Lung Cancer: how do I ask for and use molecular profiling results to guide everyday treatment decisions?

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- *Co-founder*: Trialing Health S.L

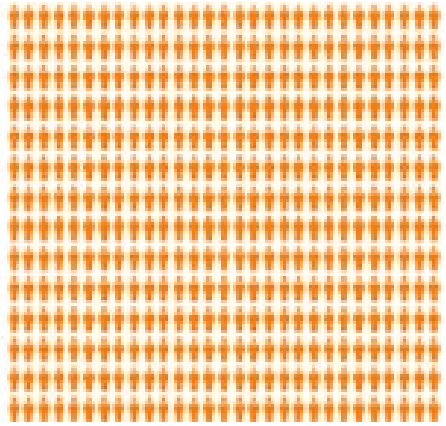
Outline

- Implications of targeted treatment
- Patient selection
- Timings
- Panel selection
- Result interpretation-Molecular tumor board
- Decision making
- Conclusions

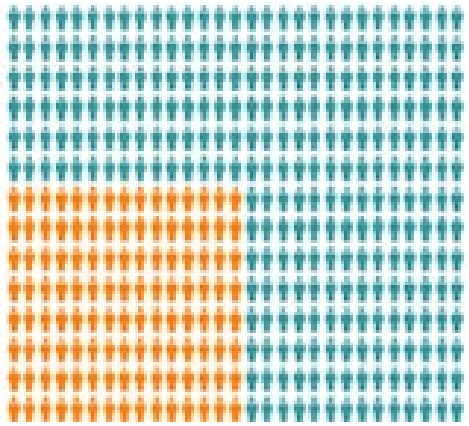
Implications of targeted treatment

The right treatment for the specific patient at the right time.

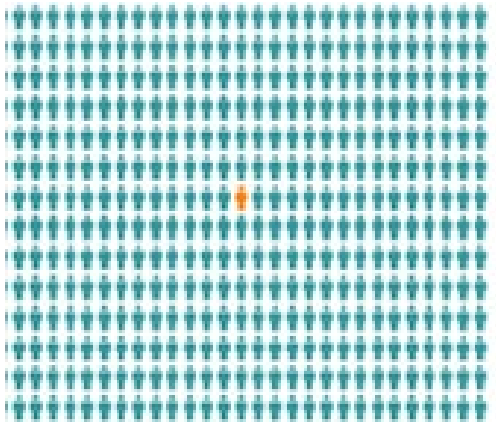
One tumor type,
same treatment for everybody



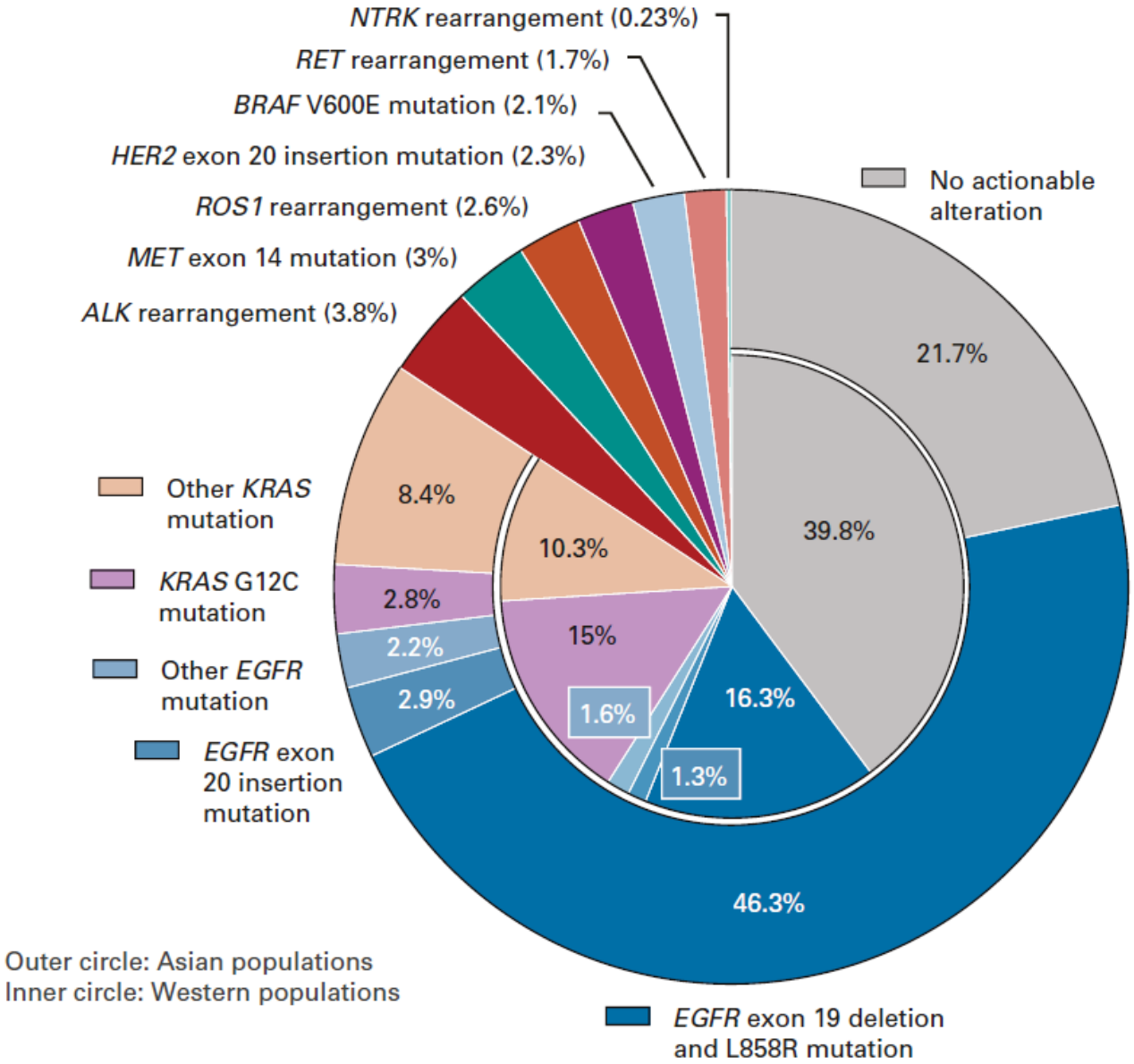
One tumor type,
one biomarker, one treatment



