Cours GOLF

TUMEURS EPITHELIALES THYMIQUES

Benjamin Besse

Nicolas Girard

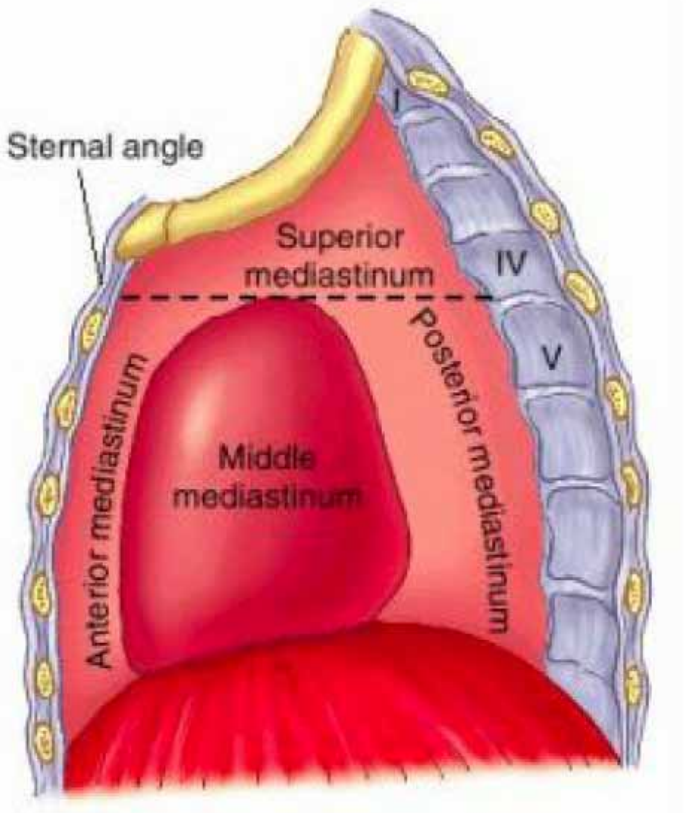
18 novembre 2015

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

rythmic.org
Réseau tumeurs THYMiques et Cancer


MOVEMBER
INSCRIVEZ-VOUS POUR PARTICIPER À MOVEMBER 2015

Tumeurs du médiastin antérieur



- **Tumeur Epithéliale Thymique (Adulte)**
  - Thymome
  - Carcinome Thymique

250 cas/an

- Kyste Thymique
- Hyperplasie Thymique

- **Lymphome** Hodgkin / non-Hodgkin

- **Tumeur Germinale**
  - Tératome
  - Seminome
  - TG non-seminomateuse

- **Pathologie de la Thyroïde**

- Pathologie de la Parathyroïde

- Kyste bronchogénique/péricardique

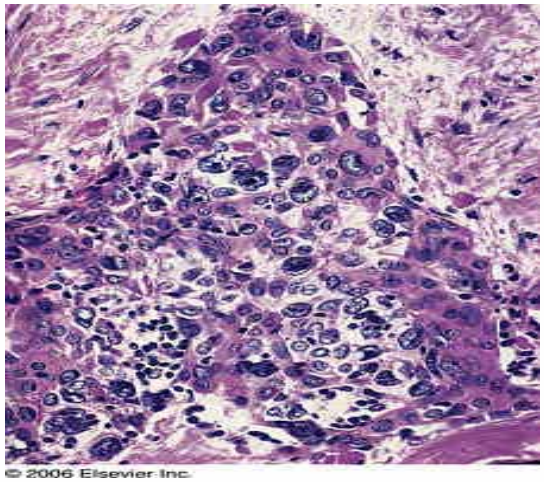
- Métastases

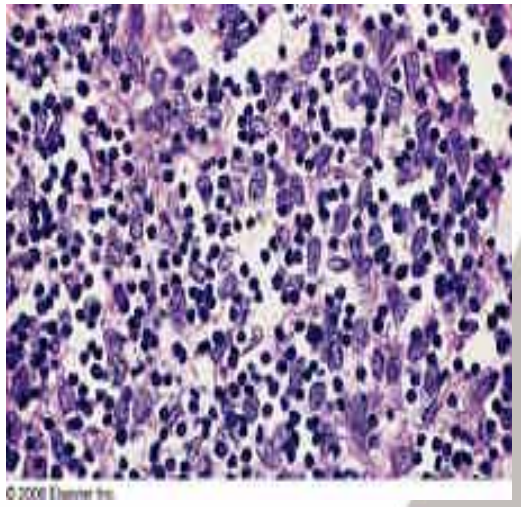
Classification O.M.S. 1999

2 composantes : épithéliales et lymphocytaires

1. Ratio lymphocytes/cellules épithéliales
2. Morphologie des cellules épithéliales
3. Atypies cellulaires – nombre de mitoses

Carcinome thymique C





Thymome B2

Révisée en 2004 et… 2014

OMS 2014

SPECIAL ARTICLE

ITMIG Consensus Statement on the Use of the WHO Histological Classification of Thymoma and Thymic Carcinoma: Refined Definitions, Histological Criteria, and Reporting

Alexander Marx, MD, Philipp Ströbel, MD,*† Sunil S. Badve, MD,‡ Lara Chalabreysse, MD,§ John K.C. Chan, MD,|| Gang Chen, MD, PhD,¶ Laurence de Leval, MD, PhD,# Frank Detterbeck, MD,** Nicolas Girard, MD, PhD,†† Jim Huang, MD,‡‡ Michael O. Kurrer, MD,§§ Libero Lauriola, MD,|||| Mirella Marino, MD,¶¶ Yoshihiro Matsuno, MD,## Thierry Jo Molina, MD, PhD,*** Kiyoshi Mukai, MD,††† Andrew G. Nicholson, MD,‡‡‡ Daisuke Nonaka, MD,§§§ Ralf Rieker, MD,|||||| Juan Rosai, MD,¶¶¶ Enrico Ruffini, MD,### and William D. Travis, MD*****

(*J Thorac Oncol.* 2014;9: 596–611)

OMS 2014

TABLE 1. Major and Minor Criteria of "Conventional" Type A Thymomas

Major criteria
Spindled and/or oval-shaped tumor cells lacking nuclear atypia (see text)
Paucity[a] or absence of immature, TdT(+) thymocytes throughout the tumor
Minor criteria
Occurrence of rosettes and/or subcapsular cysts (to be distinguished from PVS)
Presence of focal glandular formations
Pericytomatous vascular pattern
Paucity or absence of PVS contrasting with presence of abundant capillaries
Lack of Hassall's corpuscles
Complete or major encapsulation
Expression of CD20 in epithelial cells; absence of cortex-specific markers[b]

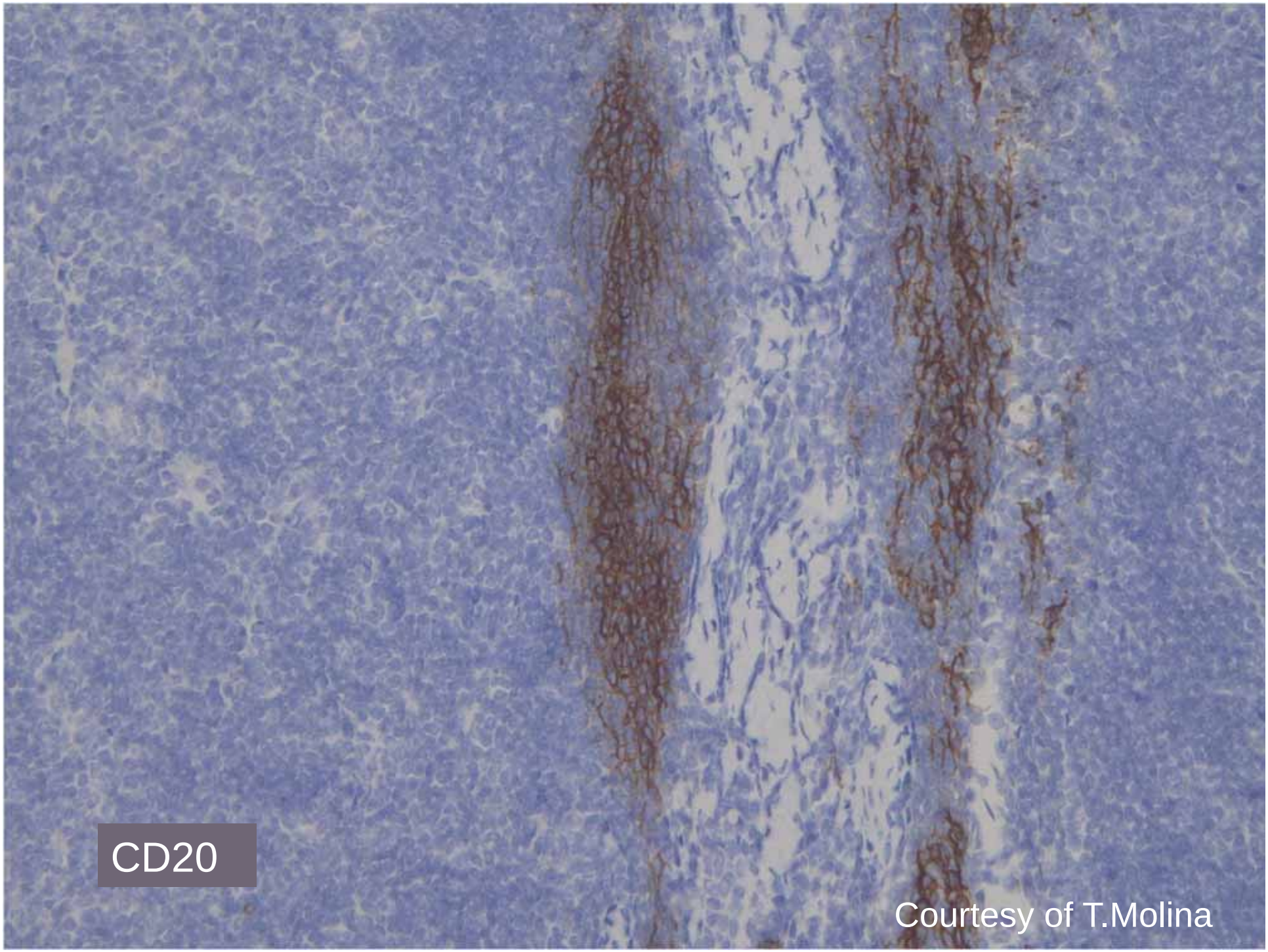
[a]Paucity implies no (immature) lymphocyte-rich regions with dense, "impossible-to-count" TdT(+) lymphocytes; or at most 10% tumor regions with moderate (see text) immature lymphocyte counts (Fig. 2).
[b]Beta5t, PRSS16, and cathepsin V by immunohistochemistry (IHC).
PVS, perivascular space.

TABLE 2. Major and Minor Histological Features Encountered in Type A and AB Thymomas

	Type A Thymoma	Type AB Thymoma
Major criteria		
Biphasic pattern at low magnification due to variable lymphocyte content	No	Common[a]
High epithelial cell content	Yes	Yes
Spindled or oval epithelial cells[b]	Yes	Yes
Paucity[c] or absence of TdT+ T cells	Yes	No
Medullary islands[d]	No	Rarely present[a,e]
Minor criteria		
Small lobular growth pattern	No	Rare
Large lobular growth pattern	Common	Common
Perivascular spaces	Rarely present	Rarely present
CD20 expression in epithelial cells	Common	Common
Cortical marker expression[f]	No	Yes

[a]These features are minor criteria in type AB thymoma.
[b]Atypia in type AB thymoma has not been addressed so far.
[c]As defined in Table 1.
[d]Detection of medullary islands is usually clear-cut on hematoxylin-eosin staining but may require immunohistochemistry (IHC), particularly when Hassall's corpuscles are missing.
[e]In lymphocyte-rich areas, usually with lack of Hassall's corpuscles.
[f]Beta5t, PRSS16, and cathepsin V (detectable by IHC in epithelial cells within lymphocyte-rich areas).

(*J Thorac Oncol.* 2014;9: 596–611)


CD20
Courtesy of T.Molina

OMS 2014

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[f]Beta5t, PRSS16, and cathepsin V (detectable by IHC in epithelial cells within lymphocyte-rich areas).

(*J Thorac Oncol.* 2014;9: 596–611)

