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PD-1/PD-L1 axis in lung cancer

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Abstract

Cancer immunotherapies have revolutionized the treatment of non-small cell lung cancer. Yet, only a small subset of patients will benefit from PD-(L)1 blockade. PD-L1 tumor cell expression is the only approved biomarker at present. Tumor mutational burden and other emerging biomarkers should improve patient selection. Combination therapy approaches with chemotherapy or CTLA-4 blockade may increase the proportion of patients who benefit from immunotherapy. Although use of immunotherapy in lung cancers with targetable oncogenes has not been particularly successful, the benefit of PD-(L)1 inhibitors in early-stage disease emerging. This review will briefly describe the evolution of the clinical development and future directions of PD-(L)1 blockade in patients with lung cancers.

Keywords

NSCLC; anti-PD-1; anti-PD-L1; immunotherapy

Introduction

Lung cancer is the most frequent cause of cancer-related mortality worldwide[1]. Fortunately, the advent of immune checkpoint inhibitors has improved the outlook for patients with advanced lung cancers. Since 2015, the US Food and Drug Administration (FDA) has approved three immunotherapies for advanced non-small cell lung cancer (NSCLC) in the first and second line setting. This review will briefly describe the evolution of the clinical development of PD-(L)1 blockade in patients with lung cancers, underscore the remaining critical opportunity to identify better tools for patient selection, and review ongoing effort to explore combinations with the PD-(L)1 blockade as the backbone for future immunotherapies.

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Early phase clinical trials of PD-(L)1 monotherapy – Proof of principle for immunogenicity of lung cancer and beginning of immunotherapy revolution

In 2010, when ipilimumab had already shown improved survival in patients with advanced melanoma[2], lung cancer was still largely regarded as non-immunogenic. But the breakthrough of PD-(L)1 blockade as a cancer immunotherapy was about to begin. In the first-in-human dose-escalation trial of a fully human anti-PD-1 IgG4 monoclonal antibody (mAB), then termed MDX-1106 and now nivolumab, 39 patients with refractory metastatic cancers were treated with a single dose of nivolumab at 0.3, 1, 3, or 10 mg*kg.[3] Six patients in this trial had NSCLC and one had evidence of radiologic response, but not sufficient to meet criteria for objective partial response. Still, this tantalizing preliminary evidence of clinical activity and mild safety profile prompted a larger, multi-dose, phase 1 study (CheckMate 003), which again included patients with NSCLC.

The presentation of this study by Topalian and colleagues at ASCO 2012 and concurrently published[4] represented the major turning point in the development of PD-(L)1 inhibitors. In addition to NSCLC, this trial enrolled patients with advanced melanoma, castration-resistant prostate cancer, renal-cell cancer or colorectal cancer to receive nivolumab at a dose of 0.1 to 10 mg*kg every two weeks. Antitumor activity was observed at all doses tested. In patients with NSCLC, response rates of 6%, 32%, and 18% were observed at doses of one, 3, or 10 mg*kg, respectively. Of responders, 8 of 14 had a response that lasted 24 weeks or more. Additional follow up of the 129 NSCLC patients demonstrated a difference in response rate between low dose and higher doses of nivolumab: 3% in the 1 mg*kg cohort, 24.3% in the 3 mg*kg, and 20.3% in 10 mg*kg cohort, respectively[5]. Based on these data, the 3 mg*kg dose was chosen for further investigation. Across all patients treated in this study, grade 3 or 4 treatment-related adverse events were observed in 14% with three (1%) drug-related deaths occurring due to pneumonitis (two in patients with NSCLC).

In parallel, pembrolizumab, another potent, highly selective, IgG4 humanized monoclonal antibody that prevents PD-1 binding with PD-L1 and PD-L2, was tested in a large, multicohort, phase 1 study (KEYNOTE-001).[6] Patients with NSCLC received pembrolizumab at a dose of 2 mg or 10 mg*kg every 3 weeks or 10 mg*kg every 2 weeks. The overall response rate was 19.4%. The response rate was similar regardless of dose, schedule, and histologic analysis. Grade 3 or higher adverse events were reported in 9.5% of patients. The most common immune related adverse events were hypothyroidism (6.9%) and pneumonitis (3.6%). Of particular importance, an analysis of tumor PD-L1 expression highlighted that patients with high PD-L1 expression (defined as >/= 50% tumor cells with membranous expression) had an enhanced likelihood of a response to pembrolizumab. In this trial, patients with high PD-L1 expression had response rates of 45%, which was significantly higher than those with low or no PD-L1 expression.

