ESMO Clinical Practice Guidelines

Cancer of Unknown Primary Clinical Case Discussion

A/Prof Linda Mileshkin
Department of Medical Oncology
Peter MacCallum Cancer Centre
Melbourne, Australia

Disclosures

No conflicts of interest to disclose

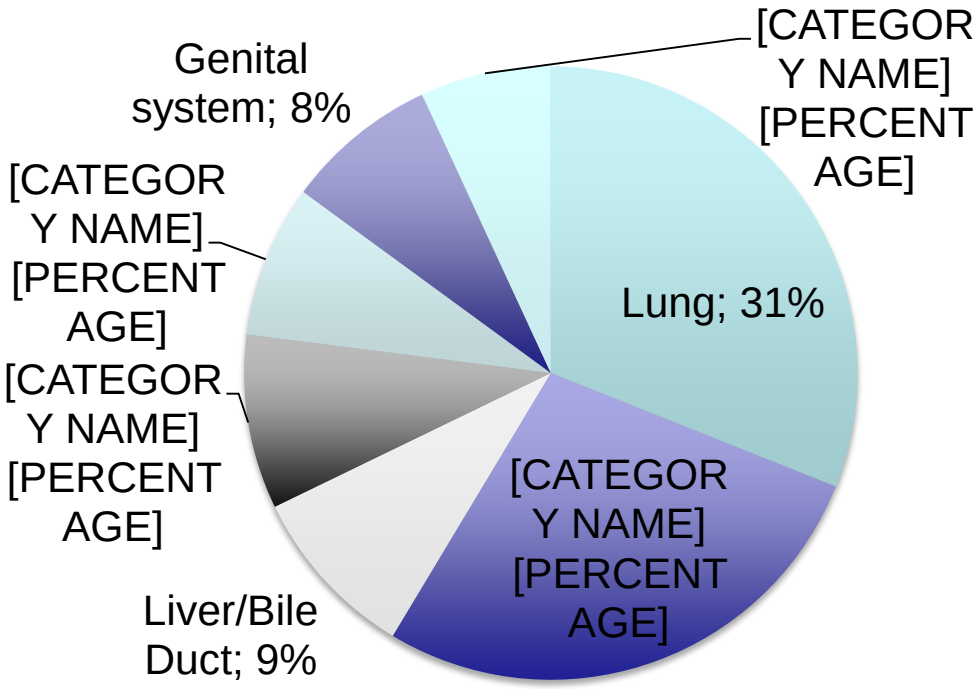
Cancer of Unknown Primary

Metastatic cancer for which the primary site of origin remains unknown despite extensive pathological and clinical investigation.

Represent 3-5% of all new cancer diagnoses

One of the 10 most frequent cancer diagnosis world-wide (Pavlidis *et al* 2003)

Sources of unknown primary tumours:



Pentheroudakis et al 2007 Eur J Cancer 2007; 43: 2026–36

CUP subsets

clinical practice guidelines

Annals of Oncology 26 (Supplement 5): v133–v138, 2015
doi:10.1093/annonc/mdv305

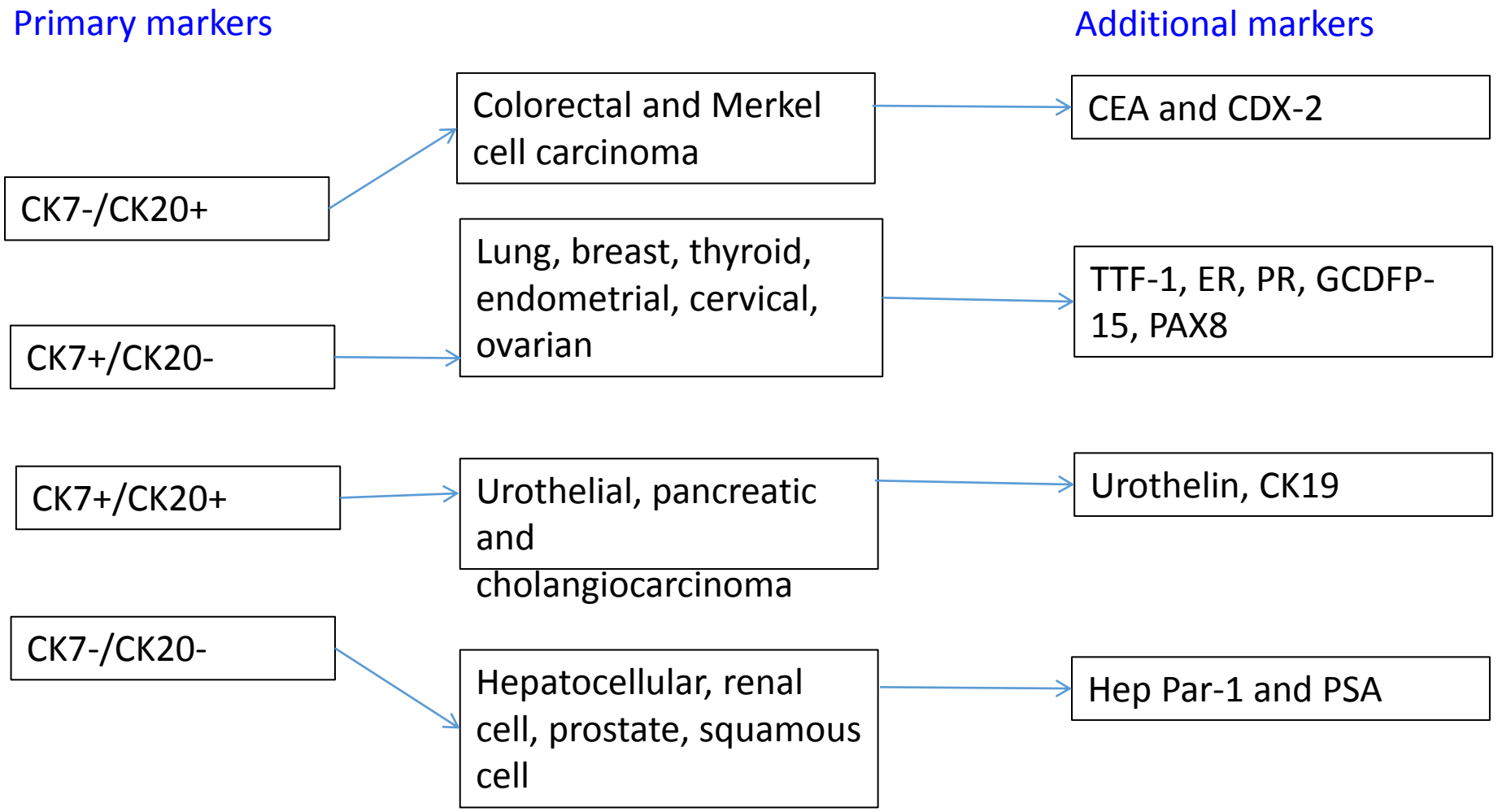
Cancers of unknown primary site: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

