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

Melissa Bersanelli, Sebastiano Buti

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

© The Author(s) 2017. Published by Baishideng Publishing Group Inc. All rights reserved.

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.

Bersanelli M, Buti S. From targeting the tumor to targeting the immune system: Transversal challenges in oncology with
the inhibition of the PD-1/PD-L1 axis. World J Clin Oncol 2017; 8(1): 37-53 Available from: URL: http://www.wjgnet.com/2218-4333/full/v8/i1/37.htm DOI: http://dx.doi.org/10.5306/wjco.v8.i1.37

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].

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.clinicaltrials.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 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.
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, \( P < 0.001 \)).

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\(^\text{[10]}\).

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\(^\text{[11]}\).

Nevertheless, the new frontier for untreated melanoma is currently represented by the combination of anti-CTLA4 and anti-PD-L1 antibodies: Larkin et al\(^\text{[12]}\) 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 mono-therapy in this setting\(^\text{[12]}\).

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

Moreover, after the Food and Drug Administration approval of ipilimumab for the adjuvant setting for melanoma\(^\text{[19]}\), 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)\(^\text{[20-31]}\).

### 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)\[22\].

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\[23\]. 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\[37\].

**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\[94\].

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 antiangiogenetic therapy. On this auriferous vein other phase III randomized trials have been planned and their results are eagerly awaited. worthy of note, a phase II 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-
Bersanelli M et al. Transversal challenges with the inhibition of the PD-1/PD-L1 axis

| Trial name/NCT | Cancer type | Immune checkpoint inhibitor | Arms | Treatment line | Primary endpoint | Expected primary completion date | No. of patients |
|----------------|-------------|-----------------------------|------|----------------|-----------------|----------------------------------|----------------|
| STOP-GAP[19]  | Melanoma    | PD-1 inhibitor (any)        | Pembrolizumab | Intermittent vs continuous therapy | Any | OS | 2025 | 550 |
| NCT02752074[14] | Melanoma    | Pembrolizumab               | Pembrolizumab + + epacadostat vs pembrolizumab + placebos | I line | PFS | 2018 | 600 |
| MASTERKEY-265[17,18] | Melanoma    | Pembrolizumab               | Pembrolizumab + talimogene cabarep + pembrolizumab + placebo | I line | PFS | 2018 | 660 |
| KEYNOTE-048[15] | HNSCC       | Pembrolizumab               | Pembrolizumab vs CT + pembrolizumab vs CT + placebo | I line | PFS | 2018 | 780 |
| KEYNOTE-049[15] | HNSCC       | Pembrolizumab               | Pembrolizumab vs methotrexate or docetaxel or cetuximab | From II line | OS | 2017 | 466 |
| KEYNOTE-204[19] | Hodgkin lymphoma | Pembrolizumab             | Pembrolizumab vs brentuximab | From II line | PFS | 2019 | 300 |
| KEYNOTE-045[14] | Urothelial cancers | Pembrolizumab          | Pembrolizumab vs paclitaxel, docetaxel or vinflunine | From II line | OS | 2017 | 470 |
| NCT02811861[18] | Renal cell carcinoma | Pembrolizumab       | Pembrolizumab + + lenvatinib vs lenvatinib + everolimus vs sunitinib | I line | PFS | 2020 | 735 |
| KEYNOTE-042[15] | Renal cell carcinoma | Pembrolizumab         | Pembrolizumab + sunitinib | I line | PFS, OS | 2019 | 840 |
| KEYNOTE-240[15] | HCC         | Pembrolizumab              | Pembrolizumab vs BSC | I line | PFS | 2019 | 408 |
| KEYNOTE-189[14] | NSqNSCLC    | Pembrolizumab             | Pembrolizumab vs platinum and paclitaxel pembrolizumab | I line | PFS | 2017 | 570 |
| KEYNOTE-407[15] | SqNSCLC     | Pembrolizumab + platinum based CT | Pembrolizumab vs sunitinib | I line | PFS | 2018 | 560 |
| KEYNOTE-042[15] | NSCLC PD-L1- positive | Pembrolizumab       | Pembrolizumab vs platinum based CT | I line | OS | 2018 | 1240 |
| KEYNOTE-010[15] | NSCLC       | Pembrolizumab + platinum based CT | Pembrolizumab vs docetaxel | From II line | OS | 2019 | 1034 |
| KEYNOTE-119[15] | Triple negative breast cancer | Pembrolizumab        | Pembrolizumab vs monochemotherapy | II-III line | PFS | 2017 | 600 |
| KEYNOTE-355[15] | Triple negative breast cancer | Pembrolizumab + pembrolizumab vs CT + placebo | Pembrolizumab vs BSC | I line | PFS | 2019 | 858 |
| KEYNOTE-177[15] | MSI-H or dMMR colorectal carcinoma | Pembrolizumab | Pembrolizumab vs CT | I line | PFS | 2019 | 270 |
| KEYNOTE-181[15] | Esophageal/esophago-gastric junction carcinoma | Pembrolizumab | Pembrolizumab vs monochemotherapy | II line | PFS | 2018 | 600 |
| KEYNOTE-061[15] | Esophageal/esophago-gastric junction adenocarcinoma | Pembrolizumab | Pembrolizumab vs paclitaxel | II line | PFS | 2017 | 720 |
| KEYNOTE-062[15] | Esophageal/esophago-gastric junction carcinoma | Pembrolizumab | Pembrolizumab vs CT + pembrolizumab vs CT | I line | PFS | 2019 | 750 |
| JAVELIN Ovarian 200[16] | Ovarian cancer (platinum resistant) | Avelumab | Avelumab vs avelumab plus PDL vs PDL | From II line | OS | 2018 | 550 |
| JAVELIN Ovarian 100[16] | Ovarian cancer | Avelumab | CT vs CT followed by avelumab vs CT + pembrolizumab | I line | PFS | 2019 | 951 |
| JAVELIN Renal 101[15] | Renal cell cancer | Avelumab | Avelumab vs avelumab with axitinib vs sunitinib | I line | PFS | 2018 | 583 |
| JAVELIN Bladder 100[15] | Urothelial cancer | Avelumab | Avelumab vs BSC (maintenance after CT) | I line | OS | 2019 | 668 |
Bersanelli M *et al.*, Transversal challenges with the inhibition of the PD-1/PD-L1 axis

