Novel Therapies for Thymic Malignancies

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Masters in Thoracic Oncology Summit
Albuquerque, New Mexico | November 16 - 19, 2023

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Thymic Epithelial Malignancies: Rules of the Road for Systemic Treatment

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- Anthracycline based regimens increase response rates in thymoma (i.e. CAP)
- Carboplatin/paclitaxel preferred 1L regimen in thymic carcinoma
- Thymic carcinoma poorer prognosis than thymoma
- R0 resection in the potentially curative setting most important intervenable prognostic factor (neoadjuvant chemo)
- Need for effective and safe targeted therapies and immune based approaches

PD-L1 score and correlation with WHO Histology

Table 3: Statistically Significant Correlation with PD-L1 High Score and WHO Histology (p=0.035)	
B3	**100% (n=7/7)**
B2	**78.9% (n=15/19)**
C	**75% (n=3/4)**
B1	71.4% (n=10/14)
AB	58.8% (n=10/17)
A	25% (n=2/8)

***Table 3*: Ranked Highest to Lowest. PD-L1 high scores are found more frequently (≥ 75%) in higher grade TETs, including WHO type B2, B3, & C. B3 and C histologies tend to have less lymphocytes; however, there was no significant correlation between PD-L1 intensity and lymphocytic infiltrate (p=0.31)**

Padda, Riess JTO 2015

PD-(L)1 Immunotherapy has activity in pts with TETs

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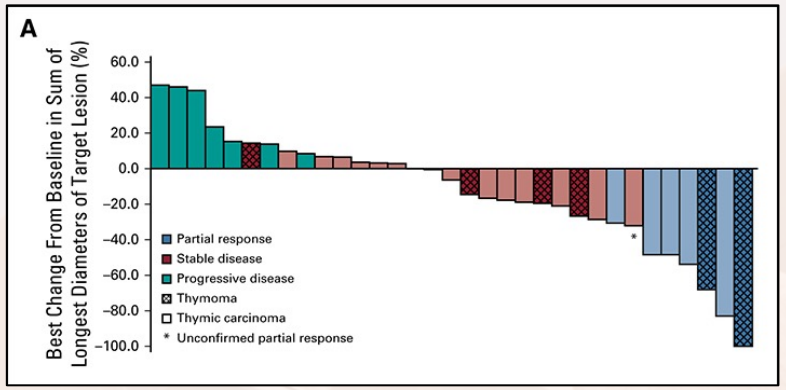
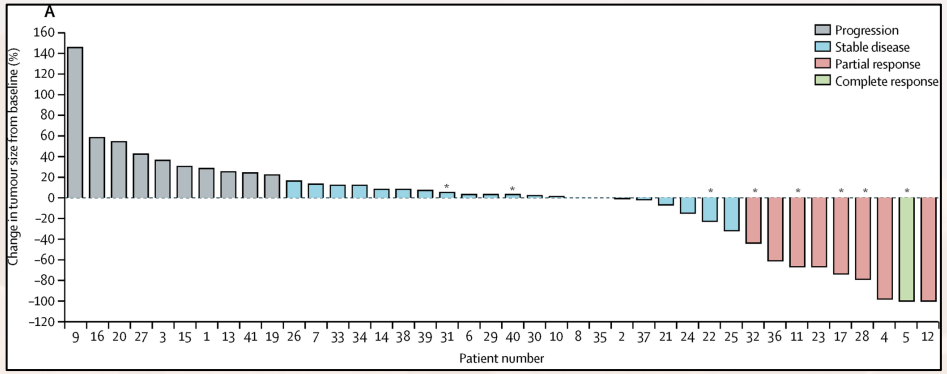
PEMBROLIZUMAB (T&TC)



N=33 (26 TC, 7 T), previously treated

- T: 2 PR (28.6%), 5 SD; mDOR not reached
- **TC: 5 PR (19.2%), 14 SD; mDOR 9.7 mo**
- mPFS 6.1 months (overall)
- mOS 13.2 mo (TC; median f/u 33.6 mo)
- Association with PD-L1 (IHC and mRNA)

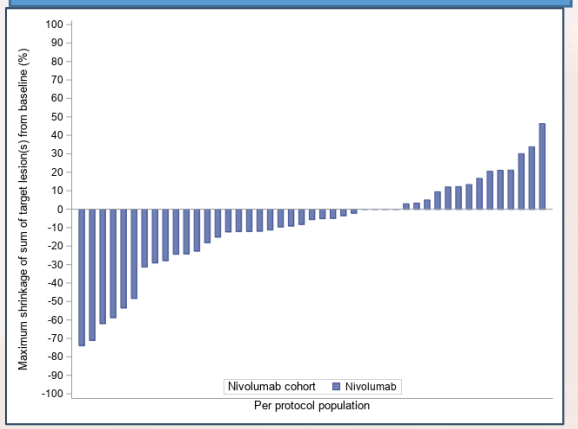
PEMBROLIZUMAB (TC)



N=40 (all TC), previously treated

- **TC: 1 CR, 8 PR (22.5% ORR), 21 SD; mDOR 35.9 mo**
- mPFS: 4.2 mo
- mOS 25.4 mo (median f/u 58.8 mo); 18% 5-year OS
- Association with PD-L1 high expression (IHC)

Nivolumab (TC)

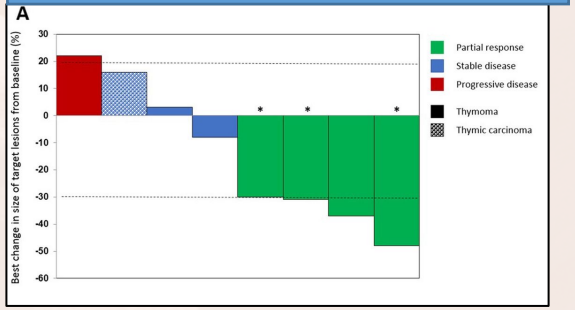


N=15 (all TC), previously treated

- 0 responses; DCR 73.3%
- mPFS 3.8 mo

N=49, ORR=12%, mPFS 6 mo

Avelumab (T)



N=7 (T), previously treated

- 4 PR (2 cPR; 29%)

Cho et al. J Clin Oncol. 2019 Aug 20;37(24):2162-2170. Giaccone et al WCLC 2019. Giaccone et al. Lancet Oncol. 2018 Mar;19(3):347-355. Giaccone et al. J Thorac Oncol. 2021 Mar;16(3):483-485. Katsuya et al. Eur J Cancer. 2019 May;113:78-86. Rajan et al. J Immunother Cancer. 2019 Oct 21;7(1):269. N. Girard et al ESMO 2021.

