CLINICAL PRESENTATION AND TREATMENT - AN OVERVIEW

Prof. Nicholas Pavlidis, MD, PhD, FRCP (Edin)

London, September 2015
What is CUP?

CUP represent a heterogenous group of metastatic tumours for which a standardized work-up fails to identify the site of origin at the time of diagnosis. It accounts for 3% - 5% of all malignancies.
THE NATURAL HISTORY OF CANCER OF UNKNOWN PRIMARY SITE
FUNDAMENTAL CHARACTERISTICS

- Early dissemination
- Clinical absence of primary at presentation
- Aggressiveness
- Unpredictable metastatic pattern, *i.e.*

Pancreatic cancer presenting as CUP has 4-fold higher incidence to affect bones, and 30% incidence to appear with lung metastases.
Cancer of Unknown Primary Site: One or more Diseases?
### HISTOLOGICAL CLASSIFICATION

<table>
<thead>
<tr>
<th>Histology</th>
<th>Incidence</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>
</tbody>
</table>
## CLINICOPATHOLOGICAL ENTITIES OF CUP

<table>
<thead>
<tr>
<th>ORGAN</th>
<th>HISTOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liver</strong> (mainly)</td>
<td>AdenoCa M or P diff</td>
</tr>
<tr>
<td>and/or other organs</td>
<td></td>
</tr>
<tr>
<td><strong>Lymph nodes</strong></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 = well, M = moderately, P = poorly, U = undifferentiated*
### Peritoneal cavity

<table>
<thead>
<tr>
<th>Condition</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peritoneal adenocarcinomatosis in females</td>
<td>Papillary or serous adenocarcinoma (± psammoma bodies)</td>
</tr>
<tr>
<td>Malignant ascites of other unknown origin</td>
<td>Mucin adenocarcinoma M or P diffuse (± signet ring cells)</td>
</tr>
</tbody>
</table>

### Lungs

<table>
<thead>
<tr>
<th>Condition</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary metastases</td>
<td>Adenocarcinoma various diffuse</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>Adenocarcinoma M or P diffuse</td>
</tr>
</tbody>
</table>

*W = well,  M = moderately,  P = poorly,  U = undifferentiated*
Bones
(solitary or multiple) AdenoCa of various diff

Brain
(solitary or 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
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?
DIAGNOSTIC AND THERAPEUTIC MANAGEMENT OF CANCER PRIMARY UNKNOWN

N. Pavlidis, E. Brásoulis, J. Hainsworth, E.A. Greco

Palliative Medical Care: The Art and the Science

Guest Editor: M. Fallon

European School of Oncology
CUP

FAVOURABLE OR GOOD PROGNOSIS SUBSETS

UNFAVOURABLE OR POOR PROGNOSIS SUBSETS
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. Poorly differentiated neuroendocrine carcinomas.
   Merkel cell carcinoma of unknown primary (localized disease)

5. Adenocarcinoma with a colon-profile (CK 20+, CK 7-, CDX 2+)

6. Men with blastic bone metastases and elevated PSA (adenocarcinoma).

7. Isolated inguinal adenopathy (squamous carcinoma).

8. Patients with a single, small, potentially resectable tumor.
WOMEN WITH OCCULT PRIMARY BREAST CARCINOMA PRESENTING AS AXILLARY LYMPHADENOPATHY
Therapeutic options applied:

1. Mastectomy and axillary dissection (M + ALND) : 59% of pts
2. Primary breast irradiation : 26% of pts
3. Observation : 15% of pts

Outcomes:

1. Observation group: 42% locoregional relapse rate
2. M + ALND or breast irradiation: adequate locoregional control and 72% 5-year survival
3. No survival difference between M + ALND or irradiation alone
N: 53 pts  TxN1-2M0  
Rx: 100% axillary surgery  
77% ipsilateral breast radiotherapy  
[32% adjuvant systemic treatment]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Irradiated pts</th>
<th>Non-irradiated pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 - yrs: 16%</td>
<td></td>
<td>5 - yrs: 36%</td>
</tr>
<tr>
<td>Local recurrence at</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[p = 0.001]</td>
<td>10 - yrs: 23%</td>
<td>10 - yrs: 52%</td>
</tr>
<tr>
<td>Breast Cancer specific survival at</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[p = 0.0073]</td>
<td>10 - yrs: 66%</td>
<td>10 - yrs: 15%</td>
</tr>
</tbody>
</table>
TREATMENT RECOMMENDATIONS

