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Patología I

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Bristol-Myers Squibb

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Spanish Lung Cancer Biomarker Testing Registry (Lungpath): Descriptive Analysis Focus in ALK Traslocation Results

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IASLC HIGHLIGHTS
7-10 DE SEPTIEMBRE 2019

SEAP-IAP Sociedad Española de Anatomía Patológica

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BACKGROUND

Oncogenic ALK gene rearrangements are found in approximately 4% of non-small cell lung cancer (NSCLC). Treatment options such as ALK tyrosine kinase inhibitors lead to improved progression free survival and overall survival. Thus, biomarker testing on pathology specimens is an essential requirement to properly treat lung cancer (LC) patients.
LungPath is an on-line tool developed by the Spanish Society of Pathology (*SEAP*) with free and voluntary participation of different Departments of Pathology to registry, monitor and trace biomarker results in clinical practice. After initial data recruitment step, first objective is to perform a descriptive analysis of *LungPath* focusing on ALK translocation testing.

METHODS

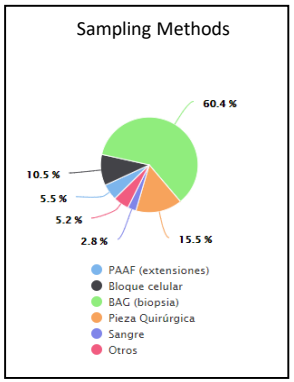
Descriptive analysis of the *LungPath* registry. Biomarker determination of LC patients were collected from March 2018 to January 2019, from 38 Spanish Departments of Pathology.

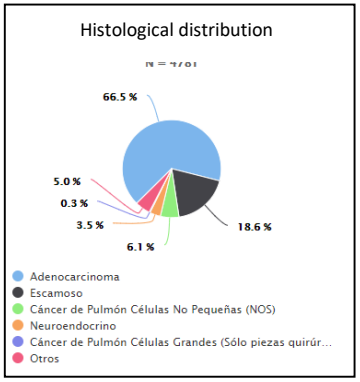
RESULTS

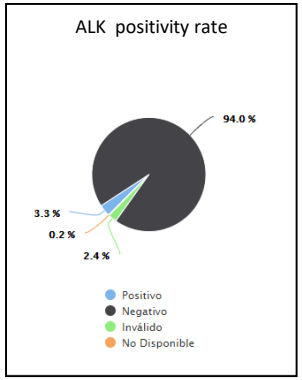
Based on this real clinical practice database, 9 biomarkers were tested over a total of 4.781 samples from LC patients. Small lung biopsies (60,4%), surgical resection specimens (15,5%) and cell block cytology (10,5%) were the mainly used samples in addition to fine needle aspiration cytology (5,5%), blood (2,5%) and other lung biopsies (5,2%).
NSCLC accounts for 95,1% of cases, principally adenocarcinoma (66,5%), squamous cell carcinoma (SCC) (18,6%), NOS (not otherwise specified) (6,1%), neuroendocrine carcinoma (3,5%) and large cell carcinoma accounting for 0,3%.
In non-squamous samples, ALK translocation was one of the most frequently analyzed biomarker (78,70%). On the other hand, in SCC, ALK translocation was shortly analyzed (52,40%), being PD-L1 expression the main biomarker analyzed (71,80%). From the adenocarcinoma samples, ALK positivity rate was 3,3%; 2,4% were invalid determinations due to several reasons.

