CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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Indication:	The treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer
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1 EXECUTIVE SUMMARY

On August 14, 2014, the applicant submitted a new drug application (NDA) to seek an approval of lenvatinib for the proposed indication *'The treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer*'. In the submission, the applicant provided clinical data from Study E7080-G000-303 (SELECT) entitled 'A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Lenvatinib (E7080) in 131^{I}-Refractory Differentiated Thyroid Cancer', and other studies.

In SELECT, a total of 392 eligible patients were randomized in a 2:1 ratio to receive either lenvatinib 24 mg by continuous once daily oral administration or matching placebo administered as blinded study drug. The randomization was stratified by geographic region (Europe, North America, and Other), age group (≤65 or >65 years), and prior VEGF/VEGFR-targeted therapy (0 or 1). The primary endpoint was progression-free survival (PFS), determined by blinded independent imaging review (IIR) conducted by the imaging core laboratory using Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria.

The primary analysis was a stratified log-rank test. Based on 220 PFS events determined by IIR, the PFS result demonstrated that patients treated with lenvatinib had statistically significant improvement in PFS compared to patients treated with placebo (stratified log-rank p-value<0.0001). The estimated median PFS was 18.3 months (95% CI: 15.1, NA) for lenvatinib arm and 3.6 months (95% CI: 2.2, 3.7) for the placebo arm. The hazards ratio was 0.21 (95% CI: 0.16, 0.28) in favor of the treatment with lenvatinib. The result of objective response rate (ORR) showed that the patients treated with lenvatinib had statistically significantly higher objective response rate than the patients treated with placebo (Cochran-Mantel-Haenszel p-value <0.0001). The estimated objective response rate for the lenvatinib arm was 64.8% (95% CI: 59.0, 70.6) with at least 16.8 months duration of response and 1.5% (95% CI: 0.0, 3.6) for the placebo arm. With 118 death events occurred, the overall survival (OS) analysis result showed that there was no statistical difference between the two treatment arms (log-rank p-value= 0.1032) with hazards ratio of 0.73 (95% CI: 0.50, 1.07). The median OS in the lenvatinib arm had not been reached at the time of the OS analysis. Among 47 deaths from placebo arm in OS analysis, 37 (79%) were crossed-over to receive lenvatinib after confirmed disease progression. The OS analyses suggested that there was a trend favoring lenvatinib.

Whether the results from study SELECT provide a favorable benefit to risk ratio to support an approval of lenvatinib for the proposed indication will be determined by the clinical review team.

2 INTRODUCTION

2.1 OVERVIEW

Lenvatinib is an oral, multiple receptor tyrosine kinase (RTK) inhibitor that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other proangiogenic and oncogenic pathway-related RTKs including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4; the platelet derived growth factor (PDGF) receptor PDGFRα; KIT; and RET. In this NDA, the applicant submitted the data from study SELECT and other studies to seek an approval of lenvatinib for a proposed indication for the patients with progressive, radioactive iodine-refractory differentiated thyroid cancer.

There were 392 randomized patients in the study SELECT. The primary objective was to compare the PFS of patients treated with lenvatinib versus placebo. SELECT was conducted at 117 study sites in Europe, North America, Asia, and Latin America. The study started on July 26, 2011and the data cutoff for the primary analysis was on Nov 15, 2013.

The secondary objectives of the study included comparisons of objective response rate (ORR) and overall survival (OS) between the two randomized treatment arms.

2.2 DATA SOURCES

Data used for this review were from the electronic submission received on August 14, 2014. The link was "\\CDSESUB1\evsprod\NDA206947\206947.enx"

3 STATISICAL EVALUATION

This section focuses on efficacy evaluation for study SELECT.

3.1 DATA AND ANALYSIS QUALITY

The quality of submitted data allowed this reviewer to verify the applicant's submitted major efficacy results and conduct the reviewer's own analyses. The protocol including its amendments and statistical analysis plan (SAP) were provided in the NDA submission.

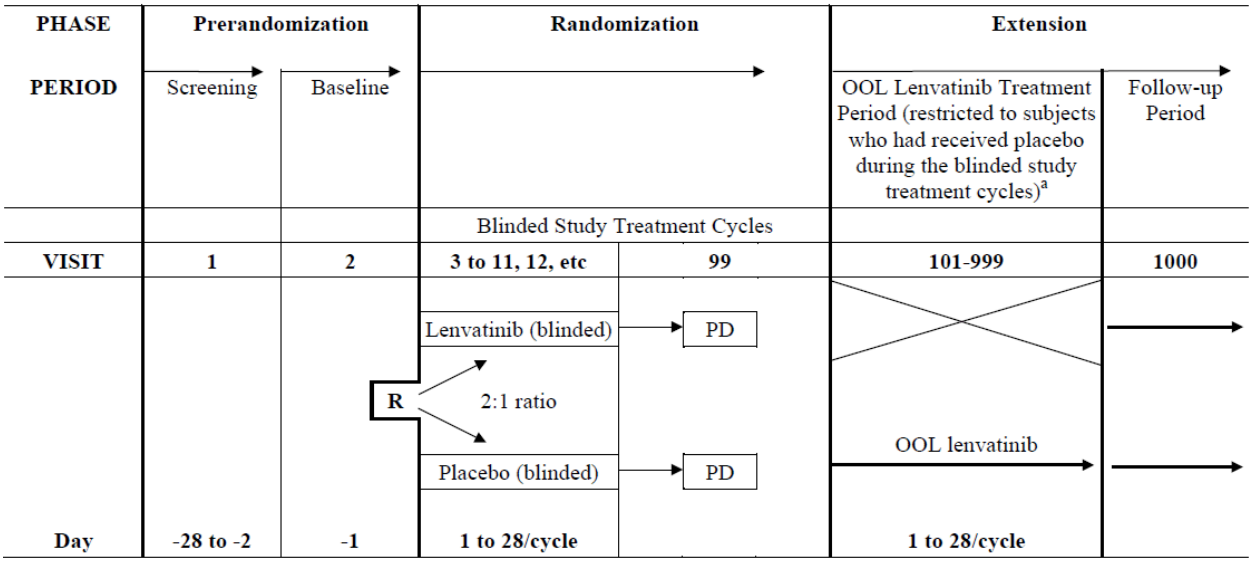
3.2 EVALUATION OF EFFICACY

Study Design and Endpoints

SELECT was a randomized, double-blind, placebo-controlled, multicenter phase III study. The study inclusion criteria included 1) the patients who had measurable disease meeting certain criteria and confirmed by central radiographic review; 2) patients with evidence of disease progression within 12 months prior to signing informed consent, according to RECIST 1.1 assessed and confirmed by central radiographic review of CT and/or MRI scans. Eligible patients were randomized with a ratio of 2:1 to receive lenvatinib 24 mg or matching placebo by continuous QD oral dosing as blinded study drug. The randomization was stratified by geographic region (Europe, North America, and Other), age group (≤65 or >65 years), and prior

VEGF/VEGFR-targeted therapy (0 or 1). Patients took blinded study drug once daily until confirmed disease progression (assessed by IIR), development of unacceptable toxicity, or withdrawal of consent. Patients in the placebo arm who had disease progression confirmed by IIR could request to enter the optional open label (OOL) lenvatinib treatment period and receive lenvatinib treatment. After the primary analysis was completed, patients treated with lenvatinib who had not experienced disease progression could request to continue open-label lenvatinib at the same dose, according to the clinical judgment of the investigator. Figure 3.1 shows the overall study design of SELECT.