K. Fizazi[1], F. A. Greco[2], N. Pavlidis[3], G. Daugaard[4], K. Oien[5] & G. Pentheroudakis[3], on behalf of the ESMO Guidelines Committee*

- Well or moderately differentiated adenocarcinomas (50%)
- Undifferentiated or poorly differentiated adenocarcinomas or carcinomas (30%)
- Squamous cell carcinomas (15%)
- Undifferentiated neoplasm (5%)

- Good prognosis or favourable subsets within these groups
  - Relies on a good quality biopsy and careful histopathological assessment

Basic IHC work-up



ESMO Diagnosis and staging guidelines

Assessment suggested	Target patient population
Thorough History and Examination	ALL
Basic blood and biochemistry analysis	ALL
CT Chest/Abdomen/Pelvis	ALL
Mammogram	ALL FEMALES
Breast MRI	Females with axillary adenocarcinoma
αFP AND βHCG	Patients with midline metastatic disease
Serum PSA	Males with adenocarcinoma bone mets
CT/PET	H+N SCC or single CUP metastasis
Endoscopies	Sign/Symptom/Laboratory oriented
Octreoscan/Chromogranin A	Patients with Neuroendocrine CUP
Additional diagnostic tests	Sign/Symptom/Laboratory oriented

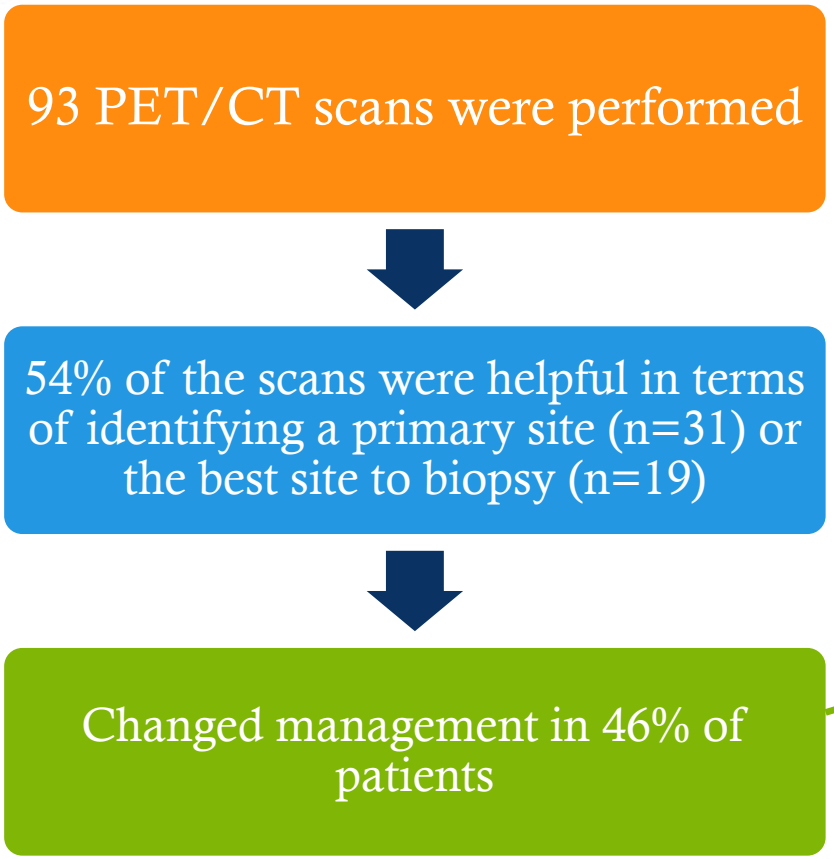
Role of PET/CT in CUP

- ESMO guidelines recommend use in squamous cell carcinoma in cervical nodes or single-site CUP
- “Limited role” in other cases so not mandatory

However

- Literature suggests
  - Ability to detect a primary in about 1/3 cases (after CT)
  - Can find additional sites of disease
  - Can change management
  - (68)Ga-DOTATATE PET may change Rx in neuroendocrine CUP
- Disadvantages
  - Cost / Lack of reimbursement
  - False positives

Utility of FDG PET/CT in 121 patients seen in PeterMac CUP clinic



- Change in Rx intent
- Change in Rx given
- Confirmation of benign disease
- Targeted site for new biopsy

