# Actualités Post ESMO en Oncologie thoracique

Mardi 18 Octobre 2022

**Dr Sophie COUSIN**

**Institut Bergonié**

Rétrospective Post Congrès 2022

# Liens d'intérêts

- Participation congrès : MSD, Pfizer, Pharmamar, Astrazeneca, Janssen
- Board: Bristol-Myers Squibb, MSD, Astrazeneca, Roche, Takeda, Sanofi
- Honoraires investigateur (recherche clinique): GSK, Novartis, Astrazeneca, MSD, Sanofi, Pharmamar, Roche, Abbvie, Takeda, Novocure, Loxo oncology, Genentech, FivePrime, Epizyme, Lilly, Bayer, OSE immunotherapeutics, Byondis, Puma Biotechnology, Bicycle therapeutics…

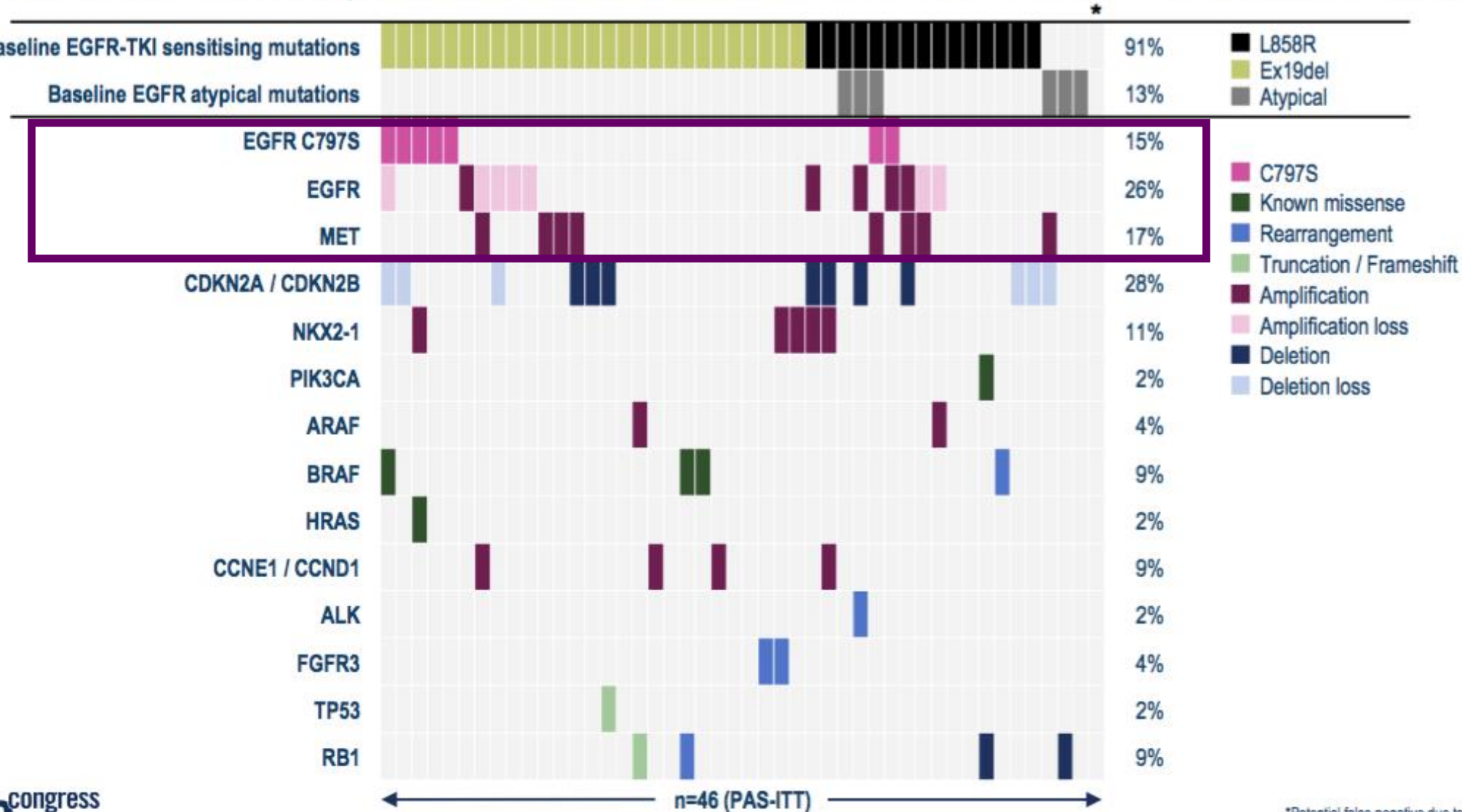
PARIS 2022 ESMO congress

# ELIOS: a multicentre, molecular profiling study of patients with EGFRm advanced NSCLC treated with first-line osimertinib

Zofia Piotrowska[1], Myung-Ju Ahn[2], Yong Kek Pang[3], Soon Hin How[4], Sang-We Kim[5], Pei Jye Voon[6], Diego Cortinovis[7], Javier de Castro Carpeno[8], Marcello Tiseo[9], Delvys Rodriguez Abreu[10], Suresh S. Ramalingam[11], Jingyi Li[12], Leslie Servidio[12], Samuel Sadow[13], Ryan Hartmaier[14], Byoung Chul Cho[15]

[1]Department of Medicine, Massachusetts General Hospital, Boston, MA, USA; [2]Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [3]Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia; [4]Department of Medicine, Kulliyyah of Medicine, International Islamic University Malaysia, Kuantan, Malaysia; [5]Department of Oncology, Asan Medical Center, Seoul, South Korea; [6]Radiotherapy and Oncology Department, Hospital Umum Sarawak, Kuching, Malaysia; [7]Oncology Unit, San Gerardo Hospital, Monza, Italy; [8]Department of Medical Oncology, Hospital Universitario La Paz, IdiPAZ, Madrid, Spain; [9]Department of Medicine and Surgery, University of Parma, Parma, Italy and Medical Oncology Unit, University Hospital of Parma, Parma, Italy; [10]Department of Medical Oncology, Gran Canaria University Hospital, Las Palmas de Gran Canaria, Spain; [11]The Winship Cancer Institute of Emory University, Atlanta, GA, USA; [12]AstraZeneca, Oncology Business Unit, Global Medical Affairs, Gaithersburg, MD, USA; [13]Biometrics & Information Sciences, AstraZeneca, Gaithersburg, MD, USA; [14]Translational Medicine, AstraZeneca Oncology R&D, Boston, MA, USA; [15]Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea

# CANDIDATE ACQUIRED ALTERATIONS WITH OSIMERTINIB




*Potential false negative due to low tumour content.



Zofia Piotrowska, MD



EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; TKI, tyrosine kinase inhibitor.

LBA52

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# Tepotinib + osimertinib for *EGFR*m NSCLC with *MET* amplification (*MET*amp) after progression on first-line (1L) osimertinib:

# Initial results from the INSIGHT 2 study

**Julien Mazieres**, Tae Min Kim, Boon Khaw Lim, Marie Wislez, Christophe Dooms, Giovanna Finocchiaro, Hidetoshi Hayashi, Chong Kin Liam, Jo Raskin, Lye Mun Tho, Filippo de Marinis, Ernest Nadal, Egbert F. Smit, Xiuning Le, Sabine Brutlach, Aurora O'Brate, Svenja Adrian, Barbara Ellers-Lenz, Niki Karachaliou, Yi-Long Wu

Toulouse, France

# INSIGHT 2: Design de l'étude

**Phase 2 en ouvert, chez mCBNPC EGFR muté après progression sous Osimertinib en 1L et présentant une amplification de MET.**

**Key inclusion criteria**

- Locally advanced or metastatic NSCLC with activating *EGFR* mutation
- Acquired resistance to 1L osimertinib
- *MET*amp detected by either central or local* FISH testing (TBx) or central NGS testing (LBx)†
- ECOG PS of 0 or 1
- Stable, treated brain metastases allowed

**Tepotinib** 500 mg QD
**+**
**Osimertinib** 80 mg QD‡

**Tepotinib monotherapy arm#**

**Primary objective**

- ORR by IRC for patients with *MET*amp centrally confirmed by TBx FISH treated with tepotinib plus osimertinib

**Secondary objectives include:**

- ORR by IRC in patients with:
  - *MET*amp by LBx NGS treated with tepotinib plus osimertinib
  - *MET*amp centrally confirmed by TBx FISH treated with tepotinib monotherapy

**Initial results are presented; global enrollment is complete, primary analysis is planned when all patients have ≥9 months' follow-up**

