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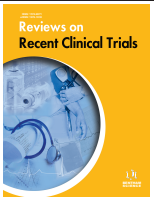

Immunotherapy for Non-Small Cell Lung Cancer - Finally a Hint of Hope

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Abstract: Lung cancer is a major public health problem worldwide and the leading cause of cancer-related mortality in developed countries. Significant advances have been made especially with the discovery of targeted agents. However, only a small proportion of patients carry activating mutations; until recently conventional chemotherapy and angiogenesis inhibitors were the preferred treatment for the vast majority of patients. Now, the successful experience of anti-PD-1 agents may have opened the door to a novel and previously unexplored dimension in the treatment of lung cancer: immunotherapy. In this mini-review we will discuss the current applications and future consequences related this topic, paying special attention to the clinical studies that constitute the scientific evidence to supports its use.

Keywords: Immunotherapy, lung cancer, nivolumab, PD-1, squamous cell carcinoma.

INTRODUCTION

Lung cancer represents a major public health problem worldwide. In most developed countries, it is the leading cause of cancer-related mortality, surpassing even breast and colon cancer when both sexes are considered [1]. Moreover, it is quite evident that this disease is not homogeneous, and multiple subtypes have been recognized for decades. From the histological perspective, the three most commonly seen subcategories are adenocarcinoma, Squamous Cell Carcinoma (SCC), and high-grade neuroendocrine (small cell) cancers [2].

Over the last couple of years, there have been virtually no advances in terms of improvements in treatment for small cell lung cancers. In contrast, the discovery of targeted agents for tumors with EFGR and ALK mutations represented major successes [3, 4]. In addition, the demonstration that novel chemotherapy agents, such as pemetrexed or bevacizumab, were particularly effective in adenocarcinomas could also be recognized as tangible progress [5, 6]. However, for SCC, there have been only small advances, mainly limited to better response rates observed with some of the newer chemotherapeutics such as nab-paclitaxel [7]. Part of the relative lack of progress could be attributed to the fact that SCC is usually related to patients' smoking habits, with consequent higher mutation rates and intrinsic resistance. Paradoxically, however, these same features may have opened the door to a novel and previously unexplored dimension in the treatment of lung cancer: immunotherapy.

The strategy of enhancing the patient's own immune system to attack malignant cells is known and has been studied for many years in multiple neoplasms, including lung cancer. However, most of the clinical research previously reported has been focused almost exclusively on different types of vaccines [8]. Unfortunately, the results were discouraging. Nonetheless, with the advent of the checkpoint inhibitors, a completely new era has clearly emerged. The publication of the CheckMate 017 clinical trial signifies a groundbreaking shift in the way we understand lung cancer, especially Squamous Cell Carcinoma Lung Cancer (SCCLC), and probably represents the most crucial progress in the fight against lung cancer since the discovery of platinum salts. Therefore, this review analyzes the implications arising from this study as well as its possible future consequences.

GROUND-BREAKING NEW EVIDENCE

In July 2015, the results of the CheckMate 017 study, a randomized, phase 3, multicenter and international clinical trial, were fully published [9]. In this trial, 272 patients with locally advanced and unresectable (Stage IIIB; ~20%) as well as metastatic (Stage IV; 80%) SCCLC were randomly assigned to receive either nivolumab or what was considered the standard of care, docetaxel. Following conventional inclusion criteria for this type of clinical trial, patients were required to be adults (>18 years old) and to have optimal performance status (Eastern Cooperative Oncology Group score 0-1) and optimal renal, hepatic, and hematological function. Given the previously known adverse events provoked by anti-PD-1 inhibitors, autoimmune diseases or use of immunosuppressant medications were logical exclusion criteria. Both study drugs were administered until confirmed disease progression or intolerable toxicity, as is

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typically done in daily practice. Pre-specified stratification variables included previous use of paclitaxel and geographical location. The primary and most important endpoint was Overall Survival (OS); secondary endpoints included, among others, Progression-Free Survival (PFS), Overall Response Rate (ORR), and safety. Correlative analyses were undertaken using PD-L1 expression as a biomarker.

The most relevant finding of this study was the confirmation that nivolumab resulted in a significant extension in the OS (9.2 *vs.* 6 months; Hazard Ratio (HR) = 0.59; P <0.001) as well as a twofold increase in the proportion of patients who remained alive by the end of the first year (42% *vs.* 24%). The OS benefit was robust across all pre-specified subgroups except for patients enrolled in countries other than the USA, Canada, and Europe and in patients older than 75 years of age.

