Supplementary Material

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Lenvatinib

Summary of data

Lenvatinib (Lenvima™) is an oral multi-kinase inhibitor approved for the treatment of adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma (DTC) that is refractory to radioactive iodine.

Lenvatinib is an inhibitor of VEGFR, EGFR, PDGFRα, RET and KIT.

The phase 3, randomised, double-blind, multi-centre SELECT trial included 392 patients with iodine refractory differentiated thyroid cancer with evidence of progression by RECIST criteria within the previous 13 months. The primary endpoint was progression free survival (PFS), and the secondary endpoints included response rate, overall survival and safety.

The study demonstrated that when compared with placebo, lenvatinib increased PFS by 14.7 months, from 3.6 months on placebo to 18.3 months on lenvatinib. There was no significant difference in overall survival. Subsequent publications have demonstrated that both older and younger patients benefit from treatment, moreover in those older than 65 years an overall survival benefit from lenvatinib has been demonstrated, in spite of cross-over to lenvatinib being allowed once patients initially receiving placebo had progressed.

The response rate was 64.8% and 1.5% in the lenvatinib and placebo arms respectively (odds ratio 28.87; 95% CI 12.46 to 66.86; $p<0.001$).

Dose reductions and interruptions occurred in 67.8% and 82.4% respectively, and 14.2% of patients had to discontinue lenvatinib. The median time to first dose reduction was 3 months.

Dose

The recommended daily dose of lenvatinib is 24mg od. Although treatment responses can be seen with lower doses it is important to start at a daily dose of 24mg and aim to maintain this dose by controlling toxicities such as hypertension and diarrhoea with additional medication where possible. A recently reported study [1] demonstrated that a starting dose of 18mg of Lenvatinib was inferior to a starting dose of 24mg, in terms of overall response rate at 24 weeks, with no clinically significant difference in treatment emergent adverse events. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs [2].

Lenvatinib capsules should be taken at about the same time each day, with or without food. They should be swallowed whole with water. Alternatively, the capsules can be added to a tablespoon of water or apple juice to produce a suspension. The capsules must be left to dissolve for 10 minutes and stirred for at least 3 minutes. Once the suspension has been swallowed the same amount of water must be added to the glass, swirled to collect any residue then swallowed. If a dose is missed and it cannot be taken within 12 hours, that dose should be skipped and the next dose taken at the usual time.

Dose interruption followed by dose reduction is recommended for ≥G3 or intolerable G2 toxicity. Once recovered to ≤G1 lenvatinib can be restarted at a lower dose. The first dose reduction is 20mg

od, with subsequent reductions being 14mg od then 10mg od. The mean half-life of lenvatinib is approximately 28 hours.

Patients of age ≥75 years, of Asian race, with comorbidities (such as hypertension, and hepatic or renal impairment), or body weight below 60 kg appear to have reduced tolerability to lenvatinib, but other than those with severe hepatic or renal impairment no specific dose adjustment is recommended.

No specific dose adjustment is required in patients with mild or moderate renal impairment. In patients with severe renal impairment the recommended starting dose is 14mg od.

No specific dose adjustment is required in patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment the recommended starting dose is 14mg od.

Common side effects (as reported in SELECT trial)

Hypertension (67.8%)
Diarrhoea (59.4%)
Fatigue (59.0%)
Decreased appetite (50.2%)
Decreased weight (46.4%)
Nausea (41%)

Whilst lenvatinib treatment can be associated with significant toxicity there is evidence within the SELECT trial data that development of side effects is associated with improved outcomes. Treatment of emergent hypertension has been shown to be associated with superior progression free and overall survival [14]. On multivariate analysis development of diarrhoea on treatment has also been shown to be associated with improved overall survival [26].

Proactive management of toxicity to allow patients to continue treatment with the minimum interruption is considered important. There is evidence that patients with shorter dose interruptions derive greater benefit from treatment with lenvatinib than those with longer dose interruptions.

Absorption

Peak plasma concentrations after oral administration of lenvatinib is fast, typically 1 to 4 hours post dose.

Interactions

No specific interactions

Treatment interruptions – eg for surgery/radiotherapy

Interruption of lenvatinib is not felt to be necessary if palliative radiotherapy is to be administered, unless large fields are to be used with expected toxicity overlapping with that of lenvatinib.

Lenvatinib should be stopped 3 days before an elective surgical procedure including dental treatment, and not restarted until wounds have fully healed.

Sorafenib

Summary of data

Sorafenib (Nexavar™) is an oral multi-kinase inhibitor approved for the treatment of adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma (DTC) that is refractory to radioactive iodine.

Sorafenib is an inhibitor of VEGF, RET and RAF.

In the multicentre, randomised, double-blind phase 3 trial (DECISION), 417 patients with locally advanced or metastatic differentiated thyroid cancer that had progressed within the past 14 months were randomised on a 1:1 basis to either sorafenib or placebo. The primary endpoint was progression free survival (PFS). Secondary endpoints were overall survival (OS), time to progression, objective response rate (ORR), disease control rate and duration of response. On progression patients in the placebo arm were permitted to cross over to open-label sorafenib.

PFS was significantly longer in the sorafenib group (10.8 months) than the placebo group (5.8 months) (hazard ratio [HR] 0.59, 95% CI 0.45-0.76; $p<0.0001$). There was no significant difference in OS between the two groups. 71.4% of patients in the placebo arm crossed over to open-label sorafenib on progression. The ORR was 12.2% and 0.5% in the sorafenib and placebo arm, respectively ($p<0.0001$). The median duration of response was 10.2 months (95% CI 7.4-16.6).

Dose reductions, interruptions and withdrawals occurred in 64.3%, 66.2% and 18.8% respectively.

Dose

The recommended dose of sorafenib is 400mg bd [3]. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

The tablets should be swallowed with water. Sorafenib should be taken without food or with a low or moderate fat meal. If a patient intends to eat a high fat meal sorafenib should be taken at least 1 hour before or 2 hours after the meal. If a dose is missed that dose should be omitted and the next dose taken at the usual time.

Dose interruption followed by dose reduction is recommended for ≥G3 or intolerable G2 toxicity. Once recovered to ≤G1 sorafenib can be restarted at a lower dose. If dose reduction is necessary, it is recommended that sorafenib is reduced to 600 mg daily in divided doses. If a further dose reduction is required sorafenib may be reduced to 400mg daily in divided doses, then to 200mg od. The half-life of sorafenib is approximately 25-48 hours.

No dose adjustment is indicated in people ≥ 65 years.

No dose adjustment is required for patients with mild, moderate or severe renal impairment. No data is available for patients requiring dialysis.

