Editorial

Immunotherapy as a targeted therapy in non-small cell lung cancer

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Introduction

In the present era, non-small cell lung cancer (NSCLC) represents the principal cause of death for cancer worldwide (about 80%), showing a high incidence (about 1,350,000 new diagnosis each year) and mortality (about 1,180,000 deaths each year) (1).

In recent years, nevertheless, the NSCLC treatment algorithm has remarkably changed, allowing to tailor therapy according to genetic mutations (*ALK+/EGFR+/ROS1+* NSCLC) and to immune system alterations [programmed death ligand-1 (PD-L1) expression/overexpression].

The PD-L1/PD-1 axis

PD-L1, encoded by the *PDCDL1* gene and found on chromosome 9, is a member of the B7 protein family expressed on B cells, T cells, dendritic cells, macrophages, and mast cells [mainly on antigen-presenting cells (APC)] (2) and its functions depend on binding with programmed death 1 (PD-1, CD279), a transmembrane receptor physiologically found on lymphocytes (preferentially on regulatory T cells) and myeloid cells (3).

The PD-1/PD-L1 axis is a keystone in the inhibition of T-cell activity and expansion, in particular the PD-L1-PD-1 ligation causes the recruitment of Src-homology 2 domain-containing phosphatases 1 and 2 (SHP-1/SHP-2) that determines the de-phosphorylation of fundamental signaling kinases in the mechanisms of central and peripheral tolerance (4,5); however, cancer cells too have adopted this PD-1/PD-L1 mechanism in order to evade immune system response (immunosurveillance) and to create an immunosuppressive microenvironment, therefore escaping from T cell cytolysis (6).

PD-L1 and NSCLC

In multiple tumor types, NSCLC among them, in fact, PD-L1 can be overexpressed, representing a therapy target and helping to determine the treatment of choice.

In particular, the American Society of Clinical Oncology (ASCO) guidelines on immune checkpoint inhibitors (ICI) recommend the use of pembrolizumab for patients with nonsquamous-histology NSCLC or squamous-histology NSCLC without any driver genes mutations (*EGFR/ALK/ROS1*), as the first-line treatment in monotherapy if they show a high PD-L1 expression (tumor proportion score ≥50%), instead immunotherapy could be administrated as second-line treatment after first-line chemotherapy in NSCLC patients positive for PD-L1 expression [Tumor Proportion Score (TPS) ≥1%], lastly, if tumor has negative or unknown PD-L1 expression, clinicians should use second-line single agent nivolumab or atezolizumab; the administration of immunotherapy is contraindicated in patients with active autoimmune disease (7).

Pembrolizumab

Pembrolizumab is a humanized monoclonal antibody against PD-1, this drug performs with high efficacy in advanced NSCLC with high level of PD-L1 expression [PD-L1 expression on at least 50% of tumor cells (TC)]. In the KEYNOTE-024 study, pembrolizumab was compared

with platinum-based chemotherapy in a basal NSCLC setting: pembrolizumab showed a high median progression-free survival (PFS) of 10.3 months [95% confidence interval (CI), 6.7 months to not reached] versus 6.0 months (95% CI, 4.2–6.2 months) [hazard ratio (HR) for disease progression (PD) or death, 0.50; 95% CI, 0.37–0.68; P<0.001], a high estimated rate of overall survival at 6 months of 80.2% versus 72.4% (HR for death, 0.60; 95% CI, 0.41–0.89; P=0.005), a response rate (RR) of 44.8% *vs.* 27.8% and a minor number of adverse events of any grade (73.4% *vs.* 90.0%) and, in particular, of grade 3, 4, or 5 (26.6% *vs.* 53.3%) (8).

Furthermore, pembrolizumab showed activity in a second line setting of NSCLC patients with PD-L1 expression on at least 1% of TC. In the KEYNOTE-010 study, pembrolizumab, when compared to docetaxel, performed with a high median overall survival (10.4 *vs.* 8.5 months) and a relevant longer overall survival (HR 0·71, 95% CI, 0.58–0.88; P=0.0008), and, as showed in the KEYNOTE-024, adverse events of any grade occurred in a minor number of patients (13% versus 35%) (9).