One patient, one molecular
profile, one precise treatment



TARGETED THERAPY. Actionable alterations



Tan JCO 2022

TARGETED THERAPY. Multiples available drugs for multiple targets

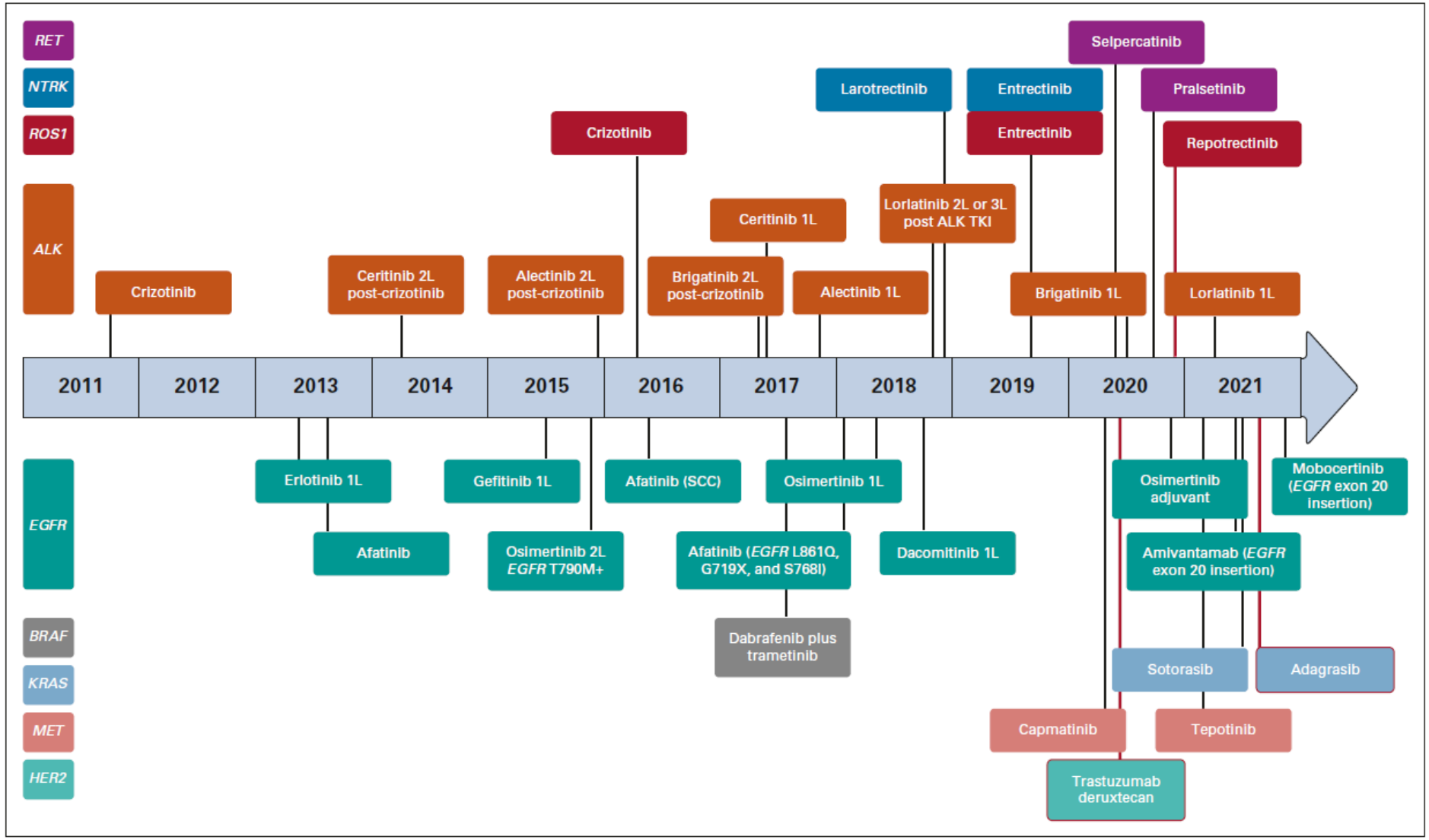


FIG 2. Timeline of FDA-approved targeted therapies for oncogene-driven NSCLC. The red lines indicate breakthrough therapy designation. 1L, first-line; 2L, second-line; FDA, US Food and Drug Administration; NSCLC, non–small-cell lung cancer; TKI, tyrosine kinase inhibitor.

