Thymic malignancies: biology, medical treatment and future perspectives

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Medical Oncology
UZ Brussel
Thymic Epithelial Tumors (TET) are mediastinal tumors that originate in the thymus and include thymoma and thymic carcinoma.

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

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

Falkson et al. JTO 2009; 4:911
Biology of TET: immunohistochemistry

- Overexpression of

<table>
<thead>
<tr>
<th>Gene overexpression</th>
<th>Thymoma</th>
<th>Thymic carcinoma</th>
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</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>70%</td>
<td>53%</td>
</tr>
<tr>
<td>IGFR-1</td>
<td>43%</td>
<td>86%</td>
</tr>
<tr>
<td>KIT</td>
<td>2%</td>
<td>79%</td>
</tr>
<tr>
<td>Mesothelin</td>
<td>infrequent</td>
<td>70%</td>
</tr>
</tbody>
</table>

- KIT expression associated with shorter PFS and OS
- Mesothelin overexpression associated with longer survival
- Cases of overexpression of ERBB2, Neutrophin receptors, VEGF-A, VEGFR-1, VEGFR-2

Biology of TET: whole exome sequencing

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

- **TC have higher TMB than thymoma**

Biology of TET: whole exome sequencing

Biology of TET: GTF2I mutation

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

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

Biology of TET: GTF2I mutation

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

Petrini et al. Nat Genet 2014; 46:844-849
Biology of TET: whole exome sequencing

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

Radovich M et al. Cancer Cell 2018; 33:244-258
Biology of TET: whole exome sequencing

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

Biology of TET: PD-L1 expression

- Data on PD-L1 expression are variable

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

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

- No randomized comparative phase 3 trials
- Relatively small single arm phase II trials
Systemic treatment: chemotherapy regimen

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

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Thymoma/TC (n)</th>
<th>ORR (%)</th>
<th>Survival</th>
<th>Line</th>
<th>Multimodal T</th>
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</thead>
<tbody>
<tr>
<td>Loehrer 1994</td>
<td>30</td>
<td>29/1</td>
<td>50</td>
<td>mOS 37.7 mo 2yS 64.5%</td>
<td>&gt;1</td>
<td>NO</td>
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<tr>
<td>Lee 1996</td>
<td>17</td>
<td>17/0</td>
<td>53</td>
<td>NR</td>
<td>1</td>
<td>NO</td>
</tr>
<tr>
<td>Kim 2004</td>
<td>22</td>
<td>10/12</td>
<td>77</td>
<td>5yS 95%</td>
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<td>YES</td>
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<tr>
<td>Liu 2007</td>
<td>28</td>
<td>7/21</td>
<td>71</td>
<td>NR</td>
<td>1</td>
<td>YES</td>
</tr>
<tr>
<td>Cardillo 2010</td>
<td>31</td>
<td>21/10</td>
<td>58</td>
<td>NR</td>
<td>1</td>
<td>YES</td>
</tr>
</tbody>
</table>
Systemic treatment: chemotherapy regimen

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

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Thymoma/TC</th>
<th>ORR</th>
<th>Survival</th>
<th>Line</th>
<th>Multimodal therapy</th>
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<tr>
<td>Fornasiero 1991</td>
<td>37</td>
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<td>92</td>
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<tr>
<td>Berruti 1993</td>
<td>6</td>
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<tr>
<td>Rea 1993</td>
<td>16</td>
<td>16/0</td>
<td>100</td>
<td>mOS 66 mo</td>
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<tr>
<td>Berruti 1999</td>
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<td>81</td>
<td>mOS 47.5 mo</td>
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<tr>
<td>Agatsuma 2011</td>
<td>34</td>
<td>0/34</td>
<td>50</td>
<td>mOS 21.3 mo 1yS 72.7%</td>
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<tr>
<td>Rea 2011</td>
<td>38</td>
<td>32/6</td>
<td>68</td>
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<td>YES</td>
</tr>
</tbody>
</table>
Systemic treatment: chemotherapy regimen

