

Management of Thyroid and Thymic Carcinomas

Belisario A. Arango, M.D.

New Orleans Summer Cancer Meeting

July 19-21, 2024

Outline

- Indications for postoperative RAI.
- Therapy for metastatic differentiated thyroid carcinoma refractory to RAI.
- Therapy for BRAF-mutated metastatic thyroid carcinoma.
- Therapy for metastatic medullary thyroid carcinoma.
- Therapy for advanced anaplastic thyroid carcinoma.

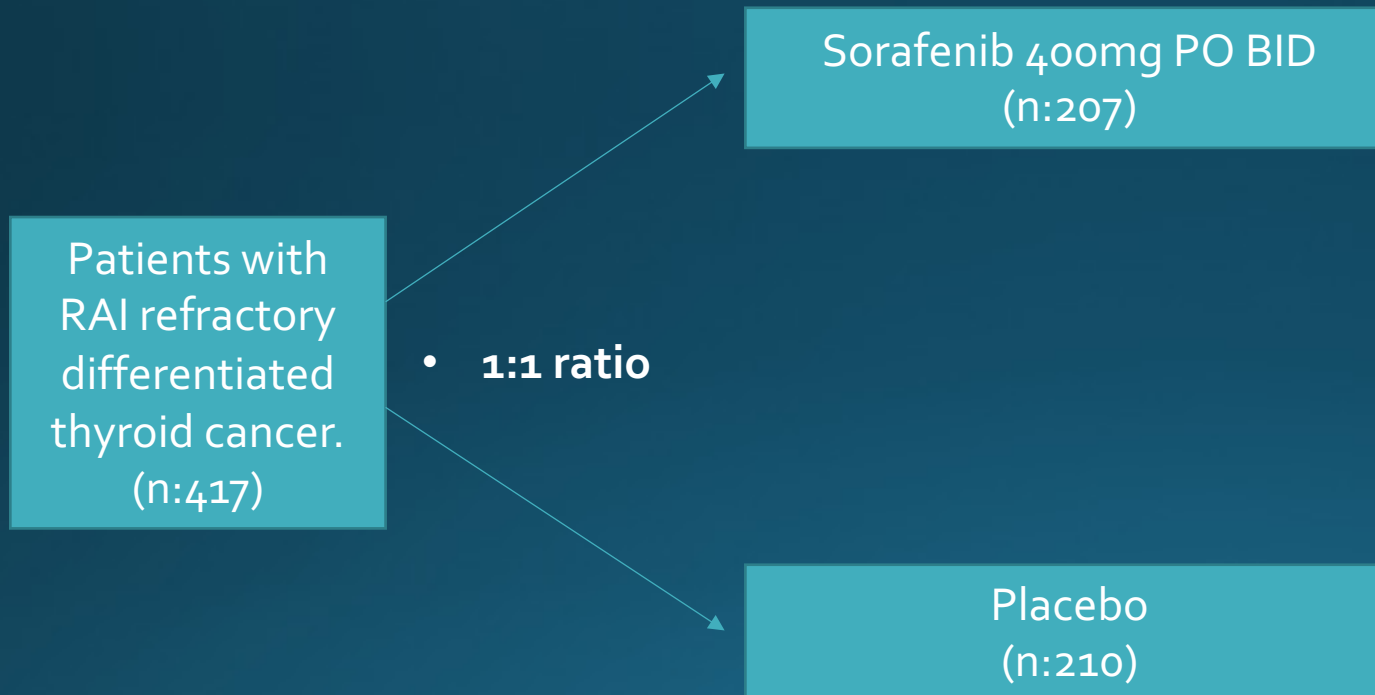
- Novel agents in the treatment for thymic carcinomas.

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.

Sorafenib for metastatic differentiated thyroid cancer refractory to RAI.

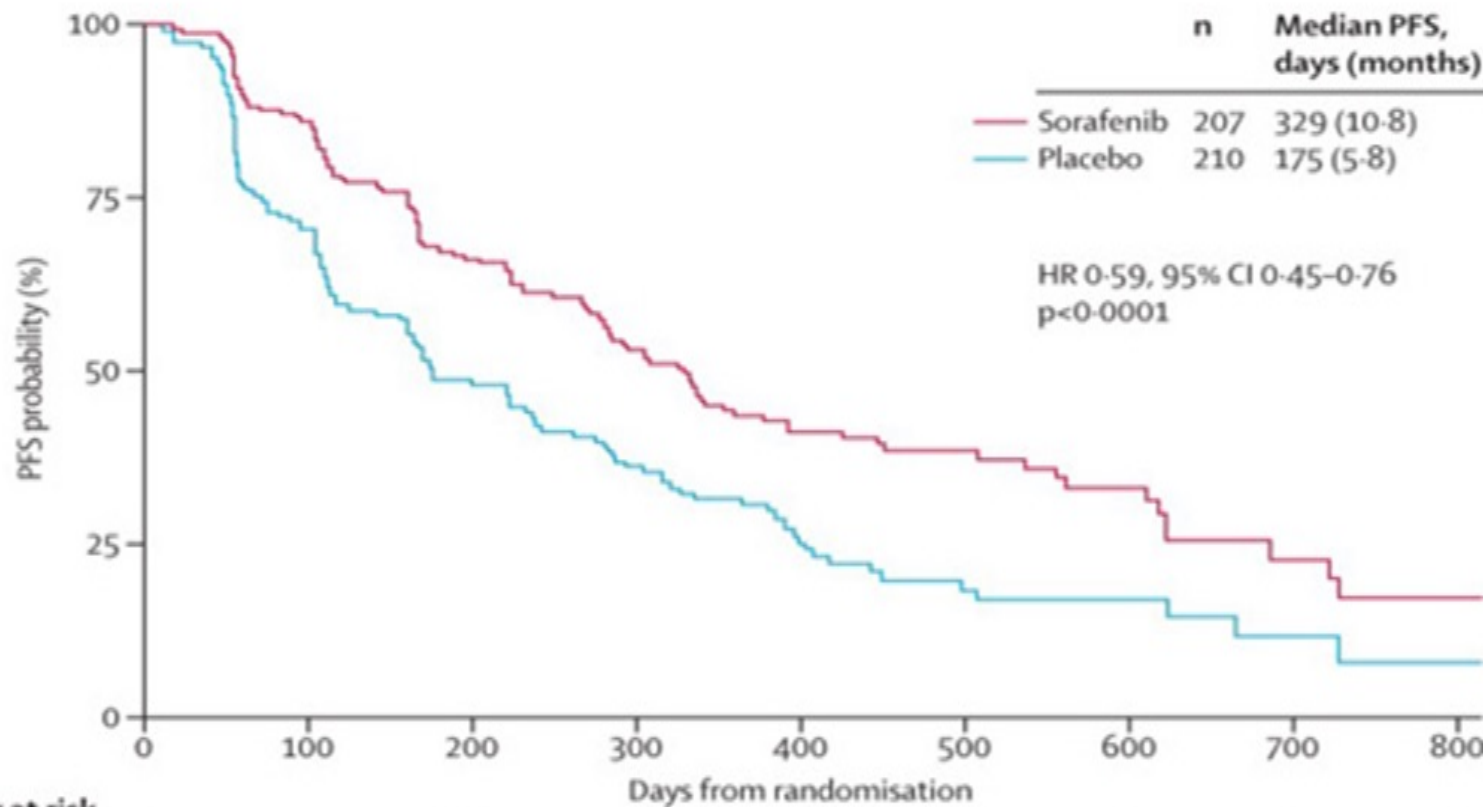
DECISION: Phase 3 randomized double-blind.



