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3Q19 Competitive Positioning in Non-Small Cell Lung Cancer (NSCLC)

TABLE 1: Key Biotech/Pharma Companies in NSCLC Market – Key Valuation Metrics

Mkt. Cap (US$)			Mkt. Price 12/11/19	Fwd P/E	YTD	Viola Advisory Rating	Viola Advisory PT	Upside Potential 52-Week High	Upside Potential PT
262.5B	RHHBY	Roche	38.49	14.1	25.0%	Buy	42.00	0%	9%
226.5B	MRK	Merck & Co.	88.98	15.7	17.7%	Buy	93.00	-3%	5%
211.5B	PFE	Pfizer Inc.	38.22	13.9	-11.6%	Buy	43.00	22%	13%
209.7B	NVS	Novartis AG	93.04	16.2	10.7%	Buy	100.00	2%	7%
146.3B	BMY	Bristol-Myers	62.41	10.0	19.0%	Buy	67.00	-5%	7%
125.6B	AZN	AstraZeneca plc	48.19	22.8	27.5%	Buy	55.00	2%	14%
116.0B	LLY	Eli Lilly and Co.	120.78	18.4	5.1%	Buy	122.00	9%	1%

Source: Yahoo Finance, Ycharts.com, Viola Advisory LLC

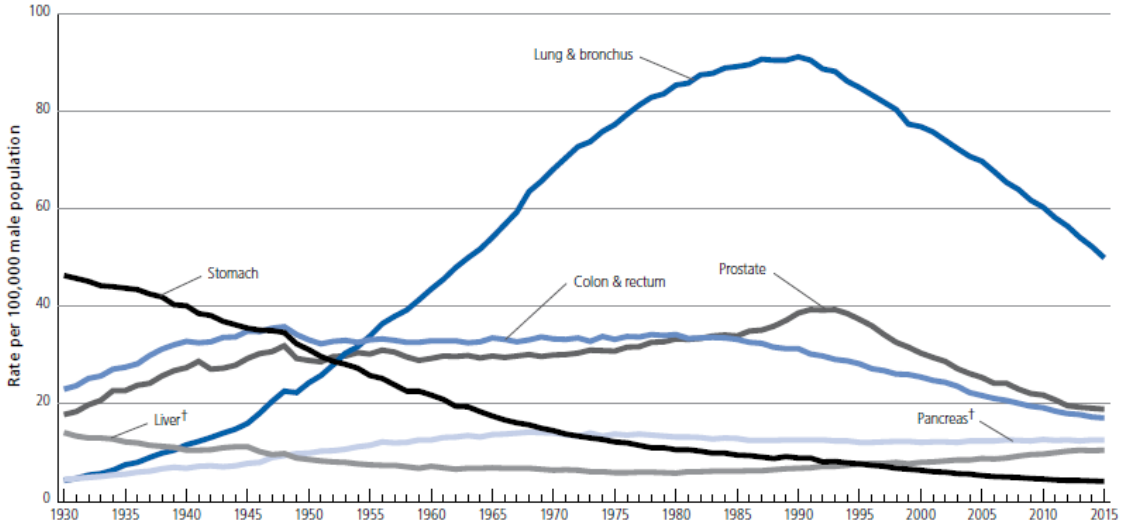
Summary: **Advances in the field of onco-genetics over the past several years and more recently in the field of immunotherapy have ushered in a new era of transformative treatments in the field of lung cancer. These novel treatments are producing deeper remissions and extending the lives of patients in the advanced stages where previously there were only limited treatment options. However, there is still much work left to be done in the areas of treatment resistance and in finding better biomarkers so more patients can be qualified to enroll in immunotherapy clinical trials. The NSCLC market is dominated by Keytruda (Merck), Opdivo (Bristol Myers) and to a lesser extent, Tagrisso (AstraZeneca). We see the NSCLC market growing by double digits and we expect Keytruda to maintain market dominance in the near term.**

I. Lung Cancer Mortality Rate and Typology

A. Lung Cancer Mortality Trend (Male vs. Female)

Around 86% of all lung cancers are caused by smoking. Lung cancer mortality rate grew during most of the 20th century mainly because of the tobacco epidemic, peaking in 1991 at 215 cancer deaths per 100,000 people (see Figure 1a and 1b). As of 2015, the overall rate had dropped to 159 per 100,000 (a decline of 26%) due to reductions in smoking, as well as improvements in early detection and treatment.