Figure 3.1 Overall Design of Study SELECT



[Source: Clinical Study Report Figure 1] OOL = optional open label, PD = progressive disease, R = randomization

[a]: After confirmation of the progression of the disease, only patients who requested to receive OOL lenvatinib were unblinded to the study drug administration. Only those patients who received placebo as the blinded study drug could receive OOL lenvatinib. Patients who did not wish to participate in the OOL Phase entered the Follow-up Period of the Extension Phase.

Per the protocol and the statistical analysis plan, the primary endpoint PFS was defined as the time from the date of randomization to the date of first documentation of disease progression or death (whichever occurred first) as determined by blinded independent imaging review (IIR) conducted by the imaging core laboratory using RECIST 1.1. Tumor assessments (CT or MRI of neck, chest, abdomen, and pelvis, and of all other known sites of disease) were performed every 8 weeks from the date of randomization during study treatment cycles in the randomization phase and every 12 weeks in the extension phase. Eligibility was confirmed by the imaging core laboratory before a patient was randomized (revised per Amendment 03). Disease progression was confirmed by the independent review prior to the investigator discontinuing study drug for a patient. The PFS censoring rules are presented in the following table.

No.	Situation	Date of Progression or Censoring	Outcome
1	No baseline tumor assessments	Date of randomization	Censored
2	Progression documented between scheduled visits	Date of first radiologic PD assessment	Progressed
3	No progression	Date of last adequate radiologic assessment	Censored
4	New anticancer treatment started	Date of last adequate radiologic assessment prior to or on date of new anticancer treatment	Censored
5	Death before first PD assessment	Date of death	Progressed
6	Death between adequate assessment visits*	Date of death	Progressed
7	Death or progression after more than one missed visit/tumor assessment**	Date of last adequate radiologic assessment before missed tumor assessments	Censored
8.	Treatment discontinuation for reasons other than PD	Date of last radiologic assessment before treatment discontinuation	Censored

CR = complete response, IIR = independent imaging review, PD = progressive disease, PR = partial response, SD =stable disease,
** Adequate tumor assessment is radiologic assessment at regular interval as defined in the protocol.*
*** More than one missed visit/adequate tumor assessment is defined as having either one of the following two durations being longer than 18 weeks - 1 day, which is 125 days (= ((8+1) x 2 x 7) – 1) for patients on the every 8 week tumor assessment schedule in this study:*

The secondary endpoints in the study included overall survival (OS), and objective response rate (ORR). OS was defined as the time from date of randomization to date of death due to any cause. ORR was defined as the proportion of patients who had best overall response (BOR) of CR or PR as determined by blinded IIR using RECIST 1.1.

Statistical Methodologies

Per the protocol and statistical analysis plan (SAP), the primary analysis of PFS was a log-rank test stratified by region (Europe, North America, Other), age group (≤65, >65years), and prior VEGF/VEGFR therapy (0, 1) at two-sided significance level of 0.01. The primary analysis was based on intent-to-treat (ITT) population, defined as all randomized patients. The Kaplan-Meier method was used to estimate the median PFS and 95% confidence intervals (CIs) for each treatment arm. Hazard ratio and its 95% confidence intervals were estimated using the Cox proportional hazards model stratified by region, age, and prior VEGF/VEGF-targeted therapy.

Assuming that the true PFS hazard ratio was 0.57 corresponding to median PFS of 8 months in the placebo arm and 14 months in the lenvatinib arm, a total of 214 events were needed to detect a hazard ratio of 0.57 with 90% power at a 2-sided alpha level of 0.01. Taking consideration of enrollment rate of 20 patients per month and 10% dropout rate, approximately 360 patients were planned to be randomized. It was estimated that the 214 PFS events would occur approximately 29 months (18 months enrollment period and 11 follow up period) after the start of the randomization phase.

Per the protocol, the secondary endpoint OS would be analyzed using Kaplan-Meier product-limit estimates and compared between lenvatinib vs. placebo using a stratified log-rank test with geographic region (Europe, North America, and Other), prior VEGF/VEGFR-targeted therapy (0 or 1), and age (≤65 years or > 65 years). Another secondary endpoint ORR was tested by using Cochran-Mantel-Haenszel (CMH) test stratified by the 3 randomization stratified factors at two-sided alpha of 0.05. According to the protocol and SAP, the secondary endpoints ORR and OS would be compared between the treatment groups by controlling the overall family-wise error rate at level $\alpha = 0.05$, using sequential testing procedure as the followings: the ORR would be tested first at the 0.05 level. Only if it was significant, OS would then be tested at the 0.05 level.

Reviewer's Comments:

1. *Notice that the primary analysis of PFS and sample size were planned at significant level of two-sided 0.01, and OS and ORR were planned at two-sided 0.05.*

2. *The applicant pre-specified in the protocol that overall survival curves compared between treatment groups using the stratified log rank test. However, the applicant stated in the SAP that not only overall survival curves compared between treatment groups using the stratified log rank test, but also the rank preserving structural failure time (RPSFT) model (Robin and Tsiatis, 1991) would be used in OS analysis to correct the bias introduced by cross-over and estimate the true treatment effect on OS.*

Patient Disposition, Demographic and Baseline Characteristics

There were 392 patients randomized in SELECT. Table 3.1 summarizes the patient disposition of ITT population at the date of data cut-off for the final PFS analysis (Nov 15, 2013).

Table 3.1 Patient Disposition

	Lenvatinib (%)	Placebo (%)
Randomized	261	131
Treated	261 (100)	131 (100)
Treatment ongoing at data cutoff date	122 (46.8)	8 (6.1)
Completed treatment – disease progression	94 (36.0)	119(90.8)
Confirmed by independent review	71	114
Not confirmed by independent review	23	5
Prematurely discontinued treatment	45 (17.2)	4 (3.1)
Primary reason for premature discontinuation		
Adverse event	37	3
Subject choice	4	0
Withdrawal of consent	4	0
Other	0	1

[Source: Clinical Study Report Table 7]

The demographics of ITT population are summarized in Table 3.2.

