Real World Evidence : Osimertinib as SoC in the management of EGFRm NSCLC

INTRODUCTION

- In patients with EGFR mutations, PFS improves after treatment with EGFR – TKIs compared with that with cytotoxic chemotherapy

- Osimertinib, an irreversible, third-generation EGFR TKI, demonstrated a clinically meaningful improvement in median progression-free survival (mPFS, 18.9 months vs. 10.2; hazard ratio [HR], 0.46; 0.37–0.57; $p < .001$) in the phase III randomized FLAURA trial

- Overall survival (OS) median OS, 38.6 months vs. 31.8; HR, 0.80; 95% CI, 0.64– 1.00), made osimertinib the best treatment option for patients with untreated EGFR-mutant aNSCLC.

aNSCLC – Advanced Non-small cell lung cancer

1. Skovlund E, Leufkens HGM, Smyth JF. The use of real-world data in cancer drug development. Eur J Cancer 2018;101:69–76.
2. Sherman RE, Anderson SA, Dal Pan GJ et al. Real-world evidence — What is it and what can it tell us? N Engl J Med 2016;375:2293–2297.

OSIMERTINIB VS COMPARATOR EGFR-TKI AS FIRST-LINE TREATMENT FOR EGFRm ADVANCED NSCLC (FLAURA): FINAL OVERALL SURVIVAL ANALYSIS

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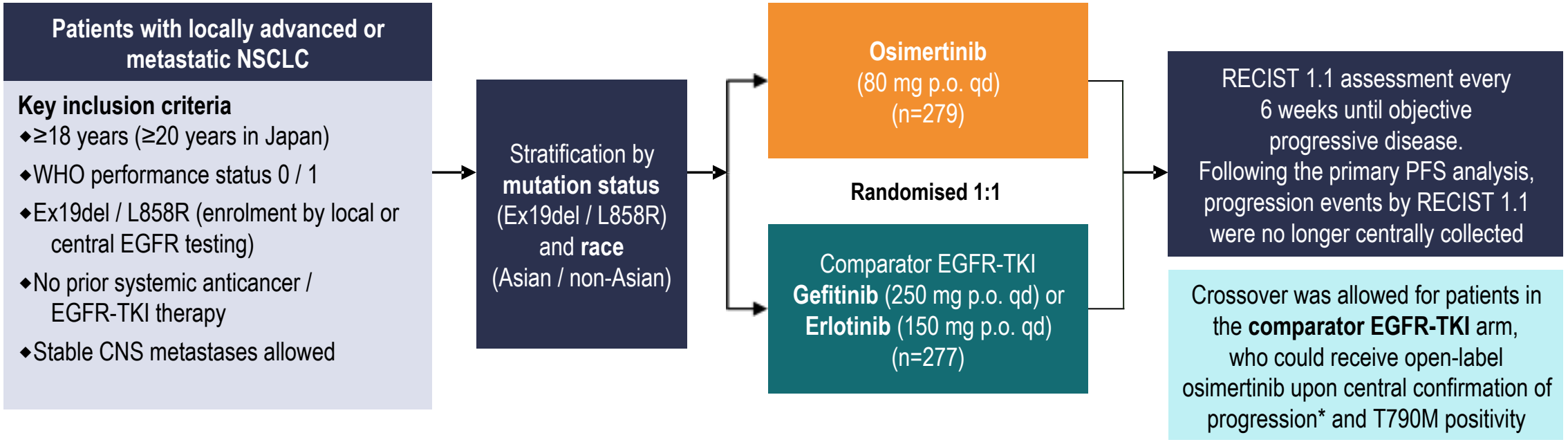
Oral presentation at ESMO 2019

FLAURA DOUBLE-BLIND STUDY DESIGN



OS was a key secondary endpoint

- Final OS analysis planned for when approximately 318 death events had occurred
- For statistical significance, a p-value of less than 0.0495, determined by O'Brien-Fleming approach, was required
  - Alpha spend for interim OS analysis was 0.0015
- At data cut-off, 61 patients (22%) in the osimertinib arm and 13 patients (5%) in the comparator arm were ongoing study treatmen t

Data cut-off: 25 June 2019

Soria et al. N Engl J Med 2018;378:113-25

*By investigator assessment if disease progression occurred after the primary analysis data cut-off

p.o., orally; qd, once daily; RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1; WHO, World Health Organization

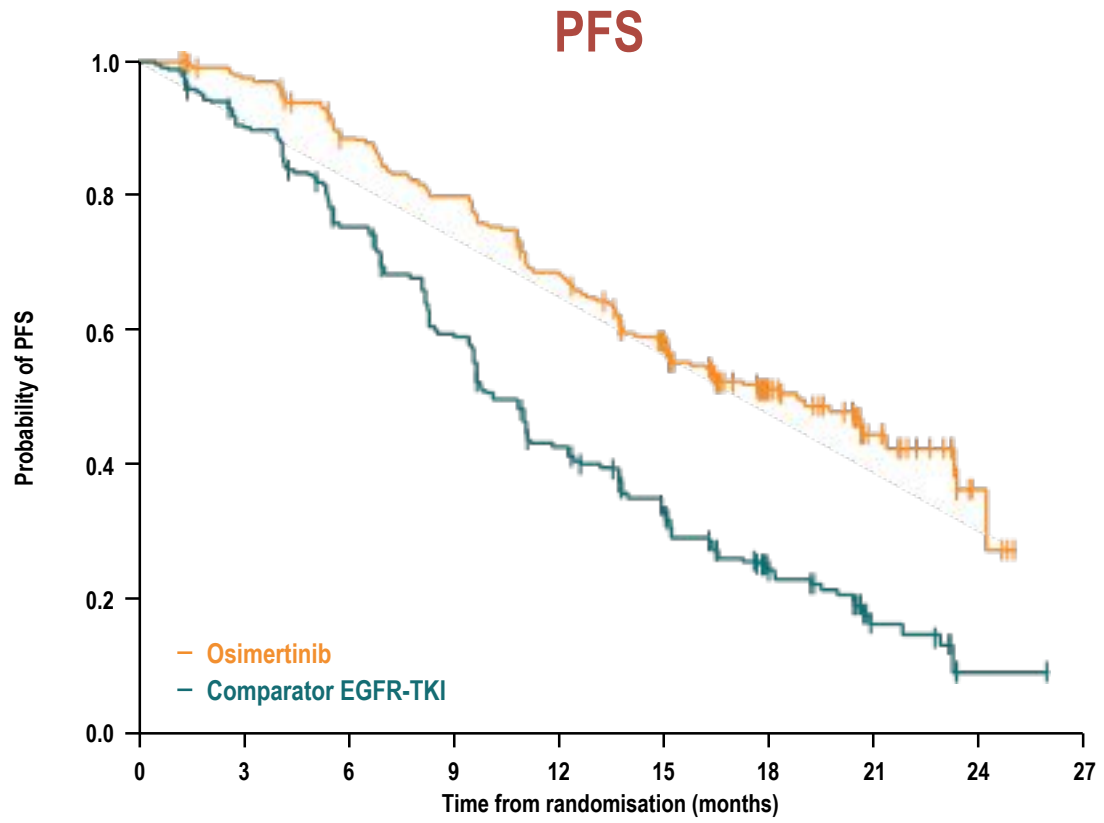
BASELINE CHARACTERISTICS

Characteristic, %	Osimertinib (n=279)	Comparator EGFR-TKI (n=277)
Sex: male / female	36 / 64	38 / 62
Age, median (range), years	64 (26–85)	64 (35–93)
Race: Asian / non-Asian	62 / 38	62 / 38
Smoking status: never / ever	65 / 35	63 / 37
CNS metastases at study entry	19	23
WHO performance status: 0 / 1	40 / 60	42 / 58
Overall disease classification: metastatic / advanced	95 / 5	95 / 5
Histology: adenocarcinoma / other	99 / 1	98 / 2
EGFR mutation at randomisation: Ex19del / L858R	63 / 37	63 / 37

Data cut-off: 12 June 2017

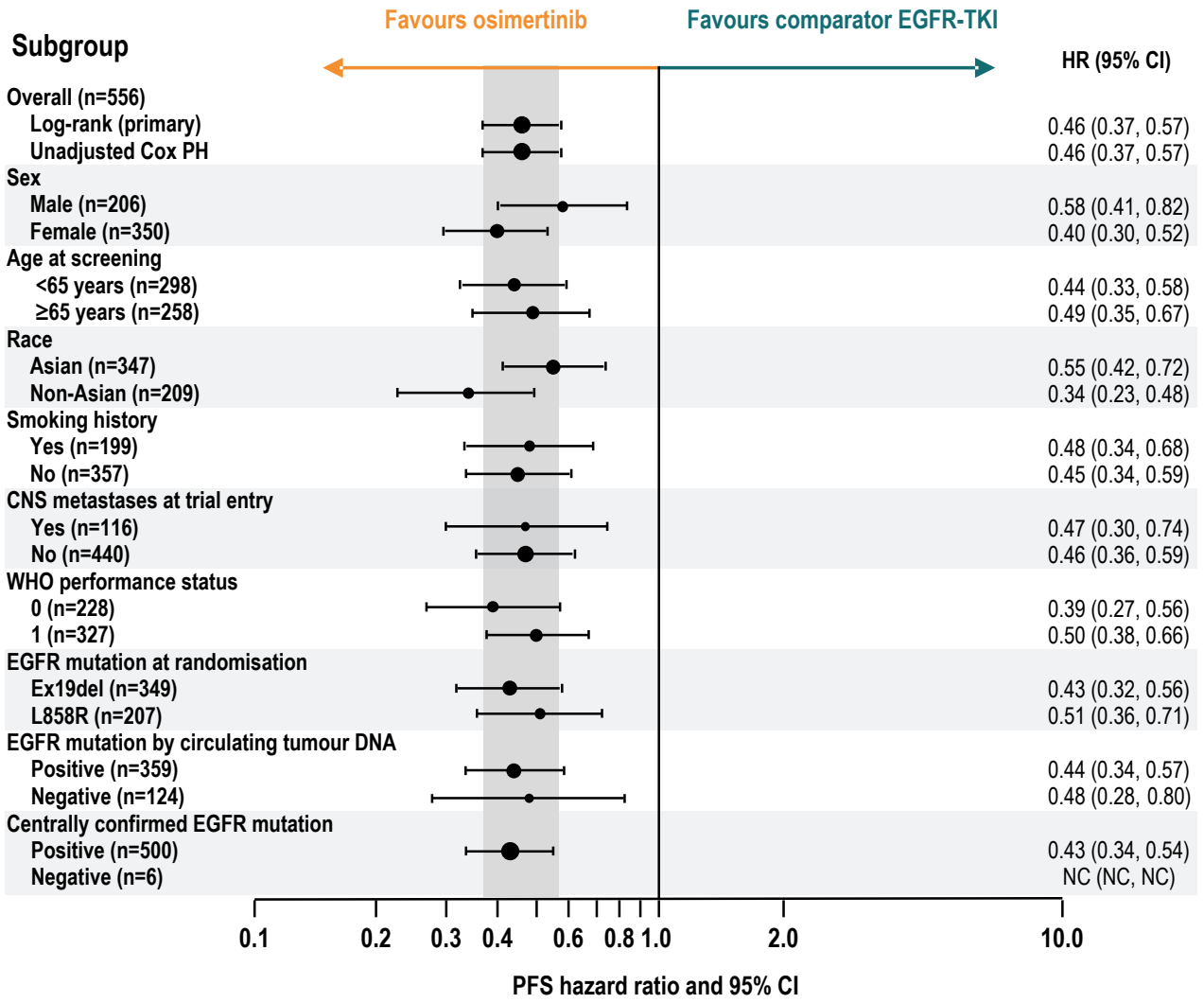
Soria et al. N Engl J Med 2018;378:113-25