No dose adjustment is required for patients with mild or moderate hepatic impairment. There are no data for patients with severe hepatic impairment.

Common side effects (as reported in DECISION trial)

Hand-foot syndrome (76.3%)
Diarrhoea (68.6%)
Alopecia (67.1%)
Rash (50.2%)
Fatigue (49.8%)
Weight loss (46.9%)
Hypertension (40.6%)

Side effects often occur early in the course of treatment (data not reported in DECISION publication). Proactive management of toxicity to enable patients to continue treatment with the minimum dose reduction or interruption is important.

Absorption

Peak plasma concentration of sorafenib is reached in around 3 hours after oral administration. Absorption is reduced by up to 30% if taken with a high fat meal, compared to being taken in the fasted state.

Interactions

CYP3A4 inducers may decrease sorafenib concentrations therefore should be used with caution.

Treatment interruptions – eg for surgery/radiotherapy

Interruption of sorafenib is not felt to be necessary if palliative radiotherapy is to be administered, unless large fields are to be used with expected toxicity overlapping with that of sorafenib. It is advisable for patients to stop taking sorafenib 6 days before planned surgery and restarted once wounds fully healed.

Cabozantinib

Summary of data

Cabozantinib (COMETRIQ™) is an oral multikinase inhibitor indicated for the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma. In addition to these licensed indications a recent randomised double-blind phase 3 trial (COSMIC 311 study) has demonstrated that cabozantinib confers a clinically and statistically significant improvement in PFS in patients with radio iodine refractory disease who have progressed during or after treatment with VEGFR targeted treatment [4]. It should be noted that Cabozantinib is available in two different preparations which are prescribed at different doses. COMETRIQ™ is licensed for the treatment of advanced medullary thyroid cancer as described above. CABOMETYX™ is currently licensed for the treatment of renal and hepatocellular cancers and is the preparation that was tested in the COSMIC-311 study.

Cabozantinib is an inhibitor of MET, VEGF, RET, AXL, KIT, and FLT3.

A multicentre, randomized double-blind study comparing cabozantinib (N = 219) with placebo (N = 111) was conducted in patients with unresectable locally advanced or metastatic MTC and documented radiographic disease progression within 14 months prior to study entry (EXAM study) [5]. The primary objective was to compare progression-free survival (PFS) in patients receiving cabozantinib versus patients receiving placebo. The secondary objectives were to compare overall response rate (ORR) and overall survival (OS). Centralized, independent, blinded review of the imaging data was used in the assessment of PFS and ORR. Patients were treated until disease progression or unacceptable toxicity.

The result of the PFS analysis, based on the central review RECIST assessment, demonstrated a statistically significant difference in the duration of PFS with cabozantinib versus placebo: the median duration was 11.2 months for subjects in the cabozantinib arm versus 4.0 months for subjects in the placebo arm (stratified Hazard Ratio [HR] = 0.28; 95% CI: 0.19, 0.40; $p<0.0001$). The PFS results were consistent across all baseline and demographic subgroups evaluated, including prior therapy with tyrosine kinase inhibitors (which may have consisted of agents targeting pathways associated with anti-angiogenesis), RET mutational status (including subjects documented not to have RET mutations), prior anticancer or radiotherapy status, or the existence of bone metastases.

The ORR was 27.9% and 0% for subjects in the cabozantinib arm and placebo arm, respectively ($p<0.0001$). The median duration of objective responses was 14.6 months (95% CI: 11.1, 17.5) for subjects in the cabozantinib arm.

Dose reductions and dose interruptions occurred in 79% and 72%, respectively. Two dose reductions were required in 41% of patients. The median time to first dose reduction was 43 days, and to first dose interruption was 33 days. Close monitoring of patients is therefore recommended during the first eight weeks of therapy.

Dose

The recommended daily dose of cabozantinib is 140 mg od. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs [6].

The capsules should be swallowed whole and not opened. Patients should be instructed to not eat anything for at least 2 hours before and for 1 hour after taking the dose. If a patient misses a dose, the missed dose should not be taken if it is less than 12 hours before the next dose.

The majority of patients will require one or more dose adjustments (reduction and/or interruption) due to toxicity. Patients therefore need to be closely monitored during the first eight weeks of therapy. When dose reduction is necessary, it is recommended to reduce to 100 mg daily, and then to 60 mg daily if a further reduction is indicated.

Dose interruptions are recommended for management of CTCAE grade 3 or greater toxicities or intolerable grade 2 toxicities. Dose reductions are recommended for events that, if persistent, could become serious or intolerable. The plasma half-life of cabozantinib is approximately 120 hours.

No specific dose adjustment is indicated in people ≥ 65 years, however, a trend in increased rate of SAEs has been observed in subjects aged 75 years and older.

Cabozantinib should be used with caution in patients with mild or moderate renal impairment.

In patients with mild or moderate hepatic impairment the recommended dose of cabozantinib is 60 mg once daily.

Osteonecrosis of the jaw has been reported in patients treated with cabozantinib. Caution is recommended if other agents associated with osteonecrosis are to be used (eg bisphosphonates), or if the patient has previously received external beam radiotherapy with high doses to the mandible.

Common side effects (as reported in EXAM trial)

Diarrhoea (63%)
Hand-foot syndrome (50%)
Nausea (43%)
Fatigue (41%)
Hypertension (33%)

Side effects that generally have early onset include hypocalcaemia, hypokalaemia, thrombocytopenia, hypertension, palmar-plantar erythrodysaesthesia syndrome (PPES), and gastrointestinal events (abdominal or mouth pain, mucosal inflammation, constipation, diarrhoea, vomiting).

The occurrence of some serious adverse reactions (e.g. GI fistula) might be dependent on the cumulative dose and could therefore present at a later stage of treatment [6].

Absorption

Peak plasma concentration after oral administration is reached at 2 to 5 hours post-dose. Plasma-concentration time profiles show a second absorption peak approximately 24 hours after administration, which suggests that cabozantinib may undergo enterohepatic recirculation.

Interactions
Avoid concomitant use of strong CYP3A4 inducers

Treatment interruptions for surgery

Cabozantinib treatment should be stopped at least 28 days prior to scheduled surgery or invasive dental procedures, if possible. The decision to resume cabozantinib therapy after surgery should be based on clinical judgment of adequate wound healing. Cabozantinib should be discontinued in patients with wound healing complications requiring medical intervention [6].

Vandetanib

Summary of data

Vandetanib (Caprelsa™) is an oral multikinase inhibitor indicated for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease.