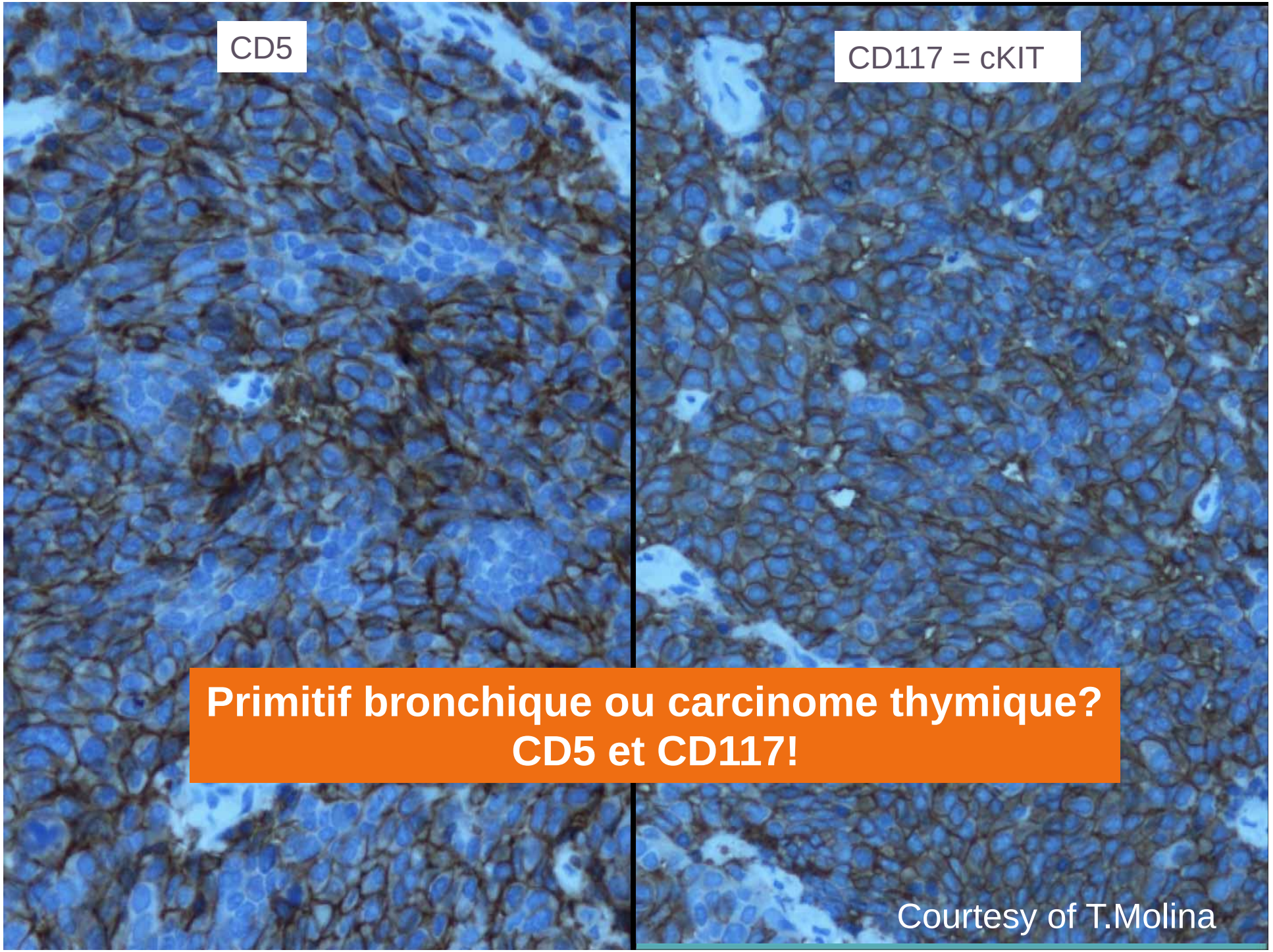
OMS 2014

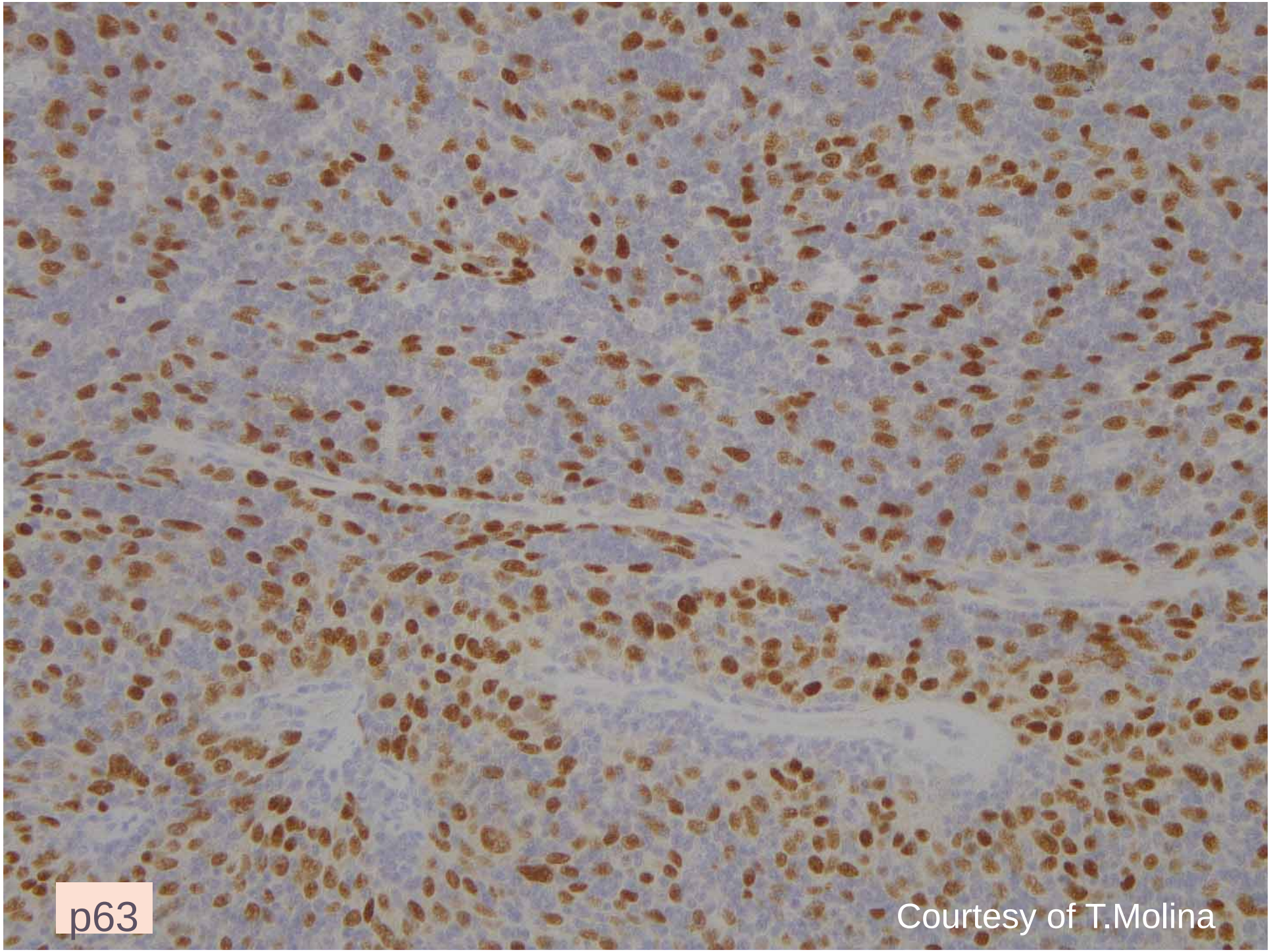
TABLE 4. Criteria for the Histological Diagnosis of TC

Major (indispensible)
Clear-cut atypia of tumor epithelial cells with the severity typical of carcinoma
Exclusion of "thymoma with atypia and/or anaplasia" and of typical or atypical carcinoids
Exclusion of metastasis to the thymus and germ cell and mesenchymal tumors with epithelial features
Minor (typical)
Infiltrative growth pattern
Small tumor cell nests within desmoplastic stroma
Absence of immature, TdT+ T cells (with rare exceptions)
Immunohistochemistry: epithelial expression of CD5, CD117; extensive expression of GLUT1, MUC1[a]
Features compatible[b] with the diagnosis of TC
Invasion with pushing borders
Occurrence of perivascular spaces
Occurrence of "Hassall-like" epidermoid whorls and/or of myoid cells
Occurrence of (usually rare) immature, TdT+ T cells

[a]CD5, CD117, GLUT1, and MUC1 are expressed by many nonthymic cancers.
[b]Although most of these features are "organotypic," that is, characteristic of thymoma, their presence does not exclude a diagnosis of TC if major diagnostic criteria of TC are fulfilled.
TC, thymic carcinoma.

(*J Thorac Oncol.* 2014;9: 596–611)


CD5
CD117 = cKIT
Primitif bronchique ou carcinome thymique?
CD5 et CD117!
Courtesy of T.Molina

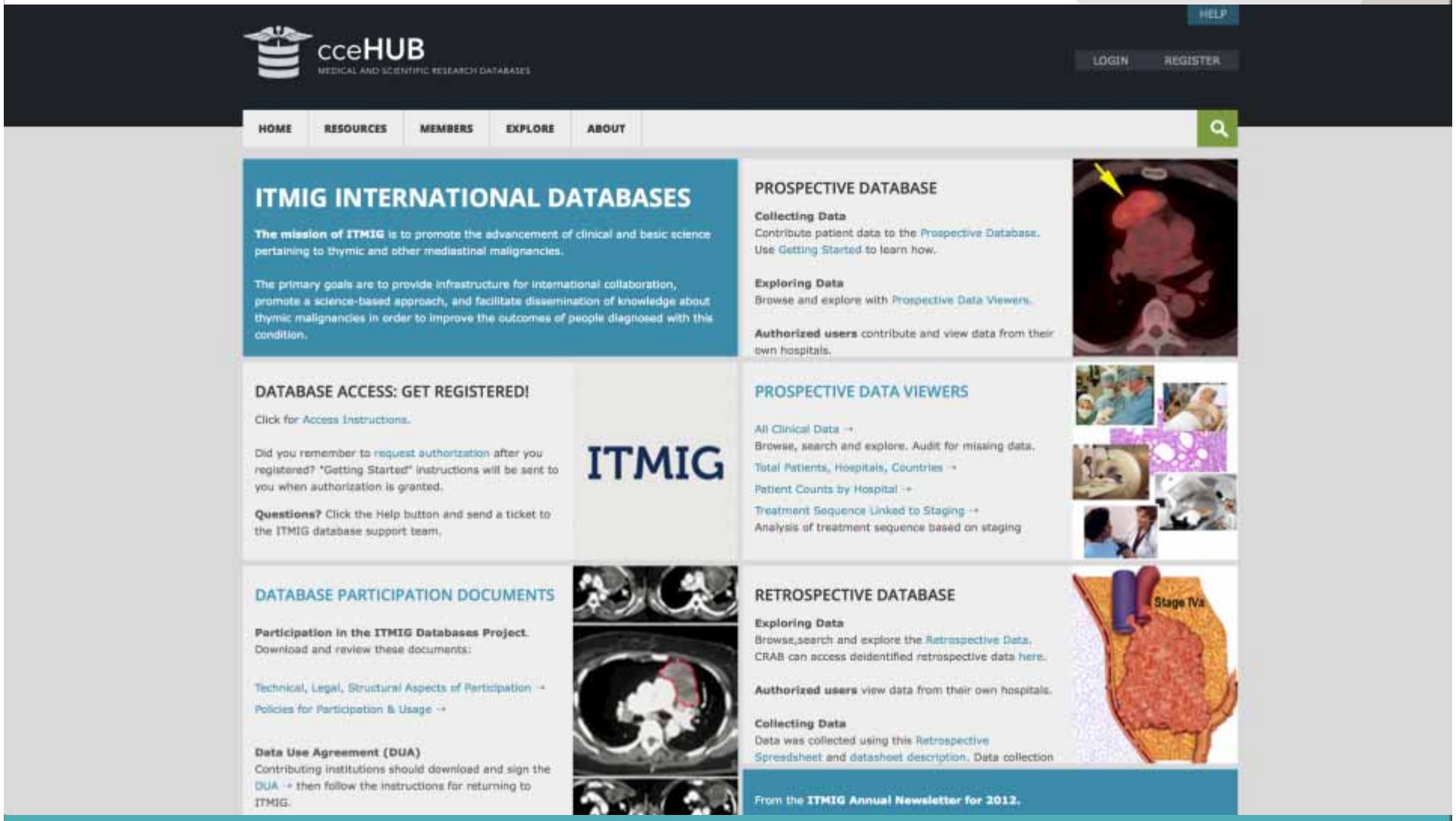

p63
Courtesy of T.Molina

Classification de Masaoka-Koga (revue par ITMIG)

Stade I	**Tumeur encapsulée** **sans envahissement de la capsule ou envahissement micro partiel (sans effraction)**
Stade II	**IIA : atteinte - de la capsule (totale)** **IIB : atteinte - de la graisse médiastinale** **- Adhérences macroscopiques, sans invasion, à la plèvre médiastinale ou au péricarde**
Stade III	**Atteinte des organes du voisinage** ***(plèvre médiastine, péricarde, n.phrénique/vague, gros vaisseaux, poumon)***
Stade IV_A	**Implants pleuraux / péricardiques**
Stade IV_B	**Dissémination lymphatique / hématogène *(métastases)***

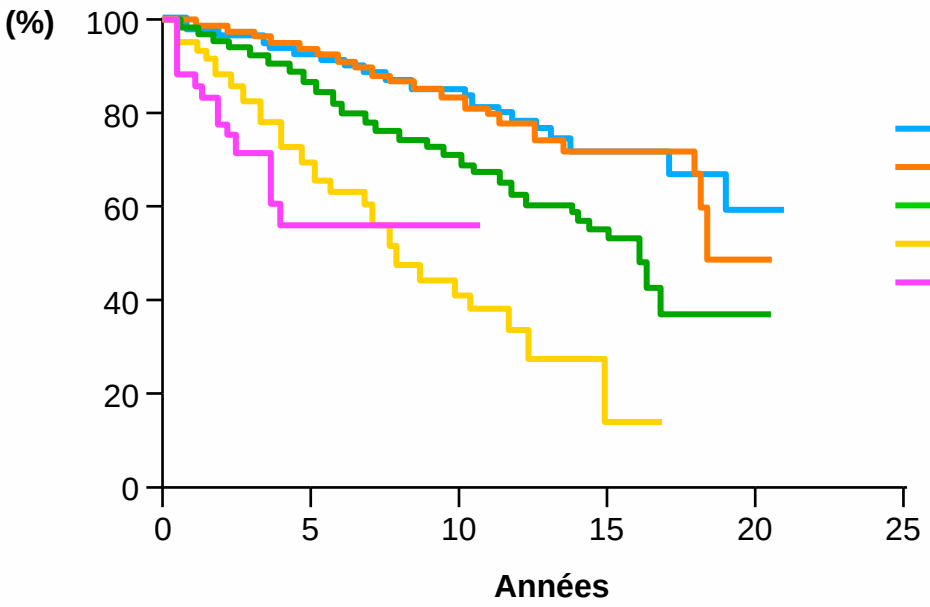
POST CHIRURGICALE

ITMIG DATABASE



Prognostic Value Of Masaoka-Koga staging

- **ITMIG database**

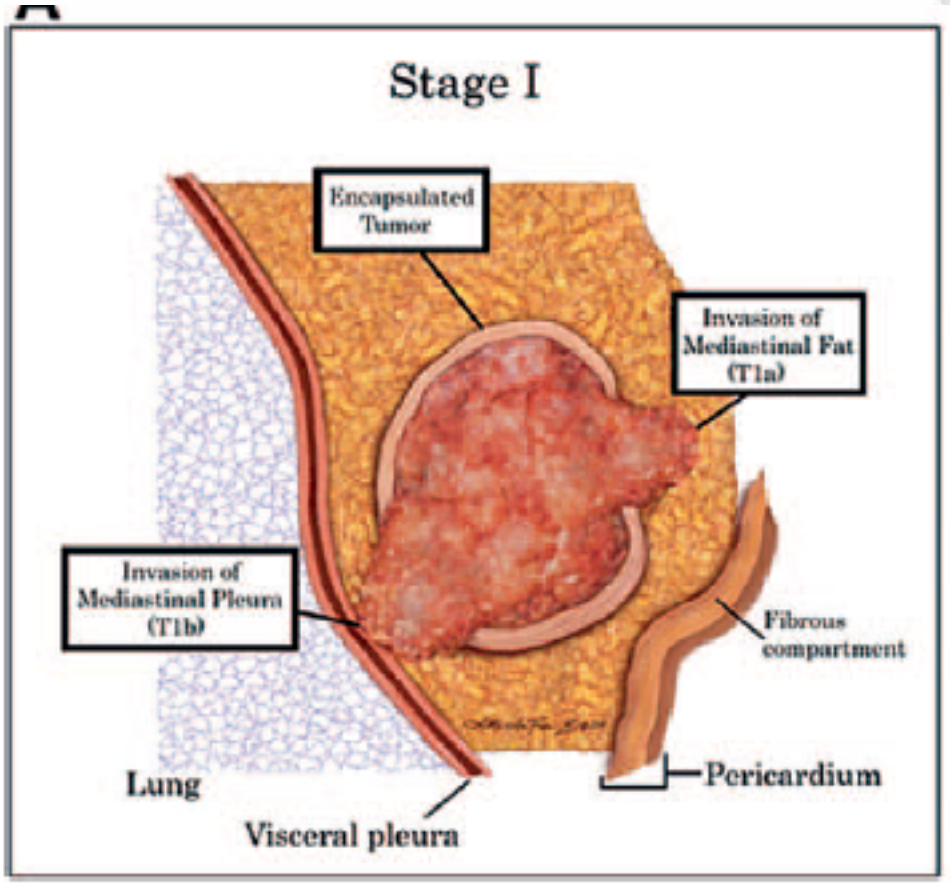


	Events/n	10 yrs OS, % (IC_{95})
Stage I	30/1 292	84 (81-86)
Stage II	78/1 878	83 (79-87)
Stage III	135/629	70 (64-75)
Stage IVA	40/106	42 (26-58)
Stage IVB	14/40	53 (32-73)

➜ **Same survival for stage I and II**

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

The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: Proposal for an Evidence-Based Stage Classification System for the Forthcoming (8th) Edition of the TNM Classification of Malignant Tumors



Masaoka-Koga : I, IIA, IIB, III

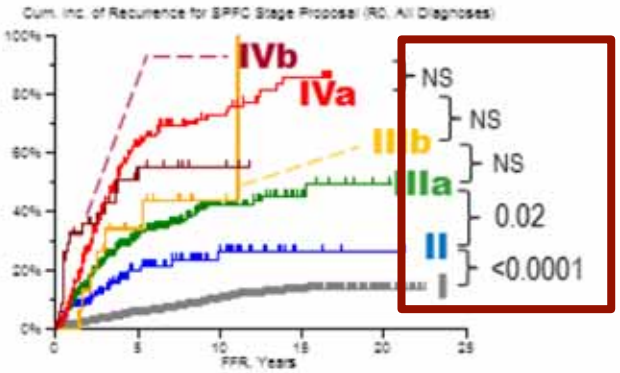
Detterbeck et al. J Thorac Oncol 2014

The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: Proposal for an Evidence-Based Stage Classification System for the Forthcoming (8th) Edition of the TNM Classification of Malignant Tumors

Frank C. Detterbeck, MD, Kelly Stratton, MS,† Dorothy Giroux, MS,† Hisao Asamura, MD,‡ John Crowley, PhD,† Conrad Falkson, MBChB,§, Pier Luigi Filosso, MD,‖, Aletta A. Frazier, MD,‖‖‖*

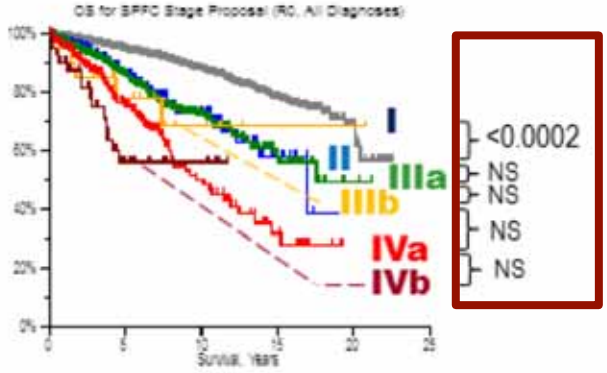
Figure e1: Outcomes of all Patients by Proposed Stage Groups

