SYNOPSIS OF RESEARCH REPORT 1120396 (PROTOCOL CO40016)

NAME OF SPONSOR/COMPANY: F. Hoffmann-La Roche Ltd. NAME OF STUDY TREATMENT: Ipatasertib (RO5532961, GDC-0068) Atezolizumab (RO5541267)	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	Final Clinical Study Report: Study CO40016, (IPATunity130). A Double-Blind, Placebo-Controlled, Randomized Phase III Study Of Ipatasertib In Combination With Paclitaxel As A Treatment For Patients With *PIK3CA/AKT1/PTEN*-Altered, Locally Advanced Or Metastatic, Triple-Negative Breast Cancer Or Hormone Receptor-Positive, HER2-Negative Breast Cancer. Report No. 1120396. August 2023
NUMBER OF STUDY CENTERS AND COUNTRIES	The number of study centers and countries for Cohort A and Cohort B were provided in the primary CSR for Cohort A (Report No. 1101889) and Cohort B (Report No. 1100941). <u>Cohort C</u> 102 centers in 11 countries: Australia (3 centers), Republic of Korea (6), Singapore (1), Taiwan (3), France (6), United Kingdom (8), Poland (10), Ukraine (14), United States (13), Brazil (27), and Peru (11).
PUBLICATIONS	Turner N, Dent RA, O'Shaughnessy J, et al. Ipatasertib plus paclitaxel for PIK3CA/AKT1/PTEN-altered hormone receptor-positive HER2-negative advanced breast cancer: primary results from cohort B of the IPATunity130 randomized phase 3 trial. Breast Cancer Res Treat. 2022; 191:565-576. Dent R, Kim S, Oliveira M, et al. Abstract GS3-04: double-blind placebo (PBO)-controlled randomized phase III trial evaluating first-line ipatasertib (IPAT) combined with paclitaxel (PAC) for PIK3CA/AKT1/PTEN-altered locally advanced unresectable or metastatic triple-negative breast cancer (aTNBC): primary results from IPATunity130 Cohort A. Cancer Res. 2021;81:GS3-04.
STUDY PHASE	III
STUDY PERIOD	First Patient Enrolled: 06-Jan-2018 Data cutoff Efficacy analysis: 30-Oct-2021 Safety analysis: 21-Mar-2023 Last Patient Last Visit: 04-Jan-2023

METHODOLOGY

Cohorts A and B of the Phase III study CO40016 were randomized, double-blind, placebo-controlled and designed to independently evaluate the efficacy, safety, and pharmacokinetics of ipatasertib + paclitaxel (Ipat + Pac) versus placebo + paclitaxel (Pbo + Pac) in patients with *PIK3CA/AKT1/PTEN*-altered, locally advanced unresectable or metastatic:

- Triple-negative breast cancer (TNBC) (Cohort A), and
- Hormone receptor-positive, HER2-negative (HR+/HER2−) breast adenocarcinoma who were not suitable for endocrine therapy (Cohort B).

Patients were randomized with a 2:1 ratio to the experimental versus control arm, and stratified by the following factors: prior adjuvant/neoadjuvant chemotherapy (yes vs. no), region (Asia-Pacific vs. Europe vs. North America vs. rest of the world), tumor *PIK3CA/AKT1/PTEN*-alteration status (PIK3CA/AKT1-activating mutations vs. PTEN alterations with no PIK3CA/AKT1-activating mutations; Cohort A only), and prior therapy with a phosphoinositide 3-kinase or mammalian target of rapamycin inhibitor (yes vs. no; Cohort B only).

Patients who initially screened for Cohort A (TNBC) but did not qualify due to the lack of a PIK3CA/AKT1/PTEN alteration (validated by central tumor tissue testing using the Foundation Medicine. Inc. Clinical Trial Assay) were eligible for Cohort C. Cohort C was an open-label, non-randomized cohort for patients with locally advanced unresectable or metastatic TNBC that assessed the safety, efficacy, and pharmacokinetics of ipatasertib in combination with paclitaxel and atezolizumab.

Cohorts A and B

All patients received paclitaxel chemotherapy (80 mg/m^2 intravenous [IV] infusion) on Days 1, 8, and 15 of each 28-day cycle and either ipatasertib at a dose of 400 mg (experimental arm) or placebo (control arm) orally once a day (QD) on Days 1−21 of each 28-day cycle.