PD-L1 expression and Pembrolizumab Activity

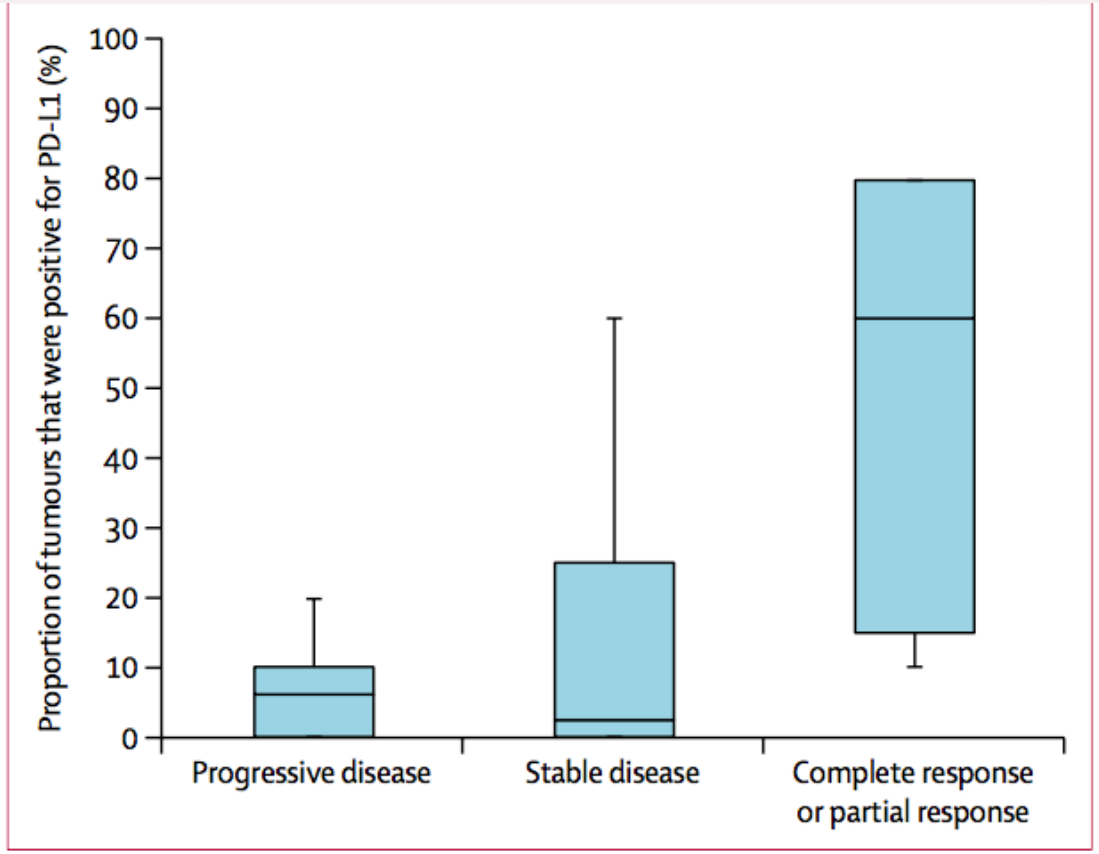
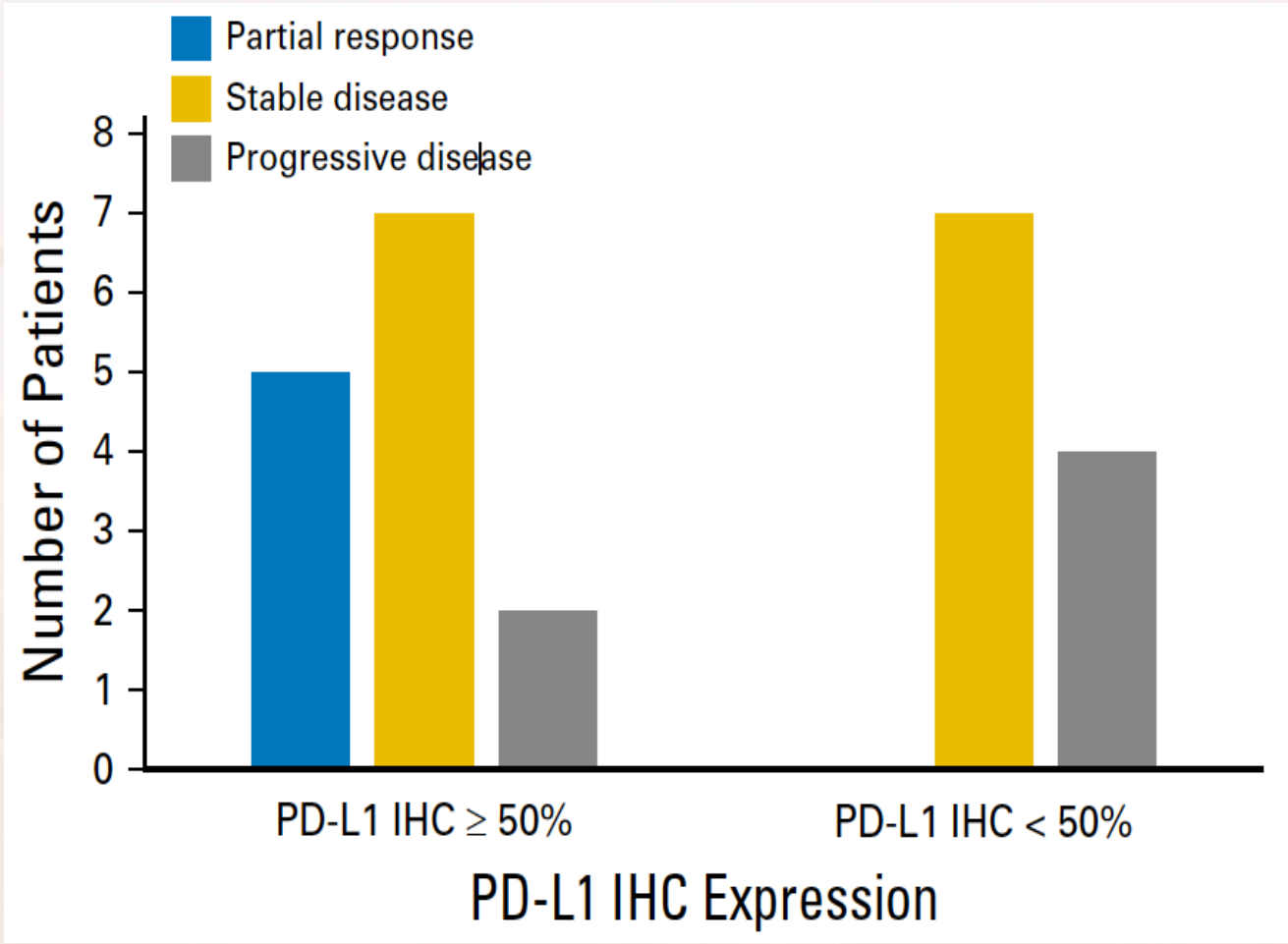