| Trial                  | Tumor Type                          | Treatment               | Efficacy Measure | Comparator | Line | OS/OSM | Year | Patients |
|------------------------|-------------------------------------|-------------------------|------------------|------------|------|--------|------|----------|
| JAVELIN Gastric 100    | Adenocarcinoma of the stomach or of the gastroesophageal junction | Avelumab                | CT1 continuation vs avelumab in maintenance after CT1 |            | I    | OS     | 2018 | 666      |
| JAVELIN Gastric 300    | Adenocarcinoma of the stomach or of the gastroesophageal junction | Avelumab                | Avelumab + BSC vs CT1 + BSC vs BSC |            | III   | OS     | 2017 | 330      |
| JAVELIN Lung 100       | NSCLC (PD-L1 positive)              | Avelumab                | Avelumab vs platinum based CT1 |            | I    | PFS    | 2017 | 420      |
| JAVELIN Lung 200       | NSCLC (PD-L1 positive)              | Avelumab                | Avelumab vs docetaxel |            | II   | OS     | 2017 | 650      |
| OAK                    | NSqNSCLC                            | Atezolizumab            | Atezolizumab vs docetaxel |            | II    | OS     | 2017 | 1225     |
| IMvigor211             | Bladder cancer                      | Atezolizumab            | Atezolizumab vs docetaxel vs monotherapy |            | I    | OS     | 2017 | 932      |
| IMvigor130             | Urothelial carcinoma (ineligible for cisplatin) | Atezolizumab            | Atezolizumab + CT1 vs placebo + CT1 |            | I    | PFS    | 2019 | 435      |
| IMpower110             | NSqNSCLC                            | Atezolizumab            | Atezolizumab vs platin + docetaxel |            | I    | PFS    | 2019 | 570      |
| IMpower111             | SqNSCLC                             | Atezolizumab            | Atezolizumab vs gemcitabine + platin |            | I    | PFS    | 2017 | ND       |
| IMpower131             | SqNSCLC                             | Atezolizumab            | Atezolizumab + nab-paclitaxel + carboplatin vs atezolizumab + paclitaxel + carboplatin vs nab-paclitaxel + carboplatin vs platin + paclitaxel + bevacizumab vs carboplatin + paclitaxel + bevacizumab |            | I    | PFS    | 2023 | 1200     |
| IMpower210             | NSCLC                               | Atezolizumab            | Atezolizumab vs docetaxel |            | II    | OS     | 2019 | 563      |
| IMpower130             | NSqNSCLC                            | Atezolizumab            | Atezolizumab + nab-paclitaxel + carboplatin vs nab-paclitaxel + carboplatin |            | I    | PFS    | 2019 | 550      |
| IMpower150             | NSqNSCLC                            | Atezolizumab            | Atezolizumab + carboplatin + paclitaxel + bevacizumab vs carboplatin + paclitaxel + bevacizumab |            | I    | PFS    | 2017 | 1200     |
| IMpower130             | Triple negative breast cancer       | Atezolizumab            | Atezolizumab + nab-paclitaxel vs placebo + nab paclitaxel |            | I    | PFS    | 2020 | 900      |
| IMmotion151            | Renal cell carcinoma                | Atezolizumab            | Atezolizumab + bevacizumab vs sunitinib |            | I    | PFS    | 2020 | 900      |
| IMpower133             | SCLC                                | Atezolizumab            | Carboplatin and etoposide ± atezolizumab vs atezolizumab |            | I    | OS     | 2019 | 400      |
| NCT02788279            | Colorectal carcinoma                | Atezolizumab            | Atezolizumab + cabimetinib vs atezolizumab |            | From III line | OS     | 2019 | 360      |
| KESTREL                | HNSCC                               | Durvalumab              | Durvalumab vs durvalumab + tremelimumab vs SOC |            | I    | PFS    | 2017 | 628      |
