UNIVERSITY OF TORINO – DEPARTMENT OF ONCOLOGY

The Evolving Paradigm of Precision Medicine in Lung Cancer: what Oncologist and Advocacies can do

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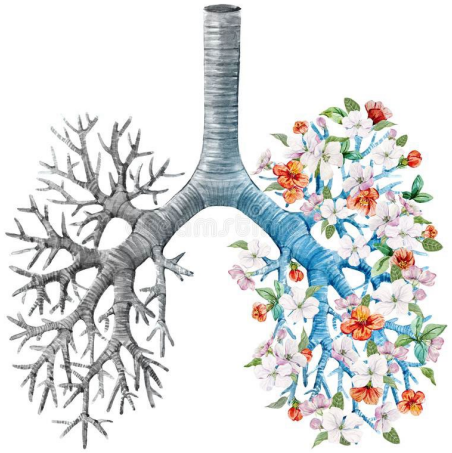
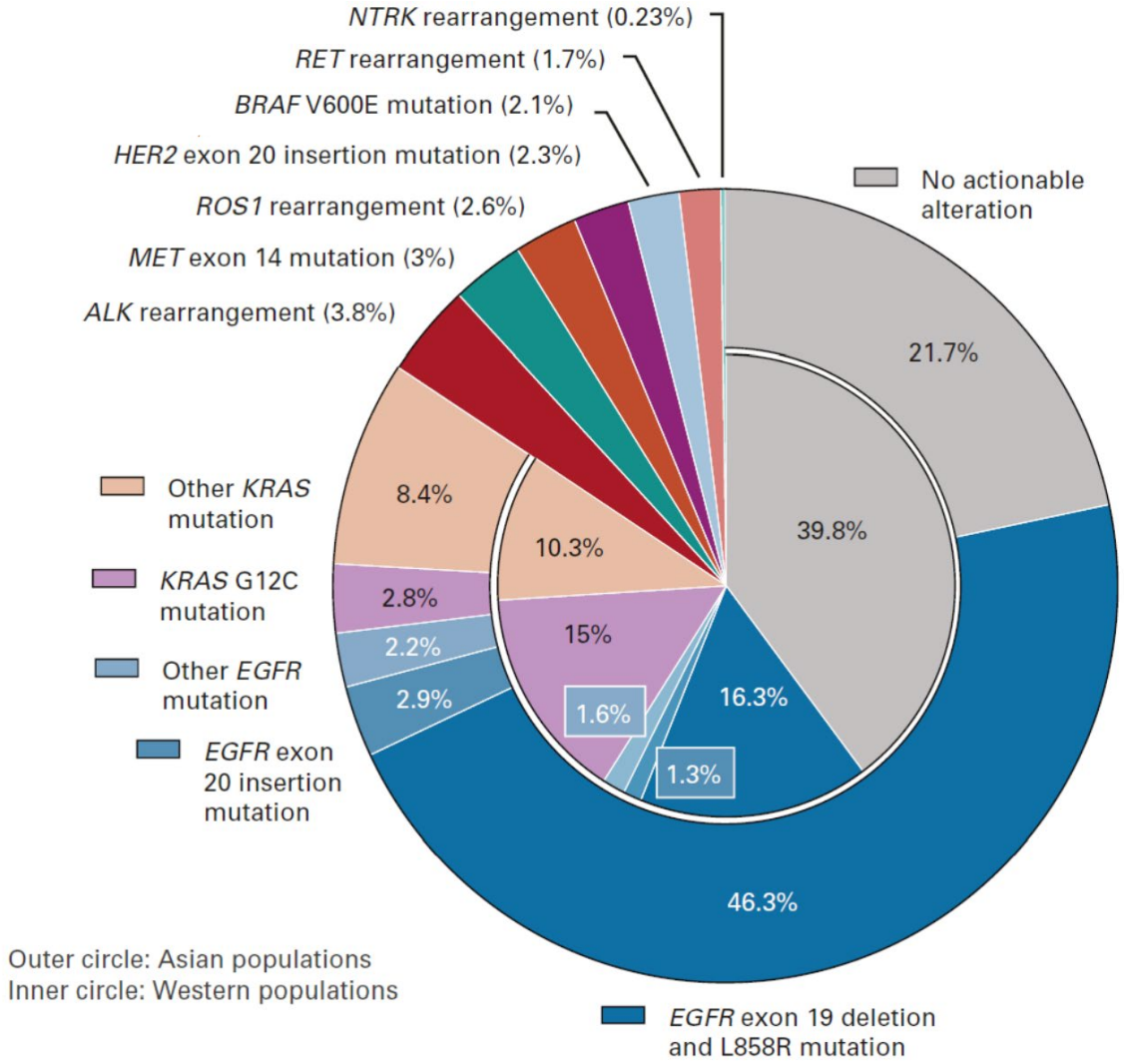
Research funding to institution from BI, MSD

