



SARAH CANNON RESEARCH INSTITUTE

Molecular Cancer Classification to Predict Tumor Type and Direct Site-Specific Therapy: A Prospective Trial of the Sarah Cannon Research Institute

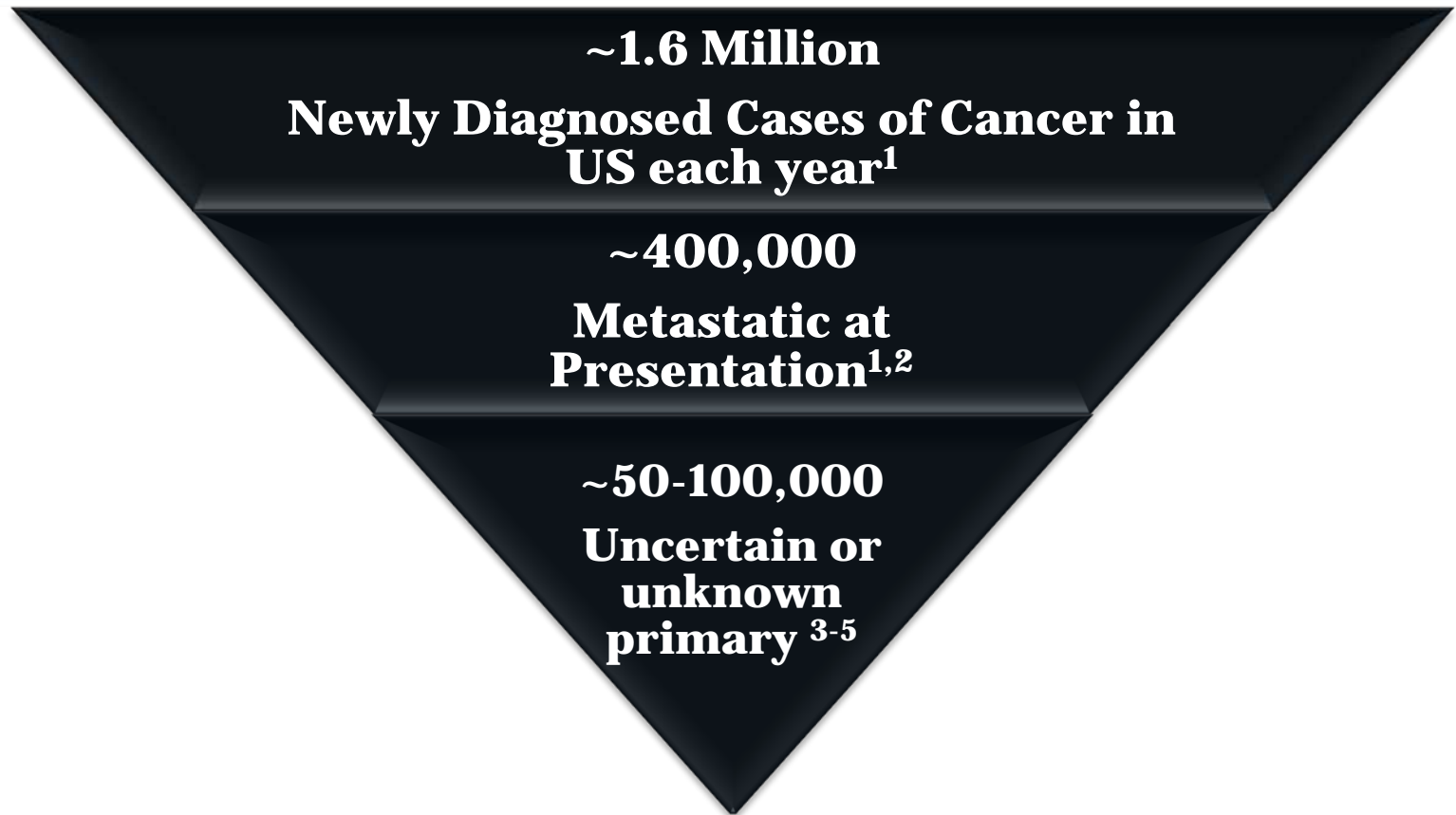
MEDCAC Meeting: May 1, 2013

Dr. F. Anthony Greco

*Sarah Cannon Cancer Center and Research Institute
Nashville, TN*

- Dr. Greco has received honoraria (>\$10,000) from bioTheranostics.