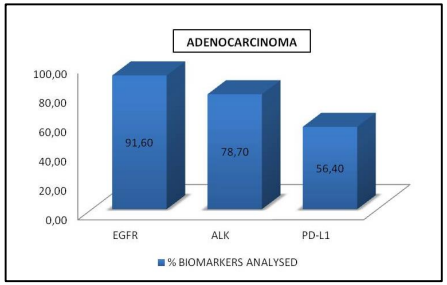
CONCLUSION

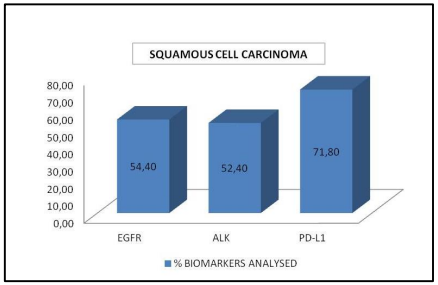
Development of central biomarker databases, such as Lungpath, provide an opportunity to registry clinical practice data and in the future could be a useful tool to monitor and correlate results between different centers and improve the available knowledge regarding biomarkers in LC.
According to international guidelines, EGFR mutations and ALK translocations should be tested in all advanced NSCLC specially in lung adenocarcinoma. ALK trasnlocation was one of the main biomarkers tested in our database with 3,4% translocation rate, similar to literature results.











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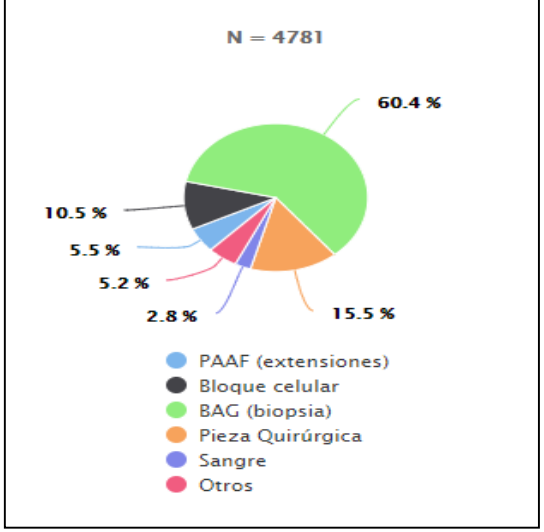
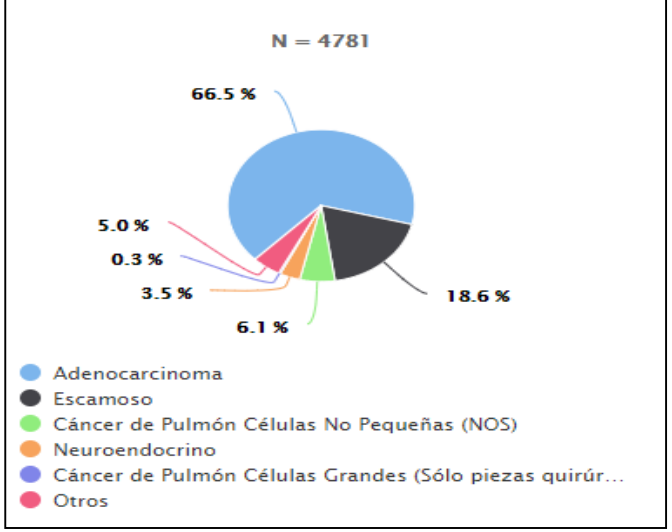
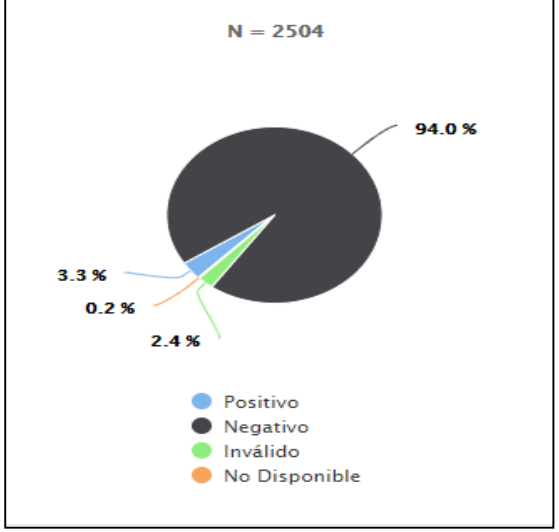
Sampling Methods

