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REVIEW

Improving Outcomes in Advanced Lung Cancer

Maintenance therapy in non-small-cell lung carcinoma

*Muhammad Furrukh,[1] Ikram A. Burney,[1] Shiyam Kumar,[1] Khwaja F. Zahid,[1] Mansour Al-Moundhri[2]

تحسين النتائج في سرطان الرئة المتقدم

العلاج المستدام في سرطان الرئة ذي الخلية غير الصغيرة

محمد فروخ، إكرام برني، شيام كومار، فرحان خوجه، منصور المنذري

الملخص: ظل العلاج الكيميائي هو العلاج التقليدي لعلاج سرطان الرئة ذي الخلية، معززا معدل البقاء على قيد الحياة في(NSCLC) غير الصغيرة المنتشرة في السنة الأولى إلى 29%. وقد استقر متوسط البقاء في حدود العشرة أشهر حتى أوائل عام 2008م. و في محاولة لتعزيز فرص الحياة في المراحل المتقدمة من المرض، بدأت دراسات العلاج المستدام الكيميائي والتي أثبتت مؤخراً إطالة أمد البقاء شهرين أو ثلاثة أشهر إضافية في حالة المرضى الذين كان إنجازهم الأدائي (0–1) مع احتفاظهم بأداء اعضاء جسمهم بشكل جيد. يتم علاج المرضى المرجو من استفادتهم الإكلينيكية بأربعة إلى ستة دورات من العلاج الكيميائي ثم يستخدم واحد من أفضل تلك العناصر المكونة للعلاج الكيميائي حتى الوصول لأفضل استجابة أو حدوث مضاعفات جانبية (المداومة المستكملة) أو تغيرها إلى عنصر آخر (المداومة المبدلة). المقالة تستعرض بإيجاز تطور العلاج الكيميائي التقليدي وتصف التجارب الرئيسية من العلاج المستدام المتكون من العلاج الكيميائي والأدوية المستهدفة في محاولة لتحسين النتائج في سرطان الرئة ذي الخلية غير الصغيرة.

مفتاح الكلمات: سرطان الرئة ذي الخلية غير الصغيرة؛ أورام الرئة؛ العلاج المستدام الكيميائي؛ العلاج الجزيئي المستهدف؛ مستقبلات؛عامل نمو البشرة؛ عامل نمو بطانة الأوعية A.

ABSTRACT: Systemic chemotherapy has remained the traditional treatment for metastatic non-small-cell lung carcinoma (NSCLC), enhancing survival rate at 1 year to 29%. The median survival had plateaued at around 10 months until early 2008, and in an attempt to enhance survival in advanced disease, maintenance chemotherapy trials were initiated which had recently demonstrated prolongation of survival by an additional 2–3 months in patients who had performance status (PS) 0–1 and well-preserved organ functions. Suitable patients with any degree of clinical benefit are treated with 4–6 cycles, and then one of the active agents is continued until best response, or toxicity (continued maintenance), or changed to a cross non-resistant single agent (switch maintenance). The article briefly reviews the evolution of systemic therapy and describes key randomised trials of maintenance therapy instituting chemotherapy and targeted agents in an attempt to improve outcomes in advanced metastatic NSCLC, based on certain clinical features, histology, and genetics.

Keywords: Carcinoma; Non-small-cell lung; Lung neoplasm; Maintenance chemotherapy; Molecular targeted therapy; Receptor; Epidermal growth factor; Vascular endothelial growth factor A.

Lung cancer is the most common cancer worldwide and a leading cause of cancer-related deaths (19.4%). The Global Cancer Incidence Project (GLOBOCAN) estimated 12.7 million new cancers and 7.6 million cancer deaths worldwide in 2008. Lung cancer accounts for 1.6 million new registered cases and 1.37 million deaths around the globe in the same year.[1] The American Cancer Society (ACS) estimated that there were 226,160 lung cancer cases and 160,340 lung cancer-related deaths in 2010 in the United States alone. The incidence of lung cancer is higher among men when compared to women, accounting for 34% and 13.5% of all cancers, respectively. The age-standardised ratio for its incidence is 33.81%, and has a 29.2% rate in men.[2] The ACS numbers currently place the adenocarcinoma subtype at 40% of all the reported cases.[3] In 2000–2003, the US Surveillance Epidemiology and End Results (SEER) database also described it as the most prevalent (47%) lung cancer subtype regardless of race, age, or gender, and the shift in histology was attributed to

Department of Medicine, [1]Sultan Qaboos University Hospital & [2]College of Medicine & Health Sciences, Sultan Qaboos University, Muscat, Oman

**Corresponding Author e-mail: furrukh_1@yahoo.com*

changes in the manufacturing of cigarettes, creating filters that allow deeper inhalation, thus channelling smoke towards the distal bronchioles.[4]

Based on a 2010 report on cancer incidence in Oman, published by the Ministry of Health, between 1998 and 2007 lung cancer was the fifth most common cancer in Oman compared to other Gulf Cooperation Council (GCC) countries. In 2010, it was the eighth commonest cause of cancer deaths among men (4.5%).[5] It was also reported to be the most common cause of cancer-related, hospital-based deaths in 2008 and the second most common cause in 2010, representing 8.78% of all cancer deaths, following stomach cancer.[5,6] The age-standardised incidence rate was 4.2 and 0.7 per 100,000 per year, and the crude incidence was 1.9 and 0.3 in men and women, respectively. The disease ranks first as a cause of cancer-related deaths in Qatar, the United Arab Emirates (UAE), and Bahrain. In Oman, small cell lung cancer (SCLC) accounted for 12% and non-small-cell lung cancer (NSCLC) for 88% of all the cancers reported in those countries. Among NSCLCs, the adenocarcinoma subtype accounted for 34%, squamous cell carcinoma around 22%, and other specified carcinomas and not otherwise specified subtypes accounted for 16% of cases.[5]

Traditionally, advanced metastatic NSCLC was treated with palliative systemic chemotherapy, but the majority of those patients experienced disease progression shortly after the cessation of chemotherapy, including those who initially responded to such an intervention. Recently, maintenance therapy has emerged as a new hope for these patients with improved outcomes and is associated with prolongation of survival by a median of two to three months. This article describes the consistent gains in survival over the past few decades and current evidence related to maintenance therapy, and also tries to identify patient subsets which are most likely to benefit from maintenance therapy.