Recurrence, R0



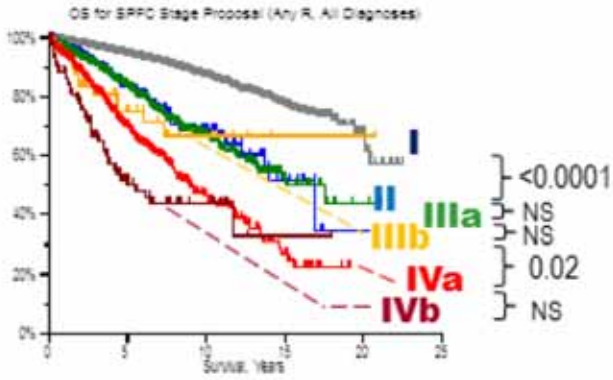
Stage	Events/N	5-Yr Estimate (CI)	10-Yr Estimate (CI)
I	192/3659	5.1% (5.1, 5.2)	9.7% (9.5, 9.9)
II	22/124	20% (17.6, 22.8)	27% (22.1, 31.1)
IIIa	142/455	32% (29.6, 34.4)	42% (37.0, 46.9)
IIIb	7/18	34% (10.6, 57.4)	42% (20.0, 58.9)
IVa	119/201	62% (47.4, 77.3)	73% (43.3, 100)
IVb	17/35	51% (23.5, 78.0)	55% (27.8, 82.4)

Overall Survival, R0



Stage	Events/N	5-Yr Estimate (CI)	10-Yr Estimate (CI)
I	363/5134	94% (93.6, 95.2)	88% (86.2, 89.2)
II	30/187	87% (80.3, 93.3)	73% (63.5, 83.1)
IIIa	100/508	86% (82.6, 89.2)	73% (67.3, 77.7)
IIIb	8/23	78% (58.7, 97.6)	68% (43.6, 93.1)
IVa	75/251	75% (68.5, 81.7)	50% (39.9, 60.2)
IVb	14/43	56% (38, 74)	56% (38, 74)

Overall Survival, any R



Stage	Events/N	5-Yr Estimate (CI)	10-Yr Estimate (CI)
I	405/5487	94% (93.5, 95)	87% (86.5, 88.5)
II	43/239	84% (77.6, 90)	69% (59.7, 78.1)
IIIa	163/778	82% (80.3, 86.5)	67% (62.4, 72.2)
IIIb	12/37	75% (61.8, 88.1)	67% (50.5, 82.6)
IVa	209/654	70% (65.7, 74.4)	46% (40.1, 52.6)
IVb	43/99	52% (40.2, 63.6)	44% (31.5, 55.9)

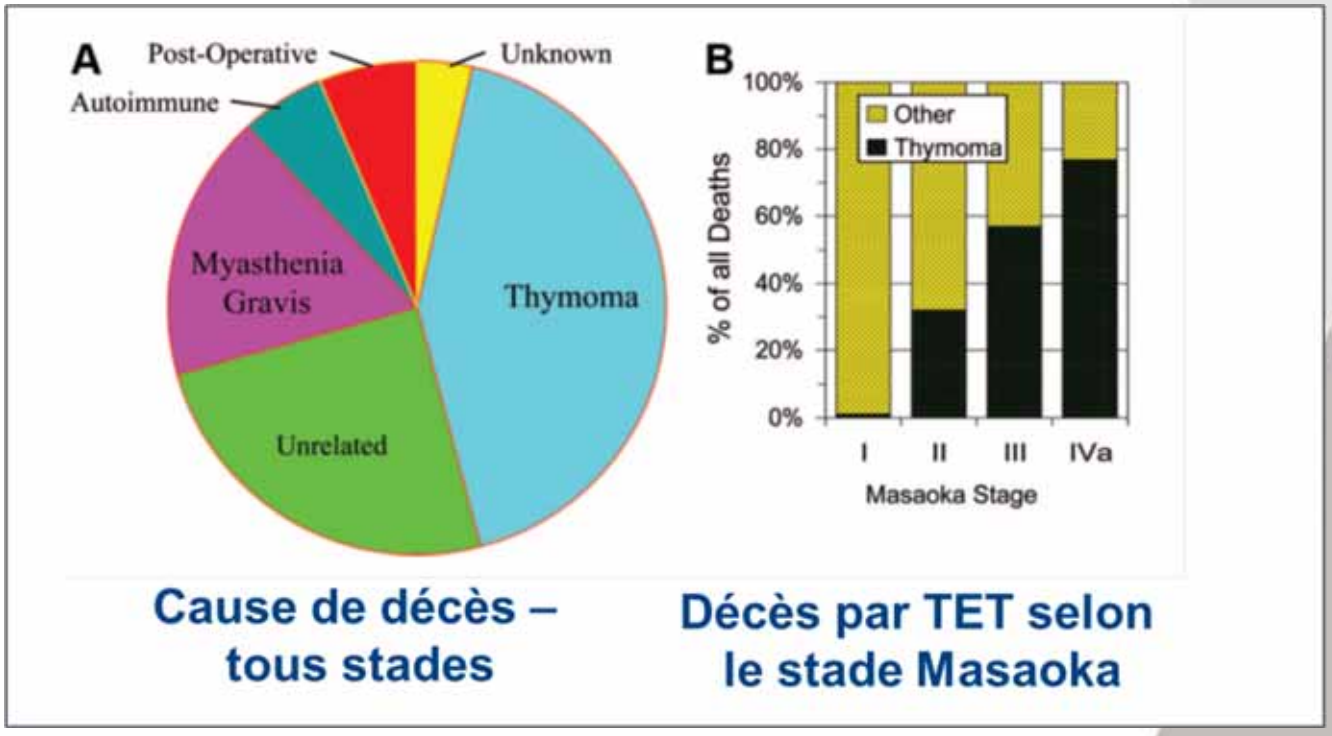
(*J Thorac Oncol.* 2014;9: S65–S72

Maladies auto-immunes et TET

- **Myasthénie (30 à 60 %)**
  - Valeur pronostique controversée
  - En fait, permet un diagnostic précoce de TET
- **Autres**
  - Erythroblastopénie
  - Hypo-gamma-globulinémie
  - Pancytopénie
  - Anémie hémolytique
  - Thyroïdite
  - Lupus érythémateux disséminé
  - Syndrôme de Sjörgren
  - Dermatomyosite

Surveillance et cause de décès

- 2,5 % mortalité opératoire



Cause de décès – tous stades

Décès par TET selon le stade Masaoka

- **Récidive tardive possible : 20 % après 10 ans**

Hunag, JTO 2011

Bilan pré-thérapeutique

- **Imagerie**
  - Tomodensitométrie thoracique avec coupes abdominales
  - TEP FDG
  - +/- IRM thoracique
- **Epreuves fonctionnelles respiratoires**
- **Recherche d'un syndrome auto-immun**
  - Hémogramme avec taux de réticulocytes
  - Electrophorèse des protéines sériques
  - Anticorps anti-nucléaires
  - Anticorps anti-récepteurs à l'acétylcholine
  - Dosage de la TSH
- **Chez l'homme!**
  - **Alpha-foetoproteine et HCG**

Biopsie ?

- **Encapsulée : résection d'emblée**

- **Non encapsulée : biopsie de taille suffisante**
  - **Eviter un ensemencement pleural**
  - **Ponction-biopsie transpariétale (*Tru-Cut*)**
  - **Médiastinotomie antérieure**
  - **Médiastinoscopie non recommandée**

Chirurgie

- Exérèse complète monobloc
- Thymomectomie et thymectomie + graisse périthymique
- Ablation des ganglions suspects
- Sternotomie médiane est la voie d'abord élective
- Option : La chirurgie vidéo-assistée pour des tumeurs de petit volume et paraissant bien encapsulées.
- Option pour les stades IVA : chimiothérapie hyperthermie intra-pleurale
- Exérèses itératives en cas de récidives sont possibles

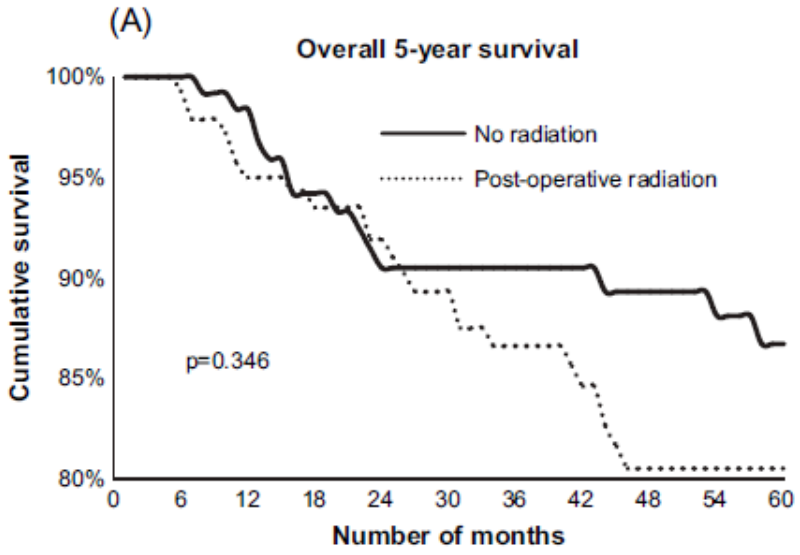
« Marginalement résécable? »

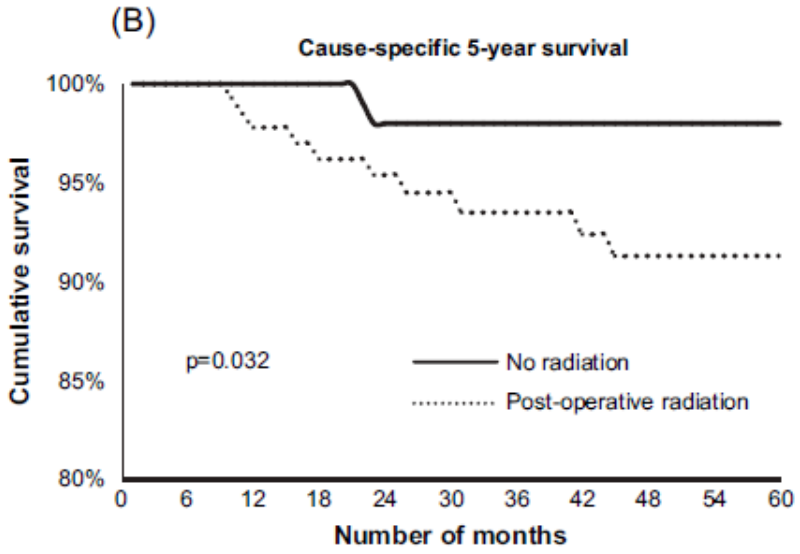
- **Stage II-IVB (TNM IASLC-ITMIG 2015) defined by:**
  - Thymic carcinoma histology
  - Phrenic nerve palsy
  - Superior vena cava syndrome
  - Occlusion of one of the innominate veins at imaging studies
- **Tumour size >8 cm**
- **Size ranging from 5 to 8 cm with one or more of the following criteria:**
  - Location at the upper aspect of the thymic area
  - Lobulated tumor contour
  - > 50% abutment of the circumference of an adjacent vessel
  - Thoracic lymphadenopathy
  - Adjacent lung changes or pleural nodularity
  - Pulmonary nodule(s)
  - Tumor invading left lung as far as hilum
  - Pericardial effusion

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%

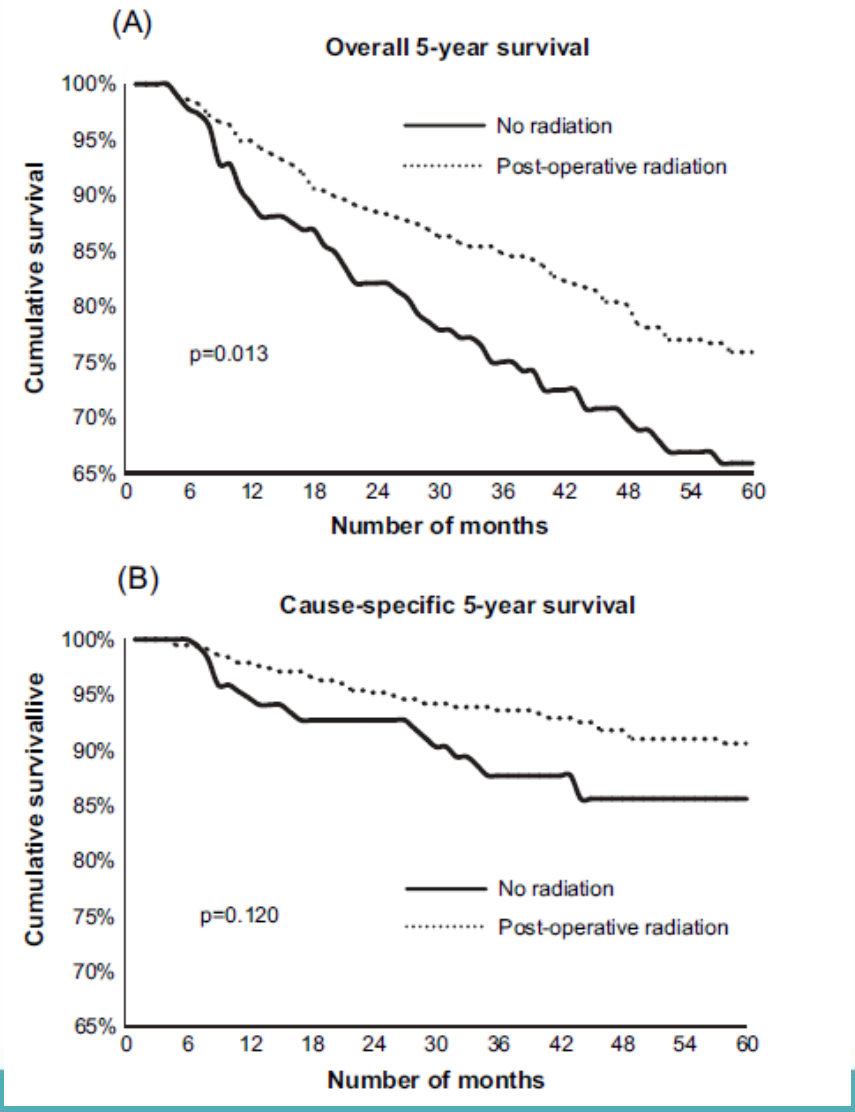
Masaoka stade I (~A localisés)





- 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**

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**

Radiothérapie post-opératoire

- **Stades I TNM 2015**
  - Stade I Masaoka-Koga-ITMIG : pas de RT post-opératoire
  - Stade IIa Masaoka-Koga-ITMIG
    - types A-B2 : pas de radiothérapie post-opératoire
    - type B3 : discuter une radiothérapie post-opératoire
  - Stade IIb Masaoka-Koga-ITMIG
    - types A-B1 : pas de radiothérapie post-opératoire
    - types B2-B3 : discuter une radiothérapie post-opératoire
- **Stades II, IIIA, IIIB TNM 2015 (stades III Masaoka-Koga-ITMIG): RT post-opératoire**
- **Résection R1 : RT post-opératoire**
- **Carcinome thymique : RT post-opératoire**

Radiothérapie post-opératoire

- **Stades I TNM 2015**
  - Stade I Masaoka-Koga-ITMIG : pas de RT post-opératoire
  - Stade IIa Masaoka-Koga-ITMIG
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    - type B3 : discuter une radiothérapie post-opératoire
  - Stade IIb Masaoka-Koga-ITMIG
    - types A-B1 : pas de radiothérapie post-opératoire
    - types B2-B3 : discuter une radiothérapie post-opératoire
- **Stades II, IIIA, IIIB TNM 2015 (stades III Masaoka-Koga-ITMIG): RT post-opératoire**
- **Résection R1 : RT post-opératoire**
- **Carcinome thymique : RT post-opératoire**

Radiothérapie post-opératoire

RECOMMANDATIONS: Dose

- **Résection complète : 50 à 56 Gy**
- **Résection incomplète :**
  - Planed Target Volume + organes critiques
  - 50 – 56 Gy + surimpression 60 – 66 Gy
  - 66 Gy en cas de simple biopsie

RECOMMANDATIONS: Modalités

- **9 à 10 Gy hebdomadaires en 5 séances**

Traitements d'induction

Protocole	Type d'étude	N (% stade III, % stade IV)	Schéma	Chirurgien	RT	Taux de réponse Objective à la chimiothérapie	Survie globale
CAP	Phase II	23 (96%, 4%)	Cisplatine 50 mg/m² J1 Doxorubicine 50 mg/m² J1 Cyclophosphamide 500 mg/m² J1 J1=J21 + RT si non progressif	4	21	69.6%	52.5% à 5 ans
CAP	Phase II	22 (50%, 50%)	Cisplatine 30 mg/m² J1 à J3 Doxorubicine 20 mg/m² en continu, J1 à J3 Cyclophosphamide 500 mg/m² J1 J1=J21-28	21	22	80%	95% à 5 ans

Loehrer PJ Sr, J. Clin. Oncol. 1997 sept;15(9):3093-9.
Kim ES, Lung Cancer. 2004 juin;44(3):369-79.

