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„Gibt es einen optimalen Zeitpunkt für den Einsatz von TKIs bei Radiojod-refraktärem Schilddrüsenkarzinom?“

Christian Pirich

Department of Nuclear Medicine & Endocrinology
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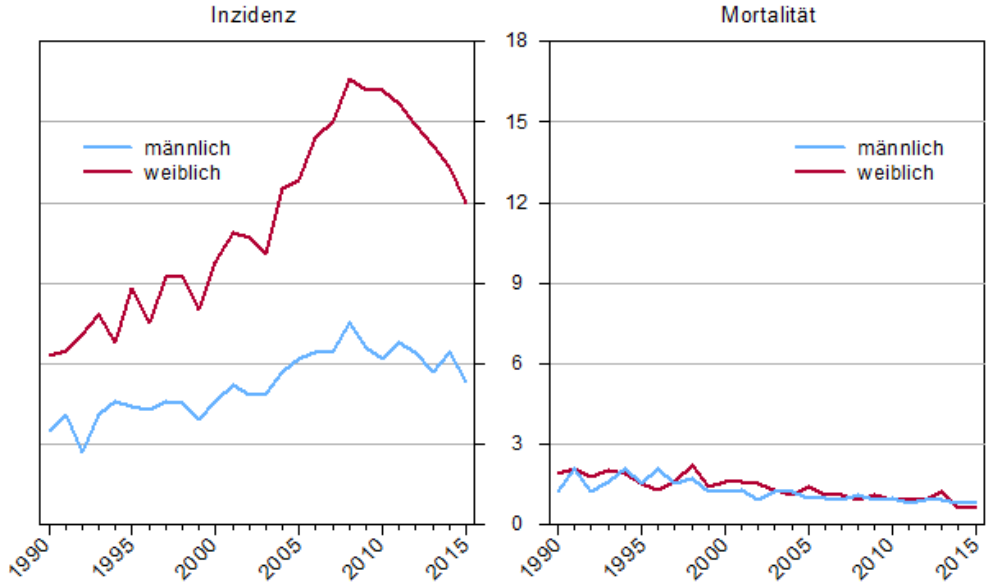
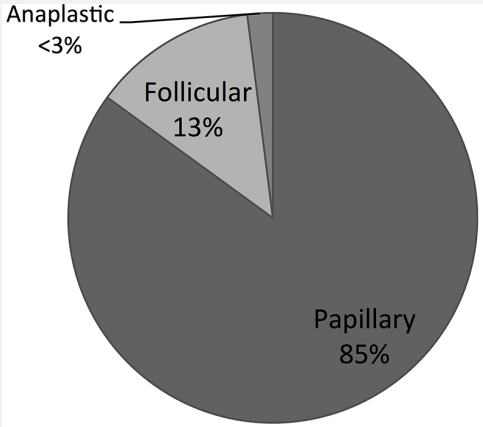
Radiojod-refraktäres, differenziertes Schilddrüsenkarzinom

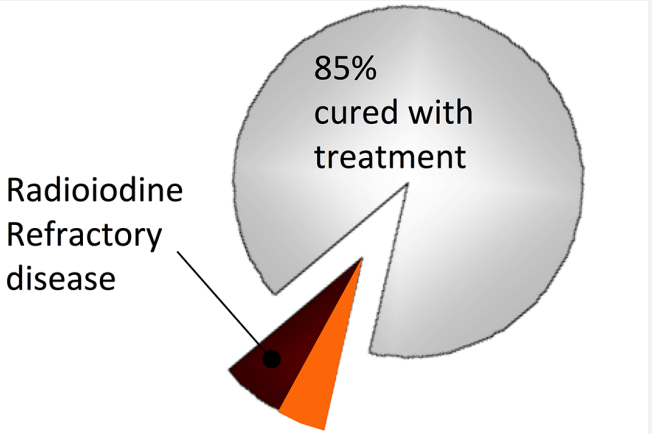
- Definition
- Häufigkeit
- Therapiestandard: Tyrosinkinase-Inhibitoren
- Kriterien für die Einleitung der Therapie: Tumorgröße, -kinetik, Klinik, Alter
- Wechsel innerhalb der Substanzklasse (Wirkungsverlust, Toxizität)

Bösartige Neubildungen der Schilddrüse im Zeitverlauf altersstandardisierte Raten auf 100.000 Personen (EUR13-Weltbevölkerung)



Q: STATISTIK AUSTRIA, Österreichisches Krebsregister (Stand 06.12.2017) und Todesursachenstatistik.
Erstellt am 18.12.2017.

