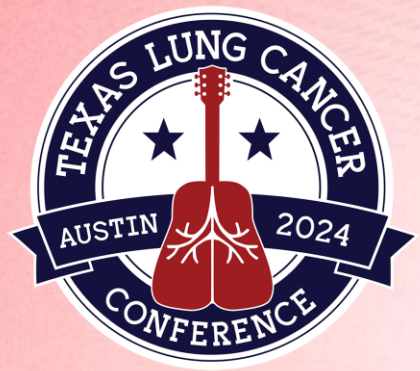


THYMIC MALIGNANCIES

Chul Kim, MD, MPH

Associate Professor of Medicine, Georgetown University

@chulkimMD

Endorsed by

IASLC INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
Conquering Thoracic Cancers Worldwide

Accredited by

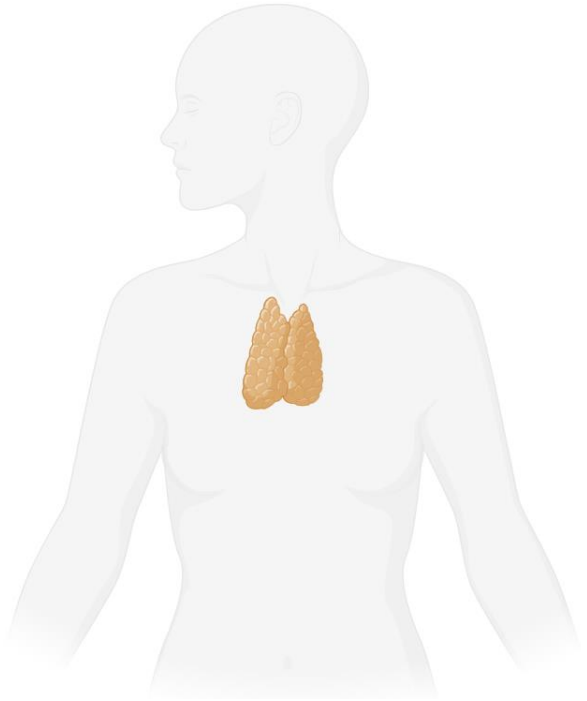
PIM Postgraduate Institute for Medicine
Professional Excellence in Medical Education

Presented by

IDEOlogy Health
Creating Aha! Moments In Healthcare

Characteristics and Management of TETs

- Histological and molecular heterogeneity
  - Thymoma (A, AB, B1, B2, B3) vs. thymic carcinoma
  - No dominant genomic alterations
- Varying clinical course
  - Relative indolent cases in some thymomas (T)
  - Highly aggressive thymic carcinoma (TC)
- Autoimmune disorders
  - More common in thymomas
  - Myasthenia gravis, pure red cell aplasia, Good's syndrome



- Complete resection whenever possible.
  - Incomplete resection is an adverse prognostic factor.
  - Role for induction therapy for marginally resectable disease
- Multidisciplinary treatment
  - Especially for locally advanced TETs
- Systemic treatment for unresectable disease
  - Platinum-based chemotherapy
  - Anti-angiogenesis therapy and ICI have emerged in the past decade

References

Kim and Giaccone. *Hematology-Oncology Therapy (3rd edition)* 2022
Image created with BioRender

Chemotherapy Trials in Advanced-Stage Inoperable TETs

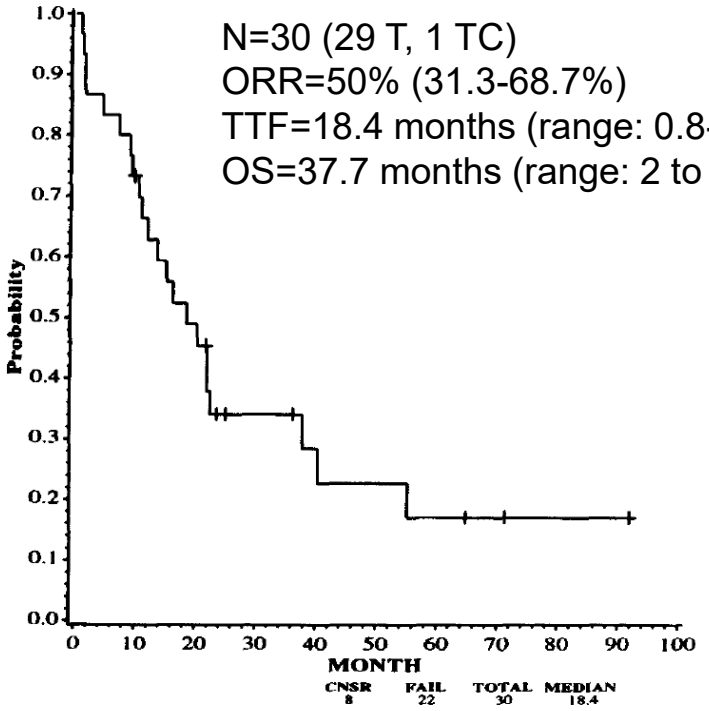
Reference	Regimen	Stage	T/TC	ORR	Median OS (years)
Front-Line Anthracycline containing Regimens					
Loehrer et al.	Cisplatin, doxorubicin, cyclophosphamide (PAC)	IV	29/1	50	3.2
Fornasiero et al.	Cisplatin, doxorubicin, cyclophosphamide, vincristine (ADOC)	III/IV	37/0	92	1.25
Front-Line Non-anthracycline containing Regimens					
Giaccone et al.	Cisplatin, etoposide (EP)	IV	16/0	56	4.3
Loehrer et al.	Cisplatin, etoposide, ifosfamide (VIP)	IV	20/8	32	2.5
Lemma et al.	Carboplatin, paclitaxel	IV	21/23	35	NR for T 1.67 for TC
Second-Line Regimens					
Palmieri et al.	Capecitabine, gemcitabine	IV	22/8	40	NR
Gbolahan et al.	Pemetrexed	IV	16/11	19	2.4

Loehrer et al. *J Clin Oncol* 1994; Fornasiero et al. *Cancer* 1991; Giaccone et al. *J Clin Oncol* 1994; Loehrer et al. *Cancer* 2001; Lemma et al. *J Clin Oncol* 2001; Palmieri et al. *Future Oncol* 2014; Gbolahan et al. *J Thorac Oncol* 2018

