Lung Cancer UPDATES
ESMO HIGHLIGTHS
09-13 SEPTIEMBRE 2022
Paris, France

Iniciativa científica de:
GECP lung cancer research

Enfermedad avanzada con mutaciones

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Mutacion KRAS G12C – Sotorasib

Estudio 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

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*Currently at Dana–Farber Cancer Institute, Boston, MA, USA.

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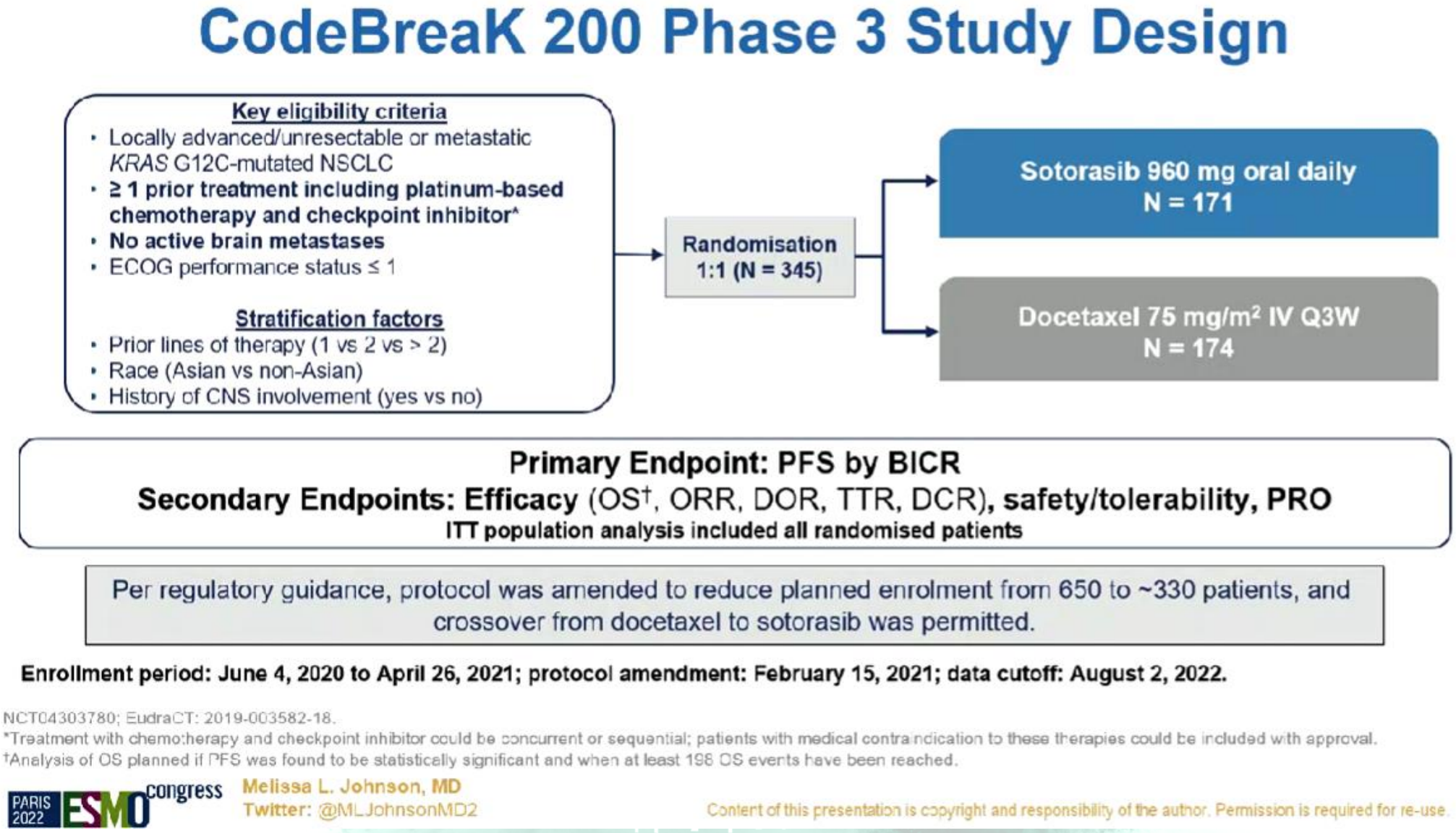

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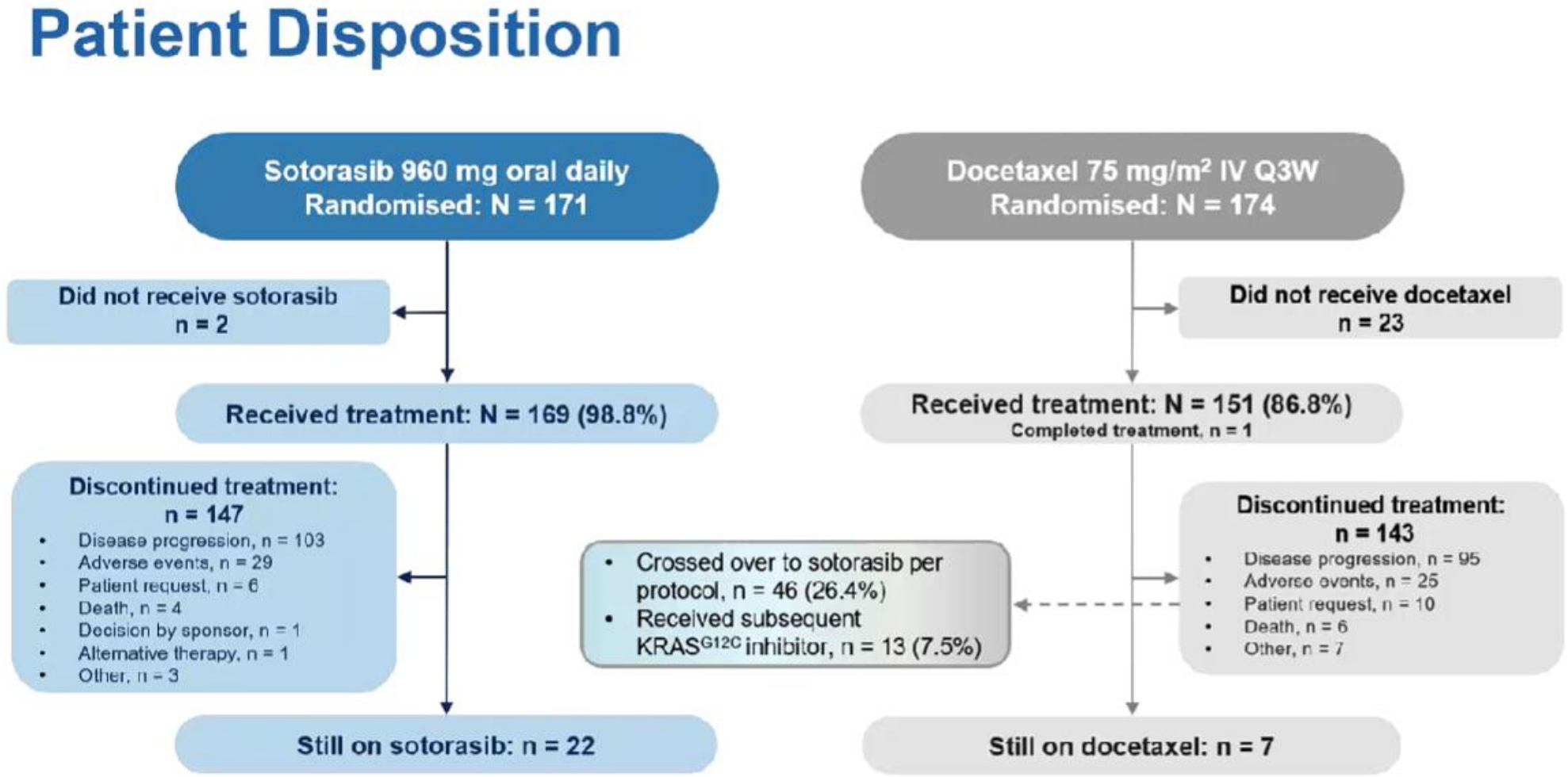