Cohort C

All patients received paclitaxel chemotherapy (80 mg/m^2 IV infusion) on Days 1, 8, and 15 and atezolizumab (840 mg IV) on Days 1 and 15 of each 28-day cycle, and ipatasertib at a dose of 400 mg orally QD on Days 1−21 of each 28-day cycle.

Study treatment was continued until disease progression, intolerable toxicity, elective withdrawal from the study, or study completion or termination. Upon treatment discontinuation, patients were followed up every 3 months for survival, patient-reported outcomes (PROs), and new anti-cancer therapies and their outcomes.

Tumor assessments based on Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) were performed every 8 weeks, regardless of treatment administration timing, during the treatment period and every 8−12 weeks after treatment discontinuation for patients who discontinued treatment without evidence of disease progression per RECIST v1.1 until documented progression per RECIST v1.1, elective withdrawal from the study, or study completion or termination. Images for tumor assessments for all patients were prospectively collected to enable retrospective blinded independent central review when needed.

PRO assessments were completed prior to the administration of study treatment or any other study assessment(s) that could bias patients' responses. During the treatment period, all PRO assessments were completed on Day 1 of each cycle and at the study drug discontinuation visit. After initiation of study drug, all adverse events (AEs), regardless of relationship to study drug, were reported until 28 days after the last dose of study. After this period, investigators were to report any serious AEs (SAEs) and AEs of special interest (AESI) that were believed to be related to prior treatment with study drug.

Rationale for an Abbreviated Clinical Study Report
This final clinical study report (CSR) is provided in an abbreviated format because ipatasertib in combination with either paclitaxel alone (i.e., Cohorts A and B) or with atezolizumab and paclitaxel (i.e., Cohort C) is no longer being pursued for use in patients with *PIK3CA/AKT1/PTEN*-altered, locally advanced or metastatic TNBC or HR+/HER2− breast cancer.

NUMBER OF PATIENTS (PLANNED AND ANALYZED)	The number of patients (planned and final enrollment) and the number of patients analyzed per analysis population for Cohort A and Cohort B were provided in the primary CSR for Cohort A (Report No. 1101889) and Cohort B (Report No. 1100941). For Cohort C, planned enrollment was approximately 100 patients and final enrollment was 102 patients. For Cohort C, the number of patients analyzed per analysis population was as follow: • ITT population: 102 patients • Safety evaluable population: 102 patients • PRO evaluable population: 101 patients
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	**Target Populations:** <u>Cohort A</u> Patients with locally advanced unresectable or metastatic TNBC with *PIK3CA/AKT1/PTEN*-altered tumor and no prior chemotherapy in the advanced setting. <u>Cohort B</u> Patients with locally advanced unresectable or metastatic HR+/HER2− breast cancer with *PIK3CA/AKT1/PTEN*-altered tumor who had no prior chemotherapy in the advanced setting and who were not suitable for endocrine therapy. <u>Cohort C</u> Patients with histologically confirmed locally advanced unresectable or metastatic TNBC without *PIK3CA/AKT1/PTEN*-altered tumors and no prior systemic chemotherapy in the advanced setting.
STUDY TREATMENTS, DOSE, MODE OF ADMINISTRATION AND BATCH NUMBER(S)	**<u>Cohort A and Cohort B</u>** Paclitaxel chemotherapy (80 mg/m^2 IV) on Days 1, 8, and 15 of each 28-day cycle and either ipatasertib at a dose of 400 mg administered orally QD on Days 1−21 of each 28-day cycle (experimental arm) or placebo orally QD on Days 1−21 of each 28-day cycle (control arm) **<u>Cohort C</u>** Paclitaxel chemotherapy (80 mg/m^2 IV) on Days 1, 8, and 15 of each 28-day cycle, ipatasertib at a dose of 400 mg administered orally QD on Days 1−21 of each

	28-day cycle, and atezolizumab 840 mg IV on Days 1 and 15 of each 28-day cycle. Batch numbers for ipatasertib/placebo, atezolizumab, and paclitaxel are provided in the study documentation of this report.
DURATION OF STUDY TREATMENT	Study treatment continued until disease progression, intolerable toxicity, elective withdrawal from the study, or study completion or termination. The end of this study was defined as the date when the last patient, last visit occurred or the date at which the last data point required for statistical analysis or safety follow-up was received from the last patient, whichever occurred later. The total length of the study, from screening of the first patient to the end of the study, was expected to be approximately 53 months. The actual study duration was approximately 62 months.