Efficacy of Cisplatin, Doxorubicin, Cyclophosphamide for TET

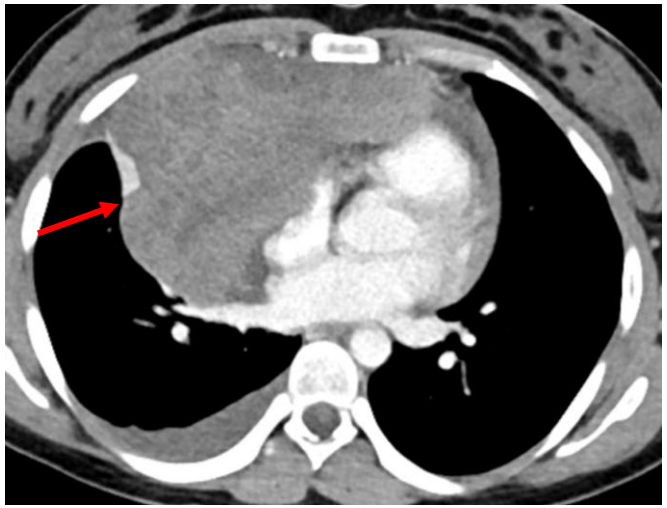
N=30 (29 T, 1 TC)
ORR=50% (31.3-68.7%)
TTF=18.4 months (range: 0.8-91.9+)
OS=37.7 months (range: 2 to 91.1+)

TTF

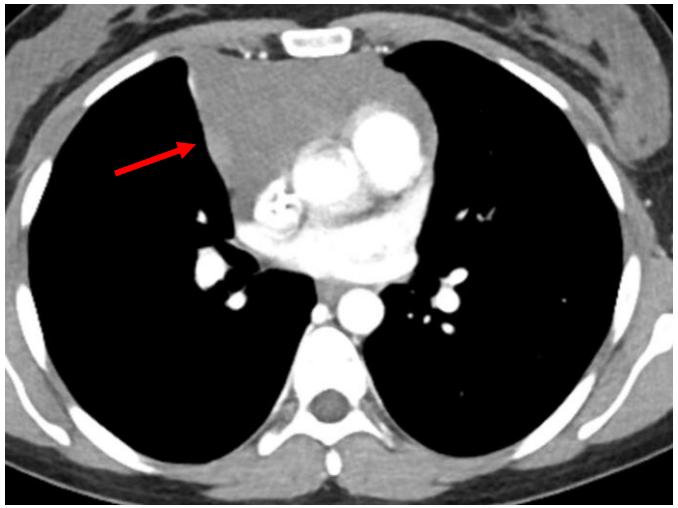


25 year old female with thymoma

Baseline



After 2 cycles of PAC



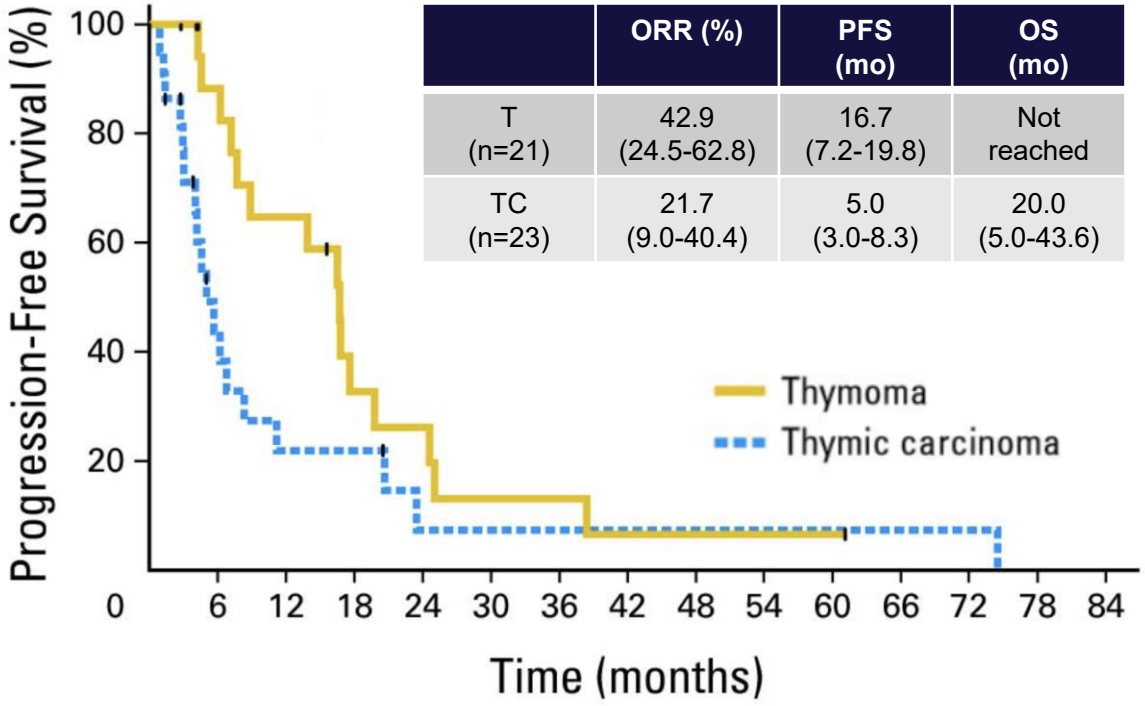
pCR achieved after 4 cycles of PAC

Loehrer et al. *J Clin Oncol* 1994

References

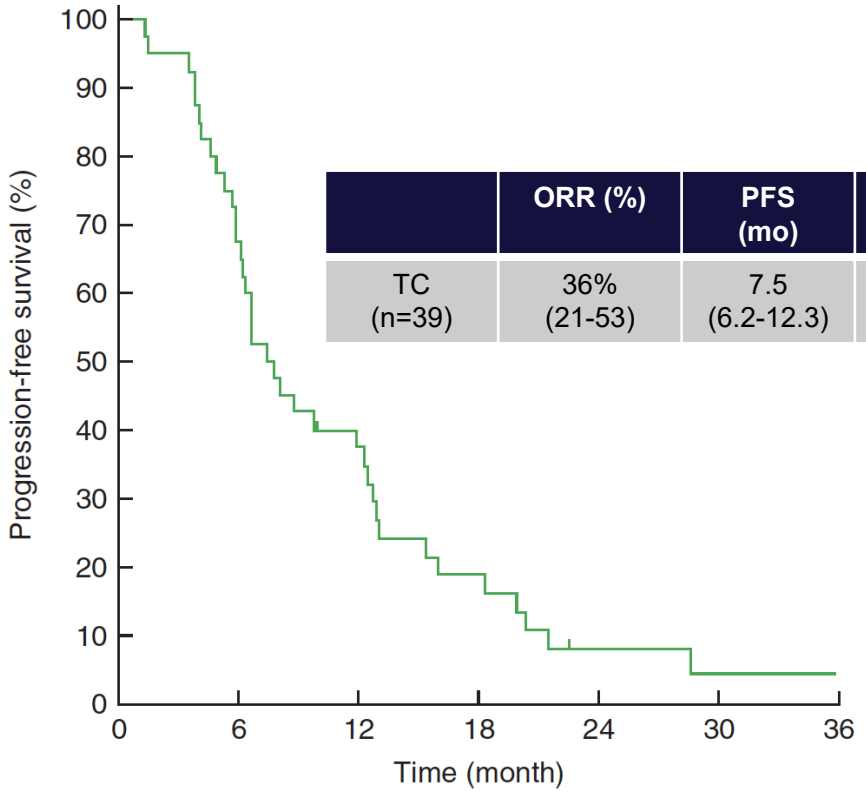
Efficacy of Carboplatin, Paclitaxel for TET

Lemma et al.