Awareness of several targets

Frequency of targetable oncogenic driver molecular alterations in NSCLC

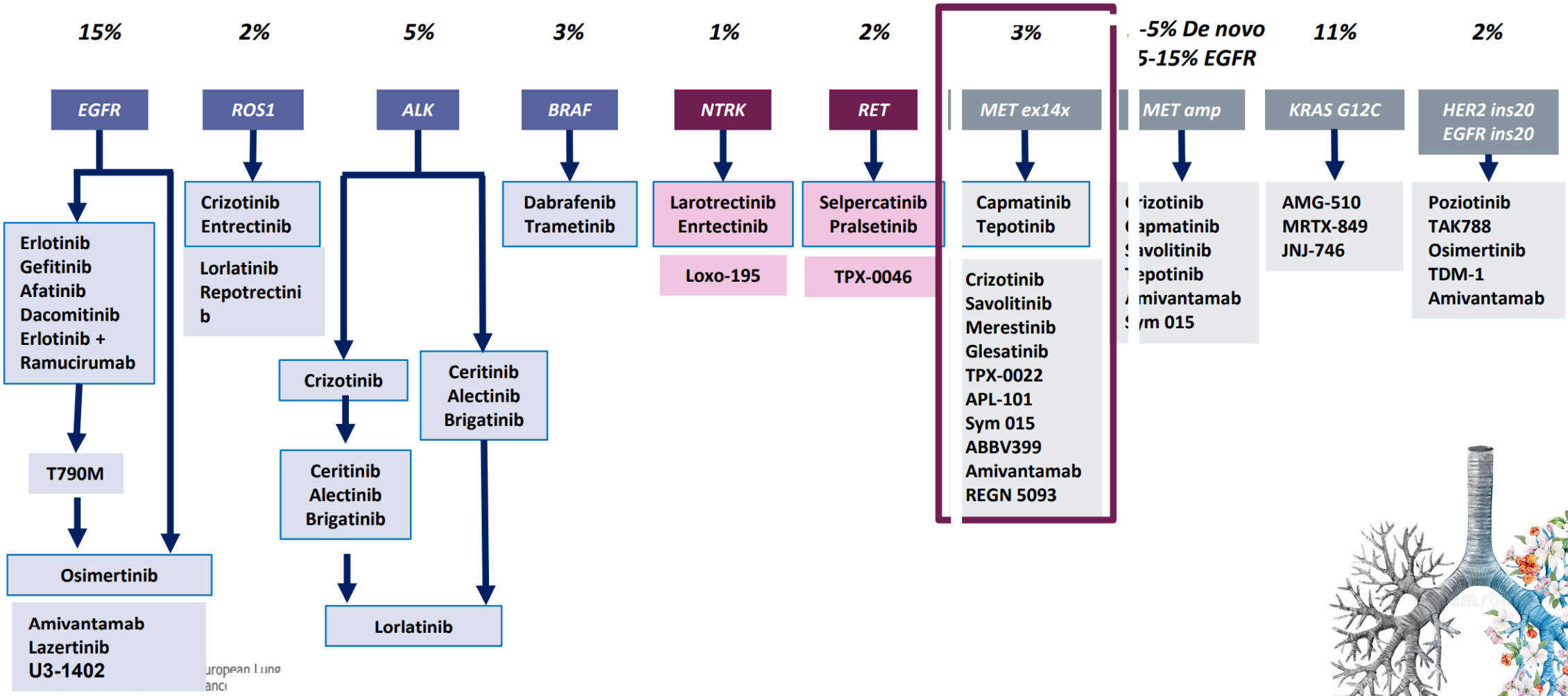




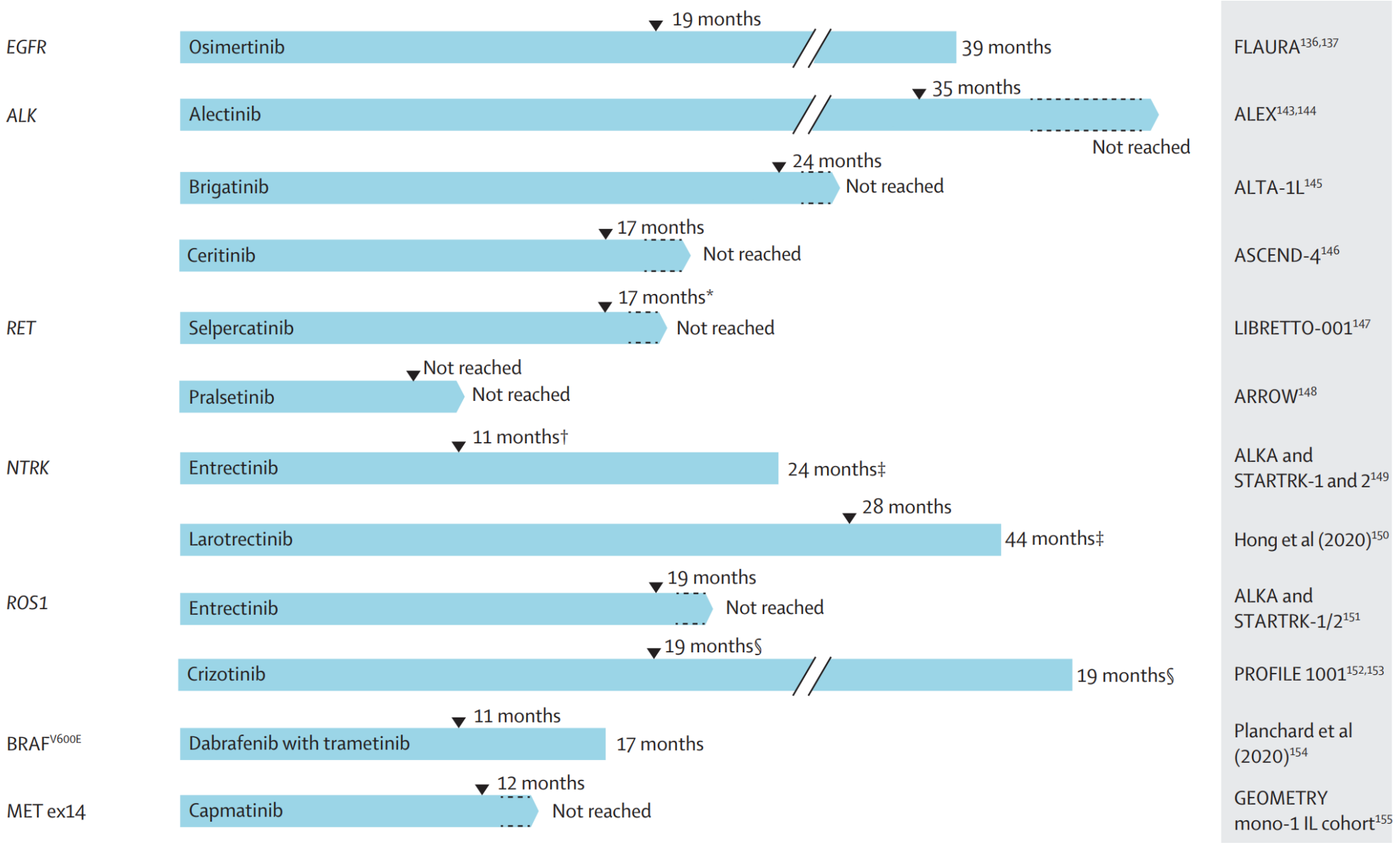
Aaron C. Tan et al, JCO 2021

Awareness of several effective drugs

Targeted therapies in NSCLC



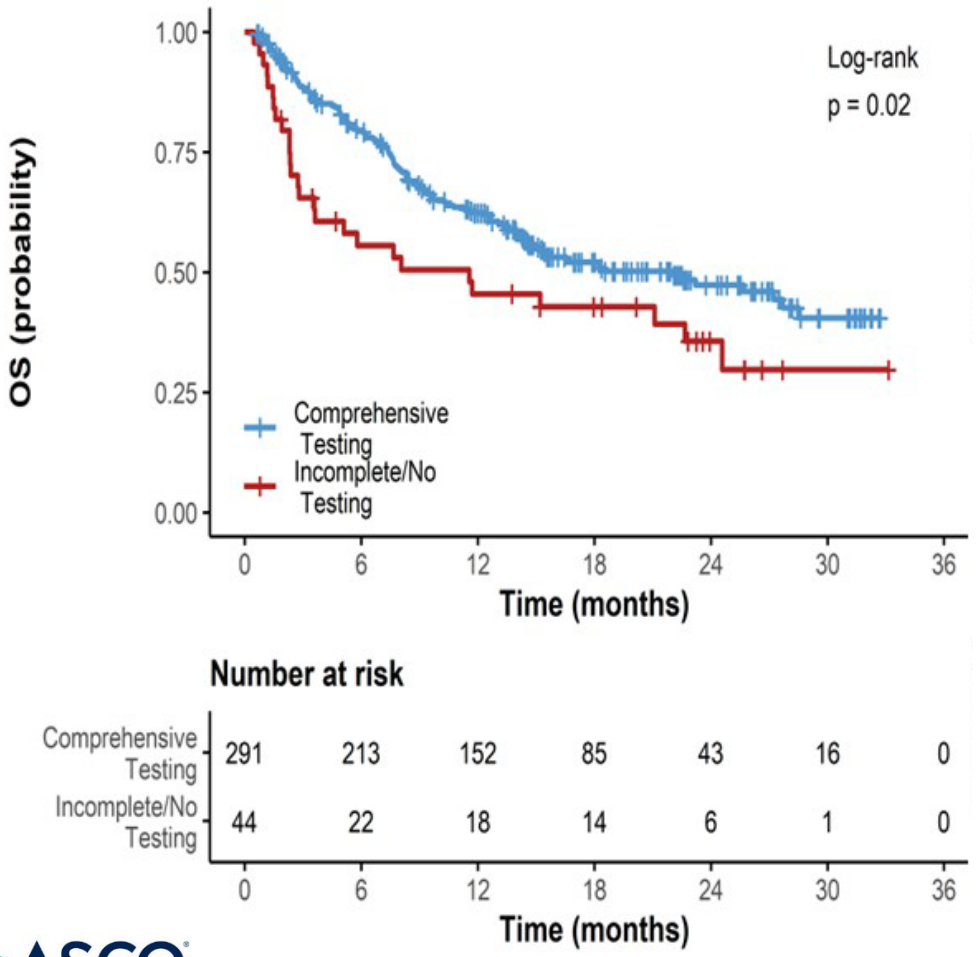
PFS and OS in oncogene addicted NSCLC pts treated with targeted therapies



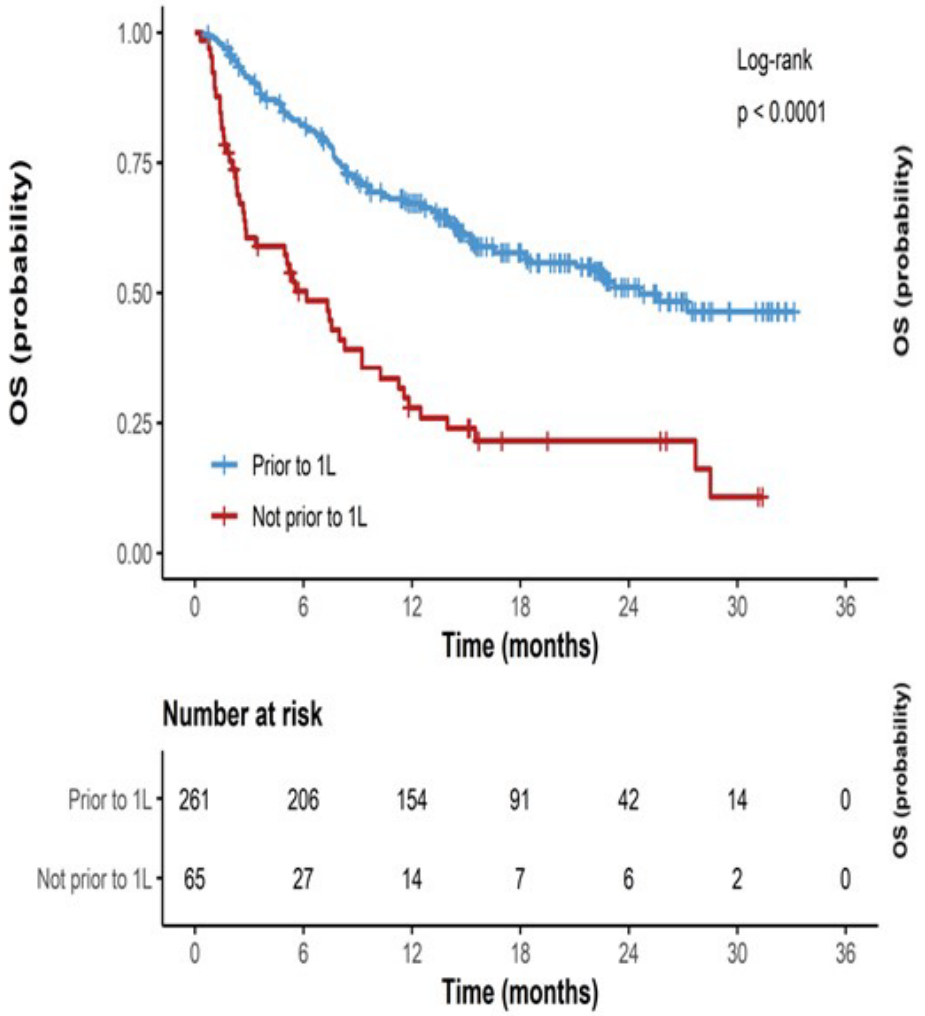
Aaron C. Tan et al, JCO 2021

Comprehensive Molecular Genotyping is associated with improved survival

OS of patients with comprehensive testing compared to patients with **incomplete/no testing**



OS of patients with comprehensive testing prior to 1L treatment compared to patients **without results available prior to 1L**



2022 ASCO ANNUAL MEETING

Charu Aggarwal, ASCO 2022

Increased need for molecular testing: What guidelines say

NCCN National Comprehensive Cancer Network®

EGFR | BRAF | KRAS | METex14 Skipping

MET amplification | HER2 | ALK Gene Fusion | ROS1 Gene Fusion

NTRK Gene Fusion | RET Gene Fusion | PD-L1

Version 3.2022, 03/16/22 © 2022 National Comprehensive Cancer Network® (NCCN®)

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE (to be updated)