SUMMARY OF OBJECTIVES AND ENDPOINTS

Objectives and corresponding endpoints for Cohort A and Cohort B of Study CO40016 were provided in the primary clinical study reports (CSRs) for Cohort A (Report No. 1101889) and Cohort B (Report No. 1100941). Objectives and corresponding endpoints for Cohort C are presented below. Exploratory objectives and results from these analyses are not presented in this final CSR.

Objectives	Corresponding Endpoints
Primary Efficacy Objective	
• To evaluate the efficacy of ipatasertib + paclitaxel + atezolizumab	• Progression-free survival (PFS), defined as the time from enrollment to the first occurrence of disease progression, as determined locally by the investigator through the use of Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), or death from any cause, whichever occurs first
Secondary Efficacy Objectives	
• To evaluate the efficacy of ipatasertib + paclitaxel + atezolizumab	• Objective response rate, defined as a CR or PR on two consecutive occasions ≥ 4 weeks apart, as determined locally by the investigator through the use of RECIST v1.1 • Duration of response, defined as the time from the first occurrence of a documented objective response to disease progression, as determined locally by the investigator through use of RECIST v1.1, or death from any cause, whichever occurs first • Clinical benefit rate, defined as an objective response (CR or PR), or stable disease for at least 24 weeks, as determined locally by the investigator through the use of RECIST v1.1 • OS, defined as the time from enrollment to death from any cause • 1-year PFS, defined as progression-free survival probabilities at 1 year • 1-year OS, defined as overall survival probabilities at 1 year

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Objectives	Corresponding Endpoints
• To evaluate PROs of GHS/QoL associated with ipatasertib + paclitaxel + atezolizumab	• Mean and mean changes from baseline GHS/QoL score as measured by the GHS/QoL scale (Questions 29 and 30) of the EORTC QLQ-C30, by cycle
Safety Objective	
• To evaluate the safety of ipatasertib + paclitaxel + atezolizumab	• Incidence of adverse events as assessed by the investigator, with severity determined through the use of NCI CTCAE v4.0 • Incidence of prespecified adverse events • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
Pharmacokinetic Objective	
• To characterize the pharmacokinetics of atezolizumab, ipatasertib and its metabolite (G-037720) when administered in combination with paclitaxel	• Plasma concentration of ipatasertib and its metabolite, G-037720 at specified timepoints for analysis using population PK methodology • Serum concentration of atezolizumab at specified timepoints
Immunogenicity Objective	
• To evaluate the immune response to atezolizumab	• Incidence ofADAs to atezolizumab during the study relative to the prevalence of ADAs at baseline

ADA = anti-drug antibody; CR = complete response; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GHS = global health status; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; OS = overall survival; PK = pharmacokinetics; PFS = progression-free survival; PR = partial response; PRO = patient-reported outcome; QoL = Quality of life; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Note: Cohort C was a single-arm cohort with no statistical hypothesis testing and the results are descriptive only.

SUMMARY OF RESULTS AND CONCLUSIONS

DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

For Cohort A and Cohort B, demographic and other baseline characteristics were provided in the primary CSR for Cohort A (Report No. 1101889) and Cohort B (Report No. 1100941).

For Cohort C, in the ITT population, all patients were women, and the majority were White (53.9%), followed by Unknown (14.7%), or Asian (11.8%). The median age was 55 years (range: 22–83 years). In accordance with the protocol inclusion criteria, all patients had a high baseline functional status (i.e., Eastern Cooperative Oncology Group Performance Status 0: 59.8% or 1: 40.2%). The majority of patients (74.5%) had metastatic disease at baseline. Prior breast cancer radiotherapy, prior anthracycline therapy, or prior taxane therapy were reported in 35.3%, 35.3%,

and 37.3% of patients, respectively. The proportion of patients with a disease-free interval and chemotherapy-free interval of >3 years were 5.9% and 3.9%, respectively. The most common diagnosed histopathological subtype was ductal (73.3%). Most patients were initially diagnosed with poorly differentiated Grade 3 breast cancer (60.8%). The most common stage at initial diagnosis was Stage IV (36.3%) followed by Stage III (30.4%) and Stage II (22.5%).