***Figure 3*: PD-L1 expression and response to pembrolizumab.**
Error bars are SD. Horizontal lines are medians.



Giaccone et al Lancet Oncol 2018

Cho et al JCO 2018

High severe irAE rate and multiple irAEs in single patients

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PEMBROLIZUMAB (T&TC)

Patien	AS (grade)	Histology	Preexisting AS	Prior Radiotherapy to Primary Mediastinal Mass	Best Response	Time to First irAE (No. of pembrolizumab cycles)	irAE Treatment	Recovery Time to Resolution Without Need for Immunosuppression (weeks)
1	Myasthenia (3) Autoimmune hepatitis (3)	Thymic carcinoma	Myasthenia	No	PR	1	Corticosteroids Pyridostigmine Azathioprine	24
2	Subacute myoclonus (3)	Thymic carcinoma	—	Yes	PR	10	Corticosteroids	6
3	Myasthenia (4)*	Thymic carcinoma	—	Yes	SD	2	Corticosteroids Pyridostigmine IVIG	16
4	Autoimmune hepatitis (4) Colitis (3) Conjunctivitis (2) Dermatitis (2) Thyroiditis (2)	Thymoma (B2)	Myasthenia	No	PR	1	Corticosteroids Mycophenolate mofetil Infliximab Tacrolimus	—
5	Myocarditis (4) Myasthenia (2)	Thymoma (B2)	Myasthenia	No	PR	1	Corticosteroids IVIG	20
6	Myocarditis (4) Autoimmune hepatitis (3) Thyroiditis (3)	Thymoma (B2)	—	No	SD	2	Corticosteroids IVIG	12
7	Glomerulonephritis (4) Dermatitis (2)	Thymoma (B3)	—	No	SD	5	Corticosteroids Cyclophosphamide	18
8	Myocarditis (4)	Thymoma (B2/B3)	—	No	SD	2	Corticosteroids IVIG	12

Abbreviations: AS, autoimmune syndrome; irAEs: immune-related adverse events; IVIG, intravenous immunoglobulin; PR, partial response; SD, stable disease.
*This patient developed myasthenia gravis without previous history of myasthenia gravis before the study and had no evidence of acetylcholine antibodies in his history by medical record.

G3-4 irAE: T: 5/7 (71.4%), TC: 4/26 (15.4%);
treatment d/c in all except 1
*3 pts had ocular MG, pyridostigmine > 1 year ago

PEMBROLIZUMAB (TC)

irAE (onset cycles)	Treatment
Polymyositis, myocarditis, hepatitis (2C)	High dose steroids, Pacemaker
Hepatitis, pancreatitis, type 1 DM (4C)	Insulin
Bullous pemphigoid (10C)	Oral steroids, topical therapy
Polymyositis, hepatitis, myocarditis, myasthenia gravis (2C)	IV steroids, Pacemaker; IVIg & steroids for MG
Polymyositis, hepatitis (4C)	IV steroids
Grade 3 transaminitis (20C)	Steroids

G3-4 irAE: 6 (15%)
*None had h/o AI disease – MG not tested
*Median duration of steroids 2.5 mo (3 wk to >2y)

Nivolumab (TC)

Grade 4/5 AEs
Respiratory failure (1 patient, G5)*
Neutropenia (1 patient, G4, treatment related)
Myocarditis (2 patients, G4, treatment related)
Immune-mediated transaminitis (1 patient, G4, treatment related)
Sepsis (1 patient, G4)
Dyspnea (1 patient, G4)*

Avelumab (T)
5/7 (71%) G3-4 autoimmune disorder
muscle weakness, myalgia, myositis, respiratory muscle insufficiency, hoarseness, paresthesia, dysphagia, dyspnea, diarrhea and elevated creatine phosphokinase (CPK)

Myositis associated with acetylcholine receptor antibodies and B-cell lymphopenia

Cho et al. J Clin Oncol. 2019 Aug 20;37(24):2162-2170. Giaccone et al WCLC 2019. Giaccone et al. Lancet Oncol. 2018 Mar;19(3):347-355. Giaccone et al. J Thorac Oncol. 2021 Mar;16(3):483-485. Katsuya et al. Eur J Cancer. 2019 May;113:78-86. Rajan et al. J Immunother Cancer. 2019 Oct 21;7(1):269. Mammen AL et al. Ann Rheum Dis. 2019 Jan;78(1):150-152. N. Girard et al ESMO 2021.

Pre-Avelumab Anti-AChR predicts Myositis

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Table 1 Serum CK levels and thymoma-associated autoantibody levels in patients with thymoma before and after avelumab treatment

Patient	Serum CK (IU/L)	Anti-AChR (nmol/L)	Anti-STR (dilutions)	Anti-VGKC (nmol/L)	Anti-GAD65 (nmol/L)	Anti-α3 (nmol/L)	Anti-CRMP5	Anti-AMPAR	Anti-GABABR	Anti-NMDA	Anti-LGI1	Anti-Caspr2
#1 Pre	55	2.59	3840	0	NT	0	Neg	Neg	Neg	Neg	Neg	Neg
#1 Day 15 post	1792	2.36	1920	0	0.02	0	Neg	Neg	Neg	Neg	Neg	Neg
#2 Pre	86	0.21	Neg	0	0	0	Neg	Neg	Neg	Neg	Neg	Neg
#2 Day 43 post	1046	0.24	Neg	0	0	0	Neg	Neg	Neg	Neg	Neg	Neg
#3 Pre	130	0.36	7680	0	0	0	Neg	Neg	Neg	Neg	Neg	Neg
#3 Day 15 post	3939	0.31	7680	0	0	0	Neg	Neg	Neg	Neg	Neg	Neg
#4 Pre	77	0	Neg	0	0	0	Neg	Neg	Neg	Neg	Neg	Neg
#4 Day 15 post	60	0	Neg	0	0	0	Neg	Neg	Neg	Neg	Neg	Neg
#5 Pre	435	0	Neg	0.11	0	0	Neg	Neg	Neg	Neg	Neg	Neg
#5 Day 15 post	473	0	Neg	0.15	0	0	Neg	Neg	Neg	Neg	Neg	Neg
#6 Pre	91	0.73	30 720	0.06	0	0	Neg	Neg	Neg	Neg	Pos	Neg
#6 Day 8 post	762	0.67	61 440	0.01	0	0	Neg	Neg	Neg	Neg	Pos	Neg
#7 Pre	87	0	Neg	0	0	0	Neg	Neg	Neg	Neg	Neg	Neg
#7 Day 15	74	0	Neg	0	0	0	Neg	Neg	Neg	Neg	Neg	Neg
#8 Pre	45	0	Neg	0	0	0	Neg	Neg	Neg	Neg	Neg	Neg
#8 Day 15	28	0	Neg	0	0	0	Neg	Neg	Neg	Neg	Neg	Neg