| MYSTIC                 | NSCLC                               | Durvalumab              | Durvalumab vs durvalumab + tremelimumab vs SOC |            | I    | PFS    | 2017 | 1092     |
| Danube                 | Bladder cancer                      | Durvalumab              | Durvalumab vs durvalumab + tremelimumab vs SOC |            | I    | PFS    | 2017 | 525      |
| Lung-MAP               | SqNSCLC (biomarker-targeted)        | Durvalumab, nivolumab   | Docetaxel vs durvalumab vs erlotinib vs AZD4547 vs ipilimumab vs palbociclib vs riluzumab vs taselisib |            | Any  | PFS    | 2022 | 10000    |
| Study Name               | Disease Location | Treatment Arm 1 | Treatment Arm 2 | Dose | Phase | Time to Progression | Duration |
|-------------------------|------------------|----------------|----------------|------|-------|---------------------|----------|
| CAURAL [59]             | NSCLC T790M mutation positive | Durvalumab | AZD9291 + durvalumab vs AZD9291 | II-III line | PFS | 2018 | 350 |
| NCT02698747 [60]        | HNSCC            | Durvalumab    | Durvalumab vs durvalumab vs tremelimumab vs SOC1 | II line | OS | 2018 | 720 |
| NEPTUNE [64]            | NSCLC            | Durvalumab    | Durvalumab + tremelimumab vs SOC1 | I line | OS | 2018 | 800 |
| ARCTIC [65]             | NSCLC            | Durvalumab    | Durvalumab vs durvalumab vs tremelimumab vs SOC1 | I[-II] line | OS | 2016 | 730 |
| NCT02224761 [66]        | Melanoma BRAFV600 mutated | Nivolumab    | Dabrafenib + trametinib followed by ipilimumab + nivolumab vs ipilimumab + nivolumab followed by dabrafenib | I line | OS | 2019 | 300 |
| NIBIT-M2 [67]           | Melanoma brain metastases | Nivolumab    | Fotemustine vs ipilimumab vs fotemustine vs ipilimumab vs nivolumab | Any | OS | 2018 | 168 |
| CheckMate 026 [72]      | NSCLC PD-L1 positive (all) | Nivolumab    | Nivolumab vs CT | I line | PFS | 2016* | 535 |
| CheckMate 65 [73]       | H&N SCC          | Nivolumab    | Nivolumab + ipilimumab vs platinum + fluorouracil + cetuximab | I line | OS | 2020 | 490 |
| CheckMate 459 [74]      | HCC              | Nivolumab    | Nivolumab vs sorafenib | I line | TTP | 2017 | 726 |
| NCT02267343 [75]        | Gastric cancer   | Nivolumab    | Nivolumab vs placebo vs docetaxel/paclitaxel | From II line | OS | 2017 | 480 |
| NCT02569242 [76]        | Esophageal cancer | Nivolumab    | Nivolumab vs sorafenib vs placebo | From II line | OS | 2019 | 390 |
| CheckMate 214 [77]      | Renal cell carcinoma | Nivolumab    | Nivolumab + ipilimumab vs sunitinib | I line | PFS | 2017 | 1070 |
| CheckMate 143 [78]      | Glioblastoma     | Nivolumab    | Nivolumab vs bevacizumab | II line | OS | 2017 | 440 |
| CheckMate 141 [79]      | H&N SCC          | Nivolumab    | Nivolumab vs cetuximab/methotrexate/docetaxel | Any | OS | 2018 | 360 |
| CheckMate 227 [80]      | NSCLC            | Nivolumab    | Nivolumab vs nivolumab + ipilimumab vs nivolumab + platinum doublet CT | I line | OS | 2018 | 1980 |
| CheckMate 451 [81]      | SCLC             | Nivolumab    | Nivolumab vs nivolumab + ipilimumab vs placebo after platinum based CT vs | Maintenance after I line | OS | 2018 | 810 |
| CheckMate 498 [82]      | Glioblastoma (unmethylated MGMT) | Nivolumab    | Nivolumab + RT vs temozolomide + RT | I line | PFS | 2019 | 550 |
| CheckMate 331 [83]      | SCLC             | Nivolumab    | Nivolumab vs topotecan/amrubicin | II line | OS | 2018 | 480 |
| CheckMate 07 [84]       | NSCLC            | Nivolumab    | Nivolumab vs docetaxel vs ipilimumab + nivolumab | From II line | OS | 2016 | 500 |
| NCT02339571 [85]        | Melanoma         | Nivolumab    | Nivolumab vs sargramostim | I line | OS | 2021 | 400 |
| CheckMate 401 [86]      | 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; 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[^89]. 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\(^{[49]}\).

