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REVIEW ARTICLE

Treatment of Advanced Non–small-cell Lung Cancer: a Fast Changing Paradigm

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ABSTRACT

Palliative chemotherapy and / or radiotherapy continue to represent the standard of care for patients with inoperable, advanced-stage non–small-cell lung cancer. However, histology and 'driving' mutations play an increasingly pertinent role in clinical decision-making in advanced non–small-cell lung cancer, with improved understanding of the molecular pathogenesis of lung cancer paving the way for tailored treatment in selected patient populations. This review describes pragmatic treatment paradigms for the first-line, maintenance, and second-line settings in advanced non–small-cell lung cancer. A key consideration in selecting a suitable treatment in the first-line setting is the presence of an actionable molecular pathway for which a specific targeted therapy is available. In the case of epidermal growth factor receptor–overexpressing tumours, treatment with an epidermal growth factor receptor–tyrosine kinase inhibitor such as erlotinib, gefitinib, or afatinib is a viable option. In patients without driving mutations, non-squamous disease can be treated with platinum-based chemotherapy plus pemetrexed with or without bevacizumab or cetuximab. Bevacizumab, in particular, is emerging as an effective option in both the first-line and maintenance settings. However, platinum-based chemotherapy that includes gemcitabine and docetaxel is preferred for squamous cell carcinomas. Failure after first-line chemotherapy with or without subsequent maintenance treatment requires a change to another targeted therapy or a change of chemotherapy. Second-line chemotherapy is currently offered to selected patients upon progression and may include pemetrexed for disease with non-squamous histology and docetaxel or erlotinib for all histological types. At present, only erlotinib is offered as a third-line option for unselected patients who have failed first- and second-line chemotherapy.

Key Words: *Bevacizumab; Carcinoma, non-small-cell lung; Erlotinib; Treatment outcome*

中文摘要

治療晚期非小細胞肺癌：一個快速變化的範例

張文龍

對於不能手術切除的非小細胞肺癌患者來說，紓緩性化療和／或放療仍然是標準的治理方法。然而，病理組織和「驅動性」基因突變在晚期非小細胞肺癌的臨床決策中漸漸發揮重要作用，對肺癌的分子發病機制更加了解可方便為個別患者進行針對性治療。本文探討晚期非小細胞肺癌實用的一線、維持和二線治療。在進行一線治療時，是否存在一個有具體標靶治療的可行分子途徑是選擇合適治療的一項重要考慮因素。對於有表皮生長因子受體（EGFR）過度表現的腫瘤，EGFR－酪胺酸激酶抑制劑，如erlotinib、gefitinib或 afatinib是可行的選擇。在沒有「驅動性」基因突變的患者中，非鱗狀細胞癌可以鉑類為基礎的化療加上pemetrexed（有或無bevacizumab或cetuximab）來治理。在

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一線和維持治療中，bevacizumab是一種新興而有效的選擇。然而，對於鱗狀細胞癌的患者，以包括gemcitabine和docetaxel的鉑類為基礎的化療方案是可取的。無論有沒有後續的維持治療，如果一線化療未見成效，便需改為進行另一種標靶治療或化療。如果患者病程惡化，便須進行二線化療，非鱗狀癌的患者可以使用pemetrexed，而對於所有肺癌種類則可以使用docetaxel或erlotinib。目前，對於一線和二線化療無效的患者來說，只有erlotinib可提供作為第三線治療。

INTRODUCTION

Advanced non–small-cell lung cancer (NSCLC) is a heterogeneous disease characterised by multiple histologies and a range of genotypes. There is an array of new drugs that endeavour to exploit actionable biochemical pathways through selective targeting of the malignant phenotype. In unresectable, locally advanced, metastatic, or recurrent NSCLC without actionable biochemical pathways, platinum-based doublet chemotherapy with third-generation agents remains the standard of care as first-line chemotherapy. However, tumour histology and targeted therapies are increasingly influencing what is becoming a fast-changing treatment paradigm. The main classes of the targeted agents used in the treatment of lung cancer are inhibitors of the epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), and echinoderm microtubule-associated protein-like 4 (EML4)–anaplastic lymphoma kinase (ALK). This article reviews the use of chemotherapy and novel targeted agents in managing advanced NSCLC in the first-line, maintenance, and second-line settings.

