Evolving targets in squamous cell lung cancer
A review of agents now under investigation
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ABSTRACT
Non-small cell lung cancer is the biggest cancer killer in North America in both men and women. The last 5 years have seen significant progress in making chemotherapy treatment choices more precise through molecular evaluation of tumours. To date, those advances have been restricted to patients with non-squamous lung cancers. In the last year, the field has changed with the discovery of potential molecular targets specific to squamous cell carcinoma. This review looks at numerous agents under active investigation in this form of lung cancer.

OVERVIEW OF LUNG CANCER EPIDEMIOLOGY
In 2013, an estimated 25,000 Canadians will develop lung cancer and over 20,000 will die of the disease. Significant improvements have been made in the management of non-small cell lung cancer (NSCLC) in the last 20 years, and it can no longer be characterized as a homogeneous disease. Therapy options diverge based on histologic subtype, with the greatest advances in patients with adenocarcinomas. Oncogenic driver mutations identify numerous subpopulations of adenocarcinomas. Mutations in genes encoding the epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), v-raf murine sarcoma viral oncogene homolog B (BRAF) protein and Kirsten rat sarcoma (KRAS) protein are all active targets. Activating gene fusions have also been discovered, including anaplastic lymphoma kinase (ALK), ROS1 and rearranged during transfection (RET) fusion genes. Using in-depth mutational analyses, drivers can be identified in nearly half of all lung adenocarcinoma tumour samples. The presence of many of these aberrations is predictive of response to targeted therapies. In general, the rate of objective response in patients with a driver mutation treated with the corresponding targeted therapy is well over 50% — double or triple the objective response rate of our most potent cytotoxic chemotherapy regimens.

Until recently, little was known about the molecular drivers of squamous lung carcinoma (SqLC) — the second most common type of NSCLC. Cytotoxic chemotherapy is the mainstay of treatment for this patient population. In the last year, data have been published providing an in-depth look into the driving factors for SqLCs, and clinical trials are currently underway evaluating the risks and benefits of therapies targeting these newly identified pathways. This review discusses some of the cutting-edge therapies under investigation in SqLC.

THE CANCER GENOME ATLAS NETWORK
In September 2012, Dr. Peter Hammerman and colleagues representing The Cancer Genome Atlas (TCGA) network published data generated from in-depth genomic and epigenomic analysis of 178 SqLCs collected from centres across the world, including several Canadian provinces. This manuscript, representing the largest research effort published on the global genetic and epigenetic regulation of SqLC, made several key observations. SqLCs are genetically complex tumours, second only to melanoma in overall mutation rate. Nearly all samples had mutations in the TP53 gene. Potentially targetable aberrations were identified in 69% of tumours. In contrast to what is seen in adenocarcinoma, SqLCs were found to have 2 or 3 major alterations simultaneously in over 15% of samples, which speaks to their complexity. Alterations that were considered targetable were found in receptor tyrosine kinases (RTKs) or signal transduction pathways such as RAS or PI3 kinase (PI3K) (Figure 1). Another identified group of mutations was in the HLA (human leukocyte antigen)-A gene, suggesting a role for immune-based therapies for SqLC. These data prompted numerous clinical trials specifically recruiting patients with SqLC.

RECEPTOR TYROSINE KINASES
Approximately 20 classes of RTKs have been identified. Blockade of aberrant signalling through these pathways has led to some of the greatest advances in cancer therapy, such as imatinib in chronic myelogenous leukemia and gastrointestinal stromal tumours, trastuzumab in breast cancer, vemurafenib in melanoma and gefitinib in adenocarcinomas of the lung. Some of the key RTKs in SqLCs include EGFR, HER2, fibroblast growth factor receptor (FGFR), discoid domain receptor 2 (DDR2) and the MET receptor.
EGFR
EGFR mutations were the first successfully targeted genetic abnormality in lung cancer. These mutations are mainly found in non-squamous histologies. Gene amplifications with protein overexpression, as well as variant III mutations, were identified by the TCGA network in up to 10% of samples. Several classes of drugs are being studied targeting EGFR in SqLC. A second-line trial of afatinib, an irreversible inhibitor of EGFR, HER2 and HER4, vs erlotinib (LUX Lung 8) is underway in SqLC. Cetuximab, a chimeric monoclonal antibody against EGFR, offers modest survival benefit in combination with chemotherapy in unselected NSCLC, as seen in the FLEX trial. In a retrospective analysis, patients with high EGFR expression (38% of enrolled squamous patients) were identified as most likely to benefit. A second-generation fully humanized monoclonal antibody, necitumumab, is now under evaluation in NSCLC. The SQUIRE trial is evaluating the addition of necitumumab to the backbone of gemcitabine and cisplatin in SqLC through a randomized phase III design. The trial completed accrual in 2011 and a recent press release confirmed that it met its primary endpoint of overall survival. These results have not yet been published or presented in a peer-reviewed format. Tissue was collected in 98% of accrued patients for biomarker analyses. Phase II studies of necitumumab with other chemotherapy backbones are also open to accrual.

