8e ÉDITION

JOURNÉES DU **GFCO 2022**

Biomarqueurs et analyses moléculaires en oncologie

Avec la participation scientifique du GFCO

BIOMARQUEURS EN ONCOLOGIE
Actualités et vision projective

Modérateurs : Lucie Karayan-Tapon, Poitiers & Pierre-Jean Lamy, Montpellier

INNOVATION DANS LES CANCERS BRONCHO-PULMONAIRES

Pr. Nicolas Girard

Institut Curie,

INSERM U932,

Université Paris-Saclay

Liens d'intérêt

- Clinical research:
- Amgen
- Astra-Zeneca
- Abbvie
- Blue
- BMS
- Boehringer-Ingelheim
- Janssen
- Hoffmann-La Roche
- Lilly
- Merck
- MSD
- Novartis
- Sivan
- Trizell

- Symposia:
- Amgen
- Astra-Zeneca
- BMS
- MSD

- Hospitality:
- BMS
- Astra-Zeneca
- Boehringer-Ingelheim
- Hoffman-La Roche
- MSD

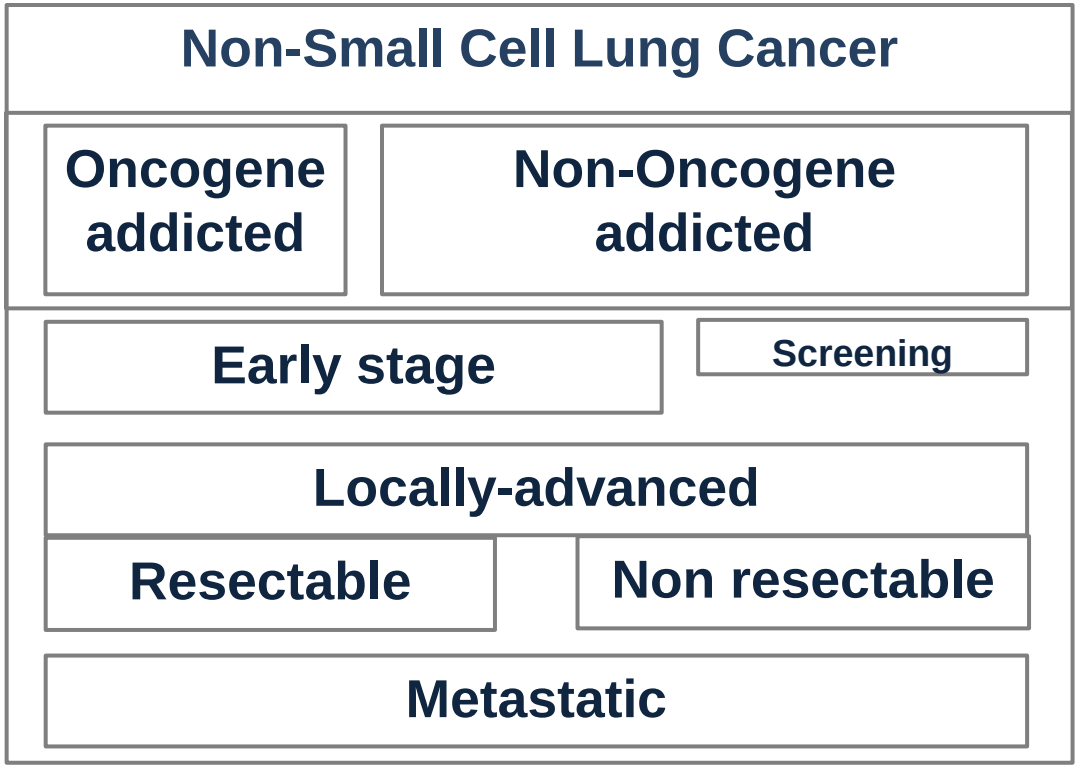
- IFCT: Treasurer

- ITMIG: President

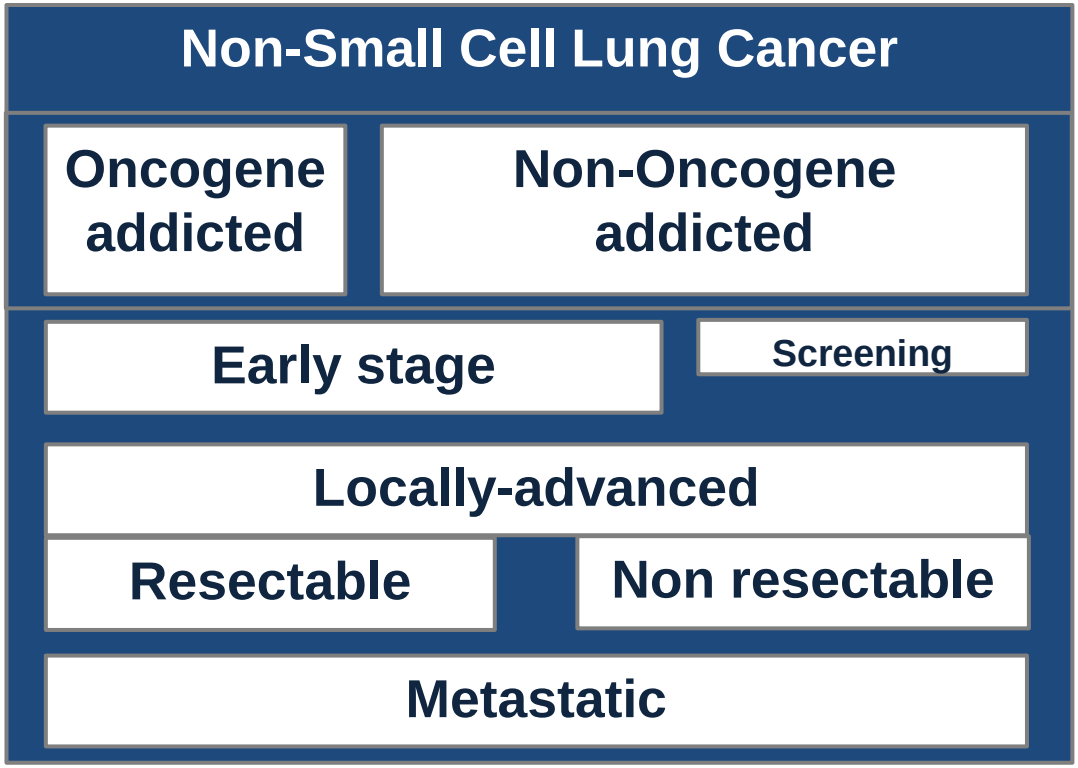
- Consultancy:
- Amgen
- Astra-Zeneca
- BMS
- Boehringer-Ingelheim
- Janssen
- Hoffman-La Roche
- Lilly
- Novartis
- Merck
- MSD
- Pfizer
- Sanofi

Public disclosure
https://dpi.sante.gouv.fr/dpi-public-webapp/app/recherche/declarant

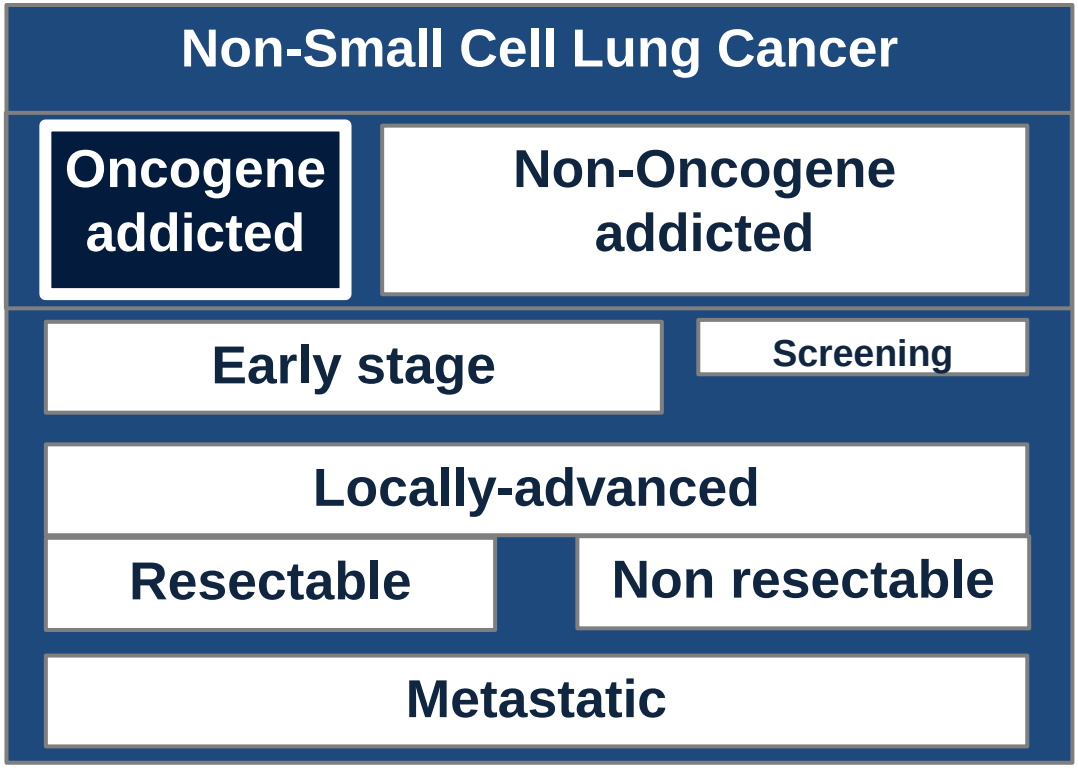
Thoracic Cancers



Thoracic Cancers



Thoracic Cancers



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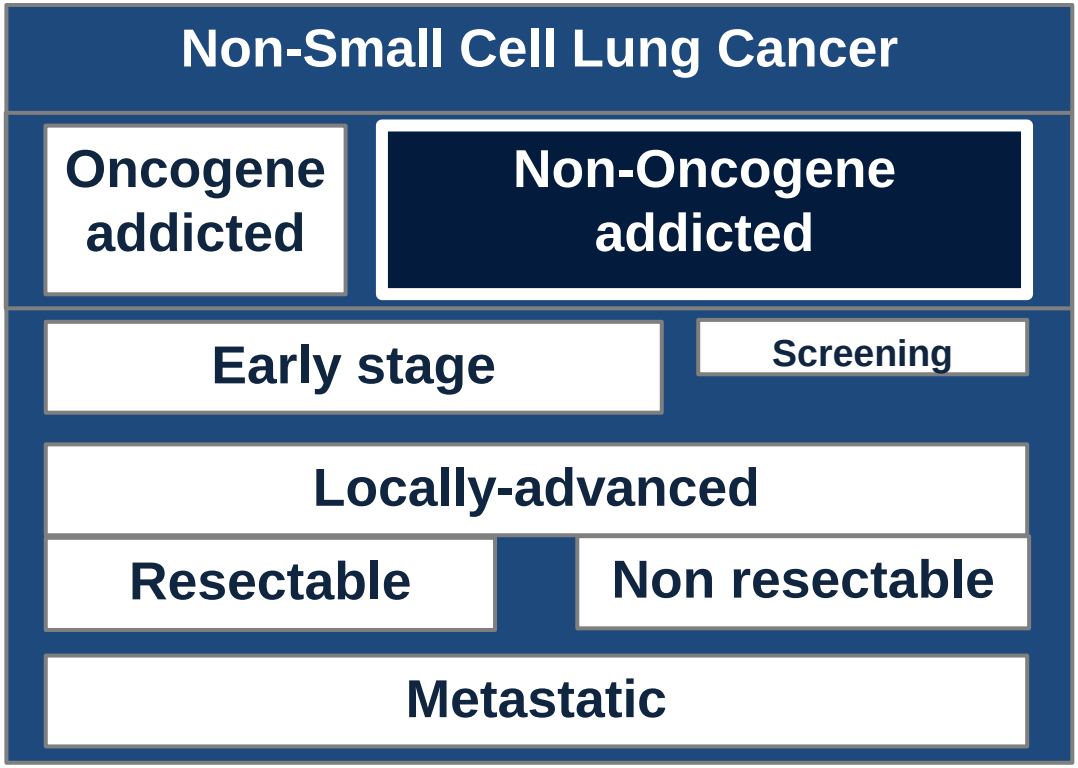

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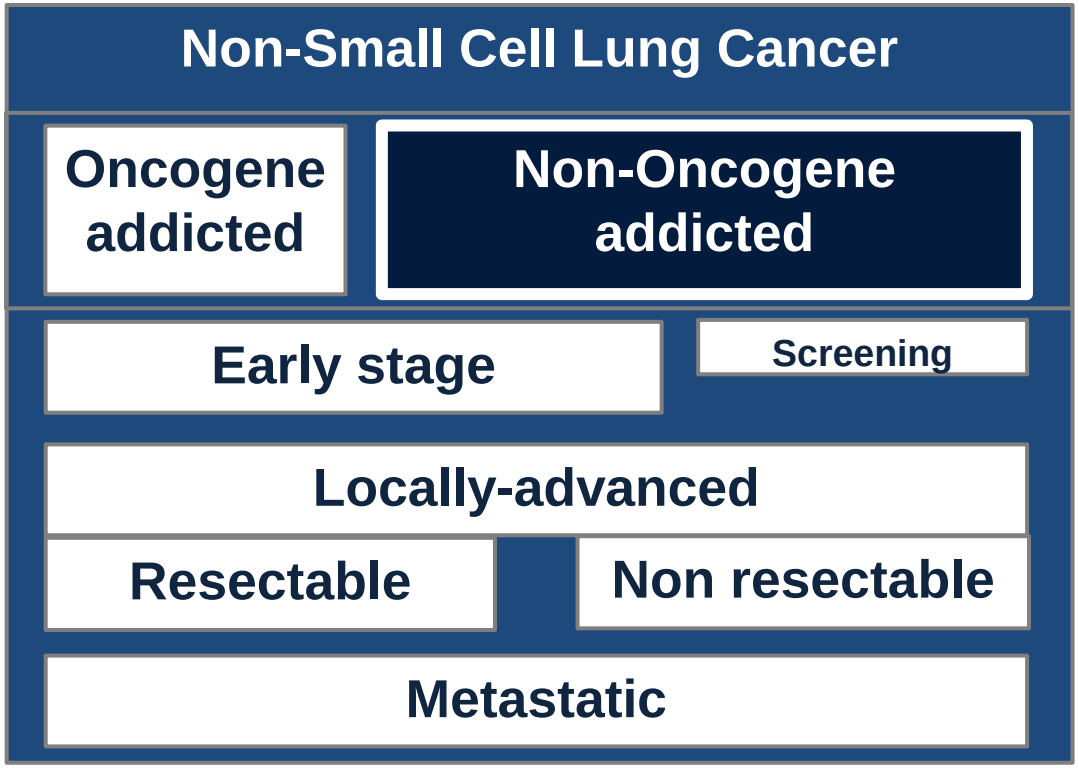
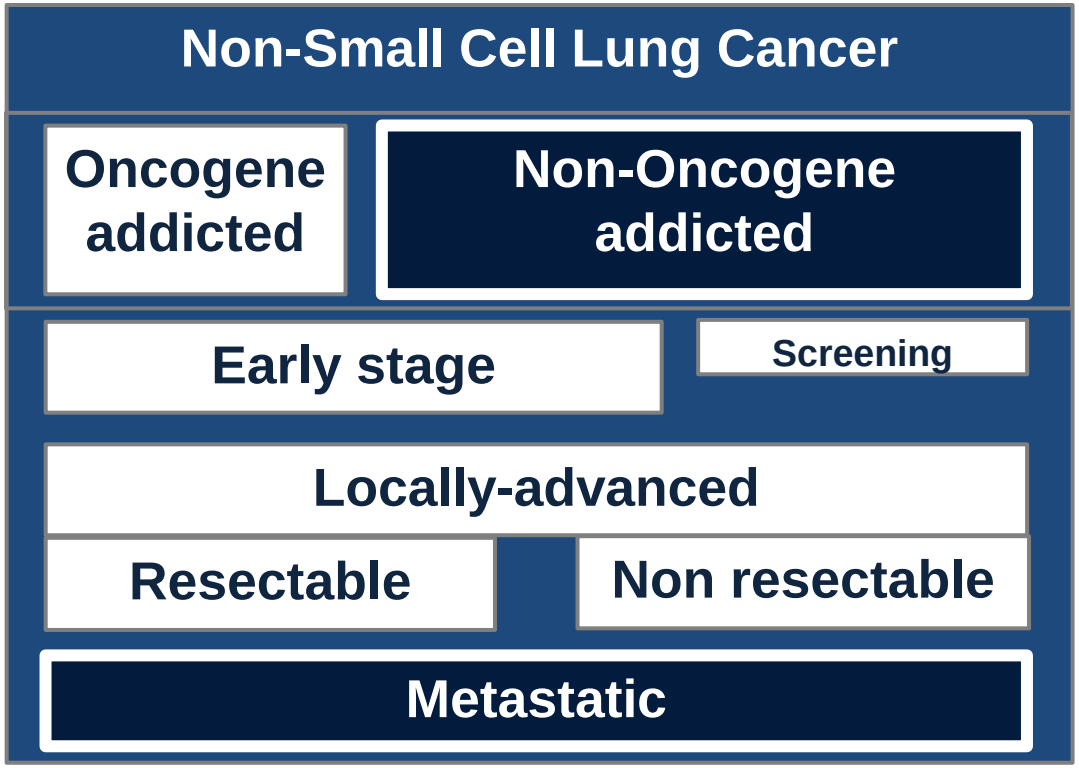


Which biomarkers?

