THYMIC TUMORS
UPDATE ON TREATMENT STRATEGIES

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DISCLOSURE

- Personal financial interests: Astra-Zeneca, Boehringer-Ingelheim, Bristol Myers Squibb, Hoffmann La Roche, Lilly, Merck Sharp Dohme, Novartis, Pfizer, Takeda

- Institutional financial interests: Astra-Zeneca, Boehringer-Ingelheim, Bristol Myers Squibb, Hoffmann La Roche, Lilly, Merck Sharp Dohme, Novartis, Pfizer, Takeda

- Non-financial interests: Former VP of International Thymic Malignancy Interest Group, Executive board of French Thoracic Cancer Intergroup, Secretary of the Oncology Group of the French Speaking Respiratory Medicine Society, Associated coordinator of RYTHMIC
THYMIC TUMORS: SYSTEMIC TREATMENT

KEY FACTORS TO CONSIDER BEFORE TREATING PATIENTS
#1 MAKE SURE OF THE DIAGNOSIS

World Health Organization 2015

<table>
<thead>
<tr>
<th>Thymoma</th>
<th>Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>SCC</td>
</tr>
<tr>
<td>AB</td>
<td></td>
</tr>
<tr>
<td>B1</td>
<td></td>
</tr>
<tr>
<td>B2</td>
<td></td>
</tr>
<tr>
<td>B3</td>
<td></td>
</tr>
</tbody>
</table>

“Médullary”  Mixed  “Cortical”
#1 MAKE SURE OF THE DIAGNOSIS

Pathological review
THYMIC TUMORS: SYSTEMIC TREATMENT

KEY FACTORS TO CONSIDER BEFORE TREATING PATIENTS
#2 STAGING IS COMPLEX
MASAOKA-KOGA TO TNM

8\textsuperscript{th} TNM staging system

Masaoka-Koga: I, IIA, IIB, III

Masaoka-Koga: III

Masaoka-Koga: IVB

Detterbeck et al. J Thorac Oncol 2014;S65-72
The most significant prognostic factor in thymic malignancies is the completion of surgical resection, whatever classification is used.
THYMIC TUMORS: SYSTEMIC TREATMENT

KEY FACTORS TO CONSIDER BEFORE TREATING PATIENTS
#3 LEVELS OF EVIDENCE ARE LIMITED: ROOM FOR MULTIDISCIPLINARY DISCUSSION

Thymic epithelial tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

N. Girard1, E. Ruffin2, A. Marx3, C. Faivre-Finn4 & S. Peters5, on behalf of the ESMO Guidelines Committee*

1Department of Respiratory Medicine, Expert Centre for Thymic Malignancies, Reference Centre for Orphan Pulmonary Diseases, Hôpital Lucile Pradel, Hospices Civils de Lyon, Lyon, France; 2Department of Thoracic Surgery, University of Turin, Turin, Italy; 3Institute of Pathology, University Medical Centre Maribor, University of Maribor, Maribor, Slovenia; 4Institute of Cancer Sciences, The University of Manchester, Manchester Academic Health Science Centre, The Christie NHS Foundation Trust, Manchester, UK; 5Department of Medical Oncology, Cantonal Hospital University Vaudois (CHUV), Lausanne, Switzerland

Table 8. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System†)

<table>
<thead>
<tr>
<th>Levels of evidence</th>
<th>NSCLC</th>
<th>Mesothelioma</th>
<th>Thymic tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>100%</td>
<td>80%</td>
<td>100%</td>
</tr>
<tr>
<td>II</td>
<td>80%</td>
<td>60%</td>
<td>60%</td>
</tr>
<tr>
<td>III</td>
<td>60%</td>
<td>40%</td>
<td>40%</td>
</tr>
<tr>
<td>IV</td>
<td>40%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>V</td>
<td>20%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

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#3 LEVELS OF EVIDENCE ARE LIMITED: ROOM FOR MULTIDISCIPLINARY DISCUSSION

RYTHMIC network

Coordinator: B. Besse  
Gustave Roussy
#3 LEVELS OF EVIDENCE ARE LIMITED: ROOM FOR MULTIDISCIPLINARY DISCUSSION

EURACAN network
THYMIC TUMORS: SYSTEMIC TREATMENT

KEY FACTORS TO CONSIDER BEFORE TREATING PATIENTS

SURGERY UPFRONT IN RESECTABLE TUMORS
**Median sternotomy** is the standard approach.