FIRST-LINE TREATMENT FOR ADVANCED NON–SMALL-CELL LUNG CANCER

Chemotherapy

Palliative chemotherapy and / or radiotherapy continue to represent the standard of care for patients with inoperable advanced-stage NSCLC without actionable biochemical pathways.[1] Platinum-based doublet chemotherapy with third-generation agents is considered standard first-line chemotherapy in this setting, producing an overall survival (OS) benefit of around 5% at 5 years.[1] However, recent evidence from a meta-analysis suggests that OS associated with non–platinum-based doublet chemotherapy is comparable to platinum-based doublet therapy.[2] In patients aged 70 years or more, the use of platinum-based and non–platinum-based doublet therapy significantly improves overall response rate (ORR), but not OS, and is associated with a higher incidence of myelosuppression.[3] For patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 2, single-agent chemotherapy with gemcitabine, vinorelbine, or a taxane might be preferred over platinum-based combination therapy, with carboplatin-based or low-dose cisplatin-based doublet therapy as alternative options.[4] In patients with non–squamous cell carcinomas and those treated with third-generation chemotherapy, carboplatin-based chemotherapy is associated with significantly higher mortality than cisplatin-based chemotherapy, although the latter is associated with more severe gastrointestinal symptoms and nephrotoxicity.[5] With regard to third-generation agents, gemcitabine-containing doublet regimens have a lower risk of progressive disease (PD) than non-gemcitabine doublet regimens.[6,7] Conversely, paclitaxel-containing doublet therapies are associated with a higher risk of PD than non–paclitaxel-containing doublet therapies.[7] In a meta-analysis comparing docetaxel with vinorelbine, OS was significantly improved with docetaxel-based regimens.[8] Current evidence also indicates that cisplatin / pemetrexed is superior to cisplatin / vinorelbine or cisplatin / gemcitabine in terms of OS in patients with advanced non-squamous NSCLC.[9,10] Conversely, in patients with squamous histology, OS was significantly greater with cisplatin / gemcitabine than with cisplatin / pemetrexed.[9,10] Thus, NSCLC histology is an important consideration when using pemetrexed. The rationale for chemotherapy selection is summarised in the Table.[2-10]

Epidermal Growth Factor Receptor–targeted Therapy

Histology plays an increasingly pertinent role in clinical decision-making in advanced NSCLC, with improved understanding of the molecular pathogenesis of lung cancer paving the way for tailored treatment in selected patient populations.[1,11] In this regard, several phase III trials have shown that, in patients with EGFR mutations, first-line EGFR tyrosine kinase inhibitors (TKIs) such as erlotinib, gefitinib, and afatinib are associated with longer progression-free survival (PFS), higher response rate, better toxicity profile, and improved quality of life compared with chemotherapy.[11] A meta-analysis confirmed that, compared with standard platinum-based

Table. Rationale for treatment selection in advanced non–small-cell lung cancer based on outcomes identified in studies.

