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REVIEW

From targeting the tumor to targeting the immune system: Transversal challenges in oncology with the inhibition of the PD-1/PD-L1 axis

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Abstract

After that the era of chemotherapy in the treatment of solid tumors have been overcome by the "translational era", with the innovation introduced by targeted therapies, medical oncology is currently looking at the dawn of a new "immunotherapy era" with the advent of immune checkpoint inhibitors (CKI) antibodies. The onset of PD-1/PD-L1 targeted therapy has demonstrated the importance of this axis in the immune escape across almost all human cancers. The new CKI allowed to significantly prolong survival and to generate durable response, demonstrating remarkable efficacy in a wide range of cancer types. The aim of this article is to review the most up to date literature about the clinical effectiveness of CKI antibodies targeting PD-1/PD-L1 axis for the treatment of advanced solid tumors and to explore transversal challenges in the immune checkpoint blockade.

Key words: Immune checkpoint inhibitors; PD-1; PD-L1; Checkpoint inhibitors; Cancer treatment; Immune checkpoint blockade; Anti-PD-1 antibodies; Anti-PD-L1 antibodies

Core tip: The onset of PD-1/PD-L1 targeted therapy in oncology has demonstrated the importance of this axis in the immune escape across almost all human cancers. A sort of revolution has been happening with the investigation of the new immune checkpoint inhibitors in the field of anticancer therapy. The aim of this article is to review the most up to date literature about the clinical effectiveness of the antibodies targeting PD-1/PD-L1 axis for the treatment of advanced solid tumors and to explore transversal challenges in the immune checkpoint blockade.

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INTRODUCTION

After that the era of chemotherapy in the treatment of solid tumors have been overcome by the "translational era", with the innovation introduced by targeted therapies, medical oncology is currently looking at the dawn of a new "immunotherapy era" with the advent of immune checkpoint inhibitors (CKI) antibodies.

The strategy to maintain physiologic self-tolerance and to restore latent anti-tumor immunity is currently going through the whole oncology, gradually revolutionizing the standard of treatment of the most chemo-resistant tumors such as melanoma, lung and renal cancer. From the first class of antibodies against cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), like ipilimumab and tremelimumab, burdened by significant autoimmune toxicity, the scenario is currently evolving in favor of the antibodies against programmed cell death protein 1 (PD-1) and its ligand PD-L1, in both cases inhibiting the PD-1/PD-L1 axis[1].

The monoclonal antibodies nivolumab and pembrolizumab (anti-PD-1), atezolizumab, durvalumab and avelumab (anti-PD-L1), have been tested against multiple cancer types in the last years and are currently under investigation in several phase Ⅱ and phase Ⅲ clinical trials. Further similar antibodies are currently undergoing phase Ⅰ experiences, in order to compete with the first arrivals on the clinical scenario[2-4]. All the antibodies cited in the text are reported in Table 1.

In all cases, the mechanism targets the inhibitory signal that contributes to the balance between co-stimulatory and inhibitory pathways in the regulation of T-cell response, starting from the antigen recognition by T-cell receptor. In fact, in contrast to other antibodies currently used for cancer therapy, CKI do not target tumor cells directly, but instead they target lymphocyte receptors or their ligands, with the aim to enhance endogenous antitumor response[5].

PD-1 belongs to the inhibitory B7-family molecules; it is upregulated and expressed by activated T-cells (but also B-cells, T regulatory and natural killer cells) and engaged through its ligands PD-L1 and PD-L2, expressed by the antigen presenting cells (APC) and by non-hematopoietic stem cells, aside from tumor cells. The role of PD-1 consists in the inhibition of the effector T-cells activity in peripheral tissues during the inflammatory response to infection and in the regulation and limitation of autoimmunity[6]. Within the tumor microenvironment, this endogenous mechanism favors immune resistance[7]. The major PD-1 ligand expressed on solid tumors cells is PD-L1, whose most important signal for induction is interferon-γ (IFN-γ), produced by T helper 1 (Th1) cells[8]. Most types of solid tumors have been demonstrated to express high levels of PD-L1 (melanoma, ovarian, lung cancer and genitourinary tumors among others), and more recently the importance of PD-L1 expression on the immune cells infiltrating the tumor also emerged, in particular on tumor-infiltrating lymphocytes (TILs). Nevertheless, the evidence about the prognostic and predictive role of these elements have not yet been clarified and it seems to be different basing on tumor type[5].

Table 1 Immune-checkpoint inhibitors antibodies with their targets

CKI	Mechanism of action
Nivolumab	Anti-PD-1
Pembrolizumab	Anti-PD-1
Atezolizumab	Anti-PD-L1
Durvalumab	Anti-PD-L1
Avelumab	Anti-PD-L1
BMS936559	Anti-PD-L1
Pidilizumab	Anti-PD-1

CKI: Checkpoint inhibitors.

Despite these unresolved issues, the findings described above provided the rationale for the capacity of the blockade of PD-1/PD-L1 axis to enhance intratumoral immune responses in a transversal way across different tumor types, firstly encouraged by preclinical evidence and then largely satisfied by the early results of several recent clinical studies.

RESEARCH

The aim of this article is to review the most up to date literature about CKI antibodies targeting PD-1/PD-L1 axis for the treatment of advanced solid tumors, particularly considering phase Ⅲ randomized trials, starting from the first performed trials on the issue. Published papers were obtained from the Medline database. The search was implemented by reviewing the most important international scientific meetings abstract databases. In addition, indirect data on the topic were achieved by reading the most recent publications related to the use of CKI in different types of solid tumors.

The ongoing trials were reached on the official website www.clincaltrials.gov, considering only randomized phase Ⅲ studies.

