# Supplementary Appendix

Supplement to: Skoulidis F, Ahn M-J, Gadgeel S, et al. Divarasib as compared with sotorasib or adagrasib in *KRAS* G12C–mutated NSCLC. N Engl J Med. DOI: 10.1056/NEJMoa2605703

This appendix has been provided by the authors to give readers additional information about the work.

**SUPPLEMENTARY APPENDIX**

Divarasib Versus Sotorasib or Adagrasib in *KRAS* G12C-Mutated NSCLC

Skoulidis et al.

**TABLE OF CONTENTS**

**Krascendo 1 Investigators and Study Group** ..... 2

**Supplementary Methods** ..... 6

**Figure S1.** Krascendo 1 Study Design. ..... 11

**Figure S2.** Patient Disposition. ..... 12

**Figure S3. A)** BICR-Assessed PFS and B) OS Across Subgroups in the Divarasib Arm Versus the Control Arm*. ..... 13

**Figure S4.** Investigator-Assessed PFS. ..... 14

**Figure S5.** Best Overall Response for Patients Treated with A) Divarasib and B) Control. . 15

**Table S1.** Representativeness of Study Participants. ..... 16

**Table S2.** Adverse Events Leading to Death in Patients in the Divarasib Arm Versus the Control Arm. ..... 17

**Table S3.** Most Common AEs Leading to Treatment Discontinuation (≥1% of Patients in Either Arm). ..... 18

**Table S4.** Safety Summary of Treatment-Related Adverse Events in Patients in the Divarasib Arm Versus the Control Arm. ..... 19

**Table S5.** Overview of AESIs*. ..... 20

**References** ..... 21

**Krascendo 1 Investigators and Study Group**

| Country | Investigator Name(s) | Site Name |
|---|---|---|
| **Argentina** | Ernesto Korbenfeld | Centro Oncologico Korben |
| | Karina Vera | Hospital Britanico |
| **Australia** | Benjamin Solomon | Peter MacCallum Cancer Centre |
| | Alexander Davis | GenesisCare North Shore |
| | Victoria Bray | Liverpool Hospital |
| | Bryan Chan | Sunshine Coast University Hospital |
| | Dainik Patel | Lyell McEwin Hospital |
| **Austria** | Maximilian Hochmair | Krankenhaus Nord - Klinik Floridsdorf |
| **Belgium** | Kristof Cuppens | Jessa Zkh (Campus Virga Jesse) |
| | Kurt Tournoy | AZORG Campus Aalst-Moorselbaan |
| | Jo Raskin | UZ Antwerpen |
| | Sebahat Ocak | CHU UCL Mont-Godinne |
| | Lore Decoster | UZ Brussel |
| | Marie Lecocq | CHU de Liège (Sart Tilman) |
| | Ingel Demedts | AZ Delta (Campus Rumbeke) |
| | Koen Deschepper | Vitaz |
| | Thomas Van Cann | ZAS Sint Augustinus Wilrijk |
| | Iuliana Angelica Tiotiu-Cepuc | Cliniques Universitaires St-Luc |
| **Brazil** | Joao Soler | Hospital de Base de Sao Jose do Rio Preto |
| | Carlos Eduardo Silva | Hospital de Cancer de Barretos |
| | Carlos Teixeira | Hospital Alemao Oswaldo Cruz |
| | Gilberto Castro Junior | Hospital Sírio-Libanês |
| | Eldsamira Sobrinho | Hospital Sao Rafael - HSR |
| **Canada** | Parneet Cheema | William Osler Health Centre - Brampton Civic Hospital |
| | Jennifer Friedmann | Jewish General Hospital |
| **Denmark** | Jon Andersen | Herlev Hospital |
| | Line Brøndum | Regionshospitalet Gødstrup |
| | Peter Meldgaard | Aarhus Universitetshospital |
| **Finland** | Okko-Sakari Kääriäinen | Kuopio Uni Hospital |
| | Katriina Jalkanen | Helsinki University Central Hospital |
| **France** | Aurelie Swalduz | Centre Leon Berard |
| | Julien Mazieres | CHU Toulouse |
| | Celine Mascaux | CHRU de Strasbourg |
| | Olivier Bylicki | Hia Sainte Anne |
| | Jacques Cadranel | Hôpitall Tenon |
| | Charles Dayen | CH de Saint Quentin |
| | Margaux Geier | CHRU Brest |
| | Benoit Roch | CHU Montpellier |
| | Victoria Ferrari | Centre Antoine Lacassagne Centre Régional de Lutte Contre Le Cancer |
| | Alexis Cortot | CHRU Lille |

