How could molecular profiling impact histology independent labels in the future?

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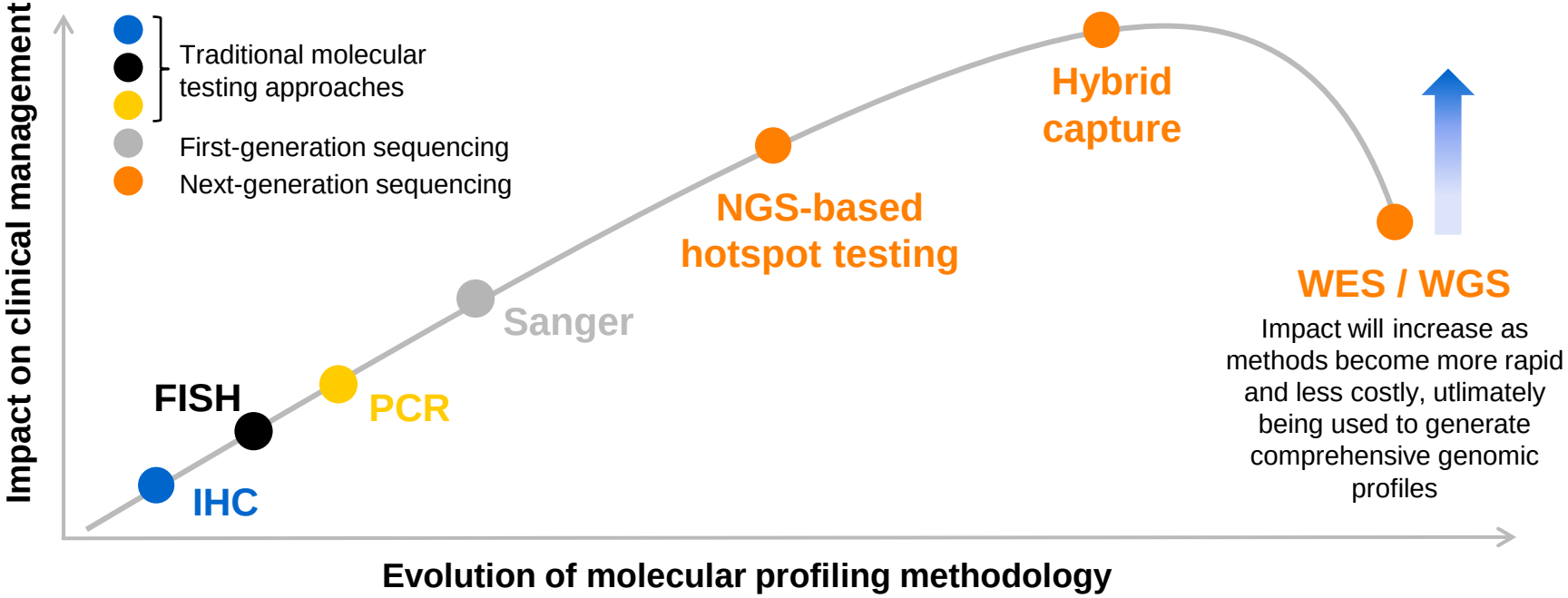
Evolvution of molecular profiling has impactecd clinical management



FISH: fluorescence in situ hybridisation; IHC: immunohistochemistry; NGS: next-generation sequencing; PCR: polymerase chain reaction; WES: whole exome sequencing; WGS: whole genome sequencing.

Netto, G.J., et al. (2003) *Proc Bayl Univ Med Cent* 16:379-83;
de Matos, L.L., et al. (2010) *Biomark Insights* 5:9-20;
Dong, L., et al. (2015) *Curr Genomics* 16:253-63.

