Thymic malignancies: biology, medical treatment and future perspectives

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Biology of thymic malignancies

- Thymic Epithelial Tumors (TET) are mediastinal tumors that originate in the thymus and include *thymoma* and *thymic carcinoma*

- Classification based on different histologic types
  - → Morphology of epithelial cells
  - → Relative proportion of the non tumoral lymphocytic component (decreasing from B1 to B3)
  - → Resemblance to normal thymic architecture

Biology of TET: WHO classification

TET	Morphological features	Frequency	10yOS
A	- Tumor composed mainly of epithelial cells with spindle/oval shape without nuclear atypia - Few or non nonneoplastic lymphocytes - Encapsulated	9%	97%
AB	- Same features as 1 - Rich in nonneoplastic lymphocytes	24%	95%
B1	- Resembles normal functional thymus, combining areas resembling normal thymic cortex and areas resembling thymic medulla. - The neoplastic epithelial cells are scant, small, with little atypia - Overwhelming rich in lymphocytes	13%	92%
B2	- Plump cells with vesicular nuclei - The neoplastic epitheliale component is scattered individually or in small clusters - Heavy population of nonneoplastic lymphocytes	24%	81%
B3	- Round or polyglonal epithelial cells with mild or no atypia - Very few lymphocytes	15%	62%
C	Thymic carcinoma	15%	29%

Falkson et al. JTO 2009; 4:911

Biology of TET: immunohistochemistry

- Overexpression of

Gene overexpression	Thymoma	Thymic carcinoma
EGFR	70%	53%
IGFR-1	43%	86%
KIT	2%	79%
Mesothelin	infrequent	70%

→ KIT expression associated with shorter PFS and OS

→ Mesothelin overexpression associated with longer survival

→ Cases of overexpression of ERBB2, Neutrophin receptors, VEGF-A, VEGFR-1, VEGFR-2

Girard N JTO 2010; 5:S291-S295; Thomas et al. Lung Cancer 2016; Petrini et al. J Thorac Oncol 2010

Biology of TET: whole exome sequencing

- Low TMB
  - → One of the lowest in adult cancers: 2 pediatric tumors have lower TMB: rhabdomyosarcoma and medulloblastoma
  - → Median 0.48 mt per megabase
    - NB lung cancer 8/Mb and melanoma 13.5/Mb
- TC have higher TMB than thymoma

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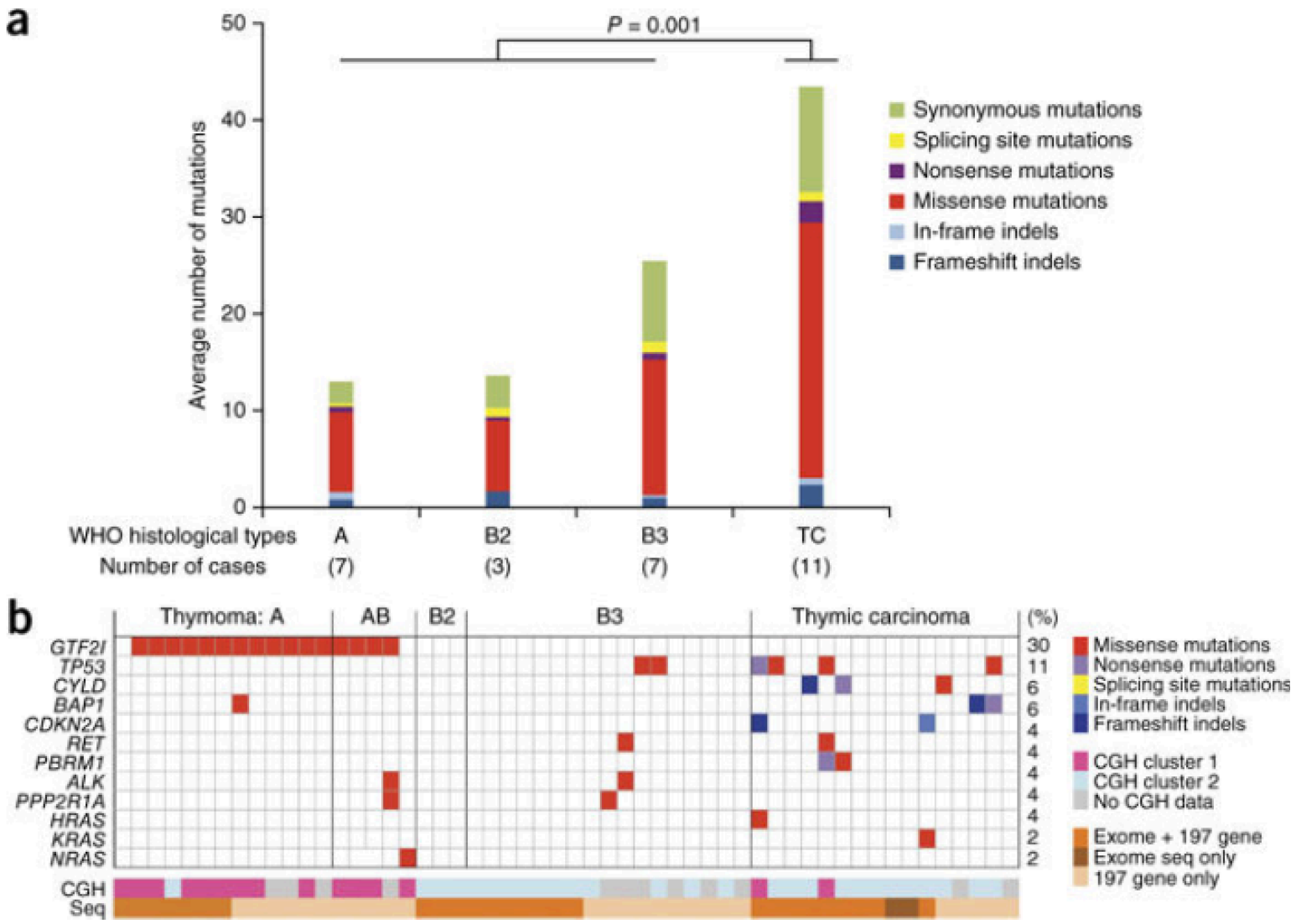
Radovich M et al. Cancer Cell 2018; 33:244-258; Petrini et al. Nat Genet 2014; 46:844-849

Biology of TET: whole exome sequencing



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Radovich M et al. Cancer Cell 2018; 33:244-258; Petrini et al. Nat Genet 2014; 46:844-849

