CANCER OF UNKNOWN PRIMARY
A DIAGNOSTIC AND THERAPEUTIC DILEMMA

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Dean, ESO College (ESCO), Milan, Italy

Limassol, January 2020
WHAT IS CANCER OF UNKNOWN PRIMARY (CUP)?

- Is a clinical disorder where patients present with histologically confirmed metastatic cancer for which standard diagnostic investigations failed to identify the primary site.

- Median age is 65 years, more common in men.
What is the Incidence of Cancer of Unknown Primary Site?
INCIDENCE AND MORTALITY OF CUP

• Before 2000 CUP accounted for the 3-5% of all cancers

  BUT

  Today accounts for almost 2% of all cancers

• [ In Europe the incidence decreased from 14 per 100,000 person in 2000 to 7.0 in 2012  (EJC 101:77-86, 2018) ]

• In USA the incidence decreased since 1980’s by 3.6% per year
  (Cancer Causes Control 25:747-757, 2014) ]
Schema of the approximate variations in the incidence-rates of cancer of unknown primary by country
WHAT ARE THE INTERPRETATIONS?

- Improved diagnostics (immunohistochemistry, molecular gene expression profiling and imaging technology) have improved the ability to detect the primary site.

- Better smoking control.
Risk Factors

• Risks of being diagnosed with CUP was strongly related to smoking.

• i) Current smokers (relative risk: 3.66) and
  ii) Heavy smokers, with 26+ cigarettes/day (relative risk: 5.12) died within 12 months

Int J Cancer 135: 2475, 2014
CLINICAL PRESENTATION OF CUP
THE NATURAL HISTORY OF CANCER OF UNKNOWN PRIMARY SITE

FUNDAMENTAL CHARACTERISTICS
FUNDAMENTAL CHARACTERISTICS

- Early dissemination
- Clinical absence of primary at presentation
- Aggressiveness
- Unpredictable metastatic pattern
Cancer of Unknown Primary Site:

One or more Diseases?
## Histological Classification

<table>
<thead>
<tr>
<th><strong>Histology</strong></th>
<th><strong>Incidence</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Well to moderately differentiated</td>
<td>50 %</td>
</tr>
<tr>
<td>Poorly or undifferentiated</td>
<td>35 %</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>10 %</td>
</tr>
<tr>
<td>Undifferentiated neoplasms</td>
<td>5 %</td>
</tr>
<tr>
<td>Not specified carcinoma</td>
<td></td>
</tr>
<tr>
<td>Neuroendocrine tumors</td>
<td></td>
</tr>
<tr>
<td>Lymphomas</td>
<td></td>
</tr>
<tr>
<td>Germ cell tumors</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>
<tr>
<td>ORGAN</td>
<td>HISTOLOGY</td>
</tr>
<tr>
<td>----------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>Liver (mainly)</td>
<td>AdenoCa M or P diff</td>
</tr>
<tr>
<td>and/or other organs</td>
<td></td>
</tr>
<tr>
<td>Lymph nodes</td>
<td></td>
</tr>
<tr>
<td>Mediastinal – Retroperitoneal (midline distribution)</td>
<td>U or P diff Ca</td>
</tr>
<tr>
<td>Axillary</td>
<td>AdenoCa W to P diff</td>
</tr>
<tr>
<td>Cervical</td>
<td>SCC Ca</td>
</tr>
<tr>
<td>Inguinal</td>
<td>U Ca, SCC, mixed SCC / adenoCa</td>
</tr>
</tbody>
</table>

\( W = \text{well, } M = \text{moderately, } P = \text{poorly, } U = \text{undifferentiated} \)
**Peritoneal cavity**

- Peritoneal adenocarcinomatosis in females
- Malignant ascites of other unknown origin

**Lungs**

- Pulmonary metastases
- Pleural effusion

AdenoCa various diff
AdenoCa M or P diff

Papillary or serous adenoCa
(± psammoma bodies)

Mucin adenoCa M or P diff
(± signet ring cells)

\[ W = \text{well}, \quad M = \text{moderately}, \quad P = \text{poorly}, \quad U = \text{undifferentiated} \]
**Bones**
(solitary or multiple)  
AdenoCa of various diff

**Brain**
(solitary of multiple)  
AdenoCa of various diff or squamous cell Ca

**Neuroendocrine tumors**
P diff Ca with neuroendocrine features (mainly), low-grade neuroendocrine Ca, small cell anaplastic Ca

**Melanoma**  
U neoplasm with melanoma features.

*W = well, M = moderately, P = poorly, U = undifferentiated*
WHAT IS THE OPTIMAL INVESTIGATIONAL DIAGNOSTIC APPROACH FOR THE IDENTIFICATION OF THE PRIMARY TUMOR?
How do we search for the primary?

