UNIVERSITY OF TORINO – DEPARTMENT OF ONCOLOGY

The Evolving Paradigm of Precision Medicine in Lung Cancer
The Oncologist Perspective

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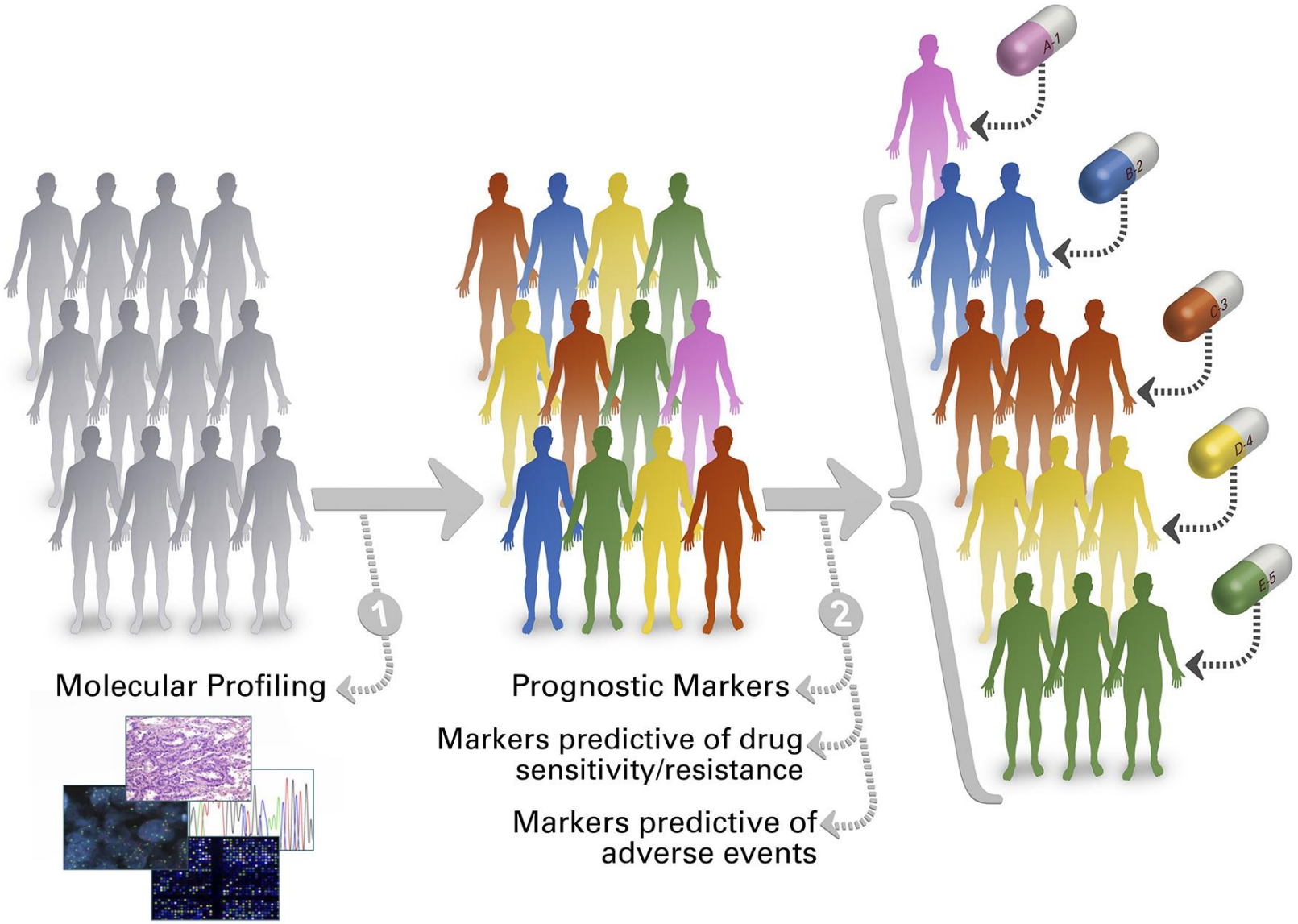
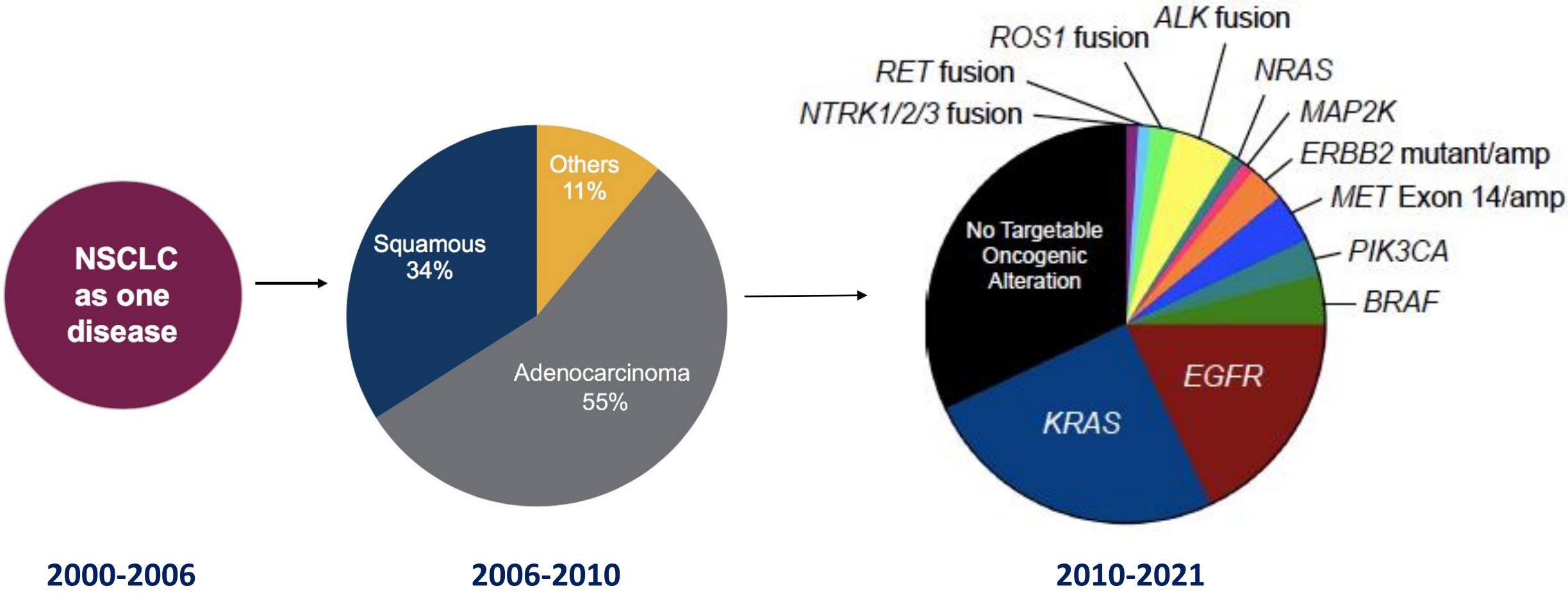
Precision Medicine in Lung Cancer