PRIMARY ANALYSIS: PROGRESSION-FREE SURVIVAL



No. at risk										
Osimertinib	279	262	233	210	178	139	71	26	4	0
Comparator EGFR-TKI	277	239	197	152	107	78	37	10	2	0

	Median PFS, months (95% CI)	HR (95% CI)
Osimertinib	18.9 (15.2, 21.4)	0.46 (0.37, 0.57); p<0.001
Comparator EGFR-TKI	10.2 (9.6, 11.1)	

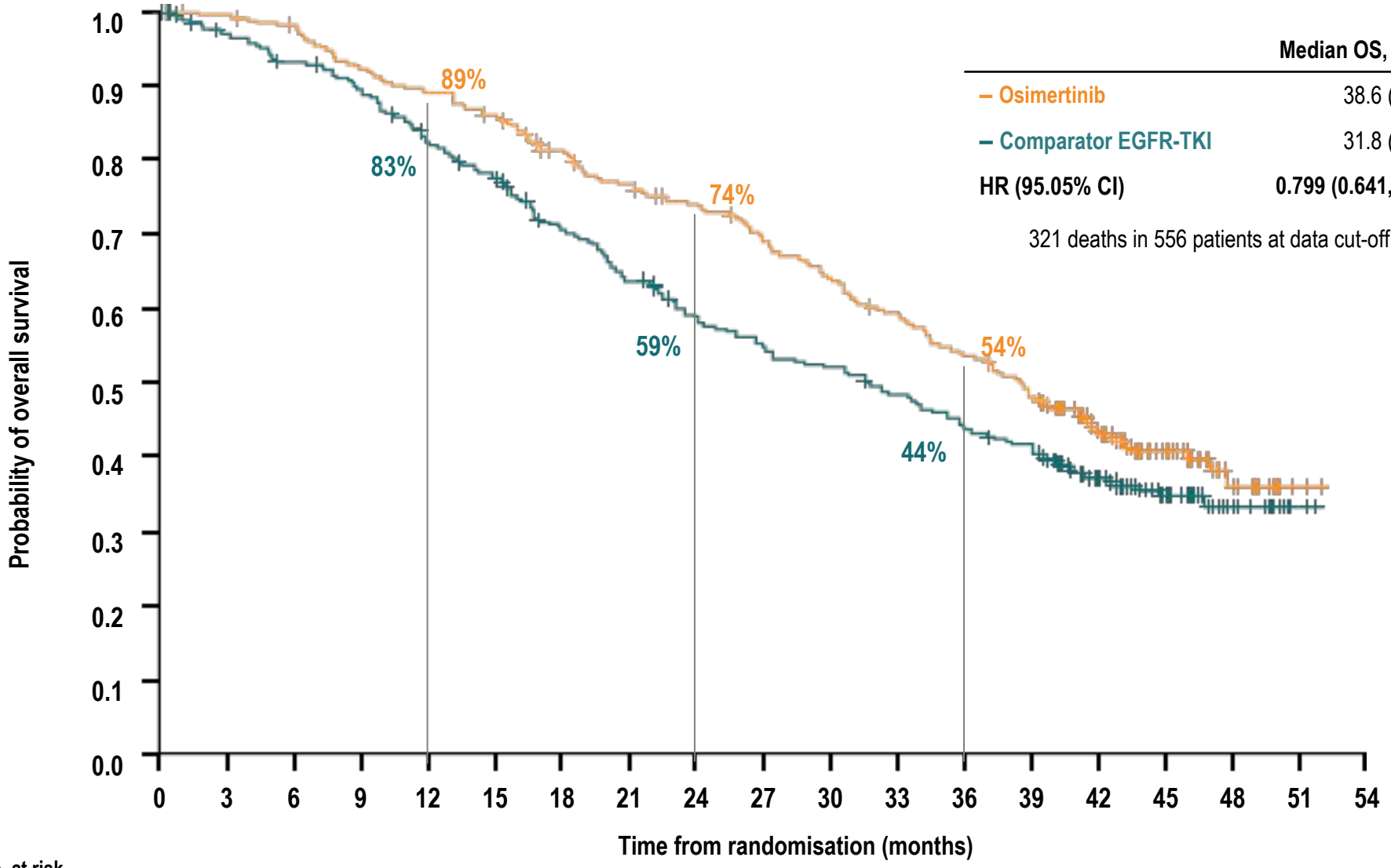


Data cut-off: 12 June 2017

1. **Soria et al. N Engl J Med 2018;378:113-25**

CI, confidence interval; ctDNA, circulating tumour DNA; NC, not calculable; PH, proportional-hazards

FINAL ANALYSIS: OVERALL SURVIVAL



Median OS, months (95% CI)	
– Osimertinib	38.6 (34.5, 41.8)
– Comparator EGFR-TKI	31.8 (26.6, 36.0)
HR (95.05% CI)	**0.799 (0.641, 0.997); p=0.0462**

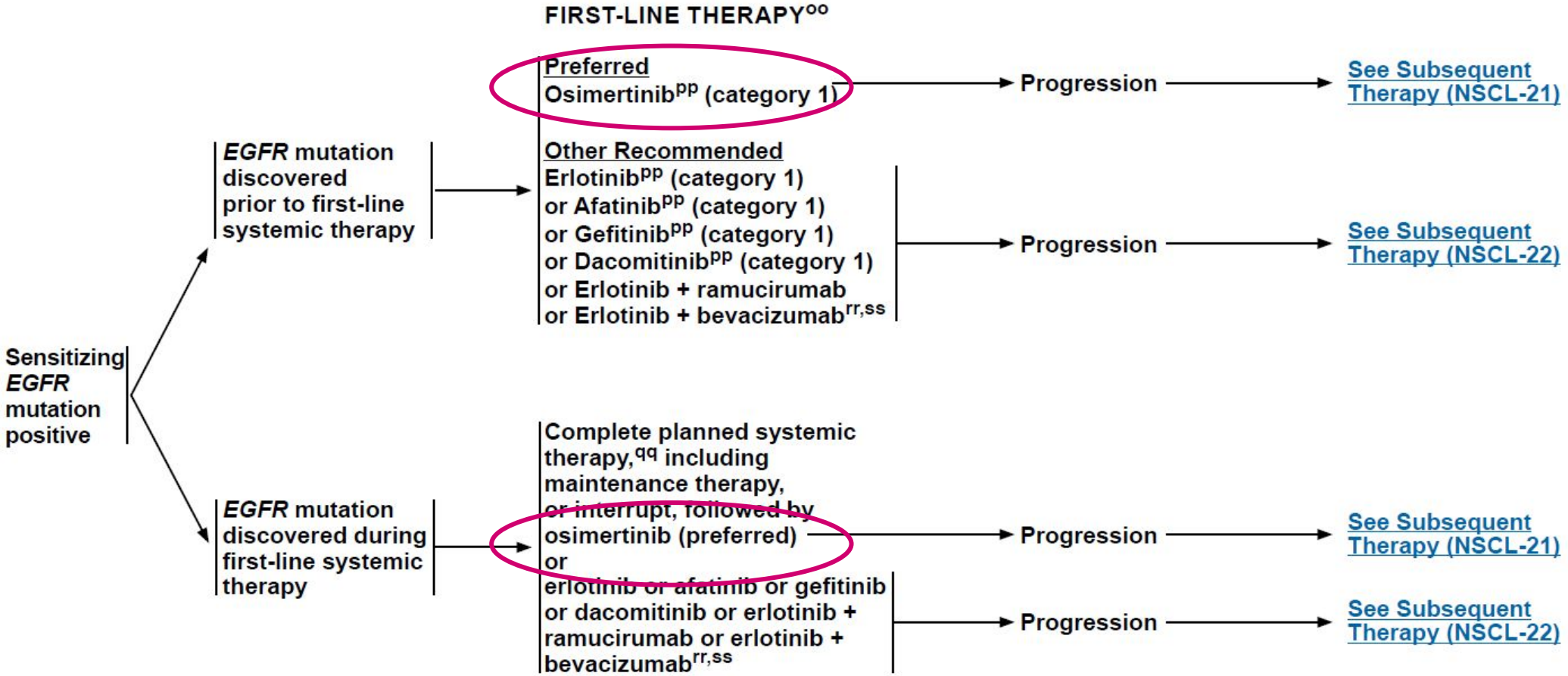
321 deaths in 556 patients at data cut-off: 58% maturity

No. at risk																			
Osimertinib	279	276	270	254	245	236	217	204	193	180	166	153	138	123	86	50	17	2	0
Comparator EGFR-TKI	277	263	252	239	219	205	182	165	148	138	131	121	110	101	72	40	17	2	0

Data cut-off: 25 June 2019

For statistical significance, a p-value of less than 0.0495, determined by O'Brien-Fleming approach, was required

SENSITIZING *EGFR* MUTATION POSITIVE[ll]



[ll] See Principles of Molecular and Biomarker Analysis (NSCL-H)

Real –World Evidence of Osimertinib

1) FLOWER STUDY
2) OSI-FACT
3) MYKONOS

First-Line Osimertinib in Patients with EGFR-Mutant Advanced Non-Small Cell Lung Cancer: : FLOWER Study

MARTINA LORENZI et al, The Oncologist 2021;9999:1–16

INTRODUCTION

- Osimertinib, an irreversible, third-generation EGFR TKI, demonstrated a clinically meaningful improvement in median progression-free survival (mPFS, 18.9 months vs. 10.2; hazard ratio [HR], 0.46; 0.37–0.57; $p < .001$) in the phase III randomized FLAURA trial

- Overall survival (OS) median OS, 38.6 months vs. 31.8; HR, 0.80; 95% CI, 0.64– 1.00), made osimertinib the best treatment option for patients with untreated EGFR-mutant aNSCLC.

- It has been estimated that only 2%–4% of patients with cancer receive treatment within RCTs, thus raising the issue of the representativeness

- Real-world data have become useful tools to assess unique insights in routine oncology practice in the post marketing setting

aNSCLC – Advanced Non-small cell lung cancer

1. Skovlund E, Leufkens HGM, Smyth JF. The use of real-world data in cancer drug development. Eur J Cancer 2018;101:69–76.
2. Sherman RE, Anderson SA, Dal Pan GJ et al. Real-world evidence — What is it and what can it tell us? N Engl J Med 2016;375:2293–2297.

KEY FEATURES: BASELINE

Variable	*n* (%)
Number of cases	126 (100.0)
Age, median (range), yr	68.0 (30–88)
Gender	
Male	45 (35.7)
Female	81 (64.3)
Recurrent	
No	107 (84.9)
Yes	19 (15.1)
Smoking status	
Never smokers	69 (54.7)
Former smokers	43 (34.1)
Smokers	10 (7.9)
Unknown	4 (3.2)
Tumor histology	
Adenocarcinoma	120 (95.2)
Squamous cell carcinoma	3 (2.4)
Adenosquamous carcinoma	2 (1.6)
Unknown	1 (0.8)
Brain metastases at diagnosis	
Present	38 (30.2)
Absent	88 (69.8)
Baseline EGFR mutation status	
Exon 19 deletion	63 (50.0)
Exon 21 L858R mutation	55 (43.7)
Rare	3 (2.4)
Complex	4 (3.3)
Unknown	1 (0.8)
Stage at diagnosis	
IIIB/IIIC	6 (4.8)
IVA	30 (23.8)
IVB	90 (71.4)
ECOG PS	
0–1	110 (87.3)
≥2	16 (12.7)

Variable	*n* (%)
Bone metastases at diagnosis	
Present	59 (46.8)
Absent	67 (53.2)
Best response to osimertinib	
CR	0 (0)
PR	92 (73.0)
SD	29 (23.0)
PD	5 (4.0)
Unknown/not evaluated	0 (0)

CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NOS, not otherwise specified; PD, progressive disease; PR, partial response; SD, stable disease.

