FROM THE ANALYST'S COUCH

The non-small-cell lung cancer drug market

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Blue sofa chair from Oksana Ariskina/Alamy Stock Photo

Non-small-cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers and is a leading cause of cancer-related deaths in the United States. It is a heterogeneous disease that includes several histologies with distinct pathophysiological characteristics and prognoses, such as adenocarcinoma and squamous-cell carcinoma. The key factors that influence treatment decisions are disease stage, histology, performance status and molecular characteristics; the latter is especially important in the treatment of metastatic disease.

Current treatment advances

Generic chemotherapy such as antitubulins and antimetabolites form the backbone of treatment for the majority of patients, often in combination with platinum-based regimens. NSCLC has evolved into a highly segmented indication defined by tumour histology and molecular status; targeted branded therapies have shaped the treatment algorithm. These include bevacizumab (Avastin; Roche), an inhibitor of angiogenesis, the first-generation epidermal growth factor receptor (EGFR) inhibitor erlotinib (Tarceva; Roche/Genentech), and the anaplastic lymphoma kinase (ALK) inhibitor crizotinib (Xalkori; Pfizer). In 2015, the US Food and Drug Administration (FDA) approved six additional therapies for NSCLC, more than for any other oncology indication in that year.

The programmed cell death protein 1 (PD1) inhibitor nivolumab (Opdivo; Bristol-Myers Squibb) became the first immunotherapy and immune checkpoint inhibitor to enter the NSCLC market, gaining approval for previously treated patients with metastatic squamous-cell carcinoma in the United States (March 2015) and Europe (July 2015). The FDA label was expanded in October 2015 to include non-squamous NSCLC. In both histologies, nivolumab demonstrated significant overall survival improvements over docetaxel, a standard-of-care taxane. A second PD1 inhibitor, pembrolizumab (Keytruda; Merck & Co.), was approved in October 2015, together with a companion diagnostic (PD-L1 IHC 22C3 pharmDx; Dako), for previously treated patients with NSCLC whose tumours express PD1 ligand 1 (PDL1). Pembrolizumab is under regulatory review for NSCLC in Europe. Several Phase III trials are ongoing for nivolumab and pembrolizumab to expand their use to earlier lines or stages of therapy.

Gefitinib (Iressa; AstraZeneca), another first-generation EGFR inhibitor, was granted FDA approval in July 2015 as a first-line treatment of metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. The third-generation EGFR tyrosine kinase inhibitor (TKI) osimertinib (Tagrisso; AstraZeneca) is the first agent to launch specifically for patients whose tumours harbour the EGFR-T790M mutation, which is associated with drug resistance. Osimertinib was approved in the United States in November 2015 under accelerated approval and in Europe in February 2016 under conditional approval. Unlike the FDA label, the European label does not restrict the use of osimertinib to patients who have received prior EGFR TKI therapy.

The anti-EGFR recombinant monoclonal antibody necitumumab (Portrazza; Eli Lilly) was granted approval in the United States in November 2015 and in Europe in February 2016 as a first-line therapy for metastatic squamous NSCLC, in combination with gemcitabine and cisplatin. Approvals were based on the Phase III SQUIRE trial, which demonstrated a statistically significant but modest 1.6-month improvement in median overall survival for the triplet combination compared with gemcitabine plus cisplatin.

First approved in Japan in July 2014, the ALK inhibitor alectinib (Alecensa; Roche/Chugai) was granted accelerated approval by the FDA in December 2015 for patients with ALK-positive metastatic NSCLC who received prior treatment with crizotinib on the basis of early-phase data. A European marketing authorization application submitted in September 2015 is under review. The Japanese Phase III J-ALEX ▸

