



## New Kinase Inhibitors Target NSCLC

### Tovok, Vargatef, and Crizotinib

Indication:

**Non-small cell lung cancer**

Products:

**Tovok** (afatinib, BIBW 2992, phase III, Boehringer Ingelheim)

**Vargatef** (BIBF 1120, phase III, Boehringer Ingelheim)

**Crizotinib** (phase III, Pfizer [PFE])

Probabilities of Approval:

**Tovok: 53%(C)**

**Vargatef: 42%(D)**

**Crizotinib: 42%(D)**

Next Catalysts:

**Data from phase III studies**, expected toward the end of 2011 for Tovok, mid-2013 for Vargatef, and in late 2012 for crizotinib.

- Despite the promise of kinase inhibitors, no drugs in this class have been approved for the treatment of non-small cell lung cancer (NSCLC) since AstraZeneca's (AZN) Iressa (gefitinib) and Astellas and Roche's (RHHBY) Tarceva (erlotinib) in 2003 and 2004, respectively.
- Hopes were raised by AstraZeneca's Zactima (vandetanib) and Pfizer's (PFE) figitumumab, but both failed phase III trials for NSCLC.
- Onyx (ONXX) and Bayer's (BAYRY) Nexavar (sorafenib) and Pfizer's Sutent (sunitinib), although approved for other cancers, have both failed to meet their primary endpoints in phase III NSCLC trials.
- Three investigational kinase inhibitors have recently entered phase III development for the treatment of NSCLC: **Tovok** (afatinib) and **Vargatef** (BIBF 1120) - both being developed by Boehringer Ingelheim (privately held) - and Pfizer's **crizotinib**.
- Although promising, all three drugs have a long way to go before approval. Examination of the clinical data available for these drugs results in our modeling *inThought* Approvability Indices of 53%(C), 42%(D), and 42%(D) for Tovok, Vargatef, and crizotinib, respectively.

Since 2003 and 2004, when **Iressa** (gefitinib) and **Tarceva** (erlotinib) were respectively approved by the FDA for the treatment of non-small cell lung cancer (NSCLC), no other kinase inhibitor has joined the armamentarium of NSCLC therapies. The last *inThought* Research Report on this indication (August 17, 2010: *Poor Track Record for Kinase Inhibitors in NSCLC*) highlighted **Nexavar** and **Sutent**, two multikinase inhibitors that have been approved for other cancers but that have failed to meet the primary endpoint of overall survival in phase III trials. This report examines three receptor tyrosine kinase inhibitors that are pursuing NSCLC as their first indication and that have reached phase III development.

### Tovok (Afatinib, BIBW 2992)

Boehringer Ingelheim's **Tovok** (afatinib) is an oral, irreversible inhibitor of both EGFR (erbB1) and HER2 (erbB2). Results presented at the 2010 ASCO (American Society of Clinical Oncology) and ESMO (European Society for Medical Oncology) meetings from the phase II LUX-Lung 2 trial indicated that the drug had high overall response rate (ORR = 57%), the primary endpoint; disease control rate (DCR = 86%); progression-free survival (PFS = 14 months); and overall survival (OS = 24 months) in lung adenocarcinoma patients with EGFR mutations (28% of patients examined). Results were just as impressive for patients with the L858R or del19 mutations, which comprised 42% and 40% of the trial population, respectively (ORR = 59% and 69%; DCR = 83% and 93%; PFS = 16.1 and 13.7 months for patients with L858R and del19 mutations). The most common serious adverse events (SAEs) were grade 3 diarrhea (19%) and rash/acne (21%).

Miller et al (*Phase IIb/III double-blind randomized trial of afatinib (BIBW 2992, an irreversible inhibitor of EGFR/HER1 and HER2) + best supportive care (BSC) versus placebo + BSC in patients with NSCLC failing 1-2 lines of chemotherapy and erlotinib or gefitinib (LUX-Lung 1)*) reported late-breaking results for afatinib at the 2010 ESMO meeting. The primary endpoint, OS, was not met (10.8 vs. 12.0 months for placebo for a hazard ratio (HR) of 1.08); however, there were significant improvements in PFS (3.3 vs. 1.1 months, HR = 0.38,  $p < 0.0001$ ), DCR (58% vs. 19%,  $p < 0.0001$ ), and ORR (7.4% vs. 0.5%,  $p < 0.01$ ). The most common SAEs were grade 3 diarrhea (17%) and rash/acne (14%).