Biology of TET: GTF2I mutation

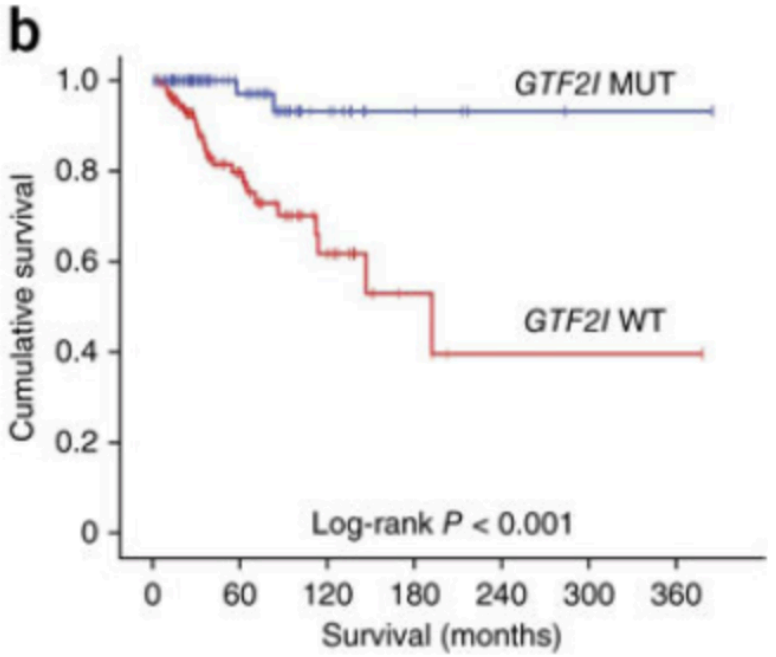
- Frequency in TET +/- 40%
  - → particularly in type A (82%) and AB (74%) vs 8% TC
  - → More frequent in early stages (I-II, 57%) than advanced disease (III-IV, 19%)

- All on the same codon: L424H
  - → GTFI2 mutations infrequent in other tumors and never this codon
  - → Alteration of the TFII-I protein structure and/or function
    - Involved in cell proliferation and cell cycle

Radovich M et al. Cancer Cell 2018; 33:244-258; Petrini et al. Nat Genet 2014; 46:844-849

Biology of TET: GTF2I mutation

- Associated with favorable outcome
  - → TETs with GTF2I mutation had longer survival
    - More prevalent in less aggressive tumors
  - → In T with GTF2I mutation 10yS 96% vs 88% in T without (p=0.057)



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Petrini et al. Nat Genet 2014; 46:844-849

Biology of TET: whole exome sequencing

- Other mutations are very rare
  - → TP53, CYLD and CDKN2A mainly in TC, some B3 thymoma
  - → KIT only reported in TC (7%)
    - Some sensitive to imatinib
  - → EGFR mutations: in one trial detected in 3/158 samples
    - all sensitive to EGFR TKI

Radovich M et al. Cancer Cell 2018; 33:244-258

Biology of TET: whole exome sequencing

- Four molecular subgroups < Lee et al.
  1. Subtype with GTF2I mutation
     - WHO class A and AB
     - Decreased prevalence of myasthenia gravis (MG)
     - Favorable DFS and OS
  2. Subtype enriched in expression of genes associated with T cell signaling
     - Enriched for WHO class B1 en B2
     - Favorable DFS and OS
  3. Subtype with Chromosomal Instability
     - Enriched for WHO B3 and TC
     - Unfavorable OS and DFS
  4. Subtype with Chromosomal Stability

Increased prevalence of MG

Lee H-S et al. Clin Cancer Res 2017;

Biology of TET: PD-L1 expression

- Data on PD-L1 expression are variable

- Tiseo et al:
  - → PD-L1 positive 18% thymoma and 65% TC
  - → No statistically significant difference in OS according PD-L1 expression

- Koh et al: meta-analysis of 6 studies
  - → In thymoma, high PD-L1 expression associated with higher Masaoka stage and with shorter OS

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Tiseo et al. Lung Cancer 2017;104:24-30; Koh et al. Thoracic Cancer 2020; 11:3086-3098

Systemic treatment

- No randomized comparative phase 3 trials
- Relatively small single arm phase II trials

Systemic treatment: chemotherapy regimen

- CAP: Cyclophosphamide-Doxorubicin-Cisplatin d1 q3w
  → ORR 50-77%

Reference	N	Thymoma/TC (n)	ORR (%)	Survival	Line	Multimodal T
Loehrer 1994	30	29/1	50	mOS 37.7 mo 2yS 64.5%	>1	NO
Lee 1996	17	17/0	53	NR	1	NO
Kim 2004	22	10/12	77	5yS 95%	1	YES
Liu 2007	28	7/21	71	NR	1	YES
Cardillo 2010	31	21/10	58	NR	1	YES

Systemic treatment: chemotherapy regimen

- ADOC: Cisplatin-Doxorubicin-Cyclophosphamide-Vincristine
  → RR 50-100%

Reference	N	Thymoma/TC	ORR	Survival	Line	Multimodal therapy
Fornasiero 1991	37	37/0	92	NR	>1	NO
Berruti 1993	6	6/0	83	NR	1	YES
Rea 1993	16	16/0	100	mOS 66 mo	1	YES
Berruti 1999	16	16/0	81	mOS 47.5 mo	1	YES
Agatsuma 2011	34	0/34	50	mOS 21.3 mo 1yS 72.7%	1	NO
Rea 2011	38	32/6	68	NR	1	YES

Systemic treatment: chemotherapy regimen

- PE: Cisplatin-Etoposide +/- epirubicin or ifosfamide

	Reference	N	Thymoma/TC	ORR	Survival	Line	Multimodal therapy
PE	Giaccone 1996	16	16/0	56	mOS 4.3 yrs 5yS 50%	>1	NO
	Mineo 2010	33	33/0	45	mOS 30 mo 5yS 37%	1	YES
	Tamiya	5	5/0	40	mOS 40.8 mo	NR	NO
PE + Epi	Venuta 1997	21	21/0	100	NR	1	YES
	Lucchi 2005	36	NR	66	NR	1	YES
	Lucchi 2006	30	30/0	73	NR	1	YES
PE +ifo	Loehrer 2001	28	20/8	32	mOS 6.1 yrs	1	NO
	Grassin 2010	16	12/4	25	NR	1	NO

Systemic treatment: chemotherapy regimen

- Carboplatin-paclitaxel
  - → Maybe somewhat lower RR 30-38%
  - → BUT all beyond 1st line and more TC

Reference	N	Thymoma/TC	ORR	Survival	Line	Multimodal therapy
Furugen 2011	16	0/16	38	mOS 49.4 mo	>1	NO
Lemma 2011	44	21/23	30	NR	>1	NO
Hirai 2015	39	0/39	36	1yS 85% 2yS 71%	NR	NO

Chemotherapy: Indications

- Adjuvant setting if resectable TET
  - → Thymoma: not recommended after R0-R1 resection
  - → TC: consider for stage III and after R1 resection for stage II

- Neoadjuvant setting if potentially resectable?
  - → Complete resection is deemed not achievable upfront (stage III/IVA)
  - → Induction chemotherapy 2-4 cycles followed by imaging and if deemed resectable than surgery

- Definitive chemotherapy if unresectable

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Girard et al. Ann Oncol 2015. ESMO guidelines thymic epithelial tumours