Atezolizumab, a human IgG1 monoclonal antibody targeting PD-L1 and containing an engineered Fc-domain designed to optimize efficacy and safety, was next to move into phase 1 studies. Atezolizumab was administered every three weeks in patients with locally advanced or metastatic solid tumors.[7] In 175 patients, the overall response rate was 21%; among NSCLC specifically, the response rate was 23%. PD-L1 tumor status seemed to

correlate with responses, although relatively few patients were assessed at the point of the initial publication.

Other notable PD-L1 inhibitors under development but not yet FDA approved include durvalumab[8] and avelumab.[9] Durvalumab has recently demonstrated profound improvement in disease-free survival in patients with stage III NSCLC following concurrent chemoradiotherapy.[10] Based on this trial, discussed further later in this review, durvalumab is expected to be FDA approved in the near future and will be a standard of care in the locally advanced setting. With regard to avelumab, in the expansion cohort of 184 patients with NSCLC treated with avelumab, there was reasonable anti-tumor activity (22 of 184 [12%] patients achieving a confirmed objective response).[9] Avelumab is unique because it is the only antibody in the PD-(L)1 category of drugs that induces natural killer cell-mediated antibody-dependent cellular cytotoxicity in vitro.

Overall, all the aforementioned anti-PD-1 and anti-PD-L1 mAbs showed promising safety and durable clinical activity in a subset of patients with NSCLC. The pharmacokinetic and pharmacodynamics profile were similar. Neither maximum tolerated dose nor dose limiting toxicities were identified in these trials.

Phase 2 and 3 trials – Path to registration and dawn of a new era

Shortly after the initial breakthrough of the clinical activity of PD-(L)1 inhibitors, several Phase 2 and 3 studies were quickly completed. By March of 2015, the first immunotherapy for lung cancer received FDA approval, establishing of a new era in thoracic oncology.

Following promising activity in a phase 2 single arm study of nivolumab in squamous NSCLC,[11] CheckMate 017[12] was a phase 3 study that compared nivolumab with docetaxel in patients with advanced squamous-cell NSCLC who had progressed during or after one prior platinum-containing chemotherapy regimen. Patients treated with nivolumab had longer overall survival (9.2 months v 6.0 months) and fewer grade 3 or 4 treatment-related adverse events than docetaxel treated patients (7% v 55%). A similarly designed study for patients with advanced non-squamous NSCLC, CheckMate057, was also completed in parallel and similar benefits were achieved[13]. Although both phase 3 trials showed longer overall survival with nivolumab than with docetaxel, they had one particular difference. Across the pre-specified expression levels (1%, 5%, and 10%), PD-L1 expression was not associated with improved outcomes in patients with squamous NSCLC while in patients with non-squamous NSCLC there was a predictive association with PD-L1 expression. Nevertheless, as responses were indeed seen across the PD-L1 spectrum and across histologies, nivolumab was FDA approved in the second line setting for all patients with NSCLC (both squamous and non-squamous, irrespective of PD-L1 expression) in 2015.

KEYNOTE-010 was the first active-control trial that enrolled patients on the basis of prospective assessment of tumor PD-L1 expression[14]. This randomized phase 2/3 clinical trial included patients with previously treated NSCLC with PD-L1 expression on at least 1% of tumor cells who were randomized to receive pembrolizumab 2 mg*kg, pembrolizumab 10 mg*kg, or docetaxel 75 mg.m^2 every 3 weeks. Pembrolizumab arms showed clearly longer

overall survival than docetaxel arm, with distinctly durable responses among those treated with pembrolizumab across all PD-L1 expression levels. There was no difference between the pembrolizumab 2 mg*kg vs pembrolizumab 10 mg*kg arms. As a result of this study and the previous KEYNOTE-001, pembrolizumab was approved by the FDA in 2015 for second line treatment of patients with PD-L1 expressing NSCLCs.