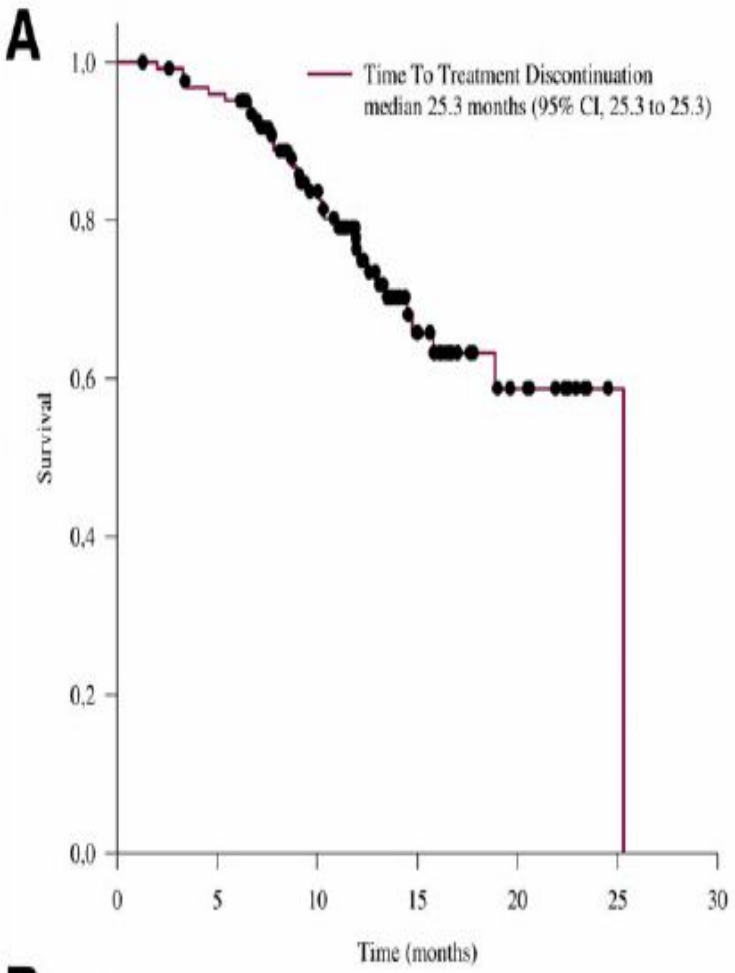
STUDY INCLUSION & EXCLUSION CRITERIA

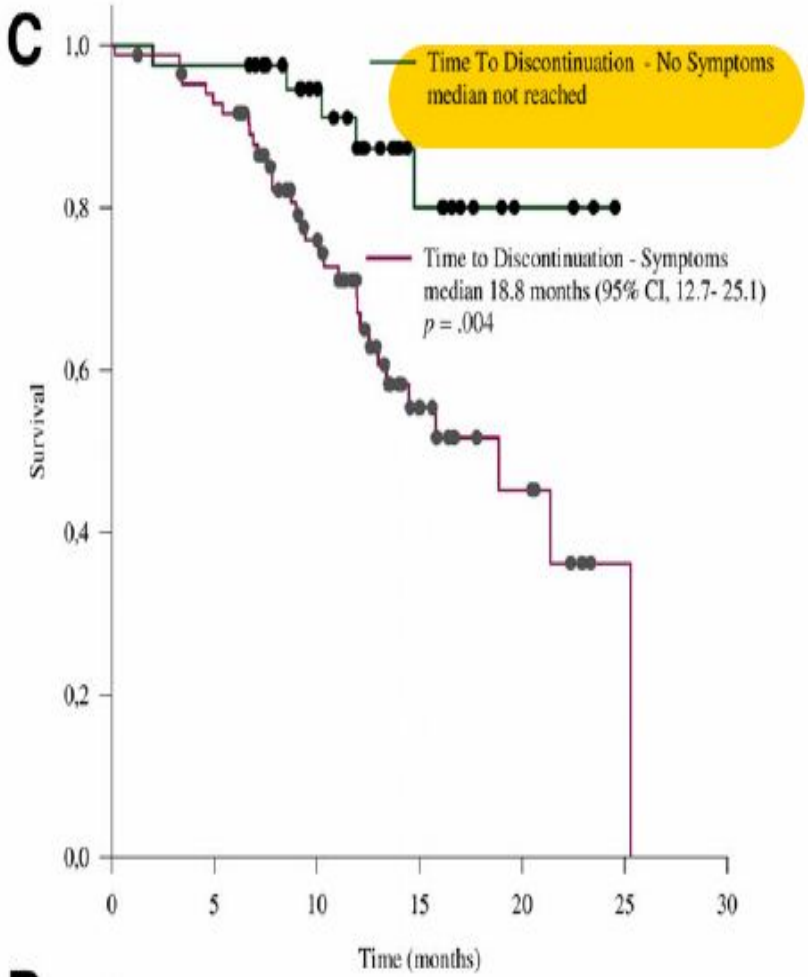
Inclusion	Exclusion
1. Age > 18 years 2. Histological and/or cytological confirmed diagnosis of NSCLC 3. Presence of one or more epidermal growth factor receptor (EGFR) mutations in exon 18–21 4. Locally advanced, recurrent or metastatic disease (stage IIIB and IV according to 8th edition of the TNM Classification of Malignant Tumors) 5. Eligible to receive first-line treatment with the third-generation EGFR TKI, Osimertinib.	Patients who received the study drug in clinical trials

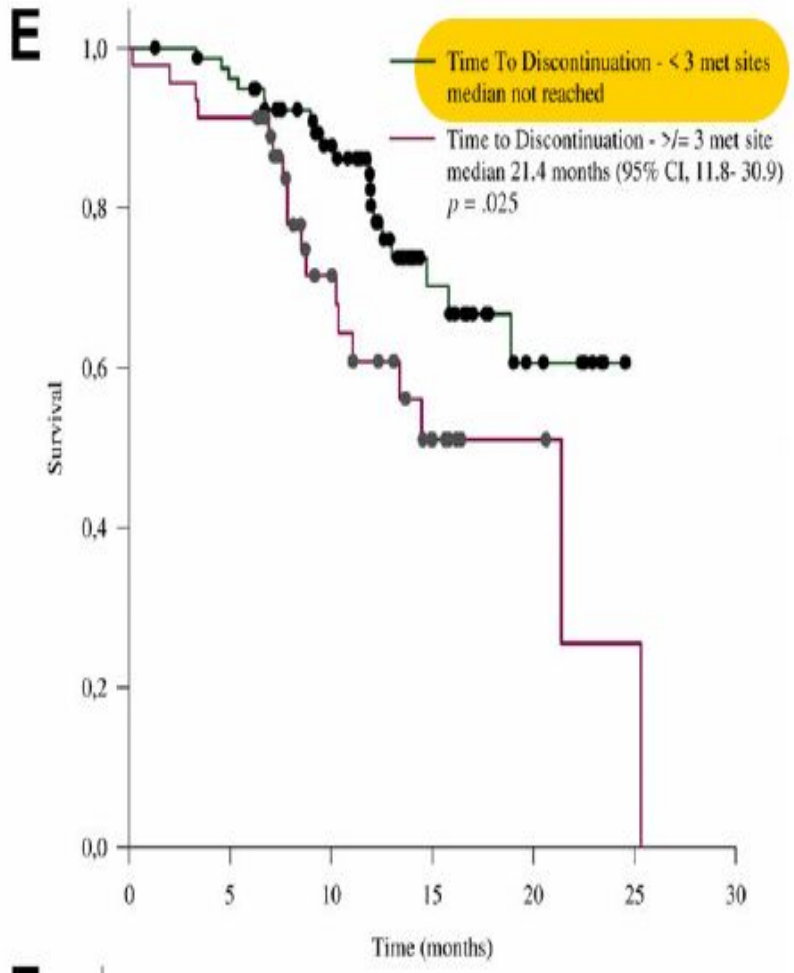
STUDY ENDPOINTS

Primary	Secondary
(a) mTTD, measured from the osimertinib start to discontinuation for any Cause (b) rate of treatment-related Aes (c) rate of dose reduction and temporary or definitive treatment interruption due to AEs. TTD is under exploration as a pragmatic real-world endpoint to assess effectiveness of anticancer therapy in NSCLC and reflects the common practice to continue treatment beyond RECIST progression, justified by the biology of oncogene addicted tumors, in which oligoprogression frequently occurs, and the favorable safety profile of targeted therapies	a) mOS (median Overall survival) b) mPFS (median progression free survival) c) ORR (Overall response rate) d) DCR (Disease control rate) e) Progression patterns to Osimertinib, in terms of number and localization of metastatic sites, new lesions, and progression related symptoms Diagnostic-therapeutic pathway: (a) The time frame between diagnostic biopsy, histologic report (b) The proportion of patients underwent locoregional treatment (c) type and frequency of rebiopsy performed at progression.

PRIMARY ASSESSMENT: EFFECTIVENESS







progression (p = .018) compared with oligo- or systemic progression.

median time to treatment discontinuation (mTTD)

mTTD in patients with or without symptoms at diagnosis

mTTD in patients with less than 3 or at least 3 metastatic sites

1) Soria JC, N Engl J Med 2017;378:113–125.

2) Blumenthal GM et al. Ann Oncol 2019;30:830–838.

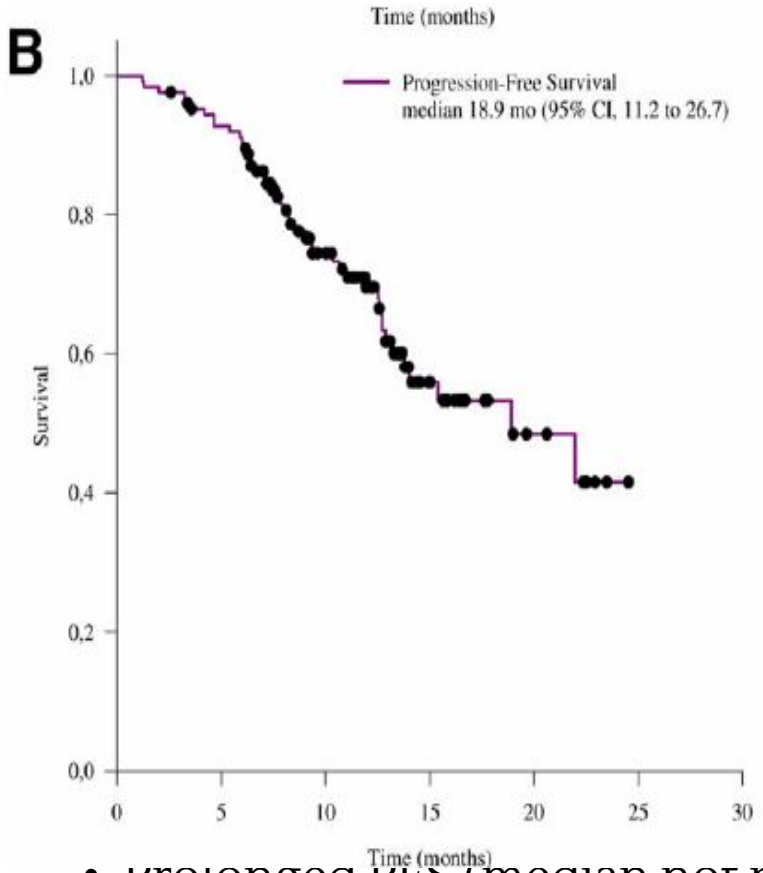
Poor treatment outcome for patients with brain metastases, presence of symptoms, and at least three metastatic sites at diagnosis, suggesting tumor load as a negative prognostic factor

