5 Things Every Internist Should Know About Lung Cancer… and Why

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Purpose and Overview

Why should internists care about lung cancer? Because of the magnitude of the problem. Carcinoma of the lung is responsible for roughly 160,000 deaths each year in the United States. This represents one-fourth of all deaths due to cancer and more than the number of deaths due to breast, colon, and prostate cancers combined. Regardless of what field one specializes in, most primary care providers will at some point encounter a patient with lung cancer – and many will be personally touched by it, through a family member, neighbor, or friend. ***It is important for all physicians to be able to recognize the disease, screen for it, and counsel their patients that that with new treatments, people are living longer and better lives.***

Objectives

The objectives of this talk are to update internists on:

1. The changing face of lung cancer
2. Screening for lung cancer
3. Status of current treatments for lung cancer
4. New targeted therapies for lung cancer
5. Understanding the biology of the disease will lead to newer treatments

Protocol

Because early-stage lung tumors are often asymptomatic and, until recently, there has been no proven approach to radiographic screening, most patients are diagnosed with advanced stage disease. Metastatic lung cancer is almost uniformly fatal, with 5 year survival rates of <2%.

Approximately 85% of cases are histologically classified as non–small-cell lung cancer (NSCLC), of which adenocarcinoma, squamous cell carcinoma, and large cell carcinoma are the primary subtypes. The incidence of adenocarcinoma in the United States is increasing, probably secondary to increased use of filtered cigarettes, which tend to cause the smoker to take deeper breaths, resulting in the inhaled smoke diffusing into the periphery of the lung, which is where adenocarcinomas tend to originate. In Europe, where non-filtered cigarettes are more commonly used, squamous cell carcinoma of the lung is more common. For unclear reasons, the incidence of small cell lung cancer is decreasing world wide.

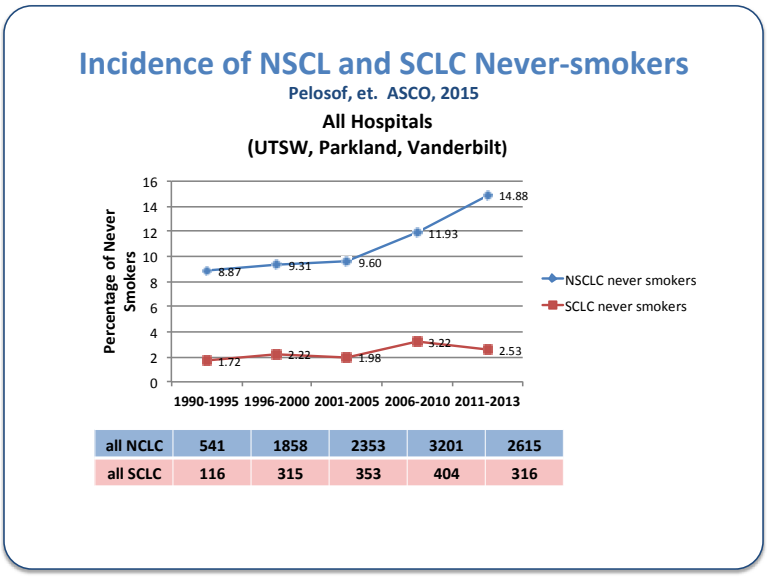
I. The changing face of lung cancer

Although cigarette smoking is the most common cause of lung cancer (responsible for approximately 85% of all cases), it is not the only cause. In the United States, about 15% of all lung cancers are in never smokers, accounting for approximately 16,000 deaths annually, similar to the number of deaths from HIV and non-Hodgkin's lymphoma[1]. If considered a separate category, lung cancer in never smokers would rank as the 6th most common cause of cancer death in females and the 8th most common cause of cancer death for both sexes, before ovarian cancer and kidney cancer[1]