Study	Patient group	Evidence
Des Guetz et al,[3] 2012	Elderly	Doublets > single-agent (ORR, but not OS)
Gridelli et al,[4] 2004	ECOG performance status 2	Single-agent chemotherapy may be preferred
Jiang et al,[2] 2012	Unselected	Non-platinum 3rd-generation doublet = platinum doublet (OS)
Le Chevalier et al,[6] 2005; Grossi et al,[7] 2009	Unselected	Gemcitabine doublet > non-gemcitabine doublet (PD)
Grossi et al,[7] 2009	Unselected	Paclitaxel doublet < non-paclitaxel doublet (PD)
Le Chevalier et al,[6] 2005	Unselected	Platinol + gemcitabine > platinol + non-gemcitabine (PD)
Douillard et al,[8] 2007	Unselected	Docetaxel > vinorelbine (OS)
Ardizzoni et al,[5] 2007	Unselected	Cisplatin + 3rd-generation > cisplatin + 3rd-generation (mortality)
Ardizzoni et al,[5] 2007	Non-squamous cell carcinoma	Cisplatin > carboplatin (mortality)
Scagliotti et al,[9] 2008; Treat et al,[10] 2012	Adenocarcinoma	Cisplatin + pemetrexed > cisplatin + gemcitabine (OS)
Scagliotti et al,[9] 2008; Treat et al,[10] 2012	Squamous cell carcinoma	Cisplatin + gemcitabine > cisplatin + pemetrexed (OS)

Abbreviations: < = inferior to; > = superior to; ECOG = Eastern Cooperative Oncology Group; ORR = overall response rate; OS = overall survival; PD = progressive disease.

doublet chemotherapy, patients receiving EGFR-TKIs as front-line therapy had significantly improved ORR and PFS, as well as a numerical improvement in median OS of 6.9 months, although this did not reach statistical significance.[12]

The combination of cisplatin / vinorelbine with cetuximab, an anti-EGFR monoclonal antibody, has demonstrated some survival benefit compared with chemotherapy alone in a phase III trial of chemotherapy-naïve patients with advanced EGFR-positive NSCLC.[13] Tumours with strong EGFR protein expression (immunohistochemistry score ≥200 out of 300)[14,15] and the development of an acneiform skin rash after the first cycle of treatment[16] are predictive biomarkers of a favourable tumour response to the combined cetuximab and chemotherapy approach. Prospectively collected tumour EGFR expression data were used to categorise patients into high and low EGFR-expressing subgroups for subsequent analysis. For patients in the high EGFR-expressing subgroup, median OS was significantly longer in the chemotherapy plus cetuximab group than in the chemotherapy alone group (median OS, 12.0 vs. 9.6 months; hazard ratio [HR] = 0.73; 95% confidence interval [CI], 0.58-0.93; p = 0.011).[15] There was no corresponding survival benefit for patients in the low EGFR-expressing subgroup. Among patients treated with chemotherapy plus cetuximab, those with first-cycle acneiform skin rash had significantly prolonged OS compared with patients without first-cycle rash (median OS, 15.0 vs. 8.8 months), indicating that first-cycle rash may be a surrogate marker for survival outcome.[16]

Targeted Therapy for Wild-type Epidermal Growth Factor Receptor Tumours

Among patients with EML4-ALK fusion oncogenes, crizotinib has been investigated in a first-in-man phase I study.[17] Among 143 patients with ALK-positive NSCLC who received crizotinib and were evaluable for response, 87 (61%) had an objective response. Median time to first objective response was 7.9 weeks and median response duration was 49.1 weeks. Median PFS was 9.7 months and estimated OS at 6 and 12 months was 88% and 75%, respectively. Adverse events (AEs) were mostly of grade 1 or 2, with visual and gastrointestinal AEs and peripheral oedema being the most common. Treatment with crizotinib was therefore well tolerated, with rapid and durable responses in patients with ALK-positive NSCLC.[17]

Two other non-EGFR TKIs in clinical development include LDK378, a selective ALK inhibitor, and selumetinib (AZD6244), a selective mitogen-activated protein kinase / extracellular signal–regulated kinase inhibitor. LDK378 has shown promising early activity in crizotinib-treated and untreated ALK-positive NSCLC patients.[18] In one study comparing selumetinib with pemetrexed in an unselected group of patients with previously treated NSCLC, selumetinib did not offer any advantage over standard treatment with pemetrexed.[19] However, in another study, the combination of selumetinib plus docetaxel compared with docetaxel alone led to a non-significant improvement in OS (9.4 vs. 5.2 months) and a significant improvement in PFS (5.3 vs. 2.1 months; p = 0.0138) in patients with Kirsten rat sarcoma (KRAS)–mutated NSCLC.[20]