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 undoubtedly a. Phase II 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\(^{[48]}\). This trial provided very promising results in platinum refractory disease, encouraging the planning of further phase III studies, currently ongoing, also for pembrolizumab\(^{[38,62]}\) 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 II 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\(^{[53,94,107]}\).

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\(^{[88,90]}\). 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\(^{[23]}\).

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 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

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)

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.

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

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. This led to the development of the immune-related response criteria (irRC), 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). 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.

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. 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.

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.

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. 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.

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.

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 antigen 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"[^417]. 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. 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 sophisticated 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.

REFERENCES

1 Lee CS, Cragg M, Glennie M, Johnson P. Novel antibodies targeting immune regulatory checkpoints for cancer therapy. Br J Clin Pharmacol 2013; 76: 233-247 [PMID: 23701301 DOI: 10.1111/bcp.12164]

2 Naing A, Gelderblom H, Gainor J, Forde PM, Butler M, Lin CC, Sharma S, Ochoa de Olza M, Schellens JHM, Soria JC, Taylor MH, Silva AP, Li Z, Bilec S, Cameron S, Jeffrey R. A first-in-human phase I study of the anti-PD-1 antibody PDR001 in patients with advanced solid tumors. 2016 ASCO Annual Meeting, Poster Discussion. J Clin Oncol 2016; 34 Suppl: abstr 3060

3 Eli Lilly and Company. A study of anti-PD-L1 checkpoint antibody (LY330054) alone and in combination in participants with advanced refractory solid tumors (PACT). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/ NCT02791334

4 Bristol-Myers Squibb. Study of Urelumab in Subjects With Advanced and/or Metastatic Malignant Tumors. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02535406

5 Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012; 12: 252-264 [PMID: 22437870 DOI: 10.1038/nrc3239]

6 Ishida Y, Agata Y, Shibahara K, Honjo T. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. EMBO J 1992; 11: 3887-3895 [PMID: 1396582]

7 Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. Nat Rev Immunol 2008; 8: 467-477 [PMID: 18500231 DOI: 10.1038/nri2236]

8 Dong J, Strome SE, Salomaa DR, Tamura H, Hirano F, Flies DB, Roche PC, Lu J, Zhu G, Tamada K, Lenton VA, Celis E, Chen L. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 2002; 8: 793-800 [PMID: 12091876 DOI: 10.1038/nm730]

9 Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, Hassel JC, Rutkowski P, McNeil C, Kalinka-Warzocha E, Savage K3, Hernberg MM, Leblé C, Charles J, Mihalceiu C, Chiariion-Sileni V, Mauch C, Cognetti F, Arance A, Schmidt H, Schadendorf D, Gogas H, Lundgren-Eriksson L, Horak C, Scarbery B, Waxman IM, Akinson V, Ascieto PA. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015; 372: 320-330 [PMID: 25399552 DOI: 10.1056/NEJMoa1412082]

10 Weber JS, D’Angelo SP, Minor D, Hodi FS, Gutzmner R, Neyns B, Hoeller C, Khushalani NI, Miller WH, Lao CD, Linette GP, Thomas L, Lorigian P, Grossmann KF, Hassel JC, Maio M, Sznol M, Ascieto PA, Mohr P, Chmielowski B, Bryce A, Svanae IM, Grob JJ, Kachhradt AM, Horak C, Lambert A, Yang AS, Larkin J. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2015; 16: 375-384 [PMID: 25795410 DOI: 10.1016/ S1470-2045(15)00768-6]

11 Robert C, Schachtet J, Long GV, Arance A, Grob JJ, Mortier L, Daud A, Carlino MS, McNeel C, Lotem M, Larkin J, Lorigian P, Neyns B, Blank CU, Hamid O, Mateus C, Shapira-Frommer R, Kosh M, Zhou H, Ibrahim N, Ebbinghaus S, Ribas A. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med 2015; 372: 2521-2532 [PMID: 25891173 DOI: 10.1056/ NEJMoa1503093]

12 Larkin J, Chiariion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, Schadendorf D, Dummer R, Smylie M, Rutkowski P, Ferrucci PF, Hill A, Wargaft J, Carlino MS, Haenen JB, Maio M, Marquez-Rodas I, McArthur GA, Ascieto PA, Long GV, Callahan MK, Postow MA, Grossmann K, Sznol M, Dreno B, Bastholt L, Yang A, Rollin LM, Horak C, Hodi FS, Wolchok JD. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med 2015; 372: 23-34 [PMID: 26027431 DOI: 10.1056/ NEJMoa1504030]

13 Bristol-Myers Squibb. A study of two different dose combinations of nivolumab in combination with ipilimumab in subjects with previously untreated, unresectable or metastatic melanoma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/ NCT02714216

14 Italian Network for Tumor Biotherapy Foundation. A study of fotemustine (FTM) vs FTM and ipilimumab (IPI) or IPI an nivolumab in melanoma brain metastasis (NIBIT-M2). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/
show/NCT02460068

