ESMO 2017 Meet-the-investigator meeting

Disease management and comprehensive genomic profiling in cancer of unknown primary

11 September 2017

IFEMA, Feria de Madrid, Spain

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NP/FMI/1709/0011

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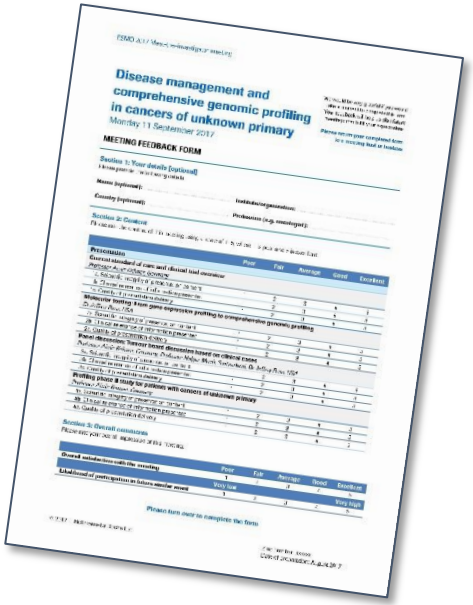

Disease management and comprehensive genomic profiling in cancers of unknown primary

Monday 11 September 2017

MEETING FEEDBACK FORM

NP/FMI/1709/0011

Agenda

Time	Topic	Presenter/Moderator
09:05 – 09:15	Current standard of care	Alwin Krämer
09:15 – 09:25	Molecular testing: from gene expression profiling to comprehensive genomic profiling	Jeffrey Ross
09:25 – 09:45	Tumor board discussion based on clinical cases	Alwin Krämer / Holger Moch / Jeffrey Ross
09:45 – 09:55	Genomic profiling study for patients with cancers of unknown primary	Alwin Krämer
09:55 – 10:00	Meeting closure	Alwin Krämer

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Current standard of care

Prof. Alwin Krämer, MD
University of Heidelberg, Germany

Disclosures

- Prof. Krämer has received research grants from Bayer and Merck, as well as honoraria for lectures or advisory board participation or consulting from Roche, and Novartis.

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Cancer of unknown primary site (CUP)

High unmet medical needs

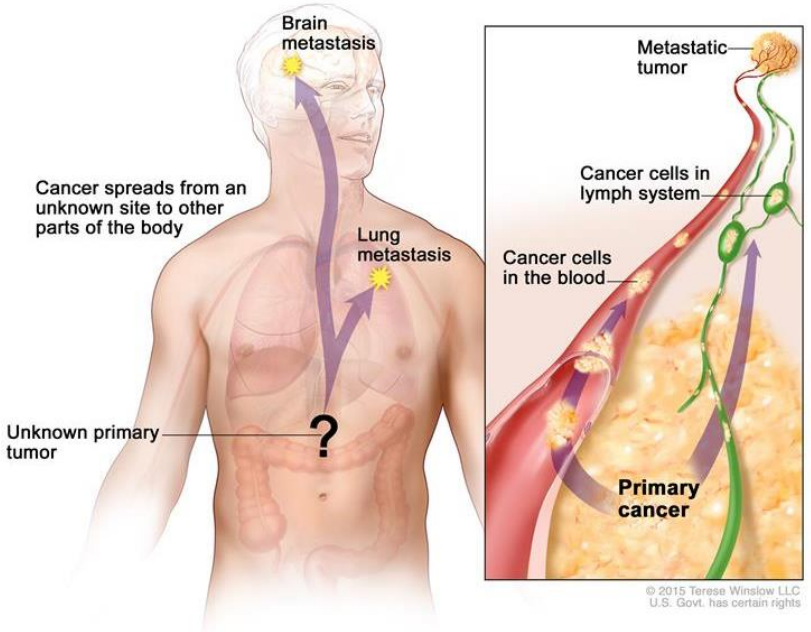

Image source: US National Cancer Institute (accessed 15/03/2017) https://www.cancer.gov/types/unknown-primary/patient/unknown-primary-treatment-pdq

- **2% – 5% of all malignancies**[1-3]
- 12-month **overall survival is 23%**[4]
- **Median overall survival is 9.1 months**[5]
- Lack of a definitive primary site often restricts treatment options to **palliative chemotherapy**[6]

1. Stella, G.M., et al. (2012) *J Transl Med* 10:12; 2. Pavlidis, N., et al. (2012) *Lancet* 379:1428; 3. Massard, C., et al. (2011) *Nat Rev Clin Oncol* 8:701; 4. Australian Institute of Health and Welfare. Cancer in Australia 2010: in brief. Canberra: Australian Institute of Health and Welfare, 2010; 5. Greco, F.A., Hainsworth, J.D.: Cancer of unknown primary site, in DeVita VT Jr, Hellman S, Rosenberg SA (eds): Cancer: Principles and Practice of Oncology (ed 9). Philadelphia, P.A., J.B. Lippincott, 2011, pp 2033-51. 6. Fizazi, K., et al. (2015) *Ann Oncol* 26(suppl 5):v133.

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CUP diagnosis follows ESMO guideline diagnostic work-up

Target patient population	Assessment suggested
All	Thorough medical history and physical examination
All	Basic blood and biochemistry analysis
All	CT scans of thorax, abdomen and pelvis
All	Histology/Immunohistology
All females	Mammography
Females with axillary adenocarcinoma	Breast MRI
Patients with midline metastatic disease	Serum α-fetoprotein and human chorionic gonadotropin
Males with adenocarcinoma bone mets	Serum prostate-specific antigen
Cervical squamous cell carcinoma	Head and neck CT / PET scan
Sign / Symptom / Laboratory oriented	Endoscopies
Patients with neuroendocrine CUP	Octreoscan / Chromogranin A
Sign / Symptom / Laboratory oriented	Additional diagnostic tests

CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.
Adapted from Fizazi, K., et al. (2015) *Ann Oncol* 26(suppl 5):v133-8.

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There are many histologies across CUP samples

Histology	Frequency
Adenocarcinoma	
• Well to moderately differentiated	50%
• Poorly or undifferentiated	30%
Squamous cell carcinoma	15%
Undifferentiated neoplasms	5%
• Not specified carcinoma	
• Neuroendocrine tumours	
• Lymphomas	
• Germ cell tumours	
• Melanomas	
• Sarcomas	
• Embryonal malignancies	

Pavlidis, N. et al. (2003) *Eur J Cancer* 39(14):1990–2005.

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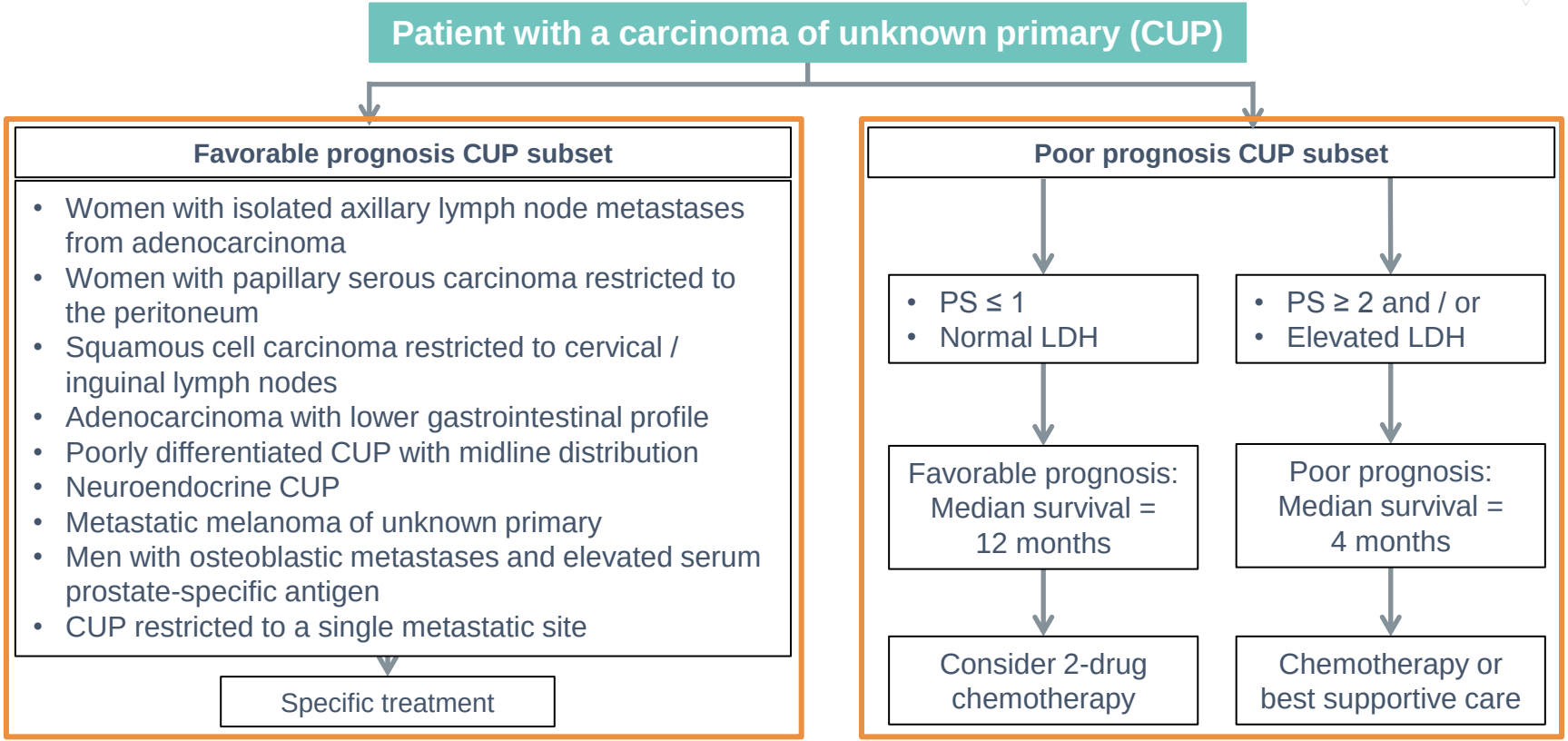
The ESMO guideline recognises distinct CUP subsets



Adapted from Fizazi, K., et al. (2015) *Ann Oncol* 26(suppl 5):v133-8.

