#ESMOUPDATES

Iniciativa científica de:

GECP lung cancer research

LUNG CANCER UPDATES

ESMO HIGHLIGHTS

27 SEPTIEMBRE - 1 OCTUBRE 2019

Con la colaboración de:

Bristol-Myers Squibb

illumina

Lilly

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Terapias dirigidas (I)

Dra. Noemí Reguart

Con la colaboración de:
Bristol-Myers Squibb
illumina
Lilly

Targeted Therapies (Friday 27, Saturday 28)

LUNG CANCER UPDATES
ESMO HIGHLIGHTS
27 SEPTIEMBRE - 1 OCTUBRE 2019

Friday 27.09.2019

Proffered Paper 1 - NSCLC, metastatic (ID 247)

- **1478O-** Results of the **ASCEND-7** phase II study evaluating ALK inhibitor ceritinib in patients with ALK+ non-small cell lung cancer metastatic to the brain (ID 4884). *Presenter Laura Q. Chow*

Saturday 28.09.2019

Presidential Symposium I (ID 263)

- **LBA5_PR-** Osimertinib vs comparator EGFR-TKI as first-line treatment for EGFRm advanced NSCLC **(FLAURA): Final overall survival analysis** (ID 567). *Presenter Suresh S. Ramalingam*

Poster Discussion – Developmental Therapeutics (ID 256)

- **LBA28-** Genomic landscape of **entrectinib resistance** from ctDNA analysis in STARTRK2. Doebele RC.
- **444PD-** Safety and preliminary clinical activity of **Repotrectinib** in pts with advanced **ROS/NTRK** fusion-positive solid tumors **(TRIDENT-1 study).** *Presenter Drillon.*
- **445PD-** Durability of response with **Larotrectinib** in adult and pediatric pts with **NTRK.** *Presenter Hyman*
- **446PD -** Phase I study of **AMG 510**, a novel molecule targeting KRAS G12C mutant solid tumours

Poster Display Session (NSCLC metastasic)

- **1532P-** Afatinib followed by Osimertinib in pts with EGFRm+ advanced NSCLC: updated data from the **GioTag real-world study**. *Presenter Hochmair*

Iniciativa científica de:
GeCP lung cancer research

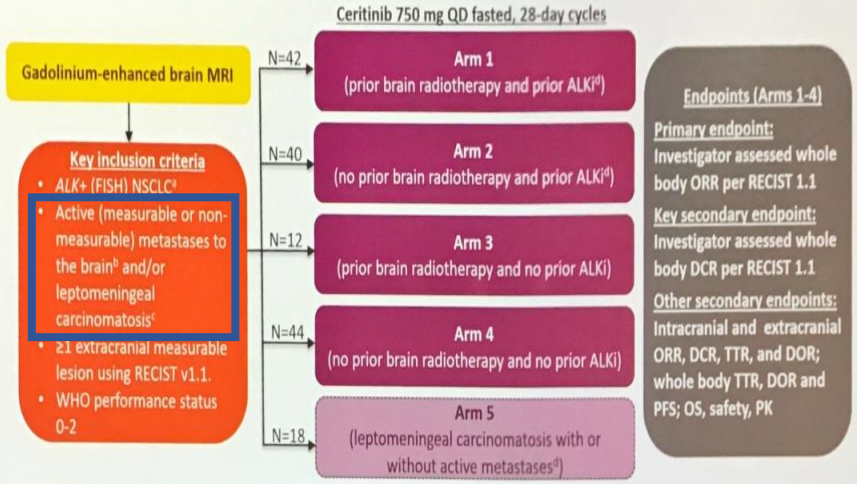
1478O- Results of the ASCEND-7 phase II study evaluating ALK inhibitor ceritinib in patients with ALK+ non-small cell lung cancer metastatic to the brain (ID 4884). Presenter *Laura Q. Chow*

BRAIN METASTASIS IN *ALK*+ NSCLC

- Brain metastases (BM) occur in approximately 30–50% of *ALK*+ NSCLC pts and are associated with poor outcomes.[1-3]
  - Crizotinib is approved for *ALK*+ NSCLC, however, acquired resistance usually develops within 1–2 years in responders and frequent progression in the brain has been reported.[4-8]
- Ceritinib is a second-generation ALKi approved for the treatment of pts with metastatic *ALK*+ NSCLC and has demonstrated promising intracranial antitumor activity.[9-12]
- The ASCEND-7 study (NCT02336451) is a phase II, open-label, multi-center, 5-arm study specifically evaluating the antitumor activity of ceritinib in pts with *ALK*+ NSCLC metastatic to the brain or leptomeninges.
- We report here the efficacy, pharmacokinetics and safety in pts with *ALK*+ NSCLC metastatic to the brain (Arms 1-4).

1. Ali A, *et al. Curr Oncol* 2013;20:e300–e306; 2. Gaspar LE, *et al. J Clin Oncol* 2005;23:2955–2961; 3. Sperduto PW, *et al. J Clin Oncol* 2012;30:419–425; 4. Solomon BJ, *et al. N Engl J Med* 2014;371:2167–2177; 5. Shaw AT, *et al. N Engl J Med* 2013;368:2385–2394; 6. Doebele RC, *et al. Clin Cancer Res* 2012;18:1472–1482; 7. Shaw AT, Engelman JA. *J Clin Oncol* 2013;31:1105–1111; 8. Costa DB, *et al. J Clin Oncol* 2015;33:1881–1888; 9. Friboulet L, *et al. Cancer Discov* 2014;4:662–673; 10. Novartis. Zykadia™ FDA-approved prescribing information; T2016-74/75. Issued September 2016; 11. Kim D-W, *et al. Lancet Oncol* 2016;17:452–463; 12. Felip E, *et al. J Clin Oncol* 2015;33(15s); abstract 8060.
ALKi, Anaplastic lymphoma kinase inhibitor; NSCLC, non-small cell lung cancer; pts, patients; WBRT, whole brain radiation therapy

ASCEND-7 STUDY DESIGN



- Intracranial and extracranial responses were assessed using modified RECIST 1.1 and RECIST 1.1, respectively.
  - As per modified RECIST, the usual criteria to select target lesions were used but maximum five target lesions located in the brain could be selected at baseline and evaluated at each assessment time point.

