SqCLC education program
Key paper summaries
October 2015
**Introduction**

This document provides brief summaries of 25 key papers supporting the agreed educational topics of the SqCLC education program for 2015, which are

1. The high unmet need in squamous NSCLC
2. The challenges to advance treatment
3. The importance of incremental innovation
4. The prevalence of currently established biomarkers
5. The emergence of new pathways

As the education program is on disease state, summaries of clinical trials describing new Lilly products, eg SQUIRE, cannot be used. For balance therefore, summaries of clinical trials of other emerging products are not included.

The summaries are presented by topic (diagnosis; epidemiology; risk factors and comorbidities; molecular biology; real-world treatment patterns; 1\textsuperscript{st}-line therapy; maintenance therapy; 2\textsuperscript{nd}-line therapy) and then in alphabetical order. There are between one and seven summaries per topic. The headings on the content page are hyperlinked to each section within the main document. Each key paper is summarized in an easy-to-digest format under the headings: Key findings; Study objective; Data highlights; and Commentary. Links are provided to the original papers.
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Bishop JA et al. p40 (ΔNp63) is superior to p63 for the diagnosis of pulmonary squamous cell carcinoma. *Mod Pathol* 2012;25:405-15


**Epidemiology**

Cetin K et al. Survival by histologic subtype in stage IV nonsmall cell lung cancer based on data from the Surveillance, Epidemiology and End Results Program. *Clin Epidemiol* 2011;3:139-48


Lee PN and Forey BA. Indirectly estimated absolute lung cancer mortality rates by smoking status and histological type based on a systematic review. *BMC Cancer* 2013;13:189-224


**Risk factors and co-morbidities**


Pesch B et al. Cigarette smoking and lung cancer – relative risk estimates for the major histological types from a pooled analysis of case-control studies. *Int J Cancer* 2012;131:1210-19

**Molecular biology**


Rekhtman N et al. Clarifying the spectrum of driver oncogene mutations in biomarker-verified squamous carcinoma of lung: lack of *EGFR/KRAS* and presence of *PIK3CA/AKT1* mutations. *Clin Cancer Res* 2012;18:1167-76

Real-world treatment patterns

Aarts MJ et al. Improvement in population-based survival of stage IV NSCLC due to increased use of chemotherapy. *Int J Cancer* 2015;136:E387-95


1st line therapy


**Maintenance therapy**


**2nd line therapy**


Diagnosis

Bishop JA et al. p40 (ΔNp63) is superior to p63 for the diagnosis of pulmonary squamous cell carcinoma. *Mod Pathol* 2012;25:405-15


Key finding

- Immunostaining with p40 antibody showed equal sensitivity and superior specificity compared with p63 antibody in the diagnosis of squamous non-small cell lung cancer (NSCLC) *in situ*

Study objective

- To compare the immunosensitivity and immunospecificity of anti-p63 (an antibody that recognizes both p63 isoforms) and anti-p40 (an antibody that recognizes only the ΔNp63 isoform) on 470 specimens of adenocarcinoma (n=237), squamous NSCLC (n=81), and large cell lymphoma (n=152; large cell lymphoma closely mimics NSCLC and up to 50% of specimens stain positive for p63 [Gualco et al 2008; Rekhtman et al 2001])

Data highlights

- 100% of squamous NSCLC, 31% of adenocarcinomas, and 54% of large cell lymphoma specimens stained positive for p63, which indicated 100% sensitivity and 60% specificity
- 100% of squamous NSCLC, 3% of adenocarcinomas, and 0% of large cell lymphoma specimens stained positive for p40, which indicated 100% sensitivity and 98% specificity
- The mean percentage of cells that immunostained for p63 vs. p40 in squamous NSCLC samples was 97% vs. 96%, respectively (p=0.73)
- The mean percentage of cells that immunostained for p63 vs. p40 in adenocarcinoma samples was 26% vs. 5%, respectively

Commentary

Treatment guidelines for NSCLC are driven by histological subtype and therefore an accurate histological diagnosis is important. p63 immunostaining has routinely been used as a diagnostic marker for squamous NSCLC but lacks specificity. This study showed that anti-p40 has equivalent sensitivity and superior specificity compared with anti-p63 for immunostaining of squamous NSCLC specimens, confirming and expanding on previous work that suggested p40 is highly squamous specific (Sniezek et al 2004; Massion et al 2003). The increased specificity of anti-p40 compared with anti-p63, with no loss of sensitivity, supports the use of p40 in the diagnosis of squamous NSCLC and may help reduce the misidentification of p63-positive adenocarcinoma and unsuspected lymphoma as squamous NSCLC.
Key finding
- Small biopsy and cytological methods are equally valid for accurately subtyping NSCLC, with similar rates of definitive, favored, and unclassified diagnoses. There was also good agreement between diagnoses based on small biopsy and cytological methods. Combining both methods produced the highest rate of definitive diagnoses and reduced the unclassified rate to 4%.

Study objective
- To compare the rate with which specific NSCLC subtyping is achieved, the concordance and accuracy of NSCLC diagnoses (N=101) in cytology and small biopsy specimens, original diagnoses were reviewed and assessed for accuracy by comparing with subsequent resection or autopsy results. In addition, immunohistochemistry (IHC) results for TTF-1 and p63, performed either as part of the initial work-up (N=38) or during the study to resolve discordant diagnoses (N=5), were reviewed.

Data highlights
- Rates of definitive diagnosis for small biopsy and cytological methods were 71% and 69%, respectively. Corresponding rates of favored diagnosis were 23% vs. 19% and for unclassified diagnosis the rates were 6% vs. 12%.
- The distribution of definitive and favored diagnoses was similar for squamous NSCLC and adenocarcinoma.
- There was good agreement between diagnoses based on small biopsy and cytological methods (93%) with a Kappa coefficient of 0.76 for squamous NSCLC and 0.88 for adenocarcinoma.
- 7% of cases had discordant diagnoses revealed by subsequent resection, autopsy, or IHC. Biopsy and cytology were equally accurate in rendering the correct diagnoses in these cases.
- Combining both biopsy and cytology methods produced the highest rate of definitive diagnoses (84%) and reduced the unclassified rate to 4%.