Sorafenib for metastatic differentiated thyroid cancer refractory to RAI.

DECISION: Phase 3 randomized double-blind.

A



Sorafenib vs Placebo
PFS: 10.8 vs 5.8 months

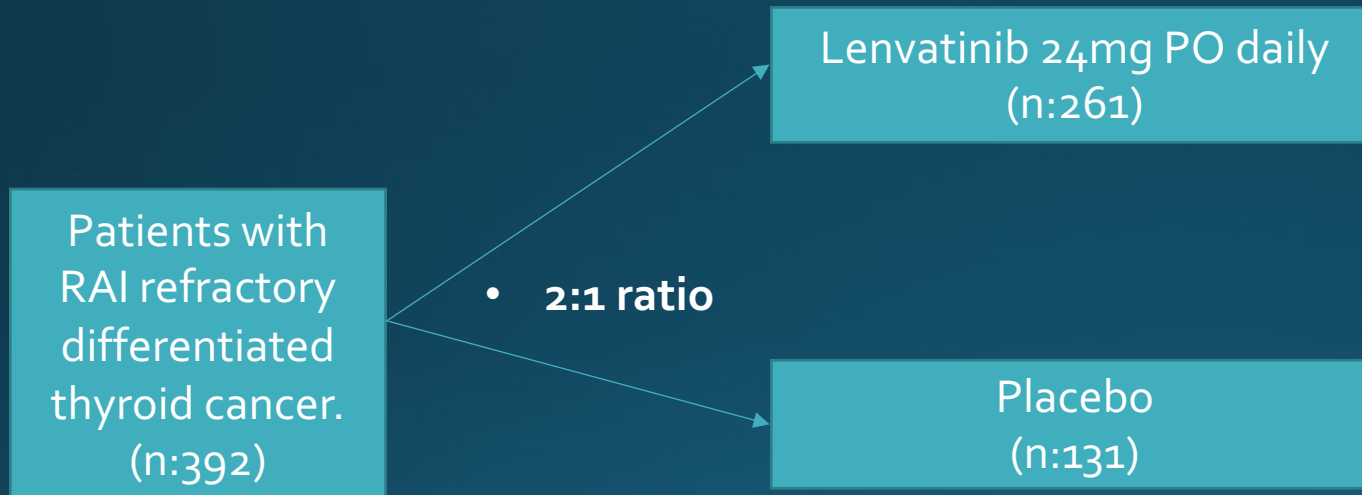
Number at risk

Sorafenib	207	157	110	81	49	33	18	8	3
Placebo	210	133	76	47	25	12	8	3	2

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

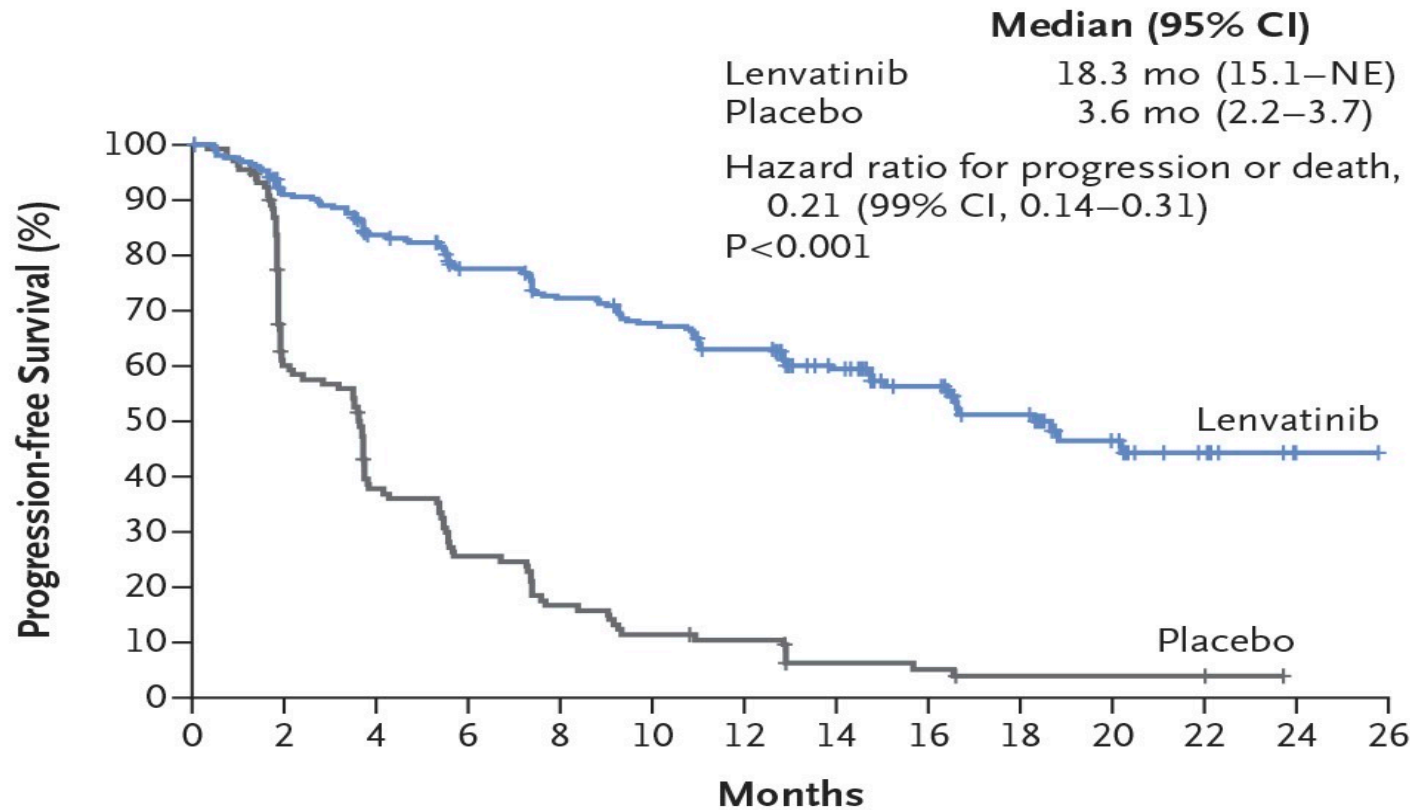
Lenvatinib for metastatic differentiated thyroid cancer refractory to RAI.