Metastatic Cancer of Unknown or Uncertain Primary Origin



- **Despite advances in imaging and pathologic techniques, tumor diagnosis remains unknown or uncertain in a significant number of new metastatic cases**

- **Cancer of Unknown Primary (CUP) Definition**
 - Metastatic cancer in the absence of a clinically-detectable anatomically-defined primary tumor site after an adequate diagnostic evaluation¹
- **CUP diagnosis can be considered a result of diagnostic failure**

INITIAL DIAGNOSTIC EVALUATION

- Complete history: including detailed review of systems
- Complete physical examination: including pelvic examination, stool for occult blood
- Complete blood cell count, comprehensive metabolic panel, lactate dehydrogenase, urinalysis
- Computed tomography scans of chest, abdomen, and pelvis
- Mammography in women
- Serum prostate-specific antigen in men
- Positron emission tomography scan in selected patients
- Pathology-including screening immunohistochemistry marker stains (CK7, CK20, TTF-1, CDX2)

¹Greco et al. Ann Oncol. 2012 Feb;23(2):298-304. Greco FA and Hainsworth JD. Cancer of unknown primary site. In: De Vita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. 2011:2033-56.

Background

- In the absence of a definitive diagnosis, CUP traditionally has been treated as a single entity, with taxane/platinum or gemcitabine/platinum chemotherapy
- Patient prognosis is poor, with median survivals of approximately 9 months.

| *Reference | Treatment | # of Patients | Median Survival |
|--|--|---------------|-----------------|
| Greco et al., Oncologist. 2004;9(6):644-52. | Paclitaxel/Carboplatin/ Etoposide followed by Gemcitabine/Irinotecan | N=111 | 9.1 months |
| Greco et al., J Clin Oncol. 2002;20(6):1651-6. | Gemcitabine/Carboplatin/ Paclitaxel | N=113 | 9.0 months |
| Piga et al., Br J Cancer. 2004;90(10):1898-904. | Carboplatin/Doxorubicin /Etoposide | N=102 | 9.0 months |
| Hainsworth et al., Cancer J. 2010;16(1):70-5. | Paclitaxel/Carboplatin/ Etoposide vs Gemcitabine/Irinotecan | N=198 | 7.4 months |
| | | | 8.5 months |

- In an effort to improve patient prognosis, a number of clinical subsets have been defined. These “favorable subsets” (~20% of patients) are treated with specific therapies and have significantly better prognosis
 - Squamous cell in the neck → Head & Neck Primary
 - Squamous cell in inguinal region → Anal/Cervical Primary
 - Adenocarcinoma in the Axilla (women) → Breast Primary
 - Peritoneal carcinoma (women) → Ovary Primary
- However, for the remaining 80% of patients, the lack of a definitive diagnosis results in empiric treatment and a poor prognosis

Prospective Outcomes with CancerTYPE ID: Background and Study Objective

■ Objective

- To evaluate the ability of gene expression-based classification with the 92-gene assay (CancerTYPE ID) to render a tumor type diagnosis in patients with CUP
- To determine the efficacy of treatment regimens based on CancerTYPE ID-predicted site of origin

■ Endpoints

- Primary endpoint: Improvement in overall survival of patients who received CancerTYPE ID-directed, site-specific therapy of at least 30% compared to previous trials from the same study group
 - 9.1 months → 11.7 months
 - Comparison in OS to 396 patients from a compilation of 4 CUP trials with contemporary chemotherapies performed by the same clinical trial network
- Secondary endpoint: Further evaluation of the accuracy of CancerTYPE ID to identify responsive vs non-responsive tumor types

■ Design

- Eligible patients had a diagnosis of CUP after diagnostic workup on initial presentation
- Patients excluded if they had a treatable CUP syndrome
- Patients were treated with standard first-line chemotherapeutic treatment regimens based on molecular results