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ESMO recommends low-toxicity palliative chemotherapy for poor-prognosis CUP patients

Chemotherapy (mg/m²)	Time	Interval	Comments
Cisplatin 60-75 + Gemcitabine 1,000	Day 1 Day 1+8	Q3 weeks	Fit patients, adequate hydration
Cisplatin 75 + Etoposide 100	Day 1 Day 1-3	Q3 weeks	Fit patients with neuroendocrine-feature CUP, adequate hydration
Paclitaxel 175 + Carboplatin AUC 5	Day 1	Q3 weeks	Convenient outpatient regimen, monitor neurotoxicity
Docetaxel 75 + Carboplatin AUC 5	Day 1	Q3 weeks	Convenient outpatient regimen, monitor neurotoxicity
Irinotecan 160 + Oxaliplatin 80	Day 1	Q3 weeks	Outpatient regimen, monitor for neurotoxicity and diarrhoea
Oral capecitabine 2,000 ± Oxaliplatin 85-130	Days 1-14 Day 1	Q3 weeks	Outpatient regimen, risk for diarrhoea and neurotoxicity
Gemcitabine 1,000/irinotecan 100	Day 1+8	Q3 weeks	Convenient outpatient regimen, monitor diarrhoea

AUC, area under the curve;
Fizazi, K., et al. (2015) *Ann Oncol* 26(suppl 5):v133-8.

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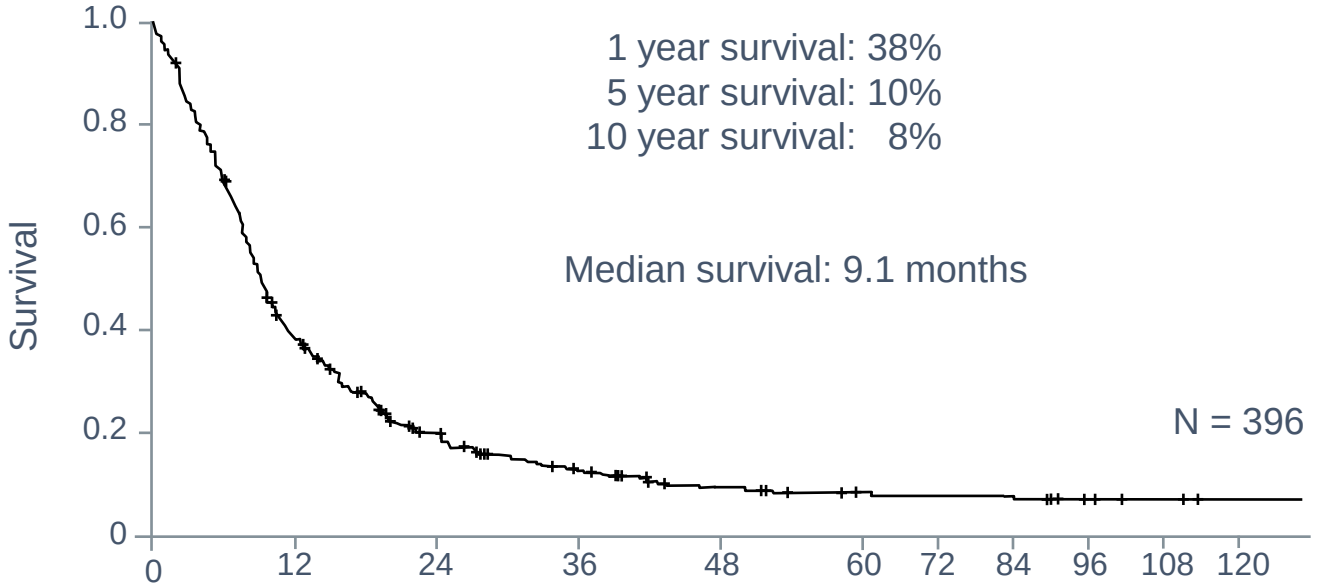
Patients with poor prognosis have low survival rates, e.g. disseminated adeno- or undifferentiated CUP

Minnie Pearl Cancer Research Network - 396 CUP Patients Treated in Phase II Studies



Greco, F.A., Hainsworth, J.D.: Cancer of unknown primary site, in DeVita VT Jr, Hellman S, Rosenberg SA (eds): Cancer: Principles and Practice of Oncology (ed 9). Philadelphia, P.A., J.B. Lippincott, 2011, pp 2033-51.

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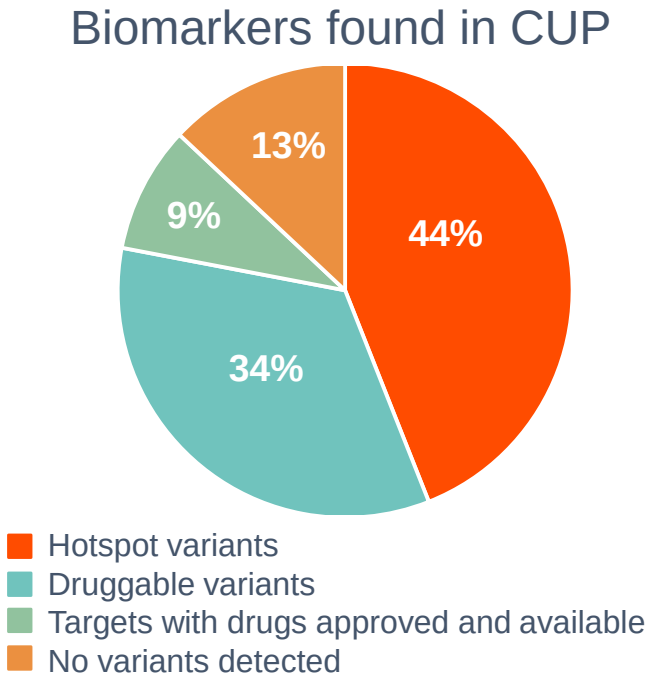
Molecular profiling can identify biomarkers associated with a potential drug benefit



Adapted from Clynick, B., et al. ESMO 2017 # 1705-PD.

- Molecular profiling was found to identify biomarkers biologically relevant and/or associated with a **potential drug benefit in most CUP cases (87%)**[1]
- It included druggable targets in key cancer related genes: BRAF, EGFR and ERBB2[1]
- In another study, expression of PD-1 and PD-L1 was observed in 63% and 21% of assessed cases respectively[2]

1.Clynick, B., et al. ESMO 2017 # 1705-PD.
2.Gatalica, Z., et al. (2014) *Oncotarget* 5:12440-7.

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Molecular testing: From gene expression profiling to comprehensive genomic profiling

Dr. Jeffrey S. Ross, MD
Foundation Medicine, Cambridge, MA USA

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Disclosures

Dr Ross is an employee, holds a leadership position and owns stock in Foundation Medicine, Inc.

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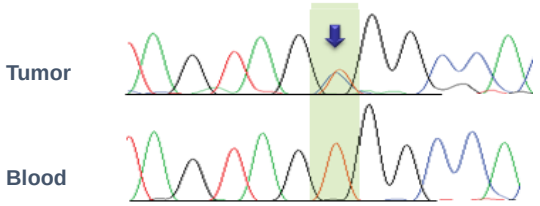
FoundationOne® identifies all classes of genomic alterations

Base Substitution

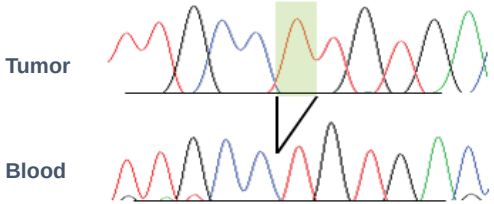
e.g. *BRAF, EGFR*



Capillary sequencing, Mass Spectrometry

Short Insertions / Deletion

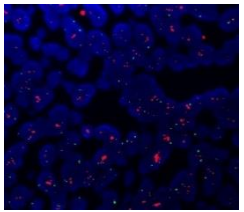
e.g. *EGFR, ERBB2*



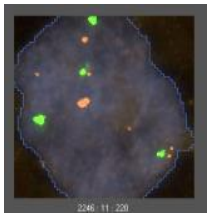
Capillary sequencing, gel size shift assays

Focal Amplification & Homozygous Deletion

e.g. *HER2, MET*



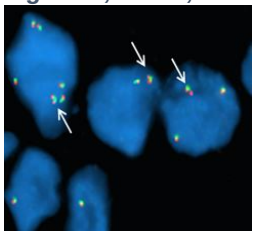
e.g. *PTEN, TSC1/2*



Fluorescence *In Situ* Hybridization

Gene Fusion

e.g. *ALK, ROS1, RET*



Real time-PCR Fluorescence *In Situ* Hybridization

PCR, polymerase chain reaction.
FMI data on file.