FIGURE 1a: Trend in age-adjusted cancer death rates, by site, Males, US, 1930-2015

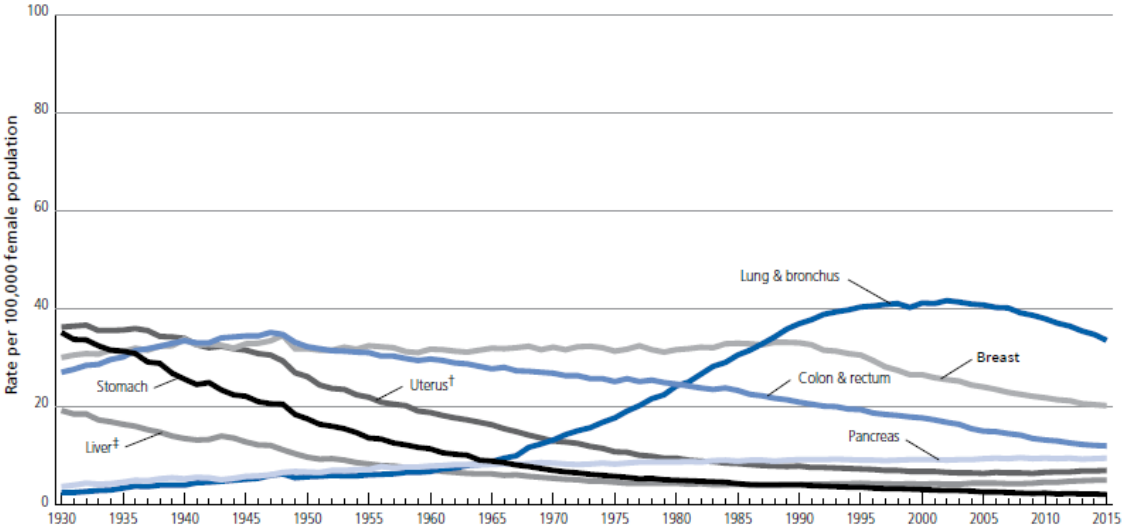


*Age adjusted to the 2000 US standard population. †Mortality rates for pancreatic and liver cancers are increasing.
Source: Cancer Facts and Figures 2018, American Cancer Society

This decline translates into more than 2.3 million fewer cancer deaths from 1991 to 2015, progress that has been driven by rapid declines in death rates for the four most common cancer types – lung, colorectal, breast, and prostate. In terms of the actual number of deaths, lung cancer claims more lives each year than do cancers of the breast, prostate, and colon combined.

Mortality trend in lung cancer for males peaked in 1991 with a mortality rate of roughly 90 per 100,000. However, between 1990 to 2015, the death rate fell sharply to around 50 per 100,000 (see Figure 1a). Despite this progress, mortality rates for pancreatic and liver cancer in males continue to gradually increase in 2015.

FIGURE 1b: Trend in age-adjusted cancer death rates, by site, Females, US, 1930-2015



*Age adjusted to the 2000 US standard population. †Uterus refers to uterine cervix and uterine corpus combined. ‡The mortality rate for liver cancer is increasing.
Source: Cancer Facts and Figures 2018, American Cancer Society

In females, the mortality trend in lung cancer peaked in the early 2000s with a mortality rate of roughly 40 per 100,000. However, the trend has gradually declined to around 35 per 100,000 from 2007 to 2015 (see Figure 1b). Despite the overall decline, mortality rate for liver cancer in females have increased steadily since 2005.