RESEARCH RESULTS

Melanoma

Treatment of advanced melanoma has been radically changed by the advent of CKI. After that the anti-CTLA4 antibody ipilimumab in the last years had become the backbone of this malignant tumor treatment, where traditional chemotherapy harvested very little success, the introduction of the anti-PD-1 antibodies nivolumab

Table 2 Phase Ⅲ randomized clinical trials currently ongoing with PD-1/PD-L1 axis blockade in adjuvant setting for solid tumors

Trial name/NCT	Cancer type	Immune checkpoint inhibitor	Arms	Primary endpoint	Expected primary completion date	No. of patients
KEYNOTE-054[20]	Melanoma	Pembrolizumab	Pembrolizumab *vs* placebo	RFS	2018	900
NCT02506153[21]	Melanoma	Pembrolizumab	Pembrolizumab *vs* high dose recombinant interferon-α-2B or ipilimumab	OS	2020	1378
KEYNOTE-091 (PEARLS)[22]	NSCLC	Pembrolizumab	Pembrolizumab *vs* placebo	DFS	2021	1380
IMvigor010[23]	Bladder cancer	Atezolizumab	Atezolizumab *vs* observation	DFS	2021	440
IMpower010[24]	NSCLC	Atezolizumab	Atezolizumab *vs* BSC after adjuvant CT[1]	DFS	2020	1127
NCT02768558[25]	NSCLC (locally advanced)	Nivolumab	Nivolumab *vs* placebo (after CT[1]-RT)	OS	2022	660
ANVIL[26]	NSCLC	Nivolumab	Nivolumab *vs* observation	DFS	2018	714
CheckMate 238[27]	Melanoma	Nivolumab	Nivolumab + placebo *vs* ipilimumab + placebo	RFS	2018	800
CheckMate 274[28]	Urothelial cancers	Nivolumab	Nivolumab *vs* placebo	DFS	2020	640
CheckMate 577[29]	Esophageal or gastroesophageal junction cancer (locally advanced)	Nivolumab	Nivolumab *vs* placebo (after CT[1]-RT and surgery)	DFS	2019	760
PACIFIC[30]	NSCLC (locally advanced)	Durvalumab	Durvalumab *vs* placebo (after CT[1]-RT)	OS	2017	702
NCT02273375[31]	NSCLC	Durvalumab	Durvalumab *vs* placebo	DFS	2025	1100

[1]According to the standard of care and basing on the choice of the investigator. RFS: Recurrence free survival; NSCLC: Non-small cell lung cancer; DFS: Disease free survival; CT: Chemotherapy; OS: Overall survival; RT: Radiotherapy.

and pembrolizumab further improved the therapeutic armamentarium for melanoma.

The first published phase Ⅲ randomized study about PD-1/PD-L1 axis inhibition in this disease demonstrated, at the beginning of 2015, the advantage of nivolumab over chemotherapy with dacarbazine both in terms of overall survival (OS) and of progression free survival (PFS) among previously untreated patients with metastatic melanoma without *BRAF* mutation. Median PFS of 5.1 mo in the nivolumab group was more than doubled when compared to dacarbazine treated patients, with 2.2 mo [hazard ratio (HR) = 0.43, 95%CI: 0.34-0.56, $P < 0.001$]. OS was not reached in the nivolumab group, instead being 10.8 mo in the group treated with chemotherapy (HR = 0.42, 99%CI: 0.25-0.73, $P < 0.001$)[9].

An analogous comparison was made in patients who progressed after anti-CTLA4 treatment in the phase Ⅲ randomized study CheckMate 037, reporting a response rate (RR) of 32% for nivolumab *vs* 11% with chemotherapy according to investigator's choice. These findings have resulted in the inclusion of nivolumab in the new treatment options for a cancer with high unmet need[10].

In parallel, pembrolizumab was compared with ipilimumab as the new standard of care for first line treatment of advanced melanoma in a phase Ⅲ randomized trial, demonstrating to prolong PFS and OS with less toxicity respect to the CTLA4 inhibitor[11].

Nevertheless, the new frontier for untreated melanoma is currently represented by the combination of anti-CTLA4 and anti-PD-L1 antibodies: Larkin *et al*[12] demonstrated that the association of nivolumab and ipilimumab resulted in a significantly longer PFS than ipilimumab alone, despite 55% of treatment-related adverse events (AEs) of grade 3 or 4 (G3-4) *vs* 16% in the nivolumab group and 27% in the ipilimumab group. This three arms phase Ⅲ randomized trial closed the matter of first line ipilimumab alone, otherwise confirming good effectiveness for nivolumab monotherapy in this setting[12].

Further phase Ⅲ-Ⅳ trials are currently ongoing to test different dosing schedules of CKI[13], others to verify their efficacy in particular subgroups of patients like those with brain metastases[14], or to establish the correct duration of anti-PD-1 therapy in metastatic melanoma, especially in the case of long responders[15]. Again, more others are investigating alternative combinations[16,17] or treatment sequences, like ipilimumab plus nivolumab followed or preceded by dabrafenib and trametinib in *BRAF* mutated patients[18].

Moreover, after the Food and Drug Administration approval of ipilimumab for the adjuvant setting for melanoma[19], as discussed below, the PD-1 and PD-L1 inhibitors are currently under investigation for the adjuvant and neoadjuvant setting also in different tumor types in several clinical trials, which results are eagerly awaited, given the lower toxicity expected from this "second generation" of CKI (Table 2)[20-31].

Lung cancer

Lung cancer immunotherapy have an historical back-

ground, but it has not shown significant survival benefit until the recent advent of CKI.

Conversely to anti-CTLA4 antibodies, which demonstrated a certain efficacy only when combined with chemotherapy, the inhibition of PD-1/PD-L1 axis clearly works as single strategy in non-small cell lung cancer (NSCLC)[32].

