# Lenvatinib (Lenvima™)

## Abbreviated National Drug Monograph

## May 2015

**VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives**

*The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.*

## FDA Approval Information

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| **Description/Mechanism of Action** | Lenvatinib is an oral tyrosine kinase inhibitor that targets multiple signaling networks, such as vascular endothelial growth factor receptor (VEGFRs 1, 2 and 3), fibroblast growth factor receptor (FGFRs 1-4), platelet-derived growth factor receptor (PDGFRα), RET and KIT. |
| **Indication(s) Under Review** | Treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer |
| **Dosage Form(s) Under Review** | Capsules: 4 mg and 10 mg |
| **REMS** | ☐ REMS ☒ No REMS |
| **Pregnancy Rating** | Embryo-fetal toxic in the animal model; Expected to cause fetal harm when given to a pregnant woman. |

## Executive Summary

**Efficacy**

- FDA Priority Review was based upon a phase 3, randomized, double-blind, placebo-controlled multicenter trial of 392 patients from 21 countries. Patients had radioiodine-refractory differentiated thyroid cancer and may have received therapy with one prior tyrosine kinase inhibitor.
- The primary endpoint, Progression-Free Survival (PFS), was greater in the lenvatinib-treated arm compared to the placebo arm. This benefit was noted in all prespecified subgroups.
- Overall survival was not different between groups, although this endpoint may have been confounded by the crossover of placebo-treated patients with progressive disease.
- Quality of life was not evaluated in this trial.

**Safety**

- Numerous adverse effects will require diligence in patient education, monitoring, dose-adjustment and adherence.
- Dose-reductions were made in a significant portion of study patients, therefore would expect reductions will be necessary among the Veteran population.
- Impact of therapy on quality of life has not been assessed in a trial population.

**Other Considerations**

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| **Outcome in clinically significant area** | PFS 18.3 vs. 3.6 mos (lenvatinib vs. placebo); median OS not different (crossover) |
| **Effect Size** | PFS HR 0.21[99% CI: 0.14-0.31; p<0.001]<br>OS unadjusted HR 0.73 [95% CI 0.5-1.07; p=0.10]<br>OS adjusted HR 0.62 [95% CI 0.4-1.0; p=0.05] |
| **Potential Harms** | ≥ Gr 3: HTN (44%) |
| **Net Clinical Benefit** | Negative<br>(low chance of benefit; high risk of harm) |

**Potential Impact**

- Place in Therapy. Patients responded to lenvatinib despite prior TKI therapy,

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| | therefore, could consider a role for lenvatinib after prior TKI therapy.<br>• Patient convenience. Blister-packaging may ease concern about taking the proper combination of dosage strengths.<br>• Dispensing a full 30-day supply may result in excess drug waste if daily dose needs to be modified. |

## Background

**Purpose for review**

Recent FDA Approval

**Issues to be determined:**
Does lenvatinib offer advantages to currently available alternatives?
What safety issues need to be considered?

**Other therapeutic options**

| Formulary Alternatives | Other Considerations |
|---|---|
| doxorubicin | Only FDA-approved cytotoxic agent;<br>ORR 25% (all PR) as monotherapy; transient effect; no OS benefit; very limited role<br>Intravenous therapy |
| **Non-formulary Alternative (if applicable)** | **Other Considerations** |
| Sorafenib | FDA-approved for differentiated thyroid cancer;<br>P3, PR 12%, PFS 11 mos (n=417); OS no diff<br>Oral agent |
| Cabozantinib | FDA-approved for medullary thyroid cancer;<br>DTC data: P1, PR 53% (n=15);<br>Oral agent |
| Sunitinib | FDA-approved for RCC, PNET, GIST;<br>DTC data: P2, PR 28%, SD 46%; TTP 13 mos (n=28);<br>Oral agent |
| Pazopanib | FDA-approved for RCC, soft tissue sarcoma;<br>DTC data: P2, PR 49% (n=39);<br>Oral agent |
| Vandetanib | FDA-approved for medullary thyroid cancer;<br>DTC data: P2, PFS 11 mos (n=145);<br>Oral agent |

## Efficacy (FDA Approved Indications)

### Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to April 2015) using the search terms lenvatinib and Lenvima. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