The Promise is becoming Reality



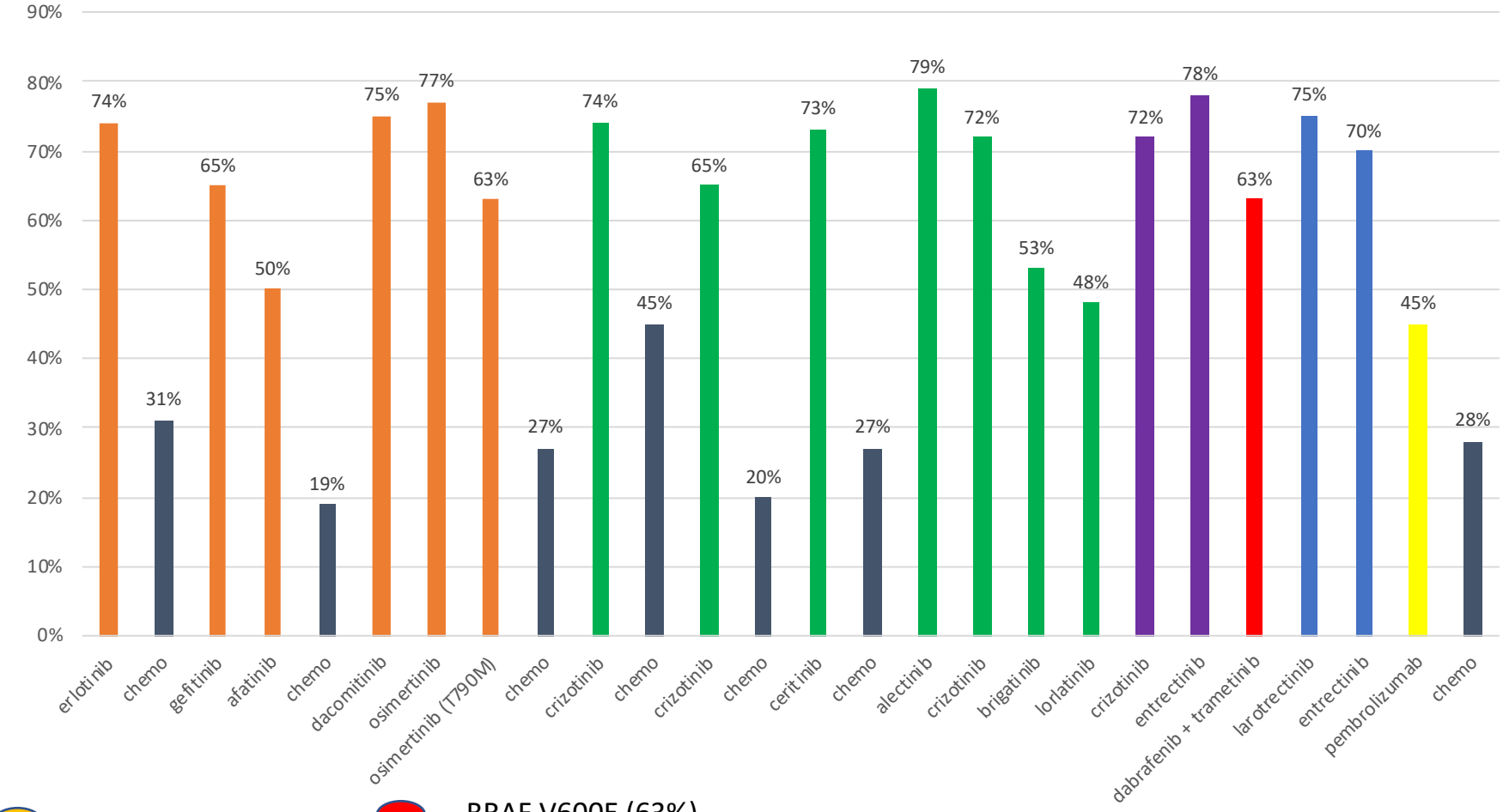
Precision Medicine in Lung Cancer

An Evolving Paradigm



Precision Medicine in Lung Cancer

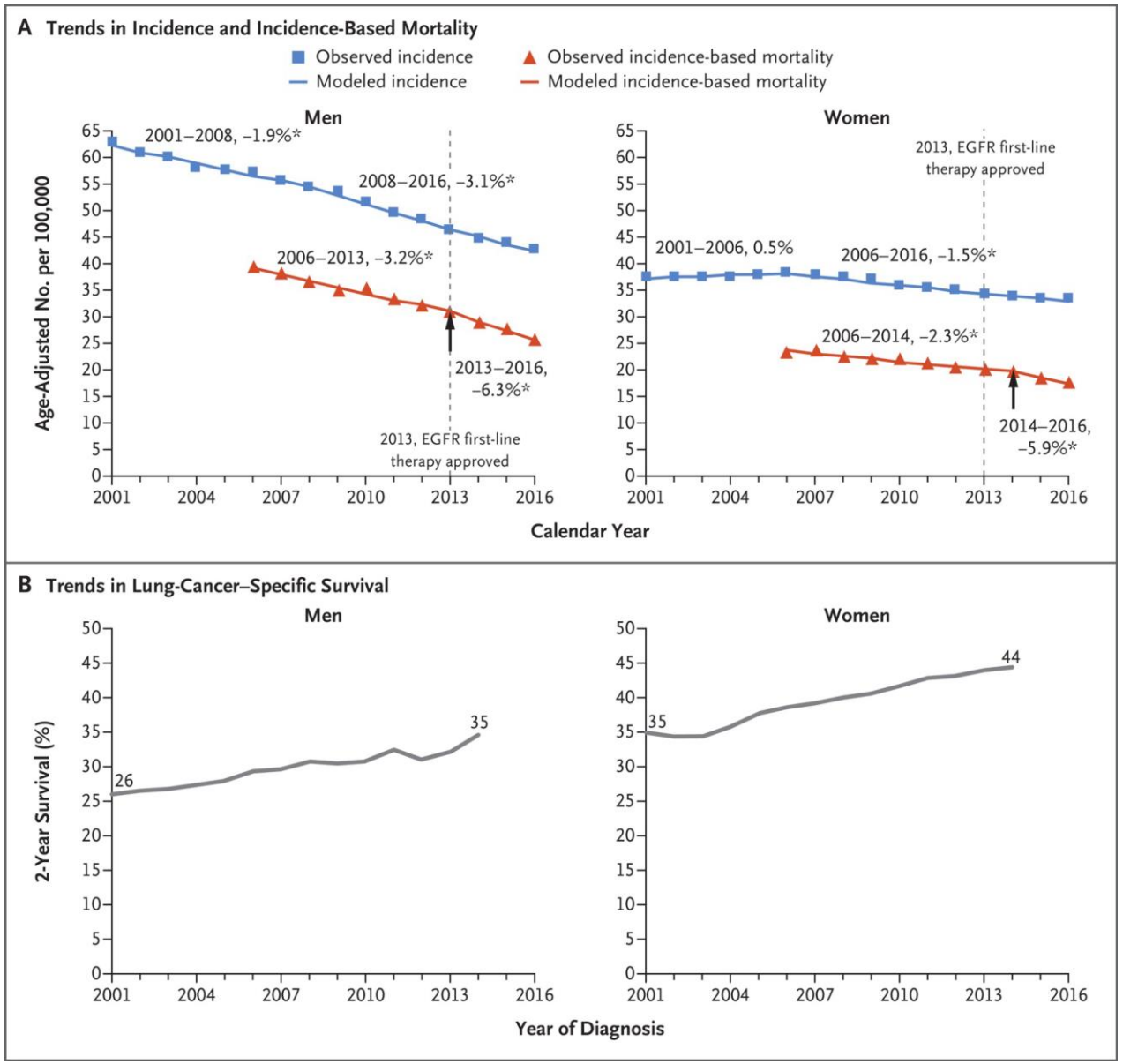
Response Rates with Targeted Therapies



- EGFR (50-77%)
- Chemo (19-45%)
- ALK (48-79%)
- ROS1 (72-78%)
- BRAF V600E (63%)
- NTRK (70-75%)
- PD-L1 ≥50% (45%)

Precision Medicine in Lung Cancer

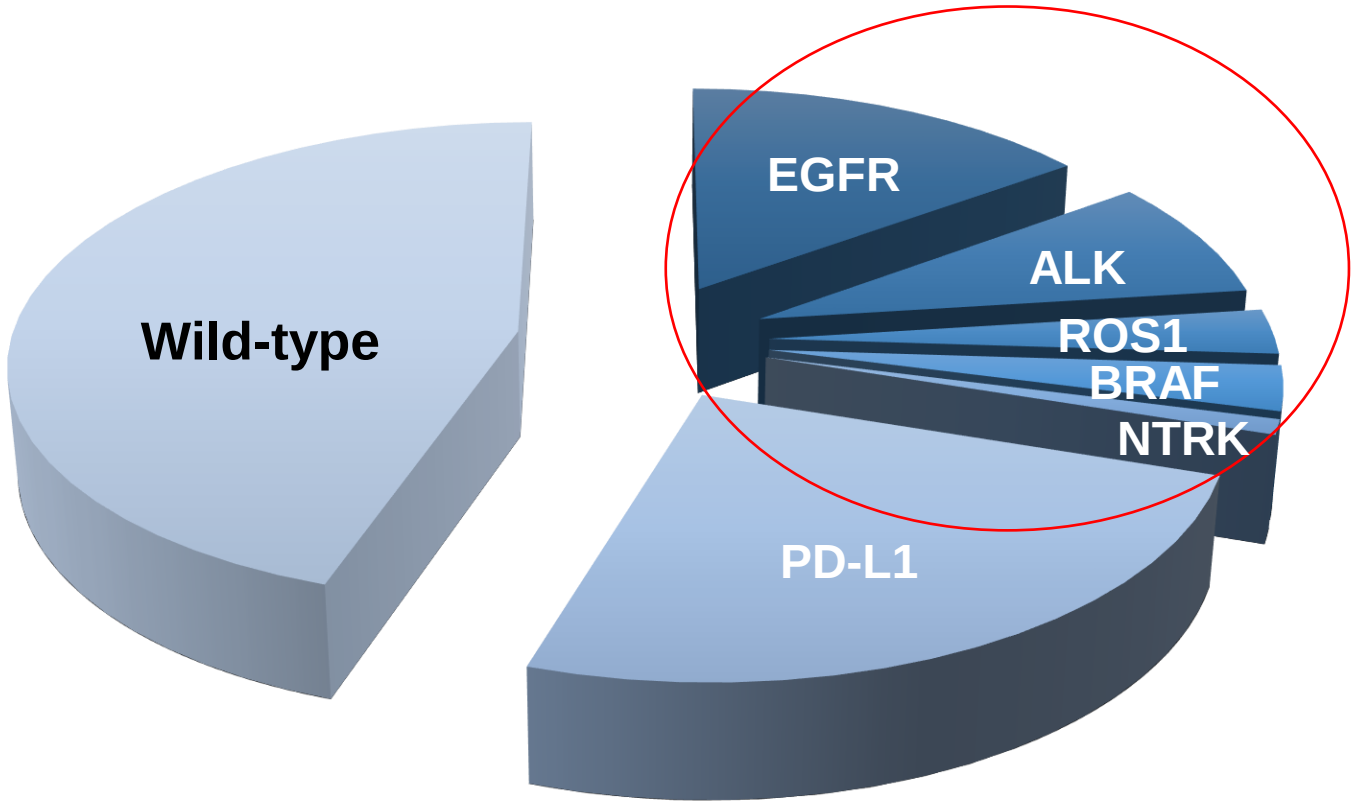
Patients' Survival with Targeted Therapies



