Supplementary Appendix

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

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SUPPLEMENTARY APPENDIX

Supplement to: Andre F, Ciruelos EM, Rubovsky G, et al. Alpelisib for *PIK3CA*-mutant, HR-positive advanced breast cancer.

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List of investigators

Table S1. Recruitment sites

Recruitment Site	Principal Investigator	Number of Patients Recruited
Országos Onkológiai Intézet	Gábor Rubovszky	14
The Chaim Sheba Medical Center	Bella Kaufman	12
Kanagawa Cancer Center	Toshinari Yamashita	11
National Taiwan University Hospital	Yen-Shen Lu	10
Hospital Universitario 12 De Octubre	Eva Maria Ciruelos Gil	9
Saitama Cancer Center Hospital	Kenichi Inoue	9
National Hospital Organization Hokkaido Cancer Center	Masato Takahashi	8
Magyar Honvedseg MH Egészségügyi Központ	Zsuzsanna Pápai	8
Gustave Roussy	Monica Arnedos	7
Rabin Medical Center Belinson	Salomon Stemmer	7
Centro Internacional de Estudios Clinicos	Humberto Cerda	7
Centre René Gauducheau	Mario Campone	7
Gemeinschaftspraxis Prof. Tesch und Dr. Grunewald	Hans Tesch	7
Hospital Universitario de Canarias	Josefina Cruz Jurado	7
Centre de Cancérologie du Grand Montpellier	Ivan Toledano	7
Instituto de Oncologia y Radioterapia de la Clinica Ricardo Palma	Wuilbert Rodriguez	6
Hospital Infanta Cristina	Juan Ignacio Delgado Mingorance	6
Tel Aviv Sourasky Medical Center Ichilov	Tamar Safra	6
Samsung Medical Center	Yeon Hee Park	6
N. N. Petrov Research Institute of Oncology	Petr Krivorotko	6
Centre Hospitalier de l'Ardenne	Frédéric Forget	6
Centre Francois Baclesse	Christelle Levy	6
National Hospital Organization Osaka National Hospital	Norikazu Masuda	6
Seoul National University Hospital	Kyung-Hun Lee	5
University of California San Francisco	Michelle Melisko	5
Universitatsklinikum Ulm	Jens Huober	5

Recruitment Site	Principal Investigator	Number of Patients Recruited
Universitaetsklinik fuer Frauenheilkunde Wien	Christian Singer	5
Centre Jean Perrin	Marie-Ange Mouret Reynier	5
Aichi Cancer Center Hospital	Hiroji Iwata	5
Kumamoto University Hospital	Hirotaka Iwase	5
Severance Hospital Yonsei University Health System YUCM	Joohyuk Sohn	5
St Luke s International Hospital	Teruo Yamauchi	5
Complex Oncology Center - Plovdiv	Antoaneta Tomova	4
SC Centrul de Oncologie Sf. Nectarie SRL	Michael Schenker	4
Tokai University Hospital	Naoki Niikura	4
Radiotherapy Center Cluj SRL, Departament Oncologie Medicala	Andrei Ungureanu	4
King Chulalongkorn Memorial Hospital	Virote Sriuranpong	4
Centro Oncologico Riojano Integral	Diego Kaen	4
Tom Baker Cancer Center	Jan-Willem Henning	4
Hospital Virgen del Rocio	Manuel Ruiz Borrego	4
Specialized Hospital for Active Treatment of Oncology	Galina Kurteva	4
Rambam Medical Center	Georgeta Fried	4
AZ Nikolaas Campus Sint Niklaas	Ines Deleu	4
Specialized Hospital for Active Treatment of Oncological Diseases “Marko Antonov Markov”	Vasil Popov	4
Hospital Clinico San Carlos	Jose Angel Garcia Saenz	4
CHU Carémeau Nimes	Miruna Timar-David	4
Seoul National University Bundang Hospital	Jeehyun Kim	4
Hospital Clinico Universitario de Santiago	Rafael Lopez Lopez	4
Hospital Son Espases	Antonia Perello Martorell	4
Toranomon Hospital	Toshimi Takano	4
Hotel Dieu de France Hospital	Joseph Kattan	4
Florida Cancer Specialists - North	Gail Wright	3
Instituto Clinico Oncologico del Sur	Eduardo Yañez	3
Uniklinikum Schleswig Holstein Campus Kiel	Christoph Mundhenke	3
Fort Wayne Medical Oncology/Hematology, Inc.	Lakshmi Aggarwal	3

Recruitment Site	Principal Investigator	Number of Patients Recruited
Osaka International Cancer Institute	Takahiro Nakayama	3
P.O. Molinette AO Citta della Salute e della Scienza Torino	Mario Airoldi	3
Arkhangelsk Regional Oncology Center	Lebedeva Ludmila	3
Hospital Universitario Virgen Arrixaca	Jose Luis Alonso Romero	3
Institut Sainte Catherine	Antoine Arnaud	3
Fondazione IRCCS Istituto Nazionale dei Tumori	Giulia Valeria Bianchi	3
Virginia Cancer Specialists	Neelima Denduluri	3
Ironwood Cancer and Research Centers	Mikhail Shtivelband	3
Clinica Viedma	Ruben Kowalyszyn	3
Cambridge Memorial Hospital	Edmond Chouinard	3
Hammoud Hospital University Medical Center	Fadi Farhat	3
Hospital Universitario HM Sanchinarro	Elena Sevillano Fernandez	3
Hospital Clinico Universitario de Valencia	Begona Bermejo de las Heras	3
Clinica Quiron Barcelona	Jose Manuel Perez Garcia	3
Hospital Gerneral de Jerez de la Frontera	Ruben De Toro Salas	3
Taipei Veterans General Hospital	Ling-Ming Tseng	3
Guys Hospital	Ines Sandri	3
CHR Verviers	Annelore Barbeaux	3
Sociedade Beneficência e Caridade de Lajeado	Leandro Brust	3
CHU de Quebec - Hopital du Saint Sacrement	Louise Provencher	3
Centre Henri Becquerel - CLCC HTE Normandie	Marianne Leheurteur	3
Gemeinschaftspraxis Drs. Kalhori, Langer Nusch	Arnd Nusch	3
Tolna County Teaching Hospital	Al-Farhat Yousuf	3
Istituto Oncologico Veneto IRCCS ex Ospedale Busonera	Pierfranco Conte	3
Hospital Quiron Madrid	Lucia Gonzalez Cortijo	3
Institut Jules Bordet	Ahmad Awada	3
Universitaetsmedizin	Marcus Schmidt	3
City Cancer Centre	Mamillapalli Gopichand	3
National Cancer Center	Keun Seok Lee	3

Recruitment Site	Principal Investigator	Number of Patients Recruited
Oncosalud Clinica Oncosalud	Carlos Vallejos	3
Regionsjukhuset i Oerebro	Kenneth Villman	3
Centro di Riferimento Oncologico della Basilicata - IRCCS	Michele Aieta	3
Scientifico Romagnolo per la Cura e lo Studio dei Tumori	Andrea Rocca	3
NHO Shikoku Cancer Center	Seiki Takashima	3
ZorgSaam Zeeuws-Vlaanderen	Marjan Van Dijk	3
Hospital Provincial de Castellon	Eduardo Martinez de Duenas	2
Tennessee Oncology	Denise Yardley	2
Peter MacCallum Cancer Centre	Marisa Grossi	2
Centro di Riferimento Oncologico IRCCS	Simon Spazzapan	2
Consultorio Privado "Dr. Joaquín Gabriel Reinoso Toledo"	Joaquín Gabriel Reinoso Toledo	2
Leicester Royal Infirmary	Samreen Ahmed	2
St.Petersburg Clinical Research Center Specialized Types of Medical Care Oncology	Nikita Volkov	2
Klinikum Suedstadt Rostock	Max Dieterich	2
Queen Mary Hospital	Joanne Chiu	2
Cancer Therapy & Research Center UT Health Science Center	Virginia Kaklamani	2
Princess Alexandra Hospital	Katharine Cuff	2
Sagara Hospital	Yasuaki Sagara	2
CENIT Centro de Neurociencias Investigacion y Tratamiento	Monica Casalnuovo	2
Universitair Ziekenhuis Antwerpen	Manon Huizing	2
Krajska Nemocnice T. Bati AS	Milan Kohoutek	2
IUCT-Oncopole	Florence Dalenc	2
Centro de Atencion e Investigacion Cardiovascular del Potosi	Pedro Figueroa Martinez	2
Hospital General Universitario de Alicante	Jose Ponce Lorenzo	2
Multifunctional Hospital for Active Treatment "Sveta Marina"	Ivan Donev	2
St Michaels Hospital	Christine Brezden-Masley	2
Hopital Prive Jean Mermoz	Olfa Derbel	2

