ESMO 2017 Meet-the-investigator meeting

Disease management and comprehensive genomic profiling in cancer of unknown primary

11 September 2017
IFEMA, Feria de Madrid, Spain
Housekeeping notes

Please remember to fill out the meeting evaluation form before leaving

This meeting is being video recorded
## Agenda

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Presenter/Moderator</th>
</tr>
</thead>
<tbody>
<tr>
<td>09:05 – 09:15</td>
<td>Current standard of care</td>
<td>Alwin Krämer</td>
</tr>
<tr>
<td>09:15 – 09:25</td>
<td>Molecular testing: from gene expression profiling to comprehensive genomic profiling</td>
<td>Jeffrey Ross</td>
</tr>
<tr>
<td>09:25 – 09:45</td>
<td>Tumor board discussion based on clinical cases</td>
<td>Alwin Krämer / Holger Moch / Jeffrey Ross</td>
</tr>
<tr>
<td>09:45 – 09:55</td>
<td>Genomic profiling study for patients with cancers of unknown primary</td>
<td>Alwin Krämer</td>
</tr>
<tr>
<td>09:55 – 10:00</td>
<td>Meeting closure</td>
<td>Alwin Krämer</td>
</tr>
</tbody>
</table>

The information contained herein may refer to use of products for indications other than those approved and/or listed in the Summary of Product Characteristics or relating to molecules currently undergoing experimental trials. The issues addressed are not meant to suggest that these products be employed for indications other than those authorised.
Current standard of care

Prof. Alwin Krämer, MD
University of Heidelberg, Germany
Disclosures

• Prof. Krämer has received research grants from Bayer and Merck, as well as honoraria for lectures or advisory board participation or consulting from Roche, and Novartis.
Cancer of unknown primary site (CUP)
High unmet medical needs

• 2% – 5% of all malignancies

• 12-month overall survival is 23%

• Median overall survival is 9.1 months

• Lack of a definitive primary site often restricts treatment options to palliative chemotherapy

Image source: US National Cancer Institute (accessed 15/03/2017)

# CUP diagnosis follows ESMO guideline diagnostic work-up

<table>
<thead>
<tr>
<th>Target patient population</th>
<th>Assessment suggested</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>Thorough medical history and physical examination</td>
</tr>
<tr>
<td>All</td>
<td>Basic blood and biochemistry analysis</td>
</tr>
<tr>
<td>All</td>
<td>CT scans of thorax, abdomen and pelvis</td>
</tr>
<tr>
<td>All</td>
<td>Histology/Immunohistology</td>
</tr>
<tr>
<td>All females</td>
<td>Mammography</td>
</tr>
<tr>
<td>Females with axillary adenocarcinoma</td>
<td>Breast MRI</td>
</tr>
<tr>
<td>Patients with midline metastatic disease</td>
<td>Serum α-fetoprotein and human chorionic gonadotropin</td>
</tr>
<tr>
<td>Males with adenocarcinoma bone mets</td>
<td>Serum prostate-specific antigen</td>
</tr>
<tr>
<td>Cervical squamous cell carcinoma</td>
<td>Head and neck CT / PET scan</td>
</tr>
<tr>
<td>Sign / Symptom / Laboratory oriented</td>
<td>Endoscopies</td>
</tr>
<tr>
<td>Patients with neuroendocrine CUP</td>
<td>Octreoscan / Chromogranin A</td>
</tr>
<tr>
<td>Sign / Symptom / Laboratory oriented</td>
<td>Additional diagnostic tests</td>
</tr>
</tbody>
</table>

CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography. Adapted from Fizazi, K., et al. (2015) *Ann Oncol* 26(suppl 5):v133-8.
There are many histologies across CUP samples