Chemotherapy: adjuvant setting in thymoma

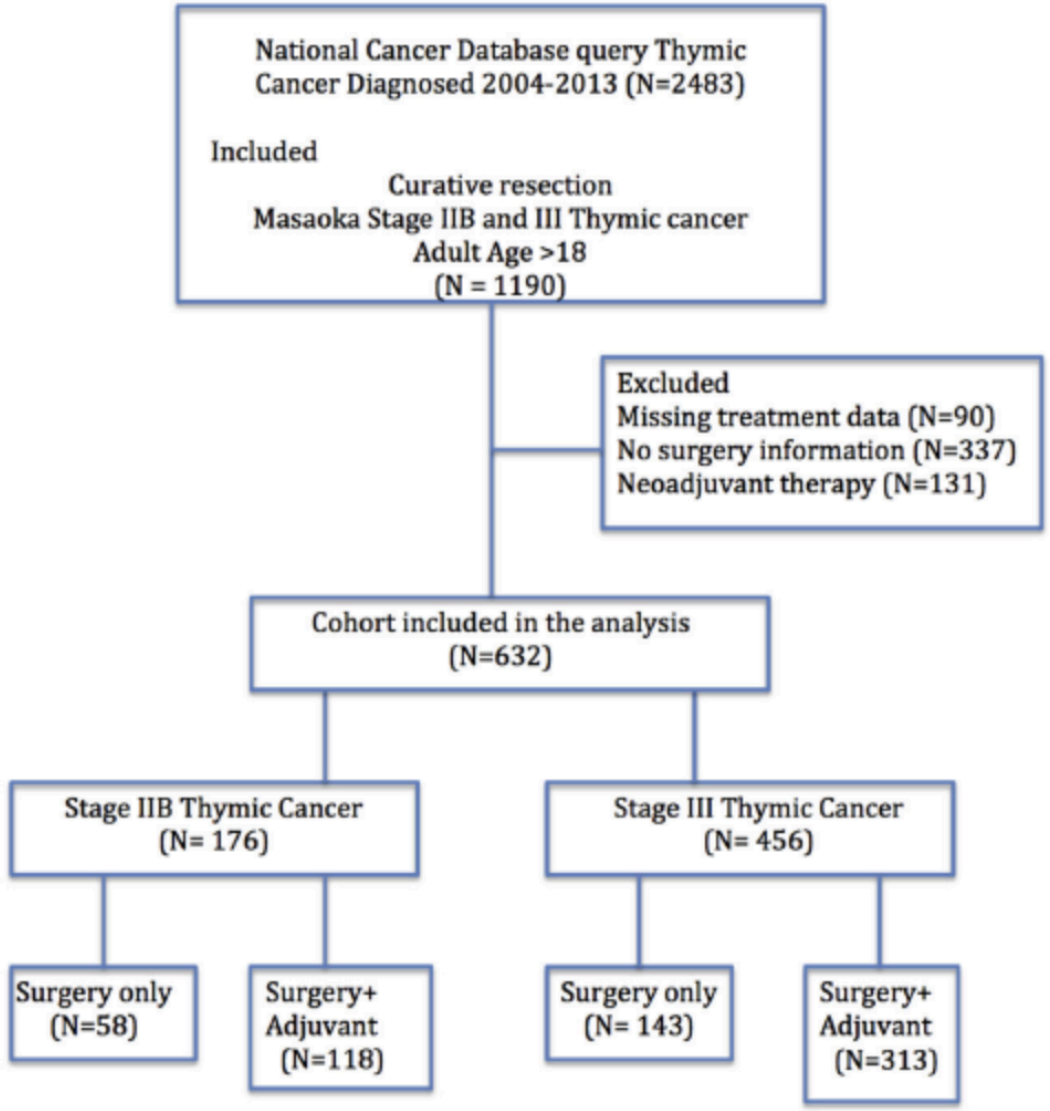
- Few data

- Retrospective analysis in 228 pts with 20y follow-up
  - → Few patients received adjuvant chemotherapy alone
  - → Adjuvant CT had no influence on the outcome of patients with thymoma type A, AB, B1 and patients with R0 resected B2 or B3 in stage II
    - Very few relapses in these tumors after surgery alone

Strobel et al. J Clin Oncol 2004

Chemotherapy: adjuvant setting in thymic carcinoma

- 176 stage IIB TC
  - → 118 adjuvant R/
    - CT 63
    - CTRT 49
    - RT 6
- 456 stage III TC
  - → 313 adjuvant R/
    - CT 129
    - CTRT 128
    - RT 56



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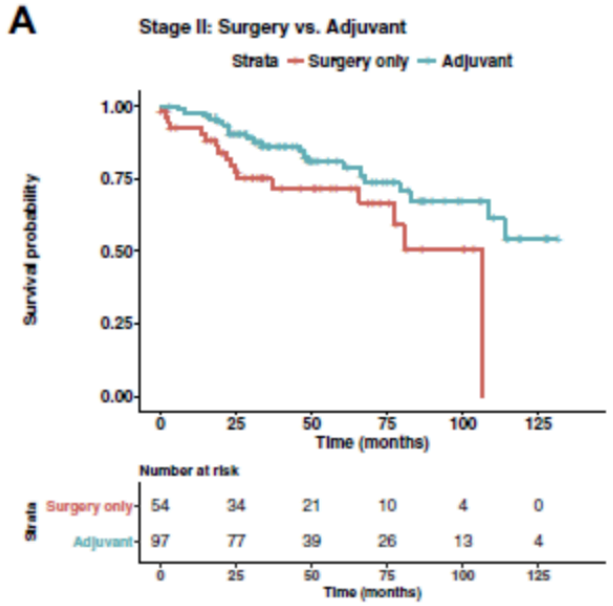
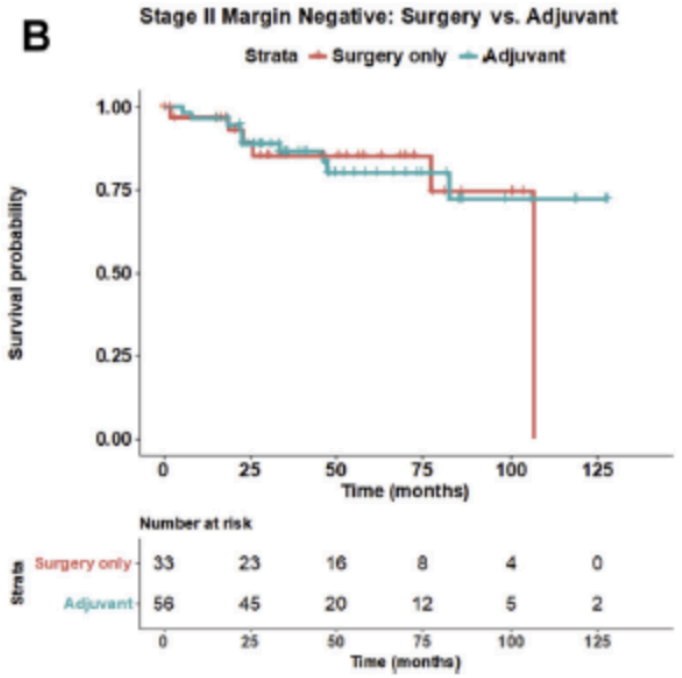
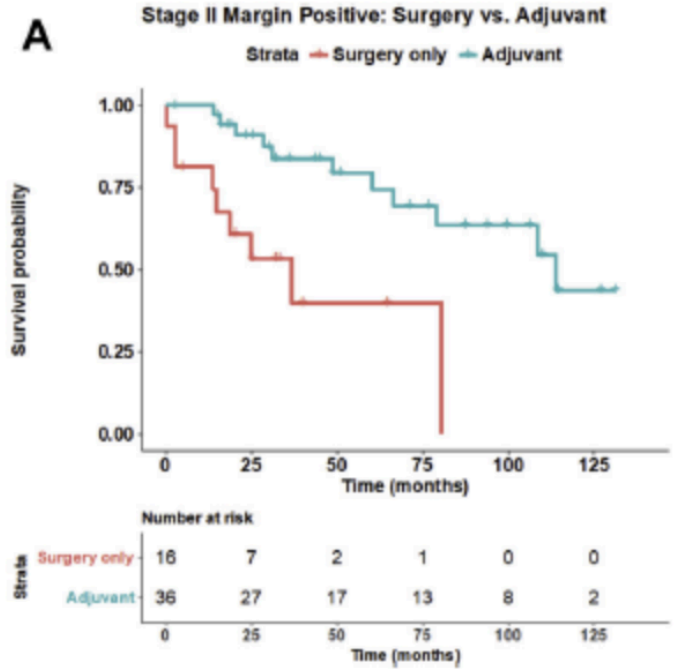
Kim et al. Ann Thorax Surg 2020

