IASLC 2023 World Conference on Lung Cancer
SEPTEMBER 9-12, 2023 | SINGAPORE

MARS2: a multicentre randomised trial comparing (extended) pleurectomy decortication versus no (extended) pleurectomy decortication for patients with malignant pleural mesothelioma

Chief Investigator:
Professor Eric Lim

Centres and PIs:
Barking, Havering & Redbridge, Dr Jonathan Shamash
Barts, Mr Kelvin Lau
Birmingham, Prof Gary Middleton
Bristol, Prof Nick Maskell
Cardiff, Dr Malgorzata Kornaszewska
Clatterbridge, Dr Anthony Pope
Colchester, Dr Dakshinamoorthy Muthukumar/Dr Charlotte Ingle
Derby, Dr Manjusha Keni
Glasgow Beatson, Dr Clinton Ali
Glasgow Golden Jubilee, Mr Alan Kirk
Guy's & St Thomas', Mr Andrea Bille
Leeds, Mr Richard Milton
Leicester, Prof Dean Fennell
Maidstone, Dr Riyaz Shah
Norwich, Dr Zacharias Tasigiannopoulos
Oxford, Prof Najib M Rahman
Papworth, Dr Robert Rintoul
Peterborough, Dr Sarah Treece
Plymouth, Dr Amy Roy
Royal Gwent, Dr Alina Ionescu
Royal Marsden, Prof Sanjay Popat
Sheffield, Mr John Edwards
South Tees, Dr Talal Mansy
South Tyneside, Dr Liz Fuller/Dr Andrew McNair
Wolverhampton, Mr Ian Morgan/Dr Pek Koh
Wythenshawe, Dr Paul Taylor

Independent Trial Steering Committee (TSC):
Prof Marcus Flather (Chair)
Dr Pauline Leonard (Previous Interim Chair)
Dr Paul Beckett
Ms Carol Tan
Prof Fergus Gleeson
Prof Fergus Macbeth
Prof David Rice
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Prof Tom Treasure (Past Chair, retired)
Prof Harvey Pass
Prof Rolf Stahel

Independent Data Monitoring Committee (DMC):
Prof Linda Sharples (Chair)
Prof Robin Rudd
Prof Mark Britton
Prof Valerie Rusch
Prof Peter Goldstraw (Retired)
Prof Joseph Friedberg

Bristol Trials Centre:
Dr Barbara Warnes
Miss Rosie Harris
Ms Kate Ashton
Miss Emma Bridgeman
Ms Surinder Kaur
Miss Samantha de Jesus
Miss Katie Joyce
Miss Holly Mckeon
Dr Athanasia Gravani
Miss Rachel Brophy
Mrs Wendy Underwood
Prof Chris Rogers

Quintet Recruitment Intervention:
Dr Daisy Elliott
Dr Nicola Mills
Dr Nicola Farrar

Trial Management Group (TMG):
Dr Robert Rintoul
Mr John Edwards
Mr David Waller
Mr Apo Nakas
Prof Dean Fennell
Prof Sanjay Popat
Ms Liz Darlison
Prof Nick Maskell
Dr Jeremy Steele

Health Economics:
Ms Liz Stokes

Sponsor:
Royal Brompton and Harefield Hospital, part of Guy's and St Thomas' NHS Foundation Trust

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NHS Guy's and St Thomas' NHS Foundation Trust

Marlene Bachler, Royal Brompton Hospital, London, United Kingdom

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mesothelioma

ESMO

SPECIAL ARTICLE

Malignant pleural mesothelioma: ESMO
diagnosis, treatment and follow-up☆

IASLC

SPECIAL ARTICLE

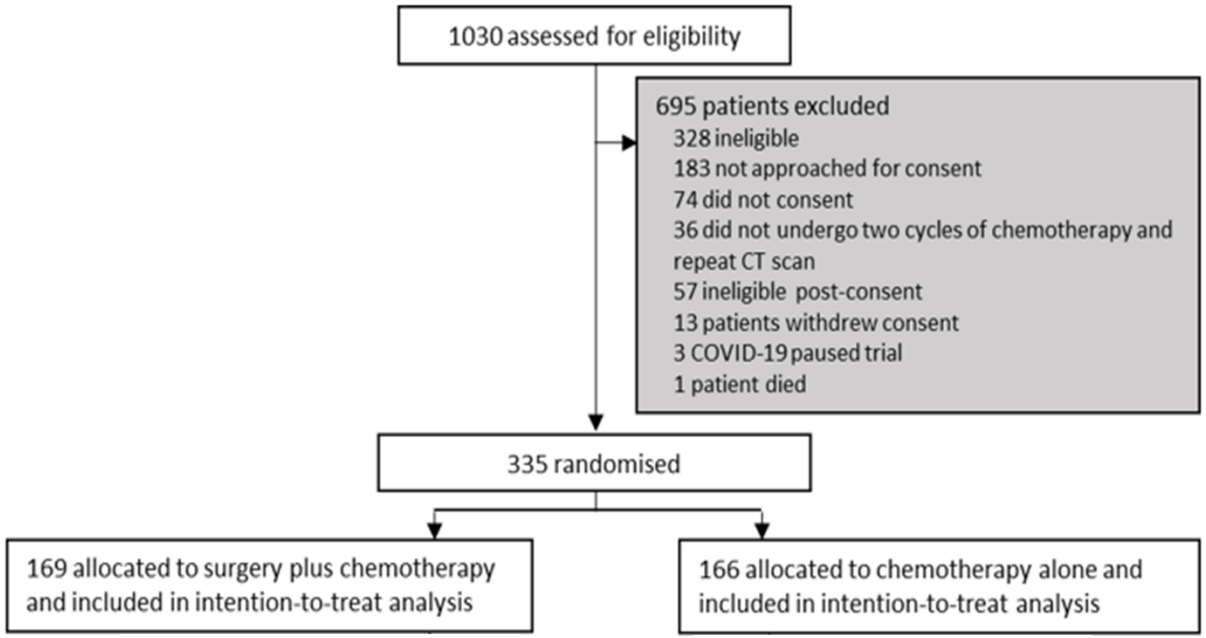
Check for updates

Current and Future Management of Malignant Mesothelioma: A Consensus Report from the National Cancer Institute Thoracic Malignancy Steering Committee, International Association for the Study of Lung Cancer, and Mesothelioma Applied Research Foundation

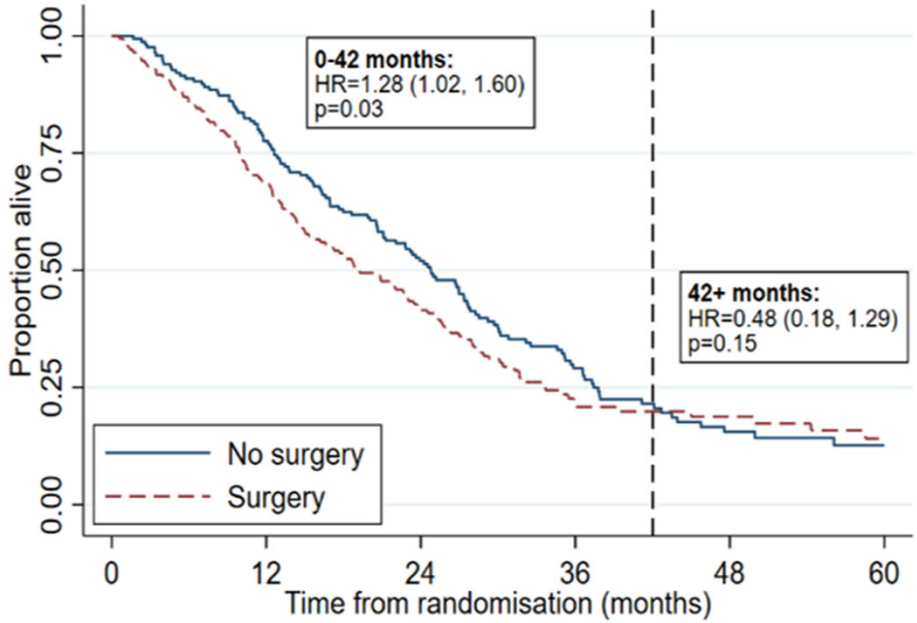
Anne S. Tsao, MD,[a] O. Wolf Lindwasser, PhD,[b] Alex A. Adjei, MD, PhD,[c] Prasad S. Adusumilli, MD,[d] Matthew L. Beyers, Msc,[e] Gideon M. Blumenthal, MD,[f] Raphael Bueno, MD,[g] Bryan M. Burt, MD,[h] Michele Carbone, MD, PhD,[i] Suzanne E. Dahlberg, PhD,[j] Marc de Perrot, MD, MSc,[k,l] Dean A. Fennell, M.B.B.S., PhD,[m,n] Joseph Friedberg, MD,[o] Ritu R. Gill, MPH,[p] Daniel R. Gomez, MD,[q] David H. Harpole Jr., MD,[r] Raffit Hassan, MD,[s] Mary Hesdorffer, NP,[t] Fred R. Hirsch, MD, PhD,[u] Julija Hmeljak, PhD,[v] Hedy L. Kindler, MD,[w] Edward L. Kom, PhD,[x] Geoffrey Liu, MD, PhD, MRCPC,[y] Aaron S. Mansfield, MD,[c] Anna K. Nowak, M.B.B.S., PhD,[z,aa] Harvey I. Pass, MD,[bb] Tobias Peikert, MD,[cc] Andreas Rimner, MD,[dd] Bruce W. S. Robinson, M.B.B.S., MD, FRACP, DTM&H,[ee,ff] Kenneth E. Rosenzweig, MD,[gg] Valerie W. Rusch, MD,[d] Ravi Salgia, MD, PhD,[hh] Boris Sepesi, MD,[ii] Charles B. Simone II, MD,[jj] Rajeshwari Sridhara, PhD,[e] Peter Szlosarek, MD, PhD,[kk] Emanuela Taioli, MD, PhD,[ll,mm] Ming-Sound Tsao, MD,[nn,oo] Haining Yang, MD, PhD,[h] Marjorie G. Zauderer, MD,[pp] Shakun M. Malik, MD[qq,*]

[a]Department of Thoracic/Head and Neck Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas
[b]Coordinating Center for Clinical Trials, National Cancer Institute, National Institutes of Health, Bethesda, Maryland
[c]Division of Medical Oncology, Mayo Clinic, Rochester, Minnesota
[d]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, New York
[e]Emmes Corporation, Rockville, Maryland
[f]U.S. Food and Drug Administration, Silver Spring, Maryland
[g]Thoracic Surgery, Brigham and Women's Hospital, Boston, Massachusetts
[h]Department of Surgery, Division of Thoracic Surgery, Baylor College of Medicine, Houston, Texas
[i]University of Hawaii Cancer Center, Honolulu, Hawaii
[j]Department of Biostatistics, Dana Farber Cancer Institute, Boston, Massachusetts
[k]Division of Thoracic Surgery, Toronto General Hospital, Toronto, Ontario, Canada
[l]Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada
[m]Department of Genetics and Genome Biology, University of Leicester, Leicester, United Kingdom
[n]University Hospitals of Leicester, Leicester, United Kingdom
[o]Department of Thoracic Surgery, University of Maryland Cancer Center, Baltimore, Maryland
[p]Department of Radiology, Brigham and Women's Hospital, Boston, Massachusetts
[q]Department of Radiation Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas
[r]Division of Cardiothoracic Surgery, Department of Surgery, Duke University, Durham, North Carolina
[s]Thoracic and GI Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland
[t]Mesothelioma Applied Research Foundation, Alexandria, Virginia
[u]University of Colorado Cancer Center, IASLC, Denver, Colorado
[v]The Company of Biologists, Cambridge, United Kingdom
[w]Department of Medicine, Section of Hematology/Oncology, University of Chicago, Chicago, Illinois
[x]Biometric Research Program, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Participant flow



Primary outcome - overall survival



Number at risk

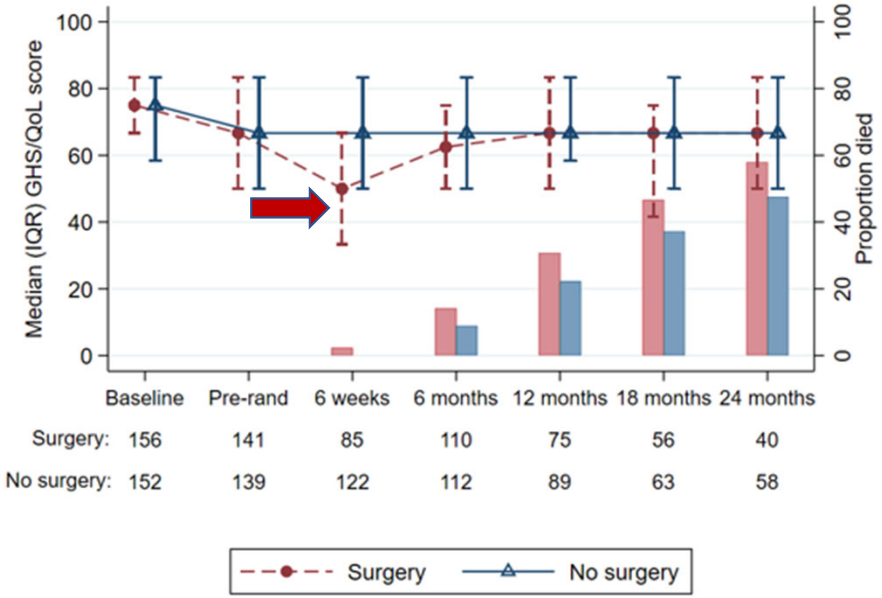
No surgery	166	128	82	37	15	6
Surgery	169	115	64	24	15	7

Safety

	Randomised to surgery (n=169)	Randomised to no surgery (n=166)	Effect (95% CI)	P value
Number of CTCAE grade 3+ events	1 (0, 3)	0 (0, 2)	IRR=3.6 (2.3, 5.5)	<0.001
0	62/169 (36.7%)	86/166 (51.8%)		
1	33/169 (19.5%)	38/166 (22.9%)		
2	22/169 (13.0%)	17/166 (10.2%)		
3	21/169 (12.4%)	12/166 (7.2%)		
4+	31/169 (18.3%)	14/166 (7.8%)		

Data are median (interquartile range) or n/N (%). CI=confidence interval, IRR=incidence rate ratio