PD-L1 50%

Thoracic Cancers



Which biomarkers?

PD-L1 50%

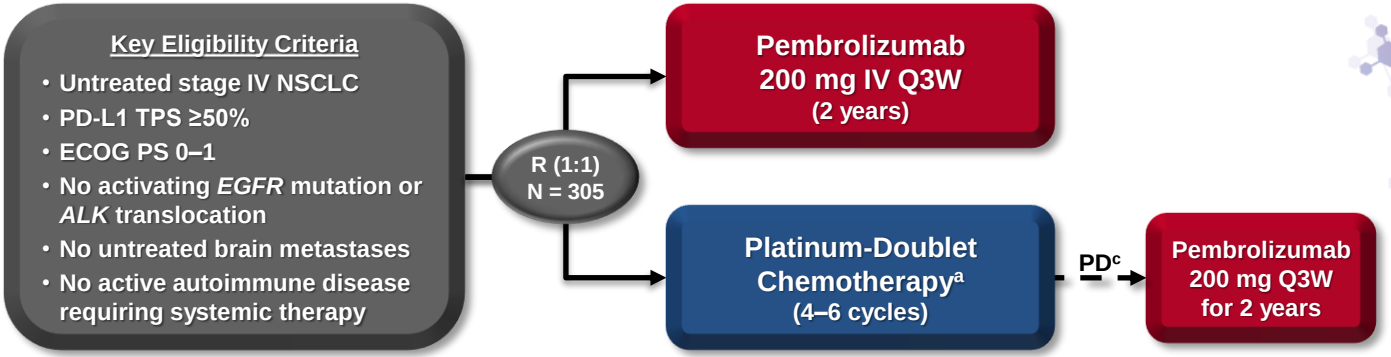
Immunotherapy as first-line for NSCLC

Immunotherapy to replace chemotherapy

Immunotherapy in addition to chemotherapy

Immunotherapy to replace chemotherapy
Selection based on PD-L1≥50%

KEYNOTE-024: design



End Points

Primary:	PFS (RECIST v1.1, blinded independent central review)
Key secondary:	OS
Secondary:	ORR, safety
Exploratory:	DOR

[a]Optional pemetrexed maintenance therapy for nonsquamous disease. [b]Permitted for nonsquamous disease only.
[c]Prior to the DMC recommendation and amendment 6, which permitted those in the chemotherapy arm to be offered pembrolizumab (based on interim analysis 2 data), patients were eligible for crossover when PD was confirmed by blinded, independent central radiology review.

Reck et al. N Engl J Med 2016; 375:1823

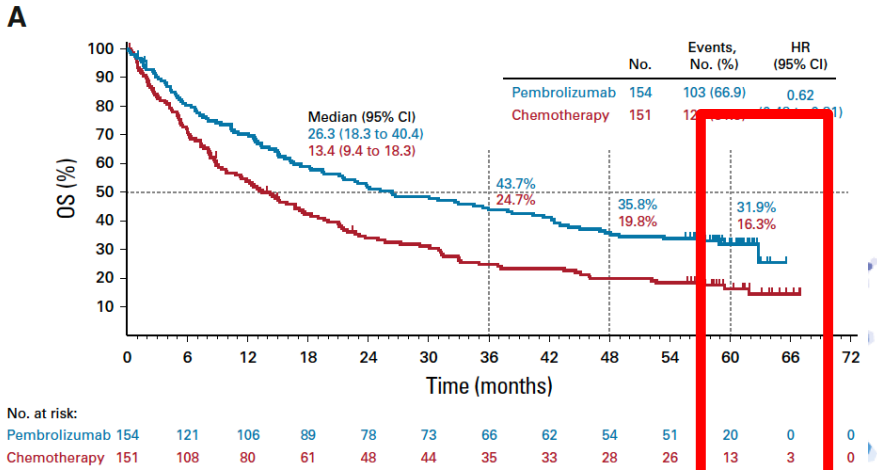
Immunotherapy to replace chemotherapy
Selection based on PD-L1≥50%

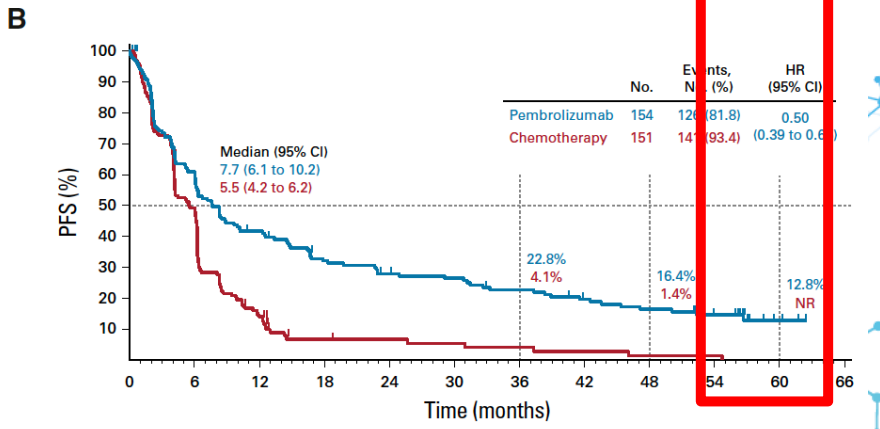
Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50%

Martin Reck, MD, PhD[1]; Delvys Rodríguez-Abreu, MD, PhD[2]; Andrew G. Robinson, MD, MSc[3]; Rina Hui, MBBS, PhD[4]; Tibor Csőszi, MD[5]; Andrea Fülöp, MD[6]; Maya Gottfried, MD[7]; Nir Peled, MD, PhD[8]; Ali Tafreshi, MD[9]; Sinead Cuffe, MD[10]; Mary O'Brien, MD[11]; Suman Rao, MD[12]; Katsuyuki Hotta, MD, PhD, MPH[13]; Ticiana A. Leal, MD[14]; Jonathan W. Riess, MD, MS[15]; Erin Jensen, MS[16]; Bin Zhao, MD, PhD[16]; M. Catherine Pietanza, MD[16]; and Julie R. Brahmer, MD[17]

Table 3. Adverse Events in the As-Treated Population.*

Adverse Event	Pembrolizumab Group (N=154)		Chemotherapy Group (N=150)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	number of patients (percent)			
Treatment-related†				
Any	113 (73.4)	41 (26.6)	135 (90.0)	80 (53.3)
Serious	33 (21.4)	29 (18.8)	31 (20.7)	29 (19.3)
Led to discontinuation	11 (7.1)	8 (5.2)	16 (10.7)	9 (6.0)
Led to death	1 (0.6)	1 (0.6)	3 (2.0)	3 (2.0)





J Clin Oncol 39:2339-2349

Brahmer et al. ESMO 2020

Immunotherapy as first-line for NSCLC

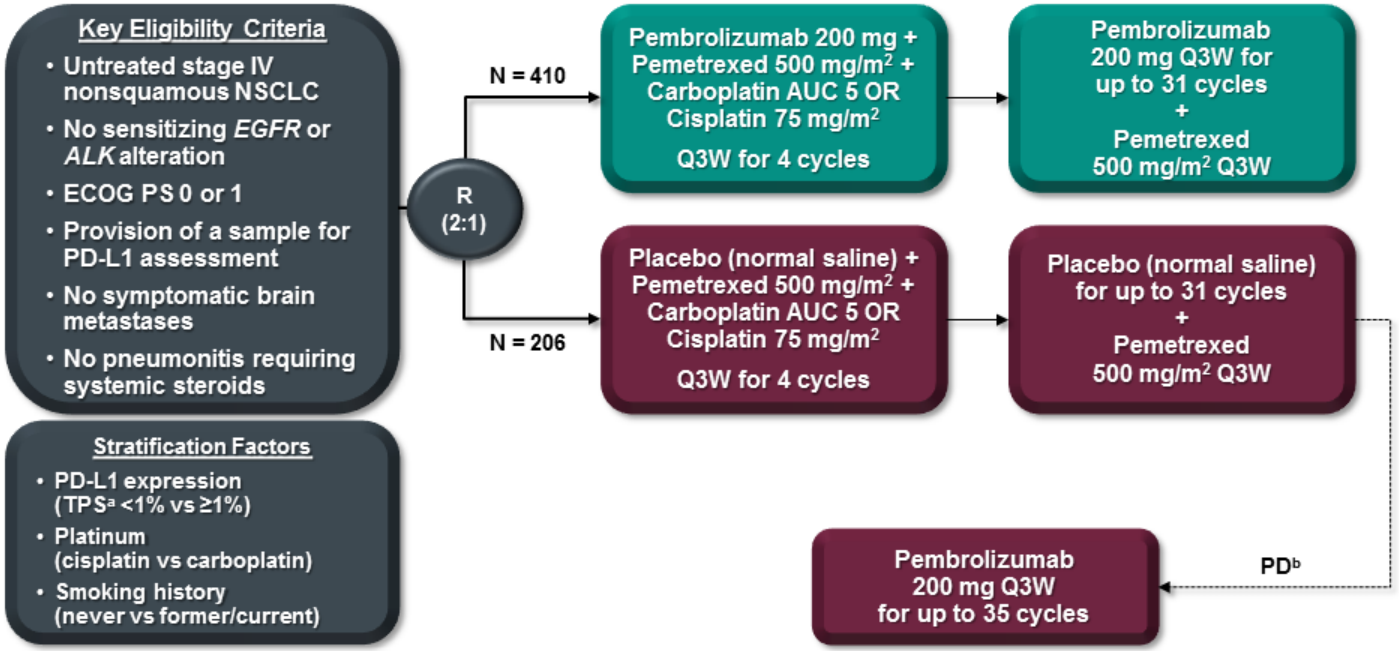
Immunotherapy *to replace* chemotherapy

Immunotherapy *in addition* to chemotherapy

Immunotherapy in addition to chemotherapy
Non-squamous cell carcinomas

Placebo
Stratification on PD-L1
Exclusion of EGFR/ALK

KEYNOTE-189: design



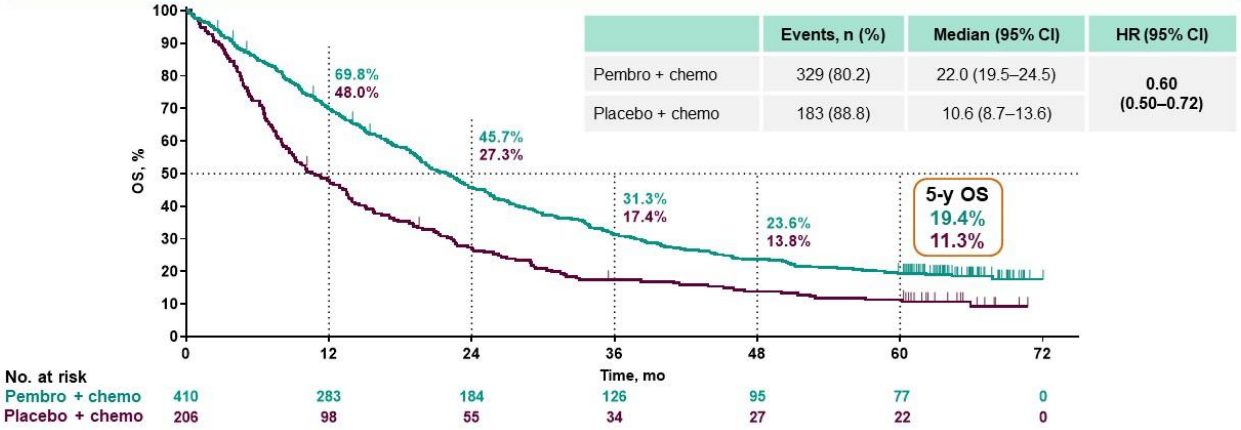
[a]Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay. [b]Patients could crossover during the induction or maintenance phases. To be eligible for crossover, PD must have been verified by blinded, independent central radiologic review and all safety criteria had to be met.

Gandhi et al. NEJM 2018;378:2078

Immunotherapy in addition to chemotherapy
Non-squamous cell carcinomas

KEYNOTE-189: results

OS: ITT Population



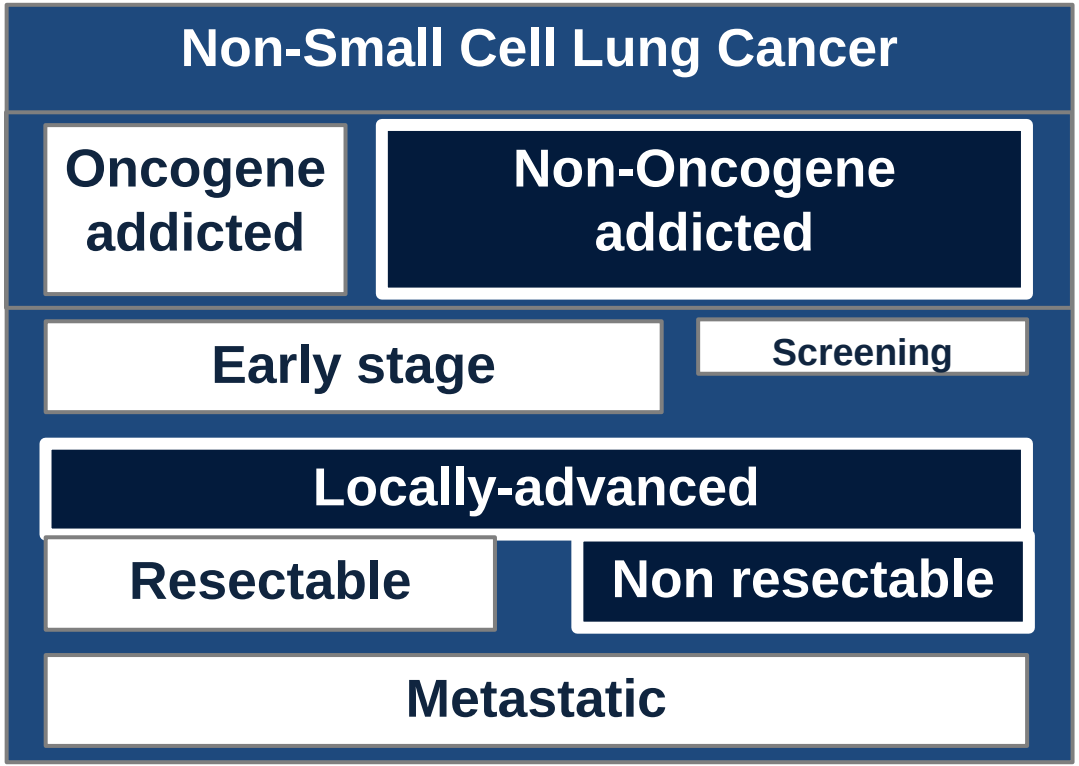
	Events, n (%)	Median (95% CI)	HR (95% CI)
Pembro + chemo	329 (80.2)	22.0 (19.5–24.5)	0.60 (0.50–0.72)
Placebo + chemo	183 (88.8)	10.6 (8.7–13.6)	

	PD-L1 TPS ≥50%		PD-L1 TPS 1%–49%		PD-L1 TPS <1%	
	Pembro + chemo (n = 132)	Placebo + chemo (n = 70)	Pembro + chemo (n = 128)	Placebo + chemo (n = 58)	Pembro + chemo (n = 127)	Placebo + chemo (n = 63)
OS HR (95% CI)	0.68 (0.49–0.96)		0.65 (0.46–0.90)		0.55 (0.39–0.76)	
5-y OS rate,[a] %	29.6	21.4	19.8	7.7	9.6	5.3

[a]Kaplan-Meier estimate. Data cutoff date: March 8, 2022.

Garassino et al. ESMO 2022

Thoracic Cancers



Which biomarkers?

