ORIGINAL RESEARCH

Incidence of immune checkpoint inhibitor-related colitis in solid tumor patients: A systematic review and meta-analysis

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Objectives: To characterize the incidence of immune-related colitis among various ICI regimens and tumor types.

Methods: Thirty-four original studies of prospective ICI trials were identified based on a PubMed search completed on November 1st, 2016. Seventeen studies compared incidences across tumor types. The incidences of all-grade, grade 3–4 (severe) colitis, and grade 3–4 (severe) diarrhea were collected.

Results: Thirty-four studies containing 8863 patients were included in the meta-analysis. The overall incidence during ipilimumab monotherapy was 9.1% for all-grade colitis, 6.8% for severe colitis, and 7.9% for severe diarrhea. The incidence was lowest during PD-1/PD-L1 inhibitor monotherapy with 1.3% for all-grade colitis, 0.9% for severe colitis and 1.2% for severe diarrhea, while combination ipilimumab and nivolumab resulted in the highest incidences of all-grade colitis (13.6%), severe colitis (9.4%) and severe diarrhea (9.2%) among ICI monotherapies. Among melanoma, NSCLC, RCC patients, incidences of colitis and diarrhea with PD-1/PD-L1 inhibitor monotherapy did not significantly differ. Severe colitis incidence was similar with ipilimumab monotherapy at 3 mg/kg and 10 mg/kg (7.1% vs 5.1%, respectively), but significantly higher for severe diarrhea with 10 mg/kg (11.5% vs 5.2%).

Conclusions: The incidence of immune-related colitis and severe diarrhea was higher with ipilimumab-containing regimens compared with PD-1/PD-L1 inhibitors. There was no significant difference in immune-related colitis between different tumor types with PD-1/L1 inhibitors.

Introduction

Immune checkpoint inhibitors (ICIs) produce impressive anti-tumor immune responses by unleashing exhausted cancer-specific T cells. In particular, monoclonal antibodies against CTLA-4 and PD-1/PD-L1 have dramatically improved clinical outcomes in a sizable subset of patients with solid and hematological cancers. With over 14 regulatory approvals in the past 5 years, immune checkpoint inhibitors are already being used increasingly in the clinical setting. Along with this expanded use, a concomitant rise in immune-related adverse events (irAEs) is inevitable. These irAEs are characterized by activated T-cell responses directed toward normal tissue, leading to inflammation of the colon, lung, endocrine glands, skin, liver, and other organs.

Colitis, or inflammation of the colon leading to abdominal pain, cramping and diarrhea, has emerged as a clinically relevant, highly morbid, and potentially life-threatening irAE that may complicate ICI therapy. While clinical trials with immune checkpoint inhibitors have adeptly reported the incidence of colitis, the variability of these events in single trials makes it difficult to accurately assess the true incidence of colitis with various immune therapy regimens and doses, and in distinct tumor types. Further, many studies report divergent incidences of “colitis” as opposed to “diarrhea,” highlighting the need for a more systemic analysis across studies. Therefore, we performed a systematic review and meta-analysis to address the incidence of ICI-related colitis and diarrhea in various solid tumor types and across different ICIs.

Methods

Design and study selection

A literature search using PubMed was performed to identify relevant articles published before November 1, 2016 that included prospective trials of anti-CTLA-4, anti-PD-1 and anti-PD-L1 therapy in solid cancer patients using ipilimumab, nivolumab, pembrolizumab, or atezolizumab either in single-agent or combination therapies. The following keywords or corresponding Medical Subject Heading terms were used: “ipilimumab,” “nivolumab,” “pembroliza-
zumab,” “atezolizumab,” or “immune checkpoint inhibitor.” The reference lists from these studies were then used to identify any further articles not found in the original search. Only prospective clinical trials were included and patients could only receive these treatments as monotherapy or in combination with each other (i.e. nivolumab and ipilimumab). Among included trials, cohorts where patients received one agent in combination with another form of therapy (e.g. vaccine, cytokine, targeted therapy, biologic therapy, or growth factor) were not included in the analysis. Articles that were published online “ahead of print” were included; unpublished abstracts were not included. These 4 agents were included as those with US. Food and Drug Administration (FDA) approval at the time of the analysis. From these studies, trials involving melanoma, renal cell carcinoma (RCC), and non-small cell lung cancer (NSCLC) were compared based on tumor types. These 3 tumor types were selected as they have the most clinical data available.