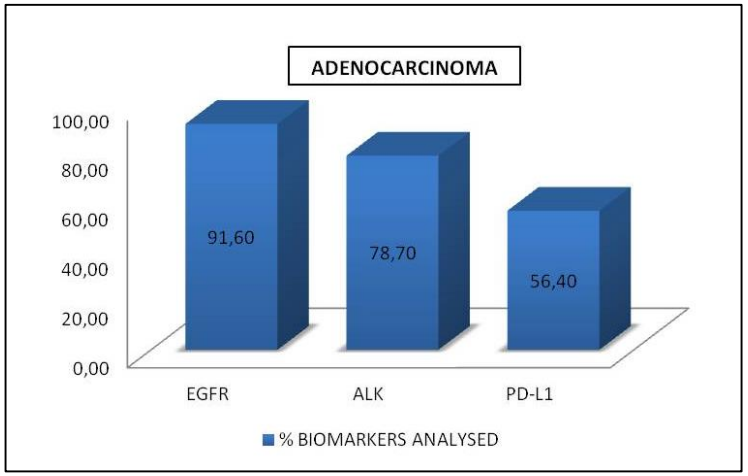


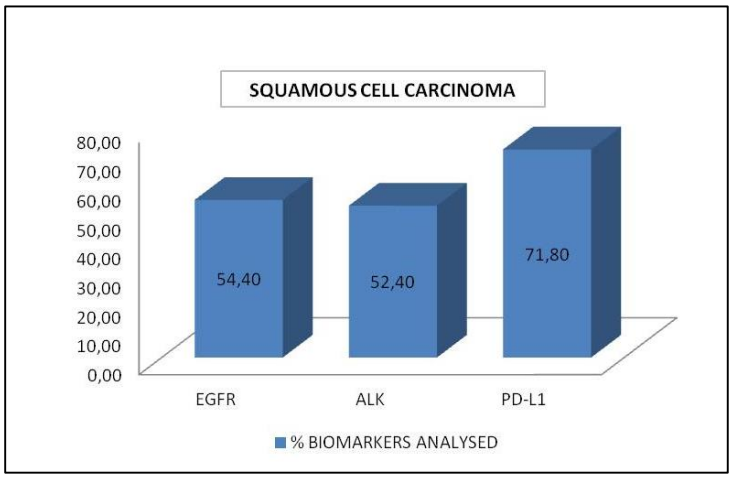
Histological distribution



ALK positivity rate







Iniciativa científica de:
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P2.04-22 - Programmed Death 1-mRNA Expression Predicts Benefit to Anti-PD1 Monotherapy in a Prospective Cohort of Advanced NSCLC (ID 1092)

LUNG CANCER UPDATES
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7-10 DE SEPTIEMBRE 2019

CLÍNIC BARCELONA Hospital Universitari

Programmed Death 1-mRNA Expression Predicts Benefit to Anti-PD1 Monotherapy in a Prospective Cohort of Advanced NSCLC

1092

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Abstract

Background: Immunotherapy (IO) targeting PD1 or PD-L1 represents a new treatment option for patients with advanced non-small cell lung cancer (NSCLC). Besides PD-L1 IHC, other predictive biomarkers are being explored as potential predictors of outcomes. Our group has recently described an association between PD1-mRNA expression and response to IO in a retrospective multi-tumor dataset (Annals Oncol 2018). We aimed to corroborate these results in a prospective cohort of advanced NSCLC.