PD-L1 1%

Consolidation IO with durvalumab is the current standard-of-care

PACIFIC: Study Design

Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study[1]

- Unresectable, Stage III NSCLC without progression after definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- If available, archived pre-cCRT tumor tissue for PD-L1 testing*

All-comers population (i.e. irrespective of PD-L1 status)

N=713 randomized

1–42 days post-cCRT

R

2:1 randomization, stratified by age, sex, and smoking history

Durvalumab 10 mg/kg q2w for up to 12 months N=476

Placebo 10 mg/kg q2w for up to 12 months N=237

Primary endpoints

- PFS by BICR using RECIST v1.1†
- OS

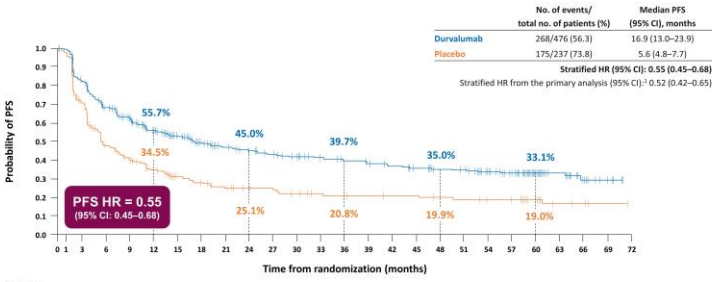
Key secondary endpoints

- ORR, DoR and TTDM by BICR
- PFS2 by investigator
- Safety
- PROs

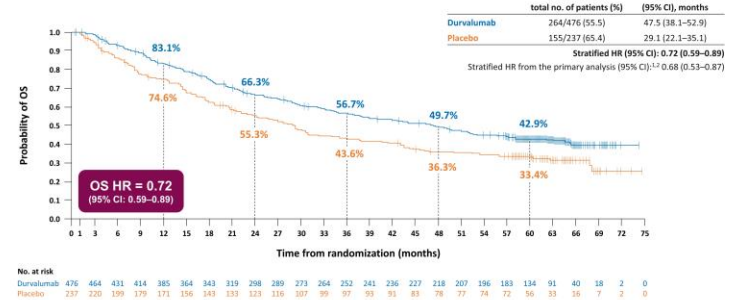
*Using the Ventana SP263 immunohistochemistry assay

†Defined as the time from randomization until the date of objective disease progression or death by any cause in the absence of progression. BICR, blinded independent central review; cCRT, concurrent CRT; PFS2, time to second progression; RECIST, Response Evaluation Criteria in Solid Tumors; TTDM, time to death or distant metastasis.
ClinicalTrials.gov number: NCT02125461

Updated PFS (ITT; BICR)



Updated OS (ITT)



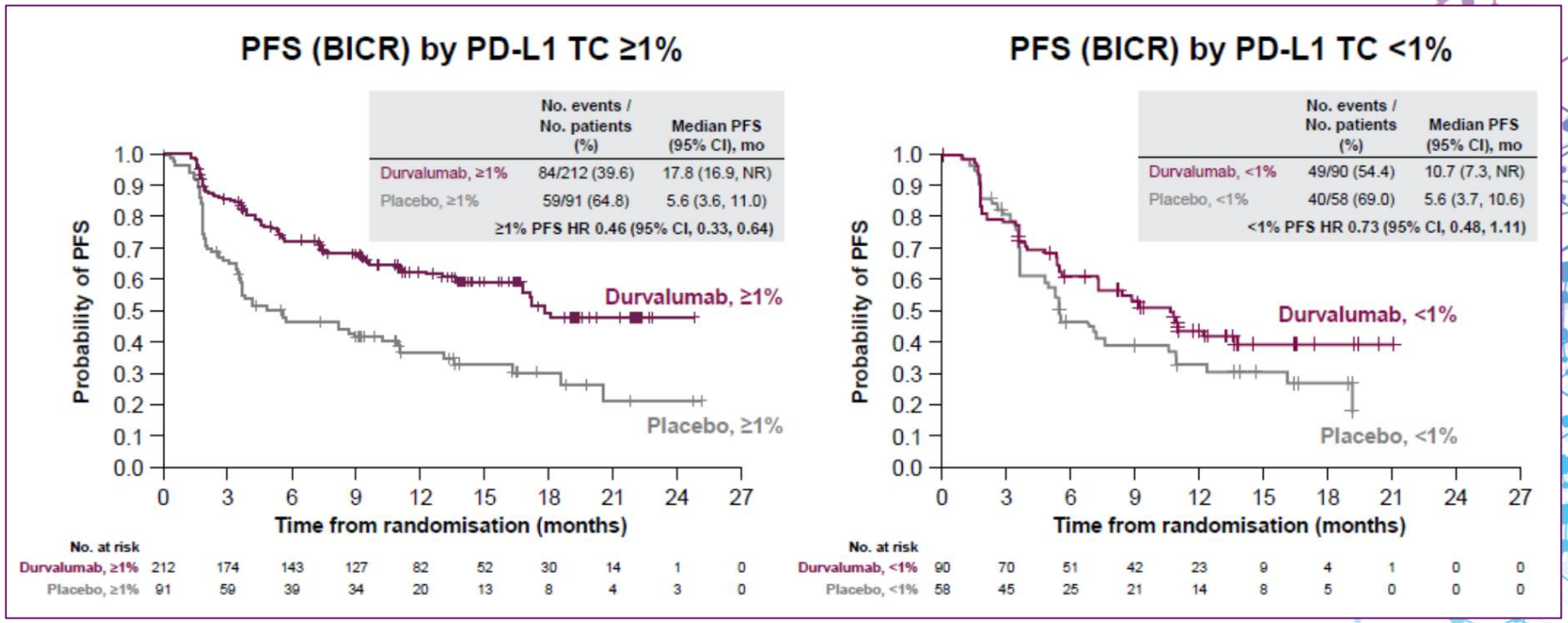
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival

Data cutoff: 11 January 2021 (median follow-up: all patients, 34.2 months [range, 0.2–74.7]; censored patients, 61.6 months [range, 0.4–74.7]).
1. Antonia SJ, et al. New Engl J Med 2018;379:2342–50; 2. European Medicines Agency. Durvalumab (Imfinzi). Summary of product characteristics 2020. Available from: https://www.ema.europa.eu/en/documents/product-information/imfinzi-epar-product-information_en.pdf 5. [Accessed April 2021]

Presented By: Dr. David R. Spigel

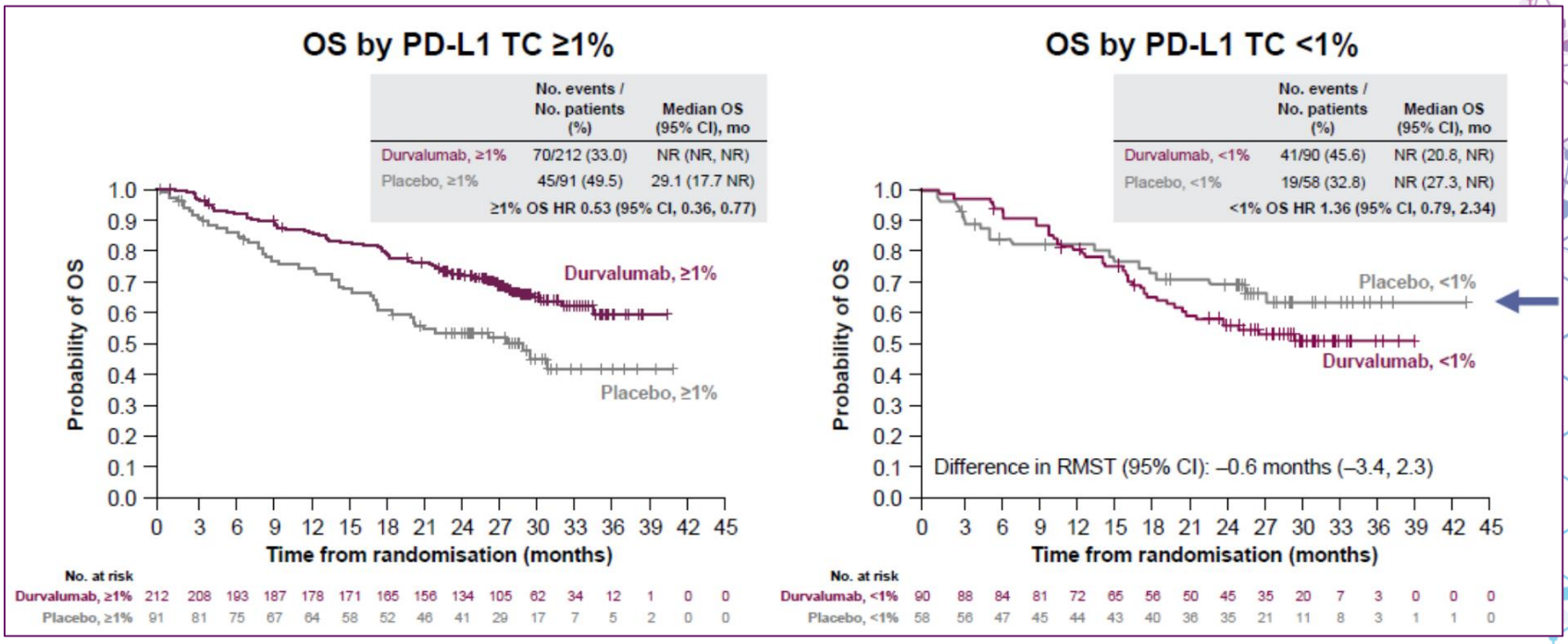
2021 ASCO ANNUAL MEETING

Analyse post-hoc: expression de PD-L1 ≥/<1%



Faivre-Finn et al. ESMO 2018

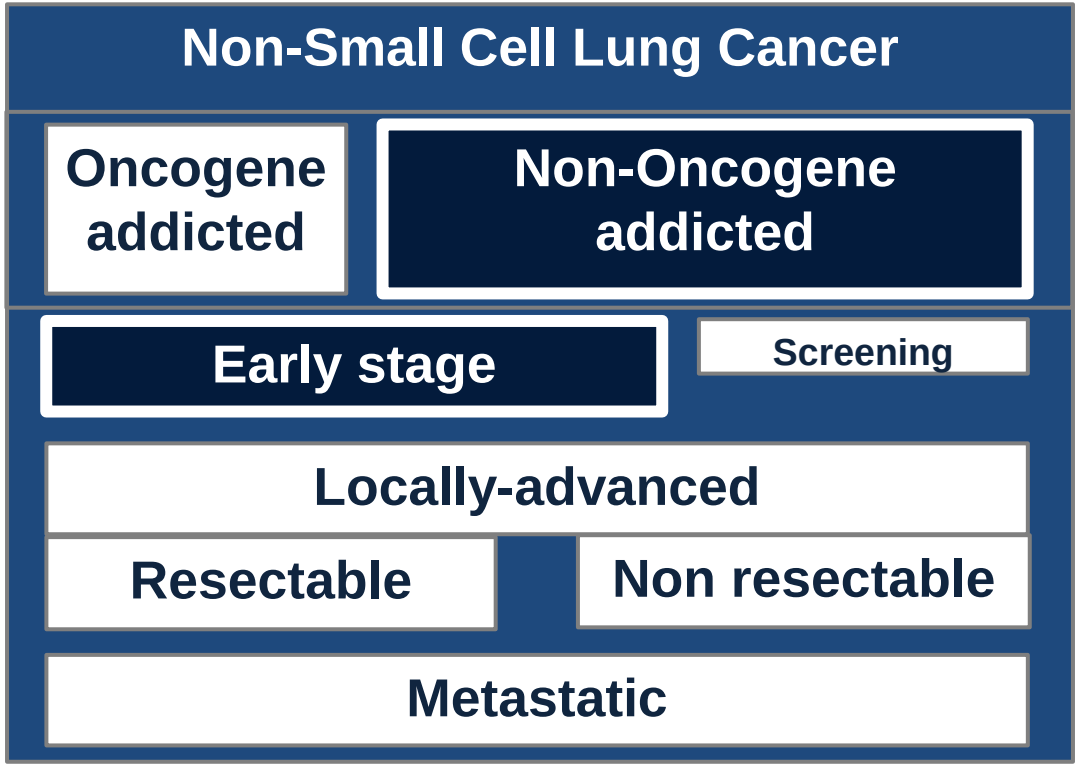
Analyse post-hoc: expression de PD-L1 ≥/<1%



- In the PD-L1 TC <1% subgroup, the number of events are low and overall the subgroup is small
- Imbalances in baseline characteristics

Faivre-Finn et al. ESMO 2018

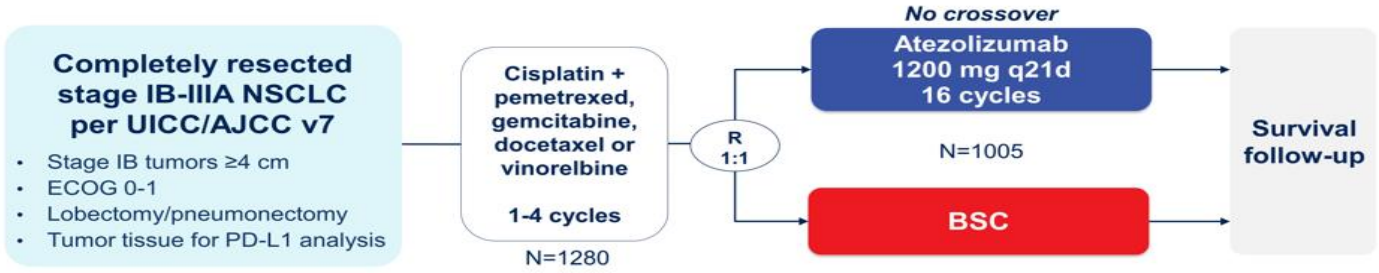
Thoracic Cancers



Which biomarkers?

PD-L1 50%

New data: IMpower-010



Stratification factors
- Male/female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status[a]: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

Primary endpoints
- Investigator-assessed DFS tested hierarchically:
  - PD-L1 TC ≥1% (per SP263) stage II-IIIA population
  - All-randomized stage II-IIIA population
  - ITT population (stage IB-IIIA)

Key secondary endpoints
- OS in ITT population
- DFS in PD-L1 TC ≥50% (per SP263) stage II-IIIA population
- 3-y and 5-y DFS in all 3 populations

Hierarchical statistical testing of endpoints

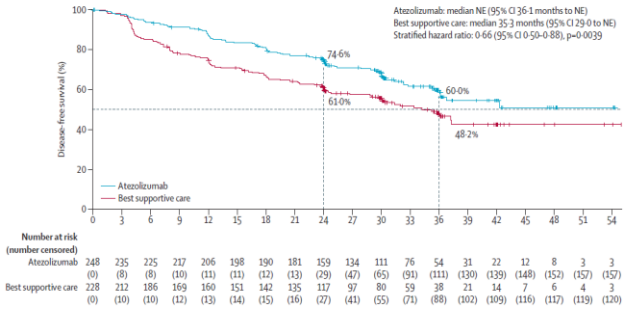
Endpoint met at IA | Endpoint not met at IA; follow-up ongoing | Endpoint not formerly tested

DFS in PD-L1 TC≥1% Stage II–IIIA population 2-sided α=0.05 → If positive → DFS in all-randomised Stage II–IIIA population 2-sided α=0.05 → If positive → DFS in ITT population (Stage IB–IIIA) 2-sided α=0.05 → If positive → OS in ITT population 2-sided α=0.05

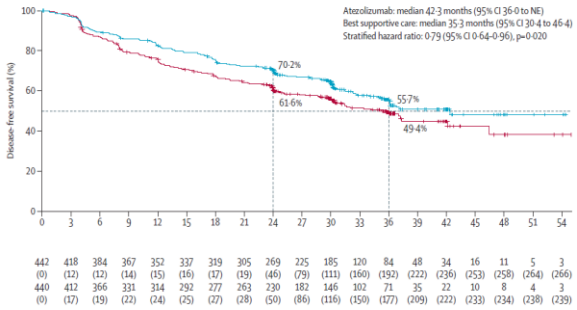
Both arms included observation and regular scans for disease recurrence on the same schedule
[a]Per SP142 assay
AJCC, American Joint Committee on Cancer; BSC, best supportive care; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; IA, interim analysis; IC, immune cell; ITT, intention-to-treat; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed cell death ligand 1; q21d, every 21 days; TC, tumour cell; UICC, Union for International Cancer Control
Wakelee HA, et al. Presented at the 2021 ASCO annual meeting (Abstract 8500); Felip E, et al. Presented at IASLC 2022 WCLC World Conference on Lung Cancer (Abstract PL03.09)

New data: IMpower-010

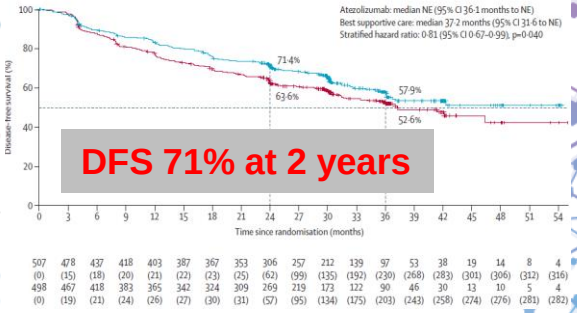
DFS in the PD-L1 TC≥1% Stage II–IIIA population[1]