Atezolizumab was explored in three pivotal phase II trials (FIR, POPLAR[15] and BIRCH[16]) and one phase III trial (OAK).[17] OAK was the first phase 3 study of an anti-PD-L1 immunotherapy in NSCLC. Overall survival was improved with atezolizumab relative to docetaxel across all spectrum of PD-L1 expression, although patients with high PD-L1 expression (measured in both tumor and immune cells) had the greatest benefit from atezolizumab. In October 2016, atezolizumab was FDA approved for the treatment of patients with metastatic NSCLC, regardless of PD-L1 expression, whose disease progressed during or following platinum-containing chemotherapy.

First line therapy and establishing role for routine PD-L1 testing

Data from KEYNOTE-001 and KEYNOTE-010 indicated that patients with a PD-L1 tumor proportion score of 50% or greater were more likely than those with lower PD-L1 expression to have a response with pembrolizumab. Therefore, in the KEYNOTE-024 trial[18], pembrolizumab was compared with the investigator's choice of cytotoxic chemotherapy as first-line therapy for patients with advanced NSCLC and a PD-L1 tumor proportion score of 50% or greater. Notably, the prevalence of a tumor proportion score of 50% or greater in the KEYNOTE-024 screened population (30.2%) was consistent with the prevalence observed in the KEYNOTE-001 trial among previously untreated patients (24.9%) and in the KEYNOTE-010 trial among previously treated patients (28%). Pembrolizumab was associated with significantly longer progression-free and overall survival compared to first-line chemotherapy. Pembrolizumab was also associated with a higher objective response rate, a longer duration of response, and a lower frequency of treatment-related adverse events than chemotherapy. Overall, the results of this trial were unequivocal and have changed the diagnostic and treatment paradigm for patients with NSCLC. Now, PD-L1 expression testing is (or should be) routine for patients with newly diagnosed NSCLC and those who are high PD-L1 expression should receive pembrolizumab as the first-line standard of care.

Updated data from KEYNOTE-024 were presented at 2017 ASCO Annual Meeting.[19] PFS2 (progression after the next line of therapy) was particularly highlighted. PFS2 is not often measured in lung cancer, however it can be used to address the impact of crossover on overall survival assessment and whether or not therapy positively impacted efficacy in the next line of therapy. The median PFS2 was 18.3 months with pembrolizumab vs 8.4 months with chemotherapy, reinforcing the conclusions that pembrolizumab is indeed the standard for first line therapy in this setting.

Conversely, in a similar but critically differently designed study of nivolumab vs platinum-based therapy, CheckMate 026 examined patients with untreated metastatic NSCLC with a PD-L1 expression level of 5% or more.[20] In this study, there was no improvement in PFS or

OS among those who received nivolumab. The major difference between this study and the KEYNOTE-024 study was the lower threshold of PD-L1 expressed used for analysis (5% vs 50% expression). But even among the patients in CheckMate 026 who had >50% PD-L1 expression, there was still no improvement in outcomes in patients treated with nivolumab vs chemotherapy. This conundrum has highlighted the importance of explore additional biomarkers. In an exploratory analysis, patients in CheckMate-026 with available tissue, whole exome sequencing was performed and mutation burden quantified. Among patients with a high tumor mutation burden, which was defined the upper tertile of mutation burden, nivolumab was associated with a higher response rate than chemotherapy (47% vs. 28%) and with a longer median progression-free survival (9.7 vs. 5.8 months). Importantly, the level of tumor mutation burden and the level of tumor PD-L1 expression did not appear to be associated. Moreover, the greatest benefit of response and progression-free survival was seen among those who had both high mutation burden and high PD-L1 expression, suggesting there may be a role for these biomarkers to be considered as a composite.

BIRCH[16] was a phase 2 trial designed to examine the efficacy of atezolizumab across lines of therapy, including first line. Patients were selected on the basis of PD-L1 expression on tumor cells (TC) or tumor-infiltrating immune cells (IC). Patients treated in the first line setting with TC3 or IC3 tumors had numerically higher ORRs versus those with TC2/3 or IC2/3 tumors, with a median overall survival of approximately two years. Ongoing randomized phase 3 trials are comparing atezolizumab monotherapy with chemotherapy.

