Treatment for Metastatic Medullary Thyroid Cancer

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Relevant Financial Relationships

Company Name: Amgen, Astra-Zeneca, Bayer, BI, Eisai, Exelixis, Genzyme, GSK, Roche.

Nature of Relationship: research grants

Objectives

Medullary thyroid cancer: definition and role of RET
Treatment of metastatic disease
Use of TKI:
  benefits
  adverse events and resistance
Increasing incidence of cancers (3%-6%/year for 30 years).

Attributed mainly to improved screening

Cancer is present in only 5% of all thyroid tumors: diagnosis is first based on FNAC
Thyroid tumors: classification

Thyroid follicle

Thyrocyte

Adenomas Cancer
- Differentiated (>90% of all cancers): Papillary, follicular, poorly differentiated
- Undifferentiated (anaplastic)

Medullary thyroid cancer (<5% of all cancers)
Epidemiology of medullary thyroid cancer

- **Incidence**
  - <5% of all thyroid cancers (1500-2000 cases/year in Europe)
  - Distant metastases requiring systemic treatment: 1 / 1.5 million population (~50 cases/year in France)

- **Genetics**
  - MTC may be hereditary:
    - Germline RET mutation. Autosomic dominant trait
    - Identification of gene carriers: prophylactic treatment
  - MTC is sporadic in >2/3 of cases:
    - Discovery at a clinical stage
    - Somatic RET mutation in >40% of tumors
Oncogenic Addiction

Figure 1. Many possible outcomes to oncogene inactivation: no effect, complete, or partial tumor reversion. Tumor death, dormancy, differentiation, or relapse.
Ret (1993): transmembrane receptor with tyrosine kinase activity. Ligand: GDNF Co-receptor: GFR alpha Ligand binding induces its dimerisation and TK activation This in turn activates several transduction pathways including the MAP kinase pathway
Signal transduction pathways in thyroid cancers

Tumor Cell

- RET
  - Y1062
  - Phosphorylated (P)
- EGFR
- C-MET
- PI3K
- AKT
- MEK
- ERK
- BRAF
- RAS
- PKC
- PLC-γ
- VEGFR
- VEGF

Endothelial cell
MTC: initial surgery

- Surgery consists for all MTCs in:
  - Total thyroidectomy
  - Bilateral dissection of lateral and central compartments.

- Success is mainly dependent upon the adequacy of the initial operation (complete protocol/skilled hands).
MTC management based on stratified genetic testing

- Genetic testing permits prophylactic surgery with cure rates >95%

- MEN 2B.
  - Thyroidectomy within the first year of life, preferably within the first month.

- RET codon 634 mutation.
  - Thyroidectomy before the age of 5 years

- RET codon 611, 618, 620 mutation and RET codon 609, 768, 790, 804 or 891 mutation.
  - Thyroidectomy possibly later than 5 years if Ct is normal, neck US is normal, familial history is not aggressive and family preference
Focus on advanced MTC

Stage IVb: **T4b** (tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels), Any N, M0.

Stage IVc: Any T, Any N, **M1**

MTC: distant metastases

- At MTC discovery: 2% (Mayo Clinic) - >15% (IGR) of patients
- During the 10 first years of follow-up, DM are detected in ~30-50% of patients with post-operative detectable Ct levels
- Diarrhea: ~30%; flushes: ~15%.
- Often present in several sites
- Often multiple in each site.

Guidelines ATA (2009) and ETA (2012)
Three problems

- Recognizing aggressive MTC
- Therapy inertia vs treatment
- Selecting adequate treatment

MTC: natural history

Thyroid nodule +/- N1: surgery

Post-operative calcitonin (Ct)

Detectable: 10-yr survival rate >90%

Undetectable = cure

Neck persistence / neck recurrence

Distant metastases

Stable disease → follow-up

Progressive disease → treatment

MDT
MTC: distant metastases

- Assessment of disease extent – standardized imaging
  - Neck: US-spiral CT scan
  - Mediastinum and lung: spiral CT scan with contrast medium
  - Liver: MRI, and if not feasible, dual-phase CT scan
  - Bone: bone scintigraphy + axial MRI
  - Brain: MRI or spiral CT scan
  - FDG or FDOPA-PET scan?