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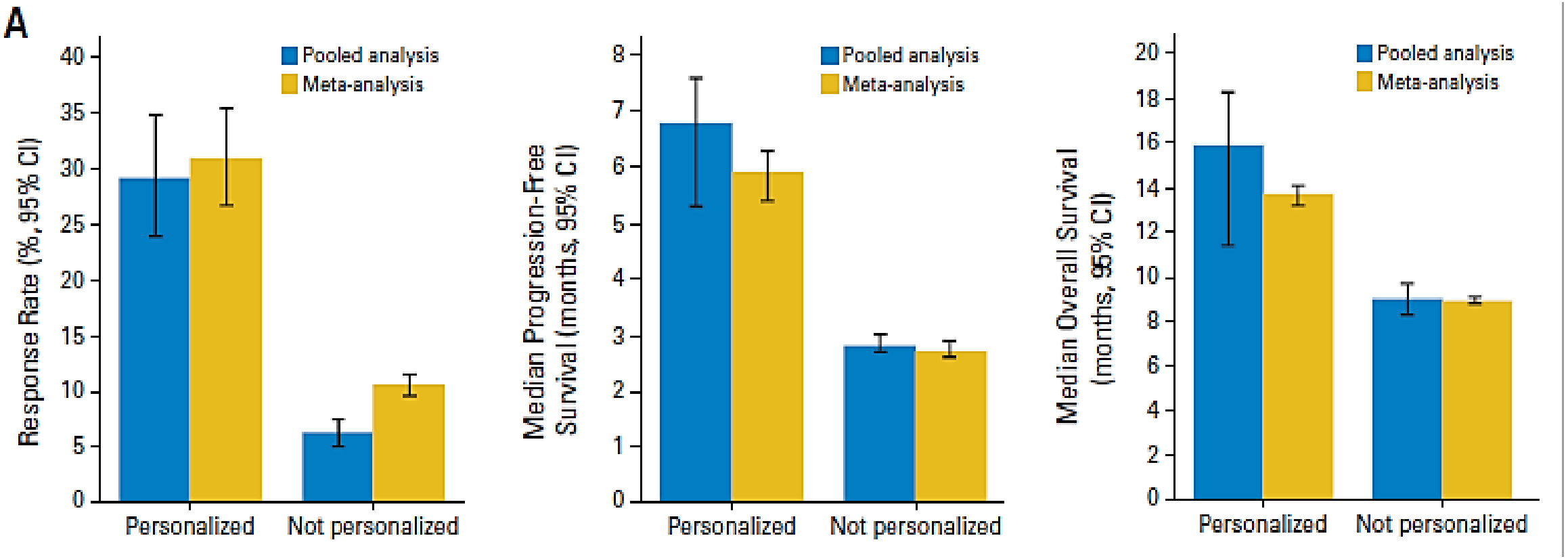
Personalized treatment improves all efficacy parameters



Schwaederle JCO 2015

Comprehensive molecular genotyping and overall survival

Patients with comprehensive molecular genotyping had superior OS (22.1 months, 95% CI 14.62 – NA), compared to those with incomplete or no testing (11.6 months, 95% CI 3.61 – NA), p=0.02, likely mediated by delivery of targeted therapy