Comprehensive genomic profiling (CGP) identifies all four classes of genomic alteration

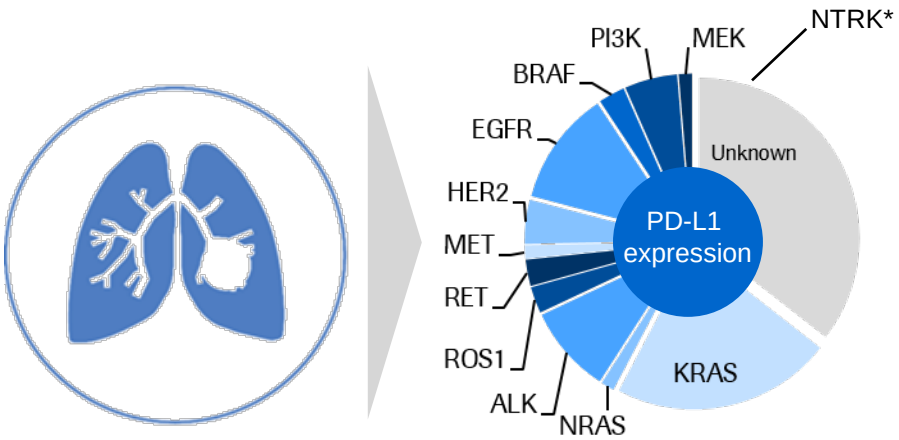
- CGP is a molecular diagnostic approach that **matches clinically relevant genomic alterations to therapeutic options** in a broad range of known cancer-related genes, **using a clinically validated platform**
- Utilizing **hybrid capture-based NGS** to **detect all 4 classes of genomic alterations**

NGS: next-generation sequencing.

Frampton, G. M., et al. (2013) Nature Biotechnol 31:1023-31; Foundation Medicine. (2017) FoundationOne® Technical Information and Test Overview. https://assets.contentful.com/vhribv12lmne/6YRrchSINOeSu48YwuesoY/0c3651c8421fa3647ccede76de9dce61/MKT-0054-02_F1_TechSpecs_digital.pdf. [Accessed December 2017]

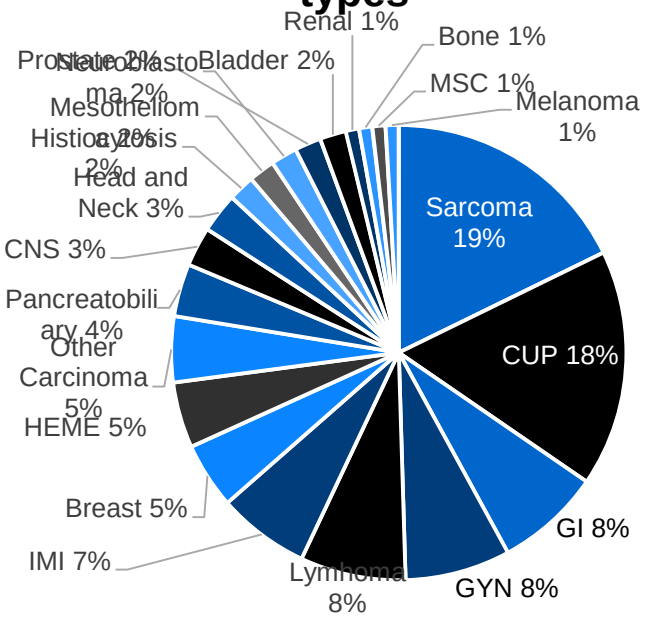
«Micro-indications» can be identified by looking at genomic subsets

Lung cancer as one example:[1,2]



Molecular alterations in NSCLC

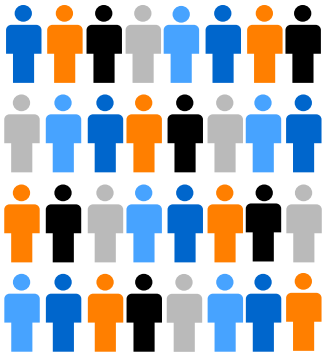
ALK-fusions across tumour types[3]



*NTRK is a potential new biomarker that is not currently included in the NCCN guidelines
NSCLC: Non-small cell lung cancer.

