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Evolving Role of Molecular Profile Diagnoses in the Management of Patients with Cancer of Unknown Primary: SCRI Studies

Dr. F. Anthony Greco
Sarah Cannon Cancer Center and Research Institute
Nashville, TN

Cancer of Unknown Primary Site

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- 2%-5% of all advanced cancer patients present with this clinicopathologic syndrome
- Most patients have carcinoma and most of these adenocarcinomas
- Despite extensive clinical and pathologic evaluation the anatomical primary site is not found in patients at the time of diagnosis
- Autopsy studies reveal small clinically undetectable primary tumor sites in 75% of patients (lung, pancreas, biliary tract, colorectal, kidney most common, but most tumors represented)
- Favorable subsets of patients represent about 20% of all patients.
- 80% of all patients (not in favorable subsets) have a poor prognosis (median survival 9 months) after empiric chemotherapy (i.e. paclitaxel/carboplatin)

Clinical Trials of Empiric Chemotherapy in Patients with Unfavorable Prognostic Factors 1997-2008

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- Includes the majority of patients –patients with favorable prognostic factors excluded
- Includes adenocarcinoma and poorly differentiated carcinoma
- Multiple phase II studies; one phase III study
- Long term survival (2,3 years and beyond) usually not reported; several exceptions

Sarah Cannon Research Institute Studies: First Six Phase II Sequential Studies (N=451) and One Phase III Study (N=198)

- Paclitaxel, carboplatin, etoposide N=71
- Docetaxel, cisplatin N=26
- Docetaxel, carboplatin N=47
- Paclitaxel, carboplatin, gemcitabine N=120
- Paclitaxel, carboplatin, etoposide followed by gemcitabine, irinotecan N=132
- Paclitaxel, carboplatin, bevacizumab, erlotinib N=55
- Paclitaxel, carboplatin, etoposide versus gemcitabine, irinotecan both followed by gefitinib N=198

Long Term Survival of 396 Patients in Five Sequential SCRI Phase II Trials

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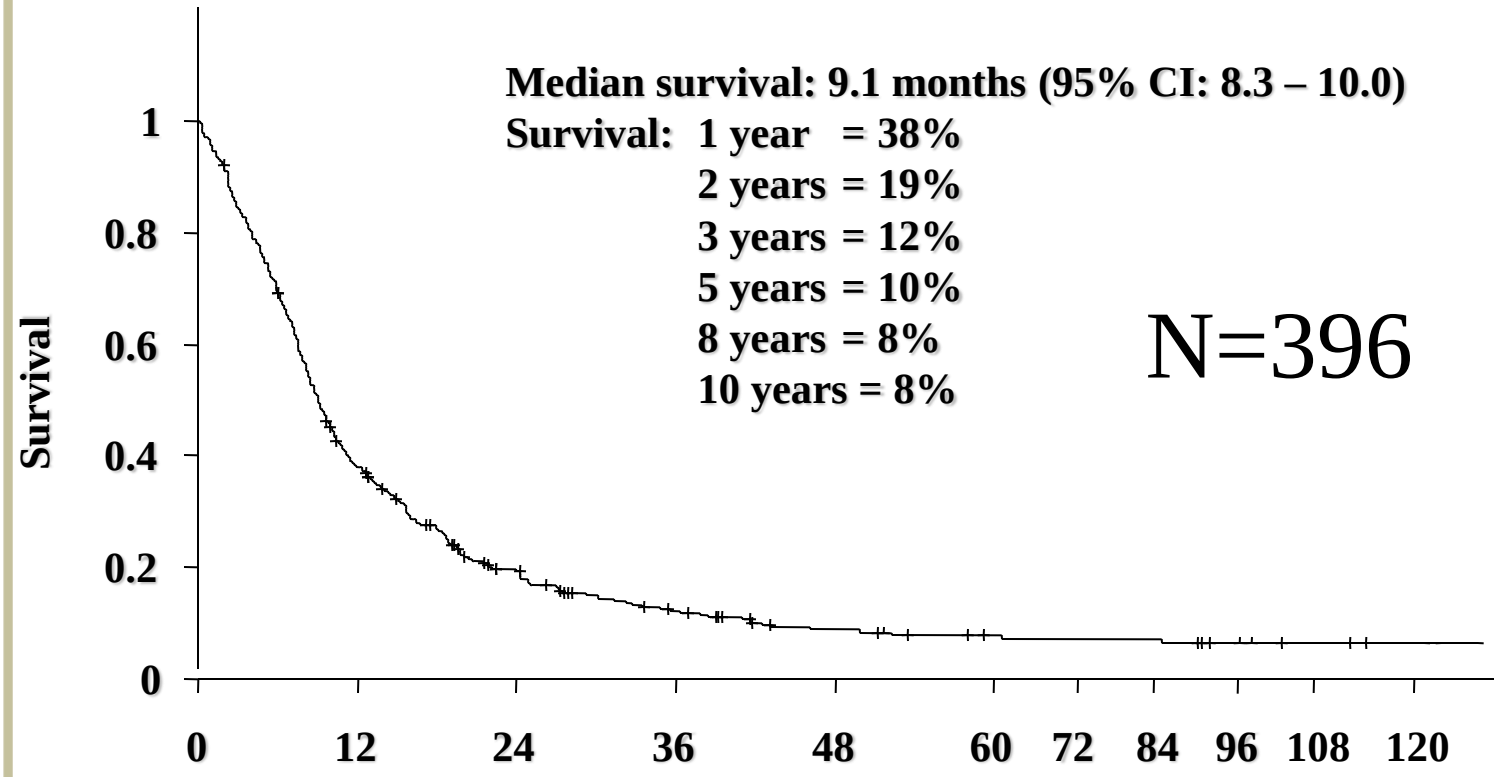