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

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Thymoma/TC</th>
<th>ORR</th>
<th>Survival</th>
<th>Line</th>
<th>Multimodal therapy</th>
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</thead>
<tbody>
<tr>
<td>Giaccone 1996</td>
<td>16</td>
<td>16/0</td>
<td>56</td>
<td>mOS 4.3 yrs 5yS 50%</td>
<td>&gt;1</td>
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<tr>
<td>Mineo 2010</td>
<td>33</td>
<td>33/0</td>
<td>45</td>
<td>mOS 30 mo 5yS 37%</td>
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<tr>
<td>Tamiya</td>
<td>5</td>
<td>5/0</td>
<td>40</td>
<td>mOS 40.8 mo NR</td>
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<td>Venuta 1997</td>
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<tr>
<td>Lucchi 2005</td>
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<td>NR</td>
<td>66</td>
<td>NR</td>
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<td>YES</td>
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<tr>
<td>Lucchi 2006</td>
<td>30</td>
<td>30/0</td>
<td>73</td>
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<td>1</td>
<td>YES</td>
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<tr>
<td>Loehrer 2001</td>
<td>28</td>
<td>20/8</td>
<td>32</td>
<td>mOS 6.1 yrs</td>
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<tr>
<td>Grassin 2010</td>
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<td>12/4</td>
<td>25</td>
<td>NR</td>
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</table>
Systemic treatment: chemotherapy regimen

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

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Thymoma/TC</th>
<th>ORR</th>
<th>Survival</th>
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<th>Multimodal therapy</th>
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<tbody>
<tr>
<td>Furugen 2011</td>
<td>16</td>
<td>0/16</td>
<td>38</td>
<td>mOS 49.4 mo</td>
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<tr>
<td>Lemma 2011</td>
<td>44</td>
<td>21/23</td>
<td>30</td>
<td>NR</td>
<td>&gt;1</td>
<td>NO</td>
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<tr>
<td>Hirai 2015</td>
<td>39</td>
<td>0/39</td>
<td>36</td>
<td>1yS 85% 2yS 71%</td>
<td>NR</td>
<td>NO</td>
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</tbody>
</table>
Chemotherapy: Indications

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

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

- **Definitive chemotherapy if unresectable**
Chemotherapy: adjuvant setting in thymoma

- Few data

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

Strobel et al. J Clin Oncol 2004
Chemotherapy: adjuvant setting in thymic carcinoma

- 176 stage IIB TC
  - 118 adjuvant R/
    - CT 63
    - CTRT 49
    - RT 6

- 456 stage III TC
  - 313 adjuvant R/
    - CT 129
    - CTRT 128
    - RT 56

Chemotherapy: adjuvant setting in thymic carcinoma

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

mOS NR vs 106 mo; p=0.01

Stage III: Survival benefit

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

mOS 94.9 mo vs 64.8 mo; p<0.01
Chemotherapy: adjuvant setting in thymic carcinoma

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

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

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>Group</th>
<th>No.</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>58</td>
<td>1.00 [Reference]</td>
<td>...</td>
<td>Surgery</td>
<td>143</td>
<td>1.00 [Reference]</td>
<td>...</td>
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<tr>
<td>Radiotherapy only</td>
<td>6</td>
<td>1.12 (0.20-6.15)</td>
<td>.90</td>
<td>Radiotherapy only</td>
<td>56</td>
<td>0.81 (0.48-1.36)</td>
<td>.42</td>
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<tr>
<td>Chemotherapy</td>
<td>63</td>
<td>0.39 (0.16-0.91)</td>
<td>.03</td>
<td>Chemotherapy</td>
<td>129</td>
<td>0.66 (0.43-0.99)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Chemoradiotherapy</td>
<td>49</td>
<td>0.43 (0.17-1.11)</td>
<td>.08</td>
<td>Chemoradiotherapy</td>
<td>128</td>
<td>0.45 (0.29-0.71)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