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FoundationOne® validation shows the high accuracy and reproducibility required for clinical use

Base Substitutions
(MAF 5-100%)

Sensitivity: > 99% PPV: > 99%

Insertions/Deletions
(1-40bp, MAF ≥ 20%)

Sensitivity: 98% PPV: > 99%

Copy Number Alterations
(> 20% tumor content, zero or ≥ 8 copies)

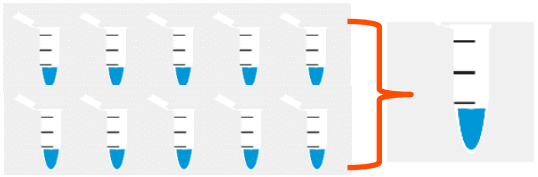
Sensitivity: > 95% PPV: > 99%

Gene Fusions
(> 30% tumor content, select introns)

Sensitivity: > 99% PPV: > 99%

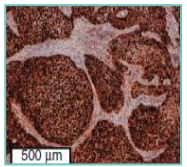
Controlled validation studies:
Cell-line pools with known alterations:

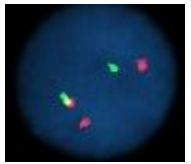
- 2,056 subs 227 indels
- 210 CNAs 32 fusions



Concordance studies with existing platforms on clinical samples:

- 118 subs/indels: Sequenom, PCR
- 185 CNAs: FISH, IHC
- 43 fusions: break-apart FISH





CNA, copy number alteration; FISH, fluorescence In Situ Hybridization; IHC, immunohistochemistry; MAF, mutant allele frequencies; PCR, polymerase chain reaction; PPV, positive predictive value.

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Frampton, G.M., et al. (2013) *Nat Biotechnol* 31:1023-31; FMI data on file.

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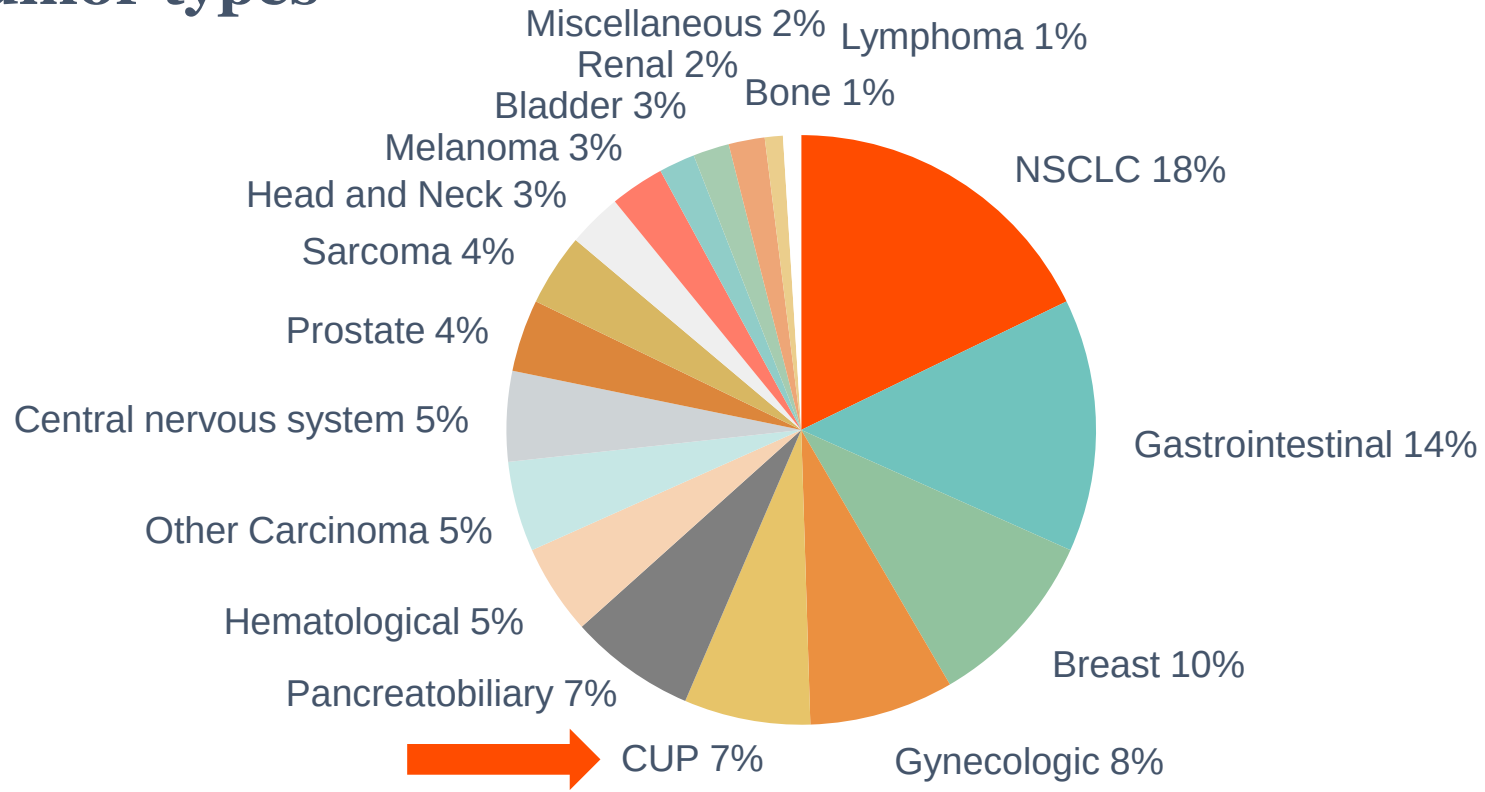
Foundation Medicine has experience across all solid tumor types



NSCLC, non-small cell lung cancer.
FMI data on file.

Of 200 cases of CUP, 96% harbored at least one genomic alteration

	ACUP	Non-ACUP
Sample	125	75
Total genomic alterations (GA)	494	347
GA/sample, mean	4.0	4.6
Base substitutions	250 (51%)	151 (44%)
Short insertions and deletions (Indels)	74 (15%)	66 (19%)
Amplifications	119 (24%)	98 (28%)
Homozygous deletions	39 (8%)	27 (8%)
Re-arrangements	12 (2%)	5 (1%)
Samples with no GA detected	0	8

Ross, J.S., et al. (2015) *JAMA Oncol* 1:40-9.

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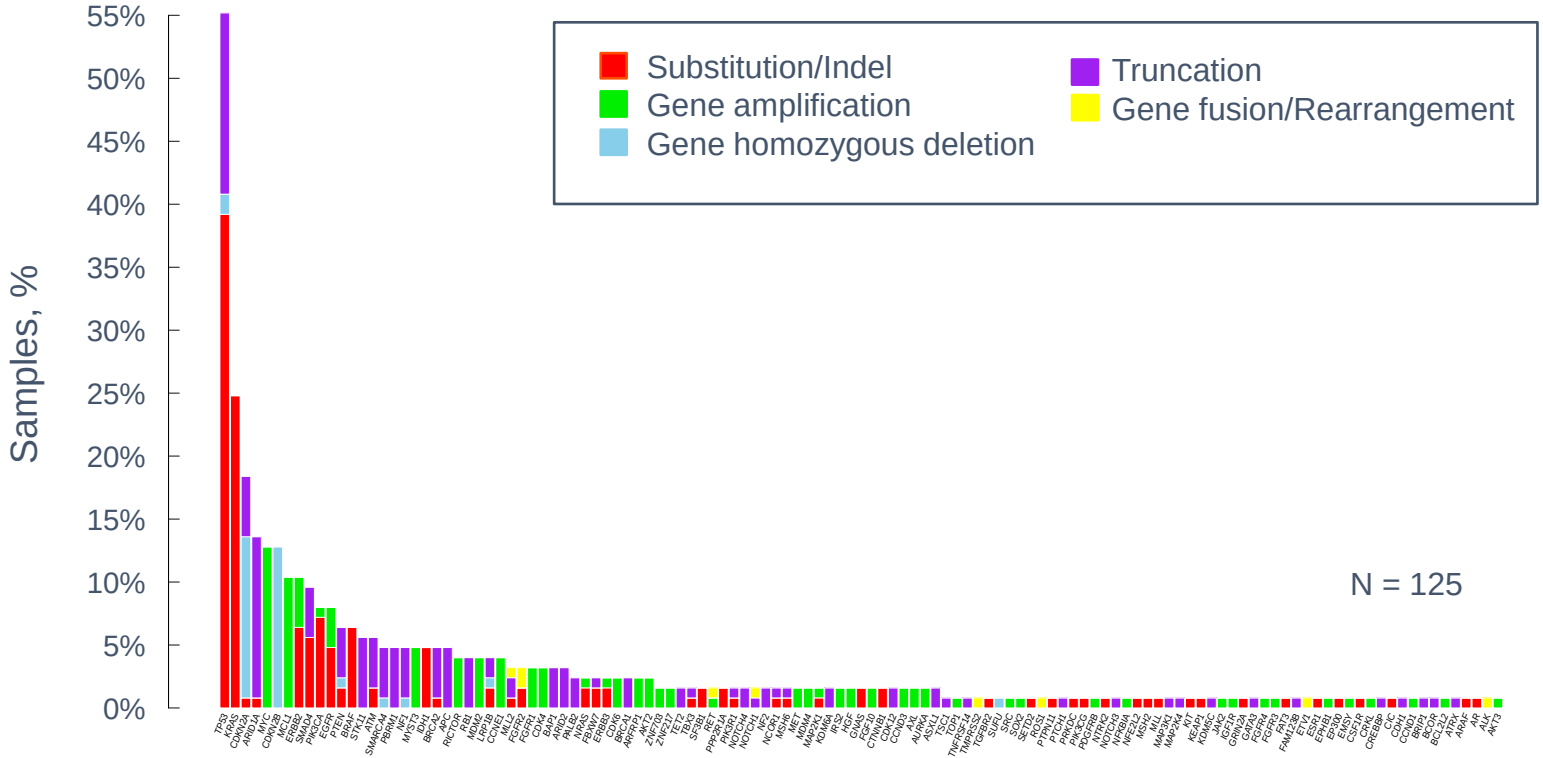
High diversity of genomic alterations and a “long tail” distribution observed across ACUP samples



ACUP, adenocarcinoma of unknown primary; Indel, insertion/deletion.