1. NSCLC NCCN Guidelines Version 2.2017;
2. Image modified and adapted from Baumgart, M. (2015) *Am J Hematol Oncol* 11:10-3.
3. Image modified and adapted from Ross J.S. et al. (2017) *Oncologist*

Clinical reality of molecularly-guided treatment



Matched targeted therapy
(outside of clinical trials)

Matched targeted therapy within clinical trials
(e.g. SHIVA, MOSCATO, PROFILER)

What proportion of cancer patients will ultimately benefit from this approach and for how long?

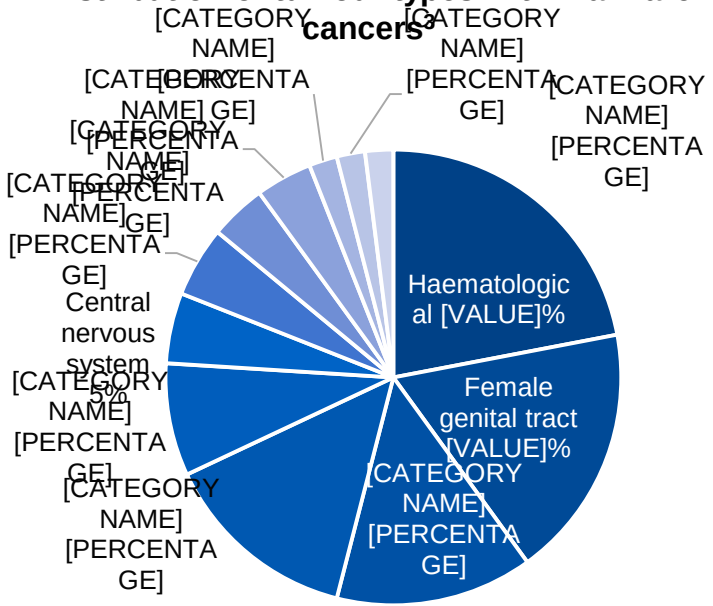
Rare cancers have high medical needs

Rare cancers: Incidence of < 6 per 100,000 persons per year[1]

Specific challenges posed by rare cancers:[2]

- Late or incorrect diagnosis
- Lack of clinical expertise
- Limited number of clinical studies due to the small number of patients
- Hurdles in developing new therapies due to limited market size
- Few available registries and tissue banks

Distribution of tumour types within all rare cancers[3]



1. http://www.rarecare.eu/rarecancers/rarecancers.asp [Accessed December 2017]
2. http://www.rarecancerseurope.org/About-Rare-Cancers/The-Burden-and-the-Challenges-of-Rare-Cancers [Accessed December 2017]
3. http://www.rarecancerseurope.org/content/download/16501/288755/file/epidemiology-rare-cancers-europe-trama.pdf [Accessed December 2017]

NGS-based molecular profiling is feasible in clinical practice and improves outcomes

MOSCATO-01: First trial to show that NGS-guided treatment can improve clinical outcomes

- **Molecular profiling performed on 843 patients** with advanced solid tumours having failed on prior lines of standard therapy
- **411 patients** (49%) had actionable alterations; 199 patients (24%) were treated with matched therapy based on genomic alterations
- Compared with previous, non-targeted therapy, **PFS was extended by 30% in a third of patients receiving targeted treatment**
- **62% of the patients had disease control** (i.e. objective response or stable disease)

NGS: next-generation sequencing.

Massard, C. et al. (2017) *Cancer Discov* 7:586-95.

Molecularly-guided therapies may improve outcomes but are limited by availability

ProfiLER-01: One of the largest trials assessing the value of NGS-based molecular profiling in a pan-cancer setting

- **Molecular profiling** performed on **1,944 patients** with advanced solid tumours
  - Routine molecular profiling was found to be **feasible** in a local and regional setting
- **> 50%** of patients had an actionable alteration
- A molecular tumour board reviewed genomic data and recommended a therapy matching
  ≥ 1 actionable alteration
- Although **35% of patients** were matched with ≥ 1 **therapy based on profiling**, **only 7% received treatment**, mainly due to the **unavailability of the matched therapy**

NGS: next-generation sequencing.

