Phase Ib Study of Ribociclib Plus Fulvestrant and Ribociclib Plus Fulvestrant Plus PI3K-Inhibitor (Alpelisib or Buparlisib) for HR+ Advanced Breast Cancer

SUPPLEMENTARY APPENDIX

Supp Table 1. Criteria for defining dose-limiting toxicities

Toxicity	DLT Criteria
Hematology	CTCAE grade 4 neutropenia for more than 4 consecutive days
	CTCAE grade 4 lymphopenia > 7 days
	CTCAE grade 4 thrombocytopenia
	CTCAE grade 3 thrombocytopenia with bleeding
	Febrile neutropenia (decrease in neutrophils associated with fever ≥ 38.5°C, ANC < 1.0×10^9/L)
Skin and subcutaneous disorders	CTCAE grade 3 rash > 7 consecutive days despite skin toxicity treatment (as per local practice) that is intolerable for the patient
	CTCAE grade 4 rash
	≥ CTCAE grade 3 photosensitivity
Metabolism	Grade 2 or 3 hyperglycemia (FG > 200 mg/dL) (confirmed with a repeat FG within 24 hours) that does not resolve to FG < 200 mg/dL within 14 days (despite optimal oral anti-diabetic therapy, e.g. glimepiride, glibenclamide and/or metformin)
	Grade 4 hyperglycemia (FG > 499 mg/dL)
	Hyperglycemia leading to diabetic keto-acidosis, hospitalization for IV insulin infusion, or non-ketotic coma
Gastrointestinal	CTCAE grade 2 pancreatitis for more than 7 consecutive days
	≥ CTCAE grade 3 pancreatitis
	≥ CTCAE grade 3 nausea or vomiting ≥ 48 hrs despite optimal anti-emetic therapy
	≥ CTCAE grade 3 diarrhea ≥ 48 hrs despite optimal anti-diarrhea treatment
	CTCAE grade 3 amylase and/or lipase, not reversible to ≤ CTCAE grade 2 for > 7 consecutive days
	CTCAE grade 4 amylase and/or lipase
Hepatobiliary	CTCAE grade 2 bilirubin for more than 7 consecutive days in the absence of liver metastases and no evidence of disease progression
	≥ CTCAE grade 3 total bilirubin
	≥ CTCAE grade 3 ALT lasting > 4 days (isolated increases in AST without concomitant increases in ALT will not be considered dose-limiting, because of the non-specific nature of AST)
	≥ CTCAE grade 2 ALT with a ≥ grade 2 bilirubin elevation of any duration in the absence of liver metastases and no evidence of disease progression
	CTCAE grade 4 ALT or AST
	CTCAE grade 4 serum alkaline phosphatase > 7 consecutive days
Cardiac	Cardiac toxicity ≥ CTCAE grade 3
	Clinical signs of cardiac disease, such as unstable angina or myocardial infarction, or troponin ≥ CTCAE grade 3
ECG QT interval	QTcF interval ≥ 501 ms on at least two separate ECGs
Mood alteration	CTCAE grade 2 mood alteration that does not resolved to ≤ grade 1 within 14 days despite medical treatment (for anxiety only, if worsened from baseline)
	≥ CTCAE grade 3 mood alteration
Renal	≥ CTCAE grade ≥ 3 serum creatinine
	CTCAE grade 2 serum creatinine for ≥ 7 consecutive days
Non-hematologic events not addressed above	≥ CTCAE grade 3, except for the exclusions noted below:
Exceptions to DLT criteria	CTCAE grade 3 fatigue < 5 days
	< 48 hours of CTCAE grade 3 edema
	Grade 3 laboratory abnormalities that are responsive to oral supplementation or deemed by the investigator to be clinically insignificant
	Leukopenia (low WBC) in the absence of dose limiting neutropenia, or lymphopenia

CTCAE version 4.03 was used for all grading. Optimal therapy for vomiting or diarrhea was based on institutional guidelines, with consideration of the prohibited medications listed in this protocol.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ANC, absolute neutrophil count; CTCAE, common terminology criteria for adverse events; DLT, dose-limiting toxicity; ECG, electrocardiogram; FG, fasting glucose; IV, intravenous; QTcF, Q-T interval corrected according to the formula of Fridericia; WBC, white blood cell count.

Supp Table 2. Guidelines for the treatment of study drug combination induced rash