Recruitment Site	Principal Investigator	Number of Patients Recruited
Klinikum Aschaffenburg, Neurologische Klinik	Manfred Welslau	2
AOU Osp. Riuniti Umberto I-GM Lancisi-G.Salesi-Univ.Studi	Rossana Berardi	2
Siriraj Hospital	Charuwan Akewanlop	2
General Hospital of Athens – Alexandra	Meletios Dimopoulos	2
Tata Memorial Hospital	Sudeep Gupta	2
Università Campus Bio-Medico	Giuseppe Tonini	2
P.O.Osp.Cliniciz.SS.Annunziata Colle dell'Ara Uni.D'Annunzio	Clara Natoli	2
VieCuri Medisch Centrum	Agnes van de Wouw	2
Instituto Nacional de Enfermedades Neoplasicas	Silvia Neciosup	2
Hospital Universitari Germans Trias i Pujol	Mireia Margeli Vila	2
Västmanlands Sjukhus	Cecilia Nilsson	2
Rutgers Cancer Institute of New Jersey	Deborah Toppmeyer	2
Sydney Adventist Hospital	Gavin Marx	2
Nemocnice Na Bulovce	Petra Holeckova	2
Luebecker Onkologische Schwerpunktpraxis	Jens Kisro	2
Medizinische Hochschule Hannover	Tjoung-Won Park-Simon	2
Szabolcs-Szatmar Bereg Megyei Onkorm. Josa Andras Korhaz	Jozsef Erfan	2
Hyogo Cancer Center	Koji Matsumoto	2
Asan Medical Center	Sung-Bae Kim	2
Wenatchee Valley Medical Center	Lindsay Overton	2
UZ Brussel	Christel Fontaine	2
Institut de Cancérologie de l'Ouest Paul Papin	Mario Campone	2
CHD Les Oudairies	Frank Priou	2
St. Elisabeth Krankenhaus Leipzig	Dagmar Langanke	2
Mercy Medical Center	David Riseberg	2
Massachusetts General Hospital	Dejan Juric	2
Beverly Hills Cancer Center	Linnea Chap	2
The Ottawa Hospital Cancer Centre	Susan Dent	1
Kaiser Permanente - California Southern	Jonathan Polikoff	1
COIBA	Mirta Varela	1

Recruitment Site	Principal Investigator	Number of Patients Recruited
Instituto Brasileiro de Controle do Câncer	Felipe José Silva Melo Cruz	1
Hospital Ramon Y Cajal	Maria Fernandez Abad	1
University Hospitals of Cleveland Seidman Cancer Center	Paula Silverman	1
Hospital de Base da Faculdade de Medicina de São José do Rio Preto	Gustavo Colangiovanni Girotto	1
Klinikum Ernst von Bergmann GmbH	Dorothea Fischer	1
Azienda USL Toscana Nord Ovest Ospedale Felice Lotti	Giacomo Allegrini	1
Liga Norte Riograndense Contra o Câncer	Sulene Cunha Souza	1
424 General Army Military Hospital	Harisios Karanikiotis	1
Hospital San Pedro de Alcantara	Pablo Borrega Garcia	1
US Oncology, P.A.	Svetislava Vukelja	1
Mayo Clinic - Arizona	Donald Northfelt	1
Highlands Oncology Group	J. Thaddeus Beck	1
Medicon AS	Renata Kozevnikovova	1
Universitaetsklinikum des Saarlandes	Ingolf Juhasz-Boess	1
Soroka University Hospital	David Geffen	1
Bellevue Medical Center	Fadi El Karak	1
Hospital La Paz	Pilar Zamora Aunon	1
Florida Cancer Specialists	Lowell Hart	1
Lyell McEwin Hospital	Jacqueline Adams	1
Instituto de Ensino e Pesquisa São Lucas	Bruno Santucci Alves da Silva	1
Hospital Clinico Viña del Mar	Alejandro Acevedo	1
Metropolitan Hospital	Christos Christodoulou	1
Central India Cancer Research Institute	Ajay Mehta	1
Pres. Osp. Civile SS. Annunziata - A.S.L. N. 1 Sassari	Antonio Pazzola	1
Länssjukhuset Gävle	Per Edlund	1
Plymouth Hospitals NHS Trust	Udaiveer Panwar	1
Scripps Clinic	Melissa Torrey	1
St. Francis Health Comprehensive Cancer Center	Andrew Meyer	1
Ordensklinikum Linz Barmherzige Schwestern	Andreas Petzer	1

Recruitment Site	Principal Investigator	Number of Patients Recruited
CHU Henri Mondor	Christophe Tournigand	1
Oncologianova GmbH	Ludger Heflik	1
Internistische Gemeinschaftspraxis Dr.Oettle und Prof. Mayer	Frank Mayer	1
Ospedale Sacro Cuore-Don Calabria	Stefania Gori	1
Institutul Regional de Oncologie Iasi	Dana Clement	1
Ryazan Regional Clinical Oncological Dispensary	Marina Shomova	1
North Shore University Health System	Teresa Law	1
Lancaster General Hospital	Elizabeth Horenkamp	1
Rush University Medical Center	Ruta Rao	1
Clinique Saint Pierre	Renaud Poncin	1
Fakultni nemocnice Hradec Kralove	Peter Priester	1
Hopital Nord Marseille	Marjorie Baciuchka-Palmaro	1
Hopital A. Mignot	Didier Mayeur	1
Institut d'Oncologie Hauts-de-Seine Nord	Alain Toledano	1
Pres. Ospedaliero di Savona Ospedale S. Paolo ASL 2 Savonese	Marco Benasso	1
ARNAS Civico-Di Cristina-Benfratelli-P.O. Civic e Benfratelli	Livio Blasi	1
Gunma University Hospital	Takaaki Fujii	1
Avera Cancer	Amy Krie	1
St. Luke's Cancer Institute	Timothy Pluard	1
St. Vincent Frontier Cancer Center	Patrick Cobb	1
Edward Cancer Center	Joseph Kash	1
El Paso, Texas Oncology	Ines Sanchez-Rivera	1
Texas Oncology PA Dallas Presbyterian Hospital	Kristi McIntyre	1
Greenville Health System	Mark O'Rourke	1
Detroit Clinical Research Center	Tallat Mahmood	1
Good Samaritan Regional Medical Center	Ike Onwere	1
City of Hope National Medical Center	Niki Patel	1
Lahey Clinic	Corrine Zarwan	1

Supplementary Methods

Trial design

Primary endpoint: Progression-free survival

Progression-free survival was defined as time from date of randomization until date of the first documented progression or death due to any cause. Progression-free survival was censored at the last adequate tumor assessment date, if no event was observed before the cut-off date; if an event was observed after ≥2 missing or inadequate tumor assessments then progression-free survival was censored at the last adequate tumor assessment.

The primary analysis was based on the distribution of progression-free survival events between the two treatment groups. Two interim analyses (one for futility, one for efficacy) were conducted after 42% and 78% of the targeted number of events of progression or death were documented, respectively. Superiority was declared at the interim efficacy analysis if the one-sided p-value from a stratified log-rank test was ≤0.0001 ($Z>3.719$; Haybittle–Peto stopping boundary). The prespecified criteria for both interim analyses were not met, and the independent data monitoring committee who reviewed the interim analyses recommended the cohort to continue in both cases. At the final analysis, superiority was to be declared if the one-sided p-value crossed the Haybittle–Peto boundary ($p\leq0.0199$).

