Evidence summary on effectiveness and safety of pazopanib in the management of metastatic soft tissue sarcoma post-chemotherapy

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Background

What is metastatic soft tissue sarcoma (mSTS)?

Soft tissue sarcomas (STS) are a rare and heterogeneous group of malignant/cancerous tumors of mesenchymal origin with more than 100 histologic subtypes as determined by the type of cell which develops genetic mutation (WHO, 2013). The most common sign of STS is a noticeable lump or swelling which causes pain when the tumor presses on nerves or muscles. A risk of STS can be inherited genetically or can be developed from exposure to chemicals or radiation. (Mayo Clinic, 2018) Biopsy and imaging tests such as x-rays, MRI, and ultrasound may be employed to detect the sarcoma, which comprises less than 1% of all new cancer cases each year (Fletcher, Bridge, Hogendoorn, & Mertens, 2013). The true frequency of rare diseases such as STS is challenging because they often go misdiagnosed or undiagnosed (National Organization for Rare Diseases, 2018).

What is the standard of care for mSTS?

The standard treatment options for adult STS includes surgery, radiation therapy, and chemotherapy. According to the National Cancer Institute's PDQ (2019), surgical resection or excision is the most common treatment for adult STS. In most cases, a combined modality treatment consisting of preoperative radiation therapy (preRT) or postoperative radiation therapy (PORT) is used to effectively treat STS while limbs are preserved. Furthermore, radiation therapy has been shown to decrease the local recurrence rate. Brachytherapy has also been investigated as an adjuvant therapy as it has possible advantages of convenience and less radiation to normal surrounding tissue relative to external beam radiotherapy (EBRT). In terms of morbidity or efficacy, the two treatment strategies have not been directly compared (PDQ® Adult Treatment Editorial Board, 2019).

On the other hand, the National Cancer Institute's PDQ (2019), noted that the role of adjuvant chemotherapy is not completely clear. In cases of recurrence, treatment of patients depends on the type of initial treatment given. After the failure of first-line chemotherapy regimen, three drugs have been approved by the US FDA since 2012 as second-line treatment of STSs: the tyrosine kinase inhibitor pazopanib for all soft tissue sarcomas except adipocytic subtypes, eribulin for liposarcoma, and trabectedin for leiomyosarcoma and liposarcoma (PDQ® Adult Treatment Editorial Board, 2019).

The World Health Organization (WHO) Essential Medicines List (EML) - Cancer Medicines Working Group (World Health Organization, 2018) advises using an overall survival interval of at least 4 months for first-line cancer treatment included in their EML. They note that likely benefits of cancer medicines tend to be overestimated when used in clinical practice due to methodological biases and they consider an overall survival of less than 3 months as marginal, because it is likely to be clinically and ethically irrelevant. Moreover, evidence on disease-free or progression-free survival may be considered for medicines with limited information on survival. However, the benefits must be large, validated, and consistent with other evidence.

What is the potential of Pazopanib as a second-line treatment for mSTS?

Second-line treatments for STS include gemcitabine, docetaxel, trabectedin, high dose ifosfamide, eribulin and pazopanib (In, Hu, & Tseng, 2017). Phase 3 trials of eribulin and pazopanib have shown strong scientific evidence after failure of anthracycline-containing regimens (Schoffski, Van Cann, & Cornillie, 2017). Pazopanib is a multi-targeted receptor tyrosine kinase inhibitor (TKI), oral therapeutic agent that impedes tumor angiogenesis and cell proliferation (Cella & Beaumont, 2015). Through its antiangiogenic properties, pazopanib binds and inhibits vascular endothelial growth factor receptors (VEGFRs), platelet-derived growth factor receptors and stem cell factor receptor c-kit which are kinase receptors that are involved in angiogenesis and proliferation. Consequently, resulting in the inhibition of angiogenesis, tumor cell growth and survival (Pick & Nystrom, 2012). In addition, pazopanib is used as a treatment for some types of soft tissue sarcoma that has not responded to chemotherapy and delays tumor growth and relieves side effects for those sarcomas that cannot be removed through surgery (American Cancer Society, 2019). In a phase 3 randomized controlled trial, pazopanib showed improvement in progression free and overall survival among patients with metastatic STS who had received at least one regimen containing anthracycline (van de Graaf, et al., 2012).