- **By Histopathology**
  - Immunohistochemistry
  - Advanced Molecular Technology

- **By Imaging**
  - Conventional Radiology
  - Ultrasonography
  - CT-scans
  - MRI
  - PET-scans
  - Mammography

- **By Endoscopy**
  - ENT panendoscopy
  - Bronchoscopy
  - Colonoscopy
  - Proctoscopy
  - Colposcopy
By
HISTOPATHOLOGY
And
IMMUNOCHEMISTRY
Cytokeratins (CKS)

Monoclonal antibodies against cytokeratin polypeptides CK7 and CK20
CK7 + CK20 +
- Urothelial tumors
- Ovarian mucinous adenocarcinoma
- Pancreatic adenocarcinoma
- Cholangiocarcinoma

CK7 + CK20 -
- Lung adenocarcinoma
- Breast carcinoma
- Thyroid carcinoma
- Endometrial carcinoma
- Cervical carcinoma
- Salivary gland carcinoma
- Cholangiocarcinoma
- Pancreatic carcinoma

CK7 - CK20 +
- Colorectal Carcinoma
- Merkel cell carcinoma

CK7 - CK20 -
- Hepatocellular carcinoma
- Renal cell carcinoma
- Prostate carcinoma
- Squamous cell & small cell lung carcinoma
- Head & neck carcinoma
MOLECULAR ANALYSIS
[Microarray Platforms]

> 80 - 90 % accuracy
<table>
<thead>
<tr>
<th>Assay</th>
<th>Platform</th>
<th>Tissue</th>
<th>No. of Tumor types</th>
<th>Number of genes</th>
<th>Accuracy in known tumors (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veridex</td>
<td>RT-PCR mRNA</td>
<td>FFPE</td>
<td>6 and ”other”</td>
<td>10</td>
<td>76</td>
</tr>
<tr>
<td>Pathwork Diagnostics</td>
<td>cDNA microarray</td>
<td>Frozen/FFPE</td>
<td>15</td>
<td>1500</td>
<td>89</td>
</tr>
<tr>
<td>Tissue of Origin test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosetta Genomics MiReview met</td>
<td>RT-PCR miRNA</td>
<td>FFPE</td>
<td>22</td>
<td>48 miRNAs</td>
<td>86</td>
</tr>
<tr>
<td>BioTheranostics CancerType ID</td>
<td>RT-PCR mRNA</td>
<td>FFPE</td>
<td>39 (including subtypes)</td>
<td>92</td>
<td>86</td>
</tr>
</tbody>
</table>
LIQUID BIOPSY IN CUP

Liquid biopsy opens a new diagnostic, predictive and prognostic window in CUP that may lead to substantial improvement in the management of patients with CUP.

El Rasy, H Khaled, N Pavlidis, Eur J Cancer 105:28-32, 2018
ENDOSCOPY

✓ Should always be symptoms - or signs oriented investigational procedures

- **ENT panendoscopy**: in cervical node involvement
- **Bronchoscopy**: in radiographic indications or symptoms
- **Colonoscopy**: in relevant symptoms and signs
- **Proctoscopy**: in inguinal node involvement
- **Colposcopy**: in inguinal node involvement
<table>
<thead>
<tr>
<th>Imaging Study</th>
<th>Diagnostic Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT-scans</td>
<td>40% accuracy / Guidance to biopsy</td>
</tr>
<tr>
<td>MRI (breast)</td>
<td>60% accuracy</td>
</tr>
<tr>
<td>FDG-PET SCAN</td>
<td>43% accuracy / more sensitive for occult H+N (80-85%)</td>
</tr>
</tbody>
</table>

**NCCN 2019:** The exact role of PET/CT remains undefined because of the lack of large prospective clinical trials comparing PET/CT with conventional imaging modalities.
SERUM TUMOR MARKERS

- Routine evaluation of current commonly used markers have not been proven of any prognostic or diagnostic assistance

- A non-specific multiple overexpression of the adenocarcinoma markers (CEA, CA 125, CA 15-3, CA 19-9) has been observed in the majority of CUP patients.

