Squamous cell carcinoma (SqCC) of the lung

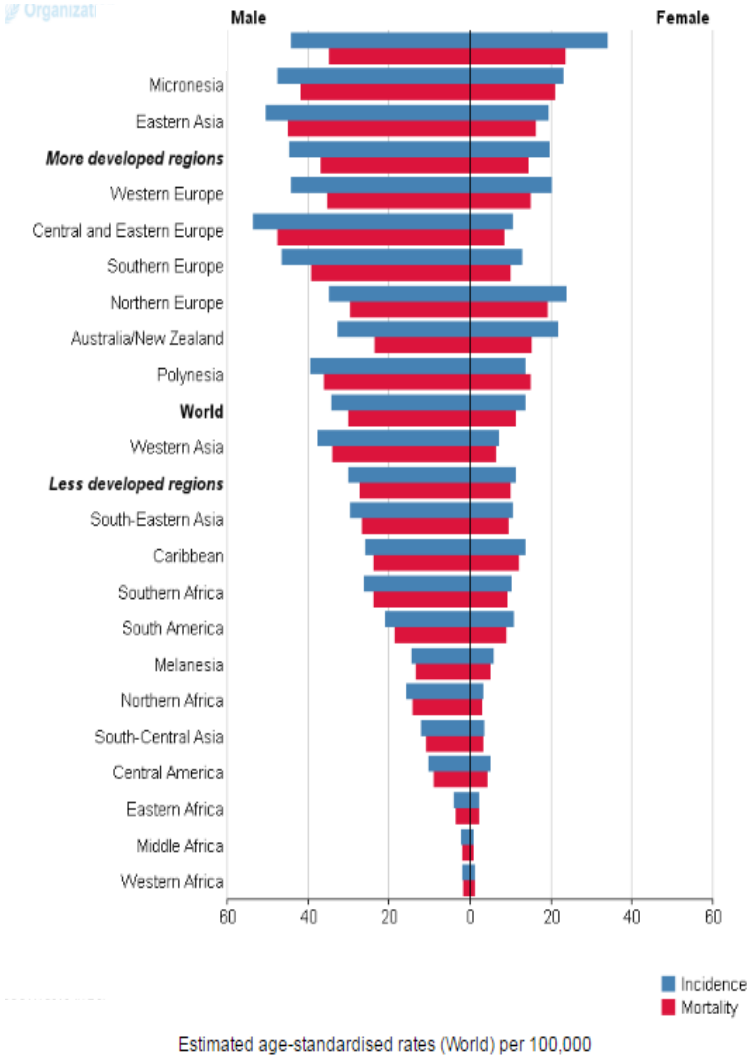
SqCC of the lung

Epidemiology and risk factors

SqCC, squamous cell carcinoma.