Under the assumption of 7 months median progression-free survival in the control arm, if the true hazard ratio was 0.6 (corresponding to a median progression-free survival of 11.67 months), a total of 243 progression-free survival events were required to have 83.8% power at a one-sided overall 2.0% level of significance to reject the null hypothesis (hazard ratio=1) using a log-rank test for a three-look group sequential design using a Haybittle–Peto boundary to determine the efficacy boundary along with (i) a gamma spending function ($\gamma=5$) and (ii) a conditional probability function to determine the non-binding futility boundaries. The non-mutant cohort was analyzed at a single look using a one-sided 0.5% level of significance. This

approach guaranteed the protection of the overall type I error (α = 2.5%, equivalent to two-sided 5%, based on a Bonferroni post-hoc adjustment).

The objectives of progression-free survival in each cohort are not treated as equally important: the overall Type I error allocation reflects the preference for testing the hypothesis in the *PIK3CA*-mutant cohort at a significance level close to the overall trial level (0.025). This preference reflects the potential of alpelisib in treating patients who have *PIK3CA*-mutant disease.

Blinded independent review committee (BIRC) data, supportive analysis of the primary endpoint

An audit-based approach was implemented for the BIRC assessment of progression-free survival. An independent random sampling process, implemented by the third party IRT vendor, selected approximately 50% of randomized patients in the *PIK3CA*-mutant cohort. The "National Cancer Institute (NCI) method"[1], based on a treatment effect estimate combining local and central review data, and the "PhRMA method"[2], based on differential discordance of early and late discrepancy rates, were used to assess whether a full blinded independent review committee review was subsequently needed.

Key secondary endpoint: Overall survival

A hierarchical testing approach was applied to the key secondary endpoint (overall survival for the *PIK3CA* mutant cohort, defined as time from date of randomization until death due to any cause), in that overall survival was only to be tested in the case of statistically significant results for progression-free survival.

Overall survival was analyzed using a stratified log-rank test at a one-sided 2.0% level of significance, and a three-look group sequential design was considered. The type I error rate for

overall survival was controlled by using a Lan–DeMets (O'Brien–Fleming) alpha spending function, independent of the Haybittle–Peto boundary used for the primary endpoint.

Other endpoints not reported in this analysis

Other endpoints which are not reported here include progression-free survival in patients with/without *PIK3CA* mutation status as measured in circulating tumor DNA, time to definitive deterioration in Eastern Cooperative Oncology Group performance status, time to response, duration of response, time to deterioration in global health status/quality-of-life scale score of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30, other patient-reported quality-of-life outcomes (brief pain index, EuroQoL [EQ-5D]), hospitalization rates, pharmacokinetics, PFS2 (progression on next-line therapy after discontinuation of study treatment; an intermediate endpoint between progression-free survival and overall survival), and exposure-response analysis.

PIK3CA status determination

Tissue-derived DNA

PIK3CA mutation status was determined by a Novartis-designated laboratory before a patient could enroll in SOLAR-1. The following was required for *PIK3CA* mutational status screening:

- One new or recent biopsy, collected at screening if feasible

OR

- Archival tumor block

OR

- Minimum 15 slides from a surgical specimen or 20 slides from a biopsy.

PIK3CA mutation analysis was performed with real time PCR assays, a Novartis clinical trial assay and QIAGEN *therascreen*® PIK3CA RGQ PCR Kit. The assays detect *PIK3CA* mutations

C420R, E542K, E545A, E545D (1635G>T only), E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y.

Grouped adverse event preferred terms

Rash

Events grouped under the term “Rash” included the preferred terms:
Dermatitis, dermatitis acneiform, dermatitis psoriasiform, drug eruption, eyelid rash, genital rash, mucocutaneous rash, perineal rash, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash maculovesicular, rash morbilliform, rash nodular, rash papular, rash papulosquamous, rash pruritic, rash pustular, rash vesicular, and rash vulvovaginal.

Gastrointestinal toxicities

Events grouped under the term “Gastrointestinal toxicities” included the following preferred terms: acetonemic vomiting, acute vestibular syndrome, cyclic vomiting syndrome, dialysis disequilibrium syndrome, diarrhea, diarrhea hemorrhagic, diarrhea neonatal, discolored vomit, fecal vomiting, hyperemesis gravidarum, infantile spitting up, infantile vomiting, Ménière’s disease, nausea, postprocedural diarrhea, post-tussive vomiting, procedural nausea, procedural vomiting, regurgitation, retching, vomiting, vomiting in pregnancy, vomiting projectile, and vomiting psychogenic.

Hyperglycemia

Events grouped under the term “Hyperglycemia” included the following preferred terms: acquired lipoatrophic diabetes, blood 1,5-anhydroglucitol decreased, blood glucose increased, diabetes complicating pregnancy, diabetes mellitus, diabetes mellitus inadequate control, diabetes with hyperosmolarity, diabetic arteritis, diabetic coma, diabetic coronary microangiopathy, diabetic hepatopathy, diabetic hyperglycemic coma, diabetic hyperosmolar

coma, diabetic ketoacidosis, diabetic ketoacidotic hyperglycemic coma, diabetic ketosis, diabetic metabolic decompensation, euglycemic diabetic ketoacidosis, fructosamine increased, fulminant type 1 diabetes mellitus, gestational diabetes, glucose tolerance impaired, glucose tolerance impaired in pregnancy, glucose urine present, glycosuria, glycosuria during pregnancy, glycosylated hemoglobin increased, hyperglycemia, hyperglycemic hyperosmolar nonketotic syndrome, hyperglycemic seizure, hyperglycemic unconsciousness, impaired fasting glucose, insulin resistance, insulin resistance syndrome, insulin resistant diabetes, insulin-requiring type 2 diabetes mellitus, ketoacidosis, ketonuria, ketosis, ketosis-prone diabetes mellitus, latent autoimmune diabetes in adults, metabolic syndrome, monogenic diabetes, neonatal diabetes mellitus, pancreatogenous diabetes, type 1 diabetes mellitus, type 2 diabetes mellitus, type 3 diabetes mellitus, and urine ketone body present.

Additional information regarding patient inclusion criteria

Definition of advanced breast cancer

Patients could enroll in SOLAR-1 if they had advanced breast cancer. This was defined by either:

- Locally advanced, recurrent breast cancer which is not amenable to curative therapy

OR

- Metastatic breast cancer.

Postmenopausal status

Women who were postmenopausal at the time of study entry were enrolled. Postmenopausal status was defined by:

- Prior bilateral oophorectomy

OR

- Age ≥60 years

OR

- Age <60 and amenorrhea for ≥12 months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and follicle-stimulating hormone (FSH) and estradiol in the postmenopausal range per local guidelines.

Note: For women with therapy-induced amenorrhea, serial measurements of FSH and/or estradiol were needed to ensure menopausal status. Enrollment was also open to men.

Prior therapy

Patients must have relapsed or progressed on one line of prior therapy. Patients must have:

- Relapsed with documented evidence of progression while on (neo)adjuvant endocrine therapy, or within 12 months after completion of (neo)adjuvant endocrine therapy, with no treatment for metastatic disease

OR

- Relapsed with documented evidence of progression >12 months after completion of (neo)adjuvant endocrine therapy, then subsequently progressed (with documented evidence of progression) on/after only one line of endocrine therapy for metastatic disease

OR

- Newly diagnosed advanced breast cancer, which then relapsed (with documented evidence of progression) on/after only one line of endocrine therapy.

Patients may not enroll with:

- Endocrine treatment-naïve advanced breast cancer

OR

- Advanced breast cancer which progressed on/within 12 months after (neo)adjuvant endocrine treatment for breast cancer and then subsequently progressed (with documented evidence of progression) after endocrine therapy for advanced disease.