- Worthwhile to request:
  - PSA in men with bone metastatic adenocarcinoma
  - B-HCG & AFP in men with an undifferentiated tumor
  - AFP in patients with hepatic tumors
  - CA 125 women with papillary adenocarcinoma of peritoneal cavity.
  - CA 15-3 women with adenocarcinoma involving only axillary lymph nodes.
WHAT IS THE OPTIMAL THERAPEUTIC APPROACH OF CANCER OF UNKNOWN PRIMARY?
DO WE HAVE EFFECTIVE DRUGS FOR CANCER OF UNKNOWN PRIMARY

OR

WE JUST HAVE RESPONSIVE SUBSETS OF PATIENTS?
CUP

FAVOURABLE OR GOOD PROGNOSIS SUBSETS

UNFAVOURABLE OR POOR PROGNOSIS SUBSETS
THE FAVOURABLE SUBSETS OR GOOD PROGNOSIS SUBSETS

20% of all CUP Cases
**Favourable Subsets**

1. Women with adenocarcinoma involving only **axillary** lymph nodes.
2. Women with **papillary** adenocarcinoma of **peritoneal** cavity.
3. Squamous cell carcinoma involving **cervical** lymph nodes.
4. Squamous cell carcinoma of the **abdomen, pelvis and retroperitoneum**.
5. Poorly differentiated **neuroendocrine** carcinomas.  
   Merkel cell carcinoma of unknown primary (localized disease).
6. Men with **blastic bone** metastases and elevated **PSA** (adenocarcinoma).
7. Patients with a **single**, small, potentially resectable tumor.
8. Isolated **inguinal** adenopathy (squamous carcinoma).
1) AdenoCa of Axillary Nodes
Should be treated as Stage II Breast Ca. 5-yr OS: 72%

2) Primary Peritoneal Serous/Papillary AdenoCa
Should be treated as Stage III-IV Ovarian Ca. RR 80%, OS 36m

3) Squamous Ca of Cervical Nodes
Should be treated as advanced Head Neck Ca. 5-yr OS 65%

4) Squamous Ca of Abdominal Cavity
Should be treated Cisplatin-based Chemo. CR 62% OS 7-76m

5) Poorly Differentiation Neuroendocrine Tumors
Should be treated with Platinum/Taxane Chemo. OR 55%
New Favorable Subsets
Detected by Immunohistochemistry or Molecular Profiling

1. CUP adenocarcinoma with a colon profile
   (CK 20+, CK7 -, CDX 2+)

2. CUP - hidden non-small cell lung cancer
   with positive biomarkers

3. CUP - hidden renal cell carcinoma
METASTATIC COLORECTAL CARCINOMA OF AN UNKNOWN PRIMARY SITE (MCCUPS)

NATURAL HISTORY
THERAPEUTIC MANAGEMENT
PROGNOSIS
DEMOGRAPHIC DATA OF MCCUPS

- **Mean Age:** 57 years (28-86 ys)
- **Gender:** Males 43%, Females 57%
- **Histology:** Adenocarcinoma 38.0%
  Poorly Differentiated AdenoCa 26.5%
  Poorly Differentiated Carcinoma 28.5%
  Squamous Carcinoma 7.0%
- **Performance Status (ECOG):**
  0: 38.5%  
  1: 50.5%  
  2: 9.5%  
  3: 3.0%
METASTATIC PROFILE OF MCCUPS

- Liver: 39%
- Abdominal Nodes: 38%
- Peritoneum: 28%
- Bones: 21%
- Lungs: 20%
- Uterus/Ovaries: 14.5%
- Adrenals: 9.0%
PROSPECTIVE TRIALS OF COLON-LIKE CHEMOTHERAPY IN PATIENTS WITH POOR PROGNOSTIC SUBSETS OF CUP