Howlader, NEJM 2020

Molecular Testing – Predictive Biomarkers

«Must Genes» recommended by ESMO Guidelines

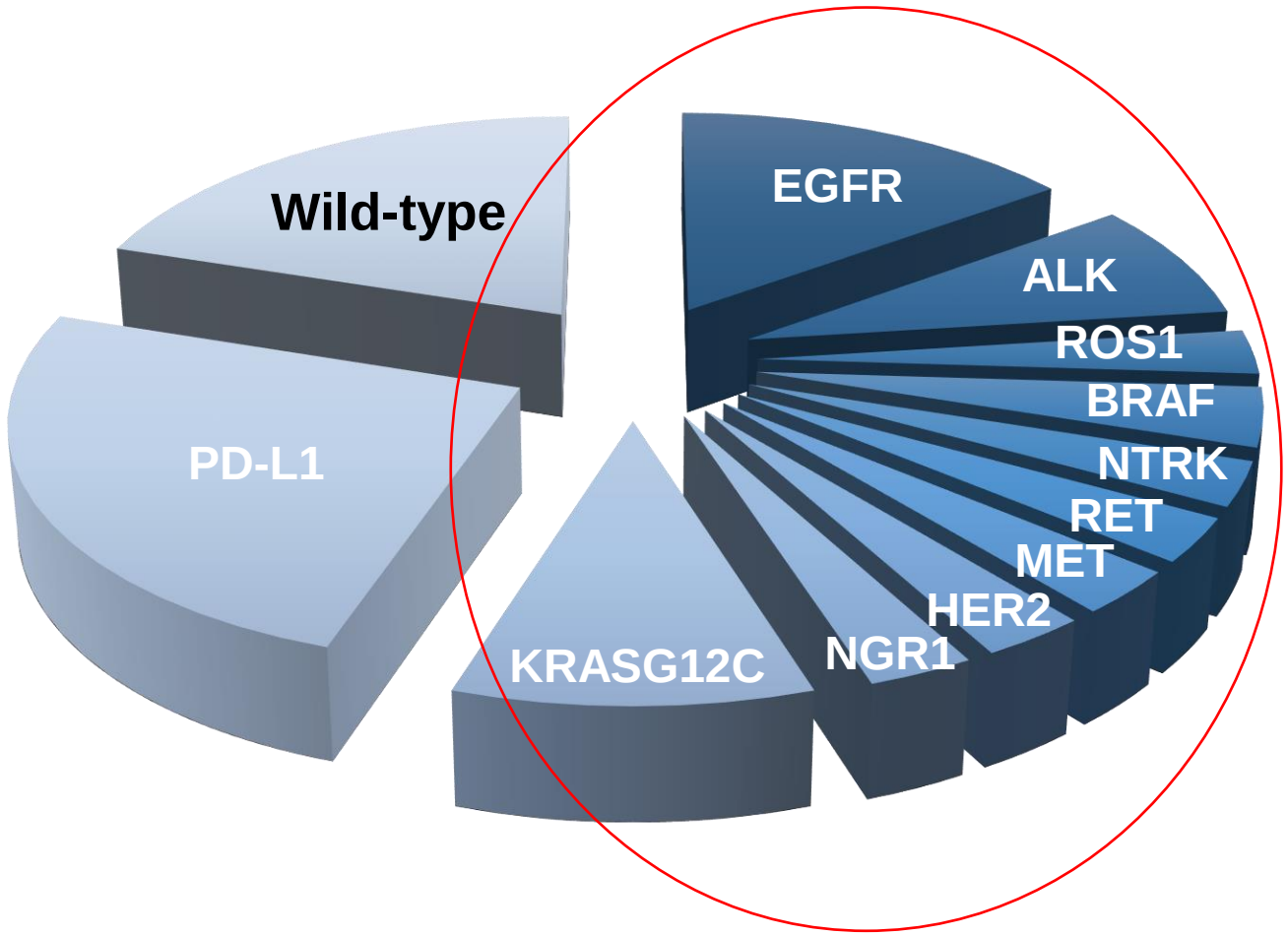


Genomic alteration	Frequency	Targeted Therapies
EGFR	12%	Osimertinib
ALK	3-8%	Alectinib
ROS1	1%	Crizotinib
BRAF	2%	Dabrafenib-Trametinib
NTRK	0.5%	Entrectinib

Planchard, Ann Oncol, Updated Sep 2020

Molecular Testing – Predictive Biomarkers

«Expanded Panel» recommended by ESMO Guidelines

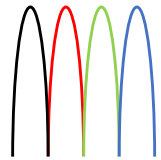
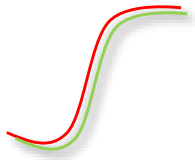
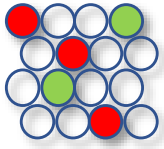
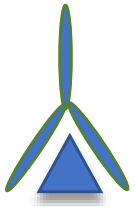
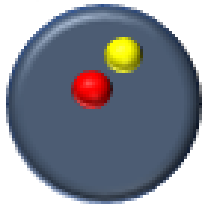
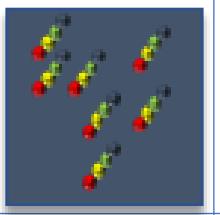
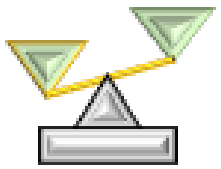
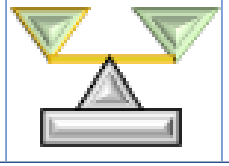
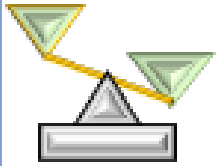
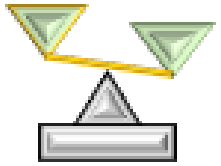
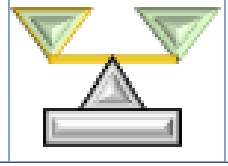
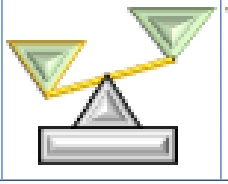
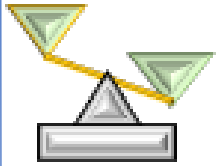


Genomic alteration	Frequency	Targeted Therapies
EGFR (classical)	12%	Osimertinib
ALK	3-8%	Alectinib
ROS1	1%	Crizotinib, Entrectinib
BRAF	2%	Dabrafenib-Trametinib
NTRK	0.5%	Entrectinib
RET	2%	Selpercatinib, Pralsetinib
METex14	2%	Capmatinib, Tepotinib
HER2	2%	Trastuzumab DxT, TDM1
KRASG12C	12%	Sotorasib
EGFR (exon20)	1-3%	Amivantamab,Mobocertinib
NRG1	0.5%	Zenocutuzumab

Planchard, Ann Oncol, Updated Sep 2020

Molecular Testing – Predictive Biomarkers

Detection Platforms

	Point mutations and Indels				Protein expression and gene fusions			
	Sanger Sequencing	Real Time PCR	Digital PCR	Next Generation Sequencing	Immuno – HistoChemistry	fluorescent In Situ Hybridization	Multiplex digital colour-coded barcode	Next Generation Sequencing
								
Limit of detection	10 – 20%	1 – 5%	0,1 – 1%	0,01– 5%	Tissue based technique (protein)	Tissue based technique (DNA)	5 – 10%	0,01– 5%
Reference Range	All the mutations present in the analyzed gene regions	Only «hot spot» Mutations (probe based)	Only «hot spot» Mutations (probe based)	All the mutations present in the analyzed gene regions	All the Fusions protein (antibody based)	Only specific fusions (probe based)	All the fusions present in the analyzed gene regions	All the fusions present in the analyzed gene regions
	FP FN	FP FN	FP FN	FP FN	FP FN	FP FN	FP FN	FP FN
								