In the year 2000, an estimated 15% of lung cancers in men and 53% of lung cancers in women occurred in never smokers. Epidemiologic studies of lung cancer in never smokers have reported significant gender and geographic variations. In addition, it has been observed that the proportion of female lung cancer cases in never smokers as compared to female lung cancer cases in smokers varies considerably from region to region. For example, the percentage of females with lung cancer who are never smokers is as high as 70-75% in Japan, Korea, Taiwan and Singapore [2]. In comparison, approximately 15% of female lung cancers in the United States are in never smokers . Among men, the proportion of never smokers is lower with less regional variation, representing about 2% of male lung cancer cases in Europe[3, 4], 5% in the United States[5, 6], and 10% in Asia[2, 7]. Other, non-smoking related causes of lung cancer include radon, cooking oil vapors and indoor coal burning (particularly in China), and environmental pollution. There have not been any viral or inheritable factors identified, although an increased susceptibility due to differences in ability to metabolize carcinogens has been postulated.

Table 1 | **Summary of selected studies of risk factors for lung cancer in never smokers** [1]

Risk factors	Risk estimate (95% CI)	Comments
Environmental ETS	1.19 (90% CI: 1.04–1.35)	Meta-analysis of 11 US studies of spousal exposure
	1.21 (1.13–1.30)	Meta-analysis of 44 case–control studies worldwide of spousal exposure
	1.22 (1.13–1.33)	Meta-analysis of 25 studies worldwide of workplace
	1.24 (1.18–1.29)	Meta-analysis of 22 studies worldwide of workplace
Residential radon	8.4% (3.0–15.8%) per 100 Be m^3 increase in measured radon	Meta-analysis of 13 European studies
	11% (0–28%) per 100 Be m^3	Meta-analysis of 7 North American studies
Cooking oil vapors	2.12 (1.81–2.47)	Meta-analysis of 7 studies from China and Taiwan (female never smokers)
Indoor coal and wood burning	2.66 (1.39–5.07)	Meta-analysis of 7 studies from China and Taiwan (both
	1.22 (1.04–1.44)	Large case–control study (2,861 cases and 3,118 controls) from Eastern and Central Europe (both
	2.5 (1.5–3.6)	Large case–control study (1,205 cases and 1541 controls) from Canada (significant for women only)
Genetic factors: family history, *CYP1A1* Ile462Val polymorphism, *XRCC1* variants	1.51 (1.11–2.06)	Meta-analysis of 28 case–control, 17 cohort and 7 twin
	2.99 (1.51–5.91)	Meta-analysis of 14 case–control studies of Caucasian never smokers
	2.04 (1.17–3.54)	Meta-analysis of 21 case–control studies of Caucasian and Asian never smokers (significant for Caucasians
	No association overall; reduced 0.65 risk (0.46–0.83) with Arg194Trp polymer and 0.56 (0.36–0.86) for with Arg280Hi heavy smokers	Large case–control study from Europe (2,188 cases and 2,198 controls)
	Increased risk for never smokers 1.3 (1.0–1.8) and decreased risk for heavy smokers 0.5 (0.3–1.0) with Arg299Gln	Large case–control study from the US (1,091 and 1240 controls)
Viral factors: HPV 16/18	10.12 (3.88–26.4) for never smoking women >60 years	Case–control (141 cases, 60 controls) study from Taiwan of never smoking women



It has been difficult to determine whether the rates of lung cancer in never-smokers are rising. However, a retrospective study done at three institutions – UTSW, Parkland, and Vanderbilt -- show a rise in the incidence of never smokers from about 9 – 10%% in the early 1990s compared to about 15% - 16% now. (Figure 1)

II. Screening for lung cancer

Three U.S. randomized screening studies in the 1980s failed to detect an impact on mortality of screening high-risk patients with chest radiography or sputum cytology, although earlier-stage cancers were detected in the screened groups. Since then, however, low-dose spiral computed tomography (CT) has emerged as a possible new tool for lung cancer screening. Spiral CT is CT imaging in which only the pulmonary parenchyma is scanned, thus negating the use of IV contrast medium and the necessity of a physician having to be present. This type of scan can usually be done quickly (within one breath) and involves low doses of radiation.

