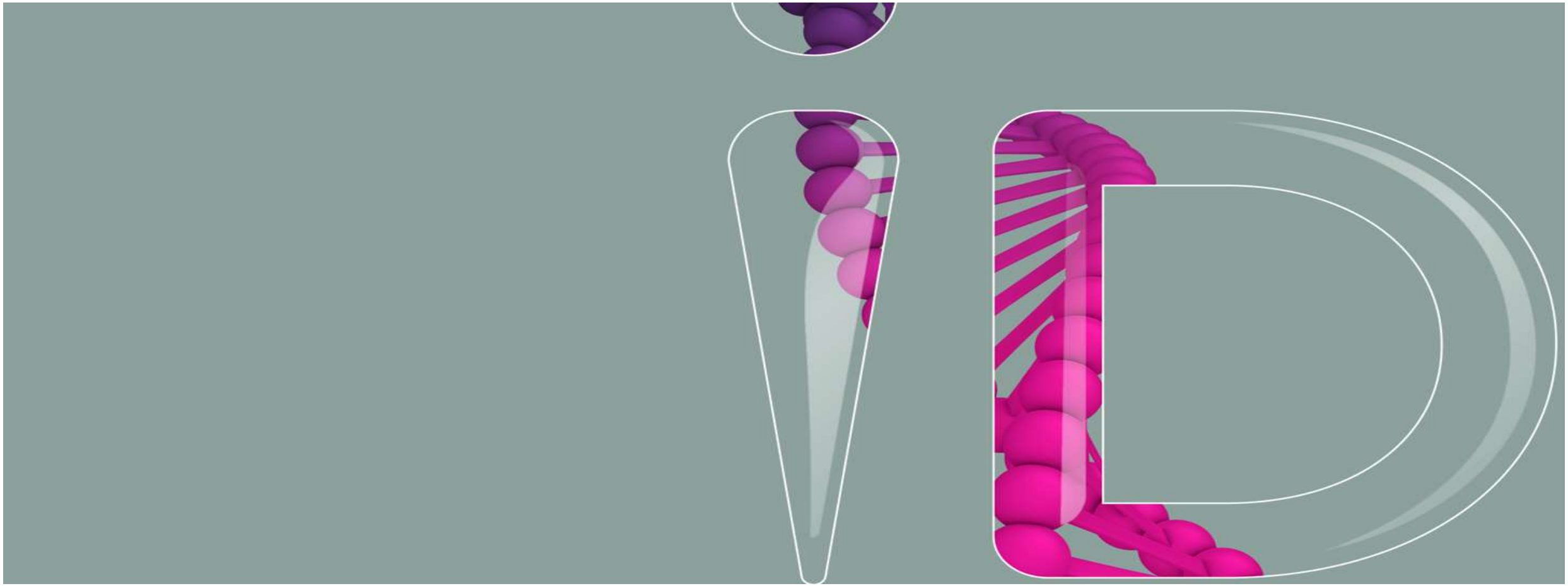
Precision oncology

EKE pathologie symposium OLV Aalst – 10 December 2019

Rudy Hovelinck, Diagnostic Manager AstraZeneca



My presentation today

Introduction of AstraZeneca

Why precision medicine in oncology matters

A long history in precision medicine

Biomarkers in Lung cancer

The important role of the Pathology Lab

our innovative science

150 Projects

50 Phase 1

37 Phase 2

23 Late-stage development

34 Life-cycle management projects

8 New molecular entities in our late-stage pipeline

5 Significant launches from each of our 3 therapy areas

53 Medicines available

Belgium

56 Clinical trials

49 Medicines available

Recognised as the most innovative pharma company

AstraZeneca has taken the **number one** spot in IDEA Pharma's Pharmaceutical Innovation Index (PII) – an index which celebrates the **most innovative companies in pharma**.

AstraZeneca

2 1 3

AstraZeneca

A global business located around 3 head offices and R&D centres

30% of total revenue is invested into R&D

Belgium
Groot-Bijgaarden

172 talented employees

Worldwide
100+ countries

61,100 talented employees

$22.1 billion total revenue

2,200 employees in **Gothenburg**, Sweden

2,900 employees in **Gaithersburg**, Maryland, US

2,200 employees in **Cambridge**, UK

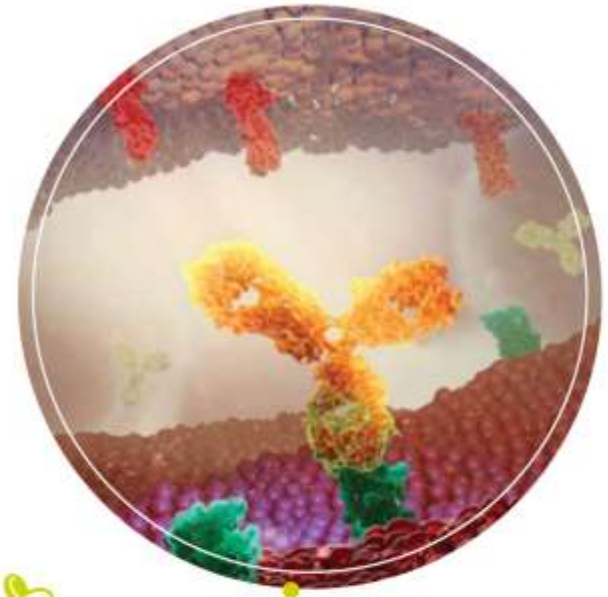
THREE MAIN THERAPY AREAS

ONCOLOGY

CARDIOVASCULAR, RENAL & METABOLISM

RESPIRATORY

Expand treatment options in
Oncology



Redefining
the treatment paradigm
to eliminate cancer
as a cause of death

The right medicine for the right patient

Our ambition is to **eliminate cancer** as a cause of death

4-FRONT OFFENSIVE AGAINST CANCER

Immuno-oncology (IO):
Using the body's immune system to help fight cancer

Antibody-drug conjugates
Arming antibodies with cancer-killing agents for specific tumour targeting

DNA damage response
Targeting the DNA repair process to block tumour cells' ability to reproduce

Tumour drivers and resistance
Developing therapies that target specific mutations to attack cancer cells

Precision oncology started in Breast cancer
>100 years of hormone treatment

Howell, A. Endocrine-related cancer 1993

1896	Oophorectomy
1922	Ovarian radiation
1939	Androgens
1951	Hypophyse irradiation
1952	Adrenalectomy
1953	Hypophysectomy
1967	Anti estrogens tamoxifen
1973	Aromatase inhibitors first generation
1982	LHRH antagonists
1987	Anti Progestins
1993	Estrogen receptor down regulators
2000	Aromatase inhibitor down regulators

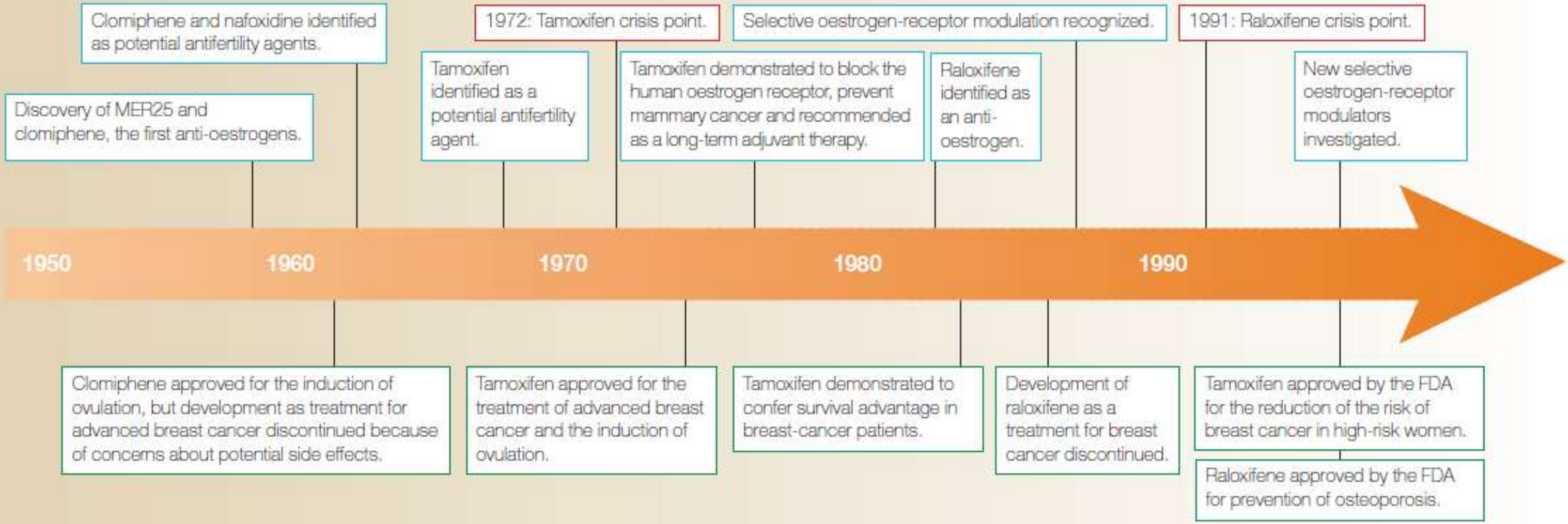
TAMOXIFEN: A MOST UNLIKELY PIONEERING MEDICINE

V. Craig Jordan

For more than 25 years, tamoxifen has been the gold standard for the endocrine treatment of all stages of oestrogen-receptor-positive breast cancer, and the World Health Organization lists tamoxifen as an essential drug for the treatment of breast cancer. It is estimated that more than 400,000 women are alive today as a result of tamoxifen therapy, and millions more have benefited from palliation and extended disease-free survival. Interestingly, tamoxifen also became the first cancer chemopreventive approved by the Food and Drug Administration (FDA) for the reduction of breast-cancer incidence in both pre- and post-menopausal women at high risk. However, 40 years ago, it was hard to imagine that a non-toxic targeted treatment for breast cancer could be developed at all.