AXILLARY LYMPH NODE

Surgical Biopsy

Compatible with Breast Cancer

Mammogram U/S MRI

Other Neoplasm

+ve for Breast Cancer

Standard treatment

-ve for Breast Cancer

Complete Axillary Dissection ± BC Surgery + Radiotherapy

Chemotherapy or hormonotherapy depending on age and menopausal status

[Type III level of evidence]
Subset 2

WOMEN WITH SEROUS PAPILLARY PERITONEAL CARCINOMA (Primary Peritoneal Carcinoma)
Serous papillary peritoneal carcinoma: Unknown primary tumour, ovarian cancer counterpart or a distinct entity? A systematic review

George Pentheroudakis, Nicholas Pavlidis*

<table>
<thead>
<tr>
<th>Years</th>
<th>1980 – 2008 (25 studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nº Pts</td>
<td>SPPCs 579</td>
</tr>
<tr>
<td></td>
<td>SOCs 1408</td>
</tr>
<tr>
<td>ORR</td>
<td>71%</td>
</tr>
<tr>
<td>OS (median)</td>
<td>24,4 mos</td>
</tr>
<tr>
<td></td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td>29 mos</td>
</tr>
</tbody>
</table>

SPPC = Serous Papillary Peritoneal Carcinoma  
SOC = Serous Ovarian Carcinoma
N: SPPCs: 38 pts  SOCs: 52 pts

High grade tumors: SPPCs 100% (p < 0.001)  
SOCs 68%

Rx: Platinum - paclitaxel combination (92 – 94% of pts)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>SPPCs</th>
<th>SOCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>12 mos</td>
<td>16.7 mos (p = 0.470)</td>
</tr>
<tr>
<td>OS</td>
<td>62 mos</td>
<td>77.5 mos (p = 0.006)</td>
</tr>
</tbody>
</table>
### Table 3. Therapy of patients with favorable risk cancers of unknown primary site (CUPs)

<table>
<thead>
<tr>
<th>CUP subtype</th>
<th>Proposed treatment</th>
<th>Potential equivalent tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peritoneal adenocarcinomatosis of a serous papillary histological type in female</td>
<td>Optimal surgical debulking followed by platinum–taxane-based chemotherapy</td>
<td>Ovarian cancer</td>
</tr>
</tbody>
</table>
SQUAMOUS CELL CARCINOMA OF AN UNKNOWN PRIMARY SITE INVOLVING CERVICAL LYMPH NODES
TREATMENT MODALITIES

[1] SURGERY

1. Excisional biopsy

2. Neck dissection
   Radical (removal of levels I-IV neck nodes, spinal accessory nerve, internal jugular vein and sternocleidomastoid muscle)
   Modified radical (removal of levels I-IV neck nodes and spares rest of neck structures)

3. Bilateral tonsillectomy (for hidden primaries)

Indications

1. Pts with $N_1$ or $N_2a$ disease without extraxapsular extension could be treated with surgery alone.

2. Locoregional control: 80% - 90%

3. 5-year overall survival: up to 65%
**Indications**

1. Excisional or incisional biopsy
2. Extracapsular extension of the tumor
3. Multiple positive nodes (stage N2b or higher)

*but also in*

4. Initial stage N2b or N3 as a sole treatment
5. Large nodes fixed to the adjacent structure (ie carotid)
6. Pts with low PS and comorbidities
**Sites**