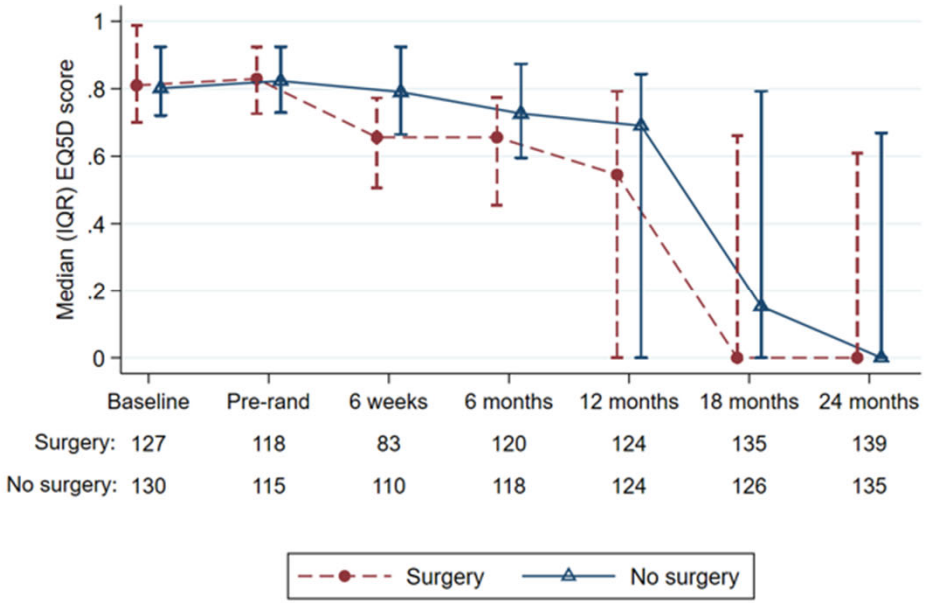
Quality of life EORTC



Outcome	Type of treatment effect estimate	Effect (95% CI)	p-value
Global health status/QoL	Test for time*treatment interaction		0.13
	Overall treatment effect	MD=-5.81 (-9.73, -1.89)	0.004
Physical functioning	Test for time*treatment interaction		0.002
	Treatment effect at 6 weeks	MD=-11.46 (-15.39, -7.52)	<0.001
	Treatment effect at 6 months	MD=-8.92 (-12.33, -5.51)	<0.001
	Treatment effect at 12 months	MD=-5.63 (-9.36, -1.91)	0.003
	Treatment effect at 18 months	MD=-2.34 (-7.27, 2.58)	0.35
	Treatment effect at 24 months	MD=0.95 (-5.60, 7.49)	0.78
Social functioning	Test for time*treatment interaction		0.16
	Overall treatment effect	MD=-10.87 (-16.07, -5.66)	<0.001
Role functioning	Test for time*treatment interaction		0.016
	Treatment effect at 6 weeks	MD=-15.77 (-22.03, -9.50)	<0.001
	Treatment effect at 6 months	MD=-13.05 (-18.61, -7.48)	<0.001
	Treatment effect at 12 months	MD=-9.51 (-15.41, -3.62)	0.002
	Treatment effect at 18 months	MD=-5.98 (-13.39, 1.44)	0.11
	Treatment effect at 24 months	MD=-2.44 (-12.01, 7.13)	0.62
Cognitive functioning	Test for time*treatment interaction		0.86
	Overall treatment effect	MD=-0.15 (-3.51, 3.22)	0.93
Emotional functioning	Test for time*treatment interaction		0.064
	Treatment effect at 6 weeks	MD=-1.04 (-4.73, 2.66)	0.58
	Treatment effect at 6 months	MD=0.28 (-3.05, 3.61)	0.87
	Treatment effect at 12 months	MD=1.99 (-1.64, 5.63)	0.28
	Treatment effect at 18 months	MD=3.70 (-0.93, 8.33)	0.12
	Treatment effect at 24 months	MD=5.41 (-0.57, 11.39)	0.076

CI=confidence interval, MD=mean difference. Scores range from 0 to 100. Higher scores represent higher levels of functioning.

Quality of life EQ5D

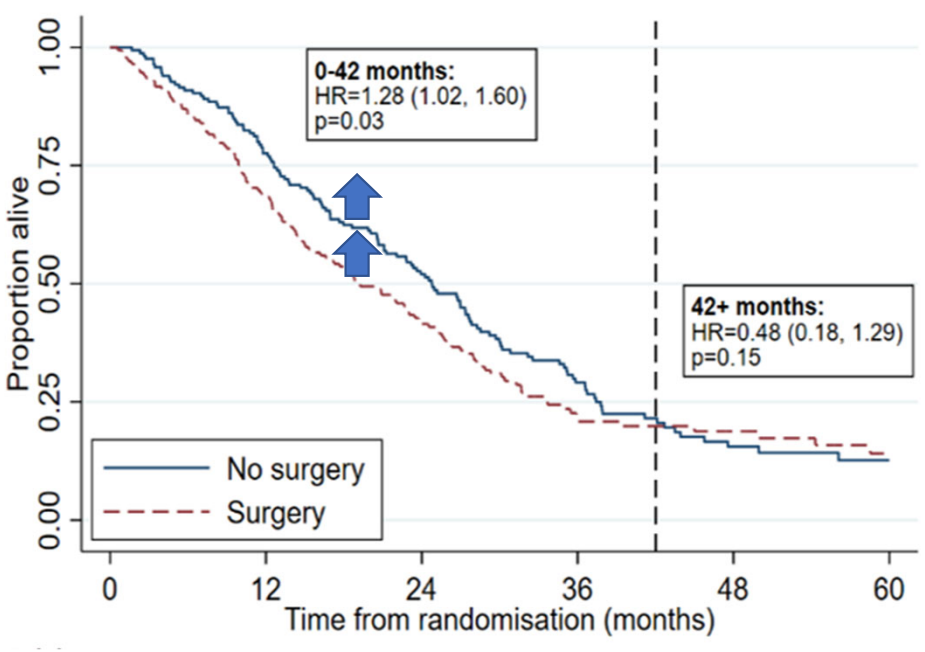


Outcome		Randomised to surgery (n=169)	Randomised to no surgery (n=166)	Effect (95% CI)	p-value
EQ5D utility score	Baseline*	0.81 (0.70, 0.99)	0.80 (0.72, 0.92)		
	Randomisation†	0.83 (0.73, 0.92)	0.82 (0.73, 0.92)		
	6 weeks‡	0.66 (0.51, 0.77)	0.79 (0.67, 0.92)		
	6 months§	0.66 (0.46, 0.77)	0.73 (0.59, 0.87)		
	12 months¶	0.55 (0.00, 0.79)	0.69 (0.00, 0.84)		
	18 months‖	0.00 (0.00, 0.66)	0.15 (0.00, 0.79)		
	24 months**	0.00 (0.00, 0.61)	0.00 (0.00, 0.67)		
Test for treatment*time interaction					0.15
Overall treatment effect estimate				MD=-0.11 (-0.15, -0.07)	<0.001

Data are median (interquartile range). CI=confidence interval, MD=mean difference. Scores range from -0.594 to 1. Higher scores indicate higher quality of life. Note EQ-5D was not collected in the pilot study. Missing data (surgery, no surgery): *78 patients with missing data (42, 36), †102 patients with missing data (51, 51), ‡ 123 patients with missing data (74, 39), § 80 patients with missing data (38, 42), ¶ 62 patients with missing data (31, 31), ‖ 59 patients with missing data (25, 34), ** 49 patients with missing data (27, 22).

Relinquishing the concept of "resectability"

- Increases survival by reducing the risk of death associated with surgery
- Open access to effective systemic treatments currently licensed for "unresectable" disease



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Slide 8

CR0 Why two blue arrow, where is the blue line going?
Chris Rogers, 2023-08-08T12:40:58.922

Conclusions

- Extended pleurectomy decortication for mesothelioma had:
  - higher risk of death
  - more serious complications
  - poorer quality of life
  - at higher cost of £14,631 ($20,102 USD)

…compared to those who were randomised to chemotherapy alone

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KRYSTAL-1: Two-Year Follow-Up of Adagrasib (MRTX849) Monotherapy in Patients With Advanced/Metastatic KRAS^{G12C}-Mutated NSCLC

Shirish M. Gadgeel[1], Pasi A. Jänne[2], Alexander I. Spira[3], Sai-Hong Ignatius Ou[4], Rebecca S. Heist[5], Jose M. Pacheco[6], Melissa L. Johnson[7], Joshua K. Sabari[8], Konstantinos Leventakos[9], Joshua A. Mason[10], Karen Velastegui[10], Xiaohong Yan[10], Richard Chao[10], Gregory J. Riely[11]

[1]Henry Ford Cancer Institute, Henry Ford Health System, Detroit, MI, USA; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]Virginia Cancer Specialists, Fairfax, VA, USA; US Oncology Research, The Woodlands, TX, USA; [4]University of California Irvine, Chao Family Comprehensive Center, Orange, CA, USA; [5]Massachusetts General Hospital, Boston, MA, USA; [6]University of Colorado Anschutz Medical Campus, Aurora, CO, USA; [7]Sarah Cannon Research Institute Tennessee Oncology, Nashville, TN, USA; [8]Perlmutter Cancer Center, New York University Langone Health, New York, NY, USA; [9]Mayo Clinic, Rochester, MN, USA; [10]Mirati Therapeutics, Inc., San Diego, CA, USA; [11]Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY, USA

Adagrasib (MRTX849) is a Differentiated KRAS^{G12C} Inhibitor

- Adagrasib, a covalent inhibitor of KRAS^{G12C}, was selected for favorable properties, including a long half-life (23 hours), dose-dependent PK, and CNS penetration[1–5]
- Based on Phase 2 Cohort A of the KRYSTAL-1 trial (n=116; median follow-up: 12.9 months; ORR: 42.9%; DOR: 8.5 months), adagrasib has been granted accelerated approval by the FDA in patients with previously treated KRAS^{G12C}-mutated NSCLC[6,7]

Key Eligibility Criteria[a]

- KRAS^{G12C}-mutated unresectable or metastatic NSCLC[b,c]
- ≥18-years-old
- ECOG PS 0–1
- Treated, stable CNS metastases were allowed

Phase 1/1b[5] Dose Escalation and Expansion	Phase 2 Cohort A[7] NSCLC Monotherapy Treatment
Adagrasib 600 mg BID N=16	**Adagrasib 600 mg BID N=116**
Key Endpoints: Safety, tolerability, recommended Phase 2 dose, and efficacy	**Primary Endpoint:** ORR (RECIST v1.1) per BICR **Secondary Endpoints:** DOR, PFS, 1-year survival rate, OS, and safety **Exploratory Endpoints:** Clinical activity in patients with CNS metastases and co-mutations[d]

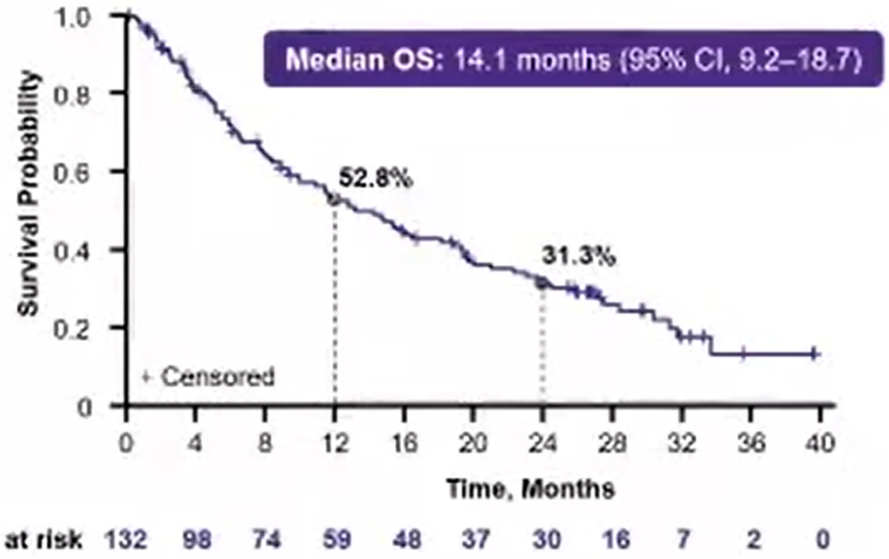
- Here we report 2-year follow-up data for 132 patients in Phase 1/1b dose escalation and expansion cohorts and Phase 2 Cohort A of KRYSTAL-1 (Data as of 1 January 2023; median follow-up: 26.9 months)
- Patients were administered adagrasib 600 mg BID orally (capsule, fasted)
- Baseline characteristics were consistent with those previously reported[5,7]

[a]Patients enrolled in Phase 2 Cohort A also had prior treatment with a PD-1/L1 inhibitor in combination or in sequence with chemotherapy. [b]KRAS^{G12C} mutation detected in tumor tissue or cfDNA by sponsor-approved local or central laboratory testing. [c]Phase 1/1b also enrolled patients with other KRAS^{G12C}-mutated unresectable or metastatic solid tumors. [d]Genetic alterations detected in tumor tissue and/or cfDNA NGS assay at baseline

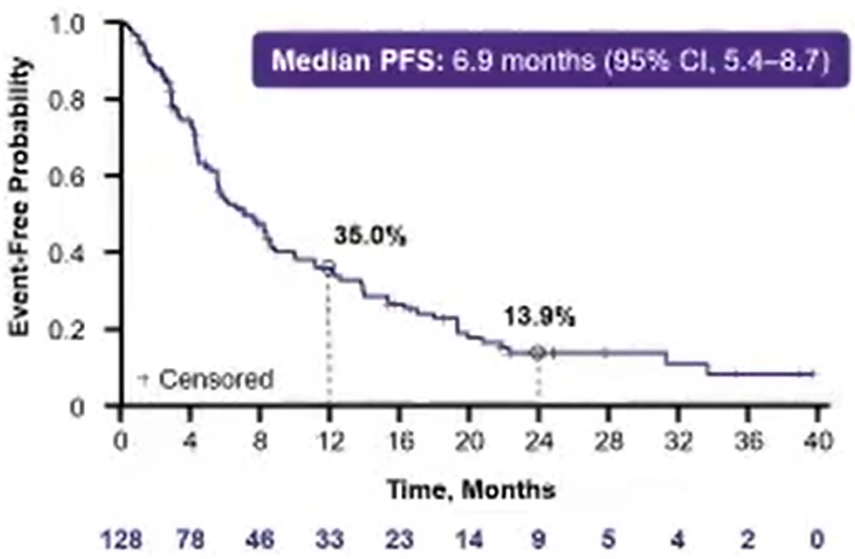
ClinicalTrials.gov: NCT03785249

Efficacy Outcomes at Two-Years

Overall Survival (N=132)



Progression-Free Survival (N=128)

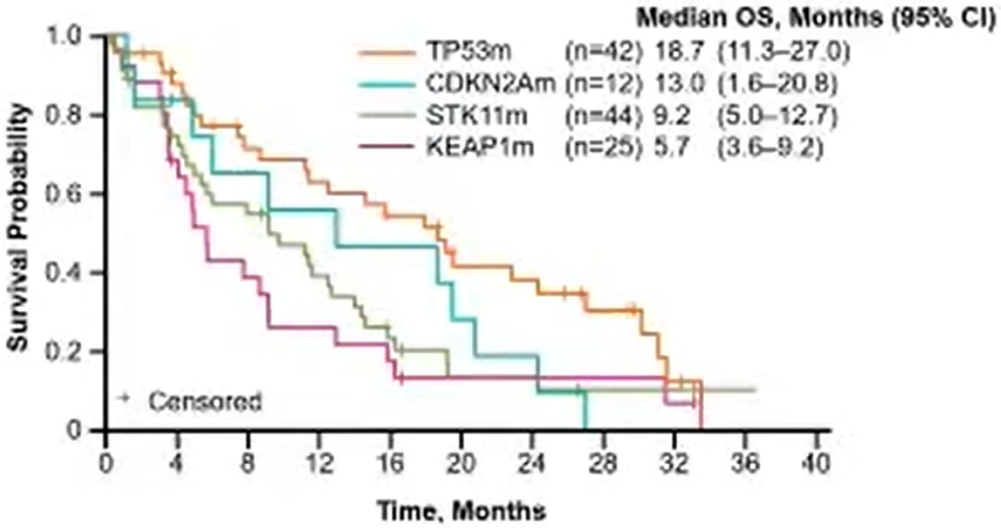


- Objective responses were observed in 43% of patients (55/128); DCR was 80%
- Median DOR was 12.4 months (95% CI, 7.0–15.1)[a]

Results are based on BICR. Missing, n=1. Full analysis set defined as all patients who had measurable disease at baseline and received ≥1 dose of adagrasib; 16 patients were not evaluable due to not having post-baseline measurement in target lesions.
[a]Twelve-month event-free rate was 50.6% (95% CI, 38.1–63.5)
Data as of 1 January 2023 (median follow-up: 26.9 months)