Methods: We prospectively evaluated the expression of 7 immune-related genes (CD4, CD8, PD1, PDL1, IFNG, GZMM and FOXP3) and 5 housekeeping genes in formalin-fixed paraffin-embedded tumor samples obtained before anti-PD1 therapy using the nCounter platform (Nanostring Technologies). The study cohort included consecutive patients with advanced NSCLC, ECOG/PS 0-1, no targetable oncogenes, treated in the first or second-line setting with anti-PD1 monotherapy from June 2017 to January 2019. Associations between the expression of PD1 mRNA (as a continuous variable and using a previously defined pre-specified cut point) and response (complete and partial response) were assessed using logistic regression analysis. Kaplan-Meier method was used for survival analysis. PD-L1 IHC tumor cell expression was assessed using the 22C3 clone. Pearson correlation between PD-L1 IHC and PD1 mRNA was explored.

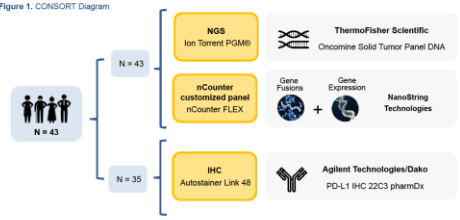
Results: A total of 43 patients were included (men 79%; adenocarcinoma 53%; nivolumab 55%; pembrolizumab 45%; first-line 30%; second-line 70%). Response occurred in 23% of patients and was significantly associated with PD1 (p=0.029) and FOXP3 (p=0.035) expression. Using the pre-established PD1 cutoff (Annals Oncol 2018), 37% and 63% samples were PD1-high and PD1-low, respectively. PD1-high was significantly associated with increased overall response rate (ORR) (43% vs 11%, OR=6.22 [CI=1.31-29.44], p=0.021) and progression-free survival (HR 0.36 [CI= 0.14-0.90], p=0.028) but not with overall survival (p=0.151). PD-L1 IHC expression was available in 35 cases, of which 46% had high (≥50%) expression levels. A moderate concordance (0.49) was observed between PD-L1 IHC and PD1-mRNA. In this subset analysis, high PD-L1 IHC was significantly associated with response (50% vs 11%, OR=8.50 [CI= 1.45-49.53], p=0.043). Importantly, when combining predefined high/low-sets for both biomarkers (PD-L1 IHC/PD1-mRNA), response was significantly increased in PD-L1-high/PD1-high compared to PD-L1-low/PD1-low (ORR 57% vs 0%, p =0.019).

Objective

We aimed to evaluate PD1-mRNA expression in a prospective cohort of advanced NSCLC of patients without relevant oncogenic alterations to define its value as potential predictor of response to immunotherapy (anti-PD1 inhibition).

Study Workflow

Figure 1. CONSORT Diagram



Results

Figure 2. Box-Plot diagrams displaying the expression of the immune genes *PDL1* (A), *FOXP3* (B) *and PD1* (C) versus overall response rate (ORR) in 43 patients with advanced NSCLC treated with anti-PD1 therapy.

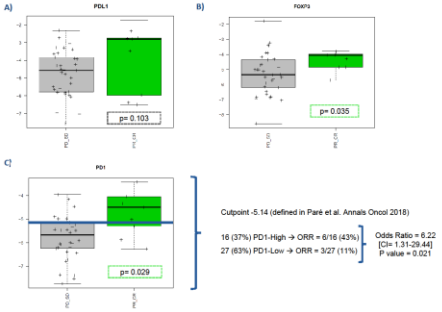


Figure 3. Progression-free survival (PFS) (A) and overall survival (B) based on *PD1*-mRNA expression. P-value was obtained from the log-rank test.

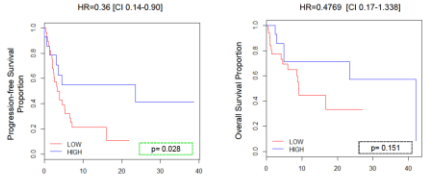
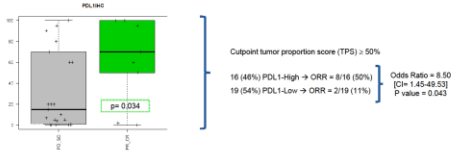


Figure 4. Association of PDL1 expression evaluated by immunohistochemistry (IHC) with overall response rate (ORR) (A) and comparison of PDL1 IHC and PD1-mRNA expression (B) in 35 samples with advanced NSCLC.