Data collection

Data was extracted by one investigator (DYW) and reviewed independently by a second investigator (DBJ). From all included trials, the number of patients treated with ICI, the number of patients that developed colitis, and the number of patients that developed diarrhea were collected. The incidence of colitis and diarrhea was characterized based on all grades and grade 3 or higher as reported by each trial using National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE) definitions. Diarrhea was also evaluated since the clinical presentation of colitis and diarrhea are often similar and the incidence may overlap. Other data, including study therapy, dosing and frequency of drug administration, phase of trial, and tumor type were also recorded.

Quality assessment

The risk of bias and quality of articles included the meta-analysis were assessed using standard methods described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Any disagreements among investigators were discussed until a consensus agreement was reached.

Data analysis

R packages meta and metaphor were used for all meta analyses. Overall incidence of colitis and diarrhea was calculated with fixed effect meta-analysis of single proportions from individual studies. Exact binomial confidence intervals were calculated for individual studies; Wald-type confidence intervals were calculated for pooled estimates, both at 5% significance level. Heterogeneity among studies were assessed using Heterogeneity I-squared and tau-squared tests with random-effects model. All analyses were performed in R 3.3.1.

Results

Literature search

Based on the literature search and evaluation of other references, a total of 2370 records were identified for screening (Fig. 1). Among these 2370 articles, 2326 were excluded based on eligibility criteria due to duplicated articles, clinical trials of ICIs in combination with other therapies, or articles that were not prospective, clinical trials. Among the 40 studies accessed, only 34 studies were included in the qualitative and quantitative synthesis. One phase 2 study that did not specify

Figure 1. PRISMA flowchart of included studies.
gastrointestinal adverse events, one phase 1/2 study using different forms of ipilimumab and one smaller single tumor type study component within a larger multi-tumor-type study (and therefore not reporting independent data) were excluded. Three studies were not included due to updated follow-up data reported from the same cohort. The 34 eligible studies included 8863 patients representing clinical trials with advanced solid tumors (N = 3), melanoma (N = 17), NSCLC (N = 8), RCC (N = 3), and other solid cancers (N = 6). These studies contained treatment arms that included ipilimumab (N = 9), nivolumab (N = 17), pembrolizumab (N = 9), atezolizumab (N = 3), and combination ipilimumab and nivolumab (N = 3). These studies are summarized in Table 1.

Incidence of colitis and diarrhea

In all 34 included studies using immune checkpoint inhibitors, the incidence of all grades of colitis was 2.4% (95% CI, 1.6% – 3.6%), 1.7% (95% CI, 1.1% – 2.5%) for grade 3–4 colitis, and 2.3% (95% CI, 1.5% – 3.3%) for grade 3–4 diarrhea. There were only 4 reported colitis-related deaths that occurred in 2 different studies, all in patients treated with single-agent ipilimumab at 10 mg/kg. We then evaluated the incidence of colitis and diarrhea based on therapy, tumor type, and dosage of ipilimumab.