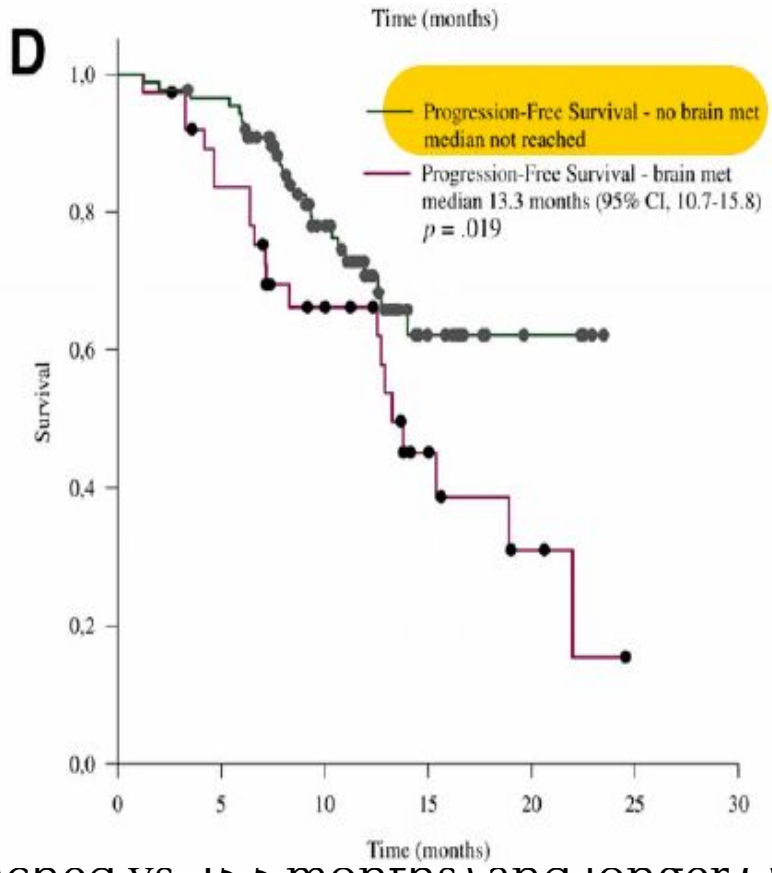
Table 2. (continued)

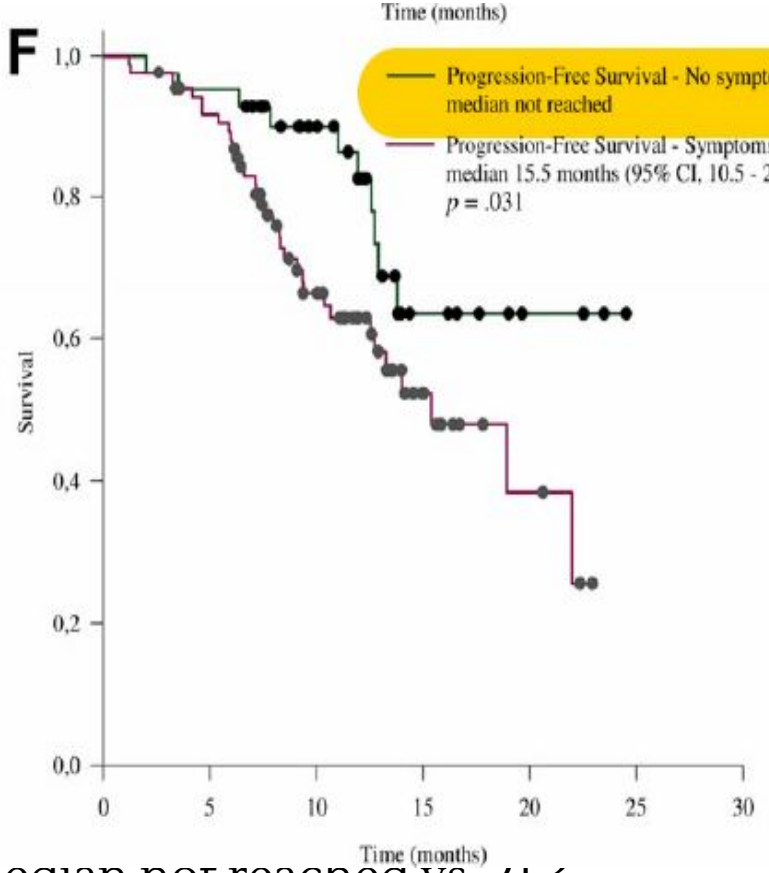
Variable	*n* (%)	PFS univariate analysis, *p* value	PFS multivariate analysis		OS univariate analysis, *p* value	OS multivariate analysis		TTD univariate analysis, *p* value	TTD multivariate analysis	
			p value	HR (95% CI)		*p* value	HR (95% CI)		*p* value	HR (95% CI)
N. of metastatic sites at diagnosis										
<3	80 (63.5)	.151	.828	1.094 (0.488–2.448)	.182	**.036**	**3.602 (1.089–11.912)**	**.025**	.085	2.182 (0.899–5.297)
≥3	46 (36.5)									
Brain metastases at diagnosis										
Present	38 (30.2)	**.019**	**.035**	**2.382 (1.061–5.344)**	.223	.916	0.941 (0.303–2.919)	.076	.284	1.631 (0.666–3.995)
Absent	88 (69.8)									
Liver metastases at diagnosis										
Present	16 (12.7)	.364	.613	1.274 (0.499–3.249)	.515	.113	0.257 (0.0481–1.377)	.724	.557	0.724 (0.247–2.126)
Absent	110 (87.3)									
Bone metastases at diagnosis										
Present	59 (46.8)	.095	.158	1.813 (0.794–4.139)	.369	.004	0.167 (0.0490–0.570)	.254	.832	0.906 (0.366–2.245)
Absent	67 (53.2)									
Best response to TKI										
CR/PR	92 (73.0)	.808	.497	1.308 (0.603–2.834)	.285	.396	1.567 (0.556–4.414)	.984	.906	1.054 (0.443–2.508)
SD/PD	34 (27.0)									
Symptoms at diagnosis										
Present	85 (67.5)	**.031**	.178	1.703 (0.785–3.695)	**.022**	.059	3.480 (0.955–12.678)	**.004**	**.028**	**3.035 (1.126–8.178)**
Absent	41 (32.5)									

Significant values are highlighted in bold.
Abbreviations: CI, confidence interval; coeff, coefficient; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; TTD, time to discontinuation.

PRIMARY ASSESSMENT : EFFECTIVENESS







- Prolonged PFS (median not reached vs. 15.5 months) and longer OS (median not reached vs. 21.3 months; p = .022) also noticed in patients at diagnosis
- TTD of 9 months or higher was significantly associated with better OS (p = .008; HR, 0.145; 95% CI, 0.035–0.599

mPFS in patients with or without brain metastases at diagnosis

mPFS in patients with and without symptoms at diagnosis

Real-world diagnostic-therapeutic pathway

- Essential element of evidence-based medicine and could help clinician in decision making

- Among patients experiencing PD (n = 44),
  - 21 cases(47.7%) underwent a rebiopsy at progression.
  - Tissue rebiopsy 14 cases (66.7%), liquid biopsy (n = 6, 28.6%)

- Molecular analysis was performed in 13 samples (61.9%)
  - Druggable resistance mechanisms included the following: MET amplification (amp) (n = 4), MET amp/EGFR amp (n = 1), EGFR amp (n = 1), HER2 amp (n = 1)

SAFETY DATA & CONCLUSION

- 110 patients (87%) experier
- Venous thromboembolism he real-world ASTRIS study, grade 3 pulr d patients receiving Osimertinib*
- No difference in rates of V ity, and tumor load.
- e of
-

Adverse event	Any grade, *n* (%)	G3/G4, *n* (%)	G1/G2, *n* (%)
Any	**110 (87.3)**	**42 (33.3)**	**68 (54.0)**
ILD/pneumonitis	12 (9.5)	3 (2.4)	9 (7.1)
Diarrhea	**49 (38.9)**	4 (3.2)	45 (35.7)
Stomatitis	17 (13.5)	1 (0.8)	16 (12.7)
Keratitis	7 (5.6)	0 (0.0)	7 (5.6)
Rash	**42 (33.3)**	2 (1.6)	40 (31.7)
Dry skin	**24 (19.0)**	0 (0.0)	24 (19.0)
Paronychia	**33 (26.2)**	1 (0.8)	32 (25.4)
Pruritus	12 (9.5)	0 (0.0)	12 (9.5)
QTcProlonged	2 (1.6)	1 (0.8)	1 (0.8)
Platelet count decrease	18 (14.3)	3 (2.4)	15 (11.9)
Leucopenia	17 (13.5)	1 (0.8)	16 (12.7)
Neutropenia	9 (7.1)	0 (0.0)	9 (7.1)
Venous thromboembolism	**12 (9.5)**	**10 (7.9)**	**2 (1.6)**
Creatinine increased	**26 (20.6)**	**0 (0.0)**	**26 (20.6)**
Heart failure	**2 (1.6)**	**1 (0.8)**	**1 (0.8)**
Arterial thromboembolism	**3 (2.4)**	**2 (1.6)**	**1 (0.8)**

Table 8. Univariate analysis of baseline patient characteristics predicting venous thromboembolism

Variable	VTE + any grade *n* (%)	VTE − any grade *n* (%)	Univariate analysis *p* value	VTE + G3–G4 *n* (%)	VTE − G3-G4 *n* (%)	Univariate analysis *p* value
Number of cases	12 (100)	114 (100)		10 (100)	116 (100)	
Age, years						
<65	8 (66.7)	42 (36.8)		6 (60)	44 (37.9)	
≥65	4 (33.3)	72 (63.2)	.0624	4 (40)	72 (62.1)	.1932
CCI						
6	2 (16.7)	6 (5.3)		2 (20)	6 (5.2)	
>6	10 (83.3)	108 (94.7)	.7570	8 (80)	110 (94.8)	.1229
Number of metastatic sites						
<3	7 (58.3)	73 (64.0)		5 (50)	75 (64.7)	
≥3	5 (41.7)	41 (36.0)	.7570	5 (50.0)	41 (35.3)	.4952
ECOG PS						
0–1	10 (83.3)	100 (87.7)		9 (90.0)	101 (87.1)	
≥2	2 (16.6)	14 (12.3)	.6496	1 (10.0)	15 (12.9)	1.0000
Peripheral sensory neuropathy	1 (0.8)	0 (0.0)			1 (0.8)	

Abbreviations: VTE, Venous Thromboembolism; +, present; -, absent; CCI, Charlson Comorbidity Index; ECOG, Eastern Cooperative Oncology Group Performance Status; N, Number.

*de Marinis F, Wu YL, Castro GD Jr. et al.. Future Oncol 2019;15:3003–3014.