Table 1. A personalised medicine synopsis table for metastatic NSCLC

Biomarker	Method	Use	LoE, GoR
EGFR mutation	Any appropriate, validated method, subject to external quality assurance	To select those patients with *EGFR*-sensitising mutations most likely to respond to EGFR TKI therapy	I, A
ALK rearrangement	Any appropriate, validated method, subject to external quality assurance. FISH is the historical standard but IHC is now becoming the primary therapy-determining test, provided the method is validated against FISH or some other orthogonal test approach. NGS is an emerging technology	To select those patients with *ALK* gene rearrangements most likely to respond to ALK TKI therapy	I, A
ROS1 rearrangement	FISH is the trial-validated standard. IHC may be used to select patients for confirmatory FISH testing but currently lacks specificity. NGS is an emerging technology. External quality assurance is essential	To select those patients with *ROS1* gene rearrangements most likely to respond to ROS1 TKI therapy	II, A
BRAF mutation	Any appropriate, validated method, subject to external quality assurance	To select those patients with *BRAF V600*-sensitising mutations most likely to respond to BRAF inhibitor, with or without MEK inhibitor therapy	II, A
PD-L1 expression	IHC to identify PD-L1 expression at the appropriate level and on the appropriate cell population(s) as determined by the intended drug and line of therapy. Only specific trial assays are validated. Internal and external quality assurance are essential	To enrich for those patients more likely to benefit from anti-PD-1 or anti-PD-L1 therapy. For pembrolizumab, testing is a companion diagnostic for nivolumab and atezolizumab, testing is complementary	I, A

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; FISH, fluorescent *in situ* hybridisation; GoR, grade of recommendation; IHC, immunohistochemistry; LoE, level of evidence; MEK, mitogen-activated protein kinase kinase; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TKI, tyrosine kinase inhibitor.

Planchard et al, Annals f Oncology 2018

Molecular testing

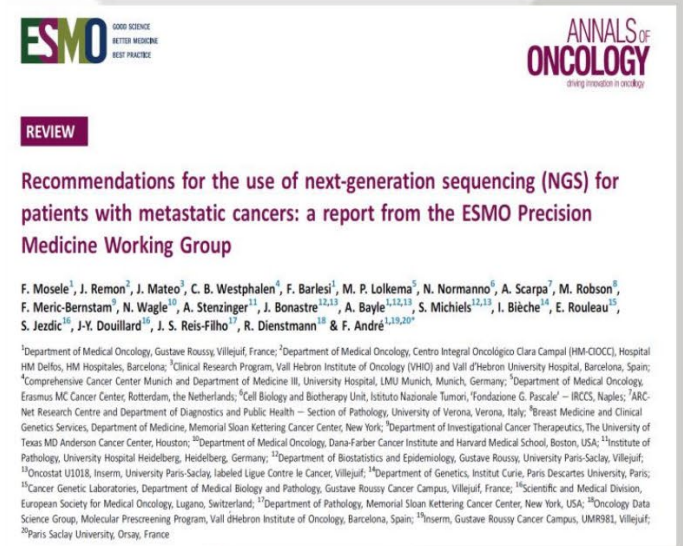
IHC	FISH	PCR	NGS
Protein expression, gene fusion products	**Gene rearrangements**	**Point mutations, small deletions/insertios** **Digital PCR may identifies rearrangements**	**Point mutations, small deletions/insertions, copy number alterations and rearrangements**
Turn-around time: 1-7 days	**Turn-around time**: 1-7 days	**Turn-around time**: 1-3 days	**Turn-around time:** 3-14 days
Benefits: Low cost Available in most laboratories Small amount of tissue needed	**Benefits:** Low cost Available in most laboratories Small amount of tissue needed	**Benefits:** Rapid test results, Available in most laboratories, Cost effective	**Benefits:** Greater ability to identify novel or heterogeneous variants; Higher sample throughput, Cost effective, Tests a wide mutational gene panel concurrently
Drawbacks Limited number of alterations Sequential testing (additional biopsy/material, more time, more costs)	**Drawbacks** Limited number of alterations Sequential testing (additional biopsy/material, more time, more costs) Fusion partner must be known	**Drawbacks** Limited number of alterations Sequential testing (additional biopsy/material, more time, more costs) Limited set of known variants	**Drawbacks** Reports can be challenging to interepret Sampling can miss tumor heterogeneity

Adapted from Pennell NA, et al . Am Soc Clin Oncol Educ Book. 2019

ESMO guidelines for NGS testing

Table 2. Summary recommendations

Tumour types	General recommendations for daily practice	Recommendation for clinical research centres	Special considerations for patients
Lung adenocarcinoma	Tumour multigene NGS to assess level I alterations. Larger panels can be used only on the basis of specific agreements with payers taking into account the overall cost of the strategy (drug included[a]) and if they report accurate ranking of alterations. NGS can either be done on RNA or DNA, if it includes level I fusions in the panel.	It is highly recommended that clinical research centres perform multigene sequencing in the context of molecular screening programmes in order to increase access to innovative drugs and to speed up clinical research. This is particularly relevant in breast, pancreatic and hepatocellular cancers where level II–IV alterations are numerous.	Using large panels of genes could lead to few clinically meaningful responders, not detected by small panels or standard testings. In this context and outside the diseases where large panels of genes are recommended, ESMO acknowledges that a patient and a doctor could decide together to order a large panel of genes, pending no extra cost for the public health care system, and if the patient is informed about the low likelihood of benefit.
Squamous cell lung cancers	No current indication for tumour multigene NGS		
Breast cancers	No current indication for tumour multigene NGS		
Colon cancers	Multigene tumour NGS can be an alternative option to PCR if it does not result in additional cost.		
Prostate cancers	Multigene tumour NGS to assess level I alterations. Larger panels can be used only on the basis of specific agreements with payers taking into account the overall cost of the strategy and if they report accurate ranking of alterations.		



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

REVIEW

Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group

F. Mosele[1], J. Remon[2], J. Mateo[3], C. B. Westphalen[4], F. Barlesi[1], M. P. Lolkema[5], N. Normanno[6], A. Scarpa[7], M. Robson[8], F. Meric-Bernstam[9], N. Wagle[10], A. Stenzinger[11], J. Bonastre[12,13], A. Bayle[1,12,13], S. Michiels[12,13], I. Bièche[14], E. Rouleau[15], S. Jezdic[16], J-Y. Douillard[16], J. S. Reis-Filho[17], R. Dienstmann[18] & F. André[1,19,20*]

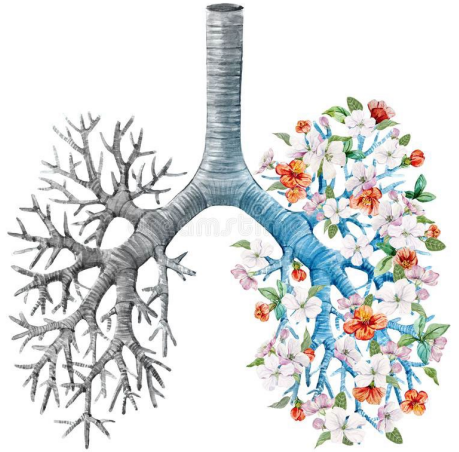
[1]Department of Medical Oncology, Gustave Roussy, Villejuif, France; [2]Department of Medical Oncology, Centro Integral Oncológico Clara Campal (HM-CIOCC), Hospital HM Delfos, HM Hospitales, Barcelona; [3]Clinical Research Program, Vall Hebron Institute of Oncology (VHIO) and Vall d'Hebron University Hospital, Barcelona, Spain; [4]Comprehensive Cancer Center Munich and Department of Medicine III, University Hospital, LMU Munich, Munich, Germany; [5]Department of Medical Oncology, Erasmus MC Cancer Center, Rotterdam, the Netherlands; [6]Cell Biology and Biotherapy Unit, Istituto Nazionale Tumori, 'Fondazione G. Pascale' – IRCCS, Naples; [7]ARC-Net Research Centre and Department of Diagnostics and Public Health – Section of Pathology, University of Verona, Verona, Italy; [8]Breast Medicine and Clinical Genetics Services, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York; [9]Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston; [10]Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, USA; [11]Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany; [12]Department of Biostatistics and Epidemiology, Gustave Roussy, University Paris-Saclay, Villejuif; [13]Oncostat U1018, Inserm, University Paris-Saclay, labeled Ligue Contre le Cancer, Villejuif; [14]Department of Genetics, Institut Curie, Paris Descartes University, Paris; [15]Cancer Genetic Laboratories, Department of Medical Biology and Pathology, Gustave Roussy Cancer Campus, Villejuif, France; [16]Scientific and Medical Division, European Society for Medical Oncology, Lugano, Switzerland; [17]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, USA; [18]Oncology Data Science Group, Molecular Prescreening Program, Vall dHebron Institute of Oncology, Barcelona, Spain; [19]Inserm, Gustave Roussy Cancer Campus, UMR981, Villejuif; [20]Paris Saclay University, Orsay, France

Mosele F. et al
Ann Oncol 2020

<u>ESMO guidelines recommend NGS testing in advanced adenocarcinomas giving the number of ESCAT grade I targets in NSCLC</u>