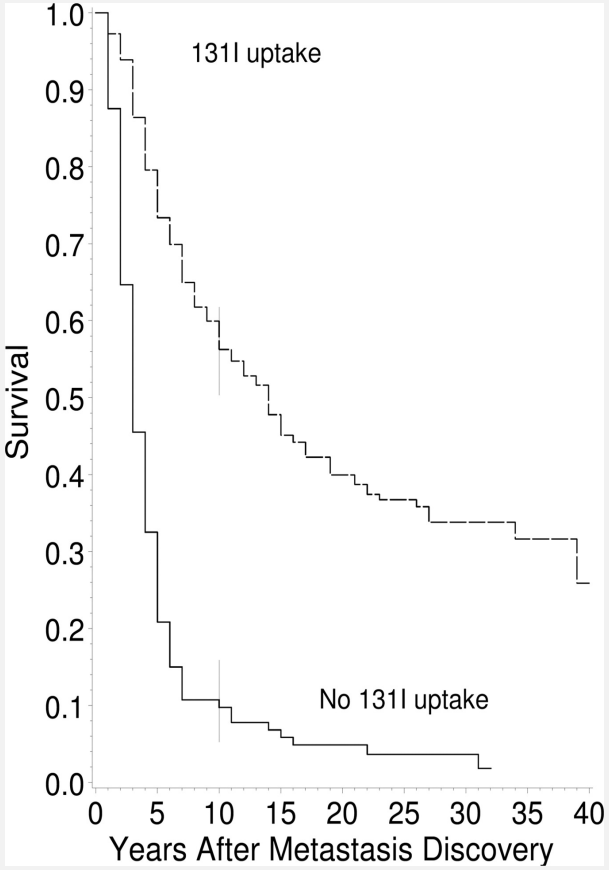


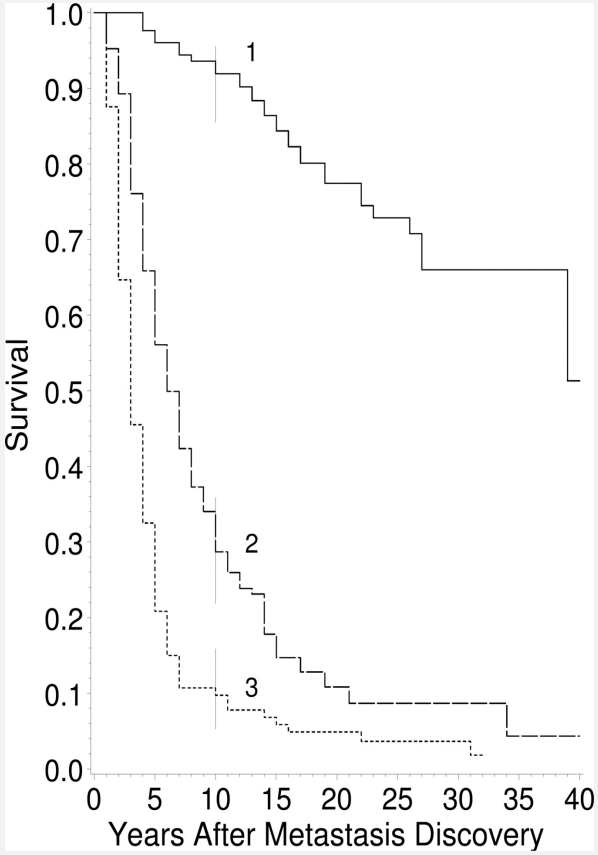


15% recurrent/metastatic disease ~1/3 controlled by I-131, T4 and/or local Rx

Clinical Endocrinology 2017; 88: 529-537

Prognose und Radiojodaufnahme in Metastasen





Überleben in Jahren nach Erstdiagnose von Fernmetastasen:
Gruppe 1: 131J-positive Pat. mit CR; *Gruppe 2* 131J-positive Pat., die positive blieben. *Gruppe 3:* 131J-negative Patienten

Durante, C. et al. J Clin Endocrinol Metab 2006;91:2892-2899

Indikationen zum Einsatz von Tyrosinkinase-Inhibitoren beim Radiojod-refraktärem differenzierten Schilddrüsenkarzinom

- 2014/2015 EMA /FDA-Zulassung der Tyrosinkinase-Inhibitoren Sorafenib u. Lenvatinib in der Indikation ***Radiojod-refraktäres differenziertes Schild-drüsenkarzinom***

Lenvatinib versus Placebo in Radioiodine-Refractory Thyroid Cancer

Martin Schlumberger, M.D., Makoto Tahara, M.D., Ph.D., Lori J. Wirth, M.D., Bruce Robinson, M.D., Marcia S. Brose, M.D., Ph.D., Rossella Elisei, M.D., Mouhammed Amir Habra, M.D., Kate Newbold, M.D., Manisha H. Shah, M.D., Ana O. Hoff, M.D., Andrew G. Gianoukakis, M.D., Naomi Kiyota, M.D., Ph.D., Matthew H. Taylor, M.D., Sung-Bae Kim, M.D., Ph.D., Monika K. Krzyzanowska, M.D., M.P.H., Corina E. Dutcus, M.D., Begoña de las Heras, M.D., Junming Zhu, Ph.D., and Steven I. Sherman, M.D.

In our phase 3, randomized, double-blind, multicenter study involving patients with progressive thyroid cancer that was refractory to iodine-131, we randomly assigned 261 patients to receive lenvatinib (at a daily dose of 24 mg per day in 28-day cycles) and 131 patients to receive placebo. At the time of disease progression, patients in the placebo group could receive open-label lenvatinib. The primary end point was progression-free survival. Secondary end points included the response rate, overall survival, and safety.

N Engl J Med 2015;372:621-30.
DOI: 10.1056/NEJMoa1406470

Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial

*Marcia S Brose, Christopher M Nutting, Barbara Jarzab, Rossella Elisei, Salvatore Siena, Lars Bastholt, Christelle de la Fouchardiere, Furio Pacini, Ralf Paschke, Young Kee Shong, Steven I Sherman, Johannes W A Smit, John Chung, Christian Kappeler, Carol Peña, István Molnár, Martin J Schlumberger, on behalf of the DECISION investigators**

Methods In this multicentre, randomised, double-blind, placebo-controlled, phase 3 trial (DECISION), v sorafenib (400 mg orally twice daily) in patients with radioactive iodine-refractory locally advanced differentiated thyroid cancer that had progressed within the past 14 months. Adult patients (≥18 years of type of cancer were enrolled from 77 centres in 18 countries. To be eligible for inclusion, participants had

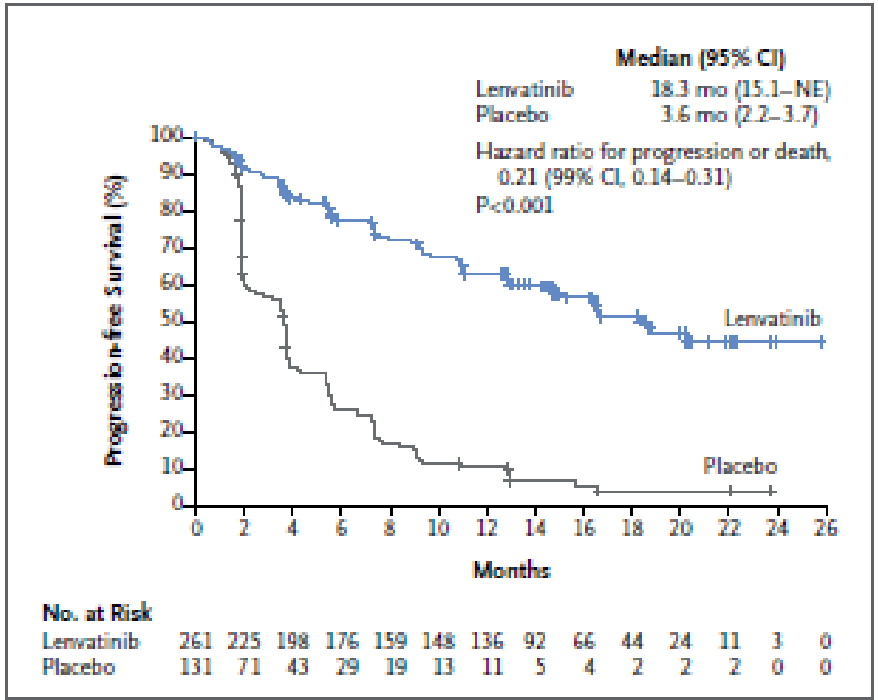


Figure 2. Kaplan–Meier Estimate of Progression-free Survival in the Intention-to-Treat Population.