Promising New Diagnostic Approaches: Determination of the Tissue of Origin

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- Improvements and New IHC stains and panels of stains
- Gene Expression Profiling of Human Cancers

Gene Expression Profiling Human Tumors

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- Microarray technology invented about 15 years ago
- Molecular profiling assays to determine primary type of cancer-several platforms now developed/available [RT-PCR-(mRNA); RT-PCR (microRNA); Microarrays (mRNA and microRNA)
- Neoplasms frequently retain normal cellular proteins from their cellular origins and mRNA serves as a template to encode these proteins
- Molecular assays were developed on basis of mRNA encoding for many normal cellular proteins from many normal tissues and testing/validation on several hundred specific known primary tumor types.
- Cancer type identification in cancer of unknown primary site (CUP) depends on comparison to library of molecular signatures of known tumor types

Molecular Diagnostics for Cancer of Uncertain Origin – Overview of Commercial Tests

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Test Providers	bioTheranostics – CancerTYPE ID	Rosetta Genomics miRview mets	Pathwork Diagnostics – Tissue of Origin Test
Number of Cancer Types	Version #1 30 types Version #2 54 types	22 types	15 types
Sample Requirement	FFPE	FFPE	Frozen or FFPE
Platform	RT PCR mRNA	RT PCR miRNA	Microarray mRNA
Sensitivity	Overall = 86%	For Primary=86% Mets=77%	88%
Specificity	99%	99%	99%
Regulatory Aspect/Clearance	CLIA Laboratory developed test	CLIA Laboratory developed test	FDA on Frozen Sample CLIA for FFPE
Pricing/ Reimbursement	~$3350	~ $3650	~$3700

Major Questions Regarding Molecular Profile Assays in CUP

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- Are molecular profile assays accurate in predicting the primary tumor site?
- Do molecular profile assays add to the standard pathologic evaluation in CUP?
- Will site-specific therapy based on molecular profile assay diagnosis improve the outcome of some CUP patients now or in the future?

Background

- There are five practical methods in various settings to determine the diagnostic accuracy of molecular tumor profiling in CUP:
    1. Evaluation of initial biopsy specimens in patients found to have latent primary tumor sites months to years after initial presentation
    2. Evaluation of biopsy specimens in patients with a single diagnosis made by immunohistochemical (IHC) staining
    3. Evaluation of clinical features
    4. Evaluation of additional targeted clinicopathological findings and IHC stains as supportive evidence after the molecular tumor profiling diagnoses
    5. Evaluation of the outcome of specific subsets of patients treated with site-specific chemotherapy based on molecular tumor profiling diagnosis
- This study was designed to access the accuracy of molecular diagnoses of the tissues of origin in the 5 settings described and to determine if molecular profiling of biopsy specimens complements standard clinicopathological evaluation in CUP.

Methods

- The CancerTYPE ID assay (bioTheranostics, Inc) was used in all patients. This molecular assay uses RT-PCR methodology, and can identify 39 tumor types and/or subtypes by assaying the expression of 87 genes (Ma XS et al; Arch Path Lab Med 2006; 130: 465). Prediction of the tissue of origin is made from an algorithm which compares the 87-gene expression profile of the test sample to each of the 39 tumor types in a reference database.
- Molecular profile assay diagnoses were correlated with standard clinical and pathologic data including clinical features, histologic diagnoses, IHC staining, and outcome after site-specific therapy (colorectal subset only).

