LBA52

PARIS 2022 ESMO congress

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

Declaration of Interests

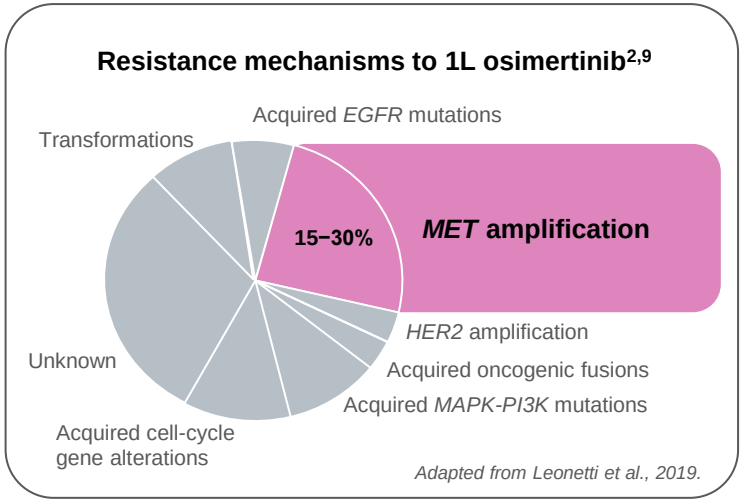
Julien Mazieres

Advisory board fees: Amgen, AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, MSD, Novartis, Pfizer, Roche, Takeda and Merck Healthcare KGaA, Darmstadt, Germany.

Research funding (institution): AstraZeneca, Bristol Myers Squibb and Roche/Genentech.

Background

- 15–30% of patients with *EGFR*m NSCLC treated with osimertinib develop resistance through *MET* amplification (*MET*amp)[1,2]
  - TBx FISH, the gold standard *MET*amp detection method has detection rates of ~30% compared with ~15% with NGS LBx[2–5]
- *MET*amp is associated with a poor prognosis[2,6]
- Tepotinib + an EGFR TKI have shown clinical activity in *EGFR*m NSCLC with *MET*amp
  - INSIGHT study (tepotinib + gefitinib)[7]
  - Real-world evidence (tepotinib + osimertinib)[8]



The combination of tepotinib plus osimertinib is being investigated in patients with *EGFR*m NSCLC with *MET*amp in INSIGHT 2: here we present initial results from this study

1. Ramalingam SS, et al. *Ann. Oncol.* 2018;29(suppl 8):viii740; 2. Wang Y, et al. *Lung Cancer.* 2018;118:105–110; 3. Smit EF, et al. *Future Oncol.* 2022;18:1039–1054;
4. Heydt C, et al. *Comput. Struct. Biotechnol. J.* 2019;17:1339–1347; 5. Cho BC, et al. *Ann. Oncol.* 2018;29:ix177. Abstract LBA8; 6. Koulouris A, et al. *Cancers*. 2022;14:3337;
7. Wu YL, et al. *Lancet Respir Med.* 2020:8(11);1132–1143; 8. Le X, et al. Poster presentation at WCLC 2022. [EP08.02-162]; 9. Leonetti A, et al. *Br J Cancer.* 2019;121(9):725–737.

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.