Table 3.2 Summary of Demographics

	Lenvatinib n=261	Placebo n=131	Total n=392
Age (year)			
Median (Min-Max)	64 (27-89)	61(21-81)	63 (21-89)
Age group, n (%)			
≤65	155 (59.4)	81 (61.8)	236 (60.2)
>65	106 (40.6)	50 (38.2)	156 (39.8)
Sex, n (%)			
Male	125 (47.9)	75 (57.3)	200 (51.0)
Female	136 (52.1)	56 (42.7)	192 (49.0)
Region, n (%)			
Europe	131 (50.2)	64 (48.9)	195 (49.7)
North America*	77 (29.5)	39 (29.8)	116 (29.6)
Other	53 (20.3)	28 (21.4)	81 (20.7)
Race, n (%)			
White	208 (79.7)	103 (78.6)	311 (79.3)
Black or African American	4 (1.5)	4 (3.1)	8 (2.0)
Asian	46 (17.6)	24 (18.3)	70 (17.9)
Japanese	30 (11.5)	11 (8.4)	41 (10.5)
Other	16 (6.1)	13 (9.9)	29 (7.4)
Native Hawaiian or other Pacific Islander	1 (0.4)	0	1 (0.3)
Other	2 (0.8)	0	2 (0.5)
Ethnicity, n (%)			
Hispanic or Latino	10 (3.8)	9 (6.9)	19 (4.8)
Not Hispanic or Latino	251 (96.2)	122 (93.1)	373 (95.2)

*[Source: Clinical Study Report Table 11] *North America includes Australia*

Reviewer's Comments:

3. *The demographics appear balanced between the two treatment arms except there were almost 10% more male patients in the placebo arm than in lenvatinib arm. This reviewer conducted a PFS analysis to evaluate whether the imbalance of sex has an impact on the PFS result (result of the analysis is summarized in Section 3.2.4.1 Table 3.7).*

The major baseline characteristics for ITT population are summarized in Table 3.3

Table 3.3 Summary of Major Baseline Characteristics

	Lenvatinib n=261	Placebo n=131	Total n=392
Thyroid Stimulating Hormone (TSH) (µIU/mL), n (%)			
≤0.5	226 (86.6)	120 (91.6)	346 (88.3)
>0.5 to ≤2.0	25 (9.6)	10 (7.6)	35 (8.9)
>2.0 to ≤5.5	10 (3.8)	1 (0.8)	11 (2.8)
Weight (kg) Median (Min-Max)	73.3 (33-155)	74 (31-165)	73.5 (31-165)
ECOG performance status, n (%)			
0	144 (55.2)	68 (51.9)	212 (54.1)
1	104 (39.8)	61 (46.6)	165 (42.1)
2	12 (4.6)	2 (1.5)	14 (3.6)
3	1 (0.4)	0	1 (0.3)
No. prior VEGF/VEGFR-targeted therapy, n (%)			
0	195 (74.7)	104 (79.4)	299 (76.3)
1	66 (25.3)	27 (20.6)	93 (23.7)

[Source: Clinical Study Report Table 11]

Table 3.4 summarizes the major baseline metastatic disease status of ITT population assessed by independent review.

Table 3.4 Baseline Metastatic Disease Status by Independent Review

	Lenvatinib n=261	Placebo n=131	Total n=392
Locally advanced DTC*	4 (1.5)	0	4 (1.0)
Metastatic DTC*	257 (98.5)	131 (100)	388(0.99)
Lung metastases	226 (86.6)	124 (94.7)	350 (89.3)
Lymph node metastases	138 (52.9)	64 (48.9)	202 (51.5)
Bone metastases	104 (39.8)	48 (36.6)	152 (38.8)
Pleural metastases	46 (17.6)	18 (13.7)	64 (16.3)
Liver metastases	43 (16.5)	28 (21.4)	71 (18.1)
Pericardium/intra-abdominal mass metastases	24 (9.2)	10 (7.6)	34 (8.6)
Musculoskeletal (non-bone)/skin metastases	10 (3.8)	5 (3.8)	15(38.2)
Brain metastases	9 (3.4)	7 (5.3)	16 (4.1)
Metastatic sites			
0	4 (1.5)	0	4 (1.0)
1	62 (23.8)	34 (26.0)	96 (24.5)
2	90 (34.5)	44 (33.6)	134 (34.2)
3	69 (26.4)	38 (29.0)	107 (27.3)
≥4	36 (13.8)	15 (11.5)	51(13.0)

*[Source: Clinical Study Report Table 13] *DTC = differentiated thyroid cancer*

Reviewer's Comments:

4. *Except for 8% more patients with lung metastases in placebo arm than lenvatinib arm, the major baseline metastatic disease status appear balanced between the two treatment arms. This reviewer conducted a PFS analysis to evaluate whether the imbalance of lung metastatses has an impact on the PFS result (result of the analysis is summarized in Section 3.2.4.1 Table 3.7)*

Results and Conclusions

Results of Primary Endpoint

Table 3.4 summarizes the primary analysis of PFS.

Table 3.4 Result of Progression-Free Survival Analysis

	Lenvatinib n=261	**Placebo n=131**
Number of Event (%)	107 (41.0)	113 (86.3)
Progression	93	109
Death	14	4
Number of Censored (%)	154 (59.0)	18 (13.7)
Median PFS in months (95% CI)	18.3 (15.1, NA)	3.6 (2.2, 3.7)
Hazard ratio* (95%CI)	0.21 (0.16, 0.28)	
p-value (stratified* log-rank)	<0.0001	

