Unmet needs in squamous cell carcinoma of the lung: potential role for immunotherapy

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Abstract Squamous cell carcinoma of the lung accounts for 20–30 % of non-small cell lung cancers (NSCLC). Despite the differences in disease characteristics between squamous and non-squamous NSCLC, both have historically been treated similarly in the clinic. Recently approved drugs have revealed differences in activity and safety profiles across histologic subtypes and have applicability in treating non-squamous, but not typically squamous, NSCLC. Exploration of immune checkpoints—co-inhibitory molecules used to regulate immune responses—has resulted in novel immunotherapies designed to interrupt signaling through the cytotoxic T lymphocyte-associated antigen-4 or programmed cell death protein-1 pathways on lymphocytes. Modulation of these pathways can lead to restored antitumor immune responses, and preliminary evidence shows that agents targeting these pathways have activity in lung cancer, including squamous NSCLC.

Keywords Non-small cell lung cancer · Squamous cell carcinoma of the lung · Programmed cell death protein-1 (PD-1) pathway · Ipilimumab · Nivolumab · Immunotherapy

Background

The first-line treatment for advanced non-small cell lung cancer (NSCLC) depends on the tumor histology and the presence of epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) rearrangements. For NSCLC with mutated EGFR or positive for ALK, treatment with an EGFR tyrosine kinase inhibitor (e.g., erlotinib or afatinib) or ALK inhibitor (e.g., crizotinib), respectively, is recommended. These molecular abnormalities are more common in patients who have adenocarcinoma. For patients with non-squamous NSCLC without an actionable molecular abnormality, the standard therapy remains chemotherapy with or without bevacizumab. Patients with squamous histology have experienced a prohibitive rate of severe pulmonary hemorrhage when treated with bevacizumab, and bevacizumab is, therefore, contraindicated in patients with squamous histology tumors [1, 2]. The activity of pemetrexed is limited to non-squamous histology [3]. Therefore, additional options to combat squamous NSCLC are needed, and based on the preliminary findings to date, there is hope that immunotherapy will prove to be a novel therapeutic approach that is not limited by histologic subtype.

Newer data are providing a better understanding of how lung cancer can avoid immune detection or elimination and persist as clinical disease. As a result, immunotherapeutic approaches for the treatment of lung cancer treatment are rapidly evolving. These include novel agents, known as immune checkpoint inhibitors, which target mechanisms used by tumors for immune evasion. This immunotherapy approach differs from antigen-specific vaccines in that it targets the entire immune system. Immune checkpoints are co-inhibitory molecules that serve to balance or attenuate co-stimulatory pathways that lead to immune activation. In normal tissues, immune checkpoint pathways prevent overactivation of the immune system to protect self-tissues. In cancer, however, tumors can utilize immune checkpoint pathways to evade immune system recognition by
expressing co-inhibitory molecules or their ligands [4–6]. Several of these co-inhibitory molecules [e.g., programmed cell death protein-1 (PD-1), its ligands PD-L1 and PD-L2, and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4)] have been linked to tumoral immune escape. Immune checkpoint inhibitors targeting CTLA-4, PD-1, and PD-L1 have shown promising clinical activity in patients with melanoma and, more recently, clinical activity in NSCLC across histologic subtypes [7–15].

This article will review differences between the histologic and immunologic characteristics of squamous versus non-squamous NSCLC, provide a brief overview of the biology of immune checkpoint inhibitors, and discuss the potential future role of antibody-mediated immune modulation in squamous NSCLC based on clinical experience to date.

Differences in histologic and immunologic characteristics between squamous and non-squamous NSCLC

Squamous and non-squamous NSCLC are recognized as distinct diseases, differing in terms of histologic and immunologic characteristics. Compared with non-squamous NSCLC, squamous NSCLC is associated with a higher likelihood of smoking, central tumor growth, and cavitation [16]. These differences between squamous and non-squamous NSCLC may influence the response to therapeutic agents, as exemplified by the differential profiles of targeted agents. Therefore, clinical trials are now starting to enroll patients by histologic type.

