BC Cancer Protocol Summary for Palliative Therapy for Metastatic Breast Cancer using Trastuzumab, Tucatinib, and Capecitabine

Protocol Code	*UBRAVTTCAP*
Tumour Group	*Breast*
Contact Physician	*Dr. Angela Chan*

ELIGIBILITY:

Patients must have:
- HER2-positive unresectable locally advanced or metastatic breast cancer
    - HER-2 overexpression defined as either IHC3+, or FISH amplification ratio greater than or equal to 2 at a quality assured laboratory,
- Prior treatment with trastuzumab, pertuzumab, and trastuzumab emtansine (KADCYLA), separately or in combination in either the adjuvant or metastatic setting
- At least one prior line of anti-HER2 therapy in the advanced setting, and
- BC Cancer "Compassionate Access Program" request approval prior to treatment

Patients should have:
- ECOG 0-2
- Adequate marrow, renal, and hepatic function
- Life expectancy of 3 months or more
- No signs or symptoms of cardiac disease. For patients with equivocal cardiac status, MUGA scan or ECHO should be done to demonstrate normal left ventricular ejection fraction
- Ability to report any severe toxicity such as diarrhea, hand/foot syndrome, severe nausea, stomatitis

Note:
- Patients with or without brain metastases are eligible for treatment with BRAVTTCAP; brain metastases may be previously treated/stable or untreated/growing but not requiring immediate local intervention
- Patients who were started on BRAVCAP or BRAVTCAP prior to 1 Dec 2022 and have not progressed, may switch to BRAVTTCAP if all other eligibility criteria are met
- Patients who completed or stopped treatment with BRAVLCAP prior to 1 Dec 2021, and have not progressed, are eligible for BRAVTTCAP if all other eligibility criteria are met

EXCLUSIONS:

Patients must not have:
- Previous progression on capecitabine in the metastatic setting
- Severe renal impairment (calculated creatinine clearance less than 30 mL/min)
- Suspected dihydropyrimidine dehydrogenase (DPD) deficiency

CAUTIONS:
- Severe hepatic dysfunction (total bilirubin greater than 50 micromol/L)

TESTS AND MONITORING:
- Baseline: CBC and differential, platelets, creatinine, bilirubin, ALT, alkaline phosphatase
- Baseline if clinically indicated: cardiac function (ECG, echocardiogram or MUGA scan)
- Prior to each cycle: CBC and differential, platelets, creatinine, bilirubin, ALT
- For patients on warfarin, weekly INR until stable warfarin dose established, then INR prior to each cycle.
- If clinically indicated: ECG, echocardiogram, MUGA, total protein, albumin, GGT, alkaline phosphatase, LDH, urea, CA15-3
- Weekly nursing assessment for tucatinib and capecitabine toxicity for Cycle 1. Consider weekly nursing assessment for toxicity in second cycle and when increasing capecitabine dose

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

SUPPORTIVE MEASURES
- all patients should be advised to obtain an adequate supply of loperamide (IMODIUM®) with directions for management of diarrhea; proactive management of diarrhea is very important.
- topical emollients (eg, Bag Balm®, Udderly Smooth®) applied liberally and frequently to the hands and feet to reduce the symptoms hand-foot syndrome, sunscreen for all sun exposed areas

TREATMENT:
If starting treatment **within 6 weeks** of previous trastuzumab-containing cycle, no need to re-load trastuzumab.

Cycle 1 only – Loading Dose

Drug	Dose	BC Cancer Administration Guideline
trastuzumab	8 mg/kg on Day 1	IV in 250 mL NS over 1 hour 30 min Observe for 1 hour post-infusion*
tucatinib	300 mg BID continuously	PO
capecitabine**	1000 mg/m^2 BID x 14 days (Days 1 to 14) (Total daily dose = 2000 mg/m^2/day)	PO

Cycle 2 onwards

Drug	Dose	BC Cancer Administration Guideline
trastuzumab	6 mg/kg on Day 1	▪ IV in 250 mL NS over 1 hour on the second dose, observe for 30 minutes post infusion*, ▪ IV IN 250 ml NS over 30 min on all subsequent doses if no adverse reactions, observe for 30 min post infusion*
tucatinib	300 mg BID continuously	PO
capecitabine**	1000 mg/m^2 BID x 14 days (Days 1 to 14) (Total daily dose = 2000 mg/m^2/day)	PO

*Observation period not required after 3 consecutive treatments with no reaction.

**Capecitabine is available as 150 mg and 500 mg tablets (refer to Capecitabine Suggested Tablet Combination Table for dose rounding).

Repeat every 3 weeks until disease progression or unacceptable toxicity.