<table>
<thead>
<tr>
<th>Histology</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>50%</td>
</tr>
<tr>
<td>• Well to moderately differentiated</td>
<td></td>
</tr>
<tr>
<td>• Poorly or undifferentiated</td>
<td>30%</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>15%</td>
</tr>
<tr>
<td>Undifferentiated neoplasms</td>
<td>5%</td>
</tr>
<tr>
<td>• Not specified carcinoma</td>
<td></td>
</tr>
<tr>
<td>• Neuroendocrine tumours</td>
<td></td>
</tr>
<tr>
<td>• Lymphomas</td>
<td></td>
</tr>
<tr>
<td>• Germ cell tumours</td>
<td></td>
</tr>
<tr>
<td>• Melanomas</td>
<td></td>
</tr>
<tr>
<td>• Sarcomas</td>
<td></td>
</tr>
<tr>
<td>• Embryonal malignancies</td>
<td></td>
</tr>
</tbody>
</table>
The ESMO guideline recognises distinct CUP subsets

Favorable prognosis CUP subset
- Women with isolated axillary lymph node metastases from adenocarcinoma
- Women with papillary serous carcinoma restricted to the peritoneum
- Squamous cell carcinoma restricted to cervical / inguinal lymph nodes
- Adenocarcinoma with lower gastrointestinal profile
- Poorly differentiated CUP with midline distribution
- Neuroendocrine CUP
- Metastatic melanoma of unknown primary
- Men with osteoblastic metastases and elevated serum prostate-specific antigen
- CUP restricted to a single metastatic site

Specific treatment

Poor prognosis CUP subset
- PS ≤ 1
- Normal LDH
- Favorable prognosis: Median survival = 12 months
- Consider 2-drug chemotherapy

- PS ≥ 2 and / or
- Elevated LDH
- Poor prognosis: Median survival = 4 months
- Chemotherapy or best supportive care

ESMO recommends low-toxicity palliative chemotherapy for poor-prognosis CUP patients

<table>
<thead>
<tr>
<th>Chemotherapy (mg/m²)</th>
<th>Time</th>
<th>Interval</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin 60-75 + Gemcitabine 1,000</td>
<td>Day 1</td>
<td>Q3 weeks</td>
<td>Fit patients, adequate hydration</td>
</tr>
<tr>
<td></td>
<td>Day 1+8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin 75 + Etoposide 100</td>
<td>Day 1</td>
<td>Q3 weeks</td>
<td>Fit patients with neuroendocrine-feature CUP, adequate hydration</td>
</tr>
<tr>
<td></td>
<td>Day 1-3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel 175 + Carboplatin AUC 5</td>
<td>Day 1</td>
<td>Q3 weeks</td>
<td>Convenient outpatient regimen, monitor neurotoxicity</td>
</tr>
<tr>
<td></td>
<td>Day 1-3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel 75 + Carboplatin AUC 5</td>
<td>Day 1</td>
<td>Q3 weeks</td>
<td>Convenient outpatient regimen, monitor neurotoxicity</td>
</tr>
<tr>
<td></td>
<td>Day 1-3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irinotecan 160 + Oxaliplatin 80</td>
<td>Day 1</td>
<td>Q3 weeks</td>
<td>Outpatient regimen, monitor for neurotoxicity and diarrhoea</td>
</tr>
<tr>
<td></td>
<td>Day 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral capecitabine 2,000 ± Oxaliplatin 85-130</td>
<td>Days 1-14</td>
<td>Q3 weeks</td>
<td>Outpatient regimen, risk for diarrhoea and neurotoxicity</td>
</tr>
<tr>
<td></td>
<td>Day 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemcitabine 1,000/irinotecan 100</td>
<td>Day 1</td>
<td>Q3 weeks</td>
<td>Convenient outpatient regimen, monitor diarrhoea</td>
</tr>
<tr>
<td></td>
<td>Day 1+8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients with poor prognosis have low survival rates, e.g. disseminated adeno- or undifferentiated CUP

Minnie Pearl Cancer Research Network - 396 CUP Patients Treated in Phase II Studies

1 year survival: 38%
5 year survival: 10%
10 year survival: 8%
Median survival: 9.1 months

Survival

0 12 24 36 48 60 72 84 96 108 120

N = 396

Molecular profiling can identify biomarkers associated with a potential drug benefit

- Molecular profiling was found to identify biomarkers biologically relevant and/or associated with a potential drug benefit in most CUP cases (87%)\(^1\)
- It included druggable targets in key cancer related genes: BRAF, EGFR and ERBB2\(^1\)
- In another study, expression of PD-1 and PD-L1 was observed in 63% and 21% of assessed cases respectively\(^2\)

Adapted from Clynick, B., et al. ESMO 2017 # 1705-PD.

