Latest Research: USA

I. Diagnosis of the cancer type in CUP

II. Outcomes of site-specific therapy of the cancer type in CUP
   a. Prospective clinical trial
   b. Retrospective clinical trials

SCRI

Latest Research: USA

III. Conclusions

IV. Current clinical research

a. Targeted therapy based on comprehensive genetic profiling – target identification

b. Immune stimulating drugs – CTLA-4 and PD-1 inhibitors

c. Prospective evaluation of site-specific therapy in CUP based on IHC and/or molecular diagnosis of cancer type

Diagnosis of the Cancer Type in CUP

- Immunohistochemistry (IHC) – improving and use of panels/patterns of positive and negative stains
- Several patterns of stains now recognized as diagnostic in appropriate clinicopathological setting
- Molecular cancer classifier assays are accurate at the 90% level in diagnosis of the cancer type
- Multiple studies in CUP now reveal ability to diagnose the cancer type in 95%+ of all patients

Immunohistochemical Staining Patterns of a Biopsy Characteristic of a Single Cancer or Tissue of Origin

Prostate	**CK7-, CK20-, PSA+**
Lung-adenocarcinoma and large cell	CK7+, CK20+, TTF-1+, Napsin A+
Lung-neuroendocrine (small cell/large cell)	chromogranin+, synaptophysin+, CD56+, TTF-1+
Thyroid carcinoma (papillary/follicular)	Thyroglobin+, TTF-1+
Melanoma	MelanA+, HMB45+, S100+

Immunohistochemical Staining Patterns of a Biopsy Characteristic of a Single Cancer or Tissue of Origin

Adrenal carcinoma	Alpha-inhibin+, Melan-A+ (A103)
Renal cell carcinoma	RCC+, PAX8+
Germ cell carcinoma	PLAP+, OCT4+
Breast carcinoma	CK7+, GCDCP-15+, ER+, mammaglobin+
Ovary carcinoma	CK7+, WT-1+, PAX8+, ER+
Hepatocellular carcinoma	Hepar-1+, CD10+, CD13+

* In the appropriate clinical and pathologic setting the staining profiles may be diagnostic of the cancer type or tissue of origin. There are many overlapping stains and not all the stains are always positive or negative as indicated above.

Outcomes of Site-Specific Therapy in CUP

- Large prospective trial – Use of molecular cancer classifier assay to diagnose cancer type and treat according to this diagnosis.

  Hainsworth JD, et al. J Clin Oncol 2013;31(2):212-223

- 194 CUP patients received standard site-specific therapy based on their molecular diagnosis of cancer type (26 cancer types diagnosed)

Outcomes of Site-Specific Therapy in CUP

- Median survival of ALL patients 12.5 months compared to about 9.0 months with standard empiric chemotherapy

- More responsive cancer types (breast, lung, ovary, others) diagnosed by the assay had median survival of 13.4 months versus 7.6 months for less responsive cancer types (biliary tract, pancreas, hepatocellular, others)

- The median survival of molecular diagnosed groups (breast, ovary, lung, pancreas, biliary tract, others) was similar to that expected from therapy of advanced cancers with known cancer types

Tissue of Origin Predicted by Molecular Assay (N=252)

Predicted Tissue of Origin	Number of Patients (%)
Biliary tract (gallbladder, bile ducts)	52 (21%)
Urothelium	31 (12%)
Colorectum	28 (11%)
Non-Small-Cell lung	27 (11%)
Pancreas	12 (5%)
Breast	12 (5%)
Ovary	11 (4%)
Gastroesophageal	10 (4%)
Kidney	9 (4%)
Liver	8 (3%)
Sarcoma	6 (2%)
Cervix	6 (2%)
Neuroendocrine	5 (2%)
Prostate	4 (2%)
Germ Cell	4 (2%)
Skin-squamous	4 (2%)
Carcinoid-intestine	3 (1%)
Mesothelioma	3 (1%)
Thyroid	2 (1%)
Endometrium	2 (1%)
Melanoma	2 (1%)
Skin-basal cell	2 (1%)
Lung, small-cell	1 (1%)
Lymphoma	1 (1%)
Head and Neck	1 (1%)
Adrenal	1 (1%)
No prediction possible (unclassifiable)	5 (2%)