Methods

Data was identified from searches in Medscape, PubMed, Google, and key cancer groups such as the American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), and the European Society for Medical Oncology (ESMO) by using terms such as 'chemotherapy in metastatic or advanced non-small-cell lung cancer', 'maintenance chemotherapy', 'consolidation therapy', and 'molecular targeted therapy'. Reference was also made to key phase II and III trials and meta-analyses published in reputable oncology journals (e.g. Journal of Clinical Oncology, the New England Journal of Medicine, Oncologist, Lancet Oncology, Journal of Thoracic Oncology).

Systemic Chemotherapy in Advanced Non-Small-Cell Lung Carcinoma

Patients with untreated advanced or metastatic disease have a median survival period of ~4 months, and can expect a one-year survival period in 10% of cases when managed with best supportive care (BSC).[7] Systemic chemotherapy remains the standard treatment for advanced or metastatic NSCLC, especially for patients who do not harbour somatic mutations of the epidermal growth factor receptor (EGFR) gene. A meta-analysis in 1995 showed that the use of cisplatin-containing chemotherapy was found to be associated with a 27% reduction in the risk of death, and improvement of 10% in survival, to attain a cumulative survival of 20% at one-year when compared to BSC alone (P <0.0001).[8]

Poly-chemotherapy with a cisplatin backbone remained the gold standard based on two meta-analyses in advanced NSCLC. In studies of cisplatin *versus* carboplatin by Hotta *et al.*, patients with metastatic lung cancer were evaluated during treatment, revealing that cisplatin was marginally superior to carboplatin. The studies also found that the addition of a third generation agent to cisplatin was associated with an 11% longer survival compared to cisplatin being used alone.[9,10] Large randomised phase III trials also have shown that platinum-doublets, (with gemcitabin, docetaxel, or vinorelbine) yielded a median overall survival (OS) of 8–10 months. A meta-analysis of 65 trials, including 13,601 patients, confirmed that the use of doublet chemotherapy increased the response rates (RR) and the median survival rates at one year by 20% when compared to single agent therapy. Adding a third agent to platinum doublets enhanced the response rates but not the survival and were more toxic.[11]

The Cochrane Collaboration Group analysed 16 randomised trials of more than 2,700 patients with advanced NSCLC.[12] Platinum doublets were found to be associated with higher RR with an absolute benefit of 9% improvement in median OS at one year (i.e. 20%) using single agents *versus* 29% using doublets (P <0.0001).

The Eastern Co-operative Oncology Group's (ECOG) E1594 trial compared various third generation agents (paclitaxel, doxetaxel, or gemcitabine) in combination with a platinum compound.[7] The response rates were 19% and the median survival was 9.2 months in females (n = 431) and 7 months in males (n = 726) and the one- and two-year survival rates were 30% and 10%, respectively. Other randomised clinical trials showed consistent results.[13-17] Socinski *et al.* reported nab paclitaxel carboplatin use in advanced squamous histology where the combination was associated with a highly significant response rate of 41% *versus* 24% for cremophor paclitaxel and carboplatin, but there was no improvement in survival rates except in elderly.[18]

In 2006, the Doulliard meta-analyses comprising 7 randomised clinical trials, including 2,867 patients, compared docetaxel to vinorelbine. The study confirmed a 11% reduction in the risk of death and a 43% reduction in the risk of febrile neutropaenia in favour of docetaxel.[19] The impact of third generation drugs on the activity of first-line chemotherapy in advanced NSCLC was published in 2009 in a meta-analysis by Francesco Grossi. The study included 45 trials of 11,867 patients. The risk of immediate progression was found to be 14% lower with gemcitabine, a statistically insignificant 9% lower with docetaxel, and 22% higher with paclitaxel. No risk of immediate progression was seen with vinorelbine.[20]

Meta-analysis of poly-chemotherapy incorporating platinum triplets certainly improved response rates (P = 0.001), but neither showed improvement in progression-free survival (PFS) or OS (P = 0.88) and was certainly associated with higher toxicity.[21] As a gold standard, platinum can be combined with any of the third generation agents (i.e. docetaxel, gemcitabine, vinorelbine, or irinotecan) with superior efficacy. The choice of agent generally depends on clinical parameters, drug availability, cost, patient convenience, and toxicity. Carboplatin is still widely used for patients with marginal renal functions and is associated with higher rates of thrombocytopenia, especially when used in combination with gemcitabine, but needs less hydration.

Two separate meta-analyses of over 12,000 patients combined compared responses, survival, toxicity, and cost of the platinum *versus* non-platinum doublets.[22,23] The RR were higher with cisplatin but the OS outcomes remained the same. One review compared platinum therapy to non-platinum agents, with a 60% increase in the odds ratio for objective RR (P <0.0001) and a 5% enhancement in patients' 12-month survival (P <0.0003) in favour of cisplatin-based chemotherapy. It was also associated with reduced risk of death and less chemo-refractoriness, while a higher likelihood of response to platinum doublets was observed in the other trial.[22,23] The rates of nausea, vomiting, delayed vomiting, myelosupression, nephrotoxicity, and gastro-intestinal (GI) toxicity remained high with the platinum compounds.

When cisplatin was compared with third generation agents, there was no difference in survival outcomes (P = 0.17), but it was associated with more neuropathy, more febrile neutropaenia, and toxic deaths. The third generation singlets were better tolerated, found less toxic in the case of ECOG performance status (PS) 2, and may also be an option in selected PS 3 patients, or in those who are elderly or with major co-morbidity. Moreover, third generation singlets remained a suitable option, when platinum compounds were contraindicated. Carboplatin was not found to be superior to these agents; in fact, it was associated with 11% higher mortality in non-squamous NSCLC.

