BC Cancer Protocol Summary for Treatment of Advanced FGFR3 Mutation-Positive Urothelial Carcinoma using Erdafitinib

Protocol Code	*UGUAVERD*
Tumour Group	*Genitourinary*
Contact Physician	*GU Systemic Therapy*

ELIGIBILITY:
Patient must have:
- Locally advanced or metastatic urothelial carcinoma,
- Susceptible FGFR3 genetic alteration:
    - Mutations: R248C, S249C, G370C, Y373C, or
    - Fusions (translocations): FGFR3–TACC3_V1, FGFR3–TACC3_V3
- Progression after at least 1 line of prior systemic therapy which includes PD-1 or PD-L1 treatment, including within 12 months of neoadjuvant or adjuvant therapy,
- A BC Cancer "Compassionate Access Program" (CAP) approval prior to treatment

Patients should have:
- Good performance status
- Adequate hematological, hepatic and renal function

TESTS:
- Baseline: CBC & Diff, creatinine, total bilirubin, ALT, alkaline phosphatase, LDH, phosphate, albumin, sodium, potassium, calcium, urea
- Baseline, if clinically indicated: urinalysis
- Day 14 and Day 21 of Cycle 1: phosphate, calcium, creatinine
- Prior to each cycle: CBC & Diff, creatinine, total bilirubin, ALT, alkaline phosphatase, phosphate, calcium, sodium, potassium
- If clinically indicated: LDH, albumin, magnesium, urinalysis, urea
- Ophthalmologic monitoring for ocular toxicity: comprehensive ophthalmologic exam prior to initiation of treatment, followed by exams every month for the first 4 months, and every 3 months thereafter is strongly recommended (provider to coordinate, review, and ensure compliance with the schedule)
- Weekly telephone nursing assessment for signs and symptoms of side effects during Cycle 1, then optional assessments in subsequent cycles

PREMEDICATIONS:
- Antiemetic protocol for low emetogenic chemotherapy protocols (see SCNAUSEA)

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
erdafitinib	8 mg* once daily	PO

*Dose may be increased to 9 mg once daily for the second cycle if phosphate level is less than 2.25 mmol/L and no significant toxicity is noted. After Cycle 1 Day 21, serum phosphate should not be used to guide further dose increases.

- Repeat every 28 days until progression or unacceptable toxicity.

DOSE MODIFICATIONS:

Dose Levels:

Starting Dose	1st Dose Reduction	2nd Dose Reduction	3rd Dose Reduction	4th Dose Reduction	5th Dose Reduction
9 mg	8 mg	6 mg	5 mg	4 mg	Discontinue
8mg	6 mg	5 mg	4 mg	Discontinue	

1. **Hyperphosphatemia:**

Phosphate Level (mmol/L)	Management
Less than 2.25	▪ Continue current erdafitinib dose. ▪ Refer to a dietitian, if not already done.
Greater than or equal to 2.25	▪ Withold erdafitinib dose and maintain low phosphate diet. ▪ Monitor phosphate levels weekly. ▪ When phosphate level returns to less than 2.25 mmol/L, restart erdafitinib at lower dose level. ▪ If there is a recurrence of phosphate elevation above 2.26 mmol/L following 2 dose reductions, permanently discontinue erdafitinib

2. **Ocular toxicity:**

Severity	Management
Asymptomatic or mild symptoms; clinical or diagnostic observations only	▪ Refer for an ophthalmologic examination (OE). If OE cannot be performed within 7 days, withhold erdafitinib until an OE can be performed ▪ If no evidence of eye toxicity on OE, continue erdafitinib at the same dose ▪ If diagnosis from OE is keratitis or retinal abnormality, withhold erdafitinib until resolution. If reversible in 4 weeks on OE, resume at next lower dose level ▪ Upon restarting erdafitinib, monitor for recurrence every 1 to 2 weeks for 1 month. Consider dose re-escalation if no recurrence
Moderate; limiting age-appropriate instrumental activities of daily living (ADL)	▪ Withhold erdafitinib and refer for OE ▪ Once symptoms resolve, resume at next lower dose level ▪ If diagnosis from OE is keratitis or retinal abnormality, withhold erdafitinib until resolution. If reversible in 4 weeks on OE, resume at lower dose level ▪ If resolved (complete resolution and asymptomatic) within 4 weeks on OE, resume erdafitinib at the next lower dose level. Upon restarting erdafitinib, monitor for recurrence every 1 to 2 weeks for 1 month
Severe or medically significant but not immediate sight-threatening; limiting self-care ADL	▪ Withhold erdafitinib until resolution ▪ If resolved (completed resolution and asymptomatic) within 4 weeks, then may resume erdafitinib at 2 dose levels lower ▪ Monitor for recurrence every 1 to 2 weeks for 1 month. If toxicity recurs, consider permanent discontinuation
Sight-threatening consequences; blindness	▪ Permanently discontinue erdafitinib ▪ Monitor until complete resolution or stabilization