Commentary
- Treatment guidelines in NSCLC require an accurate diagnosis of histological subtype (National Comprehensive Cancer Network Guidelines 2015) and subtype is crucial for correct treatment decisions, as some treatment options for non-squamous NSCLC are not indicated in patients with squamous NSCLC. Furthermore, squamous NSCLC and adenocarcinoma have distinct genetic signatures (CAGR 2012) which may be utilized for targeted therapies in future. In advanced NSCLC, diagnoses are generally obtained from small biopsy or cytology specimens. This study provides evidence that small biopsy and cytology are equally accurate diagnostic methods, although diagnostic certainty was highest when both methods were used, with the rate of unclassified diagnosis (NSCLC-NOS) reduced to just 4%.
Epidemiology

Cetin K et al. Survival by histologic subtype in stage IV nonsmall cell lung cancer based on data from the Surveillance, Epidemiology and End Results Program. Clin Epidemiol 2011;3:139-48

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3096514/

Key finding
• In the United States (US), Stage IV squamous non-small cell lung cancer (NSCLC) is more common in men than women and is associated with increased age. One-year survival rates for patients diagnosed between 1988 and 2003 were poor, with men, older patients, and those with poorly differentiated tumors having the worse prognosis

Study objective
• To provide contemporary population-based estimates of survival by histologic subtype and prognostic factors associated with survival of Stage IV NSCLC by analyzing data from 51,149 patients diagnosed in the US between 1998 and 2003 as part of the Surveillance, Epidemiology and End Results (SEER) program

Data highlights
• 69% of the 9370 patients diagnosed with squamous NSCLC were men
• Both squamous and nonsquamous NSCLC were associated with increased age; however, patients with squamous NSCLC tended to be slightly older at diagnosis than those with adenocarcinoma; ~60% of patients with squamous NSCLC were aged ≥65 years compared with ~50% of patients with adenocarcinoma
• Survival of patients with Stage IV NSCLC significantly differed between histologic subgroups; however, the prognosis was generally poor regardless of the histologic subtype (the overall 1-year survival rate was 16%)
• Diagnosis during the later years of the study period (1998-2003) was associated with increased survival across all histologic subtypes compared with a diagnosis during the early periods
• Among patients with squamous NSCLC, survival in women was 16.2% vs. 14.0% for men. Survival tended to decline with age (16.2% for patients aged <45 years; 11.3% for those aged 75-84 years), and a higher tumor grade at the time of diagnosis was associated with decreased survival compared with well-differentiated, lower-grade tumors (13.7% vs. 20%)

Commentary
This analysis from a large US database highlights that squamous NSCLC is more prevalent in men than women and is diagnosed at a slightly older age than adenocarcinoma. Many patients diagnosed with squamous NSCLC have age-related comorbidities at the time of diagnosis (Janssen-Heijnen et al 1998), which can complicate treatment. The analysis also reveals the poor overall prognosis for NSCLC including squamous NSCLC. The trend for slight improvements in survival over time are consistent with the report of Morgenzstern et al (2009). The authors suggested that this moderate increase in survival could be due in part to more advanced imaging techniques that result in stage migration, as well as the adoption of platinum-based chemotherapy as the standard of care. For patients with squamous NSCLC, there has been a paucity of new treatment options since this study, and platinum-based chemotherapy remains the recommended first-line treatment in treatment guidelines (NCCN 2015; Reck et al 2014).
Key finding
- In the United States (US), Stage IV squamous non-small cell lung cancer (NSCLC) was more common in men than women and was associated with increased age up to 79 years in both sexes. The incidence of squamous NSCLC in women rose slightly between 2004 and 2009 and fell very slightly in men.

Study objective
- To comprehensively describe recent histologic lung cancer incidence rates and trends in the US

Data highlights
- 85% of the 1,096,276 cases of lung cancer diagnosed in the US between 2004 and 2009 were NSCLC; of these cases, 240,443 were squamous NSCLC (26% of all NSCLC).
- Squamous NSCLC was more prevalent in men than women, with 63.8% of the squamous NSCLC cases diagnosed in men.
- In men, incidence rates of squamous NSCLC in those aged ≤40, 40-49, 50-59, 60-69, 70-79, and 80+ years were 0.1, 3.4, 18.8, 69.6, 128.0, and 105.7 per 100,000 population respectively. Corresponding incidence rates for women were 0.1, 1.9, 8.0, 32.8, 61, and 38.2.
- The incidence of squamous NSCLC in women rose by 1.7% per year between 2004 and 2009 and declined by 0.5% per year in men.

Commentary
This recently published comprehensive study provides an update on lung cancer incidence trends by histology across the US. Studies such as this are important because the etiology, detection, diagnosis, and treatment of lung cancer differs by histologic subtype and can change over time. The authors note that the rise in squamous NSCLC in women in the US reveals an important knowledge gap in the understanding of factors that play a role in addition to, or in combination with, smoking to impact on lung cancer incidence rates.
Lee PN and Forey BA. Indirectly estimated absolute lung cancer mortality rates by smoking status and histological type based on a systematic review. BMC Cancer 2013;13:189-224

http://www.biomedcentral.com/1471-2407/13/189

Key finding
- The mortality rate for patients with squamous non-small cell lung cancer (NSCLC) who had ever smoked was approximately twice as high as that for patients with adenocarcinoma who had ever smoked, and was also markedly higher than that for squamous NSCLC patients who had never smoked

Study objective
- To determine absolute lung cancer mortality rates using an indirect method based on a systematic review of 148 national and epidemiological studies and to estimate how mortality rates vary by sex, country, and time period separately for never, former, current, and ever smokers and separately for total lung cancer, squamous cell carcinoma, and adenocarcinoma

Data highlights
- The estimated mortality rates for ever smokers were substantially higher than those for never smokers, with a marked increase in mortality due to squamous carcinoma
- The mortality rate for patients with squamous NSCLC who had ever smoked was 117.0 per 100,000/year, compared to 58.5 per 100,000/year for patients with adenocarcinoma who had ever smoked
- Mortality rates for patients with squamous NSCLC who had smoked were approximately 11 times those of squamous NSCLC patients who have never smoked
- In never smokers, mortality rates were about twice as high for adenocarcinoma than for squamous NSCLC
- For all smoking habits and lung cancer types, mortality rates were higher in males, although the excess was less evident for never smokers
- Ever smoker mortality rates were higher in parts of Europe and America than in China, with the time trend very clear, especially for adenocarcinoma
- Never smoker mortality rates were clearly highest in China, and showed some increasing time trend, particularly for adenocarcinoma

Commentary
Although tobacco consumption is falling in some western countries, it is peaking in other regions where the incidence of lung cancer is expected to rise over the coming decades (Torre et al 2015). Active tobacco smoking has a stronger association with squamous NSCLC than with other NSCLC (Pesch et al 2012). This systematic review of 148 studies provides indirect estimates of lung cancer mortality by smoking status and histologic subtype, demonstrating that smoking also impacts on the outcome of squamous NSCLC, with mortality in patients who had ever smoked approximately twice as high for squamous NSCLC as for adenocarcinoma. The data also show that for patients with squamous NSCLC, mortality for ever smokers was substantially higher than for those who had never smoked. Although this study has several limitations, including variations in definitions between different studies, changes over time in diagnosis of lung cancer, and regional variations in smoking misclassification rates, the indirect method of estimating absolute lung cancer mortality rates used provides findings by smoking status and histologic type that are consistent with the literature.

http://dx.doi.org/10.1097/JTO.0b013e3181ba3634

Key finding:

- In the US, survival of patients with stage IV NSCLC of all histologies has been improving since 1990. However, for patients diagnosed between 2002 and 2005, survival of those with adenocarcinoma was significantly greater than for patients with squamous NSCLC.