Tumor responses were assessed with the use of Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and were confirmed by independent centralized radiologic review. Tumor responses were calculated as the maximum percentage change from baseline in the sum of the diameters of target lesions. CI denotes confidence interval, and NE not estimable.

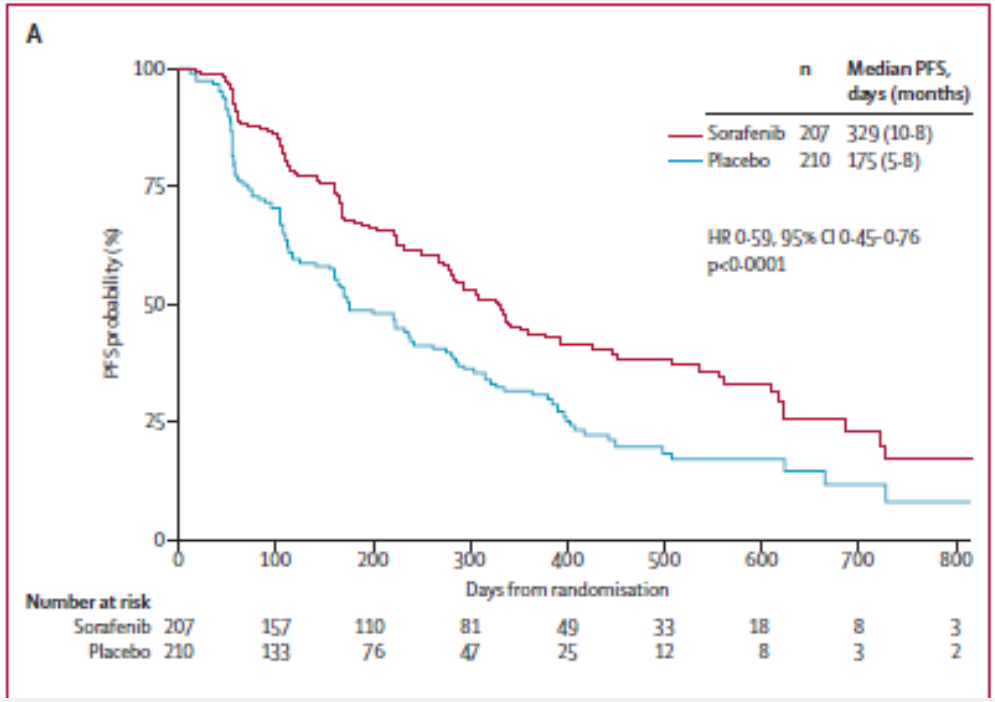


Table 2. Efficacy Measures.*

Outcome	Lenvatinib (N=261)	Placebo (N=131)	Hazard Ratio†	Odds Ratio (95% CI)
Progression-free survival				
Primary analysis, IRR and ITT populations‡				
Median (95% CI) — mo	18.3 (15.1–NE)	3.6 (2.2–3.7)	0.21 (0.14–0.31)§	
Rate — % (95% CI)				
6 mo	77.5 (71.7–82.3)	25.4 (18.0–33.6)		
12 mo	63.0 (56.5–68.9)	10.5 (5.7–16.9)		
18 mo	51.1 (43.3–58.3)	3.8 (1.1–9.2)		
24 mo	44.3 (35.1–53.1)	NE		
Prespecified sensitivity analyses				
Investigator assessment, ITT population — mo			0.24 (0.16–0.35)§	
Median	16.6	3.7		
95% CI	14.8–NE	3.5–5.4		
IRR population — mo¶			0.22 (0.15–0.32)§	
Median	16.6	3.6		
95% CI	14.8–20.3	2.2–3.7		
Secondary efficacy end points				
Overall survival, RPSFT adjusted, ITT population			0.62 (0.40–1.00)‖	
Median (95% CI) — mo	NE (22.0–NE)	NE (14.3–NE)		
Rate, RPSFT adjusted — % (95% CI)				
6 mo	90.7 (86.4–93.7)	85.3 (78.0–90.4)		
12 mo	81.6 (76.2–85.8)	70.0 (57.1–79.7)		
18 mo	72.3 (65.7–77.9)	63.0 (44.3–76.9)		
24 mo	58.7 (46.0–68.6)	NE		
Response rate — no. (%)**	169 (64.8)	2 (1.5)		28.87 (12.46–66.86)§
Complete response	4 (1.5)	0		
Partial response	165 (63.2)	2 (1.5)		
Stable disease	60 (23.0)	71 (54.2)		
Durable stable disease ≥23 wk	40 (15.3)	39 (29.8)		
Progressive disease	18 (6.9)	52 (39.7)		
Could not be evaluated	14 (5.4)	6 (4.6)		
Exploratory efficacy end points				
Disease-control rate — no. (%)††	229 (87.7)	73 (55.7)		5.05 (2.98–8.54)§
Clinical-benefit rate — no. (%)§§	209 (80.1)	41 (31.3)		7.63 (4.55–12.79)§
Time to first objective response — mo				
Median	2.0	5.6		
95% CI	1.9–3.5	1.8–9.4		

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Defining Radioiodine-Refractory Differentiated Thyroid Cancer: Efficacy and Safety of Lenvatinib by Radioiodine-Refractory Criteria in the SELECT Trial

Naomi Kiyota[1], Bruce Robinson[2], Manisha Shah[3], Ana O. Hoff[4], Matthew H. Taylor[5], Di Li[6], Corina E. Dutcus[6], Eun Kyung Lee[7], Sung-Bae Kim[8], and Makoto Tahara[9]

