Advancing the Management of Non-small Cell Lung Cancer

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Advances in the development of targeted therapies and immunotherapy have transformed the management of non-small-cell lung cancer (NSCLC). Targeting angiogenesis and molecular drivers of carcinogenesis has led to the approval of several new therapies. More recently, immunotherapeutic approaches have been investigated in the treatment setting of NSCLC. These include immune checkpoint inhibitors (e.g. anti-cytotoxic T-lymphocyte antigen-4 [CTLA-4], anti-programmed death-1 (PD-1) and anti-programmed death-ligand 1 [PD-L1] agents). The emergence of so many therapeutic options offers the potential for personalised therapy. Molecular profiling can inform treatment decisions but there is a need for more data to determine the optimal sequencing and combination of targeted and immunotherapeutic agents.

Keywords
Non-small cell lung cancer, targeted therapy, checkpoint inhibitors, immunotherapy

Disclosure: David F Heigener has participated as a consultant or advisor to Boehringer Ingelheim, Hoffmann-La Roche and Lilly and received honorarium from Lilly, Astra Zeneca, Hoffmann-La Roche, Boehringer Ingelheim and Bristol-Myers Squibb. This study involves a review of the literature and did not involve any studies with human or animal subjects performed by any of the authors.

Acknowledgements: Medical writing assistance was provided by Kat Mouret with at Touch Medical Media, UK.

Authorship: All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

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Received: 28 October 2016
Accepted: 6 January 2017
Citation: European Oncology & Haematology, 2017;13(1):53–60
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Support: The publication of this article was supported by Lilly. The views and opinions expressed are those of the authors and do not necessarily reflect those of Lilly. The authors provided Lilly with the opportunity to review the article for scientific accuracy before submission. Any resulting changes were made at the author’s discretion.

In 2015, more than 430,000 people in the US were living with lung cancer and there were around 221,000 new cases of lung cancer. Deaths from lung cancer are estimated to be in the region of 158,040.1 Lung cancer is the most frequent cause of cancer deaths in men globally and, in women, lung cancer has surpassed breast cancer as the leading cause of cancer death in developed countries.2 Data from the National Lung Cancer Audit (LUCADA) for England in 2011 show that the majority of lung cancers (87%) are classified as non-small cell lung cancer (NSCLC).3 Forty per cent of all NSCLC cases present with stage III cancer and many of them will be considered inoperable.4

Patients with stage I to III NSCLC are usually treated curatively using surgery, chemotherapy, radiation or a combined modality approach. Patients with advanced disease are generally treated with systematic chemotherapy, although response and survival rates are suboptimal; survival rates for patients diagnosed with stage IIIB and IV NSCLC are just 5% and 1%, respectively.5,6 Further, only a small proportion of patients benefit from later-line therapies.7

NSCLC comprises different histological types that are divided into two main groups that inform treatment decision-making: non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma and other cell types) and squamous cell carcinoma.8 Differences in histological and immunological characteristics of squamous and non-squamous NSCLC are summarised in Table 1.

Non-squamous cell NSCLC has benefitted from the development of targeted therapies for specific molecular subsets with epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements. Squamous cancers account for between 20% and 30% of NSCLC cases and are still treated with cytotoxic chemotherapy alone.6,9 Adenocarcinoma, the most common subtype of NSCLC, accounts for approximately 40% of lung cancers in the US, with rising prevalence also seen in Europe.6,10 Squamous cell carcinoma is closely related to smoking and has a distinct and more complex genetic signature compared with non-squamous tumours.9 In a National Institutes of Health/AARP cohort of 186,057 women and 266,074 men aged between 50 and 71 years, who were followed for 11 years, relative risks for current smoking and incidence of smoking-related cancers were similar in men and women, probably reflecting converging patterns in smoking.10 Asthma, chronic obstructive pulmonary disease (COPD) and tuberculosis (TB) were associated with an increased risk of all major subtypes of lung cancer in a Taiwanese population-based study.11 Women with TB carried the highest risk in this analysis.

Advances in the development of targeted therapies and immunotherapy has led to approval by the US Food and Drug Administration (FDA) for 12 agents in the last 10 years (see Table 2). This review aims to review these breakthroughs in the management of NSCLC.