Study Objective:

- This retrospective study assessed changes in survival per histological subtype (ie, squamous NSCLC, adenocarcinoma, large cell carcinoma, other NSCLC) by analyzing data from the Surveillance, Epidemiology, and End Results (SEER) Program for adult patients (N=129,337) with stage IV NSCLC who were diagnosed between 1990 and 2005. Study periods included: 1994-1997; 1998-2000; and 2002-2005.

Data Highlights:

- Overall, the survival of patients with NSCLC increased significantly for each successive time period
- One-year survival OS increased from 13.2% for patients diagnosed in 1990-1993 to 19.4% for those diagnosed in 2002-2005 for all histological subtypes
- One-year survival for patients with squamous NSCLC increased from 13.5% to 19.9% across the study period
- From 2002 to 2005, patients with adenocarcinoma histology had higher survival rates compared with those diagnosed with squamous NSCLC (hazard ratio, 1.033; 95% confidence interval, 1.004, 1.062; p=0.02)

Commentary

This analysis from a large US database showed that although the overall prognosis for NSCLC was poor, there have been modest but significant increases in survival among an unselected patient population with advanced NSCLC since 1990. However, for patients diagnosed between 2002 and 2005, patients with adenocarcinoma had significantly higher survival rates than those with squamous NSCLC. The authors note that EGFR tyrosine kinase inhibitors started to be used in patients with adenocarcinoma during this time period. Although more recent data from SEER are not available, data from recent clinical trials suggest there continues to be a difference between adenocarcinoma and squamous histology due to the availability of more treatment options for patients with adenocarcinoma (Scagliotti GV et al 2008, Sandler AB et al 2009, Paz-Ares L et al 2013).
Risk factors and comorbidities


**Key finding**

- A large proportion of excess deaths that occurred among current smokers in a contemporary US population were attributed to diseases that had not been formally established as being caused by smoking

**Study objective**

- This study pooled data from five contemporary US cohort studies (men, n=421,378; women, n=532,651, aged 55 years and older) over an 11-year period to estimate the number of deaths (from 52 cause-of-death categories) that were attributable to smoking.

**Data highlights**

- The rate of death from any cause was 2 to 3 times higher among current smokers compared with never-smokers (6462.7 deaths/1000 person-year vs. 2563.5 deaths/1000 person-year, respectively)
- Compared with those who had never smoked, current smokers had a higher risk of death from each of the 21 causes that are formally established as attributable to smoking, including 12 types of cancer such as lung, oral, lip and pancreatic cancers
- Approximately 17% of deaths among current smokers were caused by medical conditions that have not previously been recognized as being associated with smoking. These included: renal failure (RR 2.0; 95% CI 1.7-2.3), intestinal ischemia (RR 6.0; 95% CI 4.5-8.1), hypertensive heart disease (RR 2.4; 95% CI 1.9-3.0), infections (RR 2.3; 95% CI 2.0-2.7), various respiratory diseases (ie, pneumonia and influenza, chronic obstructive pulmonary disease, and pulmonary fibrosis) (RR 2.0; 95% CI 1.6-2.4), breast cancer (RR 1.3; 95% CI 1.2-1.5), and prostate cancer (RR 1.4; 95% CI 1.2-1.7)
- The increased risk of death from infections (p=.001), breast cancer (p=.01), and renal failure (p=.03) was proportional to the increase in the number of cigarettes smoked daily among current smokers
- The RR of death for renal failure, intestinal ischemia, hypertensive heart disease, infections, various respiratory diseases, breast cancer, and prostate cancer declined among former smokers as the number of years since smoking increased

**Commentary**

Active tobacco smoking has a greater association with squamous non-small cell lung cancer (NSCLC) than with other NSCLC (Khuder et al 2001; Pesch et al 2012). Studies such as the Million Women Study (Pirie et al 2013) have suggested that the current excess mortality in smokers vs. non-smokers cannot be fully explained by the 21 causes of deaths that are formally attributable to smoking. However, this study links smoking with several other diseases; approximately 17% of the excess mortality in smokers was found to be associated with causes that have not been formally established as being caused by smoking. The data are important to consider when treating patients with squamous NSCLC, who may have comorbidities such as renal dysfunction that can complicate treatment.

http://www.ejcancer.com/article/S0959-8049(10)00312-6/abstract

**Key findings**
- Patients with advanced non-small cell lung cancer (NSCLC) and severe comorbidities receiving platinum-doublet chemotherapy had poorer health-related quality of life (HRQoL) and more deaths from neutropenic infections than patients without severe comorbidities. However, survival and deterioration in HRQoL did not differ between patients with or without severe comorbidities.

**Study objective**
- To retrospectively analyze data from a randomized, Phase III trial of first-line platinum-doublet chemotherapy in patients with advanced NSCLC (N=436) to determine the impact of severe comorbidities on overall survival, treatment-related toxicity, and HRQoL.

**Data highlights**
- Of the 99 patients with squamous NSCLC in this study, 59 (60%) had severe comorbidities.
- Overall, fewer patients with severe comorbidities completed 4 cycles of chemotherapy, received second-line treatment or post-study radiotherapy.
- Median survival for patients with and without severe comorbidity was 6.9 vs. 8.1 months, respectively (p=.34).
- Patients with severe comorbidity developed more frequent Grade 3-4 thrombocytopenia vs. those with less comorbidity (46% vs. 36%; p=.03) although thrombocytopenic bleeds were not more frequent (3% vs. 4%; p=.65).
- Patients with severe comorbidity had significantly more neutropenic fevers (12% vs. 5%; p=.01) and more deaths from neutropenic infections (3% vs. 0%; p=.03) vs. those patients without severe comorbidity, although the incidence of Grade 3-4 neutropenia was similar (48% vs. 42%; p=.16).
- Deaths from adverse events (including neutropenic infection) occurred in 7% of patients with severe comorbidities vs. 3% of patients with no comorbidity.
- HRQoL was lower in patients with severe comorbidity, specifically with respect to global quality of life (p=.01), fatigue (p=.001), and dyspnea (p=.01).