Incidence based on therapy

The incidence of colitis and diarrhea was evaluated and stratified by therapy type, with single-agent ipilimumab, anti-PD-1 or anti-PD-L1, or combination therapy with ipilimumab and nivolumab. For treatment with ipilimumab alone, all-grade colitis occurred in 9.1% (95% CI, 6.6% – 12.5%), grade 3–4 colitis in 6.8% (95% CI, 5.3% – 8.6%), and grade 3–4 diarrhea in 7.9% (95% CI, 5.5% – 11.4%) (Fig. 2, Fig. 3, and S1). With single-agent anti-PD-1 (either nivolumab or pembrolizumab) incidences were notably lower at 1.4% (95% CI, 1.1% – 1.8%), 0.9% (95% CI, 0.7% – 1.3%), and 1.3% (95% CI, 1.0% – 1.7%) for all-grade colitis, grade 3–4 colitis, and grade 3–4 diarrhea, respectively. For single-agent anti-PD-L1 therapy (with atezolizumab), there was a 1.0% (95% CI, 0.4% – 2.2%), 0.6% (95% CI, 0.2% – 1.6%) incidence of all-grade and grade 3–4 colitis, respectively, with a 0.3% (95% CI, 0.1% – 1.1%) incidence of grade 3–4 diarrhea.
diarrhea. In contrast, combination therapy with ipilimumab and nivolumab revealed a higher incidence of all-grade colitis (13.6%, 95% CI, 7.7% – 22.9%), grade 3–4 colitis (9.4%, 95% CI, 4.8% – 17.4%), and grade 3–4 diarrhea (9.2%, 95% CI, 6.8% – 12.3%).

Incidence based on tumor type in anti-PD-1/L1 therapies

We then investigated the incidence of these events by distinct tumor types. Single-agent ipilimumab studies were exclusively in melanoma, and were thus not included in this analysis. The incidence of colitis and diarrhea based on tumor types, either melanoma, NSCLC, or RCC, was evaluated in anti-PD-1/L1 monotherapy studies only. There was low incidence of all-grade colitis (1.8%, 0.8%, 0.4%), grade 3–4 colitis (1.2%, 0.5%, 0.4%), and grade 3–4 diarrhea (1.4%, 1.2%, 1.0%) in melanoma, NSCLC and RCC trials, respectively (Fig. 4, S2 and S3). Although these incidences were low among tumor types, it is notable that the incidence of all-grade and grade 3–4 colitis appeared to occur somewhat more frequently in melanoma compared with both NSCLC and RCC.
The incidence of colitis and diarrhea was also explored in single-agent ipilimumab trials at the 2 most commonly used (and FDA-approved) doses, 10 mg/kg and 3 mg/kg. At the higher 10 mg/kg dose, the incidence of all grade colitis, grade 3–4 colitis and grade 3–4 diarrhea was 6.6% (95% CI, 2.4% – 16.7%), 5.1% (95% CI, 2.5% – 9.9%) for grade 3–4 colitis, and 11.5% (95% CI, 8.5% – 15.5%) for grade 3–4 diarrhea, respectively (S4). The lower dose at 3 mg/kg had incidences of 9.6% (95% CI, 7.6% – 12.0%), 7.1% (95% CI, 5.3% – 9.4%), and 5.2% (95% CI, 3.3% – 8.2%) for all-grade colitis, grade 3–4 colitis, and grade 3–4 diarrhea, respectively (S5). Thus, similar rates of severe colitis were noted between doses (5.1% vs. 7.1%) but substantially higher.

**Incidence based on dosage of ipilimumab**

Figure 4. Forest plot of incidence of grade 3–4 colitis in anti-PD-1/L1 therapy by tumor types: (A) melanoma, (B) renal cell carcinoma, (C) non-small cell lung cancer.
rates of severe diarrhea with 10mg/kg vs. 3mg/kg (11.5% vs. 5.2%). Notably, the only published clinical trial that evaluated ipilimumab in the adjuvant setting involved high-dose ipilimumab at 10 mg/kg. This study reported the highest incidence of all-grade colitis (15.5%) and grade 3–4 colitis (7.6%), substantially higher than all other ipilimumab studies, including others using the 10mg/kg dose.

Discussion

To our knowledge, this is the first meta-analysis assessing the rates of immune checkpoint inhibitor related colitis based on various regimens, doses, and tumor types. Importantly, there appeared to be a higher incidence of severe (grade 3–4) colitis with ipilimumab monotherapy (6.8%), and with combined immune checkpoint inhibition with ipilimumab and nivolumab (9.4%). We also observed more severe (grade 3–4) diarrhea with ipilimumab alone and in combination with nivolumab (7.9% and 9.2%, respectively) as compared with anti-PD-1 or anti-PD-L1 therapy (1.3% and 0.3%, respectively).