Note: Patients who relapsed more than 12 months from completion of (neo)adjuvant endocrine therapy, with no treatment for metastatic disease, could enroll under an earlier version of the protocol. At the time of this protocol amendment, 317 patients had been randomized to either alpelisib plus fulvestrant or placebo plus fulvestrant. Primary and secondary resistance were defined using ESMO criteria.[3]

Other investigational therapies

Patients in SOLAR-1 could not be receiving other investigational and/or neoplastic therapies while enrolled in the trial. Participation in a prior investigational study within 30 days prior to the start of study treatment, or within five half-lives of the investigational product (whichever is longer), was prohibited.

Diabetes mellitus

Patients with controlled type 2 diabetes mellitus (T2DM) were eligible for SOLAR-1. Regardless of any history of T2DM, patients must have met both of the following criteria to enroll in the trial:

- Fasting plasma glucose (FPG) ≤140 mg/dL (7.7 mmol/L)

AND

- Glycosylated hemoglobin (HbA_{1c}) ≤6.4%.

Note: Patients with HbA_{1c} ≤8% could enroll under an earlier version of the protocol.

Management of adverse events

Adverse events, including rash and the on-target adverse event of hyperglycemia, were managed actively in this trial. Protocol guidance for management of these adverse events is given in Supplementary Tables S8 and S9. General guidance for adverse events is given in Supplementary Table S10.

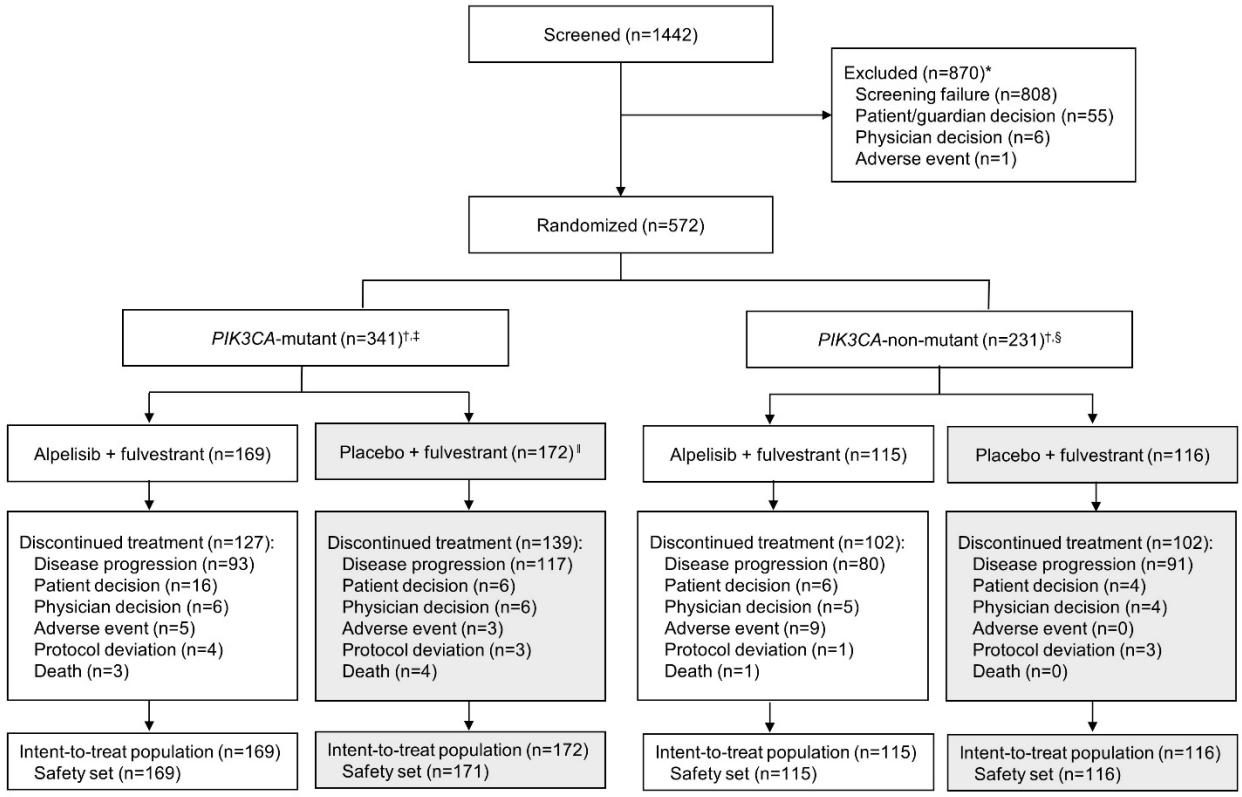
Specific guidance is also given in the protocol for management of the following adverse events: Asymptomatic amylase and/or lipase elevation, cardiac events, combined elevations of AST or ALT and total bilirubin, diarrhea, elevated serum creatinine, isolated ALT or AST elevation, isolated bilirubin elevation, left ventricular systolic dysfunction, neutropenia, pancreatitis, pneumonitis, QTc prolongation, thrombocytopenia.

Supplementary Safety Results (*PIK3CA*-mutant cohort)

Of the 187 patients with an adverse event of hyperglycemia according to grouped terms, 163 (87%) were managed with anti-diabetic medication, including 142 (76%) with metformin as single agent or in combination with other anti-diabetic medication. Other, less frequently used medications included various types of insulin (used in 52 patients, including patients with medical history of diabetes mellitus). In patients with Grade ≥2 hyperglycemia by laboratory evaluation (n=160), median time to improvement by ≥1 grade from the first event was 8 days (95% CI: 8.0–10.0). All patients with elevated FPG who discontinued alpelisib, but continued fulvestrant, had FPG levels return to grade ≤1.

Other Supplementary Figures and Tables

Figure S1. Study Overview (CONSORT Diagram)



*Primary reason for exclusion. Patients could be excluded for more than one reason. Screening failures included patients who did not meet eligibility criteria. The most common reasons for screening failure (n>100; not necessarily primary reasons for exclusion) were lack of identified *PIK3CA* mutation status (n=372) and lack of adequate tumor tissue for *PIK3CA* mutation analysis (n=128). Mutation status was identified in 76.2% patients based on primary tissue and 21.9% patients based on metastatic tissue. For 1.9% patients, tissue location was unknown.

†If a patient had an adequate archival tumor tissue sample available, then it was used to determine *PIK3CA* mutation status. If not, then a fresh tissue sample was requested. Overall, 9.4% of patients were enrolled based on mutation status from newly-obtained samples (8.8% and 10.4% for the mutant and non-mutant cohorts, respectively).

‡In the *PIK3CA*-mutant cohort, 30 patients had mutation status determined from a fresh biopsy and 311 had mutation status determined using an archival tumor sample.

[§]In the *PIK3CA*-non-mutant cohort, 24 patients had mutation status determined from a fresh biopsy and 207 had mutation status determined using an archival tumor sample.

[‖]One patient in the *PIK3CA*-mutant cohort randomized to placebo was not treated due to protocol deviation.