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>LINE</th>
<th>N</th>
<th>ORR</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>OXIRIN</td>
<td>1st</td>
<td>47</td>
<td>13.0%</td>
<td>2.7 mos</td>
<td>9.5 mos</td>
</tr>
<tr>
<td>FOLFO</td>
<td>1st</td>
<td>23</td>
<td>35.0%</td>
<td>3.0 mos</td>
<td>9.5 mos</td>
</tr>
<tr>
<td>CAPOX</td>
<td>1st</td>
<td>51</td>
<td>11.7%</td>
<td>2.5 mos</td>
<td>7.5 mos</td>
</tr>
<tr>
<td>CAPOX</td>
<td>2nd</td>
<td>25</td>
<td>13.0%</td>
<td>2.3 mos</td>
<td>3.9 mos</td>
</tr>
<tr>
<td>CAPOX</td>
<td>2nd</td>
<td>48</td>
<td>19.0%</td>
<td>3.7 mos</td>
<td>9.7 mos</td>
</tr>
<tr>
<td>FU/LV</td>
<td>2nd</td>
<td>25</td>
<td>0%</td>
<td>NR</td>
<td>3.9 mos</td>
</tr>
<tr>
<td>DIAGNOSTICS</td>
<td>LINE</td>
<td>ORR</td>
<td>OS</td>
<td></td>
<td></td>
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<td>---------------------------</td>
<td>-----------------</td>
<td>-----------</td>
<td>-------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHC</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; + 2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>100%</td>
<td>20-40 m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecul Profiling</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; + 2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>100%</td>
<td>9-31 m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecul Profiling</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; + 2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>68-84%</td>
<td>5-68 m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecul Profiling</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; + 2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>50%</td>
<td>27 m</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

THE OUTCOMES OF CUP-CCP PATIENTS TREATED WITH COLON-LIKE REGIMENS

Lancet Oncol 2008

J Clin Oncol 2008

J Cancer Ther 2012

Clin Color Ca 2012
METASTATIC RENAL CARCINOMA OF UNKNOWN PRIMARY (CUP – RENAL)
N Pts : 52       Median Age : 64 yrs
Histology : Clear Cell  39%
               Papillary  31.5%
               Unspecified  29.5%

IHC : Vimentin, CK (AE1/AE3), CD10, CK8/18, Pax8

Targeted Rx : Sunitinib, Pazopanib, Everolimus, Temsirolimus

RR : 40-50%  PR
Mean PFS : 8.5 months
Mean Survival : 6-16 months
METASTATIC LUNG CARCINOMA OF UNKNOWN PRIMARY (CUP-LUNG)
CUP - LUNG PATIENTS TREATED WITH LUNG - LIKE CHEMOTHERAPY REGIMENS

• Regimens: Platinum-containing
  • Number of pts treated: 298
  • Response Rate: 32% (18-55%)
• Overall Survival: 6.5 months – 11 months
CUP – LUNG PATIENTS TREATED WITH EGFR AND ALK INHIBITORS

• **Treatment**: Gefitinib, Erlotinib, Crizotinib, Lorlatinib
• **Number of Patients Treated**: 9
• **Histopathology**: Adenocarcinomas
• **Outcome**: CR 1, PR 7, PD 1
THE UNFAVOURABLE SUBSETS

OR

POOR PROGNOSIS SUBSETS

80% of all CUP Cases
UNFAVOURABLE SUBSETS
(80% OF CUP CASES)

1. Metastatic Carcinoma to the liver and other organs
2. Non-papillary malignant ascites (adenocarcinoma)
3. Multiple cerebral metastases (adeno or squamous Ca)
4. Multiple lung/pleural metastases (adenocarcinoma)
5. Multiple metastatic bone disease (adenocarcinoma)
OVERALL RESULTS OF CHEMOTHERAPY IN CUP PATIENTS WITH LIVER METASTASES

No of patients : 711
Response rate : < 20%
Median survival : 5.5 months

SURVIVAL OUTCOME DIFFERENCES BASED ON TREATMENTS USED AND KNOWLEDGE OF THE PRIMARY TUMOUR SITE FOR PATIENTS WITH CANCER OF UNKNOWN AND KNOWN PRIMARY IN ONTARIO

Current Oncol 2018

• From Ontario Cancer Registry: 2000-2005
  45,347 (96.3%) pts with known metastatic disease and
  1,743 (3.7%) pts with CUP

• Overall Median Survival
  Known vs CUP pts: 11.9 vs 1.9 mo
• IS THERE ANY REAL EVIDENCE THAT CUP PATIENTS TREATED AFTER MOLECULAR PROFILING TESTING HAVE A PROLONGED SURVIVAL?

• ARE THERE PROSPECTIVE RANDOMIZED STUDIES AVAILABLE?
Molecular Gene Expression Profiling to Predict the Tissue of Origin and Direct Site-Specific Therapy in Patients With Carcinoma of Unknown Primary Site: A Prospective Trial of the Sarah Cannon Research Institute

John D. Hainsworth, Mark S. Rubin, David R. Spigel, Ralph V. Boccia, Samuel Raby, Raven Quinn, and F. Anthony Greco

Conclusion

✓ The median survival time of 12.5 months for patients who received assay-directed site-specific therapy compares favorably with previous results using empiric CUP regimens.