B. Types of Lung Cancer

Lung cancers are divided into two main types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC):

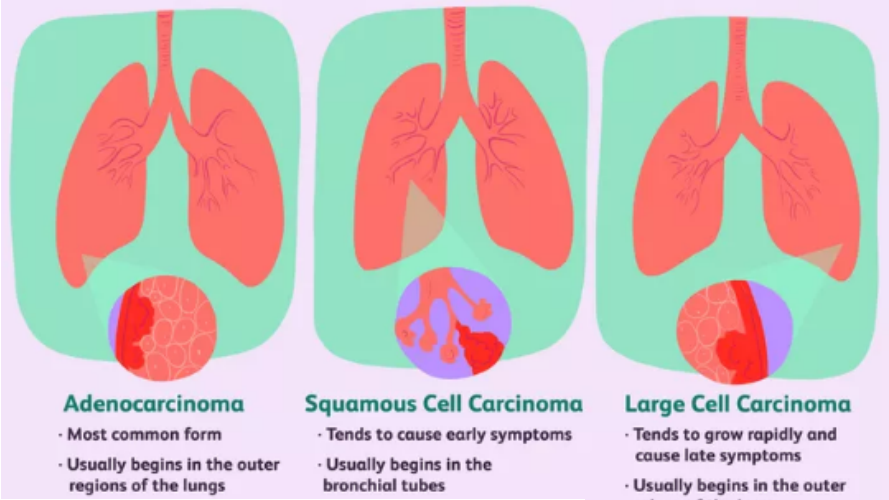
- **Small cell lung cancer (SCLC)** comprises approximately 10 - 15% of all known lung cancer cases. SCLC originates from the neuroendocrine cells in the lung.
- **Non-small cell lung cancer (NSCLC)** comprises approximately 85 - 90% of all known lung cancers cases. Within NSCLC, there are 3 various sub-types (see Figure 2):

  - Adenocarcinoma arises from the alveolar cells in the tiny air sacs in the lungs called alveoli and comprise around 40% of lung cancers);

  - Squamous cell (epidermoid) carcinoma originates from the flat squamous cells that line the inside of the airways of the lung and make up about 25 - 30% of lung cancers, and

  - Large cell (undifferentiated) carcinoma typically arises from the epithelial cells that line the outer regions of the lung and constitute around 10 - 15% of lung cancers.

FIGURE 2: Types of Non-Small Cell Lung Cancer



Source: www.verywellhealth.com (accessed 12/9/19)

II. Evolving Treatment Paradigm in NSCLC

A. Growing Role of Targeted Treatments in Cancer with Genetic Mutations

Historically, decisions on cancer therapy were based largely on histologic considerations. For example, lung cancers were categorized into small-cell lung cancer (SCLC) and non–small cell lung cancer (NSCLC) types. NSCLC was further subdivided into squamous cell carcinoma, large cell carcinoma and adenocarcinoma. Moreover, despite limited efficacy, platinum-based doublet chemotherapy was the standard treatment for patients with advanced NSCLC.

However, researchers are currently evaluating whether genetic variations of cancer have a role in treatment selection. For example, the 2 most common types of NSCLC are adenocarcinoma and squamous cell carcinoma. *EGFR* mutations, *ALK* mutations and *ROS1* mutations are more common in adenocarcinoma NSCLC. People with cancers that have these mutations are now generally treated with EGFR, ALK and ROS1 inhibitors. Over the past 10 years, a wide variety of targeted treatments have been approved for use against NSCLC, but so far, none have been approved for SCLC (see Table 2).

TABLE 2: FDA approved Targeted Treatments for Lung Cancers (by treatment type and genetic mutations)

EGFR Inhibitors			
Generic	**Brand**	**Manufacturer**	**Indication**
Gefitinib	Iressa	AstraZeneca	NSCLC with activating mutations in the *EGFR* gene
Erlotinib	Tarceva	Roche	NSCLC with activating mutations in the *EGFR* gene
Afatinib	Giotrif/Gilotrif	Boehringer Ingelheim	NSCLC with activating mutations in the *EGFR* gene
Osimertinib	Tagrisso	AstraZeneca	NSCLC with the T790M activating mutation in the *EGFR* gene
Necitumumab	Portrazza	Eli Lilly	Squamous cell NSCLCs where EGFR is present (in combo with platinum-based chemo)