**Commentary**
In this study, 60% of patients with squamous NSCLC had severe comorbidities compared with 47% of patients with adenocarcinoma, supporting previous findings by Janssen-Heijnen et al (1998). These differences are at least partly due to the older age and smoking history of patients with squamous NSCLC. Although in contrast to some other studies (Asmis et al 2008; Putlia et al 2014), this study did not find a relationship between comorbidities and survival, it does highlight the impact that the presence of severe comorbidities can have on toxicity and HRQoL in patients receiving platinum-doublet chemotherapy and the need for treatment advances with an improved risk:benefit ratio.
Key finding  
- Although all histologic subtypes of lung cancer were strongly associated with smoking, the relative risks were highest for squamous cell carcinoma

Study objective  
- To explore the impact of smoking on risks of the major histologic types of lung cancer using the pooled dataset from the SYNERGY database, which comprises 1 Canadian and 8 European case-controlled studies that enrolled a total of 13,169 patients (10,653 male) and 16,010 healthy individuals (12,758 male) between 1985 and 2005

Data highlights  
- Squamous non-small cell lung cancer (NSCLC) was the most prevalent type of lung cancer in male smokers (53.9%)
- Overall, the age-adjusted odds ratio (OR) for squamous NSCLC, estimated with logistic regression, was 45.6 in current vs. never smokers, compared to 10.8 for adenocarcinoma
- The risk of all histologic subtypes of lung cancer increased with the duration of smoking. For current male smokers of >30 cigarettes daily, age-adjusted ORs were 103.5 for squamous NSCLC and 21.9 for adenocarcinoma. For current female smokers of >30 cigarettes daily, age-adjusted ORs were 62.7 for squamous NSCLC and 16.8 for adenocarcinoma
- ORs for all histologic subtypes reduced soon after smoking cessation; however, for males, they did not return to the baseline risk of never smokers, even after 35 years

Commentary
This large study shows that although all types of lung cancer are associated with smoking, squamous NSCLC has a much stronger association with smoking than adenocarcinoma. In this study population, squamous NSCLC was the most common subtype of lung cancer in male smokers. In countries where the smoking epidemic has more recently peaked or is still increasing, such as China, the incidence of lung cancer is expected to rise over the coming decades (Torre et al 2015), and many of these cases are likely to be squamous NSCLC. In addition to the link with lung cancer, smoking has formally been established as a causative link to many other diseases, including chronic obstructive pulmonary disease and cardiovascular disease, and more recently has been linked to other respiratory diseases and renal failure (Carter et al 2015), which could complicate the treatment of patients with lung cancer.
## Molecular biology


[http://www.nature.com/nature/journal/v489/n7417/pdf/nature11404.pdf](http://www.nature.com/nature/journal/v489/n7417/pdf/nature11404.pdf)

**Key finding**
- Squamous non-small cell lung cancer (NSCLC) has a high mutation rate and a complex profile of genetic alterations that is distinct from that of adenocarcinoma

**Study objective**
- To characterize the genomic and epigenomic landscape in histopathologically validated samples from patients with previously untreated Stage I-IV squamous NSCLC (n=176), by analysis of DNA copy number, somatic exonic mutations, mRNA sequencing and expression, and promoter methylation, and in addition to identify potential therapeutic targets in squamous NSCLC

**Data highlights**
- Squamous NSCLC is characterized by multiple complex genetic alterations, with a mean of 360 exonic mutations, 165 genomic rearrangements and 323 segments of copy number alteration per tumor
- The critical tumor suppressor gene TP53 was observed to be mutated in 81% of samples, and other significantly mutated genes included CDKN2A, PTEN, PIK3CA, KEAP1, MLL2, HLA-A, NFE2L2, NOTCH1, and RB
- Significantly altered genes were found to be involved in key cellular pathways regulating squamous differentiation, cell cycle control, response to oxidative stress, and apoptotic signaling
- Screening for two common alterations seen in adenocarcinoma (KRAS and EGFR mutations) revealed that these alterations are extremely rare in squamous NSCLC
- Potentially targetable alterations distinct from those seen in adenocarcinoma were identified in 64% of tumors analyzed and included three families of tyrosine kinases (ERBBs, FGFRs, and JAKs) that were found to be mutated or amplified

**Commentary**

Advanced squamous NSCLC is an area of high unmet medical need, with few effective therapies. This study clearly demonstrates that squamous NSCLC is genetically distinct from adenocarcinoma, potentially explaining the difference in response to targeted therapies between these two subtypes. In addition, rather than single oncogenic driver mutations as in adenocarcinoma, molecular targets for therapy in squamous NSCLC involve overexpression or amplification of multiple receptors. These findings suggest that the deployment of targeted therapies is challenging in squamous NSCLC because of the genetic diversity, mutation burden, and lack of clear oncogenic drivers.

http://clincancerres.aacrjournals.org/content/18/4/1167.full.pdf+html

**Key finding**
- Combined mutational analysis and rigorous pathologic verification with immunohistochemistry (IHC) showed that EGFR/KRAS mutations do not occur in validated squamous non-small cell lung cancer (NSCLC), and the occasional detection of these mutations is due to difficulties in the diagnosis of squamous NSCLC vs. adenocarcinoma and adeno-squamous carcinoma (AD-SQC)

**Study objective**
- To screen for EGFR/KRAS mutations and 6 other therapeutically relevant mutations (BRAF, PIK3CA, NRAS, AKT1, ERBB2/HER2, and MAP2K1/MEK1) in a panel (n=95) of squamous NSCLC samples validated by IHC for TTF-1 and ΔNp63, and to conduct histological reassessment of those samples found to harbor EGFR/KRAS mutations

**Data highlights**
- None of the validated squamous NSCLC samples contained EGFR or KRAS mutations
- Four samples (4.2%) harbored PIK3CA mutations and 1 sample (1.1%) harbored an AKT1 mutation. No mutations in BRAF, NRAS, ERBB2/HER2, or MAP2K1/MEK1 were identified
- Of the reassessed samples (n=16), 10 (63%) were reclassified as AD-SQC misdiagnosed due to incomplete sampling, 5 (31%) as adenocarcinoma misdiagnosed due to morphological similarity to squamous NSCLC, and 1 (6%) was indeterminate

**Commentary**
- This study provides further evidence for the value of IHC in facilitating the accurate differentiation of NSCLC subtypes in samples that are difficult to distinguish by morphology alone. This study also clarifies the previously controversial molecular distinction between squamous NSCLC, which is shown to lack EGFR/KRAS mutations, and adenocarcinoma and AD-SQC, which can harbor these mutations. Accurate knowledge of the occurrence of clinically relevant mutations in a given lineage may aid in the assignment of patient samples to the optimal predictive molecular testing protocol for targeted therapies. Due to the low frequency of EGFR mutations in squamous NSCLC, routine testing is not recommended (NCCN 2015; Reck et al 2014). Consequently few patients with squamous NSCLC are eligible to receive EGFR tyrosine kinase inhibitors.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3262038/