- MTC patients
  - post-operative serum Ct levels ≥150 pg/mL: imaging techniques to evaluate for distant metastases.
  - If negative, should be repeated when Ct level increases by >20-100%.

MTC: FDG-PET scan

- Slowly progressive disease: low FDG uptake in metastases (standardized uptake value <6)
- Low diagnostic sensitivity/not appropriate for assessing progression or tumor response
Slowly progressive disease: **low FDG uptake in metastases (standardized uptake value <6)**

Low diagnostic sensitivity/not appropriate for assessing progression or tumor response

Exceptions: MTC patients with rapidly progressive disease

Role of F-DOPA: expensive/does it improve sensitivity of the complete imaging
Liver metastases may be difficult to visualize
US: angiomatous appearance
MRI scan (T1, T2) with arterial phase > CT scan with arterial and venous phases
MRI is more reliable than CT scan for assessment during treatment with antiangiogenic agents

25 MTC patients with liver metastases; miliary in 18 patients

<table>
<thead>
<tr>
<th></th>
<th>US</th>
<th>CT</th>
<th>MRI</th>
<th>PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>18</td>
<td>21</td>
<td>25</td>
<td>12</td>
</tr>
<tr>
<td>Lesions</td>
<td>164</td>
<td>178</td>
<td>233</td>
<td>52</td>
</tr>
</tbody>
</table>

Liver metastases: vandetanib treatment

- During antiangiogenic treatment, liver metastases may not be visible on CT but still be visible on MRI.
Metastatic MTC: prognosis

- Tumor burden: complete imaging
- Progression
  - There is no evidence that the efficacy of a systemic treatment at an early stage may be better than at a later stage
  - FU and local treatment modalities should be used as long as reasonably possible

Candidates for systemic treatment
- Large tumor burden: imaging
- Symptomatic or progressive disease on imaging (not only on DT-Ct and CEA)
Ct: doubling time (DT)

Survival rate and DT (n=65)

- DT >2 yr
- DT 0.5–2 yr
- DT <0.5 yr

Progression and DT-Ct

IGR: Progression at 1 year (RECIST: 24/45)
- DT <2 years: 94% had progressive disease
- DT >2 years: 86% had stable disease

DT < 2 years in 24/65 patients

Why is imaging so important?

During treatment with vandetanib, serum Ct and CEA levels decrease in > 80% of patients. This decrease is related to the inhibition of the ret tyrosine kinase. It may be not paralleled by a decrease in tumor masses on imaging (efficacy).

What to do in a patient with stable disease before and on treatment when toxicity appears?

Indication for treatment: progressive disease on imaging
Efficacy: tumor targets on imaging (RECIST)

Do not treat: elevated Ct levels, patients with small tumor burden; patients with no evidence of progression on imaging
Metastatic MTC: prognosis

• Candidates for local treatment modalities:
  – Before any systemic treatment
  – Local symptoms or risk of local complication:
    • Surgery
    • External radiation beam therapy,
    • Percutaneous intervention (Therapeutic imaging):
      – Radiofrequency ablation, cryoablation
      – Cement injection
      – Hepatic embolization

• Candidates for systemic treatment
  – Large tumor burden: imaging
  – Symptomatic or progressive disease on imaging (not only on DT-Ct and Dt-CEA)
## Initiation of systemic treatment in patients with metastatic MTC

<table>
<thead>
<tr>
<th>Progression</th>
<th>Tumor burden</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Small &lt;1cm</td>
<td>Large/Multiple &gt;1.5-2 cm</td>
</tr>
<tr>
<td>&lt;12-14 months</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>&gt;12-14 months</td>
<td>No</td>
<td>?? (High SUV? Symptoms?)</td>
</tr>
</tbody>
</table>
Symptomatic treatment (pain, diarrhea)

Somatostatin analogs: no benefits

Chemotherapy (ADR or 5FU/DTIC)
  - Low efficacy (ORR< 5-20%; no demonstrated benefits on survival); high toxicity

Metabolic radiation therapy (anti CEA mAb, $^{90}$Yttrium-DOTA-TOC) (Chatal JF, J Clin Oncol 2006;24:1705)
  - Low efficacy, potential toxicity

Targetted therapy (Kloos et al, Thyroid. 2009;19:565)
Local treatment for advanced disease

- Brain metastases:
  - Surgery and/or external radiation beam therapy
- Bone metastases with imaging abnormalities:
  - Surgery and ERBT
  - Radiofrequency-cryoablation, cement injection
- Lung metastases, in case of predominant lesions:
  - Radiofrequency ablation
  - Surgery

- Local treatment modalities may be used alone or in combination with systemic treatment
Surgery for bone metastases

- Single vertebral metastasis: $^{131}$I (3.7GBq x 6) and EBRT: persistent $^{131}$I uptake.
- Surgical resection after embolization: cure.

