EDITORIAL
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Squamous carcinoma of the lung: still a long and winding road to successful treatment


"…as the squamous cell lung cancer treatment landscape evolves many new therapeutic issues have arisen at the same time."

Paolo Bironzo[1] & Giorgio Vittorio Scagliotti*[,1]

Lung cancer is the leading cause of cancer-related death worldwide, accounting for approximately 1.4 million deaths in 2010 in the USA, according to the SEER database [1].

Approximately 85% of newly diagnosed lung tumors are non-small-cell lung cancer (NSCLC) and, among them, 20–30% are squamous cell lung cancer (SQCLC). The incidence of this subtype has now been surpassed by adenocarcinoma, reflecting trends in reduced tobacco exposure with the introduction of filtered and low-tar content cigarettes, as well as changes in cigarette smoke inhalation patterns [2].

The diagnosis of SQCLC is currently performed by light microscopy and relies on the presence of keratinization and/or intracellular bridges. With the increasing need of a correct histological diagnosis in order to choose the right therapeutic regimen, the dichotomy between small-cell lung cancer and NSCLC became obsolete. For such reasons when in poorly differentiated lung carcinomas there is no clear-cut cellular differentiation at light microscopy, which account for 20–30% of cases, a panel of immunohistochemistry (IHC) markers has been shown to increase the likelihood of an appropriate subtyping. This panel includes at least cytokeratin CK7, CK5, TTF-1 and p63, as demonstrated by a retrospective study performed on fine-needle aspiration cytology cell blocks [3]. Another marker, p40, an antibody that recognizes the ΔNp63-a p63 isoform, is equivalent to p63 in sensitivity but markedly superior to p63 in specificity, which eliminates the potential pitfall of misinterpreting a p63-positive adenocarcinoma or unsuspected lymphoma as a SCC [4].

Current available treatment options for advanced SQCLC rely only on systemic cytotoxic chemotherapy. Patients with a good performance status (Eastern Cooperative Oncology Group performance status 0–1) should receive a platinum agent, cisplatin (preferentially) or carboplatin, plus a third-generation drug (taxanes,

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[1]Department of Oncology, University of Turin, S. Luigi Hospital, Regione Gonzole 10, 10043, Orbassano (To), Italy
*Author for correspondence: Tel.: +390119026414; Fax: +390119015184; giorgio.scagliotti@unito.it

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vinorelbine or gemcitabine). Eastern Cooperative Oncology Group performance status 2 patients are often treated with single-agent chemotherapy, although carboplatin-based doublet could be also considered. Finally, best supportive care (BSC) represents the only option for PS 3–4 patients [5].

Several studies (for review, see [6]) have shown an inferior activity of pemetrexed in combination with cisplatin in SQCLC and this agent is currently not licensed for the treatment of this type of tumor. The histology-related activity of pemetrexed has been related to a different expression of thymidylate synthase (TS), one of the main enzymes of the folate pathway targeted by pemetrexed, with expression being higher in SQCLC and lower in nonsquamous NSCLC [7]. Other markers of chemoresistance such as ERCC1 and BRCA1 equally show higher expression in SQCLC than other histotypes [8].

A large Phase III study that compared carboplatin combined with albumin-bound paclitaxel (nab-PC) or paclitaxel demonstrated a significantly higher ORR with nab-PC than paclitaxel in the overall population (33 vs 25%; $p = 0.005$) and in patients with squamous histology (41 vs 24%; $p < 0.001$), while nab-PC was as effective as paclitaxel in patients with nonsquamous histology (26 vs 25%; $p = 0.808$) [9].

Platinum chemotherapy with poly(ADP-ribose) polymerase (PARP) inhibitors have been studied in clinical trials. Preclinical observations have shown that PARP inhibitors preferentially kill neoplastic cells and induce complete or partial regression in various human tumor xenografts in nude mice treated with platinum agents [10]. However, PARP activity in DNA repair is not fully clear [11], and as a result the biological mechanisms by which PARP inhibitors sensitize cancer cells to platinum chemotherapy remain to be resolved.