Nivolumab

Nivolumab is a fully human monoclonal antibody against PD-1, approved in pre-treated squamous and nonsquamous NSCLCs that feature negative or ≥1% PD-L1 expression (data from CheckMate-017 and CheckMate-057 trials respectively).

In the CheckMate-017 trial nivolumab was compared to docetaxel, showing a high median overall survival [9.2 (95% CI, 7.3–13.3) versus 6.0 (95% CI, 5.1–7.3) months], with a significant reduction of the risk of death [41% lower with nivolumab than with docetaxel (HR, 0.59; 95% CI, 0.44–0.79; P<0.001)] furthermore the overall survival rate at 1 year of administration was 42% (95% CI, 34–50%) versus 24% (95% CI, 17–31%); in agreement with these data, the RR is 20% with nivolumab versus 9% with docetaxel (P=0.008), moreover treatment-related adverse events of high grade (3 or 4) are less frequent (7%) with nivolumab than docetaxel (55%). Differently from pembrolizumab, this trial shows that the response to nivolumab is independent from the expression of PD-L1 (10).

On the other hand, CheckMate-057 shows that also in nonsquamous NSCLC setting the administration of nivolumab gives more benefits than treatment with docetaxel, in particular for PD-L1 positive patients (TPS ≥1%), with an increasing RR as the PD-L1 expression level increases: a median overall survival of 12.2 months (nivolumab) (95% CI, 9.7–15.0 months) versus 9.4 months (docetaxel) (95% CI, 8.1–10.7 months) (HR for death, 0.73; 96% CI, 0.59–0.89; P=0.002), 39% overall survival rate at 18 months (95% CI, 34–45%) versus 23% (95% CI, 19–28%), 19% RR versus 12% (P=0.02) and treatment-related adverse events of high grade (3 or 4) in 10% of the patients with nivolumab as compared with 54% with docetaxel; furthermore, in cases featuring no difference in overall survival between nivolumab and docetaxel (no PD-L1 expression), the safety profile and the durability of response of nivolumab compared to docetaxel qualify nivolumab as the best treatment (11).

Atezolizumab

Thanks to the OAK trial data, Atezolizumab is the first second-line humanized anti PD-L1 monoclonal antibody approved in NSCLC patients. In fact, compared to docetaxel, it shows a median overall survival of 13.8 (95% CI, 11.8–15.7) *vs.* 9.6 (95% CI, 8.6–11.2) months (HR 0.73; 95% CI, 0.62–0.87; P=0.0003) and in particular an overall survival of 15.7 (95% CI, 12.6–18.0) *vs.* 10.3 (95% CI, 8.8–12.0) months in patients with an expression of PD-L1 in the TC or in tumor-infiltrating immune cells (IC) (HR 0.74; 95% CI, 0.58–0.93; P=0.0102), however it also shows efficacy in patients with a low or undetectable PD-L1 expression, with a median overall survival of 12.6 *vs.* 8.9 months; HR 0.75; 95% CI, 0.59–0.96.

Moreover, this study shows that the overall survival improvement is similar in patients with squamous (HR 0.73; 95% CI, 0.54–0.98) or non-squamous (HR 0.73; 95% CI, 0.60–0.89, histology) and with less high-grade adverse events (15% versus 43% with docetaxel) (12).

Beyond PD-L1: tumor mutational burden (TMB)

These data show that PD-L1 is a valid biomarker of response to immunotherapy, but it also shows important limitations because it can't explain the response to therapy in patients without PD-L1 expression (10,12). To overcome these limitations, it is relevant to take into account the TMB, which represents the total number of mutations per DNA coding region.