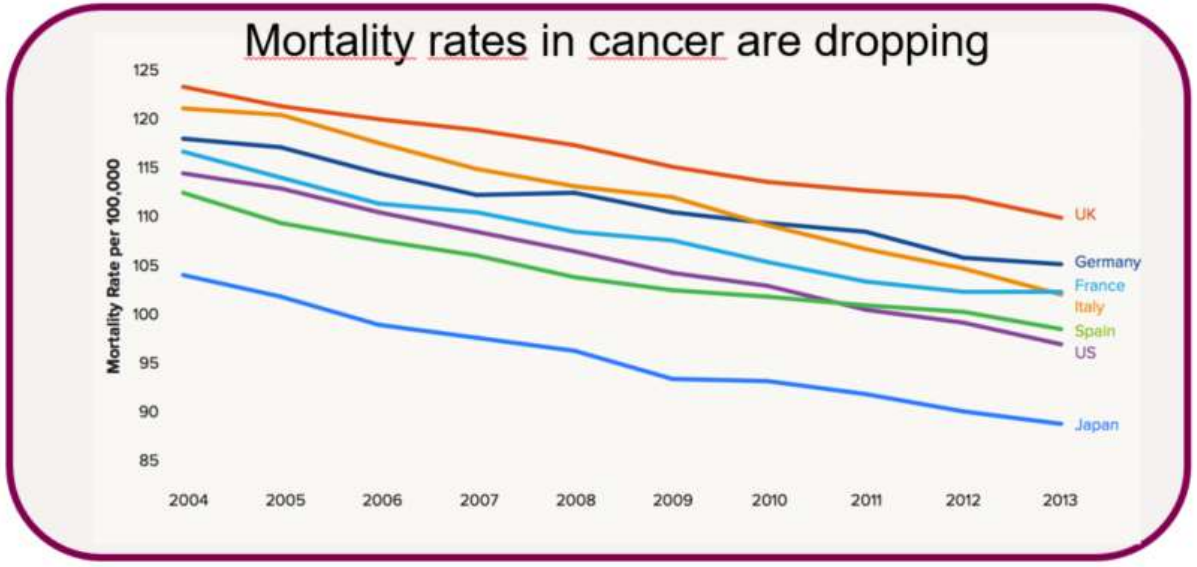
Tamoxifen triggered discovery of the ER biomarker

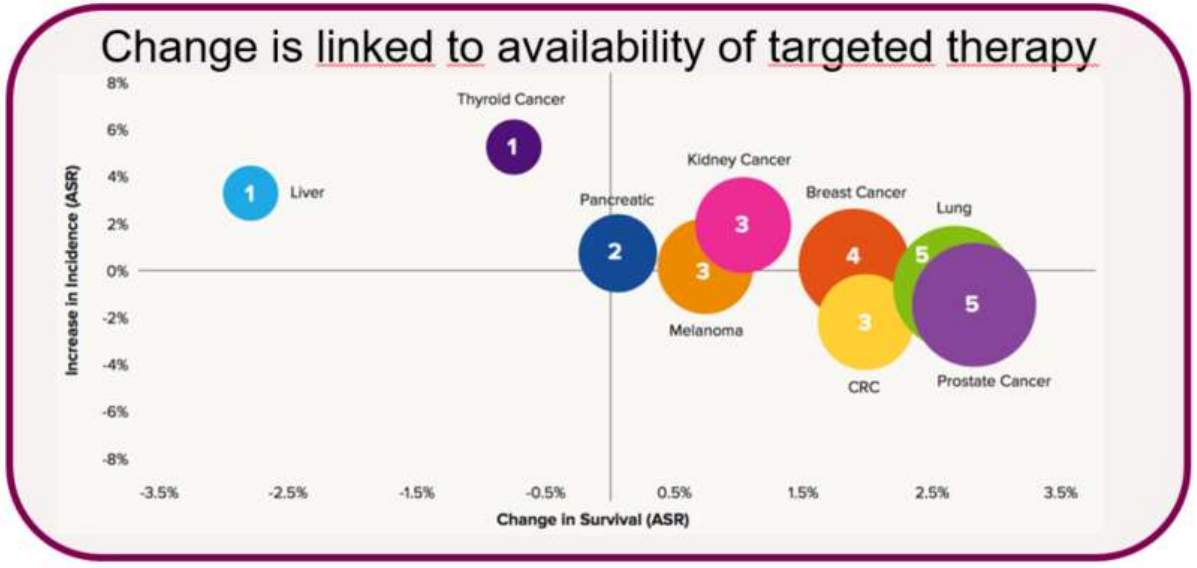
Timeline | **Milestones in the development of tamoxifen and raloxifene**

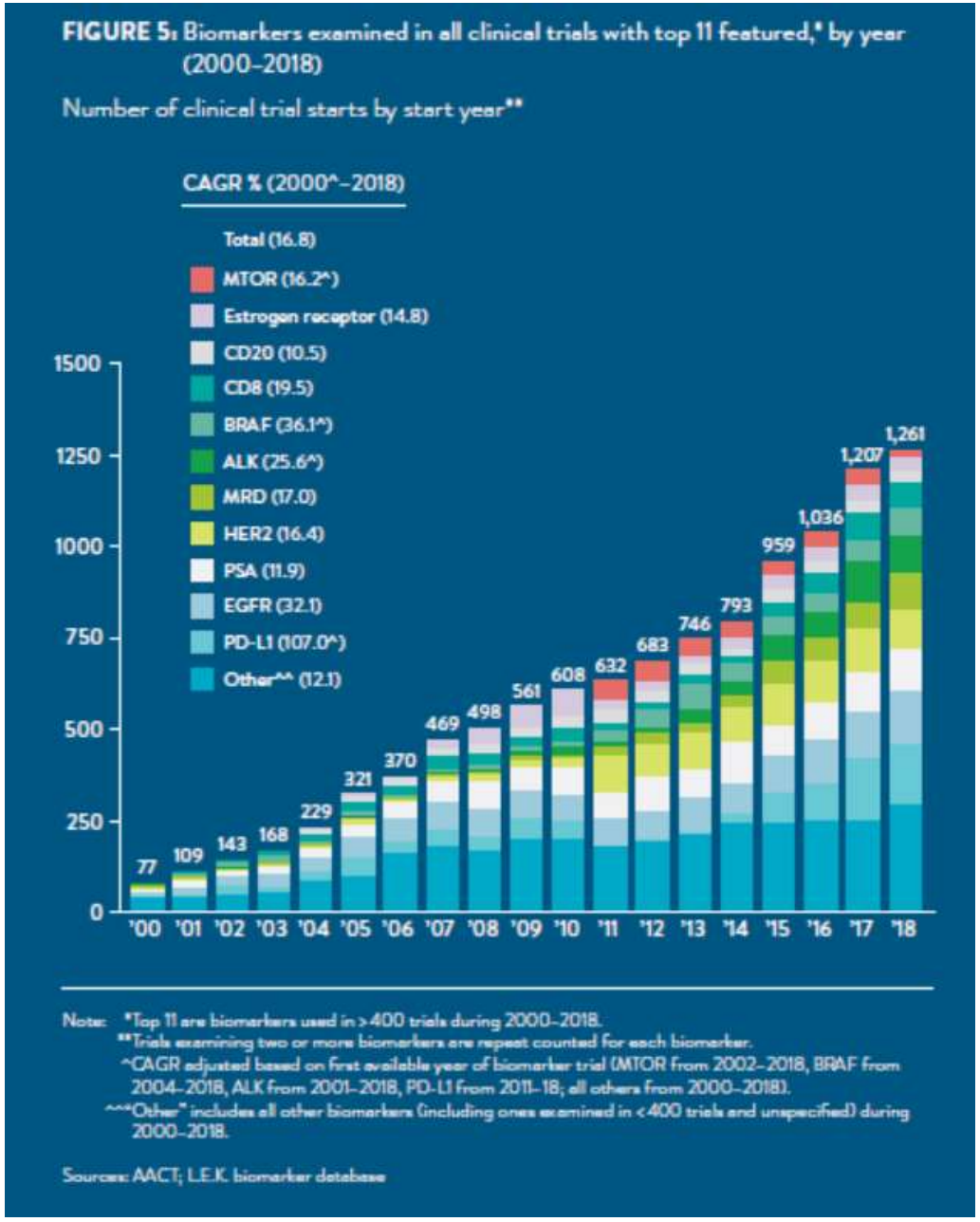


Tamoxifen and raloxifene are the pioneering selective oestrogen-receptor modulators, but both went through a crisis point at which decisions were made as to whether to terminate development; however, success occurred when the medicines were essentially re-invented for the focused application. Tamoxifen was transformed from an antifertility drug to an anti-breast-cancer drug and raloxifene was converted from an anti-breast-cancer drug to a treatment for osteoporosis. Laboratory milestones are highlighted in blue and clinical milestones are highlighted in green.

