Multidrug Combinations for First-line Therapy of Advanced Non-small-cell Lung Cancer

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Abstract

Lung cancer is a common disease with a high mortality rate. Non-small-cell lung cancer (NSCLC), which accounts for almost 85% of all cases of lung cancer, is often diagnosed at an advanced stage. Platinum-based two-drug combination regimens have become the standard of care and should be considered in patients with a good performance status (Eastern Cooperative Oncology Group performance status scale 0–1). The addition of a third chemotherapy agent is not recommended, since there is additional toxicity without a definite survival benefit. In recent years, histology has emerged as an important factor in treatment selection. In patients with non-squamous NSCLC, the cisplatin–pemetrexed regimen has demonstrated superiority over cisplatin–gemcitabine and has emerged as a preferred regimen for this subset of patients. The addition of targeted agents such as bevacizumab or cetuximab to platinum doublets has also demonstrated modest improvements in overall survival for first-line therapy of advanced NSCLC. The identification of patient-selection methods for the use of these agents remains a major challenge. Recently, the use of maintenance therapy has emerged as an option for patients who complete the recommended four to six cycles of chemotherapy. This article reviews the various first-line therapy options for advanced NSCLC.

Keywords

Lung cancer, chemotherapy, first line, platinum, bevacizumab, pemetrexed, cetuximab, gefitinib, erlotinib

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Lung cancer remains a major health problem, with nearly 222,520 cases diagnosed in the US in 2010. Although it is the second most common cancer in men and women, it is the leading cause of cancer deaths in both groups; there were an estimated 157,300 deaths in the US attributable to lung cancer in 2010.[1] Lung cancer is generally divided into small-cell lung cancer and non-small-cell lung cancer (NSCLC) based on distinct differences in disease biology and response to therapy. NSCLC accounts for 85% of all cases of lung cancer and comprises histological subtypes including adenocarcinoma, squamous cell carcinoma, bronchioloalveolar carcinoma, and large cell carcinoma. Early-stage NSCLC (stages I, II, and III) is typically treated with curative intent by surgical resection, chemotherapy, radiation therapy, and often a combination of these modalities. Treatment of advanced-stage NSCLC (stage IV disease), on the other hand, is palliative. Advanced-stage NSCLCs are defined as cancers with separate tumor nodules in the contralateral lung, tumors with pleural nodules, malignant pleural or pericardial effusions, or distant metastasis.[2] Patients presenting with these are treated with systemic chemotherapy. Improvements in both survival and quality of life have been demonstrated with systemic chemotherapy in patients with advanced-stage NSCLC. This article will focus on the systemic treatment of advanced NSCLC using multidrug combinations in the first-line setting.

Systemic Chemotherapy versus Supportive Care

Systemic chemotherapy is currently the standard of care for patients with advanced NSCLC. A number of studies have demonstrated improved outcomes for cisplatin-based regimens compared with best supportive care in advanced NSCLC. The benefit of systemic chemotherapy in patients with advanced or unresectable NSCLC was confirmed by the Big Lung Trial, a large, multicenter, randomized trial conducted in the UK. The study randomized 725 patients to treatment with cisplatin-based chemotherapy plus supportive care or supportive care alone. The chemotherapy arm had a statistically significant survival benefit compared with supportive care alone, with a median survival of eight versus 5.7 months. The one- and two-year survival rates were 29 versus 10% and 20 versus 5%, respectively.[3] An important consideration prior to recommending chemotherapy in the palliative setting is the optimization of quality of life. In the Big Lung Trial, there was a quality of life substudy in which patients in the chemotherapy arm reported a better quality of life and fewer symptoms compared with the group receiving supportive care only.[3] Rapp and colleagues have also demonstrated the superiority of cisplatin-based regimens over supportive care in the treatment of advanced NSCLC.[4] The benefit of cisplatin-based therapy in advanced NSCLC has been further

Table 1: Comparison of Platinum Doublets in the Treatment of Non-small-cell Lung Cancer (ECOG 1594)

	ORR (%)	Median Survival (Months)	Median TTP (Months)
Cisplatin–paclitaxel (n=288)	21	7.8	3.4
Cisplatin–gemcitabine (n=288)	22	8.1	4.2
Cisplatin–docetaxel (n=289)	17	7.4	3.7
Carboplatin–paclitaxel (n=290)	17	8.1	3.1

ORR = overall response rate; TTP = time to progression.

substantiated by two meta-analyses.[5,6] Based on these studies, it is clear that systemic chemotherapy improves survival and quality of life in patients with advanced NSCLC and should be considered in all patients who have a good performance status (PS), i.e. Eastern Cooperative Oncology Group (ECOG) PS 0–1.