B)

	mRNA expression		
Immunohistochemistry	PD1 Low	PD1 High	Total
PDL1 Negative – Low	10 (52.6%)	9 (47.4%)	19
PDL1 High (TPS ≥ 50%)	9 (56.3%)	7 (43.7%)	16

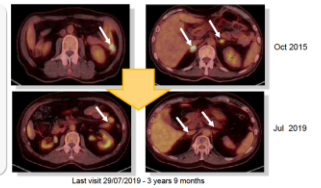
ORR based on PDL1 IHC and PD1-mRNA expression

PDL1 IHC High & PD1 High = 4/7 (57.1%)
Others = 5/18 (27.8%)
PDL1 IHC Low and PD1 Low = 0/10 (0%)

P value = 0.019

Case Report

- Male, 63 years old
- Lung ADK IIIA (T3N1M0)
- ECOG PS1
- June 2015: surgery → Chemotherapy
- Oct 2015: relapse (bilateral SRG, intestinal M1)
- Molecular:
  - TPS PDL1 100%
  - nCounter *ALK, ROS1, RET, NTRK, MET*ex14: WT
  - nCounter IO: PD1 High
  - Oncomine Solid Tumor DNA panel (NGS): WT
- Nov 2015: 1L Nivolumab (Stop 10/2017)
- Jan 2016: Partial Response (PR)
- Jul 2019: Maintained PR



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Conclusions

- PD1-mRNA expression is associated with response to anti-PD1 monotherapy .
- PD1-mRNA expression can increase the predictive ability of PD-L1 IHC.
- Further validation of these findings in pivotal clinical trials evaluating IO in advanced NSCLC patients seems

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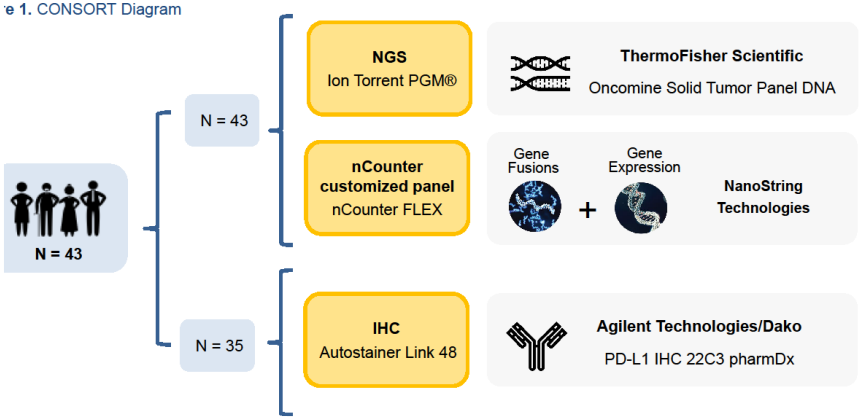

C) versus

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io = 6.22
l-29.44]
= 0.021

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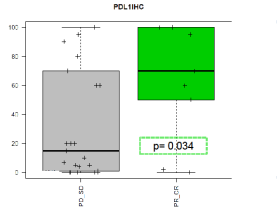
A)



Cutpoint tumor proportion score (TPS) ≥ 50%

16 (46%) PDL1-High → ORR = 8/16 (50%)
19 (54%) PDL1-Low → ORR = 2/19 (11%)

Odds Ratio = 8.50
[CI= 1.45-49.53]
P value = 0.043

B)

	mRNA expression		
Immunohistochemistry	PD1 Low	PD1 High	Total
PDL1 Negative – Low	10 (52.6%)	9 (47.4%)	19
PDL1 High (TPS ≥ 50%)	9 (56.3%)	7 (43.7%)	16