The National Lung Screening Trial (NLST) was a randomized multicenter study comparing low-dose helical CT scans with chest x-ray for the screening of older current and former heavy smokers for early detection of lung cancer [8]. From 2002-2004, over 50,000 high-risk individuals from 33 U.S. centers were randomized to three annual screenings with single-view PA chest x-ray or low-dose CT. The study enrolled individuals between the ages of 55-74 with at least a 30 pack-year smoking history (former smokers needed to have quit within the previous 15 years). Individuals with a prior lung cancer diagnosis, hemoptysis, unexplained weight loss of more than 15 lbs., or chest CT within 18 months before enrollment were excluded. The rate of screening adherence exceeded 90%. The rate of positive screening tests was 24% with CT and 7% with chest x-ray, of which about 96% were false positive. There were 247 deaths from lung cancer per 100,000 person-years in the CT group and 309 deaths per 100,000 person-years in the chest x-ray group, corresponding to a 20% relative reduction in lung cancer mortality (P=0.004). CT was also associated with a 6.7% reduction in all-cause mortality (P=0.02). Based upon these findings, screening for lung cancer with low-dose CT for high risk patients has been approved by the U.S. Preventive Services Task Force (USPSTF) and CMS for Medicare patients.

For the first time, the NLST has shown that CT-based screening reduces lung cancer mortality. However, despite a 2014 study which showed that the quality adjusted life-years was $81,000 per QALY gained [9] , numerous questions remain. Who should be screened, and how often? How will the expected large numbers of false-positive radiographic findings be managed? Can we further characterize the radiographic criteria to decrease the false positive rate? Can we more accurately identify people at high risk through the use of biomarkers?

III. People are living longer and better lives, with less side effects, with current treatments for NSCLC

Although the risk of death from advanced lung cancer remains very high, newer therapies are improving both the quantity and quality of life.

a. Early Stage Disease

Surgical resection is the mainstay of treatment for stage I NSCLC, with cure rates of 60% to 80%. Newer techniques in minimally invasive surgery, such as video-assisted thoracic surgery (VATS) or robotic assisted thoracic surgery (VATS), have resulted in shortened post-operative lengths of stay and improved pain control.

Advances in imaging and radiation delivery have led to the use of stereotactic body radiation therapy (SBRT) for lung tumors. With this technology, radiation delivery to surrounding normal lung parenchyma is substantially less than that occurring with conventional radiation. Thus, it is possible to give much higher, “ablative” radiation doses over a small number of fractions (e.g., 20 Gy per fraction for three fractions). To date, SBRT in early stage NSCLC can achieve 5-year local control rates of 85-90% [10-13].

Cure rates with Stage 2 disease (eg. hilar node involvement) drop to 25% - 35%, due primarily to distant recurrences. For that reason, the role of adjuvant, post-operative adjuvant has been explored and has shown to improve 5 year survival by roughly 5 – 15%. For example, in the JBR10 study from Canada, in which patients were randomized to receive either post-operative vinorelbine plus cisplatin vs. observation alone, the median survival after chemotherapy was significantly prolonged at 94 months (95% CI: 73 to not reached) in the vinorelbine–cisplatin group and 54%(95% CI:,48% to 61%) with observation alone (P=0.03). [14]. Five year survival was 69% and 54%, respectively. The median survival among patients with stage II non–small-cell lung cancer was 41 months in the observation group and 80 months in the chemotherapy group (hazard ratio, 0.59; 95% CI: 0.42 to 0.85; P=0.004)

b. Locally Advanced (Stage IIIA) Disease

The optimal treatment for stage IIIA NSCLC (most commonly, positive mediastinal lymph nodes) generally consists of a local approach (surgery or radiation therapy) plus a systemic treatment (chemotherapy). Current investigational efforts are directed at identifying the optimal combined-modality approach. Possibilities include surgery followed by adjuvant chemotherapy, preoperative (neoadjuvant) chemotherapy followed by surgery, chemotherapy plus radiation therapy (either concurrent or sequential), or a trimodality approach.