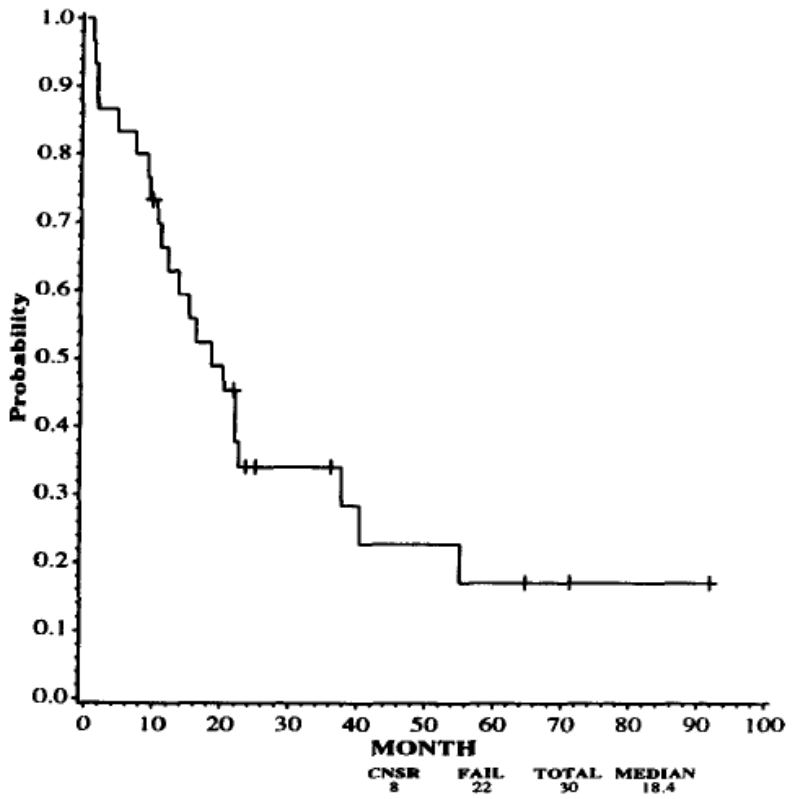
Traitements d'induction

Protocole	Type d'étude	N (% stade III, % stade IV)	Schéma	Chirurgien	RTn	Taux de réponse Objective à la chimiothérapie	Survie globale
CODE	Phase III	21 (100%, 0%)	Cisplatine 25 mg/m²/ semaine hebdomadaire Vincristine 1 mg/m²/15 jours Doxorubicine 40 mg/ m²/15 jours Etoposide 80 mg/m² J1 à J3, tous les 15 jours 9 semaines de traitement	13	12	62%	91% à 5 ans
ADOC	Phase II	16 (62.5%, 37.5%)	Doxorubicine 40 mg/m² J1 Cisplatine 50 mg/m² J1 Vincristine 0.6 mg/m² J2 Cyclophosphamide 700 mg/m² J4 J1= J21	9	13	81.2%	SG médiane 47.5 mois

Kunitoh H, Br. J. Cancer. 2010 juin 29;103(1):6-11.
Berruti A, Br. J. Cancer. 1999 nov;81(5):841-5.

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

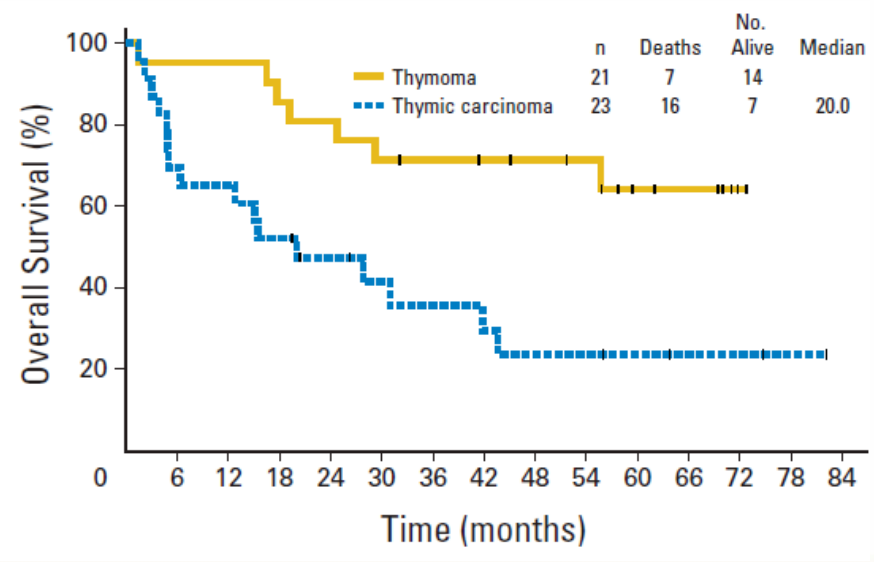
Table 1. WHO Classification of Patients With Thymic Neoplasms

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

Stades métastatiques

	Phase	N (%st III, % st IV)	Schéma	Réponses	Survie globale
VIP	Ph II	16 (50%, 50%)	Étoposide 100 mg/m² J1 à J3 Ifosfamide 1500 mg/m² J1 à J3 Cisplatine 30 mg/m² J1 à 3 J1=J21	TR : 25% (75% SD)	SG 78,1% à 2 a 58,6% à 3 a
VIP	Ph II	28 (21%, 79%)	étoposide 75 mg/m² J1 à J4 Ifosfamide 1200 mg/m² J1 à J4 Cisplatine 20 mg/m² J1 à J4 J1=J21	TR 32%	SG méd 31,6 m SG 70% à 2 a
CAP	Ph II	30	Cisplatine 50 mg/m² J1 Doxorubicine 50 mg/m² J1 Cyclophosphamide 500 mg/m² J1 J1=J21	TR 51%	SG méd : 37,7 mo SG 64 ,5% à 2 a
PE	Ph II	16	Cisplatine 60 mg/m² J1 Etoposide 120 mg/m² J1 à J3 J1=J21	TR 56%	SG médiane 4,3 a SG 69% à 3 a
Carbo/ taxol	Ph II	46 (16%, 84%)	Carboplatine AUC 6 J1 Pacltiaxel 225 mg/m² J1 J1=J21	TR 22% (C) TR 43%	SG méd 20 m (C) SG méd NA

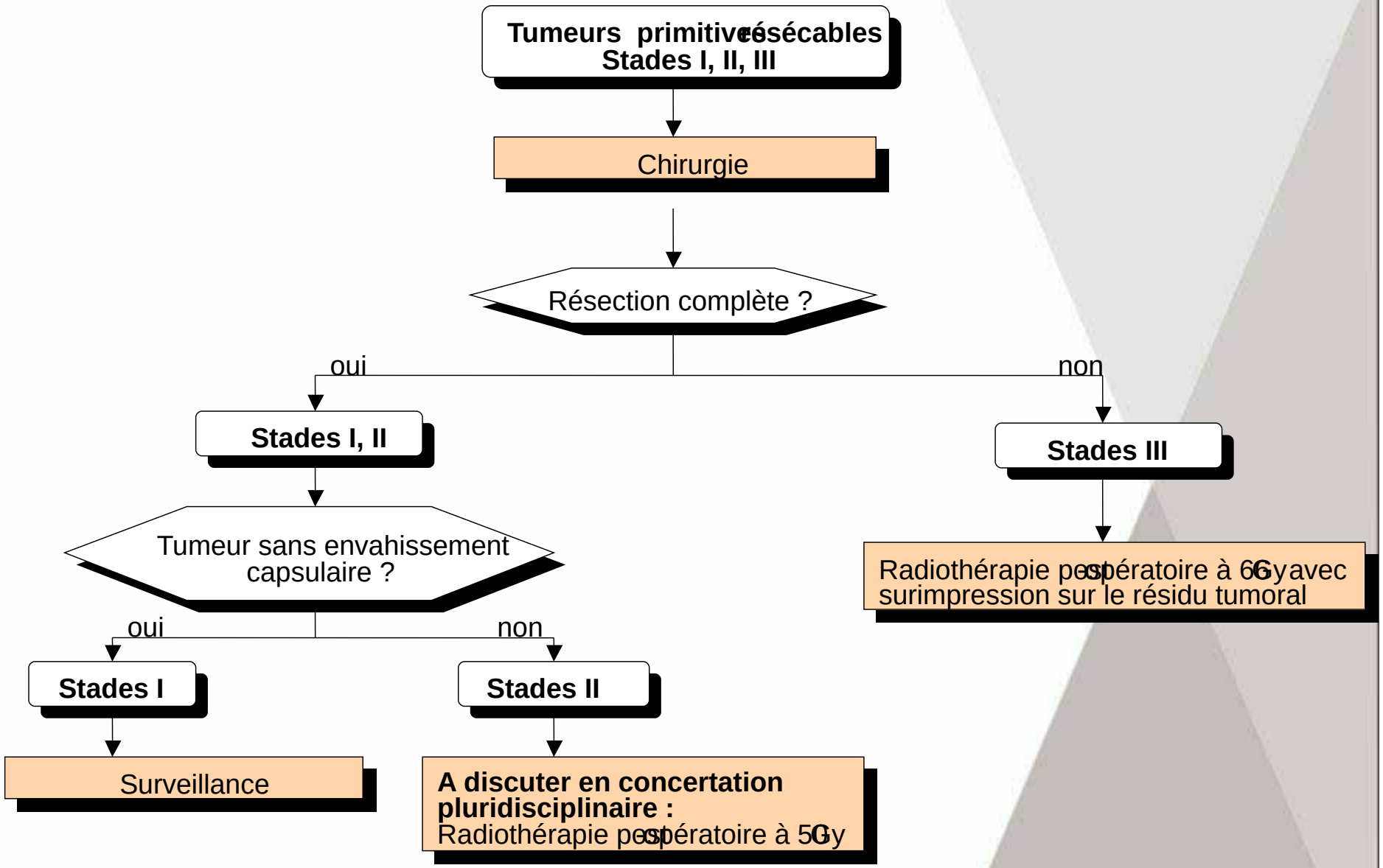
Grassin F, J Thorac Oncol. 2010 juin;5(6):893-7. - Loehrer PJ Sr, Cancer. 2001 juin 1;91(11):2010-5.
Loehrer PJ Sr, J. Clin. Oncol. 1994 juin;12(6):1164-8. - Giaccone G, J. Clin. Oncol. 1996 mars;14(3):814-20.
Lemma GL, J. Clin. Oncol. 2011 mai 20;29(15):2060-5.

Stades métastatiques

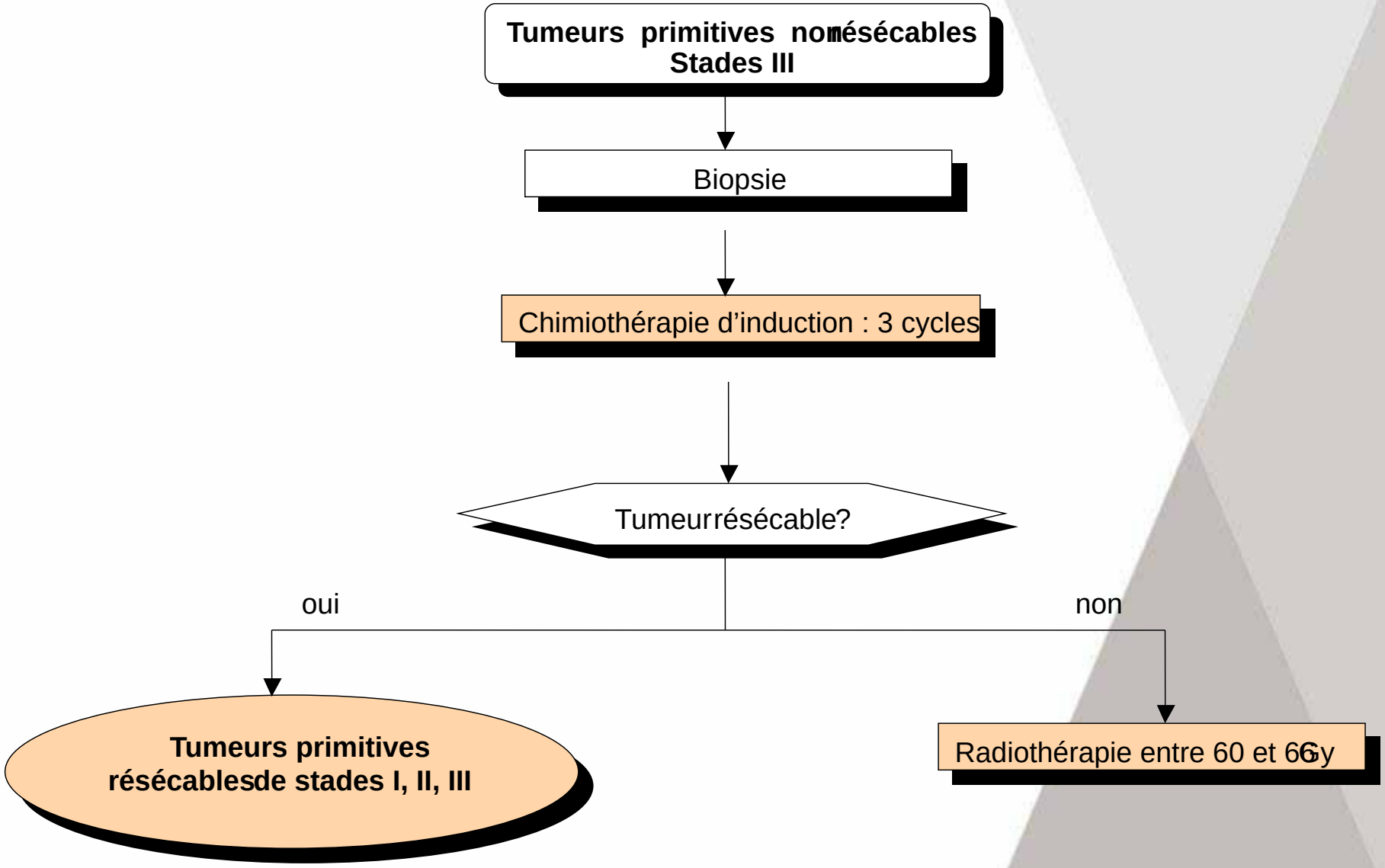
	Phase	N (% st III, % st IV)	Schéma	Réponses	Survie globale
Monothérapies					
PEM	Phase II	27 (0%, 100.5%)	Pemetrexed 500mg/m² J1= J21	TR : 17%	SSP med 11 mois SG non atteinte
CDDP	Phase II	21 (0,100%)	Cisplatine 50 mg/m² J1=J21	TR : 10% SD : 40%	SG 39% à 2 ans SG méd 19 mois
Oct	Phase II	38 (5%, 95%)	Octreotide 0.5 mg x3/j En continu, 1 a max Ajout prednisone 0,6mg/kg/j si SD à 12 sem	TR : 31.6%	SG 75,7% à 2 ans

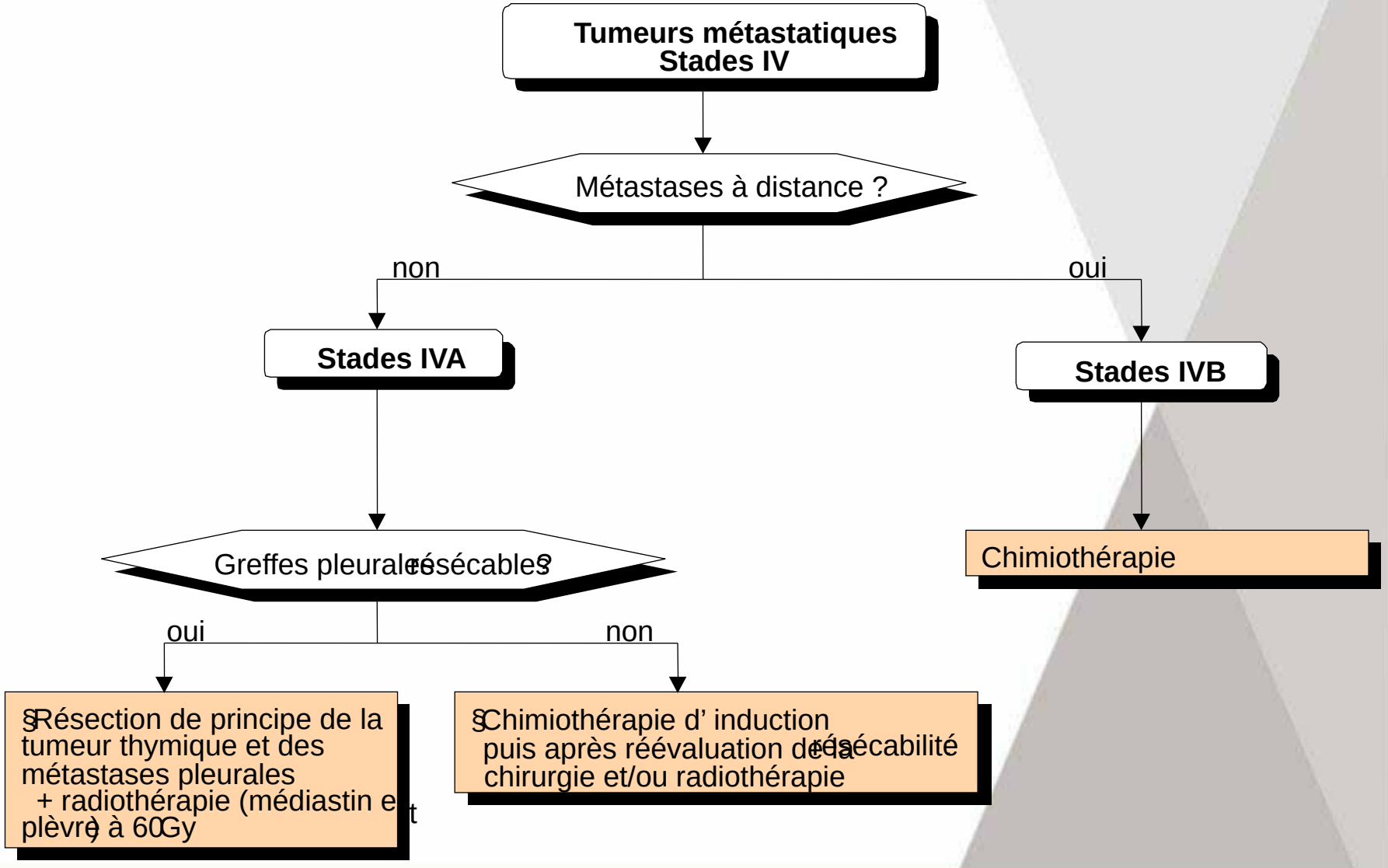
Mais aussi celltop oral, gemcitabine/xeloda…

Loehrer PJ, ASCO Meeting Abstracts. 2006 juin 16;24(18_suppl):7079.
Bonomi PD, Am. J. Clin. Oncol. 1993 août;16(4):342-5.
Loehrer PJ Sr, J. Clin. Oncol. 2004 janv 15;22(2):293-9.