# Détection de l'amplification de MET

***MET*amp definitions**

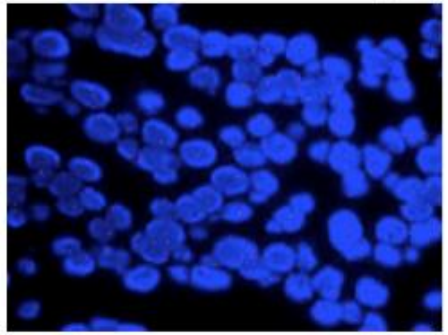
**TBx FISH:** *MET* GCN ≥5 and/or *MET/CEP7* ≥2

**and/or**

**LBx NGS:** *MET* GCN ≥2.3; Archer®

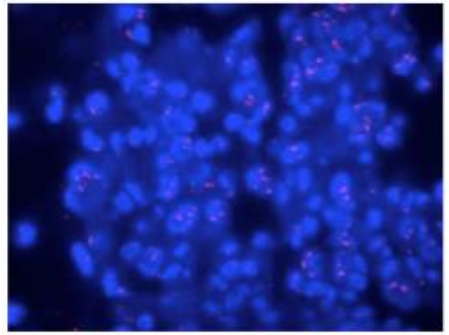
Central testing was mandatory for both

**TBx FISH: *MET*amp -**



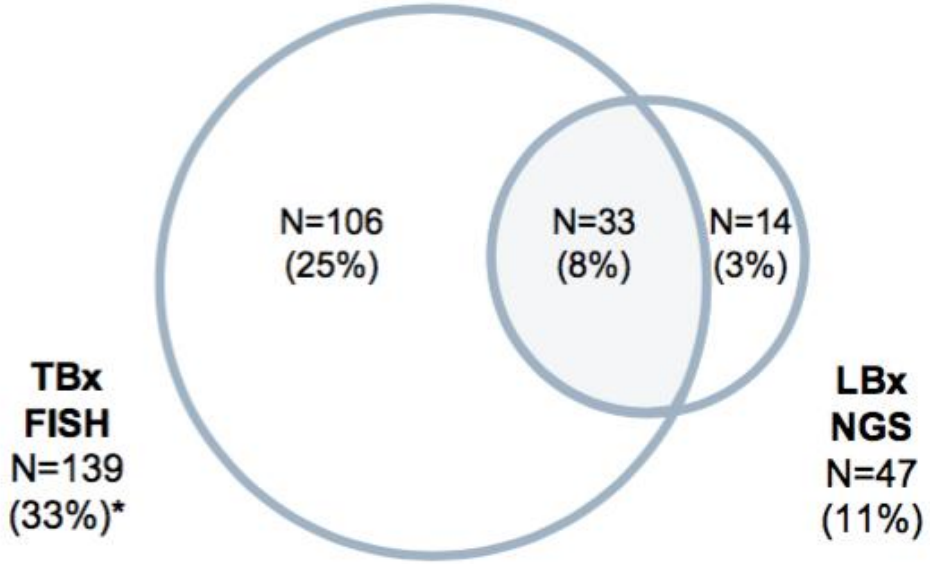
*MET* GCN, 2.33; *MET/CEP7*, 0.96

**TBx FISH: *MET*amp +**



*MET* GCN, 17.4; *MET/CEP7*, 7.35

– Among 425 pre-screened patients, *MET*amp was detected in 153 patients (36%) by:




*30 patients were local TBx FISH test positive and were also analyzed by central TBx FISH. When excluding these locally preselected patients, the central TBx FISH *MET*amp rate was 28%.

# Objective Response Rate of Tepotinib plus Osimertinib

## Tepotinib plus osimertinib (IRC)

| | *MET*amp by central TBx FISH | | *MET*amp by central LBx NGS | |
|---|---|---|---|---|
| Follow-up | ≥9 months (N=22) | ≥3 months (N=48) | ≥9 months (N=16) | ≥3 months (N=23) |
| **ORR** (95% CI) | **54.5%** (32.2, 75.6) | **45.8%** (31.4, 60.8) | **50.0%** (24.7, 75.3) | **56.5%** (34.5, 76.8) |
| **BOR, n (%)** | | | | |
| PR | 12 (54.5) | 22 (45.8) | 8 (50.0) | 13 (56.5) |
| SD | 2 (9.1) | 5 (10.4) | 1 (6.3) | 1 (4.3) |
| PD | 4 (18.2) | 10 (20.8) | 5 (31.3) | 5 (21.7) |
| NE | 4 (18.2) | 11 (22.9)* | 2 (12.5) | 4 (17.4) |

Similar ORRs were reported according to *MET*amp GCN (TBx FISH):

Patients with ≥3 months' follow-up (N=48): **≥10 GCN**: 51.9% (95% CI: 31.9, 71.3) (N=27);
**5–<10 GCN:** 40.0% (95% CI: 19.1, 63.9) (N=20)†

## Tepotinib monotherapy (IRC)

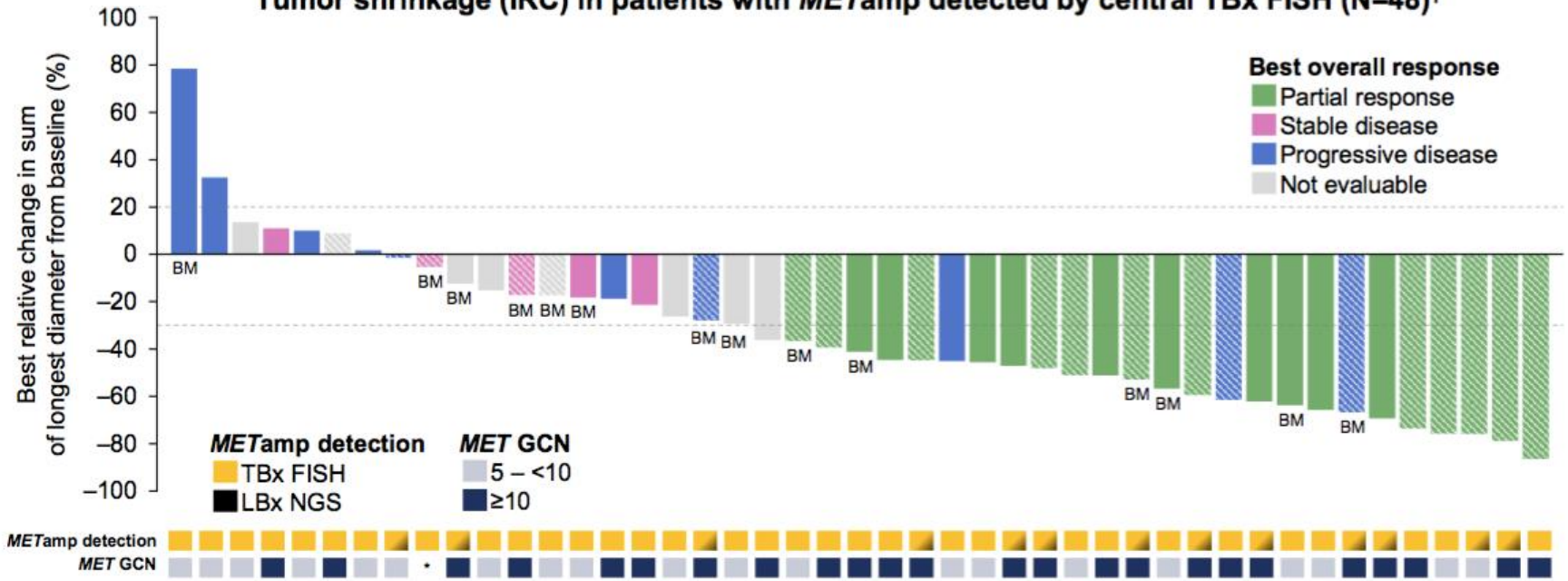
| | *MET*amp by central TBx FISH |
|---|---|
| Follow-up | ≥6 months (N=12) |
| **ORR** (95% CI) | **8.3%** (0.2, 38.5) |
| **BOR, n (%)** | |
| PR | 1 (8.3) |
| SD | 2 (16.7) |
| PD | 8 (66.7) |
| NE | 1 (8.3) |

Seven patients switched to tepotinib plus osimertinib and five of them are still on combination treatment