Platinum-based Chemotherapy

Platinum-based chemotherapy is widely used for the treatment of patients with a variety of solid tumors, including NSCLC. A number of studies have demonstrated improved survival for the combination of a platinum compound with a third-generation cytotoxic agent over therapy with either of the agents given as monotherapy.[7–10] This led to the comparison of various two-drug combination regimens in order to identify the optimal combination regimen for advanced NSCLC.

In several studies, the combination of paclitaxel and carboplatin has shown similar efficacy compared with paclitaxel–cisplatin, vinorelbine–cisplatin, cisplatin–gemcitabine, and cisplatin–docetaxel.[11,12] Paclitaxel plus carboplatin is also associated with a favorable tolerability profile for patients with advanced NSCLC (see *Table 1*).[11,12]

Belani and colleagues compared the efficacy of the carboplatin–paclitaxel combination with cisplatin–etoposide for patients with advanced NSCLC.[13] The two regimens had comparable efficacy in this randomized trial, although the quality of life parameters were more favorable for the carboplatin–paclitaxel arm.

Kelly et al. demonstrated that the combination of carboplatin–paclitaxel was associated with comparable efficacy to cisplatin–vinorelbine.[14] The experimental arm of carboplatin–paclitaxel was associated with a lower incidence of nausea and vomiting and a higher incidence of neurotoxicity. Fewer patients in the carboplatin–paclitaxel arm discontinued treatment due to toxicity.

The ECOG 1594 trial compared three regimens (cisplatin–docetaxel, cisplatin–gemcitabine, and carboplatin–paclitaxel) against the control arm of cisplatin–paclitaxel for patients with advanced NSCLC.[11] Initially, the study enrolled patients with an ECOG PS ≤2. It was closed to patients with ECOG PS 2, however, when excessive toxicity was noted among the first 64 patients with this PS.[15] Over 1,200 patients with advanced NSCLC were enrolled in this trial. While the toxicity profiles varied between the chemotherapy regimens, there were no significant differences in most of the efficacy end-points. These included overall survival (OS), one-year survival, and response rates, which were 7.9 months, 33%, and 19%, respectively. The regimen of carboplatin plus paclitaxel was chosen as the reference regimen for the next ECOG phase III study based on its favorable therapeutic index.

Carboplatin has also been safely administered in combination with docetaxel and gemcitabine in large phase III studies. Taken together, in patients with advanced-stage disease, carboplatin-based regimens are associated with a favorable therapeutic index and are used widely in the US.

Two Drugs Are Better than One, Three Drugs Are Not Better than Two

A large meta-analysis of 65 trials conducted between 1980 and 2001 compared doublet regimens versus single-agent regimens and triplet regimens in the treatment of advanced NSCLC. In monotherapy studies, a variety of chemotherapeutic agents were utilized. Most, but not all, of the doublet and triplet regimens contained a platinum compound. When single-agent regimens were compared with doublet regimens, there was a statistically significant increase in the tumor response rate from 13 to 26% (for an absolute benefit of 13%). There was also an increase in one-year survival rate (odds ratio [OR] 0.8, 95% confidence interval [CI] 0.7–0.91; p<0.001) from 30 to 35%. As expected, there was an increase in rates of grade 3 and 4 toxicity in the doublet arm.[16]

In this same meta-analysis, there was no benefit to adding a third drug to a doublet regimen. Although there was an increase in objective tumor response rate in the triplet arm (OR 0.66, 95% CI 0.58–0.75; p<0.001), the addition of a third drug resulted in an inferior one-year survival rate (OR 1.01, 95% CI 0.85–1.21; p=0.88). The addition of a third agent was associated with a higher frequency of grade 3 and 4 toxicities (OR range 1.4–2.9). Hematologic toxicities and infections accounted for the most significant differences in toxicities.[16] The combination of three cytotoxic agents is therefore not recommended for the treatment of advanced NSCLC.