Osimertinib as first-line treatment for advanced epidermal growth factor receptor mutation–positive non–small-cell lung cancer in a real-world setting (OSI-FACT)

Y. Sakata et al. European Journal of Cancer 159 (2021) 144e153

INTRODUCTION

- In patients with EGFR mutations, PFS improves after treatment with EGFR – TKIs compared with that with cytotoxic chemotherapy
- Osimertinib was shown to be superior to first generation EGFR-TKIs in terms of overall survival (OS)
- The current study, investigated the differences in efficacy with patient background and the safety of first-line Osimertinib treatment in real world scenario

1. Ramalingam SS, Vansteenkiste J, Planchard D, Cho BC, Gray JE, Ohe Y, et al. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. N Engl J Med 2020; 382:41e50.
2. Nogami N, Ramalingam SS, Imamura F, Okamoto I, Kurata T, Kato T, et al. Osimertinib as first-line therapy for EGFRm advanced NSCLC (FLAURA): final OS in Japanese subset. The 60th annual Meeting of the Japan Lung Cancer Society. 2019.

STUDY INCLUSION & EXCLUSION CRITERIA

Inclusion	Exclusion
Advanced EGFR + NSCLC with Osimertinib as the initial treatment	a) Patients concurrently using other anticancer agents or undergoing thoracic radiotherapy b) Undergoing postoperative adjuvant chemotherapy c) Receiving Osimertinib as second-line treatment

BASELINE CHARACTERISTICS

Patient characteristics.

Characteristics	Patients, No. (%) (N = 538)
Age (years)	
Median (IQR)	71 (65–78)
<75	335 (62.3)
≥75	203 (37.7)
Sex	
Male	185 (34.4)
Female	353 (65.6)
ECOG PS	
0	170 (31.6)
1	281 (52.2)
2	61 (11.3)
3	22 (4.1)
4	4 (0.7)
Smoking status	
Never	329 (61.2)
Current or former	209 (38.8)
Histology	
Adenocarcinoma	529 (98.3)
Squamous cell carcinoma	4 (0.7)
Non–small-cell carcinoma	5 (0.9)
Mutation type	
19 deletion	264 (49.1)
L858R	244 (45.4)
Uncommon mutations	30 (5.5)
Stage	
II or III	20 (3.7)
IV	354 (65.8)
Recurrence	164 (30.5)
PD-L1 TPS	
≥50%	64 (11.9)
1–49%	170 (31.6)
<1%	161 (30)
Unknown	143 (26.6)
Brain metastasis	
Symptomatic	33 (6.1)
Asymptomatic	134 (24.9)
Absent	371 (69)
Leptomeningeal metastasis	
Symptomatic	6 (1.1)
Asymptomatic	12 (2.2)
Absent	520 (96.7)
Pleural/ascites fluid	
Symptomatic	52 (9.7)
Asymptomatic	87 (16.2)
Absent	399 (74.2)
Pericardial fluid	
Symptomatic	3 (0.6)
Asymptomatic	14 (2.6)
Absent	521 (96.8)
Liver metastasis	
Present	40 (7.4)
Absent	498 (92.6)
With interstitial lung disease	
Present	9 (1.7)
Absent	529 (98.3)
With target lesions	
Present	458 (85.1)
Absent	80 (14.9)

STUDY ENDPOINTS

Primary	Secondary
PFS	a) OS b) Time to treatment failure (TTF) c) Response rate, safety and posttreatment. (Complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD] or not evaluated) d) Objective response rate (ORR; CR + PR) e) Disease control rate (DCR; CR + PR + SD)

EFFICACY ANALYSIS: PRIMARY ENDPOINT (PFS)

Category		HR	95% CI	*P* value
Age (by 10 years)		1.19	(0.96, 1.47)	0.110
Sex	Female	1.00	—	—
	Male	1.99	(1.35, 2.93)	0.001
ECOG PS	0	1.00	—	—
	1	1.14	(0.74, 1.74)	0.557
	≥2	1.44	(0.82, 2.52)	0.200
Smoking	No	1.00	—	—
	Yes	1.11	(0.73, 1.69)	0.628
Malignant effusions	No	1.00	—	—
	Yes	1.51	(1.11, 2.04)	0.008
Liver metastasis	No	1.00	—	—
	Yes	1.55	(0.03, 2.33)	0.037
Brain metastasis	No	1.00	—	—
	Yes	1.13	(0.71, 1.80)	0.600
Mutation type	19 deletion	1.00	—	—
	L858R	1.55	(1.01, 2.38)	0.043
Histology	Adenocarcinoma	1.00	—	—
	Non–small-cell lung cancer	1.06	(0.45, 2.48)	0.893
	Squamous cell carcinoma	1.63	(0.55, 4.82)	0.376
BSA	<1.5 m^2	1.00	—	—
	≥1.5 m^2	0.87	(0.52, 1.44)	0.583
Stage	Recurrence	1.00	—	—
	II, III or IV	1.71	(1.04, 2.82)	0.036
NLR	<3.1	1.00	—	—
	≥3.1	1.22	(0.88, 1.68)	0.228
LIPI	0	1.00	—	—
	1	1.24	(0.90, 1.72)	0.196
	2	1.28	(0.73, 2.25)	0.394
PD-L1 TPS	<1%	1.00	—	—
	1–49%	1.66	(1.05, 2.63)	0.029
	≥50%	2.24	(1.17, 4.30)	0.015
	Unknown	1.53	(1.05, 2.22)	0.026

TREATMENT DISCONTINUATION PROFILE
SAFETY PROFILE: ADVERSE EVENTS

Adverse events.

Adverse event	Grade	Number	Median duration of onset (range)
Pneumonitis	All grades	69 (12.8%)	56 days (7–477)
	Grade ≤III	24 (4.5%)	
	Grade V	4 (0.7%)	
Grade ≤III haematotoxicity		23 (4.3%)	33 days (2–307)
Grade ≤III non-haematotoxicity		60 (11.2%)	53 days (0–498)
QT interval prolonged	All grade	22 (4.1%)	230 days (0–565)
	Grade ≤III	6 (1.1%)	
Reduced ejection fraction/heart failure	All grade	8 (1.5%)	111 days (13–565)
	Grade ≤III	5 (0.9%)	
All AEs leading to treatment discontinuation		91 (16.9%)	56 days (5–565)

AE, adverse event.

CONCLUSION

- ORR was 76.2%, and the DCR was 94.1%. PFS is better with Osimertinib than with conventional EGFR-TKIs, irrespective of PD-L1 expression
- Median TTF was 19.1 months (95% CI:15.9 - NR)
- The median time from the start of treatment to the onset of AE was 56 days (range: 5 -565 days).
- Pneumonitis of all grades occurred in 69 patients (12.8%), grade III or higher in 24 patients (4.5%) and fatal pneumonitis in 4 patients (0.7%)

- *Conclusion:*
- PFS after first-line Osimertinib treatment in real-world practice was favourable
- The discontinuation rate due to AEs 41 (18.8%, 41/218), especially pneumonitis requires further investigation

DCR : Disease control Rate

TTF: Time to treatment failure

Real world study of patients with EGFR- mutated locally advanced or metastatic NSCLC treated with first line Osimertinib

Jorge Nieva et al. Journal of Thoracic Oncology Vol. 16 No. 3S

BACKGROUND

- Osimertinib is a third-generation, irreversible, oral EGFR-TKI that potently and selectively inhibits both *EGFR* TKI sensitizing and *EGFR* T790M resistance mutations[1–6]
- Osimertinib has demonstrated efficacy in EGFRm advanced NSCLC, including central nervous system metastases[1,2,5-7]
- In the phase 3 FLAURA study in patients with advanced EGFRm NSCLC, 1L osimertinib significantly prolonged PFS and OS compared with first-generation EGFR TKIs (erlotinib and gefitinib) with median PFS of 18.9 months vs. 10.2 months (HR, 0.46; $p < 0.001$) and median OS of 38.6 months vs. 31.8 months (HR, 0.80; $p = 0.046$)[2,6]
- There remains a need to evaluate real-world disease characteristics and clinical outcomes of patients with ERGRm NSCLC treated with 1L osimertinib monotherapy[2,3,6]

This study reports the demographic and clinical characteristics, rwTTNTD and rwTTD of patients with advanced EGFRm NSCLC who received 1L osimertinib in the US

1L, first-line; EGFR, epidermal growth factor receptor; EGFRm, *EGFR*-mutated; HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; rwTTD, real-world time to treatment discontinuation; rwTTNTD, real-world time to next treatment or death; TKI, tyrosine kinase inhibitor

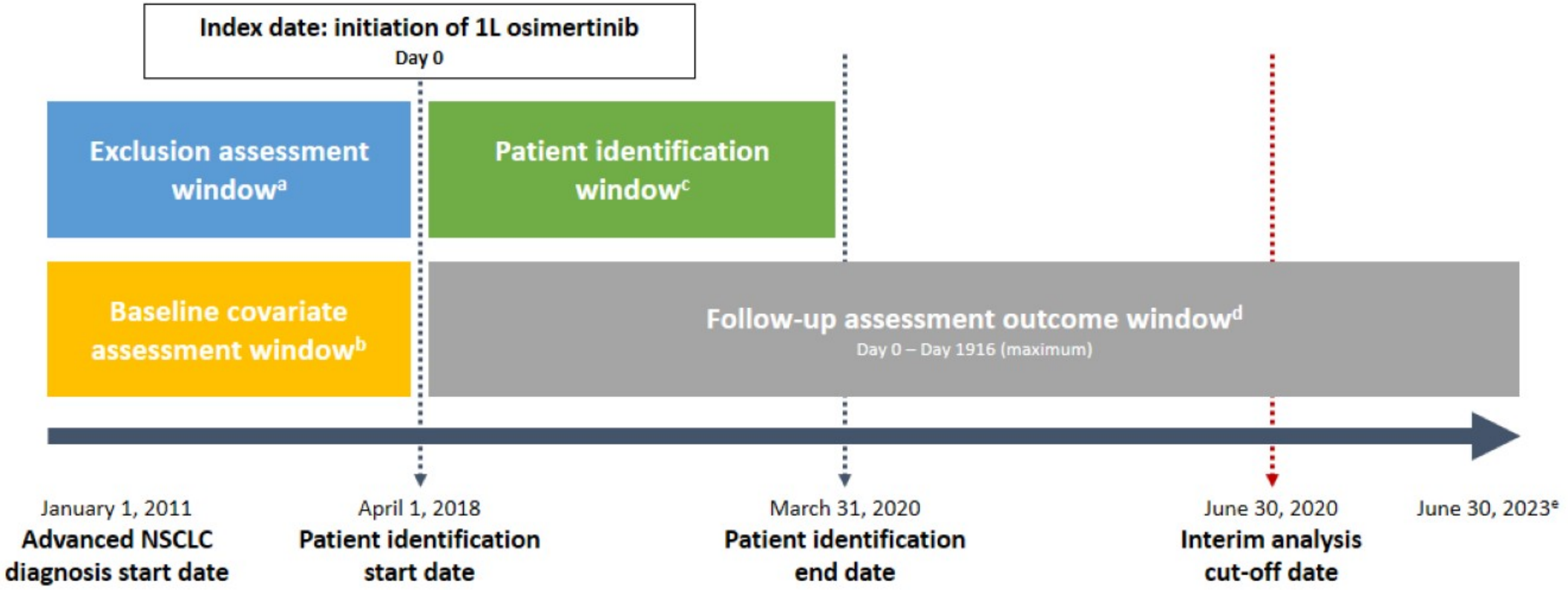
1. Cross D *et al. Cancer Discov* 2014;4:1046–61; 2. Soria JC *et al. N Engl J Med* 2018;378:113–25; 3. Mok T *et al. N Engl J Med* 2017;376:629–40; 4. Wu Y *et al. J Clin Oncol* 2018;36:2702–9; 5. Reungwetwattana T *et al. J Clin Oncol* 2018;36:3290–7; 6. Ramalingam S *et al. N Engl J Med* 2020;382:41–50; 7. Mok T *et al. Am Soc Clin Oncol* 2017;35:15suppl:9005