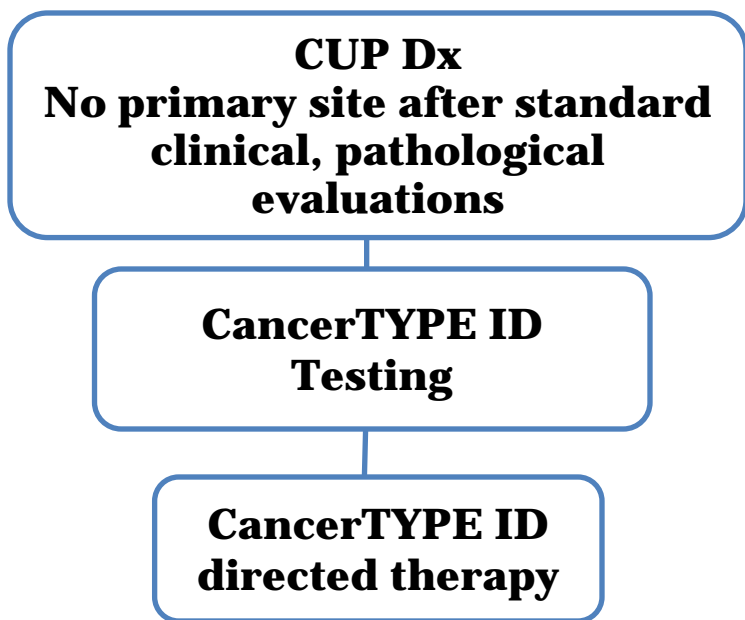


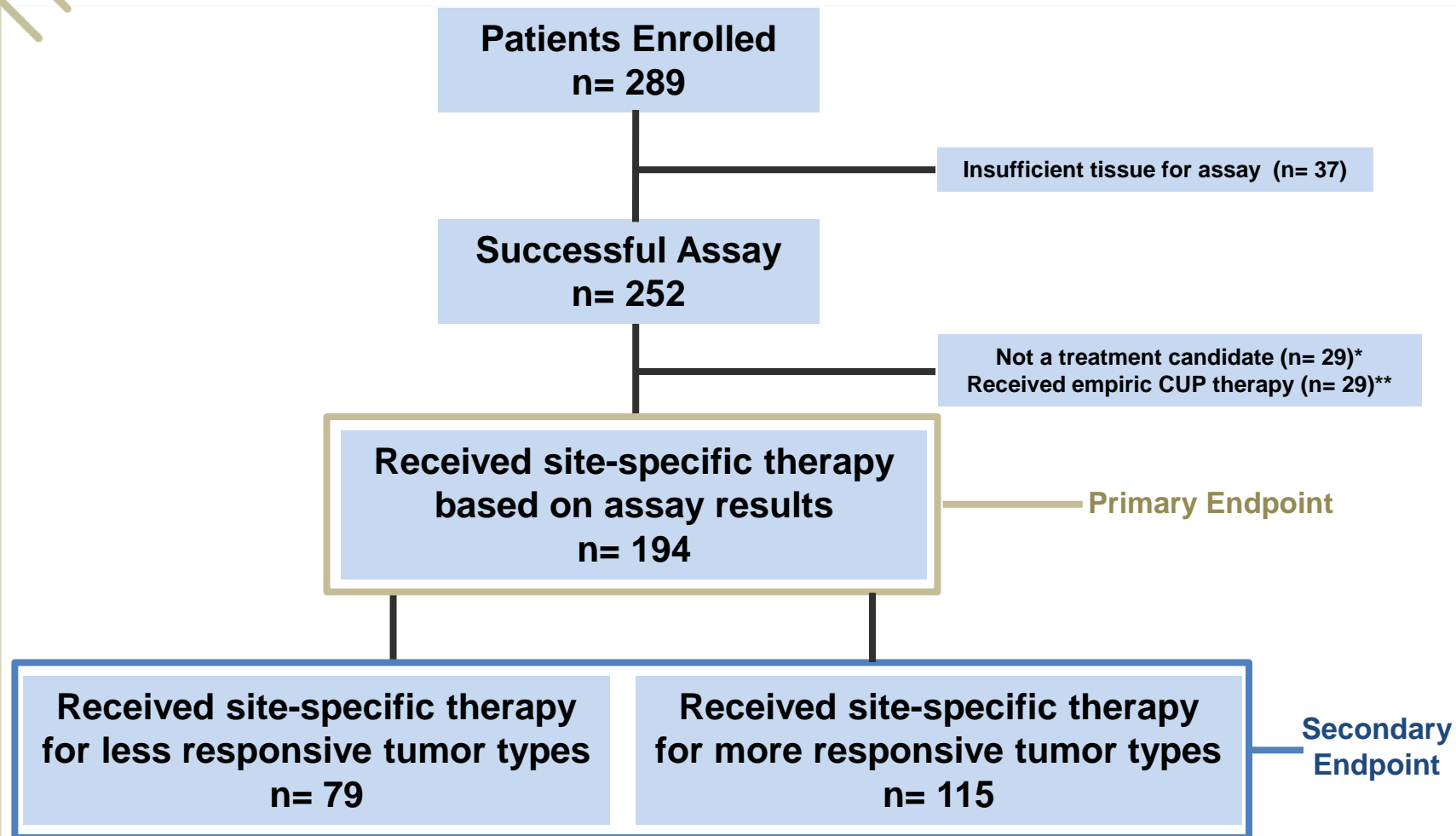
Table 1. Site-Specific Treatments

| Predicted Tissue of Origin | Treatment* |
|----------------------------|--|
| Breast | Taxane/bevacizumab |
| Colorectal | FOLFOX (or variant) + bevacizumab, or FOLFIRI (or variant) + bevacizumab |
| Lung, 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 |

Abbreviations: FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin.

