GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

rythmic.org
Réseau tumeurs THYMiques et Cancer

Cours du GOLF 2018

Thymomes et carcinomes thymiques

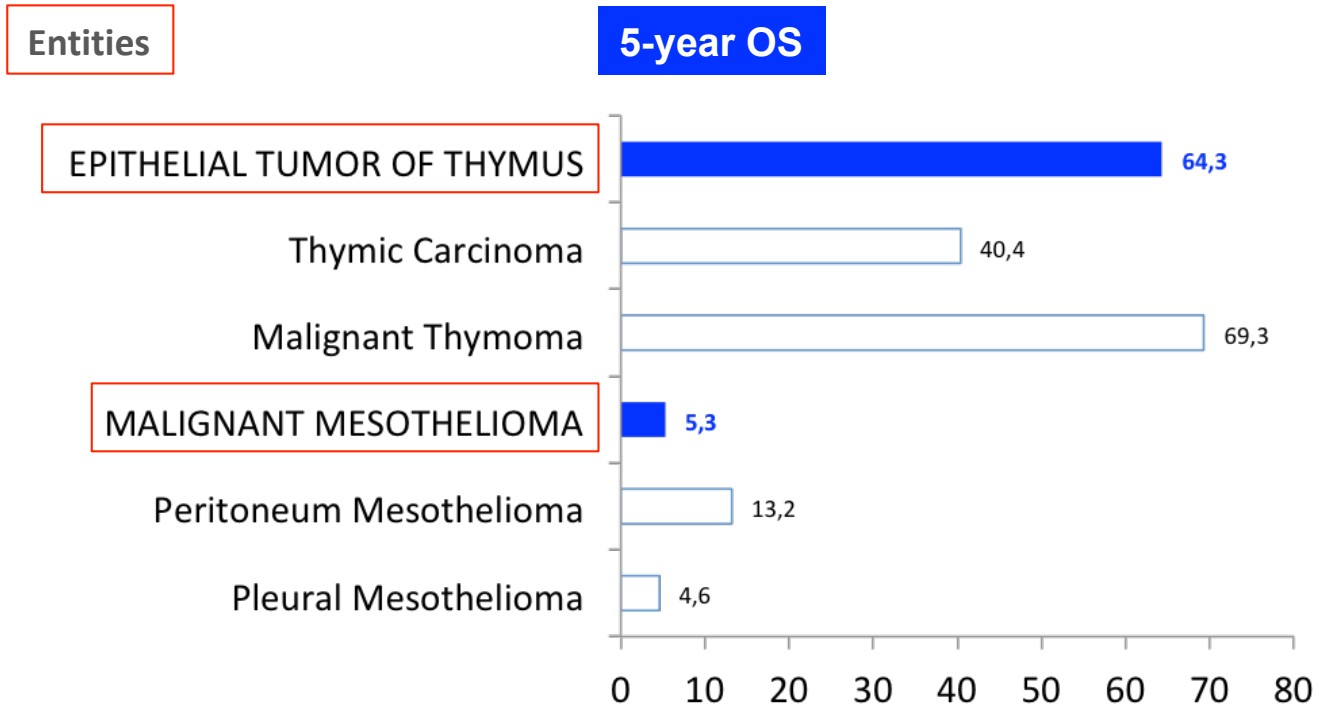
Benjamin Besse

Liens d'intérêt

- Pas de liens d'intérêt financiers personnels
- Financement de la recherche clinique et translationnelle:
  - AstraZeneca, BMS, Boehringer-Ingelheim, Lilly, Pfizer, Roche-Genentech, Sanofi-Aventis, Clovis, GSK, Servier, EOS, Onxeo, OncoMed, Inivata, OSE Pharma

RARECAREnet project

94 cancer registries to estimate incidence and OS in 2000-07. 24% rare cancers in EU.



Incidence

0.18 / 100,000 / year
Male ~ Female, 50-60 y

0.34 per 100.000 persons
In the RYTHMIC network

2.14 / 100,000 / year

RARECARENet definition:
≤ 6 cases /100,000 / year
5-y OS 48.5% (*vs.* 63.4% in common)

Courtesy of J.Remon

Gatta – Lancet Oncol 2017, Bluthgen ITMIG 2016

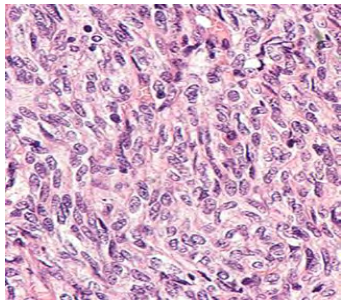
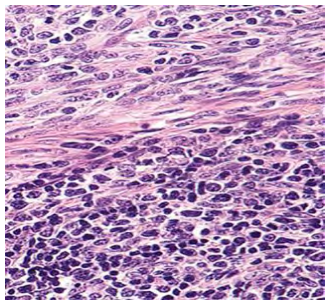
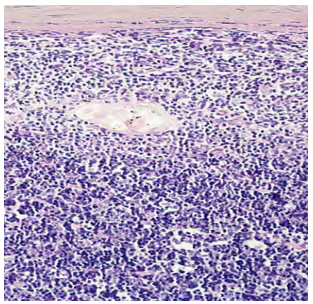
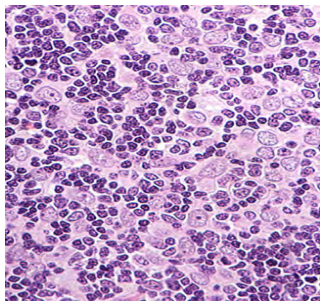
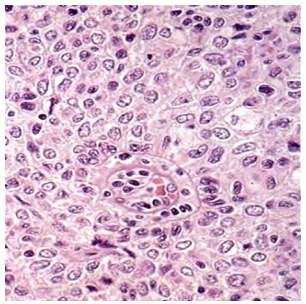
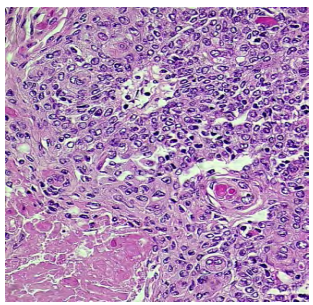
Thymic malignancies: WHO 2015

- Heterogeneous group of thoracic malignancies
- Epithelial and lymphocyte content

Thymoma

Thymic Carcinoma

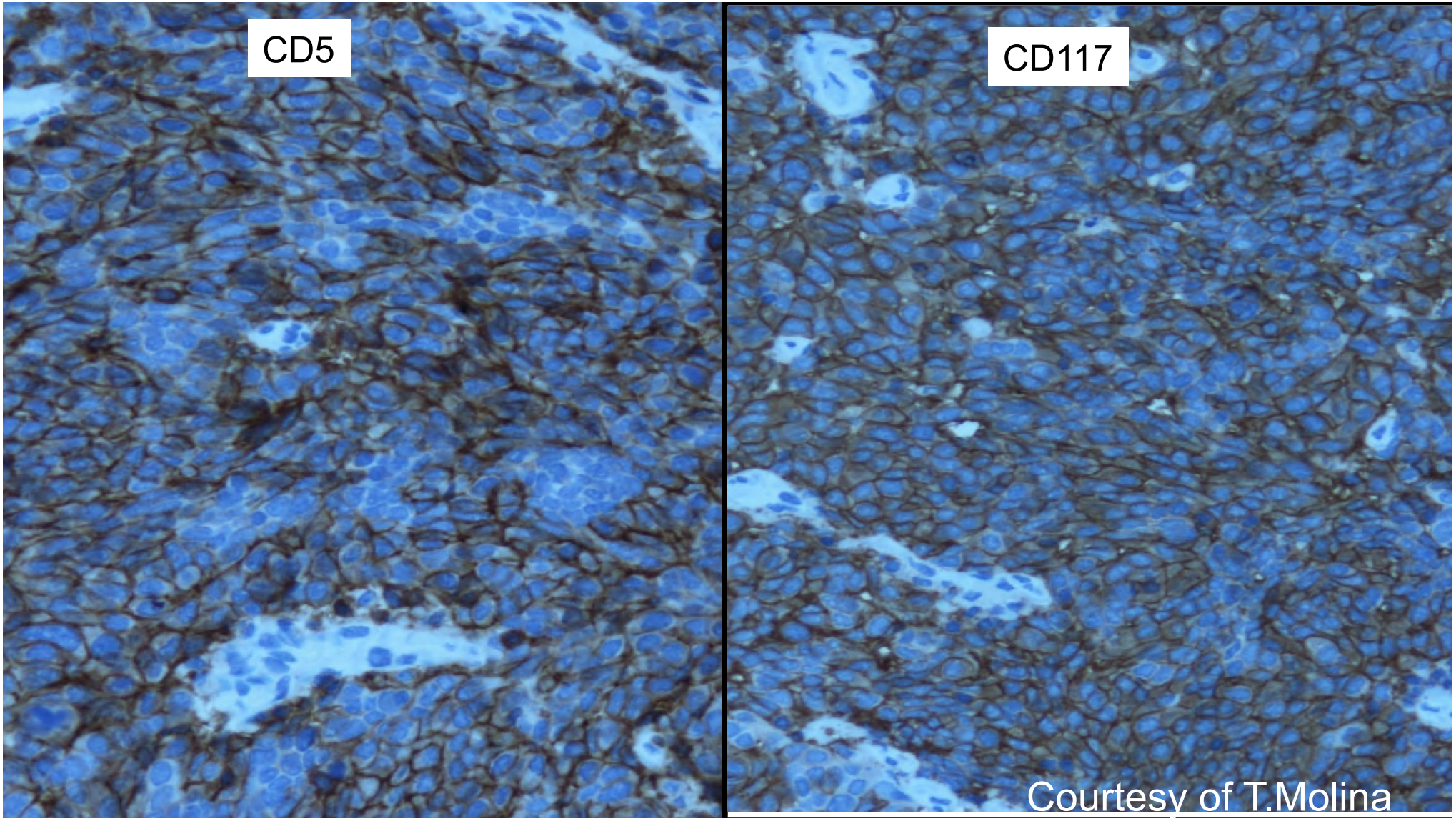
A | **AB** | **B1** | **B2** | **B3**

"Medullary" | Mixed | "Cortical" | SCC

TdT- / CD20+ | **TdT+ / CD20+** | **CD117+ / CD5+**

Marx – JTO 2014 & JTO 2015


CD5
CD117
Courtesy of T.Molina

Discordances

Patients and Methods

Pathological central review of 400 patients diagnosed with TETs from Jan 2012 to Dec 2015 by a panel of 10 expert pathologists

Assessment of agreement or disagreement between the initial institution and the panel review according

- WHO 2004/2015 for histologic typing
- Masaoka-Koga and new ITMIG proposals for staging

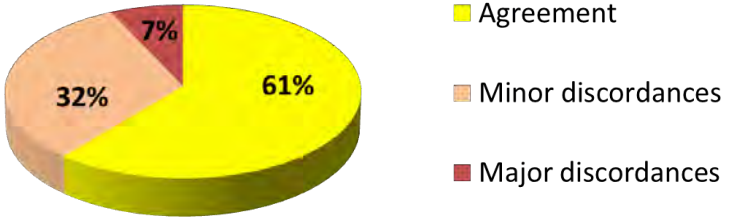
Major discordances: changed the therapy or management

Minor discordances: not change the therapy or management

According to RYTHMIC Guidelines

Post-operative recommendations are based on histopathological subtype, Masaoka-Koga stage and resection status

Discordances



Discordances	Number of discordances / number of Patients Frequency (%) n=401
Total discordances	**178 / 159 (40)**
Histologic subtype	118
Stage	60
Minor discordances	**147 / 130 (32)**
Histologic subtype	102
Stage	45
Major discordances	**31 / 29 (7)**
Histologic subtype	16
Stage	15

Masaoka-Koga-ITMIG

- Classification based on clinical and pathological items
- **After resection**

TABLE 1. Masaoka-Koga Staging System

Stage	Definition
I	Grossly and microscopically completely encapsulated tumor
IIa	Microscopic transcapsular invasion
b	Macroscopic invasion into thymic or surrounding fatty tissue, or grossly adherent to but not breaking through mediastinal pleura or pericardium
III	Macroscopic invasion into neighboring organ (i.e., pericardium, great vessel, or lung)
IVa	Pleural or pericardial metastases
b	Lymphogenous or hematogenous metastasis

Adapted from *Pathol Int* 1994;44:359–367.