Optimizing use of checkpoint inhibitor efficacy: Biomarkers and Combination approaches

Biomarkers

A substantial unmet need is the development of biomarkers of response to immunotherapeutic agents, in order to identify, before initiation of treatment, which patients are likely to experience a response to and clinical benefit from such treatments. The approval of pembrolizumab for previously untreated metastatic NSCLC with PD-L1 expression greater than 50% has established the role of PD-L1 expression as a biomarker. But there remain questions about the application of PD-L1 testing and alternative biomarkers to explore.

In the Blueprint Project[21], four PD-L1 assays were compared on the same set of tumors. Each IHC assay was developed with a unique primary antibody against PD-L1, namely, 28-8 (Dako) with nivolumab, 22C3 (Dako) with pembrolizumab, SP263 (Ventana) with durvalumab, and SP142 (Ventana) with atezolizumab. The antibodies SP142 and E1L3N bind to the cytoplasmic domain of PD-L1, while other antibodies, including 28-8, 22C3, and SP263 bind to the extracellular domain of the PD-L1. Overall, there was generally good alignment between the PD-L1 antibodies. One exception was SP142, which consistently reported fewer tumor-cells expressing PD-L1. All the assays demonstrated a greater variance on infiltrating immune-cells than on tumor cells. In a parallel independent effort, Rimm and colleagues compared the performance of four PD-L1 platforms including 28-8, 22C3, SP142 and one laboratory-developed test E1L3N (Cell Signaling).[22] Similar to Blueprint, there was

overall excellent concordance when scoring PD-L1 expression, although SP142 antibody was again an outlier that detected less PD-L1 expression in tumor cells and immune cells. In a third study[23], five pathologists scored the percentage of PD-L1 positivity in TCs and ICs of 35 resected NSCLC cases, each represented on three separate blocks. Pathologists were again highly concordant for PD-L1 tumor scoring, but not for immune cell scoring. Interestingly, a spatial heterogeneity of PD-L1 expression was observed within the area represented in a single block, but there was good concordance of PD-L1 score between blocks from the same patient. This indicates that PD-L1 testing of one block is reasonable enough, but of course intra-tumoral heterogeneity remains an important issue.

In summary, the use of PD-L1 expression on immunohistochemistry as a biomarker has important clinical utility and should be a routine test for patients with NSCLC. Most PD-L1 assays seem to have reasonable concordance. Yet, there are some inherent pitfalls, including tumor heterogeneity, sampling variability, and the dynamic expression of PD-L1, which also need to be taken into account when considering the results of PD-L1 testing.

Recent advances in genomics have provided tools to facilitate the understanding of the interaction of the intratumoral immune environment and tumor cells and will likely help the development of new biomarkers. In NSCLC, an initial clue about the impact of genetics on response to immunotherapy came from the observation that smokers are among the best responders to PD-1 therapy.[24] It is widely known that carcinogens in tobacco are largely responsible for the mutagenesis in most lung cancers, but there is a wide range of mutation burden within both smokers and never smokers, such that other pathways (e.g. related to DNA repair and replication) can define a dynamic range of mutation burden.[25] Whole exome sequencing can quantify mutation burden. In an initial report, increased mutation burden was associated with improved objective response, durable clinical benefit, and progression-free survival.[26] More recently, as noted above, an exploratory analysis from CheckMate 026 of patients treated with nivolumab or chemotherapy and profiled by whole exome sequencing confirmed that increased mutation burden associated with improved response rate and progression-free survival with nivolumab. There was no such improvement in patients treated with chemotherapy, demonstrating that mutation burden is a predictive rather than prognostic biomarker. One critique of mutation burden as a biomarker is the current infeasibility of whole exome sequencing as a clinical test. But recent data have demonstrated targeted next-generation sequencing, currently used in clinical already, can provide an accurate and expedient estimation of tumor mutation burden.[27-29]

Beyond PD-L1 and mutation burden, analyses to interrogate the inflammatory nature of the tumor microenvironment are of utmost importance for next generation biomarkers. Tests including image analyses that takes into account geographic relationships between invading T cells and tumor cells as well transcriptomic analyses[7,30,31], should permit the development of more nuanced predictive tools for identifying those most likely to benefit from anti-PD-1/PD-L1 therapies.