Angiogenesis as a target
A balance between pro-angiogenic and anti-angiogenic factors regulates angiogenesis in both physiologic and pathologic conditions.6 In many cancers, including NSCLC, proangiogenic pathways have become established as important and effective therapeutic targets because
they are essential for tumour growth, progression and metastasis. Anti-angiogenics improve tumour oxygenation, thereby improving the therapeutic efficacy of irradiation in models. Angiogenesis is regulated by complex signalling pathways with multiple cytokines and growth factors, the most important of which are vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF). Three categories of anti-angiogenic therapeutic agents have been identified:

- direct agents targeting endothelial cells and their functions (e.g. proliferation, migration and the formation of new vessels);
- indirect anti-angiogenic drugs that target cancer cells by interfering with the production of angiogenic factors or extracellular processes; and
- mixed drugs that are aimed at both endothelial and tumour cells.

The major characteristics of a selection of anti-angiogenic compounds are summarised in Table 3.

In 2006, the FDA granted approval for the use of bevacizumab, a monoclonal antibody targeting VEGF, in combination with carboplatin and paclitaxel for the initial systemic treatment of patients with squamous histology tumours and also in central tumours irrespective of histology, owing to a prohibitively high rate of severe pulmonary haemorrhage associated with bevacizumab treatment. Other approved anti-angiogenesis monoclonal antibodies include the anti-VEGFR2 agent ramucirumab whose approval was based on the randomised, double-blind, phase III Study of Docetaxel and Ramucirumab Versus Docetaxel and Placebo in the Treatment of Stage IV Non-Small Cell Lung Cancer Following Disease Progression After One Prior Platinum-Based Therapy (REVEL) trial, in which ramucirumab improved overall survival (OS) in combination with docetaxel compared with docetaxel alone in the second-line setting of NSCLC and nintedanib, which targets PDGF receptor (PDGFR), fibroblast growth factor receptor (FGFR) and VEGF receptor (VEGFR), and showed improved OS compared with docetaxel alone in the second-line setting of NSCLC, only in patients with adenocarcinoma in the BIBF 1120 Plus Docetaxel as Compared to Placebo Plus Docetaxel in 2nd Line Non Small Cell Lung Cancer (LUME-lung 1) trial.

### Targeting molecular drivers of carcinogenesis

In the last decade, an increased understanding of the molecular drivers of carcinogenesis has led to a paradigm shift in the management of NSCLC. The discovery of driver mutations in oncogenes, such as the EGFR, ALK, Kirsten rat sarcoma viral oncogene (KRAS), ROS1 proto-oncogene receptor tyrosine kinase (ROS1) and V-raf murine sarcoma viral oncogene homolog B1 (BRAF), has resulted in the clinical development of numerous targeted therapies.

### Epidermal growth factor receptor

EGFR, which belongs to the ErbB family of receptor tyrosine kinases (RTKs), is over expressed in between 40% and 80% of NSCLC patients and has been shown to be associated with poor prognosis. Its activation has been implicated in cellular proliferation, apoptosis inhibition, angiogenesis, metastases and chemoradio-resistance. It is supposed that the blockade of EGFR activation by tyrosine kinase inhibitors (TKIs), monoclonal antibodies, ligand-linked toxins and antisense approaches may ultimately lead to inhibition of cancer cell proliferation.

The incidence of EGFR mutation varies with ethnicity, with up to 50% of tumours being driven by activating EGFR mutations in Asian populations compared with 10% to 15% in Caucasians. Detection of EGFR mutations has involved tissue biopsy but less invasive methods are becoming available, including the use of circulating tumour DNA.

The use of EGFR TKIs as first-line therapy for patients with advanced EGFR mutation-positive NSCLC began with gefitinib, followed by erlotinib. Both are reversible competitive inhibitors of adenosine triphosphate (ATP) for the tyrosine kinase domain of EGFR resulting in blockade of downstream pathways. Second-generation EGFR TKIs include afatinib, which is approved for first-line treatment of EGFR-mutated tumours and dacomitinib; the latter showed promising efficacy in a phase II trial but failed to improve outcomes in two phase III trials in unselected populations.

Until recently, there were no head-to-head trials of EGFR TKIs, but the results of two trials have recently been presented. A study comparing gefitinib and afatinib showed that afatinib significantly improved efficacy versus gefitinib across a number of outcome measures, including progression-free survival (PFS), time-to-treatment failure and objective response rate. The primary analysis of OS data showed no advantage for afatinib (ESMO 2016). In a post-hoc analysis of two trials of afatinib versus chemotherapy in EGFR-positives, an OS benefit for afatinib first-line was detected in patients with Exon 19 deletions, but not for the Exon 21 point mutation L858R. This is the first proof that the sequence of therapy (i.e. afatinib first) matters. This could not be shown for either erlotinib or gefitinib. In the phase III LUX-Lung 8 trial, afatinib significantly improved OS in ‘wild type’ EGFR patients compared to erlotinib, reducing the risk of death by 19% in patients with advanced squamous cell NSCLC, who were previously treated with first-line chemotherapy.