The continued success of personalized medicine in Oncology

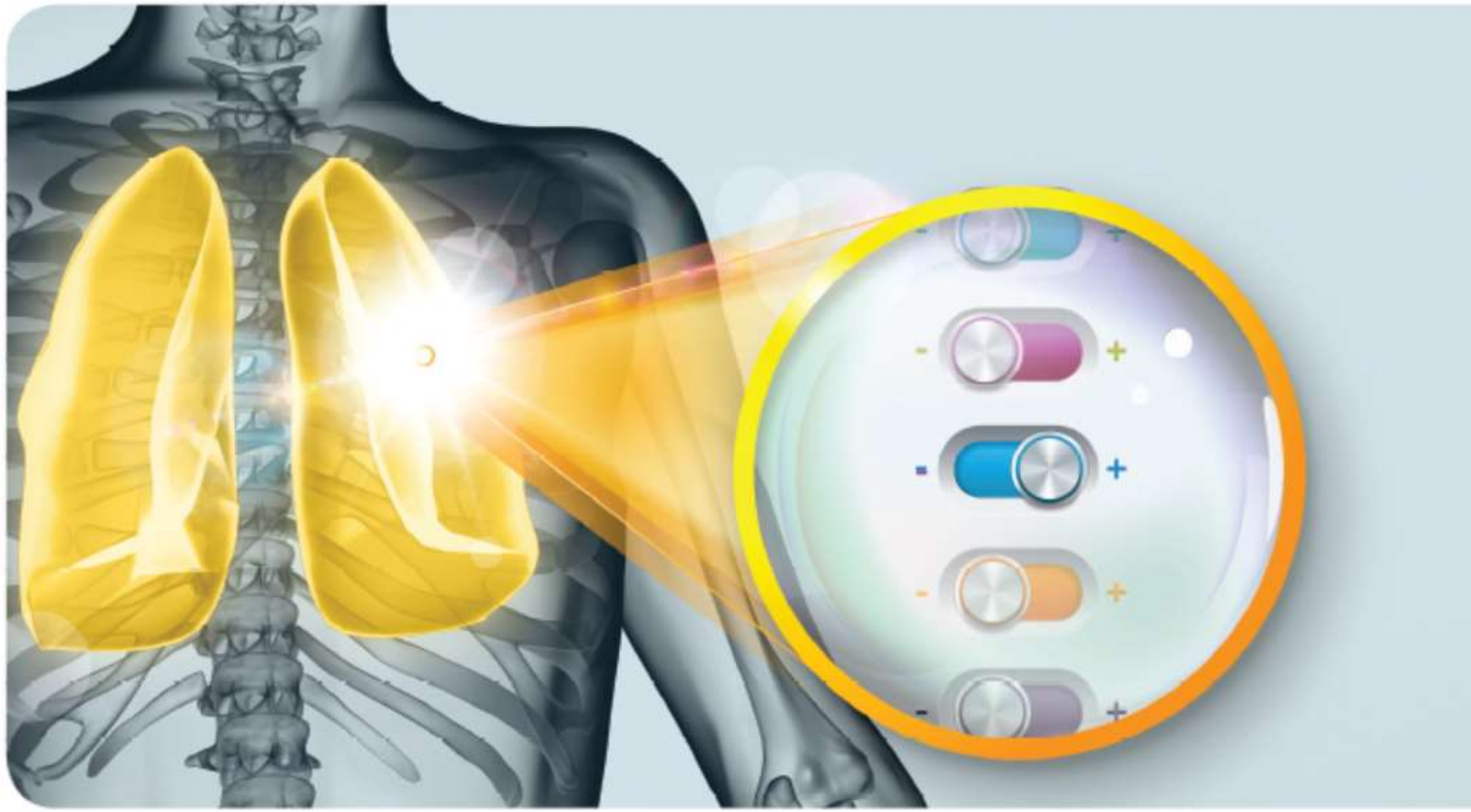






Schwaederle M,et al. Impact of Precision Medicine in Diverse Cancers: A Meta-Analysis of Phase II Clinical Trials. J Clin Oncol. 2015; 33:3817–3825.

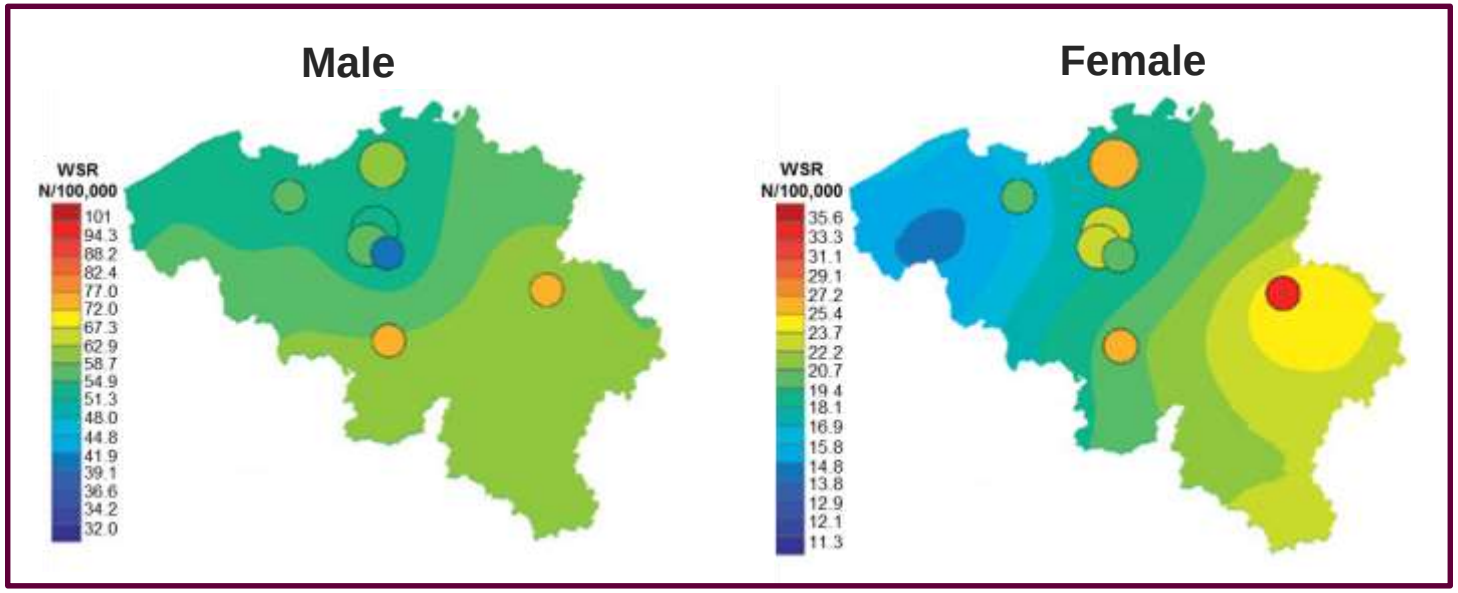
Biomarker testing for NSCLC



Lung cancer epidemiology in Belgium

- **8,174** new cases in 2016 (**66.5%** males, **33.5%** females)[1]
- The 2nd most common cancer in **males** (**13.4%** of all malignancies)[1]
- The 4th most common in **females** (**7,8%**)[1]

Age-standardized incidence by sex (2004–2013)[2]



Distribution of combined stage by sex, Belgium 2016

	Stage I	Stage II	Stage III	Stage IV	Stage X	Stage NA	Total
Males							
N	941	435	1,038	2,466	548	11	5,439
%	17.3	8.0	19.1	45.3	10.1	0.2	100
Females							
N	581	202	484	1,220	237	11	2,735
%	21.2	7.4	17.7	44.6	8.7	0.4	100

Staging according to the TNM 7th edition (Ref:Sobin LH, Gospodarowicz MK, Wittekind Ch. TNM classification of malignant tumours, UICC 7th edition)
Combined TNM stage : compilation of pathological (pTNM) and clinical (cTNM) stage. pTNM prevails over cTNM, except when cTNM stage is IV
Stage X: diagnoses with an unknown stage
Stage NA: diagnoses with a histological diagnosis where no stage can be evaluated (Not Applicable)

WSR, World Standardised incidence Rates. **1.** Cancer figures – Annual tables 2016, Belgian Cancer Registry. Available at: https://kankerregister.org/Annual%20Tables Last accessed April 25th 2019. **2**. Cancer burden in Belgium 2004–2013, Belgian Cancer Registry, Brussels 2015. Available at: https://kankerregister.org/media/docs/publications/BCR_publicatieCancerBurden2016_web160616.pdf Last accessed April 25th 2019. 3. Cancer fact sheet Lung cancer: Belgium 2016, Belgian Cancer Registry. Available at : https://kankerregister.org/media/docs/CancerFactSheets/2016/Cancer_Fact_Sheet_LungCancer_2016.pdf