- Complete exploration of the pleural cavities

- Mediastinal nodes sampling/resection (stage III tumor/thymic carcinoma)

- **Complete thymectomy**, including tumor, normal thymus, and mediastinal fat
  - *en bloc* resection of involved structures:
    - lung, vessels, pleural implants, phrenic nerves
    - surgical clips in areas of concern

- Frozen section not recommended for margins assessment
Orientation and marking in the operative room

NO

YES

D. Gossot, Montsouris Institute
Towards Minimally-Invasive Surgery?

Determinants of Complete Resection of Thymoma by Minimally Invasive and Open Thymectomy: Analysis of an International Registry

Bryan M. Burt, MD, a, Xiaopan Yao, MD, a Joseph Shraguer, MD, Alberto Antonicelli, Sukhmani Padda, MD, Jonathan Reiss, MD, Heather Wakelee, MD, Stacey Su, MD, James Huang, MD, Walter Scott, MD

Figure 1

MIT

OT

Number of Cases

% Achieving R0 Resection

Year

Time Period

MIT

OT

1997-2000
2001-2004
2005-2008
2009-2012
THYMIC TUMORS: SYSTEMIC TREATMENT

KEY FACTORS TO CONSIDER BEFORE TREATING PATIENTS

SURGERY UPFRONT IN RESECTABLE TUMORS

POST-OPERATIVE DECISION-MAKING
Recurrence rates: stage

ITMIG retrospective database

Cumulative incidence of recurrences in Masaoka-Koga groups

Thymomas (n = 7005)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Events/n</th>
<th>10-year recurrence % (IC95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>121/3097</td>
<td>8 (7-8)</td>
</tr>
<tr>
<td>III</td>
<td>140/654</td>
<td>29 (27-31)</td>
</tr>
<tr>
<td>IVA</td>
<td>64/109</td>
<td>71 (34-100)</td>
</tr>
<tr>
<td>IVB</td>
<td>17/38</td>
<td>57 (24-90)</td>
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</tbody>
</table>

Thymic carcinomas (n = 977)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Events/n</th>
<th>10-year recurrence % (IC95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I/II</td>
<td>28/112</td>
<td>25 (22-29)</td>
</tr>
<tr>
<td>III</td>
<td>68/143</td>
<td>59 (44-76)</td>
</tr>
<tr>
<td>IVA</td>
<td>19/26</td>
<td>76 (58-100)</td>
</tr>
<tr>
<td>IVB</td>
<td>20/37</td>
<td>54 (37-67)</td>
</tr>
</tbody>
</table>

Detterbeck et al. WCLC 2013, abstr. MS16.2
Failure Patterns Relative to Radiation Treatment Fields for Stage II–IV Thymoma

Andreas Rimner, MD,* Daniel R. Gomez, MD,# Abraham J. Wu, MD,* Weiji Shi, MS,†
Ellen D. Yorke, PhD,‖ Andre L. Moreira, MD,§ David Rice, MD,** Risuko Komaki, MD,#
Kenneth E. Rosenzweig, MD,†† Gregory J. Riely, MD,‡ and James Huang, MD,†

POSTOPERATIVE RADIOThERAPY GUIDELINES
THYMIC TUMORS: SYSTEMIC TREATMENT

KEY FACTORS TO CONSIDER BEFORE TREATING PATIENTS
- SURGERY UPFRONT IN RESECTABLE TUMORS
- POST-OPERATIVE DECISION-MAKING

STRATEGIES FOR SYSTEMIC THERAPY
**KEY QUESTION IS:**
WHAT IS THE INTENT OF THE SYSTEMIC TREATMENT?

<table>
<thead>
<tr>
<th>PRIMARY CHEMOTHERAPY</th>
<th>EXCLUSIVE CHEMOTHERAPY</th>
<th>SYSTEMIC THERAPIES FOR RECURRENCES</th>
</tr>
</thead>
</table>

**ITMIG Definitions and Policies**

Chemotherapy Definitions and Policies for Thymic Malignancies

Nicolas Girard, MD,* Rohit Lat, MD,† Heather Wakelee, MD,‡ Gregory J. Riely, MD,§ and Patrick J. Lochrer, MD||

J Thorac Oncol 2011;6(7 Suppl 3):S1749
KEY QUESTION IS: WHAT IS THE INTENT OF THE SYSTEMIC TREATMENT?