According to literature, it is known that patients with a history of smoking, and therefore patients with a high TMB, experience a better response to immunotherapy (13), in particular, a recent meta-analysis evaluating 6 studies (on 2,389 patients) has highlighted that in a first-line treatment setting, in patients with smoking history, the PFS increases with the administration of immunotherapy, when compared to chemotherapy (HR, 0.85; 95% CI, 0.71–1.10, P=0.07) and that, similarly, in a second-line setting, the overall survival increases (HR, 0.70; 95% CI, 0.63–0.79; P<0.00001) (14); congruently several other studies have linked a higher TMB to benefit to immunotherapy in terms of objective response, durable clinical benefit and PFS (15-17).

For this reason, TMB is now adopted as biomarker in several studies; in a recent trial naive patients with stage IV squamous or non-squamous NSCLC and with a high TMB (≥10 mutations per megabase) were treated with nivolumab with or without ipilimumab versus chemotherapy: n=1,189 patients that had an expression of PD-L1 of at least 1% were randomly assigned (in a 1:1:1 ratio), with stratification according to tumor histologic type (squamous *vs.* nonsquamous), to receive nivolumab (3 mg/kg every 2 weeks) plus ipilimumab (1 mg/kg every 6 weeks), standard of care platinum doublet chemotherapy based on tumor histologic type every 3 weeks for up to four cycles, or nivolumab (240 mg every 2 weeks), while n=550 patients with a PD-L1 expression level of less than 1% were randomly assigned (in a 1:1:1 ratio), with stratification according to tumor histologic type, to receive nivolumab (3 mg/kg every 2 weeks) plus ipilimumab (1 mg/kg every 6 weeks), standard of care platinum doublet chemotherapy based on tumor histologic type every 3 weeks for up to four cycles, or nivolumab (360 mg) plus platinum doublet chemotherapy based on tumor histologic type every 3 weeks for up to four cycles.

Patients with a high TMB showed a longer PFS when treated with nivolumab plus ipilimumab, when compared with those treated with chemotherapy, in particular, the 1-year PFS rate was 42.6% with nivolumab plus ipilimumab versus 13.2% with chemotherapy, the median PFS was 7.2 (nivolumab + ipilimumab) (95% CI, 5.5–13.2) versus 5.5 (chemotherapy) (95% CI, 4.4–5.8) months (HR for PD or death, 0.58; 97.5% CI, 0.41–0.81; P<0.001) and the objective RR was 45.3% with nivolumab plus ipilimumab versus 26.9% with chemotherapy, but, most importantly, these results were independent from the PD-L1 expression, in fact, the 1-year PFS rate was found to be 42% with nivolumab plus ipilimumab versus 16% with chemotherapy (PD-L1 ≥1% group) (HR for PD or death, 0.62; 95% CI, 0.44–0.88) and 45% with nivolumab plus ipilimumab versus 8% with chemotherapy (PD-L1 <1% group) (HR for PD or death, 0.48; 95% CI, 0.27–0.85) (18).

Future perspectives: tumor infiltrating lymphocytes (TILS)

The CD8+ TILS identified in the tumor microenvironment are related to a better survival in different tumors, including NSCLC (19). Several studies report their association with anti PD-1 therapy response, in particular, one of the most recent trials analyzed a cohort of n=26 NSCLC, showing that tumors with a CD8+ lymphocyte count under 886/mm^2 showed low RR to ICI therapy (16.7%, P=0.046), while tumors with a CD8+ lymphocyte count between 886–1,899/mm^2 showed a high RR (60%, P=0.017) and that NSCLC harboring CD8+/CD4+ ratios lower than 2 presented a low RR (13.3%), opposed to those harboring ratios higher than 2 [RR ranging between 43% and 50% (P=0.035)] (20).

Future perspectives: interleukine-8 (IL-8)

Different studies showed a key role as a predictor of response for IL-8, a member of the cysteine-X-cysteine (CXC) chemokine family, produced by malignant cells and tumor microenvironment cells in different tumor types (NSCLC included) and characterized by a protumoral activity (21).