[a] according to 7th edition of the American Joint Committee on Cancer
[b] Lesion free of local treatment (stereotactic or WBRT) or lesions in unequivocal progression after radiotherapy
[c] diagnosis requires either documentation of the presence of malignant cells detected at the cytological examination of CSF or serious suspicion of LC supported by imaging findings
[d] Previous treatment with ALKi other than crizotinib was not allowed

1478O- Results of the ASCEND-7 phase II study evaluating ALK inhibitor ceritinib in patients with ALK+ non-small cell lung cancer metastatic to the brain (ID 4884). *Presenter Laura Q. Chow*

WHOLE BODY BEST OVERALL RESPONSE PER INVESTIGATOR ASSESSMENT

Rapid response with a high DCR was seen across all 4 arms
Investigator assessed response was consistent with blinded independent review committee assessment

	ARM 1 Prior brain RT/ prior ALKi N=42	ARM 2 No prior brain RT/ prior ALKi N=40	ARM 3 Prior brain RT/ No prior ALKi N=12	ARM 4 No prior brain RT or ALKi N=44
Best overall response, n (%)				
Partial response (PR)	15 (35.7)	12 (30.0)	6 (50.0)	26 (59.1)
Stable disease (SD)	13 (31.0)	21 (52.5)	2 (16.7)	5 (11.4)
Progressive disease (PD)	7 (16.7)	6 (15.0)	1 (8.3)	7 (15.9)
Unknown	7 (16.7)	1 (2.5)	3 (25.0)	6 (13.6)
Overall response rate (CR+PR), % (95% CI)	**35.7** (21.6, 52.0)	**30.0** (16.6, 46.5)	**50.0** (21.1, 78.9)	**59.1** (43.2, 73.7)
Disease control rate (CR+PR+SD), % (95% CI)	**66.7** (50.5, 80.4)	**82.5** (67.2, 92.7)	**66.7** (34.9, 90.1)	**70.5** (54.8, 83.2)

INTRACRANIAL RESPONSE BY MODIFIED RECIST AS PER INVESTIGATOR ASSESSMENT

	ARM 1 Prior brain RT/ prior ALKi	ARM 2 No prior brain RT/ prior ALKi	ARM 3 Prior brain RT/ No prior ALKi	ARM 4 No prior brain RT or ALKi
Pts with measurable and non measurable brain metastases	N=42	N=40	N=12	N=44
Best overall response, n (%)				
Complete response (CR)	0	0	0	1 (2.3)
Partial response (PR)	11 (26.2)	8 (20.0)	2 (16.7)	17 (38.6)
Stable disease (SD)	10 (23.8)	16 (40.0)	4 (33.3)	8 (18.2)
Progressive disease (PD)	4 (9.5)	5 (12.5)	0	4 (9.1)
Non-CR/Non-PD	9 (21.4)	10 (25.0)	3 (25.0)	7 (15.9)
Unknown	8 (19.0)	1 (2.5)	3 (25.0)	7 (15.9)
Overall response rate (CR+PR), % (95% CI)	26.2 (13.9, 42.0)	20.0 (9.1, 35.6)	16.7 (2.1, 48.4)	40.9 (26.3, 56.8)
Disease control rate (CR+PR+SD+Non-CR/Non-PD), % (95% CI)	71.4 (55.4, 84.3)	85.0 (70.2, 94.3)	75.0 (42.8, 94.5)	75.0 (59.7, 86.8)
	L=11	L=8	L=2	L=18
Median DOR, months (95% CI)	9.2 (3.7, NE)	10.1 (3.8, 17.3)	NE	8.1 (5.8, 11.2)
Pts with measurable brain metastases	M=28	M=29	M=7	M=33
Overall response rate (CR+PR), % (95% CI)	**39.3 (21.5, 59.4)**	**27.6 (12.7, 47.2)**	**28.6 (3.7, 71.0)**	**51.5 (33.5, 69.2)**
Disease control rate (CR+PR+SD), % (95% CI)	**75.0 (55.1, 89.3)**	**82.8 (64.2, 94.2)**	**85.7 (42.1, 99.6)**	**75.8 (57.7, 88.9)**
	L=11	L=8	L=2	L=17
Median DOR, months (95% CI)	9.2 (3.7, NE)	10.1 (3.8, 17.3)	NE	7.5 (5.6, 11.2)

M is the number of pts with measurable brain metastasis
L is the number of pts included in DOR analysis

FUTURE (II): ALL NEXT GEN TKI PROMISING, TRIAL COMPARISON DIFFICULT

SPECIFIC CNS TRIALS WITH NEXT GEN TKI NEEDED!