Vandetanib is a selective inhibitor of vascular endothelial growth factor (VEGFR), Rearranged during Transfection (RET) and epidermal growth factor receptor (EGFR) tyrosine kinases.

The ZETA study was an international, randomised, double-blind, phase 3 trial, where 331 patients with unresectable locally advanced or metastatic hereditary or sporadic medullary thyroid cancer were randomly assigned (2:1) to receive either vandetanib (300mg od) or placebo. The primary endpoint was progression free survival (PFS). Secondary endpoints included objective response rate (ORR), disease control rate at 24 weeks, duration of response, overall survival, biochemical response and time to worsening pain.

The PFS was significantly improved with vandetanib compared to placebo. The median PFS for vandetanib was predicted to be 30.5 months vs 19.3 months in the placebo group (HR 0.46, 95% CI 0.31-0.69, P<0.001).

The ORR was 45% and 13% in the vandetanib arm and placebo arm respectively.

Dose reductions occurred in 35% patients on vandetanib.

Dose

The recommended daily dose of vandetanib is 300mg od [7].

Vandetanib should be taken around the same time each day, with or without food. If a dose is missed it should be taken as soon as the patient remembers. If it is less than 12 hours until the next dose the missed dose should not be taken, and the next dose should be taken at the usual time.

Dose interruption followed by dose reduction is recommended for ≥G3 or intolerable G2 toxicity. Once recovered to ≤G1 vandetanib can be restarted at a lower dose. If dose reduction is necessary, it is recommended that vandetanib is reduced to 200 mg od. If a further dose reduction is required vandetanib may be reduced to 100mg od. The half-life of vandetanib is 19 days.

No dose adjustment is required for elderly patients, although there is limited data in patients over the age of 75.

Vandetanib 300mg od is associated with prolongation of the QTc interval and must not be started in in patients with a QTc of >480ms. A dose interruption is required if patients develop a single QTc of ≥500ms. Vandetanib can be resumed at a reduced dose after the QTc returns to pretreatment level and any electrolyte imbalance has been corrected.

No dose adjustment is required for patients with mild renal impairment. There is limited data with 300mg daily in patients with moderate renal impairment and a dose adjustment to 200mg could be considered. Vandetanib should be avoided in patients with severe renal impairment.

There is limited data with vandetanib in patients with hepatic impairment. Vandetanib should not be used if bilirubin is >1.5 ULN, or if AST, ALT, ALP >2.5 ULN (unless due to liver metastases when a cut-off of >5 ULN can be used).

Common side effects (as reported in ZETA trial)

Diarrhoea (56%)
Rash (45%)
Nausea (33%)
Hypertension (32%)

A rare but potentially serious side effect is prolongation of the QTc interval (14% in the ZETA study, 8% ≥G3). Vandetanib has been associated with torsades de pointes and/or sudden death. Other rare but serious side effects include posterior reversible encephalopathy syndrome, Stevens-Johnson syndrome, interstitial lung disease.

Absorption

Peak plasma concentration occurs at a median 6 hours after oral administration (range 4-10). Steady state is achieved after approximately 2 months.

Interactions

Avoid concomitant use of drugs that prolong the QTc interval and/or induce torsades de pointes.
Avoid concomitant use of strong CYP3A4 inducers.

Treatment interruptions – eg for surgery/radiotherapy

Surgery – stop vandetanib for 1 week before surgery and withhold until wounds fully healed.

Palliative radiotherapy – consider withholding vandetanib for 1 week before and after radiotherapy if the target volume includes spinal cord, mediastinum, brain, pelvic organs.

Selpercatinib

Summary of data

Selpercatinib (Retsevmo^{TM}) is a highly selective small molecule RET inhibitor. It is indicated for the treatment of adults with advanced RET fusion positive thyroid cancer who require systemic therapy following treatment with sorafenib and/or lenvatinib, and also for adult and adolescent 12 years and older with advanced RET-mutant medullary thyroid cancer (MTC) who require systemic therapy following treatment with cabozantinib and/or vandetanib.

Hereditary MTC accounts for 25% of cases of MTC, and all these cases harbour a RET mutation. The remaining 75% of MTC is sporadic, and around 60% of these patients will have a somatic RET mutation. In non-medullary thyroid cancers, RET gene fusions are found in around 10% of patients. The presence of a RET mutation (MTC) or RET gene fusion must be confirmed prior to starting selpercatinib.

The LIBRETTO-001 trial was a phase 1/2 study that enrolled 55 patients with previously treated RET mutant MTC, 88 patients with RET mutant MTC who had not received prior systemic therapy, and 19 patients with RET fusion positive thyroid cancer who had previously received systemic therapy [8]. In the MTC cohorts, the objective response rate was 69% for previously treated patients, at 1 year 86% of the responses were ongoing and 82% of the patients were progression free. The objective response rate for the patients who had not previously received systemic therapy was 73%, at 1 year 91% of the responses were ongoing and 92% of the patients were progression free. In the cohort of patients with RET fusion positive thyroid cancer the objective response rate was 79%, at 1 year 71% of the responses were ongoing and 64% of the patients were progression free. Responses were seen in various subtypes of thyroid cancer including papillary, poorly differentiated, Hurthle cell and anaplastic.

Treatment related adverse events of grade 3 were seen in 28% of patients, the commonest events being hypertension, increased AST and ALT. Grade 4 adverse events were seen in 2% of patients, specifically increased AST and ALT. Treatment was discontinued due to toxicity in 2% of patients.

Dose

The recommended dose of selpercatinib depends on body weight. Patients whose weight is less than 50Kg should take 120mg twice daily, if the weight is 50kg or greater they should take 160mg twice daily.

Treatment should continue until disease progression or unacceptable toxicity.

If a dose is missed, the next dose should be taken at the scheduled time.

Selpercatinib is available as a capsule, and should be swallowed whole, with or without food (unless the patient is taking a proton pump inhibitor in which case selpercatinib should be taken with a meal).