Treatments options for Lung Cancer

Surgery

Radiotherapy

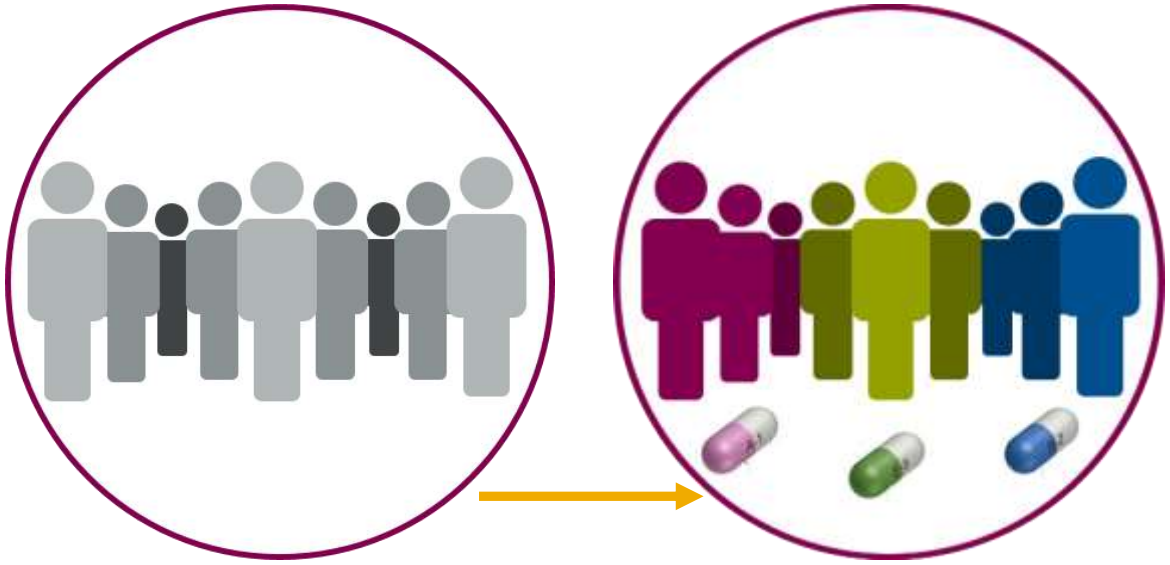
Anticancer drugs

These treatments can be given **alone or in combination** depending on the stage of disease

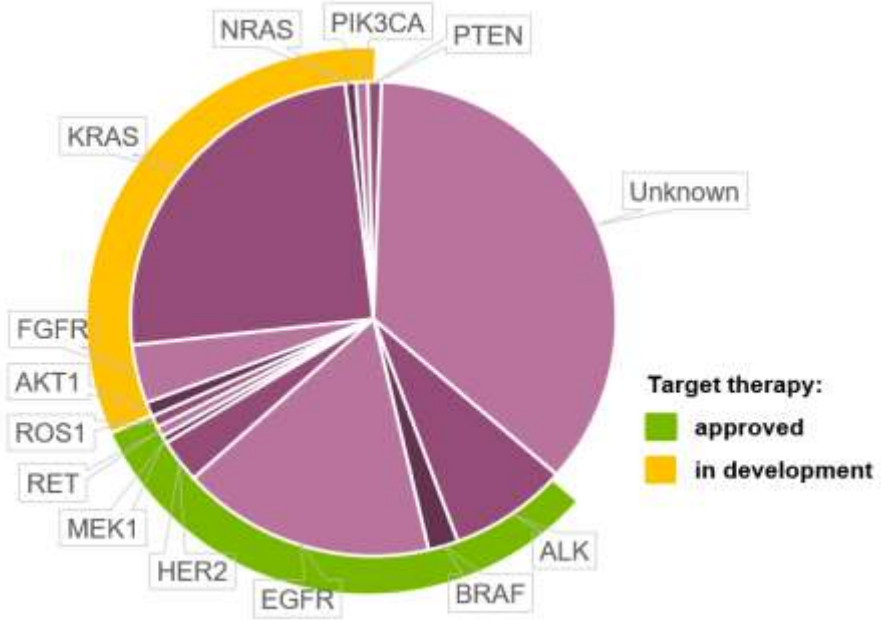
Personalized Health Care for Lung Cancer