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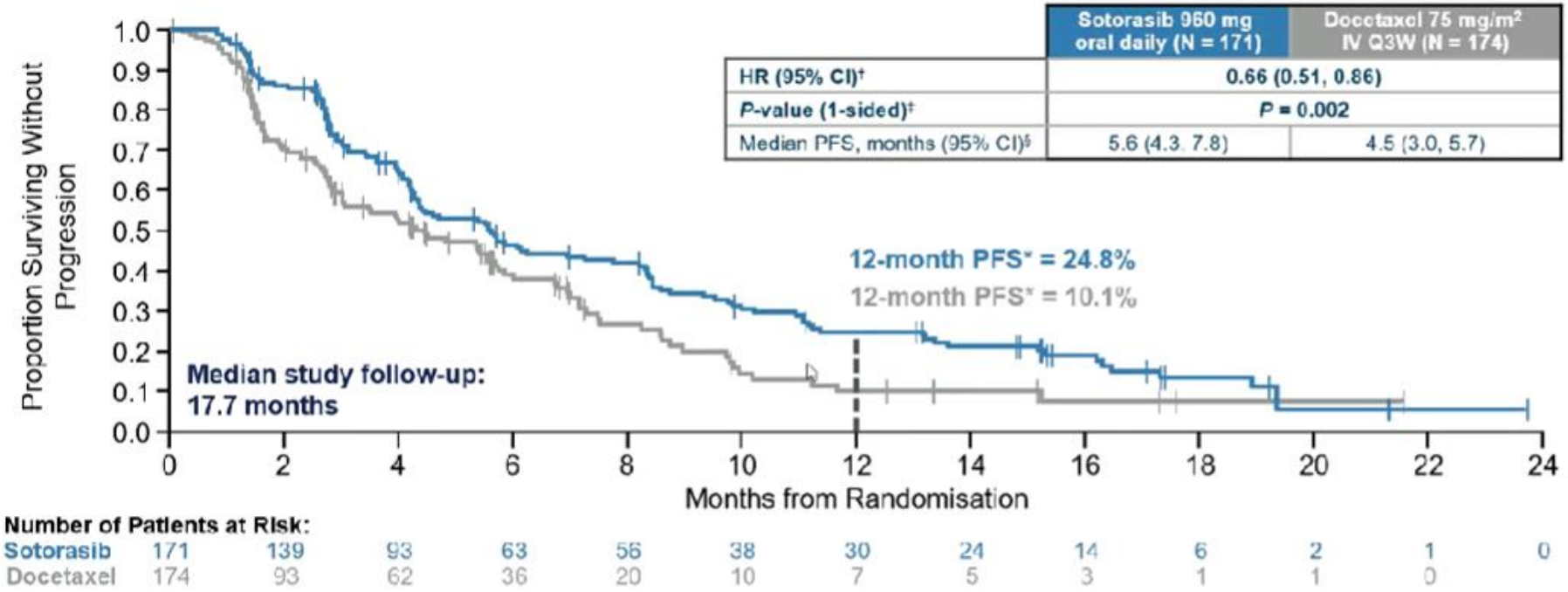
Primary Endpoint: PFS by BICR



	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)

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

*PFS rates estimated using Kaplan-Meier method; ITT population.
†HR and 95% CIs estimated using a stratified Cox proportional hazards model.
‡*P*-value calculated using a stratified log-rank test.
§Medians estimated using Kaplan-Meier method; 95% CIs estimated using the method by Klein and Moeschberger with log-log transformation.

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Mutacion KRAS G12C - Sotorasib

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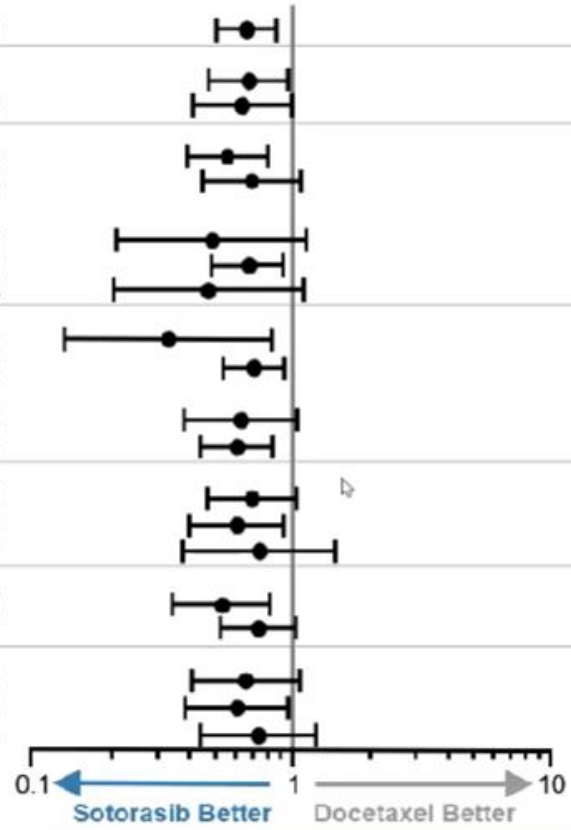
PFS Across Subgroups

Subgroup	Number of Patients: Sotorasib	Number of Patients: Docetaxel	Median PFS, months: Sotorasib	Median PFS, months: Docetaxel	Hazard Ratio (95% CI)
All randomised patients	171	174	5.6	4.5	0.66 (0.51, 0.86)
Age, at baseline (years)					
< 65	91	95	4.4	3.1	0.68 (0.48, 0.96)
≥ 65	80	79	5.9	5.6	0.64 (0.41, 0.99)
Sex					
Male	109	95	5.7	4.5	0.56 (0.39, 0.80)
Female	62	79	4.6	4.2	0.69 (0.45, 1.08)
Region					
North America	20	22	5.9	6.8	0.49 (0.21, 1.13)
Europe	126	126	5.6	4.0	0.68 (0.50, 0.92)
Other*	25	26	5.7	5.6	0.47 (0.20, 1.09)
Race					
Asian	21	22	8.3	5.6	0.33 (0.14, 0.80)
Non-Asian	149	151	5.6	4.2	0.71 (0.54, 0.95)
Baseline ECOG status					
0	59	59	8.4	6.7	0.63 (0.38, 1.05)
1	112	115	4.4	2.8	0.61 (0.44, 0.84)
Number of prior lines in advanced disease					
1	77	78	4.2	4.2	0.70 (0.47, 1.04)
2	65	69	5.7	4.8	0.61 (0.40, 0.92)
> 2	29	27	4.7	4.0	0.74 (0.37, 1.46)
History of CNS involvement					
Yes	58	60	4.4	2.9	0.53 (0.34, 0.82)
No	113	114	5.7	5.7	0.74 (0.53, 1.03)
PD-L1 protein expression					
< 1%	57	55	8.3	5.9	0.66 (0.41, 1.06)
≥ 1% and < 50%	46	70	4.6	3.0	0.61 (0.39, 0.96)
≥ 50%	60	40	5.7	5.4	0.74 (0.44, 1.23)



*Other includes South America, Asia, and Australia.