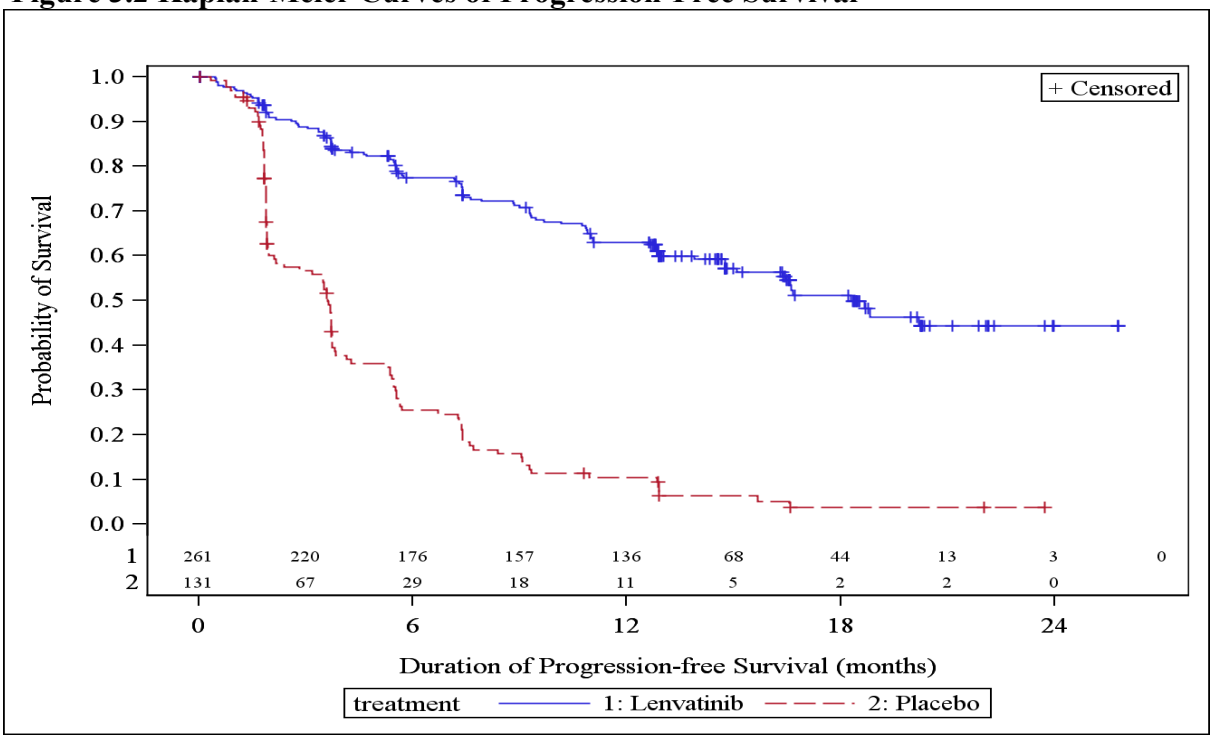
**Stratified by age, region and prior VEGF/VEGF-targeted therapy **a hazard ratio of less than 1 indicates that the treatment with lenvatinib is associated with lower risk of progression or death compared to placebo treatment.*

Reviewer's Comments:

5. *The primary PFS analysis demonstrated that the treatment with lenvatinib statistically significantly prolonged PFS compared to placebo.*

Figure 3.2 displays the reviewer's Kaplan-Meier curves of PFS.

Figure 3.2 Kaplan-Meier Curves of Progression-Free Survival



Reviewer's Comments:

6. *In order to evaluate the robustness of the observed PFS treatment effect, the applicant and this reviewer conducted several PFS sensitivity analyses. Table 3.7 summarizes the applicant's three sensitivity analyses, including analyses using the investigator assessment; using the actual reported date of progression by IIR or death to define PFS regardless of missing assessments, treatment discontinuation, or use of new anticancer therapy; and using the uniform scheduled date of radiologic assessment to define the date of censoring and events depending on equivalence of radiologic assessment intervals between 2 treatment arms.*

Table 3.7 Summary of Progression-Free Survival Sensitivity Analyses

	Lenvatinib n=261	Placebo n=131	
	Number of Events (%)		HR (99%CI)
Applicant's Analyses			
Investigators' Assessments	107 (41.0)	110 (84.0)	0.24 (0.16, 0.35)
Uniform Time of Assessment using IRR assessment	107 (41.0)	113 (86.3)	0.24 (0.16, 0.35)
No PD and Death was Censored using IRR assessment	119 (45.6)	114 (87.0)	0.22 (0.15, 0.32)
Reviewer's Analysis			
Adjusted by Lung Metastases	107 (41.0)	113 (86.3)	0.21 (0.13, 0.28)
Adjusted by Sex	107 (41.0)	113 (86.3)	0.22 (0.15, 0.32)
Had an PFS event at the date of withdraw for patients who discontinued other than PD	140 (53.6)	125 (95.4)	0.28 (0.20, 0.40)

7. *As shown in Table 3.7, the results of sensitivity analyses are consistent with the result of the primary analysis. There were 49 patients (45 patients in lenvatinib arm and 4 patients in placebo arm) who prematurely discontinued treatment due to the reasons other than PD; this reviewer conducted a sensitivity PFS analysis by considering the patient who had a PFS event at the date of withdraw for the 49 patients. See Table 3.7 for the reviewer's sensitivity analysis result.*

8. *As shown in Table 3.1 and Table 3.2, there are 10% more male patients in placebo arm than lenvatinib arm and 8% more patients with lung metastases in placebo arm than in lenvatinib arm. This reviewer conducted two PFS sensitivity analyses adjusting one demographic factor sex and one major disease characteristics lung metastases respectively to evaluate if the imbalance of the two demographic and major disease characteristic factors had impact on the result of PFS. The two reviewer's sensitivity analyses are summarized in Table 3.7.*

Results of Secondary Endpoints

Objective response rate (ORR) was a secondary endpoint in SELECT. Table 3.8 summarizes ORR analysis based on IIR assessment.

Table 3.8 Results of Objective Response and Duration of Response (IIR)

	Lenvatinib (n=261)	**Placebo (n=131)**
Response (CR+PR), n (%)	169 (64.8)	2 (1.5)
Complete response	4	0
Partial response	165	2
Applicant's 95%CI[a]	(59.0, 70.6)	(0.0, 3.6)
Reviewer's 95%CI[b]	(58.6, 70.5)	(0.19, 5.4)
P-value (CMH test)	<0.0001	
Median of Duration of Response (months) (95%CI)	NA[c](16.8, NA[c])	NA[c]

[a] obtained by using large sample normal approximation; [b] Clopper-Pearson confidence interval obtained by using exact Clopper-Pearson method; [c]NA=Not Available

Reviewer's Comments:

9. *The applicant specified using large sample normal approximation to calculate 95% confidence interval (CI) shown in Table 3.8. The reviewer's 95% CI in Table 3.8 was calculated using exact Clopper-Pearson method, which is conservative. The Applicant pre-specified a hierarchical test order for the secondary endpoints to adjust multiplicity in the SAP that the ORR would be tested first at the 0.05 level after the primary analysis of PFS shows statistical significance. The result of ORR showed that the patients treated with lenvatinib had statistically significantly higher objective response rate than patients treated with placebo.*

OS was another secondary endpoints evaluated in SELECT. Table 3.9 summarizes the applicant's OS analysis conducted at the time of final analysis of PFS.