Summary of Patients Included

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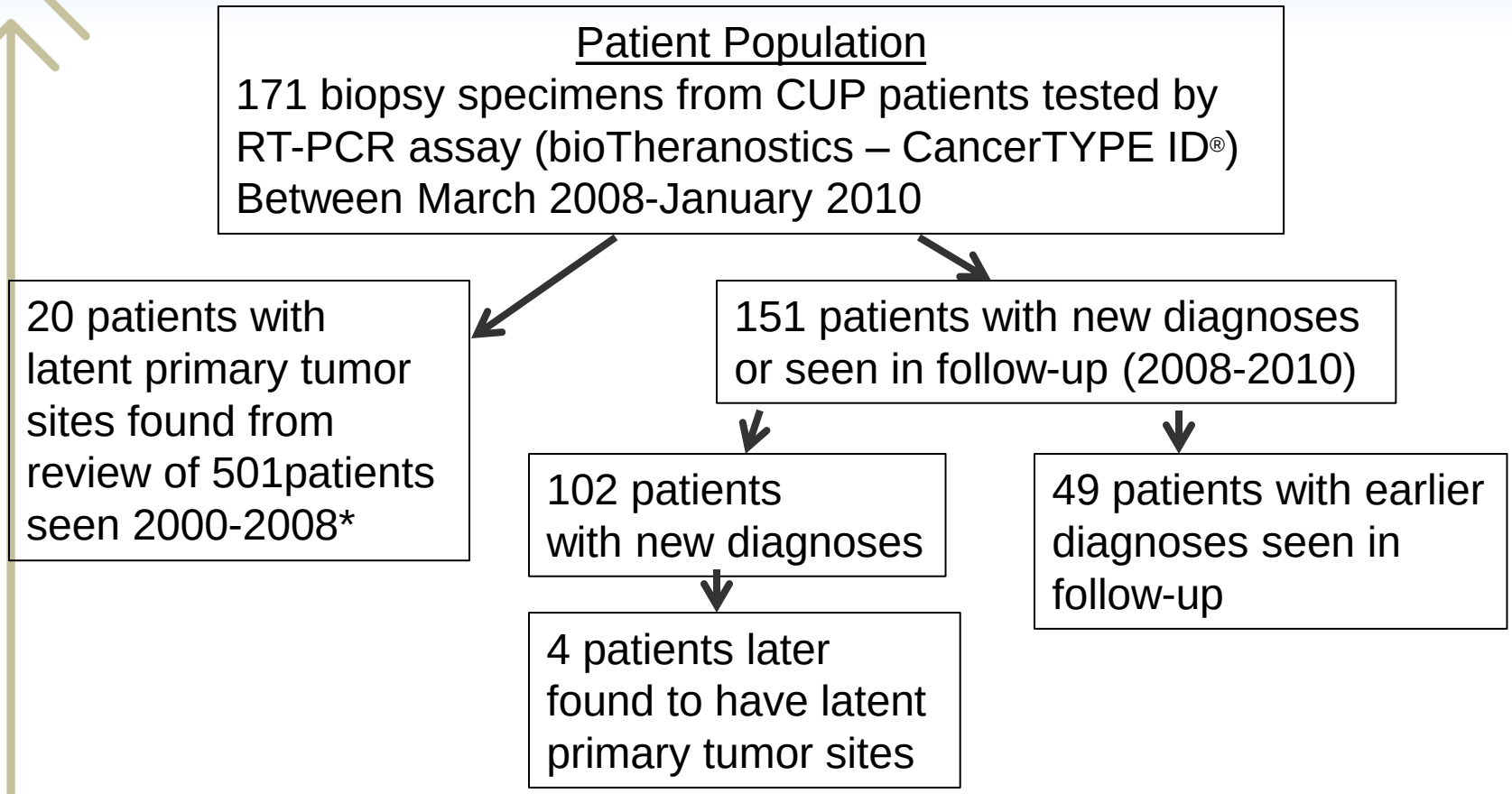

*Greco F Anthony, Spigel D R, et al. Molecular Profiling in Unknown Primary Cancer: Accuracy of Tissue of Origin Prediction. The Oncologist 2010;15:500.

Evaluation of Biopsy Specimens

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Molecular Profile Assay (CancerTYPE ID Version 1) Evaluation in CUP
March 2008 – January 2010 (N = 171)

Site	Number (%)	Site	Number (%)
Insufficient tumor	22 (12.9)	Unclassifiable	5 (3)
Intestine	26 (15.2)	Melanoma	5 (3)
Lung – Adeno/Large cell	18 (10.5)	Gallbladder	6 (3)
Lung – Neuroendocrine	6 (3.5)	Endometrium	3 (1.7)
Lung – Squamous	1 (0.6)	Testicle	3 (1.7)
Breast	15 (8.8)	Thyroid	2 (1.2)
Liver	10 (5.8)	Stomach	2 (1.2)
Pancreas	9 (5.2)	Prostate	1 (0.6)
Ovary	9 (5.2)	Brain	1 (0.6)
Kidney	7 (4)	Uterine/cervix	1 (0.6)
Urinary/bladder	7 (4)	Mesothelioma	2 (1.2)
Skin/squamous	5 (3)	Lymphoma	1 (0.6)

Correlation of Molecular Profile Assay Diagnoses with Latent Primary Tumor Sites Found Months to Years Later (N=24)

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- 38 of 501 (7.6%) patients with CUP seen from 2000-2008 had their latent primary site identified during life (median 12.25 months; range 2.25-78.5 months after initial diagnosis of CUP).
- 20 of the 38 patients with adequate biopsies had their initial diagnostic biopsy specimens tested by the molecular profile assay between March 2008 and January 2009.
- 4 additional CUP patients seen between March 2008 and January 2010 had their latent primary tumors discovered and had their initial biopsy specimens tested by molecular profile assay.
- The latent primary tumor site served as the reference known tissue of origin; 19 of 24 (79%) molecular assay diagnoses were accurate (5 breast, 4 ovary/primary peritoneal, 3 non-small cell lung, 2 colorectal, 2 melanoma, 1 stomach, 1 skin/squamous, 1 soft tissue sarcoma).
- 3 of 24 (12.5%) molecular assay diagnoses were inaccurate (testes, colorectal, sarcoma were pancreas, stomach, non-small cell lung).
- 2 of 24 (8.5%) molecular assay diagnoses were indeterminate or unclassifiable (both non-small cell lung)

Correlation of Molecular Profile Assay Diagnosis with IHC in Patients with a Single Site Predicted by IHC (*N* = 52)

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Single Suspected Primary Site Based on IHC	Number	Agreement of Molecular Assay Diagnoses with IHC Diagnoses	%
Lung/Adeno/Large Cell	19	14	74
Lung/Neuroendocrine	3	2	66
Colorectal	16	15	93
Breast	5	5	100
Melanoma	3	2	66
Germ Cell	2	1	50
Hepatocelluar	1	1	100
Ovary	1	0	0
Prostate	1	0	0
Sarcoma	1	0	0
Total	52	40	77