SELECT: Phase 3 randomized double-blind.



Lenvatinib for metastatic differentiated thyroid cancer refractory to RAI.

SELECT: Phase 3 randomized double-blind.



Lenvatinib vs Placebo
PFS: 18.3 vs 3.6 months

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

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

Sorafenib

PFS: 10.8 months

RR: 12%

HR: 0.59

Lenvatinib

PFS: 18.3 months

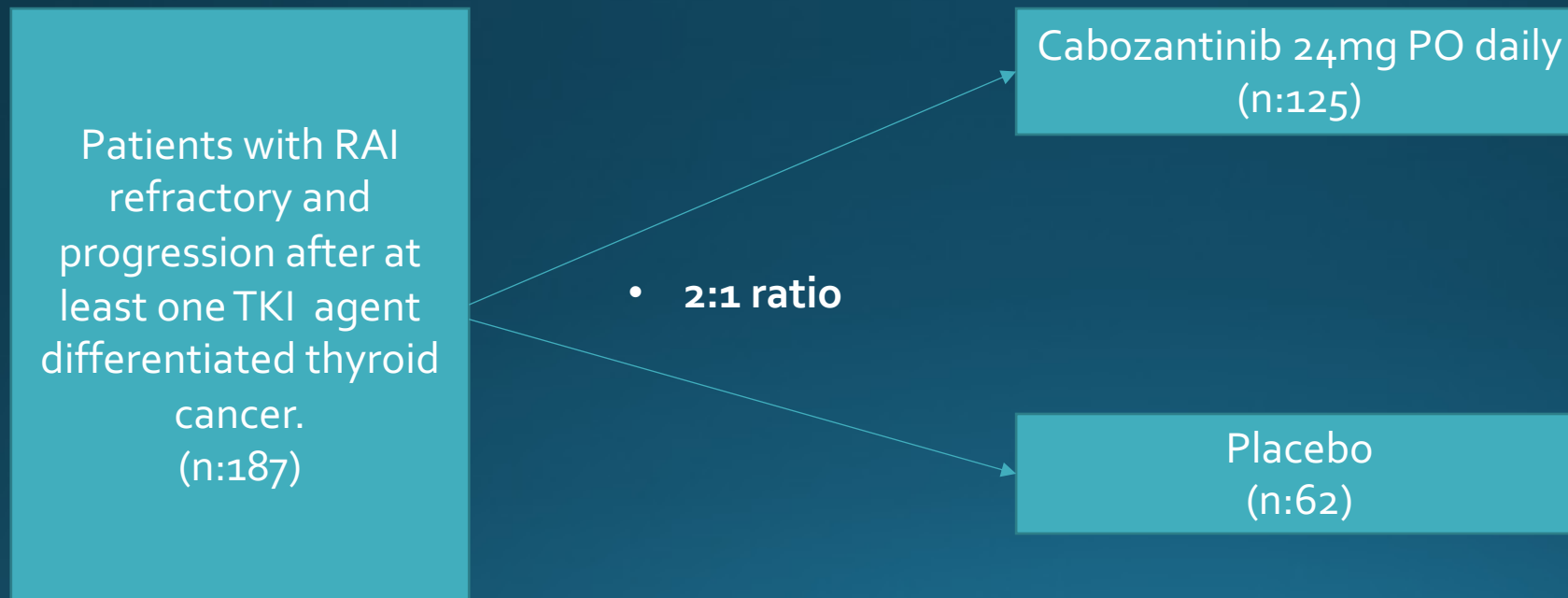
RR: 65%

HR: 0.21

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 previously treated with a TKI.