When stratifying incidences of colitis or diarrhea in PD-1 inhibitor studies based on tumor types, the incidence of all events was low in melanoma, NSCLC, and RCC. Interestingly, there was a nearly double the incidence of all-grade and grade 3–4 colitis in melanoma as compared with RCC and NSCLC, suggesting a possible tumor-specific relationship that needs to be further clarified. This type of relationship has been previously observed in another meta-analysis that revealed a higher incidence of immune-related pneumonitis in NSCLC and RCC as compared with melanoma. One could hypothesize that various tumor neoantigens could mimic normal self-antigens, potentially leading to tumor-toxicity interactions. However, our results and other studies have suggested if such interactions exist, the effects on frequency of colitis is very modest. One other possibility is that the higher response rates observed in melanoma lead to longer duration of therapy, thus contributing to the higher rates of gastrointestinal events.

The characterization and grading of colitis and diarrhea based on CTCAE definitions has significant overlap. Although the adverse event of diarrhea is graded solely on the number of bowel movements over baseline, colitis is graded based on separate clinical findings such as abdominal pain, mucus or blood in the stool, and peritoneal signs. Additionally, there is a subjective nature to the grading of symptoms which does not always translate to clinical severity and management of the symptoms. Therefore, early reporting of symptoms is emphasized to patients as delays in diagnosis often lead to more severe toxicity and comorbidity. Since clinically relevant immune-related colitis can be encapsulated by both adverse event terms, we focused on both cases of colitis and severe (grade 3–4) diarrhea to reflect this overlap as they are typically treated similarly with systemic corticosteroids. Thus, the true incidence of clinically treated immune-related colitis may need to be further explored in the post-market setting.

The complexities of irAE classification were particularly illustrated in our analysis of single-agent ipilimumab at various doses. While there was no appreciable difference in G3–4 colitis at 10 mg/kg and 3 mg/kg doses (5.1% vs 7.1%), there was a substantially higher incidence of G3–4 diarrhea with higher doses of ipilimumab (11.5% vs 5.2%). Additionally, there appeared higher incidences of both G3–4 colitis (15.5%) and diarrhea (7.6%) with adjuvant ipilimumab at 10 mg/kg in melanoma with nearly twice the incidence of the next highest incidence reported with the same dose (8.4% and 5.3% respectively). The higher rates of severe colitis and diarrhea with ipilimumab in the adjuvant setting could suggest a relationship between immune-related colitis and the lack of an immune suppressive tumor microenvironment. Clearly, this relationship remains to be established in further studies.

In this meta-analysis, ipilimumab, alone or in combination, induced more colitis than single-agent PD-1/L1 inhibitors. One possibility could be the effects of CTLA-4 inhibition in the colon microenvironment. Murine models show that the induction of T-regulatory cells in the intestines is dependent on CTLA-4 and its blockade leads to immune-related colitis. While animal and clinical studies have demonstrated that PD-1/L1 deficiency or blockade can also lead to colitis, the mechanism behind this phenomenon is less clear. One study showed that PD-1/L1-related colitis can occur through the inhibition of PD-L1 through the innate immune system, while other studies has shown the inhibition of colitis through a regulatory population of CD4+CD25-PD-1+ T cells. Data on the synergy of these therapies in a murine model of colitis has yet to be published.

The limitations of this study include inherent disadvantages with the use of meta-analyses such as quality and heterogeneity of included studies, publication bias, analysis of aggregated patient data, and generalizability of the conclusions due to these above limitations. However, we believe the strict inclusion and exclusion criteria ensured a high standard on the quality of the studies and captured all relevant trials. Additionally, studies included varying dosages and administrations schedules which could affect the heterogeneity of the meta-analysis. We felt it would be important to analyze varying doses of ipilimumab based on concerns of dose-related incidences of immune related colitis. However, this was not done for the PD-1/L1 inhibitor studies as stratifying by these parameters would lead to smaller cohorts that would be difficult to interpret statistically. In addition, we did not include any studies that combined ICI with other therapies such as targeted therapy, vaccines, or chemotherapies.