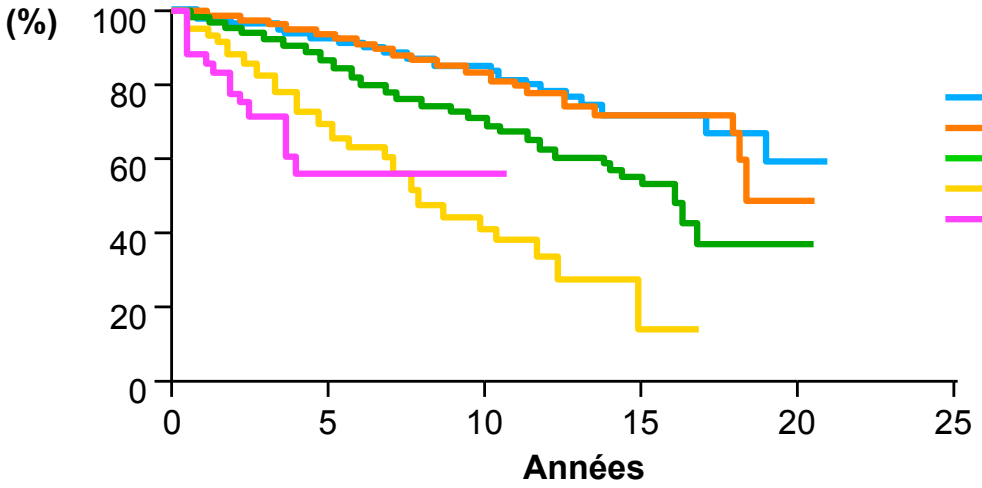
TABLE 2. ITMIG Definition of Details of the Masaoka-Koga Staging System

Stage	Definition (the ITMIG Interpretation of Details Is in Italics)
	Grossly and microscopically completely encapsulated tumor *This includes tumors with invasion into but not through the capsule, or …* *Tumors in which the capsule is missing but without invasion into surrounding tissues*
IIa	Microscopic transcapsular invasion *Microscopic transcapsular invasion (not grossly appreciated)*
b	Macroscopic invasion into thymic or surrounding fatty tissue, or grossly adherent to but not breaking through mediastinal pleura or pericardium *Gross visual tumor extension into normal thymus or perithymic fat surrounding the thymoma (microscopically confirmed), or …*

Detterbeck et al. J Thorac Oncol 2011:6:S1710

Prognostic Value Of Masaoka-Koga staging

- ITMIG database



	Events/n	10 yrs OS, % (IC_{95})
Stage I	30/1 292	84 (81-86)
Stage II	78/1 878	83 (79-87)
Stage III	135/629	70 (64-75)
Stage IVA	40/106	42 (26-58)
Stage IVB	14/40	53 (32-73)

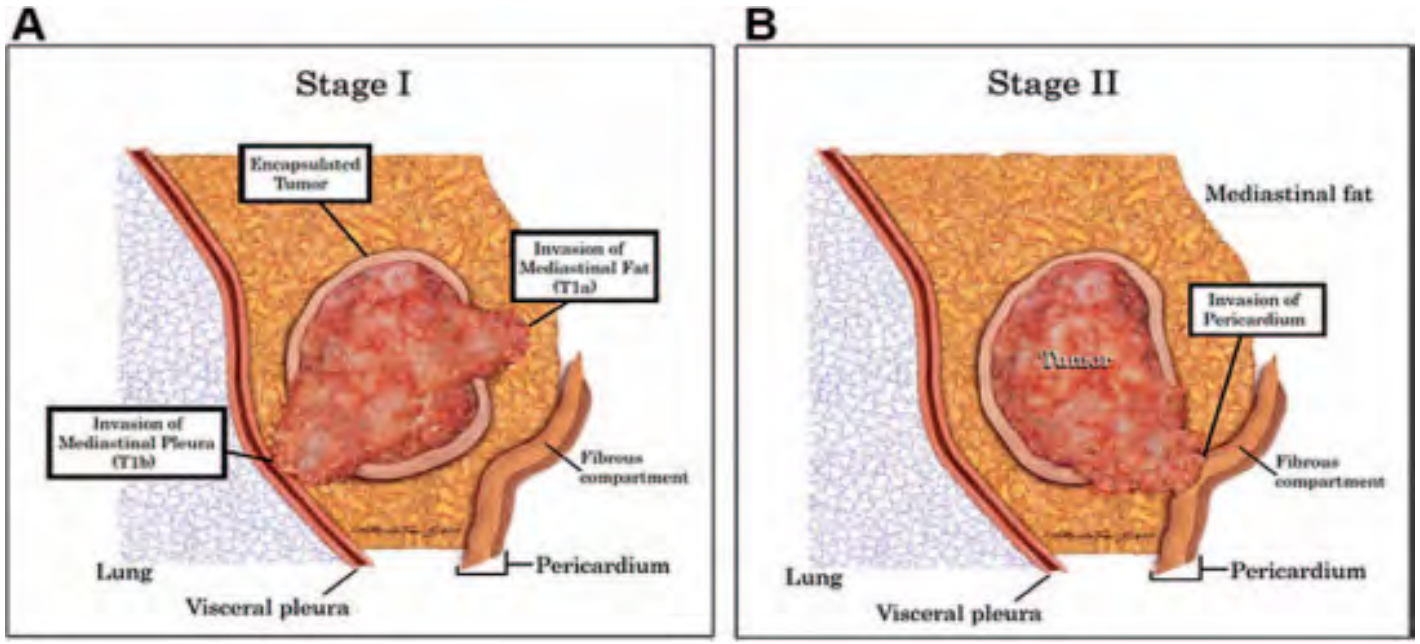
➜ Same survival for stage I and II

Detterbeck et al. WCLC 2013, abstr. MS16.2

8th TNM classification: ITMIG & IASLC

TNM

N=10.808 TET
(2000-2012)



Masaoka-Koga

Stage I, II, IIB, III **Stage III**

Detterbeck – J Thorac Oncol 2014

Incidence des Maladies AI - 2016

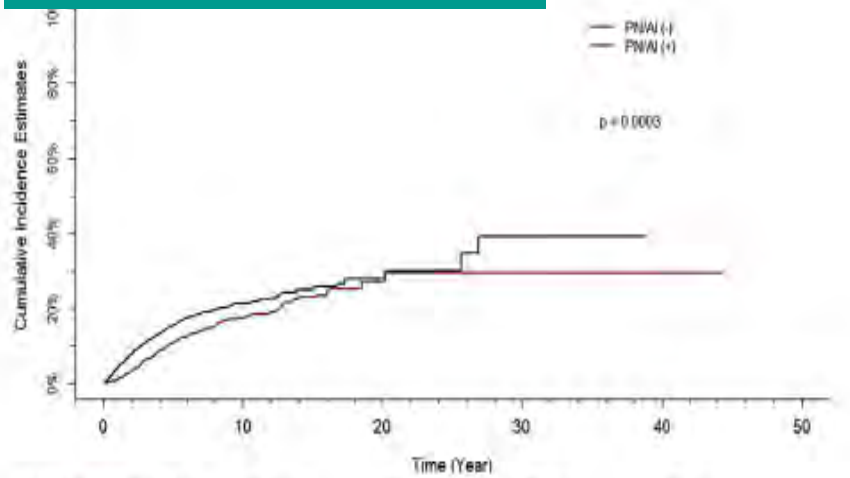
Caractéristiques cliniques	Fréquence N= 259	%
Age		
Médiane (interquartile)	63	
Sexe		
Homme	134	51.7%
Maladies auto-immunes	**55**	**21.2%**
Myasthénie	40	72.7%
Thrombopénie auto-immune	2	
Erythroblastopénie	1	
Anémie hémolytique	1	
Lupus érythémateux disséminé	1	
Polyarthrite rhumatoïde	1	
Autres	9	

Boucher CPLF 2018

Autoimmune disorders and prognosis in TET

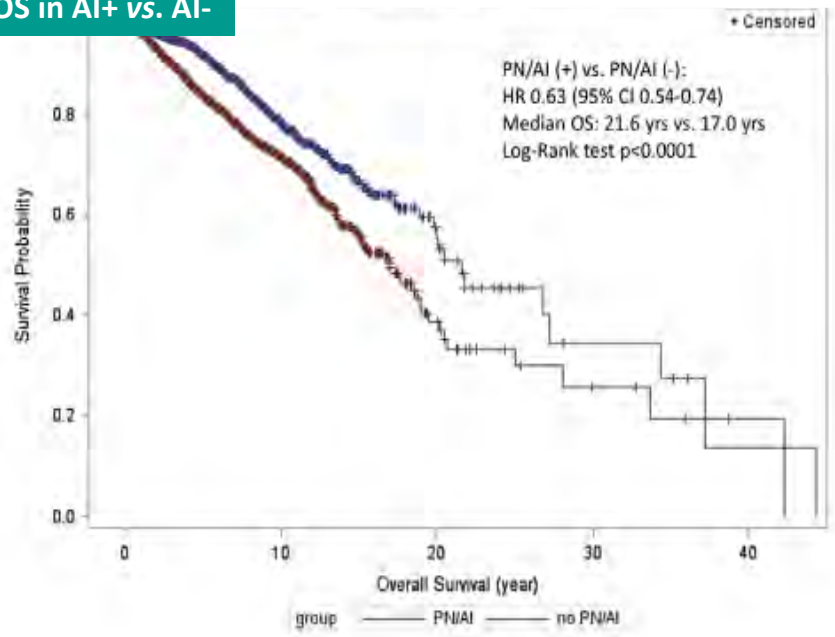
N= 6,670 patients with AI syndrome from 1951 to 2012 in ITMIG database (86% T, 12% TC)

