Critical Reviews in Oncology / Hematology 129 (2018) 27–39

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Immune-checkpoint inhibitors in non-small cell lung cancer: A tool to improve patients' selection

Giuseppe Luigi Banna[a,*], Francesco Passiglia[b], Francesca Colonese[c], Stefania Canova[c], Jessica Menis[d], Alfredo Addeo[e], Antonio Russo[b], Diego Luigi Cortinovis[c]

[a] Division of Medical Oncology, Cannizzaro Hospital, Via Messina 829, 95126, Catania, Italy
[b] Department of Surgical, Oncological and Stomatological Disciplines, University of Palermo, Italy
[c] Medical Oncology Unit, San Gerardo Hospital, Monza, Italy
[d] Department of Oncology Medicine, Gustave Roussy, Université Paris-Saclay, Villejuif, France
[e] Oncology Department, University Hospital Geneva, 1205 Geneva, Switzerland

ARTICLE INFO

Keywords:
Immune-oncology
Immune-checkpoint inhibitors
Non-small cell lung cancer
Biomarkers
Predictive factors

ABSTRACT

The identification of reliable predictive biomarkers of efficacy or resistance to immune-oncology (I–O) agents is a major issue for translational research and clinical practice. However, along with PDL1 and molecular features other clinical, radiological and laboratory factors can be considered for the selection of those patients who would not be the best candidate for immune-checkpoint inhibitors (ICPIs). We examined these factors, emerging from the results of currently available studies in non-small cell lung cancer (NSCLC), aiming to provide a useful and manageable tool which can help Oncologists in their everyday clinical practice.

A thorough patient evaluation and close clinical monitoring, due to limited, early or inconclusive currently available data, should be deserved for patients with a pre-existing symptomatic chronic obstructive pulmonary disease, age > 75 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≥ 1, a time to progression (TTP) < three months and progressive disease (PD) as the best response to the previous treatment, hepatitis or HIV-infections, high neutrophil to lymphocyte ratio (NLR), or on treatment with high-dose steroids, when the use of ICPIs is considered. Limited data are available to consider that ICPIs are safe in patients with interstitial lung disease, bronchiolitis obliterans organizing pneumonia and autommune diseases. Early evidence on steroids, vaccinations and antibiotics suggest their possible interaction with ICPIs and need to be more investigated in clinical trials. Oncogene-addicted NSCLC harboring EGFR-mutations and low tumor-infiltrating T-lymphocytes (TILs) seems not to gain benefit from I–O.

1. Introduction

Developing personalized therapies according to the tumors' molecular profile has emerged as new treatment paradigm in different tumor types including lung cancer (Banna et al., 2017a) (Novello et al., 2011). The discovery of epidermal growth factor receptor (EGFR) activating mutations as oncogene driver in 2004 and the development of the EGFR-tyrosine kinase inhibitors, represented the first example of this innovative and effective approach in lung cancer (Banna and Tiseo, 2015; Landi et al., 2014). Similarly, in NSCLC patients whose tumor harbors anaplastic lymphoma kinase (ALK) rearrangements, the ALK-inhibitors demonstrated a significant superiority over platinum chemotherapy (Califano et al., 2015). However, in those patients not harboring an EGFR or ALK molecular alterations, a limited response to chemotherapy is still observed (Banna et al., 2017b). A deeper understanding of the molecular basis of tumor immunogenicity and cancer immune-escape has subsequently led to the advent of new immunotherapeutic agents which are able to modulate the anti-tumor immune response by targeting the programmed cell death 1 (PD1)/programmed cell death 1 ligand (PD-L1) axis. The Oncology community has been celebrating the advent of the first immune-checkpoint inhibitor (ICPI) pembrolizumab as the new standard first-line option in about 30% of patients with advanced NSCLC whose tumors overexpress PD-L1 in ≥ 50% of tumor cells (Reck et al., 2016), and in combination with chemotherapy in nonsquamous NSCLC patients independently by PD-L1 tumor expression (Gandhi et al., 2018). Other first-line phase III randomized trials were reported in NSCLC patients; one of them with nivolumab in patients with PD-L1 expression ≥ 5% in tumor cells failed to demonstrate a survival benefit over chemotherapy (Carbone et al., 2017); another trial with nivolumab plus ipilimumab in patients with

* Corresponding author.
E-mail addresses: gbanna@yahoo.com, oncologiacatania@yahoo.com (G.L. Banna).

https://doi.org/10.1016/j.critrevonc.2018.06.016
Received 20 February 2018; Received in revised form 16 June 2018; Accepted 18 June 2018

Table 1
Completed phase III randomized trials with ICPIs in NSCLC.