Tan L, Medical Oncology Group of Australia ASM 2105

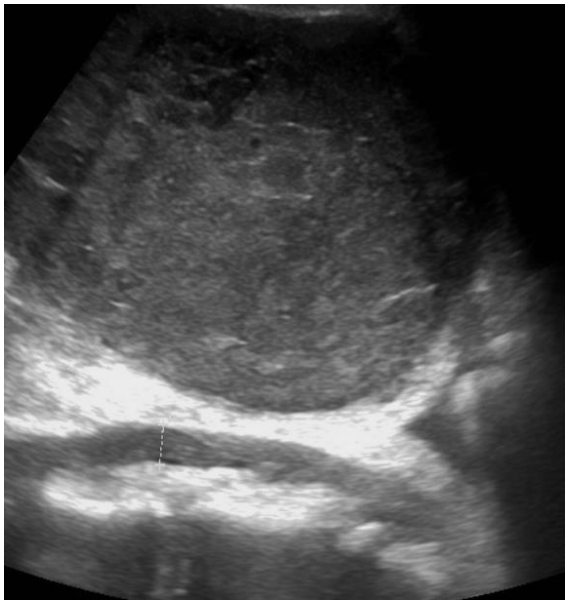
Table 3. Therapy for patients with favourable-risk cancers of unknown primary site (CUPs)

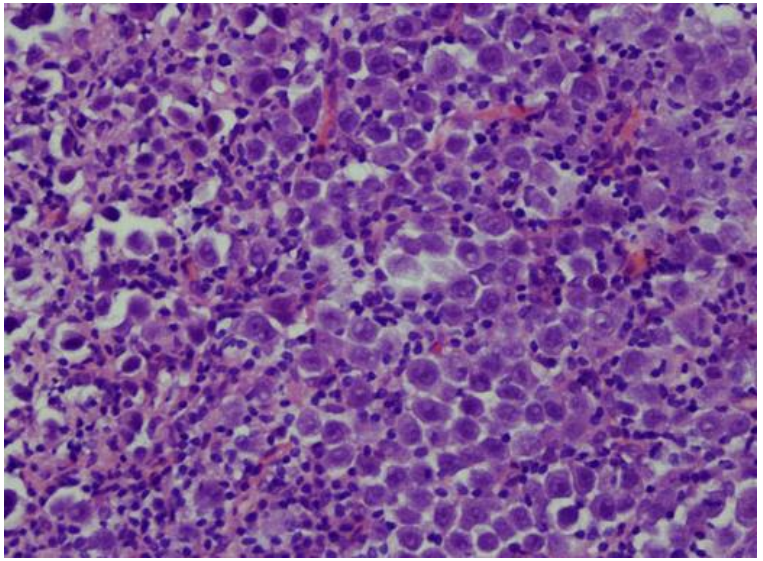
CUP subtype	Proposed treatment	Potential equivalent tumour
Poorly differentiated neuroendocrine carcinomas of an unknown primary	Platinum + etoposide combination chemotherapy	Poorly differentiated neuroendocrine carcinomas with a known primary
Well-differentiated neuroendocrine tumour of unknown primary	Somatostatin analogues, streptozocin+5-FU, sunitinib, everolimus	Well-differentiated neuroendocrine tumour of a known primary site
Peritoneal adenocarcinomatosis of a serous papillary histological type in females	Optimal surgical debulking followed by platinum–taxane-based chemotherapy	Ovarian cancer
Isolated axillary nodal metastases in females	Axillary nodal dissection, mastectomy or breast irradiation and adjuvant chemohormonotherapy	Breast cancer (found in 50%–70% when breast MRI is performed)
Squamous cell carcinoma involving non-supraclavicular cervical lymph nodes	Neck dissection and/or irradiation of bilateral neck and head–neck axis. For advanced stages induction chemotherapy with platinum-based combination or chemoradiation	Head and neck squamous cell cancer
CUP with a colorectal IHC (CK20+ CDX2+ CK7−) or molecular profile	Systemic treatment used for colorectal cancer	Metastatic colorectal cancer
Single metastatic deposit from unknown primary	Resection and/or RT ± systemic therapy	Single metastasis
Men with blastic bone metastases or IHC/serum PSA expression	Androgen deprivation therapy ± RT	Prostate cancer

5-FU, 5-fluorouracil; MRI, magnetic resonance imaging; IHC, immunohistochemistry; PSA, prostate-specific antigen; RT, radiotherapy; CK, cytokeratin.

Our case

- An abdominal ultrasound followed by guided core-needle biopsy reveals multiple hypoechoic areas in both lobes, consistent with metastases.
- Tru-cut needle biopsy yields presence of poorly differentiated adenocarcinoma.