	ORR (%)	PFS (mo)	OS (mo)
T (n=21)	42.9 (24.5-62.8)	16.7 (7.2-19.8)	Not reached
TC (n=23)	21.7 (9.0-40.4)	5.0 (3.0-8.3)	20.0 (5.0-43.6)

WJOG4207L



	ORR (%)	PFS (mo)	OS (mo)
TC (n=39)	36% (21-53)	7.5 (6.2-12.3)	Not reached

References

Lemma et al. *J Clin Oncol* 2011; Hirai et al. *Ann Oncol* 2014

Carboplatin, Paclitaxel, Ramucirumab as front-line treatment

RELEVANT: Study design

Key elegibility criteria
- Treatment-naïve advanced or metastatic thymic carcinoma or B3 thymoma with carcinoma areas
- Mesurable disease per RECIST v1.1
- ECOG PS 0-1
- No major standard controindications to antiangiogenics

→

Combination treatment
Ramucirumab 10 mg/kg iv
+ Paclitaxel 200 mg/mq iv
+ Carboplatin AUC5 iv

21-day 6 cycles

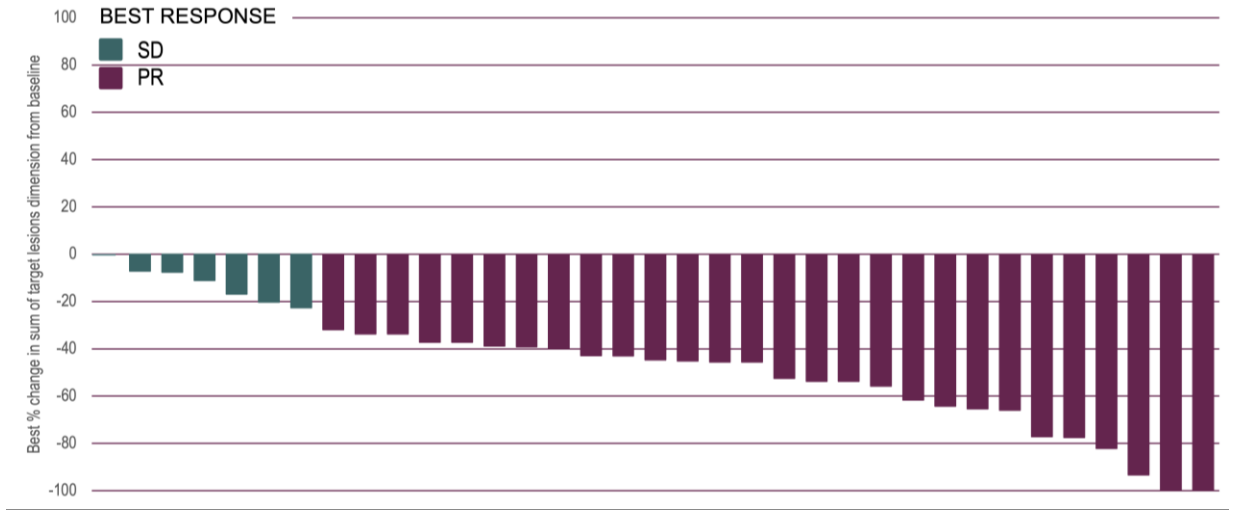
→

Mainteance phase
Ramucirumab 10 mg/kg iv

21-day cycles

EOT
Until disease progression, death or unaccettable toxicity

N=33
*ORR=80% (95% CI: 63.1-91.6)
mDOR=15.9 mo (95% CI: 12.5-50.8)
mPFS=18.1 mo (95% CI: 10.8-52.3)
mOS=43.8 mo (95% CI: 31.9-NE)



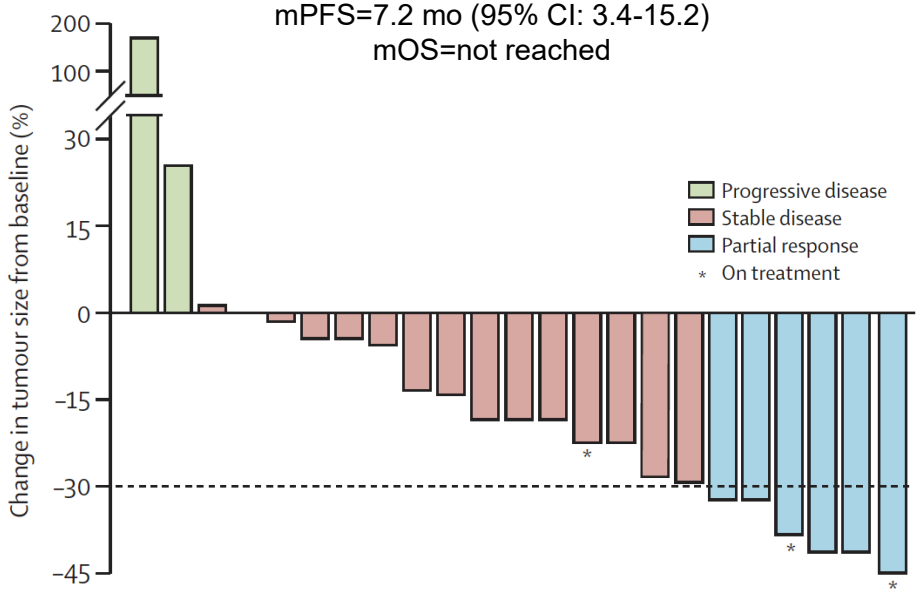
Investigator-assessed ORR

Proto et al. *ESMO* 2023

Anti-angiogenesis Therapy in Thymic Carcinoma

Sunitinib* (n=23)