DFS in the Stage II–IIIA population[1]

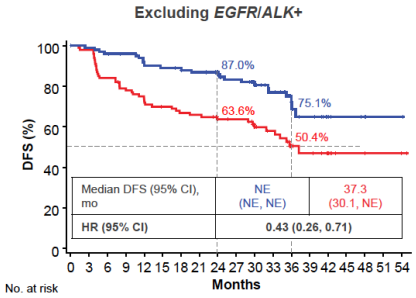


DFS in the ITT population[1]

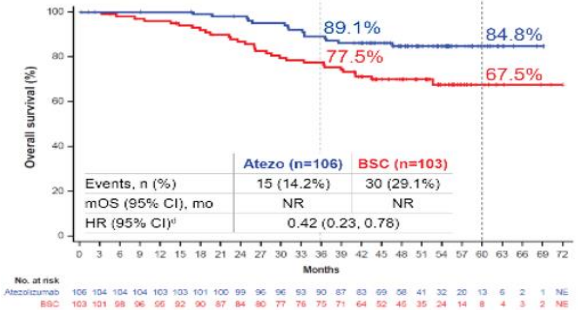


DFS 71% at 2 years

DFS in the PD-L1 TC≥50% Stage II–IIIA population[2,a,b]



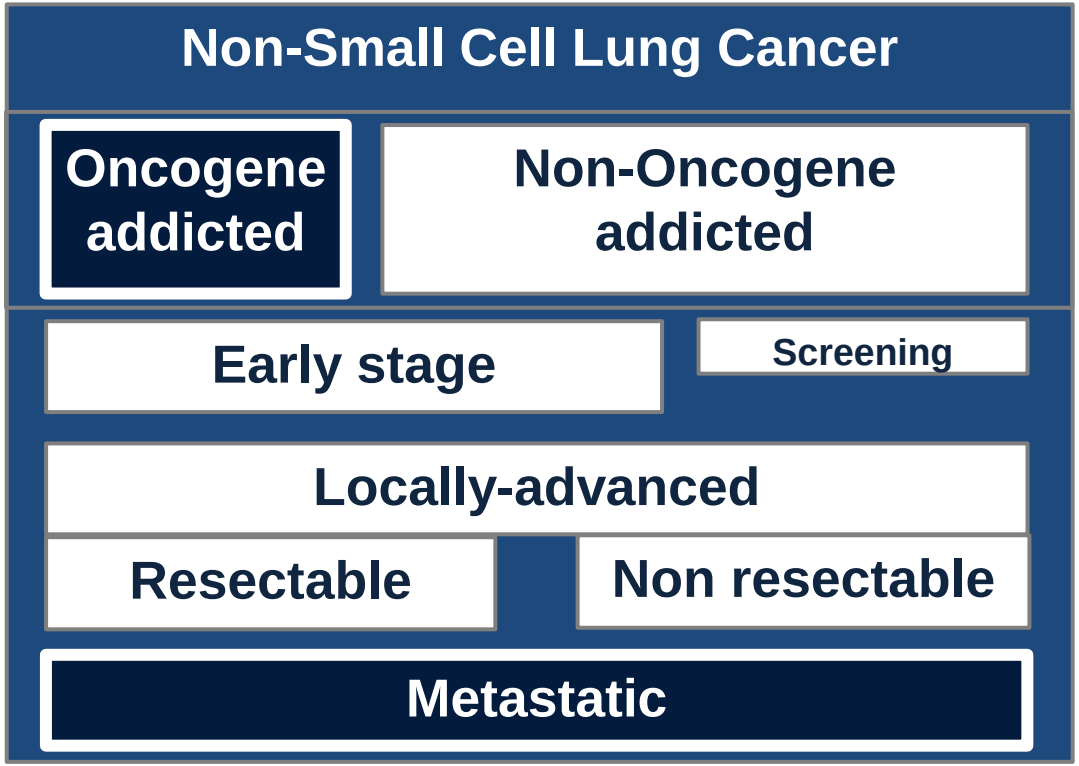
OS in the PD-L1 TC≥50% Stage II–IIIA population (excluding EGFRm/ALK-positive NSCLC)[2,a]



[a]Data cut-off: 18 April 2022; [b]Median follow-up: 46 months; [c]Stratified; [d]Unstratified
CI, confidence interval; BSC, best supportive care; EGFRm epidermal growth factor-mutated; DFS, disease-free survival; HR, hazard ratio; ITT, intention-to-treat; mOS, median OS; NE, not estimable; NR, not reached; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed cell death ligand 1; TC, tumour cell

1. Felip E, et al. Lancet 2021;398:1344–57; 2. Felip E, et al. Presented at IASLC 2022 WCLC World Conference on Lung Cancer (Abstract PL03.09)

Thoracic Cancers



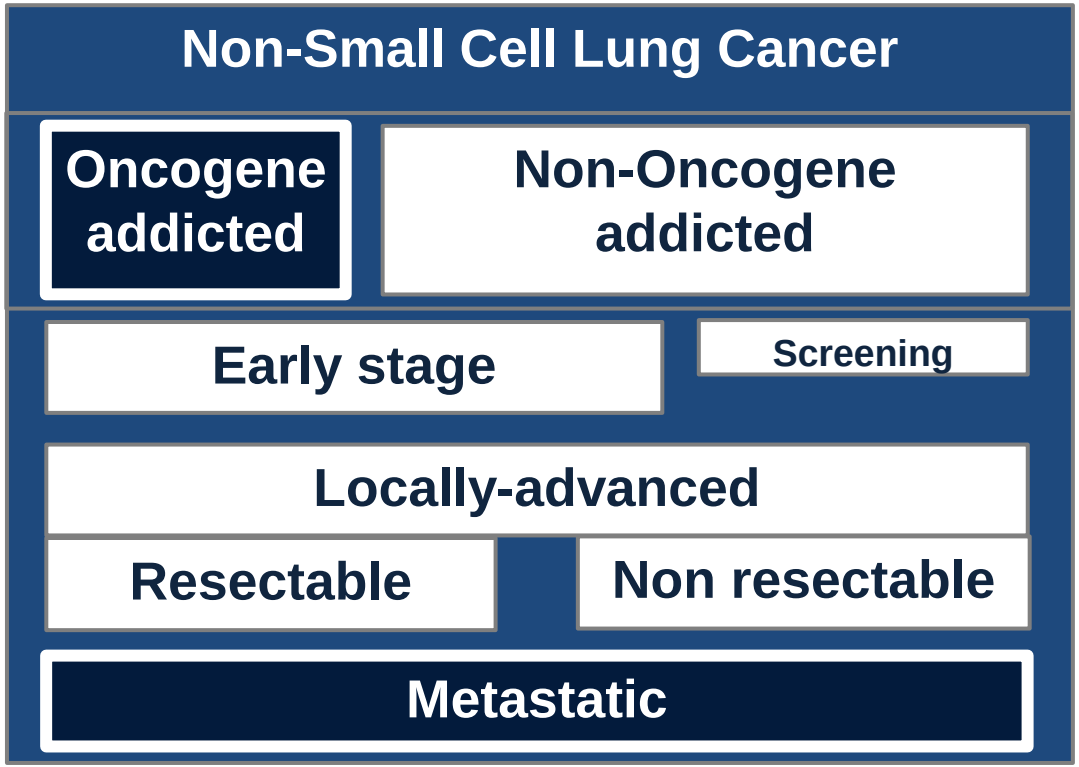
First-line

- EGFR
- ALK
- BRAF
- ROS1

Second/Late-line

- KRAS G12C
- HER2
- RET
- NTRK
- MET
- NRG1
- Ex20ins

Thoracic Cancers



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- ALK
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Second/Late-line

- KRAS G12C
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- RET
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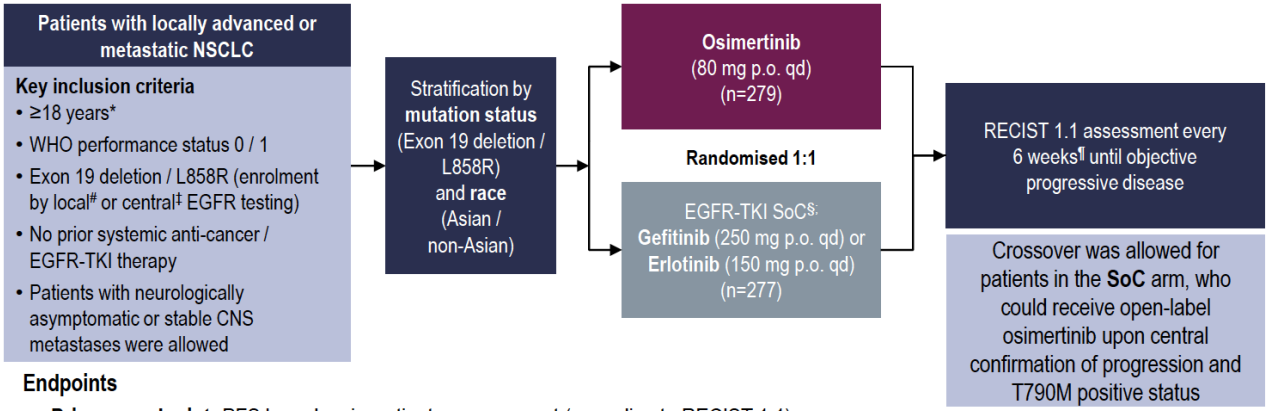
- MET
- NRG1
- Ex20ins

Mutations de l'*EGFR*
L'osimertinib est le standard de première ligne

FLAURA: Phase III, double blind, randomised open-label study to compare osimertinib vs. Gefitinib or erlotinib as first-line treatment for patients with advanced NSCLC with an *EGFR*-activating mutation



Endpoints

- **Primary endpoint:** PFS based on investigator assessment (according to RECIST 1.1)
  - The study had a 90% power to detect a hazard ratio of 0.71 (representing an improvement in median PFS from 10 months to 14.1 months) at a two-sided alpha-level of 5%
- **Secondary endpoints:** objective response rate, duration of response, disease control rate, depth of response, overall survival, patient reported outcomes, safety

SINGAPORE 2017 ESMO ASIA

FLAURA data cut-off: 12 June 2017; NCT02296125

*≥20 years in Japan; #With central laboratory assessment performed for sensitivity; ‡cobas EGFR Mutation Test (Roche Molecular Systems); § Sites to select either gefitinib or erlotinib as the sole comparator prior to site initiation; ¶Every 12 weeks after 18 months

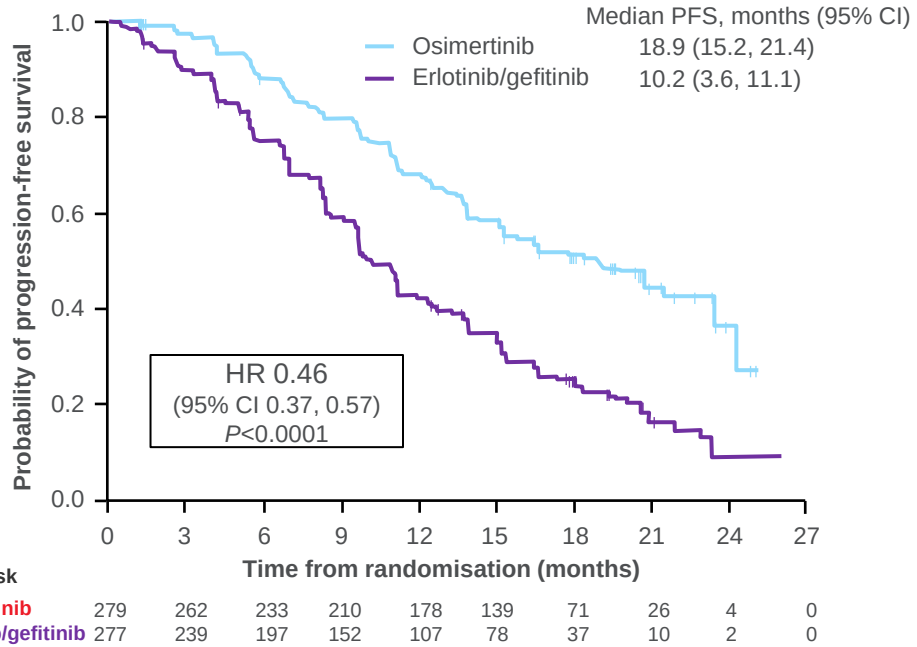
CNS, central nervous system; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PFS, progression-free survival; p.o., orally; RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1; qd, once daily; SoC, standard-of-care; TKI, tyrosine kinase inhibitor; WHO, World Health Organization

Ohe et al. ESMO Asia 2017

Mutations de l'*EGFR*
L'osimertinib est le standard de première ligne

FLAURA

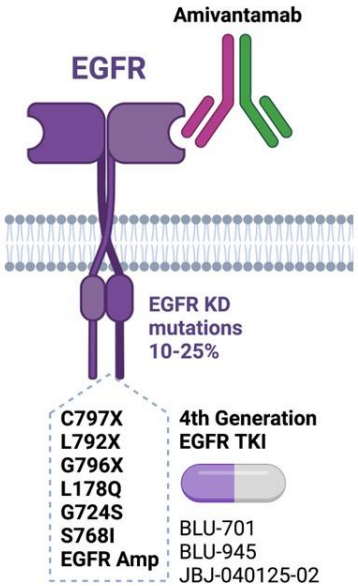
Primary endpoint: PFS (By investigator assessment)



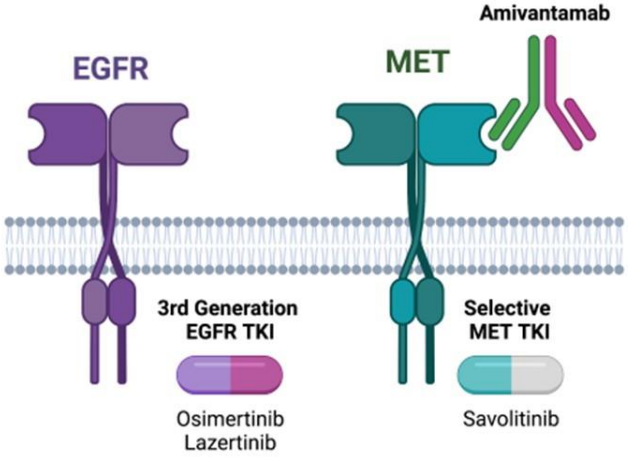
Soria JC, et al. N Engl J Med. 2018; 378:113

Challenge #1: Overcoming Osimertinib resistance

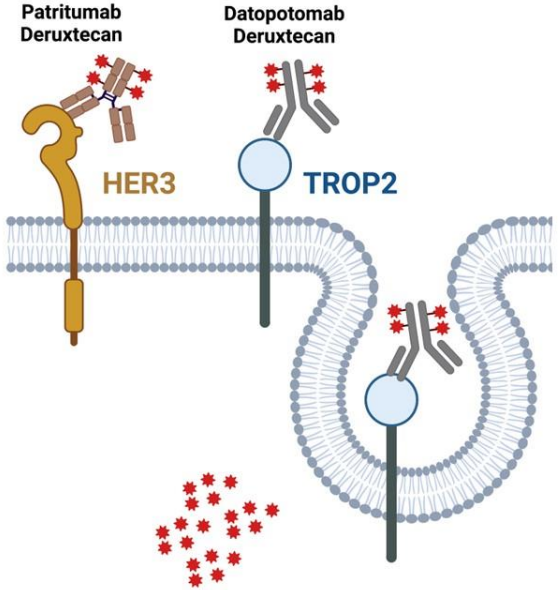
On-Target resistance



Bypass resistance



Delivering Targeted Chemotherapy - ADCs



BC Cho et al. Presnted at ASCO 2021, L. Sequist et al. Lancet Oncology 2020,
P. Janne et al Presented at ASCO 2021, EB Garon et al. Presented at ESMO 2021

PRESENTED BY:
Gonzalo Recondo MD PhD
Center for Medical Education and Clinical Research (CEMIC)

MET amplification
Tepotinib post-osimertinib: INSIGHT-2

Study Design of INSIGHT 2

An open-label, two-arm Phase II study of advanced *EGFR*m NSCLC with *MET*amp after progression on 1L osimertinib (N=~120)

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

*Enrollment could take place based on local results while central confirmation of *MET*amp was ongoing. †Submission of tumor tissue and blood sample obtained after progression on 1L osimertinib was mandatory for all patients, for *MET*amp testing. ‡Safety run-in was completed prior to combination treatment. #Patients receiving tepotinib monotherapy could switch over to the combination at the time of disease progression.