Lung cancer incidence

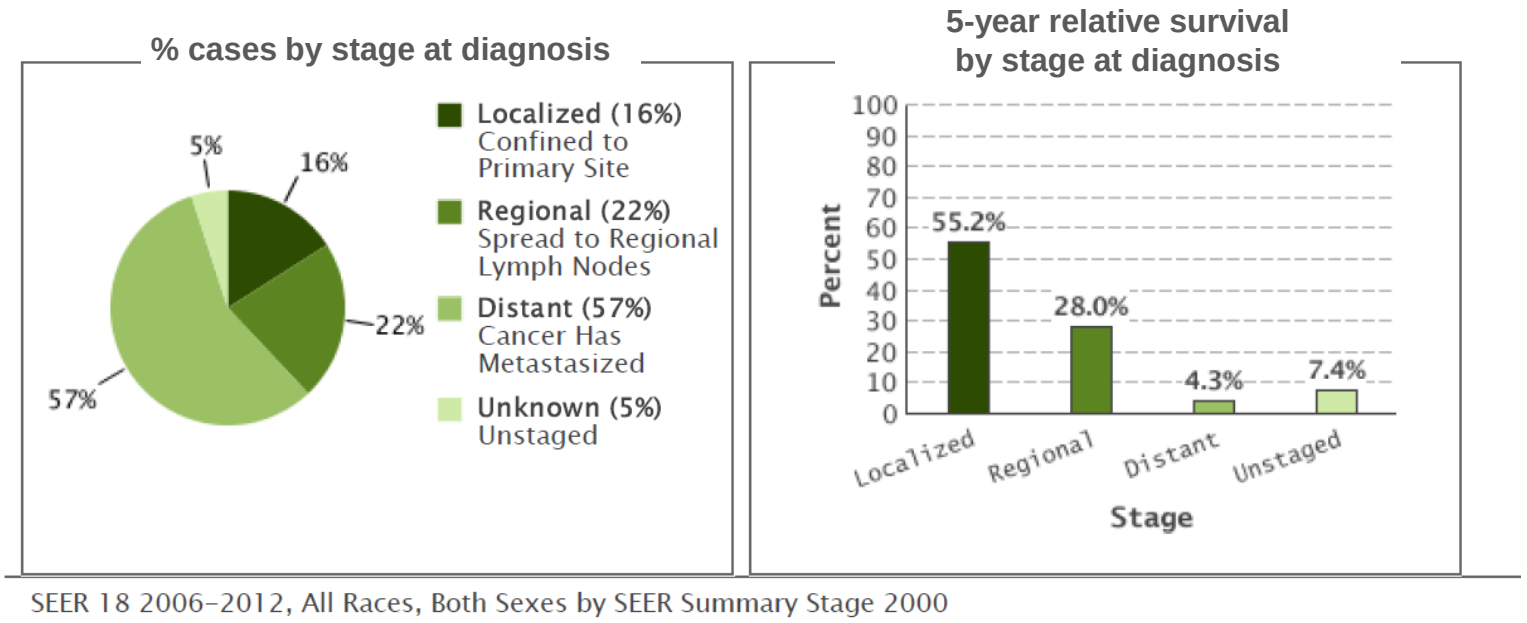
- Lung and bronchial cancer has been the **most common cancer in the world** for decades[1]
- In 2012, it was estimated there would be **1.8 million new cases** (12.9% of all new cancer cases)[1]
- Lung cancer is the **most common cancer in men** worldwide[1]
  - The highest estimated age-standardised incidence rates in men are in Central and Eastern Europe (53.5 per 100,000) and Eastern Asia (50.4 per 100,000)
  - In women, the highest estimated age-standardised incidence rates are in North America (33.8 per 100,000) and Northern Europe (23.7 per 100,000)
- Lung cancer is estimated to be responsible for nearly **one in five** deaths from cancer worldwide (1.59 million deaths; 19.4% of the total)[1]



1. Globocan 2012. Estimated Cancer Incidence, Mortality and Prevalence Worldwide 2012. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx?cancer=lung. Accessed July 2017.

Lung cancer mortality and survival rates

- Approximately **6.5%** of men and women will be diagnosed with lung and bronchus cancer at some point during their lifetime, based on 2011–2013 US data[1]
- Lung and bronchus cancer accounts for **13.3% of all new cancer cases in the US**[1]
- In 2016, lung and bronchus cancer caused an estimated **26.5% of all cancer-related deaths in the US**[1]
- The five-year survival rate is **17.7%**[1]



SEER 18 2006–2012, All Races, Both Sexes by SEER Summary Stage 2000

1. Cancer Stat Facts: Lung and Bronchus Cancer. https://seer.cancer.gov/statfacts/html/lungb.html. Accessed July 2017.

NSCLC subtypes: what is SqCC?

- ~85% of lung cancers are NSCLC[1]
- ~27–46% of NSCLC cases in men and 11–28% of NSCLC cases in women are SqCC[2]