The following tables regarding dose modifications for selpercatinib based on body weight and grade of toxicity are adapted from the SPC:

Dose modification	Adults/adolescents ≥ 50kg	Adults/adolescents < 50kg
Starting dose	160mg bd	120mg bd
First dose reduction	120mg bd	80mg bd
Second dose reduction	80mg bd	40mg bd
Third dose reduction	40mg bd	N/A

Adverse reaction		Dose modification of selpercatinib
Increased ALT or AST	G3 or G4	• Suspend until toxicity returns to baseline. Resume at a dose reduced by 2 levels • If after 2 weeks selpercatinib is tolerated without recurrent increase in ALT or AST, increase dose by 1 level • If tolerated without recurrence for at least 4 weeks, increase back to dose taken prior to onset of G3 or G4 toxicity • Permanently discontinue if G3 or G4 increases recur despite dose modifications
Hypersensitivity	All grades	• Suspend until resolves and start corticosteroids. Resume selpercatinib at 40mg bd whilst continuing steroids. Discontinue selpercatinib if symptoms recur • If selpercatinib is tolerated for at least 7 days with no recurrence of hypersensitivity incrementally increase the dose by 1 dose level each week until the dose taken prior to the onset of the hypersensitivity is reached. Taper steroid dose after selpercatinib has been tolerated for at least 7 days at the final dose.
QT interval prolongation	G3	• Suspend if QTcF interval is > 500ms until QTcF returns to < 470ms or baseline • Resume selpercatinib at the next lower dose level
	G4	• Permanently discontinue if QT prolongation remains uncontrolled after 2 dose reductions or if patient has signs or symptoms of serious arrhythmia.
Hypertension	G3	• Ensure BP is controlled before starting treatment • Suspend selpercatinib for medically significant hypertension until controlled with anti-hypertensive therapy. Resume at next lower dose
	G4	• Permanently discontinue if medically significant hypertension cannot be controlled
Haemorrhagic events	G3 or G4	• Suspend until recovery to baseline • Discontinue for severe or life threatening haemorrhagic events
Other adverse events	G3 or G4	• Suspend until recovery to baseline • Discontinue for severe or life threatening events

No dose adjustment is recommended in elderly patients, there are limited data for patients ≥ 75yrs.

No dose adjustment is required for patients with renal impairment, there are no data for patients with end stage renal disease or those on dialysis.

The dose of selpercatinib should be reduced to 80mg twice daily in patients with severe (Child-Pugh class C) hepatic impairment, no dose adjustment is required for patients with mild to moderate (Child-Pugh B or C) hepatic impairment.

Common treatment related side effects (as reported in the LIBRETTO-001 trial)

Dry mouth (39%)
Hypertension (30%)
Increased AST (28%)
Increased ALT (26%)
Fatigue (25%)
Peripheral oedema (18%)
Diarrhoea (17%)
Constipation (16%)
Nausea (15%)
QT interval prolongation (13%)

Increased AST and ALT (≥ grade 3) are reported. AST and ALT should be measured at baseline, every 2 weeks for the first 3 months of treatment with selpercatinib, then monthly. Dose reductions may be required (see table above).

QT interval prolongation is reported with selpercatinib, it should be used with caution in patients known to have pre-existing long QT syndrome. Patients should have normal electrolytes and a baseline QTcF interval of ≤ 470ms prior to starting treatment. ECG and electrolytes should be monitored in all patients after 1 week, then at least monthly. If there are risk factors that may increase the likelihood of prolonged QT interval these investigations should be carried out more frequently. There are no reports of Torsade de Pointes, sudden death, ventricular tachycardia, fibrillation or flutter.

Interactions

Selpercatinib is metabolised through CYP3A4 therefore strong inducers of CYP3A4 may reduce the efficacy of selpercatinib. CYP3A4 inhibitors may increase plasma concentration of selpercatinib and it is recommended that the dose of selpercatinib should be reduced by 50% if co-administration is necessary.

Selpercatinib may increase the concentration of CYP2C8 substrates and sensitive CYP3A4 substrates and concomitant use of these agents with selpercatinib should be avoided.

Larotrectinib

Summary of data

Larotrectinib (Vitrakvi™) is a potent and specific TRK inhibitor. It is indicated for the treatment of adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion who have locally advanced or metastatic disease and who have no satisfactory alternative treatment options. NTRK fusions are found in 5-25% of patients with thyroid cancer [9,10], and so are more prevalent than in many other solid tumours. Patients with advanced thyroid cancer should have their cancer tested for targetable alterations such as NTRK fusions. NTRK gene fusion positive status must be established prior to starting larotrectinib.

A combined report of 3 phase 1/2 trial including 55 adults and children with solid tumours with NTRK fusions treated with larotrectinib found an overall response rate of 75%, with 71% of responses on-going at 1 year. Adverse events were predominantly of grade 1, and no adverse event of grade 3 or 4 that was considered by the investigators to be related to larotrectinib occurred in more than 5% of patients. No patient discontinued larotrectinib owing to drug-related adverse events [11].

A separate analysis of 28 patients with advanced differentiated or anaplastic thyroid cancer with NTRK fusions included in these trials [12] confirmed similar findings, with an overall response rate of 75%, with 2 partial responses and 1 stable disease amongst 7 patients with anaplastic cancer.

Dose

The recommended dose in adults is 100 mg larotrectinib twice daily, until disease progression or until unacceptable toxicity occurs. Dosing in paediatric patients is based on body surface area (BSA). The recommended dose in paediatric patients is 100 mg/m^2 larotrectinib twice daily with a maximum of 100 mg per dose until disease progression or until unacceptable toxicity occurs.

Larotrectinib is available as a capsule or as an oral solution, with equivalent oral bioavailability. It can be taken with or without food but should not be taken with grapefruit or grapefruit juice.

Dose interruption followed by dose reduction is recommended for ≥G3 or intolerable G2 toxicity. If recovered to ≤G1 toxicity within 4 weeks larotrectinib can be restarted at a dose of 75mg twice daily. Subsequent recommended dose reductions are to 50mg twice daily, then to 100mg once daily. If an adverse reaction does not resolve within 4 weeks permanent discontinuation is recommended.

No dose adjustment is recommended in elderly patients.

The starting dose of larotrectinib should be reduced by 50% in patients with moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment. No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A).

No dose adjustment is required for patients with renal impairment.

Common side effects

The most common adverse drug reactions are-

increased ALT (32%)
fatigue (30%)
constipation (29%)
increased AST (27%)
dizziness (26%)
vomiting (23%)
anaemia (23%)
nausea (22%)

Neurologic reactions including dizziness, gait disturbance and paraesthesia were reported in patients receiving larotrectinib. Most of these occurred within the first 3 months of treatment. A treatment break and dose reduction should be considered depending on the severity of symptoms. Patients should be counselled about this and advised not to drive or use machines if they are affected.

ALT and AST increase are reported in patients receiving larotrectinib. The majority of ALT and AST increases occur in the first 3 months of treatment. Liver function including ALT and AST assessments should be monitored before the first dose and monthly for the first 3 months of treatment, then periodically during treatment, with more frequent testing in patients who develop transaminase elevations. Withhold or permanently discontinue larotrectinib based on the severity. If withheld, the larotrectinib dose should be reduced when restarted.