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Detection of *MET*amp

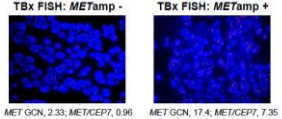
***MET*amp definitions**

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

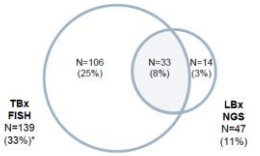
and/or

LBx NGS: *MET* GCN ≥2.3; Archer®

Central testing was mandatory for both



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



*10 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 29%.

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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.

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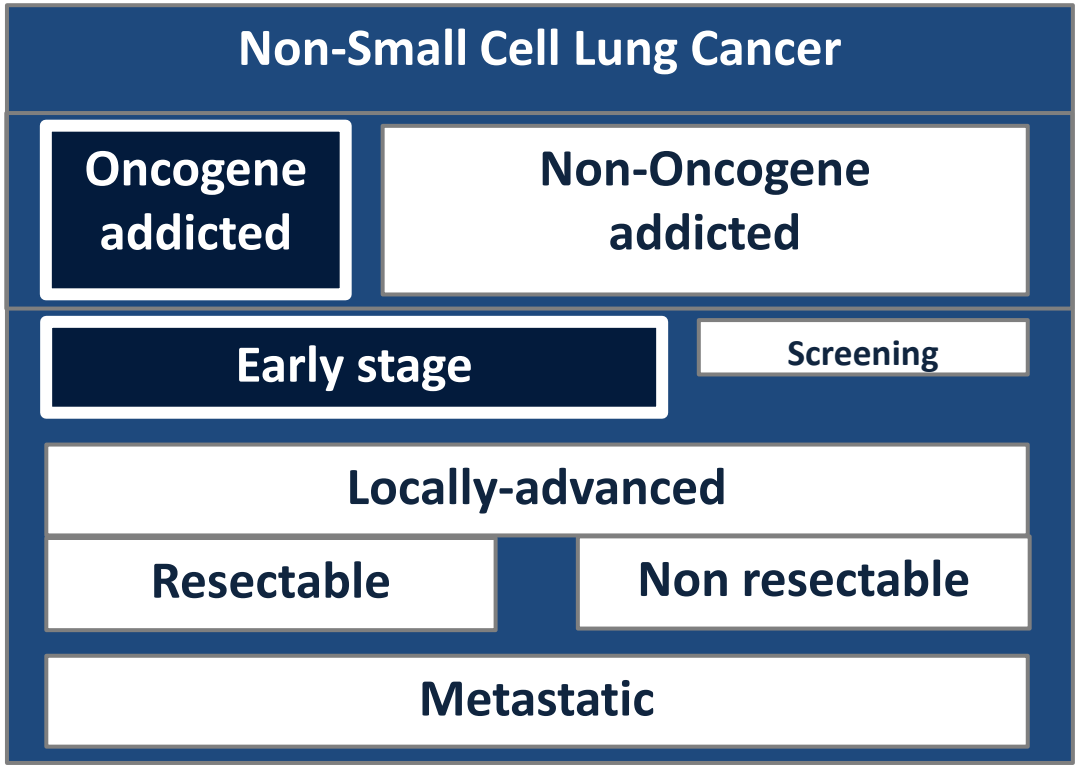
Thoracic Cancers



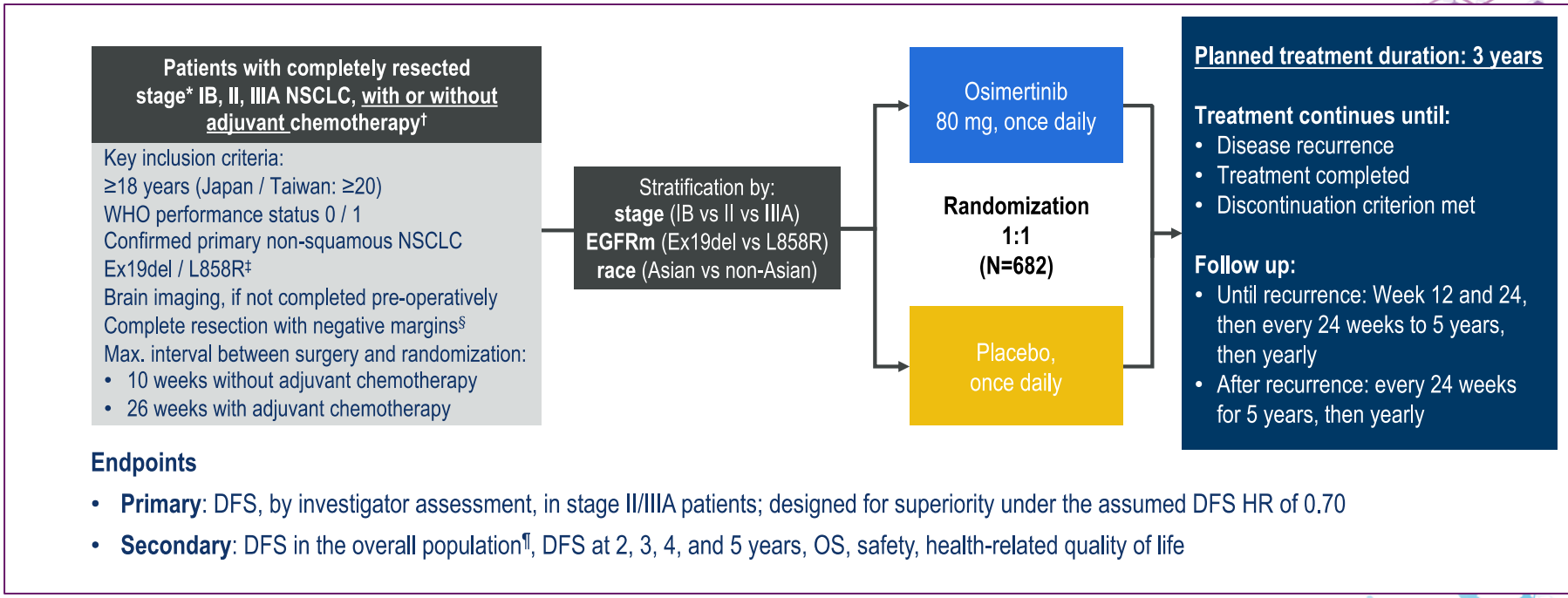
First-line

- EGFR
- ALK
- BRAF
- ROS1

Second/Late-line

- KRAS G12C
- HER2
- RET
- NTRK
- MET
- NRG1
- Ex20ins

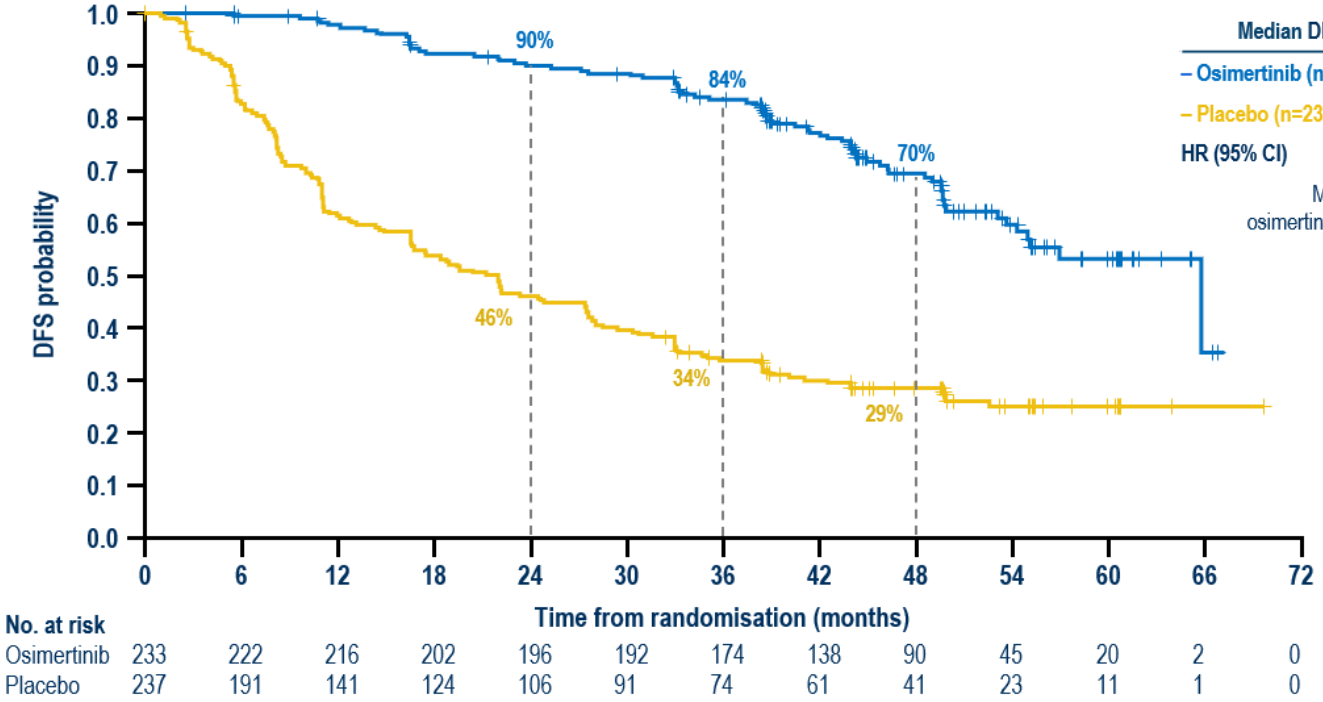
EGFR-mutant, resectable NSCLC: ADAURA



Endpoints

- **Primary**: DFS, by investigator assessment, in stage II/IIIA patients; designed for superiority under the assumed DFS HR of 0.70
- **Secondary**: DFS in the overall population¶, DFS at 2, 3, 4, and 5 years, OS, safety, health-related quality of life

EGFR-mutant, resectable NSCLC: ADAURA



Median DFS, months (95% CI)	
– Osimertinib (n=233)	65.8 (54.4, NC)
– Placebo (n=237)	21.9 (16.6, 27.5)
HR (95% CI)	**0.23 (0.18, 0.30)**

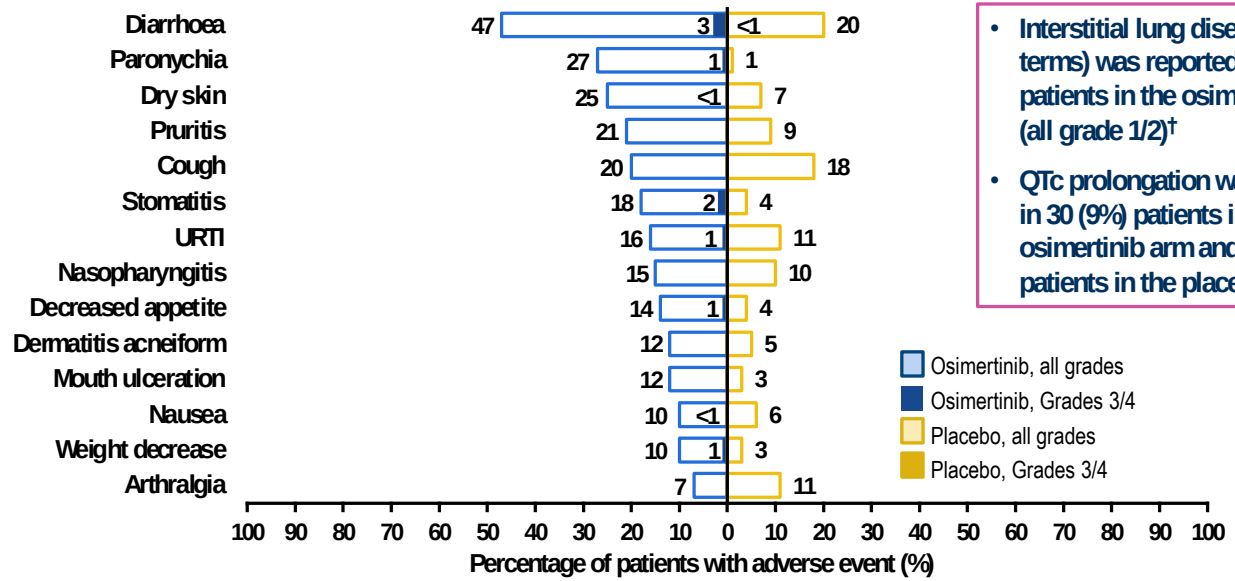
Maturity:* 51%
osimertinib 32%, placebo 70%

Data cut-off: 11 April 2022; median follow-up: osimertinib 44.2 months (range 0 to 67), placebo 19.6 months (range 0 to 70); DFS by investigator assessment; tick marks indicate censored data
*Planned maturity for DFS analysis: 50%
CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; NC, not calculable
Tsuboi M, et al. Presented at the ESMO Congress 2022 (Abstract LBA47)

EGFR-mutant, resectable NSCLC: ADAURA

ALL CAUSALITY ADVERSE EVENTS (≥10% OF PATIENTS)

- Completed planned duration of treatment of 3 years: osimertinib n=222 (66%), placebo n=139 (41%)
- Median total duration of exposure: osimertinib: 35.8 months (range 0 to 38), placebo: 25.1 months (range 0 to 39)



- **Interstitial lung disease (grouped terms) was reported in 11 (3%)* patients in the osimertinib arm (all grade 1/2)†**
- **QTc prolongation was reported in 30 (9%) patients in the osimertinib arm and 8 (2%) patients in the placebo arm‡**

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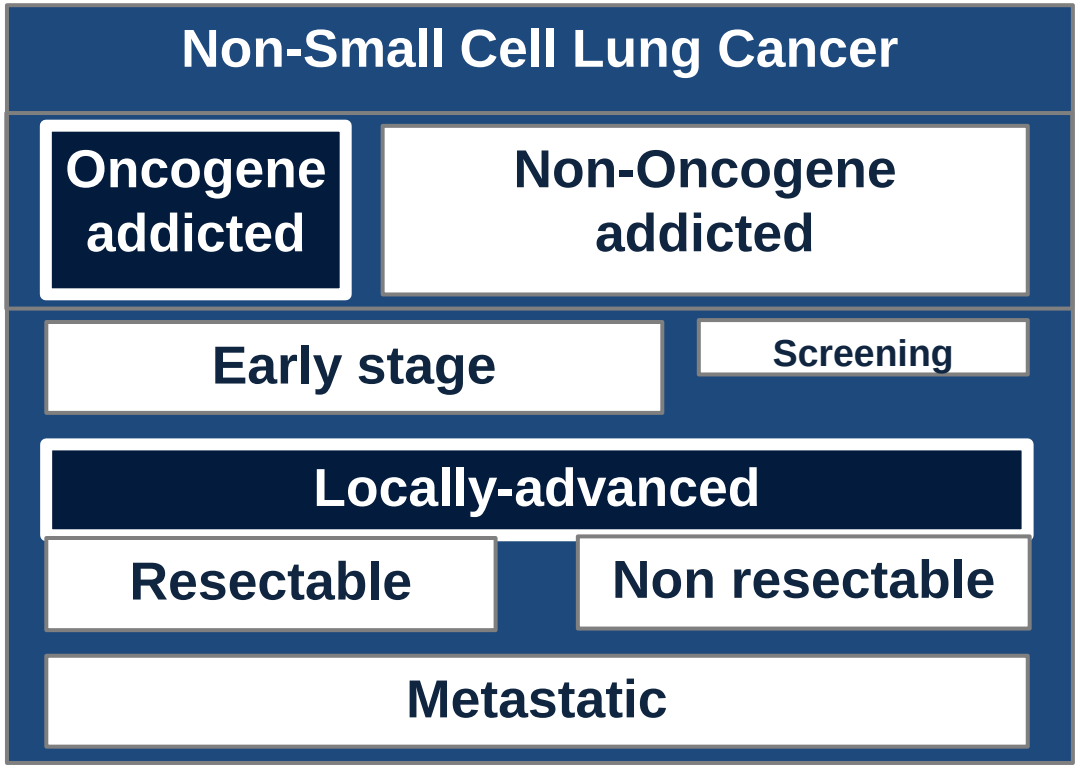
Masahiro Tsuboi, MD

*Compared with the January 17, 2020 data cut-off, one additional patient reported interstitial lung disease (grouped term): pneumonitis, Grade 2; †Grade 1, n=6; Grade 2, n=5; Grade 3, n=0; ‡Osimertinib: Grade 1, n=16; Grade 2, n=10; Grade 3, n=4; placebo: Grade 1, n=7; Grade 2, n=0; Grade 3, n=1.

QTc, electrocardiogram QT; URTI, upper respiratory tract infection
Data cut-off: April 11, 2022.