15 Canadian Cancer Trials Group. Duration of anti-PD-1 therapy in metastatic melatoma (STOP-GAP). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02821013

16 Incyte Corporation. A phase 3 study of pembrolizumab epacadotat or placebo in subjects with unresectable or metastatic melanoma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02752074

17 Amgen. Pembrolizumab with or without talimogene laherparepvec or talimogene laherparepvec placebo in unresected melanoma (MASTERKEY-265). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02263508

18 National Cancer Institute (NCI). A randomized phase III trial of dabrafenib trametinib followed by ipilimumab nivolumab at progression vs ipilimumab nivolumab followed by dabrafenib trametinib at progression in patients with advanced BRAFV600 mutant melanoma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02724781

19 FDA approves Yervoy to reduce the risk of melanoma returning after surgery. [released 2015 Oct 28]. Available from: URL: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm469944. htm

20 Merck Sharp & Dohme Corp. Study of Pembrolizumab (MK-3475) Versus Placebo After Complete Resection of High-Risk Stage III Melanoma (MK-3475-054/KEYNOTE-054). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02652504

21 National Cancer Institute (NCI). High-Dose Recombinant Interferon Alfa-2B, Ipilimumab, or Pembrolizumab in Treating Patients With Stage III-IV High Risk Melanoma That Has Been Removed by Surgery. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02506153

22 Merck Sharp & Dohme Corp. Study of Pembrolizumab (MK-3475) vs Placebo for Participants With Non-Small Cell Lung Cancer After Resection With or Without Standard Adjuvant Therapy (MK-3475-091/KEYNOTE-091) (PEARLS). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02504372

23 Hoffmann-La Roche. A Phase III Study of Atezolizumab Treatment Versus Observation as Adjuvant Therapy in Patients With PD-L1 Positive, High Risk Malignant Bladder Cancer After Cystectomy [IMvigor010]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02450331

24 Hoffmann-La Roche. Study to Assess Safety and Efficacy of Atezolizumab (MPDL3280A) Compared to Best Supportive Care Following Chemotherapy in Patients With Lung Cancer [IMpower010]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02486718

25 RTOG Foundation, Inc. Cisplatin and Etoposide Plus Radiation Followed By Nivolumab/Placebo For Locally Advanced NSCLC. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02745058

26 National Cancer Institute (NCI). Nivolumab After Surgery and Chemotherapy in Treating Patients With Stage IB-IIIA Non-small Cell Lung Cancer (ANVIL). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02559544

27 Bristol-Myers Squibb. Efficacy Study of Nivolumab Compared to Ipilimumab in Prevention of Recurrence of Melanoma After Complete Resection of Stage IIIb/c or Stage IV Melanoma (CheckMate 238). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT03889906

28 Bristol-Myers Squibb. A Study of Nivolumab, Compared to Placebo, in Patients With Bladder or Upper Urinary Tract Cancer, Following Surgery to Remove the Cancer (CheckMate 274). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02632409

29 Bristol-Myers Squibb. Study of Adjuvant Nivolumab or Placebo in Subjects With Resected Esophageal or Gastroesophageal Junction Cancer (CheckMate 577). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02125461

30 Canadian Cancer Trials Group. Double Blind Placebo Controlled Controlled Study of Adjuvant MEDI4736 In Completely Resected NSCLC. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02273375

31 AstraZeneca. A Global Study to Assess the Effects of MEDI4736 Following Concurrent Chemoradiation in Patients With Stage III Unresectable Non-Small Cell Lung Cancer (PACIFIC). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02460068

32 Steven A, Fisher SA, Robinson BW. Immunotherapy for lung cancer. Respirology 2016; 21: 821-833 [PMID: 27101251 DOI: 10.1111/resp.12789]

33 Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, Waterhouse D, Ready N, Gnjatic J, Arin Frongeri O, Havel L, Steins M, Garassino MC, Aerts JG, Domine M, Paz-Ares L, Reck M, Baudelet C, Harbison CT, Lestini B, Spigel DR. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015; 373: 123-135 [PMID: 26028407 DOI: 10.1056/NEJMoa1504627]

34 Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Feliip E, Holgado E, Barlesi F, Kohlhäuß M, Arrieta O, Burgio MA, Fayet J, Liena H, Poddubskaya E, Herber DE, Gettinger SN, Radin CM, Rizvi N, Crinò L, Blumenschein GR, Antonia SJ, Dange O, Harbison CT, Graf Finkenstein F, Brahmer JR. Nivolumab versus Docetaxel in Advanced Non-Squamous Non-Small-Cell Lung Cancer. N Engl J Med 2015; 373: 1627-1639 [PMID: 26142456 DOI: 10.1056/NEJMoa1507643]

35 ESMO 2016 Press Release. Significant survival gains with atezolizumab vs docetaxel for non-small cell lung cancer. [updated 2016 Oct 9]. Available from: URL: www.esmo.org