SCRI

Results – Assay Diagnostic Tumor Types

Responsive

Substantial benefit from standard site-specific treatment (N = 115)

- Colorectal
- NSCLC
- Bladder
- Breast
- Ovary
- Kidney
- Prostate
- Germ cell
- Others

Less Responsive

Less benefit from standard site-specific treatment (N=79)

- Biliary tract
- Pancreas
- Gastroesophageal
- Liver
- Sarcoma
- Cervix
- Others

SCRI

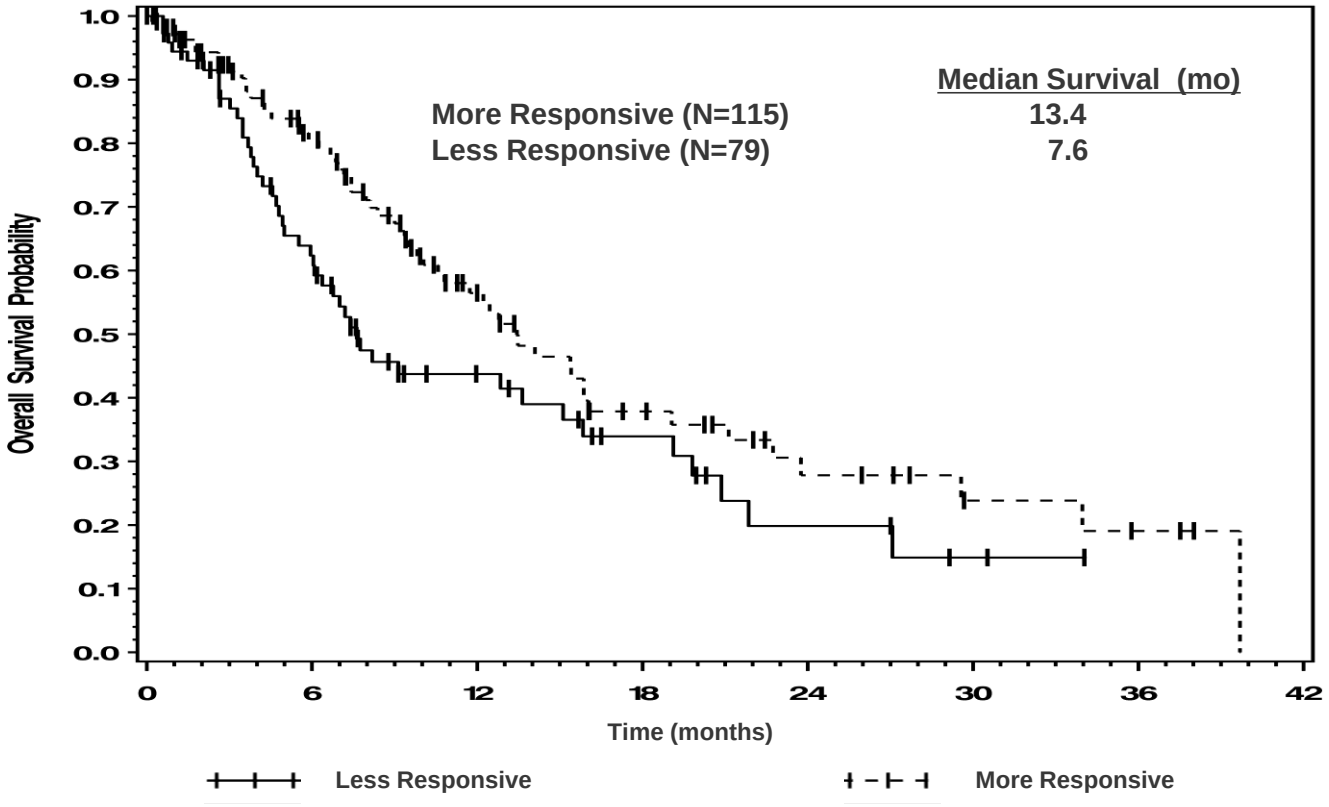
Results

- Median OS for 194 patients with assay-directed treatment was 12.5 months.
-
- Median OS for 115 patients with more responsive tumors vs. 79 patients with less responsive tumors (13.4 vs. 7.6 months).
- Median OS in specific subgroup:
-