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

Patient Flow Diagram



* Declining performance status, brain metastasis, patient decision

**Unclassifiable result, physician chose to treat with CUP regimen, non-assay directed therapy

Tumor Classification Predicted by CancerTYPE ID

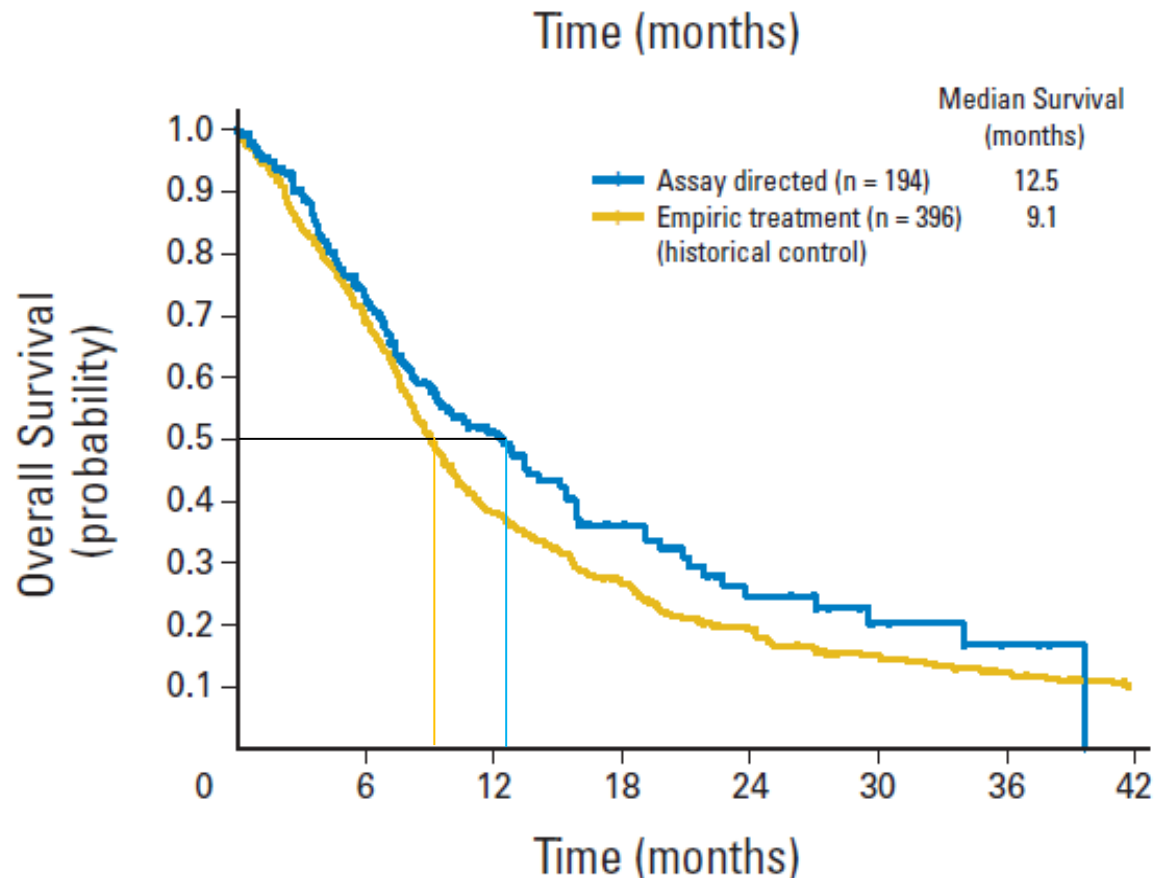
Table 3. Tissue of Origin Predicted by Molecular Assay

| Predicted Tissue of Origin | No. of Patients (N = 252) | % |
|---|------------------------------|----|
| 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 |

- CancerTYPE ID provided a primary site prediction in 98% of the cases
- 26 different tumor types predicted
 - Approximately 60% of patients had tumor types that are more likely to respond to site-directed chemotherapy (median survival >12 months)
 - 48% of identified tumors have indicated molecularly targeted therapies