Detection of *MET*amp

***MET*amp definitions**

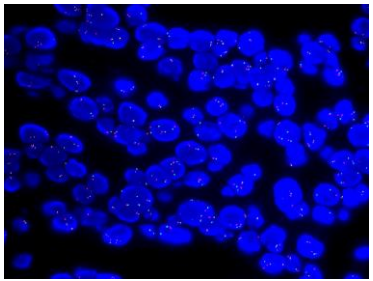
TBx FISH:
MET GCN ≥5
and/or
MET/CEP7 ≥2

and/or

LBx NGS:
MET GCN ≥2.3;
Archer®

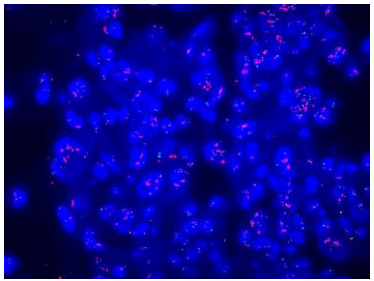
Central testing was mandatory for both

TBx FISH: *MET*amp -



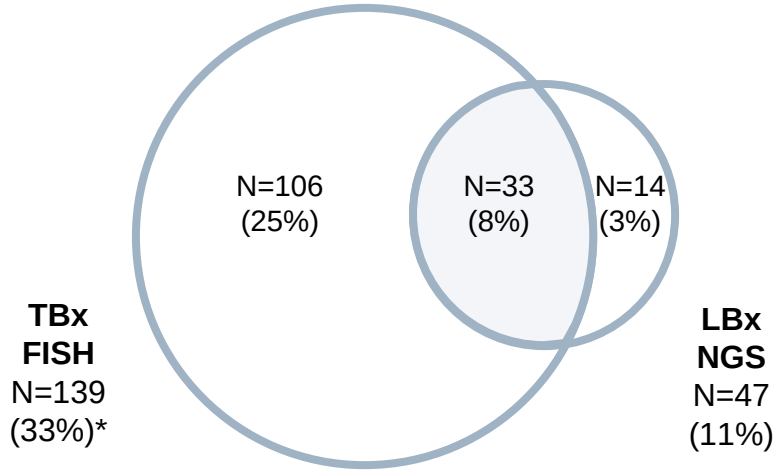
MET GCN, 2.33; *MET/CEP7*, 0.96

TBx FISH: *MET*amp +



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

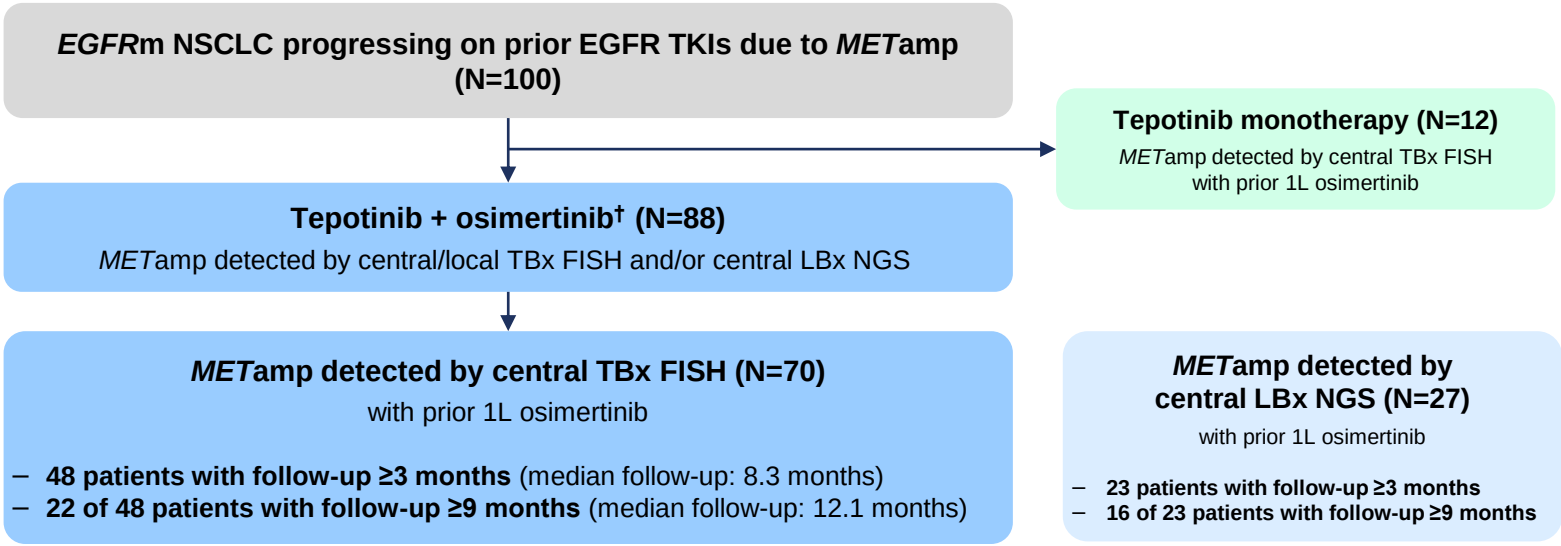
– Among 425 pre-screened patients, *MET*amp was detected in 153 patients (36%) by:



*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%.