Mammen Ann Rheum Dis 2019

Avelumab + axitinib in ADV type B3 thymomas (N=3) + thymic CA (N=27+2 mixed) (CAVEATT): a 1-arm, ph 2 trial

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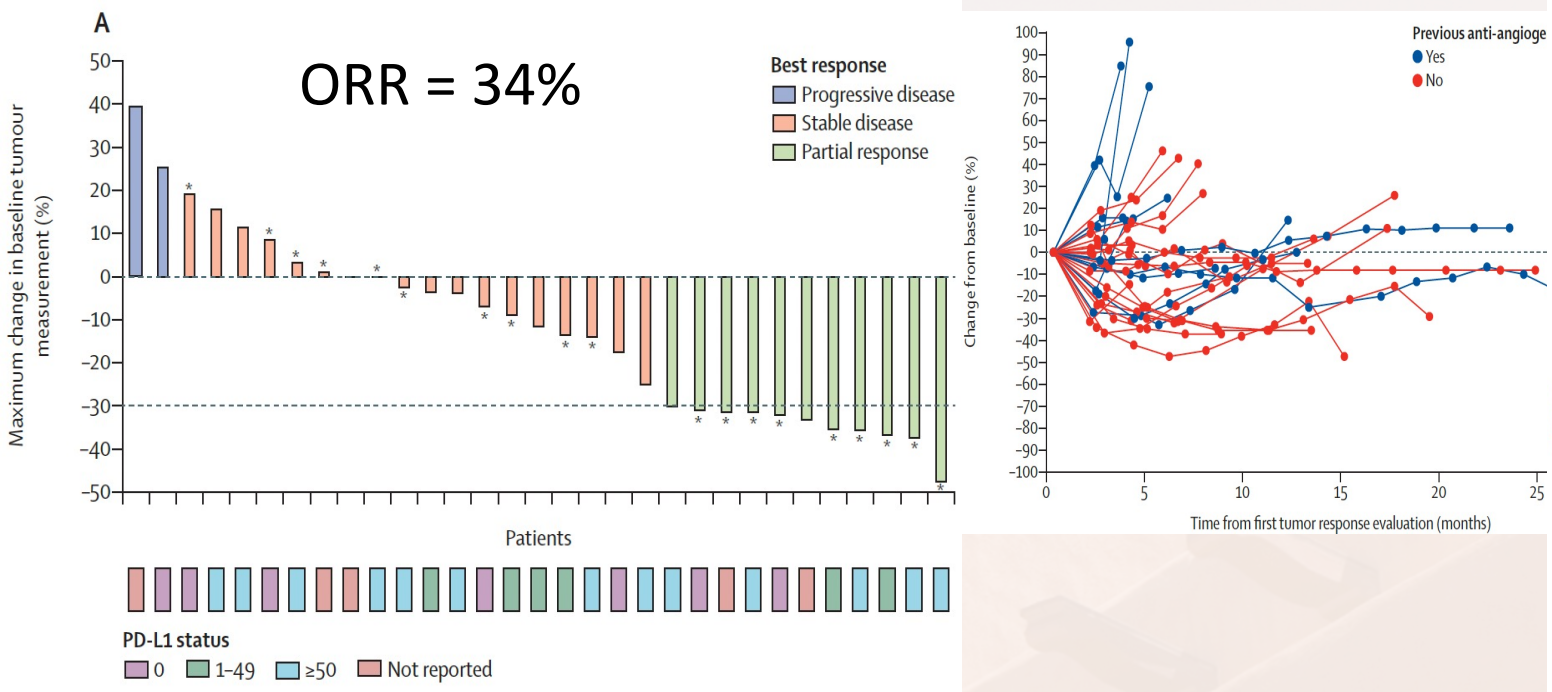

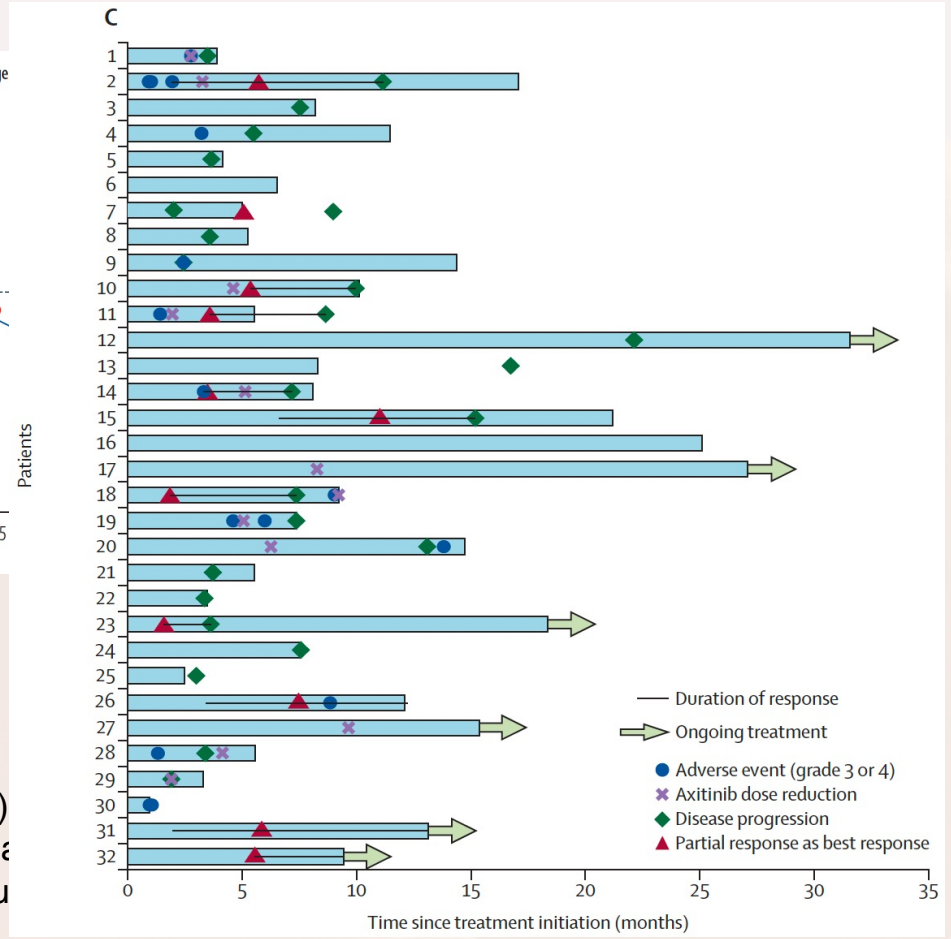

Figure ": **Overall response** (A) Waterfall plot of the best response in all eligible patients. (B) Spider plot of measurements of target lesions at each timepoint in all eligible patients (CT sca were done every 8 weeks). Red lines indicate patients naive to anti-angiogenic drugs and blu lines indicate patients previously treated with an anti-angiogenic drug. (C) Swimmer plot. *Patients not previously treated with an anti-angiogenic drug.

