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Metastatic Squamous Non-Small Cell Lung Cancer: Current Status and What Next?

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Editorial

In spite of advances in management of cancer in general, Lung cancer remains number one killer with suboptimal five year survival. Platinum containing doublet in management of Non-small cell lung cancer (NSCLC) was a major milestone achieved in 1995. This was further improved following approval of Docetaxel as second line therapy in 2000. This was followed by approval of targeted therapies like Gefitinib, Erlotinib, Afatinib, Crizotinib, Ceritinib, Brigatinib, Bevacizumab and Ramucirumab. All these advances have made significant impact in the management of non-squamous NSCLC. However, targeted therapies have not been so successful in management of the squamous NSCLC. Some of the targets identified for management of squamous NSCLC include FGFR1, FGFR2, FGFR3, PTEN, PIK3CA, DDR2 and MEK1.

Approval of Nivolumab [1], checkpoint inhibitor targeting PD-1, as a second line therapy for squamous NSCLC in 2015 was the first drug approved specifically for squamous NSCLC. It improves response rate to 27% as compared to 12% with Docetaxel and is associated with improved one year survival by 18% (42% *vs.* 24%). Pembrolizumab [2] is another checkpoint inhibitor targeting PD-1. It is approved as a first line therapy for NSCLC expressing PD-L1>50% irrespective of histology. The best results are seen in squamous NSCLC (HR=0.35 *vs.* 0.55) compared to adenocarcinoma.

Necitumumab [3] is the next product approved for squamous NSCLC as a first line therapy in combination with Gemcitabine and Cisplatin. There is a significant improvement in overall survival of 11.5 months (10.4-12.6 months) *vs.* 9.9 months (8.9-11.1 months) with hazard ratio of 0.84 (95% CI; 0.74-0.96 stratified log rank p=0.01) in spite of identical response rate (31% *vs.* 29%). Necitumumab is a recombinant human lgG1 monoclonal antibody targeting EGFR expressed on cell surface. Other EGFR antibodies evaluated include Cetuximab and Nimotuzumab. They are found to have significant adverse event profile. Cetuximab [4] was found to provide improvement in squamous NSCLC with higher EGFR expression with response rate 28.1% *vs.* 44.4% and survival benefit (9.6 months *vs.* 12.0 months; HR=0.73; p=0.011).

Small molecule EGFR inhibitors like Gefitinib, Erlotinib are not found useful in management of Squamous NSCLC. This can probably be due to site of expression and underlying pathology. EGFR is overexpressed on cell surface in Squamous NSCLC while in adenocarcinoma mutant EGFR is in cytoplasm of adenocarcinoma.

Desmocollin-3 (DSC3) is an adhesion molecule expressed on cell surface of squamous NSCLC [5] and is used to differentiate squamous from non-squamous NSCLC. CADI-05 [6] is a TLR-2 agonist and a pure potent Th1 response enhancer. It induces immune response which preferentially kills DSC3 expressing cancer cells. When combined with platinum contain doublet in management of advanced NSCLC, It improves median overall survival by 127 days (HR=0.55; 95% CI 0.32-0.95; p=0.046). This is achieved without any additional systemic side effects.

Checkpoint inhibitors provide durable response with relatively lower response rate [1,2]. To improve response rate further it is combined with various therapeutic agents. Promising amongst them is combination with CTLA4 inhibitors. In preliminary studies, combination of Nivolumab 3 mg/kg and Ipilimumab 1 mg/kg results in significant improvement in response rate of 33% in squamous NSCLC compared to response rate of 13% in non-squamous NSCLC [7].

Check point inhibitors are associated with significant discrepancy between immune response and clinical response (74% *vs.* 38%) [8]. Clinical response to anti PD-1 is associated with infiltration of tumor by immune cells [9] and recognition of antigens expressed by tumor cells [10]. It is expected that combination of check point inhibitors with CADI-05 will result into significant improvement in response rate with durable response as CADI-05 administration is known to be associated with:

- Generation of activated immune cells expressing DSC3 which recognizes and kills DSC3 expressing tumor cells.
- Increase in tumor infiltration by activated lymphocyte.
- Decrease in immune suppression (Treg as well as PD-1).
- Synergy with check point modulators.

In future we will be seeing major improvement in management of squamous NSCLC wherein check point regulator will be used with another immunotherapy to improve efficacy without significant addition of toxicity.

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