Passiglia, J Thor Oncol 2019

Molecular Testing – Predictive Biomarkers

NGS Profiling Recommended by ESMO Panel

Gene	Alteration	Prevalence	ESCAT	References
EGFR	Common mutations (*Del19, L858R*)	15% (50%—60% Asian)	IA	Midha A, et al. *Am J Cancer Res.* 2015[26]
	Acquired *T790M* exon 20	60% of *EGFR* mutant	IA	Mok T, et al. *J Clin Oncol.* 2018[27]
	Uncommon *EGFR* mutations (*G719X* in exon 18, *L861Q* in exon 21, *S768I* in exon 20)	NSCLC	IB	Soria J-C, et al. *N Engl J Med.* 2018[28]
		10%	IIB	Ramalingam S, et al. *N Engl J Med.* 2020[29]
	Exon 20 insertions	2%		Mok T, et al. *N Engl J Med.* 2017[30] Yang JC-H, et al. *Lancet Oncol.* 2015[31] Cho J, et al. *J Thorac Oncol.* 2018[32] Cardona A, et al. *Lung Cancer.* 2018[33] Heymach J, et al. *J Thorac Oncol.* 2018[34]
ALK	Fusions (mutations as mechanism of resistance)	5%	IA	Solomon B, et al. *J Clin Oncol.* 2018[35] Soria J-C, et al. *Lancet.* 2017[36] Peters S, et al. *N Engl J Med.* 2017[37] Zhou C, et al. *Ann Oncol.* 2018[38] Camidge D, et al. *N Engl J Med.* 2018[39]
MET	Mutations *ex 14 skipping*	3%	IB	Tong J, et al. *Clin Cancer Res.* 2016[40] Drilon A, et al. *Nat Med.* 2020[41]
	Focal amplifications (acquired resistance on EGFR TKI in *EGFR*-mutant tumours)	3%	IIB	Camidge D, et al. *J Clin Oncol.* 2018[52]
BRAF^{V600E}	Mutations	2%	IB	Planchard D, et al. *Lancet Oncol.* 2016[42] Planchard D, et al. *Lancet Oncol.* 2017[43] Planchard D, et al. *J Clin Oncol.* 2017[44]
ROS1	Fusions (mutations as mechanism of resistance)	1%—2%	IB	Shaw A, et al. *N Engl J Med.* 2014[45] Shaw A, et al. *Ann Oncol.* 2019[46] Drilon A, et al. *Lancet Oncol.* 2020[47]
NTRK	Fusions	0.23%—3%	IC	Drilon A, et al. *N Engl J Med.* 2018[48] Hong D, et al. *Lancet Oncol.* 2020[49] Doebele RC, et al. *Lancet Oncol.* 2020[50]
RET	Fusions	1%—2%	IC	Drilon A, et. *J Thorac Oncol.* 2019[51]
KRAS^{G12C}	Mutations	12%	IIB	Barlesi F, et al. *Lancet.* 2016[53] Fakih M, et al. *J Clin Oncol.* 2019[54]
ERBB2	Hotspot mutations Amplifications	2%—5%	IIB	Hyman D, et al. *Nature.* 2018[55] Wang Y, et al. *Ann Oncol.* 2018[56] Tsurutani J, et al. *J Thorac Oncol.* 2018[57]
BRCA 1/2	Mutations	1.2%	IIIA	Balasubramaniam S, et al. *Clin Cancer Res.* 2017[63]
PIK3CA	Hotspot mutations	1.2%—7%	IIIA	Cancer Genome Atlas Research Network. *Nature.* 2014[60] Vansteenkiste J, et al. *J Thorac Oncol.* 2015[62]
NRG1	Fusions	1.7%	IIIB	Duruisseaux M, et al. *J Clin Oncol.* 2019[59]

NTRK	Fusions	0.23%—3%	IC	Drilon A, et al. *N Engl J Med.* 2018[48] Hong D, et al. *Lancet Oncol.* 2020[49] Doebele RC, et al. *Lancet Oncol.* 2020[50]
PIK3CA	Hotspot mutations	16%	IIIA	Cancer Genome Atlas Research Network, *Nature.* 2012[61] Vansteenkiste J, et al. *J Thorac Oncol.* 2015[62]

Mosele, Ann Oncol 2020

Female, 45 years old, never smoker, stage IVB

March 12th 2021

Thoracentesis: 2500 cc blood stained pleural effusion

Histological evaluation: lung adenocarcinoma cells

***RT-PCR Molecular analyses*:** EGFR/BRAF wild-type

***FISH*:** ROS1 not rearranged

***IHC*:** ALK Not Expressed

***IHC*:** PD-L1 TPS 65%

→ **1st line immunotherapy (pembrolizumab) recommended**

Expanded biomarker panel by NGS profiling

March 18th 2021

Second opinion at S.Luigi Hospital (Orbassano)

NGS analysis by Ion Torrent Platform (Oncomine Dx Target Test)

EGFR/BRAF/KRAS/ERBB2: wild-type

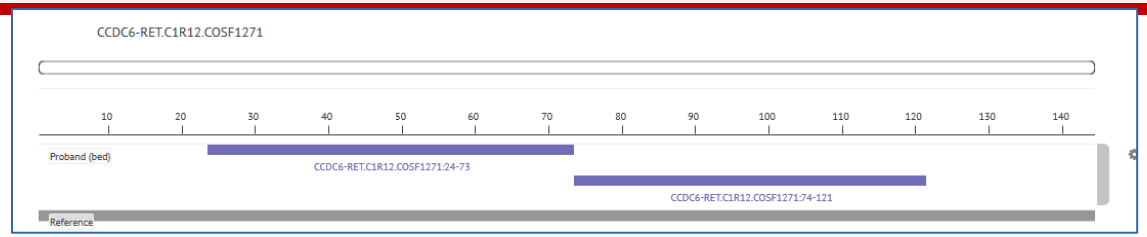
ALK/ROS1: not rearranged

METex14skipping: negative

RET-CCDC6 rearrangement

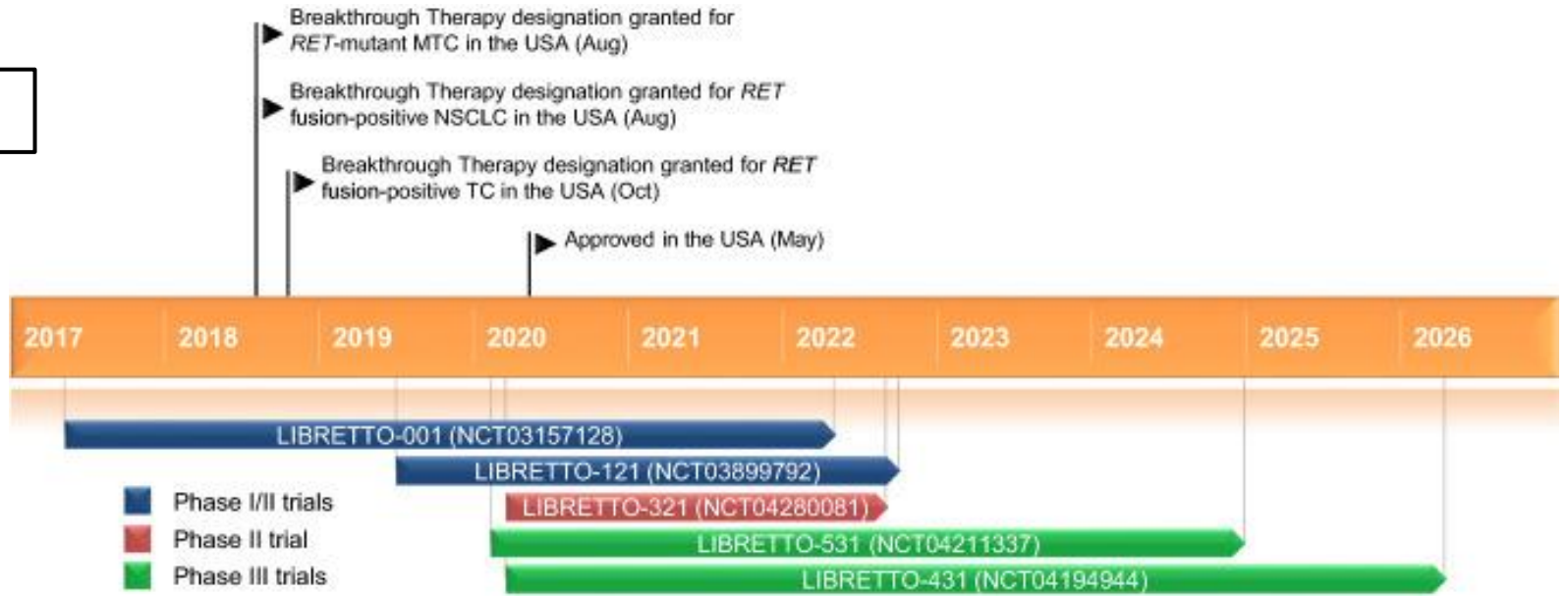
→ Randomized clinical trials (RET-TKI versus CT +/- IO)

Classification	Locus	Type	Filter	Genes (Exons)	Read	nts	Detection	3'/5' Imbalance	Ratio To Wild Type
Unclassified	chr10:43606730, chr10:43622086	ASSAYS_5P_;	NOCALL	RET		17,3848	NoCall	0.155428	
Unclassified	chr1:156834532, chr1:156851323	ASSAYS_5P_;	NOCALL	NTRK1		0,10	NoCall	4.06E-4	
Unclassified	chr2:29551347, chr2:29430138	ASSAYS_5P_;	FAIL	ALK		445,13	Absent, LOW_5P_3P_IMBA	-0.017527	
Unclassified	chr6:117711009, chr6:117632280	ASSAYS_5P_;	FAIL	ROS1		1467,1171	Absent, LOW_5P_3P_IMBA	-0.012009	
Unclassified	chr12:53585787	EXPR_CONT	PASS	ITGB7		4317	Present		
Unclassified	chr6:170871321	EXPR_CONT	PASS	TBP		5551	Present		
Unclassified	chr8:128751265	EXPR_CONT	PASS	MYC		3259	Present		
Unclassified	chr11:118960975	EXPR_CONT	PASS	HMBS		999	Present		
Unclassified	chr1:156104319	EXPR_CONT	PASS	LMNA		10522	Present		
Unclassified	chr10:61665880 - chr10:43612032	FUSION	PASS	CCDC6(1) - RET(12)		5842	Present		

