Survival Gains from First-Line Systemic Therapy in Advanced Non-Small Cell Lung Cancer in the United States, 1990-2015: Progress and Opportunities

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Disclosure: This study was supported by Genentech. Drs. Roth, Goulart, and Ramsey are consultants for Genentech.

INTRODUCTION AND OBJECTIVES

- Approximately 180,000 Americans are diagnosed with non-small cell lung cancer (NSCLC) annually, and more than half have advanced (Stage IIIB/IV) disease. [1]
- Historically, survival for these patients has been poor (e.g. 1-year survival≈23%) compared to other common cancers. [1]
- Even though standard first-line systemic therapies (e.g. platinum-doublet chemotherapy) provide a modest survival advantage, a substantial proportion (>50%) of patients do not initiate or complete treatment. [2,3]
- The advent of newer first-line systemic therapies with more favorable effectiveness and toxicity profiles affords opportunities to improve NSCLC outcomes.
- The objectives of this study were to:
  1. Quantify overall survival gains from 1990-2015, ranging from a period when best supportive care only was standard, to the present, where multiple cytotoxic and targeted therapies are available
  2. Project the potential impact of increasing use of modern systemic therapies in clinically appropriate patients.

METHODS

- **Study Design:** Simulation model that estimates overall survival (OS) for patients with advanced NSCLC in cohorts diagnosed in 5-year increments from 1990-2015 by synthesizing information about:
  1. First-line systemic therapy uptake from the peer-reviewed literature [2,3],
  2. Systemic therapy market shares conditional on receipt of treatment from a commercial database [4], and
  3. OS from clinical trials referenced in National Comprehensive Cancer Network guidelines [5-14]
- **Population and Treatments:** Adult patients with advanced NSCLC "enter" the model and receive best supportive care only or one of the first-line systemic therapies available in the given year of the analysis (Table 1). In 2010 and 2015, treatments are stratified by tumor histology (non-squamous or squamous cell carcinoma) and mutation status (EGFR or ALK).
- **Projecting Long-Term (Post-Trial) Survival**: Weibull curves were fit to in-trial overall survival curves and extrapolated to 10 years of follow-up to estimate long-term outcomes.
- **Outcomes:** Mean overall survival, 1-year overall survival proportion, and population life expectancy among all NSCLC patients diagnosed in given analysis years.
- **Model Validation:** Projected survival was validated vs. Surveillance Epidemiology and End Results (SEER) outcomes for analysis years where SEER outcomes are available (1990-2010).
- **Scenario Analyses:** Survival outcomes were evaluated in scenarios in which the proportion of patients receiving systemic therapy was increased by 10% and 30% vs. estimated use in 2015.
- **Assumptions:**
  - Treatment options restricted to most common regimens in a given analysis year
  - No consideration of the OS impacts of maintenance or second/third line therapies
  - Proportion discontinuing therapy early has equivalent OS to those receiving best supportive care only

Table 1: Market Share in NSCLC, Overall Survival Inputs, and Data Sources.

First-Line Treatment Regimen	Reference	Analysis Year					
		1990	1995	2000	2005	2010	2015
Best Supportive Care Only/Early Treatment Stopping							
Market Share (%)	[2,3]	100.0%	70.0%	70.0%	70.0%	66.4%	61.1%
Mean Overall Survival (Months)	[6]	7.1	7.1	7.1	7.1	7.1	7.1
Single Agent Chemotherapy*							
Market Share (%)	[4]	0.0%	5.0%	0.0%	0.0%	0.0%	0.0%
Mean Overall Survival (Months)	[7]	-	9.0	-	-	-	-
First Generation Platinum-Doublet^							
Market Share (%)	[4]	0.0%	25.0%	0.0%	0.0%	0.0%	0.0%
Mean Overall Survival (Months)	[8]	-	13.9	-	-	-	-
Second Generation Platinum-Doublet#							
Market Share (%)	[4]	0.0%	0.0%	30.0%	30.0%	16.0%	14.8%
Mean Overall Survival (Months)	[9]	-	-	13.8	13.8	13.8	13.8
Third Generation Platinum-Doublet& (Non-Squamous Only)							
Market Share (%)	[4]	0.0%	0.0%	0.0%	0.0%	8.9%	8.8%
Mean Overall Survival (Months)	[10]	-	-	-	-	16.7	16.7
Bevacizumab+Platinum-Doublet (Non-Squamous Only)							
Market Share (%)	[4]	0.0%	0.0%	0.0%	0.0%	3.5%	2.6%
Mean Overall Survival (Months)	[11]	-	-	-	-	18.3	18.3
Erlotinib (EGFR-Positive Only)							
Market Share (%)	[4]	0.0%	0.0%	0.0%	0.0%	5.2%	9.9%
Mean Overall Survival (Months)	[12]	-	-	-	-	24.4	24.4
Afatinib (EGFR-Positive Only)							
Market Share (%)	[4]	0.0%	0.0%	0.0%	0.0%	0.0%	1.1%
Mean Overall Survival (Months)	[13]	-	-	-	-	-	20.9
Crizotinib (ALK-Positive Only)							
Market Share (%)	[4]	0.0%	0.0%	0.0%	0.0%	0.0%	1.7%
Mean Overall Survival (Months)	[14]	-	-	-	-	-	26.6