PFS favoured sotorasib versus docetaxel across subgroups

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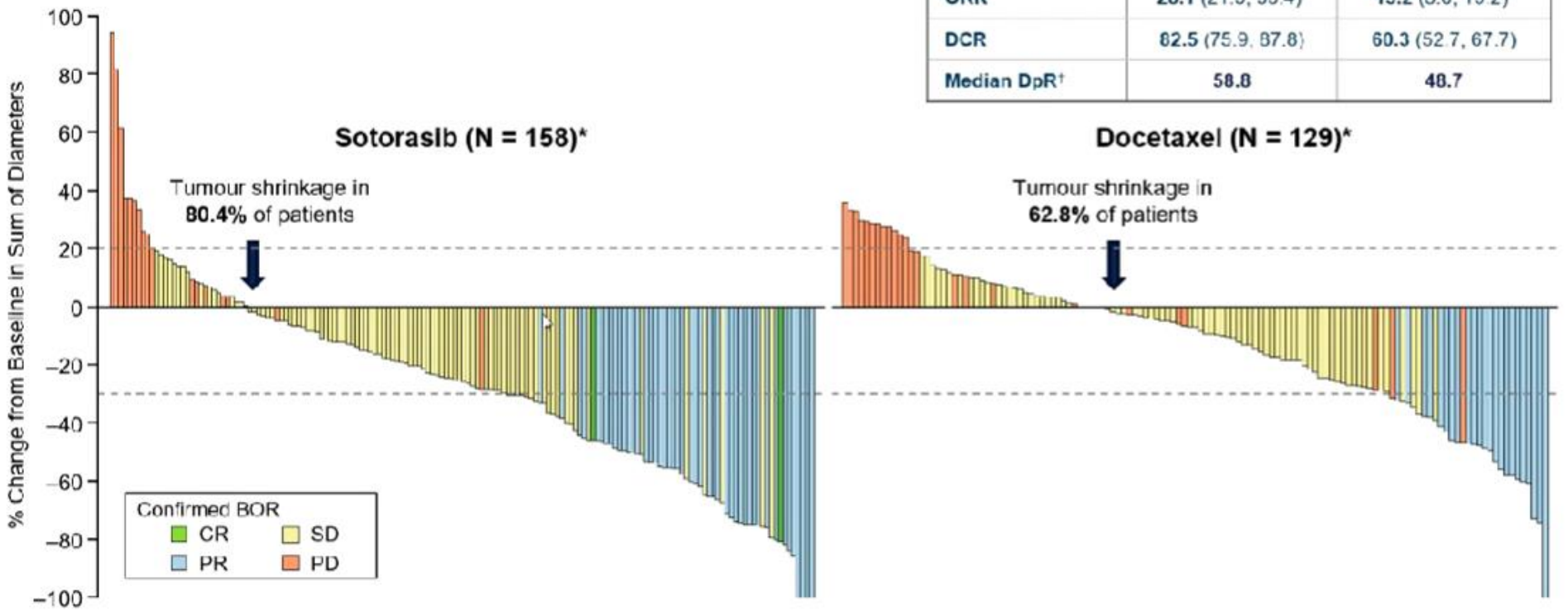
Tumour Response by BICR

% (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



Response rate was significantly higher with sotorasib versus docetaxel ($P < 0.001$)

*Patients without baseline target lesions or post-baseline percent changes, or with BOR of NE are not shown.
†Median of best percent change from baseline in sum of diameters for confirmed responders.

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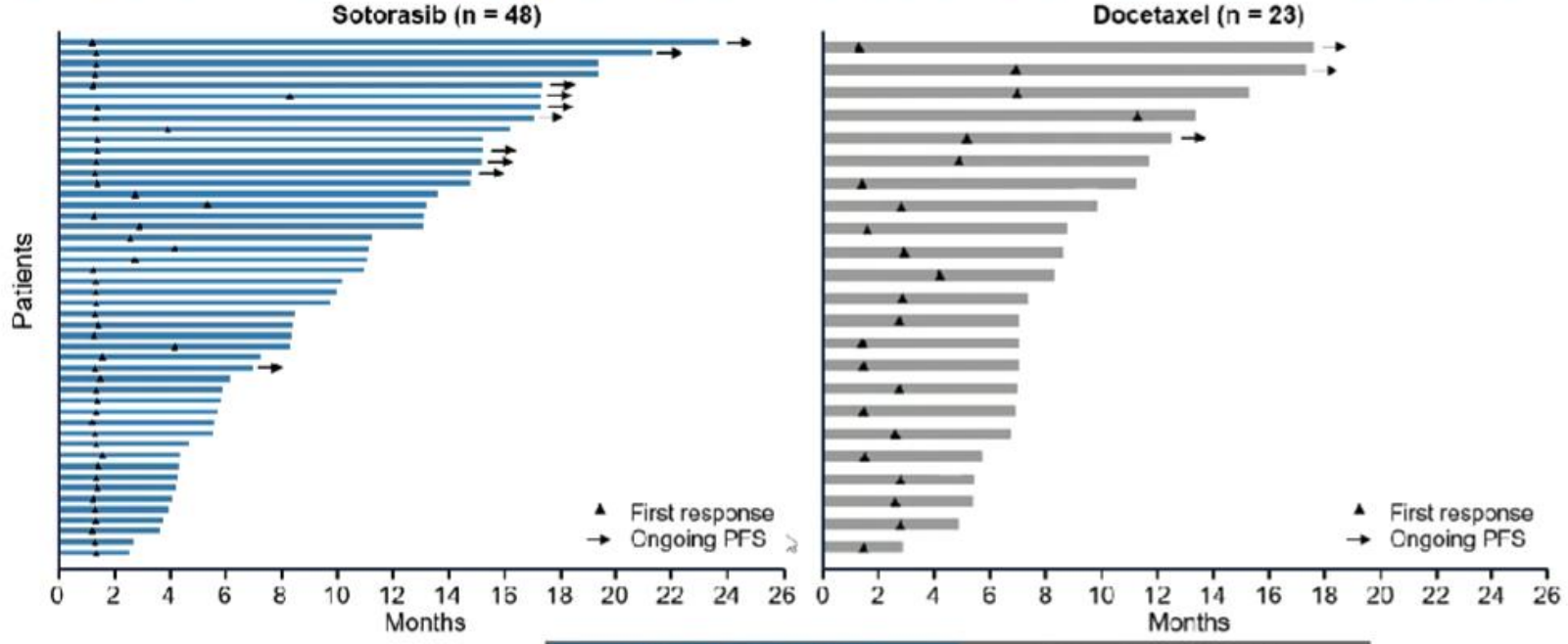
Duration of Response: Sotorasib vs Docetaxel*



	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, 6.3)

Sotorasib was associated with both faster time to response and longer duration of response

*DOR and TTR calculated only for patients who achieved a confirmed best overall response of PR or CR; ITT population.
†Number of responders.
‡Medians and 95% CIs estimated using Kaplan-Meier method.