EXPOSURE

Cohort A

At the time of the clinical cutoff date (CCOD), the median duration of ipatasertib/placebo treatment was 5.3 months (range: 0–46) in the Ipat + Pac arm and 5.7 months (range: 0–44) in the Pbo + Pac arm. The median duration of paclitaxel treatment in the Ipat + Pac arm was 5.1 months (range: 0–38) and 5.3 months (range: 0–39) in the Pbo + Pac arm.

Cohort B

At the time of the CCOD, the median duration of ipatasertib/placebo treatment was 8 months (range: 0–48) in the Ipat + Pac arm and 9.1 months (range: 0–48) in the Pbo + Pac arm. The median duration of paclitaxel treatment in the Ipat + Pac arm was 6.9 months (range: 0–48) and 8.8 months (range: 0–47) in the Pbo + Pac arm.

Cohort C

At the time of the CCOD, the median duration of ipatasertib treatment was 6.2 months (range: 0–43). The median duration of paclitaxel treatment was 6.1 months (range: 0–29). The median duration of atezolizumab treatment was 5.7 months (range: 0–41).

EFFICACY RESULTS

For Cohort A and Cohort B, primary efficacy analyses were provided in the primary CSR for Cohort A (Report No. 1101889) and Cohort B (Report No. 1100941).

This CSR describes the final efficacy data for all cohorts, specifically, final overall survival (OS) for Cohort A and Cohort B (Table 1), and PFS, OS, and other secondary efficacy endpoints for Cohort C (Table 2).

Cohorts A and B in Study CO40016 did not meet their primary endpoint, PFS. As such, the final OS analysis results were considered descriptive and there was no clinically meaningful benefit observed in OS with ipatasertib in combination with paclitaxel over paclitaxel alone in patients with *PIK3CA/AKT1/PTEN*-altered, locally advanced or metastatic TNBC (Cohort A) or HR+/HER2– breast cancer (Cohort B). The efficacy results for Cohort C were descriptive in nature, and the median duration of PFS and OS were consistent with the results in the Ipat + Pac arm in Cohort A.

Table 1 Final Overall Survival for Cohort A and Cohort B (CCOD: 30 October 2021)

Key Secondary Efficacy Endpoint				
Overall Survival (Final Analysis)				
	Cohort A		**Cohort B**	
	Pbo + Pac	**Ipat + Pac**	**Pbo + Pac**	**Ipat + Pac**
ITT Population	**n = 87**	**n = 168**	**n = 76**	**n = 146**
Patients with event (%)	39 (44.8%)	87 (51.8%)	43 (56.6%)	77 (52.7%)
Median duration of survival – months (95% CI)	24.9 (16.9, 40.4)	24.2 (19.2, 29.4)	28.4 (20.6, 37.3)	29.0 (22.4, 34.8)
Stratified Hazard Ratio (95% CI)	1.08 (0.73, 1.58)		0.94 (0.65, 1.37)	
Unstratified Hazard Ratio (95% CI)	1.05 (0.72, 1.54)		0.92 (0.64, 1.34)	

CCOD = clinical cutoff date; Ipat = ipatasertib; ITT = intent-to-treat; n = number of patients; Pac = paclitaxel; Pbo = placebo.

Table 2 Summary of Efficacy for Cohort C (CCOD: 30 October 2021)

Primary Efficacy Endpoint	
Progression-Free Survival: INV-Assessed per RECIST v1.1	
ITT Population	**Ipat + Atezo + Pac (n = 102)**
Patients with event (%)	78 (76.5%)
Median duration of PFS – months (95% CI)	7.1 (5.5, 9.1)
1-year event-free rate - % (95% CI)	31.17 (21.59, 40.76)
Key Secondary Efficacy Endpoints	
Overall Survival	
ITT Population	**Ipat + Atezo + Pac (n = 102)**
Patients with event (%)	49 (48.0%)
Median duration of survival – months (95% CI)	22.8 (17.8, NE)
1-year event-free rate - % (95% CI)	79.38 (71.31, 87.44)

