Management of Thyroid and Thymic Carcinomas

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Outline

- Background information on thyroid carcinomas.
- Postoperative RAI.
- Targeted therapy for metastatic thyroid carcinoma based on histology.

- Background information on thymic carcinomas.
- Chemotherapy combinations for treatment of metastatic thymic carcinomas.
- Novel agents in second line treatment for thymic carcinomas.

Thyroid Tumor Classification

- Follicular cells: papillary, follicular, mixed tumor histology, Hürthle cell, and anaplastic.
- Parafollicular C cells: medullary carcinoma.
- Immune cells: lymphomas.
- Stromal cells: sarcomas.

Epidemiology and Demographics

- Approximately 56,870 cases in US in 2017.
- Occurs 2-3 times more often in women than in men.
- More prevalent in Caucasians.
- Age of peak incidence is 50 years old.

Etiology and Risk Factors

- Radiation exposure.
- Age.
- Female sex.
- Family history.

*Dietary influence, sex hormones, and environmental exposures have mixed results and no clear associations.

TNM definitions (AJCC 8e)

for papillary, follicular, poorly differentiated, Hürthle cell, medullary, and anaplastic thyroid carcinomas

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤ 2 cm in greatest dimension limited to the thyroid
T1a	Tumor ≤ 1 cm in greatest dimension limited to the thyroid
T1b	Tumor > 1 cm but ≤ 2 cm in greatest dimension limited to the thyroid
T2	Tumor > 2 cm but ≤ 4 cm in greatest dimension limited to the thyroid
T3*	Tumor > 4 cm limited to the thyroid or gross extrathyroidal extension invading only strap muscles
T3a*	Tumor > 4 cm limited to the thyroid
T3b*	Gross extrathyroidal extension invading only strap muscles (sternohyoid) from a tumor of any size
T4	Includes gross extrathyroidal extension into major neck structures
T4a	Gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve from a tumor of any size
T4b	Gross extrathyroidal extension invading prevertebral fascia or encasing carotid artery or mediastinal vessels from a tumor of any size
NX	Regional lymph nodes cannot be assessed
N0	No evidence of regional lymph nodes metastasis
N0a*	One or more cytologic or histologically confirmed benign lymph node
N0b*	No radiologic or clinical evidence of locoregional lymph node metastasis
N1*	Metastasis to regional nodes
N1a*	Metastasis to level VI or VII (pretracheal, paratracheal, or prelaryngeal/Delphian, or upper mediastinal) lymph nodes; this can be unilateral or bilateral disease
N1b*	Metastasis to unilateral, bilateral, or contralateral lateral neck lymph nodes (levels I, II, III, IV, or V) or retropharyngeal lymph nodes
M0	No distant metastasis
M1	Distant metastasis

*all categories may be subdivided as solitary tumor (s) and multifocal tumor (m) – the largest tumor determines the classification

Staging guide for thyroid cancer (AJCC 8e)

Age at diagnosis	T category	N category	M category	**Stage**	Expected 10-yr DSS
		Differentiated thyroid cancer			
<55 years	any T	any N	M0	**I**	98–100%
	any T	any N	M1	**II**	85–95%
≥ 55 years	T1	N0/NX	M0	**I**	98–100%
	T1	N1	M0	**II**	85–95%
	T2	N0/NX	M0	**I**	98–100%
	T2	N1	M0	**II**	85–95%
	T3a/T3b	any N	M0	**II**	85–95%
	T4a	any N	M0	**III**	60–70%
	T4b	any N	M0	**IVA**	< 50%
	any T	any N	M1	**IVB**	< 50%
		Medullary thyroid cancer			
any	T1	N0	M0	**I**	
	T2	N0	M0	**II**	
	T3	N0	M0	**II**	
	T1-3	N1a	M0	**III**	
	T4a	any N	M0	**IVA**	
	T1-3	N1b	M0	**IVA**	
	T4b	any N	M0	**IVB**	
	any T	any N	M1	**IVC**	
		Anaplastic thyroid cancer			
any	T1-T3a	N0/NX	M0	**IVA**	
	T1-T3a	N1	M0	**IVB**	
	T3b	any N	M0	**IVB**	
	T4	any N	M0	**IVB**	
	any T	any N	M1	**IVC**	

Who should get postoperative RAI?

RAI recommended	RAI not recommended
Gross extrathyroidal extension.	Papillary microcarcinomas (<1cm) confined to the thyroid.
Primary > 4cm in size.	No detectable anti-Tg antibodies.
Postoperative unstimulated Tg >5-10 ng/ml.	Postoperative unstimulated Tg < 1 ng/ml.

Treatment for metastatic disease

- Differentiated disease
- Medullary thyroid carcinoma
- Anaplastic thyroid carcinoma

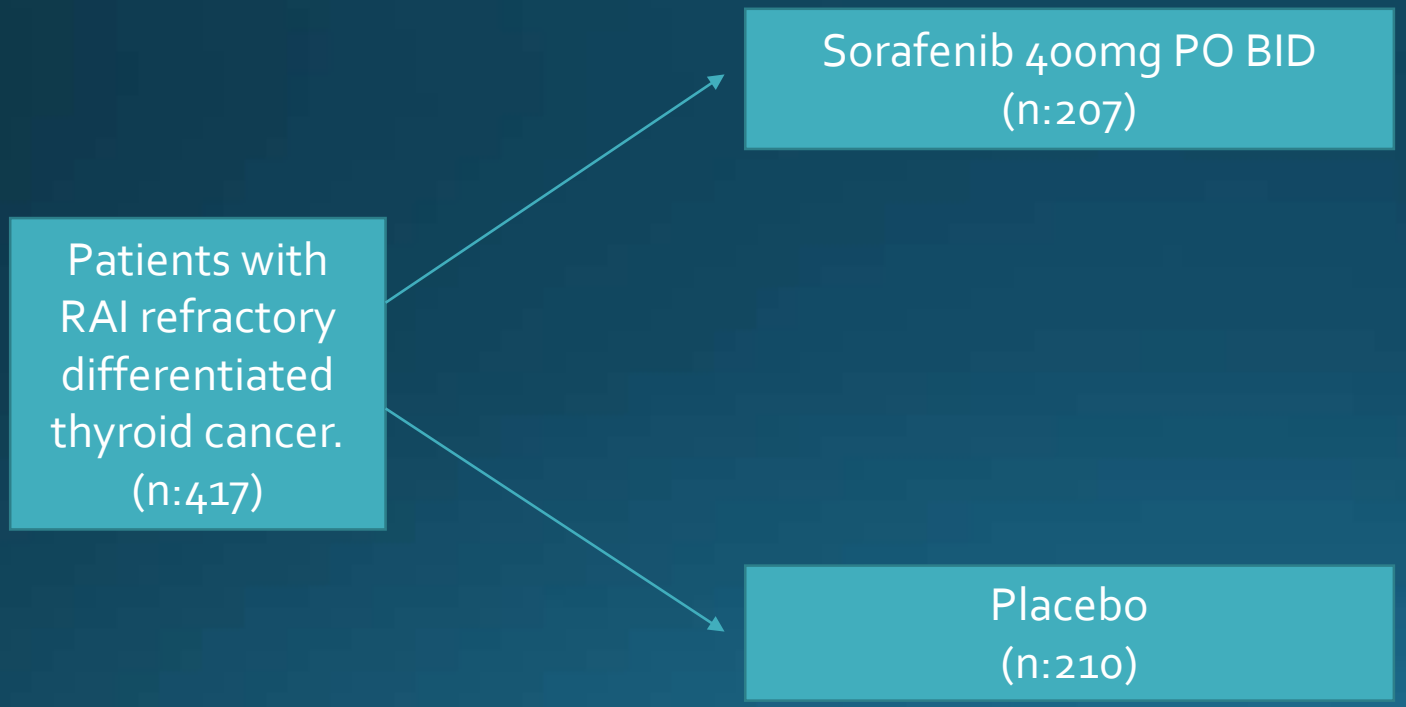
Treatments for metastatic differentiated thyroid cancer refractory to RAI