ALK Inhibitors			
Generic	**Brand**	**Manufacturer**	**Indication**
Crizotinib	Xalkori	Pfizer	NSCLC with an *ALK* gene rearrangement
Alectinib	Alecensa	Roche	NSCLC with an *ALK* gene rearrangement as 1st line treatment and for patients previously treated with crizotinib
Ceritinib	Zykadia	Novartis	NSCLC with an *ALK* gene rearrangement as 1st line treatment and for patients previously treated with crizotinib
Brigatinib	Alunbrig	Takeda Pharmaceutical	NSCLC with an *ALK* gene rearrangement previously treated with crizotinib (US only)

ROS1 Inhibitors			
Generic	**Brand**	**Manufacturer**	**Indication**
Crizotinib	Xalkori	Pfizer	NSCLC with a *ROS1* gene rearrangement

B-Raf Inhibitors			
Generic	**Brand**	**Manufacturer**	**Indication**
Dabrafenib	Tafinlar	Novartis	NSCLC with BRAF V600E mutation, in combo with the MEK inhibitor trametinib (Mekinist)

Angiogenesis Inhibitors			
Generic	**Brand**	**Manufacturer**	**Indication**
Bevacizumab	Avastin	Roche	First line treatment for: 1) NSCLC that are not squamous cell carcinoma and 2) NSCLC with EGFR gene mutation
Ramucirumab	Cyramza	Eli Lilly	Second line treatment for NSCLC in combo with docetaxel chemotherapy
Nintedanib	Vargatef	Boehringer Ingelheim	Second line treatment for NSCLC in combo with docetaxel chemotherapy (E.U. only)

Checkpoint Inhibitors			
Generic	**Brand**	**Manufacturer**	**Indication**
Nivolumab	Opdivo	Bristol-Myers Squibb	NSCLCs previously treated with chemotherapy
Pembrolizumab	Keytruda	Merck	NSCLCs previously treated with chemotherapy with >1% of cancer cells with PD-L1 on their surface or previously untreated NSCLCs with >50% of cancer cells with PD-L1 on their surface
Atezolizumab	Tecentriq	Roche	NSCLCs previously treated with chemotherapy

Note: NSCLC - non-small cell lung cancer; EGFR - epidermal growth factor receptor; ALK - anaplastic lymphoma kinase; ROS1 - ROS proto-oncogene 1; PD-L1 - programmed death ligand 1
Source: Vickers, E., "A Beginner's Guide to Targeted Cancer Treatments," Wiley Blackwell 2018

Another important factor is that lung cancers in people with a history of smoking contain different DNA mutations than non-smokers. For example, EGFR, ALK and ROS1 mutations are common in non-smokers. Moreover, lung cancers in smokers contain around 10 times the amount of DNA damage compared with lung cancers in non-smokers.

This has important implications for treatments with checkpoint inhibitors. Immunotherapy with checkpoint inhibitors has been most effective against lung cancer in smokers, probably because of their high number of mutations. Checkpoint inhibitors also look promising against SCLC. SCLC is difficult to treat, and numerous approaches have failed to improve survival times.

B. Chemoimmunotherapy Transforms Treatment in Nonsquamous NSCLC

Frontline therapy for patients with nonsquamous NSCLC has completely changed with the addition of immunotherapy drugs to chemotherapy agents. The combination of immunotherapy and chemotherapy has shown unprecedented survival in patients with newly diagnosed advanced nonsquamous non-small cell lung cancer (NSCLC). Table 3 summarizes the pivotal clinical trials in the chemoimmunotherapy NSCLC space.

However, clinicians agree that despite the tremendous benefit of immunotherapy to patients with advanced nonsquamous NSCLC, it should only be given in the absence of a genetic driver mutation (i.e., *EGFR*, *ALK* and *ROS1*). First, the clinician must determine up-front whether a driver exists before deciding whether to proceed with a targeted therapy or an immunotherapy.