Chemotherapy plus radiotherapy is the treatment of choice for patients with bulky or inoperable stage IIIA or IIIB disease without pleural effusion. Numerous randomized

studies have demonstrated an improvement in median and long-term survival with chemotherapy plus radiation therapy versus radiation therapy alone. Active areas of investigation include choice of chemotherapy, fractionation, and treatment fields. The results from two randomized studies, one conducted in Japan and the other by the Radiation Therapy Oncology Group (RTOG), showed a survival advantage with concurrent chemoradiation compared with a sequential approach, albeit at the expense of increased toxicity. In the Japanese trial, two cycles of mitomycin-C, vindesine, and cisplatin (MVP) were given concurrently or sequentially with 56 Gy of radiation.[15] Patients in either arm who experienced a response received another two cycles of MVP after radiation therapy was completed. The response rate and median survival were significantly improved with concurrent chemoradiotherapy (84% vs. 66%, p = 0.0002; 17 months vs. 13 months, p = 0.04). The confirmatory randomized RTOG 9401 trial also showed improved survival with concurrent cisplatin, vinblastine, and radiation therapy compared with sequential chemoradiation (median survival, 17 months vs. 13 months; $P = 0.08$) [16].

c. Metastatic Disease

Chemotherapy improves survival in patients with metastatic NSCLC, tripling the one year survival rate. The principal factors predicting response to chemotherapy and survival are performance status (PS) and extent of disease. Patients with a poor PS are less likely to respond to treatment and will tolerate the therapy poorly. Favorable prognostic factors include female sex, normal serum lactic dehydrogenase level, absence of bone or liver metastases, and absence of weight loss.

Systemic treatment for patients with metastatic NSCLC and adequate PS (asymptomatic or minimally symptomatic) generally includes platinum-based doublet chemotherapy. Whereas best supportive care resulted in median survival rates of 4 to 5 months and 1-year survival rates of 5% to 10%, current third-generation regimens of platinums combined with paclitaxel and docetaxel, gemcitabine, vinorelbine, and pemetrexed have yielded median survivals of 8 to 9 months and 1-year survivals of 35% to 40% [17]. One clinical trial evaluated the role of maintenance pemetrexed, a multitargeted antifolate which has greater efficacy for the treatment of nonsquamous tumors, presumably due to higher thymidylate synthase levels in squamous cell cancers. [18] Median OS was close to 14 months for patient on the pemetrexed arm, vs. 11 months on the placebo arm. 2-year survival rates were significantly longer for patients given pemetrexed (58% and 32%, respectively) than for those given placebo (45% and 21%). In addition, randomized studies have shown an improvement in symptoms and quality of life compared with patients treated with best supportive care [19].

IV. Targeted Therapy. The term “targeted therapy” has become a catch-all phrase for any systemic therapy that either involves a biological agent, or a agent which does not involve cytotoxicity by indiscriminately targeting all rapidly dividing cells, cancer or otherwise. A more “precise” definition would include one in which the drug is targeting a specific mutation found in a cancer cell, and not in normal cells. Thus, anti-angiogenic drugs and immunomodulatory drugs would not be considered targeted. The most common mutations found in NSCLC are K-ras (found in about 25%-30% of all adenocarcinomas, particularly in smokers), EGFR, also known as human epidermal growth factor receptor 1 (HER1) or ErbB1, found in about 20% of

adenocarcinomas in the Western population; and rearrangements of Anaplastic Lymphoma Kinase (ALK) gene, found in about 3-4%.

a. Targeting the Epidermal Growth Factor Receptor

EGFR is a transmembrane receptor tyrosine kinase. On ligand binding, receptor subunits dimerize, resulting in autophosphorylation of intracellular tyrosine residues and initiation of a signal transduction cascade resulting in cellular proliferation, resistance to apoptosis, cellular invasion, metastasis, and angiogenesis. Tumors harboring activating EGFR gene mutations render the cancer highly dependent on EGFR for proliferation and survival. EGFR-inhibiting drugs are tyrosine kinase inhibitors which inhibit the activation of EGFR via direct binding to the kinase activation site.

