Regimen Monograph

A - Regimen Name

ALPEFLVS Regimen

Alpelisib-Fulvestrant

Disease Site	Breast
Intent	Palliative
Regimen Category	**Evidence-Informed :** Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.
Rationale and Uses	For treatment of *PIK3CA*-mutated hormone receptor positive, HER2-negative advanced breast cancer in patients who have had previous endocrine therapy.
Supplementary Public Funding	**fulvestrant** ODB - General Benefit (fulvestrant) (ODB Formulary)

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B - Drug Regimen

Cycle 1 (loading dose):

fulvestrant	500 mg	IM	Days 1, 15
alpelisib	300 mg	PO	Daily (Continuous)

(This drug is not currently publicly funded for this regimen and intent)

Cycles 2+:

fulvestrant	500 mg	IM	Day 1
alpelisib	300 mg	PO	Daily (Continuous)

(This drug is not currently publicly funded for this regimen and intent)

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C - Cycle Frequency

REPEAT EVERY 28 DAYS

Until disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal – No routine prophylaxis; PRN recommended

- Also refer to CCO Antiemetic Recommendations.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Other Supportive Care:

- Oral antihistamine administration may be considered prophylactically for rash and severe cutaneous reactions to decrease incidence and severity, at the time of treatment initiation.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Alpelisib is only for use in hormone receptor (HR) positive, HER2-negative advanced breast cancer patients with known a PIK3CA mutation confirmed using a validated test.

Fasting plasma glucose and/or HbA1c (hemoglobin A1c test) should be performed and glucose levels should be corrected in patients with abnormal fasting glucose levels in the range of prediabetic or diabetic before initiating treatment.

A dental examination with appropriate preventive dentistry is recommended prior to treatment in patients with risk factors for ONJ, such as invasive dental procedures, concomitant therapies, poor oral hygiene and comorbid disorders.

Dosage with toxicity

Dose Level	Alpelisib Dose (mg/day)	Fulvestrant Dose (after loading dose in cycle 1)
0	300	500 mg IM q 4 weeks
-1	250	
-2	200	
-3	Discontinue	

Fulvestrant Dose Modification for Toxicity

Toxicity	Action (fulvestrant)
Hypersensitivity	Consider discontinuing if severe.
Mild hepatotoxicity	Hold until recovery and then restart.
Moderate to severe hepatotoxicity	Discontinue.

Alpelisib Dose Modification for Toxicity

Toxicity	Grade	Action
Fasting glucose	Grade 1 (> ULN - 8.9 mmol/L)	No dosage adjustment required.†
	Grade 2 (> 8.9 - 13.9 mmol/L)	No dosage adjustment required.† If fasting glucose does not decrease to ≤ 8.9 mmol/L in ≤ 21 days, ↓ alpelisib by 1 dose level.
	Grade 3 (> 13.9 - 27.8 mmol/L)	Hold.† Consider additional antidiabetic medications* for 1-2 days until hyperglycemia improves. Administer intravenous hydration and consider appropriate treatment (e.g. intervention for electrolyte/ketoacidosis/hyperosmolar disturbances). If fasting glucose decreases to ≤ 8.9 mmol/L in ≤ 3-5 days, resume at 1 dose level ↓. If fasting glucose does not decrease to ≤8.9 mmol/L within: • 3 to 5 days: consultation with a clinician with expertise in the treatment of hyperglycemia is recommended. • 21 days following appropriate treatment: discontinue.
	Grade 4 (≥ 27.8 mmol/L)	Hold.† Administer intravenous hydration and consider appropriate treatment (e.g. intervention for electrolyte/ketoacidosis/hyperosmolar disturbances). Re-check fasting glucose within 24 hours and as clinically indicated. If fasting glucose decreases to ≤ 27.8 mmol/L, follow specific recommendations for hyperglycemia above. If fasting glucose is confirmed at > 27.8 mmol/L, discontinue.

	Rash and cutaneous reactions** (excluding severe cutaneous adverse reactions etiology)	Grade 1 (< 10% body surface area (BSA) with active skin toxicity)	No dosage adjustment required; initiate topical corticosteroid treatment. Consider adding oral antihistamine treatment. If active rash does not improve within 28 days of appropriate treatment, add low dose oral corticosteroid.
		Grade 2 (10% - 30% BSA with active skin toxicity)	No dosage adjustment required; initiate/intensify topical corticosteroid and oral antihistamine treatment. Consider adding low dose systemic corticosteroid. If rash improves to ≤ grade 1 within 10 days, discontinue systemic corticosteroids.
		Grade 3 (> 30% BSA with active skin toxicity; severe rash not responsive to medical management)	Hold and initiate or intensify topical/oral corticosteroid and antihistamine treatment. When resolved to ≤ grade 1, resume at 1 dose level ↓.
		Grade 4 (e.g. severe bullous, blistering or exfoliating skin conditions; any % BSA associated with extensive superinfection, with IV antibiotics indicated; life-threatening consequences)	Discontinue
	Severe cutaneous adverse reactions, including Stevens-Johnson Syndrome /Toxic Epidermal Necrolysis, DRESS or erythema multiforme	Any	Discontinue
	Diarrhea or Colitis	Grade 1	No dosage adjustment required.†
		Grade 2	Hold until resolved to ≤ grade 1 then resume at same dose level.†