ORR based on PDL1 IHC and PD1-mRNA expression

PDL1 IHC High & PD1 High = 4/7 (57.1%)
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P value = 0.019

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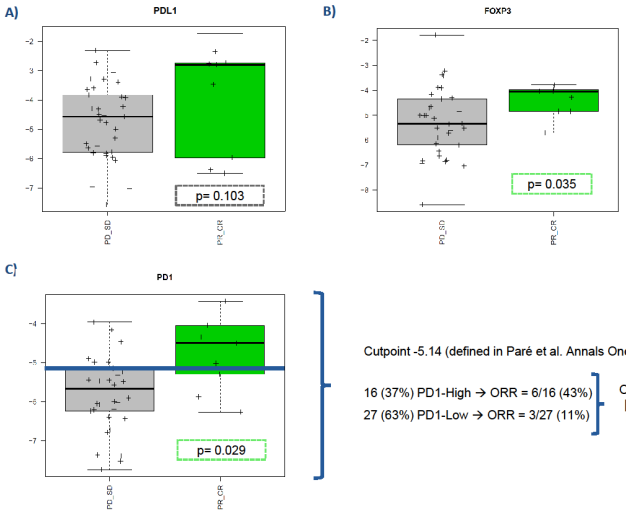

Cutpoint -5.14 (defined in Paré et al. Annals Oncol 2018)

16 (37%) PD1-High → ORR = 6/16 (43%)
27 (63%) PD1-Low → ORR = 3/27 (11%)

Odds Ratio = 6.22
[CI= 1.31-29.44]
P value = 0.021

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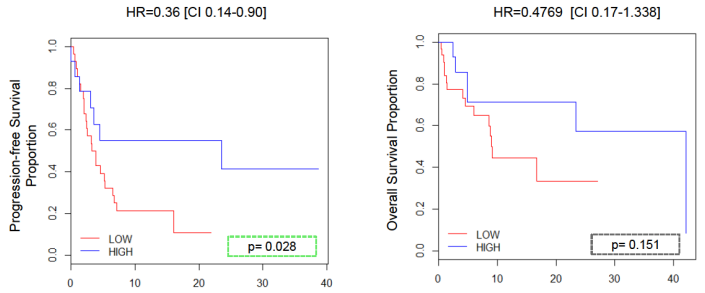