Chemotherapy: adjuvant setting in thymic carcinoma

- Stage IIB: Survival benefit
  - → Also after adjusting for confounding factors (age, grade, size, margin status and comorbidities): HR 0.63
  - → Only if R1/R2 resection HR 0.19





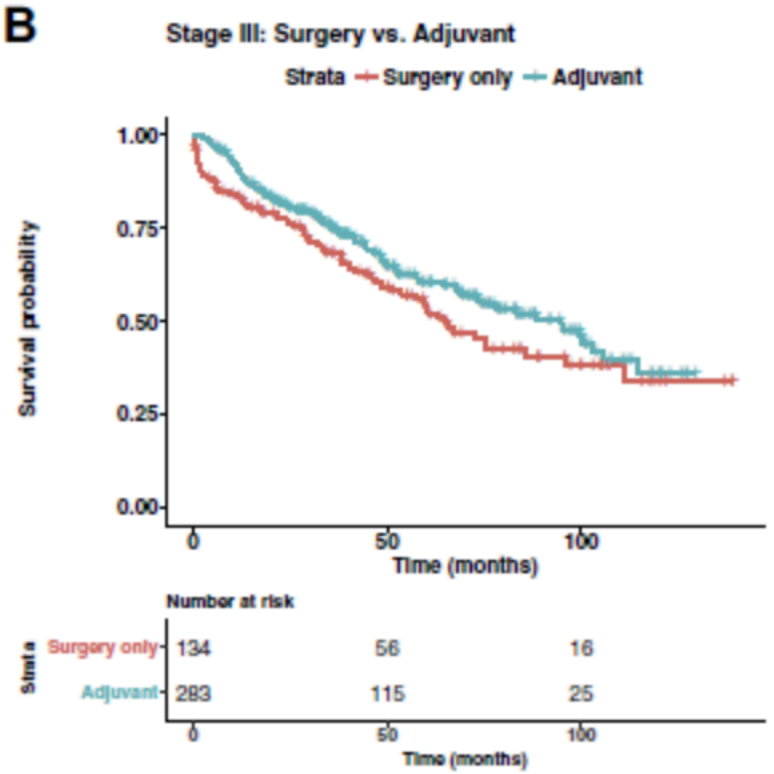


mOS NR vs 106 mo; p=0.01

Kim et al. Ann Thorax Surg 2020

Chemotherapy: adjuvant setting in thymic carcinoma

- Stage III: Survival benefit
  - → Also after adjusting for confounding factors (age, grade, size, margin status and comorbidities): HR 0.63
  - → Also benefit after R0 resection



mOS 94.9 mo vs 64.8 mo; p<0.01

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Kim et al. Ann Thorax Surg 2020

Chemotherapy: adjuvant setting in thymic carcinoma

- Subgroup analysis for type of adjuvant therapy
  → OS benefit for adjuvant chemotherapy and chemoradiotherapy

Table 4. Adjuvant Therapy Type and Association with Survival Compared With Surgery Alone

		Stage IIB				Stage III	
Group	No.	Hazard Ratio (95% CI)	*P* Value	Group	No.	Hazard Ratio (95% CI)	*P* Value
Surgery	58	1.00 [Reference]	…	Surgery	143	1.00 [Reference]	…
Radiotherapy only	6	1.12 (0.20-6.15)	.90	Radiotherapy only	56	0.81 (0.48-1.36)	.42
Chemotherapy	63	0.39 (0.16-0.91)	.03	Chemotherapy	129	0.66 (0.43-0. 99)	<.05
Chemoradiotherapy	49	0.43 (0.17-1.11)	.08	Chemoradiotherapy	128	0.45 (0.29-0.71)	<.001

CI, confidence interval.

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Kim et al. Ann Thorax Surg 2020

Chemotherapy: neoadjuvant setting

Preop Therapy for M-Stage III Thymoma/TC

Phase 2 series of preop Chemo or chemoRT

1st Author	n	% IV	% TC	Preop Chemo	Preop RT	% PR + CR	% R0	% pCR	Postop Therapy	% DFS 5-yr	% OS 5-yr	% OS 10-yr
Marulli	94	0	19	P-based	-	69	76	-	most RT/Ch	-	-	51
Leuzzi	88	0	0	undefined	few	-	65	-	±RT	85	-	-
Kunitoh	21	0	0	EAPV	-	62	39	23	RT	46	85	67
Mineo	33	0	0	PE x3	-	100	51	24	ChRT	-	37	24
Venuta	15	0	few	P-based	-	67	87	7	Ch x3→RT	-	-	90
Korst	21	0	33	PE x2	cRT	48	77	(24)[c]	-	83	71	-
Wright	10	30	10	PE x2	cRT	40	80	0	±Ch x2	-	69	-
Lucchi	36	31	25	PEEpi x3	-	67	78	-	RT	-	76	64
Lucchi	30	33	0	PEEpi x3	-	73	77	6	RT	-	83	83
Rea	38	40	16	CAPV x3-4	-	68	74	-	most RT±Ch	-	-	52
Cardillo	31	42	32	CAPPx3-4	-	58	-	6	±RT	-	-	58
Bretti	25	44	6[e]	P-based	-	72	44	14	RT	-	-	-
Kim	22	50	0	CAPPr x3	-	77	-	-	RT→Ch x3	77	95	80
Average						**67**	**68**	**11**		**73**	**74**	**63**
Average Stage III Surg ±RT							**40**		**Most RT**		**65**	**56**