It is evident that the median survival of patients with advanced (IIIB) or metastatic (IV) NSCLC has enhanced substantially over the last few decades. For those receiving BSC, the median survival time is approximately 3–4 months, around 6 months for those receiving single agent platinum, and, when patients receive 4–6 cycles of cisplatin doublets (cisplatin plus a third generation agent), the median OS reaches 8–10 months.[7]

The combination of cisplatin plus pemetrexed has lately emerged as standard of care in non-squamous NSCLC, with a resultant median survival of 12.6 and 11.4 months for adenocarcinoma and large cell carcinoma subtypes, respectively, while

Table 1: Eastern Co-operative Oncology Group (ECOG) performance status[25]

ECOG PERFORMANCE STATUS	
Grade	
ECOG	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair
5	Dead

carboplatin plus gemcitabine or docetaxel has emerged as the best combination for treating the squamous subtype.[24] Thus, histology for the first time emerged as a predictor for response, and the impression of one chemotherapy combination as the sole therapy for all histology has started to fade away.

To date, platinum doublets remain the mainstay of treatment in patients with ECOG PS 0–1 [Table 1], and with marginally higher toxicity in PS 2 patients.[25] The absolute benefit of chemotherapy at one year varied according to the PS: in PS 0 and 1, the absolute benefit was 8%; in PS 2 the benefit was 5%, and in PS 3 it was 4%.[26]

Lung cancer is a disease of the elderly and approximately one in every three patients is 70 years or above. An equal number of patients have a PS of 3 or 4. Treatment of the elderly, and those with poor performance should be individualised.[27] A third generation agent seems suitable, and there has been some evidence that these improved survival rates were as good as in younger patients when compared to BSC in the fit individuals with well-preserved organ functions at the expense of higher toxicity.[28]

In the last 5 years, the plateau in survival gains prompted researchers to drift either towards molecular profiling and targeting cells at the molecular level, or towards improving survival outcomes with maintenance therapy until patients experience best response or toxicity. BSC was considered superior to chemotherapy in the frail or elderly and for those with ECOG PS 3 or 4.[7, 45]

It had also been a matter of debate as to what constitutes the exact number of chemotherapy cycles in advanced NSCLC. By 2009, it had been established that "doublet chemotherapy should be administered for no more than 6 cycles" and for patients who attain either disease stabilisation or some response to induction chemotherapy, a treatment-free interval was offered.[29] Initiation of a different chemotherapy prior to disease progression was not the norm. A focused update in 2009 recommended that in patients with metastatic NSCLC, frontline platinum doublet should be discontinued at disease progression.[29] Those who attain disease stabilisation should be offered a total of 4 chemotherapy cycles while those with any degree of benefit should be continued until 6 cycles have been achieved.[29]

In recent times, the outcome of advanced and metastatic NSCLC has improved substantially with the integration of chemotherapy with biologics either sequentially or concurrent. The targeted agents include the EGFR-tyrosine kinase inhibitors (TKI) (erlotinib or gefitinib) and the corresponding chimeric EGFR-blocking antibody cetuximab, and the anti-angiogenic monoclonal antibody bevacizumab which targets the vascular endothelial growth factor (VEGF).[30–32] These agents are used as upfront therapy in combination with platinum doublets, and were based on large randomised clinical trials where they were continued beyond chemotherapy as maintenance therapy until progression of the disease or the appearance of toxicity.

Maintenance Therapy

The biologic basis of maintenance therapy is the Goldie-Coldman hypothesis which states that early use of non-cross resistant agents might increase the probability of killing more cells before resistant clones arise.[33] Patients tolerating and responding to treatment with 4 cycles of chemotherapy may be treated with an additional two cycles. Maintenance therapy using single agent chemotherapy is offered until progression of the disease or appearance of toxicity, while ensuring that the PS does not deteriorate. On the contrary, the day model indicates that the most active drug regimens should

Table 2: Key phase III trials of switch maintenance therapy in non-small-cell lung carcinoma

Clinical Trials	Treatment Arms	No. Patients	PFS(m)	OS (median)
Fidias *et al.*[40] 2009	Gemcitabine Carboplatin- immediate Dx Gem Carb → Docetaxel at progression	309	5.7 2.7 (*P* <0.0001)	12.3 9.7 (*P* <0.0853)
Capuzzo *et al.* (SATURN)[39]	Platinum doublet – Erlotinib (EGFR Mut) Platinum doublet – placebo	438 451	5.7 3.7 (*P* <0.0001)	12 11 (*P* <0.0088)
Ciuleanu *et al.* (JMEN)[37]	CG, PG, DG → Pemetrexed + BSC *versus* Placebo + BSC	441 222	5.2 2.6 (*P* <0.0001)	*18.6 13.6 (*P* <0.0001)
Takeda *et al.*[43] (WJTOG)	Platinum doublets x 6 Platinum doublets – Gefitinib maintenance	604	higher (*P* <0.001)	(*P* <0.11) ^22 vs 11 *15.5 vs 7.7
Zhang *et al.*[42] (INFORM C-TONG 0804)	Platinum doublets + BSC Platinum doublets – Gefitinib maintenance	296	2.6 4.8 (*P* <0.0001)	(*P* = NS)

*^never smokers vs smokers; *Adenocarcinoma vs non-adenocarcinoma.*
NS = not significant.

be used as a consolidation treatment to optimise results, and that treatment should be restricted to only 4–6 cycles.[34]

The rationale for continued intervention is simple: if one waits, allowing a chemotherapy-free interval, the disease progresses in roughly two months, with symptomatic deterioration and a possible fall in performance status. Offering immediate maintenance *versus* delayed salvage therapy at progression has always been an area of debate.[35]

Switch maintenance therapy refers to the continuation of systemic therapy using a different non-cross-resistant drug from the patient's initial chemotherapy regimen before disease progression. In a meta-analysis by Soon YY in 2009, patients with any degree of response or disease stabilisation were either subjected to maintenance treatment or were asked to watch and wait with intervention at progression.[36] There was a 50% drop rate due to the deterioration of signs and symptoms or performance status in the watch and wait group, and only 50% were found fit enough to receive second-line therapy at progression. Therefore, the benefit of such an approach was questioned and instead Soon posited continuing chemotherapy until best response or toxicity. The hypothesis generated was meant to meet a primary endpoint of enhancement in PFS and an improvement in median OS with acceptable toxicity and tolerability while maintaining the PS.