Bevacizumab, a VEGF inhibitor, is an approved first-line treatment when administered in combination with chemotherapy for patients with advanced non-squamous NSCLC.[21] History of significant haemoptysis, arterial thromboembolic events, and untreated brain

metastases contraindicates the use of bevacizumab. In a randomised open-label trial conducted in chemotherapy-naïve patients with stage IIIB / IV non-squamous NSCLC (ECOG study E4599), the combination of bevacizumab with carboplatin and paclitaxel led to a significant improvement in OS compared with carboplatin and paclitaxel alone.[22] The efficacy and safety of bevacizumab have been further evaluated in separate studies in the same setting. In the phase III Avastin in Lung Cancer (AVAiL) trial, the combination of bevacizumab 7.5 or 15 mg/kg plus cisplatin and gemcitabine was compared with cisplatin and gemcitabine alone.[23] The primary endpoint of PFS showed a significant benefit for the two bevacizumab arms, with a median PFS of 6.7 months in the low-dose group ($p = 0.003$) and 6.5 months in the high-dose group ($p = 0.03$) compared with 6.1 months in the placebo arm. Median OS was greater than 13 months in all three groups, but was not significantly increased with bevacizumab.[24] More importantly, a predefined analysis of Asian patients enrolled in AVAiL (n = 105) showed a longer PFS than in the overall study population, with a median PFS of 8.5 months in the high-dose group, 8.2 months in the low-dose group, and 6.1 months in the placebo group.[25] Moreover, median OS in the bevacizumab 7.5 mg/kg group was significantly longer than that in the placebo group (HR = 0.46; 95% CI, 0.22-0.97; $p < 0.05$). A third study, the phase IV Safety of Avastin in Lung Cancer (SAiL) study, investigated bevacizumab 7.5 or 15 mg/kg in combination with chemotherapy, with safety as the primary endpoint.[26] The incidence of grade 3 or 4 AEs of special interest was generally low, with thromboembolism occurring in 8% of patients, hypertension in 6%, bleeding in 4%, proteinuria in 3%, and pulmonary haemorrhage in 1%. Three percent of patients died due to these AEs, with thromboembolism (1%) and bleeding (1%) as the most common causes. In a predefined subgroup analysis of Asian patients enrolled in the SAiL study, the safety of first-line bevacizumab plus chemotherapy was consistent with that shown in phase III studies.[27] PFS and OS findings for the overall populations of the three studies are summarised in Figure 1.

MAINTENANCE THERAPY: A NEW APPROACH FOR ADVANCED NON–SMALL-CELL LUNG CANCER

Maintenance therapy is emerging as a potentially beneficial treatment strategy for advanced NSCLC.[28] Several agents have been investigated in this setting. A phase III study investigating the effect of docetaxel administered either immediately after gemcitabine and carboplatin induction therapy or upon PD in chemotherapy-naïve patients found no difference in OS between the two docetaxel arms, but significantly longer PFS in patients who received immediate docetaxel.[29] Another phase III study demonstrated that patients who received pemetrexed for the first time as maintenance following induction with platinum-based chemotherapy had superior PFS compared with placebo.[30] Pemetrexed maintenance therapy has been further evaluated in patients who received induction therapy with pemetrexed and cisplatin for non-squamous NSCLC in the phase III PARAMOUNT