Preoperative arteriography
CT-guidance
« Real time »

Anesthésie générale

Biopsie si indiquée
Ablation par radiofréquence d’une méta pulmonaire
Cryothérapie suivi de cimentoplastie

Résultats à 1 an

Cryothérapie suivi de cimentoplastie
### Treatment
- Anti-hypertension
- Anti-osteoporosis
- Anti-neoplastic

### Marker
- Blood pressure
- Bone mineralisation
- Tumor response (ORR, PFS)

### Aim
- Stroke
- Fracture
- Survival

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Décès

TRAITEMENT
TRAITEMENT

Décès

Guérison

Volume Tumoral
TRAITEMENT

Volume Tumoral

Décès

Guérison
Volume Tumoral

TRAITEMENT

Décès

Guérison
Tumor response: a surrogate marker of survival

Benefits on survival may be difficult to demonstrate, and this is the case for patients with a significant life expectancy who will receive several lines of treatment.

Objective response rate (ORR) that includes CR, PR and SD is measured in phase II trial but is poorly related to overall survival.

Progression free survival is better related to OS: it takes into account response duration: improvement of PFS can only be measured in randomized trials.
MTC
Activating RET mutation: 100% hereditary, > 40% sporadic MTCs
Activating RAS mutation: > 2/3 of MTCs without RET mutation
Kinase Inhibitors

ATP → KI → ATP

Activated pathway → Cancer

RET, ..... inhibition

Tumor growth

VEGFR inhibition

Tumor angiogenesis

VEGF
<table>
<thead>
<tr>
<th>Compound</th>
<th>VEGFR1</th>
<th>VEGFR2</th>
<th>VEGFR3</th>
<th>RET</th>
<th>RET/PTC3</th>
<th>RAF</th>
<th>Other targets</th>
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</thead>
<tbody>
<tr>
<td>Axitinib</td>
<td>1.2</td>
<td>0.25</td>
<td>0.29</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>1600</td>
<td>40</td>
<td>110</td>
<td>100</td>
<td>50-100</td>
<td>-</td>
<td>EGFR</td>
</tr>
<tr>
<td>Motesanib diphosphate</td>
<td>2</td>
<td>3</td>
<td>6</td>
<td>59</td>
<td>-</td>
<td>-</td>
<td>PDGF-R, C-KIT</td>
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<tr>
<td>Sunitinib</td>
<td>2</td>
<td>9</td>
<td>17</td>
<td>41</td>
<td>224</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Sorafenib</td>
<td>-</td>
<td>90</td>
<td>20</td>
<td>49</td>
<td>50</td>
<td>6</td>
<td>-</td>
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<tr>
<td>Lenvatinib (E7080)</td>
<td>22</td>
<td>4</td>
<td>5</td>
<td>35</td>
<td></td>
<td></td>
<td>PDGF-R, FGFR-1</td>
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<tr>
<td>Cabozantinib (XL184)</td>
<td>-</td>
<td>0.035</td>
<td>14</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>C-MET, C-KIT</td>
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<tr>
<td>Pazopanib</td>
<td>10</td>
<td>30</td>
<td>47</td>
<td></td>
<td></td>
<td></td>
<td>PDGF-R, C-KIT</td>
</tr>
</tbody>
</table>
### CMT: phases 1-2. Inhibiteurs de kinases