Virtually all patients with advanced, metastatic NSCLC progress after initial response to induction chemotherapy. Second-line chemotherapy improved PFS and enhanced the median OS. Soon *et al.* carried out a meta-analysis of 13 randomised trials between 1989 and 2008. Soon's meta-analysis was certainly influenced by a relatively large permetrexed maintenance therapy (JMEN) trial (excluding ATLAS and SATURN trials), comprised of over 3,000 patients, of which 10 of the 13 trials were done in the years after 2000.[37–39] The following facts were revealed in favour of maintenance therapy: 1) The improvement in OS was a statistically significant 8% reduction in the hazard of death (HR 0.92; 95%; confidence interval [CI] 0.86–0.99; *P* = 0.03) for continued therapy; 2) It was not dependent on chemotherapy use, either platinum or third-generation agents; 3) The PFS improved with maintenance therapy, with a 25% reduction in hazard for progression (HR 0.75; 95% CI; 0.69–0.81; *P* <0.00001). The use of third-generation agents was associated with higher PFS (*P* = 0.003) when compared to the older regimens; 4) Five of the 7 trials demonstrated major improvements in global quality of life (QoL) scores when using the maintenance chemotherapy arm; two of the 7 favoured the standard chemotherapy arm; 5) Two of the 7 trials suggested an increase in the adverse effects in the maintenance arm, especially myelotoxicity; 6) Cost of the drugs and associated hospital stays were reasons for concern.

There are numerous arguments against continuing chemotherapy in the palliative setting

as this is carried out without breaks in therapy, subjects advanced cancer patients to more toxicity, involves more trips to outpatient clinics, and increases the frequency of blood tests and/or transfusions. Maintenance may also be associated with poor QoL.[35]

The following text briefly describes trials and outcomes of effective, better-tolerated drugs that have emerged as agents to be used as maintenance therapy in selected lung cancer patients.

TRIALS OF SWITCH MAINTENANCE

Fidias *et al.* conducted a phase III trial of 309 patients with advanced NSCLC who did not show progression after first-line treatment with 4 cycles of carboplatin-gemcitabine. The patients were randomised to receive immediate docetaxel *versus* delayed (at progression) treatment.[40] Of those who enjoyed a chemotherapy holiday until progression of the disease, 37% had either deterioration of their PS or symptomatic deterioration, and therefore were not subsequent candidates for delayed docetaxel. However, of those in the maintenance arm, 95% could undergo immediate docetaxel. The two arms had similar RR, but the maintenance therapy was associated with significant improvement in PFS by three months (P = 0.0001). However, there was no difference in median OS (12.5 months, P = 0.08) in the delayed docetaxel arm. Though a negative trial, it is evident that a delay in salvage therapy resulted in a third of the patients falling short of subsequent intervention [Table 2].

Conducted by Cappuzzo *et al.*, the SATURN study was a non-chemotherapy, large phase III randomised trial of 1,949 patients.[39] Patients with adenocarcinoma subtypes were subjected to maintenance erlotinib after 4 cycles of standard induction chemotherapy. The trial improved PFS by two months (P = 0.0001) and median OS by one month (12 *versus* 11 months, P = 0.0088) in favour of erlotinib. Subset analyses revealed a greater benefit for patients with EGFR mutations and, interestingly, patients having wild-type EGFR also derived benefit with maintenance erlotinib (11.3 *versus* 10.2 months, P = 0.0185). All histologic subtypes benefited, but adenocarcinoma and those with stable disease benefited the most (11.9 months for erlotinib *versus* 9.6 months for placebo P = 0.0019). Based on the SATURN study[39] and retrospective exploratory data from BR.21 trials, patients with squamous-cell carcinoma (SCC) also benefited from erlotinib after induction chemotherapy as second- or third-line salvage, but use of erlotinib as maintenance in SCC remains to be defined in the context of a clinical trial.[41] A manageable acne-like rash and diarrhoea were the only toxicity reported with erlotinib use, but it was not cumulative and reduced over time.

The JMEN 663-patient trial involved pemetrexed treatment combined with BSC *versus* the use of a placebo plus BSC.[37] The study revealed improvement in PFS by 2.5 months and a landmark 5.2 months improvement in OS in the adenocarcinoma subtypes (P = 0.0001). SCC histology had a detrimental effect on survival due to differential expression of thymidylate synthase, and the survival in SCC histology was indeed inferior by one month (P = 0.9). The trial included stage IIIB/IV NSCLC, PS 0–1 stable, or responding disease post-platinum doublets. Pemetrexed also has the advantage of ease of administration (a 10 minute intravenous (IV) infusion) and therefore outpatient administration and superior tolerability with similar QoL scores. Pemetrexed maintenance was associated with higher but manageable toxicity (i.e. 16% in the pemetrexed arm *versus* 4% in the placebo arm) There was a 3% incidence of grade 3–4 neutropenia *versus* 0% in the placebo group, and 5% of patients felt fatigue in the treatment arm *versus* 1% in the placebo arm.

INFORM, a Chinese trial published by Zhang L. *et al.* used platinum doublets in non-progressing lung cancer patients who were subsequently randomised to receive gefitinib plus BSC *versus* BSC only.[42] The PFS was superior in favor of the TKI arm but the OS remained the same.

In the West Japan Thoracic Oncology Group Trial, 600 chemotherapy-naïve, stage IIIB/IV patients with NSCLC (asymptomatic brain metatstases allowed, 31% non-smokers, 78% adenocarcinoma) were randomised to 6 cycles of platinum doublets *versus* 3 cycles followed by gefitinib maintenance.[43] The gefitinib arm revealed improvement in PFS (P = 0.001) with a trend towards improvement in OS. Subset analyses showed doubling in median OS in non-smokers compared to smokers as well as in the adenocarcinoma subtypes in the gefitinib maintenance arm.