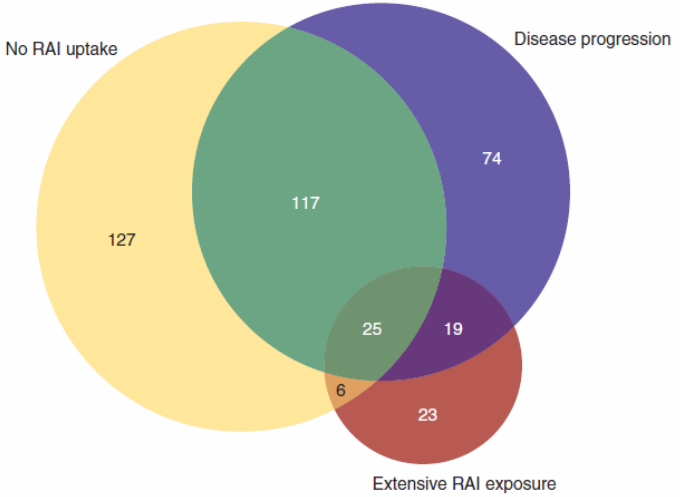

FIG. 1. Venn diagram of patients in SELECT by RR-DTC criteria group. Information is not available for one patient. RAI, radioiodine; RR-DTC, radioiodine-refractory differentiated thyroid cancer; SELECT, Study of (E7080) LEnvatinib in Differentiated Cancer of the Thyroid.

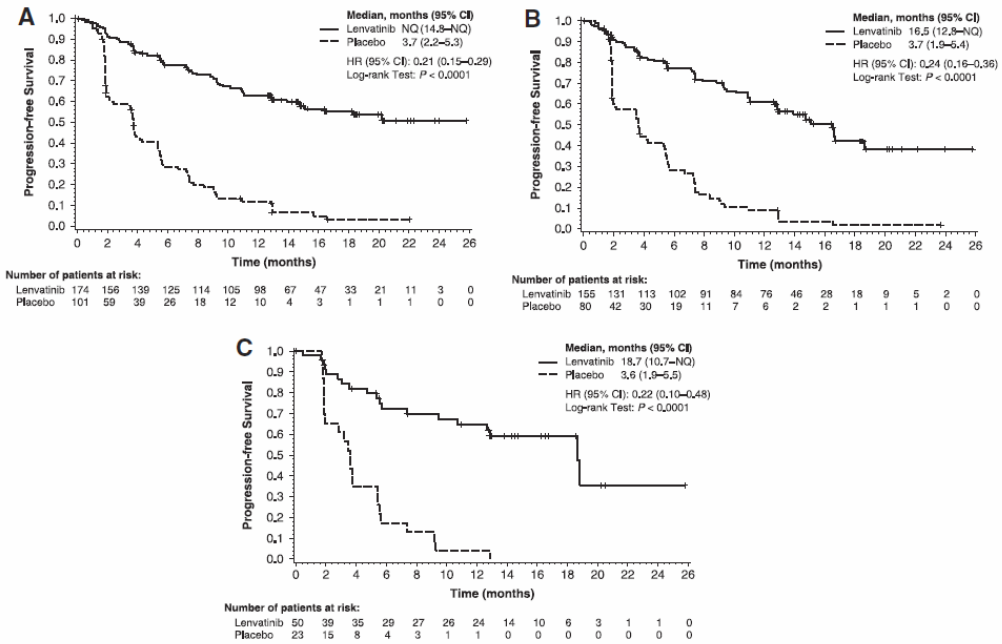

FIG. 2. Kaplan–Meier estimates of progression-free survival by RR-DTC inclusion criteria: (**A**) no RAI uptake, (**B**) disease progression, (**C**) extensive RAI exposure. CI, confidence interval; HR, hazard ratio; NQ, not quantifiable.

TABLE 1. BASELINE AND DEMOGRAPHIC CHARACTERISTICS BY RR-DTC INCLUSION CRITERIA

	No RAI uptake		*Disease progression despite RAI avidity*		*Extensive RAI exposure*	
	Lenvatinib (n=174)	*Placebo (n=101)*	*Lenvatinib (n=155)*	*Placebo (n=80)*	*Lenvatinib (n=50)*	*Placebo (n=23)*
Histology, *n* (%)						
Papillary	108 (62.1)	72 (71.3)	95 (61.3)	57 (71.3)	30 (60.0)	17 (73.9)
Poorly differentiated	17 (9.8)	16 (15.8)	14 (9.0)	11 (13.8)	4 (8.0)	3 (13.0)
Follicular, not Hürthle cell	66 (37.9)	29 (28.7)	60 (38.7)	23 (28.8)	20 (40.0)	6 (26.1)
Hürthle cell	31 (17.8)	14 (13.9)	26 (16.8)	11 (13.8)	4 (8.0)	3 (13.0)
Mean tumor burden at baseline, mm (range)	68 (15–226)	69 (15–236)	73 (15–331)	74 (15–267)	72 (15–331)	82 (20–143)
Time from most recent disease progression to randomization, *n* (%)						
<3 months	142 (81.6)	74 (73.3)	122 (78.7)	54 (67.5)	43 (86.0)	14 (60.9)
≥3 months	28 (16.1)	24 (23.8)	31 (20)	22 (27.5)	7 (14.0)	8 (34.8)
Missing	4 (2.3)	3 (3.0)	2 (1.3)	4 (5.0)	0	1 (4.3)
Median radioiodine activity received, GBq	11.1[b]	13.0[c]	11.8[d]	11.4[e]	30.6	30.1

Nuklearmedizin. 2014 Nov 25;54(1). [Epub ahead of print]

[Therapie des Patienten mit Radioiod-refraktärem, differenziertem Schilddrüsenkarzinom. Ein Konsensusstatement.]

[Article in German]

Lindner C[1], Dierneder J, Pall G, Pirich C, Hoffmann M, Raderer M, Becherer A, Niederle B, Lipp R, Lind P, Gallowitsch H, Romeder F, Virgolini I.