Ross, J.S., et al. (2015) *JAMA Oncol* 1:40-9.

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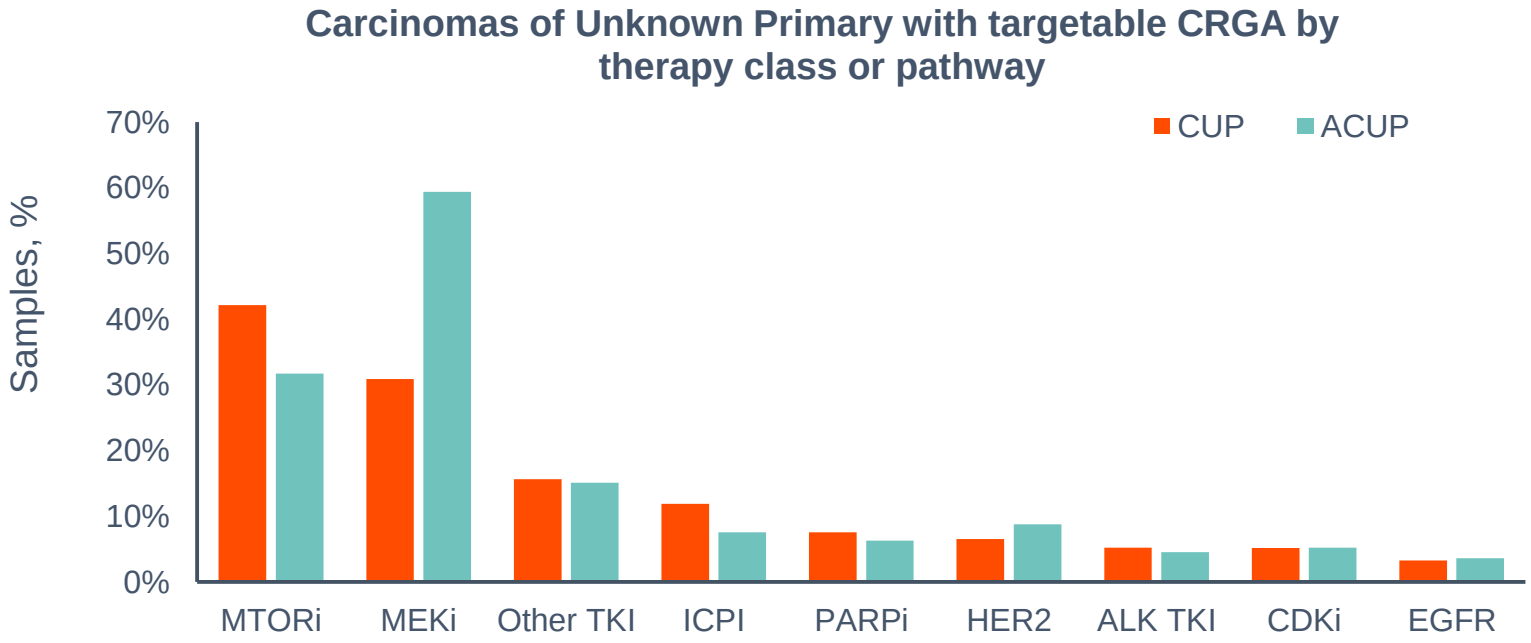
Most CUP or ACUP samples harbor targetable alterations



ACUP, adenocarcinoma of unknown primary; CRGA, clinically relevant genomic alteration.

Gay, L.M., et al. (2017) *J Clin Oncol* 35(suppl 15):3039.

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Tumor mutational burden (TMB) can help predict benefit from immune checkpoint inhibitors

- Indication of pembrolizumab ▼ for the treatment of patients with unresectable or metastatic solid tumors possessing a microsatellite instability-high (MSI-H) biomarker is the first tissue/site-agnostic approval by the FDA[1]
- FoundationOne® TMB high result will detect all MSI-high CUP cases as well as approximately 20-30% more cases where the patients are thus predicted to have a likely long term durable benefit from ICPI therapies[2]
- CUP in general features a high frequency of TMB high with over 10% of cases featuring ≥ 20 mutations per megabase similar to that seen in NSCLC (not as high as melanoma but higher than bladder cancer)[2]

1. FDA news release (2017) retrieved from: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm560167.htm.
2. FMI data on file.

Therapies marked with ▼ are subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. Adverse events should be reported to your local Merck Sharp & Dohme Limited office.

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CUP incidence and survival

Latest data from Switzerland

Prof. Holger Moch, MD
University Hospital Zurich, Switzerland

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Disclosures

Prof. Moch has received research grants from Roche and Pfizer, as well as honoraria for lectures or advisory board participation or consulting from Roche, and Astra Zeneca

CUP incidence and survival trends in Zurich, Switzerland

- 2,946 CUP patients from 1981 - 2014 (Cancer Registry Zurich)
- Age-standardized incidence:
  - 1981 and 1997: Increase from 10.5 to 17.6 / 100,000
  - 1998 - 2014: Decrease to 5.9 / 100,000
- Mean overall survival:
  - stable at 11.5 months (median 2.3 months)

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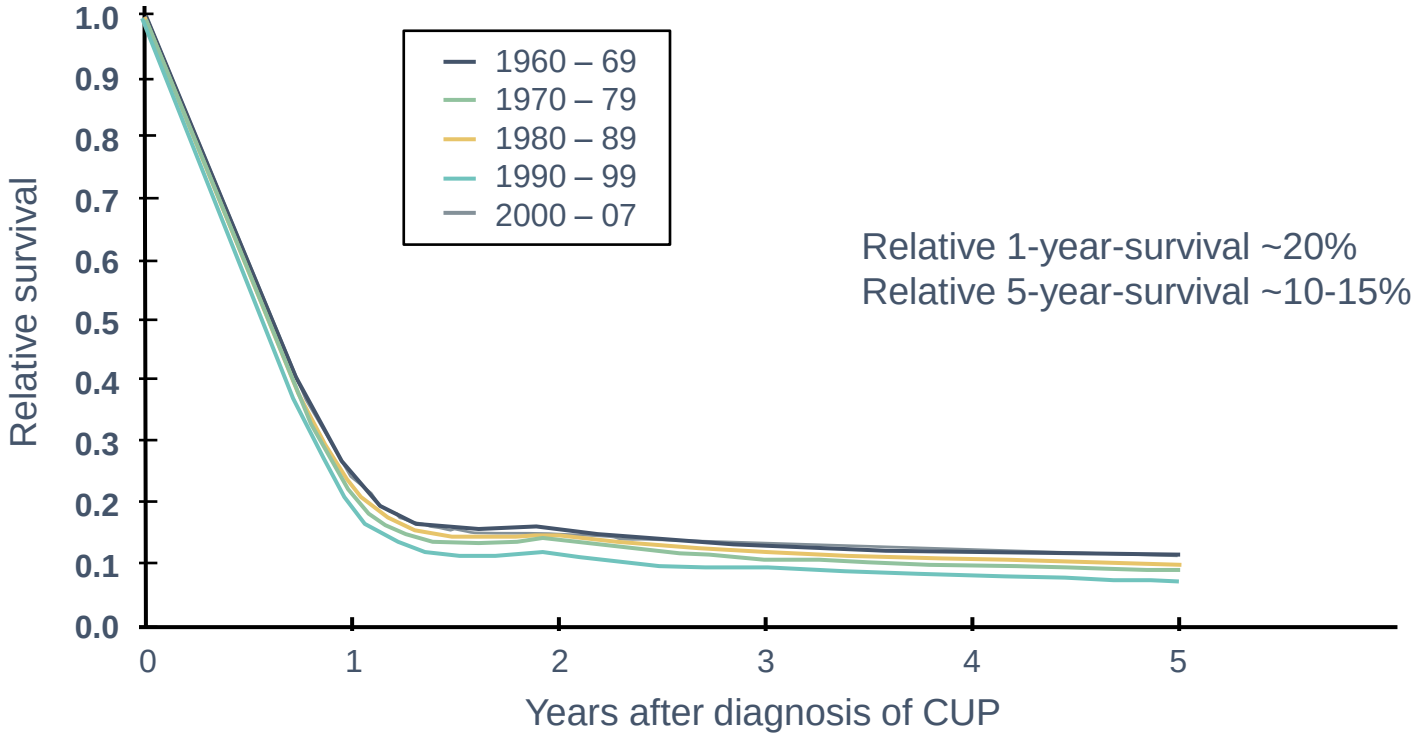
Survival has not improved in the last 40 years in Disseminated Adeno- or Undifferentiated CUP



Randén, M., et al. (2009) *Acta Oncologica* 48: 915920.