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Mutacion KRAS G12C – Sotorasib

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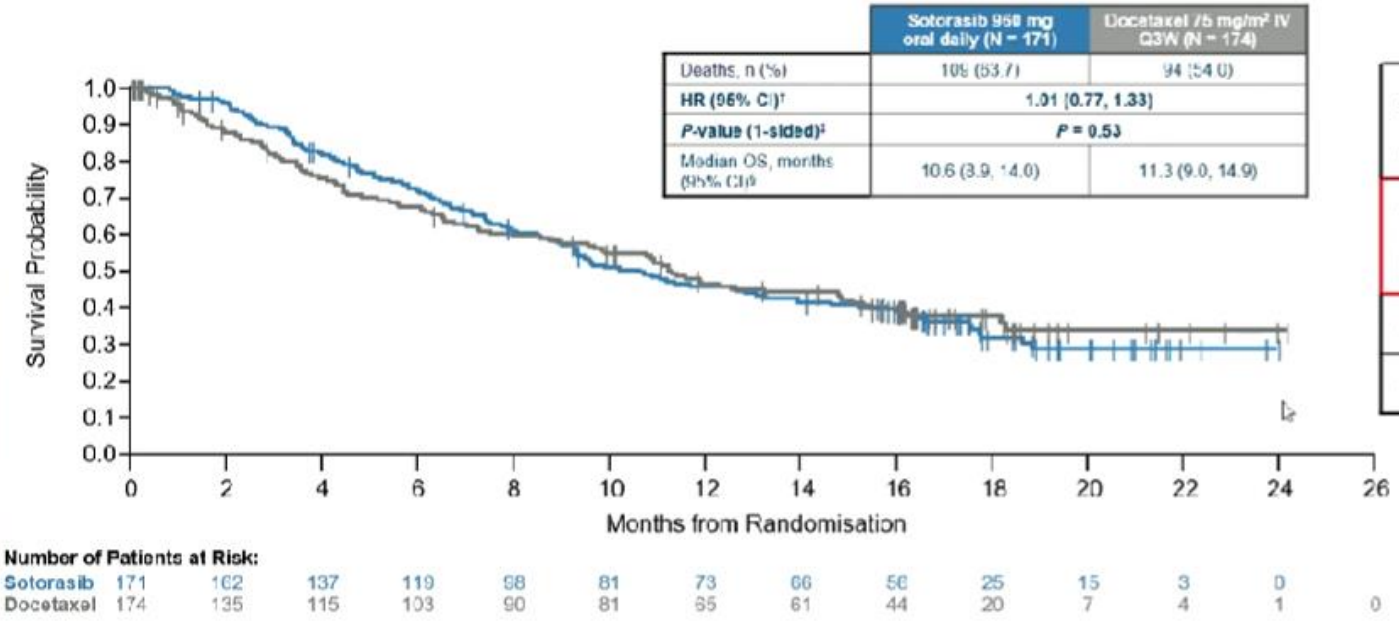
OS: Sotorasib vs Docetaxel*



	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
Deaths, n (%)	105 (53.7)	94 (54.0)
HR (95% CI)†	1.01 (0.77, 1.33)	
P-value (1-sided)‡	*P* = 0.53	
Median OS, months (95% CI)§	10.6 (8.9, 14.0)	11.3 (9.0, 14.9)

	Sotorasib	Docetaxel
Any subsequent treatment, including crossover**	36%	42%
Subsequent KRAS^{G12C} inhibitor, including crossover	4%	34%
Subsequent chemo	21%	12%
Subsequent IO	9%	6%

*OS rates estimated using Kaplan-Meier method; ITT population.
†HR and 95% CIs estimated using a stratified Cox proportional hazards model
‡*P*-value calculated using a stratified log-rank test.
§Medians estimated using Kaplan-Meier method; 95% CIs estimated using the method by Klein and Moeschberger with log-log transformation.
**Patients (16.4% in sotorasib arm, 5.2% in docetaxel arm) were treated beyond progression

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Mutacion KRAS G12C – Sotorasib

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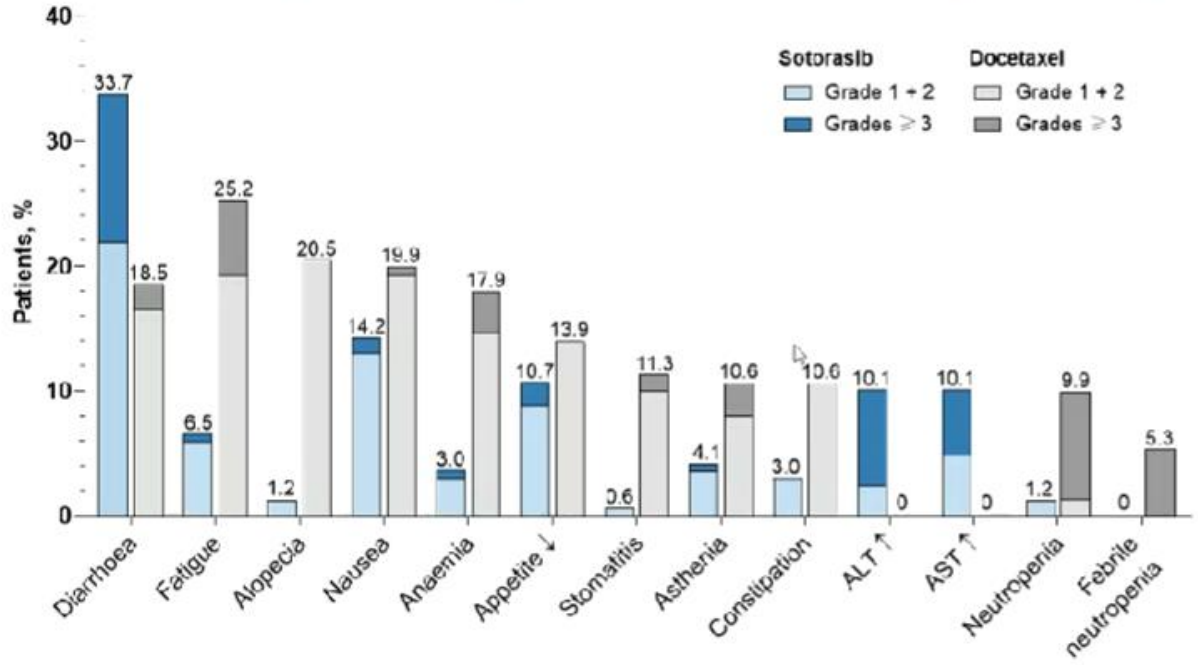
Most Common TRAEs
Any Grade TRAEs (≥ 10%) or Grade ≥ 3 (≥ 5%)



Most common Grade 3+ TRAEs with sotorasib were diarrhoea and elevated liver enzymes, and with docetaxel were neutropenia, fatigue, and febrile neutropenia

*Highest-level TRAE per preferred term reported

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Mutacion HER2 - Trastuzumab-deruxtecan (DESTINY-Lung02)

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Trastuzumab Deruxtecan in Patients With *HER2* Mutant Metastatic Non–Small-Cell Lung Cancer: Interim Results From the Phase 2 DESTINY-Lung02 Trial