- Variabler klinischer Verlauf metastasierender differenzierter Schilddrüsenkarzinome
- Patientensselektion für TKI-Einsatz unbedingt erforderlich
  - Radiojod-refraktär
  - Klinische Symptome
  - Dokumentierte Krankheitsprogression (laborchemisch: Thyreoglobulin und Bildgebung)

Table 1. Baseline Characteristics in the Intention-to-Treat Population.*

Variable	Lenvatinib (N = 261)	Placebo (N = 131)
Median age — yr	64	61
Male sex — no. (%)	125 (47.9)	75 (57.3)
Region — no. (%)		
Europe	131 (50.2)	64 (48.9)
North America	77 (29.5)	39 (29.8)
Other†	53 (20.3)	28 (21.4)
ECOG performance status — no. (%)‡		
0 or 1	248 (95.0)	129 (98.5)
2 or 3	13 (5.0)	2 (1.5)
One prior treatment regimen with a tyrosine kinase inhibitor — no. (%)§	66 (25.3)	27 (20.6)
Histologic subtype of differentiated thyroid cancer — no. (%)¶		
Papillary	132 (50.6)	68 (51.9)
Poorly differentiated	28 (10.7)	19 (14.5)
Follicular, not Hürthle cell	53 (20.3)	22 (16.8)
Hürthle cell	48 (18.4)	22 (16.8)
Metastatic lesions — no. (%)		
With bony metastases	104 (39.8)	48 (36.6)
With pulmonary metastases	226 (86.6)	124 (94.7)

	Sorafenib (n=207)	Placebo (n=210)
Female sex	103 (49·8%)	115 (54·8%)
Age (years)		
Median (range)	63 (24–82)	63 (30–87)
≥60 years	127 (61·4%)	129 (61·4%)
Ethnic origin		
White	123 (59·4%)	128 (61·0%)
Asian	47 (22·7%)	52 (24·8%)
Black	6 (2·9%)	5 (2·4%)
Hispanic	2 (1·0%)	2 (1·0%)
Not reported	29 (14·0%)	23 (11·0%)
Region		
Europe	124 (59·9%)	125 (59·5%)
North America	36 (17·4%)	36 (17·1%)
Asia	47 (22·7%)	49 (23·3%)
Metastases		
Locally advanced	7 (3·4%)	8 (3·8%)
Distant	200 (96·6%)	202 (96·2%)
Time from diagnosis (months)		
Median (range)	66·2 (3·9–362·4)	66·9 (6·6–401·8)
ECOG performance status		
0	130 (62·8%)	129 (61·4%)
1	69 (33·3%)	74 (35·2%)
2	7 (3·4%)	6 (2·9%)
Histology by central review*†		
Papillary	118 (57·0%)	119 (56·7%)
Follicular, oncocytic (Hürthle cell)	37 (17·9%)	37 (17·6%)
Follicular, non-Hürthle cell	13 (6·3%)	19 (9·0%)
Poorly differentiated	24 (11·6%)	16 (7·6%)
Well differentiated	2 (1·0%)	1 (0·5%)
Non-thyroid	0	1 (0·5%)
Medullary	0	1 (0·5%)
Oncocytic carcinoma	2 (1·0%)	0
Carcinoma, not otherwise specified	0	3 (1·4%)
Missing or nondiagnostic	13 (6·3%)	14 (6·7%)
Most common metastatic lesion sites		
Lung	178 (86·0%)	181 (86·2%)
Lymph nodes	113 (54·6%)	101 (48·1%)
Bone	57 (27·5%)	56 (26·7%)
Pleura	40 (19·3%)	24 (11·4%)
Head and neck	33 (15·9%)	34 (16·2%)
Liver	28 (13·5%)	30 (14·3%)
Baseline FDG uptake		
Positive	161 (77·8%)	159 (75·7%)
Negative	14 (6·8%)	15 (7·1%)
Missing	32 (15·5%)	36 (17·1%)
Previous treatment		
Median cumulative radioiodine activity (mCi)	400	376
Any previous systemic anticancer therapy	7 (3·4%)	6 (2·9%)
Any previous radiotherapy	83 (40·1%)	91 (43·3%)

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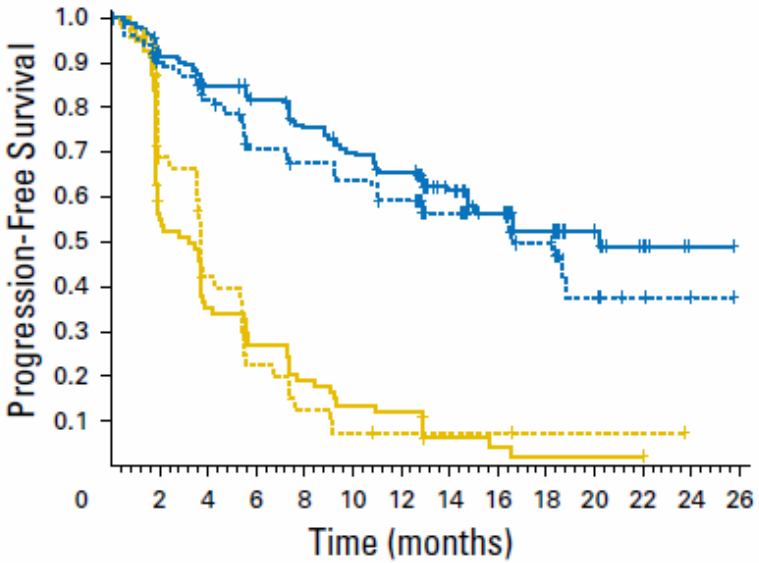
Effect of Age on the Efficacy and Safety of Lenvatinib in Radioiodine-Refractory Differentiated Thyroid Cancer in the Phase III SELECT Trial

Marcia S. Brose, Francis P. Worden, Kate L. Newbold, Matthew Guo, and Arti Hurria

A



No. of patients at risk:

Age group: Patients age ≤ 65 years														
Lenvatinib	155	138	121	113	102	94	87	60	39	25	16	8	2	0
Placebo	81	42	26	20	14	10	9	3	2	1	1	1	0	0
Age group: Patients age > 65 years														
Lenvatinib	106	87	77	63	57	54	49	32	27	19	8	3	1	0
Placebo	50	29	17	9	5	3	2	2	2	1	1	1	0	0

Conclusion

This subanalysis demonstrated improved PFS with lenvatinib treatment versus placebo in both age groups, although higher toxicity was observed in older patients. Despite the allowance of crossover after disease progression, the OS benefit was observed in older patients, suggesting that lenvatinib should be considered for treatment of patients of any age with RR-DTC.