3. **Nail Disorder:**

Severity	Management
Grade 2	▪ Consider withholding erdafitinib with reassessment in 1 to 2 weeks ▪ If first occurrence and symptoms resolve to Grade 1 or baseline within 2 weeks, restart erdafitinib at same dose ▪ If toxicity recurs or takes longer than 2 weeks to resolve to Grade 1 or baseline, restart at the next lower dose level
Grade 3	▪ Withhold erdafitinib with reassessment in 1 to 2 weeks ▪ When symptoms resolve to Grade 1 or baseline, restart at the next lower dose level
Grade 4	▪ Discontinue erdafitinib

4. **Dry Skin and Skin Toxicity:**

Severity	Management
Grade 3	▪ Withhold erdafitinib up to 28 days with weekly reassessments of clinical condition ▪ When symptoms resolve to Grade 1 or baseline, restart at the next lower dose level
Grade 4	▪ Discontinue erdafitinib

5. **Oral Mucositis:**

Severity	Management
Grade 2	▪ Consider withholding erdafitinib if patient has other drug-related concomitant Grade 2 adverse events ▪ Withhold erdafitinib if patient has received symptom management supportive care for longer than 1 week ▪ If erdafitinib is withheld, reassess in 1 to 2 weeks ▪ If first occurrence and symptoms resolve to Grade 1 or baseline within 2 weeks, restart erdafitinib at same dose ▪ If toxicity recurs or takes longer than 2 weeks to resolve to Grade 1 or baseline, restart at the next lower dose level
Grade 3	▪ Withhold erdafitinib with reassessment in 1-2 weeks ▪ When symptoms resolve to Grade 1 or baseline, restart at the next lower dose level
Grade 4	▪ Discontinue erdafitinib

6. **Dry Mouth:**

Severity	Management
Grade 3	▪ Withhold erdafitinib up to 28 days with weekly reassessments of clinical condition ▪ When symptoms resolve to Grade 1 or baseline, restart at the next lower dose level
Grade 4	▪ Discontinue erdafitinib

7. **Other Toxicity:**

Severity	Management
Grade 3	▪ Withhold erdafitinib until toxicity resolves to Grade 1 or baseline, then restart at next lower dose level
Grade 4	▪ Permanently discontinue

PRECAUTIONS:

1. **Ocular Toxicity:** Erdafitinib can cause central serous retinopathy, blurred vision and dry eyes. Reported central serous retinopathy events include chorioretinopathy, serous retinal detachment, retinopathy, and subretinal fluid. Comprehensive ophthalmological exam is strongly recommended prior to initiation of treatment, followed by monthly exams for the first 4 months and every 3 months thereafter. Referral to ophthalmology for ongoing monitoring and provision of monitoring tools such as the Amsler grid is strongly recommended. Patients reporting new onset of visual symptoms such as blurred vision, floaters, flashes of light or eye pain should be urgently evaluated. Dry eye prophylaxis with preservative-free eye lubricants is encouraged. Management of ocular toxicity may include treatment interruption, dose reduction or permanent discontinuation.
2. **Hyperphosphatemia:** Erdafitinib may cause hyperphosphatemia, and all patients should be instructed to restrict phosphate intake to 600 to 800 mg daily. Prolonged hyperphosphatemia can cause calcium precipitation and lead to soft tissue mineralization, non-uremic calciphylaxis, cutaneous calcinosis, vascular calcification, hypocalcemia, anemia, muscle cramps, pruritus, secondary hyperparathyroidism, QT interval prolongation and arrhythmias. Median onset of hyperphosphatemia is 16 days. Concurrent use with drugs that may alter serum phosphate levels such as antacids or phosphate-containing supplements should be discouraged. Referral to a dietitian at treatment initiation is strongly recommended. Management of hyperphosphatemia may include treatment interruption, dose reduction or permanent discontinuation.
3. **Nail Toxicity:** Nail discoloration, nail infection, nail ridging, onychomadesis, and onycholysis have been reported. Preventative measures and good skin care may help to reduce the frequency and severity of symptoms. Management may include erdafitinib treatment interruption and dose reduction.
4. **Palmar-plantar Erythrodysesthesia Syndrome** has been reported with erdafitinib treatment. Preventative measures and good skin care may help to reduce the frequency and severity of symptoms. Management may include treatment interruption and dose reduction.

5. **Drug Interactions:** Erdafitinib is primarily metabolized by CYP2C9 and CYP3A4. Avoid concomitant use of moderate CYP2CP9 and strong CYP3A4 inhibitors. Avoid concomitant use of dual CYP2C9 and strong CYP3A4 inducers. See BC Cancer Cancer Drug Manual for more drug interaction details.

Call the GU Systemic Therapy physician at your regional cancer centre or the GU Systemic Therapy Chair with any problems or questions regarding this treatment program.

References:

1. Erdafitinib (Balversa). CDA-AMC Reimbursement Recommendation. Canadian Journal of Health Technologies. Jan 2025; 5(1): 1-25.
2. Loriot Y, Matsubara N, Park SH et al. Erdafitinib or Chemotherapy in Advanced or Metastatic Urothelial Carcinoma. N Engl J Med 2023:389:1961-71.