Cumulative incidence of recurrence



Cumulative incidence of recurrence (95% CI)	10-year	20-year	30-year	40-year
PN/AI (-)	0.21 (0.19-0.23)	0.28 (0.24-0.33)	0.39 (0.27-0.52)	N/A
PN/AI (+)	0.17 (0.15-0.20)	0.27 (0.22-0.33)	0.30 (0.23-0.37)	0.30 (0.23-0.37)

OS in AI+ *vs.* AI-

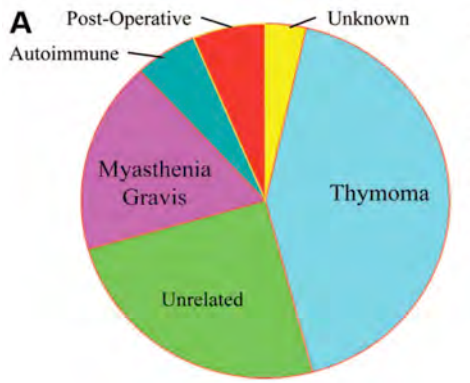


Multivariable analysis: AI is not an independent prognostic factor for patients with TET

Courtesy of J.Remon

Padda – JTO 2018

Surveillance et cause de décès



Cause de décès – tous stades

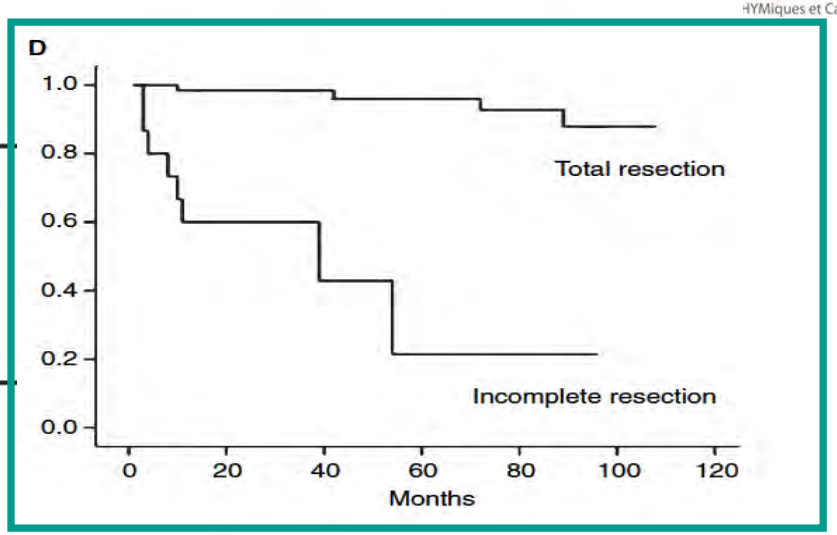
- **2,5 % mortalité opératoire**
- **Fréquence d'un second cancer (27 %)**
- **Récidive tardive possible : 20 % après 10 ans**

Hunag, JTO 2011

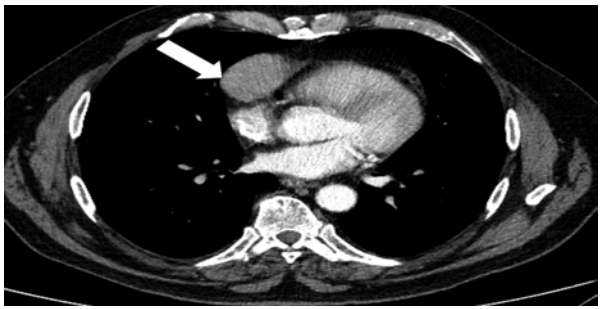
Resection

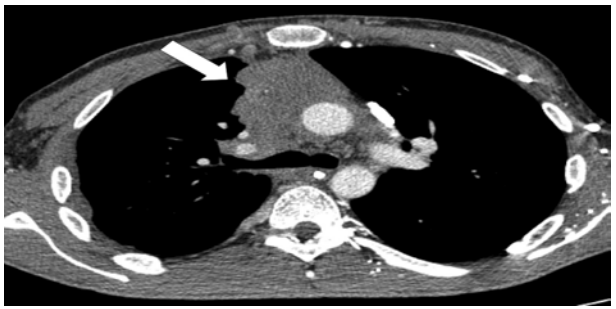
Thymic malignancy likely: All patients should be managed by a multidisciplinary team with experience in the management of thymoma

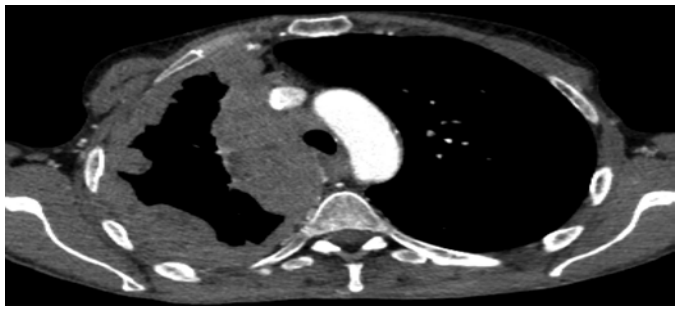
- Surgically resectable
  MEDIAN STERNOTOMY THYMECTOMY
- Locally advanced, unresectable[a]



Rossi – Histopathology 2008 * Girard – Eur Resp Rev. 2013



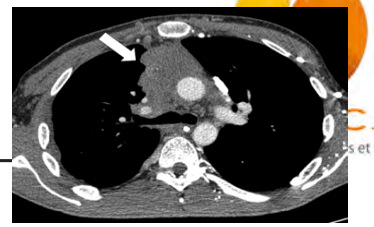




Courtesy of J.Remon

The most significant prognostic factor in TET is the completion of surgical resection

Preoperative chemotherapy



Study	Primary Chemotherapy Regimen	No. of Patients	Tumor Type	Tumor Stage	Design	Response Rate (%)
Chemotherapy						
Macchiarini et al 1991[14]	CEE	7	T/TC	III	Phase II	100
Berruti et al 1993[15]	ADOC	6	T	III-IVA	Phase II	83
Rea et al 1993[16]	ADOC	16	T	III-IVA	Retrosp	100
Berruti et al 1999[17]	ADOC	16	T	III-IVA	Phase II	81
Venuta et al 2003[18]	CEE	15	T/TC	III	Retrosp	66
Bretti et al 2004[19]	ADOC/PE	25	T/TC	III-IVA	Retrosp	72
Kim et al 2004[20]	CAPP	22	T		Phase II	77
Lucchi et al 2005[21]	CEE	36	T/TC	III-IVA	Retrosp	67
Jacot et al 2005[22]	CAP	5	T/TC	III-IVA	Retrosp	75
Yokoi et al 2007[23]	CAMP	14	T/TC	III, IV	Retrosp	93
Kunitoh et al 2009[24]	CODE	21	T	III	Phase II	62

~80%

Girard – Eur Resp Rev 2013

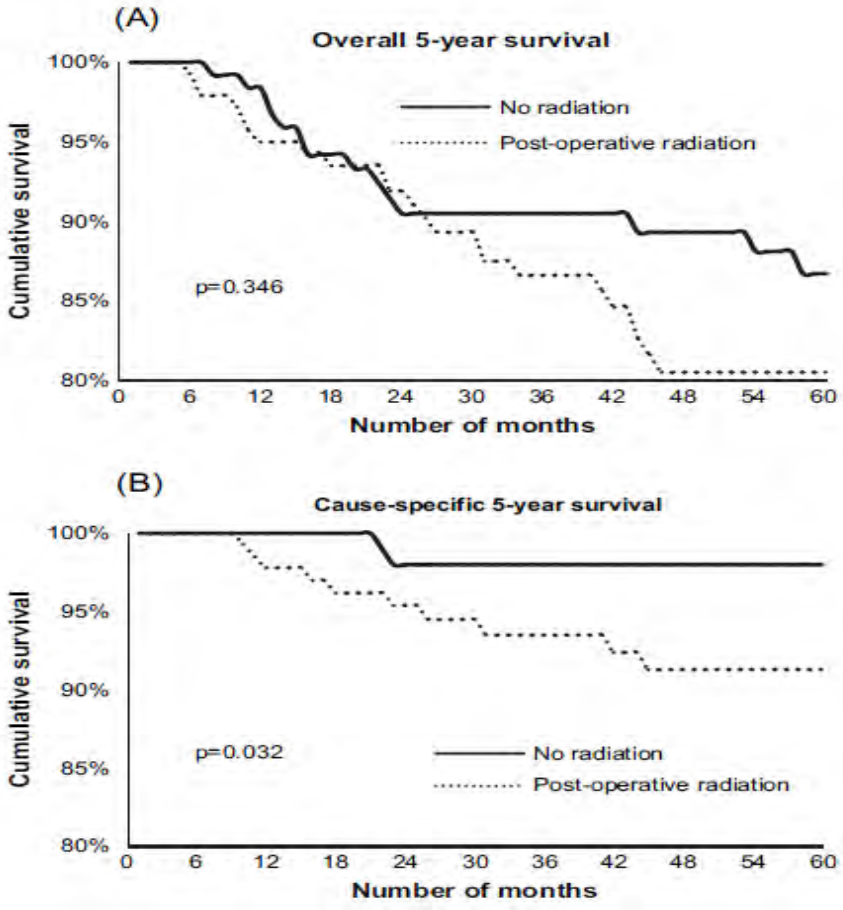
Courtesy of J.Remon

RT post-opératoire

- Base SEER (Surveillance, Epidemiology and End Results) 1973–2005.
- ‘Type A’ ‘historique’ (classif. différente de Masaoka)
- Patients décédés dans les 3 mois après la chirurgie non inclus
- N=901
- 65% traités par RT post opératoire
- 61% type TET non précisée
- Chirurgie radicale 35%