Correlation of Molecular Profile Assay Diagnosis with IHC in Patients with Uncertain IHC Diagnosis (N = 97)

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- Two possible primary sites suggested by IHC (N=47)
  - Molecular profile assay diagnosis corresponds to one IHC diagnosis N=20 (42%)
  - Molecular profile assay diagnosis does not correspond N=27 (58%)
- Three possible primary sites suggested by IHC (N=50)
  - Molecular profile assay diagnosis corresponds to one IHC diagnosis N=23(46%)
  - Molecular profile assay diagnosis does not correspond to any IHC diagnosis N=27(54%)

Results of Additional Evaluation Directed by Molecular Profile Results in Patients with Uncertain IHC Diagnosis

- In 54 patients, the molecular profile assay diagnosis did not correspond to any of the 2-3 diagnoses suggested by IHC.
  - In 41 of these 54 (75%) patients the clinical features were consistent with the assay diagnoses
  - In 35 of these 54 (64%) patients additional targeted IHC staining, review of histology, and clinical findings were evaluated for supporting evidence of the molecular profile assay diagnoses.
  - In 26 of these 35 (74%) evaluable patients additional clinicopathological findings and/or IHC supported the accuracy of the molecular profile assay diagnoses

Correlation of Molecular Profile Assay Diagnoses with Clinical Features

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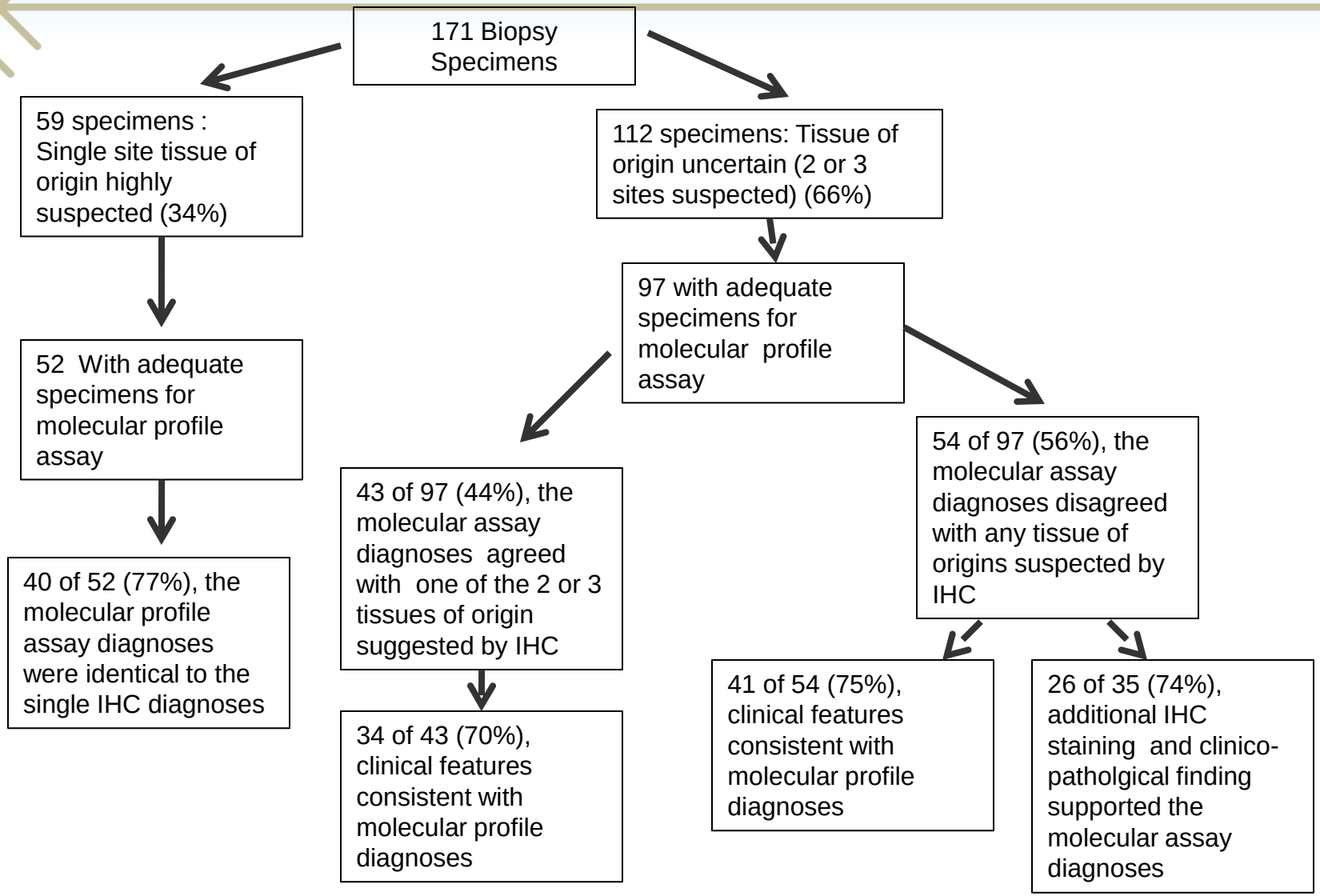
- Clinical features were consistent with molecular assay diagnoses in 112 of 149 patients (70%).
- Clinical features were consistent with molecular assay diagnoses in 41 of 52 patients (78%) with single IHC diagnoses.
- Clinical features were consistent with molecular assay diagnoses in 75 of 97 patients (77%) with uncertain IHC diagnoses.