Trédan, O., et al. (2017) ASCO Abstract #LBA100.

Frequency of biomarker testing in a German registry for NSCLC (CRISP)

		Total (n = 1208)	Non-Squamous (n = 886)	Squamous (n = 235)
Any biomarker test performed?	No	161 (13.3%)	64 (7.2%)	95 (40.4%)
	Yes	942 (78.0%)	803 (90.6%)	135 (57.4%)
	Not yet documented	105 (8.7%)	19 (2.1%)	5 (2.1%)
Test method used at least once	FISH	353 (29.2%)	329 (37.1%)	24 (10.2%)
	IHC	569 (47.1%)	470 (53.0%)	97 (41.3%)
	NGS	305 (25.2%)	277 (31.3%)	28 (11.9%)
	Other	433 (35.8%)	397 (44.8%)	33 (14.0%)
	Unknown	117 (9.7%)	103 (11.6%)	14 (6.0%)
	Missing	302 (25.0%)	114 (12.9%)	104 (44.3%)
Test performed (with at least one method)	EGFR	681 (56.4%)	626 (70.7%)	55 (23.4%)
	ALK	652 (54.0%)	600 (67.7%)	52 (22.1%)
	ROS-1	526 (43.5%)	486 (54.9%)	40 (17.0%)
	PD-L1	432 (35.8%)	348 (39.3%)	84 (35.7%)
	BRAF	319 (26.4%)	288 (32.5%)	31 (13.2%)
	RET	201 (16.6%)	186 (21.0%)	15 (6.4%)
	HER2	60 (5.0%)	49 (5.5%)	11 (4.7%)
	KRAS	345 (28.6%)	312 (35.2%)	33 (14.0%)
	CMET	265 (21.9%)	238 (26.9%)	27 (11.5%)
	P53	218 (18.0%)	196 (22.1%)	22 (9.4%)

CRISP: Clinical Research Platform Into Molecular Testing, Treatment and Outcome of NSCLC Patients; FISH: fluorescence in situ hybridisation; IHC: immunohistochemistry; NSCLC: Non-small cell lung cancer; NGS: next-generation sequencing. Total (n) = number of documented patients. Non-Squamous (n) = Number of documented patients with non-squamous tumour. Squamous (n) = number of documented patients with squamous tumour. Total might be greater than sum of non-squamous and squamous due to incomplete results

Alternative access routes to molecularly-guided targeted therapies

Network Genomic Medicine Lung Cancer

Promoting the implementation of personalised therapy in routine clinical care

Use multiplex-test, in combination with highly sensitive deep sequencing, to **identify all genomic alterations that may have therapeutic relevance now or in the future**

Provision of a comprehensive offer for **personalized trials**, in order to offer participation in a clinical trial to as many patients as possible who have detected therapeutically relevant mutations.

Network Genomic Medicine (2017) http://ngm-cancer.com/en/the-network/aims/ [Accessed December 2017]]

Country specific initiatives to facilitate access

France Genomics 2025 [1]

Objectives:

1. Position France as one of the leading countries in personalised medicine
2. Integrate genomic medicine in clinical care
3. Foster scientific and technological innovation

Genomics England 100k Genomes [2]