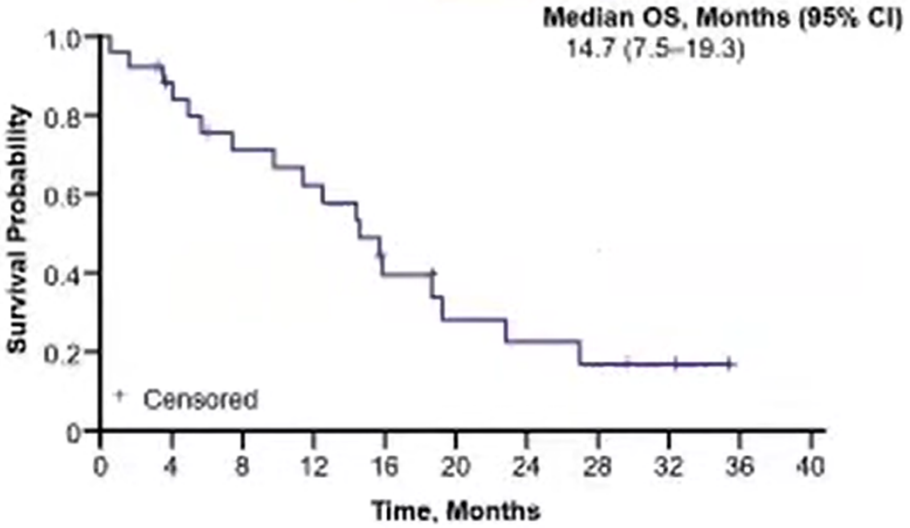
Overall Survival and Progression-Free Survival in Patients With Tumors Harboring Co-Mutations or With Baseline CNS Metastases

Overall Survival According to Co-Mutations at Baseline[a]



- Median PFS: KEAP1m, 4.1 months (95% CI, 2.7–5.6); STK11m, 4.2 months (3.9–6.1); CDKN2Am, 8.4 months (1.2–11.9); TP53m, 8.7 months (5.0–12.1)

Overall Survival in Patients With CNS Metastases at Baseline (n=26)

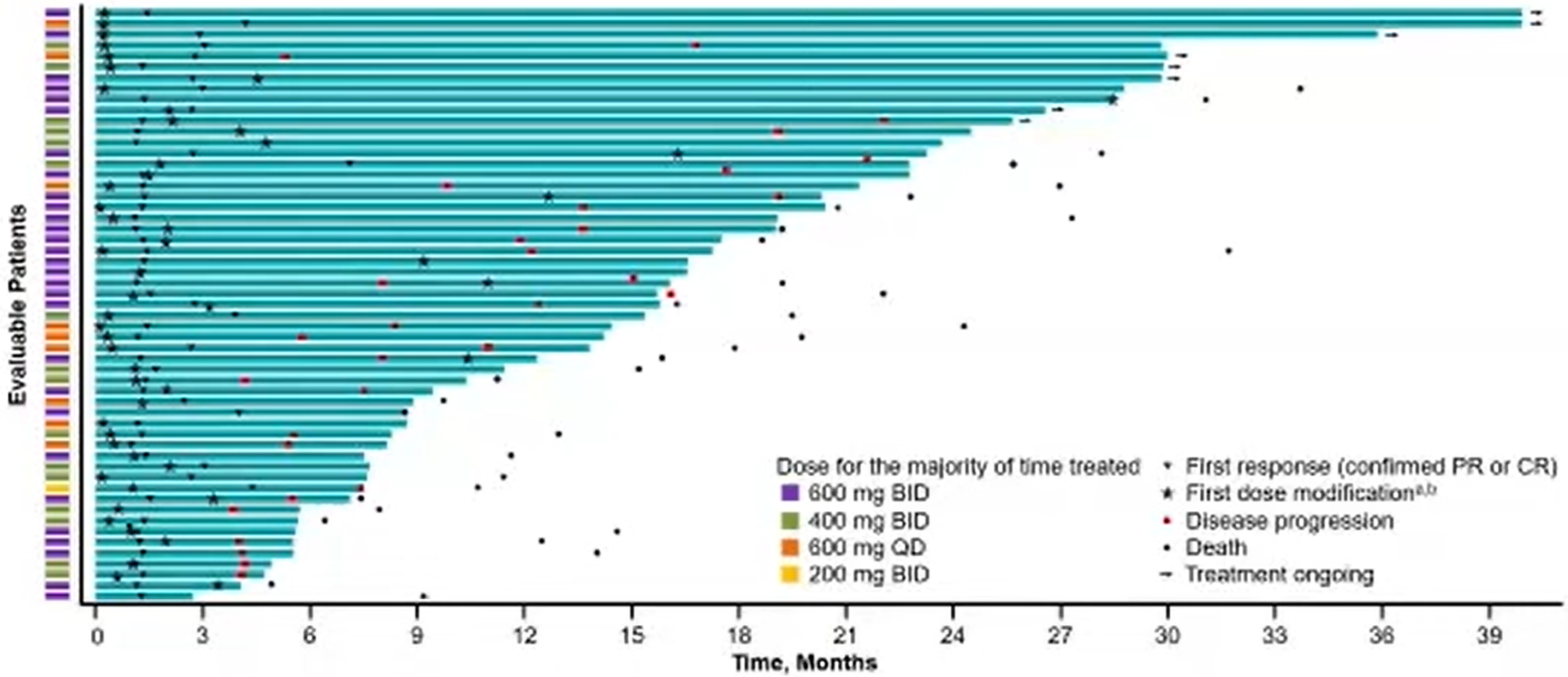


- Median PFS for patients with CNS metastases at baseline was 6.9 months (95% CI, 4.1–11.9)

PFS results are based on BICR. Full analysis set defined as all patients who had measurable disease at baseline and received ≥1 dose of adagrasib. Baseline CNS metastases were stable and treated.
[a]Co-mutations were evaluated in tissue and/or ctDNA. CDKN2Am includes homozygous deletions and inactivating mutations. Number of patients analyzed for each co-mutation: KEAP1, n=97; TP53, n=111; STK11, n=106; CDKN2A, n=70. PFS for patients with STK11m/KEAP1wt and STK11m/KEAP1m was 4.2 months (95% CI, 2.8–8.1) and 5.6 months (95% CI, 1.1–8.1), respectively. OS for patients with STK11m/KEAP1wt and STK11m/KEAP1m were 11.5 months (95% CI, 5.4–14.5) and 5.7 months (95% CI, 1.6–15.9), respectively.

Data as of 1 January 2023 (median follow-up: 25.9 months)

Duration of Treatment in Responders, Including Patients With Dose Modification



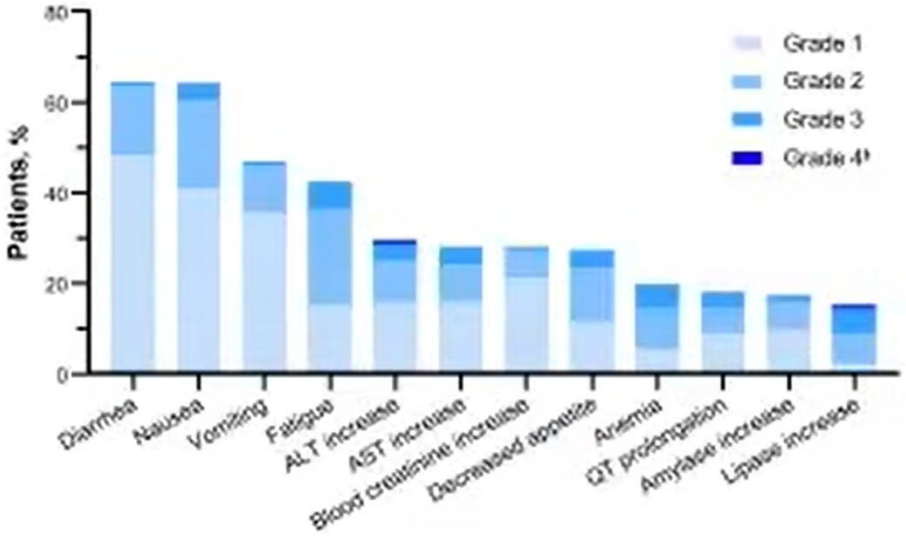
- Dose modifications were not associated with shorter treatment duration; all 33 patients (60%) who had DOT >1 year and all 12 patients (22%) who had DOT >2 years had dose modifications[b]
- For all patients with a dose modification[c], 1-year OS was 53.3% and 2-year OS was 32.1%

All results are based on BICR. [a]Time to first dose modification due to any cause, including missed dose, AE, or others. [b]Dose modification included any interruption or reduction. [c]128/132 (97%) of patients had any dose modification, 68/132 (52%) of patients had a dose reduction

Data as of 1 January 2023 (median follow-up: 26.9 months)

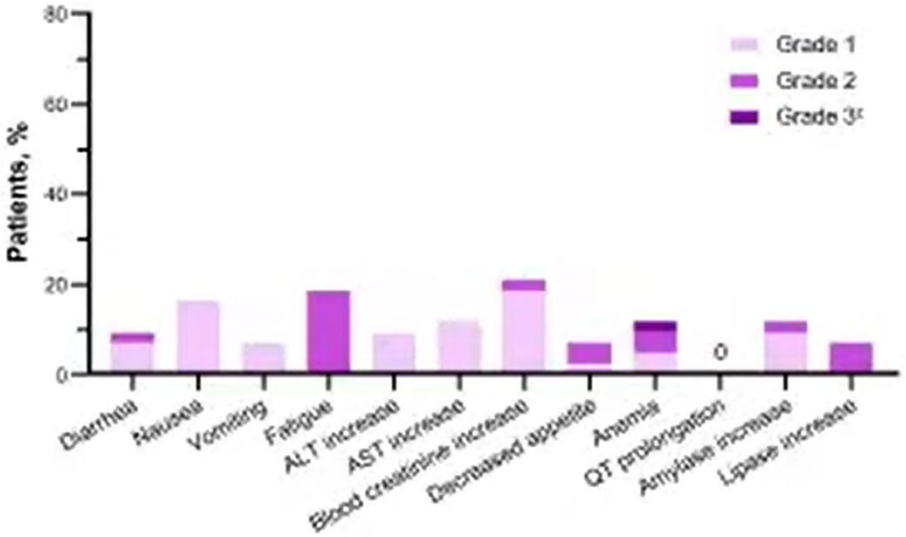
Treatment-Related Adverse Events and Long-Term Safety

TRAEs in Patients Overall (N=132)[a]



- ≥1 TRAE occurred in 128/132 (97%) patients
- 0/12 (0%) patients[c] who received IO <30 days before adagrasib had Grade ≥3 hepatotoxicity[d]
- One patient discontinued treatment due to Grade 3 hepatotoxicity

TRAEs With New Onset >1 Year (N=43)



- 43/132 patients (32.6%) received adagrasib for >1 year
- 29 of these 43 patients (67%) had a new onset TRAE after >1 year
- New onset Grade ≥2 GI TRAEs occurred in 1 patient (2%; Grade 2 diarrhea); no patients had Grade ≥2 hepatotoxicity with onset >1 year

Any grade TRAEs that occurred in >15% of patients. Overall, Grade 5 events occurred in 3 patients: cardiac failure (n=1), pneumonitis (n=1), and pulmonary hemorrhage (n=1). Overall, TRAEs led to dose reduction in 69/132 patients (52%), dose interruption in 85/132 patients (65%), and discontinuation of study drug in 12/132 patients (9%). [a]Overall, Grade 4 events comprised: neutrophil count decrease (n=2 [2%]), febrile neutropenia (n=1 [1%]), ejection fraction decrease (n=1 [1%]), ALT increase (n=1 [1%]), lipase increase (n=1 [1%]), white blood cell count decrease (n=1 [1%]), and hypokalemia (n=1 [1%]). [b]Grade 3 events that occurred >1 year after treatment onset comprised: ejection fraction decrease (n=1 [2%]), platelet count decrease (n=1 [2%]), cardiac failure (n=1 [2%]), anemia (n=1 [2%]), and nervous system disorder (n=1 [2%]). [c]Ten patients from Cohort A and 2 from Phase 1/b. [d]Hepatotoxicity included increased ALT/AST, increased liver function test, and mixed liver injury. In patients who received IO <30 days before adagrasib, 7 patients experienced Grade 3 treatment-related hepatotoxicity, 1 patient experienced Grade 4 treatment-related hepatotoxicity (ALT increase)

Data as of 1 January 2023 (median follow-up: 26.9 months)

Conclusions and Future Directions

- In this pooled analysis of patients with previously treated KRAS^{G12C}-mutated NSCLC, adagrasib demonstrated durable efficacy, with a median OS of 14.1 months and 2-year OS rate of 31%
- Exploratory analyses suggested durable clinical benefit in patients with treated, stable CNS metastases at baseline (median OS of 14.7 months), with clinical benefit noted across most baseline co-mutations
- Adagrasib had a manageable long-term safety profile; most TRAEs with onset >1 year were of low grade and included fewer GI TRAEs
- Treatment management by dose modification did not lead to a decrease in OS (2-year OS rate of 32%)
- Adagrasib was associated with a low rate of Grade ≥3 hepatotoxicity and was not observed in any patients who received adagrasib within 30 days of prior IO
- A confirmatory Phase 3 study is evaluating adagrasib vs docetaxel in previously treated patients with KRAS^{G12C}-mutated NSCLC, in North America, Europe, Asia, and Australia (KRYSTAL-12; NCT04685135)

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Osimertinib With / Without Platinum-Based Chemotherapy as First-Line Treatment in Patients with EGFRm Advanced NSCLC (FLAURA2)

Prof Pasi A. Jänne[1], Prof David Planchard[2], Prof Ying Cheng[3], Dr James Chih-Hsin Yang[4], Dr Noriko Yanagitani[5], Prof Sang-We Kim[6], Dr Shunichi Sugawara[7], Dr Yan Yu[8], Dr Yun Fan[9], Dr Sarayut Lucien Geater[10], Dr Konstantin Laktionov[11], Dr Chee Khoon Lee[12], Prof Natalia Valdiviezo[13], Prof Samreen Ahmed[14], Dr Jean-Marc Maurel[15], Dr Igor Andrasina[16], Dr Jonathan Goldman,[17] Dr Dana Ghiorghiu[18], Dr Dakshayini Kulkarni[18], Dr Xiangning Huang[19], Prof Kunihiko Kobayashi[20]

[1]Department of Medical Oncology, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [2]Department of Medical Oncology, Institut Gustave Roussy, Thoracic Unit, Villejuif, France; [3]Department of Thoracic Oncology, Jilin Cancer Hospital, Changchun, China; [4]Department of Oncology, National Taiwan University Hospital and Cancer Center, Taipei, Taiwan; [5]Department of Thoracic Medical Oncology, The Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan; [6]Department of Oncology, Asan Medical Center, Seoul, Republic of Korea; [7]Department of Pulmonary Medicine, Sendai Kousei Hospital, Hirosemachi, Aoba-ku, Sendai City, Miyagi Prefecture, Japan; [8]Department of Medical Oncology, Harbin Medical University Cancer Hospital, Harbin, China; [9]Department of Medical Oncology, Zhejiang Cancer Hospital, Hangzhou, China; [10]Department of Internal Medicine, Prince of Songkla University, Hat Yai District, Songkhla, Thailand; [11]Federal State Budgetary Institution, "N.N.Blokhin National Medical Research Center of Oncology" of the Ministry of Health of the Russian Federation, Moscow, Russia; [12]Department of Medical Oncology, Cancer Care Centre, St. George Hospital, Kogarah, Australia; [13]Department of Medical Oncology, Instituto Nacional de Enfermedades Neoplasicas, Surquillo, Peru; [14]Department of Medical Oncology, University Hospitals of Leicester, Leicester, UK; [15]Department of Clinical Oncology, Rondebosch Oncology Centre, Rondebosch, Cape Town, South Africa; [16]Department of Radiotherapy and Oncology, Východoslovenský onkologický ústav, Košice, Slovakia; [17]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [18]Department of Oncology Research & Development, AstraZeneca, Cambridge, UK; [19]Department of Oncology Biometrics, AstraZeneca, Cambridge, UK; [20]Department of Respiratory Medicine, Saitama Medical University International Medical Center, Hidaka, Saitama, Japan