Important information regarding ORR, median duration of response, PFS, toxicity, and the role of biomarkers will be discussed in the following section, contextualized with other currently available data regarding immunotherapy.

IS IMMUNOTHERAPY A NEW STANDARD OF CARE?

CheckMate 017 is undeniably a practice-changing clinical trial. As described in the preceding section, this trial compared docetaxel with nivolumab, proving the superiority of the investigational agent in terms of robust endpoints such as OS, and with the addition of a more favorable toxicity profile. Consequently, nivolumab could easily be considered the new standard of care for second-line treatment of metastatic SCCLC and a potential serious competitor to platinum doublets as first-line treatment. However, before making this statement, some issues must be discussed in more detail.

Was the Competitor Arm with Docetaxel the Right Choice?

Docetaxel has proven efficacy as second-line treatment in Non-Small Cell Lung Cancer (NSCLC). The TAX 317 clinical trial compared two doses of docetaxel, 75 and 100 mg/m2, versus placebo in 204 patients who were resistant to first-line cisplatin-based therapy. Patients were excluded if they had received paclitaxel previously. Median OS favored docetaxel by a little more than 3 months (P = 0.01) [10]. The response rate was only 6% with docetaxel and the median duration of the response was 6.5 months. Fosella and colleagues compared docetaxel to vinorelbine or ifosfamide in the second-line setting. The TAX 320 trial was a phase III trial that included 373 patients with advanced NSCLC, and 30% of the patients had SCCLC. Docetaxel again demonstrated a 6.7% ORR with 75 mg/m2, which is probably the most commonly used dose in daily practice. The competitors were virtually ineffective (ORR = 0.8%). One-year OS favored the docetaxel arm (32% *vs.* 19%, P = 0.01) [11]. Based on these results, in 2003 the American Society of Clinical Oncology changed its recommendations to include docetaxel as the standard second-line therapy in patients with adequate performance status [12].

Erlotinib and gefitinib are both Epidermal Growth Factor Receptor (EGFR)-Tyrosine Kinase Inhibitors (TKIs) with proven efficacy compared to placebo in the second-line treatment of NSCLC. Most of the original clinical trials included patients with both adenocarcinoma and SCC. In the BR21 trial, treatment with erlotinib in patients with histology other than adenocarcinoma demonstrated a non-significant improvement in OS compared to best supportive care (HR 0.8; P = 0.07). The recently published LuxLung 8 trial showed the superiority of afatinib compared to erlotinib in terms of OS and as a second-line treatment for SCCLC (7.9 *vs.* 6.8 months; HR = 0.81; P = 0.007) [13]. However, none of these drugs have proven superiority compared to docetaxel in SCCLC and may be considered as treatment only for patients with inadequate performance status [14]. Erlotinib and gefitinib were compared to docetaxel in phase III clinical trials and there was no clinical benefit between treatment arms in the SCCLC population [15-17].

Other phase III trials compared docetaxel with oral topotecan, paclitaxel poliglumex, and vinflunine in NSCLC. None of these drugs were superior to docetaxel [18-20]. The JMEI trial compared pemetrexed to docetaxel as second-line treatment. There was no difference between treatments in terms of PFS and OS [21]. However in a retrospective analysis of this trial, in patients with SCC histology treated with pemetrexed, the adjusted HRs for OS and PFS were 1.56 (P = 0.018) and 1.4 (P = 0.046), respectively. Based on this analysis, docetaxel is preferred over pemetrexed in this setting [22].

Lastly, ramucirumab is a monoclonal antibody that targets the extracellular domain of the vascular endothelial growth factor receptor 2. The REVEL study compared docetaxel with ramucirumab or placebo in the second-line treatment of patients with stage IV squamous and non-squamous NSCLC [23]. Ramucirumab and docetaxel resulted in modest improvements in OS (10.5 *vs.* 9.1 months, HR = 0.86; P = 0.023). Nonetheless, only a quarter of the patients had SCC histology, and in the subgroup analysis, there was only a non-significant trend favoring the ramucirumab arm.

On the basis of the evidence reviewed above, the docetaxel arm in the CheckMate 017 trial was, in our opinion, a valid control arm. Docetaxel showed equivalent results compared to historical response and survival rates (see Table **1**). Patients treated with docetaxel had a 9% ORR and 6-month OS comparable or even superior to the TAX 317 and 320 trials. The median duration of response in this arm was 8.4 months.

Could Previous Treatment with Paclitaxel Have Influenced the Outcomes of the Docetaxel Arm?