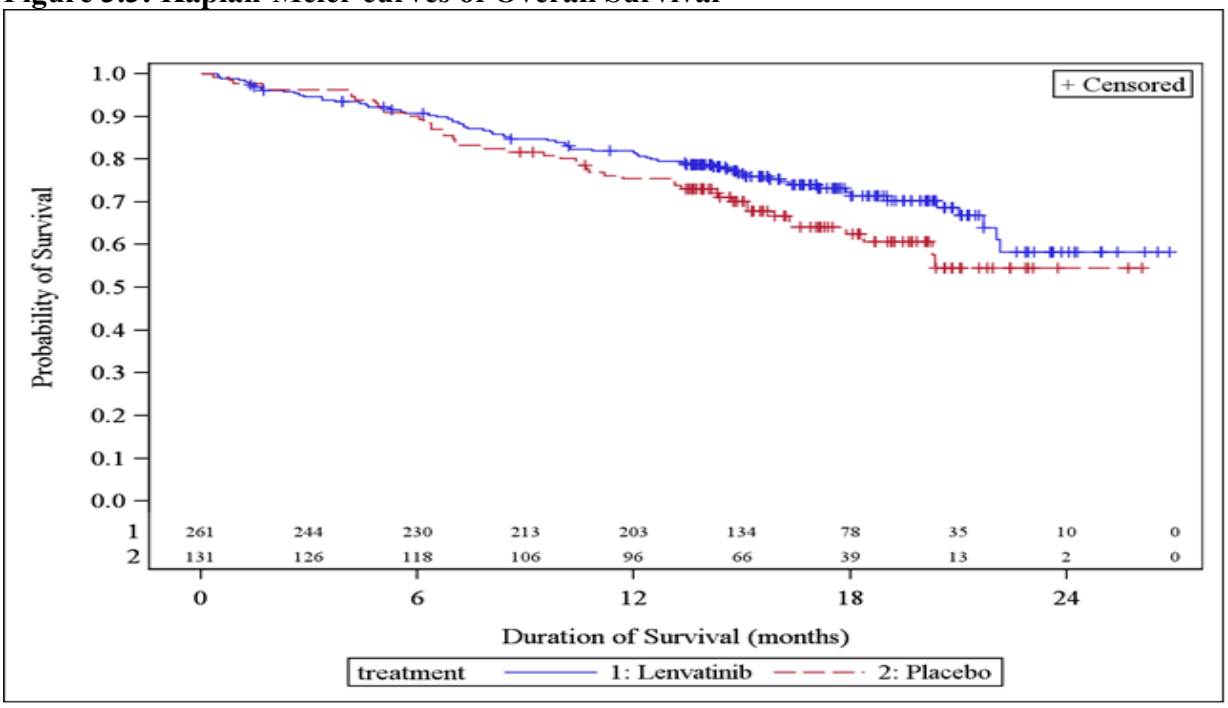
Table 3.9 Result of Overall Survival

	Lenvatinib n=261	Placebo n=131
Number of Event (%)	71 (28.2)	47 (35.9)
Number of Censored (%)	190 (72.8)	84 (64.1)
Median OS in Months (95% CI)	NA[a] (22.05, NA)	NA[a] (20.27, NA)
Hazard ratio[b] (95%CI)	0.73 (0.50, 1.07)	
p-value (stratified log-rank)	0.1032	

[a]NA=Not available due to only small number of events occurred; [b] a hazard ratio of less than 1 indicates that the treatment with lenvatinib is associated with lower risk of death compared to placebo treatment. [c] Stratified by region, age, and prior VEGF/VEGF-targeted therapy.

Figure 3.3 displays the reviewer's Kaplan-Meier curves of OS.

Figure 3.3: Kaplan-Meier curves of Overall Survival



Reviewer's Comments:

10. The OS result in Table 3.9 showed that there was no statistically significant difference in survival between the lenvatinib and placebo arms. However, the OS analysis was conducted according to ITT principle i.e. the patients were analyzed according to the randomized assigned treatment even the patients in placebo arm crossed over to receive lenvatinib. There were 109 (83%) patients in placebo arm who crossed over after confirmed PD. As a result, the OS analysis summarized in Table 3.9 may be impacted by the cross-over. Some methods have been proposed for correcting the bias introduced by cross-over. One method is 'as

treated' or 'on-treatment' analysis (Fox R. et. al 2011). The 'on treatment' method is to censor the patients when they stop receiving their randomized treatment. Table 3.10 summaries the 'on-treatment' analysis conducted by this reviewer.

Table 3.10 Reviewer's Overall Survival Sensitivity Analysis

	Lenvatinib n=261	Placebo n=131
Number of Event (%)	71	10
Number of Censored (%)	190 (72.80)	120 (92.37)
Median OS in Months (95% CI)	NA(22.05, NA)	NA (20.27, NA)
Hazard ratio[b] (95%CI)	1.64 (0.83, 3.26)	
p-value (stratified log-rank)	0.1483	

[a]NA=Not Available due to only small number of events occurred; [b] a hazard ratio of less than 1 indicates that the treatment with lenvatinib is associated with lower risk of death compared to placebo treatment. [c] Stratified by region, age, and prior VEGF/VEGF-targeted therapy.

Although it is not statistically significant, the result of OS analysis in Table 3.10 shows opposite direction of the OS result shown in Table 3.9. Censoring patients at the time when they stop receiving their randomized treatment results in informative censoring. Also, the estimates are not reliable due to more than 90% of censoring. Therefore the ''on-treatment' analysis' approach is not appropriate for this situation.

11. *Another method has been proposed for correcting the bias introduced by cross-over is rank preserving structural failure time (RPSFT) model (Robins and Tsiatis, 1991). Under certain assumptions, RPSFT model can be used to identify what survival difference that would have been observed had all patients remained on the original assigned treatment (Fox R. et. al 2011). Table 3.11 summarizes the applicant's OS analysis using RPSFT model.*

Table 3.11 Applicant's Overall Survival Analysis (using RPSFT Model)

	Lenvatinib n=261	Placebo n=131
Number of Event (%)	71(27.2)	47 (35.9)
Number of Censored (%)	190 (72.8)	84 (64.1)
Median OS in Months (95% CI)	NA (22.0, NA)	NA (14.3, NA)
Hazard ratio** (95%CI)	0.62 (0.40, 1.00)	
p-value	0.0510	

*[Source: Clinical Study Report Table 23] *NA=Not Available due to only small number of events occurred. ** a hazard ratio of less than 1 indicates that the treatment with lenvatinib is associated with lower risk of death compared to placebo treatment.*

As shown in Table 3.11, the result of OS analysis using RPSFT model seems to show a trend that lenvatinib decreases the risk of death compared to placebo. However, there is limitation when applying RPSFT model, one has to verify that one of the key assumptions of RPSFT model "common treatment effect" is satisfied. It means that the treatment effect for the patient is the same regardless of when the patient started taking the study drug. To verify this key assumption, this reviewer conducted an OS analysis for two groups of patients who received lenvatinib from cross-over or from randomization. It appears that major baseline characteristics between two groups of patients who received lenvatinib from the time of

cross-over or from randomization are similar (see Table 3.12). As shown in Table 3.13 and Figure 3.4, the OS treatment effect from lenvatinib for patients treated from randomization is not the same for patients treated from the date of crossover. Therefore, the key assumption for OS analysis using RPSFT model is not valid for the patients in study SELECT.