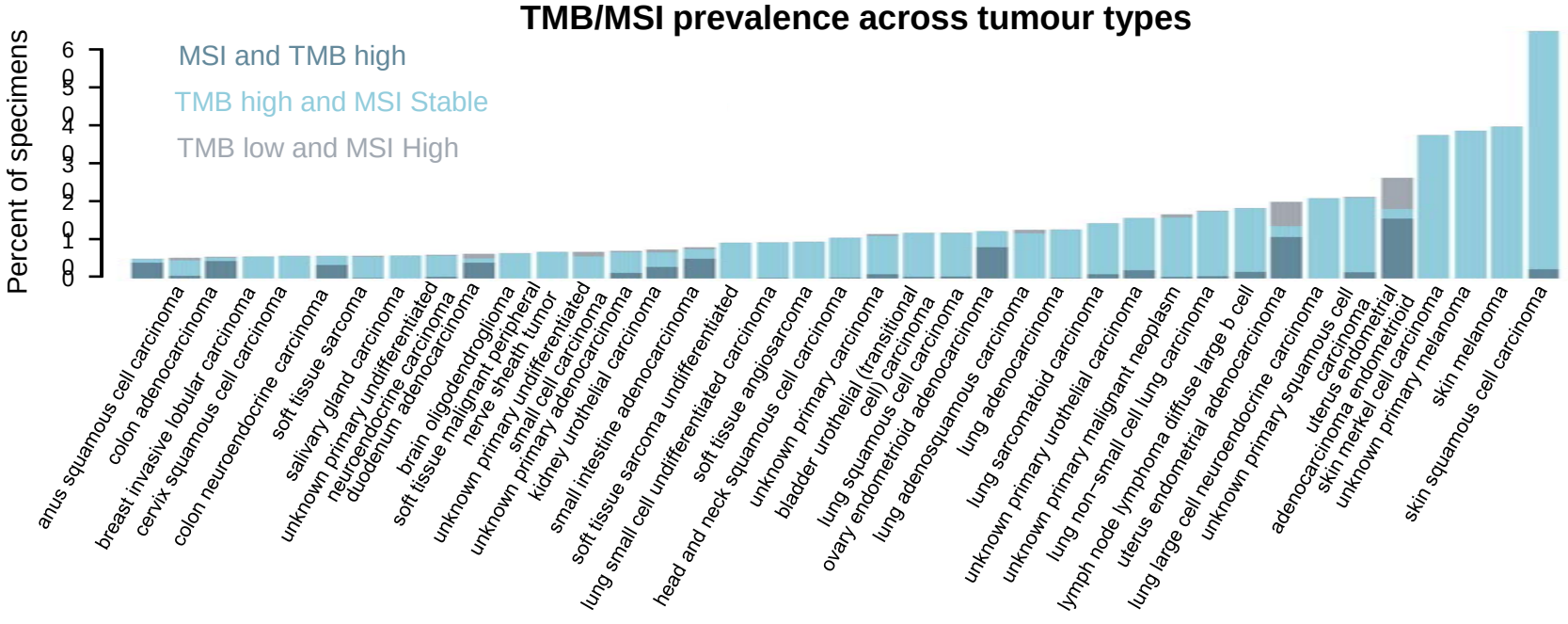
Objectives:

1. Ethical and transparent programme
2. Provide benefits of genomic medicine to patients
3. Enable new scientific discovery and medical insights
4. Kick-start the development of a UK genomics industry

1. Retrieved from: http://www.gouvernement.fr/sites/default/files/document/document/2016/06/22.06.2016_remise_du_rapport_dyves_levy_-_france_medecine_genomique_2025.pdf [Accessed September 2017];
2. Retrieved from: https://www.genomicsengland.co.uk/the-100000-genomes-project/ [Accessed September 2017].
In countries where reimbursement is not available testing is paid by patients.

Comprehensive genomic profiling can detect multiple biomarkers

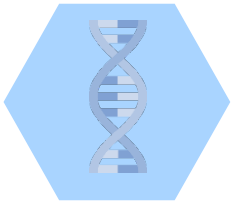
Tumour mutational burden (TMB) is the **total number of coding somatic mutations** in a tumour specimen **per megabase of coding genome assessed**



TMB: tumour mutational burden; MSI: microsatellite instability.
Chalmers, Z.R. et al. (2017) *Genome Medicine*, 9:34.

FDA approved pembrolizumab▼ based on a tumour biomarker not tumour histology

Pembrolizumab▼



Microsatellite instability-high

For the first time, the FDA has **‘approved a drug based on a tumor's biomarker without regard to the tumor's original location’** [1]

?

?

Could other drugs also be **approved based on tumour specific biomarkers**, e.g. tumour mutational burden (TMB)?

?