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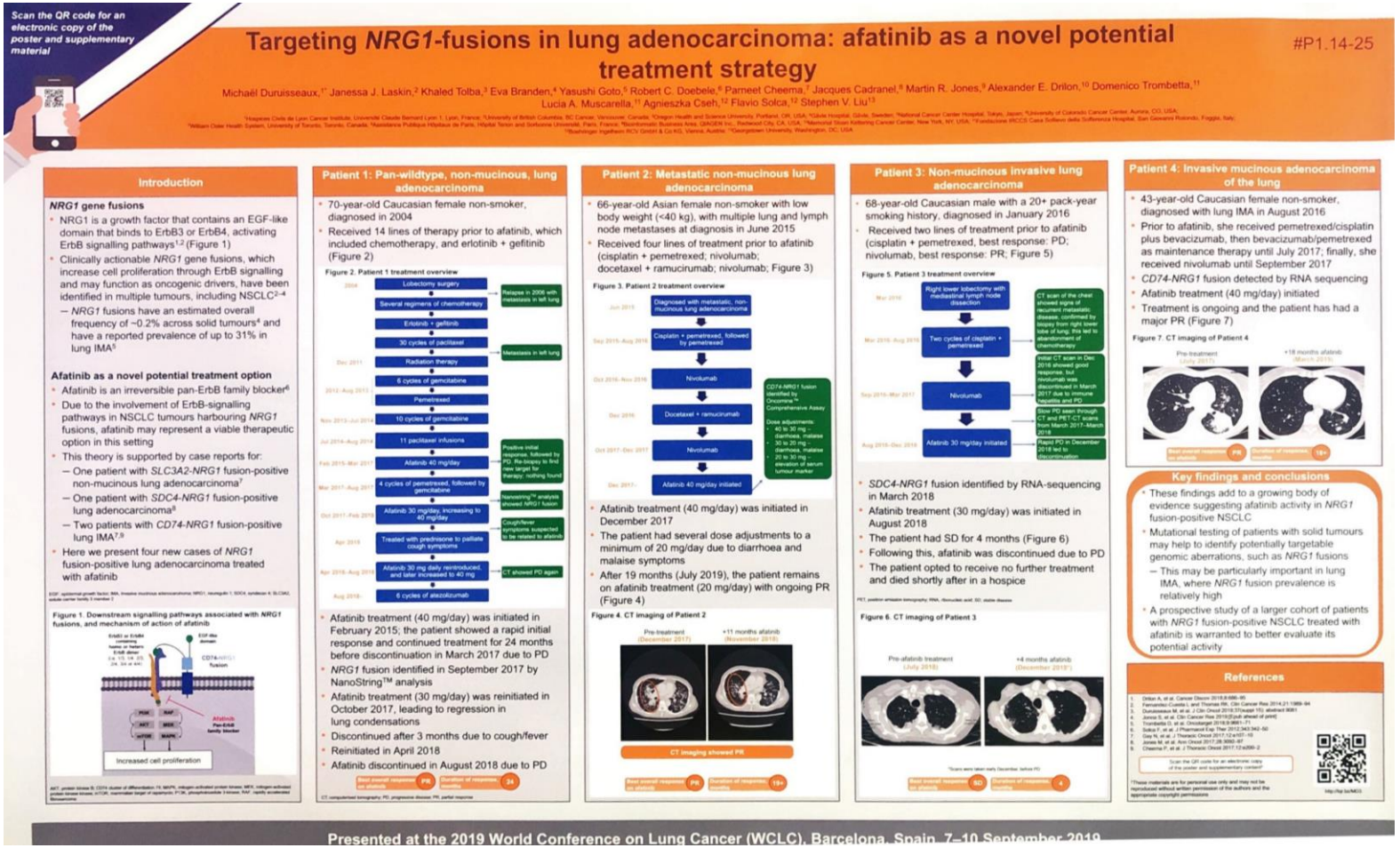
P1.14-25 - Targeting NRG1-Fusions in Lung Adenocarcinoma: Afatinib as a Novel Potential Treatment Strategy



Scan the QR code for an electronic copy of the poster and supplementary material

Targeting *NRG1*-fusions in lung adenocarcinoma: afatinib as a novel potential treatment strategy

#P1.14-25

Michaël Duruisseaux,[1*] Janessa J. Laskin,[2] Khaled Tolba,[3] Eva Branden,[4] Yasushi Goto,[5] Robert C. Doebele,[6] Parneet Cheema,[7] Jacques Cadranel,[8] Martin R. Jones,[9] Alexander E. Drilon,[10] Domenico Trombetta,[11] Lucia A. Muscarella,[11] Agnieszka Cseh,[12] Flavio Solca,[12] Stephen V. Liu[13]

Introduction

***NRG1* gene fusions**

- NRG1 is a growth factor that contains an EGF-like domain that binds to ErbB3 or ErbB4, activating ErbB signalling pathways[1,2] (Figure 1)
- Clinically actionable *NRG1* gene fusions, which increase cell proliferation through ErbB signalling and may function as oncogenic drivers, have been identified in multiple tumours, including NSCLC[2–4]
  - *NRG1* fusions have an estimated overall frequency of ~0.2% across solid tumours[4] and have a reported prevalence of up to 31% in lung IMA[5]