DOSE MODIFICATIONS:

- Dose modifications for capecitabine may occur independently of trastuzumab and/or tucatinib.
- Trastuzumab treatment can be continued while capecitabine and/or tucatinib are being held for toxicity resolution at the discretion of provider.
- If treatment with tucatinib is discontinued due to toxicity, treatment with trastuzumab and capecitabine can continue at discretion of provider.
- If either trastuzumab or capecitabine is discontinued due to toxicity, tucatinib can continue at discretion of provider.
- If both trastuzumab and capecitabine are discontinued for toxicity, tucatinib must also be discontinued.
- Maximum treatment delay of 2 weeks is allowed for resolution of toxicity. If delay of more than 2 weeks due to toxicity, treatment should be discontinued.

Tucatinib Dose Reduction Schedule

Dose Level	Tucatinib Dose
Starting dose	300 mg PO BID
First dose reduction	250 mg PO BID
Second dose reduction	200 mg PO BID
Third dose reduction	150 mg PO BID

1. Hematological – for Capecitabine

ANC (x10^9/L)		Platelets (x10^9/L)	1st Event Dose	2nd Event Dose	3rd Event Dose	4th Event Dose
greater than or equal to 1.5	and	greater than or equal to 75	100%	100%	100%	100%
1 to 1.49	or	50 to 74.9	delay* then 100%	delay* then 75%	delay* then 50%	discontinue
0.5 to 0.99	or	25 to 49.9	delay* then 75%	delay* then 50%	discontinue	discontinue
less than 0.5	or	less than The25	discontinue or delay* then 50%	discontinue	discontinue	discontinue

*delay until ANC greater than or equal to 1.5 x 10^9/L and platelets greater than or equal to 75 x 10^9/L

2. Other Non-Hematologic Toxicity- Capecitabine and Tucatinib

- if treatment is interrupted due to toxicity, retain the original stop and start dates (i.e. do not make up for missed doses when treatment is resumed)

Toxicity Criteria (Per CTCAE)

Grade	Nausea	Vomiting	Stomatitis	Hand-Foot Syndrome	Diarrhea
1	Loss of appetite without alteration in eating habits	Intervention not indicated	Asymptomatic or mild symptoms; intervention not indicated	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline
2	Oral intake decreased without significant weight loss, dehydration or malnutrition	Outpatient IV hydration; medical intervention indicated	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL
3	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	Tube feeding, TPN, or hospitalization indicated	Severe pain; interfering with oral intake	Severe skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting self care ADL	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL**
4	-	Life-threatening consequences	Life-threatening consequences ; urgent intervention indicated	-	Life-threatening consequences ; urgent intervention indicated

Other Non-Hematologic Capecitabine and Tucatinib Dose Modifications:

Grade	Occurrence	Capecitabine	Tucatinib
1	first	100%	100%
	second	100%	
	third	100%	
	fourth	100%	
2	first	delay* then 100%	100%
	second	delay* then 75%	
	third	delay* then 50%	
	fourth	discontinue	
3	first	delay* then 75%	delay*, then reduce dose to next lower dose level**
	second	delay* then 50%	
	third	discontinue	
	fourth	discontinue	
4	first	discontinue or delay* then 50%	discontinue
	second	discontinue	
	third	discontinue	
	fourth	discontinue	

* stop treatment immediately and delay until toxicity resolved to grade 0 to 1

** for grade 3 diarrhea, delay tucatinib until less than or equal to grade 1, and treat with anti-diarrheals as appropriate.

Resume at:

- same dose if patient was not taking antidiarrheal treatment when grade 3 diarrhea occurred
- next lower dose level if patient was taking anti-diarrheal treatment when grade 3 diarrhea occurred

3. Renal dysfunction: for capecitabine

Creatinine Clearance mL/min	Capecitabine Dose only
greater than 50	100%
30 to 50	75%
less than 30	Discontinue

Cockcroft-Gault Equation:

$$\text{Estimated creatinine clearance (mL/min)} = \frac{N\,(140 - \text{age})\,\text{wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

N = 1.23 male
N = 1.04 female

4. Hepatotoxicity:

Bilirubin		ALT or AST	Tucatinib Dose
Greater than 1.5 to less than or equal to 3 x ULN		_	Delay until recovery to bilirubin less than or equal to 1.5 x ULN, then restart tucatinib at the previous dose
Greater than 3 to less than or equal to 10 x ULN	or	Greater than 5 to less than or equal to 20 x ULN	Delay until recovery to bilirubin less than or equal to 1.5 x ULN or AST/ALT less than or equal to 3 x ULN, then restart tucatinib at next lower dose
Greater than 10 x ULN	or	Greater than 20 x ULN	Discontinue tucatinib
Greater than 2 x ULN	and	Greater than 3 x ULN	Discontinue tucatinib

* Capecitabine dose modification may be required for hepatotoxicity. Capecitabine has not been studied in severe hepatic dysfunction.

PRECAUTIONS:

1. **Neutropenia (uncommon):** Fever or other evidence of infection must be assessed promptly and treated aggressively.