<table>
<thead>
<tr>
<th>Levels of the neck</th>
<th>Sites to be irradiated</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Oral cavity, Waldeyer’s ring, oropharynx, both sides of the neck. Protection of larynx</td>
</tr>
<tr>
<td>II, III (upper) V</td>
<td>Nasopharynx, oropharynx, hypopharynx, larynx, both sides of the neck, to the level of the clavicles</td>
</tr>
<tr>
<td>IV only</td>
<td>Waldeyer’s ring, larynx, hypopharynx, both sides of the neck</td>
</tr>
<tr>
<td>Lower level V</td>
<td>Larynx, hypopharynx, both sides of the neck, generous regional portal to include adjacent apex of the axilla</td>
</tr>
</tbody>
</table>

**Dosage**

a. The neck, 65-70 Gy to the involved nodal stations and 50 Gy for the uninvolved sites.

b. The mucosal sites usually 50 – 60 Gy
1. **Lack of data** from prospective randomized studies

2. **Probably no benefit** for patients with pN1 neck disease without extracapsular extension

3. **For more advanced disease** (N2 or N3) chemoradiotherapy might be required (similarly to the known head/neck locally advanced disease) although they still have some negative voices.

4. **Drugs used**: cisplatin, fluorouracil, paclitaxel, cetuximab

5. Chemoradiation could be associated with significant **grade 3 toxicities** (i.e. mucositis, esophagitis, skin desquamation, laryngeal edema).
## Clinical Practice Guidelines

**Cancers of unknown primary site: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up**

K. Fizazi\(^1\), F. A. Greco\(^2\), N. Pavlidis\(^3\), G. Daugaard\(^4\), K. Oien\(^5\) & G. Petheroudakis\(^3\), on behalf of the ESMO Guidelines Committee*  

### Table 3. Therapy of patients with favorable risk cancers of unknown primary site (CUPs)

<table>
<thead>
<tr>
<th>CUP subtype</th>
<th>Proposed treatment</th>
<th>Potential equivalent tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous carcinoma involving non-supraclavicular cervical</td>
<td>Neck dissection and/or irradiation of bilateral neck and head – neck axis. For</td>
<td>Head and neck cancer</td>
</tr>
<tr>
<td>lymph node</td>
<td>advanced stages induction chemotherapy with platinum – based combination or chemoradiation</td>
<td></td>
</tr>
</tbody>
</table>
POORLY DIFFERENTIATED NEUROENDOCRINE CARCINOMA OF AN UNKNOWN PRIMARY SITE
Tumor Review

Neuroendocrine carcinoma of unknown primary: A systematic review of the literature and a comparative study with other neuroendocrine tumors

Aikaterini Stoyianni a, George Penteroudakis a, Nicholas Pavlidis *

Department of Medical Oncology, Ioanna University Hospital, Niarxou Avenue, 45500 Ioannina, Greece

Data : 1988 – 2010

No pts : 515 [Low grade = 231 (45%)]

Chemotherapy (Platinum based) : 65%

Response rate : 50-60% (CR: 20 - 30%)

Median survival : 15.5 months (11.6 – 40)
Table 3. Therapy of patients with favorable risk cancers of unknown primary site (CUPs)

<table>
<thead>
<tr>
<th>CUP subtype</th>
<th>Proposed treatment</th>
<th>Potential equivalent tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poorly differentiated neuroendocrine carcinomas of an unknown primary</td>
<td>Platinum + etoposide combination chemotherapy</td>
<td>Poorly differentiated NET with a known primary</td>
</tr>
<tr>
<td>Well differentiated NET of unknown primary</td>
<td>Somatostatin analogs, streptozocin + 5-FU, sunitinib, everolimus</td>
<td></td>
</tr>
</tbody>
</table>
Unknown primary Merkel cell carcinoma: 23 new cases and a review

Tina I. Tarantola, MD,a Laura A. Vallow, MD,c Michele Y. Halyard, MD,d Roger H. Weenig, MD,f
Karen E. Warschaw, MD,e Amy L. Weaver, MSc,b Randall K. Roenigk, MD,a Jerry D. Brewer, MD,a
and Clark C. Otley, MDa
Rochester and Minneapolis, Minnesota; Jacksonville, Florida; and Scottsdale, Arizona

• At 2 years, overall survival of patients with stage IIIB unknown primary MCC was significantly improved compared with patients with stage IIIB known primary MCC: 76.9% to 36.4% (P = .028).