Histologic characteristics

Well-differentiated squamous cell NSCLC is characterized by keratinization, intercellular bridges, and pearl formation [16, 17]. Tumor cells tend to be large with abundant dense cytoplasm, irregular hyperchromatic nuclei, and small nucleoli. For tumors without clearly differentiated morphology, analysis of p63 and thyroid transcription factor-1 (TTF-1) can be used to determine lineage [17]. Squamous cell carcinoma has a consistent histologic marker profile, namely diffuse expression of p63/CK5/6/34βE-12 and non-expression of TTF-1 [18]. In contrast, adenocarcinoma shows significant expression heterogeneity for all ‘squamous markers’; only diffuse TTF-1 expression is specific for adenocarcinoma. During attempts to refine histlogic classification based on p63 expression, investigators found that TAp63, a p53-like tumor suppressor, was detected in 100 % of squamous cell carcinomas and in only 3 % of adenocarcinomas. In contrast, expression of ΔNp63, an oncogene, was detected in 100 % of squamous cell carcinomas, but in only 3 % of adenocarcinomas [19].

Immunologic characteristics

Many tumor antigens of interest in lung cancer, including melanoma-associated antigens A3 and A4 and NY-ESO-1, have more frequent expression in squamous tumors than in non-squamous tumors [20–23]. Furthermore, immunohistochemical analyses have shown that squamous NSCLC tumors have more extensive infiltration of CD8 + effector cells than do non-squamous tumors. However, the increased numbers of tumor-infiltrating CD8 + T cells did not correlate with a survival advantage, suggesting an impotent immune response, possibly due to an immunosuppressive tumor environment [24–26]. Genomic analysis of squamous cell carcinomas found that many samples exhibited inactivating mutations in the human leukocyte antigen-A class I major histocompatibility gene, which could lead to loss-of-function and reduced expression of tumor antigens, a possible immune-evading strategy [27].

Biology of immune checkpoint inhibitors

CTLA-4 blockade

The CTLA-4 receptor is expressed on T cells, and its interaction with ligands B7-1 (CD80) and B7-2 (CD86) is thought to attenuate T cell activation early in the activation process when the T cells are in the draining lymph nodes [28, 29]. CTLA-4 competes with the co-stimulatory receptor CD28 for B7 binding, preventing sustained T cell activation [30–32]. Blockade of CTLA-4 using monoclonal antibodies induces antitumor activity in murine cancer models, via both direct enhancement of T effector cells and concomitant inhibition of regulatory T cells [33–35].

PD-1/PD-L1 blockade

Binding of the PD-1 receptor on T cells to its ligands, the most well characterized of which are PD-L1 and PD-L2, is another mechanism by which the immune system down-regulates T cell activity; this pathway is thought to act later in the antitumor process, in the tumor microenvironment [36–38]. As evidence for this pathway’s role in immune evasion, PD-1 expression has been found on tumor-infiltrating T cells [39, 40], as has expression of PD-1 ligands on various tumor types, including squamous NSCLC [36, 41, 42]. In addition to T cells, B cells and natural killer cells can also express PD-1, which may reduce their anti-tumor activity [43].
PD-1:PD-L2 binding has higher affinity and is slightly
different compared with PD-1:PD-L1 binding, although it
is unclear whether these differences translate to different
antitumor effects [44]. There is also evidence that PD-L1
may interact with CD80 (B7-1) expressed on T cells to
suppress T cell activity [45, 46]. In preclinical models,
anti-body blockade of PD-1 or its ligands induces antitumor
activity in murine cancer models through enhancement of
T cell activity, which served as the basis for clinical
development of PD-1 pathway-targeting agents [36, 47,
48].

Preliminary clinical experience with immune
checkpoint inhibitors in squamous NSCLC

Ipilimumab

Ipilimumab is an anti-CTLA-4 monoclonal antibody that
binds to the CTLA-4 receptor, which restores CD28 sig-
ning and allows immune activation to persist. In a ran-
donized phase II study in previously untreated patients
with NSCLC, the combination of ipilimumab with paclit-
axel and carboplatin as a phased regimen (i.e., 2-dose
chemotherapy lead-in) significantly improved immu-
related progression-free survival (irPFS) and modified
World Health Organization-PFS compared with chem-
otherapy alone (Table 1) [9]. The PFS advantage was not
observed when ipilimumab was administered concurrently
with chemotherapy (i.e., no chemotherapy lead-in); it is not
clear whether these observations can be applied to other
immune checkpoint inhibitors. Overall survival (OS) was
longer in the phased ipilimumab treatment group, but the
difference was not statistically significant. Subgroup ana-
lysis by histology indicated that the phased ipilimumab/
chemotherapy regimen showed activity in both squamous
and non-squamous NSCLC (Fig. 1). An ongoing phase III
study (NCT01285609) is further evaluating the clinical
efficacy of ipilimumab in combination with chemotherapy
in patients with squamous NSCLC (Table 2).