Thoracic Cancers



First-line

- **EGFR**
- **ALK**
- **BRAF**
- **ROS1**

Second/Late-line

- **KRAS G12C**
- **HER2**
- **RET**
- **NTRK**
- **MET**
- **NRG1**
- **Ex20ins**

Poster 8541

Durvalumab (durva) after chemoradiotherapy (CRT) in unresectable stage III EGFR mutation-positive (EGFRm) NSCLC: A *post hoc* subgroup analysis from PACIFIC

Jarushka Naidoo[1], Scott Antonia[2], Yi-Long Wu[3], Byoung Chul Cho[4], Piruntha Thiyagarajah[5], Helen Mann[5], Michael Newton[6], Corinne Faivre-Finn[7]

[1]Sidney Kimmel Comprehensive Cancer Center at John Hopkins University, Baltimore, MD, USA; [2]Duke University School of Medicine, Durham, NC, USA; [3]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China; [4]Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [5]Global Medicines Development, AstraZeneca, Cambridge, UK; [6]Global Medicines Development, AstraZeneca, Gaithersburg, MD, USA; [7]The University of Manchester and The Christie NHS Foundation Trust, Manchester, UK

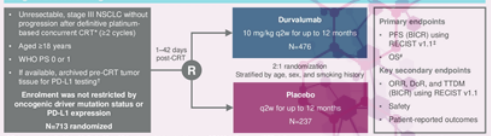
Introduction

- Standard of care for patients with unresectable stage III non-small cell lung cancer (NSCLC) includes treatment with the 'PACIFIC regimen' based on the Phase III placebo-controlled PACIFIC trial in which patients received chemoradiotherapy (CRT) followed by consolidation durvalumab in an all-comer population[1,2,3]
  - Primary analysis: overall survival (OS) hazard ratio (HR) vs placebo, 0.68; 99.73% confidence interval (CI) 0.47, 0.997; progression-free survival (PFS) HR vs placebo, 0.52; 95% CI 0.42, 0.65
  - Updated 5-year analysis: OS HR vs placebo, 0.72; 95% CI 0.59, 0.89; PFS HR vs placebo, 0.55; 95% CI 0.45, 0.68
- Epidermal growth factor receptor (EGFR) mutations are present in 10–30% of patients with unresectable stage III NSCLC of adenocarcinoma histology[4-6]. However, the benefit of immunotherapy in patients with EGFR mutation-positive (EGFRm) unresectable stage III NSCLC is unclear[7-10]
- We report a *post-hoc* exploratory analysis of efficacy and safety from a subgroup of 35 patients with EGFRm NSCLC from the PACIFIC trial

Methods

- PACIFIC (NCT02125461) was a Phase III, randomized, double-blind, placebo-controlled, multicenter, international trial of patients with World Health Organization (WHO) Performance Status (PS) 0/1 and no disease progression after platinum-based concurrent CRT (**Figure 1**)[1,2]. Enrolment was not restricted by oncogenic driver gene mutation status or programmed cell death-ligand 1 (PD-L1) expression
- Primary endpoints were PFS by blinded independent central review (BICR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and OS; key secondary endpoints included objective response rate (ORR) and safety
- Patients with EGFRm disease determined by local testing only were included in this *post-hoc* subgroup analysis
- Treatment effects for the EGFRm subgroup were estimated using unstratified Cox proportional hazard models with treatment as the only covariate; no adjustment for multiple comparisons were performed for this subgroup analysis. Medians were estimated using the Kaplan-Meier method. Statistical analyses for this subgroup were exploratory
- Data cut-off (DCO) for the EGFRm subgroup baseline characteristics and safety analysis was 13 February 2017. DCO for the EGFRm subgroup efficacy analysis was 11 January 2021

Figure 1. Trial design



*RT dosage typically 60 to 66 Gy in 30 to 33 fractions. †Using the Ventana SP263 IHC assay. ‡PFS defined as time from randomization to the date of objective disease progression, or death by any cause in the absence of progression. #OS defined as time from randomization until death by any cause.
BICR, blinded independent central review; CRT, chemoradiotherapy; DoR, duration of response; Gy, units of gray; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; q2w, every 2 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RT, radiotherapy; TTDM, time to death or distant metastasis; WHO, World Health Organization

Results and interpretation

Table 2. Subsequent treatments (any line; PACIFIC EGFRm subgroup)

Patients with post-discontinuation disease-related anti-cancer treatment, n (%)

	Durvalumab	Placebo (n=11)
		8 (73)
		7 (64)
		7 (64)
		2 (18)
		4 (36)
		3 (27)

Objective

- To report a *post hoc* exploratory analysis of the PACIFIC trial (NCT02125461) in patients with unresectable stage III EGFRm NSCLC

Conclusions

- In this exploratory analysis of durvalumab were similar to pl
- Data for this subgroup should baseline characteristics betwe according to tumor EGFRm bi
- The safety data for durvaluma profile for durvalumab monoth
- The benefit of immunotherapy
- Evidence from the early stage alternative treatment option fo
- The ongoing global Phase III osimertinib in patients with EG

Plain language sum

Why did we perform this rese

Patients with stage III non-smal unresectable NSCLC) are recor known as chemoradiotherapy ((approach was based on results durvalumab for up to 1 year or Results from the trial showed th cancer getting any worse, for lo participants who received treatr received CRT and placebo.

Around 10–30% of patients wit mutation-positive (EGFRm) NS were part of the PACIFIC trial re

How did we perform this rese

We analyzed how long 35 partic getting any worse, and how lon this type of lung cancer experie

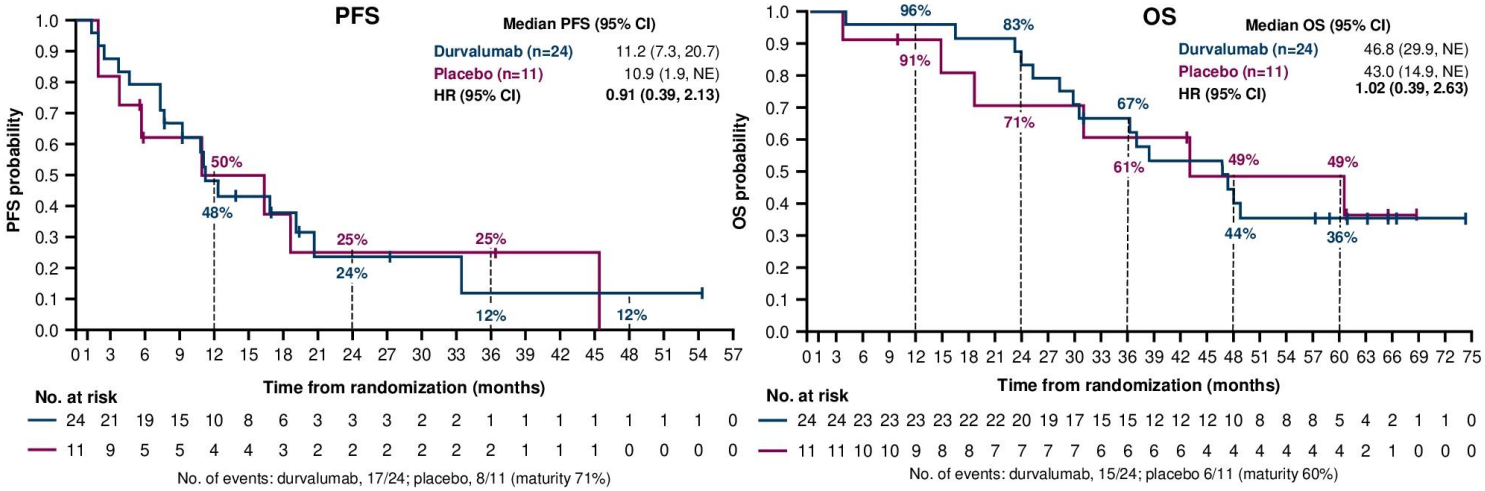
What are the findings of this

The participants with EGFRm for a similar length of time as th side effects to the rest of the PA from the PACIFIC trial, further unresectable stage III NSCLC. advanced/metastatic and resec

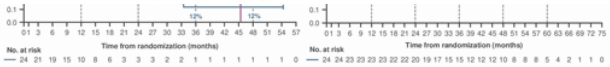
Where can I access more info

The PACIFIC trial (NCT02125461) can be accessed at: https://clinicaltrials.gov/ct2/show/NCT02125461

Figure 2. PFS (BICR) and OS (PACIFIC EGFRm subgroup)



DCO: 11 January 2021. Tick marks indicate censored data. BICR, blinded independent central review; CI, confidence interval; DCO, data cut-off; EGFRm, epidermal growth factor receptor mutation-positive; HR, hazard ratio; OS, overall survival; NE, not evaluable; NSCLC, non-small cell lung cancer; PFS, progression-free survival



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Subsequent therapies

- In the durvalumab and placebo EGFRm subgroup arms, 79% and 73% went on to receive a subsequent anti-cancer treatment, respectively
- In total, 54% and 64% of patients in the durvalumab and placebo EGFRm subgroup arms received an EGFR-TKI as post-study discontinuation anti-cancer treatment (any line) (**Table 2**)

DCO: 13 February 2017. *No grade 3/4 AEs were reported in the durvalumab arm for the AEs reported in ≥15% of patients shown in this figure.
DCO, data cut-off; EGFRm, epidermal growth factor receptor mutation-positive; LRTI, lower respiratory tract infection

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Poster

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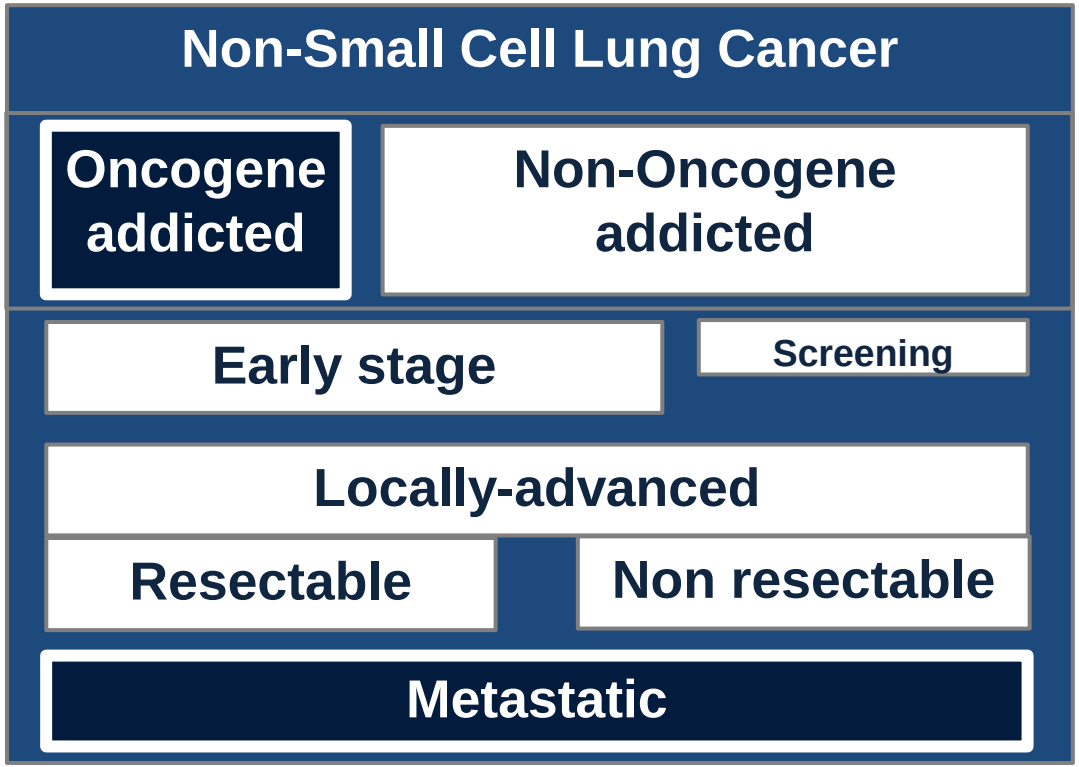
Corresponding author: Jarushka Naidoo
Corresponding author email address: jnaidoo1@jhmi.edu
Corresponding author Twitter handle: @DrJNaidoo

Poster presented at ASCO 2022; June 3–7, 2022

Thoracic Cancers



First-line

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- ROS1

Second/Late-line

- KRAS G12C
- HER2
- RET
- NTRK
- MET
- NRG1
- Ex20ins

TKIs ALK en première ligne
Efficacité

Efficacy data	ALEX[1]		ALTA-1L[2]		CROWN[3]	
	Alectinib (n=152)	Crizotinib (n=151)	Brigatinib (n=137)	Crizotinib (n=138)	Lorlatinib (n=147)	Crizotinib (n=149)
Median PFS, months	34.8*	10.9*	24.0†	11.1†	Not reached†	9.3†
HR (95% CI)	0.43 (0.32–0.58)*		0.48 (0.35–0.66)†		0.27 (0.18–0.39)†	
PFS rate at 36 months, % (95% CI)	**46.4*** (CI not reported)	**13.5*** (CI not reported)	**43.0** (34.0–51.0)†	**19.0** (12.0–27.0)†	**63.5** (CI not reported)	**18.9** (CI not reported)
Median duration of follow-up, months	37.8		40.4		36.7	

Cross-trial comparisons have significant limitations. This information is presented in order to generate discussion, not to make comparisons between study results.

*INV; †IRC.
CI, confidence interval; HR, hazard ratio; INV, investigator-assessed; IRC, independent reviewer committee;
PFS, progression-free survival.

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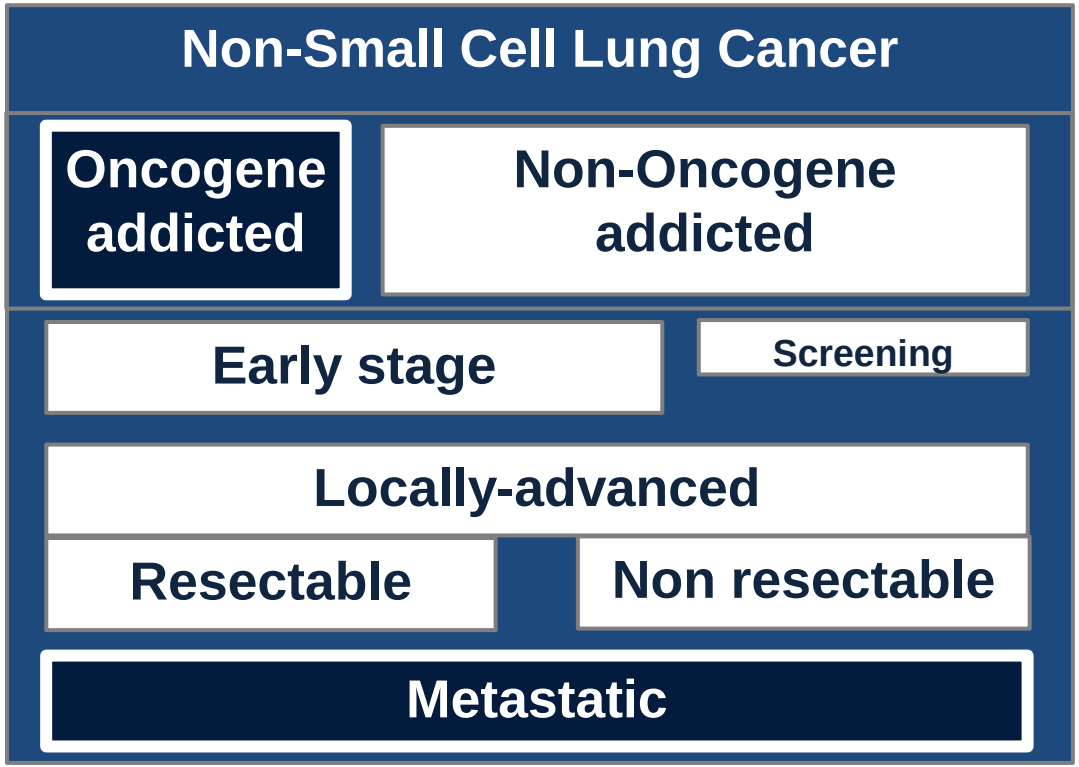
Thoracic Cancers



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ASCO 2020: BRAF

The Updated Overall Survival and Genomic Analysis from a Single-Arm Phase 2 Study of Dabrafenib plus Trametinib in Patients with *BRAF* V600E Mutant Metastatic Non-Small Cell Lung Cancer

P359

David Planchard[1], Benjamin Besse[1], Harry J.M. Groen[2], Sayed M.S. Hashemi[3], Julien Mazieres[4], Tae Min Kim[5], Elisabeth Quoix[6], Pierre-Jean Souquet[7], Fabrice Barlesi[8], Christina Baik[9], Liza Villaruz[10], Ronan J. Kelly[11], Shirong Zhang[12], Monique Tan[12], Eduard Gasal[12], Libero Santarpia[13], Bruce E Johnson[14]