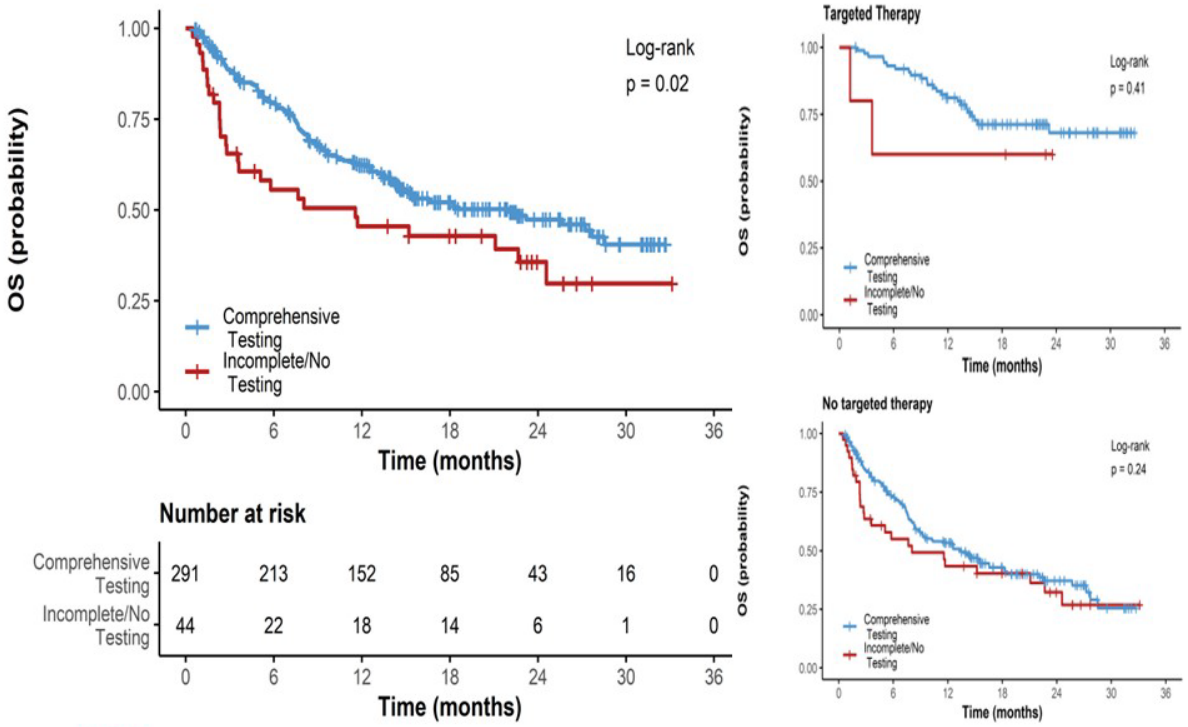


Fig 1.
Kaplan-Meier curve for OS of patients with comprehensive testing compared to patients with incomplete/no testing.

Availability of molecular genotyping results prior to first line therapy was associated with an improvement in OS (24.57 months, 95% CI, 18.56– NR), compared to patients without results available prior to first line therapy (6.18 months, 95% CI, 2.83 – 10.3), p<0.0001

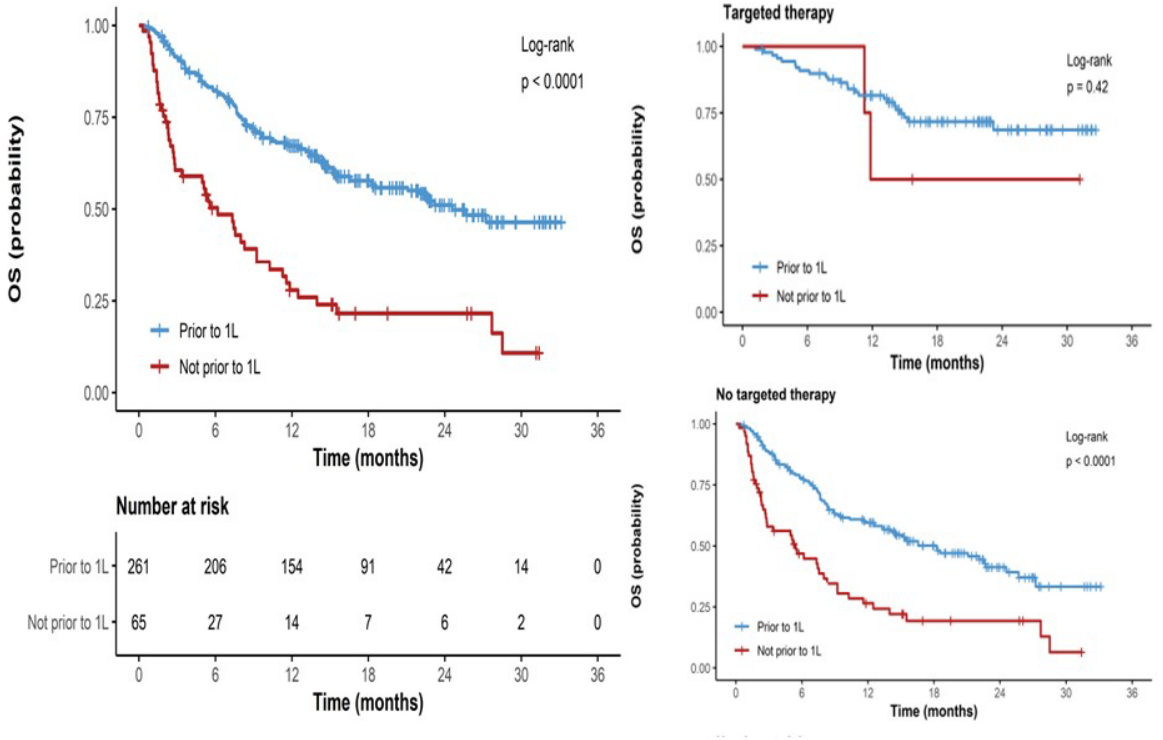


Fig 2.
Kaplan-Meier curve for OS of patients with comprehensive testing back prior to first line treatment compared to patients with results not back prior to first line treatment.