Table 1 Clinical results of ipilimumab in combination with chemo-
therapy in patients with chemotherapy-naive advanced (Stage IIIB or
IV) NSCLC [9]

|                             | Phased ipilimumab | Concurrent ipilimumab | Chemotherapy control |
|-----------------------------|-------------------|-----------------------|----------------------|
| Median time to immune-related progression | 5.7 months | 5.5 months | 4.6 months |
| HR and P value versus control | HR = 0.72, 0.05  | HR = 0.81, 0.13     |
| Median progression-free survival (WHO criteria) | 5.1 months | 4.1 months | 4.2 months |
| HR and P value versus control | HR = 0.69, 0.02  | HR = 0.88, 0.25     |
| OS, median                  | 12.2 months       | 9.7 months           | 8.3 months          |
| P value versus control      | HR = 0.87, 0.23  | HR = 0.99, 0.48     |
| OS at 1 year                | 50 %              | 42 %                 | 39 %                |

HR hazard ratio, OS overall survival, WHO World Health Organization

MK-3475

MK-3475 is a humanized antibody against PD-1. MK-3475
and nivolumab (discussed below) both target PD-1 and are
designed to inhibit PD-1 from binding its ligands, PD-L1
and PD-L2. In a phase I study, MK-3475 was administered
at 10 mg/kg every 3 weeks to NSCLC patients previously
-treated with two systemic regimens [14]. Interim data on
38 patients showed an objective response rate (ORR) by
Response Evaluation Criteria in Solid Tumors (RECIST)
v1.1 criteria of 21 %, and responses were observed in both
squamous and non-squamous histologic subtypes
(Table 3). Rapid (within 9 weeks) and long duration of
responses were reported.

A phase I trial is currently recruiting patients with stage
IIIB/IV NSCLC to evaluate combination therapy of MK-
3475 with cisplatin/pemetrexed or carboplatin/paclitaxel
(NCT01840579). Another phase I trial is assessing the
safety and activity of MK-3475 monotherapy after plati-
num failure in patients with PD-L1-positive advanced
NSCLC (NCT02007070). A phase II/III trial, also currently
recruiting, will compare two doses of MK-3475 versus
docetaxel in participants with PDL-1-positive NSCLC who
have experienced disease progression after platinum-con-
taining systemic therapy (NCT01905657) (Table 2).

Nivolumab

Nivolumab is a fully human anti-PD-1 monoclonal antibody
that binds to the PD-1 receptor, preventing it from engaging
with its ligands. A phase I dose-escalating (0.1–10.0 mg/kg
every 2 weeks) study of nivolumab initially reported results
for 296 patients with advanced solid tumors, including 122
patients with NSCLC [11]. Most NSCLC patients had been
previously treated; 94 % had received platinum-based che-
motherapy and 34 % had received tyrosine kinase inhibitors.
Objective (partial or complete) responses by RECIST v1.0
were reported in 14 of 76 evaluable NSCLC patients (18 %).
The highest ORR (32 %) occurred with 3.0 mg/kg dosing.
Six of 18 patients (33 %) with squamous NSCLC and 7 of 56
A longer-term interim analysis of 129 NSCLC patients enrolled in the study showed longer duration of responses and more sustained OS with nivolumab compared with previous reports of data from chemotherapy trials (Table 4). OS across all NSCLC patients was 42% at 1 year and 24% at 2 years [13]. Based on these findings, further investigation is being conducted with nivolumab (3.0 mg/kg) in patients with squamous NSCLC (NCT01642004) (Table 2).

An ongoing phase I trial is evaluating nivolumab as a monotherapy or in various treatment combinations in patients with stage IIIIB/IV NSCLC (NCT01454102). In the nivolumab plus chemotherapy arms, patients are randomized to receive nivolumab plus gemcitabine/cisplatin, plus either pemetrexed/cisplatin or carboplatin/paclitaxel, with safety as the primary assessment. Nivolumab is administered every 3 weeks until progression, and chemotherapy is given for four cycles at standard dosing. Interim results showed evidence of activity in patients with squamous NSCLC who received combination therapy; however, no firm conclusions can be drawn from this small phase I study [51]. This trial is also evaluating nivolumab in combination with a targeted agent (erlotinib or bevacizumab), nivolumab plus ipilimumab, nivolumab as switch maintenance monotherapy after platinum doublet, and nivolumab monotherapy in patients with asymptomatic brain metastases.