Molecular testing: From gene expression profiling to comprehensive genomic profiling

Dr. Jeffrey S. Ross, MD
Foundation Medicine, Cambridge, MA USA
Disclosures

Dr Ross is an employee, holds a leadership position and owns stock in Foundation Medicine, Inc.
FoundationOne® identifies all classes of genomic alterations

**Base Substitution**
e.g. *BRAF, EGFR*

- **Tumor**
- **Blood**
  
  Capillary sequencing, Mass Spectrometry

**Short Insertions / Deletion**
e.g. *EGFR, ERBB2*

- **Tumor**
- **Blood**
  
  Capillary sequencing, gel size shift assays

**Focal Amplification & Homozygous Deletion**
e.g. *HER2, MET*
e.g. *PTEN, TSC1/2*

- **Fluorescence In Situ Hybridization**

**Gene Fusion**
e.g. *ALK, ROS1, RET*

- **Real time-PCR Fluorescence In Situ Hybridization**
FoundationOne® validation shows the high accuracy and reproducibility required for clinical use

**Base Substitutions**  
(MAF 5-100%)  
Sensitivity: > 99%  PPV: > 99%

**Insertions/Deletions**  
(1-40bp, MAF ≥ 20%)  
Sensitivity: 98%  PPV: > 99%

**Copy Number Alterations**  
(> 20% tumor content, zero or ≥ 8 copies)  
Sensitivity: > 95%  PPV: > 99%

**Gene Fusions**  
(> 30% tumor content, select introns)  
Sensitivity: > 99%  PPV: > 99%

Controlled validation studies:  
Cell-line pools with known alterations:  
- 2,056 subs  227 indels  
- 210 CNAs  32 fusions

Concordance studies with existing platforms on clinical samples:  
- 118 subs/indels: Sequenom, PCR  
- 185 CNAs: FISH, IHC  
- 43 fusions: break-apart FISH

CNA, copy number alteration; FISH, fluorescence In Situ Hybridization; IHC, immunohistochemistry; MAF, mutant allele frequencies; PCR, polymerase chain reaction; PPV, positive predictive value.  
Foundation Medicine has experience across all solid tumor types

NSCLC 18%
Gastrointestinal 14%
Breast 10%
Gynecologic 8%
CUP 7%
Lymphoma 1%
Bone 1%
Renal 2%
Bladder 3%
Melanoma 3%
Head and Neck 3%
Sarcoma 4%
Prostate 4%
Central nervous system 5%
Other Carcinoma 5%
Hematological 5%
Pancreatobiliary 7%
Miscellaneous 2%
Of 200 cases of CUP, 96% harbored at least one genomic alteration

<table>
<thead>
<tr>
<th></th>
<th>ACUP</th>
<th>Non-ACUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample</td>
<td>125</td>
<td>75</td>
</tr>
<tr>
<td>Total genomic alterations (GA)</td>
<td>494</td>
<td>347</td>
</tr>
<tr>
<td>GA/sample, mean</td>
<td>4.0</td>
<td>4.6</td>
</tr>
<tr>
<td>Base substitutions</td>
<td>250 (51%)</td>
<td>151 (44%)</td>
</tr>
<tr>
<td>Short insertions and deletions (Indels)</td>
<td>74 (15%)</td>
<td>66 (19%)</td>
</tr>
<tr>
<td>Amplifications</td>
<td>119 (24%)</td>
<td>98 (28%)</td>
</tr>
<tr>
<td>Homozygous deletions</td>
<td>39 (8%)</td>
<td>27 (8%)</td>
</tr>
<tr>
<td>Re-arrangements</td>
<td>12 (2%)</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Samples with no GA detected</td>
<td>0</td>
<td>8</td>
</tr>
</tbody>
</table>
High diversity of genomic alterations and a “long tail” distribution observed across ACUP samples

- Substitution/Indel
- Gene amplification
- Gene homozygous deletion
- Truncation
- Gene fusion/Rearrangement