36 Reck M, Rodriguez-Abruna D, Robinson AG, Hui R, Csöszti T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O’Brien M, Rao S, Hotta K, Leiby MA, Lubiniecki GM, Shentu Y, Rangwala R, Brahmer JR. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016; 375: 1823-1833 [PMID: 27718847 DOI: 10.1056/NEJMoa1606774]

37 Bristol-Myers Squibb. An Open-Label, Randomized, Phase 3 Trial of Nivolumab Versus Investigator’s Choice Chemotherapy as First-Line Therapy for Stage IV or Recurrent PD-L1 Non-Small Cell Lung Cancer (CheckMate 026). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02486718

38 Merck Sharp & Dohme Corp. Pembrolizumab (MK-3475) Versus Standard Treatment for Recurrent or Metastatic Head and Neck Cancer (CheckMate 040). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02224781

39 Merck Sharp & Dohme Corp. Study of Pembrolizumab (MK-3475) vs Brentuximab Vedotin in Participants With Relapsed or Refractory Classical Hodgkin Lymphoma (MK-3475-204/KEYNOTE-204). In: ClinicalTrials.gov [Internet]. Bethesda (MD):
Bersanelli M et al. Transversal challenges with the inhibition of the PD-1/PD-L1 axis
Bersanelli M et al. Transversal challenges with the inhibition of the PD-1/PD-L1 axis

gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02302067

Hoffmann-La Roche. The Effect of Atezolizumab in Combination With Gemcitabine/Carboplatin and Gemcitabine/Carboplatin Alone in Participants With Untreated Locally Advanced or Metastatic Urothelial Carcinoma Who Are Ineligible for Carboplatin-based Therapy [MVigior130]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02807636

Hoffmann-La Roche. A Study of Atezolizumab (MPDL3280A) Compared With a Platinum Agent (Cisplatin or Carboplatin) (Pemetrexed or Gemcitabine) in Participants With Stage IV Non-Squamous or Squamous Non-Small Cell Lung Cancer (NSCLC) [IIMpower110]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02409342

Hoffmann-La Roche. A Study of Atezolizumab (MPDL3280A) Compared With Gemcitabine Cisplatin or Carboplatin in Patients With Stage IV Squamous Non-Small Cell Lung Cancer [IIMpower111]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02367794

Hoffmann-La Roche. A Study of Atezolizumab Compared With Docetaxel in Non-Small Cell Lung Cancer (NSCLC) After Failure With Platinum-Containing Chemotherapy [IIMpower120]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02813785

Hoffmann-La Roche. A Phase III Study of MPDL3280A (Anti-PD-L1 Antibody) in Combination With Non-Squamous Non-Small Cell Lung Cancer (IIMpower200). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02367788

Hoffmann-La Roche. A Phase III Study of MPDL3280A (Anti-PD-L1 Antibody) In Combination With Carboplatin Paclitaxel With or Without Bevacizumab in Patients With Stage IV Non-Squamous Non-Small Cell Lung Cancer (NSCLC) (IIMpower125). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02366143

Hoffmann-La Roche. A Study of Atezolizumab (Anti-PD-L1 Antibody) In Combination With Nab Paclitaxel Compared With Placebo With Nab Paclitaxel for Patients With Previously Untreated Metastatic Triple Negative Breast Cancer (IIMpassion130). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02425891

Hoffmann-La Roche. A Study Of Atezolizumab (Anti-PD-L1 Antibody) In Combination With Bevacizumab Versus Sunitinib in Patients With Untreated Advanced Renal Cell Carcinoma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02420891

Hoffmann-La Roche. A Study of Carboplatin Plus Etoposide With or Without Atezolizumab in Participants With Untreated Extensive-Stage Small Cell Lung Cancer (IIMpower133). In: ClinicalTrials. gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02763579

Hoffmann-La Roche. A Study to Investigate Efficacy and Safety of Cabotinib Plus Atezolizumab and Atezolizumab Monotherapy Versus Regorafenib in Participants With Metastatic Colorectal Adenocarcinoma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02788279

AstraZeneca. Phase III Open-label Study of MEDI4736 With/Without Tremelimumab Versus Standard of Care (SOC) in Recurrent/Metastatic Head and Neck Cancer (KESTREL). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02551159

AstraZeneca. Phase III Open Label First Line Therapy Study of MEDI 4736 (Durvalumab) With or Without Tremelimumab Versus SOC in Non Small-Cell Lung Cancer (NSCLC). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02453282

AstraZeneca. Study of MEDI4736 With or Without Tremelimumab Versus Standard of Care Chemotherapy in Urothelial Cancer. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02516421

Southwest Oncology Group. Lung-MAP: Biomarker-Targeted Second-Line Therapy in Treating Patients With Recurrent Stage IV Squamous Cell Lung Cancer. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02154400