<table>
<thead>
<tr>
<th>Inhibiteur</th>
<th>Cibles</th>
<th>n</th>
<th>RP (%)</th>
<th>SD &gt; 6 mo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vandetanib (Wells)</td>
<td>VEGFR, RET, EGFR</td>
<td>30</td>
<td>30</td>
<td>53</td>
</tr>
<tr>
<td>Sorafenib (Lam)</td>
<td>VEGFR, BRAF</td>
<td>19</td>
<td>11</td>
<td>68</td>
</tr>
<tr>
<td>Motesanib (Schlumberger)</td>
<td>VEGFR, PDGFR, C-KIT</td>
<td>83</td>
<td>2</td>
<td>43</td>
</tr>
<tr>
<td>Axitinib (Cohen)</td>
<td>VEGFR1,2,3</td>
<td>12</td>
<td>22</td>
<td>50</td>
</tr>
<tr>
<td>Sunitinib (Carr)</td>
<td>VEGFR, RET</td>
<td>6</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Cabozantinib (XL-184) (Kurzrock)</td>
<td>VEGFR, RET, C-MET</td>
<td>35</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Lenvatinib (E7080) (Schlumberger)</td>
<td>VEGFR, RET</td>
<td>59</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Gefitinib (Pennell)</td>
<td>EGFR</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C-KIT, PDGFR</td>
<td>15</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td>Imatinib (De Groot, Frank-Raue)</td>
<td></td>
<td>9</td>
<td>0</td>
<td>56</td>
</tr>
</tbody>
</table>
Toxicities associated with inhibition of kinases

Cardiovascular
- **Hypertension**
- QT prolongation
- CHF
- Acute coronary syndrome

**Diarrhea**

**Fatigue**

Weight loss

**Skin toxicity**: rashes, folliculitis, HFS, squamous cell skin cancer

**Hypothyroidism**: frequent serum TSH determination/
Increased need in LT4

Dose reduction: 11-73%
Drug withdrawal: 7-25%
Two phase 3 trials vs placebo

• Vandetanib (300mg/d) vs placebo with cross over in 331 advanced MTCs: PFS

• XL-184 (175mg/d) vs placebo without cross-over in progressive MTCs: OS
  – Improved PFS- 4.0 (placebo) vs 11.2 months (treatment) (HR: 0.28 (95%CI: 0.19-0.40, p<0.0001)
Vandetanib inhibits tyrosine kinase of VEGFR2-3, EGF et RET

RET protein
KNOWLES, JBC 2006

ZD6474
Vandetanib Inhibits Key Molecular Targets in MTC

Vandetanib inhibits EGFR, VEGFR2, wild type and mutated RET

Vandetanib treatment of nude mice

Carlomagno F et al.  
*Cancer Res* 2002;62:7284–7290
Vandetanib treatment of nude mice

NIH-RET/PTC3-injected mice
Fly eye – a model for cancer

The Drosophila retina

- Simple epithelium; few cell types
- Much is known about signaling pathways that guide development

Two cancer models

- Multiple Endocrine Neoplasia Type 2
- *Csk/Src* (breast, colon, etc)
Vandetanib suppresses RET signaling *in vivo*

Wild type  

$\text{RET}^{\text{MEN2B}}$  

$\text{RET}^{\text{MEN2B}}$ + 0.2 mM vandetanib  

$\text{RET}^{\text{MEN2B}}$ + 1 mM vandetanib

Vandetanib in metastatic hereditary medullary thyroid cancer: follow-up results of an open-label Phase II trial

SA Wells,1 JE Gosnell,2 RF Gagel,3 J Moley,1 D Pfister,4 JA Sosa,5 M Skinner,6 A Krebs,7 J Hou,7 J Vasselli7 and M Schlumberger8

1Washington University School of Medicine, St Louis, MO, USA
2University of California at San Francisco, San Francisco, CA, USA
3UTMD Anderson Cancer Center, Houston, TX, USA
4Memorial Sloan-Kettering Cancer Center, NY, USA
5Yale University School of Medicine, New Haven, CT, USA
6University of Texas, Southwestern Medical Center, Dallas, TX, USA
7AstraZeneca, Wilmington, DE, USA
8Institut Gustave Roussy, Villejuif, France
Vandetanib (300 mg): phase II, 30 patients with hereditary MTC

PR 10/30; confirmed PR: 6/30 (mean duration: 311 days+)
Stable disease >24 weeks: 16/30 (53%)

Wells S, JCO 2009
Vandetanib in Locally Advanced or Metastatic MTC: Randomized, Double-Blind Phase III Trial (ZETA)

Patients with unresectable locally advanced or metastatic MTC (N = 331)