**PRIMARY CHEMOTHERAPY**

**EXCLUSIVE CHEMOTHERAPY**

**SYSTEMIC THERAPIES FOR RECURRENCES**

*Chemotherapy Definitions and Policies for Thymic Malignancies*

Nicolas Girard, MD,* Rohit Lal, MD,† Heather Wakelee, MD,‡ Gregory J. Riely, MD,§ and Patrick J. Loehr, MD||
PRIMARY CHEMOTHERAPY: CASE REPORT

27-year old male, chest pain, no myasthenia

MTB: Is upfront complete resection achievable?
Re: « Not sure »

Biopsy: thymoma, type B3
PRIMARY CHEMOTHERAPY: CLINICAL EVIDENCE

Historical data

<table>
<thead>
<tr>
<th>Study</th>
<th>Chemotherapy Regimen</th>
<th>No. of Patients</th>
<th>Tumor Type</th>
<th>Stage</th>
<th>Design</th>
<th>Response Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macchiarini et al 1991</td>
<td>CEE</td>
<td>7</td>
<td>T/TC</td>
<td>III</td>
<td>Phase II</td>
<td>100</td>
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<tr>
<td>Baruffi et al 1993</td>
<td>ADOC</td>
<td>6</td>
<td>T</td>
<td>III-IVA</td>
<td>Phase II</td>
<td>83</td>
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<tr>
<td>Rea et al 1993</td>
<td>ADOC</td>
<td>16</td>
<td>T</td>
<td>III-IVA</td>
<td>Retros p</td>
<td>100</td>
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<tr>
<td>Baruffi et al 1999</td>
<td>ADOC</td>
<td>16</td>
<td>T</td>
<td>III-IVA</td>
<td>Phase II</td>
<td>81</td>
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<tr>
<td>Vora et al 2003</td>
<td>CEE</td>
<td>15</td>
<td>T/TC</td>
<td>III</td>
<td>Retros p</td>
<td>66</td>
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<tr>
<td>Bratii et al 2004</td>
<td>ADOC/PE</td>
<td>25</td>
<td>T/TC</td>
<td>III-IVA</td>
<td>Retros p</td>
<td>72</td>
</tr>
<tr>
<td>Kim et al 2004</td>
<td>CAP</td>
<td>22</td>
<td>T</td>
<td>Phase II</td>
<td></td>
<td>77</td>
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<tr>
<td>Lucchi et al 2005</td>
<td>CEE</td>
<td>30</td>
<td>T/TC</td>
<td>III-IVA</td>
<td>Retros p</td>
<td>67</td>
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<tr>
<td>Jacot et al 2005</td>
<td>CAP</td>
<td>5</td>
<td>T/TC</td>
<td>III-IVA</td>
<td>Retros p</td>
<td>75</td>
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<tr>
<td>Yokoi et al 2007</td>
<td>CAMP</td>
<td>14</td>
<td>T/TC</td>
<td>III, IV</td>
<td>Retros p</td>
<td>93</td>
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<tr>
<td>Kunihito et al 2009</td>
<td>CODE</td>
<td>21</td>
<td>T</td>
<td>III</td>
<td>Phase II</td>
<td>62</td>
</tr>
</tbody>
</table>

Administered regimens n=91

RYTHMICIC data

- Etoposide +/- Platin 8%
- Paclitaxel + Carboplatin 6%

Tumor response

Primary 42%
Progression 44%
Stable 8%
Partial response 67%
Complete response 67%
PRIMARY CHEMOTHERAPY: CASE REPORT

27-year old male, chest pain, no myasthenia

Then surgery!
ADVANCED TUMORS: MULTIMODAL TREATMENT

Localized tumor → Chemotherapy → Re-evaluate for surgery

Resectable → Surgical resection of primary tumor and isolated metastases

Unresectable → RT ± chemotherapy
CHEMO-RADIATION FOR THYMIC TUMORS

- Limited data in the literature...no consensus

- Sequential approach:
  - 23 patients, stage III-IV unresectable thymoma
  - induction with CAP (4 cycles), then radiotherapy
  - 5-year PFS: 54%
  - 5-year OS: 53%

- Concurrent approach:


KEY QUESTION IS: WHAT IS THE INTENT OF THE SYSTEMIC TREATMENT?

ITMIG Definitions and Policies

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Nicolas Girard, MD,* Rohit Lal, MD,† Heather Wakelee, MD,‡ Gregory J. Riely, MD,§ and Patrick J. Loehr, MD||

PRIMARY CHEMOTHERAPY

EXCLUSIVE CHEMOTHERAPY

SYSTEMIC THERAPIES FOR RECURRENCES

J Thorac Oncol 2011;6(7 Suppl 3):S1749
EXCLUSIVE CHEMOTHERAPY: CASE REPORT

67-year old male, lombalgia, hypercalcemia

Biopsy: thymic carcinoma, CD117+, CD5+
EXCLUSIVE CHEMOTHERAPY: CLINICAL EVIDENCE

Administered regimens

- **CAP**
  - Doses: 50 mg/m²/3 weeks, 100 mg/m²/3 weeks
  - Response Rate: 66%

- **Paclitaxel + Carboplatin**
  - 20%

- **Etoposide**
  - 12%

- **Others**
  - 2%

Progression

- Stable
- Partial response
- Complete response

Tumor response

- Exclusive
- Thymoma
- Lymphoma

Historical data

- **Study**
  - **No. of Patients**
  - **Period of accrual (years)**
  - **Treatment**
  - **Design**
  - **Regimen**
  - **Agents**
  - **Doses**
  - **Response Rate (%)**

RYTHMIC data

- **Patients**
- **Response Rate (%)**

References

- Girard N. Eur Respir Rev 2013;22:75
- Merveilleux du Vignaux et al. J Thorac Oncol 2018; online first

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EXCLUSIVE CHEMOTHERAPY: BETTER RESPONSE WITH ANTHRACYCLINS?