In a recent study, the levels of IL-8 in serum were evaluated at different times (at baseline and at 2–4 weeks after the first dose) in a cohort of 19 NSCLC patients treated with nivolumab or pembrolizumab: in n=12 responders to the therapy, the median serum concentration of IL-8 decreased significantly when the patients showed the best response (BR) [baseline 20.8 (Q1–Q3: 15.1–29) pg/mL versus BR 6.5 (Q1–Q3: 0–19) pg/mL; P=0.005], while in the remnant non-responders (n=7), median IL-8 serum levels significantly increased at the moment of PD, when compared with baseline levels [baseline 12 (Q1–Q3: 0–42) pg/mL versus PD 51 (Q1–Q3: 22–77) pg/mL; P=0.016].

This shows that changes in serum IL-8 levels are strongly associated with response to anti-PD-1 treatment [median change (%): responders: –45.6% (Q1/Q3: –59.1%/–15.1%)],

non-responders +27.0% (Q1–Q3: 8.3–52.1%); P<0.0001], with an area under the curve (AUC) of 1.00 (95% CI, 1.00–1.00, P=0.0004) and a sensitivity and specificity to predict response of 85.7% (95% CI, 42.1–99.6%) and 100% (95% CI, 73.5–100%), respectively, with a cut-off point of a >9.2% change; lastly early decreases in serum IL-8 levels were associated with longer overall survival (P=0.015), while increases in serum IL-8 levels were associated with poorer prognosis (HR 9.78; 95% CI, 1.0–90.1; P=0.004). Interestingly, two patients that presented pseudoprogression with an increase in the dimension of lesions showed a decrease of IL-8 concentration in serum (22).

However, although undoubtedly promising, further and larger studies are needed in order to confirm and elaborate on these results.

Future perspectives: PD-L1 amplification

In agreement with literature, another potential biomarker for immunotherapy efficacy is represented by *PD-L1* gene amplification.

In a recent study 118,187 tumor samples from different solid tumors were evaluated for *PD-L1* copy number alteration (CNA), PD-L1 expression, TMB and microsatellite instability (MSI) status: of these n=843 patient samples (0.7%) presented 6 or more CNAs in the *PD-L1* gene, in particular squamous cell carcinoma of lung [50 (1.7%); P<0.001], breast carcinoma [111 (1.9%); P<0.001], head and neck squamous cell carcinoma [39 (3.1%); P<0.001], undifferentiated soft tissue sarcoma [13 (3.9%); P<0.001], thyroid anaplastic carcinoma [9 (5.1%); P<0.001], unknown primary squamous cell carcinoma [16 (2.0%); P=0.01], nasopharyngeal carcinoma [5 (5.1%); P=0.03], and kidney sarcomatoid carcinoma [4 (6.1%); P=0.04]; conversely a low percentage of *PD-L1* amplification was identified in prostate cancer, melanoma, pancreatic and colorectal cancer. An elevated number of *PD-L1*-amplified tumors had a low to intermediate TMB (84.8%), while only 128 PD-L1-amplified tumors (15.2%) were classified as having high TMB; considerably, this study found that MSI-H(igh) and *PD-L1* amplification are not mutually exclusive, in particular n=5 out of 741 tested patients (0.7%) with *PD-L1* amplification were MSI-H.

Nine patients from one center with *PD-L1* amplification were treated with checkpoint blockade (five patients were treated with PD-1/PD-L1 inhibitor monotherapy, 3 with a PD-1/PD-L1 inhibitor plus an investigational agent and one with an anti-PD-1 and anti-CTLA4 combination therapy): six of 9 patients (66.7%) had objective responses, the median PFS among these 9 patients was 15.2 (range, 1.6 to ≥24.1) months; responders included one patient with glioblastoma (PFS, ≥5.2 months), 2 patients with head and neck squamous cell cancer (PFS, ≥9 and 15.2 months), 2 patients with metastatic basal cell cancer (PFS, 3.8 and ≥24.1 months), and 1 patient with urothelial cancer (PFS, ≥17.8 months) (23).