As of publishing this evidence summary, pazopanib is not listed on the WHO Essential Medicines List 2019 and in the current Philippine National Formulary (8th ed). The currently-listed medicines for soft tissue sarcoma in the PNF include doxorubicin, carboplatin, and ifosfamide; however, it was not mentioned at which treatment level (i.e., first line, second line, or last line of treatment) these drugs are indicated for. Upon consultation with Philippine Society of Medical Oncology (PSMO), it clarified that doxorubicin is used as initial chemotherapeutic agent for metastatic soft tissue sarcoma (citing European Society for Medical Oncology–European Reference Network for rare adult solid cancers [ESMO-EURACAN] Clinical Practice Guidelines, 2018). The society added that carboplatin, on the other hand, is used for more specific histology of rhabdomyosarcoma (citing National Comprehensive Cancer Network [NCCN] Guidelines Version 6.2019 on Soft Tissue Sarcoma) and added that it not an appropriate comparator for pazopanib. Lastly, the society added that ifosfamide can be used for soft tissue sarcoma.

The usefulness of cancer medicines differ per patient population, healthcare setting, and the capacity of low- to middle-income countries for health services and delivery of medicines. However, in this report, the appraisal of evidence on the efficacy and safety of pazopanib and its comparators were based on limited available data from published sources and medical societies. This review looked at the efficacy and safety of pazopanib as second-line treatment against other therapies or placebo among patients with metastatic soft tissue sarcoma.

Policy Question

Should pazopanib be included in the Philippine National Formulary as second-line treatment for metastatic soft tissue sarcoma?

Research Questions

Clinical effectiveness and safety

- What is the effectiveness of pazopanib compared to other therapies or placebo as second-line treatment for mSTS post chemotherapy in (a) increasing progression free survival and (b) overall survival and (c) improving quality of life among patients diagnosed with metastatic STS (mSTS)?
- What is the safety of pazopanib compared to other cytotoxic single agents and combination regimen or placebo as second-line treatment for mSTS post chemotherapy in the occurrence of (a) all adverse events (b) diarrhea (c) fatigue (d) nausea (e) weight loss (f) hypertension and (g) drug-induced transaminase elevation among patients diagnosed with mSTS?
- What are the current local and international clinical practice guidelines on the use of pazopanib as second-line treatment of mSTS?
- What is the current position/ recommendation of selected HTA agencies regarding the use of pazopanib as second-line treatment for mSTS?

Economic impact

- What is the associated medication cost of using pazopanib versus other therapies or placebo as second-line treatment for patients with mSTS?
- What is the total medication cost for the expected number of patients using pazopanib versus other therapies or placebo?

Context on the assessment framework

In alignment with our methodological framework for assessment, the results of the clinical assessment will determine if the assessment shall proceed to assessment of other HTA domains. Only health technologies that will demonstrate superiority or non-inferiority versus the comparator in the clinical assessment shall proceed to economic impact assessment, as well as the ethical, legal, social and health systems impact assessment. Since pazopanib had unconvincing evidence on clinical safety and efficacy, evidence for equity or ethical and social impact, cost-effectiveness, household financial impact, affordability and viability were no longer assessed.

Recommendation

The HTAC does not recommend the inclusion of Pazopanib as second-line treatment of metastatic soft tissue sarcoma (mSTS) in the Philippine National Formulary based on the following reasons:

- Only studies comparing pazopanib with placebo were found. These studies were *limited in number and of very low quality evidence to establish strong evidence for better efficacy/ effectiveness when compared to placebo.* While the WHO consideration on listing cancer medicine in its EML applies for first-line treatments, the HTAC deems that the consideration for overall survival can be used for second-line treatments as well. As such, the median overall survival (OS) difference of two months between the pazopanib (median OS: 12.6 months) and placebo group (median OS: 10.7 months), may be marginal and is likely to be clinically and ethically irrelevant. In terms of safety, there is an *increased risk of some adverse events based on moderate quality of evidence, when compared to placebo.*

- While the clinical guidelines NCCN, GEIS, and BSG have indicated pazopanib for STS and its subtypes, the evidence presented in this review are not sufficient to support pazopanib's claims in terms of efficacy/effectiveness and safety profile even when compared with placebo.