The first step through immunotherapy for lung cancer in clinical practice was the approval of CKI monotherapy with nivolumab (and more recently with atezolizumab) for NSCLC patients pretreated with first line chemotherapy, on the basis of the first published randomized trials[33-35].

Anti-PD1 antibodies are going to radically revolutionize lung cancer treatment regardless of the histology, especially after the recently published results of KEYNOTE 024 trial[36], providing the outstanding evidence of pembrolizumab superiority compared to chemotherapy as first line treatment for NSCLC, in terms of PFS (10.3 mo *vs* 6 mo, $P < 0.001$), OS (80% *vs* 72% at 6 mo, $P = 0.005$), RR (45% *vs* 28%) and safety among patients bearing strong PD-L1 expression on tumor cells (at least 50% was required for enrollment). This latter evidence, despite concerned to the 30% of overall NSCLC population, will provide the rationale to radically change the therapeutic paradigm for NSCLC, shifting CKI treatment option to first line in a great subgroup of patients. The selection of patients basing on a single biomarker, despite potentially harmful, has been demonstrated to be effective in this case, as proven by the recently announced failure of the analogue phase Ⅲ trial with nivolumab, whose patients were enrolled independently from PD-L1 status[37].

Several phase Ⅲ studies are currently still ongoing in order to investigate further CKI antibodies in all treatment lines, in different treatment regimens and with alternative combinations targeting PD-1/PD-L1 axis in advanced NSCLC (Table 3)[37-96].

Also adjuvant paradigm has been pursued in lung cancer: Table 2 summarizes all the ongoing phase Ⅲ studies in this field.

Squamous cell lung cancer: Squamous cell histology had the first indication for CKI therapy, basing on the outstanding results of CheckMate 017 trial comparing nivolumab *vs* docetaxel in advanced squamous NSCLC (SqNSCLC) progressive to previous chemotherapy[33]. With a median OS of 9.2 mo *vs* 6 mo, nivolumab reduced the risk of death of 41%, with an HR of 0.59 (95%CI: 0.44-0.79), $P < 0.001$. The advantage was confirmed also for RR, PFS and safety profile, finally providing an unprecedented treatment option also in terms of tolerability.

Non-squamous cell lung cancer: With a slight delay and with not as brilliant but positive results, nivolumab was also approved for non-squamous NSCLC (non-SqNSCLC) treatment after failure of chemotherapy, on the basis of an analogous phase Ⅲ randomized trial demonstrating an improvement of median OS from 9.4 mo with docetaxel to 12.2 mo (HR = 0.73, 95%CI: 0.59-0.89, $P = 0.002$)[34]. In this study, nivolumab was associated with better OS and RR but not with longer PFS compared to chemotherapy. A crossing of the PFS curves suggested a delay of the benefit with nivolumab, consistent with the results of previous immune system modulating agents, probably reflecting a pattern of response typical of immunotherapy and the use of inadequate response assessment measurements for this type of drug[97].

Other thoracic malignancies: Among other thoracic tumors, small cell lung cancer (SCLC), malignant pleural mesothelioma (MPM) and thymic epithelial tumors (TETs), under the thrust of true unmet medical needs, came across immunotherapy with CKI.

Preliminary data for PD-1/PD-L1 blockade in SCLC were encouraging and currently ongoing phase Ⅲ studies are investigating CKI both in pretreated and untreated advanced SCLC patients[72,93] or as maintenance treatment after standard treatment either in extensive or in limited disease[91].

Great expectations have been made for MPM, because of the known relationship between neoplastic and inflammatory counterpart in this tumor, recognized to have a T-cell inflamed phenotype. At the moment, only preliminary data have been published and CKI are currently under proposal for further investigations in this disease. Finally, early phases studies are ongoing to test CKI immunotherapy also in TETs[98].

Renal cancer

After the pivotal trial Checkmate 025, nivolumab has vowed to became the cornerstone of previously treated metastatic renal cell carcinoma (mRCC) therapy, finally offering an OS improvement in a setting where targeted therapies have fallen short of expectation[99]. The median OS was 25 mo (95%CI: 21.8-not estimable) with nivolumab and 19.6 mo (95%CI: 17.6-23.1) with everolimus, with a HR of 0.73 and a RR of 25% *vs* 5% ($P < 0.001$). Also in terms of toxicity, nivolumab was superior to the standard treatment everolimus, with 19% *vs* 37% of AEs.

In the light of these results, nivolumab currently represents a new standard of treatment for mRCC after disease progression to first line antiangiogenic therapy. On this auriferous vein other phase Ⅲ randomized trials have been planned and their results are eagerly awaited. Worthy of note, a phase Ⅲ randomized trial with an innovative design is comparing the combination of lenvatinib and everolimus (which recently achieved great results in phase Ⅱ[100]) with the combination of lenvatinib and pembrolizumab *vs* the standard sunitinib. Such ambitious trials will probably provide the cornerstone of the future clinical practice in RCC[41,101].