J Clin Oncol 35:2692-2699.

PFS in der Multivariatanalyse

Table 2. Univariate and Multivariate Analyses of Potential Factors Associated With PFS

	Univariate Analysis			Multivariate Analysis[a]		
Parameter	**HR[b]**	**95% CI**	***P* Value[b]**	**HR**	**95% CI**	***P* Valu**
Age (≤ vs > 65 y)	0.79	0.54–1.17	.24			
Sex (male vs female)	1.26	0.86–1.84	.24			
Baseline body weight (< vs ≥ median)	1.59	1.08–2.33	.02	1.55	1.03–2.32	004
Baseline ECOG performance status (< vs ≥ 1)	0.50	0.34–0.74	<.01	0.63	0.41–0.96	.03
Histology (follicular vs papillary)	0.64	0.43–0.97	.04	0.69	0.45–1.07	.10
Prior VEGF-targeted therapy (0 vs 1)	0.75	0.49–1.14	.18	0.86	0.55–1.34	.49
Baseline tumor size (< vs ≥ median)	0.49	0.33–0.72	<.01	0.61	0.40–0.94	.03
Percentage tumor reduction, wk 8 (< vs ≥ median)	1.67	1.11–2.50	.01	1.49	0.98–2.26	.06

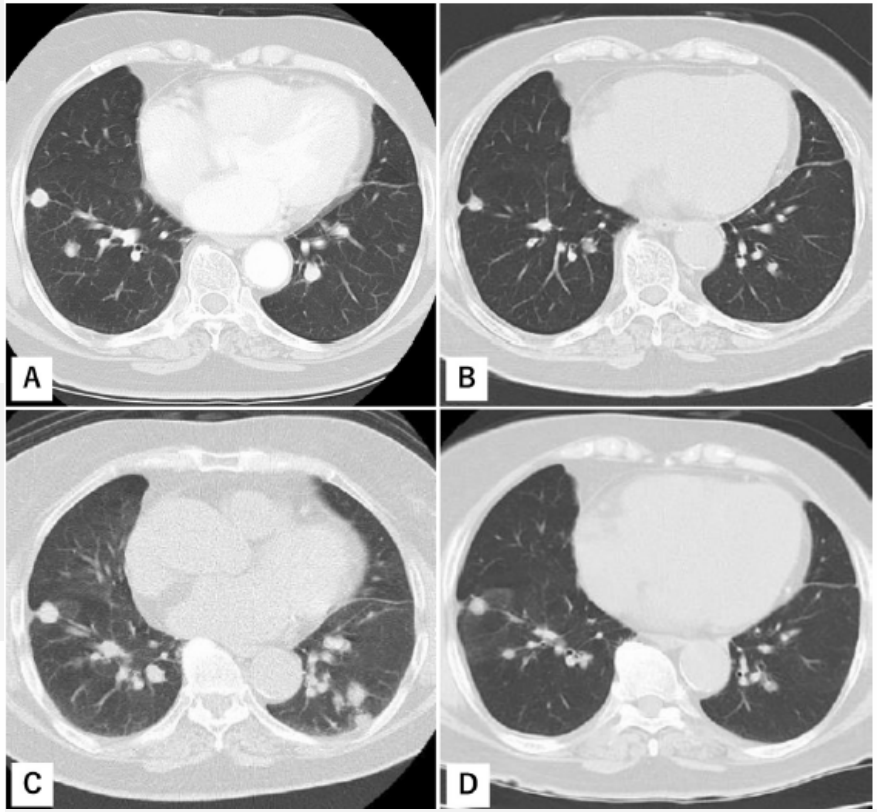
[a] Multivariate analysis includes only factors with $P < .2$ from univariate analyses.

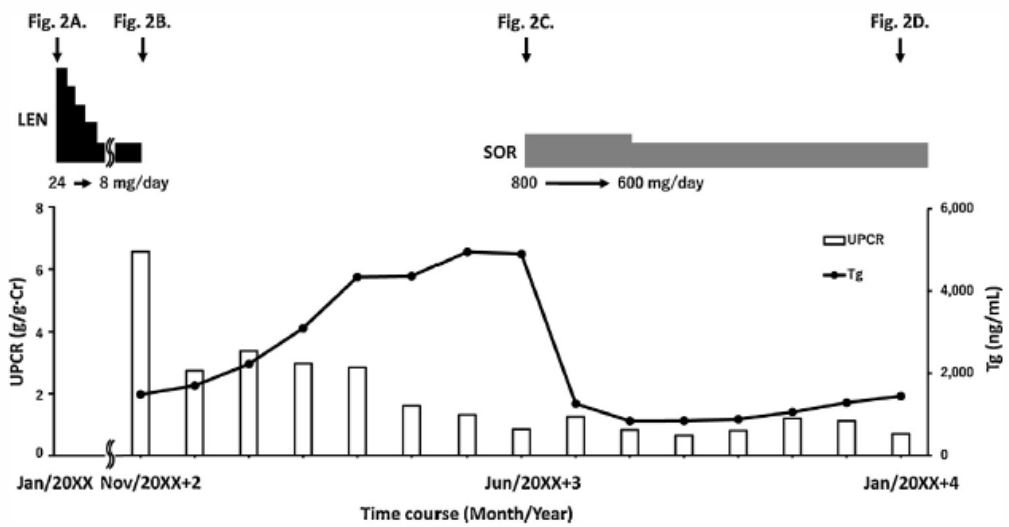
[b] HRs and *P* values were estimated with Cox proportional hazard models.