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Immunohistochemistry work-up in CUP patients

	CK	PSA	ER, PgR	CDX2+, CK20+, CK7-	TTF1, NapsinA, CK7+	Tg, CT	NSE, CG, SNP	AFP, OCT4, hCG, PLAP	LCA	S100, HMB45	Vimentin, Desmin
Undifferentiated carcinoma	+	-	±	-	-	-	-	-	-	-	±
Prostate cancer	+	+	-	-	-	-	-	-	-	-	-
Breast cancer	+	-	±	-	-	-	-	-	-	-	±
Colorectal cancer	+	-	-	+	-	-	-	-	-	-	-
Lung adenocarcinoma	+	-	-	-	+	-	-	-	-	-	-
Thyroid cancer	+	-	-	-	±	+	±	-	-	-	-
Neuroendocrine	+	-	-	-	±	±	+	-	-	-	-
Germ-cell cancer	+	-	-	-	-	-	-	+	-	-	±
Lymphoma	-	-	-	-	-	-	-	-	+	-	-
Melanoma	-	-	-	-	-	-	-	-	-	+	±
Sarcoma	-	-	-	-	-	-	-	-	-	±	+

The table shows general staining patterns but exceptions exist, especially for S100 and vimentin. Thyroid and neuroendocrine cancers often positive with CK7 and TTF1 but not with NapsinA. CK, cytokeratin; PSA, prostate specific antigen; ER, oestrogen receptor; PgR, progesterone receptor; TTF1, thyroid transrcription factor 1; Tg, thyroglobulin; CT, calcitonin; NSE, neuronspecific enolase; CG, chromogranin; SNP, synaptophysin; AFP, alpha fetoprotein; hCG, human chorionic gonadotropin; PLAP, placental alkaline phosphatase; LCA, leukocyte common antigen.

Fizazi, K., et al. (2015) *Ann Oncol* 26(suppl 5):v133-8.

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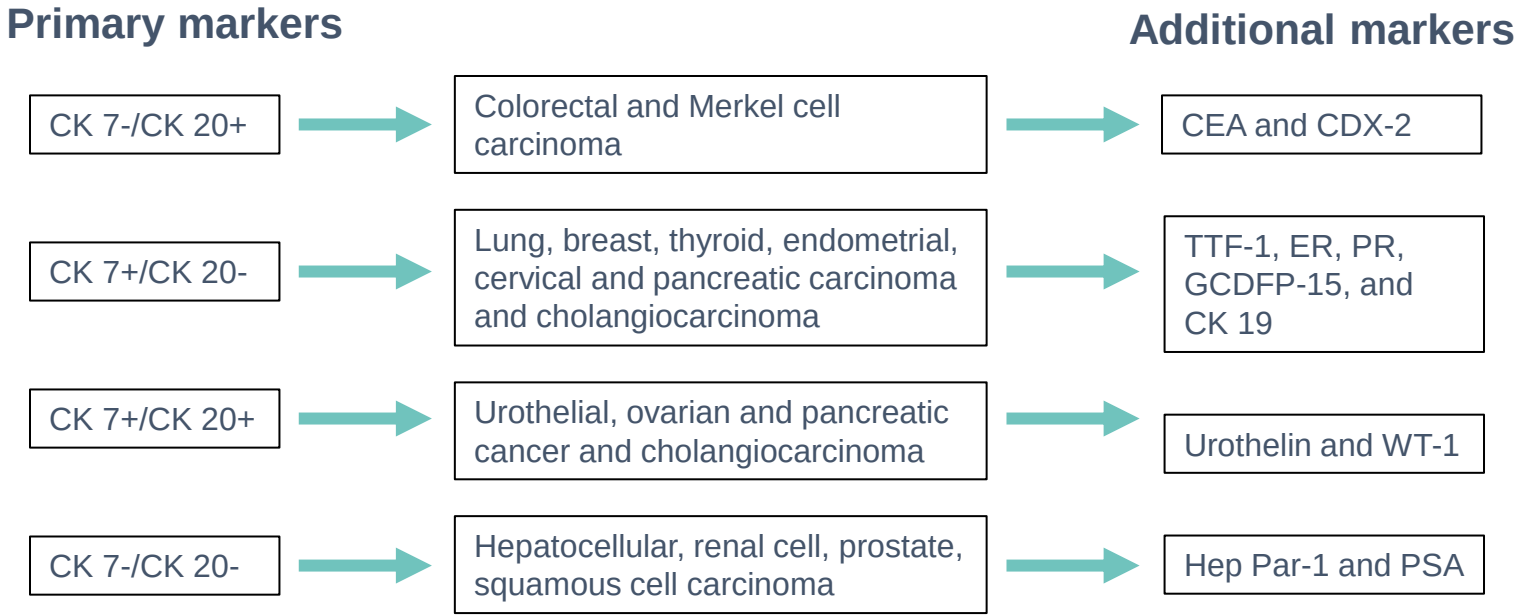
Basic immunohistochemistry work-up of CUP



CK, cyrokeratin; CEA, carcinoembryonic antigen; TTF1, thyroid transcription factor 1; ER, oestrogen receptor; PgR, progesterone receptor; GCDFP-15, gross cystic disease fluid protein-15; WT-1, Wilms tumor gene 1; PSA, prostate specific antigen.
Adapted from Fizazi, K., et al. (2015) *Ann Oncol* 26(suppl 5):v133-8.

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Tumor board discussion on clinical cases

Dr. Jeffrey S. Ross, MD
Foundation Medicine, Cambridge, MA USA

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Clinical case 1

Dr. Jeffrey S. Ross, MD
Foundation Medicine, Cambridge, MA USA

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Clinical case 1

Patient medical background

Medical background

- A 53-year old Caucasian female
- No history of smoking
- 3-week history of worsening fatigue and severe exertional dyspnea

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Chung, J.H., et al. (2014) *Case Rep Oncol* 7:628-32.

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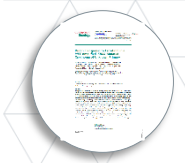
Clinical case 1

Clinical examination



Physical examination

- 3 cm non-tender, hard, subcutaneous, proximal right upper extremity mass with erythematous overlying skin
- 1 cm non-tender, subcutaneous nodule in the left parietal area of the scalp

PET and CT imaging

- Multiple metabolically active masses in the right lung; largest mass in the upper lobe measuring 5.8 x 5.0 cm
- Left lung mass measuring 2.3 x 2.2 cm
- Right hilar and mediastinal lymphadenopathy and subcarinal lymphadenopathy noted
- Extrathoracic, metabolically active lesions noted, including masses in the celiac nodal basin and the anterior right upper arm

CT, computed tomography; PET, positron emission tomography.

Chung, J.H., et al. (2014) *Case Rep Oncol* 7:628-32.

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Clinical case 1

Laboratory assessment results

Immunohistochemical staining	
Positive	**Negative**
Vimentin	TTF1, Napsin A, AE1/AE3, CK5, CK6, CK7, CAM5.2, and mCEA

Morphologic examination of the biopsy from the right upper extremity mass	Overall results
Malignant neoplasm of unknown histogenesis	Lung origin of tumor could not be confirmed

Chung, J.H., et al. (2014) *Case Rep Oncol* 7:628-32.

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Based on the initial investigation and laboratory results, what would you advise?

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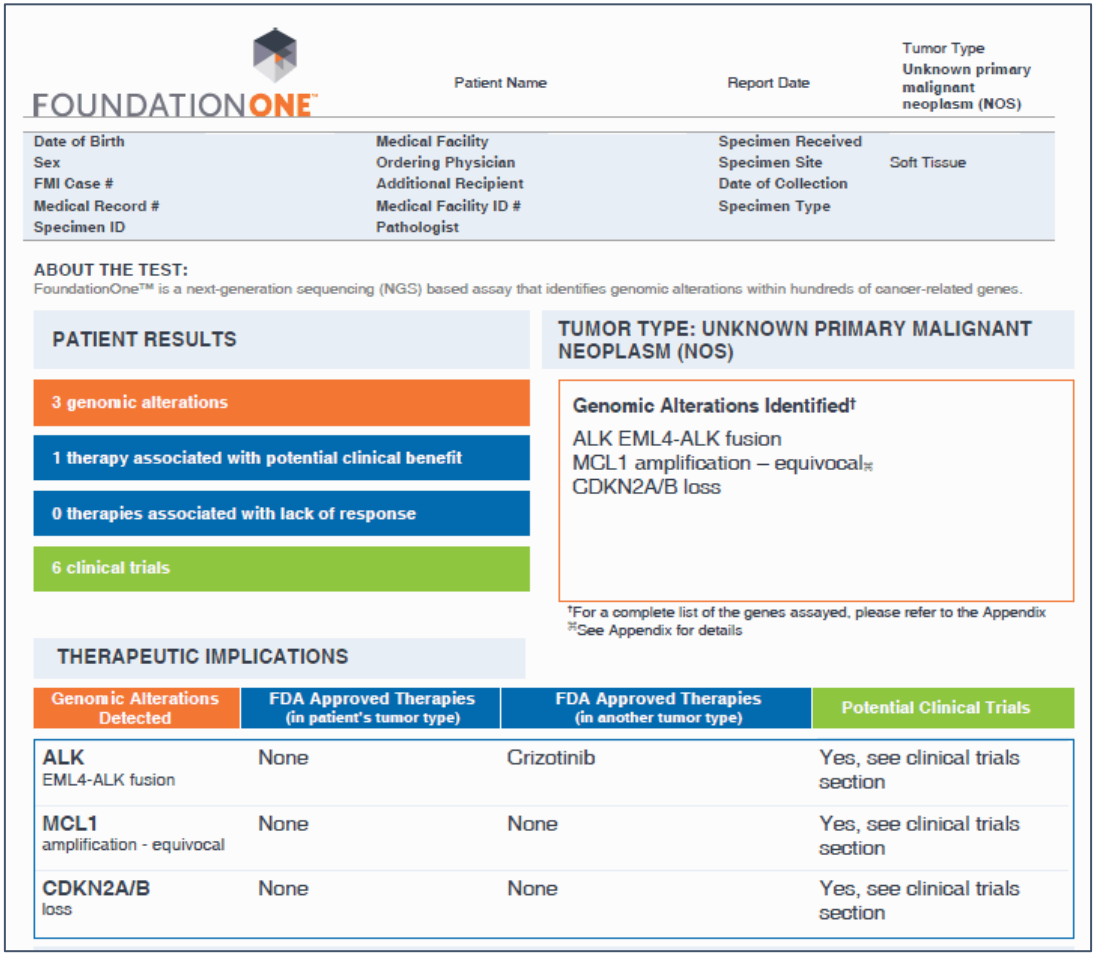
Foundation Medicine report results