Table 3.12 Major Baseline Characteristics Between two Groups of Patients Who Received Lenvatinib from the Time of Cross-over or from Randomization

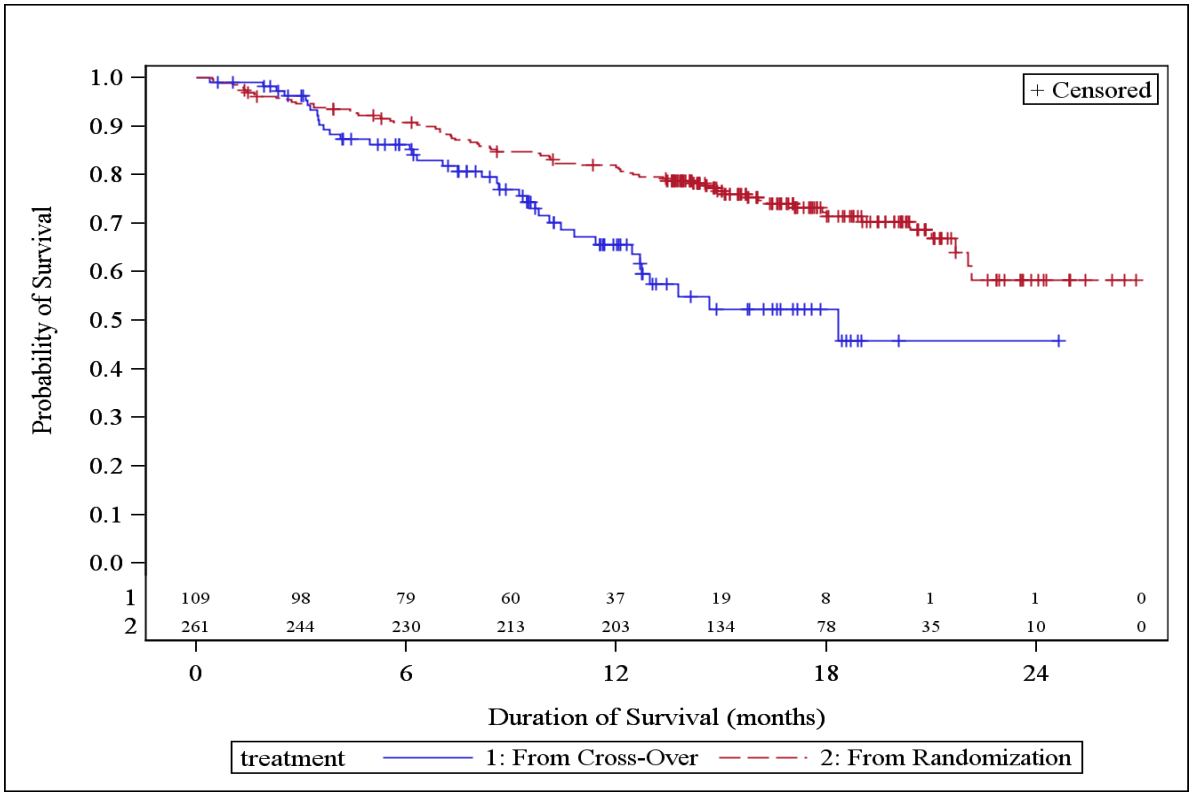
	From Randomization (n=261)	From Crossover (n=109)
Age		
<=65	155 (59.4)	69 (63.3)
>65	106 (40.6)	40 (36.7)
Sex		
Female	136 (52.1)	43 (39.5)
Male	125 (47.9)	66 (60.6)
Prior VEGF/VEGFR-targeted therapy		
No	196 (75.1)	80 (73.4)
Yes	65 (24.9)	29 (26.6)
Region		
Europe	131 (50.2)	52 (47.7)
North America	77 (29.5)	31 (28.4)
Other	53 (20.3)	26 (23.9)
Baseline ECOG Status		
0	144 (55.2)	57 (52.3)
1	104 (39.9)	51 (46.8)
2	12 (4.6)	1 (0.9)

Table 3.13 Reviewer's OS Analysis for two Groups of Patients Who Received Lenvatinib from the Time of Cross-over or from Randomization

	From Randomization (n=261)	From Cross-over (n=109)
Number of Event (%)	71 (27.2)	37 (33.9)
Number of Censored (%)	190 (72.8)	72 (66.1)
Median OS in months (95% CI)	NA (22.0, NA)	18.3 (12.7, NA)
Nominal p-value (log-rank)	0.0005	

Please note that the analysis shown in Table 3.13 is considered as exploratory and the p-value shown in Table 3.13 is not interpretable due to lack of randomization between the two groups.

Figure 3.4 Kaplan-Meier curves of Overall Survival for two Groups of Patients Who Received Lenvatinib Either from the Time of Cross-Over or from Randomization



12 *For an OS analysis, the situation when 83% of placebo patients crossed over the treatment after they had disease progression results in a challenge to estimate the true OS treatment effect. It will be very helpful if the true effect of active treatment on overall survival can be estimated. Since there are 22 placebo patients who never crossed over to receive lenvatinib, one approach is to estimate the treatment effect on OS based on the data from these 22 placebo treated patients. Table 3.14 summarizes some baseline characteristics between 22 patients who never crossed over and 109 patients who crossed-over to receive lenvatinib in placebo arm.*

Table 3.14 Some Baseline Characteristics between Two Placebo Patient Groups

	Never Cross-over (n=22)	Crossover (n=109)
Age		
<=65	12 (54.6)	65 (59.6)
>65	10 (45.5)	44 (40.4)
Prior VEGF/VEGFR-targeted therapy		
No	20 (90.9)	80 (73.4)
Yes	2 (9.1)	29 (26.6)
Region		
Europe	12 (54.6)	52 (47.7)
North America	8 (36.4)	31 (28.4)
Other	2	26 (23.9)
Baseline ECOG Status		
0	11 (50.0)	57 (52.3)
1	10 (45.5)	51 (46.8)
2	1 (4.6)	1 (0.9)

As shown in Table 3.14, some baseline characteristics between the two placebo groups are similar. This reviewer performed one exploratory analysis based on simulation. In the simulation analysis, the survival time for the 109 cross-over placebo patients was randomly generated from the survival distribution derived from the 22 placebo patients who never crossed over to receive lenvatinib, assuming that the survival distributions are the same between these 2 groups of placebo patients. In the simulation analysis, the survival time was assumed to follow an exponential distribution and estimated using the Kaplan-Merier method. The analysis was performed based on 10,000 simulation runs to estimate the hazard ratio (HR). The nominal p-value and the 95% CI was calculated based a t-distribution derived from the estimates of the log(HR) and their standard deviation (Robin 1987). Table 3.15 summarizes the reviewer's simulation analysis.

