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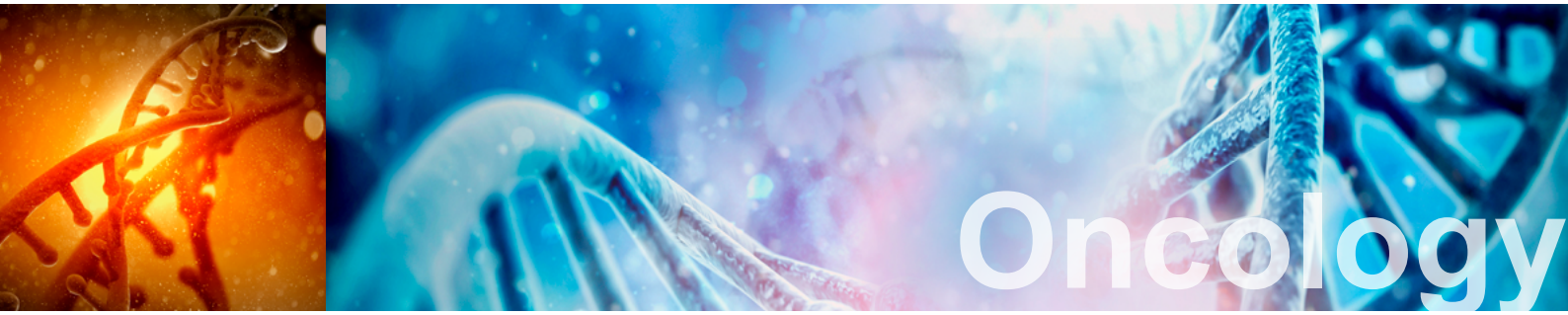
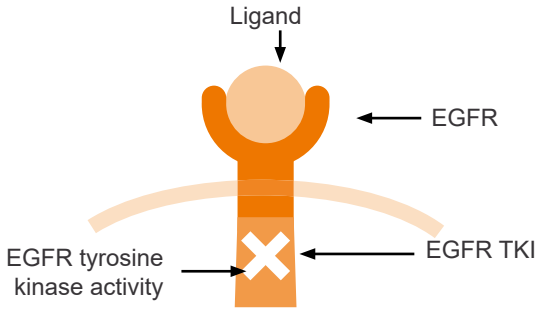


Pulmonology

Lung cancer is the leading cause of death around the world in men and the second most common cause in women (after breast cancer). The main histological types are NSCLC and SCLC. NSCLC accounts for 85% of cases and SCLC 15%. This histological distinction and the stage of the cancer are important because the treatments and prognoses differ according to these two factors.

In the 2000's, there was a treatment revolution in locally advanced or metastatic NSCLCs based on personalised medicine (targeted therapy) linked to molecular abnormalities in genes involved in lung carcinogenesis (gene mutations, rearrangements or amplifications). These abnormalities are known as "driver" events. EGFR TKIs have been the first-line targeted therapy for NSCLC. Extensive analysis of these genes is thus a key step in treating patients. Eurofins Biomnis offers two NGS panels (LUNG1 and LUNG2) and targeted FISH tests to meet the needs of MDCM clinicians. The list of analyses offered has been created based on international guidelines (ASCO-CAP, ESMO).



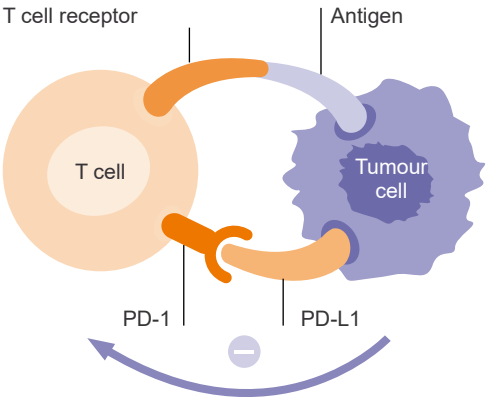
Example of a targeted anti-EGFR therapy: action against the INTRACELLULAR domain of the receptor