Clinical parameters that appear to predict response to EGFR TKIs include never-smoking history, East Asian ethnicity, adenocarcinoma histology (particularly tumors with bronchioloalveolar features), and female gender. Molecular analysis of tumor specimens from individuals with these characteristics has revealed high rates of activating mutations in the EGFR tyrosine kinase domain. These mutations hyperactivate the EGFR tyrosine kinase, rendering cancer cells highly dependent on EGFR oncogenic pathways and thus exquisitely sensitive to EGFR inhibition. Among patients with “classic” EGFR mutations [exon 19 in-frame deletions of amino acids 747–750 and exon 21 L858R substitutions which account for more than 90% of EGFR mutations,[20] response rates to EGFR TKIs exceed 60% and median survival exceeds 2 years. In the first-line Iressa Pan-Asia Study (IPASS) [21], in which over 1200 previously untreated nonsmokers or former light smokers in East Asia who had advanced adenocarcinoma NSCLC were randomized to gefitinib at 250 mg orally daily or carboplatin-paclitaxel, progression-free survival was superior in the gefitinib arm (HR 0.74; p <0.001), with 12-month progression-free survival rates 25% for gefitinib and 7% for carboplatin-paclitaxel. Among those patients whose tumors harbored EGFR mutations, progression-free survival was significantly longer with gefitinib (HR 0.48; p <0.001); by contrast, in the mutation-negative group, gefitinib resulted in significantly shorter progression-free survival compared with carboplatin-paclitaxel (HR 2.85; p <0.001). No benefit in overall survival was observed, likely due to subsequent TKI therapy in patients originally treated on the chemotherapy arm.[22]

Two drugs are approved in the United States for treatment of patients harboring EGFR mutations -- erlotinib or afatinib. Afatinib was compared to two different chemotherapy regimens in two Phase 3 studies for patients with first line EGFR mutations. Although the drug did not improve overall survival in the whole population of either trial (it did improve progression free survival), when combined overall survival was significantly longer for patients with del19-positive tumors in the afatinib group than in the chemotherapy group in both trials: in LUX-Lung 3, median overall survival was 33.3 months in the afatinib group versus 21.1 month) in the chemotherapy group; in LUX-Lung 6, it was 31.4 months versus 18.4 months, respectively [23].

The primary toxicities of these drugs are acneiform rash and diarrhea.

b. ALK gene rearrangements

The anaplastic lymphoma kinase (*ALK*) gene, which encodes a tyrosine kinase, was originally identified in a subset of anaplastic large cell lymphomas with a t (2; 5)(p23;q35) translocation. In a rare subset (2% to 7% of cases) of NSCLC, chromosome 2p inversion results in fusion of the protein encoded by the echinoderm microtubule-associated protein-like 4 (*EML4*) gene with the intracellular signaling portion of the ALK receptor tyrosine kinase. Analogous to *EGFR* mutations, *EML4-ALK* fusions result in constitutive tyrosine kinase activity, dependence of the cancer cell on activated downstream mitogenic pathways, and sensitivity to ALK inhibition. 3-5% of NSCLC tumors have rearrangements in the ALK gene with some overlap in the demographics with NSCLC patients with EGFR mutations (younger, never smokers), although the two are rarely found in the same patient. Crizotinib is an oral small molecule TKI, also active against ALK, ROS1, and MET, that is approved for the treatment of advanced NSCLC harboring ALK rearrangements. Clinical studies have demonstrated response rates of 60-75% and the recent Phase III trial comparing first-line crizotinib to cisplatin (or carboplatin) plus pemetrexed in advanced, ALK-positive NSCLC demonstrated a PFS of 10.9 months with crizotinib compared to 7.0 months with chemotherapy ($p < 0.001$) [24, 25]. Ceritinib is a second-generation ALK inhibitor that has recently been approved in ALK-positive patients who have either progressed on crizotinib or are intolerant to it. This approval is based on a phase I study demonstrating response rates of greater than 50% even in patients who had been previously treated with crizotinib.

c. K-ras and FAK inhibitor

KRAS mutations, which occur in approximately 30% of lung adenocarcinoma cases, represent a major unmet clinical need in thoracic oncology. KRAS acts as a molecular on/off switch. Once it is turned on, it recruits and activates proteins necessary for the propagation of growth factor and other receptors' signal such as c-Raf and PI 3-kinase. KRAS binds to GTP in the active state and possesses an intrinsic enzymatic activity which cleaves the terminal phosphate of the nucleotide converting it to GDP. Upon conversion of GTP to GDP, KRAS is turned off. In the majority of cases, these mutations are missense mutations which introduce an amino acid substitution at position 12, 13, or 61. The result of these mutations is constitutive activation of *KRAS* signaling pathways.