After reaching the indication for second line treat-

Table 3 Phase III randomized clinical trials currently ongoing with PD-1/PD-L1 axis blockade in advanced setting for solid tumors

Trial name/NCT	Cancer type	Immune checkpoint inhibitor	Arms	Treatment line	Primary endpoint	Expected primary completion date	No. of patients
STOP-GAP[15]	Melanoma	PD-1 inhibitor (any)	Intermittent *vs* continuous therapy	Any	OS	2025	550
NCT02752074[16]	Melanoma	Pembrolizumab	Pembrolizumab + epacadostat *vs* pembrolizumab + placebo	I line	PFS	2018	600
MASTERKEY-265[17]	Melanoma	Pembrolizumab	Pembrolizumab + talimogene laherparepvec *vs* pembrolizumab + placebo	I line	PFS	2018	660
KEYNOTE-048[82]	HNSCC	Pembrolizumab	Pembrolizumab *vs* CT[1] + pembrolizumab *vs* CT[1]	I line	PFS	2018	780
KEYNOTE-040[38]	HNSCC	Pembrolizumab	Pembrolizumab *vs* methotrexate or docetaxel or cetuximab	From II line	OS	2017	466
KEYNOTE-204[39]	Hodgkin lymphoma	Pembrolizumab	Pembrolizumab *vs* brentuximab	From II line	PFS	2019	300
KEYNOTE-045[40]	Urothelial cancers	Pembrolizumab	Pembrolizumab *vs* paclitaxel, docetaxel or vinflunine	From II line	OS	2017[2]	470
NCT02811861[41]	Renal cell carcinoma	Pembrolizumab	Pembrolizumab + lenvatinib *vs* lenvatinib + everolimus *vs* sunitinib	I line	PFS	2020	735
KEYNOTE-426[102]	Renal cell carcinoma	Pembrolizumab	Pembrolizumab + axitinib *vs* sunitinib	I line	PFS, OS	2019	840
KEYNOTE-240[42]	HCC	Pembrolizumab	Pembrolizumab *vs* BSC	II line	PFS	2019	408
KEYNOTE-189[43]	NSqNSCLC	Pembrolizumab	Platinum and pemetrexed ± pembrolizumab	I line	PFS	2017	570
KEYNOTE-407[44]	SqNSCLC	Pembrolizumab	CT[1] ± pembrolizumab	I line	PFS	2018	560
KEYNOTE-042[45]	NSCLC PD-L1-positive	Pembrolizumab	Pembrolizumab *vs* platinum based CT[1]	I line	OS	2018	1240
KEYNOTE-010[46]	NSCLC	Pembrolizumab	Pembrolizumab *vs* docetaxel	From II line	OS	2019	1034
KEYNOTE-119[47]	Triple negative breast cancer	Pembrolizumab	Pembrolizumab *vs* monochemotherapy	II-III line	PFS	2017	600
KEYNOTE-355[48]	Triple negative breast cancer	Pembrolizumab	CT[1] + pembrolizumab *vs* CT[1] + placebo	I line	PFS	2019	858
KEYNOTE-177[49]	MSI-H or dMMR colorectal carcinoma	Pembrolizumab	Pembrolizumab *vs* CT[1]	I line	PFS	2019	270
KEYNOTE-181[50]	Esophageal/ esophago-gastric junction carcinoma	Pembrolizumab	Pembrolizumab *vs* monochemotherapy[1]	II line	PFS	2018	600
KEYNOTE-061[51]	Esophageal/ esophago-gastric junction adenocarcinoma	Pembrolizumab	Pembrolizumab *vs* paclitaxel	II line	PFS	2017	720
KEYNOTE-062[52]	Esophageal/ esophago-gastric junction carcinoma	Pembrolizumab	Pembrolizumab *vs* CT[1] + pembrolizumab *vs* CT[1]	I line	PFS	2019	750
JAVELIN Ovarian 200[53]	Ovarian cancer (platinum resistant)	Avelumab	Avelumab *vs* avelumab plus PLD *vs* PLD	From II line	OS	2018	550
JAVELIN Ovarian 100[54]	Ovarian cancer	Avelumab	CT[1] *vs* CT[1] followed by avelumab maintenance *vs* CT[1] + avelumab followed by avelumab maintenance	I line	PFS	2019	951
JAVELIN Renal 101[55]	Renal cell cancer	Avelumab	Avelumab with axitinib *vs* sunitinib	I line	PFS	2018	583
JAVELIN Bladder 100[56]	Urothelial cancer	Avelumab	Avelumab *vs* BSC (maintenance after CT[1])	I line maintenance	OS	2019	668