Conclusions

In this meta-analysis, we identified a higher incidence of immune-related colitis with ipilimumab-based regimens as compared with PD-1/PD-L1 inhibitors. Immune-related colitis can be a challenging clinical dilemma for both patients and physicians, including a decrease in functional status and frequent clinical monitoring. Additionally, the cost on the healthcare system is substantial with one study estimating the cost to be over $20,000 and 5 hospital days for inpatient hospitalization for severe episodes of colitis and diarrhea in the United States. With the increasing use of immune checkpoint inhibitors (ICI) in oncology, there will be a concomitant rise in the incidence of immune-related colitis. This systematic review provides a basis to increase clinician awareness. We believe further studies are needed to fully characterize the natural history and management of this significant adverse event.
Disclosure of potential conflicts of interest
Dr. Johnson has consulted for BMS and Genoptix, and has received research funding from Incyte. No other disclosures are reported.

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References
1. Weber JS, O’Day S, Urba W, Powderly J, Nichol G, Yellin M, Snively J, Hersh E. Phase ii study of ipilimumab for patients with metastatic melanoma. J Clin Oncol 2008; 26(36):3590-56; PMID:19018089; https://doi.org/10.1200/JCO.2008.16.1927
2. Weber J, Thompson JA, Hamid O, Amin A, Ron I, Riddolfi R, Assi H, Maraveyas A, Berman D, et al. A randomized, double-blind, placebo-controlled, phase ii study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage iii or iv melanoma. Clin Cancer Res 2009; 15(17):5591-98; PMID:19671877; https://doi.org/10.1158/1078-0432.CCR-09-1024
3. Wolchok JD, Neyns B, Linette G, Negrin S, Lutzky J, Thomas L, Waterfield W, Schadendorf D, Smylie M, Guthrie T, Jr, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: A randomised, double-blind, multicentre, phase 2, dose-ranging study. Lancet Oncol 2010; 11(2):155-64; PMID:20004617; https://doi.org/10.1016/S1470-2045(09)70334-1
4. O’Day SJ, Maio M, chiarion-sileni V, Gajewski TF, Pehamberger H, Bondarenko IN, Queirolo P, Lundgren L, Mikhaliov S, Roman L, et al. Efficacy and safety of ipilimumab monotherapy in patients with pretreated advanced melanoma: A multicenter single-arm phase ii study. Ann Oncol 2010; 21(8):1712-17; https://doi.org/10.1093/annonc/mdq013
5. Brahmer JR, Drake CG, Wollner I, Powderly JD, Picus J, Sharifman WH, Stankevich E, Pons A, Salay TM, McMiller TL, et al. Phase i study of single-agent anti-programmed death-1 (mdx-1106) in refractory solid tumors: Safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol 2010; 28(19):3167-75; PMID:20516446; https://doi.org/10.1200/JCO.2009.26.7609
6. Hodi FS, O’Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, Robert C, Schadendorf D, Hassel JC, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010; 363(8):711-23; PMID:20525992; https://doi.org/10.1056/NEJMoa1001859
7. Margolin K, Ernstoff MS, Hamid O, Lawrence D, McDermott D, Puzanov I, Wolchok JD, Clark JJ, Snol M, Logan TF, et al. Ipilimumab in patients with melanoma and brain metastases: An open-label, phase 2 trial. Lancet Oncol 2012; 13(5):459-65; PMID:22454629; https://doi.org/10.1016/S1470-2045(12)70090-6
8. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, Powderly JD, Carvajal RD, Sosman JA, Atkins MB, et al. Safety, activity, and immune correlates of anti-pd-1 antibody in cancer patients. J Clin Oncol 2013; 31(34):4311-18; PMID:24145345; https://doi.org/10.1200/JCO.2013.53.4802