Almost all patients with initial response to EGFR TKIs eventually relapse due to acquired resistance. Around half of patients develop secondary
include rociletinib (CO-1686),\textsuperscript{50} osimertinib (AZD9291)\textsuperscript{51,52} and olmutinib. Inhibitors in clinical development target the T790M mutation; these tracks and unknown mechanisms in 15–20%\textsuperscript{49}. Third-generation EGFR accounted for by point mutations, $\text{EGFR}^\alpha$, \text{EGFR}^\text{amplification}, bypass mutation: T790M within the EGFR kinase domain,\textsuperscript{47,48} the rest are resistance to EGFR TKIs has been attributed to a recurrent missense mutation within 9–12 months of starting an EGFR TKI.\textsuperscript{46} Around half of NSCLC = non-small cell lung cancer; PDGF = platelet-derived growth factor; VEGF = vascular endothelial growth factor; VEGFR = VEGF receptor.

### Table 2: Agents approved for the treatment of non-small cell lung cancer from 2006 to 2015

<table>
<thead>
<tr>
<th>Agent</th>
<th>Year of FDA approval</th>
<th>Mechanism of action</th>
<th>Indication</th>
</tr>
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<tbody>
<tr>
<td>Aflatinib (Gilotrif)</td>
<td>2013</td>
<td>EGFR TKI</td>
<td>Metastatic NSCLC with EGFR mutations</td>
</tr>
<tr>
<td>Alecinitib (Alcetinasa)</td>
<td>2015</td>
<td>ALK inhibitor</td>
<td>ALK-positive, metastatic NSCLC who have progressed on or are intolerant to crizotinib</td>
</tr>
<tr>
<td>Atezolizumab (Fecentriq)</td>
<td>2016</td>
<td>Anti-PD-L1 mAb</td>
<td>Metastatic NSCLC whose disease progressed during or following platinum-containing chemotherapy</td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>2006*</td>
<td>Anti-VEGF mAb</td>
<td>In combination with carboplatin and paclitaxel, as first-line therapy of unresectable, locally advanced, recurrent or metastatic, non-squamous, NSCLC</td>
</tr>
<tr>
<td>Cetinib (Zykadia)</td>
<td>2014</td>
<td>ALK inhibitor</td>
<td>ALK-positive, metastatic NSCLC with disease progression on or who are intolerant to crizotinib</td>
</tr>
<tr>
<td>Crizotinib (Xalkori)</td>
<td>2011</td>
<td>ALK inhibitor</td>
<td>ALK-positive, metastatic NSCLC</td>
</tr>
<tr>
<td>Erlotinib (Tarceva)</td>
<td>2013</td>
<td>EGFR TKI</td>
<td>Metastatic NSCLC with EGFR mutations</td>
</tr>
<tr>
<td>Gefitinib (Iressa)</td>
<td>2015</td>
<td>EGFR TKI</td>
<td>Metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test</td>
</tr>
<tr>
<td>Nivolumab (Opdivo)</td>
<td>2015</td>
<td>Anti-PD-1 mAb</td>
<td>Non-squamous NSCLC with progression on or after platinum-based chemotherapy</td>
</tr>
<tr>
<td>Nintedanib (Portrazza)</td>
<td>2015</td>
<td>Anti-EGFR mAb</td>
<td>In combination with gemcitabine and cisplatin for first-line therapy of metastatic squamous NSCLC</td>
</tr>
<tr>
<td>Osimertinib (Tagrisso)</td>
<td>2015</td>
<td>EGFR TKI</td>
<td>EGFR T790M mutation positive NSCLC after progression on or after EGFR TKI therapy</td>
</tr>
<tr>
<td>nab-Paclitaxel (Abraxane)</td>
<td>2012</td>
<td>Chemotherapy</td>
<td>Untreated locally advanced or metastatic NSCLC who are not candidates for surgery or radiation</td>
</tr>
<tr>
<td>Pembrolizumab (Keytruda)</td>
<td>2015</td>
<td>Anti-PD-L1 mAb</td>
<td>Metastatic NSCLC with tumours that express PD-L1 and with disease progression on or after platinum-containing chemotherapy</td>
</tr>
<tr>
<td>Ramucirumab (Cyramza)</td>
<td>2014</td>
<td>Anti-VEGF mAb</td>
<td>In combination with docetaxel for metastatic NSCLC with disease progression on or after platinum-based chemotherapy</td>
</tr>
<tr>
<td>Necitumumab (Portrazza)</td>
<td>2015</td>
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*These studies were restricted to non-squamous histology as life-threatening or fatal haemoptysis episodes were reported in patients with squamous histology treated with bevacizumab plus chemotherapy.\textsuperscript{133} Predictive factors to enable selection of patients in whom bevacizumab is likely to be effective have yet to be established. ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; FDA = Food and Drug Administration; mAb = monoclonal antibody; NSCLC = non-small cell lung cancer; PD-1 = programmed death-1; PD-L1 = programmed death-ligand 1; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor.