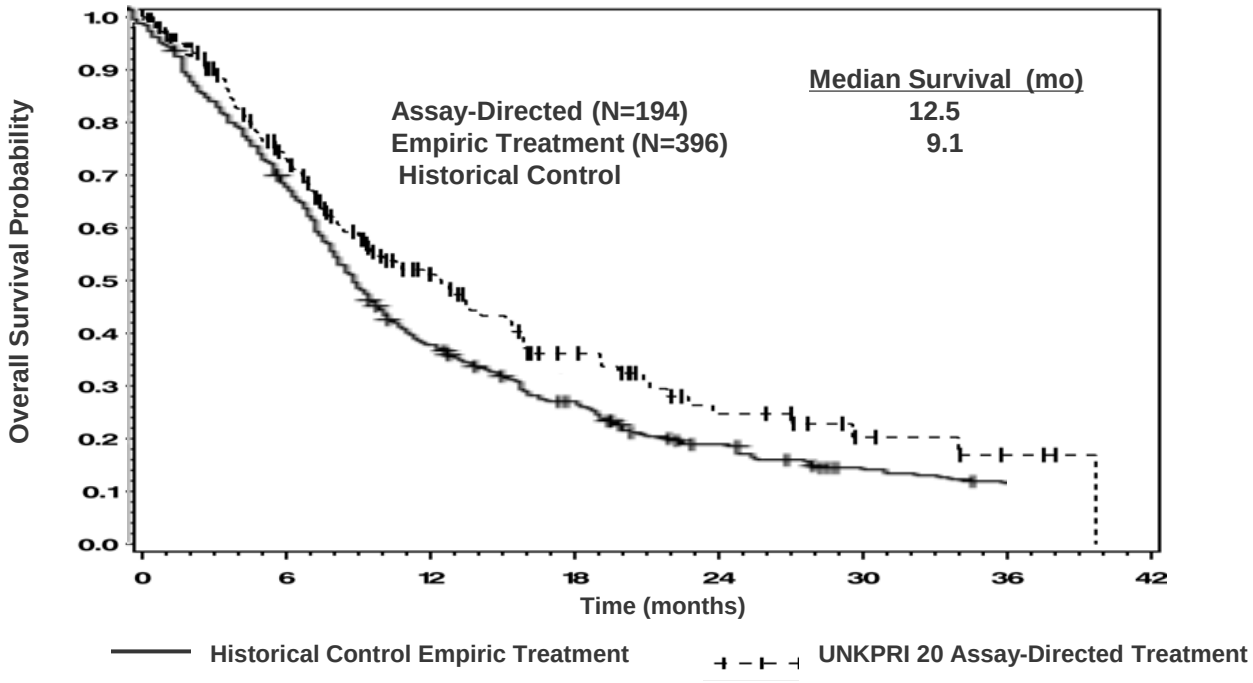
  - Biliary Tract 6.8 months
  - Pancreas 9 months
  - Kidney 12 months
  - Colon 12 months
  - NSCLC 16 months
  - Ovary 30 months
  - Breast > 24 months

SCRI

Survival Curve comparison of Responsive versus Less Responsive Tumor Types, Assay Directed Treatment only



Survival Curve Comparison of UNKPRI 20 Assay-Directed Treatment versus Empiric Treatment Historical Control



Outcomes of Site-Specific Therapy – Retrospective Trials

- Colorectal adenocarcinoma – Two studies with diagnosis by molecular cancer classifier assays and/or IHC
- 74 CUP patients were diagnosed as colorectal and received site-specific colorectal chemotherapy (FOLFOX or similar regimens)
- Median survival of all 74 patients was 24 months (27 months in 42 patient study and 21 months in 32 patient study)

