PCN197

Estimation of the Population of Patients with RET-Altered Tumors in the United States

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BACKGROUND

- The REarranged during Transfection (RET) is an activating oncogenic driver in various tumor types.
- The oncogenic activation of RET can occur by one of the two major known alteration mechanisms: point mutations and fusions[1,2]
- The most common tumor types with RET alterations include[2]
  - medullary thyroid cancer (RET mutations)
  - other thyroid cancer (RET fusions)
  - non-small cell lung cancer (RET fusions)
- Selpercatinib is an oral agent that targets the RET proto-oncogene and other kinases that is currently being studied in patients diagnosed with RET-altered advanced solid tumors and other tumors with RET activation[3,4]
  - List of the ongoing clinical trials: LIBRETTO-001 (NCT03157128), LIBRETTO-321 (NCT04280081), LIBRETTO-431 (NCT04194944), LIBRETTO-531 (NCT04211337), and LIBRETTO-121 (NCT03899792)

Objective

- To estimate the annual population of patients with non-small cell lung cancer, medullary thyroid cancer, and other thyroid cancer potentially eligible for RET-targeted therapy in the United States (US)

METHODS

Cancer Incidence and Disease Progression

- Surveillance, Epidemiology, and End Results (SEER) registry data from 2012-2016 were used to estimate the annual rates of tumor- and histology-specific incidence per 100,000 US population including males and females of all ages and races/ethnicities
- The weighted average of the age-specific rates in individuals aged ≥ 65 years from SEER was used to estimate the annual incidence rates for the Medicare population
- The rates of tumor-specific advanced stage at diagnosis were estimated from SEER statistics (2009-15 for NSCLC & other TC; 2003-12 for MTC), while the rates of tumor-specific disease progression were estimated through review of literature
- The rates referenced above were used as point estimates for a budgetary impact analysis (BIA). Point estimate variable uncertainty was handled via one-way sensitivity analyses in subsequent BIA

Prevalence of RET Alterations by Tumor Type

- The literature was reviewed to estimate the prevalence of RET alterations across tumor types included in this study

Key Assumptions

- Tumor genetic profile testing was assumed to have been done on all patients
- Patients who received radioactive iodine (RAI) therapy were assumed to receive only one round of RAI prior to becoming eligible for RET-targeted therapy upon progression

Population Estimation

- For each tumor type, the potential number of patients eligible for RET-targeted therapy was estimated per 1,000,000 persons per year
  - Estimates were also calculated for patients ≥ 65 years of age (e.g. Medicare population)
- Calculations and chart creation was performed using MS Excel® and were validated by multiple independent reviewers

RESULTS

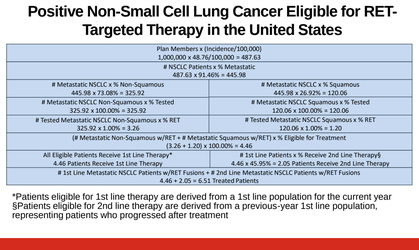
Non-small Cell Lung Cancer (NSCLC)

- The annual incidence of NSCLC was estimated at 48.8 per 100,000 persons in the US[5,6]
- Calculations are provided in Figure 1 (all ages) and Figure 2 (≥ 65 years)
- Among 1 million persons of all ages, it was estimated that 6.5 patients with RET fusion-positive metastatic NSCLC will be eligible to receive RET-targeted therapy in the first-line or second-line settings combined (Table 1)
- Among 1 million persons of age ≥ 65 years, it was estimated that 38.2 patients with RET fusion-positive NSCLC will be eligible for receiving RET-targeted therapy in either the first-line or second-line setting combined (Table 2)

Table 1. All Ages: Estimation of Number of Patients with RET Fusion-Positive Non-Small Cell Lung Cancer Eligible for RET-Targeted Therapy in the United States