| | | |
|---|---|---|
| | Remi Veillon | CHU Bordeaux |
| | Michael Duruisseaux | Hôpital Louis Pradel |
| **Germany** | Sebastian Ertl | KEM/Evang. Kliniken Essen Mitte gGmbH |
| | Sabine Bohnet | Universitätsklinikum Schleswig-Holstein |
| | Eva-Lotte Buchmeier | Klinikum Koeln-Merheim |
| | Daniel Misch | Helios Klinikum Emil von Behring GmbH |
| | Georg Evers | Universitätsklinikum Münster, Medizinische Klinik A, Translationale Onkologie |
| | Christian Schulz | Universitätsklinikum Regensburg |
| | Martin Schuler | Universitätsklinikum Essen |
| | Farastuk Bozorgmehr | Thoraxklinik Heidelberg gGmbH |
| | Karsten Schulmann | Lungenklinik Hemer |
| | Martin Reck | LungenClinic Großhansdorf GmbH |
| | Christian Grohé | Evangelische Lungenklinik Berlin |
| | Jan Stratmann | Universität Des Saarlandes |
| | Konrad Kokowski | Klinikum Bogenhausen |
| | Jens Kern | Klinikum Würzburg Mitte gGmbH |
| | Niels Reinmuth | Asklepios Fachkliniken GmbH |
| | Martin Faehling | Klinikum Esslingen |
| | Jonas Kuon | SLK Kliniken Heilbronn GmbH, Standort Fachklinik Löwenstein |
| **Greece** | Giannis Mountzios | Errikos Dynan Hospital |
| | Konstantinos Syrigos | Uoa Sotiria Hospital |
| | Grigorios Rallis | Theageneio Hospital |
| | Eleni Fountzila | Ag. Loukas Hospital |
| | Athanasios Kotsakis | University Hospital of Larissa |
| **Hong Kong** | Siu Ching Molly Li | Prince of Wales Hosp |
| | Shi Feng Nyaw | Tuen Mun Hospital |
| **Italy** | Marcello Tiseo | A.O. Universitaria Di Parma |
| | Laura Bonanno | IRCCS Istituto Oncologico Veneto (IOV) |
| | Antonio Chella | Azienda Ospedaliero Universitaria Pisana |
| | Giovanni Maria Fadda | Ospedale Civile SS Annunziata |
| | Annamaria Catino | Irccs Ist. Tumori Giovanni Paolo Ii |
| | Lorenzo Antonuzzo | Azienda Ospedaliero-Universitaria Careggi |
| | Carlo Genova | Ospedale Policlinico San Martino |
| | Lorenza Landi | IRCCS Istituto Regina Elena (IFO) |
| **Japan** | Shunichi Sugawara | Sendai Kousei Hospital |
| | Yasushi Goto | National Cancer Center Hospital |
| | Noriko Yanagitani | The Cancer Institute Hospital of JFCR |
| | Hiroaki Akamatsu | Wakayama Medical University Hospital |
| | Isamu Okamoto | Kyushu University Hospital |
| | Hiroaki Kanemura | Kindai University Hospital |
| **Mexico** | Eleazar Macedo | ARKE Estudios Clínicos S.A. de C.V. |
| **Netherlands** | Bianca Van Veggel | Jeroen Bosch Ziekenhuis |
| | Kornelis Van Der Leest | Amphia Ziekenhuis |
| | Niels Claessens | Ziekenhuis Rijnstate |

| | | |
|---|---|---|
| | Sevim Uzun | Medisch Centrum Haaglanden, locatie Antoniushove |
| | Peter Plomp | Isala |
| | Lisenka Boom | Ziekenhuis St. Jansdal |
| **Poland** | Marcin Skrzypski | Uniwersyteckie Centrum Kliniczne, Klinika Onkologii i Radioterapii |
| | Krzysztof Rogoziewicz | Dolnośląskie Centrum Onkologii, Pulmonologii i Hematologii |
| | Mateusz Polaczek | Instytut Gruzlicy I Chorob Pluc |
| **Portugal** | Rita Felix | IPO do Porto |
| | Ana Marques | Hospital de Braga |
| | Antonio Araujo | Centro Hospitalar do Porto – Hospital de Santo António |
| | Ana Figueiredo | CHUC - Unidade de Pneumologia Oncológica |
| | Marcos Pantarotto | Centro Clinico Champalimaud |
| **Republic of Korea** | Hyun Ae Jung | Samsung Medical Center |
| | Tae Min Kim | Seoul National University Hospital |
| | Se Hyun Kim | Seoul National University Bundang Hospital |
| | In-Jae Oh | Chonnam National University Hwasun Hospital |
| | Byoung Yong Shim | St. Vincent's Hospital |
| | Joo-Hwan Park | Gachon University Gil Medical Center |
| **Singapore** | Geet Yi Gillianne Lai | National Cancer Centre |
| **Spain** | Rosa Alvarez Alvarez | Hospital General Universitario Gregorio Marañon |
| | Oscar Juan Vidal | Hospital Universitario la Fe |
| | Angel Artal Cortes | Hospital Universitario Miguel Servet |
| | Ernest Nadal | Institut Catala d Oncologia Hospitalet |
| | Enriqueta Felip | Hospital Vall Hebron |
| | Vanesa Gutierrez | Hospital Regional Universitario de Malaga |
| | Margarita Majem Tarruella | Hospital de la Santa Creu i Sant Pau |
| | Jose Fuentes Pradera | Hospital Nuestra Senora de Valme |
| **Sweden** | Johan Isaksson | Gävle Sjukhus |
| **Taiwan** | Jin-Yuan Shih | National Taiwan University Hospital |
| | Yung-Hung Luo | Taipei Veterans General Hospital |
| | How-Wen Ko | Chang Gung Medical Foundation - Linkou |
| **Thailand** | Pongwut Danchaivijitr | Siriraj Hospital |
| | Sarayut Geater | Songklanagarind Hospital |
| | Yotsawaj Runglodvatana | Vajira Hospital |
| **United Kingdom** | Katy Clarke | St James University Hospital |
| | Nicola Steele | Beatson West Of Scotland Cancer Centre |
| | Nicola Thompson | Addenbrooke's Hospital |
| | Louise Medley | Torbay Hospital |
| | Jason Adhikaree | Nottingham City Hospital |
| | Sanjay Popat | Royal Marsden Hospital - London<br>Royal Marsden Hospital (Sutton) |
| | Alexandros Georgiou | Guy's Hospital - Cancer Centre |
| | Victoria Brown | Castle Hill Hospital |
| | Ariel Lopez-Chavez | Allegheny Cancer Center |

| | | |
|---|---|---|
| **United States of America** | Ferdinandos Skoulidis | MD Anderson Cancer Center |
| | Wade Iams | Tennessee Oncology<br>Tennessee Oncology, PLLC - Chattanooga |
| | Jiaxin Niu | Banner Health MD Anderson AZ |
| | Angel Qin | University of Michigan |
| | Amy Cummings | UCLA Hematology / Oncology Clinic |
| | Marina Chiara Garassino | University of Chicago Medical Center |
| | James Yoo | Oregon Health & Science University |
| | Christian Thomas | New England Cancer Specialists |
| | Bassam Ghabach | JPS Health Network |
| | Benjamin Herzberg | Columbia University Medical Center |
| | Collin Blakely | University of California, San Francisco |
| | Raymond Osarogiagbon | Baptist Clinical Research Institute |
| | Jia Luo | Dana Farber Cancer Institute |
| | Estelamari Rodriguez | University of Miami |
| | John Nemunaitis | Taylor Cancer Research Center |
| | Bo Wang | Oncology Associates of Oregon, P.C |
| | Eric Santos | Cancer and Hematology Centers of Western Michigan |
| | Ernesto Bustinza-Linares | Florida Cancer Specialists - North |
| | So Yeon Kim | Yale Cancer Center |
| | Parth Desai | Fox Chase Cancer Center |
| | Ronald Tang | Los Angeles Cancer Network |
| | Neeraj Sharma | Texas Oncology - Northeast Texas |
| | Eric Lander | Minnesota Oncology Edina |