Auris Nasus Larynx 45 (2018) 1249–1252

Successful treatment switch from lenvatinib to sorafenib in a patient with radioactive iodine-refractory differentiated thyroid cancer intolerant to lenvatinib due to severe proteinuria

Hideaki Goto [a], Naomi Kiyota [a,b,*], Naoki Otsuki [c], Yoshinori Imamura [a], Naoko Chayahara [a], Hirotaka Suto [a], Yoshiaki Nagatani [a], Masanori Toyoda [a], Toru Mukohara [a], Ken-ichi Nibu [c], Toshihiko Kasahara [d], Yasuhiro Ito [e], Akihiro Miya [e], Mitsuyoshi Hirokawa [f], Akira Miyauchi [e], Hironobu Minami [a,b]



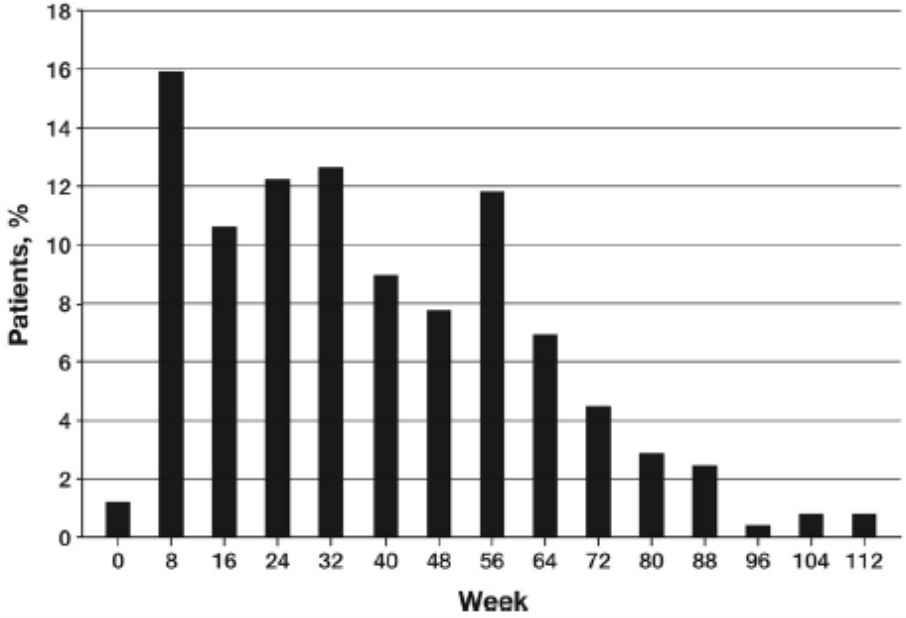


Time course of urine protein to creatinine ratio (UPCR) and thyroglobulin (Tg) values. LEN, lenvatinib; SOR, so

A before LENVATINIB
B before suspension of LENVA
C after 7-month without LENVA
D after 7-month SORAFENIB

Characterization of Tumor Size Changes Over Time From the Phase 3 Study of Lenvatinib in Thyroid Cancer

Bruce Robinson, Martin Schlumberger, Lori J. Wirth, Corina E. Dutcus, James Song, Matthew H. Taylor, Sung-Bae Kim, Monika K. Krzyzanowska, Jaume Capdevila, Steven I. Sherman, and Makoto Tahara*



Results: The median maximum percentage change in tumor size was −42.9% for patients receiving lenvatinib (responders, −51.9%; nonresponders, −20.2%). Tumor size reduction was most pronounced at first assessment (median, −24.7% at 8 wk after randomization); thereafter, the rate of change was slower but continuous (−1.3% per mo). In a multivariate model, percentage change in tumor size at the first assessment was a marginally significant positive predictor for PFS ($P = .06$).

Conclusions: The change in tumor size conferred by lenvatinib was characterized by two phases: an initial, rapid decline, followed by slower, continuous shrinkage. (*J Clin Endocrinol Metab* 101: 4103–4109, 2016)

Characterization of Tumor Size Changes Over Time From the Phase 3 Study of Lenvatinib in Thyroid Cancer

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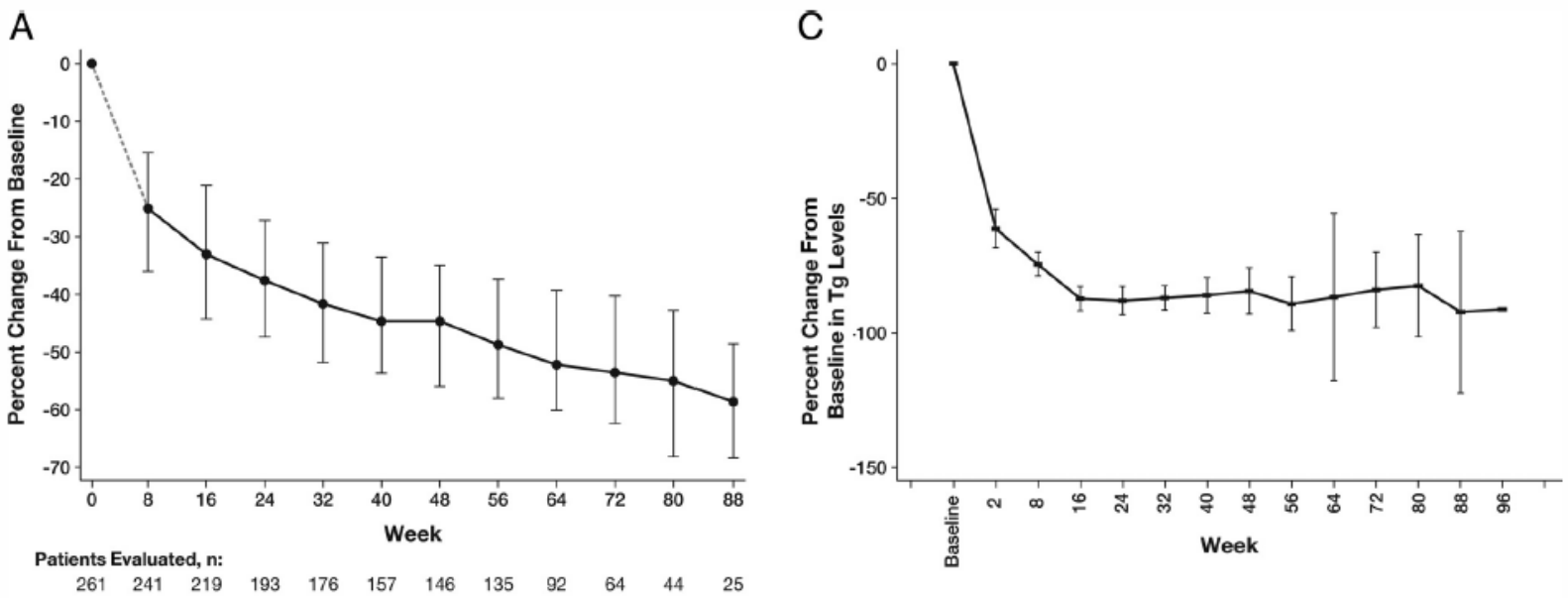