Summary: Correlation of Molecular Profile Assay Diagnoses with IHC Diagnoses and Clinicopathological Features



Outcomes of CUP "colorectal assay profile" subset of patients treated with colorectal site-specific chemotherapy

- The standard chemotherapy for CUP has been with empiric regimens, usually a platinum with paclitaxel or gemcitibine.
- The outcomes have been poor with response rates of 25-35% and median survivals of 9 to 11 months.
- In the last decade chemotherapy for patients with advanced colorectal carcinoma has improved. Response rates are usually greater the 50% and the median survival approaches 2 years.
- Colorectal molecular profile assay diagnoses in CUP were selected to determine the outcome with site-specific colorectal chemotherapy and to correlate the assay diagnoses with the expected superior outcomes versus expected outcomes after empiric regimens.
- 21 of 26 CUP patients with "colorectal profile assay" diagnoses were evaluable
- 17 of 21 patients received chemotherapy known to be effective in colorectal carcinoma in the first-line setting ; 12 of 17 (70%) had objective responses
- 6 of 21 patients received chemotherapy known to be effective in colorectal carcinoma in the second line setting ; 2 of 6 (33%) had objective responses
- The median survival of all 21 patients was 21 months (95% CI=16.02-25.99 months) with 2 and 4 year survivals of 38% and 24% respectively; these responses and survivals are similar to known advanced colorectal carcinomas and superior to empiric chemotherapy for CUP patients.

Conclusions

- In CUP the molecular profile RT-PCR assay (CancerTYPE –ID®) predicted single tissues of origin diagnoses in 144 of 171 tumor biopsy specimens tested (84%) and 144 of 149 (96%) with adequate tumor specimens; 23 different tumor types and/or subtypes were predicted; colorectal (15%), lung (15%), breast (9%), hepatocellular (6%), ovary(5%), and pancreas (5%) were the most common diagnoses.
- The accuracy of the molecular profile assay diagnoses were supported by ;
  - A correct diagnosis in 19 of 24 (79%) patients with a latent primary tumor site identified months to years after the initial diagnosis of CUP.
  - Consistent clinical features in 70% of all patients including 41 of 52 (78%) patients given a single diagnosis by IHC and 75 of 97 (77%) with uncertain IHC diagnoses.
  - High correlation with IHC single diagnoses; 40 of 52 (77%) patients had the same diagnoses by IHC including 14 of 19 (74%) with lung, 15 of 16 (93%) with colorectal and 5 of 5 (100%) with breast.

Conclusions (continued)

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  - When an unexpected molecular profile assay diagnosis led to further IHC tests and/or clinical diagnostic procedures, the [molecular assay diagnosis was supported in 26 of 35 patients (74%)].
  - Outcome after site-specific chemotherapy for the "colorectal assay profile" CUP subset of patients similar to known advanced colorectal carcinoma (objective response rate 70%; median , 2 year and 4 year survivals 21 months , 38% and 24% respectively).
- Molecular profile assay diagnoses appear accurate in CUP (about 80% overall) and are particularly useful in those patients with an uncertain IHC diagnosis (97 of 149 patients 65%).
- The molecular profile assay is a valuable diagnostic test in CUP and complements standard clinicopathological evaluation.

Are Outcomes/Survivals Improved in CUP by Site-Specific Therapy Based on Tissue of Origin Diagnoses by Molecular Profiling?

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1. Retrospective data (colorectal diagnoses)
2. Prospective data

Site Specific Treatment for CUP with a "Colorectal" Molecular Profile Assay Diagnosis

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Journal of Cancer Therapy, 2012, 3, 37-43

- 32 patients; 11 from Veridex assay and our previous publication. (Varadhachary et al JCO 2008: 26: 442); 21 from the current prospective evaluation of 171 patients
- 30 of 32 had normal colonoscopies; 2 not done
- Clinical features consistent with metastatic colorectal carcinoma in 28 of 32 patients (liver, peritoneal metastasis)
- ALL were treated in either the first-line (23) or second-line (13) setting with colorectal type regimens
- IHC consistent with colorectal carcinoma in 17 of 32 (53%)
- Objective response rates 74% (17 of 23 evaluable) first-line; 54% (7 of 13 evaluable) second-line
- Median survival – 21 months; 2 year survival 42%; 4 year survival 35%

Retrospective Study of Treatment Outcomes in CUP and a Colorectal Molecular Profile

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Clinical Colorectal Cancer, Oct 2011 online and in print

- Review of bioTheranostics (CancerTYPE ID) RT-PCR colorectal predictions (125 of 1544 assays from March 2008-August 2009)
- Surveys sent to oncologists: 42 of 125 patients (34%) completed
- Clinical and pathological features consistent with occult colorectal primary; 69% had intra-abdominal mets. Colonoscopy in 32/all normal; immunostaining typical in 17 of 39 patients (44%)
- 32 patients received either 1st or 2nd line therapy with regimens used for colorectal cancer: response rates 48% 1st line, 53% 2nd line
- Median survival of patients who received site-specific therapy for colorectal cancer was 27 months
- Patients with high probability of having an occult colorectal primary site on the basis of molecular profiling had survival similar to patients with known metastatic colorectal cancer when treated with site-specific regimens