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Introduction

- EGFR-TKIs are standard of care first-line treatment for EGFRm advanced NSCLC;[1,2] however, despite efficacy, most patients will progress following treatment,[3,4] and clinical factors associated with poor prognosis include CNS metastases or L858R mutation[5–7]
- Osimertinib, a third-generation, CNS active EGFR-TKI, is the preferred first-line treatment for EGFRm advanced NSCLC based on superior PFS / OS benefit with osimertinib vs comparator EGFR-TKIs in the FLAURA study[1–4,8–12]
- Clinical data on first-generation EGFR-TKIs combined with chemotherapy have suggested an additive effect[13–17]
- Osimertinib plus platinum-pemetrexed recently showed encouraging activity in the Phase II OPAL study in Japanese patients with untreated EGFR-mutated advanced NSCLC (ORR 90.9% [95% CI 84.0, 97.8]; median PFS 31.0 months [95% CI 26.8, NC]);[18] however, this combination has not been evaluated in a randomized trial

The global, open-label, randomized FLAURA2 study (NCT04035486) aims to assess the efficacy and safety of osimertinib plus platinum-pemetrexed vs osimertinib monotherapy as first-line treatment for EGFRm advanced NSCLC

1. Hendriks et al. Ann Oncol 2023;34:P339–57; 2. Hanna et al. J Clin Oncol 2021;39:1040–91; 3. Soria et al. N Engl J Med 2018;378:113–25; 4. Ramalingam et al. N Engl J Med 2020;382:41–50; 5. Bhatt et al. J Glob Oncol 2016;3:208–17; 6. Peters et al. Cancer Treat Rev 2016;45:139–62; 7. Lee CK. J Natl Cancer Inst 2017;109; 8. Cross et al. Cancer Discov 2014;4(9):1046–61; 9. Mok et al. N Engl J Med 2017;376:629–40; 10. Wu et al. N Engl J Med 2020;383:1711–23; 11. Wu et al. J Clin Oncol 2018;36:2702–09; 12. Reungwetwattana et al. J Clin Oncol 2018;36:3290–97; 13. Hosomi et al. J Clin Oncol 2020;38:115–23; 14. Noronha et al. J Clin Oncol;38:124–36; 15. Oizumi et al. ESMO Open 2018;3:e000313; 16. Sugawara et al. Ann Oncol 2015;26:888–94; 17. Hou et al. JAMA Netw Open 2023;6:e2255050; 18. Saito et al. Eur J Cancer 2023;185:83–93

CI, confidence interval; CNS, central nervous system; EGFRm, epidermal growth factor receptor-mutated; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; NC, not calculable; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival

FLAURA2 Phase III study design

Safety run-in period (N=30)
Published in ESMO Open, 2021[1]

Patients with untreated locally advanced / metastatic EGFRm NSCLC

Key inclusion criteria:

- Aged ≥18 years (Japan: ≥20 years)
- Pathologically confirmed non-squamous NSCLC
- Ex19del / L858R (local / central test)
- WHO PS 0 / 1
- No prior systemic therapy for advanced NSCLC
- Stable CNS metastases were allowed*
- CT / MRI scan at baseline

Stratification by:

- **Race** (Chinese Asian / non-Chinese Asian / non-Asian)
- **EGFRm** (local / central test)
- **WHO PS** (0 / 1)

Randomization 1:1 (N=557)

Osimertinib 80 mg (QD) + pemetrexed 500 mg/m² + carboplatin AUC5 or cisplatin 75 mg/m² (Q3W for 4 cycles for platinum-based treatments)

Maintenance osimertinib 80 mg (QD) + pemetrexed (Q3W)†

Osimertinib 80 mg (QD)

Follow-up:

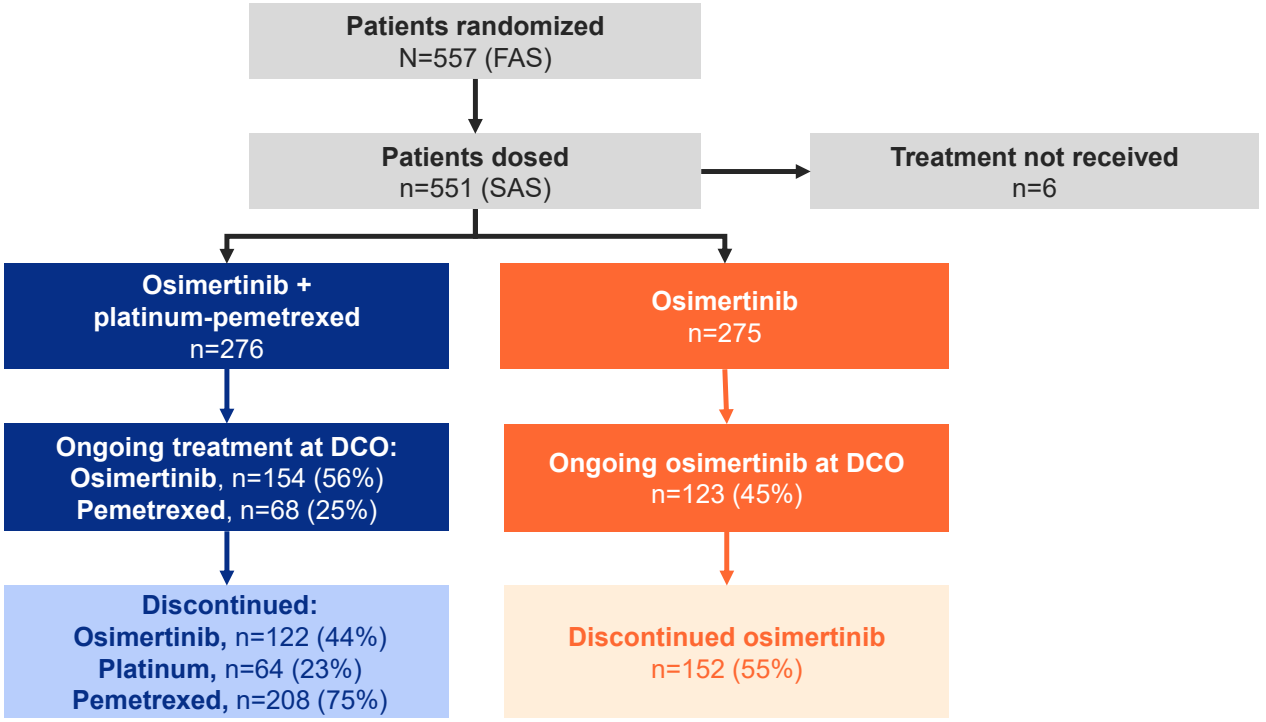
- RECIST 1.1 assessment at 6 and 12 weeks, then every 12 weeks until RECIST 1.1 defined radiological disease progression or other withdrawal criteria were met

- **Primary endpoint:** PFS (by investigator and BICR assessment per RECIST 1.1)‡§
- **Secondary endpoints:** OS, ORR, DoR, DCR, HRQoL, safety (AEs by CTCAE v5) and PFS2‡

1. Planchard et al. ESMO Open 2021;6(5):100271. *Not requiring steroids for at least two weeks; †Pemetrexed maintenance continued until a discontinuation criterion was met; ‡Efficacy analyses in the full analysis set, defined as all patients randomized to study treatment regardless of the treatment actually received, and safety analyses in the safety analysis set, defined as all randomized patients who received ≥1 dose of study treatment – one patient who was randomized to osimertinib plus platinum-pemetrexed received only osimertinib and was therefore included in the osimertinib monotherapy safety analysis set; §The study provided 90% power to demonstrate a statistically significant difference in PFS assuming HR=0.68 at 5% two-sided significance level

AE, adverse event; AUC, area under curve; BICR, blinded independent central review; CNS, central nervous system; CT, computerised tomography; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; DoR, duration of response; EGFR, epidermal growth factor receptor; EGFRm, EGFR-mutated; EGFR-TKI, EGFR-tyrosine kinase inhibitor; Ex19del, exon 19 deletion; HR, hazard ratio; HRQoL, health-related quality of life; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival; QD, once-daily; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; WHO PS, World Health Organization performance status

Patient disposition



- Disease progression and AEs were the most common reasons for discontinuation of any study treatment*

Data cut-off: 03 April 2023
*Progression includes both RECIST 1.1 objective disease progression and subjective disease progression
AE, adverse event; DCO, data cut-off; FAS, full analysis set; RECIST, Response Evaluation Criteria in Solid Tumors; SAS, safety analysis set

Baseline characteristics

- Patient demographics / clinical characteristics were balanced between arms, and almost half of patients had CNS metastases at baseline

Characteristics, %*	Osimertinib + platinum-pemetrexed (n=279)†	Osimertinib monotherapy (n=278)†
Sex: male / female	38 / 62	39 / 61
Age: median (range), years	61 (26–83)	62 (30–85)
Race: Chinese Asian / non-Chinese Asian / non-Asian	25 / 39 / 35	25 / 38 / 36
WHO PS: 0 / 1‡	37 / 62	37 / 63
Smoking status: never / current / former	67 / 1 / 31	65 / 1 / 33
Histology: adenocarcinoma / adenosquamous / other	99 / 1 / 1	99 / 0 / 1
EGFR mutation at randomization§: Ex19del / L858R	61 / 38	60 / 38
Locally advanced / metastatic	5 / 95	3 / 97
CNS metastases	42	40
Extra-thoracic visceral metastases	53	54
Baseline tumor size, mean (SD) / median (range), mm	65 (42) / 57 (10–284)	64 (39) / 57 (11–221)

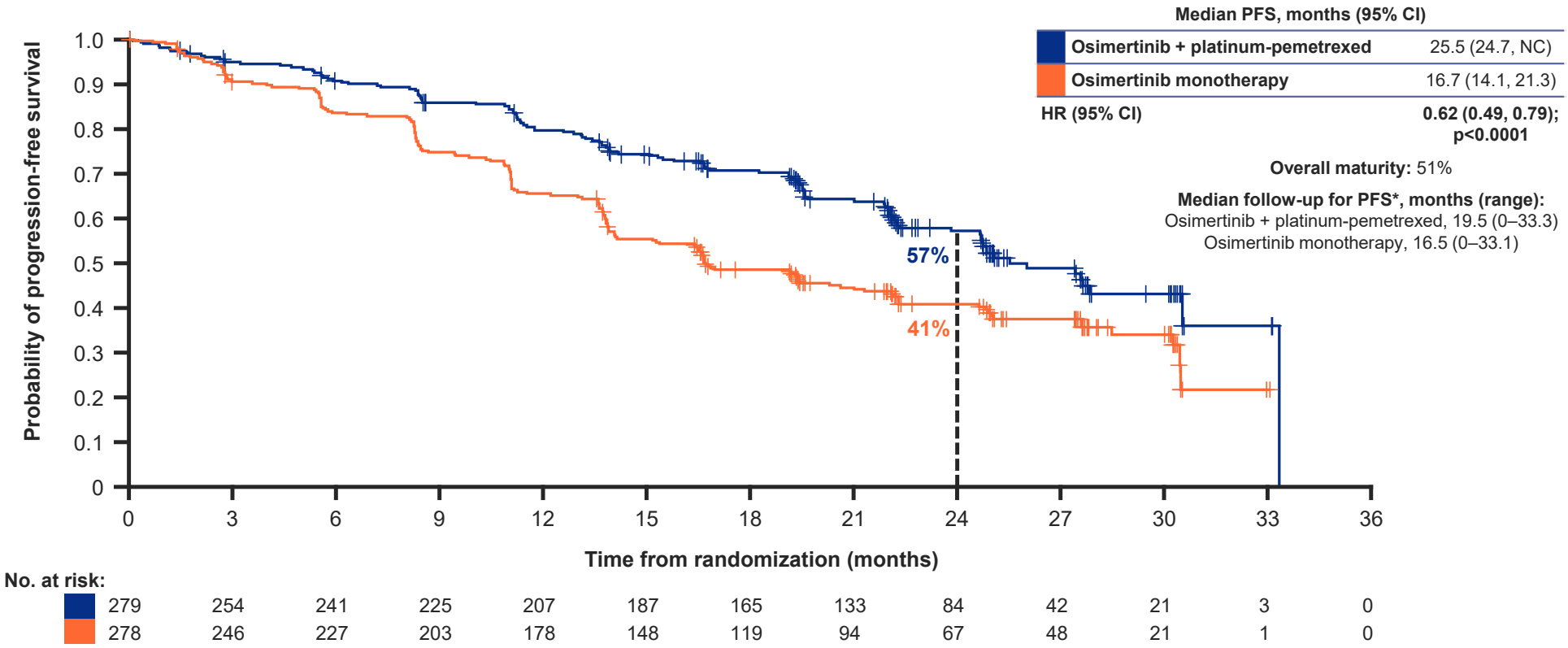
Data cut-off: 03 April 2023

*Percentages calculated and rounded to nearest whole number; †Three patients in each arm were randomized to either treatment arm, but received no study treatment; ‡One patient had a WHO PS of 2; §Central and local EGFR mutation test

CNS, central nervous system; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; SD, standard deviation; WHO PS, World Health Organization performance status

Progression-free survival per investigator

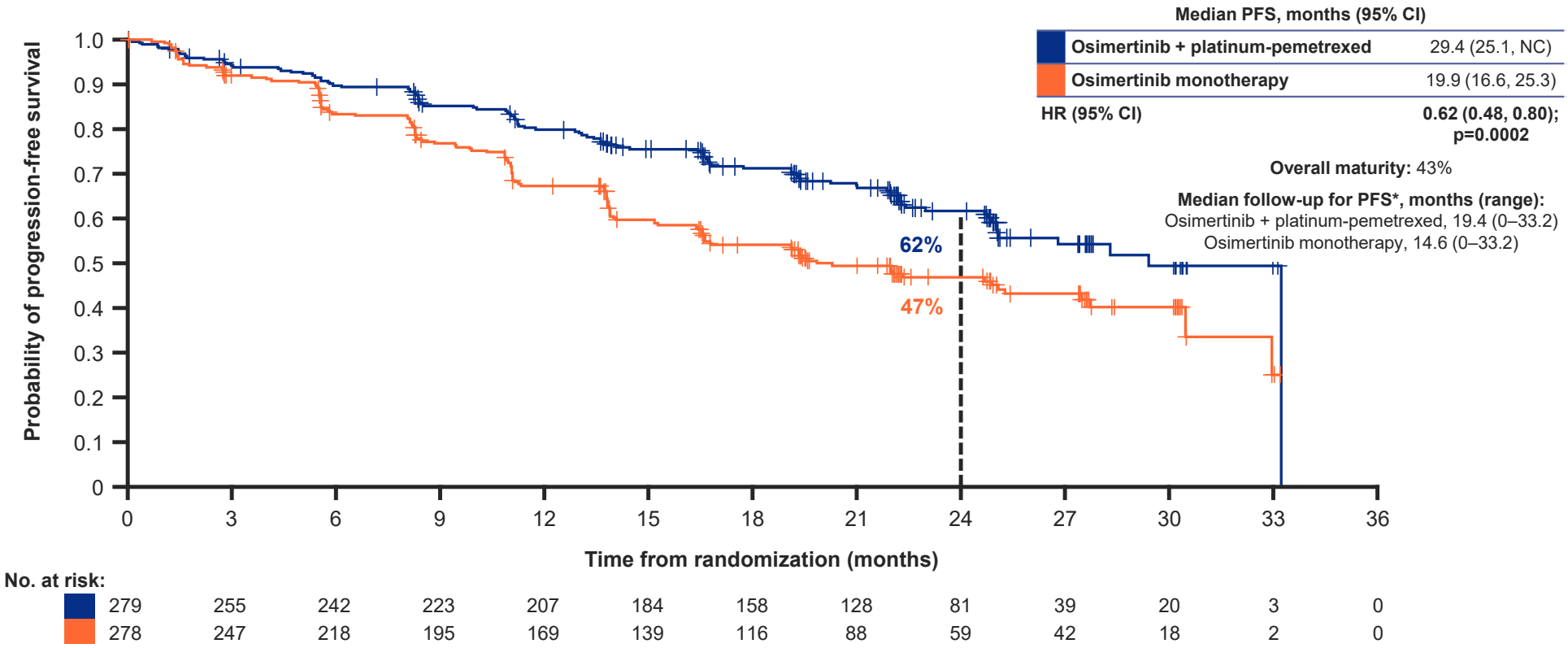
- Median PFS was improved by 8.8 months with osimertinib plus platinum-pemetrexed vs osimertinib monotherapy