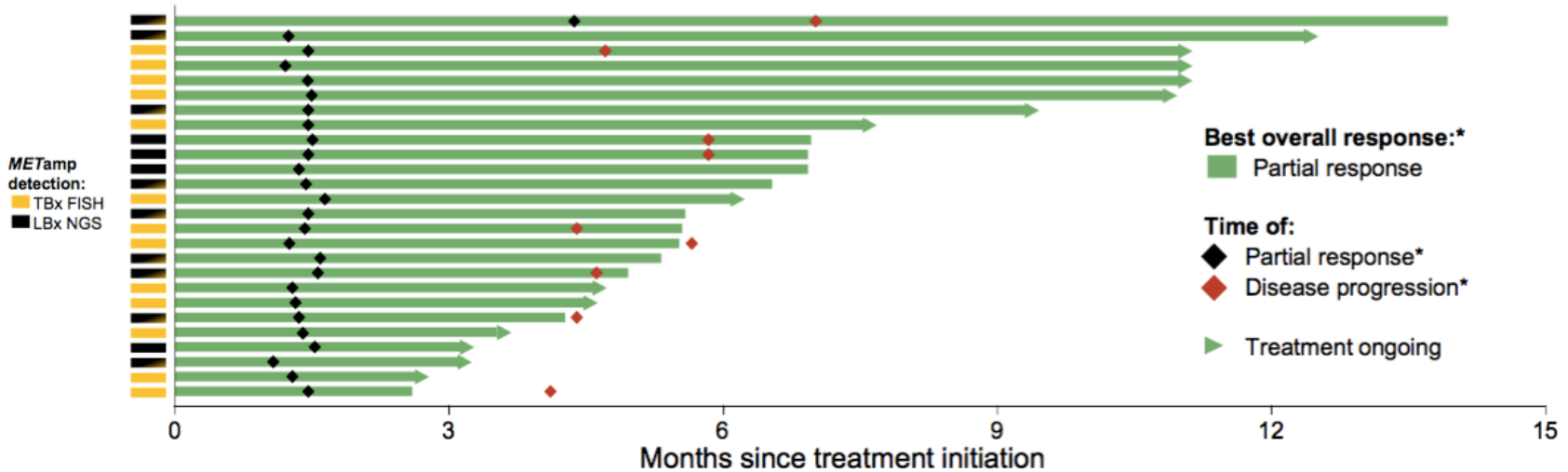
**Confirmed ORR was 54.5% in patients with *MET*amp detected by TBx FISH with ≥9 months' follow-up**

*Incomplete post-baseline assessments (n=2), SD <12 weeks (n=3), COVID-19-related early discontinuation (n=1), and PD/AE-related early discontinuations (n=5). †One patient had GCN 4.96 and enrolled through a *MET/CEP7* ratio ≥2.

## Tumor shrinkage (IRC) in patients with *MET*amp detected by central TBx FISH (N=48)†




## Time on treatment in responders (IRC) with *MET*amp detected by central TBx FISH and/or LBx NGS treated with tepotinib plus osimertinib (N=26)




**Responses mostly occurred within 6 weeks; half of responders had a duration of treatment ≥6 months**
**Median DOR was not reached**

CodeBreaK 200

PARIS 2022 ESMO congress

# Sotorasib versus Docetaxel for Previously Treated Non-Small Cell Lung Cancer with *KRAS* G12C Mutation: CodeBreaK 200 Phase 3 Study

**Melissa L. Johnson**,[1] Adrianus Johannes de Langen,[2] David Waterhouse,[3*] Julien Mazieres,[4] Anne-Marie C. Dingemans,[5] Giannis Mountzios,[6] Miklos Pless,[7] Jürgen Wolf,[8] Martin Schuler,[9] Hervé Lena,[10] Ferdinandos Skoulidis,[11] Isamu Okamoto,[12] Sang-We Kim,[13] Helena Linardou,[14] Silvia Novello,[15] Yuanbin Chen,[16] Benjamin Solomon,[17] Cynthia Obiozor,[18] Yang Wang,[18] Luis Paz-Ares[19]

[1]Sarah Cannon Research Institute at Tennessee Oncology, Nashville, TN, USA; [2]Netherlands Cancer Institute, Amsterdam, The Netherlands; [3]Oncology Hematology Care, Cincinnati, OH, USA; [4]Centre Hospitalier Universitaire de Toulouse, Toulouse, France; [5]Erasmus MC Cancer Institute, University Medical Center, Rotterdam, The Netherlands; [6]Henry Dunant Hospital Center, Athens, Greece; [7]Kantonsspital Winterthur, Winterthur, Switzerland; [8]Center for Integrated Oncology, University Hospital Cologne, Cologne, Germany; [9]West German Cancer Center, University Hospital Essen, Essen, Germany; [10]Centre Hospitalier Universitaire de Rennes - Hopital Pontchaillou, Rennes, France; [11]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [12]Kyushu University Hospital, Fukuoka, Japan; [13]Asan Medical Center, Seoul, South Korea; [14]Metropolitan Hospital, Athens, Greece; [15]Department of Oncology, Università Degli Studi Di Torino – San Luigi Hospital Orbassano, Italy; [16]Cancer & Hematology Centers of Western Michigan, Grand Rapids, MI, USA; [17]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [18]Amgen Inc., Thousand Oaks, CA, USA; [19]Hospital Universitario 12 de Octubre, CNIO-H12O Lung Cancer Unit, Complutense University and Ciberonc, Madrid, Spain.
*Currently at Dana–Farber Cancer Institute, Boston, MA, USA.

# CodeBreak 200

## Design de l'étude

**Key eligibility criteria**

- Locally advanced/unresectable or metastatic *KRAS* G12C-mutated NSCLC
- **≥ 1 prior treatment including platinum-based chemotherapy and checkpoint inhibitor***
- **No active brain metastases**
- ECOG performance status ≤ 1

**Stratification factors**

- Prior lines of therapy (1 vs 2 vs > 2)
- Race (Asian vs non-Asian)
- History of CNS involvement (yes vs no)

**Randomisation 1:1 (N = 345)**

**Sotorasib 960 mg oral daily N = 171**

**Docetaxel 75 mg/m² IV Q3W N = 174**

**Primary Endpoint: PFS by BICR**

**Secondary Endpoints: Efficacy** (OS†, ORR, DOR, TTR, DCR), **safety/tolerability, PRO**

**ITT population analysis included all randomised patients**

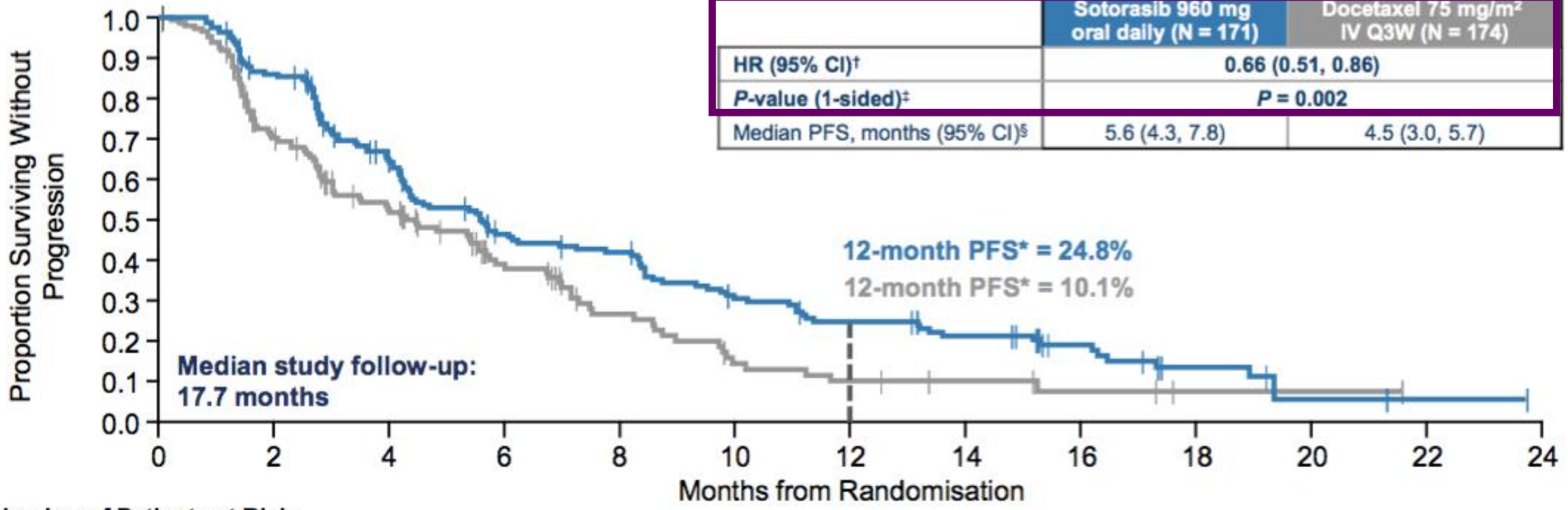
Per regulatory guidance, protocol was amended to reduce planned enrolment from 650 to ~330 patients, and crossover from docetaxel to sotorasib was permitted.