Treatment Based on Histology

All NSCLCs have traditionally been treated alike, regardless of their histologic subtype. With the recent development of novel cytotoxic and targeted agents, however, histology has been found to play a major role in the prediction of toxicity and benefit. Accurate identification of histology at the time of diagnosis has therefore gained additional importance.

Certain molecular abnormalities, such as epidermal growth factor receptor (EGFR) mutation and EML4-ALK translocation, are more commonly present in patients with adenocarcinoma histology. Since specific agents that target these abnormalities are available, it has become critical to obtain core biopsies for establishing the diagnosis of NSCLC. Fine-needle aspiration specimens, which were the primary method of diagnosis of NSCLC, may not provide adequate tissue for the identification of histologic subtype and to conduct specific biomarker analyses.

Cisplatin–Pemetrexed

Pemetrexed, a multitargeted folate antagonist, exerts anticancer effects by inhibiting thymidylate synthase, dihydrofolate reductase, and glycinamide

ribonucleotide formyltransferase. This results in dysfunctional purine and pyrimidine synthesis, thereby disrupting DNA and RNA synthesis and causing arrest in cell growth.[17,18]

Pemetrexed is approved in combination with cisplatin as first-line therapy and as monotherapy in the second-line treatment of advanced NSCLC.[19] It was initially approved for all histologic subtypes of NSCLC (second-line), but in 2008 the indication was changed to non-squamous histology only. This was based on a phase III study by Scagliotti et al. that compared cisplatin and pemetrexed versus the combination of cisplatin plus gemcitabine in chemotherapy-naïve patients with advanced NSCLC.[19] The primary end-point was to demonstrate non-inferiority for the cisplatin–pemetrexed arm compared with the standard cisplatin–gemcitabine regimen. In fact, the study demonstrated an identical response rate, progression-free survival (PFS), and OS for both regimens. The cisplatin–pemetrexed regimen was associated with a more favorable tolerability profile.

Interestingly, a prospectively designed subset analysis demonstrated superior outcomes for patients with adenocarcinoma and non-squamous histology who were treated with cisplatin–pemetrexed.[19] For patients with squamous histology, cisplatin–gemcitabine therapy was associated with a better outcome (see *Table 2*). Subsequently, a retrospective subset analysis of the phase III second-line trial by Hanna et al. also demonstrated an inferior outcome with pemetrexed in quamous histology.[20]

Overexpression of thymidylate synthase, a major target of pemetrexed, has been shown to be associated with reduced sensitivity to pemetrexed.[21,22] The differences in expression of thymidylate synthase between squamous and adenocarcinoma might explain the variable outcome of efficacy based on histology.[23]

The use of combination therapy with pemetrexed (500mg/m^2 given intravenously on day 1, repeated every 21 days) and a platinum agent is now frequently used in patients with non-squamous histology. This is because of its comparable efficacy with other platinum-based chemotherapy doublets and its relatively favorable toxicity profile. Patients who receive pemetrexed should also receive folic acid (350–1,000µg orally daily) and vitamin B_{12} (1,000µg intramuscularly/subcutaneously, repeated every nine weeks) supplementation to reduce the severity of hematological toxicity. These supplements should be started one week prior to the beginning of therapy. Patients should also receive dexamethasone (4mg orally twice daily the day before, the day of, and the day after each treatment) in order to minimize dermatologic toxicity.[24]

Combination of Targeted Agents with Chemotherapy—Bevacizumab

Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor (VEGF), has been shown to have anticancer activity in a variety of cancers.[25,26] VEGF is the principal regulator of angiogenesis in both normal and malignant tissues, including NSCLC.[27–30] Bevacizumab has been approved by the US Food and Drug Administration (FDA) for the treatment of advanced non-squamous NSCLC in the first-line setting in combination with carboplatin and paclitaxel.