Focal adhesion kinase (FAK) is a nonreceptor tyrosine kinase that was identified at adhesion sites between cells and the extracellular environment. FAK activation relies upon autophosphorylation of the unique Y-397 site that is found in the N-terminal domain. This region binds a number of signaling proteins such as src, PI-3 kinase, and Grb-7. It also binds EGFR, VEGFR, and p53 and other molecules that are critical for carcinogenesis. Interestingly, p53 can inhibit FAK expression, and FAK can inhibit p53 expression. In breast cancer cells, p53 mutation is highly correlated with FAK over expression. FAK also activates proteins that promote cell motility and migration, invasion, survival, angiogenesis, lymphangiogenesis, and proliferation [26].

Scaglioni and colleagues demonstrated that *KRAS* mutant NSCLC cell lines and xenografts with alterations in either *p53* or *INK4a/Arf (CDKN2A)* are sensitive to FAK inhibition. [27] Defactinib (VS-6063) is a selective oral inhibitor of FAK. Gerber, et al are examining the effects of FAK inhibition in patients with *KRAS* mutant NSCLC and various permutations of *p53* and *CDKN2A* alterations in a multi-center, non-randomized, open-label, multi-cohort trial for patients with advanced *KRAS* mutant

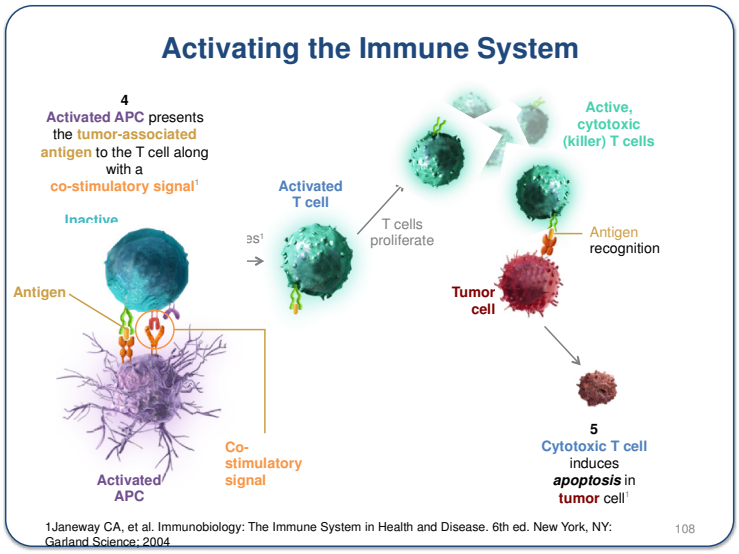
NSCLC who had received at least one prior (platinum-based doublet) line of therapy. The primary endpoint is progression-free survival at 12 weeks. Patients are enrolled into one of four molecularly defined cohorts: (A) wild type *INK4a/Arf* and wild type *p53*, (B) *INK4a/Arf* alteration and wild type *p53*, (C) wild type *INK4a/Arf* and *p53* alteration, (D) *INK4a/Arf* alteration and *p53* alteration. In all cohorts, patients received defactinib 400 mg orally BID until disease progression. Fifty-three patients with *KRAS* mutant NSCLC have been enrolled across 9 sites; results are pending [28].

d. Incidence and significance of driver mutations in lung cancer.