Forquer IJROBJ 10

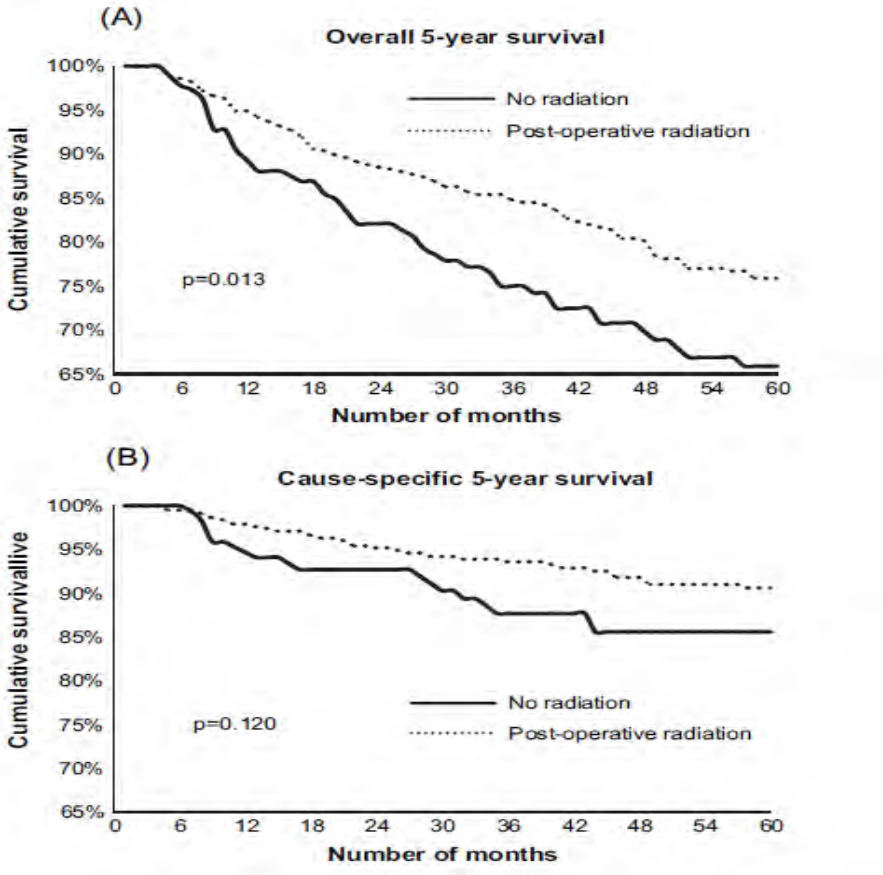
Masaoka stade I (~A localisés)



- N= 275
- Effet délétère
  - **Survie spécifique à 5 ans : 98% (C) vs. 91% (C+RT) p = 0.03**
  - **Survie globale: 87% (C) vs. 81% (C+RT) p = 0.35**

Forquer IJROBJ 10

Masaoka stade II-III (=A régionaux)



- N= 626
- Effet bénéfique
  - **Survie spécifique à 5 ans : 86% (C) vs. 91% (C+RT) p = 0.12**
  - **Survie globale: 66% (C) vs. 76% (C+RT) p = 0.01**
- Persiste si chirurgie radicale
  - **Survie globale: 62% (C) vs. 75% (C+RT) p = 0.12**

Forquer IJROBJ 10

Radiothérapie post-opératoire

RECOMMANDATIONS : Indication

La proposition de stratégie pour la radiothérapie post-opératoire, à valider en réunion de concertation pluri-disciplinaire, est la suivante[49-51] :

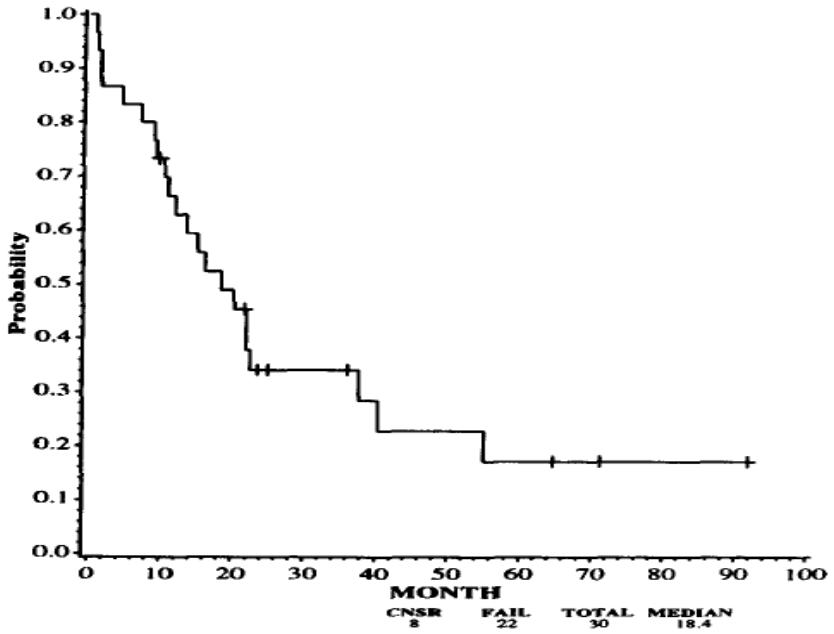
- en cas de résection complète :
  - stade I : pas de radiothérapie post-opératoire
  - stade IIa :
    - types A-B2 : pas de radiothérapie post-opératoire
    - type B3 : discuter une radiothérapie post-opératoire
  - stade IIb
    - types A-B1 : pas de radiothérapie post-opératoire
    - types B2-B3 : discuter une radiothérapie post-opératoire
  - stades III:
    - radiothérapie post-opératoire
- en cas de résection R1 : - radiothérapie post-opératoire
- en cas de carcinome thymique : - radiothérapie post-opératoire

- Irradier la totalité de la loge thymique ainsi que les éventuelles extensions tumorales
- Irradiation creux sus-claviculaires non recommandée

Référentiel RYHTMIC

Stades métastatiques

CAP (CDDP, Adriamycine, Cyclophosphamide)



- **Traitement historique**
- **CAP X 8**
- **N=30 (1 carcinome thym.)**
- **Pas de classification OMS anatomo-pathologique**

- **Evaluation tumorale OMS (TDM)**

- **ORR=50%**
- **TTF=18 mois**
- **Survie médiane 37 mois**

Lehrer, JCO 94

Stades métastatiques
Paclitaxel - carboplatine

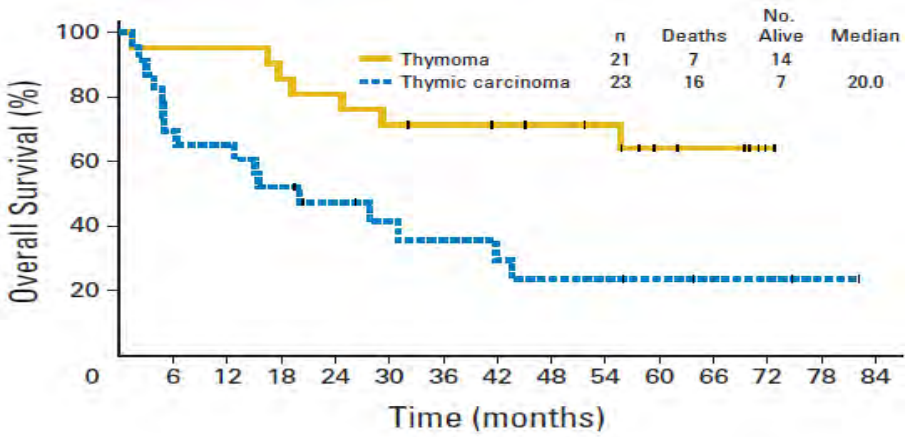
Table 1. WHO Classification of Patients With Thymic Neoplasms

WHO Classification	Thymic Tumor No.	Thymic Tumor %
A	1	2.3
AB	1	2.3
B1	8	18.1
B2	7	15.9
B3	10	22.7
C	13	29.6
Thymoma-NOS*	4	9.1

N=21

N=23

*Thymoma-NOS classification indicates not otherwise specified because of limited material.



- **Carboplatin AUC 6 + paclitaxel (225 mg/m2) X6**
- **RECIST**

- **Thymomes**
- **PFS = 16.7 mois**
- **ORR 42.9%**
- **OS non atteinte**

- **Carcinomes thymiques**
- **PFS 5 mois**
- **ORR = 21.7%**
- **OS 20.0 mois**

Lemma, JCO 11

Chemotherapy in advanced disease

Table 1. Chemotherapy for advanced thymic carcinoma in previous studies

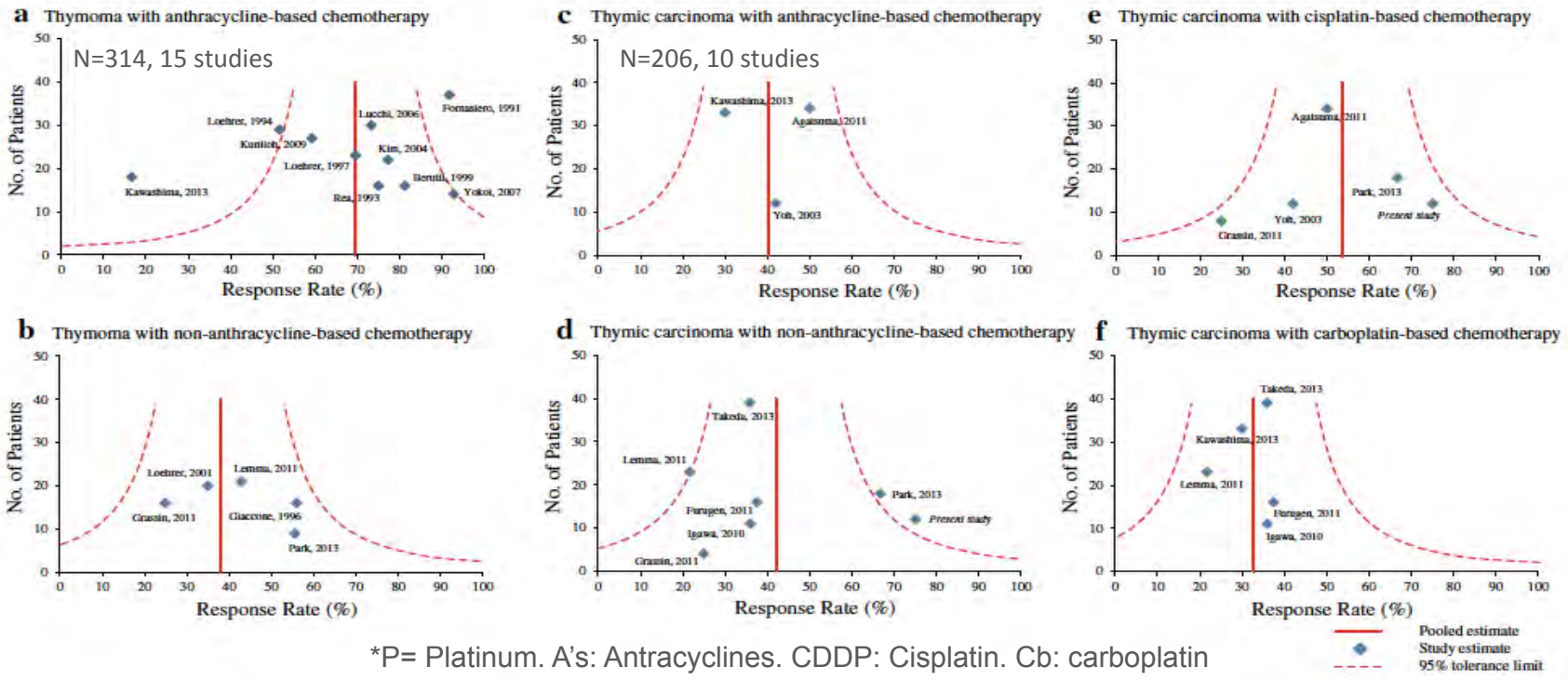
Authors	P or R	Regimen	No. of patients	Response rate (%)	PFS (month)	MST (month)	
Loehrer et al. [11]	P (Phase II)	CAP 8 cycles	30 (T = 29, TC-1)	50	18.4	37.7	~50%
Koizumi et al. [7]	R (Case series)	ADOC	8 (TC = 8)	75	—	19	~75%
Agatsuma et al. [12]	R	ADOC	34 (TC = 34)	50	—	21.3	
Fornasiero et al. [13][a]	R (Case series)	ADOC	37 (T = 37, TC = 0)	91.8	12	15	
Loehrer et al. [8]	P (Phase II)	VIP	28 (T = 20, TC = 8)	32	11.9	31.6	~30%
Grassin et al. [9]	P (Phase II)	VIP	16 (T = 12, TC = 4)	25	—	Not reached	
Igawa et al. [14]	R	CbP	11 (TC = 11)	36	7.9	22.7	
Furugen et al. [15]	R	CbP	16 (TC = 16)	37.5	8.6	49.4	
Lemma et al. [16]	P (Phase II)	CbP 6 cycles AUC=6/P=225	46 (T = 23, TC = 23)	21.7 (TC) 41.9 (T)	5 (TC) 16.7 (T)	20 (TC) Not reached (T)	~25%
Okuma et al. [17]	R	Cisplatin irinotecan	9 (TC = 9)	55.6	7.9	33.8	
Palmieri et al. [18]	P (Phase II) [a]second-line	Carboplatin gemcitabine	15 (T = 12, TC = 3)	40	11	Not reached	
Oshita et al. [19]	P	PACE	14 (T = 7, TC = 7)	42.9	—	14.7 (no prior Tx; 8.9)	
Yoh et al. [10]	R	CODE	12 (TC = 12)	42	5.6	46	
Hirai	**P**	**CbP** AUC=6/P=200	**39 (T=0, TC=39)**	**36**	**7.5**	**NR, 2-y OS 71%**	**~36%**