## Supplementary Methods

*Patients*

*KRAS* G12C mutation was confirmed by central laboratory testing of tumor samples provided at screening on Qiagen *therascreen* KRAS RGQ PCR Kit or pre-existing results from blood or tumor tissue samples via a Clinical Laboratory Improvement Amendments (CLIA)-approved laboratory. *KEAP1* mutational status was confirmed through central laboratory testing of blood samples with FoundationOne® Liquid CDx (F1LCDx) or pre-existing results from approved next-generation sequencing tests. Programmed death-ligand 1 (PD-L1) levels were determined by local testing. Required prior systemic treatment included a platinum-based doublet chemotherapy and a programmed cell death protein 1 (PD-1)/ PD-L1 inhibitor, either given in combination as one line of therapy (i.e., PD-L1/PD-1 inhibitor plus platinum-based doublet chemotherapy) or as individual lines of therapy (i.e., PD-L1/PD-1 inhibitor preceded or followed by platinum-based doublet chemotherapy) unless the individual had a medical contraindication to one of the required therapies.

Patients with known actionable concomitant second oncogenic driver mutations were excluded (*EGFR* mutations, *ALK* rearrangement, *ROS1* rearrangement, *BRAF* V600E mutation, *HER2* mutations, *NTRK* fusions, *RET* fusions, and *MET* Exon 14 skipping mutations). While patients with untreated or active central nervous system (CNS) metastases were excluded, patients were eligible if CNS metastases were adequately treated and neurologically stable.

*Trial oversight and author responsibilities*

| Contribution | Authors |
|---|---|
| Study design | Ferdinandos Skoulidis, Myung-Ju Ahn, Shirish Gadgeel, Sanjay Popat, Niels Reinmuth, Youyou Hu, Sarah M Shagan, Mark T Lin, Uyi Osaghae, Tien Hoang, Felice Wu, Raymond Meng, Michael S Mathisen, Benjamin J Solomon |
| Data collection | All authors |
| Data analysis | All authors |
| Manuscript drafting/providing critical review | All authors<br>The first draft, under the direction of the authors, was written by Rebecca Benatan, BSc, of Ashfield MedComms, an Inizio company, and funded by F. Hoffmann-La Roche Ltd. Third-party medical writing assistance, under the direction of the authors, was provided by Rebecca Benatan, BSc, and Claire White, PhD, of Ashfield MedComms, an Inizio company, and funded by F. Hoffmann-La Roche Ltd. |
| Approval of final manuscript | All authors |

*Trial design and treatment*

Randomization was conducted via an Interactive Voice/Web Response System (IxRS) using a permuted-block randomization method.

For the stratification factor intended KRAS G12C inhibitor in the control arm, investigators declared which control treatment (sotorasib or adagrasib) they would assign the patient to in the event the patient was randomized to the control arm. Patients were then randomized to receive divarasib or the investigator-assigned control treatment.

Treatment beyond disease progression was permitted if there was evidence of clinical benefit (per investigator), absence of signs and symptoms of unequivocal disease progression (including worsening laboratory results), no decline in Eastern Cooperative Oncology Group performance status attributed to disease progression, absence of tumor progression at critical sites that could not be managed with protocol-allowed medical interventions, and written patient consent.

The dose of divarasib could be reduced to 200 mg then 100 mg for management of treatment-related toxicities. If further dose reductions were required, divarasib treatment was discontinued. Dose modifications for sotorasib and adagrasib were permitted per local prescribing information. If the dose of divarasib was interrupted for >1 cycle (21 days) due to toxicity, treatment was discontinued unless clinically indicated.

*Endpoints and assessments*

Progression-free survival (PFS) was defined as the time from randomization to the first occurrence of disease progression, according to RECIST v1.1, or death from any cause (whichever occurred first). Overall survival (OS) was defined as the time from randomization to death from any cause. Confirmed overall response rate (ORR) was defined as complete response or partial response on two occasions ≥4 weeks apart, as determined by blinded independent central review (BICR) according to RECIST v1.1. Duration of response was defined as the time from the first occurrence of a documented confirmed objective response to disease progression, as determined by BICR according to RECIST v1.1, or death from any cause (whichever occurred first).

Patient-reported outcome (PRO) assessments included time to confirmed deterioration (TTCD) of dyspnea and physical functioning using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and cough using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 (EORTC QLQ-LC13). TTCD was defined as the time from the date of randomization until the first confirmed clinically meaningful deterioration that was maintained for at least two consecutive assessments or an initial clinically meaningful decrease or increase from baseline followed by death (attributable to cancer progression within 6 weeks). The proportion of missing data at each assessment timepoint was summarized to facilitate interpretation of the data.

The primary endpoint of the trial was originally investigator-assessed PFS and was updated to PFS by BICR to align with Health Authority and Ethics Committee requests. BICR-assessed PFS was a requirement in the original protocol and was therefore assessed for all patients.

Key biomarkers including *KEAP1* and PD-L1 were evaluated for their association with efficacy in a pre-planned analysis.

Participants who discontinued treatment prior to radiographic disease progression continued to have tumor assessments, even if they started new anticancer therapy, until disease progression, withdrawal of consent, loss to follow-up, or death. Participants who were treated beyond disease progression continued to undergo tumor assessments every 6 weeks after initial documentation of progression, or more frequently if clinically indicated, regardless of time in the study until treatment was discontinued.