- While some of the HTA agencies reviewed cited that pazopanib demonstrated moderate benefit on progression free survival, it lacked benefit in terms of overall survival. In addition, improvement of quality of life studies were lacking. PBAC acknowledges that there is an unclear, potentially high incremental cost-effectiveness ratio for pazopanib, and unsupported claim for overall survival benefit.

Responsiveness to Disease Magnitude, Severity, and Equity

Current prevalence/ severity of the disease

According to the 2012-2016 data of Surveillance, Epidemiology, and End Results (SEER) Program of the United States (US) National Cancer Institute, the annual incidence of STS worldwide was 3.5 per 100,000. For 2019, American Cancer Society estimates that there have been 12,750 new soft tissue sarcoma cases in the United States.

In the Philippines, there is no recent data available for the prevalence of STS. However, DOH reported in 2005 that rhabdomyosarcoma, the most common soft tissue cancer in children, comprises 2.2% of the reported 2,707 cases of cancer in 1998.

Effectiveness and safety

The following subsections report the evidence on pazopanib based on published evidence effectiveness and safety, local and international clinical practice guidelines on the use of pazopanib, as well as recommendations of HTA agencies on its use.

Based on the results of the systematic search, the Evidence Review Group (ERG) did not find any studies comparing pazopanib to other treatments; hence, the evidence that will be presented in this report are relative treatment effects of pazopanib compared with placebo.

Review of published evidence on clinical effectiveness

The ERG found only one systematic review by Sharma et al. (2013) comparing pazopanib with placebo in terms of clinical effectiveness.

While the outcomes *median overall survival* (12.6 months vs 10.7 months) and *median progression free survival* (4.6 months vs 1.6 months) favored pazopanib versus placebo, these were only based on one randomized controlled trial (RCT) called the PALETTE (2011) trial. The median follow-up period was 14.9 months (interquartile range: 11.0–18.2) for pazopanib and 14.6 months (interquartile range: 11.3–19.7) in the placebo group. The reported outcomes were based on very low quality evidence using GRADE assessment. Further, no studies were found reporting the outcome *quality of life*.

Table 1.
Key Findings on the Review of Published Evidence on the Clinical Effectiveness of Pazopanib

Outcome	Results
median Overall survival[1] (OS)	Pazopanib group = 12.6 months vs. Placebo group = 10.7 months ● Pazopanib arm had longer median OS than placebo, based on one systematic review ● The quality of evidence is very low

median Progression free survival (PFS)	Pazopanib group = 4.6 months vs. Placebo group = 1.6 months ● Pazopanib arm had longer median PFS than placebo, based on one systematic review ● The quality of evidence is very low
Quality of Life	no data found

[1]Median follow-up period: 14.9 months (interquartile range: 11.0–18.2) for pazopanib and 14.6 months (interquartile range: 11.3–19.7) in the placebo group

Review of published evidence on clinical safety

The ERG found three systematic reviews (Sharma et al., 2013; Colosia et al., 2016; Kappadia et al., 2013) comparing pazopanib with placebo in terms of clinical safety.

The evidence shows an increased occurrence of the following adverse events when taking pazopanib: diarrhea (All Grade), fatigue (All Grade, Grade 3), nausea and vomiting (All Grade), weight loss (High Grade, All Grade), hypertension (All Grade), increased ALT (High Grade, All Grade), increased AST (High Grade, All Grade), and increased bilirubin (All Grade). These are all based on moderate quality of evidence using GRADE assessment. Table 2 summarizes the results.

Table 2.
Key Finding on the Review of Published Evidence on the Clinical Safety of Pazopanib