PAS DE CT ADJUVANTE!!


Tumeurs primitives non résécables
Stades III
Biopsie
Chimiothérapie d'induction : 3 cycles
Tumeur résécable?
oui
non
Tumeurs primitives
résécables de stades I, II, III
Radiothérapie entre 60 et 66 Gy


Tumeurs métastatiques
Stades IV
Métastases à distance ?
non
oui
Stades IVA
Stades IVB
Greffes pleurales résécables ?
Chimiothérapie
oui
non
Résection de principe de la tumeur thymique et des métastases pleurales
+ radiothérapie (médiastin et plèvre) à 60 Gy
Chimiothérapie d' induction
puis après réévaluation de la résécabilité
chirurgie et/ou radiothérapie

Apport de la biologie et des nouvelles thérapies ?

EVEROLIMUS: phase II study

N=55, Everolimus 10 mg/d
ORR = 22%

EFFICACY

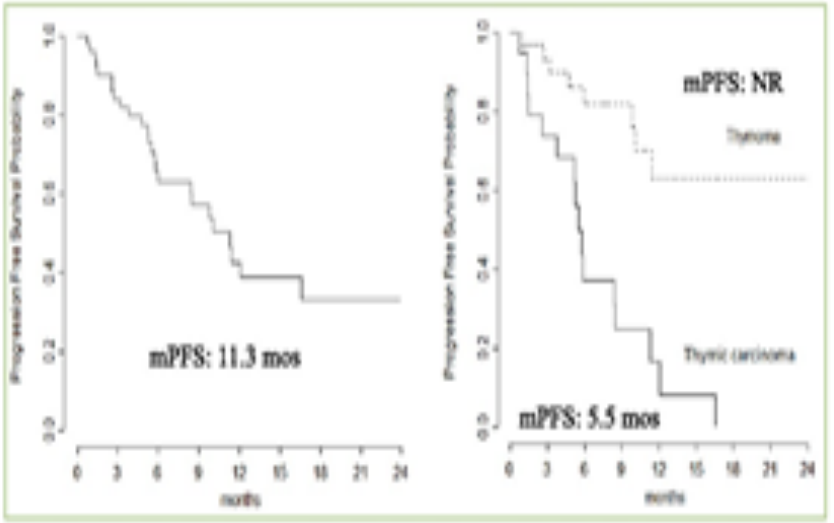
First 41 pts	N	%
CR	1	2.4
PR	8	19.5
SD	29	70.7
PD	3	7.3

DCR: 92.7% (N=38)*
Thymomas (26): 100%
Thym. Carc. (11): 78.5%
*1 pt without histotype

All 50 treated pts	N	%
CR	1	2.0
PR	10	20.0
SD	32	64.0
PD	4	8.0
Missing	3	6.0

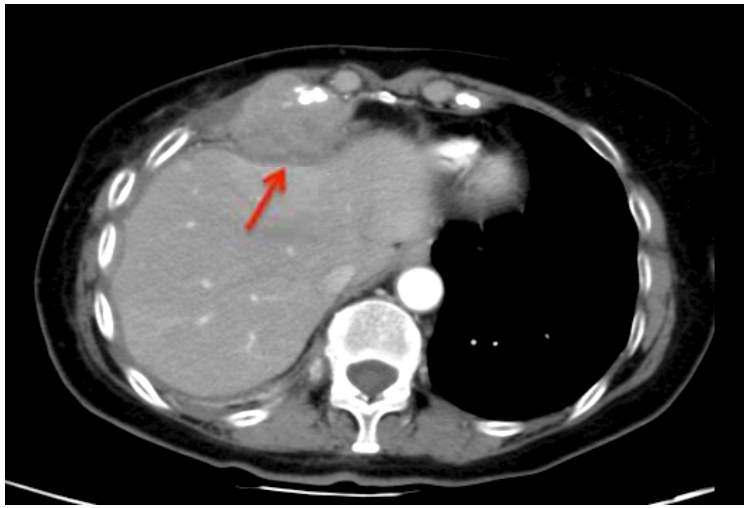
DCR: 86.0% (N= 43)*
Thymomas (28): 93.3%
Thym. Carc. (14): 73.7%
*1 pt without histotype

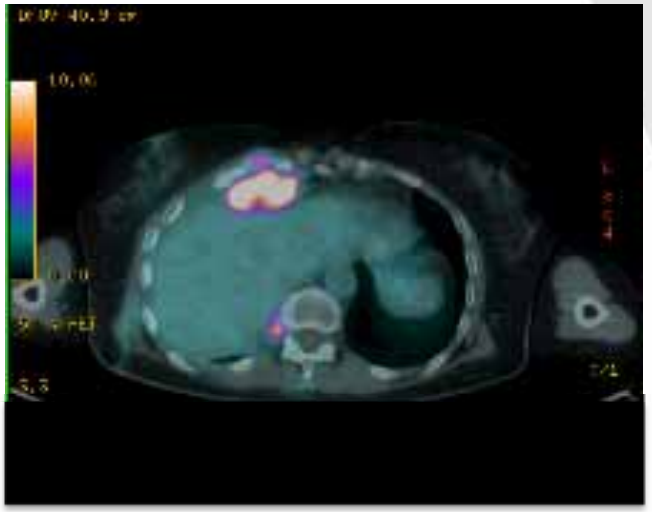
PROGRESSION FREE SURVIVAL



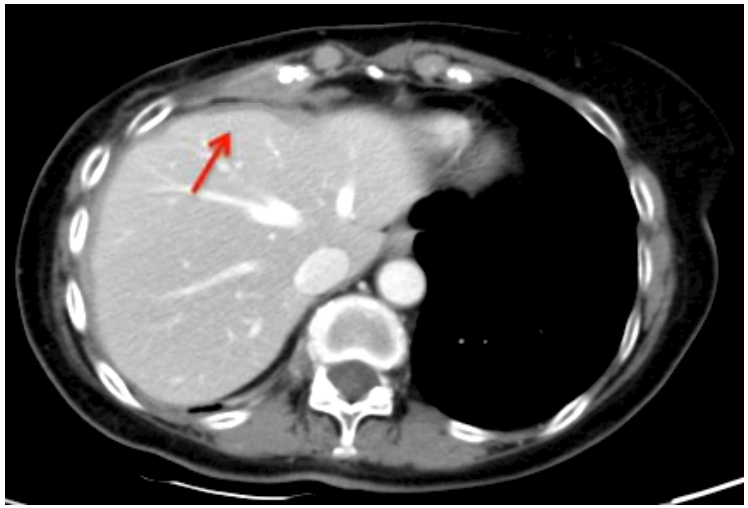
Median Follow up (mos): 12.4, range: 0.7-36.9
1 year PFS , ALL: 42.7%, Thymoma: 70.2%, thymic carcinoma: 16.6%

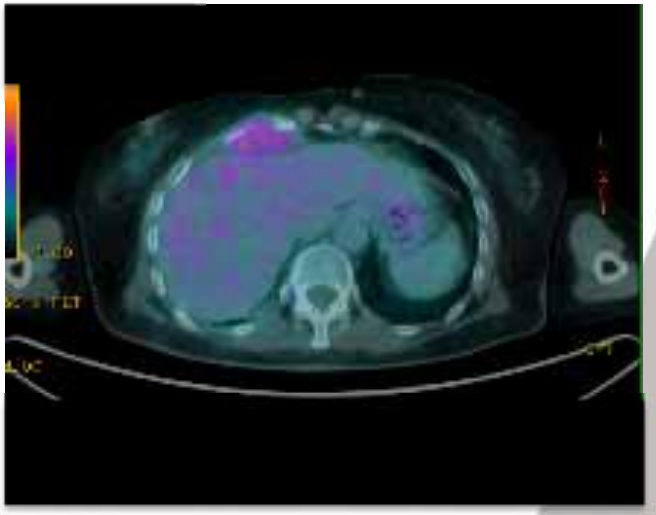
Response to Everolimus





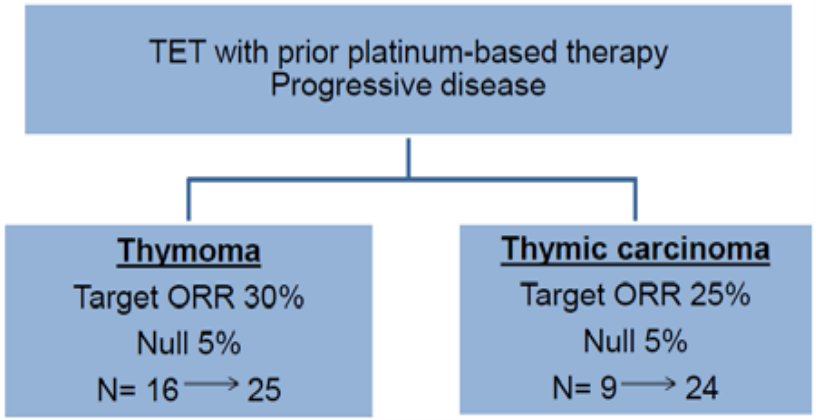
BASELINE





AFTER 6 WKS

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)

SUNITINIB : phase II study

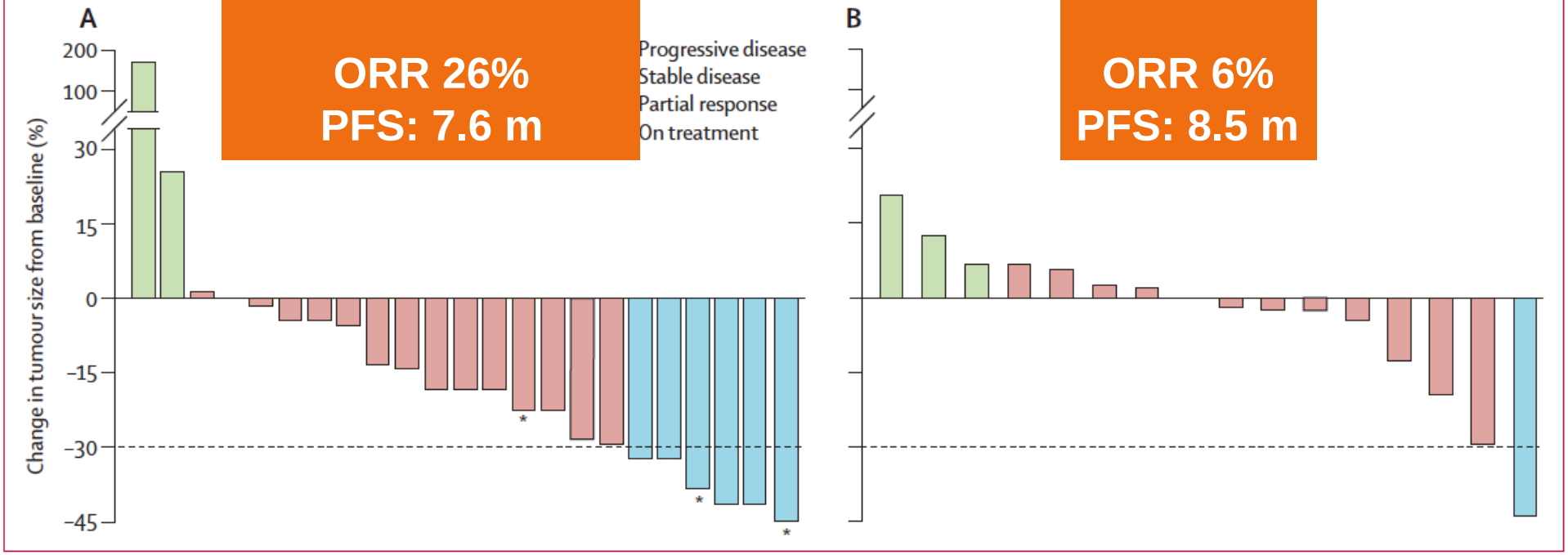
Sunitinib 50 mg/d
4 weeks out of 6

Thymic carcinoma
N=23

ORR 26%
PFS: 7.6 m

Thymoma
N=16

ORR 6%
PFS: 8.5 m

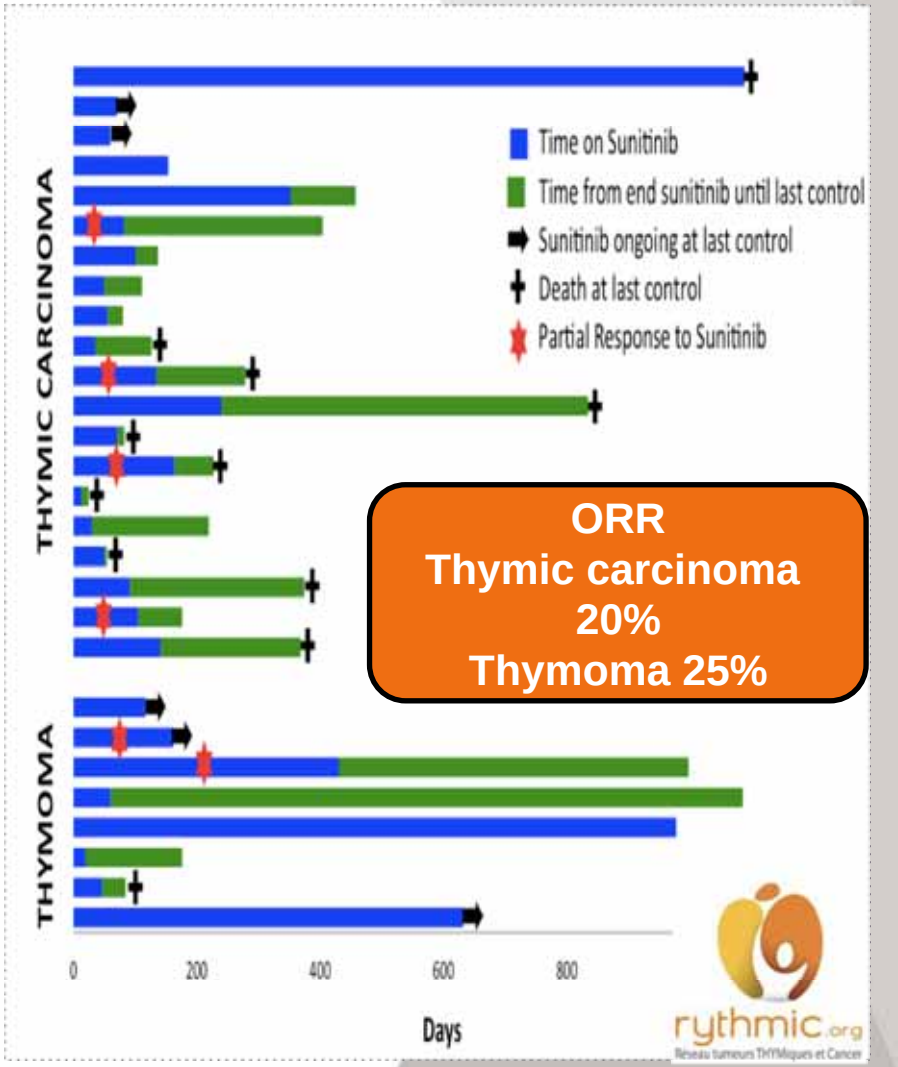


Thomas, Lancet Oncol 2015

SUNITINIB : RYTHMIC data

Characteristics	Population (N=28)	
	Thymoma (N=8)	Thymic Carcinoma (n=20)
Median age (years)	40.1 (24-61)	53.9 (17-75)
Sex:		
Male / Female	5 (68%) / 3 (32%)	14 (70%) / 6 (30%)
Masaoka Stage:		
III / IV	3 (32%) / 5 (68%)	3 (15%) / 17 (85%)
Thymoma*:		
B1 / B2 / B3 / UK	1 /3 / 2 / 2	NA
Sunitinib treatment Line:		
1^{st} / 2^{nd} / 3^{rd} / 4^{th} / ≥ 5^{th}	1 / 2 /2 / 1 / 2	1 /2 / 5 / 6 / 6