		If it recurs, hold until ≤ grade 1 then resume at 1 dose level ↓.†
	Grade 3	Hold until resolution to ≤ grade 1 then resume at 1 dose level ↓.†
	Grade 4	Discontinue
Pancreatitis	Grade 2 or 3	Hold until resolved to ≤ grade 1 then resume at 1 dose level ↓. If toxicity re-occurs, discontinue.
	Grade 4	Discontinue
Symptoms of pneumonitis	Any	Hold and investigate; discontinue if confirmed
Bilirubin	Grade 2	Hold until resolved to ≤ grade 1: • if improved within 14 days, resume at same dose. • if improved in > 14 days, resume at 1 dose level ↓.
	Grade 3	Hold until resolution to ≤ grade 1 then resume at 1 dose level ↓.
	Grade 4	Discontinue
Serious hypersensitivity reactions / Anaphylactic reactions	Any	Discontinue
All other toxicities	Grade 1 or 2	No dosage adjustment required.†
	Grade 3	Hold until resolved to ≤ grade 1 then resume at 1 dose level ↓.
	Grade 4	Discontinue.

†Initiate or intensify appropriate medical therapy (e.g. oral anti-diabetic or anti-diarrhea treatment) and monitor as clinically indicated. For Grade 2 or 3 colitis, consider additional treatment, such as steroids.

*As recommended in the phase III clinical study, insulin may be used for 1-2 days until hyperglycemia resolves. However, this may not be necessary in the majority of alpelisib-induced hyperglycemia, given the short half-life of alpelisib and the expectation of glucose levels normalizing after dose interruption.

**For all grades of rash, consider consultation with a dermatologist.

Hepatic Impairment

Fulvestrant is metabolized primarily in the liver. There are no efficacy and safety data in patients with breast cancer and hepatic impairment. Decreased clearance (by 2.2 fold) and changes in exposure (↑ 70%) were observed in women with moderate hepatic impairment compared to patients with normal hepatic function.

Hepatic Impairment	Alpelisib Dose	Fulvestrant Dose
Child-Pugh Class A or B	No dose adjustment required.	Use with caution. No dose adjustment required.
Child-Pugh Class C		Not studied. Use not recommended.

Renal Impairment

Creatinine Clearance (mL/min)	Alpelisib Dose	Fulvestrant Dose
≥ 30	No dose adjustment required.	No dosage adjustment required.
< 30	Effect on alpelisib pharmacokinetics is unknown.	Use with caution; no data.

Dosage in the Elderly

No dose adjustment is required for alpelisib or fulvestrant. For alpelisib, no overall differences in safety or efficacy were observed between patients ≥ 65 years of age and younger patients; however, gastrointestinal toxicity (primarily diarrhea and nausea), hyperglycemia, weight loss, hypokalemia and dyspnea were reported more frequently in older patients.

Dosage based on ethnicity

No dose adjustment is required for alpelisib or fulvestrant. For alpelisib however, rash, severe cutaneous reactions, hypersensitivity and anaphylactic reaction, and pancreatitis were more frequently reported in Asian patients compared to Caucasian patients.

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F - Adverse Effects

Refer to fulvestrant, alpelisib drug monograph(s) for additional details of adverse effects.

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Hyperglycemia (may be severe) • Diarrhea (may be severe) • Rash, pruritus (may be severe)	• Nausea, vomiting • Fatigue • Anorexia, weight loss • Mucositis	• Alopecia • Mucosal dryness • Joint disorder • Dysgeusia • Headache • Edema • ↑ LFTs • Fever • Injection site reaction • Dyspepsia • Anemia • Creatinine increased • Infection	• Myelosuppression, bleeding • Acute kidney Injury • Osteonecrosis of jaw • Pneumonitis • Arterial/venous thromboembolism • Osteoporosis • Colitis • Pancreatitis • Hyperglycemic hyperosmolar non-ketotic syndrome • Ketoacidosis • Estrogen deprivation symptoms • Hypersensitivity • DRESS • Erythema multiforme • Stevens-Johnson syndrome • Toxic epidermal necrolysis • Hypertension

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G - Interactions

Refer to fulvestrant, alpelisib drug monograph(s) for additional details.

- Avoid co-administration with strong CYP3A4 inducers due to decreased alpelisib concentration/efficacy.
- Avoid co-administration of alpelisib with BCRP inhibitors due to increased alpelisib concentration and/or toxicity. If concomitant use is unavoidable, closely monitor for increased alpelisib adverse reactions.
- Fulvestrant may interfere with estradiol immunoassay measurements (falsely elevated estradiol levels) due to its structural similarity with estradiol.