What we often get to work with

Biopsy report

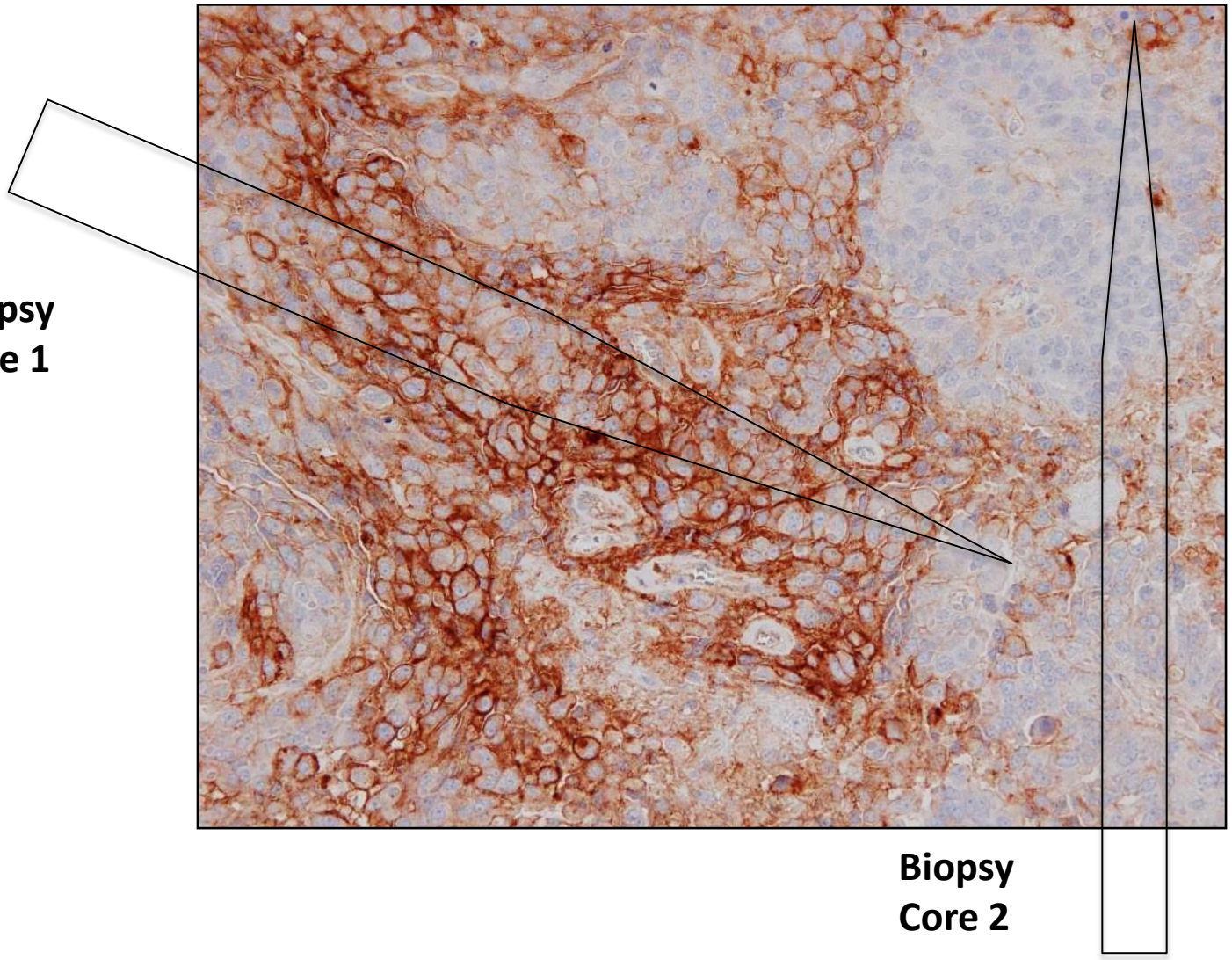
Macroscopic description

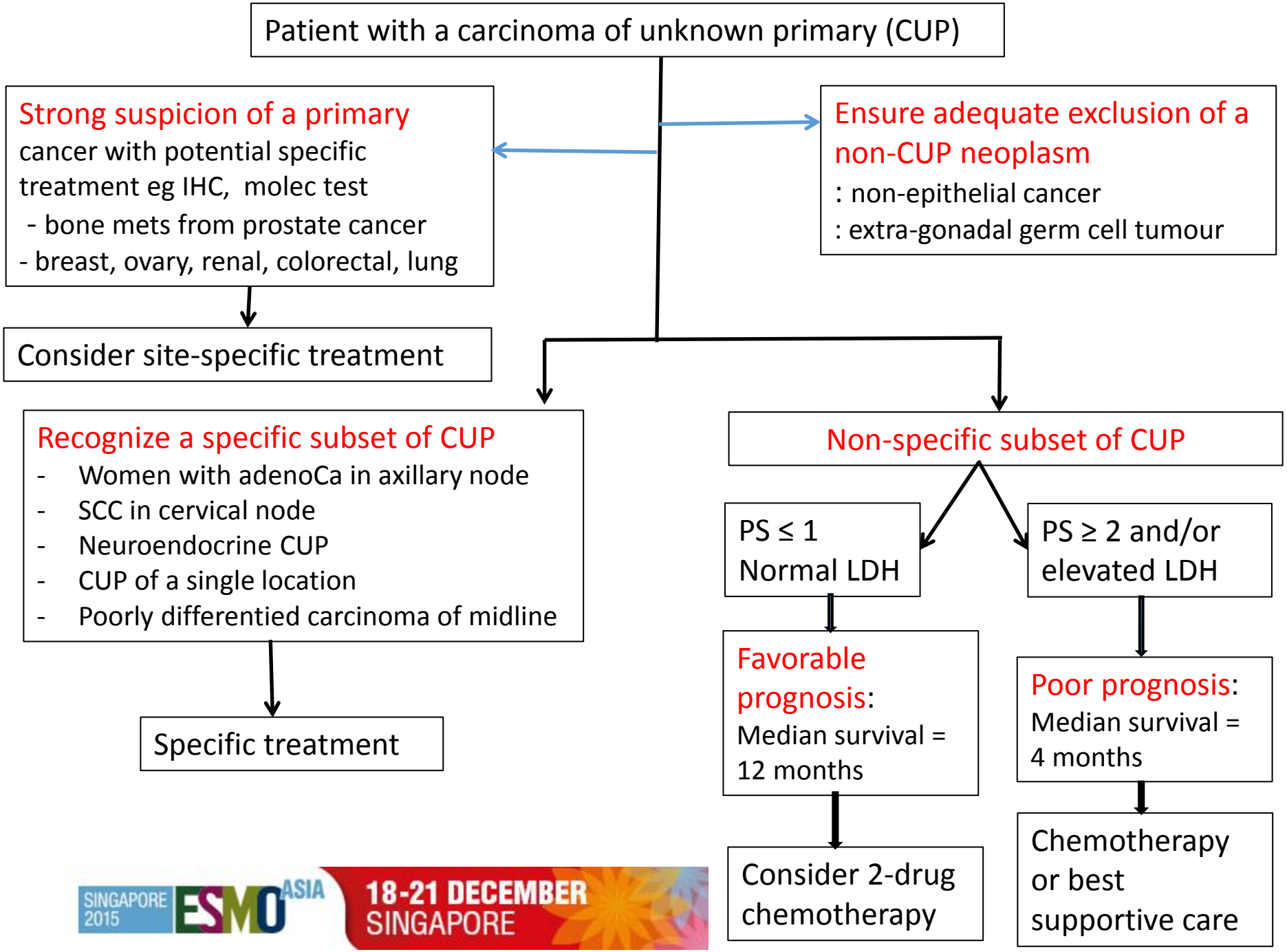
“The specimen consists of one core of tissue measuring 6mm in length and less than 1mm in diameter”

Reported to show poorly differentiated adenocarcinoma

Immunohistochemically the population is positive with CK20, EMA and CDX2. The population is negative with CK7, PSA, TTF1, PAX8 and GATA3. This pattern suggests a large bowel or appendiceal primary, while not excluding pancreatic duct.