AstraZeneca. Study of AZD9291 Plus MEDI4736 Versus AZD9291 Monotherapy in NSCLC After Previous EGFR TKI Therapy in T790M Mutation Positive Tumours (CAURAL). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02454933

AstraZeneca. Study of MEDI4736 Monotherapy and in Combination With Tremelimumab Versus Standard of Care Therapy in Patients With Head and Neck Cancer. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02689784

AstraZeneca. Study of 1st Line Therapy Study of MEDI4736 With Tremelimumab Versus SoC in Non Small-Cell Lung Cancer (NSCLC) (NEPTUNE). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02422929

AstraZeneca. A Global Study to Assess the Effects of MEDI4736, Given as Monotherapy or in Combination With Tremelimumab Determined by PD-L1 Expression Versus Standard of Care in Patients With Locally Advanced or Metastatic Non Small Cell Lung Cancer (ARCTIC). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02352948

Merck Sharp & Dohme Corp. A Study of Pembrolizumab (MK-3475) for First Line Treatment of Recurrent or Metastatic Squamous Cell Cancer of the Head and Neck (MK-3475-048: KEYNOTE-048). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02558031

Bristol-Myers Squibb. Study of Nivolumab in Combination With Ipilimumab Compared to the Standard of Care (Extreme Study Regimen) as First Line Treatment in Patients With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (CheckMate 651). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02741570

Bristol-Myers Squibb. A Study of Nivolumab Compared to Sostesabin as a Primary Treatment in Patients With Advanced Hepatocellular Carcinoma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02765009

Ono Pharmaceutical Co. Ltd. Study of ONO-4538 in Unresectable Advanced or Recurrent Gastric Cancer. In: ClinicalTrials.
A Study of Nivolumab, or Nivolumab
Gorantla V, Weiss K, Tawbi H. Immunotherapy in 2015; 2015; 2016; 2016. Effectiveness Study of Nivolumab
Bersanelli M. Combination therapy in kidney cancer: Nivolumab Combined With Ipilimumab
Bauer TW, Slingluff CL, Rahma OE. From bench to
Study of Nivolumab Compared to
96
94
93
89
86
85
83
80
78
76
74
72
70
68
66
64
62
60
58
56
54
52
50
48
46
44
42
40
38
36
34
32
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0