- FDA approved: Sorafenib
  Lenvatinib

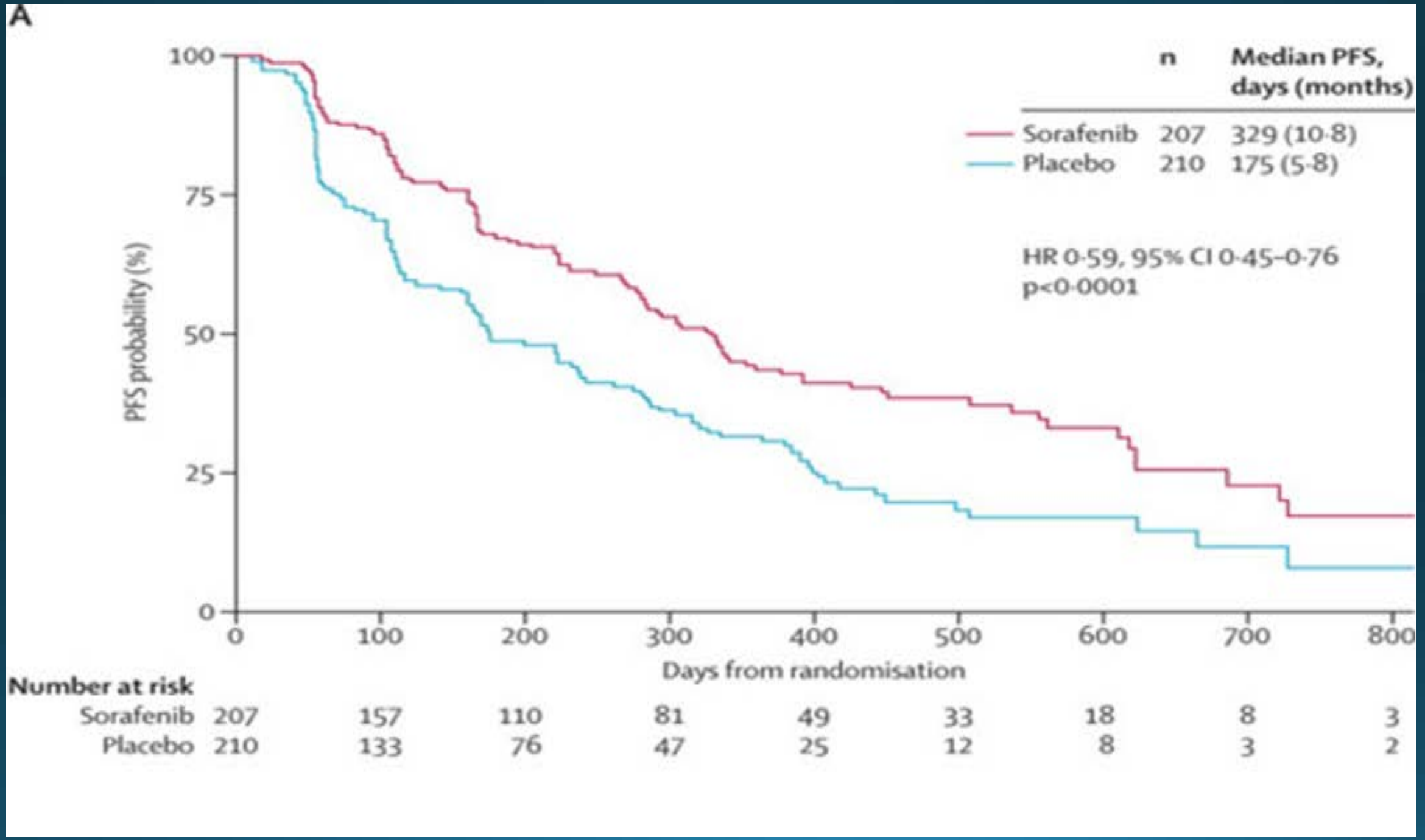
- Non-FDA approved: Axitinib
  Pazopanib
  Sunitinib
  Vandetinib
  Cabozantinib
  Everolimus

Sorafenib for metastatic differentiated thyroid cancer refractory to RAI.

Phase 3 randomized double-blind.