BMS-936559

The fully human anti-PD-L1 antibody BMS-936559 was studied in a phase I trial of patients with advanced cancer, including 75 NSCLC patients [7]. The NSCLC patients experienced responses when treated with the 3.0 mg/kg or the 10.0 mg/kg dose. Overall, 5 of 49 patients with NSCLC had an objective response and these responses lasted for 24 weeks in 3 of these 5 patients. One of 13 patients with squamous histology and 4 of 36 patients with non-squamous histology had a response; reported ORRs were 8 and 11%, respectively. Six additional patients, three with squamous and three with non-squamous histology, had stable disease lasting at least 24 weeks. At 6 months, the rates of PFS were 43 and 26% for patients with squamous and non-squamous NSCLC, respectively.

MPDL3280A

MPDL3280A is a human anti-PD-L1 monoclonal antibody containing an engineered immunoglobulin G Fc-domain designed to optimize efficacy and safety. A phase I dose-ranging study of MPDL3280A monotherapy in patients with locally advanced or metastatic NSCLC reported an initial ORR of 23% (12 of 53 patients); three patients with squamous NSCLC and nine patients with non-squamous NSCLC had a response [15]. Additional patients who were

| Response | Patient group | Events/Patients | HR (95% CI) |
|----------|--------------|----------------|-------------|
| IrPFS    | All          | 54/68 vs 56/66  | 0.72 (0.50-1.06) |
|          | Non-Squamous | 36/47 vs 41/51  | 0.82 (0.52-1.28) |
|          | Squamous     | 18/21 vs 15/15  | 0.55 (0.27-1.12) |
| mWHO-PFS | All          | 56/68 vs 61/66  | 0.69 (0.48-1.00) |
|          | Non-Squamous | 37/47 vs 46/51  | 0.81 (0.53-1.26) |
|          | Squamous     | 19/21 vs 15/15  | 0.40 (0.18-0.87) |
| OS       | All          | 51/68 vs 51/66  | 0.87 (0.59-1.28) |
|          | Non-Squamous | 38/47 vs 37/51  | 1.17 (0.74-1.86) |
|          | Squamous     | 13/21 vs 14/15  | 0.48 (0.22-1.03) |

Fig. 1 Clinical efficacy of phased ipilimumab + carboplatin/paclitaxel by histologic subtype in patients with NSCLC [49]. IrPFS, progression-free survival (PFS) by modified WHO (mWHO) criteria and overall survival (OS) in the phase II randomized study of ipilimumab administered either in a phased schedule or currently with paclitaxel/carboplatin in patients with NSCLC, analyzed by histologic subtype. Comparison of the phased ipilimumab arm versus placebo arm. Phased ipilimumab plus paclitaxel/carboplatin appeared to have a greater effect on patients with squamous histology than those with non-squamous histology. The hazard ratio (HR) point estimates for irPFS, mWHO-PFS, and OS were significantly smaller with phased ipilimumab plus paclitaxel/carboplatin in the squamous population compared with the non-squamous population; however, small sample size warrants caution in interpretation. Reproduced with permission from Zielinski et al. [49]
not included in the ORR (RECIST v1.1) had delayed responses after apparent radiographic progression.

An additional phase I study, currently recruiting patients, will evaluate MPDL3280A in combination with carboplatin/paclitaxel, with carboplatin/pemetrexed, and with carboplatin/nab-paclitaxel in patients with advanced or metastatic NSCLC (NCT01633970). Two additional phase II studies in patients with advanced or metastatic NSCLC are ongoing. One trial is evaluating objective responses in patients with PD-L1-positive NSCLC receiving single-agent MPDL3280A therapy (NCT01846416). The other trial is evaluating OS and safety of MPDL3280A compared with docetaxel after platinum therapy failure (NCT01903993) (Table 2). A phase III trial of similar design, comparing MPDL3280A with docetaxel, is planned to start in early 2014 (NCT02008227).