FDA: Food and Drug Administration.
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. Merck Sharp & Dohme Ltd: pembrolizumab.
1. FDA news release retrieved from: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm560167.htm [Accessed December 2017].

Novel approaches to evidence generation are needed to demonstrate efficacy and safety of molecularly-guided therapy in a pan-tumour setting

Accumulated data approach	Basket trials	Rare molecular subtypes
Robust efficacy/safety signals in a "lead" tumor type → pan-tumor data	Robust efficacy seen across a multitude of tumor types	How to create robust efficacy and safety signals in microindications?
Biological plausibility supports extrapolation to other tumor types	High/consistent ORR across tumor types	First two approaches not practical
Molecular marker status can be assessed with a validated test	Unmet medical need and acceptable tolerability across tumor types	Example: **Cancer of unknown primary**
High unmet medical need supports iterative or full approval	Ability to gather confirmatory data through PMC registries/RWD	**How do we efficiently validate molecularly-guided treatments for patients irrespective of tumour type in rare indications?**
Confirmatory data gained through registries RWD or CTs	Example: **Larotrectinib** in TRK fusion cancers (not approved)[2]	
Example: **Pembrolizumab▼** in advanced MSI-H/dMMR solid tumours[1]		

dMMR: mismatch repair deficient; MSI-H: microsatellite instability high; TRK: tropomyosin receptor kinase.
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. Merck Sharp & Dohme Ltd: pembrolizumab.

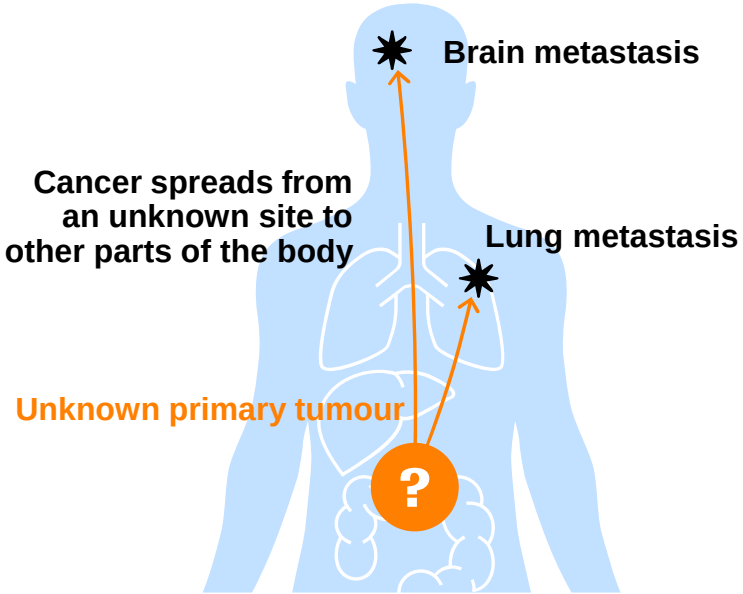
1. FDA news release retrieved from: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm560167.htm [Accessed December 2017];
2. Loxo Oncology news release retrieved from: https://ir.loxooncology.com/docs/press-releases/2114.pdf [Released 3 June 2017, accessed December 2017].

CANCER OF UNKNOWN PRIMARY (CUP) TO ASSESS THE UTILITY OF PAN-TUMOUR MOLECULAR PROFILING

CUP is unique relative to other cancers and has limited treatment options

3 – 5% of all cancers[1]

A heterogeneous group of cancers with a **high unmet need** for effective treatment options[1]



4th most common cause of cancer-related deaths[2]