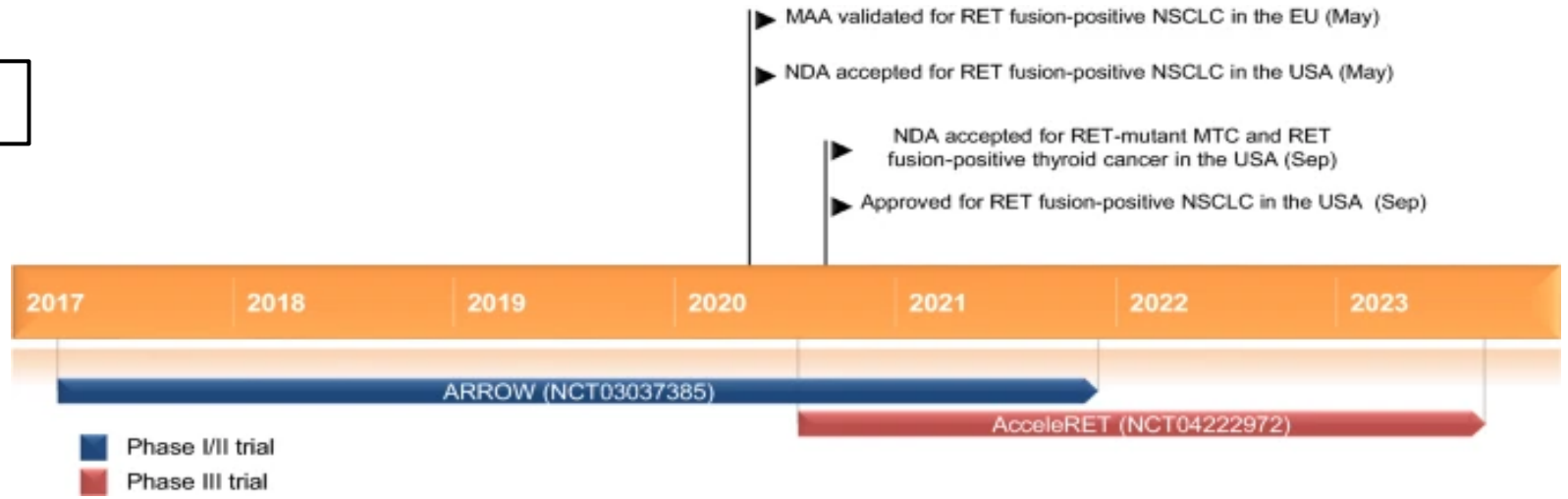


RET-TKI under clinical development

Selpercatinib



Pralsetinib



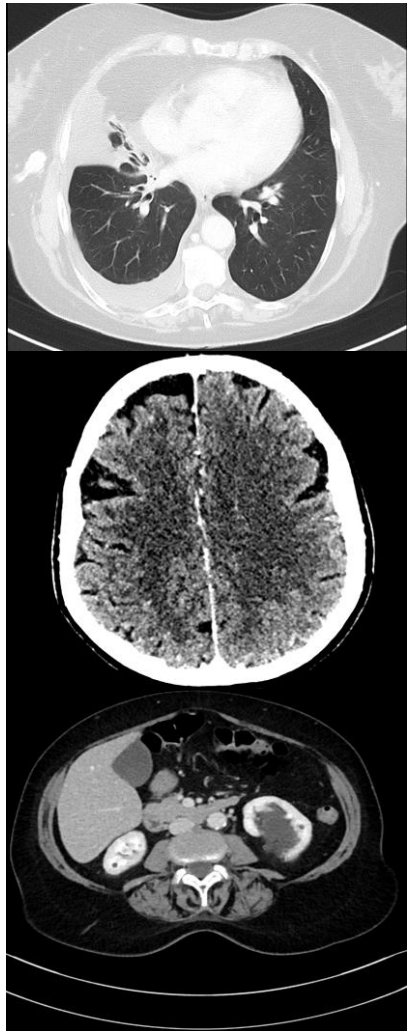
RET-TKI activity in RET-CCDC6 rearranged NSCLC patient

Baseline March 2021

CT-scan Report after 3 months

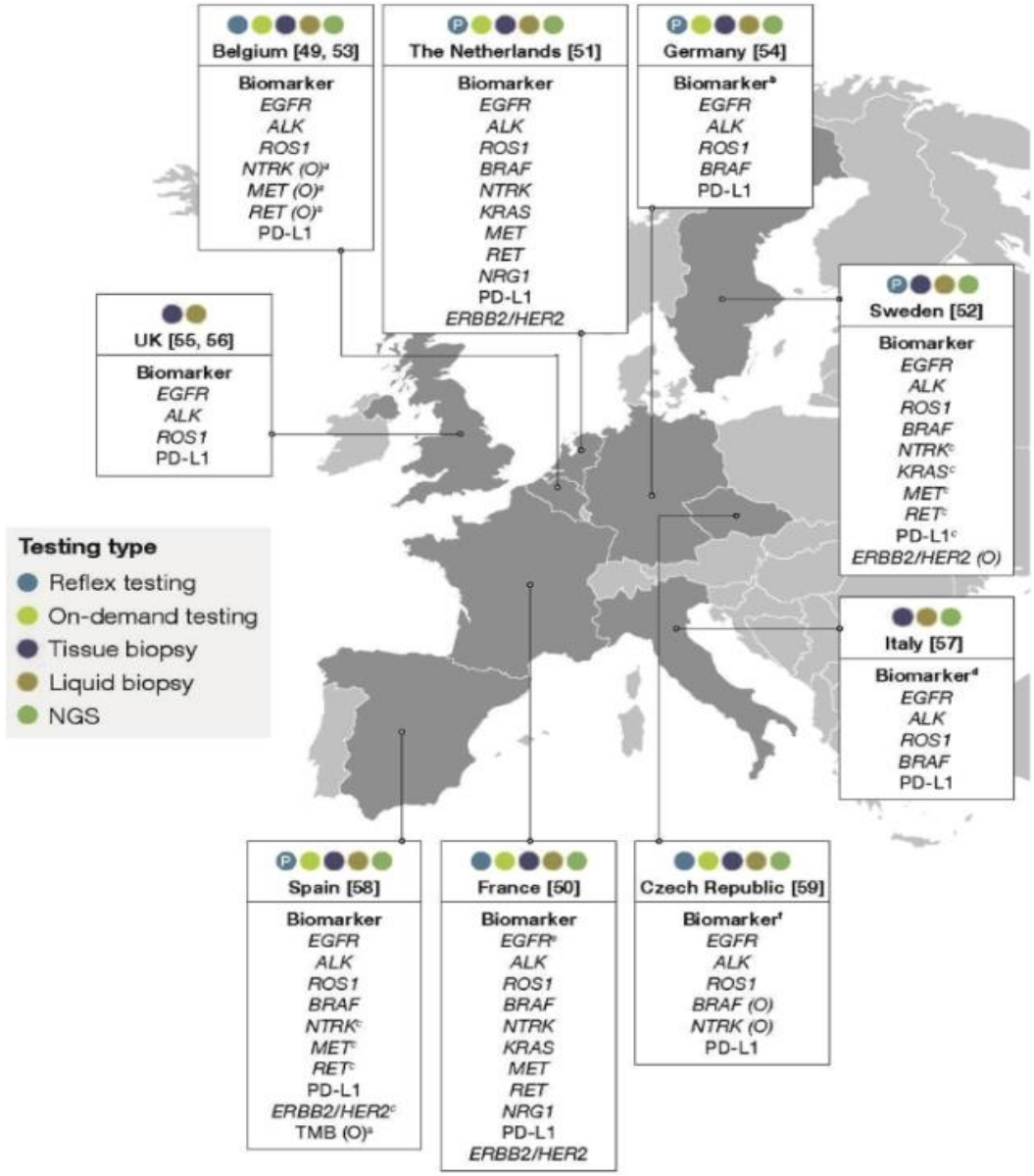
- **Partial regression** of the *voluminous lesion in the right perihilar site*
- Almost **complete regression** of the multiple *lung bilateral parenchymal nodules*
- **Complete regression** of the *cerebral nodules*
- **Partial response** of the multiple bilobular *hepatic hypodense lesions*

After 3 months June 2021



Molecular Testing – Predictive Biomarkers

Disparities across European Countries



	ALK	EGFR	PD-L1	ROS1	BRAF	MET	KRAS
Croatia							
Denmark							
Finland							No data
France							
Germany							
Ireland							
Israel							
Italy							
Latvia							No data
Norway							No data
Poland							
Portugal							No data
Romania							
Slovenia							
Spain							
Sweden							
Switzerland							No data
The Netherlands							
Turkey		No data		No data		No data	
United Kingdom							

Table 1. Availability of lung cancer molecular tests (November 2019).