[1]Gustave Roussy, Villejuif, France; [2]University of Groningen and University Medical Centre Groningen, Groningen, The Netherlands; [3]VU University Medical Center Amsterdam, The Netherlands; [4]Hospital Larrey, Toulouse, France; [5]Seoul National University Hospital, Seoul, South Korea; [6]University Hospital of Strasbourg, Strasbourg, France; [7]Hôpital de Jour, Pierre Benitef, France; [8]Aix-Marseille University, Marseille, France; [9]Fred Hutchinson Cancer Research Center, Seattle, Washington, United States; [10]University of Pittsburgh Medical Center - Hillman Cancer Center, Pittsburgh, Pennsylvania, United States; [11]Baylor University Medical Center, Dallas, Texas, United States; [12]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, United States; [13]Novartis Pharma AG, Basel, Switzerland; [14]Dana-Farber Cancer Institute, Boston, Massachusetts, United States

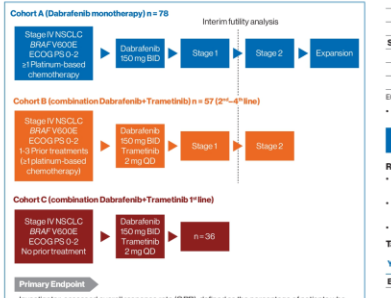
Background

- *BRAF* V600E mutations have been observed in 2%–4% of NSCLC; this mutation drives cellular growth and proliferation through constitutive activation of the mitogen-activated protein kinase pathway[1–4]
- Primary analysis of this trial showed robust clinical activity for dabrafenib + trametinib with manageable safety profile in patients with *BRAF* V600E mutant metastatic Non-Small Cell Lung Cancer (NSCLC)[5–7]
- Here we present the updated overall survival (OS) and genomic analysis data for combination therapy population in Cohort B (pretreated) and Cohort C (treatment-naive) patients

Methods

- This was a Phase 2, multicohort, multicenter, non-randomized, open-label (NCT01336634) study where patients were sequentially enrolled into 3 different cohorts based on the number of prior lines of systemic treatment for metastatic disease **(Figure 1)**

Figure 1. Study Design



BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer; ORR, overall response rate QD, once daily

Assessments and Statistical Methods

- The data cutoff date for this updated analysis was June 22, 2019
- Central confirmatory testing of *BRAF* V600E mutation was performed using the next generation sequencing OncomineTM assay developed by Thermo Fisher Scientific
- Potential associations between baseline genomic landscape and patient efficacy endpoints were evaluated using Kaplan-Meier curves, Log rank tests and Cox regression models

Results

Baseline Characteristics and Patient Disposition

- The median age of the patients was 67.0 years (range: 44–91 years) with a higher proportion (22 patients; 61%) of older patients (≥ 65 years old) enrolled in cohort C
- In cohort C, 30 versus 3 patients were Caucasian and Asian

Table 1. Patient Demographics and Baseline Characteristics

	Pretreated (Cohort B) N = 57	Treatment-naïve (Cohort C) N = 36
Age (years)		
Median (range)	64.0 (41–88)	67.0 (44–91)
Age group (years), n (%)		
≥18 to <65	29 (51)	14 (39)
≥65	28 (49)	22 (61)
Sex, n (%), Female	28 (49)	22 (61)
ECOG PS, n (%)		
0	17 (30)	13 (36)
1	35 (61)	22 (61)
2	5 (9)	1 (3)
Smoking History, n (%)		
Never smoked	16 (28)	10 (28)
Current smoker	6 (11)	5 (14)
Former smoker	35 (61)	21 (58)

ECOG PS, Eastern Cooperative Oncology Group performance status

- At data cutoff, 4 pretreated patients and 7 treatment-naïve patients were still in follow-up

Efficacy

Response Rate

- The median duration of follow-up was 16.6 and 16.3 months for pretreated and treatment-naïve patients, respectively
- Four patients each from pretreated and treatment-naïve cohorts with partial response also had complete disappearance of target lesions
- Response rates are mentioned in **Table 2** below

Table 2. Summary of Investigator-Assessed Best Response (RECIST v1.1 Criteria)

Year	Pretreated (Cohort B) N = 57	Treatment-naïve (Cohort C) N = 36
Best Response, n (%)		
CR	3 (5)	2 (6)
PR	36 (63)	21 (58)
SD	7 (12)	4 (11)
PD	7 (12)	5 (14)
NE	4 (7)	4 (11)
Response Rate		
CR + PR, n (%)	39 (68.4)	23 (63.9)
95% CI, %	54.8–80.1	46.2–79.2
Disease Control Rate		
CR + PR + SD, n (%)	46 (80.7)	27 (75.0)
95% CI, %	68.1–90.0	57.8–87.9

CI, confidence interval; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease

Duration of Response (DOR)

- Investigator-assessed median DOR was 9.8 months (95% CI, 6.9–18.3) and 10.2 months (95% CI, 8.3–15.2) in pretreated and treatment-naïve patients, respectively

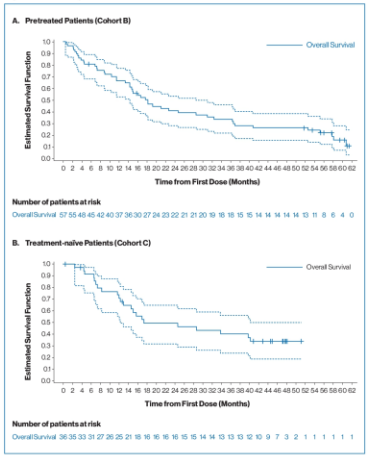
Progression free survival (PFS)

- Updated investigator assessed median PFS was 10.2 months (95% CI, 6.9–16.7) and 10.8 months (95% CI, 7.0–14.5) for pretreated and treatment-naïve patients, respectively

Overall Survival (OS)

- The estimated median OS was 18.2 months (95% CI, 14.3–28.6) and 17.3 months (95% CI, 12.3–40.2) in pretreated and treatment-naïve cohorts **(Figure 2)**

Figure 2. Plot of Kaplan- Meier Overall Survival Curve with 95% Confidence Band



Safety

- For patients in the combination treatment cohorts the median duration of treatment with dabrafenib and trametinib was 10.55 months (range: 0.3–62.2 months)
- The most frequent adverse events (AEs) regardless of study treatment relationship in ≥ 30% of patients were pyrexia (56%), nausea (49%), vomiting (41%), dry skin (39%), edema peripheral (38%), diarrhea (37%), decreased appetite (33%), and cough (31%) **(Table 3)**
- Overall, 56 (60%) patients died due to progressive disease and 12 (13%) patients died due to other reasons

Table 3. Adverse Events in Patients Receiving Dabrafenib + Trametinib (all grade incidence ≥ 20%)

Adverse Event, n (%)	All Grade	Grade 3	Grade 4
Pyrexia	52 (56)	6 (6)	0
Nausea	46 (49)	0	0
Vomiting	38 (41)	3 (3)	0
Dry skin	36 (39)	1 (1)	0
Oedema peripheral	35 (38)	0	0
Diarrhoea	34 (37)	2 (2)	0
Decreased appetite	31 (33)	0	0
Cough	29 (31)	0	0
Asthenia	27 (29)	4 (4)	0
Fatigue	26 (28)	3 (3)	0
Chills	25 (27)	0	0
Rash	24 (26)	1 (1)	0
Dyspnoea	24 (26)	6 (6)	0
Arthralgia	21 (23)	1 (1)	0

Genomic Analysis

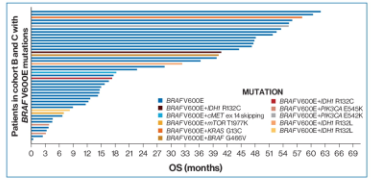
- Fifty seven of 62 tumor samples retrieved from 93 patients were centrally confirmed to have *BRAF* V600E mutation; 5 non-confirmed BRAF tumors (3 patients had PR) were positive for *c-MET T1010I, KRAS G12V, ALK* fusion and 2 *JAK3* S493C with median PFS of 13.8 months while OS was not estimable due to limited data points
- Eleven (22%) of 50 NSCLC patients analyzed for additional genomic alterations had concomitant somatic mutations and/or genetic alterations in addition to *BRAF* V600E mutation (**Table 4**)
- Log Rank test and Cox proportional hazards regression were used to test the significance
- NSCLC patients whose tumors had concomitant genetic alterations in the PI3K pathway showed a trend toward decreased OS
  - Median OS for patients with co-activated MAPK and PI3K pathways and single *BRAF* V600E mutation was 5.4 and 22.7 months, respectively ($P = 0.0660$ by the log-rank test)
- Landscape of baseline DNA alterations for *BRAF* V600E NSCLC patients with available data where patients are ranked according to OS is shown in **Figure 3**

Table 4. Genomic Alterations Detected by NGS in Archival Biopsies of Metastatic *BRAF* V600E–mutant NSCLC Patients and their Association with Clinical Outcome

	Cohort	Genetic alterations	Cohort	Best response	PFS, months	OS, months
D + T (Cohort B) (ORR, 68.4%; mPFS, 10.2 months; mOS, 18.2 months)		*BRAF* V600E + *IDH1* R132C	B	CR	6.9	40.7
		BRAF V600E + *KRAS* G13C	B	PR	5.8†	5.8†
		BRAF V600E + *IDH1* R132L[^]	B	PR	32.4	32.4
		BRAF V600E + *PIK3CA* E542K	B	PR	16.7	55.2
		BRAF V600E + *cMET* ex 14 skipping	B	PR	10.2	18.2
		BRAF V600E + *PIK3CA* E545K	B	NE	1.4**	3.8
		BRAF V600E + *PIK3CA* E545K	B	PD	1.4	3.1
		cMET T1010I^	B	PR	27.6	59.4
		JAK3 S493C^	B	PR	5.6	10.3
		KRAS G12V^	B	PD	2.9	4.4
D + T (Cohort C) (ORR, 63.9%; mPFS, 10.8 months; mOS, 17.3 months)		*BRAF* V600E + *mTOR* T1977K	C	PR	7.0	7.0
		BRAF V600E + *IDH1* R132C	C	PR	10.4	17.3
		BRAF V600E + *IDH1* R132L	C	PR	5.5	8.2
		BRAF V600E + *BRAF* G466V	C	SD	19.4	40.2
		ALK fusion^	C	SD	13.8	40.9‡
		JAK3 S493C^	C	PR	19.3	51.2‡

CR, complete response, D, Dabrafenib; mOS, median overall survival; mPFS, median progression-free survival; NE, not evaluable; NGS, next-generation sequencing; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; T, Trametinib. †Patient reported no history of former or current smoking at baseline (never smoker). **These patients are reported as BRAFV600E wild type after central lab testing. ‡Censored, follow-up ongoing. **Censored due to follow up ended. ^A CTNNB1 S33C mutation was also detected in this patient.

Figure 3. Genomic Landscape of Baseline DNA Alterations for *BRAF* V600E NSCLC Patients



NSCLC patients' data with non-confirmed *BRAF* V600E mutation have not been reported in this figure

Conclusions

- The combination of dabrafenib at 150 mg twice daily with trametinib 2 mg once daily provided durable clinical benefit with a favorable benefit/risk ratio for patients with *BRAF* V600E mutation positive, metastatic NSCLC regardless of prior treatment for their metastatic disease
- The safety profile of dabrafenib plus trametinib in patients with NSCLC was consistent with that reported in patients with melanoma treated with this combination. AEs were manageable and no new safety signals were identified
- Co-occurring genetic alterations might influence clinical outcomes for patients with *BRAF* V600E mutation positive, metastatic NSCLC

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Acknowledgements

We would like to thank our patients, their families and caregivers, the participating clinical sites and teams. Medical editorial assistance with this presentation was provided by Shivani Patel (Novartis Healthcare Pvt Ltd).

Disclosures

- Consulting or Advisory Role: AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Novartis, Roche, Pfizer, MSD Oncology, Celgene, MedImmune, BeiGene; Honoraria: Prime Oncology, Peer CME; Research Funding: AstraZeneca/MedImmune, Bristol-Myers Squibb, Boehringer Ingelheim, Lilly, Merck, Novartis, Roche, Pfizer, Sanofi/Aventis, Taiho Pharmaceutical, Daiichi Sankyo, Abbvie

Presented at the ASCO Virtual Meeting, May 29 – 31, 2020.
This study was sponsored by Novartis Pharmaceuticals Corporation.

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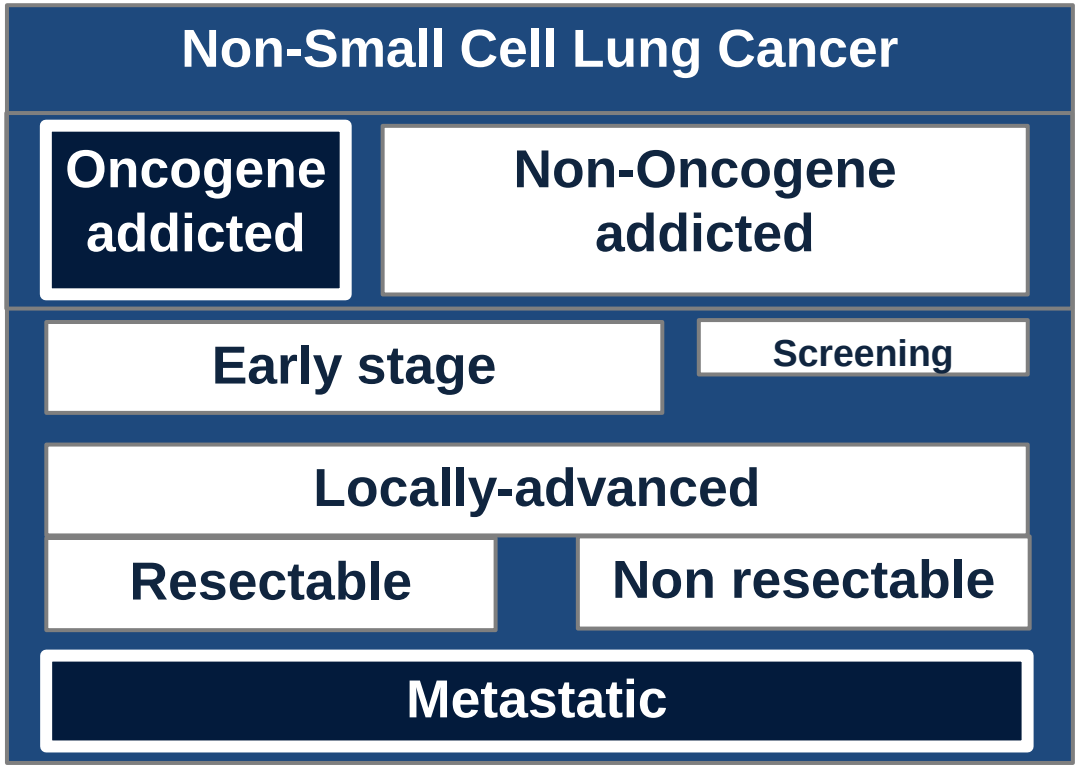
Thoracic Cancers