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Other Secondary Efficacy Endpoints	
Objective Response Rate: INV-Assessed per RECIST v1.1	
Patients with Measurable Disease at Baseline	**Ipat + Atezo + Pac (n = 102)**
Responders 95% CI	54 (52.9%) (42.80, 62.90)
Complete Response (CR) 95% CI	7 (6.9%) (2.80, 13.63)
Partial Response (PR) 95% CI	47 (46.1%) (36.16, 56.23)
Duration of Response: INV-Assessed per RECIST v1.1	
Patients with Objective Response	**Ipat + Atezo + Pac (n = 54)**
Patients with event (%)	32 (59.3%)
Patients without event (%)	22 (40.7%)
Median duration of response – months 95% CI	8.7 (5.7,12.7)
Clinical Benefit Rate: INV-Assessed per RECIST v1.1	
Patients with Measurable Disease at Baseline	**Ipat + Atezo + Pac (n = 102)**
Patients with clinical benefit 95% CI	56 (54.9%) (44.74, 64.78)
Patient-Reported Outcomes – GHS/QoL – EORTC QLQ-C30	
PRO Evaluable Population	N = 101
Please refer below for an overview of the PRO results.	

Atezo = atezolizumab; CCOD = clinical cutoff date; CR = complete response; EORTC QLQ C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GHS = Global Health Status; INV = investigator; Ipat = ipatasertib; ITT = intent-to-treat; n = number of patients; Pac = paclitaxel; PFS = progression-free survival; PR = partial response; PRO = patient-reported outcome; QoL = Quality of Life; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Patient Reported Outcomes – GHS/QoL – EORTC QLQ-C30 (Cohort C Only)
Beyond Cycle 7, less than half of the PRO evaluable population were still on treatment, precluding a meaningful analysis following the Cycle 7 assessment. The mean Global Health Status/Quality of Life (GHS/QoL) score at baseline was 74.92. No clinically meaningful deterioration (i.e., a ≥10-point decrease) in the mean change from baseline values was observed, indicating patients' baseline GHS/QoL was maintained through Cycle 7.

SAFETY RESULTS

The safety profile of ipatasertib in combination with paclitaxel remained consistent with the safety profile reported in the primary CSR for Cohorts A and B. The safety profile of ipatasertib in combination with atezolizumab and paclitaxel (Cohort C) was consistent with the known risks of each individual study drug and no new safety signals were identified across cohorts. Key safety findings for each cohort are provided below.

Cohort A

- The median duration of ipatasertib/placebo treatment was 5.3 months in the Ipat+Pac arm and 5.7 months in the Pbo+Pac arm. The median duration of paclitaxel treatment was 5.1 months in the Ipat + Pac arm and 5.3 months in the Pbo + Pac arm.
- The most frequent AEs (by Preferred Term [PT]) of any grade (reported in ≥30% of patients) were diarrhea, alopecia, nausea, and vomiting in the Ipat + Pac arm and diarrhea, alopecia and constipation in the Pbo+Pac arm.
- Grade≥3 AEs were reported in a similar proportion of patients in the Ipat+Pac arm and the Pbo+Pac arm (50.6% vs. 46.0%). The most frequent Grade ≥3 AEs (by PT) with ≥5% incidence were diarrhea and neutropenia in the Ipat+Pac arm, and neutrophil count decreased in the Pbo+Pac arm.
- A total of 132 deaths were reported in the safety evaluable population (Ipat+Pac: 91 patients [54.8%] vs. Pbo+Pac: 41 patients [47.1%]). The primary cause of death was progressive disease.
- Grade 5 AEs were reported in 2 patients in both Ipat+Pac (1.2%) and Pbo+Pac (2.3%) arms. Of these, 1 AE (by PT) of tumor lysis syndrome in the Pbo+Pac arm was considered related to both placebo and paclitaxel by the investigator.
- Serious adverse events (SAEs) were reported in a similar proportion of patients in the Ipat+Pac arm and the Pbo+Pac arm (20.5% vs. 23.0%). SAEs (by PT) reported in ≥1% of patients (i.e., ≥2 patients) in the Ipat+Pac arm were: diarrhea, febrile neutropenia, pulmonary embolism, pneumonia, nausea, and vomiting. SAEs (by PT) reported in more than 1 patient in the Pbo+Pac arm were: pneumonia and pleural effusion.
- The proportion of patients who experienced AEs leading to ipatasertib/placebo treatment discontinuation was higher in the Ipat+Pac arm compared with Pbo+Pac arm (10.2% vs. 6.9%)
- AEs leading to discontinuation of paclitaxel was reported in 15.1% of patients in the Ipat+Pac arm and 16.1% of patients in the Pbo + Pac arm.
- Selected AEs were reported in both treatment arms (Ipat + Pac: 94.6% vs. Pbo + Pac: 90.8%). Selected AEs of diarrhea, asthenia, nausea, rash, vomiting, hyperglycemia and oral mucositis were observed with a higher frequency (≥5% difference) in the Ipat + Pac arm compared with the Pbo + Pac arm. Peripheral neuropathy, neutropenia, erythropenia, hepatotoxicity, hyperlipidemia, pneumonia, thrombocytopenia, pneumonitis, colitis, and erythema multiforme were reported with < 5% difference between treatment arms. Of the safety evaluable patients, for selected AEs, 51.8% experienced a highest Grade of 1–2 in the Ipat + Pac arm, 57.5% experienced a highest Grade of 1–2 in the Pbo + Pac arm, 42.8% experienced a highest Grade of 3–4 in the Ipat + Pac arm, and 33.3% experienced a highest Grade of 3–4 in the Pbo + Pac arm.