The majority of side effects are G1 or G2. The majority of adverse reactions leading to dose reduction occur in the first 3 months of treatment. Permanent discontinuation of larotrectinib for treatment emergent adverse events occurred in 5% of patients.

Interactions

If co-administration with a strong CYP3A4 inhibitor is necessary, the larotrectinib dose should be reduced by 50%. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, larotrectinib should be resumed at the dose taken prior to initiating the CYP3A4 inhibitor.

Entrectinib

Summary of data

Entrectinib (Rozlytrek^{TM}), like Larotrectinib, is a potent and specific TRK inhibitor. It is indicated for the treatment of adult and paediatric patients 12 years of age and older with solid tumours expressing a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion who have locally advanced or metastatic disease and who have no satisfactory alternative treatment options. NTRK gene fusion positive status must be established prior to starting entrectinib.

A combined report of 3 phase 1/2 trial including 54 adults and children with solid tumours with NTRK fusions (10 different tumour types including 5 patients with thyroid cancer) treated with entrectinib found an overall response rate of 57%. Median duration of response was 10 months [13]. The same study reported safety data for 355 patients who had received entrectinib across 4 clinical trials. Most adverse events were of G1 or G2 and were reversible. The most common serious treatment-related event was cognitive disorder in 3% of patients.

Dose

The recommended dose for adults is 600 mg entrectinib once daily.

The recommended dose for paediatric patients 12 years of age and older is 300 mg/m^2 body surface area (BSA) entrectinib once daily. In practice for BSA 1.11-1.50m^2 the dose is 400mg once a day and for BSA >1.5m^2 the dose is 600mg once a day.

Entrectinib is available as a capsule. It should be swallowed whole. It may be taken with or without food but should not be taken with grapefruit or grapefruit juice.

Dose interruption followed by dose reduction may be required to manage adverse reactions. The dose may be reduced to 400mg once a day and then to 200mg once a day if further reduction is required. Entrectinib should be permanently discontinued if the patient is unable to tolerate a dose of 200mg once a day.

No dose adjustment is required in patients ≥ 65 years of age.

No dose adjustment is recommended for patients with mild hepatic impairment. Entrectinib has not been studied in patients with moderate and severe hepatic impairment.

No dose adjustment is required in patients with mild or moderate renal impairment. Entrectinib has not been studied in patients with severe renal impairment.

Common side effects

The most common adverse reactions are-
Fatigue
Constipation
Dysgeusia
Oedema
Dizziness

Diarrhoea
Nausea
Dysaesthesia
Dyspnoea
Anaemia
Increased weight
Increased blood creatinine
Pain
Cognitive disorders
Vomiting
Cough
Pyrexia

Cognitive disorders, including confusion, mental status changes, memory impairment, and hallucinations, were reported in clinical trials with entrectinib. Patients over the age of 65 years experienced a higher incidence of these events than younger patients. Patients should be monitored for signs of cognitive changes and should be instructed not to drive or use machines if they do experience these symptoms.

Fractures have been reported, especially in paediatric patients treated with entrectinib. Patients with signs or symptoms of fractures should be assessed promptly.

Hyperuricemia has been observed in patients treated with entrectinib. Serum uric acid levels should be assessed prior to initiating entrectinib and periodically during treatment. Urate-lowering medication may be indicated.

Congestive heart failure has been reported in clinical trials of entrectinib. Patients with symptoms or known risk factors for congestive heart failure should have left ventricular ejection fraction assessed prior to starting treatment and should be carefully monitored on treatment.

QTc interval prolongation has been observed in patients receiving entrectinib. Treatment should be avoided in patients with a baseline QTc interval longer than 450ms, with congenital long QTc interval, and those taking other drugs known to prolong QTc interval. Assessment of ECG and electrolytes at baseline and after 1 month on treatment is recommended.

Overall 4.4% of patients discontinued entrectinib due to treatment related adverse events.

Interactions

The concomitant use of strong or moderate CYP3A inhibitors in adults and paediatric patients 12 years and older, should be avoided. For adults, if coadministration is unavoidable, the use of strong or moderate CYP3A inhibitors with entrectinib should be limited to 14 days and the dose should be reduced as follows:

- 100 mg once daily for use with strong CYP3A inhibitors
- 200 mg once daily for use with moderate CYP3A inhibitors.

Dabrafenib and Trametinib

Summary of data

Dabrafenib (Tafinlar™) is a BRAF inhibitor, and Trametinib (Mekinist™) is a MEK inhibitor. The combination of these drugs is used in the management of unresectable or metastatic BRAF V600E mutated ATC.

The presence of a BRAF V600E mutation must be confirmed prior to starting dabrafenib and trametinib. It is reported that 20-50% of anaplastic thyroid cancers harbour a BRAF V600E mutation.

A study of 100 patients with BRAF V600E mutated rare cancers treated with dabrafenib and trametinib included 16 patients with anaplastic thyroid cancer. An overall response rate of 69% was demonstrated in the ATC cohort. Median duration of response, progression-free survival and overall survival could not be assessed as responses were ongoing at the time of data cut-off, but Kaplan-Meier estimates at 12 months were 90%, 79% and 80% respectively.

Responses were reported early in the course of treatment, typically within the first few weeks.

Adverse events were assessed across the entire study population. Events of ≥ G3 were seen in 42% of patients. Dose reduction, dose interruption, permanent discontinuation was seen in 30%, 38%, and 8% respectively.

Further evidence for the efficacy of dabrafenib and trametinib was demonstrated in a series of 6 patients who received the combination prior to surgery. All 6 patients had complete resection of the thyroid tumour, and the resected specimens showed significant pathological response with reduction in ATC viability.

Dabrafenib dose

The recommended dose of dabrafenib is 150mg bd [14]. The capsules should be swallowed whole with water, approximately 12 hours apart. The dose should be taken at least 1 hour before, or 2 hours after a meal. If a dose is missed it should not be taken if it is less than 6 hours until the next dose is due.

No dose adjustment is required for patients with mild or moderate renal impairment, there are no data for patients with severe renal impairment.

No dose adjustment is required for patients with mild hepatic impairment. There are no clinical data in patients with moderate or severe hepatic impairment. Dabrafenib is primarily metabolised by the liver to so caution is recommended if moderate or severe liver impairment is present.

No dose adjustment is required for patients ≥65yrs.

Trametinib dose

The recommended dose of trametinib is 2mg od [15]. The tablets should be swallowed whole with water at least 1 hour before or 2 hours after a meal. The trametinib can be taken with either the

morning or evening dose of dabrafenib but should be taken at the same time every day. If a dose is missed it should only be taken if it is more than 12 hours until the next dose.