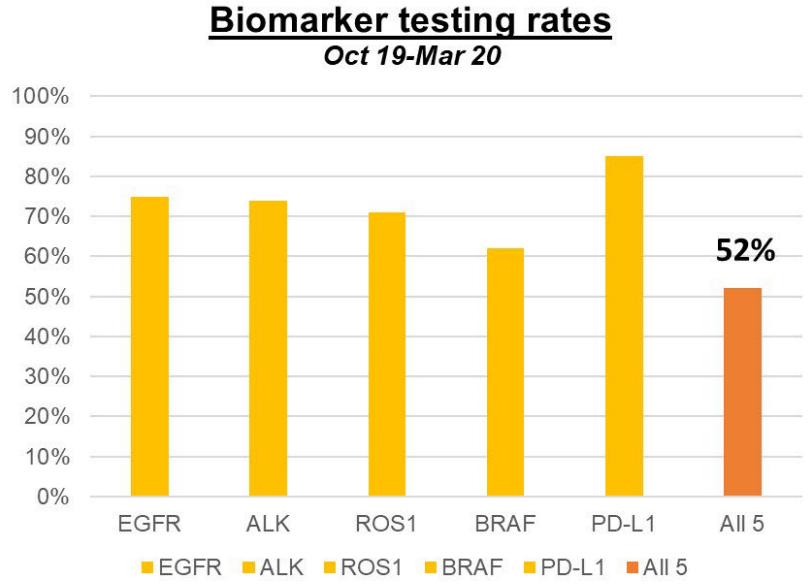
..But not all that glitters is gold

…last year 2021 ASCO ANNUAL MEETING



The US Oncology Network of community oncology practices

Screening by NGS in patients with NSCLC
N=3474 from Apr.18 to Mar.20



Robert, ASCO 2021

Challenges in the Implementation of Precision Medicine in Clinical Practice

DISEASE-SPECIFIC
Tumor evolution
Spatial heterogeneity
Difficult to access metastatic biopsies
Tissue quality

TECHNOLOGY ACCESS
Inequalities in healthcare access
Test for individual biomarker vs multiplexed profiling

DATA INTERPRETATION
Rapid knwoledge development
Data sharing
Expertise at molecular tumor boards

PRACTICE
Availability of investigations
Expertise
Funding

DATABASES

TRIALS

DRUGS

CLINICAL SUPPORT
Integrated Data
Multidisciplinary Tumor Board

TWO EXAMPLES

EPROPA
(European Program for ROutine testing of Patients with Advanced lung cancer)

EPROPA launched in December 2020, is a program addressed at European patients with advanced NSCLC.

It represents an effective diagnostic and therapeutic opportunity that allows patients to have a broad and complete molecular characterization with the optimization of the management of the biopsy material and the time required for the outcome of the molecular analysis.

WALCE - www.womenagainstlungcancer.org – www.epropa.eu

WALCE
Women Against Lung Cancer in Europe

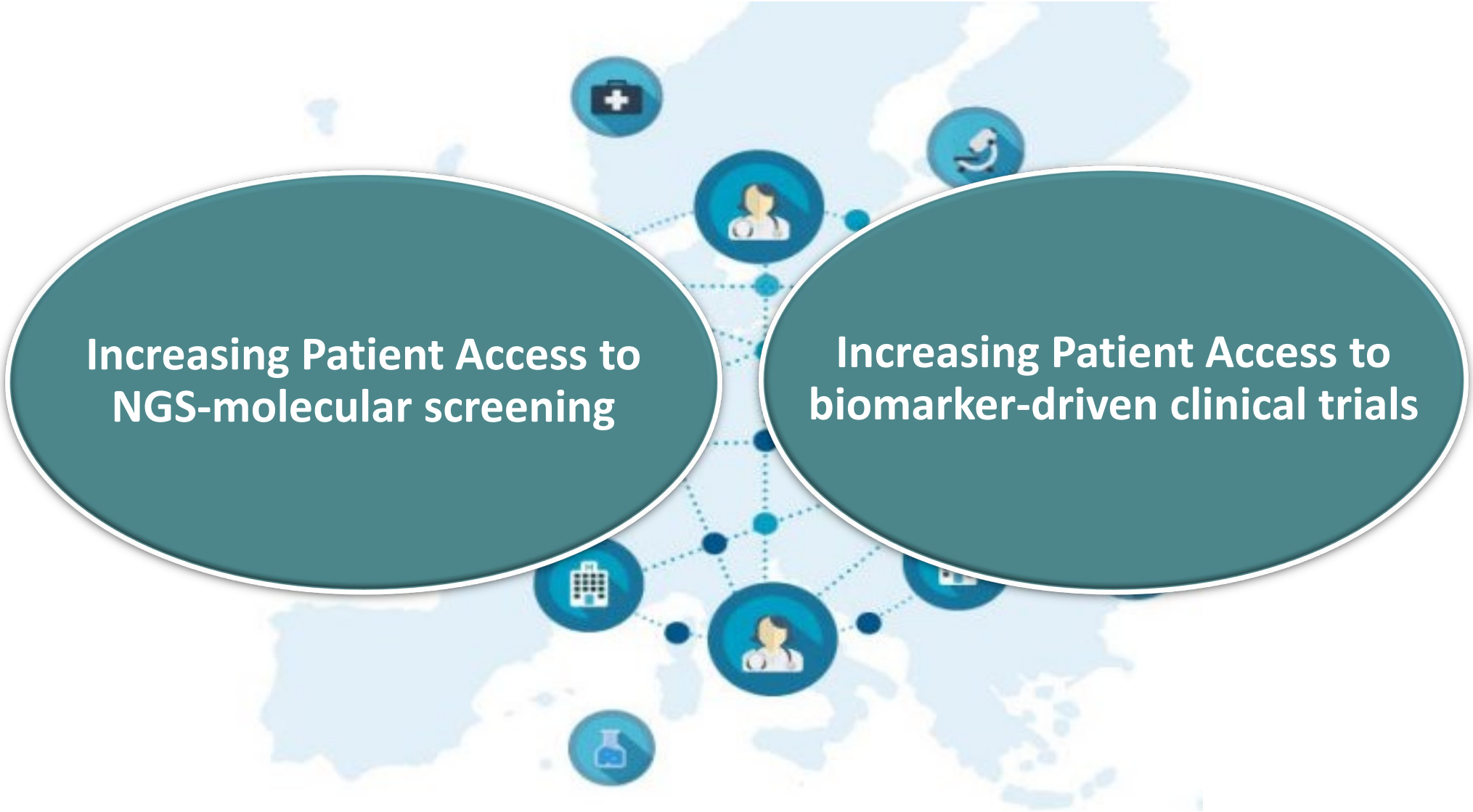
Department of Oncology
University of Turin

IASLC

EPROPA

EPROPA: goals

European Program for ROutine testing of Patients with Advanced lung cancer



EPROPA

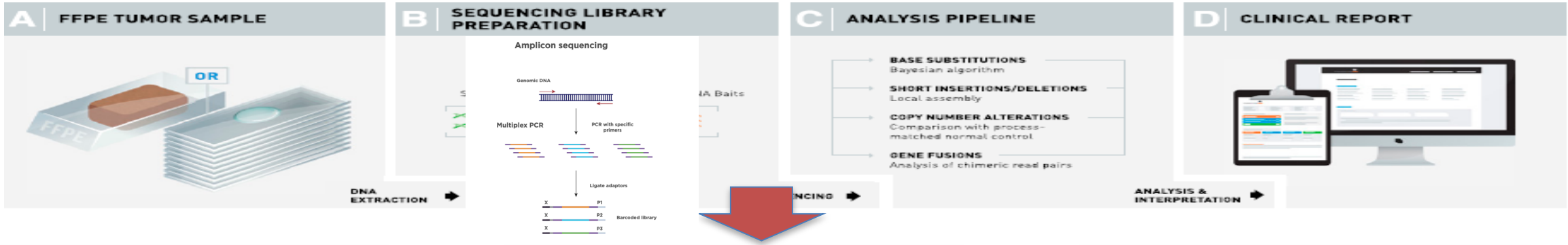
Increasing Patients' Access to NGS Molecular Screening

Patient case/Tumor samples are derived from his **doctor**

- Free shipping of tissue samples
- Free Comprehensive Molecular Profiling
- Economic and logistic support to patients and one caregiver moving throughout Europe

Molecular Tumor Board

Oncologist | **Surgeon** | **Molecular Pathol.** | **Molecular Biol.** | **Bioinformatics**

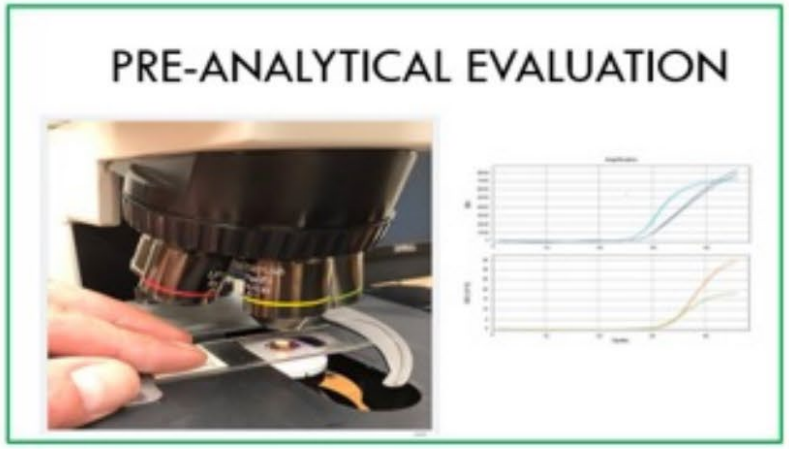


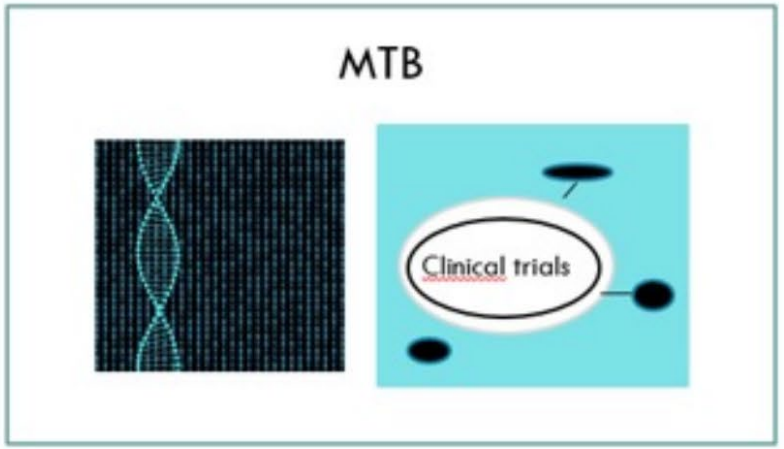
Molecular Screening → Report with therapeutic proposal → Discussion with patient and his **doctor**