Patient Disposition

At the cut-off date of April 26, 2022, 425 patients had been assessed: *MET*amp was detected centrally in 153 patients and 100 patients had received treatment*



*Main reasons for pre-screening (n=35)/screening (n=18) failures: no measurable disease, worsening of performance status, out of range laboratory values. †Seven patients did not receive 1L osimertinib; four patients were local TBx FISH test positive; seven patients had *MET*amp detected by central LBx NGS only (TBx FISH was not evaluable in five patients; TBx FISH was negative in two patients).

Baseline Characteristics of Patients in INSIGHT 2

n (%)		All treated N=100	Tepotinib + osimertinib N=88	Tepotinib monotherapy N=12
Age	Median, years (range)	61 (20–84)	61 (20–84)	60 (44–73)
Sex	Female	62 (62.0)	53 (60.2)	9 (75.0)
	Male	38 (38.0)	35 (39.8)	3 (25.0)
Race	Asian	56 (56.0)	50 (56.8)	6 (50.0)
	White	36 (36.0)	32 (36.4)	4 (33.3)
	Other/not collected	8 (8.0)	6 (6.8)	2 (16.7)
Smoking status*	Never	66 (66.0)	57 (64.8)	9 (75.0)
	Former/current	31 (31.0)	28 (31.8)	3 (25.0)
ECOG PS	0	32 (32.0)	28 (31.8)	4 (33.3)
	1	68 (68.0)	60 (68.2)	8 (66.7)
Brain metastases at study entry†	Yes	27 (27.0)	22 (25.0)	5 (41.7)
EGFR mutation	Del19	58 (58.0)	51 (57.9)	7 (58.3)
	L858R	40 (40.0)	35 (39.8)	5 (41.7)
	L861Q	2 (2.0)	2 (2.3)	0 (0.0)
Time on prior 1L osimertinib‡	<12 months	30 (30.0)	25 (28.4)	5 (41.7)
	≥12 months	63 (63.0)	56 (63.6)	7 (58.3)

In patients treated with tepotinib plus osimertinib with *MET*amp detected by central TBx FISH, median GCN was 10.45 (range: 2.08–45.26) and median *MET/CEP7* was 1.96 (range: 0.92–10.06)

*Smoking status missing for three patients. †Target and/or non-target lesions as assessed by investigator and/or IRC. ‡Seven patients did not receive 1L osimertinib.

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)

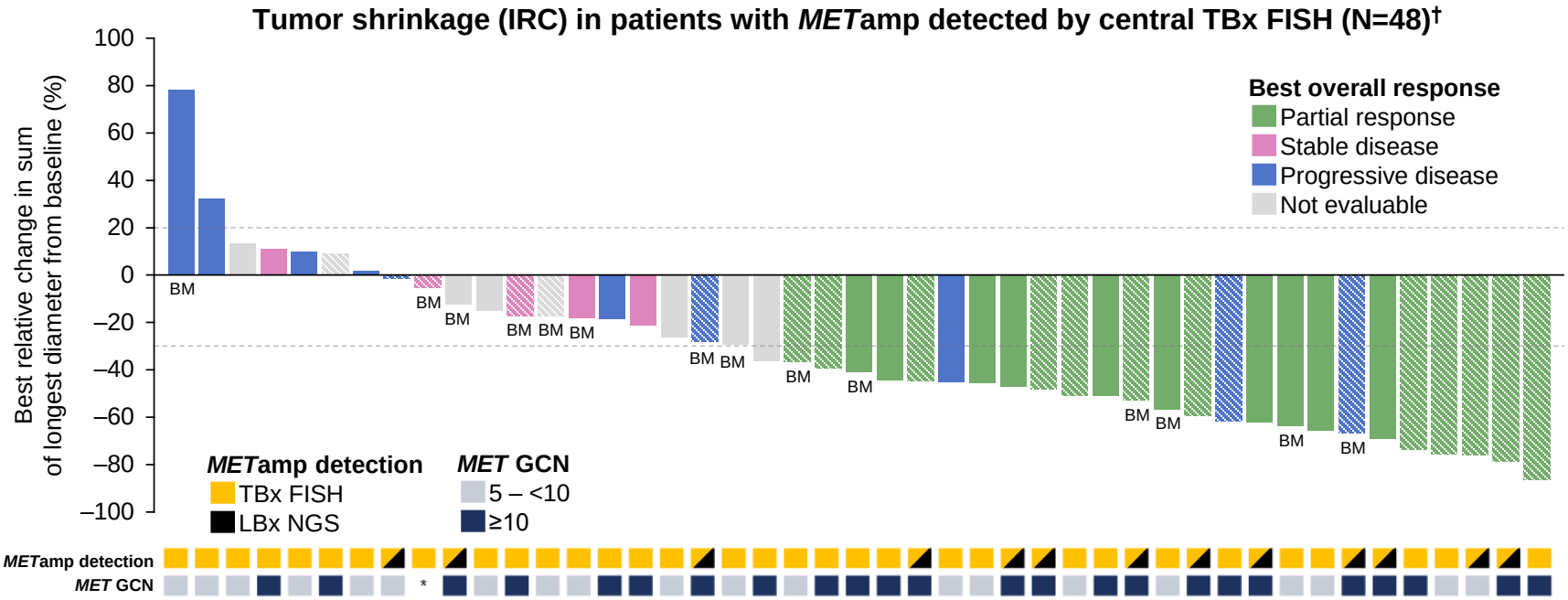
	*MET*amp by central TBx FISH
Follow-up	≥6 months (N=12)
ORR (95% CI)	**8.3%** (0.2, 38.5)
BOR, n (%)	
PR	1 (8.3)
SD	2 (16.7)
PD	8 (66.7)
NE	1 (8.3)