Koichi Goto, MD, PhD,[a] Sang-We Kim, Toshio Kubo, Yasushi Goto, Myung-Ju Ahn, David Planchard, Dong-Wan Kim, James Chih-Hsin Yang, Tsung-Ying Yang, Kaline Pereira, Kapil Saxena, Ryota Shiga, Yingkai Cheng, Mehreteab Aregay, Pasi A. Jänne

On behalf of the DESTINY-Lung02 investigators

[a]National Cancer Center Hospital East, Kashiwa, Japan

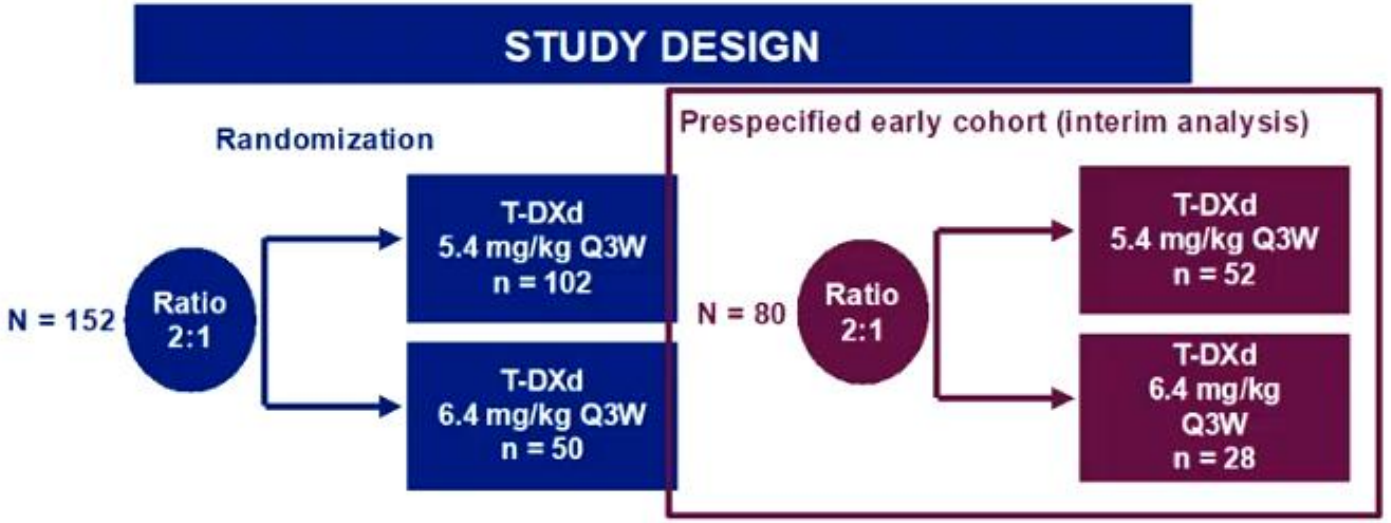
Mutacion HER2 - Trastuzumab-deruxtecan (DESTINY-Lung02)

Diseño del estudio

Design = Prespecified EARLY cohort

KEYPOINTS

- ***HER2* mut** advaced NSCLC (PS 0-1)
- **≥ 1 prior therapy** (platinum based chemo)
- **Adecuate washout** of prior treatment
- **CNS+ allowed** if treated/asymphomatic
- **Stratification:** prior PD-(L)1 inhibitor



- PRIMARY ENDPOINT: **ORR by BIRC**
- **The early cohort** = patients randomized **≥ 4.5 mo**. before the interim analysis data cutoff (≥3 post-baseline assessments)

Mutacion HER2 - Trastuzumab-deruxtecan (DESTINY-Lung02)

Eficacia reportada

CLÍNIC BARCELONA Hospital Universitari

AntiHER2 therapies in NSCLC

	Study	N	ORR (%)	DCR (%)	DoR (mo.)	PFS (mo.)	OS (mo.)	G3/4 AEs (%)	ILD (%)	FU (mo.)
Destiny Lung 02 T-Dxd, 5.4 mg/kg	Ph 2	52	54%	90%	8.7mo*	-	-	37%	8%	5.6 mo
Destiny Lung 02 Tx-Dxd, 6.4 mg/kg	Ph 2	28	43%	93%	5.9 mo	-	-	71%	18%	5.4 mo
Destiny Lung 01 T-Dxd, 5.4 mg/kg	Ph 2	91	55%	92%	9.3 mo	8.2 mo	17.8 mo	46%	26%	13 mo
TDM-1	Ph 2	18	44.4%	83.3%	4 mo	5 mo	-	5.6%	-	10 mo
Novel TKIs	Ph 2	78-90	21-30%	70-85%	~ 9 mo	5- 6 mo	10-14 mo	20.5-79%	-	~ 9 mo.

Goto, ESMO 2022; Lin, NEJM 2022, Le X, JCO 2022; Song, BMC Medicine 2022, Mazières J, https://dailynews.ascopubs.org/do/10.1200/ADN.22.201105/full/

** Data with 3 months of extended FU*

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Cross trial comparisons should be made with caution and might be confounded by various factors

Mutacion HER2 - Trastuzumab-deruxtecan (DESTINY-Lung02)

Toxicidad pulmonar (neumonitis intersticial)

Adjudicated drug-related ILD

Hospital Universitari

	Study	N	ILD (%)	G1 (%)	G2 (%)	G3 (%)	G4 G5	Median time ILD (days)	Cases resolved	FU (mo)
DESTINY LUNG 02, Safety analysis set										
T-Dxd, 5.4 mg/kg	Phase 2	101	**6%**	3%	2%	**1%**	-	67.5 (40-207)	50%	5.6 mo
Tx-Dxd, 6.4 mg/kg		50	**14%**	2%	12%	**0%**	-	41.0 (36-208)	14%	5.4 mo
DESTINY LUNG 01, Previous data										
T-Dxd, 5.4 mg/kg	Phase 2	91	**26%**	3.3%	16.5%	**4.4%**	G5 **2.2%**	141 (14-462)	54%	13 mo

↑ ILD rate with ↑ dose, ↓ % than in DESTINY lung 01???

No severe ILD
Early ILD if higher dose
Different from prior data

Different FU

Dr. Laura Mezquita

Goto, ESMO 2022; Lin, NEJM 2022, Le X, JCO 2022

Cross trial comparisons should be made with caution and might be confounded by various factors

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Mutacion EGFR resistente a TKI