A modest 1.2 months of improvement in median PFS was seen in a French IFC trial (EORTC 08021) trial of maintenance gefitinib, but no gains

Table 3: Key phase II-III trials of continuous maintenance therapy in non-small-cell lung carcinoma

Clinical Trials	Treatment Arms	No. of Patients	PFS	Median OS (m)
Belani *et al.*[47]	Carboplatin Gemcitabine Carboplatin Gemcitabine → Gemcitabine	390 -ive trial as 66% patients KPS<80	(*P* <0.124)	(*P* <0.243)
Brodowicz *et al.*[9]	Cisplatin Gemcitabine Cisplatin Gemcitabine → Gemcitabine	519 (OS for KPS<80-12.2m) (OS for KPS>80-25.3m)	5.5 6.6 (*P* <0.001)	11 13 (*P* <0.2)
Perol *et al.*[51]	Cisplatin Gemcitabine → Gemcitabine Cisplatin Gemcitabine → Observation Cisplatin Gemcitabine → Erlotinib	464	3.8 (*P* <0.0001) 1.9 2.9 (*P* <0.002)	*P* = NS
Paz-Ares *et al.*[2] (PARAMOUNT)	Cisplatin Pemetrexed → Pemetrexed + BSC Cisplatinu Pemetrexed – Placebo + BSC	539	4.1 2.8 (*P* <0.0006)	13.9 11 (*P* <0.0195)

NS = not significant.

were witnessed in the OS.[44] Switch maintenance by virtue of increase in PFS and OS (pemetrexed or erlotinib) has emerged as a new standard of care in adenocarcinoma patients with preserved organ function who maintain PS 0–1, and therefore has been approved by the NCCN Guidelines version 3.2012.[45]

TRIALS OF CONTINOUS MAINTENANCE

Continuous maintenance refers to the prolonged use of one or more agents which the patient has been exposed to in his/her initial regimen in the absence of disease progression. There are several published randomised and ongoing clinical trials addressing the role of continuation maintenance therapy for advanced/metastatic NSCLC [Table 3].

Socinski *et al.* reported a negative trial of 230 patients with advanced NSCLC.[46] Patients were treated with carboplatin paclitaxel doublets for a total of 4 cycles and then were either subsequently treated with weekly paclitaxel until progression or given a chemotherapy-free interval (CFI). The same agent was then given again at disease progression. The continuation paclitaxel failed to improve the RR, the median survival rate, or QoL scores. However, the extended therapy arm resulted in a higher incidence of neuropathy; 40% compared to 20% in the observation arm.

In 2003, Belani *et al.* described the use of weekly maintenance paclitaxel in 390 non-progressing advanced and metastatic NSCLC cases.[47] Using 3 different schedules of paclitaxel and carboplatin, the study revealed neither improvement in time to progression (TTP) (38 *versus* 29 weeks; *P* = 0.124) nor in the median survival (75 *versus* 60 weeks; *P* = 0.243).

Von Plessen *et al.* demonstrated, in another negative trial, that 6 *versus* 3 cycles of vinorelbine and carboplatin did not translate into a meaningful prolongation of PFS (21 *versus* 16 weeks; *P* = 0.21) or OS (32 *versus* 28 weeks; *P* = 0.75), and more blood transfusions were used in the maintenance arm.[48]

The use of gemcitabine as continuation therapy after initial treatment with 4 cycles of gemcitabine and cisplatin remains one of the most promising of the continuous maintenance therapies. Brodowicz *et al.* showed that maintenance therapy with gemcitabine resulted in a longer median time to progression (6.6 *versus* 5.0 months; *P* < 0.001) without any significant improvement in median OS (13 *versus* 11 months; *P* = 0.195).[49] However a pre-planned subgroup analysis revealed that in those with a Karnofsky performance status (KPS) score of greater than 80, the median survival doubled (25.3 *versus* 12.2 months). Gemcitabine maintenance following gemcitabine carboplatin combination reported by Belani *et al.* was a negative trial for PFS (*P* 0.57) and OS (*P* 0.83), possibly because 66% of the patients had PS 2 and only 34% had a PS 0–1.[50] A subgroup analysis, where patients' KPS was >80, clearly favoured the gemcitabine maintenance arm. Until those studies, continuation maintenance therapy was associated with a modest improvement in PFS with no gains in OS at the expense of more but manageable side-effects. KPS emerged as a strong predictor for response and a clinically meaningful outcome for maintenance therapy.

In the IFCT-GFPC 0502 French trial of 464

patients with stable disease or responders, 4 cycles of cisplatin gemcitabine were used and later subgroups were continued on gemcitabine or a placebo, or were switched to erlotinib maintenance.[51] All patients who subsequently progressed were offered pemetrexed. PFS was superior in the erlotinib group (2.9 months; $P = 0.002$) *versus* the gemcitabine group (3.8 months; $P < 0.0001$) *versus* the observation arm (1.9 months), but the OS was only numerically superior in the maintenance arms.

The PARAMOUNT trial incorporated maintenance pemetrexed in a phase III setting in patients receiving initial platinum pemetrexed doublets for 4 cycles. A group of 359 non-progressive patients were randomly assigned to maintenance pemetrexed plus BSC, while 180 patients were assigned to a placebo plus BSC. The test arm revealed superior PFS (4.1 months *versus* 2.8 months; $P = 0.0006$) in all age groups, irrespective of smoking status. All responders indicated an equal QoL, with 3–4% indicating grade 3 or 4 toxicity including nausea, anaemia, fatigue, etc. However, fatigue was significant (5% *versus* 1% in those receiving ≤12 cycles) and may be managed by increasing the cycle interval to 4 weeks. The OS data were presented at the 2012 ASCO Conference where maintenance pemetrexed plus BSC was associated with a 22% reduction in risk of death (HR 0.78; 95% CI; 0.64-0.96) and the OS was 13.9 *versus* 11 months for the placebo plus BSC group ($P = 0.0195$), and was maintained when calculated from the beginning of induction therapy (17 *versus* 14 months). A third of the patients lived beyond 24 months.[52]

FAST ACT-I was a phase II study by Tony Mok *et al.* employing platinum gemcitabine doublets every 4 weeks for 6 cycles in untreated stage IIIB/IV NSCLC, concurrent with erlotinib or a placebo followed by continuous maintenance erlotinib in non-progressing patients in the experimental arm *versus* erlotinib at progression in the placebo arm.[53] PFS was increased, but not OS in the continuous maintenance arm. Based on this encouraging result, a phase III trial (FAST ACT-II) with a similar design has completed patient accrual in September 2010 and the results are keenly awaited.[54] Some institutes, including ours, finds it reasonable to continue pemetrexed, or gemcitabine, or erlotinib in patients with adenocarcinoma subtypes and gemcitabine in SCC.