The second treatment revolution for these tumours was immunotherapy, which is based on the principle of activating (via blocking inhibitory checkpoints) the immune response via immune checkpoint inhibitors. Analysing the expression of cell receptors (in particular PD-L1) using IHC can be useful for the prescription of these ICIs (analysis offered by Eurofins

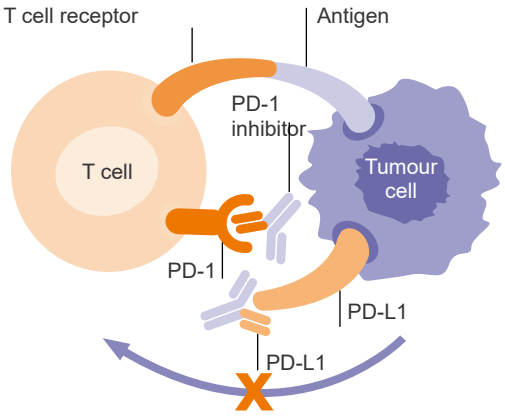
DS83-INTGB – October 2020

Pathology). A future area of investigation will be the role of immunotherapy in NSCLC with one or more actionable molecular abnormalities. Other biomarkers are being evaluated for use in immunotherapy, such as tumour mutational burden (TMB).

Tumour cell defence mechanism: inhibition of the immune response (T cells)



Activity of anti-PD-1 or anti-PDL-1: inhibitors



"Targeted therapy: sensitivity and resistance": What analyses are available? What techniques are used? What are potential targets for the future?

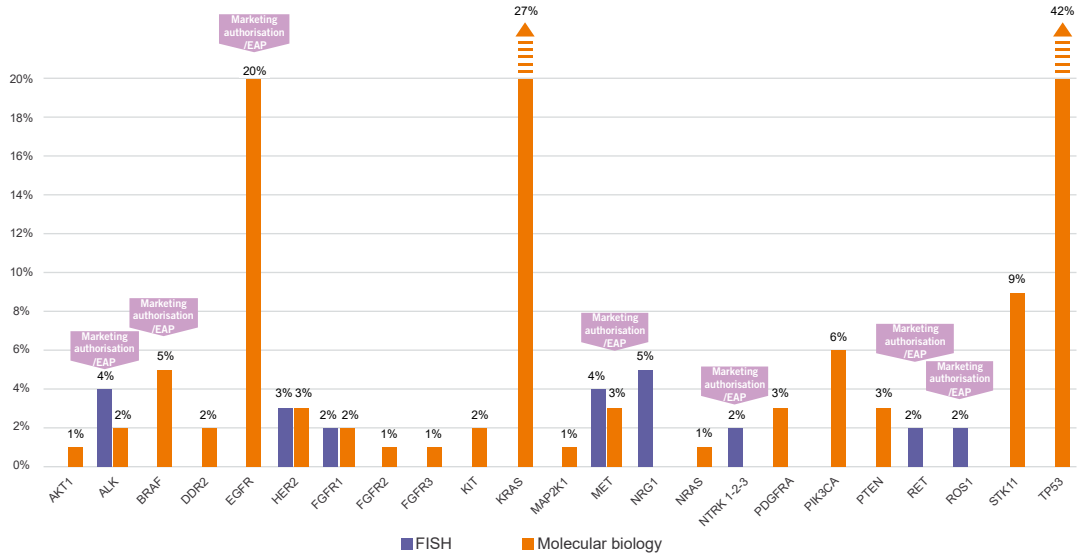
"LUNG1" NGS panel	EGFR – BRAF – MET – KRAS (4 genes)
FISH unitary tests – LUNG	ALK, ROS1, RET, NTRK 1-2-3, MET, HER2, FGFR1, NRG1
"LUNG2" NGS panel	AKT1 – ALK – BRAF – DDR2 – EGFR – HER2 – FGFR1 – FGFR2 – FGFR3 – KIT – KRAS – MAP2K1 – MET – NRAS – PDGFRA – PIK3CA – PTEN – STK11 – TP53 (19 genes)
Liquid biopsy (circulating tumour DNA)	EGFR (1 gene)

The NGS "LUNG1" panel associated with the FISH unitary test fulfil the routine needs of clinicians for prescribing targeted therapies for locally advanced or metastatic NSCLC. In 2020, the EGFR (mutation), ALK (rearrangement), ROS1 (rearrangement), RET (rearrangement), BRAF (mutation), NTRK (rearrangement) and MET (mutation) status can be used to guide the selection of targeted therapy (TMA (temporary marketing authorization)). In addition, KRAS status is included in this panel.

