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Cost-effectiveness in the Second-line Treatment of Non-Small Cell Lung Cancer (NSCLC) in the U.S.

Christopher N Graham MS[1], Hediyyih N Knox MS[1], Lisa M Hess PhD[2], Min-Hua Jen PhD[2], Gebra Cuyun Carter PhD[2], Kumari Chandrawansa PhD[2], Mark Boye PhD[2]

[1]RTI-Health Solutions, Research Triangle Park NC; [2]Eli Lilly and Company, Indianapolis IN

ABSTRACT

OBJECTIVES

The objective of this study was to develop a cost-effectiveness model from a third-party payer perspective to evaluate second-line treatment strategies for NSCLC in the U.S. and to investigate the value of ramucirumab + docetaxel (RAM+DOC) across histological subtypes.

METHODS

Model comparators include the most commonly used second-line treatment regimens for NSCLC for which clinical trial data were available in the squamous, non-squamous, and overall population. We used a lifetime horizon, 3% cost discounting rate, and semi-Markov structure to account for time-dependent variation in probabilities of progression-free and overall survival. The structure of the model incorporated 21-day cycles and four health states including second-line treatment, third-line treatment, best supportive (palliative) care, and death. Clinical trial data were supplemented by other published data, when necessary. Probabilistic and one-way sensitivity analyses were conducted to test the robustness of findings.

RESULTS

Based on the results of this cost-effectiveness analysis, RAM+DOC in the second-line treatment of patients may be considered a cost-effective option in the non-squamous populations given an oncology willingness-to-pay threshold of $200,000 per life-year gained (ICER=$192,833 versus docetaxel alone). For the overall NSCLC population, comparators were limited and the incremental cost effectiveness ratio was slightly higher (ICER=$222,224 versus docetaxel). There were very limited data to evaluate the squamous population, and the ICER for RAM+DOC was high. The lack of complete data in the histological subgroups was a limitation; analyses were only possible for a subset of the comparators of interest.

CONCLUSIONS

The treatment patterns and cost data used to inform this model are US-specific and would require adaptation to be generalizable elsewhere. Depending on the threshold used by the decision maker, RAM+DOC may be a cost-effective option for the overall and non-squamous NSCLC population.

BACKGROUND

- Lung cancer is the second most commonly diagnosed malignancy in the U.S.
  - 221,200 new cases of lung cancer are projected to occur in 2015 (Siegel et al., 2015)
- Lung cancer is the leading cause of cancer death in the U.S.
  - Cause of more deaths annually than prostate, breast, colon, and pancreatic cancers combined
- An estimated 83% of all lung cancers are non-small cell lung cancers (NSCLC)
  - Approximately 30% of cancers are categorized as squamous, which is associated with lower survival outcomes than non-squamous NSCLC
- The majority of NSCLC patients present with advanced disease, which has poor prognosis
  - The 5-year survival for metastatic disease is less than 5% (SEER)
- The standard treatment for initial therapy of advanced disease involves platinum-based therapy
  - Pemetrexed and bevacizumab have shown to improve survival outcomes when added to a first-line platinum-based regimen for patients with non-squamous NSCLC
- Patients with advanced disease well enough for treatment will require additional therapy as the disease progresses

STUDY OBJECTIVE

- To develop a cost-effectiveness model to evaluate the costs and benefits of second-line treatment strategies for NSCLC in the U.S.

METHODS AND ASSUMPTIONS

- Perspective: Third-party payer
  - The model considers only direct medical care costs in the U.S.
- Population: The model considers only direct medical care costs in the U.S.
  - Previously treated metastatic NSCLC
  - Patients whose disease has progressed on or after prior therapy
  - Three approaches were modeled: all NSCLC patients, those with squamous histology, and those with non-squamous histology, respectively
- Time horizon: Lifetime (assumed 10 years)
- Discounting: 3%
- Cost inputs: 2014 U.S. dollars (Table 1)
- Other inputs
  - 51% of patients will require subsequent (third-line) therapy ($2,644 per cycle) for all regimens other than single-agent docetaxel (54.6% received additional treatment in the REVEL trial, Garon et al., 2015)
  - End of life care = $15,323 (Chastek et al., 2012)
  - Toxicity rates are limited to grade 3/4 toxicities reported in the clinical trials

METHODS AND ASSUMPTIONS (CONT)

- Other inputs (continued)
  - Additional treatment- and outcome-related values are listed in Table 2
- Outcomes: Life-years
- Model structure
  - Semi-Markov (Figure 1)
  - Structure allows for time-dependent probabilities of both progression-free survival (PFS) and overall survival (OS)
  - Cycle length = 21 days (equivalent to a NSCLC treatment cycle)
- Sensitivity analyses
  - One-way and probabilistic (10,000 iterations, Monte Carlo simulation) sensitivity analyses were conducted