First-line

- EGFR
- ALK
- BRAF
- ROS1

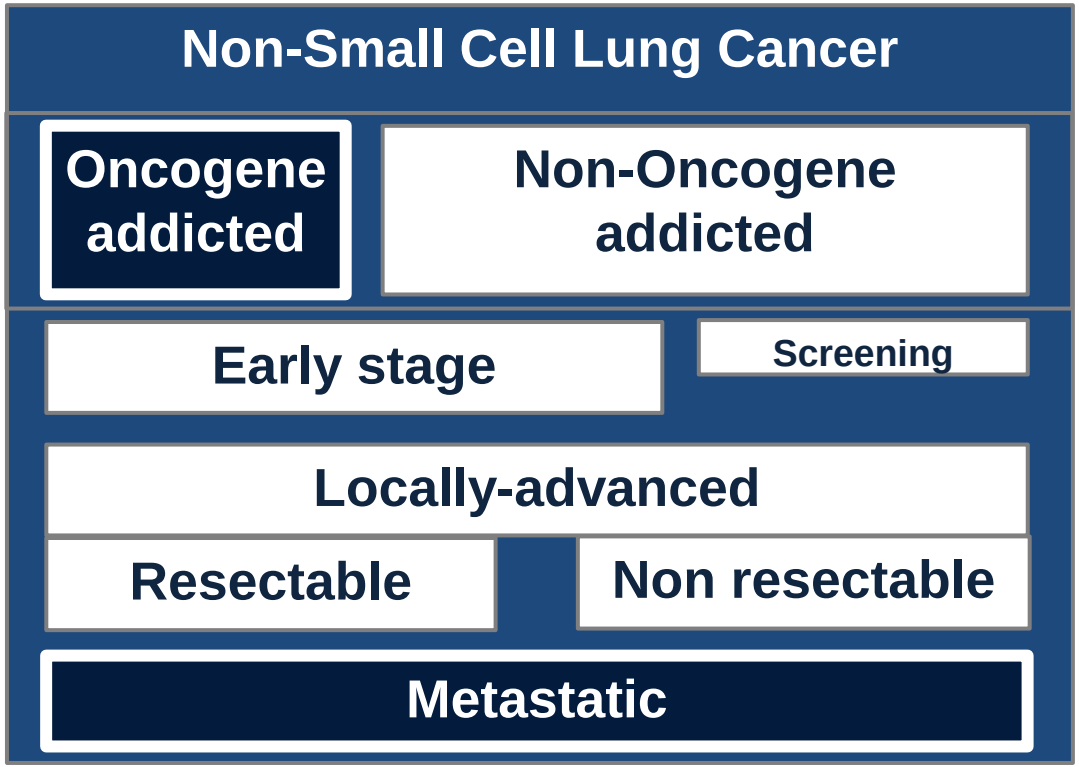
Second/Late-line

- KRAS G12C
- HER2
- RET
- NTRK
- MET
- NRG1
- Ex20ins

ROS1-1: les données

Auteur	Pop majoritaire	Année	Phase	N	Lignes	Taux de réponse	PFS (mois)	SG (mois)
Shaw et al (1001)	Caucasienne	2014	I/II	53	1L 13% 2L 38% 3L 49%	**69,8%**	**19,3**	Non atteinte
Mazières et al (EUROS cohort)	Caucasienne	2015	Recueil retrospectif	31	1L 3% 2L 29% 3L et + 68%	**80%**	**9,1**	Non rapporté
Moro-Sibilot et al (AcSé crizo)	Caucasienne	2015	II	37	1L 5% 2L 27% 3L et + 68%	**53%** (à 2 cycles)	**10**	Non atteinte Estimée à 18,4 mois
Goto et al (Oxford Oncology Study - OO 12-01)	Asiatique	2016	II	127	1L 19% 2L 42% 3L et + 39%	**69,3%**	**13,4**	Non atteinte

Thoracic Cancers



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Most frequent alteration for 2L: KRAS G12C
CodeBeak 200: Sotorasib

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

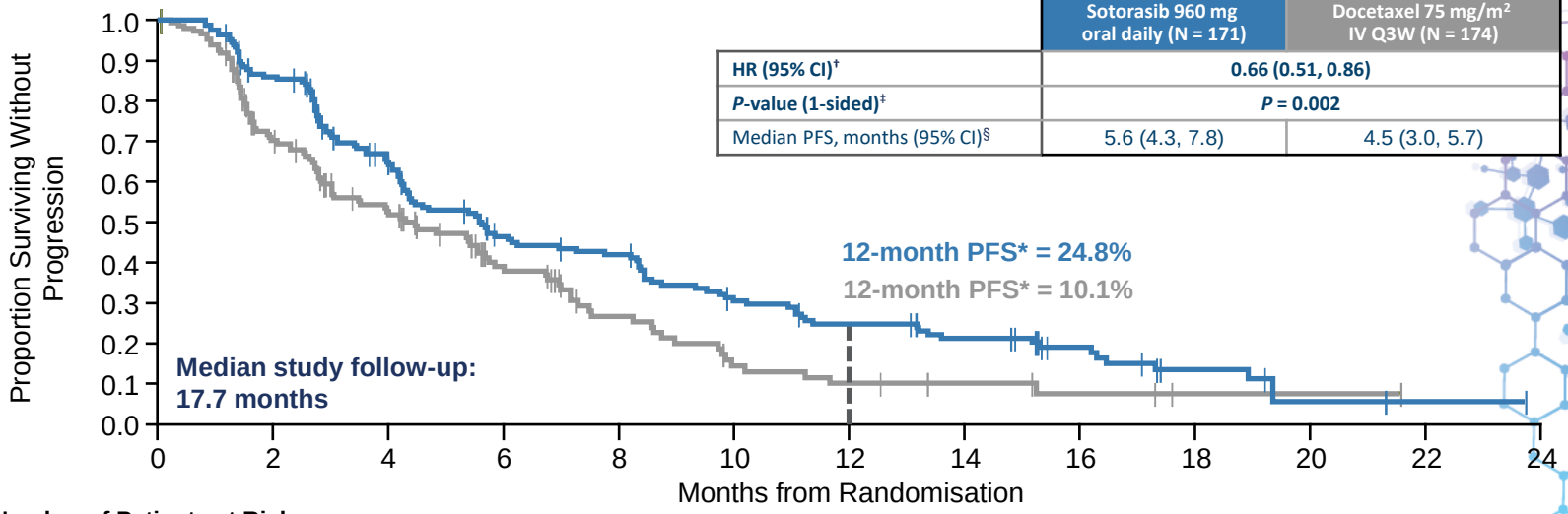
Per regulatory guidance, protocol was amended to reduce planned enrolment from 650 to ~330 patients, and crossover from docetaxel to sotorasib was permitted.

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

Johnson ML, et al. Presented at European Society for Medical Oncology (ESMO) 2022 Annual Meeting, September 9-13, 2022; Paris, France.

Most frequent alteration for 2L: KRAS G12C
CodeBeak 200: Sotorasib

	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)



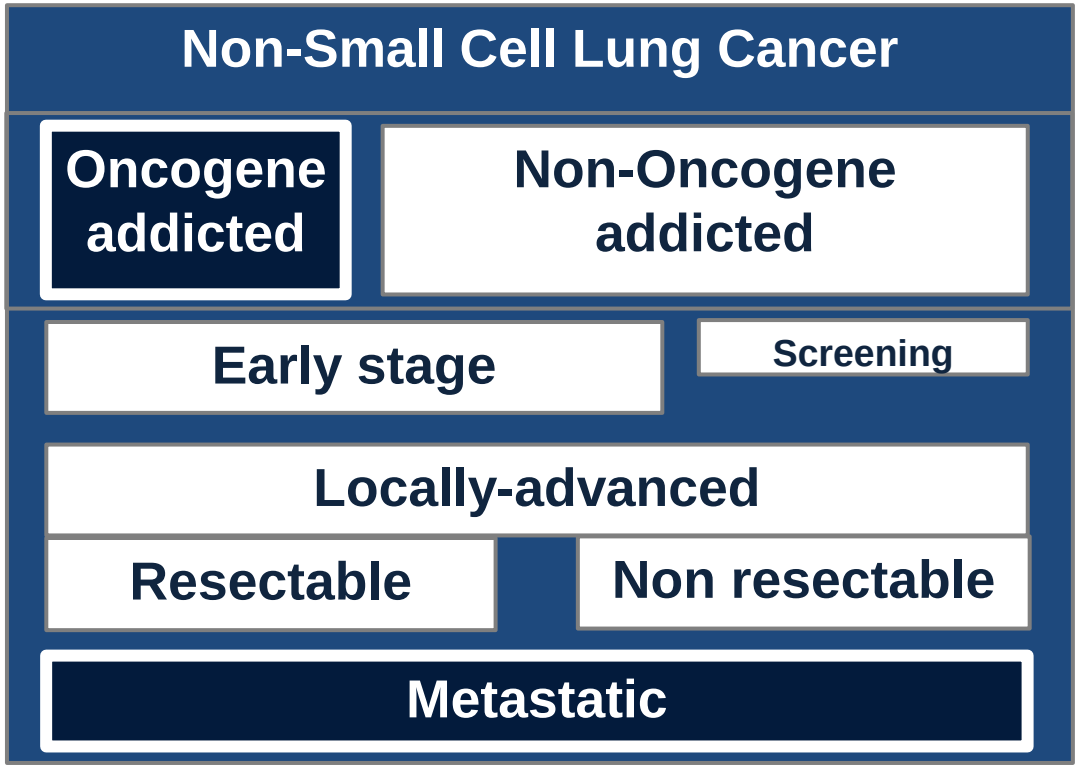
Number of Patients at Risk:

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 met its primary endpoint with sotorasib demonstrating superior PFS over docetaxel (HR 0.66, *P* = 0.002); 12-month PFS rate was 24.8% for sotorasib and 10.1% for docetaxel

Johnson ML, et al. Presented at European Society for Medical Oncology (ESMO) 2022 Annual Meeting, September 9-13, 2022; Paris, France

Thoracic Cancers



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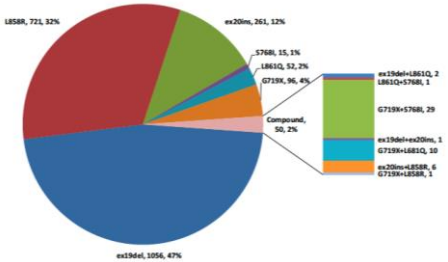
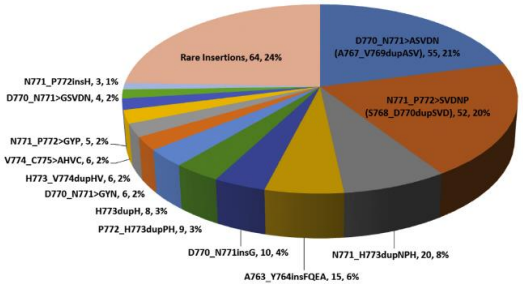
EGFR Exon 20 insertions: key features

FREQUENCY and HETEROGENEITY

- - 12% of EGFR
- mutations
- - >100 subtypes
- - NGS required
- for diagnosis
- - Insensive to
- EGFR TKIs
- (except FQE



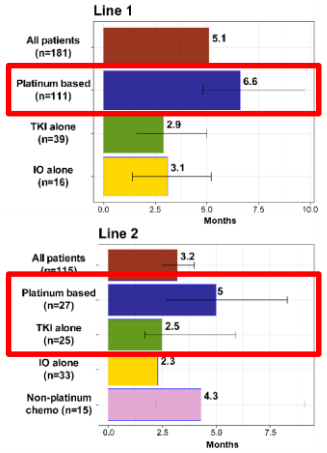


Riess et al. J Thorac Oncol 2018;13:1560

TREATMENT: REAL-WORLD EVIDENCE (Flatiron database)

Treatment, n (%)	Line 1	Line 2
Number of patients	181	115
Platinum-based regimen	111 (61.3)	27 (23.5)
Platinum doublet	50 (27.6)	13 (11.3)
Platinum + IO	32 (17.7)	8 (7.0)
Platinum + VEGFi	25 (13.8)	5 (4.3)
Other platinum combinations[a]	4 (2.2)	0
Platinum alone	0	1 (0.9)
TKI alone	39 (21.5)	25 (21.7)
Other TKI combinations	1 (0.6)	0
IO alone	16 (8.8)	33 (28.7)
VEGFi alone	1 (0.6)	11 (9.6)
Non-platinum chemotherapy	5 (2.8)	15 (13.0)
Others	8 (4.4)	4 (3.5)

Median (95% CI) rwPFS by Therapy



Girard et al. MA04.07. WCLC 2020

EGFR Exon 20 insertions: targeted therapies

POZIOTINIB: ZENITH20 phase 2 trial

- 115 patients

- **Response rate by BIRC: 15%** (95%CI 9-23%)

- **mPFS: 5.5 mo** (95% CI, 0-13.1)

- Grade ≥3 TRAE: 30%
- AEs leading to discontinuation: ?

Socinski et al. LBA60. ESMO 2020
Cornelissen. MA11.04. WCLC 2020

MOBOCERTINIB: Phase ½ and EXCLAIM cohorts

- 114 and 96 patients

- **Response rate per IRC: 23/26%** (95%CI 15-33/19-35%)

- **mPFS: 7.3 mo** (95% CI, 5.5-10.2)

- Grade ≥3 TRAE: 30%
- AEs to discontinuation: 17/10%

Ramalingam et al. OA04.03. WCLC 2020

AMIVANTAMAB: CHRYSALIS PHASE 1 trial

- 81 patients

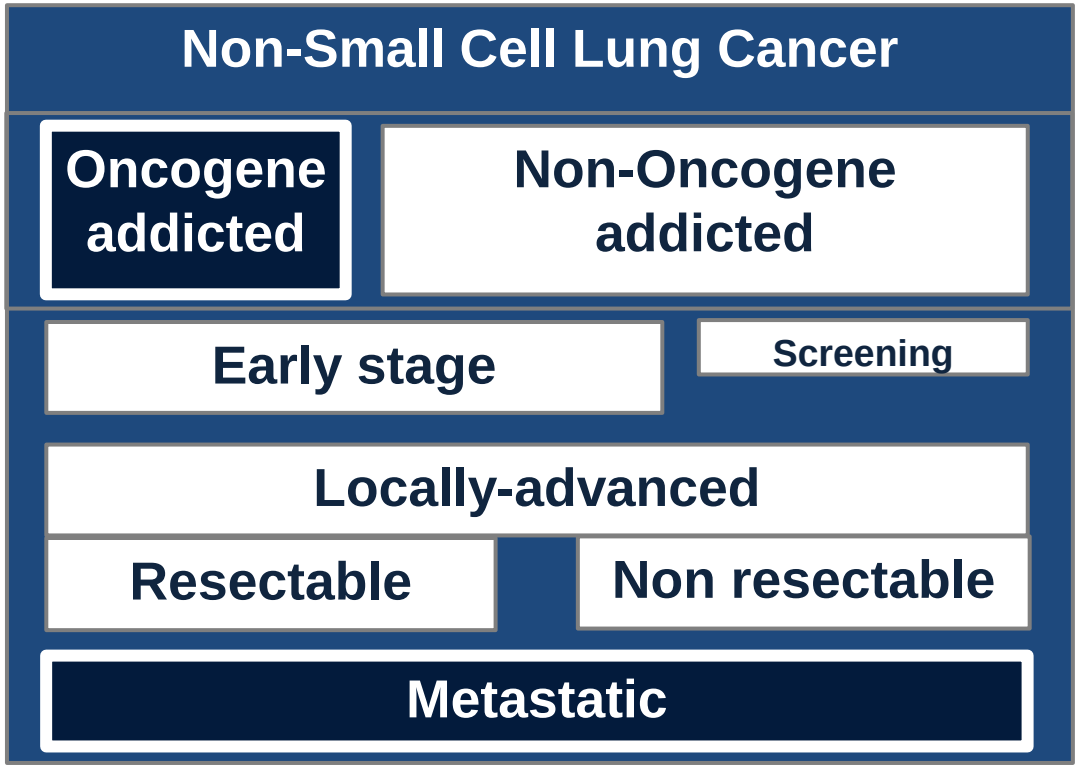
- **Response rate by BIRC: 40%** (95%CI 29-51%)

- **mPFS: 8.3 mo** (95% CI, 6.5-10.9)

- Grade ≥3 TRAE: 16%
- AEs to discontinuation: 4%

Sabari et al. OA04.04. WCLC 2020

Thoracic Cancers



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- Ex20ins

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

REVIEW

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[1], J. Remon[2], J. Mateo[3], C. B. Westphalen[4], F. B
F. Meric-Bernstam[9], N. Wagle[10], A. Stenzinger[11], J. Bonas
S. Jezdic[16], J-Y. Douillard[16], J. S. Reis-Filho[17], R. Dienstma

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	NSCLC	IB	Soria J-C, et al. *N Engl J Med.* 2018[28]
	18, *L861Q* in exon 21, *S768I* in exon 20)	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	2%–5%	IIB	Hyman D, et al. *Nature.* 2018[55]
	Amplifications			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]

Merci!

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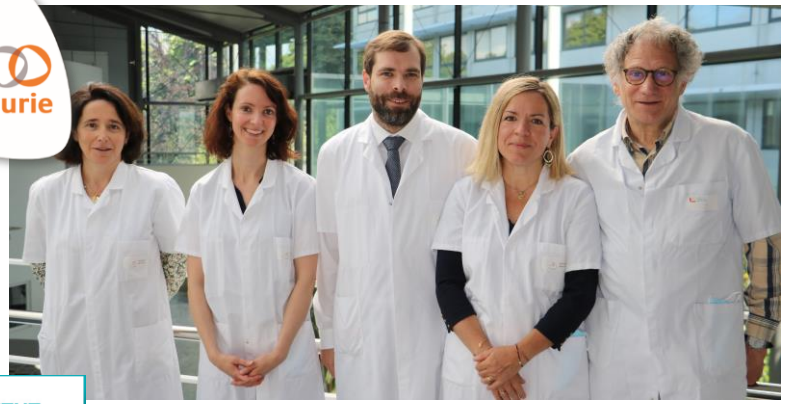

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