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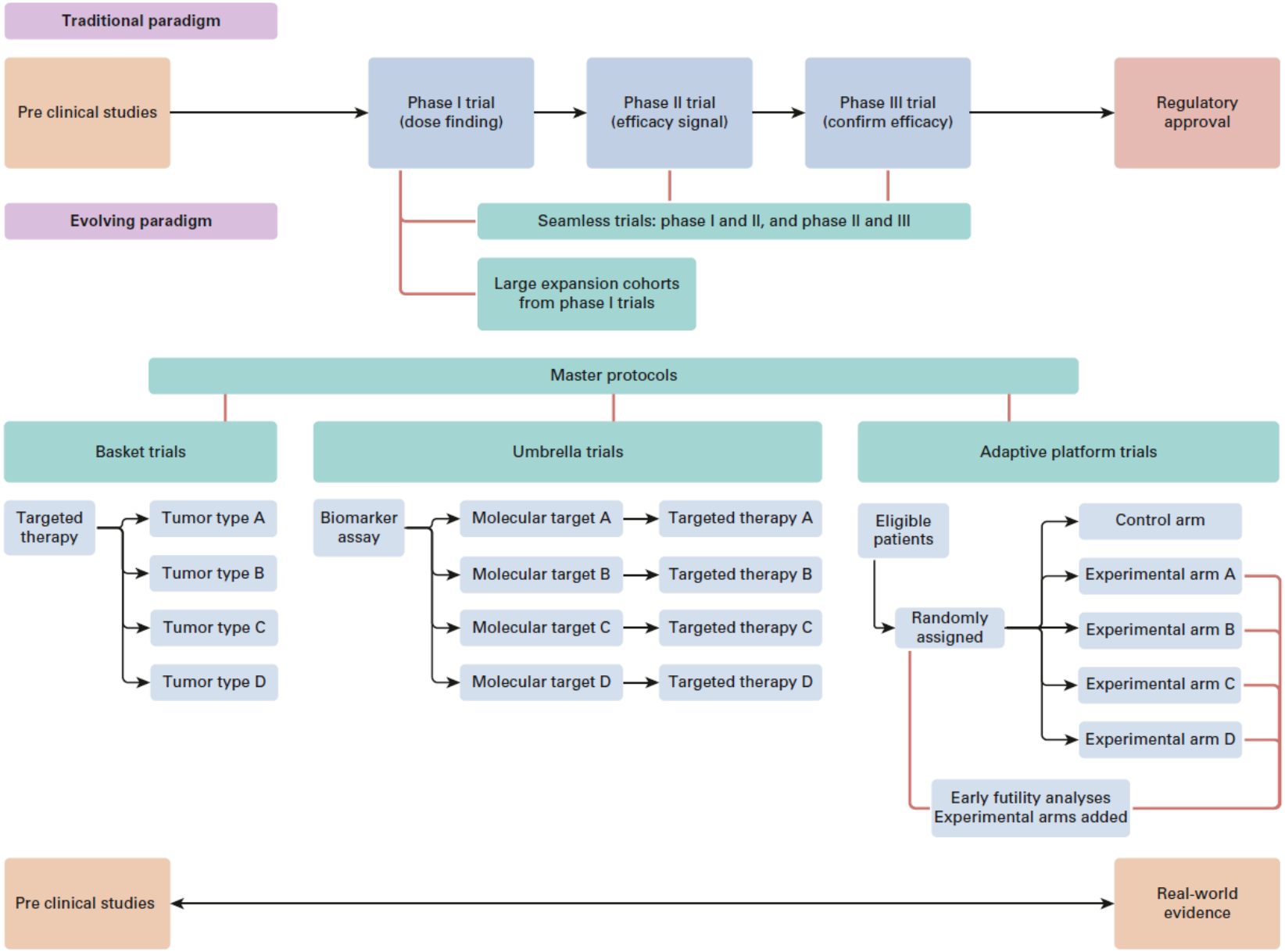
Impact on drug development paradigm



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Patient selection

- Non-squamous NSCLC amenable for systemic treatment
  - Stage IV or relapsed
- Squamous histogy
  - Non-smokers or les than 10 pack/year
  - Under 50y
  - Some targets might be infrequent but present (RET, KRAS G12C)
- Discussed at the weekly MDT