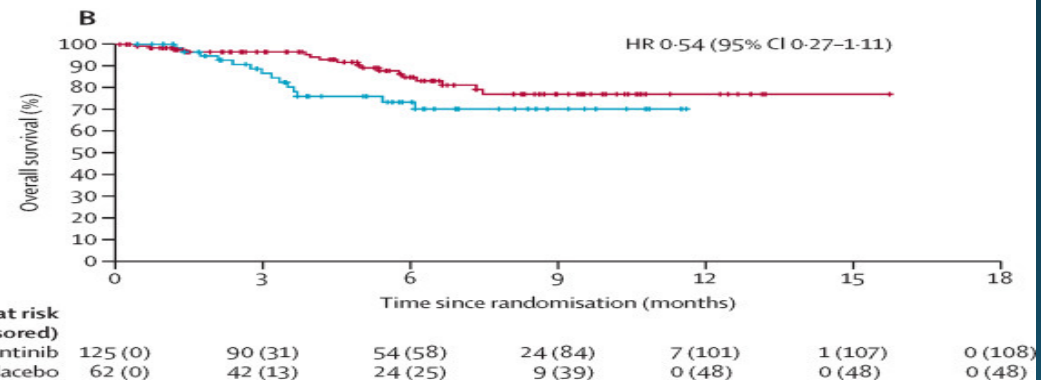
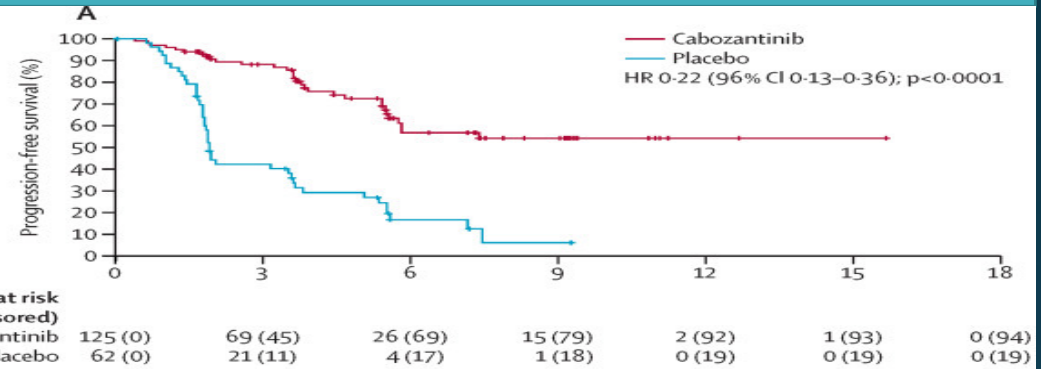
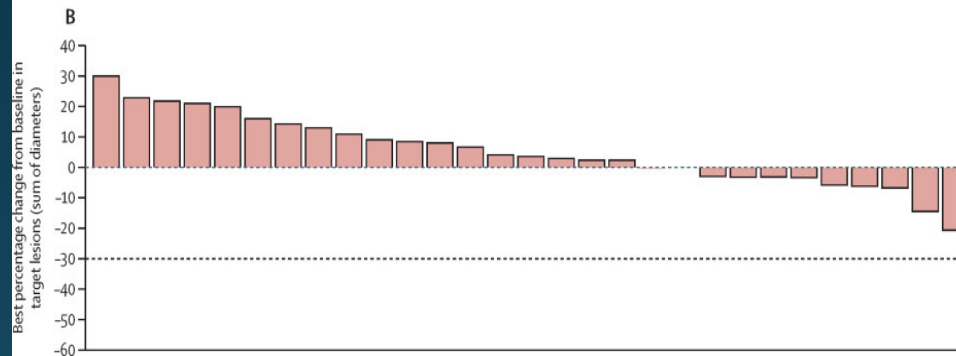
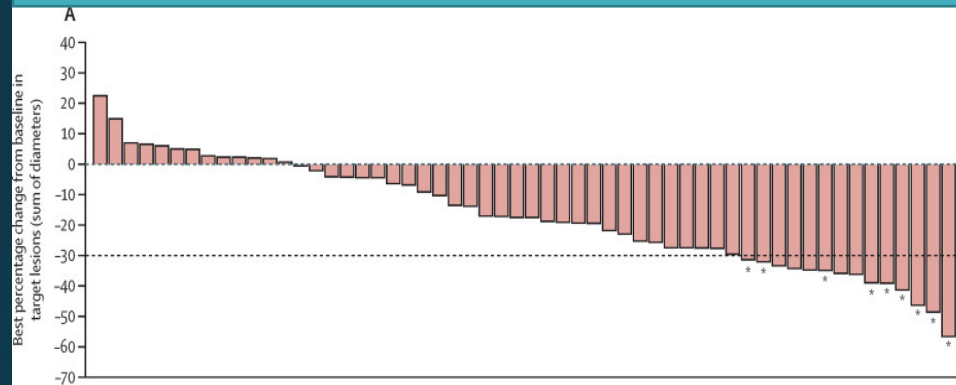
COSMIC-311: Phase 3 randomized double-blind.



Brose MS, et al. Lancet Oncol 2021;22:1126-38.

Cabozantinib for metastatic differentiated thyroid cancer refractory to RAI.

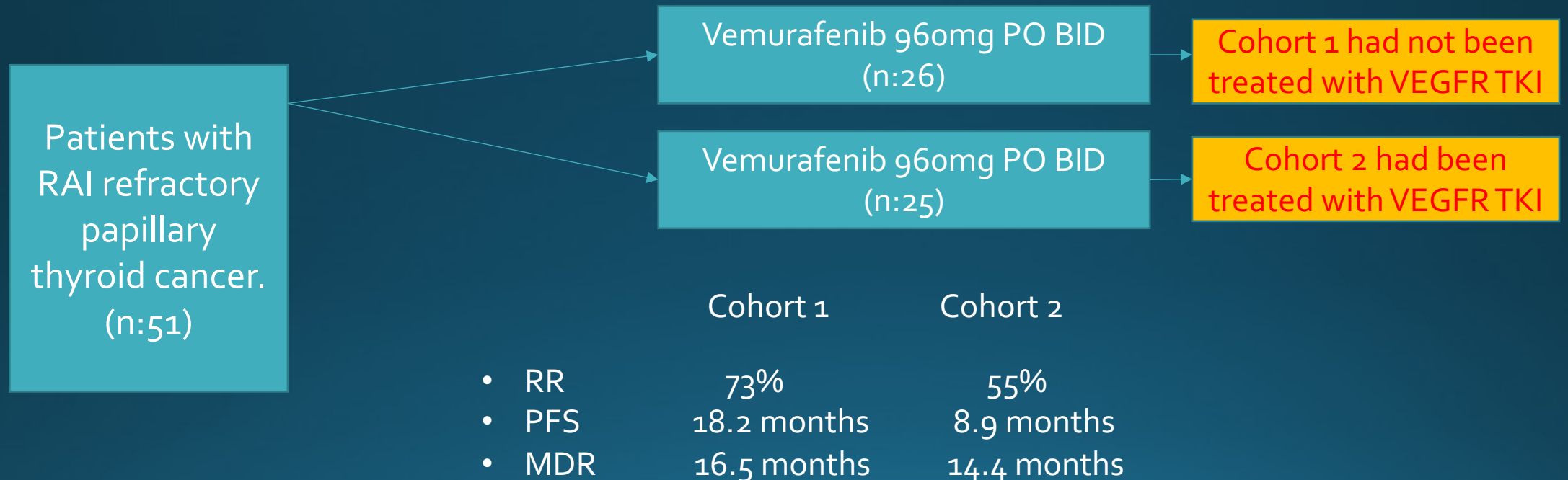
COSMIC-311: Phase 3 randomized double-blind.