No dose adjustment is required for patients with mild or moderate renal impairment, there are no data for patients with severe renal impairment.

No dose adjustment is required for patients with mild hepatic impairment. There are no clinical data in patients with moderate or severe hepatic impairment so caution is recommended.

No dose adjustment is required for patients ≥65yrs.

Common treatment related side effects

Fatigue (44%)
Pyrexia (31%)
Nausea (31%)
Chills (25%)
Vomiting (25%)
Headache (19%)

Both dabrafenib and trametinib should be interrupted for G3 or intolerable G2 toxicity, then resumed with a dose reduction when toxicity has resolved to G0 or G1. If G4 toxicity is experienced, consideration should be given to permanent discontinuation of dabrafenib and trametinib , or the treatment could be resumed with a dose reduction once toxicity resolves to G0 or G1.

Dose level	Dabrafenib dose	Trametinib dose
Starting dose	150 mg twice daily	2 mg once daily
1st dose reduction	100 mg twice daily	1.5 mg once daily
2nd dose reduction	75 mg twice daily	1 mg once daily
3rd dose reduction	50 mg twice daily	1 mg once daily

Adapted from https://www.medicines.org.uk/emc/product/5190/smpc#gref and https://www.medicines.org.uk/emc/product/5072/smpc#gref

In general, if a dose reduction is required, both dabrafenib and trametinib should be reduced. Exceptions are as follows:

- Pyrexia – dabrafenib should be withheld if temperature is ≥ 38.5c, trametinib should be continued. The patient should be assessed to exclude infection, and anti-pyretics such as paracetamol or ibuprofen should be commenced. If this is not effective corticosteroids can be considered. Once the pyrexia has resolved dabrafenib can be recommenced with anti-pyretic prophylaxis, either at the same dose or with a dose reduction. Serious non-infectious

febrile events tend to occur within the first few weeks of treatment and usually respond well to dose interruption.

- Uveitis – discussion with ophthalmologist is advised. Symptoms should be managed with local therapies, but if these do not control the symptoms dabrafenib should be withheld until symptoms resolve then recommenced with a dose reduction. Trametinib may continue without dose reduction.
- Left ventricular ejection fraction (LVEF) reduction – if the LVEF falls by >10% and the ejection fraction is below the lower limit of normal trametinib should be interrupted until the ejection fraction recovers at which point it may be restarted with a dose reduction. Trametinib should be permanently discontinued following G3 or G4 toxicity. Dabrafenib does not need to be interrupted. In all patients LVEF should be monitored at baseline, 1 month, then 3 monthly.
- Retinal vein occlusion – trametinib should be permanently discontinued, dabrafenib may continue. Trametinib should not be used in patients with a prior history of retinal vein occlusion.
- Retinal pigment epithelial detachment (RPED) – trametinib should be withheld for G2-3 RPED then can be restarted with a dose reduction if symptoms resolve to G0-1 within 3 weeks. If symptoms do not resolve within 3 weeks trametinib should be permanently stopped. Dabrafenib may continue.
- Interstitial lung disease – trametinib should be withheld if the patient has suspected pneumonitis, and permanently withheld if pneumonitis is confirmed.

Interactions

Strong inhibitors or inducers of CYP2C8 or CYP3A4 may increase or decrease concentrations of dabrafenib.

Dabrafenib is an inducer of metabolising enzymes and concomitant use of dabrafenib with warfarin or digoxin may lead to reduced exposure to warfarin or digoxin.

There are no particular cautions with regard to co-administration of trametinib with other drugs.

Treatment interruption for surgery

Occasional patients may be considered for surgery if they have an exceptional response to treatment. It is recommended that Trametinib is discontinued 5 days prior to surgery. Dabrafenib can be taken up to the day of surgery.

Postoperatively the patient should be kept under close review and treatment restarted as soon as the surgical wound is healed.

References

1. Brose M., Panaseykin Y., Konda B., de la Fouchardiere C., Hughes B., Gianoukakis A., et al. A randomized study of lenvatinib 18 mg vs 24 mg in patients with radioiodine-refractory differentiated thyroid cancer. J Clin Endocrinol Metab 2022;107(3):776–787. doi:10.1210/clinem/dgab731.

2. Lenvatinib S.P.C. https://www.medicines.org.uk/emc/product/6840/smpc; 2019.

3. Haddad R., Schlumberger M., Wirth L.J., Sherman E., Shah M., Robinson B., et al. Incidence and timing of common adverse events in lenvatinib-treated patients from the SELECT trial and their association with survival outcomes. Endocrine 2017;56:121–128. doi:10.1007/s12020-017-1233-5.

4. Brose M.S., Robinson B., Sherman S., Jarzab B, Lin C, Vaisman F, et al. Cabozantinib versus placebo in patients with radio-iodine refractory differentiated thyroid cacner who have progressed after prior VEGFR-targeted therapy: results from the phase 3 COSMIC-311 trial. Oral abstract ASCO; 2021.

5. Schlumberger M., Elisei R., Müller S., Schöffski P., Brose M., Shah M., et al. Overall survival analysis of exam, a phase III trial of cabozantinib in patients with radiographically progressive medullary thyroid carcinoma. Ann Oncol 2017;28:2813–2819. doi:10.1093/annonc/mdx479.

6. Cometriq SPC. https://www.medicines.org.uk/emc/medicine/32559; 2019.

7. Vandetanib SPC. https://www.medicines.org.uk/emc/product/3944/smpc; 2019.

8. Wirth L.J., Sherman E., Robinson B., Solomon B., Kang H., Lorch J., et al. Efficacy of selpercatinib in RET-altered thyroid cancers. N Engl J Med 2020;383:825–835. doi:10.1056/NEJMoa2005651.

9. Amatu A., Sartore-Bianchi A., Bncardino K., Pizzutilo E., Tosi F., Siena S. Tropomyosin receptor kinase (TRK) biology and the role of NTRK gene fusions in cancer. Ann Oncol 2019;30. doi:10.1093/annonc/mdz383. viii5–15.

10. Cocco E., Scaltriti M., Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. Nat Rev Clin Oncol 2018;15:731–747. doi:10.1038/s41571-018-0113-0.

11. Drilon A., Laetsch T., Kummar S., DuBois S., Lassen U., Demetri G., et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 2018;378:731–739. doi:10.1056/NEJMoa1714448.

12. Cabanillas M., Drilon A, Farago A, Brose M, McDermott R, Sohal D, et al. Larotrectinib treatment of advanced TRK fusion thyroid cancer. Presented at the ESMO Virtual Congress 2020;19–21. September 2020.