9. Topalian SL, Sznol M, McDermott DF, Kluger HM, Carvajal RD, Sharfman WH, Braham JR, Lawrence DP, Atkins MB, Powderly JD, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J Clin Oncol 2014; 32(10):1020-30; PMID:24590637; https://doi.org/10.1200/JCO.2013.53.0105
10. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, Hassel JC, Rutkowski P, McNeil C, Kalinka-Warzocha E, et al. Nivolumab in previously untreated melanoma without braf mutation. N Engl J Med 2015; 372(4):320-30; PMID:25399552; https://doi.org/10.1056/NEJMoa1412082
11. Herbst RS, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, Sosman JA, McDermott DF, Powderly JD, Gettinger SN, et al. Predictive correlates of response to the anti-pd-l1 antibody mdp3280a in cancer patients. Nature 2014; 515(7528):563-7; PMID:25428504; https://doi.org/10.1038/nature14011
12. Motzer RJ, Rini BI, McDermott DF, Redman BG, Kuzel TM, Harrison MR, Vaishampayan UN, Drabkin HA, George S, Logan TF, et al. Nivolumab for metastatic renal cell carcinoma: Results of a randomized phase ii trial. J Clin Oncol 2015; 33(13):1430-7; PMID:25452452; https://doi.org/10.1001/jco.2014.59.0703
13. Rizvi NA, Mazieres I, Planchard D, Stinchcombe TE, Dy GK, Antoni SJ, Horn L, Lenza M, Menenecier B, et al. Activity and safety of nivolumab, an anti-pd-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (checkmate 063): A phase 2, single-arm trial. Lancet Oncol 2015; 16(3):257-65; PMID:25704439; https://doi.org/10.1016/S1470-2045(15)70054-9
14. Weber JS, D’Angelo SP, Minid O, Hodi FS, Gutzmer R, Negrin S, Hoeller C, Khushalani NI, Miller WH, Jr., Lao CD, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-cila-4 treatment (checkmate 037): A randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2015; 16(4):375-84; PMID:25795410; https://doi.org/10.1016/S1470-2045(15)70076-8
15. McDermott DF, Drake CG, Sznol M, Choueiri TK, Powderly JD, Smith DC, Brahmer JR, Carvajal RD, Hammers HJ, Puzanov I, et al. Survival, durable response, and long-term safety in patients with previously treated advanced renal cell carcinoma receiving nivolumab. J Clin Oncol 2015; 33(18):2013-20; PMID:25800770; https://doi.org/10.1200/JCO.2014.58.1041
16. Garon EB, Rizvi NA, Hui R, Leigh N, Balmanoukian AS, Eder JP, Patnaik A, Aggarwal C, Gubens M, Horn L, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015; 372(21):2018-28; PMID:25891174; https://doi.org/10.1056/NEJMoa1510824
17. Robert C, Schachter J, Long GV, Arance A, Grob JH, Mortier L, Daud A, Carlino MS, McNeil C, Lotem M, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 2015; 372(26):2521-32; PMID:25891173; https://doi.org/10.1056/NEJMoa1503093
18. Gettinger S, Rizvi NA, Chow LQ, Borghaei H, Brahmer J, Ready N, Gerber DE, Shepherd FA, Antonia S, Goldman JW, et al. Nivolumab monotherapy for first-line treatment of advanced non-small-cell lung cancer. J Clin Oncol 2016; 34(25):2980-87; PMID:27354485; https://doi.org/10.1200/JCO.2016.66.9929
19. Postow MA, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, Linette GP, Meyer N, Giguere JK, Agarwala SS, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med 2015; 372(21):2006-17; PMID:25891304; https://doi.org/10.1056/NEJMoa1414428
20. Patnaik A, Kang SP, Rosco D, Papadopoulos KP, Ellassa-Schaap J, Brem T, Drengler R, Chen C, Smith M, Espino G, et al. Phase I study of pembrolizumab (mk-3475; anti-pd-1 monoclonal antibody) in patients with advanced solid tumors. Clin Cancer Res 2015; 21(19):4286-93; PMID:25977344; https://doi.org/10.1158/1078-0432.CCR-14-2607
21. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, Skora AD, Luber BS, Azad NS, Laheru D, et al. Pd-1 blockade in tumors