*Statistical analysis*

To control the overall two-sided type I error rate at 0.05, hierarchical testing was conducted for PFS, OS, ORR, and TTCD (evaluated sequentially for EORTC QLQ-LC13 cough, QLQ-C30 dyspnea, and QLQ-C30 physical functioning). Each endpoint was tested only if the preceding endpoint reached statistical significance.

At the interim analysis for OS, the stopping boundary for early rejection of the null hypothesis for an overall two-sided 5% significance level was 0.0128 for 156 events. Since the prespecified efficacy threshold for OS was crossed at this analysis, no further formal testing of this hypothesis will occur.

Median duration of follow-up was calculated using the inverse Kaplan-Meier method. A stratified log-rank test was used to compare PFS and OS between treatment groups. The hazard ratios and associated 95% confidence intervals (CIs) for PFS and OS were estimated using a stratified Cox regression model. The Kaplan-Meier method and the Brookmeyer-

Crowley method were used to estimate the median PFS, OS, and DoR for each arm with associated 95% CIs. In addition, for descriptive purposes, the PFS rates were estimated using the Kaplan-Meier method for each treatment arm and the 95% CIs calculated by using the standard error derived from Greenwood's formula. For subgroup analyses of BICR-assessed PFS and OS, hazard ratios and 95% CIs were estimated using unstratified Cox proportional hazards models. All subgroups were prespecified. CI widths were not adjusted for multiplicity and should not be used in place of hypothesis tests.

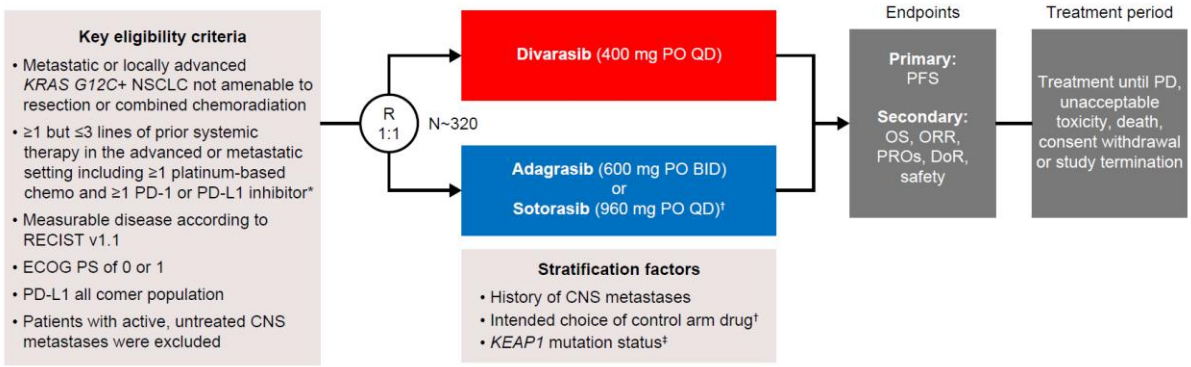
An estimate of ORR and its 95% CI was calculated using the Clopper-Pearson method for each treatment arm. For formal testing of difference in confirmed ORR between the treatment arms, a covariate-adjusted analysis for the difference of proportions was conducted using G-Computation where a logistic regression model was fitted adjusting for the stratification factors specified in randomization, with 95% CIs estimated by bootstrap resampling. Statistical significance was inferred if the 95% CI for difference in confirmed ORR excluded zero.

Key assumptions were needed in the interpretation of the reported estimates. PFS assumed proportional hazards, evaluated under a treatment policy strategy (assessed regardless of treatment early discontinuation, or subsequent therapies), with sample size calculations assuming an exponential survival distribution. OS assumed a treatment policy strategy and proportional hazards, with sample size and interim efficacy stopping boundaries governed by an exponential survival distribution. ORR assumed a composite variable strategy treating patients with early discontinuations or pre-response non-protocol therapies as non-responders, with treatment arm differences evaluated via covariate-adjusted G-computation and bootstrap resampling.

Dose intensity with respect to total dose was the total dose actually received divided by the planned total dose and multiplied by 100.

Details on statistical analysis can be found in the protocol and the statistical analysis plan.

**Figure S1.** Krascendo 1 Study Design.




*In the advanced or metastatic setting.

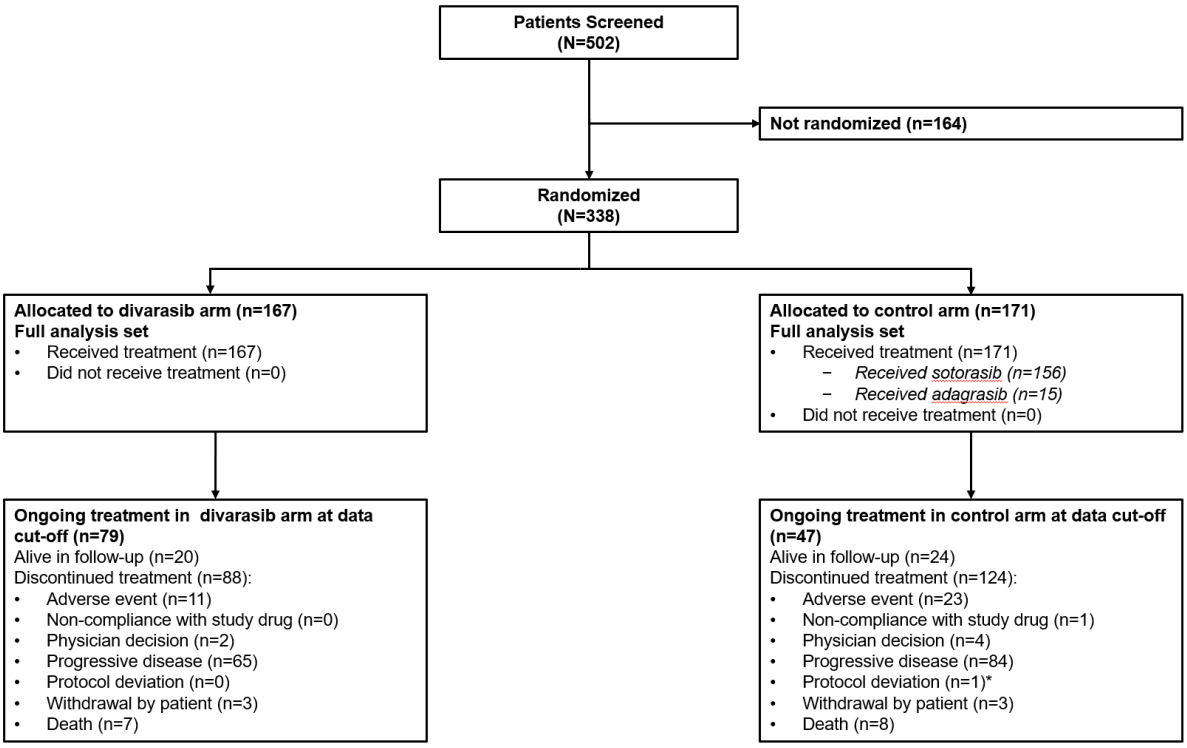
†The control arm drug will depend on local approvals and availability; if both drugs are locally approved and readily available, the investigators will choose and participants will receive the same drug for the duration of treatment.