ALK-TKI	CNS ORR (%) TKI naive	CNS DoR (months) TKI naive	CNS ORR (%) TKI pretreated[2]	CNS DoR (months) TKI pretreated[2]
Crizotinib	18-40	3.7-26.4	NA	NA
Ceritinib	29-62	7.5	28-39	6.9-10.1
Alectinib	79	NR	64	10.8
Brigatinib	78	NA	53-67	NA – 18.9
Lorlatinib	77[1]	NR	53-87	14.5 - NR

NA: not available; NR: not reached;1: 2 out of 3 patients; 2: crizotinib and/or next gen TKI

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Costa JCO 2015 *Chow ESMO 2019 * Soria Lancet 2017 *Gadgeel JCO 2016 *Solomon Lancet Oncol 2018 * Gadgeel Ann Oncol 2018 *Shaw Lancet Oncol 2017 * Gettinger Lancet Oncol 2016 * Camidge NEJM 2018

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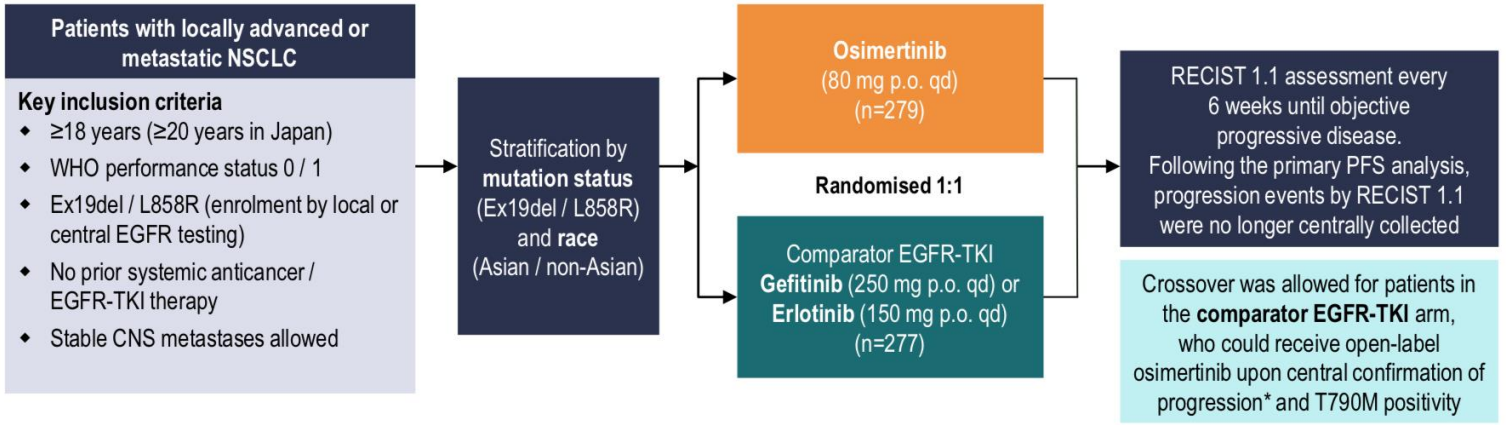
OSIMERTINIB VS COMPARATOR EGFR-TKI AS FIRST-LINE TREATMENT FOR EGFRm ADVANCED NSCLC (FLAURA): FINAL OVERALL SURVIVAL ANALYSIS

Suresh S Ramalingam[1], Jhanelle E Gray[2], Yuichiro Ohe[3], Byoung Chul Cho[4], Johan Vansteenkiste[5], Caicun Zhou[6], Thanyanan Reungwetwattana[7], Ying Cheng[8], Busayamas Chewaskulyong[9], Riyaz Shah[10], Ki Hyeong Lee[11], Parneet Cheema[12], Marcello Tiseo[13], Thomas John[14], Meng-Chih Lin[15], Fumio Imamura[16], Rachel Hodge[17], Yuri Rukazenkov[17], Jean-Charles Soria[18,19], David Planchard[19]

[1]Emory University, Winship Cancer Institute, Atlanta, GA, USA; [2]Department of Thoracic Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; [3]Department of Internal Medicine, National Cancer Center Hospital, Tokyo, Japan; [4]Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [5]University Hospital KU Leuven, Leuven, Belgium; [6]Pulmonary Hospital of Tongji University, Shanghai, China; [7]Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [8]Jilin Provincial Cancer Hospital, Changchun, China; [9]Oncology Unit, Department of Medicine, Chiang Mai University, Chiang Mai, Thailand; [10]Kent Oncology Centre, Maidstone Hospital, Maidstone and Tunbridge Wells NHS Trust, Maidstone, UK; [11]Division of Medical Oncology, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheong-ju, Korea; [12]William Osler Health System, University of Toronto, Toronto, ON, Canada; [13]Medical Oncology Unit, University Hospital of Parma, Parma, Italy; [14]Department of Medical Oncology, Austin Health, Melbourne, Australia; [15]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan; [16]Department of Thoracic Oncology, Osaka International Cancer Institute, Chuo-ku, Osaka, Japan; [17]Global Medicines Development, AstraZeneca, Cambridge, UK; [18]Early Oncology Research & Development, AstraZeneca, Gaithersburg, Maryland / Université Paris-Sud, Orsay, France; [19]Department of Medical Oncology, Gustave Roussy, Villejuif, France

LBA5_PR- Osimertinib vs comparator EGFR-TKI as first-line treatment for EGFRm advanced NSCLC (FLAURA): Final overall survival analysis (ID 567). *Presenter Suresh S. Ramalingam*