Samples, %

N = 125

ACUP, adenocarcinoma of unknown primary; Indel, insertion/deletion.
Most CUP or ACUP samples harbor targetable alterations

Carcinomas of Unknown Primary with targetable CRGA by therapy class or pathway

- MTORi
- MEKi
- Other TKI
- ICPI
- PARPi
- HER2
- ALK TKI
- CDKi
- EGFR

Tumor mutational burden (TMB) can help predict benefit from immune checkpoint inhibitors

• Indication of pembrolizumab ▼ for the treatment of patients with unresectable or metastatic solid tumors possessing a microsatellite instability-high (MSI-H) biomarker is the first tissue/site-agnostic approval by the FDA\(^1\)

• FoundationOne\(^\circ\) TMB high result will detect all MSI-high CUP cases as well as approximately 20-30% more cases where the patients are thus predicted to have a likely long term durable benefit from ICPI therapies\(^2\)

• CUP in general features a high frequency of TMB high with over 10% of cases featuring \(\geq 20\) mutations per megabase similar to that seen in NSCLC (not as high as melanoma but higher than bladder cancer)\(^2\)

2. FMI data on file.

Therapies marked with ▼ are subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. Adverse events should be reported to your local Merck Sharp & Dohme Limited office.
CUP incidence and survival

Latest data from Switzerland

Prof. Holger Moch, MD
University Hospital Zurich, Switzerland
Disclosures

Prof. Moch has received research grants from Roche and Pfizer, as well as honoraria for lectures or advisory board participation or consulting from Roche, and Astra Zeneca
CUP incidence and survival trends in Zurich, Switzerland

• 2,946 CUP patients from 1981 - 2014 (Cancer Registry Zurich)

• Age-standardized incidence:
  – 1981 and 1997: Increase from 10.5 to 17.6 / 100,000
  – 1998 - 2014: Decrease to 5.9 / 100,000

• Mean overall survival:
  – stable at 11.5 months (median 2.3 months)
Survival has not improved in the last 40 years in Disseminated Adeno- or Undifferentiated CUP

Relative 1-year-survival ~20%
Relative 5-year-survival ~10-15%

## Immunohistochemistry work-up in CUP patients

<table>
<thead>
<tr>
<th></th>
<th>CK</th>
<th>PSA</th>
<th>ER, PgR</th>
<th>CDX2+, CK20+, CK7-</th>
<th>TTF1, NapsinA, CK7+</th>
<th>Tg, CT</th>
<th>NSE, CG, SNP</th>
<th>AFP, OCT4, hCG, PLAP</th>
<th>LCA</th>
<th>S100, HMB45</th>
<th>Vimentin, Desmin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undifferentiated carcinoma</td>
<td>+</td>
<td>-</td>
<td>±</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>±</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>+</td>
<td>-</td>
<td>±</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>±</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lung adenocarcinoma</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>±</td>
<td>+</td>
<td>±</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>±</td>
<td>±</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Germ-cell cancer</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>±</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Melanoma</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>±</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

The table shows general staining patterns but exceptions exist, especially for S100 and vimentin. Thyroid and neuroendocrine cancers often positive with CK7 and TTF1 but not with NapsinA. CK, cytokeratin; PSA, prostate specific antigen; ER, oestrogen receptor; PgR, progesterone receptor; TTF1, thyroid transcription factor 1; Tg, thyroglobulin; CT, calcitonin; NSE, neuronspecific enolase; CG, chromogranin; SNP, synaptophysin; AFP, alpha fetoprotein; hCG, human chorionic gonadotropin; PLAP, placental alkaline phosphatase; LCA, leukocyte common antigen.