**Key finding**
- Squamous non-small cell lung cancer (NSCLC) tumors grow quickly, with a median doubling time of less than half that of adenocarcinoma (160 vs. 387 days)

**Study objective**
- To analyze doubling times in CT-screen-detected lung cancers detected as part of the Pittsburgh Lung Screening Study

**Data highlights**
- 63 NSCLC specimens were included in the analysis. Overall, there were 10 cancers with rapid doubling times (<183 days), 23 with doubling times of 183-365 days), and 30 with slow doubling times (>365 days)
- Squamous NSCLC tumors comprised 60% of the rapid-doubling-time group and only 3.3% of the slow-doubling-time group
- Median doubling time of squamous NSCLC tumors was 160 days compared with 387 days for adenocarcinomas (p=.0031)
- Prevalent cancers had a significantly slower doubling time than non-prevalent cancers

**Commentary**
This study added to limited existing knowledge about the doubling time of NSCLC tumors and highlights the rapid doubling times of squamous NSCLC tumors. Another study in CT-screen-detected cancers reported median doubling times of 77 days for squamous NSCLC and 303 days for adenocarcinoma (Veronesi et al 2012). Although the reported doubling times differ across studies, Honda et al (2009) and MacKintosh et al (2014) report similar trends.
Real-world treatment patterns

Aarts MJ et al. Improvement in population-based survival of stage IV NSCLC due to increased use of chemotherapy. *Int J Cancer* 2015;136:E387-95


Key finding

- In a study from the Netherlands, fewer patients with newly diagnosed advanced squamous non-small cell lung cancer (NSCLC) received chemotherapy compared with patients with advanced adenocarcinoma (38% vs. 52%); in the overall population, patients who did not receive chemotherapy had poorer survival than those who did receive chemotherapy

Study objective

- To assess use of chemotherapy and survival of patients from the Netherlands Cancer Registry newly diagnosed with Stage IV NSCLC between 2001 and 2012 in the Eindhoven area (N=5428)

Data highlights

- Overall, use of chemotherapy increased over time, from 30% of patients in 2001 to 48% in 2012
- In the overall population, median survival increased from 18 to 21 weeks over the study period
- Across the study period, 38% of patients with Stage IV squamous NSCLC (N=985) received chemotherapy, compared with 52% of Stage IV adenocarcinoma patients (N=2112)
- In the overall population, 64% of patients aged 65-74 years who received chemotherapy survived 6 months, compared with 19% who did not receive chemotherapy; median survival was 35 vs. 10 weeks
- Other factors significantly associated with use of chemotherapy included younger age, high socioeconomic status, no comorbidity, hospital of diagnosis, and recent diagnosis

Commentary

This large European study found that fewer patients with Stage IV squamous NSCLC received chemotherapy, compared with those patients with Stage IV adenocarcinoma, and highlights that patients who did not receive chemotherapy had significantly poorer survival. These data compliment the studies of Davis et al 2012 (US) and Sacher et al 2015 (Canada). Taken together, these studies emphasize the significant unmet need in squamous NSCLC and the importance of advancing treatment options for all patients. Amongst other factors, lower chemotherapy uptake was associated with advanced age and presence of comorbidities, both of which are more common in patients with squamous NSCLC (Janssen-Heijnen et al 1998). The authors speculate that squamous NSCLC patients may also have lower performance scores due to more centrally located disease.

http://dx.doi.org/10.1016/j.lungcan.2014.11.002

**Key finding**
- More than 25% of patients with metastatic squamous non-small cell lung cancer (NSCLC) in a US Medicare population received no cancer-directed treatment and fewer than 50% of patients received chemotherapy. Prognosis was poor, particularly among those who only received supportive care

**Study objective**
- Data from the Surveillance, Epidemiology, and End Results Program – Medicare database on patients aged ≥65 years and diagnosed with metastatic squamous NSCLC between 2001 and 2009 (N=17,133) were analyzed retrospectively to assess treatment patterns

**Data highlights**
- Overall, 72% of patients received cancer-directed therapy (radiation, chemotherapy, cytoreductive surgery, and/or biologic therapy) and 45% received at least 1 line of chemotherapy
- Patients who received cancer-directed therapy had a significantly longer median survival compared with those managed with supportive care only (8 months vs. 2 months, respectively; p<.0001)
- Among those patients for whom a first-line chemotherapeutic regimen was identified (n=7029), carboplatin plus paclitaxel was the most commonly used regimen (n=3215; 46%), followed by carboplatin plus gemcitabine (n=711; 10.1%)
- Older age (≥85 years), metastatic disease at initial diagnosis and the presence of comorbidities were independently associated with decreased odds of receiving cancer-directed therapy and chemotherapy

**Commentary**
This large real-world study found that patients with metastatic squamous NSCLC who were older and had a higher burden of comorbidity were less likely to receive any cancer-directed therapy. Many patients with squamous NSCLC have age- and smoking-related comorbidities at the time of diagnosis (Janssen-Heijnen et al 1998; Asmis et al 2008; Putila and Guo 2014). This study highlights that these comorbid conditions increase the difficulty of treating these patients, with many receiving only supportive care. Patient prognosis was poor, with a median survival of 8 months for those who received cancer-directed therapy and 2 months for those who received supportive care only, highlighting the high unmet medical need in this population.


Key finding
- The majority of patients with metastatic non-small cell lung cancer (NSCLC), and particularly those with squamous NSCLC, do not receive chemotherapy

Study objective
- This large, retrospective, population-based study of all patients diagnosed with Stage IV NSCLC in Canada between 2005-2009 (N=8113) examined practice patterns with respect to systemic treatment and survival outcomes over time

Data highlights
- Overall, only 24% of patients received first-line chemotherapy and of those receiving first-line chemotherapy, only 31% subsequently received second-line therapy
- Patients with adenocarcinoma were more likely to receive systemic therapy than those with Squamous NSCLC (odds ratio 1.3; p<.0001)
- Patients aged >70 years were less likely to receive systemic therapy than younger patients (odds ratio 0.3; p<.0001)
- Median survival from time of diagnosis for patients who did not receive systemic therapy was 3.3 months, whereas patients selected for first-line systemic therapy had a median survival of 8.2 months and those who received both first-and second-line therapy had a median survival of 16.2 months

