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Should anti-mesothelin therapies be explored in lung cancer?

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Drugs targeting driver mutations and immune checkpoint inhibitors have led to substantial improvements in outcomes of patients with advanced non-small cell lung cancer (NSCLC). Unfortunately, therapeutic resistance to these treatment modalities is almost inevitable. Additionally, a substantial proportion of patients do not respond to these treatments. There is therefore an unmet need to develop new and effective therapies for advanced NSCLC.

Mesothelin is a cell-surface glycoprotein overexpressed in a number of epithelial cancers including malignant mesothelioma and pancreatic and ovarian carcinoma. Mesothelin was discovered by Ira Pastan and Mark Willingham at the National Cancer Institute[1, 2]. Laboratory and clinical work done by Raffit Hassan and colleagues over last 20 years have validated it as an attractive target for treating cancer[3]. A number of agents therapeutically targeting mesothelin are now in various phases of clinical development[4]. These include an immunotoxin (SS1P), antibody drug conjugates (anetumab ravtansine, DMOT4039A), a chimeric monoclonal antibody (amatuximab), chimeric antigen receptor T-cells and a tumor vaccine (CRS207) that encodes mesothelin. Clinical trials of these agents have provided additional evidence that mesothelin is a bona fide tumor specific antigen and offer several key insights into therapeutic targeting of mesothelin in cancer. Targeting mesothelin has been proven safe despite its expression in the lining of the pleura and pericardium; toxicities that can be attributable to its expression in essential normal tissues are limited[5]. Tumor responses have been observed as exemplified by the durable responses seen in patients with advanced epitheloid mesothelioma. These patients received anti-mesothelin immunotoxin, SS1P in combination with pentostatin and cyclophosphamide, the latter administered to minimize the human antibody response to the immunotoxin[6].

Several lines of evidence support the development of mesothelin-targeted therapies in lung adenocarcinoma. Recent studies have demonstrated the expression of mesothelin in lung adenocarcinoma. A study from Memorial Sloan-Kettering Cancer Center observed mesothelin expression by immunohistochemistry in about 70% of early stage (stages I–III) lung adenocarcinoma (n=1209). After adjusting for known prognostic factors, increased mesothelin expression was associated with poor overall survival and relapse free survival[7]. Mesothelin expression was also observed in advanced stage (stages III–IV) lung adenocarcinoma (n=93). Over 50% of such tumors expressed mesothelin in a series reported

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by this author and colleagues at the National Cancer Institute[8]. In this study, high mesothelin expression, defined by mesothelin expression in more than 25% of cells, was found in 24% of patients and was associated with inferior survival. In both studies, patients with high mesothelin expression were more likely to have KRAS mutations, compared with patients with low expression. Earlier studies have also documented mesothelin expression in 41% to 53% of lung adenocarcinoma[9, 10]. Consistent with these findings, mesothelin expression is significantly elevated in approximately 30% of the lung adenocarcinoma cell lines of the Broad-MIT-Novartis cancer cell line database. In vitro and in vivo studies that demonstrate cytotoxic activity of anti-mesothelin therapies in mesothelin expressing lung cancers lend further support to clinical evaluation of mesothelin-targeted therapies in lung adenocarcinoma[11, 12].

Mesothelin-directed therapies are already in clinical testing in NSCLC patients. A phase I clinical trial is evaluating the safety and immunogenicity of JNJ-64041757, a live attenuated Listeria Monocytogenes vaccine (NCT02592967). Previous studies have found the mesothelin expressing live attenuated Listeria Monocytogenes vaccine, CRS207 to be safe and effective in patients with pancreatic cancer and mesothelioma[13, 14]. JNJ-64041757 is engineered to encode and express human mesothelin and to efficiently deliver this tumor-associated antigen into both major histocompatibility complex Class I and Class II antigen-processing pathways. The purpose of this study is to determine the recommended Phase 2 dose, preliminary clinical activity and immune induction of JNJ-64041757 when administered intravenously to patients with advanced (Stage IIIB/IV) lung adenocarcinoma.

Another approach that is undergoing clinical evaluation is the use of mesothelin-targeted chimeric antigen receptors (CAR), synthetic receptors that target T cells to cell-surface antigens and augment T-cell function and persistence. Systemic (NCT01583686) and intrapleural (NCT02414269) administration of mesothelin- CAR T cells are being evaluated in clinical trials in patients with mesothelin-expressing lung cancers[15]. The purpose of these phase I clinical trials are to determine the safety and the maximum tolerated dose of mesothelin CAR T cells. In pre-clinical studies, intrapleural delivery resulted in greater T-cell proliferation, T-cell redistribution to extra-thoracic metastatic sites, tumor eradication, and survival than a 30-fold higher T-cell dose administered systemically[16].

Does mesothelin-targeting have a role in squamous lung cancer or small cell lung cancer? Although these histologies account for only a fraction of all lung cancers, they are associated with substantial morbidity and mortality. Based on limited available data, mesothelin expression in squamous cell lung cancer seems to occur at a much lower frequency than lung adenocarcinoma. In the series by Miettinen and Sarlomo-Rikala only 23% (29 of 124) of squamous cell carcinoma expressed mesothelin[10]. In the same study, none of the 41 small cell lung cancers expressed mesothelin. These results are consistent with cell line data obtained from the Broad-MIT-Novartis cancer cell line database [17] and indicate that additional studies are needed to further characterize mesothelin as a target for squamous lung cancer. Available data does not support its development in small cell lung cancer.

Dramatic improvements in outcomes of NSCLC in the last decade are a result of characterization of NSCLC subtypes based on genotype and histology. The translation of

these understandings to patients- referred to as precision oncology- is contingent on identification of individual genomic or molecular subtypes. As with antigen-directed therapies, expression of antigen is essential for the targeted therapy to be effective. Mesothelin-targeted therapies are most advanced in clinical development in epitheloid mesothelioma and pancreatic cancer. In both these tumors, mesothelin expression is found in over 95% of cases, precluding for the most part the need for patient selection. Unlike these tumors, mesothelin expression is found in only about half of lung adenocarcinomas. Furthermore, expression in these tumors tends to be heterogeneous with mesothelin observed both in the cytoplasm and on the cell surface. Currently there are no standardized methods to assess mesothelin expression in tumors. In this context, detection of serum mesothelin- which represents the fraction of mesothelin that enters the circulation by various mechanisms including shedding of the membrane bound portion- represents an attractive adjunct to assessment of tumor mesothelin expression. While the reliability of serum mesothelin has been extensively studied in mesothelioma [18], its role in NSCLC warrants thorough evaluation. As clinical development moves forward, it is imperative to develop validated methods to detect mesothelin expression while accounting for heterogeneity of expression preferably using less invasive methods in order to select patients who are most likely to respond to anti-mesothelin therapies.

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