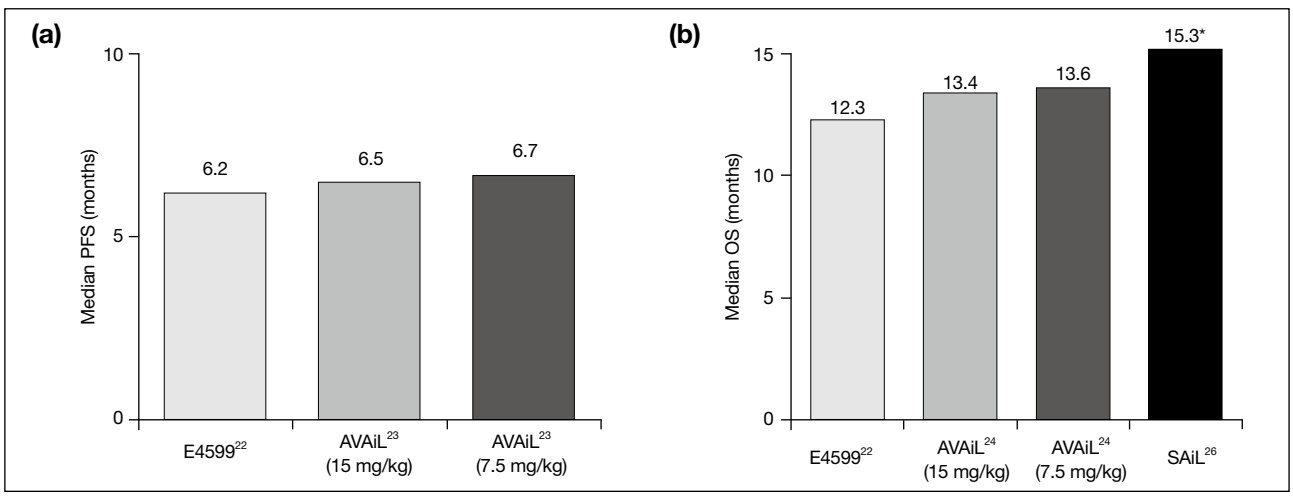


Figure 1. Summary of (a) progression-free survival (PFS) and (b) overall survival (OS) with bevacizumab 7.5 and 15 mg/kg in the Eastern Cooperative Oncology Group E4599, Avastin in Lung Cancer (AVAiL), and Safety of Avastin in Lung Cancer (SAiL) studies.
Time to progression in SAiL was 7.8 months for the overall population.
SAiL shows consistent efficacy with E4599 and AVAiL.
* Preliminary OS.

study (Phase III Study of Maintenance Pemetrexed Plus Best Supportive Care Versus Placebo Plus Best Supportive Care Immediately Following Induction Treatment with Pemetrexed Plus Cisplatin for Advanced Nonsquamous NSCLC).[31] Compared with maintenance with placebo plus best supportive care (BSC), pemetrexed plus BSC was associated with a significant reduction in risk of PD (HR = 0.62; 95% CI, 0.49-0.79; $p < 0.0001$) and improved PFS. Final data from several unpublished studies, including AVAPERL (M022089), ABIGAIL (B021015), SATURN (Sequential Tarceva in Unresectable NSCLC), and ATLAS (Avastin and Tarceva in Lung With NSCLC), which have all been conducted in the maintenance setting, are yet to be revealed. In AVAPERL, previously untreated patients with non-squamous NSCLC received induction therapy with bevacizumab, pemetrexed, and cisplatin before randomisation to maintenance with either bevacizumab alone or in combination with pemetrexed. Preliminary data show that PFS was doubled in the bevacizumab and pemetrexed maintenance arm compared with bevacizumab alone (7.4 vs. 3.7 months), with this benefit consistently observed across all patient subgroups.[32] In ABIGAIL, previously untreated patients with non-squamous NSCLC were randomised to induction therapy with platinum-based chemotherapy plus either bevacizumab 7.5 or 15 mg/kg, followed by bevacizumab maintenance therapy until PD. In this study, preliminary evidence indicates that lower plasma VEGF-A levels at baseline are associated with longer PFS.[33] Both arms were associated with OS in excess of 13 months, without any difference between low- and high-dose bevacizumab. Finally, the SATURN study compared erlotinib with placebo as maintenance therapy after first-line platinum-based doublet therapy. Preliminary findings show that PFS significantly favours erlotinib maintenance therapy across all patient subgroups, including those with squamous and non-squamous cell disease, smokers, ex-smokers, never-smokers, and both sexes.[34] Although a significant benefit was observed for erlotinib in EGFR wild-type tumours, the difference between erlotinib and placebo was more pronounced in those patients with EGFR-mutated tumours. More importantly, OS was significantly improved in the erlotinib arm, irrespective of EGFR wild-type status.