Based on the compelling data above, the focused update in 2011 recommended that a patient with any degree of clinical benefit after 4 cycles of frontline platinum doublet therapy, an immediate alternative, or a single agent should continue maintenance treatment. This should be offered for patients with adenocarcinoma subtype having PS 0–1.[55] Maintenance therapy in frail and elderly patients should be individualised in the absence of controlled randomised trials. With their ease of administration at home, lack of the serious side effects that are generally seen with chemotherapy, and potential use in ECOG PS ≥2 patients, oral TKIs remain a viable therapeutic option in this set of patients.

MOLECULAR TARGETS AND MONOCLONAL ANTIBODIES AS MAINTENANCE

Vascular Targets and Bevacizumab (Monoclonal antibody targeting the VEGF (vascular edothelial growth factor A)

Tumour angiogenesis has long been established. In 1971, Folkman proposed a hypothesis regarding the presence of vascular factor, and it took almost two decades to discover vascular endothelial growth factor (VEGF).[56] Tumours require a rich vascular supply in order to grow and metastasise. A tumour of 1–2 mm can survive without acquiring a blood supply, but as it grows it evolves an independent blood supply by the release of VEGF that binds to corresponding receptors (VEGFR), initiating angiogenesis, cell proliferation, invasion, and metastases.

In a 2004 study whereby researchers locked VEGF pathways and thus tumourigenesis by monoclonal antibodies, patients showed higher response rates and superior survival outcomes. In the initial phase II trial of bevacizumab, two different dose schedules (7.5 and 15 mg/kg) were used, with a carboplatin paclitaxel doublet for a maximum of 6 cycles, whereas in the third arm, bevacizumab was added to the same combination therapy at disease progression and maintained until best response or toxicity.[57] Patients with SCC were excluded in subsequent trials because of an increased risk of fatal haemoptysis (9% pulmonary haemorrhage), especially if the lesions were cavitating, central, or adherent to a mediastinal blood vessel. Also excluded were patients with CNS metastases, due

Table 4a: Key phase II-IV trials of addition of continuous Bevacizumab +M. Bev – therapy in non-small-cell lung carcinoma

Author/ Study	# of Patients	Phase	Regimen	RR (%)	PFS (m)	*P* value	OS (m)	*P* value
Johnson *et al.*[57]	99	II	Chemo alone + M. Bev	30 40	7 7.4	0.023	14.9 17.7	0.63
Seiji Niho[58]	180	II	Carbo/ Pac + M. Bev	31 60.7	5.9 6.9	0.009	22 22	0.9
Jyoti *et al.*[64]	50	II	CDDP/ Pem + M. Bev.		8		14.6	
Sandler *et al.* (ECOG E4599)[59]	878	III	CDDP/ Pac M. Bev.	15 35	4.5 6.2		10.3 12.3	0.003
Subgroup analyses: -adenocarcinoma -developing hypertension							14.2 15.9	0.03
Reck Martin *et al.* (AVAIL)[61]	1043	III	CDDP/ Gem + Bev 7.5 mg/ kg + Bev 15 mg/ kg	22 38 35	6.1 8.5 8.2		13.1 13.6 3.4	0.76
Lucio Crino *et al.* (SAiL)[62]	2212	IV	Chemo + M. Bev		8.3		19.3	
Miller *et al.* (ATLAS)[38]	740	III	Platinum doublet + bev + M. bev + M. bev + erlotinib		3.7 4.8		~	NS 0.0012
AVAPERL1[65] (ongoing)	362	IIIb	CDDP Pem Bev. + M. Bev. + M. Bev. + Pem		3.7 7.4	<0.001	15.7 not reached	0.23

Table 4b: Phase II & III trials of cetuximab in advanced metastatic non-small-cell lung carcinoma

Study/Author	# of Patients	Phase	Regimen	RR (%)	PFS	OS (m)
LUCAS[76] Rosell	86	II	CDDP / Vin + Cetuximab	28 35	4.6 5	7.3 8.3
BMS 100[75] Butt	130	II	CDDP / Gem + Cetuximab	18 28	4.2 5.1	9 12
FLEX[71] Pirker	1135	III	CDDP / Vin + cetuximab	29 36	4.8 4.8	10.1 11.3
BMS 099[74] Lynch	676	III	Carb / Taxane + Cetuximab	17 26	4.4 8.4	4.2 9.7

RR = response rate; PFS = progression-free survival; OS = overall survival; Chemo = chemotherapy; +MBev = bevacizumab maintenance after induction with chemo + bevacizumab; Carb = carboplatin; Pac = paclitaxel; Pem = pemetrexed; Gem = gemcitabine; CCDP = cisplatin; Vin = vinorelbine; NS = not significant.

to a fear of intra-tumoural bleed. RR were enhanced from 30% with platinum doublets to 40% with doublets plus bevacizumab at 15 mg/kg weight. The median PFS (7 months *versus* 5.9 months; *P*= 0.023) and OS (17.7 months *versus* 14.9 months; *P* = 0.63) were superior in the 15 mg/kg bevacizumab arm. In another phase II Japanese trial, J 019907, paclitaxel and carboplatin were used alone or with bevacizumab, and the addition improved RRs and the PFS by one month (*P* = 0.009).[58]

In an open label prospective, randomised, ECOG E4599 trial [Table 4], the addition of bevacizumab to the paclitaxel and cisplatin arm was associated with enhanced RR (35% *versus* 15%), superior PFS (6.2 *versus* 4.5 months), and a median OS (12.3 *versus* 10.3 months; *P* = 0.003).[59]

The one- and two-year survival rates improved from 44% to 56%, and 17% to 27%, respectively. Subgroup analyses revealed that patients with adenocarcinoma subtypes showed median survival improvement to 14.2 months (a 3.9 month improvement). For those who developed

hypertension (defined as >150/100 mm/Hg or a 20% increase in diastolic blood pressure (BP) from the baseline) because of bevacizumab, the median OS was longer (15.9 months; $P = 0.03$).[59] In retrospect, subset analyses in patients above 70 years show a trend towards higher RR and PFS with the addition of bevacizumab, but there was no increase in OS ($P = 0.4$). It is not clear as yet if the improvement in efficacy was because of induction or because of the maintenance effects of bevacizumab.