Data cut-off: 03 April 2023
*In all patients
CI, confidence interval; HR, hazard ratio; NC, not calculable; PFS, progression-free survival

Progression-free survival per BICR

- Median PFS was improved by 9.5 months with osimertinib plus platinum-pemetrexed vs osimertinib monotherapy

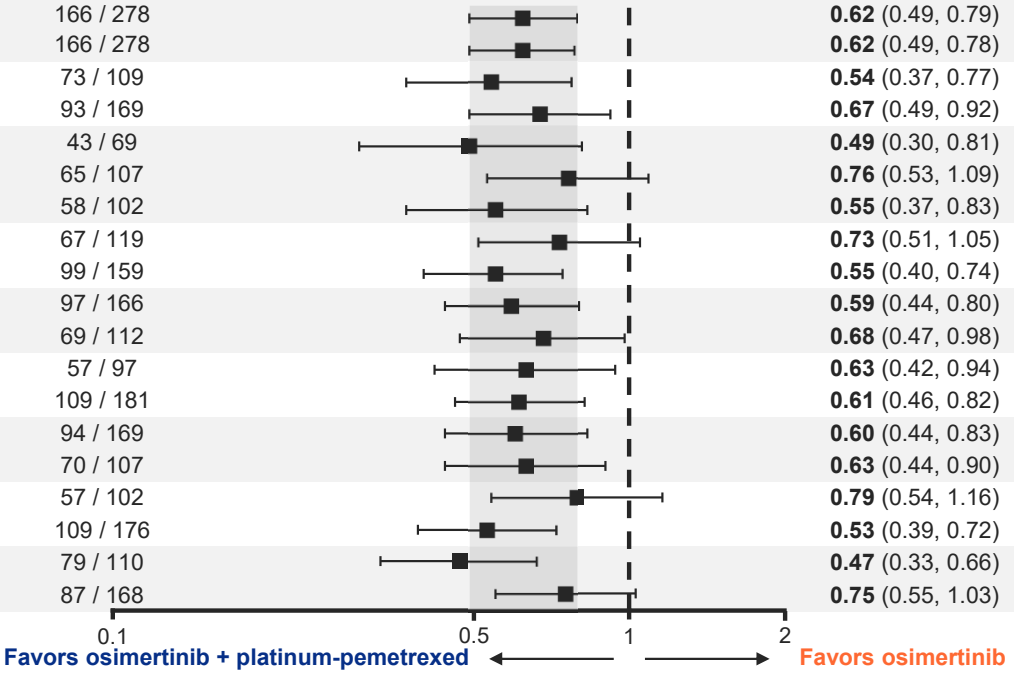


Data cut-off: 03 April 2023
*In all patients
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NC, not calculable; PFS, progression-free survival

Progression-free survival across subgroups

- PFS benefit was consistent across all pre-defined subgroups

Subgroup		Osimertinib + platinum-pemetrexed (Events / patients)	Osimertinib monotherapy (Events / patients)	HR (95% CI)
All patients	Stratified log-rank	120 / 279	166 / 278	**0.62** (0.49, 0.79)
	Unadjusted Cox PH	120 / 279	166 / 278	**0.62** (0.49, 0.78)
Sex	Male	51 / 106	73 / 109	**0.54** (0.37, 0.77)
	Female	69 / 173	93 / 169	**0.67** (0.49, 0.92)
Race	Chinese Asian	26 / 71	43 / 69	**0.49** (0.30, 0.81)
	Non-Chinese Asian	54 / 107	65 / 107	**0.76** (0.53, 1.09)
	Non-Asian	40 / 101	58 / 102	**0.55** (0.37, 0.83)
EGFR mutation test method	Central	52 / 121	67 / 119	**0.73** (0.51, 1.05)
	Local	68 / 158	99 / 159	**0.55** (0.40, 0.74)
Age at screening	<65 years	73 / 174	97 / 166	**0.59** (0.44, 0.80)
	≥65 years	47 / 105	69 / 112	**0.68** (0.47, 0.98)
Smoking history	Yes	43 / 91	57 / 97	**0.63** (0.42, 0.94)
	No	77 / 188	109 / 181	**0.61** (0.46, 0.82)
EGFR mutation type*	Ex19del	65 / 172	94 / 169	**0.60** (0.44, 0.83)
	L858R	55 / 106	70 / 107	**0.63** (0.44, 0.90)
WHO PS	0	48 / 101	57 / 102	**0.79** (0.54, 1.16)
	1	72 / 178	109 / 176	**0.53** (0.39, 0.72)
CNS status at baseline	Yes	52 / 116	79 / 110	**0.47** (0.33, 0.66)
	No	68 / 163	87 / 168	**0.75** (0.55, 1.03)



Data cut-off: 03 April 2023

*For EGFR mutation type, patients with both Ex19del and L858R were included in Ex19del group

CI, confidence interval; CNS, central nervous system; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletion; HR, hazard ratio; PFS, progression-free survival; PH, proportional hazard; WHO PS, World Health Organization performance status

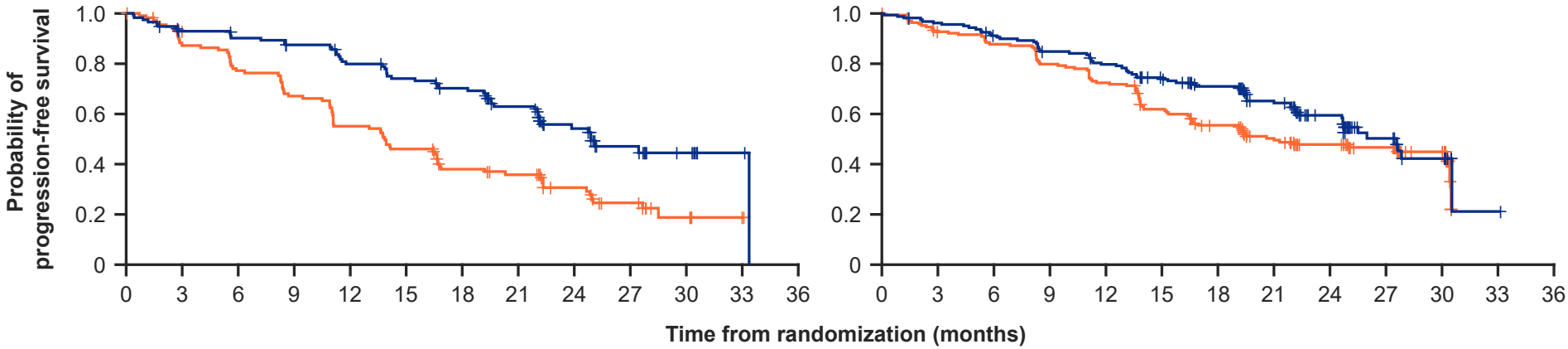
PFS* with / without CNS metastases at baseline

With CNS metastases

Median PFS, months (95% CI)	
Osimertinib + platinum-pemetrexed	24.9 (22.0, NC)
Osimertinib monotherapy	13.8 (11.0, 16.7)
HR (95% CI)	0.47 (0.33, 0.66)

Without CNS metastases

Median PFS, months (95% CI)	
Osimertinib + platinum-pemetrexed	27.6 (24.7, NC)
Osimertinib monotherapy	21.0 (16.7, 30.5)
HR (95% CI)	0.75 (0.55, 1.03)



No. at risk:

Osimertinib + platinum-pemetrexed	116	101	98	93	84	77	70	58	34	19	8	2	0
Osimertinib monotherapy	110	95	84	73	60	50	37	32	21	13	5	1	0

Osimertinib + platinum-pemetrexed	163	153	143	132	123	110	95	75	50	23	13	1	0
Osimertinib monotherapy	168	151	143	130	118	98	82	62	46	35	16	0	0

Data cut-off: 03 April 2023
*Per investigator; CNS metastases determined by the investigator and recorded in the eCRF
CI, confidence interval; CNS, central nervous system; eCRF, electronic case report form; HR, hazard ratio; NC, not calculable; PFS, progression-free survival

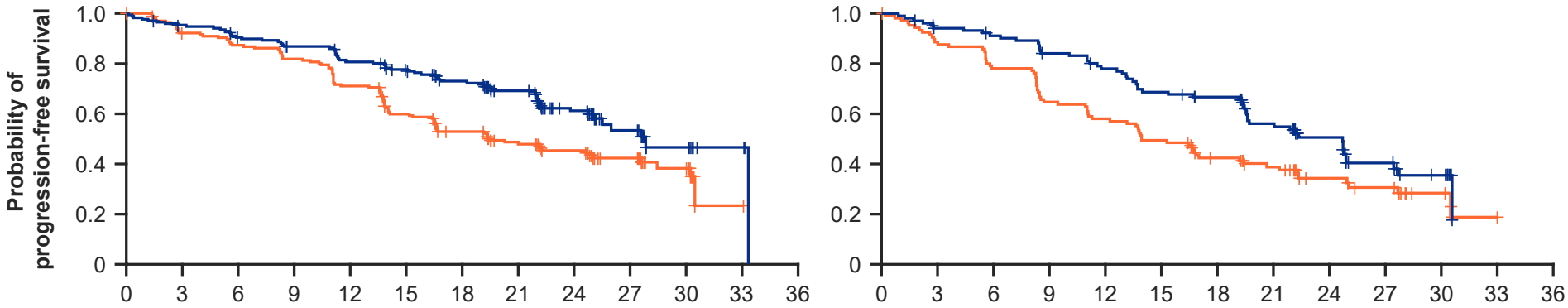
PFS* by EGFR mutation type at baseline

Ex19del

Median PFS, months (95% CI)	
Osimertinib + platinum-pemetrexed	27.9 (25.1, NC)
Osimertinib monotherapy	19.4 (16.5, 27.6)
HR (95% CI)	0.60 (0.44, 0.83)

L858R

Median PFS, months (95% CI)	
Osimertinib + platinum-pemetrexed	24.7 (19.5, 27.4)
Osimertinib monotherapy	13.9 (11.1, 19.4)
HR (95% CI)	0.63 (0.44, 0.90)



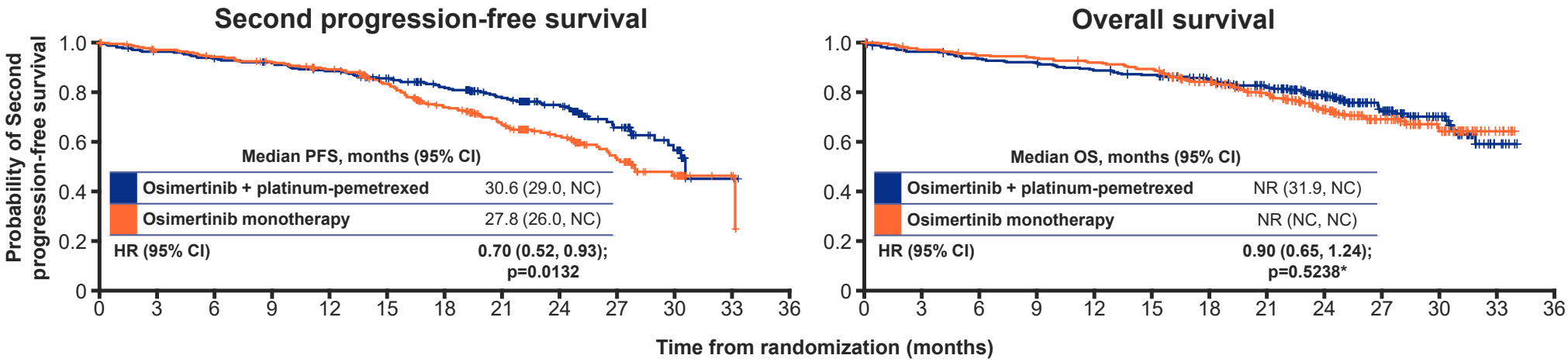
No. at risk:

Osimertinib + platinum-pemetrexed	172	159	150	142	131	120	103	86	53	23	9	3	0
Osimertinib monotherapy	169	152	144	135	117	96	79	63	48	33	16	1	0

Osimertinib + platinum-pemetrexed	106	95	91	83	76	67	62	47	31	19	12	0	0
Osimertinib monotherapy	107	92	82	68	61	52	40	31	19	15	5	0	0

Data cut-off: 03 April 2023
*Per investigator
CI, confidence interval; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; HR, hazard ratio; NC, not calculable; PFS, progression-free survival

PFS2 and OS interim analysis



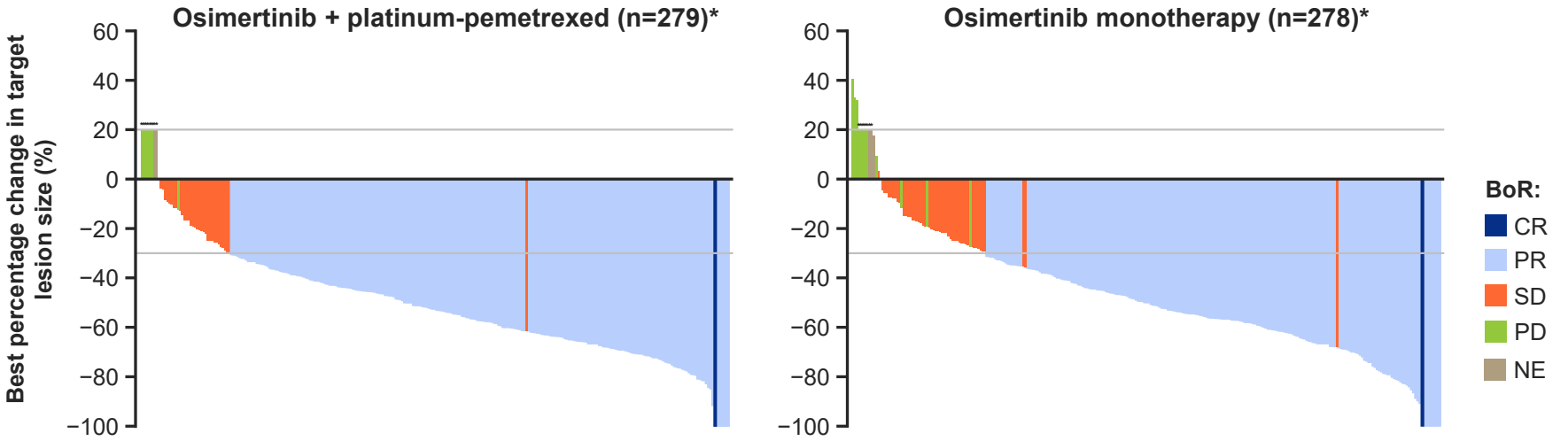
No. at risk:

	279	263	254	247	236	220	194	158	107	54	26	3	0		279	267	258	253	244	237	219	191	139	84	46	7	0
	278	265	255	246	232	206	166	130	90	58	26	3	0		278	267	260	257	251	244	214	185	133	85	46	10	0

- PFS2 and OS were immature at this interim analysis (34% and 27% data maturity, respectively)
- At DCO, of those that discontinued treatment, 57 / 123 patients (46%) in the osimertinib plus platinum-pemetrexed arm and 91 / 151 patients (60%) in the osimertinib monotherapy arm had received any subsequent anti-cancer treatment†
- In both arms, cytotoxic chemotherapy was the most common second-line treatment (65% and 82% of those who received subsequent anti-cancer treatment in the combination and monotherapy arms, respectively)†

Data cut-off: 03 April 2023
*Significance level is p-value <0.00158 at this interim for OS; †Subsequent anti-cancer treatments included those with a start date after the date of the last dose of study treatment. Patients could have received more than one subsequent anti-cancer treatment
Percentages of patients by treatment type are calculated from the number of patients who received a subsequent anti-cancer treatment
CI, confidence interval; HR, hazard ratio; NC, not calculable; NR, not reached; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival

Tumor response per investigator



	Osimertinib + platinum-pemetrexed (n=279)	Osimertinib monotherapy (n=278)
Median best percentage change in target lesion size, % (range)	-52.6 (-100.0, 20.0)	-50.0 (-100.0, 40.4)
Objective response rate, % (95% CI)	83.2 (78.2, 87.4)	75.5 (70.1, 80.5)
Odds ratio (95% CI)	1.61 (1.06, 2.44)	
Complete response, n (%)	1 (<1)	2 (1)
Partial response, n (%)	231 (83)	208 (75)
Stable disease ≥35 days, n (%)	34 (12)	51 (18)
Progression, n (%)	7 (3)	12 (4)
Median duration of response, months (95% CI)	24.0 (20.9, 27.8)	15.3 (12.7, 19.4)

Data cut-off: 03 April 2023
*Overall, 275 patients from the osimertinib + platinum-pemetrexed arm and 276 from the osimertinib monotherapy arm had best percentage change in target lesion size available, including imputed values – indicated by * on the graphs
BoR, best overall response; CI, confidence interval; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease

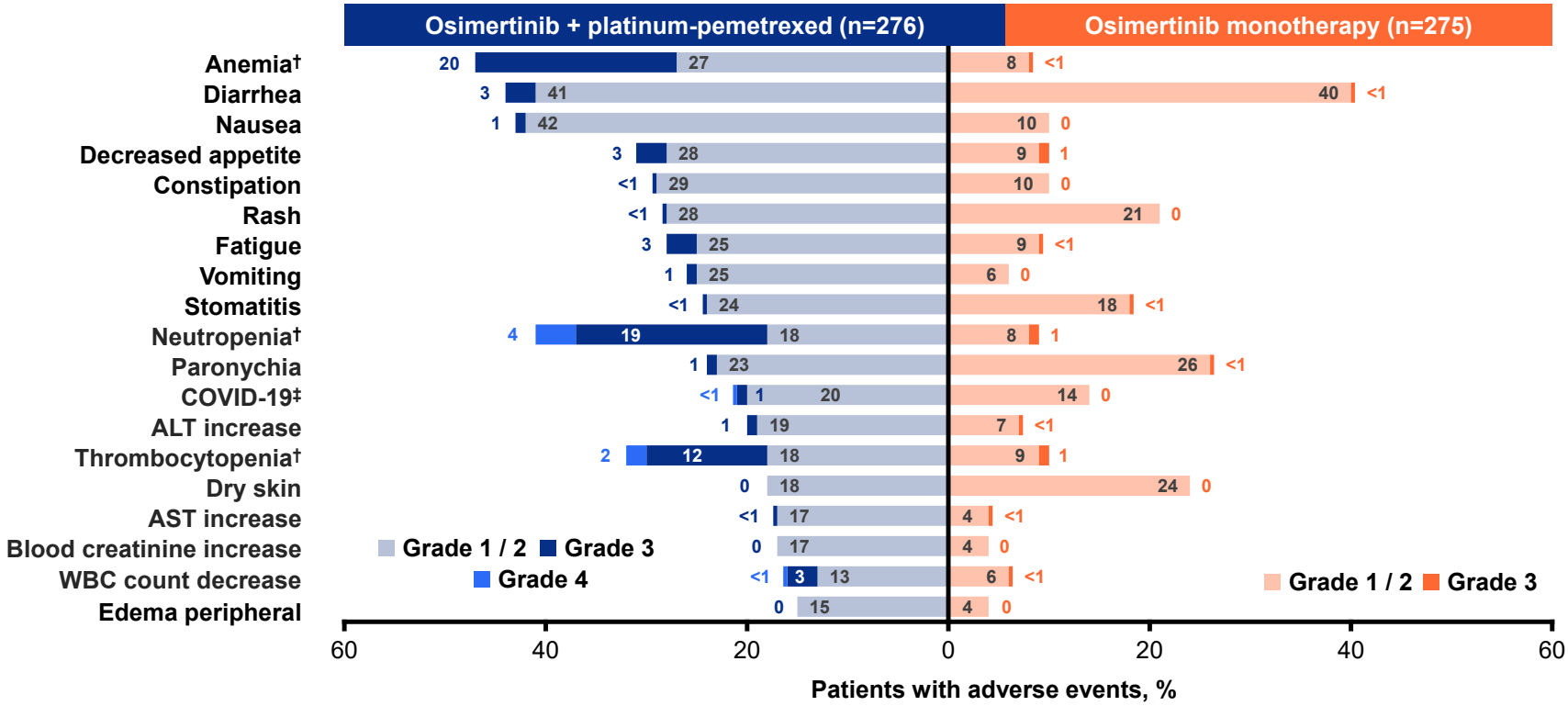
Safety summary

- Median total duration of osimertinib exposure was 22.3 months (range 0.1–33.8) in the osimertinib plus platinum-pemetrexed arm and 19.3 months (range 0.1–33.8) in the osimertinib monotherapy arm
- In the combination arm patients received a median of 12 cycles of pemetrexed (range 1–48) and 212 patients (77%) completed 4 cycles of platinum-based chemotherapy

Patients with AEs, n (%)*	Osimertinib + platinum-pemetrexed (n=276)	Osimertinib monotherapy (n=275)
AE any cause	**276 (100)**	**268 (97)**
Any AE Grade ≥3	176 (64)	75 (27)
Any AE leading to death	18 (7)	8 (3)
Any serious AE	104 (38)	53 (19)
Any AE leading to discontinuation	132 (48)	17 (6)
Osimertinib / carboplatin or cisplatin / pemetrexed discontinuation	30 (11) / 46 (17) / 119 (43)	17 (6) / NA / NA
AE possible causally related to treatment†	**269 (97)**	**241 (88)**
Any AE Grade ≥3	146 (53)	29 (11)
Causally related to osimertinib / carboplatin or cisplatin / pemetrexed	81 (29) / 104 (38) / 130 (47)	29 (11) / NA / NA
Any AE leading to death	5 (2)	1 (<1)
Causally related to osimertinib / carboplatin or cisplatin / pemetrexed	3 (1) / 2 (1) / 3 (1)	1 (<1) / NA / NA
Any serious AE	52 (19)	15 (5)

Data cut-off: 03 April 2023
*Percentages calculated and rounded to nearest whole number; †Per investigator assessment
AE, adverse event; NA, not applicable

Common adverse events (≥15% of patients)*



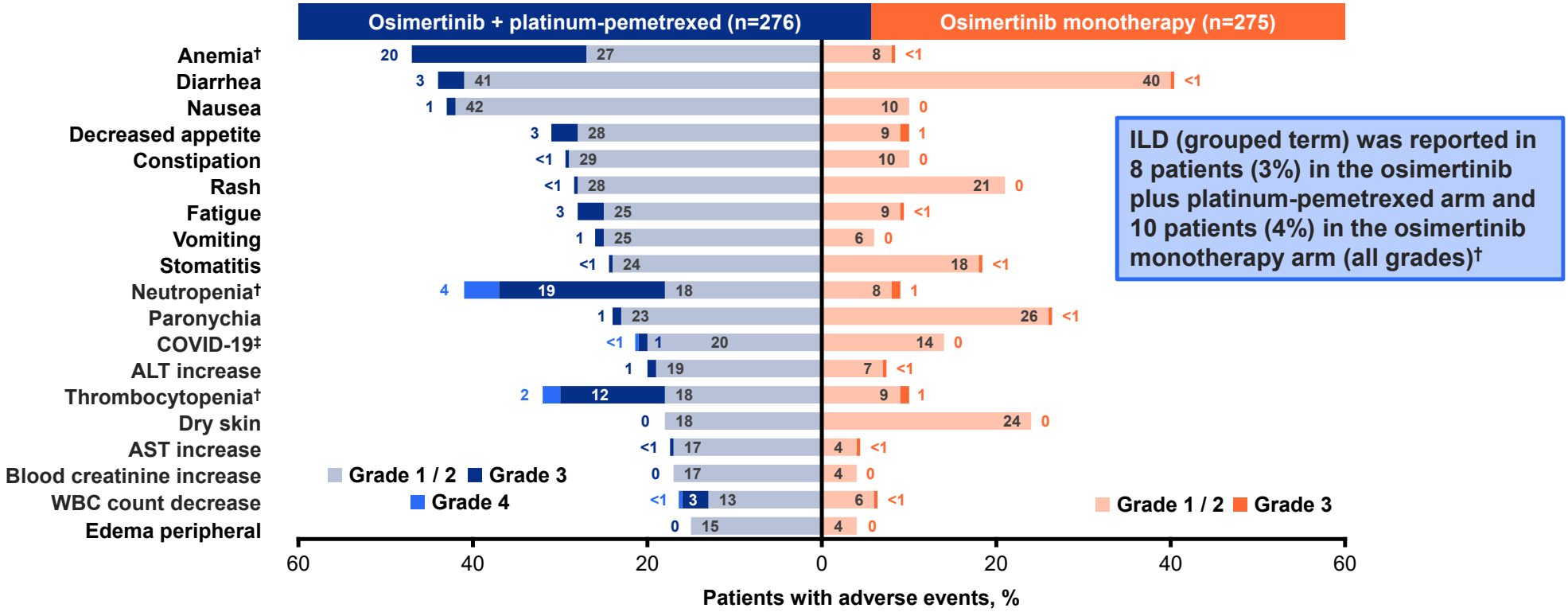
- Of most common AEs (occurring in ≥15% of patients in either arm), all Grade 4 AEs in the osimertinib plus platinum-pemetrexed arm were hematological toxicities, known to be associated with chemotherapy; there were no common Grade 4 AEs in the monotherapy arm

Data cut-off: 03 April 2023

*In commonly reported AEs, defined as occurring in ≥15% of patients in either treatment arm, by MedDRA preferred terms (unless stated as a grouped term of the same medical concepts); †Grouped term: anemia / hemoglobin decreased, thrombocytopenia / platelet count decreased, and neutropenia / neutrophil count decreased by preferred terms); ‡Of common AEs (≥15% of patients), one Grade 5 AE of COVID-19 was reported in the osimertinib plus platinum-pemetrexed arm

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities; WBC, white blood cell

Common adverse events (≥15% of patients)*



ILD (grouped term) was reported in 8 patients (3%) in the osimertinib plus platinum-pemetrexed arm and 10 patients (4%) in the osimertinib monotherapy arm (all grades)†

- Of most common AEs (occurring in ≥15% of patients in either arm), all Grade 4 AEs in the osimertinib plus platinum-pemetrexed arm were hematological toxicities, known to be associated with chemotherapy; there were no common Grade 4 AEs in the monotherapy arm

Data cut-off: 03 April 2023

*In commonly reported AEs, defined as occurring in >15% of patients in either treatment arm, by MedDRA preferred terms (unless stated as a grouped term of the same medical concepts); †Grouped term: anemia / hemoglobin decreased, thrombocytopenia / platelet count decreased, neutropenia / neutrophil count decreased, and interstitial lung disease / pneumonitis / organizing pneumonitis (by preferred terms); ‡Of common AEs (≥15% of patients), one Grade 5 AE of COVID-19 was reported in the osimertinib plus platinum-pemetrexed arm

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ILD, interstitial lung disease; MedDRA, Medical Dictionary for Regulatory Activities; WBC, white blood cell

Conclusions

- Osimertinib in combination with platinum-pemetrexed has demonstrated a statistically significant and clinically meaningful improvement in PFS over osimertinib monotherapy in patients with EGFRm advanced NSCLC (HR: 0.62 [95% CI 0.49, 0.79])
    - **Median improvements in PFS were 8.8 and 9.5 months with combination vs monotherapy, per investigator and BICR, respectively (median 25.5 vs 16.7 and 29.4 vs 19.9 months per investigator and BICR, respectively)**
- PFS benefits were consistent across all pre-defined subgroups
- PFS2 and OS data were immature at this interim analysis
- The safety profiles were as expected for each treatment and were manageable with standard medical practice
- Further ongoing analyses include CNS response and progression, post-progression endpoints, subsequent therapies, and ctDNA analyses

Osimertinib plus platinum-pemetrexed offers a new first-line treatment option for patients with EGFRm advanced NSCLC

BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; EGFRm, epidermal growth factor receptor-mutated; HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival

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557 patients from 21 countries randomized in the FLAURA2 study

Plain language summary

Treatment with osimertinib plus chemotherapy significantly increases progression-free survival rate for patients with EGFR-mutated advanced non-small cell lung cancer (NSCLC)

Why did we perform this research?

- Epidermal growth factor receptor (EGFR) is a gene that controls cell growth and division. EGFR-tyrosine kinase inhibitors (EGFR-TKIs), including osimertinib, block the activity of EGFR on cancer cells, reducing their growth and spread
- EGFR-TKIs are recommended as the first treatment for patients diagnosed with advanced NSCLC; however, while receiving EGFR-TKIs, the disease can get worse
- FLAURA2 is a study designed to compare treatment with osimertinib, either in combination with chemotherapy or on its own, for patients with advanced NSCLC who have an EGFR gene mutation

How did we perform this research?

- Patients with EGFR-mutated advanced NSCLC were randomly assigned to treatment with either osimertinib plus chemotherapy or osimertinib alone and were followed closely to monitor disease progression
- Here, we report results on the effectiveness and side effects of these treatment options

What were the findings and implications of this research?

- Overall, patients who received osimertinib plus chemotherapy had a significantly longer time without disease progression, with a 38% lower risk of disease progression or death, compared to treatment with osimertinib alone
- These data highlight a potential new treatment regimen of osimertinib plus chemotherapy for patients with EGFR-mutated advanced NSCLC
- The side effects of osimertinib and chemotherapy were consistent with the well-established individual drug profiles, and were considered manageable

Where can I access more information?