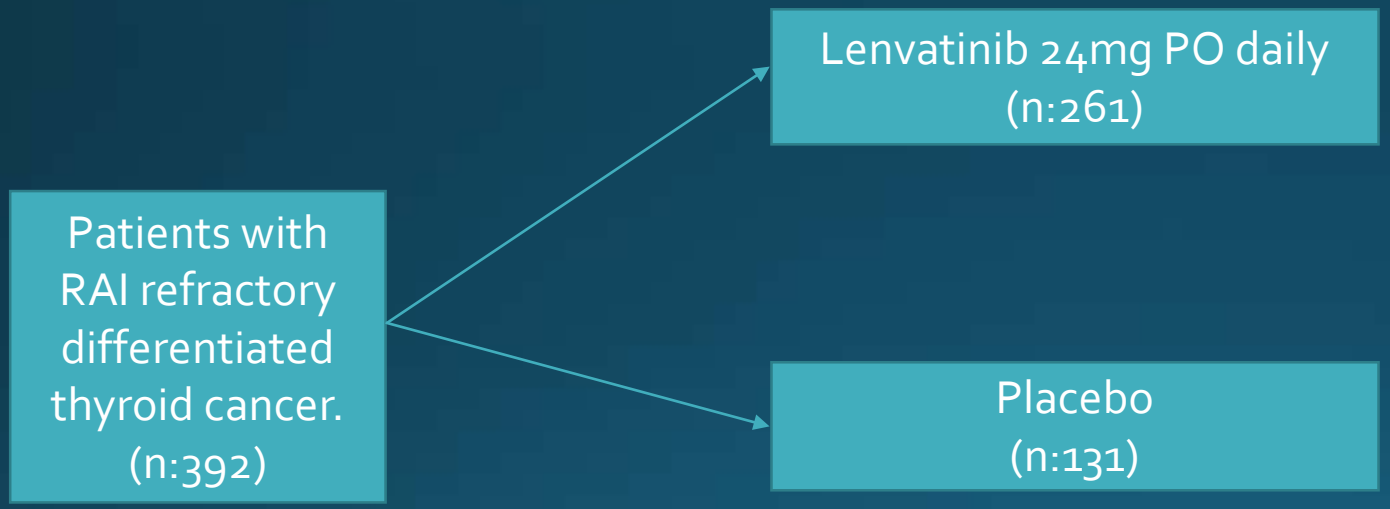


Brose MS, et al. Lancet 2014;384(9940):319-328.

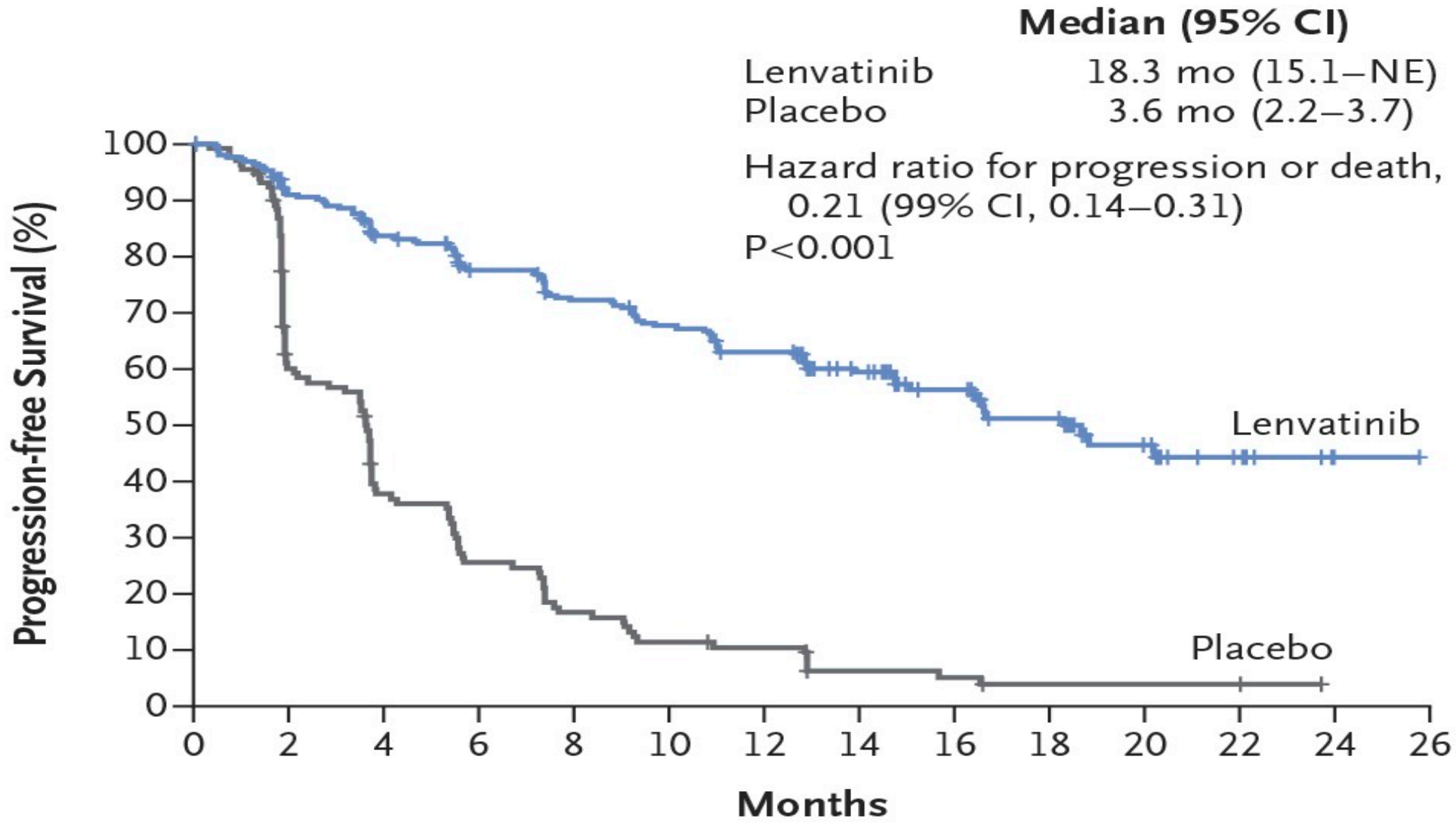

A
n
Median PFS, days (months)
Sorafenib 207 329 (10·8)
Placebo 210 175 (5·8)
HR 0·59, 95% CI 0·45–0·76
p<0·0001
PFS probability (%)
100
75
50
25
0
0
100
200
300
400
500
600
700
800
Days from randomisation
Number at risk
Sorafenib 207 157 110 81 49 33 18 8 3
Placebo 210 133 76 47 25 12 8 3 2

Lenvatinib for metastatic differentiated thyroid cancer refractory to RAI.

Phase 3 randomized double-blind.



Schlumberger M, et al. NEJM 2015;372:621-630.



No. 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

Sorafenib	Lenvatinib
PFS: 10.8 months	PFS: 18.3 months
RR: 12%	RR: 65%
HR: 0.59	HR: 0.21

Cabozantinib for metastatic differentiated thyroid cancer refractory to RAI.

Phase 2 single-arm.