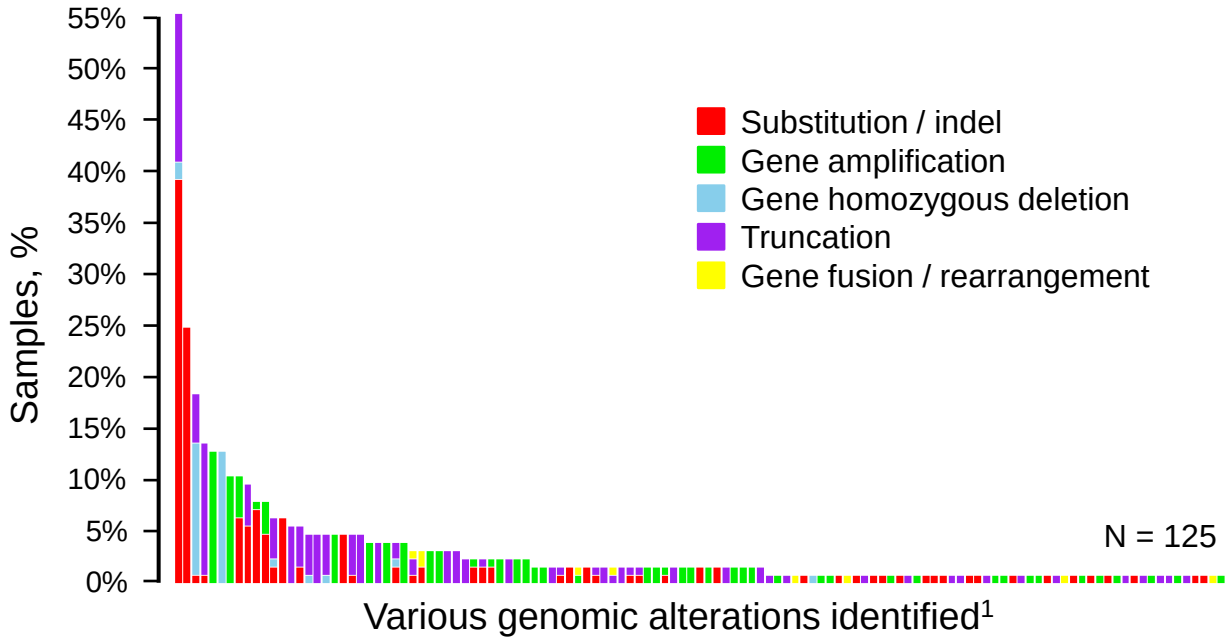
Poor prognosis cases[1] (80% – 85%)

- **median overall survival of < 1 year**
- **treatment limited to low toxicity palliative chemotherapy**

Cancer of unknown primary (CUP) is defined by the **lack of a primary site**, unidentifiable by standard diagnostics[1]

1. Fizazi, K., et al. (2015) *Ann Oncol* 26(suppl 5):v133-8;
2. Pavlidis, N. and Pentheroudakis, G. (2012) *Lancet* 379:1428-35.