Commentary
These recently published data support the findings of other studies (eg, Ritzwoller et al 2012; Davis et al 2015) that many patients diagnosed with advanced squamous NSCLC still receive only supportive care. Although the authors suggest that more research is needed to better understand patient characteristics that contribute to lack of treatment, older age is shown here to be a factor. Older NSCLC patients (≥70 years) have a higher prevalence of serious comorbidity, including cardiovascular disease and chronic obstructive pulmonary disease, compared with younger (<70 years) patients, and in patients aged ≥70 years, those with squamous NSCLC have a higher incidence of comorbidity compared with adenocarcinoma (Janssen-Heijnen et al 1998). Research across a broad range of cancers has found that patients with comorbidities are less likely to receive cancer treatments such as surgery, radiotherapy, and chemotherapy (Søgaard et al 2013).
1\textsuperscript{st}-line therapy


http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4264629/?report=reader

**Key finding**
- Histological subtype was not a predictor of survival benefit in patients with Stage III/IV non-small cell lung cancer (NSCLC) who received first-line treatment with one of four platinum-based chemotherapy doublets. Median overall survival (OS) for patients with squamous NSCLC ranged from 6.9 to 9.4 months.

**Study objective**
- To re-analyze data from a Phase 3 trial (E1594) by histological subtype (squamous \([n=224]\), adenocarcinoma \([n=647]\), large cell \([n=74]\), and other \([n=194]\)) to compare OS after 1\textsuperscript{st}-line treatment with one of four platinum-based doublets: cisplatin-paclitaxel, cisplatin-gemcitabine, cisplatin-docetaxel, and carboplatin-paclitaxel.

**Data highlights**
- Median OS for patients with squamous NSCLC and adenocarcinoma was 8.1 and 8.3 months, respectively.
- Median OS for the 4 platinum-based chemotherapy doublets were not statistically different, regardless of histological subtype; median OS for patients with squamous NSCLC ranged from 6.9 months for those treated with cisplatin-paclitaxel to 9.4 months for those treated with cisplatin-gemcitabine.

**Commentary**
Patients with squamous NSCLC have fewer available treatment options than those with nonsquamous disease. This study highlights the poor OS of patients with advanced squamous NSCLC treated in clinical trials with first-line, platinum-based doublets, which are the currently recommended approach in treatment guidelines for squamous NSCLC considered suitable for chemotherapy (Reck et al 2014; National Comprehensive Cancer Network Guidelines 2015) and highlights the high unmet need in squamous NSCLC.

http://jco.ascopubs.org/content/22/11/2184.full.pdf

Key finding
- Although bevacizumab combined with carboplatin and paclitaxel improved overall response rate and time to progression in patients with advanced or recurrent non-small cell lung cancer (NSCLC), it was associated with risk of major hemoptysis in patients with squamous NSCLC histology

Study objective
- This randomized, open-label, placebo-controlled, multicenter, Phase 2 study assessed the efficacy and safety of two different doses of bevacizumab in combination with carboplatin and paclitaxel for the treatment of patients with advanced or recurrent NSCLC (N=99)

Data highlights
- The addition of bevacizumab (15 mg/kg) to carboplatin and paclitaxel increased the overall response rate versus carboplatin-paclitaxel (31.5% vs. 18.8%, respectively), however, major hemoptysis occurred in 6 patients, with 4 events being fatal
- When considered by histological subtype, 31% (4/13) of patients with squamous NSCLC experienced life-threatening hemoptysis, compared with 3.7% (2/54) of patients with adenocarcinoma
- Major hemoptysis appeared to be associated with squamous NSCLC histology, tumor necrosis, cavitation, and tumors that were localized close to major blood vessels

Commentary
Squamous histology was a risk factor for life-threatening hemoptysis with bevacizumab in this Phase 2 study. Major hemoptysis was also associated with tumors that were centrally localized and close to major blood vessels, and with the presence or development of tumor cavitation. Because these features are more common in lung tumors of squamous histology compared with adenocarcinomas, the authors noted that it is not clear if histology alone is the key risk factor or if it is a surrogate for these other risk factors. Based on these results, patients with squamous NSCLC were excluded from the subsequent Phase 3 trials of bevacizumab and the drug is contraindicated in patients with squamous NSCLC.


**Key finding**
- There was no association between histologic subtype and treatment outcome following treatment with different platinum doublets in patients with advanced non-small cell lung cancer (NSCLC). Median overall survival (OS) for patients with squamous NSCLC was 8.4 months

**Study objective**
- To re-analyze data from 4 randomized SWOG trials of first-line platinum-doublet chemotherapy for advanced NSCLC (S9308, S9509, S9806, and S0003) by histologic subtype (adenocarcinoma [n=640], squamous [n=220], large cell [n=121], and other [n=165])

**Data highlights**
- Median OS for patients with all histologies was between 8 and 9 months, and median PFS was around 4 months
- Median OS for patients with nonsquamous and squamous histology was 8.8 and 8.4 months, respectively
- For patients with squamous NSCLC, median OS with paclitaxel-carboplatin was 8.8 months while median OS with vinorelbine-cisplatin was 6.9 months

**Commentary**
Patients with squamous NSCLC have fewer available treatment options than those with nonsquamous disease. This study highlights the poor OS of patients with advanced squamous NSCLC treated in clinical trials with platinum combination chemotherapy, the recommended first-line treatment in treatment guidelines (NCCN 2015; Reck et al 2014), and highlights the high unmet need in squamous NSCLC.
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**Key finding**
- The combined regimen of gemcitabine plus cisplatin for first-line treatment of patients with Stage III/IV non-small cell lung cancer (NSCLC) demonstrated superior overall survival, response rate, and time to disease progression compared with cisplatin alone

**Study objective**
- This prospective, randomized, Phase 3 clinical study compared the efficacy and safety of gemcitabine plus cisplatin with cisplatin for first-line treatment of patients with advanced NSCLC (N=522; n=220 adenocarcinoma; n=145 squamous NSCLC; n=62 large cell carcinoma; n=84 NSCLC; n=11 other)

**Data highlights**
- Patients treated with gemcitabine plus cisplatin showed significant increase in overall survival compared with cisplatin alone (9.1 months vs. 7.6 months, respectively; p=.004)
- Patients treated with gemcitabine plus cisplatin showed significant increase in response rates compared with cisplatin alone (30.4% vs. 11.1%, respectively; p<.0001)
- Patients treated with gemcitabine plus cisplatin showed significant increase in median time to disease progression compared with cisplatin alone (5.6 months vs. 3.7 months, respectively; p=.0013)
- Grade 4 neutropenia and thrombocytopenia occurred at a higher rate in patients treated with gemcitabine plus cisplatin compared with cisplatin alone; however, thrombocytopenia was not associated with serious hemorrhagic events