**Enrollment period: June 4, 2020 to April 26, 2021; protocol amendment: February 15, 2021; data cutoff: August 2, 2022.**

# CodeBreak 200

## Objectif primaire: la PFS

| | Sotorasib 960 mg oral daily (N = 171) | Docetaxel 75 mg/m² IV Q3W (N = 174) |
|---|---|---|
| HR (95% CI)† | 0.66 (0.51, 0.86) | |
| *P*-value (1-sided)‡ | *P* = 0.002 | |
| Median PFS, months (95% CI)§ | 5.6 (4.3, 7.8) | 4.5 (3.0, 5.7) |



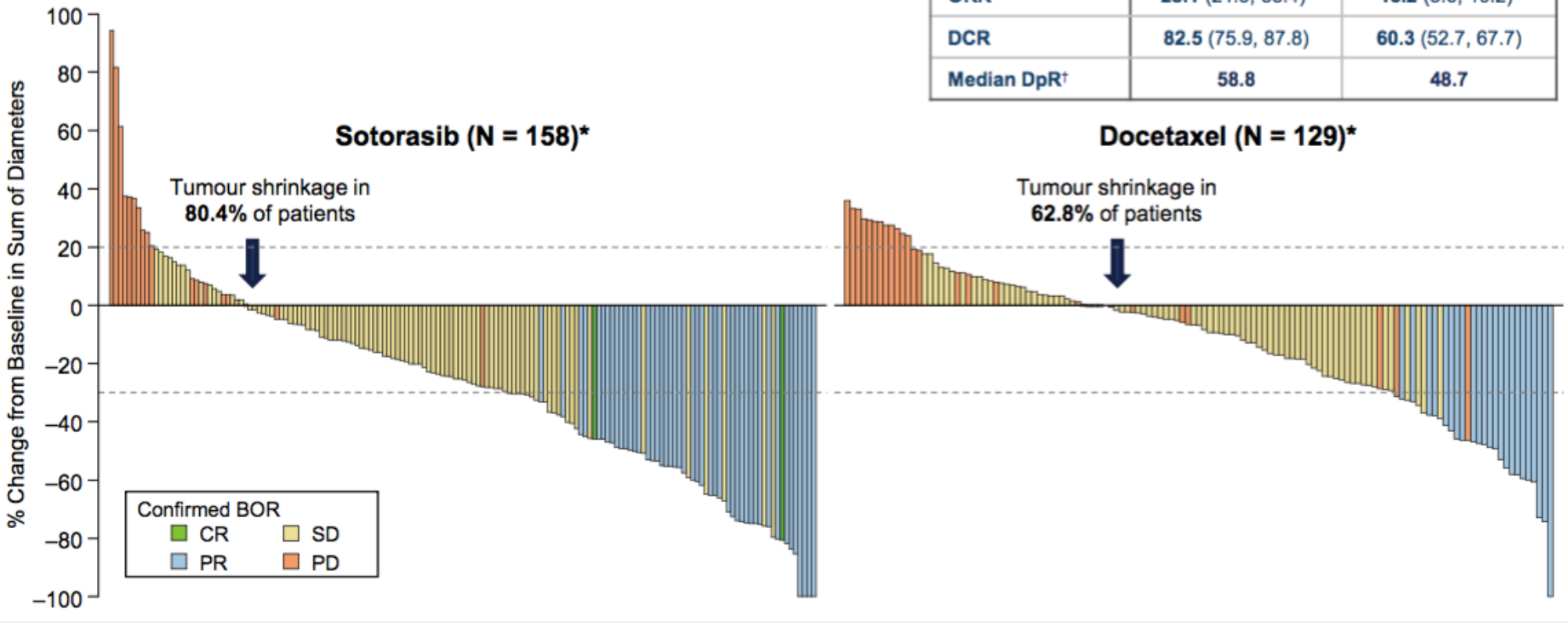

**Number of Patients at Risk:**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sotorasib | 171 | 139 | 93 | 63 | 56 | 38 | 30 | 24 | 14 | 6 | 2 | 1 | 0 |
| Docetaxel | 174 | 93 | 62 | 36 | 20 | 10 | 7 | 5 | 3 | 1 | 1 | 0 | |

# CodeBreak 200

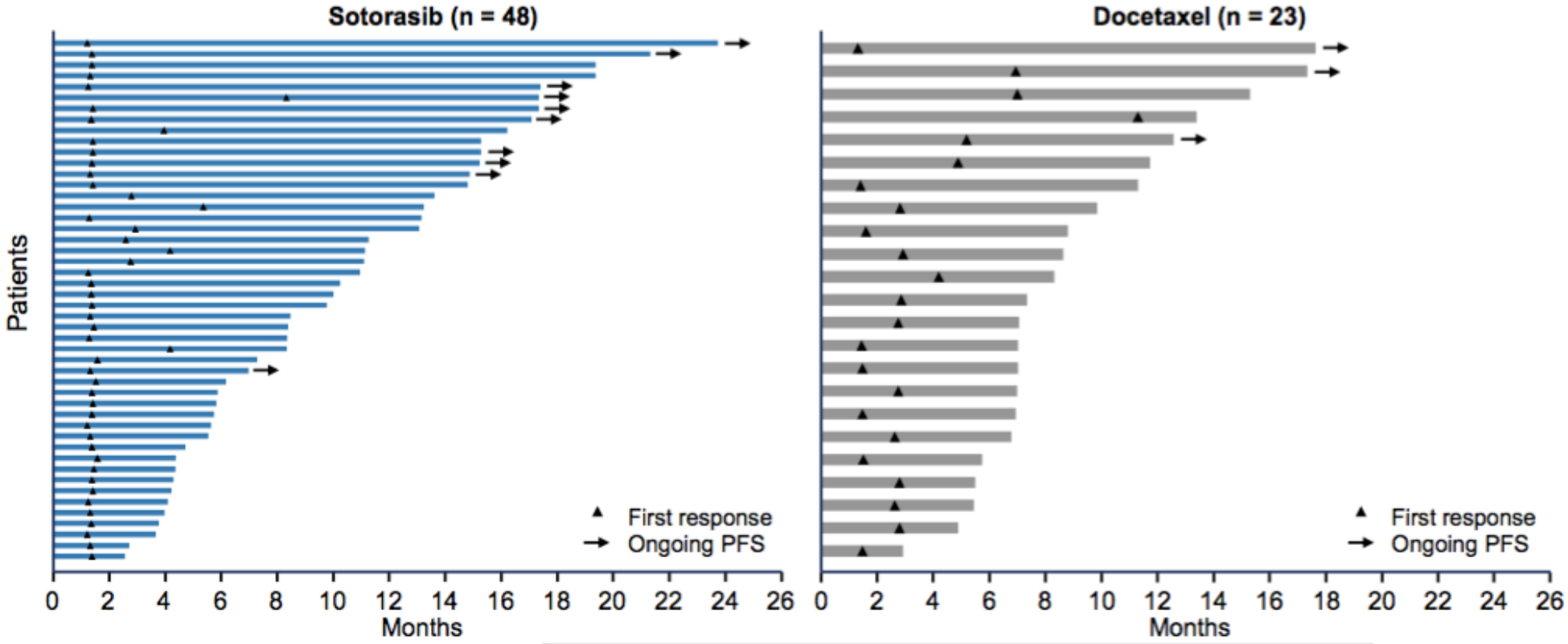
## Réponse objective

| % (95% CI) | Sotorasib | Docetaxel |
|---|---|---|
| ORR | **28.1** (21.5, 35.4) | **13.2** (8.6, 19.2) |
| DCR | **82.5** (75.9, 87.8) | **60.3** (52.7, 67.7) |
| Median DpR† | **58.8** | **48.7** |