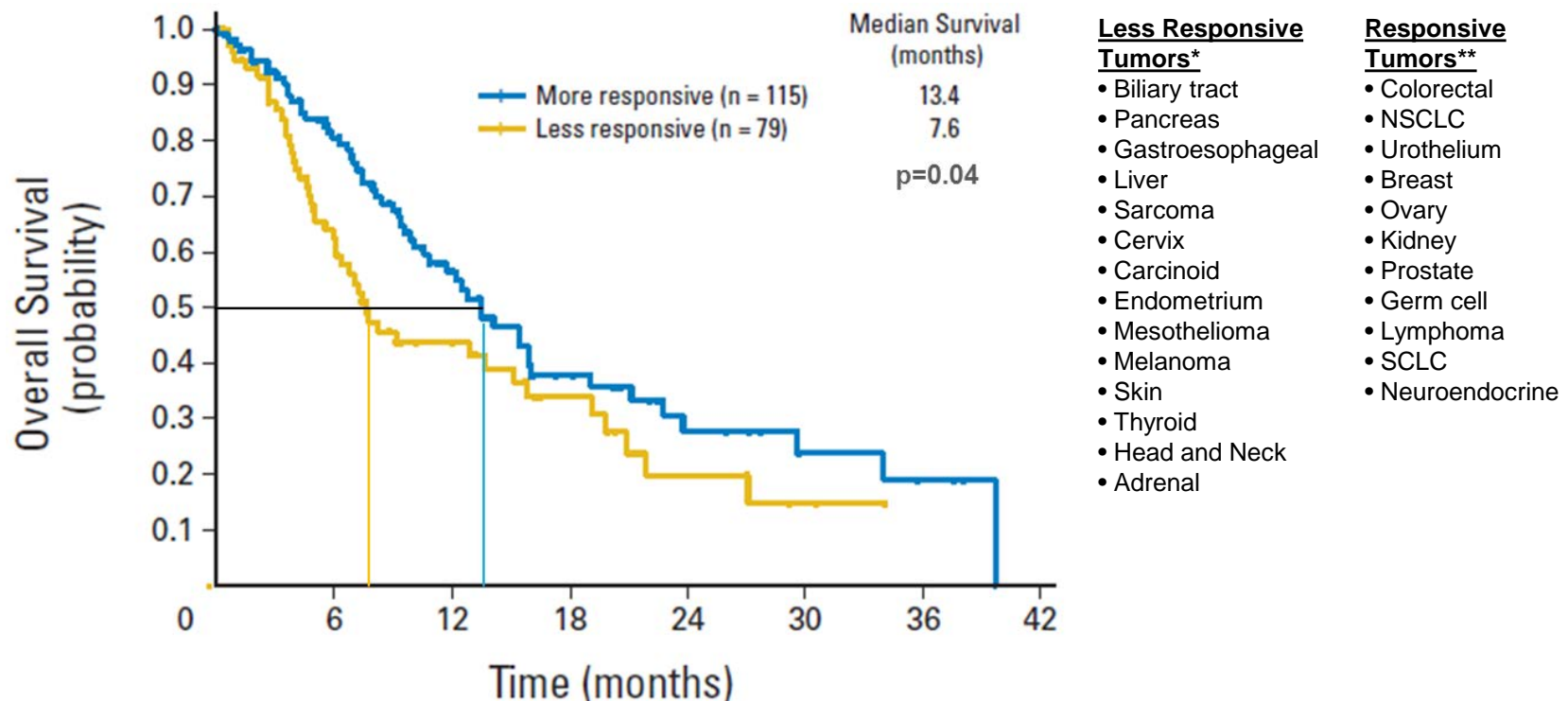
Primary Endpoint: Assay Directed Treatment vs. Empiric Treatment Historical Control

- **The primary endpoint of the study was met: 37% increase in overall survival with assay-directed therapy**



Identification of Responsive Clinical Subsets

- **Patients identified by CancerTYPE ID to have responsive tumor types had a statistically significant increase in overall survival compared to those with less responsive tumor types ($p=0.04$)**
- **Provides evidence that when more effective therapies are available, CancerTYPE ID has an even greater impact on patient outcome**



*Less Responsive (Median OS ≤ 12 mo with standard treatment)

**Responsive (Median OS ≥ 12 mo with standard treatment)

Summary

- First and only prospective trial in which molecular cancer classification has directed site-specific therapy.
- CancerTYPE ID provided a primary site prediction in 98% of cases.
- Approximately 60% of patients were predicted to have responsive tumor types and as treatment options improve, CancerTYPE ID may have an even greater impact on patient outcome.
- Primary endpoint of the study was met resulting in 37% increase in overall survival denoting superiority of assay-directed therapy.
- Observed toxicities in CUP patients were similar to those reported in other trials with specific cancer types.
- Gene expression-based classification is recommended as part of the standard evaluation for patients with CUP.