Patients with RAI refractory differentiated thyroid cancer. (n:35)

Cabozantinib 140mg PO QD (n:35)

- RR: 54%
- PFS: Not reached.

Brose MS, et al. JCO 36, 2018(suppl;abstract 6088).

Nintedanib as second line metastatic differentiated thyroid cancer refractory to RAI.

Phase 2 randomized double-blind.

Patients with RAI refractory differentiated thyroid cancer with progression after 1 or 2 lines of treatment. (n:70)

- Nintedanib 400mg PO daily (n:45)
- Placebo (n:25)

Progression-free survival

- **Nintedanib: 3.7 months**
- **Placebo: 2.8months**

***HR: 0.6**

25% of patients had received 2 prior lines of treatment.

Schlumberger M, et al. JCO 36, 2018(suppl;abstract 6021).

Medullary thyroid carcinoma (MTC)

- MTC arises from the neuroendocrine parafollicular cells.
- 80% of MTC are sporadic.
- 20% are related to MEN type 2A and MEN type 2B.
- MTC can cause paraneoplastic syndromes.

*RET mutations seen in 25% of sporadic cases and up to 95% of familial MTC.

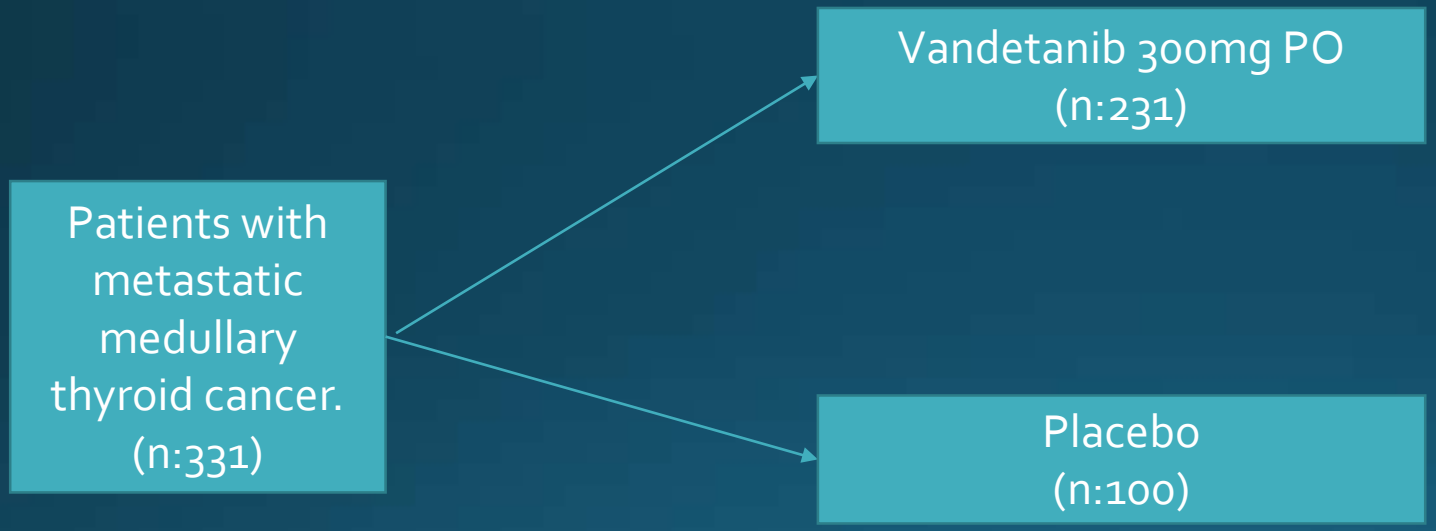
Treatment for metastatic medullary thyroid cancer.

- FDA approved: Vandetanib
  Cabozantinib

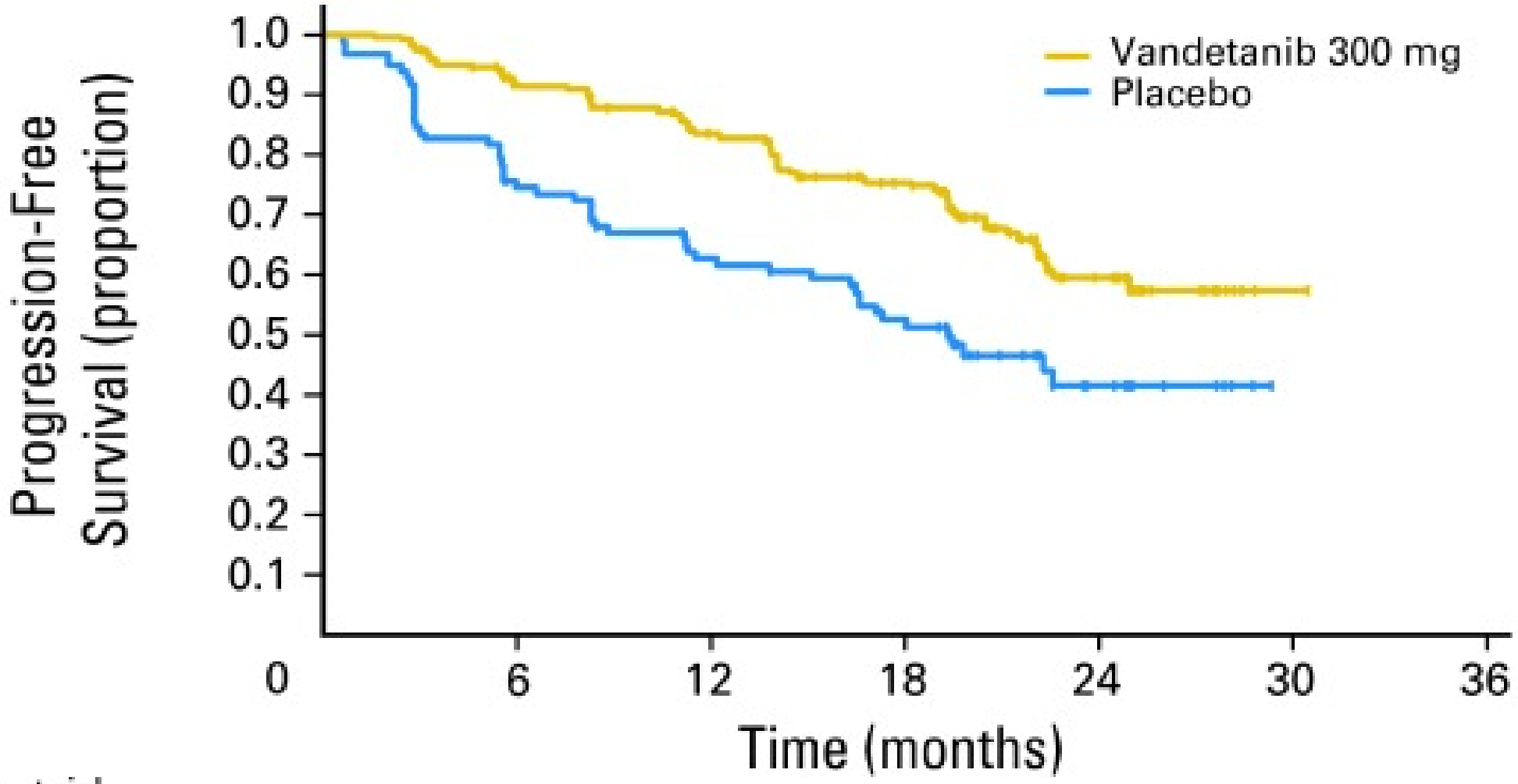
- Non-FDA approved: Anlotinib
  Pazopanib
  Sunitinib
  Sorafenib
  Lenvatinib
  Dacarbazine based chemotherapy