- ORR: 11%
- SD: 69%
- CR: 1%
- PFS: 11 vs 1.9 months.

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

Phase 2 open label non-randomised.



Dabrafenib vs Dabrafenib + Trametinib in BRAF-mutated RAI metastatic DTC.

Phase 2 double-arm randomised.

Patients with BRAF-mutated RAI refractory and metastatic differentiated thyroid cancer. (n:53)

• 1:1 ratio

Dabrafenib 150mg PO twice daily (n:26)

Dabrafenib 150mg PO twice daily + Trametinib 2mg PO daily (n:27)

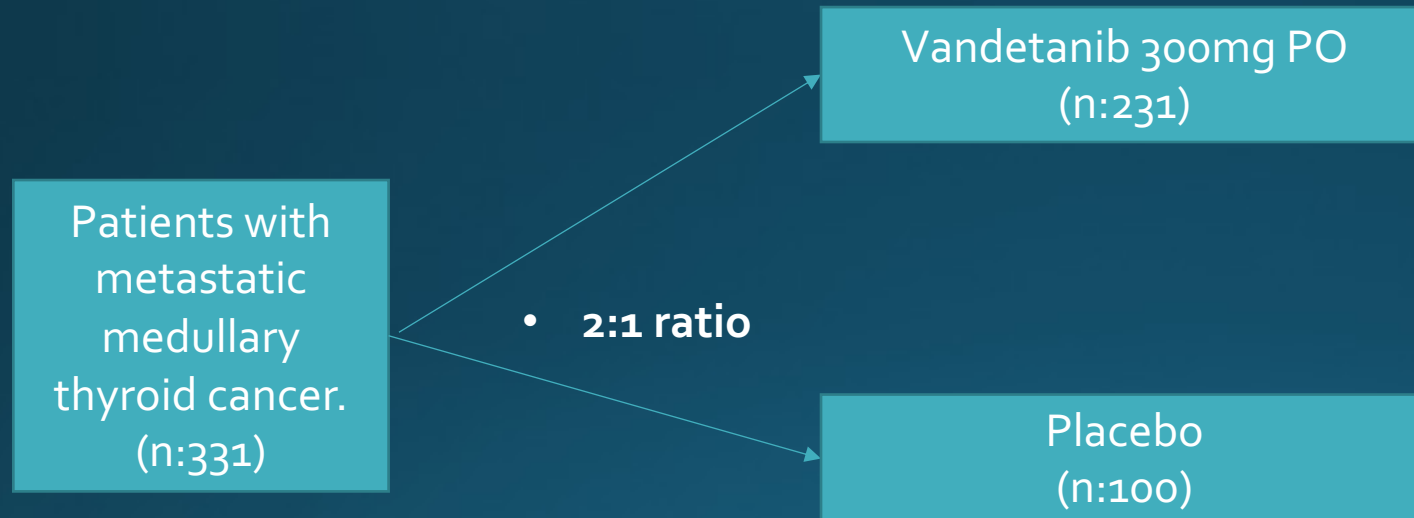
Dabrafenib

Dabrafenib + Trametinib

• RR	42%	48%	(<i>p</i> =0.67)
• PR	35%	30%	
• PFS	10.5	15.1 months	(<i>p</i> =0.65)
• OS	37.9	47.5 months	(<i>p</i> =0.99)

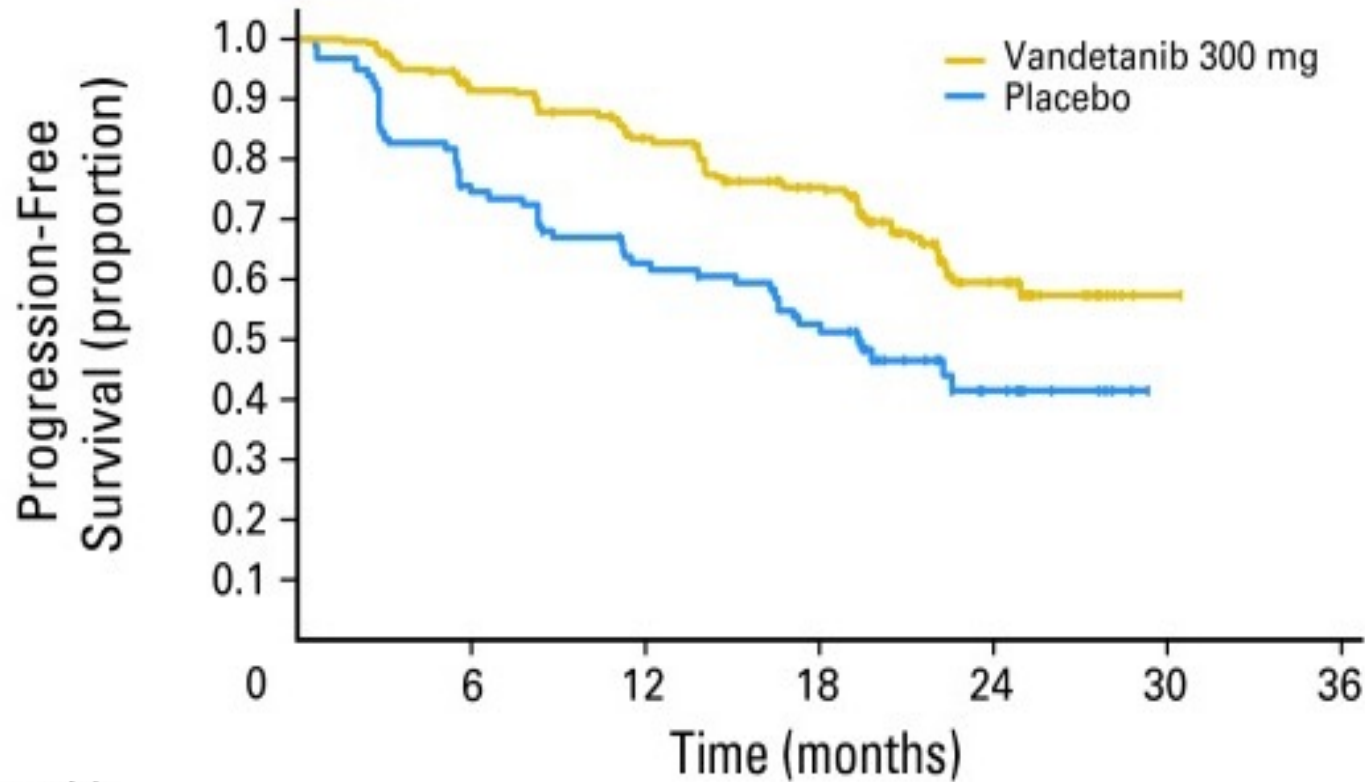
Vandetanib for metastatic medullary thyroid cancer.