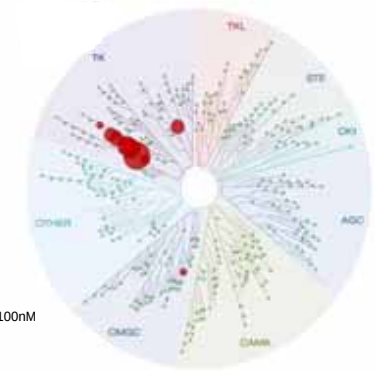
UK: unknown. *2 T patients and 1 TC patient had auto-immune disorders



Median follow-up 4.7 months

Lucitanib Phase I

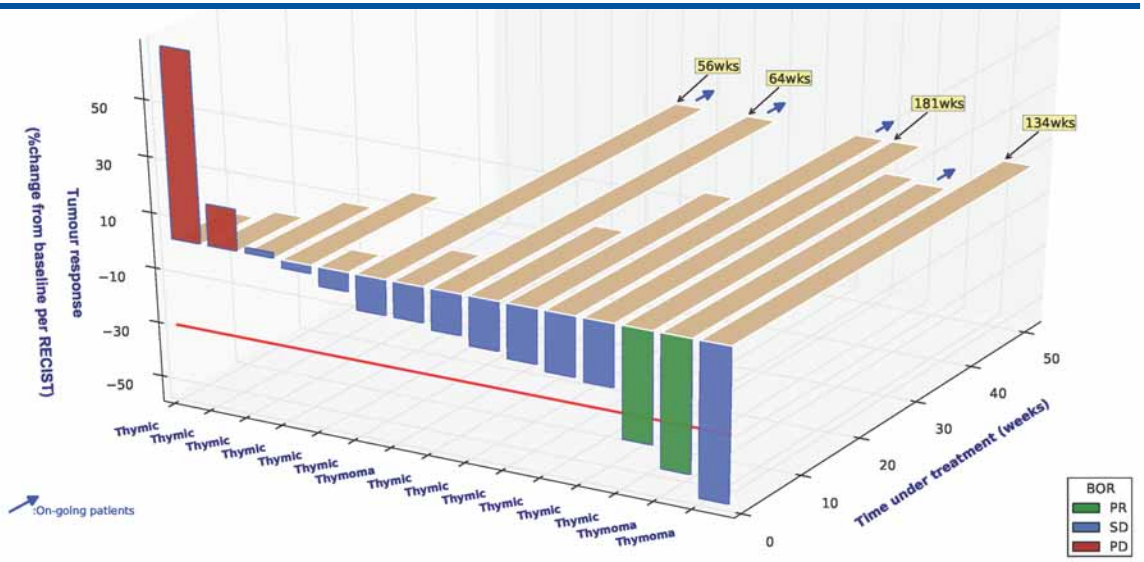
Lucitanib kinase profile binding



456 Assays tested
17 interaction mapped at 100nM
S(35) = 0,03

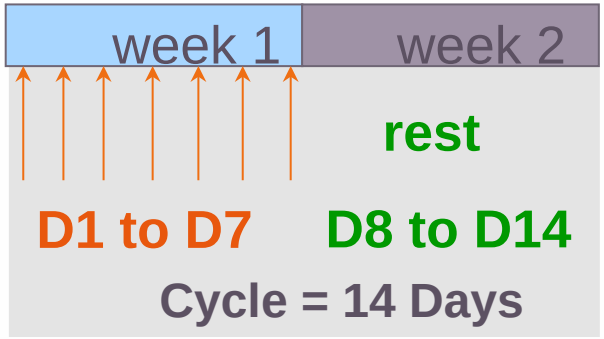
Kinase	Kd (nM)
FGFR1	21
FGFR2	41
FGFR3	51
VEGFR1	1.0
VEGFR2	1.1
VEGFR3	7.1
PDGFRα	0.4
PDGFRß	0.3
CSF1R	0.9
RET	5.0
RET M918T	4.6
KIT	0.3

Thymoma B-type N=3	Thymic Carcinoma N=12	All patients N=15



ORR 13%
PFS 36 weeks

Phase II study - Milciclib

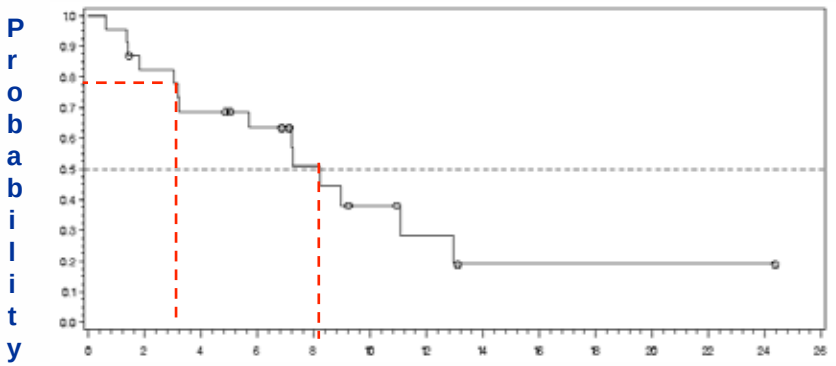


Patients received 150 milciclib orally once daily for 7 days on, 7 days off, in a 2-week cycle

Patients' baseline characteritics (n=49)	
Characteristics	**Value**
Median age, years (range)	55 (21-80)
ECOG PS 0 -1*	22 / 13
Tumor types (WHO classification)* B3 - Well Differentiated Thymic Carcinoma C - Thymic carcinoma	 11 33
Prior therapies* None Systemic only Surgery + Systemic Systemic + Radiotherapy Surgery + Systemic + Radiotherapy	 4 6 9 2 19

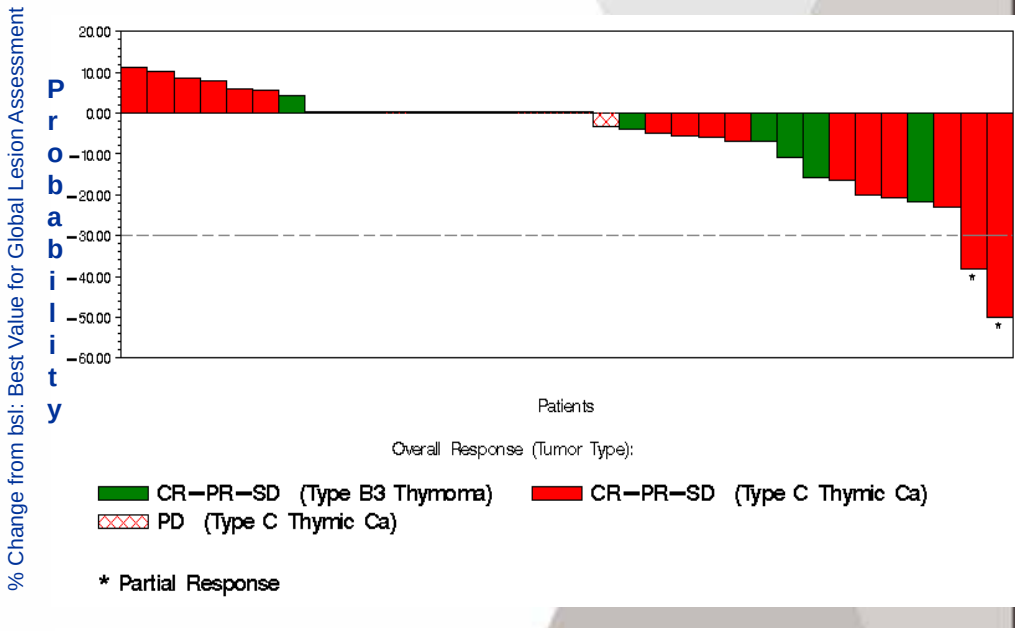
Milciclib

Progression-Free Survival



months

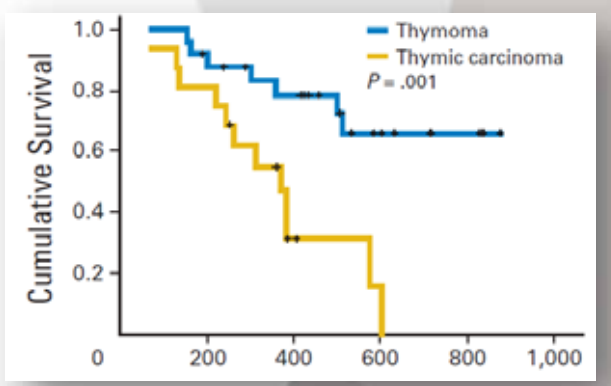
Median PFS (95% CI)
8.2 (3.2- 12.9) mo



Evaluable pts : 12 SDs + 2 PRs/28 pts
Treated pts : 18 SDs + 2 PRs/39 pts

Histone deacetylase inhibitors

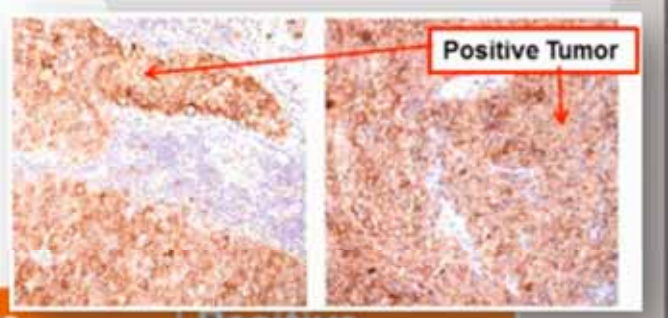
- **Belinostat alone**:
  - phase II trial in refractory tumors
  - 25 thymomas, 16 thymic carcinomas
  - PR in 8%, SD in 68% of thymomas, vs. 0%/50% in carcinomas



- **Belinostat and CAP: phase I/II**
  - 7 thymomas: 1 CR, 4 PR, 2SD
  - 6 carcinomas: 2 PR, 4 SD

Giaccone et al. J Clin Oncol 2011;29:2052; Thomas et al. J Clin Oncol 2012;30 (suppl; abstr 7103)

PD-L1



Study	Antibody	Definition of Positive	Positive thymomas	Positive thymic carcinomas
Brown 2003	Ab 29E.5A9 or 29E.2A3	Not stated	81% (21/26)	88% (7/8)
Padda 2015	rabbit MoAb clone 15	High intensity	68% (44/65)	75% (3/4)
Naidoo ASCO 2015	rabbit MoAb E1L3N	≥ 25% tumor cells positive	94% (11/12)	34% (4/12)
Katsuya ASCO 2015	rabbit MoAb E1L3N	H-score ≥3	67% (6/9)	41% (7/17)
		TOTAL	73% (82/112)	51% (21/41)

Giaccone ASCO 2015

Study design – open label phase II

with a close monitor of toxicity for the first 10 patients

Primary objective:

To detect activity of nivolumab as single agent versus the best investigator's choice as second line treatment for thymic malignancies

Eligible patients Second-line → **Nivolumab 3 mg/kg IV q2 weeks**

Primary endpoint: PFS at 6 months

Secondary endpoints: TTP, Response,
Duration of response, OS
QOL, Safety

Biomarkers

PD-L1 at baseline and PD
Others: immune patterns, molecular profile

+ Initiative INCa AcSé Pembro

Screening Patients with Thoracic Malignancy for Efficient Clinical Trial Access

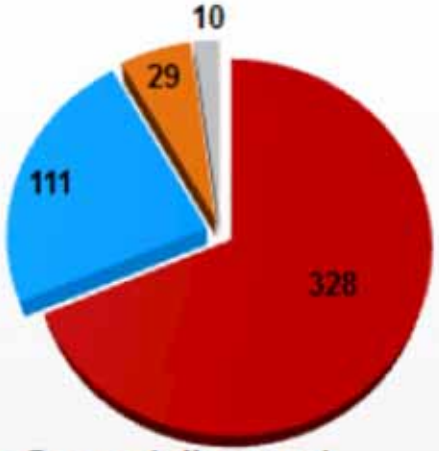
EORTC European Organisation for Research and Treatment of Cancer

etop

14MG Solid tumour panel v1

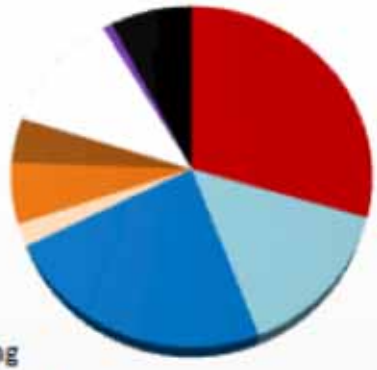
Panel footprint: 2.2 Mb

Panel features: 478



■ Genes (all exons)

■ Copy number variants

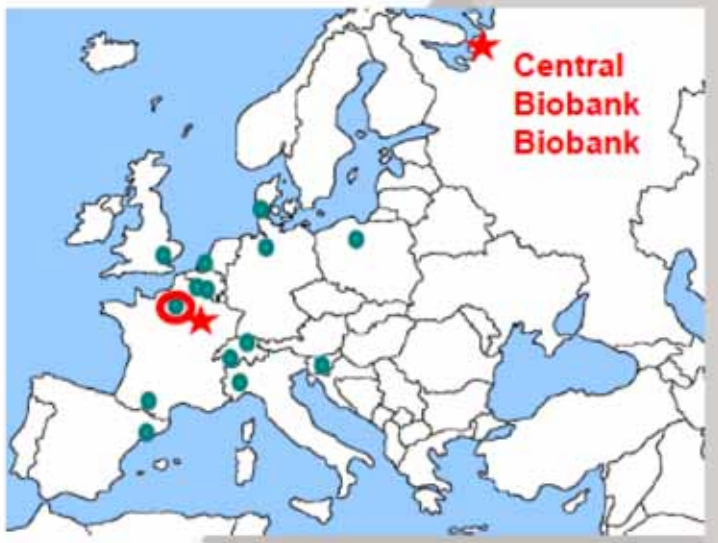


Function (genes)

- Signalling
- Transcription factor
- Transcriptional control
- Apoptosis
- DNA damage response
- Cell cycle control
- Miscellaneous/Unknown
- Immune-related
- Structural components