Overall Turnaround Time: **7-10 days**

EPROPA WORKFLOW

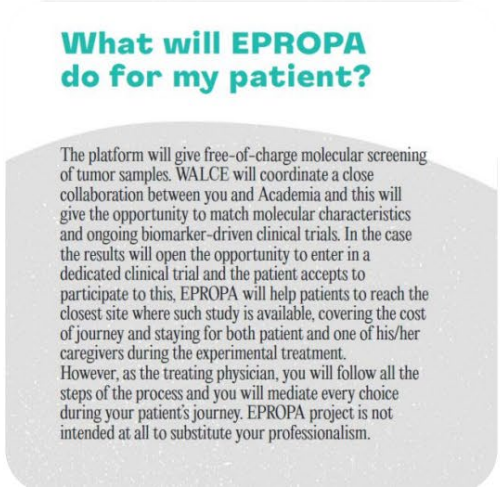
- FFPE DNA/RNA extraction, quantifications and quality control; amplicon-based NGS analysis;
- Molecular data check within genomic database (Clinvar – NCBI - NIH, COSMIC, Polyphen)



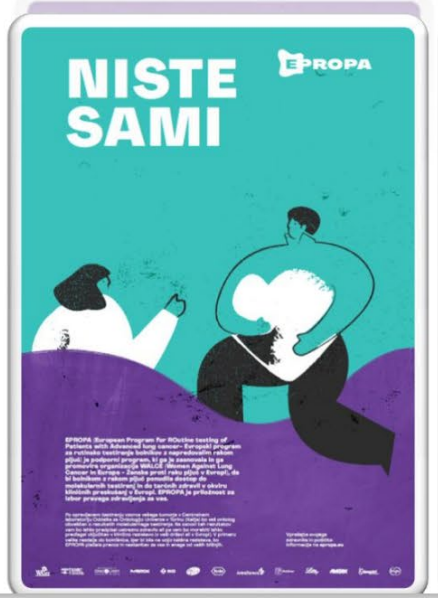


EPROPA
(European Program for ROutine testing of Patients with Advanced lung cancer)

Promotional materials:
landing page, poster, flyer for clinicians and for patients



EPROPA
(European Program for ROutine testing of Patients with Advanced lung cancer)



POSTER:
Greek
Slovenian
Spanish
Portuguese

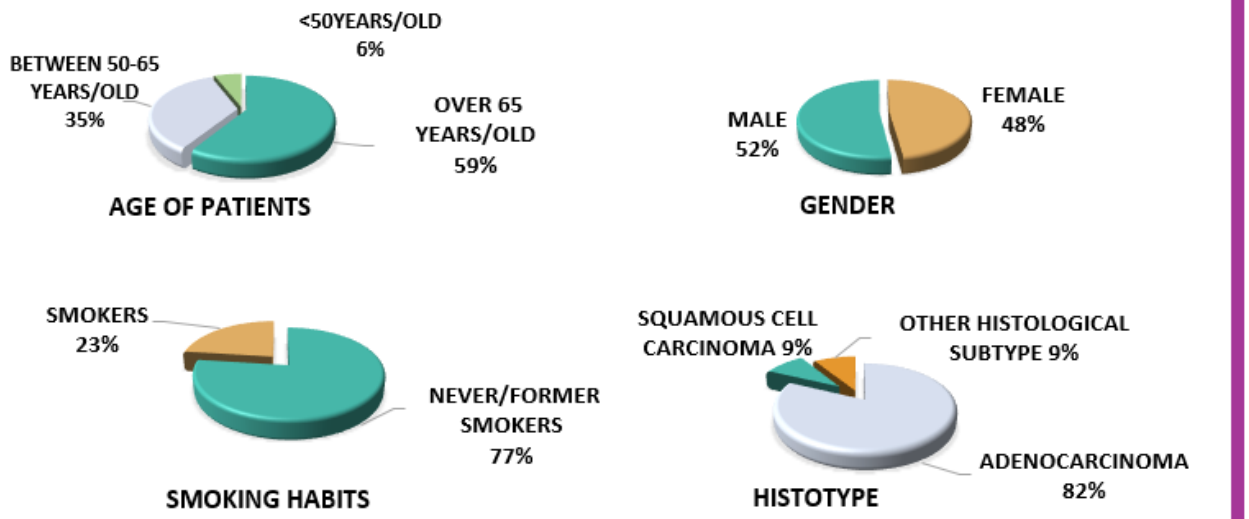
Polish
Romanian
Serbian
Italian

EPROPA Update (1/2)

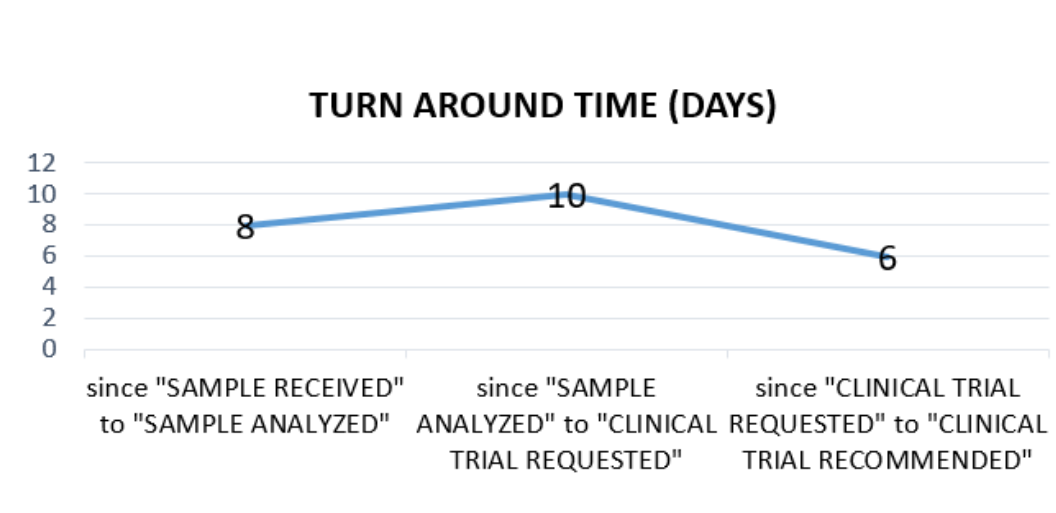
Number of patients registered: 205

Number of centers registered: 27

Number of active European countries: 6



CLINICAL PATHOLOGICAL FEATURES OF PATIENTS INCLUDED IN EPROPA



TURN AROUND TIME OF EPROPA STEPS

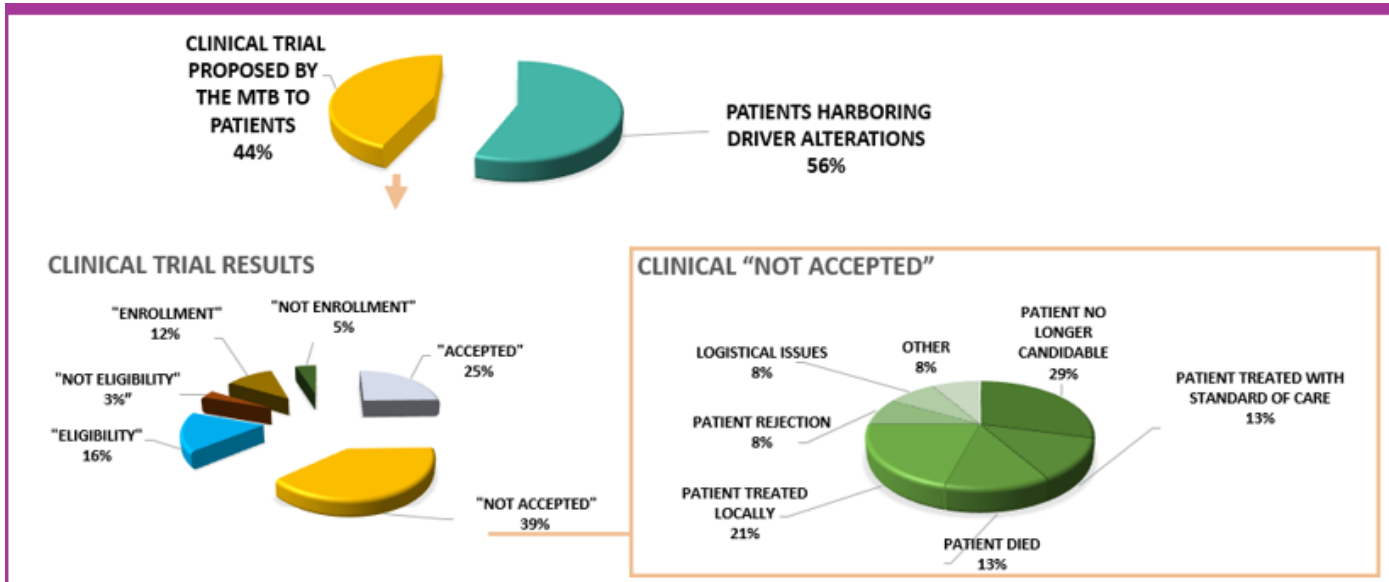
Passiglia F, WCLC 2022

EPROPA Update (2/2)