Table S2. Serious Adverse Events by Single Preferred Term Regardless of Treatment Relationship (Overall Population)

Adverse Event	Alpelisib Group (n=284)		Placebo Group (n=287)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
	number of patients (percent)			
Any adverse event	99 (34.9)	82 (28.9)	48 (16.7)	43 (15.0)
Hyperglycemia	28 (9.9)	26 (9.2)	0	0
Diarrhea	8 (2.8)	4 (1.4)	0	0
Abdominal pain	6 (2.1)	4 (1.4)	2 (0.7)	1 (0.3)
Acute kidney injury	5 (1.8)	3 (1.1)	1 (0.3)	1 (0.3)
Anemia	5 (1.8)	3 (1.1)	0	0
Nausea	5 (1.8)	4 (1.4)	2 (0.7)	1 (0.3)
Osteonecrosis of jaw	5 (1.8)	4 (1.4)	1 (0.3)	1 (0.3)
Rash	5 (1.8)	4 (1.4)	0	0
Vomiting	5 (1.8)	2 (0.7)	3 (1.0)	1 (0.3)
Pyrexia	4 (1.4)	0	0	0
Stomatitis	4 (1.4)	2 (0.7)	0	0
Dehydration	3 (1.1)	1 (0.4)	3 (1.0)	3 (1.0)
Erythema multiforme	3 (1.1)	2 (0.7)	0	0
Hypersensitivity	3 (1.1)	1 (0.4)	0	0
Hypokalemia	3 (1.1)	3 (1.1)	1 (0.3)	0
Mucosal inflammation	3 (1.1)	3 (1.1)	0	0
Pleural effusion	3 (1.1)	3 (1.1)	5 (1.7)	4 (1.4)
Pneumonia	3 (1.1)	3 (1.1)	5 (1.7)	5 (1.7)
Maculopapular rash	3 (1.1)	2 (0.7)	0	0
Back pain	2 (0.7)	2 (0.7)	2 (0.7)	2 (0.7)
Blood creatinine increased	2 (0.7)	2 (0.7)	0	0

Brain edema	2 (0.7)	1 (0.4)	0	0
Cellulitis	2 (0.7)	1 (0.4)	2 (0.7)	2 (0.7)
Decreased appetite	2 (0.7)	0	0	0
Dyspnea	2 (0.7)	1 (0.4)	4 (1.4)	4 (1.4)
General physical health deterioration	2 (0.7)	1 (0.4)	0	0
Hyponatremia	2 (0.7)	2 (0.7)	1 (0.3)	1 (0.3)
Muscular weakness	2 (0.7)	2 (0.7)	0	0
Pneumonitis	2 (0.7)	1 (0.4)	0	0
Pulmonary embolism	2 (0.7)	2 (0.7)	3 (1.0)	2 (0.7)
Renal failure	2 (0.7)	2 (0.7)	0	0
Upper gastrointestinal hemorrhage	2 (0.7)	2 (0.7)	0	0
Urinary tract infection	2 (0.7)	1 (0.4)	3 (1.0)	3 (1.0)
Abscess jaw	1 (0.4)	1 (0.4)	0	0
Asthenia	1 (0.4)	0	0	0
Bacteremia	1 (0.4)	1 (0.4)	0	0
Bipolar disorder	1 (0.4)	1 (0.4)	0	0
Cardiac arrest	1 (0.4)	1 (0.4)	0	0
Chest pain	1 (0.4)	0	0	0
Dermatitis acneiform	1 (0.4)	1 (0.4)	0	0
Dermatitis allergic	1 (0.4)	1 (0.4)	0	0
Diabetic ketoacidosis	1 (0.4)	1 (0.4)	0	0
Dyspepsia	1 (0.4)	0	0	0
Enterocolitis	1 (0.4)	1 (0.4)	0	0
Erysipelas	1 (0.4)	1 (0.4)	0	0
Erythema	1 (0.4)	1 (0.4)	0	0

Fatigue	1 (0.4)	0	0	0
Febrile neutropenia	1 (0.4)	1 (0.4)	0	0
Hemoglobin decreased	1 (0.4)	1 (0.4)	0	0
Headache	1 (0.4)	1 (0.4)	0	0
Hepatic enzyme increased	1 (0.4)	1 (0.4)	0	0
Hepatic failure	1 (0.4)	1 (0.4)	0	0
Hepatitis acute	1 (0.4)	1 (0.4)	0	0
Herpes zoster	1 (0.4)	0	0	0
Hip fracture	1 (0.4)	1 (0.4)	1 (0.3)	1 (0.3)
Hypertension	1 (0.4)	1 (0.4)	0	0
Hypertensive crisis	1 (0.4)	1 (0.4)	0	0
Hypochloremia	1 (0.4)	0	0	0
Ileus	1 (0.4)	0	0	0
Interstitial lung disease	1 (0.4)	0	1 (0.3)	1 (0.3)
Intestinal obstruction	1 (0.4)	1 (0.4)	0	0
Ketoacidosis	1 (0.4)	1 (0.4)	0	0
Lipase increased	1 (0.4)	1 (0.4)	0	0
Malaise	1 (0.4)	0	0	0
Melena	1 (0.4)	0	0	0
Metastases to meninges	1 (0.4)	1 (0.4)	0	0
Multiple organ dysfunction syndrome	1 (0.4)	1 (0.4)	0	0
Musculoskeletal chest pain	1 (0.4)	0	0	0
Nephrolithiasis	1 (0.4)	0	1 (0.3)	1 (0.3)
Esophagitis	1 (0.4)	0	0	0
Pancreatitis	1 (0.4)	1 (0.4)	0	0
Peritonsillar abscess	1 (0.4)	1 (0.4)	0	0

Pulmonary edema	1 (0.4)	1 (0.4)	0	0
Pyelonephritis acute	1 (0.4)	1 (0.4)	0	0
Radiation proctitis	1 (0.4)	1 (0.4)	0	0
Rash generalized	1 (0.4)	1 (0.4)	0	0
Rash macular	1 (0.4)	1 (0.4)	0	0
Respiratory failure	1 (0.4)	1 (0.4)	0	0
Rib fracture	1 (0.4)	1 (0.4)	0	0
Second primary malignancy	1 (0.4)	1 (0.4)	0	0
Seizure	1 (0.4)	1 (0.4)	0	0
Spinal column stenosis	1 (0.4)	1 (0.4)	0	0
Spinal compression fracture	1 (0.4)	1 (0.4)	1 (0.3)	1 (0.3)
Stevens–Johnson syndrome	1 (0.4)	1 (0.4)	0	0
Syncope	1 (0.4)	1 (0.4)	0	0
Thrombotic microangiopathy	1 (0.4)	1 (0.4)	0	0
Tumor pain	1 (0.4)	1 (0.4)	0	0
Type 2 diabetes mellitus	1 (0.4)	1 (0.4)	0	0
Ureterolithiasis	1 (0.4)	0	0	0
Urosepsis	1 (0.4)	0	0	0
Urticaria	1 (0.4)	0	0	0
Weight decreased	1 (0.4)	0	0	0
Wrist fracture	1 (0.4)	0	0	0
Acute respiratory failure	0	0	1 (0.3)	1 (0.3)
Altered state of consciousness	0	0	1 (0.3)	1 (0.3)
Appendicitis	0	0	1 (0.3)	1 (0.3)
Aspiration	0	0	1 (0.3)	1 (0.3)

Atrial fibrillation	0	0	1 (0.3)	0
Blood bilirubin increased	0	0	1 (0.3)	1 (0.3)
Bone pain	0	0	1 (0.3)	1 (0.3)
Bronchostenosis	0	0	1 (0.3)	1 (0.3)
Cancer pain	0	0	1 (0.3)	1 (0.3)
Cardiac failure	0	0	2 (0.7)	0
Cerebrovascular accident	0	0	1 (0.3)	1 (0.3)
Colitis	0	0	1 (0.3)	1 (0.3)
Constipation	0	0	1 (0.3)	0
Femur fracture	0	0	1 (0.3)	1 (0.3)
Gallstone ileus	0	0	1 (0.3)	0
Gastrointestinal hemorrhage	0	0	1 (0.3)	1 (0.3)
Hypercalcemia	0	0	2 (0.7)	1 (0.3)
Mediastinitis	0	0	1 (0.3)	1 (0.3)
Motor dysfunction	0	0	1 (0.3)	1 (0.3)
Myocardial infarction	0	0	1 (0.3)	1 (0.3)
Osteitis	0	0	1 (0.3)	1 (0.3)
Overdose	0	0	1 (0.3)	0
Pelvic pain	0	0	1 (0.3)	1 (0.3)
Pericardial effusion	0	0	1 (0.3)	1 (0.3)
Procedural complication	0	0	1 (0.3)	0
Pulmonary tuberculosis	0	0	1 (0.3)	0
Pyelonephritis	0	0	1 (0.3)	1 (0.3)
Respiratory tract infection	0	0	1 (0.3)	1 (0.3)
Septic shock	0	0	1 (0.3)	1 (0.3)