‡Detected versus not detected/unknown.

§Including time to confirmed deterioration.

BID, twice daily; CNS, central nervous system; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer; OS, overall survival; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PO, orally; PRO, patient-reported outcome; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; TTCD, time to confirmed deterioration.

**Figure S2.** Patient Disposition.



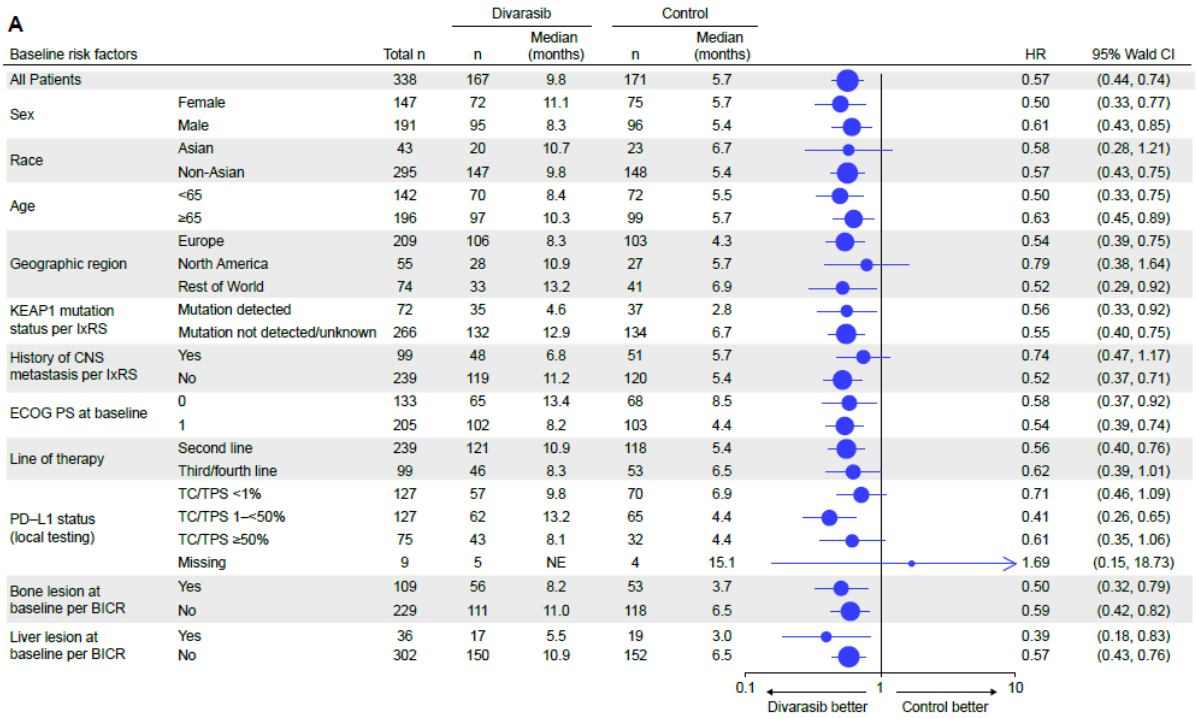

**Data cut-off: May 19, 2026.**

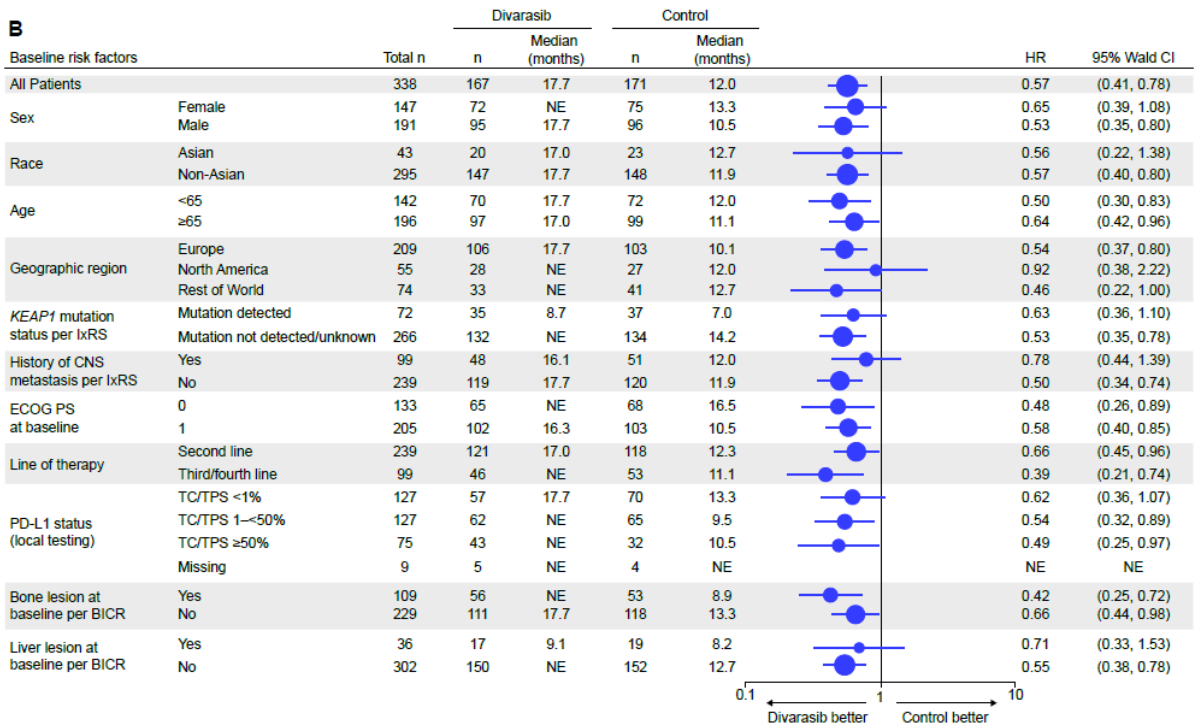
Control arm included treatment with sotorasib or adagrasib. Patients could be treated beyond progressive disease and therefore the number of