Vandetanib for metastatic medullary thyroid cancer.

Phase 3 randomized double-blind.



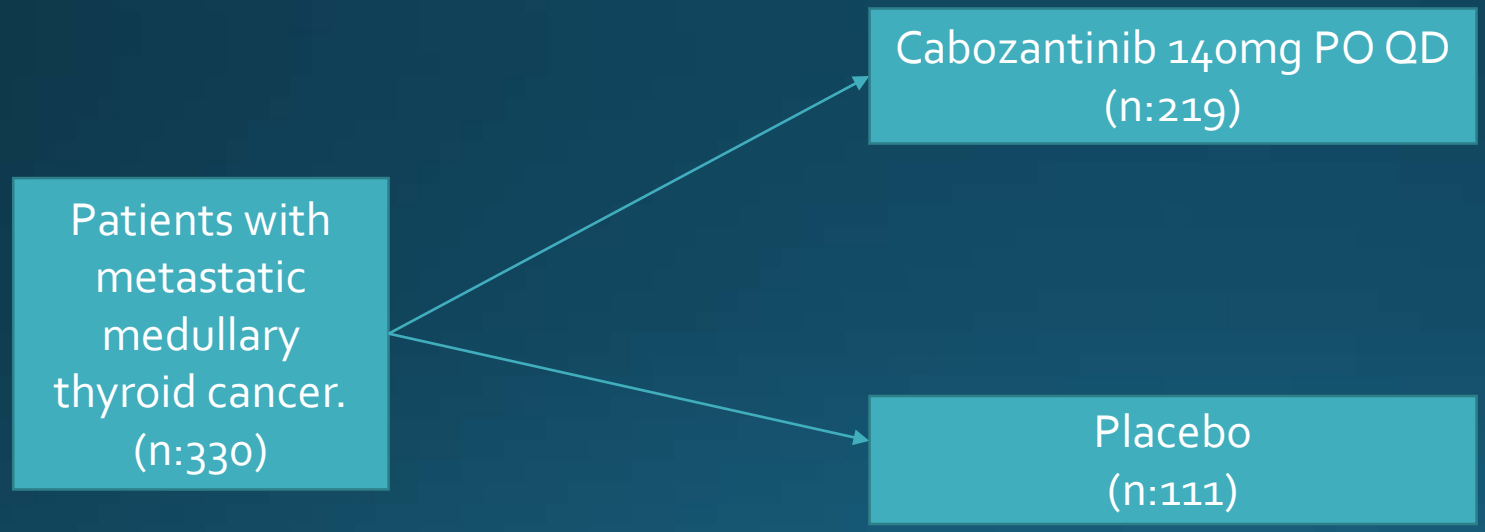
Wells SA, et al. JCO 2012;30(2):134-141.



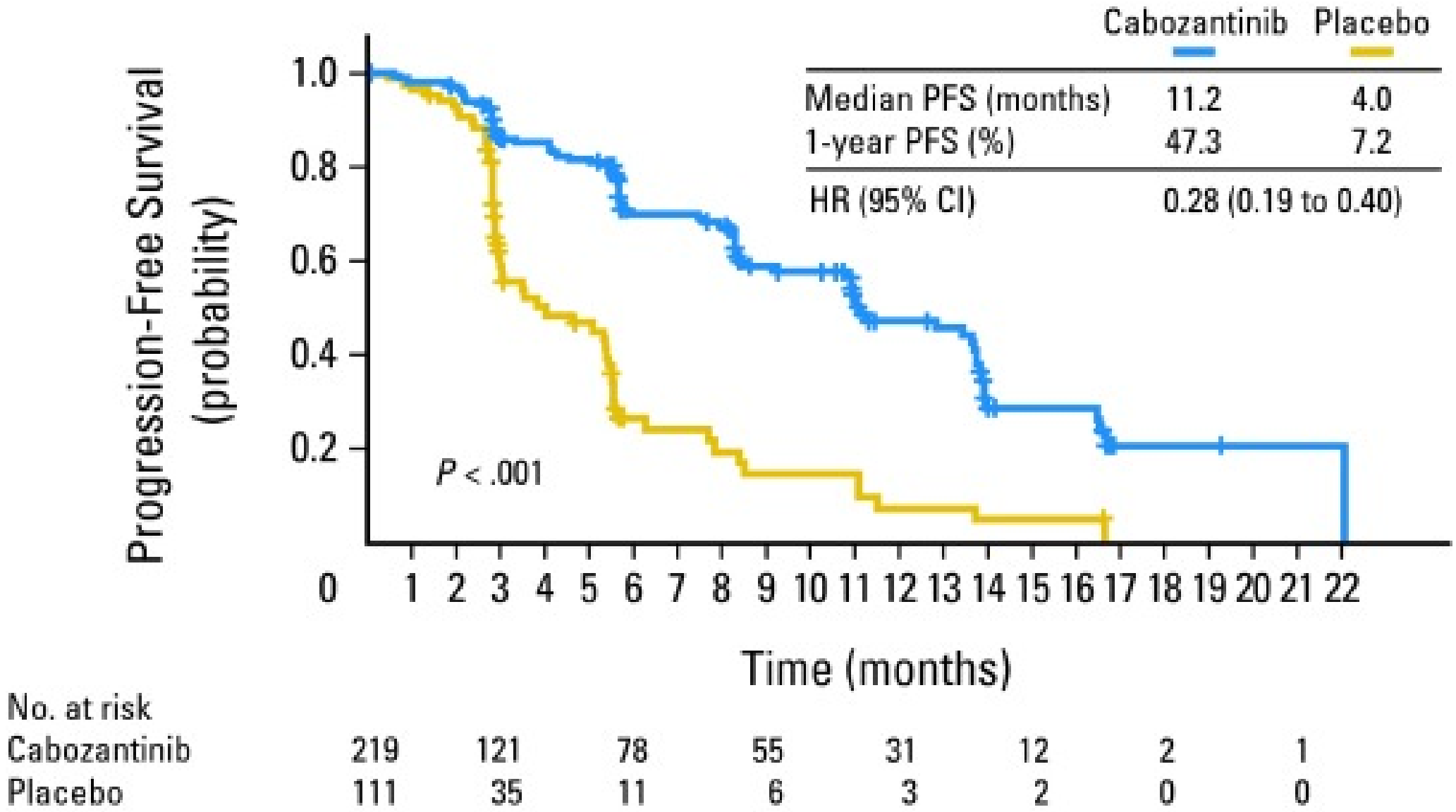
No. at risk							
Vandetanib 300 mg	231	196	169	140	40	1	0
Placebo	100	71	57	45	13	0	0