### Review of Efficacy

Lenvatinib vs. Placebo in Radioiodine-Refractory Thyroid Cancer

| Study design | Inclusion/Demographics | Intervention | Outcomes |
|---|---|---|---|
| SELECT[2]<br>P3, R, DB, PC, MC<br>N=392 (L 261; P 131)<br>21 countries<br>Americas, Europe, Asia, Australia | Inclusion Criterion:<br>Adult patients; measurable disease based on RECIST 1.1, path confirmed DTC, iodine-131-refractory/resistant; PD in previous 13 months; one prior VEGF/VEGFR-targeted agent permitted; clinically stable brain metastases without need for steroids eligible; currently receiving thyroxine suppression therapy; TSH ≤ 0.5 mCi/mL; ECOG PS 0-2; BP ≤ 150/90 mmHg; CrCl ≥ 30 ml/min; ANC ≥ 1500/mm$^3$; platelets ≥ 100,000/mm$^3$; hemoglobin ≥ 9 g/dL; INR ≤ 1.5; bilirubin ≤ 1.5x ULN (except for unconjugated hyperbilirubinemia or Gilbert's syndrome); Alk phos, ALT, AST ≤ 3x ULN (or ≤ 5x ULN if liver mets);<br><br>Exclusion criterion:<br>Urine protein ≥ 1 g/24 hrs; GI malabsorption; CHF (greater than NYHA Class II), unstable angina, MI or CVA within 6 mos, cardiac arrhythmia requiring medical treatment; QTcF interval > 480 ms; active hemoptysis; anticoagulants (LMWH allowed); bleeding/thrombotic disorder; active infection (requiring treatment); pregnancy; breastfeeding | Lenvatinib (L) 24 mg PO daily vs. placebo (PBO) for 28 days<br><br>R 2:1<br>Stratified by: age, geography, prior TKI (yes/no)<br><br>At PD, PBO-treated patients could receive open-label L.<br><br>Tumor assessments every 8 weeks (random phase);<br>Every 12 weeks (extension phase) via RECIST criteria | Lenvatinib (L) 24 mg PO daily vs. placebo (PBO) for 28 days<br><br>Primary endpoint: PFS<br>Secondary: OS<br>Exploratory: DCR, CBR<br><br>Median follow-up 17.1 mos:<br>Lenvatinib vs. PBO<br>PFS 18.3 vs. 3.6 mos<br>HR 0.21 (0.14-0.31); p< 0.001<br><br>Benefit maintained in all pre-specified subgroups.<br><br>Prior TKI vs. no TKI<br>PFS 18.7 vs. 15.1 mos<br><br>RR 64.8 vs. 1.5%<br>OR 28.87(12.46-66.86); p<0.001<br>Median time to OR ~ 2 mos<br>OS no significant difference<br>HR 0.73 (0.50-1.07); p=0.10<br>Median duration of tx 13.8 mos vs. 3.9 mos<br><br>Tx-related AEs (all grades)<br>97.3 vs. 59.5%<br>Tx-related AEs (≥ gr 3)<br>75.9 vs. 9.9%<br>AEs: HTN, proteinuria, ATE, VTE, ARF, hepatic failure, GI fistula<br>AEs led to DC of tx:<br>14.2 vs. 2.3%<br>AEs: asthenia, HTN<br>Dose-interruption:<br>82.4 vs. 18.3%<br>Dose-reduction<br>67.8 vs. 4.6%<br>AEs: diarrhea (23%), HTN (20%), proteinuria (19%), ↓ appetite (18%)<br>Fatal events<br>7.7 vs. 4.6%<br>2.3% Tx-related (PE, hemorrhagic stroke)<br>Mean levatinib dose 17.2 |