Courtesy of J.Remon

Antracyclines / Non-antracyclines schedules

Hirai – Ann Oncol 2015

Chemotherapy in advanced disease



*P= Platinum. A's: Antracyclines. CDDP: Cisplatin. Cb: carboplatin

P-A's* *vs*. P-non-A's in T
69% *vs*. 38%, p<0.0001

P-A's *vs*. P-non-A's in TC
41.8% vs. 41%, p<0.91

CDDP* *vs*. Cb in TC
54% vs. 33%, p<0.003

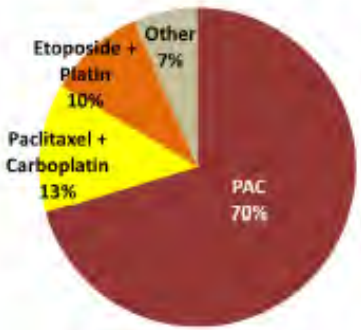
Courtesy of J.Remon

Okuma – J Cancer Res Clin Oncol 2015

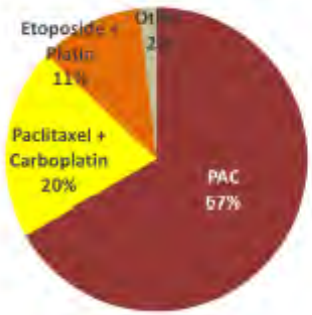
Real-life data of CT efficacy in TETs

RYTHMIC database

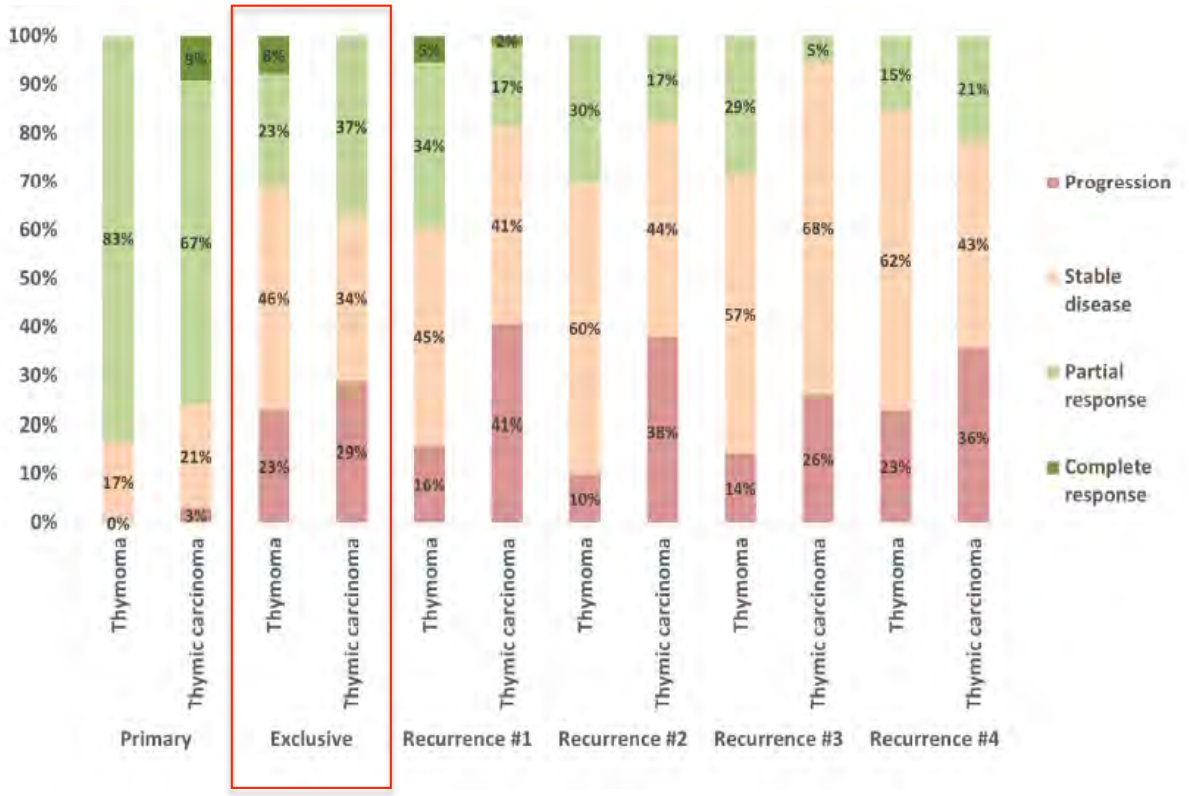
Primary Treatment N=91



Exclusive Treatment N=54



ORR ~30%
PFS 6.2 mo.
OS: not reached



Merveilleux du Vignaux – JTO 2018

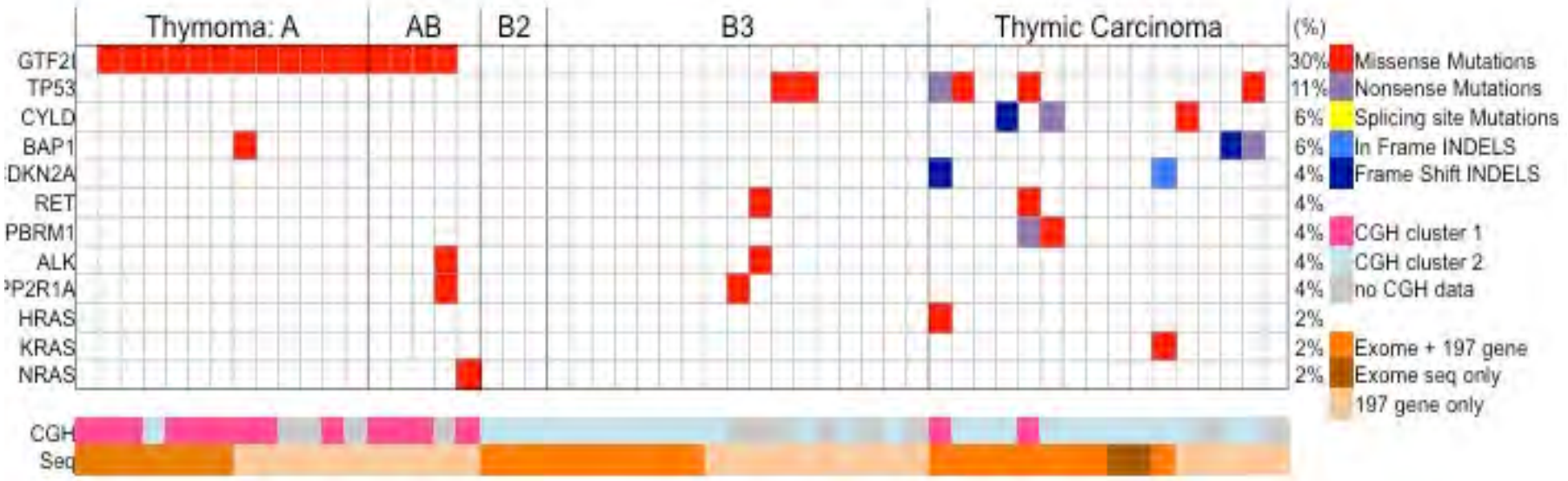
Second-line treatment in TET

~20% 4-8 mo. 12-20 mo.

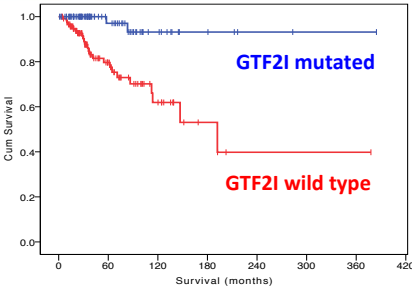
	Phase	N		RR (%)		PFS		OS	
		T	TC	T	TC	T	TC	T	TC
Pemetrexed [12]	Retrospective	6	10	PR: 17% SD: 83%	PR: 10% SD: 50%	13.8	6.5	20.1	12.7
Pemetrexed [13]	II	16	11	17%	0%	TTP 6.5	TTP 1.3	29	
Etoposide oral [14]	Retrospective	5	8	PR 15%, SD 70%	PR 13% SD 63%	53	4	98	22
Amrubicin [15]	II	14	19	ORR: 18% 29%	11%	8.7	8.5	NR	18.1
Capecitabine/gemcitabine [17	II	22	8	ORR: 40% *In TC:* 38%		11	6	1-y OS: 90% 2-y OS: 66%	
Everolimus [49]	II	30	19	DCR: 93%	DCR: 74% ORR: 22% (PR 20%)	NR	5.5	NR 1 y: 82%	18.6 1 y: 62%
Cixutumumab [52]	II	37	12	PR: 14% SD: 28%	SD: 42%	*TTP* 9	*TTP* 1.7	27.5	8.4
Belinostat [54]	II	25	16	PR: 8% SD: 43%	PR: 0% SD: 40%	TTP 11.4	TTP 2.7	NR	12.4
Sunitinib [60]	II	16	25	6%	26%	8.5	7.2	15.5	NR
Sunitinib [61]	Retrospective	8	20	27%	20%	5.4	3.3	NR	12.3
Lucitanib [64]	I	3	12	33.3%	8.3%	DOR: 7 m			
Saracatinib [66]	II	12	9	0%	0%	5.7	3.6		
Milciclib [68]	II	9	26	20%		8.2		NR	