FOUNDATIONONE

Patient Name

Report Date

Tumor Type
Unknown primary malignant neoplasm (NOS)

Date of Birth	Medical Facility	Specimen Received	
Sex	Ordering Physician	Specimen Site	Soft Tissue
FMI Case #	Additional Recipient	Date of Collection	
Medical Record #	Medical Facility ID #	Specimen Type	
Specimen ID	Pathologist		

ABOUT THE TEST:
FoundationOne™ is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

PATIENT RESULTS

- 3 genomic alterations
- 1 therapy associated with potential clinical benefit
- 0 therapies associated with lack of response
- 6 clinical trials

TUMOR TYPE: UNKNOWN PRIMARY MALIGNANT NEOPLASM (NOS)

Genomic Alterations Identified†

ALK EML4-ALK fusion
MCL1 amplification – equivocal‡
CDKN2A/B loss

†For a complete list of the genes assayed, please refer to the Appendix
‡See Appendix for details

THERAPEUTIC IMPLICATIONS

Genomic Alterations Detected	FDA Approved Therapies (in patient's tumor type)	FDA Approved Therapies (in another tumor type)	Potential Clinical Trials
ALK EML4-ALK fusion	None	Crizotinib	Yes, see clinical trials section
MCL1 amplification - equivocal	None	None	Yes, see clinical trials section
CDKN2A/B loss	None	None	Yes, see clinical trials section

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After seeing the Foundation Medicine report results, would you change your treatment strategy?

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Clinical case 1

Medical decision

Medical decision	Reason given
Crizotinib ▼ (250 mg orally twice daily)	Presence of the EML4-ALK rearrangement, a known oncogenic driver in a subset of pulmonary adenocarcinomas

Palma, N.A., et al. (2014) *Case Rep Oncol* 7:503-8.

Therapies marked with ▼ are subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. Adverse events should be reported to your local Pfizer Limited office.

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Clinical case 1

Therapy results and follow up – CT scan

Pre-treatment

+ 1 month

Computed tomography (CT) scan of the chest before starting crizotinib ▼ and 1 month after starting crizotinib ▼, respectively.

Chung, J.H., et al. (2014) *Case Rep Oncol* 7:628-32.

Therapies marked with ▼ are subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. Adverse events should be reported to your local Pfizer Limited office.

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Clinical case 2

Dr. Jeffrey S. Ross, MD
Foundation Medicine, Cambridge, MA USA

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Clinical case 2

Patient medical background and initial medical investigation

Medical background	Biology	Preliminary diagnosis
44-year-old Caucasian female with metastatic cancer of unknown primary (CUP) Diagnosed with multiple metastatic lesions in the mesentery of the small intestines and the duodenojejunal flexure	Histopathology analyses were inconclusive • High-grade neoplasm with pleomorphic tumor • Positive for vimentin • ~30% of the tumor cells: MIB-1 positive	CUP with sarcomatoid features

MIB-1, monoclonal antibody to KI67.
Gröschel, S., et al. (2016) *Cold Spring Harb Mol Case Stud* 2: a001180.

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Clinical case 2

Patient follow up

Initial medical decision	16 months Relapse	Medical decision	21 months Relapse	Medical decision
• Tumor lesions completely resected • 4 cycles: **doxorubicin and ifosfamide** (EORTC)	• Progressive pain in the right shoulder • Mass in the right deltoid muscle • Second metastatic lesion in the right axilla	• Complete surgical excision • **Adjuvant radiotherapy** to the right shoulder and axilla	• 5 new tumors formation • Surgical resection of multiple lesions • Tumor progressed rapidly	• **Trabectedin** initiated • Stopped : progressive disease and Grade IV thrombocytopenia

Gröschel, S., et al. (2016) *Cold Spring Harb Mol Case Stud* 2: a001180.

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Based on the patient status, what would you advise?

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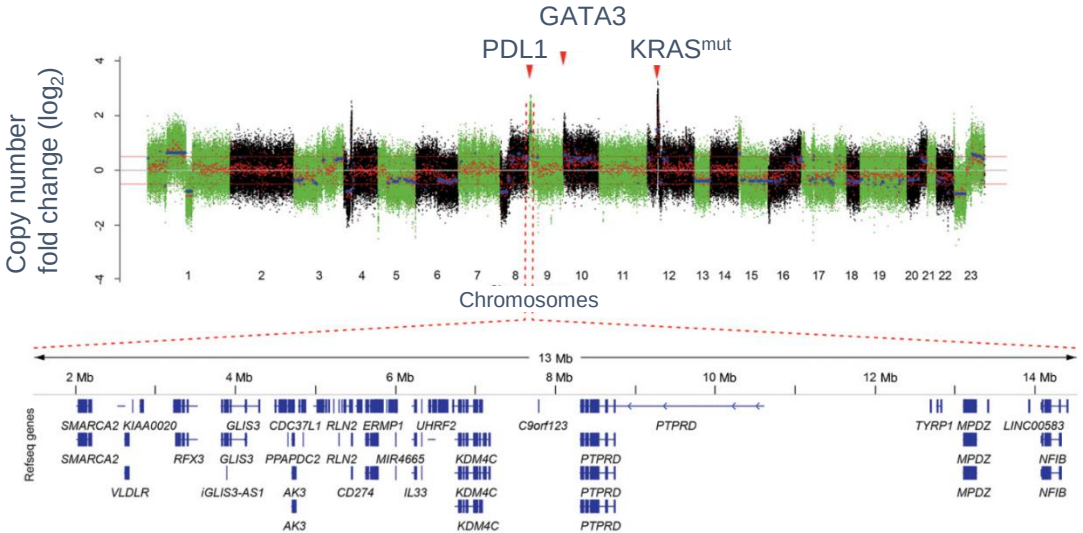
Clinical case 2

Molecular profiling

Enrollment in MASTER (Molecularly Aided Stratification for Tumor Eradication Research), a cross-entity molecular stratification program for advanced-stage cancer and patients with rare tumors (Kordes et al. 2016)

Molecular profiling results (Whole-exome sequencing and RNA-sequencing)



Gröschel, S., et al. (2016) *Cold Spring Harb Mol Case Stud* 2: a001180.

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After seeing the profiling results, would you change your treatment strategy?

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Clinical case 2

Medical decision

Rationale	Medical decision	Therapy selected 24 months after initial diagnosis
• Amplification and overexpression of PDL1 • Hypermutated tumor genome	ICI treatment with the anti-PD1 monoclonal antibody **pembrolizumab ▼**	**Pembrolizumab ▼** 2 mg/kg 3 week cycles

Gröschel, S., et al. (2016) *Cold Spring Harb Mol Case Stud* 2: a001180.

Therapies marked with ▼ are subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. Adverse events should be reported to your local Merck Sharp & Dohme office.

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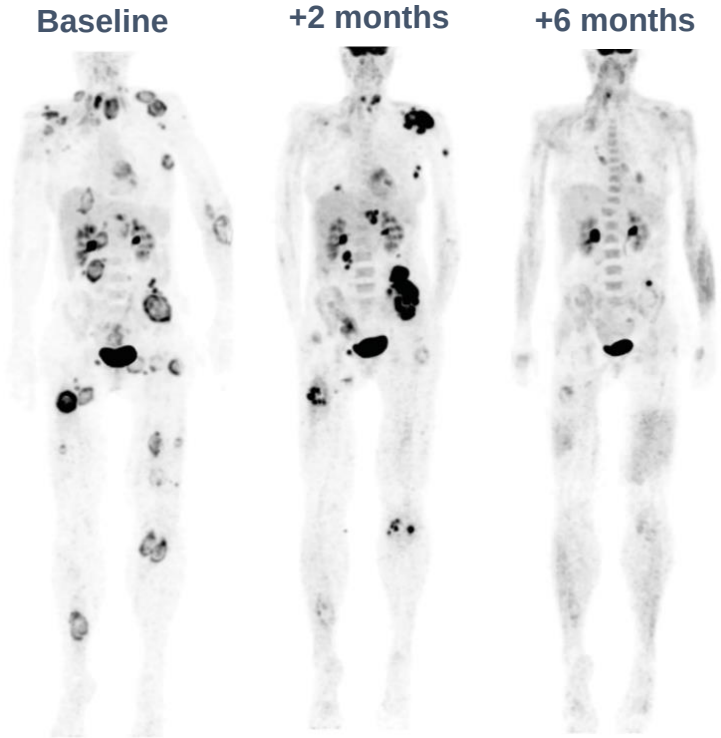
Clinical case 2

Follow up: PET/CT scans



6 months follow up

- Near-complete remission
- Response Evaluation Criteria In Solid Tumors: very good partial remission

14 months follow up

- Remained in continuous **near-complete remission**
- **Free of disease-specific symptoms**

Gröschel, S., et al. (2016) *Cold Spring Harb Mol Case Stud* 2: a001180.