- More information on the FLAURA2 study can be found on ClinicalTrials.gov (NCT04035486): https://beta.clinicaltrials.gov/study/NCT04035486

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Benmelstobart with Anlotinib plus Chemotherapy as First-line Therapy for ES-SCLC: A Randomized, Double-blind, Phase III Trial (ETER701)

Ying Cheng[1], R. Yang[2], J. Chen[3], W. Zhang[4], C. Xie[5], Q. Hu[6], N. Zhou[7], C. Huang[8], S. Wei[9], H. Sun[10], X. Li[11], Y. Yu[12], J. Lai[13], H. Yang[14], H. Fang[15], H. Chen[16], P. Zhang[17], K. Gu[18], Q. Wang[19], J. Shi[20], T. Yi[21], X. Xu[22], X. Ye[23], D. Wang[24], C. Xie[25], C. Liu[26], Y. Zheng[27], D. Lin[28], W. Zhuang[29], P. Lu[30], G. Yu[31], J. Li[32], Y. Gu[33], B. Li[34], R. Wu[35], O. Jiang[36], Z. Wang[37], G. Wu[38], H. Lin[39], D. Zhong[40], Y. Xu[41], Y. Shu[42], D. Wu[43], X. Chen[44], J. Wang[45], M. Wang[46]

[1]**Jilin Cancer Hospital, Changchun**, [2]Yunnan Cancer Hospital, Kunming, [3]Hunan Cancer Hospital, Changsha, [4]The First Affiliated Hospital of Nanchang University, Nanchang, [5]Shandong Cancer Hospital and Institute, Jinan, [6]The Affiliated Hospital of Inner Mongolia University, Hohhot, [7]Sun Yat-sen University Cancer Center, Guangzhou, [8]Tianjin Medical University Cancer Institute and Hospital, Tianjin, [9]Gansu Provincial Cancer Hospital, Lanzhou, [10]The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, [11]The First Affiliated Hospital of Zhengzhou University, Zhengzhou, [12]Harbin Medical University Cancer Hospital, Harbin, [13]Fujian Medical University Union Hospital, Fuzhou, [14]Xiangya Hospital Central South University, Changsha, [15]Anhui Chest Hospital, Hefei, [16]Affiliated Hospital of Guangdong Medical University, Zhanjiang, [17]Shanghai Pulmonary Hospital, Shanghai, [18]The First Affiliated Hospital of Anhui Medical University, Hefei, [19]Henan Cancer Hospital, Zhengzhou, [20]Linyi Cancer Hospital, Linyi, [21]Xiangyang Central Hospital, Xiangyang, [22]Northern Jiangsu People's Hospital, Yangzhou, [23]Guizhou Provincial People's Hospital, Guiyang, [24]Hengshui People's Hospital, Hengshui, [25]Zhongnan Hospital of Wuhan University, Wuhan, [26]Cancer Hospital Affiliated to Xinjiang Medical University, Urumqi, [27]The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, [28]Jiangmen Central Hospital, Jiangmen, [29]Fujian Cancer Hospital, Fuzhou, [30]The First Affiliated Hospital of Xinxiang Medical College, Xinxiang, [31]Weifang People's Hospital, Weifang, [32]Qinghai University Affiliated Hospital, Xining, [33]Qinghai Provincial People's Hospital, Xining, [34]Beijing Chest Hospital, Capital Medical University, Beijing, [35]Shengjing Hospital of China Medical University, Shenyang, [36]The Second People's Hospital of Neijiang, Neijiang, [37]The First Affiliated Hospital of Xinjiang Medical University, Urumchi, [38]Maoming People's Hospital, Maoming, [39]The Second Affiliated Hospital of Hainan Medical University, Haikou, [40]Tianjin Medical University General Hospital, Tianjin/CN, [41]Jingzhou Central Hospital, Jingzhou, [42]Jiangsu Province Hospital, Nanjing, [43]Shenzhen People's Hospital, Shenzhen, [44]The First Affiliated Hospital of Wannan Medical College, Wuhu, [45]Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, [46]Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou

China

Background

- Small-cell lung cancer (SCLC) is a recalcitrant malignancy.
- Despite immunochemotherapy showed promise with a 2-4 month overall survival (OS) benefits in extensive-stage SCLC (ES-SCLC), improving long-term survival remains an unmet need.
- The limited benefit might attribute to the complicated SCLC microenvironment, which is characterized by immunosuppression, angiogenesis and vascularization. Tumor microenvironment reprogramming and tumor vessel normalization could promote immune cell infiltration, obtaining synergistic effects with immunotherapy.
- Therefore, considering the complexity and heterogeneity of SCLC microenvironment, we made an advanced design to combine Benmelstobart (a novel developed PD-L1 inhibitor) with anlotinib (an antivascular agent) plus standard chemotherapy, aiming to obtain improved efficacy, longer survival benefits and manageable safety in ES-SCLC.

Study Design

- A multicenter, placebo-controlled, randomized phase III trial in first-line ES-SCLC.

Key Eligibility Criteria

- 18-75 years
- Pathologically confirmed diagnosis of ES-SCLC
- No prior systemic therapy
- Measurable lesion (RECIST1.1)
- Asymptomatic or treated and stable brain metastases permitted
- ECOG PS 0 or 1
- Adequate organ function

R (1:1:1)
N=738

Induction (Four 21-day cycles)	*Maintenance**
Benmelstobart (1200mg, d1) + **Anlotinib** (12mg, d1-14) + Etoposide + Carboplatin	Benmelstobart + Anlotinib
Placebo + **Anlotinib** (12mg, d1-14) + Etoposide + Carboplatin	Placebo + Anlotinib
Placebo + Placebo + **Etoposide** + **Carboplatin**	Placebo +Placebo

Primary Endpoints
- OS (IRC, RECIST1.1)
- PFS (IRC, RECIST1.1)

Secondary Endpoints
- PFS (investigator, RECIST1.1 and iRECIST)
- ORR
- DCR
- DOR
- 6-mo/12-mo PFS rate
- 12-mo/18-mo OS rate
- Quality of Life
- Safety and tolerability

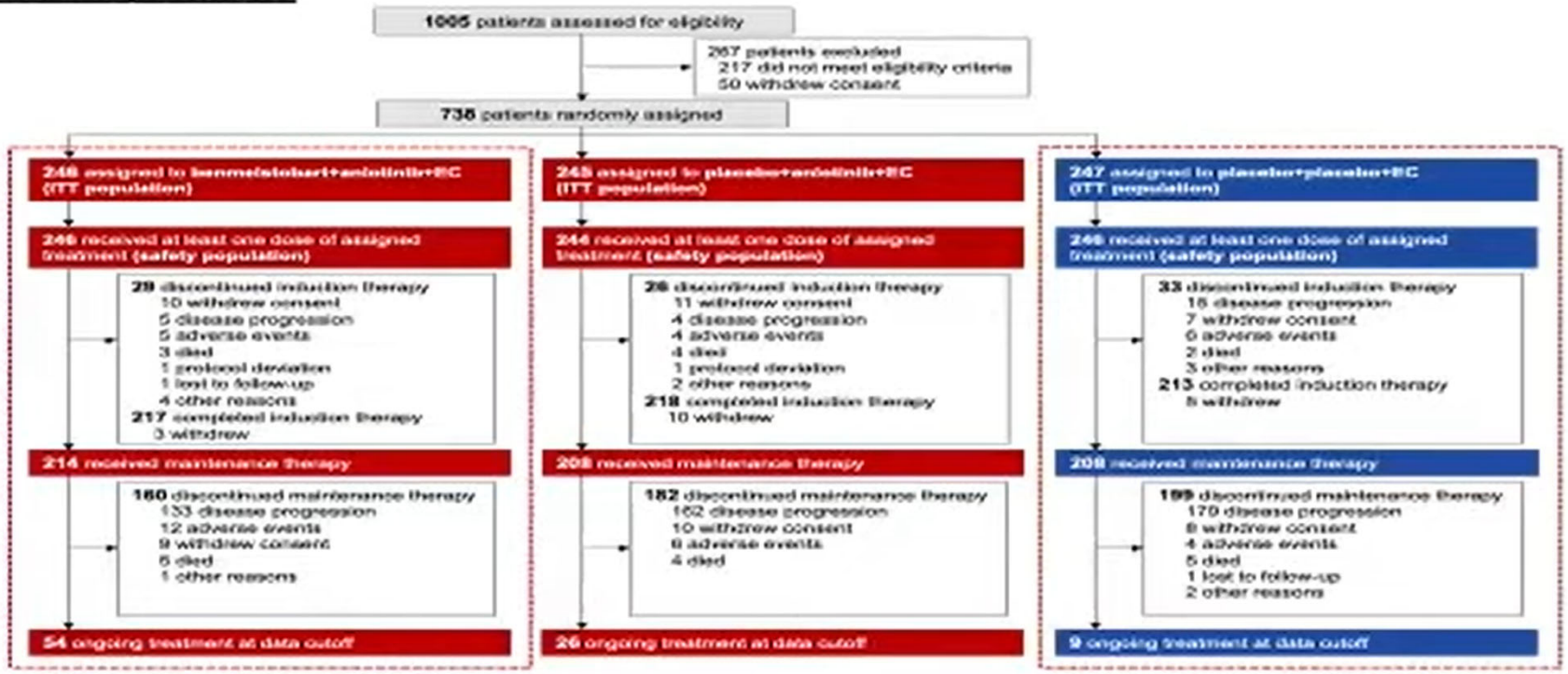
➢ **Stratified by:** ECOG PS (0/1); brain metastases (Y/N); liver metastases (Y/N).

➢ **Statistical Consideration**

- The primary efficacy endpoints of this trial are PFS and OS. In this study, a fixed-sequence test will be used for comparisons between treatment groups.
- The previous study showed that the median OS and PFS in the control group were 10 and 4 months, respectively. Patients were enrolled within a 12-month accrual period with an 18-month follow-up and were randomly assigned (1:1:1) to three groups. The power was 85% with a type I error rate of 0.050 and a dropout incidence of 10%. The type I error rate in the interim analysis for PFS will be controlled by the Method Based on the Sum of P-values (MSP). The initial sample size in this study will be estimated based on PFS using a computer simulation program.

* During maintenance therapy, patients are allowed to receive PCI, but not thoracic radiation.

Patients Disposition



Subsequent Treatment: 117 (47.6%)
Subsequent Immunotherapy: 32 (13.0%)

Subsequent Treatment: 184 (74.8%)
Subsequent Immunotherapy: 53 (21.5%)

Baseline Characteristics (ITT Population)

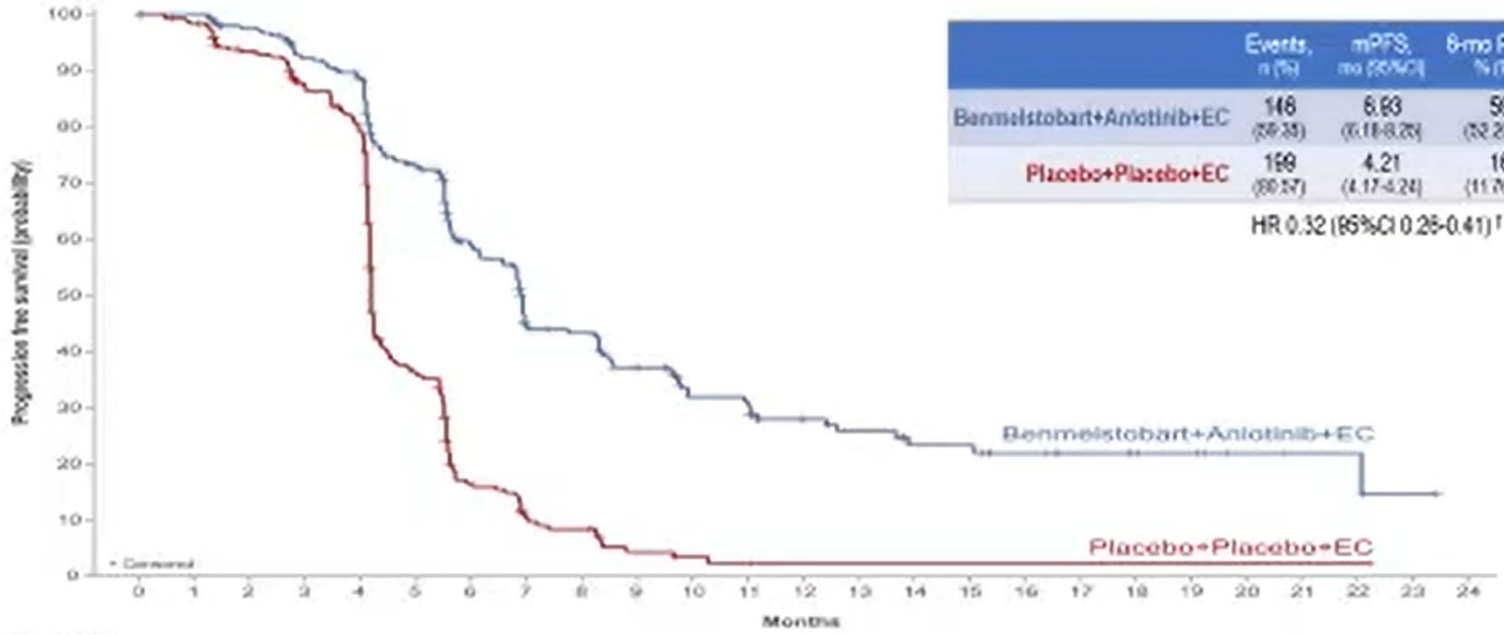
	Benmelstobart+Anlotinib+EC (N=246)	Placebo + Placebo + EC (N=247)
Median Age (range), years	62.0 (36-75)	63.0 (30-75)
Gender, n (%)		
Male	209 (85.0)	207 (83.8)
ECOG PS, n (%)		
0 / 1	47 (19.1) / 199 (80.9)	48 (19.4) / 199 (80.6)
Smoking status, n (%)		
Never	59 (24.0)	54 (21.9)
Former / Current	154 (62.6) / 33 (13.4)	158 (64.0) / 35 (14.2)
Clinical stage[*], n (%)		
Limited-stage	1 (0.4)	7 (2.8)
Extensive-stage	245 (99.6)	240 (97.2)
Disease stage[#] (AJCC 8th), n (%)		
II	0 (0.0)	1 (0.4)[a]
III	30 (12.2)	21 (8.5)
IV	216 (87.8)	225 (91.1)
Brain / Liver / Bone metastases, n (%)	25 (10.2) / 79 (32.1) / 69 (28.0)	26 (10.5) / 79 (32.0) / 69 (27.9)

From Mar 18, 2020 to Dec 10, 2021, 738 patients randomized.

Data cutoff date: May 14, 2022.

[a] The tumor lesions of this stage II patient included the primary tumor in right lung (Tumor >3 cm but ≤4 cm in greatest dimension), regional lymph nodes metastases in ipsilateral hilar and inferior lobe, which cannot be delineated in a target area of radiation therapy and determined as ES-SCLC (assessed by IRC and investigator).