patients who discontinued due to progressive disease is less than the number of patients with a progressive disease event.

*Patient did not have *KRAS* G12C-mutated NSCLC and was mis-enrolled.

NSCLC, non-small cell lung cancer.

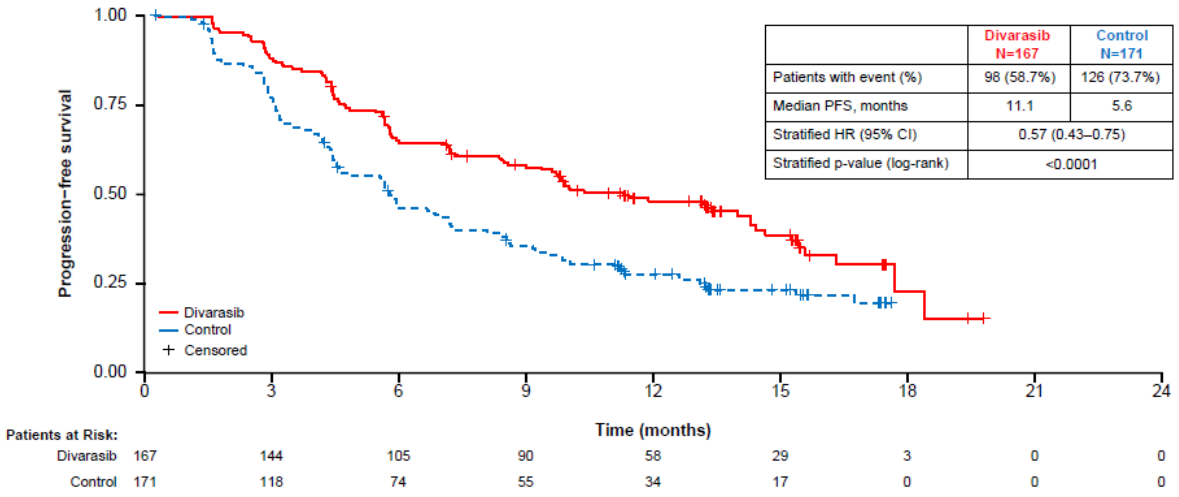
**Figure S3. A)** BICR-Assessed PFS and B) OS Across Subgroups in the Divarasib Arm Versus the Control Arm*.




*Control arm included treatment with sotorasib or adagrasib.
Hazard ratios across pre-specified subgroups are exploratory. Proportional hazards assumptions were evaluated; non-proportionality was observed in the North America overall survival subgroup. Subgroup estimates should be interpreted with caution.