Patient Population	Value	Reference
Plan Members	1,000,000	Assumption
Annual Incidence Rate of NSCLC per 100,000	48.7627	SEER Incidence (NSCLC)[5]
% Metastatic Disease	91.46%	SEER Stage Distribution (NSCLC)[6], NSCLC Meta-analyses Collaborative Group[8]
% of NSCLC Patients that are Non-Squamous	73.08%	SEER Data by Histology (NSCLC)[7]
% Patients Tested	100%	Assumption
% of NSCLC Patients with RET Fusions	1.0%	Kato et al., 2017[2]
% of Patients Eligible for Treatment	100.0%	Assumption
# 1st Line Metastatic NSCLC Patients w/RET Fusions	4.46	Calculated Value
Proportion of 1L Patients who Receive 2nd Line Therapy	45.95%	Simeone et al., 2019[9]
# 2nd Line Metastatic NSCLC Patients w/RET Fusions	2.05	Calculated Value
Total # Metastatic NSCLC Patients w/RET Fusions (1L + 2L)	6.51	Calculated Value

Figure 1. All Ages: Patient Flow and Calculations for the Estimation of Number of Patients with RET Fusion-Positive Non-Small Cell Lung Cancer Eligible for RET-Targeted Therapy in the United States

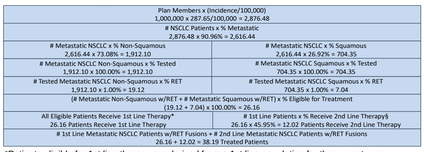


*Patients eligible for 1st line therapy are derived from a 1st line population for the current year
§Patients eligible for 2nd line therapy are derived from a previous-year 1st line population, representing patients who progressed after treatment

Table 2. Age ≥65 Years: Estimation of Number of Patients with RET Fusion-Positive Non-Small Cell Lung Cancer Eligible for RET-Targeted Therapy in the United States

Patient Population	Value	Reference
Plan Members	1,000,000	Assumption
Annual Incidence Rate of NSCLC per 100,000	287.6478	SEER Incidence (NSCLC)[5]
% Metastatic Disease	90.96%	SEER Stage Distribution (NSCLC)[6], NSCLC Meta-analyses Collaborative Group[8]
% of NSCLC Patients that are Non-Squamous	73.08%	SEER Data by Histology (NSCLC)[7]
% Patients Tested	100%	Assumption
% of NSCLC Patients with RET Fusions	1.0%	Kato et al., 2017[2]
% of Patients Eligible for Treatment	100.0%	Assumption
# 1st Line Metastatic NSCLC Patients w/RET Fusions	26.16	Calculated Value
Proportion of 1L Patients who Receive 2nd Line Therapy	45.95%	Simeone et al., 2019[9]
# 2nd Line Metastatic NSCLC Patients w/RET Fusions	12.02	Calculated Value
Total # Metastatic NSCLC Patients w/RET Fusions (1L + 2L)	38.19	Calculated Value

Figure 2. Age ≥65 Years: Patient Flow and Calculations for the Estimation of Number of Patients with RET Fusion-positive Non-Small Cell Lung Cancer Eligible for RET-Targeted Therapy in the United States



*Patients eligible for 1st line therapy are derived from a 1st line population for the current year
§Patients eligible for 2nd line therapy are derived from a previous-year 1st line population, representing patients who progressed after treatment

Medullary Thyroid Cancer (MTC)

- The annual incidence of thyroid cancer was estimated at 15.8 per 100,000 persons in the US, of which approximately 1.6% have medullary thyroid cancer[10,11]
- Calculations are provided in Figure 3 (all ages) and Figure 4 (≥ 65 years)
- Among 1 million persons of all ages, it was estimated that ~1 patient with RET mutation-positive MTC will be eligible to receive RET-targeted therapy (Table 3)
- Among 1 million persons of age ≥ 65 years, it was estimated that ~1.3 patients with RET mutation-positive MTC will be eligible for receiving RET-targeted therapy (Table 4)

Table 3. All Ages: Estimation of Number of Patients with RET-Mutant Medullary Thyroid Cancer Eligible for RET-Targeted Therapy in the United States