Sinus tachycardia	0	0	1 (0.3)	0
Skin infection	0	0	1 (0.3)	1 (0.3)
Spinal cord compression	0	0	2 (0.7)	2 (0.7)
Subileus	0	0	1 (0.3)	1 (0.3)
Thrombosis	0	0	1 (0.3)	0
Ulna fracture	0	0	1 (0.3)	1 (0.3)

Table S3. Most Frequent Adverse Events by Single Preferred Term Regardless of Treatment Relationship (*PIK3CA*-mutant Cohort)*

Adverse Event	Alpelisib Group (n=169)			Placebo Group (n=172)†		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	168 (99.4)	116 (68.6)	20 (11.8)	152 (88.9)	46 (26.9)	11 (6.4)
Hyperglycemia‡	110 (65.1)	54 (32.0)	8 (4.7)	15 (8.8)	0	1 (0.6)
Diarrhea§	92 (54.4)	13 (7.7)	0	19 (11.1)	1 (0.6)	0
Nausea§	77 (45.6)	4 (2.4)	0	34 (19.9)	0	0
Rash¶	67 (39.6)	22 (13.0)	0	11 (6.4)	1 (0.6)	0
Decreased appetite	57 (33.7)	1 (0.6)	0	13 (7.6)	0	0
Stomatitis	45 (26.6)	5 (3.0)	0	11 (6.4)	0	0
Decreased weight	45 (26.6)	6 (3.6)	0	1 (0.6)	0	0
Vomiting§	43 (25.4)	0	0	16 (9.4)	0	0
Fatigue	40 (23.7)	5 (3.0)	0	26 (15.2)	0	0
Alopecia	36 (21.3)	0	0	5 (2.9)	0	0
Headache	29 (17.2)	2 (1.2)	0	23 (13.5)	0	0
Dysgeusia	28 (16.6)	0	0	6 (3.5)	0	0
Asthenia	27 (16.0)	2 (1.2)	0	22 (12.9)	0	0
Mucosal inflammation	27 (16.0)	3 (1.8)	0	3 (1.8)	0	0
Pruritis	26 (15.4)	2 (1.2)	0	6 (3.5)	0	0
Arthralgia	21 (12.4)	1 (0.6)	0	26 (15.2)	1 (0.6)	0

*Events listed were reported as a single term in ≥15% of patients for any grade in either group.

†One patient who was randomly assigned to the placebo group did not receive either placebo or fulvestrant.

‡As a whole, all-grade events of hyperglycemia (including the following preferred terms: diabetes mellitus, hyperglycemia, insulin resistance, metabolic syndrome, and others [see Supplementary Methods for

complete list]) were reported in 66.9% of patients in the alpelisib group (grade ≥3: 37.9%) and 9.9% of patients in the placebo group (grade ≥3: 0.6%).

[§]All-grade gastrointestinal toxicities (including the following preferred terms: nausea, vomiting, diarrhea, and others [see Supplementary Methods for complete list]) were reported in 73.4% of patients in the alpelisib group (grade ≥3: 9.5%) and 29.8% of patients in the placebo group (grade ≥3: 0.6%).

[¶]All-grade events of any rash (including the following preferred terms: rash follicular, rash generalized, rash maculo-papular, and others [see Supplementary Methods for complete list]) were reported in 59.2% of patients in the alpelisib group (grade ≥3: 23.7%) and 8.2% of patients in the placebo group (grade ≥3: 0.6%).

Three adverse events of special interest (pancreatitis, severe cutaneous reactions and pneumonitis) fell below the reporting threshold listed here. Hypersensitivity, which occurred in 17.2% of patients in the alpelisib group (grade ≥3: 1.8%) and 3.5% of patients in the placebo group (grade ≥3: 0%), did not contain any single preferred terms that reached the reporting threshold listed here.

Table S4. Most Frequent Adverse Events by Single Preferred Term Regardless of Treatment Relationship (*PIK3CA*-non-mutant Cohort)*

Adverse Event	Alpelisib Group (n=115)			Placebo Group (n=116)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	114 (99)	67 (58)	13 (11)	112 (97)	41 (35)	4 (3)
Diarrhea‡	72 (63)	6 (5)	0	26 (22)	0	0
Hyperglycemia†	71 (62)	39 (34)	3 (3)	13 (11)	1 (<1)	0
Nausea‡	50 (44)	3 (3)	0	30 (26)	1 (<1)	0
Decreased appetite	44 (38)	1 (<1)	0	17 (15)	1 (<1)	0
Rash§	34 (30)	6 (5)	0	6 (5)	0	0
Vomiting‡	34 (30)	2 (2)	0	12 (10)	1 (<1)	0
Asthenia	31 (27)	3 (3)	0	15 (13)	0	0
Decreased weight	31 (27)	5 (4)	0	5 (4)	0	0
Fatigue	29 (25)	5 (4)	0	23 (20)	3 (3)	0
Mucosal inflammation	25 (22)	3 (3)	0	0	0	0
Pruritis	25 (22)	0	0	10 (9)	0	0
Stomatitis	25 (22)	2 (2)	0	7 (6)	0	0
Peripheral edema	22 (19)	0	0	5 (4)	0	0
Headache	21 (18)	0	0	15 (13)	0	0
Alopecia	20 (17)	0	0	2 (2)	0	0
Dry skin	19 (17)	0	0	5 (4)	0	0
Dysgeusia	19 (17)	0	0	4 (3)	0	0
Pyrexia	19 (17)	1 (<1)	0	2 (2)	0	0
Back pain	14 (12)	1 (<1)	0	20 (17)	3 (3)	0
Arthralgia	11 (10)	0	0	21 (18)	2 (2)	0

Constipation	9 (8)	0	0	20 (17)	1 (<1)	0

*Events listed were reported in ≥15% of patients for any grade in either group.

†As a whole, all-grade events of hyperglycemia (including the following preferred terms: diabetes mellitus, hyperglycemia, insulin resistance, metabolic syndrome, and others [see Supplementary Methods for complete list]) were reported in 64.3% of patients in the alpelisib plus fulvestrant arm (grade ≥3: 38.3%) and 11.2% of patients in the placebo plus fulvestrant arm (grade ≥3: 0.9%).

‡All-grade gastrointestinal toxicities (including the following preferred terms: nausea, vomiting, diarrhea, and others [see Supplementary Methods for complete list]) were reported in 78.3% of patients in the alpelisib plus fulvestrant arm (grade ≥3: 7.8%) and 42.2% of patients in the placebo plus fulvestrant arm (grade ≥3: 1.7%).

§All-grade events of any rash (including the following preferred terms: rash follicular, rash generalized, rash maculo-papular, and others [see Supplementary Methods for complete list]) were reported in 46.1% of patients in the alpelisib plus fulvestrant arm (grade ≥3: 14.8%) and 8.6% of patients in the placebo plus fulvestrant arm (no grade ≥3 events).

Three adverse events of special interest (pancreatitis, severe cutaneous reactions and pneumonitis) fell below the reporting threshold listed here. Hypersensitivity, which occurred in 15.7% of patients in the alpelisib group (grade ≥3: 1.7%) and 5.2% of patients in the placebo group (grade ≥3: 0%), did not contain any single preferred terms that reached the reporting threshold listed here.