✓ Molecular tumor profiling contributes to the management of patients with CUP and should be a part of their standard evaluation.
OVERALL SURVIVAL: Assay-directed treatment vs. empiric treatment

Presented by: F. Anthony Greco, MD
Epigenetic profiling to classify cancer of unknown primary: a multicentre, retrospective analysis

Based on the microarray DNA methylation signatures (EPICUS)

Interpretation We show that the development of a DNA methylation based assay can significantly improve diagnoses of cancer of unknown primary and guide more precise therapies associated with better outcomes. Epigenetic profiling could be a useful approach to unmask the original primary tumour site of cancer of unknown primary cases and a step towards the improvement of the clinical management of these patients.
Figure: Outcome of patients with cancer of unknown primary who receive a site-specific treatment that matches the EPICUP prediction.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Design</th>
<th>Arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEFCAPI 04</td>
<td>GEFCAPI</td>
<td>Phase III</td>
<td>Platinum-based Cx vs Pathwork-based Rx [Reported-ESMO 2019]</td>
</tr>
<tr>
<td>CUPISCO</td>
<td>ROCHE</td>
<td>Phase II</td>
<td>Platinum-based Cx vs Targeted Rx or Immunotherapy (Atezolizumab) [Ongoing]</td>
</tr>
</tbody>
</table>
Randomized Phase II Trial Comparing Site-Specific Treatment (SST) Based on Gene Expression Profiling With Empirical Carboplatin/Paclitaxel (ECP) for Patients with CUP  [OSAKA JAPAN]

- The primary end point was 1-year survival rate.
- 130 pts were randomly assigned.

**RESULTS**

<table>
<thead>
<tr>
<th></th>
<th>SST (site specific)</th>
<th>ECP (empirical)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>5.1 m</td>
<td>4.8 m</td>
</tr>
<tr>
<td>OS</td>
<td>9.8 m (p=0.890)</td>
<td>12.5 m (p=0.550)</td>
</tr>
<tr>
<td>1-YR OS</td>
<td>44%</td>
<td>54.9% (p=0.264)</td>
</tr>
</tbody>
</table>

**CONCLUSION:**

- Site-specific treatment that was based on microarray profiling did not result in a significant improvement in 1-year survival compared with empirical PC.
A PHASE 3 TRIAL OF EMPIRIC CHEMOTHERAPY WITH CISPLATIN AND GEMCITABINE OR SYSTEMIC TREATMENT TAILORED BY MOLECULAR GENE EXPRESSION ANALYSIS IN PATIENTS WITH CARCINOMAS OF AN UNKNOWN PRIMARY SITE

GEFCAPI 04

Karim Fizazi, Aline Maillard, Nicolas Penel, Giulia Baciarello, Djelila Allouache, Gedske Daugaard, Agnes Van de Wouw, Gemma Soler, Elodie Vauleon, Loic Chaigneau, Rob Jansen, Fernando Losa Gaspa, Rafael Morales-Barrera, Carmen Balana, Diego Tosi, Bruno Chauffert, Catherine A. Schnabel, Geraldine Martineau, Stephane Culine, Isabelle Borget

Gustave Roussy, University of Paris Sud, Villejuif, France
GEFCAPI 04 Phase III design

Control arm: Empiric chemotherapy

- Cisplatin 100 mg/m² d1
- Gemcitabine 1250 mg/m², day 1 and 8, q3w x 6 cycles

CUP → R

PS=0-2
No previous systemic Rx
Excluded: subsets with favourable prognosis

Molecular Test → Personalized Treatment

= Standard treatment of the suspected primary
GEFCAPI-04: Suspected primary cancers (CancerTYPE ID)

Control arm  Experimental arm

Not available/non contributive
Pancreaticobiliary
Squamous Cell Carcinoma
Kidney
Lung Adenocarcinoma
Intestine
Gastroesophageal Adenocarcinoma
Sarcoma
Urinary Bladder
Breast Adenocarcinoma
Liver Hepatocellular Carcinoma
Head and Neck Salivary Gland Carcinoma
Mesothelioma
Ovary
Cervix Adenocarcinoma
Melanoma
Neuroendocrine
Germ Cell
Prostate Adenocarcinoma
### Primary endpoint: PFS (central review)