Four (12%) of 32 patients developed irAE SAEs; Gr 3 interstitial pneumonitis, Gr 4 polymyositis, Gr 3 polymyositis (N=2). There were no treatment-related deaths

Conforti Lancet Oncol 2022

Immune Checkpoint Blockade in Thymic Malignancies

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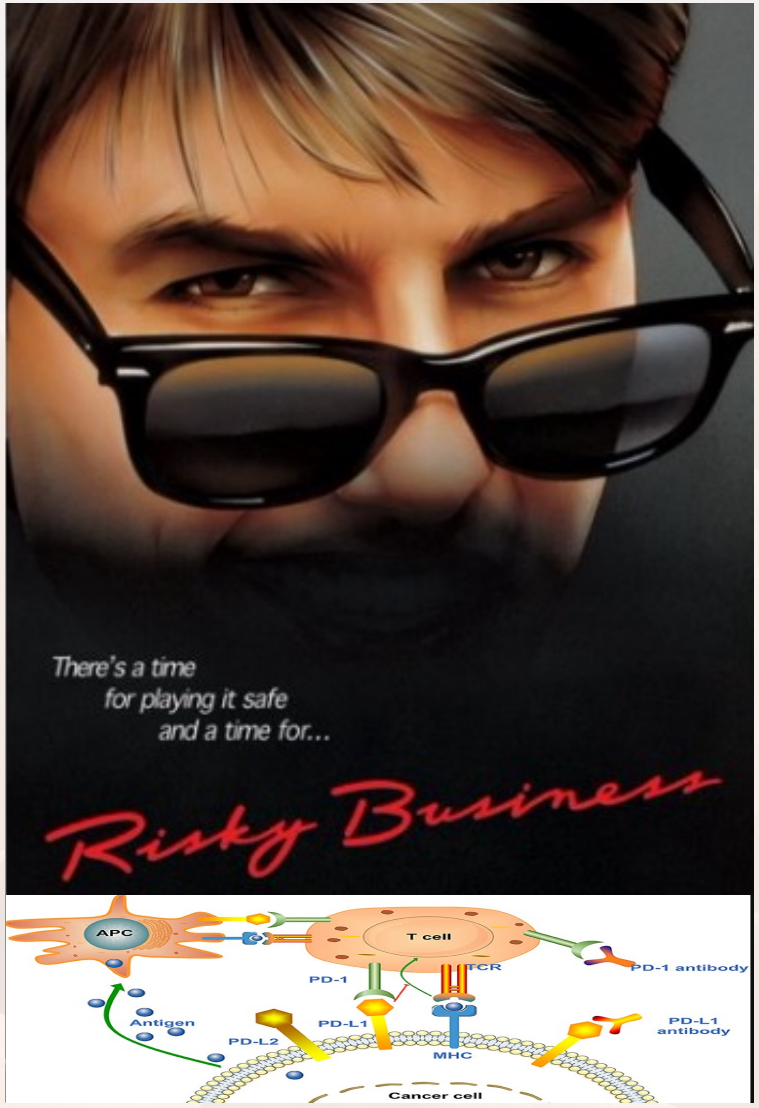


- PD-(L)1 ICI Never in Thymoma
- In thymic carcinoma (TC) after informed discussion of risks and PD on Several lines of treatment and no autoimmune disease
- I do use PD-L1 IHC to inform decision making in TC

CD47 expression patterns in thymic epithelial tumors

Thomas Sun MD, [1] Brandon Nguyen,[2] Simon Chen MD, [1] Natkunam Yaso MD, [1] Sukhmani Padda MD,[3] Matt van de Rijn MD, [1] Heather Wakelee MD, [1] Jonathan W Riess MD[2]

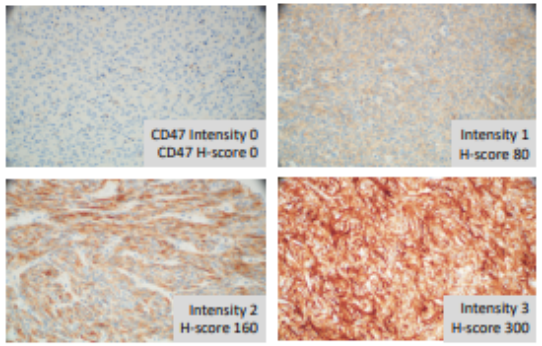
[1]Stanford University School of Medicine, [2]University of California, Davis, [3]Cedars-Sinai Medical Center; Correspondence: jwriess@ucdavis.edu; Abstract #8586

Background

- Anti-CD47 therapy is a new class of immunotherapy that acts thru macrophage checkpoint inhibition
- For thymomas and thymic carcinomas, existing PD-1/PD-L1 checkpoint inhibitors have excessively high rates of immune-related adverse effects
- Are there high levels of CD47 protein expression in thymic tumors to suggest anti-CD47 therapy may be effective?