Basic immunohistochemistry work-up of CUP

**Primary markers**

- **CK 7-/CK 20+**
  - Colorectal and Merkel cell carcinoma

- **CK 7+/CK 20-**
  - Lung, breast, thyroid, endometrial, cervical and pancreatic carcinoma and cholangiocarcinoma

- **CK 7+/CK 20+**
  - Urothelial, ovarian and pancreatic cancer and cholangiocarcinoma

- **CK 7-/CK 20-**
  - Hepatocellular, renal cell, prostate, squamous cell carcinoma

**Additional markers**

- **CEA and CDX-2**

- **TTF-1, ER, PR, GCDFP-15, and CK 19**

- **Urothelin and WT-1**

- **Hep Par-1 and PSA**

CK, cyokeratin; CEA, carcinoembryonic antigen; TTF1, thyroid transcription factor 1; ER, oestrogen receptor; PgR, progesterone receptor; GCDFP-15, gross cystic disease fluid protein-15; WT-1, Wilms tumor gene 1; PSA, prostate specific antigen.

Tumor board discussion on clinical cases

Dr. Jeffrey S. Ross, MD
Foundation Medicine, Cambridge, MA USA
Clinical case 1

Dr. Jeffrey S. Ross, MD
Foundation Medicine, Cambridge, MA USA
Clinical case 1
Patient medical background

Medical background

- A 53-year old Caucasian female
- No history of smoking
- 3-week history of worsening fatigue and severe exertional dyspnea

Clinical case 1

Clinical examination

Physical examination

- 3 cm non-tender, hard, subcutaneous, proximal right upper extremity mass with erythematous overlying skin
- 1 cm non-tender, subcutaneous nodule in the left parietal area of the scalp

PET and CT imaging

- Multiple metabolically active masses in the right lung; largest mass in the upper lobe measuring 5.8 x 5.0 cm
- Left lung mass measuring 2.3 x 2.2 cm
- Right hilar and mediastinal lymphadenopathy and subcarinal lymphadenopathy noted
- Extrathoracic, metabolically active lesions noted, including masses in the celiac nodal basin and the anterior right upper arm

CT, computed tomography; PET, positron emission tomography.
Clinical case 1
Laboratory assessment results

**Immunohistochemical staining**

<table>
<thead>
<tr>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vimentin</td>
<td>TTF1, Napsin A, AE1/AE3, CK5, CK6, CK7, CAM5.2, and mCEA</td>
</tr>
</tbody>
</table>

**Morphologic examination of the biopsy from the right upper extremity mass**

<table>
<thead>
<tr>
<th>Malignant neoplasm of unknown histogenesis</th>
<th>Overall results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lung origin of tumor could not be confirmed</td>
</tr>
</tbody>
</table>

Based on the initial investigation and laboratory results, what would you advise?
### Foundation Medicine report results

**About the Test:**
FoundationOne® is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

### Patient Results
- 3 genomic alterations
- 1 therapy associated with potential clinical benefit
- 0 therapies associated with lack of response
- 6 clinical trials

### Tumor Type: Unknown Primary Malignant Neoplasm (NOS)

**Genomic Alterations Identified**
- ALK EML4-ALK fusion
- MCL1 amplification – equivocal
- CDKN2A/B loss

### Therapeutic Implications

<table>
<thead>
<tr>
<th>Genomic Alterations Detected</th>
<th>FDA Approved Therapies (in patient’s tumor type)</th>
<th>FDA Approved Therapies (in another tumor type)</th>
<th>Potential Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK EML4-ALK fusion</td>
<td>None</td>
<td>Crizotinib</td>
<td>Yes, see clinical trials section</td>
</tr>
<tr>
<td>MCL1 amplification – equivocal</td>
<td>None</td>
<td>None</td>
<td>Yes, see clinical trials section</td>
</tr>
<tr>
<td>CDKN2A/B loss</td>
<td>None</td>
<td>None</td>
<td>Yes, see clinical trials section</td>
</tr>
</tbody>
</table>
After seeing the Foundation Medicine report results, would you change your treatment strategy?
Clinical case 1

Medical decision

<table>
<thead>
<tr>
<th>Medical decision</th>
<th>Reason given</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crizotinib ▼</strong> (250 mg orally twice daily)</td>
<td>Presence of the EML4-ALK rearrangement, a known oncogenic driver in a subset of pulmonary adenocarcinomas</td>
</tr>
</tbody>
</table>

Therapies marked with ▼ are subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. Adverse events should be reported to your local Pfizer Limited office.

Clinical case 1
Therapy results and follow up – CT scan

Computed tomography (CT) scan of the chest before starting crizotinib ▼ and 1 month after starting crizotinib ▼, respectively.