Cabozantinib for metastatic medullary thyroid cancer.

Phase 3 randomized double-blind.

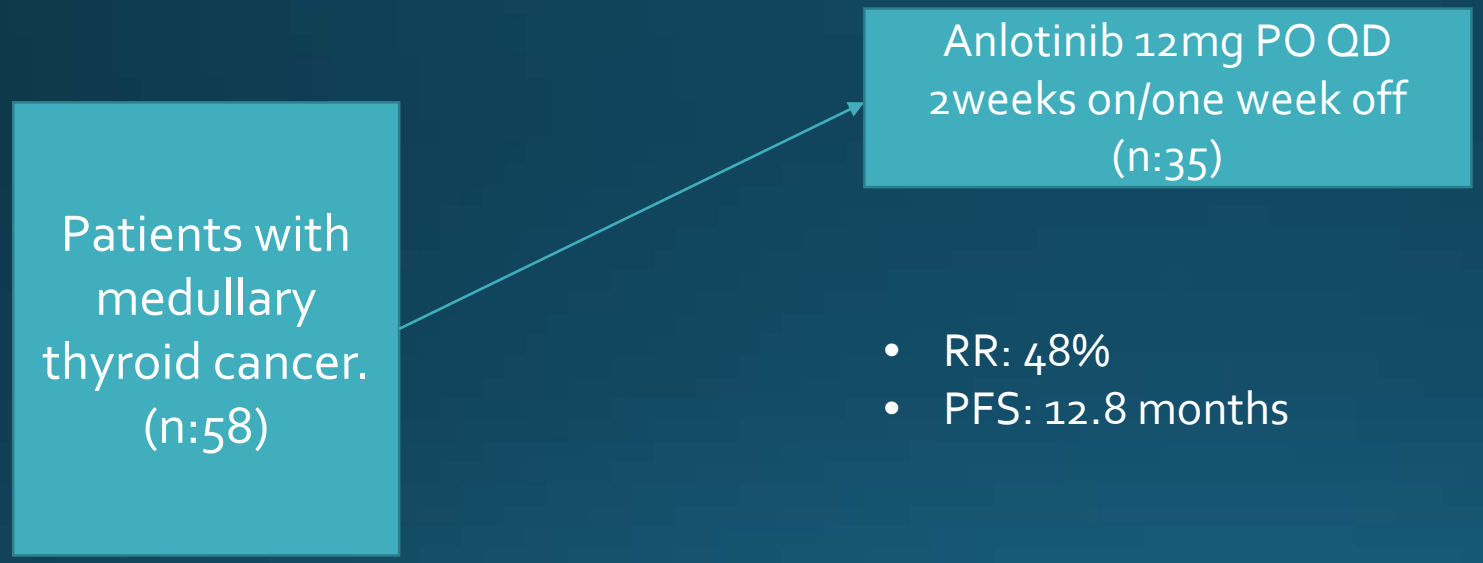


Elisei R, et al. JCO 2013;31(29):3639-3646.


Cabozantinib
Placebo
Median PFS (months) 11.2 4.0
1-year PFS (%) 47.3 7.2
HR (95% CI) 0.28 (0.19 to 0.40)
Progression-Free Survival (probability)
1.0
0.8
0.6
0.4
0.2
0
P < .001
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Time (months)
No. at risk
Cabozantinib 219 121 78 55 31 12 2 1
Placebo 111 35 11 6 3 2 0 0

Anlotinib for metastatic medullary thyroid cancer.

- **Phase 2 single-arm.**



Sun Y, et al. JCO 34, 2016(suppl;abstract 6015).

BRAF inhibition in thyroid cancer

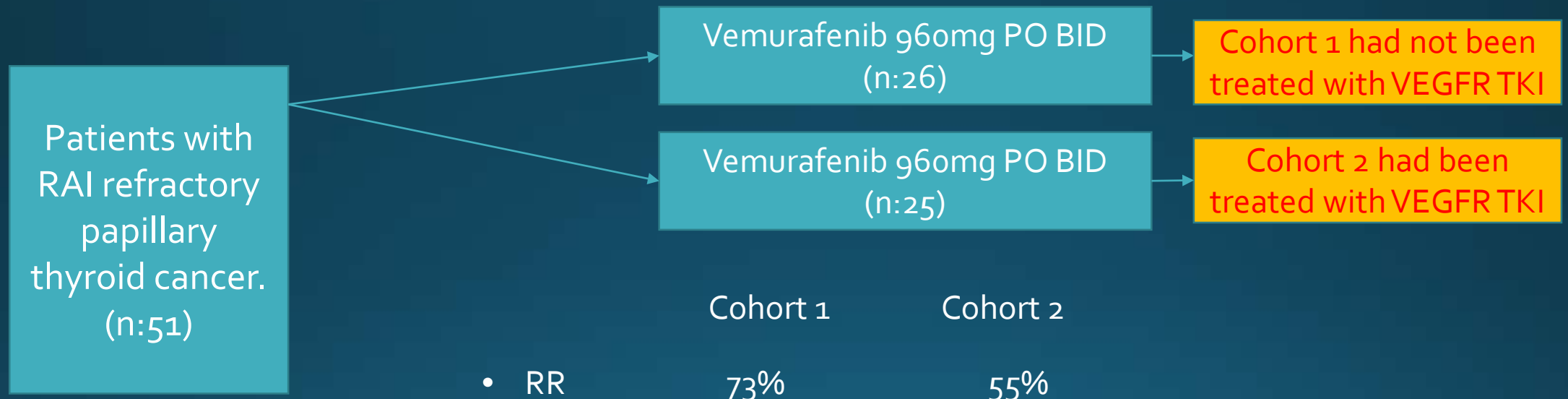
- BRAF mutation is found in approximately 37-50% of papillary thyroid carcinomas and in approximately 25% of anaplastic thyroid carcinomas.