This data has not been published, but there is evidence based on the TAX 320 and TAX 317 trials that previous treatments with paclitaxel did not affect the response rate when docetaxel was administered as second-line (10.5% *vs.* 8.5% with and without previous paclitaxel, respectively) [24]. In the CheckMate 017 study, 34% of patients in both arms had been treated previously with paclitaxel. In a pre-specified analysis, both groups of patients—those treated with paclitaxel or those receiving other chemotherapies—

Table 1. Comparison of docetaxel performance as second line therapy throughout different clinical trials.

Clinical Trial	Description	Median OS	1-Year OS	ORR	Duration of Response
TAX 317 [10]	Docetaxel 75 mg/m^2 *vs.* Docetaxel 100 mg/m^2 *vs.* Placebo	7.5 months *vs.* 5.9 months *vs.* 4.6 months	37% *vs.* 19% *vs.* 19%	5.8%.	6.5 months (23.7 - 31.0)
TAX 320 [11]	Docetaxel 75 mg/m^2 *vs.* Docetaxel 100 mg/m^2 *vs.* Ifosfamide or Vinorelbine	5.5 months *vs.* 5.7 months *vs.* 5.6 months	21% *vs.* 32% *vs.* 19%	10.8% *vs.* 6.7% *vs.* 0.8%	7.5 months *vs.* 9.1 months *vs.* 5.9 months
INTEREST [15]	Docetaxel 75 mg/m^2 *vs.* Gefitinib	8 months *vs.* 7.6 months	34% *vs.* 32%	7.6% *vs.* 9.1%	Not described
V-15-32 [16]	Docetaxel 60 mg/m^2 *vs.* Gefitinib	14 months *vs.* 11.5 months	53.7% *vs.* 47.8%	12.8% *vs.* 22.5%	Not described
Ramlau R. *et al.* [18]	Docetaxel 75 mg/m^2 *vs.* Oral Topotecan days 1-5	7.75 months *vs.* 7.0 months	29% *vs.* 25%	5% in each group	6.25 months *vs.* 5.75 months
Paz-Ares L. *et al.* [19]	Docetaxel 75 mg/m^2 *vs.* Paclitaxel poliglumex	6.9 months (both arms)	29% *vs.* 25%	12% *vs.* 8%	45% *vs.* 40% (at 12 wks)
Krzakowski M. *et al.* [20]	Docetaxel 75 mg/m^2 *vs.* Vinflunine 320 mg/m2	7.2 months *vs.* 6.7 months	Not described	5.5% *vs.* 4.4 %	4.3 *vs.* 4.7 months
Hana N *et al.* [21]	Docetaxel 75 mg/m^2 *vs.* Pemetrexed 500 mg/m2	7.9 months *vs.* 8.3 months	29.7%	8.8 % *vs.* 9.1%	5.3 months *vs.* 4.6 months
Garon E *et al.* [23]	Docetaxel 75 mg/m2 +/- Ramucirumab 10 mg/kg	10.5 months *vs.* 9.1 months	Not described	23% *vs.* 14%	3.75 months *vs.* 3.25 months
CheckMate 017 [9]	Docetaxel 75 mg/m^2 *vs.* Nivolumab 3 mg/kg	6 months *vs.* 9.2 months	24% *vs.* 42%	9% *vs.* 20%	8.4 months *vs.* Not reached

benefited from treatment with nivolumab. Hence, we can assume that the use of paclitaxel as first-line treatment did not significantly influence the ultimate outcomes.

Would it be Possible that Most of the Benefit Observed in OS with Nivolumab Could be Explained Exclusively by Sustained Response?

This presumption is probably correct; however, subsequent treatments might have influenced outcomes in the nivolumab arm. Patients treated with nivolumab experienced a 20% response rate with a median duration of response that was not reached in this interim analysis. At the time of cutoff, 16% of patients continued treatment with nivolumab compared to 1.6% of patients receiving docetaxel. In concordance with the results observed in other tumors in which PD-1 inhibitors proved to have a clear therapeutic benefit, such as melanoma, patients who respond to treatment can achieve a prolonged benefit [25]. This phenomenon is extremely unusual with chemotherapy but it is sometimes observed with the use of immunotherapy in advanced cancers. Interestingly, in the CheckMate 017, although the median PFS was statistically significant, it was not clinically relevant. Moreover, 40% of patients in the nivolumab arm and 38% in the docetaxel arm received subsequent therapies once they showed disease progression. Specifically, 29% of the patients originally allocated to receive nivolumab were treated with docetaxel afterward. The outcomes of this subgroup of patients were not published and it is unknown how this treatment could have affected this arm in terms of OS.