Afatinib as a novel potential treatment option

- Afatinib is an irreversible pan-ErbB family blocker[6]
- Due to the involvement of ErbB-signalling pathways in NSCLC tumours harbouring *NRG1* fusions, afatinib may represent a viable therapeutic option in this setting
- This theory is supported by case reports for:
  - One patient with *SLC3A2-NRG1* fusion-positive non-mucinous lung adenocarcinoma[7]
  - One patient with *SDC4-NRG1* fusion-positive lung adenocarcinoma[8]
  - Two patients with *CD74-NRG1* fusion-positive lung IMA[7,9]
- Here we present four new cases of *NRG1* fusion-positive lung adenocarcinoma treated with afatinib

Figure 1. Downstream signalling pathways associated with *NRG1* fusions, and mechanism of action of afatinib

Patient 1: Pan-wildtype, non-mucinous, lung adenocarcinoma

- 70-year-old Caucasian female non-smoker, diagnosed in 2004
- Received 14 lines of therapy prior to afatinib, which included chemotherapy, and erlotinib + gefitinib (Figure 2)

Figure 2. Patient 1 treatment overview

- Afatinib treatment (40 mg/day) was initiated in February 2015; the patient showed a rapid initial response and continued treatment for 24 months before discontinuation in March 2017 due to PD
- *NRG1* fusion identified in September 2017 by NanoString™ analysis
- Afatinib treatment (30 mg/day) was reinitiated in October 2017, leading to regression in lung condensations
- Discontinued after 3 months due to cough/fever
- Reinitiated in April 2018
- Afatinib discontinued in August 2018 due to PD

Patient 2: Metastatic non-mucinous lung adenocarcinoma

- 66-year-old Asian female non-smoker with low body weight (<40 kg), with multiple lung and lymph node metastases at diagnosis in June 2015
- Received four lines of treatment prior to afatinib (cisplatin + pemetrexed; nivolumab; docetaxel + ramucirumab; nivolumab; Figure 3)

Figure 3. Patient 2 treatment overview

- Afatinib treatment (40 mg/day) was initiated in December 2017
- The patient had several dose adjustments to a minimum of 20 mg/day due to diarrhoea and malaise symptoms
- After 19 months (July 2019), the patient remains on afatinib treatment (20 mg/day) with ongoing PR (Figure 4)

Figure 4. CT imaging of Patient 2

Patient 3: Non-mucinous invasive lung adenocarcinoma

- 68-year-old Caucasian male with a 20+ pack-year smoking history, diagnosed in January 2016
- Received two lines of treatment prior to afatinib (cisplatin + pemetrexed, best response: PD; nivolumab, best response: PR; Figure 5)

Figure 5. Patient 3 treatment overview

- *SDC4-NRG1* fusion identified by RNA-sequencing in March 2018
- Afatinib treatment (30 mg/day) was initiated in August 2018
- The patient had SD for 4 months (Figure 6)
- Following this, afatinib was discontinued due to PD
- The patient opted to receive no further treatment and died shortly after in a hospice

Figure 6. CT imaging of Patient 3

Patient 4: Invasive mucinous adenocarcinoma of the lung

- 43-year-old Caucasian female non-smoker, diagnosed with lung IMA in August 2016
- Prior to afatinib, she received pemetrexed/cisplatin plus bevacizumab, then bevacizumab/pemetrexed as maintenance therapy until July 2017; finally, she received nivolumab until September 2017
- *CD74-NRG1* fusion detected by RNA sequencing
- Afatinib treatment (40 mg/day) initiated
- Treatment is ongoing and the patient has had a major PR (Figure 7)

Figure 7. CT imaging of Patient 4

Key findings and conclusions

- These findings add to a growing body of evidence suggesting afatinib activity in *NRG1* fusion-positive NSCLC
- Mutational testing of patients with solid tumours may help to identify potentially targetable genomic aberrations, such as *NRG1* fusions
  - This may be particularly important in lung IMA, where *NRG1* fusion prevalence is relatively high
- A prospective study of a larger cohort of patients with *NRG1* fusion-positive NSCLC treated with afatinib is warranted to better evaluate its potential activity

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