Insights in cancer etiology resulted in targeted drug development

Histology based **Personalized**

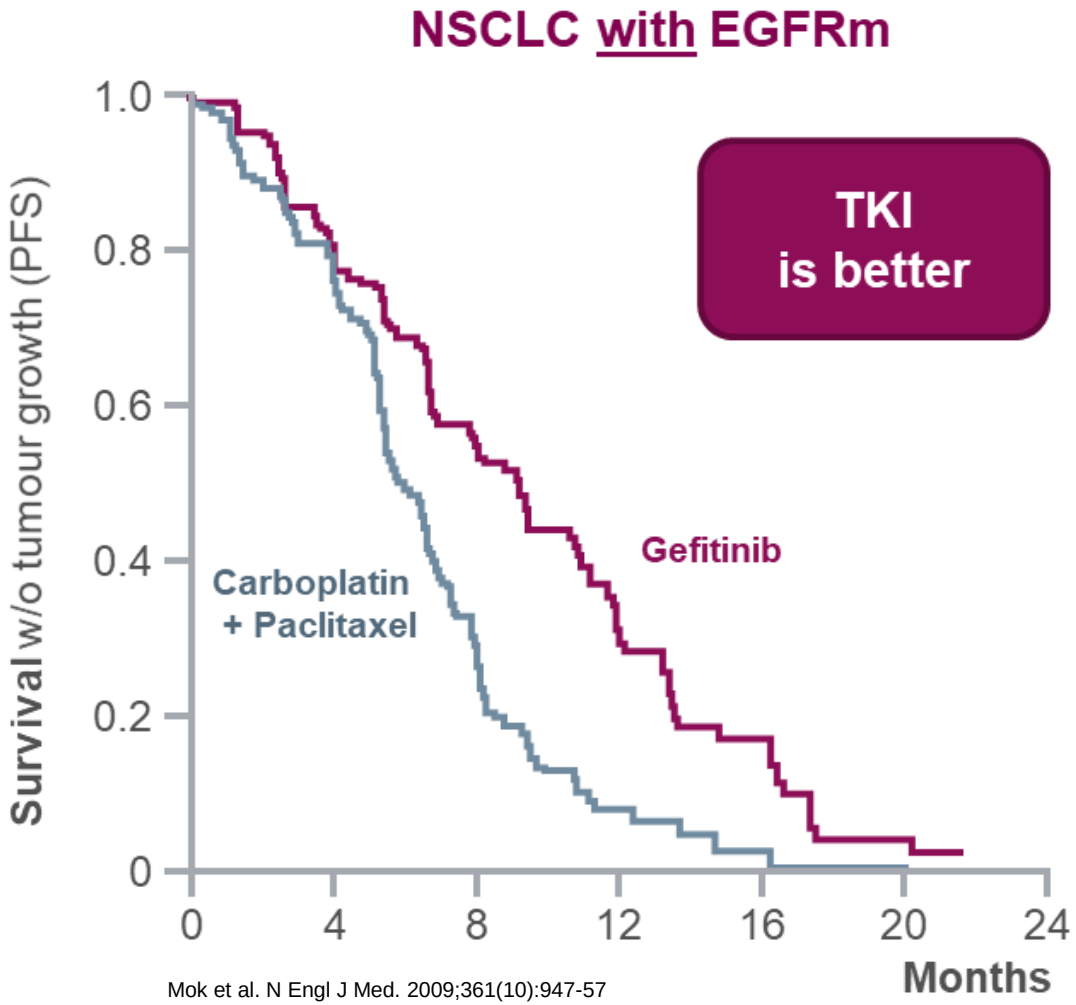


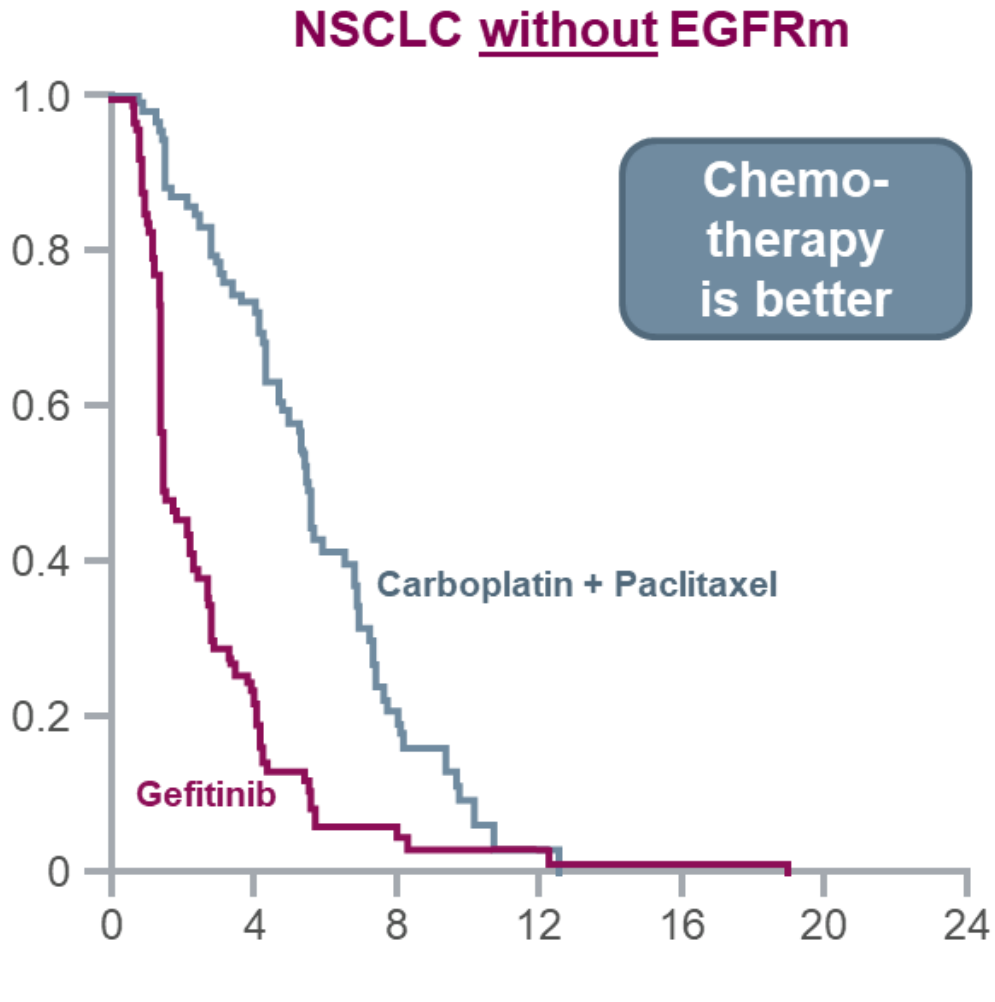
Biomarker status



Kris MG et al. JAMA 2014;311:1998–2006
http://www.ema.europa.eu/ema/ (accessed November 24, 2016)

Understanding of Biomarker status is essential for correct therapy choice

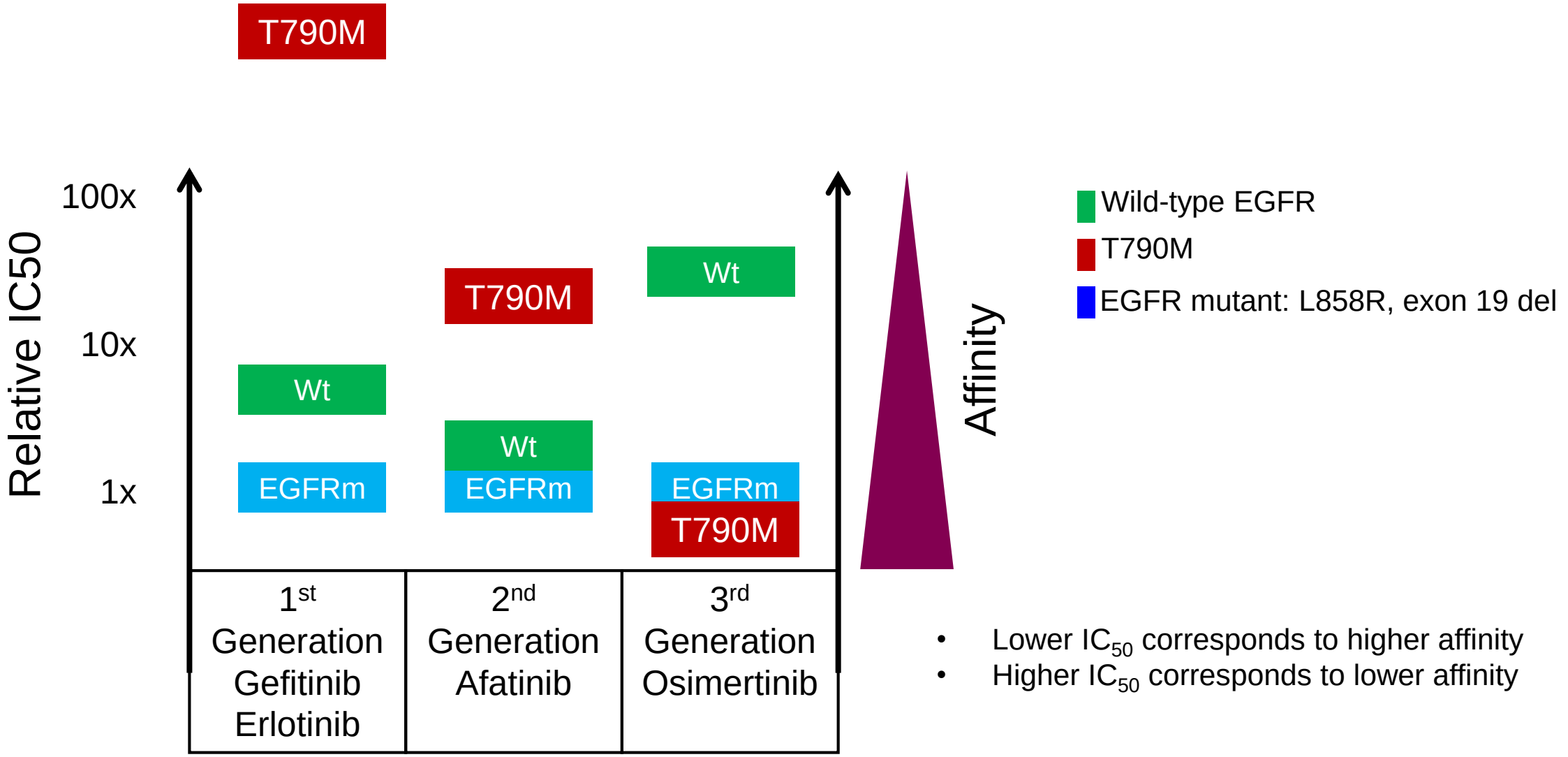




Mok et al. N Engl J Med. 2009;361(10):947-57

Details on specific mutations in biomarker needed

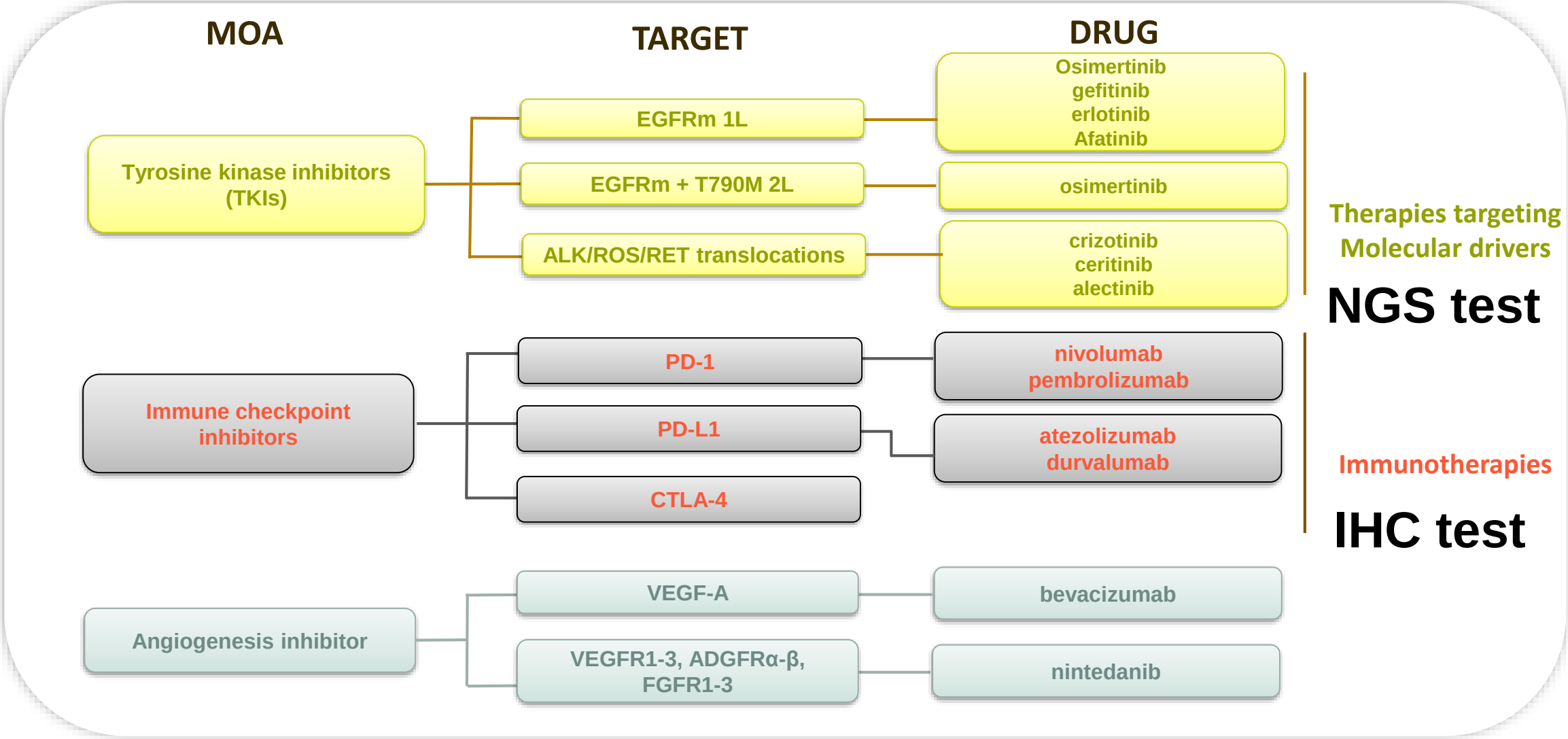
EGFR TKIs were redesigned for optimal affinity to activating/resistance mutations