CI, confidence interval.
## Chemotherapy: neoadjuvant setting

### Preop Therapy for M-Stage III Thymoma/TC

<table>
<thead>
<tr>
<th>1st Author</th>
<th>n</th>
<th>IV</th>
<th>TC</th>
<th>Preop Chemo</th>
<th>Preop RT</th>
<th>% PR + CR</th>
<th>% R0</th>
<th>% pCR</th>
<th>Postop Therapy</th>
<th>% DFS 5-yr</th>
<th>% OS 5-yr</th>
<th>% OS 10-yr</th>
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<tr>
<td>Marulli</td>
<td>94</td>
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<td>19</td>
<td>P-based</td>
<td>-</td>
<td>69</td>
<td>76</td>
<td>-</td>
<td>most RT/Ch</td>
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<td>-</td>
<td>51</td>
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<td>Leuzzi</td>
<td>88</td>
<td>0</td>
<td>0</td>
<td>undefined</td>
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<td>-</td>
<td>65</td>
<td>-</td>
<td>±RT</td>
<td>85</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Kunitoh</td>
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<td>0</td>
<td>0</td>
<td>EAPV</td>
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<td>62</td>
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<td>23</td>
<td>RT</td>
<td>46</td>
<td>85</td>
<td>67</td>
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<tr>
<td>Mineo</td>
<td>33</td>
<td>0</td>
<td>0</td>
<td>PE x3</td>
<td>-</td>
<td>100</td>
<td>51</td>
<td>24</td>
<td>ChRT</td>
<td>-</td>
<td>37</td>
<td>24</td>
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<tr>
<td>Venuta</td>
<td>15</td>
<td>0</td>
<td>few</td>
<td>P-based</td>
<td>-</td>
<td>67</td>
<td>87</td>
<td>7</td>
<td>Ch x3→RT</td>
<td>-</td>
<td>-</td>
<td>90</td>
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<tr>
<td>Korst</td>
<td>21</td>
<td>0</td>
<td>33</td>
<td>PE x2 cRT</td>
<td>(24)</td>
<td>48</td>
<td>77</td>
<td>0</td>
<td>-</td>
<td>83</td>
<td>71</td>
<td>-</td>
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<tr>
<td>Wright</td>
<td>10</td>
<td>30</td>
<td>10</td>
<td>PE x2 cRT</td>
<td>-</td>
<td>40</td>
<td>80</td>
<td>0</td>
<td>±Ch x2</td>
<td>-</td>
<td>-</td>
<td>69</td>
</tr>
<tr>
<td>Lucchi</td>
<td>36</td>
<td>31</td>
<td>25</td>
<td>PEEpi x3</td>
<td>-</td>
<td>67</td>
<td>78</td>
<td>-</td>
<td>RT</td>
<td>-</td>
<td>76</td>
<td>64</td>
</tr>
<tr>
<td>Lucchi</td>
<td>30</td>
<td>33</td>
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<td>PEEpi x3</td>
<td>-</td>
<td>73</td>
<td>77</td>
<td>6</td>
<td>RT</td>
<td>-</td>
<td>83</td>
<td>83</td>
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<td>Rea</td>
<td>38</td>
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<td>CAPV x3-4</td>
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<td>74</td>
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<td>most RT±Ch</td>
<td>-</td>
<td>-</td>
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<td>Cardillo</td>
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<td>42</td>
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<td>58</td>
<td>77</td>
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<td>±RT</td>
<td>-</td>
<td>-</td>
<td>58</td>
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<tr>
<td>Bretty</td>
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<td>6e</td>
<td>P-based</td>
<td>-</td>
<td>72</td>
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<td>RT</td>
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<td>-</td>
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<tr>
<td>Kim</td>
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<td>50</td>
<td>0</td>
<td>CAPPr x3</td>
<td>-</td>
<td>77</td>
<td>-</td>
<td>-</td>
<td>RT→Ch x3</td>
<td>77</td>
<td>95</td>
<td>80</td>
</tr>
</tbody>
</table>

**Average**

- 67
- 68
- 11
- 73
- 74
- 63

**Average Stage III Surg ±RT**

- 40
- Most RT
- 65
- 56
Chemotherapy: which regimen?