Table 2: Cisplatin–Pemetrexed versus Cisplatin–Gemcitabine

	Median OS (Months) (Adjusted HR, 95% CI)	Median PFS (Months) (Adjusted HR, 95% CI)
All Patients		
Cisplatin–pemetrexed	10.3 (0.94, 0.84–1.05)	4.8 (1.05, 0.94–1.15)
Cisplatin–gemcitabine	10.3	5.1
Non-squamous Histology		
Cisplatin–pemetrexed	11.8 (0.81, 0.70–0.94)	5.3 (0.90, 0.79–1.02)
Cisplatin–gemcitabine	10.4	4.7
Squamous Histology		
Cisplatin–pemetrexed	9.4 (1.23, 1.00–1.51)	4.4 (1.36, 1.12–1.65)
Cisplation–gemcitabine	10.8	5.5

CI = confidence interval; HR = hazard ratio; OS = overall survival; PFS = progression-free survival.

Table 3: Bevacizumab in the First-line Treatment of Advanced Non-squamous Non-small-cell Lung Cancer

	PFS (months) (HR, 95% CI; p-value)	OS (months) (HR, 95% CI; p-value)
4599 Study		
Bevacizumab 15mg/kg + CP	6.2 (0.66, 0.57–0.77; p<0.001)	12.3 (0.79, 0.67–0.92; p=0.003)
Placebo + CP	4.5	10.3m
AVAil Study		
Bevacizumab 7.5mg/kg + CG	6.7 (0.75, 0.64–0.87; p=0.0003)	13.6 (0.93, 0.78–1.11; p=0.420)
Bevacizumab 15mg/kg + CG	6.5 (0.85, 0.73–1.00; p=0.03)	13.4 (1.03, 0.86–1.23; p=0.761)
Placebo + CG	6.1	13.1

CG = cisplatin + gemcitabine; CI = confidence interval; CP = carboplatin + paclitaxel; HR = hazard ratios, which are compared with the placebo arms; OS = overall survival; PFS = progression-free survival.

In a phase II trial comparing bevacizumab plus carboplatin plus paclitaxel versus carboplatin and paclitaxel alone, the bevacizumab-containing arm showed a statistically significant improvement in time to progression (7.4 versus 4.2 months; p=0.023) and a trend toward improvement in OS. A subset analysis revealed a higher incidence of hemorrhage and hemoptysis among patients with squamous cell carcinoma histology.[31]

Consequently, in the subsequent phase III study ECOG 4599, patients with squamous cell histology were excluded. This study compared bevacizumab in combination with carboplatin and paclitaxel versus carboplatin plus paclitaxel in patients with recurrent or advanced NSCLC. There was an improvement in OS (hazard ratio [HR] 0.79; p=0.003) and PFS (HR 0.66; p<0.001) in the bevacizumab arm (see *Table 3*). There was also a higher incidence of certain toxicities, such as hypertension, proteinuria, bleeding, and febrile neutropenia, in the paclitaxel–carboplatin–bevacizumab arm. There were 15 deaths in the bevacizumab arm compared with two deaths in the chemotherapy-alone arm.[32]

The efficacy of bevacizumab in combination with chemotherapy was also evaluated by the AVAil study.[33] In this study, 1,043 patients received one of two doses of bevacizumab (7.5 or 15mg/kg) or placebo in combination with cisplatin and gemcitabine. The primary end-point of

Table 4: Epidermal Growth Factor Receptor Inhibitors in the First-line Treatment of Advanced Non-squamous Non-small-cell Lung Cancer

	HR for Progression with Gefitinib Compared with CP (95% CI; p-value)	HR for Death with Gefitinib Compared with CP (95% CI)
All patients	0.74 (0.65–0.85; p<0.001)	0.91 (0.76–1.10)
EGFR+	0.48 (0.36–0.64; p<0.001)	0.78 (0.50–1.20)
EGFR-	2.85 (2.05–3.98; p<0.001)	1.38 (0.92–2.09)

Results of the Iressa Pan-Asia (IPASS) study. Hazard ratios (HRs) for progression and death with gefitinib compared with carboplatin and paclitaxel (CP) with 95% confidence intervals (CIs). EGFR = epidermal growth factor receptor.

