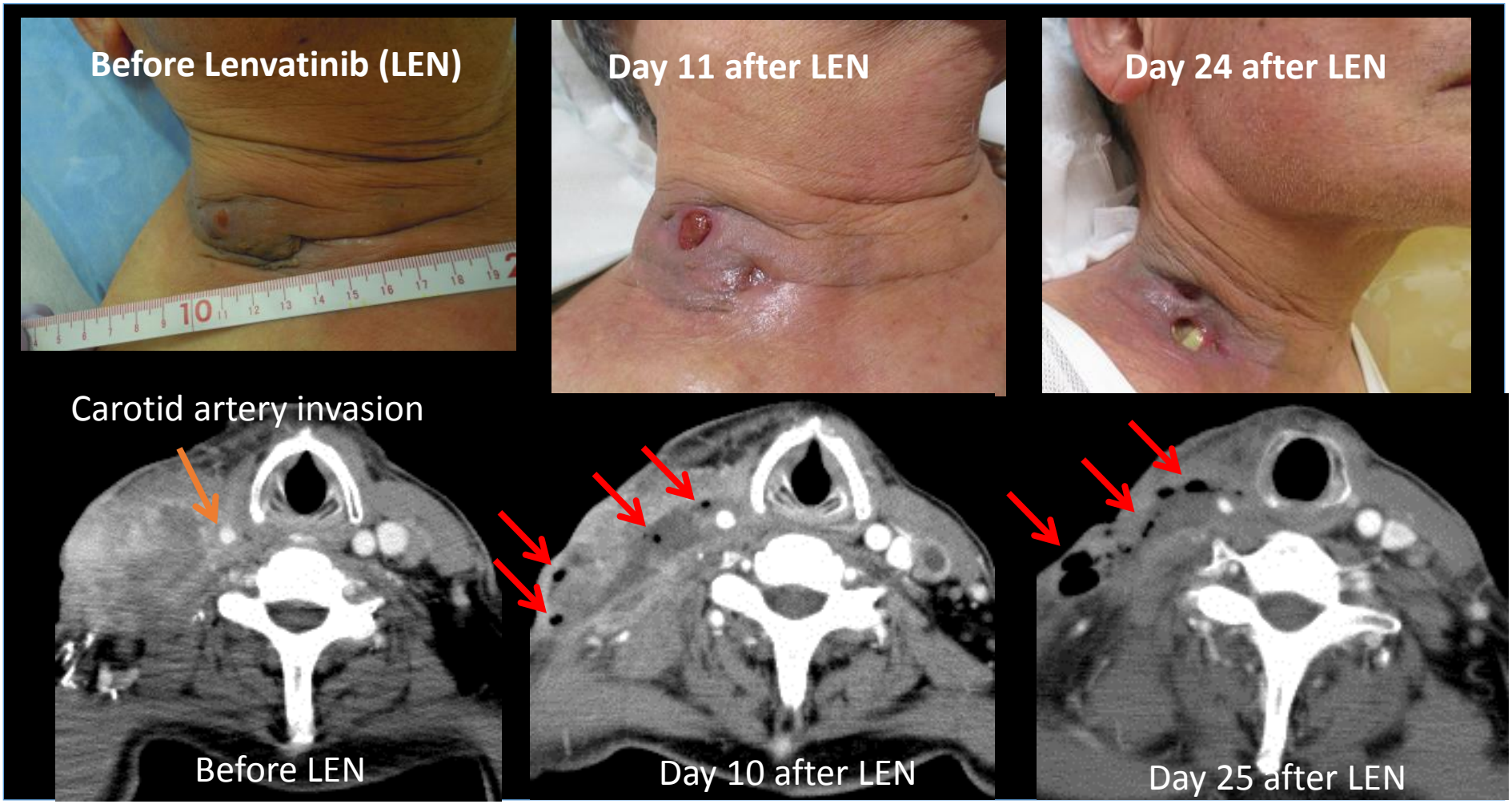
A large ulcer with subsequent carotid rupture in an area that was previously irradiated



Machiels J H et al. JCO 2010;28:21-28

Risk of Bleeding by TKI

- 73-yr-old male with recurrent PTC who had prior RT therapy in neck LN metastasis



Slide courtesy of Dr Akifumi Suzuki

Delayed Use of TKI

- Merits
  - Cost
  - Recognize improved QOL
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  - Worsened outcomes in patients with older age or FTC
  - Increased risk of bleeding by watch & wait
    - ✓ Invasion to the carotid artery in an area that was previously irradiated
    - ✓ Skin invasion and disintegration

Take Home Message: Early or Delayed use of TKI for Thyroid Cancer

- Both early and delayed use of TKI for thyroid cancer have merits and demerits.
- Appropriate timing to start TKI should be considered based on assessment of the individual
  - Symptomatic disease and/or rapidly growing
  - Risk of worsening patient QOL
  - Aggressive disease features
    - Elderly or FTC patients
  - Increased risk of being unable to receive TKI by watch & wait
    - Poor PS
    - Brain metastasis
    - Risk of bleeding