Thymoma: yes

Thymic carcinoma: not sure
KEY QUESTION IS: WHAT IS THE INTENT OF THE SYSTEMIC TREATMENT?

ITMIG Definitions and Policies

Chemotherapy Definitions and Policies for Thymic Malignancies

Nicolas Girard, MD,* Rohit Lai, MD,† Heather Wakelee, MD,‡ Gregory J. Riely, MD,§ and Patrick J. Loehr, MD||

PRIMARY CHEMOTHERAPY

EXCLUSIVE CHEMOTHERAPY

SYSTEMIC THERAPIES FOR RECURRENCES

J Thorac Oncol 2011;6(7 Suppl 3):S1749
RECURRENCES: CASE REPORT

32 year-old male, Morvan syndrome

2011 chemo and resection for thymoma, type B2-B3

2014 Resection of implant

2016
RECURRCES: CLINICAL EVIDENCE FOR SYSTEMIC TREATMENT

First recurrence
n=79

Recurrence 2
n=54

Recurrence 3
n=29

Recurrence 4
n=13

Merveilleux du Vignaux et al. J Thorac Oncol 2018; online first

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RECURRENCES: CLINICAL EVIDENCE FOR SYSTEMIC TREATMENT

RYTHMIC data

Merveilleux du Vignaux et al. J Thorac Oncol 2018; online first
RECURRENCES:
CLINICAL EVIDENCE FOR SYSTEMIC TREATMENT

RYTHMIC data

<table>
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<tr>
<th></th>
<th>PFS</th>
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<tbody>
<tr>
<td>Primary</td>
<td>20.7</td>
</tr>
<tr>
<td>Exclusive</td>
<td>6.2</td>
</tr>
<tr>
<td>Recurrence 1</td>
<td>7.6</td>
</tr>
<tr>
<td>Recurrence 2</td>
<td>6.2</td>
</tr>
<tr>
<td>Recurrence 3</td>
<td>6.9</td>
</tr>
<tr>
<td>Recurrence 4</td>
<td>8.7</td>
</tr>
</tbody>
</table>

Merveilleux du Vignaux et al. J Thorac Oncol 2018; online first
THYMIC TUMORS: SYSTEMIC TREATMENT

KEY FACTORS TO CONSIDER BEFORE TREATING PATIENTS

SURGERY UPFRONT IN RESECTABLE TUMORS

POST-OPERATIVE DECISION-MAKING

STRATEGIES FOR SYSTEMIC THERAPY

PRECISION MEDICINE APPROACHES?
THYMIC CARCINOMAS
FOUNDATION MEDICINE PANEL

Thymic squamous cell carcinomas

<table>
<thead>
<tr>
<th>Squamous Cell</th>
<th>Patients</th>
<th>Median Age (y)</th>
<th>Gender (% Female)</th>
<th>Avg GA/tumor</th>
<th>Avg CRGA/tumor</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>69</td>
<td>57</td>
<td>34%</td>
<td>4.1</td>
<td>1.0</td>
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</tbody>
</table>

Significant Genomic Alterations

- KIT
- FGFR3
- PIK3CA

TMB >10 mutations/Mb: 9%
TMB >20 mutations/Mb: 9%

Mutation Frequency by Gene

- CDKN2A
- TP53
- CYLD
- KIT
- ARID1A
- KDM6A
- CDKN2B
- TP53
- KIT
- SETD2
- CDKN1B
- KDM6A
- CDKN1B
- PIK3CA
- PIK3CA
- PIK3CG
- EZH2
- BRAF
- FGFR1
- PTEN
- FAT1
- MLL3
- CHD4
- TNKS2
- FGF6
- FGFR3
- CREBBP
- ATM
- EZH2
- BRAF