Primary Endpoint: PFS (ITT Population)



	Events, n (%)	mPFS, mo (95%CI)	6-mo PFS rate, % (95%CI)	12-mo PFS rate, % (95%CI)
Benmelstobart+Anlotinib+EC	148 (59.9)	6.93 (5.59-8.28)	59.11 (52.29-65.33)	27.91 (21.26-34.94)
Placebo+Placebo+EC	199 (80.57)	4.21 (4.17-4.24)	18.55 (11.76-22.95)	2.29 (0.56-6.38)

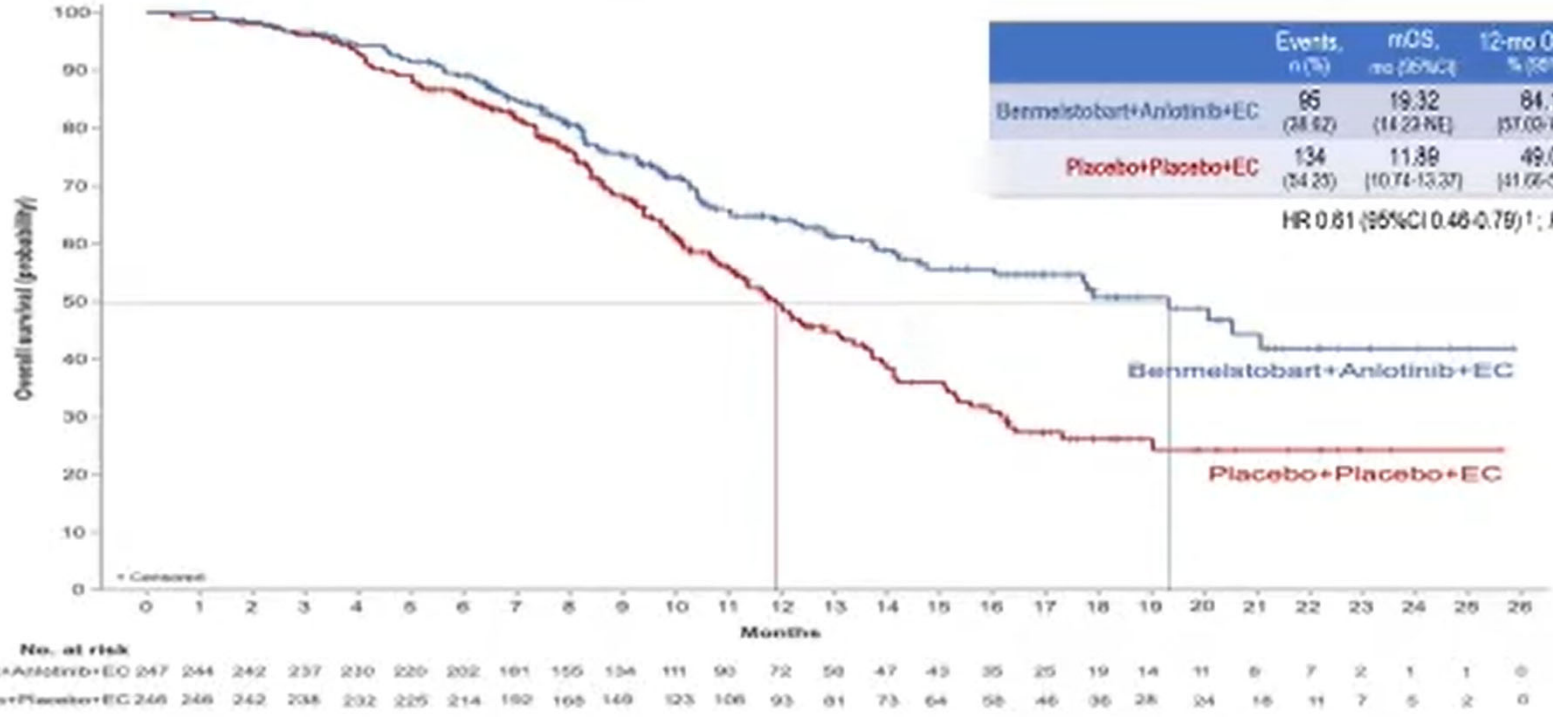
HR 0.32 (95%CI 0.26-0.41)[†] ; $P < 0.0001$ *

Data cutoff date: May 14, 2022; median follow-up was 14.0 months (range, 12.8-15.5)
*P value in sensitivity analysis was done using unstratified log-rank test. †Hazard ratios (HR) in sensitivity analysis was estimated using unadjusted Cox proportional hazards model

Primary Endpoint: OS (ITT Population)

	Events, n (%)	mOS, mo (95%CI)	12-mo OS rate, % (95%CI)	24-mo OS rate, % (95%CI)
Benmelstobart+Anlotinib+EC	85 (38.62)	19.32 (14.23-NE)	64.12 (57.09-70.34)	41.83 (34.98-48.66)
Placebo+Placebo+EC	134 (54.23)	11.89 (10.74-13.37)	49.00 (41.66-55.93)	24.24 (18.96-32.26)

HR 0.61 (95%CI 0.46-0.79)[1]; P = 0.0002 *



Data cutoff date: May 14, 2022; median follow-up was 14.0 months (range, 12.8-15.5).
*P value in sensitivity analysis was done using unstratified log-rank test. [1]Hazard ratios (HR) in sensitivity analysis was estimated using unadjusted Cox proportional hazards model.

PFS and OS in Subgroups

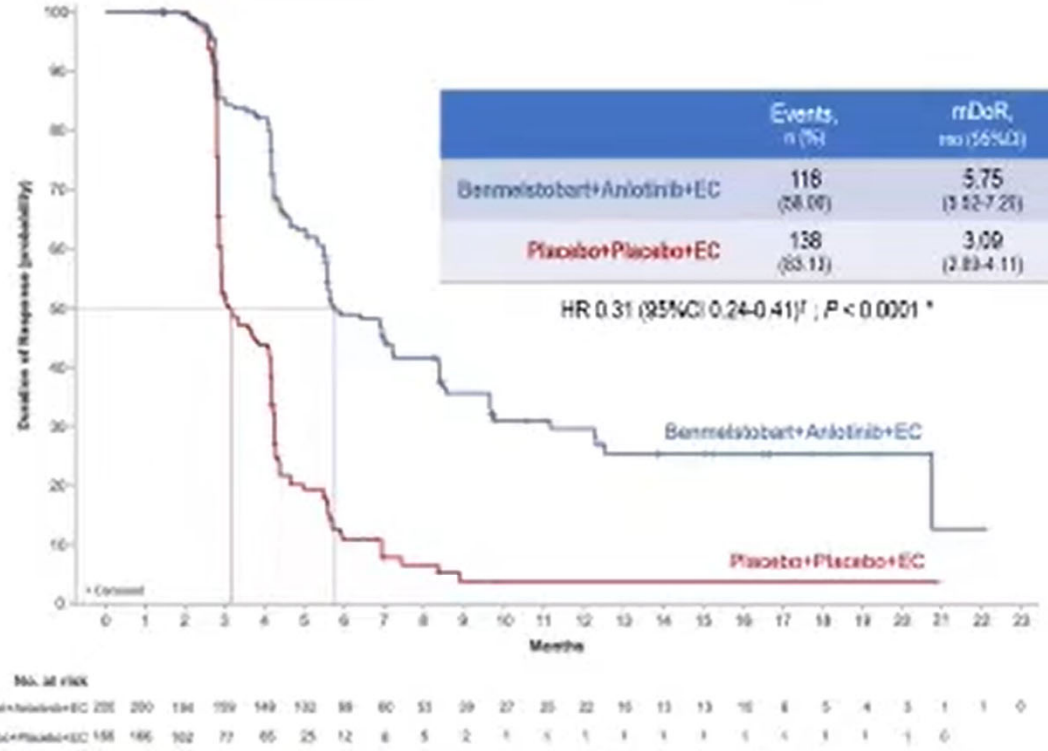
OS

Subgroups	N (Events)	Bevmelotcobart+Azlotinib+EC vs. Placebo+Placebo+EC Hazard Ratio for Death (95%CI)
All the patients	400 (220)	0.61 (0.47-0.79)
ECOG PS, n (%)		
0	95 (35)	0.49 (0.24-0.98)
1	308 (184)	0.63 (0.47-0.84)
Brain metastases		
Yes	51 (27)	0.64 (0.29-1.41)
No	442 (202)	0.60 (0.45-0.79)
Liver metastases		
Yes	158 (98)	0.79 (0.53-1.18)
No	335 (133)	0.51 (0.36-0.72)
Bone metastases		
Yes	138 (73)	0.55 (0.34-0.88)
No	355 (156)	0.62 (0.45-0.86)
Age		
≥65	196 (96)	0.54 (0.35-0.81)
<65	297 (133)	0.66 (0.49-0.92)
Lactate Dehydrogenase (LDH)		
≥ULN	232 (127)	0.61 (0.43-0.87)
<ULN	269 (102)	0.55 (0.37-0.82)
Clinical stage* at first diagnosis		
Limited-stage	8 (5)	0.62 (0.47-0.80)
Extensive-stage	485 (224)	
Gender		
Male	416 (201)	0.64 (0.49-0.85)
Female	77 (28)	0.30 (0.12-0.73)
Disease stage*		
IV	441 (209)	0.63 (0.49-0.82)
IIIB	52 (20)	0.43 (0.16-1.07)
Smoking status		
Former	312 (150)	0.67 (0.49-0.93)
Never	113 (41)	0.38 (0.20-0.74)
Current	60 (36)	0.62 (0.32-1.18)

PFS

Subgroups	N (Events)	Bevmelotcobart+Anlotinib+EC vs. Placebo+Placebo+EC Hazard Ratio for Disease Progression or Death (95%CI)
All the patients	400 (345)	0.32 (0.26-0.41)
ECOG PS, n (%)		
0	95 (80)	0.22 (0.12-0.40)
1	308 (265)	0.38 (0.30-0.49)
Brain metastases		
Yes	51 (45)	0.59 (0.30-1.16)
No	442 (365)	0.33 (0.26-0.42)
Liver metastases		
Yes	158 (123)	0.36 (0.24-0.53)
No	335 (222)	0.31 (0.23-0.41)
Bone metastases		
Yes	138 (100)	0.29 (0.20-0.60)
No	355 (245)	0.33 (0.25-0.44)
Age		
≥65	196 (135)	0.31 (0.22-0.45)
<65	297 (209)	0.37 (0.28-0.50)
Lactate Dehydrogenase (LDH)		
≥ULN	232 (167)	0.35 (0.25-0.48)
<ULN	269 (177)	0.33 (0.24-0.44)
Clinical stage* at first diagnosis		
Limited-stage	8 (7)	0.78 (0.09-6.88)
Extensive-stage	485 (338)	0.35 (0.28-0.44)
Gender		
Male	416 (299)	0.34 (0.27-0.43)
Female	77 (46)	0.32 (0.17-0.60)
Disease stage*		
IV	441 (313)	0.34 (0.27-0.43)
IIIB	52 (36)	0.40 (0.20-0.80)
Smoking status		
Former	312 (227)	0.40 (0.30-0.52)
Never	113 (75)	0.28 (0.15-0.44)
Current	66 (48)	0.28 (0.13-0.58)

Secondary Endpoints: DoR, ORR, DCR (ITT Population)



	Events, n (%)	rmDoR, mo (95%CI)
Benmelstobart+Anlotinib+EC	118 (58.00)	5.75 (3.52-7.23)
Placebo+Placebo+EC	138 (83.13)	3.09 (2.83-4.11)

HR 0.31 (95%CI 0.24-0.41)[†] ; *P* < 0.0001 *

Tumor response (IRC, RECIST 1.1)

	Benmelstobart + Anlotinib + EC (N=246)	Placebo + Placebo + EC (N=247)
Objective confirmed response, n (%) [95%CI]	200 (81.30) [75.86-85.97]	165 (66.80) [60.55-72.64]
Complete Response, n (%)	3 (1.22)	0 (0.00)
Partial Response, n (%)	197 (80.08)	165 (66.80)
Stable Disease, n (%)	23 (9.35)	50 (20.24)
Progressive Disease, n (%)	8 (3.25)	16 (6.48)
Not Evaluable*, n (%)	15 (6.10)	16 (6.48)
P	0.0001	
Disease Control Rate, n (%) [95%CI]	223 (90.65) [86.30-93.98]	215 (87.04) [82.21-90.97]
P	0.2003	

* The best overall response could not be evaluated for patients who had no baseline or no postbaseline tumor assessments, and at least one lesion that could not be evaluated.
IRC= Independent Review Committee.

† *P* value in sensitivity analysis was done using unstratified log-rank test. Hazard ratio (HR) in sensitivity analysis was estimated using unadjusted Cox proportional hazards model.

Saftey Summary	Benmelstobart + Anlotinib + EC (N=246)		Placebo + Placebo + EC (N=246)*	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Any TRAEs, n (%)	246 (100.0)	229 (93.1)	245 (99.6)	214 (87.0)
Leading to any dose reduction or interruption	124 (50.4)	83 (33.7)	57 (23.2)	39 (15.9)
Leading to any discontinuation	21 (8.5)	14 (5.7)	7 (2.8)	5 (2.0)
Leading to death	11 (4.5)	11 (4.5)	4 (1.6)	4 (1.6)
Any irAEs, n (%)	105 (42.7)	41 (16.7)	47 (19.1)	17 (6.9)
Leading to any dose reduction	16 (6.5)	13 (5.3)	5 (2.0)	3 (1.2)
Leading to any discontinuation	20 (8.1)	15 (6.1)	4 (1.6)	3 (1.2)
Leading to death	5 (2.0)	5 (2.0)	1 (0.4)	1 (0.4)
Any SAEs, n (%)	135 (54.9)	115 (46.7)	101 (41.1)	84 (34.1)
Benmelstobart-related ≥ Grade 3 SAEs	/	51 (20.7)	/	22 (8.9)
Anlotinib-related ≥ Grade 3 SAEs	/	56 (22.8)	/	33 (13.4)
Chemotherapy-related ≥ Grade 3 SAEs	/	92 (37.4)	/	63 (25.6)

TRAEs	Benmelstobart + Anlotinib + EC (N=246)		Placebo + Placebo + EC (N=246)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Any TRAEs, n (%)	246 (100.0)	229 (93.1)	245 (99.6)	214 (87.0)
TRAEs reported in ≥10% of patients, n (%)				
Neutrophil count decreased	224 (91.1)	171 (69.5)	223 (90.7)	169 (68.7)
Platelet count decreased	219 (89.0)	122 (49.6)	201 (81.7)	88 (35.8)
White-cell count decreased	223 (90.7)	94 (38.2)	225 (91.5)	85 (34.6)
ALT increased	68 (27.6)	2 (0.9)	73 (29.7)	5 (2.0)
AST increased	66 (26.8)	3 (1.2)	60 (24.4)	1 (0.4)
Weight loss	45 (18.3)	3 (1.2)	17 (6.9)	1 (0.4)
TSH increased	33 (13.4)	1 (0.4)	8 (3.3)	0 (0.0)
Occult blood positive	29 (11.8)	0 (0.0)	17 (6.9)	2 (0.8)
Lymphocyte count decreased	29 (11.8)	8 (3.25)	24 (9.8)	7 (2.9)
Total bilirubin increased	29 (11.8)	2 (0.8)	17 (6.9)	2 (0.8)
γ-GT increased	27 (11.0)	4 (1.6)	28 (11.4)	3 (1.2)

TEAEs= Treatment emergent adverse events; TRAEs= Treatment-related adverse events; irAEs= immune-related adverse events; EC= Etoposide + Carboplatin
* The population that could be evaluated for safety included 245 patients who received at least 1 dose of Placebo+Placebo+EC and 246 patients who received Benmelstobart+Anlotinib+EC

Summary

- Benmelstobar+Anlotinib+EC showed significant benefits over Placebo+EC as first-line therapy in ES-SCLC patients, with the historically longest PFS and OS.
  - -mPFS: Benmelstobart+Anlotinib+EC vs Placebo+EC, 6.9 vs 4.2 months, P<0.0001;
  - -mOS: Benmelstobart+Anlotinib+EC vs Placebo+EC, 19.3 vs 11.9 months, P=0.0002.
- The safety profile is tolerable and manageable.
- The addition of anti-angiogenic agent to immunochemotherapy in the first-line treatment of ES-SCLC resulted in the historically longest PFS and OS, supporting the use of immunochemotherapy plus Anlotinib (a small-molecule, multitargeted anti-angiogenic agent) as a new treatment option for the patients population.