Table 2 Ongoing phase II and III clinical trials of immune checkpoint inhibitors in NSCLC [50]

| Target (trial identifier) | Trial phase | Trial stage (expected accrual) | Treatment setting | Clinical end points |
|---------------------------|-------------|-------------------------------|-------------------|---------------------|
| Ant-CTLA-4                | III         | Recruiting (n = 920)           | Stage IV/recurrent squamous NSCLC | Primary: OS secondary: OS, PFS, BORR |
| Ipilimumab + paclitaxel/carboplatin versus placebo + paclitaxel/carboplatin (NCT01285609) | III         | Recruiting (n = 920)           | Stage IV/recurrent squamous NSCLC | Primary: OS secondary: OS, PFS, PFS, DOR |
| Anti-PD-1                 | II/III      | Recruiting (n = 920)           | Second-line, PD-L1-positive NSCLC | Primary: OS, PFS, safety Secondary: ORR, DOR |
| MK-3475 monotherapy versus docetaxel (NCT01905657) | II/III      | Recruiting (n = 920)           | Second-line, PD-L1-positive NSCLC | Primary: ORR, OS secondary: PFS, PD-L1 biomarker, DOR, TTR, QOL |
| Nivolumab monotherapy (NCT01721759) | II          | Ongoing (n = 100)             | ≥Third-line, advanced, or metastatic squamous NSCLC | Secondary: Investigator-assessed ORR |
| Nivolumab monotherapy after azacitidine + entinostat versus after oral azacitidine (epigenetic priming study) (NCT01928576) | II          | Recruiting (n = 120)           | ≥Second-line, advanced, or metastatic NSCLC | Primary: response (progression-free at 32 weeks) Secondary: PFS, time to progression, OS, safety |
| Nivolumab monotherapy versus docetaxel (NCT01642004) | III         | Ongoing (n = 264)             | Second-line, advanced, or metastatic squamous NSCLC | Primary: ORR, OS secondary: PFS, PD-L1 biomarker, DOR, TTR, QOL |
| Nivolumab monotherapy versus docetaxel (NCT01673867) | III         | Ongoing (n = 574)             | Second-line, advanced, or metastatic non-squamous NSCLC | Primary: OS Secondary: ORR, PFS, PD-L1 expression, QOL |
| Anti-PD-L1                | II          | Recruiting (n = 130)           | Advanced or metastatic PD-L1-positive NSCLC | Primary: investigator-assessed ORR Secondary: ORR, DOR, PFS, safety, PK |
| MPDL3280A monotherapy (NCT01846416) | II          | Recruiting (n = 180)           | ≥Second-line, advanced or metastatic NSCLC | Primary: OS secondary: ORR, PFS, safety, QOL |
| MPDL3280A monotherapy versus docetaxel (NCT01903993) | II          | Recruiting (n = 180)           | ≥Second-line, advanced or metastatic NSCLC | Primary: OS secondary: ORR, PFS, safety, QOL |

Ongoing trials of immunotherapy in squamous cell NSCLC

Table 2 lists ongoing phase II and III trials of immune checkpoint inhibitors in NSCLC, including three trials specifically in squamous cell carcinoma of the lung.

An ongoing double-blind placebo controlled phase III study (NCT01285609) is comparing carboplatin (area under the curve of six) and paclitaxel (175 mg/m²) every 3 weeks with ipilimumab or placebo. The primary endpoint is OS. Patients will receive ipilimumab or placebo in combination with chemotherapy in a phased schedule, similar to that used in the phase II study described above: ipilimumab 10 mg/kg once every 3 weeks for four doses and then every 12 weeks beginning at week 24.
CI confidence interval, CR complete response, NSCLC non-small cell lung cancer, NR not reached, ORR objective response rate, OS overall survival, PFS progression-free survival, PR partial response, RECIST response evaluation criteria in solid tumors

Table 3  Interim phase I efficacy results of MK-3475 monotherapy (10 mg/kg) in evaluable patients with NSCLC [14]

| Nivolumab dose (mg/kg) | Squamous (n = 54) | Non-squamous (n = 74) | All NSCLC<sup>c</sup> (n = 129) | Squamous (n = 54) | Non-squamous (n = 74) | All NSCLC<sup>c</sup> (n = 129) | Squamous (n = 54) | Non-squamous (n = 74) | All NSCLC<sup>c</sup> (n = 129) |
|------------------------|-----------------|---------------------|-------------------------------|-----------------|---------------------|-------------------------------|-----------------|---------------------|-------------------------------|
| 1.0                    | 0/15 (0)        | 1/18 (5.6)          | 1/33 (3.0)                   | 0               | 63.9 (63.9, 63.9)   | 63.9 (63.9, 63.9)             | 8.0 (2.6, 13.3)  | 9.9 (5.6, 22.7)      | 9.2 (5.6, 11.1)               |
| 3.0<sup>d</sup>        | 4/18 (22.2)     | 5/19 (26.3)         | 9/37 (24.3)                  | NR (16.1, 133.9+) | 74.0 (24.3, 74.0+) | 74.0 (133.9+)                 | 9.5 (6.7, NE)    | 18.2                 | 14.9 (9.5, NE)           |
| 10.0                   | 5/21 (23.8)     | 7/37 (18.9)         | 12/59 (20.3)                | 83.1 (16.1, 117+) | NR (61.1+, 65.7+)  | 83.1 (133.9+)                 | 10.5 (7.8, 12.5) | 7.4 (4.6, 12.4)      | 9.2 (5.2, 12.4)             |
| All doses              | 9/54 (16.7)     | 13/74 (17.6)        | 22/129 (17.1)               | NR (16.1, 133.9+) | 63.9                | 74.0 (61.1+, 74.0+)           | 9.2 (7.3, 12.5)  | 10.1 (7.2, 13.7)     | 9.6 (7.8, 12.4)             |