- Lower IC_{50} corresponds to higher affinity
- Higher IC_{50} corresponds to lower affinity

Li D et al. Oncogene 2008; Cross DA et al. Cancer Discov 2014; Hirano T et al. Oncotarget 2015

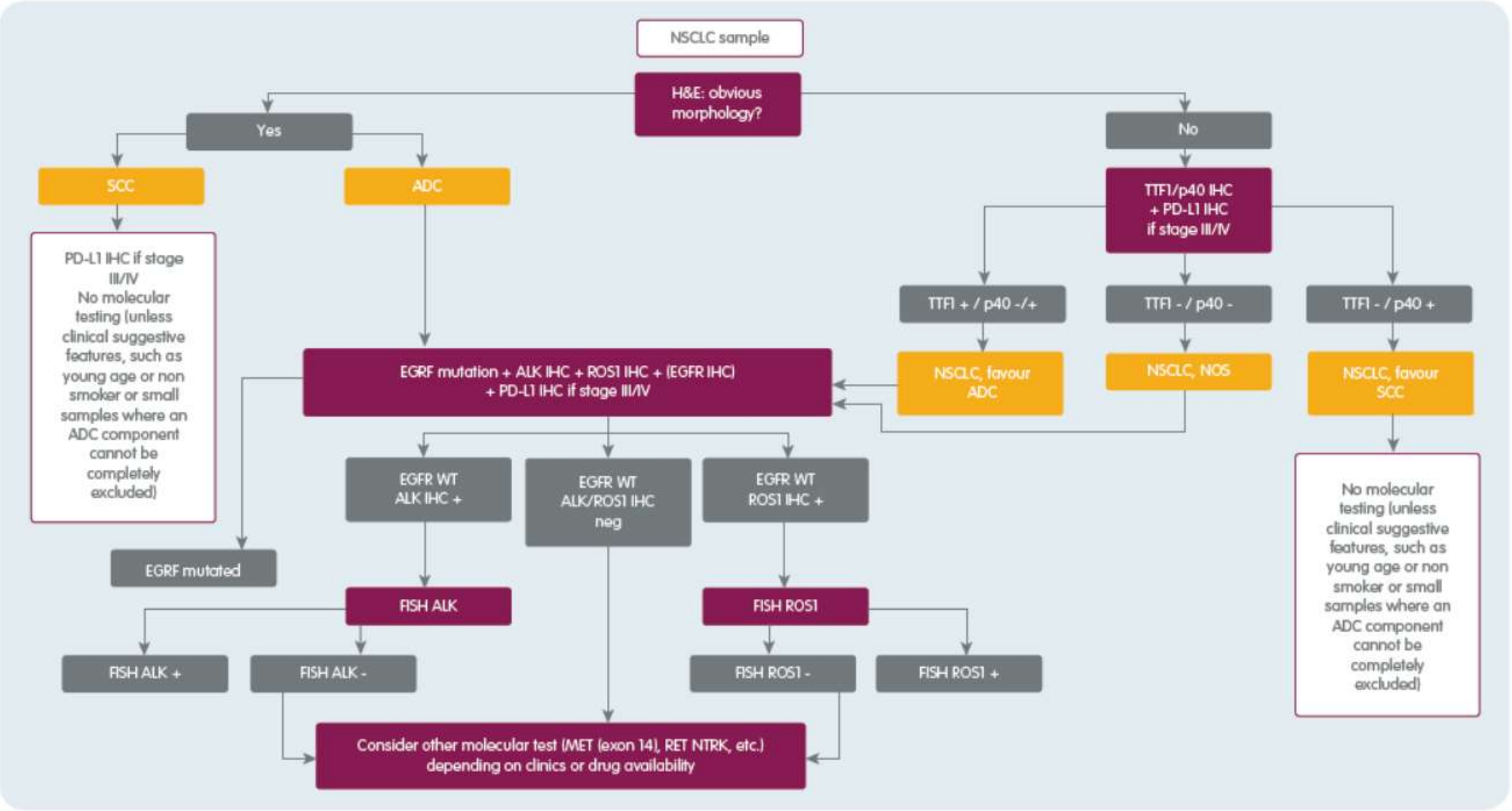
Specialized therapies available in NSCLC today in Belgium



Korpanty GJ, et al. Front Oncol. 2014;4:204; Hoos A. Nat Rev Drug Discov. 2016;15(4):235-247;
www.inami.fgov.be , www.ema.europa.eu accessed 5th of September 2019: Durvalumab: SmPC Imfinzi, latest version;

Belgian guidelines

New diagnostic algorithm for NSCLC biomarkers



PD-L1 test drives clinical decision in Stage 3 and Stage 4

Available PD-L1 antibody assays for identifying patients

The variety of drugs with specific PD-L1 IHC assays poses challenges for the pathologists on how to implement PD-L1 testing

The clinical data generated during the clinical trials of these drugs was based on different antibody assays, that are now available as in CE marked vitro Diagnostic assays (CE-IVD).

Associated drug	Positivity Threshold	Antibody assay	Platform	Minimum tumour cells
Pembrolizumab[2]	* 1L NSCLC (Stage IV) - all histologies: TPS ≥ 50% (monotherapy) - non-squamous: no PD-L1 threshold (in combination with chemotherapy) * ≥2L NSCLC (Stage IV): TPS ≥ 1%	22C3 (Dako)	Link 48 Autostainer	100
Nivolumab[3]	≥ 2L NSCLC (Stage IV): no PD-L1 threshold	28-8 (Dako)	Link 48 Autostainer	100
Atezolizumab[4]	≥ 2L NSCLC (Stage IV): no PD-L1 threshold	SP142 (Ventana)	Benchmark ULTRA	50
Durvalumab (Imfinzi)[5]	≥ 1% TPS (**Stage III** NSCLC)	SP263 (Ventana)	Benchmark	100

This table does not reflect the complete EMA labels of the mentioned drugs and only highlights the differences in PD-L1 scoring and cut-offs between the different drugs.

- European Medicines Agency recommends a validated test without antibody specification.
- Scientific investigation was needed to prove equivalence of the different antibody assays.[6,7]
  - Comparable performance in NSCLC was observed for the 28-8, 22C3 and SP263 CE-IVD assays.
  - The SP142 CE-IVD assay is different because it stains less tumour cells and cannot be used.
  - Lab developed assays can provide comparable results but lack clinical performance data and need extensive validation.

EGFR TKI's cannot be given after chemo therapy
This reemphasis the need for fast testing

	Reimbursed in Belgium[30] for
Osimertinib	as monotherapy is indicated for: - **the first-line*** treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) **with Exon 19 deletions or exon 20 L858R epidermal growth factor receptor (EGFR) mutations.** - the treatment of adult patients with locally advanced or metastatic **EGFR T790M** mutation-positive **NSCLC at or after progression on a first line tki.**
afatinib	as monotherapy for the treatment of - Epidermal Growth Factor Receptor (EGFR) **TKI-naïve** adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with **activating EGFR mutation(s);** - Adult patients with locally advanced or metastatic NSCLC of squamous histology **progressing on or after platinum-based chemotherapy.**
erlotinib	is indicated as monotherapy - first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) **with EGFR activating mutations.** - maintenance treatment after first-line chemotherapy in patients with locally advanced or metastatic NSCLC **with an expression of EGFR determined by IHC in at least 10% of the tumor cells.**

Available tests for EGFR

Real-time PCR

- Multiple hot spots in a gene
- Semi automated – fully automated
- Fast – very fast (same day)
- only the alterations that are targeted by the specific assay will be detected
- Intermediate sensitivity