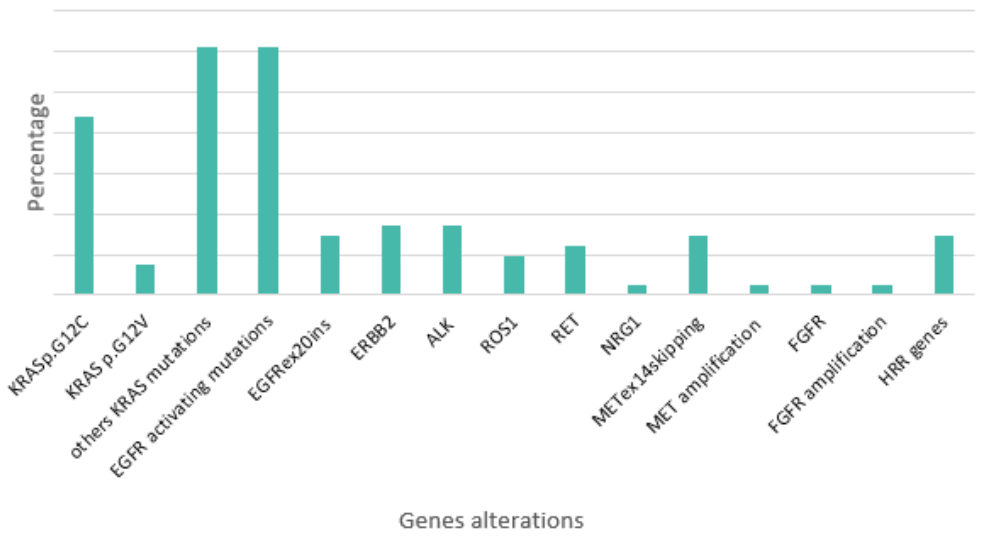
Number of patients registered: 205

Number of centers registered: 27

Number of active European countries: 6



CLINICAL TRIAL RESULTS AND ENROLLMENT IN EPROPA

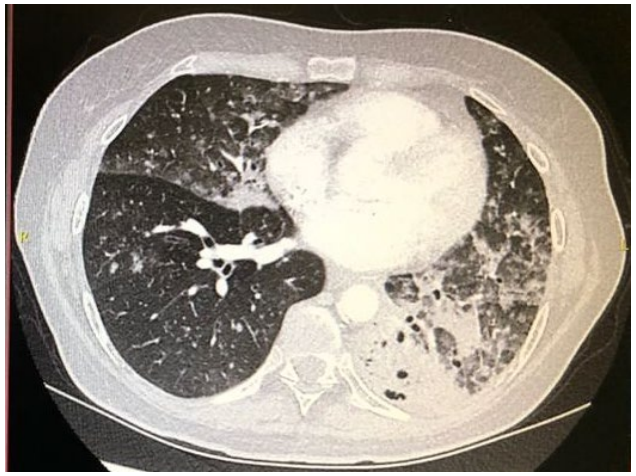


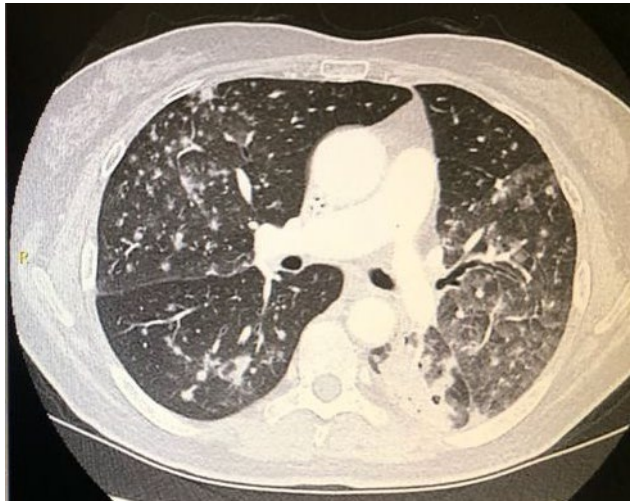
PATHOGENIC MOLECULAR ALTERATIONS (%) DETECTED IN EPROPA

Passiglia F, WCLC 2022

Female, 65 years old, never smoker, stage IVA

February 22th 2021





FNA left lung lesion

Histological evaluation: lung mucinous adenocarcinoma cells

NGS analysis by Ion Torrent Platform
(Oncomine Dx Target Test - Thermo Fisher Scientific):

EGFR/BRAF/KRAS/ERBB2: wild-type

ALK/ROS1/RET: not rearranged

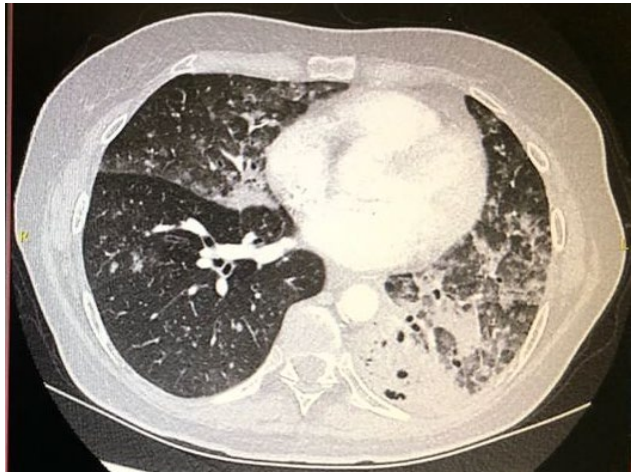
METex14skipping: negative

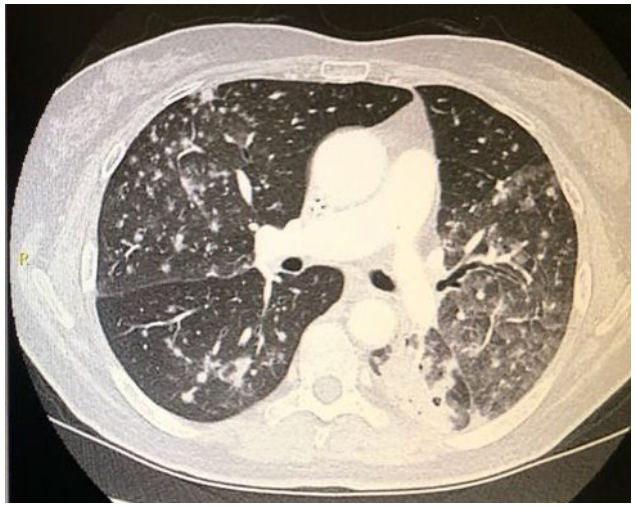
PD-L1 IHC: negative

→ **1st line chemo-immunotherapy recommended**

Chemo-Immunotherapy activity in WT NSCLC patient

Baseline Feb 2021

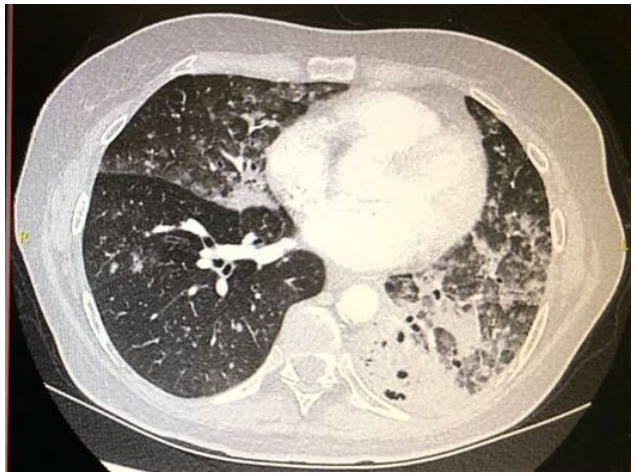


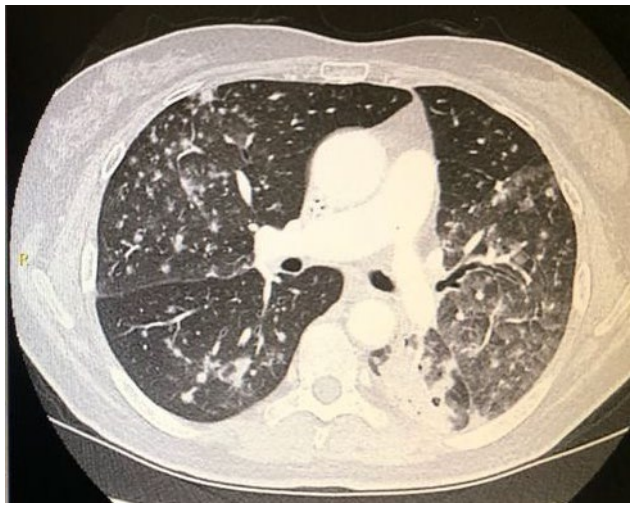


CT-scan Report after 3 months

- **SD** of the *voluminous lesion in the left inferior lobe*
- Occurrence of left pleural effusion
- Increase of the multiple *lung bilateral parenchymal nodules*