How Toxic is the New Standard?

In addition to the survival benefit, nivolumab showed a better toxicity profile compared to docetaxel. Patients with SCCLC often have other morbidities related to tobacco consumption. Quality of life is a major concern in treating patients with advanced NSCLC. Docetaxel is generally poorly tolerated among patients, with neutropenia and peripheral neuropathy the main dose-limiting toxicities for patient care. All grade adverse events including grades 3 and 4 were less frequent with nivolumab. Severe immune-related adverse events with nivolumab were seen in a relatively small proportion (~5%) and these can be safely managed with drug discontinuation and systemic steroids.

To conclude, when adding up all the information available we find that nivolumab clearly demonstrated a 40% reduction in the risk of death with a significant benefit in terms of toxicities. Hence, it will be appropriate to consider this drug as the new standard of care for the second-line treatment of patients with advanced SCCLC.

What is the Cost of this New Standard Approach?

Treatment costs are key determinants of patient's access to cancer drugs worldwide, especially in low and middle income countries [26]. The financial burden of medical treatment in cancer is a concern for patients, their families, health systems and country economics. Nivolumab costs - all in US dollars - $2,454 per 100 mg/10 ml vial and $991 for the 40 mg/4 ml. Based on the recommended dose of 3 mg/Kg every 2 weeks, the monthly cost to treat a patient weighting 75 kg and measuring 1.7 meters is $6,890 and $20,670 every trimester. The cost of docetaxel varies between brands from $2,762 to $888, and it is widely available in multiple countries. Taking into account the lowest price, one trimester of treatment with docetaxel costs $7,105 almost one third compared to nivolumab. Because 1.8 million people were diagnosed with lung cancer in 2013 and 1.6 million people died of the disease, the costs of treating patients with immunotherapy is a mayor financial problem [27]. Together with the encouraging clinical data with nivolumab, cost effectiveness studies should prompt more information and evidence on the cost-efficacy of this drug. The EGFR inhibitors proved to be cost-efficient in patients with sensitizing EGFR mutated lung adenocarcinomas compared to first line, previous standard of care, cisplatin and pemetrexed [28]. Hopefully, immune checkpoints inhibitors could meet this endpoint with reliable biomarkers that could select patients benefiting the most of these treatments. Developing effective drugs for cancer treatment is as important as guaranteeing population access to these medications. Pharmaceutical companies, insurance and governments should work together to provide adequate access to these beneficial drugs.

WHAT IS THE POTENTIAL ROLE PLAYED BY THE BIOMARKERS?

Effective biomarkers that can predict which patients will benefit the most from these new agents are undoubtedly required to optimize costs and benefits. In parallel to the development of multiple new molecules that are currently in the pipeline at many pharmaceutical companies, different platforms for PD-L1 expression are currently also under investigation. In the case of nivolumab for SCCLC, CheckMate 017 showed that different expression levels of PD-L1 (negative <1% and positive with >1%, >5%, and >10% in tumor cells) did not necessarily correlate with tumor response. ORRs ranged from 17% in PD-L1 negative tumors to 19% with >10% expression level in 117 evaluable patients.

In another clinical trial that was similar but performed in patients with non-squamous histology, the CheckMate 057, patients with <1% of PD-L1 expression had equivalent OS compared to patients treated with docetaxel [29]. On the other side, patients whose tumors expressed >1%, >5%, and >10% PD-L1 in cell membranes experienced higher ORRs and longer OS than their counterparts. In patients with >10% expression of PD-L1, the OS observed with nivolumab was 19.4 months in comparison with a modest 8 months seen with docetaxel (HR = 0.40; interaction P = 0.0002). Thus, it is apparent that in non-squamous NSCLC, PD-L1 expression seems to better correlate with clinical outcomes. However, considering that both trials used the same immunohistochemical method for PD-L1 quantification and exactly the same drug, why such an obvious difference?

The KEYNOTE-001 study is an extended phase I trial that evaluated treatment with pembrolizumab (an anti-PD-1 monoclonal antibody) in 495 patients with advanced NSCLC at three different dosing schedules [30]. In the whole population, ORR was 19.5% and median duration of response was 12.5 months. This trial evaluated PD-L1 expression using the DAKO EnVision FLEX plus HRP-Polymer Kit (DAKO K8012; Dako, Carpinteria, CA, USA) with the 22C3 monoclonal antibody (Merck & Co., Inc., Kenilworth, NJ, USA). When stratifying by PD-L1 expression (<1%, 1-49%, and >50% of tumor cells) tumor expression of >50% correlated with a higher ORR and prolonged PFS and OS. In this study, 85 patients had SCC histology and a 23.5% ORR was documented. In some of these patients (N = 44), PD-L1 expression was correlated with response rates. In 14 cases with >50% PD-L1 expression, the ORR was 64%, compared to an ORR of only 23% in 22 patients with PD-L1 levels of 1-49%. No responses were seen in 8 patients with <1% of PD-L1 expression. Despite the small sample size in this trial, there seems to be at least some correlation between PD-L1 expression and response rate in patients with SCCLC.