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Molecular gene expression profiling to predict the tissue of origin and direct site-specific therapy in patients with carcinoma of unknown primary site (CUP): Results of a prospective Sarah Cannon Research Institute Trial

F. Anthony Greco, MD[1,2]; Mark S. Rubin, MD[3]; Ralph V. Boccia, MD[4] ; Michael A. Scola, MD[5]; David R. Spigel, MD[1,2]; Samuel Raby[1]; Thabiso Chirwa[1]; Raven Quinn, MS[1]; Catherine A. Schnabel, Ph.D.[6]; Mark G. Erlander, Ph.D.[6]; John D. Hainsworth, MD[1,2]

[1]Sarah Cannon Research Institute (SCRI), Nashville, TN ; [2]Tennessee Oncology, PLLC, Nashville, TN; [3]Florida Cancer Specialists/SCRI, Ft Myers, FL; [4]The Center for Cancer and Blood Disorders, Bethesda, MD; [5]Hematology-Oncology Associates of Northern New Jersey, Morristown, NJ; [6]bioTheranostics, Inc., San Diego, CA

Background and Rationale

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- CUP is a common clinical syndrome, accounting for 3-4% of cancer diagnoses. Most patients receive empiric chemotherapy of moderate efficacy, resulting in a median survival of approximately 9 months.

- As treatment for specific advanced solid tumors improves (e.g. colorectal, renal, melanoma), the accurate identification of these tumor types among the heterogeneous group of CUP patients would allow site-specific therapy, and may improve treatment outcome.

- Molecular tumor profiling is a promising diagnostic technique to determine the tissue of origin in patients with CUP. However, neither the accuracy nor the clinical value of these molecular predictions is known.

- In this large, prospective, multicenter, community-based clinical trial, we performed a 92-gene molecular profiling assay (CancerTYPE ID; bioTheranostics Inc.) on tumor biopsies from patients with newly diagnosed CUP. Tissue of origin predictions were used to guide selection of first-line chemotherapy.

Study Objectives

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- To define the utility of the 92-gene assay in identifying a tissue of origin in patients with CUP.

- To evaluate the impact of the molecular assay prediction on the efficacy of therapy for patients with CUP. Overall survival was determined in the following groups:
  - All patients who received assay-directed site-specific therapy (primary endpoint)
  - Subsets of patients predicted to have more responsive versus less responsive cancer types
  - Subsets of patients with specific tumor diagnoses

Key Eligibility Criteria

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- Diagnosis of CUP following a standard evaluation (complete medical history, physical examination, complete blood counts, chemistry profile, CT scans of the chest and abdomen, PET scan, and directed evaluation of all symptomatic areas).
- One of the following pathologic diagnoses after histologic exam and appropriate IHC stains: adenocarcinoma, poorly differentiated adenocarcinoma, poorly differentiated carcinoma, or poorly differentiated squamous carcinoma.
- Sufficient archived biopsy tissue from a surgical or core needle tumor biopsy to perform the molecular profiling assay.
- ECOG performance status of 0, 1, or 2
- No previous systemic therapy
- Measurable or evaluable disease (RECIST)
- Adequate organ function
- Specific treatable CUP syndromes were excluded: extragonadal germ cell syndrome, neuroendocrine carcinoma; women with adenocarcinoma isolated to axillary lymph nodes; women with peritoneal carcinomatosis; squamous carcinoma limited to cervical, supraclavicular, or inguinal lymph nodes; patients with a single resectable metastasis.

Methods

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- Upon study entry, all patients had a formalin-fixed paraffin-embedded biopsy sample collected and sent to bioTheranostics, Inc. for the 92-gene assay. No treatment was given until results of the molecular assay were available.

