**Lung Cancer**

**RESULTS FROM THE PHASE III PARAMOUNT TRIAL**

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**TRIAL SUMMARY:** Improved overall survival with continuation maintenance therapy in NS NSCLC Paz-Ares L, De Marinis F, Dediu M et al. PARAMOUNT: Final overall survival (OS) results of the phase III study of maintenance pemetrexed (pem) plus best supportive care (BSC) versus placebo (pbl) plus BSC immediately following induction treatment with pem plus cisplatin (cis) for advanced nonsquamous (NS) non-small cell lung cancer (NSCLC). ASCO 2012 J Clin Oncol 2012;30(suppl):Abstract IBA7507.

The PARAMOUNT trial showed that pemetrexed (pem) continuation maintenance therapy significantly reduced the risk of disease progression over placebo (hazard ratio [HR]=0.62; 95% confidence interval [CI] 0.49–0.79; p<0.0001) in patients with advanced nonsquamous non-small cell metastatic lung cancer (NS NSCLC) who had not progressed during pemetrexed (cis) induction. In a double-blind, placebo-controlled study, alpha-controlled for overall survival (OS), 939 patients received induction (4 cycles of pem 500 mg/m² and cis 75 mg/m² on day 1 of 21-day cycles), and 539 patients who had not progressed and had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0/1 were randomized (2:1) to maintenance pem (500 mg/m² on day 1 of 21-day cycles) + best supportive care (BSC) or placebo + BSC until disease progression. All received B12, folic acid and dexamethasone. After 397 deaths, a log-rank test compared overall survival (OS) between arms using a nominal α level of 0.0498. Patient characteristics were balanced between arms: median age 61 years, 58% men, 32% PS 0, 95% Caucasian, 86% adenocarcinoma and 45% complete/partial response (CR/PR) to induction.

Pem resulted in a statistically significant 22% reduction in risk of death (HR=0.78). The HR was the same when measured from the beginning of induction. Survival improvement was similar for patients with an induction outcome of CR/PR vs stable disease. The authors concluded that pem continuation maintenance therapy offers superior OS vs placebo. These final results confirm that pem-cis induction followed by continuation pem further benefits patients compared with induction therapy alone, offering a change in the treatment paradigm for advanced NS NSCLC.

**COMMENTARY:** In the past, the standard of care in metastatic non-small cell lung cancer (NSCLC) has been to treat patients with a platinum doublet for 4 to 6 cycles and to offer second-line therapy upon progression. Maintenance therapy in NSCLC is defined as a therapeutic agent that is administered after completion of first-line chemotherapy but before the disease progresses. While maintenance therapy is not yet universally accepted as a therapeutic approach, data have demonstrated its potential to improve survival in a clinically significant way.

The benefits of maintenance therapy have been demonstrated in 2 Phase III randomized trials using pemetrexed and erlotinib. Pemetrexed maintenance after 4 cycles of a platinum doublet not containing pemetrexed met its primary endpoint of progression-free survival (PFS). Patients given maintenance pemetrexed had improved PFS compared to placebo (HR=0.50; p<0.0001). Erlotinib, an oral tyrosine kinase inhibitor (TKI) of the epidermal growth factor receptor (EGFR) was studied in a maintenance fashion in the SATURN trial. Erlotinib maintenance after 4 cycles of a platinum doublet not containing erlotinib also met the primary endpoint of PFS (improved PFS HR=0.71; p=0.0001). Both pemetrexed and erlotinib have efficacy in the second-line setting, it was not difficult to understand that initiating these agents earlier (maintenance) would improve PFS. In fact, it was expected. A more important and necessary endpoint was an improvement in overall survival (OS). Both maintenance pemresulted (HR=0.79; p=0.012) and erlotinib (HR=0.81; p=0.0088) trials were positive for OS. Subsequently, many centres adopted the practice of early second-line or “switch” maintenance.

The PARAMOUNT trial differed in concept and design from the above-mentioned trial. Unlike switch maintenance, PARAMOUNT examined the effect of continuous maintenance, where one of the agents in the induction doublet was continued after 4 cycles. At ASCO 2011, the PARAMOUNT trial was presented as a late-breaking abstract after meeting the primary endpoint of PFS. Patients received 4 cycles of cisplatin/pemetrexed and were randomized to pemetrexed or placebo if they did not progress. An improvement in PFS in favour of maintenance pemetrexed was seen (HR=0.62; p<0.001). PARAMOUNT was powered to meet its secondary and more meaningful endpoint of OS. OS was positive: 13.9 months in the pemetrexed arm vs 11.0 for placebo (HR=0.78; p=0.0195). From the beginning of induction therapy, OS was 16.9 vs 14 months (HR=0.78; p=0.0191).

Of the 1022 patients with nonsquamous histology and Stage 4 disease screened, 939 were enrolled. Patients consented to the trial at that time. Enrolled patients were given 4 cycles of cisplatin and pemetrexed. Patients who had not progressed were randomized to maintenance pemetrexed or placebo. It is important to note that 217 patients did progress and were not eligible for the maintenance portion. Also important, 183 patients were not eligible to be random-
ized for other reasons including adverse events and death. This emphasizes the importance of using your best drugs upfront and not saving them for subsequent lines as patients may deteriorate or decline further therapy. Pemetrexed and cisplatinum induction followed by maintenance pemetrexed improves OS. Drug holidays are still an option and reintroduction of pemetrexed may be appropriate in selected patients. This strategy of continuous maintenance with pemetrexed allowed patients to live from the beginning of maintenance to almost 14 months and from the beginning of all therapy to almost 17 months. This is a great step forward in the world of lung cancer.

### REFERENCES


### IN BRIEF

### Already known
- Switch maintenance therapy improves survival. Patients given pemetrexed or erlotinib after 4 cycles of a platinum doublet not containing pemetrexed or erlotinib showed improvement in both PFS and OS.

### What this study showed
- Continuation maintenance therapy improves survival. Patients given pemetrexed after 4 cycles of a platinum doublet that contained pemetrexed showed improvement in both PFS and OS. This now becomes an option for our patients.

### Next steps
- PARAMOUNT confirms an OS benefit of first-line cisplatin/pemetrexed followed by maintenance pemetrexed until progression in patients with Stage IV NSCLC with nonsquamous histology. This is a paradigm shift in the treatment of lung cancer.