### Table 3: Listing of key anti-angiogenic drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mode of action</th>
<th>Supporting data</th>
</tr>
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| Afiblercept                 | Antagonist that binds and inactivates circulating VEGF                       | A phase II trial in patients with platinum- and erlotinib-resistant, locally advanced or metastatic adenocarcinoma revealed an acceptable safety profile but only minor activity as a single agent.\textsuperscript{134}  
A more recent phase II trial showed no benefit from adding afiblercept to docetaxel in patients with platinum-resistant advanced or metastatic NSCLC\textsuperscript{135} |
| Bevacizumab                 | Anti-VEGF monoclonal antibody, hypothesised to create an imbalance in the angiogenesis regulatory process, favouring anti-angiogenesis in the tumour microenvironment\textsuperscript{136} | Two pivotal phase III trials provide support for using bevacizumab in combination with chemotherapy in NSCLC\textsuperscript{137,138} |
| Nintedanib                 | A small molecule triple angiokinase inhibitor of VEGF1–3, PDGF-β and -α and FGFRI–3 | First anti-angiogenic agent to demonstrate a survival benefit in the second-line treatment of patients with adenocarcinoma NSCLC versus an active comparator.\textsuperscript{139,140} In the LUME-Lung 1 study nintedanib plus docetaxel significantly improved progression-free survival versus docetaxel alone regardless of histology (hazard ratio, 0.79; 95% confidence interval 0.68–0.92; 3.4 months versus 2.7 months; p=0.002) |
| Ramucirumab                 | A fully humanised monoclonal antibody directed against VEGFR-2             | Ramucirumab plus docetaxel improved survival as second-line treatment of patients with stage IV NSCLC in the multicentre, double-blind, randomised phase III trial (REVEL)\textsuperscript{141} |

NSCLC = non-small cell lung cancer; PDGF = platelet-derived growth factor; VEGF = vascular endothelial growth factor; VEGFR = VEGF receptor.

resistance within 9–12 months of starting an EGFR TKI.\textsuperscript{4} Around half of resistance to EGFR TKIs has been attributed to a recurrent missense mutation: T790M within the EGFR kinase domain,\textsuperscript{43,44} the rest are accounted for by EGFR point mutations, EGFR amplification, bypass tracks and unknown mechanisms in 15–20%.\textsuperscript{45} Third-generation EGFR inhibitors in clinical development target the T790M mutation; these include rociletinib (CO-1660),\textsuperscript{46} osimertinib (AZD9291)\textsuperscript{132} and olmutinib (HM61713).\textsuperscript{13} Osimertinib received FDA and EMA approval in this setting in 2015. In addition, osimertinib has demonstrated high efficacy (overall response rate [ORR] 75%, 72% of PFS at 12 months) in preliminary data in the first-line setting.\textsuperscript{14,15} Other mechanisms of resistance can currently only be treated with chemotherapy: these include the activation of alternative signalling pathways (Met, hepatocyte growth factor [HGF], AXL, Hedgehog [Hh], insulin-like growth factor receptor [IGF-1R], PDK4, mTOR, AKT, AKT2, and BCL6).\textsuperscript{16,17}
[IGF-1R]), alterations to downstream pathways (AKT mutations, loss of PTEN), impairment of the EGFR-TKIs-mediated apoptosis pathway and histological transformation.56

Anti-EGFR monoclonal antibodies bind EGFR on the surface of tumour cells and block the binding of EGF. Monoclonal antibodies may also act via immunological mechanisms, for example, antibody-dependent cellular cytotoxicity.57

Cetuximab is a monoclonal antibody targeted at the EGFR signalling pathway. Two randomised, open-label phase III trials compared chemotherapy and cetuximab with chemotherapy alone in patients with advanced NSCLC.61,62 Improved OS for cetuximab added to chemotherapy was shown in the Cetuximab plus chemotherapy in patients with advanced non-small cell lung cancer (FLEX) trial; in contrast, the BMS099 trial failed to demonstrate an improvement in PFS. A meta-analysis of individual patient data concluded that the combination of cetuximab plus chemotherapy significantly improved clinical outcomes including OS, and had an acceptable safety profile, however, due to the small benefit, approval was not pursued by the company.60