Combinations: Chemotherapy and Dual Checkpoint Blockade

For decades, chemotherapy was the only treatment available for advanced NSCLC. The potential rationale to combine chemotherapy with immune checkpoint blockade is to reduce the tumor burden, augment tumor antigen presentation, and affect stromal cells in ways that may selectively reduce immunosuppressive cells (e.g. T-regulatory cells and myeloid derived suppressor cells). Chemotherapy has also been shown to induce PD-L1 expression on tumor cells.[32] But there are also reasons for uncertainty about the synergism of chemotherapy with immunotherapy, including imprecise choice of chemotherapy to achieve immunogenic effects, detriment of concurrent steroids used for supportive care during chemotherapy, direct immunosuppressive effects of chemotherapy, and additive toxicity.

This debate has been put to the test in the phase 1/2 KEYNOTE-021 study, where pembrolizumab was initially added to carboplatin plus paclitaxel (cohort A), carboplatin plus paclitaxel plus bevacizumab (cohort B), or carboplatin plus pemetrexed (cohort C). The greatest antitumor activity was observed in 24 patients treated in the cohort C, where the combination of carboplatin, pemetrexed, and pembrolizumab resulted in 71% of patients achieving an overall response and a median progression-free survival of 10.2 months. Based on the latter, Langer and colleagues reported the results of a randomized phase 2 study of a fixed dose of 200 mg of pembrolizumab plus carboplatin and pemetrexed versus chemotherapy alone as first-line therapy for patients with advanced NSCLC of non-squamous histology[33]. The combination arm significantly prolonged progression-free survival (13 months v 8.9 months) and improved the proportion of patients who achieved an objective response (55% v 29%). The incidence of grade 3 or worse treatment-related adverse events was somewhat higher in those treated with the combination (39% v 26%). Of note, there was no improvement in overall survival.

On the basis of these results, the FDA granted accelerated approval in May 2017 to this combination of carboplatin, pemetrexed, and pembrolizumab for patients with untreated advanced non-squamous NSCLC. A larger Phase 3 trial (KEYNOTE-189) is ongoing now and is expected to provide top-line results later in 2017. Particularly close attention will be paid to whether overall survival is improved and how benefit is achieved in PD-L1-defined subgroups, especially given the now established standard of pembrolizumab monotherapy for patients with high PD-L1 expression.

In addition to chemotherapy, dual immune checkpoint blockade has also been examined as a combination approach to improve responses for patients with NSCLC. Dual anti-CTLA-4 and anti-PD-(L)1 blockade is the combination that has been most extensively studied in NSCLC. Early studies have demonstrated particularly promising response rates, but with a concomitant increase in the frequency and severity of adverse events. The CTLA-4 and PD-(L)1 pathways have different mechanisms for inhibiting the function of T cells, highlighting the rational opportunity for synergy.[34]

In CheckMate 012[35], an open-label phase 1 study for nivolumab and ipilimumab (anti-CTLA-4 mAb) as first-line treatment of advanced NSCLC, patients treated with nivolumab 3 mg*kg every two weeks and ipilimumab 1mg*kg every 6 or 12 weeks had overall

response rate of 43% among all-comers, and up to 86% in a small cohort of patients with PD-L1 expression greater than 50%. Grades 3 and 4 treatment-related adverse events were observed in 33% of the patients. No treatment-related deaths were reported. Although tantalizing, Phase 2 and 3 results are ongoing and still awaited.

The combination of anti-PD-L1 plus CTLA-4 has also been evaluated in a Phase 1 study, which also demonstrated potentially promising activity, especially among PD-L1 low expressers.[36] This activity prompted a Phase 3 study MYSTIC, in which patients with untreated, advanced NSCLC were randomized to platinum-based chemotherapy, durvalumab monotherapy, or durvalumab plus tremelimumab. The top-line results were recently reported in a press release that no significant improvement in progression-free survival was seen among those treated with the combination. However, the full results have not yet been reported and, importantly, analysis of overall survival is still pending.