JAVELIN Gastric 100[57]	Adenocarcinoma of the stomach or of the gastro-esophageal junction	Avelumab	CT[1] continuation *vs* avelumab in maintenance after CT[1]	I line	OS	2018	666
JAVELIN Gastric 300[58]	Adenocarcinoma of the stomach or of the gastro-esophageal junction	Avelumab	Avelumab + BSC *vs* CT[1] + BSC *vs* BSC	III line	OS	2017	330
JAVELIN Lung 100[59]	NSCLC (PD-L1 positive)	Avelumab	Avelumab *vs* platinum based CT[1]	I line	PFS	2017	420
JAVELIN Lung 200[60]	NSCLC (PD-L1 positive)	Avelumab	Avelumab *vs* docetaxel	From II line	OS	2017	650
OAK[61]	NSqNSCLC	Atezolizumab	Atezolizumab *vs* docetaxel	From II line	OS	2017	1225
IMvigor211[62]	Bladder cancer	Atezolizumab	Atezolizumab *vs* monochemotherapy	II line	OS	2017	932
IMvigor130[63]	Urothelial carcinoma (ineligible for cisplatin)	Atezolizumab	Atezolizumab + CT[1] *vs* placebo + CT[1]	I line	PFS	2019	435
IMpower110[64]	NSqNSCLC	Atezolizumab	Atezolizumab *vs* platin + pemetrexed	I line	PFS	2019	570
IMpower111[65]	SqNSCLC	Atezolizumab	Atezolizumab *vs* gemcitabine + platin	I line	PFS	2017	ND
IMpower131[66]	SqNSCLC	Atezolizumab	Atezolizumab + nab-paclitaxel + carboplatin *vs* atezolizumab + paclitaxel + carboplatin *vs* nab-paclitaxel + carboplatin	I line	PFS	2023	1200
IMpower210[67]	NSCLC	Atezolizumab	Atezolizumab *vs* docetaxel	II line	OS	2019	563
IMpower130[68]	NSqNSCLC	Atezolizumab	Atezolizumab + nab-paclitaxel + carboplatin *vs* nab-paclitaxel + carboplatin	I line	PFS	2019	550
IMpower150[69]	NSqNSCLC	Atezolizumab	Atezolizumab + carboplatin + paclitaxel ± bevacizumab *vs* carboplatin + paclitaxel + bevacizumab	I line	PFS	2017	1200
IMpassion130[70]	Triple negative breast cancer	Atezolizumab	Atezolizumab + nab-paclitaxel *vs* placebo + nab paclitaxel	I line	PFS	2020	900
IMmotion151[71]	Renal cell carcinoma	Atezolizumab	Atezolizumab + bevacizumab *vs* sunitinib	I line	PFS	2020	900
IMpower133[72]	SCLC	Atezolizumab	Carboplatin and etoposide ± atezolizumab	I line	OS	2019	400
NCT02788279[73]	Colorectal carcinoma	Atezolizumab	Atezolizumab + cobimetinib *vs* atezolizumab *vs* regorafenib	From III line	OS	2019	360
KESTREL[74]	HNSCC	Durvalumab	Durvalumab *vs* durvalumab + tremelimumab *vs* SOC	I line	PFS	2017	628
MYSTIC[75]	NSCLC	Durvalumab	Durvalumab *vs* durvalumab + tremelimumab *vs* SOC	I line	PFS	2017	1092
Danube[76]	Bladder cancer	Durvalumab	Durvalumab *vs* durvalumab + tremelimumab *vs* SOC[1]	I line	PFS	2017	525
Lung-MAP[77]	SqNSCLC (biomarker-targeted)	Durvalumab, nivolumab	Docetaxel *vs* durvalumab *vs* erlotinib *vs* AZD4547 *vs* ipilimumab *vs* palbociclib *vs* rilotumumab *vs* taselisib	Any	PFS	2022	10000

CAURAL[78]	NSCLC T790M mutation positive	Durvalumab	AZD9291 + durvalumab *vs* AZD9291	II-III line	PFS	2018	350
NCT02369874[79]	HNSCC	Durvalumab	Durvalumab *vs* durvalumab + tremelimumab *vs* SOC[1]	II line	OS	2018	720
NEPTUNE[80]	NSCLC	Durvalumab	Durvalumab + tremelimumab *vs* SOC[1]	I line	OS	2018	800
ARCTIC[81]	NSCLC	Durvalumab	Durvalumab *vs* durvalumab + tremelimumab *vs* SOC[1]	II-III line	OS	2016	730
NCT02224781[18]	Melanoma BRAFV600 mutated	Nivolumab	Dabrafenib + trametinib followed by ipilimumab + nivolumab *vs* ipilimumab + nivolumab followed by dabrafenib + trametinib	I line	OS	2019	300
NIBIT-M2[14]	Melanoma brain metastases	Nivolumab	Fotemustine *vs* ipilimumab + fotemustine *vs* ipilimumab + nivolumab	Any	OS	2018	168
CheckMate 026[37]	NSCLC PD-L1 positive (all)	Nivolumab	Nivolumab *vs* CT[1]	I line	PFS	2016[2]	535
CheckMate 651[83]	H&N SCC	Nivolumab	Nivolumab + ipilimumab *vs* platinum + fluorouracil + cetuximab	I line	OS	2020	490
CheckMate 459[84]	HCC	Nivolumab	Nivolumab *vs* sorafenib	I line	TTP	2017	726
NCT02267343[85]	Gastric cancer	Nivolumab	Nivolumab *vs* placebo	From II line	OS	2017	480
NCT02569242[86]	Esophageal cancer	Nivolumab	Nivolumab *vs* docetaxel/paclitaxel	From II line	OS	2019	390
CheckMate 214[87]	Renal cell carcinoma	Nivolumab	Nivolumab + ipilimumab *vs* sunitinib	I line	PFS	2019	1070
CheckMate 143[88]	Glioblastoma	Nivolumab	Nivolumab *vs* bevacizumab	II line	OS	2017	440
CheckMate 141[89]	H&N SCC	Nivolumab	Nivolumab *vs* cetuximab/ methotrexate/docetaxel monotherapy	Any	OS	2018	360
CheckMate 227[90]	NSCLC	Nivolumab	Nivolumab *vs* nivolumab + ipilimumab *vs* nivolumab + platinum doublet CT[1]	I line	OS	2018	1980
CheckMate 451[91]	SCLC	Nivolumab	Nivolumab *vs* nivolumab + ipilimumab *vs* placebo after platinum based CT[1]	Maintenance after I line	OS	2018	810
CheckMate 498[92]	Glioblastoma (unmethylated MGMT)	Nivolumab	Nivolumab + RT *vs* temozolomide + RT	I line	PFS	2019	550
CheckMate 331[93]	SCLC	Nivolumab	Nivolumab *vs* topotecan/amrubicin	II line	OS	2018	480
CheckMate 078[94]	NSCLC	Nivolumab	Nivolumab *vs* docetaxel	From II line	OS	2018	500
NCT02339571[95]	Melanoma	Nivolumab	Nivolumab + ipilimumab ± sargramostim	I line	OS	2021	400
CheckMate 401[96]	Melanoma	Nivolumab	Nivolumab + ipilimumab *vs* nivolumab	I line	OS	2021	615