Further evidence can be added from other experiences with different drugs still under investigation. MEDI4736 is an anti-PD-L1 monoclonal antibody (AstraZeneca, London, UK). In an extended phase I study in patients with NSCLC, ORR was 21% among 88 patients with SCC histology [31]. In this population, a 33% response rate was observed in patients with PD-L1 positive tumors compared with a rate of only 8% in the PD-L1 negative counterpart. This trial used the SP263 monoclonal antibody and considered staining positive when PD-L1 was expressed in >25% of tumor cells at any intensity. The Poplar phase II clinical trial evaluated the efficacy of treatment with atezolizumab, another anti-PD-L1 monoclonal antibody (Roche, Basel, Switzerland), versus docetaxel in previously treated patients with NSCLC [32]. PD-L1 expression was evaluated with SP142 monoclonal antibody and the Ventana automated immunohistochemistry platform (Ventana Medical Systems, Tucson, AZ, USA). PD-L1 staining was assessed in both tumoral and tumor-infiltrating immune cells, and the intensity of expression was scored from 1 to 3 in both groups. In the whole population, OS was not significantly prolonged, but when stratified by PD-L1 staining, patients with 3+ staining intensity had a 54% risk reduction of death compared to docetaxel. In contrast, in patients with no staining, there was no difference in OS compared to docetaxel. A total of 34% of the population in both arms had SCC histology, and data on response rate and immunohistochemical scoring in this subtype have not yet been presented. Interestingly, this is the first trial to evaluate PD-L1 expression in the tumor and immune cells in NSCLC.

By considering this information, we could confirm that PD-L1 expression probably corresponds with better outcome; however, it is important to remark that some patients with PD-L1 negative tumors can still achieve benefit from these therapies. This last issue clearly affects the

credibility of PD-L1 as a solid biomarker especially when it is compared with other well-established and clinically validated biomarkers such as human epidermal growth factor receptor 2 (HER2) or the hormone receptors. In that sense, some issues may affect the biomarker assessment. Tumor heterogeneity, point in the treatment when the sample is taken, tumor sample handling, and anatomical site of the biopsies (*i.e*., primary or metastatic), as well as the sensitivity and specificity of the different methodologies applied are some of the variables that can modify the results. Other variables to assess include the subtype of cells evaluated (*i.e*., tumoral or immune cells), the subcellular location of the protein expression, the cutoff value chosen to confirm positive expression, and the pattern of distribution within the tumor itself [33].

Moreover, it has been reported that in NSCLC, tobacco carcinogen exposure corresponds with a high mutational rate, which subsequently results in a higher tumoral neoantigen burden [30, 34, 35]. In the CheckMate study discussed in this review, 92% of patients were smokers or former smokers. We could hypothesize that this fact may explain why PD-L1 expression was not as efficient a biomarker as it had been reported to be in other subtypes. More investigation is needed to support this presumption.

Lastly, it is undeniable that further research focused on reliable biomarkers is sorely needed. It is fairly obvious that one biomarker alone might be insufficient to explain the complex interaction between immunity and cancer cells. Beyond the PD-1/PD-L1 interaction, other ligands such as PD-L2 also participate in immune regulation. Multiple immune checkpoints play major roles in tumor immunological tolerance including LAG3, TIM3, and OX40, among others. It is expected that these and other markers will soon be employed as part of our daily practice [36].

CONCLUSION

To conclude, we can realistically state that we are probably witnessing the beginning of a completely revolutionary approach to the treatment of lung cancer. Immunotherapy clearly represents a treatment modality that has very little in common with conventional chemo-therapeutic agents. The latter used to be the cornerstone of treatment for patients with metastatic lung cancer. This paradigm has now been challenged for the first time. From the practical perspective, clinicians will now begin to rapidly learn and perfect the best ways in which to administer these new drugs in daily practice, adapting to the more complex types of patients who are usually not selected for clinical trials. However, if adverse events and excessive financial costs do not limit the widespread use of immunotherapy, we can only foresee an auspicious future ahead.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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PATIENT'S CONSENT

Declared none.

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