HER2
Lung adenocarcinomas with aberrations in HER2 classically have insertions in exon 20, at a reported incidence of 2% to 4%. In contrast, HER2 amplification was identified in 4% of SqLC samples in TCGA, and non-canonical mutations were found in 3% of samples. Potential agents targeting these abnormalities include afatinib, dacomitinib, lapatinib and neratinib. No benefit has been shown from trastuzumab for HER2-overexpressing NSCLC. One response to dacomitinib in a patient with amplified HER2 has been reported. No specific trials in SqLC are currently accruing.

FGFR
Amplifications and mutations in the FGF RTKs were the most common genetic derangement in RTKs of SqLCs in the TCGA publication. Recent reports have documented that dysregulation of the FGFR pathway confers a poorer prognosis in resected lung cancers, is associated with heavy smoking and behaves like an oncogenic driver. Multiple agents are in development that selectively target FGFRs, such as AZD4547, BGJ398 and LY2874544. Numerous less-selective agents that block multiple RTKs, including FGFR, have been identified, such as brivanib, dovitinib, nintedanib, pazopanib, ponatinib and regorafenib. Pharmaceutical companies are also developing monoclonal antibodies to FGFR, as well as FGF ligand traps. AZD4547 is being studied in 2 clinical trials in FGFR-amplified SqLC patients: a trial in the UK with AZD4547 alone and another by the Eastern Cooperative Oncology Group with AZD4547 combined with docetaxel. A phase I trial of BGJ398 has presented results showing responses in FGFR-amplified patients. Ponatinib is being evaluated as a single agent in patients with aberrant FGFR in Boston. Nintedanib is being studied in combination with gemcitabine and cisplatin in unselected first-line SqLC patients. The results of LUME Lung 1, a phase III trial of nintedanib +/- docetaxel, were presented at the American Society of Clinical Oncology Annual Meeting in 2013. Improvements in progression-free survival were seen across all histologies. Overall survival benefit was demonstrated in adenocarcinomas, but not the full cohort. Tumour samples were not mandated, so we are unlikely to obtain data from this trial on the benefit in the subpopulation of patients with FGFR derangements.

DDR2
DDR2 is involved in cell adhesion and proliferation. Mutations have been identified in 4% of SqLCs. Both dasatinib and ponatinib block DDR2 signalling. A trial of dasatinib in patient with DDR2 mutations is actively accruing patients, including at sites in Canada. Objective responses have been described in patients with DDR2 mutations treated with dasatinib.

c-MET
c-MET is an oncogene that encodes the MET receptor, which is stimulated by the hepatocyte growth factor (HGF). c-MET is amplified in 12% and mutated in 1% of SqLCs. Aberrations in MET are associated with chemotherapy and EGF RTK resistance. A phase II clinical trial of onartuzumab (MetMAb), a monoclonal antibody that blocks MET receptor signalling, in combination with paclitaxel and platinum is currently underway in first-line SqLC.

RAS PATHWAY DYSREGULATION
The RAS signalling pathway is frequently activated in lung adenocarcinomas through mutations in KRAS. In contrast, RAS signalling in SqLCs is most commonly aberrantly acti-
vated through inactivating deletions of neurofibroma 1 (NF1), which normally suppresses KRAS signalling.7 MEK inhibitors such as selumetinib and trametinib may be useful agents in targeting SqLCs with activation of the RAS pathway, given the downstream location of MEK to RAS (Figure 1). No trials have been conducted aimed specifically at SqLCs with RAS activation.