Papel de sintilimab +/- IBI305 + Quimio: ORIENT-31 trial

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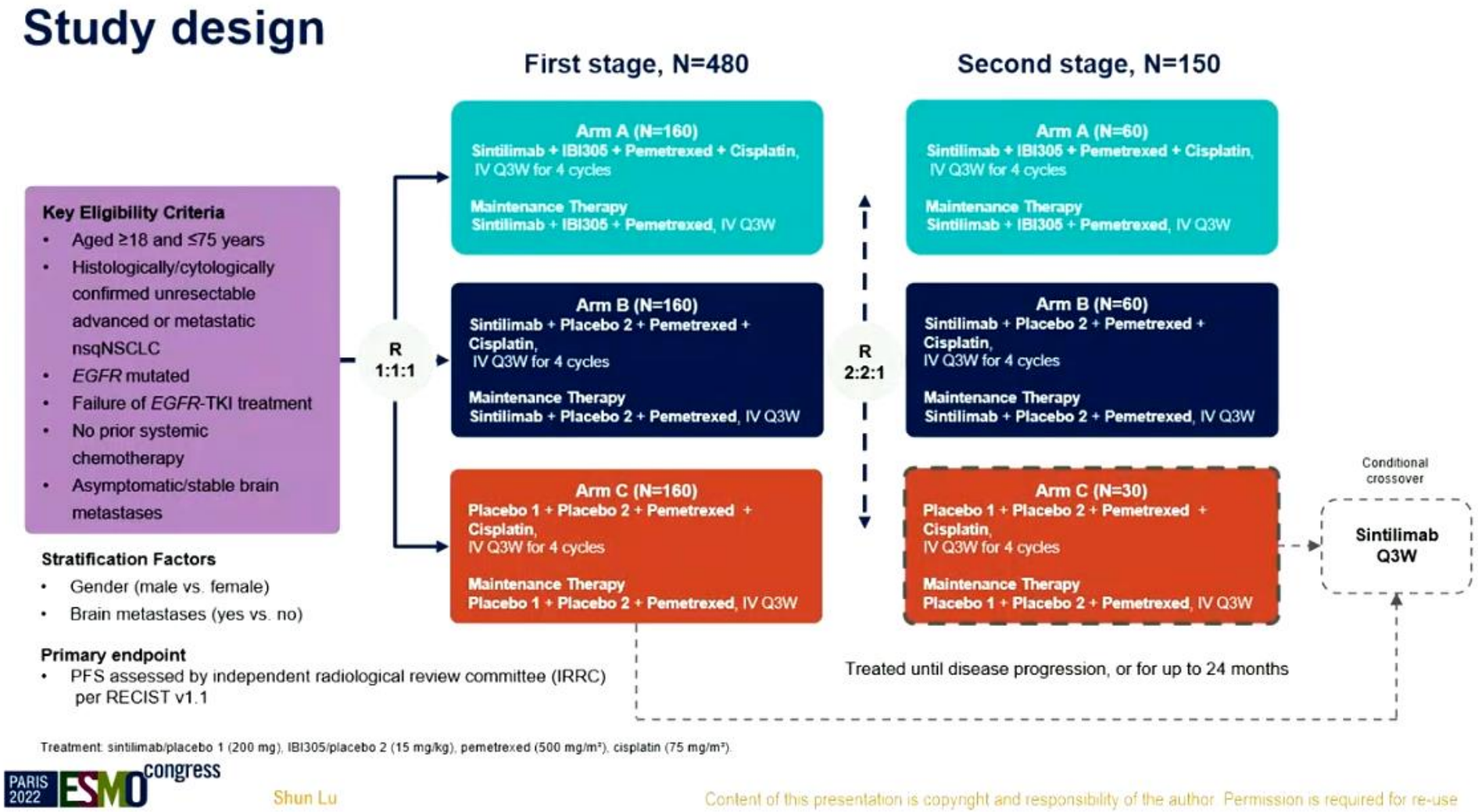
Sintilimab with or without IBI305 plus chemotherapy in patients with EGFR mutated non-squamous non-small-cell lung cancer (EGFRm nsqNSCLC) who progressed on EGFR tyrosine-kinase inhibitors (TKIs) therapy: second interim analysis of phase 3 ORIENT-31 study

Shun Lu, MD
Department of Medical Oncology, Shanghai Chest Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

September 11, 2022

Mutacion EGFR resistente a TKI

Papel de sintilimab +/- IBI305 + Quimio: ORIENT-31 trial



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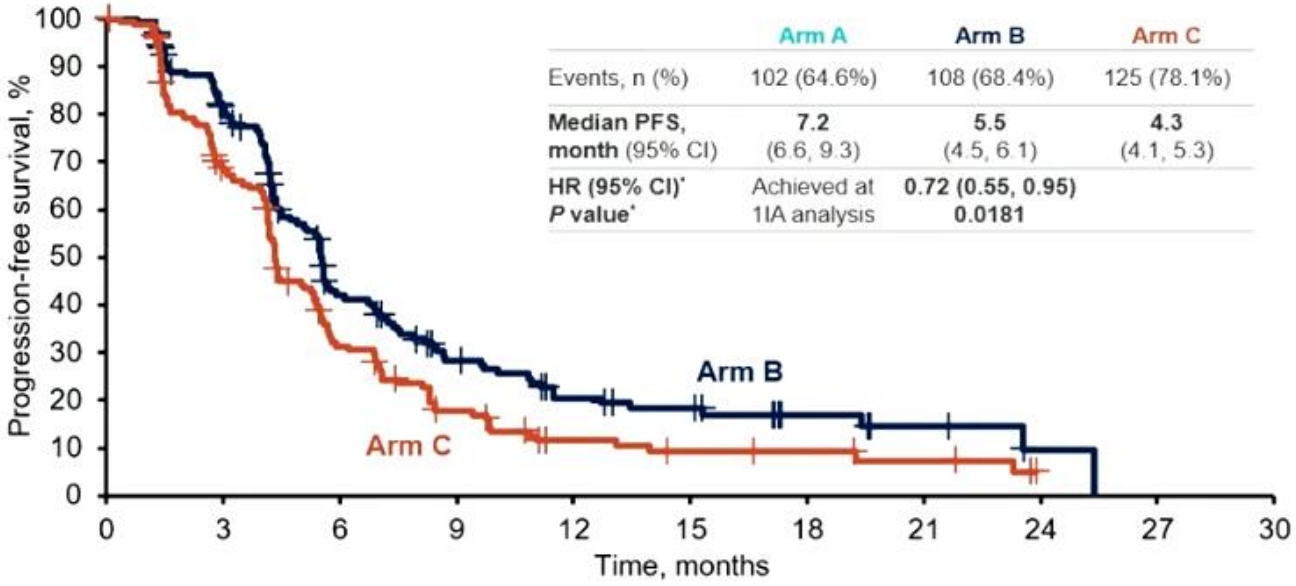
Mutacion EGFR resistente a TKI

Papel de sintilimab +/- IBI305 + Quimio: ORIENT-31 trial

Study met primary endpoint of PFS (by IRRC) in Arm B vs Arm C



	Arm A	Arm B	Arm C
Events, n (%)	102 (64.6%)	108 (68.4%)	125 (78.1%)
Median PFS, month (95% CI)	**7.2** (6.6, 9.3)	**5.5** (4.5, 6.1)	**4.3** (4.1, 5.3)
HR (95% CI)*	Achieved at 1IA analysis	**0.72 (0.55, 0.95)**	
P* value		**0.0181**	

Number at risk

Arm B	158	111	52	31	19	15	7	4	1	0
Arm C	160	97	41	21	10	7	6	3	0	

* Compared with Arm C. HR and *P* value were calculated with stratified Cox model and log rank test, and were stratified by gender (male vs. female), presence of brain metastases (yes vs. no) and prior EGFR-TKI treatment (1 line vs. 2 lines). The two-sided α boundary is 0.0444 as calculated using Lan-Demets spending function with O'Brien-Fleming approximation.
Data cutoff, 31 Mar 2022; median follow up, 13.1 months. IA, interim analysis; HR, hazard ratio; CI, confidence interval