**Figure S4.** Investigator-Assessed PFS.

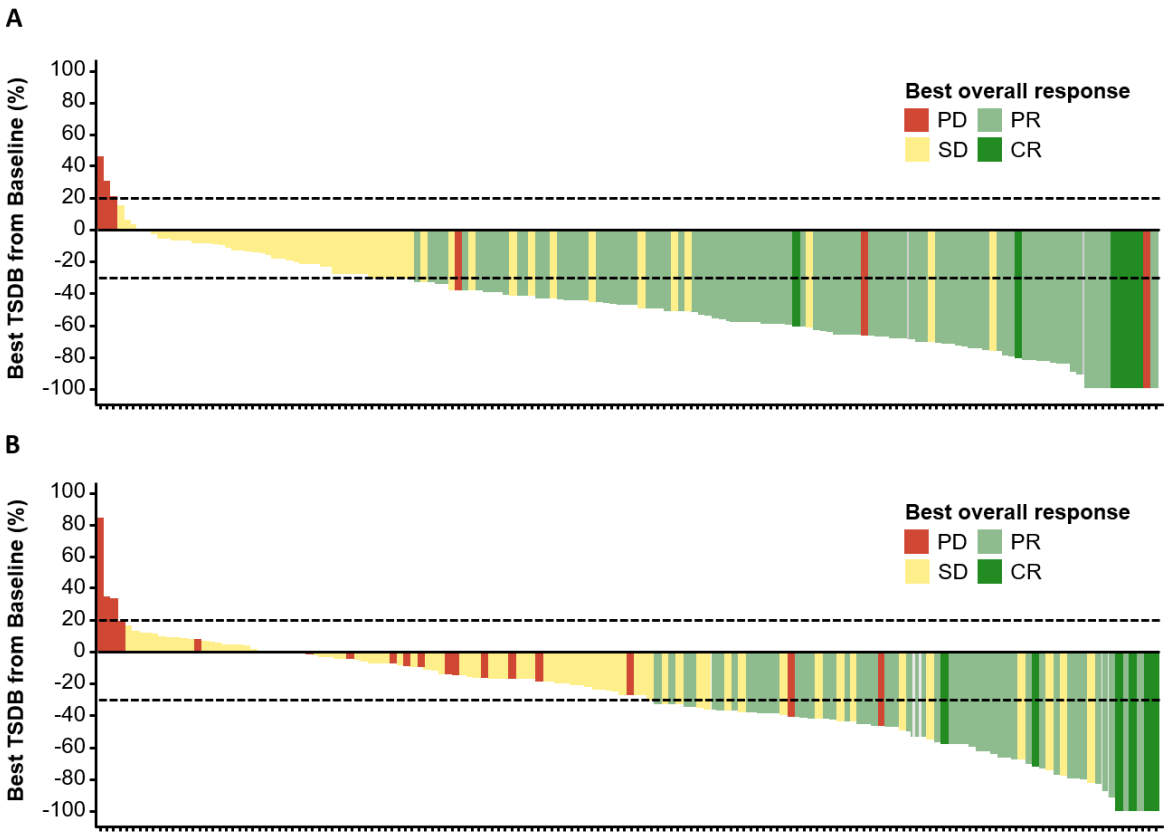



| | Divarasib N=167 | Control N=171 |
|---|---|---|
| Patients with event (%) | 98 (58.7%) | 126 (73.7%) |
| Median PFS, months | 11.1 | 5.6 |
| Stratified HR (95% CI) | 0.57 (0.43–0.75) | |
| Stratified p-value (log-rank) | <0.0001 | |

Control arm included treatment with sotorasib or adagrasib.

CI, confidence interval; OS, overall survival; PFS, progression-free survival.

**Figure S5.** Best Overall Response for Patients Treated with A) Divarasib and B) Control.




Control arm included treatment with sotorasib or adagrasib.

**Table S1.** Representativeness of Study Participants.

| Category | Details |
|---|---|
| Disease under investigation | *KRAS* G12C-mutated NSCLC |
| Special consideration related to: | |
| Sex and gender | *KRAS* G12C mutations are more prevalent in female patients than male patients.[1-3] |
| Age | The median age of patients with locally advanced/metastatic *KRAS* G12C-mutated NSCLC is approximately 68 years, which is comparable with that of patients with *KRAS* wild-type NSCLC.[3,4] |
| Race or ethnic group | In NSCLC, the frequency of *KRAS* G12C mutations varies by race or ethnicity.[1,3] White populations have the highest frequency of *KRAS* G12C mutations (~13%), followed by Black/African American populations (~11%); *KRAS* G12C mutations occur at a relatively low frequency in Asian populations (~4%). |
| Geography | Real-world studies have shown geographic variation in *KRAS* G12C prevalence in advanced NSCLC: 9–20% in the US, 9–18% in Europe, and 1–4% in Asia.[5] |
| Other considerations | *KRAS* G12C mutations are strongly associated with a history of tobacco smoking.[3,6] |
| Overall representativeness of this trial | Demographic and disease characteristics in the Krascendo 1 trial were generally consistent with those previously reported. The median age of patients was 66 years, and most patients were White (77.5%) and previous or current smokers (97%). A notable exception was that there was a higher proportion of male patients (56.5%) than female patients (43.5%); however, the proportion of female patients was higher in Krascendo 1 than in phase III studies for *KRAS* G12C inhibitors, sotorasib and adagrasib (36.3% and 36%, respectively).[7,8] |

NSCLC, non-small cell lung cancer.

**Table S2.** Adverse Events Leading to Death in Patients in the Divarasib Arm Versus the Control Arm.

| **Grade 5 AE, n (%)** | **Divarasib (n=167)** | **Control* (n=171)** |
|---|---|---|
| Pneumonia | 3 (1.8) | 0 |
| Death | 0 | 2 (1.2) |
| Urinary tract infection | 1 (0.6) | 0 |
| Gastrointestinal hemorrhage | 2 (1.2)† | 0 |
| Transitional cell carcinoma | 1 (0.6) | 0 |
| Depressed level of consciousness | 1 (0.6) | 0 |
| Confusional state | 1 (0.6) | 0 |
| Chronic obstructive pulmonary disease | 1 (0.6) | 0 |
| Device-related sepsis | 0 | 1 (0.6) |
| Acute myeloid leukemia | 0 | 1 (0.6) |
| Ischemic stroke | 0 | 1 (0.6) |
| Myocardial infarction | 0 | 1 (0.6) |
| Road traffic incident | 0 | 1 (0.6) |

*Control arm included treatment with sotorasib or adagrasib.

†Includes GI hemorrhage and Upper GI hemorrhage (n=1, each)

AE, adverse event.

**Table S3.** Most Common AEs Leading to Treatment Discontinuation (≥1% of Patients in Either Arm).

| **AE, n (%)** | **Divarasib (n=167)** | **Control* (n=171)** |
|---|---|---|
| Alanine aminotransferase increased | 1 (0.6%) | 6 (3.5%) |
| Aspartate aminotransferase increased | 0 | 5 (2.9%) |
| Drug-induced liver injury | 2 (1.2%) | 1 (0.6%) |
| Diarrhea | 2 (1.2%) | 1 (0.6%) |
| Blood alkaline phosphatase increased | 0 | 3 (1.8%) |
| Gamma-glutamyltransferase increased | 0 | 3 (1.8%) |
| Hepatitis | 0 | 3 (1.8%) |
| Pneumonitis | 0 | 3 (1.8%) |
| Lipase increased | 0 | 2 (1.2%) |
| Liver function test increased | 0 | 2 (1.2%) |

*Control arm included treatment with sotorasib or adagrasib.

AE, adverse event.