Methods:

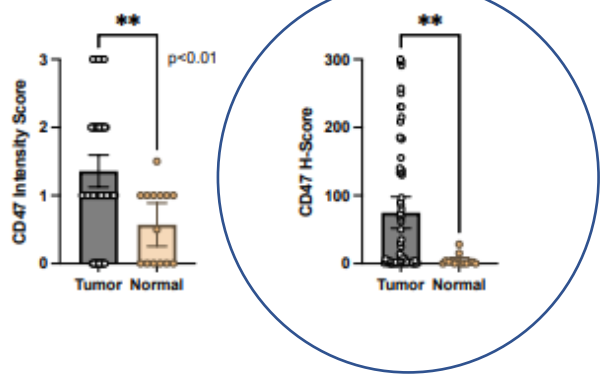
- Tissue microarray of 64 thymomas, 3 thymic carcinomas and 14 thymic controls
- Stained for CD47 epithelial expression in intensity and H-score (intensity x percentage of tumor involved)
  - CD47 low (intensity 0-1; H-score 0-149)
  - CD47 high (intensity 2-3; H-score 150-300)

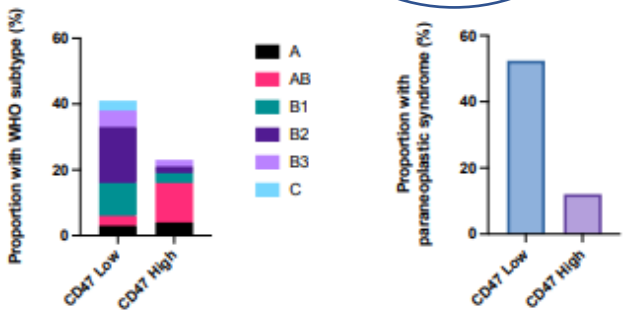


CD47 is highly expressed in thymomas and much less in normal thymus

Raises possibility of anti-CD47 therapy to treat thymic epithelial cancers

Results:





Conclusions:

- Thymic tumors had higher CD47 expression than normal tissue by 16-fold (mean H-Score 75 vs 4.6, p = 0.003)
- CD47-high tumors were more often WHO subtype AB (61.5% vs 13.7%)
- CD47-low tumors were more frequently associated with presence of a paraneoplastic syndrome (52.4% vs 12.0%, p = 0.0014)

T. Sun et al. JTOCRR 2023

Everolimus (mTORC1 inhibitor) in pts with thymic epithelial tumors

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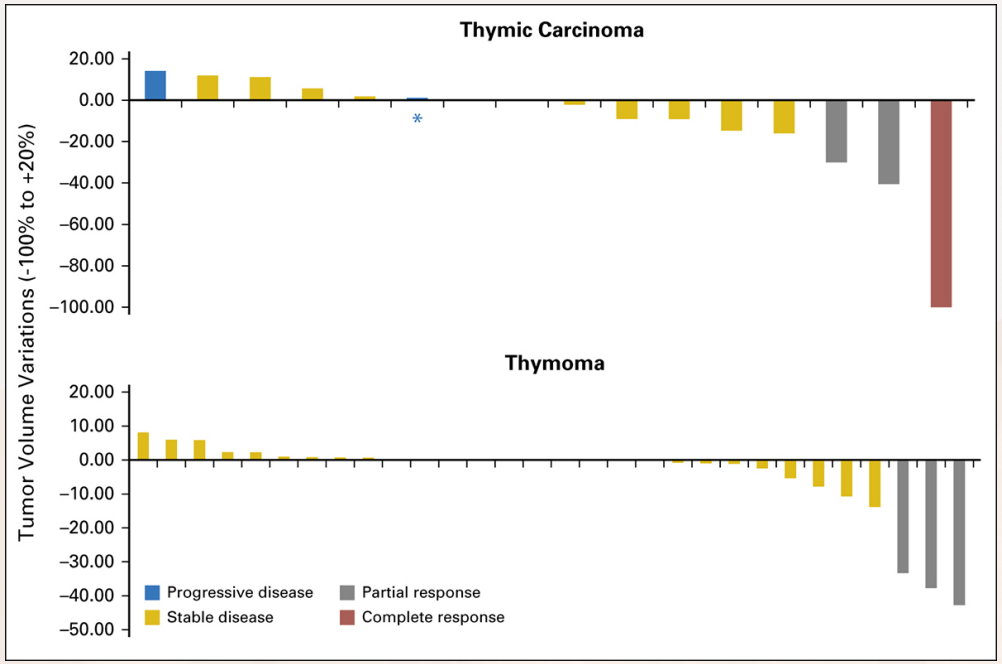
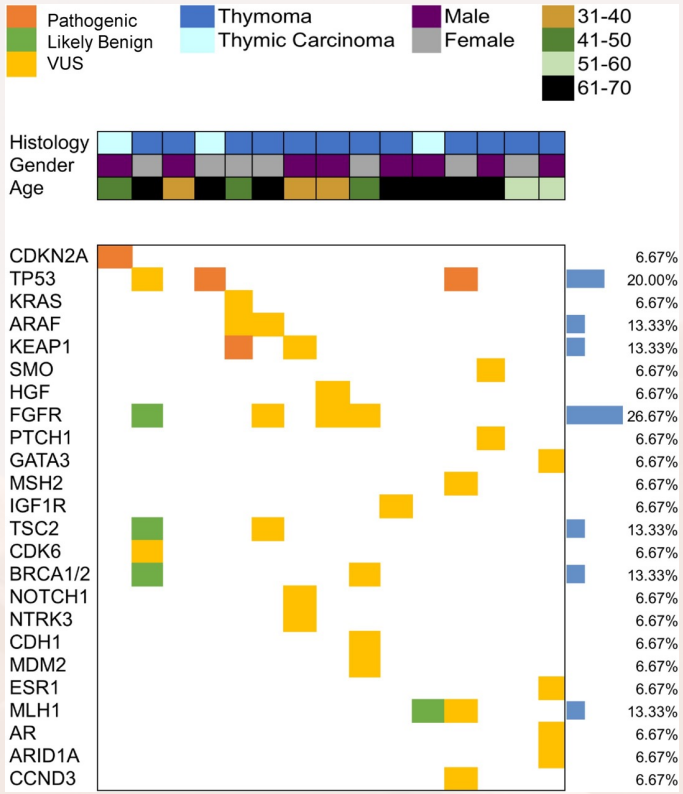


N= 51 (32 T, 18 TC), previously treated

- ORR: T 9.4%, TC 16.7%
- DCR: T 93.8%, TC 77.8%
- mTTF T 11.3 mo, TC 5.6 mo
- mPFS T 16.6 mo, TC 5.6 mo
- mOS T NR, TC 14.5 mo
- *18 pneumonitis (8 infectious, 10 noninfectious); 3 fatal



N=15 (12 T, 3 TC), previously treated

- mTTF T 14.7 mo, TC 2.6 mo
- mOS 27.6 mo (T NR, TC 5.3 mo)

***2/7 patients had improvement in autoimmunity (enteropathy, PRCA)**

No association with pathogenic mutations

-observed in 4/15 (27 %): *TP53, KEAP1* and *CDKN2A*

No pneumonitis

Zucali et al. J Clin Oncol. 2018 Feb 1;36(4):342-349. Hellyer et al. Lung Cancer. 2020 Nov;149:97-102.