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Ross et al. ESMO 2017
<table>
<thead>
<tr>
<th></th>
<th>Adeno.</th>
<th>Basaloid</th>
<th>Lymphoepitheliomatous</th>
<th>Neuroendocrine</th>
<th>NOS</th>
<th>Squamous Cell</th>
<th>Sarcomatoid</th>
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<tbody>
<tr>
<td>Patients</td>
<td>7</td>
<td>5</td>
<td>5</td>
<td>30</td>
<td>54</td>
<td>69</td>
<td>4</td>
</tr>
<tr>
<td>Median Age (y)</td>
<td>48</td>
<td>58</td>
<td>50</td>
<td>48</td>
<td>57</td>
<td>57</td>
<td>61</td>
</tr>
<tr>
<td>Gender (% Female)</td>
<td>43%</td>
<td>60%</td>
<td>20%</td>
<td>37%</td>
<td>24%</td>
<td>34%</td>
<td>50%</td>
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<tr>
<td>Avg GA/tumor</td>
<td>4.0</td>
<td>2.8</td>
<td>1.0</td>
<td>3.3</td>
<td>4.1</td>
<td>4.1</td>
<td>4.8</td>
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<tr>
<td>Avg CRGA/tumor</td>
<td>0.9</td>
<td>0.3</td>
<td>--</td>
<td>0.9</td>
<td>0.8</td>
<td>1.0</td>
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<tr>
<td>Significant Genomic Alterations</td>
<td>PDGFR A</td>
<td>FGFR3</td>
<td>CDKN2A</td>
<td>KIT</td>
<td>BRCA2</td>
<td>IDH1</td>
<td>KIT</td>
</tr>
<tr>
<td></td>
<td>KIT</td>
<td>MET</td>
<td>CDKN2A</td>
<td>PTEN</td>
<td>PTEN</td>
<td>ERBB2</td>
<td>PIK3CA</td>
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<td></td>
<td>FBXW7</td>
<td>PTCH1</td>
<td>MEN1</td>
<td>ERBB3</td>
<td>KIT</td>
<td>PIK3CA</td>
<td>PIK3CA</td>
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<tr>
<td>TMB &gt;10 mutations/Mb</td>
<td>14%</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>3%</td>
<td>5%</td>
<td>9%</td>
</tr>
<tr>
<td>TMB &gt;20 mutations/Mb</td>
<td>0%</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>3%</td>
<td>5%</td>
<td>9%</td>
</tr>
</tbody>
</table>
WHICH PATHWAYS FOR PRECISION MEDICINE APPROACHES?

- KIT inhibitors
- Cyclin-dependent kinase inhibitors
- IGF-1R inhibitors
- PI3K inhibitors
- Proapoptotic agents
- Histone deacetylase inhibitors
- VEGFRs inhibitors
- VEGFRs overexpression
- Mutated epigenetic regulatory genes
- PI3K subunits mutations
- BCL2 gains
- IGF-1R overexpression
- KIT activating mutations
- Loss of CDKN2A/B
- Immune checkpoints inhibitors
- PD-L1 expression