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| | | | mg/day |

- Lenvatinib was processed through the FDA Priority Review process.
- The FDA approval of lenvatinib was based on a phase 3, randomized, double-blind, placebo-controlled, multicenter study in patients with radioiodine-refractory DTC.
- Patients were permitted therapy with one prior TKI. Although the response was slightly higher in those who did not receive a prior TKI (median PFS 18.7 mos) vs. those who did (median PFS 15.1 mos), the differences between groups did not appear to be great.
- The median duration of follow-up was 17 months. Median PFS was greater in the lenvatinib arm (18.3 vs. 3.6 mos). Benefit was noted in all prespecified subgroups, which included age, sex, race, prior treatment with a TKI, geography, histology and baseline thyrotropin levels).
- Median time to objective response was 2 months; ORR 64.8 vs. 1.5% in lenvatinib vs. placebo groups, respectively. Overall survival difference was not significant; patients crossing over from placebo to lenvatinib may have confounded the analysis.
- Median duration of treatment was 13.8 months among lenvatinib-treated patients. Adverse events were higher in those who received lenvatinib; Grade 3 or greater events were also higher. Dose interruptions (82 vs. 18%) and dose reductions (68 vs. 5%) were higher in the lenvatinib arm. Discontinuation due to adverse events was 14.2%. Patients received a mean daily lenvatinib dose of 17.2 mg with the first dose-reduction occurring around 3 months.
- Quality of life was not evaluated.

## Potential Off-Label Use

According to www.clinicaltrials.gov website, lenvatinib is being actively researched in the following:

- First-line treatment of unresectable hepatocellular carcinoma
- Unresectable or advanced metastatic renal cell carcinoma
- Treatment of advanced Non-Small Cell Lung Cancer
- In combination with temozolomide for metastatic melanoma

## Safety

(for more detailed information refer to the product package insert)

| | Comments |
|---|---|
| **Boxed Warning** | • None |
| **Contraindications** | • None |
| **Warnings/Precautions** | • **Hypertension** (HTN). HTN reported in 73% of lenvatinib vs. 16% of placebo-treated patients; median time to onset was 16 days; Grade 3 HTN in 44 vs. 4%; Grade 4 HTN in <1 vs. 0% (lenvatinib vs. placebo, respectively); control blood pressure prior to starting treatment; monitor after one week, then every 2 weeks for the first 2 months, then at least monthly thereafter; withhold lenvatinib for Grade 3 HTN despite optimal antihypertensive therapy; resume at reduced dose when HTN is controlled (≤ Grade 2); discontinue for life-threatening HTN.<br>• **Cardiac Dysfunction**. Cardiac dysfunction (reduced left or right ventricular function, cardiac failure or pulmonary edema) was reported in 7 vs. 2% of lenvatinib vs. placebo-treated patients; 2 vs. 0% were ≥ grade 3 severity; reduced ejection fraction (EF) was noted in the majority of cases; severity > 20% reduction in EF noted in 2 vs. 0% of lenvatinib vs. placebo-treated patients, respectively. Monitor for signs/symptoms of cardiac decompensation. Withhold lenvatinib for development of Grade 3 cardiac dysfunction until improvement to Grade 0 or 1 or baseline. Either resume at reduced dose or discontinue lenvatinib depending on the severity and |

persistence of cardiac dysfunction. Discontinue lenvatinib for Grade 4 cardiac dysfunction.