Outcome	Results
Diarrhea ***(risk ratio, RR)***	High Grade Diarrhea: **RR: 5.64 [95% CI: 0.74 - 43.16][1], RR: 5.66 [95% CI: 0.74 - 43.34][2]** ● There is no statistically significant difference for high grade diarrhea, based on 2 systematic reviews. The direction of the risk ratios favors placebo over pazopanib while the 95% confidence interval for "High grade" crossed the line of no effect (i.e., the value of 1). This means that the observed effect is inconclusive as it ranges from favorable to non-favorable outcomes. ● The quality of evidence is moderate All Grade Diarrhea, %reported[2] : **Pazopanib group = 57.74% vs. Placebo group= 16.26%** ● There were more all-grade events of diarrhea from the Pazopanib group compared to placebo, based on 1 systematic review. The result favors placebo for all grade diarrhea. ● The quality of evidence is moderate
Fatigue ***(risk ratio, RR)***	High Grade Fatigue (Grade 3 and Grade 4) :**RR: 1.88 [95% CI: 0.78 - 4.51][1]** ● There is no statistically significant difference for high grade fatigue based on 1 systematic review. The 95% confidence interval for "High grade" crossed the line of no effect (i.e., the value of 1). This means that the observed effect is inconclusive as it ranges from favorable to non-favorable outcomes. ● The quality of evidence is moderate

	Grade 3 fatigue: **RR: 2.57 [95% CI: 1.10 - 8.16][2]** ● The result statistically favors placebo for Grade 3 fatigue, based on 1 systematic review. The risk of having Grade 3 fatigue when taking pazopanib is 2.57 times higher vs. placebo. ● The quality of evidence is moderate Grade 4 fatigue: **RR: 0.51 [95% CI: 0.03 - 8.16][2]** ● There is no statistically significant difference for grade 4 fatigue, based on 1 systematic review. The 95% confidence interval for "grade 4" crossed the line of no effect (i.e., the value of 1). This means that the observed effect is inconclusive as it ranges from favorable to non-favorable outcomes. ● The quality of evidence is moderate All Grade Fatigue, %reported[2]: **Pazopanib group =64.85% vs. Placebo group = 48.78%** ● There were more all-grade events of fatigue from the Pazopanib group compared to placebo, based on 1 systematic review. The result favors placebo for all grade fatigue. ● The quality of evidence is moderate
Nausea and Vomiting (N/V) ***(risk ratio, RR)***	High Grade N/V (Grade 3 and Grade 4): **RR: 2.06 [95% CI: 0.44 - 9.55][2]** High Grade Vomiting: **RR: 4.10 [95% CI: 0.52 - 32.41][1]** High Grade nausea: **RR: 2.05 [95% CI: 0.44 - 9.51][1]** ● There is no statistically significant difference for high grade N/V, based on 2 systematic reviews. The direction of the risk ratios favors placebo over pazopanib, but the 95% confidence interval for "High grade" crossed the line of no effect (i.e., the value of 1). This means that the observed effect is inconclusive as it ranges from favorable to non-favorable outcomes. ● The quality of evidence is moderate Grade 3 N/V: **RR: 2.06 [95% CI: 0.44 - 9.55][2]** ● There is no statistically significant difference for grade 3 N/V, based on 1 systematic review. The direction of the risk ratios favors placebo over pazopanib but the 95% confidence interval for "grade 3" crossed the line of no effect (i.e., the value of 1). This means that the observed effect is inconclusive as it ranges from favorable to non-favorable outcomes. ● The quality of evidence is moderate Grade 4 N/V: **RR: Cannot be estimated[2]** All Grade N/V, %reported[2]: **Pazopanib group = 53.97% vs.Placebo group = 27.64%** ● There were more all-grade events of N/V from the Pazopanib group compared to placebo, based on 1 systematic review. The result favors placebo for all grade N/V. ● The quality of evidence is moderate
Weight Loss	High Grade Weight loss (Grade 3 and Grade 4), %reported[1]: **Pazopanib group = 3.75% vs. Placebo group = 0%** ● There were more high grade events of weight loss from the Pazopanib group