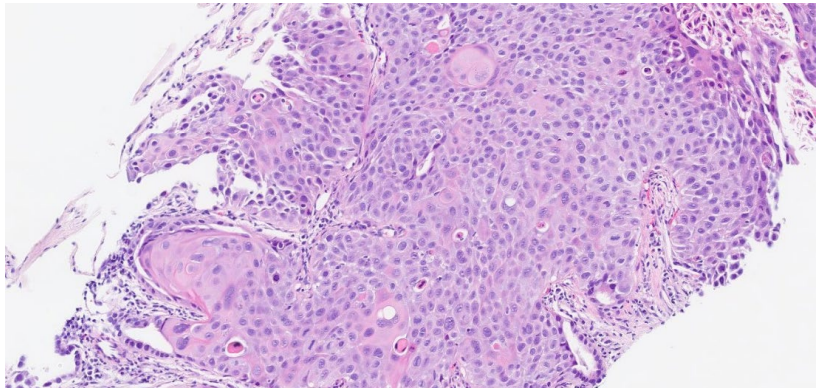
Kerr et al. Lung Cancer 2021

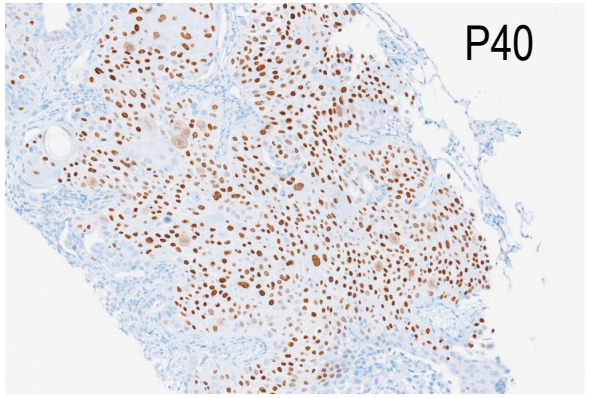
Timings

- Pathology review-MDT
  - Enough and good quality sample?
  - Reflex testing (pathologists requests appropriate biomarkers)
  - Alternative sources-liquid biopsy
- Turn around time
  - 7-15 days acceptable?
  - First consultation with medical oncologists with molecular results
  - New technology (i.e.Fast NGS): 48hours

Case 1

- 59 year old woman, non-smoker
- Chinese
- Referred to our center with advance *squamous* NSCLC with no molecular testing. Stage IV with brain metastases
- No additional material
- Liquid biopsy and recovered tumor block from referring center





Liquid biopsy:
-No mutations detected
CAST PCR:
-EGFR L858R
Biopsy:
-EGFR L858R, TP53 muts

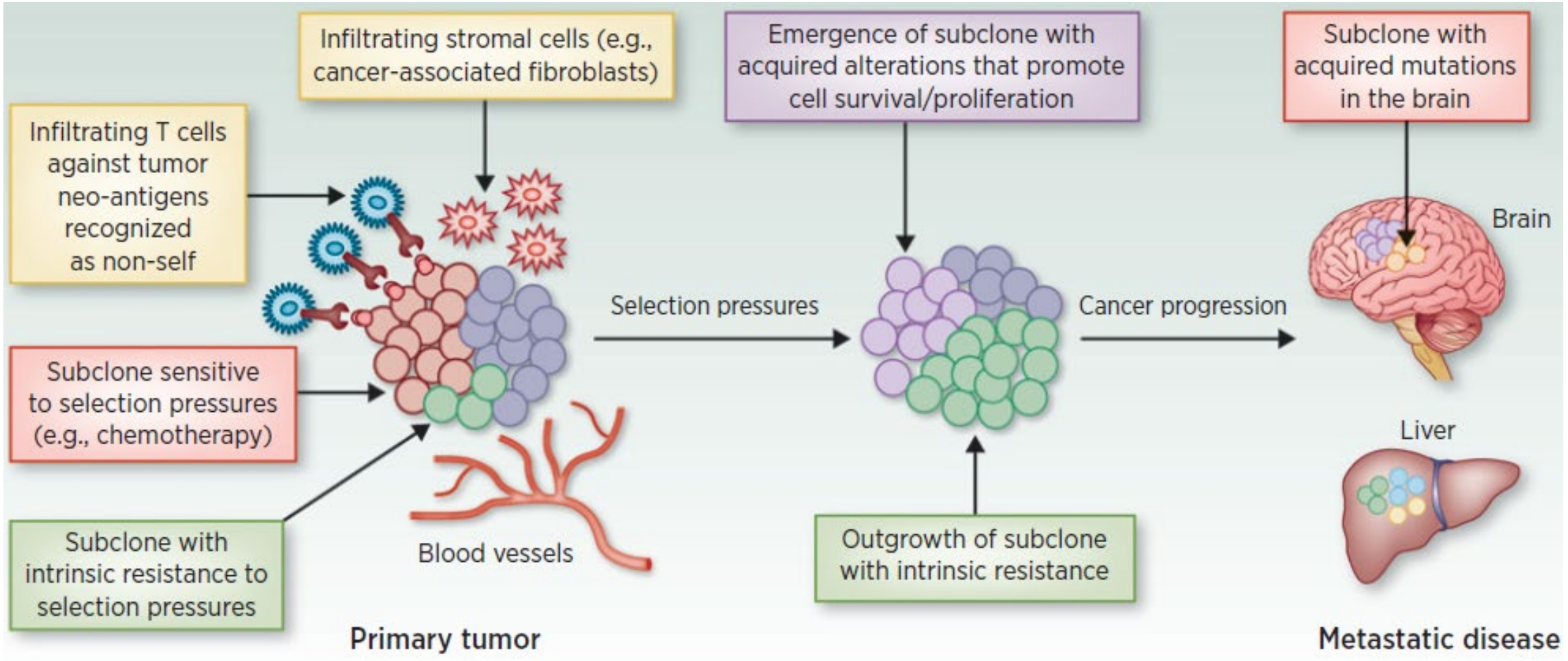
Panel selection

- Protocols in place
- Targeted panels
  - Small: 20-60 genes: all essential biomarkers for marketed drugs
  - Large: 300-500 genes
    - TMB, MSI, relevant co-mutations?
    - More costly and complex to report
    - VUS-how to do the reporting?
  - Liquid biopsy: depending on clinical scenario (diagnosis vs relapse)