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Genomic profiling study for patients with cancers of unknown primary

Prof. Alwin Krämer, MD
University of Heidelberg, Germany

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Genomic profiling study for patients with CUP

Rationale

- Current diagnostics can help to identify patients with CUP who have a favourable prognosis
- Treatment options are limited in poor prognosis patients with CUP
- Comprehensive genomic profiling has the potential to identify new treatment options without the need to know the primary tumor site
- Checkpoint inhibitor might be effective in CUP similarly to other tumor types
- Majority of CUP samples harbor targetable alterations

Roche data on file, study concept MX39795.

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Study objective

To compare the efficacy and safety of molecularly-guided therapy versus standard platinum-containing chemotherapy in patients with cancer of unknown primary site

Roche data on file, study concept MX39795.

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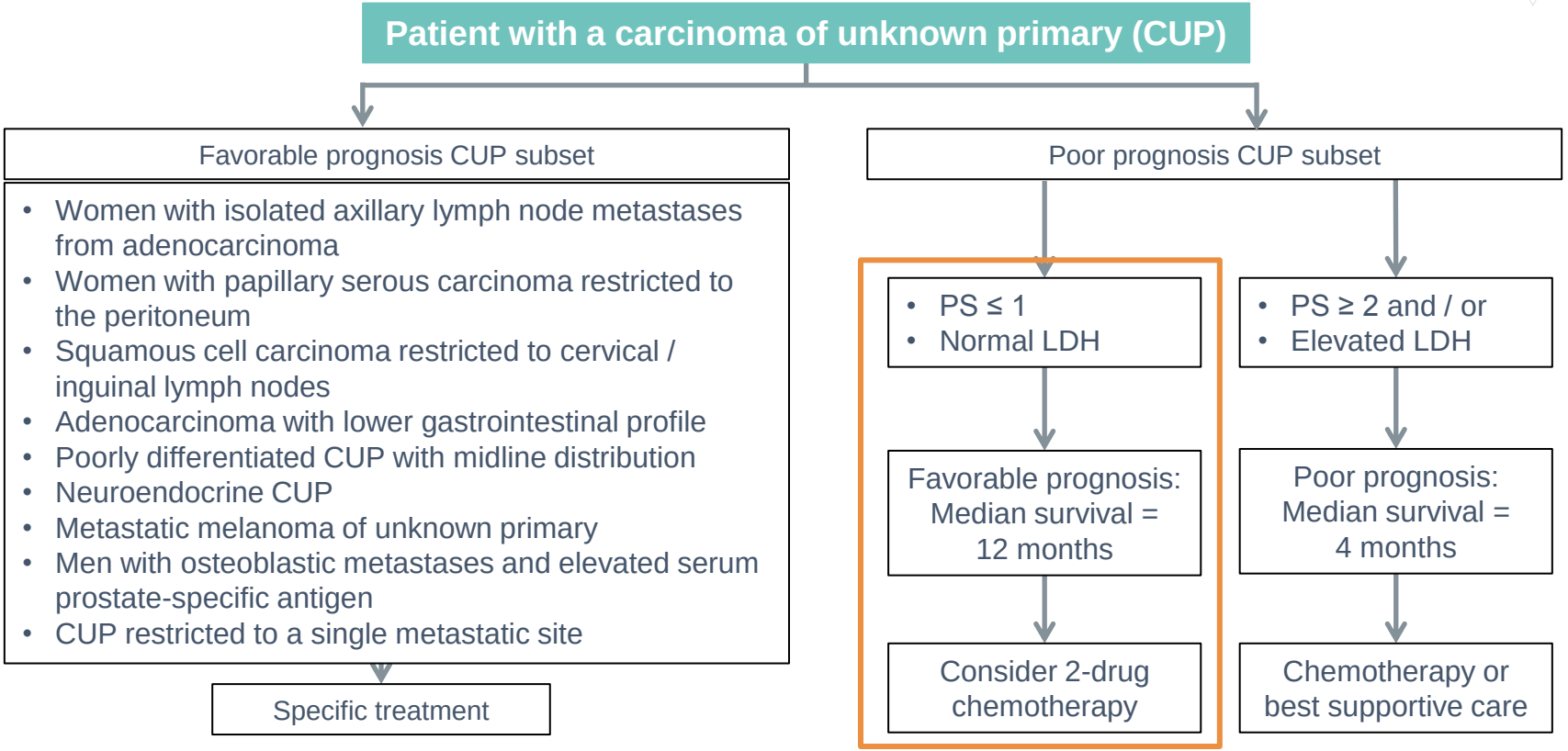
Study target population



Adapted from Fizazi, K., et al. (2015) *Ann Oncol* 26(suppl 5):v133-8.
Roche data on file, study concept MX39795.

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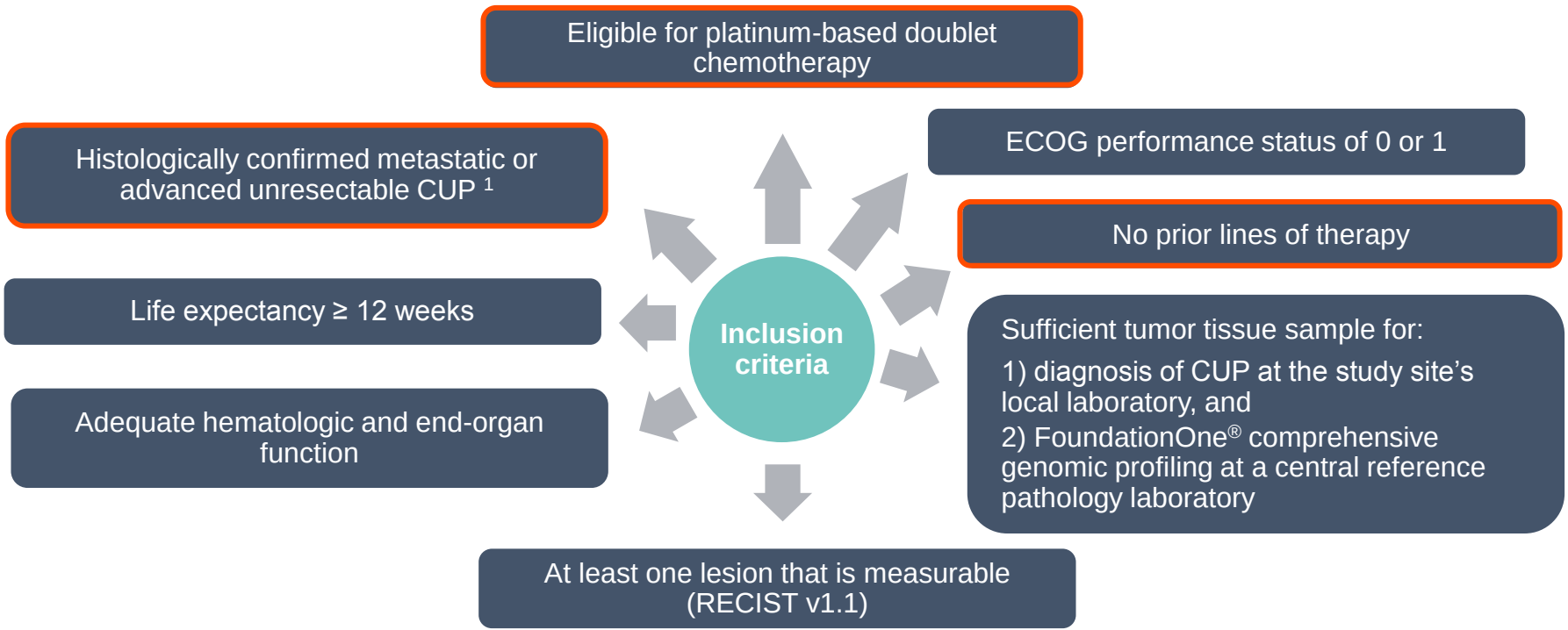
Selected inclusion criteria for the CUP profiling study

Preliminary design



ECOG, Eastern Cooperative Oncology Group.

1. Fizazi, K., et al. (2015) *Ann Oncol* 26(suppl 5):v133-8.

Roche data on file, study concept MX39795.