High diversity of genomic alterations observed across ACUP samples

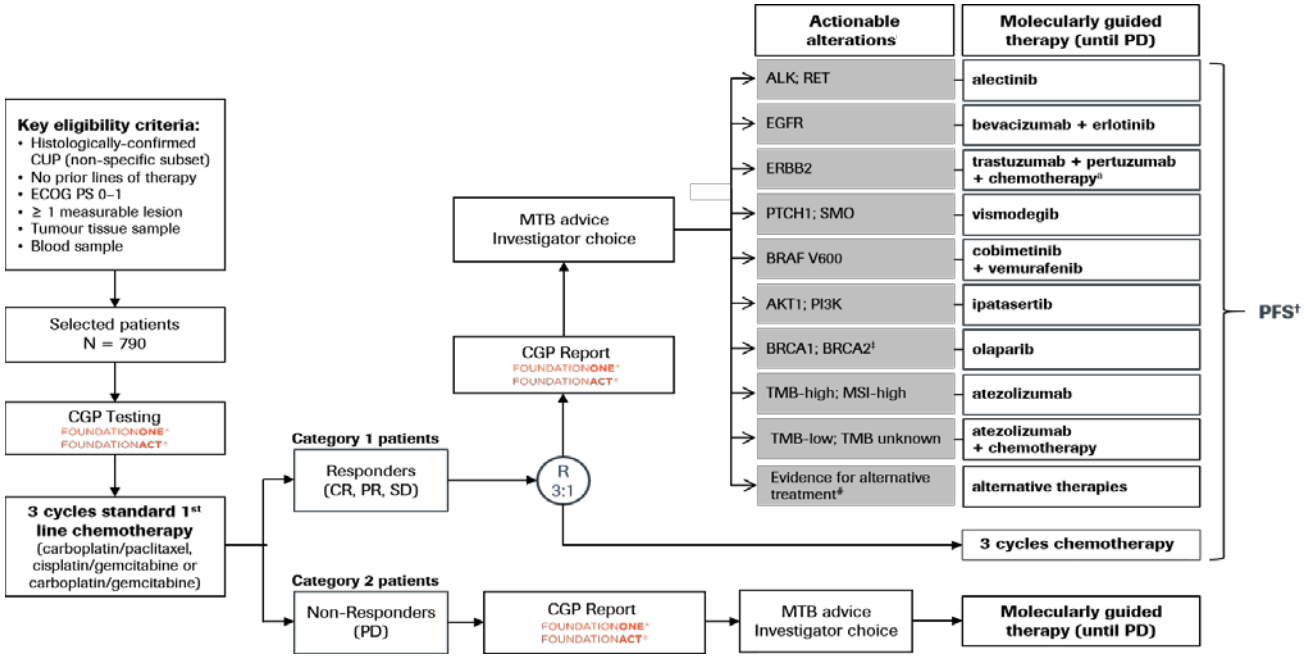


Comprehensive genomic profiling has shown that almost all CUP samples harbour targetable alterations[1,2]

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

1. Ross, J.S., *et al.* (2015) *JAMA Oncol* 1:40-9; 2. Subbiah, I.M., *et al.* (2017) *Oncoscience* 4:47-56.

Global study on CUP to assess utility of molecular profiling in a pan-tumour setting



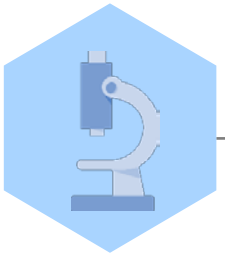
[a] continuation of the initial platinum doublet induction chemotherapy; † primary endpoint; ‡ or homologous recombination deficiency based on loss of heterozygosity; # potential rationales for alternative treatments: (i) strong suspicion of a primary tumour revealed by CGP, (ii) strong rationale for alternative commercially-available, targeted therapy, (iii) negative predictor of response to anti-PD-1/PD-L1 agents, (iv) no genetic alteration allowing assignment to a protocol-mandated targeted therapy and contraindication for atezolizumab.

CGP, comprehensive genomic profiling; CUP, cancer of unknown primary site; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; MTB, Molecular Tumour Board; MSI, microsatellite instability; PD, progressive disease; PFS, progression free survival; PR, partial response; R, randomisation; SD, stable disease; TMB, tumour mutational burden.

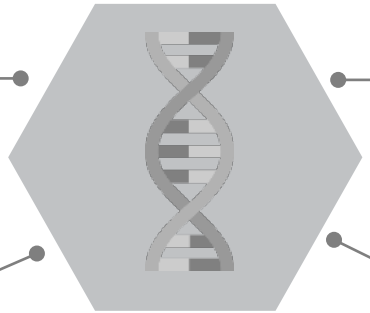
Roche data on file, study concept MX39795.

ARE HISTOLOGY INDEPENDENT LABELS THE WAY FORWARD?

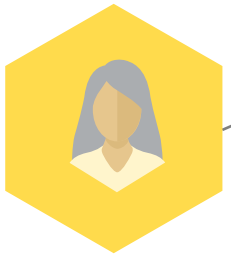
What impact will molecular profiling have on histology independent labels?



What will be the recognised standard for NGS testing?



What type and volume of data will be needed to get a histology independent label?



Will therapies be limited to patients with no alternative treatment options or as last line?

How will clinical benefit be measured?

Will different types of post-licensing evidence generation be required?

NGS: next-generation sequencing.

Doing now what patients need next