Table 3.15 Reviewer's Overall Survival Exploratory Simulation Analysis

Analysis	p-value	HR (95%CI)
Based on 22 placebo patients who did not cross over*	0.0616	0.646 (0.408, 1.021)

**The estimated hazard was 0.02658.*

13. *Please note that all OS analyses except the primary analysis shown in Table 3.9 should be considered exploratory because the underlying assumptions used in these analyses are difficult to be verified.*

3.3 Evaluation of Safety

Please refer to Dr. Abhilasha Nair's clinical review for safety evaluation of lenvatinib.

3.4 Benefit-Risk Assessment

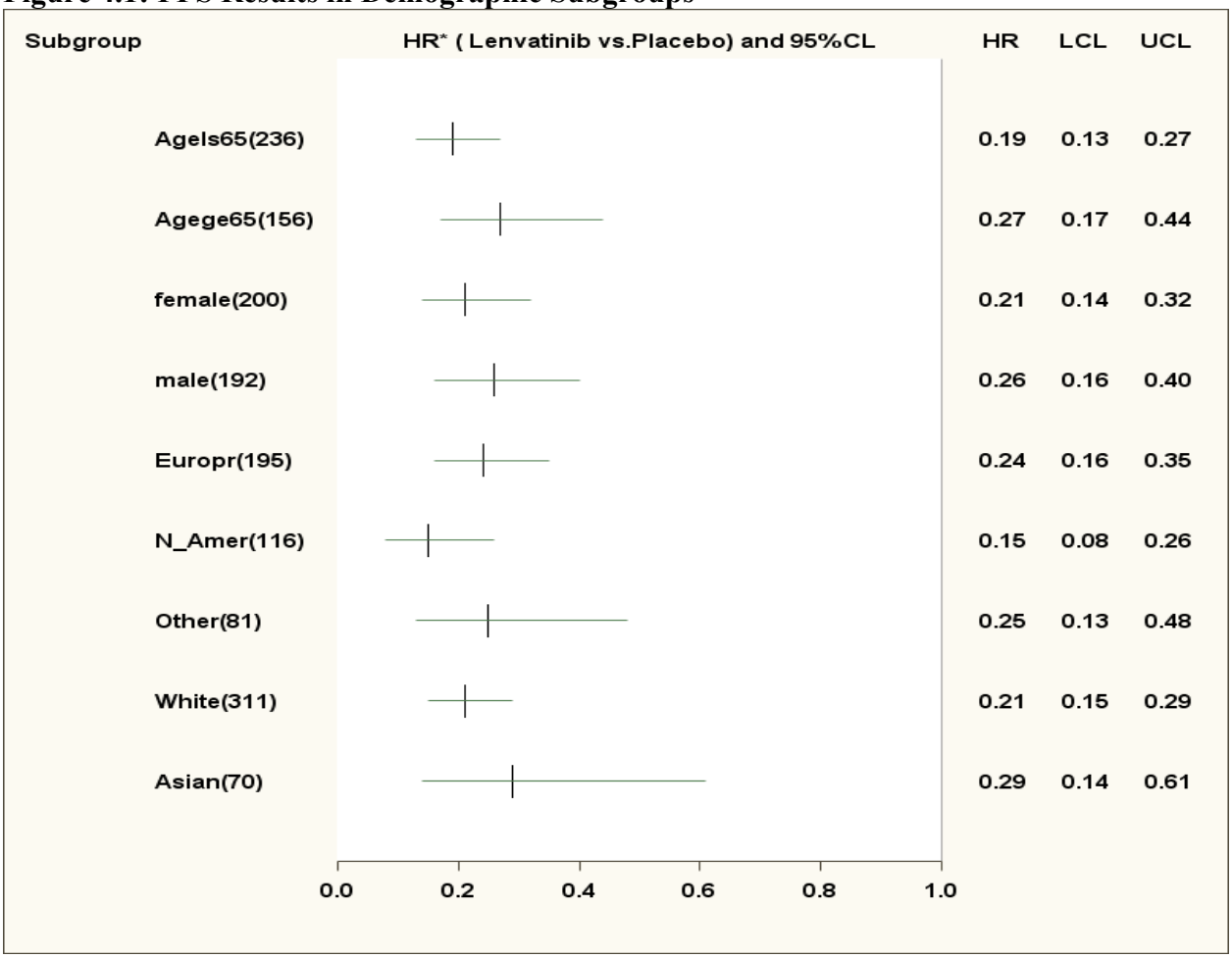
For the patients with 131^{I}-refractory differentiated thyroid cancer (RR-DTC) and radiographic evidence of disease progression within the prior 12 months, the results of PFS and ORR from study SELECT show that treatment with lenvatinib statistically improves PFS and ORR significantly compared to treatment with placebo. Whether the results from SELECT provide a favorable benefit to risk ratio to support an approval of lenvatinib for the proposed indication will be deferred to the clinical review team.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Age, Race, and Geographic Region

This reviewer conducted PFS analyses in the subgroups defined by age, gender, race, and geographic region. Figure 4.1 displays the forest plot of PFS analyses in the demographic subgroups.

Figure 4.1: PFS Results in Demographic Subgroups



**a hazard ratio of less than 1 indicates that the treatment with lenvatinib is associated with lower risk of progression or death compared to the placebo treatment.*