Fig 1. Overall survival among 18 patients with stage IIIB unknown primary Merkel cell carcinoma (MCC) and 27 patients with stage IIIB known primary MCC from same time period. Kaplan-Meier estimates are provided at 1, 2, 3, 4, and 5 years. Number at risk are included in parentheses.
Subset 5

ADENOCARCINOMA WITH A COLON–PROFILE (CK 20+, CK 7−, CDX 2+, CEA+) OF AN UNKNOWN PRIMARY SITE
A Retrospective Study of Treatment Outcomes in Patients With Carcinoma of Unknown Primary Site and a Colorectal Cancer Molecular Profile

John D. Hainsworth,1,2 Catherine A. Schnabel,3 Mark G. Erlander,3 David W. Haines III,1 F. Anthony Greco1,2

Carcinoma of unknown primary with gastrointestinal profile: immunohistochemistry and survival data for this favorable subset

G. R. Varadhachary · S. Karanth · W. Qiao · H. R. Carlson · M. N. Raber · J. D. Hainsworth · F. A. Greco
CUP ADENOCARCINOMA WITH A COLON-PROFILE

Cases reported : 74

Gender M/F : 36 % / 64 %  Median Age : 57 years

IHC : CK 20⁺, CK 7⁻, CDX2⁺, ± CEA⁺

Molecular Profiling : 83 – 97 % sensitivity for colon Ca

Disease extension  (Intraabdominal) :
- Abdominal nodes = 51 %  - Carcinomatosis = 50%
- Liver mets = 30%  - Ascites = 27%

Overall RR to site specific regimen : 50% [ CR: 15%, PR : 35% , SD: 25% ]

Overall RR to empirical Rx : 17% [ (CR: 0%, PR : 17% , SD: 33% ]

Median Survival : 21 – 37 months

OTHER FAVOURABLE SUBSETS

- Men with blastic bone metastases from an adenocarcinoma and elevated serum PSA ⇒ treat as advanced prostate cancer
- Isolated inguinal adenopathy from squamous cell carcinoma ⇒ local excision ± radiation
- Patients with a single, small, potentially resectable tumours ⇒ local excision ± radiation
THE UNFAVOURABLE SUBSETS
OR
POOR PROGNOSIS SUBSETS
UNFAVOURABLE SUBSETS

1. Adenocarcinoma metastatic to the liver or other organs
2. Poorly differentiated carcinoma
3. Non-papillary malignant ascites (adenocarcinoma)
4. Multiple cerebral metastases (adeno or squamous Ca)
5. Multiple lung/pleural metastases (adenocarcinoma)
6. Multiple metastatic bone disease (adenocarcinoma)
7. Squamous–cell carcinoma of the abdominal cavity
Table 4. Long-Term Survival in Patients With Unknown Primary Carcinoma and Unfavorable Prognostic Factors