<u>Trastuzumab</u>

2. **Cardiac toxicity**: Trastuzumab can produce ventricular dysfunction and congestive heart failure in about 2% of patients. The majority of patients who develop cardiac dysfunction are symptomatic. Regular monitoring of asymptomatic patients is not routinely necessary but may be ordered within 4 to 6 months of treatment with trastuzumab. If no significant decline in cardiac function is apparent, repeated testing is not generally necessary, unless the patient's medical condition changes. Discontinue treatment for symptomatic congestive heart failure or serious cardiac arrhythmias. Most patients who develop cardiac dysfunction respond to appropriate medical therapy and in some cases (where the benefit outweighs the risk) may continue trastuzumab under close medical supervision.
3. **Trastuzumab infusion-associated symptoms,** usually chills and fever, occur in 40% of patients during the first trastuzumab infusion (infrequent with subsequent infusions). Other signs and symptoms may include nausea, vomiting, pain (sometimes at tumour sites), rigors, headache, dizziness, dyspnea, hypotension, rash and asthenia. Symptoms may be treated with acetaminophen, diphenhydramine and meperidine with or without an infusion rate reduction.

   Rarely, serious infusion-related reactions have been reported (3 per 1000 patients) sometimes leading to death (4 per 10,000). Reactions include dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress, and, uncommonly, allergic-like reactions. Patients experiencing dyspnea at rest due to pulmonary metastases and other pulmonary/cardiac

conditions may be at increased risk of a fatal infusion reaction and should be treated with extreme caution, if at all. For serious reactions, discontinue the trastuzumab infusion and provide supportive therapy such as oxygen, beta-agonists and corticosteroids.

4. **A possible interaction with trastuzumab and warfarin** has been reported. An increased INR and bleeding may occur in patients previously stabilized on warfarin. The interaction was noted in two patients after 8 to 10 doses of trastuzumab. An INR prior to starting the trastuzumab is recommended, then every 2 weeks for the first 3 months and then monthly if stable. Inform patient to watch for any bleeding. Modification of the warfarin dose may be needed.

Tucatinib

5. **Diarrhea:** severe diarrhea associated with dehydration, hypotension, acute kidney injury, and death has been reported. Median time to first episode is 12 days and 80% of events will resolve in about 8 days. Consider diagnostic tests to exclude infectious causes of severe diarrhea or diarrhea with complicating features (e.g., dehydration, fever, neutropenia). Use antidiarrheal treatment to manage diarrhea as clinically indicated. Based on the severity of the event, tucatinib treatment interruption, dose reduction, or treatment discontinuation may be required.
6. **Palmar-plantar erythrodysesthesia** has been reported during treatment with tucatinib, trastuzumab and capecitabine. Delay tucatinib for grade 3 toxicity until ≤ grade 1. Once recovered, reduce tucatinib dose to next lower dose level.
7. **Hepatotoxicity** has been reported during treatment with tucatinib. Monitor throughout treatment. See table above for dose modification parameters.
8. Patients **65 years or older** may experience a higher incidence of grade 3 (or higher) diarrhea and vomiting during treatment. Monitor closely throughout treatment.
9. **Drug interactions:** tucatinib is a major substrate of CYP2C8, and a strong inhibitor of CYP3A4. Dose modification may be required. See cancer drug manual for more information.
10. **Increased creatinine** has been observed during treatment with tucatinib, secondary to inhibition of renal tubular transport of creatinine via OCT2 and MATE1 transporters by tucatinib. Glomerular function is unaffected. Creatinine elevation usually occurs within the first 21 days of treatment, remains elevated but stable throughout treatment, and is reversible upon treatment discontinuation.

Capecitabine

11. **Dihydropyrimidine dehydrogenase (DPD) deficiency** can result in severe and unexpected toxicity – stomatitis, diarrhea, neutropenia, neurotoxicity - secondary to reduced drug metabolism of capecitabine. This deficiency is thought to be present in about 3% of the population.
12. **Myocardial ischemia and angina occurs rarely in patients receiving fluorouracil or capecitabine.** Development of cardiac symptoms including signs suggestive of ischemia or of cardiac arrhythmia is an indication to discontinue treatment. If there is development of cardiac symptoms patients should have urgent cardiac assessment. Generally re-challenge with either fluorouracil or capecitabine is not recommended as symptoms potentially have a high likelihood of recurrence

which can be severe or even fatal. Seeking opinion from cardiologists and oncologists with expert knowledge about fluorouracil or capecitabine toxicity is strongly advised under these circumstances. The toxicity should also be noted in the patient's allergy profile.

13. **Possible drug interactions with capecitabine and warfarin, phenytoin or fosphenytoin** have been reported and may occur at any time. Close monitoring is recommended (eg, for warfarin, monitor INR weekly during capecitabine therapy and for 1 month after stopping capecitabine).

Call Dr. Angela Chan or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Murthy RK, Loi S, Okines A et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. N Engl J Med. 2020 Feb 13;382(7):597-609.