Remon – Cancer Treat Rev 2016

GT2FI mutation in TET



Missense mutation (ch 7 c.74146970T>A) in GTF2I in type A thymomas
In a serie with 274 TET, GT2Fi mutation in 82% Type A and 74% Type AB

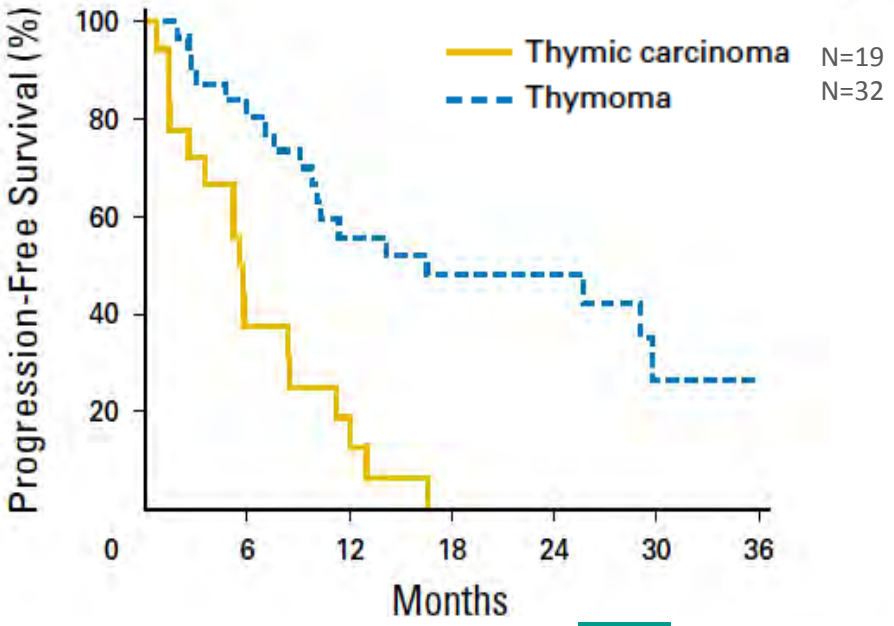


Courtesy of J.Remon

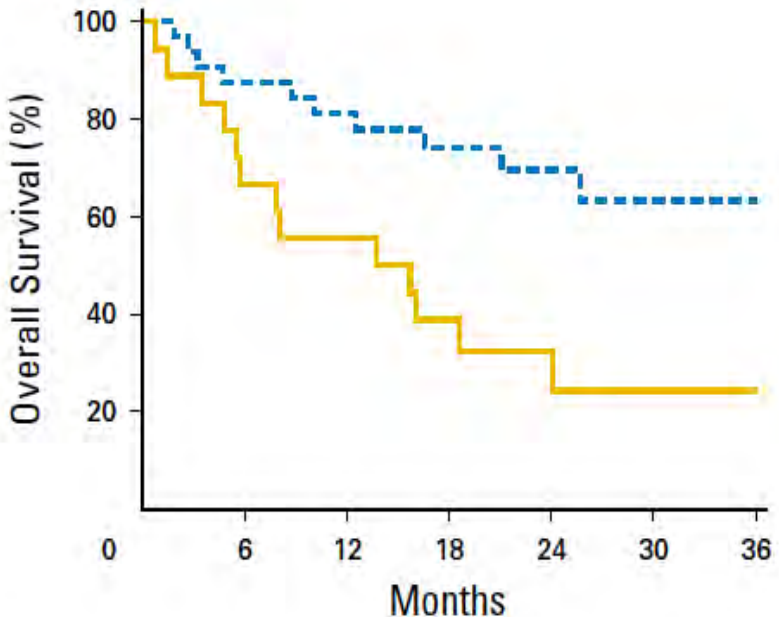
Petrini – Nature Genet 2014

Everolimus, phase II

PFS 10.1 months (16.6 *vs*. 5.6 mo.)



OS 25.7 months (NR *vs*. 14.7 mo.)

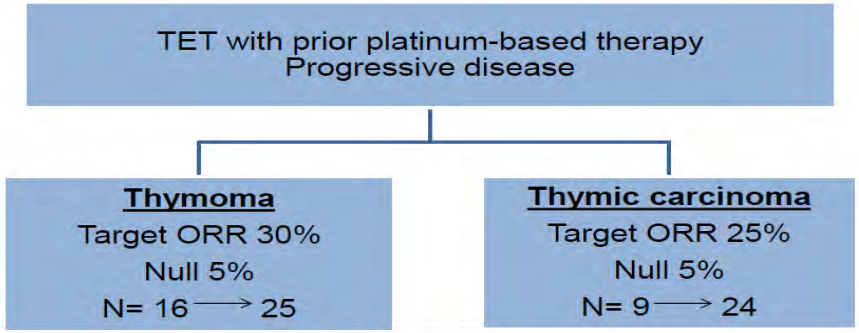


RR 12% (10% *vs*. 16%). DCR 88%

Courtesy of J.Remon

Zuccali –JCO 2018

SUNITINIB : phase II study



Sunitinib 50 mg/d

4 weeks out of 6

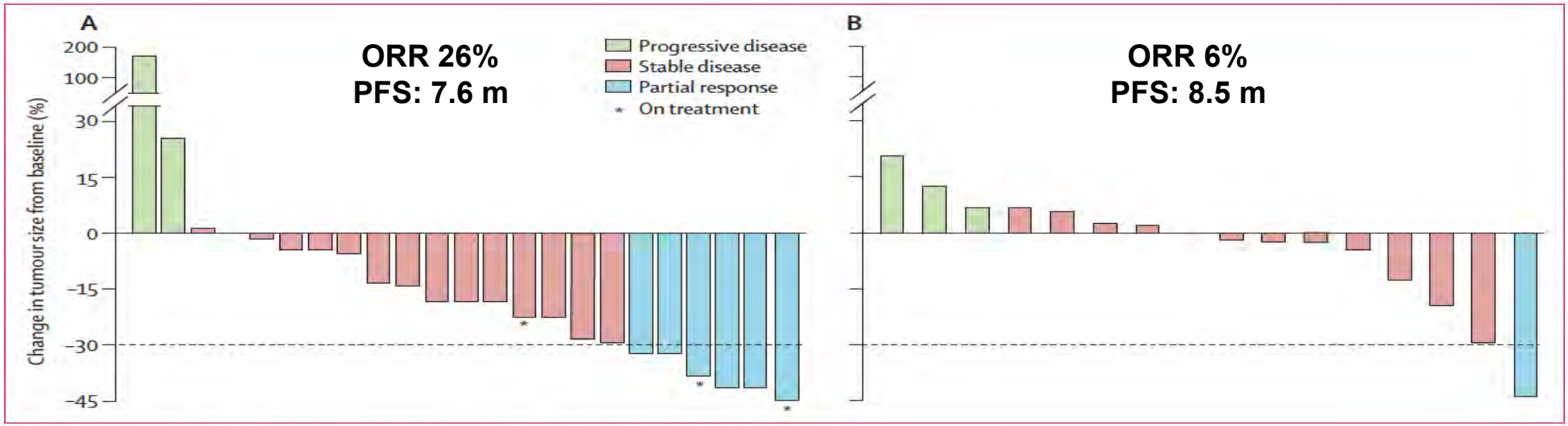
Patient characteristics			
	Thymoma	Thymic carcinoma	Total
Number of patients	16	24	40
Age Median (Range)	54 (31-74)	58 (41-81)	57.5 (31-81)
Sex Male Female	7 9	15 9	22 18
ECOG PS 0- 1 2	15 1	21 3	36 4
Race: Caucasian African-American	13 3	23 1	36 4
Histology B1 B2 B3 Uncategorized	2 5 8 1	24	40
Prior systemic therapies Median (Range) ≥ 2 prior therapies	2 (1-7) 13	2 (1-5) 14	2 (1-7) 27
No. of cycles administered Median (Range)	5 (1-13)	4 (1-13)	4 (1-13)

Thomas ASCO 2014

SUNITINIB : phase II study

Thymic carcinoma
N=23

Thymoma
N=16

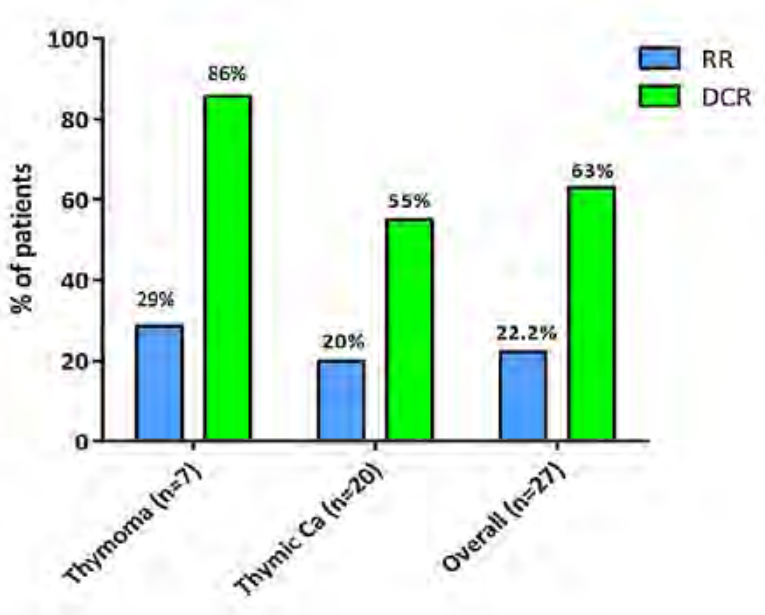


Thomas, Lancet Oncol 2015

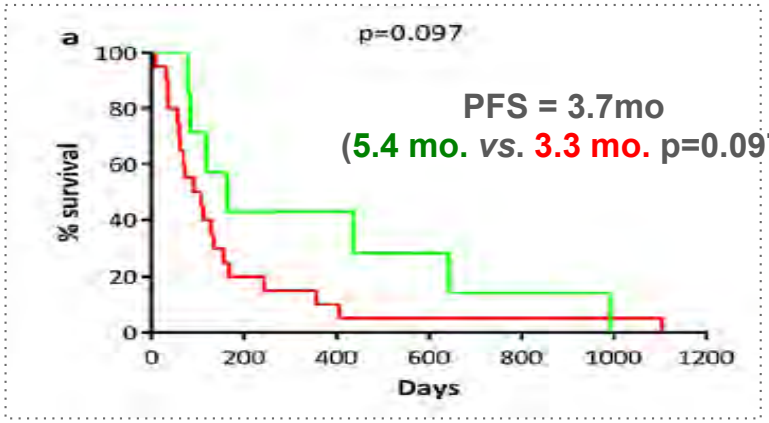
Sunitinib off-label

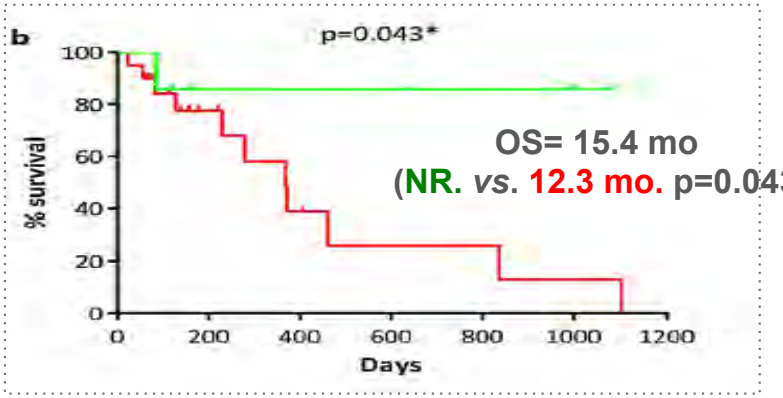
RYTHMIC database. N=28 (20 TC, 8 T). 54% sunitinib 4th line