# CodeBreak 200

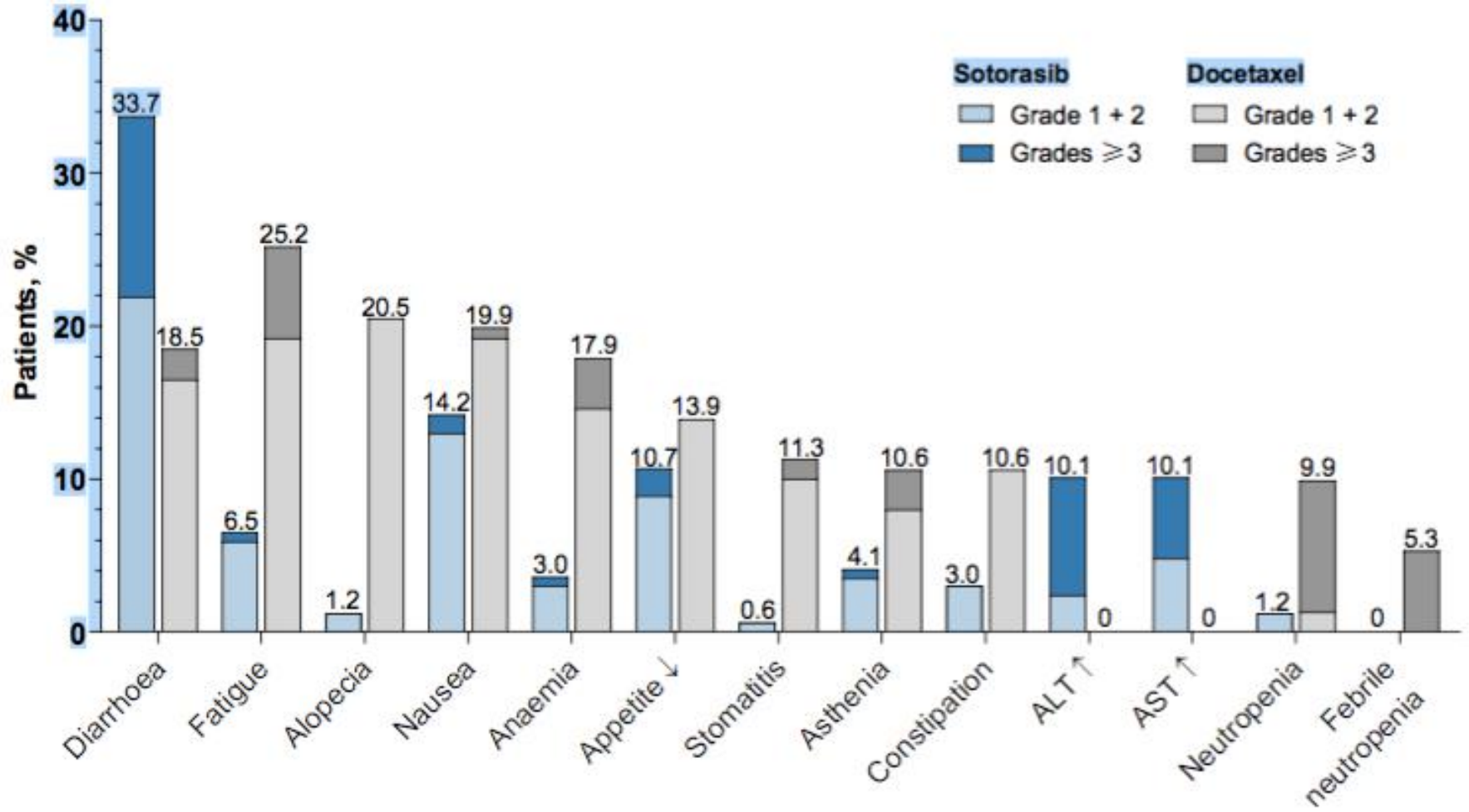
## Durée de la réponse




| | Sotorasib 960 mg oral daily (n = 48)† | Docetaxel 75 mg/m² IV Q3W (n = 23)† |
|---|---|---|
| Median TTR, months (range)‡ | 1.4 (1.2, 8.3) | 2.8 (1.3, 11.3) |
| Median DOR, months (95% CI)‡ | 8.6 (7.1, 18.0) | 6.8 (4.3, 8.3) |

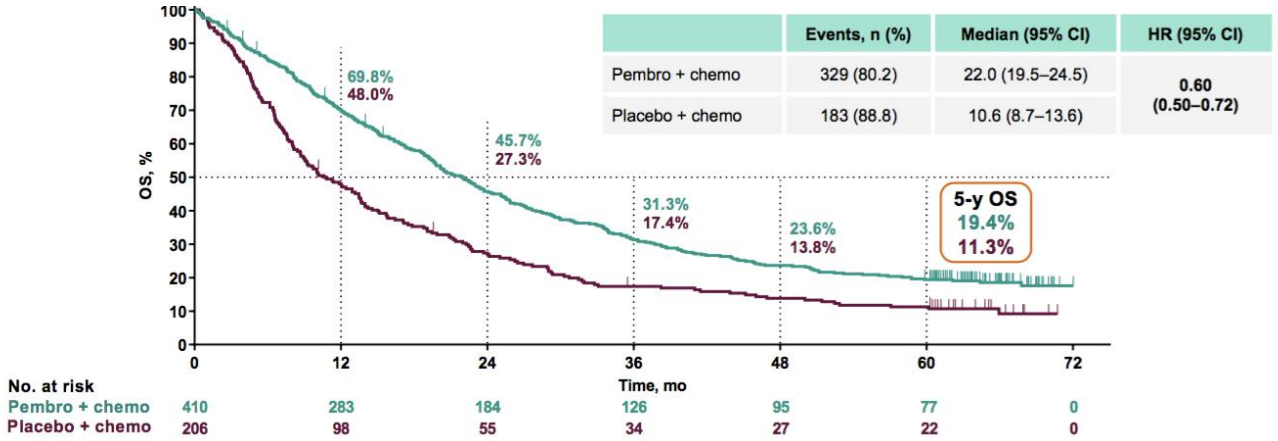
# CodeBreak 200

## Profil de toxicité



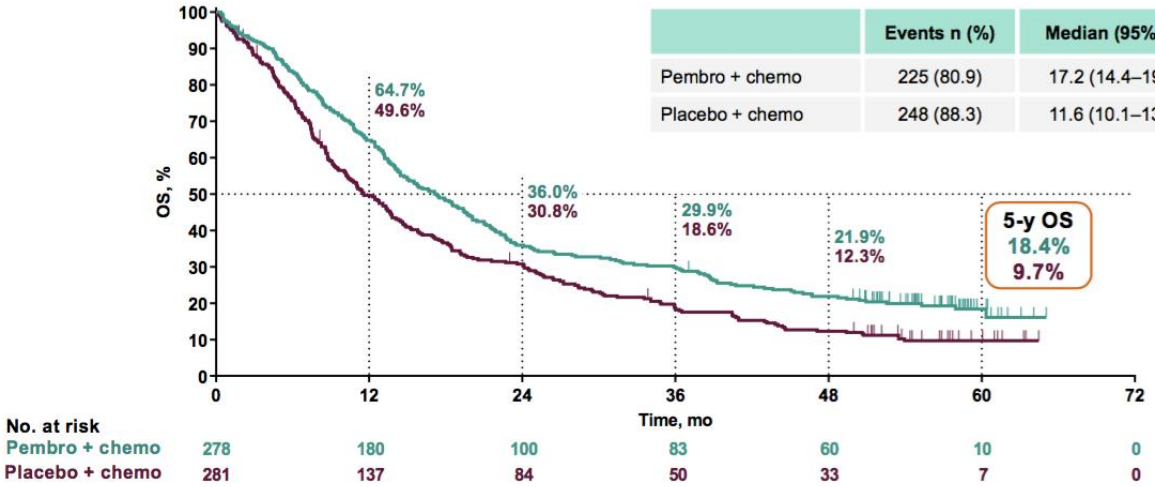
# Up-date à 5 ans des doublets + Pembrolizumab en 1ere ligne métastatique

**Keynote 189**
Non épidermoide
64,5 mois de médiane de follow-up




| | Events, n (%) | Median (95% CI) | HR (95% CI) |
|---|---|---|---|
| Pembro + chemo | 329 (80.2) | 22.0 (19.5–24.5) | 0.60 (0.50–0.72) |
| Placebo + chemo | 183 (88.8) | 10.6 (8.7–13.6) | |

**Keynote 407**
Epidermoide
56 mois de médiane de follow-up




| | Events n (%) | Median (95% CI) | HR (95% CI) |
|---|---|---|---|
| Pembro + chemo | 225 (80.9) | 17.2 (14.4–19.7) | 0.71 (0.59–0.85) |
| Placebo + chemo | 248 (88.3) | 11.6 (10.1–13.7) | |

Novello et al. Esmo 2022; Garassino et al. Esmo 2022

PARIS 2022 ESMO congress

# A randomized phase II study of preoperative nivolumab plus relatlimab or nivolumab in patients with resectable non-small-cell lung cancer

NEOpredict-Lung

**Martin Schuler**[1], Kristof Cuppens[2], Till Ploenes[1], Michel Vanbockrijck[2], Marcel Wiesweg[1], Kaid Darwiche[1], Alexander Schramm[1], Brigitte Maes[2], Balazs Hegedus[1], Hans-Ulrich Schildhaus[1], Hubertus Hautzel[1], Dirk Theegarten[1], Paul Baas[3], Koen Hartemink[3], Bert Du Pont[2], and Clemens Aigner[1]

[1]West German Cancer Center, University Medicine Essen, Essen, Germany
[2]Jessa Hospital, Hasselt, Belgium
[3]Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands

# NEOpredict-Lung

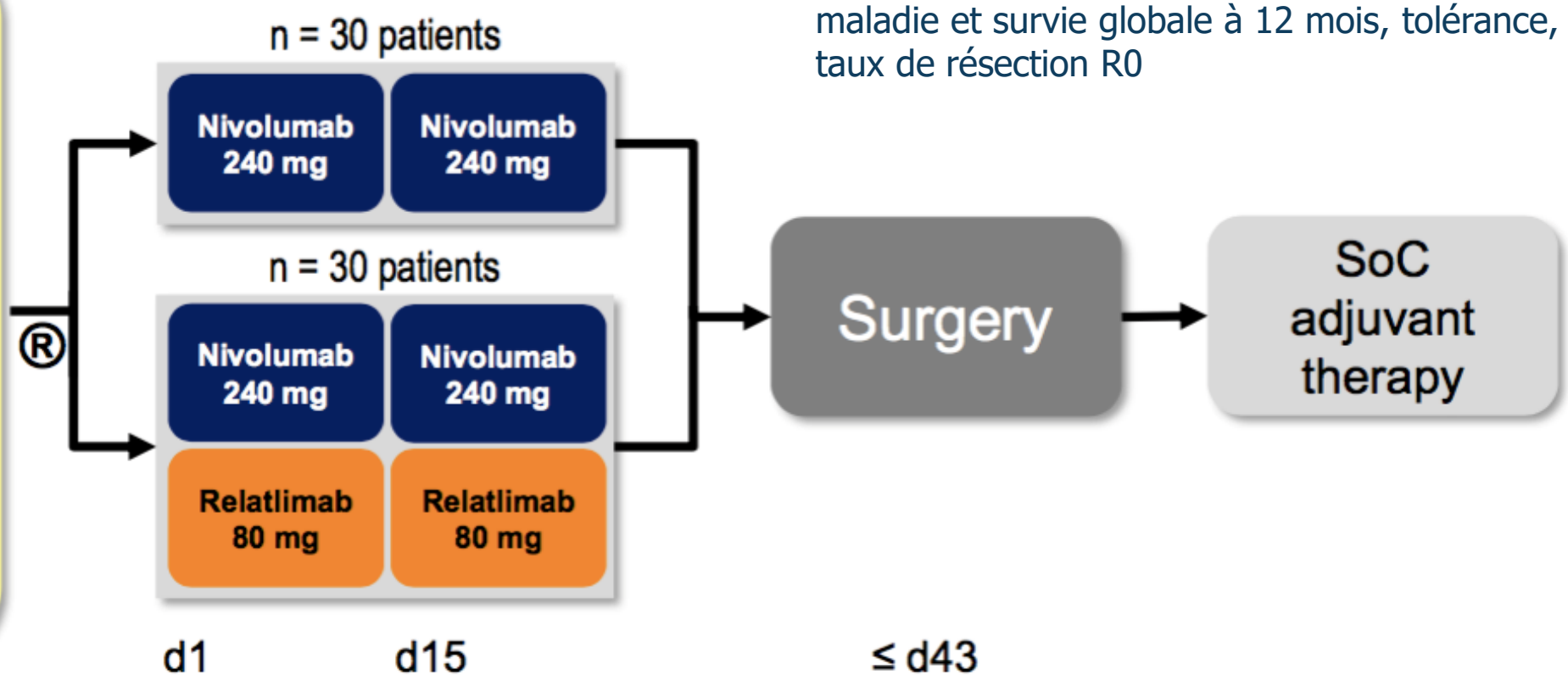
## Design de l'étude: phase II randomisée

**Objectif primaire:** faisabilité d'une chirurgie curative dans les 43 jours

**Objectifs secondaires:** Réponse objective radiologique et histopathologique, survie sans maladie et survie globale à 12 mois, tolérance, taux de résection R0

### Key eligibility

- Histologically confirmed non-small-cell lung cancer
- Stage I B, II or III A (UICC 8th edition)
- Curative resectability as determined by the multidisciplinary lung cancer board
- Sufficient organ function



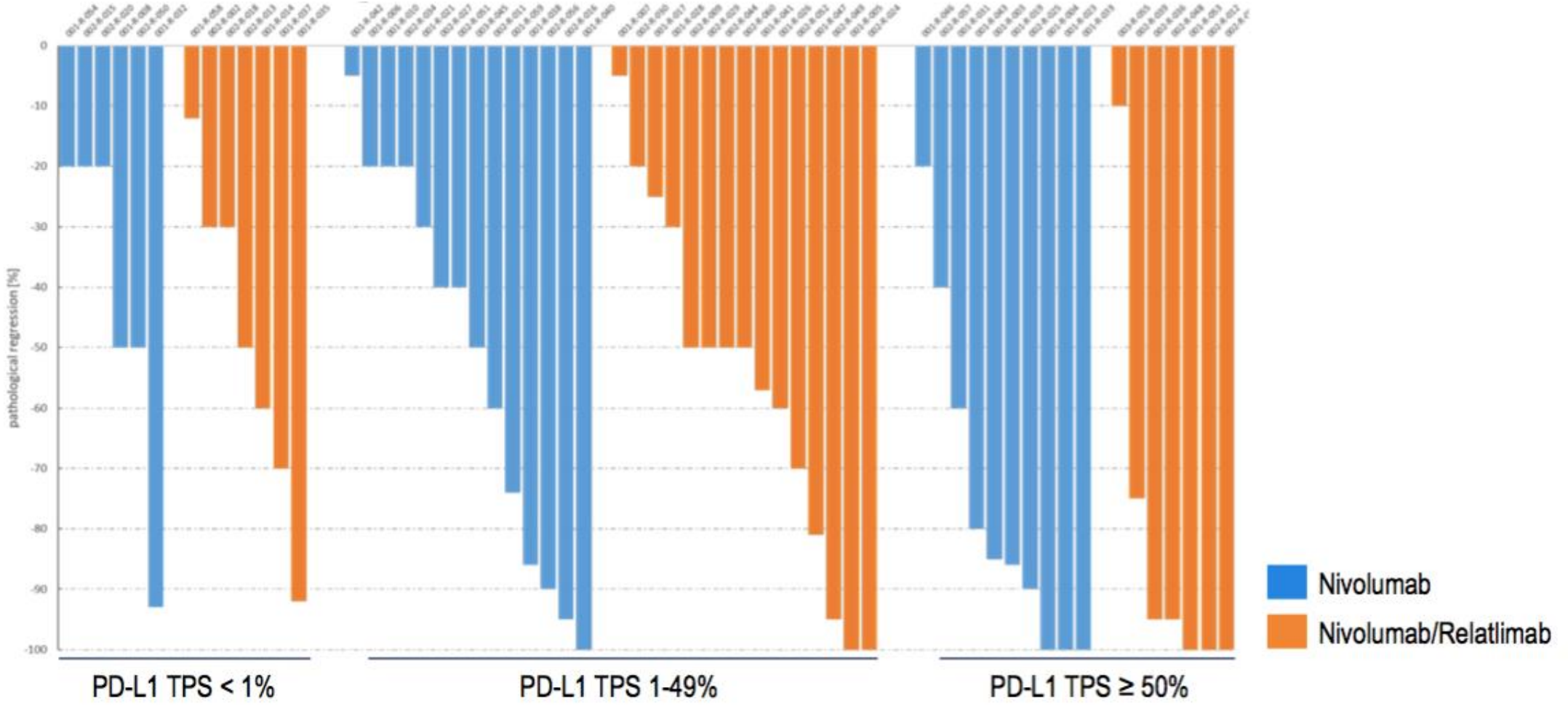
# NEOpredict-Lung

## Critères de jugement

| | Nivolumab | Nivolumab/Relatlimab |
|---|---|---|
| Primary endpoint: | | |
| ▪ Feasibility (surgery ≤ d43) | 100% | 100% |
| Secondary endpoints: | | |
| ▪ ORR (RECIST version 1.1) | 10% | 27% |
| ▪ ORR (PERCIST version 1.0)* | 38% | 38% |
| ▪ Complete/major pathological response** | 27% | 30% |
| ▪ DFS at 12 months | 92% (70-98%) | 91% (66-98%) |
| ▪ OS at 12 months | 92% (70-98%) | 100% |
| ▪ R0 resection rate** | 100% | 97% |