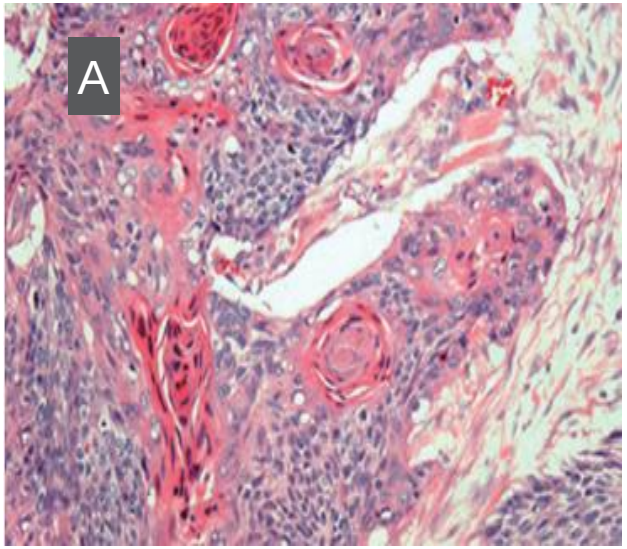
WHO diagnostic categories of NSCLC*[3]	Key histological features	Clinical features
Adenocarcinoma	Gland formation and papillary structures; IHC marker is thyroid transcription factor-1[3]	Typically located peripherally; related to surface alveolar epithelium or bronchial mucosal glands. Most common histology in women[3]
SqCC	Characterized by areas of keratinization and the presence of intercellular bridges; IHC markers are p63 and p40, and possibly cytokeratin 5/6[3]	Typically centrally located, making it more likely to invade larger blood vessels in the mediastinum, and more likely to cause bronchial obstruction. Begins in early versions of flat cells that line the inside of the lung airways and arises in the proximal bronchi. Commonly associated with tumour cavitation and a higher risk of pulmonary haemorrhage than adenocarcinoma. Stronger association with smoking than adenocarcnoma[3]
NSCLC NOS	No clear adenocarcinoma, squamous or neuroendocrine morphology or staining pattern. Classified as large cell carcinoma in resection specimens[4] NOS may also be diagnosed if the biopsy only contains a poor quality or little bronchial tissue, which lacks distinctive features[5]	Poor prognosis compared with other subtypes of NSCLC, even if diagnosed in the early stages of disease[5]

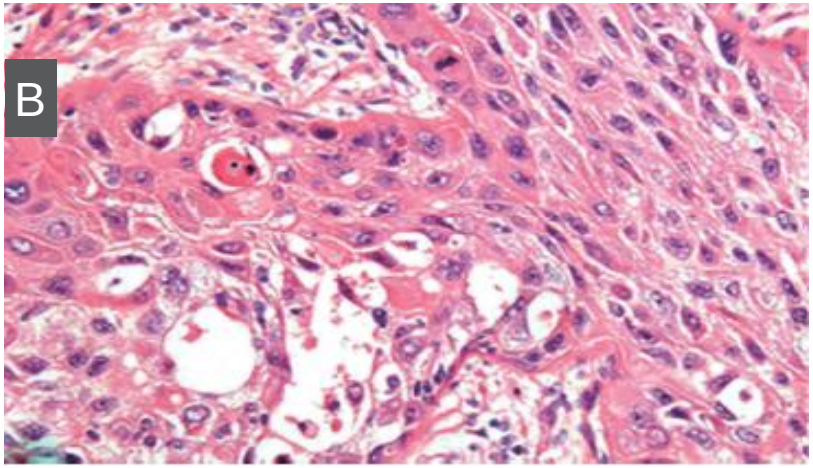
*by small biopsy and cytology.
IHC, immunohistochemistry; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; SqCC, squamous cell carcinoma.
This information is from an international website which is intended for healthcare professionals not located in the United States of America (US) and the United Kingdom (UK).

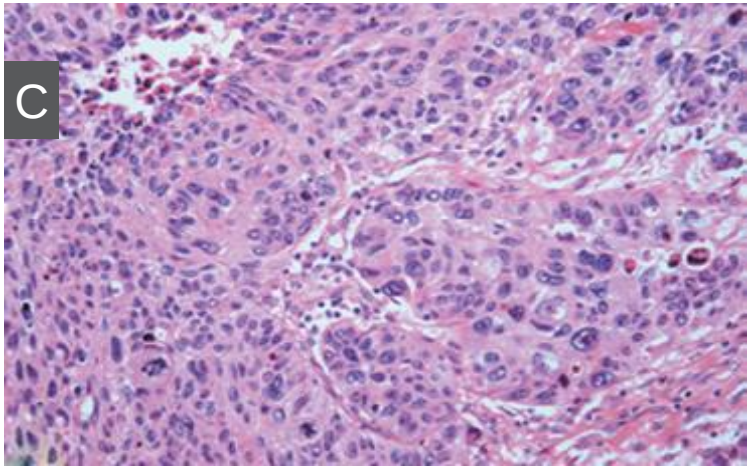
1. Houston KA, et al. Lung Cancer 2014;86:22–8; 2. Youlden DR, et al. J Thorac Oncol 2008;3:819–31; 3. Socinski MA, et al. J Thorac Oncol 2016;11:1411–22;
4. Travis WD, et al. J Thorac Oncol 2015;10:1243–60; 5. Tane S, et al. Oncol Lett 2014;8:1017–24.