- **Arterial Thromboembolic Events** (ATE). ATEs were reported in 5 vs. 2%; ≥ Grade 3 events in 3 vs. 1% of lenvatinib vs. placebo-treated patients, respectively; discontinue lenvatinib following ATE; safety of resuming lenvatinib after ATE has not been established; lenvatinib has not been studied in patients having an ATE within prior 6 months.
- **Hepatotoxicity**. ≥ Grade 3 ALT increases noted in 4%; and AST increases in 5% of lenvatinib-treated patients; none seen in the placebo arm. Monitor liver function before start of lenvatinib, then every 2 weeks for the first 2 months and at least monthly thereafter. Withhold lenvatinib for Grade 3 or greater liver impairment until resolved to Grade 0 to 1 or baseline. Either resume at a reduced dose or discontinue lenvatinib depending on severity and persistence of hepatotoxicity. Discontinue lenvatinib for hepatic failure.
- **Proteinuria**. Proteinuria was reported in 34 vs. 3%; greater than or equal to Grade 3 events were reported in 11 vs. 0% of lenvatinib vs. placebo-treated patients, respectively. Monitor for proteinuria before start of and periodically throughout treatment. For urine dipstick proteinuria ≥ 2+, obtain a 24-hour urine protein. Withhold lenvatinib for ≥ 2 gm proteinuria/24 hours and resume at a reduced dose when proteinuria < 2 gm/24 hours. Discontinue lenvatinib for nephrotic syndrome.
- **Renal Failure & Impairment**. Renal impairment was reported in 14 vs. 2%; ≥ Grade 3 events were 3 vs. 1% of lenvatinib vs. placebo-treated patients, respectively; the primary risk factor for severe renal impairment was dehydration/hypovolemia due to diarrhea and vomiting. Withhold lenvatinib for development of Grade 3 or 4 renal failure/impairment until resolved to Grade 0 to 1 or baseline. Either resume at a reduced dose or discontinue lenvatinib depending on the severity and persistence of renal impairment.
- **Gastrointestinal Perforation & Fistula Formation**. Events were reported in 2 vs. 0.8%, lenvatinib vs. placebo-treated patients, respectively. Discontinue lenvatinib in patients who develop gastrointestinal perforation or life-threatening fistula.
- **QT Interval Prolongation**. QT/QTc interval prolongation was reported in 9 vs. 2%; ≥ Grade 3 events reported in 2 vs. 0% of lenvatinib vs. placebo-treated patients, respectively. Monitor electrocardiograms in patients with congenital long QT syndrome, CHF, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Monitor and correct electrolyte abnormalities in all patients. Withhold lenvatinib for the development of ≥ Grade 3 QT interval prolongation. Resume lenvatinib at a reduced dose when QT prolongation resolves to Grade 0 or 1 or baseline.
- **Hypocalcemia**. Hypocalcemia ≥ Grade 3 severity was reported in 9 vs. 2% of lenvatinib vs. placebo-treated patients, respectively; in most cases, hypo-calcemia responded to replacement and dose interruption/reduction. Monitor blood calcium levels at least monthly and replace calcium as necessary during treatment. Interrupt and adjust dosing as necessary, depending on severity, presence of ECG changes, and persistence of hypocalcemia.
- **Reversible Posterior Leukoencephalopathy Syndrome** (RPLS). Across all clinical studies there were 3 reported events of RPLS in a

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| | total of 1108 patients who received lenvatinib. Confirm diagnosis with MRS. Withhold drug for RPLS until fully resolved. Upon resolution, resume at a reduced dose or discontinue lenvatinib depending on severity/persistence of neurologic symptoms.<br>• **Hemorrhage Events**. The most common hemorrhage event was epistaxis; Events occurred in 35 vs. 18% (all Grades); ≥ Grade 3 in 2 vs. 3% of lenvatinib vs. placebo-treated patients. Discontinuation due to these events was reported in 1% of patients. There was one case of fatal intracranial hemorrhage among 16 patients with CNS metastases, who received lenvatinib. Withhold lenvatinib for the development of Grade 3 hemorrhage until resolved to Grade 0 or 1. Either resume at a reduced dose or discontinue lenvatinib depending on the severity and persistence of hemorrhage. Discontinue lenvatinib in Grade 4 hemorrhage.<br>• **Impairment of Thyroid Stimulating Hormone Suppression**. Exogenous thyroid suppression is impaired with lenvatinib. Elevation of TSH level above 0.5 mU/L was noted in 57 vs. 14% of lenvatinib vs. placebo-treated patients, respectively. Monitor TSH levels monthly; adjust thyroid replacement medication as needed in patients with DTC.<br>• **Embryofetal Toxicity**. Lenvatinib can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to their fetus. Advise females of reproductive potential to use effective contraception during treatment and for at least 2 weeks following completion of therapy. |

**Safety Considerations**

- Lenvatinib is an oral formulation that is available in two dosage strengths. The capsules are supplied in cartons of 6 cards. Each card is a 5-day blister card. The drug can be purchased as a 30-day supply of the following daily strengths: 24 mg, 20 mg, 14 mg and 10 mg. The reduced doses correspond to the recommended dose modifications provided by the manufacturer. Due to the high rate of dose interruptions and reductions, with a mean daily dose of 17 mg taken by study patients, there is a potential for drug waste as patients change dosage.
- Patient education and diligent monitoring is necessary to ensure safe use.
- Careful consideration of patient history and comorbidities, particularly with regard to potential toxicities consistent with VEGF inhibition (i.e. risk of bleed, HTN, impaired wound healing).
- Fistula formation is rare but potentially life-threatening. Upper airway fistulas that develop while on antiangiogenic tyrosine kinase inhibitor therapies have been associated with prior external beam radiotherapy and large tumors invading neck structures[13].