Endocrine (2017) 56:121–128

Table 1 Common lenvatinib-emergent adverse events

Lenvatinib-emergent adverse events	Grade 1–2n (%)	Grade 3n (%)	Median time to first onset, weeks (IQR)	Median time to last resolution, weeks (IQR)
Diarrhea[a]	152 (58)	23 (9)	12.1 (4.1, 23.7)	18.1 (2.3, 40.9)
Fatigue/asthenia/malaise	147 (56)	27 (10)	3.0 (1.1, 7.0)	16.3 (4.6, 36.6)
Proteinuria	58 (22)	26 (10)	6.1 (4.0, 15.6)	8.8 (4.0, 24.6)
Rash[b]	58 (22)	1 (0)	7.3 (2.9, 16.3)	5.9 (2.0, 18.6)
PPES	76 (29)	9 (3)	5.9 (3.1, 12.0)	20.0 (8.6, 32.1)

IQR, interquartile range, *PPES*, palmar-plantar erythrodysesthesia syndrome

[a] Includes diarrhea, colitis, bowel movement irregularity, frequent bowel movements, functional gastrointestinal disorder, gastrointestinal disorder, and change in bowel habit

[b] Includes macule, papule, rash, rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, and rash pruritic

Incidence and timing of common adverse events in Lenvatinib-treated patients from the SELECT trial and their association with survival outcomes

Robert I. Haddad[1] · Martin Schlumberger[2] · Lori J. Wirth[3] · Eric J. Sherman[4] · Manisha H. Shah[5] · Bruce Robinson[6] · Corina E. Dutcus[7] · Angela Teng[7] · Andrew G. Gianoukakis[8] · Steven I. Sherman[9]

Characterization of Tumor Size Changes Over Time From the Phase 3 Study of Lenvatinib in Thyroid Cancer

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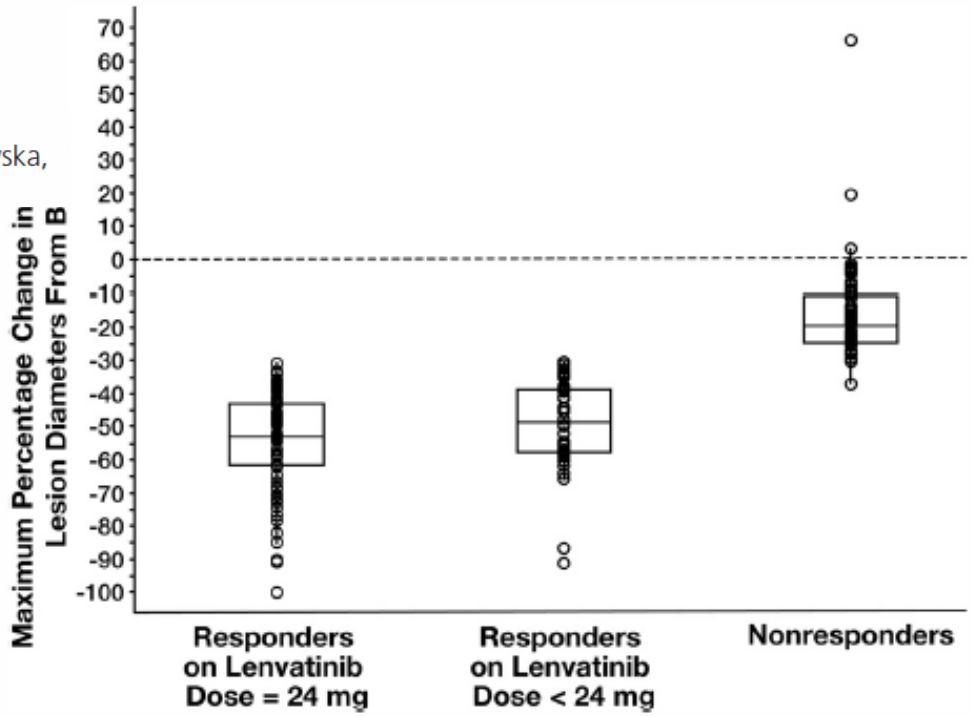

Figure 1. Maximum percentage change in sum of target lesion diameters from baseline in patients with RR-DTC who were randomized to receive lenvatinib in SELECT. Patients with best overall response of partial or complete response were considered responders. Patients whose earliest responses occurred within 30 days of receiving 24 mg/d lenvatinib were defined as responders at 24-mg lenvatinib; otherwise, patients were considered responders at less than 24-mg lenvatinib. Nonresponders shown include the 76 patients who had at least one postbaseline target lesion measurement.

Patientenselektion für den Einsatz von TKIs beim RJ-refraktären Schilddrüsenkarzinom

- rascher Progress (biochemisch / bildgebend: 10-20mm Zunahme in 3 Monaten, FDG PET/CT: Knochenmets.)
- kurze Thyreoglobulin Verdoppelungszeit
- hohe Tumorlast
- symptomatische Metastasen (vertebrogene Schmerzen, Pleurerguss, Hämoptysen)

Startdosierung

- Lenvatinib 24 mg tgl
- Sorafenib 2 x 400 mg

Dosisreduktion (bis *drug holiday*) und **proaktives Management** bei schwerer Hypertonie, höhergradiger Asthenie, Diarrhoe, Proteinurie, sowie in jedem Fall Hepatotoxizität od. QTc-Verlängerung

- **Bei Progress unter 1st line TKI ist 2nd line TKI indiziert**

Caveats und relative Kontraindikationen für den Einsatz von TKIs beim RJ-refraktären SD-Karzinom

- minimale Progression bei asymptomatische Patienten
- lokoregionäre Erkrankungen mit Therapieoptionen

- Hirnmetastasen mit hoher Tumorlast
- Hoch-Risiko Situation bei Hämorrhagien