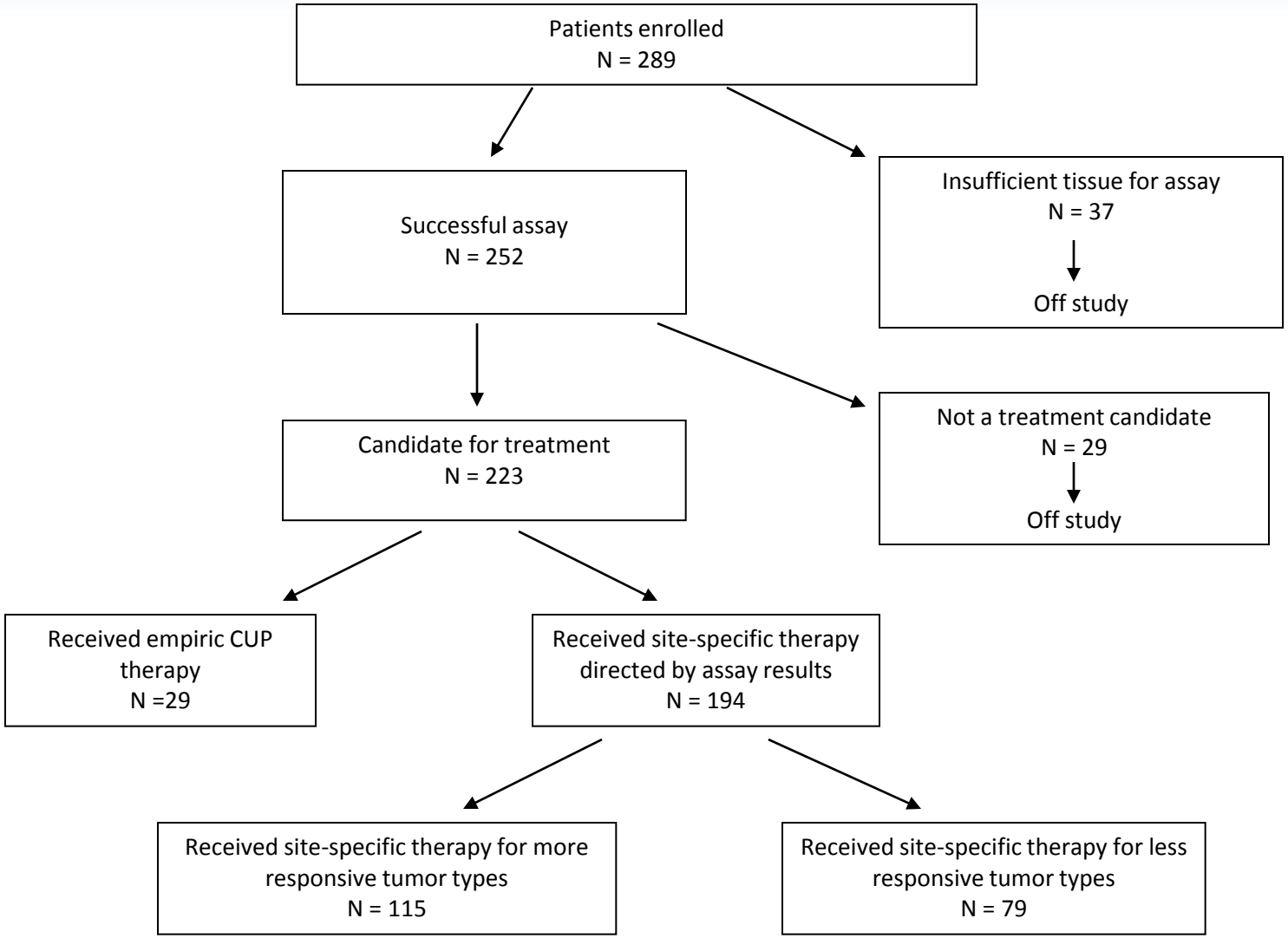
- If a tissue of origin was predicted by the assay, standard site-specific therapy for advanced cancer of the type predicted was administered. Standard treatments for the tumor types anticipated to be predicted most commonly were specified in the protocol. For patients with predictions of other sites of origin not specified in the protocol, standard treatments were to be determined by the treating physician, using NCCN or equivalent guidelines.

- Patients were not treated further in this study if the assay could not be successfully completed (usually due to an inadequate amount of tumor in the biopsy specimen). If the assay was completed but was unable to predict a tissue of origin, patients received standard empiric chemotherapy for CUP.

- Since all chemotherapy regimens were anticipated to be standard and therefore familiar to treating oncologists, treatment was administered (including dose modifications and management of toxicity) following standard practice guidelines.

- Patients were re-evaluated for response after completion of two cycles of therapy; responding or stable patients continued therapy, with re-evaluations every 6-8 weeks, until tumor progression occurred or the treatment course was completed. All patients were followed for survival.

Patient Flow Diagram



Site Specific Treatments

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Predicted Tissue of Origin	Treatment*
Breast	Taxane/bevacizumab
Colorectal	FOLFOX (or variant) + bevacizumab, or FOLFIRI (or variant) + bevacizumab
Lung cancer, non-small cell	Platinum-based doublet + bevacizumab
Ovary	Paclitaxel/carboplatin + bevacizumab
Pancreas	Gemcitabine/erlotinib
Prostate	Androgen ablation therapy
Renal	Sunitinib or bevacizumab ± interferon
Other diagnoses	Standard first-line treatment per guidelines

*Bevacizumab was omitted from the treatment regimen for patients with contraindications

Statistical Considerations

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- Standard empiric chemotherapy for patients with CUP produces a median survival of approximately 9 months. We postulated that accurate prediction of the site of origin by the molecular assay would result in more effective, site-specific therapy and would therefore improve the median survival of the entire group. A 30% improvement (i.e. 9 months → 12 months) in survival was considered clinically significant and supportive of the clinical value of molecular tumor profiling.

- Patients with tumor types that are sensitive to available treatment would be expected to derive greater benefit than less sensitive tumors when accurate identification directs site-specific therapy. We compared the efficacy of assay-directed therapy in patients with assay predictions of "more responsive" versus "less responsive" tumor types. Tumor types were separated into these 2 categories based on the impact of standard treatment for each specific tumor type.
  - More responsive: colorectal, breast, ovary, kidney, prostate, bladder, NSCLC, germ cell, poorly differentiated neuroendocrine, lymphoma, small cell lung cancer
  - Less responsive: biliary tract, pancreas, gastroesophageal, liver, sarcoma, cervix, carcinoid, endometrium, mesothelioma, melanoma, skin, thyroid, head/neck, adrenal

- We planned to enroll enough patients so that the subgroups of patients with the more commonly predicted tumor types would be large enough to analyze separately for survival. Overall survival was determined for the subgroups of patients with the following tumor predictions: biliary tract, pancreas, colorectal, NSCLC, ovary, breast