The present results suggest that further prospective clinical trials regarding ICI treatment in *PD-L1*-amplified cancers are needed in order to validate these findings.

Predictor of hyperprogression: MDM2

Careful attention should be paid on an important adverse event of immunotherapy: hyperprogression. According to Kato *et al.*, hyperprogression is defined as a time to treatment failure (TTF) <2 months, with the association of an increase >50% in tumor burden compared with pre-immunotherapy imaging obtained within 2 months of the initiation of immunotherapy and a >2-fold increase in progression pace.

In a recent study, 155 patients with different cancers receiving immunotherapy were analyzed by next generation sequencing: in six patients (4%) *MDM2* family amplification (*MDM2/4*) was identified, this finding was associated with poorer clinical outcomes (TTF <2 months) (OR >11.9; P=0.001) and was still statistically significant after multivariate analysis (P=0.02) and bootstrap analysis (P=0.001). In fact, four of these patients experienced hyperprogression (24).

Conclusions

Taking into account the recent findings coming from the studies evaluating the role of new predictors and comparing them with the existing data reported in the literature (*Table 1*), immuno-oncology could—and currently is starting to—gain some additional arrows to its quiver, helping to tailor therapy to the patients' characteristics and shifting the existing paradigm of biomarkers for immunotherapy.

Table 1 Biomarkers and immunotherapy

Study and drug used	Biomarker	Outcome measure	P*
Keynote-024, Reck *et al.* (1st line pembrolizumab)	PD-L1 ≥50%	HR for death: 0.60	0.005
Keynote-010, Herbst *et al.* (2nd line pembrolizumab)	PD-L1 ≥1%	HR for death: 0.71	0.0008
Checkmate-017, Brahmer *et al.* (2nd line nivolumab)	PD-L1 ≥1%	HR for death: 0.59	<0.001
	PD-L1 <1%	HR for death: 0.59	
Checkmate-057, Borghaei *et al.* (2nd line nivolumab)	PD-L1 ≥1%	HR for death: 0.73	0.002
	PD-L1 <1%	Not significant	
OAK, Rittmeyer *et al.* (2nd line atezolizumab)	TC1/2/3 or IC1/2/3	HR for death: 0.74	0.0003
	TC0 or IC0	HR for death: 0.75	
Checkmate-227, Hellmann *et al.* (1stline: nivolumab + ipilimumab)	TMB ≥10 MPM + PD-L1 ≥1%	HR for PD or death: 0.62	<0.001
	TMB ≥10 MPM + PD-L1 <1%	HR for PD or death: 0.48	
Uryvaev *et al.* (ICI therapy)	CD8+ count: under 886/mm^2	RR to ICI: 16.7%	0.046
	CD8+ count:886 to 1,899/mm^2	RR to ICI: 60%	0.017
	CD8+/CD4+ ratios <2	RR to ICI: 13.3%	0.035
	CD8+/CD4+ ratios >2	RR to ICI: 43% to 50%	
Sanmamed *et al.* (ICI therapy)	Serum IL-8 early change >9.2%	AUC: 1.00; sensitivity: 85.7%; specificity: 100%;	0.0004
Kato *et al.* (ICI therapy)	MDM2 family amplification	OR for TTF >11.9	0.001

*, statistically significant results for P<0.05. ICI, immune checkpoint inhibitors; PD-L1, programmed death ligand 1; TC, tumor cells; IC, immune cells; TMB, tumor mutational burden; MPM, mutations per megabase; CD8+, CD8-expressing tumor infiltrating lymphocytes; CD4+, CD4-expressing tumor infiltrating lymphocytes; IL-8, interleukine-8; MDM2, mouse double minute 2 homolog; HR, hazard ratio; PD, progression of disease; RR, response rate; AUC, area under the curve; OR, odds ratio; TTF, time to treatment failure.

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