Sunitinib 50 mg 4weeks on / 2 week off



Thymoma / Thymic Carcinoma





Remon – Lung Cancer 2016

PD-L1 expression in TET

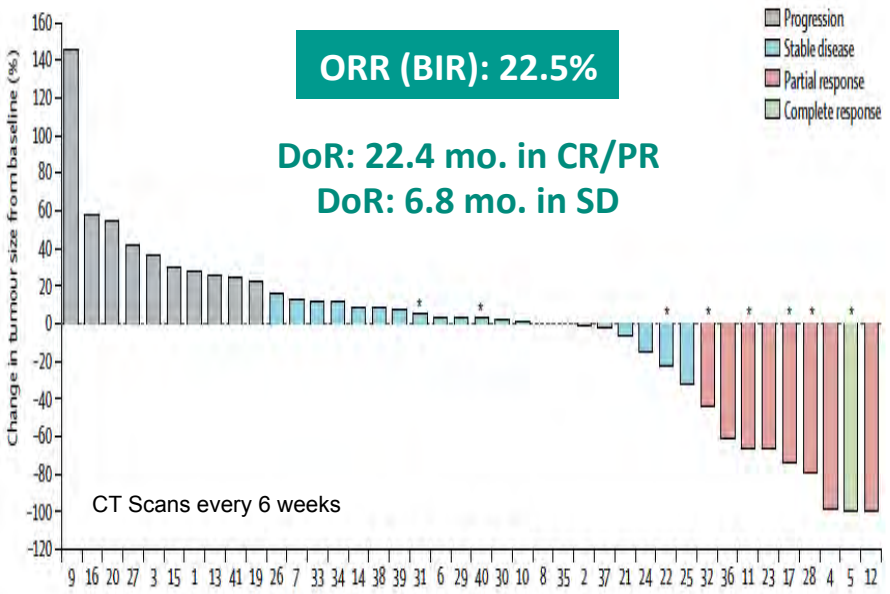
	Technique	Thymoma	Thymic Carcinoma	Prognostic value
Weissferdt	E1L3N ≥5%	**64%**	**54%**	**NO**
Arbour	E1L3N, M-score 25%	**92%**	**36%**	**Better OS**
Katsuya	E1L3N, ≥ 1%	**67%**	**41%**	**NO**
Tiseo	E1L3N, H-Score ≥ 3	**55%**	**45%**	**NO**
Katsuya	E1L3N H-Score ≥ 3, 1%	**23%**	**70%**	**NO**
Padda	TMA, clone 5H1	**68%**	**75%**	**Worse OS**
Marchevsy	SP142, staining 1%	**92%**	**50%**	**NO**
Yokoyama	EPR1161 ≥ 38% for T EPR1161, H-score>20, TC	**54%**	**80%**	**Worse DFS in T** **Better OS in TC**

Weissferdt- Mod Pathol 2017 * Katsuya – Lung Cancer 2016 * Tiseo – Lung Cancer 2017 * Katsuya – Lung Cancer 2015 * Padda – JTO 2015 * Marchevsky – Hum Pathol 2017 *Yokoyama – Ann Thoracic Surg 2016 & Clin Cancer Res 2016

Courtesy of J.Remon

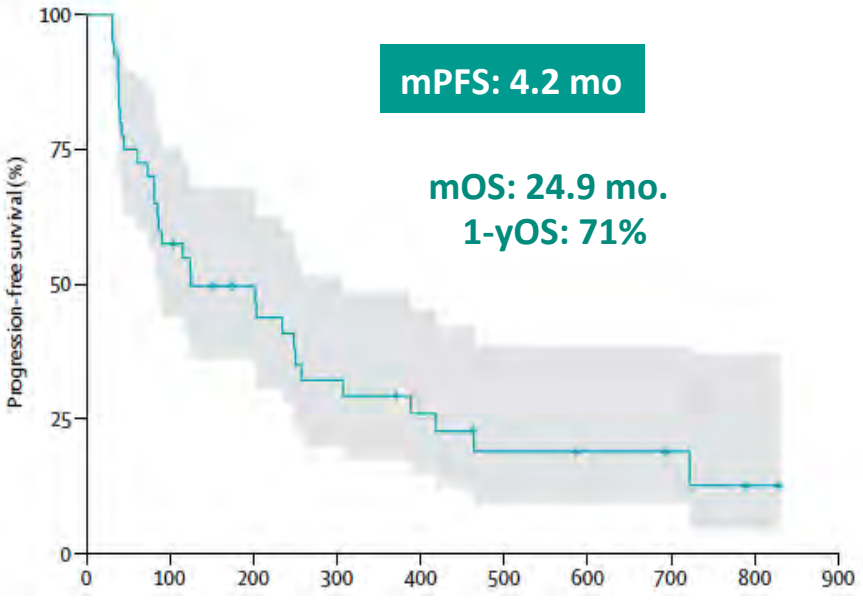
Pembrolizumab in TET

N=40 Thymic Carcinoma with PD at least 1 previous CT. 25% PD-L1≥ 50%. Fw: 20 months



ORR (BIR): 22.5%

DoR: 22.4 mo. in CR/PR
DoR: 6.8 mo. in SD



mPFS: 4.2 mo

mOS: 24.9 mo.
1-yOS: 71%

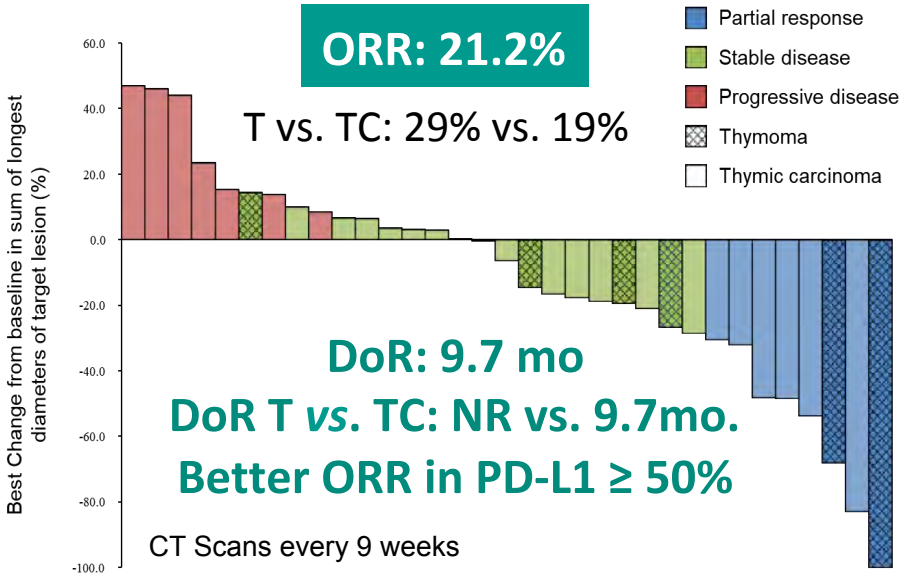
Outcome correlated with PD-L1 expression
Six (15%) developed sever irAE's with two (5%) with myocarditis

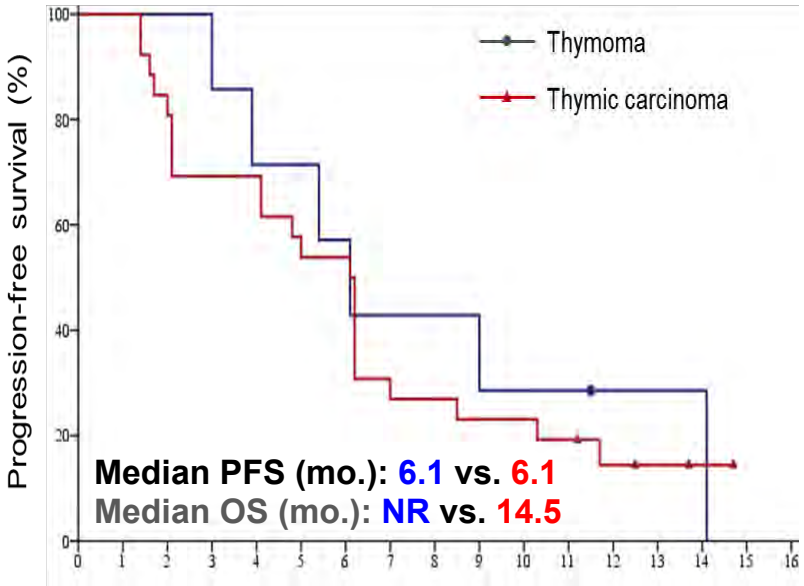
Courtesy of J.Remon

Giaccone – Lancet Oncol 2018

Pembrolizumab in TET

N=33 (7 T + 26 TC). 9% of patients with previous MG. Pembrolizumab until PD.