Reimbursed

Not reimbursed

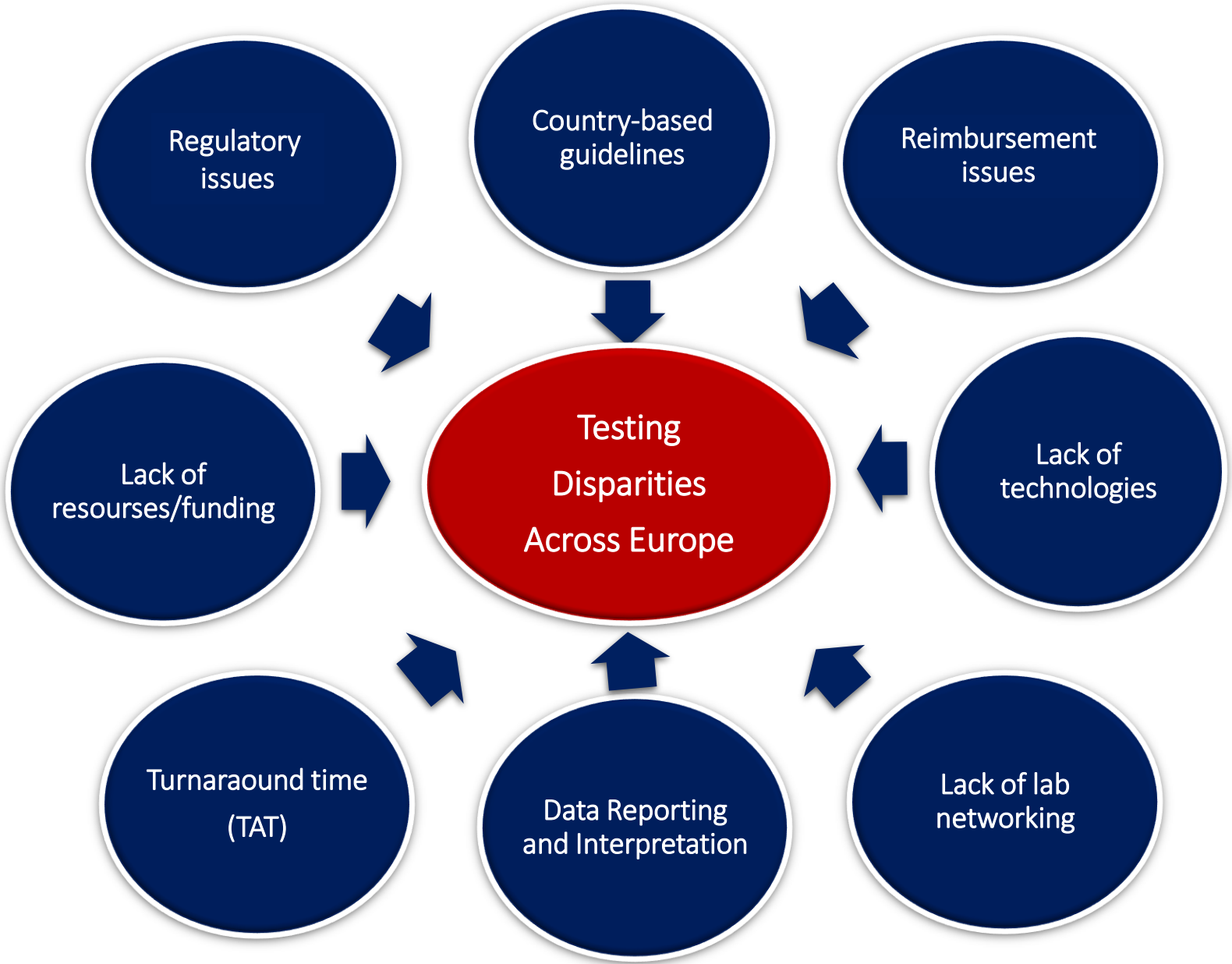
Contradictory data

With reimbursement, we refer to tests that are available for all patients, and therefore are not self-paid by the patient

Kerr, Lung Cancer 2021, LuCE Position Paper 2019

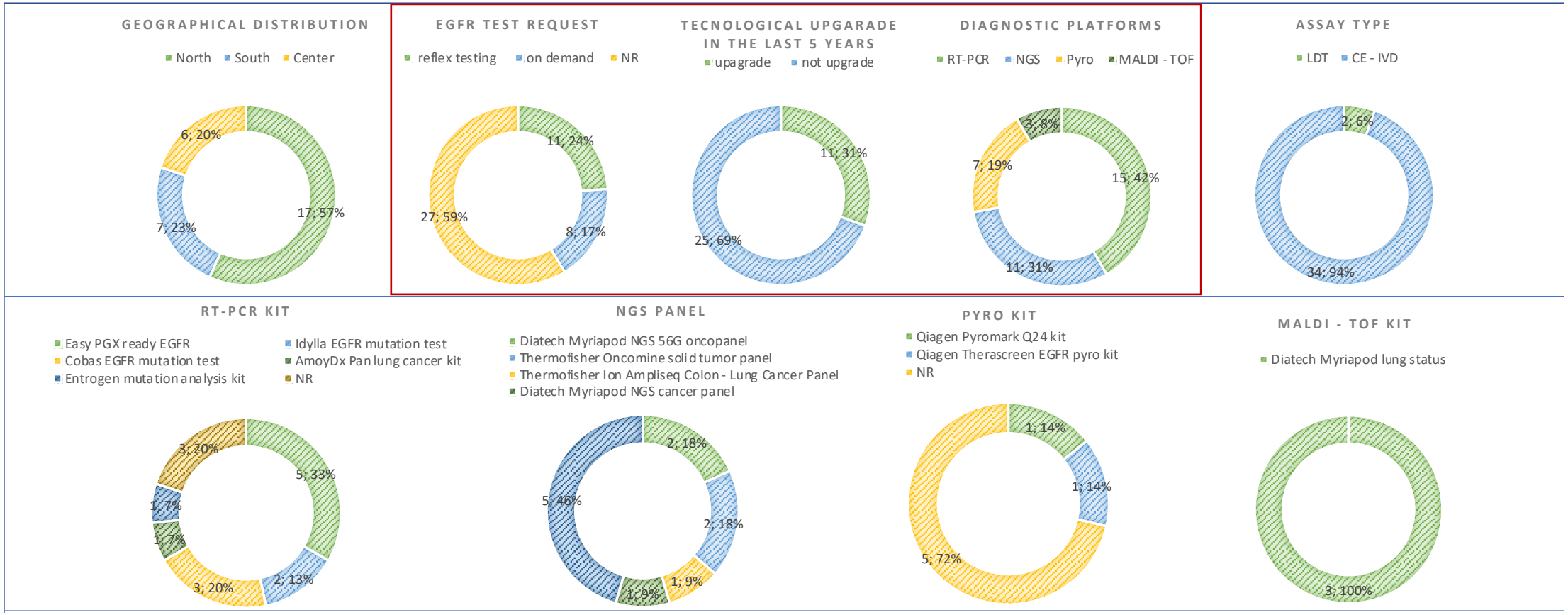
Molecular Testing – Predictive Biomarkers

Challenges and Barriers across European Countries



Molecular Testing – Predictive Biomarkers

Italian Scenario in 2021

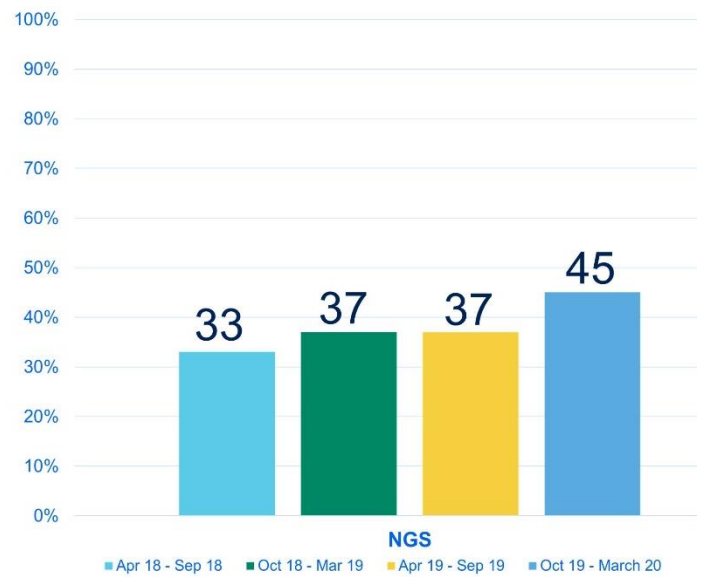


Malapelle, Crit Rev Oncol/Haematol 2021

Molecular Testing - Predictive Biomarkers

US Scenario in 2021

Test types	Overall N=3474	Nonsquamous N=2820
EGFR	70%	76%
ALK	70%	76%
ROS1	68%	73%
BRAF	55%	59%
PD-L1	83%	83%
Any biomarker	90%	91%
All 5 biomarker tests	46%	49%
NGS	37%	39%



Patients with non-squamous NSCLC	Non-squamous N=10,333	White N=6,705	Black/AA N=922	P-value, White vs Black/AA
Ever tested	8,786 (85.0%)	5,699 (85.0%)	764 (82.9%)	0.09
Tested prior to first line therapy		4,881 (72.8%)	662 (71.8%)	0.52
Ever NGS tested	5,494 (53.2%)	**3,668 (54.7%)**	**404 (43.8%)**	**<0.0001**
NGS tested prior to first line therapy		**2,452 (36.6%)**	**274 (29.7%)**	**<0.0001**

Adapted from Lovly, ASCO 2021

#ASCO21
Equity: Every Patient. Every Day. Everywhere.

Biomarker testing in Lung Cancer

- ✓ ***Represents the standard of care***
- ✓ ***Assists in identifying therapeutic options for our patients***
- ✓ ***Important eligibility criteria for clinical trials***

Are we meeting the mark??