After 3 months May 2021



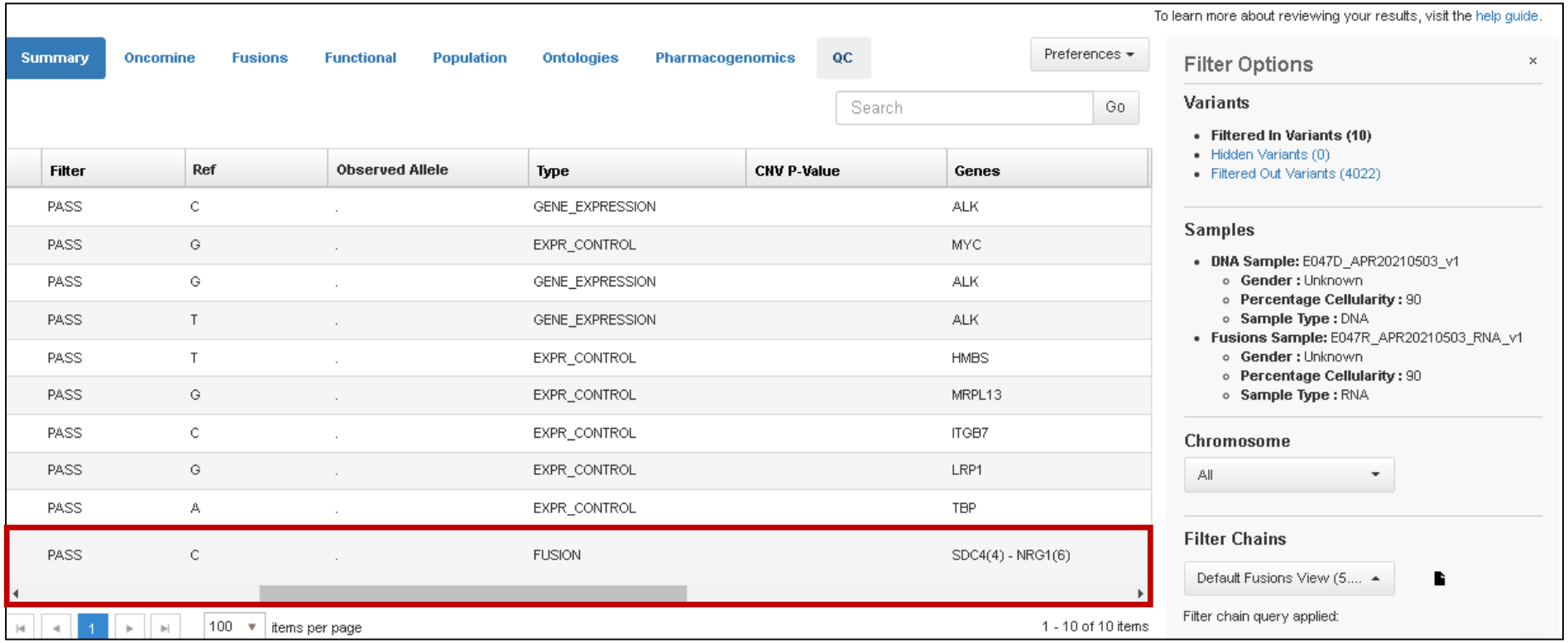


Expanded biomarker panel by EPROPA NGS profiling

May 11th 2021

NGS analysis by Ion Torrent Platform (161 genes) (Oncomine Comprehensive Panel v3 - Thermo Fisher Scientific*):

NRG1-SCDA rearrangement

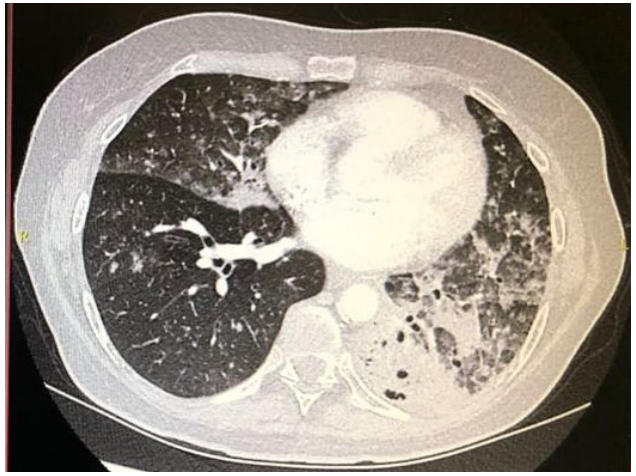


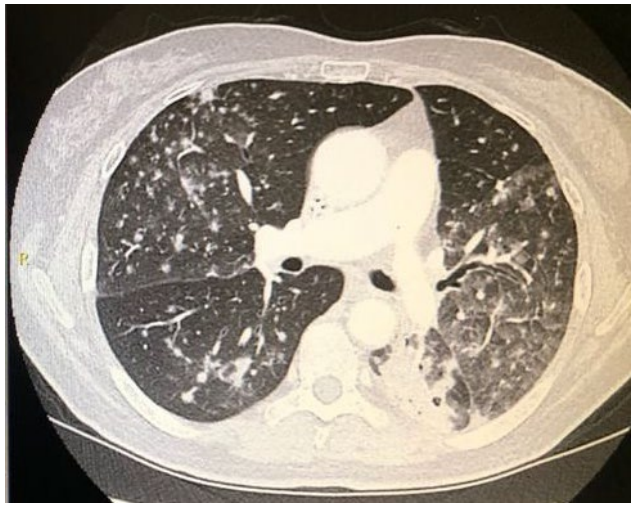
→ Phase I-II clinical trial testing Monoclonal Antibody in NRG1+ solid tumors (Milan)

** For Research Use Only*

NRG1 Inhibitor (MoAb) activity in NRG1-rearranged NSCLC patient

Baseline May 2021

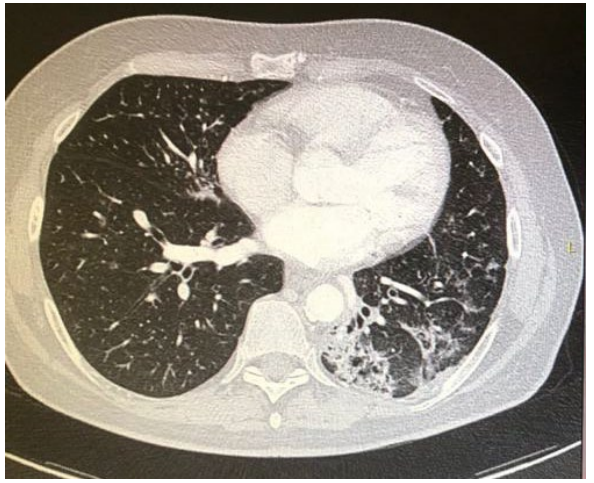


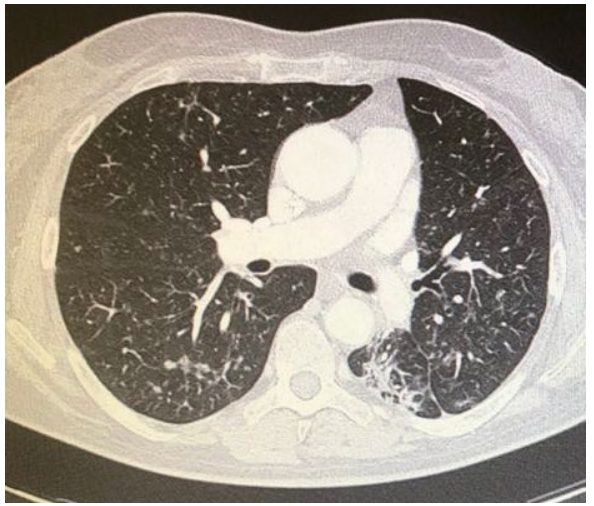


CT-scan Report after 3 months

- **Partial regression** of the *voluminous lesion in the left inferior lobe*
- Regression of left pleural effusion
- Partial regression of the multiple *lung bilateral parenchymal nodules*

After 3 months August 2021





The patient's voice:

"I have stage 4 mucinous adenocarcinoma of the lung. These words may be enough to describe my situation. If today I am still here I owe it to the competence and the humanity of my oncologist for having promptly offered me the possibility of carrying out a test for the identification of molecular alterations through a program developed by WALCE. The results of the molecular tests came after an exhausting third cycle of chemotherapy and found a genetic mutation "treatable" with an experimental molecular therapy. From May 2021, every 15 days with my daughter, I go to Milan supported by the Association and there I undergo molecular the treatment without incurring any financial expense. I am happy to have had the opportunity to do these tests and to continue receiving assistance."

(Felicina, 66 years old - Turin - Italy)

The voice of the Italian Centers

"The study in NGS in our reality is not yet reimbursed and, for about three months thanks to EPROPA program, the reality of our patients with lung cancer has completely changed. The effectiveness of this project confirms the need to centralize the molecular characterization in highly specialized centers with the availability of NGS and a dedicated team for the analysis and interpretation of the results with the aim of optimizing the diagnostic-therapeutic path of patients with lung cancer ."

(Dr. Claudio Sini - John Paul II Hospital of Olbia - Medical Oncology and CPDO Unit)

PROMOTED BY

ENDORSED BY

Supported by unrestricted grants of:

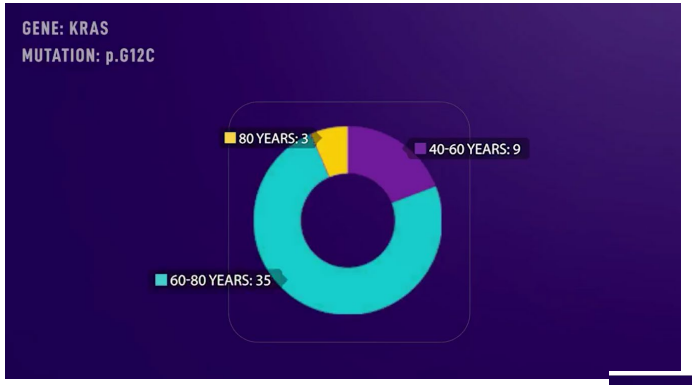
https://biomarkersatlas.com/

The application of innovative techniques and methods of analysis allows Biomarkers Atlas to guarantee complete, easily accessible and always updated data on gene mutations affecting DNA.