SqCC of the lung: pathology

- The characteristic morphological features of SqCC include flattened appearance, intercellular bridges, individual cell keratinisation and squamous pearl formation[1]
- Well-differentiated tumours show[1]
  - keratin pearl formation (A)
  - individual cell keratinisation and intercellular bridges evident at high power (B)
- These are less obvious in poorly differentiated examples (C)[1]







SqCC, squamous cell carcinoma.
This information is from an international website which is intended for healthcare professionals not located in the United States of America (US) and the United Kingdom (UK).

1. Davidson M, et al. J Thorac Dis 2013;5(Suppl. 5):S463-S478.

SqCC of the lung: the major risk factor is smoking

- SqCC is associated more strongly with smoking than any other lung cancer[1]
  - In a pooled analysis (n=13,169 cases and 16,010 controls from Europe and Canada), the OR for SqCC in male current vs never smokers was 45.6 (95% CI: 34.3–60.6), compared with 10.8 (95% CI 8.7–13.3) for adenocarcinoma[2]
- In patients with SqCC who are ever smokers, the estimated mortality rate is almost twice that reported in ever smokers with adenocarcnoma[3]

CI, confidence interval; OR, odds ratio; SqCC, squamous cell carcinoma.
This information is from an international website which is intended for healthcare professionals not located in the United States of America (US) and the United Kingdom (UK).

1. Derman BA, et al. Transl Lung Cancer Res 2015;4(5):524–32; 2. Pesch B, et al. Int J Cancer 2012;131:1210–19; 3. Lee PN and Forey BA. BMC Cancer 2013;13:189.

SqCC of the lung

Clinical features, diagnosis and staging

SqCC, squamous cell carcinoma.

SqCC of the lung: clinical presentation and symptoms

- Patients with early-stage SqCC of the lung may have no obvious or defining symptoms[1]
- As the disease progresses, the following symptoms might be observed[1]

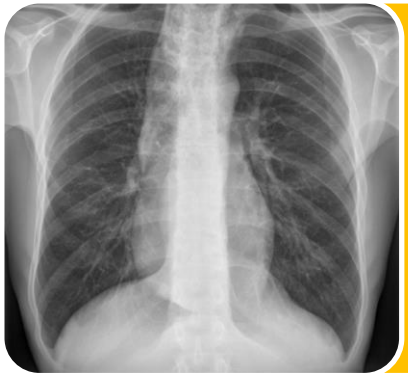
Symptoms may include:	
Persistent cough	Coughing up blood
Persistent chest infections	Loss of appetite
Unexplained weight loss	Shortness of breath
Ache when breathing	Fatigue
Hoarseness	Discomfort when swallowing
Finger clubbing	Persistent chest or shoulder pain

SqCC, squamous cell carcinoma.
This information is from an international website which is intended for healthcare professionals not located in the United States of America (US) and the United Kingdom (UK).

1. NHS Choices: symptoms of lung cancer. http://www.nhs.uk/Conditions/Cancer-of-the-lung/Pages/Symptoms.aspx. Accessed July 2017.

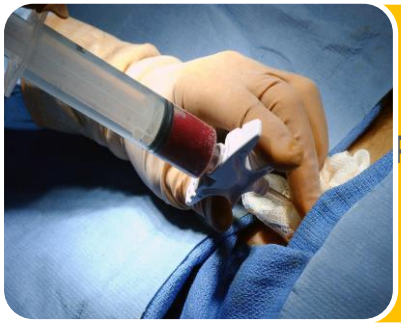
SqCC of the lung: diagnosis

Medical history, imaging, pulmonary function[1]



- Medical history, including smoking history
- CT scan of chest and upper abdomen, with contrast
- FDG PET/CT scan
- Brain MRI with contrast
- MRI to establish whether disease has spread
- Pulmonary function tests

Biopsy and sampling[1]



- Bronchoscopy
- Mediastinal lymph node evaluation
- Pathologic confirmation, e.g. via mediastinoscopy, thoracoscopy, needle biopsy, lymph node biopsy, mediastinotomy, EUS/EBUS biopsy
- Thoracentesis or pericardiocentesis

CT, Computed tomography; EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography; SqCC, squamous cell carcinoma.
This information is from an international website which is intended for healthcare professionals not located in the United States of America (US) and the United Kingdom (UK).