Digital droplet PCR

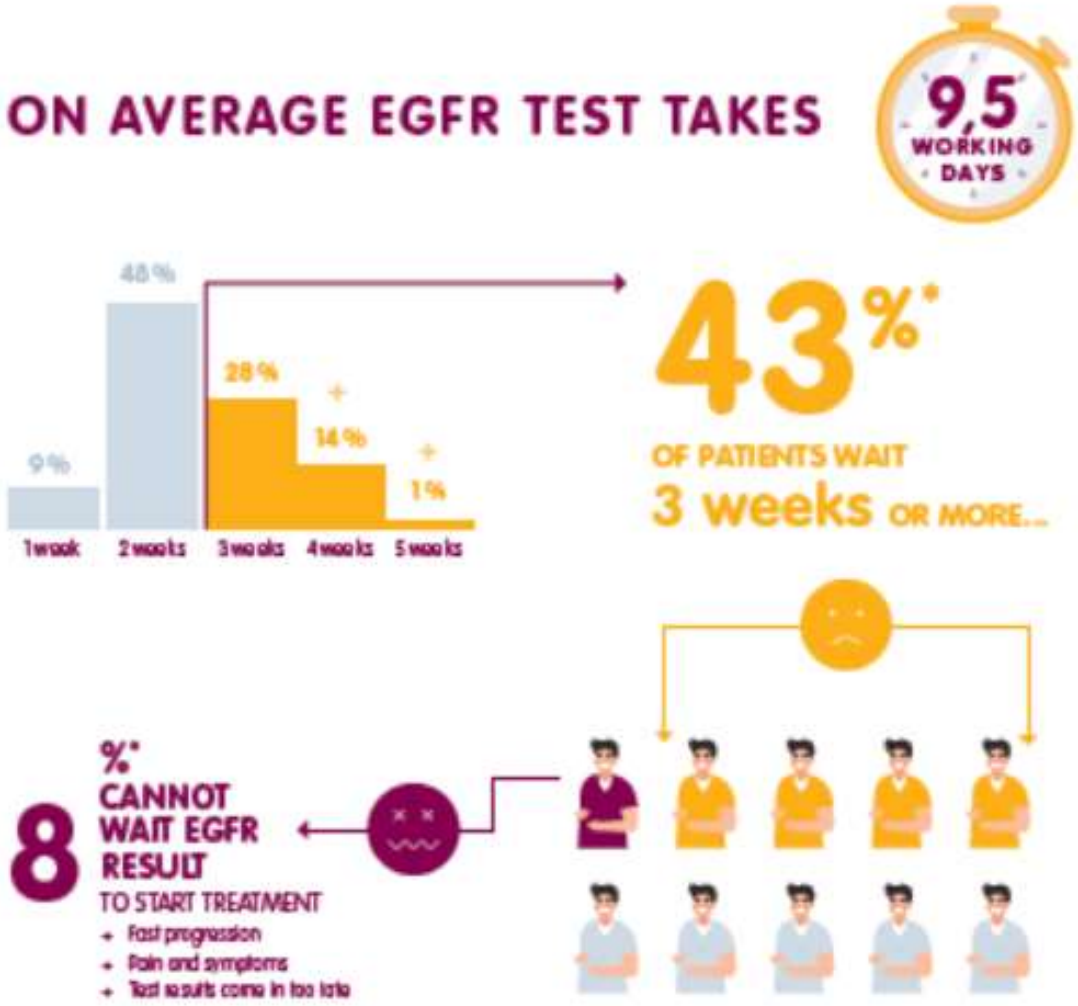
- A few selected hot spots in a gene
- Semi automated
- Fast
- only the alterations that are targeted by the specific assay will be detected
- Most sensitive

Next Generation Sequencing

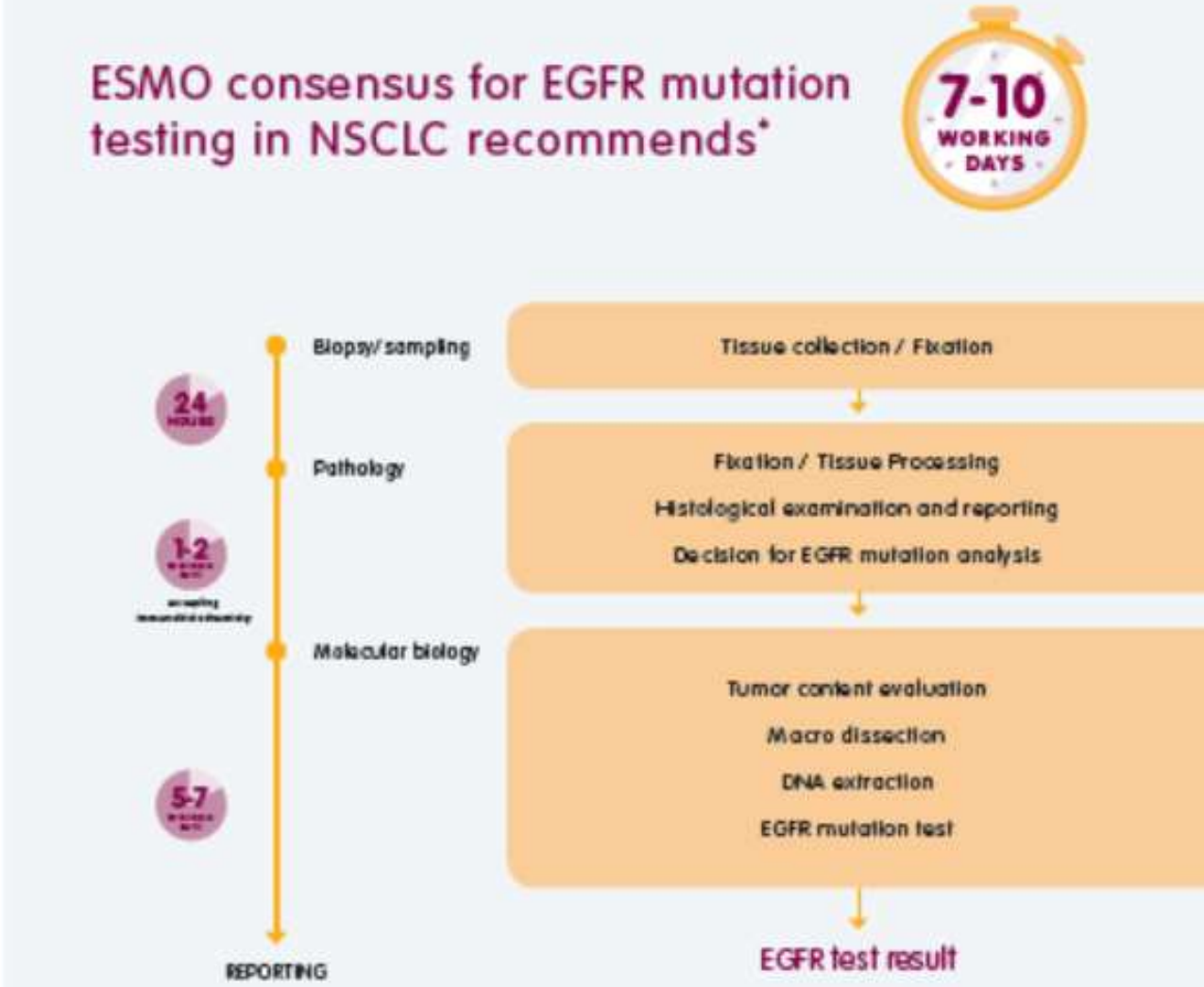
- Gene panel
- More laborious
- Slower
- All mutations found
- Sensitivity ifct number of reads


All test results need to be available for clinical decision making, but tests have different TAT
IHC
NGS

Molecular test results can arrive too late for therapeutic decision making



EGFR: Epidermal Growth Factor Receptor
* Market research done in Belgium in April 2019 in n=106 patient files of patients with locally advanced or metastatic NSCLC



ESMO: European Society for Medical Oncology
NSCLC: Non-small cell lung cancer
* Pirker R. et al J Thorac Oncol. 2010;5: 1706–1713

PD-L1 and EGFRm are overlapping biomarkers

EXPRESS Study: Prevalence of PD-L1 TPS ≥ 50% and TPS ≥ 1% among patients with stage IIIB/IV NSCLC:

- In the group of PD-L1 < 50% the EGFRm prevalence is 23%
- in the PD-L1 > 50% the EGFRm prevalence is 16%.

➢ The EGFR prevalence is lower but not sufficient to make the assumption that most PD-L1 > 50% samples will return negative for EGFR mutations and it's not important to wait for the EGFR test result.

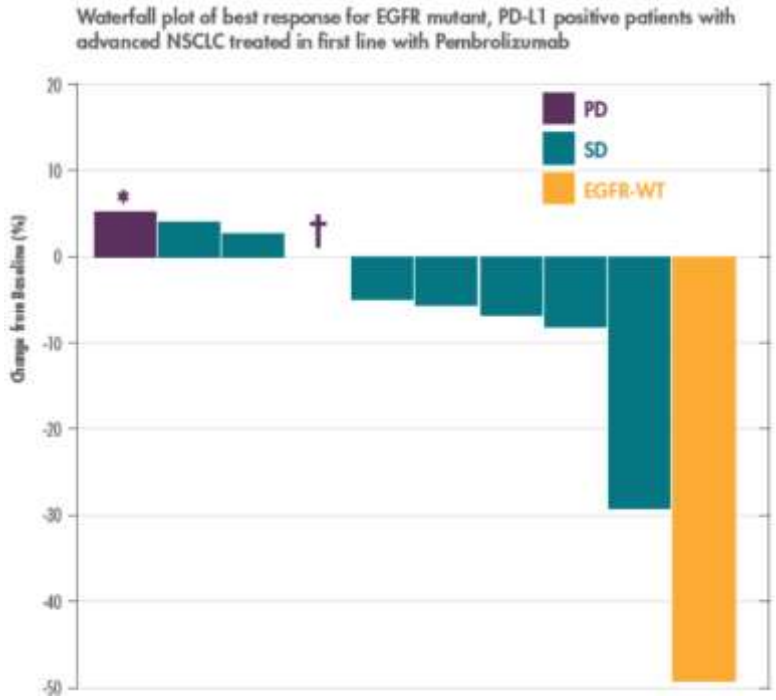
Characteristic, n (%)	N	TPS >= 50%	TPS >= 1%	TPS < 1%
All patients	2368	530 (22)	1232 (52)	1136 (48)
ALK translocation status				
Positive	74	15 (20)	48 (65)	26 (35)
Negative	1433	347 (24)	753 (53)	680 (47)
Unknown	861	168 (20)	431 (50)	430 (50)
EGFR mutation status				
Positive	448	60 (13)	197 (44)	251 (56)
Negative	1260	319 (25)	673 (53)	587 (47)
Unknown	660	151 (23)	362 (55)	298 (45)

Dietel et al Lung Cancer 134, 2019, 174-179 Real-world prevalence of programmed death ligand 1 expression in locally advanced or metastatic non–small cell lungcancer: The global, multicentre EXPRESS study

When the therapy does not match with the biomarker..