Result interpretation-Molecular tumor board

- Clinical scenario
  - At diagnosis
  - At relapse/progression from targeted agents
  - Clinical situation-urgency
- Reporting
  - Tiers (only 1 and 2)
  - All variants
  - What to do with non-reported info (potentially relevant in the future?)
- Discussion of potentially germline findings, clonal hematopoyesis
- Discussion of dynamic changes in biomarkers (liquid biopsy)

TARGETED THERAPY. Adaptive clonal dynamics



Jamal-Hanjani CCR 2015

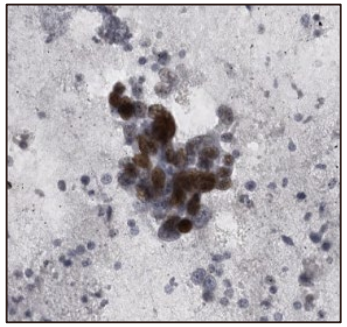
Decision making

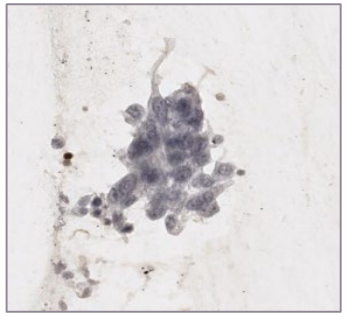
- Different access to NGS (precision medicine programs)
- Linked to drugs
- Different approval and reimbursment situations
- Compassionate use and clinical trial referrals

Case 2

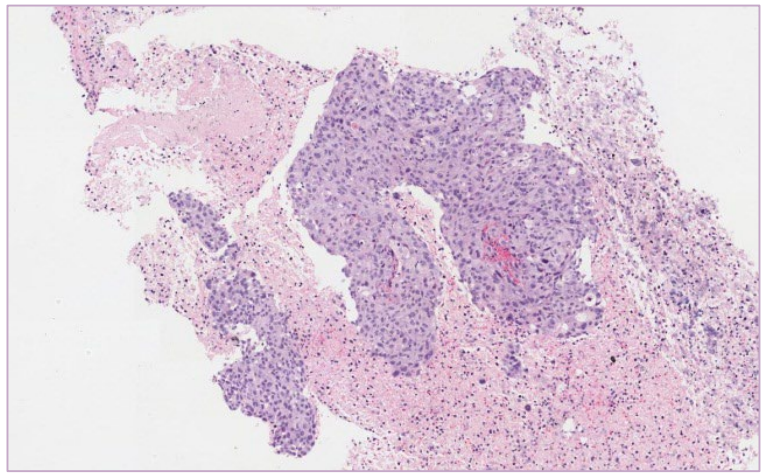
58 yo female. Heavy smoker

- April 2018: Lung adenocarcinoma T2bN2M1c (brain and bone mets)