<sup>a</sup> ORR = (|CR + PR|)/n) × 100; RECIST v1.0
<sup>b</sup> OS estimates after 1 year reflect censoring and shorter follow-up for patients enrolling later in the study
<sup>c</sup> One patient had unknown histologic type
<sup>d</sup> 3.0 mg/kg dosing is being further evaluated in phase III trials

NCT01721759 is a single arm, multicenter, phase II study of nivolumab monotherapy in patients with advanced or metastatic squamous NSCLC who have received at least two prior treatment regimens. The trial has completed its enrollment. The primary endpoint is ORR, as determined by an independent radiology review committee. An ongoing, randomized open-label phase III study is comparing ORR and OS with nivolumab monotherapy versus docetaxel in patients with squamous cell NSCLC who progressed on or after platinum-based chemotherapy (NCT01642004).

With the exception of one trial enrolling patients with non-squamous NSCLC (NCT01673867), the additional ongoing trials listed in Table 2 are enrolling NSCLC patients who are not segregated at enrollment by histologic type. However, reports of these clinical trials may present results based on squamous or non-squamous histology, as this is frequently a stratification factor.

Potential role of biomarkers in lung cancer immunotherapy

Predictive biomarkers for checkpoint inhibitor therapy would help to select patients who are most likely to respond to this treatment. However, a definitive predictive biomarker for any of these agents has not been identified. Expression of the PD-L1 ligand on tumor cells is the most promising predictive biomarker candidate reported to date for PD-1 pathway-targeting agents, but data are very limited at present.
In an immunohistochemical analysis of pretreatment biopsy specimens from several tumor types, tumor cell-surface expression of PD-L1 was significantly correlated with an objective clinical response to nivolumab monotherapy in a dose-ranging phase I study [11]. Nine of 25 patients (36%) with PD-L1-positive tumors had an objective response versus 0 of 17 patients with PD-L1-negative tumors. However, this was a posthoc analysis on a subset of patients and the investigators urged caution in interpreting the results. Data correlating anti-PD-1/PD-L1 agent activity with PD-L1 tumor status are starting to emerge. Although some associations between PD-L1-positive status and increased activity have been noted, findings of several studies, including some in lung cancer, have reported responses in patients with tumors considered negative for PD-L1 expression [11, 12, 14, 15, 52]. Additional research is needed to determine the role of PD-L1 as a potential predictive marker of response to anti-PD-1 antibody therapy.

Discussion

Histology is now an important consideration for treatment selection in NSCLC. Currently, patients with squamous NSCLC have more limited treatment options compared with patients with NSCLC of non-squamous histology. Immuno-therapy with checkpoint inhibitors has the promise of being effective in various subtypes of NSCLC, as it directly targets tumoral escape mechanisms. Preliminary evidence suggests that activity with these agents may not be restricted by specific tumor cell characteristics or histology, and these results indicate that this novel approach to treatment may increase treatment options available to patients with squamous NSCLC. The results of ongoing phase II and III clinical trials of these agents will more clearly determine the future role for immunotherapy in the management of lung cancer, particularly for squamous cell carcinoma of the lung.

Acknowledgments The author takes full responsibility for the content of this publication and confirms that it reflects his viewpoint and medical expertise. The author also wishes to acknowledge StemScientific, funded by Bristol-Myers Squibb, for providing editorial support. Neither Bristol-Myers Squibb nor StemScientific influenced the content of the manuscript, nor did the author receive financial compensation for authoring the manuscript.

Conflict of interest Dr. Stinchcombe’s institution has received research grants from Bristol-Myers Squibb for the participation in clinical trials; Dr. Stinchcombe has served on advisory boards for Celgene, Genentech, and Lilly.

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