<table>
<thead>
<tr>
<th>Author and Year of Publication</th>
<th>No. of Patients</th>
<th>Regimen</th>
<th>Median Survival (mo)</th>
<th>1-Year Survival (%)</th>
<th>2-Year Survival (%)</th>
<th>3-Year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Briasoulis et al, 2000\textsuperscript{34}</td>
<td>33</td>
<td>PCB</td>
<td>10</td>
<td>25</td>
<td>5</td>
<td>NR</td>
</tr>
<tr>
<td>Dowell et al, 2001\textsuperscript{35}</td>
<td>34</td>
<td>P5FUL (17)</td>
<td>8.3</td>
<td>26</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CbE (17)</td>
<td>6.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balaña et al, 2003\textsuperscript{38}</td>
<td>30</td>
<td>GCE</td>
<td>7.2</td>
<td>36</td>
<td>14</td>
<td>NR</td>
</tr>
<tr>
<td>Park et al, 2004\textsuperscript{40}</td>
<td>37</td>
<td>PC</td>
<td>11</td>
<td>38</td>
<td>11</td>
<td>NR</td>
</tr>
<tr>
<td>Piga et al, 2004\textsuperscript{39}</td>
<td>102</td>
<td>CbDoxE</td>
<td>9</td>
<td>35.3</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Pouessel et al, 2004\textsuperscript{41}</td>
<td>35</td>
<td>GD</td>
<td>10</td>
<td>43</td>
<td>7</td>
<td>NR</td>
</tr>
<tr>
<td>El-Rayes et al, 2005\textsuperscript{43}</td>
<td>22</td>
<td>PCB</td>
<td>6.5</td>
<td>27</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Pittman et al, 2006\textsuperscript{36}</td>
<td>51</td>
<td>GCB</td>
<td>7.8</td>
<td>26</td>
<td>12</td>
<td>NR</td>
</tr>
<tr>
<td>Palmeri et al, 2006\textsuperscript{44}</td>
<td>66</td>
<td>GPC (33)</td>
<td>9.6</td>
<td>30</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GVC (33)</td>
<td>13.6</td>
<td>52</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Berry et al, 2007\textsuperscript{46}</td>
<td>42</td>
<td>PCB</td>
<td>8.5</td>
<td>33</td>
<td>17</td>
<td>NR</td>
</tr>
<tr>
<td>Briasoulis et al, 2007\textsuperscript{42}</td>
<td>47</td>
<td>OxIr</td>
<td>9.5</td>
<td>40</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Schneider et al, 2007\textsuperscript{45}</td>
<td>33</td>
<td>GCaCb</td>
<td>7.6</td>
<td>35.6</td>
<td>14.2</td>
<td>NR</td>
</tr>
<tr>
<td>MPCRN (5 trials) 1997-2008\textsuperscript{1,21-24}</td>
<td>396</td>
<td>Multiple regimens (see text)</td>
<td>9.1</td>
<td>38</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>928</strong></td>
<td></td>
<td><strong>8.9</strong></td>
<td><strong>34.6</strong></td>
<td><strong>13</strong></td>
<td><strong>12</strong></td>
</tr>
</tbody>
</table>
THE SUBSET OF ADENOCARCINOMA METASTATIC TO THE LIVER
OVERALL RESULTS OF CHEMOTHERAPY IN CUP PATIENTS WITH LIVER METASTASES

N° of patients : 711
Response rate : < 20%
Median survival : 5.5 months
Prognostication in cancer of unknown primary (CUP): Development of a prognostic algorithm in 311 cases and review of the literature

Dimitrios Petrakis, George Pentheroudakis, Evangelos Vougaris, Nicholas Pavlidis*
Fig. 1. Overall Survival by CUP Clinicopathologic Subgroups in univariate analysis.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hazard Ratio for death</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS 0–1</td>
<td>0.56</td>
<td>0.39–0.81</td>
<td>0.002</td>
</tr>
<tr>
<td>CUP Subgroup Visceral</td>
<td>1.75</td>
<td>0.98–3.5</td>
<td>0.001</td>
</tr>
<tr>
<td>WBC up to 10.000/mm3</td>
<td>0.512</td>
<td>0.34–0.76</td>
<td>0.001</td>
</tr>
<tr>
<td>Total Bilirubin &gt;1 mg/dl</td>
<td>0.67</td>
<td>0.45–1.001</td>
<td>0.054</td>
</tr>
</tbody>
</table>
DOES THE IDENTIFICATION OF PRIMARY SITE BY MOLECULAR PROFILING FOLLOWING SITE-SPECIFIC THERAPY IMPROVE PATIENTS’ OUTCOME?

WHAT IS THE EVIDENCE TODAY?
STEPS IN DIAGNOSTIC AND THERAPEUTIC MANAGEMENT

DIAGNOSIS OF METASTATIC CARCINOMA (by histopathology)

SEARCH 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

TREAT THE PATIENT

STEP III

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