2:1 Randomization

Vandetanib 300 mg/day
n = 231

Follow for progression

Discontinued blinded treatment at progression

Optional open-label vandetanib 300 mg/day

Follow for survival

Primary endpoint: PFS

Placebo
n = 100

Follow for progression

PFS, Progression-free survival

Phase 3 trial: vandetanib vs placebo (Zeta study)

Figure 1. Kaplan-Meier plot of PFS (Full Analysis Set)

Median PFS:
Placebo: 19.3 mo
Vandetanib: >30.5 mo, not reached (HR: 0.46; p<10^{-4})

ORR: 44%

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Vandetanib 300 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>231</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>198</td>
<td>72</td>
</tr>
<tr>
<td>12</td>
<td>171</td>
<td>57</td>
</tr>
<tr>
<td>18</td>
<td>141</td>
<td>45</td>
</tr>
<tr>
<td>24</td>
<td>42</td>
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<tr>
<td>30</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>36</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Vandetanib: toxicity

• Adverse event profile consistent with EGFR and VEGFR inhibition: diarrhea, rash and folliculitis, nausea, hypertension, fatigue

• QT prolongation common (>20ms in 90% of patients): (long QTc before treatment (450ms), other treatments, electrolyte abnormalities (diarrhea)), but “torsades de pointes” and sudden death are rare

• Long median duration of treatment (21 months): AEs managed with dose reduction / standard medical treatment. Tolerance is usually good

• Rate of discontinuation for AE – 13%
Vandetanib benefited all patient groups in a predefined subgroup analysis of PFS.

The analyses were performed using a log-rank test with treatment as the only factor.
**PFS by tumor size at baseline**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size ≥10cm (n=114)</td>
<td>57</td>
<td>50.0%</td>
</tr>
<tr>
<td>Tumor size &lt;10cm (n=17)</td>
<td>47</td>
<td>40.2%</td>
</tr>
</tbody>
</table>
Vandetanib treatment significantly prolonged time to worsening of pain*

Hazard ratio = 0.61 (0.43–0.87); \(P=0.006\)

Median (months): 7.85 (vandetanib); 3.25 (placebo)

* Determined from patient-reported opioid analgesic use and responses to the Brief Pain Inventory questionnaire

Hazard ratio <1 favours vandetanib
A delay of 11 months in initiating vandetanib treatment does not alter OS in a “Vandetanib-phase III MTC patients”

OS is affected by the cross over (93% in the placebo group)

Mature OS analysis : >=2012
Data on RET mutation status (Study 58)

- **298 Sporadic MTC Patients on Study 58**
  - **155** proven RET mutation positive – 92% with 918T mutation
  - **79** proven to have No mutation at M918T and No other mutation identified:
    - 8 patients found negative by all other mutation tests
    - 71 patients had some or all of the other tests failed, but those that worked demonstrated no mutation
  - **64** No information on M918T mutation
### Benefit in 79 M918T mutation negative patients

<table>
<thead>
<tr>
<th>Efficacy Endpoint</th>
<th>RET Mutation Positive Patients (n=187)*</th>
<th>Patients with No M918T Mutation and No Other Identified Mutation (n=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS HR (95%) confidence interval</td>
<td>0.45 (0.26, 0.78)</td>
<td>0.57 (0.29, 1.13)</td>
</tr>
<tr>
<td>Predicted Median PFS (months)</td>
<td>29 vs 18</td>
<td>28 vs 18</td>
</tr>
<tr>
<td>(vandetanib vs placebo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Objective Response Rate (vandetanib arm)</td>
<td>52%</td>
<td>35%</td>
</tr>
<tr>
<td>Duration of Response (months)</td>
<td>22</td>
<td>18</td>
</tr>
</tbody>
</table>

* This includes RET mutation positive hereditary MTC patients
Kaplan-Meier plot of PFS and RET M918T

PFS in RET positive patients

HR 0.45  95% CI (0.26–0.78)

PFS in RET M918T negative patients

HR 0.57  95% CI (0.29–1.13)
RET mutation negative MTC: patient 2801035

Baseline November 2008

Vandetanib 300mg/d. November 2009

Calcitonin: 35,000pg/mL

850 pg/ml
Molecular Biological Rationale for Vandetanib Activity in RET Mutation Negative MTC

Vandetanib- multi-kinase inhibitor: VEGFR, EGFR and RET:

RET: Vandetanib inhibits Non Mutated RET
RET mutation negative MTC – express Non-Mutated RET
Functional role of Non-Mutated RET carried over to MTC
– Calcitonin secretion decreases on RET inhibition

VEGFR: Expressed by MTC cells
Increased expression in both hereditary and sporadic MTC
Increased expression in RET mutation negative MTC

EGFR: Evidence for amplification and overexpression in MTC
Cross talk between EGFR and RET leading to trans-activation of the receptors has also been described

RAS: Frequent in RET<0 MTCs. Paradigms of EGFR/KRAS mutations in colon carcinoma may not apply

Metastatic MTC: vandetanib

- Higher efficacy than any other systemic treatment:
  - High ORR with many long lasting responses (> 3-5 years)
  - Significantly prolonged PFS
  - Symptomatic benefits in many patients

- Vandetanib was available in the frame of an Autorisation Temporaire d’Utilisation (ATU) in France since august 2010: on august 2011, 47 MTC patients have been included (1/1.5 millions/year). 30 AEs have been reported, including 18 serious AEs, but no unexpected toxicities.

- Vandetanib was approved
  - By FDA in april 2011
  - By EMA in november 2011 for the treatment of aggressive and symptomatic MTC in patients with unresectable locally advanced or metastatic disease, but further data are needed to quantify drug benefits in patients with no RET mutation in their metastatic tissue.
  - By France in april 2012.
Pour mieux soigner : des médicaments à écartter

le vandétanib (Caprelsa°), sans efficacité démontrée sur la survie dans les cancers médullaires de la thyroïde, expose à des effets indésirables graves chez 1 patient sur 3 (diarrhées, pneumonies, hypertensions) et à des morts subites (n° 342 p. 256-259) ;
XL184: preclinical rationale

- Inhibits MET, VEGFR2, RET
- Including usual mutants of MET and RET
- Active in animal models
  - *In vivo*: inhibition of MET, VEGFR2, RET
  - Regression of tumors
MTC phase 3 trial: cabozantinib vs placebo

- Cabozantinib (XL-184) (175mg/d) vs placebo without cross-over:
  - 330 patients with progressive disease in <14 months
  - Randomization 2/1
  - ORR: 28%.
  - PFS: 4.0 (placebo) vs 11.2 months (cabozantinib) (HR: 0.28 (95%CI: 0.19-0.40, p<0.0001))
  - OS not mature
Phase 3. Cabozantinib: progression free survival

Schöffski P et al., ASCO Annual Meeting, Chicago, 04 June 2012
Cabozantinib: best tumor response

Prior tyrosine kinase inhibitor therapy (21% of patients)
Median response duration: 14.7 months

Schöffski et al., ASCO Annual Meeting, Chicago, 04 June 2012
Adverse reactions observed in ≥ 25% and grade 3-4 in ≥ 5%: diarrhea, stomatitis, palmar-plantar erythrodysesthesia syndrome (PPES), decreased weight, decreased appetite, nausea, fatigue, hypertension, abdominal pain.

Laboratory abnormalities (≥25%): increased AST-ALT, lymphopenia, increased alkaline phosphatase, hypocalcemia, neutropenia, thrombocytopenia, hypophosphatemia, and hyperbilirubinemia.

The following serious adverse reactions attributed to cabozantinib included osteonecrosis of the jaw (n=1), reversible posterior leukoencephalopathy syndrome (n=1), pancreatitis (n=3), nephrotic syndrome (n=1), fatal hemorrhage (n=2), and fatal perforation/fistula (n=2).

Dose reduction was required in 79% of patients.
<table>
<thead>
<tr>
<th></th>
<th>ZETA Vandetanib</th>
<th>EXAM Cabozantinib</th>
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</thead>
<tbody>
<tr>
<td>Dose reduction (%)</td>
<td>35</td>
<td>79</td>
</tr>
<tr>
<td>Discontinuation for toxicity (%)</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Grade 3 &amp; 4 toxicity (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11</td>
<td>15.9</td>
</tr>
<tr>
<td>HFS</td>
<td>N/A</td>
<td>12.6</td>
</tr>
<tr>
<td>Rash</td>
<td>4</td>
<td>0.9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9</td>
<td>8.4</td>
</tr>
<tr>
<td>QTc prolongation</td>
<td>8</td>
<td>N/A</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6</td>
<td>9.3</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>4</td>
<td>4.7</td>
</tr>
</tbody>
</table>
MTC
Activating RET mutation: 100% hereditary, > 40% sporadic MTCs
Activating RAS mutation: > 2/3 of MTCs without RET mutation
Response to cabozantinib and mutational status  
(ASCO, 2013)