Cohort B

- The median duration of ipatasertib/placebo treatment was 8 months in the Ipat + Pac arm and 9.1 months in the Pbo + Pac arm. The median duration of paclitaxel treatment was 6.9 months in the Ipat + Pac arm and 8.8 months in the Pbo + Pac arm.

- The most frequent AEs (by PT) of any grade (reported in ≥30% of patients) were: diarrhea, alopecia, anemia, neuropathy peripheral, vomiting and nausea in the Ipat + Pac arm and diarrhea, alopecia, peripheral sensory neuropathy, and constipation in the Pbo + Pac arm.
- Grade≥3 AEs were reported in a higher proportion of patients in the Ipat + Pac arm and the Pbo + Pac arm (57.2% vs. 49.3%). The most frequent Grade ≥3 AEs (by PT) with ≥5% incidence were diarrhea, neutrophil count decreased, neuropathy peripheral and neutropenia in the Ipat + Pac arm, and neutrophil count decreased, peripheral sensory neuropathy, neutropenia, and hypertension in the Pbo + Pac arm.
- A total of 122 deaths were reported in the safety evaluable population (Ipat + Pac: 78 patients [53.8%] vs. Pbo + Pac: 44 patients [58.7%]). The primary cause of death was progressive disease.
- Grade 5 AEs were reported in 5 patients (3.4%) in the Ipat + Pac arm and 1 patient (1.3%) in the Pbo + Pac arm. Of these, SAE (by PT) of sepsis in the Pbo + Pac arm was considered related to paclitaxel and SAE of febrile neutropenia in the Ipat + Pac arm was considered related to ipatasertib and paclitaxel by the investigator.
- SAEs were reported in a higher proportion of patients in the Ipat+Pac arm compared with the Pbo+Pac arm (20.7% vs. 14.7%). SAEs (by PT) reported in ≥1% of patients (i.e., ≥2 patients) in the Ipat+Pac arm were: diarrhea, pneumonia, pneumonitis, febrile neutropenia, and neutropenia. No SAE (by PT) was reported in more than 1 patient in the Pbo+Pac arm.
- The proportion of patients who experienced AEs leading to ipatasertib/placebo treatment discontinuation was higher in the Ipat+Pac arm compared with Pbo+Pac arm (11.7% vs. 4.0%)
- AEs led to discontinuation of paclitaxel in 29% of patients in the Ipat+Pac arm and 16% of patients in the Pbo + Pac arm.
- Selected AEs were reported in both treatment arms (Ipat+Pac: 97.2% vs. Pbo+Pac: 97.3%). Selected AEs of diarrhea, nausea, rash, erythropenia, vomiting, and oral mucositis were observed with a higher frequency (≥5% difference) in the Ipat+Pac arm compared with the Pbo+Pac arm. Peripheral neuropathy, neutropenia, asthenia, hyperglycemia, hyperlipidemia, pneumonia, pneumonitis, and thrombocytopenia were reported with < 5% difference between treatment arms. Of the safety evaluable patients, for selected AEs, 51.7% experienced a highest Grade of 1–2 in the Ipat + Pac arm, 65.3% experienced a highest Grade of 1–2 in the Pbo + Pac arm, 44.1% experienced a highest Grade of 3–4 in the Ipat + Pac arm, 32% experienced a highest Grade of 3–4 in the Pbo + Pac arm, and 1.4% experienced a highest Grade of 5 in the Ipat + Pac arm.