Chung, J.H., et al. (2014) Case Rep Oncol 7:628-32. Therapies marked with ▼ are subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. Adverse events should be reported to your local Pfizer Limited office.
Clinical case 2

Dr. Jeffrey S. Ross, MD
Foundation Medicine, Cambridge, MA USA
## Clinical case 2

**Patient medical background and initial medical investigation**

<table>
<thead>
<tr>
<th>Medical background</th>
<th>Biology</th>
<th>Preliminary diagnosis</th>
</tr>
</thead>
</table>
| 44-year-old Caucasian female with metastatic cancer of unknown primary (CUP) | Histopathology analyses were inconclusive  
  • High-grade neoplasm with pleomorphic tumor  
  • Positive for vimentin  
  • ~30% of the tumor cells: MIB-1 positive | CUP with sarcomatoid features |

Diagnosed with multiple metastatic lesions in the mesentery of the small intestines and the duodenojejunal flexure

Clinical case 2
Patient follow up

**Initial medical decision**
- Tumor lesions completely resected
- 4 cycles: doxorubicin and ifosfamide (EORTC)

**16 months Relapse**
- Progressive pain in the right shoulder
- Mass in the right deltoid muscle
- Second metastatic lesion in the right axilla

**Medical decision**
- Complete surgical excision
- **Adjuvant radiotherapy** to the right shoulder and axilla

**21 months Relapse**
- 5 new tumors formation
- Surgical resection of multiple lesions
- Tumor progressed rapidly

**Medical decision**
- Trabectedin initiated
- Stopped: progressive disease and Grade IV thrombocytopenia

Based on the patient status, what would you advise?
Clinical case 2

Molecular profiling

Enrollment in MASTER (Molecularly Aided Stratification for Tumor Eradication Research), a cross-entity molecular stratification program for advanced-stage cancer and patients with rare tumors (Kordes et al. 2016)

Molecular profiling results (Whole-exome sequencing and RNA-sequencing)
After seeing the profiling results, would you change your treatment strategy?
Clinical case 2

Medical decision

Rationale

- Amplification and overexpression of PDL1
- Hypermutated tumor genome

Medical decision

ICI treatment with the anti-PD1 monoclonal antibody pembrolizumab ▼

Therapy selected 24 months after initial diagnosis

Pembrolizumab ▼
- 2 mg/kg
- 3 week cycles


Therapies marked with ▼ are subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. Adverse events should be reported to your local Merck Sharp & Dohme office.
Clinical case 2
Follow up: PET/CT scans

Baseline | +2 months | +6 months

6 months follow up
- Near-complete remission
- Response Evaluation Criteria In Solid Tumors: very good partial remission

14 months follow up
- Remained in continuous near-complete remission
- Free of disease-specific symptoms

Genomic profiling study for patients with cancers of unknown primary

Prof. Alwin Krämer, MD
University of Heidelberg, Germany
Genomic profiling study for patients with CUP

**Rationale**

- Current diagnostics can help to identify patients with CUP who have a favourable prognosis
- Treatment options are limited in poor prognosis patients with CUP
- Comprehensive genomic profiling has the potential to identify new treatment options without the need to know the primary tumor site
- Checkpoint inhibitor might be effective in CUP similarly to other tumor types
- Majority of CUP samples harbor targetable alterations
Study objective

To compare the efficacy and safety of molecularly-guided therapy versus standard platinum-containing chemotherapy in patients with cancer of unknown primary site
Study target population

Patient with a carcinoma of unknown primary (CUP)

Favorable prognosis CUP subset
- Women with isolated axillary lymph node metastases from adenocarcinoma
- Women with papillary serous carcinoma restricted to the peritoneum
- Squamous cell carcinoma restricted to cervical / inguinal lymph nodes
- Adenocarcinoma with lower gastrointestinal profile
- Poorly differentiated CUP with midline distribution
- Neuroendocrine CUP
- Metastatic melanoma of unknown primary
- Men with osteoblastic metastases and elevated serum prostate-specific antigen
- CUP restricted to a single metastatic site