Palbociclib (CDK 4/6 inhibition) in pts with thymic epithelial tumors

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Patient Characteristics	No of patients	%
Age (median: 54 years,32-92)		
<60 years	33	68.8%
≥60 years	15	31.2%
Sex		
Male	26	54.2%
Female	22	45.8%
ECOG PS		
0	2	4.2%
1	46	95.8%
Histology		
A	1	2.1%
B1	2	4.2%
B2	8	16.7%
B3	13	27.1%
C	23	47.9%
Unknown	1	2.1%
Masaoka stage		
IV-A	13	27.1%
IV-B	33	68.8%
Unknown	2	4.2%
History of thymectomy		
Yes	21	43.8%
No	27	56.2%
Line of previous chemotherapy		
1	31	64.6%
2	11	22.9%
3	5	10.4%
4	1	2.1%

Majority thymic carcinoma (48%) and type B3 thymoma (27%)

- Cyclin D→ activates CDK 4/6→ phosphorylates retinoblastoma protein (RB) → transition from G1 to S phase
- Rb and phosphorylated-Rb noted to be highly expressed in TETs (94.6% and 83.8% respectively)
- Palbociclib, CDK4/6 inhibitor, studied and given 125 mg ORAL daily 3 weeks on/1 week off

Adverse Event	Any grade	Grade=>3
Neutropenia	30 (62.5%)	20 (41.7%)
Anemia	18 (37.5%)	7 (14.6%)
Thrombocytopenia	13(27.1%)	5 (10.4%)
Fever	9(18.8%)	0 (0%)
Fatigue	8 (16.7%)	0 (0%)
Anorexia	5 (10.4%)	0 (0%)
Diarrhea	5 (10.4%)	0 (0%)
Nausea	4 (8.4%)	0 (0%)
Constipation	4 (8.4%)	0 (0%)
Alopecia	4 (8.4%)	0 (0%)
Pneumonitis	4 (8.4%)	2 (4.2%)
Herpes zoster	3 (6.25%)	0 (0%)
Increased blood creatinine	2 (4.2%)	0 (0%)
Increased AST	1 (2.1%)	0 (0%)
Increased ALT	1(2.1%)	1(2.1%)
Increased bilirubin	1(2.1%)	0 (0%)

Myelosuppression common, including neutropenia

Keziers et al. Diagn Pathol. 2015 Nov 4;10:201. Ahn et al. Abstr #8576. ASCO 2021

Palbociclib (CDK4/6 inhibition) has activity in thymic epithelial tumors

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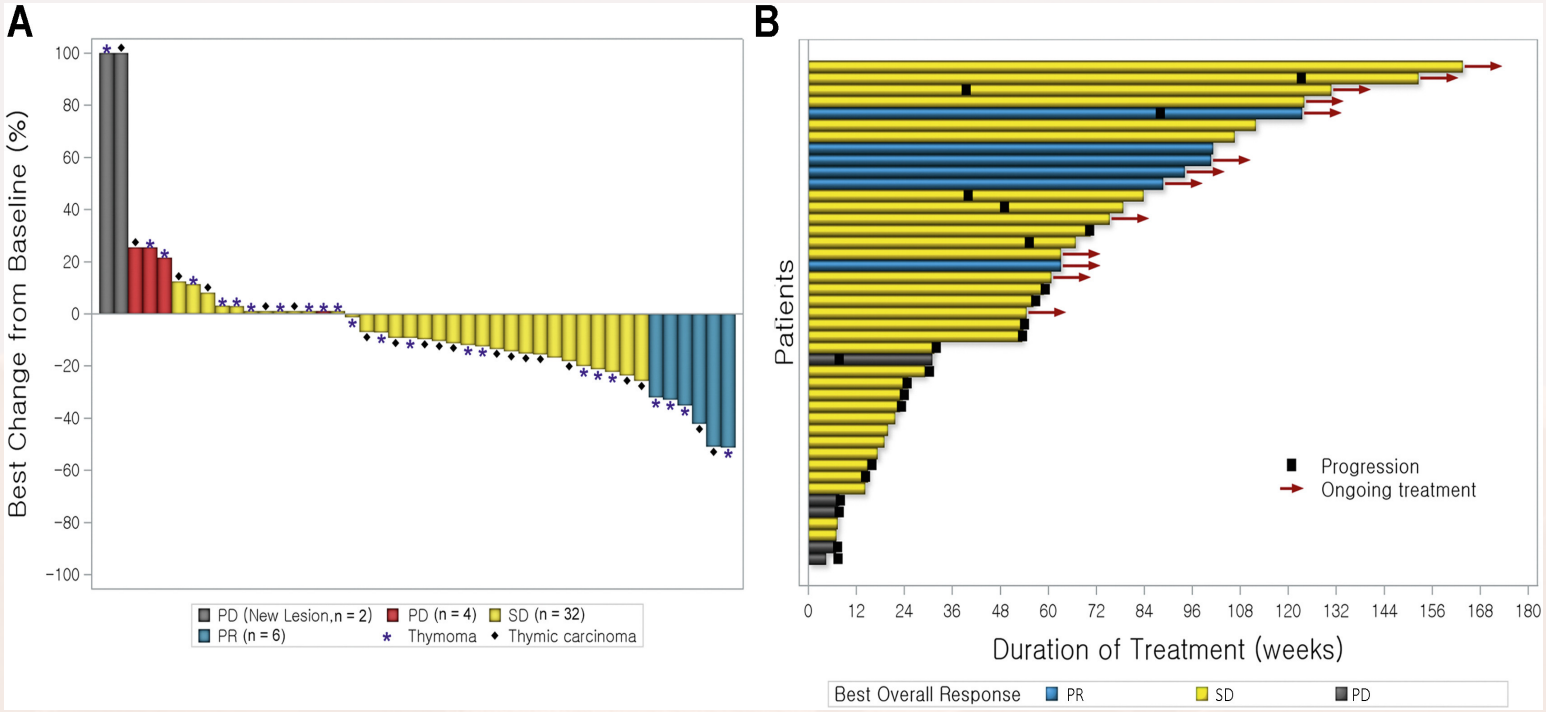
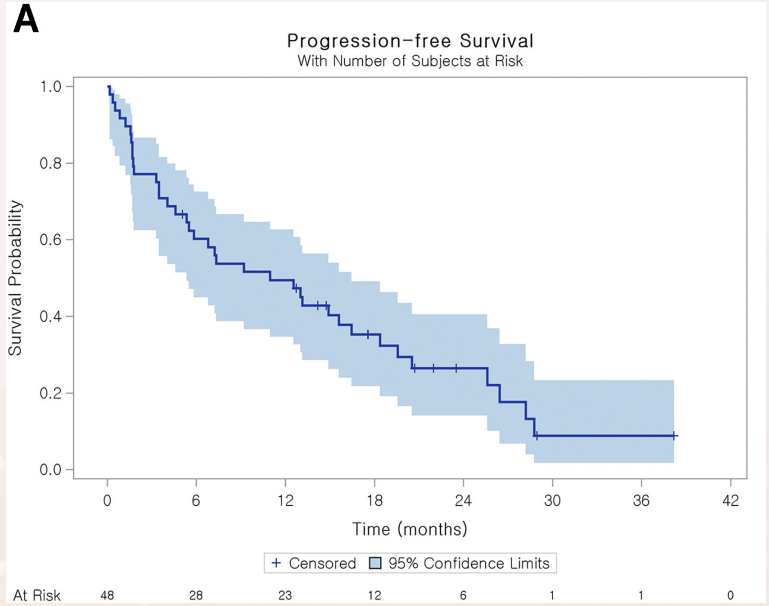
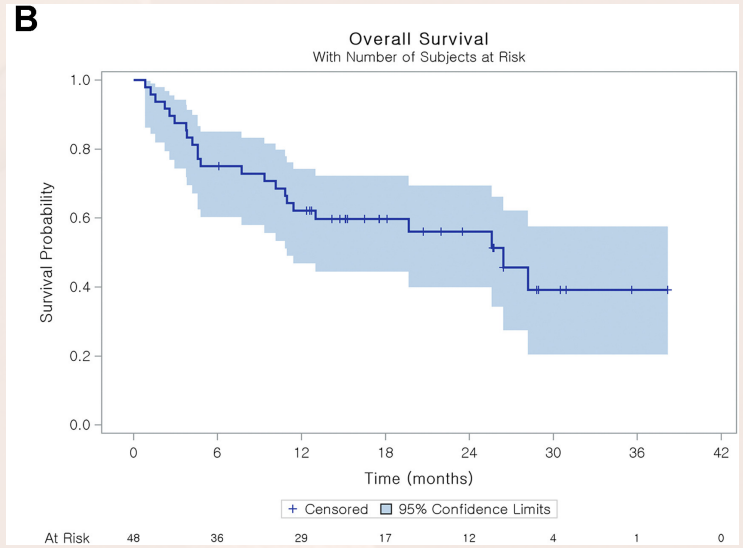