TABLE 3: Cross-study comparison in first-line metastatic NSCLC

Trial	Treatment	Population	mOS	Result
Checkmate-227 part 1	Opdivo + Yervoy	TMB high (≥10mut/MB)	23.0 mo. vs 16.4 mo.	Unclear*
Neptune	Imfinzi + tremelimumab	TMB high (≥20mut/MB)	not disclosed	Miss
Keynote-042	Keytruda (approved)	PD-L1 ≥ 1%	16.4 mo. vs 12.1 mo.	Hit
Checkmate-227 part 1a	Opdivo + Yervoy	PD-L1 ≥ 1%	17.1 mo. vs 14.9 mo.	Hit
Keynote-189	Keytruda + chemo (approved)	Non-squamous all-comers	22.0 mo. vs 10.7 mo.	Hit
Checkmate-227 part 1	Opdivo + Yervoy	All-comers	17.1 mo. vs 13.9 mo.	Exploratory
Checkmate-227 part 2	Opdivo + chemo	Non-squamous all-comers	18.8 mo. vs 15.6 mo.	Miss
Checkmate-9LA	Opdivo + Yervoy + chemo	All-comers	not disclosed	Hit
Poseidon	Imfinzi + chemo +/- tremelimumab	All-comers	2Q 2021	TBC

Note: * called into question by a similar result in TMB low subjects and FDA request for more data.
Source: Vantage 10/23/19

However, if immediate treatment is needed (due to disease burden or progressive symptoms), then the consensus recommendation is to give chemotherapy alone. If it is later determined that the patient does not have a driver mutation, then immunotherapy can be added to the treatment plan.

The Keynote-189 trial changed the entire treatment paradigm for advanced nonsquamous NSCLC (see Table 3). In the trial, investigators evaluated the combination of carboplatin, pemetrexed, and pembrolizumab (Keytruda). The combination led to outstanding responses and overall survival and has become the gold standard for first-line treatment for patients with advanced nonsquamous NSCLC. Furthermore, a patient does not need to have high PD-L1 status to be eligible for this regimen. Single-agent pembrolizumab can be used in patients with higher PD-L1 expression.

Other novel immunotherapy combinations are also being investigated like the CheckMate-227 trial (see Table 3 for multiple iterations of that trial). Results of the trial were presented at the 2019 ESMO Congress.

CheckMate-227 (part 1a) compared the combination immunotherapy arm versus the chemotherapy arm. The combination of ipilimumab (Yervoy) and nivolumab (Opdivo) reached statistical significance in patients with PD-L1 TPS >1%. Patients without PD-L1 expression also seemed to benefit from the combination. The trial results may offer an alternate treatment for patients who might prefer a chemotherapy-free backbone. Furthermore, a significant number of complete responses with the combination were observed and toxicity was well managed.

III. Overview of the NSCLC Market

A. NSCLC Market: Market Participants, Annual Sales and Y/Y Growth Rates

Table 4 examines the size of the NSCLC market, the growth rate on a Y/Y basis and the market participants. Moreover, it shows the companies that are taking share and companies that are losing share. The data points were collected from company financial statements (SEC filings) and were consolidated into our proprietary database for further analysis. The data will be updated annually at the end of the 4Q reporting period and will comprise of annual sales figures of all FDA approved oncology drugs for that year.

TABLE 4: NSCLC Market – Size, Growth rate and Mkt. Players (by US$ Million Sales, 2017-2018)