STUDY DESIGN

- A global observational prospective cohort study is ongoing in the US, Europe and Asia and involves analysis of registry and electronic health records data from country-specific data sources in participating countries
- This US sub-analysis includes data from the nationwide Flatiron Health electronic health record-derived de-identified database. The Flatiron Health database is comprised of de-identified patient-level structured and unstructured data, curated via technology-enabled abstraction
- During the study period, the de-identified data originated from approximately 280 US cancer clinics (~ 800 sites of care)
- For this interim sub-analysis, data were collected through June 30, 2020
- The study is ongoing; the follow-up period is planned until June 2023
- Patient inclusion criteria
  - ✓ ≥ 18 years at the time of advanced NSCLC diagnosis
  - ✓ Advanced (stage IIIB and IV) NSCLC
  - ✓ *EGFR* mutation documented prior to initiation of 1L osimertinib monotherapy
  - ✓ Initiated 1L osimertinib from April 1, 2018 to March 31, 2020

1L, first-line; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer

STUDY DESIGN



[a]Excludes age < 18 years and use of osimertinib within a clinical trial; [b]Including clinical characteristics, biomarker testing, demographics, comorbidities, CNS imaging and (neo)adjuvant treatments; [c]1L osimertinib initiation; [d]Including treatment pathways, biomarker testing, overall survival, progression-free survival, CNS metastases incidence; [e]Or until a median follow-up of ~ 38 months; the cohort exit date will be defined as the earliest instance of either: the last day of available follow-up, date of death, or end of study period

1L, first-line; CNS, central nervous system; NSCLC, non-small cell lung cancer

ASSESSMENT AND STATISTICAL ANALYSIS

- Baseline clinical and demographic characteristics and treatment patterns were summarized using descriptive statistics
- Kaplan–Meier analyses were used to generate estimates of TTNTD and TTD
  - rwTTNTD was defined as time from index date until the start of the next systemic therapy or death in the absence of next systemic therapy
  - rwTTD is time from index date until the earliest end date of osimertinib associated with discontinuation on or prior to the end of 1L therapy
- Unadjusted and adjusted Cox proportional hazards models were used to assess associations between baseline covariates and clinical outcomes
- The index date for time-to-event analyses was defined as the date of 1L osimertinib initiation

1L, first-line; rwTTD, real-world time to treatment discontinuation; rwTTNTD, real-world time to next treatment or death

SOCIODEMOGRAPHIC CHARACTERISTICS

Characteristic	N = 548
Age[a], years, median (IQR)	70.0 (61.0–78.0)
Age[a], years, n (%)	
18–64	179 (32.7)
65–74	176 (32.1)
≥ 75	193 (35.2)
Sex, n (%)	
Female	379 (69.2)
Male	169 (30.8)
Race, n (%)	
White	295 (53.8)
Black or African American	40 (7.3)
Asian	75 (13.7)
Other	63 (11.5)
Unknown	75 (13.7)

Characteristic	N = 548
Practice type, n (%)	
Academic	89 (16.2)
Community	459 (83.8)
Region, n (%)	
Midwest	59 (10.8)
Northeast	102 (18.6)
South	180 (32.8)
West	110 (20.1)
Other/unknown	97 (17.7)

[a]At index date
IQR, interquartile range

CLINICAL CHARACTERISTICS

Characteristic, n (%)	N = 548
Stage at initial diagnosis of NSCLC[a]	
I–IIIA	89 (16.2)
IIIB	5 (0.9)
IV	448 (81.8)
NR	6 (1.1)
Histology	
Non-squamous	534 (97.4)
Squamous	7 (1.3)
NOS	7 (1.3)
ECOG PS	
0–1	295 (53.8)
≥ 2	79 (14.4)
Unknown	174 (31.8)
History of smoking	
Yes	237 (43.2)
No	311 (56.8)

Characteristic, n (%)	N = 548
Charlson comorbidity index[b]	
0	367 (67.0)
1	104 (19.0)
2	46 (8.4)
> 3	31 (5.7)
Metastatic sites prior to index date	
0–1	254 (46.3)
2–3	228 (41.6)
≥ 4	66 (12.0)
Evidence of liver metastases	
Yes	79 (14.4)
No/unknown	469 (85.6)
Evidence of brain metastases at baseline imaging	
Yes	184 (33.6)
No	243 (44.3)
Unknown (assessment unavailable)	121 (22.1)

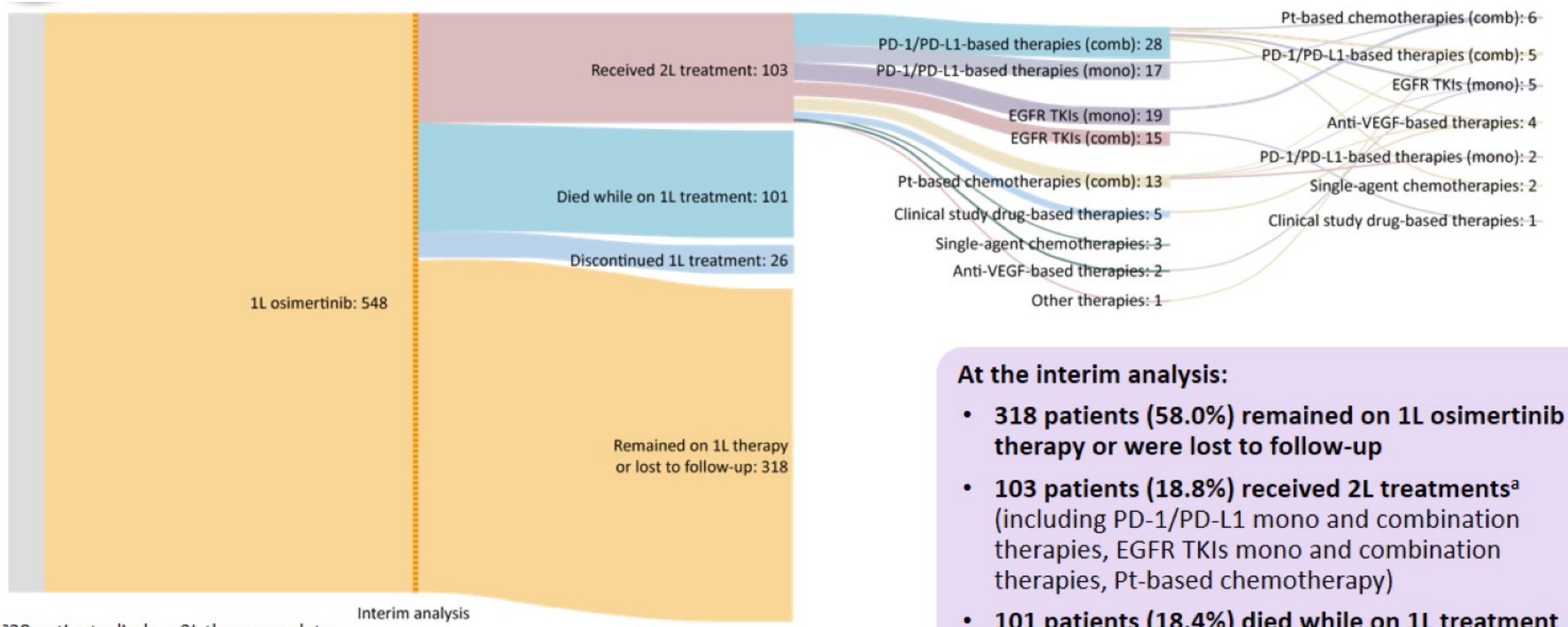
[a]Clinician-documented stage at the chronologically first diagnosis of NSCLC (from clinical notes); [b]Comorbidities documented at any time prior to index date
ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified; NR, not reported; NSCLC, non-small cell lung cancer; PS, performance status

EGFR MUTATIONS

EGFR mutation, n (%)	N = 548
***EGFR*-mutation positive**	**548 (100)**
Common mutations only	**469 (85.6)**
Exon 19 del	280 (51.1)
L858R	185 (33.7)
Exon 19 del plus L858R	4 (0.7)
Both common and uncommon mutations	**22 (4.0)**
Uncommon mutations only	**52 (9.5)**
Unknown mutation	**5 (0.9)**

EGFR, epidermal growth factor receptor

TREATMENT SEQUENCING



[a]38 patients died on 2L therapy or later

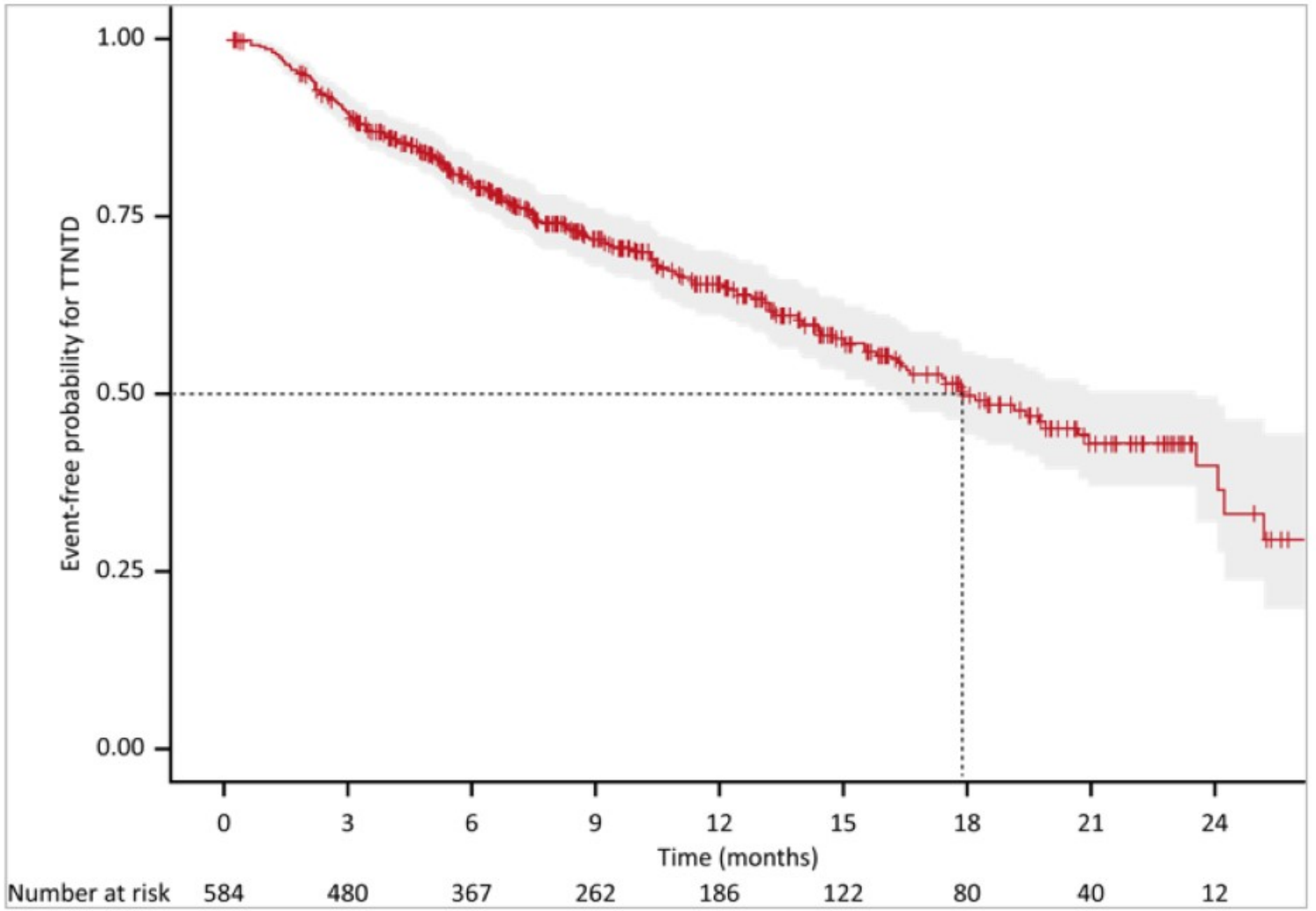
1L/2L, first/second-line; EGFR, epidermal growth factor receptor; PD-1, programmed cell death 1 receptor; PD-L1, programmed death-ligand 1; Pt, platinum; TKIs, tyrosine kinase inhibitors; VEGF, vascular endothelial growth factor