Median f/u 14.5 mo (range 0.8-38.2)

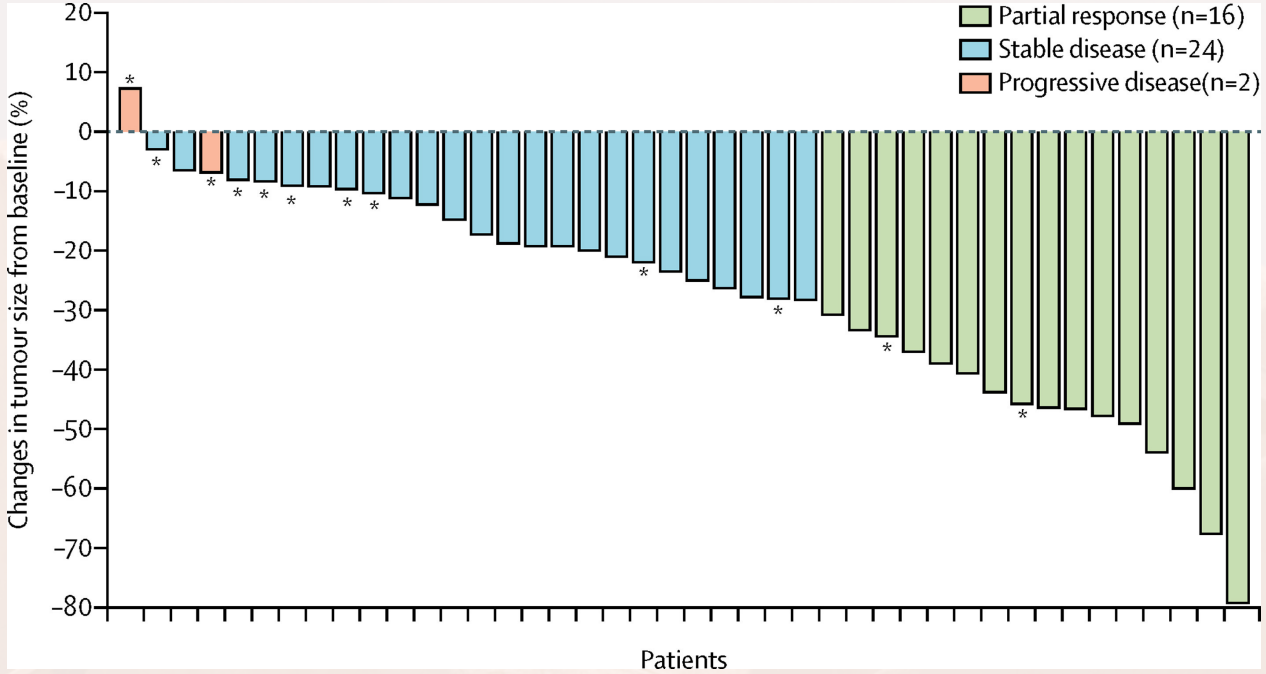
- Median cycle 10 (range 1-40)
- ORR: 6/48 (12.5%)
- mPFS 11.0 mo (95% CI 4.6-17.4)
- mOS 26.4 months (95% CI 17.4-35.4)

- 16.7 (4/24) ORR Thymoma, 8.7% TC (2/23)

Jung et al. Journal of Thoracic Oncology 2023 18223-231DOI: (10.1016/j.jtho.2022.10.008)

Lenvatinib in Thymic Malignancies

Lenvatinib in Thymic Carcinoma



ORR=38%, mPFS = 8.3 months
AEs included PPE, diarrhea, HTN (27/42 pts), thrombocytopenia

J. Sato et al Lancet Onc 2020, A. Thomas et al Lancet Onc 2015.

Real Life Multicenter Experience with Lenvatinib (J Benitez et al. ASCO 2022)

- N=29
- TC = 62% of pts
- ORR 17%. PR only in TC. DCR=76%
- Responses observed in lower doses than used in study (69% started at 14 mg daily dose rather than 24 mg daily in study)
- Sunitinib in TET (N=41)

- TC=26% ORR, N=25
- T=6% ORR, N=16

Conclusions

- Significant activity of chemotherapy in thymic malignancies
- Be aware of autoimmunity
- Anthracycline regimens for thymoma when possible (increase response rate)
- Carboplatin/paclitaxel is 1L option in thymic carcinoma
- Multiple drugs with single agent activity
- Newer targeted option VEGF(R) (Lenvatinib/sunitinib), mTOR (everolimus), PD-L1 (caution)
- Need more clinical trials