The NGS "LUNG2" panel approach expands the range of tested mutations in the genes implicated in resistance mechanisms for targeted therapies, emerging markers for targeted therapies or immunotherapy response, or potential targets for clinical research. This approach should be complemented by targeted FISH tests.

DS83-INTGB – October 2020

Frequency of FISH or molecular abnormalities in NCSLC and available targeted therapies (marketing authorisation/EAP)



"LUNG1" NGS panel

EGFR Presence of an EGFR activating mutation (exons 18-19-20 and 21) allows the use of EGFR TKIs (first, second or third generation TKIs) with greater effectiveness than chemotherapy. However, EGFR mutations associated with resistance to first or second generation (e.g. T790M) and recently third generation (e.g. C797X) targeted therapies have also been observed during treatment. Other EGFR TKI resistance mechanisms are listed below. EGFR mutations can also result in resistance to ALK TKIs.

BRAF Presence of a BRAF mutation (V600X) allows the use of a BRAF inhibitor. These mutations can also result in resistance to EGFR TKIs.

MET Presence of an MET mutation (exon 14) allows the use of an MET inhibitor.

KRAS A KRAS mutation does not provide the basis for targeted NSCLC therapy, however the mutated status is associated with a poor prognosis. It may result in a resistance mechanism against EGFR and ALK TKIs or conversely, in increased sensitivity to immunotherapy. All this makes it a molecular marker of interest.

"LUNG2" NGS panel

ALK ALK mutations represent a resistance mechanism against ALK TKIs.

HER2 HER2 mutations do not currently provide basis for targeted therapy, however it appears that there is some form of anti-tumour activity of anti-HER2s in combination with chemotherapy in the presence of an HER2 mutation.

AKT1, DDR2, FGFR1, FGFR2, FGFR3, KIT, MAP2K1, NRAS, PDGFRA, PIK3CA, PTEN, STK11 and TP53 are emerging potential markers for the treatment of NSCLC, either through a targeted therapy or a response to immunotherapy.

DS83-INTGB – October 2020

Targeted FISH unitary tests

		Rearrangement	Amplification
ALK	The presence of an ALK rearrangement allows the use of ALK TKIs (first, then second or third generation TKIs) with a greater efficacy than chemotherapy. As with EGFR, resistance mechanisms have been observed such as ALK mutations (e.g. G1202R).	●	●
ROS1	Presence of a ROS1 rearrangement allows the use of ALK TKIs.	●	
RET	Presence of an RET rearrangement allows the use of anti-RET antibodies.	●	
NTRK 1/2/3	The presence of NTRK 1, 2 or 3 rearrangement allows the use of a TKI.	●	
MET	MET amplification is a resistance mechanism against EGFR and ALK TKIs.		●
HER2	HER2 amplification is a resistance mechanism against EGFR TKIs. Trials are also ongoing for a targeted therapy, analogous to that for breast cancer, however they appear less promising than for HER2 mutations.		●
FGFR1	FGFR1 amplification could have a predictive effect on the prescription of anti-angiogenics.		●
NRG1	A targeted therapy could be considered if there is a NRG1 rearrangement.	●	

Note: IHC tests can be carried out to determine the level of expression of ALK, ROS1 or NTRK. Confirmation using FISH is required for ROS1 and NTRK.

Liquid biopsy (circulating tumour DNA): EGFR

For diagnosis, this analysis should not be used as a substitute for the molecular analysis of tissue tumour except if the tissue sample is not accessible or not useable (all of sample used, low tumour infiltration, quantity of extracted DNA insufficient for FISH or molecular biology techniques). The value of testing for an EGFR mutation in the plasma is in the characterisation of progression mechanisms under targeted therapy (e.g. testing for resistance to EGFR TKI (T790M)).