14m genomics

Online molecular portrait
Prospective clinical data
500-1000 tumors / yr



RYTHMIC: a regional network of expert centers

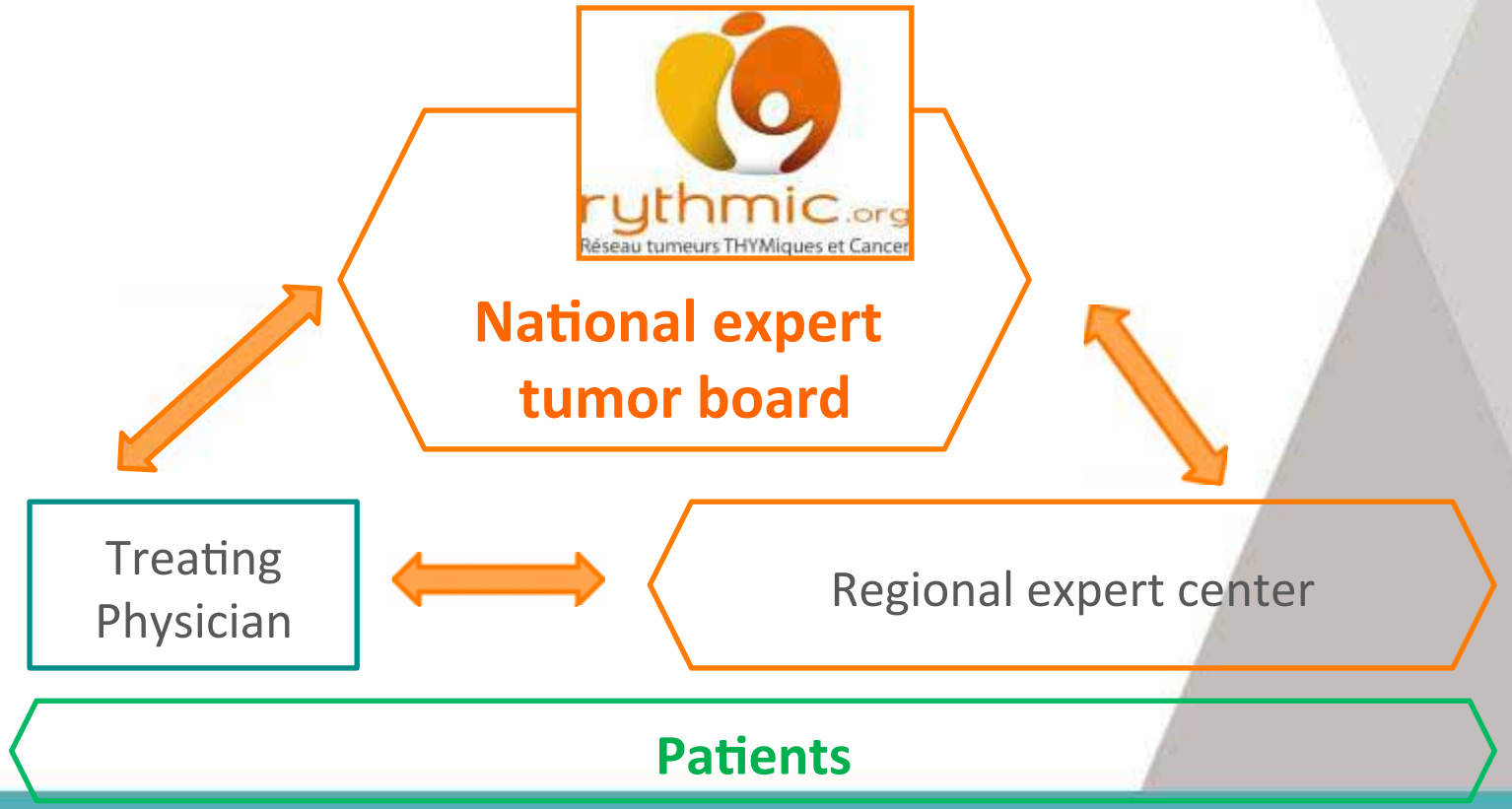
rythmic.org
Réseau tumeurs THYMiques et Cancer

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

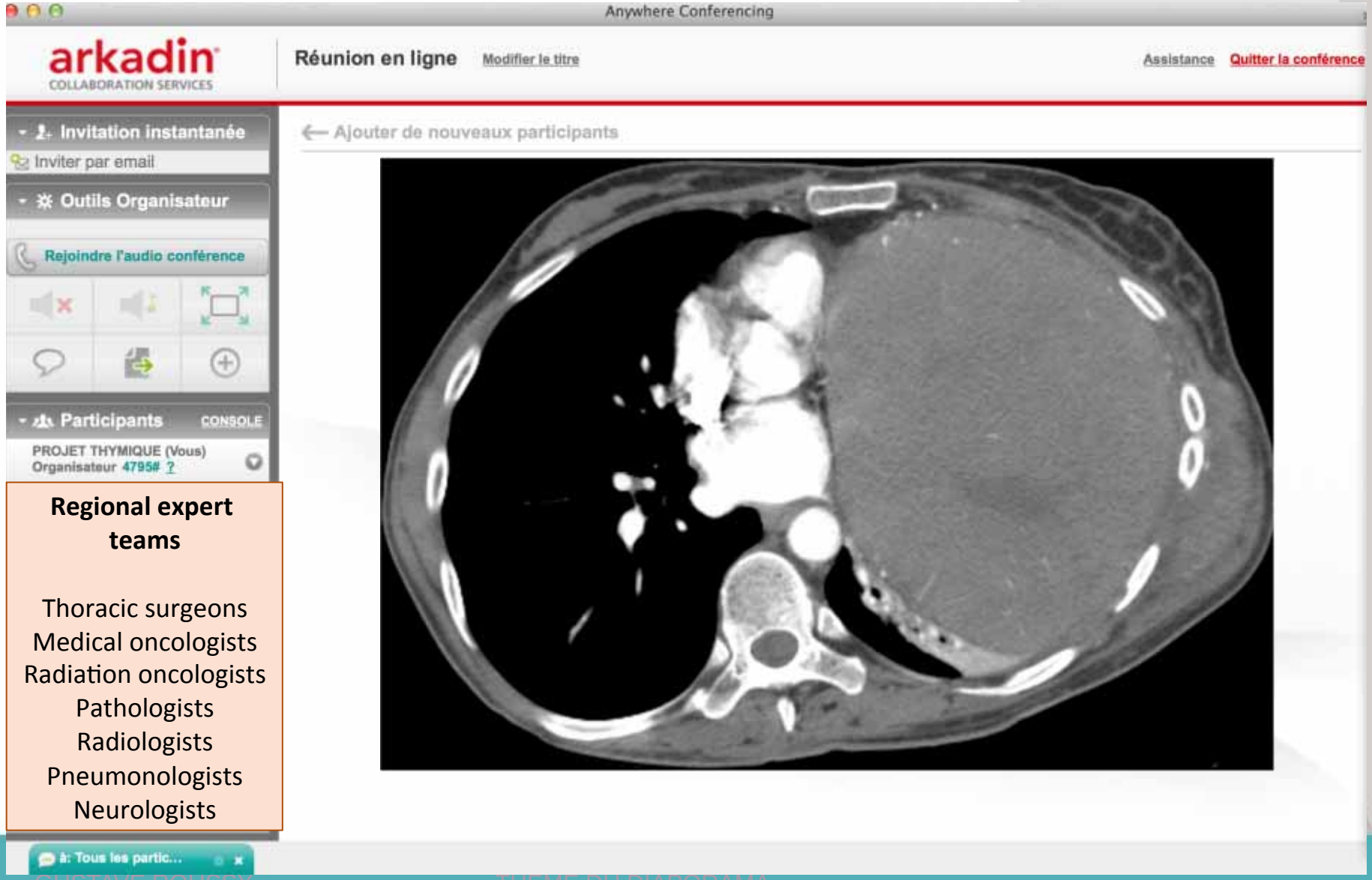
Coordinator:
B. Besse
Gustave Roussy

Hospices Civils de Lyon

RYTHMIC: Infrastructure of the network



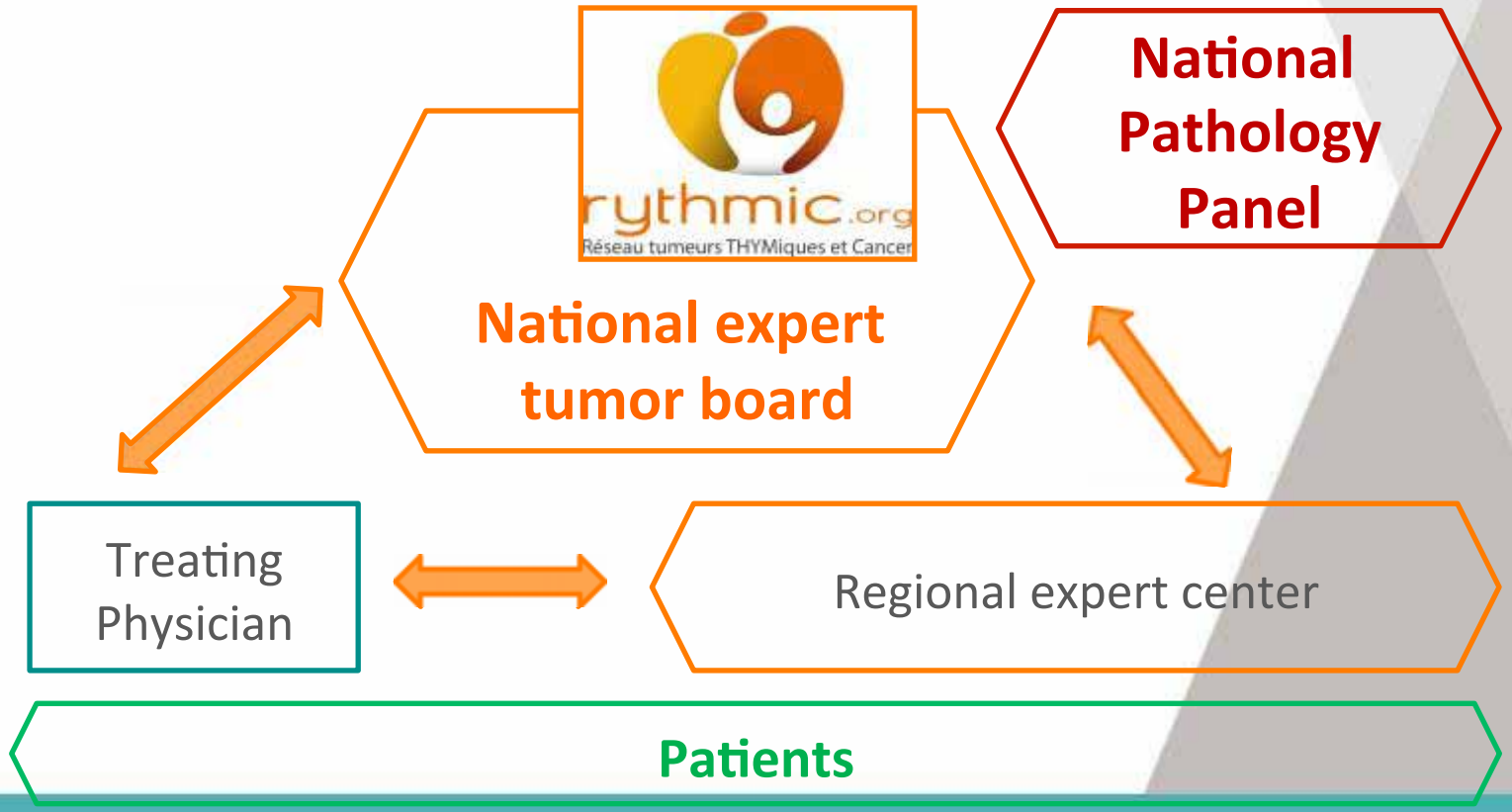
Online virtual tumor board



Regional expert teams

Thoracic surgeons
Medical oncologists
Radiation oncologists
Pathologists
Radiologists
Pneumonologists
Neurologists

RYTHMIC: Infrastructure of the network



RYTHMIC: Infrastructure of the network

Guidelines

CME activities

Prospective database and trials

IFCT

rythmic.org
Réseau tumeurs THYMiques et Cancer

National expert tumor board

National Pathology Panel

Treating Physician

Regional expert center

Patients

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
16TH WORLD CONFERENCE ON LUNG CANCER
SEPTEMBER 6–9, 2015 → DENVER, COLORADO, USA

Systemic Treatment in Advanced Thymic Epithelial Tumors. Insights From a Prospective Cohort of 1000 Patients Enrolled in RYTHMIC

N. Girard, E. Dansin, H. Léna, E. Pichon, PA. Thomas, J. Mazières, L. Thiberville,
V. Westeel, G. Zalcman, C. Clément-Duchêne, G. Massard, X. Quantin, J. Bennouna, P. Fournel, T. Molina, B. Besse

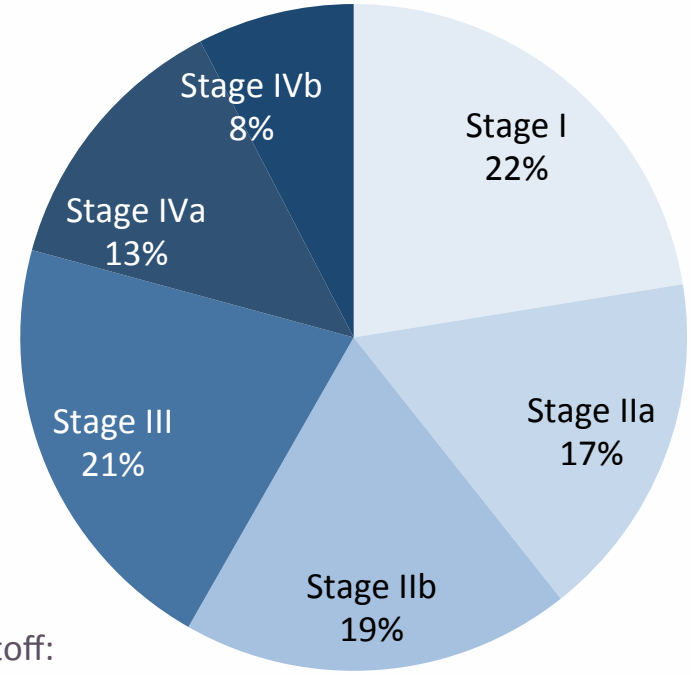
GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS
Hospices Civils de Lyon
IFCT
10 ANS INSTITUT NATIONAL DU CANCER
rythmic.org
Reseau tumeurs THYMiques et Cancer

RYTHMIC: Characteristics of patients

- A global view of the disease, from early to late stage

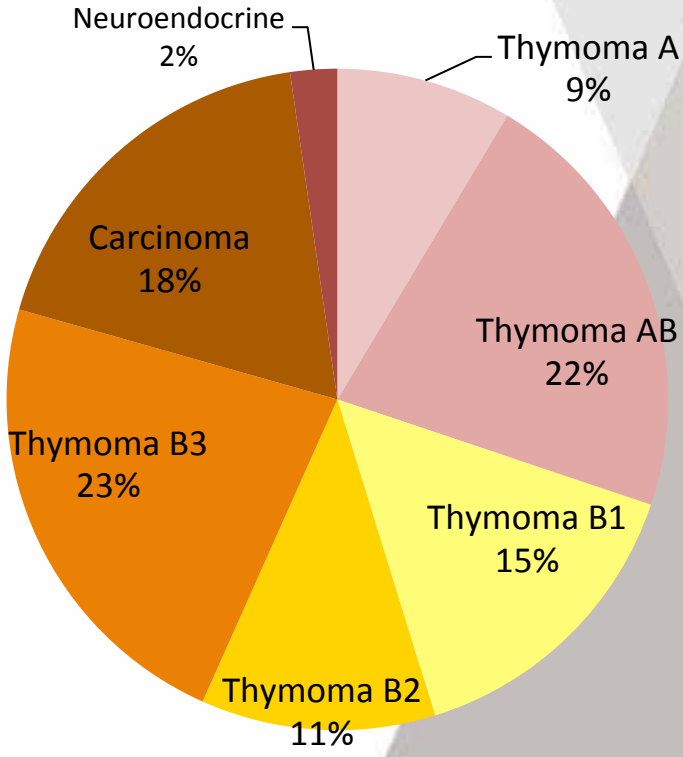
- 42% of stage III-IV tumors
- Histology was of higher grade (B2, B3, Carc) in those cases (p<0.001)