Grade (CTCAE v4.03)	Actions and recommended concomitant medications
Grade 1	Maintain ribociclib, buparlisib, or alpelisib dosing Initiate antihistamine dosing. Recommend non-sedating regimen (e.g. hydroxyzine 25 mg bid) for at least 28 days Topical corticosteroid preparation** bid for affected areas for at least 28 days
Grade 2	Maintain ribociclib, buparlisib, and alpelisib dosing Initiate antihistamine dosing. Recommend non-sedating regimen during the daytime and sedating at QHS (e.g. hydroxyzine 25 mg AM and noon followed by diphenhydramine 25-50 mg QHS) for at least 28 days Topical corticosteroid preparation** bid for affected areas for at least 28 days Oral corticosteroid (recommend prednisone 0.5-0.75 mg per kg QD or equivalent for 10 days). If rash resolves to Grade 0-1 within 10 days, oral corticosteroid may be discontinued, tapered dosing not needed. If oral prednisone is administered continuously for >10 days, tapered dosing is indicated. Intravenous steroid administration can be substituted for oral administration If rash is not grade ≤1 in 14 days, continue or readminister oral corticosteroid (recommend prednisone 0.5-0.75 mg QD or equivalent for 10 days; longer periods of dosing require tapered dosing) If hyperglycemia has been noted prior to initiating corticosteroid dosing, continue daily fingerstick and change FPG monitoring to twice weekly, and adjust oral antiglycemic regimen according to hyperglycemia management guidance, as needed with corticosteroid dosing (per study protocol)
Grade 3/ intolerable Grade 2	Hold ribociclib, alpelisib, and/or buparlisib dosing until rash resolves to Grade 0-1 and consider dermatology consultation for skin biopsy and photographs Initiate antihistamine dosing. Recommend non-sedating regimen during the daytime and sedating at QHS (e.g. hydroxyzine 25 mg AM and noon followed by diphenhydramine 25-50 mg QHS) for at least 28 days Topical corticosteroid preparation** bid for affected areas for at least 28 days Oral corticosteroid (recommend prednisone 0.5-0.75 mg QD or equivalent for 10 days). If rash resolves to Grade 0-1 within 10 days (and does not recur with redosing; see below for guideline on rechallenge), oral corticosteroid may be discontinued, tapered dosing not needed. If oral prednisone administered continuously for >10 days, tapered dosing is indicated. Intravenous steroid administration can be substituted for oral administration If rash is not grade ≤ 1 in 14 days, continue or readminister oral corticosteroid (recommend prednisone 0.5-0.75mg QD or equivalent) until resolved and alpelisib and ribociclib is restarted If hyperglycemia has been noted prior to initiating corticosteroid dosing, continue daily fingerstick and change FPG monitoring to twice weekly, and adjust oral antiglycemic regimen according to hyperglycemia management guidance, as needed with corticosteroid dosing (per study protocol) A dose reduction of one dose level is recommended if this is a second occurrence. Dose reduction is not necessary following the first occurrence of grade 3 or intolerable grade 2 rash Upon rechallenge with alpelisib, or buparlisib and ribociclib (once rash grade ≤ 1), continue oral corticosteroid for at least 48 hours. If rash and/or pruritus do not recur in 48 hours, discontinue corticosteroid dosing. Antihistamine regimen should be continued for a minimum of 28 days after rechallenge with alpelisib and ribociclib
Grade 4	Permanently discontinue alpelisib and/or buparlisib and ribociclib, and consider a dermatology consultation Treatment of rash should follow guidelines for grade 3/intolerable grade 2 rash above, with the exception of rechallenge, and with any additional measures needed. (alpelisib and ribociclib should be permanently discontinued)

**Topical corticosteroid preparation recommended regimens: for face and/or intertriginous areas (including genitalia) recommend alclometasone 0.05% or hydrocortisone 2.5% creams; for other body areas (i.e trunk and extremities), recommend clobetasol or betamethasone 0.05% creams. Consider spray preparation for ease of application on trunk. For scalp involvement, consider a foam preparation.

Abbreviations: bid, twice a day; CTCAE, common terminology criteria for adverse events; FPG, fasting plasma glucose; QD, once a day; QHS, every night at bedtime.

Supp Table 3. Prior anti-neoplastic therapies

	Ribociclib 600 mg + fulvestrant (*n* = 13)	**Ribociclib 400 mg (continuous) + fulvestrant (*n* = 15)**	**Triple combination ribociclib + alpelisib + fulvestrant (*n* = 18)**	**Triple combination ribociclib + buparlisib + fulvestrant (*n* = 24)**	**All patients (*N* = 70)**
Therapy type at last treatment, *n* (%)					
Chemotherapy	4 (30.8)	1 (6.7)	7 (38.9)	7 (29.2)	19 (27.1)
Hormonal therapy	8 (61.5)	12 (80.0)	10 (55.6)	16 (66.7)	46 (65.7)
PI3K/AKT/mTOR	1 (7.7)	2 (13.3)	1 (5.6)	3 (12.5)	7 (10.0)
Other	1 (7.7)	2 (13.3)	1 (5.6)	1 (4.2)	5 (7.1)

Abbreviations: mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol-3-kinase.

Supp Table 4. Patients requiring dose reductions and interruptions of ribociclib

	Ribociclib 600 mg + fulvestrant (*n* = 13)	**Ribociclib 400 mg (continuous) + fulvestrant (*n* = 15)**	**Triple combination ribociclib + alpelisib + fulvestrant (*n* = 18)**	**Triple combination ribociclib + buparlisib + fulvestrant (*n* = 24)**	**All patients (*N* = 70)**
Patients with at least one dose reduction, *n* (%)	3 (23.1)	4 (26.7)	10 (55.6)	16 (66.7)	33 (47.1)
Adverse event	3 (23.1)	4 (26.7)	8 (44.4)	12 (50.0)	27 (38.6)
As per protocol	0	0	3 (16.7)	3 (12.5)	6 (8.6)
Dispensing error	0	0	0	2 (8.3)	2 (2.9)
Dosing error	0	0	0	1 (4.2)	1 (1.4)
Physician decision	0	0	0	3 (12.5)	3 (4.3)
Missing	0	0	0	1 (4.2)	1 (1.4)
Patients with at least one dose interruption, n (%)	9 (69.2)	11 (73.3)	15 (83.3)	23 (95.8)	58 (82.9)
Adverse event	7 (53.9)	6 (40.0)	12 (66.7)	19 (79.2)	44 (62.9)
As per protocol	6 (46.2)	1 (6.7)	10 (55.6)	14 (58.3)	31 (44.3)
Dispensing error	0	1 (6.7)	0	0	1 (1.4)
Dosing error	5 (38.5)	7 (46.7)	8 (44.4)	11 (45.8)	31 (44.3)
Physician decision	1 (7.7)	2 (13.3)	3 (16.7)	6 (25.0)	12 (17.1)
Technical problems	0	1 (6.7)	2 (11.1)	1 (4.2)	4 (5.7)

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