13. Doebele R., Drilon A., Paz-Ares L., Siena S., Shaw A., Farago A., et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1–2 trials. Lancet Oncol 2020;21:271–282. doi:10.1016/S1470-2045(19)30691-6.

14. Dabrafenib S.P.C. https://www.medicines.org.uk/emc/product/5190/smpc#gref; 2021.

15. Trametinib S.P.C. https://www.medicines.org.uk/emc/product/5072/smpc#gref; 2021.

Materials to support patients

Link to CRUK consent forms

https://www.cancerresearchuk.org/health-professional/treatment-and-other-post-diagnosis-issues/consent-forms-for-sact-systemic-anti-cancer-therapy

Link to Macmillan Cancer Information

https://www.macmillan.org.uk/cancer-information-and-support/treatments-and-drugs

Thyroid Genomics: Patient Information Leaflet

What is genomic testing?

Genomics is the study of the body's genes, their functions and their influence on the growth, development and working of the body. Changes in the genes in an individual cell can lead to unregulated growth of that cell and this can lead to the development of a cancer. By testing the genetic material in cancer cells we are now able to detect which genes have been affected in an individual cancer.

Genomic data is increasingly used alongside information about the morphology (visual appearance) of a tumour to inform diagnosis, treatment selection and management of the patient.

Why are genomics tests helpful?

They can help

• guide doctors in deciding what drug treatment might be best for you

• guide doctors on whether you're able to join a clinical trial. Clinical trials of new targeted anti-cancer drugs are increasingly being designed so that they are open to patients with a range of tumour types as long as they share specific DNA mutation profiles, instead of being used for just one tumour type

They are also sometimes used to help determine if a thyroid nodule is benign (non cancerous) or malignant (cancerous).

Are genomics tests always helpful?

The tests always provide us with information on the tumour but this information doesn't always lead to changes in treatment or additional treatment options.

Do all thyroid cancer tumours get tested?

No. It isn't always necessary to test a tumour for genetic mutations as it will not change what is the best treatment. Some patients will only require surgery whilst others may only need a combination of surgery and radioactive iodine or radiotherapy. Only a minority of thyroid cancer patients with more advanced disease will need targeted drug therapy, which is increasingly guided by genomic information.

What does it mean if you do or don't have a particular genetic mutation?

The most common time we use genomic information is when patients' cancer has spread from the thyroid gland to other parts of the body and is causing symptoms. If we find a mutation that is linked to a targeted drug we may then be able to use that drug to treat the cancer.

For differentiated thyroid cancers (papillary and follicular) the first line of treatment in this setting will be lenvatinib or sorafenib. If these drugs stop working or cause significant side effects the next step will be to check tumour tissue for mutations that may be suitable for more specific targeted therapies. The mutations we are looking for are called NTRK and RET fusions.

For medullary thyroid cancer patients, the first line of treatment may involve drugs such as cabozantinib or vandetanib. If these types of drugs stop working or cause significant side effects the next step will be to check tumour tissue for mutations that may be suitable for more specific targeted therapies. The mutation we are looking for is called RET.

For anaplastic thyroid cancer patients we are interested in BRAF, ALK and RET mutations.

If we discover that a patient's tumour does not have any of the relevant mutations we know those treatments are not appropriate and we can avoid using drugs that will not be helpful but could cause side effects.

In the future we may be use these tests to look for signs that a tumour may be becoming resistant to a drug treatment or to understand how it may behave.

Is thyroid cancer hereditary?

In the vast majority of cases there is no family risk. The tumour tissue is tested to detect mutations that have arisen in the cancer. There is no reason why other family members should also develop the same cancer.

However, a small number of patients with differentiated thyroid cancer (papillary and follicular), will have an inherited condition such as Cowden's syndrome or PTEN Hamartoma syndrome which increases the risk of developing a thyroid cancer.

Medullary thyroid cancer is different. Approximately one quarter of patients will have inherited their cancer. This can be determined by a genetic blood test looking for what is called a germline RET mutation. This is a mutation that is found in every cell in the body and has been inherited from a parent. The genetic changes we discuss in the rest of this leaflet are known as somatic changes. These are only found in the cancer cells, and it is the development of these changes that leads to a cancer.

How are genomics tests performed?

The tests are performed on a sample of thyroid cancer tissue, usually taken from the original thyroid operation. Occasionally a new tissue sample may be required in which case a biopsy from another part of the body will be organised.

How long does it take to get the results?

This can vary but is likely to be in the order of 2-3 weeks.

Do all hospitals perform these tests?

These are specialised tests and are therefore done in specialist laboratories. For example in England there are seven designated centres and in Wales there is one centralised service. However, every hospital should have access to testing by sending samples away to the designated centres.

Lenvatinib Assessment Form

Patient name: **Hospital no:** **Review date:**

Dose Levels: 24mg; 20mgs; 14mgs and 10mgs

Common side effects: Hypertension, proteinuria, maculopapular and/or acneiform rash, decreased appetite, bleeding, changes to thyroid function levels, altered bowel habits, hypocalaemia and fatigue.

Physical Assessment:

System	Normal	Abnormal	Specification of abnormalities
Hair and skin			
Lymph Nodes			
Eyes/vision			
Ears, Nose, and Throat			
Oral cavity			e
Respiratory			
Cardiovascular			Most recent ECG and cQTc result:
Abdomen/ Gastrointestinal			
Appetite			
Musculoskeletal			
Mental status & sleep patterns			
Neurological			
Pain			
Performance Status			WHO Score
Other concerns?			

BP: HR: Temp: RR: O_2 Sats: Urinalysis:

Base Line Weight: Today's Weight:

Current dose of Lenvatinib:

Dose of Levothyroxine:
(Aiming for TSH to be <0.1mU/L)

Any other relevant tests/information Scans: Last date of scan: Next date of scan:
Current cardiac medication
Analgesia
Other Medication
ALLERGIES

Patient Fit for Treatment ☐

Treatment Delayed ☐

Treatment Dose Adjusted ☐ Please Specify:

Treatment Permanently Withdrawn ☐

Clinicians Name: ……

Position: …… Signature: ……

Sorafenib Assessment Form

Patient name: **Hospital no:** **Review date:**

Dose Levels: 800mg; 600mgs, 400mgs and 200mgs. Doses should be reduced by 200mg as required.

Common side effects: Common side effects: Hypertension, maculopapular and/or acneiform rash, decreased appetite, altered bowel habits and fatigue.