Patient Characteristics (N = 252; all patients with successful assays)

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Characteristic	Number of Patients (%)
Median age, yrs (range)	64 (26-89)
Gender	
Male	116 (46%)
Female	136 (54%)
Number of metastatic sites	
1	78 (31%)
> 1	174 (69%)
Histology	
Adenocarcinoma	130 (51%)
Poorly differentiated adenocarcinoma	62 (24%)
Poorly differentiated carcinoma	45 (18%)
Squamous carcinoma	13 (5%)
Poorly differentiated neuroendocrine carcinoma	1 (1%)
Poorly differentiated neoplasm	1 (1%)

Tissue of origin predicted by Molecular Assay (N = 252)

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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%)

Survival in 223 Treated Patients and in Subsets

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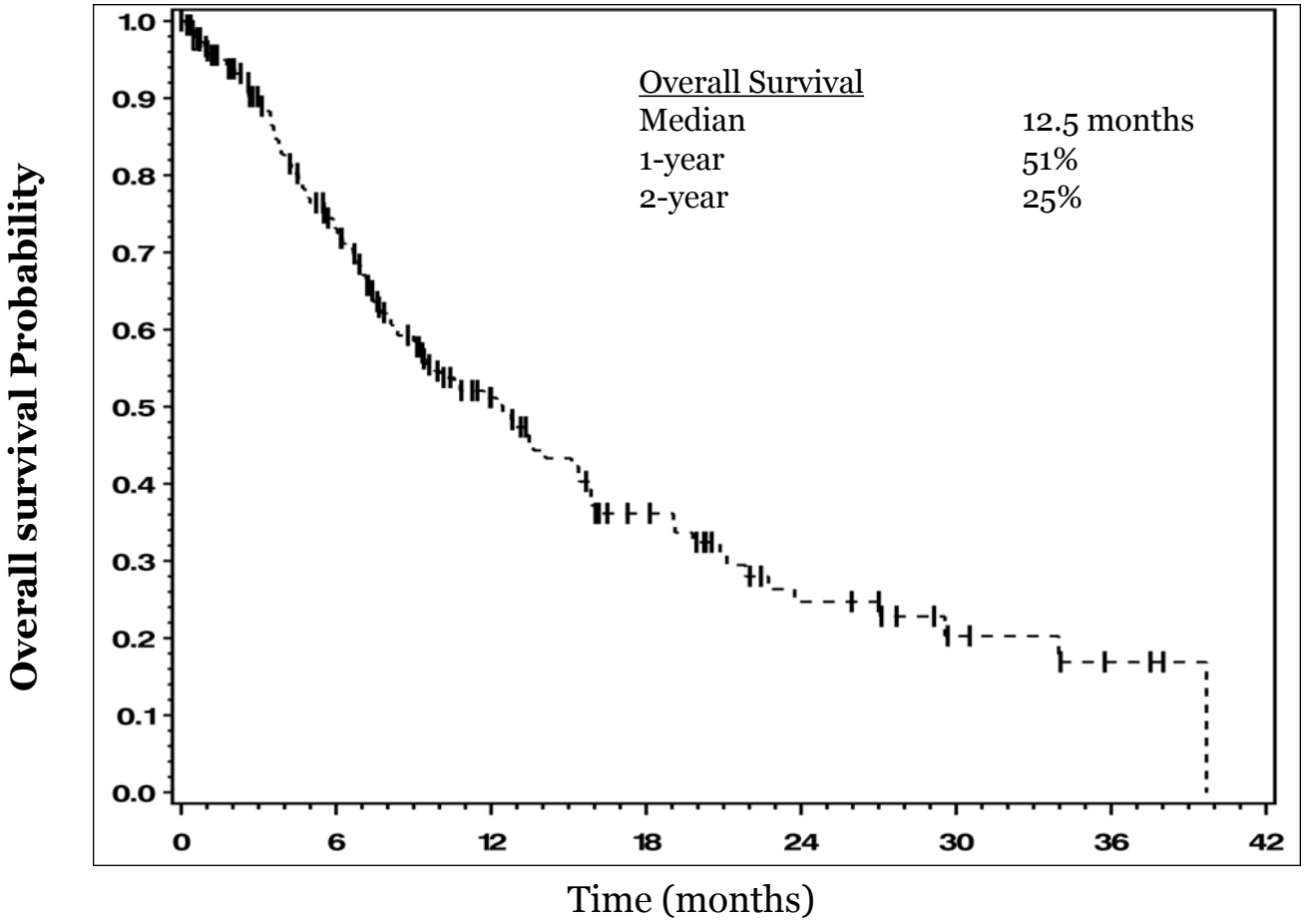
Patient Group	Number	Median survival (mo.)
All treated	223	10.8
Assay-directed treatment	194	12.5, p=0.02
Empiric treatment	29	4.7
Tumor type*		
Treatment responsive	115	13.4, p=0.04
Less treatment responsive	79	7.6
Individual tumor types		
Biliary tract	45	6.8
Pancreas	12	8.2
Colorectal	26	12.5
NSCLC	23	15.9
Ovary	10	29.6
Breast	10	NYR (>24)

NYR = not yet reached; *Includes 194 patients who received assay-directed treatment

Overall Survival: All patients who received site-specific treatment (N = 194)



Overall Survival: Assay-directed treatment, more responsive vs. less responsive tumor types