Patient Population	Value	Reference
Commercial Plan Members	1,000,000	Assumption
Annual Incidence Rate of Thyroid Cancer per 100,000	15.7606	SEER Incidence (TC)[10]
% of Thyroid Cancer Patients that are MTC	1.55%	SEER Data by Histology (TC)[11]
% Advanced/Metastatic Disease	57.20%	Randle et al., 2017[12] & Sippel et al., 2008[13]
% MTC Patients - Sporadic	75.00%	Wells et al., 2013[14]
% MTC Patients - Hereditary	25.00%	Wells et al., 2013[14] (1 – 0.75) = 0.25
% MTC Patients Tested	100.00%	Assumption
Sporadic MTC Patients*		
# Tested Advanced Sporadic MTC	1.05	Calculated Value
% Sporadic MTC Patients with RET Mutations	50.00%	Wells et al., 2015[15]
# Tested Advanced Sporadic MTC Patients with RET Mutations	0.52	Calculated Value
Hereditary MTC Patients*		
# Tested Advanced Hereditary MTC	0.35	Calculated Value
% Hereditary MTC Patients w/RET Mutations	95.00%	Wells et al., 2015[15]
# Tested Advanced Hereditary MTC Patients with RET Mutations	0.33	Calculated Value
Advanced MTC Patients w/RET Mutations		
Total # of Advanced Sporadic + Hereditary MTC w/RET Mutations	0.86	Calculated Value

*The sporadic and hereditary MTC patients are discrete patient populations. Refer to funnel on the next slide to see derivation of the total # of patients with advanced MTC w/RET mutations who are eligible for treatment.

Figure 3. All Ages: Patient Flow and Calculations for the Estimation of Number of Patients with RET-Mutant Medullary Thyroid Cancer Eligible for RET-Targeted Therapy in the United States

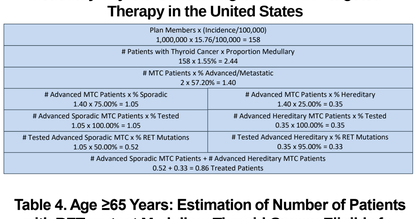
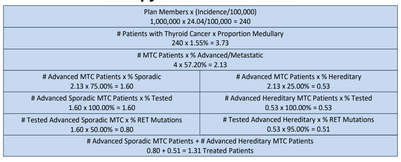


Table 4. Age ≥65 Years: Estimation of Number of Patients with RET-mutant Medullary Thyroid Cancer Eligible for RET-targeted Therapy in the United States

Patient Population	Value	Reference
Plan Members	1,000,000	Assumption
Annual Incidence Rate of Thyroid Cancer per 100,000	24.0391	SEER Incidence (TC)[10]
% of Thyroid Cancer Patients that are MTC	1.55%	SEER Data by Histology (TC)[11]
% Advanced/Metastatic Disease	57.20%	Randle et al., 2017[12] & Sippel et al., 2008[13]
% MTC Patients - Sporadic	75.00%	Wells et al., 2013[14]
% MTC Patients - Hereditary	25.00%	Wells et al., 2013[14] (1 – 0.75) = 0.25
% MTC Patients Tested	100.00%	Assumption
Sporadic MTC Patients*		
# Tested Advanced Sporadic MTC	1.60	Calculated Value
% Sporadic MTC Patients with RET Mutations	50.00%	Wells et al., 2015[15]
# Tested Advanced Sporadic MTC Patients with RET Mutations	0.80	Calculated Value
Hereditary MTC Patients*		
# Tested Advanced Hereditary MTC	0.53	Calculated Value
% Hereditary MTC Patients w/RET Mutations	95.00%	Wells et al., 2015[15]
# Tested Advanced Hereditary MTC Patients with RET Mutations	0.51	Calculated Value
Advanced MTC Patients w/RET Mutations		
Total # of Advanced Sporadic + Hereditary MTC w/RET Mutations	1.31	Calculated Value

*The sporadic and hereditary MTC patients are discrete patient populations. Refer to funnel on the next slide to see derivation of the total # of patients with advanced MTC w/RET mutations who are eligible for treatment.

Figure 4. Age ≥65 Years: Patient Flow and Calculations for the Estimation of Number of Patients with RET-Mutant Medullary Thyroid Cancer Eligible for RET-Targeted Therapy in the United States



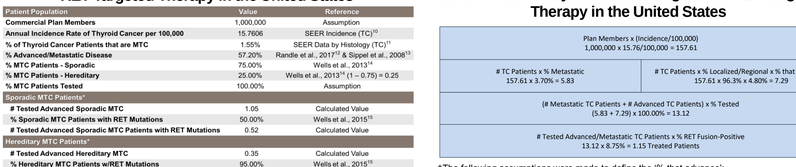
Other Thyroid Cancer (TC)