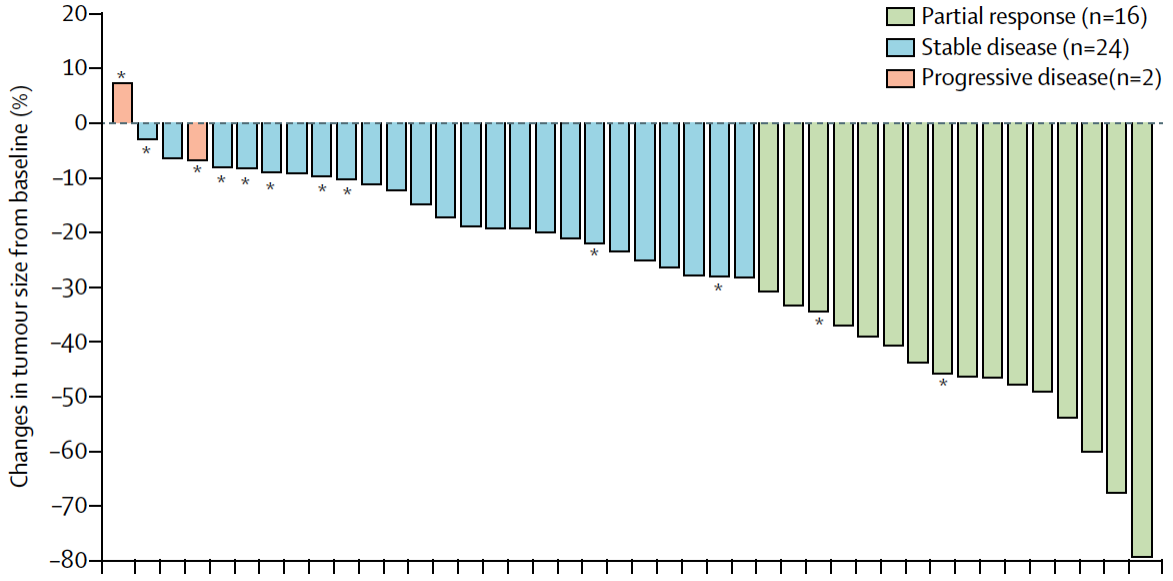
ORR=26% (95% CI: 10.2-48.4)
mDOR=16.4 mo (range: 1.4-16.4)
mPFS=7.2 mo (95% CI: 3.4-15.2)
mOS=not reached



*Thymoma cohort closed after enrollment of 16 patients due to insufficiency activity (ORR=6%)

Lenvatinib (n=42)

ORR=38% (95% CI: 23.6-54.4)
mDOR=11.6 mo (95% CI: 5.8-18.0)
mPFS=9.3 mo (95% CI: 7.7-13.9)
mOS=not reached



Thomas et al. *Lancet Oncol* 2015; Sato et al. *Lancet Oncol* 2020

Summary of Anti-angiogenesis Therapy in TET

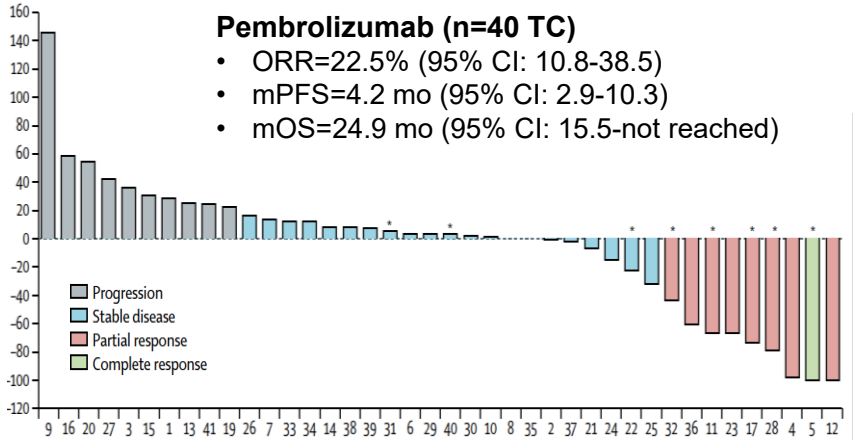
Treatment	T TC	ORR (%)	mDOR (mo.)	mPFS (mo.)	mOS (mo.)	Rate of ≥ G3 of TRAEs
Sunitinib[1]	16	6	-	8.5	15.5	70%
	25	26	16.4	7.2	NR	
Sunitinib[2]	12*	0	-	7.7	47.9	44.2%
	32	21	20.8	8.8	27.8	
Lenvatinib[3]	-	-	-	-	-	NA**
	42	38	11.6	9.3	NR	
Regorafenib[4]	10	10	5.5	9.6	NR	52.6%
	7	14	3.9	9.2	20.1	

* B3 thymoma; **Most common ≥ G3 TRAEs included HTN (64%), palmar-plantar erythrodysesthesia syndrome (7%); NR: not reached; NA: not available

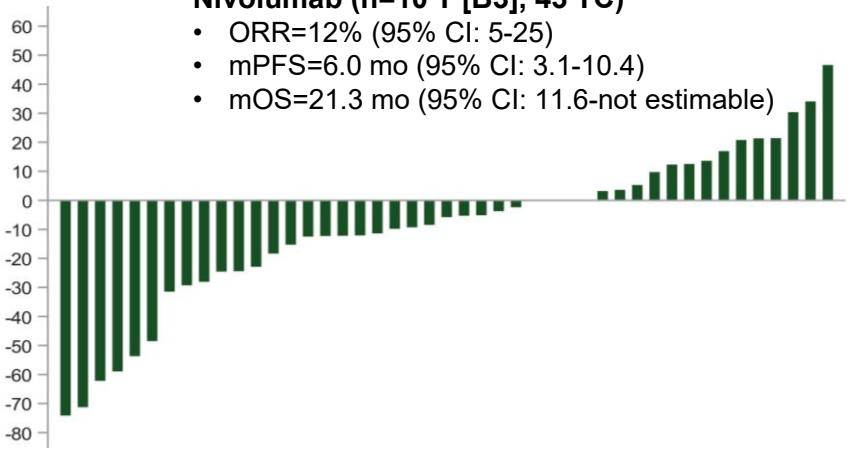
[1]Thomas et al. *Lancet Oncol* 2015; [2]Proto et al. *J Thorac Oncol* 2023; [3]Sato et al. *Lancet Oncol* 2020; [4]Perrino et al. *Cancer* 2022