**Adverse Reactions**

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| Common adverse reactions | Incidence ≥ 30%: HTN, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, decreased weight, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia (PPE) syndrome, abdominal pain, dysphonia |
| Death/Serious adverse reactions | Incidence ≥ 2%: pneumonia (4%), HTN (3%), dehydration (3%) |
| Discontinuations due to adverse reactions | Dose-reductions: 68 vs. 5% (lenvatinib vs. placebo, respectively)<br>Dose-reductions due to adverse reactions: HTN, proteinuria, decreased appetite, diarrhea<br>DC due to adverse reactions: 18 vs. 5% (lenvatinib vs. placebo, respectively)<br>Reactions leading to DC: HTN (1%), asthenia (1%) |

**Drug Interactions**

**Drug-Drug Interactions**

- No dose adjustment of lenvatinib is recommended for co-administration with CYP3A, P-glycoprotein and breast cancer resistance protein (BCRP) inhibitors or CYP3A4, P-glycoprotein inducers.

## Risk Evaluation

As of April, 2015

**Comments**

Sentinel event advisories

- None
- Sources: ISMP, FDA, TJC

Look-alike/sound-alike error potentials

| NME Drug Name | Lexi-Comp | First DataBank | ISMP | Clinical Judgment |
|---|---|---|---|---|
| Lenvatinib 4, 10mg cap | Cabozantinib<br>Lapatinib,<br>Vandetanib | None | None | None |
| Lenvima | Lynparza | None | None | Lentrada<br>Fetzima<br>Levimir<br>Levitra<br>Lexiva |

- Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

## Other Considerations

- FDA Medical Reviewer notes that perhaps lower doses should be evaluated for safety/efficacy.
- VA procurement of lenvatinib is through the specialty pharmacy, Biologics, Inc.
- Lenvatinib is an oral formulation that is available in two dosage strengths that are blister packed. The capsules are supplied in cartons of 6 cards. Each card is a 5-day blister card. The drug can be purchased as a 30-day supply of the following daily strengths: 24 mg, 20 mg, 14 mg and 10 mg. The reduced doses correspond to the recommended dose modifications provided by the manufacturer. Due to the rate of dose interruptions and reductions, with a mean daily dose of 17 mg taken by study patients, there is a potential for drug waste as patients change dosage.
- Updated ATA Guidelines for the Management of Thyroid Nodules and Differentiated Thyroid Cancer are still in development. A specific release/publication date is not available at this time. The 2009 Guideline note potential benefit with anti-angiogenic therapies that have numerous common side effects. Although noted that these toxicities are responsive to supportive care measures, suggest that treatment with these agents should be limited to specialists experienced in their use.
- NCCN Guidelines version 2.2014 does not include lenvatinib. Sorafenib is noted as a category 2A recommendation in iodine-refractory, recurrent, locally advanced or soft tissue/bony metastatic disease; NCCN also notes that other small molecule TKI's (axitinib, pazopanib, sunitinib, vandetinib) can be considered if clinical trials are not available or appropriate.
- NCCN also provides Principles of Kinase Inhibitor Therapy in Advanced Thyroid Cancer, which points out that several factors should be considered regarding TKI therapy:
    - Therapy is not curative, but can prolong PFS
    - Therapy can be expected to cause significant side effects that can affect quality of life
    - The natural history of DTC and MTC is variable, ranging from months to years
    - Pace of disease progression should be considered as those asymptomatic with indolent disease may not benefit; those with rapidly progressive disease may benefit despite side effect profile
    - Optimal management of kinase inhibitor side effects is essential; guidelines to address dermatologic, hypertensive and GI side effects can be used, as well as dose modification and holding therapy