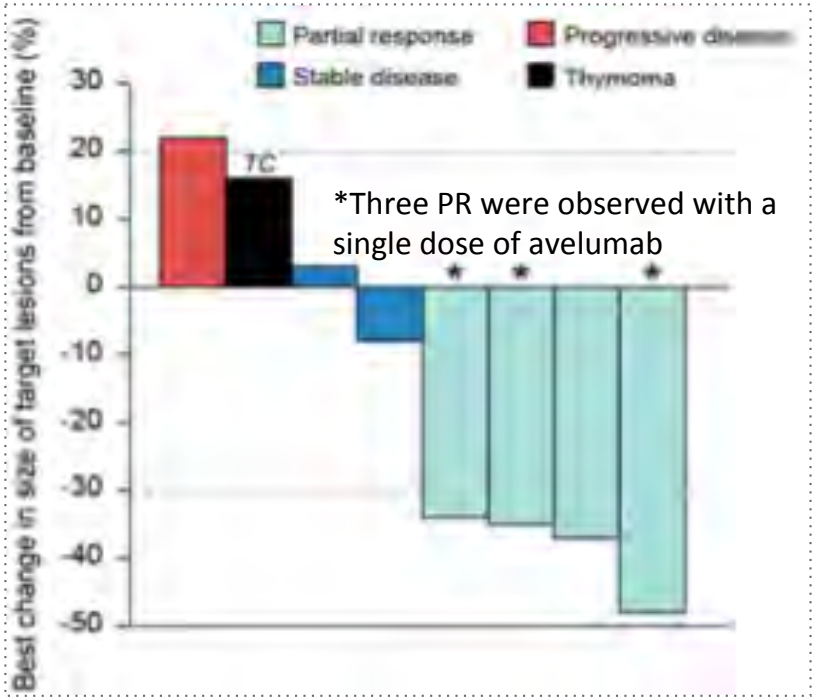


24.2% patients (5 T, 3 TC) discontinued study treatment due to grade ≥3 irAEs
Hepatitis (12%), Myocarditis (9%), MG (6%), Thyroiditis (3%)

Courtesy of J.Remon

Cho – JCO 2018

Avelumab (anti-PDL1) in TET



Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Tumor pain	1 (13%)			
Back pain		1 (13%)		
Extremity pain	1 (13%)			
Fever	1 (13%)			
Flu-like symptoms	1 (13%)			
Chills	1 (13%)			
Fatigue	3 (38%)	1 (13%)		
Nausea	1 (13%)			
Wheezing	1 (13%)			
Bronchial infection		1(13%)		
Ear and labyrinth disorder (fullness)		1 (13%)		
Urinary urgency		1 (13%)		
Autoimmune disorder			**3 (38%)**	**2 (25%)**

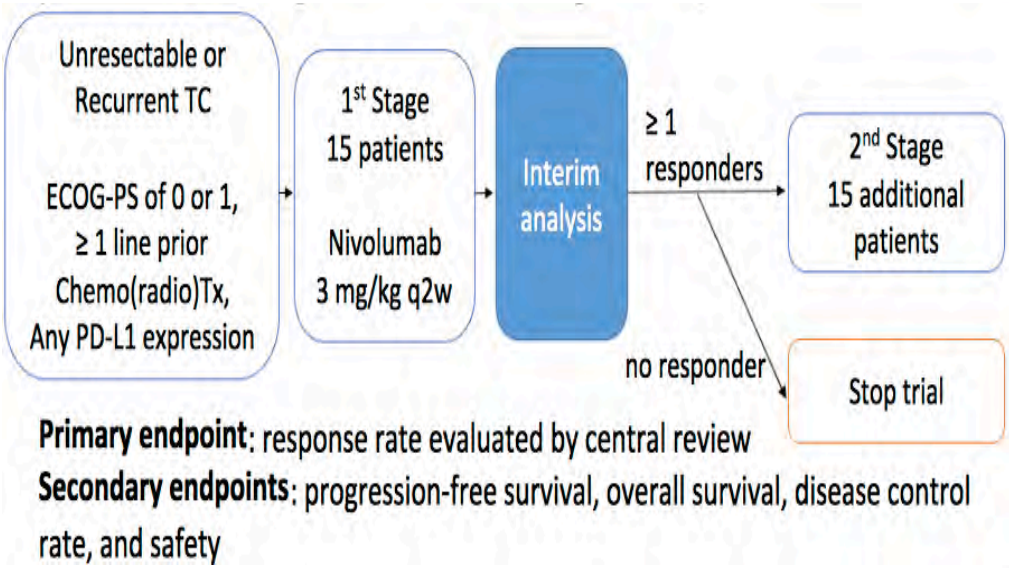
4/8 patients with partial response

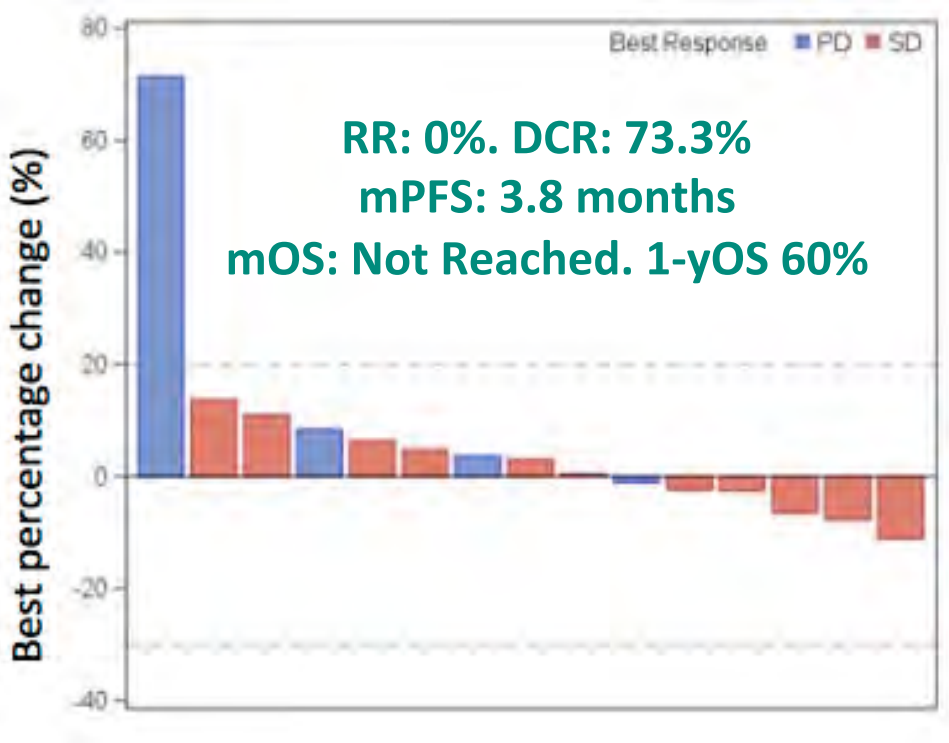
Immune related AE's in 5 patients. G3-4 AE's: 68%

Rajan – WCLC 2016 * Heery – Lancet Oncol 2017
Courtesy of J.Remon

All 4 responders experienced irAE's (3 myositis 1 enteritis)

Nivolumab in TET: PRIMER study





Courtesy of J.Remon

Seto – ELCC 2018

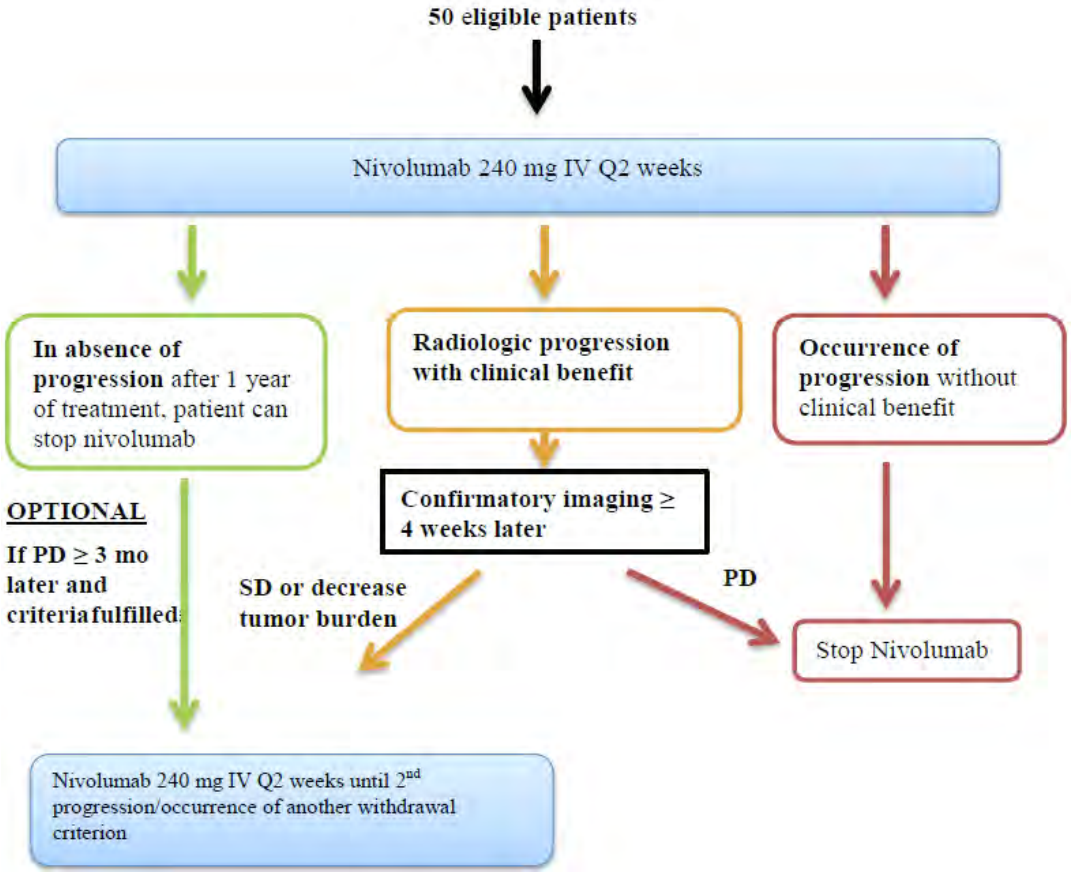
ICI in pre-treated TET

	Pembrolizumab			Nivolumab	Avelumab
	Giaccone et al. Phase II	Cho et al. Phase II		Seto et al. PRIMER study. Phase II	Rajan et al. Phase I
N	41	33		15	8
TC / T	40 / 0	26	7	15	1 / 7
RR / DCR	22.5% / 70%	19.2% / 73%	29% / 100%	0% / 73%	50%
PFS	4.2 mo. CT-scans / **6 w.**	6.1 mo. in TC CT-scans / **9 w.**		3.8 mo. CT-scans / **NR.**	Not reported (NR)
OS / 1-y OS	24.9 mo. / 71%	15 mo. / NR	Not reached	Not reached / 60%	NR
Predictive	**PD-L1 expression** 25% PD-L1 ≥ 50% RR 60%, PFS 24 mo.	**PD-L1 expression** 58.3% PD-L1 ≥ 50% RR=36%		NR	NR
Ir-AE G3-4	15%	15.4%		13%	68%

Courtesy of J.Remon

Giaccone – Lancet Oncol 2017 * Cho – JCO 2018 * Seto – ELCC 2018 * Rajan – WCLC 2016

NIVOTHYM



Interim analysis on 17 pts
If no activity (PFS at 6 months)

Nivo 3 mg/Kg Q2W +
Ipi 6 mg/kg Q6W until PD

RYTHMIC

- **2 RCP nationale / mois**
- **RCP régionales hebdomadaires**
- **1 fiche + CR anapath + CR opératoire**
- **www.rythmic.org**

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Guidelines

CME activities

Prospective database and trials

IFCT

National Pathology Panel

National expert tumor board

Treating Physician

Regional expert center

Patients

Conclusions

- TET are heterogeneous group
- Histology, resection, stage : main prognostic factors.
- Multidisciplinary approach is required
- Surgery has to be discussed upfront
- CAP, paclitaxel/carboplatin most frequent chemo.
- Immunotherapies may play a role in the next future, but careful monitoring is strongly recommended.