AVAIL was a randomised phase III trial using cisplatin, or gemcitabine and bevacizumab in three groups: Group A received chemotherapy alone; Group B received chemotherapy and 7.5 mg/kg of cisplatin, and Group C received chemotherapy plus 15 mg/kg of bevacizumab.[61] The RRs improved (Group A - 22%; Group B - 38%; Group C - 35%) but there was no improvement in survival with the bevacizumab addition. The primary endpoint of the trial was not an investigation of maintenance.

SAIL, an open label phase IV trial of 2,212 patients from 40 countries, analysed the addition of bevacizumab to platinum doublets followed by maintenance bevacizumab, which suggested an improvement in time to progression (TTP) to 8+ months and a median OS to a landmark 19.3 months.[62] These figures were reproduced by another US-based study, ARIES, where the median OS also approached 13.6 months.[63]

A phase II trial, combining pemetrexed-carboplatin with or without bevacizumab also improved survival outcomes.[64] The PFS was 8 months and there was an OS of 14.6 months with the addition of bevacizumab. Based on these findings, a randomised trial (AVAPERL 1) was initiated in patients with advanced adenocarcinoma, incorporating pemetrexed-cisplatin with or without bevacizumab and then continued with maintenance bevacizumab, with or without pemetrexed.[65] The maintenance combination of bevacizumab and pemetrexed revealed better RR and a superior PFS. The median OS was 15.6 months in the bevacizumab arm, which has not yet been reached in the bevacizumab-pemetrexed maintenance arm. In summary, the addition of bevacizumab to the standard platinum doublets gives a definitive hint at improving the median survival in adenocarcinoma subgroups way beyond the 12 months seen in PS 0–1 patients.

Information on continuing bevacizumab beyond progression came from preclinical data in animal xenografts, where it not only enhanced the effects of chemotherapy, but also delayed regrowth and improved survival.[66] An observational study of bevacizumab use beyond progression in metastatic colorectal cancer has confirmed significant improvement in medial survival, from 26 months to 31 months.[67] In a retrospective analysis from the electronic medical records of NSCLC in the US, in a total of 498 non-squamous NSCLC patients, 403 received first line chemotherapy plus bevacizumab; 154 received bevacizumab monotherapy on progression; and 249 did not. Median OS was 20.9 months for the bevacizumab group *versus* 10.2 months for the chemotherapy only group, and a PFS of 10.3 months for the bevacizumab group *versus* 6.5 months in the chemotherapy only group.[68] A large multi-institutional, prospective, controlled randomised trial by Avastin in all lung lines was initiated by Roche Pharmaceuticals, and is currently recruiting patients.[69] It incorporates induction platinum doublets plus bevacizumab which is continued post-progression, with salvage single-agent sequential chemotherapy with each progression in an attempt to improve survival figures, without compromising QoL and with acceptable toxicity.

Miller *et al.* published the ATLAS, a phase III trial on advanced NSCLC patients (n = 768) treated with platinum doublets for 4 cycles using bevacizumab as a third agent during induction and then continued in non-progressing patients alone or with concurrent erlotinib.[38] The combination arm had a superior PFS by 1.1 months (4.8 *versus* 3.7 months; $P = 0.0012$), but there was no improvement in OS; therefore, it is a struggle to find a place for the use of two targeted agents in the presence of better options [Table 4]. The ongoing study design of the ERACLE trial (induction pEmetrexed and cisplatin followed by maintenance pemetrexed *versus* carboplatin-paclitaxel and bevacizumab followed by maintenance bevacizumab) compares the two drug combinations in non-squamous NSCLC in a maintenance setting.[70] Point break trial is a negative trial for OS, yet the maintenance arm comprising of pemetrexed & bevacizumab revealed 1.7 & 2 months improvement in PFS and OS respectively compared to bevacizumab maintenance alone.

Epidermal Growth Factor Receptor and Cetuximab (Monoclonal Antibody Targeting the EGFR)

The First Line Erbitux in Lung Cancer (FLEX) trial was a phase III, prospective, randomised trial of 1,125 patients from 155 treatment centres comparing the addition of cetuximab to cisplatin and vinorelbine given for 6 cycles.[71] In the test arm, cetuximab was continued as maintenance until progression of disease or unacceptable toxicity. Median OS was 11.3 months in the experimental arm (n = 557) and 10.1 months in the chemotherapy alone arm (n = 558 patients; *P* = 0.044). Interestingly, women survived longer than men (12.7 months *versus* 9.3 in men), Asians did better compared to Caucasians (19.5 months *versus* 9.6), and patients with a better performance status, as well as those who had never smoked, did statistically better. Patients with an acne-like rash (grade 1–3 rash seen in 56%, grade 3 in 10%) had a longer overall survival than those without (15 months *versus* 8.8; *P* <0.001). The addition of monoclonal antibodies improved the RRs, which was statistically significant (36% *versus* 29%). Adenocarcinoma subtype (46% of overall patient population) expressing EGFR (defined as at least one EGFR protein on immunohistochemistry (IHC) showed a survival of 20.2 months in the experimental arm and 13.6 months in the chemotherapy-only arm.[72] The researchers looked at the EGFR expression in a qualitative manner (i.e. product of the staining intensity [1+, 2+, 3+]) and the number of cells stained on IHC were scored between 0–300. A total of 30% of the patients had an EGFR H-score >200, which was considered strongly expressive, and a median survival of 12 months was seen in the cetuximab plus chemotherapy arm as compared to those with an EGFR H-score <200, which was considered negative, where the survival was 9.3 months (HR 0.75). Patients with SCC (34% of the patient population) had a median OS of 10.2 months in cetuximab group *versus* 8.9 months in chemotherapy-only arm. A subgroup analysis revealed an EGFR overexpression in 30% of SCC patients, and when these were subjected to cetuximab and chemotherapy, the survival improved to 11.2 months for the combination arm *versus* 8.9 months for the chemotherapy-only arm, and also improved one-year survival to 44% in the combination arm *versus* 25% in the chemotherapy-only arm. Unlike colon carcinoma, the *k*-ras mutation did not predict the response to cetuximab.