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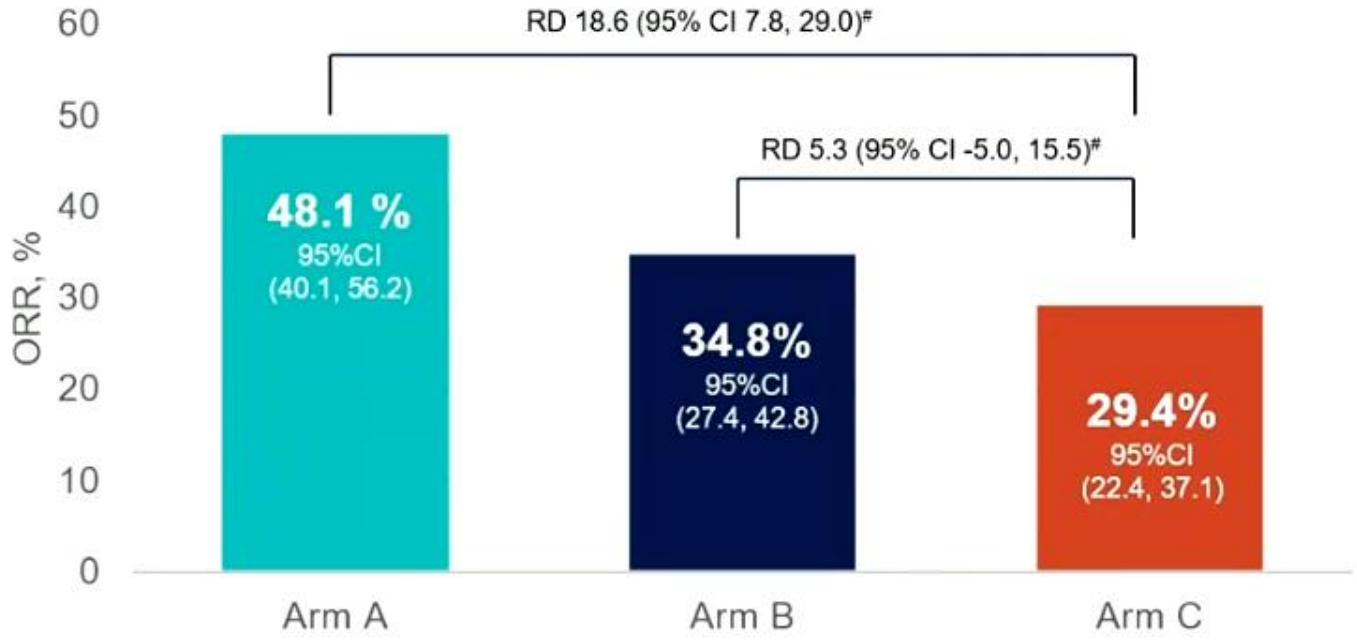
Mutacion EGFR resistente a TKI

Papel de sintilimab +/- IBI305 + Quimio: ORIENT-31 trial

Secondary endpoint: ORR, DCR and DOR (by IRRC)



	Arm A	Arm B	Arm C
DCR (95% CI)	86.1% (79.7%, 91.1%)	81.6% (74.7%, 87.3%)	75.6% (68.2%, 82.1%)
Median DOR, month (95% CI)	8.5 (5.6, 11.7)	7.4 (4.7, 12.0)	5.7 (4.1, 7.1)

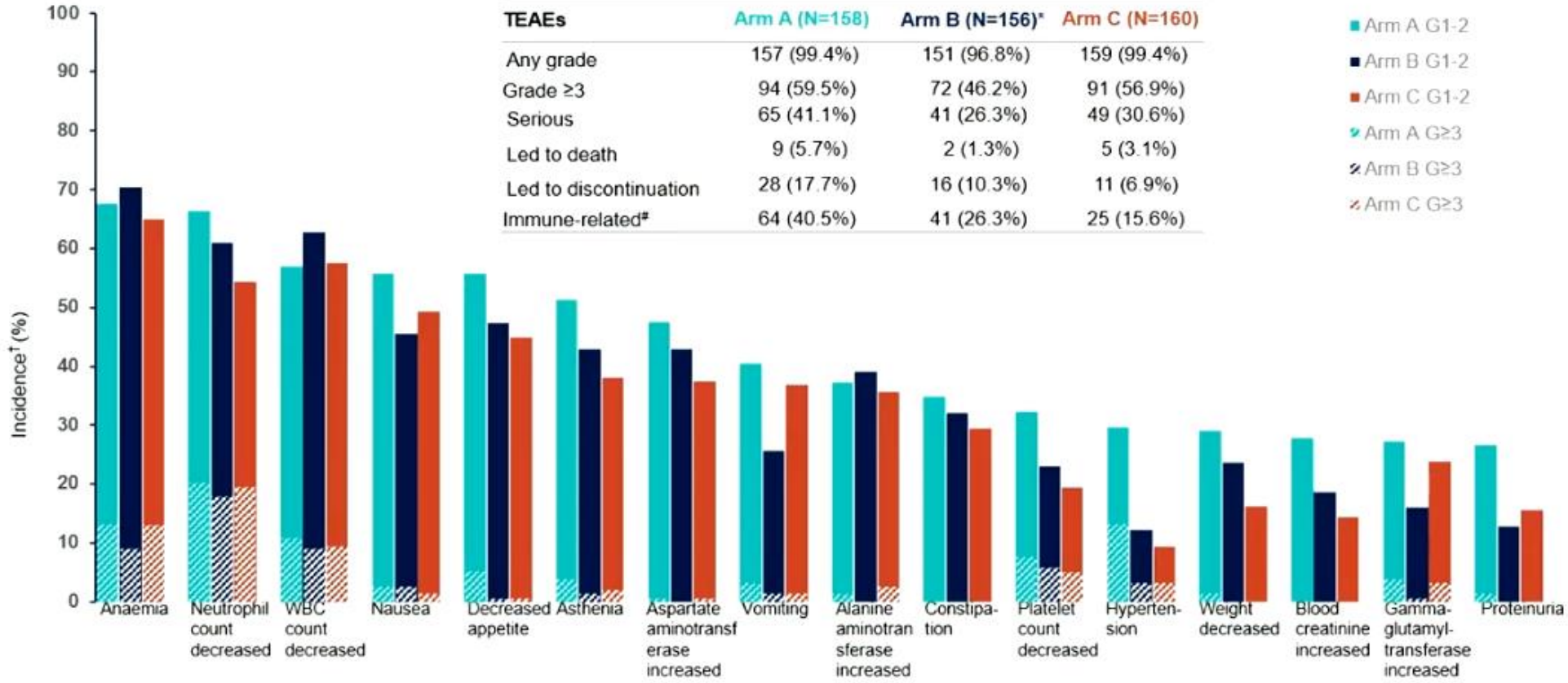
ORR, objective response rate; DCR, disease control rate; DOR, duration of response; RD, rate difference; CI confidence interval.
RD and CI was calculated using Miettinen & Nurminen method stratified by gender (male vs. female), presence of brain metastases (yes vs. no) and prior EGFR-TKI treatment (1 line vs. 2 lines)

Mutacion EGFR resistente a TKI

Papel de sintilimab +/- IBI305 + Quimio: ORIENT-31 trial

Safety summary in all treated patients

TEAEs	Arm A (N=158)	Arm B (N=156)*	Arm C (N=160)
Any grade	157 (99.4%)	151 (96.8%)	159 (99.4%)
Grade ≥3	94 (59.5%)	72 (46.2%)	91 (56.9%)
Serious	65 (41.1%)	41 (26.3%)	49 (30.6%)
Led to death	9 (5.7%)	2 (1.3%)	5 (3.1%)
Led to discontinuation	28 (17.7%)	16 (10.3%)	11 (6.9%)
Immune-related#	64 (40.5%)	41 (26.3%)	25 (15.6%)



* Two patients didn't receive any study treatment and were excluded from safety analysis set. # immune-related AE per investigator's assessment. † TEAEs with ≥20% incidence in any treatment arm; data cutoff, 31 Mar 2022.
TEAEs, treatment-emergent adverse events.