Masaoka-Koga-ITMIG stage



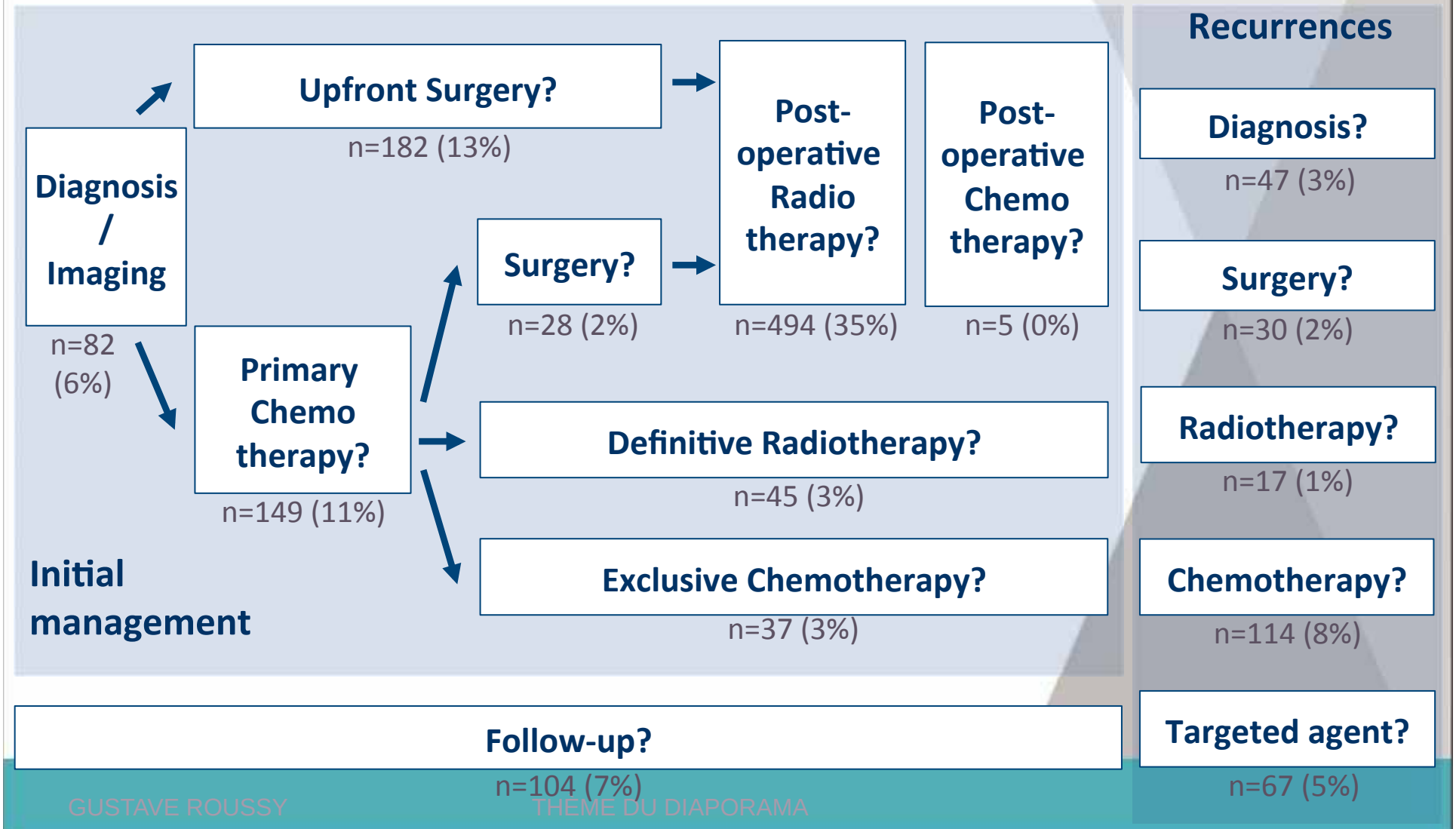
Data cutoff:
August 15th, 2015

Histology



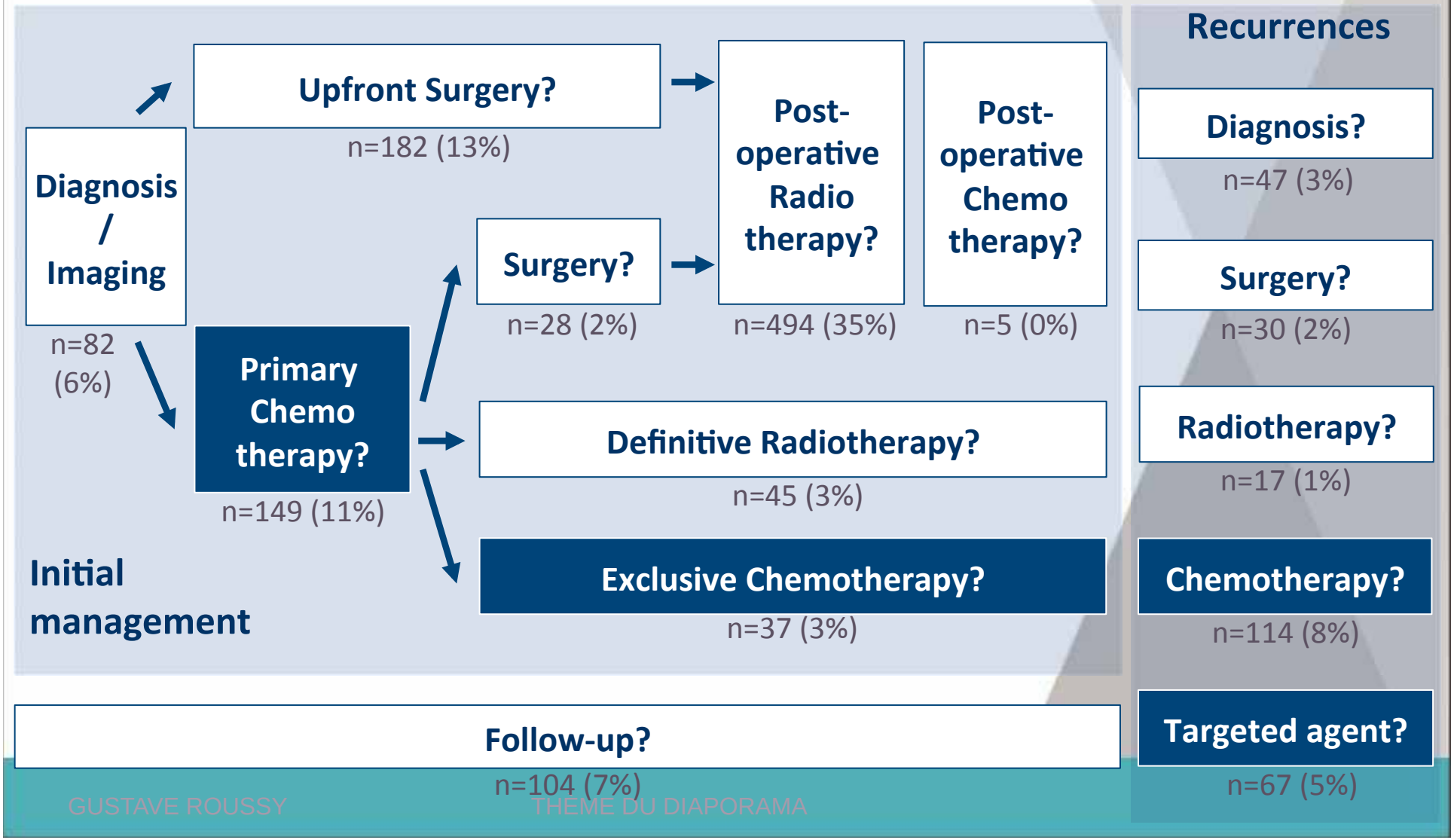
RYTHMIC: Multidisciplinary tumor board

- 1337 questions raised at the multi-disciplinary tumor board

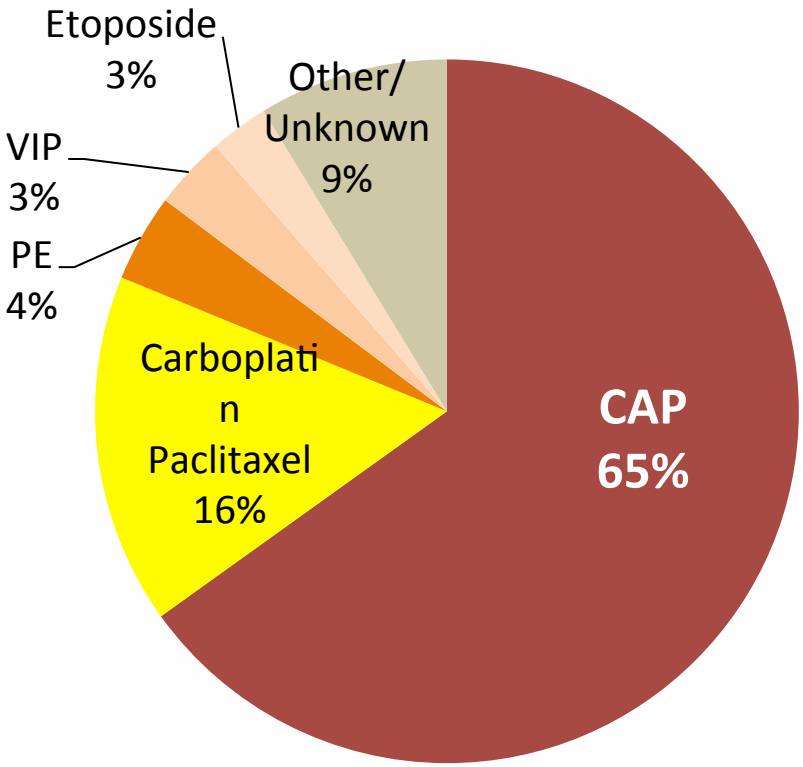


RYTHMIC: Multidisciplinary tumor board

- 1337 questions raised at the multi-disciplinary tumor board

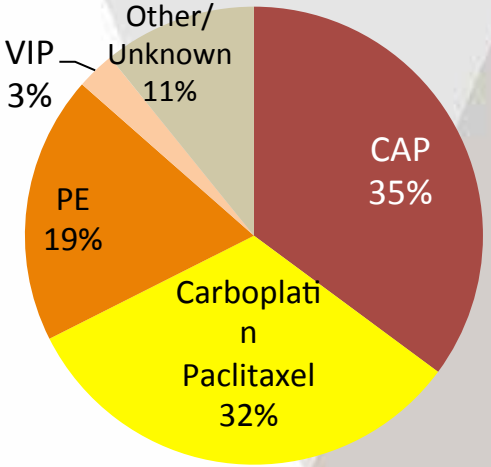


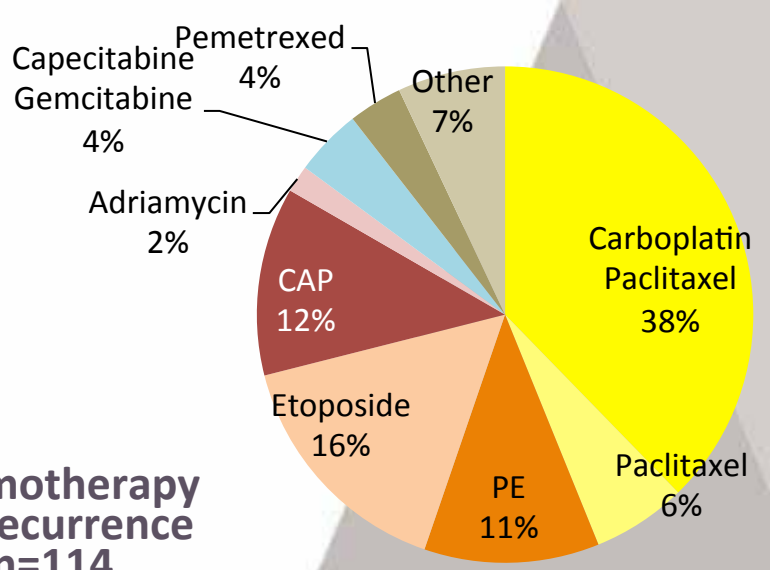
RYTHMIC: Proposed chemotherapy regimens



Primary chemotherapy
n=149

Exclusive chemotherapy
n=37

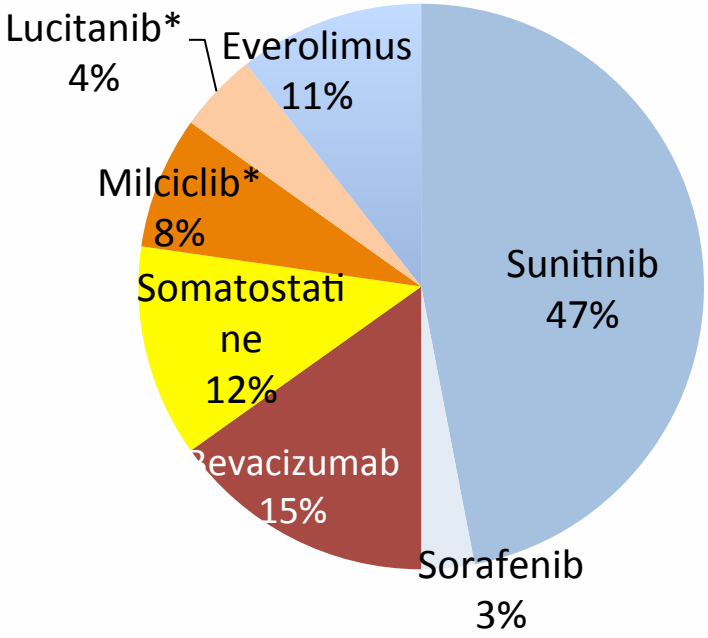




Chemotherapy for recurrence
n=114

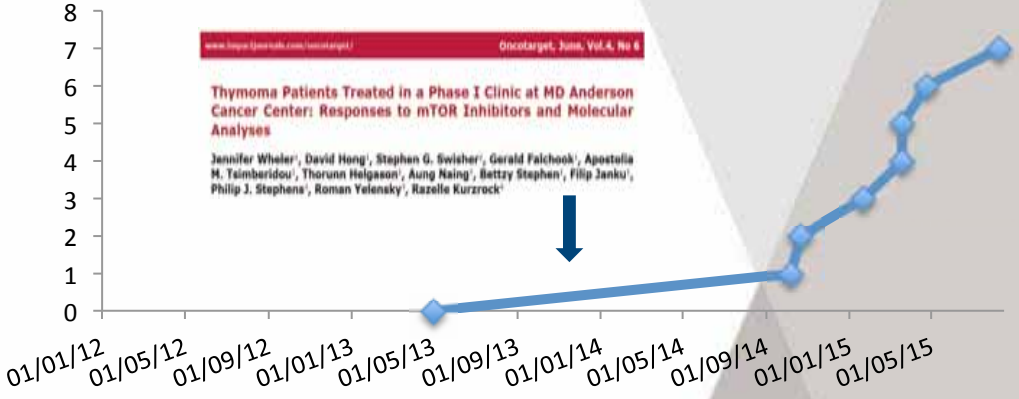
RYTHMIC: Proposed targeted agents

- 67 patients, recurrent tumors: rapid and equal access to innovation



* Phase I/II trial

EVEROLIMUS



Oncotarget, June, Vol.4, No 6

Thymoma Patients Treated in a Phase I Clinic at MD Anderson Cancer Center: Responses to mTOR Inhibitors and Molecular Analyses

Jennifer Wheler[1], David Hong[1], Stephen G. Swisher[2], Gerald Falchook[1], Apostolia M. Tsimberidou[1], Thorunn Helgason[1], Aung Naing[1], Bettzy Stephen[1], Filip Janku[1], Philip J. Stephens[3], Roman Yelensky[3], Razelle Kurzrock[1]

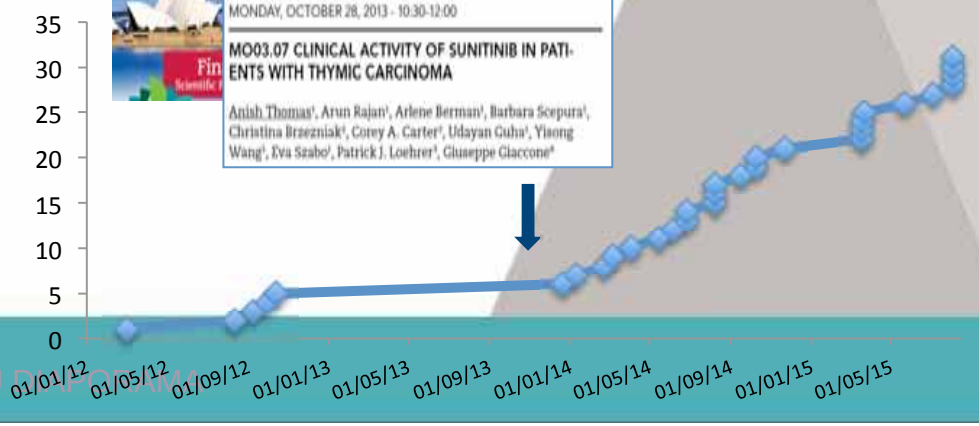
SUNITINIB

IASLC

THYMIC MALIGNANCIES
MONDAY, OCTOBER 28, 2013 - 10:30-12:00

MO03.07 CLINICAL ACTIVITY OF SUNITINIB IN PATIENTS WITH THYMIC CARCINOMA

Anish Thomas[1], Arun Rajan[1], Arlene Berman[1], Barbara Scepura[1], Christina Brzezniak[1], Corey A. Carter[2], Udayan Guha[1], Yiaong Wang[1], Eva Szabo[1], Patrick J. Loehrer[3], Giuseppe Giaccone[4]



Wheler et al. Oncotarget 2013;4:890
J Thorac Oncol 2013;8:S268

Conclusion

- **Nouvelles classifications**
  - TNM et OMS
- **Chirurgie : l'acte central**
  - Centre spécialisé
- **RT adjuvante à discuter**
  - Selon stade et histologie
- **CAP et Paclitaxel/carboplatine**
  - Les traitements de première intention
- **Sunitinib et everolimus**
  - Nouvelles options