In 2015, another monoclonal antibody, necitumumab, was approved for the first-line treatment of metastatic squamous NSCLC in combination with gemcitabine and cisplatin. In Europe, approval was given for necitumumab in combination with gemcitabine and cisplatin chemotherapy is indicated for the treatment of adult patients with locally advanced or metastatic EGFR expressing squamous NSCLC who had not received prior chemotherapy for this condition. Approval was based on data from the First-line Treatment of Participants With Stage IV Squamous Non-Small Cell Lung Cancer With Necitumumab and Gemcitabine-Cisplatin (SQuIRE) trial, studied necitumumab in combination with cisplatin and gemcitabine in patients with squamous cell NSCLC (n=1,093).64 The primary endpoint of OS was improved by the addition of necitumumab to chemotherapy. The hazard ratio (HR) was 0.84. Median survival times were 11.5 and 9.9 months for the chemotherapy and necitumumab arm and versus chemotherapy alone, respectively, one-year survival rates were 47.7% versus 42.8% and two-year survival rates were 19.9% and 16.5%. PFS was also improved (HR 0.85; p=0.02). The survival benefit was more pronounced in the German SQUIRE subpopulation with 16.5%. PFS was also improved (HR 0.85; p=0.02). The survival benefit were 47.7% versus 42.8% and two-year survival rates were 19.9% and 9.9 months for the chemotherapy and necitumumab arm and chemotherapy alone, respectively, one-year survival rates were not reached versus 10.2 months) compared with crizotinib and was well tolerated.59 Although ALK inhibitors are generally well tolerated, they are associated with a wide range of treatment-emergent adverse events (AEs), including gastrointestinal AEs and hepatotoxicity, but most are manageable and reversible.74

Several other agents are in clinical development. The dual ALK/EGFR inhibitor brigatinib showed promising activity in ALK-positive NSCLC patients with brain metastasis following crizotinib.75 Other agents include ASP8026,73 X-396,74 TSR-011 and the dual ALK/ROS 1 inhibitor lorlatinib (PF-06463922).75

ROS1
Another molecular subgroup, around 1% of NSCLC patients,72 have chromosomal rearrangements of the gene encoding ROS1 proto-oncogene receptor tyrosine kinase (ROS1). Following evidence suggesting that that ROS1 is another therapeutic target of the ALK inhibitor crizotinib,76 crizotinib was approved in this patient subgroup after demonstrating an ORR of 72% in patients with advanced ROS1-rearranged NSCLC.76

BRAF
Mutations of the BRAF gene have been identified in 1% to 2% of patients with NSCLC,72 leading to the investigation of the BRAF inhibitor dabrafenib, which has demonstrated an ORR of 63% in combination with the MEK inhibitor trametinib.77 An ORR of 42% was also reported in a phase II study of vemurafenib.77

KRAS
Activating mutations in KRAS are found in about 30% of adenocarcinoma and 4% of squamous cell carcinomas.83 However, development of effective KRAS inhibitors has proved challenging. Selumetinib, a MEK1/MEK2 inhibitor, showed promising efficacy in combination with docetaxel in a phase II trial,84 however, the consecutive phase III trial failed to meet its primary endpoint.74

Other molecular driver targets
Other molecular targets are currently under investigation. These include ROS1 fusions, RET fusions, neurotrophic tyrosine kinase receptor type 1 (NTRK1) fusions, Met gene amplification, FGFR1 gene amplification, HER2 mutations.85 Amplification of mesenchymal-epithelial transition (MET) factor is found in about 5% of lung adenocarcinoma. Promising data were obtained from two phase II trials, one investigating dual EGFR and MET inhibition, with erlotinib and tivantinib,86 the other evaluating
Asian race and never-smoking status. There is a need to identify smoking status and mutations were strongly associated with ERBB2 were associated with female sex, Asian race and never-smoking EGFR detected in 22%, 25%, 8.5% and 2.4%, respectively. 

Despite demonstrating impressive efficacy, targeted therapies have limitations. In many cases, known mutations are not present: squamous NSCLC rarely have EGFR and ALK mutations. There is a need to identify driver mutations; the Lung Cancer Mutation Consortium was formed to enable collaborative multi-institutional analyses of ten potential oncogenic driver mutations. Among 1,007 patients on whom mutation analysis were performed, EGFR, KRAS, ALK and ERBB2 alterations were detected in 22%, 25%, 8.5% and 2.4%, respectively. EGFR mutations were associated with female sex, Asian race and never-smoking status; ALK rearrangements were strongly associated with never-smoking status and ERBB2 mutations were strongly associated with Asian race and never-smoking status. There is a need to identify predictive biomarkers for targeted therapies. The biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE)-2 clinical study aims to identify biomarkers for optimal patient selection for EGFR, PI3K/AKT and MEK inhibitors.