Immune Checkpoint Inhibitor Therapy in TETs

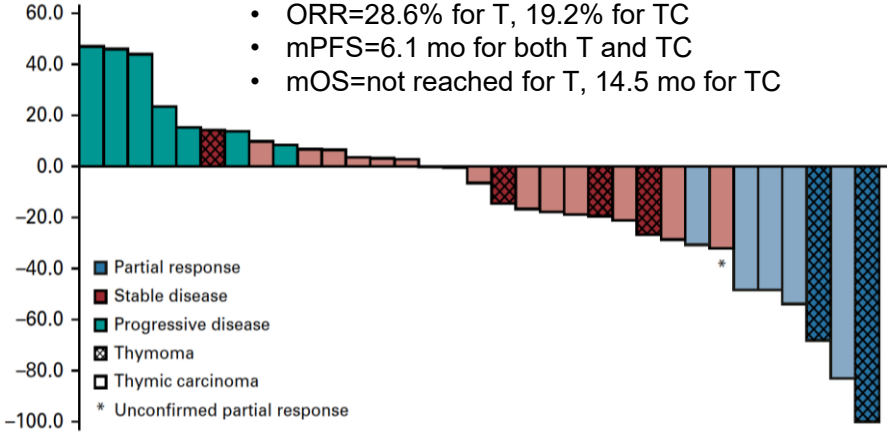
Pembrolizumab (n=40 TC)
- ORR=22.5% (95% CI: 10.8-38.5)
- mPFS=4.2 mo (95% CI: 2.9-10.3)
- mOS=24.9 mo (95% CI: 15.5-not reached)



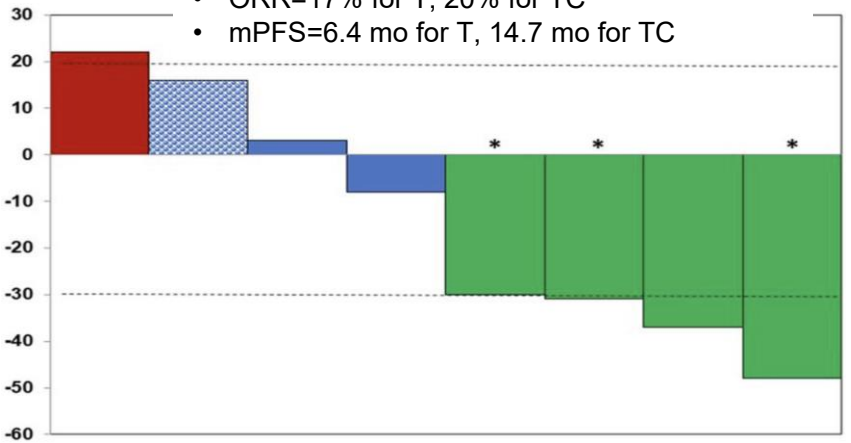
Nivolumab (n=10 T [B3], 43 TC)
- ORR=12% (95% CI: 5-25)
- mPFS=6.0 mo (95% CI: 3.1-10.4)
- mOS=21.3 mo (95% CI: 11.6-not estimable)



Pembrolizumab (n=26 TC, 7 T)
- ORR=28.6% for T, 19.2% for TC
- mPFS=6.1 mo for both T and TC
- mOS=not reached for T, 14.5 mo for TC



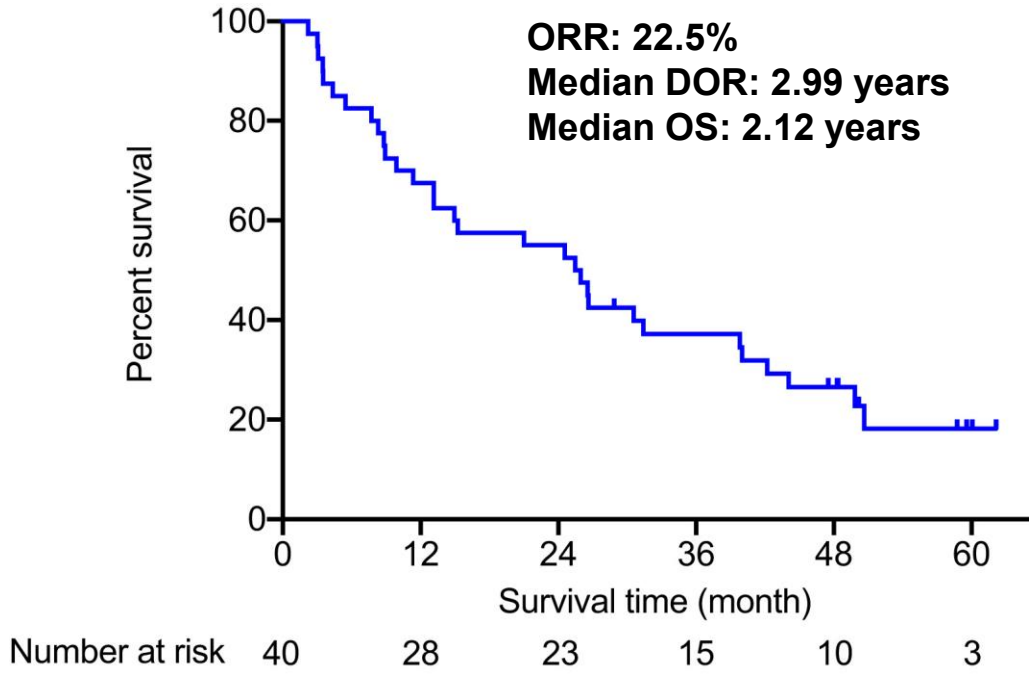
Avelumab (n=12 T, 11 TC)*
- ORR=17% for T, 20% for TC
- mPFS=6.4 mo for T, 14.7 mo for TC