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

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

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

- Anti-angiogenesis
- cKIT inhibitors
- mTOR inhibitors
- IGFR-1 inhibitors
Anti-angiogenesis: Sunitinib

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

- Real life retrospective analysis from the French RYTHMIC network
  → N= 28 (8 T and 20 TC)

<table>
<thead>
<tr>
<th></th>
<th>Thymoma</th>
<th>Thymic Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (%)</td>
<td>28.6 (2/7)</td>
<td>20 (4/20)</td>
</tr>
<tr>
<td>DCR (%)</td>
<td>86 (6/7)</td>
<td>55 (11/20)</td>
</tr>
<tr>
<td>mPFS (mo)</td>
<td>5.4</td>
<td>3.3</td>
</tr>
<tr>
<td>mOS (mo)</td>
<td>NR</td>
<td>12.3</td>
</tr>
</tbody>
</table>

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

Anti-angiogenesis: Lenvatinib

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

Anti-cKIT inhibition: Imatinib

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

- BUT case reports of activity in KIT mutant TC

mTOR inhibitor: everolimus

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

<table>
<thead>
<tr>
<th></th>
<th>Thymoma (n=32)</th>
<th>TC (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>9.4%</td>
<td>16.7%</td>
</tr>
<tr>
<td>DCR</td>
<td>78%</td>
<td>94%</td>
</tr>
<tr>
<td>mPFS</td>
<td>16.6 mo</td>
<td>5.6 mo</td>
</tr>
<tr>
<td>mOS</td>
<td>NR</td>
<td>14.7 mo</td>
</tr>
</tbody>
</table>

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

IGFR-1 inhibitor: cixutumumab

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

<table>
<thead>
<tr>
<th></th>
<th>Thymoma (n=37)</th>
<th>TC (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>14%</td>
<td>0%</td>
</tr>
<tr>
<td>DCR</td>
<td>89%</td>
<td>42%</td>
</tr>
<tr>
<td>mPFS</td>
<td>9.9 mo</td>
<td>1.7 mo</td>
</tr>
<tr>
<td>mOS</td>
<td>27.5 mo</td>
<td>8.4 mo</td>
</tr>
</tbody>
</table>

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

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

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

Immunotherapy: Nivolumab

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

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

Giaccone et al. Lancet Oncol 2018
Immunotherapy: Pembrolizumab

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

<table>
<thead>
<tr>
<th></th>
<th>Thymoma (n=7)</th>
<th>TC (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>28.6%</td>
<td>19.2%</td>
</tr>
<tr>
<td>DCR</td>
<td>100%</td>
<td>73.1%</td>
</tr>
<tr>
<td>mDOR</td>
<td>NR</td>
<td>9.7 mo</td>
</tr>
<tr>
<td>mPFS</td>
<td>6.1 mo</td>
<td>6.1 mo</td>
</tr>
<tr>
<td>mOS</td>
<td>NR</td>
<td>14.5 mo</td>
</tr>
<tr>
<td>irAE G3/4</td>
<td>71.4% (5/7)</td>
<td>15.4% (4/26)</td>
</tr>
</tbody>
</table>

**TABLE 4. Immune-Related Adverse Events at Any Frequency**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Thymoma (n = 7)</th>
<th>Thymic Carcinoma (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis</td>
<td>Grade 1-2: 0</td>
<td>Grade 3-4: 2 (28.6%)</td>
</tr>
<tr>
<td></td>
<td>Grade 1-2: 0</td>
<td>Grade 3-4: 2 (7.7%)</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>1 (14.3%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>2 (7.7%)</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>0</td>
<td>3 (42.9%)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>1 (14.3%)</td>
<td>1 (14.3%)</td>
</tr>
<tr>
<td></td>
<td>1 (3.8%)</td>
<td>0</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>2 (28.6%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Colitis</td>
<td>0</td>
<td>1 (14.3%)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>0</td>
<td>1 (14.3%)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nephritis</td>
<td>0</td>
<td>1 (14.3%)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subacute myoclonus</td>
<td>0</td>
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</tr>
<tr>
<td></td>
<td>0</td>
<td>1 (3.8%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0</td>
<td>3 (11.5%)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin rash</td>
<td>0</td>
<td>2 (7.7%)</td>
</tr>
</tbody>
</table>

**NOTE.** Data presented as No. (%).
Future perspectives

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

● Tumor biology
  → TET have low TMB
  → Tumor biology differs between the histological subtypes and there is an increase of mutations with more aggressive histology

● Chemotherapy
  → Different chemotherapy regimens are used, most frequently CAP
  → Indications:
    ● Adjuvant chemotherapy may be considered for stage III and incompletely resected stage II TC
    ● Induction chemotherapy for potentially resectable TETs
    ● Unresectable TETs
Take home messages

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