Targeted therapy in squamous cell non-small cell lung cancer

Although many of the targeted agents described apply to non-squamous NSCLC, targeted therapy for squamous cell NSCLC is now an area of active clinical research. Characterisation of squamous cell carcinoma by The Cancer Genome Atlas has identified mutations in receptor tyrosine kinase pathways PI3K, AKT and FGFR, which may lead to targeted drugs being developed in the future. In addition, the Lung Master Protocol LUNG-MAP (LUNG-MAP) was recently launched to study the potential for biomarker-driven targeted therapy for second-line treatment of patients with squamous cell lung cancer.

Immunotherapy

Recently, immune checkpoint inhibitors (e.g. anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4); anti-programmed death-1 (PD-1); and anti-programmed death-ligand 1 (PD-L1) have emerged as new therapeutic options. In a phase II study, ipilimumab in combination with first-line chemotherapy showed promise in treating patients with metastatic NSCLC. In another phase II study, tremelimumab did not demonstrate superiority over best supportive care in NSCLC patients but a partial response rate was seen in 4.8%, suggesting that tremelimumab warrants further investigation.

In 2015, the FDA, and in 2016, the EMA, approved the anti-PD-1 agent nivolumab for the treatment of non-squamous NSCLC. In Europe, the regulators noted the higher risk of death in patients with aggressive disease. Approval was based on data from the phase III CheckMate 057 trial, which found that nivolumab improved OS compared with docetaxel (12.2 months versus 9.4 months) in the second-line treatment of non-squamous cell NSCLC. However, CheckMate 026, a study investigating nivolumab in the first-line treatment setting, did not meet its primary endpoint: the PFS was 4.2 months with nivolumab compared with 5.9 months with chemotherapy.

Pembrolizumab has also received accelerated FDA-approval for the second-line treatment of NSCLC following data from the KEYNOTE clinical trials. Recent long-term data from KEYNOTE-001 (median follow-up duration 23.1 months) reported an OS of 22.1 months for treatment-naive patients and 10.6 months for previously treated patients. The survival benefit increases with increasing PD-L1 positivity. In the recently published KEYNOTE-024 study, pembrolizumab was associated with significantly longer PFS (10.3 months versus 6.0 months) and OS (80.2% at 6 months versus 72.4%) and with fewer AEs compared with platinum-based chemotherapy. The KEYNOTE-042 study is also investigating pembrolizumab in the first-line setting.

Anti-PD-L1 agents including atezolizumab, durvalumab (MEDA736) and avelumab (MSB0010718C) are also being developed for NSCLC. In the phase II POPLAR trial, atezolizumab significantly improved OS and ORRs versus docetaxel in patients with non-squamous and squamous NSCLC with strong PD-L1 expression. In the phase II BIRCH trial, atezolizumab showed an ORR of up to 27% in patients with strong PD-L1 expression. Recently presented data from the OAK trial showed superior survival (13.8 months versus 9.6 months) for atezolizumab versus docetaxel in previously treated patients with NSCLC. In October 2016, atezolizumab was approved by the FDA for the treatment of patients with metastatic NSCLC whose disease progressed during or following platinum-containing chemotherapy.

Immunotherapeutic approaches are also in development for squamous cell NSCLC. Nivolumab was approved for use in squamous NSCLC in March 2015 following data from the phase III CheckMate 017 trial, in which nivolumab significantly improved over docetaxel (9.2 months versus 6 months) in the second-line setting in patients with squamous cell NSCLC. In a phase II study of nivolumab in refractory patients (two or more previous lines of treatment) with squamous cell NSCLC, CheckMate 063, the response rate was only 14.5%. However, almost all responders had ongoing responses at study end (median duration of response not reached).

Combined therapeutic approaches involving immunotherapy are also a promising approach. Ipilimumab has shown efficacy in treating patients with metastatic NSCLC in combination with first-line chemotherapy in one phase II trial. The combination of durvalumab and tremelimumab, has demonstrated antitumor activity in patients with locally advanced or metastatic NSCLC. In addition, KEYNOTE-189 is investigating the combination of pembrolizumab (MK-3475) and platinum-pemetrexed chemotherapy.