EPROPA

European Program for ROutine testing of Patients with Advanced lung cancer

Increasing Patient Access to NGS-molecular screening

Increasing Patient Access to biomarker-driven clinical trials

https://www.epropa.eu/it/

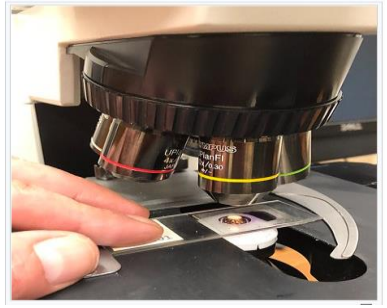
EPROPA

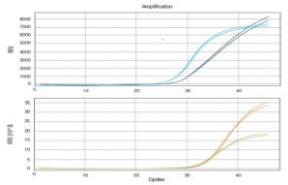
Project and Workflow

All patients with histological diagnosis of NSCLC; stage IIIB/C-IV (8th TNM); FFPE tissue sample availability for molecular analysis may participate

- FFPE DNA/RNA extraction, quantifications and quality control;
- NGS analysis by Ion Torrent Platform (161 genes) (Thermo Fisher Scientific);
- Molecular data check within genomic database (Clinvar - NCBI – NIH, COSMIC, *Polyphen*);
- MTB Discussion and Clinical Trials Identification (Clinicaltrialgov.It);
- Logistic Support to the patients during the diagnostic/therapeutic process

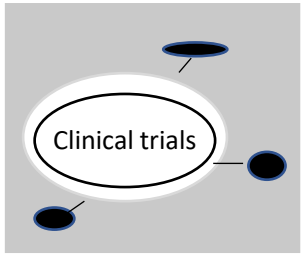
PRE-ANALYTICAL EVALUATION





NGS ANALYSIS WORKFLOW

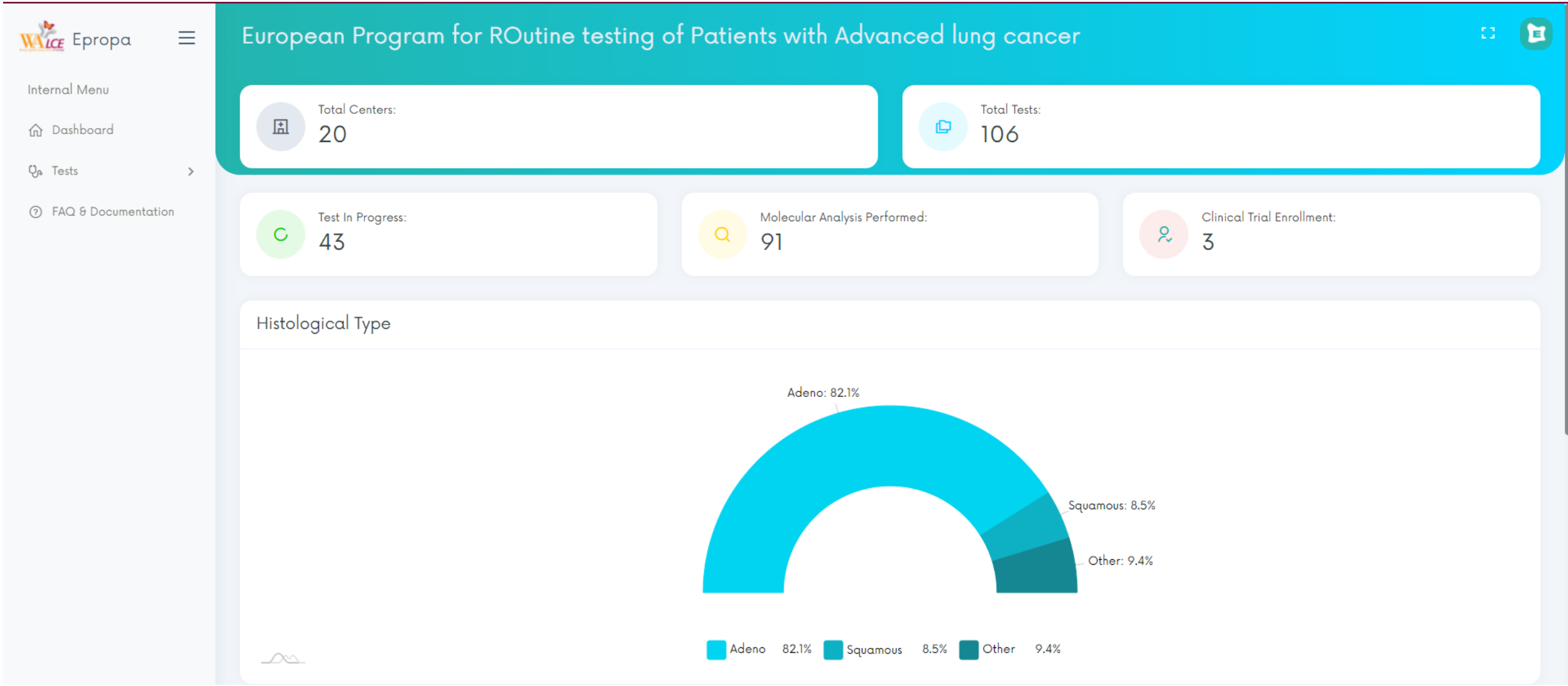
MTB



EPROPA

The Website Platform

https://www.epropa.eu/



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):

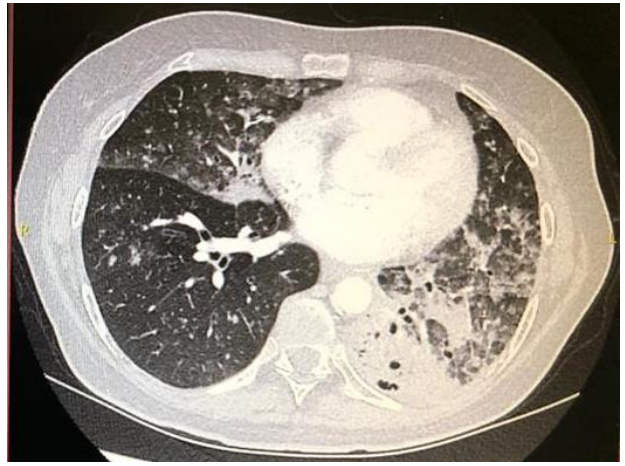
EGFR/BRAF/KRAS/ERBB2: wild-type

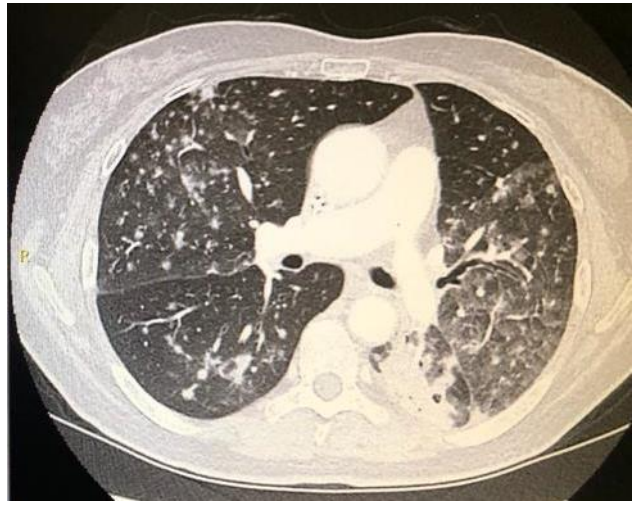
ALK/ROS1/RET: not rearranged

METex14skipping: negative

PD-L1 IHC: negative

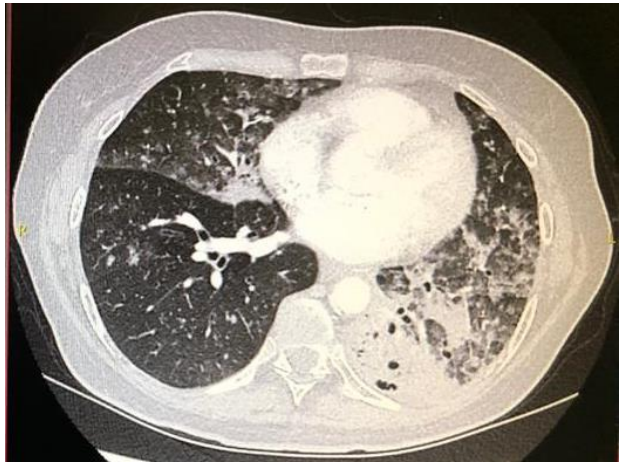
→ **1st line chemo-immunotherapy recommended**