Drug Reference	Line Setting	Histology	Trial	PDL1 expression	HR OS (95% CI) P value	HR PFS (95% CI) P value
Pembrolizumab (Reck et al., 2016)	First Advanced	NSCLC	KN-024	≥50%	0.60 (0.41 -0.89) P = 0.005	0.50 (0.37-0.68) P < 0.001
Nivolumab (Carbone et al., 2017)	First Advanced	NSCLC	CM-026	≥5%	1.02 (0.80-1.30) NR	1.15 (0.91-1.45) P = 0.25
Pembrolizumab + Chemotherapy (Gandhi et al., 2018)	First Advanced	NonSq	KN-189	any	0.49 (0.38-0.64) P < 0.001	0.52 (0.43-0.64) P < 0.001
Nivolumab + Ipilimumab[a] (Hellmann et al., 2018)	First Advanced	NSCLC	CM-227	any	NR	0.58[a] (0.41-0.81) P < 0.001
Nivolumab + Chemotherapy (Borghaei et al., 2018)	First Advanced	NSCLC	CM-227	< 1%	NR	0.74 (0.58-0.94) P = NR
Pembrolizumab + Chemotherapy (Lopes et al., 2018)	First Advanced	NSCLC	KN-042	≥1%	0.81 (0.71-0.93) P = 0.0018	1.07 (0.94-1.21) P = NR
Pembrolizumab + Chemotherapy (Paz-Ares et al., 2018)	First Advanced	Sq	KN-407	any	0.64 (0.49-0.85) P = 0.0008	0.56 (0.45-0.70) P < 0.0001
Atezolizumab + Bevacizumab- Chemotherapy (Socinski et al., 2018)	First Advanced	NonSq	IMPower150	any	0.78 (0.64-0.96) P = 0.0164	0.59 (0.50-0.70) P < 0.0001
Atezolizumab + Chemotherapy (Jotte et al., 2018)	First Advanced	Sq	IMPower131	any	0.96[b] (0.78-1.18) P = 0.69	0.71 (0.60-0.85) P = 0.0001
Pembrolizumab (Rittmeyer et al., 2017)	Second Advanced	NSCLC	KN-010	≥1%	0.71 (0.58-0.88) p = 0.0008	0.88 (0.74-1.05) p = 0.07
Nivolumab (Brahmer et al., 2015)	Second Advanced	Sq	CM-017	NA	0.59 (0.44-0.79) P < 0.001	0.62 (0.47-0.81) P < 0.001
Nivolumab (Borghaei et al., 2015)	Second Advanced	NonSq	CM-057	NA	0.73 (0.59-0.89) P = 0.002	0.92 (0.77–1.11) P = 0.39
Atezolizumab (Herbst et al., 2016)	Second Advanced	NSCLC	OAK	NA	0.73 (0.62–0.87) p = 0.0003	0.95 (0.82–1.10) NR
Durvalumab (Antonia et al., 2017)	After CTRT Stage III	NSCLC	PACIFIC	NA	NR	0.52 (0.42-0.65) P < 0.001

Abbreviations: CM, Checkmate; ICPIs, immune-checkpoint inhibitors; CTRT, chemo-radiotherapy; KN, Keynote; NonSq, non-squamous; NR, not reported; NSCLC, non-small cell lung cancer; Sq, squamous.
[a]Results refer only to patients with high tumor mutational burden, as defined by at least 10 mutations per megabase.
[b]Results refer to first interim analysis.

high tumor mutational burden (as defined by at least 10 mutations per megabase) met its primary endpoint of progression-free survival (PFS) (Hellmann et al., 2018); the results of other five trials (Borghaei et al., 2018; Lopes et al., 2018; Paz-Ares and Luft, 2018; Jotte et al., 2018; Socinski et al., 2018) (Socinski et al., 2018) were presented at the 2018 American Society for Clinical Oncology Conference and are summarized in Table 1. However, also the patients who currently do not receive an ICPI upfront, may benefit from ICPIs in further lines of treatment.

Four completed phase III randomized trials have consistently demonstrated that ICPIs, including nivolumab, pembrolizumab, and atezolizumab significantly improve overall survival (OS) and quality of life (QoL) as compared with the standard second-line therapy, docetaxel, in both squamous and non-squamous NSCLC patients who progressed to first-line therapy (Borghaei et al., 2015; Brahmer et al., 2015; Herbst et al., 2016; Rittmeyer et al., 2017). The phase III randomized trials with ICPIs in NSCLC are summarized in Table 1.

Based on these data, the US Food and Drug Administration (FDA) and the European Medical Agency (EMA) have approved pembrolizumab in pre-treated NSCLC patients with tumor PD-L1 expression > 1% while both nivolumab and atezolizumab received regulatory approval regardless of tumor PD-L1 expression. A recent survival update of the CheckMate-003 phase I study revealed that about 15% of NSCLC highly pre-treated patients were still alive after 5 years of therapy with nivolumab, suggesting that these drugs could offer the potential for a durable disease control and long-term survival in a limited subgroup of patients (Brahmer and Jackman, 2017). Conversely, about 50% of pre-treated patients do not gain benefit from ICPIs, and about 10–15% of them even develop “hyper-progression” (Champiat et al., 2017; Ferrara et al., 2017a), suggesting that identifying selection criteria for I–O represents an urgent and unmet clinical need.

Beyond the tumor PDL1 expression, other biological parameters, such as the tumor mutation burden (TMB) or tumor-infiltrating T-lymphocytes (TILs), have been explored as possible predictive biomarkers, including both genomic and immunological features.

Besides these biomarkers, some other clinical, laboratory and pathological parameters should be considered in the clinical practice to improve the selection of patients who are more likely to benefit from