[1]According to the standard of care and basing on the choice of the investigator; [2]The trial has results but it is still unpublished. OS: Overall survival; PFS: Progression free survival; HNSCC: Head and neck squamous cell carcinoma; HCC: Hepatocarcinoma; NSqNSCLC: Non-squamous non-small cell lung cancer; SqNSCLC: Squamous non-small cell lung cancer; CT: Chemotherapy; NSCLC: Non-small cell lung cancer; MSI-H: High microsatellite instability; dMMR: Deficient mismatch repair; PLD: Pegylated liposomal doxorubicin; SCLC: Small cell lung cancer; TTP: Time to progression; ORR: Objective response rate.

ment, also first line setting has been investigated, with the planning of interesting trials currently still ongoing. In previously untreated RCC patients, atezolizumab in combination with bevacizumab is being compared to sunitinib[71]; the same standard of treatment is in turn compared to pembrolizumab combined with axitinib[102] and then to nivolumab plus ipilimumab[87]. Eventually, also avelumab plus axitinib is being investigated *vs*

sunitinib[55]. In all cases, the control arm is represented by such a big standard of therapy (sunitinib) that, in case of positive results, the clinical practice for RCC will completely change, switching from angiogenesis inhibition to immune-checkpoint blockade.

Urothelial cancers

Since no significant improvements have been achieved in metastatic bladder cancer for long time, the impressive results of recent trials with CKI, in particular with the anti-PD-L1 atezolizumab, have given new hope to finally cure urothelial cancer[103,104].

Atezolizumab is currently been approved for treatment of urothelial cancer on the basis of a randomized phase Ⅱ trial comparing this anti-PD-L1 with standard treatment, demonstrating its advantage over chemotherapy in both platinum pretreated ineligible patients and in chemotherapy pretreated patients[105]. At the same time, phase Ⅲ studies in second line setting are ongoing and both atezolizumab and pembrolizumab have been compared to different second line chemotherapeutic regimens in all urothelial cancers: The trial with pembrolizumab has been recently early stopped due to the meeting of the primary endpoint (OS)[40,62]. Also avelumab and durvalumab reached phase Ⅲ investigation in bladder cancer, but in the first line setting; the latter combined with the anti-CTLA4 tremelimumab *vs* standard first line chemotherapy[56,76]. A further interesting study in metastatic urothelial cancer is recruiting naive patients ineligible to cisplatin to receive atezolizumab in combination with chemotherapy (gemcitabine and carboplatin) as first line treatment[63].

Not less significant the promising evidence about the role of CKI in the adjuvant setting of urothelial cancer: Atezolizumab is under investigation *vs* only observation after cystectomy in PD-L1 positive high risk muscle-invasive bladder cancer[23] and also nivolumab is being tested in this setting[28].

Head and neck cancer

Head and neck squamous cell carcinoma (HNSCC) undoubtedly a promising candidate for CKI because of the profound immune suppression from which is characterized. As the matter of fact, a phase Ⅲ randomized study comparing nivolumab to the standard of treatment in pretreated HNSCC patients was early stopped after the clear demonstration of an improvement in terms of OS for nivolumab[89]. This trial provided very promising results in platinum refractory disease, encouraging the planning of further phase Ⅲ studies, currently ongoing, also for pembrolizumab[38,82] and early phases trials with durvalumab and avelumab[106].

Despite an apparently not so favorable toxicity profile, also anti-CTLA4 antibodies are being tested in combination with anti-PD-1 or anti-PD-L1 agents in HNSCC. Phase Ⅲ studies with this therapeutic strategy are currently ongoing both in pretreated patients and in first line setting[74,79].

Other tumors

The PD-1/D-L1 axis has been targeted in other tumor types than those cited above, with an interesting rationale and supported by phase Ⅰ-Ⅱ experiences, despite still remaining in shadow waiting for phase Ⅲ results.

In ovarian cancer, despite several early phase studies currently ongoing with nivolumab, pembrolizumab, BMS936559 (an anti-PD-L1) and avelumab, the emerged response rates are relatively low, in front of a manageable safety profile[53,54,107].

Pembrolizumab, aside from early investigations in soft tissue and bone sarcomas[108], is currently under phase Ⅲ investigation in hepatocellular carcinoma[42], in esophageal and gastric carcinoma[50-52], in Hodgkin and non-Hodgkin lymphoma[39].

In these latter malignancies also nivolumab and pidilizumab, anti-PD-1 antibodies, besides from atezolizumab and durvalumab, anti-PD-L1 antibodies, are being evaluated in early phases[109]. Furthermore, different treatment lines of advanced gastric cancer are being tested with avelumab[57,58].

Some initial encouraging data are emerging from ongoing studies in favor of the employment of CKI also in central nervous system (CNS) malignancies, such as glioblastoma, where unmet clinical needs are leading to new investigations[88,92]. Disappointing results were instead obtained for pancreatic cancer, despite a certain evidence for durvalumab[110].

About colorectal cancer, despite the initial evidence to be not responsive to nivolumab, a subset of patients has been identified as potentially best responders to pembrolizumab, revealing that the mismatch repair (MMR) status can predict clinical benefit with enhanced responsiveness in tumors with microsatellite instability (MSI)[111]. With this rationale, phase Ⅲ randomized studies have been initiated in order to compare standard therapy with pembrolizumab in MSI colorectal cancer patients[49]. Furthermore, atezolizumab is currently under investigation alone or in combination with cobimetinib (mitogen activate protein kinase-inhibitor) *vs* regorafenib (antiangiogenic multi-kinase inhibitor) in all advanced colorectal tumors[73].

Eventually, a great interest for PD-1/PD-L1 blockade is represented by triple negative breast cancer: Phase Ⅲ trials are currently ongoing with pembrolizumab compared to chemotherapy and with atezolizumab combined with nab-paclitaxel both in neo-adjuvant and advanced setting[47,48,70,112].