A retrospective analysis of FLEX trial reveals the maintenance cetuximab arm is associated with a significant improvement in median OS (1.3 months) in patients with stable disease while median survival was unchanged in patients with any kind of response.[73] The US (BMS-099)[74] trial looked at unselected patients with NSCLC to taxane plus cetuximab, and reached its primary endpoint of enhanced median OS (9.7 *versus* 8.4 months) but not PFS. A review by Pirker *et al.* (FLEX[71], BMS 099[74], BMS 100[75], LUCAS[76] [see Table 4]) confirmed the consistent benefit of adding cetuximab to chemotherapy in patients with advanced NSCLC of all histological subtypes in terms of OS (*P* <0.01), PFS (*P* <0.03), and OS rate (OR 1.463, *P* <0.001).[77]

The Southwest Oncology Group trial is a phase II study that combined cetuximab to carboplatin, paclitaxel and bevacizumab for 6 cycles, followed by bevacizumab weekly until disease progression.[78] The primary endpoint of the trial was the frequency and severity of haemorrhagic toxicity that was grade 4 or higher in advanced stage non-squamous NSCLC and was found to have a tolerable safety profile with 2% incidence of haemorrhage that was grade > 4. SWOG 0819 is a similar, ongoing phase III trial comparing the same 4 drug combination with the 3 drug combination of ECOG 4599 trial.[79] Cetuximab was also evaluated concurrently with paclitaxel carboplatin or sequentially after the same regimen and then continued as maintenance. The outcomes were similar but sensory neuropathy was higher in the former (15% *versus* 5% *P* <0.036).[80] Acne-like rash, infusion related reactions and hypomagnesaemia were encountered in cetuximab recipients.

Eight trials including 3,736 patients were analysed for either maintenance therapy for patients with any clinical benefit in NSCLC compared to watchful waiting or placebo. The study analyses included the OS as a primary outcome and PFS and toxicity as a secondary outcome. The switch maintenance was associated with improvement in OS (*P* <0.001), while the continuous arm showed a trend towards better OS but lacked statistical significance (*P* = 0.124). An interaction test was applied between the two maintenance therapies (switch and continuous), yet the difference in OS between the two maintenance strategies was not statistically significant (*P* = 0.777) and

Table 5a: Maintenance strategies in non-small-cell lung carcinoma

Maintenance Strategies (Options):	
Adenocarcinoma Subtypes:	
1. **Switch maintenance**	
Induction Chemotherapy	***Maintenance Agent***
Gemcitabine + Carboplatin/ or Cisplatin	Docetaxel
Pemetrexed + Cisplatin	*Erlotinib / or Gefitinib (TKI)
Pemetrexed + Cisplatin	Docetaxel
Gemcitabine/or docetaxel/ or Paclitaxel + Cisplatin	Pemetrexed
2. **Continued Maintenance**	
Pemetrexed + Cisplatin	Pemetrexed
Gemcitabine + Cisplatin	†Gemcitabine
TKI	TKI
3. **Monoclonal Antibody Addition:**	
Platinum doublets + ‡Bevacizumab	‡Bevacizumab
Platinum doublets + Cetuximab	Cetuximab
Squamous Histology:	
Platinum + Gemcitabine/ or docetaxel + §Cetuximab	§Cetuximab
	†Gemcitabine

**May be used in frail & elderly; †KPS>80; ‡In nonsquamous histology only tumor not abutting major vessel and no hemoptysis; §data favors use in cases with stable disease after post induction chemotherapy.*

an improvement in PFS was found with both maintenance strategies (P = 0.128).[81] Subgroup analyses could not find any differences in the survival outcome in switch maintenance using chemotherapy or that with the TKI. However, maintenance therapy was associated with higher toxicity. It is therefore reasonable to consider any maintenance therapy at the expense of reasonable toxicity and tolerability.

Table 5b: Maintenance therapy in non-small-cell lung carcinoma

Who gets maintenance therapy?
(Non-small-cell lung carcinoma):
Histology:
Adenocarcinoma subtypes
Squamous cell carcinoma
Clinical Features:
Age: Adults 18-70 years (fit, elderly)
Gender: Any
ECOG PS 0-1, †KPS>80
ECOG PS 2 (selected cases for TKI)
Genetics:
EGFR Wild type – chemotherapy
EGFR Mutant – *TKI
(TKI responders; Asian, women, never smoker, having adenocarcinoma)
k-ras mutation – chemotherapy
EML4 Alk – Crizotinib
Suitable subset of patients;
-Clinical benefit; Stable disease or regression after induction chemotherapy
-Well-preserved organ function
-No major co-morbidity

**May also be used in frail & elderly; ‡In nonsquamous histology only tumor not abutting major vessel and no hemoptysis; §data favors use in cases with stable disease after post induction chemotherapy.*

Conclusion

Maintenance therapy has emerged as a new treatment paradigm in the management of NSCLC. Patients with well-preserved organ function, who are maintaining their PS and responding to chemotherapy, or who are experiencing disease stabilisation after induction chemotherapy may now be effectively treated with maintenance therapy, taking tolerability into account. Others may be followed closely and therapy may be individualised according to clinical course, age, and the presence of co-morbidity. Salvage chemotherapy may be instituted at any time before the PS declines to levels beyond intervention, or the patient experiences significant symptomatic deterioration. Careful patient and drug selection, long term safety, and QoL should all be considered while patient participation remains integral in final decision making. Details of patients' clinical features, histology, and genetics should be taken into account for optimisation of therapy [Tables 5a and b]. However, retrospective data and subgroup analyses should be read with extreme caution, as the number of patients in these analyses are often

reduced and the studies are subject to biases.

Patient and tumour characteristics derived from molecular biology and cancer genetics continue to evolve and are helping oncology decision-makers to define subsets of patients that would derive benefit from customised maintenance therapy. The data from large numbers of randomised phase III trials is very compelling, and the year 2012 provided a variety of options for treating any given patient, but what remains to be defined is the exact sequencing of these strategies.

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