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| **Outcome in clinically significant area** | PFS 18.3 vs. 3.6 mos (lenvatinib vs. placebo);<br>median OS not significant (crossover) |
| **Effect Size** | PFS HR 0.21[99% CI: 0.14-0.31; p<0.001]<br>OS unadjusted HR 0.73 [95% CI 0.5-1.07; p=0.10]<br>OS adjusted HR 0.62 [95% CI 0.4-1.0; p=0.05] |
| **Potential Harms** | ≥ Gr 3: HTN (44%) |
| **Net Clinical Benefit** | Negative<br>(low chance of benefit with high risk of harm) |

Definitions

**Outcome in clinically significant area:** morbidity, mortality, symptom relief, emotional/physical functioning, or health-related quality of life
**Effect Size:** odds ratio, relative risk, NNT, absolute risk reduction, relative risk reduction, difference in size of outcomes between groups, hazard ratio
**Potential Harms:** Low risk (Grade 3 or 4 toxicity in <20%) versus High risk (Grade 3 or 4 toxicity in ≥20%)
**Net Clinical Benefit:** Substantial (high benefit with low risk of harm), moderate (high benefit with high risk of harm), minimal (low benefit with low risk of harm), negative (low benefit with high risk of harm)

## Dosing and Administration

- The recommended dose of lenvatinib is 24 mg orally, on a once daily basis. A 24 mg dose consists of 2 x 10mg capsules and 1 x 4 mg capsule taken with or without food. Take each dose at the same time every day. If a dose is missed and cannot be taken within 12 hours, skip the dose and take the next dose at the usual time of administration. Continue therapy until disease progression or unacceptable toxicity.
- Refer to the package insert for full dosing information, with dose modifications based upon blood pressure, cardiac dysfunction, hemorrhage, ATE, renal impairment, hepatotoxicity, proteinuria, GI perforation or fistula, QT prolongation, RPLS or other adverse events.

## Special Populations (Adults)

| | Comments |
|---|---|
| **Elderly** | • No overall differences in safety or efficacy noted between younger patients and those over age 65 or 75 years. |
| **Pregnancy** | • Fetal harm can result when administered to a pregnant woman. |
| **Lactation** | • Due to the potential for serious adverse reactions in nursing infants, it is advisable to discontinue breastfeeding during treatment. |
| **Renal Impairment** | • No dose adjustment recommended in mild or moderate renal impairment. The recommended dose in severe renal impairment is 14 mg take once daily. Drug was not studied in end stage renal disease. |
| **Hepatic Impairment** | • No dose adjustment is recommended in mild or moderate hepatic impairment. In severe hepatic impairment, the recommended dose is 14 mg taken once daily. |
| **Pharmacogenetics/genomics** | • No data identified. |
| **Females and Males of Reproductive Potential** | • Advise females of reproductive potential to use effective contraception during treatment and for at least 2 weeks following completion of therapy.<br>• Reduced fertility of unknown duration, in both males and females, may result. |