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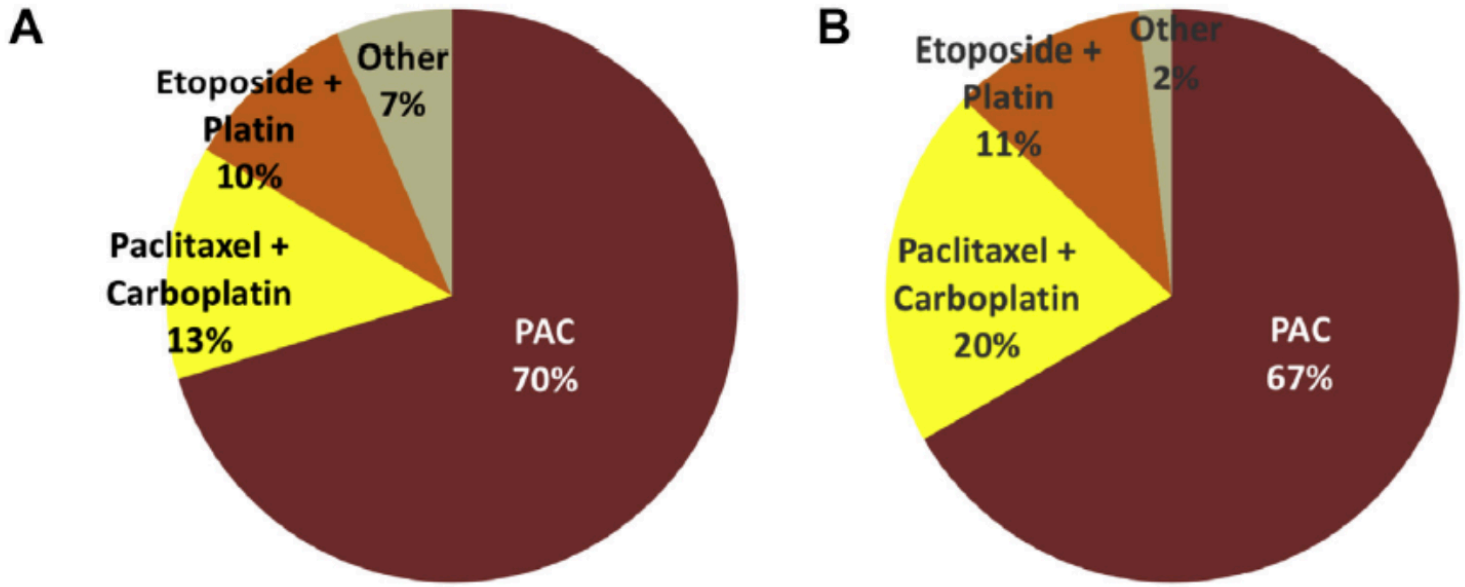
Courtesy FC Detterbeck

Chemotherapy: which regimen?

- French RYTHMIC prospective cohort
  - → Primary chemotherapy (n=91): ORR 83% T and 75% TC
  - → Exclusive chemotherapy (n=54): ORR 31% T and 37% TC



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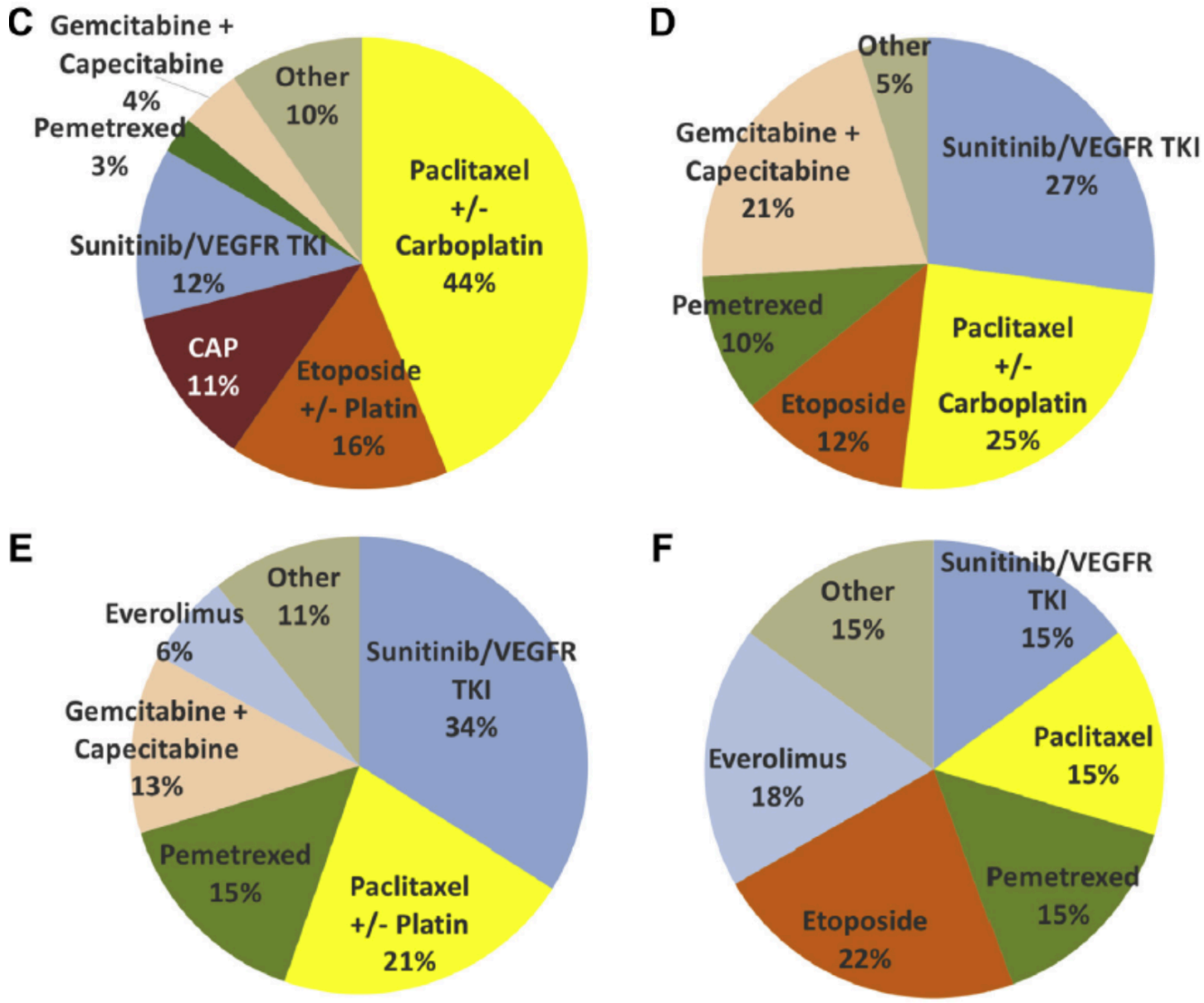
Merveilleux du Vignaux et al. JTO 2018;13:1762-1770

Chemotherapy: which regimen?

- Multiple lines of systemic treatment are delivered…
- Different options



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Merveilleux du Vignaux et al. JTO 2018;13:1762-1770

Targeted therapies: options

- Anti-angiogenesis
- cKIT inhibitors
- mTOR inhibitors
- IGFR-1 inhibitors
- Octreotide

Anti-angiogenesis: Sunitinib

- Open label phase II trial after failure of at least one previous platinum-containing regimen
  - → NB also a KIT inhibitor!
  - → Thymoma (n=16)
    - PR 6% and DCR 81%
    - mPFS 8.5 mo and mOS 15.5 mo
  - → Thymic carcinoma (n=25)
    - PR 26% and DCR 91%
    - mPFS 7.2 mo and mOS NR
  - → AEs: 13% decrease in LVEF with three patients grade 2; one patient died of cardial arrest possibly treatment related!