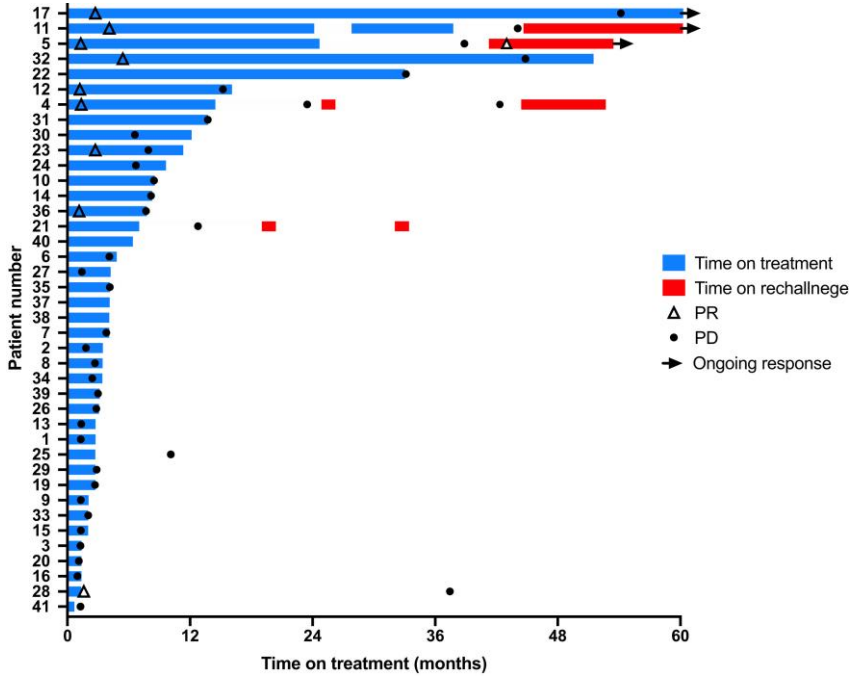


Giaccone et al. *Lancet Oncol* 2018; Cho et al. *J Clin Oncol* 2018; Girard et al. *ESMO Open* 2023; Rajan et al. *J Immunother Cancer* 2019; *Rajan et al. SITC 2019

Durable Response with ICI in Subsets of TETs

- Phase II trial of **pembrolizumab** in patients with thymic carcinoma (N=40)
- Median follow-up: 4.9 years

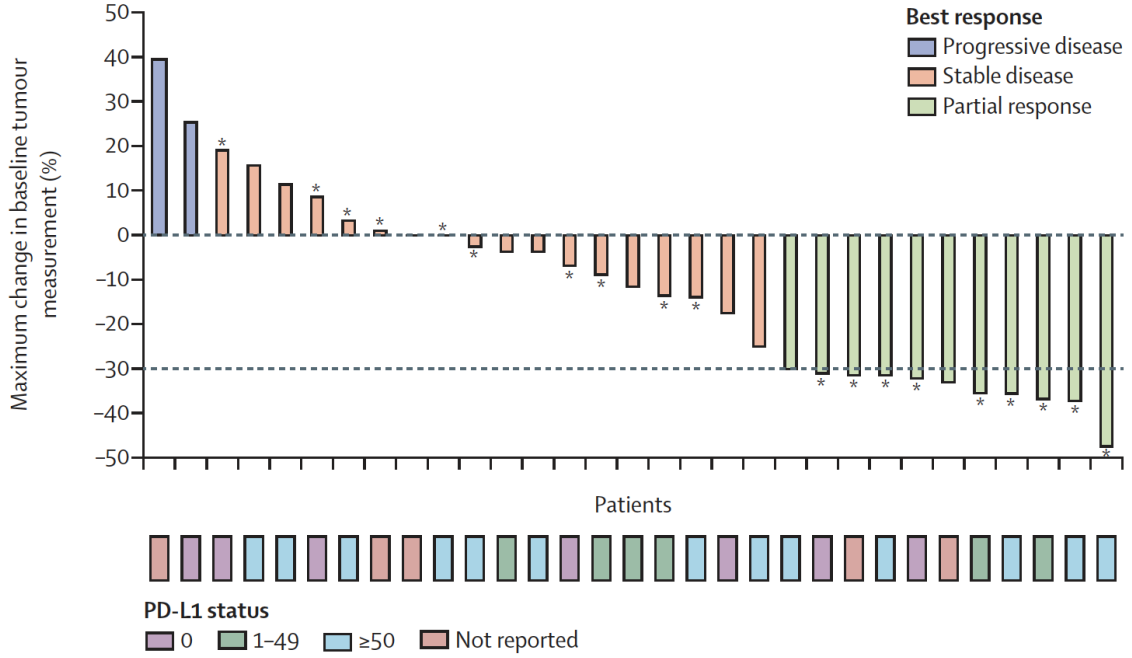


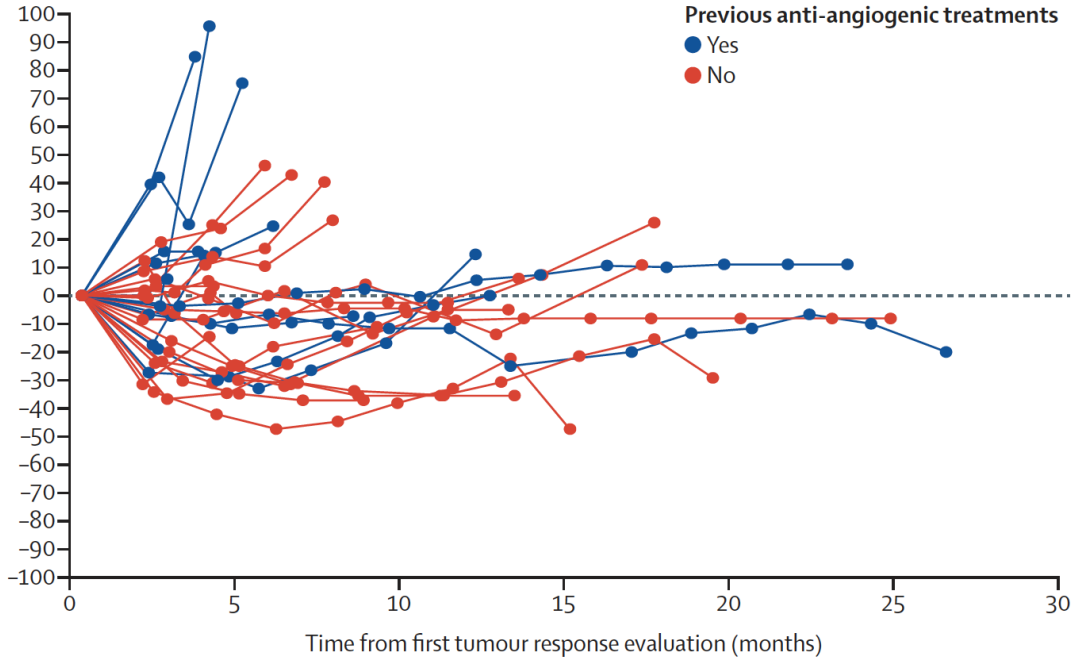


Giaccone and Kim *J Thorac Oncol* 2021

ICI and Anti-angiogenesis Therapy

- Phase II trial of **avelumab** plus **axitinib** in patients with type B3 thymoma and thymic carcinoma (n=32)
- Efficacy: ORR 38%, 33%, 28% in PD-L1 50%, 1-49%, and 0%, respectively
- More pronounced benefit in patients without previous anti-angiogenic therapy
- *PBRM1* mutations were associated with response.