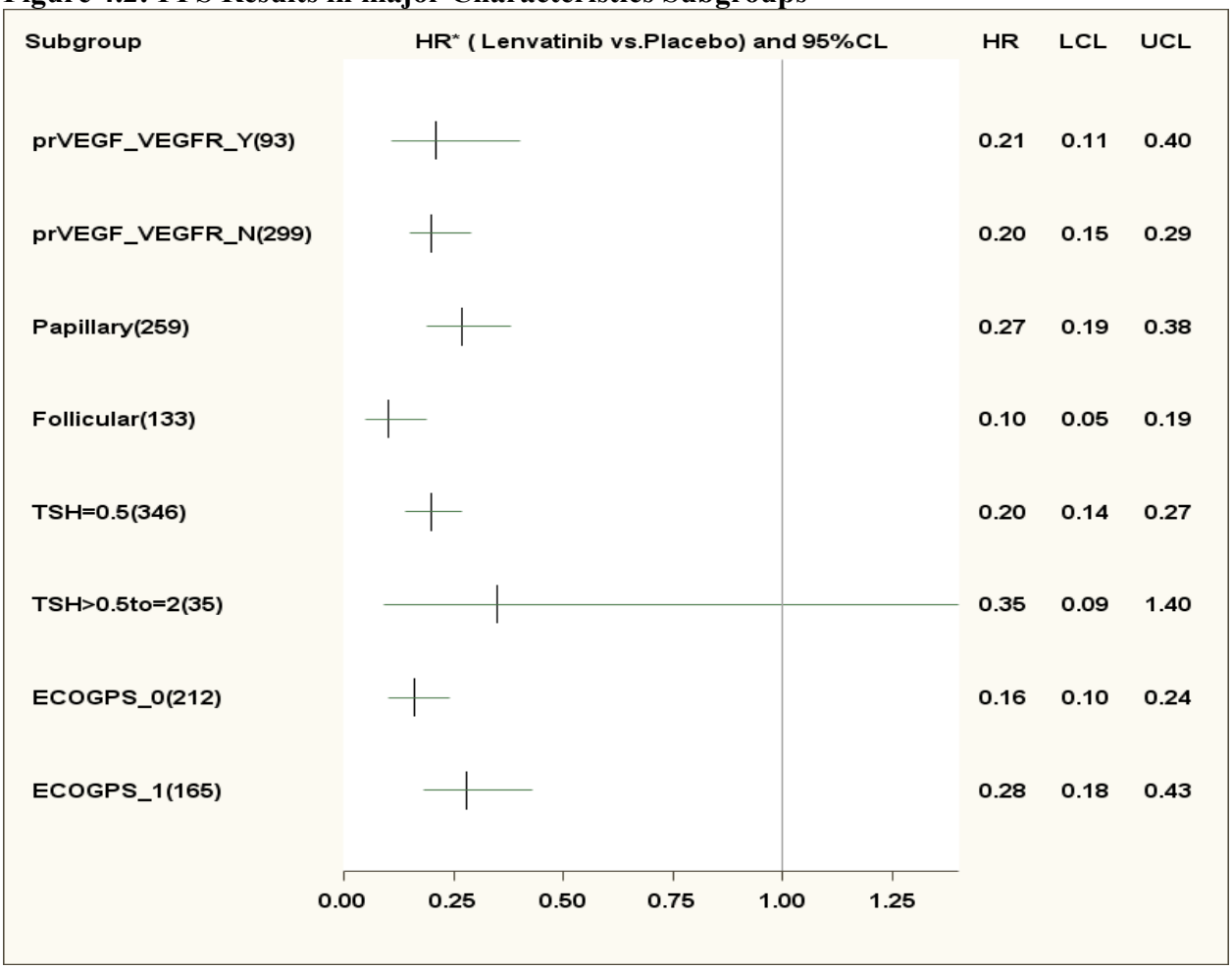
Reviewer's Comments:

14. The subgroup analyses results are considered exploratory. The subgroup analyses results appear to be consistent with the results from overall population.

4.2 Statistical Issues Other Special/Subgroup Population

This reviewer conducted the PFS analyses in subgroups defined by major baseline disease characteristics. Figure 4.2 displays the forest plot of the PFS analyses in the major characteristic subgroups.

Figure 4.2: PFS Results in major Characteristics Subgroups



**a hazard ratio of less than 1 indicates that the treatment with lenvatinib is associated with lower risk of progression or death compared to the placebo treatment.*

Abbreviations: prVEGF_VEGFR_Y/N= subgroup of patients who had/had no prior VEGF/VEGFR-targeted therapy ECOGPS_0/1= subgroup of patients whose Eastern Cooperative Oncology Group performance status=0/1; Papillary/ Fllclr = subgroup of patients whose histology subtype was Papillary/ Follicular; TSH=0.5/>0.5 to =2 = subgroup of patients who had TSH>0.5 to =2;

Reviewer's Comments:

15. The results of the major characteristic subgroup analyses are considered exploratory. The subgroup analyses results appear to be consistent with the results from overall population.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

This reviewer found no major statistical issue that impacted the primary analysis. However, it is noted that the study which allows patients to cross over after PD may impose a challenge to estimate true OS treatment effect.

5.2 Collective Evidence

Based on the data from the study SELECT, the primary analysis result of PFS demonstrated that patients with 131^{I}-refractory differentiated thyroid cancer (RR-DTC) and radiographic evidence of disease progression within the prior 12 months had statistically significant improvement in PFS when treated with lenvatinib compared to those treated with the placebo (stratified log-rank p-value <0.0001). The estimated median PFS was 18.3 months (95% CI: 15.1, NA (not yet reached at the time of analysis)) for lenvatinib arm and 3.6 months (95% CI: 2.2, 3.7) for the placebo arm. The hazards ratio of PFS was 0.21 (95% CI: 0.16, 0.28) in favor of the treatment with lenvatinib. The result of secondary endpoint ORR showed that there was statistically significantly higher objective response rate for patients treated with lenvatinib compared to patients treated with placebo. Given that 83% of patient in placebo arm crossed over to lenvatinib arm after confirmed PD, the OS analysis (according to ITT principle) result failed to show that there was statistically significant improvement between the two the treatment arms (stratified log-rank p-value=0.1032) with hazards ratio of 0.73 (95% CI: 0.50, 1.07).

5.3 Conclusions and Recommendations

This reviewer concludes that patients treated with lenvatinib have statistically significant improvement in progression free survival and objective response rate compared to the patients treated with placebo. The result of overall survival shows that there is no statistically significant difference between the two treatment arms. The OS analysis suggests that there is a trend favoring lenvatinib. Whether the results from SELECT provide a favorable benefit to risk ratio to support an approval of lenvatinib for the proposed indication will be determined by the clinical review team.

5.4 Labeling Recommendations

This reviewer recommends use the primary analyses results of PFS, ORR and OS that were specified in the protocol and statistical analysis plan in the label of lenvatinib.

REFERENCES

1. Robins JM, Tsiatis AA. Correcting for non-compliance in randomized trials using rank preserving structural failure time models. Commun Stat Theory Methods. 1991; 20(8): 2609-31.
2. Fox R, Lucinda B, Abrams K: Evaluation of methods to adjust for treatment switching in clinical trials. Trials 2011, 12 (Suppl 1): A139
3. Rubin, D.B. (1987), Multiple Imputation for Nonresponse in Surveys, New York: John Wiley & Sons, Inc.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

XIAOPING JIANG
01/14/2015

KUN HE
01/14/2015

RAJESHWARI SRIDHARA
01/14/2015

STATISTICS FILING CHECKLIST FOR NDA206947

NDA Number: 206947 **Applicant: Eisai Inc.** **Stamp Date: August 14, 2014**

Drug Name: Lenvatinib **NDA Type: Type 1- New Molecular Entity**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	×			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	×			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	×			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	×			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	×			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	×			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			×	
Appropriate references for novel statistical methodology (if present) are included.			×	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	×			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	×			

File name: Statistics Filing Checklist for NDA206947

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/s/

XIAOPING JIANG
09/16/2014

KUN HE
09/16/2014