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EGFR resistente con MET amplificación

Tepotinib + osimertinib : Estudio INSIGHT 2

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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

EGFR resistente con MET amplificación

Tepotinib + osimertinib : Estudio 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.

EGFR resistente con MET amplificación

Tepotinib + osimertinib : Estudio INSIGHT 2

Detection of *MET*amp

***MET*amp definitions**

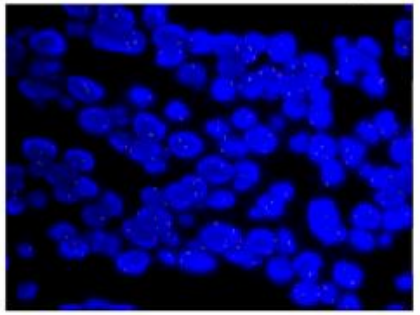
TBx FISH: *MET* GCN ≥5 and/or *MET*/*CEP7* ≥2

and/or

LBx NGS: *MET* GCN ≥2.3; Archer®

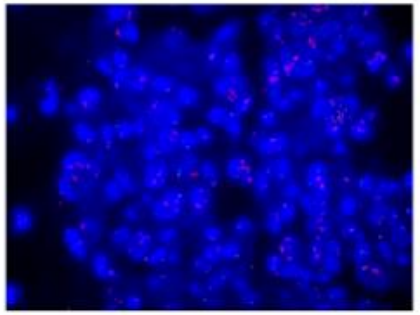
Central testing was mandatory for both

TBx FISH: *MET*amp -



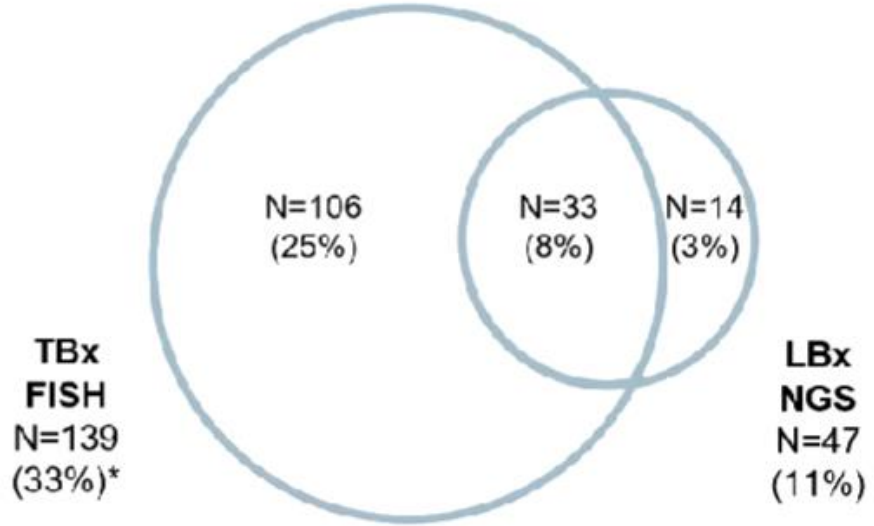
MET GCN, 2.33; *MET*/*CEP7*, 0.96

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%.

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Julien Mazieres

EGFR resistente con MET amplificación

Tepotinib + osimertinib : Estudio INSIGHT 2

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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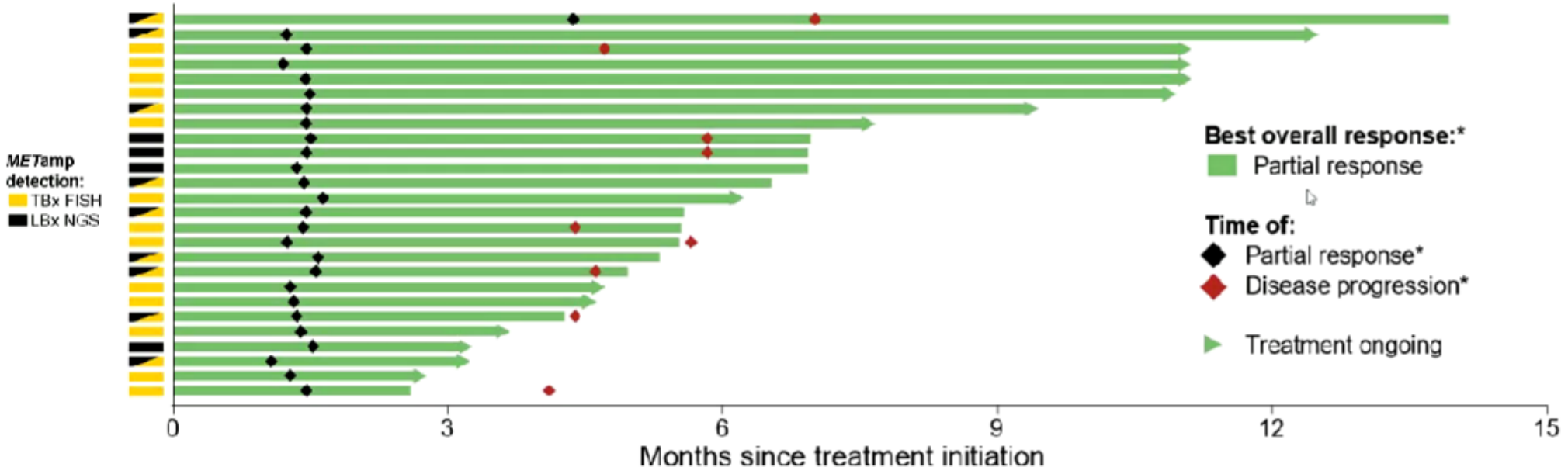
Responses to Tepotinib Plus Osimertinib were Rapid and Long-lasting

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

*By IRC; treatment-end decisions were based on investigator-assessed disease progression.

PARIS 2022 ESMO congress

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Safety Profile of Tepotinib plus Osimertinib

TRAEs of any grade in >10% all patients, n (%)	Tepotinib + osimertinib N=88	
	Any grade	Grade ≥3
Any	**65 (73.9)**	**21 (23.9)**
Diarrhea	36 (40.9)	0
Peripheral edema	21 (23.9)	4 (4.5)
Paronychia	15 (17.0)	1 (1.1)
Nausea	12 (13.6)	0
Decreased appetite	10 (11.4)	2 (2.3)
Vomiting	10 (11.4)	1 (1.1)

- AEs led to a dose reduction in 16 patients (18.2%)
  - Tepotinib dose was reduced in 14 patients (15.9%)
  - Osimertinib dose was reduced in four patients (4.5%)
  - Two patients had a dose reduction in both drugs
- Primary reason for treatment discontinuation was AEs in six patients (6.8%)
- Two patients had AEs leading to death that were considered potentially related to either trial drug by the investigator
  - One patient had pneumonia/pneumonitis
  - One patient had pleural effusion

The safety profile of the combination was consistent with the known safety profiles of tepotinib and osimertinib