ZETA trial: phase 3 randomized double-blind.



Vandetanib for metastatic medullary thyroid cancer.

ZETA trial: phase 3 randomized double-blind.



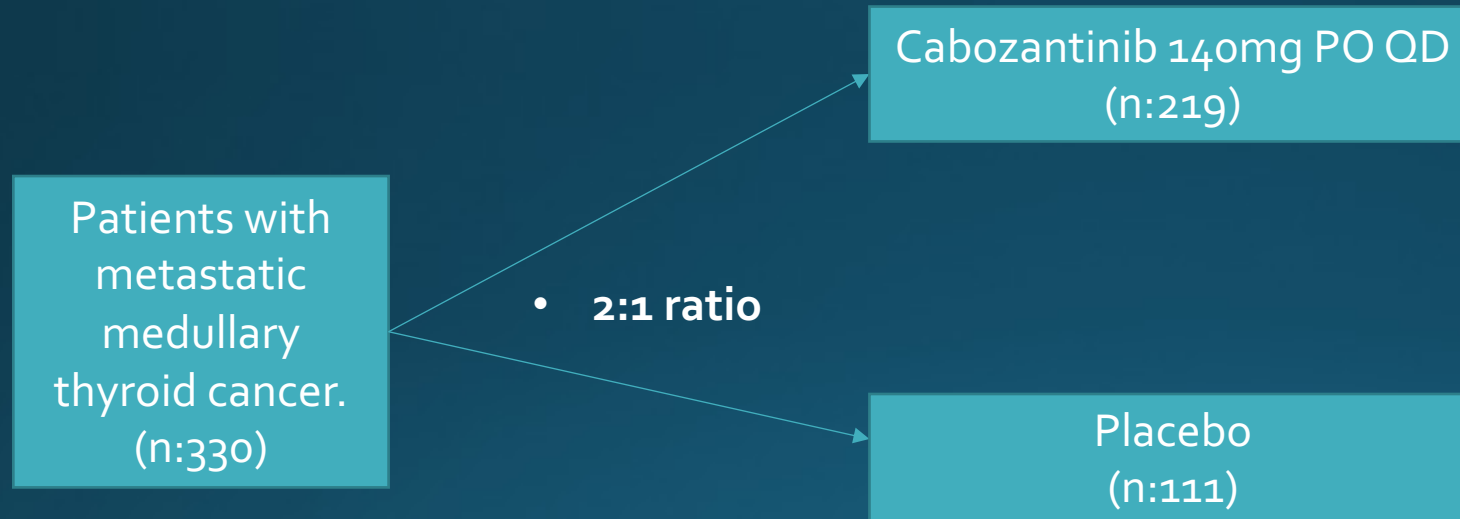
No. at risk	0	6	12	18	24	30	36
Vandetanib 300 mg	231	196	169	140	40	1	0
Placebo	100	71	57	45	13	0	0

Vandetanib vs Placebo
PFS: 30.5 vs 19.3 months

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

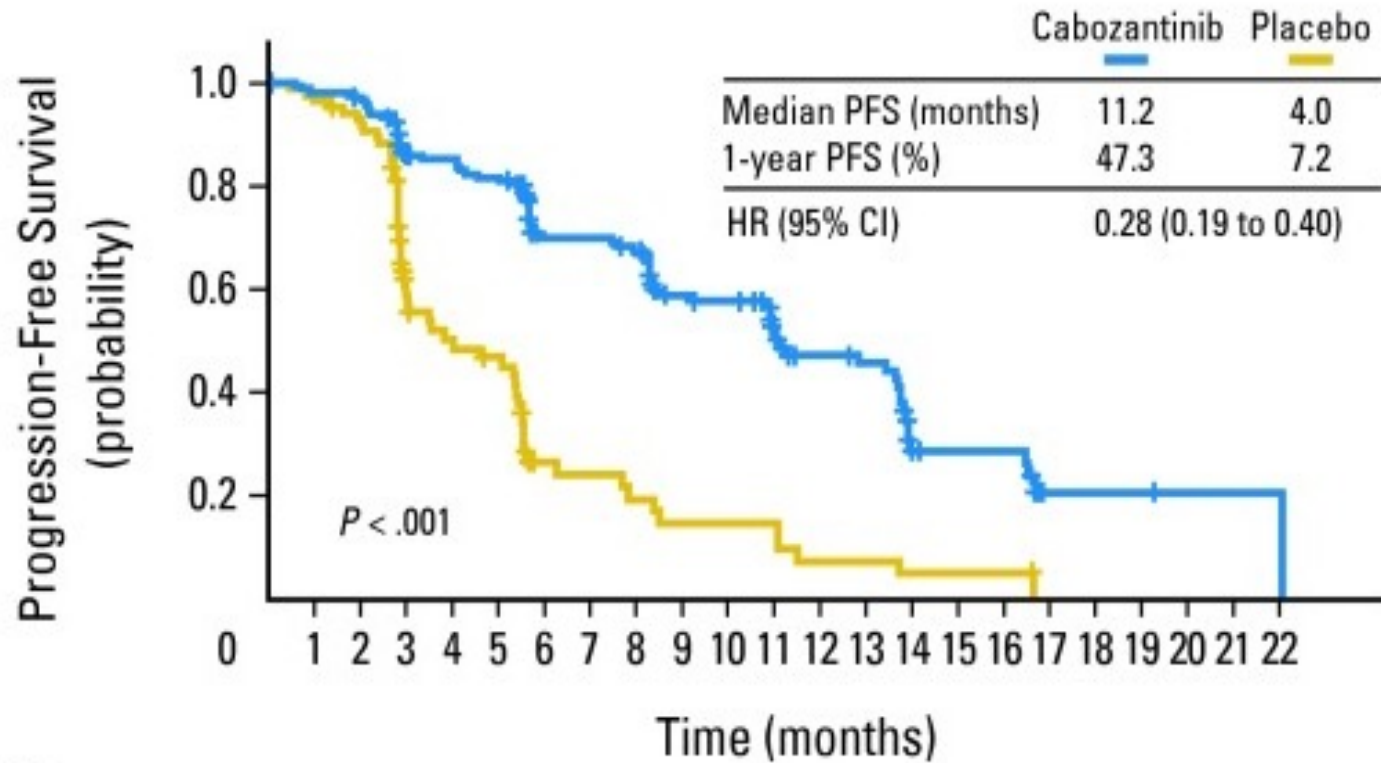
Cabozantinib for metastatic medullary thyroid cancer.