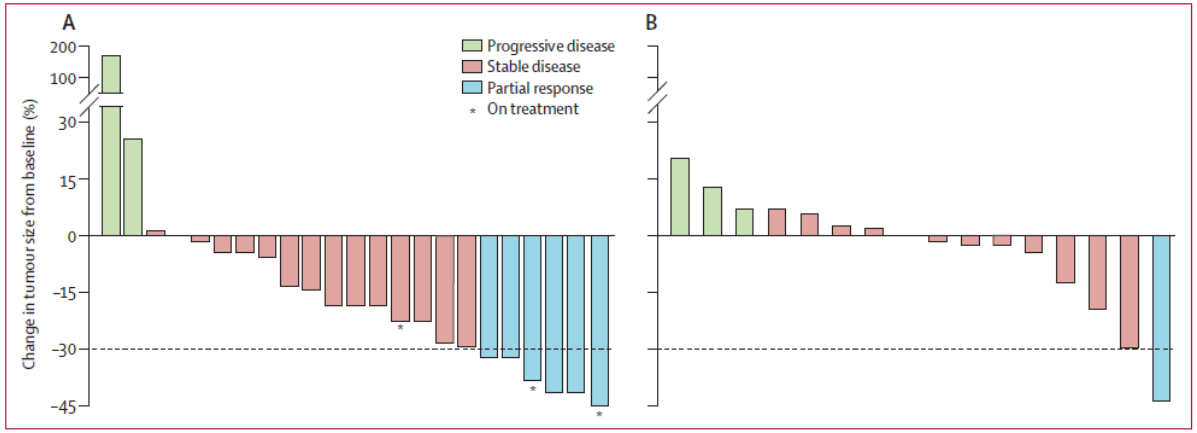

Figure 1: **Waterfall plots of tumour responses to sunitinib**
Responses in patients with (A) thymic carcinoma and (B) thymoma. Of three patients with thymoma who had progressive disease, two came off treatment because of the appearance of new lesions and one stopped treatment owing to a 20% increase in tumour size. All three had progressive disease at the first restaging timepoint.

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Thomas A et al. Lancet Oncol 2015

Anti-angiogenesis: Sunitinib

- Real life retrospective analysis from the French RYTHMIC network

→ N= 28 (8 T and 20 TC)

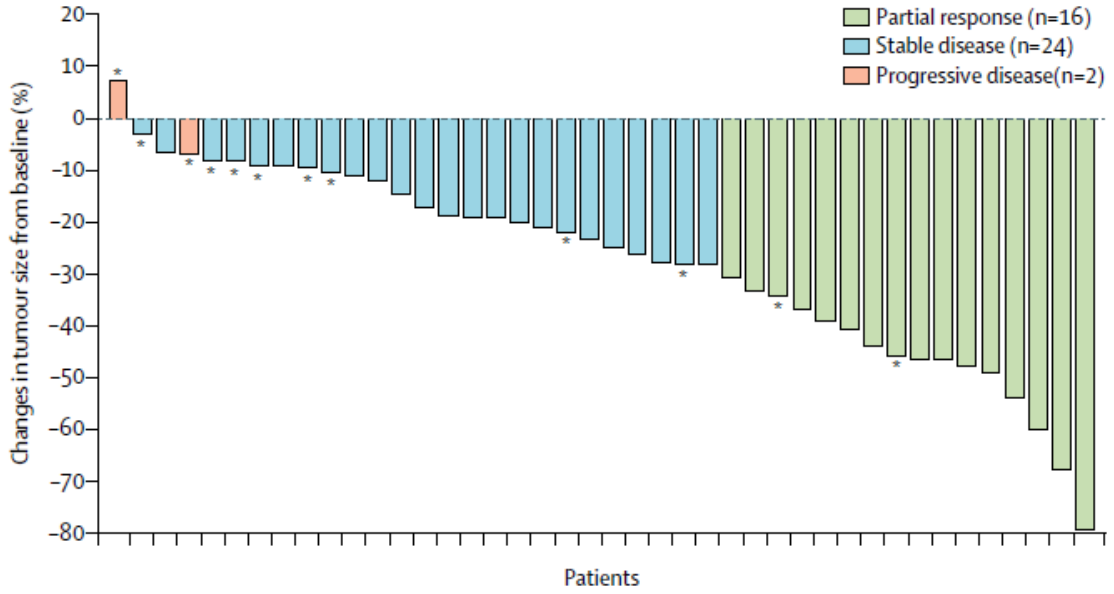
	Thymoma	Thymic Carcinoma
ORR (%)	28.6 (2/7)	20 (4/20)
DCR (%)	86 (6/7)	55 (11/20)
mPFS (mo)	5.4	3.3
mOS (mo)	NR	12.3

→ 8/28 pts stopped because of AE>G2: stomatitis, asthenia, diarrhoea, LVEF decline in 1 pt

Remon J et al. Lung Cacner 2016

Anti-angiogenesis: Lenvatinib

- Open label phase II after progression of at least one platinum-based chemotherapie in thymic carcinoma (n=42)
  - → PR 38% and SD 57%
  - → DCR 95%
  - → mDOR 11.6 mo
  - → mPFS 9.3 mo and mOS NR
  - → AEs: 2% LVEF dysfunction and 2% pneumonitis; 64% G3 AHT



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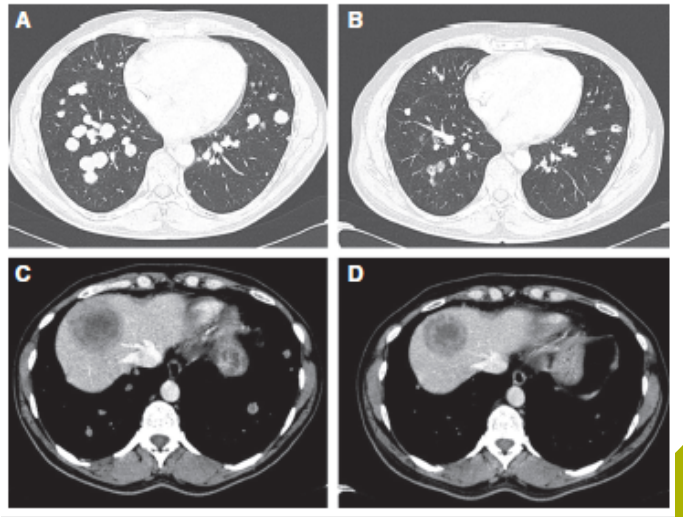
Sato et al. Lancet Oncol 2020; 21:843-850

Anti-cKIT inhibition: Imatinib

- Two phase 2 trials of imatinib in TETs
  - → One regardless of KIT expression and one in TETs with KIT overexpression
  - → No mutations of KIT identified in either trial
  - → NO responses!!