*Cisplatin
^Cisplatin/Carboplatin + Etoposide
#Cisplatin/Carboplatin + Vinorelbine/Gemcitabine/Docetaxel
&Cisplatin/Carboplatin + Pemetrexed

Figure 1: Estimated advanced non-small cell lung cancer treatment mix by analysis year. In 1990, advanced NSCLC patients received best supportive care only. Over the subsequent 25 years, an increasing proportion received first line systemic therapy as a number of cytotoxic and targeted therapies were approved by the U.S. Food and Drug Agency (FDA).

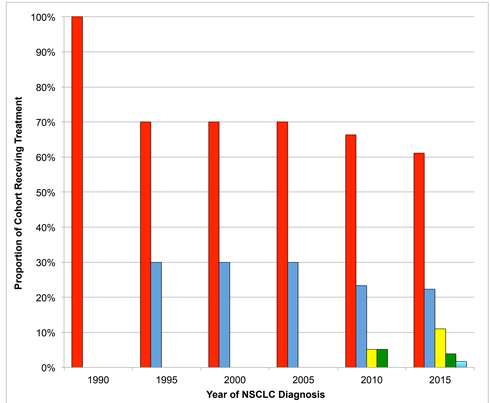
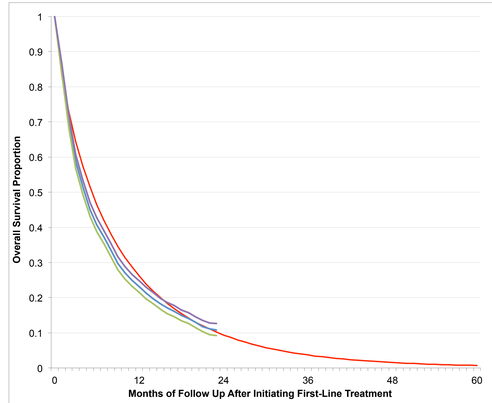


Figure 2: Survival outcome validation. The figure displays a comparison of survival projected by the simulation model for 2010 versus SEER outcomes for patients diagnosed with non-small cell lung cancer in 2010. Similar comparisons were done for 1990-2005.



RESULTS

Table 2: Advanced non-small cell lung cancer estimated outcomes by year of diagnosis. From 1990 to 2015, the expected one-year survival proportion doubled (13.5% in 1990 to 29.2%), and mean per-patient survival improved by 4.3 months (32,967 population life years).

Analysis Year	Expected: 1-Year Survival (%)	Expected: Mean Per-Patient Survival (Months)	Expected: Population Life Years*
1990	13.5%	7.1	54,433
1995	21.7%	8.9	68,233
2000	20.9%	9.1	69,767
2005	20.9%	9.1	69,767
2010	26.2%	10.3	78,967
2015	29.2%	11.4	87,400

*Assumed that 92,000 patients are diagnosed with advanced NSCLC in each analysis year

Figure 3: Advanced NSCLC estimated overall survival by year of diagnosis, 2015 vs. 1990. When the proportion of patients receiving systemic therapy in 2015 was increased by 10% (Scenario 1) or 30% (Scenario 2), the improvement in survival relative to 1990 increased by 4.6 months (35,267 population life years) and 5.3 months (40,633 population life years), respectively**.**