Chemo-Immunotehrapy activity in WT NSCLC patient

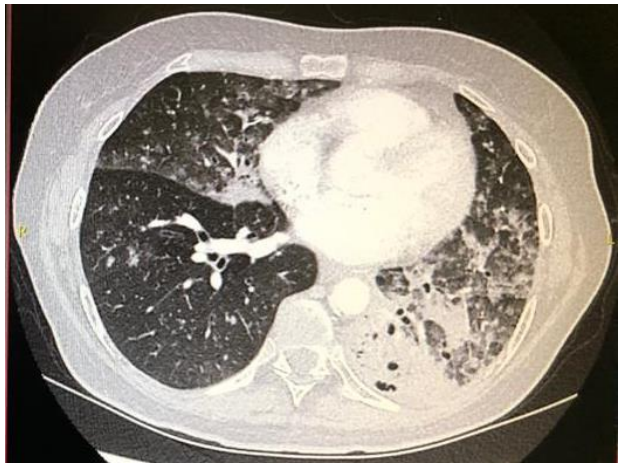
Baseline Feb 2021

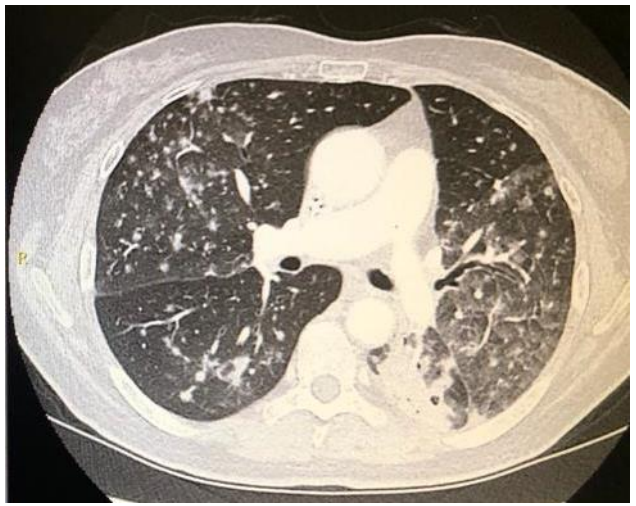


CT-scan Report after 3 months

- **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



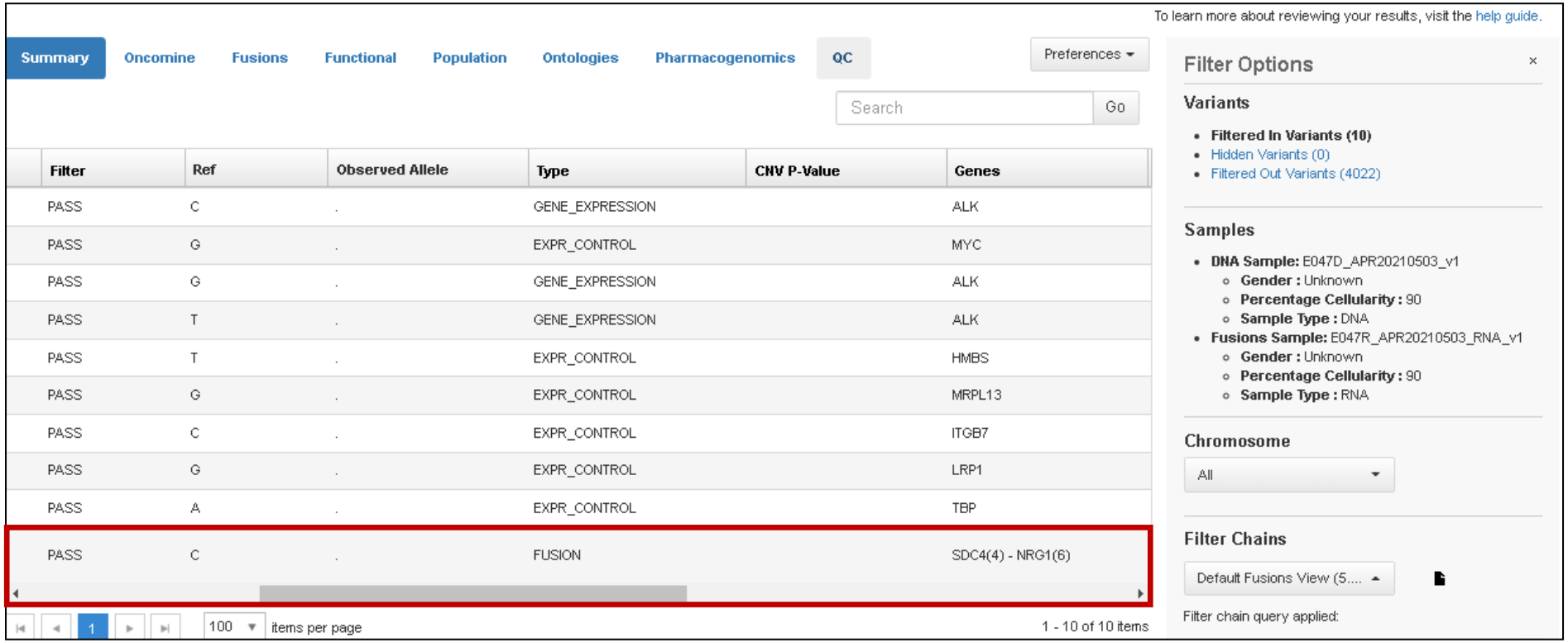


Expanded biomarker panel by ERPOPA NGS testing

May 11th 2021

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

NRG1-SCDA rearrangement

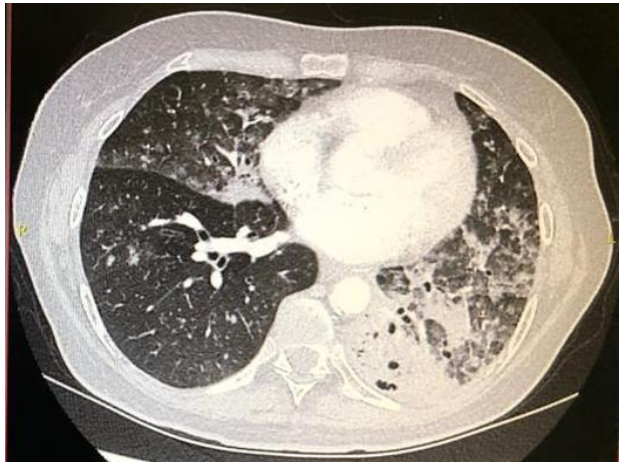


Filter	Ref	Observed Allele	Type	CNV P-Value	Genes
PASS	C	.	GENE_EXPRESSION		ALK
PASS	G	.	EXPR_CONTROL		MYC
PASS	G	.	GENE_EXPRESSION		ALK
PASS	T	.	GENE_EXPRESSION		ALK
PASS	T	.	EXPR_CONTROL		HMBS
PASS	G	.	EXPR_CONTROL		MRPL13
PASS	C	.	EXPR_CONTROL		ITGB7
PASS	G	.	EXPR_CONTROL		LRP1
PASS	A	.	EXPR_CONTROL		TBP
PASS	C	.	FUSION		SDC4(4) - NRG1(6)

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

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

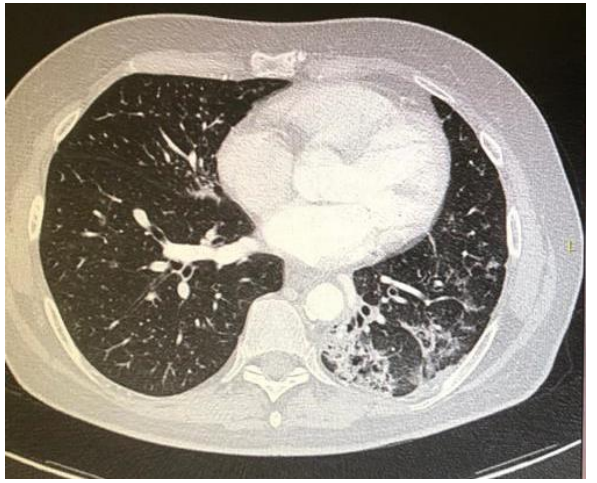
Baseline May 2021

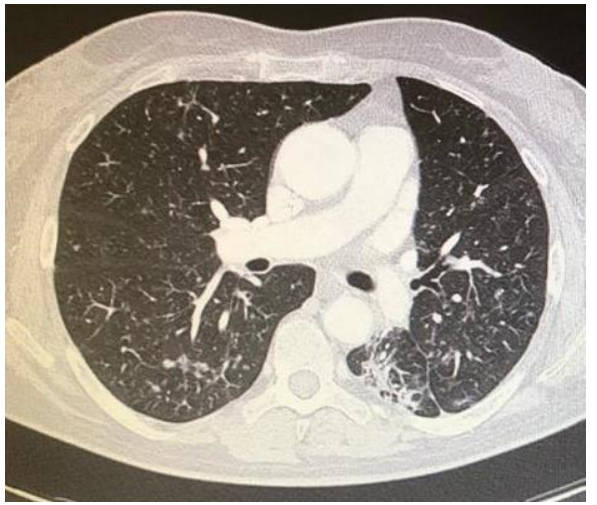


CT-scan Report after 3 months

- **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 Evolving Paradigm of Precision Medicine in Lung Cancer

The oncologist perspective

- Precision medicine is the way forward
- Rapidly increasing of predictive biomarkers and targeted therapies
- Molecular testing is standard of care
- Aiming to broad biomarker testing by NGS analysis upfront
- Overcoming barriers to NGS molecular testing
- Reducing patients' access disparities to biomarker testing and cancer care

“Providing equitable care for our patients is our North Star, and it requires constant attention and reinforcement…”
– Dr. Lori J. Pierce, MD, FASCO, FASTRO

Polaris, image: Wikisky

… and PARTNERSHIPS between academic centers, community centers, patients, patient advocates, pharma / biotech, payers, and regulatory bodies. A team approach to show solidarity towards generating solutions, advancing knowledge, attaining equity for all.