# NEOpredict-Lung

## Réponse histopathologique



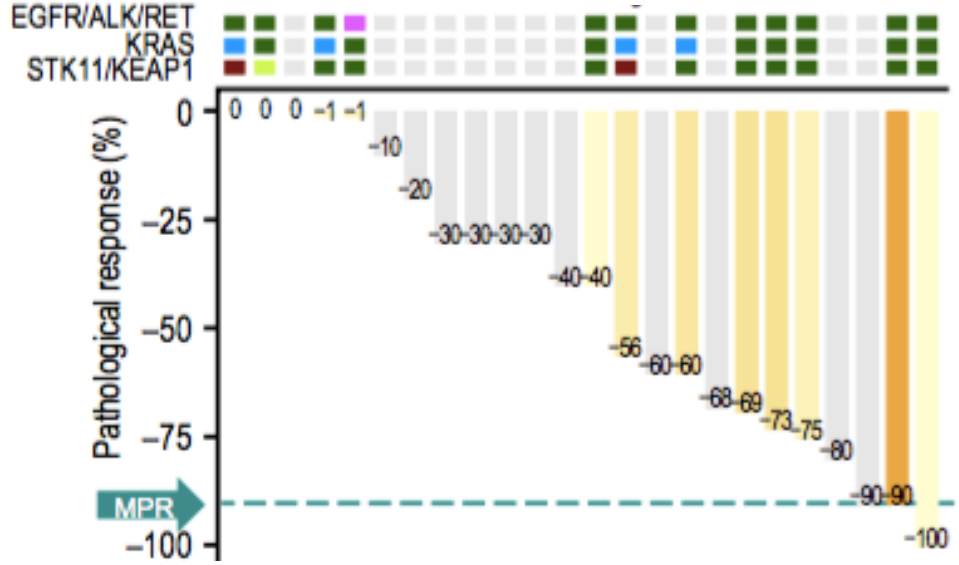
PARIS 2022 ESMO congress

# Platform study of neoadjuvant durvalumab (anti-PD-L1) alone or combined with oleclumab (anti-CD73), monalizumab (anti-NKG2A), or danvatirsen (anti-STAT3) in patients with resectable, early-stage non-small-cell lung cancer: pharmacodynamic correlates and ctDNA dynamics in the NeoCOAST study

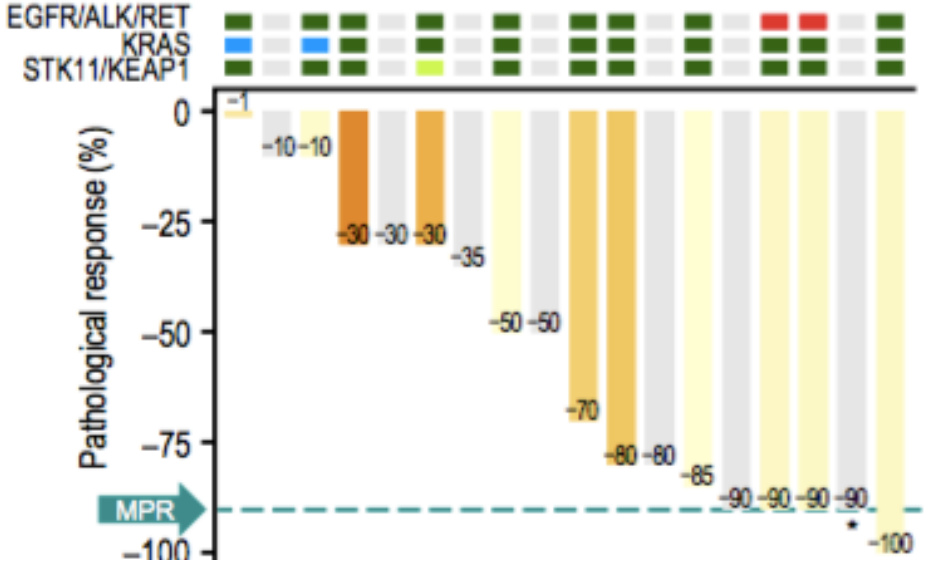
**Jonathan Spicer[1], Tina Cascone[2], Gozde Kar[3], Ying Zheng[4], Jorge Blando[4], Tze Heng Tan[5], Lin-Yang Cheng[4], Ray Mager[4], Oday Hamid[4], Yee Soo-Hoo[6], Patrick Forde[7], Walter Weder[8], Rosario Garcia-Campelo[9], Italia Grenga[10], Rakesh Kumar[4], and Lara McGrath[10]**

[1]McGill University, Montreal, QC, Canada; [2]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]AstraZeneca, Cambridge, UK; [4]AstraZeneca, Gaithersburg, MD, USA; [5]AstraZeneca, Munich, Germany; [6]AstraZeneca, Wilmington, DE, USA; [7]Bloomberg–Kimmel Institute for Cancer Immunotherapy, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA; [8]Thoracic surgery, Clinic Bethanien, Zurich, Switzerland; [9]Medical Oncology Unit, University Hospital A Coruña, A Coruña, Spain; [10]AstraZeneca, Waltham, MA, USA.

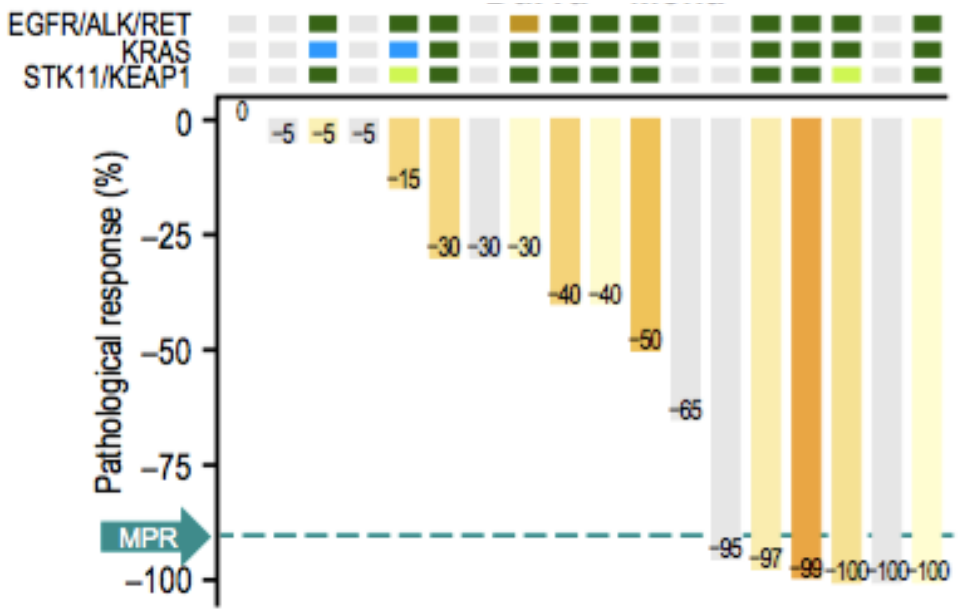
Durvalumab seul



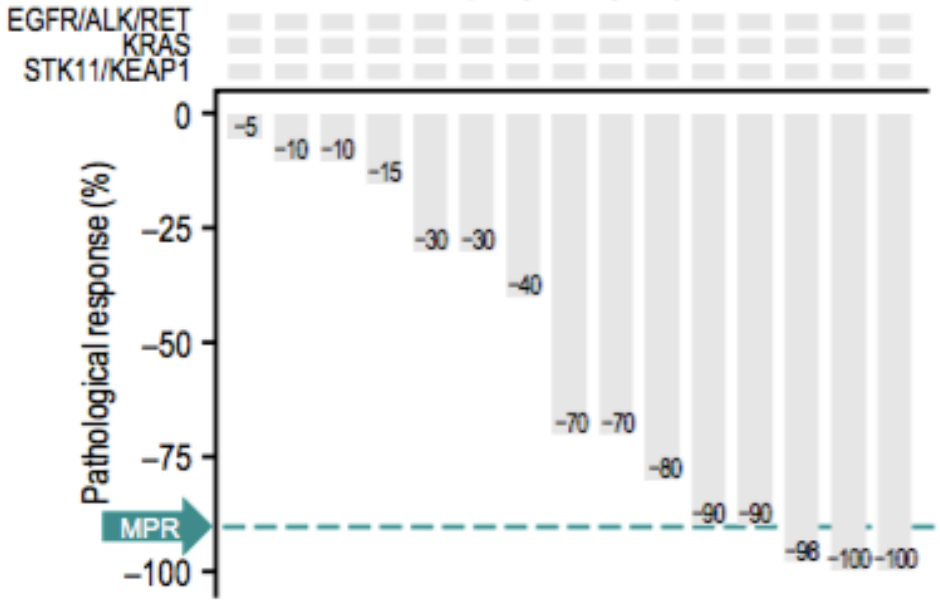

Durvalumab + oleclumab (anti CD73)




Durvalumab + monalizumab (anti NKG2A)