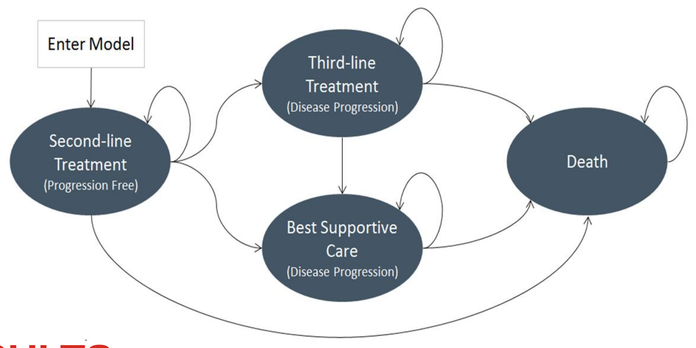
Table 1. Cost Inputs

Drug Costs	Wholesale Acquisition Cost	Source
Ramucirumab	$1,020	Truven REDBOOK
Docetaxel	$167	
Pemetrexed	$596	
Erlotinib	$6,212	
Bevacizumab	$664	
Infusion Costs	**Cost**	**Source**
Initial infusion		Centers for Medicare and Medicaid Services (CMS) Physician Fee Schedule Search National Payment Amount (2014) multiplied by public insurer vs. Medicare cost difference factor of 1.49 from the American Hospital Association Trendwatch Chartbook (2011)
First hour	$199	
Subsequent hour(s)	$42	
Subsequent infusion	$92	
Premedication	$45	
Toxicity Costs	**Cost**	**Source**
Neutropenia	$12,422	Toxicities mapped ICD-9 codes and inpatient costs from HCUPnet (2014). Costs adjusted using the medical component of the Consumer Price Index to September 2014 US dollars (US Bureau of Labor Statistics, 2014).
Febrile neutropenia	$19,091	
Fatigue	$7,019	
Nausea and vomiting	$6,381	
Diarrhea	$7,159	
Rash	$6,372	
Dyspnea	$6,008	
Leukopenia	$8,485	
Anemia	$6,305	
Hypertension	$5,793	
Pulmonary hemorrhage	$9,234	
CNS hemorrhage	$16,784	
Thromboembolic event	$21,429	
Interstitial lung disease	$12,853	
Physician Visits and Disease Monitoring	**Cost**	**Source**
Physician visit	$161	Centers for Medicare and Medicaid Physician Fee Schedule Search National Payment Amount (2014) multiplied by public insurer vs. Medicare cost difference factor of 1.49 from the American Hospital Association Trendwatch Chartbook (2011).
Oncologist visit	$215	
Computed tomography scan	$288	
Chest x-ray	$36	

Table 2. Other Input Values

Item	Probability/Input Value			Source
	All NSCLC	Non-squamous	Squamous	
Number of Infusions				
Ramucirumab + Docetaxel				
Ramucirumab	6.10	6.30	5.80	REVEL trial (Garon et al., 2014)
Docetaxel	5.50	5.60	5.10	
Docetaxel	4.90	5.10	4.30	
Pemetrexed	N/A	5.10	N/A	Assumed similar to mean number of administrations for docetaxel given median number of administrations reported for pemetrexed (Hanna et al., 2004) and docetaxel alone (Garon et al., 2014) are the same and non-significant PFS HR from Hanna et al. (2004)
Bevacizumab + Erlotinib				
Bevacizumab	N/A	6.30	N/A	Assumed same number of infusions as ramucirumab
Treatment Duration (weeks)				
Ramucirumab + Docetaxel	19.7	20.0	18.1	REVEL trial (Garon et al., 2014)
Docetaxel	16.9	17.6	14.2	
Pemetrexed	--	17.6	--	Assumed similar to non-squamous treatment duration for docetaxel given non-significant PFS HR from Hanna et al. (2004).
Bevacizumab + Erlotinib	--	20.0	--	Assumed same treatment duration as ramucirumab
Progression-free Survival Hazard Ratios				
Docetaxel		Referent		
Ramucirumab + Docetaxel	0.762	0.766	0.761	REVEL trial (Garon et al., 2014)
Pemetrexed	--	0.970	--	Hanna et al., 2004
Erlotinib	1.203	1.140	1.203	Overall population fixed-effects meta-analysis of DELTA (Kawaguchi et al., 2014) and TITAN (Ciuleanu et al., 2012) . Non-squamous: assumed similar to adenocarcinoma in DELTA (Kawaguchi et al., 2014). Squamous: not reported. Assumed equal to overall population
Bevacizumab + Erlotinib	--	0.707	--	Herbst et al., 2011
Overall Survival Hazard Ratios				
Docetaxel		Referent		
Ramucirumab + Docetaxel	0.857	0.830	0.883	REVEL trial (Garon et al., 2014)
Pemetrexed	--	0.990	--	Hanna et al., 2004
Erlotinib	0.943	0.950	0.890	Overall population: fixed-effects meta-analysis of DELTA (Kawaguchi et al., 2014) and TITAN (Ciuleanu et al., 2012). Nonsquamous: assumed similar to adenocarcinoma in TITAN (Ciuleanu et al., 2012). Squamous: Ciuleanu et al., 2012
Bevacizumab + Erlotinib	--	1.016	--	Herbst et al., 2011