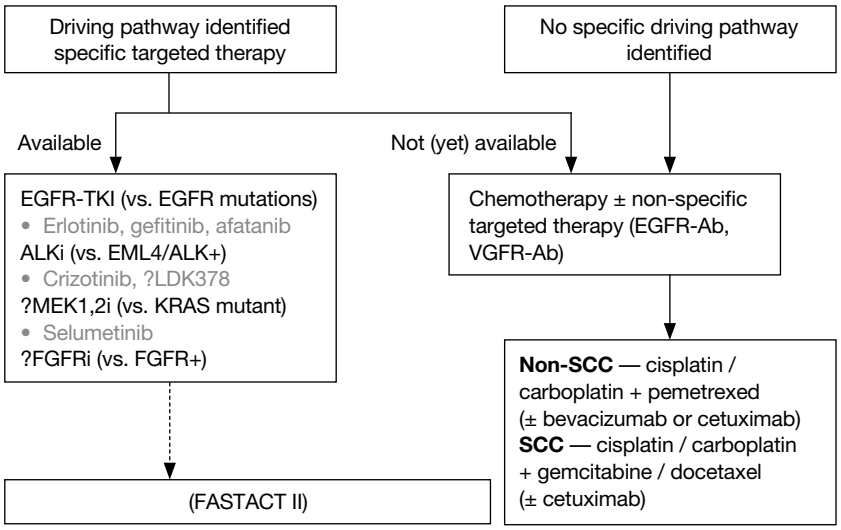
SECOND-LINE CHEMOTHERAPY FOR ADVANCED NON–SMALL-CELL LUNG CANCER

Second-line chemotherapy is currently offered to selected patients upon disease progression and may include pemetrexed in non-squamous disease and docetaxel or erlotinib in all NSCLC.[35] At present, only erlotinib is offered as a third-line option in unselected patients who have failed first- and second-line chemotherapy. However, there are numerous treatment regimens currently under investigation in patients who have failed first-line chemotherapy. Preliminary data have indicated that selumetinib plus docetaxel produced superior PFS than docetaxel alone in KRAS-mutated patients, erlotinib was inferior to docetaxel as single-agent therapy in patients with wild-type EGFR,[36] and cetuximab combined with either docetaxel or pemetrexed was not beneficial in the second-line setting.[37] A further study is investigating post-progression erlotinib in patients with EGFR-mutated NSCLC.