There is a need to identify patients who are most likely to benefit from immunotherapy. The expression of PD-1 ligands (PD-L1 or PD-L2) on tumours has been found to predict clinical benefit of immune checkpoint blockade in melanoma, and from anti-PD-1 therapy in NSCLC. Somatic mutations arising from mismatch-repair defects have also been found to predict clinical benefit of immune checkpoint blockade with pembrolizumab.

Chemotherapy

Despite advances in targeted therapies and immunotherapy, chemotherapy involving a platinum agent combined with a third-generation therapeutic, most commonly taxanes, gemcitabine, vinorelbine or pemetrexed, remains central to the treatment advanced NSCLC. Research into new chemotherapeutic agents appeared to have reached a plateau. However, in 2012, the FDA approved nab-paclitaxel, a nanoparticle albumin-bound (nab) formulation of paclitaxel which,
Figure 1: Proposed algorithm for chemotherapies, immunotherapy and targeted therapies in the management of non-small cell lung cancer

Conclusions
The treatment landscape for NSCLC has expanded greatly in the last decade, and the availability of immunotherapy and therapies targeted towards a specific driver mutation has allowed treatment to be tailored to the patient. Outcomes may be improved by correctly profiling the tumour and using this to inform the appropriate sequence of treatments. There may be a way to either cycle or combine treatments to prevent cancer cells from adapting to specific drugs. However, few biological and clinical data are available to direct the sequencing of immunotherapies and targeted drugs, though an algorithm has recently been proposed by Thomas et al. (see Figure 1). More progress also remains to be made towards personalised treatment and shift away from the ‘one-size-fits-all’ approach. Identification of the specific molecular alterations that contribute to the response to targeted therapy will become an important part of selecting appropriate therapies. Reliable biomarkers to predict which patients might benefit from targeted therapy and immunotherapy are also urgently needed. The few treatment advances achieved so far for lung cancer patients with metastatic squamous cell carcinoma contrasts with the progress seen in NSCLC, highlighting another unmet need for improved treatment options for this group of patients.

33. Fukuoka M, Wu YL, Thongprasert S, et al., Biomarker analyses
30. Pao W, Miller VA, Epidermal growth factor receptor mutations,
29. Gridelli C, Maione P, Ferrara ML, et al., Cetuximab and other
27. Pirker R, Epidermal growth factor receptor-directed monoclonal
18. Bergers G, Benjamin LE, Tumorigenesis and the angiogenic
afatinib or cisplatin plus pemetrexed in patients with metastatic
chemotherapy as first-line treatment for European patients
positive non-small-cell lung cancer (OPTIMAL, CTONG-0802):
EGFR,
harbouring mutations of the epidermal growth factor receptor
paclitaxel in clinically selected patients with advanced
open-label, first-line study of gefitinib versus carboplatin/
N Engl J Med
advanced non-small-cell lung cancer of adenocarcinoma
epidemiology study of EGFR mutations in Asian patients with
untreated locally advanced or metastatic non-small-cell lung
cancer (ASCEND-4), 2015;34:Suppl; abstr 9008.
Ganem D, Chen E, Gelbart J, et al., Antitumor activity of the
second-generation, irreversible, pan-EGFR tyrosine kinase inhibitor
permeability and coaptation as first-line therapy in patients with
LDK378 as an open-label, randomised, controlled phase 3 study
Soda M, Choi YL, Enomoto M, et al., Identification of the
J Thoracic Oncol
Terasu H, Nakamura E, Otsuka T, et al., Evaluation of the
EGFR-directed monoclonal antibody as first-line therapy in
EGFR-directed monoclonal antibody in previously untreated

drug resistance, and growth in tumors mediated by angiopoietins
endothelial growth factor expression in non-small cell lung
diseases on histologic types of lung cancer in both sexes: a
NIH-AARP cohort,
Mechanisms
56. Morgillo F, Della Corte CM, Fasano M, Ciardiello F, Mechanisms
53. Kim DW, Lee DH, Kang JH, et al., Clinical activity and safety of
AZD9291 in EGFR
Oncol Res
J Clin Oncol
non-small cell lung cancer (NSCLC) patients (pts) with EGFR
update Phase I and pooled Phase II results, Presented at:

diseases on histologic types of lung cancer in both sexes: a
NIH-AARP cohort,

Advancing the Management of Non-small Cell Lung Cancer
90. Spigel DR, Chaft JE, Gettinger SN et al., Clinical activity and
89. Sequist LV, von Pawel J, Garmey EG, et al., Randomized phase
80. Bergethon K, Shaw AT, Ou SH, et al., ROS1 rearrangements
75. Kerstein D, Gettinger S, Gold K, et al., LBA4 - Evaluation of
72. De Castro Gea, First-line Ceritinib Versus Chemotherapy
69. Zini E, Calzetti V, Greco F, et al., Angiogenesis: the
disregarding the presence of EGFR and KRAS mutations, but
permeability and coaptation as first-line therapy in patients with
stage IV non-squamous non-small-cell lung cancer (NESSPIRLE)
with non-small cell lung cancer (NSCLC)
and a second mutation in the EGFR kinase domain,
PLoS Med
, 2008;5:253-63.