Table 1 | **Select therapies in the late-phase pipeline for NSCLC**

Product	Companies	Target or drug subclass	Phase
Dacomitinib	Pfizer	Pan-HER (EGFR and HER2/4)	III
Patritumab	Daiichi Sankyo	HER3	III
Rociletinib	Clovis Oncology	EGFR	III
ASP8273	Astellas Pharma	EGFR	III
Atezolizumab	Roche/Chugai	PDL1	III
Durvalumab	AstraZeneca	PDL1	III
Avelumab	Merck KGaA/Pfizer	PDL1	III
Tremelimumab	AstraZeneca	CTLA4	III
BV-NSCLC-001	Bioven	EGF antigen vaccine	III
TG-4010	Transgene	Viral vector vaccine	III
Tergenpumatucel-L	NewLink Genetics	Whole-cell tumour vaccine	IIb/III
OSE-2101 (Tedopi)	OSE Pharma	Multi-antigen vaccine	III
Selumetinib	AstraZeneca	MEK	III
Tafinlar (dabrafenib)	Novartis	BRAF	II
Mekinist (trametinib)	Novartis	MEK	II
Veliparib	Abbvie	PARP	III
Abemaciclib	Eli Lilly	CDK4/6	III

CDK4/6, cyclin-dependent kinase 4/6; CTLA4, cytotoxic T lymphocyte antigen 4; EGF, epidermal growth factor; EGFR, EGF receptor; HER, human epidermal growth factor receptor; MEK, MAPK/ERK kinase; NSCLC, non-small-cell lung cancer; PARP, poly(ADP-ribose) polymerase; PDL1; programmed cell death protein 1 ligand 1.

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trial, which evaluated alectinib versus crizotinib in ALK-inhibitor-naive patients, was stopped early in February 2016 for meeting its primary end point, progression-free survival. A similarly designed Phase III trial (ALEX) is ongoing in the United States and other countries.

Late-phase pipeline

The NSCLC late-phase pipeline is one of the busiest in oncology. The majority of late-phase agents focus on improving outcomes for metastatic disease, the largest drug-treatable patient population. The pipeline includes existing drug classes (for example, immune checkpoint inhibitors and EGFR inhibitors) as well as novel agents.

Most excitement surrounds immune checkpoint inhibitors, and combination therapies involving these agents are a prominent feature of the late-phase pipeline. Several PDL1 inhibitors are in Phase III development for NSCLC, including atezolizumab (Roche), durvalumab (AstraZeneca/Celgene) and avelumab (Merck KGaA/Pfizer). Atezolizumab is being evaluated as a monotherapy and in combination with other agents, including bevacizumab, and chemotherapy. Durvalumab is being evaluated as a monotherapy and in combination with tremelimumab (AstraZeneca/Pfizer) — which targets cytotoxic T lymphocyte antigen 4 (CTLA4) — and to date is the only immune checkpoint inhibitor in Phase III development for unresectable stage III NSCLC. Like pembrolizumab, atezolizumab and durvalumab are also in late-phase development as adjuvant therapies for completely resected stage IB-IIIA disease, a setting in which drug treatment relies solely on chemotherapy at present. In 2015, a total of seven and four Phase III trials were initiated in NSCLC for atezolizumab and durvalumab, respectively, highlighting their ambitious clinical development programmes. However, enrolment into the Phase III CAURAL trial of durvalumab plus osimertinib was suspended in October 2015 because of safety concerns. Avelumab entered Phase III development for NSCLC in 2015, and two Phase III trials are ongoing in the metastatic setting.

Rociletinib (Clovis Oncology), a third-generation EGFR TKI, is under regulatory review for NSCLC positive for the EGFR-T790M mutation in the United States and Europe. Like osimertinib, rociletinib was granted FDA breakthrough therapy designation (BTD) and regulatory submissions were based on promising early-phase clinical data.