Table S5. Summary of Adverse Events Leading to Discontinuation

Adverse Event	Alpelisib Group (n=284)		Placebo Group (n=287)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
	number of patients (percent)			
Any adverse event	71 (25.0)	37 (13.0)	13 (4.5)	11 (3.8)
Hyperglycemia	18 (6.3)	12 (4.2)	0	0
Rash	9 (3.2)	3 (1.1)	0	0
Diarrhea	8 (2.8)	1 (0.4)	0	0
Fatigue	6 (2.1)	3 (1.1)	0	0
Nausea	5 (1.8)	1 (0.4)	0	0
Decreased appetite	4 (1.4)	0	0	0
Stomatitis	4 (1.4)	1 (0.4)	1 (0.3)	0
Hypersensitivity	3 (1.1)	2 (0.7)	0	0
Lipase increased	3 (1.1)	1 (0.4)	4 (1.4)	4 (1.4)
Pneumonitis	3 (1.1)	1 (0.4)	0	0
Rash maculo-papular	3 (1.1)	1 (0.4)	0	0
Vomiting	3 (1.1)	0	0	0
Dry mouth	2 (0.7)	1 (0.4)	0	0
Erythema	2 (0.7)	2 (0.7)	0	0
Erythema multiforme	2 (0.7)	0	0	0
Mucosal inflammation	2 (0.7)	1 (0.4)	0	0
Weight decreased	2 (0.7)	0	0	0
Dyspnea	1 (0.4)	0	1 (0.3)	0
Interstitial lung disease	1 (0.4)	0	1 (0.3)	1 (0.3)
Pneumonia	1 (0.4)	1 (0.4)	1 (0.3)	1 (0.3)
Spinal cord compression	0	0	2 (0.7)	1 (0.3)

*Events listed caused discontinuation in >1 patient.

Table S6. Treatment Exposure and Dose Adjustments for Alpelisib/Placebo

Treatment exposure	*PIK3CA*-mutant		*PIK3CA*-non-mutant	
	Alpelisib + fulvestrant (N=169)	Placebo + fulvestrant (N=171)*	Alpelisib + fulvestrant (N=115)	Placebo + fulvestrant (N=116)
Exposure to alpelisib/placebo				
Median duration of exposure, months (range) [n exposed]	5.5 (0.0–29.0) [168]	4.6 (0.0–30.1) [170]	5.6 (0.3–30.8) [115]	6.2 (0.5–29.5) [116]
Median relative dose intensity, %	82.7	100	84.5	100
Dose adjustments, n (%)				
Patients with dose interruptions (≥1)	125 (74.0)	55 (32.2)	80 (69.6)	31 (26.7)
Dose interruptions due to AEs	116 (68.6)	27 (15.8)	73 (63.5)	13 (11.2)
Patients with dose reductions (≥1)	108 (63.9)	15 (8.8)	60 (52.2)	6 (5.2)
Dose reductions due to AEs	105 (62.1)	8 (4.7)	59 (51.3)	5 (4.3)
Dose discontinuations due to AEs	43 (25.4)	8 (4.7)	28 (24.3)	4 (3.4)

*1 patient in the placebo arm of the *PIK3CA*-mutant cohort did not receive fulvestrant or placebo. AE denotes adverse event.

Table S7. Protocol Guidance for Treatment of Hyperglycemia in SOLAR-1

Hyperglycemia	

Grade 1	• **Maintain dose level** and remind patient of lifestyle changes.
	  o If FPG <140 mg/dL, consider adding metformin*
	  o If FPG 140–60 mg/dL, start or intensify metformin*
	• Initiate metformin 500 mg once daily with dinner.
	  o If no GI intolerance after several days, increase to 500 mg twice daily with breakfast and dinner
	  o If tolerated, 1 g twice daily with breakfast and dinner
	  o If not tolerated, reduce to prior tolerated dose
	• Monitor FPG as clinically indicated and at least weekly for 8 weeks, then every 2 weeks until FPG is within baseline values.

Grade 2	• **Maintain dose level** and remind patient of lifestyle changes.
	  o Metformin 500 mg twice daily with breakfast and dinner
	  o If no GI intolerance, increase to 500 mg with breakfast, 1000 mg with dinner
	  o If tolerated, 1000 mg bid with breakfast and dinner
	  o If not tolerated, reduce to prior tolerated dose
	  o Titrate to the maximum tolerated dose over a period of 3 weeks
	• Exclude confounding factors such as UTI and consider consultation with a diabetologist.
	• If FPG continues to rise, or is persistently >160 mg/dL (>8.9 mmol/L), on MTD of metformin, add an insulin-sensitizer, e.g. pioglitazone 30 mg.
	• Monitor FPG as clinically indicated, and at least weekly, until FPG resolves to ≤Grade 1.
	  o If FPG does not resolve to ≤Grade 1 within 21 days after initiation of appropriate antidiabetic treatment, reduce alpelisib/placebo by one dose level.
	  o Continue with antidiabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks.
	  o Alert treating physician if FPG >250 mg/dL.

Grade 3	• **Interrupt treatment with alpelisib/placebo** and confirm fasting status of the assessment. If non-fasting, re-check within 24 hours.
	• Exclude confounding factors such as UTI and consider consultation with a diabetologist.
	• Administer IV hydration and intervention for electrolyte/ketoacidosis/hyperosmolar disturbances as clinically appropriate.
	• Start metformin and titrate as outlined for Grade 2, add pioglitazone as outlined for Grade 2.
	• Insulin may be used for 1–2 days until hyperglycemia resolves; however this may not be necessary in the majority of cases of alpelisib-induced hyperglycemia, given the short half-life of alpelisib.
	• Monitor FPG as clinically indicated and at least twice weekly until FPG resolves to ≤Grade 1.
	  o If FPG resolves to ≤Grade 1 within 3–5 days, while off study treatment and on metformin, re-start alpelisib/placebo and reduce one dose level, continue with antidiabetic treatment and check FPG at least weekly for 8 weeks, then continue checking at least every 2 weeks, alert treating physician if FPG >250 mg/dL.
	  o If FPG does not resolve to Grade 1 within 3–5 days while off study treatment and on metformin, consultation with a diabetologist for management of diabetes is strongly recommended.
	  o If FPG does not resolve to ≤Grade 1 within 21 days after initiation of appropriate antidiabetic treatment in cooperation with a diabetologist, and exclusion of confounding factors e.g. urinary tract infection, permanently discontinue patient from alpelisib/placebo treatment.

Grade 4	• **Interrupt treatment with alpelisib/placebo**, confirm fasting status of the assessment. If non-fasting, re-check within 24 hours.
	• Exclude confounding factors such as UTI and consider consultation with a diabetologist.
	• Initiate or intensify medication with appropriate antidiabetic treatment (see Grade 3), re-check within 24 hours.
	  ○ If grade improves then follow specific grade recommendations.
	  ○ If FPG is confirmed at Grade 4 and confounding factors can be excluded, permanently discontinue patient from alpelisib/placebo.

Always consider consultation with a diabetologist and reinforce advice on lifestyle changes recommended by the ADA, i.e. exercise and dietary advice.[4]

*The preferred option for treating alpelisib-induced hyperglycemia is metformin, given its wide availability and well-characterized safety profile. However, in case of intolerance or unavailability of metformin, investigator's judgment should be exercised and other insulin sensitizers such as thiazolidinediones or DPP4 inhibitors can be used.

Table S8. Protocol Guidance for Treatment of Skin and Subcutaneous Disorders in SOLAR-1

Skin and subcutaneous tissue disorders	
Grade 1 (<10% BSA with active skin toxicity)	• **Maintain dose level.** • Initiate topical corticosteroids 3–4 times daily. ○ Preferred compounds to use are triamcinolone, betamethasone while skin toxicity is active, during maximum 28 days. • For patients with symptoms like burning and/or pruritus add non-sedating antihistamine, consider adding a sedating antihistamine at night. • If active rash is not resolved within 28 days of appropriate treatment, consider adding low-dose systemic corticosteroid (20–40 mg daily).
Grade 2 (10–30% BSA with active skin toxicity)	• **Maintain dose level.** • Initiate topical corticosteroids 3–4 times daily. ○ Preferred compounds to use are triamcinolone or betamethasone while skin toxicity is active, for up to 28 days. • Consider adding systemic corticosteroids 20–40 mg daily. • If rash resolves to ≤Grade 1 within 10 days systemic corticosteroid may be discontinued. • For patients with symptoms like burning, stinging and/or pruritus, add non-sedating antihistamine, consider adding a sedating antihistamine at night.