	compared to placebo, based on 1 systematic review. The result favors placebo for high grade weight loss. ● The quality of evidence is moderate All Grade Weight Loss, %reported[2]: **Pazopanib group = 48.12% vs. Placebo group = 20.33%** ● There were more all-grade events of weight loss from the Pazopanib group compared to placebo, based on 1 systematic review. The result favors placebo for all grade weight loss. ● The quality of evidence is moderate
Hypertension (HTN) ***(risk ratio, RR)***	High Grade HTN (Grade 3 and Grade 4): **RR: 2.05 [95% CI: 0.70 - 6.00][1]** ● There is no statistically significant difference for high grade HTN, based on 1 systematic review. The direction of the risk ratios favors placebo over pazopanib but the 95% confidence interval for "high grade" crossed the line of no effect (i.e., the value of 1). This means that the observed effect is inconclusive as it ranges from favorable to non-favorable outcomes. ● The quality of evidence is moderate Grade 3 HTN: **RR: 2.06 [95% CI:0.70 - 6.02][2]** ● There is no statistically significant difference for grade 3 HTN, based on 1 systematic review.. The direction of the risk ratios favors placebo over pazopanib but the 95% confidence interval for "grade 3" crossed the line of no effect (i.e., the value of 1). This means that the observed effect is inconclusive as it ranges from favorable to non-favorable outcomes. ● The quality of evidence is moderate Grade 4 HTN: **RR: Cannot be estimated[2]** All Grade HTN, %reported[1]: **Pazopanib group = 41.42% vs. Placebo group = 20.33% 6.50%** ● There were more all-grade events of HTN from the Pazopanib group compared to placebo, based on 1 systematic review. The result favors placebo for all grade HTN. ● The quality of evidence is moderate
Increased ALT ***(risk ratio, RR)***	High Grade Increased ALT: **RR: 2.95 [95% CI: 1.04 - 8.33][1], RR=2.96 [95% CI: 1.05 - 8.37][3]** ● The results statistically favor placebo for high grade increased ALT, based on 2 systematic reviews. There is statistically higher risk of increased ALT in pazopanib by 2.95 to 2.96 times when compared with placebo. ● The quality of evidence is moderate Grade 3 Increased ALT: **RR=3.09 [95% Ci: 0.93 - 10.28][2]** ● There is no statistically significant difference for grade 3 increased ALT, based on 1 systematic review. The 95% confidence interval for "grade 3" crossed the line of no effect (i.e., the value of 1). This means that the observed effect is inconclusive as it ranges from favorable to non-favorable outcomes. ● The quality of evidence is moderate

	Grade 4 Increased ALT: **RR=2.57 [95% Ci: 0.30 - 21.78][2]** ● There is no statistically significant difference for grade 4 increased ALT, based on 1 systematic review.. The 95% confidence interval for "grade 4" crossed the line of no effect (i.e., the value of 1). This means that the observed effect is inconclusive as it ranges from favorable to non-favorable outcomes. ● The quality of evidence is moderate All Grade Increased AL, %reported[1]: **Pazopanib group = 46.03% vs Placebo group = 17.89%[2]** ● There were more all-grade events of increased ALT from the Pazopanib group compared to placebo, based on 1 systematic review. The result favors placebo for all grade increased ALT. ● The quality of evidence is moderate
Increased AST ***(risk ratio, RR)***	High grade increased AST(Grade 3 and 4): **RR: 4.89 [95% CI:1.15 - 20.56][1], RR: 4.87 [95% CI: 1.16 - 20.65][3]** ● The results statistically favor placebo for high grade increased AST, based on 2 systematic reviews. There is statistically higher risk of increased AST in pazopanib by 4.87 to 4.89 times when compared with placebo. ● The quality of evidence is moderate Grade 3 increased AST: **RR: 3.35 [95% CI: 0.77 - 14.59][2]** ● There is no statistically significant difference for grade 3 increased AST, based on 1 systematic review.. The 95% confidence interval for "grade 3" crossed the line of no effect (i.e., the value of 1). This means that the observed effect is inconclusive as it ranges from favorable to non-favorable outcomes. ● The quality of evidence is moderate Grade 4 increased AST: **RR: 6.72 [95% CI: 0.38 - 118.26][2]** ● There is no statistically significant difference for grade 4 increased AST, based on 1 systematic review. The 95% confidence interval for "grade 4" crossed the line of no effect (i.e., the value of 1). This means that the observed effect is inconclusive as it ranges from favorable to non-favorable outcomes. ● The quality of evidence is moderate All Grade Increased AST, %reported[2]: **Pazopanib group = 51.05% vs Placebo group = 21.95%** ● There were more all-grade events of increased AST from the Pazopanib group compared to placebo, based on 1 systematic review.. The result favors placebo for all grade increased AST. ● The quality of evidence is moderate
Increased Bilirubin	High grade increased bilirubin: **RR=0.77 [95% CI: 0.13 - 4.54][1] , RR=1.03 [95% CI: 0.19 - 4.54][3]** ● There is no statistically significant difference for high grade increased