Figure 1. Cost-effectiveness Model Structure



RESULTS

- The base case total and incremental costs and effectiveness results are provided in Table 3.
- One-way sensitivity analyses found that ramucirumab drug acquisition costs and ramucirumab + docetaxel PFS and OS hazard ratios had the largest impact on model results across all histological subgroups
  - Importantly, the REVEL trial was not powered to detect differences at the histological subgroup level; these sensitivity analyses suggest that caution should be used when interpreting the cost-effectiveness by histology
- Probabilistic sensitivity analyses found that as the willingness-to-pay threshold for life-years gained increases, the more likely ramucirumab + docetaxel is to be the preferred treatment option
- In the overall, non-squamous, and squamous populations, 27.8%, 32.5%, and 8.0%, respectively, of the 10,000 iterations performed showed ramucirumab + docetaxel to have a net monetary benefit below a willingness-to-pay threshold of $200,000
  - Likely due to insufficient data, the net monetary benefit (NMB) is lower for the squamous subgroup

Table 3. Cost-effectiveness

Regimen	Incremental Cost per Life-Year Gained				
	Total		Incremental		ICER
	Costs	Life-Years	Costs	Life-Years	
All NSCLC					
Docetaxel	$91,914	1.292	—	—	—
Erlotinib	$112,766	1.388	$20,852	0.096	$216,344
Ramucirumab + Docetaxel	$150,714	1.559	$58,800	0.267	$222,224
Non-squamous Population					
Docetaxel	$96,669	1.365	—	—	—
Pemetrexed	$112,884	1.382	$16,215	0.017	Dominated (extended dominance)[a]
Erlotinib	$117,430	1.453	$20,762	0.088	Dominated (extended dominance)[a]
Ramucirumab + Docetaxel	$162,547	1.707	$65,878	0.342	$192,833
Bevacizumab + Erlotinib	$163,937	1.339	$67,269	−0.026	Dominated[b]
Squamous Population					
Docetaxel	$68,403	0.921	—	—	—
Erlotinib	$88,847	1.031	$20,444	0.110	$185,072
Ramucirumab + Docetaxel	$115,487	1.039	$47,084	0.118	$3,329,265

[a] Dominated (extended dominance) means a combination of regimens has both lower total costs and higher life years than the current regimen
[b] Dominated means another regimen has both lower total costs and higher life years than the current regimen

LIMITATIONS

- This study was conducted with U.S.-specific cost, comparator, and treatment pattern inputs that are not generalizable to other countries or regions.
  - Additional studies must be conducted to understand the cost effectiveness of ramucirumab + docetaxel outside the U.S.
- While bevacizumab is used in the U.S. in the post-progression setting, there are little data supporting the use of this agent after initial therapy. The only randomized trial identified in the second-line setting includes a combination with erlotinib that is atypical of U.S. treatment patterns.
- Data for the histological subgroups are very limited, and these results must be interpreted with caution
  - Due to lack of power to detect significant differences by histologic subgroup in the REVEL trial, sensitivity analyses show that the ICER for the squamous population is reduced by 75% when the overall population outcomes are applied
- Healthcare resource use and outcomes in the real world may differ from those reported in randomized trials
- Data are limited to randomized trial data, and may have limited generalizability to the patient population that does not meet study eligibility criteria

CONCLUSIONS

- Based on the results of this cost-effectiveness analysis, ramucirumab + docetaxel in the second-line treatment of patients may be considered a cost-effective option in the overall NSCLC and non-squamous populations given a willingness-to-pay threshold of $200,000 per life-year gained for oncology treatments
- In the squamous population, the ICER for ramucirumab + docetaxel was higher, though with limited options in second-line NSCLC treatment available, ramucirumab + docetaxel may have value for selected patients

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