Currently the role of targeted therapies in SQCLC remains elusive. Bevacizumab, a monoclonal antibody against VEGF, is an established treatment option combined with chemotherapy in nonsquamous advanced NSCLC only. Such restriction is related to life-threatening or fatal episodes of hemoptysis in bevacizumab-treated patients with SQCLC, as observed in one of the early Phase II trials [12], and the drug is not currently licensed for SQCLC. Several multitargeted, antiangiogenic agents including sorafenib, motesanib and nintedanib have been studied in clinical trials for patients with advanced NSCLC. For most of these agents antitumor activity has not been seen in SQCLC and occasionally only additive toxicity has been reported (for review see [13]).

Nintedanib, which inhibits VEGF receptor (VEGFR), PDGF receptor (PDGFR) and FGF receptor (FGFR), has been extensively investigated. The LUME-Lung 1 study comparing docetaxel plus nintedanib versus docetaxel plus placebo as second-line treatment in NSCLC patients and in SQCLC showed only a small statistically significant improvement in progression-free survival and no effect on overall survival [14].

SQCLC lacks EGF receptor (*EGFR*) mutations and *ALK* gene fusions, and the occasional detection of these mutations in SQCLC is due to challenges with differential diagnosis with adenosquamous carcinoma and adenocarcinoma, an issue mostly resolved by incorporating IHC markers [15]. Independently from the abovementioned issue, when EFGR mutations are detected in SQCLC they are in almost invariably in never smokers.

In a Phase III trial (FLEX) a statistically nonsignificant correlation in SQCLC between increased survival and chemotherapy plus cetuximab, a monoclonal antibody against EGFR, was observed in the subgroup of patients with SQCLC [16] and high EGFR expression was associated with survival in the study population [17].

When compared with adenocarcinoma, SQCLC is characterized by a more complex genetic profile. Chromosome 3q amplification and chromosome 3p and 9p deletions have been frequently reported. In particular, *SOX2* is amplified in approximately 20% of SQCLC series and, by contrast, *FOXP1* is inactivated in 4% of tumors [18]. The TCGA Cancer Genome Atlas (TCGA) found that the genes significantly mutated include *TP53*, *CDKN2A*, *PTEN*, *PIK3CA*, *KEAP1*, *MLL2*, *HLA-A*, *NFE2L2*, *NOTCH1* and *RB1* [18]. Smokers affected by SQCLC frequently carry *DDR2* and *FGFR2* mutations, while *EGFR*, *MET* and *PIK3CA* mutations are prevalent in never-smokers [19]. Among mutations, the most interesting from a therapeutic point of view are represented by *MDM2*, a negative regulator of p53 [20], *PIK3CA* and *PTEN*, *DDR2*, *FGFR1*, *MLL2* and *ERBB2*.

Constitutive activation of FGFR1 by gene amplification, translocation or mutation is associated with various malignancies such as breast cancer or myeloproliferative diseases. It has been recently reported that FGFR1 amplification

occurs in 20% of SQCLC, and preclinical tests have shown that these alterations are therapeutically tractable. These findings make FGFR1 amplification a potential biomarker for lung cancer treatment [21].

The NRF2 pathway, involved in cell response to oxidative stress, and the Eph-ephrin signaling system, especially related to EPHB3 overexpression, have been detected in SQCLC, but the development of effective targeting agents is lacking [22,23].

Several checkpoint receptors expressed on T cells modulate the immune response as part of normal physiological processes to maintain self-tolerance, prevent autoimmunity, suppress inappropriate responses to host antigens and protect nontumor tissues from damage [24]. Tumors can exploit these immune checkpoint pathways to evade the immune response and develop resistance against attack from the immune system. Two such pathways with the potential for therapeutic anticancer targeting include PD-1 and CTLA-4.