Special attention must be paid to the clinical and biological data provided with the sample. For this, we recommend the use of our dedicated test request form (reference B9-INTGB).

In conclusion, the molecular and FISH approaches for pulmonary tumours are constantly changing. This document was written according to the state of knowledge in 2020, however the therapeutic targets are continously evolving, which makes decision-making by chest MDCMs complex.

Note: Alongside FISH and molecular analyses, Eurofins Biomnis also offers the ProGRP, NSE, CYFRA 21, SCC and ACE serum marker tests for pulmonary oncology.

The evaluation of tumour mutational burden (TMB) as a predictive test for response to immunotherapy is also available from Eurofins Biomnis.

DS83-INTGB – October 2020

Molecular characteristics of genes analysed using NGS:

Gene	NM_	EXONS	LUNG1	LUNG2
AKT1	NM_005163.2	3		●
ALK	NM_004304.4	21, 22, 23, 25		●
BRAF	NM_004333.5	11, 15	●	●
DDR2	NM_006182	5, 8, 12–15, 17		●
EGFR	NM_005228	12, 18–21	●	●
HER2	NM_004448.3	19–21		●
FGFR1	NM_023110	3, 4		●
FGFR2	NM_000141	7, 9, 12		●
FGFR3	NM_000142	7, 9, 14, 16, 18		●
KIT	NM_000222	8, 9, 11, 13, 17		●
KRAS	NM_004985	2, 3, 4	●	●
MAP2K1	NM_002755	2		●
MET	NM_001127500	2, 14, 16, 19	●	●
NRAS	NM_002524	2, 3, 4		●
PDGFRA	NM_006206	12, 14, 18		●
PIK3CA	NM_006218	2, 8, 10, 14, 21		●
PTEN	NM_000314.6	1, 3, 6–8		●
STK11	NM_000455	1, 4, 6, 8		●
TP53	NM_000546	2, 4-10		●

Before taking any samples, view the key information for each test (pre-analytical requirements, turnaround time, required documents*, etc.) on **www.eurofins-biomnis.com** > Test Guide section > **Test Code**

Analysis codes

Lung 1 NGS Panel – 3 genes: **POUM1**
Lung 2 NGS Panel – 23 genes: **POUM2**
Targeted FISH unit tests: **MOHC4**
EGFR liquid biopsy: **EGFRS**
TMB test: **TMB**

Required documents

Test request form - Oncology-Solid tumors (ref. B9-INTGB)
Histopathology report

Turnaround time (FISH and NGS): 13 days (one extra week if verification by Sanger is required)

Literature references

WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. WHO Classification of Tumours, 4th Edition, Volume 7. Edited by Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG

Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors: Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. Lindeman NI et al, Arch Pathol Lab Med. 2018 Mar;142(3):321-346. PMID: 29355391

Pan-Asian adapted Clinical Practice Guidelines for the management of patients with metastatic non-small-cell lung cancer: a CSCO-ESMO initiative endorsed by JSMO, KSMO, MOS, SSO and TOS. Wu YL, Planchard D, Lu S, Sun H, Yamamoto N, Kim DW, Tan DSW, Yang JC, Azrif M, Mitsudomi T, Park K, Soo RA, Chang JWC, Alip A, Peters S, Douillard JY. Ann Oncol. 2019 Feb 1;30(2):171-210. PMID: 30596843

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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 et al. Ann Oncol 2020 Aug 24;S0923-7534(20)39971-3. PMID: 32853681

Website https://www.mycancergenome.org/
https://www.e-cancer.fr/
https://www.cancer.gov/

Abbreviations

SMLC	Small cell lung cancer
NSMLC	Non-small cell lung cancer
ICI	Immune checkpoint inhibitor
IHC	Immunohistochemistry
TKI	Tyrosine-kinase inhibitor
MDCM	Multidisciplinary consultation meeting
TMB	Tumour mutational burden

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DS83-INTGB – October 2020