Ann Oncol

targeted therapy and chemotherapy for advanced NSCLC:
ongoing research questions, J Clin Oncol, 2017;35:2637-81.

84. Tsuchihashi A, Katoh H, Sakuma H, et al., Topoisomerase II alpha
expression with safety and efficacy outcomes in SQUIRE:
Oncol Res
with Stage IV non-small-cell lung cancer (NSCLC)
LBA1_PR, 2016;.

82. Huang D, Coffee AM, Smith R, et al., Expression of angiopoietins
and their receptors in human lung cancer: an immunohistochemical

55. Ng ML, Tazelaar HD, Johnson BE, et al., Microarray analysis of
egf-ligated endothelial cells identifies a novel mechanism that
regulates cell proliferation: the role of angiopoietins, Angiogenesis,

48. Lortat-Jacob S, Brouet D, et al., Inhibition of endogenous

factor-β is an essential autocrine and vascular regulator of
eroducts of endothelial growth factor expression in non-small cell

36. Zou HY, Cucek SE, Zou L, et al., A phase II study of crizotinib
without prior treatment of ALK-positive NSCLC (AP26113): a
randomized, open-label, uncontrolled, phase 2 trial, J Clin Oncol, 2014;32:3702-09.

20. Bergers G, Benjamin LE, Tumorigenesis and the angiogenic

14. Friedman NA, Abott CC, Capelosse NE, et al., impact of changing
U.S. cigarette smoking patterns on incident cancer risks: 20 smoking
related cancers among the women and men of the
National Health Interview Surveys, 1976 to 2001, Cancer Causes Control,

15. Huang Y, Jani A, Nair NS, et al., The effects of pulmonary


38. Inui M, Ohtani T, Ohno S, et al., Angiogenesis in the tumor

dogma: from basic science to clinical application, Adv Drug Deliv Rev,

17. Iwata H, Kato S, Imamura M, et al., Ceritinib in ALK-positive
non-small-cell lung cancer that is resistant to crizotinib,

37. Inoue A, Sugimoto K, Sakamoto H et al., Changes in the
angiogenic switch during metastasis in human colorectal cancer:
Identification of a novel microRNA as a potential therapeutic target,

40. Soria JC, Felip E, Cobo M, et al., Anti-EGFR mAbs as second line
therapy in patients with advanced NSCLC harboring EGFR exon 20

with bevacizumab for non-small-cell lung cancer (N9031C01),

of pemtuzumab removed according to NSCLC histology: a review of

25. Sano T, Yoshikawa H, Nonomura A et al., Development of an
inhibitory monoclonal antibody against EGFR in NSCLC cell line,


13. Inoue A, Sugimoto K, Sakamoto H et al., Changes in the
angiogenic switch during metastasis in human colorectal cancer:
Identification of a novel microRNA as a potential therapeutic target,
107. Gulley JL, Spigel D, Kelly K, et al., Avelumab (MSB0010718C), 
106. Rivzi NA, Brahmer JR, Ou S-HI, et al., Safety and clinical activity
105. NCT02220894, Study of MK-3475 (Pembrolizumab) Versus
101. Garon EB, Rizvi NA, Hui R, et al., Pembrolizumab for the
100. Socinski MA, Bondarenko I, Karaseva NA, et al., Weekly nab-
small-cell lung cancer: a multicentre, phase 1b study,
98. EMA, Opdico: Summary of Product Characteristics. Available
97. Lynch TJ, Bondarenko I, Luft A, et al., Ipilimumab in combination
95. Lynch TJ, Bondarenko I, Luft A, et al., Ipilimumab in combination
tumor imaging and radiation therapy: considerations for successfully combining
radiation into the paradigm of immunoncology drug
93. Golden EB, Demaria S, Scher PB, et al., An abscopal response to radiation and 
sipulemmab in a patient with metastatic non-small cell lung cancer,
92. Thomas A, Lu SC, Subramaniam D, et al., Refining the treatment of 