Monoclonal antibodies (mAbs) against PD-1 and PDL-1 demonstrated activity in both pretreated and naive patients. In a Phase I trial nivolumab, a fully human mAb directed against the cytotoxic T-cell protein PD1, led to a 23% response rate in previously treated SQCLC patients [25]. In a heavily pretreated group of patients the median OS was 10.1 months, with a 1-year OS of 42% and a 2-year OS of 24% [26]. Another anti-PD1 mAb, pembrolizumab, was tested in a Phase II trial in previously untreated PD-L1-positive NSCLC patients. In the 42 evaluable patients the objective response rate by immune-related response criteria (irRC) was 36% [27]. Two mAbs that target PD-L1, MPDL3280A and MEDI4736, have recently been tested, reporting comparable results, as reported with nivolumumab and pembrolizumab [28,30]. The immunohistochemistry score for PD-L1 expression directly correlated with response rate as smoking status, with 26% of responses in current or former smokers versus 10% in never smokers [29].

In conclusion, as the SQCLC treatment landscape evolves many new therapeutic issues have arisen at the same time. Molecular alterations proven to be predictive tools in oncogene-addicted adenocarcinomas do not apply to SQCLC, probably as a consequence of its more complex genetic profile. However, at the same time the expanding role of next-generation sequencing and its vastly reduced cost paves the way for a more appropriate use of targeted agents, possibly leading to better results even in SQCLC. Moreover, the immunotherapy, with its promising results, has opened exciting new roads that will be thoroughly explored in the near future, both in the advanced and early disease setting. While our knowledge of tumors genetics and microenvironment evolve rapidly, the challenge is to correctly put in the right place each piece of the evolving puzzle to gradually improve patient outcome.

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References

1 National Cancer Institute. http://seer.cancer.gov/

2 Siegel R, Naishadham D, Jemal A. Cancer statistic 2013. *CA Cancer J. Clin.* 63, 11–30 (2013).

3 Righi L, Graziano P, Fornari A *et al.* Immunhistochemical subtyping of nonsmall cell lung cancer not otherwise specified in fine-needle aspiration cytology: a retrospective study of 103 cases with surgical correlation. *Cancer* 117, 3416–3423 (2011).

4 Bishop JA, Teruya-Feldstein J, Westra WH *et al.* p40(ΔNp63) is superior to p63 for the diagnosis of pulmonary squamous cell carcinoma. *Mod. Pathol.* 25, 405–415 (2012).

5 Reck M, Popat S, Reinmuth N *et al.* Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* doi:10.1093/annonc/mdu199 (2014) (Epub ahead of print).

6 Scagliotti G, Brodowicz T, Shepherd FA *et al.* Treatment-by-histology interaction analyses in three Phase III trials show superiority of pemetrexed in nonsquamous non-small cell lung cancer. *J. Thorac. Oncol.* 6, 64–70 (2011).

7 Ceppi P, Volante M, Saviozzi S *et al.* Squamous cell carcinoma of the lung compared with other histotypes shows higher messenger RNA and protein levels for thymidylate synthase. *Cancer* 107, 1589–1596 (2006).

8 Bonanno L, Favaretto A, Rosell R. Platinum drugs and DNA repair mechanisms in lung cancer. *Anticancer Res.* 34, 493–501 (2014).

9 Socinski MA, Bondarenko I, Karaseva NA *et al.* Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a Phase III trial. *J Clin. Oncol.* 30, 2055–2062 (2012).

10 Miknyoczki SJ, Jones-Bolin S, Pritchard S *et al.* Chemopotentiation of temozolomide, irinotecan, and cisplatin activity by CEP-6800, a poly(ADP-ribose) polymerase

inhibitor. *Mol. Cancer Ther.* 2, 371–382 (2003).

11 Ahel I, Ahel D, Matsusaka T *et al.* Poly (ADP-ribose)-binding zinc finger motifs in DNA repair/checkpoint proteins. *Nature* 451, 81–85 (2008).

12 Johnson DH, Fehrenbacher L, Novotny WF *et al.* Randomized Phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small cell lung cancer. *J. Clin. Oncol.* 22, 2184–2191 (2004).

13 Scagliotti G, Govindan R. Targeting angiogenesis with multitargeted tyrosine kinase inhibitors in the treatment of non-small cell lung cancer. *Oncologist* 15, 436–446 (2010)

14 Reck M, Kaiser R, Mellemgaard A *et al.* Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a Phase 3, double-blind, randomised controlled trial. *Lancet Oncol.* 15, 143–155 (2014).