- BRAF mutation might confer a more aggressive behavior and worst prognosis.

- Tumors with BRAF mutations have a decreased ability to incorporate RAI resulting in treatment failure.

Vemurafenib for metastatic BRAF mutated papillary thyroid carcinoma refractory to RAI.

Phase 2 open label non-randomised.

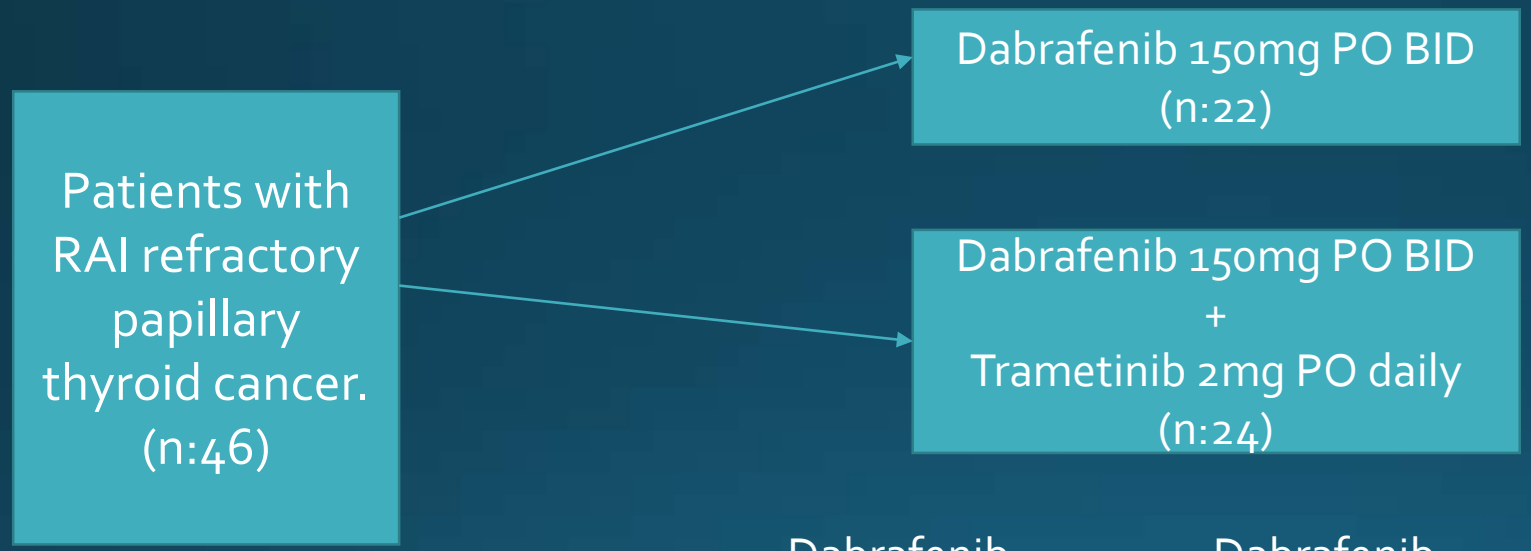


	Cohort 1	Cohort 2
• RR	73%	55%
• PFS	18.2 months	8.9 months
• MDR	16.5 months	14.4 months

Brose MS, et al.Lancet Oncol 2016(9):1272-1282.

Dabrafenib versus dabrafenib plus trametinib in BRAF mutated papillary thyroid carcinoma.

Phase 2 randomized double-blind.



	Dabrafenib	Dabrafenib + Trametinib
• RR:	50%	54%

Shah MH, et al. JCO 35, 2017(suppl;abstract 6022).

Anaplastic thyroid carcinoma (ATC)

- Aggressive undifferentiated tumors.
- Stage IV at diagnosis.
- Disease-specific mortality approaching 100%.
- 50% of patients had either a prior or coexisting differentiated thyroid carcinoma.
- Carboplatin/Paclitaxel, Docetaxel/Doxorubicin; RR <15%.
- 20-50% of ATC have BRAF mutations.

Dabrafenib plus trametinib in BRAF mutated anaplastic thyroid carcinoma.

Phase 2 open label non-randomised.

Patients with BRAF mutated anaplastic thyroid cancer. (n:16)

Dabrafenib 150mg PO BID
+
Trametinib 2mg PO daily
(n:24)

- RR: 69%
- PFS: Not reached.

Subbiah V, et al. JCO 2018, 36(1):7-13.

Thymic carcinomas

- Very rare and aggressive tumors. Approx. 1.5 cases/ 1 million.
- Squamous and undifferentiated carcinomas.
- Unknown etiology.
- No clear identifiable risk factors.
- Worst prognosis than thymomas.
- Surgical resection for localized disease.
- Postoperative radiation indicated for residual disease.

Table 1 Masaoka staging system

Stage	Description
I	Macroscopically encapsulated and no microscopic capsular invasion
II	Macroscopic invasion into adjacent tissues (fatty or mediastinal pleura) or microscopic capsular invasion
III	Macroscopic invasion into adjacent organ(s)
IVA	Pleural or pericardial dissemination
IVB	Lymphogenous or hematogenous metastasis

Table 9 The relationship between the IASLC/ITMIG TNM proposal staging categories and Masaoka-Koga staging system

The 8th edition TNM stage	TNM	Definition (involvement of)	Masaoka-Koga
Stage I	T1aN0M0	Encapsulated or unencapsulated, with or without extension into mediastinal fat	Stage I and II
	T1bN0M0	Extension into mediastinal pleura	Stage III (partial-pleura)
Stage II	T2N0M0	Pericardium	Stage III (partial-pericardium)
Stage IIIa	T3N0M0	Lung, brachiocephalic vein, superior vena cava, chest wall, phrenic nerve, hilar (extrapericardial) pulmonary vessels	Stage III (partial-completeness of resection)
Stage IIIb	T4N0M0	Aorta, arch vessels, main pulmonary artery, myocardium, trachea, or esophagus	Stage III (partial-incompleteness of resection)
Stage IVa	TxN1M0	Anterior (perithymic) nodes	Stage IVb
	TxN0M1a	Separate pleural or pericardial nodule(s)	Stage IVa
	TxN1M1a	Anterior (perithymic) nodes, Separate pleural or pericardial nodule(s)	Stage IVb
Stage IVb	TxN2M0	Deep intrathoracic or cervical nodes	Stage IVb
	TxN2M1a	Deep intrathoracic or cervical nodes, Separate pleural or pericardial nodule(s)	Stage IVb
	TxNxM1b	Pulmonary intraparenchymal nodule or distant organ metastasis	Stage IVb

IASLC, the International Association for the Study of Lung Cancer; ITMIG, the International Thymic Malignancies Interest Group.