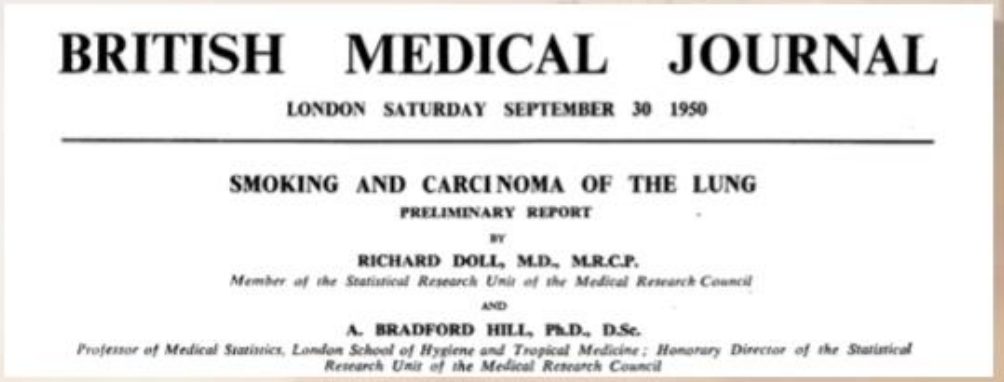



Durvalumab + danvatirsen (STAT3i)



# An Actionable Inflammatory Axis for Air Pollution Induced Non-Small Cell Lung Cancer

Charles Swanton Francis Crick Institute and UCL Hospitals



BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 30 1950

SMOKING AND CARCINOMA OF THE LUNG

PRELIMINARY REPORT

BY

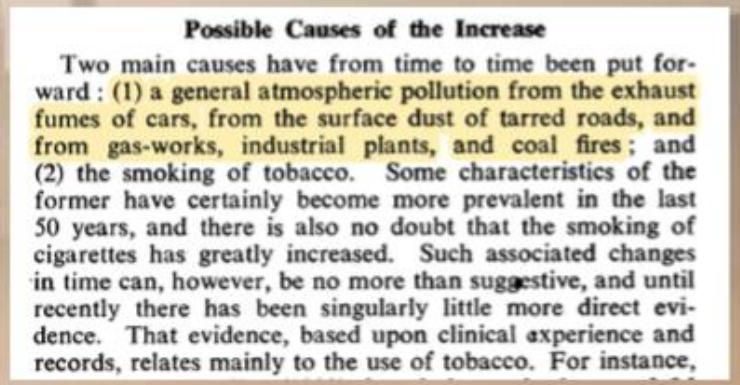
RICHARD DOLL, M.D., M.R.C.P.

*Member of the Statistical Research Unit of the Medical Research Council*

AND

A. BRADFORD HILL, Ph.D., D.Sc.

*Professor of Medical Statistics, London School of Hygiene and Tropical Medicine; Honorary Director of the Statistical Research Unit of the Medical Research Council*



**Possible Causes of the Increase**

Two main causes have from time to time been put forward: (1) a general atmospheric pollution from the exhaust fumes of cars, from the surface dust of tarred roads, and from gas-works, industrial plants, and coal fires; and (2) the smoking of tobacco. Some characteristics of the former have certainly become more prevalent in the last 50 years, and there is also no doubt that the smoking of cigarettes has greatly increased. Such associated changes in time can, however, be no more than suggestive, and until recently there has been singularly little more direct evidence. That evidence, based upon clinical experience and records, relates mainly to the use of tobacco. For instance,

@charlesswanton

THE FRANCIS CRICK INSTITUTE

UCL Cancer Institute

UCL

NHS University College London Hospitals NHS Foundation Trust

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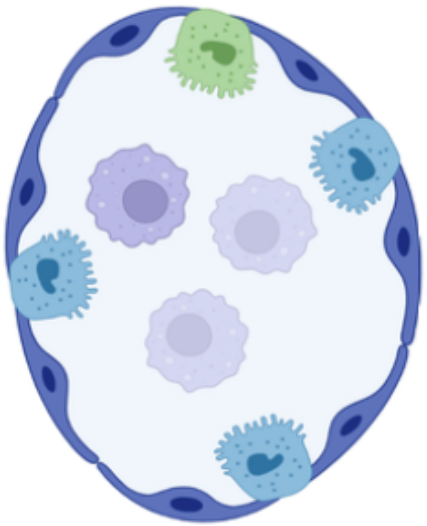
# Rôle de la pollution dans la carcinogénèse

**Initiator**
**Pre-existing mutation**

**Promoter**
**PM2.5 drives clonal outgrowth**

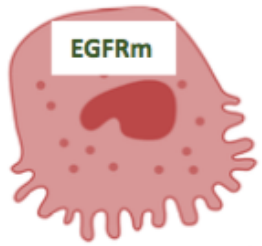
**Pre-Existing Oncogenic Mutations** in **Normal** Lung in Non-smoking Adults Increase with Age

**EGFRm**



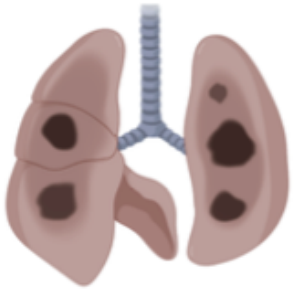
**Pollution**

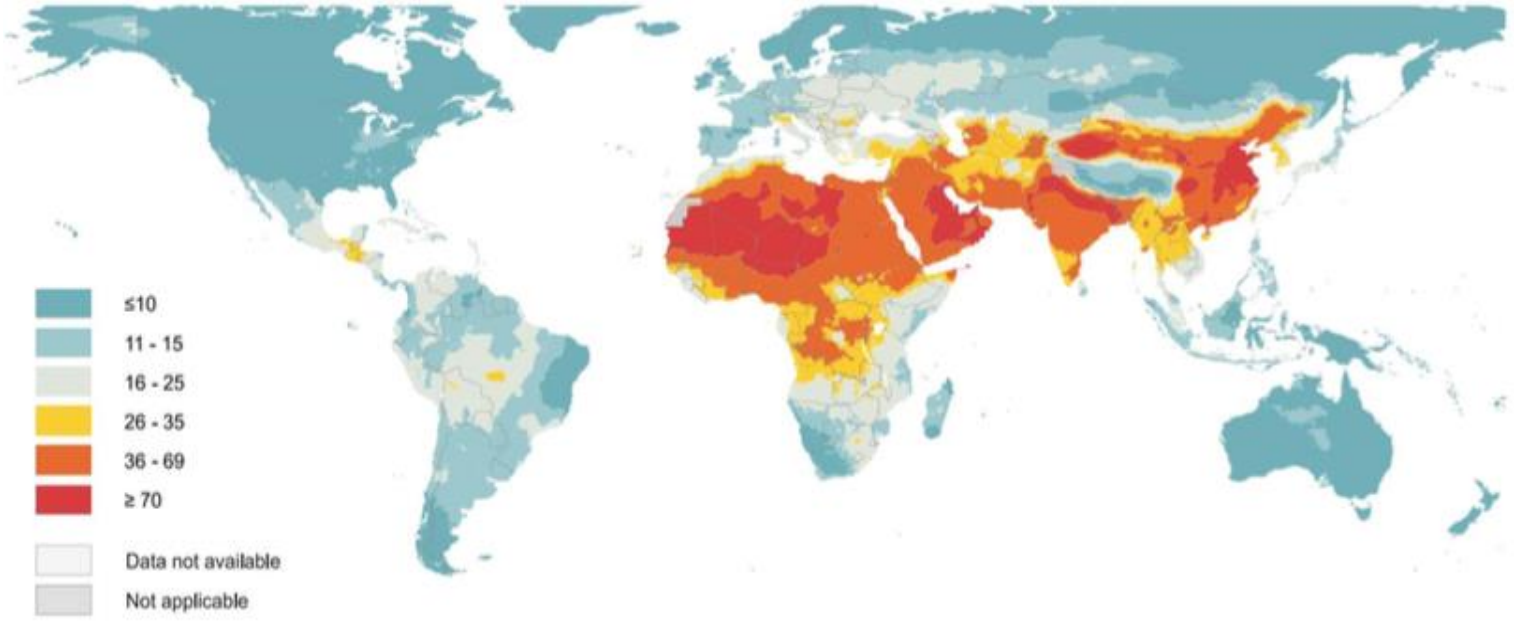
**PM2.5 Induced**
Interleukin 1 Beta




Trans-differentiation to a progenitor stem-cell state

**Tumour Formation**






$PM_{2.5}$ : Fine particulate matter of 2.5 microns or less.

**Pollution de l'air:**

- Responsable de 267000morts par cancer bronchique en 2017
- Seconde cause de cancer bronchique derrière le tabac
- > 95% de la population vit avec des taux de pollution de l'air > aux recommandations de la WHO

# Synthèse

- Lutte contre la pollution
- Trémulation immunologique en néoadjuvant
- Sotorasib comme 2eme ligne après platine et immunothérapie
- Bloquer l'amplification de MET en post Osimertinib dans le CBNPC muté EGFR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