Immunohistochemistry: Expression Heterogeneity and Potential for Sampling Error





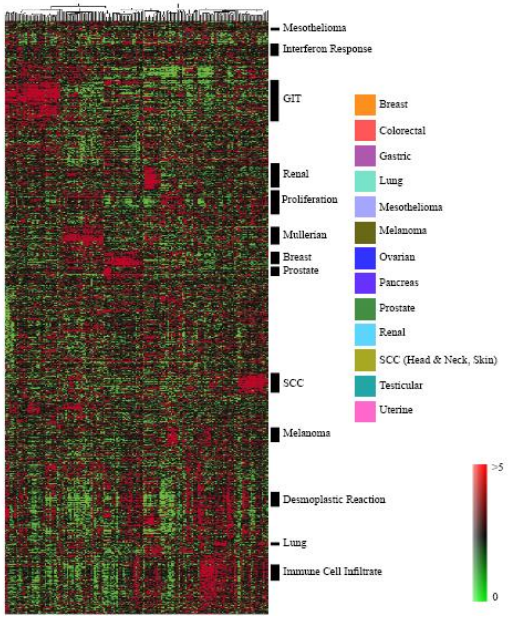
Patients and clinicians prefer to make a site-specific diagnosis!

- On-line survey responses from 86 Australian medical oncologists
- 27% stated that they would prefer to provide a best guess of the primary site of the cancer rather than diagnose CUP as a specific diagnostic entity
- 83% of respondents stated that they would label CUP cases with a specific primary in an effort to obtain access to government funded drugs only available for certain cancer types

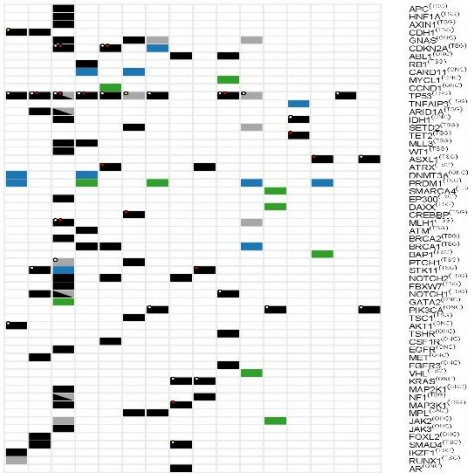
Karapetis et al, manuscript in preparation 2015

Molecular approaches to improving the clinical management of CUP

Detection of likely site of origin



Mutational profiling for actionable mutations



Site of origin gene-expression classification

Molecular Classification of Human Carcinomas by Use of Gene Expression Signatures[1]

Andrew I. Su, John B. Welsh, Lisa M. Sapinoso, Suzanne G. Kern, Petre Dimitrov, Hilmar Lapp, Peter G. Schultz, Steven M. Powell, Christopher A. Moskaluk, Henry F. Frierson, Jr., and Garret M. Hampton[2]

Department of Chemistry, The Scripps Research Institute, La Jolla, California 92037 [A.I.S., P.G.S.]; Genomics Institute of the Novartis Research Foundation, San Diego, California 92121 [J.B.W., L.M.S., S.G.K., P.D., H.L., P.G.S., G.M.H.]; and Departments of Medicine [S.M.P.] and Pathology [C.A.M., H.F.F.], University of Virginia Health System, Charlottesville, Virginia 22908