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Non-small cell lung cancer. Version 8. 2017. https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed July 2017.

SqCC of the lung: staging and TNM classification

- The system used most often to stage lung cancer is the American Joint Committee on Cancer TNM system, which is based on[1]
  - The size of the main tumour (T) and whether it has grown into nearby areas
  - Whether the cancer has spread to nearby (regional) lymph nodes (N)
  - Whether the cancer has metastasised (M) to other organs of the body
- Once the T, N, and M categories have been defined, this information is combined to assign an overall Stage of 0, I, II, III, or IV[1]
- This process is called stage grouping[1]
- It produces a range of anatomic stage or prognostic groups (right)[1]

ANATOMIC STAGE/PROGNOSTIC GROUPS			
Occult Carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
	T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T1a	N1	M0
	T1b	N1	M0
	T2a	N1	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a	N2	M0
	T1b	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T3	N2	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	T1a	N3	M0
	T1b	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N3	M0
	T4	N2	M0
	T4	N3	M0
Stage IV	Any T	Any N	M1a
	Any T	Any N	M1b

M, metastasis; N, node; SqCC, squamous cell carcinoma; T, tumour.

This information is from an international website which is intended for healthcare professionals not located in the United States of America (US) and the United Kingdom (UK).

1. American Joint Committee on Cancer. AJCC Lung Cancer Staging Poster 7th ed., 2009. https://cancerstaging.org/references-tools/quickreferences/Documents/LungMedium.pdf. Accessed July 2017.

SqCC of the lung: TNM classification in more detail

T	Comments
TX	Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualised by imaging or bronchoscopy
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (for example, not in the main bronchus)*
T1a	Tumour 2 cm or less in greatest dimension
T1b	Tumour more than 2 cm but 3 cm or less in greatest dimension
T2	Tumour more than 3 cm but 7 cm or less or tumour with any of the following features (T2 tumours with these features are classified T2a if 5 cm or less): involves main bronchus, 2 cm or more distal to the carina; invades visceral pleura (PL1 or PL2); associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumour more than 3 cm but 5 cm or less in greatest dimension
T2b	Tumour more than 5 cm but 7 cm or less in greatest dimension
T3	Tumour more than 7 cm or one that directly invades any of the following: parietal pleural (PL3), chest wall (including superior sulcus tumours), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumour in the main bronchus less than 2 cm distal to the carina* but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumour nodule(s) in the same lobe
T4	Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina, separate tumour

*The uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.

M, metastasis; N, node; SqCC, squamous cell carcinoma; T, tumour.

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1. American Joint Committee on Cancer. AJCC Lung Cancer Staging Poster 7th ed., 2009. https://cancerstaging.org/references-tools/quickreferences/Documents/LungMedium.pdf. Accessed July 2017.

SqCC of the lung: TNM classification in more detail

N	Comments
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M	**Comments**
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumour nodule(s) in a contralateral lobe, tumour with pleural nodules or malignant pleural (or pericardial) effusion*
M1b	Distant metastasis (in extrathoracic organs)

*Most pleural (and pericardial) effusions with lung cancer are due to tumour. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumour, and the fluid is non-bloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging element and the patient should be classified as M0.
M, metastasis; N, node; SqCC, squamous cell carcinoma; T, tumour.
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1. American Joint Committee on Cancer. AJCC Lung Cancer Staging Poster 7th ed., 2009. https://cancerstaging.org/references-tools/quickreferences/Documents/LungMedium.pdf. Accessed July 2017.