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.

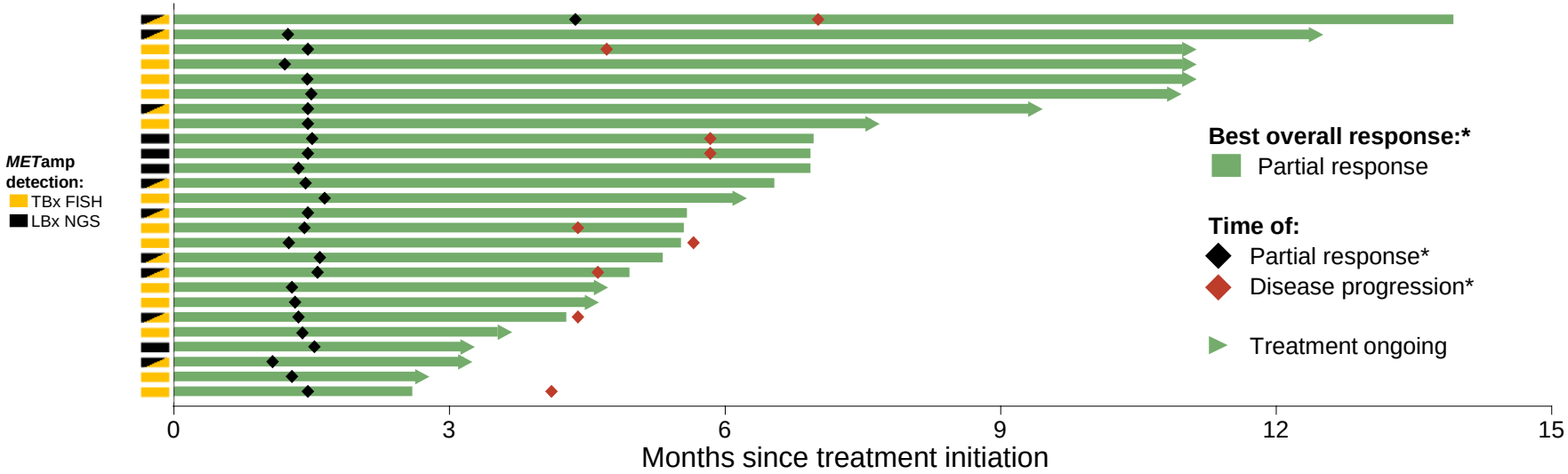
Antitumor Activity of Tepotinib plus Osimertinib



*One patient had GCN 4.96 and enrolled through a *MET/CEP7* ratio ≥2. †Three patients were excluded due to a baseline/post-baseline measurement not being available.
Hashed bars indicate patients with ≥9 months' follow-up. BM, brain metastases at baseline.

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.