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 treatment

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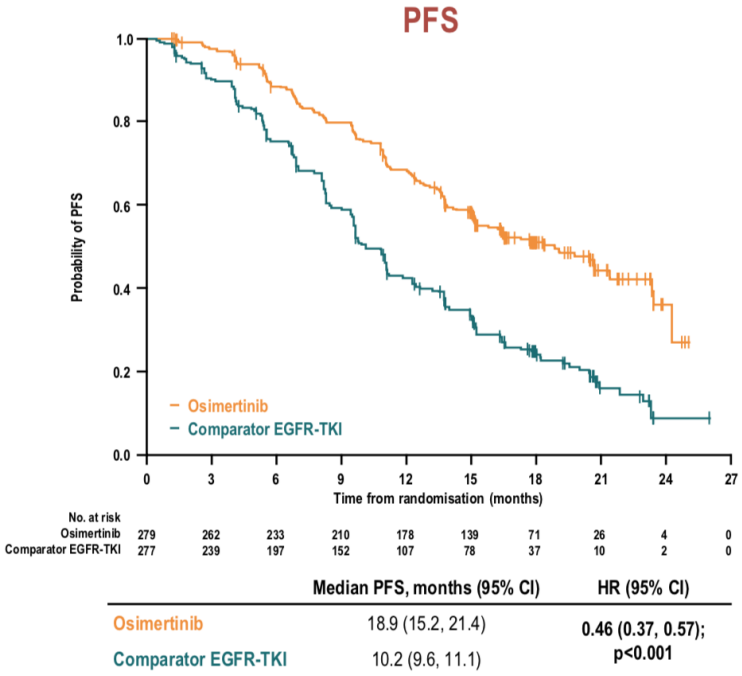
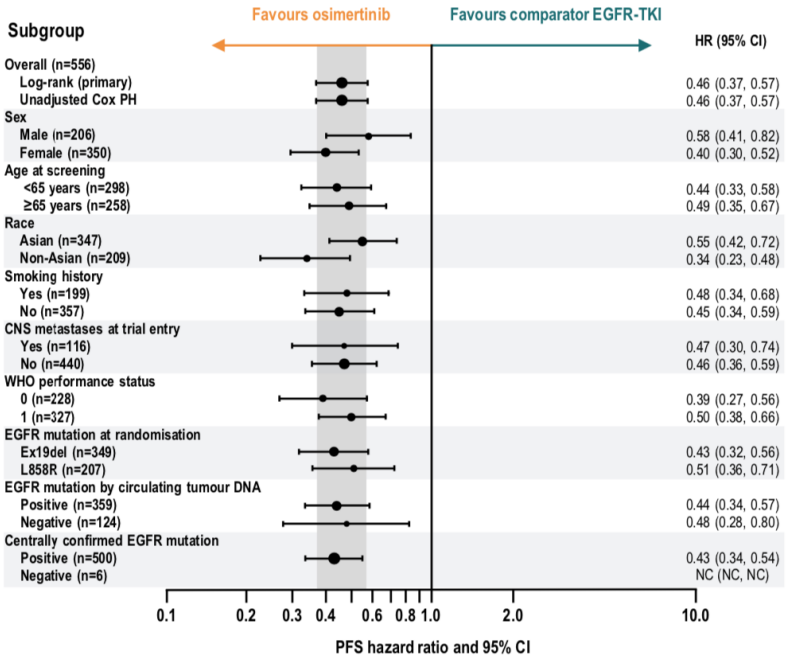
Data cut-off: 25 June 2019
Soria et al. N Engl J Med 2018;378:113-25
*By investigator assessment if disease progression occurred after the primary analysis data cut-off
p.o., orally; qd, once daily; RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1; WHO, World Health Organization

LBA5_PR- Osimertinib vs comparator EGFR-TKI as first-line treatment for EGFRm advanced NSCLC (FLAURA): Final overall survival analysis (ID 567). *Presenter Suresh S. Ramalingam*

PRIMARY ANALYSIS: PROGRESSION-FREE SURVIVAL



	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)	



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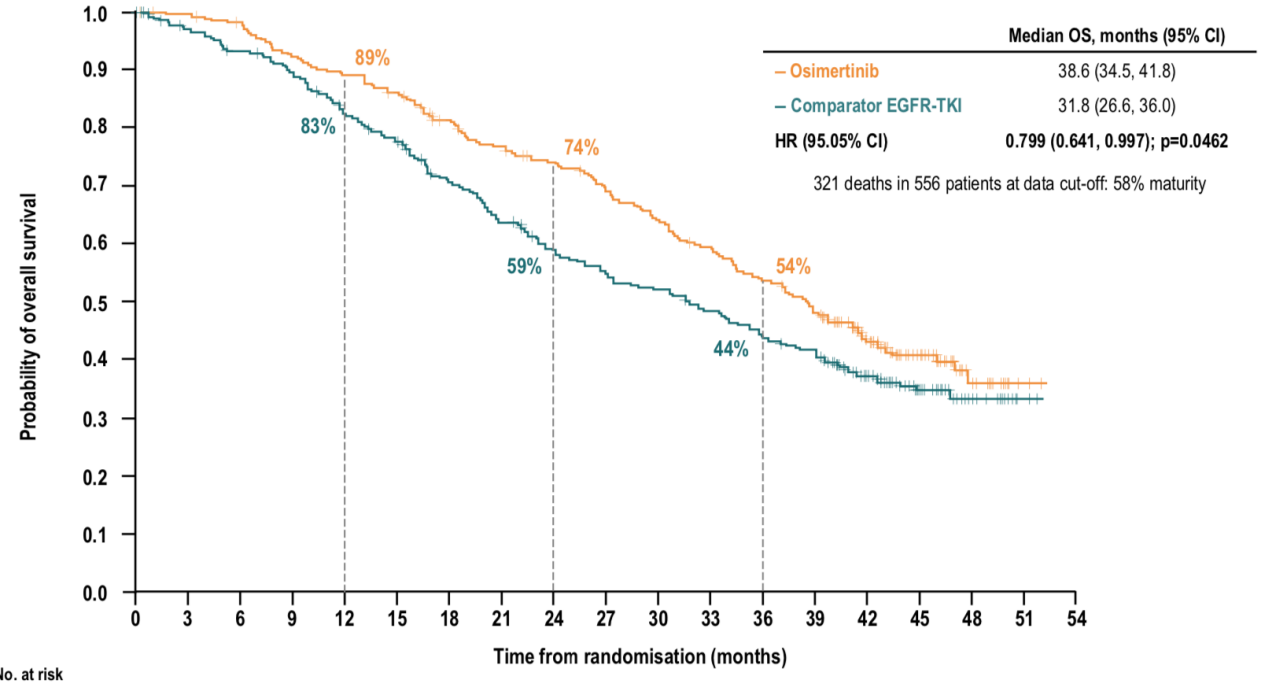
Data cut-off: 12 June 2017