SqCC of the lung: genetic profile

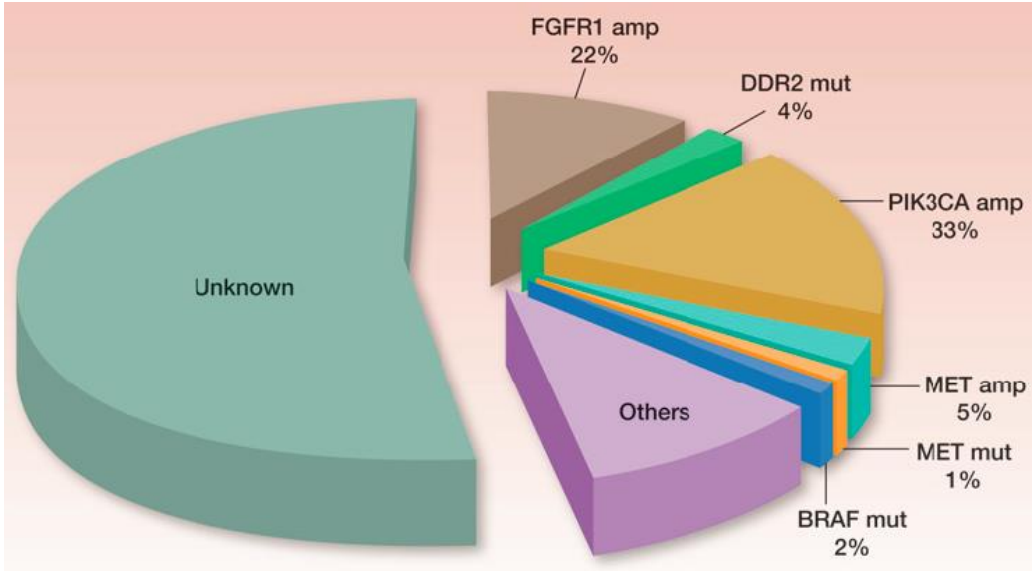
- Most SqCC lung tumours express:[1]
  - p40/p63
  - Cytokeratins 5/6
  - High molecular weight keratin
  - Carcinoembryonic antigen
- Most SqCC lung tumours do not express cytokeratin 7 and TTF-1[1]
- In the case of small biopsy specimens or poorly differentiated tumours that lack histologic signs of squamous differentiation, IHC staining for both p40/p63 (positive in SqCC) and TTF-1 (negative in SqCC) is often informative[1]

IHC, immunohistochemistry; SqCC, squamous cell carcinoma; TTF-1, thyroid transcription factor-1.
This information is from an international website which is intended for healthcare professionals not located in the United States of America (US) and the United Kingdom (UK).

1. Gerber DE, et al. Am Soc Clin Oncol Educ Book. 2014:e353–65.

SqCC of the lung is characterised by complex genomic alterations

- Frequency of potentially targetable genetic abnormalities in SqCC of the lung include membrane receptor alterations, signalling pathway alterations, and transcription factor alterations
- Patients whose tumours harbour specific molecular defects such as these may be enrolled in prospective clinical trials of relevant targeted agents
- Potential targets include FGFR1 amplification, alterations in the PI3K pathway, and DDR2 mutations



DDR, discoidin death receptor 2; FGFR1, fibroblast growth factor receptor 1; PI3K, phosphatidyl 3-kinases; SqCC, squamous cell carcinoma.

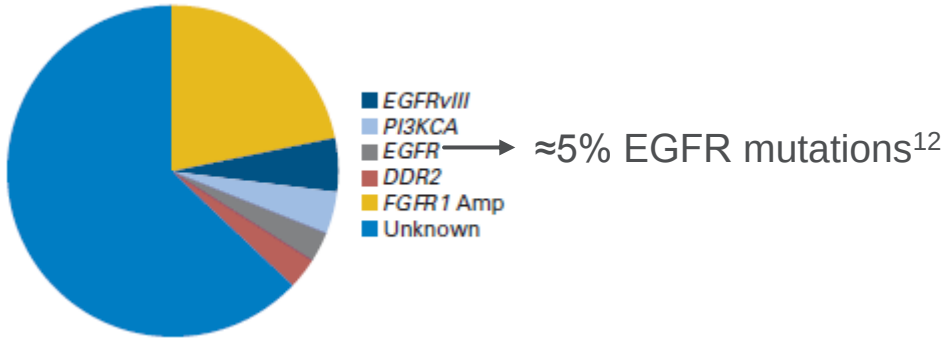
1. Perez-Moreno P, et al. Clin Cancer Res 2012;18:2443–51.