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

Conclusions

- The initial analysis of INSIGHT 2 showed that tepotinib plus osimertinib had promising activity in patients with *EGFR*m NSCLC who progressed on 1L osimertinib with *MET*amp centrally confirmed by TBx FISH
  - ORR was 54.5% in patients with ≥9 months' follow-up (N=22) and 45.8% in patients with ≥3 months' follow-up (N=48)
- Our data indicate that FISH *MET* GCN of ≥5 and/or *MET/CEP7* ratio of ≥2 in TBx samples define a *MET*amp-positive population with an original sensitizing *EGFR* mutation that derives clinical benefit from the combination of tepotinib plus osimertinib
- The safety profile of the combination was consistent with the known safety profiles of tepotinib and osimertinib

Tepotinib plus osimertinib is an active oral regimen, providing a potential chemotherapy-sparing targeted therapy option for patients with *EGFR*m NSCLC with *MET*amp after progression on 1L osimertinib, who have a high unmet need

Acknowledgments

- The authors would like to thank all the patients and their families, all investigators and co-investigators, and the study teams at all participating centers and at Merck Healthcare KGaA, Darmstadt, Germany
- The study was sponsored by Merck Healthcare KGaA, Darmstadt, Germany
- Medical writing and editorial assistance was provided by Syneos Health, UK, and funded by Merck Healthcare KGaA, Darmstadt, Germany

INSIGHT 2 investigators

Spain: D Vicente Baz, E Felip Font, G Garcia Ledo, E Nadal Alforja, A Aguilar Hernandez, A Taus Garcia, O Juan Vidal, M Cobo Dols, T Moran, B Rubio Viqueira, D Rodriguez Abreu, A Azkarate Martinez, R Bernabe Caro

Italy: A Chella, F De Marinis, V Guarneri, M Milella, G Finocchiaro, D Cortinovis, F Verderame, D Rocco, F Grossi, F Cappuzzo, E Bria

Germany: N Reinmuth, M Thomas, S Michels, F Griesinger, T Wehler, T Overbeck, M Wermke, H Hummel, M Lamprecht, C Gessner, B Eul, S Bohnet

Belgium: J Raskin, I Demedts, C Dooms

Netherlands: A van der Wekken, L Hendriks, A de Langen

USA: X Le, J Cuevas, C Bestvina, H Jhangiani, M Johnson, S Rao, U Tapan, J Hamm, G de Lima Lopes, J Sabari, O Marathe, L Raez, R Scheff, P Lammers

Vietnam: C Phuong, K Nguyen, N Nguyen, D Nguyen, K Do, A Le

Malaysia: C Liam, P Voon, S How, A Ahmad, I Bin Hyder Ali, L Tho, B Lim

France: R Veillon, J Mazieres, A Cortot, A Vergnenegre, C Chouaid, R Gervais, M Wislez, M Perol

Russia: S Orlov, E Poddubskaya, A Poltoratsky, E Ovchinnikova, A Zimina, D Saenko, N Musaeva

Japan: H Mizutani, T Kato, T Tokito, M Morise, H Hayashi, H Tanaka, K Chikamori, M Karayama, H Daga, T Kijima, K Ohashi

China: J Yang, J Fang, C Huang, G Chen, N Yang, J Zhao, Y Shu, R Ma, J Zhou, J Shi, Y Cheng, Z Han, Q Zhou, Y Zhang, J Cui, L Li, J Wang, G Wu, L Zhang, S Hu, B Han, X Min

Taiwan: C Yang, T Yang, C Chian, Y Chen, T Hsia, C Wang, C Chen

Hong Kong: H Loong, J Ho, V Lee, K Wong

Thailand: V Sriuranpong, S Geater, P Danchaivijitr, T Suksomboon charoen

Singapore: D Tan, P Chia, W Hsieh

Republic of Korea: T Kim, S Kim, Y Kim, J Lee, J Kang, J Han, J Ahn, Y Min, S Shin

Abbreviations

1L, first line
AE, adverse event
BOR, best overall response
CEP7, chromosome 7 centromere
DOR, duration of response
ECOG PS, Eastern Cooperative Oncology Group performance status
EGFR, epidermal growth factor receptor
FISH, fluorescence in situ hybridization
GCN, gene copy number
HER2, human epidermal growth factor receptor 2
IRC, independent review committee
LBx, liquid biopsy
m, mutation
MAPK, mitogen-activated protein kinase
MET, mesenchymal–epithelial transition factor
*MET*amp, *MET* amplification
NE, not evaluable
NGS, next-generation sequencing
NSCLC, non-small cell lung cancer
ORR, objective response rate
PD, progressive disease
PI3K, phosphoinositide 3-kinase
PR, partial response
QD, once daily
SD, stable disease
TBx, tissue biopsy
TKI, tyrosine kinase inhibitor
TRAE, treatment-related adverse event