Anti PD-L1/PD-1 has not shown significant benefit in patients with EGFRm patients

In first-line, EGFRm patients were excluded from most studies
In Keynote-00131 in the 10 patients on trial with documented EGFR mutations, the ORR was 0%



Toxicity concerns rising when osimertinib is used after Anti PD-L1/PD-1 monotherapy

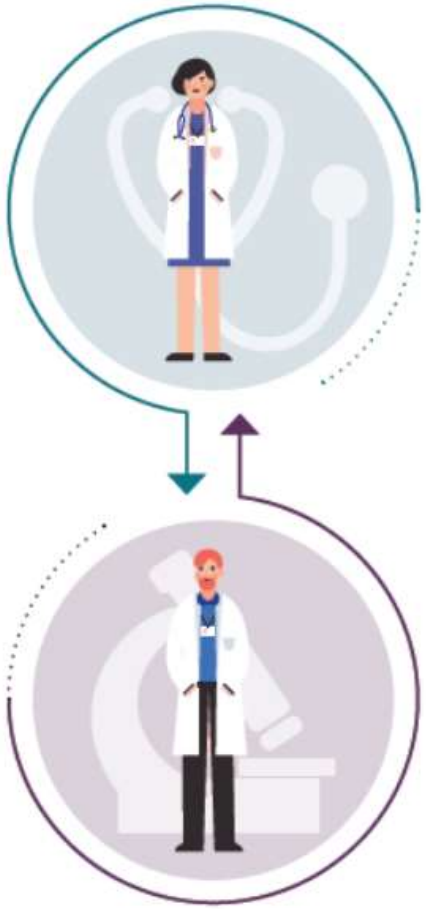
Characteristic	PD-L1 Then OSI (n=41)	OSI Then PD-L1 (n=29)
Age, y	61 (30-79)	56 (36-85)
PD-L1, n (%)		
NIV	24 (59)	16 (55)
PEMBRO	9 (22)	10 (35
ATE	8 (19)	3 (10)
Time between PD-L1 and OSI, d	61 (12-1,446)	5 (1-256)
Severe immune-related AE, n (%)	6 (15)	0 (0)

*Subject deemed to have progression based on dural thickening on brain MRI
† subject with complete response of target lesion but nontarget progression on first scan
ORR: objective response rate, PD: progressive disease, SD: stable disease, EGFR-WT:epidermal growth factor wild type , Anti PDL-1/PD-1: programmed death-lignad 1 inhibitors, ATE: atezolizumab, DUR: durvalumab, NIV: nivolumab, OSI: osimertinib

What can I do in the pathology lab to secure fast test results for every patient?

Be proactive and communicate

- Install reflex testing procedures with the multi disciplinary team
- Educate your physician, especially when the sample does no meet your requirements:
  - missing sample identification
  - request form incomplete
  - sample too small in size
  - …
- Communicate test results asap
- Report a clear test result with sufficient detail



Avoid test failures that lead to repeat testing and resampling

- Protect the DNA quality in the sample:
  - Pre analytical steps: 4% NBF, Time to fixation, fixation time 6-48h, temperature
  - Use non acid Bone lesion decalcification
- Preserve as much tissue as possible during sectioning
- Do not perform unnecessary tests
  - HE only if clear histology
  - IHC tests - only p40/TTF1!
  - mucin stain

https://www.youtube.com/watch?time_continue=35&v=TXi_KpR3LYU&feature=emb_logo

Thank you for your attention and your daily work

AstraZeneca

“ TWO WEEKS
to receive the results!
It’s horrible to live with*.”

Waiting for the result, a stressful time for patients and their relatives

* Reported from a market research done in April 2019 with n=20 lung cancer patients and relatives

ODYSSEY

AZ team in contact with all experts involved.

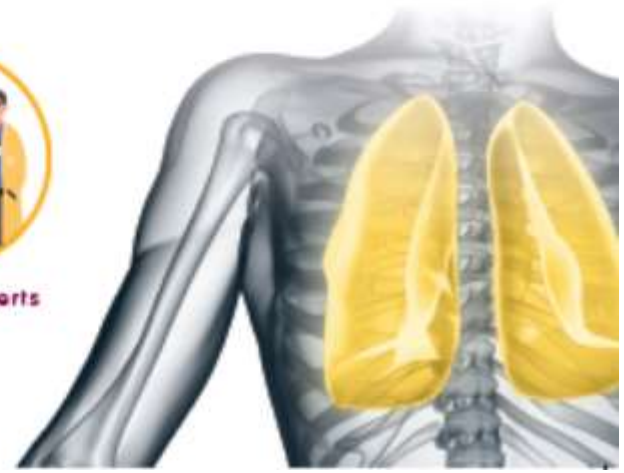
OBJECTIVE DATA ON YOUR SAMPLE JOURNEY

Chart sample flow

Only 10 minutes of your time

Full chart delivered

Involve all experts



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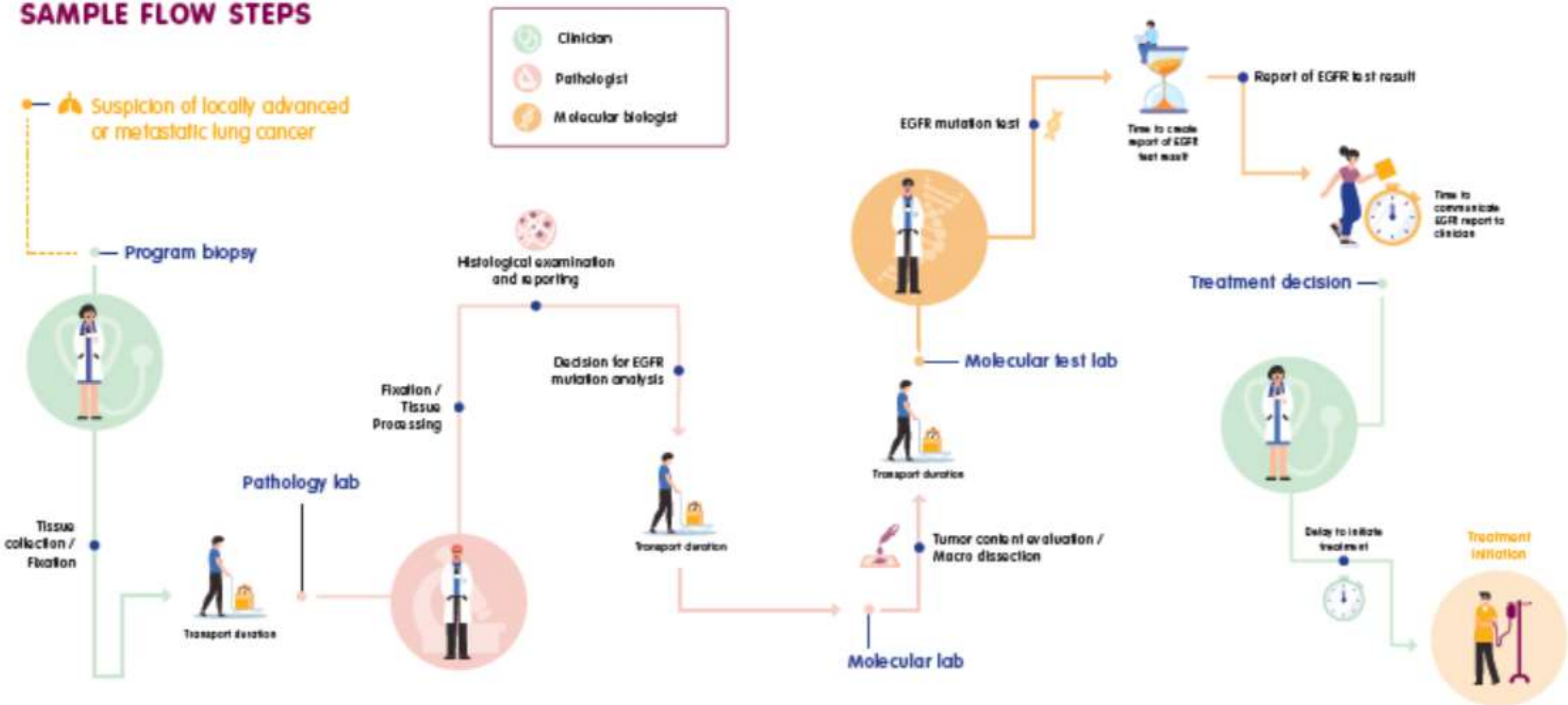
SAMPLE FLOW STEPS



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