PRAGMATIC TREATMENT ALGORITHMS FOR ADVANCED NON–SMALL-CELL LUNG CANCER

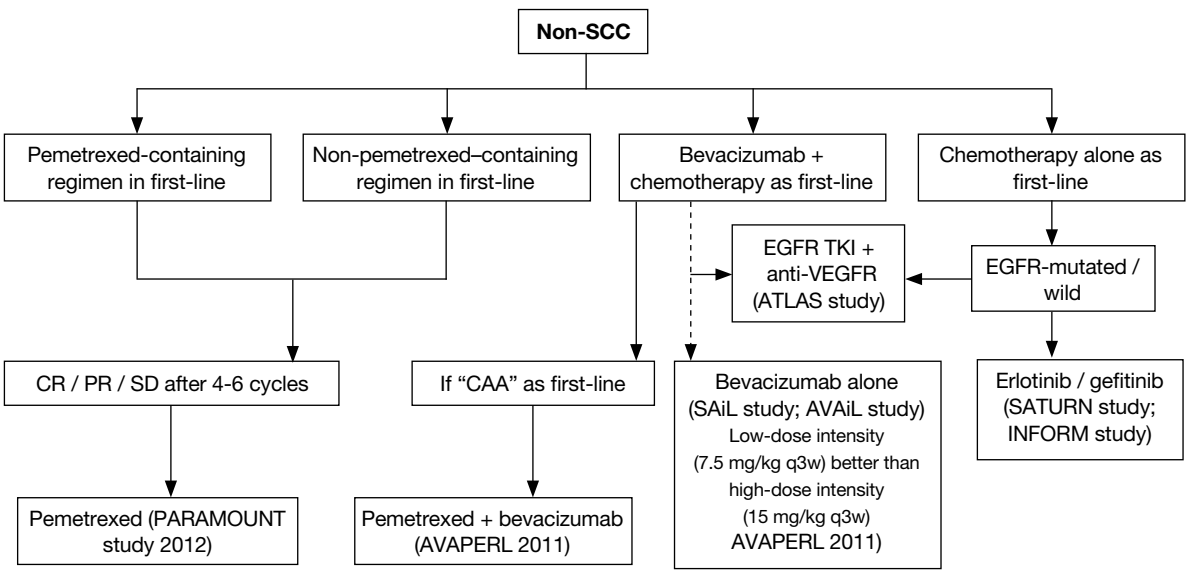
Figure 2 summarises the pragmatic treatment algorithms that are proposed for patients with advanced NSCLC in the first-line, maintenance, and second-line settings. These algorithms include treatments that have yet to receive regulatory approval for these indications, but may nevertheless emerge as viable treatment options in the near future. A key consideration in selecting a suitable treatment in the first-line setting is the presence of an actionable molecular pathway for which a specific targeted therapy is available (Figure 2a). The proposed treatment algorithm also accounts for histology, with pemetrexed and bevacizumab deemed suitable for non-squamous disease only. Similarly, in the maintenance setting, treatment selection is also determined by histology, with pemetrexed and bevacizumab emerging as dominant options in non-squamous disease (Figure 2b). On the other hand, erlotinib and docetaxel can be effective as maintenance therapy for all histology types. Docetaxel- or gemcitabine-based platinum doublets are preferred in squamous disease as first-line treatment. In addition, cetuximab plus chemotherapy is a viable option in NSCLC with high EGFR expression (Figure 2c). Lastly, failure after first-line chemotherapy with or without subsequent maintenance treatment requires a change to another EGFR-TKI in the case of EGFR-mutated NSCLC, or a change of chemotherapy (Figure 2d). Ultimately, the patient's own wishes and physical condition need to be factored into the final formulation of individualised treatment.

(a) First-line setting



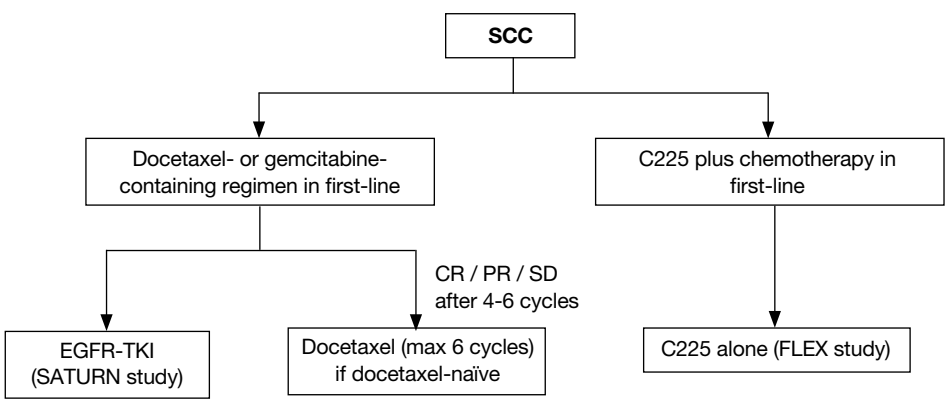
(b) Maintenance setting: non-squamous histology

Maintenance therapy (only applicable after first-line chemotherapy)



(c) Maintenance setting: squamous histology

Maintenance therapy (only applicable after first-line chemotherapy)