Su *et al* 2001

Multiclass cancer diagnosis using tumor gene expression signatures

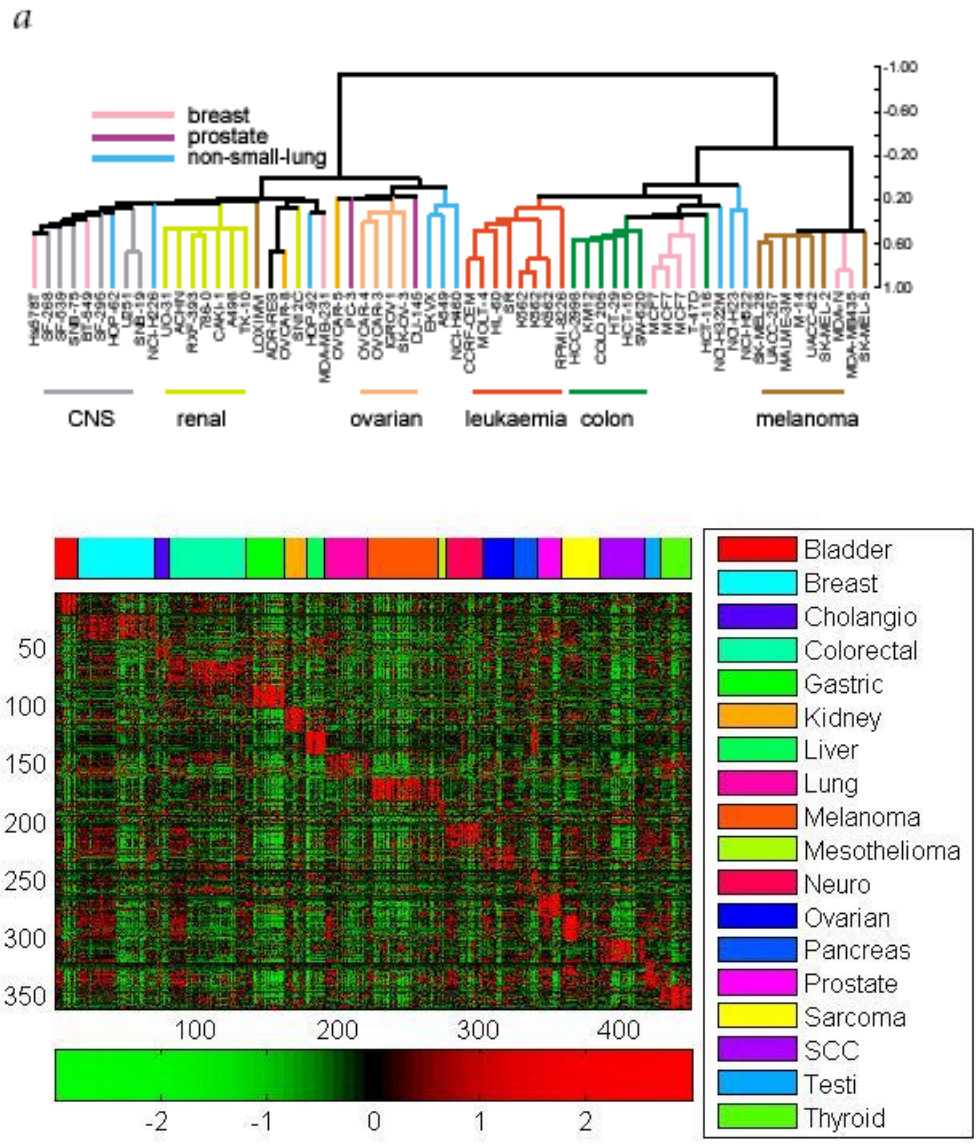
Sridhar Ramaswamy*†, Pablo Tamayo*, Ryan Rifkin*†, Sayan Mukherjee*†, Chen-Hsiang Yeang*§, Michael Angelo*, Christine Ladd*, Michael Reich*, Eva Latulippe¶, Jill P. Mesirov*, Tomaso Poggio‖, William Gerald¶, Massimo Loda#, Eric S. Lander*,**, and Todd R. Golub*†**

Ramaswamy *et al* 2001

An Expression-Based Site of Origin Diagnostic Method Designed for Clinical Application to Cancer of Unknown Origin

Richard W. Tothill,[1] Adam Kowalczyk,[1] Danny Rischin,[2] Alex Bousioutas,[1] Izhak Haviv,[1] Ryan K. van Laar,[1] Paul M. Waring,[3,4] John Zalcberg,[2] Robyn Ward,[5] Andrew V. Biankin,[6] Robert L. Sutherland,[6] Susan M. Henshall,[6] Kwun Fong,[7] Jonathan R. Pollack,[8] David D.L. Bowtell,[1] and Andrew J. Holloway[1]