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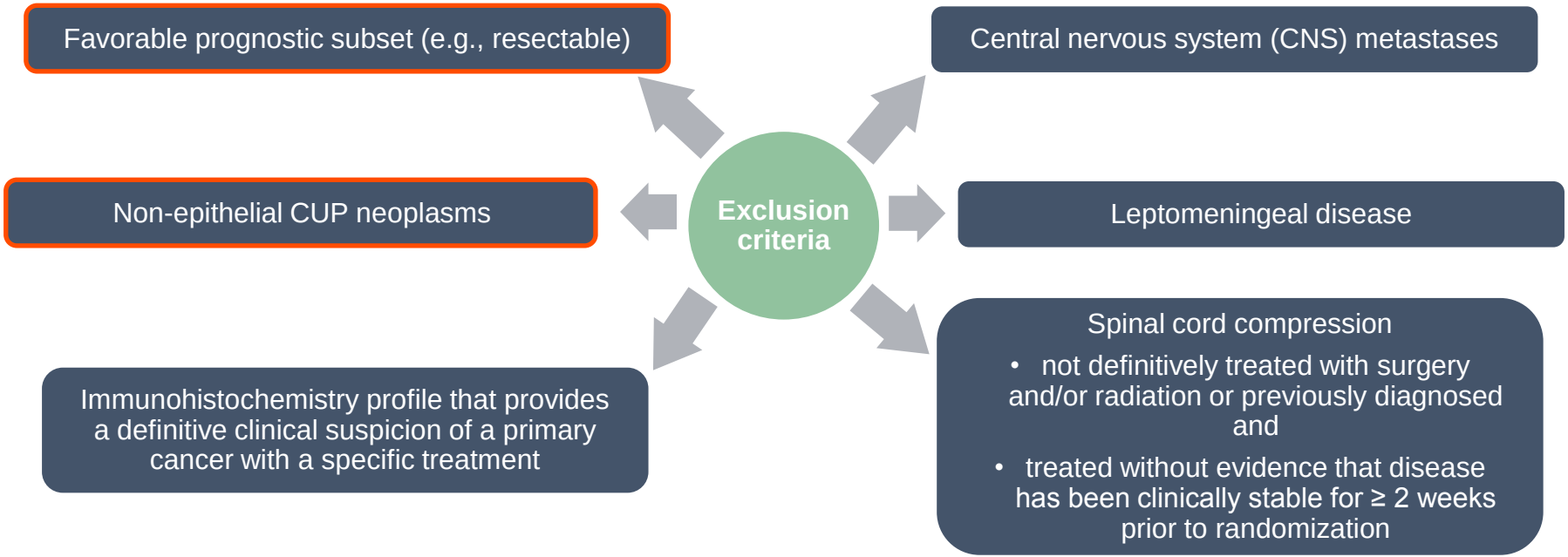
Selected exclusion criteria for the CUP profiling study

Preliminary design



Roche data on file, study concept MX39795.

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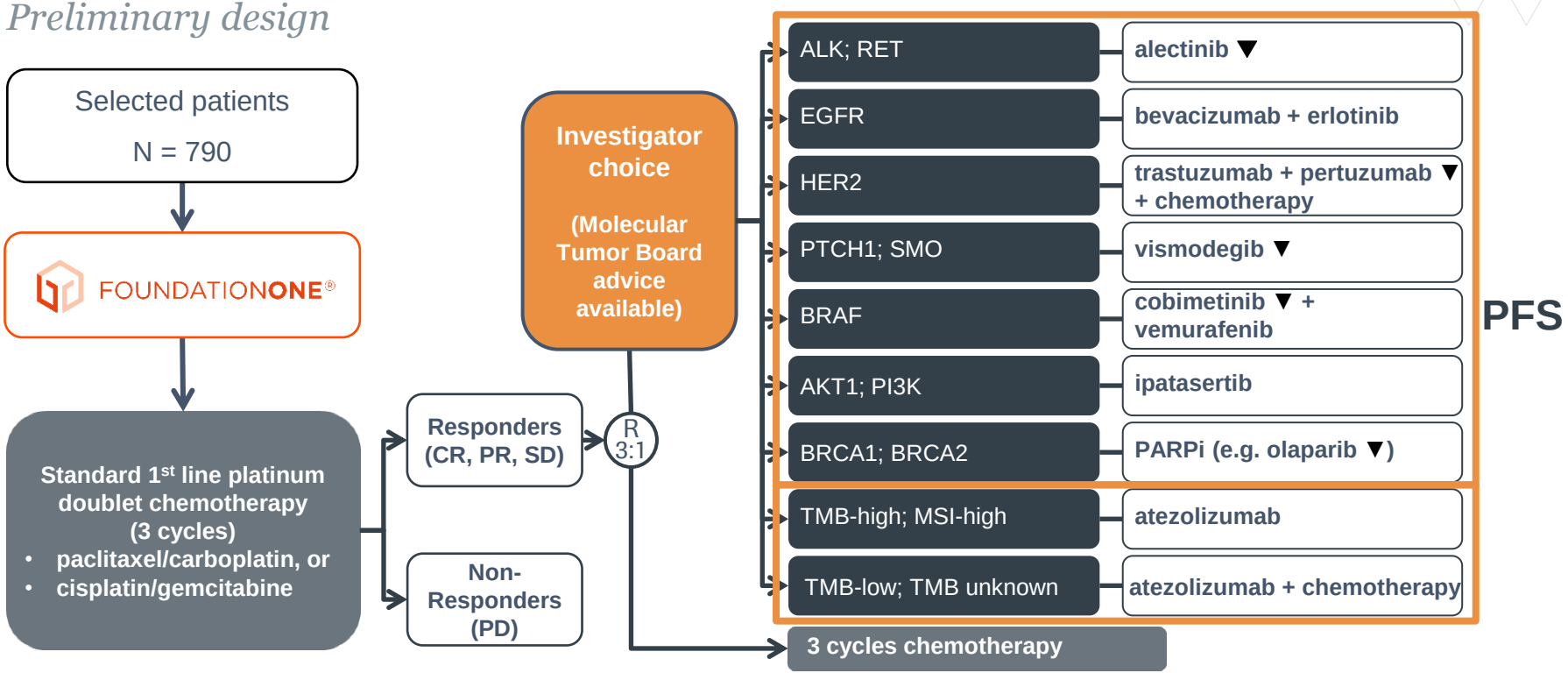
Genomic profiling study for patients with CUP

Preliminary design



CR, complete response; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TMB, tumor mutational burden; MSI: microsatellite instability. Roche data on file, study concept MX39795. Therapies marked with ▼ are subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. Adverse events should be reported to your respective local office: AstraZeneca for olaparib; Roche for alectinib, pertuzumab, cobimetinib and vismodegib.

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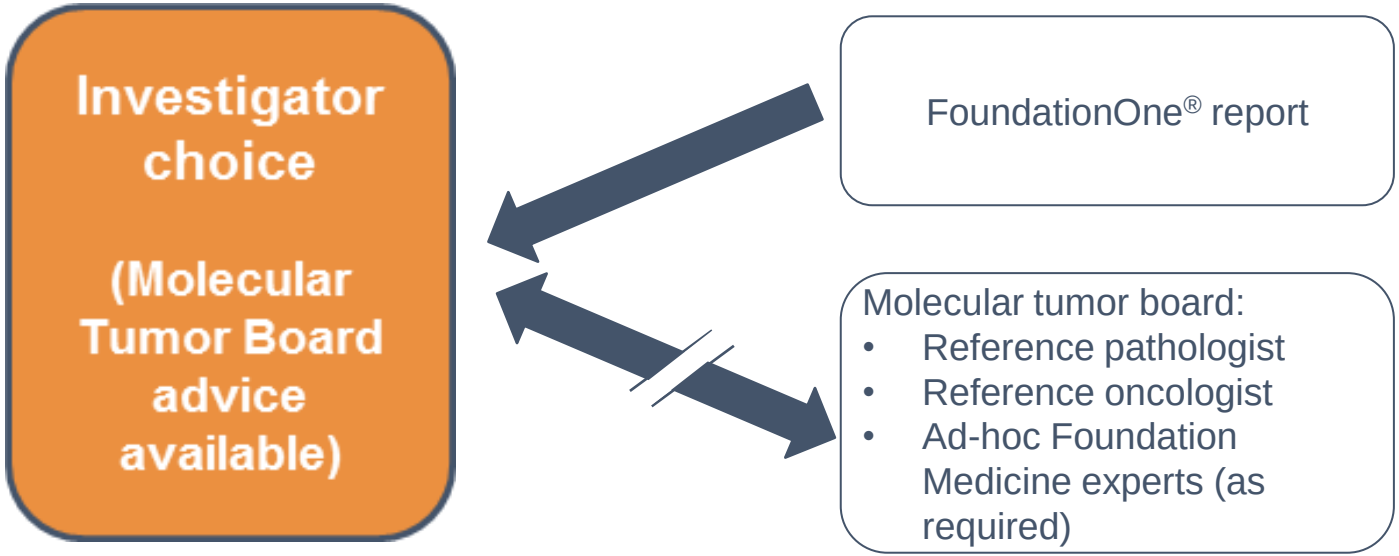
Targeted therapy selection by investigator choice

Preliminary allocation process



A **central molecular tumor board** will be available to **provide advice** on therapy choice and to **ensure consistency** across treatment options

Roche data on file, study concept MX39795.

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“NAVIFY Tumor Board solution” summarises clinical data for use by molecular tumor board

1. Collect

Gather medical records across specialties

2. Coordinate

Schedule tumor board meetings

3. Prepare

Create presentation of patient data

4. Conduct

Support patient case discussion

5. Next Steps

Capture and document treatment plan decisions

- For software demonstration, please visit the Roche booth (Hall 7)

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Study set-up initiated: 80+ sites planned in 20+ countries

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Meeting closure

Prof. Alwin Krämer, MD
University of Heidelberg, Germany

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Conclusions

- The ESMO guideline recommends low-toxicity palliative chemotherapy for poor-prognosis CUP patients
- Comprehensive genomic profiling can detect targetable genomic alterations in CUP samples
- The presented genomic profiling CUP study will evaluate the efficacy of molecularly guided therapy versus platinum chemotherapy

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Doing now what patients need next

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