# KIT INHIBITORS FOR KIT MUTATIONS

## Activating c-KIT mutations in a subset of thymic carcinoma and response to different c-KIT inhibitors


<table>
<thead>
<tr>
<th>Reference</th>
<th>Age/sex</th>
<th>Histologic type</th>
<th>c-KIT mutation</th>
<th>Stage</th>
<th>Therapy</th>
<th>Drug</th>
<th>Clinical response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strobel et al. [7]</td>
<td>54/M</td>
<td>TC, squamous cell, G3</td>
<td>V560del ex11</td>
<td>Metastatic</td>
<td>None</td>
<td>Imatinib</td>
<td>SD (6 months)</td>
</tr>
<tr>
<td>Bisagni et al. [10]</td>
<td>46/M</td>
<td>TC, squamous cell, G3</td>
<td>D816F ex17</td>
<td>pT3, N2, M1</td>
<td>S + CT + RT</td>
<td>Sorafenib</td>
<td>PR (&gt;15 months)</td>
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<tr>
<td>Disel et al. [13]</td>
<td>47/F</td>
<td>TC, squamous cell, G3</td>
<td>del577-578-579 ex11</td>
<td>IVA</td>
<td>CT + RT</td>
<td>Sorafenib</td>
<td>SD</td>
</tr>
<tr>
<td>Buti et al. [14]</td>
<td>48/M</td>
<td>TC, squamous cell, G3</td>
<td>Y535N</td>
<td>IV</td>
<td>CT</td>
<td>Imatinib</td>
<td>PR (&gt;8 months)</td>
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<tr>
<td>Li et al. [19]</td>
<td>46/M</td>
<td>TC, squamous cell, G3</td>
<td>ND</td>
<td>IV</td>
<td>CT</td>
<td>Sorafenib</td>
<td>SD (&gt;9 months)</td>
</tr>
<tr>
<td>Chua et al. [20]</td>
<td>NA</td>
<td>Type-B2</td>
<td>ND</td>
<td>I</td>
<td>Imatinib + CT</td>
<td>Dasatinib</td>
<td>LR</td>
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<tr>
<td>Hamada et al. [21]</td>
<td>Case 1: 62/M</td>
<td>Atypical carcinoma</td>
<td>None</td>
<td>Invasive</td>
<td>CT</td>
<td>Imatinib</td>
<td>Good clinical response</td>
</tr>
<tr>
<td></td>
<td>Case 2: 58/M</td>
<td>Atypical carcinoma</td>
<td>ND</td>
<td>Invasive</td>
<td>S + RT</td>
<td>Nessuno</td>
<td>Recurrence and metastasis</td>
</tr>
<tr>
<td>Giaccone et al. [22]</td>
<td>Case 1: 36/M</td>
<td>TC</td>
<td>ND</td>
<td>IVB</td>
<td>CT</td>
<td>Imatinib</td>
<td>PD</td>
</tr>
<tr>
<td></td>
<td>Case 2: 67/M</td>
<td>Type-B3</td>
<td>ND</td>
<td>IVA</td>
<td>S + RT + CT</td>
<td>Imatinib</td>
<td>SD</td>
</tr>
<tr>
<td></td>
<td>Case 3: 47/M</td>
<td>Type-B2/3</td>
<td>ND</td>
<td>IVA</td>
<td>CT</td>
<td>Imatinib</td>
<td>SD</td>
</tr>
<tr>
<td></td>
<td>Case 4: 76/M</td>
<td>TC</td>
<td>ND</td>
<td>IVB</td>
<td>CT</td>
<td>Imatinib</td>
<td>PD</td>
</tr>
<tr>
<td></td>
<td>Case 5: 36/M</td>
<td>TC</td>
<td>ND</td>
<td>IVB</td>
<td>CT</td>
<td>Imatinib</td>
<td>PD</td>
</tr>
<tr>
<td></td>
<td>Case 6: 71/M</td>
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<td>ND</td>
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<td>PD</td>
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<tr>
<td></td>
<td>Case 7: 69/F</td>
<td>TC, squamous cell type</td>
<td>None</td>
<td>IVB</td>
<td>None</td>
<td>Imatinib</td>
<td>PD</td>
</tr>
<tr>
<td>Strobel et al. [23]</td>
<td>Case 1: 35/M</td>
<td>TC, squamous cell type</td>
<td>None</td>
<td>IVA</td>
<td>CT + imatinib</td>
<td>Sunitinib</td>
<td>PR</td>
</tr>
<tr>
<td></td>
<td>Case 2: 60/M</td>
<td>TC, squamous cell type</td>
<td>None</td>
<td>IVA</td>
<td>S + RT + CT</td>
<td>Sunitinib</td>
<td>PR</td>
</tr>
<tr>
<td></td>
<td>Case 3: 77/M</td>
<td>TC, squamous cell type</td>
<td>None</td>
<td>II</td>
<td>S</td>
<td>Sunitinib</td>
<td>PR</td>
</tr>
<tr>
<td></td>
<td>Case 4: 28/F</td>
<td>TC, undifferentiated</td>
<td>None</td>
<td>IVB</td>
<td>CT + RT</td>
<td>Sunitinib</td>
<td>PR (2 months)</td>
</tr>
<tr>
<td>Palmieri et al. [24]</td>
<td>15 cases</td>
<td>4 type B2</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>Imatinib</td>
<td>PD</td>
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<tr>
<td></td>
<td>2 type B2/B3</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Imatinib</td>
<td>PD</td>
</tr>
<tr>
<td></td>
<td>6 type B3</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Imatinib</td>
<td>1 SD</td>
</tr>
<tr>
<td></td>
<td>3 TC</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Imatinib</td>
<td>PD</td>
</tr>
</tbody>
</table>
Sunitinib in patients with chemotherapy-refractory thymoma and thymic carcinoma: an open-label phase 2 trial

Aneel Thomas, Anun Rojan, Adene Berman, Yusuke Tamita, Christina Brzoznick, Min-Jung Lee, Sunmin Lee, Alexander Ling, Aaron Spitzler, Corey A Carter, Udayan Guha, Yisong Wang, Eva Szabo, Paul Meltzer, Seth M Steinberg, Jane B Trepel, Patrick J Lechner, Giuseppe Giaccone

<table>
<thead>
<tr>
<th></th>
<th>Thymic carcinoma (n=23)</th>
<th>Thymoma (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>95% CI</td>
<td>Patients (%)</td>
</tr>
<tr>
<td>Objective response†</td>
<td>6 (26%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>15 (65%)</td>
<td>12 (75%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2 (9%)</td>
<td>3 (19%)</td>
</tr>
<tr>
<td>Disease control</td>
<td>21 (91%)</td>
<td>13 (81%)</td>
</tr>
</tbody>
</table>

Figure 1: Waterfall plots of tumour responses to si
Expression of mesothelin in thymic carcinoma and its potential therapeutic significance