Table 5: Cetuximab in Combination with Chemotherapy in the First-line Treatment of Advanced Non-small-cell Lung Cancer

	PFS (Months) (HR, 95% CI; p-value)	OS (Months) (HR, 95% CI; p-value)	ORR (%)
Flex Study			
Cetuximab + CV	4.4 (0.93, 0.825–1.077; p=0.39)	11.3 (0.871, 0.762–0.996; p=0.044)	36 (p=0.01)
CV	4.4	10.0	29
BMS-099			
Cetuximab + TC	4.40 (0.902, 0.761–1.069; p=0.236)	9.69 (0.89, 0.754–1.051; p=0.169)	25.7 (p=0.007)
TC	4.24	8.38	17.2

CI = confidence interval; CV = cisplatin + vinorelbine; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; TC = taxane + carboplatin.

improvement in PFS was met with both doses of bevacizumab in combination with chemotherapy (HR 0.75; p=0.003 for the low-dose arm and HR=0.82; p=0.03 for the high-dose arm; see *Table 3*). This study was not powered to compare the two bevacizumab arms. Improvements in PFS with bevacizumab did not, however, translate into a survival benefit in the follow-up analysis of this study (see *Table 3*).[34] As in previous studies, there were similar trends of increased adverse events in the bevacizumab arm compared with the chemotherapy-alone arm.

In patients with non-squamous NSCLC who have no contraindications to receiving a VEGF inhibitor—such as severe bleeding (hemoptysis), risk for intracranial bleeding (untreated brain metastasis), or uncontrolled hypertension—bevacizumab can be used in combination with a platinum doublet. Based on the results with bevacizumab, a number of agents that inhibit the VEGF receptor are currently under investigation. This class of agents includes sorafenib, sunitinib, and axitinib, which have a demonstrated response rate of 5–25% as monotherapy in advanced NSCLC. These results have led to ongoing studies evaluating the combination of these agents with either standard chemotherapy doublets or with molecularly targeted agents.

First-line Therapy with Epidermal Growth Factor Receptor Inhibitors

EGFR are cell-surface membrane receptors that can activate tyrosine kinases, which can in turn control intracellular pathways that partake in regulating cell proliferation, apoptosis, angiogenesis, adhesion, and motility. NSCLC patients with mutations in the tyrosine kinase domain of the EGFR receptor (base-pair deletion at exon 19 or point mutation at exon 21) are exquisitely sensitive to treatment with EGFR tyrosine kinase inhibitors.[35,36] EGFR mutations are relatively more common in patients who have never smoked or are light smokers, those that have adenocarcinoma histology and in patients of Asian ethnicity.[37]

Gefitinib

Although EGFR inhibitors are approved for the treatment of recurrent or refractory NSCLC, a recent study demonstrated their utility for first-line therapy in selected patients. In the Iressa Pan-Asia (IPASS) study,[38] 1,217 previously untreated patients with advanced lung adenocarcinomas were randomized to receive either single-agent gefitinib or combination chemotherapy with carboplatin and paclitaxel. Of note, the patients included had never smoked or were former light smokers. In the overall analysis, PFS was significantly better in patients who received single-agent gefitinib (HR 0.75, 95% CI 0.65–0.85). There was also an improved objective response rate in the gefitinib arm (43 versus 32%, OR 1.59, 95% CI 1.25–2.01). OS, however, was not significantly different between the two groups (see *Table 4*).

In a pre-planned biomarker analysis of the IPASS study, patients with tumors that contained the EGFR mutation had a significantly longer PFS when treated with gefitinib compared with chemotherapy (median survival 9.5 versus 6.3 months, HR 0.48, 95% CI 0.36–0.64). In patients without the EGFR mutation, however, PFS was significantly shorter for those who received gefitinib (HR for progression or death with gefinitib 2.85, 95% CI 2.05–3.98; p<0.001). The most common adverse effects in the gefitinib arm were rash or acne (66.2% of patients) and diarrhea (46.6%).[38] Two other recent studies have also documented the superiority of gefitinib to chemotherapy in the first-line therapy of patients with an EGFR mutation.[39,40]

Based on these observations, single-agent EGFR tyrosine kinase inhibitors should be considered in the first-line therapy of patients whose tumors harbor the EGFR mutation. Patients with wild-type EGFR or those with unknown EGFR mutation status should continue to receive standard first-line chemotherapy. The combination of chemotherapy with EGFR tyrosine kinase I does not improve survival over of chemotherapy alone and is not recommended for routine use.[41,42]