Tovok improved PFS, DCR, and ORR, but it did not meet its primary endpoint of OS.

The phase II results spurred the initiation of three randomized, open-label phase III trials in patients with stage IIIB/IV adenocarcinoma - LUX-Lung 3, begun in August 2009; LUX-Lung 5, begun in February 2010; and LUX-Lung 6, begun in April 2010.

LUX-Lung 3 seeks to enroll 330 patients with EGFR mutations, who will be given either cisplatin + pemetrexed or afatinib as first-line therapy. Primary endpoint is PFS.

LUX-Lung 5 seeks to enroll 900 patients with EGFR mutations or who have failed at least one regimen of platinum-based chemotherapy. Patients will be given either paclitaxel + afatinib or investigator's choice of chemotherapy. Primary endpoint is OS.

LUX-Lung 6 seeks to enroll 330 patients in China and Korea with EGFR mutations, who will be given either gemcitabine + cisplatin or afatinib monotherapy. Primary endpoint is PFS.

While the results of the LUX-Lung-1 trial are reasonably encouraging, the failure to meet its primary endpoint of OS was disappointing. As we await data from the phase III trials in progress, which are expected to start becoming available toward the end of 2011, we model an *inThought* Approvability Index (IAI) score of 53%(C).

### Vargatef (BIBF 1120)

Boehringer Ingelheim's **Vargatef** (BIBF 1120) is touted as an orally active triple angiokinase inhibitor, with activity against three families of receptor tyrosine kinases: vascular endothelial growth factor receptors (VEGFRs), platelet-derived growth factor receptors (PDGFRs), and fibroblast growth factor receptors (FGFRs).

In a small (73 patients with advanced, relapsed NSCLC) phase II trial, Vargatef was given as 1<sup>st</sup>- or 2<sup>nd</sup>-line therapy. The primary endpoint of PFS was 1.6 months, and the incidence of dose-limiting grade 3/4 toxicity was 3%. DCR, a secondary endpoint, was 48%.

Based on the "undiscouraging" phase II results, two pivotal, randomized, double-blind phase III trials were begun in December 2008, both planning to enroll about 1300 patients with advanced or recurrent NSCLC. LUME-Lung 1, a multinational, ex-US trial, will administer docetaxel ± Vargatef as 2<sup>nd</sup>-

line therapy. LUME-Lung 2, a multinational trial that includes the US, will administer pemetrexed (and folic acid) ± Vargatef as 2<sup>nd</sup>-line therapy to NSCLC patients with a nonsquamous histology. The primary endpoint is PFS for both trials.

Interim results for Vargatef are less revealing and thus less encouraging than those for afatinib; therefore, we model an IAI score of 42%(D). Phase III results are not expected until mid-2013.

### Crizotinib

Pfizer's crizotinib is an orally bioavailable inhibitor of both c-Met (hepatocyte growth factor receptor) and ALK (anaplastic lymphoma kinase), two receptor tyrosine kinases. The former is overexpressed in about 22% of NSCLC cases, and the latter is involved in a mutation (EML4-ALK) that is found in about 5% of NSCLC cases.

Bang et al (*Clinical activity of the oral ALK inhibitor PF-02341066 in ALK-positive patients with non-small cell lung cancer (NSCLC)*) and Camidge et al (*Clinical activity of crizotinib (PF-02341066) in ALK-positive patients with non-small cell lung cancer (NSCLC)*) presented impressive results for crizotinib at the 2010 ASCO and ESMO meetings, respectively. When preclinical results suggested that tumors with an ALK mutation would be particularly responsive to crizotinib, an ongoing phase I trial of this drug (Kwak et al, "Anaplastic Lymphoma Kinase Inhibition in Non-Small-Cell Lung Cancer." *N Engl J Med* 363;18:1693-1703) enrolled 82 heavily pretreated ALK+ (by FISH) NSCLC patients. Within this population ORR = 57% and DCR = 90%. The most frequent adverse events were gastrointestinal (54% nausea, 48% diarrhea, and 44%

vomiting), but they were minor (grade 1/2). Grade 3/4 SAEs consisted mostly of AST and ALT elevation (6% of each) but were reversible upon cessation of treatment.