Outcomes of Site-Specific Therapy – Retrospective Trials

- IHC colorectal adenocarcinoma – one study with diagnosis by IHC
- 74 CUP patients – all CDX2+

2 cohorts – 34 patients, CDX2+, CK20+, CK7-;
40 patients CDX2+, irrespective of CK7/CK20

Median survival 30 months all patients

37 months – cohort #1, 21 months – cohort #2

SCRI

Outcomes of Site-Specific Therapy – Retrospective Trials

- Renal cell carcinoma – one study with diagnosis by molecular cancer classifier assay
- 22 CUP patients from a series of 488 CUP patients (4.5%) had renal cell diagnosis
- As in all CUP an anatomical primary site not found (all 22 had normal kidneys on CT scan)
- Subtypes diagnosed by molecular assay – clear cell (7), papillary (8), unknown (7)

Outcomes of Site-Specific Therapy – Retrospective Trials

- Sites of metastasis – retroperitoneum (63%), mediastinum (31%), lung (22%), bone (18%)
- IHC (RCC, PAX 8) supportive of renal cell in 7 of 9 studied after the molecular diagnosis
- 16 of 22 received first-line targeted drugs (site-specific for renal) and median survival was 13.4 months

Outcomes of Site-Specific Therapy – Retrospective Trials

- Poorly differentiated neoplasms – diagnosis of cancer type by molecular cancer classifier assay
- 30 of 751 CUP patients (4%) seen over 12 years
- No cancer type diagnosed by extensive IHC (median 18 stains, range 9-46)
- 25 of 30 patients diagnosed by molecular assay [8 sarcomas (3 mesotheliomas, 5 others), 5 melanomas, 2 lymphomas, 10 carcinomas (3 germ cell tumors, 2 neuroendocrine tumors, 5 other)]

Outcomes of Site-Specific Therapy – Retrospective Trials

- Additional IHC data and genetic testing supports the molecular diagnosis in 12 of 16 patients
- 7 patients tested at the time of diagnosis received site-specific therapy based upon molecular diagnosis (germ cell 2, neuroendocrine 2, mesothelium 2, lymphoma 1)
- All 7 responded favorably and 5 remain in remission 25+ - 72+ months

Parallel Knowledge in the Last Several Years

- Evolving and improving therapy for several cancer types – site-specific approach
- Acquired genetic alterations – common and important in the etiology and growth/metastasis of human cancers
- Targeted therapeutics developing at rapid pace for several solid tumors and at least now rather site-specific
- CUP needs to be diagnosed to offer the best therapy to these patients

Conclusions

- In CUP a specific or single cancer type can be diagnosed in 90%+ by IHC and/or molecular cancer classifier assays.
- In CUP the primary tumor site is very small and by definition not found.
- The size of the primary tumor site does not change the approach to treatment for a patient with metastatic cancer.
- The aim to “make the unknown, known” is reality.

Conclusions

- Site-specific therapy based on the diagnosis of the cancer type from a metastatic site by IHC and/or molecular cancer classifier assay results in outcomes expected for that type of cancer
- The outcomes for patients with CUP diagnosed with cancer types with relatively effective therapies initially or in sequence is improved compared to empiric regimens of the past
- More solid tumors (lung, breast, colorectal, gastric/GE junction, melanoma) are now associated with actionable driver genetic abnormalities and their diagnosis in CUP patients is important
- CUP patients with poorly responsive cancer types will do poorly until improved therapies are developed for their cancer type

FDA-Approved Targeted Agents for Cancer Treatment – USA (N=34)

Drug	FDA-Approved Indication	Target(s)
Ado-trastuzumab emtansine	Breast cancer	HER2
Afatinib	NSCLC	EGFR
Axitinib	RCC	VEGFR
Bevacizumab	Colorectal, NSCLC, RCC, cervix, GBM	VEGF-A
Bosutinib	CML	Bcr-abl
Cabozantinib	MTC	RET, VEGFR, MET, TRKB, TIE2
Ceritinib	NSCLC	ALK, ROS
Cetuximab	Colon, NSCLC, HNC	EGFR
Crizotinib	NSCLC	EML4-ALK, ROS1, MET
Dabrafenib	Melanoma	BRAFV600E