Analysis Year	Scenario (% Completing Systemic Therapy)	Per-Patient Mean Overall Survival (Months)	Incremental Per-Patient Mean Overall Survival (Months)	Incremental Population Mean Overall Survival (Years)
1990	Reference (0%)	7.1	Reference	Reference
2015	Base Case (38.9%)	11.4	4.3	32,967
2015	Scenario 1 (42.8%)	11.7	4.6	35,267
2015	Scenario 2 (50.6%)	12.4	5.3	40,633

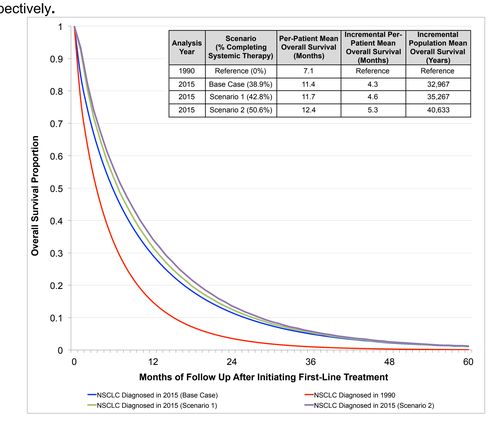


Figure 4: Mean overall survival by histological sub-group (squamous or non-squamous) and for all NSCLC patients, 2010-2015. Squamous cell carcinoma patients receiving first line therapy received either platinum-doublet chemotherapy or targeted therapy (if EGFR+ or ALK+). Non-squamous cell carcinoma patients received any of the first line therapies available in the given analysis year. From 2010-2015, overall survival gains in NSCLC were predominately driven by gains in the non-squamous sub-group.

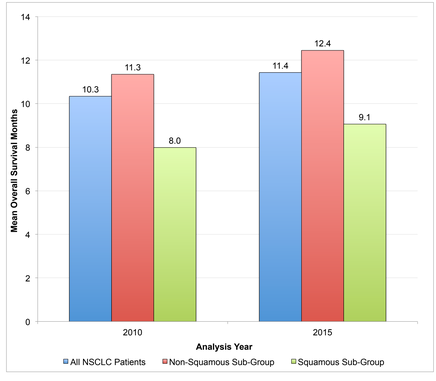
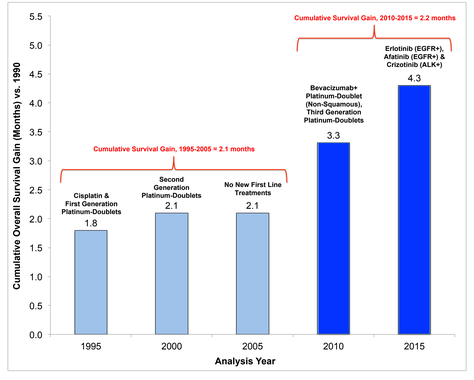


Figure 5: Cumulative mean overall survival gain (vs. 1990) by analysis year and introduction of new first-line systemic therapies. Of the overall 4.3 month mean advanced NSCLC overall survival improvement from 1990 to 2015, 2.2 months (51%) is attributable to FDA approvals of targeted therapies in the past 10 years.



Note: Figure 5 presents FDA approved first line therapies by the year in which they became available in this analysis (as the analysis is divided into 5-year increments). In actuality, Bevacizumab was approved in 2006, Pemetrexed was approved in 2008, Crizotinib was approved in 2011, and Erlotinib and Afatinib were approved in 2013.

DISCUSSION AND CONCLUSIONS

- Our findings are limited by the fact that we did not also evaluate the survival impacts of new maintenance and second-line therapies—though the survival gains attributable to those therapies are likely small relative to those of first line therapies.
- Survival remains poor in advanced NSCLC relative to other common cancers, but the development of new first line therapies over the past 25 years has resulted in modest per-patient survival gains, and substantial population-level life year gains.
- Considering the proportion receiving each treatment, and the size of overall survival treatment effects, the NSCLC survival gain of 4.3 months between 1990 and 2015 is predominately attributable to the advent of platinum-based chemotherapy, followed by EGFR, VEGF, and ALK targeted and biomarker driven therapies, respectively.
- Advances in NSCLC health outcomes can be improved even further by increasing use of systemic therapies in the substantial proportion of patients who are suitable for treatment, yet currently receive best supportive care only or discontinue systemic therapy too early to derive discernable clinical benefit.

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