Phase 3 randomized double-blind.



Cabozantinib for metastatic medullary thyroid cancer.

Phase 3 randomized double-blind.



No. at risk	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	
Cabozantinib	219	121	78	55	31	12	2	1																
Placebo	111	35	11	6	3	2	0	0																

	Cabozantinib	vs	Placebo
PFS:	11.2		4 months
1yPFS:	47.3%		7.2%

Selpercatinib in advanced RET-mutated medullary thyroid cancer.

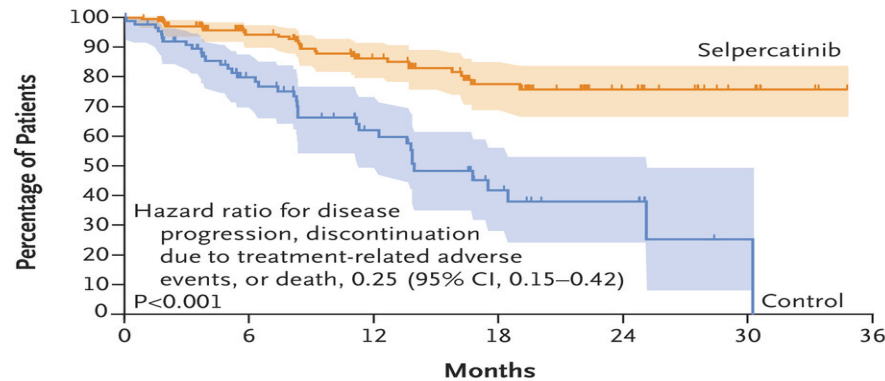
LIBRETTO-531 trial: phase 3 randomized double-blind.



Selpercatinib in advanced RET-mutated medullary thyroid cancer.

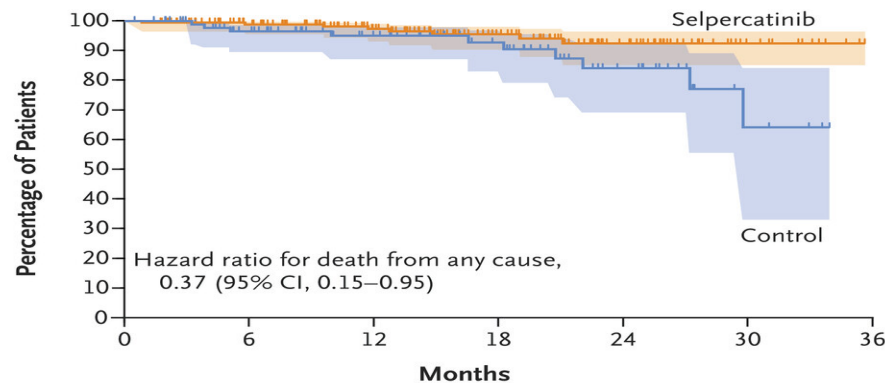
LIBRETTO-531 trial: phase 3 randomized double-blind.

A Treatment Failure-free Survival



No. at Risk	0	6	12	18	24	30	36
Selpercatinib	193	127	84	45	20	7	0
Control	98	51	28	12	7	1	0

B Overall Survival



No. at Risk	0	6	12	18	24	30	36
Selpercatinib	193	158	120	77	40	11	0
Control	98	77	58	39	20	5	0

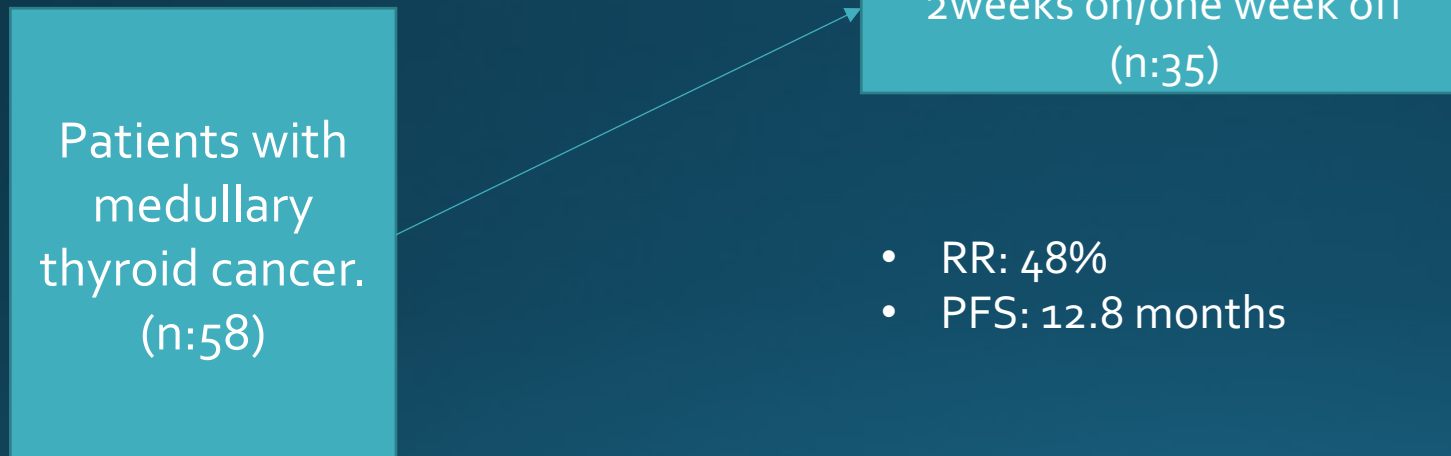
Selpercatinib

Control

- RR 69% 38%
- CR 12% 4%
- PR 57% 34%
- PFS Not reached 16.8 months ($p < 0.001$)
- 12mPFS 89% 65%
- TFFS Not reached 13.9 months ($p < 0.001$)
- 12mTFFS 86% 62%

Anlotinib for metastatic medullary thyroid cancer.