Although KRAS, EGFR, and also are the most common mutations found in adenocarcinoma of` the lung, they are not the only ones. From 2009 through 2012, the Lung Cancer Mutation Consortium, a group of 14 academic sites in the US, tested adenocarcinomas of the lung for driver mutations in 10 genes. An oncogenic driver was found in 466 of 733 patients (64%). Among these 733 tumors, 182 tumors (25%) had a KRAS mutation; 122 (17%) had a sensitizing EGFR; and 57 (8%) had a ALK rearrangements. Other mutations included other EGFR 299 (4%); 2 or more genes, 24 (3%); ERBB2 (formerly HER2), 19 (3%); BRAF, 16 (2%); PIK3CA, 6 (<1%); MET amplification, 5 (<1%); NRAS, 5 (<1%); MEK1, 1 (<1%); AKT1, 0. Results were used to select a targeted therapy or trial in 275 of 1007 patients (28%). The median survival was 3.5 years for the 260 patients with an oncogenic driver and genotype-directed therapy compared with 2.4 years for the 318 patients with any oncogenic driver(s) who did not receive genotype-directed therapy (propensity score–adjusted hazard ratio, 0.69 [95%CI, 0.53-0.9], P = .006) [29].

V. The importance of understanding biology to identify new treatments… Activating the immune system

Immune “checkpoints” are proteins that block the immune response by inhibiting T cell activation, thus helping control the balance of costimulatory and co-inhibitory signals that have essential roles in maintaining self-tolerance. The immune checkpoint inhibitors intensify the anti-tumor immune response by disrupting these negative feedback signals, thus releasing the breaks on the immune system, allowing the T cells to attack the cancer. For example, binding of the protein called programmed death-1 ligand (PD-L1), which is expressed on cancer cells, to its receptor on T cells (PD1) results in dampening of the immune response, whereas disrupting it through the use of monoclonal antibodies activates T cells. Similarly, binding of a monoclonal antibody to cytotoxic T lymphocyte antigen (CTLA-4) on the surface of T cells also “releases the brakes” on T cells, freeing the immune system to attack cancer cells..



Melanoma research has been at the forefront of immune checkpoint inhibitors and the FDA approved ipilimumab (an anti-CTLA4 antibody) in 2011 and nivolumab (an anti-PD1 antibody) and pembrolizumab (a anti-PDL1 antibody) in 2014 for the treatment of metastatic melanoma. These agents have been intensely studied in several tumor types including in NSCLC. A phase II, multisite, single-arm trial (CheckMate 063) of nivolumab in patients with advanced, refractory squamous cell carcinoma demonstrated an objective response in 14.5% of patients and stable disease in 30% of the patients. Grade 3-4 adverse events included fatigue, diarrhea, and pneumonitis [30]. CheckMate 017 is a Phase 3 study comparing docetaxel with nivolumab as a second line treatment for patients with metastatic squamous NSCLC following prior platinum-based treatment. The study was stopped early based on an interim data analysis which showed an improved overall survival (9.2 versus 6.0 months, p = 0.00025) for nivolumab compared to docetaxel in. Although the final results have not yet been published, in March 2015, nivolumab was approved for use in metastatic squamous NSCLC after progression on platinum-based therapy.

Bavituximab is a first-in-class phosphatidylserine (PS)-targeting monoclonal antibody that was developed at UTSW by Dr. Phil Thorpe. PS is a highly immunosuppressive molecule usually located inside the membrane of healthy cells, but "flips" in the presence of stress, creating a specific target for anti-cancer treatments. [31] Preclinical studies have shown that PS expands M2-like tumor associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs), and results in a immunosuppressive cytokine milieu. The PS-targeting antibody bavituximab binds to PS and blocks this immunosuppressive signal, increasing the presence of M1-like TAMs and mature dendritic cells in the tumors, and markedly altered the cytokine balance in the tumor microenvironment from immunosuppressive to immunostimulatory. The drug is currently in a phase III trial evaluating bavituximab plus docetaxel versus docetaxel plus placebo in second line non-squamous cell lung cancer.

Of note, the side effects associated with these therapies are very different than the side effects associated with chemotherapy. Adverse effects are generally related to a hyperimmune system, and include inflammation of the thyroid, colon, lungs, skin, and pituitary gland.

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