<table>
<thead>
<tr>
<th></th>
<th>Control arm</th>
<th></th>
<th>Experimental arm</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>IC95%</td>
<td>Estimate</td>
<td>IC95%</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>5.29</td>
<td>[4.30;6.24]</td>
<td>4.6</td>
<td>[3.68;6.01]</td>
</tr>
<tr>
<td>24 months PFS (%)</td>
<td>7.92</td>
<td>[3.86;13.87]</td>
<td>9.02</td>
<td>[4.64;15.18]</td>
</tr>
<tr>
<td>36 months PFS (%)</td>
<td>5.66</td>
<td>[2.29;11.27]</td>
<td>5.84</td>
<td>[2.41;11.48]</td>
</tr>
</tbody>
</table>

Median follow-up:
- 43.4 months [29.4-52.8] control arm
- 47.9 months [28.6-51.8] experimental arm

Central review not available: 20 pts (8.2%)

![Kaplan-Meier Survival Estimates with Number of Subjects at Risk](image)

HR: 0.95 (0.72-1.25)

Logrank p = 0.7102

---

**1:** A - Gemcitabin/Cisplatin

**2:** B - Treatment of the primary suspected by molecular analysis

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Overall Survival

Kaplan-Meier Survival Estimates
With Number of Subjects at Risk

<table>
<thead>
<tr>
<th></th>
<th>Control arm</th>
<th></th>
<th>Experimental arm</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>IC95%</td>
<td>Estimate</td>
<td>IC95%</td>
</tr>
<tr>
<td>Median OS (mo)</td>
<td>9.99</td>
<td>[7.06;11.96]</td>
<td>10.68</td>
<td>[7.33;11.93]</td>
</tr>
<tr>
<td>12 months OS (%)</td>
<td>40.68</td>
<td>[31.79;49.36]</td>
<td>41.32</td>
<td>[32.51;49.91]</td>
</tr>
<tr>
<td>24 months OS (%)</td>
<td>20.4</td>
<td>[13.46;28.36]</td>
<td>18.97</td>
<td>[12.34;26.70]</td>
</tr>
<tr>
<td>36 months OS (%)</td>
<td>11.2</td>
<td>[5.87;18.45]</td>
<td>11.41</td>
<td>[6.16;18.44]</td>
</tr>
</tbody>
</table>

HR: 0.92 (0.69-1.23)

Logrank p=0.7152

Barcelona ESMO Congress 2019

Arm
1: A - Gemcitabin/Cisplatin
2: B - Treatment of the primary suspected by molecular analysis

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Outcomes for selected suspected cancers

Kidney cancer

Colo-rectal cancer

Melanoma

Each bar represents single subject in the study.
Until more robust outcomes and comparative effectiveness data are available, pathologists and oncologists must collaborate on the judicious use of these modalities (IHC and GEP) on a case–by–case basis, with the best possible individualized patient outcome in mind...
GENOMIC ALTERATIONS IN CUP

Cancer Medicine 7:4814-4824, 2018

• METHODS: 10 peer-reviewed publications (2013-2018) of comprehensive genomic profiling in CUP patients

• FINDINGS: 85% clinically relevant mutations or targetable biomarkers were identified, of which 13%-64% may benefit from currently available drugs
CRITICAL QUESTIONS ON DIAGNOSTIC AND THERAPEUTIC UTILITY OF MOLECULAR PROFILING (MP) IN CUP PATIENTS

Q 1 : Does MP assay, increases accuracy of identifying the primary site?

Q 2 : Does MP helps in utilizing targeted treatment?

Q 3 : Does identification of primary site improves patient outcome (survival)?
STEPS IN DIAGNOSTIC AND THERAPEUTIC MANAGEMENT

DIAGNOSIS OF METASTATIC CARCINOMA (by histopathology)

SEACH FOR PRIMARY SITE

STEP I
Clinical, immunohistochemistry, imaging, endoscopy studies

RULE-OUT POTENTIALLY TREATABLE OR CURABLE TUMORS
(Immunohistochemistry or other studies)

STEP II
i.e. Breast Cancer, Germ-cell Tumors, Lymphomas

CHARACTERIZE THE SPECIFIC CLINICOPATHOLOGICAL ENTITY

STEP III

TREAT THE PATIENT

FAVOURABLE SUBSETS
[Similarly to relevant primaries with “Curative Intent”]

UNFAVOURABLE SUBSETS
[With empirical chemotherapy with “Palliative Intent” or with specific Rx following gene profiling]
Thank you