- Phase 2 single-arm.



Dabrafenib plus trametinib in BRAF mutated anaplastic thyroid carcinoma.

ROAR trial: phase 2 open label non-randomised.

Patients with
BRAF mutated
anaplastic
thyroid cancer.
(n:36)

Dabrafenib 150mg PO BID
+
Trametinib 2mg PO daily

- ORR: 56%
- CR: 3 patients
- PFS: 6.7 months.
- OS: 14.5 months.

Nivolumab plus ipilimumab in patients with advanced anaplastic thyroid cancer

Single institution retrospective analysis

- Patients with anaplastic thyroid cancer. (n:19)

Nivolumab plus ipilimumab

- RR: 33%
- PD-L1 TPS<50: RR 0%.
- Grade 3 irAEs 58%
- BRAF wild-type 63%

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 ON
2 weeks OFF
(n:20)

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

Everolimus for advanced thymic carcinoma previously treated with cisplatin.

- Phase 2 single-arm.

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

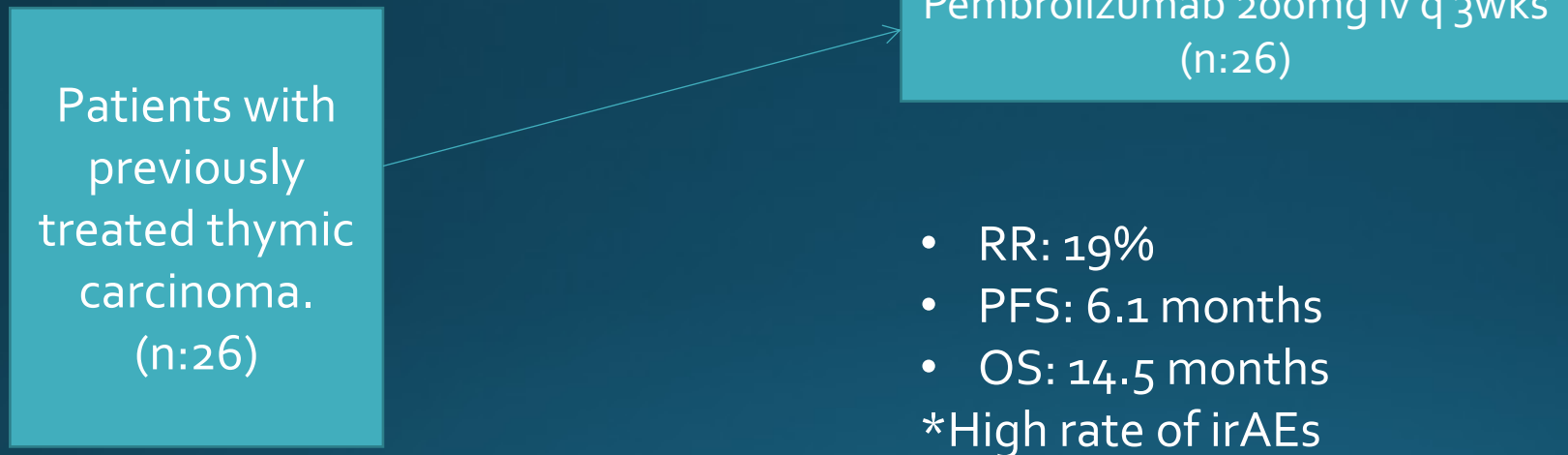
Everolimus 10mg PO QD
(n:18)

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

*36% incidence of pneumonitis. 3 deaths pneumonitis.

Pembrolizumab for advanced thymic carcinoma previously treated with cisplatin.

- Phase 2 single-arm.



Pembrolizumab for recurrent metastatic thymic carcinoma.

- Phase 2 single-arm.

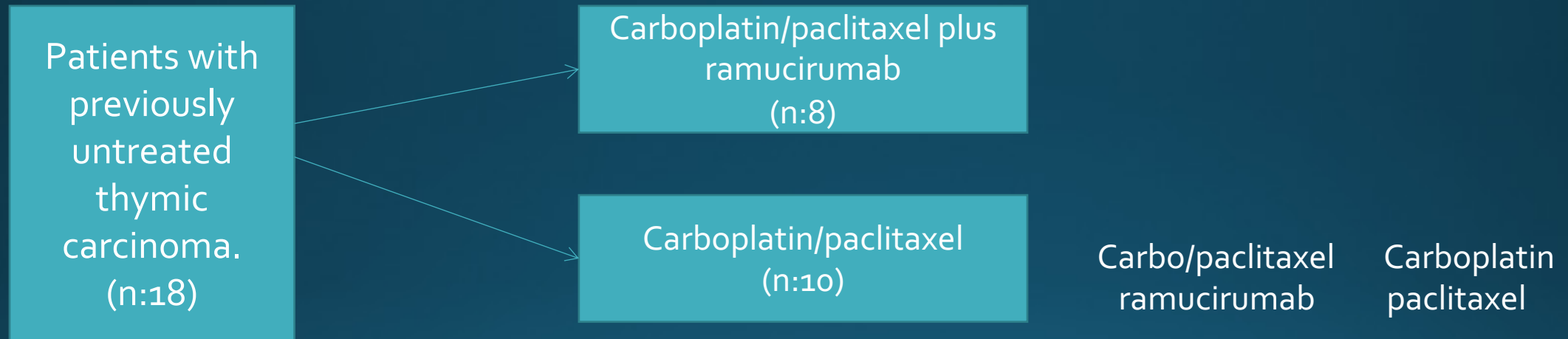
Patients with previously treated thymic carcinoma.
(n:40)

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

- RR: 22%
- *High rate of irAEs

S1701: Carboplatin/paclitaxel with or without ramucirumab in thymic cancer.

- Phase 2 double-arm.



	Carbo/paclitaxel ramucirumab	Carboplatin paclitaxel
• PR	88%	40%
• DCR	100%	70%
• PFS	8 months	7 months

*50% grade 3 AEs in ramucirumab arm.

Conclusions

Thyroid carcinomas

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