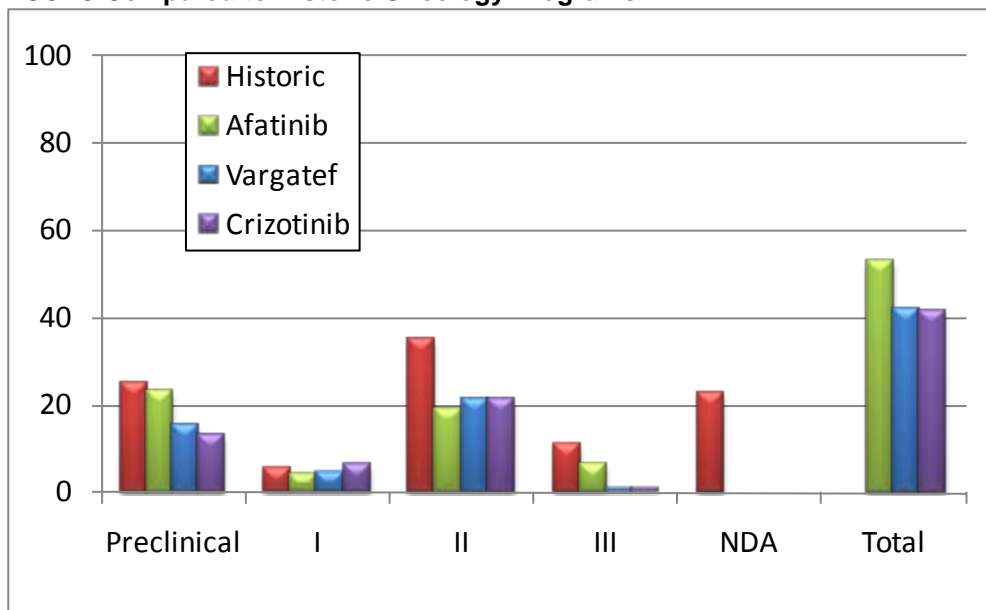
The "striking" efficacy and "minimal" toxicity found in the phase I trial prompted the initiation of a randomized, open-label phase III trial (PROFILE 1007) in September 2009 as 2<sup>nd</sup>-line therapy in advanced NSCLC patients carrying the EML4-ALK fusion gene. The trial expects to enroll 318 patients, who will receive either crizotinib or chemotherapy (pemetrexed or docetaxel). The primary endpoint is PFS.

The leap from phase I to phase III reflects the faith the investigators have in this drug. Among the risks in this strategy is the proper application of a diagnostic test to identify those patients with ALK+ NSCLC who could benefit from crizotinib. Although an open-label, single-arm phase II trial (PROFILE 1005) has subsequently been initiated, the lack of phase II and phase III data, which are expected in 2012, constrain our forecasting capacity. We model an IAI score 42%(D).

### Addendum

Since the inThought Research Report of August 17, 2010, Pfizer announced that Sutent has failed to meet its primary endpoint of OS in the SUN 1087 trial (although it met the secondary endpoint of PFS). This resulted in our lowering the IAI score for Sutent by 3 points from 49%(D) to 46%(D). The IAI score for Nexavar remains unchanged at 40%(D).

**Figure 1: Approvability Index Points for Afatinib, Vargatef, and Crizotinib for NSCLC Compared to Historic Oncology Programs**



Source: inThought estimates

### inThought Approvability Index

The inThought Approvability Index is a dynamic tool that assesses the progress of a drug candidate through clinical development, evaluating strength of clinical data and trial design, benchmarked against historical parameters and likelihood to maintain forward momentum. Points are assigned for specific line items relating to safety, efficacy, and other factors in each phase of clinical development. Possible points total 100 upon drug approval, and are allocated in each phase according to the historical approval rate of similar drugs, such that the current points of a drug relate to its probability of approval. In addition, a letter grade is assigned and reflects the momentum of a drug candidate in its current phase, with "A" indicating significantly above average/likely to progress, "C" indicating average, and "F" indicating significantly below average/unlikely to progress.

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