**Commentary**
At the time this trial was initiated, no other trial had demonstrated an advantage for combination therapy vs. cisplatin monotherapy for patients with Stage III/IV NSCLC. In 1998, results published by Wozniak et al demonstrated advantage for cisplatin plus vinorelbine compared with cisplatin alone in patients with Stage III/IV NSCLC (N=432). Other platinum-based chemotherapy combinations have demonstrated comparable efficacy to gemcitabine plus cisplatin in first-line treatment of Stage IIIIB/IV squamous NSCLC, with overall survival of ~8-11 months (Hoang et al 2013). Various therapies approved for nonsquamous NSCLC, such as pemetrexed and bevacizumab, are not approved for squamous NSCLC and despite a number of trials, there are no targeted agents specifically approved for the first-line treatment of squamous NSCLC. Platinum-based (cisplatin or carboplatin) doublet chemotherapy remains the only first-line treatment option for most patients with squamous NSCLC (Reck et al 2014; National Comprehensive Cancer Network Guidelines 2015), reflecting a significant unmet need for treatment advances in this patient population.

http://jco.ascopubs.org/content/26/21/3543.full.pdf+html

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<th>Key finding</th>
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<td>Differences in the efficacy of pemetrexed plus cisplatin vs. gemcitabine plus cisplatin, as assessed by overall survival (OS), were observed between patients with Stage IIIB / IV squamous non-small cell lung cancer (NSCLC) and other histologies, with pemetrexed plus cisplatin associated with longer survival in adenocarcinoma patients, but inferior survival vs. gemcitabine plus cisplatin in squamous NSCLC</td>
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<td>This inferiority, prospective, randomized, open-label, multicenter, Phase 3 clinical study compared the efficacy and safety of gemcitabine plus cisplatin and pemetrexed plus cisplatin in 1725 chemotherapy-naïve patients with Stage IIIB/IV NSCLC and performance status 0-1</td>
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<td>In the overall population, OS for treatment with pemetrexed plus cisplatin was noninferior to gemcitabine plus cisplatin (median survival 10.3 months vs. 10.3 months, respectively; hazard ratio [HR] 0.94; 95% confidence interval [CI] 0.84-1.05)</td>
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<td>However, when OS was analyzed by histology, compared with gemcitabine plus cisplatin, treatment with pemetrexed plus cisplatin showed statistically superior OS in patients with adenocarcinoma (n=847; 12.6 months vs. 10.9 months, respectively) and large-cell carcinoma (n=153; 10.4 months vs. 6.7 months, respectively)</td>
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<td>In contrast, in patients with squamous NSCLC (n=473), treatment with gemcitabine plus cisplatin provided statistically superior OS (10.8 months vs. 9.4 months)</td>
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<td>This Phase 3 trial demonstrated differences in OS in chemo-naïve patients with NSCLC according to histological subtype, with the efficacy of the platinum doublet pemetrexed plus cisplatin differing between patients with squamous and nonsquamous histology, with pemetrexed-based therapy associated with inferior OS compared with gemcitabine-cisplatin in patients with squamous NSCLC. It has subsequently been shown that 1st-line maintenance therapy and 2nd-line therapy with pemetrexed also provides no benefit in patients with squamous NSCLC (Ciuleanu et al 2009; Scagliotti G et al 2009). These findings may be due to significantly higher levels of thymidylate synthase in patients with squamous NSCLC compared with adenocarcinoma (Ceppi et al 2006), as overexpression of this protein has been shown to reduce the sensitivity to pemetrexed (Sigmond et al 2003; Giovannetti et al 2005).</td>
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http://jco.ascopubs.org/content/30/17/2055.full.pdf+html

Key finding
- Treatment with albumin-bound paclitaxel (nab-paclitaxel) plus carboplatin led to a significant improvement in overall response rate (ORR) vs. treatment with solvent-based paclitaxel (sb-paclitaxel) plus carboplatin (41% vs. 24%) in patients with squamous non-small cell lung cancer (NSCLC)

Study objective
- To investigate the effect on ORR, progression-free survival (PFS), and overall survival (OS) of nab-paclitaxel plus carboplatin vs. sb-paclitaxel plus carboplatin in untreated patients (n=1052) with Stage IIIIB-IV NSCLC

Data highlights
- Treatment with nab-paclitaxel provided a significantly higher ORR than treatment with sb-paclitaxel by both independent radiological assessment (33% vs. 25%) and by the investigator’s assessment (38% vs. 33%)
- Patients with squamous histology receiving nab-paclitaxel plus carboplatin demonstrated a greater response rate than those with adenocarcinoma (41% vs. 26%)
- In the overall population, no significant differences were observed between treatment arms in terms of PFS (6.3 vs. 5.8 months) or OS (12.1 vs. 11.2 months)
- There were no significant differences in OS by histology subtype between treatment arms; median OS of patients with squamous NSCLC was 10.7 months in the nab-paclitaxel arm vs. 9.5 months in the sb-paclitaxel arm (p=NS)
- Nab-paclitaxel was better tolerated than sb-paclitaxel

Commentary
This study shows a significant benefit for patients with squamous NSCLC receiving treatment with nab-paclitaxel plus carboplatin vs. one of the most commonly used standard of care combinations in the treatment of advanced NSCLC (sb-paclitaxel plus carboplatin). However, this improvement in ORR did not translate into a PFS or OS benefit, highlighting the continued high level of unmet need for patients with the squamous NSCLC subtype, for whom more effective therapies are urgently needed.
Key finding

- In this Phase 3 study of alternating oral and i.v. vinorelbine plus cisplatin vs. docetaxel plus cisplatin as first-line treatment of advanced non-small cell lung cancer (NSCLC), both treatment arms provided similar efficacy in terms of response, time-related parameters and quality of life (QoL), though median survival for patients with squamous NSCLC was lower in both treatment arms than for those patients with adenocarcinoma.

Study objective

- This randomized, multinational, Phase 3 study compared the efficacy of alternating i.v. and oral vinorelbine (day 1 i.v. vinorelbine and day 8 oral vinorelbine) plus cisplatin as first-line treatment vs. docetaxel (DCT) in a cisplatin-based combination in patients with advanced NCSLC (n=390; Stage IIIIB or IV), in terms of time to treatment failure (TTF), overall response, progression-free survival (PFS), overall survival (OS), tolerance, and QoL.