- BUT case reports of activity in KIT mutant TC



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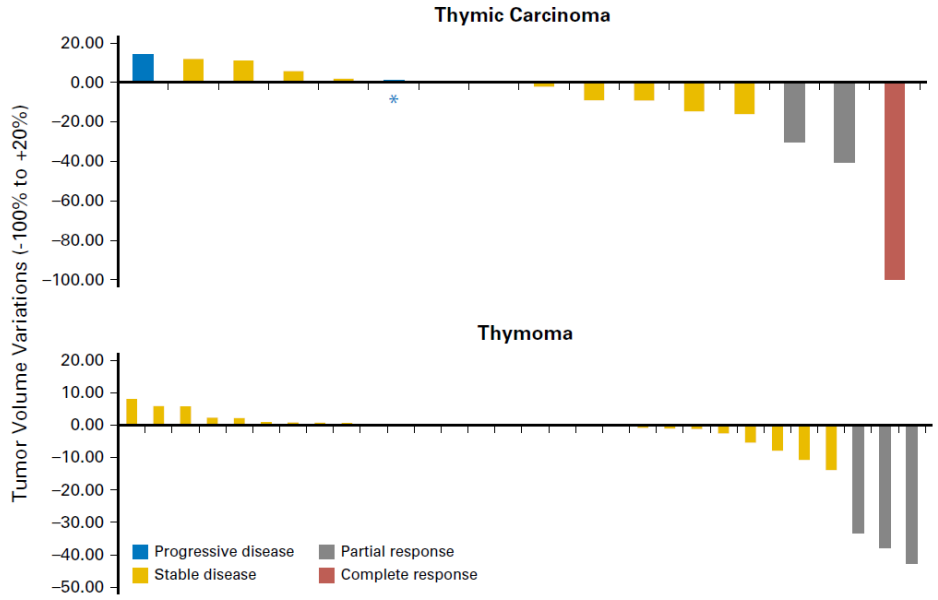
Giaccone et al. J Thorac Oncol 2009; Palmieri et al. Cancer Chemothera Pharmacol 2012; Buti et al JCO 2011; Hirai et al. Mol and clin oncol 2016

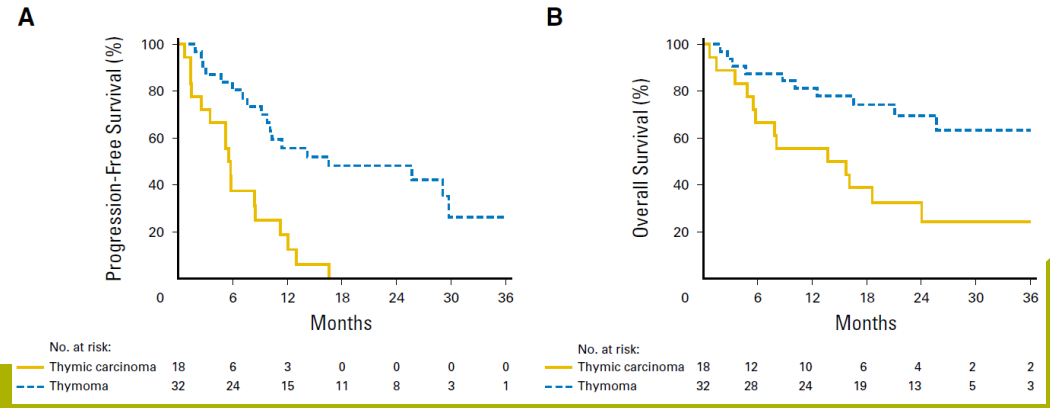
mTOR inhibitor: everolimus

- Open label phase II after progression on platinum-based chemotherapy (n=50)
  - → Thymoma and TC

	Thymoma (n=32)	TC (n=18)
ORR	9.4%	16.7%
DCR	78%	94%
mPFS	16.6 mo	5.6 mo
mOS	NR	14.7 mo

  - → Significant toxicity
    - SAEs in 14/51 pts
    - Common diarrhea and mucositis
    - Three cases of fatal pneumonitis





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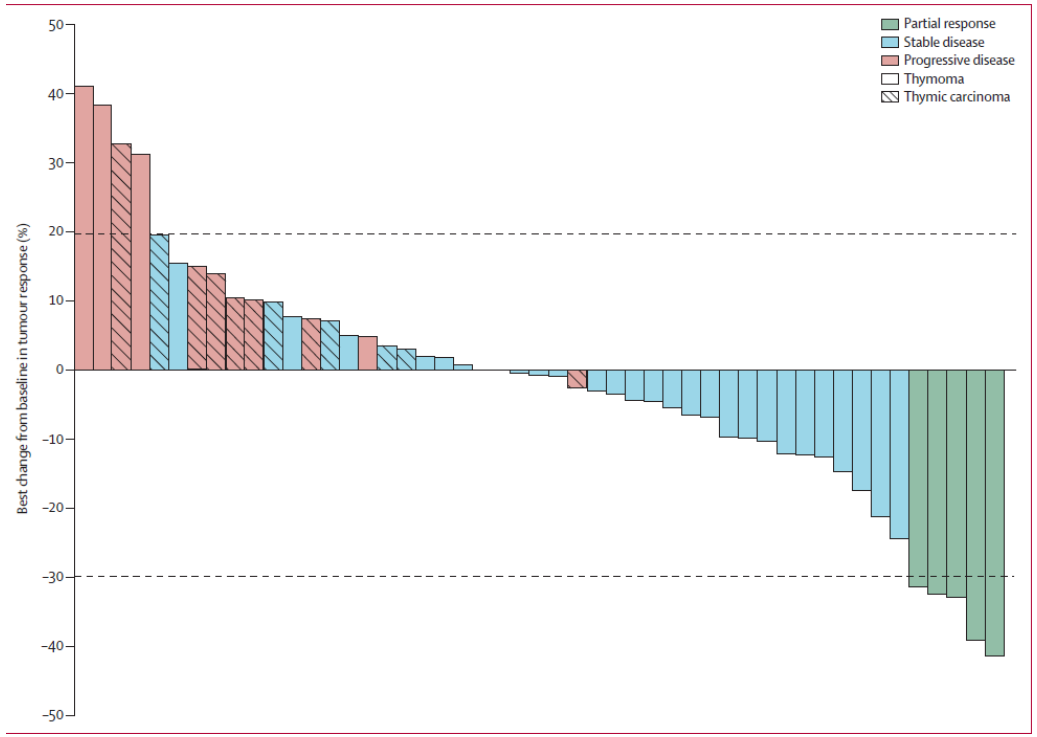
Zucali P et al. J Clin Oncol 2017; 36:342-349

IGFR-1 inhibitor: cixutumumab

- Open label phase II, in TETs after failure of at least one chemotherapy regimen (n=49)

	Thymoma (n=37)	TC (n=12)
ORR	14%	0%
DCR	89%	42%
mPFS	9.9 mo	1.7 mo
mOS	27.5 mo	8.4 mo



→ 24% of thymoma pts developed autoimmune disease, most frequently pure red cell aplasia

Octreotide

- Retrospective analysis
  - → 12/27 pts with positive octreoscan treated with octreotide
  - → ORR 3/12 (25%) and SD 5/12 (42%)
  - → mPFS 8 mo

- Phase II octreotide plus prednisone as neoadjuvant treatment in primary or recurrent unresectable TETs
  - → ORR 15/17 (88%)
  - → Subsequent complete surgical resection in 9/17 (52%)