ErbB Receptor Family is a valid therapeutic target for SqCC of the lung

- Dysregulation of the ErbB pathway is frequently observed in SqCC of the lung[1,2]

ErbB Receptor	Frequency (%)
EGFR overexpression[2-5]	26-86
EGFR amplification[2,5]	15-27
*EGFR*vIII mutation[6]	5
EGFR kinase domain mutation[7]	<5
ERBB2 mutation/amplification[2]	5
ERBB3 mutation[8]	1
ERBB3 overexpression[9]	10
ERBB4[10]	8

Frequency of known drivers in SqCC[11]



DDR, discoidin death receptor 2; EGFR, epidermal growth factor receptor; FGFR1, fibroblast growth factor receptor 1; PI3K, phosphatidyl 3-kinases; SqCC, squamous cell carcinoma.

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1. Hirsch et al. J Clin Oncol 2003;21:3798-807; 2. Lopez-Malpartida et al. Lung Cancer 2009;65:25-33; 3. Lee et al. Lung Cancer 2010;68:375-82; 4. Gately et al. Clin Lung Cancer 2014;15:58-66; 5. Dacic et al. Am J Clin Pathol 2006;125:860-5; 6. Ji et al. PNAS 2006;103:7817-22; 7. Dearden et al. Ann Oncol 2013;24: 2371–76; 8. Jaiswal et al. Cancer Cell. 2013;23:603-17; 9. Gorgoulis et al. Pathol Res Pract 1995;191:973-81.10. Kan et al. Nature 2010;466:869-75; 11. Li et al. J Clin Oncol 2013;31:1039-49; 12. Pao et al. Lancet Oncol 2011;12:175-80.

SqCC of the lung

Treatment options

SqCC, squamous cell carcinoma.
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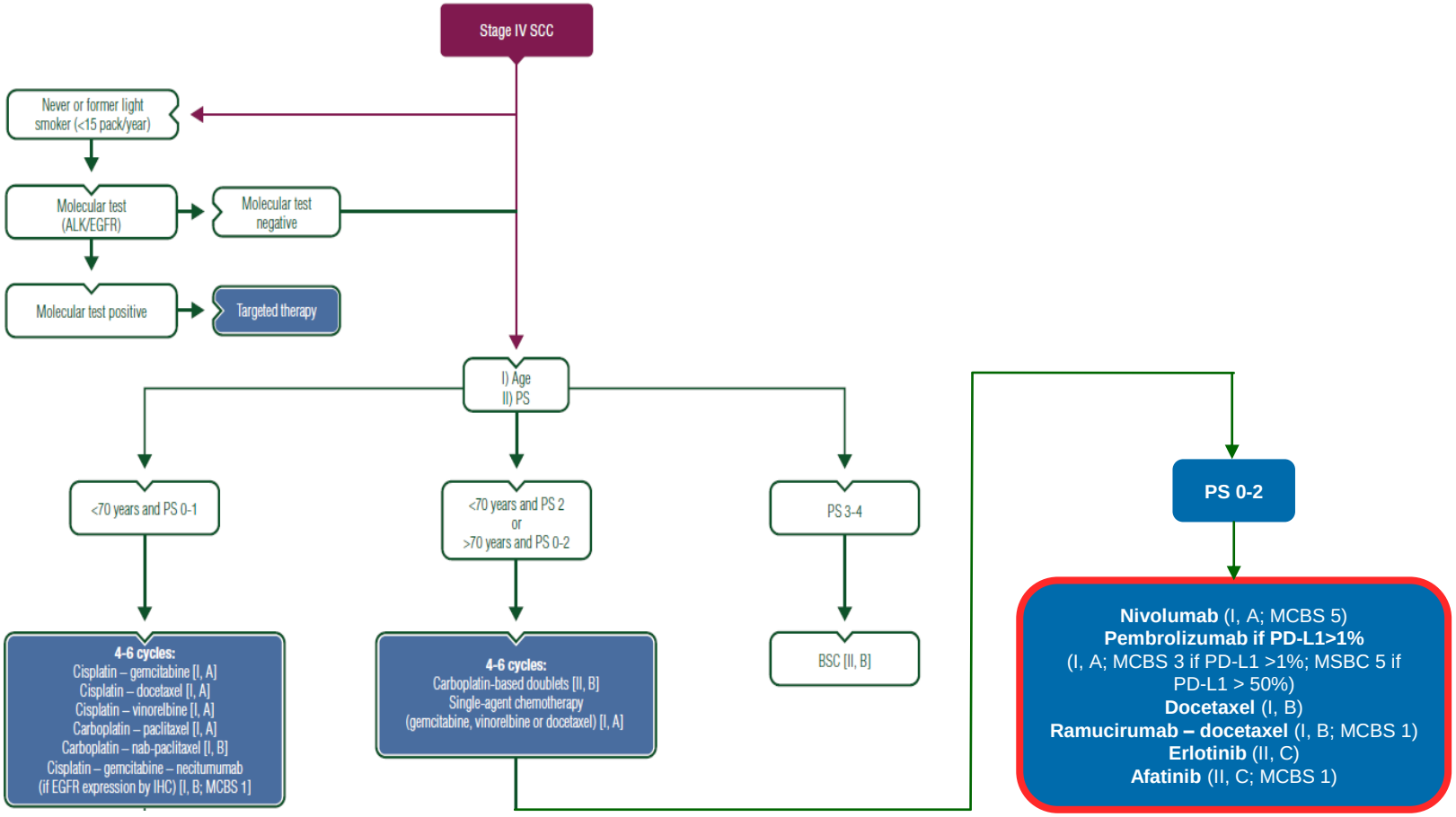
Current treatment recommendations for metastatic SqCC of the lung (ESMO guidelines)