Conforti et al. *Lancet Oncol* 2022

Summary of IO Trials in TETs

Treatment	Thymoma Thymic Carcinoma	ORR (%)	mDOR (mo.)	mPFS (mo.)	mOS (mo.)
Pembrolizumab[1,2]	-	-	-	-	-
	40	22.5	35.8	4.2	24.9
Pembrolizumab[3]	7	28.6	NR	6.1	NR
	26	19.2	9.7	6.1	14.5
Nivolumab[4]	10	12	5.3	6.0	21.3
	43				
Nivolumab[5]	-	-	-	-	-
	15	0	-	3.8	14.1
Nivolumab/Vorolanib[6]	-	-	-	-	-
	9	11	-	9.1	21.1
Avelumab[7,8]	12	17	-	6.4	-
	11	20	-	14.7	-
Avelumab/axitinib[9]	5*	40	5.5	7.5	26.6
	27	33			
KN046[10]	-	-	-	-	-
	46	16.3	10.1	5.6	NR

* 3 patients with type B3 thymoma, 2 patients with mixed type B3/TC; NR: not reached

[1]Giaccone et al. *Lancet Oncol* 2018; [2]Giaccone and Kim J *Thorac Oncol* 2021; [3]Cho et al. *J Clin Oncol* 2018; [4]Girard et al. *ESMO Open* 2023; [5]Katsuya et al. *Eur J Cancer* 2019; [6]Beckermann et al. *JTO Clin Res Rep* 2024; [7]Rajan et al. *J Immunother Cancer* 2019; [8]Rajan et al. SITC 2019; [9]Conforti et al. *Lancet Oncol* 2022; [10]Fang et al ESMO 2023

Risk of irAEs Associated with ICI Therapy in TETs

Serious irAEs can be seen in about 15% patients with TC and up to 70% in patients with T.

Treatment related AEs (all grade)	Pembrolizumab[1]	Pembrolizumab[2]		Avelumab[3]	Avelumab/axitinib[4]	Nivolumab[5+]
	TC (N=40)	T (n=7)	TC (n=26)	T (n=7)	B3 T & TC (N=32)	B3 T & TC (N=55)
Polymyositis	3 [7.5%]	0	0	4 [57.1%]	3 [9.4%]	0
Myocarditis	2 [5.0%]	3 [42.9%]	0	4 [57.1%]	0	2 [3.6%]
Myasthenia gravis	2 [5.0%]	1 [14.3%]	2 [7.7%]	0	0	0
Subacute myoclonus	0	0	1 [3.8%]	0	0	0
Cranial neuropathy	0	0	0	1 [14.3%]	0	0
Conjunctivitis	0	1 [14.3%]	0	0	0	0
Enteritis/colitis	0	1 [14.3%]	0	1 [14.3%]	-	2 [3.6%]
Diarrhea	9 [22.5%]	-	-	-	18 [56.3%]	6 [10.9%]
AST elevation	16 [40.0%]	2 [28.6%]	2 [7.7%]	4 [57.1%]	6 [18.8%]	6 [10.9%]
ALT elevation	10 [25.0%]	2 [28.6%]	2 [7.7%]	4 [57.1%]	6 [18.8%]	7 [12.7%]
Pancreatitis	1 [2.5%]	0	0	0	0	3 [5.5%]
Pneumonitis	0	0	0	0	1 [3.1%]	4 [7.3%]
Nephritis	0	1 [14.3%]	0	0	0	-
Proteinuria	-	-	-	-	-	1 [1.8%]
Hypothyroidism	5 [12.5%]	-	-	0	0	3 [5.5%]
Hyperthyroidism	2 [5.0%]	2 [28.6%]	1 [3.8%]	0	0	-
Bullous pemphigoid	1 [2.5%]	0	0	0	0	0
Rash	0	0	2 [7.7%]	0	8 [25%]*	4 [7.3%]
Pruritis	-	-	-	-	6 [18.8%]	6 [10.9%]

* Palmar-plantar erythrodysesthesia syndrome

\+ **In this trial, patients with the presence of acetylcholine receptor antibodies at baseline were excluded.**

[1]Giaccone et al. *Lancet Oncol* 2018; [2]Cho et al. *J Clin Oncol* 2018; [3]Rajan et al. *J Immunother Cancer* 2019; [4]Conforti et al. *Lancet Oncol* 2022; [5]Girard et al. *ESMO Open* 2023

Ongoing Immunotherapy Trials in TETs

Setting	Treatment	N	Histology	Phase	Primary Endpoint(s)	Region	NCT
Resectable TET (Neoadjuvant/Perioperative)	**Platinum-based chemotherapy/toripalimab**	15	Stage III-IVA T/TC	2	Rate of severe AEs mPR	China	NCT04667793
	Cisplatin/docetaxel/pembrolizumab	40	Stage III-IVA T/TC	2	mPR	South Korea	NCT03858582
	Radiation/envolizumab	25	Stage III-IVA TC	2	ORR	China	NCT06019468
Advanced TET (First-line)	**Carboplatin/taxane/pembrolizumab**	40	T/TC	4	ORR	China	NCT04554524
	Carboplatin/taxol/lenvatinib/pembrolizumab	35	TC	2	ORR	Japan	NCT05832827
Advanced TET (Second-line and beyond)	**Avelumab**	55	T/TC	2	Safety, tolerability ORR	USA	NCT03076554
	Atezolizumab	34	TC	2	ORR	China	NCT04321330
	Pembrolizumab	37	T/TC	1	Incidence of AEs	USA	NCT03295227
	Pembrolizumab/lenvatinib	43	B3 T/TC	2	5-month PFS	France, Italy, Spain	NCT04710628
	Pembrolizumab/sunitinib	40	TC	2	ORR	USA	NCT03463460
	Nivolumab +/- ipilimumab	55	B3 T/TC	2	6-month PFS	Europe	NCT03134118
	Bintrafusp Alfa (Anti-PD-L1/TGFβ Trap fusion protein)	38	T/TC	2	ORR	USA	NCT04417660
	KN046 (PD-L1/CTLA-4 bispecific antibody)	66	TC	2	ORR	China	NCT04469725
	XmAb20717						
	KFA115 +/- tislelizumab	220	TC among other cancers	1	DLT Dose intensity	International	NCT05544929
	SO-C101 (IL-15 superagonist) +/- pembrolizumab	200	TC among other cancers	1	DLT	International	NCT04234113