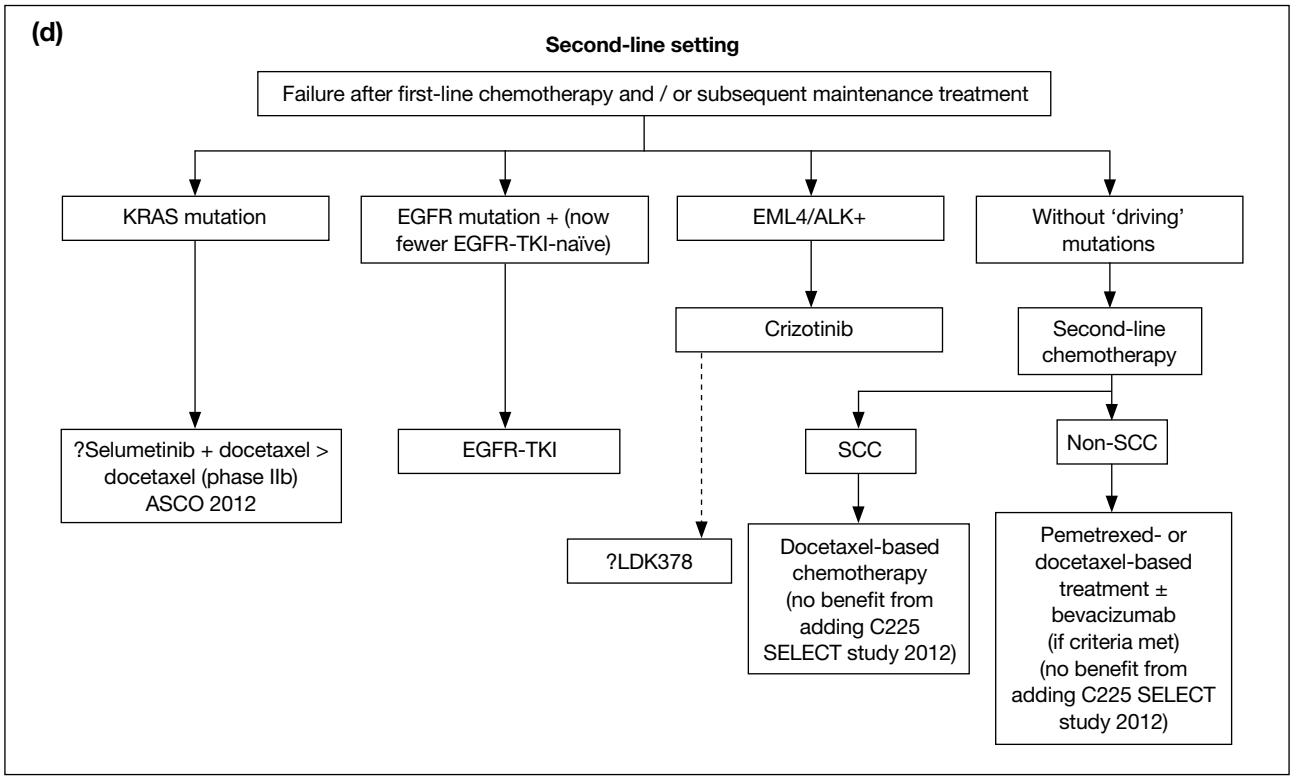


Figure 2. Proposed treatment paradigms in the (a) first-line, (b) maintenance of non-squamous, (c) maintenance of squamous, and (d) second-line settings for patients with advanced non–small-cell lung cancer.
Abbreviations: ALK = anaplastic lymphoma kinase; CAA = cisplatin + alimta + avastin; CR = complete response; EGFR = epidermal growth factor receptor; EML = echinoderm microtubule-associated protein-like; FGFR = fibroblast growth factor receptors; KRAS = Kirsten rat sarcoma; PD = progressive disease; PR = partial response; Rx = treatment; SCC = squamous cell carcinoma; TKI = tyrosine-kinase inhibitor; VEGFR = vascular endothelial growth factor receptor; VGFR = vascular growth factor receptor.

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