(risk ratio, RR)	bilirubin, based on 2 systematic reviews. The direction of the risk ratios generally favors placebo over pazopanib but the 95% confidence interval for "high grade" crossed the line of no effect (i.e., the value of 1). This means that the observed effect is inconclusive as it ranges from favorable to non-favorable outcomes. ● The quality of evidence is moderate Grade 3 increased bilirubin: **RR=0.77 [95% CI: 0.13 - 4.56][2]** ● There is no statistically significant difference for grade 3 increased bilirubin, based on 1 systematic review. The direction of the risk ratios generally favors placebo over pazopanib but the 95% confidence interval for "grade 3" crossed the line of no effect (i.e., the value of 1). This means that the observed effect is inconclusive as it ranges from favorable to non-favorable outcomes. ● The quality of evidence is moderate Grade 4 increased bilirubin: **Cannot be estimated[2]** All Grade Increased Bilirubin,%reported[2]: **Pazopanib group = 28.45% vs. Placebo group = 7.32%[2]** ● There were more all-grade events of increased bilirubin from the Pazopanib group compared to placebo, based on 1 systematic review.. The result favors placebo for all grade increased bilirubin, ● The quality of evidence is moderate

[1] Sharma, et al. (2013) ; [2] Colosia, et al. (2016); [3] Kapadia, et al. (2013)

Review of local and international clinical practice guidelines

In the four clinical practice guidelines reviewed, three guidelines [National Comprehensive Cancer Network (NCCN), Spanish Group for Research on Sarcoma (GEIS), British Sarcoma Group (BSG)] recommended the use of pazopanib as second-line therapy. One guideline [Philippine Cancer Society Inc. (PSCI)] did not mention pazopanib as an option for chemotherapy. We summarize the key recommendations of different clinical practice guidelines below:

- PSCI**:** The society did not mention pazopanib as an option for chemotherapy, either in combination or as a single agent (Philippine Cancer Society Inc., 2014)
- NCCN: for STS subtypes with non-specific histologies, pazopanib is recommended as a single agent for palliative therapy only except for lipogenic sarcomas in which the drug must not be administered; for Gastrointestinal stromal tumor (GIST), pazopanib is recommended for when there is disease progression after imatinib, sunitinib, and regorafenib (the three aforementioned are FDA approved for treatment of GIST) (von Mehren, et al., 2018)
- GEIS: pazopanib is apt as post-first line treatment for non-adipocytic sarcomas (Garcia del Muro, et al., 2016)
- BSG: pazopanib can be used for post-second-line therapy if patient fitness and funding allow for it (Dangoor, et al., 2016)

Review of recommendations by HTA Agencies

In the four HTA agencies reviewed, one (PBAC) recommended it for funding, one (Pan-Canadian Oncology Drug Review) did not recommend it for funding, and two (National Horizon Scanning Center; All Wales Medicines Study Group) did not specify their recommendations but mentioned their key findings. We summarize the key recommendations of different HTA agencies below:

Table 3.
Key recommendations of different HTA agencies on the use of Pazopanib

HTA Agency	Recommendation
Pharmaceutical Benefits Advisory Committee (PBAC) (2013)	● Recommended funding for pazopanib for advanced STS, based on: ○ Benefit seen for PFS (4.6 mos. vs. 1.6 mos for pazopanib versus placebo; HR = 0.31, 95% CI: 0.24 to 0.40, P < 0.0001) ○ High unmet clinical need ○ Moderate overall cost ● PBAC acknowledges that there is an unclear, potentially high ICER for pazopanib, and unsupported claim for overall survival benefit
National Horizon Scanning Centre (2010)	● Speculative potential impact to lower mortality or higher length of survival ● Uncertain unit cost with respect to alternative therapies ● Disparity of available data on disease prevalence: there is difficulty in ascertaining the number of patients who may benefit from the drug
All Wales Medicines Study Group (2013)	● Recommendation for funding was not specified ● Moderate benefit on progression free survival ● Lack of benefit for overall survival ● The lack of measured improvement of quality of life
Pan-Canadian Oncology Drug Review (2012)	● Did not recommend funding for pazopanib ● Moderate benefit on progression free survival, lack of benefit for overall survival, and the lack of measured improvement of quality of life ● Treatment is not cost-effective

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