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H - Drug Administration and Special Precautions

Refer to fulvestrant, alpelisib drug monograph(s) for additional details.

Administration: Fulvestrant

- Each dose consists of 2 pre-filled syringes (250 mg/5mL). Administer each pre-filled syringe as SLOW intramuscular injection (1-2 minutes per injection) into EACH buttock.
- Caution should be taken due to proximity of the sciatic nerve and large blood vessels.
- Administer according to local guidelines at the Cancer Centre or physician's office.
- Store refrigerated at 2 to 8°C in original package.

Administration: Alpelisib

- Alpelisib should be administered once daily at approximately the same time each day immediately following a meal.
- Tablets should be swallowed whole (tablets should not be chewed, crushed or split prior to swallowing). Tablets that are broken, cracked, or otherwise not intact should not be ingested.
- If a dose is missed, it can be taken immediately following food and within 9 hours after the time it is usually administered. After more than 9 hours, the dose should be skipped for that day and the next dose should be taken at its usual time. Missed doses should not be made up the next day.

- If a dose is vomited, do not administer an additional dose on that day; resume the dosing schedule the next day at the usual time.
- Do not store above 30°C.
- Store in the original package to protect from moisture.

Contraindications

- Patients who are hypersensitive to alpelisib or fulvestrant or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container.
- Fulvestrant is contraindicated in pregnant or breastfeeding women.

Other Warnings /Precautions

- Due to the route of administration of fulvestrant, use with caution in patients with bleeding disorders or on anticoagulants.
- There is a potential osteoporosis risk due to fulvestrant's mechanism of action.
- Caution should be exercised when alpelisib and drugs known to cause ONJ are used either simultaneously, or sequentially. Alpelisib treatment should not be initiated in patients with ongoing ONJ.
- Do not initiate alpelisib treatment in patients with history of severe cutaneous reactions.
- Alpelisib is associated with QT prolongation. Exercise caution if alpelisib is used concomitantly with medicinal products that are known to prolong the QTc interval. Patients with uncontrolled heart disease and/or recent cardiac events (including long QT syndrome, QTcF > 450 ms for males or > 460 ms for females) were excluded from the phase III clinical study.
- The safety of alpelisib in patients with Type 1 and uncontrolled Type 2 diabetes has not been established as these patients were excluded from the phase III clinical study. Patients with pre-diabetes, diabetes, BMI ≥ 30, elevated FPG or HbA1c >/= ULN, or age ≥ 75 years have a higher risk of developing severe hyperglycemia and/or associated complications (e.g. ketoacidosis).
- It is currently unknown whether alpelisib may reduce the effectiveness of systemically acting hormonal contraceptives.

Pregnancy/Lactation

- This regimen is **contraindicated** for use in pregnancy. Adequate contraception should be used by patients and their partners while on treatment and after the last treatment dose.

Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.

- Breastfeeding is **contraindicated** during this treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).
- Fertility effects: Probable

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

- CBC; Baseline and as clinically indicated
- Liver function tests, bilirubin; Baseline and as clinically indicated
- Renal function tests; Baseline and as clinically indicated
- ECG; Baseline and as clinically indicated. More frequently if taken concomitantly with medications known to prolong the QTc interval
- Electrolytes, including potassium and calcium; Baseline and in patients experiencing gastrointestinal toxicity as clinically indicated
- Fasting glucose; Baseline and at least weekly for the first 2 weeks of treatment, followed by every 4 weeks and as clinically indicated. Monitor more frequently for the first few weeks in patients with pre-diabetes, diabetes, BMI ≥ 30, or age ≥ 75 years
- Fasting glucose (if patient experiences hyperglycemia after initiating alpelisib); Regularly, at least until fasting glucose decreases to normal levels. During treatment with antidiabetic medications, monitor at least once a week for 8 weeks, followed by once every 2 weeks and as clinically indicated
- HbA1c; Baseline, every 3 months and as clinically indicated
- Clinical toxicity assessment for injection site reactions, estrogen deprivation symptoms, fatigue, thromboembolism, edema, fever/infection, ONJ, pancreatitis,

dysgeusia, pneumonitis, hypersensitivity, musculoskeletal, dermatological and gastrointestinal effects (including mucositis); As clinically indicated

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Administrative Information

- Outpatient prescription for home administration (alpelisib)
- Outpatient prescription; drug administered at Cancer Centre or physician's office (fulvestrant)

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K - References

Alpelisib and fulvestrant drug monographs, Ontario Health (Cancer Care Ontario).

Andre F, Ciruelos E, Rubovsky G, et al. Alpelisib for PIK3CA-mutated, hormone receptor–positive advanced breast cancer. N Engl J Med 2019; 380:1929-1940.

July 2023 Updated Dose modifications, Adverse effects, Drug administration/Special Precautions, and Clinical monitoring sections

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not

undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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