Data highlights

- Both treatment arms provided similar efficacy in terms of TFF, overall response, PFS, and OS.
- The median survival of patients with squamous NSCLC (n=129) was lower in both treatment arms than for those patients with adenocarcinoma:
  - Squamous histology: 8.87 months (i.v./oral vinorelbine) and 9.82 months (DCT)
  - Adenocarcinoma: 11.73 months (i.v./oral vinorelbine) and 11.60 months (DCT)
- Both treatment arms had an acceptable tolerance profile:
  - Main hematologic toxicity was Grade 3-4 neutropenia: 24.4% (i.v./oral vinorelbine) and 28.8% (DCT)
- QoL as measured by the Lung Cancer Symptom Scale was similar in both treatment arms.

Commentary

Platinum combination chemotherapy is the recommended first-line approach in treatment guidelines for patients with squamous NSCLC (NCCN 2015; Reck et al 2014). This Phase 3 study is one of several demonstrating the poor OS of patients with advanced squamous NSCLC (Kelly et al 2013; Hoang et al 2013; Scagliotti et al 2008), with median survival of 9-10 months, highlighting the high unmet need in squamous NSCLC.
Maintenance therapy


http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(09)61497-5/abstract

**Key finding**
- In patients with Stage III/IV nonsquamous non-small cell lung cancer (NSCLC) who had not progressed after 4 cycles of first-line platinum-based chemotherapy, maintenance pemetrexed therapy improved progression-free survival (PFS) and overall survival (OS) in those patients whose tumors had nonsquamous histologies but not in patients with squamous NSCLC

**Study objective**
- This randomized, double-blind, placebo-controlled, Phase 3, multicenter study assessed pemetrexed as maintenance therapy in patients with Stage III/IV NSCLC who had not progressed after 4 cycles of platinum-based chemotherapy (N=663), including 182 patients with squamous NSCLC

**Data highlights**
- In the overall population, treatment with pemetrexed significantly improved PFS (p<.0001) and OS (p=.012) compared with placebo
- However, when analyzed by histology, benefits of maintenance pemetrexed were only seen in patients with nonsquamous NSCLC. In the squamous NSCLC population, median PFS was 2.4 months with pemetrexed compared with 2.5 months with placebo (HR 1.03; p=.896). Corresponding median OS was 9.9 months and 10.8 months, respectively (HR 1.07; p=.678)

**Commentary**
Differential effects of pemetrexed by histology have previously been demonstrated in the first-line setting, with benefits of the pemetrexed-cisplatin doublet only seen in patients with nonsquamous NSCLC (Scagliotti et al 2008). This study also demonstrates a significant treatment-by-histology interaction with maintenance pemetrexed, with no benefit for OS or PFS seen in patients with squamous histology. These data contribute to the limited range of treatment options for patients with squamous NSCLC.
2nd-line therapy


http://jco.ascopubs.org/content/22/9/1589.full?sid=326770d2-946b-4aca-a060-45fc12f8fe37

http://theoncologist.alphamedpress.org/content/14/3/253.full.pdf+html

Key finding
- Second-line treatment with pemetrexed resulted in clinically equivalent efficacy outcomes, but with significantly fewer side effects compared with docetaxel in patients with advanced non–small cell lung cancer (NSCLC); however, patients with squamous NSCLC had significantly better overall survival (OS) with docetaxel

Study objective
- This randomized Phase 3 trial compared the efficacy and toxicity of pemetrexed vs. docetaxel in patients (n=571) with advanced (Stage III/IV) NSCLC previously treated with chemotherapy

Data highlights
- In the overall population, overall response rates were 9.1% and 8.8% (analysis of variance \( P = 0.105 \)) for pemetrexed and docetaxel, respectively. Median progression-free survival (PFS) was 2.9 months for each arm, and median survival time was 8.3 vs. 7.9 months (\( P = \) not significant), respectively
- A retrospective analysis of the data, presented by Peterson et al (*J Thorac Oncol* 2007;2(suppl 4):s316-s317) and published by Scagliotti in 2009 showed a significant survival benefit for pemetrexed only in patients with non-squamous NSCLC (9.3 vs. 8.0 months; hazard ratio [HR] 0.78, \( p=.048 \)), while those with squamous NSCLC fared better with docetaxel (6.2 vs. 7.4; HR 1.56, \( p=.018 \)).
- Patients receiving docetaxel experienced significantly higher rates of neutropenia, neutropenic fever, infections, and hospitalization due to neutropenic events compared to patients receiving pemetrexed

Commentary
- The data presented by Hanna et al supported the use of pemetrexed as a standard treatment option for second-line NSCLC based on equivalent efficacy with docetaxel but with a favorable safety profile. However, the subsequent retrospective analysis of the data by Peterson et al (*J Thorac Oncol* 2007;2(suppl 4):s316-s317), showing a significant survival benefit for pemetrexed only in patients with non-squamous NSCLC, led to the loss of pemetrexed's indication in squamous NSCLC in the second-line setting. The differential effects of pemetrexed by histology have also been demonstrated in the first-line setting, with benefits of the pemetrexed-cisplatin doublet seen only in patients with non-squamous NSCLC (Scagliotti et al 2008), and also in the maintenance setting with no benefit for OS or PFS seen in pemetrexed-treated patients with squamous histology (Ciuleanu et al 2013).

http://jco.ascopubs.org/content/30/28/3516.full.pdf+html

**Key finding**
- The evidence for a clinical benefit with first-line maintenance treatment was not conclusive for patients with squamous non-small cell lung cancer (NSCLC)

**Study objective**
- To investigate the efficacy of two maintenance strategies (gemcitabine continuation maintenance and erlotinib switch maintenance) vs. observation alone in randomly assigned patients with Stage IIIB/IV NSCLC whose disease was controlled after gemcitabine-cisplatin induction chemotherapy (n=464)

**Data highlights**
- Maintenance with both gemcitabine and erlotinib significantly prolonged progression-free survival (PFS) vs. observation alone (3.8 and 2.9 vs. 1.9 months, respectively)
- However, neither gemcitabine or erlotinib maintenance provided a significant increase in overall survival (OS) vs. observation (12.1 and 11.4 vs. 10.8 months, respectively)
- The PFS benefit was greater in patients with adenocarcinoma vs. patients with non-adenocarcinoma (includes squamous cell carcinoma and unknown) for both gemcitabine (hazard ratio: 0.54, adenocarcinoma; 0.60, non-adenocarcinoma) and erlotinib (hazard ratio: 0.63, adenocarcinoma; 0.79, non-adenocarcinoma)

**Commentary**
- This study is inconclusive regarding the benefit of maintenance therapy for patients with squamous NSCLC and shows a poorer outcome for these patients than for those with adenocarcinoma receiving maintenance therapy, highlighting the high unmet need in squamous NSCLC. Maintenance treatment may be an option for patients with squamous NSCLC depending on factors such as performance status, patient preference, and toxicity after first-line treatment but is not currently recommended in treatment guidelines (NCCN 2015; Reck et al 2014).