Transversal challenges

Immune-related toxicity: The management of the "new toxicities" of CKI is transversal to all malignancies and to all cited antibodies, unavoidably involving other specialists beyond the oncologist, such as the endocrinologist and the immunologist in first line.

These immune-related adverse events (irAEs) are due to the infiltration of tissues by activated T-lymphocytes responsible of autoimmunity. As a consequence, the block of the immune-checkpoint can amplify any immune response in all organs: Skin, gastrointestinal tract, endocrine glands, lung, CNS, liver, kidney, hematological cells, muscular-articular system, heart and eyes can all be affected. Nevertheless, most of these irAEs are rare and only fatigue, rash, pruritus, diarrhea, nausea and arthralgia occurs in > 10% of cases. On the other hand, despite being rare, interstitial pneumonitis is the main life-threatening toxicity for anti PD-1/PD-L1 agents[113].

Potentially predisposing conditions for irAEs development could be represented by personal or family history of autoimmune disease (genetic determinants), by underlying silent autoimmunity, chronic viral infections or other personal ecological factors (such as the microbiome in the case of enterocolitis)[114].

The prevention, the anticipation, the detection and then the treatment (with multidisciplinary approach) and monitoring of irAEs are the principles of their correct clinical management. Depending on their severity, irAEs require temporary or permanent discontinuation of CKI therapy, use of high doses corticosteroids or, in severe cases, of anti-TNF treatment with infliximab. The current management guidelines are based on recent expert consensus recommendations published about the issue[115].

Response assessment: RECIST *vs* immune-related criteria: Based on survival analysis, traditional response evaluation criteria in solid tumors (RECIST) might underestimate the benefit of CKI[116].

The pattern of response of immunotherapy, radically different from those of standard chemotherapy and also of antiangiogenic agents, is frequently not captured by the conventional RECIST[117]. This led to the development of the immune-related response criteria (irRC)[118], assessing tumor burden as a continuous variable and evaluating percentage changes in several target lesions overtime. In this system, the appearance of new lesions does not mean progressive disease but it is considered and reassessed in the context of a dynamic evaluation. Moreover, the thresholds to determine progression or response (25% increase and 50% decrease) are higher than those of RECIST (20% increase and 30% decrease)[119]. Given the reported evidence, modified criteria are undoubtedly mandatory in the response assessment to the new immunotherapy, in order to prevent premature discontinuation of treatment.

PD-L1 expression as response predictor: In the context of solid tumors treated with PD-1/PD-L1 inhibitors, the predictive role of PD-L1 expression on tumor cells and, as more recently discovered, on immune infiltrating cells, represents an actual issue of great interest and constitutes a significant cue of discussion for clinical researchers[120].

Currently, on the basis of the state of art, the predictive value of PD-L1 on tumor cells is limited to NSCLC and melanoma, especially for anti-PD-1 antibodies, whilst a more predictive significance of PD-L1 expression on the immune cells infiltrating the tumor seems to emerge for urothelial cancers in the case of anti-PD-L1 antibodies[121,122]. Nevertheless, a great limit of such speculations is represented by the scarce reliance and reproducibility of the different methods used for the biomarker's detection, with controversial results depending on the staining technique, on the different anti-PD-L1 antibodies and finally on the sample used for immune-histochemical assay (primary tumor *vs* metastases samples, with the challenge of heterogeneity). Moreover, confusing data emerged from the use (and the lack of validation) of different cut-off for PD-L1 expression, from 1%, to 5%, to 50% threshold in different trials[120].

Aside from PD-L1 expression, further multiple factors have been explored and are currently undergoing investigations as predictive elements for response to CKI: Among these, an increasing interest is being acquired by the micro-environmental features of the tumor, such as the infiltrating immune cells sub-populations and their biomarkers expression[123].

Microsatellite instability and hyper-mutational status: The MSI phenotype, as a consequence of a defective DNA-MMR system, characterizes a subgroup of tumors harboring a large number of somatic mutations (high mutational load). Since these mutations have the potential to encode a great number of immunogenic neoantigens, a particular susceptibility of MSI-hypermutated cancers to PD-1/PD-L1 axis blockade have been hypothesized and more recently proven[124]. As the matter of fact, MSI tumors have a microenvironment characterized by abundant T-cell infiltrate, with activated $CD8^+$ cytotoxic T lymphocyte (CTL) and activated Th1 producing IFN-γ, high expression of PD-L1 (in particular by TILs and myeloid cells infiltrating the tumor) and great overexpression of immune-checkpoint related proteins[125]. All these elements configure the elective candidate cancer for immune-checkpoint inhibition and suggest to investigate CKI in all cancer types with MMR defects.

Additionally, tumors with polymerase E (POLE) mutations, despite stable microsatellites, have been demonstrated to contain a high mutational load. Also these POLE-ultra-mutated cancers are characterized by an active Th1/CTL microenvironment and upregulated immune checkpoints, constituting an ideal target for CKI therapy as well as MSI tumors[126].

In conclusion, among apparently resistant cancer types (such as colon cancer), CKI have been proven to exert an effect in case of MMR defects and trials on this selected population are currently ongoing to investigate

the efficacy of anti-PD-1 antibodies[49].

Immune system modulation with sequential or association strategies: Given the great benefit in terms of OS and the long lasting impact of CKI therapy on patients' survival in the responding cases, probably due to immunological memory, two major issues remain to be addressed: The sensitization of non-responders and the disease control in patients initially pseudo-progressive. With these aims, combination strategies have been planned and investigated in the last years, either combining immunotherapy with chemotherapy, radiotherapy and targeted agents or associating different CKI[127].

The strategy to increase the immunogenicity of tumors can be pursued through the enhancement of antigen presentation (boosting antigens release or stimulating APC function), the stimulation of major histocompatibility complex (MHC) class Ⅰ expression, the down-regulation of the T-reg cells and the stimulation of the T-cells infiltration. Some of these mechanisms can be achieved with promising combination strategies.