- RET status was determined in 216/330 pts
- 79% harbored an activating mutation, and 21% were mutation negative.
- All RET mutational subgroups (positive, negative, and unknown) showed hazard ratios indicating PFS benefit from cabo treatment, and an ORR between 22% and 32%.
- Pts with RET M918T mutation showed a statistically significant longer median PFS on cabo treatment (61 weeks) than other RET mutation positive pts (36 weeks, p=0.049).
- 16/85 tested pts with negative or unknown RET-mutation status had a RAS gene mutation: the RAS-positive pts showed a similar ORR (31%) and PFS (47 weeks) as the RET positive population.
On November 29, 2012, the U. S. Food and Drug Administration approved cabozantinib (COMETRIQ capsules, Exelixis, Inc), for the treatment of patients with progressive metastatic medullary thyroid cancer (MTC).
On March 2014 by EMA.
### Natural history of a 52-year-old sporadic MTC patient

<table>
<thead>
<tr>
<th>Year</th>
<th>Event/Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986</td>
<td>Total thyroidectomy + lymph node dissection (T4, N1, M0) Radiation therapy to the neck</td>
</tr>
<tr>
<td>1987</td>
<td>Ct = 134 pg/mL Negative imaging</td>
</tr>
<tr>
<td>1993</td>
<td>Ct = 698 pg/mL Liver mets: 7, 7, 7 mm</td>
</tr>
<tr>
<td>1996</td>
<td>Ct = 1,500 pg/mL Liver mets: 12, 16, 17 mm</td>
</tr>
<tr>
<td>1999</td>
<td>Ct = 3,400 pg/mL Liver mets: 10, 15, 16, 20 mm</td>
</tr>
<tr>
<td>2002</td>
<td>Ct = 5,500 pg/mL Liver mets: 14, 18, 15, 24 mm Good quality of life, no diarrhea</td>
</tr>
<tr>
<td>2004</td>
<td>Ct = 12,200 pg/mL Lung and bone mets Bone surgery and chemotherapy (no benefits) TKI</td>
</tr>
<tr>
<td>2005</td>
<td>Brain mets Radiation therapy</td>
</tr>
<tr>
<td>July 2006</td>
<td>Death</td>
</tr>
</tbody>
</table>

Ct and tumor doubling times ~3 years
Metastatic MTC: molecular targeted therapies

• Duration of treatment (years?), short and long-term toxicity, quality of life, improvement of survival are still under evaluation: local treatment modalities of distant metastases may control the disease and delay the initiation of systemic treatment

• There is no indication:
  – For patients with elevated Ct and or CEA levels and no other evidence of disease
  – For patients with minimal disease (< 2cm), when asymptomatic and stable

• Decision to treat has to be validated by a multidisciplinary team

• Control of toxicities
Advanced MTC’s new unmet need: progression following treatment with TKIs

- Patients progress, but maintain good performance status
- Many patients respond, then progress in a new lesion or a subset of lesions.
- Need for studies:
  - Get tissue! – Perform translational analysis - perform trials
    - Sequential treatment with MKIs, but all molecules are anti-angiogenic
    - Find other targets. New agents in development may also play a role in the treatment of thyroid cancer in the first- or second-line settings (PI3K) and PD-1-PDL-1
French network for rare cancers: TUTHYREF: TUmeurs de la THYroïde REfractaires supported by the French Institut National du Cancer
- Referral center: IGR
- 30 competence centres
- Web conference every 2 weeks, annual meeting, protocols
- Objectives:
  - Recommendations: ATA/ETA
  - Research
  - Access to innovation for all patients
Several compounds are partially effective, and there is a need for:
  • Improving drug efficacy
  • Decreasing drug toxicity
  • Predicting drug efficacy (biomarkers, ....)

Need for large series of patients (Phase II and III trials) in National, European (Endocrine Group of the EORTC) and International (ITOG) networks

Inclusion of patients in trials rather than off label use of drugs.

Getting the right drug to each patient.