At the interim analysis:

- **318 patients (58.0%) remained on 1L osimertinib therapy or were lost to follow-up**
- **103 patients (18.8%) received 2L treatments[a]** (including PD-1/PD-L1 mono and combination therapies, EGFR TKIs mono and combination therapies, Pt-based chemotherapy)
- **101 patients (18.4%) died while on 1L treatment**
- **26 patients (4.7%) discontinued 1L treatment**

REAL WORLD TIME TO NEXT TREATMENT OR DEATH (rwTTNTD)

- **Median follow-up time was 9.6 months**
- **Median rwTTNTD was 17.9 months (95% CI: 16.2–23.6)**
- **204 (37.2%) events[a]**
  - **101 (18.4%) died**
  - **103 (18.8%) switched to 2L**

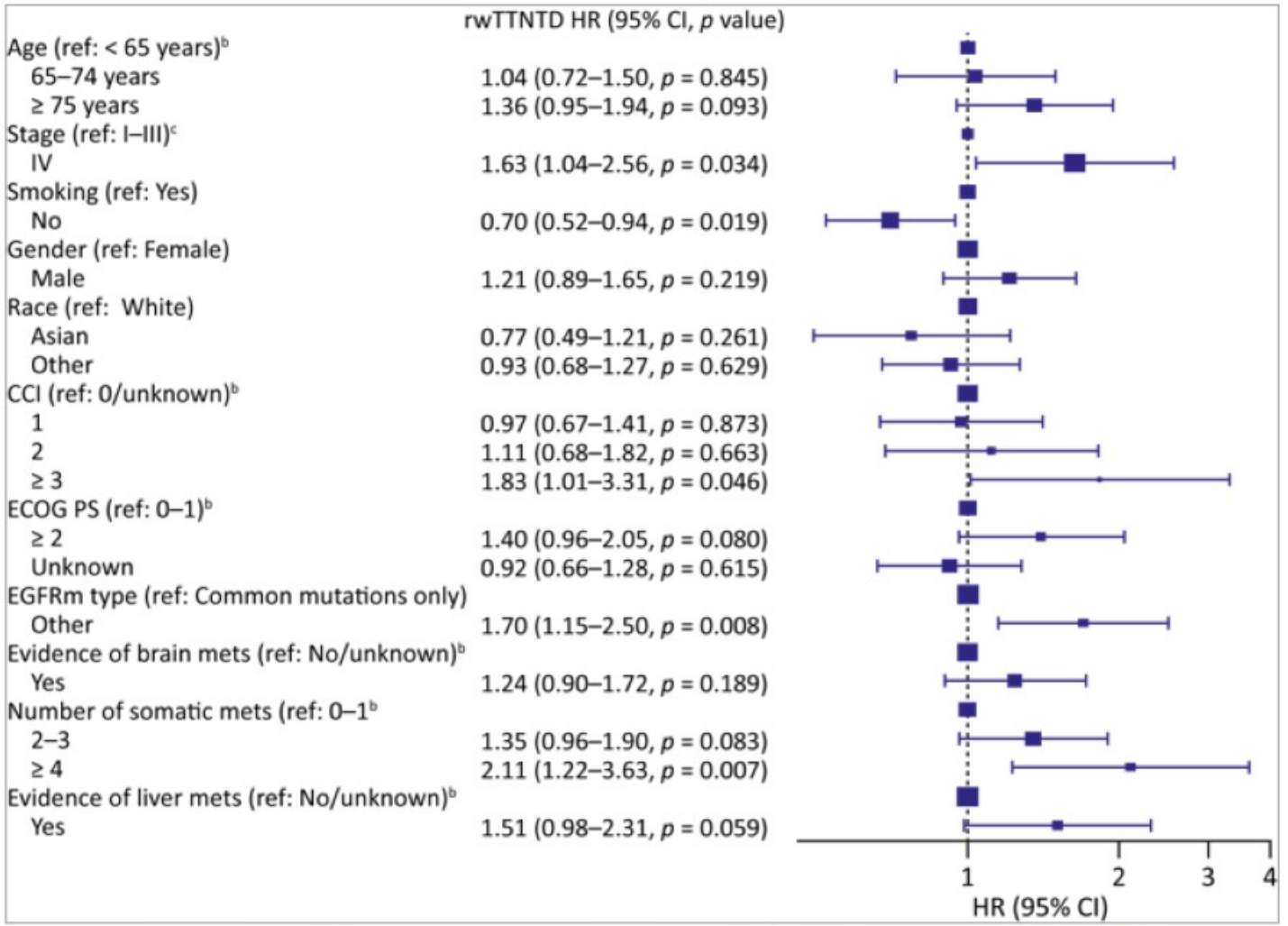


[a]Event date was defined as the date of start of the next systemic therapy or death in the absence of next systemic therapy; data were censored at the last day of available follow-up or end of study period

2L, second-line; rwTTNTD, real-world time to next treatment or death

REAL WORLD TIME TO NEXT TREATMENT OR DEATH (rwTTNTD)

- **In the multivariate analysis, the following variables were significantly associated with rwTTNTD[a]**
  - **Stage at initial diagnosis of NSCLC**
  - **Smoking status**
  - **Charlson comorbidity index ≥ 3**
  - ***EGFR* mutation type**
  - **Number of metastatic sites ≥ 4**

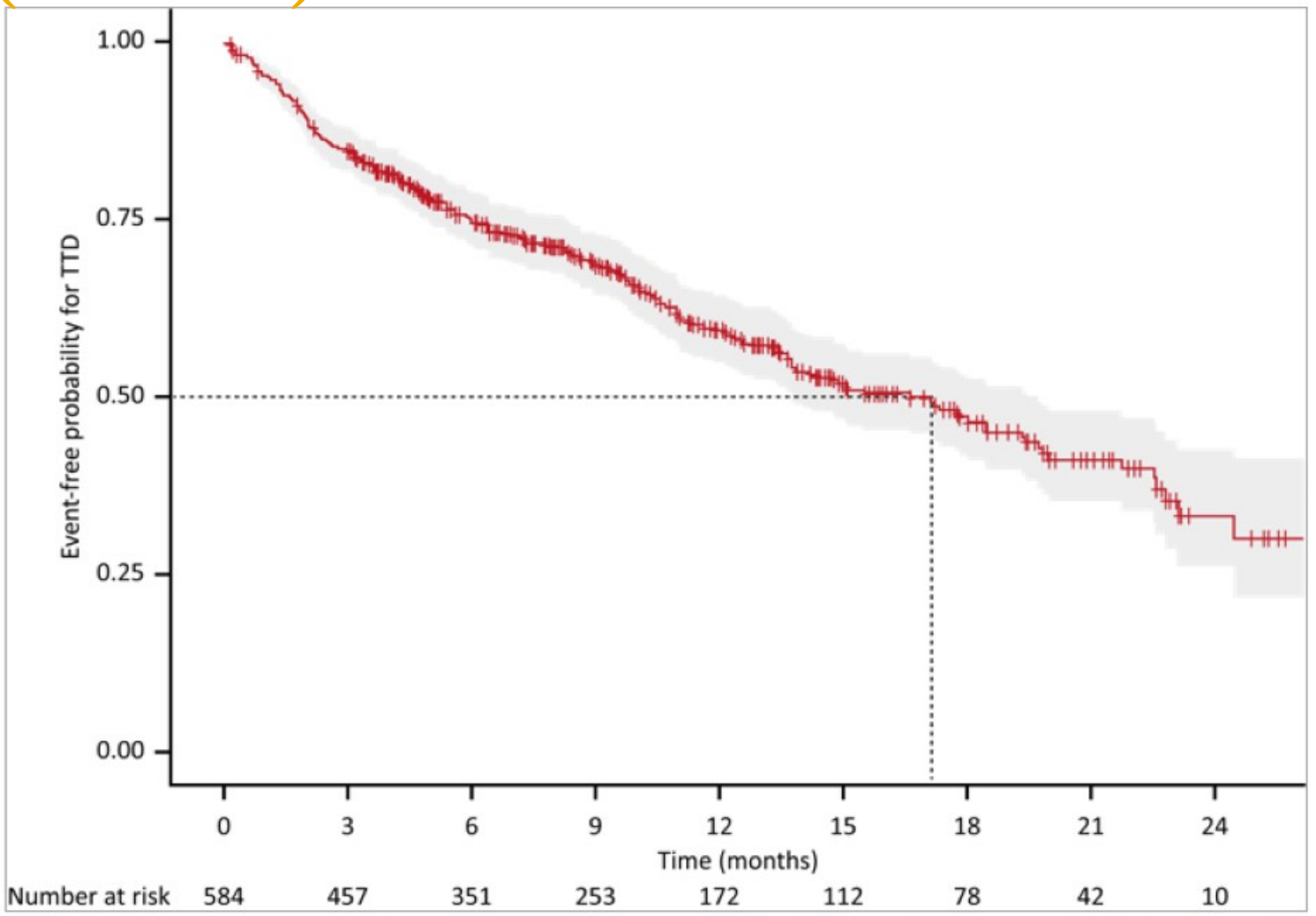


[a]Statistical significance threshold was 0.05 (two-sided); there were no adjustments for multiple testing; [b]At index date; [c]Stage at initial diagnosis, before progressing to advanced NSCLC

CCI, Charlson comorbidity index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HR, hazard ratio; mets, metastases; PS, performance status; ref, reference; rwTTNTD, real-world time to next treatment or death

REAL WORLD TIME TO TREATMENT DISCONTINUATION (rwTTD)

- **Median rwTTD was 17.2 months (95% CI: 13.8–19.8)**
- **230 (42.0%) events[a]**
  - **101 (18.4%) died**
  - **103 (18.8%) switched to 2L**
  - **26 (4.7%) discontinued**