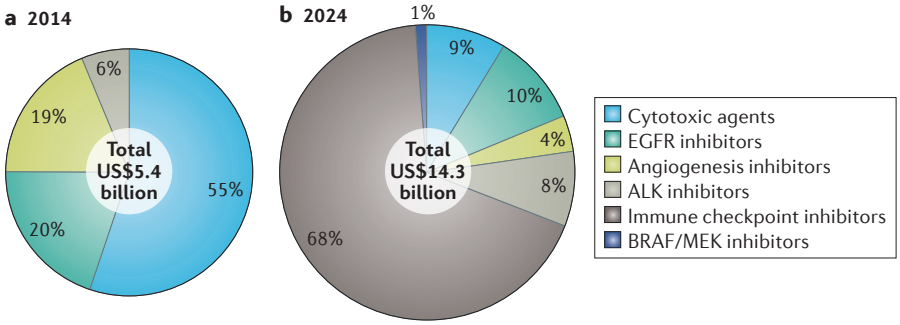

Figure 1 | **NSCLC markets.** The figure shows the 2014–2024 forecast for the seven major markets: United States, France, Germany, Italy, Spain, United Kingdom and Japan. ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; MEK, MAPK/ERK kinase; NSCLC, non-small-cell lung cancer.

The Phase III TIGER-3 trial is ongoing in patients with EGFR activating mutations (excluding exon 20) but does not require patients to harbour EGFR-T790M. The Phase II/III TIGER-1 trial explores rociletinib as a first-line therapy for EGFR-mutation-positive NSCLC. Another third-generation EGFR TKI, ASP8273 (Astellas Pharma), is also in a Phase III trial as a first-line therapy for NSCLC patients with EGFR activating mutations.

Dacomitinib (Pfizer), an irreversible pan-HER inhibitor, is being evaluated as a first-line treatment for metastatic NSCLC; however, two separate Phase III trials in previously treated patients failed to meet their primary end point. The anti-HER3 monoclonal antibody patritumab (Daiichi Sankyo) is also in Phase III development for NSCLC.

Other drug classes in late-phase development include inhibitors of BRAF/MEK (MAPK/ERK kinase), CDK4 (cyclin-dependent kinase 4) and CDK6, as well as poly(ADP-ribose) polymerase (PARP) inhibitors (TABLE 1). The BRAF inhibitor dabrafenib (Tafinlar; Novartis) was granted FDA BTD for BRAF-V600E-positive patients as a single agent in 2014 and in combination with trametinib (Mekinist; Novartis), a MEK inhibitor, in 2015. The MEK inhibitor selumetinib (AstraZeneca) is being evaluated in the Phase III SELECT-1 trial in KRAS-mutation-positive NSCLC. A diverse array of therapeutic vaccines are also in late-phase development for NSCLC (TABLE 1). However, the field of therapeutic vaccines has been marred by high-profile failures.

Market indicators

In 2014, the NSCLC market totalled US$5.4 billion and was dominated by sales of three branded agents — the chemotherapy drug pemetrexed (Alimta; Eli Lilly), erlotinib and bevacizumab — that held a combined 70% market share. Despite the patent expiry and ensuing competition from generic and biosimilar agents during our 2014–2024 forecast period, the NSCLC market is forecast to increase to approximately $14.3 billion in 2024 (a 10% annual growth) (FIG. 1). Sales growth will be fuelled by the entry of premium-priced agents, including the six therapies approved by the FDA in 2015.

The NSCLC market is expected to become increasingly fragmented, driven by emerging therapies in biomarker-defined populations. In 2024, the NSCLC market is likely to be composed of six major drug classes, but immune checkpoint inhibitors are expected to dominate with a market share of 68%. By 2014, the PD1 inhibitors nivolumab and pembrolizumab are forecast to generate in excess of $2.5 billion and $2.1 billion in the NSCLC market, respectively (nearly half of the immune checkpoint inhibitor market share). Sales of ALK TKIs are expected to increase over the forecast period owing to the continued uptake of currently marketed agents. Despite the small size of the eligible population (patients with ALK-positive NSCLC account for approximately 8% of all NSCLC cases), ALK TKIs will generate $1.2 billion in 2024. Next-generation EGFR TKIs and BRAF/MEK inhibitors are other notable market entrants, but their market impact (less than $1 billion) will be limited by the size of the eligible patient population.

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