Cohort C

- The median duration of ipatasertib, atezolizumab, and paclitaxel treatment were 6.2, 5.7, and 6.1 months, respectively.
- The most frequent AEs (by PT) of any grade (reported in ≥30% of patients) were diarrhea, alopecia, nausea, anemia, and rash.
- Grade ≥3 AEs were reported in 60.8% of patients. The most frequent Grade ≥3 AEs (by PT) with ≥5% incidence were alanine aminotransferase increased, aspartate aminotransferase increased, neuropathy peripheral, diarrhea and neutropenia.
- A total of 50 deaths were reported in the safety evaluable population. The primary cause of death was progressive disease.
- Grade 5 AEs were reported in 4 patients (3.9%). Of these, a SAE (by PT) of pulmonary embolism was considered related to atezolizumab by the investigator.

- SAEs (by PT) reported in ≥2 patients were diarrhea, pneumonia, urinary tract infection, pyrexia, fatigue, pneumonitis, cholecystitis, dehydration, tumor necrosis, rash, febrile neutropenia, and vomiting.
- The proportions of patients who experienced AEs leading to ipatasertib, atezolizumab, and paclitaxel treatment discontinuation were 10.8%, 13.7%, and 22.5%, respectively.
- The proportion of patients who experienced at least one selected AE was 99%. The most frequent (≥30%) selected AEs (by PT) were diarrhea, rash, nausea, and anemia. Of the safety evaluable patients, for selected AEs, 48% experienced a highest Grade of 1–2, 50% experienced a highest Grade of 3–4, and 1% experienced a highest Grade of 5.

PHARMACOKINETICS RESULTS

Pharmacokinetic analyses for Cohorts A and B are described in the primary CSRs (Cohort A Report No. 1101889; Cohort B Report No. 1100941).
For Cohort C, concentrations of ipatasertib and its metabolite, G-037720, increased after multiple dosing compared with that following a single dose. This is consistent with what is expected for ipatasertib given its half-life and the once daily dosing regimen. The steady state plasma exposures of ipatasertib and G-037720 were comparable on Cycle 1 Day 15 and Cycle 3 Day 15. The variability of ipatasertib and G-037720 concentrations at each time point observed in this study is high, partially due to the wide window of time (time range) allowed for sample collection for PK analysis.

IMMUNOGENICITY RESULTS

For Cohort C, the incidence of treatment-emergent anti-drug antibodies (ADAs) was 17.8% (18/101) in the treatment-emergent ADA-evaluable population.

IMPACT OF COVID-19 PANDEMIC ON STUDY CONDUCT AND ANALYSES

The coronavirus disease 2019 pandemic had minor impact on the study conduct and data collection. Data analysis has not been impacted:

- The study protocol or conduct has not been altered.
- The study had minimal missing data.
- The impact on safety data collection was minor. The observed overall safety findings from the study were not confounded by the pandemic, still hold scientific validity and are clinically meaningful.
- The risk/benefit ratio of ipatasertib remains unchanged, as both efficacy and safety results have not been impacted.

CONCLUSIONS

In Study CO40016, Cohorts A and B did not meet their primary endpoint: Ipatasertib in combination with paclitaxel did not demonstrate a statistically significant and clinically meaningful improvement in investigator-assessed PFS compared with paclitaxel alone in patients with *PIK3CA/AKT1/PTEN*-altered, locally advanced or metastatic TNBC or HR+/HER2- breast cancer. The final OS results were consistent with those of the primary endpoint, with no clinically meaningful benefit observed for ipatasertib in combination with paclitaxel over paclitaxel alone for both Cohorts A and B. The efficacy results from Cohort C (ipatasertib in combination with paclitaxel and atezolizumab) were consistent with the results in the ipatasertib and paclitaxel arm in Cohort A. For patient-reported GHS/QOL, the result of adding ipatasertib to paclitaxel and atezolizumab (Cohort C) was consistent with that of adding ipatasertib to paclitaxel alone (Cohorts A and B), such that it did not result in a detrimental effect to patients' overall health-related quality of life.
The safety profile of the combination of ipatasertib with either paclitaxel alone (Cohort A and B) or with atezolizumab and paclitaxel (Cohort C) was consistent with the known risks of each individual study treatment component. No new safety signals were identified.

Signature Page for 1120396-co40016-synopsis
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Approval Task	Chenglin Ye Company Signatory 11-Aug-2023 03:14:32 GMT+0000