Anish Thomas (MD), Yuanbin Chen (MD PhD), Arlene Berman (MS),
David S. Schrump (MD), Giuseppe Giaccone (MD PhD),
David J. Venzon (PhD), David J. Lieuwehr (MS), Seth M. S.
Markku Miettinen (MD), Raffit Hassan (MD), Arun Raja

* A. Immunohistochemistry of mesothelin in thymic carcinoma. (A) Thymic carcinoma with strong mesothelin expression in tumor cells. (B) Thymic carcinoma with moderate mesothelin expression in tumor cells. (C) Thymic carcinoma with weak mesothelin expression in tumor cells. (D) Thymic carcinoma with no mesothelin expression in tumor cells.
OTHER STRATEGIES: SELINEXOR
THYMIC TUMORS: SYSTEMIC TREATMENT

KEY FACTORS TO CONSIDER BEFORE TREATING PATIENTS

SURGERY UPFRONT IN RESECTABLE TUMORS

POST-OPERATIVE DECISION-MAKING

STRATEGIES FOR SYSTEMIC THERAPY

PRECISION MEDICINE APPROACHES?

IMMUNE CHECKPOINT INHIBITORS
IMMUNOTHERAPY FOR THYMIC TUMORS
RATIONALE

Expression of PD-L1

Low tumor mutation burden
IMMUNOTHERAPY FOR THYMIC TUMORS AUTO-IMMUNE DISORDERS

Paraneoplastic Syndromes and Thymic Malignancies: An Examination of the International Thymic Malignancy Interest Group Retrospective Database

Sukhmani K. Padda, MD, Xiaopan Yao, PhD, Alberto Antonielli, MD, Jonathan W. Riess, MD/MS, Yue Shang, PhD, Joseph B. Shrager, MD, Robert Korst, MD, Frank Detterbeck, MD, James Huang, Heather A. Wakelee, MD, Sunil S. Badve, MD

<table>
<thead>
<tr>
<th>PN/AI</th>
<th>Yes</th>
<th>2143 (34.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Myasthenia gravis</td>
<td>2068 (32.8)</td>
</tr>
<tr>
<td></td>
<td>Pure red cell aplasia</td>
<td>47 (0.7)</td>
</tr>
<tr>
<td></td>
<td>Hypogammaglobulinemia</td>
<td>13 (0.2)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>15 (0.3)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>4154 (66.0)</td>
</tr>
</tbody>
</table>

A

Product-Limit Survival Estimates

PN/AI(+) vs. PN/AI (-): HR 0.82 (95% CI 0.70-0.97)
Median OS: 21.6 yrs vs. 18.7 yrs
Log-Rank test p=0.02

B

Product-Limit Survival Estimates

PN/AI(+) vs. PN/AI (-): HR 0.56 (95% CI 0.39-1.0)
Median OS: 13.6 yrs vs. 7.4 yrs
Log-Rank test p=0.09

J Thorac Oncol 2017;13:436
**AUTO-IMMUNE DISORDERS**

**THYMOMA VS. THYMIC CARCINOMA**

Thymomas: loss of AIRE

Thymic carcinomas: shared antigens

Darnell et al. NEJM 2003;349:1543
AUTO-IMMUNE DISORDERS MAY BE EXACERBATED BY TREATMENT

Sunitinib in patients with chemotherapy-refractory thymoma and thymic carcinoma: an open-label phase II

Anish Thomas, Arun Rajan, Arlene Berman, Yusuke Tomitaka, Christina Brzezniak, Min-Jung Lee, Sumin Lee, Alexander Ling, Aaron Corey A Carter, Udayan Guha, Yisong Wang, Eva Szabo, Paul Meltzer, Seth M Steinberg, Jane B Trepel, Patrick J Loehrer, Giuseppe G

In the thymoma cohort, two (13%) patients—one with pure red-cell aplasia and one with hypogammaglobulinaemia—developed autoimmune disorders while on treatment. The frequency of autoimmune disorders before, during, and after treatment with sunitinib is summarised in the appendix (p 10).

Table S2. Autoimmune conditions before, during and after treatment with sunitinib in thymoma patients

<table>
<thead>
<tr>
<th>Before treatment</th>
<th>During treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Uveitis</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>None</td>
<td>PRCA</td>
</tr>
<tr>
<td>8</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>11</td>
<td>MG, PRCA</td>
<td>None</td>
</tr>
<tr>
<td>12</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>13</td>
<td>None</td>
<td>None</td>
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<td>14</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>15</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>16</td>
<td>MG, myasthenia gravis; PRCA, pure red cell aplasia</td>
<td>Hypogammaglobulinaemia</td>
</tr>
</tbody>
</table>

MG, myasthenia gravis; PRCA, pure red cell aplasia
†7 months after stopping treatment
‡2 months after stopping treatment

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Lancet Oncol 2015; 16:177
IMMUNOTHERAPY FOR THYMIC TUMORS
SAFETY IS THE FIRST CONCERN

Major risk of immune-related toxicity in thymomas

Waterfall plot. Three PRs were observed with a single dose of avelumab (*).