Grade 3
(>30% BSA with active skin toxicity)
	• **Interrupt treatment with alpelisib/placebo** dose until rash/skin toxicity is no longer active but fading to Grade 1, consider exploratory skin biopsy for central assessment.
	• Initiate topical corticosteroids 3–4 times daily, preferred compounds to use are triamcinolone or betamethasone for at least 28 days.
	• Add systemic corticosteroids 20–40 mg daily.
	• If rash resolves to ≤Grade 1 within 10 days, systemic corticosteroid may be discontinued.
	• For patients with symptoms like burning, stinging and/or pruritus, add non-sedating antihistamine during the day, consider adding a sedating antihistamine at night.
	• When re-starting alpelisib/placebo dose:
	  ○ At same dose in case of first occurrence, at reduced dose level in case of second occurrence.
	  ○ If rash/skin toxicity still active in up to 10% BSA after more than 14 days, continue oral corticosteroid for at least 48 hours upon re-initiation of alpelisib/placebo.
	  ○ If rash and/or pruritus do not reoccur within 48 hours after re-challenge with alpelisib, systemic corticosteroid may be discontinued.
	• For patients with symptoms like burning, stinging and/or pruritus, antihistamine regimen should be continued for a minimum of 28 days after re-initiation of alpelisib/placebo.

Grade 4 (skin toxicity associated with extensive superinfection, with IV antibiotics indicated;	• **Permanently discontinue alpelisib/placebo** and consider consultation with a dermatologist. • Treatment of rash should follow guidelines for Grade 3 above, except that alpelisib/placebo must not be re-initiated. • Consider exploratory skin biopsy for central assessment.

life-threatening consequences)

Consultation with a dermatologist is highly recommended for better assessment and management of alpelisib-induced skin toxicity.

Table S9. Protocol Guidance for Other Adverse Events in SOLAR-1

Other investigations	
Grade 1 or 2	• **Maintain dose level.**
Grade 3	• **Interrupt treatment with alpelisib/placebo** until the event is resolved to ≤Grade 1, then re-initiate at the next lower dose level.
Grade 4	• **Permanently discontinue alpelisib/placebo** • **Interrupt dose for ≥Grade 3 vomiting or Grade 3 nausea** only if the vomiting or nausea cannot be controlled with optimal antiemetic (as per local practice)

Table S10. Additional Characteristics of Patients at Baseline*

Characteristic	*PIK3CA*-mutant Cohort		*PIK3CA*-non-mutant Cohort	
	Alpelisib Group (n=169)	**Placebo Group (n=172)**	**Alpelisib Group (n=115)**	**Placebo Group (n=116)**
Median age (range) — yr	63.0 (25–87)	64.0 (38–92)	62.0 (39–82)	63.0 (32–88)
Sex — no. (%)				
Female	168 (99.4)	172 (100)	115 (100)	116 (100)
Male	1 (0.6)	0	0	0
Race — no. (%)				
White	117 (69.2)	109 (63.4)	82 (71.3)	69 (59.5)
Asian	34 (20.1)	40 (23.3)	25 (21.7)	26 (22.4)
Black or African American	1 (0.6)	3 (1.7)	1 (0.9)	3 (2.6)
Other or unknown	17 (10.1)	20 (11.6)	7 (6.1)	18 (15.5)
Region — no. (%)				
Europe	86 (50.9)	87 (50.6)	67 (58.3)	58 (50.0)
North America	19 (11.2)	24 (14.0)	10 (8.7)	13 (11.2)
Asia	32 (18.9)	38 (22.1)	24 (20.9)	26 (22.4)
Latin America	14 (8.3)	17 (9.9)	3 (2.6)	9 (7.8)
Other	18 (10.7)	6 (3.5)	11 (9.6)	10 (8.6)
ECOG performance status — no. (%)				
0	112 (66.3)	113 (65.7)	84 (73.0)	79 (68.1)
1	56 (33.1)	58 (33.7)	30 (26.1)	37 (31.9)
Missing	1 (0.6)	1 (0.6)	1 (0.9)	0
Sites of metastases — no. (%)†				
Breast	1 (0.6)	3 (1.7)	5 (4.3)	4 (3.4)

Bone				
Any	131 (77.5)	121 (70.3)	79 (68.7)	89 (76.7)
Only	42 (24.9)	35 (20.3)	26 (22.6)	23 (19.8)
Visceral				
Any	93 (55.0)	100 (58.1)	66 (57.4)	74 (63.8)
Liver	49 (29.0)	54 (31.4)	41 (35.7)	36 (31.0)
Lung	57 (33.7)	68 (39.5)	37 (32.2)	55 (47.4)
Lung/liver	84 (49.7)	86 (50.0)	56 (48.7)	56 (48.3)
Other	3 (1.8)	1 (0.6)	1 (0.9)	4 (3.4)
Lymph nodes	56 (33.1)	65 (37.8)	43 (37.4)	53 (45.7)
Other	29 (17.2)	26 (15.1)	19 (16.5)	23 (19.8)
Number of metastatic sites — no. (%)				
0	0	1 (0.6)	0	0
1	63 (37.3)	52 (30.2)	44 (38.3)	33 (28.4)
2	58 (34.3)	60 (34.9)	35 (30.4)	38 (32.8)
≥3	48 (28.4)	59 (34.3)	36 (31.3)	45 (38.8)
Prior treatment — no. (%)‡				
Any CDK4/6 inhibitor	9 (5.3)	11 (6.4)	7 (6.1)	8 (6.9)
Tamoxifen	59 (34.9)	62 (36.0)	37 (32.2)	50 (43.1)
Chemotherapy§	101 (59.8)	107 (62.2)	78 (67.8)	72 (62.1)
Neoadjuvant	25 (14.8)	29 (16.9)	20 (17.4)	23 (19.8)
Adjuvant	78 (46.2)	86 (50.0)	64 (55.7)	58 (50.0)
Line of treatment in advanced disease — no. (%)‖				
First line	88 (52.1)	89 (51.7)	71 (61.7)	62 (53.4)
Second line	79 (46.7)	82 (47.7)	42 (36.5)	53 (45.7)

Endocrine status — no. (%)¶				
Primary resistance	23 (13.6)	22 (12.8)	31 (27.0)	26 (22.4)
Secondary resistance	120 (71.0)	127 (73.8)	66 (57.4)	65 (56.0)
Sensitive	20 (11.8)	19 (11.0)	16 (13.9)	20 (17.2)

*Any differences between treatment groups were below 10% for the *PIK3CA*-mutant cohort. CDK denotes cyclin-dependent kinase, ECOG denotes Eastern Cooperative Oncology Group.

†One patient in the placebo group in each cohort had locally advanced disease with no metastases.

‡All patients previously received treatment with an aromatase inhibitor.

§(Neo)adjuvant disease only. Patients may have received chemotherapy in both the neoadjuvant and adjuvant settings. One patient in the placebo group of the *PIK3CA*-mutant cohort received chemotherapy for advanced disease (protocol deviation).

‖Three patients in the *PIK3CA*-mutant cohort (two from the alpelisib group and one from the placebo group) were excluded due to protocol deviations.

¶Primary endocrine resistance: Relapse <24 months while on endocrine therapy in adjuvant setting, or progression <6 months while on endocrine therapy in the metastatic setting. Secondary endocrine resistance: Relapse ≥24 months while on endocrine therapy in adjuvant setting or relapse <12 months after end of endocrine therapy in adjuvant setting, or progression ≥6 months while on endocrine therapy in the metastatic setting. The study protocol was updated after enrollment began, to exclude patients who relapsed ≥12 months after completion of (neo)adjuvant endocrine therapy with no treatment for metastatic disease (endocrine sensitive).

References

1. Dodd LE, Korn EL, Freidlin B, Gray R, Bhattacharya S. An audit strategy for progression-free survival. Biometrics 2011;67:1092-9.

2. Amit O, Mannino F, Stone AM, et al. Blinded independent central review of progression in cancer clinical trials: results from a meta-analysis. Eur J Cancer 2011;47:1772-8.

3. Cardoso F, Senkus E, Costa A, et al. 4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). Ann Oncol 2018;29:1634-57.

4. American Diabetes Association. 4: Lifestyle Management. Diabetes Care. 2017;40(Suppl 1):S33–S43.