Consider 2-drug chemotherapy

Specific treatment

Poor prognosis CUP subset
- PS ≥ 2 and / or
- Elevated LDH

Favorable prognosis: Median survival = 12 months

Poor prognosis: Median survival = 4 months

Chemotherapy or best supportive care

Selected inclusion criteria for the CUP profiling study

Preliminary design

Histologically confirmed metastatic or advanced unresectable CUP

Eligible for platinum-based doublet chemotherapy

ECOG performance status of 0 or 1

No prior lines of therapy

Sufficient tumor tissue sample for:
1) diagnosis of CUP at the study site’s local laboratory, and
2) FoundationOne® comprehensive genomic profiling at a central reference pathology laboratory

At least one lesion that is measurable (RECIST v1.1)

Life expectancy ≥ 12 weeks

Adequate hematologic and end-organ function

Inclusion criteria

ECOG, Eastern Cooperative Oncology Group.
Roche data on file, study concept MX39795.
Selected exclusion criteria for the CUP profiling study

Preliminary design

- Favorable prognostic subset (e.g., resectable)
- Central nervous system (CNS) metastases
- Non-epithelial CUP neoplasms
- Leptomeningeal disease
- Immunohistochemistry profile that provides a definitive clinical suspicion of a primary cancer with a specific treatment
- Spinal cord compression
  - not definitively treated with surgery and/or radiation or previously diagnosed and
  - treated without evidence that disease has been clinically stable for ≥ 2 weeks prior to randomization

Roche data on file, study concept MX39795.
Genomic profiling study for patients with CUP

Preliminary design

Selected patients
N = 790

Investigator choice
(Molecular Tumor Board advice available)

Responders (CR, PR, SD) R 3:1
Non-Responders (PD)

Standard 1st line platinum doublet chemotherapy (3 cycles)
- paclitaxel/carboplatin, or
- cisplatin/gemcitabine

3 cycles chemotherapy

ALK; RET
ALK; RET
alectinib ▼

EGFR
EGFR
bevacizumab + erlotinib

HER2
HER2
trastuzumab + pertuzumab ▼ + chemotherapy

PTCH1; SMO
PTCH1; SMO
vismodegib ▼

BRAF
BRAF
cobimetinib ▼ + vemurafenib

AKT1; PI3K
AKT1; PI3K
ipatasertib

BRCA1; BRCA2
BRCA1; BRCA2
PARPi (e.g. olaparib ▼)

TMB-high; MSI-high
TMB-high; MSI-high
atezolizumab

TMB-low; TMB unknown
TMB-low; TMB unknown
atezolizumab + chemotherapy

CR, complete response; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TMB, tumor mutational burden; MSI: microsatellite instability. Roche data on file, study concept MX39795. Therapies marked with ▼ are subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. Adverse events should be reported to your respective local office: AstraZeneca for olaparib; Roche for alectinib, pertuzumab, cobimetinib and vismodegib.
Targeted therapy selection by investigator choice

Preliminary allocation process

Investigator choice

(Molecular Tumor Board advice available)

FoundationOne® report

Molecular tumor board:
• Reference pathologist
• Reference oncologist
• Ad-hoc Foundation Medicine experts (as required)

A central molecular tumor board will be available to provide advice on therapy choice and to ensure consistency across treatment options

Roche data on file, study concept MX39795.
“NAVIFY Tumor Board solution” summarises clinical data for use by molecular tumor board

1. Collect
Gather medical records across specialties

2. Coordinate
Schedule tumor board meetings

3. Prepare
Create presentation of patient data

4. Conduct
Support patient case discussion

5. Next Steps
Capture and document treatment plan decisions

• For software demonstration, please visit the Roche booth (Hall 7)
Study set-up initiated: 80+ sites planned in 20+ countries
Meeting closure

Prof. Alwin Krämer, MD
University of Heidelberg, Germany
Conclusions

• The ESMO guideline recommends low-toxicity palliative chemotherapy for poor-prognosis CUP patients

• Comprehensive genomic profiling can detect targetable genomic alterations in CUP samples

• The presented genomic profiling CUP study will evaluate the efficacy of molecularly guided therapy versus platinum chemotherapy
Doing now what patients need next