FDA-Approved Targeted Agents for Cancer Treatment – USA (N=34)

Drug	FDA-Approved Indication	Target(s)
Dasatinib	CML	Bcr-abl, SRC, cKIT, PDGFR
Erlotinib	NSCLC	EGFR
Everolimus	RCC, breast, pNET	mTOR, TSC1, TSC2
Ibrutinib	MCL, CLL	BTK
Imatinib	CML, GIST	Bcr-abl, cKIT
Lapatinib	Breast	EGFR
Lenvatinib	Thyroid	VEGFR, FGFR, RET, KIT, PDGFR
Nilotinib	CML	Bcr-abl
Olaparib	Ovary	BRCA
Palbociclib	Breast	CDK 4/6
Panitumumab	Colon	EGFR

FDA-Approved Targeted Agents for Cancer Treatment – USA (N=34)

Drug	FDA-Approved Indication	Target(s)
Pazopanib	RCC, STS	VEGFR, PDGFR, EGFR, KIT
Pertuzumab	Breast	HER2
Ramucirumab	Gastric	VEGFR2
Regorafenib	Colon	VEGFR, TIE2, PDGFR, RET, cKIT
Ruxolitinib	Myelofibrosis	JAK1, JAK2
Sorafenib	RCC, HCC, DTC	BRAF, KIT, FLT-3, RET, VEGFR, PDGFR
Sunitinib	RCC, GIST, pNET	PDGFR, VEGFR, KIT, FLT-3, RET
Temsirolimus	RCC	mTOR
Trametinib	Melanoma	MEK1, MEK2
Trastuzumab	Breast, gastric	HER2
Vandetanib	MTC	RET, EGFR, VEGFR, TIE2
Vemurafenib	Melanoma	BRAFV600E
Vismodegib	BCC	SMO

Ongoing and Upcoming Clinical Trials

- Molecular analysis for therapy choice (NCI-MATCH TRIAL)
  - Solid tumors – umbrella protocol for multiple, single-arm phase II trials, each molecular subgroup matched to a targeted agent
  - Currently 20 arms (targeted drugs): EGFR, ALK, ROS-1, BRAF, HER2, NF2, cKIT, MET, GNAQ, GNA 11, TSC 1/2, PTEN, Patch, FGFR

- ASCO TAPUR Trial(Targeted agent profiling utilization registry)
  - 5 Big Pharma Companies to provide drugs

Ongoing and Upcoming Clinical Trials

- Basket Trial (SCRI) Selected Targeted Agents
  - Solid tumors
  - HER2, EGFR, BRAF, SMO or loss of function PTCH-1
  - Trastuzumab / Pertuzumab, erlotinib, vemurafenib, vismodegib
- FGFR: (SCRI) Selected Targeted Agents
  - Solid tumors
  - FGFR alterations
  - BGJ393 (FGFR inhibitor)

Ongoing and Upcoming Clinical Trials

- ALK/ROS1: (SCRI) Selected Targeted Agent-Any solid tumor (except ALK/ROS1+ NSCLC

  -Ceritinib (ALK/ROS1 inhibitor)

- Prospective Trial Evaluating Outcomes of Directed Matched Targeted Therapy in CUP

  -CUP

  -21 genetic alterations

  -Multiple targeted agents

- Immune stimulating Therapy in CUP

  -- PD-1 inhibitor (MED14736) alone or with CTLA-4 inhibitor (tremilimumab)

Ongoing and Upcoming Clinical Trials

- Prospective Evaluation of CUP: Site-Specific Therapy Based on IHC and/or Molecular Diagnosis of Single Cancer Type. Genomic analysis now for selected diagnoses.

  - Colorectal, renal, breast, ovary, NSCLC, gastric/GE junction, neuroendocrine, lung, urothelial, cholangiocarcinoma, others