Physical Assessment:

System	Normal	Abnormal	Specification of abnormalities
Hair and skin			
Lymph Nodes			
Eyes/vision			
Ears, Nose, and Throat			
Oral cavity			
Respiratory			
Cardiovascular			Most recent ECG and cQTc result:
Abdomen/ Gastrointestinal			
Appetite			
Musculoskeletal			
Mental status & sleeping pattern			
Neurological			
Pain			
Performance Status			WHO Score
Other concerns?			

BP: HR: Temp: RR: O_2 Sats: Urinalysis:
Base Line Weight: Today's Weight:

Current dose of Sorafenib: Dose of Levothyroxine:

(Aiming for TSH to be <0.1mU/L)

Any other relevant tests/information Scans: Last date of scan: Next date of scan:
Current cardiac medication
Analgesia
Other Medication
ALLERGIES

Patient Fit for Treatment ☐

Treatment Delayed ☐

Treatment Dose Adjusted ☐ Please Specify:

Treatment Permanently Withdrawn ☐

Clinicians Name: ……

Position: ……Signature: ……

Vandetanib Assessment Form

Patient name: **Hospital no:** **Review date:**

Dose Levels: 300mg; 200mgs, 100mgs (dose reduce by 100mg as required)

Common side effects: hypertension, acneiform rash, maculopapular rash, photosensitivity, altered bowel habits and fatigue

Physical Assessment:

System	Normal	Abnormal	Specification of abnormalities
Hair and skin			
Lymph Nodes			
Eyes/vision			
Ears, Nose, and Throat			
Oral cavity			
Respiratory			
Cardiovascular			Most recent ECG and QTc result:
Abdomen/ Gastrointestinal			
Appetite			
Musculoskeletal			
Mental status & sleep patterns			
Neurological			
Pain			
Performance Status			WHO Score
Other concerns?			

BP: HR: Temp: RR: O_2 Sats: Urinalysis:

Base Line Weight: Today's Weight:

Current dose of Vandetanib: Dose of Levothyroxine:

Any other relevant tests/information Scans: Last date of scan: Next date of scan:
Current cardiac medication
Analgesia
Other Medication
ALLERGIES

Patient Fit for Treatment ☐

Treatment Delayed ☐

Treatment Dose Adjusted ☐ Please Specify:

Treatment Permanently Withdrawn ☐

Clinicians Name: ……

Position: ……Signature: ……

Cabozantinib Assessment Form

Patient name: **Hospital no:** **Review date:**

Dose Levels: 140mg; 100mgs or 60mgs

Common side effects: Nausea, altered bowel habits, mucositis, altered taste, fatigue, decreased appetite, weight loss, hoarse voice, hair colour changes and delayed wound healing

Physical Assessment:

System	Normal	Abnormal	Specification of abnormalities
Hair and skin			
Lymph Nodes			
Eyes/vision			
Ears, Nose, and Throat			
Oral cavity			
Respiratory			
Cardiovascular			Most recent ECG and QTc result:
Abdomen/ Gastrointestinal			
Appetite			
Musculoskeletal			
Mental status & sleeping pattern			
Neurological			
Pain			
Performance Status			WHO Score
Other concerns?			

BP: HR: Temp: RR: O_2 Sats: Urinalysis:

Base Line Weight: Today's Weight:

Current dose of Cabozantinib: Dose of Levothyroxine:

Any other relevant tests/information Scans: Last date of scan: Next date of scan:
Current cardiac medication
Analgesia
Other Medication
ALLERGIES

Patient Fit for Treatment ☐

Treatment Delayed ☐

Treatment Dose Adjusted ☐ Please Specify:

Treatment Permanently Withdrawn ☐

Clinicians Name: ……

Position: ……Signature: ……

Selpercatinib Assessment Form

Patient name: **Hospital no:** **Review date:**

Dose Levels: <50Kgs 120mg BD, >50Kgs 160mg BD

Common side effects: Nausea, vomiting, constipation, cough, dyspnoea, diarrhoea, pneumonitis, fatigue, myalgia, hypertension, oedema, rash, blurred vision, headaches, bleeding and delayed wound healing.

Physical Assessment:

System	Normal	Abnormal	Specification of abnormalities
Hair and skin			
Lymph Nodes			
Eyes/vision			
Ears, Nose, and Throat.			
Oral cavity			
Respiratory			
Cardiovascular			Most recent ECG and QTc result:
Abdomen/ Gastrointestinal			
Appetite			
Musculoskeletal			
Mental status & sleep patterns			
Neurological			
Pain			
Performance Status			WHO Score
Other concerns?			

BP: HR: Temp: RR: O_2 Sats: Urinalysis:

Base Line Weight: Today's Weight:

Current dose of Selpercatinib: Dose of Levothyroxine:

Any other relevant tests/information
Scans: Last scan date: Next scan date:
Current cardiac medication
Analgesia
Other Medication
ALLERGIES

Patient Fit for Treatment ☐

Treatment Delayed ☐

Treatment Dose Adjusted ☐ Please Specify:

Treatment Permanently Withdrawn ☐

Clinicians Name: ……

Position: …… Signature: ……

Dabrafenib and Trametinib Assessment Form

Patient name: **Hospital no:** **Review date:**

Dose Levels: Dabrafenib 150mgs BD; Trametinib 2mgs OD (take at night with evening dose of Dabrafenib to reduce nausea)

Common side effects: anaemia, alopecia, hyperglycaemia, hypophosphatemia. Cough, headache, photosensitivity, skin reactions, thrombocytopenia, bradycardia, blurred vision, eye irritation, mucositis, lymphoedema, fever, haemorrhage, hypersensitivity, delayed wound healing, hypertension, altered bowels and nausea

Physical Assessment:

System	Normal	Abnormal	Specification of abnormalities
Hair and skin			
Lymph Nodes			
Eyes/vision			
Ears, Nose, and Throat			
Oral cavity			
Respiratory			
Cardiovascular			Most recent ECG and QTc result:
Abdomen/ Gastrointestinal			
Appetite			
Musculoskeletal			
Mental status and sleep pattern			
Neurological			
Pain			
Performance Status			WHO Score
Other concerns?			

BP: HR: Temp: RR: O_2 Sats: Urinalysis:
Base Line Weight: Today's Weight:

Current dose of Dabrafenib: Current dose of Trametinib:
Dose of Levothyroxine:

Any other relevant tests/information Scans: Last date of scan: Next date of scan:
Current cardiac medication
Analgesia
Other Medication
ALLERGIES

Patient Fit for Treatment ☐

Treatment Delayed ☐

Treatment Dose Adjusted ☐ Please Specify:

Treatment Permanently Withdrawn ☐

Clinicians Name:……

Position:……Signature:……