- A real-world mutation knowledge-based system to support the healthcare personnel in the clinical management of oncogene-addicted NSCLC patients.
- An overview of the mutation subtypes and testing practice across >10 Italian institutions in order to cover all clinically relevant genomic alterations within the actionable biomarkers in the setting of advanced NSCLC.
- 5 different categories (sex, age, smoking status, tumor histotype, and PD-L1) are also collected from included patients with metastatic NSCLC and matched with their molecular background.

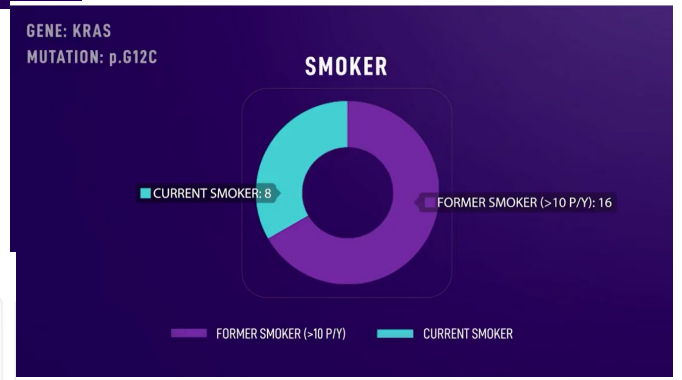
https://biomarkersatlas.com/

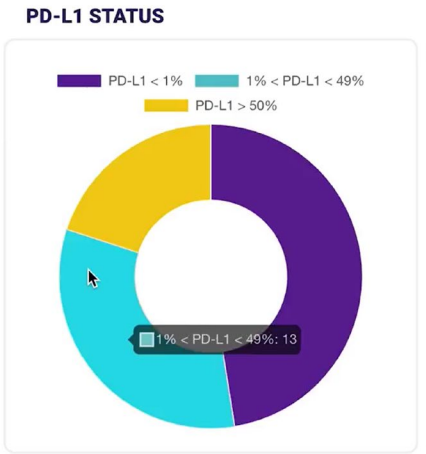
Analyze available data to get insight about pt characteristics and the correlation with a specific mutational status



age

smoking habit





PDL1 expression

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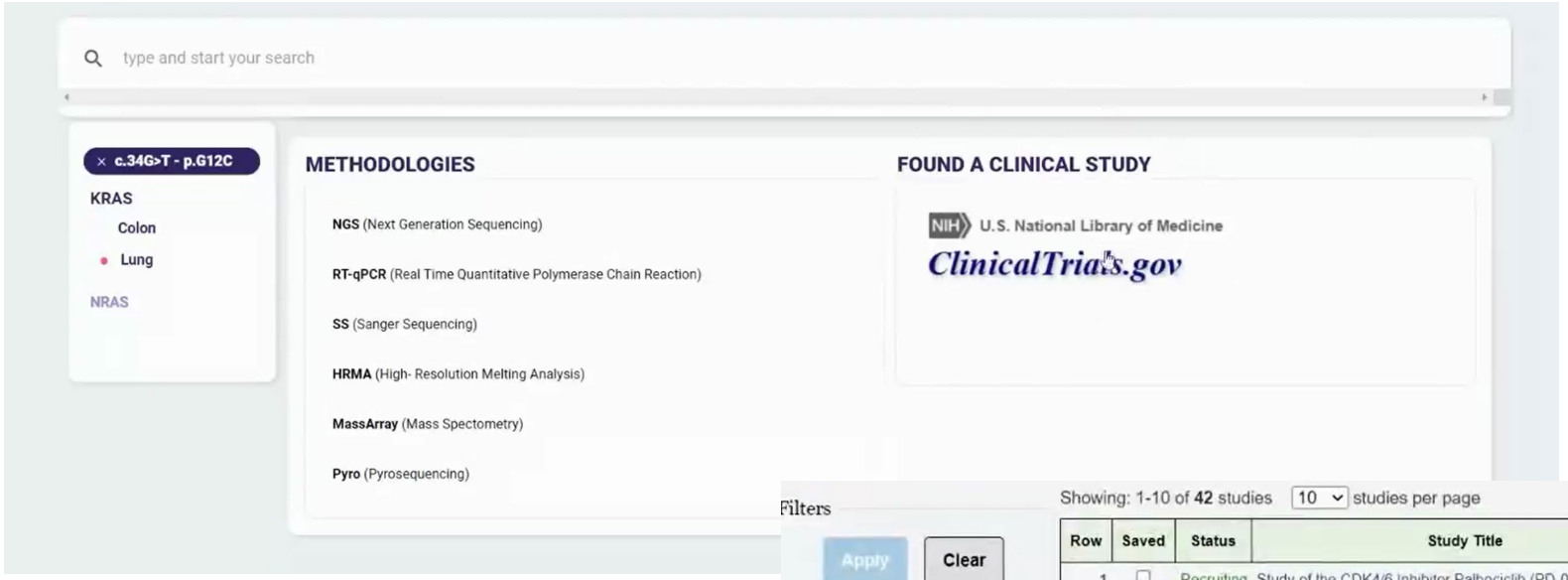
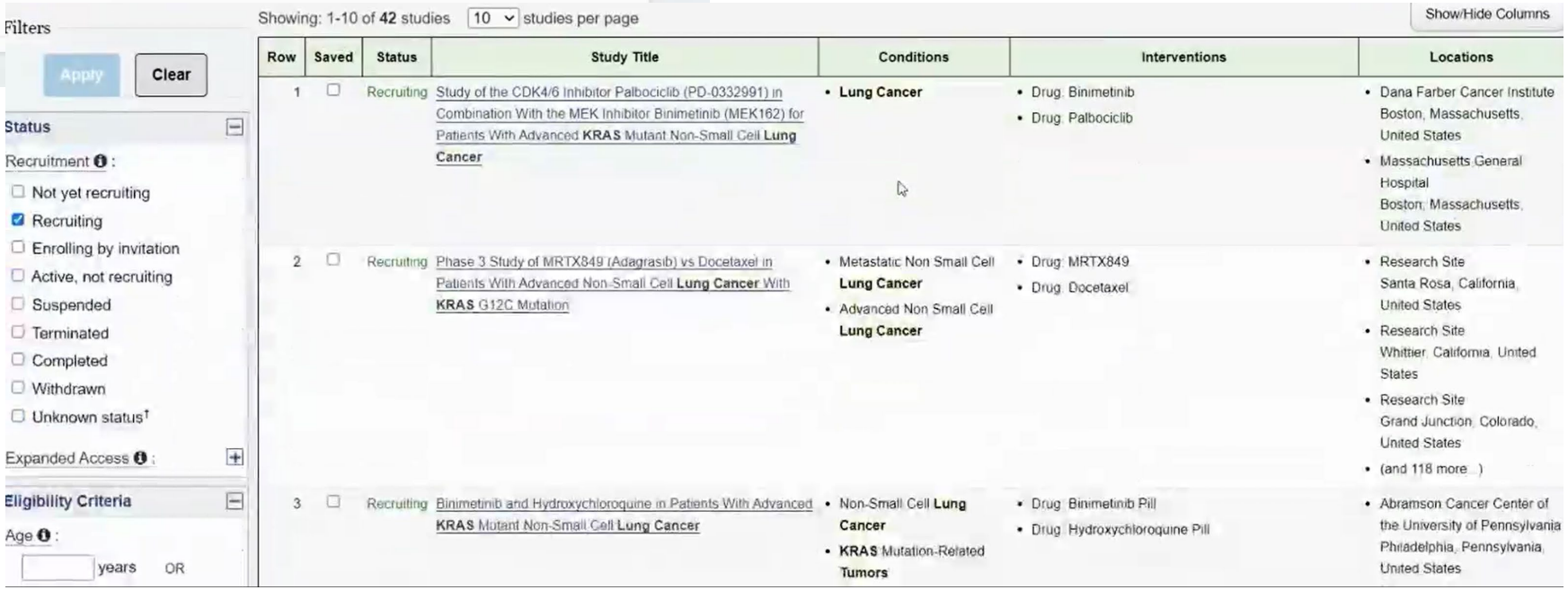


Each mutation reported in the biomarkers ATLAS is connected to pubmed indexed references and *clinicaltrials.gov*



https://biomarkersatlas.com/

Update

- 62 unique genomic alterations across 4 different genes

  (n= 35 EGFR, n=20 KRAS, n=5 NRAS and n=2 BRAF)
- Molecular data of 608 advanced NSCLC patients
- Complete clinical data of 269 patients

The program is expanding to include a total of 23 Italian institutions during the course of 2022

Malapelle U, et al WCLC 2022

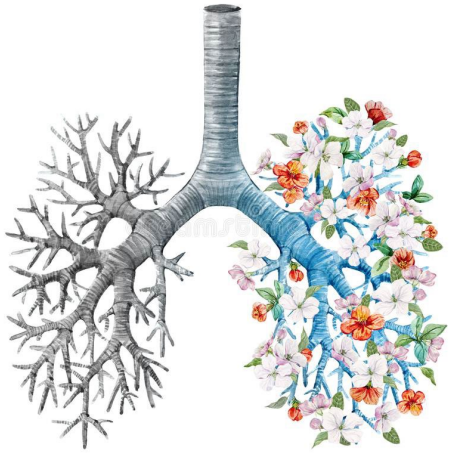
Towards a real precision medicine

1 ***Knowing more about the patient***

2 ***Knowing more about the tumor***

3 ***Knowing more about the target***

4 ***Knowing more about the drug***



TOWARDS A REAL EQUITABLE CANCER CARE