			Sales (US$ Million)					
Generic	**Brand**	**Manufacturer**	**FY 2017**	**Y/Y chg.**	**% of Total**	**FY 2018**	**Y/Y chg.**	**% of Total**
osimertinib	Tagrisso	AstraZeneca	955	126%	12%	1,860	95%	14%
gefitinib	Iressa	AstraZeneca	528	3%	6%	518	-2%	4%
durvalumab	Imfinzi*	AstraZeneca	--	--	--	418	*	3%
afatinib	Gilotrif/Giotrif (sNDA 1/16/18)	Boehringer Ingelheim	--	--	--	--	--	--
nivolumab	Opdivo*	Bristol-Myers Squibb	2,492	10%	30%	3,570	43%	27%
ramucirumab	Cyramza*	Eli Lilly	538	25%	7%	591	10%	4%
necitumumab	Portrazza	Eli Lilly	10	-30%	0%	--	--	--
pembrolizumab	Keytruda*	Merck & Co.	2,519	225%	30%	4,661	85%	35%
ceritinib	Zykadia	Novartis	--	--	--	--	--	--
---	Xalkori	Pfizer	594	6%	7%	524	-12%	4%
dacomitinib	Vizimpro	Pfizer	--	--	--	--	--	--
lorlatinib	Lorbrena (US)/ Lorviqua (EU)	Pfizer	--	--	--	--	--	--
alectinib	Alecensa	Roche	364	101%	4%	640	76%	5%
atezolizumab	Tecentriq*	Roche	250	295%	3%	372	49%	3%
brigatinib	Alunbrig	Takeda Pharmaceutical	26	2%	0%	48	84%	0%
		Total	8,276	58%	100%	13,202	60%	100%

Source: Viola Advisory Oncology Database
*Viola Advisory sales breakdown by cancer sub-type.

The NSCLC market grew substantially in 2017 ($8.3 billion +58% y/y) and in 2018 ($13.2 billion +60% y/y). There are two drugs that dominate the market – Keytruda (Merck) and Opdivo (Bristol Myers) – both anti PD-1 checkpoint inhibitors. The dominance of immunotherapy drugs in the NSCLC market is due to their impressive efficacy and safety profile and the confidence that clinical oncologists have in prescribing these therapeutic agents in both the front-line and in the advanced setting of NSCLC.

B. NSCLC Market: Potential Share Gainers and Losers

Opdivo and Keytruda were early comers in the NSCLC market with Opdivo receiving its initial approval in March 2015 for advanced squamous NSCLC. Keytruda was granted accelerated approval on October 2015 to treat patients with advanced NSCLC whose disease progressed after other treatments and with tumors that expressed PD-L1.

First mover advantage for both Opdivo and Keytruda enabled each of them to carve out a 30% market share in a fast-growing market (+58% y/y) in 2017. Both drugs also continued to maintain their market dominance in 2018 with Merck almost doubling Keytruda sales for that year to around $4.7 billion (+85% y/y) and substantially increasing its y/y market share by 5 percentage points to 35% in 2018 from 30% in 2017.

Bristol-Myers, on the other hand, also managed to grow Opdivo sales in 2018 but at half the growth rate (+43% y/y) of its main competitor Merck. This slower growth rate in 2018 caused Bristol-Myers to lose market share dropping from 30% in 2017 to around 27% in 2018, a loss of around 3 percentage points.

The rapid growth of Merck's Keytruda in the lung cancer market in 2018 can be attributed to several factors: First, the impressive clinical trial results of Keynote-189 established Keytruda as the gold standard for treating metastatic nonsquamous NSCLC in the first-line setting; second, Keytruda was able to secure a second approval in the front-line setting in advanced nonsquamous NSCLC irrespective of PD-L1 expression in May 2017, and third, Keytruda was given FDA approval (also in May 2017) as the first cancer treatment for any solid tumor with a specific genetic feature. Until now, the FDA approved cancer treatments based on where in the body the cancer started – for example, lung or breast cancer. This is the first FDA approval of a drug based on a tumor's biomarker without regard to the tumor's original location.

AstraZeneca's Tagrisso is the third largest drug in the NSCLC market with a 12% market share in 2017 and a 14% market share in 2018. Unlike immunotherapy drugs, Tagrisso is a targeted therapy intended for treatment naïve NSCLC patients that exhibit EGFR mutated tumors. EGFR inhibitors produce very high response rates to tumors that test positive for EGFR mutations. Tagrisso showed an overall response rate of 61% in clinical trials which enabled it to secure an FDA approval in March 2017 for metastatic NSCLC and later expanded its label to first-line treatment for EGFR-mutated NSCLC in April 2018.

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