- The annual incidence of thyroid cancer was estimated at 15.8 per 100,000 persons in the US[10]
- Calculations are provided in Figure 5 (all ages) and Figure 6 (≥ 65 years)
- Among 1 million persons of all ages, it was estimated that 1.15 patients with RET fusion-positive TC will be eligible to receive RET-targeted therapy (Table 5)
- Among 1 million persons of age ≥ 65 years, it was estimated that 3 patients with RET fusion-positive TC will be eligible for receiving RET-targeted therapy (Table 6)

Table 5. All Ages: Estimation of Number of Patients with RET Fusion-Positive Thyroid Cancer Eligible for RET-Targeted Therapy in the United States

Patient Population	Value	Reference
Plan Members	1,000,000	Assumption
Annual Incidence Rate of Thyroid Cancer (TC) per 100,000	15.7606	SEER Incidence (TC)[10]
% Metastatic	3.7%	SEER Incidence (TC)[10]
% Localized/Regional Disease (not Metastatic)	96.3%	1 - % Metastatic = 1 – 0.037
% Localized/Regional Patients that Advance	4.8%	Tsang et al., 1998[16]
% Advanced/Metastatic Patients Tested	100.0%	Assumption
% RET Fusion-Positive TC	8.75%	Weighted – Agrawal et al., 2014[17], Guerra et al., 2000[18] & Adeniran et al., 2000[19]
# Advanced/Metastatic RET Fusion-Positive TC Patients	1.15	Calculated value

Figure 5. All Ages: Patient Flow and Calculations for the Estimation of Number of Patients with RET Fusion-Positive Thyroid Cancer Eligible for RET-Targeted Therapy in the United States

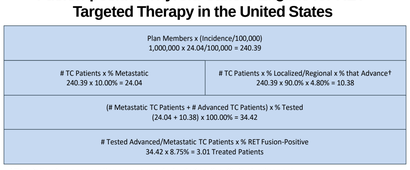


†The following assumptions were made to define the '% that advance':
Patients with surgery who progress will receive radioactive iodine (RAI) treatment; Patients will be eligible for systemic therapy after one round of RAI

Table 6. Age ≥65 Years: Estimation of Number of Patients with RET Fusion-Positive Thyroid Cancer Eligible for RET-Targeted Therapy in the United States

Patient Population	Value	Reference
Plan Members	1,000,000	Assumption
Annual Incidence Rate of Thyroid Cancer (TC) per 100,000	24.0391	SEER Incidence (TC)[10]
% Metastatic	10.0%	SEER Incidence (TC)[10]
% Localized/Regional Disease (not Metastatic)	90.0%	1 - % Metastatic = 1 – 0.10
% Localized/Regional Patients that Advance	4.8%	Tsang et al., 1998[16]
% Advanced/Metastatic Patients Tested	100.0%	Assumption
% RET Fusion-Positive TC	8.75%	Weighted – Agrawal et al., 2014[17], Guerra et al., 2000[18] & Adeniran et al., 2000[19]
# Advanced/Metastatic RET Fusion-Positive TC Patients	3.01	Calculated value

Figure 6. Age ≥65 Years: Patient Flow and Calculations for the Estimation of Number of Patients with RET Fusion-positive Thyroid Cancer Eligible for RET-Targeted Therapy in the United States



*†The following assumptions were made to define the '% that advance':
Patients with surgery who progress will receive radioactive iodine (RAI) treatment; Patients will be eligible for systemic therapy after one round of RAI

Limitations

- The estimated numbers of patient population presented in this study are limited to the US
- The estimates presented in this study are based on currently available literature, however, the actual number of patients eligible for RET-targeted therapy may vary along with improvements in estimated prevalence of RET
- The assumption of 100% testing used in this study is an ideal best case scenario, however, not all patients currently receive genomics-based testing at diagnosis

CONCLUSION

- We estimate that in the United States a total of about 8.52 patients per million persons, or approximately 2,800 patients (assuming US population of 328 million) are eligible for RET-targeted therapy each year
- These findings provide a specific quantification of the anticipated number of patients potentially eligible for treatment with novel agents targeting RET
- The estimated number of patients in this study are small relative to the overall population of patients with NSCLC or thyroid cancer

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Virtual ISPOR 2020
May 18 – 20, 2020

Sponsored by Eli Lilly and Company