can be considered SN-negative and that these patients can be spared the morbidity associated with CLND. They also suggest that by treating these patients as SN-positive, other studies may have found unrealistically good outcomes in SN-positive patients.

Original article van Akkooi ACJ *et al.* (2006) Clinical relevance of melanoma micrometastases (<0.1 mm) in sentinel nodes: are these nodes to be considered negative? *Ann Oncol* **17:** 1578–1585

Identification of lung adenocarcinoma subtypes by DNA microarray analysis

Morphological classifications of non-small-cell lung cancers using gene-expression profiling have been previously reported, but, because of significant variations in classifications, little consensus regarding their number and nature exists. By directly comparing the results from three studies reporting subclassification of lung adenocarcinomas by gene-expression profiling, Hayes *et al.* validated adenocarcinoma subtypes from independent clinical patient cohorts.

The trial compared the results from studies conducted at the Stanford University, the University of Michigan and the Dana-Farber Cancer Institute. Hierarchical consensus clustering identified three tumor subtypes (bronchioid, squamoid and magnoid) in each cohort. In stage I and II patients from the Dana-Farber group, the squamoid and magnoid subtypes were associated with considerably shorter survival than the bronchioid tumors ($P = 0.01$ and $P = 0.04$, respectively), while recurrence was reported in 27% of patients with bronchioid, 61% of patients with squamoid and 37% of patients with magnoid subtypes ($P = 0.04$). In advanced stages of the disease, improved survival was noted in the squamoid subtype compared with the magnoid ($P = 0.03$) and bronchioid ($P = 0.2$) subtypes. Overall, patients with magnoid tumors had a worse survival compared with patients with other tumor subtypes ($P = 0.04$ and $P = 0.10$). Genes regulating growth, development, differentiation, survival and cisplatin resistance were characteristic of bronchioid tumors. Squamoid tumors were characterized by genes associated with angiogenesis, while the magnoid subtype exhibited a strong inflammatory signature and was associated with genes regulating metabolism and proliferation.

This study validates the use of DNA microarray analysis in the identification of adenocarcinoma subtypes with different clinically significant behaviors such as stage-specific survival.

Original article Hayes DN *et al.* (2006) Gene expression profiling reveals reproducible human lung adenocarcinoma subtypes in multiple independent patient cohorts. *J Clin Oncol* **24:** 5079–5090

Improved survival in gefitinib-treated NSCLC patients with high *EGFR* gene copy numbers

Response to the *EGFR* inhibitor gefitinib is correlated with mutations in *EGFR* and with phosphorylated Akt in some patients, although the association of *KRAS* and *BRAF* mutations with gefitinib resistance is unclear. Hirsch *et al.* recently assessed the relationship between such biomarkers and clinical outcome in patients with advanced non-small-cell lung cancer (NSCLC) treated with gefitinib.

The phase III trial included 1,629 patients randomly assigned to receive either 250 mg of gefitinib, or placebo. Patients who had a high *EGFR* copy number had a significantly improved survival following gefitinib treatment compared with patients with low *EGFR* copy numbers ($P = 0.045$), and a 39% lower risk of death than patients who received placebo ($P = 0.067$). Gefitinib also prolonged median survival in individuals with a high *EGFR* copy number when compared with placebo (8.3 vs 4.5 months), but this difference was not observed for those with a low *EGFR* copy number ($P = 0.417$). Gefitinib-treated patients with *EGFR*-positive tumors had significantly better survival ($P = 0.049$) and improved response rates (8.2% vs 1.5%) compared with patients with *EGFR*-negative tumors. Objective tumor response rates were also higher in gefitinib-treated patients with mutated *EGFR* than in those without such mutations (37.5% vs 2.6%). In contrast to previous studies, there was no correlation between phosphorylated Akt protein expression and survival outcome; the role of *KRAS* and *BRAF* mutations in relation to clinical outcome could not be assessed.

The authors conclude that *EGFR* copy number is a potential biomarker that could identify the patients with NSCLC who are most likely to benefit from gefitinib treatment.

Original article Hirsch FR *et al.* (2006) Molecular predictors of outcome with gefitinib in a phase III placebo-controlled study in advanced non-small-cell lung cancer. *J Clin Oncol* **24:** 5034–5042

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