Tothill *et al* 2005



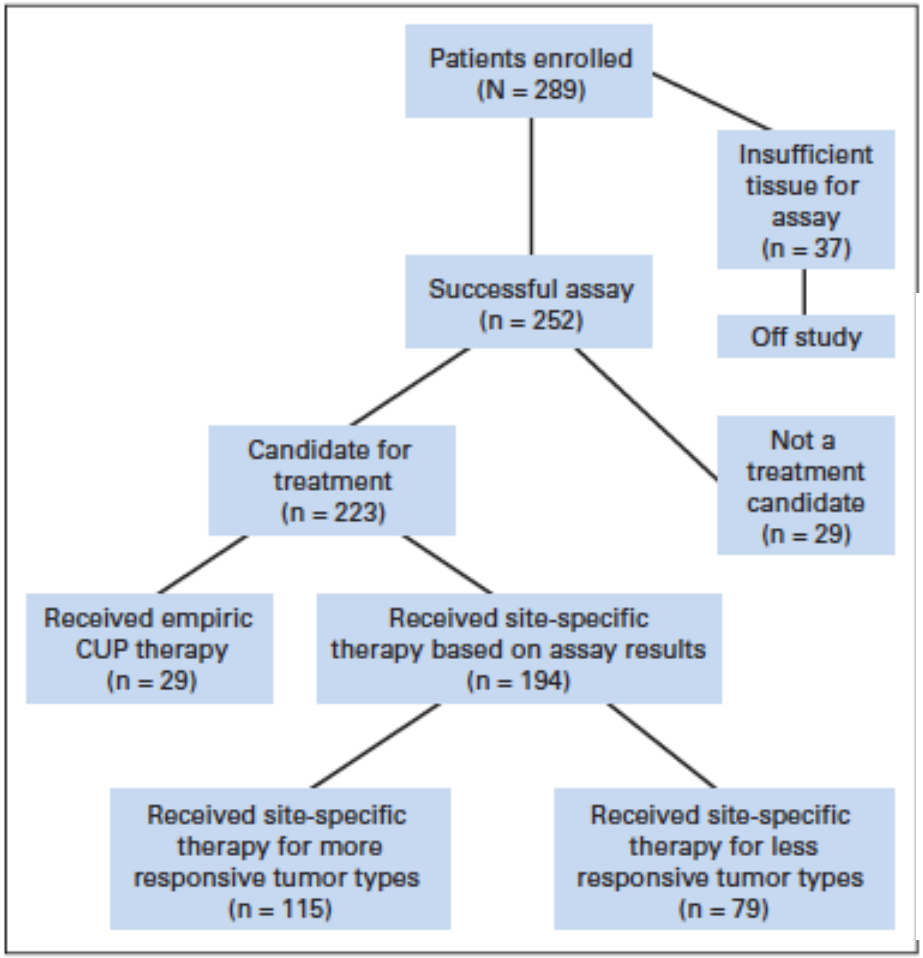
eg. CUPGuide from Healthscope pathology

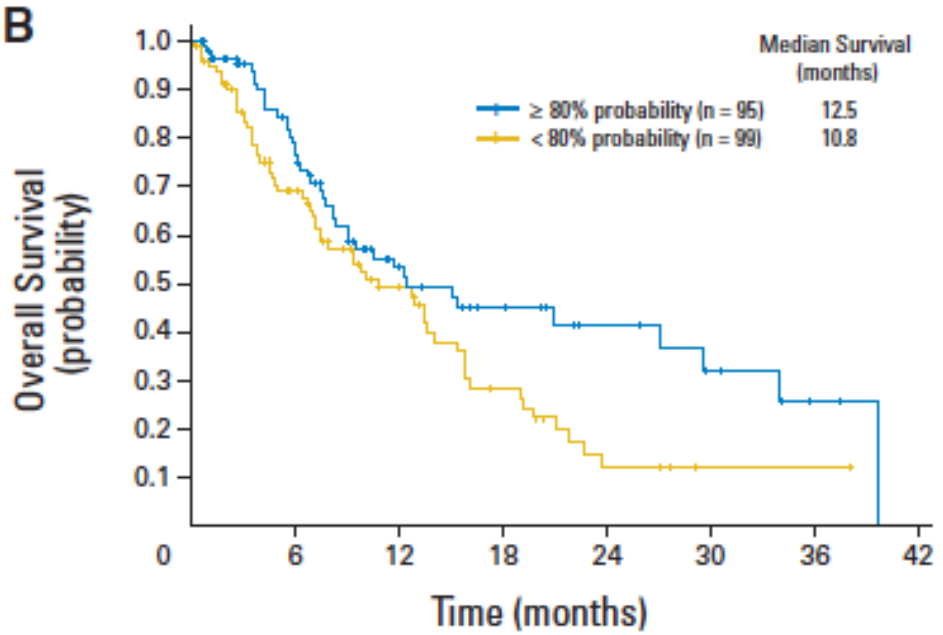
VOLUME 31 · NUMBER 2 · JANUARY 10 2013

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Molecular Gene Expression Profiling to Predict the Tissue o Origin and Direct Site-Specific Therapy in Patients With Carcinoma of Unknown Primary Site: A Prospective Trial o 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





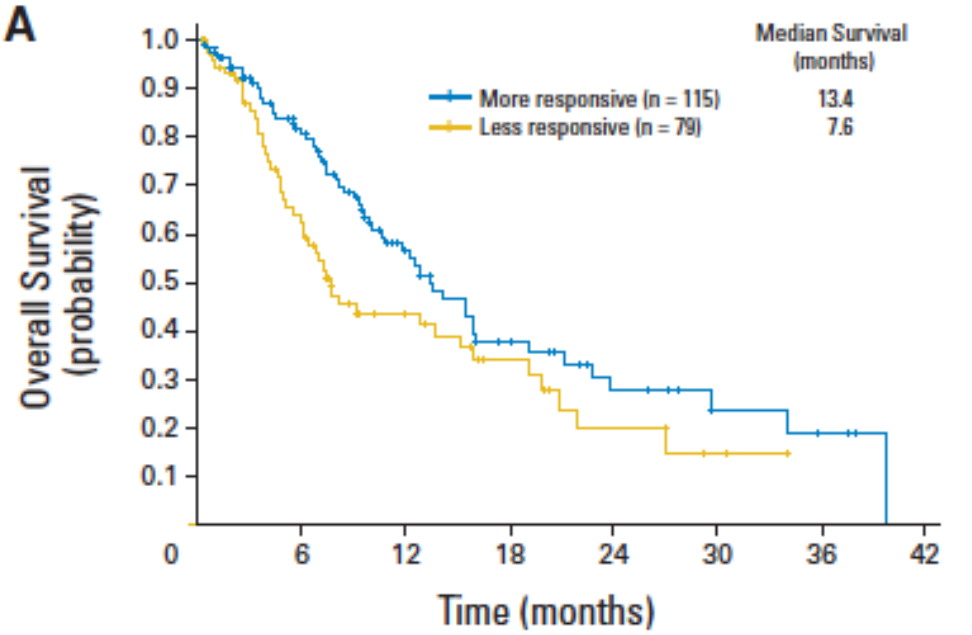
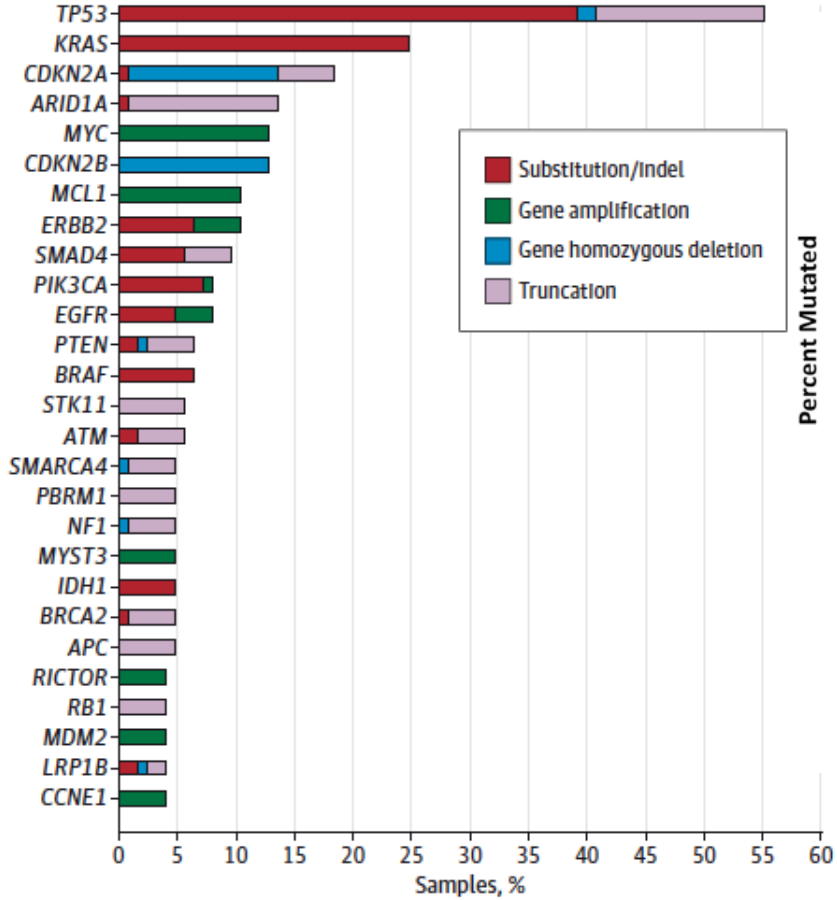
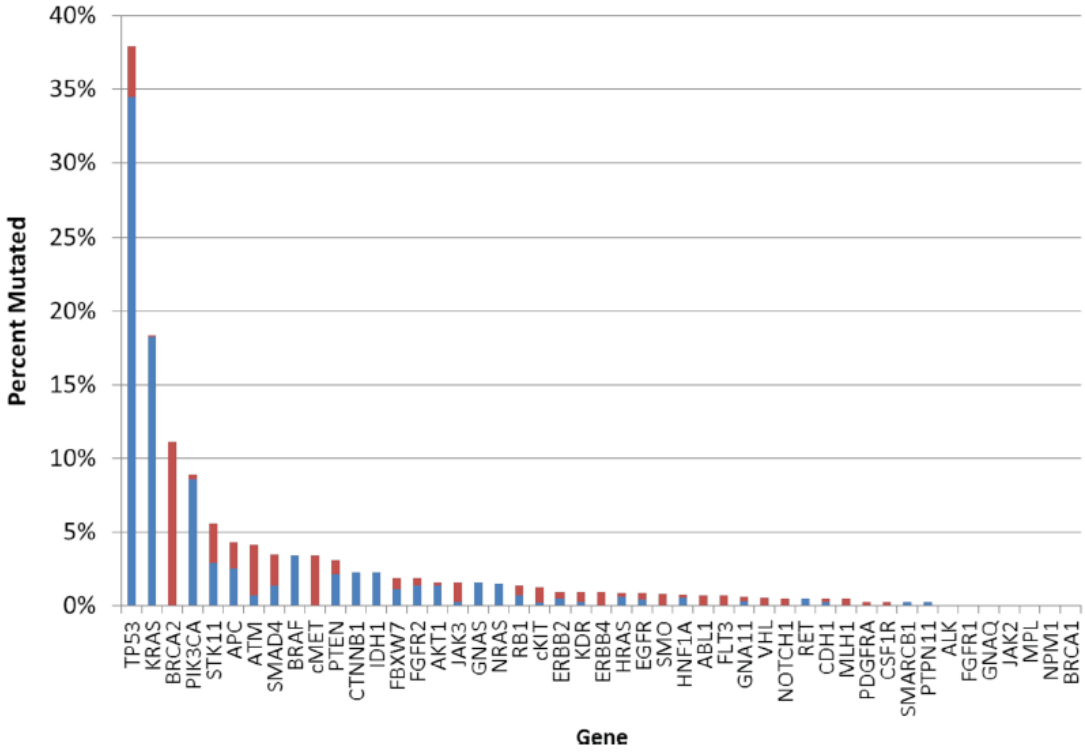