Smears PATb 4R
TTF1 + / p40 -



Cell block cel PATb 4R

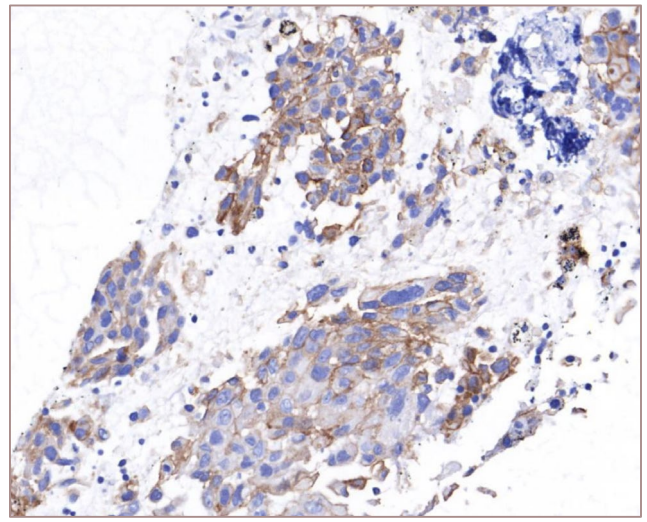
Realtime PCR/Sanger:
EGFR

FISH:
ALK
ROS1
MET

IHQ:
PD-L1: 100 %

NEG

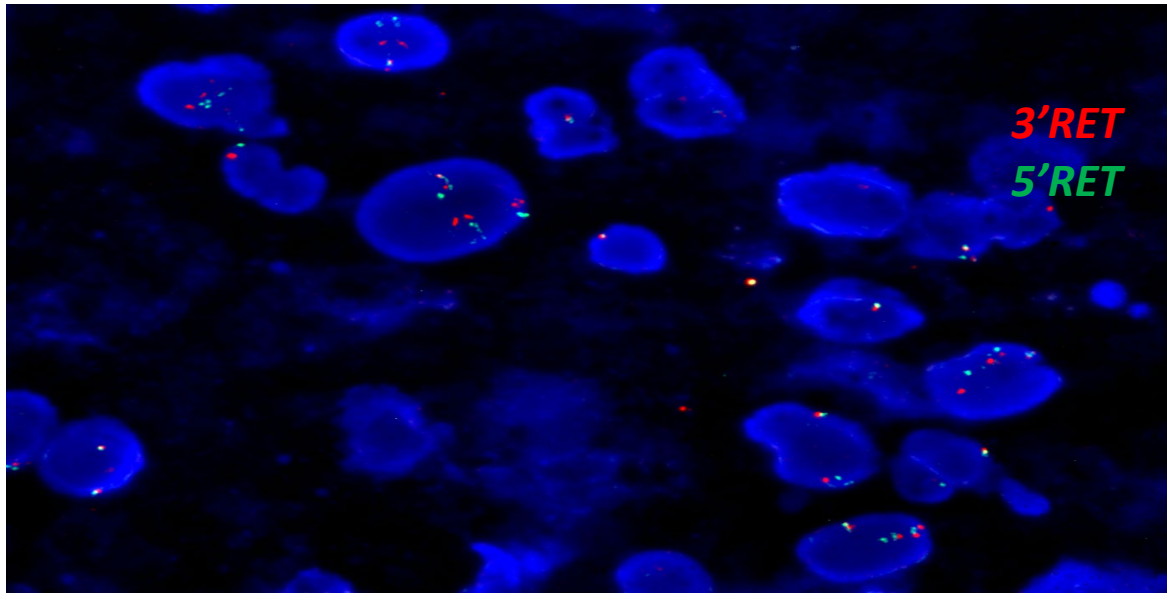
Biopsy:tumor cell representation
10 %



WBRT and pembrolizumab- Severe neurological toxicity- Guillain Barre syndrome

Liquid biopsy assay

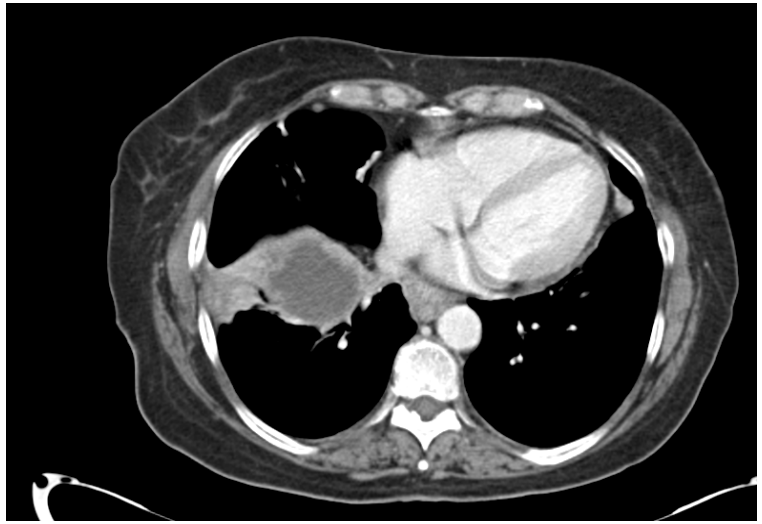
Gene	Variant	Allele fraction
TP53	p.Glu339* p.Glu328*	1.2%
PIK3CA	p.Glu545Val	0.02%
***KIF5B*(15) - *RET*(12)**	Gene fusion	



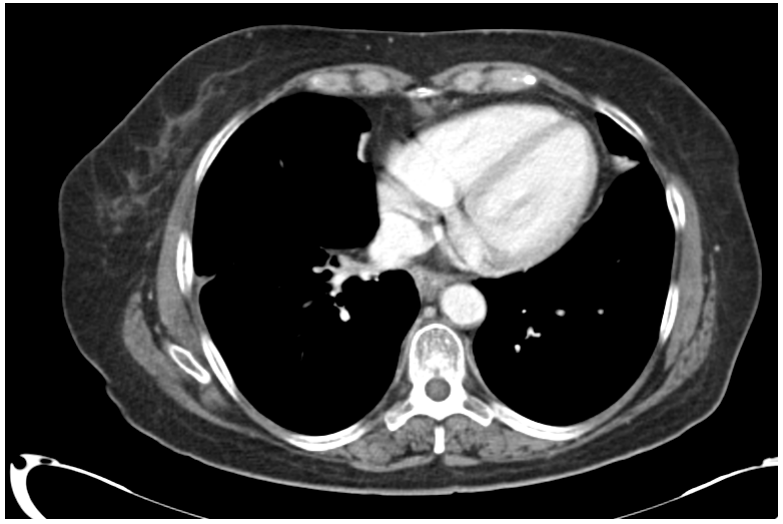
No targeted therapy approved at that moment in Spain

Clinical trial of selpercatinib ongoing (LOXO-292 120mg BID)

Basal



C5D1



Conclusions

- In recent years molecular diagnosis of patients with lung cancer has improved survival and quality of life
- New challenges emerge
  - Panel size selection
  - Alternative sources for genomic studies (role of liquid biopsy)
  - Funding for diagnostics
  - Real world applications of findings (approvals and reimbursement)
  - Reporting of VUS
- Multidisciplinary assesment of findings is essential for best use of NGS
- Early disease settings-should NGS be used?