Longo et al. Am J Clin Oncol 2012 and Kirzinger et al PLoS One 2016

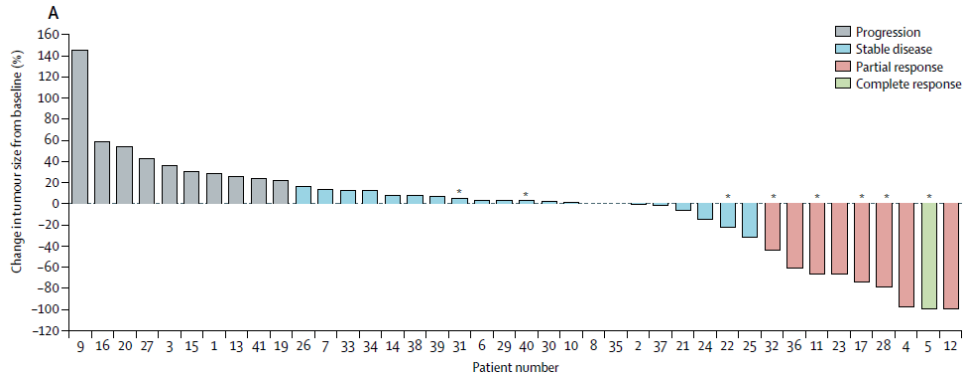
Immunotherapy: Nivolumab

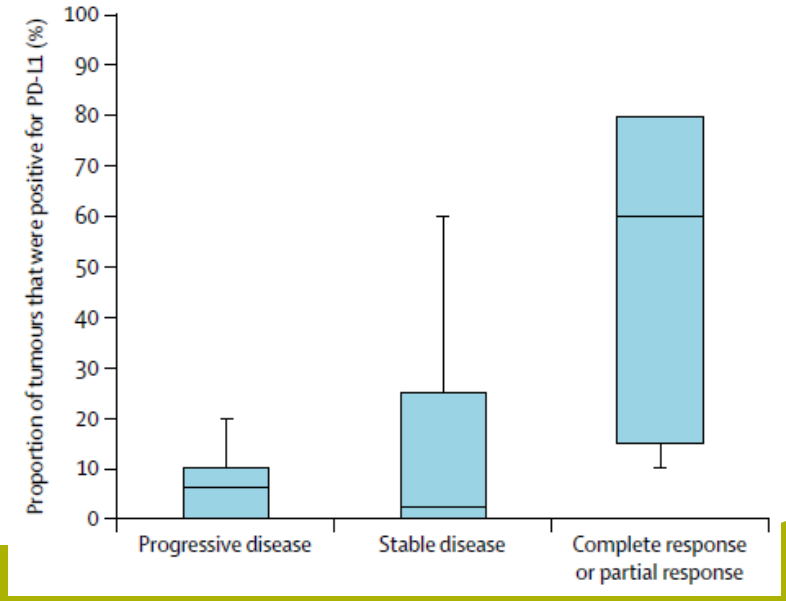
- Phase II study in TC after failure of at least one chemotherapy regimen (n=15)
  - → ORR 0% and DCR 73.3 %
  - → mOS 14.1 mo
  - → 2 serious AEs:
    - G3 AST increase
    - G3 adrenal insufficiency

Katsuya et al. Eur J Cancer 2019; 113

Immunotherapy: Pembrolizumab

- Open label phase II in thymic carcinoma refractory to chemotherapy (n=40)
  - → ORR 22.5% with median DOR 22 mo
    - More responses in PDL1 pos
  - → 1y PFS 29% and mOS 24.9 mo
  - → Six patients (15%) with severe irAE
    - Myocarditis
    - Hepatitis
    - MG
    - Bulleus pemphigoid
    - Type 1 diabetes mellitus





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Giaccone et al. Lancet Oncol 2018

Immunotherapy: Pembrolizumab

- Open label phase in TET after at least one line of chemotherapy (n=33)

	Thymoma (n=7)	TC (n=26)
ORR	28.6%	19.2%
DCR	100%	73.1%
mDOR	NR	9.7 mo
mPFS	6.1 mo	6.1 mo
mOS	NR	14.5 mo
irAE G3/4	71.4% (5/7)	15.4% (4/26)

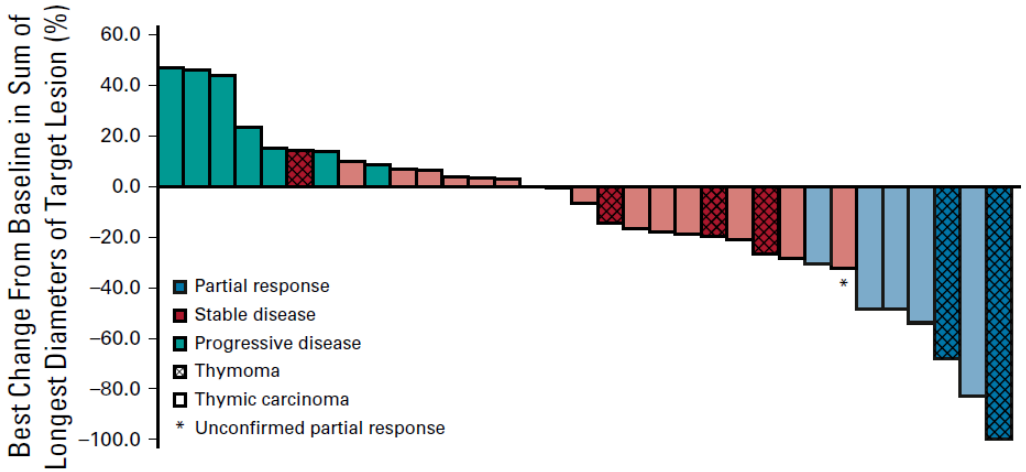

TABLE 4. Immune-Related Adverse Events at Any Frequency

	Thymoma (n = 7)		Thymic Carcinoma (n = 26)	
Adverse Event	**Grade 1-2**	**Grade 3-4**	**Grade 1-2**	**Grade 3-4**
Hepatitis	0	2 (28.6)	0	2 (7.7)
Myasthenia gravis	1 (14.3)	0	0	2 (7.7)
Myocarditis	0	3 (42.9)	0	0
Thyroiditis	1 (14.3)	1 (14.3)	1 (3.8)	0
Dermatitis	2 (28.6)	0	0	0
Colitis	0	1 (14.3)	0	0
Conjunctivitis	0	1 (14.3)	0	0
Nephritis	0	1 (14.3)	0	0
Subacute myoclonus	0	0	0	1 (3.8)
Pruritus	0	0	3 (11.5)	0
Skin rash	0	0	2 (7.7)	0

NOTE. Data presented as No. (%).

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Future perspectives

- Ongoing studies in TET
  - → Immunotherapy trials
    - Atezolizumab/ Avelumab/ Nivolumab (NIVOTHYM) also in Belgium
  - → Combination anti-angiogenesis and chemotherapy
    - RELEVENT trial: single arm phase 2 trial in TC/B3 T with ramucirumab+ chemotherapy (carboplatin/)paclitaxel
  - → Combination immunotherapy en chemotherapy
    - Pembrolizumab + chemotherapy (carbo/paclitaxel) in 1st line
  - → Combination anti-angiogenesis and immunotherapy
    - Phase 2 pembrolizumab + sunitinib

Take home messages

- Tumor biology
  - → TET have low TMB
  - → Tumor biology differs between the histological subtypes and there is an increase of mutations with more aggressive histology
- Chemotherapy
  - → Different chemotherapy regimens are used, most frequently CAP
  - → Indications:
    - Adjuvant chemotherapy may be considered for stage III and incompletely resected stage II TC
    - Induction chemotherapy for potentially resectable TETs
    - Unresectable TETs

Take home messages

- Recurrent TETs may be candidate for multiple lines of treatment
  - → Chemotherapy
  - → Anti-angiogenesis
  - → Imatinib only if KIT mutated TC
  - → Octreotide if positive on Dotanoc scan
  - → Immunotherapy in TC, high risk of irAEs in thymoma