Figure 1. The Most Prevalent Genomic Alterations in 125 Samples of Adenocarcinoma of Unknown Primary Site





Original Investigation

Comprehensive Genomic Profiling of Carcinoma of Unknown Primary Site

New Routes to Targeted Therapies

Jeffrey S. Ross, MD; Kai Wang, MD, PhD; Laurie Gay, PhD; Geoff A. Otto, PhD; Emily White, BS; Kiel Iwanik, BS; Gary Palmer, MD; Roman Yelensky, PhD; Doron M. Lipson, PhD; Juliann Chmielecki, PhD; Rachel L. Erlich, PhD; Andrew N. Rankin, PhD; Siraj M. Ali, MD, PhD; Julia A. Elvin, MD, PhD; Deborah Morosini, MD; Vincent A. Miller, MD; Philip J. Stephens, PhD

www.impactjournals.com/oncotarget/ Oncotarget, Vol. 5, No. 23

Comprehensive tumor profiling identifies numerous biomarkers of drug response in cancers of unknown primary site: Analysis of 1806 cases

Zoran Gatalica[1], Sherri Z. Millis[1], Semir Vranic[2], Ryan Bender[1], Gargi D. Basu[1], Andreas Voss[1], Daniel D. Von Hoff[3]

[1]Caris Life Sciences, Phoenix, United States of America

[2]Department of Pathology, Clinical Center, University of Sarajevo, Sarajevo, Bosnia and Herzegovina

[3]Translational Genomic Research Institute and Virginia G Piper Cancer Center, Phoenix, United States of America

Clinical decision making:

Site of origin CUP test versus mutation profile – or both?

- Which result makes most sense clinically
- Likely efficacy of anatomically-based therapy
- Likely efficacy of targeted agent
- Practical availability of targeted agent for a given patient
- Ability to combine or sequence therapies

URGENT NEED FOR TRIALS TO DETERMINE IF IMPACTS ON PATIENT OUTCOMES!

LETTER

doi:10.1038/nature10868

Unresponsiveness of colon cancer to BRAF(V600E) inhibition through feedback activation of EGFR

Anirudh Prahallad[1]*, Chong Sun[1]*, Sidong Huang[1]*, Federica Di Nicolantonio[2,3]*, Ramon Salazar[4], Davide Zecchin[2], Roderick L. Beijersbergen[1], Alberto Bardelli[2,3] & René Bernards[1]

Context matters!

Melbourne, Australia