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

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

LBA5_PR- Osimertinib vs comparator EGFR-TKI as first-line treatment for EGFRm advanced NSCLC (FLAURA): Final overall survival analysis (ID 567). *Presenter Suresh S. Ramalingam*

FINAL ANALYSIS: OVERALL SURVIVAL



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

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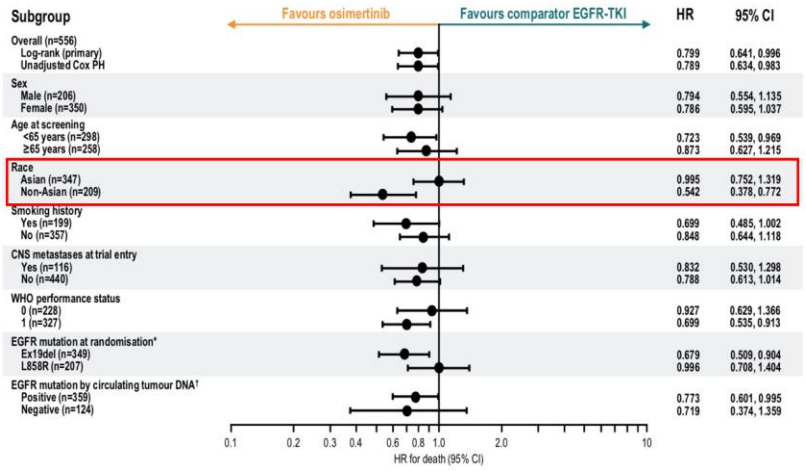
Data cut-off: 25 June 2019
For statistical significance, a p-value of less than 0.0495, determined by O'Brien-Fleming approach, was required

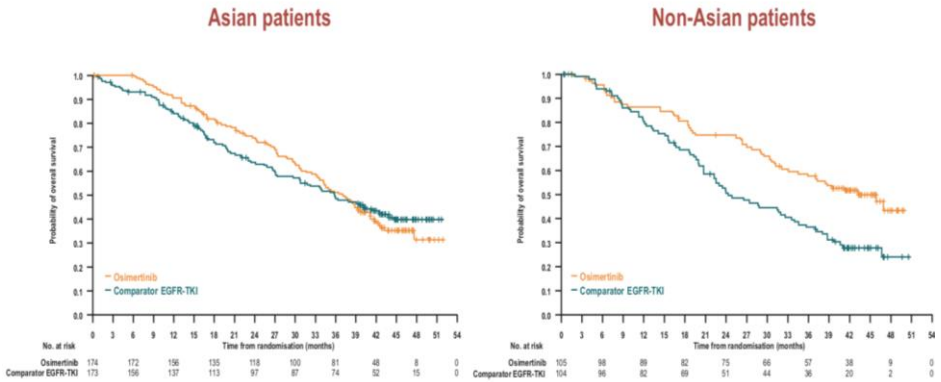
LBA5_PR- Osimertinib vs comparator EGFR-TKI as first-line treatment for EGFRm advanced NSCLC (FLAURA): Final overall survival analysis (ID 567). *Presenter Suresh S. Ramalingam*

OVERALL SURVIVAL ACROSS SUBGROUPS



Data cut-off: 25 June 2019
Hazard ratio <1 implies a lower risk of death on osimertinib
*Local or central test; †Result missing for 36 patients in the osimertinib arm and 37 patients in the comparator EGFR-TKI arm

OVERALL SURVIVAL IN ASIAN AND NON-ASIAN PATIENTS



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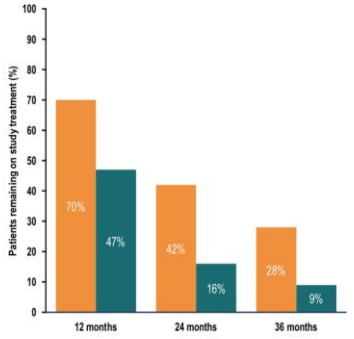
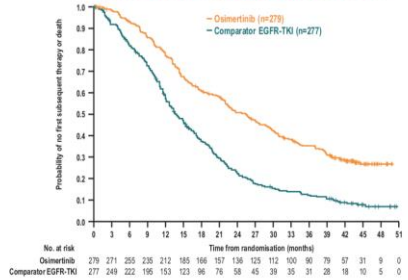
LBA5_PR- Osimertinib vs comparator EGFR-TKI as first-line treatment for EGFRm advanced NSCLC (FLAURA): Final overall survival analysis (ID 567). *Presenter Suresh S. Ramalingam*

PATIENTS REMAINING ON STUDY TREATMENT AND TIME TO FIRST SUBSEQUENT TREATMENT OR DEATH

Patients remaining on study treatment



Time to first subsequent treatment*



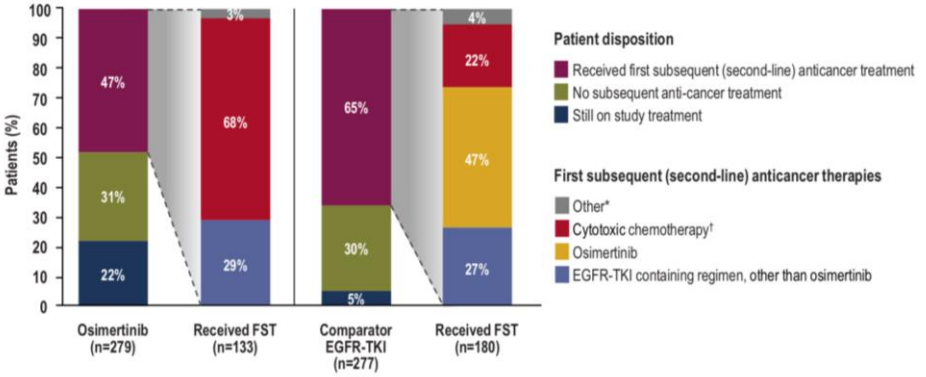
Time to first subsequent therapy or death	Events	Median, months (95% CI)
Osimertinib	194	25.5 (22.0, 29.1)
Comparator EGFR-TKI	242	13.7 (12.3, 15.7)
HR (95% CI)		0.478 (0.393, 0.581) p<0.0001