## Projected Place in Therapy

- Thyroid cancer is considered rare in the U.S. The lifetime incidence of developing thyroid cancer is less than 1%. It is estimated that 63,000 new cases will be diagnosed in in the U.S. in 2014; resulting in 1900 deaths. It is more commonly seen in women and ranks as the 5$^{th}$ most common malignancy among women. The peak age of incidence is 49 years.
- Three main types of thyroid cancer are: differentiated (includes papillary, follicular, Hurthle), medullary and anaplastic (undifferentiated). Differentiated thyroid cancers are the most common (>90%) followed by medullary (~4%) and anaplastic (~2%).
- Overall, DTC is the least aggressive type of thyroid cancer and has an excellent prognosis, although a small percentage of patients will have more aggressive disease. Five-year survival rates are best among patients with local or regional disease (96-99%), whereas those with distant disease fare worse (56%).
- Factors associated with poorer prognosis in DTC include: age > 45 years, male gender, radioactive iodine resistance, PET scan with positive FDG uptake.
- Genetic alterations within the MAPK and/or PI3 signaling pathways have been identified in the pathogenesis of thyroid cancer. VEGF is a noted contributor to progression. The focus of research has been on the development of novel agents that affect these targets.
- Cytotoxic chemotherapy has a very limited role, if any, in the management of thyroid cancer. International guidelines no longer support its use.
- Multiple tyrosine kinase inhibitors have activity in thyroid cancer, though not all have FDA-approval for this indication. Only sorafenib and lenvatinib have received FDA-approval for DTC.
- There are no comparative trials evaluating sorafenib to lenvatinib for DTC. Both are oral formulations. Indirect differences to consider include dosing frequency (sorafenib BID vs. lenvatinib QD), toxicity profile (more cardiovascular, renal effects, but no dermatologic toxicity with lenvatinib), and experience.
- Some patients exhibit an indolent course of disease with minimal to no symptoms. There does not appear to be a benefit of targeted therapy in these patients, as there is a great risk of toxicity. No benefit in overall survival or quality of life has been shown to date. In symptomatic patients with an aggressive disease course, the potential benefit of disease stabilization needs to be weighed against the toxicity profile and commitment to intensive management strategies.
- Patients responded to lenvatinib despite prior TKI therapy, therefore, would consider a role for lenvatinib in the second-line setting.
- Blister-packaging may ease concern about taking the proper combination of dosage strengths. Although dispensing a full 30-day supply may result in excess drug waste if daily dose needs to be modified.

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## Appendix 1: Approval Endpoints

**Table 1. A Comparison of Important Cancer Approval Endpoints**

| Endpoint | Regulatory Evidence | Study Design | Advantages | Disadvantages |
|---|---|---|---|---|
| Overall Survival | Clinical benefit for regular approval | • Randomized studies essential<br>• Blinding not essential | • Universally accepted direct measure of benefit<br>• Easily measured<br>• Precisely measured | • May involve larger studies<br>• May be affected by crossover therapy and sequential therapy<br>• Includes noncancer deaths |
| Symptom Endpoints (patient-reported outcomes) | Clinical benefit for regular approval | • Randomized blinded studies | • Patient perspective of direct clinical benefit | • Blinding is often difficult<br>• Data are frequently missing or incomplete<br>• Clinical significance of small changes is unknown<br>• Multiple analyses<br>• Lack of validated instruments |
| Disease-Free Survival | Surrogate for accelerated approval or regular approval* | • Randomized studies essential<br>• Blinding preferred<br>• Blinded review recommended | • Smaller sample size and shorter follow-up necessary compared with survival studies | • Not statistically validated as surrogate for survival in all settings<br>• Not precisely measured; subject to assessment bias, particularly in open-label studies<br>• Definitions vary among studies |
| Objective Response Rate | Surrogate for accelerated approval or regular approval* | • Single-arm or randomized studies can be used<br>• Blinding preferred in comparative studies<br>• Blinded review recommended | • Can be assessed in single-arm studies<br>• Assessed earlier and in smaller studies compared with survival studies<br>• Effect attributable to drug, not natural history | • Not a direct measure of benefit in all cases<br>• Not a comprehensive measure of drug activity<br>• Only a subset of patients with benefit |
| Complete Response | Surrogate for accelerated approval or regular approval* | • Single-arm or randomized studies can be used<br>• Blinding preferred in comparative studies<br>• Blinded review recommended | • Can be assessed in single-arm studies<br>• Durable complete responses can represent clinical benefit<br>• Assessed earlier and in smaller studies compared with survival studies | • Not a direct measure of benefit in all cases<br>• Not a comprehensive measure of drug activity<br>• Small subset of patients with benefit |
| Progression- Free Survival (includes all deaths) or Time to Progression (deaths before progression censored) | Surrogate for accelerated approval or regular approval* | • Randomized studies essential<br>• Blinding preferred<br>• Blinded review recommended | • Smaller sample size and shorter follow-up necessary compared with survival studies<br>• Measurement of stable disease included<br>• Not affected by crossover or subsequent therapies<br>• Generally based on objective and quantitative assessment | • Not statistically validated as surrogate for survival in all settings<br>• Not precisely measured; subject to assessment bias particularly in open-label studies<br>• Definitions vary among studies<br>• Frequent radiological or other assessments<br>• Involves balanced timing of assessments among treatment arms |

*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. See text for details.

**Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2007.**