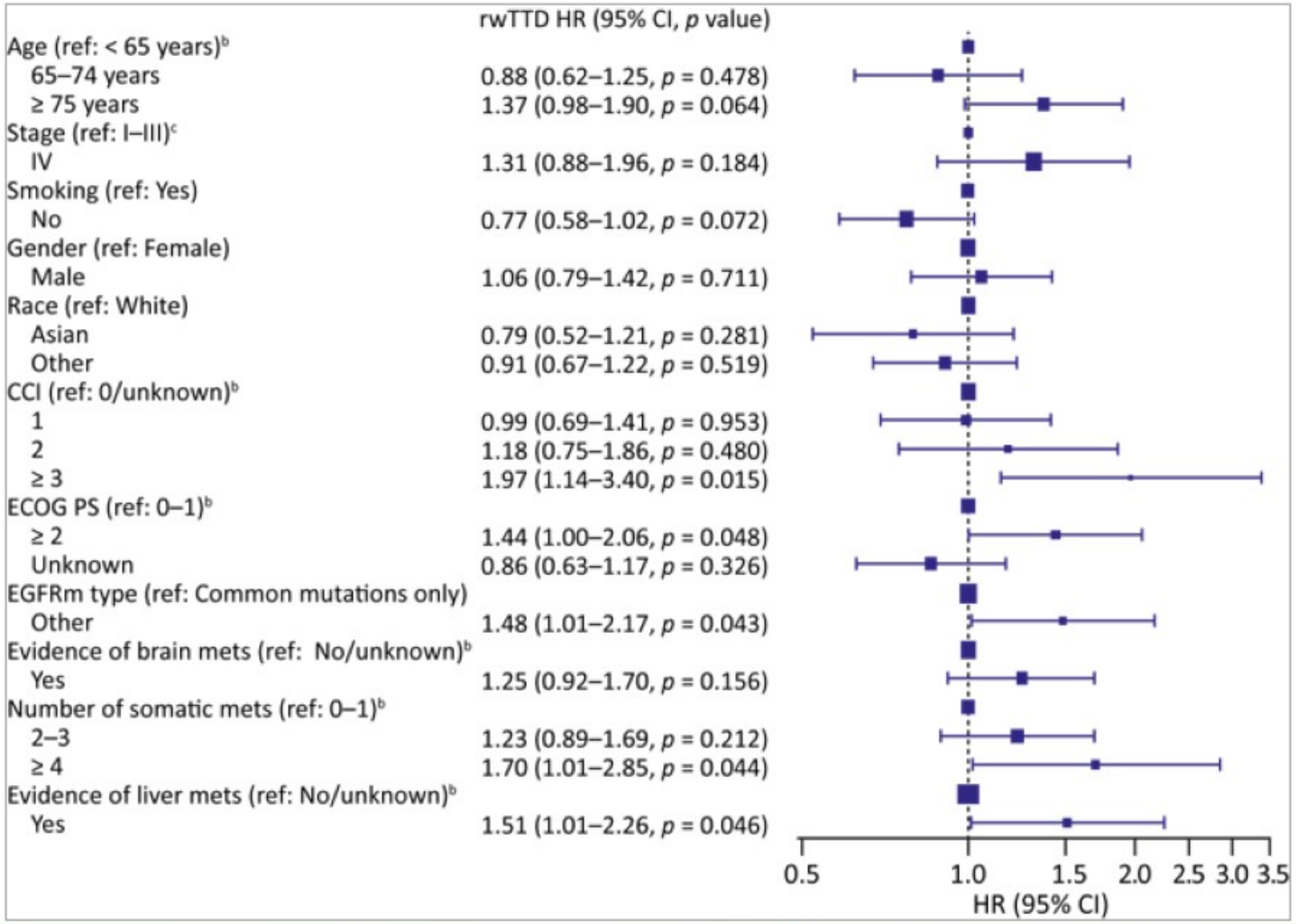


[a]Event date was defined as the earliest end date of osimertinib associated with discontinuation on or prior to the end of 1L therapy; data were censored at the earliest of the end date of the last episode of osimertinib treatment or the end of 1L osimertinib therapy

1L, first-line; rwTTD, real-world time to treatment discontinuation

REAL WORLD TIME TO TREATMENT DISCONTINUATION (rwTTD)

- **In the multivariate analysis, the following variables were significantly associated with rwTTD[a]**
  - **Charlson comorbidity index ≥ 3**
  - **ECOG performance status ≥ 2**
  - ***EGFR* mutation type**
  - **Number of metastatic sites ≥ 4**
  - **Evidence of liver metastases**



[a]Statistical significance threshold was 0.05 (two-sided); there were no adjustments for multiple testing; [b]At index date; [c]Stage at initial diagnosis, before progressing to advanced NSCLC

1L, first-line; CCI, Charlson comorbidity index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HR, hazard ratio; mets, metastases; PS, performance status; ref, reference; rwTTD, real-world time to treatment discontinuation

TAKE HOME MESSAGES

- The study provides real-world insights into the use of 1L osimertinib in patients with advanced EGFRm NSCLC, based on the first data-cut analysis of the US subpopulation
- The interim rwTTNTD and rwTTD results support the effectiveness of osimertinib in this real-world population
- Longer-term outcomes will be evaluated in final analysis

1L, first-line; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non-small cell lung cancer; PFS, progression-free survival; rwTTD, real-world time to treatment discontinuation; rwTTNTD, real-world time to next treatment or death

OSIMERTINIB TABLETS
TAGRISSO™ 40 mg & 80 mg
Abbreviated Prescribing Information
QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 80 mg tablet contains a dose of 80 mg osimertinib (as mesylate).
Each 40 mg tablet contains a dose of 40 mg osimertinib (as mesylate).
THERAPEUTIC INDICATIONS
Osimertinib as monotherapy is indicated for:
•The adjuvant treatment after complete tumour resection in patients with non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.
•The first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC whose tumours have epidermal growth receptor (EGFR exon 19 deletions or exon 21 (L858R) substitutions mutations.
•The treatment of patient with metastatic epidermal growth factor receptor (EGFR T790M mutation -positive non-small cell lung cancer (NSCLC as detected by an appropriate test, whose disease has progressed on or after EGFR TKI therapy
POSOLOGY AND METHOD OF ADMINISTRATION
The recommended dose is 80 mg osimertinib once a day with or without food, at the same time each day.
•Patients in the adjuvant setting should receive treatment until disease recurrence or unacceptable toxicity. Treatment duration for more than 3 years was not studied.
•Patients with locally advanced or metastatic lung cancer should receive treatment until disease progression or unacceptable toxicity.
If a dose of TAGRISSO is missed, the dose should be made up unless the next dose is due within 12 hours.
CONTRAINDICATIONS
None **WARNINGS & PRECAUTIONS**
•**Assessment of EGFR mutation status** When considering the use of TAGRISSO as adjuvant treatment after complete tumour resection in patients with NSCLC, EGFR mutation positive status (exon 19 deletions or exon 21 (L858R) substitution mutations) indicates treatment eligibility. A validated test should be performed in aclinical laboratory using tumour tissue DNA from biopsy or surgical specimen.When considering the use of TAGRISSO as a treatment for locally advanced or metastatic NSCLC, it is important that the EGFR mutation positive status is determined. A validated test should be performed using either tumour DNA derived from a tissue sample or circulating tumour DNA(ctDNA) obtained from a plasma sample.
Only robust, reliable and sensitive tests with demonstrated utility for the determination of EGFR mutation status should be used.Positive determination of EGFR mutation status (activating EGFR mutations for first-line treatment or T790M mutations following progression on or after EGFR TKI therapy) using either a tissue-based or plasma-based test indicates eligibility for treatment with TAGRISSO.However, if a plasma-based ctDNA test is used and the result is negative, it is advisable to follow-up with a tissue test wherever possible due to the potential for false negative results using a plasma-based test.I**nterstitial lung disease (ILD) -** Withhold TAGRISSO and promptly investigate for ILD in any patient who presents with worsening of respiratory symptoms which may be indicative of ILD (e.g. dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmedPlease refer to full prescribing information.**Erythema multiforme and Stevens-Johnson syndrome-** Case reports of Erythema multiforme (EM) and Stevens-Johnson syndrome (SJS) have been rarely reported, in association with TAGRISSO treatment. If signs and symptoms suggestive of SJS appear, TAGRISSO should be interrupted or discontinued immediately.**QTc interval prolongation -** When possible, avoid use of TAGRISSO in patients with congenital long QT syndrome. Consider periodic monitoring with electrocardiograms (ECGs) and electrolytes in patients with congestive heart failure, electrolyte abnormalities, or those who are taking medications that are known to prolong the QTc interval.**Changes in cardiac contractility -** In patients with cardiac risk factors and those with conditions that can affect LVEF, cardiac monitoring, including an assessment of LVEF at baseline and during treatment, should be considered. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered.
•**Keratitis** - Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist.
FERTILITY, PREGNANCY AND LACTATION
•Women of childbearing potential should be advised to avoid becoming pregnant while receiving TAGRISSO.TAGRISSO is not recommended during pregnancy and in women of childbearing potential not using contraception. Breast-feeding should be discontinued during treatment with TAGRISSO..Results from animal studies have shown that TAGRISSO has effects on male and female reproductive organs and could impair fertility.
UNDESIRABLE EFFECTS
The safety data of reflect exposure to TAGRISSO in 1479 patients with EGFR mutation-positive non-small cell lung cancer. These patients received TAGRISSO at a dose of 80 mg daily in three randomised Phase 3 studies (ADAURA Adjuvant, FLAURA, first line and AURA3, second line only), two single-arm studies (AURAex and AURA2, second line or greater) and one Phase 1 study (AURA1, first-line or greater). Most adverse reactions were Grade 1 or 2 in severity.
The most commonly reported adverse drug reactions (ADRs) were diarrhoea (47%) rash (45%), paronychia (33%), dry skin (32%), and stomatitis (24%). Grade 3 and Grade 4 adverse reactions with Tagrisso were 8.5% and 0.1%, respectively. I
n patients treated with TAGRISSO 80 mg once daily, dose reductions due to adverse reactions occurred in 3.2 % of the patients. Discontinuation due to adverse reactions was 4.6%.
Please refer to full prescribing information or detailed assessment of adverse events.**INTERACTIONS**It is recommended that concomitant use of strong CYP3A inducers with TAGRISSO should be avoided. If not possible, then increase TAGRISSO dose to 160 mg during the treatment with strong CYP3A inducer and resume at 80 mg, 3 weeks after discontinuation of the strong CYP3A inducer. No dose adjustments are required when TAGRISSO is used with moderate and/or weak CYP3A inducers. CYP3A4 inhibitors are not likely to affect the exposure of osimertinib. Gastric pH modifying agents can be concomitantly used with TAGRISSO without any restrictions. Patients taking concomitant medications with disposition dependent upon BCRP and with narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving TAGRISSO.
PHARMACOLOGICAL PROPERTIES *Mechanism of action*
Osimertinib is a Tyrosine Kinase Inhibitor (TKI). It is an oral potent and selective irreversible inhibitor of Epidermal Growth Factor Receptors (EGFRs) harboring sensitising mutations (EGFRm) and TKI-resistance mutation T790M.
Pharmacokinetic properties
Based on population pharmacokinetic analysis, osimertinib apparent plasma clearance is 14.3 L/h, apparent volume of distribution is 918 L and terminal half-life of approximately 44 hours.
***PHARMACEUTICAL PARTICULARS* EXCIPIENTS** Tablet core :- Mannitol, Microcrystalline cellulose, Low-substituted hydroxpropyl cellulose, Sodium stearyl fumarate.Tablet coating:- Polyvinyl alcohol, Titanium dioxide, Macrogol 3350, Talc, Yellow iron oxide, Red iron oxide & Black iron oxide. **SHELF LIFE**3 years. **STORAGE** This medicinal product does not require any special storage conditions. **PRESENTATION** Film-coated tablet (tablet). The TAGRISSO 80 mg tablet is a beige, 7.25 x 14.5 mm, oval, biconvex tablet, debossed with “AZ” and “80” on one side and plain on the reverse.
The TAGRISSO 40 mg tablet is a beige, 9 mm, round, biconvex tablet, debossed with “AZ” and “40” on one side and plain on the reverse.
Tagrisso™ is a trademark of AstraZeneca Group Companies.
TM: Trademark Applied for
For full prescribing information, please contact: AstraZeneca India Pharma Ltd. Block N1, 12th Floor, Manyata Embasssy Business Park, Rachenahalli, Outer Ring Road, Bangalore – 560045. www.astrazeneca.india.com. For more information please refer Prescribing information version 4 dated 10th March 2021

THANK YOU!