Data cut-off: 25 June 2019

*Time from the date of randomisation to the earlier of the date of anti-cancer therapy start date following study drug discontinuation or death

SECOND-LINE TREATMENT FOLLOWING PROGRESSION

- Of the 180 patients in the comparator EGFR-TKI arm who received a first subsequent treatment, **85 patients (47%) crossed over to osimertinib** (31% of all patients randomised from the comparator EGFR-TKI arm)



Data cut-off: 25 June 2019

*Refers to those patients who did not receive either chemotherapy or an EGFR-TKI; †The majority of patients who received cytotoxic chemotherapy received a platinum-based chemotherapy regimen
FST, first subsequent treatment

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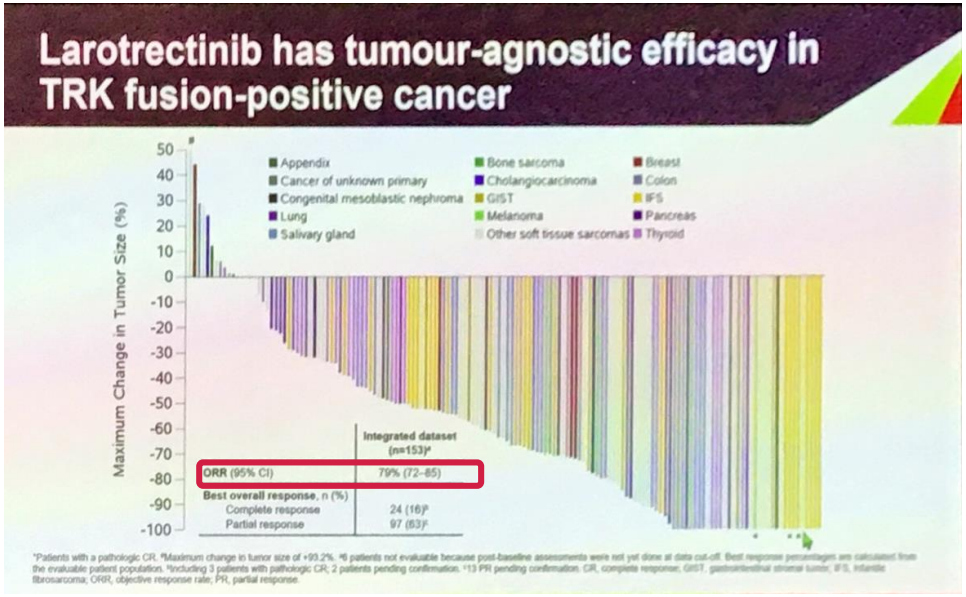
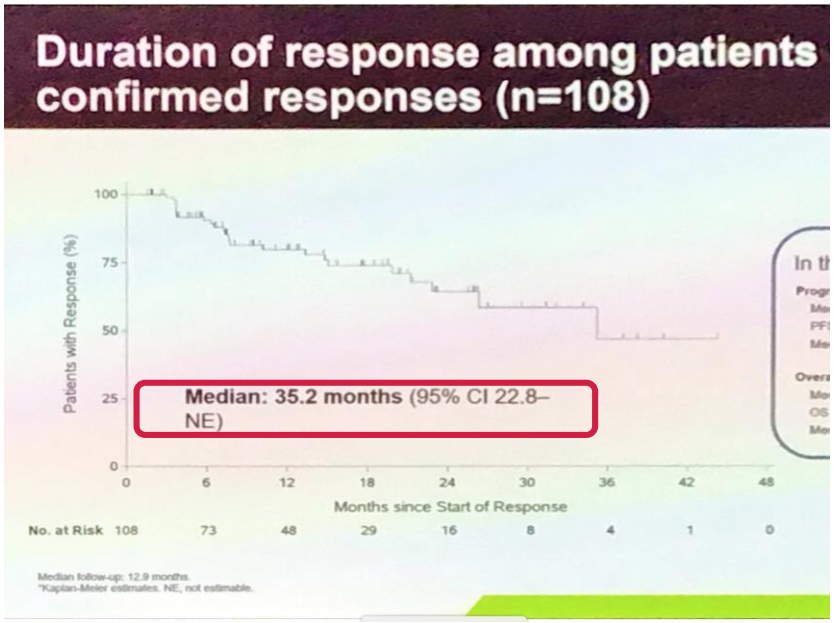
445PD- Durability of response with Larotrectinib in adult and pediatric pts with NTRK. *Presenter Hyman*

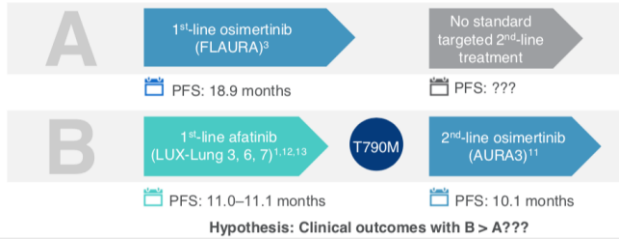




1532P- Afatinib followed by Osimertinib in pts with EGFRm+ advanced NSCLC: updated data from the GioTag real-world study. *Presenter Hochmair*