Chemotherapeutic agents are capable to induce immunogenic cancer death, generating a strong immune stimulation. Among these, cyclophosphamide have additionally been shown to reduce the number of circulating T-reg cells, removing a key element of immunosuppression, and moreover to sensitize tumor cells to T-cell mediated apoptosis, potentially boosting the effect of the immune checkpoint blockade[128-130]. Considering the criticism of a combination between CKI and chemotherapy, given expected short term immunosuppressive effect of the latter, in our opinion a sequential strategy could represent a good opportunity to take advantage of cell death and antigen release caused by an induction chemotherapy, in order to prepare a more immunogenic environment for the subsequent CKI[131].

A great interest for the potential stimulation of the immune-response through radiotherapy has been suggested by the evidence about the immune-mediated abscopal effect[132]. Aside from interesting case reports, clinical trials in this field are currently in early phases and eagerly awaited[133].

Targeted therapy combinations with immunotherapy are currently under investigation, in early phases, with interesting results[127]. The rationale of such strategies could be represented by the aim to obtain a more rapid RR and to boost PFS with the targeted agent, in expectation of the long-term effect on survival of the CKI.

Finally, the combination of anti-PD-1 and anti-CTLA4 antibodies, despite the increased immune-related toxicity, has been shown to improve the outcomes in a phase Ⅲ randomized trial in metastatic melanoma, early changing the standard of treatment a few years after the onset of the new immunotherapy with ipilimumab[134]. Several trials investigating such association of CKI are currently ongoing: The management of irAEs will probably represent the main criticism of such strategies[127].

Targeting PD-1/PD-L1 axis in adjuvant setting: The rationale for the PD-1/PD-L1 axis inhibition for adjuvant purposes is in the concept of "immunological memory", generated by the cancer-immunity cycle, starting from the release of cancer cell antigens also in the early phases of tumorigenesis. After the APC migration in the lymph nodes and the presentation of antigens in the context of MHC-I molecules to $CD8^+$ T cells, aside from effector T-lymphocytes capable of activation against cancer neo-antigens, memory T-cells are also generated. These quiescent lymphocytes are appointed to the subsequent immune-response and could contribute to avoid disease relapse[135].

Considering the widely acceptable toxicity profile of CKI, the proposal of using them as adjuvant therapy, to prevent relapses after surgery of early disease while maintaining a good quality of life, appears very favorable. In support of this, we have the approval of the CTLA4 inhibitor ipilimumab for adjuvant treatment in melanoma, on the basis of a recent pivotal trial[136]. For PD-1/PD-L1 axis inhibitors, nevertheless, the investigation in adjuvant setting is quite early, in spite of a more favorable safety management. A noteworthy issue about immune-adjuvant treatment with these compounds (unlike the case of ipilimumab) is the correct duration of therapy, ranging from one to more years in different planned trials. The currently ongoing studies are reported in Table 2.

PERSPECTIVES

Considering the wide range of settings and combinations covered by the ongoing clinical trials with CKI treatment, we think that the future directions for immunotherapy are still to be written and they are probably different basing on cancer types. The reason of this latter statement, not so obvious as it may seem, is likely due to the other different therapies to whom immune-checkpoint blockade needs to be sequenced and alternated in each tumor, more than to a real difference in the target, which is always represented by the immune system and by its relationship with the tumor rather than by the tumor itself.

From this point of view, a key issue could be represented by the immunomodulating potential of the current standard of treatment in each case, sometimes widely unknown and rarely explored before the "immunotherapy era"[137].

The great advantage of anti-PD-1/PD-L1 agents is undoubtedly represented by their very favorable safety profile, with large tolerability in almost all patients. Combinations of CKI with standard chemotherapy or targeted therapies, despite possibly more effective, have the risk of became unsustainable both in terms of costs and of toxicity, significantly impacting on the final outcome. Nevertheless, alternating targeted and

immunotherapy might permit to modulate tumor metabolism, inflammation and immune infiltration, allowing to modify the relationship between cancer and immune system.

Thus, in order to fully take advantage of its potential, the winning strategy with immune-checkpoint blockade could be represented by an ingenious sequence, exploiting the immunomodulating properties of previous and subsequent drugs with the aim of boosting immune system activation against the tumor.

CONCLUSION

The onset of PD-1/PD-L1 targeted therapy has demonstrated the importance of this axis in the immune escape across almost all human cancers. Despite being burdened by some issues not still addressed, such as the correct duration of therapy in the responsive patients, the new CKI allowed to significantly prolong survival and to generate durable response, demonstrating remarkable efficacy in a wide range of cancer types. However, such benefit is not extended to all patients, and some of them experienced immune escape despite therapy. The investigation about mechanisms leading to the development of primary or secondary immune escape must represent the key element of future studies in the whole immuno-oncology, with the aim of resensitize these patients to the immune checkpoint blockade. The future approach to the problem may be represented by a personalized cancer immunotherapy, allowed only by multiparameter biomarkers approaches, as interestingly suggested by Kim *et al*[138] in a recent review about the "step to success (or failure)" to PD-1/PD-L1 blockade. In their proposal, a hypothetical algorithm could provide the assessment of specific immune-related biomarkers in each patient's tumor, allowing to create a personal mapping according to which characteristics the oncologist could chose (or exclude) the optimal immunotherapy or immunotherapeutic combination for each single case.

Waiting for the possible realization of such sophistication of therapy, the immune checkpoint blockade in oncology is currently experiencing promising huge advances, shifting the classical paradigm of anticancer treatment from targeting the tumor to targeting the immune system and increasing our hopes to gain the immune control of oncological disease.

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