15 Rekhtman N, Paik PK, Arcila ME *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.* 18, 1167–1176 (2012).

16 Pirker R, Pereira JR, Szczesna A *et al.* Cetuximab plus chemotherapy in patients with advanced non-small cell lung cancer (FLEX): an open-label randomised Phase III trial. *Lancet* 373, 1525–1531 (2009).

17 Pirker R, Pereira JR, von Pawel J *et al.* EGFR expression as a predictor of survival for first-line chemotherapy plus cetuximab in patients with advanced non-small-cell lung cancer: analysis of data from the Phase 3 FLEX study. *Lancet Oncol.* 13, 33–42 (2012).

18 Hammerman PS, Hayes DN, Wilkerson MD *et al.* Comprehensive genomic characterization of squamous cell lung cancers. *Nature* 489, 519–525 (2012).

19 An SJ, Chen ZH, Su J *et al.* Identification of enriched driver gene alterations in subgroups of non-small cell lung cancer patients based on histology and smoking status. *PLoS ONE* 7, e40109 (2012).

20 Wade M, Li YC, Wahl GM. MDM2, MDMX and p53 in oncogenesis and cancer therapy. *Nat. Rev. Cancer* 13, 83–96 (2012).

21 Dienstmann R, Rodon J, Prat A *et al.* Genomic aberrations in the FGFR pathway: opportunities for targeted therapies in solid tumors. *Ann. Oncol.* 25, 552–563 (2014).

22 Sasaki H, Suzuki A, Shitara M *et al.* Genotype analysis of the *NRF2* gene mutation in lung cancer. *Int. J. Mol. Med.* 31(5), 1135–1138 (2013).

23 Li JJ, Xie D. The roles of and therapeutic potentials of Ephs and ephrins in lung cancer. *Exp. Cell Res.* 319, 152–159 (2013).

24 Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat. Rev. Cancer* 12, 252–264 (2012).

25 Brahmer JR, Horn L, Antonia SJ *et al.* Survival and long-term follow-up of the Phase I trial of nivolumab (anti-PD-1; BMS-936558; ONO-4538) in patients (PTS) with previously treated advanced non-small cell lung cancer (NSCLC). Presented at: *2013 ASCO Annual Meeting.* Chicago, IL, USA, 31 May–4 June 2013 (Abstract 8030).

26 Brahmer JR, Horn L, Antonia SJ *et al.* Nivolumab (anti-PD-1; BMS-936558; ONO-4538) in patients with non-small cell lung cancer (NSCLC): overall survival and long-term safety in a Phase 1 trial. Presented at: *15th World Conference on Lung Cancer.* Sydney, Australia, 27–30 October 2013 (Abstract MO18.03).

27 Rizvi NA, Garon EB, Patnaik A *et al.* Safety and clinical activity of MK-3475 as initial therapy in patients with advanced non-small cell ling cancer (NSCLC). Presented at: *2014 ASCO Annual Meeting.* Chicago, IL, USA, 30 May–3 June 2014 (Abstract 8007).

28 Horn L, Herbst RS, Spigel D *et al.* An analysis of the relationship of clinical activity to baseline EGFR status, PD-L1 expression and prior treatment history in patients with non-small cell lung cancer (NSCLC) following PD-L1 blockade with MPDL3280A (anti-PDL1). Presented at: *15th World Conference on Lung Cancer.* Sydney, Australia, 27–30 October 2013 (Abstract MO18.01).

29 Brahmer JR, Rizvi NA, Lutzky J *et al.* Clinical activity and biomarkers of MEDI4736, an anti-PD-L1 antibody, in patients with NSCLC. Presented at: *2014 ASCO Annual Meeting.* Chicago, IL, USA, 30 May–3 June 2014 (Abstract 8021).

30 Spigel DR, Gettinger SN, Horn L *et al.* Clinical Activity, safety, and biomarkers of MPDL3280A, an engineered PD-L1 antibody in patients with localiy advanced or metastatic non-small cell lung cancer (NSCLC). Presented at: *2013 ASCO Annual Meeting.* Chicago, IL, USA, 31 May–4 June 2013 (Abstract 8008).