Another common activating mutation in the RAS signalling pathway involves BRAF. The most well-known cancers that possess mutated BRAF are melanoma and thyroid carcinomas carrying V600E mutations.36,37 The mutations in SqLC are not the canonical V600E mutations, in contrast to adenocarcinomas in which half of the mutations in BRAF are V600E.7 Many of the agents developed to block this pathway are specific for V600E mutations (vemurafenib and dabrafenib).10 MEK inhibitors such as selumetinib are being studied in non-melanoma tumours that have mutant BRAF.38 SqLCs have been reported to have both activated and inactivated BRAF protein.39 Dasatinib is being evaluated in a clinical trial enrolling patients with inactive BRAF. An objective response has been reported in a SqLC patient with a BRAF-inactivating mutation treated with dasatinib.39,40

**PI3 KINASE DYSREGULATION**

PI3K alterations were found in 47% of the SqLC samples analyzed by TCGA.7 Multiple mechanisms have been described to aberrantly activate the PI3K signal transduction cascade, including mutations in PIK3CA, amplification of AKT3 and inactivation of PTEN.7 Nearly 30% of these alterations overlap with aberrations in RTKs or RAS, suggesting that many of them are “passenger” alterations.7 At least 2 PI3K-targeted agents are in active phase II clinical trials in SqLC: buparlisib (a pan-PI3K inhibitor) and piltlisib (a class I PI3K inhibitor).41-43 Buparlisib is being studied in comparison with docetaxel in second-line SqLC.41 Both buparlisib and piltlisib are being evaluated in combination with paclitaxel and carboplatin in first-line SqLC treatment.41,43 Both trials require tissue for biomarker development.

**IMMUNE-DIRECTED THERAPIES IN SQUAMOUS LUNG CANCER**

Interest has developed recently in immune-based therapies in lung cancer. Two articles published simultaneously in the New England Journal of Medicine described the results of 2 phase I trials of monoclonal antibodies that block tumoural evasion of immune surveillance.44,45 Nivolumab blocks programmed cell death protein 1 (PD-1), an inhibitory receptor found on activated leukocytes, while BMS-936559 (MDX-1105) blocks programmed cell death protein 1 ligand 1 (PD-L1) found on tumour cells that interact with PD-1.44,45 In these phase I trials, objective responses were seen in 10% to 18% of refractory lung cancer patients, several of which were durable over one year.44,45 Moving forward, a phase III trial of nivolumab vs docetaxel accruing second-line SqLC patients and a phase II trial of nivolumab vs placebo in third-line treatment of SqLC are in development.46,47 Phase I evaluations of several PD-1 inhibitors, including AMP-224, MK-3475 and nivolumab, either alone or in combination with chemotherapies, are underway.48-51 The only PD-L1 inhibitor under active investigation is MPDL3280A, which has shown safety in phase I trials.52 A phase II trial of MPDL3280A compared to docetaxel is underway.53 SqLCs may make optimal targets for immune therapy, given genetic predispositions suggested in TCGA data.7 Inactivating mutations were identified in HLA-A, which were previously unreported.7 Overexpression of PD-L1 and its ligands have been reported in SqLC.54

Another immune-targeted agent is ipilimumab, a monoclonal antibody against cytotoxic T-lymphocyte antigen 4 (CTLA-4)55 that is approved for use in melanoma. A phase II clinical trial of ipilimumab with paclitaxel and carboplatin in SqLC has been reported showing tolerability,56 and a phase III trial of this combination is recruiting.56 Combinations of ipilimumab and nivolumab are also being evaluated.49

Another novel way to stimulate the immune system is by targeting the tumour with cancer-seeking (oncolytic) viruses.57 Oncolytic viruses have direct cytotoxic effects, while also stimulating the host immune system. NCIC is evaluating one agent, reolysin, a reovirus, in a pan-Canadian effort in lung cancer.58 The trial has an arm specifically for relapsed SqLCs assessing reolysin in combination with docetaxel.

**CONCLUSION**

In the past 5 years, the field of precision medicine in NSCLC has come of age with our ability to molecularly test patients for aberrations and select them for targeted therapies based on these results. Until recently, that opportunity was restricted to patients with adenocarcinomas, but in the last year the field has also opened for our patients with SqLCs. Dozens of trials focused on this subtype of NSCLC are using rational designs aimed at allowing physicians to more precisely choose therapies for patients based on their individual characteristics. Our hope is that individualizing patient treatment selections will demote lung cancer from its position as the number 1 cancer killer in North America.

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**References**