**Table S4.** Safety Summary of Treatment-Related Adverse Events in Patients in the Divarasib Arm Versus the Control Arm.

| **Safety parameter, n (%)** | **Divarasib (n=167)** | | **Control* (n=171)** | |
|---|---|---|---|---|
| | **All grade** | **Grade ≥3** | **All grade** | **Grade ≥3** |
| TRAE | 155 (92.8) | 41 (24.6) | 137 (80.1) | 59 (34.5) |
| Treatment-related SAE | 13 (7.8) | NA | 26 (15.2) | NA |
| TRAE leading to any dose action | 60 (35.9) | NA | 77 (45.0) | NA |
| TRAE leading to treatment discontinuation | 8 (4.8) | NA | 20 (11.7) | NA |
| TRAE leading to dose reduction | 44 (26.3) | NA | 51 (29.8) | NA |
| TRAE leading to dose interruption | 33 (19.8) | NA | 40 (23.4) | NA |
| TRAEs that occurred in ≥10% patients in either treatment arm | | | | |
| Diarrhea | 110 (65.9) | 15 (9.0) | 65 (38.0) | 5 (2.9) |
| Nausea | 89 (53.3) | 2 (1.2) | 35 (20.5) | 4 (2.3) |
| Vomiting | 65 (38.9) | 0 | 14 (8.2) | 2 (1.2) |
| Alanine aminotransferase increased | 25 (15.0) | 9 (5.4) | 39 (22.8) | 16 (9.4) |
| Aspartate aminotransferase increased | 23 (13.8) | 3 (1.8) | 36 (21.1) | 15 (8.8) |
| Fatigue | 17 (10.2) | 0 | 23 (13.5) | 1 (0.6) |
| Decreased appetite | 21 (12.6) | 1 (0.6) | 17 (9.9) | 3 (1.8) |
| Lipase increased | 17 (10.2) | 5 (3.0) | 20 (11.7) | 9 (5.3) |
| Blood alkaline phosphatase increased | 8 (4.8) | 1 (0.6) | 27 (15.8) | 7 (4.1) |
| Constipation | 22 (13.2) | 0 | 5 (2.9) | 0 |

*Control arm included treatment with sotorasib or adagrasib.

TRAE, treatment-related adverse event

**Table S5.** Overview of AESIs*.

| **AESI, n (%)** | **Divarasib (n=167)** | **Control† (n=171)** |
|---|---|---|
| Total number of patients with at least one AESI | 156 (93.4) | 130 (76.0) |
| Total number of AESIs | 718 | 418 |
| **Total number of patients with at least one:** | | |
| Grade 1–2 AESI | 118 (70.7) | 78 (45.6) |
| Grade 3–4 AESI | 38 (22.8) | 52 (30.4) |
| Grade 5 AESI | 0 | 0 |
| Serious AESI | 12 (7.2) | 18 (10.5) |
| AESI leading to any dose action | 59 (35.3) | 68 (39.8) |
| AESI leading to study treatment discontinuation | 7 (4.2) | 16 (9.4) |
| AESI leading to dose reduction | 38 (22.8) | 43 (25.1) |
| AESI leading to drug interruption | 37 (22.2) | 32 (18.7) |
| Treatment-related AESI | 146 (87.4) | 108 (63.2) |
| Treatment-related grade 3–4 AESI | 31 (18.6) | 47 (27.5) |
| Treatment-related grade 5 AESI | 0 | 0 |
| Treatment-related serious AESI | 8 (4.8) | 16 (9.4) |
| **Medical concept categories, n (%)** | | |
| GI toxicity | 152 (91.0) | 117 (68.4) |
| Hepatotoxicity | 45 (26.9) | 67 (39.2) |

*Adverse event terms per Standard MedDRA Query for GI toxicity include: gastrointestinal nonspecific symptoms and therapeutic procedure (narrow), non-infectious diarrhea (narrow), and colitis (exclude infective). Adverse event terms per Standard MedDRA Query for hepatotoxicity include: hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (narrow), liver-related investigation, signs and symptoms (narrow), and hepatitis, non-infectious (narrow).

†Control arm included treatment with sotorasib or adagrasib.

AESI, adverse event of special interest; GI, gastrointestinal; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, Standard MedDRA Query.

**References**

1. Nassar AH, Adib E, Kwiatkowski DJ. Distribution of KRAS (G12C) somatic mutations across race, sex, and cancer type. N Engl J Med 2021;384:185-7.

2. Isaksson J, Berglund A, Louie K, et al. KRAS G12C mutant non-small cell lung cancer linked to female sex and high risk of CNS metastasis: population-based demographics and survival data from the National Swedish Lung Cancer Registry. Clin Lung Cancer 2023;24:507-18.

3. Julian C, Pal N, Gershon A, et al. Overall survival in patients with advanced non-small cell lung cancer with KRAS G12C mutation with or without STK11 and/or KEAP1 mutations in a real-world setting. BMC Cancer 2023;23:352.

4. Judd J, Abdel Karim N, Khan H, et al. Characterization of KRAS mutation subtypes in non-small cell lung cancer. Mol Cancer Ther 2021;20:2577-84.

5. Lim TKH, Skoulidis F, Kerr KM, et al. KRAS G12C in advanced NSCLC: prevalence, co-mutations, and testing. Lung Cancer 2023;184:107293.

6. Salem ME, El-Refai SM, Sha W, et al. Landscape of KRASG12C, associated genomic alterations, and interrelation with immuno-oncology biomarkers in KRAS-mutated cancers. JCO Precis Oncol 2022:e2100245.

7. de Langen AJ, Johnson ML, Mazieres J, et al. Sotorasib versus docetaxel for previously treated non-small-cell lung cancer with KRAS G12C mutation: a randomised, open-label, phase 3 trial. Lancet 2023;401:733-46.

8. Barlesi F, Yao W, Duruisseaux M, et al. Adagrasib versus docetaxel in KRAS(G12C)-mutated non-small-cell lung cancer (KRYSTAL-12): a randomised, open-label, phase 3 trial. Lancet 2025;406:615-26.