A Study of Nivolumab Compared to Bevacizumab and of Nivolumab With or Without Ipilimumab in Glioblastoma Patients (CheckMate 143). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02017717
Nivolumab. A Study of Nivolumab Combined With Ipilimumab Versus Sunitinib in Previously Untreated Advanced or Metastatic Renal Cell Carcinoma (CheckMate 214). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02569242
Nivolumab. A Study of the Effectiveness and Safety of Nivolumab Compared to Bevacizumab and of Nivolumab With or Without Ipilimumab in Glioblastoma Patients (CheckMate 143). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02331749
Nivolumab. A Trial of Nivolumab, or Nivolumab Plus Ipilimumab, or Nivolumab Plus Platinum-doublet Chemotherapy, Compared to Platinum Doublet Chemotherapy in Patients With Stage IV Non-Small Cell Lung Cancer (NSCLC) (CheckMate 227). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02105636
Nivolumab. A Study of Nivolumab, or Nivolumab Plus Ipilimumab, or Nivolumab Plus Platinum-doublet Chemotherapy, Compared to Platinum Doublet Chemotherapy in Patients With Extensive-Stage Disease Small Cell Lung Cancer (ED-SCLC) After Completion of Platinum-based Chemotherapy (CheckMate 451). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02535666
Nivolumab. Study of Nivolumab Compared to Temozolomide, Given With Radiation Therapy, for Newly-diagnosed Patients With Glioblastoma (GBM, a Malignant Brain Cancer) (CheckMate 498). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02617589
Nivolumab. Effectiveness Study of Nivolumab Compared to Docetaxel in Subjects Previously Treated With Advanced or Metastatic Non Small Cell Lung Cancer (CheckMate 078). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02481830
Nivolumab Combined With Ipilimumab Followed by Nivolumab Monotherapy as First-Line Treatment for Patients With Advanced Melanoma (CheckMate 401). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: URL: https://clinicaltrials.gov/ct2/show/NCT02599402
Bersanelli M. The ‘nivolution’ in renal cell carcinoma: behind the scenes of clinical trials. Future Oncol 2016; 12: 2061-2063 [PMID: 27168416 DOI: 10.2217/fon-2016-0040]
Facchetti F, Marabelli A, Rossi G, Soria JC, Besse B, Tiseo M. Moving Immune Checkpoint Blockade in Thoracic Tumors beyond NSCLC. J Thorac Oncol 2016; 11: 1819-1836 [PMID: 27289878 DOI: 10.1016/j.jtho.2015.06.027]
Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Sinirinas S, Tykodi SS, Somesan JA, Procopio G, Plimack ER, Castellano D, Choueiri TK, Gunney H, Downs V, Bonp O, Wagaqta J, Gauler TC, Ueda T, Tomita Y, Schutz FA, Kollmannsberger C, Larkin J, Ravaud A, Simon JS, Xu LA, Waxman IM, Sharma P. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med 2015; 373: 1803-1813 [PMID: 26460148 DOI: 10.1056/NEJMoa1510065]
Motzer RJ, Hutson TE, Glen H, Michaelson MD, Molina A, Eisen T, Jassm J, Zolnikewich J, Marote JP, Bellando B, Melichar B, Tomasek J, Kremer A, Kim HJ, Wood K, Dutcus E, Larkin J, Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. Lancet Oncol 2015; 16: 1473-1482 [PMID: 26842279 DOI: 10.1016/S1470-2045(15)00299-9]
Buti S, Bersanelli M. Combination therapy in kidney cancer: the next revolution? Lancet Oncol 2015; 16: 1441-1442 [PMID: 26682275 DOI: 10.1016/S1470-2045(15)00325-3]
A Phase III Randomized, Open-label Study to Evaluate Efficacy and Safety of Pembrolizumab (MK-3475) in Combination With Axitinib Versus Sunitinib Monotherapy as a First-line Treatment for Locally Advanced or Metastatic Renal Cell Carcinoma (mRCC) (KEYNOTE-426). NCT02853331
Kim J. Immune checkpoint blockade therapy for bladder cancer treatment. Invest Clin Urol 2016; 57 Suppl 1: S98-S105 [PMID: 27326412 DOI: 10.1111/ica.2016.57.S1.S98]
Fahmy O, Khairul-Ari MI, Stenzl A, Gakis G. The current status of checkpoint inhibitors in metastatic bladder cancer. Clin Exp Metastasis 2016; 33: 629-635 [PMID: 27380916 DOI: 10.1007/s10585-016-9807-9]
Rosenberg JE, Hoffmann-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A, Dawson N, O’Donnell PH, Balmanoukian A, Loriot Y, Srinivas S, Retz MM, Grivas P, Joseph RW, Galsky MD, Fleming MT, Petrylak DP, Perez-Gracia JL, Bursi H, Castellano D, Canil C, Bellmant J, Dajorin D, Nickles D, Bourgon R, Frampton GM, Cui N, Marathasan S, Abidoye O, Fine GD, Dreizer R, Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016; 387: 1909-1920 [PMID: 26952546 DOI: 10.1016/S0140-6736(16)00561-4]
Economopoulos P, Kotsantis I, Psyrri A. Checkpoint Inhibitors in Head and Neck Cancer: Rationale, Clinical Activity, and Potential Biomarkers. Curr Treat Options Oncol 2016; 17: 40 [PMID: 27315066 DOI: 10.1007/s11864-016-0419-z]
Hamanishi J, Mandai M, Konishi I. Immune checkpoint inhibition in ovarian cancer. Int Immunol 2016; 28: 339-348 [PMID: 27055470 DOI: 10.1093/intimm/dxw020]
Burgess M, Goranta V, Weiss K, Tawbi H. ImmunoTherapy in Sarcoma: Future Horizons. Curr Oncol Rep 2015; 17: 52 [PMID: 26423769 DOI: 10.1007/s11921-015-0476-7]
Matsuki E, Younes A. Checkpoint Inhibitors and Other Immune Therapies for Hodgkin and Non-Hodgkin Lymphoma. Curr Treat Options Oncol 2016; 17: 31 [PMID: 27193488 DOI: 10.1007/s40425-016-0119-z]
Kunk PR, Bauer TW, Stingluff CL, Rahma OE. From bench to bedside a comprehensive review of pancreatic cancer immunotherapy. J Immunother Cancer 2016; 4: 14 [PMID: 26981244 DOI: 10.1186/s40425-016-0119-z]
Sanchez-Castañón M, Er TK, Bujanda L, Herreros-Villanueva M. Immunotherapy in colorectal cancer: What have we learned so far? Clin Chim Acta 2016; 460: 78-87 [PMID: 27350293 DOI: 10.1016/j.cca.2016.06.027]
Hoos A, de Pril V, Gurunath RK, de Schaetzen G, Suciu S, Testori A. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. Lancet Oncol 2015; 16: 522-530 [PMID: 25840693 DOI: 10.1016/S1470-2045(15)70122-1]

van der Most RG, Currie AJ, Robinson BW, Lake RA. Decoding dangerous death: how cytotoxic chemotherapy invokes inflammation, immunity or nothing at all. Cell Death Differ 2008; 15: 13-20 [PMID: 18007666 DOI: 10.1038/sj.cdd.4402255]

Kim JM, Chen DS. Immune escape to PD-L1/PD-1 blockade: seven steps to success (or failure). Ann Oncol 2016; 27: 1492-1504 [PMID: 27207108 DOI: 10.1093/annonc/mdw217]

P- Reviewer: Qin JM, Tirumani SH, Tomizawa M, Tsikouras PPT, Zhang L  S- Editor: Ji FF  L- Editor: A  E- Editor: Wu HL