*ESMO guidelines do not recommend maintenance therapy in the treatment of squamous cell carcinoma NSCLC.
BSC, best standard of care, EGFR, epidermal growth factor receptor; MCBS, Magnitude of Clinical Benefit Scale; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; PS, performance status; SqCC, squamous cell carcinoma.
This information is from an international website which is intended for healthcare professionals not located in the United States of America (US) and the United Kingdom (UK).

1. Novello S, et al. Ann Oncol 2016;27(Suppl .5):v1–v27.

Abbreviated EU SmPC

EGFR M+ NSCLC and sqNSCLC

GIOTRIF®: Irreversible ErbB family blocker. **Active substance:** Afatinib. **Indications:** GIOTRIF is indicated as monotherapy for (1) patients with locally advanced or metastatic NSCLC with activating EGFR mutations not previously treated with EGFR TKIs, (2) patients with NSCLC of squamous histology progressing on or after platinum-based chemotherapy. **Posology:** The recommended dose is 40 mg once daily, orally. Not recommended in patients with an eGFR <15ml/min and severe hepatic impairment. **Contraindications:** Hypersensitivity to afatinib or any of the excipients. **Interactions:** Potent P-gp inhibitors may lead to increased afatinib exposure, concomitant treatment with potent P-gp inducers may lead to a reduction in afatinib exposure. Afatinib is not an inhibitor or inducer of CYP enzymes. **Undesirable effects:** Paronychia, cystitis, decreased appetite, dehydration, hypokalaemia, dysgeusia, conjunctivitis, dry eye, epistaxis, rhinorrhoea, diarrhoea, stomatitis, nausea, vomiting, cheilitis, dyspepsia, alanine aminotransferase increased, aspartate aminotransferase increased, rash, acneiform dermatitis, pruritus, dry skin, palmar-plantar erythrodysaesthesia syndrome, nail disorders, Stevens-Johnson syndrome, toxic epidermal necrolysis, muscle spasms, renal impairment/renal failure, pyrexia, weight decreased, interstitial lung disease, keratitis, pancreatitis. **Presentations:** 20 mg, 30 mg, 40 mg, and 50 mg film-coated tablets. For detailed information, please refer to the published Prescribing Information.

Supply classification: POM.

This medicine is subject to additional monitoring.

Boehringer Ingelheim International GmbH, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany

EGFR M+, epidermal growth factor receptor mutation positive; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

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