Duration of Treatment and Response

OA18.03: Safety and Clinical Activity of Avelumab (MSB0010718C; Anti-PD-L1) in Patients with Advanced Thymic Epithelial Tumors (TETs) – Arun Rajan

J Thorac Oncol 2016;11:e147

Rajan et al. WCLC 2016
IMMUNOTHERAPY FOR THYMIC TUMORS
PHASE II TRIALS

Response rate: 23%
Median DOR: 22 months
Severe irAE: 15%

Lancet Oncol 2018;19:347
IMMUNOTHERAPY FOR THYMIC TUMORS
PHASE II TRIALS

Table 2. Response to Treatment

<table>
<thead>
<tr>
<th></th>
<th>Thymoma (n = 7)</th>
<th>Thymic Carcinoma (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best response, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>2 (28.6)</td>
<td>5 (19.2)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>5 (71.4)</td>
<td>14 (53.8)</td>
</tr>
<tr>
<td>Progression</td>
<td>0 (0.0)</td>
<td>7 (26.9)</td>
</tr>
<tr>
<td>Overall response rate, % (95% CI)</td>
<td>28.6 (6.2 to 61.4)</td>
<td>19.2 (6.5 to 37.9)</td>
</tr>
<tr>
<td>Disease control rate, % (95% CI)</td>
<td>100 (64.6 to 100)</td>
<td>73.1 (63.9 to 86.3)</td>
</tr>
<tr>
<td>PFS, months, median (95% CI)</td>
<td>6.1 (4.3 to 7.9)</td>
<td>6.1 (6.1 to 7.1)</td>
</tr>
</tbody>
</table>

Table 5. Treatment-Related Autoimmune Syndromes in Patients Who Discontinued Pembrolizumab Treatment

<table>
<thead>
<tr>
<th>Patient</th>
<th>AS (grade)</th>
<th>Histology</th>
<th>Prior Radiotherapy</th>
<th>Prior Palliative Medicinal Mass</th>
<th>Best Response</th>
<th>Time to First sAE (No. of pembrolizumab cycles)</th>
<th>Recovery Time to Resolution Without Need for Immunosuppression (weeks)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Myasthenia (3)</td>
<td>Thymoma</td>
<td>No</td>
<td>PR</td>
<td>1</td>
<td>Curicosteroids Penicillamine Azathioprine</td>
<td>24</td>
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<tr>
<td>2</td>
<td>Myasthenia (3)</td>
<td>Thymoma</td>
<td>No</td>
<td>PR</td>
<td>10</td>
<td>Curicosteroids Penicillamine Azathioprine</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>Myasthenia (3)</td>
<td>Thymoma</td>
<td>No</td>
<td>SD</td>
<td>2</td>
<td>Curicosteroids Penicillamine Azathioprine</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>Myasthenia (3)</td>
<td>Thymoma</td>
<td>No</td>
<td>PR</td>
<td>1</td>
<td>Curicosteroids Penicillamine Azathioprine</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>Myasthenia (3)</td>
<td>Thymoma</td>
<td>No</td>
<td>SD</td>
<td>6</td>
<td>Curicosteroids Penicillamine Azathioprine</td>
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<td>6</td>
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<td>Thymoma</td>
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<td>SD</td>
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<td>12</td>
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</tbody>
</table>
IMMUNOTHERAPY FOR THYMIC TUMORS
NOT A STANDARD, ADDITIONAL TRIALS NEEDED

EORTC-ETOP NIVOTHYM

Primary objective:
To detect activity of nivolumab as single agent as second line treatment for type B3 thymoma and thymic carcinoma

Primary endpoint: PFS rate at 6 months

Secondary endpoints:
- ORR and DCR, Duration of response
- OS
- QOL
- Safety

Eligible patients

Nivolumab 240 mg IV q2 weeks

Biomarkers: SPECTA
- PD-L1
- Cytokines
- Molecular profiling

PIs: N. Girard, S. Peters

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THYMIC TUMORS: SYSTEMIC TREATMENT

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PRECISION MEDICINE APPROACHES?

IMMUNE CHECKPOINT INHIBITORS
TEAM IS THE KEY!

Pr Nicolas Girard  Dr Sophie Beaucaire-Daniel  Dr Catherine Daniel  Dr Alain Livartowski

Contact: nicolas.girard2@curie.fr