Rationale for sequential afatinib and osimertinib

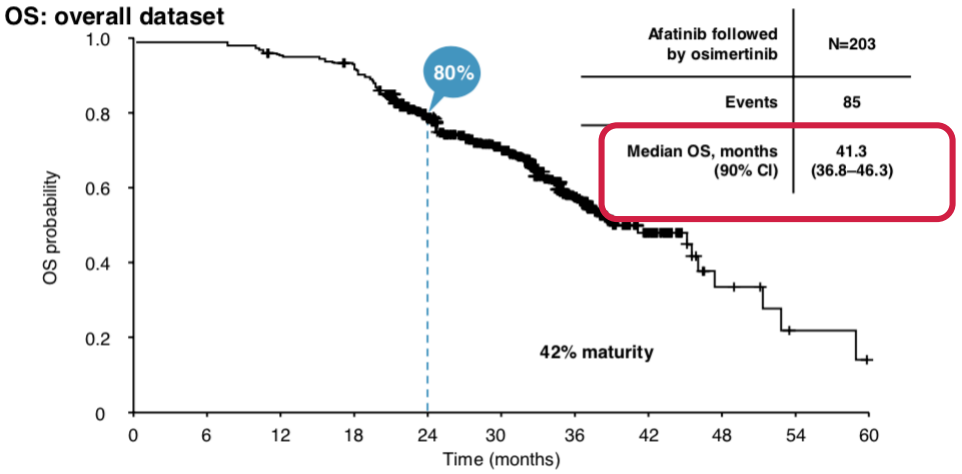
- Most patients progressing on afatinib will be eligible for second-line treatment with osimertinib
- Osimertinib has shown first- and second-line (against T790M) activity[3,11]
- There is currently no standard targeted treatment for patients progressing on osimertinib



- The GioTag study is a global observational study across 10 countries (Austria, Canada, Israel, Italy, Japan, Singapore, Slovenia, Spain, Taiwan and the USA)[14]
- A maximum of 15 consecutive patients were enroled from each site

The first global, observational study to evaluate outcomes of patients who received first-line afatinib followed by osimertinib (NCT03370770)

- Medical charts (62%) and electronic health records (38%) of consecutive patients treated in real-world practice were retrospectively reviewed
- Patients had *EGFR*m+ (Del19/L858R) TKI-naïve advanced NSCLC and were treated with first-line afatinib, developed T790M-mediated acquired resistance, and received second-line osimertinib treatment
- **Primary outcome:** TTF
- **Exploratory outcome:** OS



- Median follow-up 30.3 months
- Median OS almost 3.5 years and 80% of patients alive at 2 years
- In patients treated with 40 mg/day dose of afatinib, mOS 45.3 month
- Median TTF with osimertinib was 15.6 months, (AURA-3 10 mo)

444PD- Safety and preliminary clinical activity of Repotrectinib in pts with advanced ROS/NTRK fusion-positive solid tumors (TRIDENT-1 study). *Presenter Drillon.*

RESULTS: EFFICACY

Figure 3. Preliminary Efficacy of Repotrectinib in TKI-Naïve *ROS1*+ NSCLC by BICR

	TKI Naïve (N=11)
Confirmed ORR, n/N (%)	10/11 (91%)
95% CI (%)	(59 – 100)
ORR at 160mg QD or above	6/7 (86%)
Duration of response (DOR), months	
% DOR ≥ 18 months[1]	65%
Range	3.7+ – 23.3+
Intracranial ORR (IC-ORR)[2], n/N (%)	3/3 (100%)
95% CI (%)	(29 – 100)
Clinical Benefit Rate, n/N (%)	11/11 (100%)
95% CI (%)	(72 – 100)
Median follow-up time, months	20.1
Range	5.3 – 24.9+

- Median duration of response is not mature, 5 out of 10 (50%)* responders by BICR were ongoing without an event at the time of this analysis: 3.7+, 14.8+, 16.4+, 17.6+, and 23.3+ months.
- Duration of cPR in 3 patients with IC-ORR were 14.8+, 17.6+, and 23.1 months.

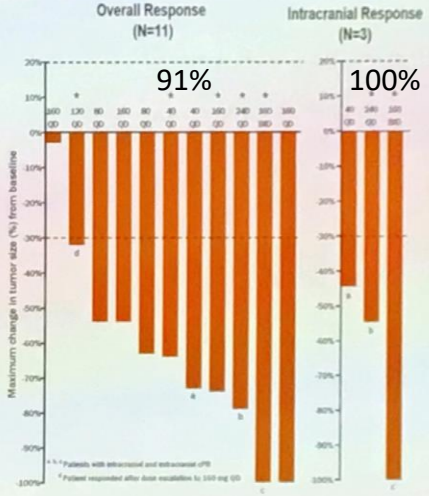
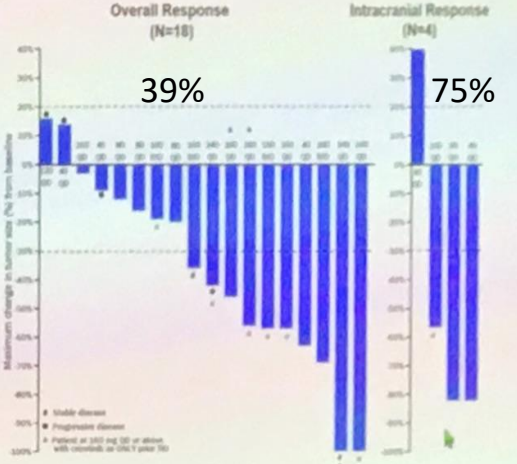


Figure 4. Preliminary Efficacy of Repotrectinib by BICR in Patients with *ROS1*+ NSCLC Pretreated with 1 TKI

	Pretreated with 1 PRIOR TKI (N=18)
Confirmed ORR, n/N (%)	7/18 (39%)
95% CI (%)	(17 – 64)
ORR at 160 mg QD or above	6/11 (55%)
IC-ORR[1], n/N (%)	3/4 (75%)
95% CI (%)	(19 – 99)
Clinical benefit rate, n/N (%)	14/18 (78%)
95% CI (%)	(52 – 94)
Median follow-up time, months[2]	7.3
Range	0.6 – 19.3+

* 2 of 7 patients remain in cPR both at 5.5+ months.