Novel Therapies in Development

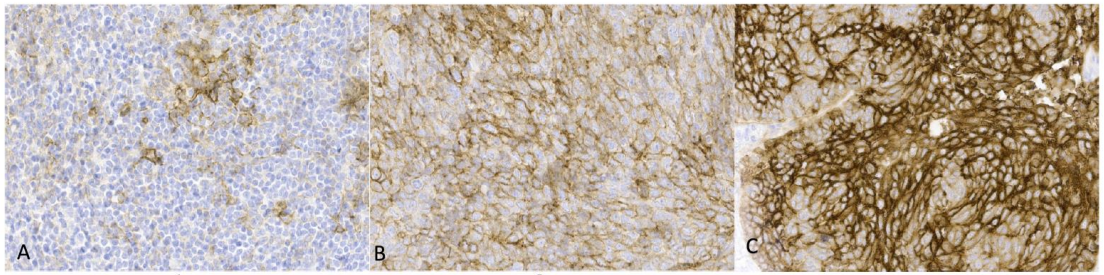
Treatment	Target(s)	N	Histology	Phase	Primary Endpoint(s)	Region(s)	NCT
Rivoceranib	VEGFR2	40	T/TC	2	ORR	Korea	NCT06200233
KC1036	VEGFR2, AXL, FLT	30	T/TC	2	ORR	China	NCT05683886
^{177}Lu-DOTA-TATE / Olaparib	SSTR, PARP	18	Somatostatin receptor+ tumors (including thymoma)	1	TRAEs	Sweden	NCT04375267
Lutathera vs. everolimus	SSTR	120	Lung and thymic NET	3	PFS	France, Italy, Spain	NCT05918302
PT-112	Ribosomal biogenesis	53	T/TC	2	ORR	USA	NCT05104736
VMD-928	TrkA	74	Solid tumors (including TET) or lymphoma	1	TEAEs	USA	NCT03556228
IDE397	MAT2A	130	MTAP-deleted solid tumors	1	DTL, MTD	International	NCT04794699
AMG 193	PRMT5	527	MTAP-null solid tumors	1/2	MTD, RP2D, ORR	International	NCT05094336
MRTX1719	PRMT5	370	MTAP-deleted solid tumors	1/2	DLT, ORR	USA	NCT05245500

Clinicaltrials.gov; Conforti et al. *Expert Opin Investig Drugs* 2022; Sun et al. *JTO Clin Res Rep* 2023; Chen et al. *Br J Cancer* 2022

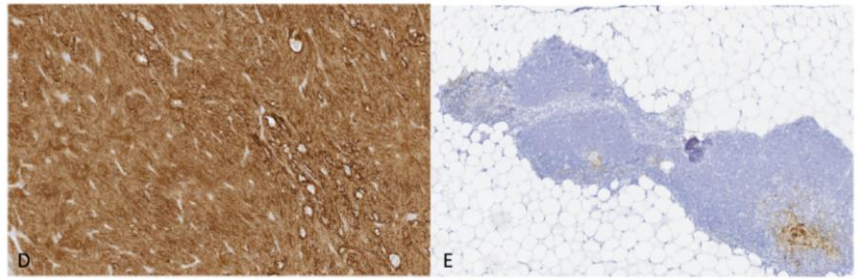
High Levels of Expression of Trop-2 in TETs

	Normal Thymus Tissue (n=13)	Thymoma (n=17)						Thymic carcinoma (n=12)
		A (n=2)	AB (n=6)	B1 (n=3)	B2 (n=4)	B3 (n=2)	Thymoma Total	
Trop-2 IHC Score								
0	8	0	0	0	0	1	1	0
1+	5	0	1	1	1	0	3	3
2+	0	1	5	2	3	1	12	8
3+	0	1	0	0	0	0	1	2

Examples of grading of Trop-2 IHC

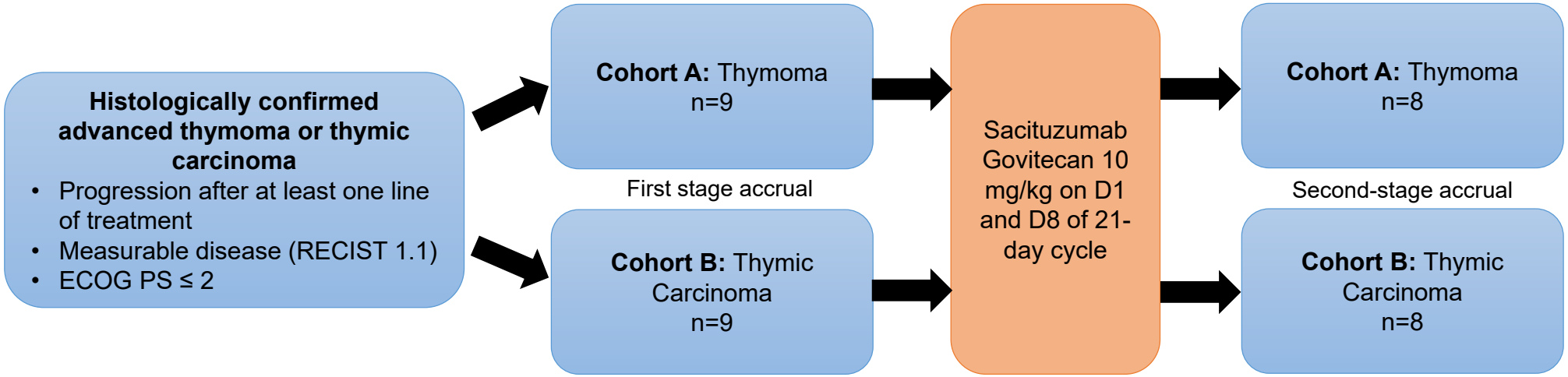


Trop-2 staining of thymoma & normal thymic tissue



Yeung et al. *Lung Cancer* 2023

Phase II Multicenter Trial of Sacituzumab Govitecan



- Primary endpoint: ORR
- Secondary endpoints: DOR, PFS, OS, adverse events
- Exploratory analyses: Expression of Trop-2 in tissue and circulating tumor cells and its correlation with treatment outcomes
- NCT06248515

Conclusions

- Multidisciplinary management plays a crucial role in treating TETs.
- For advanced stages of TETs, platinum-based cytotoxic chemotherapy continues to be the primary treatment option. The addition of ramucirumab to a regimen of carboplatin and paclitaxel has shown to enhance treatment outcomes.
- The inclusion of small molecule VEGFR inhibitors and immune checkpoint inhibitors (ICIs) has become increasingly significant in the therapeutic strategy for TETs. However, the use of ICIs in treating thymomas is generally not recommended unless within a clinical trial setting.
- There is a pressing need for innovative therapies that target the specific molecular weaknesses of TETs.