Cetuximab

Cetuximab, a monoclonal antibody against EGFR, has been shown to be active as first-line therapy in advanced NSCLC when added to a platinum-based doublet. In the FLEX trial, 1,125 previously untreated patients with EGFR-positive advanced NSCLC were randomized to receive either cisplatin–vinorelbine plus weekly cetuximab or cisplatin–vinorelbine alone.[43] Patients who received cetuximab continued to take the drug as maintenance therapy after the completion of chemotherapy until unacceptable toxicity or disease progression. The median OS was significantly prolonged in the chemotherapy–cetuximab group (11.3 months) compared with chemotherapy-alone (10.1 months; see *Table 5*). The side effects of cetuximab included acne-like skin rash, diarrhea, and infusion reactions.

The BMS-099 trial also evaluated the benefit of adding cetuximab to chemotherapy in the first-line setting.[44] It was a multicenter, open-label, phase III study that randomized 676 chemotherapy-naïve patients to

either cetuximab plus carboplatin–taxane (paclitaxel or docetaxel) or the same chemotherapy alone. Chemotherapy in both arms was administered every three weeks and cetuximab was given weekly. In contrast to the FLEX study, EGFR status was not an inclusion criterion for this study. The primary end-point of BMS-099 was PFS. This was not significantly improved in the cetuximab–chemotherapy arm compared with the chemotherapy-alone arm when analyzed by the independent radiologic review committee (median PFS 4.4 versus 4.24 months, HR 0.92, 95% CI 0.761–1.069; p=0.2358). The overall response rate was significantly better in the cetuximab–chemotherapy arm compared with the chemotherapy-alone arm (25.7 versus 17.2%; see *Table 5*). There was no statistically significant difference in OS, although a modest numerical trend was noted in favor of cetuximab (9.7 versus 8.4 months).

Efforts to identify biomarkers that predict a more favorable outcome with cetuximab have been unsuccessful to date. In both the BMS-099 and FLEX studies, K-RAS mutational status was not predictive of response to cetuximab in patients with NSCLC.[45]

Duration of Therapy

Chemotherapy has cumulative toxicities; therefore, it is important to define the optimum number of cycles of treatment in order to maximize benefit without sacrificing quality of life.

In a phase III trial by Socinski et al., 230 patients with advanced NSCLC were randomized to receive either four cycles of carboplatin plus paclitaxel or to continue receiving the same therapy until disease progression. There was no statistically significant difference in OS, response rate, or one-year survival rates between the two trial arms.[46] There was, however, a higher incidence of neuropathy in the 'treatment until progression' arm.

In a more recent phase III study, 452 patients with advanced NSCLC who did not progress after receiving two cycles of a cisplatin-based doublet regimen were randomized to receive either two or four additional cycles of chemotherapy. Four cycles of chemotherapy was shown to be non-inferior to six cycles. Although there was a significant time-to-progression benefit in the arm receiving six cycles of chemotherapy (6.2 versus 4.6 months), this did not translate into a survival benefit. Patients in the four-cycle chemotherapy arm experienced an improved quality of life, improved performance status, and decreased toxicity compared with the six-cycle chemotherapy arm.[47]

These data support the administration of either four total cycles of chemotherapy or two cycles beyond best response (up to six cycles in total). These data are reflected in the 2004 American Society of Clinical Oncology (ASCO) guidelines[48] and the 2008 National Comprehensive Cancer Network clinical practice guidelines[49] for patients with advanced NSCLC.

Conclusions

A number of novel treatment options are available for patients with advanced-stage NSCLC. Although the treatment is still palliative, more efficacious front-line and salvage therapy options have recently become available. The introduction of targeted therapies and improved supportive care have contributed to the improvements in outcomes noted for advanced NSCLC in the past few years. The use of maintenance therapy with pemetrexed and erlotinib has recently demonstrated improved survival and has emerged as a novel option in the first-line therapy of advanced NSCLC.

A number of newer classes of targeted agents are currently in the advanced stages of clinical investigations. For these agents, identification of biomarkers that will identify patient subgroups most likely to benefit from treatment is an important priority. At present, for the routine care of patients with advanced NSCLC, specific knowledge regarding histology and EGFR mutation status are useful in selecting therapy.

As research continues, it is hoped that new agents will emerge that will lead to further changes in the current landscape of treatment for patients with lung cancer. ■

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