Emerging Clinical Situations: Oncogene-Driven Lung Cancer and Locally Advanced Disease

In patients with NSCLCs harboring specific alterations in oncogenic drivers, such as mutations in *EGFR*, *ALK* or *ROS1*, tyrosine kinase inhibitors have offered impressive antitumor activity. However, resistance almost inevitably develops, highlighting the understandable eagerness to explore how immunotherapies may play a role in these diseases as well. From a biologic perspective, although oncogene-driver lung cancers tend to occur in never smokers and therefore have lower tumor burden (and thereby may be less responsive to immunotherapies), there are some reasons for enthusiasm.[37] For example, NSCLC cell lines with activated *EGFR* mutations demonstrated induced PD-L1 expression, and mouse models of EGFR-driven lung cancer are associated with increased markers of T cell exhaustion which may be primed for reinvigoration with PD-(L)1 blockade.[38] Also, PD-L1 expression level was higher in NSCLC cell lines positive for *EML4–ALK* rearrangement than in those wild-type for the fusion gene.[39] Nevertheless, the overall clinical data to date has suggested relatively low activity of PD-(L)1 therapies in these types of lung cancers.

A meta-analysis to assess the role of immune checkpoint inhibitors as second-line therapy in patients with *EGFR* mutant advanced NSCLC showed that immunotherapy does not improve overall survival over docetaxel in this population[40]. In a separate report, Gainor and colleagues observed a low objective response rate in a cohort of 58 patients treated with PD-1/PD-L1 inhibitor (3.6% in EGFR-mutant or ALK-positive patients versus 23.3% in EGFR wild-type and ALK-negative/unknown patients).[41] In addition, a retrospective analysis of patients with *MET* exon 14 skipping altered lung cancers showed a similarly low response rate, with few responses even among those with high PD-L1 expression or high mutation burden.[42]

By contrast, there is quite promising data to support an anticipated standard role for immunotherapies in earlier stage disease. Multimodality therapy is recommended for most patients with Stage III NSCLC. In addition to generating adaptive immunity, fractionated radiotherapy leads to upregulation of tumor cell expression of PD-L1 and blockade of the PD-1/PD-L1 axis can enhance the immune response to fractionated radiotherapy in multiple

syngeneic models.[43,44] PACIFIC is the first phase III trial to test an immune checkpoint inhibitor as sequential therapy in patients with stage III NSCLC who had not progressed following platinum-based chemotherapy concurrent with radiation therapy.[10] Patients were randomized to receive durvalumab for up to 12 months or placebo. The median disease-free survival was 16.8 months in the durvalumab arm compared to 5.6 months with placebo. It is important to highlight the acceptable toxicity profile of durvalumab in this setting, particularly the relatively low rate grade 3 or 4 pneumonitis (3.4%). Although overall survival data is still pending, regulatory approval is expected for durvalumab in this setting and will likely be a new standard for patients with stage III NSCLC treated with chemoradiation.

In addition to the adjuvant setting, there is intriguing data about the potential role of neoadjuvant PD-(L)1 therapy as well. In an early-phase study, 22 patients with early-stage resectable NSCLC safely received two cycles of neoadjuvant nivolumab followed by surgery.[45] There were no delays in surgery or concerning safety signals, while 43% of patients had a major pathologic response to nivolumab at the time of surgery, defined as ≤10% residual viable tumor.[46] Phase 3 studies of neoadjuvant PD-(L)1 therapy are now ongoing.

Conclusion

The rapid development of anti-PD-1/PD-L1 inhibitors for treatment of advanced NSCLC has profoundly improved the outcomes for patients, revealed critical new biology about lung cancer and immunity, and initiated a booming opportunity for drug development. Albeit quite uncommon, it is now possible with anti-PD-(L)1 inhibitors for some patients with advanced NSCLC to be alive and progression-free several years after diagnosis, some with no evidence of residual disease.[47,48] The potential for durable benefit is nothing short of transcendent. And yet, only a subset of NSCLC patients will respond to immune checkpoint blockade monotherapy; put another way, the vast majority of patients with NSCLC do not respond to PD-(L)1 blockade. In ongoing effort to stimulate non-responders to achieve therapeutic benefit, numerous additional immunomodulatory pathways are being explored in clinical trials. Also, understanding of the mechanisms of primary and acquired resistance to immune checkpoint blockade will help define the future of combination therapies.

Ultimately, a personalized immunotherapy program may prove to be the keystone of future cancer therapy. Pretreatment assessment of immune-related biomarkers, PD-L1 expression, quantitative and qualitative assessments of the molecular landscape of tumors, and location and signature of the immune infiltrate, may help inform the best treatment strategy for each patient. Toward this goal, there has been progress, but much more work left to be done.

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