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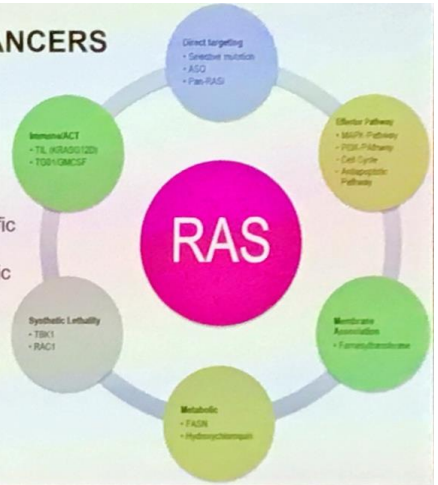
446PD - Phase I study of AMG 510, a novel molecule targeting KRAS G12C mutant solid tumours

TARGETING RAS-MUTANT CANCERS

- RAS genes are the most commonly mutated oncogenes in cancer – so far very limited success in targeting the *'undruggable'*.
- Recent approaches of directly targeting specific mutations (KRAS G12C) or indirectly through Effector- and Metabolic-Pathways, or Synthetic Lethality has resulted promising strategies.



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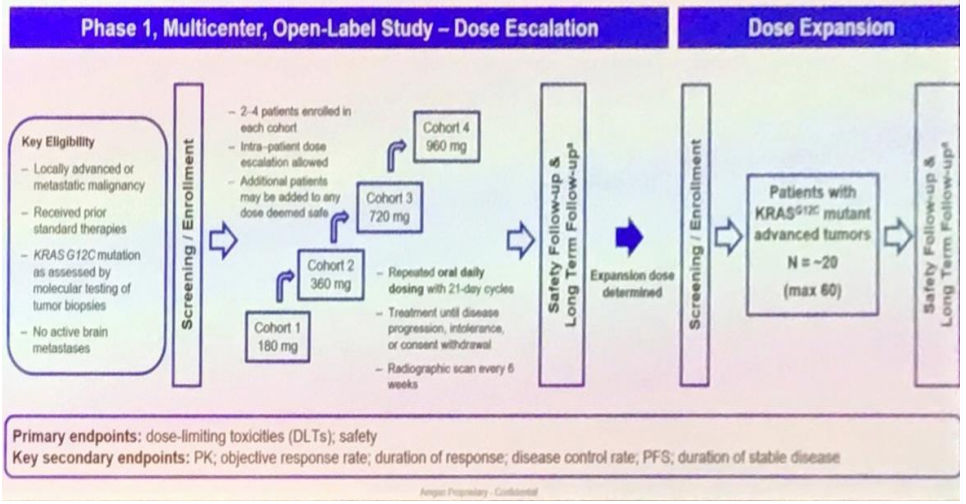
Study Design

- *KRAS G12C* mutation is found in approximately **1%–3% of solid tumors**[3] **and 13% of NSCLC**
- AMG 510 is a small molecule that specifically and irreversibly inhibits $KRAS^{G12C}$ by permanently locking it in an inactive GDP-bound state



446PD - Phase I study of AMG 510, a novel molecule targeting KRAS G12C mutant solid tumours

Patient Incidence of Adverse Events (AEs): Summary

	All AEs N = 76 n (%)	All treatment-related AEs N = 76 n (%)
Any grade Grade ≥ 2 Grade ≥ 3 Grade ≥ 4	57 (75.0) 44 (57.9) 24 (31.6) 8 (10.5)	26 (34.2) 14 (18.4) 6 (7.9) 0 (0.0)
Dose limiting toxicity	0 (0)	0 (0)
Serious adverse events	17 (22.4)	0 (0)[c]
Fatal adverse events	7 (9.2)[a]	0 (0)
AEs leading to treatment discontinuation	2 (2.6)[b]	0 (0)

- No dose limiting toxicities were reported
- No treatment-related serious or fatal AEs were reported
- There were no treatment-related AEs leading to treatment discontinuation

960mg oral daily dose was identified as the expansion dose and recommended phase 2 dose

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Best Tumor Response, All Tumor Types

All Dose Levels

Efficacy outcomes with all dose levels	NSCLC, evaluable patients N = 23	CRC, evaluable patients N = 29	Other tumor types, evaluable patients N = 3
Best overall response			
Partial response – n (%)	11 (48)	1 (3)	1 (33)[f]
Stable disease – n (%)	11 (48)	22 (76)	1 (33)[f]
Progressive disease – n (%)	1 (4)	6 (21)	1 (33)[f]
Objective response rate[a]	48%	3%	N/A
Disease control rate[b]	96%	79%	N/A

960mg Dose

Efficacy outcomes with 960mg dose	NSCLC, evaluable patients N = 13	CRC, evaluable patients N = 12	Other tumor types, evaluable patients N = 1
Best overall response			
Partial response – n (%)	7 (54)	1 (8)	0 (0)
Stable disease – n (%)	6 (46)	10 (83)	0 (0)
Progressive disease – n (%)	0 (0)	1 (8)	1 (100)[f]
Objective response rate[a]	54%	8%	N/A
Disease control rate[b]	100%	92%	N/A

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