Metastatic Thymic carcinomas

*Anthracycline and platinum based chemotherapy combinations.

- Cis/dox/vin/cyclophos (ADOC)
- Cis/adria/cyclophos (PAC)
- Cis/adria/etoposide (PAE)
- Adria/cis/vinc/etoposide (CODE)
- Carbo/paclitaxel
- Cis/etoposide (PE)
- Vinc/ifos/cis (VIP)

Table 1 Unified response rates of advanced thymoma patients treated with anthracycline-based or non-anthracycline-based chemotherapy regimens

Regimen	Author, year	Study design	Stage	No. of patients	Responders	RR	PFS	OS
Anthracycline-containing regimens								
ADOC	Fornasiero et al. (1991)	S	III/IVa/IVb	37	34	91.8 %	12 mos	15 mos
PAC	Loehrer et al. (1994)	G	IV	29	15	51.7 %	11.8 mos	37.7 mos
PAC (+XRT)	Loehrer et al. (1997)	G	III	23	16	69.6 %	–	93 mos
ADOC	Rea et al. (1993)	S	III/IVa	16	12	75.0 %	–	66 mos
ADOC	Berruti et al. (1999)	S	III/IVa	16	13	81.3 %	33.2 mos	47.5 mos
PAC	Kim et al. (2004)	G	III/IVa/IVb	22	17	77.3 %	–	–
PAE (+XRT)	Lucchi et al. (2006)	S	III/IVA	30	22	73.3 %	–	–
CAMP	Yokoi et al. (2007)	S	IVa/IVb	14	13	92.9 %	–	–
Dose-dense CODE	Kunitoh et al. (2009)	G	IVa/IVb	27	16	59.3 %	0.79 year	6.1 year
CarboAMR	Kawashima et al. (2013)	G	Invasive	18	3	16.7 %	7.6 mos	Not reached
Total				232	161	69.4 %		
Non-anthracycline-containing regimens								
PE	Giaccone et al. (1996)	G	III/IV/rec	16	9	56 %	2.2 year	4.3 year
VIP	Loehrer et al. (2001)	G	III/IVa/IVb	20	7	35 %	11.9 mos	31.6 mos
VIP	Grassin et al. (2011)	G	IIIB/IVA/IVB	16[a]	4[a]	25 %[a]	13.1 mos	Not reached
CarboPTX	Takeda et al. (2013)	G	III/IVa/IVb	21	6	42.9 %	16.7 mos	Not reached
CDDP/DTX	Park et al. (2013)	G	III/IVa/IVb	9	5	55.6 %	–	–
Total				82	31	37.8 %		

G prospective multicenter group phase II trial, *S* single-center experience, *mos* months, *RR* objective response rate, *ADOC* adriamycin, cisplatin, vincristine and cyclophosphamide, *PAC* cisplatin, adriamycin and cyclophosphamide, *PAE* cisplatin, adriamycin and etoposide, *CAMP* PAC = cisplatin, adriamycin, methylprednisolone and cyclophosphamide, *CODE* adriamycin, cisplatin, vincristine and etoposide,

PE cisplatin and etoposide, *VIP* vincristine, ifosfamide and cisplatin, *CarboPTX* carboplatin and paclitaxel

Sunitinib for previously treated advanced thymic carcinoma.

- **Phase 2 single-arm.**

Patients with previously treated thymic carcinoma. (n:20)

Sunitinib 50mg PO QD for 4 wks the 2 weeks off (n:20)

- RR: 16%
- PFS: 3.3 months
- OS: 12.3 months

Remon J, et al. Lan Onc 2016;(97):99-104.

Everolimus for advanced thymic carcinoma previously treated with cisplatin.

- **Phase 2 single-arm.**

Patients with previously treated thymic carcinoma. (n:18)

→ Everolimus 10mg PO QD (n:18)

- RR: 20%
- PFS: 5.6 months
- OS: 14.7 months

*36% incidence of pneumonitis. 3 deaths pneumonitis.

Zucali PA, et al. JCO 2018;36(4):342-349.

Pembrolizumab for advanced thymic carcinoma previously treated with cisplatin.

- **Phase 2 single-arm.**

Patients with previously treated thymic carcinoma. (n:26)

→ Pembrolizumab 200mg iv q 3wks (n:26)

- RR: 19%
- PFS: 6.1 months
- OS: 14.5 months

*High rate of irAEs

Cho J, et al. JCO 2018;36. ahead of print.

Pembrolizumab for recurrent metastatic thymic carcinoma.

- **Phase 2 single-arm.**

Patients with previously treated thymic carcinoma. (n:40)

Pembrolizumab 200mg iv q 3wks (n:26)

- RR: 22%

*High rate of irAEs

Giaccone G, et al. Lancet Oncol 2018;19(3):347-355.

Conclusions

Thyroid carcinomas

- Small-molecules TKI are the treatment of choice of metastatic differentiated thyroid carcinoma refractory to RAI.
- Small-molecules TKI that target the RET gene mutations are the treatment of choice for metastatic medullary carcinoma.
- BRAF inhibitors offer an alternative treatment pathway for BRAF mutated thyroid carcinomas.
- BRAF inhibitors should be the treatment of choice for BRAF mutated ATC.

Thymic carcinomas

- Anthracycline and platinum based chemotherapy combinations remain the standard treatment of choice for metastatic thymic carcinomas.
- Sunitinib and everolimus are treatment options in second-line. Everolimus has a high incidence of pneumonitis.
- Pembrolizumab demonstrates activity second line but is associated with a high rate of severe immune related adverse events.